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A Convenient Synthesis of (*S*)-2-Azidonitriles, (*S*)-2-Aminonitriles and (*S*)-1,2-Diamines[1]

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Abstract: (*S*)-2-Azidonitriles (*S*)-**4** are easily accessible from (*R*)-2-(sulfonyloxy)nitriles (*R*)-**2** by nucleophilic substitution with alkali azides **3** under complete inversion of configuration. The azidonitriles (*S*)-**4** can be converted by catalytic hydrogenation into (*S*)-2-aminonitriles (*S*)-**8** and by hydrogenation using $LiAlH_4$ into (*S*)-1,2-diaminoalkanes (*S*)-**9**, respectively, both, (*S*)-**8** and (*S*)-**9**, isolated as hydrochlorides. Hydrolysis of the aminonitrile hydrochlorides (*S*)-**8**·HCl in a saturated solution of HCl in alcohol gives (*S*)-2-amino carboxamide hydrochlorides (*S*)-**10**·HCl with enantiomeric excesses >99% after recrystallization.

In a preliminary communication[3] we have described the first synthesis of optically active 2-azidonitriles by stereoselective nucleophilic substitution of (*R*)-2-(sulfonyloxy)nitriles with potassium azide.
In the present publication we report comprehensively on the preparation of optically active 2-azidonitriles, their hydrogenation to optically active 2-aminonitriles as well as to optically active 1,2-diamines. We also describe the preparation of enantiomerically pure (*S*)-2-amino carboxamides by hydrolysis of the corresponding (*S*)-2-aminonitriles.

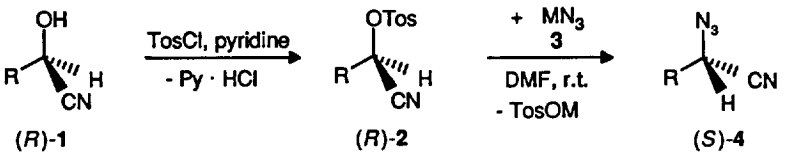
Aliphatic 2-Azidonitriles (*S*)-4 from 2-(4-Tosyloxy)nitriles (*R*)-2 with Alkali Azides 3

Whereas stereoselective nucleophilic substitution of α-substituted carboxylic acids and carboxylates, respectively, are quite common,[4] very little is known about the comparable reactions of α-substituted nitriles.[5]
From nitriles with a leaving group in α-position, only α-halonitriles have been prepared in optically active form.[5] Nucleophilic substitutions of optically active α-halonitriles, however, occur with a great deal of racemization, caused by nucleophilic attack of halide ions liberated during substitution. Optically active α-sulfonyloxynitriles which are easily accessible by sulfonylation of the corresponding cyanohydrins[3,6] are configurationally considerably more stable because of the lower nucleophilic potential of sulfonate leaving groups.[4]
Only a few examples of racemic 2-azidonitriles are described in the literature. 2-Azidopropionitrile[7a] and 2-azido-2,2-diphenylacetonitrile,[7b] for example, were prepared by nucleophilic substitution of the corresponding 2-bromonitriles with NaN_3. 2-Azido-2,2-diphenylacetonitrile was also obtained starting from diphe-

nylacetonitrile by azide transfer with tosyl azide.[7c] Dehydration of 2-azidoaldehyde oximes represents a general procedure for the synthesis of racemic 2-azidonitriles.[8]

We have now prepared optically active alkyl and cycloalkyl 2-azidonitriles (*S*)-**4** by nucleophilic substitution of the corresponding (*R*)-2-(4-tosyloxy)nitriles **2**[3,6] with various azides **3** in dimethylformamide (DMF) as solvent at room temperature whereby complete inversion of configuration occurs (Scheme 1, Table 1).

Scheme 1



1,2,4	a	b	c	d	e	f
R	*n*-C_3H_7	Me_2CHCH_2	Me_3C	*c*-C_6H_{11}	*c*-C_6H_9	$MeS(CH_2)_2$

3	a	b	c
M	K^+	Na^+	Bu_4N^+

Table 1. (*S*)-2-Azidonitriles **4** from (*R*)-2-(4-Tosyloxy)nitriles **2** by Nucleophilic Substitution with Alkali Azides **3** in DMF at Room Temperature

