A reappraisal of the Ni-[(Benzylprolyl)amino]benzophenone complex in the synthesis of α,α-disubstituted amino acid derivatives

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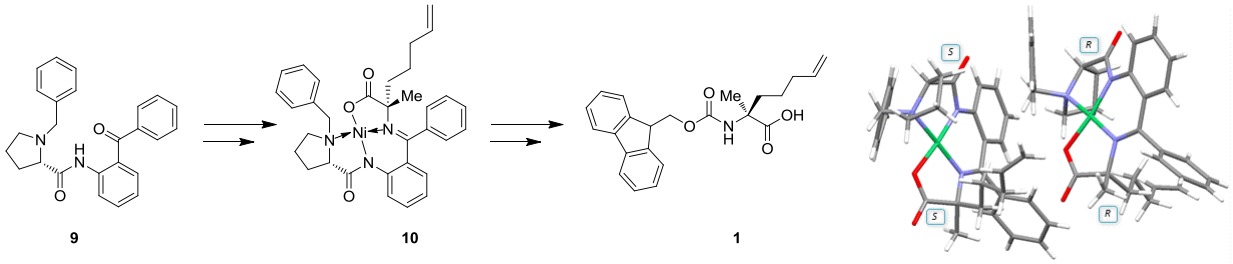


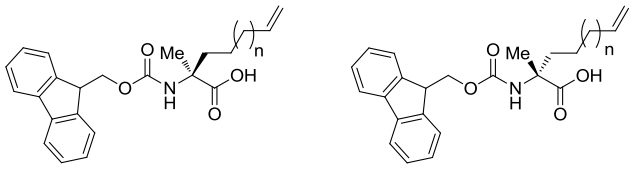
Abstract

α,α-Disubstituted alkenyl amino acid derivatives (e.g. Fmoc-S_5-OH) are valuable monomers in the construction of stapled peptide derivatives. Synthetic access to these is possible using the Ni-[(Benzylprolyl)amino]benzophenone (BPB) complex as a chiral auxiliary. We discuss a reappraisal of the use of this, and demonstrate that epimerisation of the proline α-center occurs during formation of the complex, leading to erosion in the enantiomeric excess of the final product. Modified conditions have been developed, providing the target compounds in high enantiomeric excess.

Introduction

The synthesis of homochiral, non-proteinogenic amino acid derivatives is an important objective for many applications in the area of peptide science.[1,2] First introduced by Verdine,[3] the α,α-disubstituted alkenyl amino acids **1** – **4** (Figure 1) are pivotal building blocks in the construction of peptide staples, which represent stabilised epitopes of larger protein assemblies designed to mimic α-helical secondary structure.[4] These peptide derivatives have found utility in a number of biological applications, including as drug candidates for clinical studies. Accordingly, having access to robust methods for the

synthesis of the requisite amino acid monomers used to construct target peptide staples is a pivotal consideration in enabling the preparation of these biologically useful entities.

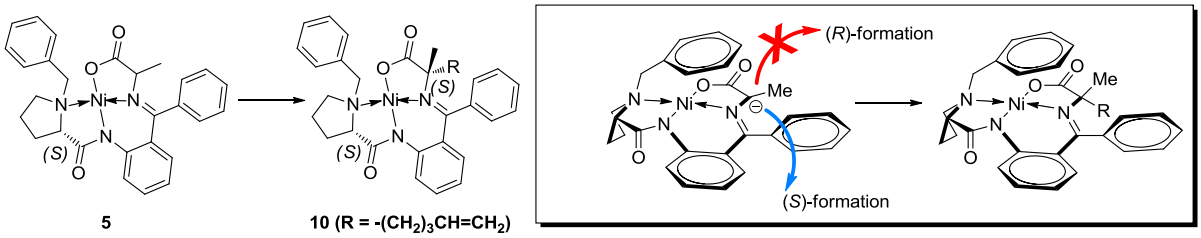


1 Fmoc S_5-OH (n = 1)
2 Fmoc S_8-OH (n = 4)

3 Fmoc R_5-OH (n = 1)
4 Fmoc R_8-OH (n = 4)

Figure 1. Verdine amino acids used for construction of peptide staples.

To this end, a number of chiral auxiliary based approaches to **1** and related derivatives have been reported.[3,5,6] From this set, an auxiliary which has been of particular interest to a number of groups has been the Ni-BPB based system (**5**)[7] and related analogues which have been used in the construction of both mono-[8] and α,α-disubstituted alkenyl[9,10] amino acids exemplified by **1** and its derivatives. Application of compound **5** in this context is attractive given the predictable sense of stereoinduction imparted by the proline α–centre of the auxiliary (Figure 2),[7] and the fact that large scale synthesis of the Schiff-base complex (up to 1 kg) has been reported.[11]



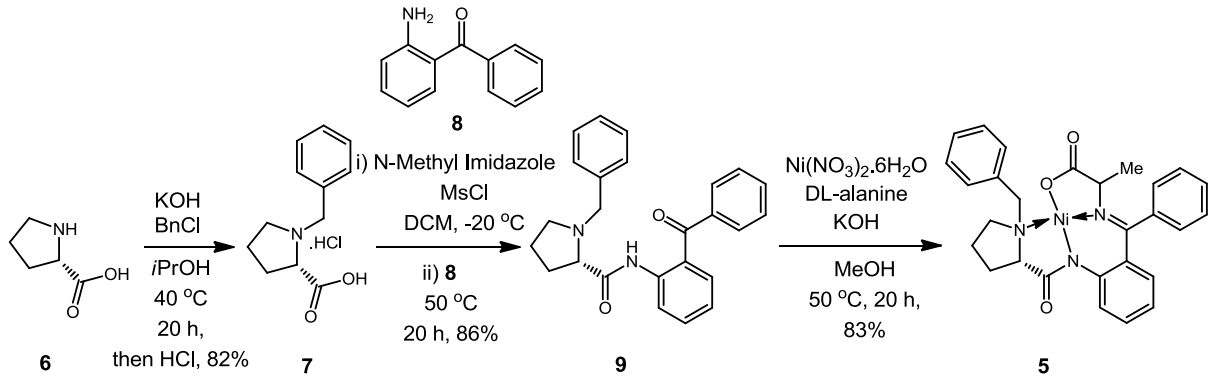
5 **10** (R = $-(CH_2)_3CH=CH_2$)

Figure 2. Mnemonic developed to rationalise stereoinduction.

