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Enantioselective Pd-catalyzed allylic amination with self-assembling and non-assembling monodentate phosphine ligands

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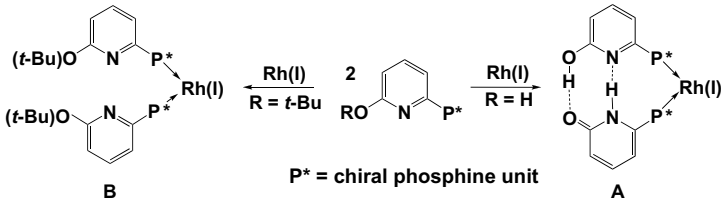
Abstract—New chiral phospholanes were prepared by coupling of bromo-substituted heterocycles with the enantiopure, building block (2*R*,5*R*)-2,5-dimethyl-1-chlorophospholane. Some of the new phosphine ligands have the potential for self-assembling via hydrogen bondings in a metal complex. By application of these and related ligands in the palladium catalyzed allylic amination reaction, high enantioselectivities (up to 99%) were achieved. The influence of the construction of the cyclic phosphine ligands on the enantioselectivity is analyzed.

1. Introduction

Chiral heterocyclic phosphines, such as phosphetanes, phospholanes, phosphinanes or phosphepines play a central role as ligands in homogeneous metal catalyzed reactions.[1] In most cases, bidentate ligands bearing these heterocycles have been used, but also monodentate ligands may induce high enantioselectivities. In particular, bulky monodentate phosphepines, developed by Gladiali et al. and Beller et al., showed excellent stereodiscriminating properties in a range of different catalytic reactions, for example, Rh-catalyzed hydrogenations.[2]

For sometime we have been interested in finding correlations between steric and electronic features in the ligand and the degree of enantioselectivity induced in the chiral product.[3] In a recent approach, we showed evidence that self-assembling catalysts (Scheme 1) based on *P*-pyridone phosphines **4b**, **5b** and **6b** (Scheme 2) can be used for efficient stereocontrol in the Rh-catalyzed asymmetric



Scheme 1. Coordination behaviour of self-assembling ligands versus monodentate ligands.

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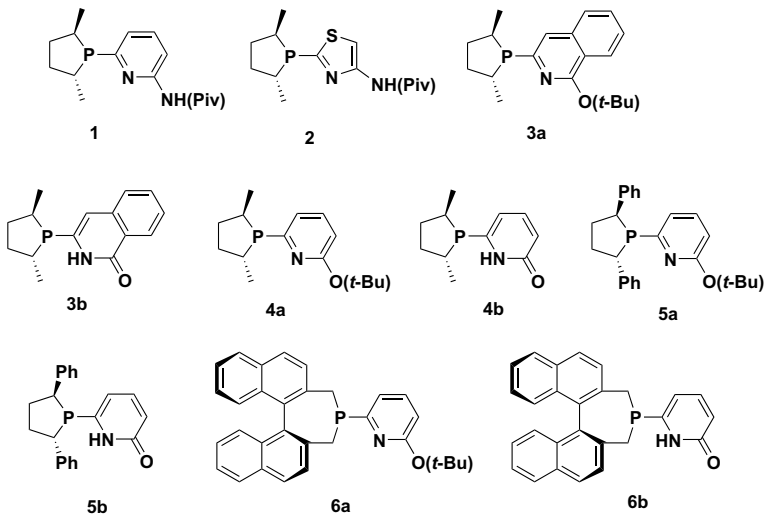


Scheme 2. Ligands tested in the asymmetric allylic amination.

hydrogenation.[4] The general concept of self-assembling catalysts was developed by one of us (B.B.) and successfully applied to numerous catalytic reactions.[5]

