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Stereoselective synthesis of (1*R*)- and (1*R*,2*S*)-1-aryl-2-alkylamino alcohols from (*R*)-cyanohydrins[1]

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Abstract: Hydrogenation of (*R*)-cyanohydrins (*R*)-**1** with $LiAlH_4$ occurs without racemization to give the (*R*)-2-amino alcohols (*R*)-**3**. (1*R*,2*S*)-2-Amino alcohols (1*R*,2*S*)-**4** are obtained with high diastereoselectivity by addition of methyl Grignard to O-silyl protected cyanohydrins (*R*)-**2** and subsequent hydrogenation with $NaBH_4$. The N-alkylated 2-amino alcohols (*R*)-**8** and (1*R*,2*S*)-**9** can be prepared either by reductive alkylation of the corresponding 2-amino alcohols (*R*)-**3** and (1*R*,2*S*)-**4**, respectively, or by a transimination reaction of the Grignard addition products with primary amines and subsequent hydrogenation with $NaBH_4$. The lower diastereoselectivity of hydrogenation in case of the N-alkylimino compounds in comparison to the N-unsubstituted imines is explained by a weaker chelating effect. © 1997 Elsevier Science Ltd. All rights reserved.

The 2-amino alcohol skeleton is a structural unit found in a substantial number of bioactive natural products.[2] Because of their biological activity, many of these compounds are of great interest as pharmaceuticals,[3] and a variety of methods have been developed for their stereoselective preparation.[2,4] Optically active cyanohydrins which became easily available in the last decade,[5] especially via enzyme catalyzed reactions,[5,6] are excellent starting compounds for the stereoselective synthesis of α-hydroxy carboxylic acids, α-hydroxy aldehydes, α-hydroxy ketones and 2-amino alcohols.[5,7]

1-Aryl-2-amino alcohols structurally derived from adrenaline and ephedrine, respectively, are sympathomimetics of particular pharmacological interest.[3] The biological activity of adrenaline derivatives is restricted to the (*R*)-enantiomer, and in the ephedrine-type compounds the (1*R*,2*S*)-stereoisomers present the pharmacological potent species. Furthermore, the different biological activities of the various sympathomimetics depend strongly on the size of the substituent at the amino group which influences the interaction with the α and β receptors, respectively.

(*R*)-2-Amino alcohols of the adrenaline type are accessible from (*R*)-cyanohydrins without any racemization either directly by hydrogenation of (*R*)-cyanohydrins with $LiAlH_4$[8] or by various hydrogenating procedures from the O-protected cyanohydrins.[9] (1*R*,2*S*)-2-Amino alcohols of the ephedrine type can be prepared from O-protected (*R*)-cyanohydrins by addition of Grignard reagents to the nitrile group and subsequent hydrogenation of the imino intermediate with $NaBH_4$ or $Zn(BH_4)_2$.[10] The reactions proceed without racemization at C-1.[10c] The hydrogenation in 2-position is highly diastereoselective.[10c]

Since, as mentioned before, the biological activity of sympathomimetics significantly depends on the substituents at the amino function, the introduction of N-substituents in 2-amino alcohols is of great importance for the preparation of pharmaceuticals.

Brussee *et al.* have developed a convenient procedure for the introduction of N-substituents in ephedrine-type 2-amino alcohols.[11a–c] The imine intermediate which is formed after addition of a Grignard reagent to the nitrile group of O-protected cyanohydrins is liberated with methanol and by

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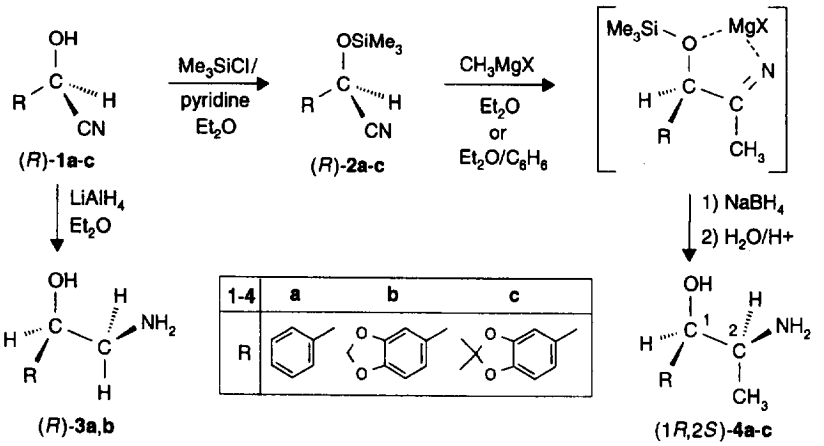