Educts			MN_3	Products			
(*R*)-**2**	R =	(*ee*%)[a]	**3**	(*S*)-**4**	Yield [%]	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)	bp [°C/Torr]
a	*n*-C_3H_7	95.5	**a**	**a**	74	-113.5 (1.05)	78/15
a	*n*-C_3H_7	94.5	**b**	**a**	90		
b	$(CH_3)_2CHCH_2$	96.4	**a**	**b**	79	-83.3 (1.22)	70-71/12
b	$(CH_3)_2CHCH_2$	96.4	**b**	**b**	75		
c	$(CH_3)_3C$	82.5	**c**[b]	**c**	67	-149.0 (1.15)	57/10
d	*c*-C_6H_{11}	94.0	**b**	**d**	77	-105.4 (1.17)	112/10
e	*c*-C_6H_9	95.9	**b**	**e**	78	-111.6 (1.08)	113/10
f	$CH_3S(CH_2)_2$	91.6	**b**	**f**	83	-121.4 (1.55)	116/10

[a] ee-Values of the starting cyanohydrins (*R*)-**1**, see Ref.[6] [b] 48 h in boiling benzene.

The azidonitriles (*S*)-**4a,b** and **d-f** were obtained in good yields by reacting (*R*)-**2a,b,d-f** with a 1.5 fold excess of azide **3a** or **3b** (Table 1). The use of NaN_3 (**3b**) instead of KN_3 (**3a**) in the reaction of **2a,b** led to comparable yields, therefore NaN_3 was applied in most cases (Table 1). Under the given conditions (DMF, room temperature) the neopentyl derivative 3,3-dimethyl-2-(4-toluenesulfonyloxy)butanenitrile (*R*)-**2c** did not react with KN_3, even after several weeks. By using tetrabutylammonium azide (**3c**)[9] in boiling benzene, however, (*R*)-**2c** was converted to (*S*)-**4c** in 48 h with 67% yield (Table 1).

For determination of the *ee*-values of the azidonitriles (*S*)-**4** a direct method could not be developed. There-

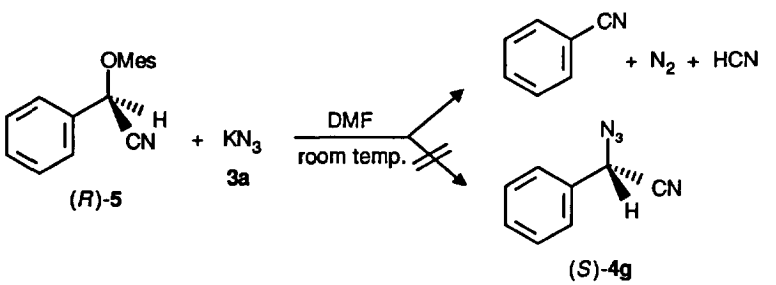
fore the *ee*-values of the azidonitriles (*S*)-**4** were determined after their hydrogenation to the corresponding 2-aminonitriles or 1,2-diamines, respectively, as will be described later.

The *S*-configuration of the 2-azidonitriles was confirmed by comparison of specific rotation values of (*S*)-2-amino-4-methylpentanenitrile (**8b**) $[[\alpha]_D^{22} = +16.8$ (*c* 0.80, $H_2O)]$[10a] and (*S*)-1,2-diamino-4-methylpentane (**9b**) $[[\alpha]_D^{18} = -10.9$ $(H_2O)]$[10b] with the published literature data.[10]

Reaction of 2-(Methanesulfonyloxy)-2-phenylacetonitrile (*R*)-(5) with Azides 3

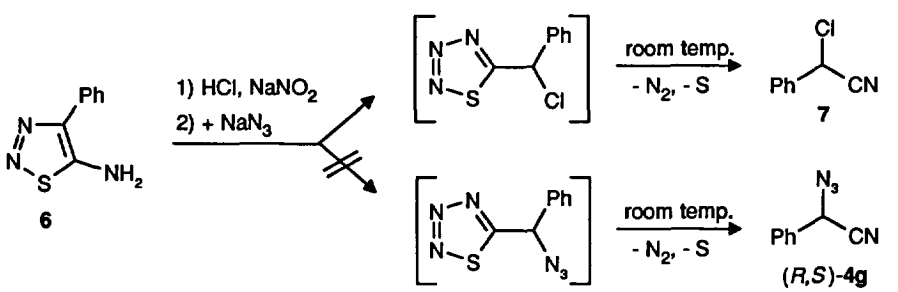
(*R*)-2-(methanesulfonyloxy)-2-phenylacetonitrile (*R*)-**5**, a benzylic type of an α-substituted nitrile, reacts with KN_3 (**3a**) under the reaction conditions described (DMF, 20°C) in a few minutes completely with releasing of nitrogen. Surprisingly, however, 2-azido-2-phenylacetonitrile (*S*)-**4g** was not formed in this reaction but benzonitrile (Scheme 2).