Our hydrogenation studies revealed that hydrogen bonding between parts of the ligand in the relevant Rh(I)-catalysts (**A**, Scheme 1) can significantly enhance the enantioselectivity of the hydrogenation of α-(*Z*)-*N*-acetamido acrylates and dimethyl itaconate. Whereas catalysts based on common monodentate ligands (**B**, Scheme 1) gave inferior results.[4]

In particular, in non-polar solvents, ligands **4b**, **5b** and **6b** were superior in comparison to their *O*-*tert*-Bu-protected pyridinol analogues **4a**, **5a** and **6a**, which are not capable of self-assembling. Moreover, these studies showed that the size of the phosphine heterocycle is crucial for the achievement of high ee-values. Thus, ligands with the bulky phosphepine ligands induced the highest enantioselectivities in the product (99% ee).

In order to enlarge the family of self-associating phosphine ligands, and to study this particular effect in other asymmetric transformations, we herein report on the synthesis of phospholanes **1**, **2** and **3a** and **3b**. The new ligands were tested together with phosphines of types **4**–**6** in the asymmetric allylic amination (Tsuji–Trost reaction).[6,7]

2. Results and discussion

2.1. Synthesis

The new phospholanes **1**, **2** and **3a** and **3b** were synthesized in one step by coupling of the enantiopure *P*-chlorodimethylphospholane **8**,[8] easily available from 2,5-dimethyl-1-trimethylsilyl-phospholane[9] **7** by treatment with hexachloroethane in CH_2Cl_2 at reflux, with the corresponding bromides **9**, **10** and **11** in yields of 30–72% (Scheme 3).

Cleavage of the *tert*-butyl ether in **3a** with concentrated formic acid furnished (2*R*,5*R*)-2,5-dimethyl-1-(1*H*-isochinoyl-2-on)-phospholane **3b**. Syntheses of ligands **4a** and **4b**, **5a** and **5b** and **6a** and **6b** were reported recently.[4]

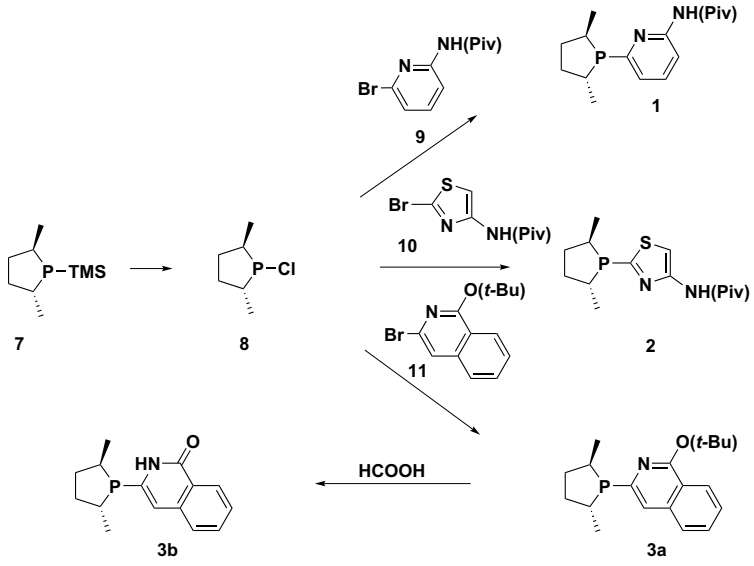
2.2. Enantioselective allylic amination

With these ligands in hand, we evaluated their enantioselective discrimination ability in the allylic amination. As a benchmark test, we studied the reaction of *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with benzylamine.[10]

In most cases, the required precatalysts were prepared in situ from 2 equiv of the ligands and 1 equiv of the metal precursor ($Pd_2(dba)_3{\cdot}CHCl_3$ and $[PdCl(allyl)]_2$), respectively. In the catalytic reaction, in addition to the effect of different ligands, the influence of the solvent was studied.

