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Preparation of enantiomerically pure pyridyl amino acids from serine

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A range of substituted pyridyl amino acids have been prepared by palladium catalysed cross-coupling of serine-derived organozinc reagents with differently substituted halopyridines. Following this procedure a DMAP analogue has been synthesised and used as a building block in the preparation of two related tripeptides, which have been tested as catalysts in the kinetic resolution of *trans*-2-(*N*-acetylamino)cyclohexan-1-ol, resulting in modest enantioselectivity.

Introduction

Pyridylalanines (Fig. 1) and substituted analogues are extremely interesting because of their use as components of bioactive compounds and as chiral building blocks in organic synthesis. They have been studied for several pharmaceutical applications,[1,2] including use as components of anti-inflammatory[3] and antitumour agents.[4] There is therefore an ongoing interest in developing good routes for the synthesis of these compounds. In the last ten years, several approaches to the synthesis of pyridylalanines have been reported, including catalytic asymmetric hydrogenation,[5] enzymatic resolution[6,7] and the use of chiral auxiliaries.[8]

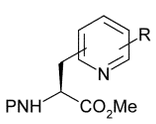


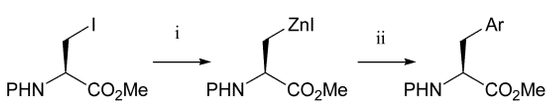
Fig. 1

Some time ago, we reported the synthesis of protected 2-pyridylalanine by the palladium catalysed coupling of a serine-derived organozinc reagent with 2-bromopyridine.[9] The organozinc reagent was prepared from the corresponding iodoalanine-derivative by treatment with a Zn/Cu couple using ultrasonic irradiation. This approach has since been successfully adapted and employed by several groups for the synthesis of other pyridylalanine derivatives,[10–15] and extended to the synthesis of related heterocyclic derivatives.[16,17]

Different groups have commented,[11,19] in short communications, upon the reliability of the methods available for formation of the organozinc reagents needed for these coupling reactions, and given our recent advances in this area,[20–22] we now report, in full, the results of a systematic study of methods for the synthesis of a range of substituted pyridylalanine derivatives. In the context of a study to assess the use of pyridyl amino acids as chiral DMAP analogues,[23–26] we have considered the synthesis of amino-substituted pyridine derivatives, to be used as components of potentially catalytically active peptides.[27] In order to allow maximum flexibility in the incorporation of these pyridyl amino acids into peptides, we have investigated the synthesis of both Fmoc and Boc-protected derivatives.

Results and discussion

The key findings from our work are that proper activation of zinc is essential for efficient formation of zinc reagents from iodoalanine derivatives, and that DMF is an excellent solvent for performing both the insertion reaction and the subsequent coupling.[20] The organozinc reagents were prepared using commercial zinc dust activated sequentially with 1,2-dibromoethane and TMSCl in dry DMF,[28] or with zinc activated using iodine in the absence of solvent. The use of zinc activated with iodine allows complete zinc reagent formation within 2 hours at room temperature, as well as the use of smaller amounts of solvent. Cross-coupling reactions of the zinc reagents **2** with bromopyridine derivatives were performed using bis(triphenylphosphine)palladium dichloride as catalyst, and gave the desired pyridyl amino acid derivatives **3**–**9** in consistent yields ranging from 40 to 60% (Scheme 1, Table 1).



a, P = Fmoc **1** **2** **3 - 9**
b, P = Boc

Scheme 1 *Reagents and conditions:* i, activated Zn; ii $Pd(PPh_3)_2Cl_2$ (5.4 mol%), electrophile, DMF, rt.

The 2- and 4-bromopyridines are better substrates than 3-bromopyridine in this reaction. Compounds **3b**, **4b** and **5b** have been prepared by Walker *et al.*[10] using the same approach and the same trend was observed. Indeed, 2,5-dibromopyridine gave **6**, the product of coupling at the 2-position, with none of the other compounds arising from coupling at the 5-position detected. 2-Amino-6-bromopyridine was successfully employed as an electrophile to give the adducts **8a** and **8b**. Although we had previously demonstrated that anilines can be tolerated in cross-coupling reactions with organozinc reagents,[29] the compatibility with the substantially more acidic 2-aminopyridine is noteworthy. Coupling of **2a** with 2-amino-5-iodopyridine was attempted unsuccessfully. Unfortunately, coupling in position 5, as noted previously, is less favourable than in position 2, even with an iodide rather than a bromide. Finally, hydrolysis of the ester moiety using LiOH[6,30] in a representative number of cases gave the corresponding carboxylic acids **10**–**13**.

Coupling of 2,6-dibromopyridine with 1 equivalent of either zinc reagent **2a** or **2b** gave the corresponding mono-coupled products, **7a** and **7b** as the only products isolated, while treatment of 2,6-dibromopyridine with an excess of zinc reagent **15** (derived from iodoalanine **14**)[31] did give the expected dicoupled product **16** (10%), along with the mono-coupled product **17** (30%) (Scheme 2). This result suggests that bromopyridylalanines might be useful as starting materials for further palladium-catalysed coupling reactions.

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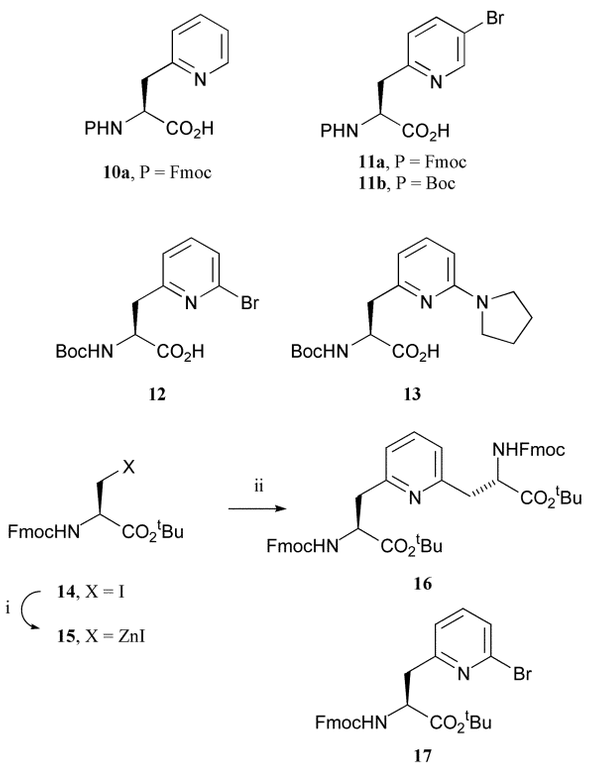
Table 1 Preparation of pyridylalanines

Electrophile	Zinc reagent	Product	Ar	Protecting group	Yield (%)
2-Bromopyridine	**2a**	**3a**[a]	2-Pyridyl	Fmoc	57
3-Bromopyridine	**2a**	**4a**	3-Pyridyl	Fmoc	45
4-Bromopyridine	**2a**	**5a**	4-Pyridyl	Fmoc	57
2,5-Dibromopyridine	**2a**	**6a**	5-Bromo-2-pyridyl	Fmoc	60
2,5-Dibromopyridine	**2b**	**6b**	5-Bromo-2-pyridyl	Boc	45
2,6-Dibromopyridine	**2a**	**7a**	6-Bromo-2-pyridyl	Fmoc	57
2,6-Dibromopyridine	**2b**	**7b**	6-Bromo-2-pyridyl	Boc	52
2-Amino-6-bromopyridine	**2a**	**8a**	6-Amino-2-pyridyl	Fmoc	56
2-Amino-6-bromopyridine	**2b**	**8b**	6-Amino-2-pyridyl	Boc	40
2-Bromo-6-pyrrolidinopyridine	**2b**[b]	**9b**	6-Pyrrolidino-2-pyridyl	Boc	50

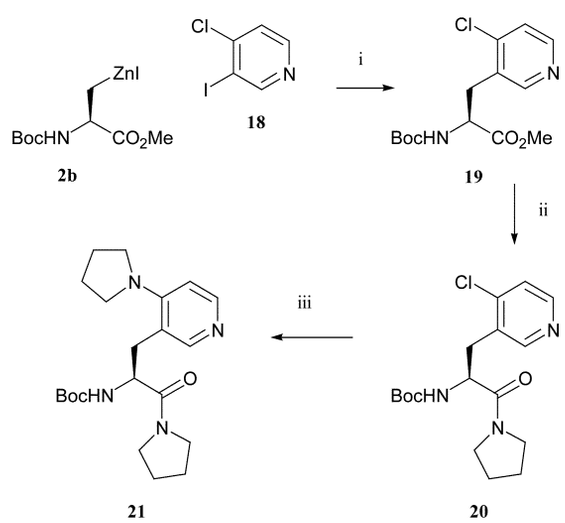
[a] The X-ray crystal structure of this compound has been determined.[18] [b] Iodine activation of zinc.



Scheme 2 *Reagents and conditions:* i, activated Zn; ii $Pd(PPh_3)_2Cl_2$, 2,6-dibromopyridine, DMF, rt.

