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A practical asymmetric synthesis of homochiral α-arylglycines

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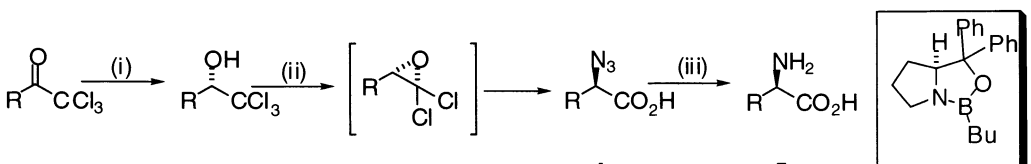
Abstract—Enantioselective reduction of a series of substituted aryl trichloromethyl ketones with the CBS-catecholborane reagent afforded homochiral aryl trichloromethyl carbinols which have been elaborated to give homochiral α-arylglycines in high e.e.

1. Introduction

The development of methodology for the asymmetric synthesis of homochiral α-arylglycines continues to attract attention within the synthetic community due to their potential pharmacological properties and their use as precursors for the synthesis of chiral ligands and novel oligopeptide structures.[1] A range of strategies exist for the enantioselective synthesis of this class of α-amino acids, including asymmetric Strecker reactions,[2] *C*-arylation of electrophilic chiral glycinates,[3] electrophilic amination of chiral benzylic enolates,[4] and enantioselective carboxylation of metallated benzylamine derivatives.[5] In practice, however, the asymmetric synthesis of α-arylglycines can prove problematical since this class of α-amino acids are prone to racemisation at their α-stereocentre.[6] As part of our studies directed towards the synthesis of a small library of homochiral α-arylglycines, we wished to determine whether the methodology first developed by Corey and Link for the asymmetric synthesis of aliphatic α-amino acids,[7] based on the enantioselective reduction of trichloromethyl ketones with the CBS catalyst, could be employed for the asymmetric synthesis of aryl α-amino acids. We wish to report herein that a key modification to the reaction conditions originally described by Corey and Link[7] has enabled us to employ this methodology for the asymmetric synthesis of a representative range of α-arylglycines in >97% e.e.



Scheme 1. *Reagents and conditions:* (i) catecholborane, CBS catalyst **6**, toluene, −78°C; (ii) 4 equiv. of NaOH, 2 equiv. of NaN_3, DME/H_2O; (iii) H_2, Pd/C, EtOAc.

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2. Results and discussion

The original report by Corey and Link[7] on the asymmetric synthesis of homochiral aliphatic α-amino acids relied on a strategy in which enantioselective reduction of easily prepared alkyl trichloromethyl ketones **1** with the chiral CBS catalyst **6** gave homochiral trichloromethyl carbinols **2**. Treatment of these compounds with excess NaOH gave dichloroepoxide intermediates **3**, which underwent ring opening with an azide anion to afford homochiral α-azido acids **4**. Subsequent hydrogenolysis of these α-azido acids afforded homochiral α-amino acids **5** in very high e.e. (Scheme 1).

We decided to investigate the extension of this methodology to the asymmetric synthesis of α-arylglycine derivatives, an application which had not been reported previously.

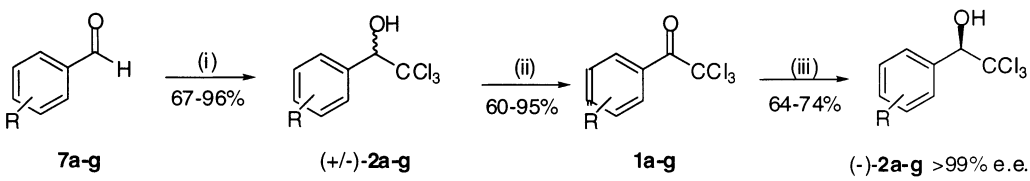
2.1. Asymmetric synthesis of homochiral aryl trichloromethyl carbinols

A series of commercially available *ortho*-, *meta*- and *para*-substituted aryl aldehydes **7a–g** were treated with trichloromethyl anion, generated in situ by treatment of chloroform with KOH in MeOH/DMF,[8] to afford the corresponding racemic aryl trichloromethyl carbinols (±)-**2a–g** in 67–96% yield (Scheme 2).[9] Subsequent oxidation of these aryl trichloromethyl carbinols (±)-**2a–g** using 1 equivalent of sodium dichromate and two equivalents of sulphuric acid in glacial acetic acid afforded the desired aryl trichloromethyl ketones (±)-**1a–g** in 60–95% yield.[10] Reduction of aryl trichloromethyl ketones **1a–g** with (*S*)-CBS catalyst **6**, using catecholborane as the stoichiometric reducing agent,[7] gave the desired homochiral aryl trichloromethyl carbinols (−)-**2a–g** in acceptable yield (64–74%) and in >99% e.e. (Scheme 2).[11–13]