Scheme 1.

addition of a primary amine transimination occurs by release of NH_3. The subsequent hydrogenation with $NaBH_4$ yields N-substituted 2-amino alcohols. N-Alkylated compounds of the adrenaline type are available by selective hydrogenation of O-protected cyanohydrins to imines using diisobutylaluminium hydride, transimination with a primary amine and subsequent hydrogenation.[11b]

Alternative to the transimination reaction, N-substituents can also be introduced by direct alkylation of 2-amino alcohols. N-Monoalkylation, for example, can best be performed by reductive alkylation, i.e. initial formation of a Schiff's base with the corresponding aldehydes or ketones followed by hydrogenation. The important introduction of a *tert*-butyl group, however, is not possible by this route.

In the present publication we report on the synthesis of N-alkylated (*R*)- and (1*R*,2*S*)-2-amino alcohols starting from (*R*)-cyanohydrins by both routes, reductive alkylation of 2-amino alcohols and transimination of the corresponding imino intermediates, respectively.

2-Alkylamino alcohols (*R*)-8 and (1*R*,2*S*)-9 by reductive alkylation of 2-amino alcohols (*R*)-3 and (1*R*,2*S*)-4, respectively

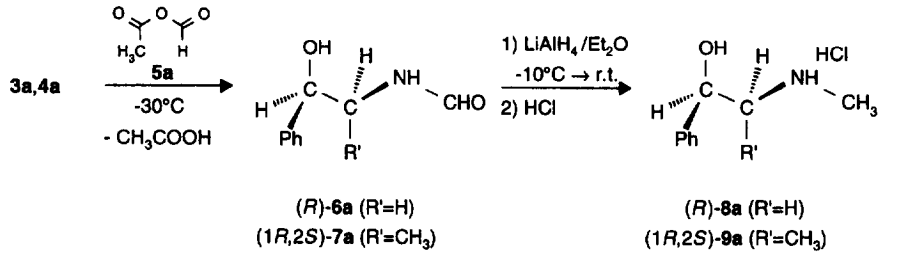
The reductive alkylation of 2-amino alcohols was investigated with the already described adrenaline derivatives (*R*)-**3a,b**[8] and the ephedrine analogues (1*R*,2*S*)-**4a–c** (Scheme 1).

The amino alcohols (1*R*,2*S*)-**4b,c** were prepared from the corresponding cyanohydrins (*R*)-**1b,c** according to the synthesis of **4a**.[10c] The cyanohydrins (*R*)-**1a,b** are accessible in high enantiomeric purity by (*R*)-oxynitrilase catalyzed addition of HCN to the corresponding aldehydes.[8,12] Analogously (*R*)-**1c** was obtained at 30°C with 51% conversion and 96%*ee*. The amino alcohols (1*R*,2*S*)-**4b** and **4c** are obtained from (*R*)-**2b** and **c**, respectively, with high diastereoselectivity (95%*de*).

The reductive methylation of amino alcohols **3** and **4** was performed via the corresponding N-formyl derivatives **6** and **7**, respectively,[13] as outlined in Scheme 2.

The use of the reactive acetic formic anhydride **5a** as formylation agent in twofold excess based on the amino alcohols **3** or **4** enables mild reaction conditions. After removal of the solvent and acetic acid the N-formylamino alcohols **6a** and **7a** were hydrogenated with $LiAlH_4$ in diethyl ether at room temperature to give the corresponding N-methylamino alcohols **8a** und **9a** (Table 1).[13] The *ee*- and *de*-values could not be determined by gas chromatography. The optical purity of (*R*)-halostachine (**8a**) and (1*R*,2*S*)-ephedrine (**9a**) was determined by specific rotation (Table 1). The specific rotation of **9a** corresponds with literature data[14] and thus confirms that the reductive methylation of (1*R*,2*S*)-**4a** to (−) ephedrine (1*R*,2*S*)-**9a** proceeds without racemization.