Scheme 2



The synthesis of racemic 2-azido-2-phenylacetonitrile (*R,S*)-**4g** by diazotisation of 5-amino-4-phenyl-1,2,3-thiadiazole (**6**) is described in the literature.[11] According to this procedure published[11] we have tried to prepare **4g** for spectroscopic comparisons. In contrast to the literature data,[11] however, the only product we obtained by diazotisation of **6** was 2-chloro-phenylacetonitrile (**7**)[5a,12] (Scheme 3).

Scheme 3

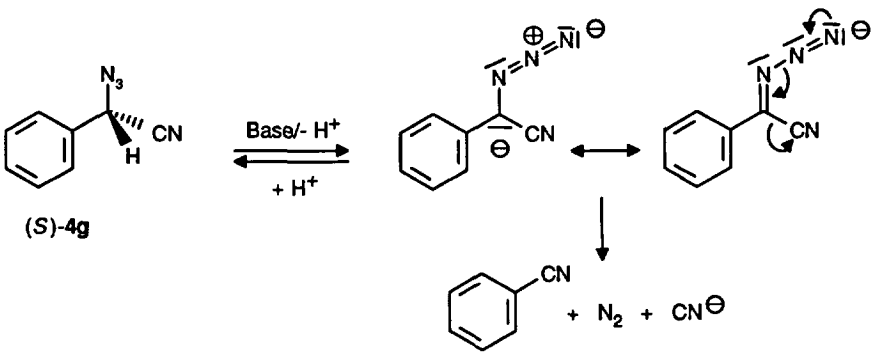


For structure proof we have prepared the α-chloronitrile **7** by reaction of the racemic mesylate **5** with tetrabutylammonium chloride.[13] Compound **7** was unambiguously characterized. The NMR spectra correspond with literature data[5a,12] as well as with the data of the product obtained by diazotation of **6**.[11]

The reaction of 2-hydroxy-phenylacetonitrile with HN_3 under conditions of the Mitsunobu reaction[14] to get the azidonitrile (*R,S*)-**4g** yielded also exclusively benzonitrile and nitrogen.

The formation of benzonitrile and nitrogen during the reaction of (*R*)-**5** with KN_3 can be explained by a base catalyzed fragmentation of the primarily formed azidonitrile **4g** as shown in Scheme 4. The easily occuring deprotonation of **4g** could be proved by H/D exchange in CD_3OD with a weak base like pyridine. After 24 hours at room temperature the H/D exchange is complete.

Scheme 4



Avoiding basic conditions in the reaction of (*R*)-**5** with an azide should prevent the fragmentation. Indeed, by dropping a solution of tetrabutylammonium azide (**3c**) in benzene slowly to a solution of (*R*)-**5** in benzene a mixture of (*S*)-**4g** (52.3%*ee*) and benzonitrile in the ratio 92:8 was obtained in 74% yield.

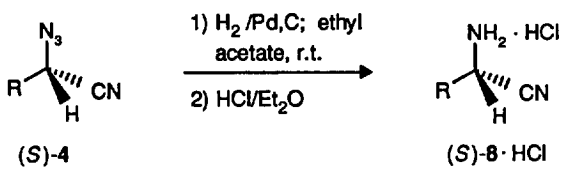
For improving the enantiomeric excess in this substitution reaction, we have applied more acidic reaction conditions to avoid the base catalyzed racemization of both the starting compound (*R*)-**5** as well as the resulting azidonitrile (*S*)-**4g**. So (*R*)-**5** was reacted with a 10 fold molar excess of NaN_3 in acetic acid as solvent. Because of the competition between azide and acetate as nucleophiles, 54% of a mixture of (*S*)-**4g**, (*S*)-2-acetoxy-phenylacetonitrile and benzonitrile in the ratio 85%:10%:5% was obtained. The enantiomeric excess of 82.2% for (*S*)-**4g**, determined after hydrogenation to the corresponding aminonitrile, is comparable with the best *ee*-values obtained for (*S*)-2-acetoxy-2-phenylacetonitrile in the reaction of (*R*)-**5** with potassium acetate in acetic acid.[6]

Preparation of (*S*)-2-Aminonitrile Hydrochlorides (*S*)-8 · HCl

2-Aminonitriles are important starting compounds for the synthesis of 2-amino acids and biologically interesting heterocycles.[15] A well known procedure for the preparation of optically active 2-aminonitriles is the asymmetric Strecker synthesis.[15,16] The optical induction in the case of the addition of HCN to the imino function has been realized with optically active sulfinimines[17a] or imines prepared of aldehydes with chiral amines such as L-1-phenylethylamine,[17b] tetra-*O*-pivaloyl-β-D-galactosylamine[17c,d] and (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-1,3-dioxane.[17e] A further method for the preparation of chiral aminonitriles is the resolution of racemic aminonitriles by formation of salts with optically active organic acids.[15,18a] A kinetic resolution of racemic 2-aminonitriles is possible by enzyme catalyzed enantioselective hydrolysis of the nitrile group yielding (*R*)-2-aminonitriles and (*S*)-2-amino acids.[16,18b] (*S*)-2-aminonitriles can be generally prepared from naturally occuring *N*-protected (*S*)-2-amino carboxamides by dehydration.[10a,18c]