As part of an on-going medicinal chemistry effort in our laboratories utilising peptide staples, we sought to prepare alkenyl amino acids **1** – **4** using the Ni-BPB Schiff base complexes given the apparently robust precedence already established. In this report, however, we report the epimerisation of the proline under conditions used to facilitate formation of the Schiff base complex resulting in sub-optimal measured enantiomeric excess of the final Fmoc amino acid product. Based on these observations, we have then developed modified procedures for complex formation, enabling synthesis target amino acid derivatives in high enantiomeric excess.

Our synthetic approach commenced through formation of the auxiliary using a combination of reported procedures[11,12] to form the Schiff base complex **5** (Scheme 1). In particular, the final complexation step proved difficult to perform on larger scale without compromising

yield. It was found that extended reaction times and increasing the equivalents of KOH used was necessary to achieve high yields.

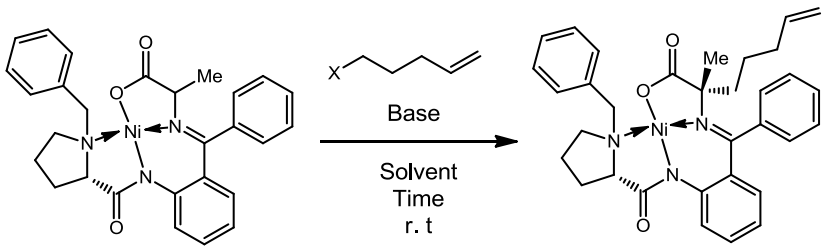


Scheme 1. Access to the BPB auxiliary.

With adequate quantities of the BPB auxiliary in hand, we next turned our attention to the alkylation step. More recent reports[8,9] had suggested that this could be capricious in nature, therefore a focused optimisation was undertaken. From consideration of the primary literature, some of the highest yields for enantioselective alkylation with haloalkenes had been achieved using sodium hydroxide.[9,13] The published conditions employing sodium hydroxide as a base used dry acetonitrile and DMF as solvents, therefore acetonitrile was chosen for initial screening as the resulting work-up and isolation was reasoned to be less problematic. 5-bromopentene was selected as the substrate due to its commercial availability and success reported elsewhere.[9,10] Finally, the reaction temperature was maintained at ambient as increasing the temperature was anticipated to lower the diastereomeric ratio. The results of this survey are reported in Table 1.

The use of sodium hydroxide as a base was not successful (Entry 1), nor was potassium *tert*-butoxide in acetonitrile although traces of product could be observed when used in THF (Entries 2 and 3). Purifying potassium *tert*-butoxide by sublimation and addition of tetra-*N*-butylammonium iodide (TBAI) as an additive gave modest isolated yields (Entry 4), whereas exchanging the electrophile for the corresponding alkyl iodide resulted in an increased yield, particularly when used in conjunction with TBAI (Entries 5 and 6). The precise reasons for the elevation in yield observed with TBAI are not clear, however, this could be attributable to the tertiary butylammonium cation minimizing enolate aggregation which could otherwise supress reactivity. The overall process reported compares favourably with previously reported conditions, where isolated yields of 55-68% were obtained.[9,10] The diasteromeric ratio of compound **10** was found to be in excess of 98% as determined by ^{1}H NMR, implying that the enolate alkylation had occurred in a stereoselective manner.

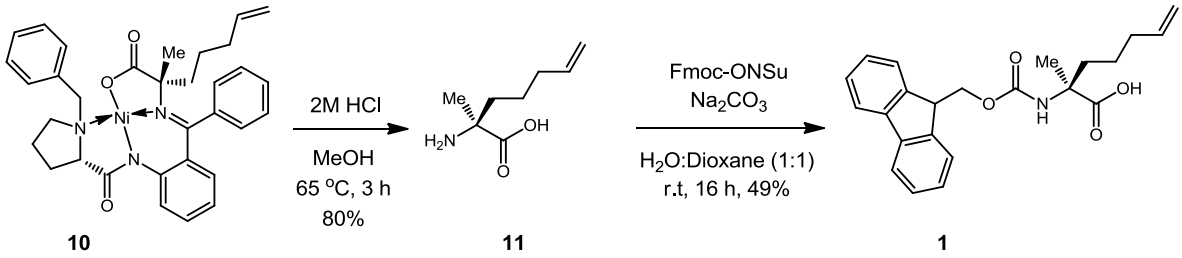
Table 1. Optimisation of alkylation of BPB auxiliary.



5 **10**

	X	Base	Solvent	Additive	Reaction time	Yield 10
1	Br	NaOH	MeCN	-	2 h	No reaction
2	Br	*t*BuOK	MeCN	-	2 h	No reaction
3	Br	*t*BuOK	THF	-	2 h	Trace
4	Br	*t*BuOK (sub.)	THF (dry)	TBAI (0.1 equiv)	5 h	35%
5	I	*t*BuOK (sub.)	THF (dry)	-	5 h	43%
6	I	*t*BuOK (sub.)	THF (dry)	TBAI (0.1 equiv)	16 h	70%

Having enabled optimal conditions for the synthesis of complex **10**, we next sought to generate the free amino acid before subsequently installing the N^{α}-Fmoc protecting group, at which point the enantiomeric excess of the final product could be determined through chiral HPLC with UV-detection. Acidolysis of the complex proceeded smoothly using dilute HCl (Scheme 2), with the amino acid being isolated using ion exchange chromatography. Incorporation of the Fmoc group using 9-Fluorenylmethyl *N*-succinimidyl carbonate gave the final compound in acceptable yield following reverse phase purification.



Scheme 2. Hydrolysis and Fmoc protection of final alkenyl amino acid.