The enantiomeric excess of each (−)-aryl trichloromethyl carbinol **2a–g** was shown to be >99% by derivatisation using Alexakis' chiral phosphoramide methodology[14] and comparison of the ^{31}P NMR spectra with those of authentic racemic standards. Interestingly, the Mosher's ester chiral derivatisation method, previously employed to determine the enantiomeric purity of both aryl methyl carbinols[15] and aryl trifluoromethyl carbinols,[16] proved ineffective in this case, since resonances in both the ^{1}H and ^{19}F NMR spectra of the derivatives of racemic aryl trichloromethyl carbinols **2a–g** were not resolved. The absolute configuration of the stereogenic centre of each homochiral aryl trichloromethyl carbinol (−)-**2a–g** was assigned as *R* using the previously established model for the CBS reduction system in which reduction of trichloromethyl ketones with the (*S*)-enantiomer of CBS catalyst **6** afforded (*R*)-trichloromethyl carbinols.[11] These assignments were confirmed for (−)-2,2,2-trichloro-1-phenylethanol **2a** by comparison of the sign of its specific rotation of $[\alpha]_D^{23} = -36.0$ with that of the known (*S*)-enantiomer, (+)-**2a** ($[\alpha]_D^{25} = +36.9$, $CHCl_3$).[17]

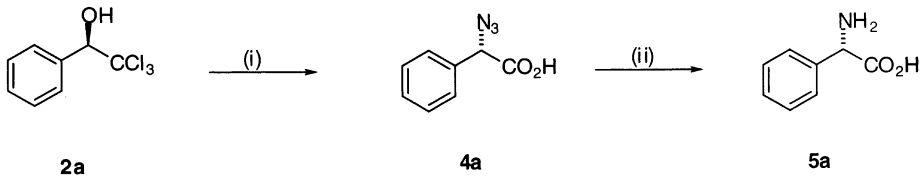
2.2. Enantioselective synthesis of α-arylglycines

With the desired homochiral aryl trichloromethyl carbinols **2a–g** in hand, our attention turned towards their elaboration to the desired homochiral α-arylglycines **5a–g**. Since we were aware of the increased capacity of the stereogenic centres of the intermediate α-azido acids **4a–g** to undergo racemisation under alkaline conditions, we first optimised conditions for the conversion of (*R*)-2,2,2-trichloro-1-phenylethanol **2a** into (*S*)-phenylglycine **5a** (Scheme 3). Application of the original Corey–Link conditions,[7] involving treatment of carbinol (−)-**2a** with four equivalents of NaOH and two equivalents of NaN_3 in aqueous dimethoxyethane, gave α-azido acid **4a**, which was immediately reduced by catalytic hydrogenation (10% Pd/C as catalyst) to afford *racemic* (±)-phenylglycine **5a** in 70% yield (Table 1, entry 1). Given that racemisation was unlikely to have occurred during hydrogenolysis of α-azido acid **4a** to phenylglycine **5a**,[18] we investigated a variety of basic conditions for the conversion of carbinol (−)-**2a** to its corresponding (*S*)-α-azido acid **4a** in an effort to suppress the racemisation. Thus, treatment of carbinol (−)-**2a** with either one or two equivalents of NaOH afforded, after hydrogenolysis, enantiomerically enriched (*S*)-phenylglycine **5a** in 70% e.e. but in low yield (12 and 49%, respectively; Table 1, entries 2 and 3). Similarly, when LiOH, K_2CO_3 and Cs_2CO_3 were employed as bases, phenylglycine **5a** was obtained, after hydrogenolysis, in very low yield (18–37%) and in 65–70% e.e. (Table 1, entries 4–6). Attempts to employ the organic bases Et_3N and DABCO did not afford any of the desired product (Table 1, entries 7 and 8). A review of the literature revealed that DBU had previously been employed as an alternative to NaOH for the base-promoted conversion of alkyl trichloromethyl carbinols **2** into derivatives of α-azido acids **4**.[19] We found that treatment of the aryl trichloromethyl carbinol (−)-**2a** with exactly one equivalent of DBU and two



a: R = H; **b:** R = 2-MeO; **c:** R = 2-Me; **d:** R = 2-Br; **e:** R = 3-Me; **f:** R = 4-Me; **g:** R = 4-F

Scheme 2. *Reagents and conditions:* (i) $CHCl_3$, KOH, MeOH/DMF, −10°C; (ii) $Na_2Cr_2O_7$, H_2SO_4/AcOH; (iii) catecholborane, CBS catalyst **6** (10 mol%), toluene, −70 to 0°C.



