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Novel chiral P,O-ligands for homogeneous Pd(0) catalysed asymmetric allylic alkylation reactions

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Abstract—Two novel P,O-coordinating chiral phoshine–amide ligands with hydroxymethyl side chains **5a** and **5b** were prepared and tested in some benchmark Pd(0) catalysed asymmetric allylic alkylations. The conversions and enantioselectivities were generally good, with a highest conversion of 92% and a highest ee of 62% obtained using 1,3-diphenylpropenyl acetate as substrate. A number of palladium pre-catalysts were used, but it was $[Pd(allyl)Cl]_2$ which gave the best results. Ligand **5b** was seen to give better enantioselectivities.

1. Introduction

Catalytic asymmetric synthesis has currently considerable application in providing useful enantiomerically pure compounds. One of the outstanding endeavours in the area is the creation of new C–C and C–X bonds. Since 1977, the asymmetric allylic alkylation (AAA) reaction has become a standard approach for achieving this objective.[1,2] Many chiral ligands have been screened for this particular reaction; these generally contain P or N, possess C_2 or C_1 symmetry and can be of a homobidentate type (e.g., diphosphines and bisoxazolines) or of a heterobidentate nature (e.g., phosphinooxazolines).[1]

Trost's ligand **1** (Fig. 1) has shown considerable applicability for this particular reaction,[2,3] and has elicited much interest from the chemical community.

An interesting study of this ligand in Pd(0) catalysed allylic alkylations by Lloyd-Jones and co-workers[4] demonstrated that under certain circumstances, an alternative P,O mode of coordination of this ligand with Pd was possible giving a catalytically active complex (Fig. 1). Amatore et al.[5] have unambiguously shown this type of coordination in a Pd–allyl complex formed with Trost's diaminocyclohexane-2-diphenylphosphinonapthoyl ligand. Clayden et al.[6] developed an atropisomeric phosphinamide that showed excellent enantioselectivities in the benchmark allylic alkylation of 1,3-diphenylpropenyl acetate. Also worthy of note are the phosphine–amide ligands **3** and **4** (Fig. 2) derived from *O*-methoxy (*S*)-phenylalaninol developed by Mino et al.[7] that were successfully used in palladium catalysed asymmetric allylic alkylations giving a highest ee of 85%. Sinou and co-workers[8] have also developed a series of sugar-derived amides that have also been successful for this

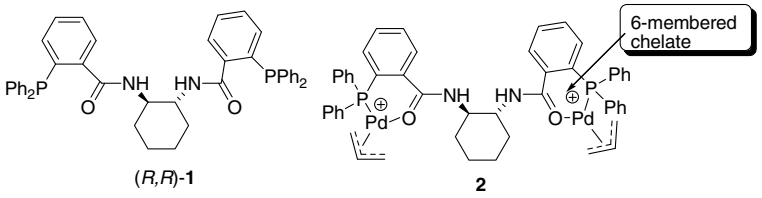

Figure 1.

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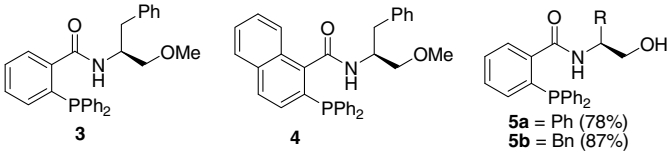
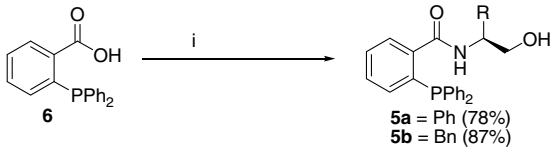


Figure 2.



Scheme 1. Reagents and conditions: (i) (*S*)-phenylglycinol or (*S*)-phenylalaninol, DCC, DMAP, CH_2Cl_2, rt, 24 h.

reaction. Jiang and Huang[9] prepared a series of P,O-type ligands based on (*S*)-prolinol that gave ees of up to 90% in the asymmetric allylic alkylation of dimethyl malonate with 1,3-diphenyl propenyl acetate. Gilbertson and coworkers[10] have shown that certain β-turn derived palladium phosphine complexes give ees up to 95% in the alkylation of 3-acetoxycyclopentene with dimethyl malonate.

