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Synthesis of Pseudo-*geminal*-, Pseudo-*ortho*-, and *ortho*-Phosphinyl-oxazolinyl-[2.2]paracyclophanes for Use as Ligands in Asymmetric Catalysis

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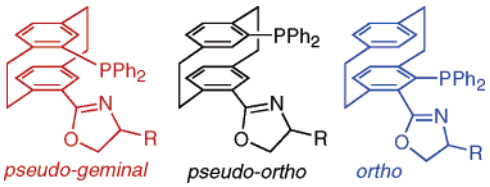

Syntheses of three regioisomers of aromatic-substituted phosphinyl-oxazolinyl-[2.2]paracyclophanes, pseudo-*geminal*, pseudo-*ortho*, and *ortho*, have been carried out or, in the latter two cases, newly developed. It has, therefore, been demonstrated that all aromatic-substituted isomers relevant for 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, among 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 that 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 pseudogeminal 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] sul-

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foxidations,[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 oxazolinyl-phosphinyl-[2.2]paracyclophanes, *P*,*N*-ligands[22,23] designed by Pelter et al. and Hou et al.[24,25] Hou showed that the use of the pseudogeminal 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.

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-oxazolinyl-[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 that 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 conditions[29] to give an inseparable mixture of diastereoisomers **5** (Scheme 1). The pseudogeminal 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 $FeBr_2$ or $FeBr_3$ 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 $ClPPh_2$. Interestingly, it was found that the diastereomeric phosphines **1a** and **1b** could be far more easily separated from the

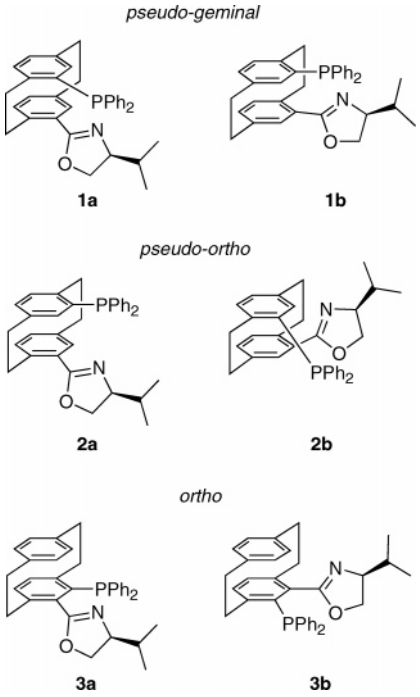
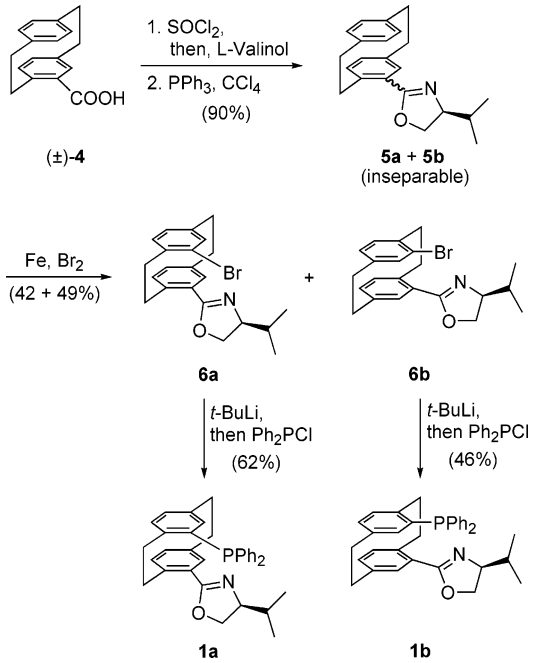


FIGURE 1. All isomers of the aromatic-substituted [2.2]paracyclophane for use as *P*,*N*-ligands.

SCHEME 1. Synthesis of Pseudo-*geminal*-phosphinyl-oxazolinyl-[2.2]paracyclophanes



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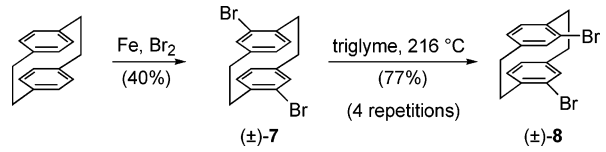
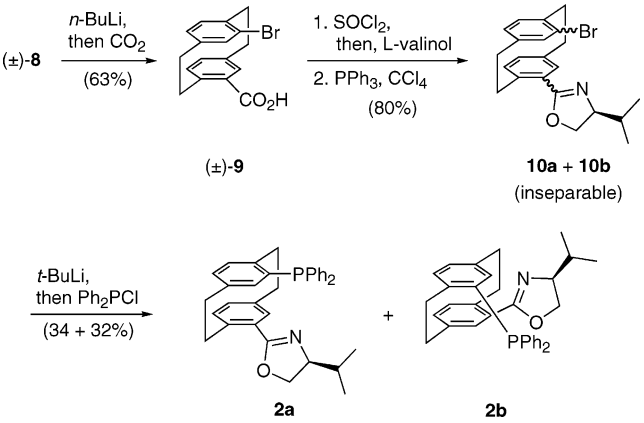
SCHEME 2. Access to Pseudo-*ortho*-Substituted [2.2]Paracyclophanes



SCHEME 3. Synthesis of Pseudo-*ortho*-phosphinyl-oxazolinyl-[2.2]paracyclophanes



oxazolinyl[2.2]paracyclophane byproducts (resulting from protonation of the lithium intermediates) by column chromatography if a three-component solvent system (pentane/DCM/EtOAc [20:4:1]) was used instead of the more usual two-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]

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 et al.[8] and Braddock et al.[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.

Dibromide **8** was converted to the monocarboxylic 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 $ClPPh_2$, 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 workup 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 workup procedure was developed, and the yields improved to 34 and 32%. This procedure is described later in the "Asymmetric Catalysis" section.

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-oxazolinyl-[2.2]paracyclophanes similar to **3** (Figure 1) have been previously synthesized in our group by a metal−phosphine exchange of *ortho*-oxazolinyl-palladacycles.[28] Although efficient, the use of stoichiometric (1.1 equiv) palladium acetate is expensive, so an alternative procedure was sought. Attempted *ortho*-directed lithiations proved problematic due to the competitive 1,2-addition of the alkyllithium to the oxazoline and the 1,4-addition to the [2.2]paracyclophane backbone.[28] Hou, however, showed that *ortho*-lithiation of the diastereotopic mixture of oxazolinyl[2.2]paracyclophanes **5**, using *n*-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 $ClPPh_2$ 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 workup leads to the *ortho*-hydroxy-aldehyde FHPC (see Introduction), in 64% yield, as a result of the facile hydrolysis of the carbamate during workup. We desired the carboxylic acid rather than the aldehyde, so gaseous CO_2 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 the 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 byproducts **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**

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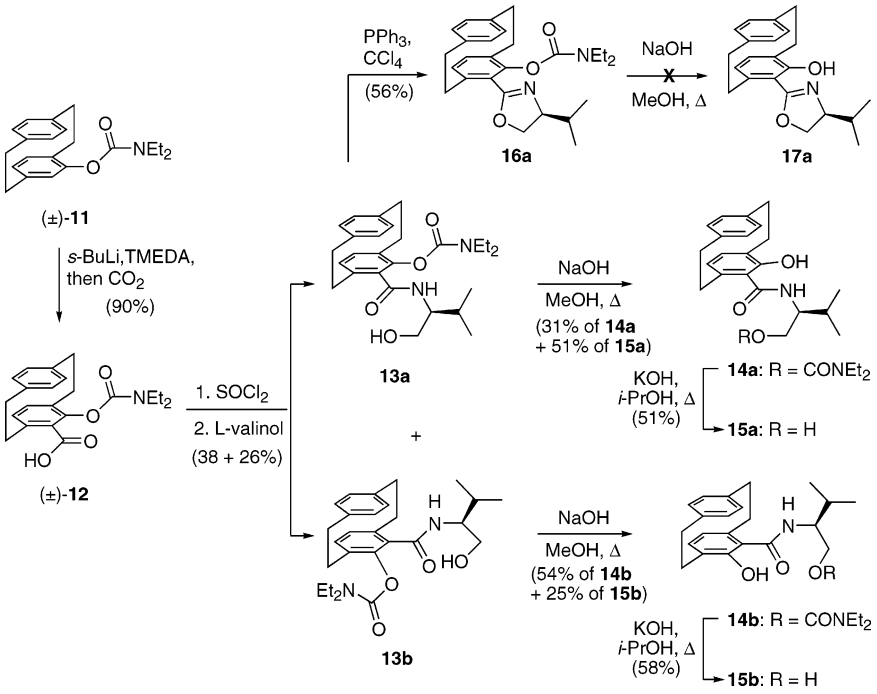
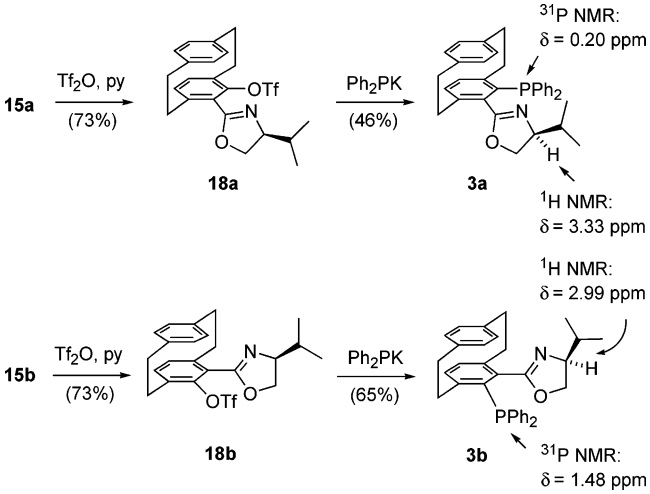
SCHEME 4. Synthesis of *ortho*-Phosphinyl-oxazolinyl-[2.2]paracyclophanes, Part 1