However, despite the encouraging levels of diastereomeric purity of alkylated BPB complex **10** observed using ^{1}H NMR, this did not translate into appreciably high levels of enantiomeric purity when analysing Fmoc-*S*$_5$-OH by chiral HPLC. This study indicated that the target amino acid was obtained in only 82% enantiomeric excess, which was deemed to be unsuitable for use in solid phase peptide synthesis. The cause of this apparent erosion in enantiomeric excess was initially not clear given the high diastereomeric purity of the precursor complex **10** and the predictable sense of stereoinduction associated with the BPB-based auxiliary systems in general. Some insight into the precise reasons behind this disappointingly low level of enantiomeric excess was obtained through acquisition of a small molecule X-ray structure of complex **10** (Figure 3).

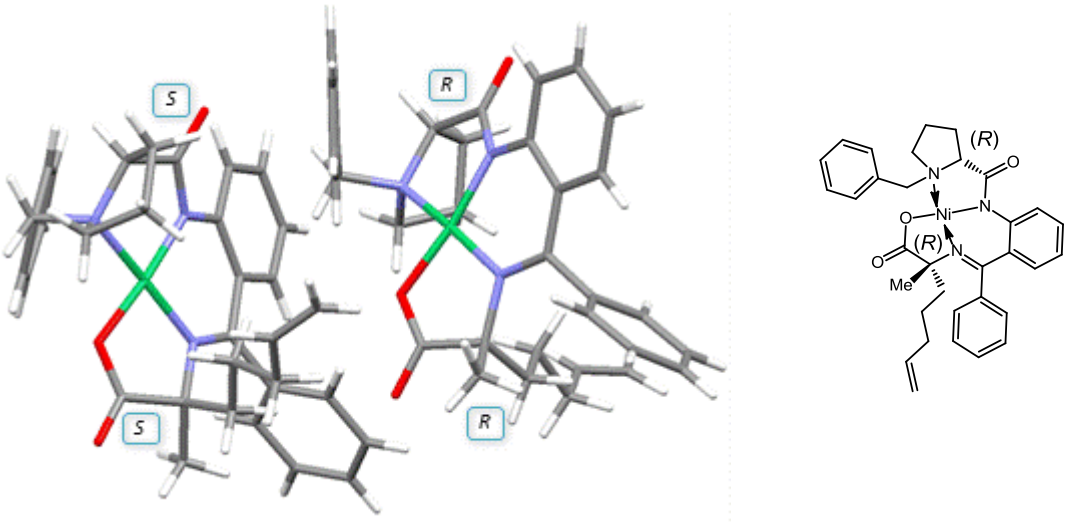


Figure 3. X-ray diffraction derived structure of BPB-complex **10** showing presence of opposite enantiomer.

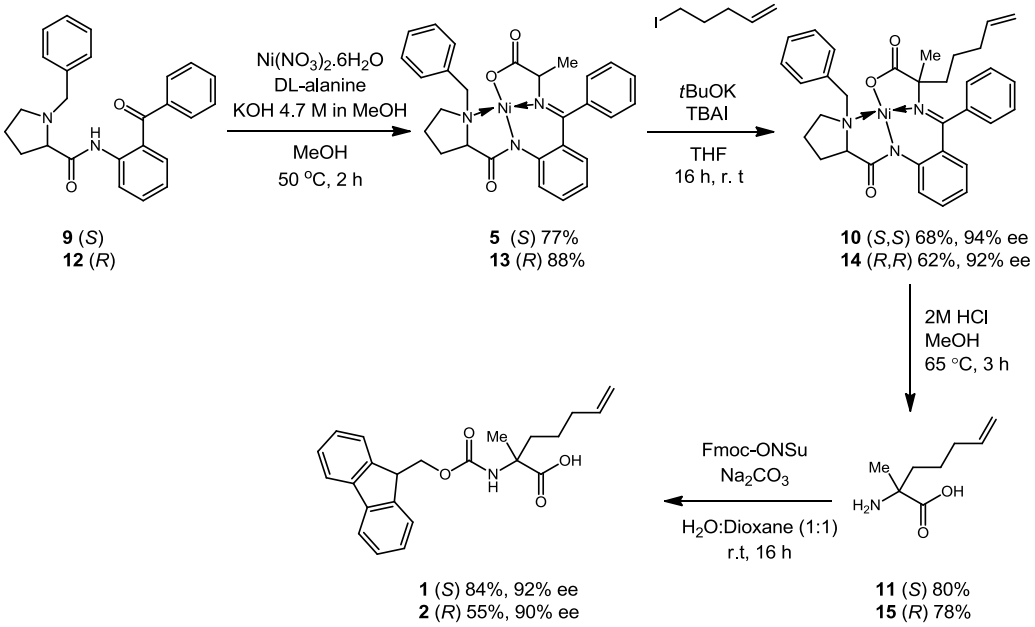
The isolation of centrosymmetric crystals of complex **10** revealed that although this species was predominately a single diastereomer, a significant amount of both the corresponding enantiomers is present. This ultimately results in the lower than expected enantiomeric

excess observed. Although the single crystal shows a 1:1 mix of (*R*, *R*) and (*S*, *S*) complexes, the bulk must in fact be a scalemate given the higher enantiomeric excess (82%) observed by chiral HPLC of the final quaternary amino acid product.

Formation of the (*R*, *R*) complex is a result of alkylation of the (*R*)-proline based auxiliary which arises through epimerisation of the α-centre of the auxiliary during its synthesis. This observation is perhaps surprising as a lower enantiomeric excess of final amino acid **1** would be more likely be attributable to poor diastereocontrol during enolate alkylation rather than inherent issues with the auxiliary itself. Detection of the presence of the (*R*, *R*) complex is not possible by ^{1}H NMR, however, chiral HPLC indicated the enantiomeric excess of complex **10** was 84% and is, therefore, in very close accord with the result obtained for Fmoc-S_5-OH confirming that the alkylation step is indeed relatively diastereoselective in nature. It was then important to establish at what point in the preparation of the BPB auxiliary epimerisation of the proline center occurred. Development of a chiral HPLC assay to determine the enantiomeric excess of the immediate precursor **5** was not possible as this was likely to be a mixture of up to 4 diastereomers given the fact that DL-Ala is generally used in the complexation step as this center is enolised when the α,α-disubstituted amino acid is prepared. It was, however, possible to determine the enantiomeric excess for the benzophenone amide derivative **9** which was shown to have an ee of in excess of 98%, indicating that epimerisation of the proline derivative was not taking place during amide bond formation. From this result, it was inferred that the conditions used in the formation of the BPB-Ala complex **5** itself (prolonged treatment with base at elevated temperatures) were more than likely the cause of the erosion in chiral integrity of the auxiliary.