Due to our interest in the catalytic asymmetric allylic alkylation,[11] we became interested in preparing the free OH derivative of Mino's ligand[7] **5b** (Fig. 2) and its phenyl glycinol analogue **5a**. We postulated that the free OH group might act as a third coordination site with the metal leading to more rigid transition states that promote greater enantiocontrol in the reaction.

Herein, we report our preliminary results on the synthesis of ligands **5a** and **5b**, and their application in some Pd(0) catalysed asymmetric allylic alkylations.

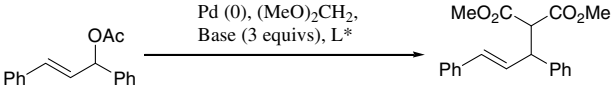
2. Results and discussion

Ligands **5a** and **5b** were prepared in good yields after much experimentation from *o*-(diphenylphosphine)benzoic acid **6** using (*S*)-phenylglycinol and (*S*)-phenylalanine according to the conditions shown in Scheme 1.

Purification of these ligands was hampered by the tendency of the dicyclohexylurea by-product to adhere to these ligands.

Once in hand, these ligands were first tested in the asymmetric allylic alkylation reaction of dimethyl malonate with *rac*-1,3-diphenylpropenyl acetate (Table 1). Overall, the results were quite encouraging with a number of good to excellent conversions and with generally good enantioselectivites (a highest of 62% was obtained, Table 1, entry 4). It was ligand **5b** that gave the best ees, which is attributed to the greater stereochemical hindrance associated with the benzyl group over a phenyl group. Ligand **5a** afforded the (*R*)-enantiomer as the major enantiomer for the malonate product when $[Pd(allyl)Cl]_2$ was used, but afforded the (*S*)-enantiomer when the other two Pd pre-catalysts were used. Ligand **5b** gave the (*S*)-enantiomer as the major enantiomer, except when DMF was used as the solvent where it was found that the (*R*)-enantiomer was the major enantiomer (19% ee and a conversion of 12%). We find it difficult to explain this 'chiral switching' phenomenon, but are aware that a similar phenomenon was shown by Sinou and co-workers[8c] when the reaction solvent was changed. Elevated temperatures were needed to achieve the highest conversions in all the systems studied, and in some cases there was an increase in the enantioselectivity. For example, when $[Pd(allyl)Cl]_2$ was used as the pre-catalyst at room temperature with ligand **5a** in DCE, a conversion of 44% was registered and an ee of 16%, but, when the reaction was conducted at reflux (Table 1, entry 2), a conversion of 91% was registered with a rise in the ee to 37%. This trend was also observed when ligand **5b** was used under the same conditions. When DCM was used with **5b** (Table 1, entry 5), there was also a substantial rise in the conversion (38% was obtained at rt), although the ee remained about the same (59% and 55%, respectively). However, this was not a general effect, for instance, when

Table 1. Asymmetric allylic alkylation of *rac*-1,3-diphenylpropenyl acetate using ligands **5a** and **5b**[a]

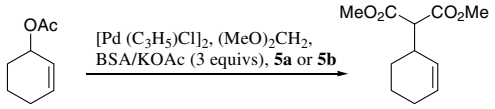


Entry	Pre-catalyst	Ligand	Solvent	Temp (°C)	Base(s)	Conver.[b] (%)	ee[c] (%)
1	$[Pd(allyl)Cl]_2$	**5a**	DCM	Reflux	BSA/KOAc	48	23 (*R*)
2	$[Pd(allyl)Cl]_2$	**5a**	DCE	Reflux	BSA/KOAc	91	37 (*R*)
3	$[Pd(allyl)Cl]_2$	**5a**	THF	Reflux	BSA/KOAc	92	20 (*R*)
4[d]	$[Pd(allyl)Cl]_2$	**5b**	DCM	rt	BSA/KOAc	63	62 (*S*)
5	$[Pd(allyl)Cl]_2$	**5b**	DCM	Reflux	BSA/KOAc	90	55 (*S*)
6	$[Pd(allyl)Cl]_2$	**5b**	THF	Reflux	BSA/KOAc	90	17 (*S*)
7	$Pd_2(dba)_3{\cdot}CHCl_3$	**5a**	DCE	Reflux	BSA/KOAc	86	46 (*S*)

[a] Reaction conditions: 2.5 mol % of ligand and 1 mol % pre-catalyst, complexation conducted at reflux temperature for 2 h and then rt or at reflux for 20 h (when Base = BSA/KOAc, 1 mol % KOAc was used).
[b] Pertains to the ratio of substrate to product as determined by HPLC.
[c] Determined by HPLC using a Chiralcel OD-H column.
[d] 5 mol % ligand to 2.5 mol % pre-catalyst.

