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Direct synthesis of unprotected phenols using palladium-catalysed cross coupling reactions of functionalised organozinc reagents

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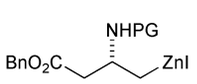
Palladium-catalysed reaction of unprotected 2-, 3-, and 4-iodophenols with a range of amino acid derived organozinc reagents (*not* used in excess) gives the expected products in good to excellent yield, demonstrating that carbon–zinc bonds are not protonated by acidic phenols under the conditions of palladium-catalysed coupling reactions.

Introduction

A key goal in improving the efficiency of synthetic routes is to reduce, as far as is possible, the need for protecting groups. In the context of reactions of electrophiles with organometallic nucleophiles, protection of alcohols in the electrophile is almost always considered necessary, and was one of the key driving forces for the development of a wide range of hydroxyl protecting groups,[1,2] notably silyl ethers. The enhanced acidity of phenols (the p*K*a of phenol measured in water is 10) means that the need for protection of the phenolic hydroxyl group in reactions involving organometallic reagents goes largely unquestioned.

It has been known for some time that carbon–zinc bonds can tolerate the presence of acidic protons, for example in the organozinc reagents **2**–**5**.[3–5] Knochel *et al*. have shown that organozinc halides can be formed in the presence of a range of additives containing acidic protons, although the presence of these additives does reduce the yield of the organozinc reagent.[6] Most interestingly, it was demonstrated that reactions that proceed rapidly at low temperature, for example reaction of organocopper reagents with allylic electrophiles, can be carried out in the presence of additives containing free hydroxyl groups, including phenol (although the yield of product was slighly reduced).[6] These results imply that, under the right circumstances, protection of free hydroxyl groups may not be required. Since this is important for the application of organozinc chemistry to the chemical modification of peptides, which may incorporate a range of acidic protons, we have decided to test it experimentally.



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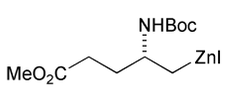
1b, PG = Boc



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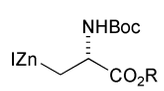

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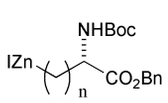
3b, R = Me

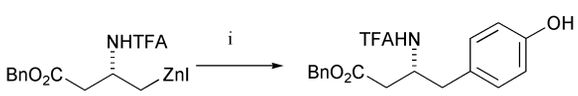


4, n = 2
5, n = 3

Our recent discovery that it is possible to prepare the methyl ester analogue of the trifluoroacetyl-protected organozinc reagent **1a**,[7] in which the p*K*a of the NH proton is estimated to be around 17 (in DMSO),[8] prompted us to consider whether other protons of comparable acidity might also be tolerated in the electrophile, and the most obvious and useful functional group that fulfils this criterion appeared to be phenol (the p*K*a of phenol measured in DMSO is 18).[8] We have therefore explored the cross-coupling of free iodophenols with a range of functionalised zinc reagents, since this would give direct access to tyrosine analogues, without the need for hydroxyl protection. †

Results and discussion

Our first experiment involved the attempted coupling of *N*-TFA protected zinc reagent **1a** with 4-iodophenol (1.3 eq.) under standard Pd-catalysed conditions (Scheme 1). We were delighted to isolate the desired product **6** in 66% yield, comparable with the yields obtained from the reaction of the same zinc reagent with electrophiles not containing acidic protons.[7] The fact that the yield was greater than 50% established that protonation of the organozinc reagent by the phenol was occurring at a slower rate than the cross coupling reaction, and did not compromise the viability of the reaction.



1a **6**

Scheme 1 *Reagents and conditions*: 4-IC_6H_4OH, DMF, $Pd_2(dba)_3$ (2.5 mol%), P(*o*-tol)$_3$ (10 mol%), r.t.

