Concise Synthesis of Enantiomerically Pure Phenylalanine, Homophenylalanine, and Bishomophenylalanine Derivatives Using Organozinc Chemistry: NMR Studies of Amino Acid-Derived Organozinc Reagents

Richard F. W. Jackson,* Rebecca J. Moore, and Charles S. Dexter

Department of Chemistry, Bedson Building, The University of Newcastle, Newcastle upon Tyne, NE1 7RU, UK

Jason Elliott[†] and Charles E. Mowbray[‡]

Merck Sharpe and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK and Department of Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, CT13 9NJ, UK

Received June 12, 1998

Protected phenylalanines **23** (seven examples), homophenylalanines **7** (eight examples), and bishomophenylalanines **8** (seven examples) have been prepared by palladium-catalyzed coupling of the amino acid-derived organozinc reagents **13**, **5**, and **6**, respectively, with aryl iodides. While the reactions of the zinc reagent **13** may be conducted in both THF and DMF as solvent, the results obtained in DMF are generally superior. In the case of the reagents **5** and **6** the results are far superior in DMF. NMR investigations on the structure of the zinc reagents **13** in THF suggest that there is strong intramolecular coordination of the urethane carbonyl group, whereas in DMF this interaction is completely suppressed.

There continues to be substantial interest in the synthesis of nonproteinogenic α-amino acids.[1,2] Analogues of phenylalanine, for example homophenylalanine **1** and bishomophenylalanine **2**, are significant components of a range of biologically active compounds.[3,4] We have developed the use of organozinc reagent **4a** and zinc/copper reagent **4b** (each prepared from protected iodoalanine **3**) as a route for the synthesis of enantiomerically pure α-amino acids,[5,6] including a widely used method for the synthesis of simple phenylalanine derivatives by palladium-catalyzed coupling of the organozinc reagent **4a**.[7−18] The success of this approach encouraged us to explore the use of homologous reagents **5** and **6** for the synthesis of homophenylalanine **7** and bishomophenylalanine **8** derivatives by a similar method.

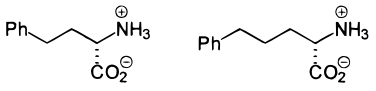
Previous routes to homophenylalanine **7** and bishomophenylalanine **8** derivatives have employed enzymatic methods,[4,19,20] and have also made use of the chiral pool.[21−23] Asymmetric routes have included the reaction of nucleophilic glycine equivalents with 2-arylethyl- and 3-arylpropyl halides,[24] and the reaction of silyl enol ethers with electrophilic glycine equivalents,[25] as well as the use of catalytic asymmetric hydrogenation.[26] An indirect approach, based on catalytic asymmetric reduction of trichloromethyl ketones followed by reaction with azide anion and hydrogenation, has been developed,[27] as have routes relying on precursors prepared by asymmetric catalysis.[28]

In preliminary work, we had explored the generation of the reagent **5** by ultrasonic treatment of the iodide **9**

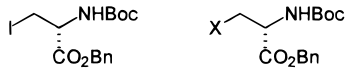
[†] Merck Sharpe and Dohme Research Laboratories.
[‡] Department of Discovery Chemistry, Pfizer Central Research.

(1) Williams, R. M. *Synthesis of Optically Active* α-Amino Acids; Pergamon: New York, 1989.
(2) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1650.
(3) Sahoo, S. P.; Caldwell, C. G.; Chapman, K. T.; Durette, P. L.; Esser, C. K.; Kopka, I. E.; Polo, S. A.; Sperow, K. M.; Niedzwiecki, L. M.; Izquierdomartin, M.; Chang, B. C.; Harrison, R. K.; Stein, R. L.; Maccoss, M.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2441−2446.
(4) Hashimoto, K.; Sakai, M.; Okuno, T.; Shirahama, H. *J. Chem. Soc., Chem. Commun.* **1996**, 1139−1140.
(5) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397−3404.
(6) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210−2215.
(7) Dow, R. L.; Bechle, B. M. *Synlett* **1994**, 293−294.
(8) Smyth, M. S.; Burke, T. R., Jr. *Tetrahedron Lett.* **1994**, *35*, 551−554.
(9) Ye, B.; Burke, T. R. *J. Org. Chem.* **1995**, *60*, 2640−2641.
(10) Ye, B.; Otaka, A.; Burke, T. R. *Synlett* **1996**, 459−460.
(11) Smyth, M. S.; Burke, T. R. *Org. Prep. Proced. Int.* **1996**, *28*, 77−81.
(12) Swahn, B.-M.; Claesson, A.; Pelcman, B.; Besidski, Y.; Molin, H.; Sandberg, M. P.; Berge, O.-G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1635−1640.
(13) Malan, C.; Morin, C. *Synlett* **1996**, 167−168.
(14) Chen, P.; Cheng, P. T. W.; Alam, M.; Beyer, B. D.; Bisacchi, G. S.; Dejneka, T.; Evans, A. J.; Greytok, J. A.; Hermsmeier, M. A.; Humphreys, W. G.; Jacobs, G. A.; Kocy, O.; Lin, P. F.; Lis, K. A.; Marella, M. A.; Ryono, D. E.; Sheaffer, A. K.; Spergel, S. H.; Sun, C. Q.; Tino, J. A.; Vite, G.; Colonno, R. J.; Zahler, R.; Barrish, J. C. *J. Med. Chem.* **1996**, *39*, 1991−2007.
(15) Swahn, B.-M.; Andersson, F.; Pelcman, B.; Söderberg, J.; Claesson, A. *J. Labeled Compd Radiopharm.* **1997**, *39*, 259−266.
(16) Jung, M. E.; Starkey, L. S. *Tetrahedron* **1997**, *53*, 8815−8824.
(17) Walker, M. A.; Kaplita, K. P.; Chen, T.; King, H. D. *Synlett* **1997**, 169−170.
(18) Kawata, S.; Ashizawa, S.; Hirama, M. *J. Am. Chem. Soc.* **1997**, *119*, 12012−12013.
(19) Asano, Y.; Yamada, A.; Kato, Y.; Yamaguchi, K.; Hibino, Y.; Hirai, K.; Kondo, K. *J. Org. Chem.* **1990**, *55*, 5567−5571.
(20) Crich, J. Z.; Brieva, R.; Marquart, P.; Gu, R. L.; Flemming, S.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 3252−3258.
(21) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833−1843.
(22) El Marini, A.; Roumestant, M.-L.; Pappalardo, L.; Viallefont, P. *Bull. Soc. Chim. Fr.* **1989**, *4*, 554−558.
(23) Giannis, A.; Henk, T. *Liebigs Ann. Chem.* **1991**, 789−793.
(24) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277−5292.
(25) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547−1557.
(26) Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143−5150.

10.1021/jo981133u CCC: $15.00
Published on Web 10/14/1998

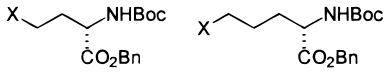


1 **2**



3

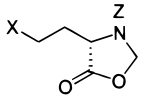
4a, X = IZn
4b, X = IZn(NC)Cu



5, X = IZn
7, X = Ar
9, X = I

6, X = IZn
8, X = Ar
10, X = I

with zinc/copper couple in benzene/dimethylacetamide (DMA) (according to the successful method developed for the zinc reagent **4a**), and also by treatment of iodide **9** with zinc activated using the Knochel procedure employing 1,2-dibromoethane and chlorotrimethylsilane in tetrahydrofuran as solvent.[29,30] Although in both cases we were able to generate the zinc reagent, substantial amounts of the corresponding 2-aminobutanoic acid derivative were formed by protonation, presumably due to the presence of an acidic carbamate proton (in marked contrast to the behavior of the reagent **4a**). The reaction conditions required for the formation of the zinc reagent **5** (35 °C, 30 min) were slightly less mild than those required for the formation of the reagents **4a** and **13**, which could both be prepared at ambient temperature, and this difference was considered responsible for the protonation observed. The relative ease of formation of the zinc reagents **4a** and **13** is presumably due to the greater proximity of the electron-withdrawing substituents. These observations lead us to explore the use of the fully protected zinc reagent **11**, in turn generated from the iodide **12**.[31,32] While this proved a successful tactic, it was slightly limiting. An efficient *general* method for the preparation and use of simply protected amino acid-derived organozinc reagents was clearly highly desirable.

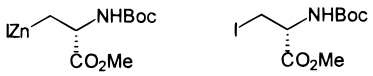


11, X = IZn
12, X = I

Results and Discussion

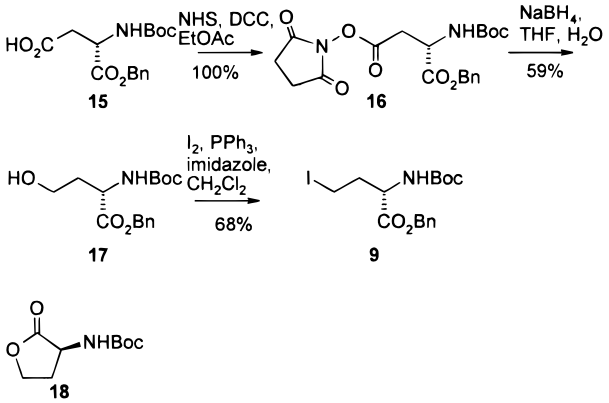
Two reports encouraged us to explore this area in a systematic manner. First, it had been reported that use of an excess of the zinc reagent **5** gave good yields in a coupling reaction with an iodohistidine derivative, provided DMA was used as the solvent.[33] Subsequently, it was reported that simple N-protected iodoethylamine derivatives could be converted into stable zinc reagents provided a DMSO/THF mixture was used as the solvent.[34] We felt that the use of dipolar aprotic solvents in these processes might be significant.

While organozinc reagents have usually been prepared in solvents of moderate Lewis basicity (e.g., THF),[30] the benefits of using dipolar aprotic solvents as a minor component of the solvent mixture has already been highlighted.[35] It has also been reported that use of DMF allows the preparation of arylzinc iodides from aryl iodides,[36] a process which does not generally occur efficiently in THF, except using highly reactive Rieke zinc.[37] The benefits of using DMF for palladium-catalyzed coupling reactions have been known for some time.[38] We have therefore undertaken a systematic study of the use of DMF for the preparation of the zinc reagents **4a**, **5**, **6**, and **13**, and the subsequent palladium-catalyzed coupling of reagents **5**, **6**, and **13** (prepared from the iodide **14**) with aryl iodides.



