Palladium(0) catalysed and copper(I) promoted reactions of the secondary zinc reagent derived from L-threonine

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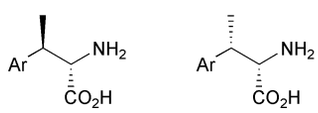
C-3 epimeric secondary zinc reagents **2a/b** were prepared from either diastereoisomeric iodide **3a** or **3b** using DMF as solvent, and characterised by ^{1}H NMR methods. Palladium catalysed cross couplings and copper promoted allylations yielded protected β-methyl substituted amino acids.

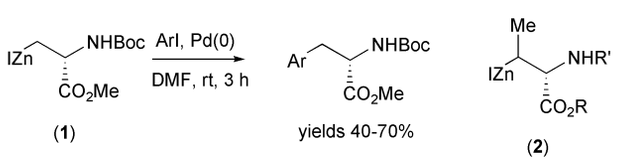
Introduction

There is continued interest in methodology directed towards the synthesis of non-proteinogenic amino acids.[1,2] To this end we have prepared a wide range of non-natural enantiomerically pure α-/β-/γ- amino acids *via* the palladium(0)-catalysed cross couplings and copper(I) catalysed allylations of zinc reagents derived from serine, aspartic acid and glutamic acid.[3–5] However our methodology cannot yet access C-3 disubstituted α-amino acids, for example 3-methyl-3-arylalanines.



In view of the interest in modified amino acids that can confer conformational rigidity in small peptides,[6,7] various groups have investigated the synthesis of 3-methyl-3-aryl-alanines. Many of those reported have relied on the use of chiral enolates,[8,9] catalytic asymmetric process (*i.e.* Katsuki–Jacobsen or Sharpless epoxidations)[10,11] or asymmetric hydrogenation[12] to introduce chirality. Despite the attractiveness of using L-threonine as a starting material, to our knowledge only one report has used this strategy.[13]

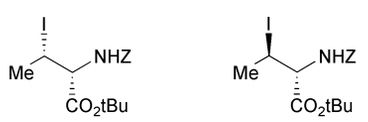
The efficient and reliable palladium and copper(I)-catalysed reactions of iodozinc alanine **1** in DMF encouraged us to extend this methodology to the secondary zinc reagent **2**. It was envisaged that a range of C(3)-methyl substituted α-amino acids could be accessed using this reagent.



(**1**) yields 40-70% (**2**)

However when preparing a secondary alkylzinc reagent from an optically pure alkyl iodide precursor, stereochemical scrambling is usually seen at the secondary C_{sp^3}–I bond. For example, Rieke[14–16] has shown that optically pure secondary alkyl bromides yield racemic secondary alkylzinc bromides when treated with activated zinc dust. Similarly, Knochel[17,18] reported that diastereoisomerically pure iodides give a 1:1 mixture of diastereoisomers after treatment with zinc dust, followed by transmetallation with a source of Cu(I) and allyl bromide. A recent report has shown that an analogue of the zinc reagent derived from iodide **3a** (protected as the *N*-Boc methyl ester) reacted with phosphorus electrophiles in an overall non-stereoselective manner,[19] and this has prompted us to report our own synthetic endeavours.

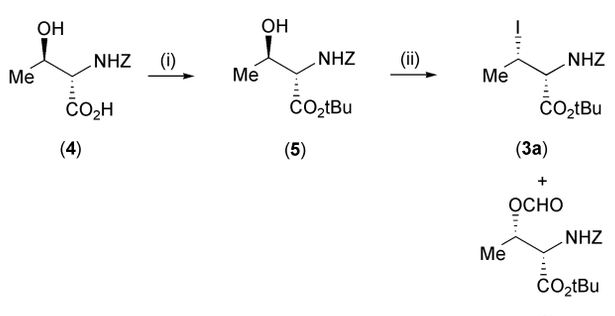
Therefore to address both the stereochemical issues and to access a range of 3-methyl α-amino acids we aimed to prepare pure samples of diastereoisomeric iodides **3a/b**, and then using our now optimum conditions (activated zinc dust in DMF at room temperature) convert them both into the corresponding zinc reagent. Its stability would be apparent through deuterium quenching, Pd(0) cross-coupling with aryl halides/ Cu(I) promoted allylations and ^{1}H/ ^{13}C NMR spectroscopy.



(**3a**) (**3b**)

Results and discussion

Iodide **3a** was prepared in two steps from commercially available *N*-Cbz-L-threonine **4** (Scheme 1). Selective *tert*-butyl esterification of **4** with *t*BuBr, potassium carbonate and benzyltriethylammonium chloride in dimethylacetamide[20] proceeded to give **5** in 50–55% yield after recrystallisation. Though this method did avoid *tert*-butyl ether formation it proved capricious, and was not amenable to scale up beyond 30 mmol.



(**4**) (**5**) (**3a**) (**6**)

Scheme 1 *Reagents and conditions:* i. *t*BuBr, benzyltriethylammonium chloride (BTEAC), K_2CO_3, DMA, 55 °C, 48 h. ii. 2 eq. $Me(PhO)_3P^+I^-$, DMF, rt, 4 h.