Scheme 3. *Reagents and conditions:* (i) base, 2 equiv. of NaN_3, DME/H_2O (see Table 1); (ii) H_2, Pd/C, EtOAc.

equivalents of sodium azide in aqueous dimethoxyethane afforded, after hydrogenolysis, phenylglycine (+)-**5a** in 62% yield and >99% e.e. (Table 1, entry 9). The importance of carrying out this transformation with exactly one mole equivalent of DBU was demonstrated by carrying out the conversion of **2a** to **4a** in the presence of either 1.2 or 2 equivalents of DBU, which resulted in partial racemisation and afforded, after hydrogenolysis, enantiomerically enriched **5a** in 90 and 82% e.e., respectively, albeit in improved yield (Table 1, entries 9 and 10). To the best of our knowledge, this is the first demonstration of the superiority of DBU over inorganic bases for the transformation of non-racemic trichloromethyl carbinols **2** into α-azido acids **4** without racemisation.

Table 1. Transformation of carbinol (−)-**2a** into α-azido acid **4a** then (*S*)-phenylglycine **5a** according to Scheme 3[a]

Base	Equiv. used	Yield of **5a** (%)	E.e. of **5a** (%)
NaOH	4	70	0
NaOH	2	49	70
NaOH	1	12	70
LiOH	4	37	70
K_2CO_3	5	20	60
Cs_2CO_3	6	18	65
Et_3N	5	0	–
DABCO	1	0	–
DBU	2	80	82
DBU	1.2	71	90
DBU	1	62	≥99

[a] The intermediate α-azido acid was not isolated but was immediately hydrogenated to give the amino acid **5a**. Enantiomeric excesses were determined by Mosher's amide analysis.

As a consequence of these findings, the optimised conditions employing a stoichiometric quantity of DBU were then employed for the conversion of the series of homochiral (*R*)-aryl trichloromethyl carbinols (−)-**2b**–**g** into their corresponding (*S*)-α-arylglycines **5b**–**g**, which were isolated in overall yields of between 40 and 62% yield and in ≥97% e.e. in all cases (Scheme 4).

The enantiomeric excesses of the homochiral α-arylglycines **5a**–**g** prepared in this study were determined by conversion to the corresponding Mosher's amide derivatives and comparison of the ^{19}F NMR spectra with those of authentic racemic standards. The absolute configuration of the homochiral α-arylglycines **5a**–**g** was assigned as *S* on the basis of the following mechanistic arguments: cyclisation of homochiral (*R*)-aryl trichloromethyl carbinols **2a**–**g** affords epoxide intermediates **3a**–**g**, which are attacked by azide anion with inversion at their stereogenic centre to afford (*S*)-α-azido acids **4a**–**g**; the configuration of these derivatives is conserved on hydrogenolysis to the corresponding (*S*)-α-arylglycines **5a**–**g**. These stereochemical assignments were confirmed for **5a** and **5g**, for which the positive sign of the specific rotations of the (*S*)-enantiomers are known from the literature.[20]

3. Conclusions

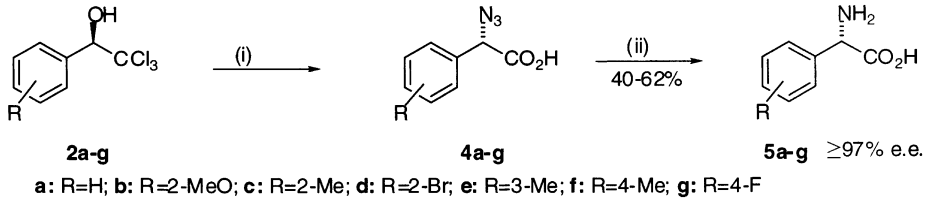
In conclusion, we have demonstrated that a key modification to the methodology first developed by Corey and Link for the asymmetric synthesis of homochiral aliphatic α-amino acids, based on enantioselective reduction of alkyl trichloromethyl ketones with CBS catalyst **6**, has enabled us to prepare a representative series of diversely substituted α-arylglycines in reasonable yield and very high e.e. The strategy employed is practical and straightforward, involves commercially available materials, and should be applicable to the preparation of a wide range of homochiral α-aryl glycines.

4. Experimental

4.1. General

Melting points were determined on a Thermovar apparatus. ^1H (300.13 MHz), $^{13}C\{^1H\}$ (75.43 MHz), ^{19}F (282.39 MHz) and ^{31}P (121.49 MHz) NMR spectra were recorded on a Bruker AC-300 instrument. Chemical shifts (δ) are given in ppm, coupling constants (J) are given in hertz. IR spectra were recorded on a Perkin–Elmer FTIR 1600 spectrometer as solutions in $CHCl_3$ or as dispersions in Nujol. Principal diagnostic absorptions are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a Perkin–Elmer 141 MC polarimeter in a 1 dm cell. Electron impact mass spectra (EIMS) and chemical ionisation mass spectra (CIMS) were obtained on a Nermag R10-10C quadrupole spectrometer, using ammonia as the vector gas for the latter technique. High resolution chemical ionisation mass spectra (HRMS) were recorded on a Kratos MS-80 spectrometer using methane as the vector gas. For simplicity, diagnostic peak data from mass spectra are presented only for isotopes ^{35}Cl and ^{79}Br, although the expected statistical isotopic distributions were invariably observed.