13 **14**

Iodide **9** had been synthesized previously from *N*-(*tert*-butoxycarbonyl)-L-glutamic acid α-benzyl ester **19** using a Barton decarboxylative iodination.[39] While this method was convenient on a small scale, the chromatography necessary to remove excess iodoform was somewhat tedious, and an alternative preparation of the compound was used. Treatment of *N*-(*tert*-butoxycarbonyl)-L-aspartic acid α-benzyl ester **15** with *N*-hydroxysuccinimide/



DCC gave succinimide ester **16**. Subsequent reduction gave the homoserine derivative **17**, which was converted into iodide **9** using iodine, triphenylphosphine, and

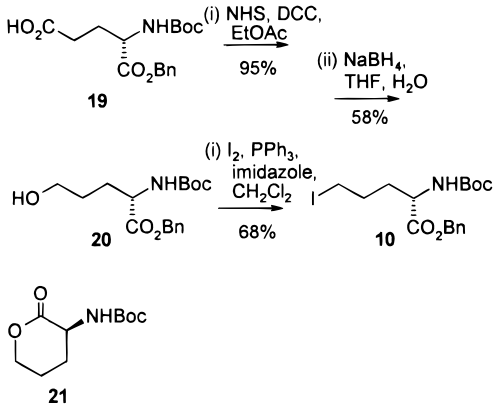
(27) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906−1908.
(28) Poch, M.; Alcon, M.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1993**, *34*, 7781−7784.
(29) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390−2392.
(30) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.
(31) Fraser, J. L.; Jackson, R. F. W.; Porter, B. *Synlett* **1994**, 379−380; Fraser, J. L.; Jackson, R. F. W.; Porter, B. *Synlett* **1995**, 819−820.
(32) Jackson, R. F. W.; Fraser, J. L.; Wishart, N.; Porter, B.; Wythes, M. J. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1903−1912.
(33) Evans, D. A.; Bach, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1326−1327.
(34) Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H. P.; Berger, S.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415−2432.
(35) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 5559−5562.
(36) Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413−4416.
(37) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445−1453.
(38) Negishi, E.-i.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453−4456.
(39) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479−5486.

Table 1. Changes in Carbonyl Shifts on Zinc Reagent Formation in THF-d_8

$\Delta\delta$ ($\delta_{(R-ZnI)} - \delta_{(R-I)}$)	**4a**	**5**	**6**	**13**
carbamate	+2.711	+0.526	+0.431	+2.711
ester	+5.386	+1.506	+0.848	+5.347

imidazole.[40] The reduction step was inefficient and the byproducts formed were the starting material **15** and lactone **18**.[3] Work carried out by Miller indicates that replacement of the α-benzyl ester with an α-*tert*-butyl ester could significantly increase the yield of the desired alcohol by reducing lactonization.[41]

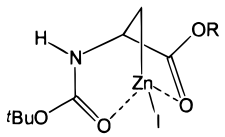
The alkyl iodide **10** was prepared from *N*-(*tert*-butoxycarbonyl)-L-glutamic acid α-benzyl ester **19**, via the alcohol **20**, in an analogous manner. As observed in the preparation of iodide **9**, the reduction step was inefficient and significant amounts of the starting material **19** and lactone **21** were retrieved.



NMR Studies of the Zinc Reagents in THF. As an initial measure of zinc reagent stability and structure in THF, the zinc reagents **4a**, **5**, **6**, and **13** were prepared in THF-d_8 using zinc activated by treatment with 1,2-dibromoethane and chlorotrimethylsilane. As already indicated, while the reagents **4a** and **13** could be prepared at ambient temperature, the reagents **5** and **6** required gentle warming (to 35 °C) to achieve zinc insertion in a comparable time. ^{1}H NMR spectra of the serine-derived reagents **4a** and **13** indicated efficient formation of the zinc reagent, whereas the spectra of the homologous reagents **5** and **6** showed that substantial amounts of protected 2-aminobutanoic acid and 2-aminopentanoic acid, respectively, were already present. The sample of zinc reagent **4a** was heated at 50 °C to establish its stability and the identity of its decomposition products. Heating for 3 days was required before all the zinc reagent had decomposed. Some protonation of the zinc reagent (to give protected alanine) was observed, but the major decomposition product was benzyl acrylate formed by β-elimination.

^{13}C NMR spectra of the same samples were also informative. One of the most striking aspects of the data was the downfield shift of the carbonyl carbon resonances (both of the ester group and the carbamate group) upon conversion of the starting iodides into the corresponding alkylzinc iodides. These changes in chemical shift are reported in Table 1 and are indicative of coordination of the ester carbonyl group to zinc in all cases. The carbamate carbonyl group is also certainly coordinated to zinc in **4a** and **13**, but this effect is less pronounced in the case of **5** and **6**.[42] The observation that the magnitude of $\Delta\delta$ for the ester carbonyl decreases as the zinc becomes more remote from the α-center is consistent with intramolecular coordination of this carbonyl group to zinc, which we suggest becomes decreasingly favorable as the ring size increases from 5 (**4a**, **13**) to 7 (**6**). The coordination of the carbamate carbonyl group to zinc would be expected to lead to β-elimination in the case of the β-aminozinc reagents **4a** and **13** (since the zinc can act as an internal Lewis acid). Similar observations have been made on other amino acid-derived organozinc reagents.[43]

We believe that the (relatively) high stability of the zinc reagents **4a** and **13** in THF is best accounted for by invoking an internally chelated structure **22**. Circumstantial evidence for structure **22** is provided by the significantly different magnetic environments of the two diastereotopic protons observed for **4a** and **13** in THF. A further piece of evidence that is consistent with this monomeric structure is that a ^{1}H NMR spectrum of a racemic mixture of **13** was identical to that observed for enantiomerically pure **13**.[44] The fact that the ester carbonyl binds strongly to zinc in both **4a** and **13** can be used to explain the low rate of β-elimination, since although the urethane carbonyl is also coordinated to zinc, the necessary conformation for elimination (either a syn or anti arrangement of the C−Zn and C−NHBoc bonds) cannot be achieved.



22a, R = Bn
22b, R = Me

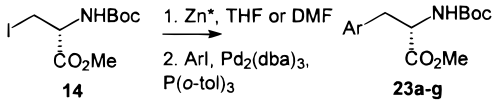
NMR Studies of the Zinc Reagents in DMF. Given the precedent for the use of dipolar aprotic solvents for zinc reagent formation,[33,34] we have investigated the influence of such solvents on the structure of the amino acid-derived zinc reagents, with a view to establishing whether the stability of the reagents could be improved, without compromising their reactivity. Therefore, an analogous set of NMR spectra of the zinc reagents **4a**, **5**, **6**, and **13** were obtained using DMF-d_7 as the solvent, again employing zinc activated with 1,2-dibromoethane and chlorotrimethylsilane. The reaction conditions used for the formation of the reagents were identical to those used in THF (zinc insertion at ambient temperature for **4a** and **13**, and at 35 °C for **5** and **6**). In this case, the ^{1}H NMR spectra indicated that each of the zinc reagents **4a**, **5**, **6**, and **13** had been formed efficiently, and much smaller amounts of the corresponding protonated zinc reagents were detected in the case of the reagents **5** and **6** compared to that observed in THF. The ^{13}C NMR spectra of the same samples indicated that the carbamate carbonyl experienced a small upfield shift, while the ester

(40) Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473−1479.
(41) Lee, B. H.; Gerfen, G. J.; Miller, M. J. *J. Org. Chem.* **1984**, *49*, 2418−2423.
(42) Nakamura, E.; Shimada, J.-i.; Kuwajima, I. *Organometallics* **1985**, *4*, 641−646.
(43) Dexter, C. S.; Jackson, R. F. W. *Chem. Commun.* **1998**, 75−76.
(44) Turner, D. Ph. D. Thesis, University of Newcastle, 1996.

Table 2. Changes in Carbonyl Shifts on Zinc Reagent Formation in DMF-d_7

$\Delta\delta$ ($\delta_{(R-ZnI)} - \delta_{(R-I)}$)	**4a**	**5**	**6**	**13**
carbamate	−0.896	−0.789	−0.873	−0.868
ester	+5.692	+0.831	+0.256	+5.786

Scheme 1



carbonyl carbon atoms showed similar downfield shifts to those observed in THF. These results are presented in Table 2.

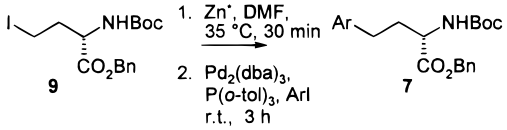
The decrease in $\Delta\delta$ for the ester carbonyl carbon from **4a** to **5** to **6** is again consistent with intramolecular coordination of this carbonyl group to zinc,[42] which mirrors the behavior in THF. The coordination of the carbamate carbonyl group to zinc appears to be completely suppressed in DMF.

Comparison of the Coupling of Zinc Reagent 13 with Aryl Iodides in THF and in DMF. The evidence that the nature of the zinc reagent **13** is significantly altered when it is prepared in DMF, rather than THF, prompted us to undertake a comparative study of the use of these solvents for the preparation of phenylalanine derivatives **23a-g** (Scheme 1). The zinc reagent **13** was prepared from the iodide **14** using activated zinc in THF or DMF at room temperature[36] and then coupled under palladium catalysis with a representative range of aryl iodides as reported in Table 3.

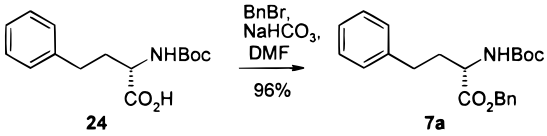
Some clear trends are evident from the results described in Table 3. The results indicate that the coupling process is more effective in DMF, but that in some cases in THF, the yield of coupled product can be increased by conducting the reaction at a higher temperature. The most significant results are the increased yields with *ortho*-substituted aryl iodides when using DMF, and the most striking result is the successful preparation of the 2-fluorophenyl derivative **23e**, which completely eluded us using our previously developed protocol.[5] The ability to conduct the coupling reaction in DMF at room temperature makes the whole process extremely convenient to carry out, and these conditions are the best that we have identified to date for the reaction.

Synthesis of Homophenylalanine Derivatives. Given the efficiency with which the organozinc reagent **5** had been prepared in DMF, it was important to establish whether this reagent could be exploited for the synthesis of homophenylalanine derivatives. Thus the organozinc reagent **5** was generated from iodide **9** using zinc dust, activated by the Knochel method,[30] in DMF. Total conversion into the organozinc reagent **5** occurred after 30 min at 35 °C. The enhanced stability of the zinc reagent **5** in DMF meant that these conditions were the best compromise between the rate of formation of the reagent and its rate of decomposition. Subsequent palladium-catalyzed cross-coupling reactions were carried out at room temperature in the presence of the active catalyst bis-(tri-*o*-tolylphosphine)palladium(0) to give the homophenylalanine deraivatives **7** (Scheme 2, Table 4). Bis(tri-*o*-tolylphosphine)palladium(0) was prepared from $Pd_2(dba)_3$ and tri-*o*-tolylphosphine. A report by Amatore and co-workers has indicated that the concentration of the active catalyst is likely to be lower than expected.[45] This arises because, in contradiction with usual assumptions, dba is a better ligand for the low-ligated active species than mono-dentate phosphorus-based ligands such as tri-*o*-tolylphosphine.