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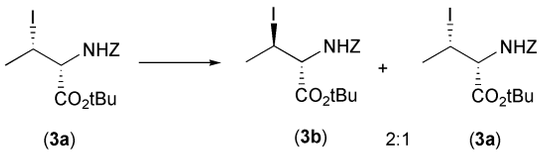
Treatment of **5** with methyl triphenoxyphosphonium iodide[21] in dry DMF at room temperature afforded **3a** as a single diastereoisomer typically in 50–55% yield after chromatography. Formate **6** was isolated as a minor product (2%).

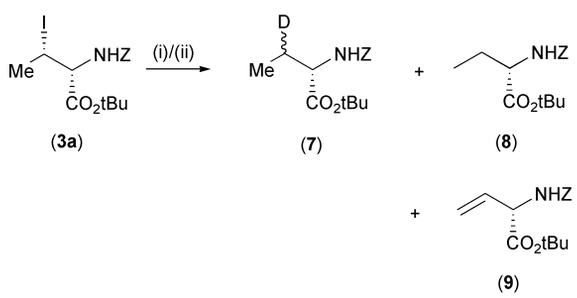
Iodide **3b** was prepared by treatment of **3a** with sodium iodide in acetone at room temperature (Scheme 2). A sample of the pure diastereoisomer **3b** was obtained by flash chromatography.



Scheme 2 *Reagents and conditions:* 2 eq. NaI, acetone, rt.

Preparation and deuteration of zinc reagent 2

Zinc reagent **2** was generated in dry DMF using activated zinc dust (Scheme 3). TLC analysis of the reaction, as a means to verify that **3a** had been transformed to the zinc reagent, proved ineffective. A slight exotherm that ensued as **3a** reacts became a more reliable sign that zinc reagent **2** had formed. Consumption of **3a** was complete after 2 min at room temperature. Immediate quenching of the zinc reagent with d_1-acetic acid (2 eq.) led to a 1:1 mixture of **7** and **8**, as judged from integration of their C(2)H protons. ^{13}C and MS data confirmed deuterium incorporation. The overall sequence of forming zinc reagent **2** and its quench to give **7** gave a 1:1 mixture of C-3 epimeric deuterated compounds, as evident from the C(3)H proton signal integrals. *N*-Cbz-L-vinylglycine *tert*-butyl ester **9** was formed in small amounts (~5%) on all occasions, though it proved to be inseparable from protonated zinc reagent **8**.



Scheme 3 *Reagents and conditions:* (i) Zn* (prepared from Zn dust using 1,2-dibromoethane followed by Me_3SiCl in DMF). (ii) Iodide **3a** in DMF 2 min then 2 eq. CH_3COOD.

Longer time lapse before addition of D^+ led to a relatively smaller amount of the deuterated compound **7**, with the protonated compound **8** being the major decomposition product. Though these reactions proceeded with complete conversion of the iodide, only 60–65% recovery of material was the norm.

NMR experiments: structure and stability of secondary zinc reagent 2

We have previously reported that the ^{13}C NMR spectrum of zinc reagent **1** in DMF-d_7 indicates the presence of intramolecular ester carbonyl-zinc(II) coordination (Fig. 1), as evidenced by a substantial (~5 ppm) downfield shift of the ester carbon signal following zinc insertion.[5]

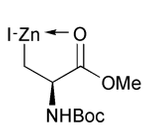


Fig. 1 Proposed structure of *N*-Boc iodozincalanine methyl ester **1** in DMF.

The zinc reagent **2** was prepared as before, but in d_7-DMF, and then transferred to an NMR tube fitted with Youngs' tap under a nitrogen atmosphere. The ^{1}H NMR spectrum obtained ~10 min after formation of zinc reagent confirmed the absence of the iodide **3a** and the formation of a 1:1 mixture of the two diastereoisomeric zinc reagents **2a/b** (Fig. 2). Reduced compound **8** and **9** were present in small amounts (~5% each). The diagnostic signals for the zinc reagents **2a/b** were two doublets (1.02 ppm and 1.045 ppm), corresponding to the zinc reagent methyl group, and two pentets (0.79 ppm and 0.88 ppm) corresponding to the methine proton adjacent to zinc.

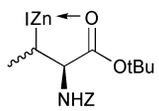


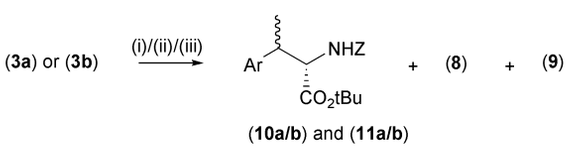
Fig. 2 Proposed structure of zinc reagents **2a/b** in DMF.

In the ^{13}C spectrum of **2a/b**, two signals (174.46 and 174.54 ppm) corresponding to the ester carbonyls were observed, each shifted downfield from the signal (169.0) due to the ester carbonyl in the starting iodide **3a**. These shifts are indicative of diastereoisomeric zinc reagents with internal Zn–O coordination, in a similar manner to that observed with the serine-derived reagent **1**.

In order to assess the stability of the reagents **2a/b**, a second ^{1}H NMR spectrum was obtained 2 hours later, and this proved to be essentially identical to the original spectrum. Thus, the secondary zinc reagents **2a/b** appeared to be stable at room temperature.

Synthesis of 3-methyl-3-arylalanines

Palladium catalysed cross coupling of reagents **2a/b** with a series of aryl iodides was effected using the catalyst prepared *in situ* from $Pd_2(dba)_3$ and tri-*o*-tolylphosphine (Scheme 4).