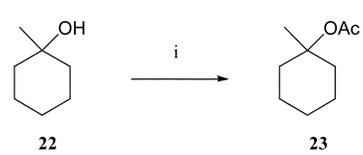
Preparation of a DMAP analogue

While the 2-pyrrolidinopyridine **9b** is a potential acylation catalyst, it is known that introduction of substituents in the 2- and 6-positions of DMAP analogues results in a very substantial decrease in their activity as catalysts in acylation reactions. We therefore identified the 4-chloropyridine derivative **19** as a suitable precursor of a DMAP analogue. The chloropyridine **19** could, in principle, be prepared from 3-iodo-4-chloropyridine **18**, although the failure of the coupling reaction between zinc reagent **2a** and 2-amino-5-iodopyridine was a cause for concern. 3-Iodo-4-chloropyridine **18** was prepared using a modification of a known procedure,[32] in which the hydrochloride salt of 4-chloropyridine was treated directly with 2 equivalents of LDA at low temperature, followed by quenching with iodine. This modification obviated the need to isolate volatile, easily polymerisable 4-chloropyridine. Coupling of zinc reagent **2b** with **18** gave the desired product **19** after overnight reaction at 40 °C using $Pd(PPh_3)_2Cl_2$ as catalyst, albeit in very poor yield (20%) (Scheme 3). Efforts to improve the yield of this coupling using more reactive palladium catalysts (including $(^tBu_3P)_2Pd$ and the combination of 2-($^tBu_2P$)biphenyl with $Pd(OAc)_2$) proved even less effective, so this is not a problem relating to the activity of the catalyst. We established that one of the reasons for the low yield was that the electrophile **18** was not stable to the reaction conditions, and that a substantial amount of 4-chloropyridine was recovered from the reaction mixture.† By the simple expedient of adding a second equivalent of electrophile to the reaction, the yield of **19** could be significantly improved (36%). The replacement of chloride was performed by refluxing a solution of **19** in pyrrolidine, which initially gave the amide **20**, which was subsequently converted into the 4-pyrrolidinopyridine **21** on further reaction (47%). While this compound had a substantial optical rotation, we have not been able to determine whether any racemisation occurred in its formation. The higher reactivity of the methyl ester function towards pyrrolidine means that a different protecting group regime would be required if the free amino acid corresponding to the DMAP-analogue **21** is required.



Scheme 3 *Reagents and conditions:* i, $Pd(PPh_3)_2Cl_2$, DMF, rt; ii, pyrrolidine, reflux, 3 h; iii, pyrrolidine, reflux, 3 d.

Since our purpose was to use this residue as building block, we checked the catalytic activity of **21** as a nucleophilic catalyst. As a test reaction we chose the acetylation of 1-methylcyclohexanol **22** to give **23** (Scheme 4). Acetylation of **22** occurs in the presence of DMAP but not of pyridine.[24] GC analyses after 24 hours indicated 79% conversion. As expected, compound **9b** under the same conditions only gave rise to traces of the acetylated product.

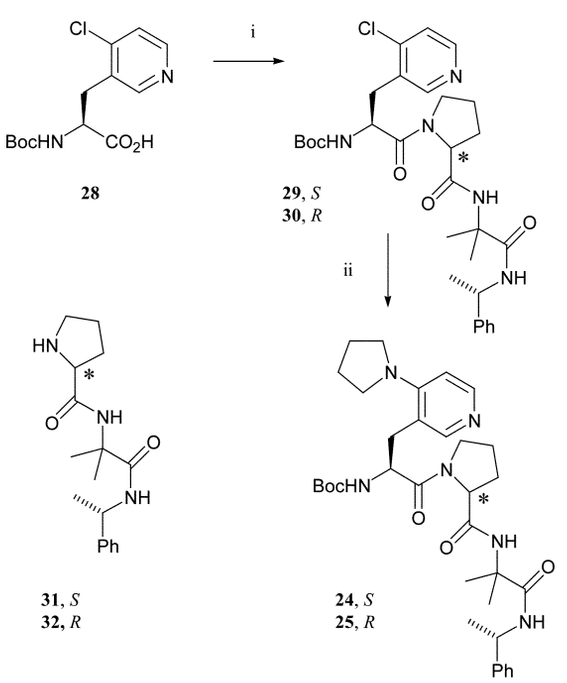


Scheme 4 *Reagents and conditions:* i, Ac_2O, Catalyst **21** or **9b**, NEt_3, rt.

† The synthesis of pyridylzinc halides by oxidative addition of active zinc to halopyridines has been reported,[41] so we suspect that this is the cause.

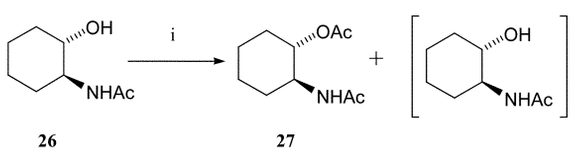
Synthesis of catalysts for kinetic resolution

In the last ten years there has been growing interest in developing asymmetric nucleophilic catalysts. A particularly relevant approach was the tripeptidic system developed by Miller and co-workers.[33–36] Their design involves a catalytically active residue, 3-imidazoylalanine, at the *N*-terminus. We have therefore synthesised analogues of Miller's catalyst, **24** and **25**, in which the *N*-terminal amino acid was replaced with our DMAP analogue precursor **28**. The tripeptide **29** was synthesised using standard peptide solution coupling conditions, and then treatment with pyrrolidine gave the desired tripeptide **24** (Scheme 5). This strategy overcame the problem that we had not prepared the free carboxylic acid corresponding to the DMAP amide derivative **21**. Tripeptide **25**, where L-proline was replaced by D-proline, was also synthesised following the same procedure. The overall isolated yields of both **24** and **25** were each around 40%, and while there was no evidence for the presence of diastereoisomers in these reactions, we cannot exclude the possibility that some epimerisation of the compound occurred under the conditions of the pyrrolidine displacement reaction. What is clear, however, is that products **24** and **25** are diastereoisomerically pure, as judged by their NMR data, and that they are therefore also enantiomerically pure since they each contain one nonlabile stereogenic centre (in the methylbenzylamine fragment).



Scheme 5 *Reagents and conditions:* i, EDCI (1.1 eq.), HOBt (1.1 eq.), **31** or **32**, DMF, rt; ii, pyrrolidine, reflux, 3 d.

Both **24** and **25** were tested as asymmetric catalysts in the kinetic resolution of racemic *trans*-aminoacetyl-2-cyclohexanol **26**, with formation of the acetylated product **27**, since this was the process which Miller and co-workers investigated. Catalyst **24** gave 50% yield (based on the amount of acetic anhydride) and 41% ee when used at a level of 0.5 mol% under the conditions reported in Scheme 6. No enantiomeric excess was observed by using 1 eq of acetic anhydride and lowering the temperature to −50 °C. Catalyst **25** under the same conditions shown in Scheme 6 gave 100% yield and no ee. Complete conversion was also observed by reducing the temperature to −78 °C. Our interpretation of these data is that the DMAP residue confers too great a catalytic activity upon the tripeptides under the conditions under which they have been tested, with the result that the catalysts show low selectivity.



Scheme 6 *Reagents and conditions:* i, **24** (0.5 mol%), Ac_2O (0.1 eq), 0 °C.

Conclusions

Our approach to the synthesis of pyridyl amino acids has proved to be efficient and reliable. Cross coupling with a particularly unreactive electrophile has been investigated and the DMAP analogue precursor **19** was obtained, albeit in modest yield. This residue has shown very good activity as a nucleophilic catalyst.

Experimental

Unless otherwise stated, NMR spectra were obtained at room temperature on either a Bruker WP200 (200 MHz), a Jeol Lambda 500 (500 MHz) or a Bruker AMX 2–400 NMR spectrometer (400 MHz). Coupling constants are quoted in Hertz and chemical shifts in ppm. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 and at 500 MHz, reference TMS. ^{13}C NMR spectra were recorded in $CDCl_3$ at 125 and 100 MHz and referenced to TMS. Mass spectra were obtained using a micromass Autospec M machine or a Micromass LCT. Peaks due to ^{79}Br and ^{35}Cl only are recorded. Infrared spectra were measured on a Nicolet 20 SX instrument or on a Paragon 1000. Elemental analyses were performed using a Carlo Erba 1106 machine or a Perkin Elmer 2400 CHN Elemental Analyser. Melting points were determined on an Agar 600C Heating Stage used in conjunction with a B300 Prior Laboratory Microscope. A polAAr 2001 instrument or an AA-10 from Optical Activity Ltd at room temperature was used for obtaining $[a]_D$ readings. Optical rotations are given in 10^{-1} deg cm^2 g^{-1}. Chiral phase HPLC was carried out on a Beckman System Gold machine attached to a 166 detector, 127 solvent module and 507 autosampler using a Daicel OD (0.46 cm ϕ × 25 cm) chiral column. Chiral phase GC was carried out on a heptakis (2,6-di-*O*-methyl-3-*O*-pentyl)-*β*-cyclodextrin chiral GC column using a Perkin-Elmer 8500 gas chromatograph, with H_2 as carrier gas at 15 psi. All reaction solvents were distilled. Petroleum ether refers to the fraction with a boiling point from 40–60 °C. Dry DMF, toluene and dichloromethane were distilled from calcium hydride. DMF and toluene were stored over 4 Å molecular sieves. Dry THF was distilled from potassium benzophenone ketyl. TMSCl was distilled from and stored over poly(2-vinylpyridine). TsCl was purified by recrystallisation from chloroform–petroleum. TLC was performed using Merck silica gel 60 F254 aluminium backed plates, and were visualised under UV light first, then by using a ninhydrin solution (approx. 0.1% w/v in ethanol) followed by warming. Flash chromatography was performed on BDH silica gel, 0.2–0.5 mm, 30–70 mesh. All organic extracts were dried using magnesium sulfate and concentrated under reduced pressure by rotary evaporation. All reactions requiring anhydrous conditions were conducted under a positive nitrogen atmosphere in oven-dried glassware using standard syringe techniques. *N*-(Fluorenylmethoxycarbonylamino)-3-iodo-propionic acid *t*-butyl ester **14** was prepared according to a known procedure.[31] 4-Bromopyridine,[37] 2-amino-6-bromopyridine,[38] and 2-bromo-6-pyrrolidinopyridine[39] were prepared by literature methods. Dipeptides **31** and **32** were prepared by standard methods.