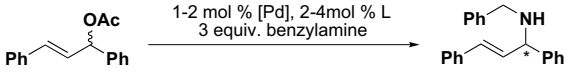
In general, in all trials, full conversion was observed under the conditions displayed in Table 1. Due to the low solubility of catalysts derived from phosphepine ligands **6**, higher substrate:catalyst ratios were necessary. The enantioselectivites achieved with this set of 10 related ligands varied over a range of 3–99% ee.

To our surprise, the highest enantioselectivity (99% ee, run 3) was obtained with the 'small' 2,5-dimethyl substituted phospholane ligand **3a** in toluene as a solvent. It should be noted that due to the *O*-*tert*-Bu protection, this monodentate ligand cannot aggregate with a second ligand at the palladium centre by hydrogen bonding. Incorporation of isochinolone backbone **3b** decreased the enantioselectivity (run 4). Lower ee-values, but similar tendencies have been noted for the 2-(*O*-*tert*-Bu)-pyridinol/pyridone-based pair of phospholanes **4a** and **4b** (runs 5 and 6). Replacement of the methyl groups at the 2,5-position of the phospholane by phenyls, **5a** and **5b**, further diminished the ee. In contrast to the ligands of types **3** and **4**, the relevant *P*-pyridone ligand **5b** was superior in comparison to the *P*-(*O*-*tert*-Bu-pyridinol) ligand **5a** (runs 7 and 8). Unexpectedly, inferior enantioselectivities were also observed with the bulky phosphepines **6a** and **6b**. Poor ee-values are characteristic for *P*-(*O*-*tert*-Bu-pyridinol) ligand **6a** (runs 9 and 10). Enhancement of the ee was obtained by employing the



Scheme 3. Convergent synthesis of phospholanes **1**, **2** and **3a** and **3b**.

Table 1. Pd-catalyzed enantioselective allylic amination of *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene using phosphines **1**–**6** as ligands



Run	Ligand	Pd precursor	Solvent	L/[Pd]	% ee[a]
1	(*R*,*R*)-**1**[b]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	2	76 (*R*)
2	(*R*,*R*)-**2**[b]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	2	20 (*S*)
3	(*R*,*R*)-**3a**[b]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	2	99 (*R*)
4	(*R*,*R*)-**3b**[b]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	2	91 (*R*)
5	(*R*,*R*)-**4a**[b]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	2	92 (*R*)
6	(*R*,*R*)-**4b**[b]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	2	83 (*R*)
7	(*S*,*S*)-(−)-**5a**[b]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	2	8 (*S*)
8	(*S*,*S*)-(−)-**5b**[b]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	2	45 (*R*)
9	(*S*)-**6a**[c]	$[PdCl(allyl)]_2$	THF	2	3 (*R*)
10	(*S*)-**6a**[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	1,2-Dichloroethane	2	14 (*S*)
11	(*S*)-**6b**[c]	$[PdCl(allyl)]_2$	CH_2Cl_2	2	82 (*S*)
12	(*S*)-**6b**[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	CH_2Cl_2	2	82 (*S*)
13	(*S*)-**6b**[c]	$[PdCl(allyl)]_2$	Toluene	2	40 (*S*)
14	(*S*)-**6b**[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	4	42 (*S*)
15	(*S*)-**6b**[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	Toluene	2	40 (*S*)
16	(*S*)-**6b**[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	THF	2	41 (*S*)
17	(*S*)-**6b**[c]	$[PdCl(allyl)]_2$	THF	2	57 (*S*)
18	(*S*)-**6b**[c]	$[PdCl(allyl)]_2$	1,2-Dichloroethane	2	87 (*S*)
19	(*S*)-**6b**[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	1,2-Dichloroethane	2	84 (*S*)

[a] Determined by HPLC analysis, Chiracel OJ-H.
[b] Reaction conditions: 0.5 mmol substrate, 0.005 mmol $Pd_2(dba)_3{\cdot}CHCl_3$, 0.01 mmol ligand, 1.5 mL solvent; 25 °C.
[c] Reaction conditions: 0.32 mmol substrate, 0.0064 mmol Pd precursor, 0.0128 mmol ligand, 3.5 mL solvent; 25 °C.

