The Synthesis of *Pseudo-Geminal*, *Pseudo-Ortho* and *Ortho* Phosphinyl-Oxazolinyl-[2.2]Paracyclophanes for Use as Ligands in Asymmetric Catalysis

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pseudo-geminal

pseudo-ortho

ortho

Abstract

Syntheses of three regioisomers of aromatic-substituted oxazolinyl-phosphinyl-[2.2]paracyclophanes, *pseudo-geminal*, *pseudo-ortho* and *ortho*, have been carried out or, in the latter two cases, newly developed. It has therefore been demonstrated that all aromatic-substituted isomers relevant for use as chelating ligands for asymmetric catalysis are accessible. These *P,N*-ligands, along with their diastereoisomers, were shown to exhibit widely differing activity and enantioselectivity (up to 89% ee) in the Pd-catalyzed asymmetric allylic alkylation reaction.

Introduction

Planar chiral substituted [2.2]paracyclophanes have often been used as ligands in asymmetric catalysis.^{1,2} Perhaps the most famous example is PHANEPHOS, a planar chiral equivalent of BINAP, which, amongst other applications,³⁻⁷ exhibited a higher activity and enantioselectivity than BINAP in the Rh-catalyzed hydrogenation of the tetrahydropyrazine precursor to the HIV protease inhibitor Crixivan (86 vs. 56% ee).⁸

There are three aromatic disubstitution patterns available to [2.2]paracyclophane which give compounds geometrically capable of chelating a metal and therefore applicable as chiral ligands for asymmetric catalysts. Despite this, all studies to date have concentrated on the development and use of ligands based on only one of these patterns. The closest exception involves the synthesis of *iso*-FHPC, the *pseudo-geminal* analogue of 5-formyl-4-hydroxy[2.2]paracyclophane (FHPC).⁹⁻¹³ FHPC is an established precursor to [2.2]paracyclophane Schiff bases, salens^{14,15} and hydroxy-amines^{16,17} which have been used in asymmetric additions of diorganozincs to aldehydes and imines,^{18,19} sulfoxidations,²⁰ and the trimethylsilylcyanation of benzaldehyde.²¹ However, to the best of our knowledge, the conversion of *iso*-FHPC into similar ligands and their use in asymmetric catalysis has not yet been published. We therefore decided to address this general absence by demonstrating that all three aromatic-disubstituted [2.2]paracyclophane isomers can be synthesized using established [2.2]paracyclophane chemistry and that they are all effective as ligands in asymmetric catalysis. The compounds chosen were the oxazoliny-phenylphosphinyl-[2.2]paracyclophanes, *P,N*-ligands^{22,23} designed by Pelter and Hou.^{24,25} Hou showed that use of the *pseudo-geminal* isomers gave up to 90% ee in the Pd-catalyzed allylic alkylation reaction.²⁶ **This paper** will describe the syntheses of the *pseudo-geminal*, *pseudo-ortho* and *ortho* analogues of these compounds (Figure 1) and compare their effectiveness as ligands in the same allylic alkylation reaction.

FIGURE 1

Results and Discussion

By taking advantage of literature-described directing effects, we were able to synthesize both diastereoisomers of each of the three desired aryl-substituted regioisomers of phosphinyl-oxazoliny[2.2]paracyclophane **1-3**. *iso*-Propyl was chosen as the substituent on the oxazoline ring on account of the inexpense of the amino alcohol required (valinol) and its effectiveness as a sterically demanding group which is not so bulky as to inhibit reactions.

Synthesis of *Pseudo-Geminal* Isomers

Following previously described syntheses of **1** and similar derivatives,^{24,25,27,28} racemic carboxylic acid **4** was converted to the acid chloride, reacted with L-valinol and cyclized under Bryce's conditions²⁹ to give an inseparable mixture of diastereoisomers **5** (Scheme 1). The *pseudo-geminal* substitution pattern was attained by exploiting a directing effect, which occurs during iron-catalyzed bromination.³⁰ The resulting bromides **6a** and **6b** were separable by column chromatography. However, this reaction rarely proceeded to completion, even if commercial FeBr₂ or FeBr₃ was used as catalyst, and bromide **6a** often had to be used in the next step as an inseparable mixture with **5**. The bromides **6** were converted to the target compounds **1** by bromo-lithium exchange using *t*-BuLi followed by reaction with ClPPh₂. Interestingly, it was found that the diastereomeric phosphines **1a** and **1b** could be far more easily separated from the oxazolinyl[2.2]paracyclophane by-products (resulting from protonation of the lithium intermediates), by column chromatography, if a 3-component solvent system (pentane/DCM/EtOAc [20:4:1]) was used instead of the more usual 2-component system (pentane/EtOAc).

The absolute configurations of **1** were checked by preparation of **6a**, in the same manner, from enantiopure carboxylic acid (–)-(R_P) **4**.³¹

SCHEME 1

Synthesis of *Pseudo-Ortho* Isomers

The *pseudo-ortho* substitution pattern was set up early on in the synthesis by starting from dibromide **8**, prepared according to the procedure by Reich and Cram^{32a} with the improvements of Pye and Rossen⁸ and Braddock^{32b} (Scheme 2). Its synthesis involves dibromination of [2.2]paracyclophane to give a mixture of isomers from which the highly insoluble *pseudo-para* dibromide **7** can be crystallized. Thermal isomerization of **7** leaves the pure *pseudo-ortho* dibromide **8** alone in solution after cooling.

SCHEME 2

Dibromide **8** was converted to the mono-carboxylic acid **9** as previously described.³³ This was then converted to the diastereotopic bromo-oxazolinyl [2.2]paracyclophanes **10** (Scheme 3) in the same manner as for the *pseudo-geminal* compounds described above. Oxazolines **10a** and **10b** were inseparable at this stage, but the corresponding phosphines **2**, synthesized by lithiation and reaction with ClPPh₂, had different *R_f* values on silica, so could be separated by chromatography. Using the standard technique, yields of only 9 and 11%, of **2a** and **2b**, respectively, were obtained and this was attributed to phosphine oxidation during work-up and lengthy chromatographic separation. This was despite degassing of the solvents prior to use by bubbling argon through them while under sonication. However, during later research with 4-methoxyphenylphosphine derivatives, a novel work-up procedure was developed and the yields improved to 34 and 32%. This procedure is described later in the ‘Asymmetric Catalysis’ section.

SCHEME 3

The absolute configurations of **2a** and **2b** were determined by the synthesis of **2b** from enantiopure dibromide (+)-(S_P) **8**. This was obtained by resolution of the racemate by preparative chiral HPLC (see Experimental Section).

Synthesis of *Ortho* Isomers

Ortho-substituted phosphinyl-oxazolinyll[2.2]paracyclophanes similar to **3** (Figure 1) have been previously synthesized in our group by a metal-phosphine exchange of *ortho* oxazolinyll-palladacycles.²⁸ Although efficient, the use of stoichiometric (1.1 eq) palladium acetate is expensive so an alternative procedure was sought. Attempted *ortho*-directed lithiations proved problematic due to competitive 1,2-addition of the alkyl lithium to the oxazoline, and 1,4-addition to the [2.2]paracyclophane backbone.²⁸ Hou, however, showed that *ortho*-lithiation of the diastereotopic mixture of oxazolinyll[2.2]paracyclophanes **5**, using $n\text{-BuLi}$ with TMEDA in Et_2O , was successful, and that after quenching with PhSSPh or PhSeSePh , a mixture of the desired *ortho* products, as well as those resulting

from lithiation at the benzylic position, were obtained.^{34,35} An attempt by us to synthesize phosphines **3** by carrying out Hou's lithiation and then adding ClPPh₂ led to a mixture of products (including 17% starting material), none of which could be identified as the desired phosphines **3**.

Hence, the *ortho* substitution pattern was obtained by *ortho* lithiation of the carbamate **11** (Scheme 4), a reaction which has been shown to proceed readily and highly regioselectively when *s*-BuLi is used in the presence of TMEDA.^{10,36,37} According to the literature, lithiation of **11** followed by reaction with DMF and an acidic work-up leads to the *ortho* hydroxy-aldehyde FHPC (see Introduction), in 64% yield, due to facile hydrolysis of the carbamate during work-up. We desired the carboxylic acid rather than the aldehyde, so gaseous CO₂ was used as the electrophile in place of DMF. Interestingly, the yield was higher and the carbamate was left intact. In view of our synthetic plan, this was actually a useful result as it acted as a protecting group during subsequent amidation of the carboxylic acid to give separable diastereoisomers **13**. The absolute configurations of **13** were determined by synthesis of **13b** from enantiopure (–)-(R_P) **11**, which itself was obtained in two steps from enantiopure bromo[2.2]paracyclophane. The latter compound was synthesized by monolithiation and protonation of enantiopure dibromide **8**. Unfortunately, removal of the carbamate from **13** was impossible under acidic conditions and forcing basic conditions (NaOH, MeOH, reflux, 20 h), although successful, gave **15** in low yields along with the carbamate-migrated by-products **14**. The carbamates **14** could only be hydrolyzed under yet harsher conditions (KOH, *i*-PrOH, reflux, 51 h). The overall calculated yields of **15a** and **15b**, from **13a** and **13b**, over these two steps are 69 and 56%, respectively. Strangely, when these same conditions were applied to the starting carbamates **13** directly, a reduced overall yield of **15a**, but increased yield of **15b**, was observed (hydrolysis of **13a**: 34% of product, 8% of SM; hydrolysis of **13b**: 60% of product, 0% of SM). An attempt was also made to carry out carbamate hydrolysis after

formation of the oxazoline **16a**, but this was unsuccessful and only the ring-opened product **13a** (actually the precursor of **16a**) could be isolated in 10% yield.

SCHEME 4

On treatment with TiF_2O , the hydroxy-amides **15** underwent simultaneous cyclization and triflation³⁸ of the phenol group to give oxazoliny-triflates **18** (Scheme 5). Subsequent nucleophilic aromatic substitution of the triflate with Ph_2PK gave the desired *ortho* phosphinyl-oxazolines **3**. Inspection of the NMR spectra of **3a** and **3b** is very interesting and reveals information about the compounds' conformations. The chemical shift of the *CH* proton in the oxazoline ring (identified by COSY, DEPT

and HETCOR NMR experiments) is 3.33 ppm for **3a** and 2.99 ppm for **3b**. The increased shielding occurring in **3b** is attributed to delocalization of electron density from the P-lone pair, through the π -system, onto the N-atom of the oxazoline ring. Correspondingly, ^{31}P NMR of **3b** shows the P-atom to be more deshielded (1.48 ppm) than that of **3a** (0.20 ppm). In conclusion, **3b** must have the oxazoline, P-lone pair and [2.2]paracyclophane aromatic ring in conjugation, whereas **3a** does not.

SCHEME 5

Asymmetric Catalysis

Asymmetric allylic alkylation was chosen as a test reaction for the new ligands to make a good comparison with Hou's work with compounds **1**.²⁵ As hoped, a different positional isomer of the same ligand gave a much higher ee; *pseudo-ortho* **2a** gave 82% ee where the original *pseudo-geminal* derivative gave 56% ee (Table 1).

TABLE 1. Palladium-Catalyzed Asymmetric Allylic Alkylation

Entry	Ligand	Substitution	Time (h)	Yield (%)	ee (%)	abs. config.
1	1a	<i>pseudo-gem.</i>	6	>98	56 ^a	(<i>S</i>)
2	1b	<i>pseudo-gem.</i>	8	96	30	(<i>S</i>)
3	2a	<i>pseudo-ortho</i>	10	>98	82	(<i>S</i>)
4	2b	<i>pseudo-ortho</i>	10	>98	28	(<i>R</i>)
5	3a	<i>ortho</i>	8	>98	23	(<i>S</i>)
6	3b	<i>ortho</i>	7	>98	47	(<i>S</i>)
7	19a	<i>pseudo-ortho</i>	5	>98	89	(<i>S</i>)
8	19b	<i>pseudo-ortho</i>	20	>98	63	(<i>R</i>)
9	22a^b	<i>pseudo-ortho</i>	5	>98	89	(<i>R</i>)
10	22b^b	<i>pseudo-ortho</i>	20	>98	62	(<i>S</i>)

^a Hou obtained 62% ee (ref. 25). ^b *Pseudo*-enantiomer of **2** (see text).

Rather than simply being an effect of the bite angle at the metal in the active catalyst, this result must arise from the chiral environment being entirely different to that of the complex formed with **1a**. As shown in Figure 2, in **1a**, half of the [2.2]paracyclophane backbone shields one side of the active site, whereas **2a** could form a *pseudo* C₂-symmetric type complex. This argument is especially relevant when one considers that the opposite diastereoisomers of the *pseudo-ortho* ligands gave opposite enantiomers of the product (entries 3 and 4), whereas the *pseudo-geminal* and *ortho* ligands gave the same enantiomer (entries 1, 2, 5 and 6). The latter selectivities must depend more strongly on the stereochemistry of the oxazoline substituent than that of the [2.2]paracyclophane backbone and the conformations shown in Figure 2 are in accord with this.

FIGURE 2

Possible conformation of
active catalyst with **1a** Possible conformation of
active catalyst with **2a**

Hou showed that the allylic alkylation could be optimized by using derivatives of the *pseudo-geminal* compounds with a di(4-methoxyphenyl)phosphinyl group in place of the diphenylphosphinyl group. We therefore synthesized such derivatives **19** of the *pseudo-ortho* compounds (Figure 3), using the same technique as for **2**, but using (MeOC₆H₄)₂PCl instead of Ph₂PCl. These electron rich phosphines were found to be more susceptible to oxidation and the oxides could not be reduced by the usual method using HSiCl₃.⁸ However, the yields could be improved from 9 and 6% (of **19a** and **19b**, respectively) to 32 and 31% by modifying the work-up. Hence, in place of the addition of degassed aq NH₄Cl and extraction with degassed DCM, 2 equiv of Et₃N were added (to quench HCl formed later) along with Et₂O and the mixture suspended directly onto silica. After drying, this was placed atop a silica column and chromatography carried out as quickly as possible to give the separated diastereoisomers.

FIGURE 3

Use of compounds **19** as ligands in the allylic alkylation reaction gave improved enantioselectivities of 89 and 63% ee, respectively (Table 1, entries 7 and 8). Further attempted ligand optimization involved the synthesis of compounds **22** (Scheme 6) possessing phenyl-substituted oxazoline units. (It should be noted that the Ph-substituted products **22** were *pseudo* enantiomers of the *i*-Pr-analogues **2** because D-phenylglycinol was used. Accordingly, the products from the allylic alkylation reaction were the opposite enantiomers.) It was also found that the diastereoisomers could be separated at the amide stage. Cyclization to the oxazolines **21** required harsher conditions than the *i*-Pr analogues; an extra equiv of each reagent was added and the mixture heated at 50 °C for a further 4 h. Heating was necessary due to the lower solubility of the starting amides **20**. Once again, the absolute configurations of **21** were assigned by synthesis of **21a** from enantiopure (+)-(*S_p*) **9**.