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-*para*-toluenesulfonatepropionic acid methyl ester

Fmoc-serine methyl ester (10 g, 29.3 mmol) was dissolved in pyridine (100 cm^3) and cooled to −5 °C. *para*-Toluenesulfonyl

chloride (11.16 g, 58.58 mmol), freshly recrystallised from toluene–petroleum, was added to the solution. The reaction mixture was left overnight and then poured into ice–water and the aqueous mixture was extracted into ethyl acetate (50 cm^3). The organic layer was washed with 1 M citric acid (3 × 30 cm^3), saturated sodium bicarbonate (2 × 30 cm^3), brine (30 cm^3), 1 M hydrochloric acid (2 × 20 cm^3), saturated sodium bicarbonate (2 × 20 cm^3) and brine (3 × 20 cm^3). The organic extracts were finally dried, filtered, and concentrated under reduced pressure. The compound crystallised when ether was added. The tosylate was recrystallised from ethanol–petroleum and white crystals were obtained (13.6 g, 27.45 mmol, 94%); mp 125–127 °C; $[\alpha]_D$ +17.6 (*c* 1 in CH_2Cl_2); found C 62.7%, H 5.1, N 2.8, $C_{26}H_{25}NO_7S$ requires C 62.9%, H 5.0, N 2.8; ν_{max} (KBr disc)/cm^{-1}: 3450, 3050, 2950, 1720, 1350, 1160; δ_H (125 MHz, $CDCl_3$) 7.77 (2H, d, *J* 7.5), 7.75 (2H, d, *J* 8.0), 7.59 (2H, t, *J* 8.0), 7.46–7.39 (2H, m), 7.32 (2H, t, *J* 7.0), 7.27 (2H, d, *J* 8.0), 5.62 (1H, d, *J* 7.5), 4.56–4.60 (1H, m), 4.44 (1H, dd, J_{AX} 5.5, J_{AB} 10.5), 4.37–4.33 (2H, m), 4.27 (1H, dd, J_{BX} 4.5, J_{AB} 10.5), 4.18 (1H, t, *J* 7.5), 3.73 (3H, s), 2.36 (3H, s); δ_C (500 MHz, $CDCl_3$) 168.6, 155.5, 145.2, 143.7, 143.6, 141.3, 132.2, 129.9, 128.0, 127.8, 127.1, 125.2, 120.0, 67.5, 53.3, 53.1, 46.9, 21.6; *m*/*z* (EI) 495 (M^+, 35%), 436 (23), 178 (100) 59 (35).

(2*R*)-(*N*-Fluorenylmethoxycarbonylamino)-3-iodopropionic acid methyl ester 1a

A solution of sodium iodide (8.16 g, 54.4 mmol) in acetone (25 cm^3) was added dropwise to a solution of the tosylate (13.5 g, 27.2 mmol) prepared above in acetone (55 cm^3), under nitrogen. The resulting yellow solution was stirred overnight, at room temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The gum was taken up with chloroform (150 cm^3), washed with water (3 × 80 cm^3), sodium thiosulfate (2 × 50 cm^3) and brine (2 × 50 cm^3). The organic layer was dried, filtered and concentrated under reduced pressure to give a pale-yellow solid. The iodide **1a** was recrystallised from ethanol–petroleum ether to give white crystals, (11.3 g, 92 %); mp 153–154 °C (from ethanol–petroleum); $[\alpha]_D$ +5.2 (*c* 1 in ethyl acetate); found C 50.6%, H 3.7, N 3.0, $C_{19}H_{18}NO_4I$ requires C 50.5%, H 4.0, N 3.1; ν_{max} (KBr disc)/cm^{-1} 3316, 3053, 2944, 1736, 1691, 1537, 1278, 739; δ_H (500 MHz, $CDCl_3$) 7.77 (2H, d, *J* 7.5), 7.62 (2H, d, *J* 7.5), 7.41 (2H, t, *J* 7.5), 7.35–7.32 (2H, m), 5.66 (1H, d, *J* 7.0), 4.65–4.56 (1H, m), 4.45–4.36 (2H, m), 4.25 (1H, t, *J* 7.5), 3.83 (3H, s), 3.62–3.59 (2H, m); δ_C (125 MHz, $CDCl_3$) 169.8, 155.5, 143.7, 141.1, 127.9, 127.2, 125.2, 120.2, 67.5, 54.2, 53.3, 47.2, 7.49; *m*/*z* (EI) 451 (M^+, 45%), 392 (35), 323 (30), 228 (27), 178 (100), 165 (80), 59 (30).

General procedure A for zinc insertion:

Zinc dust (0.27 g, 4.2 mmol, 6 eq.), was weighed into a 50 cm^3 flask with side arm. The flask was heated, then evacuated and flushed with nitrogen 3 times. Dry DMF (0.5 cm^3) and 1,2-dibromoethane (18 µl, 0.21 mmol, 0.3 eq.) were added, and the mixture was heated on a hot water bath (90 °C) with vigorous stirring for 30 min. The reaction mixture was allowed to cool to room temperature. Trimethylsilylchloride (5 µl, 0.042 mmol, 0.06 eq.) was added to the mixture which was allowed to stir for a further 30 min. The iodide **1a**,**b** (0.7 mmol, 1 eq.) was dissolved in dry DMF (0.9 cm^3), and transferred *via* syringe to the reaction mixture, which was then heated to 35 °C. Monitoring the reaction by TLC, petroleum–ethyl acetate, 2 : 1, typically showed complete consumption of starting material after 2 h.

General procedure B for zinc insertion:

Zinc dust (2 eq.) was weighed into a 50 cm^3 flask with side arm. Iodine (0.03 eq.) was added. The flask was evacuated, heated with a heat gun and flushed with nitrogen 3 times. The iodide derivative (1 eq.) was dissolved in dry DMF (1.3 cm^3 $mmol^{-1}$) and transferred *via* syringe to the reaction mixture, which was previously cooled to 0 °C. Monitoring the reaction by TLC, petroleum ether–ethyl acetate, 2 : 1, typically showed complete consumption of the starting material after 90 min.

Palladium-catalysed cross coupling procedure C:

The ice bath was removed and the electrophile (1.33 eq.) was added to the flask, followed by bis(triphenylphosphine)-palladium(II) dichloride (0.054 eq.). The reaction was heated at different temperatures and periods depending on the electrophile and then allowed to cool to room temperature. The mixture was diluted with ethyl acetate, washed with water and brine and dried. Flash column chromatography on silica gel, with an appropriate petroleum–ethyl acetate gradient, furnished the expected protected pyridyl α-amino acid.

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-(pyrid-2′-yl)propionic acid methyl ester 3a

Coupling of zinc reagent **2a**, prepared from iodide **1a** (0.31 g, 0.7 mmol) using procedure A, with 2-bromopyridine (89 µl, 0.9 mmol) using procedure C, gave **3a** (0.16 g, 57%) as colourless crystals; mp 98–100 °C (from ethanol–petroleum); $[\alpha]_D$ +16.3 (*c* 1 in CH_2Cl_2); found C 71.8%, H 5.4, N 6.7, $C_{24}H_{22}N_2O_4$ requires C 71.6%, H 5.5, N 6.9; ν_{max} (cap. film)/cm^{-1} 3337, 3064, 2951, 1722, 1510, 1437, 739; δ_H (500 MHz, $CDCl_3$) 8.49 (1H, d, *J* 4.0), 7.71 (2H, d, *J* 7.5), 7.58–7.54 (3H, m), 7.35 (2H, t, *J* 7.5), 7.27 (2H, t, *J* 7.5), 7.12–7.09 (2H, m), 6.43 (1H, d, *J* 8.0), 4.79–4.75 (1H, m), 4.33 (2H, dd, *J* 3.0, 7.5), 4.20 (1H, t, *J* 7.5), 3.67 (3H, s), 3.34 (1H, dd, J_{AX} 5.0, J_{AB} 15.0), 3.30 (1H, dd, J_{BX} 6.0, J_{AB} 15.0); δ_C (125 MHz, $CDCl_3$) 173.4, 158.5, 157.5, 150.6, 145.3, 142.7, 138.0, 129.0, 128.4, 126.6, 125.1, 123.3, 121.3, 68.5, 54.9, 53.7, 48.6, 40.4; *m*/*z* (EI) 402 (M^+, 17%), 343 (11), 238 (38), 207 (39), 196 (69), 178 (100), 165 (31).