Having established this principle, we have explored the coupling of a range of other amino acid-derived organozinc reagents with unprotected 2-, 3- and 4-iodophenol, which allowed us to isolate the free phenols **7**–**11**, and our results are given in Table 1. The very high yields obtained in the cross coupling with 3- and 4-iodophenol using zinc reagent **1b** are a striking demonstration of the tolerance exhibited by this reagent towards acidic protons. The lower yield obtained with 2-iodophenol reflects the behaviour of other 2-substituted iodobenzene derivatives in similar coupling reactions.[4] Finally, attempted reaction of **3b** with 3,4-dihydroxyiodobenzene

† There is a report[14] concerning the coupling of zinc reagent **3a** with unprotected 2-iodo-3-hydroxypyridine[15] which gave the expected product in 33% yield, but the reaction used 2 equivalents of the organozinc reagent, so the possibility that the free hydroxyl group might have been tolerated in the reaction was not addressed. In another report, which highlights the desirability of avoiding the use of protecting groups, 2-chloro-3-hydroxy-6-iodopyridine was protected as its TBS-ether prior to Pd-catalysed coupling with the zinc reagent **3a**, and the protecting group was removed immediately afterwards.[16]

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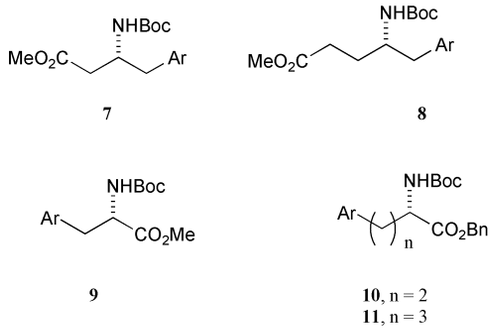
Table 1 Cross-coupling of organozinc reagents with unprotected iodophenols

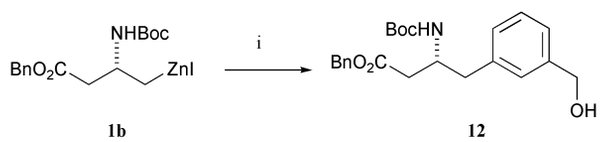
Organozinc	Electrophile	Product	Ar	Yield (%)[a]
1a	4-IC_6H_4OH	**6**	4-HOC_6H_4	66
1b	2-IC_6H_4OH	**7a**	2-HOC_6H_4	42
1b	3-IC_6H_4OH	**7b**	3-HOC_6H_4	88
1b	4-IC_6H_4OH	**7c**	4-HOC_6H_4	85
2	4-IC_6H_4OH	**8**	4-HOC_6H_4	64
3b	4-IC_6H_4OH	**9a**	4-HOC_6H_4	59
3b	3-IC_6H_4OH	**9b**	3-HOC_6H_4	54
4	4-IC_6H_4OH	**10**	4-HOC_6H_4	48
5	4-IC_6H_4OH	**11**	4-HOC_6H_4	49

[a] Isolated yields refer to homogeneous material purified by flash chromatography.

unfortunately gave none of the desired product, L-DOPA, indicating the enhanced acidity of catechol is sufficient to ensure competitive protonation of the zinc reagent.



In a single experiment, we have also established that an unprotected benzylic alcohol functionality can be tolerated; the cross-coupling reaction of zinc reagent **1b** with 3-iodobenzyl alcohol gave the product **12** (Scheme 2), although the yield was modest (42%).



Scheme 2 *Reagents and conditions*: 3-$IC_6H_4CH_2OH$, DMF, $Pd_2(dba)_3$ (2.5 mol%), P(*o*-tol)$_3$ (10 mol%), r.t.

Conclusions

In summary we have demonstrated that the protection of iodophenols is unnecessary in the Pd-catalysed cross coupling of organozinc iodides, and thereby broadened the potential scope of these reagents in synthesis. These results reinforce the notion that p*K*a values measured in water need to be used with care, especially when reactions are conducted in aprotic solvents, and that p*K*a values measured in DMSO[8] are a more reliable guide to potential incompatibility.