Three different procedures for the metallation of **21b** were tested, including using *n*-BuLi, *t*-BuLi (both at −78 °C) and *s*-Bu₂Mg.LiCl at rt, a reagent recently described by Knochel as highly effective for the metallation of aryl bromides.³⁹ Reaction of the organometallics, generated in these ways, with the chlorophosphine gave 70, 33 and 0% of the desired product **22b**, respectively. The reaction starting with *t*-BuLi gave an unidentified by-product which was difficult to separate from the product and that starting with Knochel's reagent gave 29% starting material and 33% oxazoliny[2.2]paracyclophane, resulting

from quenching of the unreacted paracyclophanyl metallic during work-up. Hence, for the metallation of the opposite diastereoisomer **21a**, *n*-BuLi became the reagent of choice, but strangely, in this case, the procedure was completely unsuccessful. Instead, lithiation at $-78\text{ }^{\circ}\text{C}$ gave a mixture of products (including one with $m/z=487/489$, corresponding to addition of a butyl group to the starting material). It was hypothesized that problems were arising due to either deprotonation of the oxazoline at the benzylic position or migration of the anion resulting from bromo-lithium exchange. To avoid this, the reaction was carried out at $-95\text{ }^{\circ}\text{C}$ using a diethyl ether/liquid nitrogen bath. The desired product **22a** was now formed and isolated in 57% yield. Its use as a ligand in allylic alkylation, however, gave the same ee (89%) as the *i*-Pr-oxazoline **19a**. Similarly, the diastereoisomer **22b** acted with almost the equivalent selectivity as **19b**. This is understandable since the phenyl group is only ‘longer’ than the *i*-Pr group and the steric bulk is in fact less (A values ($-\Delta G$ of interconversion between equatorial and axial substituents on a cyclohexane ring): Ph = 2.9, *i*-Pr = 2.15 kcal mol $^{-1}$).⁴⁰ This explanation agrees with the conformation of the active catalyst with **2a**, proposed in Figure 2.

SCHEME 6

Conclusion

We have devised synthetic routes to all aromatic-substituted regioisomers of phosphinyl-oxazoliny[2.2]paracyclophanes which are relevant for use as chelating ligands in asymmetric catalysis. In the allylic alkylation reaction, use of the *pseudo-ortho* version of a previously reported *pseudo-geminal i*-Pr-substituted compound gave higher enantioselectivity. However, the Ph-substituted *pseudo-ortho* phosphinyl-oxazoliny[2.2]paracyclophane was less selective than the published *pseudo-geminal* analogue which shows that the conformation of the active catalyst with the *pseudo-ortho* ligand forms a chiral environment which obeys different rules for selectivity.

Experimental

All air sensitive manipulations were carried out under an inert atmosphere of Ar. Toluene, THF and Et₂O for reactions were distilled, under nitrogen, from sodium/benzophenone ketyl radical. DCM for reactions was distilled, under nitrogen, from CaH₂. Et₂O, pentane, petroleum ether, DCM, EtOAc and CHCl₃ for column chromatography were distilled before use. Flash column chromatography was carried out using silica gel (bead size 40-63 μ m). Analytical thin layer chromatography (TLC) was performed using precoated aluminium-backed plates (silica gel 60 F₂₅₄) and visualized with UV radiation at 254 nm, or by staining with a solution of potassium permanganate (3 g), K₂CO₃ (20 g) and NaOH (5%, 5 mL) in water (300 mL). ¹H, ¹³C, ³¹P and ¹⁹F NMR spectra were recorded at 300, 400 or 500 MHz and are reported as follows: chemical shift (ppm), (number of protons, multiplicity, coupling constant *J* (Hz), assignment, when confirmed by using DEPT, COSY and HETCOR experiments). IR spectra were measured as KBr pellets, neat (in the case of liquid compounds) or in CHCl₃ solution; absorptions are given in wave numbers (cm⁻¹). MS was carried out using EI or CI (methane). Optical rotation measurements were conducted at room temperature at a wavelength of 589 nm.

(±)-[2.2]Paracyclophane-4-carboxylic acid (**4**),²⁴ (±)-4,12-dibromo[2.2]paracyclophane (**7**),³² (±)-4-bromo[2.2]paracyclophane-12-carboxylic acid (**9**) (and its enantiopure forms),³³ (±)-*O*-(4-[2.2]paracyclophanyl) diethylcarbamate (**11**)¹⁰ and 1,3-diphenyl-2-propenyl acetate⁴¹ were prepared according to literature procedures. Acid **4** was resolved according to Rozenberg's procedure³¹ and dibromide **7** by preparative chiral HPLC [OD column, 55 mm ID, *n*-hexane:*i*-PrOH = 95:5), flow rate = 30 mL min⁻¹, 2 bar, *t*_{(R)-(-)} = 17 min, *t*_{(S)-(+)} = 23 min]; HPLC analysis (Chiralcel OD column, *n*-hexane:*i*-PrOH = 95:5, flow rate = 1 mL min⁻¹, *t*_{(R)-(-)} = 5.9 min, *t*_{(S)-(+)} = 7.5 min).

(-)-(S,4R_P)- and (+)-(S,4S_P)-4-(4-*iso*-Propyloxazolin-2-yl)[2.2]paracyclophane (5a** and **5b**)**

Thionyl chloride (16.8 mL, 230.3 mmol) was added to carboxylic acid **4** (10.31 g, 40.91 mmol) and the resulting mixture heated at 60 °C for 4 h. The excess thionyl chloride was removed by evaporation and the final traces by azeotropic distillation with toluene. The resulting crude acid chloride was dissolved in DCM (67 mL) and cooled to 0 °C. A solution of L-valinol (8.36 g, 81.00 mmol) and Et₃N (11.4 mL, 81.00 mmol) in DCM (10 mL) was added, the reaction mixture allowed to warm to rt and stirred for 24 h. DCM (500 mL) was then added and the solution washed with aq NaHCO₃ solution (3.5% w/v, 2 × 600 mL) and brine (600 mL). The organic phase was dried over MgSO₄, filtered, concentrated and dried *in vacuo* to give the crude amide. PPh₃ (18.78 g, 71.59 mmol), MeCN (859 mL), CCl₄ (6.9 mL, 71.6 mmol) and Et₃N (10.1 mL, 71.6 mmol) were added and the mixture stirred for 18 h. DCM (850 mL) was then added and the solution washed with brine (2 × 850 mL), dried over MgSO₄, filtered and concentrated. Flash column chromatography, gradient elution [pentane/EtOAc (19:1),(9:1)] gave an inseparable mixture of the title compounds as a pale yellow solid (11.63 g, 89%); *R*_f (petroleum ether:EtOAc = 8:2) 0.52.

A pure sample of (–)-(S,4R_P) **5a** was prepared in the same manner as that described above, but on a smaller scale, from enantiopure (–)-(4R_P)-carboxylic acid **4**.³¹ Colorless oil; [α]_D²⁰ –170 (*c* 0.88, CHCl₃); ¹H NMR (400 MHz) δ 7.04 (1 H, d, *J* = 1.7, H-5), 6.61–6.46 (6 H, m, H-7, 8, 12, 13, 15, 16), 4.40 (1 H, dd, *J* = 9.3, 7.7, OCHH), 4.20–4.08 (3 H, m, OCHH, NCH, H-2a), 3.19–2.97 (6 H, m, H-1a, 1b, 9a, 9b, 10a, 10b), 2.85 (1 H, ddd, *J* = 12.6, 10.2, 6.6, H-2b), 1.93 (1 H, oct, *J* = 6.7, CH(CH₃)₂), 1.11 (3 H, d, *J* = 6.7, CH₃), 1.01 (3 H, d, *J* = 6.7, CH₃); ¹³C NMR (100 MHz) δ 163.4, 140.7, 139.8, 139.4, 139.2, 135.6, 134.6, 134.2, 132.8, 132.6, 132.2, 131.1, 128.4, 72.9, 69.3, 35.9, 35.3, 35.1, 34.9, 32.9, 19.2, 18.2; IR (neat, cm^{–1}) $\nu_{\max}$ 1640 (C=N); MS (EI, *m/z*) 320 (14), 319 (M⁺, 57), 276 (M⁺–*i*-Pr, 9), 216 (15), 215 (CH₂C₆H₃(oxazoline)CH₂⁺, 100), 159 (11), 147 (11), 104 (14); HRMS Found 319.193581. C₂₂H₂₅NO requires 319.193614.

A pure sample of (+)-(S,4S_P) **5b** was obtained as a by-product from the synthesis of **1b** as a pale yellow solid; mp 93.5–95.0 °C; [α]_D²⁰ +26 (*c* 1.20, CHCl₃); ¹H NMR (400 MHz) δ 7.04 (1 H, d, *J* = 1.9, H-5), 6.58 (1 H, dd, *J* = 8.0, 1.9, H-7), 6.57–6.48 (5 H, m, H-8, 12, 13, 15, 16), 4.37–4.30 (2 H, m, OCHH, H-2a), 4.17–4.08 (2 H, m, OCHH, NCH), 3.20–2.98 (6 H, m, H-1a, 1b, 9a, 9b, 10a, 10b), 2.87 (1 H, ddd, *J* = 12.9, 10.2, 6.9, H-2b), 1.95 (1 H, oct, *J* = 6.7, CH(CH₃)₂), 1.17 (3 H, d, *J* = 6.7, CH₃), 1.05 (3 H, d, *J* = 6.7, CH₃); ¹³C NMR (100 MHz) δ 162.9, 140.9, 139.8, 139.3, 139.2, 135.7, 134.6, 134.1, 132.8, 132.6, 132.2, 131.2, 128.3, 73.0, 69.2, 35.8, 35.3, 34.9, 34.7, 33.4, 19.3, 18.7; IR (KBr, cm^{–1}) $\nu_{\max}$ 1637 (C=N); MS (EI, *m/z*) 320 (14), 319 (M⁺, 56), 276 (M⁺–*i*-Pr, 8), 216 (16), 215 (CH₂C₆H₃(oxazoline)CH₂⁺, 100), 159 (10), 147 (10), 104 (13); HRMS Found xxxSUBMITTEDxx. C₂₂H₂₅NO requires xxxxx.

(–)-(S,4S_p,13R_p)-4-Bromo-13-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (6a)²⁷

The diastereomeric mixture of oxazolines **5** (0.13 g, 0.40 mmol) was dissolved in dry DCM (11 mL). Iron powder (3 mg, 0.05 mmol) was added followed by bromine (0.03 mL, 0.48 mmol) [Note: On larger scales, a solution of bromine should be added dropwise, according to the literature procedure.²⁴ and the mixture heated at reflux for 16 h. The reaction mixture was washed with saturated NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organic phase was dried over MgSO₄, filtered and concentrated. Flash column chromatography, gradient elution [petroleum ether/EtOAc (9:1), (8:2)] gave the title compound as a white solid (0.07 g, 42%); *R_f* (petroleum ether:EtOAc = 8:2) 0.58; mp 131.0-133.0 °C; [α]_D²⁰ –5 (*c* 1.00, CH₂Cl₂); ¹H NMR (500 MHz) δ 7.19 (1 H, br.s, H-12), 6.64 (1 H, d, *J* = 1.5, H-5), 6.62 (1 H, dd, *J* = 7.8, 2.0, H-16), 6.58 (1 H, d, *J* = 7.8, H-15), 6.55 (1 H, d, *J* = 7.8, H-8), 6.53 (1 H, dd, *J* = 7.8, 1.5, H-7), 4.56 (1 H, ddd, *J* = 13.7, 10.4, 4.1, H-1a), 4.40 (1 H, dd, *J* = 9.4, 8.2, OCHH), 4.11 (1 H, ddd, *J* = 9.4, 8.2, 6.6, NCH), 4.04 (1 H, t, *J* = 8.2, OCHH), 3.56 (1 H, ddd, *J* = 12.9, 10.4, 4.1, H-2a), 3.06 (2 H, m, H-10a, 10b), 3.01 (3 H, m, H-9a, 9b, 1b), 2.93 (1 H, ddd, *J* = 12.9, 10.4, 4.1, H-2b), 1.89 (1 H, oct, *J* = 6.6, CH(CH₃)₂), 1.05 (3 H, d, *J* = 6.6, CH₃), 0.89 (3 H, d, *J* = 6.6, CH₃); ¹³C NMR (75 MHz) δ 163.0, 141.1, 141.0, 139.2, 138.6, 136.6, 136.0 (C-15), 135.9 (C-5), 134.9 (2 C, s, C-8, 16), 132.9 (C-12), 131.6 (C-7), 126.3, 73.2 (NCH), 68.7 (OCH₂), 35.1 (C-2), 34.9 (C-10), 34.5 (C-9), 33.6 (C-1), 32.5 (CH(CH₃)₂), 19.6 (CH₃), 18.1 (CH₃); IR (KBr, cm^{–1}) $\nu_{\max}$ 1637 (C=N); MS (CI, methane *m/z*) 428 (M+C₂H₅⁺, 22), 426 (M+C₂H₅⁺, 21), 401 (24), 400 (M+H⁺, 100), 399 (46), 398 (M+H⁺, 98), 397 (24), 215 (CH₂C₆H₃(oxazoline)CH₂⁺, 7).

(–)-(S,4R_p,13S_p)-4-Bromo-13-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (6b)²⁷

Further elution gave the title compound as a white solid (0.08 g, 49%); *R_f* (petroleum ether:EtOAc = 8:2) 0.47; mp 147.5-149.0 °C; [α]_D²⁰ –104 (*c* 1.00, CH₂Cl₂); ¹H NMR (500 MHz) δ 7.24 (1 H, br.s, H-

12), 6.66 (1 H, br.s, H-5), 6.61 (1 H, dd, $J = 7.9, 1.8$, H-16), 6.56 (1 H, br.s, H-7, 8), 6.55 (1 H, d, $J = 7.9$, H-15), 4.53 (1 H, ddd, $J = 13.1, 10.0, 4.3$, H-1a), 4.42 (1 H, dd, $J = 9.5, 8.4$, OCHH), 4.13 (1 H, t, $J = 8.4$, OCHH), 4.00 (1 H, m, NCH), 3.54 (1 H, ddd, $J = 13.2, 10.0, 4.0$, H-2a), 3.09 (3 H, m, H-10a, 10b, 1b), 3.02 (2 H, m, H-9a, 9b), 2.93 (1 H, ddd, $J = 13.2, 10.4, 4.3$, H-2b), 1.96 (1 H, oct, $J = 6.9$, CH(CH₃)₂), 1.16 (3 H, d, $J = 6.9$, CH₃), 0.97 (3 H, d, $J = 6.9$, CH₃); ¹³C NMR (75 MHz) δ 164.2 (C=N), 141.2, 140.6, 139.0, 138.6, 136.1, 136.0, 135.1, 134.7, 132.7 (C-12), 131.5, 126.9, 126.6, 73.0 (NCH), 69.8 (OCH₂), 35.4 (C-2), 34.8 (C-10), 34.5 (C-9), 33.2 (C-1), 33.1 (CH(CH₃)₂), 19.8 (CH₃), 18.9 (CH₃); IR (KBr cm⁻¹) $\nu_{\max}$ 1643 (C=N); MS (CI, methane, m/z) 428 (M+C₂H₅⁺, 20), 426 (M+C₂H₅⁺, 21), 401 (21), 400 (M+H⁺, 88), 399 (45), 398 (M+H⁺, 100), 397 (25), 215 (CH₂C₆H₃(oxazoline)CH₂⁺, 7); Anal. Found C, 66.08; H, 5.94; N, 3.26. C₂₂H₂₄BrNO requires C, 66.34; H, 6.07; N, 3.52.