Accordingly, the formation of complex **5** was re-examined, with particular focus on reaction time and stoichiometry of KOH used (Scheme 3). Employing shorter reaction times and using fewer equivalents of base added as a solution rather than a powder was successful in forming complex **10** in good yield. Subsequent alkylation using the conditions developed above and assessment of enantiomeric excess by chiral HPLC indicated that alkylated complex **10** was primarily a single enantiomer (94% ee), confirming that epimerisation of the auxiliary during its formation is largely responsible for the erosion in enantiomeric excess observed. Following acidolysis of the complex and installation of the Fmoc protecting group, measurement of enantiomeric excess of **1** indicated a superior ee of 92% (compared to the ee of 82% previously obtained in the preparation of this compound), consistent with what was observed for the alkylation step, and supporting the fact that high measured enantio- and diastereomeric ratios of complex **10** translated into a final product of near identical levels

of enantiopurity. The antipode **3** could also be prepared using the same route commencing from the (*R*)-BPB derived auxiliary **13** (prepared in an analogous fashion to the corresponding (*S*)-auxiliary), again with enantiomeric excess of alkylated complex **14** translating to measured optical purity of the final amino acid Fmoc-R_5-OH (**3**, Scheme 3). Based on all of the above, limiting the exposure of Ni-BPB complexes to base is crucial in maintaining the stereochemical integrity of the auxiliary in order to obtain amino acid products of appropriate optical purity.



Scheme 3. Modified route to **1** and application to synthesis of **2**.

A corollary to the current work relates to recent reports[14,15,16] using the BPB auxiliary to kinetically resolve or invert the stereochemistry of amino acids ligated to a Ni Schiff base complex. Both of these studies report conditions which involve prolonged treatment of BPB auxiliaries with base. In addition to this, a recent report from Li and co-workers[17] indicate the choice of base being crucial when using a related BPP auxiliary for the synthesis of amino acids of the type **1** – **4**, with *tert*-butoxide derived bases being optimal. These reports, together with consideration of our observations, some degree of caution therefore needs to be exercised in exposing Ni-BPB complexes to base as epimerisation of the proline may occur, leading to compromised optical purity of final products.

In conclusion, through a combination of X-ray crystallographic input and chiral HPLC analysis, this study has shown that the variable nature of stereoinduction observed using Ni-BPB complexes is not solely attributable to poor levels of facial control upon enolate alkylation of complexes such as **5** but is a consequence of epimerisation of the auxiliary itself. We anticipate these findings will be of use in developing robust and scalable

syntheses of alkenyl amino acids **1** – **4** which are of value in the area of peptide staples, and may also impact on other applications of the BPB auxiliary as noted above.

Experimental Section

General Methods. All reagents and solvents were used as obtained unless otherwise stated. Purification was carried out according to standard laboratory methods.[18] Thin layer chromatography was carried out using aluminium-backed silica plates which were analysed under 254 nm UV light or developed using potassium permanganate solution. Flash chromatography was carried out using prepacked silica cartridges. ^{1}H NMR spectra were recorded at 400 or 500 MHz and ^{13}C NMR spectra were recorded at 101 or 126 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.27 (^{1}H) and 77.23 ppm (^{13}C), and DMSO referenced at 2.50 (^{1}H) and 39.51 ppm (^{13}C). Mass spectrometry data was generated using a TOF analyser at the University of Swansea, UK. Optical rotations were measured at 589 nm, with concentrations reported in g per 100 mL. Normal-phase chiral HPLC was carried out using a Chiralpak IA (Amylose tris(3,5-dimethylphenylcarbamate)) column at room temperature with a flow rate of 1 mL/min. Analysis of Nickel complexes was achieved using an isocratic system of 40% IPA in hexane over 40 minutes. Chiral separation of Fmoc amino acids was achieved using a gradient of 5 – 20% IPA in hexane with a flow rate of 1 mL/min over 20 minutes. Strong cation exchange chromatography was carried out using sulfonic acid functionalised DOWEX resin, 50WX8 H-form. 1-iodopent-4-ene was prepared as previously reported.[19]

Benzyl-L-proline hydrochloride (7)[11]

To a round bottomed flask containing 2-propanol (60 mL) at 40 ^{o}C was added L-proline (10.0 g, 86.6 mmol, 1 equiv.) and the reaction mixture stirred at this temperature until fully in solution. The reaction mixture was then cooled to 0 ^{o}C and KOH (19.5 g, 347 mmol, 4 equiv.) was added and stirred for 5 minutes. Benzyl chloride (15 mL, 130 mmol, 1.5 equiv.) was added dropwise over 15 minutes, maintaining the temperature between 0 ^{o}C and 5 ^{o}C. Once addition was complete, the reaction mixture was heated to 40 ^{o}C and stirred for 17 h. Once complete, the reaction mixture was cooled to room temperature and acidified to pH 4 with conc. HCl. DCM (150 mL) was added and the flask placed in the fridge overnight. The precipitate was then filtered off and the filtrate concentrated *in vacuo*. The residue was suspended in acetone to give a white solid. Filtration and washing with cold acetone afforded the title compound as a white solid (17.2 g, 82%).

v_{max} (neat): 3005, 2993, 2953, 1713, 1672, 1498 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.45 – 7.42 (m, 2H), 7.40 – 7.32 (m, 3H), 5.12 (br s, 1H), 4.19 (d, 1H, *J* = 13.2 Hz), 3.91 (d, 1H, *J* = 13.2 Hz), 3.59 (dd, 1H, *J* = 6.0, 3.2 Hz), 3.20 – 3.15 (m, 1H), 2.81 – 2.74 (m, 1H), 2.24 – 2.14 (m, 1H), 1.96 – 1.81 (m, 2H), 1.78 – 1.71 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.6, 134.8, 129.6, 128.4, 128.1, 65.8, 57.2, 53.1, 28.4, 22.6. HRMS: ($C_{12}H_{16}O_2N_1$) $[M+H]^+$ requires 206.1176, found $[M+H]^+$ 206.1175. $[\alpha]^{20}_D$ = -28.8 (c = 1, MeOH).