Experimental

The iodide precursors to the zinc reagents **2**,[5] **3b**,[4] **4**[4] and **5**[4] were prepared by literature methods. The precursor to **1b** was prepared from Boc-L-aspartic acid β-benzyl ester by an analogous method to that used for the preparation of the corresponding methyl ester.[5] An alternative method has been described.[9]

Synthesis of iodide precursor to zinc reagent 1a

2*S*-(2,2,2-Trifluoroacetylamino)succinic acid 4-benzyl ester. This compound was synthesised according to the literature procedure.[10] Phenyl trifluoroacetate (5.00 g, 23.6 mmol) and L-aspartic acid β-benzyl ester (3.00 g, 13.4 mmol) were heated together at 125–130 °C with stirring under an atmosphere of nitrogen. After the formation of a transparent liquid, the mixture was heated for a further 5 min (10 min total heating). Upon cooling, the product was triturated with petroleum ether (10 × 20 mL) and the remaining solvent evaporated under reduced pressure to yield a white powder (3.96 g, 93%), mp 89–91 °C, literature value 88–90 °C.[10] ν_{max}/cm^{-1} 3308 (N–H); 1729 (C=O); 1708 (C=O); 1180 (C–O). Found C, 48.85; H, 3.70; N, 4.32. $C_{13}H_{12}NO_5F_3$ requires C, 48.91; H, 3.79; N, 4.39%. δ_H (250 MHz, $CDCl_3$) 2.98 (1H, dd, *J* 17.5 and 4.0), 3.22 (1H, dd, *J* 17.5 and 4.5), 4.82–4.98 (1H, m), 5.27 (2 H, s), 7.28–7.41 (5H, m) and 7.45 (1H, d, *J* 8.5); δ_C (62.5 MHz, $CDCl_3$) 35.3, 48.7, 67.6, 115.5 (q, *J* 283), 128.4, 128.7, 129.7, 134.7, 157.3 (q, *J* 34), 170.8 and 173.9; *m*/*z* (EI) 319.0668 (8%, M^+, $C_{13}H_{12}NO_5F_3$ requires 319.0667), 184(6), 166(3), 140(5), 108(100), 107(56) and 99(10); $[a]_D^{22.5}$ +59.1 (*c* 1.02 in $CHCl_3$).

2*S*-(2,2,2-Trifluoroacetylamino)succinic acid 1-(2,5-dioxopyrrolidin-1-yl) ester 4-benzyl ester. To a stirred solution of *N*-TFA aspartic acid β-benzyl ester (10.77 g, 33.7 mmol) in ethyl acetate (80 mL) at 0 °C was added solid *N*-hydroxysuccinimide (3.88 g, 33.7 mmol). A solution of dicyclohexylcarbodiimide (6.96 g, 33.7 mmol) in ethyl acetate (30 mL) was added over a period of 5 min. The reaction was allowed to attain room temperature and left for 3 h. The precipitate of dicyclohexylurea was filtered off, and the filtrate was washed successively with saturated aqueous sodium hydrogen carbonate (2 × 15 mL) and brine (2 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give crude succinimide ester as a white solid (13.92 g, 99%), mp 116–118 °C. ν_{max}/cm^{-1} 3329 (N–H); 1744 (C=O); 1710 (C=O); 1209 (C–O). Found C, 49.19; H, 3.53; N, 6.69. $C_{17}H_{15}O_7N_2F_3$ requires C, 49.05; H, 3.63; N, 6.73%. δ_H (250 MHz, $CDCl_3$) 2.85 (4H, s), 3.02 (1H, dd, *J* 17.5 and 4.5), 3.27 (1H, dd, *J* 17.5 and 4.5), 5.11–5.28 (2H, m), 5.28–5.38 (1H, m), 7.36 (5H, s) and 7.72 (1H, d, *J* 8.5); δ_C (62.5 MHz, $CDCl_3$) 25.5, 35.5, 47.4, 67.7, 115. 5 (q, *J* 285), 128.6, 128.7, 129.6, 134.8, 157.0 (q, *J* 39), 165.3, 168.5 and 169.7; *m*/*z* (EI) 416.0835 (12%, M^+, $C_{17}H_{15}O_7N_2F_3$ requires 416.0835), 273(4), 224(6), 184(24), 166(4), 139(18), 115(11), 108(25) and 107(43); $[a]_D^{22.5}$ + 7.0 (*c* 1.01 in $CHCl_3$).

