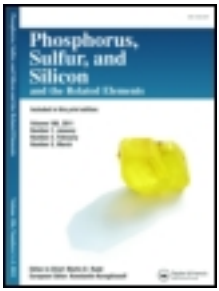

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Palladium-Catalyzed Asymmetric Allylic Alkylation Using Phosphine-Amide Derived from Chiral *trans*-2-Aminocyclohexanol

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A novel phosphine-amide derived from resolved trans*-2-aminocyclohexanol has been synthesized and studied in palladium-catalyzed asymmetric allylic alkylation of racemic (E)-1,3-diphenyl-2-propenyl acetate with various nucleophiles.*

Keywords Asymmetric allylic alkylation; ^{1}H-^{15}N HMBC NMR; Pd-complexes; phosphine-amide ligand; resolved *trans*-2-aminocyclohexanol

INTRODUCTION

Palladium-catalyzed asymmetric allylic alkylation is certainly one of the most useful processes for asymmetric carbon-carbon or carbon-heteroatom bond formation.[1] Since the first example described by Trost and Strege in 1977,[2] a large variety of chiral ligands have been studied. Among them, for example, the bidentate Trost's *P*,*P*-ligand based on *trans*-1,2-diaminocyclohexane[3] and a phosphine-oxazoline known as Pfaltz's *P*,*N*-ligand,[4] rank among the best and afford enantioselectivities up to 99%.

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.
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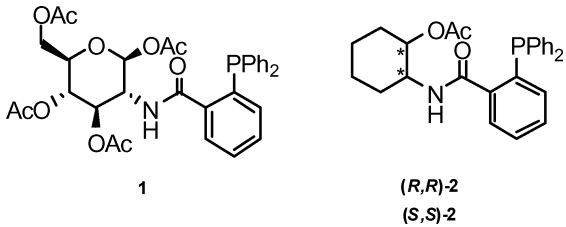


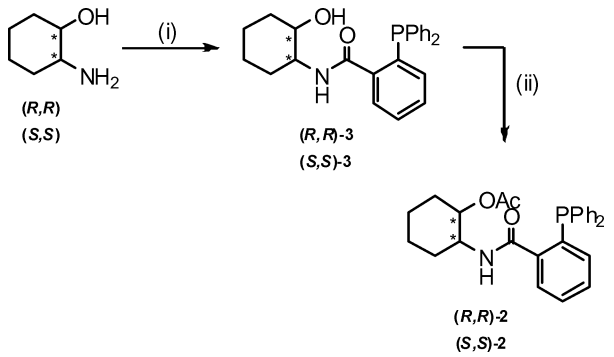
FIGURE 1 Ligands used in the studied Pd-catalyzed allylic alkylation.

High catalyst performance requires careful choice of the activating metal but also of the chiral ligands. During the last 10 years, carbohydrates including xylose, glucose, D-glucosamine, galactose, mannitol, and trehalose backbones have appeared as good sources of chiral ligands for asymmetric catalysis.[5] For example, Ruffo et al.[6] have prepared bis(phosphine-amides) based on 2,3-glucodiamine, closely resembling (1*S*, 2*S*)-cyclohexanediamine. In 2003, our group reported on the potential of the monophosphine-amide ligand **1** derived from D-glucosamine (Figure 1).[7] Using this ligand, enantioselectivities up to 97% have been obtained in the allylic alkylation of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with various nucleophiles, despite the fact that the chiral information of the auxiliary was considerably distant from the ligating achiral phosphorus center. We have also studied the infuence of the stereochemistry of the D-glucosamine moiety on the enantioselectivity of allylic alkylation by modifying the configuration and the nature of the substituent at the anomeric position in the ligand and in order to reveal its potential modes of interactions with the metal center.[8]

In this article, we present the synthesis of structurally simplified phosphine-amide ligands **2** (Figure 1) derived from chiral *trans*-2-aminocyclohexanol and the evaluation of these ligands in the model palladium-catalyzed asymmetric allylic substitution reactions. By comparing the results obtained with the both types of phosphine-amides **1** and **2**, we can demonstrate that the presence of the structurally rich carbohydrate framework in the ligand is crucial for the achievement of a high level of enantioselectivity in the studied reaction.