Scheme 2



Scheme 3



Excellent yields of the cross-coupled products **7** were obtained. The *o*-nitro derivative **7b** was the only example for which a modest yield was obtained, even in DMF. This result is not entirely surprising as unfavorable steric effects may have influenced the course of this reaction. The successful preparation of the *o*-amino derivative **7h** was very pleasing as this had not been possible in THF even using the organozinc reagent **11**, fully protected on nitrogen.

Conversion of commercially available *N*-(*tert*-butoxycarbonyl)-(L)-homophenylalanine **24** into the corresponding benzyl ester **7a** (Scheme 3)[46] gave a material that exhibited specific rotation identical to that of compound **7a** prepared via the palladium-catalyzed cross-coupling reaction.

The availability of the 2-amino derivative **7h** led to the development of a concise, stereocontrolled route to 3-aminobenzazepin-2-ones. (*R*)-3-Amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one *ent*-**25** is an important component of some angiotensin converting enzyme (ACE) inhibitors[47] and a novel class of compounds that stimulate release of growth hormones.[48] Previous syntheses have required fractional crystallization of tartaric acid salts to obtain a single enantiomer of the 3-aminobenzazepin-2-one.[48] However, more recently the first enantioselective synthesis of the 3-aminobenzazepin-2-one *ent*-**25** was published.[49]

Simply heating benzyl 2-(*S*)-((*tert*-butoxycarbonyl)-amino)-4-(2′-aminophenyl)butanoate **7h**[50] in the absence of solvent leads to the formation of the protected 3-aminobenzazepin-2-one **26** in good yield. Subsequent removal of the Boc group[49] afforded (*S*)-3-amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one **25** (Scheme 4). The excellent agreement of the optical rotation for **25** with the literature value provides additional support for

(45) Amatore, C.; Jutand, A.; Khalil, F.; Mbarki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168−3178.

(46) Hecker, S. J.; Minich, M. L.; Lackey, K. *J. Org. Chem.* **1990**, *55*, 4904−4911.

(47) Watthey, J. W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. *J. Med. Chem.* **1985**, *28*, 1511−1516.

(48) Schoen, W. R.; Pisano, J. M.; Prendergast, T. K.; Wyvratt, M. J.; Fisher, M. H.; Cheng, K.; Chan, W. W. S.; Butler, B.; Smith, R. G.; Ball, R. G. *J. Med. Chem.* **1994**, *37*, 897−906.

(49) Armstrong, J. D.; Eng, K. K.; Keller, J. L.; Purick, R. M.; Hartner, F. W.; Choi, W. B.; Askin, D.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 3239−3242.

(50) Ito, Y.; Kobayashi, K.; Maeno, M.; Saegusa, T. *Chem. Lett.* **1980**, 487.

Table 3. Preparation of Phenylalanine Derivatives 23

aryl iodide	Ar	Product	yield(%)[a] in DMF[b]	yield(%)[a] in THF[b]	yield(%)[a] in THF[c]
PhI	Ph	**23a**	64	58	41
2-NO_2-C_6H_4I	2-NO_2-C_6H_4	**23b**	28	5	13
4-NO_2-C_6H_4I	4-NO_2-C_6H_4	**23c**	57	62	60
2-MeO-C_6H_4I	2-MeO-C_6H_4	**23d**	57	19	36
2-F-C_6H_4I	2-F-C_6H_4	**23e**	40	16	0
4-F-C_6H_4I	4-F-C_6H_4	**23f**	58	24	49
1-naphthyl iodide	1-naphthyl	**23g**	69	57	48

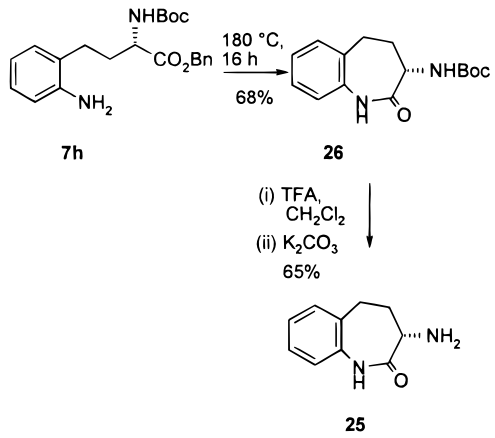
[a] Yields are based on iodide **14**. [b] Zinc reagent prepared at room temperature, coupling at room temperature. [c] Zinc reagent prepared at 35 °C, coupling reaction conducted at 50 °C.

Table 4. Preparation of Homophenylalanine Derivatives 7

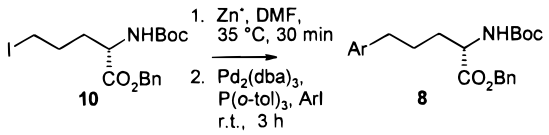
aryl iodide	product	Ar	yield (%)[a]
PhI	**7a**	Ph	70
2-NO_2−C_6H_4I	**7b**	2-NO_2−C_6H_4	40
4-NO_2−C_6H_4I	**7c**	4-NO_2−C_6H_4	84
2-MeO−C_6H_4I	**7d**	2-MeO−C_6H_4	74
4-MeO−C_6H_4I	**7e**	4-MeO−C_6H_4	74
4-Me-C_6H_4I	**7f**	4-Me-C_6H_4	87
1-naphthyl iodide	**7g**	1-naphthyl	88
2-NH_2−C_6H_4I	**7h**	2-NH_2−C_6H_4	53

[a] Yields are based on aryl iodide.

Scheme 4



Scheme 5



complete retention of stereochemical integrity in the coupling process.

Synthesis of Bishomophenylalanine Derivatives. Organozinc reagent **6** was prepared by treating iodide **10** with zinc in DMF using the same procedure used for iodide **9**. Complete insertion of zinc into the carbon−iodine bond had occurred after 30 min at 35 °C. Subsequent palladium-catalyzed cross-couplings with aryl iodides employed identical reaction conditions to those used to generate the protected homophenylalanine derivatives, which gave a range of protected bishomophenylalanine derivatives **8** (Scheme 5, Table 5).

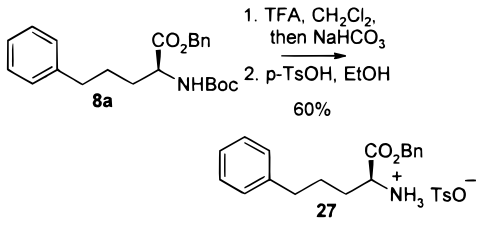
A number of 5-aryl α-amino acids **8** were prepared in excellent yields. However, in the reactions with *ortho*-substituted aromatic iodides (which are more sterically hindered), the yields were only moderate, and in the reaction with 1-iodo-2-nitrobenzene the yield of the product **8b** was poor (as had been observed in the preparation of the analogous homophenylalanine derivative **7b**).

Table 5. Preparation of Bishomophenylalanine Derivatives 8

aryl iodide	product	Ar	yield (%)[a]
PhI	**8a**	Ph	77
2-NO_2−C_6H_4I	**8b**	2-NO_2−C_6H_4	10
4-NO_2−C_6H_4I	**8c**	4-NO_2−C_6H_4	75
2-MeO−C_6H_4I	**8d**	2-MeO−C_6H_4	42
4-MeO−C_6H_4I	**8e**	4-MeO−C_6H_4	62
4-Me-C_6H_4I	**8f**	4-Me-C_6H_4	84
1-naphthyl iodide	**8g**	1-naphthyl	41

[a] Yields are based on aryl iodide.

Scheme 6



Benzyl 2-(*S*)-amino-5-phenylpentanoate *p*-toluenesulfonate **27** was prepared from benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-5-phenylpentanoate **8a** in good yield (Scheme 6). The specific rotation of this compound was comparable with the literature value.[51]

Conclusions

A general method for the synthesis of enantiomerically pure 4-aryl and 5-aryl α-amino acids has been established. The utility of these compounds has been demonstrated in the concise synthesis of (*S*)-3-amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one **25**. More importantly, we have identified the profound beneficial effect of DMF on the preparation, stability, and cross-coupling reactions involving organozinc reagents **5** and **6**, as well as a rationalization for the unique behavior of the serine-derived organozinc reagents **4a** and **13** (which can be prepared and used effectively in both THF and DMF).

Experimental Section

General experimental procedures have already been described.[5] DMF was distilled from calcium hydride and stored over 4 Å molecular sieves. Specific rotations were measured at 20 °C, unless otherwise stated. ^{1}H NMR spectra were recorded in $CDCl_3$ as solvent at 500 MHz, referenced to TMS, unless stated otherwise. ^{13}C NMR spectra were recorded at 125 MHz. Coupling constants are given in hertz. Organic

(51) Shimohigashi, Y.; Izumiya, N. *Int. J. Pept. Protein Res.* **1978**, *12*, 7.

extracts were dried over $MgSO_4$, and the solvent then removed using a rotary evaporator.

Benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-hydroxybutanoate (17). *N*-*tert*-Butoxycarbonyl-L-aspartic acid α-benzyl ester **15** (3.23 g, 10.0 mmol) and *N*-hydroxysuccinimide (1.27 g, 11.0 mmol) were dissolved in ethyl acetate (40 mL) with stirring under nitrogen. The solution was cooled to 0 °C, and 1,3-dicyclohexylcarbodiimide (2.27 g, 11.0 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirring continued for 6 h. The resulting suspension was filtered, and the filtrate was dried and concentrated under reduced pressure to give succinimide ester **16** as a colorless solid. Sodium borohydride (0.57 g, 15.0 mmol) was dissolved in a 4:1 mixture of THF and water (40 mL) at 0 °C. The succinimide ester **16** was dissolved in THF (28 mL) and added to the sodium borohydride solution. The reaction mixture was stirred vigorously for several minutes until gas evolution ceased and then quenched with a saturated aqueous solution of ammonium chloride (20 mL) and left to stir for 10 min. The reaction mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were dried. The solvent was removed to give a colorless oil which was purified by flash column chromatography on silica gel eluting with 2:1 petroleum ether/ethyl acetate to give ester **17** as a colorless oil (1.82 g, 59%). (Found MH^+ 310.1668. $C_{16}H_{24}NO_5$ requires 310.1654). $[\alpha]^{27}_D$ −39.9 (*c* 1.0, MeOH) (lit. value of enantiomer $[\alpha]_D$ +35 (*c* 1.0, MeOH)).[52] IR (film, cm^{-1}) 3377, 2977, 1740, 1713. NMR: δ_H 1.44 (9H, s), 1.60−1.65 (1H, m), 2.13−2.19 (1H, m), 2.76 (1H, br s), 3.60−3.66 (1H, m), 3.68−3.72 (1H, m), 4.51−4.55 (1H, m), 5.18 (1H, d, *J* 12.2), 5.21 (1H, d, *J* 12.2), 5.41 (1H, d, *J* 7.7), 7.34−7.37 (5H, m); δ_C 28.2, 36.1, 50.6, 58.2, 67.3, 80.5, 126.9, 128.2, 128.5, 135.2, 156.4, 172.7. *m*/*z* (EI) 310 (MH^+, 5%).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-5-hydroxypentanoate (20). *N*-*tert*-Butoxycarbonyl-L-glutamic acid α-benzyl ester **19** (3.37 g, 10.0 mmol) was treated under the same reaction conditions as those described in the preparation of succinimide ester **16**. This led to the formation of succinimide ester which, without further purification, was reduced using the procedure developed for the preparation of benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-hydroxybutanoate **17**. Purification by flash column chromatography (2:1 petroleum ether/ethyl acetate) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanoate **20** as a colorless oil (1.78 g, 55%). (Found $M^+ - C_4H_8$ 267.1114. $C_{13}H_{17}NO_5$ requires 267.1107). $[\alpha]^{27}_D$ −3.0 (*c* 1.0 in $CHCl_3$) (lit. value −2.9 (*c* 1.0 in $CHCl_3$)).[53] IR (film, cm^{-1}) 3373, 2978, 1739, 1704. NMR δ_H 1.42 (9H, s), 1.52−1.59 (2H, m), 1.69−1.76 (1H, m), 1.86−1.92 (1H, m), 2.74 (1H, br s), 3.58 (2H, t, *J* 6.1), 4.31−4.36 (1H, m), 5.14 (1H, d, *J* 12.5), 5.19 (1H, d, *J* 12.5), 5.39 (1H, d, *J* 8.2), 7.33−7.35 (5H, m). δ_C 28.2, 29.2, 53.2, 60.4, 61.8, 66.9, 79.9, 128.2, 128.3, 128.5, 135.3, 155.5, 172.6. *m*/*z* (EI) 267 ($M^+ - C_4H_8$, 25%).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-4-iodobutanoate (9). Triphenylphosphine (6.29 g, 24.0 mmol) and imidazole (1.63 g, 24.0 mmol) were dissolved in dry dichloromethane (60 mL) with stirring under nitrogen. Iodine (6.10 g, 24.0 mmol) was added slowly, and after 5 min a solution of benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-hydroxybutanoate **17** (6.18 g, 20.0 mmol) in dry dichloromethane (20 mL) was also added. Stirring was continued for 1 h at room temperature by which time no starting material remained (as judged by TLC). The solvent was evaporated under reduced pressure, the residue was filtered through a short column of silica gel eluting with diethyl ether (300 mL), and the filtrate was concentrated to give a pale yellow oil. Purification by flash column chromatography eluting with 5:1 petroleum ether/ethyl acetate yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-iodobutanoate **9** as a colorless solid which was recrystallized from pentane, mp 54−55 °C (lit. value mp 54 °C)[39] (5.70 g, 68%). (Found $M^+ - CO_2Bn$ 284.0141. $C_8H_{15}INO_2$ requires 284.0149). $[\alpha]^{27}_D$ −32.6 (*c* 1.0 in MeOH) (lit. value −33.0 (*c* 1.0 in MeOH)).[39] IR (KBr, cm^{-1}) 3356, 2979, 1756, 1680. δ_H (200 MHz) 1.42 (9H, s), 2.14−2.22 (1H, m), 2.30−2.38 (1H, m), 3.12 (2H, t, *J* 7.8), 4.32−4.38 (1H, m), 5.10 (1H, d, *J* 8.0), 5.16 (2H, s), 7.33−7.35 (5H, m). δ_C (50 MHz) −0.5, 28.3, 37.0, 54.5, 67.5, 80.3, 128.4, 128.6, 128.7, 135.1, 156.2, 171.5. *m*/*z* (EI) 284 ($M^+ - CO_2Bn$, 17%).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-5-iodopentanoate (10). Benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanoate **20** (6.46 g, 20.0 mmol) was treated under the same reaction conditions as those described in the preparation of benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-iodobutanoate **9**. Purification by flash column chromatography (5:1 petroleum ether/ethyl acetate) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-5-iodopentanoate **10** as a colorless oil (5.89 g, 68%), which solidified with time in the freezer, mp 34−35 °C (from light petroleum ether/Et_2O). (Found $M^+ - C_4H_8$ 377.0125. $C_{13}H_{16}INO_4$ requires 377.0126). $[\alpha]^{27}_D$ −19.9 (*c* 1.0 in MeOH). IR (film, cm^{-1}) 3364, 2976, 1743 and 1713. NMR δ_H 1.44 (9H, s), 1.71−1.82 (2H, m), 1.85−1.95 (2H, m), 3.11−3.18 (2H, m), 4.34−4.39 (1H, m), 5.06 (1H, d, *J* 8.2), 5.16 (1H, d, *J* 12.2), 5.22 (1H, d, *J* 12.2), 7.34−7.37 (5H, m). δ_C 5.3, 28.3, 29.2, 33.7, 52.6, 67.2, 80.1, 128.3, 128.5, 128.6, 135.2, 155.3, 172.2. *m*/*z* (EI) 377 ($M^+ - C_4H_8$, 14%).

NMR Studies of the Zinc Reagents 4a, 5, 6, and 13. Zinc dust (325 mesh, 300 mg, 4.5 mmol) was added to a nitrogen-purged flask. THF-d_8 [or DMF-d_7] (0.5 mL) and 1,2-dibromoethane (19.4 μL, 0.225 mmol) were added, and the flask was repeatedly heated using a hot water bath and allowed to cool over a period of 15 min. The reaction mixture was allowed to cool to room temperature, trimethylsilyl chloride (6.0 μL, 0.046 mmol) was added, and the resultant mixture was stirred vigorously for 30 min under nitrogen. The amino acid-derived iodides **3**, **9**, **10**, or **14** (0.75 mmol) in THF-d_8 [or DMF-d_7] (0.5 mL) was added to the flask which was either stirred at room temp (for **3** and **14)** or heated at 35 °C (for **9** and **10**) until no starting material remained (as judged by TLC, 2:1, petroleum ether:ethyl acetate). The zinc was allowed to settle, and the supernatant was then transferred to a nitrogen-filled NMR tube fitted with a Young's tap (a small amount of residual zinc dust was unavoidably transferred, but its presence did not adversely affect the spectra). References used for the deuterated solvents: DMF-d_7 δ_H 2.9, δ_C 161.7; THF-d_8 δ_H 1.8, δ_C 26.7.

Iodide 3. δ_H (DMF-d_7) 1.41 (9 H, s), 3.55 (1 H, dd, *J* 8.5 and 10.2), 3.68 (1 H, dd, *J* 4.7 and 10.2) 4.45−4.49 (1 H, m), 5.22 (2 H, br s), 7.31 (1 H, br d, *J* 8.1), 7.32−7.45 (5 H, m); δ_C (DMF-d_7) 4.0, 27.4, 55.5, 66.4, 78.5, 127.6, 127.8, 128.1, 135.7, 155.2, 169.0. δ_H 1.50 (THF-d_8) (9 H, s), 3.57 (1 H, dd, *J* 6.2 and 10.0), 3.62−3.66 (1 H, m), 4.54−4.58 (1 H, m), 5.24 (2 H, s), 6.65 (1 H, d, *J* 7.2), 7.30−7.46 (5 H, m); δ_C (THF-d_8) 7.9, 30.0, 57.2, 69.1, 81.0, 130.3, 130.4, 130.6, 138.2, 157.2, 171.4.

Zinc Reagent 4a. δ_H (DMF-d_7) 0.49 (1 H, dd, *J* 9.0 and 12.5), 0.55 (1 H, dd *J* 7.1 and 12.5), 1.35 (9 H, s), 4.19−4.23 (1 H, m), 5.06 (1 H, d, *J* 12.7), 5.11 (I H, d, *J* 12.7), 6.12 (1 H, d, *J* 6.6), 7.29−7.39 (5 H, m); δ_C (DMF-d_7) 12.0, 26.9, 53.6, 64.1, 76.8, 126.4, 126.7, 127.3, 135.8, 154.3, 174.7. δ_H (THF-d_8) 0.48−0.56 (1 H, m), 0.62−0.71 (1 H, m), 1.45 (9 H, s), 4.23−4.28 (1 H, m), 5.14−5.17 (2 H, m), 6.79 (1 H, br s), 7.30−7.78 (5 H, m); δ_C (THF-d_8) 15.0, 30.4, 57.4, 68.3, 82.5, 130.1, 130.6, 138.8, 156.0, 176.8. Remaining signal obscured by peaks at 130.

Iodide 9. δ_H (DMF-d_7) 1.39 (9 H, s), 2.19−2.36 (2 H, m), 3.33−3.41 (2 H, m), 4.28 (1 H, td, *J* 4.6 and 13.2), 5.16 (1 H, d, *J* 12.5), 5.22 (1 H, d, *J* 12.5), 6.91 (1 H, br d, *J* 7.5), 7.31−7.44 (5 H, m); δ_C (DMF-d_7) 1.8, 27.4, 35.0, 54.4, 65.9, 78.2, 127.5, 127.8, 128.1, 136.0, 155.7, 171.4. δ_H (THF-d_8) 1.48 (9 H, s), 2.21 (1 H, dt, *J* 8.3 and 14.6), 2.41 (1 H, dt, *J* 7.9 and 13.5), 3.29 (2 H, t, *J* 8.3), 4.33 (1 H, dt, *J* 4.9 and 8.9), 5.19 (1 H, d, *J* 12.5), 5.22 (1 H, d, *J* 12.4), 6.61 (1 H, d, *J* 8.2), 7.33−7.44 (5 H, m); δ_C (THF-d_8) 2.2, 30.0, 38.7, 56.9, 80.6, 130.2, 130.5, 138.5, 157.8, 173.4. Remaining two signals obscured by solvent peak, and by peaks at 130, respectively.

Zinc Reagent 5. δ_H (DMF-d_7) 0.02−0.08 (1 H, m), 0.129 (1 H, dt, *J* 5.5 and 12.2), 1.35 (9 H, s), 1.84−1.92 (1 H, m),

(52) Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1991**, *32*, 923−926.

(53) Olsen, R. K.; Ramasamy, K.; Emery, T. *J. Org. Chem.* **1984**, *49*, 3527−3534.

1.93−2.01 (1 H, m), 4.00 (1 H, d, *J* 7.6 and 13.1), 6.62 (1 H, d, *J* 7.8), 7.03 (1 H, d, *J* 7.8), 7.29−7.39 (5 H, m); δ_C (DMF-d_7) 3.5, 26.9, 30.0, 57.8, 64.3, 76.9, 126.5, 126.8, 127.3, 135.6, 154.9, 172.3. δ_H (THF-d_8) 0.11−0.22 (2 H, m), 1.44 (9 H, m), 1.90−2.08 (2 H, m), 4.05 (1 H, m), 5.16 (2 H, m), 6.23 (1 H, d, *J* 6.7), 7.31−7.38 (5 H, m); δ_C (THF-d_8) 12.0, 30.2, 32.9, 57.4, 68.3, 80.6, 130.2, 130.6, 130.8, 138.6, 158.3, 174.9.