The other alkyl substituents were introduced by reaction of the amino alcohols (*R*)-**3a** and (1*R*,2*S*)-

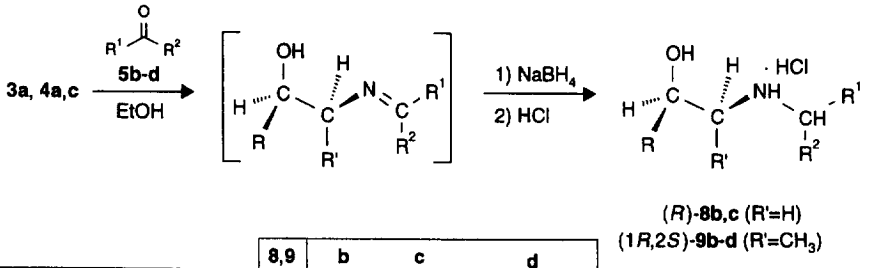


Scheme 2.

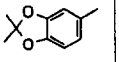
Table 1. Synthesis of 2-alkylamino alcohols (*R*)-**8** and (1*R*,2*S*)-**9** by reaction of 2-amino alcohols **3** and **4** with **5a** and carbonyl compounds **5b–d**, respectively, and subsequent hydrogenation with $LiAlH_4$ or $NaBH_4$

2-Amino Alcohols **3,4**		Compd	2-Alkylamino Alcohols (*R*)-**8**, (1*R*,2*S*)-**9**[a]					
	ee (*de*) [%]	**5**		Yield [%]	*ee* [%][b]	*de* [%][b]	$[\alpha]_D^{20}$ (*c*, solvent)	mp [°C]
(*R*)-**3a**	98	**5a**	**8a**	75	88[c]	-	-46.2 (1.16, H_2O)[d]	109-110[e]
(1*R*,2*S*)-**4a**	>99 (>99)	**5a**	**9a**	77	>99[c]	>99	-34.5 (3.78, H_2O)[f]	218-219[f]
(*R*)-**3a**	98	**5b**	**8b**	64	96	-	-46.4 (1.1, H_2O)	161-161.5
(1*R*,2*S*)-**4a**	>99 (>99)	**5b**	**9b**	76	>99	>99	-24.4 (1.0, H_2O)[g]	207-208[g]
(*R*)-**3a**	96	**5c**	**8c**	64	96	-	-62.9 (0.97, MeOH)[h]	133-136[i]
(1*R*,2*S*)-**4a**	98 (99)	**5c**	**9c**	76	99	>98	-2.64 (1.48, EtOH)	102-103
(1*R*,2*S*)-**4c**	- (95)	**5d**	**9d**	15	-	-	-1.08 (1.2, $CHCl_3$)	94-96

[a]With the exception of **8b** and **9c,d** isolated as hydrochloride. [b]From the crude product determined by gas chromatography after pivaloylation. [c]Determined by specific rotation. [d]Ref. [17]. [e]Ref. [18]. [f]Ref. [14]. [g]Ref. [19]. [h]$[\alpha]_{20}^{578}$, Ref.[20]. [i]Ref.[21].