RESULTS AND DISCUSSION

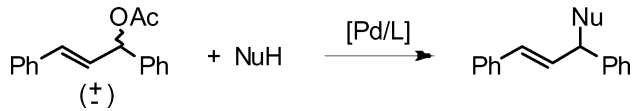
The new phosphine-amide ligands **2** were obtained from resolved *trans*-2-aminocyclohexanol (Scheme 1). The latter compound can be easily obtained by several methods: resolution of the racemic compound as salts of tartaric acid,[9] ring-opening reaction of cyclohexene oxide by



SCHEME 1 Synthesis of ligands **(*R*,*R*)-2** and **(*S*,*S*)-2**: (i) 2-(diphenylphiosphino)benzoic acid, EDC, HOBT, DMF, rt, 18 h; (ii) Ac_2O, DMAP, Py, rt, 5 h.

chiral methylbenzylamine resulting in diastereomers, which can be separated and debenzylated (Overman's method),[10] or the same ring-opening reaction by TMS-azide in the presence of chiral chromium complex followed by reduction.[11] As Nishida et al.[12] have described, Overman's protocol was the best one to obtain both enantiomers of *trans*-2-aminocyclohexanol in enantiomerically pure form, and we repeated this protocol also in our study. In order to obtain the corresponding phosphine-amide derivatives, a condensation reaction between (1*R*,2*R*)- or (1*S*,2*S*)-2-aminocyclohexanol and 2-(diphenylphosphino)benzoic acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBT) as coupling reagents was performed in DMF at room temperature for 18 h. After purification by flash chromatography, the chiral 2-(diphenylphosphino)-*N*-(2-hydroxycyclohexyl)-benzamides (***R*,*R*)-3** and (***S*,*S*)-3** were isolated in 80% yield. Then, the intermediates (***R*,*R*)-3** and (***S*,*S*)-3** were acetylated to give the chiral 2-[2-(diphenylphosphino)benzoyl]amino cyclohexyl acetates (***R*,*R*)-2** and (***S*,*S*)-2** in 75% and 79% yield, respectively.

The new ligands **2** were examined in the palladium-catalyzed asymmetric allylic alkylation of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with several nucleophiles, using $[(\eta^3\text{-}C_3H_5)PdCl]_2$ as the palladium source (Scheme 2). The obtained results were compared to



SCHEME 2 Allylic alkylation of racemic 1,3-diphenylprop-2-enyl acetate.

TABLE I Palladium-Catalyzed Asymmetric Allylic Alkylation of Racemic 1,3-Diphenylprop-2-enyl Acetate with Several Nucleophiles at 60°C and Using (*R*,*R*)-2 as Ligand[a]

Pd/L	NuH	Time	Yield (%)[b]	e.e. (%)[c] (config)[d]
1/1	$CH_2(CO_2Me)_2$	24 h	30	57 (*S*)
1/2	$CH_2(CO_2Me)_2$	24 h	97	80 (*S*)
1/1	$CH_3CH(CO_2Me)_2$	96 h	92	37 (*R*)
1/2	$CH_3CH(CO_2Me)_2$	96 h	95	67 (*R*)
1/1	$AcNHCH(CO_2Me)_2$	96 h	15	63 (*R*)
1/2	$AcNHCH(CO_2Me)_2$	96 h	50	54 (*R*)
1/1	Benzylamine	96 h	35	31 (*R*)
1/2	Benzylamine	96 h	10	57 (*R*)
1/1	Morpholine	96 h	30	33 (*R*)
1/2	Morpholine	96 h	50	48 (*R*)

[a][substrate]/[NuH]/[Base]/[Pd] = 25/75/75/1.

[b]Yields of isolated pure product after column chromatography.

[c]Enantiomeric excess determined by HPLC analysis (column Chiralpak AD 0.46 × 25 cm).

[d]The absolute configuration was determined by comparison with an authentic sample.

[e]K_2CO_3 used as base.