We have now prepared (*S*)-2-aminonitrile hydrochlorides (*S*)-**8** · HCl starting from (*S*)-2-azidonitriles (*S*)-**4** by catalytic hydrogenation of the azide group[19] (Scheme 5, Table 2). Under the reaction conditions applied (Pd/C, room temperature), only the azido but not the nitrile function was hydrogenated.

Scheme 5



4, 8	R	4, 8	R
a	*n*-C_3H_7	**d**	*c*-C_6H_{11}
b	Me_2CHCH_2	**e**	*c*-C_6H_9
c	Me_3C	**g**	Ph

Table 2. Palladium Catalyzed Hydrogenation of (*S*)-2-Azidonitriles (*S*)-**4** to (*S*)-2-Aminonitrile Hydrochlorides (*S*)-**8** · HCl in Ethyl Acetate at Room Temperature

Educts		Reaction	Products (*S*)-**8** · HCl				
(*S*)-**4**	(*ee*%)[a]	Time [h]		Yield [%]	*ee* [%][b]	$[\alpha]_D^{20}$ (*c*, MeOH)	mp [°C]
a	96.0	5	**a**	73	95.8	+10.9 (1.115)	147.5-148.5
b	96.8	15	**b**	77	97.7	+17.2 (1.070)	176-178.5
						+9.6 (2.013)[c]	
c	82.5	16	**c**	58	79.7	-21.6 (1.215)	-
d	95.4	15	**d**	81	92.9	+8.2 (1.050)	194-195
e	95.9[d]	72	**e**	60	97.9	-24.3 (1.110)	181-183
g[e]	98.0	24	**g**	40	52.3	-27.5 (1.215)	158-160
g[f]	99.5	4	**g**	30	82.2	+33.0 (1.001)[c]	152-155

[a] *ee*-Values of the starting cyanohydrins (*R*)-**1** before sulfonylation (see Ref.[6]) and nucleophilic substitution with azides. [b] Determination of *ee*-values after acetylation by GC on β-cyclodextrin phases. [c] In H_2O. [d] Diastereomers. [e] Prepared by reaction of (*R*)-**5** with **3c** in benzene. [f] Prepared by reaction of (*R*)-**5** with **3b** in acetic acid as solvent.

Free 2-aminonitriles are not very stable. By complete protonation of the amino group, however, racemization and condensation reaction to iminobisnitriles[20] are inhibited.[21] Because of this instability the aminonitriles (*S*)-**8** were isolated as hydrochlorides (Scheme 5, Table 2).

In (*S*)-2-azido-2-(3-cyclohexenyl)acetonitrile (*S*)-**4e** the C-C double bond was also hydrogenated under the usual reaction conditions and a mixture of (*S*)-**8e**·HCl/(*S*)-**8d**·HCl was isolated in the ratio 66:34. By using the Lindlar catalyst with addition of 2,2-(ethylenedithio)diethanol, solely (*S*)-**8e**·HCl was obtained in 60% yield with 97.9%*ee* (Table 2).

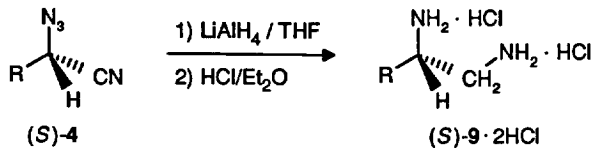
For the hydrogenation of the azido function a triazene is postulated as an intermediate which, in the case of 2-azidonitriles, can react intramolecularly to give an aminotriazol.[22] The formation of triazols is favored in case of aromatic substituents (**4g**: R = Ph).[23] This is probably the reason for the relatively low yield of (*S*)-**8g**·HCl in the hydrogenation of **4g** (Table 2).

Preparation of (*S*)-1,2-Diamine Dihydrochlorides (*S*)-9·2HCl

Optically active 1,2-diamines, which are of interest as ligands in platinum II complexes with efficient antitumor properties,[24a] are generally prepared by hydrogenation of 2-amino carboxamides derived from naturally occuring amino acids with $LiAlH_4$ or diborane.[10b,24]

As outlined in Scheme 6, (*S*)-1,2-diaminoalkane dihydrochlorides (*S*)-**9**·2HCl can easily be obtained by hydrogenation of (*S*)-2-azidonitriles (*S*)-**4** using $LiAlH_4$ which hydrogenates both the azide and the nitrile function (Table 3).[25] By this route optically active diamines can be prepared, which are not accessible via naturally occuring 2-amino acids.