4-Hydroxy-3*S*-(2,2,2-trifluoroacetylamino)butanoic acid benzyl ester. To a cooled (0 °C) suspension of sodium borohydride (0.47 g, 12.49 mmol) in water (3 mL) and THF (23 mL) was added a solution of the precursor succinimide ester (3.25 g, 7.81 mmol) in THF (4 mL) over 30 s. The reaction was quenched after 4 min with saturated aqueous ammonium chloride and the product extracted into ethyl acetate (2 × 20 mL). The combined organic fractions were washed with brine (2 × 20 mL), dried ($MgSO_4$), evaporated under reduced pressure, and the crude product purified by column chromatography on silica with DCM–ethyl acetate (4 : 1) to give the alcohol as a white crystalline solid (1.61 g, 67%), mp 70–71 °C. ν_{max}/cm^{-1} 3455 (O–H); 3253 (N–H); 1711 (C=O). Found C, 51.25; H, 4.66; N, 4.60. $C_{13}H_{14}O_4NF_3$ requires C, 51.15; H, 4.62; N, 4.59%. δ_H (250 MHz, $CDCl_3$) 2.22 (1H, br t), 2.77 (2H, d, *J* 6), 3.69–3.87 (2H, m), 4.28–4.43 (1H, m), 5.15 (2H, s) and 7.36 (5H, s); δ_C (62.5 MHz, $CDCl_3$) 34.8, 48.7, 62.9, 67.1, 115.8 (q, *J* 287), 128.4, 128.6, 128.7, 135.1, 157.4 (q, *J* 38), and 171.3. *m*/*z* (EI) 306.0955 (1 %, MH^+, $C_{13}H_{15}O_4NF_3$ requires 306.0953), 305(3), 198(7), 139(24), 108(91), 107(43), 91(100) and 79(44); $[a]_D^{22.5}$ + 9.1 (*c* 0.99 in $CHCl_3$).

4-Iodo-3*S*-(2,2,2-trifluoroacetylamino)butanoic acid benzyl ester. Triphenylphosphine (5.13 g, 19.5 mmol), imidazole (1.33 g, 19.5 mmol) and iodine (4.96 g, 19.5 mmol) were added to dry DCM (60 mL) under nitrogen with stirring. A solution of the precursor alcohol (5.68 g, 18.6 mmol) in dry DCM

(20 mL) was added under nitrogen *via* syringe. The reaction was monitored by TLC (petrol–ethyl acetate, 1 : 1) and was complete after 5 min. The precipitate was removed by filtration and the filtrate washed with aqueous sodium thiosulfate solution (1 M, 3 × 20 mL) and brine (50 mL), followed by drying ($MgSO_4$). The DCM was evaporated under reduced pressure and the crude product purified by column chromatography on silica with petrol–ethyl acetate (2 : 1) to give the iodide as white crystals (5.87 g, 76%), mp 75–77 °C. ν_{max}/cm^{-1} 3277 (N–H); 1725 (C=O); 1702 (C=O); 1186 (C–O). Found C, 37.88; H, 3.06; N, 3.21; I, 30.57. $C_{13}H_{13}O_3NF_3I$ requires C, 37.61; H, 3.16; N, 3.37; I, 30.57%. δ_H (250 MHz, $CDCl_3$) 2.75 (1H, dd, *J* 17.0 and 5.5), 2.95 (1H, dd, *J* 17.0 and 5.0), 3.30–3.50 (2H, m), 4.23–4.40 (1H, m), 5.17 (2H, s), 7.14 (1H, d, *J* 17.0) and 7.30–7.50 (5H, m); δ_C (62.5 MHz, $CDCl_3$) 7.1, 37.7, 47.7, 67.2, 115.7 (q, *J* 288), 128.4, 128.6, 128.7, 135.1, 156.8 (q, *J* 37), and 170.2; *m*/*z* (EI) 414.9906 (13%, M^+, $C_{13}H_{13}O_3NF_3I$ requires 414.9892), 308(5), 266(7), 195(9), 154(3), 139(7), 108(100) and 107(32); $[\alpha]_D^{22.5}$ + 7.0 (*c* 1.00 in $CHCl_3$).