Scheme 4 *Reagents and conditions:* (i) Zn* in DMF. (ii) iodide **3a** or **3b** in DMF, 2 min. (iii) ArI (1.33 eq.), $Pd_2(dba)_3$ (2.5 mol%), $P(o\text{–}MeC_6H_4)_3$ (10 mol%), room temp., 3 h.

Compounds **10a/b** and **11a/b** were formed as a 1:1 mixture of C-3 epimers in modest yields (see Table 1). Diastereoisomers with a polar aromatic substituent (*i.e.* *p*-nitro and *p*-methoxy, **10a/b** and **11a/b**) were separable by careful chromatography on silica gel with an appropriate petrol–ethyl acetate gradient. In these reactions reduced compound **8** was typically formed in 30–35% yield, along with inseparable **9** in ~5% yield. Absolute configurations at C-3 were assigned by comparison with those reported for *N*-acetyl methyl ester analogues,[22] for which in all cases the (2*S*,3*S*) diastereoisomer displayed its C(3)H signal downfield from that of the corresponding signal in the (2*S*,3*R*) diastereoisomer. Our best, albeit still modest, yield (for **11a/b**) was obtained from a reaction on a 2.3 mmol scale, the largest scale that we employed.

Reactions with iodobenzene and 4-iodotoluene did produce the expected products as mixtures of diastereoisomers, but it proved not to be possible to isolate analytically pure samples of the products. No cross-coupled product was obtained when using 1-iodonaphthalene or 1-iodo-4-bromobenzene, the major product in these cases being **8**, formed by protonation. Reaction of iodide **3b** under the same conditions again gave a 1:1 mixture of diastereoisomers (entry 2, Table 1). The low yields reflect the small scale (0.17 mmol) on which this reaction was carried out, and again the major by-product was **8**.

Table 1 Preparation of 3-methyl-3-arylalanines **10a/b**, **11a/b**

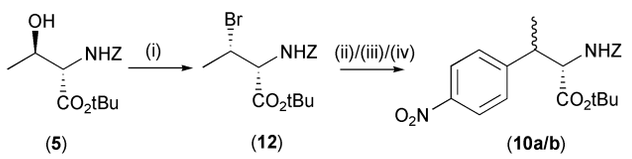
Aryl iodide	Alkyl iodide	Ar	Products	Yield (%)[a]	Yield **8**[a]
4–NO_2–C_6H_4I	**3a**	4–NO_2–C_6H_4	**10a/b**	37	31
4–NO_2–C_6H_4I	**3b**	4–NO_2–C_6H_4	**10a/b**	17	11
4–MeO–C_6H_4I	**3a**	4–MeO–C_6H_4	**11a/b**	44	7

[a] Based on starting iodide **3a** or **3b**.

Table 2 Preparation of 3-methyl 3-alkenyl substituted α-amino acids

Electrophile	R	Product	Yield (%)
CH_2=$CHCH_2Br$	H_2C=$CHCH_2$	**13a/b**	38
CH_2=$C(Br)CH_2Br$	H_2C=$C(Br)CH_2$	**14a/b**	34
CH_2=$C(CO_2Et)CH_2Br$	CH_2=$C(CO_2Et)CH_2$	**15a/b**	36

Formation of zinc reagent **2** from bromide **12**, prepared as a single diastereoisomer from **5** using CBr_4/PPh_3 in toluene, required a slightly elevated temperature (35 °C) (Scheme 5).



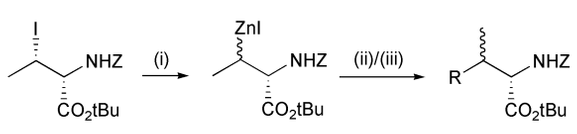
Scheme 5 *Reagents and conditions:* (i) CBr_4/PPh_3, toluene, rt 5 h. (ii) Zn*, DMF. (iii) bromide **5** in DMF, 1 h 35 °C. (iv) 4–NO_2–C_6H_4I (1.33 eq.), $Pd_2(dba)_3$ (2.5 mol%), P(*o*–$MeC_6H_4)_3$ (10 mol%), room temp., 3 h.

Subsequent Pd(0) cross coupling with *p*-iodonitrobenzene led to the isolation of **10a/b** and **8** in 30% yield each, though vinyl glycine derivative **9** was not formed. This represented no improvement on using iodide **3a**.

Our conclusion from these results is that the zinc reagent **2a/b** is perfectly stable at room temperature, but that it reacts substantially more slowly with aryl iodides under palladium catalysis than the analogous zinc reagent **1**. We therefore turned our attention to the possibility of copper-catalysed reactions.

Copper(I) catalysed reactions

Treatment of alkylzinc halides with Cu(I) salts gives more reactive organometallics which can be trapped with allylic or propargylic halides.[4] We have previously employed Hiemstra's variant[23] using a catalytic amount of Cu(I)Br·DMS (0.1 eq.) in dry DMF with α-amino acid zinc reagents.[24] Extension of this methodology to iodide **3a** permitted the preparation of 3 examples of 3-methyl 3-alkenyl substituted α-amino acids **13a/b**–**15a/b** (Scheme 6) in typically 30–40% yield (Table 2).



Scheme 6 *Reagents and conditions:* (i) Zn*, DMF. (ii) CuBr·SMe_2 (0.1 eq.), −10 °C, electrophile, warm to room temp., 3 h.