Elemental analyses were carried out at the Institut de Chimie des Substances Naturelles du CNRS, Gif-sur-Yvette, France. Flash chromatography was performed



Scheme 4. *Reagents and conditions:* (i) 1 equiv. of DBU, 2 equiv. of NaN_3, DME/H_2O; (ii) H_2, Pd/C, EtOAc.

using Merck Kieselgel 60 (230–400 mesh) as the stationary phase. Analytical TLC was carried out on Merck Kieselgel 60 F_{254} plates of 0.2 mm thickness which were developed using a 5% solution of phosphomolybdic acid in ethanol. All R_f values are given for the solvent system which was used for preparative chromatography. CBS catalyst **6** was prepared as a solution in toluene, as previously described.[13a] Chloroform, DMF, methanol and toluene were dried and purified by standard procedures before use; other solvents and all reagents were obtained commercially and used as supplied.

4.2. Preparation of racemic aryl trichloromethyl carbinols 2a–g. General procedure

A solution of KOH (1.12 g, 20 mmol) in MeOH (4 ml) was added dropwise to a stirred solution of aryl aldehyde **7a**–**g** (20 mmol) and chloroform (3.5 ml, 44 mmol) in DMF (15 ml) at −10°C under an inert atmosphere. After 1 h at this temperature, the reaction mixture was treated with a 1 M HCl solution (4 ml) and toluene (4 ml). This vigorously stirred mixture was allowed to warm to room temperature over 30 min. The organic phase was collected and washed with water (2×4 ml), stirred with active charcoal for 10 min and filtered through Celite, washed with a 5% $NaHCO_3$ solution (4 ml) and then water (4 ml). The organic phase was then dried over $MgSO_4$, filtered and evaporated. The crude product thus obtained was purified by flash chromatography using cyclohexane/CH_2Cl_2 (7:3) as the mobile phase. Solid products were then recrystallised from petroleum ether.

4.2.1. (±)-2,2,2-Trichloro-1-phenylethanol 2a. A yellow oil, 91%. R_f 0.42; IR ($CHCl_3$): 3396br; CIMS: m/z 242 $[MH+NH_3]^+$, 259 $[MH+2NH_3]^+$; ^1H NMR ($CDCl_3$): δ 3.30 (s, 1H), 5.21 (s, 1H), 7.39 (m, 3H), 7.61 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 84.4, 103.0, 127.8, 129.2, 129.5, 134.7. Anal. calcd for $C_8H_7Cl_3O$: C, 42.61; H, 3.13. Found: C, 42.38; H, 3.27.

4.2.2. (±)-2,2,2-Trichloro-1-(2-methoxyphenyl)ethanol 2b. An off-white solid, 91%. R_f 0.34; mp 45°C (petroleum ether); IR ($CHCl_3$): 3586br; CIMS: m/z 255 $[MH]^+$; ^1H NMR ($CDCl_3$): δ 3.89 (s, 3H), 4.21 (d, $J=6.9$, 1H), 5.61 (d, $J=6.9$, 1H), 7.00 (m, 1H), 7.39 (dd, $J=7.8$ and 1.6, 2H), 7.62 (dd, $J=7.7$ and 1.5, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 55.6, 80.1, 103.6, 111.4, 120.6, 123.7, 130.6, 130.8, 157.9. Anal. calcd for $C_9H_9Cl_3O_2$: C, 42.30; H, 3.55. Found: C, 42.64; H, 3.44.

4.2.3. (±)-2,2,2-Trichloro-1-(2-methylphenyl)ethanol 2c. A white solid, 83%. R_f 0.22; mp 60°C (petroleum ether); IR ($CHCl_3$): 3582br; CIMS: m/z 204 $[MH-Cl]^+$; ^1H NMR ($CDCl_3$): δ 2.52 (s, 3H), 3.20 (d, $J=4.5$, 1H), 5.57 (d, $J=4.5$, 1H), 7.19–7.35 (m, 3H), 7.82 (dd, $J=6.5$ and 2.6, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 20.5, 79.9, 103.6, 126.0, 127.9, 129.5, 130.8, 134.2, 137.7. Anal. calcd for $C_9H_9Cl_3O$: C, 45.13; H, 3.79; Cl, 44.40. Found: C, 45.21; H, 3.79; Cl, 44.36.