SCHEME 5. Synthesis of *ortho*-Phosphinyl-oxazolinyl-[2.2]paracyclophanes, Part 2



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.

On treatment with Tf_2O, the hydroxy-amides **15** underwent simultaneous cyclization and triflation[38] of the phenol group to give oxazolinyl-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 C*H* 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.

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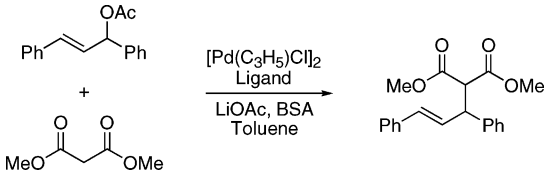
TABLE 1. Palladium-Catalyzed Asymmetric Allylic Alkylation



entry	ligand	substitution	time (h)	yield (%)	ee (%)	abs. config.
1	**1a**	pseudogem.	6	>98	56[a]	(*S*)
2	**1b**	pseudogem.	8	96	30	(*S*)
3	**2a**	pseudo-ortho	10	>98	82	(*S*)
4	**2b**	pseudo-ortho	10	>98	28	(*R*)
5	**3a**	ortho	8	>98	23	(*S*)
6	**3b**	ortho	7	>98	47	(*S*)
7	**19a**	pseudo-ortho	5	>98	89	(*S*)
8	**19b**	pseudo-ortho	20	>98	63	(*R*)
9	**22a**[b]	pseudo-ortho	5	>98	89	(*R*)
10	**22b**[b]	pseudo-ortho	20	>98	62	(*S*)

[a] Hou et al. obtained 62% ee (ref 25). [b] Pseudoenantiomer of **2** (see text).

Asymmetric Catalysis. Asymmetric allylic alkylation was chosen as a test reaction for the new ligands to make a good comparison with the work with compounds **1** of Hou et al.[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).

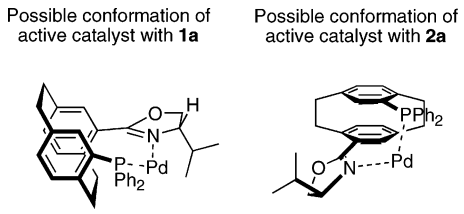


FIGURE 2. Cartoons of speculative Pd complexes with pseudogeminal and pseudo-ortho ligands.

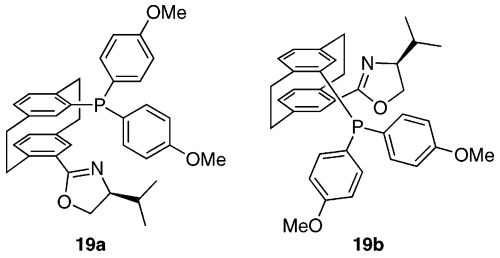


FIGURE 3. Ligand optimization: 4-methoxyphenylphosphines.

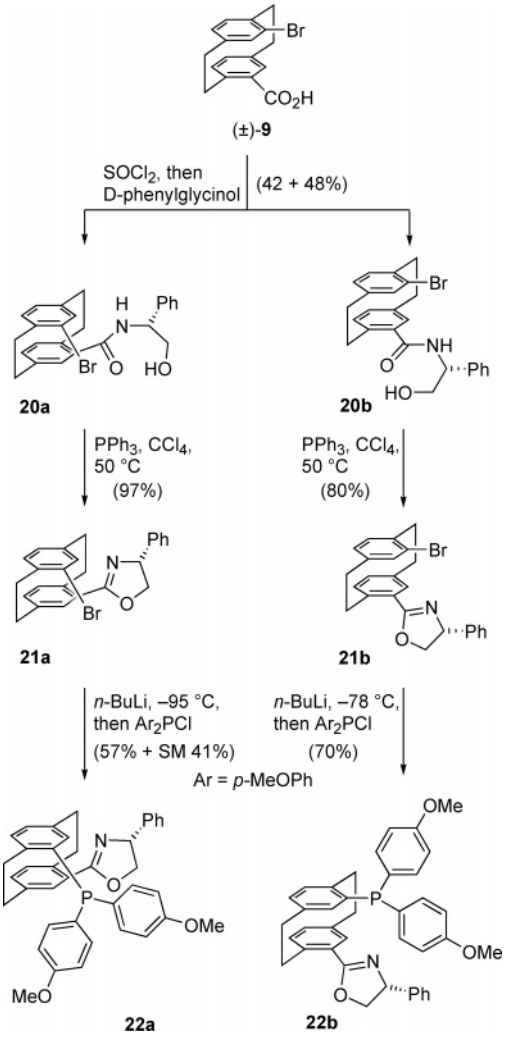
Rather than simply being an effect of the bite angle at the metal in the active catalyst, this result must arise from the chiral environment being entirely different to that of the complex formed with **1a**. As shown in Figure 2, in **1a**, half of the [2.2]-paracyclophane backbone shields one side 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.

Although these arguments account for the selectivity differences stemming from the various ligand types, they cannot fully explain the observed selectivity values, because the complete mechanistic scenario must also consider the exo/endo isomerism of the substrate allyl fragment. However, no information is available on that aspect at the present time.

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 $(MeOC_6H_4)_2PCl$ instead of Ph_2PCl. These electron-rich phosphines were found to be more susceptible to oxidation, and the oxides could not be reduced by the usual method using $HSiCl_3$.[8] However, the yields could be improved from 9 and 6% (of **19a** and **19b**, respectively) to 32 and 31% by modifying the workup. Hence, in place of the addition of degassed aq NH_4Cl and the extraction with degassed DCM, 2 equiv of Et_3N were added (to quench HCl formed later) along with Et_2O, and the mixture was suspended directly onto silica. After drying, this was placed atop a silica column, and chromatography was carried out as quickly as possible to give the separated diastereoisomers.

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

SCHEME 6. Ligand Optimization: Synthesis of Phenyl-oxazolines



6) possessing phenyl-substituted oxazoline units. (It should be noted that the Ph-substituted products **22** were pseudoenantiomers 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 equivalent of each reagent was added, and the mixture was heated at 50 °C for an additional 4 h. Heating was necessary as a result of the lower solubility of the starting amides **20**. Once again, the absolute configurations of **21** were assigned by the synthesis of **21a** from enantiopure (+)-(S_p)-**9**.

Three different procedures for the metalation of **21b** were tested, including using *n*-BuLi, *t*-BuLi (both at −78 °C), and *s*-Bu_2Mg·LiCl at room temperature, a reagent recently described by Knochel et al. as highly effective for the metalation of aryl bromides.[39] The 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 byproduct that was difficult to separate from the product and that, starting with Knochel's

(39) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **1996**, *45*, 159.

reagent, gave 29% starting material and 33% oxazolinyl[2.2]-paracyclophane, resulting from quenching of the unreacted paracyclophanylmetallic during workup. Hence, for the metalation 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 °C gave a mixture of products (including one with m/z = 487/489, corresponding to the addition of a butyl group to the starting material). It was hypothesized that problems were arising as a result of 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 °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 because 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 and *i*-Pr = 2.15 kcal mol^{-1}).[40]

Conclusion

We have devised synthetic routes to all aromatic-substituted regioisomers of phosphinyl-oxazolinyl-[2.2]paracyclophanes that are relevant for use as chelating ligands in asymmetic 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-oxazolinyl-[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 that obeys different rules for selectivity.

