PERKIN 1

Efficient synthesis of protected β-phenylethylamines, enantiomerically pure protected β-phenyl-α-benzylethylamines and β-phenyl-α-isopropylethylamines using organozinc chemistry

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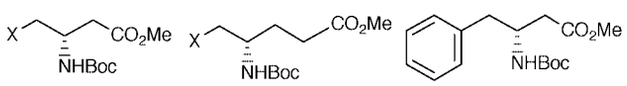
The β-aminoalkylzinc reagents **9a**, **10** and **11** have been efficiently prepared using DMF as a solvent. Palladium-catalysed coupling of these reagents with substituted aryl iodides, under mild and convenient conditions, gives protected β-phenylethylamines **6** in 72–80% yield (three examples), enantiomerically pure protected β-phenyl-α-benzylethylamines **7** in 53–61% yield (four examples), and protected β-phenyl-α-isopropylethylamines **8** in 53–79% yield (four examples).

We have developed substantial expertise in the conversion of readily available enantiomerically pure natural amino acids (serine, aspartic acid, glutamic acid) into unnatural amino acids using organometallic chemistry without loss of stereochemical integrity.[1–3] Recently, we have established that β- and γ-amino acids can be prepared from the zinc reagents **1** and **3** provided



1, X = ZnI
2, X = I

3, X = ZnI
4, X = I

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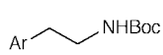
dipolar aprotic solvents are used.[4] In dimethylformamide, for example, we have found zinc insertion into precursor iodides **2** and **4** to be a rapid and reliable process which works well at high concentration (typically 1 molar). For example, coupling of zinc reagent **1** with aryl iodides under palladium catalysis has given the corresponding arylated products **5** in satisfactory to excellent yield.[4]

There continues to be great interest in the synthesis of compounds containing β-aminoaryl functionality.[5] Phenylethylamines are widely found as components of alkaloid natural products, and are known to affect serotonin,[6] dopamine,[7] and noradrenaline[8] receptors. There have been many approaches to the synthesis of β-aminoaryl compounds, in particular β-phenylethylamines, and these have been extensively reviewed.[9] Previous routes to β-phenylethylamine derivatives have employed the Heck arylation reaction followed by reduction[10,11] and have also made use of a boron trifluoride–diethyl ether promoted ring opening reaction of aziridines with lithium diorganocuprates.[12] Other methods involving halogen–lithium exchange followed by nucleophilic substitution,[13] and the addition of lithium salts to styrene derivatives,[14] have been used as routes to β-phenylethylamine derivatives. In this paper, we describe a concise route to β-phenylethylamine derivatives



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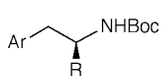
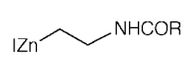


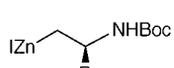
7, R = Bn
8, R = ^{i}Pr



9a, R = O^{t}Bu
9b, R = Ph

6, and analogues **7** and **8** with an additional substituent (benzyl and isopropyl) α to nitrogen, by use of organozinc chemistry.

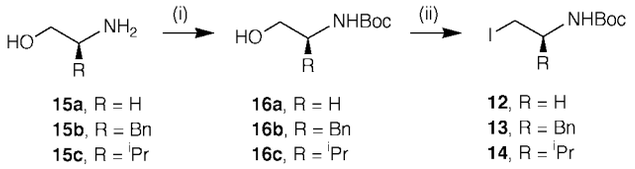
Simple β-amido zinc reagents, without additional ester functionality, which would be required for the preparation of compounds **6** and **7**, have been prepared by Knochel and co-workers.[15] Transmetallation to the corresponding zinc/copper reagent allowed reaction with a range of electrophiles. These reagents were reported to display a reduced reactivity relative to zinc/copper reagents bearing oxygen functionality. Our early efforts to prepare simple organozinc reagents such as **9a** were thwarted by the instability of the reagents, but we were interested by Knochel and co-workers' report that the zinc reagent **9b**, in which the nitrogen was protected as a benzamide, could be prepared in a THF–DMSO mixture at 0 °C.[15] All our recent results concerning the structures of amino acid-derived β-amino zinc reagents, in which the use of a dipolar aprotic solvent suppresses β-elimination, suggested that a likely explanation for Knochel and co-workers' observation was that the DMSO disrupted internal coordination between the amide carbonyl and the zinc, thus suppressing β-elimination. We therefore felt it would be possible to prepare the novel organozinc reagent **9a** in a dipolar aprotic solvent, and that coupling with aryl iodides would provide an efficient route for the synthesis of protected β-phenylethylamines **6**. Applications of enantiomerically pure zinc reagents **10**[15] and **11** could also be explored.



10, R = Bn
11, R = ^{i}Pr

Results and discussion

The *N*-protected alkyl iodides **12**, **13** and **14** were prepared in two simple steps. Treatment of aminoalcohols **15a–c** in an alkaline solution of THF with di-*tert*-butyl dicarbonate gave the protected alcohols **16a–c**, which were converted into iodides **12**, **13** and **14** using iodine, triphenylphosphine and imidazole (Scheme 1, Table 1).[16]



15a, R = H
15b, R = Bn
15c, R = ^{i}Pr

16a, R = H
16b, R = Bn
16c, R = ^{i}Pr

12, R = H
13, R = Bn
14, R = ^{i}Pr

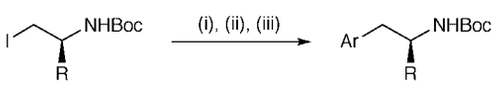
Scheme 1 *Reagents and conditions*: i, Boc_2O (1.1 equiv.), 1 M NaOH, THF, room temp., 12 h; ii, I_2 (1.1 equiv.), PPh_3, imidazole, room temp.