Iodide 10. δ_H (DMF-d_7) 1.39 (9 H, s), 1.79−1.84 (1 H, m), 1.89−1.97 (3 H, m), 3.26−3.32 (2 H, m), 4.19 (1 H, dt, *J* 4.5 and 10.0), 5.16 (1 H, d, *J* 12.5), 5.21 (1 H, d, *J* 12.5), 7.26 (1 H, d, *J* 7.9), 7.33−7.43 (5 H, m): δ_C (DMF-d_7) 6.0, 27.5, 31.8, 52.8, 54.4, 65.7, 78.0, 127.5, 127.7, 128.1, 136.1, 155.6, 172.0 δ_H (THF-d_8) 1.38 (9 H, s), 1.64−1.69 (1 H, m), 1.80−1.88 (3 H, m), 4.23 (1 H, td, *J* 8.8 and 4.6), 5.08 (1 H, d, *J* 12.5), 5.11 (1 H, d, *J* 12.5), 6.45 (1 H, d, *J* 8.6), 7.23−7.34 (5 H, m): δ_C (THF-d_8) 7.3, 30.0, 32.2, 35.3, 56.3, 80.6, 130.1, 130.2, 130.5, 138.7, 157.8, 175.0. Remaining signal obscured by solvent peak.

Zinc Reagent 6. δ_H (DMF-d_7) 0.04−0.15 (2 H, m), 1.35 (9 H, s), 1.55−1.74 (4 H, m), 4.08−4.15 (1 H, m), 5.08 (1 H, d, *J* 12.5), 5.17 (1 H, d, *J* 12.5), 6.84 (1 H, d, *J* 7.9), 7.29−7.39 (5 H, m); δ_C (DMF-d_7) 7.6, 23.8, 26.9, 36.2, 53.0, 64.6, 77.0, 126.5, 126.8, 127.4, 135.4, 154.8, 172.2. δ_H (THF-d_8) 0.22−0.24 (2 H, m), 1.45 (9 H, s), 1.58−1.74 (3 H, m), 1.76−1.85 (1 H, m), 4.30−4.38 (1 H, m), 5.12 (1 H, d, *J* 12.5), 5.16 (1 H, d, *J* 12.5), 6.42 (1 H, d, *J* 6.0), 7.30−7.42 (5 H, m); δ_C (THF-d_8) 15.6, 30.3, 55.8, 68.2, 80.8, 130.1, 130.5, 130.6, 138.7, 158.2, 175.0. *The two remaining methylene peaks are not easily assigned due to other degradation products.*

Iodide 14. δ_H (DMF-d_7) 1.42 (9 H, s), 3.49 (1 H, dd, *J* 8.2 and 10.0), 3.62 (1 H, dd, *J* 4.5 and 10.0), 3.71 (3 H, s), 4.40 (1 H, m), 7.21 (1H, br d, *J* 8.2); δ_C (DMF-d_7) 4.1, 27.4, 51.7, 55.3, 78.5, 155.1, 169.6. δ_H (THF-d_8) 1.49 (9 H, s), 3.53 (1 H, dd, *J* 6.1 and 10.0), 3.61 (1 H, dd, *J* 4.5 and 10.0), 3.78 (3 H, s), 4.50 (1 H, m), 6.59 (1 H, br d, *J* 7.0); δ_C (THF-d_8) 8.1, 30.0, 57.0, 58.6, 81.0, 157.2, 171.9.

Zinc Reagent 13. δ_H (DMF-d_7) 0.38 (1 H, dd, *J* 8.5 and 12.8), 0.42 (1 H, dd, *J* 7.6 and 12.8), 1.31 (9 H, s), 3.53 (3 H, s), 4.09 (1 H, m), 6.99 (1 H, br d, *J* 6.7); δ_C (DMF-d_7) 12.0, 28.6, 50.0, 53.3, 76.8, 154.2, 175.4. δ_H (THF-d_8) 0.44 (1 H, m), 0.58 (1 H, m), 1.47 (9 H, s), 3.70 (3 H, s), 4.16 (1 H, m), 6.38 (1 H, br); δ_C (THF-d_8) 14.9, 30.3, 53.6, 57.2, 82.5, 159.9, 177.3.

Reaction with Aromatic Iodides with Zinc Reagent 13. General Procedure for reactions in THF. The zinc reagent **13** was prepared in THF from iodoalanine **14** (0.75 mmol), using an identical procedure to that used for THF-d_8, but it was not removed from the excess zinc. The aromatic iodide (1 mmol) was added, followed by $Pd_2(dba)_3$ (20 mg, 0.019 mmol) and P(*o*-tol)$_3$ (22 mg, 0.076 mmol). The reaction mixture was stirred at 50 °C for 1 h. The mixture was filtered, partitioned between ethyl acetate (25 mL) and water (25 mL), and washed with brine (25 mL) and water (25 mL). The organic extracts were dried, filtered, and evaporated. The crude product was purified by flash column chromatography using a petroleum ether:ethyl acetate gradient to give the pure phenylalanine derivatives **23a**−**g**.

Reaction with Aromatic Iodides. General Procedure for Reactions in DMF. The zinc reagent **13** was prepared in DMF using an identical procedure to that used for DMF-d_7, but it was not removed from the excess zinc. The coupling reaction was carried out at room temp according to the procedure described for above for THF.

All the following data refer to compounds prepared using DMF as solvent.

Methyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-3-phenylpropanoate (23a). Treatment with iodobenzene gave **23a** (0.1314 g, 64%), isolated as a colorless oil which solidified with time, mp 41−42 °C. $[\alpha]^{20}_D$ +46.9 (*c* 3.43, CH_2Cl_2). $[\alpha]^{23}_D$ −5.6 (*c* 1.0, MeOH), lit. value[54] $[\alpha]^{27}_D$ −4.6 (*c* 1.0, MeOH). IR (film, cm^{-1}) 3367, 1716. NMR δ_H 1.42 (9 H, s), 3.05 (1 H, dd, *J* 6.1 and 13.7), 3.12 (1 H, dd, *J* 5.5 and 13.7), 3.71 (3 H, s), 4.59 (1 H, dd, *J* 6.1 and 13.4), 4.98 (1 H, d, *J* 7.0), 7.22−7.31 (5 H, m); δ_C 28.3, 38.4, 52.2, 54.4, 79.9, 127.0, 128.5, 129.3, 136.0, 155.1, 172.4; *m*/*z* (EI) 279 (M^+, 0.5%).

Methyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-3-(2′-nitrophenyl)propanoate (23b). Treatment with 1-iodo-2-nitrobenzene gave **23b** (0.0681 g, 28%), isolated as fine pale brown needles, mp 83−84 °C. (Found: C, 55.67; H, 6.22; N, 8.64%: $C_{15}H_{20}N_2O_6$ requires C, 55.55; H, 6.22; N, 8.64%). $[\alpha]^{20}_D$ +42.7 (*c* 0.185, CH_2Cl_2). IR (KBr, cm^{-1}) 3362, 1747, 1684. NMR δ_H 1.34 (9 H, s), 3.20−3.27 (1 H, dd, *J* 9 and 14), 3.48−3.53 (1 H, dd, *J* 5.8 and 14), 3.70 (3 H, s), 4.65−4.66 (1 H, m), 5.16 (1 H, d, *J* 6.7), 7.36−7.40 (2 H, m), 7.53 (1 H, t, *J* 7.3), 7.91−7.96 (1 H, d, *J* 7.9); δ_C 28.2, 35.6, 52.6, 54.0, 80.0, 125.1, 128.1, 131.8, 133.1, 133.0, 149.7, 154.9, 172.0; *m*/*z* (EI) 265 ($M^+ - C_2H_3O_2$, 2%).

Methyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-3-(4′-nitrophenyl)propanoate (23c). Treatment with 1-iodo-4-nitrobenzene gave **23c** (0.1370 g, 57%), isolated as fine brown needles, mp 95−97 °C (lit. value[55] mp 92−94 °C). (Found C, 55.25; H, 5.91; N, 8.51%: $C_{15}H_{20}N_2O_6$ requires C, 55.55; H, 6.22; N, 8.64). $[\alpha]^{20}_D$ +30.4 (*c* 1.055, CH_2Cl_2). IR (KBr, cm^{-1}) 3358, 1735, 1730, 1689, 1676. NMR δ_H 1.41 (9 H, s), 3.12 (1 H, dd, *J* 6.1 and 13.5), 3.27 (1 H, dd, *J* 6.1 and 13.5), 3.74 (3 H, s), 4.64−4.67 (1 H, m), 5.01−5.09 (1 H, d, *J* 6.4), 7.31 (2 H, d, *J* 8.6), 8.16 (2 H, d, *J* 8.6); δ_C 28.3, 38.4, 52.5, 54.1, 80.4, 123.7, 130.2, 144.0, 147.2, 154.9, 171.6; *m*/*z* (EI) 324 (M^+, 0.05%).

Methyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-3-(2′-methoxyphenyl)propanoate (23d). Treatment with 2-iodoanisole gave **23d** (0.1272 g, 57%), isolated as pale orange oil, which solidified with time, mp 75−76 °C. (Found C, 62.36; H, 7.55; N, 4.53% $C_{16}H_{23}NO_5$ requires C, 62.12; H, 7.49; N, 4.53%). $[\alpha]^{20}_D$ +14.9 (*c* 0.68, CH_2Cl_2). IR (film, cm^{-1}) 3379, 2976, 1746, 1716. NMR δ_H 1.38 (9 H, s), 3.02−3.11 (2 H, m), 3.69 (3 H, s), 3.82 (3 H, s), 4.51 (1 H, dd, *J* 7.3 and 13.7), 5.22 (1 H, d, *J* 7.3), 6.86 (1 H, d, *J* 8.2,), 6.89 (1 H, t, *J* 7.3), 7.09 (1 H, dd, 1.5 and 7.3), 7.23 (1 H, dt, *J* 1.5 and 8.2); δ_C 28.3, 32.4, 52.0, 54.0, 55.3, 79.5, 110.4, 120.6, 124.7, 131.2, 155.3, 157.6, 172.9; *m*/*z* (EI) 309 (M^+, 0.3%).

Methyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-3-(2′-fluorophenyl)propanoate (23e). Treatment with 2-fluoro-1-iodobenzene gave **23e** (0.0923 g, 40%), isolated as a pale yellow oil. (Found C, 60.53; H, 4.57; N, 6.78% $C_{15}H_{20}NO_4F$ requires C, 60.60; H, 4.71; N, 6.78%). $[\alpha]^{19}_D$ +40.0 (*c* 1.02, CH_2Cl_2). IR (film, cm^{-1}) 3440, 2979, 1747, 1717. NMR δ_H 1.40 (9 H, s), 3.08 (1 H, dd, *J* 6.8 and 13.8), 3.18 (1 H, dd, *J* 5.8 and 13.8), 3.73 (3 H, s), 4.59 (1 H, dd, *J* 6.4 and 14.1), 5.06 (1 H, d, *J* 7.6), 7.03 (1 H, t, *J* 8.9), 7.10 (1 H, dt, *J* 0.9 and 7.3), 7.15 (1 H, dt, *J* 1.5 and 7.7), 7.10−7.25 (1 H, m); δ_C 28.3, 31.9, 52.33, 53.6, 79.9, 115.4 (d, J_{CF} 22.7), 123.2 (d, J_{CF} 66), 124.1, 128.9 (d, J_{CF} 8.25), 131.7 (d, J_{CF} 4.1), 155.0, 161.4 (d, J_{CF} 243.8), 172.2; *m*/*z* (EI) 297 (M^+, 0.4%).

Methyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-3-(4′-fluorophenyl)propanoate (23f). Treatment with 4-fluoro-1-iodobenzene gave **23f** (0.1203 g, 58%), isolated as beige needles, mp 38−41 °C. (Found M^+ 297.1355. $C_{15}H_{20}NO_4F$ requires 297.1376). $[\alpha]^{20}_D$ +30.5 (*c* 0.1, CH_2Cl_2). IR (KBr, cm^{-1}) 3356, 1738, 1689, 1512, 1219, 1162; NMR δ_H 1.42 (9 H, s), 3.01 (1 H, dd, *J* 6.1 and 14), 3.10 (1 H, dd, *J* 5.8 and 14), 3.71 (3 H, s), 4.57 (1 H, dd, *J* 6.1 and 13.8), 4.98 (1 H, d, *J* 7.3), 6.96−7.00 (2 H, m), 7.07−7.12 (2 H, m); δ_C 28.3, 37.6, 52.3, 54.4, 80.0, 115.4 (d, J_{CF} 20.7), 130.8 (d, J_{CF} 7.3), 131.8, 155.0, 162.0 (d, J_{CF} 245.0), 172.2; *m*/*z* (EI) 297 (M^+).

Methyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-3-naphthylpropanoate (23g). Treatment with 1-iodonaphthalene gave **23g** (0.1714 g, 69%), isolated as a pale brown oil. (Found M^+ 329.1631. $C_{19}H_{23}NO_4$ requires 329.1627). $[\alpha]^{20}_D$ +27.5 (*c* 1.47, CH_2Cl_2). IR (film, cm^{-1}) 3369, 2977, 1745, 1713. NMR δ_H 1.39 (9 H, s), 3.46 (1 H, dd, *J* 6.7 and 13.7), 3.56−3.60 (1 H, m), 3.60 (3 H, s), 4.72 (1 H, dd, *J* 6.8 and 13.7), 5.09 (1 H, d, *J* 7.3), 7.26 (1 H, d, *J* 7.0), 7.38 (1 H, t, *J* 7.9), 7.47 (1 H, t, *J* 7.2), 7.53 (1 H, t, *J* 7.1), 7.75 (1 H, d, *J* 8.0), 7.84 (1 H, d, *J* 8.0), 8.07 (1 H, d, *J* 8.5); δ_C 28.3, 35.6, 52.1, 54.3, 79.9, 123.6,

(54) Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.; Mizuno, Y.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, 1063−1066.

(55) Tokutake, S.; Imanishi, Y.; Sisido, M. *Mol. Cryst. Liq. Cryst.* **1989**, *170*, 245−257.

125.6, 125.7, 126.3, 127.4, 127.9, 128.8, 132.2, 132.5, 133.9, 155.0, 172.6. *m*/*z* 329 (M^+, 1%).

Preparation of Protected Homophenylalanines (7). General Procedure. Zinc dust (325 mesh, 0.40 g, 6.0 mmol) was placed in a nitrogen-purged flask. Dry DMF (0.45 mL) and 1,2-dibromoethane (25.9 μL, 0.3 mmol) were added, and the flask was heated at 60 °C for 30 min using a hot water bath. The mixture was allowed to cool to room temperature, trimethylsilyl chloride (8.0 μL, 0.06 mmol) was added, and the resulting mixture was stirred vigorously for 30 min. A solution of benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-iodobutanoate **9** (0.42 g, 1.0 mmol) in dry DMF (0.45 mL) was added to the activated zinc. The reaction mixture was heated to 35 °C for 30 min, after which time TLC analysis (5:1 petroleum ether/ethyl acetate) revealed that no starting material remained. The reaction mixture was cooled to room temperature, and then $Pd_2(dba)_3$ (17.3 mg, 0.02 mmol), tri-*o*-tolylphosphine (22.8 mg, 0.08 mmol), and the aromatic iodide (0.75 mmol) were added sequentially. Stirring was continued for 3 h at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL), and the organic layer was washed with brine (3 × 30 mL), dried, and concentrated under reduced pressure to give the crude product as an oil. Purification by flash column chromatography (petroleum ether/ethyl acetate gradient) afforded the pure 4-aryl α-amino acid derivative.

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-4-phenylbutanoate (7a). Treatment with iodobenzene (83.9 μL, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate **7a** as a pale yellow oil which solidified on standing, mp 45−46 °C (0.19 g, 70%). (Found $M^+ - C_4H_8$ 313.1311. $C_{18}H_{19}NO_4$ requires 313.1314). $[\alpha]^{17}_D$ +7.7 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3369, 2978, 1740, 1715. NMR δ_H 1.45 (9H, s), 1.90−1.97 (1H, m), 2.11−2.17 (1H, m), 2.55−2.68 (2H, m), 4.38−4.43 (1H, m), 5.09−5.12 (2H, m), 5.19 (1H, d, *J* 12.2), 7.11 (2H, d, *J* 7.4), 7.18 (1H, t, *J* 7.4), 7.26 (2H, t, *J* 7.4), 7.33−7.37 (5H, m); δ_C 28.3, 31.5, 34.4, 53.4, 67.0, 79.9, 126.1, 128.2, 128.3, 128.4, 128.5, 128.6, 135.3, 140.7, 155.3, 172.5. *m*/*z* (EI) 313 ($M^+ - C_4H_8$, 60%).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-4-(2′-nitrophenyl)butanoate (7b). Treatment with 1-iodo-2-nitrobenzene (0.18 g, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-(2′-nitrophenyl)butanoate **7b** as an orange oil (0.12 g, 40%). (Found $MH^+ - C_4H_8$ 359.1260. $C_{18}H_{19}N_2O_6$ requires 359.1243). $[\alpha]^{17}_D$ +24.5 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3374, 2978, 1740 and 1713, 1610, 1577, 1527, 1500, 1391, 1366, 1349. NMR δ_H 1.46 (9H, s), 2.00−2.04 (1H, m), 2.17−2.23 (1H, m), 2.88−2.93 (2H, m), 4.41−4.45 (1H, m), 5.16−5.19 (2H, m), 5.22 (1H, d, *J* 12.2), 7.34−7.37 (7H, m), 7.49−7.52 (1H, m), 7.92 (1H, d, *J* 8.3); δ_C 28.3, 29.2, 33.5, 53.5, 67.3, 80.1, 124.8, 125.0, 127.4, 128.5, 128.6, 132.2, 133.2, 135.3, 136.1, 149.1, 155.4, 172.1. *m*/*z* (EI) 359 ($MH^+ - C_4H_8$, 1%).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-4-(4′-nitrophenyl)butanoate (7c). Treatment with 1-iodo-4-nitrobenzene (0.18 g, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-(4′-nitrophenyl)butanoate **7c** as an orange oil (0.26 g, 84%). (Found M^+ 414.1793. $C_{22}H_{26}N_2O_6$ requires 414.1791). $[\alpha]^{17}_D$ +10.8 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3379, 2978, 1740, 1714, 1605, 1576, 1520, 1499, 1391, 1367, 1347. NMR δ_H 1.45 (9H, s), 1.92−1.99 (1H, m), 2.14−2.20 (1H, m), 2.63−2.69 (1H, m), 2.72−2.78 (1H, m), 4.38−4.42 (1H, m), 5.11−5.14 (2H, m), 5.24 (1H, d, *J* 12.2), 7.23 (2H, d, *J* 8.6), 7.35−7.38 (5H, m), 8.10 (2H, d, *J* 8.6). δ_C 28.3, 31.4, 33.9, 53.2, 67.3, 80.2, 123.6, 123.7, 128.5, 128.6, 129.2, 135.1, 146.5, 148.6, 155.0, 172.0. *m*/*z* (EI) 414 (M^+, 0.1%), 358 ($M^+ - C_4H_8$, 3).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-4-(2′-methoxyphenyl)butanoate (7d). Treatment with 2-iodoanisole (97.6 μL, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-(2′-methoxyphenyl)butanoate **7d** as a pale orange oil which solidified on standing, mp 51−52 °C (0.22 g, 74%). (Found M^+ 399.2059. $C_{23}H_{29}NO_5$ requires 399.2045). $[\alpha]^{17}_D$ +6.7 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3371, 2975, 1740, 1716, 1589, 1559 1495 1384, 1367. NMR δ_H 1.45 (9H, s), 1.93−1.98 (1H, m), 2.08−2.14 (1H, m), 2.64 (2H, t, *J* 7.8), 3.78 (3H), 4.36−4.40 (1H, m), 5.10 (1H, d, *J* 12.3), 5.14 (1H, d, *J* 12.3), 5.18 (1H, d, *J* 8.3), 6.82 (1H, d, *J* 8.0), 6.84−6.87 (1H, m), 7.04 (1H, dd, *J* 7.3 and 1.5), 7.15−7.19 (1H, m), 7.33−7.36 (5H, m); δ_C 26.2, 28.4, 32.4, 53.6, 55.1, 66.9, 79.7, 110.2, 120.5, 127.5, 128.2, 128.4, 128.6, 129.1, 130.0, 135.5, 155.4, 157.3, 172.6. *m*/*z* (EI) 399 (M^+, 1%), 343 ($M^+ - C_4H_8$, 11).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-4-(4′-methoxyphenyl)butanoate (7e). Treatment with 4-iodoanisole (0.18 g, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-(4′-methoxyphenyl)butanoate **7e** as a yellow oil (0.22 g, 74%). (Found M^+ 399.2048. $C_{23}H_{29}NO_5$ requires 399.2045). $[\alpha]^{19}_D$ +7.2 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3364, 2977, 2835, 1740, 1715. NMR δ_H 1.45 (9H, s), 1.87−1.94 (1H, m), 2.08−2.14 (1H, m), 2.50−2.61 (2H, m), 3.77 (3H), 4.36−4.40 (1H, m), 5.07 (1H, d, *J* 7.7), 5.12 (1H, d, *J* 12.2), 5.19 (1H, d, *J* 12.2), 6.79 (2H, d, *J* 8.6), 7.02 (2H, d, *J* 8.6), 7.34−7.37 (5H, m); δ_C 28.3, 30.6, 34.6, 53.3, 55.2, 67.0, 79.9, 113.9, 128.3, 128.4, 128.6, 129.3, 132.8, 135.4, 155.7, 158.0, 172.5. *m*/*z* (EI) 399 (M^+, 4%), 343 ($M^+ - C_4H_8$, 42).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-4-(4′-methylphenyl)butanoate (7f). Treatment with 4-iodotoluene (0.16 g, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-(4′-methylphenyl)butanoate **7f** as a pale orange oil which solidified on standing, mp 60.5−61.5 °C (0.25 g, 87%). (Found M^+ 383.2099. $C_{23}H_{29}NO_4$ requires 383.2096). $[\alpha]^{17}_D$ +6.9 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3362, 2976, 1740, 1716. NMR δ_H 1.44 (9H, s), 1.88−1.95 (1H, m), 2.09−2.15 (1H, m), 2.30 (3H, s), 2.54−2.62 (2H, m), 4.37−4.41 (1H, m), 5.06 (1H, d, *J* 8.0), 5.12 (1H, d, *J* 12.2), 5.22 (1H, d, *J* 12.2), 7.00 (2H, d, *J* 7.9), 7.07 (2H, d, *J* 7.9), 7.34−7.37 (5H, m); δ_C 21.0, 28.3, 31.1, 34.5, 53.5, 67.1, 79.9, 128.2, 128.3, 128.4, 128.6, 129.1, 135.4, 135.6, 137.6, 155.3, 172.5. *m*/*z* (EI) 383 (M^+, 1%), 327 ($M^+ - C_4H_8$, 19).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-4-naphthylbutanoate (7g). Treatment with 1-iodonaphthalene (109.5 μL, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-naphthylbutanoate **7g** as a pale yellow oil which solidified on standing, mp 84−85 °C (0.28 g, 88%). (Found M^+ 419.2089. $C_{26}H_{29}NO_4$ requires 419.2096). $[\alpha]^{17}_D$ +13.3 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3355, 2977, 1735, 1714. NMR δ_H 1.47 (9H, s), 2.06−2.13 (1H, m), 2.25−2.31 (1H, m), 3.00−3.14 (2H, m), 4.49−4.54 (1H, m), 5.15 (1H, d, *J* 12.2), 5.20 (1H, d, *J* 12.2), 5.22 (1H, d, *J* 8.2), 7.25 (1H, d, *J* 7.0), 7.33−7.37 (6H, m), 7.43−7.47 (2H, m), 7.70 (1H, d, *J* 8.3), 7.82−7.85 (1H, m), 7.87−7.89 (1H, m); δ_C (125 MHz, $CDCl_3$) 28.3, 33.6, 53.6, 60.4, 67.2, 79.1, 123.4, 125.5, 125.9, 126.1, 126.9, 127.0, 128.3, 128.4, 128.5, 128.6, 128.8, 131.6, 133.9, 135.3, 155.3, 172.3. *m*/*z* (EI) 419 (M^+, 2%), 363 ($M^+ - C_4H_8$, 30).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-4-(2′-aminophenyl)butanoate (7h). Treatment with 2-iodoaniline (0.16 g, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-(2′-aminophenyl)butanoate **7h** as a pale yellow oil which solidified on standing, mp 112−113 °C (0.15 g, 53%). (Found M^+ 384.2053. $C_{22}H_{28}N_2O_4$ requires 384.2049). $[\alpha]^{19}_D$ +6.7 (*c* 1.0, CH_2Cl_2). IR (KBr, cm^{-1}) 3435, 3354 2970, 1735 and 1678. NMR δ_H 1.44 (9H, s), 1.93−2.00 (1H, m), 2.12−2.17 (1H, m), 2.41−2.47 (1H, m), 2.50−2.55 (1H, m), 3.56 (2H, s), 4.40−4.45 (1H, m), 5.14 (1H, d, *J* 12.2), 5.19−5.21 (2H, m), 6.64 (1H, dd, *J* 7.6 and 1.2), 6.68−6.71 (1H, m), 6.94 (1H, dd, *J* 7.4 and 1.2), 7.00−7.04 (1H, m), 7.33−7.36 (5H, m); δ_C 26.9, 28.3, 31.7, 53.5, 67.1, 80.0, 115.7, 118.8, 124.9, 127.4, 128.4, 128.5, 128.6, 129.4, 135.3, 144.1, 155.4, 172.4. *m*/*z* (EI) 384 (M^+, 34%), 328 ($M^+ - C_4H_8$, 40).