In this case, products were isolated as inseparable 1:1 mixtures of diastereoisomers. Significantly lower amounts of reduced compound **8**, typically 5–10%, were isolated from these Cu(I) promoted reactions along with nearly equal amounts of inseparable vinyl glycine **9**.

Conclusions

Our final conclusion from this work is that the threonine derived zinc reagents **2a/b** are of limited synthetic value, but that further optimisation, particularly of the copper-promoted reactions, may render this approach to the synthesis of β-methyl substituted α-amino acids more practically useful. The difficulties in separating the products of the reaction from the by-products **8** and **9** is a major limitation at present.

Experimental

Melting points were determined on a Linkham HFS91 heating stage, with a TC92 controller. Optical rotations were determined with a PolAAR 2001 instrument. Mass spectra were obtained using a Micromass Autospec M machine in E.I. mode. Infra red spectra were obtained using a Nicolet 20PCIR instrument. ^{1}H NMR spectra were acquired at 500 MHz with a JEOL Lambda spectrometer and at 200 MHz with a Bruker WP-200. Chemical shifts (δ) are given in ppm, relative to tetramethylsilane (0 ppm), and coupling constants are given in Hz. ^{13}C NMR spectra were acquired at 125 MHz with the JEOL Lambda spectrometer and at 50 MHz with the Bruker WP-200. All chemical shifts (δ) are given in ppm, and are referenced to tetramethylsilane (0 ppm) or $CDCl_3$ (77.0 ppm).

DMF, DMA and toluene were distilled from calcium hydride and stored over 4 Å molecular sieves. TLC analysis was performed on aluminium plates coated with Kieselgel 60 F_{254} (0.25 mm). TLC plates were analysed by UV (254 nm) where appropriate, otherwise plates were developed by treatment with aqueous ammonium molybdate followed by heating. Chemicals were purchased from the Aldrich or Lancaster Synthesis chemical companies, and used as supplied.

tert-Butyl (2*S*,3*R*)-2-(benzyloxycarbonyl)amino-3-hydroxybutanoate (5)

N-Benzyloxycarbonyl-L-threonine **4** (2.53 g, 10 mmol) was dissolved in *N,N*-dimethylacetamide (75 cm^3) at room temperature in the presence of benzyltriethylammonium chloride (2.28 g, 10 mmol). Anhydrous potassium carbonate (35.9 g, 260 mmol) was added to the stirred solution, followed by the addition of *tert*-butyl bromide (55 cm^3, 480 mmol). The mixture was stirred at 55 °C for 24 h. The reaction was allowed to cool, poured into water (1000 cm^3) and the product extracted with ethyl acetate (250 cm^3). The organic layer was separated, washed with water (2 × 100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow solid. Recrystallisation from diethyl ether–hexane afforded ester **5** as colourless needles (1.57 g, 3.1 mmol, 51%). Mp 66 °C. (Found $M^+ - C_4H_8$, 253.0954. $C_{12}H_{15}NO_5^+$ requires 253.0950); $[\alpha]_D^{20}$ −3.8 (*c.* 1.0, CH_2Cl_2); ν_{max}/cm^{-1} (KBr disc) 1514, 1740, 2975, 3407; δ_H (500 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.5), 1.47 (9H, s), 1.94 (1H, br s), 4.15–4.23 (1H, m), 5.12 (2H, s), 5.51 (1H, br s), 7.26–7.37 (5H, m); δ_C (125 MHz, $CDCl_3$) 20.0, 28.0, 59.7, 67.1, 68.4, 82.6, 128.1 (2×), 128.2, 136.3, 156.7, 170.0; *m/z* (EI) 253 ($M^+ - C_4H_8$, 4%), 209 (97), 164 (25), 148 (75), 107 (30), 91 (96), 57 (100). Anal. Calc'$C_{16}H_{23}O_5N$: C 62.10%, H 7.49%, N 4.53%. Found C 62.20%, H 7.46%, N 4.43%.

tert-Butyl (2*R*,3*S*)-2-(benzyloxycarbonyl)amino-3-iodobutanoate (3a)

(2*S*,3*R*)-*tert*-Butyl 2-(benzyloxycarbonyl)amino-3-hydroxybutanoate **5** (2.1 g, 5 mmol) was added in four portions over 10 minutes to a solution of methyltriphenoxyphosphonium iodide (4.52 g, 10 mmol) in anhydrous *N,N*-dimethylformamide

(15 cm^3) under nitrogen at room temperature. The flask was covered with foil and the mixture stirred at room temperature for 3 h. Methanol (15 cm^3) was added and the reaction left to stir for a further 15 minutes. The reaction mixture was poured into water (75 cm^3) and extracted with ether (2 × 50 cm^3). The combined organic fractions were washed with water (2 × 75 cm^3), 5% NaOH (25 cm^3), water (3 × 50 cm^3) and dried ($MgSO_4$). Concentration under reduced pressure gave a pale yellow oil. Flash chromatography on silica gel using petrol–ethyl acetate (20:1) gave **3a** as a pale yellow oil (1.14 g, 2.72 mmol, 54%). (Found: [$MH^+ - C_4H_9$], 362.9972. $C_{12}H_{14}NO_4^+$ requires 362.9968); $[\alpha]_D^{22}$ 40.2 (*c.* 1.05, CH_2Cl_2); ν_{max}/cm^{-1} (cap. film) 1394, 1504, 1724, 2978, 3033; δ_H (500 MHz, $CDCl_3$) 1.51 (9H, s), 1.99 (3H, d, *J* 7), 4.19 (1H, dd, *J* 8 and 3.5), 4.44 (1H, dq, *J* 7 and 3.5), 5.12 (2H, m), 5.61 (2H, d, *J* 8), 7.31–7.39 (5H, s); δ_C (125 MHz, $CDCl_3$) 25.3, 28.1, 60.7, 67.2, 83.6, 128.1, 128.3, 128.6, 129.6, 136.1, 155.6, 167.6; *m*/*z* (EI) 363 ($MH^+ - {}^tBu$, 30%), 318 (42), 292 (9), 236 (40), 107 (33), 91 (100), 57 (40).