Scheme 6



(*S*)-**4** (*S*)-**9**·2HCl

4, 9	R	4, 9	R
b	Me_2CHCH_2	d	c-C_6H_{11}
c	Me_3C	e	c-C_6H_9

Table 3. Hydrogenation of 2-Azidonitriles (*S*)-**4** with $LiAlH_4$ to 1,2-Diamine Dihydrochlorides (*S*)-**9**·2HCl

Educts		Products (*S*)-**9**·2HCl			
(*S*)-**4**	(ee %)[a]		Yield [%]	*ee* [%][b]	$[\alpha]_D^{20}$ (*c*, H_2O)
b	96.4	b	81	-	-10.2 (3.57)[c]
c	90.9	c	23	84.9	+7.8 (1.09)
d	94.0	d	76	88.3	-7.1 (1.02)[d]
e	96.3[e]	e	44	93.2	+1.0 (1.00)

[a] *ee*-Values of the starting cyanohydrins (*R*)-**1** (see Ref.[6]). [b] *ee*-Values were determined after acetylation by GC on a chiral bornyl amide phase. [c] See Ref.[10b] [d] See Ref.[26] [e] Diastereomers.

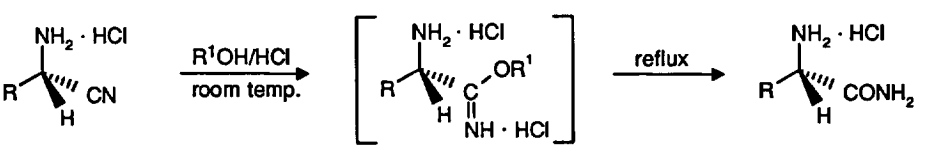
As shown in Table 3, the diamine dihydrochlorides (*S*)-**9b,d** · 2HCl were obtained in fairly good yields. The diminished yields of diamine dihydrochlorides (*S*)-**9c,e** · 2HCl indicate that hydrogenation was probably accompanied by side reactions forming di- or trialkylamines.[27] The hydrogenation of (*S*)-2-azido-2-phenylacetonitrile (*S*)-**4g** with $LiAlH_4$ gives not only (*S*)-1,2-diamino-1-phenylethane dihydrochloride (*S*)-**9g** · 2HCl, since the starting material besides (*S*)-**4g** contains also 10% (*S*)-2-acetoxy-phenylacetonitrile (see above). Moreover **4g** partly decomposes to benzonitrile, caused by $LiAlH_4$ which also reacts as a base. The hydrogenation of **4g** gives therefore besides (*S*)-**9g** · 2HCl also (*S*)-2-amino-1-hydroxy-1-phenylethane and benzylamine. Whereas in the hydrogenation of the alkyl azidonitriles (*S*)-**4c-e** (Table 3) a small decrease of enantiomeric purity was observed, 2-azido-phenylacetonitrile (*S*)-**4g** was hydrogenated with considerable racemization (16.8%*ee*).

Preparation of (*S*)-2-Amino Carboxamide Hydrochlorides (*S*)-10 · HCl

Optically active 2-amino carboxamides are normally prepared by ammonolysis of the corresponding 2-amino acid esters[10a,18c,24b] or by resolution of racemic 2-amino carboxamides via the formation of diastereomeric salts with chiral organic acids.[28a,b] Also the enantioselective hydrolysis of racemic α-aminonitriles using chiral carbonyl catalysts is described.[28c]

Under specific conditions, for example by hydrolysis in conc. H_2SO_4, nitriles can be converted selectively into acid amides.[29] We have applied the conditions of the Pinner reaction[30] for hydrolyzing (*S*)-2-aminonitrile hydrochlorides (*S*)-**8** · HCl selectively to the corresponding 2-amino carboxamide hydrochlorides (*S*)-**10** · HCl (Scheme 7, Table 4). Analogous to a procedure described in the literature,[31] the hydrolysis was performed in a saturated solution of hydrogen chloride in alcohol. On heating, 2-amino carboxamide hydrochlorides (*S*)-**10** · HCl were obtained from the primarily formed imido ester hydrochlorides **A**[31] (Scheme 7). The course of the reaction depends on the alcohol used.[31] If R in (*S*)-**8** · HCl is alkyl, unbranched in β-position, a secondary alcohol R^1OH should be applied, otherwise ester formation results from intermediate **A**.[31] Therefore we have used isopropanol ($R^1 = i$Pr) as solvent in case of (*S*)-**8a,b** · HCl, whereas (*S*)-**8d** · HCl was hydrolyzed in ethanol (R^1 = Et) and (*S*)-**8e** · HCl in allyl alcohol ($R^1 = CH_2{=}CHCH_2$) according to Ref.[31]