General procedure for the coupling reactions of iodides with aryl iodides

Zinc dust (0.236 g, 3.6 mmol, 6.0 eq.) was placed in a dry 25 mL round bottom flask, with sidearm, containing a rugby ball shaped stirrer. The flask was flushed with nitrogen and dry DMF (0.75 mL) and TMSCl (100 μL, 0.8 mmol) were added under nitrogen *via* syringe. The solution was observed to effervesce and the mixture was vigorously stirred at room temperature for 5 min (the DMF occasionally changes to a yellow colour during this period). The zinc was allowed to settle and the supernatant solution was removed *via* syringe, followed by drying of the zinc under vacuum by heating with a hot air gun. A solution of the zinc reagent precursor iodide (0.6 mmol, 1.0 eq.) was dissolved in DMF (0.75 mL) under nitrogen and transferred to the zinc *via* syringe. The solution was stirred at room temperature and the insertion judged to be complete by TLC within 5 min. $Pd_2(dba)_3$ (17.9 mg, 0.02 mmol), P(*o*-tol)$_3$ (23.8 mg, 0.08 mmol) and the aryl iodide (1.3 eq. relative to the iodide) were added to the flask. The flask was covered with aluminium foil and left at room temperature overnight. The reaction was diluted with EtOAc (50 mL), filtered and evaporated under reduced pressure. The residue was warmed at 40 °C under high vacuum to remove the DMF. The crude product was purified by column chromatography.

4-(4-Hydroxyphenyl)-3*R*-(2,2,2-trifluoroacetylamino)butanoic acid methyl ester (6). This product was prepared following the procedure outlined above, using 4-iodophenol as the aryl iodide (172 mg, 0.78 mmol, 1.3 eq.) and the zinc reagent **1a**. Purification of the crude product by column chromatography on silica with DCM–MeOH (10 : 1) yielded a white solid (151 mg, 66%), mp 156–159 °C. ν_{max}/cm^{-1} 3300 (C–H); 1698 (C=O); 1516 (N–H). Found C, 59.36; H, 4.67; N, 3.52. $C_{19}H_{18}F_3NO_4$ requires C, 59.84; H, 4.76; N, 3.67. δ_H (400 MHz, CD_3OD) 2.58 (1H, dd, *J* 15.5 and 8.5), 2.64 (1H, dd, *J* 15.5 and 5.5), 2.69 (1H, dd, *J* 13.5 and 8), 2.75 (1H, dd, *J* 14 and 6.5), 4.39–4.49 (1H, m), 5.04 (1H, d, *J* 12), 5.09 (1H, d, *J* 12), 6.69 (2H, d, *J* 8.5) and 6.96 (2H, d, *J* 8.5). δ_C (100 MHz, CD_3OD) 39.0, 40.0, 50.5, 67.6, 116.2, 117.4 (q, *J* 287), 129.2, 129.3, 129.4, 129.5, 131.3, 137.3, 157.3, 158.3 (q, *J* 37) and 172.1; *m*/*z* (TOF MS ES$^+$) 382.1262 (7%, MH^+, $C_{19}H_{19}F_3NO_4$ requires 382.1266), 304(10) and 251(100).

3*R*-*tert*-Butoxycarbonylamino-4-(2-hydroxyphenyl)butanoic acid benzyl ester (7a). This product was prepared following the procedure outlined above, using 2-iodophenol as the aryl iodide (172 mg, 0.78 mmol, 1.3 eq.) and the zinc reagent **1b**. Purification of the crude product by column chromatography on silica with DCM–EtOAc (20 : 1) yielded a white solid (97 mg, 42%), mp 84–86 °C. ν_{max}/cm^{-1} 3357 (C–H); 3313 (O–H); 1687 (C=O); 1534 (N–H). Found C, 68.69; H, 6.96; N, 3.49. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.06; N, 3.63%. δ_H (250 MHz, $CDCl_3$) 1.44 (9H, s), 2.59 (2H, br d, *J* 5), 2.60 (1H, m (signal partially obscured)), 3.01–3.12 (1H, m), 3.83–4.01 (1H, m), 5.16 (2H, s), 5.53 (1H, br d, *J* 7.5), 6.79 (1H, t, *J* 7.5), 6.88 (1H, d, *J* 7.6), 6.96 (1H, d, *J* 7.5), 7.13 (1H, t, *J* 7.5), 7.37 (5H, s) and 7.85 (1H, br s). δ_C (62.5 MHz, $CDCl_3$) 28.2, 36.1, 36.7, 48.5, 66.6, 80.4, 116.3, 119.8, 123.2, 128.3, 128.4, 128.6, 130.8, 135.4, 155.4, 156.4, and 171.7 (one signal obscured); *m*/*z* (EI$^+$) 385.1875 (3%, M^+, $C_{22}H_{27}NO_5$ requires 385.1889), 385(3), 222(19), 178(64) and 91(100); $[\alpha]_D^{22.1}$ +19.6 (*c* 1.02 in $CHCl_3$).