P-pyridone-based ligand **6b** (runs 11–19). As shown the reaction is rather sensitive to the solvent used; best ee-values were observed in 1,2-dichloroethane (up to 87% ee, runs 18 and 19), but did not reach the value obtained with ligand **3a**. Apparently, the amination reaction gets benefit from a small cyclic phospholane unit, but a large *N*-heterocycle. Thus, the isochinoline ligand **3b** gave higher enantioselectivities than the pyridine-based phosphine **4b** (runs 3 and 5). The same trend was observed for the related pair **3a** and **4a** (runs 4 and 6). An exchange of the pyridinol/pyridinone substituent at the phosphorus atom with other heterocycles (ligands **1** or **2**) did not improve the results (runs 1 and 2).

3. Conclusion

Some new chiral phospholanes have been prepared by a convergent approach using enantiopure *P*-chloro-dimethylphospholane as a building block. The new ligands were tested together with related and known heterocyclic phosphines in the Pd-catalyzed asymmetric amination. Excel-

lent enantioselectivities (up to 99%) were obtained in this reaction. Surprisingly, ligands **3a** and **4a** based on small heterocyclic phosphines provided the highest ee-values. Interestingly, these ligands were not capable of self-assembling. Conversely large phosphine ligands **5b** and **6b** take profit from the property of self-assembling. This is in strong contrast to the results recently observed in the Rh-catalyzed asymmetric hydrogenation.[4]

4. Experimental

General: All reagents unless otherwise mentioned were purchased from commercial sources and used without additional purification. The solvents were dried and freshly distilled under argon before use. All reactions involving phosphines were performed under an argon atmosphere by using standard Schlenk techniques. Elementary analyses were performed on an elementar vario (Fa. Elementar Analysensysteme GmbH). Optical rotations were measured on a Perkin–Elmer 241 polarimeter. NMR spectra were recorded on the following spectrometers: Varian Mercury spectrometer (300 MHz, 121 MHz and 75 MHz for ^{1}H, ^{31}P and ^{13}C, respectively), Bruker AMX 400 (400 MHz, 162 MHz and 100 MHz for ^{1}H, ^{31}P and ^{13}C, respectively) and Bruker DRX 500 (500 MHz, 202 MHz and 125 MHz for ^{1}H, ^{31}P and ^{13}C, respectively) and are referenced according to residual proton solvent signals. Chemical shifts of ^{1}H, ^{13}C and ^{31}P NMR spectra are reported in ppm. Chemical shifts of ^{31}P NMR spectra are referred to H_3PO_4 as an external standard. Elemental analyses were performed with a LECO CHNS-932. High-resolution mass spectra were obtained on a Finnigan MAT 8200 instrument and ESI mass spectrometry was performed on a Finnigan *LCQ Advantage*.

4.1. General procedure for the preparation of phospholanes 1, 2 and 3a

To a solution of bromide **9** or **10** or **11** (7.78 mmol) in dry THF (40 ml), a solution of *n*BuLi [1.6 M in hexane; for **9** and **10** 9.72 ml (15.56 mmol); for **11** 4.86 ml (7.78 mmol), respectively] was added dropwise under stirring at −110 °C. The reaction mixture was stirred for 1 h at this temperature. It was then warmed up to ambient temperature and stirred for a further 1.5 h. A solution of (2*R*,5*R*)-2,5-dimethyl-1-chlorophospholane[8] **8** (1.17 g, 7.78 mmol) in dry THF (10 ml) was then slowly added. The solution was warmed up to −40 °C and quenched with water (0.14 ml, 7.78 mmol). The mixture was concentrated in vacuum. After the addition of pentane the suspension was filtered. The solution was concentrated in vacuum to give the crude products.