Table 1 Yields of protected aminoalcohols and corresponding iodides

R	Alcohol	Yield (%)	Iodide	Yield (%)
H	**16a**	92	**12**	58
Bn	**16b**	95	**13**	55
^{i}Pr	**16c**	93	**14**	56

Synthesis of phenylethylamine derivatives

The organozinc reagent **9a** was generated from the iodide **12** using activated zinc dust,[17] in DMF. Complete conversion into the organozinc reagent **9a** occurred within 15 min at ambient temperature (19 °C). Subsequent palladium-catalysed cross-coupling reactions were carried out at ambient temperature in the presence of the active catalyst bis(tri-*o*-tolylphosphine)palladium(0), prepared from $Pd_2(dba)_3$ and tri-*o*-tolylphosphine, to give the phenylethylamine derivatives **6**. Analogous treatment of the iodides **13** and **14** gave the coupled products **7** and **8**, respectively (Scheme 2, Table 2). The only



12, R = H
13, R = Bn
14, R = ^{i}Pr

6, R = H
7, R = Bn
8, R = ^{i}Pr

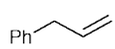
Scheme 2 *Reagents and conditions*: i, Zn* (prepared from Zn dust using 1,2-dibromoethane, followed by Me_3SiCl, in DMF), 15–45 min, room temp.; ii, iodides **12**–**14** in DMF, 15 min, room temp.; iii, ArI (1.33 equiv.), $Pd_2(dba)_3$ (2.5 mol%), P(*o*-$MeC_6H_4)_3$ (10 mol%), room temp., 3 h.

significant differences are the rates of formation of the zinc reagents, and the slightly lower yields obtained in coupling reactions of the zinc reagent **10**. The zinc reagent **10** took 45 minutes to be formed completely, whilst the reagent **11** formed in 30 minutes on the same scale.

The successful preparation of coupled products **6** in DMF stands in stark contrast to our initial efforts to prepare the zinc reagent **9a** using the Knochel procedure[17] in THF. For example, formation and coupling of zinc reagent **9a** with 1-iodo-4-nitrobenzene gave the coupled product **6b** in only 40% yield, compared to 80% in DMF. The enantiomeric purity of two representative products, **7b** and **8a**, was checked by the preparation of a racemic sample, followed by chiral phase HPLC analysis. This established that no detectable racemisation had occurred during the coupling process.

NMR Experiments: structural study of organozinc reagent 10

In order to explore our hypothesis that the use of DMF as solvent results in the disruption of coordination by the carbamate group to zinc,[4] the NMR spectra of the zinc reagent **10** was recorded in both THF-d_8 and DMF-d_7. The ^{1}H NMR spectrum of **10** in THF-d_8 showed that significant β-elimination of the carbamate group had occurred, yielding 3-phenylprop-1-ene **17** and Boc-NH_2, whereas in DMF-d_7 the ^{1}H NMR spectrum revealed much cleaner formation of the zinc reagent. These observations are entirely consistent with our previous observations on zinc reagents **1** and **3**.[4]



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The ^{13}C spectra also proved to be informative. Upon formation of the zinc reagent **10** in THF-d_8, the carbamate carbon is observed to shift downfield (+4.226) relative to the same carbon in the parent iodide, suggesting coordination of the carbamate to zinc. This is the largest such shift we have observed in β-amino zinc reagents,[4] and supports the general hypothesis that the additional presence of an ester function, capable of coordination to zinc (for example in **1** and **3**), can suppress coordination of the carbamate to zinc. This would be expected, in turn, to reduce the tendency towards β-elimination. In DMF-d_7 a very small upfield shift (−0.388) of the carbamate carbon is observed, implying that coordination of the carbamate to zinc is suppressed.

Conclusions

A method, employing mild and convenient conditions, for the synthesis of β-phenylethylamines **6**, enantiomerically pure β-phenyl-α-benzylethylamine **7** and β-phenyl-α-isopropylethylamine derivatives **8** has been established. We have confirmed the profound beneficial effect of using DMF on the preparation, stability and cross coupling reactions involving the β-amino organozinc reagents **9a**, **10** and **11**, and provided some evidence for the role of DMF in stabilising the zinc reagent **10**. In addition we have demonstrated that for the chiral zinc reagents **10** and **11**, complete retention of stereochemical integrity occurs during the coupling process.

Table 2 Preparation of phenylethylamine derivatives **6**, **7** and **8**

	Aryl iodide	Iodoamine	R	Ar	Product	Yield (%)[a]
	PhI	**12**	H	Ph	**6a**	72
	4-NO_2-C_6H_4I	**12**	H	4-NO_2-C_6H_4	**6b**	80
	1-Naphthyl iodide	**12**	H	1-Naphthyl	**6c**	80
	PhI	**13**	Bn	Ph	**7a**	53
	4-MeO-C_6H_4I	**13**	Bn	4-MeO-C_6H_4	**7b**	57
	4-Me-C_6H_4I	**13**	Bn	4-Me-C_6H_4	**7c**	59
	1-Naphthyl iodide	**13**	Bn	1-Naphthyl	**7d**	61
	PhI	**14**	^{i}Pr	Ph	**8a**	71
	4-NO_2-C_6H_4I	**14**	^{i}Pr	4-NO_2-C_6H_4	**8b**	79
	1-Naphthyl iodide	**14**	^{i}Pr	1-Naphthyl	**8c**	63
	4-MeO-C_6H_4I	**14**	^{i}Pr	4-MeO-C_6H_4	**8d**	53

[a] Based on starting iodide, **12**, **13** or **14**.

Experimental

Dry DMF was distilled from calcium hydride and stored over 4 Å molecular sieves. Dry dichloromethane was distilled from calcium hydride. Dry THF was distilled from potassium benzophenone ketyl. Petroleum ether refers to the fraction with a boiling point between 40–60 °C. Specific rotations were measured at 20 °C, unless otherwise stated. $[a]_D$ values are given in 10^{-1} deg cm^2 cm^{-1}. ^{1}H NMR spectra were recorded in $CDCl_3$ solvent at 500 MHz, referenced to TMS. ^{13}C NMR spectra were recorded in $CDCl_3$ at 125 MHz and referenced to TMS. Chemical shifts are given in ppm. Coupling constants are given in Hertz. Organic extracts were dried over $MgSO_4$ and the solvent removed on a rotary evaporator.

The following starting materials: *N*-*tert*-butoxycarbonyl-2-aminoethanol **16a**,[18] (2*S*)-(*N*-*tert*-butoxycarbonyl)-2-amino-2-benzylethanol **16b**,[15] and (2*S*)-(*N*-*tert*-butoxycarbonyl)-2-amino-3-methylbutanol **16c**[19] were prepared using the method described below.