4.2.4. (±)-2,2,2-Trichloro-1-(2-bromophenyl)ethanol 2d. A white solid, 95%. R_f 0.33; mp 50°C (petroleum ether); IR ($CHCl_3$): 3570br; CIMS: m/z 303 $[MH]^+$; ^1H NMR ($CDCl_3$): δ 4.21 (s, 1H), 5.61 (s, 1H), 7.28 (ddd, $J=7.9$, 1.9 and 1.7, 1H), 7.32 (ddd, $J=8.1$, 7.9 and 1.4, 1H), 7.63 (dd, $J=7.9$ and 1.4, 1H), 7.90 (dd, $J=8.1$ and 1.7, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 81.8, 102.7, 125.7, 127.3, 130.0, 130.9, 132.9, 135.0. Anal. calcd for $C_8H_6BrCl_3O$: C, 31.58; H, 1.97. Found: C, 31.46; H, 1.88.

4.2.5. (±)-2,2,2-Trichloro-1-(3-methylphenyl)ethanol 2e. A colourless oil, 73%. R_f 0.34; IR ($CHCl_3$): 3584br; CIMS: m/z 239 $[MH]^+$; ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H), 3.78 (d, $J=4.5$, 1H), 5.18 (d, $J=4.5$, 1H), 7.25–7.47 (m, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 21.6, 84.6, 103.2, 126.5, 127.8, 129.8, 130.3, 134.9, 137.6. Anal. calcd for $C_9H_9Cl_3O$: C, 45.13; H, 3.79; Cl, 44.40. Found: C, 45.44; H, 3.76; Cl, 45.08.

4.2.6. (±)-2,2,2-Trichloro-1-(4-methylphenyl)ethanol 2f. A colourless oil, 96%. R_f 0.45; IR ($CHCl_3$): 3384br; CIMS: m/z 239 $[MH]^+$; ^1H NMR ($CDCl_3$): δ 2.36 (s, 3H), 3.34 (d, $J=3.9$, 1H), 5.15 (d, $J=3.9$, 1H), 7.18 (d, $J=8.1$, 2H), 7.47 (d, $J=8.1$, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 21.2, 84.3, 103.2, 128.5, 129.0, 131.8, 139.4. Anal. calcd for $C_9H_9Cl_3O$: C, 45.13; H, 3.79. Found: C, 45.23; H, 3.81.

4.2.7. (±)-2,2,2-Trichloro-1-(4-fluorophenyl)ethanol 2g. A colourless oil, 67%. R_f 0.28; IR ($CHCl_3$): 3433br; CIMS: m/z 260 $[MH+NH_3]^+$; ^1H NMR ($CDCl_3$): δ 3.49 (s, 1H), 5.18 (s, 1H), 7.07 (m, 2H), 7.56 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 83.8, 103.2, 114.8 (d, $J=22.6$), 129.8, 131.0 (d, $J=7.5$), 163.3 (d, $J=242$). Anal. calcd for $C_8H_6Cl_3FO$: C, 39.46; H, 2.48. Found: C, 39.88; H, 2.63.

4.3. Oxidation of aryl trichloromethyl carbinols 2a–g. General procedure

A solution of sodium dichromate dihydrate (1.49 g, 5.00 mmol) and concentrated sulphuric acid (0.54 ml,

10.0 mmol) in glacial acetic acid (10 ml) was added dropwise to a stirred solution of racemic aryl trichloromethyl carbinol (±)-**2a**–**g** (5.00 mmol) in glacial acetic acid (10 ml). The mixture was stirred at room temperature for 1 h, then the excess oxidant was destroyed by the addition of 2-propanol (1.5 ml). After a further 10 min, a saturated NaCl solution (25 ml) was added and the mixture was extracted with CH_2Cl_2 (2×15 ml). The combined organic extracts were washed with a 5% $NaHCO_3$ solution (12 ml) and then a saturated NaCl solution (12 ml). The organic phase was then dried over $MgSO_4$, filtered and evaporated. The crude product thus obtained was purified by flash chromatography using cyclohexane/CH_2Cl_2 (1:1) as the mobile phase.

4.3.1. 2,2,2-Trichloro-1-phenylethanone 1a. An oil, 78%. R_f 0.83; IR ($CHCl_3$): 1654; EIMS: m/z 187 (M^+–Cl), 105 (M^+–CCl_3); ^{1}H NMR ($CDCl_3$): δ 7.49 (t, J=8.4, 2H), 7.63 (tt, J=8.3 and 1.6, 1H), 8.26 (dd, J=8.4 and 1.6, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 96.0, 128.5, 129.1, 131.6, 134.4, 181.3. Anal. calcd for $C_8H_5Cl_3O$: C, 43.07; H, 2.26; Cl, 47.59. Found: C, 43.19; H, 2.31; Cl, 47.49.