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-(pyrid-3′-yl)-propionic acid methyl ester 4a

Coupling of zinc reagent **2a**, prepared from iodide **1a** (0.31 g, 0.7 mmol) using procedure A, with 3-bromopyridine (91 µl, 0.9 mmol) using procedure C, gave **4a** (0.13 g, 45%) as pale yellow solid; mp 40–43 °C; $[\alpha]_D$ +20.6 (*c* 1 in CH_2Cl_2); ν_{max} (KBr disc)/cm^{-1} 3309, 3036, 2949, 1717, 1532, 740; δ_H (500 MHz, $CDCl_3$) 8.50 (1H, s), 8.38 (1H, s), 7.77 (2H, d, *J* 7.3), 7.57–7.53 (2H, m), 7.41–7.38 (3H, m), 7.33–7.30 (2H, m), 7.21 (1H, t, *J* 7.0), 5.34 (1H, d, *J* 7.5), 4.67 (1H, d, *J* 7.0), 4.45 (1H, t, *J* 7.0), 4.38 (1H, t, *J* 7.0), 4.20 (1H, t, *J* 7.0), 3.74 (3H, s), 3.16 (1H, dd, J_{AX} 6.0, J_{AB} 14.0), 3.08 (1H, dd, J_{BX} 5.0, J_{AB} 14.0); δ_C (125 MHz, $CDCl_3$) 171.5, 155.5, 150.4, 148.6, 143.6, 141.3, 136.8, 132.1, 128.5, 127.1, 125.0, 123.4, 120.2, 67.0, 54.5, 52.6, 47.1, 35.5; *m*/*z* (EI) 402 (M^+, 52%), 178 (100), 165 (12), 93 (20). Acc. Mass. calcd for $C_{24}H_{22}N_2O_4^+$ requires *m*/*z* 402.1579. Found 402.1566.

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-(pyrid-4′-yl)-propionic acid methyl ester 5a

Coupling of zinc reagent **2a**, prepared from iodide **1a** (0.31 g, 0.7 mmol) using procedure A, with 4-bromopyridine (0.15 g, 0.9 mmol) using procedure C gave **5a** (0.16 g, 57%) as a white foam; mp 54–56 °C; $[\alpha]_D$ +24.4 (*c* 1 in CH_2Cl_2); ν_{max} (KBr disc)/cm^{-1} 3326, 3036, 2950, 1719, 1603, 1215, 741; δ_H (500 MHz, $CDCl_3$) 8.50 (2H, s), 7.77 (2H, d, *J* 7.5), 7.56 (2H, d, *J* 7.5), 7.41 (2H, t, *J* 7.5), 7.31 (2H, t, *J* 7.5), 7.01–7.00 (2H, m), 5.29 (1H, d, *J* 7.5), 4.69 (1H, dd, J_{AX} 6.0, J_{BX} 5.0), 4.50 (1H, dd, *J* 7.0, 11.0), 4.40 (1H, dd, *J* 6.0, 11.0), 4.20 (1H, t, *J* 6.5), 3.74 (3H, s), 3.15 (1H, dd, J_{AX} 6.0, J_{AB} 14.0), 3.05 (1H, dd, J_{BX} 5.0, J_{AB} 14.0); δ_C (125 MHz, $CDCl_3$) 171.2, 155.4, 149.7, 143.7, 141.4, 132.1, 127.8, 127.0, 125.0, 124.9, 124.6, 120.0, 66.9, 54.0, 52.6, 47.2, 37.6; *m*/*z* (EI) 402 (M^+, 68%), 343 (12), 277 (78), 196 (92), 178

(100), 165 (18). Acc.Mass calcd for $C_{24}H_{22}N_2O_4^+$ requires *m/z* 402.1579. Found 402.1564.

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-(5′-bromopyrid-2′-yl)propionic acid methyl ester 6a

Coupling of zinc reagent **2a** (0.31 g, 0.7 mmol), prepared from iodide **1a** (0.31 g, 0.7 mmol) using procedure A, with 2,5-dibromopyridine (0.22 g, 0.9 mmol) using procedure C, gave **6a** (0.20 g, 60%), as a yellow solid; mp 99–101 °C; $[\alpha]_D$ +22.5 (*c* 1 in CH_2Cl_2); found C 60.1%, H 4.1, N 5.8, $C_{24}H_{21}N_2O_4Br$ requires C 59.9%, H 4.4, N 5.8; ν_{max} (cap. film)/cm^{-1} 3333, 3064, 2951, 1721, 1516, 1450, 759, 739; δ_H (500 MHz, $CDCl_3$) 8.58 (1H, s), 7.76–7.73 (3H, m), 7.57 (2H, t, *J* 7.5), 7.40 (2H, t, *J* 7.5), 7.30 (2H, t, *J* 7.5), 7.03 (1H, d, *J* 8.0), 6.04 (1H, d, *J* 7.5), 4.78–4.74 (1H, m), 4.37 (2H, d, *J* 7.0), 4.22 (1H, t, *J* 7.0), 3.72 (3H, s), 3.34 (1H, dd, J_{AX} 5.5, J_{AB} 15.0), 3.29 (1H, dd, J_{BX} 4.5, J_{AB} 15.0); δ_C (125 MHz, $CDCl_3$) 172.1, 155.7, 155.0, 150.2, 143.9, 141.3, 139.4, 127.7, 127.0, 125.1, 125.1, 119.9, 118.6, 67.1, 53.2, 52.5, 47.2, 38.4; *m/z* (EI) 480 (M$^+$, 20%), 421 (12), 284, (81), 257, (32), 178 (100), 165 (62).

(2*S*)-(*N*-*tert*-Butoxycarbonylamino)-3-(5′-bromopyrid-2′-yl)-propionic acid methyl ester 6b

Coupling of zinc reagent **2b**, prepared from iodide **1b** (0.46 g, 1.4 mmol) using procedure A, with 2,5-dibromopyridine (0.44 g, 1.8 mmol) using procedure C, gave **6b** (0.27 g, 54%) as a yellow oil; found C 46.5%, H 5.4, N 7.5, $C_{14}H_{19}N_2O_4Br$ requires C 46.8%, H 5.3, N 7.8; ν_{max} (cap. film)/cm^{-1} 3369, 2977, 2953, 1746, 1714, 1501, 1366, 861, 632; δ_H (500 MHz, $CDCl_3$) 8.56 (1H, s), 7.73 (1H, dd, *J* 8.0, 2.0), 7.06 (1H, d, *J* 8.0), 5.73 (1H, d, *J* 8.0), 4.71–4.66 (1H, m), 3.70 (3H, s), 3.28 (1H, dd, J_{AX} 6.0, J_{AB} 14.5), 3.24 (1H, dd, J_{BX} 5.0, J_{AB} 14.5), 1.42 (9H, s); δ_C (125 MHz, $CDCl_3$) 172.1, 155.7, 155.3, 150.2, 139.0, 125.0, 118.9, 79.8, 52.7, 52.3, 38.8, 28.3; *m/z* (EI) 358 (M$^+$, 30%), 302 (46), 284 (55), 171 (35), 57 (100).

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-(6′-bromopyrid-2′-yl)propionic acid methyl ester 7a

Coupling of zinc reagent **2a** (0.31 g, 0.7 mmol), prepared from iodide **1a** (0.31 g, 0.7 mmol) using procedure A, with 2,6-dibromopyridine (0.22 g, 0.9 mmol) using procedure C, gave **7a** (0.19 g, 57%) as a yellow solid; mp 97–99 °C (from ethanol–petroleum); $[\alpha]_D$ +32.2 (*c* 1 in CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 3339, 3064, 2950, 1732, 1555, 1437, 759, 739; δ_H (500 MHz, $CDCl_3$) 7.74 (2H, d, *J* 7.5), 7.58 (2H, dd, *J* 7.5, 14.0), 7.43 (2H, t, *J* 7.5), 7.38 (2H, t, *J* 7.5), 7.34 (1H, d, *J* 8.0), 7.29 (1H, app t, *J* 7.5), 7.06 (1H, d, *J* 7.5), 5.99 (1H, d, *J* 8.0), 4.75–4.71 (1H, m), 4.35 (2H, d, *J* 7.0), 4.21 (1H, t, *J* 7.0), 3.75 (3H, s), 3.32–3.30 (2H, m); δ_C (125 MHz, $CDCl_3$) 171.6, 158.2, 155.8, 143.8, 143.7, 138.9, 127.6, 127.0, 126.3, 125.1, 122.6, 119.9, 67.0, 53.3, 52.5, 47.0, 38.7; *m/z* (EI) 480 (M$^+$, 15%), 421 (23), 297 (67), 285 (63), 178 (100). Acc. Mass for *m/z* $C_{24}H_{21}N_2O_4Br$ requires 480.0684. Found 480.0673.

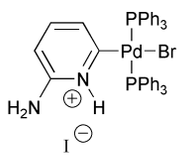
(2*S*)-(*N*-*tert*-Butoxycarbonylamino)-3-(6′-bromopyrid-2′-yl)-propionic acid methyl ester 7b

Coupling of zinc reagent **2b**, prepared from iodide **1b** (0.46 g, 1.4 mmol) using procedure A, with 2,6-dibromopyridine (0.44 g, 1.8 mmol) using procedure C, gave **7b** (0.26 g, 52%) as pale yellow oil; $[\alpha]_D$ −29.7 (*c* 1.65 in acetone); found C 47.0%, H 5.1, N 7.7, $C_{14}H_{19}N_2O_4Br$ requires C 46.8%, H 5.3, N 7.8; ν_{max} (cap film)/cm^{-1} 3365, 2978, 1746, 1715, 1502, 1166; δ_H (500 MHz, $CDCl_3$) 7.48 (1H, app t, *J* 8.0), 7.34 (1H, d, *J* 8.0), 7.12 (1H, d, *J* 7.5), 5.44 (1H, d, *J* 7.5), 4.71–4.63 (1H, m), 3.76 (3H, s), 3.33–3.23 (2H, m), 1.42 (9H, s); δ_C (125 MHz, $CDCl_3$) 172.0, 158.5, 155.2, 141.4, 138.7, 126.2, 122.6, 79.9, 52.9, 52.4, 39.3, 28.2; *m/z* (EI) 359 (MH$^+$, 45%), 285 (35), 259 (55), 199 (80), 171 (55), 57 (100).