1 M NaOH (70 mL) was added to a stirred solution of the aminoalcohol, **15a**, **b** or **c** (65 mmol) in dry THF (160 mL). The alkaline solution was treated with di-*tert*-butyl dicarbonate (14.20 g, 65 mmol). The resulting solution was left stirring for 12 h at room temperature after which THF was removed at reduced pressure and the remaining aqueous solution was acidified to pH 2 with sodium hydrogen sulfate. The aqueous phase was extracted with ethyl acetate (2 × 50 mL) and dried over $MgSO_4$ before concentrating to give the protected aminoalcohols, **16a**, **b** or **c**. (See Table 1 for yields.) ^{1}H NMR data was consistent with the literature[15,18,19] and these compounds were used without further purification in the next step.

Preparation of *N*-*tert*-butoxycarbonyl-2-amino-1-iodoalkanes. General procedure

The precursor iodides, **12**, **13** and **14**, were all prepared using the following method:[16] triphenylphosphine (1 equiv.) and imidazole (1 equiv.) were dissolved in dry dichloromethane with stirring under nitrogen. Iodine (1.1 equiv.) was added slowly and after 5 min a solution of Boc-protected aminoalcohol **16a**, **b** or **c** (1 equiv.) in dry dichloromethane was also added. Stirring was continued at room temperature until no starting material remained as judged by TLC (2:1, petroleum ether–ethyl acetate). The solvent was evaporated under reduced pressure, the residue was filtered through a short column of silica gel eluting with diethyl ether, and the filtrate was concentrated to give crude product iodides as oils. Purification by flash column chromatography eluting with a suitable petroleum ether–ethyl acetate gradient yielded the precursor iodides **12**, **13** and **14** as solids.

***N*-*tert*-Butoxycarbonyl-2-amino-1-iodoethane 12.**[20] Isolated as a pale orange solid, *N*-*tert*-butoxycarbonyl-2-amino-1-iodoethane **12** was recrystallised from petroleum ether–ethyl acetate, (6.00 g, 58%). Mp 42–43 °C (Found $M^+ - C_4H_8$ 214.9453; $C_3H_6NO_2I$ requires 214.9443) (Found: C, 31.0; H, 5.0; N, 5.1%: $C_7H_{14}NO_2I$ requires C, 31.0; H, 5.2; N, 5.2%); IR (KBr disc)/cm^{-1} 3353, 2978, 1682, and 1521; NMR δ_H 1.45 (9H, s, C(CH_3)$_3$), 3.24 (2H, t, *J* 6.0, CH_2I), 3.46–3.51 (2H, m, CH_2N), 4.96–5.01 (1H, br s, N*H*); δ_C 5.95 (CH_2), 28.35 (CH_3), 43.00 (CH_2), 79.81 (quat.), and 155.46 (CO); *m*/*z* (EI) 171 (ICH_2-CH_2NH_2, 25%), 57 (45), and 44 (30).

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-amino-3-phenyl-1-iodopropane 13.[15] Isolated as a white solid, *N*-*tert*-butoxycarbonyl-2-amino-3-phenyl-1-iodopropane **13** was recrystallised from petroleum ether–ethyl acetate, (6.32 g, 55%). Mp 120–121 °C (lit.[15] 118 °C) (Found M^+ 361.0522; $C_{14}H_{20}NO_2I$ requires 361.0539); $[a]_D^{26}$ 18.8 (*c* 1.00 in $CHCl_3$) [lit.[15] 18.87 (*c* 2.93 in $CHCl_3$)] (Found C, 46.6; H, 5.3; N, 3.8%: $C_{14}H_{20}NO_2I$ requires C, 46.6; H, 5.6; N, 3.9%); IR (KBr disc)/cm^{-1} 3352, 3031, 2974, and 1690; δ_H 1.45 (9H, s, C(CH_3)$_3$), 2.85 (2H, m, CH_2Ph), 3.15 (1H, dd, *J* 4.5, 10, C(1)*H*), 3.40 (1H, dd, *J* 4.5, 10, C(1)*H*′), 3.57–3.64 (1H, m, C(2)*H*), 4.67–4.73 (1H, d, *J* 7, N*H*), and 7.18–7.40 (5H, m, Ar*H*); δ_C 13.97 (CH_2), 28.35 (CH_3), 40.60 (CH_2), 51.02 (CH), 79.81 (quat.), 126.85 (Ar), 128.54 (Ar), 129.06 (Ar), 137.05 (Ar), and 154.84 (CO); *m*/*z* (EI) (M^+ 361, 15%), 305 (40), 288 (15), 270 (26), 170 (40), 91 (44), and 57 (100).

A racemic sample *rac*-**13** of the above material was prepared in an identical manner using *rac*-**16b** as the starting material.

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-amino-3-methyl-1-iodobutane 14.[21] Isolated as a white solid, *N*-*tert*-butoxycarbonyl-2-amino-3-methyl-1-iodobutane **14** was recrystallised from petroleum ether–ethyl acetate (4.12 g, 56%). Mp 49–51 °C (lit.[21] 48–51 °C) (Found M^+ 313.0541; $C_{10}H_{20}NO_2I$ requires 313.0539); $[a]_D^{21}$ −18.1 (*c* 1.75 in $CHCl_3$), [lit.[21] −18.7 (*c* 2.10 in $CHCl_3$)] (Found C, 38.6; H, 6.7; N, 4.5%: $C_{10}H_{20}NO_2I$ requires C, 38.4; H, 6.4; N, 4.5%); IR (KBr disc)/cm^{-1} 3292, 2965, 1675, and 533; δ_H 0.95 (3H, d, *J* 7, CH(CH_3)$_2$), 0.97 (3H, d, *J* 7, CH(CH_3′)$_2$), 1.45 (9H, s, C(CH_3)$_3$), 1.74–1.81 (1H, m, C*H*(CH$_3$)$_2$), 3.09–3.14 (1H, m, C(2)*H*), 3.33 (1H, dd, *J* 10, 5, C(1)*H*), 3.42 (1H, dd, *J* 10, 5, C(1)*H*′), and 4.56–4.62 (1H, m, N*H*); δ_C 13.65 (CH_2), 18.43 (CH_3), 19.54 (CH_3), 28.59 (CH_3), 32.51 (CH), 55.70 (CH), 79.76 (quat.), and 155.59 (CO); *m*/*z* (EI) (M^+ 313, 71%), 298 (7), 277 (10), 270 (21), 170 (30), 143 (6), 116 (7), 72 (13), and 57 (100).