Experimental Section

General. For instrumental details, see Supporting Information. Starting materials: (±)-[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 acetate[41] were prepared according to literature procedures. Acid **4** was resolved according to the procedure of Rozenberg et al.[31] and dibromide **7** was resolved 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*,4*R*$_P$)- and (+)-(*S*,4*S*$_P$)-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 was heated at 60 °C for 4 h. The excess thionyl chloride was removed by evaporation, and the final traces were removed 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 Et_3N (11.4 mL, 81.00 mmol) in DCM (10 mL) was added, and the reaction mixture was allowed to warm to room temperature and stir for 24 h. DCM (500 mL) was then added, and the solution was washed with aq $NaHCO_3$ solution (3.5% w/v, 2 × 600 mL) and brine (600 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated, and dried in vacuo to give the crude amide. PPh_3 (18.78 g, 71.59 mmol), MeCN (859 mL), CCl_4 (6.9 mL, 71.6 mmol), and Et_3N (10.1 mL, 71.6 mmol) were added, and the mixture stirred for 18 h. DCM (850 mL) was then added, and the solution was washed with brine (2 × 850 mL), dried over $MgSO_4$, 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*,4*R*$_P$)-**5a** was prepared in the same manner as that described above, but on a smaller scale, from enantiopure (−)-(4*R*$_P$)-carboxylic acid **4**.[31] Colorless oil; $[\alpha]^{20}_D$ −170 (*c* 0.88, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.04 (1H, d, J = 1.7 Hz, H-5), 6.61−6.46 (6H, m, H-7, 8, 12, 13, 15, 16), 4.40 (1H, dd, J = 9.3, 7.7 Hz, OC*H*H), 4.20−4.08 (3H, m, OCH*H*, NC*H*, H-2a), 3.19−2.97 (6H, m, H-1a, 1b, 9a, 9b, 10a, 10b), 2.85 (1H, ddd, J = 12.6, 10.2, 6.6 Hz, H-2b), 1.93 (1H, oct, J = 6.7 Hz, C*H*(CH$_3$)$_2$), 1.11 (3H, d, J = 6.7 Hz, C*H*$_3$), 1.01 (3H, d, J = 6.7 Hz, C*H*$_3$); ^{13}C 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}) ν_{max} 1640 (C═N); MS (EI, m/z) 320 (14), 319 (M$^+$, 57), 276 (M$^+$ − *i*-Pr, 9), 216 (15), 215 (CH$_2$C$_6$H$_3$(oxazoline)CH$_2^+$, 100), 159 (11), 147 (11), 104 (14); HRMS calcd for $C_{22}H_{25}NO$, 319.1936; found, 319.1936.

A pure sample of (+)-(*S*,4*S*$_P$)-**5b** was obtained as a byproduct from the synthesis of **1b** as a pale yellow solid; mp 93.5−95.0 °C; $[\alpha]^{20}_D$ +26 (*c* 1.20, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.04 (1H, d, J = 1.9 Hz, H-5), 6.58 (1H, dd, J = 8.0, 1.9 Hz, H-7), 6.57−6.48 (5H, m, H-8, 12, 13, 15, 16), 4.37−4.30 (2H, m, OC*H*H, H-2a), 4.17−4.08 (2H, m, OCH*H*, NC*H*), 3.20−2.98 (6H, m, H-1a, 1b, 9a, 9b, 10a, 10b), 2.87 (1H, ddd, J = 12.9, 10.2, 6.9 Hz, H-2b), 1.95 (1H, oct, J = 6.7 Hz, C*H*(CH$_3$)$_2$), 1.17 (3H, d, J = 6.7 Hz, C*H*$_3$), 1.05 (3H, d, J = 6.7 Hz, C*H*$_3$); ^{13}C 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}) ν_{max} 1637 (C═N); MS (EI, m/z) 320 (14), 319 (M$^+$, 56), 276 (M$^+$ − *i*-Pr, 8), 216 (16), 215 (CH$_2$C$_6$H$_3$(oxazoline)-CH$_2^+$, 100), 159 (10), 147 (10), 104 (13); HRMS calcd for $C_{22}H_{25}$-NO, 319.1936; found, 319.1938.

(−)-(*S*,4*S*$_P$,13*R*$_P$)-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), and the mixture was heated at reflux for 16 h [Note: On larger scales, a solution of bromine should be added dropwise, according to the literature procedure.[24]] The reaction mixture was washed with saturated $NaHCO_3$ solution (2 × 10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography with 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; $[\alpha]^{20}_D$ −5 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 7.19 (1H, br s, H-12), 6.64 (1H, d, J = 1.5 Hz, H-5), 6.62 (1H, dd, J = 7.8, 2.0 Hz, H-16), 6.58 (1H, d, J = 7.8 Hz, H-15), 6.55 (1H, d, J = 7.8 Hz, H-8), 6.53 (1H, dd, J = 7.8, 1.5 Hz, H-7), 4.56 (1H, ddd, J = 13.7, 10.4, 4.1 Hz, H-1a), 4.40 (1H, dd, J = 9.4, 8.2 Hz, OC*H*H), 4.11 (1H, ddd, J = 9.4, 8.2, 6.6 Hz, NC*H*), 4.04 (1H, t, J = 8.2 Hz, OCH*H*), 3.56 (1H, ddd, J = 12.9, 10.4, 4.1 Hz, H-2a), 3.06 (2H, m, H-10a, 10b), 3.01 (3H, m, H-9a, 9b, 1b), 2.93 (1H, ddd, J = 12.9, 10.4, 4.1 Hz, H-2b), 1.89 (1H, oct, J = 6.6 Hz, C*H*(CH$_3$)$_2$), 1.05 (3H, d, J = 6.6 Hz, C*H*$_3$), 0.89 (3H, d, J = 6.6 Hz, C*H*$_3$); ^{13}C 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 (2C, s, C-8, 16), 132.9 (C-12), 131.6 (C-7), 126.3, 73.2 (NC*H*), 68.7 (O*C*H$_2$), 35.1 (C-2), 34.9 (C-10), 34.5 (C-9), 33.6 (C-1), 32.5 (*C*H(CH$_3$)$_2$), 19.6 (*C*H$_3$), 18.1 (*C*H$_3$); IR (KBr, cm^{-1}) ν_{max} 1637

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(C═N); MS (CI, methane, *m*/*z*) 428 (M + $C_2H_5^+$, 22), 426 (M + $C_2H_5^+$, 21), 401 (24), 400 (M + H^+, 100), 399 (46), 398 (M + H^+, 98), 397 (24), 215 ($CH_2C_6H_3$(oxazoline)CH_2^+, 7).

(−)-(*S*,4*R*$_p$,13*S*$_p$)-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; $[\alpha]^{20}_D$ −104 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 7.24 (1H, br s, H-12), 6.66 (1H, br s, H-5), 6.61 (1H, dd, *J* = 7.9, 1.8 Hz, H-16), 6.56 (1H, br s, H-7, 8), 6.55 (1H, d, *J* = 7.9 Hz, H-15), 4.53 (1H, ddd, *J* = 13.1, 10.0, 4.3 Hz, H-1a), 4.42 (1H, dd, *J* = 9.5, 8.4 Hz, OC*H*H), 4.13 (1H, t, *J* = 8.4 Hz, OCH*H*), 4.00 (1H, m, NC*H*), 3.54 (1H, ddd, *J* = 13.2, 10.0, 4.0 Hz, H-2a), 3.09 (3H, m, H-10a, 10b, 1b), 3.02 (2H, m, H-9a, 9b), 2.93 (1H, ddd, *J* = 13.2, 10.4, 4.3 Hz, H-2b), 1.96 (1H, oct, *J* = 6.9 Hz, C*H*(CH_3)$_2$), 1.16 (3H, d, *J* = 6.9 Hz, C*H*$_3$), 0.97 (3H, d, *J* = 6.9 Hz, C*H*$_3$); ^{13}C 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 (N*C*H), 69.8 (O*C*H$_2$), 35.4 (C-2), 34.8 (C-10), 34.5 (C-9), 33.2 (C-1), 33.1 (*C*H(CH_3)$_2$), 19.8 (*C*H$_3$), 18.9 (*C*H$_3$); IR (KBr, cm^{-1}) ν_{max} 1643 (C═N); MS (CI, methane, *m*/*z*) 428 (M + $C_2H_5^+$, 20), 426 (M + $C_2H_5^+$, 21), 401 (21), 400 (M + H^+, 88), 399 (45), 398 (M + H^+, 100), 397 (25), 215 ($CH_2C_6H_3$(oxazoline)-CH_2^+, 7); Anal. Calcd for $C_{22}H_{24}BrNO$: C, 66.34; H, 6.07; N, 3.52. Found: C, 66.08; H, 5.94; N, 3.26.