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-(6′-aminopyrid-2′-yl)propionic acid methyl ester 8a

Coupling of zinc reagent **2a**, prepared from iodide **1a** (0.62 g, 1.4 mmol) using procedure B, with 2-amino-6-bromopyridine (0.32 g, 1.9 mmol), using procedure C, gave **8a** (0.32 g, 56%) as a yellow solid; mp 47–49 °C; $[\alpha]_D$ +7.6 (*c* 1 in CH_2Cl_2); ν_{max} (KBr disc)/cm^{-1} 3365, 3038, 2949, 1717, 1615, 1464, 1449, 1214, 759, 740; δ_H (500 MHz, $CDCl_3$) 7.75 (2H, d, *J* 7.5), 7.57 (2H, dd, *J* 7.5, 7.5), 7.37 (2H, d, *J* 7.5), 7.29 (2H, d, *J* 7.5), 6.47 (1H, d, *J* 7.5), 6.37 (1H, d, *J* 8.0), 6.33 (1H, d, *J* 7.5), 4.67 (1H, dd, *J* 5.5, 13.0), 4.47 (2H, s), 4.35–4.33 (2H, m), 4.24 (1H, t, *J* 7.5), 3.74 (3H, s), 3.17 (1H, dd, J_{AX} 6.5, J_{AB} 14.5), 3.12 (1H, dd, J_{BX} 5.0, J_{AB} 14.5) (NH obscured); δ_C (125 MHz, $CDCl_3$) 172.1, 157.7, 156.0, 154.8, 144.0, 141.3, 138.6, 127.6, 127.0, 125.2, 120.0, 113.7, 106.9, 67.0, 53.4, 52.3, 47.1, 38.5; *m/z* (EI) 417 (M$^+$, 45%), 358 (25), 239 (40), 196 (21), 178 (100), 165 (12). Acc. Mass calcd for *m/z* $C_{24}H_{23}N_3O_4^+$ requires 417.1688. Found 417.1672

When the dried ethyl acetate extracts were evaporated, crystals were formed which were identified as the pyridyl palladium salt **33** by X-ray crystallography.[40]



33

(2*S*)-(*N*-*tert*-Butyloxycarbonylamino)-3-(6′-aminopyrid-2′-yl)-propionic acid methyl ester 8b

Coupling of zinc reagent **2b**, prepared from iodide **1b** (0.46 g, 1.4 mmol) using procedure A, with 2-amino-6-bromopyridine (0.32 g, 1.9 mmol) using procedure C, gave **8b** (0.16 g, 40%) as a yellow solid; mp 90–92 °C; $[\alpha]_D$ +6.0 (*c* 1 in CH_2Cl_2); found C 57.0%, H 6.9, N 13.9, $C_{14}H_{21}N_3O_4$ requires C 56.9%, H 7.1, N 14.2; ν_{max} (KBr disc)/cm^{-1} 3462, 3358, 2976, 2960, 1745, 1682, 1517, 1504, 1464, 1440, 1243, 1226, 784; δ_H (500 MHz, $CDCl_3$) 7.33–7.27 (1H, m), 6.42 (1H, dd, *J* 2.0, 4.0), 6.33 (1H, dd, *J* 2.0, 8.0), 5.91 (1H, d, *J* 8.0), 4.71–4.63 (2H, br s), 4.61 (1H, app q, *J* 5.0), 3.68 (3H, s), 3.11 (1H, dd, J_{AX} 5.5, J_{AB} 14.0), 3.03 (1H, dd, J_{BX} 4.5, J_{AB} 14.0), 1.42 (9H, s); δ_C (125 MHz, $CDCl_3$) 172.7, 158.2, 155.5, 155.2, 138.2, 113.2, 106.7, 79.6, 53.1, 52.1, 38.9, 28.3; *m/z* (EI) 295 (M$^+$, 16%), 239 (18), 222 (16), 195 (50), 108 (78), 57 (100).

(2*S*)-(*N*-*tert*-Butoxycarbonylamino)-3-(6′-pyrrolidin-1′-yl-pyridine)propionic acid methyl ester 9b

Coupling of zinc reagent **2b**, prepared from iodide **1b** (0.32 g, 1 mmol) using procedure B, with 2-bromo-6-pyrrolydinylpyridine (0.30 g, 1.3 mmol) using procedure C, gave **9** (0.17 g, 50%) as a yellow oil; $[\alpha]_D$ +22 (*c* 1, DCM); ν_{max} (thin film)/cm^{-1} 3339, 2973, 1750, 1715, 1495, 1165; δ_H (500 MHz, $CDCl_3$) 7.30–7.28 (1H, m), 6.87 (1H, d, *J* 7.5), 6.29 (1H, d, *J* 7.5), 6.17 (1H, d, *J* 8.5), 4.47–4.45 (1H, m), 3.55 (3H, s), 3.30–3.27 (4H, m), 3.09 (1H, dd, *J* 15.0, 5.0), 2.94 (1H, dd, *J* 15.0, 4.5), 1.84–1.81 (4H, m), 1.31 (9H, s); δ_C (125 MHz, $CDCl_3$) 172.4, 156.3, 155.6, 155.0, 137.3, 110.4, 104.4, 78.9, 52.8, 51.8, 46.3, 37.7, 28.1, 25.3; *m/z* (EI) 349 (M$^+$, 100%), 276 (37), 234 (89), 190 (42), 162 (60), 57 (97); *m/z* (ES) 350 (MH$^+$, 100%); Acc.Mass. (ES) calcd for $C_{18}H_{27}N_3O_4$+H requires *m/z* 350.2080. Found 350.2070.

General procedure D for hydrolysis of methyl esters:

The amino acid was dissolved in THF–H_2O (3 : 2) (4 cm^3 mmol^{-1}). Two equivalents of LiOH were added and the mixture stirred at rt until TLC indicated complete consumption of the

starting material. The solvent was removed under reduced pressure. Water was added and the solution extracted with ethyl acetate. The aqueous layer was acidified to pH 3 with HCl (0.1 M) and extracted with ethyl acetate. The organic layer was dried and the solvent evaporated under reduced pressure yielding the carboxylic acid.

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-(pyrid-2′-yl)-propionic acid 10a

According to general procedure D, **10a** (0.46 g, 1.2 mmol) was obtained from the methyl ester **3a** (0.80 g, 2 mmol), as a yellow solid in 60% yield; mp 160–162 °C; $[a]_D$ +71.5 (*c* 1 in CH_2Cl_2); found C 70.9%, H 5.2, N 6.9, $C_{23}H_{20}N_2O_4$ requires C 71.1%, H 5.2, N 7.2; ν_{max} (KBr disc)/cm^{-1} 3323, 3036, 2886, 1733, 1698, 1544, 1443, 1260, 738; δ_H (500 MHz, $CDCl_3$) 11.0–10.8 (1H, br s), 8.57 (1H, d, *J* 4.5), 7.78–7.76 (3H, m), 7.61 (2H, d, *J* 7.5), 7.40 (2H, t, *J* 7.5), 7.35–7.30 (3H, m), 7.26 (1H, d, *J* 4.5), 6.05 (1H, d, *J* 6.0), 4.60–4.58 (1H, m), 4.47 (1H, dd, J_{AX} 7.5, J_{AB} 10.5), 4.39 (1H, dd, J_{BX} 7.0, J_{AB} 10.5), 4.23 (1H, app t, *J* 7.0), 3.49–3.45 (2H, m); δ_C (125 MHz, $CDCl_3$) 175.5, 172.7, 155.6, 146.2, 143.7, 141.3, 139.3, 127.7, 127.1, 125.7, 125.1, 123.0, 119.9, 66.8, 53.2, 47.2, 38.1; *m*/*z* (EI) 297 ($M^+ - CH_2$-pyr, 20%), 196 (5), 178 (100), 165 (15), 94 (6).

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-(5′-bromopyrid-2′-yl)propionic acid 11a

According to general procedure D, **11a** (0.79 g, 1.7 mmol) was obtained, from the methyl ester **6a** (0.96 g, 2 mmol), as a yellow solid in 85% yield; mp 219–221 °C, found *M* 466.0497, $C_{23}H_{19}N_2O_4Br$ requires 466.0528; ν_{max} (KBr disc)/cm^{-1} 3321, 3037, 1695, 1421, 838, 757; δ_H (500 MHz, $CDCl_3$) 8.65 (1H, s), 7.85 (1H, d *J* 8.0), 7.78 (2H, d, *J* 7.5), 7.59 (2H, d, *J* 7.5), 7.42 (2H, d, *J* 7.5), 7.33 (2H, t, *J* 7.5), 7.09 (1H, d, *J* 8.0), 5.97–5.90 (1H, br s), 4.62–4.56 (1H, m), 4.48 (1H, dd, *J* 10.5, 7.0), 4.41 (1H, dd, *J* 10.5, 6.5), 4.23 (1H, t, *J* 7.0), 3.40–3.34 (2H, m) (carboxylic acid proton not observed); δ_C (125 MHz, $CDCl_3$) 175.5, 172.7, 155.6, 146.2, 143.7, 141.3, 139.3, 127.7, 127.1, 125.7, 125.1, 123.0, 119.9, 66.8, 52.3, 47.2, 38.1; *m*/*z* (EI) 466 (M^+, 13%), 448 (63), 242 (25), 227 (80), 196 (17), 178 (100), 165 (80).