A racemic sample *rac*-**14** of the above material was prepared in an identical manner using *rac*-**16c** as the starting material. Compound *rac*-**14** exhibited identical spectroscopic data to the enantiomerically pure sample **14**, but had a mp of 67–68 °C.

Preparation of protected β-phenylethylamines 6, protected β-phenyl-α-benzylethylamines 7 and β-phenyl-α-isopropylethylamines 8. General procedure

Zinc dust (325 mesh, 0.294 g, 4.5 mmol, 6.0 equiv.) was weighed into a 50 mL round bottom flask with side arm which was repeatedly evacuated (with heating using a hot air gun) and flushed with nitrogen. Dry DMF (0.5 mL) and 1,2-dibromoethane (30 μL, 0.355 mmol) were added, and the flask was repeatedly heated using a hot water bath before being allowed to cool over a period of 20 min. The reaction mixture was allowed to cool to room temperature, trimethylsilyl chloride (20 μL, 0.250 mmol) was added, and the resultant mixture and was allowed to stir for a further 30 min under nitrogen. The iodides **12**, **13** or **14** (0.75 mmol) in dry DMF (0.5 mL under nitrogen) were added to the flask and stirred at room temperature until no starting material remained as judged by TLC (2:1, petroleum ether–ethyl acetate). Tris(dibenzylideneacetone)dipalladium (0.0228 g, 0.025 mmol, 0.025 equiv.), tri-*o*-tolylphosphine (0.0304 g, 0.10 mmol, 0.10 equiv.) and the aromatic iodide (1.00 mmol) were added sequentially to the reaction mixture. Stirring was continued for 3 h at room temperature. The reaction mixture was diluted with ethyl acetate (60 mL), and the organic layer was washed with water (2 × 30 mL), brine (2 × 30 mL), dried and concentrated under reduced pressure to give the crude product as an oil. Purification by flash column chromatography over silica with a suitable petroleum ether–ethyl acetate gradient furnished the pure protected products **6**, **7** and **8**.

***N*-*tert*-Butoxycarbonyl-2-phenylethylamine 6a.** Treatment with iodobenzene (111 μL, 1.00 mmol) gave **6a** (0.120 g, 72%), isolated as a beige solid, mp 55–56 °C (lit.[22] 56–57 °C) (Found M^+, 221.1410; $C_{13}H_{19}NO_2$ requires 221.1416) (Found: C, 70.7; H, 8.7; N, 6.3%: $C_{13}H_{19}NO_2$ requires C, 70.5; H, 8.7; N, 6.3%); IR (KBr disc)/cm^{-1} 3380, 2979, 1688, and 1169; NMR δ_H 1.43 (9H, s, C(CH_3)$_3$), 2.79 (2H, t, *J* 7.0, C(2)H_2), 3.38 (2H, q, *J* 7.0, C(1)H_2), 4.52–4.60 (1H, br s, N*H*), and 7.20–7.30 (5H, m, Ar*H*); δ_C 28.41 (CH_3), 36.21 (CH_2), 41.78 (CH_2), 79.20 (quat.), 126.39 (Ar), 128.57 (Ar), 128.81 (Ar), 139.01 (Ar), and 155.86

(CO); *m/z* (EI) 221 (M^+, 10%), 165 (100), 104 (56), 91 (10) and 57 (92).

***N-tert*-Butoxycarbonyl-2-(4-nitrophenyl)ethylamine 6b.** Treatment with 1-iodo-4-nitrobenzene (0.249 g, 1.00 mmol) gave **6b** (0.159 g, 80%), isolated as fine orange needles, mp 94–95 °C (lit.[23] 94–95 °C) (Found M^+, 266.1264; $C_{13}H_{18}N_2O_4$ requires 266.1267) (Found: C, 58.4; H, 7.0; N, 10.2%: $C_{13}H_{18}N_2O_4$ requires C, 58.6; H, 6.8; N, 10.5%); IR (KBr disc)/cm^{-1} 3364, 2981, 1680, 1521, and 1346; NMR δ_H 1.43 (9H, s, $C(CH_3)_3$), 2.93 (2H, t, *J* 7, C(2)H_2), 3.42 (2H, q, *J* 7, C(1)H_2), 4.57–4.64 (1H, br s, N*H*), 7.37 (2H, d, *J* 8.5, Ar*H*), and 8.17 (2H, d, *J* 8.5, Ar*H*); δ_C 28.36 (CH_3), 36.25 (CH_2), 41.34 (CH_2), 79.60 (quat.), 123.78 (Ar), 129.70 (Ar), 146.78 (Ar), 146.93 (Ar), and 155.78 (CO); *m/z* (EI) 266 (M^+, 34%), 251 (25), 193 (56), 149 (35), 137 (60), and 57 (100).

***N-tert*-Butoxycarbonyl-2-(1-naphthyl)ethylamine 6c.** Treatment with 1-iodonaphthalene (146 μL, 1.00 mmol) gave **6c** (0.163 g, 80%) isolated as an orange crystalline solid. Mp 88–89 °C (Found M^+ 271.1562; $C_{17}H_{21}NO_2$ requires 271.1572) (Found: C, 75.1; H, 7.9; N, 4.8%: $C_{17}H_{21}NO_2$ requires C, 75.3; H, 7.8; N, 5.2%); IR (KBr disc)/cm^{-1} 3338, 3037, 2976, 1681, and 1527; NMR δ_H 1.44 (9H, s, $C(CH_3)_3$), 3.27 (2H, t, *J* 7, C(2)H_2), 3.50 (2H, q, *J* 7, C(1)H_2), 4.59–4.64 (1H, br s, N*H*), 7.32 (1H, d, *J* 7, Ar*H*), 7.37–7.42 (1H, m, Ar*H*), 7.46–7.49 (1H, m, Ar*H*), 7.51–7.54 (1H, m, Ar*H*), 7.74 (1H, d, *J* 8.2, Ar*H*), 7.85 (1H, d, *J* 7.7, Ar*H*), and 8.08 (1H, d, *J* 8.3, Ar*H*); δ_C 28.43 (CH_3), 33.36 (CH_2), 41.29 (CH_2), 79.20 (quat.), 123.69 (Ar), 125.51 (Ar), 125.64 (Ar), 126.11 (Ar), 126.77 (Ar), 127.21 (Ar), 128.76 (Ar), 132.00 (Ar), 133.90 (Ar), 135.16 (Ar), and 155.92 (CO); *m/z* (EI) 271 (M^+, 23%) 215 (58), 198 (12), 154 (100), 141 (67), and 57 (83).

