Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 7, pp. 1061–1067, 1997

Printed in Great Britain

PII: S0957-4166(97)00066-9

0957-4166/97 $17.00 + 0.00

Direct conversion of chiral cyanohydrins to chiral nitrones by transimination

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Abstract: A new method for the preparation of enantiomerically pure *N*-benzyl nitrones is described. By using either a one-pot reduction-transimination or a one-pot Grignard addition-transimination sequence chiral *O*-protected α-hydroxynitriles can be converted into chiral aldo- and ketonitrones, respectively. © 1997 Elsevier Science Ltd

Introduction

Over the past decades numerous examples of the application of nitrones in organic synthesis, mostly by way of 1,3 dipolar cycloaddition reactions, have been published[1]. The preparation of these nitrones has usually been carried out by condensation of aldehydes with hydroxylamines in the presence of a heterogeneous drying agent or by direct oxidation of amines and hydroxylamines[2]. Only recently a general procedure for the preparation of chiral nitrones starting from aldehydes was published[3], and applied to the synthesis of a large number of chiral and achiral aldonitrones. We hereby report a new and simple one-pot procedure for the synthesis of chiral nitrones starting from *O*-protected chiral α-hydroxynitriles (cyanohydrins).

The synthesis and application of chiral cyanohydrins is a major interest in our group. In recent years a simple system has been developed by which these cyanohydrins can be prepared in excellent enantiomeric purity by the addition of HCN to aldehydes in a reaction catalyzed by the enzyme *R*-oxynitrilase, as present in almond meal (E.C. 4.1.2.10)[4]. The cyanohydrins thus obtained generally possess the (*R*)-configuration and have been shown to be excellent chiral building blocks in organic synthesis. Further modification can produce a wide range of enantio- and diastereomerically pure chiral compounds, including β-hydroxy-α-amino acids[5], α-hydroxy-β-amino acids[6] and β-γ-unsaturated-α-hydroxy esters[7].

Since cyanohydrins are unstable under basic or reductive conditions a protecting group on oxygen has to be introduced in most instances to prevent decomposition and racemization. Silyl protecting groups, in particular the *tert*-butyldimethylsilyl (TBS), and mixed acetals, in particular 2-methoxy *iso*propyl (MIP) and tetrahydropyranyl (THP) were shown to be especially useful, since these groups can be introduced and removed under mild conditions without loss of enantiomeric purity.

A particularly attractive method for converting a cyano group is a transimination based reaction sequence[8,9]. First the nitrile is converted to a primary imine, either by DIBAL reduction or Grignard addition. The imine reacts in a transimination step with an added amine to give a secondary imine, while ammonia is liberated. This method has been used to prepare *N*-substituted β-ethanolamines[9] as well as diethanolamines[10].

The thermodynamic stability of the C=N bond in the obtained imine increases with the type of amine used, in the order NH_3 < aliphatic amines < aromatic amines < amines with an adjacent electronegative atom bearing a free electron pair[11] (e.g. RNH–OH). We therefore concluded that it should be possible to prepare nitrones using this transimination step.

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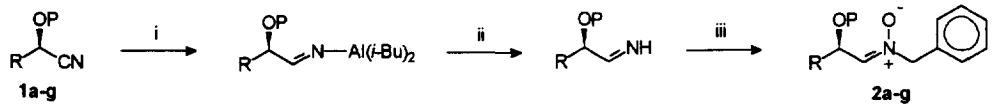
Results and discussion

The TBS and MIP protected cyanohydrins **1a–g** (Scheme 1) were used as starting materials for the projected nitrone synthesis. The THP protective group is less attractive in this case because the extra stereogenic centre which is introduced complicates both the synthesis and the spectral properties.



a: R = C_6H_5, P = TBS; **b**: R = C_6H_5, P = MIP; **c**: R = 4-Cl-C_6H_5, P = MIP; **d**: R = 4-MeO-C_6H_5, P = MIP;
e: R = 4-MeO-C_6H_5, P = TBS; **f**: R = propenyl, P = TBS; **g**: R = 5-Me-furanyl, P = TBS.
i) DIBAL; ii) MeOH; iii) *N*-benzylhydroxylamine.