4.3.2. 2,2,2-Trichloro-1-(2-methoxyphenyl)ethanone 1b. An oil, 60%. R_f 0.77; IR ($CHCl_3$): 1710; EIMS: m/z 252 (M^+), 135 (M^+–CCl_3); ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H), 7.08 (m, 2H), 7.55 (t, J=7.4, 1H), 7.66 (d, J=6.4, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 55.7, 95.8, 111.5, 120.1, 123.1, 129.1, 132.9, 157.4, 186.1. Anal. calcd for $C_9H_7Cl_3O_2$: C, 42.64; H, 2.78. Found: C, 42.91; H, 2.65.

4.3.3. 2,2,2-Trichloro-1-(2-methylphenyl)ethanone 1c. An oil, 76%. R_f 0.89; IR ($CHCl_3$): 1710; EIMS: m/z 236 (M^+), 119 (M^+–CCl_3); ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H), 7.35 (m, 3H), 7.95 (dd, J=6.4 and 2.1, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 20.5, 96.0, 125.2, 128.4, 131.6, 131.8, 134.2, 134.6, 174.0. Anal. calcd for $C_9H_7Cl_3O$: C, 45.51; H, 2.97. Found: C, 45.23; H, 3.81.

4.3.4. 2,2,2-Trichloro-1-(2-bromophenyl)ethanone 1d. An oil, 95%. R_f 0.83; IR ($CHCl_3$): 1744; EIMS: m/z 183 (M^+–CCl_3); ^{1}H NMR ($CDCl_3$): δ 7.40 (m, 2H), 7.68 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 94.8, 120.5, 126.8, 128.6, 132.1, 133.4, 135.7, 185.4. Anal. calcd for $C_8H_4BrCl_3O$: C, 31.77; H, 1.33. Found: C, 32.56; H, 1.38.

4.3.5. 2,2,2-Trichloro-1-(3-methylphenyl)ethanone 1e. An oil, 83%. R_f 0.81; IR ($CHCl_3$): 1706; EIMS: m/z 236 (M^+), 119 (M^+–CCl_3); ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 7.44 (m, 2H), 8.06 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 21.3, 95.6, 128.3, 128.8, 129.3, 132.1, 135.3, 138.6, 181.7. Anal. calcd for $C_9H_7Cl_3O$: C, 45.51; H, 2.97. Found: C, 45.23; H, 2.68.

4.3.6. 2,2,2-Trichloro-1-(4-methylphenyl)ethanone 1f. An oil, 83%. R_f 0.82; IR ($CHCl_3$): 1707; EIMS: m/z 236 (M^+), 119 (M^+–CCl_3); ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H), 7.27 (d, J=8.3, 2H), 8.15 (d, J=8.3, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 21.8, 95.6, 126.1, 129.1, 131.7, 145.6, 180.8; HRMS: $[C_9H_7Cl_3O+H]^+$ requires 236.9641. Found: 236.9647.

4.3.7. 2,2,2-Trichloro-1-(4-fluorophenyl)ethanone 1g. An oil, 88%. R_f 0.85; IR ($CHCl_3$): 1744; EIMS: m/z 240 (M^+), 123 (M^+–CCl_3); ^{1}H NMR ($CDCl_3$): δ 7.18 (m, 2H), 7.32 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 94.9, 115.5 (d, J=21.6), 124.9, 134.6 (d, J=7.2), 165.9 (d, J=257), 179.3; HRMS: $[C_8H_4Cl_3FO+H]^+$ requires 240.9389. Found: 240.9372.

4.4. Asymmetric reduction of aryl trichloromethyl ketones 1a–g. General procedure

A solution of aryl trichloromethyl ketone **1a**–**g** (5.00 mmol) in toluene (50 ml) was added to a 1 M solution of catalyst **6** in toluene (0.50 ml, 0.50 mmol). This mixture was cooled to −70°C and a 1 M solution of catecholborane in THF (10 ml, 10 mmol) was added slowly. The mixture was stirred at −70°C for 8 h and then at room temperature for 16 h, then water (10 ml) and EtOAc (10 ml) were added. The organic phase was washed with a 1 M NaOH solution (3×10 ml) and then with a 1 M HCl solution (2×10 ml), dried over $MgSO_4$, filtered and evaporated. The crude product thus obtained was purified in the same manner as described above for the racemic preparation (Section 4.2).

4.4.1. (*R*)-2,2,2-Trichloro-1-phenylethanol 2a. A yellow oil, 73%. Spectral data as for racemic preparation; $[\alpha]_D^{23}=-36$ (c 1.00, $CHCl_3$); e.e. >98% (derivatisation method A).

4.4.2. (*R*)-2,2,2-Trichloro-1-(2-methoxyphenyl)ethanol 2b. A pale yellow solid, 64%. Spectral data as for racemic preparation; $[\alpha]_D^{23}=-52$ (c 0.26, $CHCl_3$); e.e. >98% (derivatisation method A).