***N-tert*-Butoxycarbonyl-1,3-diphenyl-2-propylamine 7a.** Treatment with iodobenzene (111 μL, 1.00 mmol) gave **7a** (0.124 g, 53%), isolated as white prisms. Mp 133–135 °C (Found $MH^+ - (CH_3)_2CHCH_2$ 256.1349; $C_{16}H_{16}NO_2$ requires 256.1338) (Found: C, 77.2; H, 8.3; N, 4.6%: $C_{20}H_{25}NO_2$ requires C, 77.1; H, 8.1; N, 4.5%); IR (KBr disc)/cm^{-1} 3387, 3028, 2976, and 1678; NMR δ_H 1.35 (9H, s, $(C(CH_3)_3)$, 2.71–2.83 (4H, m, CH_2Ph), 4.07–4.16 (1H, m, C(1)*H*), 4.32–4.39 (1H, br s, N*H*), and 7.16–7.39 (10H, m, Ar*H*); δ_C 28.38 (CH_3), 40.21 (CH_2), 52.52 (CH), 79.07 (quat.), 126.32 (Ar), 128.35 (Ar), 129.46 (Ar), 138.16 (Ar), and 155.22 (CO); *m/z* (EI) 256 ($MH^+ - (CH_3)_2CHCH_2$ 92%), 238 (64), 220 (21), 120 (81), 91 (45), and 57 (100).

(1*S*)-*N-tert*-Butoxycarbonyl-1-(4-methoxyphenyl)-3-phenyl-2-propylamine 7b. Treatment with 1-iodo-4-methoxybenzene (0.234 g, 1.00 mmol) gave **7b** (0.152 g, 57%), isolated as white needles. Mp 113–114 °C (Found M^+ 341.1996; $C_{21}H_{27}NO_3$ requires 341.1990); $[a]_D^{26}$ −0.89 (*c* 0.300 in $CHCl_3$) (Found: C, 74.0; H, 7.9; N, 3.9%: $C_{21}H_{27}NO_3$ requires C, 73.9; H, 7.9; N, 4.1%); IR (KBr disc)/cm^{-1} 3376, 3032, 2977, 2836, and 1687; NMR δ_H 1.35 (9H, s, $(C(CH_3)_3)$, 2.67–2.83 (4H, m, CH_2Ph and $CH_2C_6H_4OMe$), 4.05–4.10 (1H, m, C(1)*H*), 4.31–4.36 (1H, br s, N*H*), 6.84 (2H, d, *J* 8.5, Ar*H*), 7.10, (2H, d, *J* 8.5, Ar*H*), and 7.16–7.31 (5H, m, Ar*H*); δ_C 28.34 (CH_3), 39.26 (CH_3), 40.10 (CH_2), 52.64 (CH), 55.26 (CH_3) 79.12 (quat.), 113.82 (Ar), 126.32 (Ar), 128.37 (Ar), 129.42 (Ar), 130.15 (Ar), 130.36 (Ar), 138.25 (Ar), 155.28 (CO), and 158.19 (Ar); *m/z* (EI) 341 (M^+, 37%), 286 (29), 268 (22), 250 (25), 220 (94), 194 (39), 165 (22), 120 (78), 91 (19), 77 (5), and 57 (100).

A racemic sample *rac*-**7b** of the above material was prepared in an identical manner using *rac*-**13** as the starting material. Compound *rac*-**7b** exhibited identical spectrosopic data to the enantiomerically pure sample **7b**, but had a mp of 103–104 °C. The racemic sample was analysed by chiral phase HPLC (Chiralpack AD, eluent 90 : 10 hexane–ethanol, flow rate 1 ml min^{-1}, detection at 215 nm), which gave baseline enantiomer separation. Analysis of **7b** indicated an enantiomeric excess of at least 99.5%.

(1*S*)-*N-tert*-Butoxycarbonyl-1-(4-methylphenyl)-3-phenyl-2-propylamine 7c. Treatment with 1-iodo-4-methylbenzene (0.218 g, 1.00 mmol) gave **7c** (0.143 g, 59%), isolated as white prisms. Mp 107–108 °C (Found MH^+ 326.2114; $C_{21}H_{28}NO_2$ requires 326.2120); $[a]_D^{25}$ −1.03 (*c* 1.165 in $CHCl_3$) (Found: C, 76.6; H, 8.5; N, 4.4%: $C_{21}H_{27}NO_3$ requires C, 77.5; H, 8.4; N, 4.3%); IR (KBr disc)/cm^{-1} 3378, 2976, and 1687; NMR δ_H 1.36 (9H, s, $(C(CH_3)_3)$, 2.32 (3H, s, ArCH_3), 2.65–2.83 (4H, m, CH_2Ph and $CH_2C_6H_4Me$), 4.05–4.15 (1H, m, C(1)*H*), 4.30–4.40 (1H, br s, N*H*), and 7.06–7.31 (9H, m, Ar*H*); δ_C 21.01 (CH_3), 28.41 (CH_3), 39.71 (CH_3), 40.09 (CH_2), 52.55 (CH), 79.08 (quat.), 126.31 (Ar), 128.30 (Ar), 129.08 (Ar), 129.31 (Ar), 129.43 (Ar), 135.00 (Ar), 135.84 (Ar), 138.26 (Ar), and 155.28 (CO); *m/z* (EI) 326 (MH^+, 14%), 270 (36), 252 (82), 234 (9), 220 (17), 178 (19), 164 (30), 120 (69), 91 (27), and 57 (100).