Scheme 1. One-pot synthesis of aldonitrones via a reduction-transimination pathway.

Reduction of the cyano group of **1a** with DIBAL, was followed by addition of dry methanol to liberate the free imine and to destroy the excess of DIBAL. Then *N*-benzylhydroxylamine, conveniently prepared by addition of NH_2OH to benzaldehyde followed by a $NaBH_3CN$ reduction[12], was added to start the transimination reaction. Work up after 4 hours provided **2a** in essentially quantitative yield with an enantiomeric purity of 98% as determined by HPLC (see experimental part). The same procedure was followed for the conversion of protected cyanohydrins **1b–g** into aldonitrones **2b–g** (Table 1). No side products were observed and the nitrones obtained can be used without further purification. For the preparation of analytical samples the nitrones may be purified by means of recrystallization or by column chromatography. Compound **2g**, carrying a 5-methylfuryl substituent, appeared to be less stable. When this compound is stored for a longer period of time it starts decomposing, probably under the influence of light.

NMR-spectroscopy revealed that a single geometric isomer was obtained in all cases. On the basis of literature data this was expected to be the *Z*-isomer[13]. This was confirmed in the case of **2b** by X-ray analysis.

Ketonitrones can be prepared by carrying out a Grignard addition, rather than a hydride reduction, prior to the transimination step[9]. They are more difficult to synthesize than aldonitrones, probably because of the known instability of the former[2a]. To the best of our knowledge, enantiomerically pure ketonitrones have not yet been described in literature. The one-pot Grignard addition-transimination sequence is depicted in Scheme 2.

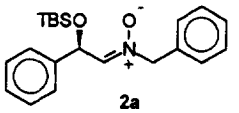
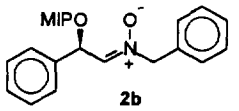
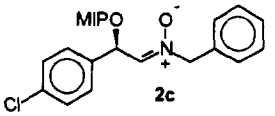
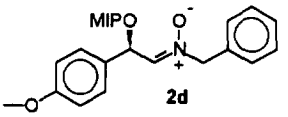
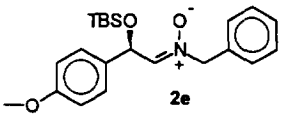
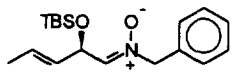
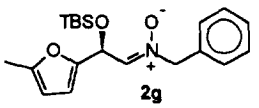
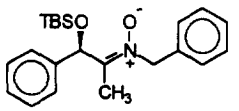
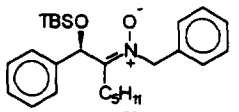
TBS-protected cyanohydrin **1a** was treated with MeMgI. The free imine was liberated and the excess of MeMgI was destroyed by addition of dry methanol. After transimination with *N*-benzylhydroxylamine ketonitrone **3a** was obtained in 51% yield with an enantiomeric purity of >99% as determined by HPLC after work-up and purification by column chromatography. Compound **3a** was prepared with a TBS protective group. The MIP-protective group seemed a bad choice in the same reaction. With this group the crude product contains only a small amount of the desired ketonitrone. Similarly, the *n*-pentylsubstituted ketonitrone **3b** was obtained in 47% yield also with excellent e.e.

As transimination is known to be strongly influenced by substituent effects the lower yields observed in the case of ketonitrones **3a** and **3b** may be caused by a slower transimination reaction. Also partial decomposition during aqueous work-up may occur.