4.2. (2*R*,5*R*)-2,5-Dimethyl-1-(2′-pivaloylamino-pyrid-6′-yl)-phospholane 1

The crude product was purified by bulb to bulb distillation (180 °C, 10^{-3} mbar) to give a white solid. Yield: 1.22 g (54%); Mp 55–58 °C, $[\alpha]_D^{19} = -74$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 8.52–8.49 (m, CH, 1H), 7.92 (br s, NH, 1H), 7.12–7.07 (m, CH, 2H), 3.39–3.27 (m, 1H), 2.25–2.08 (m, 2H), 1.82–1.74 (m, 1H), 1.58–1.47 (m, 1H), 1.36 (dd, CH_3–CP, $J = 18.3$ Hz, $J = 7.3$ Hz, 3H), 1.25–1.15 (m, 1H), 0.96 (s, CH_3, 9H), 0.89 (dd, CH_3–CP, $J = 10.1$ Hz, $J = 7.0$ Hz, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 176.9 (s, C=O), 161.9 (d, $J = 24.5$ Hz, arom. C–NH), 152.7 (d, $J = 4.1$ Hz, arom. C–P), 137.1 (d, $J = 8.5$ Hz, arom. CH), 127.4 (d, $J = 34.0$ Hz, arom. CH), 113.3 (s, arom. CH), 40.1 (s, CH_2), 38.0 (d, $J = 2.6$ Hz, CH_2), 37.1 (d, $J = 13.5$ Hz, CH–P), 33.6 (d, $J = 8.9$ Hz, CH–P), 30.7 (s, quat. C), 27.8 (s, $C(CH_3)_3$), 20.8 (d, $J = 33.8$ Hz, CH_3), 15.7 (s, CH_3). ^{31}P NMR (122 MHz, C_6D_6) δ 10.6. MS (CI, NH_3) *m*/*z* (%) 309 $[M+O]^+$ (100), 293 $[M]^+$ (14), 225 (15), 179 (72), 150 (29), 133 (52). HRMS (CI) calcd for $C_{16}H_{25}N_2OP$: 292.1704. Found: 292.1708. Elemental Anal. Calcd for $C_{16}H_{25}N_2OP$ (M = 292.36): C, 65.73; H, 8.62; P, 9.58. Found: C, 65.22; H, 8.72; P, 9.43.

4.3. (2*R*,5*R*)-2,5-Dimethyl-1-(3′-pivaloylamino-thiazol-4′-yl)-phospholane 2

The crude product was purified by bulb to bulb distillation (160 °C, 10^{-3} mbar) and subsequent flash chromatography (CH_2Cl_2/petrol ether 9/1) to give a white solid. Yield: 0.70 g (30%); Mp 117–120 °C, $[\alpha]_D^{19} = -61$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, C_6D_6) δ 8.22 (br s, NH, 1H), 8.09 (s, arom. H, 1H), 3.10–3.01 (m, CH, 1H), 2.15–2.08 (m, CH_2, 1H), 2.00–1.88 (m, CH, 1H), 1.76–1.70 (m, CH_2, 1H), 1.66–1.57 (m, CH_2, 1H), 1.24 (dd, $J = 19.2$ Hz, $J = 7.3$ Hz, CH_3, 3H), 1.08–1.00 (m, CH_2, 1H), 0.95 (dd, $J = 11.3$ Hz, $J = 6.9$ Hz, CH_3, 3H), 0.92 (s, $C(CH_3)_3$, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 175.2 (s, C=O), 168.5 (d, $J = 46.2$ Hz, arom. C–P), 151.2 (d, $J = 6.5$ Hz, arom. C), 105.9 (s, arom. CH), 39.6 (s, quat. C), 38.0 (s, CH_2), 37.9 (d, $J = 3.2$ Hz, CH_2), 37.8 (d, $J = 4.3$ Hz, CH–P), 37.7 (d, $J = 7.5$ Hz, CH), 27.8 (s, $C(CH_3)_3$), 21.3 (d, $J = 33.3$ Hz, CH_3), 15.5 (s, CH_3). ^{31}P NMR (122 MHz, C_6D_6) δ 6.2. MS (CI, NH_3) *m*/*z* (%) 314 $[M+O]^+$ (13), 298 $[M]^+$ (71), 198 (23), 57 (100) HRMS (CI) calcd for $C_{14}H_{23}N_2OPS$: 298.1261. Found: 298.1269. Elemental Anal. Calcd for $C_{14}H_{23}N_2OPS$ (M = 298.39): C, 56.35; H, 7.77; N, 9.39; S, 10.75. Found: C, 56.61; H, 7.87; N, 9.23; S, 10.87.