Scheme 7



(*S*)-**8** · HCl **A** (*S*)-**10** · HCl

8, 10	**a**	**b**	**d**	**e**
R	*n*-C_3H_7	Me_2CHCH_2	*c*-C_6H_{11}	*c*-C_6H_9

Table 4. Hydrolysis of (*S*)-2-Aminonitrile Hydrochlorides (*S*)-**8** · HCl to (*S*)-2-Amino Carboxamide Hydrochlorides (*S*)-**10** · HCl

(*S*)-**8** · HCl		R^1OH	Products (*S*)-**10** · HCl					
	(ee%)	(ml)		Yield [%][a]	*ee* [%][a]	Yield [%][b]	*ee* [%][b]	$[\alpha]_D^{20}$ (*c*, solvent)
a	97.3	*i*PrOH (15)	**a**	-	-	64	>99.5	+18.3 (1.00, MeOH)
b	97.7	*i*PrOH (14)	**b**	79	98.7	54	>99.5	+8.3 (1.94, H_2O)[c]
d	95.4	EtOH (19)	**d**	77	99.3	62	>99.5	-29.7 (1.06, MeOH)
e	98.7[d]	AllylOH (40)	**e**	-	-	44	97.2[d]	+44.8 (1.035, MeOH)

[a] Crude products. [b] After recrystallization. [c] See Ref.[28a] [d] Diastereomers.

As shown in Table 4, the amino carboxamide hydrochlorides (*S*)-**10** · HCl were isolated with good chemical yields and excellent enantiomeric excesses. The enantiomeric excesses of compounds (*S*)-**10** · HCl were determined by HPLC an a chiral crown ether phase with aqueous perchloric acid (pH 2) as eluent.[32]

Experimental

Materials and Methods: 5-Amino-4-phenyl-1,2,3-thiadiazole (**6**) was prepared according to Ref.[33] and tetrabutylammonium azide (**3c**) according to Ref.,[9] but extraction was performed with diethyl ether instead of dichloromethane. All solvents were purified and dried as described in the literature. Melting points were determined in a Büchi SMP-20 and are uncorrected. ^1H NMR spectra were recorded on a Bruker ACF 250 and CXP 300 with TMS as internal standard. Optical rotations were performed in a Perkin-Elmer polarimeter 241 LC. Gas chromatography: Hewlett Packard 5700A with FID, Spectra Physics Minigrator, 30 ml/min nitrogen, glass columns 2.3 m x 2 mm, phase OV7 on Chromosorb W. GC for determination of enantiomeric excess: a) Carlo Erba Fractovap 2150 with FID, Carlo Erba Mega Series integrator, 0.7 bar helium or 0.3-0.5 bar hydrogen, column 20 m, phase PS 086 with 10% permethylated β-cyclodextrin; b) Carlo Erba HRGC 5300 Mega Series with FID, Carlo Erba Mega Series integrator, 0.7 bar helium or 0.3-0.5 bar hydrogen, column 20 m, phase polydimethylsiloxane with 3.5% valeroyl-L-valine-(*R*)-bornylamide. HPLC for determination of enantiomeric excess: Pharmacia HPLC Pump 2248 with Pharmacia VWM2141 photometer, column Chiral Crownpak CR, size 5 µm (0.4 x 15 cm) (Daicel Chemical Ind. Ltd.), eluent: aqueous perchloric acid, pH 2.0.

*(S)-2-Azidonitriles **4a,b,d-f**; General Procedure*: A solution of (*R*)-**2** (1 equivalent) in DMF (5 ml/mmol **2**) was dropped within 1 h to a solution of **3a** or **3b** (1.5 equivalents) and dibenzo-18-crown-6 (5 mol% based on **3**) in DMF. The reaction mixture was stirred at room temperature for 3-5 d. Then it was hydrolyzed with water and extracted with diethyl ether or dichloromethane. The combined extracts were washed six to eight times with 1 N sodium bicarbonate solution and water, dried ($MgSO_4$) and concentrated. The residue was fractionally distilled *in vacuo* yielding compounds **4** as colorless oils (data see Table 1).