Conclusion

By using a hydride reduction-transimination sequence with *N*-benzylhydroxylamine aldonitrones of high enantiomeric purity were obtained starting from enantiomerically pure *O*-protected cyanohydrins,

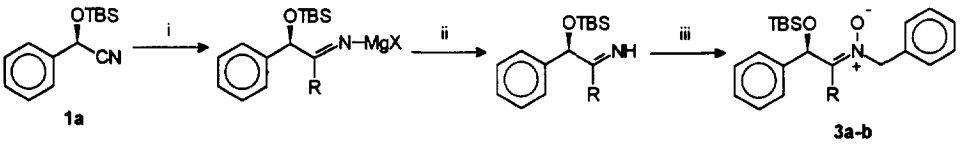
Table 1. Nitrones obtained from cyanohydrins **1a–g**

Product	e.e. (%)[a]	Yield (%)	mp (°C)	$[\alpha]_D^{20}$ [b]	e.e. (%)[c]
 **2a**	99	99	35-36	+ 86	98
 **2b**	>99	84	109	+ 136	>99
 **2c**	99	99	91	+ 116	97
 **2d**	>99	91	105	+ 125	96
 **2e**	>99	99	oil	+ 104	99
 **2f**	97	98	oil	+ 48	97
 **2g**	>99	82	33	+ 57	99
 **3a**	99	51	oil	+ 120	99
 **3b**	99	47	oil	+ 42	97

a) E.e. of starting material. b) (c=1, $CHCl_3$). c) E.e. of nitrone.

all in good to excellent yield. By using a Grignard addition instead of hydride reduction as the first step, the method was extended to ketonitrones.

Intra- and intermolecular 1,3-dipolar cycloaddition reactions of these compounds are under current investigation.



a: R = CH_3 ; **b**: R = *n*-C_5H_{11}.

i) RMgX; ii) MeOH; iii) *N*-benzylhydroxylamine.

Scheme 2. One-pot synthesis of ketonitrones via a Grignard addition-transimination pathway.

Experimental

Enantiomeric purities were determined by HPLC using a *Chiralcel OD* column (250 * 4.6 mm) for **2a–2g** and **3a**, and a *Chiralcel OD* column (500 * 4.6 mm) for compound **3b**. As eluents, mixtures of hexane (H) and 2-propanol (I), which are specified in each case, were applied. The nitrones were also prepared in racemic form to optimize the conditions for peak separation. Optical rotations were measured using a *Propol* automatic polarimeter. Melting points were measured on a *Büchi* melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a *JEOL FX-200* instrument. The ^{13}C-NMR of compound **2a** was recorded on a *Bruker WM-300* instrument. Samples were measured in $CDCl_3$, with Me_4Si as an internal standard for ^{1}H-NMR, and $CDCl_3$ as an internal standard for ^{13}C-NMR; δ in ppm.

The protected cyanohydrins **1a–g** were prepared as described earlier[14]. *N*-Benzylhydroxylamine was prepared by addition of NH_2OH to benzaldehyde followed by a $NaBH_3CN$ reduction (yield: 80%; M.p. 57°C (recryst. from ethanol and petroleum-ether 40/60).

General procedure for the preparation of aldonitrones

All reactions were carried out under a dry nitrogen atmosphere. In a three-necked flask, 3 mmol of the nitrile was dissolved in 25 ml of dry diethyl ether. At −70°C 4.5 ml (4.5 mmol) of 1M DIBAL in cyclohexane was added to the stirred solution. The cooling bath was removed and the mixture was allowed to warm to −10°C. After cooling to −90°C 1.5 ml of dry MeOH was added and at −60°C 0.4 g (3 mmol) *N*-benzylhydroxylamine was added as a solid. The mixture was stirred at r.t. for 4 h, poured into H_2O (50 ml) and extracted with diethyl ether (3×100 ml). The combined organic layers were washed with saturated brine (1×50 ml), dried ($MgSO_4$) and the solvents evaporated.