4.4. (2*R*,5*R*)-2,5-Dimethyl-1-(1′-*tert*-butoxy-isoquinolin-3′-yl)-phospholane 3a

The crude product was purified by bulb to bulb distillation (160 °C, 10^{-3} mbar) and subsequent flash chromatography (CH_2Cl_2/petrol ether 9/1, R_f 0.19) to give a white solid. Yield: 1.77 g (72%); $[\alpha]_D^{19} = -97$ (*c* 0.65, $CHCl_3$). ^{1}H NMR (500 MHz, C_6D_6) δ 8.31–8.27 (m, arom. H, 1H), 7.68 (d, $J = 8.5$ Hz, arom. H, 1H), 7.34–7.31 (m, arom. H, 1H), 7.24–7.18 (m, arom. H, 2H), 3.44–3.35 (m, CH–P, 1H), 2.40–2.20 (m, CH–P and CH_2, 2H), 1.96–1.92 (m, CH_2, 2H), 1.67 (br s, $C(CH_3)_3$, 9H), 1.46 (dd, $J = 18.5$ Hz, $J = 6.9$ Hz, CH_3–CP, 3H) 1.38–1.30 (m, 1H), 0.98 (dd, $J = 11.3$ Hz, $J = 6.9$ Hz, CH_3–CP, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 159.6 (d, $J = 3.2$ Hz, arom. C–O), 152.3 (d, $J = 24.8$ Hz, arom. C–P), 138.4 (d, $J = 12.9$ Hz, quart. C), 131.0 (s, arom. CH), 127.6 (s, arom. CH), 126.9 (s, arom. CH), 125.7 (s, arom. CH), 125.0 (d,

$J = 46.2$ Hz, arom. CH), 121.7 (s, quat. C), 80.5 (s, quat. C), 38.7 (s, CH_2), 38.5 (d, $J = 4.7$ Hz, CH_2), 37.3 (d, $J = 11.83$ Hz, CH–P), 35.2 (d, $J = 8.7$ Hz, CH–P), 29.3 (s, $C(CH_3)_3$), 21.2 (d, $J = 33.3$ Hz, CH_3), 16.1 (s, CH_3). ^{31}P NMR (122 MHz, C_6D_6) δ 13.9. MS (EI) m/z (%) 315 $[M]^+$ (25), 259 (100), 217 (54), 186 (53). HRMS (EI) calcd for $C_{19}H_{26}NOP$: 315.1747. Found: 315.1745. Elemental Anal. Calcd for $C_{19}H_{26}NOP$ (M = 315.39): C, 72.36; H, 8.31; N, 4.44. Found: C, 72.06; H, 8.51; N, 4.36.