(+)-(*S*,4*S*$_p$,13*R*$_p$)-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, $ClPPh_2$ (0.75 mL, 4.20 mmol) was added dropwise. The resulting pale yellow solution was allowed to warm to room temperature and stirred for 18 h. A degassed (by argon bubbling under sonication), saturated aq solution of NH_4Cl (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 Na_2SO_4, 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; $[\alpha]^{20}_D$ +4 (*c* 0.44, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.33 (4H, m, P−C$_6$*H*$_5$), 7.24 (6H, m, P−C$_6$*H*$_5$), 7.06 (1H, br s, H-12), 6.64 (2H, br s, H-15, 16), 6.50 (2H, m, H-7, 8), 5.84 (1H, dd, J_{H-P} = 7.9 Hz, *J* = 1.5 Hz, H-5), 4.61 (2H, m, OC*H*H, H-1a), 4.20 (1H, td, *J* = 9.2, 7.0 Hz, NC*H*), 4.10 (1H, dd, *J* = 9.2, 7.2 Hz, OCH*H*), 3.49 (1H, m, H-2a), 3.07 (1H, m, H-10a), 2.85 (5H, m, H-1b, 2b, 9a, 9b, 10b), 1.92 (1H, oct, *J* = 7.0 Hz, C*H*(CH_3)$_2$), 1.13 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 0.92 (3H, d, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (75 MHz) δ 162.7 (*C*═N), 144.0 (d, J_{C-P} = 17.3 Hz, C-4), 141.6, 138.83 (d, J_{C-P} = 14.3 Hz), 138.80, 138.6, 138.0 (d, J_{C-P} = 10.7 Hz), 137.5 (d, J_{C-P} = 13.7 Hz), 136.1, 135.0, 134.8, 134.2, 133.7, 133.6 (d, J_{C-P} = 2.4 Hz), 133.4 (2C, s), 133.3 (d, J_{C-P} = 2.9 Hz), 133.2, 128.52, 128.49, 128.40, 128.3, 128.2, 128.1, 127.0, 73.8 (N*C*H), 69.1 (O*C*H2), 36.3, 34.9, 34.8, 33.6 (d, J_{C-P} = 14.9 Hz, C-2), 32.7 (*C*H(CH_3)$_2$), 20.0 (*C*H$_3$), 18.5 (*C*H$_3$); ^{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 (M^+ − Me, 18) 460 (M^+ − *i*-Pr, 18), 434 (19), 289 (11), 288 ($CH_2C_6H_3(PPh_2)CH_2^+$, 38), 287 (18), 208 (16), 198 (19), 178 (11). Data agrees with that published.[25]

(−)-(*S*,4*R*$_p$,13*S*$_p$)-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; $[\alpha]^{20}_D$ −80 (*c* 0.39, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.35 (4H, m, P−C$_6$*H*$_5$), 7.23 (6H, m, P−C$_6$*H*$_5$), 7.15 (1H, br s, H-12), 6.62 (2H, br s), 6.51 (2H, m, H-7, 8), 5.83 (1H, dd, J_{H-P} = 8.2 Hz, *J* = 1.7 Hz, H-5), 4.55 (1H, dd, *J* = 9.9, 8.1 Hz, OC*H*H), 4.51 (1H, m, H-1a), 4.31 (1H, t, *J* = 8.1 Hz, OCH*H*), 4.10 (1H, m, NC*H*), 3.43 (1H, m, H-2a), 3.06 (1H, m, H-10a), 2.87 (5H, m, H-1b, 2b, 9a, 9b, 10b), 2.19 (1H, oct, *J* = 6.8 Hz, C*H*(CH_3)$_2$), 1.19 (3H, d, *J* = 6.8 Hz, C*H*$_3$), 1.02 (3H, d, *J* = 6.8 Hz, C*H*$_3$); ^{13}C NMR (75 MHz) δ 163.5 (*C*═N), 143.7 (d, J_{C-P} = 17.2 Hz, C-4), 141.1, 139.2 (d, J_{C-P} = 14.3 Hz), 138.9, 138.0 (d, J_{C-P} = 10.7 Hz), 137.2 (d, J_{C-P} = 13.7 Hz), 136.1, 135.1, 134.8, 134.5, 133.7, 133.6, 133.4 (2C, s), 133.2 (d, J_{C-P} = 4.2 Hz), 128.6, 128.52, 128.48, 128.38, 128.2, 128.1, 127.0, 73.1 (N*C*H), 69.9 (O*C*H$_2$), 35.7, 34.9, 34.8, 34.1 (d, J_{C-P} = 15.5 Hz, C-2), 32.9 (*C*H(CH_3)$_2$), 20.0 (*C*H$_3$), 19.1 (*C*H$_3$); ^{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 (M^+ − Me, 19) 460 (M^+ − *i*-Pr, 27), 434 (16), 289 (20), 288 ($CH_2C_6H_3(PPh_2)CH_2^+$, 58), 287 (33), 208 (31), 198 (27), 178 (18). Data agrees with that published.[25]

(±)-*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. CO_2 gas was then bubbled through the solution for 2 h. The reaction mixture was allowed to warm to room temperature and stirred for 18 h with slow bubbling of CO_2. The mixture was extracted twice with water (1 L, 500 mL) and then aq NaOH solution (6 M, 50 mL). The combined aq layers were washed with DCM (500 mL) and Et_2O (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), and 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; ^{1}H NMR (300 MHz) δ 6.82 (1H, dd, *J* = 7.9, 1.7 Hz), 6.70 (1H, dd, *J* = 7.9, 1.7 Hz), 6.67 (1H, d, *J* = 8.2 Hz), 6.62 (1H, dd, *J* = 7.9, 1.7 Hz), 6.53 (1H, dd, *J* = 7.9, 1.7 Hz), 6.50 (1H, d, *J* = 7.9 Hz), 3.59 (2H, m, C*H*$_2$CH$_3$), 3.50 (1H, m), 3.39 (2H, m, C*H*$_2$CH$_3$), 3.25 (1H, ddd, *J* = 12.6, 10.6, 4.9 Hz), 3.16−3.04 (4H, m), 2.88 (1H, ddd, *J* = 12.6, 10.4, 5.2 Hz), 2.79 (1H, m), 1.42 (3H, t, *J* = 6.9 Hz, CH$_2$C*H*$_3$), 1.21 (3H, t, *J* = 7.2 Hz, CH$_2$C*H*$_3$); ^{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 (*C*H$_2$CH$_3$), 42.0 (*C*H$_2$CH$_3$), 34.7, 34.3 (2C, s), 30.6, 14.2 (*C*H$_3$), 13.2 (*C*H$_3$); IR (KBr, cm^{-1}) ν_{max} 3433 (O−H), 1723 (Et_2NC═O), 1678 (C═OOH); MS (EI, *m*/*z*) 368 (17), 367 (M^+, 72), 251 (17), 250 (ParacyclophanylCHO$^+$, 90), 104 ($CH_2C_6H_4CH_2^+$, 58), 100 (100); HRMS calcd for $C_{22}H_{25}NO_4$, 367.1784; found, 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; $[\alpha]^{20}_D$ +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 was heated at 60 °C for 4 h. The excess thionyl chloride was removed by evaporation, and the final traces were removed 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 was allowed to warm to room temperature and stirred for 24 h. DCM (120 mL) was then added, and the solution was washed with aq $NaHCO_3$ solution (3.5% w/v, 2 × 120 mL) and brine (120 mL). The organic phase was dried over Na_2SO_4, 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; $[\alpha]^{20}_D$ −23 (*c* 0.90, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.10 (1H, dd, *J* = 7.9, 1.7 Hz), 6.72 (1H, dd, *J* = 7.9, 1.7 Hz), 6.58 (1H, dd, *J* = 7.9, 1.7 Hz), 6.54 (1H, d, *J* = 7.9 Hz), 6.52 (1H, dd, *J* = 7.9, 1.7 Hz), 6.44 (1H, d, *J* = 7.9 Hz), 5.78 (1H, br d, *J* = 8.9 Hz, N*H*), 3.81 (1H, dddd, *J* = 8.9, 7.2, 5.4, 3.5 Hz, NC*H*), 3.59 (3H, m, C*H*$_2$OH, C*H*$_2$CH$_3$), 3.44 (1H, m, CH*H*CH$_3$), 3.28 (1H, m, C*H*HCH$_3$), 3.23 (2H, m), 3.19−2.98

(5H, m), 2.74 (1H, m), 1.81 (1H, oct, J = 6.7 Hz, CH(CH$_3$)$_2$), 1.43 (3H, t, J = 7.2 Hz, CH$_2$CH_3), 1.20 (3H, t, J = 7.2 Hz, CH$_2$CH_3), 0.95 (3H, d, J = 6.7 Hz, CH(CH_3)CH$_3$), 0.91 (3H, d, J = 6.7 Hz, CH(CH$_3$)CH_3); ^{13}C 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 (*C*H$_2$OH), 57.3 (N*C*H), 42.12 (*C*H$_2$CH$_3$), 42.08 (*C*H$_2$CH$_3$), 35.1, 34.5, 33.4, 30.4, 28.9 (*C*H(CH$_3$)$_2$), 19.5 (CH(*C*H$_3$)-CH$_3$), 18.8 (CH(CH$_3$)*C*H$_3$), 14.0 (CH$_2$*C*H$_3$), 13.2 (CH$_2$*C*H$_3$); IR (CHCl$_3$, cm^{-1}) ν_{max} 3411 (br, O—H and N—H), 1699 (Et$_2$NC═O), 1657 (C═OONH); MS (EI, *m*/*z*) 453 (21), 452 (M$^+$, 78), 350 (9), 348 (M$^+$ − CH$_2$C$_6$H$_4$CH$_2$, 7), 335 (12), 248 (14), 231 (60), 104 (CH$_2$—C$_6$H$_4$—CH$_2^+$, 23), 100 (100); HRMS calcd for C$_{27}$H$_{36}$N$_2$O$_4$, 452.2675; found, 452.2675.