(+)-(S,4S_p,13R_p)-4-Diphenylphosphinyl-13-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (1a)²⁵

t-BuLi (15% w/v solution in *n*-pentane, 2.3 mL, 4.2 mmol) was added dropwise to a solution of bromide **6a** (0.80 g, 2.00 mmol) in THF (20 mL) at -78 °C to give an orange solution. After stirring for 1.5 h, ClPPh₂ (0.75 mL, 4.20 mmol) was added dropwise. The resulting pale yellow solution was allowed to warm to rt and stirred for 18 h. A degassed (by argon bubbling under sonication), saturated aq solution of NH₄Cl (10 mL) was added and shaken vigorously. The aq layer was separated and extracted with degassed DCM (2 × 14 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography (degassed pentane:DCM:EtOAc = 20:4:1) gave the title compound as a white solid (0.63 g, 62%); R_f (petroleum ether:EtOAc = 8:2) 0.64; mp 134.0-137.0 °C; $[\alpha]_D^{20} +4$ (*c* 0.44, CHCl₃); ¹H NMR (300 MHz) δ 7.33 (4 H, m, P-C₆H₅), 7.24 (6 H, m, P-C₆H₅), 7.06 (1 H, br.s, H-12), 6.64 (2 H, br.s, H-15, 16), 6.50 (2 H, m, H-7, 8), 5.84 (1 H, dd, $J_{H-P} = 7.9, J = 1.5$, H-5), 4.61 (2 H, m, OCHH, H-1a), 4.20 (1 H, td, $J = 9.2, 7.0$, NCH), 4.10 (1 H, dd, $J = 9.2, 7.2$, OCHH), 3.49

(1 H, m, H-2a), 3.07 (1 H, m, H-10a), 2.85 (5 H, m, H-1b, 2b, 9a, 9b, 10b), 1.92 (1 H, oct, $J = 7.0$, $\text{CH}(\text{CH}_3)_2$), 1.13 (3 H, d, $J = 7.0$, CH_3), 0.92 (3 H, d, $J = 7.0$, CH_3); ^{13}C NMR (75 MHz) δ 162.7 (C=N), 144.0 (d, $J_{\text{C-P}} = 17.3$, C-4), 141.6, 138.83 (d, $J_{\text{C-P}} = 14.3$), 138.80, 138.6, 138.0 (d, $J_{\text{C-P}} = 10.7$), 137.5 (d, $J_{\text{C-P}} = 13.7$), 136.1, 135.0, 134.8, 134.2, 133.7, 133.6 (d, $J_{\text{C-P}} = 2.4$), 133.4 (2C, s), 133.3 (d, $J_{\text{C-P}} = 2.9$), 133.2, 128.52, 128.49, 128.40, 128.3, 128.2, 128.1, 127.0, 73.8 (NCH), 69.1 (OCH₂), 36.3, 34.9, 34.8, 33.6 (d, $J_{\text{C-P}} = 14.9$, C-2), 32.7 ($\text{CH}(\text{CH}_3)_2$), 20.0 (CH_3), 18.5 (CH_3); ^{31}P NMR (121 MHz) δ -4.12; IR (KBr, cm^{-1}) ν_{max} 1637 (C=N); MS (EI, m/z) 504 (26), 503 (M^+ , 100), 502 (58), 488 ($\text{M}^+ - \text{Me}$, 18) 460 ($\text{M}^+ - i\text{-Pr}$, 18), 434 (19), 289 (11), 288 ($\text{CH}_2\text{C}_6\text{H}_3(\text{PPh}_2)\text{CH}_2^+$, 38), 287 (18), 208 (16), 198 (19), 178 (11). Data agrees with that published.²⁵

(-)-(S,4R_p,13S_p)-4-Diphenylphosphinyl-13-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (1b)²⁵

Treatment of bromide **6b**, according to the procedure for the synthesis of **1a**, gave the title compound as a white solid (0.46 g, 46%); R_f (petroleum ether:EtOAc = 8:2) 0.67; mp 159.0-161.0 °C; $[\alpha]_{\text{D}}^{20}$ -80 (c 0.39, CHCl_3); ^1H NMR (300 MHz) δ 7.35 (4 H, m, P-C₆H₅), 7.23 (6 H, m, P-C₆H₅), 7.15 (1 H, br.s, H-12), 6.62 (2 H, br.s), 6.51 (2 H, m, H-7, 8), 5.83 (1 H, dd, $J_{\text{H-P}} = 8.2$, $J = 1.7$, H-5), 4.55 (1 H, dd, $J = 9.9$, 8.1, OCHH), 4.51 (1 H, m, H-1a), 4.31 (1 H, t, $J = 8.1$, OCHH), 4.10 (1 H, m, NCH), 3.43 (1 H, m, H-2a), 3.06 (1 H, m, H-10a), 2.87 (5 H, m, H-1b, 2b, 9a, 9b, 10b), 2.19 (1 H, oct, $J = 6.8$, $\text{CH}(\text{CH}_3)_2$), 1.19 (3 H, d, $J = 6.8$, CH_3), 1.02 (3 H, d, $J = 6.8$, CH_3); ^{13}C NMR (75 MHz) δ 163.5 (C=N), 143.7 (d, $J_{\text{C-P}} = 17.2$, C-4), 141.1, 139.2 (d, $J_{\text{C-P}} = 14.3$), 138.9, 138.0 (d, $J_{\text{C-P}} = 10.7$), 137.2 (d, $J_{\text{C-P}} = 13.7$), 136.1, 135.1, 134.8, 134.5, 133.7, 133.6, 133.4 (2C, s), 133.2 (d, $J_{\text{C-P}} = 4.2$), 128.6, 128.52, 128.48, 128.38, 128.2, 128.1, 127.0, 73.1 (NCH), 69.9 (OCH₂), 35.7, 34.9, 34.8, 34.1 (d, $J_{\text{C-P}} = 15.5$, C-2), 32.9 ($\text{CH}(\text{CH}_3)_2$), 20.0 (CH_3), 19.1 (CH_3); ^{31}P NMR (162 MHz) δ -5.46; IR (KBr, cm^{-1}) ν_{max} 1624 (C=N); MS (EI, m/z) 504 (38), 503 (M^+ , 100), 502 (67), 488 ($\text{M}^+ - \text{Me}$, 19) 460 ($\text{M}^+ - i\text{-Pr}$, 27), 434 (16), 289 (20),

288 ($\text{CH}_2\text{C}_6\text{H}_3(\text{PPh}_2)\text{CH}_2^+$, 58), 287 (33), 208 (31), 198 (27), 178 (18). Data agrees with that published.²⁵

(-)-(S,4*R*_p,12*R*_p)- and (+)-(S,4*S*_p,12*S*_p)-4-Bromo-12-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (10a and 10b)

Thionyl chloride (1.35 mL, 18.49 mmol) was added to (±)-bromo-carboxylic acid **9**³³ (1.08 g, 3.28 mmol) and the resulting mixture heated at 60 °C for 4 h. The excess thionyl chloride was removed by evaporation and the final traces by azeotropic distillation with toluene. The resulting crude acid chloride was dissolved in DCM (5 mL) and cooled to 0 °C. A solution of L-valinol (0.67 g, 6.50 mmol) and Et₃N (0.91 mL, 6.50 mmol) in DCM (1 mL) was added and the reaction mixture allowed to warm to rt and stirred for 24 h. DCM was then added (60 mL) and the solution washed with aq NaHCO₃ solution (3.5% w/v, 2 × 70 mL) and brine (70 mL). The organic phase was dried over MgSO₄, filtered, concentrated and dried *in vacuo* to give the crude amide. PPh₃ (1.51 g, 5.75 mmol), MeCN (69 mL), CCl₄ (0.56 mL, 5.75 mmol) and Et₃N (0.81 mL, 5.75 mmol) were added and the mixture stirred for 18 h. DCM (70 mL) was then added and the solution washed with brine (2 × 70 mL), dried over MgSO₄, filtered and concentrated. Flash column chromatography, gradient elution (petroleum ether:EtOAc = 14:1 → 9:1) gave an inseparable mixture of the title compounds as a pale yellow solid (1.04 g, 80%); *R_f* (petroleum ether:EtOAc = 1:4) 0.69.

A pure sample of (-)-(S,4*R*_p,12*R*_p)-**10a** was prepared in the same manner as that described above, but on a smaller scale, from enantiopure (-)-(4*R*_p,12*R*_p)-4-bromo[2.2]paracyclophane-12-carboxylic acid (**9**).³³ White solid; mp 61.5-63.5 °C; $[\alpha]_{\text{D}}^{20}$ -114 (*c* 0.95, CHCl₃); ¹H NMR (300 MHz) δ 7.68 (1 H, br.s, H-13), 6.65 (1 H, d, *J* = 1.3, H-5), 6.59 (2 H, br.s, H-15, 16), 6.56 (1 H, dd, *J* = 7.9, 1.3, H-7), 6.49 (1 H, d, *J* = 7.9, H-8), 4.41 (1 H, m, OCHH), 4.20-4.08 (3 H, m, OCHH, NCH, H-10a), 3.46 (1 H, ddd, *J* = 13.4,

9.7, 1.7, H-2a), 3.20 (1 H, ddd, $J = 12.9, 9.7, 6.7$), 3.06 (2 H, m), 2.96 (1 H, ddd, $J = 12.6, 9.4, 7.2$), 2.79 (2 H, m) 1.87 (1 H, oct, $J = 6.7$, $\text{CH}(\text{CH}_3)_2$), 1.11 (3 H, d, $J = 6.7$, CH_3), 1.01 (3 H, d, $J = 6.7$, CH_3); ^{13}C NMR (75 MHz) δ 163.3 (C=N), 142.0, 140.3, 139.2, 138.8, 135.6, 135.0, 134.94, 134.87, 131.2, 130.3 (C-13), 128.2, 126.6, 72.9 (NCH), 69.6 (OCH_2), 36.1, 35.8, 34.0, 33.1 ($\text{CH}(\text{CH}_3)_2$), 32.5, 19.1 (CH_3), 18.5 (CH_3); IR (CHCl_3 , cm^{-1}) ν_{max} 1639 (C=N); MS (EI, m/z) 400 (12), 399 (M^+ , 48), 398 (13), 397 (M^+ , 47), 356 ($\text{M}^+ - \text{i-Pr}$, 6), 354 ($\text{M}^+ - i\text{-Pr}$, 6), 216 (17), 215 ($\text{CH}_2\text{C}_6\text{H}_3(\text{oxazoline})\text{CH}_2^+$, 100), 214 (11), 172 (5), 159 (11), 147 (9), 146 (5); HRMS Found 397.1042. $\text{C}_{22}\text{H}_{24}^{79}\text{BrNO}$ requires 397.1041.

Similarly, a pure sample of (+)-(S,4S_p,12S_p)-**10b** was prepared from enantiopure (+)-(4S_p,12S_p)-4-bromo[2.2]paracyclophane-12-carboxylic acid (**9**).³³ White solid; mp 101.0-102.0 °C; $[\alpha]_{\text{D}}^{20} +17$ (c 0.89, CHCl_3); ^1H NMR (300 MHz) δ 7.62 (1 H, d, $J = 1.5$, H-13), 6.62 (1 H, d, $J = 1.7$, H-5), 6.58 (1 H, d, $J = 7.9$), 6.55 (2 H, m), 6.47 (1 H, d, $J = 7.7$), 4.32 (2 H, m, H-10, OCHH), 4.07 (2 H, m, OCHH, NCH), 3.45 (1 H, ddd, $J = 13.4, 9.9, 1.7$), 3.17 (1 H, ddd, $J = 13.1, 9.9, 6.7$), 3.05 (3 H, m), 2.78 (2 H, m), 1.92 (1 H, oct, $J = 6.7$, $\text{CH}(\text{CH}_3)_2$), 1.17 (3 H, d, $J = 6.7$, CH_3), 1.05 (3 H, d, $J = 6.7$, CH_3); ^{13}C NMR (75 MHz) δ 162.8 (C=N), 142.1, 140.6, 139.0, 138.8, 135.6, 135.0, 134.94, 134.86, 131.3, 130.0 (C-13), 128.1, 126.6, 73.4 (NCH), 69.3 (OCH_2), 35.73, 35.68, 33.5 (2C, s, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{-CH}_2$), 32.6, 19.4 (CH_3), 18.9 (CH_3); IR (KBr, cm^{-1}) ν_{max} 1633 (C=N); MS (EI, m/z) 400 (7), 399 (M^+ , 29), 398 (11), 397 (M^+ , 32), 356 ($\text{M}^+ - i\text{-Pr}$, 5), 354 ($\text{M}^+ - i\text{-Pr}$, 5), 216 (16), 215 ($\text{CH}_2\text{C}_6\text{H}_3(\text{oxazoline})\text{CH}_2^+$, 100), 214 (25), 172 (5), 147 (9), 146 (5); HRMS Found 397.1042. $\text{C}_{22}\text{H}_{24}^{79}\text{BrNO}$ requires 397.1041.

(+)-(S,4R_p,12R_p)-4-Diphenylphosphinyl-13-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (2a)

n-BuLi (15% w/v solution in *n*-hexane, 0.35 mL, 0.81 mmol) was added dropwise to a solution of the diastereomeric mixture of bromides **10** (0.22 g, 0.54 mmol) in THF (5.4 mL) at -78 °C to give an orange solution. After stirring for 1.5 h, Ph_2PCl (0.20 mL, 1.14 mmol) was added dropwise to give a black

solution, which slowly became orange. After 10 min, the cooling bath was removed and the reaction mixture stirred for a further 3 h. Ordinary 'wet' Et₃N (0.15 mL, 1.08 mmol) was added followed by Et₂O (5 mL) and the resulting mixture added to silica gel (2.3 g) and DCM (5 mL). The solvent was evaporated to leave the crude product mixture suspended on silica which was added to the top of a column of silica gel for flash chromatography, gradient elution (petroleum ether:DCM:EtOAc = 20:3:1 - > 15:4:1 -> 7:2:1. This gave the title product as a white solid (0.09 g, 34%); *R_f* (petroleum ether:CHCl₃:EtOAc = 7:2:1) 0.57; mp 105.0-106.0 °C; [α]_D²⁰ +33 (*c* 0.62, CHCl₃); ¹H NMR (400 MHz) δ 7.60 (1 H, d, *J* = 1.4, H-13), 7.39 (2 H, m, P-C₆H₅), 7.36-7.20 (8 H, m, P-C₆H₅), 6.64 (1 H, dd, *J* = 7.8, 1.4, H-15), 6.59 (1 H, d, *J* = 7.8, H-16), 6.57 (1 H, dd, *J* = 7.9, 1.8, H-7), 6.49 (1 H, dd, *J* = 7.9, *J*_{H-P} = 5.5, H-8), 5.87 (1 H, dd, *J*_{H-P} = 8.2, *J* = 1.8, H-5), 4.33 (1 H, dd, *J* = 8.8, 7.4, OCHH), 4.18 (1 H, dd, *J* = 12.5, 9.4, H-10a), 3.94-3.85 (2 H, m, NCH, OCHH), 3.44 (1 H, ddd, *J* = 12.8, 10.2, 6.9, H-1a), 3.30 (1 H, dd, *J* = 13.7, 10.2, H-2a), 3.08 (1 H, dd, *J* = 12.8, 10.2, H-1b), 3.01 (1 H, dd, *J* = 12.5, 9.9, H-9a), 2.86 (1 H, ddd, *J* = 12.5, 9.4, 7.7, H-9b), 2.78-2.66 (2 H, m, H-2b, 10b), 1.74 (1 H, oct, *J* = 6.7, CH(CH₃)₂), 1.00 (3 H, d, *J* = 6.7, CH₃), 0.88 (3 H, d, *J* = 6.7, CH₃); ¹³C NMR (100 MHz) δ 161.7 (C=N), 143.0 (d, *J*_{C-P} = 18.2, C-4), 141.1, 140.2, 139.4, 138.6 (d, *J*_{C-P} = 9.8), 137.2 (d, *J*_{C-P} = 11.4), 136.5 (d, *J*_{C-P} = 9.8), 136.0, 135.7, 135.3, 134.7, 134.2, 133.8, 133.0, 132.83, 132.76, 130.9 (d, *J*_{C-P} = 4.5), 129.1, 128.3, 128.2 (2C, s), 128.1, 128.0, 127.5, 73.6 (NCH), 68.8 (OCH₂), 36.2 (C-10), 35.5 (d, *J*_{C-P} = 9.9, C-2), 33.14 (C-1), 33.09 (2 C, s, C-9, CH(CH₃)₂), 19.3 (CH₃), 18.4 (CH₃); ³¹P NMR (121 MHz) δ -1.03; IR (KBr ???, cm⁻¹) ν _{max} 1636 (C=N); MS (EI, *m/z*) 504 (36), 503 (M⁺, 100), 502 (6), 488 (M⁺-Me, 3) 460 (M⁺-*i*-Pr, 7), 418 (7), 289 (15), 288 (CH₂C₆H₃(PPh₂)CH₂⁺, 63), 287 (24), 215 (19), 209 (12), 178 (9); HRMS Found 503.2378. C₃₄H₃₄PNO requires 503.2378.