4.5. (2*R*,5*R*)-2,5-Dimethyl-1-(1′-oxo-1′,2′-dihydro-isoquinolin-3′-yl)-phospholane 3b

A mixture of (2*R*,5*R*)-3,5-dimethyl-1-(1′-*tert*-butoxy-isoquinolin-3-yl)-phospholane **3a** (0.35 g, 1.11 mmol) in concd formic acid (5 ml) was stirred at ambient temperature for 10 min. The solvent was then evaporated. The residue was dried in vacuum at 40 °C for 1 h. Subsequently, the substance was crystallized from 10 ml of dry diethyl ether and filtered. The crude product was purified by flash chromatography (CH_2Cl_2/ethyl acetate 1/1, R_f 0.38) to give a white solid. Yield: 0.273 g (95%); Mp 161–162 °C, $[\alpha]_D^{19} = -129$ (c 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, C_6D_6) δ 11.80 (br s, NH, 1H), 8.70 (d, $J = 7.3$ Hz, arom. H, 1H), 7.28–7.18 (m, arom. H, 3H), 6.76 (d, $J = 8.3$ Hz, arom. H, 1H), 3.08–2.98 (m, CH–P, 1H), 2.42–2.33 (m, CH_2, 1H), 2.26–2.09 (m, CH–P, 1H), 1.88–1.79 (m, CH_2, 2H), 1.32 (dd, $J = 19.2$ Hz, $J = 7.2$ Hz, CH_3, 3H), 1.26–1.13 (m, CH_2, 1H), 0.97 (dd, $J = 10.4$ Hz, $J = 7.1$ Hz, CH_3, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 165.7 (s, arom. C=O), 140.7 (d, $J = 44.0$ Hz, arom. C–P), 138.4 (d, $J = 11.5$ Hz, quat. C), 133.2 (s, arom. CH), 128.3. (s, arom. CH), 127.7 (s, arom. CH), 127.3 (s, quat. C), 126.9 (s, arom. CH), 116.5 (d, $J = 30.6$ Hz, arom. CH), 38.4 (d, $J = 3.9$ Hz, CH_2), 38.2 (s, CH_2), 36.6 (d, $J = 11.5$ Hz, CH–P), 33.7 (d, $J = 8.7$ Hz, CH–P), 21.3 (d, $J = 34.5$ Hz, CH_3), 16.0 (s, CH_3). ^{31}P NMR (122 MHz, C_6D_6) δ 10.8. MS (CI, NH_3) m/z (%) 259 $[M]^+$ (100), 202 (96), 186 (60), 176 (51). HRMS (CI) calcd for $C_{15}H_{18}NOP$: 259.1121. Found: 259.1112. Elemental Anal. Calcd for $C_{15}H_{18}NOP$ (M = 259.28): C, 69.48; H, 7.00; N, 5.40. Found: C, 69.27; H, 7.17; N, 5.31.

4.6. Pd-catalyzed asymmetric allylic amination (with ligands 1–5)

A mixture of Pd precursor (0.005 mmol), chiral ligand (0.01 mmol) and *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene (0.5 mmol) in a solvent (1.5 ml) was stirred at room temperature for 20 min. Benzylamine (0.160 g, 1.50 mmol) was then added and the resulting mixture was stirred for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 ml) and diethyl ether (10 ml) was added. The organic layer was extracted with Et_2O (3×10 ml). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give the crude product. Ee values were determined by chiral HPLC on a Chiralcel OJ column (hexane/*i*-propanol 80/20, 0.5 ml/min).

4.7. Procedure for the Pd-catalyzed asymmetric allylic amination (with ligands 6a and 6b)

Due to the low solubilities of **6a** and **6b** in nonpolar solvents, the procedure for Pd-catalyzed asymmetric allylic amination was modified.

A mixture of the Pd precursor (0.0064 mmol) and chiral ligand (0.0128 mmol) in a solvent (3.5 ml) was stirred at room temperature for 30 min. *rac*-(*E*)-1,3-Diphenyl-3-acetoxyprop-1-ene (0.32 mmol) and benzylamine (0.103 g, 0.96 mmol) were then added and the resulting mixture was stirred for 12 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution and diethyl ether (10 ml) was added. The organic layer was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give the crude product.

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