*(R)-(Z)-N-{2-[(*tert*-Butyldimethylsilyl)oxy]-2-phenyl-ethylidene}-benzylamine* N-*oxide* **2a**

Compound **2a** was prepared by the general procedure from **1a** (3.7 g, 15 mmol) (e.e. 99%) affording 5.6 g (>99%) of **2a** as a yellow oil. The oil was chromatographed (silica gel, petroleum ether 40–60/diethyl ether 2:3) and a white solid was obtained mp. 35–36°C; $[\alpha]_D^{20}$=+86 (c=1, $CHCl_3$); e.e. 98% (HPLC eluent H:I=90:10). ^{1}H-NMR δ: 0.01 (s, 3H, MeSi), 0.02 (s, 3H, MeSi), 0.87 (s, 9H, *t*-Bu), 4.84 (s, 2H, $C_6H_5CH_2$), 6.01 (d, 1H, J=6.69 Hz, C_6H_5CH), 6.77 (d, 1H, J=6.68 Hz, $^+$N=CH), 7.27–7.51 (m, 10H, H-arom). ^{13}C-NMR δ: −5.33 (MeSi), −5.25 (MeSi), 17.83 (Me_3C), 25.48 (Me_3C), 68.18 (C_6H_5CH), 69.11 ($C_6H_5CH_2$), 125.50, 127.48, 128.05, 128.55, 128.65, 128.93 (C-arom), 132.34 (CH_2C_{ipso}), 140.45 (CHC_{ipso}), 140.56 (C=N$^+$).

(R)-(Z)-N-{2-[(Methoxy-isopropyl)oxy]-2-phenyl-ethylidene}-benzylamine N-*oxide* **2b**

Compound **2b** was prepared by the general procedure from **1b** (2.1 g, 10 mmol) (e.e. >99%) affording 2.6 g (84%) of **2b** as a white solid. An analytical sample was recrystallized from diethyl ether, mp. 109°C; $[\alpha]_D^{20}$=+136 (c=1, $CHCl_3$); e.e. >99% (HPLC eluent H:I=90:10). ^{1}H-NMR δ: 1.30 (s, 3H, MeC), 1.32 (s, 3H, MeC), 3.02 (s, 3H, MeO), 4.83 (s, 2H, $C_6H_5CH_2$), 6.04 (d, 1H, J=6.68Hz, C_6H_5CH), 6.79 (d, 1H, J=6.69 Hz, $^+$N=CH), 7.29–7.52 (m, 10H, H-arom). ^{13}C-NMR δ: 24.15 (*Me*C),

24.38 (*Me*C), 48.04 (MeO), 66.05 (C_6H_5CH), 68.50 ($C_6H_5CH_2$), 100.54 (Me_2C), 125.68, 126.99, 127.52, 127.66, 127.95, 128.36 (C-arom), 132.28 (CH_2C_{ipso}), 138.90 (CHC_{ipso}), 139.37 ($C=N^+$).

*(R)-(Z)-*N*-{2-[(Methoxy-isopropyl)oxy]-2-(4-chlorophenyl)-ethylidene}-benzylamine* N*-oxide* ***2c***

Compound **2c** was prepared by the general procedure from **1c** (0.7 g, 3 mmol) (e.e. 99%) affording 1.1 g (>99%) of **2c** as a white solid. An analytical sample was recrystallized from diethyl ether, mp. 91°C; $[\alpha]_D^{20}$=+116 (c=1, $CHCl_3$); e.e. 97% (HPLC eluent H:I=90:10). ^{1}H-NMR δ: 1.28 (s, 3H, MeC), 1.31 (s, 3H, MeC), 3.01 (s, 3H, MeO), 4.83 (s, 2H, $C_6H_5CH_2$), 5.99 (d, 1H, J=6.68 Hz, C_6H_5CH), 6.75 (d, 1H, J=6.68 Hz, $^+$N=CH), 7.29–7.47 (m, 10H, H-arom). ^{13}C-NMR δ: 24.59 (*Me*C), 24.79 (*Me*C), 48.62 (MeO), 66.11 (C_6H_5CH), 69.12 ($C_6H_5CH_2$), 101.18 (Me_2C), 127.55, 128.25, 128.60, 128.71, 128.89 (C-arom), 132.28 (CH_2C_{ipso}), 133.15 (*C*Cl), 137.79 (CHC_{ipso}), 139.52 ($C=N^+$).