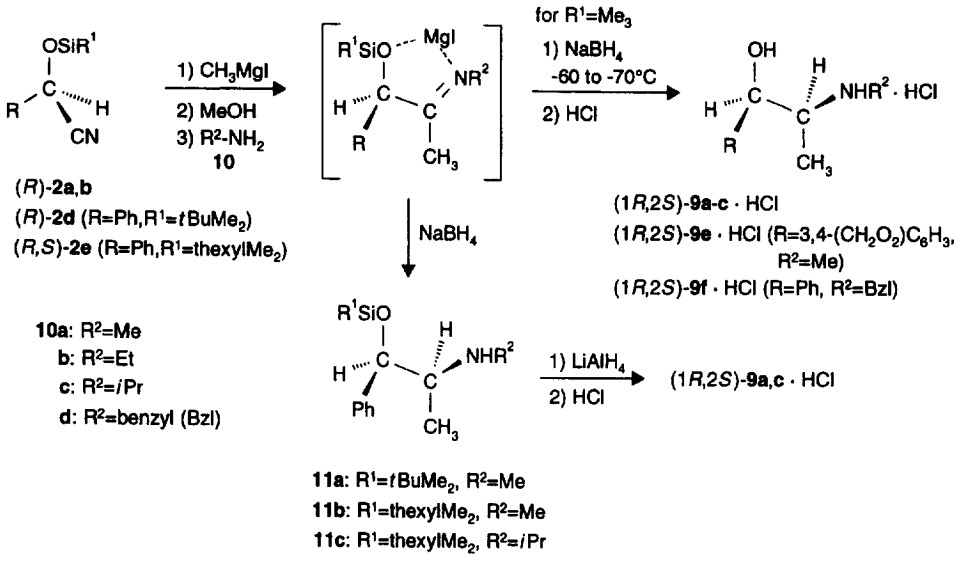
5	b	c	d
R^1	CH_3	CH_3	$(CH_2)_2C_6H_5$
R^2	H	CH_3	H

8,9	b	c	d
R	C_6H_5	C_6H_5	
R^1	CH_3	CH_3	$(CH_2)_2C_6H_5$
R^2	H	CH_3	H

Scheme 3.

4a,c with carbonyl compounds **5b–d** to the imino intermediates, which are hydrogenated with $NaBH_4$ to give the 2-alkylamino alcohols **8b,c** and **9b–d** as outlined in Scheme 3. The results are summarized in Table 1. The reaction of **3a** and **4a** with acetaldehyde **5b** in equimolar amounts at 0°C in ethanol, in order to avoid polymerisation,[15] followed by hydrogenation with $NaBH_4$ at 0°C yielded (*R*)-**8b** and (1*R*,2*S*)-**9b** without racemization in 64 and 76% yield, respectively (Table 1). The enantiomeric and diastereomeric excesses were determined from the obtained crude products by gas chromatography.

The 2-isopropylamino alcohols (*R*)-**8c** and (1*R*,2*S*)-**9c** were obtained from **3a** and **4a**, respectively,



Scheme 4.

with threefold excess of absolute acetone (**5c**) at 0°C[16] in ethanol and subsequent hydrogenation with $NaBH_4$. As can be seen from Table 1, isopropylation proceeds without loss of stereochemical integrity to (*R*)-**8c** and (1*R*,2*S*)-**9c**. 2-(3-Phenylpropyl)amino alcohol **9d** was obtained with only 15% yield by reaction of (1*R*,2*S*)-**4c** with 3-phenylpropionaldehyde (**5d**) in twofold excess based on **4c** at room temperature and subsequent hydrogenation at −8 to −13°C (Table 1).

2-Alkylamino alcohols (1*R*,2*S*)-9 from O-silylated cyanohydrins (*R*)-2 by grignard addition, *in situ* transimination with primary amines 10, and subsequent hydrogenation with $NaBH_4$

Based on the method developed by Brussee[11] we have prepared the 2-alkylamino alcohols (1*R*,2*S*)-**9a–c,e,f**. The O-silyl protected cyanohydrins (*R*)-**2a,b,d** and **e** were added dropwise at 0°C to a solution of the Grignard reagent. The primarily formed imino intermediates were treated with dry methanol and converted into the N-alkyl imino derivatives by addition of the corresponding primary amine **10**. We have varied the O-silyl protecting groups in order to investigate their influence on the diastereoselectivity of the hydrogenation of the imino intermediates. By using trimethylsilyl as protecting group the N-alkylated 2-amino-1-arylpropanols **9a–c,e,f** were obtained directly after hydrogenation and the usual acidic work-up. Both the *tert*-butyldimethylsilyl[11a] and thexyldimethylsilyl protected compounds, however, give first the still protected 2-alkylamino alcohols **11a–c**. $LiAlH_4$ is required for deprotection of compounds **11** to give the desired products **9a** and **9c**[10a,11a] (Scheme 4, Table 2).