$[Pd(allyl)Cl]_2$ was used as the pre-catalyst at rt in DCM with ligand **5a**, a conversion of only 5% was registered and an ee of 43%, but when carried out at reflux (Table 1, entry 1), a conversion of 48% was registered at the expense of a decrease in the ee to 23%. When one compares the various pre-catalysts used, it can be seen that it was $[Pd(allyl)Cl]_2$ which gave the best conversions in all cases. For example, using ligand **5a** with DCE and THF, conversions of 91% and 92% (Table 1, entries 2 and 3) could be obtained. Ligand **5b** also afforded a conversion of 90% in THF (Table 1, entry 6). Using $Pd(dba)_2$ it was found that both ligands **5a** and **5b** gave low conversions, but **5b** gave the highest ee (53%). When 5 mol % ligand **5b** (with 2.5 mol % $[Pd(allyl)Cl]_2$) was used under the same conditions (Table 1, entry 4), there was an increase in the substrate conversion from 38% to 63%, while the enantioselectivity remained constant.

The results were poorer when *rac*-3-acetoxycyclohexene was used as substrate under standard conditions (Scheme 2). The reactions only proceeded when DCM was used as the solvent and with $[Pd(allyl)Cl]_2$ as the palladium source. The conversions were poor (6–12%). Reactions using other solvents (DCE and THF) and pre-catalysts ($Pd(dba)_2$, $Pd_2(dba)_3{\cdot}CHCl_3$) failed to give a product. It was ligand **5b** that furnished the best enantioselectivity (36% ee).



Scheme 2.

It is presumed that the generally lower conversions obtained in the reactions performed at room temperature were possibly a consequence of coordination of the free ligand hydroxyl group with Pd, with concomitant deactivation of the metal. Sinou et al. and Desimoni et al. have previously observed that certain chiral pybox ligands give low conversions for this particular reaction, no matter what conditions were used,[12] which might imply that coordination of an additional binding group (such as an hydroxyl) to the Pd has a deactivating effect.

For the malonate alkylation reaction using 1,3-diphenylpropenyl acetate with allyl palladium dimer, it is apparent that Mino's ligand gives slightly better enantiocontrol (76% ee in DCM) than with our ligands **5a** (37% ee in DCE, Table 1, entry 2) and **5b** (62% in DCM, Table 1, entry 4) contrary to what had been predicted at the outset. A very recent publication by Pons and Rós et al.[13] has shown that coordinating solvents lead to an enhanced fluxional behaviour of the allyl Pd complex (η^3-η^1-η^3 isomerisation or allyl rotation) with enhanced *endo*/*exo* (M/W) isomerisation,[1] which we expect should reduce the reaction enantioselectivity. To test their hypothesis, these workers prepared a pyridylpyrazole probe bearing an hydroxyethyl appendage and ^1H NMR spectroscopy implied coordination of the OH group with the palladium atom.

It was not possible to confirm this experimentally by ^1H NMR in our case, due to the poor resolution of the spectra, but the following mechanism based on the observations of Pons and Ros is presented in Scheme 3.

In an attempt to garner additional support for this hypothesis, we prepared the following Pd complexes **7a** and **7b** (Fig. 3) using the procedure previously reported[11] in the hope of obtaining crystals of these complexes appropriate for X-ray analysis. Unfortunately, these complexes could not be characterised by this technique due to their instability (neither was it possible to do so by NMR due to the poor spectral resolution) and were thus characterised by mass spectrometry.