4.4.3. (*R*)-2,2,2-Trichloro-1-(2-methylphenyl)ethanol 2c. A white solid, 74%. Spectral data as for racemic preparation; $[\alpha]_D^{23}=-72$ (c 0.25, $CHCl_3$); e.e. >98% (derivatisation method A).

4.4.4. (*R*)-2,2,2-Trichloro-1-(2-bromophenyl)ethanol 2d. A white solid, 67%. Spectral data as for racemic preparation; $[\alpha]_D^{23}=-79$ (c 0.26, $CHCl_3$); e.e. >98% (derivatisation method A).

4.4.5. (*R*)-2,2,2-Trichloro-1-(3-methylphenyl)ethanol 2e. A colourless oil, 71%. Spectral data as for racemic preparation; $[\alpha]_D^{23}=-45$ (c 1.00, $CHCl_3$); e.e. >98% (derivatisation method A).

4.4.6. (*R*)-2,2,2-Trichloro-1-(4-methylphenyl)ethanol 2f. A colourless oil, 67%. Spectral data as for racemic preparation; $[\alpha]_D^{23}=-35$ (c 1.00, $CHCl_3$); e.e. >98% (derivatisation method A).

4.4.7. (*R*)-2,2,2-Trichloro-1-(4-fluorophenyl)ethanol 2g. A colourless oil, 68%. Spectral data as for racemic preparation; $[\alpha]_D^{23}=-33$ (c 1.00, $CHCl_3$); e.e. >98% (derivatisation method A).

4.5. Preparation of (*S*)-arylglycines 5a–g. General procedure

A solution of DBU (0.31 g, 2.00 mmol) and sodium azide (0.26 g, 4.00 mmol) in water (6 ml) was added to a vigorously stirred solution of (*R*)-2,2,2-trichloromethyl-1-arylethanol (–)-**2a**–**g** (2.00 mmol) in dimethoxyethane (5 ml) at 10°C. After 5 min the mixture was warmed to room temperature and stirred for a further 24 h. Ether (3 ml) was added, and the two phases separated. The organic phase was extracted with a 5% NaOH solution (3 ml), and the aqueous phases combined. The resulting aqueous solution was cooled to 0°C and was treated with a 1 M KH_2PO_4 solution until pH 3 was attained. The solution was then extracted with EtOAc (4×3 ml) and the combined extracts were dried over $MgSO_4$. The resulting solution of α-azido acid **4a**–**g** was concentrated to a volume of 7 ml, and 10% palladium on carbon (10 mg) was added. This mixture was stirred vigorously under hydrogen at atmospheric pressure for 24 h. The solid catalyst was recovered by careful filtration and the filtrate discarded. The solids were washed with a mixture of water (50 ml) and EtOH (3 ml) at 70°C, and a clear solution was obtained by filtration. Evaporation of this solution left the required (*S*)-arylglycine **5a**–**g**, which was purified by passage through a column of Dowex 50X8 ion exchange resin.

4.5.1. (*S*)-Phenylglycine 5a. A white solid, 62%. Mp >250°C; IR (Nujol): 1730; CIMS: *m*/*z* 152 $[MH]^+$; ^1H NMR (CD_3OD): δ 4.86 (s, 1H), 7.32–7.60 (m, 5H); $^{13}C\{^1H\}$ NMR (CD_3OD): δ 56.6, 128.0, 129.6, 130.3, 131.5, 170.8; $[\alpha]_D^{23}=+154$ (*c* 0.50, 5 M HCl); e.e. ≥99% (derivatisation method B).

4.5.2. (*S*)-(2-Methoxyphenyl)glycine 5b. A white solid, 40%. Mp >250°C; IR (Nujol): 1740; CIMS: *m*/*z* 182 $[MH]^+$; ^1H NMR (CD_3OD): δ 3.87 (s, 3H), 4.83 (s, 1H), 7.02 (m, 2H), 7.36 (m, 2H); $^{13}C\{^1H\}$ NMR (CD_3OD): δ 55.7, 56.1, 108.5, 112.2, 121.9, 130.6, 131.4, 131.7, 168.9; $[\alpha]_D^{23}=+163$ (*c* 0.10, 5 M HCl); e.e. = 97% (derivatisation method B).

4.5.3. (*S*)-(2-Methylphenyl)glycine 5c. A white solid, 45%. Mp >250°C; IR (Nujol): 1744; CIMS: *m*/*z* 166 $[MH]^+$; ^1H NMR (CD_3OD): δ 2.49 (s, 3H), 4.56 (s, 1H), 7.24 (m, 2H), 7.41 (m, 2H); $^{13}C\{^1H\}$ NMR (CD_3OD): δ 19.6, 56.1, 123.6, 127.7, 128.2, 129.9, 132.0, 136.2, 169.2; $[\alpha]_D^{23}=+91$ (*c* 0.10, 5 M HCl); e.e. ≥99% (derivatisation method B).