tert-Butyl (2*S*,3*S*)-2-(benzyloxycarbonyl)amino-3-formyloxybutanoate (6)

Isolated as a pale yellow oil from the above reaction (33 mg, 0.1 mmol, 2%). (Found: [$MH^+ - C_4H_9$] 281.0907. $C_{13}H_{15}NO_6^+$ requires 281.0899); $[\alpha]_D^{30}$ 5.9 (*c.* 1.5, CH_2Cl_2); ν_{max}/cm^{-1} (cap. film) 1155, 1522, 1726, 2938, 2980 3350; δ_H (500 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.5), 1.48 (9H, s), 4.56 (1H, dd, *J* 8 and 3), 5.11 (2H, s), 5.30–5.35 (1H, m), 5.56 (1H, d, *J* 8), 7.17–7.36 (5H, m), 8.01 (1H, s); δ_C (125 MHz, $CDCl_3$) 16.9, 30.0, 57.3, 67.2, 70.6, 83.3, 128.2 (×2), 128.5, 136.1, 155.9, 160.2, 167.9. *m*/*z* (EI) 281 ($M^+ - C_4H_8$, 9%), 236 (4), 107 (9), 91 (100), 57 (31).

tert-Butyl (2*R*,3*R*)-2-(benzyloxycarbonyl)amino-3-iodobutanoate (3b)

Iodide **3a** (3.06 g, 7.3 mmol) was added to a stirred solution of sodium iodide (3.29 g, 20 mmol, 2.7 eq.) in acetone (200 cm^3) under nitrogen at room temperature then heated at reflux for 24 h. The reaction mixture was concentrated under reduced pressure. Residue was extracted into ethyl acetate (200 cm^3), washed with brine (250 cm^3), 1 M sodium thiosulfate solution (100 cm^3) and water (250 cm^3). Concentration of the organic layer gave a 2:1 mixture of the (2*R*,3*R*)- and (2*R*,3*S*)-diastereoisomers as a pale yellow oil. Flash chromatography on silica gel using petrol–ethyl acetate gave **3b** (0.37 g, 0.88 mmol, 12%) and a 1:1 mixture of **3a/b** (1.824 g, 4.35 mmol, 60%). (Found: M^+, 419.0594. $C_{16}H_{22}NO_4I^+$ requires 419.0593); $[\alpha]_D^{22}$ −14.4 (*c.* 1.2, CH_2Cl_2); ν_{max}/cm^{-1} (cap. film) 1394, 1507, 1728, 2978; δ_H (500 MHz, $CDCl_3$) 1.49 (9H, s), 1.92 (3H, d, *J* 7), 4.17 (1H, dd, *J* 2.5 and 9.5), 4.69 (1H, dq, *J* 7 and 2.5), 5.14 (2H, s), 5.44 (1H, d, *J* 9.5), 7.26–7.40 (5H, m); δ_C (125 MHz, $CDCl_3$) 26.0, 28.0, 29.6, 60.2, 67.3, 83.2, 128.1, 128.2, 128.5, 136.1, 156.6, 168.5; *m*/*z* (EI) 419 (M^+, 28%), 363 (40), 318 (28), 236 (5), 192 (65), 107 (13), 91 (100), 57 (30).

tert-Butyl (2*R*,3*S*)-2-(benzyloxycarbonyl)amino-3-bromobutanoate (12)

Carbon tetrabromide (0.958 g, 2.89 mmol) and triphenylphosphine (0.758 g, 2.89 mmol) were dissolved in anhydrous toluene (16 cm^3) in a dry flask under nitrogen at room temperature. Ester **5** (0.618 g, 2.00 mmol) was added in four portions over 30 minutes. The reaction was stirred at room temperature for 3 hours, then filtered and the solid washed with toluene (20 cm^3). The filtrate was concentrated under reduced pressure to give a pale yellow oil. Flash chromatography on silica gel using petrol–ethyl acetate (3:1) gave *tert*-butyl (2*R*,3*S*)-2-(benzyloxycarbonyl)amino-3-bromobutanoate **12** as a yellow oil (0.373 g, 1.00 mmol, 50%); (Found $MH^+ - C_4H_9$ 315.0091, $C_{12}H_{14}NO_4Br^+$ requires 315.0106); $[\alpha]_D^{22}$ 31.0 (*c.* 1.05, CH_2Cl_2); ν_{max}/cm^{-1} (cap. film) 1394, 1506, 1725, 3034, 3348; δ_H (500 MHz, $CDCl_3$) 1.50 (9H, s), 1.81 (3H, d, *J* 7), 4.37 (1H, dq, *J* 3 and 7), 4.46 (1H, dd, *J* 3 and 8), 5.12 (2H, s), 5.65 (1H, d, *J* 8), 7.30–7.40 (5H, m); δ_C (125 MHz, $CDCl_3$) 23.0, 28.0, 50.0, 60.0, 67.3, 83.5, 128.1, 128.2, 128.6, 136.1, 155.6, 167.4. *m*/*z* (EI) 315 ($M^+ - {}^tBu$, 70%), 272 (11), 264 (13), 191 (100) 91 (100), 57 (31).