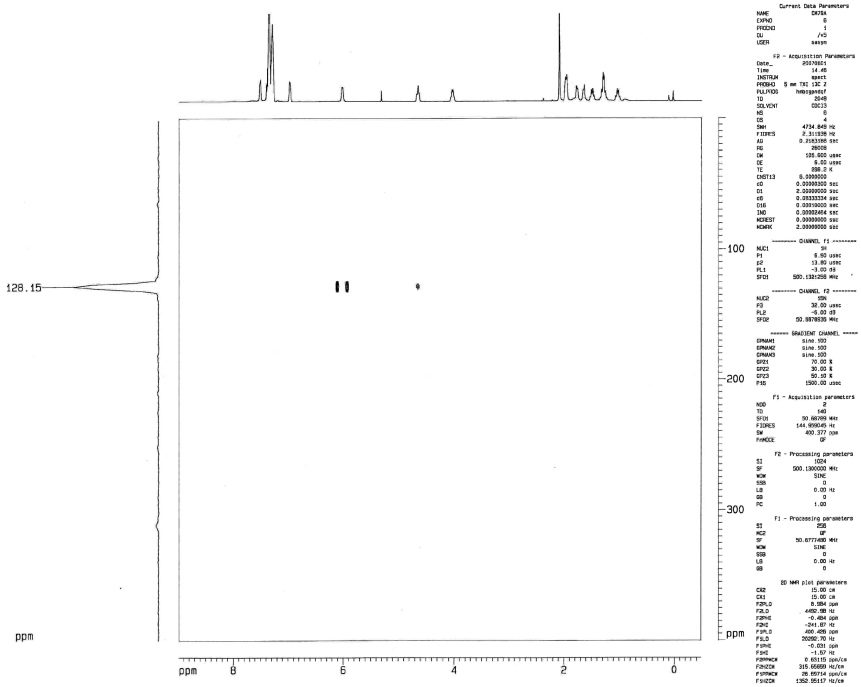
those observed previously using ligand **1** derived from D-glucosamine[7] (Table I). The reactions were performed in THF (0.125 M) at 60°C, using 2 mol % of $[(\eta^3\text{-}C_3H_5)PdCl]_2$, 4 or 8 mol % of ligand **2**, 3 equiv. of nucleophile (NuH), a mixture of *N*, *O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv.), and KOAc (2 mol %) as the base.

In Table I, we have reported only the results obtained with ligand (***R***,***R***)**-2**. However, the allylic alkylations were also performed using ligand (***S***,***S***)**-2** under the same reaction conditions as reported above and using the same nucleophile. The allylic products showed almost the same level of enantioselectivity as for the other enantiomer, as could have been predicted.

Compared with phosphine-amide **1** based on D-glucosamine,[7] the efficacy of ligands (***R***,***R***)**-2** and (***S***,***S***)**-2** in the studied reaction was generally lower. In fact, high yields were obtained with difficulty and the reactions required higher temperature (Table I). At room temperature, independently of which ligands and nucleophiles were used, no conversion was observed. The best yields (97% and 95%) were obtained for the $CH_2(CO_2Me)_2$ and $CH_3CH(CO_2Me)_2$ with the Pd/ligand ratio of 1/2 (Table I) at 60°C during 24 and 96 h, respectively. The enantiomeric excesses were moderate to good (31% to 80%) and were lower than those measured for the same allylic product obtained using derivative

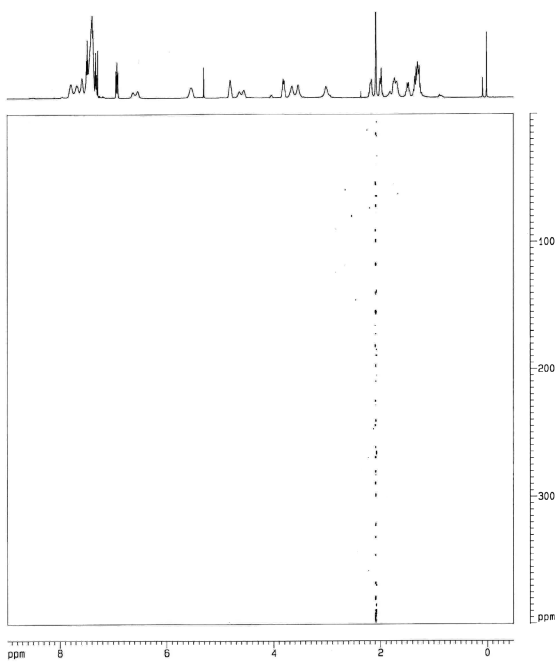
1 as ligand with a Pd/ligand ratio of 1:1. In contrast, with the ligand based on D-glucosamine, in all cases except when $AcNHCH(CO_2Me)_2$ was used as nucleophile (Table I), the enantioselectivity was higher when the Pd/ligand **2** ratio of 1:2 was applied.