(S)-2-Azido-3,3-dimethylbutanenitrile [(S)-4c]: A solution of (*R*)-**2c** (5.89 g, 22.03 mmol) and **3c** (7.52 g, 26.44 mmol) in benzene (80 ml) was treated with ultrasound for 5 min and then refluxed for 48 h. After the reaction was complete (TLC control) benzene was removed and the residue chromatographed on silica gel (column 5 x 10 cm) with petroleum ether/dichloromethane (1:1). The product containing fractions were concentrated and fractionally distilled *in vacuo* to give **4c** as colorless oil (data see Table 1).

Elemental Analysis of Compounds **4**

4	Molecular Formula (Mol. Weight)	Calcd./Found (%) C	H	N	4	Molecular Formula (Mol. Weight)	Calcd./Found (%) C	H	N	S
a	$C_5H_8N_4$	48.37	6.50	45.13	**d**	$C_8H_{12}N_4$	58.52	7.37	34.12	
	(124.2)	48.58	6.63	45.01		(164.2)	58.44	7.31	34.05	
b	$C_6H_{10}N_4$	52.16	7.29	40.55	**e**	$C_8H_{10}N_4$	59.24	6.21	34.54	
	(138.2)	52.19	7.17	40.32		(162.2)	59.09	6.25	34.78	
c	$C_6H_{10}N_4$	52.16	7.29	40.55	**f**	$C_5H_8N_4S$	38.45	5.16	35.87	20.52
	(138.2)	52.19	7.28	40.66		(156.2)	38.66	5.17	35.98	20.36

Reaction of (R,S)-5 with 3a: A solution of **5** (0.50 g, 2.37 mmol) in DMF (7 ml) was added dropwise at room temperature to a stirred solution of **3a** (0.29 g, 3.57 mmol) and dibenzo-18-crown-6 (5 mol% based on **3a**) in DMF (30 ml). After stirring for a further 12 h, the reaction mixture was poured into water (140 ml) and extracted with dichloromethane. The combined extracts were washed with sodium bicarbonate solution and water, dried ($MgSO_4$), concentrated and chromatographed on silica gel with petroleum ether/dichloromethane (1:1) to give benzonitrile instead of **4g**, characterized by ^1H, ^{13}C NMR and by GC (co-injection of benzonitrile).

Diazotation of 6: A conc. aqueous solution of $NaNO_2$ (0.69 g, 10.0 mmol) was added dropwise at -2°C to a solution of **6** (1.77 g, 10.0 mmol) in conc. HCl (50 ml), followed by addition of a catalytic amount of urea and **3b** (3.25 g, 50.0 mmol). The reaction mixture was stirred at -2°C for 2 h, warmed to room temperature (16 h), neutralized with NaOH and extracted with diethyl ether. The combined extracts were washed with sodium bicarbonate solution, dried ($MgSO_4$), concentrated, and the residue chromatographed on silica gel with petroleum ether/ethyl acetate (1:1). The thiatriazole containing fractions (turbid by sulfur precipitation) were concentrated, and the residue taken up in chloroform and allowed to stand at room temperature for 8 d. Evaporation and chromatography on silica gel with petroleum ether/dichloromethane (1:1) yielded 0.61 g (40%) **7** instead of **4g** as brown oil. ^1H NMR ($CDCl_3$): δ = 5.56 (s, 1 H, CH), 7.43-7.59 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$): δ = 44.15 (C2), 116.05 (CN), 127.62 (*m*-Ph), 129.47 (*o*-Ph), 130.47 (*p*-Ph), 133.07 (*i*-Ph). Anal. Calcd. for C_8H_6ClN: C, 63.38; H, 3.99; N, 9.24; Cl, 23.39. Found: C, 63.50; H, 4.08; N, 9.22; Cl, 23.56.

2-Chloro-2-phenylacetonitrile (7): A solution of tetrabutylammonium chloride[13] (3.52 g, 12.67 mmol) in dichloromethane (30 ml) was added dropwise at room temperature to a stirred solution of **5** (1.90 g, 8.99

mmol) in dichloromethane (30 ml). The solvent was removed and the residue chromatographed on silica gel with petroleum ether/dichloromethane (1:1) to give 1.19 g (87%) **7** as a colorless, eye-irritant oil.