Preparation of protected β-methylarylalanines (10a/b–13a/b). General procedure

Zinc dust (0.294 g, 4.5 mmol, 6.0 eq.) was weighed into a 50 cm^3 round bottom flask that was repeatedly evacuated and flushed with nitrogen. Dry DMF (0.5 cm^3) and 1,2-dibromoethane (19 μL, 0.225 mmol) were added *via* syringe and the mixture was stirred vigorously. The mixture was then heated until ethane was evolved before being allowed to attain room temperature. Trimethylsilylchloride (15 μL, 0.115 mmol) was added to the mixture and stirred for 30 min. Iodide **3a** or **3b** (0.314 g, 0.75 mmol) was dissolved in dry DMF (0.5 cm^3) under nitrogen. The iodide solution was added to the activated zinc at room temperature in a water bath *via* syringe. After 2 minutes aryl iodide (1.0 mmol), $Pd_2(dba)_3$ (0.0228 g, 0.025 mmol, 0.025 eq.) and tri-*o*-tolyl-phosphine (0.0304 g, 0.10 mmol, 0.10 eq.) were added in that order to the reaction mixture. The reaction mixture was left to stir at room temperature for 3 h and then diluted with ethyl acetate (50 cm^3). The organic extract was washed with brine (50 cm^3), water (50 cm^3) and dried ($MgSO_4$).

tert-Butyl (2*S*,3*R*/*S*)-2-(benzyloxycarbonyl)amino-3-(*p*-nitrophenyl)butanoate (10a/b)

Treatment with *p*-iodonitrobenzene (0.249 g, 1.0 mmol) followed by flash chromatography on silica gel using petrol–ethyl acetate (8:1) yielded (2*S*,3*R*) diastereoisomer **10a** (52 mg, 0.13 mmol, 17%) as a thick dark oil. (Found: M^+ 414.1799. $C_{22}H_{26}N_2O_6^+$ requires 414.1791); $[\alpha]_D^{22}$ 16.3 (*c.* 0.27, CH_2Cl_2); ν_{max}/cm^{-1} (cap. film) 1347, 1521, 1724, 2935, 2978, 3340. δ_H (500 MHz, $CDCl_3$) 1.33 (3H, d, *J* 7), 1.35 (9H, s), 3.33 (1H, pent, *J* 6.5), 4.51 (1H, dd, *J* 6 and 9), 4.99 (1H, d, *J* 12), 5.09 (1H, d, *J* 12), 5.37 (1H, d, *J* 9), 7.28–7.40 (7H, m), 8.12 (2H, m); δ_C (125 MHz, $CDCl_3$) 16.1, 27.9, 42.8, 59.1, 67.1, 82.9, 123.9, 128.2, 128.4, 128.6, 128.9, 137.9, 147.0, 149.6, 155.9, 169.9. *m*/*z* (EI) 414 (M^+, 15%), 358 (10), 313 (45), 151 (6), 91 (100), 57 (9%).

(2*S*,3*S*) Diastereoisomer **10b** (63 mg, 0.15 mmol, 20%). (Found $M^+ - CO_2{}^tBu$ 313.1193. $C_{17}H_{17}N_2O_4^+$ requires 313.1188); $[\alpha]_D^{22}$ 15.9 (*c.* 0.27, CH_2Cl_2); ν_{max}/cm^{-1} (cap. film) 1346, 1718, 2935, 2978, 3342; δ_H (500 MHz, $CDCl_3$) 1.40 (9H, s), 1.80 (3H, d, *J* 7), 3.43 (1H, pent, *J* 6.5), 4.51 (1H, dd, *J* 5.5 and 8.5), 5.05 (1H, d, *J* 12), 5.09 (1H, d, *J* 12), 5.26 (1H, d, *J* 9), 7.25–7.45 (7H, m), 8.14 (2H, m); δ_C (125 MHz, $CDCl_3$) 16.6, 28.0, 42.4, 59.1, 67.1, 82.9, 123.4, 128.0, 128.3, 128.5, 128.8, 136.0, 146.9, 149.1, 156.0, 169.6; *m*/*z* (EI) 358 ($MH^+ - {}^tBu$, 0.3%), 313 (1), 223 (1), 151 (6), 107 (30), 91 (100).

tert-Butyl (2*S*,3*R*/*S*)-2-(benzyloxycarbonyl)amino-3-(*p*-methoxyphenyl)butanoate (11a/b)

Using iodide **3a** (0.98 g, 2.34 mmol) to generate the organozinc reagent **2a/b** and *p*-methoxyiodobenzene (0.73 g, 3.12 mmol) followed by flash chromatography on silica gel using petrol–ethyl acetate 8:1 gave (2*S*,3*S*) diastereoisomer **11a** (221 mg, 0.55 mmol, 24%) as a dark red oil. $[\alpha]_D^{21}$ 16.3 (*c.* 0.27, CH_2Cl_2). ν_{max}/cm^{-1} (cap. film) 1514, 1726, 3344. δ_H (500 MHz, $CDCl_3$) 1.33 (3H, d, *J* 7), 1.41 (9H, s), 3.30 (1H, pent, *J* 6.5), 3.76 (3H, s), 4.44 (1H, dd, *J* 9 and 5), 5.07 (2H, s), 6.81 (2H, m), 7.11 (2H, m), 7.25–7.30 (5H, m); δ_C (125 MHz, $CDCl_3$) 17.9, 27.9, 41.3, 55.2, 59.8, 66.8, 81.6, 113.7, 128.0, 128.1 (×2), 128.8, 133.0, 136.4, 156.2, 158.6, 170.5. *m*/*z* (EI) 400 (MH^+, 0.1%), 344 (0.5), 327 (0.1), 298 (1.3), 248 (5), 135 (100), 91 (52), 57 (12%).