In order to obtain an insight into the possible mode of chelation of ligand **2** to palladium, we performed a NMR study of ***(R,R)*-2** and its Pd-complexes with a Pd/ligand ratio of 1:1 and 1:2. We focused our NMR study on the chemical shifts of the carbon atoms of the two carbonyl groups of the ligand before and after the complexation, as well as on the chemical shifts of the phosphorus and nitrogen atoms. Before complexation of the ligand (***R*,*R*)-2**, the two signals corresponding to carbonyl groups linked to NH and an oxygen atom were detected at 168.8 and 172.3 ppm, respectively. The chemical shift of the phosphorus atom was at –8.9 ppm. Using a ^1H-^{15}N HMBC NMR sequence, the chemical shift of the nitrogen atom was found at 128.1 ppm (Figure 2a).

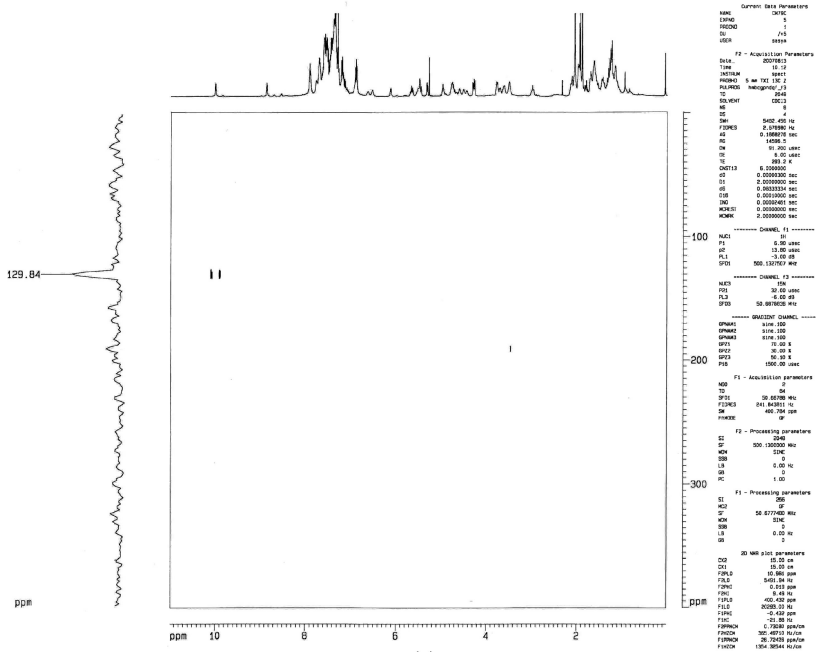


(a)

FIGURE 2 ^1H-^{15}N HMBC NMR ($CDCl_3$) spectra for ***(R,R)*-2** (a) and for the corresponding Pd-complexes: Pd/L ratio of 1:1 (b) and of 1:2 (c). *(Continued)*



(b)



(c)

FIGURE 2 (Continued)

After complexation with palladium, in the case of a Pd/ (***R***,***R***)**-2** ratio of 1:1, no change was observed for the chemical shifts of the carbonyl groups. Two signals were detected in the ^{31}P NMR spectrum at 26.9 and 27.6 ppm, indicating two types of chelation to palladium (the chemical shift of the corresponding phosphine oxide is at 35 ppm). In addition, no signal was observed in the ^{1}H-^{15}N HMBC NMR spectrum (Figure 2b), indicating a possible chelation to the metal. Recently, Amatore et al.[13] reported on the basis of X-ray analysis that, in the case of Trost's ligand, the bidentate *P*, *P*-complex can generate a *P*, *O*-chelate as well as a *P*, *N*-chelate after intramolecular deprotonation. The ^{1}H-^{15}N HMBC NMR sequence uses a polarization transfer between the two nuclei, so the absence of a signal seems to indicate that the nitrogen atom is deprotonated in favor of the coordination to palladium. In the spectrum of Pd/ (***R***,***R***)**-2** with a ratio of 1:2, in the region typical for carbonyl groups, two new signals for the carbonyl group linked to NH at 166.5 and 167.4 ppm, as well as two signals for the carbonyl group linked to the oxygen atom at 170.8 and 172.1 ppm, were detected, in addition to the two signals appearing at 168.8 and 172.3 ppm. In the ^{31}P NMR spectra, we observed four signals at 20.4, 24.4, 26.9, and 27.6 ppm, with the first two displaying a high intensity. In the ^{1}H-^{15}N HMBC NMR spectrum (Figure 2c) one signal at 129.8 ppm was detected, indicating no chelation between the palladium and the nitrogen atoms. This NMR study shows that various complexes were obtained from the studied ligand and the palladium. It seems that there is equilibrium between mono- and bidentate chelates. In the case of Pd/ (***R***,***R***)**-2** ratio of 1:1, the bidentate *P*, *N*-complex and monodendate *P*, *P*-complexes are probably in equilibrium. In the case of Pd/ (***R***,***R***)**-2** ratio of 1:2, the monodentate *P*, *P*-complex seems to be in equilibrium with two bidentate *P*, *O*-complexes involving the oxygen atoms of the carbonyl groups of the acetamido function and acetoxy function.