(*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide (9)[11]

To a round bottomed flask containing dry DCM (475 mL) under N_2 was added **7** (34.5 g, 143 mmol, 1 equiv.) to form a cloudy suspension. The reaction mixture was cooled to -20 °C using a mixture of ice and NaCl (1:3), giving (on average) an internal temperature of -5 °C. *N*-Methyl imidazole (31.8 mL, 399 mmol, 2.8 equiv.) was then added and stirred for 5 minutes. Methanesulfonyl chloride (12.2 mL, 157 mmol, 1.1 equiv.) was then added slowly over 5 minutes, maintaining the internal temperature at between -5 °C to 0 °C. The reaction mixture was then left to stir at -5 °C to 0 °C for 30 minutes. 2-Aminobenzophenone (25.3 g, 128 mmol, 0.9 equiv.) was then added and the reaction mixture left to stir at room temperature for 17 h. The reaction mixture was quenched with sat. NH_4Cl and separated with DCM (3 x 400 mL). The organic layers were combined, dried and concentrated in vacuo to give the crude as a dark brown oil. The crude was then purified by silica chromatography (0-100% EtOAc in Pet. Ether 40/60) to give the title compound as a yellow solid (42.3 g, 86%).

v_{max} (neat): 3248, 2968, 2839, 2810, 1687, 1643, 1576, 1510, 1442 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 11.54 (s, 1H), 8.59 (dd, 1H, *J* = 7.6, 1.2 Hz), 7.82 – 7.80 (m, 2H), 7.67 – 7.61 (m, 1H), 7.57 – 7.45 (m, 4H), 7.41 – 7.39 (m, 2H), 7.18 – 7.15 (m, 3H), 7.13 – 7.09 (m, 1H), 3.95 (d, 1H, *J* = 13.2 Hz), 3.62 (d, 1H, *J* = 13.2 Hz), 3.37 (dd, 1H, *J* = 5.2, 4.8 Hz), 3.27 – 3.22 (m, 1H), 2.47 – 2.40 (m, 1H), 2.33 – 2.23 (m, 1H), 2.03 – 1.96 (m, 1H), 1.90 – 1.76 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.5, 174.1, 138.7, 138.1, 137.7, 132.9, 132.1, 132.0, 129.6, 128.7, 127.8, 127.7, 126.6, 124.9, 121.7, 121.1, 67.8, 59.4, 53.4, 30.5, 23.7. HRMS: ($C_{25}H_{25}O_2N_2$) $[M+H]^+$ requires 385.1911, found $[M+H]^+$ 385.1908. $[\alpha]^{20}_D$ = -106.7 (c = 1, MeOH). ee = >98 % by chiral HPLC, retention time = 11.95 min.

(*R*)-N-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide (12)[11]

To a round bottomed flask containing dry DCM (50 mL) under N_2 was added benzyl-L-proline hydrochloride (7.4 g, 30.6 mmol, 1 equiv.) to form a cloudy suspension. The reaction mixture was cooled to -20 °C using a mixture of ice and NaCl (1:3), giving (on average) an

internal temperature of -5 °C. *N*-Methyl imidazole (9.8 mL, 85.7 mmol, 2.8 equiv.) was then added and stirred for 5 minutes. Methanesulfonyl chloride (2.4 mL, 33.6 mmol, 1.1 equiv.) was then added slowly over 5 minutes, maintaining the internal temperature at between -5 °C to 0 °C. The reaction mixture was then left to stir at -5 °C to 0 °C for 30 minutes. 2-Aminobenzophenone (**138**) (5.4 g, 27.5 mmol, 0.9 equiv.) was then added and the reaction mixture left to stir at room temperature for 17 h. The reaction mixture was quenched with sat. NH_4Cl and separated with DCM (3 x 100 mL). The organic layers were combined, dried and concentrated in vacuo to give the crude as a dark brown oil. The crude was then purified by silica chromatography (0-100% EtOAc in Pet. Ether 40/60) to give the title compound as a yellow solid (9.0 g, 85%).

ν_{max} (neat): 3250, 2963, 2822, 1688, 1640, 1515, 1442 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.52 (s, 1H), 8.58 (dd, 1H, *J* = 7.6, 0.8 Hz), 7.80 – 7.78 (m, 2H), 7.64 – 7.60 (m, 1H), 7.56 – 7.49 (m, 4H), 7.40 – 7.37 (m, 2H), 7.17 – 7.14 (m, 3H), 7.12 – 7.08 (m, 1H), 3.93 (d, 1H, *J* = 12.8 Hz), 3.61 (d, 1H, *J* = 12.8 Hz), 3.35 – 3.31 (dd, 1H, *J* = 5.2, 4.8 Hz), 3.23 – 3.21 (m, 1H,), 2.45 – 2.40 (m, 1H), 2.30 – 2.22 (m, 1H), 2.00 – 1.96 (m, 1H), 1.83 – 1.77 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.5, 174.2, 138.7, 138.1, 137.7, 132.9, 132.1, 132.0, 129.6, 128.7, 127.8, 127.7, 126.6, 124.9, 121.7, 121.1, 67.8, 59.4, 53.4, 30.5, 23.7; HRMS: ($C_{25}H_{25}O_2N_2$) $[M+H]^+$ requires 385.1911, found $[M+H]^+$ 385.1910; $[\alpha]^{20}_D$ = +106.6 (c = 1, MeOH); ee = >98 % by chiral HPLC, retention time 11.42 min.