Also (2*S*,3*R*) diastereoisomer **11b** (190 mg, 0.48 mmol, 20%) as a dark red oil. (Found M^+ 399.2022. $C_{23}H_{29}NO_5^+$ requires 399.2046); $[\alpha]_D^{21}$ 16.3 (*c.* 0.27, CH_2Cl_2); ν_{max}/cm^{-1} (cap. film)

1155, 1248, 1514, 1725, 3341. δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, ^{t}Bu), 1.31 (3H, d, *J* 6.5), 3.08 (1H, pent, *J* 7), 3.76 (3H, s), 4.41 (1H, dd, *J* 7 and 9), 5.08 (2H, m), 5.37 (1H, d, *J* 9), 6.81 (2H, m), 7.12 (2H, m), 7.30–7.36 (5H, m); δ_C (125 MHz, $CDCl_3$) 17.3, 27.7, 42.2, 55.1, 59.7, 66.7, 81.7, 113.6, 128.0, 128.4. 128.8 (×2), 133.6, 136.3, 155.8, 158.5, 170.6. *m*/*z* (EI) 399 (M^+, 0.01%), 343 (0.05), 298 (1.3), 207 (0.7), 163 (0.5, 135 (100), 91 (37).

tert-Butyl (2*S*)-2-(benzyloxycarbonyl)aminobutanoate (8)

Obtained as a by product in all palladium(0) couplings as result of protonation of the zinc reagent **2**. Isolated from those reactions as an inseparable mixture with *N*-Cbz-L-vinylglycine *tert*-butyl ester **9**. The title compound was prepared as a pure compound as follows: (2*R*,3*S*)-*tert*-butyl 2-(benzyloxycarbonyl)amino-3-iodobutanoate **3a** was dissolved in a small amount of DMF, acetic acid was then added followed by zinc dust. A strong exotherm then ensued. After filtration of the zinc dust and aqueous work up the title compound was isolated as a pale yellow oil. (Found $M^+ - C_4H_8$, 237.1011. $C_{12}H_{15}NO_4^+$ requires 237.1001); $[a]_D^{24}$ 6.2 (*c.* 1.25, CH_2Cl_2). ν_{max}/cm^{-1} (cap. film) 3340, 3091, 2976, 1723, 1524, 1157. δ_H (500 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.5), 1.45 (9H, s), 1.66–1.75 (1H, m), 1.82–1.90 (1H, m), 4.20–4.26 (1H, m), 5.10 (2H, s), 5.33 (1H, d, *J* 7.5), 7.30–7.38 (5H, m). δ_C (125 MHz, $CDCl_3$) 9.2, 26.0, 28.0, 55.3, 66.8, 81.9, 128.1, 128.5 (×2), 136.4, 155.8, 171.5. *m*/*z* (EI) 237 (4%, $M^+ - C_4H_8$), 192 (12), 148 (17) 91 (100), 57 (20).

Copper(I)-promoted couplings. General procedure

Zinc dust (0.150 g, 2.3 mmol, 3 eq.) was weighed into a 50 cm^3 round bottom flask which was evacuated four times (twice with heating) and flushed with nitrogen four times. Dry DMF (0.5 cm^3) was added *via* syringe and the reaction stirred vigorously. Trimethylsilylchloride (30 cm^3, 0.23 mmol) was added to the mixture and stirred for 30 min. (2*R*,3*S*)-*tert*-butyl 2-(benzyloxycarbonyl)amino-3-iodobutanoate **3a** (0.314 g, 0.75 mmol) was dissolved in dry DMF (0.5 cm^3) under nitrogen and added to the activated zinc at room temperature. An exotherm after 2–3 min corresponded to the formation of the zinc reagent after which the stirring was stopped and zinc allowed to settle. The supernatent and further dry DMF (5 cm^3) used to wash the zinc was transferred to a solution of copper(I) bromide dimethyl sulfide complex (20 mg, 0.1 mmol, 0.1 eq.) and electrophile (1 mmol). The reaction mixture was stirred at −15 °C for 5 min then allowed to warm to room temperature, and left to stir overnight. The reaction mixture was diluted with ethyl acetate (50 cm^3), washed with 1 M sodium thiosulfate (20 cm^3), water (2 × 20 cm^3), brine (40 cm^3) and dried ($MgSO_4$).

tert-Butyl (2*S*,3*R*/*S*)-2-(benzyloxycarbonyl)amino-3-methylhex-5-enoate (13a/b)