CONCLUSION

To summarize, in our previous study using derivative **1** as ligand, we proposed in the case of Pd:**1** ratio of 1:1 the existence of bidentate complexes in equilibrium, in which the palladium was chelated to the phosphorus atom and also to the oxygen atom of the carbonyl groups linked to C-1, C-3, and NH of the carbohydrate skeleton.[8] No complexation of the palladium atom to the nitrogen atom was observed. By comparing the results on allylic alkylation using ligand **1** with the results obtained with ligand (***R***,***R***)**-2**, we have demonstrated that the presence of an acetoxy group at the β-position at the anomeric center

of the D-glucosamine residue is crucial but not sufficient for obtaining allylic products with high enantioselectivity. The other carbonyl groups linked to carbohydrate moiety, most probably those linked to C-3 and NH, seem thus to play a very important role in stabilizing and rigidifying the formed complexes with palladium and in effecting higher induction in the allylic substitutions studied.

EXPERIMENTAL

Solvents were purified by standard methods and dried if necessary. All commercially available reagents were used as received. All reactions were monitored by TLC (TLC plates GF_{254} Merck). Air- and moisture-sensitive reactions were performed using the usual inert atmosphere techniques. Reactions involving organometallic catalysis were carried out in a Schlenk tube under an inert atmosphere. Column chromatography was performed on silica gel 60 (230–240 mesh, Merck). Optical rotations were recorded using a Perkin-Elmer 241 polarimeter. NMR spectra were recorded with a Bruker AMX 300 spectrometer and referenced as follows: ^{1}H (300 MHz) internal $SiMe_4$ at δ 0.00 ppm, ^{13}C (75 MHz) internal $CDCl_3$ at δ 77.2 ppm, and ^{31}P (121 MHz) external 85% H_3PO_4 at δ 0.0 ppm. Conversion was determined by GC using a Quadrex OV1 column (30 m $\times$ 0.25 mm), and enantiomeric excess was determined by HPLC with a Chiralpak^{AD} column (25 cm $\times$ 4.6 mm) using a ratio of hexane:*i*-propanol as eluent.

Synthesis of (*R,R*)- and (*S,S*)-3: General Procedure

In a Schlenk tube under nitrogen 2-(diphenylphosphino)benzoic acid (0.34 g, 1.11 mmol), (1*R*,2*R*)- or (1*S*,2*S*)-2-aminocyclohexanol (0.18 g, 1.56 mmol), EDC · HCl (0.25 g, 1.33 mmol), HOBT (0.18 g, 1.33 mmol), and $NaHCO_3$ (0.11 g, 1.33 mmol) were stirred in DMF (10 mL) for 18 h at rt. After evaporation of the solvent, the product was purified by flash chromatography (CH_2Cl_2:MeOH 10:1) to afford (***R***,***R***)**-** or (***S***,***S***)**-3**.

2-(Diphenylphosphino)-N-[(1R,2R)-2-hydroxy-cyclohexyl]-benzamide (R,R)-3

Yield: 80%; white solid; mp = 140–142°C; R_f = 0.30 (CH_2Cl_2/MeOH 10 : 1); $[\alpha]_D^{25}$ -9.0 (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.65–7.60 (m, 1H, arom-H), 7.42–7.22 (m, 12H, arom-H), 6.99–6.92 (m, 1H, arom-H), 5.84 (d, J = 6.8 Hz, 1H, NH), 3.78–3.66 (m, 1H, C*H*NH), 3.19 (ddd, J = 10.0, 9.8, 4.3 Hz, 1H, C*H*OH), 2.03–1.99 (m, 1H, CH_2), 1.89–1.82 (m,