(+)-(*S*,4*R*$_P$,5*S*$_P$)-*O*-[4-(5-(1-Hydroxymethyl-2-methyl-propyl-carbamoyl)-[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]$^{20}_D$ +20.7 (*c* 1.09, CHCl$_3$); ^{1}H NMR (300 MHz) δ 7.13 (1H, dd, J = 7.9, 1.7 Hz), 6.67 (1H, dd, J = 7.9, 2.0 Hz), 6.59 (1H, dd, J = 7.7, 1.7 Hz), 6.53 (1H, d, J = 7.8 Hz), 6.52 (1H, dd, J = 7.7, 2.0 Hz), 6.43 (1H, d, J = 7.8 Hz), 6.08 (1H, br d, J = 7.9 Hz, N*H*), 3.71 (1H, m, NC*H*), 3.64 (1H, m, C*H*HCH$_3$), 3.52 (3H, m, CH*H*CH$_3$, C*H*$_2$OH), 3.37 (1H, m, C*H*HCH$_3$), 3.33−3.17 (3H, m), 3.06−2.91 (4H, m), 2.86 (1H, m), 2.76 (1H, m), 1.83 (1H, oct, J = 6.8 Hz, C*H*(CH$_3$)$_2$), 1.40 (3H, t, J = 7.2 Hz, CH$_2$CH_3), 1.18 (3H, t, J = 7.2 Hz, CH$_2$CH_3), 0.89 (3H, d, J = 6.8 Hz, CH(CH_3)CH$_3$), 0.88 (3H, d, J = 6.8 Hz, CH(CH$_3$)CH_3); ^{13}C 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 (N*C*H), 57.9 (*C*H$_2$OH), 42.0 (2C, s, 2 × *C*H$_2$CH$_3$), 35.1, 34.4, 33.4, 30.3, 28.8 (*C*H(CH$_3$)$_2$), 19.1 (CH(*C*H$_3$)-CH$_3$), 19.0 (CH(CH$_3$)*C*H$_3$), 14.2 (CH$_2$*C*H$_3$), 13.2 (CH$_2$*C*H$_3$); IR (KBr, cm^{-1}) ν_{max} 3493 (br, O—H), 3259 (N—H), 1719 (Et$_2$NC═O), 1661 (C═OONH); MS (EI, *m*/*z*) 453 (25), 452 (M$^+$, 90), 350 (10), 348 (M$^+$ − CH$_2$C$_6$H$_4$CH$_2$, 7), 335 (14), 248 (14), 231 (60), 104 (CH$_2$C$_6$H$_4$CH$_2^+$, 24), 100 (100); HRMS calcd for C$_{27}$H$_{36}$N$_2$O$_4$, 452.2675; found, 452.2676.

(−)-(*S*,4*S*$_P$,5*R*$_P$)-*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. Aqueous HCl (3 M, 45 mL, 135 mmol) was added, and the mixture was extracted with EtOAc (4 × 50 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated. Flash column chromatography, gradient elution (pentane/EtOAc = 19:1 → 9:1 → 8:2 → 7:3) gave the title compound as a colorless oil (0.26 g, 31%): R_f (petroleum ether/EtOAc = 1:1) 0.71; [α]$^{20}_D$ −117 (*c* 0.95, CHCl$_3$); ^{1}H NMR (300 MHz) δ 11.65 (1H, s, O*H*), 7.04 (1H, dd, J = 7.9, 1.7 Hz), 6.58 (1H, dd, J = 7.9, 1.7 Hz), 6.48 (1H, dd, J = 7.7, 1.7 Hz), 6.44 (1H, d, J = 7.7 Hz), 6.43 (1H, dd, J = 7.7, 1.7 Hz), 6.25 (1H, d, J = 7.7 Hz), 4.25 (2H, m, NC*H*, CH*H*O), 4.06 (1H, dd, J = 15.6, 8.3 Hz, C*H*HO), 3.57 (1H, m, H-9a), 3.39 (1H, ddd, J = 12.7, 9.9, 2.7 Hz, H-2a), 3.20−2.80 (9H, m, H-10a, 10b, 9b, 1a, 1b, 2 × C*H*$_2$CH$_3$), 2.53 (1H, ddd, J = 12.7, 10.6, 5.2 Hz, H-2b), 1.99 (1H, m, C*H*(CH$_3$)$_2$), 1.12 (6H, d, J = 6.9 Hz, CH(CH_3)$_2$), 0.93 (6H, m, 2 × CH$_2$CH_3); ^{13}C 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 (*C*H$_2$OH), 54.3 (N*C*H), 42.0 (*C*H$_2$CH$_3$), 41.4 (*C*H$_2$CH$_3$), 36.1, 35.0, 33.8, 30.2 (2C, s, *C*H(CH$_3$)$_2$, C-2), 19.6 (CH(*C*H$_3$)CH$_3$), 18.9 (CH(CH$_3$)*C*H$_3$), 13.9 (CH$_2$*C*H$_3$), 13.1 (CH$_2$*C*H$_3$); IR (CHCl$_3$, cm^{-1}) ν_{max} 3309 (O—H and N—H), 1686 (Et$_2$NC═O), 1624 (C═OONH); MS (EI, *m*/*z*) 453 (30), 452 (M$^+$, 100), 348 (M$^+$ − CH$_2$C$_6$H$_4$CH$_2$, 30), 347 (33), 335 (M$^+$ − HOC(O)NEt$_2$, 15), 232 (14), 231 (71), 230 (15), 146 (10), 104 (CH$_2$—C$_6$H$_4$—CH$_2^+$, 27), 100 (16); HRMS calcd for C$_{27}$H$_{36}$N$_2$O$_4$, 452.2675; found, 452.2675.

(−)-(*S*,4*S*$_P$,5*R*$_P$)-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. Aqueous HCl (3 M, 7 mL, 21 mmol) was added, and the mixture was extracted with Et$_2$O (2 × 22 mL) and DCM (22 mL). The combined organic layers were washed with NaHCO$_3$ (30 mL) to remove any [2.2]paracyclophane carboxylic acid byproduct, and the aq layer was extracted with DCM (22 mL). All organic layers were combined, dried over Na$_2$SO$_4$, filtered, and concentrated. Flash column chromatography with 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; [α]$^{20}_D$ −148 (*c* 1.30, CHCl$_3$); ^{1}H NMR (400 MHz) δ 11.52 (1H, s, O*H*), 7.05 (1H, dd, J = 8.0, 1.9 Hz), 6.59 (1H, dd, J = 8.0, 1.9 Hz), 6.51 (1H, dd, J = 8.0, 1.9 Hz), 6.48 (1H, d, J = 7.7 Hz), 6.45 (1H, dd, J = 8.0, 1.9 Hz), 6.25 (1H, d, J = 7.7 Hz), 6.08 (1H, br d, J = 8.7 Hz, N*H*), 3.95 (1H, tdd, J = 8.7, 6.8, 4.1 Hz, NC*H*), 3.68 (2H, m, C*H*$_2$OH), 3.53 (1H, m, H-9a), 3.48 (1H, q, J = 7.0 Hz), 3.41 (1H, ddd, J = 12.9, 10.2, 2.8 Hz), 3.17 (1H, ddd, J = 12.9, 10.4, 5.2 Hz), 3.11 (1H, m), 3.02 (1H, ddd, J = 12.9, 10.7, 2.8 Hz), 2.96−2.82 (2H, m), 2.55 (1H, ddd, J = 13.2, 10.7, 5.2 Hz, H-2b), 2.05 (1H, oct, J = 6.8 Hz, C*H*(CH$_3$)$_2$), 1.10 (3H, d, J = 6.8 Hz, C*H*$_3$), 1.09 (3H, d, J = 6.8 Hz, C*H*$_3$); ^{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 (*C*H$_2$OH), 56.8 (N*C*H), 36.1, 35.0, 33.8, 30.2, 29.4 (*C*H-(CH$_3$)$_2$), 19.8 (*C*H$_3$), 19.2 (*C*H$_3$); IR (KBr, cm^{-1}) ν_{max} 3419 (br, O—H and N—H), 1622 (C═OONH); MS (EI, *m*/*z*) 354 (24), 353 (M$^+$, 100), 322 (M$^+$ − CH$_2$OH, 13), 310 (M$^+$ − *i*-Pr, 21), 268 (34), 250 (33), 249 (M$^+$ − CH$_2$C$_6$H$_4$CH$_2$, 52), 248 (12), 218 (62), 206 (22), 164 (15), 163 (15), 147 (21), 146 (17), 104 (CH$_2$C$_6$H$_4$-CH$_2^+$, 74), 102 (22); HRMS calcd for C$_{22}$H$_{27}$NO$_3$, 353.1991; found, 353.1990..