*(R)-(Z)-*N*-{2-[(Methoxy-isopropyl)oxy]-2-(4-methoxyphenyl)-ethylidene}-benzylamine* N*-oxide* ***2d***

Compound **2d** was prepared by the general procedure from **1d** (5.88 g, 25 mmol) (e.e. >99%) affording 7.80 g (91%) of **2d** as a white solid. An analytical sample was recrystallized from *n*-pentane, mp. 105°C; $[\alpha]_D^{20}$=+125 (c=1, $CHCl_3$); e.e. 96% (HPLC eluent H:I=90:10). ^{1}H-NMR δ: 1.29 (s, 3H, MeC), 1.31 (s, 3H, MeC), 3.02 (s, 3H, MeO), 3.79 (s, 3H, MeOPh), 4.82 (s, 2H, $C_6H_5CH_2$), 5.96 (d, 1H, J=6.68 Hz, C_6H_4CH), 6.78 (d, 1H, J=6.68 Hz, $^+$N=CH), 6.85 (d, 2H, J=8.73 Hz, MeO–C_6H_4), 7.30–7.36 (m, 5H, H-arom), 7.41 (d, 2H, J=8.73 Hz, MeO–C_6H_4). ^{13}C-NMR δ: 24.87 (*Me*C), 25.05 (*Me*C), 48.82 (MeO), 55.13 (*Me*OPh), 66.58 ($MeOC_6H_4CH$), 69.32 ($C_6H_5CH_2$), 101.24 (Me_2C), 113.73, 114.00, 127.69, 128.83, 129.18 (C-arom), 131.48 (CH_2C_{ipso}), 132.11 (CHC_{ipso}), 140.34 ($C=N^+$), 158.01 (MeO-*C*).

*(R)-(Z)-*N*-{2-[(*tert*-Butyldimethylsilyl)oxy]-2-(4-methoxyphenyl)-ethylidene}-benzylamine* N*-oxide* ***2e***

Compound **2e** was prepared by the general procedure from **1e** (6.93 g, 25 mmol) (e.e. >99%) affording 9.23 g (99%) of **2e** as a yellow oil; $[\alpha]_D^{20}$=+104 (c=1, $CHCl_3$); e.e. 99% (HPLC eluent H:I=90:10). ^{1}H-NMR δ: 0.03 (s, 6H, MeSi), 0.87 (s, 9H, *t*-BuSi), 3.80 (s, 3H, MeOPh), 4.83 (s, 2H, $C_6H_5CH_2$), 5.95 (d, 1H, J=6.68 Hz, C_6H_4CH), 6.77 (d, 1H, J=6.68 Hz, $^+$N=CH), 6.86 (d, 2H, J=8.73 Hz, MeO–C_6H_4), 7.27–7.37 (m, 5H, H-arom), 7.41 (d, 2H, J=8.73 Hz, MeO–C_6H_4). ^{13}C-NMR δ: −5.20 (*Me*Si), 17.90 (Me_3C), 25.55 (*Me*$_3$C), 54.93 (*Me*OPh), 68.07 ($MeOC_6H_4CH$), 69.09 ($C_6H_5CH_2$), 113.41, 113.50 ($MeOC_{meta}$), 126.84, 126.93, 128.63, 128.71, 128.92, 129.01, 129.15 (C-arom), 132.39 (CH_2C_{ipso}), 132.60 (CHC_{ipso}), 141.09 ($C=N^+$), 158.99 (MeO–C_{para}).

*(R)-(Z)-*N*-{2-[(*tert*-Butyldimethylsilyl)oxy]-3-*E*-pentenylidene}-benzylamine* N*-oxide* ***2f***