(–)-(S,4S_p,12S_p)-4-Diphenylphosphinyl-13-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (2b)

Further elution gave the title compound as a white solid (0.09 g, 32%); *R_f* (petroleum ether:CHCl₃:EtOAc = 7:2:1) 0.47; mp 115.0-118.0 °C; [*α*]_D²⁰ –49 (*c* 0.59, CHCl₃); ¹H NMR (400 MHz) δ 7.69 (1 H, br.s, H-13), 7.48 (2 H, m, P-C₆H₅), 7.34-7.19 (8 H, m, P-C₆H₅), 6.65 (1 H, d, *J* = 7.7, 1.4, H-15), 6.61 (1 H, d, *J* = 7.7, H-16), 6.58 (1 H, dd, *J* = 7.7, 1.3, H-7), 6.49 (1 H, dd, *J* = 7.7, *J*_{H-P} = 5.5, H-8), 5.86 (1 H, dd, *J*_{H-P} = 8.2, *J* = 1.3, H-5), 4.23 (2 H, m, OCHH, H-10a), 3.94 (2 H, m, NCH, OCHH), 3.45 (1 H, ddd, *J* = 12.9, 10.2, 6.9, H-1a), 3.30 (1 H, dd, *J* = 13.7, 10.2, H-2a), 3.06 (2 H, m, H-9a, 1b), 2.73 (3 H, m, H-2b, 10b, 9b), 1.51 (1 H, m, CH(CH₃)₂), 0.98 (3 H, d, *J* = 6.7, CH₃), 0.87 (3 H, d, *J* = 6.9, CH₃); ¹³C NMR (100 MHz) δ 162.7 (C=N), 143.2 (d, *J*_{C-P} = 18.2, C-4), 140.8, 139.8, 139.5, 139.1, 139.0, 137.3 (d, *J*_{C-P} = 12.1), 136.5, 136.4, 136.2, 135.6, 134.9, 134.3, 134.2, 132.8, 132.7, 132.6, 131.7, 131.6, 131.0, 129.1, 128.2, 128.13, 128.06, 72.9 (NCH), 69.2 (OCH₂), 36.5, 35.6 (d, *J*_{C-P} = 14.9, C-2), 34.1, 33.5 (CH(CH₃)₂), 33.1, 19.5 (CH₃), 18.9 (CH₃); ³¹P NMR (162 MHz) δ –0.92; IR (KBr, cm^{–1}) ν_{max} 1637 (C=N); MS (EI, *m/z*) 504 (34), 503 (M⁺, 100%), 502 (12), 488 (M⁺–Me, 4), 460 (M⁺–*i*-Pr, 8), 418 (8), 289 (15), 288 (CH₂C₆H₃(PPh₂)CH₂⁺, 63), 287 (15), 215 (18), 209 (11), 178 (8); HRMS Found 503.2379. C₃₄H₃₄PNO requires 503.2378.

(±)-O-[4-(5-Carboxy-[2.2]paracyclophanyl)]diethylcarbamate (12)

s-BuLi [1.2 M solution in cyclohexane/hexane (92:8), 99.3 mL, 119.2 mmol] was added to a solution of carbamate **11**¹⁰ (32.6 g, 101.0 mmol) and TMEDA (18.2 mL, 121.2 mmol) in THF (1.5 L) at 0 °C. The resulting orange solution was stirred for 1.25 h. CO₂ gas was then bubbled through the solution for 2 h. The reaction mixture was allowed to warm to rt and stirred for 18 h with slow bubbling of CO₂. The mixture was extracted twice with water (1 L, 500 mL) then aq NaOH solution (6 M, 50 mL). The combined aq layers were washed with DCM (500 mL) and Et₂O (2 × 500 mL). The aq layer was

acidified to pH 1 with aq HCl (6 M) to give a white precipitate. The mixture was then extracted with DCM (3×500 mL), the combined organic layers were dried over Na_2SO_4 , filtered, concentrated and dried *in vacuo* to give the title compound as a white solid (33.4 g, 90%); R_f (DCM:EtOAc = 8:2) 0.07; mp 125.0-127.0 °C; ^1H NMR (300 MHz) δ 6.82 (1 H, dd, $J = 7.9, 1.7$), 6.70 (1 H, dd, $J = 7.9, 1.7$), 6.67 (1 H, d, $J = 8.2$), 6.62 (1 H, dd, $J = 7.9, 1.7$), 6.53 (1 H, dd, 7.9, 1.7), 6.50 (1 H, d, $J = 7.9$), 3.59 (2 H, m, CH_2CH_3), 3.50 (1 H, m), 3.39 (2 H, m, CH_2CH_3), 3.25 (1 H, ddd, $J = 12.6, 10.6, 4.9$), 3.16-3.04 (4 H, m), 2.88 (1 H, ddd, $J = 12.6, 10.4, 5.2$), 2.79 (1 H, m), 1.42 (3 H, t, $J = 6.9$, CH_2CH_3), 1.21 (3 H, t, $J = 7.2$, CH_2CH_3); ^{13}C NMR (75 MHz) δ 170.2, 153.8, 148.1, 142.8, 139.4, 139.3, 137.8, 133.2, 132.9, 132.7, 132.2, 131.0, 129.2, 125.4, 42.3 (CH_2CH_3), 42.0 (CH_2CH_3), 34.7, 34.3 (2 C, s), 30.6, 14.2 (CH_3), 13.2 (CH_3); IR (KBr, cm^{-1}) ν_{max} 3433 (O-H), 1723 ($\text{Et}_2\text{NC}=\text{O}$), 1678 ($\text{C}=\text{OOH}$); MS (EI, m/z) 368 (17), 367 (M^+ , 72), 251 (17), 250 (Paracyclophanyl CHO^+ , 90), 104 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2^+$, 58), 100 (100); HRMS Found 367.1784. $\text{C}_{22}\text{H}_{25}\text{NO}_4$ requires 367.1784.

Enantiopure (+)-(4*R*_p,5*S*_p)-**12** was prepared from enantiopure carbamate **11**^{16a} (see Results and Discussion). White solid; mp 140.0-142.0 °C; $[\alpha]_{\text{D}}^{20} +53$ (c 0.70, CHCl_3).

(–)-(S,4*S*_p,5*R*_p)-O-[4-(5-(1-hydroxymethyl-2-methyl-propylcarbamoyl)-[2.2]paracyclophanyl)]-diethylcarbamate (13a)

Thionyl chloride (2.0 mL, 27.8 mmol) was added to (±)-carboxylic acid **12** (1.81 g, 4.94 mmol) and the resulting mixture heated at 60 °C for 4 h. The excess thionyl chloride was removed by evaporation and the final traces by azeotropic distillation with toluene. The resulting crude acid chloride was dissolved in DCM (8 mL) and cooled to 0 °C. A solution of L-valinol (1.01 g, 9.78 mmol) and Et_3N (1.37 mL, 9.78 mmol) in DCM (1 mL) was added and the reaction mixture allowed to warm to rt and stirred for 24 h.

DCM (120 mL) was then added and the solution washed with aq NaHCO₃ solution (3.5% w/v, 2 × 120 mL) and brine (120 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, gradient elution (pentane:DCM:EtOAc = 6:2:2 → 5:2:3 → 4:2:4) gave the title compound as a white solid (0.85 g, 38%); *R_f* (DCM:EtOAc = 8:2) 0.21; mp 61.5-63.0 °C; [α]_D²⁰ -23 (*c* 0.90, CHCl₃); ¹H NMR (300 MHz) δ 7.10 (1 H, dd, *J* = 7.9, 1.7), 6.72 (1 H, dd, *J* = 7.9, 1.7), 6.58 (1 H, dd, *J* = 7.9, 1.7), 6.54 (1 H, d, *J* = 7.9), 6.52 (1 H, dd, *J* = 7.9, 1.7), 6.44 (1 H, d, *J* = 7.9), 5.78 (1 H, br.d, *J* = 8.9, *NH*), 3.81 (1 H, dddd, *J* = 8.9, 7.2, 5.4, 3.5, *NCH*), 3.59 (3 H, m, CH₂OH, CH₂CH₃), 3.44 (1 H, m, CHHCH₃), 3.28 (1 H, m, CHHCH₃), 3.23 (2 H, m), 3.19-2.98 (5 H, m), 2.74 (1 H, m), 1.81 (1 H, oct, *J* = 6.7, CH(CH₃)₂), 1.43 (3 H, t, *J* = 7.2, CH₂CH₃), 1.20 (3 H, t, *J* = 7.2, CH₂CH₃), 0.95 (3 H, d, *J* = 6.7, CH(CH₃)CH₃), 0.91 (3 H, d, *J* = 6.7, CH(CH₃)CH₃); ¹³C NMR (75 MHz) δ 167.1, 154.7, 146.0, 140.0, 139.2, 138.9, 136.1, 132.8, 132.5, 132.0 (2C, s), 131.6, 129.6, 129.5, 63.3 (CH₂OH), 57.3 (*NCH*), 42.12 (CH₂CH₃), 42.08 (CH₂CH₃), 35.1, 34.5, 33.4, 30.4, 28.9 (CH(CH₃)₂), 19.5 (CH(CH₃)CH₃), 18.8 (CH(CH₃)CH₃), 14.0 (CH₂CH₃), 13.2 (CH₂CH₃); IR (CHCl₃, cm⁻¹) $\nu_{\max}$ 3411 (br., O-H and N-H), 1699 (Et₂NC=O), 1657 (C=OONH); MS (EI, *m/z*) 453 (21), 452 (M⁺, 78), 350 (9), 348 (M⁺-CH₂C₆H₄CH₂, 7), 335 (12), 248 (14), 231 (60), 104 (CH₂-C₆H₄-CH₂⁺, 23), 100 (100); HRMS Found 452.2675. C₂₇H₃₆N₂O₄ requires 452.2675.

(+)-(S,4*R*_P,5*S*_P)-O-[4-(5-(1-hydroxymethyl-2-methyl-propylcarbamoyl)-[2.2]paracyclophanyl)]-diethylcarbamate (13b)

Further elution gave the title compound as a white solid (0.58 g, 26%); *R_f* (DCM:EtOAc = 8:2) 0.10; mp 136.5-137.0 °C; [α]_D²⁰ +20.7 (*c* 1.09, CHCl₃); ¹H NMR (300 MHz) δ 7.13 (1 H, dd, *J* = 7.9, 1.7), 6.67 (1 H, dd, *J* = 7.9, 2.0), 6.59 (1 H, dd, *J* = 7.7, 1.7), 6.53 (1 H, d, *J* = 7.8), 6.52 (1 H, dd, *J* = 7.7, 2.0), 6.43 (1 H, d, *J* = 7.8), 6.08 (1 H, br.d, *J* = 7.9, *NH*), 3.71 (1 H, m, *NCH*), 3.64 (1 H, m, CHHCH₃), 3.52 (3 H,

m, CHHCH₃, CH₂OH), 3.37 (1 H, m, CHHCH₃), 3.33-3.17 (3 H, m), 3.06-2.91 (4 H, m), 2.86 (1 H, m), 2.76 (1 H, m), 1.83 (1 H, oct, $J = 6.8$, CH(CH₃)₂), 1.40 (3 H, t, $J = 7.2$, CH₂CH₃), 1.18 (3 H, t, $J = 7.2$, CH₂CH₃), 0.89 (3 H, d, $J = 6.8$, CH(CH₃)CH₃), 0.88 (3 H, d, $J = 6.8$, CH(CH₃)CH₃); ¹³C NMR (75 MHz) δ 167.6, 154.5, 146.0, 140.6, 139.6, 138.8, 136.1, 132.7, 132.5, 132.3, 132.1, 132.0, 129.3, 128.8, 63.7 (NCH), 57.9 (CH₂OH), 42.0 (2C, s, 2×CH₂CH₃), 35.1, 34.4, 33.4, 30.3, 28.8 (CH(CH₃)₂), 19.1 (CH(CH₃)CH₃), 19.0 (CH(CH₃)CH₃), 14.2 (CH₂CH₃), 13.2 (CH₂CH₃); IR (KBr, cm⁻¹) $\nu_{\max}$ 3493 (br., O-H), 3259 (N-H), 1719 (Et₂NC=O), 1661 (C=OONH); MS (EI, m/z) 453 (25), 452 (M⁺, 90), 350 (10), 348 (M⁺-CH₂C₆H₄CH₂, 7), 335 (14), 248 (14), 231 (60), 104 (CH₂C₆H₄CH₂⁺, 24), 100 (100); HRMS Found 452.2676. C₂₇H₃₆N₂O₄ requires 452.2675.

(-)-(S,4S_P,5R_P)-O-[2-(5-(4-hydroxy[2.2]-paracyclophanyl))-3-methylbutyl] diethylcarbamate (14a)

Carbamate **13a** (0.85 g, 1.89 mmol) was dissolved in a mixture of MeOH (53 mL) and aq NaOH (6 M, 19.8 mL, 118.9 mmol). The reaction mixture was then heated at reflux for 20 h. Aq HCl (3 M, 45 mL, 135 mmol) was added and the mixture extracted with EtOAc (4 × 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, gradient elution (pentane:EtOAc = 19:1 → 9:1 → 8:2 → 7:3) gave the title compound as a colourless oil (0.26 g, 31%); R_f (petroleum ether:EtOAc = 1:1) 0.71; $[\alpha]_D^{20}$ -117 (c 0.95, CHCl₃); ¹H NMR (300 MHz) δ 11.65 (1 H, s, OH), 7.04 (1 H, dd, $J = 7.9, 1.7$), 6.58 (1 H, dd, $J = 7.9, 1.7$), 6.48 (1 H, dd, $J = 7.7, 1.7$), 6.44 (1 H, d, $J = 7.7$), 6.43 (1 H, dd, $J = 7.7, 1.7$), 6.25 (1 H, d, $J = 7.7$), 4.25 (2 H, m, NCH, CHHO), 4.06 (1 H, dd, $J = 15.6, 8.3$, CHHO), 3.57 (1 H, m, H-9a), 3.39 (1 H, ddd, $J = 12.7, 9.9, 2.7$, H-2a), 3.20-2.80 (9 H, m, H-10a, 10b, 9b, 1a, 1b, 2×CH₂CH₃), 2.53 (1 H, ddd, $J = 12.7, 10.6, 5.2$, H-2b), 1.99 (1 H, m, CH(CH₃)₂), 1.12 (6 H, d, $J = 6.9$, CH(CH₃)₂), 0.93 (6 H, m, 2×CH₂CH₃); ¹³C NMR (75 MHz) δ 170.9, 159.5, 155.9, 140.1, 137.8, 137.5, 137.4, 133.0, 131.8, 131.3, 129.0, 127.7, 127.1, 117.9, 64.6 (CH₂OH), 54.3 (NCH),

42.0 (CH₂CH₃), 41.4 (CH₂CH₃), 36.1, 35.0, 33.8, 30.2 (2 C, s, CH(CH₃)₂, C-2), 19.6 (CH(CH₃)CH₃), 18.9 (CH(CH₃)CH₃), 13.9 (CH₂CH₃), 13.1 (CH₂CH₃); IR (CHCl₃, $\nu_{\max}$ 3309 (O-H and N-H), 1686 (Et₂NC=O), 1624 (C=OONH); MS (EI, m/z) 453 (30), 452 (M⁺, 100), 348 (M⁺-CH₂C₆H₄CH₂, 30), 347 (33), 335 (M⁺-HOC(O)NEt₂, 15), 232 (14), 231 (71), 230 (15), 146 (10), 104 (CH₂-C₆H₄-CH₂⁺, 27), 100 (16); HRMS Found 452.2675. C₂₇H₃₆N₂O₄ requires 452.2675.