4.5.4. (*S*)-(2-Bromophenyl)glycine 5d. A white solid, 55%. Mp >250°C; IR (Nujol): 1740; CIMS: *m*/*z* 230 $[MH]^+$; ^1H NMR (CD_3OD): δ 4.92 (s, 1H), 7.02–7.25 (m, 4H); $^{13}C\{^1H\}$ NMR (CD_3OD): δ 56.8, 127.0, 127.3, 128.0, 129.1, 129.6, 134.2, 171.2; $[\alpha]_D^{23}=+67$ (*c* 0.25, 5 M HCl); e.e. = 98% (derivatisation method B).

4.5.5. (*S*)-(3-Methylphenyl)glycine 5e. A white solid, 49%. Mp >250°C; IR (Nujol): 1738; CIMS: *m*/*z* 166 $[MH]^+$; ^1H NMR (CD_3OD): δ 2.35 (s, 3H), 4.52 (s, 1H), 7.08–7.25 (m, 4H); $^{13}C\{^1H\}$ NMR (CD_3OD): δ 21.3, 60.2, 126.1, 129.6, 129.8, 130.3, 132.1, 138.5, 169.8; $[\alpha]_D^{23}=+146$ (*c* 0.20, 5 M HCl); e.e. ≥99% (derivatisation method B).

4.5.6. (*S*)-(4-Methylphenyl)glycine 5f. A white solid, 41%. Mp >250°C; IR (Nujol): 1735; CIMS: *m*/*z* 166 $[MH]^+$; ^1H NMR (CD_3OD): δ 2.35 (s, 3H), 4.78 (s, 1H), 7.18 (d, $J=8.1$, 2H), 7.47 (d, $J=8.1$, 2H); $^{13}C\{^1H\}$ NMR (CD_3OD): δ 21.1, 60.2, 128.5, 129.1, 131.3, 139.2, 170.5; $[\alpha]_D^{23}=+149$ (*c* 0.50, 1 M HCl); e.e. ≥99% (derivatisation method B).

4.5.7. (*S*)-(4-Fluorophenyl)glycine 5g. A white solid, 60%. Mp >250°C; IR (Nujol): 1736; CIMS: *m*/*z* 170 $[MH]^+$; ^1H NMR (CD_3OD): δ 4.65 (s, 1H), 7.21 (m, 2H), 7.54 (m, 2H); $^{13}C\{^1H\}$ NMR (CD_3OD): δ 65.4, 131.1, 117.1 (d, $J=22.7$), 131.4 (d, $J=8.0$), 166.4 (d, $J=245$), 170.6; $[\alpha]_D^{23}=+131$ (*c* 0.50, 1 M HCl); e.e. ≥99% (derivatisation method B).

4.6. Determination of enantiomeric purity of carbinols 2 (derivatisation method A)

In an NMR tube, (1*S*,2*S*)-*N*,*N*′-dimethyl-1,2-bis[3-(trifluoromethyl)phenyl]-1,2-ethanediamine (10 mg, 27 μmol) was dissolved in $CDCl_3$ (0.6 ml). Pyridine (11 μl, 136 μmol) was added, followed by PCl_3 (3 μl, 34 μmol), then the aryl trichloromethyl carbinol **2a**–**g** (27 μmol). After 5 min, the sample was analysed by ^{31}P NMR spectroscopy. For all compounds **2a**–**g** studied here, the (*R*)-enantiomer gave a derivative having a ^{31}P NMR signal at δ 140.0 (±5.0) ppm, while the (*S*)-enantiomer gave a lower field signal at δ 145.0 (±5.0) ppm; baseline resolution was always achieved. The detection limit was established using **2a**, by incremental contamination of enantiomerically pure material with racemic material, and was found to be an enantiomeric ratio of 99:1 (i.e. at e.e. = 98%).

4.7. Determination of enantiomeric purity of arylglycines 5a–g (derivatisation method B)

Chiral derivatisation of each arylglycine **5a**–**g** with (*R*)-MTPA-Cl was carried out essentially according to Williams' procedure[3] on a 70 μmol scale. The resulting (*R*)-MTPA-amide was dissolved in $CDCl_3$ (0.6 ml) and analysed by ^{19}F NMR spectroscopy. For all compounds **5a**–**g** studied here, the (*R*)-enantiomer gave a derivative having a ^{19}F NMR signal at δ 8.75 (±0.05) ppm, while the (*S*)-enantiomer gave a lower field signal at δ 9.00 (±0.05) ppm; baseline resolution was always achieved. The detection limit was established using **5a**, by incremental contamination of enantiomerically pure material with racemic material, and was found to be an enantiomeric ratio of 99.5:0.5 (i.e. at e.e. = 99%).

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