Compound **2f** was prepared by the general procedure from **1f** (5.25 g, 25 mmol) (e.e. 97%) affording 7.75 g (98%), of **2f** as a yellow oil; $[\alpha]_D^{20}$=+48 (c=1, $CHCl_3$); e.e. 97% (HPLC eluent H:I=97:3). ^{1}H-NMR δ: 0.03 (s, 6H, MeSi), 0.84 (s, 9H, *t*-BuSi), 1.68 (dd, 3H, J=6.69 Hz and J=1.55, *Me*C=C), 4.84 (s, 2H, $C_6H_5CH_2$), 5.32 (m, 1H, C=C*CH*), 5.48 (m, 1H, CH_3CH=*CH*), 5.81 (m, 1H, CH_3CH=CH), 6.58 (d, 1H, J=5.65 Hz, $^+$N=CH), 7.38 (s, 5H, H-arom). ^{13}C-NMR δ: −5.20 (*Me*Si), −5.05 (*Me*Si), 17.93 (*Me*C=C), 17.93 (Me_3C), 25.55 (*Me*$_3$C), 67.86 (C=*C*CH), 69.06 ($C_6H_5CH_2$), 127.05, 127.25 (*C*=*C*), 127.98, 128.68, 128.77, 129.15, 129.27 (C-arom), 132.36 (C_{ipso}), 140.36 ($C=N^+$).

*(S)-(Z)-*N*-{2-[(*tert*-Butyldimethylsilyl)oxy]-2-(5-methylfuranyl)-ethylidene}-benzylamine* N*-oxide* ***2g***[15]

Compound **2g** was prepared by the general procedure from **1g** (0.8 g, 3 mmol) (e.e. >99%) affording 1.2 g of **2g** as an orange oil. This compound seemed to be less stable compared to the other aldonitrones. The oil was chromatographed (silica gel, petroleum ether 40–60/diethyl ether 2:3) and 0.9 g (82%) of **2g** was obtained as a white solid, mp. 33°C; $[\alpha]_D^{20}$=+57 (c=1, $CHCl_3$); e.e. 99% (HPLC eluent H:I=95:5). ^{1}H-NMR δ: −0.01 (s, 3H, MeSi), 0.05 (s, 3H, MeSi), 0.83 (s, 9H, *t*-Bu), 2.25 (s, 3H, Me),

4.88 (s, 2H, $C_6H_5CH_2$), 5.89 (m, 2H, C*H*OTBS+CH), 6.14 (d, 1H, 3.08 Hz, CH), 6.95 (d, 1H, J=6.68 Hz, $^+$N=CH), 7.39 (s, 5H, H-arom). ^{13}C-NMR δ: −5.90 (MeSi), −5.84 (MeSi), 12.62 (Me), 17.29 (Me_3C), 24.91 (Me_3C), 62.31 (C_6H_5CH), 68.47 ($C_6H_5CH_2$), 105.50 (CH), 107.66 (CH), 127.81, 127.87, 128.28 (C_6H_5), 132.22 (C_{ipso}), 136.86 (C=N$^+$), 149.68 (C_qO), 151.08 (C_qO).

*(R)-(Z)-*N*-{2-[(*tert*-Butyldimethylsilyl)oxy]-1-methyl-2-phenyl-ethylidene}-benzylamine* N*-oxide* ***3a***

The reaction was carried out under a dry nitrogen atmosphere. In a three-necked flask **1a** (2.2 g, 9 mmol) (e.e. 99%) was dissolved in 25 ml of dry diethyl ether. Then 4.5 ml (13.5 mmol) of 3M MeMgI in diethyl ether was added and the mixture was stirred for 1 h. After cooling to 5°C, 15 ml of dry MeOH was added immediately, followed by 1.2 g (9 mmol) *N*-benzylhydroxylamine. The mixture was stirred at r.t. for 4 h, poured into H_2O (150 ml) and extracted with diethyl ether (3×200 ml). The combined organic layers were washed with saturated brine (1×50 ml), dried ($MgSO_4$), and the solvents evaporated affording 3.2 g of **3a** as a yellow oil. The oil was chromatographed (silica gel, petroleum ether 40–60/ethylacetate 2:3) and 1.68 g (51%) of **3a** was obtained as a colourless oil; $[\alpha]_D^{20}$=+120 (c=1, $CHCl_3$); e.e. 99% (HPLC eluent H:I=95:5). ^{1}H-NMR δ: 0.01 (s, 3H, MeSi), 0.02 (s, 3H, MeSi), 0.90 (s, 9H, *t*-Bu), 1.99 (s, 3H, Me), 5.01 (s, 2H, $C_6H_5CH_2$), 6.52 (s, 1H, C_6H_5CH), 7.28–7.58 (m, 10H, H-arom). ^{13}C-NMR δ: −5.78 (Me_2Si), 12.24 (Me), 17.41 (Me_3C), 25.14 (Me_3C), 64.09 ($C_6H_5CH_2$), 68.44 (C_6H_5CH), 124.77, 126.84, 127.02, 127.46, 127.98 (C-arom), 132.71 (CH_2C_{ipso}), 139.96 (CHC_{ipso}), 147.61 (C=N$^+$).