Preparation of an Authentic Sample of Enantiomerically Pure Benzyl 2-(*S*)-(*tert*-butoxycarbonyl)amino)-4-phenylbutanoate (7a). *N*-(*tert*-Butoxycarbonyl)-(L)-homophenylalanine **25** (0.42 g, 1.5 mmol, purchased from BACHEM in its enantiomerically pure form) was dissolved in dry DMF (3 mL) under nitrogen. Sodium hydrogen carbonate (0.32 g, 3.8 mmol) followed by benzyl bromide (0.54 mL, 4.5 mmol) were added to the reaction mixture, and it was heated at 60 °C for 4 h. The mixture was then allowed to cool to room temperature, and it was diluted with water. The aqueous layer was extracted with ethyl acetate (30 mL), and the organic extract was subsequently washed with water (2 × 50 mL) and brine (50 mL). The organic extract was dried and concentrated under reduced pressure to give an oil which was purified by

flash column chromatography (10:1 petroleum ether/ethyl acetate). This yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)-amino)-4-phenylbutanoate **7a** as a colorless solid, mp 45−46 °C (0.53 g, 96%). $[\alpha]^{16}_D$ +7.7 (*c* 1.0, CH_2Cl_2) [compared with $[\alpha]^{17}_D$ +7.7 (*c* 1.0, CH_2Cl_2) from the sample of **7a** prepared via the palladium-catalyzed cross-coupling reaction]. All other data was consistent with that quoted above.

(*S*)-(2-Oxo-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-3-yl)-carbamic Acid *tert*-Butyl Ester (26). Benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-4-(2′-aminophenyl)butanoate **7h** (0.38 g, 1.0 mmol) was heated at 180 °C for 16 h under an atmosphere of nitrogen. The crude product was allowed to cool and then purification by flash column chromatography (petroleum ether/ethyl acetate gradient) afforded (2-oxo-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-3-yl)carbamic acid *tert*-butyl ester **26** as a colorless crystalline solid, mp 233−235 °C (0.19 g, 68%). (Found M^+ 276.1470. $C_{15}H_{20}N_2O_3$ requires 276.1474). $[\alpha]^{20}_D$ −189.6 (*c* 1.0, MeOH). IR (KBr, cm^{-1}) 3290 3192, 2980, 1719, 1679. NMR δ_H 1.41 (9H, s), 1.96−2.02 (1H, m), 2.62−2.70 (2H, m), 2.90−2.96 (1H, m), 4.27−4.32 (1H, m), 5.53 (1H, d, *J* 7.3), 7.01 (1H, d, *J* 7.3), 7.12−7.15 (1H, m), 7.20−7.23 (2H, m), 8.36 (1H, s); δ_C 28.3, 28.6, 36.7, 50.5, 79.7, 122.5, 126.4, 127.7, 129.8, 134.0, 136.2, 155.1, 173.3. *m*/*z* (EI) 276 (M^+, 1%), 220 ($M^+ - C_4H_8$, 36).

(*S*)-3-Amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one (25). (2-Oxo-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-3-yl)-carbamic acid *tert*-butyl ester **26** (55.3 mg, 0.2 mmol) was dissolved in dry dichloromethane (2 mL) at 0 °C under an atmosphere of nitrogen. Trifluoroacetic acid (TFA) (0.5 mL) was added, and the reaction mixture was stirred for 1.5 h, during which time the temperature was allowed to warm to room temperature. The reaction mixture was concentrated, and the residue was dissolved in water (10 mL). The pH of the aqueous solution was brought up to 10 using solid potassium carbonate, and then the solution was extracted with dichloromethane (4 × 10 mL). The organic extracts were combined, dried, and concentrated. This yielded (*S*)-3-amino-2,3,4,5-tetrahydro-1*H*-[1]-benzazepin-2-one **25** as a pale yellow solid, mp 147−149 °C (22.9 mg, 65%). (Found M^+ 176.0947. $C_{10}H_{12}N_2O$ requires 176.0950). −445.7 (*c* 0.5, MeOH) (lit. value −446 (*c* 1.0, MeOH)).[48] IR (KBr, cm^{-1}) 3355, 3180, 2942, 1684. NMR δ_H 1.75 (2H, br s), 1.90−1.96 (1H, m), 2.48−2.56 (1H, m), 2.63−2.67 (1H, m), 2.88−2.95 (1H, m), 3.45 (1H, br s), 6.99 (1H, d, *J* 7.6), 7.13−7.16 (1H, m), 7.23−7.26 (2H, m), 8.03 (1H, br s); δ_C 29.1, 39.1, 51.5, 122.0, 126.1, 127.6, 129.7, 134.5, 136.6, 177.5. *m*/*z* (EI) 176 (M^+, 37%).

Preparation of 5-Aryl α-Amino Acids (8). General Procedure. Zinc reagent **6** was prepared from iodide **10** in DMF on a 1 mmol scale and then coupled to aryl iodides (0.75 mmol) to give the 5-aryl α-amino acids **8**, in an identical manner to that described above for zinc reagent **5**.