(+)-(*S*,4*R*$_P$,5*S*$_P$)-*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; [α]$^{20}_D$ +74 (*c* 0.76, CHCl$_3$); ^{1}H NMR (400 MHz) δ 11.42 (1H, s, O*H*), 7.04 (1H, dd, J = 7.9, 1.9 Hz), 6.57 (1H, dd, J = 7.9, 1.9 Hz), 6.49 (1H, dd, J = 7.9, 1.9 Hz), 6.48 (1H, d, J = 7.7 Hz), 6.44 (1H, dd, J = 7.9, 1.9 Hz), 6.26 (1H, d, J = 7.7 Hz), 6.02 (1H, br d, J = 9.1 Hz, N*H*), 4.40 (1H, dd, J = 11.5, 5.8 Hz, CH*H*O), 4.27 (1H, dd, J = 11.5, 3.3 Hz, C*H*HO), 4.19 (1H, m, NC*H*), 3.47 (1H, ddd, J = 13.6, 9.3, 2.7 Hz, H-9a), 3.44−3.30 (5H, m, H-2a, 2 × C*H*$_2$CH$_3$), 3.17 (1H, ddd, J = 12.9, 10.2, 5.2 Hz, H-1a), 3.04 (2H, m, H-1b, 10a), 2.88 (1H, ddd, J = 13.6, 9.3, 6.7 Hz, H-9b), 2.78 (1H, ddd, J = 12.6, 9.3, 6.7 Hz, H-10b), 2.54 (1H, ddd, J = 13.2, 10.7, 5.2 Hz, H-2b), 1.88 (1H, oct, J = 6.8 Hz, C*H*(CH$_3$)$_2$), 1.18 (6H, t, J = 7.1 Hz, 2 × CH$_2$CH_3), 0.97 (3H, d, J = 6.8 Hz, CH-(CH_3)CH$_3$), 0.92 (3H, d, J = 6.8 Hz, CH(CH$_3$)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 (*C*H$_2$OH), 54.0 (N*C*H), 41.9 (*C*H$_2$CH$_3$), 41.3 (*C*H$_2$CH$_3$), 35.9, 35.0, 33.8, 30.2, 29.7 (*C*H(CH$_3$)$_2$), 19.2 (CH(*C*H$_3$)CH$_3$), 18.8 (CH(CH$_3$)*C*H$_3$), 14.2 (CH$_2$*C*H$_3$), 13.5 (CH$_2$*C*H$_3$); IR (KBr, cm^{-1}) ν_{max} 3308 (O—H and N—H), 1682 (Et$_2$NC═O), 1622 (C═OONH); MS (EI, *m*/*z*) 453 (29), 452 (M$^+$, 100), 348 (M$^+$ − CH$_2$C$_6$H$_4$CH$_2$, 33), 347 (38), 335 (M$^+$ − HOC(O)NEt$_2$, 13), 232 (13), 231 (69), 230 (13), 146 (8), 104 (CH$_2$C$_6$H$_4$CH$_2^+$, 21), 100 (15); HRMS calcd for C$_{27}$H$_{36}$N$_2$O$_4$, 452.2675; found, 452.2674.

(+)-(*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; [α]$^{20}_D$ +58 (*c* 1.95, CHCl$_3$); ^{1}H NMR (400 MHz) δ 11.46 (1H, s, O*H*), 7.05 (1H, dd, J = 7.7, 1.7 Hz),

6.59 (1H, dd, J = 8.0, 1.7 Hz), 6.54 (1H, dd, J = 7.7, 1.9 Hz), 6.49 (1H, d, J = 7.7 Hz), 6.44 (1H, dd, J = 8.0, 1.9 Hz), 6.28 (1H, d, J = 7.7 Hz), 6.14 (1H, br d, J = 8.5 Hz, N*H*), 3.97 (1H, m, NC*H*), 3.88 (2H, m, CH_2OH), 3.59 (1H, m, H-9a), 3.42 (1H, ddd, J = 13.0, 10.3, 2.8 Hz, H-2a), 3.17 (1H, ddd, J = 12.6, 10.3, 5.0 Hz, H-1a), 3.13 (1H, m, H-10a), 3.01 (1H, ddd, J = 12.6, 10.7, 2.8 Hz, H-1b), 2.88 (2H, m, H-9b, 10b), 2.55 (1H, ddd, J = 13.0, 10.7, 5.0 Hz, H-2b), 1.91 (1H, oct, J = 6.9 Hz, C*H*(CH_3)$_2$), 0.98 (3H, d, J = 6.9 Hz, CH_3), 0.94 (3H, d, J = 6.9 Hz, 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 (*C*H_2OH), 56.7 (N*C*H), 36.3, 35.0, 33.8, 30.1 (C-2), 29.1 (*C*H(CH_3)$_2$), 19.5 (*C*H_3), 19.0 (*C*H_3); IR ($CHCl_3$, cm^{-1}) ν_{max} 3434 (br, O—H and N—H), 1619 (C═OONH); MS (EI, *m*/*z*) 354 (22), 353 (M^+, 100), 322 (M^+ − CH_2OH, 15), 310 (M^+ − *i*-Pr, 25), 268 (38), 250 (28), 249 (M^+ − $CH_2C_6H_4CH_2$, 46), 248 (14), 218 (56), 206 (19), 164 (14), 163 (13), 147 (13), 146 (11), 104 ($CH_2C_6H_4CH_2^+$, 44), 102 (18); HRMS calcd for $C_{22}H_{27}NO_3$, 353.1991; found, 353.1991.

(−)-(*S*,4*S*$_P$,5*R*$_P$)-*O*-[4-(5-(4-*iso*-Propyloxazolin-2-yl)-[2.2]paracyclophanyl)]diethylcarbamate (16a). Carbamate **13a** (65 mg, 0.143 mmol) was dissolved in MeCN (3.0 mL) and PPh_3 (65 mg, 0.250 mmol), Et_3N (35 μl, 0.250 mmol), and CCl_4 (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 Na_2SO_4. The mixture was filtered and concentrated. Flash column chromatography with gradient elution (pentane/EtOAc = 9:1 → 8:2 → 7:3) gave the title compound as a colorless oil that 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; $[\alpha]^{20}_D$ −50 (*c* 0.79, $CHCl_3$); ^{1}H NMR (400 MHz) δ 6.98 (1H, dd, J = 7.7, 1.9 Hz), 6.71 (1H, dd, J = 7.7, 1.9 Hz), 6.60 (1H, dd, J = 8.0, 1.9 Hz), 6.58 (1H, d, J = 8.0 Hz), 6.53 (1H, dd, J = 8.0, 1.9 Hz), 6.46 (1H, d, J = 8.0 Hz), 4.25 (1H, dd, J = 9.6, 8.0 Hz, CH*H*O), 4.08 (1H, ddd, J = 9.6, 8.0, 6.6 Hz, NC*H*), 3.98 (1H, t, J = 8.0 Hz, C*H*HO), 3.68 (1H, m, CH*H*CH_3), 3.52 (1H, ddd, J = 12.6, 10.6, 2.5 Hz, H-9a), 3.44 (2H, m, 2 × C*H*HCH_3), 3.30 (1H, m, CH*H*CH_3), 3.21 (1H, ddd, J = 12.4, 10.6, 4.7 Hz, H-10a), 3.10 (1H, m, H-2a), 3.04 (3H, m, H-1a, 1b, 10b), 2.87 (1H, ddd, J = 12.6, 10.4, 4.7 Hz, H-9b), 2.75 (1H, m, H-2b), 1.82 (1H, oct, J = 6.6 Hz, C*H*(CH_3)$_2$), 1.41 (3H, t, J = 6.9 Hz, CH_2CH_3), 1.18 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.09 (3H, d, J = 6.6 Hz, CH(CH_3)CH_3), 0.98 (3H, d, J = 6.6 Hz, $CH(CH_3)CH_3$); ^{13}C 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 (N*C*H), 69.3 (*C*H_2O), 42.2 (*C*H_2-CH_3), 42.0 (*C*H_2CH_3), 34.8, 34.4, 34.1, 33.2 (*C*H(CH_3)$_2$), 30.7 (C-2), 19.2 (CH(*C*H_3)CH_3), 18.8 ($CH(CH_3)$*C*H_3), 14.5 (CH_2*C*H_3), 13.5 (CH_2*C*H_3); IR ($CHCl_3$, cm^{-1}) ν_{max} 1716 (Et_2NC═O), 1653 (C═N); MS (EI, *m*/*z*) 435 (28), 434 (M^+, 100), 391 (M^+ − *i*-Pr, 3), 361 (8), 334 (M^+ − $CONEt_2$, 28), 305 (6), 271 (8), 257 (6),243 (12), 230 ($CH_2C_6H_2$(O)(oxazoline)CH_2^+, 40), 100 (60); HRMS calcd for $C_{27}H_{34}N_2O_3$, 434.2569; found, 434.2569.