1H, CH_2), 1.71–1.60 (m, 2H, CH_2), 1.42–1.07 (m, 3H, CH_2), 1.00–0.86 (m, 1H, CH_2). ^{13}C NMR ($CDCl_3$): δ = 174.3, 142.1 (d, J = 27.9 Hz), 136.3 (d, J = 9.3 Hz), 136.2 (d, J = 8.7 Hz), 134.5 (d, J = 16.1 Hz), 134.3, 134.1 (d, J = 7.5 Hz), 133.8 (d, J = 7.5 Hz), 130.4, 129.3 (d, J = 5.5 Hz), 129.2, 129.0 (d, J = 6.8 Hz), 128.8 (d, J = 6.8 Hz), 128.5 (d, J = 5.6 Hz), 74.9, 56.3, 33.8, 31.2, 24.7, 24.1. ^{31}P NMR ($CDCl_3$): δ = -10.3. Anal. Calcd for $C_{25}H_{26}NO_2P$: C 74.42, H 6.50; found C 74.02, H 6.56%.

2-(Diphenylphosphino)-N-*[(1S,2S)-2-hydroxy-cyclohexyl] benzamide (S,S)-3*

Yield: 80%; white solid; mp = 135–137°C; R_f = 0.30 (CH_2Cl_2/MeOH 10 : 1); $[\alpha]_D^{25}$+9.7 (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.65–7.62 (m, 1H, arom-H), 7.42–7.24 (m, 12H, arom-H), 6.99–6.95 (m, 1H, arom-H), 5.76 (d, J = 6.8 Hz, 1H, NH), 3.79–3.67 (m, 1H, C*H*NH), 3.21 (ddd, J = 9.9, 9.9, 4.3 Hz, 1H, C*H*OH), 2.03–2.00 (m, 1H, CH_2), 1.85–1.82 (m, 1H, CH_2), 1.71–1.60 (m, 2H, CH_2), 1.39–0.98 (m, 3H, CH_2), 0.95–0.86 (m, 1H, CH_2). ^{13}C NMR ($CDCl_3$): δ = 170.6, 142.3 (d, J = 27.7 Hz), 136.6 (d, J = 8.7 Hz), 136.5 (d, J = 8.7 Hz), 134.7 (d, J = 18.8 Hz), 134.6, 134.4 (d, J = 7.5 Hz), 134.1 (d, J = 7.5 Hz), 130.7, 129.6, 129.5 (d, J = 5.6 Hz), 129.3 (d, J = 8.7 Hz), 129.1 (d, J = 9.3 Hz), 128.5 (d, J = 5.6 Hz), 75.1, 56.6, 34.1, 31.5, 25.0, 24.4; ^{31}P NMR ($CDCl_3$): δ = -10.3. Anal. Calcd for $C_{25}H_{26}NO_2P$: C 74.42, H 6.50; found C 74.10, H 6.49%.

Synthesis of (*R,R*)- and (*S,S*)-2: General Procedure

In a Schlenk tube under nitrogen, (***R***,***R***)- or (***S***,***S***-**3** (0.20 g, 0.49 mmol) and a few crystals of DMAP were dissolved in pyridine (5 mL). At 0°C, Ac_2O (0.06 g, 0.58 mmol) was added dropwise, and the mixture was stirred at rt for 5 h. After evaporation of the pyridine, the residue was dissolved in CH_2Cl_2 (10 mL), washed with cold water (2 × 5 mL), dried over Na_2SO_4, concentrated, and purified by flash chromatography (CH_2Cl_2:MeOH 30:1) to afford (***R***,***R***)-**2** or (***S***,***S***)-**2**.