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-5-phenylpentanoate (8a). Treatment with iodobenzene (83.9 μL, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-5-phenylpentanoate **8a** as a yellow oil (0.22 g, 77%). (Found MH^+ 384.2196. $C_{23}H_{30}NO_4$ requires 384.2174). $[\alpha]^{17}_D$ −0.8 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3371, 2977, 1741, 1715. NMR δ_H 1.43 (9H, s), 1.61−1.69 (3H, m), 1.81−1.86 (1H, m), 2.53−2.63 (2H, m), 4.36−4.40 (1H, m), 5.02 (1H, d, *J* 7.6), 5.11 (1H, d, *J* 12.2), 5.18 (1H, d, *J* 12.2), 7.10 (2H, d, *J* 7.3), 7.16 (1H, t, *J* 7.3), 7.24 (2H, t, *J* 7.3), 7.32−7.36 (5H, m); δ_C 26.9, 28.3, 32.2, 35.2, 53.3, 66.9, 79.9, 125.9, 128.2, 128.3, 128.4, 128.5, 128.6, 135.4, 141.6, 155.3, 172.7. *m*/*z* (EI) 384 (*M*H$^+$, 1%), 327 ($M^+ - C_4H_8$, 10).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-5-(2′-nitrophenyl)pentanoate (8b). Treatment with 1-iodo-2-nitrobenzene (0.18 g, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-5-(2′-nitrophenyl)pentanoate **8b** as an orange oil (0.03 g, 10%). (Found $MH^+ - C_4H_8$ 373.1399. $C_{19}H_{21}N_2O_6$ requires 373.1400). $[\alpha]^{18}_D$ −4.0 (*c* 0.5, CH_2Cl_2). IR (film, cm^{-1}) 3378, 2977, 1741, 1713, 1609, 1577, 1526, 1499, 1391, 1366, 1349. NMR δ_H 1.43 (9H, s), 1.62−1.75 (3H, m), 1.89−1.94 (1H, m), 2.81−2.88 (2H, m), 4.37−4.42 (1H, m), 5.06 (1H, d, *J* 8.2), 5.14 (1H, d, *J* 12.2), 5.21 (1H, d, *J* 12.2), 7.25 (1H, dd, *J* 7.6 and 1.5), 7.32−7.37 (6H, m), 7.46−7.49 (1H, m), 7.89 (1H, dd, *J* 8.3 and 1.3); δ_C 26.3, 28.3, 32.3, 32.5, 53.2, 67.1, 79.9, 124.7, 126.8, 127.1, 128.4, 128.6, 131.8, 132.9, 135.3, 136.7, 149.2, 155.3, 172.5. *m*/*z* (EI) 373 (*M*H$^+ - C_4H_8$, 3%).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-5-(4′-nitrophenyl)pentanoate (8c). Treatment with 1-iodo-4-nitrobenzene (0.18 g, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-5-(4′-nitrophenyl)pentanoate **8c** as an orange oil (0.24 g, 75%). (Found MH^+ 429.2022. $C_{23}H_{29}N_2O_6$ requires 429.2022). $[\alpha]^{24}_D$ −1.6 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3390, 2977, 1741, 1713, 1605, 1599, 1519, 1499, 1384, 1367, 1346. NMR δ_H 1.44 (9H, s), 1.58−1.70 (3H, m), 1.83−1.87 (1H, m), 2.63−2.76 (2H, m), 4.39−4.42 (1H, m), 5.07−5.12 (2H, m), 5.21 (1H, d, *J* 12.2), 7.23 (2H, d, *J* 8.6), 7.32−7.36 (5H, m), 8.09 (2H, d, *J* 8.6); δ_C 26.4, 28.2, 32.2, 34.9, 53.0, 67.1, 80.0, 123.6, 128.3, 128.5, 128.6, 129.1, 135.2, 146.4, 149.5, 155.3, 172.3. *m*/*z* (EI) 373 (*M*H$^+ - C_4H_8$, 4%).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-5-(2′-methoxyphenyl)pentanoate (8d). Treatment with 2-iodoanisole (97.6 μL, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-5-(2′-methoxyphenyl)pentanoate **8d** as an orange oil (0.13 g, 42%). (Found M^+ 413.2224. $C_{24}H_{31}NO_5$ requires 413.2202). $[\alpha]^{24}_D$ +1.0 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3379, 2977, 1741, 1715. NMR δ_H 1.43 (9H, s), 1.61−1.67 (3H, m), 1.82−1.89 (1H, m), 2.56−2.64 (2H, m), 3.78 (3H), 4.34−4.39 (1H, m), 5.01 (1H, d, *J* 7.7), 5.12 (1H, d, *J* 12.3), 5.19 (1H, d, *J* 12.3), 6.81−6.86 (2H, m), 7.04 (1H, dd, *J* 6.1 and 1.3), 7.15−7.18 (1H, m), 7.31−7.36 (5H, m); δ_C 25.5, 28.3, 29.5, 32.3, 53.5, 55.2, 66.9, 79.8, 110.2, 120.3, 127.1, 128.2, 128.3, 128.6, 129.2, 129.8, 135.5, 155.3, 157.4, 172.3. *m*/*z* (EI) 413 (M^+, 0.2%), 357 ($M^+ - C_4H_8$, 20).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-5-(4′-methoxyphenyl)pentanoate (8e). Treatment with 4-iodoanisole (0.18 g, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)-amino)-5-(4′-methoxyphenyl)pentanoate **8e** as an orange oil (0.19 g, 62%). (Found M^+ 413.2216. $C_{24}H_{31}NO_5$ requires 413.2202). $[\alpha]^{19}_D$ −1.0 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3372, 2977, 1742, 1714. NMR δ_H 1.43 (9H, s), 1.61−1.66 (3H, m), 1.80−1.84 (1H, m), 2.47−2.59 (2H, m), 3.78 (3H), 4.34−4.39 (1H, m), 5.00 (1H, d, *J* 8.0), 5.12 (1H, d, *J* 12.2), 5.20 (1H, d, *J* 12.2), 6.79 (2H, d, *J* 8.6), 7.02 (2H, d, *J* 8.6), 7.31−7.36 (5H, m); δ_C 27.1, 28.3, 32.2, 34.3, 53.4, 55.3, 66.9, 79.8, 113.8, 128.3, 128.6, 129.2, 129.3, 133.7, 135.4, 155.3, 157.8, 172.7. *m*/*z* (EI) 413 (M^+, 3%), 357 ($M^+ - C_4H_8$, 58).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-5-(4′-methylphenyl)pentanoate (8f). Treatment with 4-iodotoluene (0.16 g, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)-amino)-5-(4′-methylphenyl)pentanoate **8f** as a yellow oil (0.25 g, 84%). (Found $M^+ - C_4H_8$ 341.1623. $C_{20}H_{23}NO_4$ requires 341.1627). $[\alpha]^{17}_D$ −1.5 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3374, 2977, 1741, 1715. NMR δ_H 1.43 (9H, s), 1.61−1.67 (3H, m), 1.81−1.85 (1H, m), 2.30 (3H, s), 2.50−2.60 (2H, m), 4.34−4.38 (1H, m), 5.00 (1H, d, *J* 7.9), 5.12 (1H, d, *J* 12.2), 5.20 (1H, d, *J* 12.2), 6.99 (2H, d, *J* 7.9), 7.05 (2H, d, *J* 7.9), 7.31−7.35 (5H, m); δ_C 21.0, 27.0, 28.3, 32.2, 34.8, 53.3, 66.9, 79.8, 128.2, 128.3, 128.4, 128.6, 129.0, 135.3, 135.4, 138.5, 155.3, 172.7. *m*/*z* (EI) 341 ($M^+ - C_4H_8$, 7%).

Benzyl 2-(*S*)-((*tert*-Butoxycarbonyl)amino)-5-naphthylpentanoate (8g). Treatment with 1-iodonaphthalene (109.5 μL, 0.75 mmol) yielded benzyl 2-(*S*)-((*tert*-butoxycarbonyl)-amino)-5-naphthylpentanoate **8g** as a yellow oil (0.13 g, 41%). (Found M^+ 433.2245. $C_{27}H_{31}NO_4$ requires 433.2253). $[\alpha]^{24}_D$ +0.3 (*c* 1.0, CH_2Cl_2). IR (film, cm^{-1}) 3371, 2977, 1741, 1714. NMR δ_H 1.43 (9H, s), 1.73−1.85 (3H, m), 1.93−1.98 (1H, m), 2.99−3.13 (2H, m), 4.39−4.44 (1H, m), 5.02 (1H, d, *J* 8.0), 5.11 (1H, d, *J* 12.5), 5.17 (1H, d, *J* 12.5), 7.25 (1H, d, *J* 6.1), 7.28−7.36 (6H, m), 7.45−7.49 (2H, m), 7.70 (1H, d, *J* 8.3), 7.82−7.85 (1H, m); 7.96−7.98 (1H, m). δ_C 26.3, 28.3, 32.4, 53.3, 60.5, 67.0, 79.9, 123.7, 125.4, 125.5, 125.8, 126.0, 126.7, 127.0, 128.2, 128.4, 128.6, 128.8, 131.6, 133.9, 135.4, 155.4, 172.7. *m*/*z* (EI) 433 (M^+, 2%), 377 ($M^+ - C_4H_8$, 48).

Benzyl 2-(*S*)-Amino-5-phenylpentanoate *p*-Toluenesulfonate (27). Redistilled trifluoroacetic acid (TFA) (2 mL) was added to a stirred solution of benzyl 2-(*S*)-((*tert*-butoxycarbonyl)amino)-5-phenylpentanoate **8a** (95.8 mg, 0.25 mmol) in dry dichloromethane (2 mL) at − 10 °C under an atmo-

sphere of nitrogen. The cooling bath was removed, and the solution was stirred at room temperature for 1 h, after which time TLC analysis showed that no starting material remained. Concentration under reduced pressure gave an oil which was redissolved in dichloromethane (10 mL). Neutralization by careful addition of a saturated aqueous solution of sodium hydrogen carbonate was carried out, and then the organic layer was further washed with aqueous sodium hydrogen carbonate (3 × 5 mL, 1 M), water (3 × 5 mL), and brine (5 mL). Drying and concentrating under reduced pressure gave an oil which was purified by flash column chromatography (petroleum ether/ethyl acetate gradient). This yielded benzyl 2-(*S*)-amino-5-phenylpentanoate as a straw-colored oil, which was dissolved in ethanol (2 mL), and *p*-toluenesulfonic acid monohydrate (47.5 mg, 0.25 mmol) in ethanol (5 mL) was added to the solution. The mixture was left at room temperature for 16 h, after which time a colorless solid had precipitated. This was filtered and rinsed with cold diethyl ether leaving benzyl 2-(*S*)-amino-5-phenylpentanoate *p*-toluenesulfonate **27** as a colorless crystalline solid, mp 125−126 °C (lit.[51] value mp 125−127 °C) (68.0 mg, 60%). (Found M^+ − TsOH 283.1558. $C_{18}H_{21}NO_2$ requires 283.1572). $[\alpha]^{15}_D$ +1.8 (*c* 1.0, $CHCl_3$). (lit.[51] value $[\alpha]^{20}_D$ +1.6 (*c* 1.0, $CHCl_3$)). IR (KBr, cm^{-1}) 3062, 2937, 1743. NMR δ_H 1.43−1.50 (1H, m), 1.60−1.68 (1H, m), 1.80−1.85 (2H, m), 2.28 (3H, s), 2.34−2.38 (2H, m), 4.01−4.05 (1H, m), 4.94 (1H, d, *J* 12.2), 5.09 (1H, d, *J* 12.2), 6.92 (2H, dd, *J* 7.9 and 1.7), 7.05 (2H, d, *J* 8.0), 7.10−7.28 (8H, m), 7.72 (2H, d, *J* 8.0), 8.26 (3H, s); δ_C 21.3, 26.0, 29.9, 34.9, 53.0, 67.8, 125.8, 126.1, 128.2, 128.3, 128.4, 128.5, 128.5, 128.9, 134.7, 140.6, 140.9, 141.2, 169.3. *m*/*z* (EI) 283 (M^+ − TsOH, 0.5%).

Acknowledgment. We thank Pfizer Central Research (studentship award to R.J.M.), EPSRC (studentship to C.S.D.) and Merck Sharpe and Dohme (CASE award to C.S.D.) for support, and the Nuffield Foundation for a One Year Science Research Fellowship (R.F.W.J). We also thank Dr. N. Wishart for developing the techniques for measuring NMR spectra of amino acid derived zinc reagents, Drs. M.N.S. Hill and Dr. N.H. Rees for recording NMR spectra, and Dr. D. Turner for the initial preparation of substituted phenylalanine derivatives from **14** in THF, and the NMR spectra of racemic **13**.

Supporting Information Available: ^1H and ^{13}C NMR spectra for all compounds (78 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO981133U