The O-trimethylsilyl protected alkylimino compounds were hydrogenated at low temperatures (−60 to −70°C) to obtain high *de*-values.[10c] The diastereomeric excesses observed, however, are lower than those reached with the N-unsubstituted derivatives (R^2=H).[10c] The O-silyl protected 2-alkylamino alcohols **11a–c** were isolated in yields between 89 and 95%. Deprotection gave the 2-alkylamino-1-phenylpropanols (1*R*,2*S*)-**9a** and **9c** with 80–87%*de*, determined from the crude products **11a–c** by ^1H NMR spectroscopy (Table 2).

As can be seen in the reactions of O-silylated cyanohydrins **2a,d** and **e** with methylamine **10a**, the silyl groups only slightly influence the *de*-value of the obtained **9a** (Table 2). The N-isopropyl and N-benzylamino alcohols (1*R*,2*S*)-**9c** and **9f** were obtained with 90 and >95%*de*, respectively, whereas

Table 2. Synthesis of 2-N-alkylamino alcohols (1*R*,2*S*)-**9** by grignard reaction of O-silyl protected cyanohydrins **2**, transimination with primary amines **10** and subsequent hydrogenation with $NaBH_4$

O-Silylated Cyanohydrins (*R*)-**2**			Amines **10**		Temp.	2-Alkylamino-1-arylpropanols (1*R*,2*S*)-**9**·HCl			
	R	R^1		R^2	[°C]		Yield [%]	*de* [%][a]	$[\alpha]_D^{20}$ (c, solvent)
2a	Ph	Me_3	**10a**	Me	-70	**9a**	63	81	-34.5 (3.25, H_2O)
2d	Ph	$tBuMe_2$	**10a**	Me	-60	**9a**[b]	75	87[c]	
2e	Ph	$thexylMe_2$	**10a**	Me	0	**9a**[b]	75	80[c]	
2a	Ph	Me_3	**10b**	Et	-60	**9b**	49	75	-25.0 (1.78, H_2O)
2a	Ph	Me_3	**10c**	*i*Pr	-60	**9c**	63	90	-4.03 (1.15, EtOH)
2e	Ph	$thexylMe_2$	**10c**	*i*Pr	0	**9c**[b]	83	84[c]	
2b	$(CH_2O_2)C_6H_3$	Me_3	**10a**	Me	-60	**9e**	35	77	-41.6 (0.78, MeOH)
2a	Ph	Me_3	**10d**	Bzl	-60	**9f**	62	>95	-17.6 (0.5, MeOH)[d]

[a]Determined from the crude products by ^1H NMR spectroscopy. [b]After removal of the protecting group in compounds **11** with $LiAlH_4$. [c]*de*-Value determined from crude **11** by ^1H NMR spectroscopy. [d]Ref. [11a].

the 2-ethylamino-1-phenylpropanol (1*R*,2*S*)-**9b** was isolated with only 75%*de*. We were not able to introduce the *tert*-butyl group via the transimination process although this method is described in the literature.[11d]

A comparison of the specific rotations of (1*R*,2*S*)-**9a,b** and **f** with literature data[11a,14,19] confirms that the preparation of (1*R*,2*S*)-2-alkylamino-1-arylpropanols proceeds without racemization from compounds (*R*)-**2** via the described one-pot reaction.

As described in the literature,[11b] 2-N-alkylamino-1-phenylethanols (*R*)-**8** can be prepared via selective hydrogenation of the nitrile group of optically active cyanohydrins (*R*)-**1** to the corresponding imino compounds with diisobutylaluminium hydride, transimination with primary amines **10** and hydrogenation with $NaBH_4$ in 80–97% yield using *tert*-butyldimethylsilyl as protecting group. We have applied this method for the reaction of the O-trimethylsilyl protected cyanohydrin (*R*)-**2a** with methylamine (**10a**) to give (*R*)-halostachine (*R*)-**8a**. Contrary to the literature data,[11b] however, we obtained (*R*)-**8a** only in very low yield (7%) and with partly racemization. By reductive alkylation of the corresponding 2-amino alcohol, however, we were able to isolate (*R*)-**8a** in 75% yield and almost no racemization (see Table 1).