(−)-(*S*,4*S*$_P$,5*R*$_P$)-Trifluoromethansulfonic Acid [4-(5-(4-*iso*-Propyloxazolin-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 Tf_2O (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 room temperature and stirred for an additional 2 h. Water (6 mL) was added, and the aq layer was separated and extracted with DCM (3 × 6 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography with 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; $[\alpha]^{20}_D$ −26 (*c* 1.35, $CHCl_3$); ^{1}H NMR (400 MHz) δ 6.90 (1H, dd, J = 7.7, 1.9 Hz), 6.82 (1H, dd, J = 7.7, 1.7 Hz), 6.63 (1H, dd, J = 7.7, 1.7 Hz), 6.62 (1H, d, J = 8.0 Hz), 6.60 (1H, dd, J = 7.7, 1.9 Hz), 6.58 (1H, d, J = 8.0 Hz), 4.42 (1H, dd, J = 9.1, 7.7 Hz, CH*H*O), 4.18 (1H, td, J = 9.1, 6.6 Hz, NC*H*), 4.10 (1H, dd, J = 9.1, 7.7 Hz, C*H*HO), 3.43 (1H, m), 3.36 (1H, ddd, J = 13.5, 9.9, 4.1 Hz, H-2a), 3.23 (1H, ddd, J = 12.9, 9.9, 4.1 Hz), 3.07−2.96 (4H, m), 2.90 (1H, ddd, J = 13.5, 10.2, 4.1 Hz, H-2b), 2.00 (1H, oct, J = 6.6 Hz, C*H*(CH_3)$_2$), 1.13 (3H, d, J = 6.6 Hz, CH_3), 1.04 (3H, d, J = 6.6 Hz, CH_3); ^{13}C 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, *C*F_3), 73.5 (N*C*H), 69.6 (*C*H_2O), 34.8, 34.4, 34.1, 32.6 (*C*H(CH_3)$_2$), 30.8 (C-2), 19.6 (*C*H_3), 18.5 (*C*H_3); ^{19}F NMR (376 MHz) δ −73.8 (3F, 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 ($CH_2C_6H_2$(O)(oxazoline)CH_2^+, 89), 104 ($CH_2C_6H_4CH_2^+$, 19); HRMS calcd for $C_{23}H_{24}SF_3NO_4$, 467.1378; found, 467.1379.

(−)-(*S*,4*R*$_P$,5*S*$_P$)-Trifluoromethansulfonic Acid [4-(5-(4-*iso*-Propyloxazolin-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 colorless oil: R_f (petroleum ether/EtOAc = 8:2) 0.42; $[\alpha]^{20}_D$ −69 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz) δ 6.80 (1H, dd, J = 7.9, 1.7 Hz), 6.75 (1H, dd, J = 7.9, 1.7 Hz), 6.63 (1H, dd, J = 7.9, 1.7 Hz), 6.61 (2H, s, H-7, 8), 6.58 (1H, dd, J = 7.9, 1.7 Hz), 4.50 (1H, dd, J = 9.9, 8.7 Hz, CH*H*O), 4.17 (1H, t, J = 8.7 Hz, C*H*HO), 4.05 (1H, m, NC*H*), 3.70 (1H, ddd, J = 12.1, 9.6, 4.0 Hz, H-9a), 3.36 (1H, ddd, J = 13.4, 9.9, 3.7 Hz), 3.21 (1H, m), 3.12−2.84 (5H, m), 1.92 (1H, oct, J = 6.7 Hz, C*H*(CH_3)$_2$), 1.17 (3H, d, J = 6.7 Hz, CH_3), 1.05 (3H, d, J = 6.7 Hz, CH_3); ^{13}C 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, *C*F_3), 72.9 (N*C*H), 70.3 (*C*H_2O), 34.7, 34.3, 34.2, 33.3 (*C*H(CH_3)$_2$), 30.8, 19.4 (*C*H_3), 19.0 (*C*H_3); ^{19}F NMR (376 MHz) δ −73.8 (3F, 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 ($CH_2C_6H_2$(O)(oxazoline)CH_2^+, 85), 104 ($CH_2C_6H_4CH_2^+$, 21); HRMS calcd for $C_{23}H_{24}SF_3NO_4$, 467.1378; found, 467.1378.

(−)-(*S*,4*S*$_P$,5*R*$_P$)-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 Ph_2PK (0.5 M w/v solution in THF, 0.43 mL, 0.21 mmol) was added. The solution was stirred at room temperature for 20 h. Degassed water (75 mL) and DCM (45 mL) were added, and the mixture was shaken vigorously. The aq layer was separated and extracted with DCM (45 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography with 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; $[\alpha]^{20}_D$ −12 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.56 (2H, m), 7.34 (2H, m), 7.15 (3H, m), 7.10 (3H, m), 6.87 (1H, br d, J = 8.0 Hz), 6.77 (1H, br d, J = 8.0 Hz), 6.55 (2H, m), 6.40 (1H, d, J = 7.8 Hz, H-7), 6.35 (1H, dd, J = 7.8 Hz, J_{H-P} = 3.7 Hz, H-8), 3.52 (1H, t, J = 8.1 Hz, CH*H*O), 3.33 (1H, m, NC*H*), 3.16 (1H, dd, J = 9.9, 8.1 Hz, C*H*HO), 3.09−2.80 (5H, m), 2.68 (2H, m), 2.41 (1H, m, H-2b), 1.65 (1H, oct, J = 6.7 Hz, C*H*(CH_3)$_2$), 0.94 (3H, d, J = 6.7 Hz, CH(CH_3)CH_3), 0.83 (3H, d, J = 6.7 Hz, $CH(CH_3)$CH_3); ^{13}C NMR (75 MHz) δ 163.2 (*C*═N), 145.5 (d, J_{C-P} = 8.9 Hz), 142.0 (d, J_{C-P} = 12.5 Hz), 140.1 (d, J_{C-P} = 9.5 Hz), 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 (2C, s), 127.9, 72.7 (N*C*H), 68.5 (*C*H_2O), 36.4 (d, J_{C-P} = 6.5 Hz, C-2), 34.7, 34.6, 33.5, 32.2 (*C*H(CH_3)$_2$), 19.7 (*C*H_3), 18.2 (*C*H_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 (M^+ − Me, 8) 461 (13), 460 (M^+ − *i*-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 ($CH_2C_6H_4CH_2^+$, 8); HRMS calcd for $C_{34}H_{34}PNO$, 503.2378; found, 503.2379.