(*S*)-Ni(II)-Ala-BPB (5)[11]

To a round bottomed flask containing MeOH (70 mL) under N_2 was added **9** (7.68 g, 20.0 mmol, 1 equiv.), DL-Alanine (3.60 g, 40.0 mmol, 2 equiv) and $Ni(NO_3)_2.6H_2O$ (11.6 g, 40.0 mmol, 2 equiv.) and the contents heated to 40 °C. A solution of KOH (7.84 g, 140 mmol, 7 equiv.) in MeOH (30 mL) was added dropwise to the reaction vessel over 10 minutes. Once addition was complete, the reaction mixture was heated to 50 °C and left to react for 2 h. The reaction was cooled to room temperature and neutralised with conc. acetic acid. Water (400 mL) and DCM (200 mL) were added to the reaction vessel and left to stir overnight. The mixture was then separated with DCM (3 x 300 mL) and the organic layers combined, dried and concentrated *in vacuo* to give the crude product as a red oil. The crude material was then purified by silica chromatography (0-100% EtOAc in Pet. Ether 40-60, 0-5% MeOH in EtOAc) to give the title compound as a bright red solid (7.55 g, 74%).

ν_{max} (neat): 2976, 2872, 1678, 1622, 1591, 1440 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.06 (m, 3H), 7.54 – 7.44 (m, 3H), 7.39 (t, 2H, *J* = 8.4 Hz), 7.27 – 7. 12 (m, 3H), 6.96 (d, 1H, *J* = 7.6 Hz), 6.68 – 6.61 (m, 2H), 4.43 – 4.40 (m, 1H), 3.91 (q, 1H, *J* = 7.2 Hz), 3.75 – 3.69

(m, 1H), 3.56 (d, 1H, *J* = 12.8 Hz), 3.53 – 3.47 (m, 1H), 2.77 – 2.72 (m, 1H), 2.59 – 2.51 (m, 1H), 2.25 – 2.18 (m, 1H), 2.11 – 2.04 (m, 1H), 1.61 – 1.59 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 180.3, 170.1, 170.1, 142.0, 133.4, 133.3, 133.0, 131.9, 131.4, 129.6, 128.8, 128.7, 127.4, 127.1, 126.3, 123.8, 120.7, 70.1, 66.4, 63.0, 57.2, 30.7, 24.0, 21.7. 1C not observed. HRMS: ($C_{28}H_{28}O_3N_3Ni$) $[M+H]^+$ requires 512.1479, found $[M+H]^+$ 512.1467. $[\alpha]^{20}_D$ = +2669 (c = 0.03, MeOH).

(*R*)-Ni(II)-Ala-BPB (13)

To a round bottomed flask containing MeOH (20 mL) under N_2 was added **12**[11] (2.0 g, 5.2 mmol, 1 equiv.), DL-Alanine (0.93 g, 10.4 mmol, 2 equiv) and $Ni(NO_3)_2.6H_2O$ (3.02 g, 10.4 mmol, 2 equiv.) and the contents heated to 40 ^oC. A solution of KOH (2.04 g, 36.4 mmol, 7 equiv) in MeOH (10 mL) was added dropwise to the reaction vessel over 10 minutes. Once addition was complete, the reaction mixture was heated to 50 ^oC and left to react for 2 h. The reaction was cooled to room temperature and neutralised with conc. acetic acid. Water (100 mL) and DCM (50 mL) were added to the reaction vessel and left to stir for 3 h. The mixture was then separated with DCM (3 x 100 mL) and the organic layers combined, dried and concentrated *in vacuo* to give the crude product as a red oil. The crude material was then purified by silica chromatography (0-100% EtOAc in Pet. Ether 40-60, 0-5% MeOH in EtOAc) to give the title compound as a bright red solid (2.36 g, 88%).

ν_{max} (neat): 2978, 2872, 1678, 1624, 1591, 1438 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.07 (m, 3H), 7.55 – 7.44 (m, 3H), 7.38 (t, 2H, *J* = 8.4 Hz), 7.31 – 7. 15 (m, 3H), 7.14 – 7.11 (m, 1H), 6.95 (d, 1H *J* = 7.6 Hz), 6.69 – 6.61 (m, 2H), 4.44 – 4.41 (m, 1H), 3.91 (q, 1H, *J* = 7.2 Hz), 3.76 – 3.68 (m, 1H), 3.55 (d, 1H, *J* = 12.8 Hz), 3.51 – 3.43 (m, 1H,), 2.77 – 2.71 (m, 1H), 2.59 – 2.48 (m, 1H), 2.26 – 2.18 (m, 1H), 2.11 – 2.04 (m, 1H), 1.61 – 1.59 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 180.4, 180.3, 170.2, 142.0, 133.4, 133.3, 133.0, 132.0, 131.4, 129.6, 128.9, 128.4, 127.4, 127.1, 126.4, 123.8, 120.7, 70.0, 66.5, 63.0, 57.2, 30.7, 24.0, 21.8. HRMS: ($C_{28}H_{28}O_3N_3Ni$) $[M+H]^+$ requires 512.1479, found $[M+H]^+$ 512.1470. $[\alpha]^{20}_D$ = -2043 (c = 0.03, MeOH).

(*S*)-Ni(II)-S_5-BPB (10)

To a dry round bottomed flask containing dry THF (25 mL) was added **5** (1.0 g, 1.9 mmol, 1 equiv.) and cooled to 0 ^oC under N_2. TBAI (72 mg, 0.20 mmol, 0.1 equiv.) and sublimed *t*BuOK (547 mg, 4.90 mmol, 2.5 equiv.) were added and the mixture left to stir for 5 minutes. 5-iodopentene (957 mg, 4.90 mmol, 2.5 equiv.) was added dropwise over 5 minutes and the reaction mixture left to stir at room temperature for 17 h. The reaction mixture was quenched

with 0.1 M HCl and separated with DCM (3 x 40 mL). The organic layers combined, dried and concentrated *in vacuo* to give the crude product as a red oil. The crude material was then purified by silica chromatography (0-2% MeOH in EtOAc) to give the title compound as a bright red solid (778 mg, 68%).