*(R)-(Z)-*N*-{2-[(*tert*-Butyldimethylsilyl)oxy]-1-*n*-pentyl-2-phenyl-ethylidene}-benzylamine* N*-oxide* ***3b***

The reaction was carried out under a dry nitrogen atmosphere. To a three-necked flask 0.16 g (6.6 mmol) of magnesium and 10 ml of dry diethyl ether were added. Then 0.74 ml (6 mmol) of 1-pentylbromide were added and the reaction mixture was refluxed for 45 minutes. After cooling the reaction mixture in an ice-bath, 0.74 g (3 mmol) of **1a** (e.e. 99%) in 20 ml of dry diethyl ether were added dropwise. The mixture was stirred for 1h at room temperature. After cooling to 0°C, 15 ml of dry methanol were added, followed by 0.74 g (6 mmol) of *N*-benzylhydroxylamine. The mixture was stirred at r.t. for 4 h, poured into H_2O (150 ml) and extracted with diethyl ether (3×100 ml). The combined organic layers were washed with saturated brine (1×50 ml), dried ($MgSO_4$), and the solvents evaporating affording 1.48 g of **3b** as a yellow oil. The oil was chromatographed (silica gel, petroleum ether 40–60/ethyl acetate 7:3) and 0.60 g (47%) of **3b** was obtained as a colourless oil; $[\alpha]_D^{20}$=+48 (c=1, $CHCl_3$); e.e. 97% (HPLC eluent H:I=97:3). ^{1}H-NMR δ: 0.05 (s, 6H, MeSi), 0.83 (m, 3H, Me), 0.91 (s, 9H, *t*-Bu), 1.26 (m, 6H, CH_2), 2.40 (m, 2H, CH_2), 5.00 (s, 2H, $C_6H_5CH_2$), 6.53 (s, 1H, C_6H_5CH), 7.24–7.61 (m, 10H, H-arom). ^{13}C-NMR δ: −5.05 (Me_2Si), 13.81 (Me), 18.08 (Me_3C), 22.05 (CH_2), 25.75 (Me_3C), 27.51, 27.83, 31.98 (CH_2), 63.66 ($C_6H_5CH_2$), 69.50 (C_6H_5CH), 125.79–130.64 (C-arom), 133.65 (CH_2C_{ipso}), 140.69 (CHC_{ipso}), 149.04 (C=N$^+$).

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14. Preparation of cyanohydrins: see reference 4; MIP-protection: see reference 8; TBS-protection: Brussee, J.; Loos, W.T.; Kruse, C.G.; van der Gen, A.; *Tetrahedron*, **1990**, *46*, 979. Compound **1c** was prepared following the preceding procedures. **(+)-(*R*)-α-Hydroxy-4-chlorobenzeneacetonitrile** ^{1}H-NMR: δ(ppm) 5.53 (s, 1H, CH), 7.26–7.49 (m, 4H, H-arom); ^{13}C-NMR: δ(ppm) 62.75 (COH), 105.94 (CN), 127.33, 133.48 (C-arom), 183.48 (C-para). M.p. 40°C (dec); $[\alpha]_D^{20}$=+36 (c=1, $CHCl_3$).
15. Compound **2g** possesses a similar spatial arrangement as **2a–f**. Due to the priority rules its configuration must be assigned as (*S*).

(Received in UK 27 January 1997)