3*R*-*tert*-Butoxycarbonylamino-4-(3-hydroxyphenyl)butanoic acid benzyl ester (7b). This product was prepared following the procedure outlined above, using 3-iodophenol as the aryl iodide (172 mg, 0.78 mmol, 1.3 eq.) and the zinc reagent **1b**. Purification of the crude product by column chromatography on silica with DCM–EtOAc (6 : 1) yielded a white solid (201 mg, 88%), mp 88–90 °C. ν_{max}/cm^{-1} 3384 (C–H); 1729 (C=O); 1691 (C=O); 1513 (N–H). Found C, 68.48; H, 7.02; N, 3.51. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.06; N, 3.63%. δ_H (250 MHz, $CDCl_3$) 1.40 (9H, s), 2.49 (1H, dd, *J* 16.5 and 6), 2.56 (1H, dd, *J* 16.5 and 6), 2.73 (1H, dd, *J* 13 and 7.9), 2.85 (1H, dd, *J* 13.5 and 6.5), 4.07–4.26 (1H, m), 5.09 (1H, d, *J* 12), 5.10 (1H, signal partially obscured), 5.17 (1H, d, *J* 12), 5.85 (1H, s), 6.58–6.78 (3H, m), 7.11 (1H, t, *J* 8) and 7.36 (5H, s). δ_C (62.5 MHz, $CDCl_3$) 28.3, 37.6, 40.2, 48.7, 66.5, 79.7, 113.7, 116.2, 121.2, 128.3, 128.5, 129.5, 135.5, 139.0, 155.4, 156.3 and 171.6 (one signal obscured); *m*/*z* (EI$^+$) 385.1888 (5%, M^+, $C_{22}H_{27}NO_5$ requires 385.1889), 278(62), 222(62) and 178(100); $[\alpha]_D^{22.1}$ +6.9 (*c* 1.02 in $CHCl_3$).

3*R*-*tert*-Butoxycarbonylamino-4-(4-hydroxyphenyl)butanoic acid benzyl ester (7c). This product was prepared following the procedure outlined above, using 4-iodophenol as the aryl iodide (172 mg, 0.78 mmol, 1.3 eq.) using zinc reagent **1b**. Purification of the crude product by column chromatography on silica with DCM–EtOAc (10 : 1) yielded a white solid (194 mg, 85%), mp 124–126 °C. ν_{max}/cm^{-1} 3358 (C–H); 1702 (C=O); 1686 (C=O); 1529 (N–H). Found C, 68.32; H, 6.96; N, 3.41. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.06; N, 3.63%. δ_H (400 MHz, $(CD_3)_2CO$) 1.40 (9H, s), 2.58 (2H, d, *J* 6.5), 2.75 (1H, dd, *J* 13.5 and 7), 2.83 (1H, dd, *J* 13.5 and 7), 4.07–4.23 (1H, m), 5.06–5.20 (2H, m), 5.95 (1H, br d, *J* 7.5), 6.79 (2H, d, *J* 8), 7.07 (2H, d, *J* 8), 7.27–7.54 (5H, m) and 8.19 (1H, s). δ_C (100 MHz, $(CD_3)_2CO$) 28.7, 39.4, 40.4, 50.7, 66.7, 78.9, 116.0, 128.9, 129.0, 129.4, 130.0, 131.3, 137.5, 156.0, 156.9 and 171.9; *m*/*z* (EI$^+$) 385.1887 (3%, M^+, $C_{22}H_{27}NO_5$ requires 385.1889), 268(56), 222(42), 178(82) and 91(100); $[\alpha]_D^{22.1}$ +6.9 (*c* 1.02 in $CHCl_3$).