ν_{max} (neat): 2924, 2854, 1670, 1630, 1577, 1533, 1437, 1352 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, 2H, *J* = 7.2, 0.8 Hz), 8.02 (dd, 1H, *J* = 8.4, 1.2 Hz), 7.51 – 7.44 (m, 2H), 7.42 – 7.36 (m, 3H), 7.33 – 7.26 (m, 3H), 7.15 – 7.11 (m, 1H), 6.98 (d, 1H, *J* = 6.8 Hz), 6.67 – 6.60 (m, 2H), 5.92 – 5.82 (m, 1H), 5.11 – 5.01 (m, 2H), 4.51 (d, 1H, *J* = 13.2 Hz), 3.71 (d, 1H, *J* = 12.4 Hz), 3.67 – 3.63 (m, 1H), 3.44 (dd, 1H, *J* = 6.0, 4.4 Hz), 3.30 – 3.22 (m, 1H), 2.74 – 2.66 (m, 1H), 2.51 – 2.37 (m, 2H), 2.15 – 2.01 (m, 5H), 1.77 – 1.65 (m, 2H), 1.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 182.4, 180.5, 172.4, 141.5, 137.9, 136.6, 133.3, 131.7, 131.5, 130.3, 129.4, 129.0, 128.9, 128.7, 127.9, 127.3, 127.0, 124.0, 120.7, 115.4, 78.0, 70.0, 63.4, 57.0, 39.9, 33.7, 30.7, 29.6, 30.7, 25.3, 23.3. HRMS: ($C_{33}H_{36}O_3N_3Ni$) $[M+H]^+$ requires 580.2105, found $[M+H]^+$ 580.2095. $[\alpha]^{20}_D$ = +1273 (c = 0.03, MeOH). dr = >98% by ^1H NMR. ee = 94% by chiral HPLC, retention time = 12.64 min.

(*R*)-Ni(II)-R_5-BPB (14)

To a dry round bottomed flask containing dry THF (150 mL) was added **13** (6.00 g, 11.7 mmol, 1 equiv.) and cooled to 0 °C under N_2. TBAI (433 mg, 1.2 mmol, 0.1 equiv.) and sublimed *t*BuOK (2.63 g, 23.4 mmol, 2 equiv.) were added and the mixture left to stir for 5 minutes. 5-iodopentene (4.59 g, 23.4 mmol, 2 equiv.) was added dropwise over 5 minutes and the reaction mixture left to stir at room temperature for 17 h. The reaction mixture was quenched with 0.1 M HCl and separated with DCM (3 x 250 mL). The organic layers combined, dried and concentrated *in vacuo* to give the crude product as a red oil. The crude material was then purified by silica chromatography (0-2% MeOH in EtOAc) to give the title compound as a bright red solid (4.24 g, 62%).

ν_{max} (neat): 2968, 2942, 2858, 1664, 1635, 1571, 1533, 1435, 1355 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, 2H, *J* = 6.8 Hz), 8.03 (d, 1H, *J* = 9.2 Hz), 7.51 – 7.48 (m, 2H), 7.44 – 7.40 (m, 3H), 7.35 – 7.27 (m, 3H), 7.17 – 7.12 (m, 1H), 7.00 (dd, 1H, *J* = 6.4, 1.2 Hz), 6.68 – 6.62 (m, 2H), 5.93 – 5.83 (m, 1H), 5.13 – 5.03 (m, 2H), 4.51 (d, 1H, *J* = 12.4 Hz), 3.72 (d, 1H, *J* = 12.4 Hz), 3.69 – 3.64 (m, 1H), 3.45 (dd, 1H, *J* = 6.0, 4.8 Hz), 3.31 – 3.24 (m, 1H), 2.76 – 2.68 (m, 1H), 2.53 – 2.39 (m, 2H), 2.19 – 2.03 (m, 5H), 1.79 – 1.69 (m, 2H), 1.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 182.2, 180.4, 172.3, 141.4, 136.5, 133.3, 131.7, 131.5, 130.2, 129.4, 129.0, 128.8, 128.6, 127.8, 127.3, 126.9, 123.9, 120.7, 115.4, 78.0, 69.9, 63.3, 56.9, 39.8, 33.7, 30.6, 29.5, 25.3, 23.2. HRMS: ($C_{33}H_{36}O_3N_3Ni$) $[M+H]^+$ requires 580.2105, found

$[M+H]^+$ 580.2099. $[\alpha]^{20}_D$ = -1262 (c = 0.03, MeOH). dr = >98% by ^1H NMR. ee = 90% by chiral HPLC, retention time = 7.66 min.

(*S*)-2-amino-2-methylhept-6-enoic acid (11)[9]

To a round bottomed flask containing MeOH (13 mL, 0.08 M) was added **10** (583 mg, 1.1 mmol, 1 equiv.) and 2M HCl (18 mL, 0.06 M). The reaction mixture was heated to reflux for 3 h turning from a dark red to a yellow solution. The mixture was cooled to room temparature and basified to pH 9 with conc. NH_3. Water (50 mL) was added and the mixture separated with DCM (3 x 100 mL). The aqueous layer was concentrated *in vacuo* to give a crude turquoise solid. 40 g of Dowex resin (50WX8 hydrogen form) was swollen in water and packed into a column and washed with water. The crude solid was then dissolved in MeOH:water (1:1) and added to the resin. The column was then washed with MeOH (120 mL) and water (120 mL) to elute impurities. The product was then eluted using 25% NH_3 in water (200 mL) and concentrated *in vacuo*. The white solid was then dissolved in water and freeze dried to give the title compound as a flocculent white solid (101 mg, 80%).

ν_{max} (neat): 3053, 2947, 1585, 1539, 1458, 1404 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.61 (br s, 3H), 5.81 - 5.72 (m, 1H), 5.04 – 4.94 (m, 2H), 2.00 – 1.95 (m, 2H), 1.68 – 1.60 (m, 1H), 1.55 – 1.43 (m, 2H), 1.30 – 1.23 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 138.4, 114.8, 59.7, 37.4, 33.3, 23.2, 22.7 1C not observed (C=O). HRMS: ($C_8H_{16}O_2N$) $[M+H]^+$ requires 158.1176, found $[M+H]^+$ 158.1176. $[\alpha]^{20}_D$ = +12 (c = 0.15, MeOH)

(*R*)-2-amino-2-methylhept-6-enoic acid (15)