(1*S*)-*N-tert*-Butoxycarbonyl-1-(1-naphthyl)-3-phenyl-2-propylamine 7d. Treatment with 1-iodonaphthalene (146 μL, 1.00 mmol) gave **7d** (0.165 g, 61%), isolated as pale platelets. Mp 133–134 °C (Found M^+ 361.2046; $C_{24}H_{27}NO_2$ requires 361.2042); $[a]_D^{26}$ 36.40 (*c* 0.450 in $CHCl_3$) (Found: C, 79.8; H, 7.8; N, 3.9%: $C_{24}H_{27}NO_3$ requires C, 79.8; H, 7.5; N, 3.9%); IR (KBr disc)/cm^{-1} 3375, 3031, 2974, 1678, and 1625; NMR δ_H 1.34 (9H, s, $(C(CH_3)_3)$, 2.87 (2H, d, *J* 6.5, CH_2Ar), 3.27 (2H, m, CH_2naphthyl), 4.20–4.28 (1H, m, C(1)*H*), 4.41–4.46 (1H, br s, N*H*), 7.20 (2H, d, *J* 7, Ar*H*), 7.23 (1H, d, *J* 7, Ar*H*), 7.29 (1H, d, *J* 7.5, Ar*H*), 7.32 (2H, m, Ar*H*), 7.39 (1H, t, *J* 7.5, Ar*H*), 7.45–7.56 (2H, m, Ar*H*), 7.74 (1H, d, *J* 7.5, Ar*H*), 7.84 (1H, m, Ar*H*), and 7.97 (1H, m, Ar*H*); δ_C 28.31 (CH_3), 37.40 (CH_2), 40.37 (CH_2), 52.20 (CH), 79.10 (quat.), 125.31 (Ar), 125.53 (Ar) 126.06 (Ar), 126.42 (Ar), 127.26 (Ar), 127.45 (Ar), 128.43 (Ar), 128.72 (Ar), 128.88 (Ar), 129.30 (Ar), 132.22 (Ar), 133.92 (Ar), 134.57 (Ar), 137.78 (Ar), and 155.30 (CO); *m/z* (EI) 361 (M^+, 25%), 306 (15), 288 (89), 270 (46), 244 (29), 220 (28), 141 (48), 120 (94), 91 (16), and 57 (100).

(2*S*)-*N-tert*-Butoxycarbonyl-3-methyl-1-phenyl-2-butylamine 8a

Treatment with iodobenzene (111 μL, 1.00 mmol) gave **8a** (0.141 g, 71%), isolated as a white powder. Mp 78–79 °C (Found MH^+ 264.1971; $C_{16}H_{26}NO_2$ requires 264.1964); $[a]_D^{27}$ 11.7 (*c* 1.650 in $CHCl_3$) (Found: C, 72.6; H, 9.7; N, 5.2%: $C_{16}H_{25}NO_2$ requires C, 73.0; H, 9.6; N, 5.3%); IR (KBr disc)/cm^{-1} 3386, 2983, 1680, and 1645; δ_H 0.92 (3H, d, *J* 7, $CH(CH_3)_2$), 0.96 (3H, d, *J* 7, $CH(CH_3')_2$), 1.36 (9H, s, $C(CH_3)_3$), 1.65–1.73 (1H, m, $CH(CH_3)_2$), 2.66 (1H, dd, *J* 14, 6, C(1)*H*), 2.78 (1H, dd, *J* 14, 6, C(1)*H*), 3.70–3.78 (1H, m, C(2)*H*), 4.28–4.36 (1H, m, N*H*), and 7.16–7.29 (5H, m, Ar*H*); δ_C 17.24 (CH_3), 19.68 (CH_3), 28.35 (CH_3), 30.69 (CH), 38.69 (CH_2), 56.54 (CH), 78.87 (quat.), 126.31 (Ar), 128.30 (Ar), 129.33 (Ar), 138.76 (Ar), and 155.69 (CO); *m/z* (EI) (MH^+, 264, 11%), 208 (76), 190 (10), 172 (100), 147 (9), 116 (57), 91 (44), 77 (78), and 57 (98).

A racemic sample *rac*-**8a** of the above material was prepared in an identical manner using *rac*-**14** as the starting material. Compound *rac*-**8a** exhibited identical spectrosopic data to the enantiomerically pure sample **8a**, but had a mp of 64–65 °C. The racemic sample was analysed by chiral phase HPLC (Chiralpack AD, eluent 98 : 2 hexane–ethanol, flow rate 1 ml min^{-1}, detection at 215 nm), which gave baseline enantiomer separation. Analysis of **8a** indicated an enantiomeric excess of 99%.

(2*S*)-*N-tert*-Butoxycarbonyl-3-methyl-1-(4-nitrophenyl)-2-butylamine 8b. Treatment with 1-iodo-4-nitrobenzene (0.249 g, 1.00 mmol) gave **8b** (0.183 g, 79%), isolated as orange needles. Mp 141–142 °C (Found $M^+ - OC(CH_3)_3$ 235.1090; $C_{12}H_{15}N_2O_3$ requires 235.1083); $[a]_D^{25}$ 38.7 (*c* 0.315 in $CHCl_3$) (Found: C, 61.7; H, 7.6; N, 8.9%: $C_{16}H_{24}N_2O_4$ requires C, 62.3; H, 7.8; N, 9.1%); IR (KBr disc)/cm^{-1} 3355, 2987, 1682, 1521, and

1371; NMR δ_H 0.95 (3H, d, *J* 7, CH(CH_3)$_2$), 0.98 (3H, d, *J* 7, CH(CH_3')$_2$), 1.33 (9H, s, C(CH_3)$_3$), 1.70–1.76 (1H, m, C*H*(CH$_3$)$_2$), 2.74 (1H, dd, *J* 14, 6, C(1)*H*), 2.92 (1H, dd, *J* 14, 6, C(1)*H′*), 3.74–3.80 (1H, m, C(2)*H*), 4.34–4.37 (1H, m, N*H*), 7.37 (2H, d, *J* 8.5, Ar*H*), and 8.14 (2H, d, *J* 8.5, Ar*H*); δ_C 17.41 (CH$_3$), 19.57 (CH$_3$), 28.42 (CH$_3$), 31.42 (CH), 38.98 (CH$_2$), 56.45 (CH), 79.29 (quat.), 123.49 (Ar), 130.03 (Ar), 146.59 (Ar), 147.02 (Ar), and 155.51 (CO); *m*/*z* (EI) (M$^+$ − OC(CH$_3$)$_3$ 235, 52%), 220 (22), 72 (84) and 57 (100).