Treatment with allyl bromide (0.09 cm^3, 0.121 g, 1 mmol) followed by flash chromatography on silica gel using petrol–ethyl acetate 20:1 gave *tert*-butyl-(2*R*,3*R*/*S*)-2-(benzyloxycarbonyl)amino-3-methylhex-5-enoate **13a/b** (96 mg, 0.29 mmol, 38%) as a mixture of diastereoisomers in a 1:1 ratio. (Found $M^+ - C_4H_8^+$ 277.1313. $C_{15}H_{19}NO_4^+$ requires 277.1314). ν_{max}/cm^{-1} (cap. film) 1156, 1222, 1368, 1511, 1723, 3347. δ_H (500 MHz, $CDCl_3$) 0.85 (3H, d, *J* 7) and 0.94 (3H, d, *J* 7), 1.46 and 1.47 (9H, s), 1.86–2.23 (3H, m), 4.20 (1H, dd, *J* 4.5 and 8.5), 4.26 (1H, dd, *J* 3.5 and 9), 5.04–5.15 (4H, m), 5.27 (1H, d, *J* 9), 5.38 (1H, d, *J* 8.5). δ_C (125 MHz, $CDCl_3$) 14.2, 15.6, 28.2,* 36.1, 36.5, 37.0, 37.7, 57.7, 58.3, 67.2,* 82.0, 82.2, 116.8, 116.9, 128.1,* 128.2,* 128.5, 128.6, 136.2,* 136.4,* 156.0, 156.3, 170.8, 171.2 (* indicates signals common to both diastereoisomers); *m*/*z* 277 ([$MH^+ - C_4H_8$], 0.3%), 232 (13), 91 (100), 57 (22). Anal. Calc'd for $C_{19}H_{27}NO_4$: C 68.4%, H 8.2%, N 4.4%. Found C 68.37%, H 8.31%, N 4.36%.

tert-Butyl (2*S*,3*R*/*S*)-2-(benzyloxycarbonyl)amino-5-bromo-3-methylhex-5-enoate (14a/b)

Treatment with 2,3-dibromopropene followed by followed by flash chromatography on silica gel (10:1 petrol–ethyl acetate) gave **14a/b** (104 mg, 0.25 mmol, 34%) as a pale yellow oil. (Found $M^+ - C_4H_9 - CO_2$, 310.0443. $C_{14}H_{17}NO_2Br^+$ requires 310.0443). δ_H (500 MHz, $CDCl_3$) 0.87 (3H, d, *J* 7), 0.93 (3H, d, *J* 7), 1.48 (9H, s), 1.49 (9H, s), 2.21 (2H, m), 2.40 (1H, m), 2.49 (2H, m), 2.58 (1H, m), 4.32 (2H, m), 5.10 (4H, m), 5.26 (1H, d, *J* 9), 5.34 (1H, d, *J* 8), 5.48 (2H, m), 5.63 (2H, s), 7.30–7.38 (5H, m). δ_C 13.5, 15.1, 28.0,* 34.5, 35.0, 44.1, 45.2, 57.0, 57.9, 67.0, 67.2, 82.3, 82.6, 118.9, 119.1, 128.2,* 128.5 (×2),* 132.0,* 136.2,* 156.1, 156.3, 170.5, 170.9 (* indicates signals common to both diastereoisomers). *m*/*z* (EI) 266 ([$MH - C_4H_8 - PhCH_2$]$^+$, 5.5%), 232 (7), 91 (100), 57 (14).

tert-Butyl (2*S*,3*R*/*S*)-2-(benzyloxycarbonyl)amino-3-methyl-5-methylenehexanedioic acid 6-ethyl ester (15a/b)

Treatment with ethyl 2-bromomethylacrylate (0.14 cm^3, 1 mmol) followed by flash chromatography on silica gel (10:1 petrol–ethyl acetate) gave the title compounds **15a/b** (95 mg, 0.27 mmol, 36%) as a 1:1 mixture of diastereoisomers. (Found $M^+ - C_4H_8$ 349.1523. $C_{18}H_{23}NO_6^+$ requires 349.1525). ν_{max}/cm^{-1} (cap. film) 1158, 1218, 1521, 1717, 2935, 2978, 3556. δ_H (500 MHz, $CDCl_3$) 0.84 (3H, d, *J* 7), 0.90 (3H, d, *J* 7), 1.30 (3H, t, *J* 7), 1.46 (9H, s), 1.48 (9H, s), 2.05–2.14 (2× 1H, m), 2.22 (1H, m), 2.29 (1H, m), 2.45 (2× 1H, m), 4.14–4.24 (2× 2H, m), 4.31 (1H, dd, *J* 3 and 9), 5.11 (2H, m, $PhCH_2$), 5.30 (1H, d, *J* 9), 5.46 (1H, d, *J* 8), 5.60 (2H, s), 6.23 (2H, d, *J* 7.5), 7.30–7.40 (10H, m). δ_C (125 MHz, $CDCl_3$) 14.2, 14.3, 15.7,* 28.0,* 35.0,* 35.5, 35.9, 57.4, 58.4, 60.7, 60.8, 66.9, 67.0, 82.1, 82.3, 126.8, 127.2, 128.1,* 128.5,* 136.4,* 138.4,* 156.1, 156.4, 166.9,* 170.7, 171.1 (* indicates signals common to both diastereoisomers; two signals obscured between 128.0 and 128.5). *m*/*z* (EI) 349 ($M^+ - C_4H_8$, 1.3%), 332 (0.4), 304 (20), 260 (40), 91 (100), 57 (13).

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