(1R,2R)-2-[2-(Diphenylphosphino)benzoyl]amino Cyclohexyl Acetate (R,R)-2

Yield: 75%; white solid; mp = 69–70°C; R_f = 0.60 (CH_2Cl_2/MeOH 30 : 1); $[\alpha]_D^{25}$ -28.8 (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.49–7.45 (m, 1H, arom-H), 7.38–7.21 (m, 12H, arom-H), 6.95–6.90 (m, 1H, arom-H), 5.94 (d, J = 9.1 Hz, 1H, NH), 4.61 (ddd, J = 10.5, 10.5, 4.3 Hz, 1H, CHOAc), 4.05–3.94 (m, 1H, C*H*NH), 2.06 (s, 3H, CH_3), 1.96–1.91 (m, 2H, CH_2), 1.76–1.60 (m, 2H, CH_2), 1.50–1.40 (m, 1H, CH_2), 1.30–1.20

(m, 2H, CH_2), 1.05–0.90 (m, 1H, CH_2). ^{13}C NMR ($CDCl_3$): $\delta = 172.3$, 168.8, 141.8 (d, $J = 25.4$ Hz), 137.9 (d, $J = 11.8$ Hz), 137.8 (d, $J = 11.8$ Hz), 136.7 (d, $J = 21.1$ Hz), 134.8, 134.4 (d, $J = 4.5$ Hz), 134.2 (d, $J = 4.5$ Hz), 130.6, 129.1 (d, $J = 9.9$ Hz), 129.0 (d, $J = 5.0$ Hz), 128.9 (d, $J = 9.8$ Hz), 128.8, 127.6 (d, $J = 4.9$ Hz), 75.0, 53.4, 32.1, 31.1, 24.5, 24.4, 21.8. ^{31}P NMR ($CDCl_3$): $\delta = -8.9$. HRMS (ESI) $[M]^+$ $C_{27}H_{28}NO_3P$: calcd 445.1806, found 445.1790.

(1R,2R)-2-[2-(Diphenylphosphino)benzoyl]amino Cyclohexyl Acetate (S,S)-2

Yield: 79%; white solid; mp = 60–62°C; $R_f = 0.60$ (CH_2Cl_2/MeOH 30 : 1); $[\alpha]_D^{25}$ +30.0 (*c* 0.5, CH_2Cl_2). ^1H NMR ($CDCl_3$): $\delta = 7.41–7.38$ (m, 1H, arom-H), 7.29–7.17 (m, 12H, arom-H), 6.87–6.84 (m, 1H, arom-H), 5.92 (d, $J = 8.6$ Hz, 1H, NH), 4.53 (ddd, $J = 10.4$, 10.4, 4.5 Hz, 1H, CHOAc), 3.98–3.86 (m, 1H, C*H*NH), 2.08 (s, 3H, CH_3), 1.88–1.83 (m, 2H, CH_2), 1.67–1.64 (m, 1H, CH_2), 1.55–1.52 (m, 1H, CH_2), 1.45–1.33 (m, 1H, CH_2), 1.27–1.08 (m, 2H, CH_2), 0.97–0.85 (m, 1H CH_2). ^{13}C NMR ($CDCl_3$): $\delta = 172.4$, 168.8, 141.7 (d, $J = 26.0$ Hz), 137.9 (d, $J = 11.0$ Hz), 137.8 (d, $J = 11.8$ Hz), 136.7 (d, $J = 21.0$ Hz), 134.8, 134.3 (d, $J = 19.8$ Hz), 134.1 (d, $J = 20.4$ Hz), 130.6, 129.1, 129.0 (d, $J = 6.2$ Hz), 128.9 (d, $J = 5.0$ Hz), 128.8 (d, $J = 4.9$ Hz), 127.6 (d, $J = 4.9$ Hz), 75.0, 53.3, 32.0, 31.4, 24.5, 24.4, 21.8. ^{31}P NMR ($CDCl_3$): $\delta = -8.9$. HRMS (ESI) $[M]^+$ $C_{27}H_{28}NO_3P$: calcd 445.1806, found 445.1794.

Allylic Alkylation: General Procedure

In a Schlenk tube, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (8.8 mg, 24 μmol) and the ligand (21.3 mg, 48 μmol, or 42.7 mg, 96 μmol) were dissolved in THF (1 mL). After stirring for 1 h at rt, a solution of racemic 1,3-diphenyl-2-propenyl acetate (302 mg, 1.2 mmol) in THF (1 mL) was added. After 30 min, this solution was transferred to a Schlenk tube containing dimethyl malonate (475 mg, 3.6 mmol), BSA (732 mg, 3.6 mmol), and KOAc (2.3 mg, 24 μmol) in THF (2 mL). The reaction mixture was stirred at 60°C for the desired time. The conversion was determined by GC analysis. The mixture was then diluted with diethyl ether (15 mL) and water (5 mL). The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by chromatography (petroleum ether:ethyl acetate 10:1). The enantiomeric excesses were determined by HPLC analysis.

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