(−)-(*S*,4*R*$_P$,5*S*$_P$)-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; $[\alpha]^{20}_D$ −242 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.58 (2H, m), 7.45 (2H, m), 7.23−7.18 (6H, m), 6.81 (1H, dd, J = 8.0, 1.7 Hz), 6.63 (3H, m), 6.53 (1H, d, J = 7.7 Hz, H-7), 6.42 (1H, dd, J = 7.7 Hz, J_{H-P} = 3.8 Hz, H-8), 3.79 (1H, t, J = 8.6 Hz, CH*H*O), 3.68 (1H, dd, J = 9.9, 8.6 Hz, C*H*HO), 3.63 (1H, ddd, J = 13.0, 12.4, 5.8 Hz, H-9a), 3.08 (1H, ddd, J = 13.2, 9.6, 3.9 Hz), 2.99 (2H, m, NC*H*, CH*H*CH_2), 2.93−2.84 (3H, m), 2.76 (1H, ddd, J = 13.0, 9.6, 4.7 Hz), 2.49 (1H, ddd, J = 13.7, 9.9, 4.4 Hz, H-2b), 1.65 (1H, m, C*H*$(CH_3)_2$), 1.01 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)CH_3), 0.88 (3H, d, J = 6.9 Hz, CH(CH_3)C*H*$_3$); ^{13}C NMR (100 MHz) δ 162.4 (*C*═N), 145.4 (d, J_{C-P} = 9.9 Hz), 142.0 (d, J_{C-P} = 11.4 Hz), 139.4, 138.90, 138.95, 138.0 (d, J_{C-P} = 9.1 Hz), 137.0, 136.8, 135.3 (2C, 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 (N*C*H), 69.3 (*C*H_2O), 36.5 (d, J_{C-P} = 9.1 Hz, C-2), 35.0, 34.8, 34.2, 33.1 (*C*H-$(CH_3)_2$), 19.6 (CH(*C*H_3)CH_3), 19.2 (CH(CH_3)*C*H_3); ^{31}P NMR (162 MHz) δ 1.48; IR ($CHCl_3$, cm^{-1}) ν_{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 ($CH_2C_6H_4CH_2^+$, 22); HRMS calcd for $C_{34}H_{34}PNO$, 503.2378; found, 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 that slowly became orange. After 10 min, the cooling bath was removed, and the reaction mixture was stirred for an additional 3 h. Ordinary "wet" Et_3N (0.1 mL, 0.71 mmol) was added, followed by Et_2O (3 mL), and the resulting mixture was 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 with gradient elution (pentane/Et_2O = 9:1 → 8:2 → 7:3. This gave the title product as a white solid (0.06 g, 32%): R_f (petroleum ether/Et_2O = 8:2) 0.21; mp 79.0−81.0 °C; $[\alpha]^{20}_D$ +19 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.61 (1H, br s, H-13), 7.32 (2H, br dd, J_{H-P} = 8.7 Hz, J = 7.9 Hz, P−C_6H_4OMe (ortho)), 7.23 (2H, br dd, J_{H-P} = 8.7 Hz, J = 7.6 Hz, P−C_6H_4OMe (ortho)), 6.85 (2H, br d, J = 7.6 Hz, P−C_6H_4-OMe (meta)), 6.77 (2H, br d, J = 7.9 Hz, P−C_6H_4OMe (meta)), 6.62 (1H, dd, J = 7.9, 1.7 Hz, H-15), 6.58 (1H, d, J = 7.9 Hz, H-16), 6.54 (1H, dd, J = 7.7, 1.8 Hz, H-7), 6.45 (1H, dd, J = 7.7 Hz, J_{H-P} = 5.4 Hz, H-8), 5.88 (1H, dd, J_{H-P} = 8.4 Hz, J = 1.8 Hz, H-5), 4.34 (1H, m, OC*H*H), 4.18 (1H, br dd, J = 12.4, 9.3 Hz, H-10a), 3.92 (2H, m, NC*H*, OCH*H*), 3.80 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.43 (1H, ddd, J = 12.9, 9.9, 6.7 Hz, H-1a), 3.26 (1H, br dd, J = 13.6, 9.9 Hz, H-2a), 3.02 (2H, m, H-1b, 9a), 2.86 (1H, ddd, J = 12.6, 9.3, 7.4 Hz, H-9b), 2.78−2.61 (2H, m, H-2b, 10b), 1.74 (1H, oct, J = 6.7 Hz, C*H*$(CH_3)_2$), 1.00 (3H, d, J = 6.7 Hz, C*H*$_3$), 0.88 (3H, d, J = 6.7 Hz, C*H*$_3$); ^{13}C NMR (75 MHz) δ 161.9 (*C*═N), 160.4 (MeO*C*), 159.9 (MeO*C*), 142.9 (d, J_{C-P} = 17.9 Hz), 141.1, 140.1, 139.5, 138.8 (d, J_{C-P} = 12.0 Hz), 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 Hz), 130.0 (d, J_{C-P} = 7.5 Hz), 127.9 (d, J_{C-P} = 8.3 Hz), 127.6, 113.9, 113.8 (2C, s), 113.7, 73.6 (N*C*H), 68.8 (O*C*H_2), 55.13 (O*C*H_3), 55.06 (O*C*H_3), 36.1 (C-10), 35.3 (d, J_{C-P} = 9.5 Hz, C-2), 33.8, 33.0 (2C, s), 19.3 (*C*H_3), 18.3 (*C*H_3); ^{31}P NMR (121 MHz) δ −4.64; IR ($CHCl_3$, cm^{-1}) ν_{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 ($CH_2C_6H_3$(P(C_6H_4OMe)$_2$)CH_2^+, 50), 347 (13), 282 (8), 240 (8), 239 (9), 215 (10), 178 (9); HRMS calcd for $C_{36}H_{38}PNO_3$, 563.2589; found, 563.2588.

(−)-(*S*,4*S*$_p$,12*S*$_p$)-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/Et_2O = 8:2) 0.08; mp 147.0−149.0 °C; $[\alpha]^{20}_D$ −50 (*c* 0.87, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.69 (1H, d, J = 1.5 Hz, H-13), 7.40 (2H, dd, J = 8.7 Hz, J_{H-P} = 8.2 Hz, P−C_6H_4-OMe (ortho)), 7.24 (2H, br dd, J = 8.7 Hz, J_{H-P} = 7.2 Hz, P−C_6H_4-OMe (ortho)), 6.85 (2H, br d, J = 8.7 Hz, P−C_6H_4OMe (meta)), 6.76 (2H, br d, J = 8.7 Hz, P−C_6H_4OMe (meta)), 6.63 (1H, dd, J = 7.7, 1.5 Hz, H-15), 6.59 (1H, d, J = 7.7 Hz, H-16), 6.55 (1H, dd, J = 7.8, 1.7 Hz, H-7), 6.45 (1H, dd, J = 7.8 Hz, J_{H-P} = 5.7 Hz, H-8), 5.89 (1H, dd, J_{H-P} = 8.4 Hz, J = 1.7 Hz, H-5), 4.32−4.18 (2H, m, OC*H*H, H-10a), 4.00−3.90 (2H, m, NC*H*, OCH*H*), 3.79 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.45 (1H, ddd, J = 12.9, 9.7, 6.7 Hz, H-1a), 3.27 (1H, br dd, J = 13.6, 9.7 Hz, H-2a), 3.05 (2H, m, H-1b, 9a), 2.81−2.62 (3H, m, H-9b, H-2b, 10b), 1.53 (1H, oct, J = 6.7 Hz, C*H*$(CH_3)_2$), 1.00 (3H, d, J = 6.7 Hz, CH(CH_3)-C*H*$_3$), 0.88 (3H, d, J = 6.7 Hz, CH(C*H*$_3$)CH_3); ^{13}C NMR (75 MHz) δ 162.7 (*C*═N), 160.4 (MeO*C*), 159.9 (MeO*C*), 143.0 (d, J_{C-P} = 17.9 Hz), 140.8, 139.7, 139.5, 138.7 (d, J_{C-P} = 10.7 Hz), 137.7, 137.3, 135.6, 134.9, 134.4, 134.3, 134.2, 134.1, 132.5, 131.6 (d, J_{C-P} = 4.8 Hz), 130.5 (d, J_{C-P} = 7.1 Hz), 127.8 (d, J_{C-P} = 7.7 Hz), 127.6, 113.9 (2C, s), 113.8, 113.7, 73.1 (N*C*H), 69.1 (O*C*H_2), 55.08 (O*C*H_3), 55.05 (O*C*H_3), 36.4 (C-10), 35.5 (d, J_{C-P} = 9.5 Hz, C-2), 34.0, 33.5 (*C*H$(CH_3)_2$), 33.0, 19.4 (CH(CH_3)*C*H_3), 18.9 (CH(*C*H_3)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 (M^+ − Me, 4) 478 (5), 349 (12), 348 ($CH_2C_6H_3$(P(C_6H_4-OMe)$_2$)CH_2^+, 49), 347 (12), 282 (8), 240 (7), 239 (9), 215 (9); HRMS calcd for $C_{36}H_{38}PNO_3$, 563.2589; found, 563.2590.

General Procedure for the Palladium-Catalyzed Allylic Alkylation of 1,3-Diphenyl-2-propenyl Acetate.[25] [Pd(η^3-C_3H_5)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 acetate[41] (0.13 g, 0.50 mmol) in toluene (1.0 mL) was added, and the solution was stirred for 0.5 h. Dimethylmalonate (0.17 mL, 1.50 mmol), then *N*,*O*-bis(trimethylsilyl)acetamide (0.37 mL, 1.50 mmol), and LiOAc (1 mg, 0.015 mmol) were added. The reaction was monitored by TLC [starting material, R_f (petroleum ether/EtOAc = 9:1) 0.51; product, R_f 0.34] until completion. DCM (15 mL) was then added, and the solution was washed with aq saturated NH_4Cl solution (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (petroleum ether/EtOAc = 9:1) gave the product as a clear oil that 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: Detailed preparative descriptions for compounds **10a**,**b**, **2a**,**b**, and **20**−**22a**,**b**. ^{1}H and ^{13}C 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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