(2*S*)-*N*-*tert*-Butoxycarbonyl-3-methyl-1-(1-naphthyl)-2-butylamine 8c. Treatment with iodonaphthalene (146 μL, 1.00 mmol) gave **8c** (0.148 g, 63%), isolated as orange crystals. Mp 100–101 °C (Found M$^+$ 313.2046; $C_{20}H_{27}NO_2$ requires 313.2042); $[a]_D$ 42.6 (*c* 0.580 in $CHCl_3$ (Found: C, 75.61; H, 8.69; N, 4.46%: $C_{20}H_{27}NO_2$ requires C, 76.64; H, 8.68; N, 4.47%); IR (KBr disc)/cm^{-1} 3324, 2972, and 1681; NMR δ_H 0.95–1.05 (6H, m, CH(CH_3)$_2$), 1.32 (9H, s, C(CH_3)$_3$), 1.77–1.89 (1H, m, C*H*(CH$_3$)$_2$), 3.13–3.25 (2H, m, C(1)H_2), 3.92–4.00 (1H, m, C(2)*H*), 4.40–4.45 (1H, m, N*H*), and 7.36–7.39 (1H, m, Ar*H*), 7.45–7.48 (1H, m, Ar*H*), 7.52–7.55 (1H, m, Ar*H*), 7.72 (1H, d, *J* 8 Ar*H*), and 7.84 (1H, d, *J* 8, Ar*H*); δ_C 16.88 (CH$_3$), 19.78 (CH$_3$), 28.32 (CH$_3$), 30.63 (CH), 35.98 (CH$_2$), 55.81 (CH), 78.85 (quat.), 123.85 (Ar), 125.28 (Ar), 125.47 (Ar), 126.06 (Ar), 126.20 (Ar), 127.05 (Ar), 128.71 (Ar), 128.71, 132.31 (Ar), 133.90 (Ar), 134.94 (Ar), and 155.68 (CO); *m*/*z* (EI) (M$^+$ 313, 22%), 258 (47), 240 (45), 196 (26), 181 (29), 172 (35), 141 (59), 116 (70), 72 (100), and 57 (89).

(2*S*)-*N*-*tert*-Butoxycarbonyl-3-methyl-1-(4-methoxyphenyl)-2-butylamine 8d. Treatment with 1-iodo-4-methoxybenzene (0.218 g, 1.00 mmol) gave **8d** (0.116 g, 53%), isolated as a white solid. Mp 104–105 °C (Found M$^+$ 293.1990; $C_{17}H_{27}NO_3$ requires 293.1991); $[a]_D^{25}$ 13.6 (*c* 0.580 in $CHCl_3$) (Found: C, 69.3; H, 9.8; N, 4.6%: $C_{17}H_{27}NO_3$ requires C, 69.6; H, 9.3; N, 4.8%); IR (KBr disc)/cm^{-1} 3389, 2979, 2837, and 1683; NMR δ_H 0.90 (3H, d, *J* 7, CH(CH_3)$_2$), 0.95 (3H, d, *J* 7, CH(CH_3')$_2$), 1.38 (9H, s, C(CH_3)$_3$), 1.67–1.75 (1H, m, C*H*(CH$_3$)$_2$), 2.62 (1H, dd, *J* 15, 5, C(1)*H*), 2.71 (1H, dd, *J* 15, 5, C(1)*H′*), 3.64–3.72 (1H, m, C(2)*H*), 3.78 (3H, s), 4.26–4.35 (1H, m, N*H*), 6.82 (2H, d, *J* 8.5, Ar*H*), and 7.10 (2H, d, *J* 8.5, Ar*H*); δ_C 17.22 (CH$_3$), 19.72 (CH$_3$), 28.38 (CH$_3$), 30.51 (CH), 37.75 (CH$_2$), 55.25 (CH), 78.86 (quat.), 113.74 (Ar), 130.14 (Ar), 130.78 (Ar), 155.74 (Ar), and 158.04 (CO); *m*/*z* (EI) (M$^+$ 293, 19%), 220 (54), 194 (19), 172 (30), 161 (6), 150 (7), 121 (85), 72 (100), and 57 (90).

NMR experiments: structural study of the phenylalaninol 10 derived organozinc reagent in both THF-d_8 and DMF-d_7

The organozinc reagent **10** was generated using the general procedure described above using THF-d_8 and DMF-d_7 in place of non-deuterated solvents. When no starting material remained (as judged by TLC) the excess zinc was allowed to settle. The supernatent was transferred *via* syringe into a nitrogen-filled NMR tube fitted with a Young's tap. Unavoidably, a small amount of zinc dust was transferred into the NMR tube, however this did not appear to affect the quality of the spectra. References used for the deuterated solvents; THF-d_8 (δ_H 1.80, δ_C 26.70) and DMF-d_7 (δ_H 2.90, δ_C 161.70).