A comparison of both alkylation procedures described in this paper shows, that the reductive alkylation gives higher diastereomeric excesses than the transimination process in the preparation of (1*R*,2*S*)-2-alkylamino-1-arylpropanols. This is probably due to the more stable chelate complexes of the imino compounds obtained primarily by addition of Grignard reagents to nitriles compared with the chelates of the N-alkylimino compounds obtained by transimination. Since the diastereomeric 2-alkylamino alcohols (1*R*,2*S*)-**9** can be obtained in high enantiomeric purity after recrystallization, the transimination procedure offers a simplier approach to these compounds than the reductive alkylation. For the preparation of (*R*)-2-alkylamino-1-arylethanols, however, the reductive alkylation is preferable. As can be seen in the preparation of (*R*)-**8a**, the selective hydrogenation of the nitrile group to the imino product and the subsequent transimination step are obviously difficult and results in very poor yields.

For the introduction of the *tert*-butyl group in adrenaline analogues, which is of particular interest for important pharmaceuticals, reductive alkylation is not possible and the transimination was not successful so far. In a forthcoming publication therefore we will report on alternative routes for the preparation of (*R*)-2-N-*tert*-butylamino derivatives of the adrenaline type.

Experimental

Materials and methods

Avicel cellulose was purchased from Merck and piperonal from Fluka. (*R*)-Oxynitrilase was prepared according to Ref.[22], 2,2-dimethyl-5-formyl-benzo[1,3]dioxol according to Ref.[23], racemic

cyanohydrins **1** according to Ref.[24], silylation of (*R*)-**1** according to Ref.[10c] All solvents were purified and dried as described in the literature. Melting points were determined on a Büchi SMP-20 and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP 80 and ACF 250 with TMS as internal standard. Optical rotations were performed in a Perkin–Elmer polarimeter 241 LC. Preparative column chromatography was performed with glass columns of different size packed with silica gel S, grain size 0.032–0.063 mm (Riedel-de Haen). GC for determination of enantiomeric and diastereomeric excess: a) Carlo Erba Fractovap 2150 with FID, Carlo Erba Mega Series integrator, 0.5 bar hydrogen, column 20 m, phase polydimethylsiloxane, OV 1701 with 10% permethylated β-cyclodextrin; b) Carlo Erba HRGC 5300 Mega Series with FID, Carlo Erba Mega Series integrator, 0.5 bar hydrogen, column 20 m, phase polydimethylsiloxane with 3.5% valeroyl-L-valine-(*R*)-bornylamide or PS086 with 10% permethylated β-cyclodextrin.

*Preparation of 2-amino alcohols (1*R,2S*)-**4b,c**; general procedure*[10c]

At 0°C a solution of **2b** (48 mmol) or **2c** (3.6 mmol) in diethyl ether was added via syringe to a solution of Grignard reagent, prepared from Mg (82 or 20 mmol) and methyl iodide (80 or 20 mmol) in diethyl ether under argon atmosphere, and the reaction mixture stirred for 4–5 h at room temperature. After cooling to −60°C, diethyl ether was added followed by solid $NaBH_4$ (80 or 18 mmol) and methanol (20 or 5 ml). The stirred reaction mixture was allowed to warm to 5–10°C within 16 h. After hydrolyzing with water the reaction mixture was set to pH 1–2 with HCl, the aqueous phase washed with diethyl ether, set to pH 10–12 with NaOH and extracted four times with diethyl ether. The combined extracts were dried ($MgSO_4$), concentrated and **4b** and **4c** isolated as hydrochlorides in 51 and 38% yield, respectively. The *de*-values were determined from crude **4** by ^{1}H NMR spectroscopy.