(2*S*)-(*N*-*tert*-Butyloxycarbonylamino)-3-(5′-bromopyrid-2′-yl)-propionic acid 11b

According to general procedure D, **11b** (0.76, 2.2 mmol) was obtained from the methyl ester **6b** (1 g, 3 mmol), as a yellow solid in 75% yield; mp 165–166 °C, $[a]_D$ −9.0 (*c* 1 in acetone); found C 44.9%, H 4.9, N 7.8, $C_{13}H_{17}N_2O_4Br$ requires C 45.2%, H 5.0, N 8.1; ν_{max} (KBr disc)/cm^{-1} 3378, 2985, 2973, 1737, 1687, 1548, 1165, 650; δ_H (500 MHz, $CDCl_3$) 8.48 (1H, s), 7.74 (1H, d, *J* 7.0), 7.15 (1H, d, *J* 7.0), 6.02–5.98 (1H, br s), 4.48–4.45 (1H, m), 3.29–3.27 (1H, m), 3.20–3.18 (1H, m), 1.35 (9H, s) (carboxylic acid proton not observed); δ_C (125 MHz, $CDCl_3$) 176.6, 156.7, 155.9, 149.5, 140.0, 125.9, 118.9, 80.0, 54.8, 38.9, 28.3; *m*/*z* (EI) 300 (33%), 288 (30), 271 (65), 244 (80), 171 (40), 57 (100).

(2*S*)-(*N*-*tert*-Butyloxycarbonylamino)-3-(6′-bromopyrid-2′-yl)-propionic acid 12

According to general procedure D, **12** (0.61, 1.3 mmol) was obtained from the methyl ester **7b** (0.72 g, 1.5 mmol) as a white solid in 87% yield; mp 156–158 °C; $[a]_D$ −12.0 (*c* 1 in acetone); found C 44.9%, H 4.9, N 7.9, $C_{13}H_{17}N_2O_4Br$ requires C 45.2%, H 4.9, N 7.9; ν_{max} (KBr disc)/cm^{-1} 3330, 2980, 1725, 1686, 1518, 1166; δ_H (500 MHz, $CDCl_3$) 7.58 (1H, app t, *J* 7.5), 7.43 (1H, d, *J* 7.5), 7.27 (1H, d, *J* 7.5), 5.81 (1H, d, *J* 6.0), 4.59–4.56 (1H, m), 3.36–3.26 (2H, m), 1.44 (9H, s); δ_C (125 MHz, $CDCl_3$) 173.3, 158.7, 155.6, 140.4, 140.0, 126.7, 123.1, 80.4, 52.6, 38.9, 28.3; *m*/*z* (EI) 345 (MH^+, 80%), 300 (40), 244 (35), 201, 199 (100), 171 (95), 57 (95).

(2*S*)-(*N*-*tert*-Butoxycarbonylamino)-3-(6′-pyrrolidin-1′-ylpyridine)propionic acid 13

According to general procedure D, **13** (0.28 g, 0.84 mmol) was obtained from the methyl ester **9b** (0.35 g, 1 mmol) as a brown solid in 84% yield. Mp 193–195 °C; $[a]_D$ +95 (*c* 1, $CHCl_3$); found C 59.7%, H 7.7, N 12.1, $C_{17}H_{25}N_3O_4$ requires C 59.9%, H 7.5, N 12.5; ν_{max} (KBr disk)/cm^{-1} 3378, 2976, 2878, 1708, 1629, 1479; δ_H (400 MHz, $CDCl_3$) 7.60–7.58 (1H, m), 6.71 (1H, d, *J* 7.5); 6.45 (1H, d, *J* 9.0), 6.05–6.03 (1H, br s), 4.25–4.23 (1H, m), 3.65–3.50 (4H, m), 3.20–3.18 (2H, m), 2.10–2.0 (4H, m), 1.45 (9H, s) (carboxylic acid proton not observed); δ_C (125 MHz, $CDCl_3$) 174.8, 155.9, 153.4, 152.7, 141.4, 111.8, 108.1, 79.8, 53.1, 48.3, 38.7, 30.1, 25.7; *m*/*z* (ES) 336 (MH^+, 100%), 280 (50).

(2′*S*)-2,6-Bis-[2′-(*N*-Fluorenylmethoxycarbonylamino)-2′-(*tert*-butoxycarbonyl)ethyl]pyridine 16

Coupling of the zinc reagent **15**, prepared from **14** (0.34 g, 0.7 mmol) using general procedure A, with 2,6-dibromopyridine (0.11 g, 0.5 mmol) using procedure C, gave the product **16** (46 mg, 10%) as a yellow solid; mp 73–75 °C; $[a]_D$ +23.8 (*c* 0.5 in CH_2Cl_2); ν_{max} (KBr disc)/cm^{-1} 3341, 3003, 2976, 2932, 1724, 1520, 1222, 1154, 739; δ_H (500 MHz, $CDCl_3$) 7.74 (2H, d, *J* 7.5), 7.67 (4H, t, *J* 7.0), 7.57 (4H, t, *J* 7.5), 7.50–7.45 (2H, m), 7.34–7.27 (4H, m), 7.17 (1H, q, *J* 8.0), 7.00 (2H, d, *J* 8.0), 6.71 (2H, d, *J* 8.5), 4.88–4.85 (2H, m), 4.22–4.13 (4H, m), 4.05 (2H, t, *J* 7.5), 3.38 (2H, dd, J_{AX} 6.5, J_{AB} 15.5), 3.27 (2H, dd, J_{BX} 4.0, J_{AB} 15.5), 1.38 (18H, s); δ_C (125 MHz, $CDCl_3$) 171.2, 157.0, 156.5, 143.9, 141.1, 136.7, 127.7, 127.0, 125.5, 121.8, 119.8, 81.6, 67.1, 53.2, 47.0, 39.9, 28.0; *m*/*z* (EI) 809 (M^+, 18%), 708 (8), 631 (16), 587 (65), 486 (34), 430 (40), 178 (100), 165 (31).

(2*S*)-(*N*-Fluorenylmethoxycarbonylamino)-3-(6′-bromopyrid-2′-yl)propionic acid *tert*-butyl ester 17

Also obtained in the above reaction was product **17** (0.11 g, 30%); mp 49–51 °C; δ_H (500 MHz, $CDCl_3$) 7.76 (2H, d, *J* 7.5), 7.60 (2H, dd, *J* 7.5, 11.5), 7.45 (2H, t, *J* 7.5), 7.39 (2H, t, *J* 7.5), 7.35 (1H, d, *J* 8.5), 7.30 (1H, t, *J* 7.5), 7.10 (1H, d, *J* 7.5), 5.95 (1H, d, *J* 8.0), 4.64–4.60 (1H, m), 4.35 (2H, d, *J* 7.0), 4.22 (1H, t, *J* 7.0), 3.32 (1H, dd, J_{AX} 5.5, J_{AB} 14.5), 3.27 (1H, dd, J_{BX} 5.0, J_{AB} 14.5), 1.42 (9H, s); δ_C (125 MHz, $CDCl_3$) 170.0, 158.7, 155.8, 143.8, 143.7, 141.2, 138.7, 127.6, 127.0, 126.6, 126.2, 122.7, 120.0, 82.4, 66.9, 53.7, 47.1, 39.0, 27.9.

4-Chloro-3-iodopyridine 18

A solution of LDA (13.2 mmol) in dry THF (10 cm^3) was prepared as follows: to a magnetically stirred solution of dry diisopropylamine (1.70 cm^3, 13.2 mmol) in dry THF (4 cm^3) under nitrogen at −78 °C, *n*-BuLi (4.87 cm^3 of solution 2.5 M in hexanes, 13.2 mmol) was added *via* syringe. This solution was stirred at −78 °C for 20 min and then transferred to a suspension of 4-chloropyridine hydrochloride (1 g, 6.6 mmol) in dry THF (2 cm^3) keeping the temperature below −70 °C. The resulting lithiopyridine precipitated as a white solid in an orange solution. The mixture was stirred for 20–30 min at −78 °C and then treated over 10 min with a solution of I_2 (1.67 g, 6.6 mmol) in dry THF (4 cm^3) keeping the internal temperature below −65 °C. The reaction mixture was allowed to warm to r.t. over 4 h, poured into 8% aqueous sodium bisulfite (20 cm^3) and extracted with Et_2O (20 cm^3). The combined organic extracts were washed with 8% aqueous sodium bisulfite (20 cm^3), 5% aqueous sodium hydrogencarbonate (20 cm^3), water (20 cm^3) and brine (20 cm^3), dried and concentrated to yield a dark brown solid. Purification *via* chromatography (eluent: dichloromethane) afforded 0.97 g of **18** (61%). Mp 78–80 °C; found C 25.1%, H 0.9, N 5.8, C_5H_3NClI requires C 25.1%, H 1.2, N 5.8; ν_{max} (KBr disc)/cm^{-1} 3300, 2000–1800, 1550–1430; δ_H (500 MHz, $CDCl_3$) 8.95 (1H, s), 8.43 (1H, d, *J* 5.0), 7.42 (1H,

d, *J* 6.0); δ_C (125 MHz, $CDCl_3$) 158.4, 149.6, 147.9, 124.9, 98.4; *m*/*z* (EI) 239 (M^+, 100%), 112 (43).