(-)-(S,4S_p,5R_p)-4-Hydroxy-[2.2]paracyclophane-5-carboxylic acid (1-hydroxymethyl-2-methyl-propyl)-amide (15a)

i) Further elution gave the title compound (0.34 g, 51%).

ii) Alternatively, carbamate **14a** (0.22 g, 0.48 mmol) and KOH (0.27 g, 4.8 mmol) were dissolved in *i*-PrOH (10 mL). The reaction mixture was then heated at reflux for 51 h. Aq HCl (3 M, 7 mL, 21 mmol) was added and the mixture extracted with Et₂O (2 × 22 mL) and DCM (22 mL). The combined organic layers were washed with NaHCO₃ (30 mL), to remove any [2.2]paracyclophane carboxylic acid by-product, and the aq layer was extracted with DCM (22 mL). All organic layers were combined, dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, gradient elution (pentane:EtOAc = 9:1 -> 8:2 -> 7:3) first gave unreacted starting material **14a** (0.04 g, 16%) and then the title compound as a white solid (0.10 g, 59%); R_f (petroleum ether:EtOAc = 1:1) 0.50; mp 43.0-48.0 °C; $[\alpha]_D^{20}$ -148 (*c* 1.30, CHCl₃); ¹H NMR (400 MHz) δ 11.52 (1 H, s, OH), 7.05 (1 H, dd, *J* = 8.0, 1.9), 6.59 (1 H, dd, *J* = 8.0, 1.9), 6.51 (1 H, dd, *J* = 8.0, 1.9), 6.48 (1 H, d, *J* = 7.7), 6.45 (1 H, dd, *J* = 8.0, 1.9), 6.25 (1 H, d, *J* = 7.7), 6.08 (1 H, br.d, *J* = 8.7, NH), 3.95 (1 H, tdd, *J* = 8.7, 6.8, 4.1, NCH), 3.68 (2 H, m, CH₂OH), 3.53 (1 H, m, H-9a), 3.48 (1 H, q, *J* = 7.0), 3.41 (1 H, ddd, *J* = 12.9, 10.2, 2.8), 3.17 (1 H, ddd, *J* = 12.9, 10.4, 5.2), 3.11 (1 H, m), 3.02 (1 H, ddd, *J* = 12.9, 10.7, 2.8), 2.96-2.82 (2 H, m), 2.55 (1 H, ddd, *J* = 13.2, 10.7, 5.2, H-2b), 2.05 (1 H, oct, *J* = 6.8, CH(CH₃)₂), 1.10 (3 H, d, *J* = 6.8, CH₃), 1.09 (3 H, d, *J* = 6.8,

CH_3); ^{13}C NMR (75 MHz) δ 171.0, 159.4, 140.1, 137.9, 137.7, 137.3, 133.0, 131.8, 131.4, 129.2, 127.7, 127.1, 117.9, 63.1 (CH_2OH), 56.8 (NCH), 36.1, 35.0, 33.8, 30.2, 29.4 ($\text{CH}(\text{CH}_3)_2$), 19.8 (CH_3), 19.2 (CH_3); IR (KBr, cm^{-1}) ν_{max} 3419 (br., O-H and N-H), 1622 ($\text{C}=\text{OONH}$); MS (EI, m/z) 354 (24), 353 (M^+ , 100), 322 ($\text{M}^+-\text{CH}_2\text{OH}$, 13), 310 ($\text{M}^+-i\text{-Pr}$, 21), 268 (34), 250 (33), 249 ($\text{M}^+-\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2$, 52), 248 (12), 218 (62), 206 (22), 164 (15), 163 (15), 147 (21), 146 (17), 104 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2^+$, 74), 102 (22); HRMS Found 353.1990. $\text{C}_{22}\text{H}_{27}\text{NO}_3$ requires 353.1991.

(+)-(S,4R_P,5S_P)-O-[2-(5-(4-hydroxy[2.2]-paracyclophanyl))-3-methylbutyl] diethylcarbamate (14b)

Treatment of carbamate **13b** (0.58 g, 1.29 mmol) according to the procedure for the synthesis of **14a** gave the title compound as a pale yellow solid (0.31 g, 54%); R_f (petroleum ether:EtOAc = 1:1) 0.68; mp 111.0-113.0 °C; $[\alpha]_{\text{D}}^{20} +74$ (c 0.76, CHCl_3); ^1H NMR (400 MHz) δ 11.42 (1 H, s, OH), 7.04 (1 H, dd, $J = 7.9, 1.9$), 6.57 (1 H, dd, $J = 7.9, 1.9$), 6.49 (1 H, dd, $J = 7.9, 1.9$), 6.48 (1 H, d, $J = 7.7$), 6.44 (1 H, dd, $J = 7.9, 1.9$), 6.26 (1 H, d, $J = 7.7$), 6.02 (1 H, br.d, $J = 9.1$, NH), 4.40 (1 H, dd, $J = 11.5, 5.8$, CHHO), 4.27 (1 H, dd, $J = 11.5, 3.3$, CHHO), 4.19 (1 H, m, NCH), 3.47 (1 H, ddd, $J = 13.6, 9.3, 2.7$, H-9a), 3.44-3.30 (5 H, m, H-2a, $2\times\text{CH}_2\text{CH}_3$), 3.17 (1 H, ddd, $J = 12.9, 10.2, 5.2$, H-1a), 3.04 (2 H, m, H-1b, 10a), 2.88 (1 H, ddd, $J = 13.6, 9.3, 6.7$, H-9b), 2.78 (1 H, ddd, $J = 12.6, 9.3, 6.7$, H-10b), 2.54 (1 H, ddd, $J = 13.2, 10.7, 5.2$, H-2b), 1.88 (1 H, oct, $J = 6.8$, $\text{CH}(\text{CH}_3)_2$), 1.18 (6 H, t, $J = 7.1$, $2\times\text{CH}_2\text{CH}_3$), 0.97 (3 H, d, $J = 6.8$, $\text{CH}(\text{CH}_3)\text{CH}_3$), 0.92 (3 H, d, $J = 6.8$, $\text{CH}(\text{CH}_3)\text{CH}_3$); ^{13}C NMR (100 MHz) δ 170.0, 159.1, 155.4, 139.9, 137.7, 137.5, 137.2, 132.7, 131.6, 131.2, 128.9, 127.5, 126.9, 118.0, 65.1 (CH_2OH), 54.0 (NCH), 41.9 (CH_2CH_3), 41.3 (CH_2CH_3), 35.9, 35.0, 33.8, 30.2, 29.7 ($\text{CH}(\text{CH}_3)_2$), 19.2 ($\text{CH}(\text{CH}_3)\text{CH}_3$), 18.8 ($\text{CH}(\text{CH}_3)\text{CH}_3$), 14.2 (CH_2CH_3), 13.5 (CH_2CH_3); IR (KBr, cm^{-1}) ν_{max} 3308 (O-H and N-H), 1682 ($\text{Et}_2\text{NC}=\text{O}$), 1622 ($\text{C}=\text{OONH}$); MS (EI, m/z) 453 (29), 452 (M^+ , 100), 348 (M^+-

$\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2$, 33), 347 (38), 335 ($\text{M}^+ - \text{HOC}(\text{O})\text{NEt}_2$, 13), 232 (13), 231 (69), 230 (13), 146 (8), 104 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2^+$, 21), 100 (15); HRMS Found 452.2674. $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_4$ requires 452.2675.

(+)-(S,4*R*_P,5*S*_P)-4-Hydroxy-[2.2]paracyclophane-5-carboxylic acid (1-hydroxymethyl-2-methyl-propyl)-amide (15b)

i) Further elution gave the title compound (0.11 g, 25%).

ii) Alternatively, treatment of carbamate **14b** (0.29 g, 0.64 mmol) according to procedure (ii) for the synthesis of **15a** first gave the starting material **14b** (0.04 g, 12%) and then the title compound as a white solid (0.13 g, 58%); R_f (petroleum ether:EtOAc = 1:1) 0.50; mp 85.5-87.0 °C; $[\alpha]_D^{20} +58$ (c 1.95, CHCl_3); ^1H NMR (400 MHz) δ 11.46 (1 H, s, OH), 7.05 (1 H, dd, $J = 7.7, 1.7$), 6.59 (1 H, dd, $J = 8.0, 1.7$), 6.54 (1 H, dd, $J = 7.7, 1.9$), 6.49 (1 H, d, $J = 7.7$), 6.44 (1 H, dd, $J = 8.0, 1.9$), 6.28 (1 H, d, $J = 7.7$), 6.14 (1 H, br.d, $J = 8.5$, NH), 3.97 (1 H, m, NCH), 3.88 (2 H, m, CH_2OH), 3.59 (1 H, m, H-9a), 3.42 (1 H, ddd, $J = 13.0, 10.3, 2.8$, H-2a), 3.17 (1 H, ddd, $J = 12.6, 10.3, 5.0$, H-1a), 3.13 (1 H, m, H-10a), 3.01 (1 H, ddd, $J = 12.6, 10.7, 2.8$, H-1b), 2.88 (2 H, m, H-9b, 10b), 2.55 (1 H, ddd, $J = 13.0, 10.7, 5.0$, H-2b), 1.91 (1 H, oct, $J = 6.9$, $\text{CH}(\text{CH}_3)_2$), 0.98 (3 H, d, $J = 6.9$, CH_3), 0.94 (3 H, d, $J = 6.9$, CH_3); ^{13}C NMR (100 MHz) δ 170.6, 159.2, 139.8, 137.9, 137.5, 137.4, 132.9, 131.6, 131.2, 129.0, 127.4, 127.2, 117.9, 63.6 (CH_2OH), 56.7 (NCH), 36.3, 35.0, 33.8, 30.1 (C-2), 29.1 ($\text{CH}(\text{CH}_3)_2$), 19.5 (CH_3), 19.0 (CH_3); IR (CHCl_3 , cm^{-1}) ν_{max} 3434 (br., O-H and N-H), 1619 ($\text{C}=\text{OONH}$); MS (EI, m/z) 354 (22), 353 (M^+ , 100), 322 ($\text{M}^+ - \text{CH}_2\text{OH}$, 15), 310 ($\text{M}^+ - i\text{-Pr}$, 25), 268 (38), 250 (28), 249 ($\text{M}^+ - \text{CH}_2\text{C}_6\text{H}_4\text{CH}_2$, 46), 248 (14), 218 (56), 206 (19), 164 (14), 163 (13), 147 (13), 146 (11), 104 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2^+$, 44), 102 (18); HRMS Found 353.1991. $\text{C}_{22}\text{H}_{27}\text{NO}_3$ requires 353.1991.

(–)-(S,4S_p,5R_p)-O-[4-(5-(4-Isopropylloxazolin-2-yl)-[2.2]paracyclophanyl)]diethylcarbamate (16a)

Carbamate **13a** (65 mg, 0.143 mmol) was dissolved in MeCN (3.0 mL) and PPh₃ (65 mg, 0.250 mmol), Et₃N (35 μL, 0.250 mmol) and CCl₄ (24 μL, 0.250 mmol) were added. The resulting solution was stirred for 23 h. It was then diluted with DCM (3 mL), washed with brine (2 × 3 mL) and dried over Na₂SO₄. The mixture was filtered and concentrated. Flash column chromatography, gradient elution (pentane:EtOAc = 9:1 → 8:2 → 7:3) gave the title compound as a colorless oil which became a white crystalline solid on standing (35 mg, 56%); R_f (petroleum ether:EtOAc = 8:2) 0.12; mp 62.0-64.0 °C; [α]_D²⁰ –50 (c 0.79, CHCl₃); ¹H NMR (400 MHz) δ 6.98 (1 H, dd, *J* = 7.7, 1.9), 6.71 (1 H, dd, *J* = 7.7, 1.9), 6.60 (1 H, dd, *J* = 8.0, 1.9), 6.58 (1 H, d, *J* = 8.0), 6.53 (1 H, dd, *J* = 8.0, 1.9), 6.46 (1 H, d, *J* = 8.0), 4.25 (1 H, dd, *J* = 9.6, 8.0, CHHO), 4.08 (1 H, ddd, *J* = 9.6, 8.0, 6.6, NCH), 3.98 (1 H, t, *J* = 8.0, CHHO), 3.68 (1 H, m, CHHCH₃), 3.52 (1 H, ddd, *J* = 12.6, 10.6, 2.5, H-9a), 3.44 (2 H, m, 2×CHHCH₃), 3.30 (1 H, m, CHHCH₃), 3.21 (1 H, ddd, *J* = 12.4, 10.6, 4.7, H-10a), 3.10 (1 H, m, H-2a), 3.04 (3 H, m, H-1a, 1b, 10b), 2.87 (1 H, ddd, *J* = 12.6, 10.4, 4.7, H-9b), 2.75 (1 H, m, H-2b), 1.82 (1 H, oct, *J* = 6.6, CH(CH₃)₂), 1.41 (3 H, t, *J* = 6.9, CH₂CH₃), 1.18 (3 H, t, *J* = 7.1, CH₂CH₃), 1.09 (3 H, d, *J* = 6.6, CH(CH₃)CH₃), 0.98 (3 H, d, *J* = 6.6, CH(CH₃)CH₃); ¹³C NMR (100 MHz) δ 160.4, 153.3, 148.2, 142.2, 139.4, 139.2, **136.2**, 132.8, 132.5, 132.3, 131.5, 131.1, 129.3, 123.1, 73.3 (NCH), 69.3 (CH₂O), 42.2 (CH₂CH₃), 42.0 (CH₂CH₃), 34.8, 34.4, 34.1, 33.2 (CH(CH₃)₂), 30.7 (C-2), 19.2 (CH(CH₃)CH₃), 18.8 (CH(CH₃)CH₃), 14.5 (CH₂CH₃), 13.5 (CH₂CH₃); IR (CHCl₃, cm^{–1}) ν_{max} 1716 (Et₂NC=O), 1653 (C=N); MS (EI, *m/z*) 435 (28), 434 (M⁺, 100), 391 (M⁺–*i*-Pr, 3), 361 (8), 334 (M⁺–CONEt₂, 28), 305 (6), 271 (8), 257 (6), 243 (12), 230 (CH₂C₆H₂(O)(oxazoline)CH₂⁺, 40), 100 (60); HRMS Found 434.2569. C₂₇H₃₄N₂O₃ requires 434.2569.