4*S*-*tert*-Butoxycarbonylamino-5-(4-hydroxyphenyl)pentanoic acid methyl ester (8). This product was prepared following the procedure outlined above, using 4-iodophenol as the aryl iodide (172 mg, 0.78 mmol, 1.3 eq.) and zinc reagent **2**. Purification of the crude product by column chromatography on silica with DCM–EtOAc (10 : 1) yielded a white solid (108 mg, 64 %), mp 149–151 °C. ν_{max}/cm^{-1} 3370 (C–H); 1713 (C=O); 1683 (C=O); 1516 (N–H). Found C, 63.08; H, 8.13; N, 4.22. $C_{17}H_{25}NO_5$ requires C, 63.14; H, 7.79; N, 4.33%. δ_H (400 MHz, CD_3OD) 1.36 (9H, s), 1.50–1.64 (1H, m), 1.76–1.88 (1H, m), 2.29 (1H, dd, *J* 16.5 and 7), 2.36 (1H, dd, *J* 16.5 and 6.5), 3.62 (4H, s (two overlapping signals)), 6.68 (2H, d, *J* 8.5) and 7.00 (2H, d, *J* 8.5). δ_C (100 MHz, CD_3OD) 28.8, 30.6, 31.7, 41.8, 52.1, 53.1, 79.8, 116.0, 130.7, 131.3, 156.8, 158.1 and 175.6; *m*/*z* (EI$^+$) 323.1731 (3%, M^+, $C_{17}H_{25}NO_5$ requires 323.1733), 216(32), 160(17), 116(72) and 107(59); $[\alpha]_D^{22.5}$ +1.0 (*c* 1.02 in MeOH).

2*S*-*tert*-Butoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid methyl ester (9a). This product was prepared following the procedure outlined above, using 4-iodophenol as the aryl iodide

(172 mg, 0.78 mmol, 1.3 eq.) and zinc reagent **3b**. Purification of the crude product by column chromatography on silica with DCM–MeOH (40 : 1) yielded a white solid (106 mg, 59 %), mp 106–107 °C, literature value 101–105 °C.[11] $[\alpha]_D^{22.5}$ +48.8 (*c* 1.03 in $CHCl_3$), literature value $[\alpha]_D^{20}$ +48.2 (*c* 1 in $CHCl_3$).[12]

2*S*-*tert*-Butoxycarbonylamino-3-(3-hydroxyphenyl)propionic acid methyl ester (9b). This product was prepared following the procedure outlined above, using 3-iodophenol as the aryl iodide (172 mg, 0.78 mmol, 1.3 eq.) and zinc reagent **3b**. Purification of the crude product by column chromatography on silica with DCM–MeOH (40 : 1) yielded a colourless oil (96 mg, 54%). ν_{max}/cm^{-1} 3384 (C–H); 1745 (C=O); 1720 (C=O); 1690 (C=O). Found C, 60.88; H, 7.82; N, 4.42. $C_{15}H_{21}NO_5$ requires C, 61.00; H, 7.17; N, 4.74%; *m*/*z* (EI^+) 295.1409 (4%, M^+, $C_{22}H_{27}NO_5$ requires 295.1420), 239(25), 178(100), 136(22) and 107(24); $[\alpha]_D^{22.5}$ +38.6 (*c* 1.04 in $CHCl_3$), literature value $[\alpha]_D^{25}$ +34.2 (*c* 1.18 in $CHCl_3$).[13]

2*S*-*tert*-Butoxycarbonylamino-4-(4-hydroxyphenyl)butanoic acid benzyl ester (10). This product was prepared following the procedure outlined above, using 4-iodophenol as the aryl iodide (172 mg, 0.78 mmol, 1.3 eq.) and zinc reagent **4**. Purification of the crude product by column chromatography on silica with DCM–EtOAc (20 : 1) yielded a colourless oil (113 mg, 48%). ν_{max}/cm^{-1} 3393 (C–H); 1743 (C=O); 1716 (C=O); 1689 (C=O); 1516 (N–H). Found C, 68.14; H, 7.45; N, 3.51. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.06; N, 3.63%. δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s), 1.80–1.95 (1H, m), 2.00–2.14 (1H, m), 2.43–2.60 (2H, m), 4.32–4.43 (1H, m), 5.09 (1H, d, *J* 12.5), 5.18 (1H, d, *J* 12.5), 5.18 (1H, signal partially obscured), 6.21 (1H, s), 6.72 (2H, d, *J* 8.5), 6.91 (2H, d, *J* 8.5) and 7.33 (5H, s). δ_C (100 MHz, $CDCl_3$) 28.3, 30.5, 34.4, 53.2, 67.1, 80.3, 115.3, 128.3, 128.4, 128.6, 129.4, 132.2, 135.2, 154.3, 155.5 and 172.6; *m*/*z* (EI^+) 385.1880 (6%, M^+, $C_{22}H_{27}NO_5$ requires 385.1889), 329(31), 238(24), 209(15), 177(100) and 107(35); $[\alpha]_D^{22.5}$ −18.5 (*c* 1.08 in MeOH).