To a round bottomed flask containing MeOH (90 mL, 0.08 M) was added **14** (4.2 g, 7.2 mmol, 1 equiv.) and 2M HCl (121 mL, 0.06 M). The reaction mixture was heated to reflux for 3 h turning from a dark red to a yellow solution. The mixture was cooled to r.t and basified to pH 9 with conc. NH_3. Water (150 mL) was added and the mixture separated with DCM (3 x 200 mL). The aqueous layer was concentrated *in vacuo* to give a crude turquoise solid. 40 g of Dowex resin (50WX8 hydrogen form) was swollen in water and packed into a column and washed with water. The crude solid was then dissolved in MeOH:water (1:1) and added to the resin. The column was then washed with MeOH (150 mL) and water (150mL) to elute impurities. The product was then eluted using 25% NH_3 in water (250 mL) and concentrated *in vacuo*. The white solid was then dissolved in water and freeze dried to give the title compound as a flocculent white solid (675 mg, 78%).

v_{max} (neat): 3049, 2980, 2947, 1585, 1458, 1402 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.49 (br s, 3H), 5.82 - 5.72 (m, 1H), 5.04 – 4.94 (m, 2H), 1.20 – 1.94 (m, 2H), 1.68 – 1.60 (m, 1H), 1.54 – 1.43 (m, 2H), 1.30 – 1.23 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 138.4, 114.8, 59.7, 37.4, 33.3, 23.1, 22.7 1C not observed (C=O). HRMS: ($C_8H_{14}O_2N$) $[M-H]^-$ requires 156.1030, found $[M-H]^-$ 156.1032. $[\alpha]^{20}_D$ = -12 (c = 0.15, MeOH).

(*S*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-methylhept-6-enoic acid (1)[9]

To a round bottomed flask containing H_2O (9 mL) and dioxane (9 mL) was added **11** (170 mg, 1.10 mmol, 1 equiv.) and Na_2CO_3 (229 mg, 2.20 mmol, 2 equiv.) to form a cloudy solution. The reaction mixture was cooled to 0 °C and 9-Fluorenylmethyl *N*-succinimidyl carbonate (730 mg, 2.20 mmol, 2 equiv.) was added in small portions over 2 h, with the reaction temperature being maintained between 0 °C to 5 °C. Once addition was complete the reaction was left to stir at r.t for 17 h. The reaction mixture was then concentrated *in vacuo* and the residue separated with water (3 x 100 mL) and Et_2O 100 mL). The aqueous washings were back extracted with Et_2O (100 mL), combined and acidified to pH4 using 1 M HCl. The aqueous solution was then extracted with EtOAc (2 x 100 mL) and the organic layers washed with 1M HCl (2 x 100 mL). The organic layers combined, dried and concentrated *in vacuo* to give the crude product as a yellow oil. The crude material was then purified by silica chromatography (0 - 3% MeOH in DCM) to give the title compound as a yellow gummy solid (344 mg, 84%).

v_{max} (neat): 2939, 1705, 1641, 1506, 1450 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, 2H, *J* = 7.6 Hz), 7.73 (d, 2H, *J* = 7.6 Hz), 7.46 – 7.40 (m, 3H), 7.34 (td, 2H*J* = 6.8, 0.8 Hz), 5.83 – 5.73 (m, 1H), 5.03 – 4.95 (m, 2H), 4.28 – 4.19 (m, 3H), 2.01 – 1.97 (m, 2H), 1.78 – 1.68 (m, 2H), 1.36 – 1.26 (m, 5H). ^{13}C NMR (101 MHz, DMSO-d_6): 175.3, 154.7, 143.8, 140.7, 138.5, 127.6, 127.0, 125.2, 120.0, 114.9, 65.2, 58.2, 46.7, 36.2, 33.2, 22.5, 22.3. HRMS: ($C_{23}H_{26}O_4N$) $[M+H]^+$ requires 380.1856, found $[M+H]^+$ 380.1858. $[\alpha]^{20}_D$ = +18.1 (c = 0.15, MeOH). ee = 92% by chiral HPLC, retention time = 9.55 min.

(*R*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-methylhept-6-enoic acid (2)

To a round bottomed flask containing H_2O (27.5 mL) and dioxane (27.5 mL) was added **15** (517 mg, 3.30 mmol, 1 equiv.) and Na_2CO_3 (697 mg, 6.60 mmol, 2 equiv.) to form a cloudy solution. The reaction mixture was cooled to 0 °C and 9-Fluorenylmethyl *N*-succinimidyl carbonate (2.2 g, 6.6 mmol, 2 equiv.) was added in small portions over 2 h, with the reaction temperature being maintained between 0 °C to 5 °C. Once addition was complete the

reaction was left to stir at r.t for 17 h. The reaction mixture was then concentrated *in vacuo* and the residue separated with water (3 x 200 mL) and Et_2O (200 mL). The aqueous washings were back extracted with Et_2O (200 mL), combined and acidified to pH4 using 1 M HCl. The aqueous solution was then extracted with EtOAc (2 x 200 mL) and the organic layers washed with 1M HCl (2 x 200 mL). The organic layers combined, dried and concentrated in vacuo to give the crude product as a yellow oil. The crude material was then purified by silica chromatography (0 -3% MeOH in DCM) to give the title compound as a yellow gummy solid (690 mg, 55%).

ν_{max} (neat): 2939, 1705, 1641, 1504, 1448 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, 2H, *J* = 7.6 Hz), 7.73 (d, 2H, *J* = 7.6 Hz), 7.42 (dd, 3H, *J* = 7.6, 7.2), 7.34 (dd, 2H *J* = 7.6, 7.2), 5.82 – 5.75 (m, 1H), 5.03 – 4.94 (m, 2H), 4.28 – 4.19 (m, 3H), 2.01 – 1.99 (m, 2H), 1.78 – 1.69 (m, 2H), 1.36 – 1.26 (m, 5H). ^{13}C NMR (101 MHz, DMSO-d_6): 175.4, 154.8, 143.9, 140.7, 138.4, 127.6, 127.1, 125.3, 120.0, 114.9, 65.2, 58.3, 46.8, 36.2, 33.3, 22.5, 22.4 HRMS: ($C_{23}H_{26}O_4N$) $[M+H]^+$ requires 380.1856, found $[M+H]^+$ 380.1859. $[\alpha]^{20}_D$ = -13.5 (c = 0.15, MeOH). ee = 90% by chiral HPLC**,** retention time = 10.96 min.

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Supplementary Data

Copies of spectroscopic data (^1H and ^{13}C NMR) for all products, chiral HPLC and crystallography data. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1543445. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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