(–)-(S,4S_p,5R_p)-Trifluoromethansulfonic acid [4-(5-(4-isopropylloxazolin-2-yl)-[2.2]paracyclophanyl)] ester (18a)

A solution of diol **15a** (0.19 g, 0.53 mmol) and pyridine (0.1 mL, 1.27 mmol) in DCM (1.5 mL) was added dropwise to a solution of Tf₂O (0.19 mL, 1.11 mmol) in DCM (0.5 mL) at 0 °C. After stirring for 1.5 h, the solution was warmed to rt and stirred for a further 2 h. Water (6 mL) was added, the aq layer separated and extracted with DCM (3 × 6 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, gradient elution (pentane:EtOAc = 19:1 → 9:1) gave the title compound as a colorless oil (0.18 g, 73%); *R_f* (petroleum ether:EtOAc = 8:2) 0.52; [*α*]_D²⁰ –26 (*c* 1.35, CHCl₃); ¹H NMR (400 MHz) *δ* 6.90 (1 H, dd, *J* = 7.7, 1.9), 6.82 (1 H, dd, *J* = 7.7, 1.7), 6.63 (1 H, dd, *J* = 7.7, 1.7), 6.62 (1 H, d, *J* = 8.0), 6.60 (1 H, dd, *J* = 7.7, 1.9), 6.58 (1 H, d, *J* = 8.0), 4.42 (1 H, dd, *J* = 9.1, 7.7, CHHO), 4.18 (1 H, td, *J* = 9.1, 6.6, NCH), 4.10 (1 H, dd, *J* = 9.1, 7.7, CHHO), 3.43 (1 H, m), 3.36 (1 H, ddd, *J* = 13.5, 9.9, 4.1, H-2a), 3.23 (1 H, ddd, *J* = 12.9, 9.9, 4.1), 3.07–2.96 (4 H, m), 2.90 (1 H, ddd, *J* = 13.5, 10.2, 4.1, H-2b), 2.00 (1 H, oct, *J* = 6.6, CH(CH₃)₂), 1.13 (3 H, d, *J* = 6.6, CH₃), 1.04 (3 H, d, *J* = 6.6, CH₃); ¹³C NMR (100 MHz) *δ* 159.3 (C=N), 145.5, 143.5, 139.2, 138.9, 137.2, 134.3, 132.7, 132.4, 132.3, 131.9, 130.2, 124.1, 118.5 (q, *J*_{C-F} 317.9, CF₃), 73.5 (NCH), 69.6 (CH₂O), 34.8, 34.4, 34.1, 32.6 (CH(CH₃)₂), 30.8 (C-2), 19.6 (CH₃), 18.5 (CH₃); ¹⁹F NMR (376 MHz) *δ* –73.8 (3 F, s); IR (neat, cm^{–1}) *ν*_{max} 1659 (C=N); MS (EI, *m/z*) 468 (13), 467 (M⁺, 44), 424 (M⁺–*i*-Pr., 2), 335 (29), 334 (M⁺–Tf, 100), 249 (8), 248 (11), 231 (14), 230 (CH₂C₆H₂(O)(oxazoline)CH₂⁺, 89), 104 (CH₂C₆H₄CH₂⁺, 19); HRMS Found 467.1379. C₂₃H₂₄SF₃NO₄ requires 467.1378.

(–)-(S,4R_P,5S_P)-Trifluoromethansulfonic acid [4-(5-(4-*isopropyl*oxazolin-2-yl)-[2.2]paracyclophanyl)] ester (18b**)**

Treatment of diol **15b** (90 mg, 0.255 mmol) according to the procedure for the synthesis of **18a** gave the title compound as a colourless oil; R_f (petroleum ether:EtOAc = 8:2) 0.42; $[\alpha]_D^{20}$ –69 (c 0.66, CHCl₃); ¹H NMR (300 MHz) δ 6.80 (1 H, dd, J = 7.9, 1.7), 6.75 (1 H, dd, J = 7.9, 1.7), 6.63 (1 H, dd, J = 7.9, 1.7), 6.61 (2 H, s, H-7, 8), 6.58 (1 H, dd, J = 7.9, 1.7), 4.50 (1 H, dd, J = 9.9, 8.7, CHHO), 4.17 (1 H, t, J = 8.7, CHHO), 4.05 (1 H, m, NCH), 3.70 (1 H, ddd, J = 12.1, 9.6, 4.0, H-9a), 3.36 (1 H, ddd, J = 13.4, 9.9, 3.7), 3.21 (1 H, m), 3.12–2.84 (5 H, m), 1.92 (1 H, oct, J = 6.7, CH(CH₃)₂), 1.17 (3 H, d, J = 6.7, CH₃), 1.05 (3 H, d, J = 6.7, CH₃); ¹³C NMR (75 MHz) δ 159.8 (C=N), 145.7, 143.7, 139.2, 139.1, 137.1, 134.6, 132.7, 132.5, 132.3, 130.1, 124.4, (q, J_{C-F} 319.5, CF₃), 72.9 (NCH), 70.3 (CH₂O), 34.7, 34.3, 34.2, 33.3 (CH(CH₃)₂), 30.8, 19.4 (CH₃), 19.0 (CH₃); ¹⁹F NMR (376 MHz) δ –73.8 (3 F, s); IR (neat, cm^{–1}) ν_{max} 1654 (C=N); MS (EI, m/z) 468 (12), 467 (M⁺, 39), 424 (M⁺–*i*-Pr, 2), 335 (26), 334 (M⁺–Tf, 100), 249 (7), 248 (10), 231 (13), 230 (CH₂C₆H₂(O)(oxazoline)CH₂⁺, 85), 104 (CH₂C₆H₄CH₂⁺, 21); HRMS Found 467.1378. C₂₃H₂₄SF₃NO₄ requires 467.1378.

(–)-(S,4S_P,5R_P)-4-Diphenylphosphinyl-5-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (3a**)**

Triflate **18a** (1.05 g, 2.24 mmol) was dissolved in THF (6.5 mL) and Ph₂PK (0.5 M w/v solution in THF, 0.43 mL, 0.21 mmol) was added. The solution was stirred at rt for 20 h. Degassed water (75 mL) and DCM (45 mL) were added and the mixture shaken vigorously. The aq layer was separated and extracted with DCM (45 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography, gradient elution (petroleum ether:DCM:EtOAc = 32:7:1 - > 31:7:2) gave the title compound as a white crystalline solid (0.52 g, 46%); R_f (petroleum ether:DCM:EtOAc = 7:2:1) 0.55; mp 88.0–91.0 °C; $[\alpha]_D^{20}$ –12 (c 0.30, CHCl₃); ¹H NMR (300 MHz) δ

7.56 (2 H, m), 7.34 (2 H, m), 7.15 (3 H, m), 7.10 (3 H, m), 6.87 (1 H, br.d, $J = 8.0$), 6.77 (1 H, br.d, $J = 8.0$), 6.55 (2 H, m), 6.40 (1 H, d, $J = 7.8$, H-7), 6.35 (1 H, dd, $J = 7.8$, $J_{\text{H-P}} = 3.7$, H-8), 3.52 (1 H, t, $J = 8.1$, CHHO), 3.33 (1 H, m, NCH), 3.16 (1 H, dd, $J = 9.9$, 8.1, CHHO), 3.09-2.80 (5 H, m), 2.68 (2 H, m), 2.41 (1 H, m, H-2b), 1.65 (1 H, oct, $J = 6.7$, $\text{CH}(\text{CH}_3)_2$), 0.94 (3 H, d, $J = 6.7$, $\text{CH}(\text{CH}_3)\text{CH}_3$), 0.83 (3 H, d, $J = 6.7$, $\text{CH}(\text{CH}_3)\text{CH}_3$); ^{13}C NMR (75 MHz) δ 163.2 (C=N), 145.5 (d, $J_{\text{C-P}} = 8.9$), 142.0 (d, $J_{\text{C-P}} = 12.5$), 140.1 (d, $J_{\text{C-P}} = 9.5$), 139.5, 138.8, 138.7, 138.3, 138.0, 135.5, 134.6, 133.3, 133.2, 133.0, 132.9, 131.7, 131.64, 131.57, 131.2, 128.5, 128.4, 128.3, 128.0 (2 C, s), 127.9, 72.7 (NCH), 68.5 (CH_2O), 36.4 (d, $J_{\text{C-P}} = 6.5$, C-2), 34.7, 34.6, 33.5, 32.2 ($\text{CH}(\text{CH}_3)_2$), 19.7 (CH_3), 18.2 (CH_3); ^{31}P NMR (121 MHz) δ 0.20; IR (CHCl_3 , cm^{-1}) ν_{max} 1653 (C=N); MS (EI, m/z) 504 (37), 503 (M^+ , 100), 502 (17), 488 ($\text{M}^+ - \text{Me}$, 8), 461 (13), 460 ($\text{M}^+ - i\text{-Pr}$, 39), 434 (17), 433 (36), 432 (45), 413 (9), 412 (31), 358 (15), 357 (24), 356 (27), 330 (22), 329 (49), 328 (58), 322 (14), 308 (20), 104 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2^+$, 8); HRMS Found 503.2379. $\text{C}_{34}\text{H}_{34}\text{PNO}$ requires 503.2378.

(–)-(S,4R_P,5S_P)-4-Diphenylphosphinyl-5-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (3b)

Treatment of triflate **18b** (0.84 g, 1.81 mmol) according to the procedure for the synthesis of **3a** gave the title compound as a white crystalline solid (0.59 g, 65%); R_f (petroleum ether:DCM:EtOAc = 7:2:1) 0.32; mp 170.0-172.0 °C; $[\alpha]_{\text{D}}^{20}$ –242 (c 1.04, CHCl_3); ^1H NMR (400 MHz) δ 7.58 (2 H, m), 7.45 (2 H, m), 7.23-7.18 (6 H, m), 6.81 (1 H, dd, $J = 8.0$, 1.7), 6.63 (3 H, m), 6.53 (1 H, d, $J = 7.7$, H-7), 6.42 (1 H, dd, $J = 7.7$, $J_{\text{H-P}} = 3.8$, H-8), 3.79 (1 H, t, $J = 8.6$, CHHO), 3.68 (1 H, dd, $J = 9.9$, 8.6, CHHO), 3.63 (1 H, ddd, $J = 13.0$, 12.4, 5.8, H-9a), 3.08 (1 H, ddd, $J = 13.2$, 9.6, 3.9), 2.99 (2 H, m, NCH, CHHCH_2), 2.93-2.84 (3 H, m), 2.76 (1 H, ddd, $J = 13.0$, 9.6, 4.7), 2.49 (1 H, ddd, $J = 13.7$, 9.9, 4.4, H-2b), 1.65 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 1.01 (3 H, d, $J = 6.6$, $\text{CH}(\text{CH}_3)\text{CH}_3$), 0.88 (3 H, d, $J = 6.9$, $\text{CH}(\text{CH}_3)\text{CH}_3$); ^{13}C NMR (100 MHz) δ 162.4 (C=N), 145.4 (d, $J_{\text{C-P}} = 9.9$), 142.0 (d, $J_{\text{C-P}} = 11.4$), 139.4, 138.90, 138.95, 138.0 (d, $J_{\text{C-P}} =$

9.1), 137.0, 136.8, 135.3 (2 C, s), 133.4, 133.2, 133.1, 132.9, 132.2, 132.1, 131.4, 130.9, 128.4, 128.34, 128.26, 128.2, 127.9, 127.8, 72.6 (NCH), 69.3 (CH₂O), 36.5 (d, J_{C-P} = 9.1, C-2), 35.0, 34.8, 34.2, 33.1 (CH(CH₃)₂), 19.6 (CH(CH₃)CH₃), 19.2 (CH(CH₃)CH₃); ³¹P NMR (162 MHz) δ 1.48; IR (CHCl₃, cm⁻¹) $\nu_{\max}$ 1651 (C=N); MS (EI, m/z) 504 (37), 503 (M⁺, 100), 502 (19), 488 (M⁺-Me, 10), 461 (10), 460 (M⁺-*i*-Pr, 28), 434 (25), 433 (57), 432 (63), 413 (19), 412 (64), 358 (13), 357 (24), 356 (36), 330 (39), 329 (75), 328 (93), 322 (27), 308 (22), 104 (CH₂C₆H₄CH₂⁺, 22); HRMS Found 503.2378. C₃₄H₃₄PNO requires 503.2378.

(+)-(S,4*R*_p,12*R*_p)-4-Di(4-methoxyphenyl)phosphinyl-13-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (19a)

n-BuLi (15% w/v solution in *n*-hexane, 0.23 mL, 0.53 mmol) was added dropwise to a solution of the diastereomeric mixture of bromides **10** (0.14 g, 0.35 mmol) in THF (3.5 mL) at -78 °C to give an orange solution. After stirring for 1.5 h, a solution of chlorodi(4-methoxyphenyl)phosphine (0.21 g, 0.74 mmol) in THF (0.5 mL) was added dropwise to give a black solution which slowly became orange. After 10 min, the cooling bath was removed and the reaction mixture stirred for a further 3 h. Ordinary 'wet' Et₃N (0.1 mL, 0.71 mmol) was added followed by Et₂O (3 mL) and the resulting mixture added to silica gel (1.4 g) and DCM (3 mL). The solvent was evaporated to leave the crude product mixture suspended on silica which was added to the top of a column of silica gel for flash chromatography, gradient elution (pentane:Et₂O = 9:1 → 8:2 → 7:3. This gave the title product as a white solid (0.06 g, 32%); R_f (petroleum ether:Et₂O = 8:2) 0.21; mp 79.0-81.0 °C; $[\alpha]_D^{20}$ +19 (*c* 0.96, CHCl₃); ¹H NMR (300 MHz) δ 7.61 (1 H, br.s, H-13), 7.32 (2 H, br.dd, J_{H-P} = 8.7, J = 7.9, P-C₆H₄OMe (*ortho*)), 7.23 (2 H, br.dd, J_{H-P} = 8.7, J = 7.6, P-C₆H₄OMe (*ortho*)), 6.85 (2 H, br.d, J = 7.6, P-C₆H₄OMe (*meta*)), 6.77 (2 H, br.d, J = 7.9, P-C₆H₄OMe (*meta*)), 6.62 (1 H, dd, J = 7.9, 1.7, H-15), 6.58 (1 H, d, J = 7.9, H-16), 6.54 (1 H, dd, J =

7.7, 1.8, H-7), 6.45 (1 H, dd, $J = 7.7$, $J_{H-P} = 5.4$, H-8), 5.88 (1 H, dd, $J_{H-P} = 8.4$, $J = 1.8$, H-5), 4.34 (1 H, m, OCHH), 4.18 (1 H, br.dd, $J = 12.4$, 9.3, H-10a), 3.92 (2 H, m, NCH, OCHH), 3.80 (3 H, s, OCH₃), 3.74 (3 H, s, OCH₃), 3.43 (1 H, ddd, $J = 12.9$, 9.9, 6.7, H-1a), 3.26 (1 H, br.dd, $J = 13.6$, 9.9, H-2a), 3.02 (2 H, m, H-1b, 9a), 2.86 (1 H, ddd, $J = 12.6$, 9.3, 7.4, H-9b), 2.78-2.61 (2 H, m, H-2b, 10b), 1.74 (1 H, oct, $J = 6.7$, CH(CH₃)₂), 1.00 (3 H, d, $J = 6.7$, CH₃), 0.88 (3 H, d, $J = 6.7$, CH₃); ¹³C NMR (75 MHz) δ 161.9 (C=N), 160.4 (MeOC), 159.9 (MeOC), 142.9 (d, $J_{C-P} = 17.9$), 141.1, 140.1, 139.5, 138.8 (d, $J_{C-P} = 12.0$), 137.3, 137.0, 135.3, 134.8, 134.5, 134.2, 134.1, 133.9, 132.6, 130.9 (d, $J_{C-P} = 4.7$), 130.0 (d, $J_{C-P} = 7.5$), 127.9 (d, $J_{C-P} = 8.3$), 127.6, 113.9, 113.8 (2 C, s), 113.7, 73.6 (NCH), 68.8 (OCH₂), 55.13 (OCH₃), 55.06 (OCH₃), 36.1 (C-10), 35.3 (d, $J_{C-P} = 9.5$, C-2), 33.8, 33.0 (2 C, s), 19.3 (CH₃), 18.3 (CH₃); δ_P (121 MHz) -4.64; IR (CHCl₃, cm⁻¹) $\nu_{\max}$ 1642 (C=N); MS (EI, m/z) 564 (33), 563 (M⁺, 100), 562 (11), 548 (M⁺-Me, 4), 460 (M⁺-*i*-Pr, 9), 478 (6), 349 (13), 348 (CH₂C₆H₃(P(C₆H₄OMe)₂)CH₂⁺, 50), 347 (13), 282 (8), 240 (8), 239 (9), 215 (10), 178 (9); HRMS Found 563.2588. C₃₆H₃₈PNO₃ requires 563.2589.