2*S*-*tert*-Butoxycarbonylamino-5-(4-hydroxyphenyl)pentanoic acid benzyl ester (11). This product was prepared following the procedure outlined above, using 4-iodophenol as the aryl iodide (172 mg, 0.78 mmol, 1.3 eq.) and zinc reagent **5**. Purification of the crude product by column chromatography on silica with toluene–MeOH (20 : 1) yielded a white solid (91 mg, 49%) mp 99–101°C. ν_{max}/cm^{-1} 3401 (C–H); 1738 (C=O); 1716 (C=O); 1688 (C=O); 1516 (N–H). Found C, 68.72; H, 7.60; N, 3.42. $C_{23}H_{29}NO_5$ requires C, 69.15; H, 7.32; N, 3.51%. δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s), 1.54–1.73 (3H, m), 1.79–1.93 (1H, m), 2.45–2.60 (2H, m), 4.37–4.35 (1H, m), 5.12 (1H, d, *J* 12.5), 5.20 (1H, signal partially obscured), 5.23 (1H, d, *J* 12.5), 6.20 (1H, s), 6.77 (2H, d, *J* 8.5), 6.95 (2H, d, *J* 8.5) and 7.32–7.43 (5H, m). δ_C (100 MHz, $CDCl_3$) 27.6, 28.7, 32.5, 34.7, 53.8, 67.5, 80.7, 115.6, 128.7, 128.9, 129.0, 129.8, 133.7, 135.7, 154.6, 156.0 and 173.3; *m*/*z* (EI^+) 399.2055 (1%, M^+, $C_{23}H_{29}NO_5$ requires 399.2046), 320(29), 305(100), 208(13), 165(13) and 91(23); $[\alpha]_D^{22.5}$ −21.3 (*c* 1.04 in MeOH).

3*R*-*tert*-Butoxycarbonylamino-4-(3-hydroxymethylphenyl)butanoic acid benzyl ester (12). This product was prepared following the procedure outlined above, using 3-iodobenzyl alcohol as the aryl iodide (183 mg, 0.78 mmol, 1.3 eq.) and zinc reagent **1b**. Purification of the crude product by column chromatography on silica with DCM–EtOAc (2 : 1) yielded a colourless oil (101 mg, 42%). ν_{max}/cm^{-1} 3343 (O–H); 1722 (C=O); 1685 (C=O); 1530 (N–H). δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s), 2.25 (1H, br s), 2.46 (1H, dd, *J* 16 and 6), 2.54 (1H, dd, *J* 16 and 6), 2.77 (1H, dd, *J* 13.5 and 8), 2.90 (1H, dd, *J* 13.5 and 6.5), 4.09–4.21 (1H, m), 4.60 (2H, s), 5.08 (1H, d, *J* 12.5), 5.09 (1H, signal partially obscured), 5.14 (1H, d, *J* 13.5) and 7.01–7.46 (9H, m). δ_C (100 MHz, $CDCl_3$) 28.3, 37.6, 40.2, 48.8, 65.0, 66.4, 79.4, 125.2, 127.9, 128.3, 128.5, 128.6, 132.0, 132.9, 135.6, 137.9, 141.2, 155.1 and 171.5; *m*/*z* (EI^+) 422.1935 (8%, MNa^+, $C_{23}H_{29}NO_5Na$ requires 422.1943), 400(9), 344(29), 321(100), 300(33) and 282(28); $[\alpha]_D^{22.5}$ +9.7 (*c* 1.04 in MeOH).

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