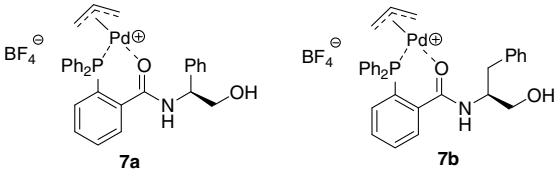
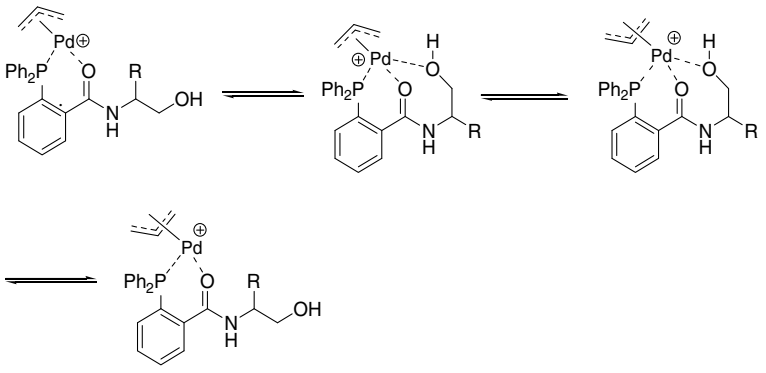


Figure 3.

Another possibility might be the displacement of the amide carbonyl by the free hydroxyl group giving a competing chiral catalyst.[14]

3. Conclusions

The simple phosphine–amides **5a** and **5b** were obtained in very good yields from *o*-(diphenylphosphine)benzoic acid



Scheme 3.

6 and the readily available amino-alcohols (*S*)-phenylglycinol and (*S*)-phenylalaninol. Compounds **5a** and **5b** complexed with various palladium pre-catalysts in situ to form chiral catalysts that catalyse the asymmetric alkylation reactions of 1,3-diphenylpropenyl acetate and 3-acetoxycyclohexene with moderate to good enantioselectivities. In the case of the former substrate, very good substrate conversions were obtained when the reaction was carried out at an elevated temperature. Further work is currently in progress at immobilising these ligands onto solid supports and applying these ligands in other catalytic asymmetric reactions.

4. Experimental

4.1. General information

All reagents were obtained from Aldrich, Fluka, Alfa Aesar or Acros. Solvents were dried using common laboratory methods.[15]

Column chromatography was carried out on silica gel (sds, 70–200 μm) and flash column chromatography (Merck, 40–63 μm and sds, 40–63 μm). TLC was carried out on aluminium backed Kisel-gel 60 F_{254} plates (Merck). Plates were visualised either by UV light or with phosphomolybdenic acid in ethanol.

High performance liquid chromatographic (HPLC) analysis was performed on an Agilent 1100 series instrument. The following conditions were used: $p_{max} = 50$ bar, flux = 1 ml/min, detector = DAD ($\lambda = 210,10$ nm), eluent—*n*-hexane/isopropanol (98:2). The column used was a Chiralcel OD-H (0.46 cm × 25 cm) fitted with a guard column composed of the same stationary phase.

Gas chromatographic (GC) analyses of the products were performed on a Hewlett Packard (HP) 6890 series instrument equipped with a flame ionisation detector (FID). The chromatograph was fitted with a cyclosil-B capillary column (30 m, 250 μm, 0.25 μm) (Agilent 112-2532).

In all cases, the acetate conversions were calculated by determining the ratio of the peak areas for the substrate (both enantiomers) and the alkylated product (both enantiomers).

The melting points were recorded on a Barnstead Electrothermal 9100 apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on either a Bruker AMX300 (^{1}H: 300.13 MHz) instrument using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on a VG Autospec M (Waters-Micromass) spectrometer using the FAB technique. Infra-red spectra were measured with a Perkin Elmer Paragon 1000 model.