(-)-(S,4S_p,12S_p)-4-Di(4-methoxyphenyl)phosphinyl-13-(4-*iso*-propyloxazolin-2-yl)[2.2]paracyclophane (19b)

Further elution gave the title compound as a white crystalline solid (0.06 g, 31%); R_f (petroleum ether:Et₂O = 8:2) 0.08; mp 147.0-149.0 °C; [α]_D²⁰ -50 (*c* 0.87, CHCl₃); ¹H NMR (300 MHz) δ 7.69 (1 H, d, $J = 1.5$, H-13), 7.40 (2 H, dd, $J = 8.7$, $J_{H-P} = 8.2$, P-C₆H₄OMe (*ortho*)), 7.24 (2 H, br.dd, $J = 8.7$, $J_{H-P} = 7.2$, P-C₆H₄OMe (*ortho*)), 6.85 (2 H, br.d, $J = 8.7$, P-C₆H₄OMe (*meta*)), 6.76 (2 H, br.d, $J = 8.7$, P-C₆H₄OMe (*meta*)), 6.63 (1 H, dd, $J = 7.7$, 1.5, H-15), 6.59 (1 H, d, $J = 7.7$, H-16), 6.55 (1 H, dd, $J = 7.8$, 1.7, H-7), 6.45 (1 H, dd, $J = 7.8$, $J_{H-P} = 5.7$, H-8), 5.89 (1 H, dd, $J_{H-P} = 8.4$, $J = 1.7$, H-5), 4.32-4.18 (2 H, m, OCHH, H-10a), 4.00-3.90 (2 H, m, NCH, OCHH), 3.79 (3 H, s, OCH₃), 3.74 (3 H, s, OCH₃), 3.45 (1 H, ddd, $J = 12.9$, 9.7, 6.7, H-1a), 3.27 (1 H, br.dd, $J = 13.6$, 9.7, H-2a), 3.05 (2 H, m, H-1b, 9a), 2.81-

2.62 (3 H, m, H-9b, H-2b, 10b), 1.53 (1 H, oct, $J = 6.7$, $\text{CH}(\text{CH}_3)_2$), 1.00 (3 H, d, $J = 6.7$, $\text{CH}(\text{CH}_3)\text{CH}_3$), 0.88 (3 H, d, $J = 6.7$, $\text{CH}(\text{CH}_3)\text{CH}_3$); ^{13}C NMR (75 MHz) δ 162.7 (C=N), 160.4 (MeOC), 159.9 (MeOC), 143.0 (d, $J_{\text{C-P}} = 17.9$), 140.8, 139.7, 139.5, 138.7 (d, $J_{\text{C-P}} = 10.7$), 137.7, 137.3, 135.6, 134.9, 134.4, 134.3, 134.2, 134.1, 132.5, 131.6 (d, $J_{\text{C-P}} = 4.8$), 130.5 (d, $J_{\text{C-P}} = 7.1$), 127.8 (d, $J_{\text{C-P}} = 7.7$), 127.6, 113.9 (2 C, s), 113.8, 113.7, 73.1 (NCH), 69.1 (OCH_2), 55.08 (OCH_3), 55.05 (OCH_3), 36.4 (C-10), 35.5 (d, $J_{\text{C-P}} = 9.5$, C-2), 34.0, 33.5 ($\text{CH}(\text{CH}_3)_2$), 33.0, 19.4 ($\text{CH}(\text{CH}_3)\text{CH}_3$), **18.9** ($\text{CH}(\text{CH}_3)\text{CH}_3$); ^{31}P NMR (121 MHz) δ -4.70; IR (CHCl_3 , cm^{-1}) ν_{max} 1638 (C=N); MS (EI, m/z) 564 (35), 563 (M^+ , 100), 562 (18), 548 ($\text{M}^+ - \text{Me}$, 4), 478 (5), 349 (12), 348 ($\text{CH}_2\text{C}_6\text{H}_3(\text{P}(\text{C}_6\text{H}_4\text{OMe})_2)\text{CH}_2^+$, 49), 347 (12), 282 (8), 240 (7), 239 (9), 215 (9); HRMS Found 563.2590. $\text{C}_{36}\text{H}_{38}\text{PNO}_3$ requires 563.2589.

(+)-(R,4S_P,12S_P)-4-Bromo-[2.2]paracyclophane-12-carboxylic acid (1-hydroxymethyl-2-methyl-propyl)-amide (20a)

Thionyl chloride (2.47 mL, 33.90 mmol) was added to ($\pm$)-bromo-carboxylic acid **9**³³ (1.99 g, 6.02 mmol) and the resulting mixture heated at 60 °C for 4 h. The excess thionyl chloride was removed by evaporation and the final traces by azeotropic distillation with toluene. The resulting crude acid chloride was dissolved in DCM (5 mL) and cooled to 0 °C. A solution of D-phenylglycinol (1.64 g, 11.92 mmol) and Et_3N (1.68 mL, 11.92 mmol) in DCM (6 mL) was added and the reaction mixture allowed to warm to rt and stirred for 24 h. DCM was then added (150 mL) and the solution washed with aq NaHCO_3 solution (3.5% w/v, 2×150 mL) and brine (150 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated. Flash column chromatography, gradient elution (pentane:DCM:EtOAc = 5:2:3 $\rightarrow$ 4:2:4 $\rightarrow$ 3:2:5) was carried out and the title compound was found to crystallize in several of the fractions. This was removed by filtration. The remaining fractions consisted of mixtures of both diastereoisomers so these were evaporated and recrystallized from EtOAc and a small amount of

petroleum ether. This gave more of the pure title compound. This chromatography-recrystallization procedure was repeated several times to give the title compound as a white crystalline solid (1.14 g, 42%); R_f (pentane:DCM:EtOAc = 3:2:5) 0.56; mp 222.5-223.0 °C; $[\alpha]_D^{20} +58$ (c 0.84, CHCl₃); ¹H NMR (400 MHz) δ 7.40-7.31 (5 H, m, *Ph*), 7.29 (1 H, d, J = 1.7, H-13), 6.90 (1 H, d, J = 1.7, H-5), 6.65-6.59 (4 H, m, *NH*, H-7, 15, 16), 6.54 (1 H, d, J = 7.7, H-8), 5.32 (1 H, ddd, J = 6.0, 5.8, 4.4, *NCH*), 4.09 (2 H, br.s, CH₂OH), 3.81 (1 H, m, H-10a), 3.47 (1 H, ddd, J = 13.7, 9.6, 1.9), 3.17 (1 H, ddd, J = 12.9, 9.6, 6.9), 3.13-3.03 (3 H, m), 2.89-2.79 (2 H, m), 2.64 (1 H, br.s, *OH*); ¹³C NMR (75 MHz) δ 169.1 (C=O), 142.3, 139.9, 139.5, 138.6, 138.5, 136.0, 135.4, 135.0, 134.9, 134.6, 131.5, 128.9 (2 C, s), 127.9, 126.8 (2 C, s), 126.7, 126.4, 67.2 (CH₂OH), 56.3 (*NCH*), 35.7, 34.7, 34.4, 32.6; IR (KBr, cm⁻¹) $\nu_{\max}$ 3422 (br., O-H), 3315 (N-H), 1639 (C=OONH); MS (EI, m/z) 452 (9), 451 (M⁺, 35), 450 (14), 449 (M⁺, 37), 420 (M⁺-CH₂OH, 6), 419 (5), 418 (M⁺-CH₂OH, 5), 332 (21), 331 (10), 330 (25), 316 (6), 315 (M⁺-HOCH₂C(Ph)(H)NH, 11), 314 (8), 313 (M⁺-HOCH₂C(Ph)(H)NH, 12), 267 (M⁺-CH₂C₆H₃(Br)CH₂, 32), 147 (100), 131 (46), 121 (17); HRMS Found 449.0990. C₂₅H₂₄BrNO₂ requires 449.0991.

(-)-(R,4R_P,12R_P)-4-Bromo-[2.2]paracyclophane-12-carboxylic acid (1-hydroxymethyl-2-methyl-propyl)-amide (20b)

The title compound was isolated, during the procedure described above, as a white amorphous solid (1.30 g, 48%); R_f (pentane:DCM:EtOAc = 3:2:5) 0.49; mp 60.0-62.0 °C; $[\alpha]_D^{20} -46$ (c 0.81, CHCl₃); ¹H NMR (400 MHz) δ 7.44 (2 H, m, *Ph*), 7.38-7.31 (3 H, m, *Ph*), 7.30 (1 H, br.s, H-13), 6.69 (1 H, d, J = 7.4, *NH*), 6.61-6.52 (4 H, m), 6.48 (1 H, d, J = 8.0), 5.12 (1 H, m, *NCH*), 3.85 (2 H, d, J = 4.7, CH₂OH), 3.73 (1 H, ddd, J = 12.4, 6.9, 4.9, H-10a), 3.41 (1 H, ddd, J = 13.5, 9.6, 1.9, H-2a), 3.15-2.93 (5 H, m, *OH*, H-1a, 1b, 9a, 9b), 2.83-2.72 (2 H, m, H-2b, 10b); ¹³C NMR (100 MHz) δ 168.9 (C=O), 142.0, 139.7, 139.4, 139.0, 138.4, 135.7, 135.4, 135.0, 134.6, 134.0, 131.2, 128.7 (2 C, s), 127.6, 126.9, 126.7

(2 C, s), 126.4, 66.1 (CH₂OH), 55.9 (NCH), 35.6 (C-2), 34.7 (C-10), 34.3, 32.4; IR (KBr, cm⁻¹) $\nu_{\max}$ 3398 (br., O-H), 3284 (N-H), 1655 (C=OONH); MS (EI, m/z) 452 (10), 451 (M⁺, 40), 450 (9), 449 (M⁺, 38), 421 (5), 420 (M⁺-CH₂OH, 5), 419 (6), 418 (M⁺-CH₂OH, 5), 332 (24), 331 (10), 330 (25), 316 (7), 315 (M⁺-HOCH₂C(Ph)(H)NH, 10), 314 (8), 313 (M⁺-HOCH₂C(Ph)(H)NH, 10), 267 (M⁺-CH₂C₆H₃(Br)CH₂, 30), 147 (100), 131 (42), 121 (6); HRMS Found 449.0990. C₂₅H₂₄BrNO₂ requires 449.0991.

(+)-(R,4S_p,12S_p)-4-Bromo-12-(4-phenyloxazolin-2-yl)[2.2]paracyclophane (21a)

Amide **20a** (1.14 g, 2.54 mmol), PPh₃ (1.16 g, 4.44 mmol), CCl₄ (0.43 mL, 4.44 mmol) and Et₃N (0.62 mL, 4.44 mmol) were dissolved in MeCN (53 mL) and the solution was stirred for 15 h. The reaction was monitored by tlc and, in order to force it to completion, an extra eq of PPh₃ (0.67 g, 2.54 mmol), CCl₄ (0.25 mL, 2.54 mmol) and Et₃N (0.35 mL, 2.54 mmol) were added and the mixture heated at 50 °C for 4 h. DCM (66 mL) was then added and the solution washed with brine (2 × 66 mL), dried over MgSO₄, filtered and concentrated. Flash column chromatography, gradient elution (pentane:EtOAc = 24:1 -> 19:1 -> 9:1) gave the title compound as a waxy semi-solid (1.07 g, 97%); R_f (petroleum ether:EtOAc = 8:2) 0.63; [α]_D²⁰ +28 (c 0.95, CHCl₃); ¹H NMR (300 MHz) δ 7.80 (1 H, br.s, H-13), 7.39 (4 H, m, *Ph*), 7.30 (1 H, m, *Ph*), 6.69 (1 H, d, *J* = 1.7, H-5), 6.62 (2 H, m, H-15, 16), 6.57 (1 H, dd, *J* = 7.9, 1.7, H-7), 6.50 (1 H, d, *J* = 7.9, H-8), 5.48 (1 H, dd, *J* = 10.1, 8.3, NCH), 4.79 (1 H, dd, *J* = 10.1, 8.3, OCHH), 4.24 (1 H, ddd, *J* = 12.6, 9.2, 2.0, H-10a), 4.19 (1 H, t, *J* = 8.3, OCHH), 3.48 (1 H, ddd, *J* = 13.1, 9.7, 1.5, H-2a), 3.22 (1 H, ddd, *J* = 12.9, 9.9, 6.9), 3.13-2.94 (3 H, m), 2.81 (2 H, m); ¹³C NMR (75 MHz) δ 164.8 (C=N), 142.8, 142.1, 140.8, 139.3, 138.8, 135.8, 135.4, 135.1, 135.0, 131.2, 130.6 (C-13), 128.7 (2 C, s), 127.7, 127.4, 126.7 (2 C, s), 126.6, 74.1 (OCH₂), 70.3 (NCH), 36.2, 35.8, 34.0, 32.6; IR (CHCl₃, cm⁻¹) $\nu_{\max}$ 1632 (C=N); MS (EI, m/z) 434 (14), 433 (M⁺, 56), 432 (14), 431 (M⁺, 57), 250

(18), 249 ($\text{CH}_2\text{C}_6\text{H}_3(\text{oxazoline})\text{CH}_2^+$, 100), 248 (12), 158 (54), 131 (12), 104 (12), 103 (20); HRMS Found 431.0885. $\text{C}_{25}\text{H}_{22}^{79}\text{BrNO}$ requires 431.0885.

(+)-(R,4R_p,12R_p)-4-Bromo-12-(4-phenyloxazolin-2-yl)[2.2]paracyclophane (21b)

Treatment of amide **20b** (1.29 g, 2.87 mmol) according to the procedure for the synthesis of **21a** gave the title compound as a white crystalline solid (0.99 g, 80%); R_f (petroleum ether:EtOAc = 8:2) 0.51; mp 115.0-118.0 °C; $[\alpha]_{\text{D}}^{20} +15$ (c 0.86, CHCl_3); ^1H NMR (400 MHz) δ 7.75 (1 H, br.d, J = 1.5, H-13), 7.48-7.40 (4 H, m, *Ph*), 7.32 (1 H, m, *Ph*), 6.66 (1 H, d, J = 1.7, H-5), 6.61 (1 H, d, J = 7.9, H-16), 6.60 (1 H, dd, J = 7.9, 1.5, H-15), 6.55 (1 H, dd, J = 8.0, 1.7, H-7), 6.49 (1 H, d, J = 8.0, H-8), 5.39 (1 H, dd, J = 9.9, 8.2, NCH), 4.70 (1 H, dd, J = 9.9, 8.2, OCHH), 4.29 (1 H, t, J = 8.2, OCHH), 4.28 (1 H, ddd, J = 13.2, 8.2, 2.5, H-10a), 3.47 (1 H, ddd, J = 13.2, 9.9, 1.7, H-2a), 3.21 (1 H, ddd, J = 12.9, 9.9, 6.6, H-1a), 3.09 (1 H, m, H-1b), 2.99 (2 H, m, H-9a, 9b), 2.80 (2 H, m, H-10b, 2b); ^{13}C NMR (100 MHz) δ 164.0 (C=N), 142.7, 142.0, 140.8, 139.1, 138.7, 135.6, 135.2, 135.0, 134.8, 131.2, 130.1 (C-13), 128.7 (2 C, s), 127.5, 127.4, 126.8 (2 C, s), 126.6, 73.5 (OCH₂), 70.8 (NCH), 35.8, 35.7, 33.8 (C-9), 32.6 (C-1); IR (CHCl_3 , cm^{-1}) ν_{max} 1632 (C=N); MS (EI, m/z) 434 (14), 433 (M^+ , 61), 431 (M^+ , 58), 250 (18), 249 ($\text{CH}_2\text{C}_6\text{H}_3(\text{oxazoline})\text{CH}_2^+$, 100), 248 (12), 158 (51), 131 (15), 104 (12), 103 (19); HRMS Found 431.0884. $\text{C}_{25}\text{H}_{22}^{79}\text{BrNO}$ requires 431.0885.