*2-Methylamino alcohols (*R*)-**8a** and (1*R,2S*)-**9a** via the N-formylamino compounds **6** and **7**; general procedure*[13]

Acetic formic anhydride (**5a**) (2 equivalents based on **3,4**) was added dropwise at −30°C to a solution of (*R*)-**3a** (1.9 mmol) and (1*R*,2*S*)-**4a** (1.85 mmol), resp., in 10 ml diethyl ether. After stirring for 1 h the volatile compounds were removed *in vacuo*. The residue was taken up in diethyl ether and reduced at −10°C with $LiAlH_4$ (ca. 1.5 equivalents based on **3,4**). After stirring for 2 h at room temperature the reaction mixture was hydrolyzed with NaOH (10%). The aqueous phase was extracted several times with diethyl ether. The combined extracts were dried (Na_2SO_4), concentrated, and **8a** and **9a** were isolated as hydrochlorides.

*2-Alkylamino alcohols (*R*)-**8b,c** and (1*R,2S*)-**9b–d**; general procedure*[16]

The carbonyl compound **5b** (1 equivalent) or **5c,d** (2 equivalents based on **3,4**) was added dropwise at 0°C (**5b**) or room temperature (**5c,d**) to a solution of (*R*)-**3a** or (1*R*,2*S*)-**4a,c** (0.7–6.6 mmol) in abs. ethanol. The reaction mixture was stirred for 30 min (**5b,5c**) or 2.5 h (**5d**) and was reduced either at 0°C with 2 equivalents $NaBH_4$ (**5b,5c**) or at −8°C with 3 equivalents $NaBH_4$ (**5d**). After stirring for 1 h (**5b,5c**) or 12 h (**5d**) the reaction mixture was hydrolyzed with water and NaOH (5%), and the aqueous phase extracted with diethyl ether. The combined extracts were dried (Na_2SO_4) and concentrated. The products **8c** and **9b** were isolated as hydrochlorides, **8b** and **9c** were chromatographed on silica gel with THF/ethanol/25% NH_3 (20:1:1), **9d** with petroleum ether/ethyl acetate (3:7) and was recrystallized from diethyl ether/hexane.

*2-Alkylamino alcohols (1*R,2S*)-**9a–c,e,f** from silyl-protected cyanohydrins (*R*)-**2a,b** via transimination with **10**[11a]; general procedure*

At 0°C **2** (5–20 mmol) was dropped to a solution of the Grignard reagent[11a] in diethyl ether, and the reaction mixture stirred for 6 h at room temperature. After cooling to 0°C a solution of **10** (2 equivalents based on **2**) in methanol was added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for further 1–3 h and reduced with $NaBH_4$ (2 equivalents based on **2**) at −60 to −70°C. After stirring for 12 h the reaction mixture was hydrolyzed with dil. HCl and

Table 3. ^{1}H NMR data of compounds **1c**, **4b,c**, **8b** and **9c,d** (80 or 250 MHz, $CDCl_3$, δ)

1c	1.69 (s, 6 H, CH_3), 2.77 (d, *J*=6.6 Hz, 1 H, OH), 5.42 (d, *J*=6.6 Hz, 1 H, CH), 6.73-6.76 (m, 1 H, Ph), 6.91-6.95 (m, 2 H, Ph)
4b	1.00 (d, *J*=6.0 Hz, 3 H, CH_3), 1.85 (bs, 3 H, NH_2, OH), 2.95-3.30 (m, 1 H, C*H*NH_2), 4.40 (d, *J*=5.0 Hz, 1 H, C*H*OH), 5.95 (s, 2 H, CH_2), 6.75-6.85 (m, 3 H, Ph)
4c	1.01 (d, *J*=6.4 Hz, 3 H, C*H*$_3$CH), 1.66, 1.67 (2 s, 6 H, CH_3), 3.06-3.16 (m, 1 H, CH_3C*H*), 4.37 (d, *J*=5.2 Hz, 1 H, C*H*OH), 6.61-6.84 (m, 3 H, Ph)
8b	1.09 (t, *J*=7.1 Hz, 3 H, CH_3), 2.40-2.75 (m, 2 H, CH_2), 2.70 (dd, J_1=-12.1, J_2=8.9 Hz, 1 H, CH_2), 2.86 (dd, J_1=-12.1, J_2=3.7 Hz, 1 H, CH_2), 4.72 (dd, J_1=3.7, J_2=8.9 Hz, 1 H, C*H*OH), 7.20-7.44 (m, 5 H, Ph)
9c	0.80 (d, *J*=6.0 Hz, 3 H, CH_3), 1.08 (d, *J*=6.0 Hz, 6 H, CH(C*H*$_3$)$_2$), 2.75-3.20 (m, 2 H, C*H*NHC*H*(C*H*$_3$)$_2$), 4.65 (d, *J*=4.0 Hz, 1 H, C*H*OH), 7.30 (s, 5 H, Ph)
9d	0.85 (d, *J*=6.5 Hz, 3 H, C*H*$_3$CH), 1.65, 1.67 (2 s, 6 H, CH_3), 1.77-1.88 (m, 2 H, CH_2C*H*$_2$C*H*$_2$), 2.27-2.89 (m, 5 H, CH_3C*H*, C*H*$_2$C*H*$_2$C*H*$_2$), 2.27-2.89 (bs, 1 H, CHO*H*), 4.60 (d, *J*=4.1 Hz, 1 H, C*H*OH), 6.59-6.74 (m, 3 H, Ph), 7.16-7.32 (m, 5 H, Ph)