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-amino-3-phenyl-1-iodopropane 13

NMR δ_H (THF-d_8) 1.43 (9H, s, C(CH_3)$_3$), 2.90 (2H, d, *J* 7, C(3)H_2), 3.26 (1H, dd, *J* 5, 12, C(1)*H*), 3.52 (1H, dd, *J* 5, 12, C(1)*H′*), 3.63–3.71 (1H, m, C(2)*H*), 6.28 (1H, br d, *J* 7, N*H*), and 7.22–7.31 (5H, m, Ar*H*); δ_C (THF-d_8) 14.62 (CH$_2$), 30.04 (CH$_3$), 42.21 (CH$_2$), 54.82 (CH), 80.18 (quat.), 128.58 (Ar), 130.50 (Ar), 131.42 (Ar), 140.41 (Ar), and 157.16 (CO). NMR δ_H (DMF-d_7) 1.34 (9H, s, C(CH_3)$_3$), 2.83 (1H, dd, *J* 8, 14, C(3)*H*), 2.94 (1H, dd, *J* 8, 14, C(3)*H′*), 3.33 (1H, dd, *J* 7, 10, C(1)*H*), 3.46 (1H, dd, *J* 5, 10, C(1)*H′*), 3.70–3.77 (1H, m, C(2)*H*), 6.91 (1H, br d, *J* 8, N*H*), and 7.20–7.31 (5H, m, Ar*H*); δ_C (DMF-d_7) 11.66 (CH$_2$), 27.47 (CH$_3$), 39.49 (CH$_2$), 53.32 (CH), 77.60 (quat.), 125.99 (Ar), 127.98 (Ar), 128.87 (Ar), 138.25 (Ar), and 155.01 (CO).

(2*S*)-*N*-tert-Butoxycarbonyl-2-amino-3-phenyl-1-iodozinciopropane 10. NMR δ_H (THF-d_8) 0.33–0.49 (2H, m, C(1)H_2), 1.37 (9H, s, C(CH_3)$_3$), 2.63 (1H, dd, *J* 6, 13, C(3)*H*), 2.82 (1H, dd, *J* 7, 13, C(3)*H′*), 3.68–3.76 (1H, m, C(2)*H*), 6.50–6.54 (1H, br s, N*H*), and 7.04–7.20 (5H, m, Ar*H*); δ_C (THF-d_8) 16.40 (CH$_2$), 30.76 (CH$_3$), 42.50 (CH$_2$), 58.33 (CH), 82.73 (quat.), 117.58 (Ar), 128.33 (Ar), 131.67 (Ar), 140.05 (Ar), and 161.39 (CO). NMR δ_H (DMF-d_7) 0.32 (1H, dd, *J* 5.5, 13, C(1)*H*), 0.36 (1H, dd, *J* 5.5, 13 (C(1)*H′*), 1.32 (9H, s, C(CH_3)$_3$), 2.74 (1H, dd, *J* 6, 13, C(3)*H*), 2.83 (1H, dd, *J* 6, 13, C(3)*H′*), 3.99–4.06 (1H, m, C(2)*H*), 5.88 (1H, br d, *J* 8.5, N*H*), 7.10–7.25 (5H, m, Ar*H*); δ_C (DMF-d_7) 15.72 (CH$_2$), 27.28 (CH$_3$), 44.38 (CH$_2$), 52.88 (CH), 76.45 (quat.), 124.64 (Ar), 126.96 (Ar), 128.60 (Ar), 140.30 (Ar), and 154.62 (CO).

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References

1 R. F. W. Jackson, N. Wishart, A. Wood, K. James and M. J. Wythes, *J. Org. Chem.*, 1992, **57**, 3397.
2 M. J. Dunn, R. F. W. Jackson, J. Pietruszka and D. Turner, *J. Org. Chem.*, 1995, **60**, 2210.
3 R. F. W. Jackson, R. J. Moore, C. S. Dexter, J. Elliott and C. E. Mowbray, *J. Org. Chem.*, 1998, **63**, 7875.
4 C. S. Dexter and R. F. W. Jackson, *Chem. Commun.*, 1998, 75.
5 G. A. Cordell, *Introduction to Alkaloids-A Biogenic Approach*, Wiley, New York, 1981.
6 D. E. Nichols, S. E. Synder, R. Oberlander, M. P. Johnson and X. Haung, *J. Med. Chem.*, 1991, **34**, 276.
7 F. Claudi, M. Cardellini, G. M. Cingolani, A. Piergentilli, P. Guidubaldo and W. Balduini, *J. Med. Chem.*, 1990, **33**, 2408.
8 H. F. Bradford, *Chemical Neurobiology*, Freeman, New York, 1986.
9 K. W. Bentley, *Nat. Prod. Rep.*, 1998, **15**, 341.
10 Z. Zhuangyu, P. Yi, H. Hongwen and T. Kao, *Synth. Commun.*, 1990, **20**, 3563.
11 C. A. Busacca, R. E. Johnson and J. Swestock, *J. Org. Chem.*, 1993, **58**, 3299.
12 M. J. Eis and B. Ganem, *Tetrahedron Lett.*, 1985, **26**, 1153.
13 J. Barluenga, F. Foubela, F. J. Fañanás and M. Yus, *Tetrahedron*, 1989, **45**, 2183.
14 J. A. Sejas, M. P. Vasquez-Tato, C. Entanza and M. M. Martinez, *Tetrahedron Lett.*, 1998, **39**, 5073.
15 R. Duddu, M. Eckhardt, M. Furlong, H. P. Knoess, S. Berger and P. Knochel, *Tetrahedron*, 1994, **50**, 2415.
16 G. L. Lange and C. Gottardo, *Synth. Commun.*, 1990, **20**, 1473.
17 P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93**, 2117.
18 P. G. Mattingly, *Synthesis*, 1990, 366.
19 A. W. Konradi, S. J. Kemp and S. F. Pedersen, *J. Am. Chem. Soc.*, 1994, **116**, 1316.
20 A. M. Doherty, J. S. Kaltenbronn, J. P. Hudspeth, J. T. Repine, W. H. Roark, I. Sircar, F. J. Tinney, C. J. Connolly, J. C. Hodges, M. D. Taylor, B. L. Batley, M. J. Ryan, A. D. Essenburg, S. T. Rapundalo, R. E. Weishaar, C. Humblet and E. A. Lunney, *J. Med. Chem.*, 1991, **34**, 1258.
21 R. Caputo, E. Cassano, L. Longobardo and G. Palumbo, *Tetrahedron Lett.*, 1995, **36**, 167.
22 K. Ninomiya, *J. Med. Chem.*, 1974, **30**, 2151.
23 P. A. Stark, B. D. Thrall, G. G. Meadows and M. M. Abdel-Monem, *J. Med. Chem.*, 1992, **35**, 4264.

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