(-)-(R,4S_p,12S_p)-4-Di(4-methoxyphenyl)phosphinyl-12-(4-phenyloxazolin-2-yl)[2.2]paracyclophane (22a)

n-BuLi (15% w/v solution in *n*-hexane, 0.28 mL, 0.65 mmol) was added dropwise to a solution of the bromide **21a** (0.20 g, 0.47 mmol) in THF (4.7 mL) at -95 °C (obtained by addition of liquid nitrogen to a bath of diethyl ether) to give an orange solution which slowly turned dark brown over 4 min. After this

time, a solution of chlorodi(4-methoxyphenyl)phosphine (0.26 g, 0.93 mmol) in THF (1.5 mL) was added dropwise to give a pale orange solution. After 12 min, the cooling bath was removed and the reaction mixture stirred for a further 1.5 h. Ordinary 'wet' Et₃N (0.13 mL, 0.93 mmol) was then added followed by Et₂O (4 mL) and the resulting mixture added to silica gel (2.0 g) and DCM (4 mL). The solvent was evaporated to leave the crude product mixture suspended on silica which was added to the top of a column of silica gel for flash chromatography, gradient elution (petroleum ether:DCM:EtOAc = 23:6:1 -> 15:4:1). This gave first unreacted starting material **21a** (0.08 g, 42%) and then the title compound as a white solid (0.16 g, 57%); *R_f* (petroleum ether:DCM:EtOAc = 7:2:1) 0.45; mp 88.0-90.0 °C; $[\alpha]_D^{20}$ -26 (*c* 0.92, CHCl₃); ¹H NMR (400 MHz) δ 7.70 (1 H, d, *J* = 1.7, H-13), 7.35 (4 H, m, *Ph*, P-C₆H₄OMe (*ortho*)), 7.29-7.21 (5 H, m, *Ph*, P-C₆H₄OMe (*ortho*)), 6.83 (2 H, br.d, *J* = 8.0, P-C₆H₄OMe (*meta*)), 6.77 (2 H, br.d, *J* = 8.0, P-C₆H₄OMe (*meta*)), 6.67 (1 H, dd, *J* = 7.9, 1.7, H-15), 6.62 (1 H, d, *J* = 7.9, H-16), 6.57 (1 H, dd, *J* = 7.7, 1.8, H-7), 6.48 (1 H, dd, *J* = 7.7, *J_{H-P}* = 5.8, H-8), 5.93 (1 H, dd, *J_{H-P}* = 8.5, *J* = 1.8, H-5), 5.24 (1 H, m, NCH), 4.71 (1 H, dd, *J* = 10.2, 8.2, OCHH), 4.24 (1 H, br.dd, *J* = 12.4, 9.4, H-10a), 4.02 (1 H, dd, *J* = 9.1, 8.2, OCHH), 3.81 (3 H, s, OCH₃), 3.75 (3 H, s, OCH₃), 3.47 (1 H, ddd, *J* = 13.2, 10.1, 6.7, H-1a), 3.30 (1 H, br.dd, *J* = 13.2, 10.1, H-2a), 3.09 (1 H, m, H-1b), 3.03 (1 H, m, H-9a), 2.90 (1 H, ddd, *J* = 12.6, 9.4, 7.4, H-9b), 2.77 (1 H, ddd, *J* = 12.4, 9.9, 7.4, H-10b), 2.70 (1 H, m, H-2b); ¹³C NMR (100 MHz) δ 163.7 (C=N), 160.3 (MeOC), 159.8 (MeOC), 142.8 (d, *J_{C-P}* = 19.7), 142.7, 141.3, 140.0, 139.5, 138.7 (d, *J_{C-P}* = 9.9), 137.3, 137.0, 135.4, 135.1, 134.4, 134.2, 134.1, 134.0, 132.6 (C-13), 131.1 (d, *J_{C-P}* = 5.3), 129.9 (d, *J_{C-P}* = 7.0), 128.6 (2 C, s), 127.8 (d, *J_{C-P}* = 7.6), 127.3, 127.2, 126.6 (2 C, s), 113.9, 113.8 (2 C, s), 113.7, 73.4 (OCH₂), 70.8 (NCH), 55.2 (OCH₃), 55.1 (OCH₃), 36.2 (C-10), 35.4 (d, *J_{C-P}* = 9.8, C-2), 33.9 (C-9), 33.1 (C-1); ³¹P NMR (121 MHz) δ -4.72; IR (KBr, cm⁻¹) $\nu_{\max}$ 1636 (C=N); MS (EI, *m/z*) 598 (37), 597 (M⁺, 100), 596 (23), 568 (M⁺-OMe, 5), 478

(5), 449 (3%), 349 (17), 348 ($\text{CH}_2\text{C}_6\text{H}_3(\text{P}(\text{C}_6\text{H}_4\text{OMe})_2)\text{CH}_2^+$, 63), 347 (14), 317 (7), 299 (10), 249 (6), 240 (11), 239 (19), 209 (6); HRMS Found 597.2433. $\text{C}_{39}\text{H}_{36}\text{PNO}_3$ requires 597.2433.

(+)-(R,4S_p)-4-(4-phenyloxazolin-2-yl)[2.2]paracyclophane

The title compound was sometimes isolated as a by-product from the above synthesis. Pale yellow solid; mp 124.5-125.0 °C; $[\alpha]_{\text{D}}^{20} +115$ (c 0.83, CHCl_3); ^1H NMR (400 MHz) δ 7.39 (4 H, m, *Ph*), 7.31 (1 H, m, *Ph*), 7.16 (1 H, br.s, H-5), 6.64 (2 H, m), 6.54 (4 H, m), 5.47 (1 H, br.t, $J = 8.8$, NCH), 4.80 (1 H, dd, $J = 9.9, 8.8$, OCHH), 4.21 (2 H, m, OCHH, H-2a), 3.20-2.98 (6 H, m, H-1a, 1b, 9a, 9b, 10a, 10b), 2.88 (1 H, ddd, $J = 13.2, 9.9, 6.9$, H-2b); ^{13}C NMR (100 MHz) δ 165.0 (C=N), 142.6, 141.2, 139.8, 139.6, 139.3, 135.8, 135.0, 134.4, 132.9, 132.7, 132.2, 131.2, 128.7 (2 C, s), 128.0, 127.5, 126.7 (2 C, s), 74.2 (OCH₂), 70.4 (NCH), 36.1 (C-2), 35.4, 35.1, 35.0; IR (KBr, cm^{-1}) ν_{max} 1624 (C=N); m/z (EI, m/z) 354 (28), 353 (M^+ , 100), 250 (17), 249 ($\text{CH}_2\text{C}_6\text{H}_3(\text{oxazoline})\text{CH}_2^+$, 93), 248 (12), 158 (51), 131 (9), 105 (26), 104 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2^+$, 23%), 103 (18%); HRMS 353.177981. $\text{C}_{25}\text{H}_{23}\text{NO}$ requires 353.177964.

(+)-(R,4R_p,12R_p)-4-Di(4-methoxyphenyl)phosphinyl-12-(4-phenyloxazolin-2-yl)[2.2]paracyclophane (22b)

n-BuLi (15% w/v solution in *n*-hexane, 0.15 mL, 0.35 mmol) was added dropwise to a solution of bromide **21b** (0.10 g, 0.23 mmol) in THF (2.3 mL) at -78 °C. The resulting orange solution was stirred for 2 h, after which time a solution of chlorodi(4-methoxyphenyl)phosphine (0.14 g, 0.49 mmol) in THF (0.7 mL) was added dropwise to give a pale yellow solution. After 15 min, the cooling bath was removed and the reaction mixture stirred for a further 2 h. Ordinary 'wet' Et_3N (0.06 mL, 0.46 mmol)

was added followed by Et₂O (2 mL) and the resulting mixture added to silica gel (1.0 g) and DCM (2 mL). The solvent was evaporated to leave the crude product mixture suspended on silica which was added to the top of a column of silica gel for flash chromatography, gradient elution (pentane:DCM:EtOAc = 23:6:1 → 7:2:1. This gave the product as a white solid (0.10 g, 70%); *R_f* (petroleum ether:DCM:EtOAc = 7:2:1) 0.39; mp 208.0-210.0 °C; [α]_D²⁰ +131 (*c* 0.77, CHCl₃); ¹H NMR (400 MHz) δ 7.69 (1 H, d, *J* = 1.5, H-13), 7.39 (2 H, t, *J* = 8.6, *J_{H-P}* = 8.6, P-C₆H₄OMe (*ortho*)), 7.26 (5 H, m, *Ph*, P-C₆H₄OMe (*ortho*)), 7.08 (2 H, m, *Ph*), 6.77 (2 H, br.d, *J* = 8.6, P-C₆H₄OMe (*meta*)), 6.73 (2 H, br.d, *J* = 8.0, P-C₆H₄OMe (*meta*)), 6.67 (1 H, dd, *J* = 7.9, 1.5, H-15), 6.62 (1 H, d, *J* = 7.9, H-16), 6.56 (1 H, dd, *J* = 7.6, 1.8, H-7), 6.48 (1 H, dd, *J* = 7.6, *J_{H-P}* = 5.5, H-8), 6.00 (1 H, dd, *J_{H-P}* = 8.2, *J* = 1.8, H-5), 5.27 (1 H, dd, *J* = 10.2, 8.2, NCH), 4.62 (1 H, dd, *J* = 10.2, 8.2, OCHH), 4.26 (1 H, m, H-10a), 4.17 (1 H, t, *J* = 8.2, OCHH), 3.74 (3 H, s, OCH₃), 3.59 (3 H, s, OCH₃), 3.48 (1 H, ddd, *J* = 12.8, 9.9, 7.1, H-1a), 3.29 (1 H, br.dd, *J* = 13.5, 9.9, H-2a), 3.08 (1 H, br.dd, *J* = 12.8, 10.4, H-1b), 3.02 (1 H, m, H-9a), 2.77-2.65 (3 H, m, H-9b, 10b, 2b); ¹³C NMR (75 MHz) δ 163.9 (C=N), 160.4 (MeOC), 159.9 (MeOC), 143.0 (d, *J_{C-P}* = 17.9), 142.6, 141.4, 139.9, 139.7, 138.9 (d, *J_{C-P}* = 10.7), 137.6, 137.3, 135.7, 135.3, 134.4 (3 C, s), 134.1, 132.5 (C-13), 131.8 (d, *J_{C-P}* = 4.8), 130.4 (d, *J_{C-P}* = 7.2), 128.6 (2 C, s), 127.6 (d, *J_{C-P}* = 7.7), 127.3, 127.1, 126.8 (2 C, s), 114.0, 113.9 (2 C, s), 113.8, 73.2 (OCH₂), 70.5 (NCH), 55.0 (OCH₃), 54.9 (OCH₃), 36.5 (C-10), 35.5 (d, *J_{C-P}* = 9.5, C-2), 34.2 (C-9), 32.9 (C-1); ³¹P NMR (121 MHz) δ -4.67; IR (KBr, cm⁻¹) $\nu_{\max}$ 1630 (C=N); MS (EI, *m/z*) 598 (37), 597 (M⁺, 100), 596 (19), 568 (M⁺-OMe, 5), 493 (5), 349 (17), 348 (CH₂C₆H₃(P(C₆H₄OMe)₂)CH₂⁺, 61), 347 (15), 317 (7), 299 (9), 249 (8), 240 (11), 239 (20), 225 (5), 209 (7); HRMS Found 597.2434. C₃₉H₃₆PNO₃ requires 597.2433.

(+)-(R,4R_p)-4-(4-phenyloxazolin-2-yl)[2.2]paracyclophane

The title compound was sometimes isolated as a by-product from the above synthesis. Pale yellow solid; mp 148.0-148.5 °C; $[\alpha]_D^{20} -72$ (*c* 0.97, CHCl₃); ¹H NMR (400 MHz) δ 7.40 (4 H, m, *Ph*), 7.32 (1 H, m, *Ph*), 7.16 (1 H, br.s, H-5), 6.62 (2 H, m), 6.53 (4 H, m), 5.43 (1 H, dd, *J* = 10.2, 8.2, NCH), 4.76 (1 H, dd, *J* = 10.2, 8.2, OCHH), 4.28 (1 H, t, *J* = 8.2, OCHH), 4.26 (1 H, ddd, *J* = 13.0, 9.6, 2.2, H-2a), 3.20-2.97 (6 H, m, H-1a, 1b, 9a, 9b, 10a, 10b), 2.87 (1 H, ddd, *J* = 13.0, 10.2, 6.6, H-2b); ¹³C NMR (100 MHz) δ 164.7 (C=N), 142.7, 141.2, 139.8, 139.5, 139.3, 135.9, 135.1, 134.4, 132.9, 132.7, 132.3, 131.3, 128.7 (2 C, s), 127.9, 127.5, 126.7 (2 C, s), 73.9 (OCH₂), 70.4 (NCH), 35.9 (C-2), 35.4, 35.1, 35.0; IR (IR (KBr, cm⁻¹) $\nu_{\max}$ 1636 (C=N); MS (EI, *m/z*) 354 (25), 353 (M⁺, 100), 250 (16), 249 (CH₂C₆H₃(oxazoline)CH₂⁺, 87), 248 (13), 158 (50), 131 (11), 105 (26), 104 (CH₂C₆H₄CH₂⁺, 23%), 103 (18%); HRMS Found 353.1780. C₂₅H₂₃NO requires 353.1780.

General procedure for the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate²⁵

[Pd(η^3 -C₃H₅)Cl]₂ (3.7 mg, 0.01 mmol) and the appropriate ligand (0.03 mmol) were dissolved in toluene (2.0 mL) and stirred for 1 h. A solution of 1,3-diphenyl-2-propenyl acetate⁴¹ (0.13 g, 0.50 mmol) in toluene (1.0 mL) was added and the solution stirred for 0.5 h. Dimethylmalonate (0.17 mL, 1.50 mmol), then *N,O*-bis(trimethylsilyl)acetamide (0.37 mL, 1.50 mmol), then LiOAc (1 mg, 0.015 mmol) were added. The reaction was monitored by tlc [SM: R_f (petroleum ether:EtOAc = 9:1) 0.51, product: R_f 0.34] until completion. DCM (15 mL) was then added, the solution washed with aq saturated NH₄Cl solution

(2 × 10 mL), dried over MgSO₄, filtered and concentrated. Flash column chromatography (petroleum ether:EtOAc = 9:1) gave the product as a clear oil which slowly crystallized. The ee was determined by HPLC analysis (Chiralcel AD column, heptane:*i*-PrOH = 95:5), flow rate = 0.5 mL min⁻¹, *t*_R = 30.6 min, *t*_S = 43.3 min].

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Supporting Information Available. ¹H and ¹³C NMR spectra of all new compounds (PDF). This material is available free of charge via the internet at <http://pubs.acs.org>.

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