(2*S*)-(*N*-*tert*-Butoxycarbonylamino)-3-(4′-chloropyridin-3′-yl)-propionic acid methyl ester 19

Coupling of zinc reagent **2b**, prepared from iodide **1b** (0.2 g, 0.35 mmol) using procedure B, with 4-chloro-3-iodopyridine was carried out using procedure C. After stirring for 16 h at room temp., additional electrophile (0.186 g, 0.78 mmol) was added to give a crude product, which was purified by chromatography (ethyl acetate–petroleum ether: 2 : 1) to give **19** (0.067 g, 36%). $[\alpha]_D$ +11 (*c* 1, $CHCl_3$); ν_{max} (hexachlorobutadiene)/cm^{-1} 3437, 2979, 2953, 1748, 1721, 1688, 1495; δ_H (400 MHz, $CDCl_3$) 8.35–8.33 (2H, m), 7.25 (1H, d, *J* 5.5); 5.25 (1H, d, *J* 8.0), 4.62 (1H, dd, *J* 14.0, 8.0), 3.71 (3H, s), 3.33 (1H, dd, *J* 14.0, 5.5), 3.05 (1H, dd, *J* 14.0, 8.0), 1.33 (9H, s); δ_C (125 MHz, $CDCl_3$) 171.8, 154.8, 155.6, 151.9, 149.1, 144.3, 130.5, 124.4, 80.0, 52.7, 52.5, 37.7, 28.1; *m*/*z* (FAB) 315 (MH^+, 21%), 259 (12), 186 (33), 154 (100), 149 (62), 136 (72). Acc. Mass. (ES) calcd for $C_{14}H_{19}N_2O_4Cl$+H requires *m*/*z* 315.1112. Found 315.1101.

[1(*R*)-(4-Chloropyridin-3-ylmethyl)-2-oxo-2-pyrrolidin-1-ylethyl]carbamic acid *tert*-butyl ester 20

A solution of chloropyridine **19** 0.24 g (0.7 mmol) in pyrrolidine (3 cm^3) was kept at reflux for 3 h. After evaporating the solvent, the residue was recrystallised from ethyl acetate–petroleum ether to give amide **20** (0.17 g, 68%). Mp 138–142 °C; $[\alpha]_D$ −2 (*c* 0.5, $CHCl_3$); found C 57.6%, H 6.8, N 11.8, $C_{17}H_{24}N_3O_3Cl$ requires C 57.8%, H 6.8, N 11.9; ν_{max} (KBr disk)/cm^{-1} 3274, 2977, 1702, 1632; δ_H (400 MHz, $CDCl_3$) 8.36 (1H, s), 8.35 (2H, d, *J* 5.5), 7.23 (1H, d, *J* 5.5), 5.54 (1H, d, *J* 9.0), 4.86–4.84 (1H, m), 3.68–3.18 (4H, m), 3.08–2.97 (1H, dd, *J* 6.0, 13.5), 2.94 (1H, dd, *J* 8.5, 13.5), 2.01–1.88 (4H, m), 1.35 (9H, s); δ_C (125 MHz, $CDCl_3$) 169.1, 154.8, 154.8, 152.3, 149.1, 130.6, 124.2, 79.6, 50.1, 46.4, 45.9, 34.4, 28.1, 25.9, 24.0; *m*/*z* (ES) 354 (MH^+, 100%), 298 (25).

[2-Oxo-2-pyrrolidin-1-yl-1-(4-pyrrolidin-1-yl-pyridin-3-ylmethyl)ethyl]carbamic acid *tert*-butyl ester 21

A solution of chloropyridine **19** (0.24 g, 0.7 mmol) in pyrrolidine (3 cm^3) was kept at reflux for 3 d. After evaporating the solvent, the residue was recrystallised from ethyl acetate–petroleum ether to give the pyrrolidinopyridine **21** (0.12 g, 47%). Mp 153–155 °C; $[\alpha]_D$ −44 (*c* 0.41, MeOH); found C 61.9%, H 8.3, N 13.6, $C_{21}H_{32}N_4O_3$ requires C 62.3%, H 8.3, N 13.9; ν_{max} (KBr disk)/cm^{-1} 3260, 2977, 1695, 1636; δ_H (400 MHz, $CDCl_3$) 8.06 (1H, d, *J* 6.0), 7.95 (1H, s), 6.46 (1H, d, *J* 6.0), 5.47 (1H, d, *J* 9.0), 4.55 (1H, dt, *J* 18.5, 9.0, 5.0), 3.50–3.40 (8H, m), 2.99–2.97 (1H, m), 2.50–2.48 (1H, m), 2.0–1.8 (4H, m), 1.65–1.40 (4H, m), 1.35 (9H, s); δ_C (125 MHz, $CDCl_3$) 169.4, 154.9, 153.5, 151.9, 147.5, 117.2, 108.8, 79.5, 52.0, 50.4, 46.1, 36.5, 36.5, 28.2, 25.7, 25.6, 23.9; *m*/*z* (ES) 389 (MH^+, 100%), 333 (5).

(2*S*)-(*N*-*tert*-Butoxycarbonylamino)-3-(4′-chloropyridin-3′-yl)-propionic acid 28

According to general procedure D, **28** (0.14 g, 0.46 mmol) was obtained from the methyl ester **19** (0.25 g, 0.8 mmol) as a white solid in 58% yield. Mp 146–148 °C; $[\alpha]_D$ −43 (*c* 7.5, MeOH); ν_{max} (KBr disk)/cm^{-1} 3430, 1732, 1684, 1458; δ_H (400 MHz, DMSO) 13.8–13.6 (1H, b), 8.45 (1H, s); 7.68 (1H, d, *J* 5.5), 7.21 (1H, d, *J* 5.5), 7.26 (1H, d, *J* 8.0), 4.18 (1H, m), 3.21–3.18 (1H, dd, *J* 5.0, 14.0), 2.95–2.91 (1H, m), 1.21 (9H, s); δ_C (125 MHz, DMSO) 172.9, 155.4, 152.3, 149.1, 143.0, 131.5, 124.3, 78.2, 52.4, 31.9, 28.1; *m*/*z* (ES) 301 (MH^+, 68%), 279 (23), 247 (17), 245 (100). Acc. Mass. calcd for $C_{13}H_{17}ClN_2O_4$ requires *m*/*z* 301.0940, found 301.0950.

[(*S*)-2-((*S*)-2-{Methyl-1-[1-(*R*)-phenylethylcarbamoyl]ethyl-carbamoyl}pyrrolidin-1-yl)-2-oxo-1-(4-pyrrolidin-1-ylpyridin-3-ylmethyl)ethyl]carbamic acid *tert*-butyl ester 24

Acid **28** (0.11 g, 0.42 mmol) and dipeptide **31** (0.11 g, 0.42 mmol) were dissolved in DMF (5 cm^3) in the presence of *N*-methylmorpholine (0.05 cm^3, 0.42 mmol). HOBt (0.07 g, 0.42 mmol) was added and the solution was cooled to −23 °C. After adding EDCl (0.08 g, 0.42 mmol) the mixture was stirred for 2 h at −23 °C and for 15 h at rt. A saturated solution of $NaHCO_3$ (10 cm^3) was poured into the reaction flask and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine and then dried over $MgSO_4$. After evaporating the solvent under reduced pressure, the crude product was purified *via* chromatography (eluent: AcOEt) to yield peptide **29** (0.12 g, 52%). Peptide **29** (0.05 g, 0.08 mmol) was dissolved in pyrrolidine (2 cm^3) and the solution was kept at reflux for 3 days. After evaporating the solvent, the residue was purified by chromatography (eluent DCM–MeOH: 9 : 1) and the pyrrolidinopyridine **24** (0.021 g, 40%) was obtained. $[\alpha]_D$ +2.8 (*c* 0.36, $CHCl_3$); ν_{max} (KBr)/cm^{-1}3436, 2925, 2953, 1683, 11652, 1639; δ_H (400 MHz, $CDCl_3$) 8.10 (1H, d, *J* 6.0), 7.98 (1H, s); 7.40–7.10 (5H, m), 6.79–6.78 (1H, br s), 6.66 (1H, d, *J* 6.0), 5.25 (1H, m), 5.05 (1H, m), 4.68 (1H, m), 4.05–4.03 (1H, b), 3.70–3.40 (6H, m), 3.12 (1H, dd, *J* 5.5, 14.0), 2.99 (1H, m), 2.05–1.80 (4H, m), 1.51–1.48 (4H, m), 1.43 (3H, d, *J* 7.0), 1.40 (6H, s), 1.35 (9H, s); δ_C (125 MHz, $CDCl_3$) 173.5, 170.8, 155.0, 153.8, 150.9, 146.5, 144.2, 128.3, 126.6, 126.2, 119.9, 109.2, 80.0, 61.3, 57.4, 52.5, 50.6, 48.7, 47.2, 35.6, 28.5, 28.3, 26.4, 25.6, 25.1, 24.8, 21.9; *m*/*z* (ES) 621 (MH^+, 48%), 500 (20), 404 (65), 403 (100), 347 (48); Acc. Mass. calcd for $C_{34}H_{48}N_6O_5$+H requires *m*/*z* 621.3764, found 621.3760.