Reaction of (R)-5 with azides 3 in different solvents: a) A solution of HN_3 (2.5 M in acetonitrile,[34] 2 ml) was added to a solution of **3c** (3.19 g, 11.22 mmol) in benzene (150 ml). This mixture was added dropwise at room temperature within 11 h to a vigorous stirred solution of (*R*)-**5** [2.37 g, 11.22 mmol, $[\alpha]_D^{20}$ = +20.6 (*c* 1.105, CH_2Cl_2)] in benzene (150 ml). The reaction mixture was concentrated, and the residue chromatographed on silica gel with petroleum ether/dichloromethane (1:1, 2.5‰ acetic acid) to give 1.43 g (74%) of a light yellow oil composed of 92% (*S*)-**4g** and 8% benzonitrile (determined by GC); $[\alpha]_D^{20}$ = -28.6 (*c* 1.040, CH_2Cl_2).

b) **3b** (9.23 g, 142.0 mmol) was added at 37°C to a solution of (*R*)-**5** [3.0 g, 14.2 mmol, $[\alpha]_D^{20}$ = +20.8 (*c* 1.080, CH_2Cl_2)] in acetic acid (40 ml), and the reaction mixture stirred for 24 h. Then it was poured into water (200 ml) and extracted with diethyl ether. The combined extracts were washed with 1 N sodium bicarbonate solution, dried ($MgSO_4$), concentrated, and the residue dried *in vacuo* to give 1.44 g (54%) of a yellow oil composed of 85% (*S*)-**4g**, 10% (*S*)-2-acetoxy-phenylacetonitrile, 5% benzonitrile (determined by GC); $[\alpha]_D^{20}$ = -29.9 (*c* 1.110, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 5.23 (s, 1 H, CH), 7.49 (s, 5 H, Ph); ^{13}C NMR ($CDCl_3$): δ = 54.40 (C2), 115.45 (CN), 127.40 (*o/m*-Ph), 129.57 (*m/o*-Ph), 130.44 (*p*-Ph), 130.95 (*i*-Ph).

(S)-2-Aminonitrile hydrochlorides (S)-8 · HCl; General Procedure: The Pd catalyst (10 mg/mmol **4**) was added to a solution of **4** in ethyl acetate (40 ml for **4b,d**; 55 ml for **4e** and 70 ml for **4a,c,g**) and with vigorous stirring hydrogen was passed through the solution in the given time (Table 2). The catalyst was filtered off, and the filtrate concentrated. The residue was taken up in diethyl ether. By passing HCl through the ice-cooled solution the hydrochlorides (*S*)-**8** · HCl were precipitated, filtered off and recrystallized from acetonitrile (**8a,b**), acetonitrile/ethanol (**8c,e**), acetonitrile/diethyl ether (**8d**) and ethanol/H_2O (**8g**).

Determination of ee-values of (S)-8 · HCl: Acetic anhydride (40 µl) and pyridine (10 µl) were added to a solution of **8** · HCl (10 mg) in dichloromethane (300 µl). After standing at room temperature for 16 h, the reaction mixture was filtered through a silica gel column (3 x 0.5 cm) with dichloromethane (4-5 ml). The enantiomeric excess was determined directly from the filtrate by gas chromatography on a β-cyclodextrin phase.

(S)-1,2-Diamine dihydrochlorides (S)-9 · 2HCl; General Procedure: The azidonitrile (*S*)-**4** was dropped with stirring at -40°C to $LiAlH_4$ (4 equivalents) in abs. THF (30 ml/mmol **4**). The reaction mixture was allowed to warm up to room temperature, stirred for 16 h and then heated to 40°C for 2 h. The ice-cooled reaction mixture was hydrolyzed with 10% KOH solution until lithium and aluminium hydroxides precipitated. The reaction mixture was extracted with diethyl ether or THF in a Soxhlet apparatus for 16 h. The extract was dried ($MgSO_4$). The product was precipitated by passing HCl into the solution, filtered off and recrystallized from ethanol (**9c,d** · 2HCl) and ethanol/diethyl ether (**9e** · 2HCl).

Determination of ee-values of (S)-9 · 2HCl: The crude **9** · 2HCl (10 mg), pyridine (20 µl) and trifluoroacetic anhydride (30 µl) were added to dichloromethane (200 µl), and after standing at room temperature for 16 h, the reaction mixture was filtered through a silica gel column (3 x 0.5 cm) with dichloromethane or ethyl acetate (3-4 ml). The enantiomeric excess was determined directly from the filtrate by gas chromatography on a chiral bornylamide phase.

(S)-2-Amino carboxamide hydrochlorides (S)-10 · HCl; General Procedure: With cooling HCl was passed into a solution of aminonitrile hydrochloride **8** · HCl (4.0-7.0 mmol) in the corresponding alcohol (Table 4) until the solution was saturated. Then the reaction mixture was stirred for 16 h at room temperature and refluxed for further 1-2 h. The product either precipitate on cooling or was precipitated by addition of diethyl ether and was recrystallized from ethanol.

Determination of ee-values of (S)-10 · HCl: 20 µl of a solution of (*S*)-**10** · HCl (1 mg) in H_2O (1 ml) were used for the *ee* determination on a Chiral Crownpak CR column by HPLC with aqueous $HClO_4$, pH 2.0 as eluent; detection wavelength 200 nm.

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