4.2. Synthesis of (*S*)-*N*-(2-hydroxy-1-phenylethyl)-2-(diphenylphosphino)benzamide 5a

A solution of DCC (0.841 g, 4.1 mmol), DMAP (0.399 g, 3.3 mmol), amino alcohol (3.3 mol) and *o*-(diphenylphosphine)benzoic acid **6** (0.500 g, 1.6 mmol) in CH_2Cl_2 (5 mL) was stirred under nitrogen at rt for 24 h. A white precipitate was formed. The reaction was monitored by TLC. The precipitate was filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica using hexane/AcOEt (3:2) as eluent giving the *title compound* as a white solid as product (78%). Mp 113.6–116.3 °C. IR [ν (cm^{-1})]: 1032.12, 1055.82, 1456.56, 1548.00, 1622.60, 2882.76, 2930.84, 3054.97, 3257.98; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.1 (s, 1H, –O*H*), 3.7–3.8 (m, 2H, –CH_2OH), 5.1–5.2 (m, 1H, –C*H*Ph), 6.4–6.5 (d, $J = 6.7$ Hz, 1H, –N*H*), 7.2–7.7 (m, 19H, H aromatics); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 57 (–*C*HCH$_2$OH), 66.5 (–CH-*C*H$_2$OH), 127–142 (C aromatics), 169 (–*C*O); MS (FAB, *m*/*z*): 426.08 (M+1); $[\alpha]_D^{21} = +22.4$ (*c* 0.41, $CHCl_3$).

4.3. Synthesis of (*R*)-*N*-(1-benzyl-2-hydroxyethyl)-2-(diphenylphosphino)benzamide 5b

This compound was prepared in the same manner as for **5a**. Giving the *title compound* **5b** as a white solid (87%). Mp 138.7–141.1 °C. IR [ν (cm^{-1})]: 1034.77, 1094.46, 1456.58, 1520.47, 1627.97, 2854.15, 2922.92, 3053.82, 3333.02; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.2 (s, 1H, –O*H*), 2.6–2.8 (m, 2H, –CHCH_2Ph), 3.55 (m, 2H, –C*H*HOH), 3.75 (m, 2H, –CH*H*OH), 4.2 (m, 1H, –C*H*CH$_2$Ph), 5.8 (d, $J = 6.8$ Hz, 1H, –N*H*), 7.1–7.5 (m, 19H, H aromatics); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 37 (–CH*C*H$_2$Ph), 54 (–*C*HCH$_2$Ph), 64 (–*C*H$_2$OH), 127–138 (C aromatics), 169 (–*C*O); MS (FAB, *m*/*z*): 440.08 (M+1). $[\alpha]_D^{23} = -39$ (*c* 0.55, $CHCl_3$).

4.4. Preparation of [allylPd-5a]BF_4 complex 7a and [allylPd-5b]BF_4 complex 7b

The chiral ligand (**5a**; 0.04 mmol, **5b**; 0.09 mmol) was added to a solution of $[Pd(C_3H_5)Cl]_2$ (0.5 equiv) in CH_2Cl_2 under a nitrogen atmosphere. After stirring the solution for 10 min, $AgBF_4$ (1 equiv) was added. The mixture was stirred for 5 min and then the precipitate ($AgCl_2$) was removed by filtration. The solvent was evaporated and the resultant solid was washed with pentane and dried under vacuum.

4.4.1. [AllylPd-5a]BF_4 7a. Black solid (quantitative yield). Mp 124.5–128.6 (°C). MS (FAB, *m*/*z*): 307.08 (M+2−Pd^+(allyl)−C_8H_8O).

4.4.2. [AllylPd-5b]BF_4 7b. Black solid (quantitative yield). MS (FAB, *m*/*z*): 584.20 (M+1−H_2O), 438.21 (M+1−Pd^+(allyl)), 305.07 (M−C_8H_8O).

4.5. Catalytic reactions

4.5.1. General procedure for the homogeneous catalytic asymmetric allylic alkylation reactions. The ligand was added to a solution of Pd (1–2 mol %) in solvent under a nitrogen atmosphere. The reaction mixture was refluxed for 2 h. A solution of *rac*-1,3-diphenylpropenyl acetate or *rac*-3-acetoxycyclohexene (0.200 g), dimethyl malonate (0.3 mL, 2.4 mmol), BSA (0.6 mL, 2.4 mmol) and KOAc (0.800 mg, 1 mol %) in solvent (1 mL) was added to the

catalyst solution at rt. The resulting mixture was stirred for 20 h at rt or at reflux. The reaction mixture was filtered over a pad of Celite and silica gel and washed with hexane/AcOEt (2:1). The solvent was evaporated and the products were analysed by HPLC (malonate product derived from *rac*-1,3-diphenylpropenyl acetate) or GC (malonate product derived from *rac*-3-acetoxycyclohexene).

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