[(*S*)-2-{(*R*)-2-[Methyl-1-(1-phenylethylcarbamoyl)ethyl-carbamoyl]pyrrolidin-1-yl}-2-oxo-1-(4-pyrrolidin-1-ylpyridin-3-ylmethyl)ethyl]carbamic acid *tert*-butyl ester 25

Acid **28** (0.11 g, 0.42 mmol) and dipeptide **32** (0.10 g, 0.45 mmol) were dissolved in 3 cm^3 of DMF in the presence of *N*-methylmorpholine (0.05 cm^3, 0.45 mmol). HOBt (0.06 g, 0.4 mmol) was added and the solution was cooled to −23 °C. After adding EDCl (0.08 g, 0.38 mmol) the mixture was stirred for 2 h at −23 °C and for 15 h at rt, 10 cm^3 of saturated solution of $NaHCO_3$ were poured into the reaction flask and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine and then dried over $MgSO_4$. After evaporating the solvent under reduced pressure, the crude product was purified *via* chromatography (eluent: AcOEt) to yield peptide **30** (0.09 g, 50%). Peptide **30** (0.04 g, 0.07 mmol) was dissolved in pyrrolidine (2 cm^3) and the solution was kept at reflux for 3 days. After evaporating the solvent, the residue was purified by chromatography (eluent DCM–MeOH: 9 : 1) and the pyrrolidinopyridine **25** (0.02 g, 40%) was obtained. $[\alpha]_D$ −7.7 (*c* 0.26, $CHCl_3$); mp 103–105 °C; ν_{max} (KBr)/cm^{-1} 3436, 2926, 1693, 1686, 1638; δ_H (400 MHz, $CDCl_3$) 8.10 (1H, d, *J* 6.0), 7.98 (1H, s); 7.40–7.20 (5H, m), 6.55 (1H, d, *J* 6.0), 5.47 (1H, d, *J* 8.5), 5.05–5.03 (1H, m), 4.85 (1H, m), 4.20–4.18 (1H, b), 3.65–3.15 (6H, m), 3.12 (1H, dd, *J* 5.5, 14.0), 3.05–3.02 (1H, m), 2.05–1.80 (4H, m), 1.75–1.10 (24H, m); δ_C (125 MHz, $CDCl_3$) 171.3, 169.3, 154.9, 154.1, 150.9, 146.5, 128.3, 126.2, 117.6, 109.2, 79.6, 61.4, 52.0, 50.5, 49.1, 46.5, 45.8, 43.1, 36.8, 28.2, 26.2, 25.6, 25.3, 24.2; *m*/*z* (ES) 644 (MNa^+, 7%), 621 (MH^+, 100), 619 (14). Acc. Mass: $C_{34}H_{48}N_6O_5$+H requires 621.3764, found 621.3756.

General procedure for the determination of the catalytic activity of pyridyl amino acid derivatives

1-Methylcyclohexanol **22** (0.228 g, 2 mmol) was dissolved in toluene (5 cm^3). Triethylamine (0.42 cm^3, 3 mmol) and catalyst (0.08 mmol) were added. Acetic anhydride (0.40 cm^3, 4.2 mmol)

was added. The mixture was stirred for 24 h, after which the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (10 cm^3) and the solution was washed with water (10 cm^3) and 1 M HCl (5 cm^3). After drying, the solvent was removed. The crude product was purified *via* chromatography (eluent: petroleum ether–ethyl acetate: 1 : 1). Two samples were taken during the reaction after 10 and 24 h and their composition was checked by GC. GC conditions: isotherm at 60 °C; retention times: starting material **22** 2.52, product **23** 6.96. δ_H (200 MHz, $CDCl_3$) 2.01 (3H, s), 1.65–1.40 (10H, m), identical to an authentic sample.

Kinetic resolution of trans-*N*-(2-hydroxycyclohexyl)acetamide

Alcohol (±)-**26** (157 mg, 1 mmol) and catalyst **24** (0.0005 mmol) were dissolved in $CHCl_3$ (1 cm^3), and toluene (9 cm^3) was added to produce a white suspension. The reaction mixture was cooled to 0 °C and acetic anhydride (9.4 µl, 0.10 mmol) was then added and the reaction was allowed to stir for 48 h at 0 °C. The reaction mixture was applied directly to a silica gel column. The product was eluted with ethyl acetate to afford acetylated product **27** (10 mg). δ_H (400 MHz, $CDCl_3$) 5.79 (1H, b), 4.60 (1H, dt, *J* 4.4, 10.8), 3.81–3.75 (1H, m), 1.99 (3H, s), 1.87 (3H, s), 2.19–1.10 (8H, m); δ_C (125 MHz, $CDCl_3$) 171.8, 169.6, 74.6, 52.7, 32.0, 31.0, 24.1, 24.0, 23.3, 21.1. The enantiomers were separated by GC. Conditions: isotherm 110 °C; retention times for the two enantiomers: 27.9 min, 30.0 min.

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References

1 E. C. Jorgensen and K. Hsiek, *J. Med. Chem.*, 1979, **22**, 1199.
2 P. T. Sullivan, M. Kester and S. J. Norton, *J. Med. Chem.*, 1968, **11**, 1172.
3 H. Shimeno, S. Soeda and S. H. Nagamatsu, *Chem. Pharm. Bull.*, 1977, 2983.
4 J. E. Rivier, J. Porter, C. L. Rivier, M. Perrin, A. Corrigan, W. A. Hook, R. P. Siraganian and W. W. Vale, *J. Med. Chem.*, 1986, **29**, 1846.
5 M. Adamczyk, S. R. Akireddy and R. E. Reddy, *Org. Lett.*, 2001, **3**, 3157.
6 C. Hoes, J. Raap, W. Bloemhoff and K. E. T. Kerling, *Recl. Trav. Chim. Pays-Bas*, 1980, **99**, 99.
7 M. S. Cooper, A. W. Seton, A. W. Stevens, M. F. G. Stevens and A. D. Westwell, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2613.
8 P. Dalla Croce, C. La Rosa and E. Pizzatti, *Tetrahedron: Asymmetry*, 2000, **11**, 2635.
9 R. F. W. Jackson, N. Wishart, A. Wood, K. James and M. J. Wythes, *J. Org. Chem.*, 1992, **57**, 3397.
10 M. A. Walker, K. P. Kaplita, T. Chen and H. D. King, *Synlett*, 1997, 740.
11 B. Schmidt and D. K. Ehlert, *Tetrahedron Lett.*, 1998, **39**, 3999.
12 S. Kawata, S. Ashizawa and M. Hirama, *J. Am. Chem. Soc.*, 1997, **119**, 12012.
13 B. Ye and T. R. Burke, *J. Org. Chem.*, 1995, **60**, 2640.
14 B. Ye, A. Otaka and T. R. Burke, *Synlett*, 1996, 459.
15 A. W. Seton, M. F. G. Stevens and A. D. Westwell, *J. Chem. Res.*, 2001, (S)546.
16 B.-M. Swahn, A. Claesson, B. Pelcman, Y. Besidski, H. Molin, M. P. Sandberg and O.-G. Berge, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1635.
17 B.-M. Swahn, F. Andersson, B. Pelcman, J. Söderberg and A. Claesson, *J. Labelled Compd. Radiopharm.*, 1997, **39**, 259.
18 W. Clegg and L. Horsburgh, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2003, **59**, o1257.
19 M. A. Walker, K. P. Kaplita, T. Chen and H. D. King, *Synlett*, 1997, 169.
20 R. F. W. Jackson, R. J. Moore, C. S. Dexter, J. Elliot and C. E. Mowbray, *J. Org. Chem.*, 1998, **63**, 7875.
21 C. S. Dexter, R. F. W. Jackson and J. Elliott, *J. Org. Chem.*, 1999, **64**, 7579.
22 C. S. Dexter, C. Hunter and R. F. W. Jackson, *J. Org. Chem.*, 2000, **65**, 7417.
23 G. Hoefle, W. Steglich and H. Vorbrueggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 569.
24 E. F. V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129.
25 A. C. Spivey, A. Maddaford and A. J. Redgrave, *Org. Prep. Proced. Int.*, 2000, **32**, 331.
26 S. Arai, S. Bellemin-Laponnaz and G. C. Fu, *Angew. Chem., Int. Ed.*, 2001, **40**, 234.
27 E. R. Jarvo and S. J. Miller, *Tetrahedron*, 2002, **58**, 2481.
28 P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390.
29 R. F. W. Jackson, D. Turner and M. H. Block, *J. Chem. Soc., Perkin Trans. 1*, 1997, 865.
30 T. R. Burke, M. S. Smyth, A. Otaka and P. P. Roller, *Tetrahedron Lett.*, 1993, **34**, 4125.
31 H. J. C. Deboves, C. Hunter and R. F. W. Jackson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 733.
32 P. Rocca, F. Marsais, A. Godard and G. Queguiner, *Tetrahedron*, 1993, **49**, 49.
33 G. T. Copeland, E. R. Jarvo and S. J. Miller, *J. Org. Chem.*, 1998, **63**, 6784.
34 S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann and E. M. Ruel, *J. Am. Chem. Soc.*, 1998, **120**, 1629.
35 E. R. Jarvo, G. T. Copeland, N. Papaioannou, P. J. Bonitatebus and S. J. Miller, *J. Am. Chem. Soc.*, 1999, **121**, 11638.
36 G. T. Copeland and S. J. Miller, *J. Am. Chem. Soc.*, 2001, **123**, 6496.
37 G. Lunn, *J. Org. Chem.*, 1992, **57**, 6317.
38 H. J. Den Hertog and J. P. Wibault, *Recl. Trav. Chim. Pays-Bas*, 1936, **55**, 122.
39 T. Sammakia and T. B. Hurley, *J. Org. Chem.*, 1999, **64**, 4652.
40 W. Clegg and L. Horsburgh, *Acta Crystallogr., Sect. E.: Struct. Rep. Online*, 2003, **E59**, m700.
41 T. Sakamoto, Y. Kondo, N. Takazawa and H. Yamanaka, *Tetrahedron Lett.*, 1993, **34**, 5955.