Table 4. Elemental analysis data of amino alcohols **4b,c**, **8b** and **9c,d**

	Molecular Formula (Mol. Weight)	Calcd./Found C	H	N	Cl		Molecular Formula (Mol. Weight)	Calcd./ Found C	H	N
4b	$C_{10}H_{13}NO_3$	61.53	6.71	7.17		**9c**	$C_{12}H_{19}NO$	74.57	9.91	7.25
	(195.2)	61.47	6.76	7.31			(193.3)	74.76	10.02	7.40
4c	$C_{12}H_{17}NO_3$·HCl	55.49	6.99	5.39	13.65	**9d**	$C_{21}H_{27}NO_3$	73.87	7.97	4.10
	(259.7)	55.49	6.84	5.13	13.45		(341.5)	73.97	7.83	4.03
8b	$C_{10}H_{15}NO$	72.69	9.15	8.48						
	(165.2)	72.57	9.30	8.31						

extracted three times with diethyl ether. The aqueous phase was set to pH 10 with NaOH and extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$), concentrated, and the products isolated as hydrochlorides.

*2-Alkylamino alcohols (1*R*,2*S*)-**9a,c** from silyl-protected cyanohydrins (*R*)-**2d,e**; general procedure*

A solution of **2** (6–20 mmol) in diethyl ether was dropped at 0°C to a solution of the Grignard reagent in diethyl ether, and the reaction mixture refluxed for 4 h. At room temperature 10 ml methanol and **10a,c** (2 equivalents based on **2**) were added. After stirring for 30 min the reaction mixture was reduced at 0°C with $NaBH_4$ (2 equivalents), stirred for 12 h, hydrolyzed with water and extracted three times with 50 ml diethyl ether each. The combined extracts were washed twice with NaCl solution, dried ($MgSO_4$), concentrated, and the *de*-value was determined by ^{1}H NMR spectroscopy. The residue was taken up in diethyl ether, added dropwise to a suspension of $LiAlH_4$ (1–1.5 equivalents based on **2**) in diethyl ether, and the reaction mixture refluxed for 1 h. After hydrolysis with water at 0°C and extraction with diethyl ether the products **9a,c** were isolated as hydrochlorides.

Determination of ee-*and* de-*values of (*R*)-**1**, and amino alcohols **3,4,8,9***

a) Acetic anhydride (50 μl) and pyridine (10 μl) were added to a solution of **1** (10 μl) in dichloromethane (100 μl). After heating to 60°C for 2 h, the reaction mixture was filtered through a silica gel column (3×0.5 cm) with dichloromethane (4 ml) as eluent. The enantiomeric excess was determined directly from the filtrate by gas chromatography.

b) Pivaloyl chloride (50 μl) was added to a solution of crude amino alcohol **3,4,8** or **9** (5 μl or 5 mg) in pyridine (100 μl), and after standing at room temperature for 16 h, the reaction mixture was filtered through a silica gel column (3×0.5 cm) with dichloromethane (2 ml) as eluent. The enantiomeric and

diastereomeric excess was determined directly from the filtrate by gas chromatography (Table 3 and Table 4).

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