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Palladium catalysed enantioselective asymmetric allylic alkylations using the Berens' DIOP analogue

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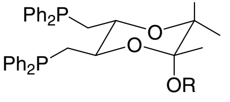
Abstract—Berens' DIOP analogue **1a** was evaluated in a series of Pd(0) catalysed asymmetric allylic alkylations of both acyclic and cyclic substrates using both C- and N-nucleophiles. The reaction conditions were exhaustively analysed and a maximum ee of 60% was obtained using *rac*-1,3-diphenylpropenyl acetate **3** and malonate as the nucleophile. *rac*-3-Acetoxycyclohexene **5** gave inferior ee's. Various solvents were applied including [bmim]PF_6. The results using benzylamine were comparable to those obtained using malonate. For **3**, in all cases the reaction exclusively gave the branched alkylated product **4** and allylic amine **8**, with no trace of their linear regioisomers. The [allylPd-**1a**]BF_4 complex **7** was prepared, characterised and screened in the asymmetric allylic alkylation of *rac*-1,3-diphenylpropenyl acetate **3**. It was also immobilised on montmorillonite K-10 support and preliminary solid phase reactions were conducted with **3**.

1. Introduction

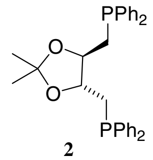
Presently, catalytic asymmetric synthesis (CAS) is finding considerable application in providing important enantiomerically pure compounds. Asymmetric allylic alkylation (AAA) reactions[1] are powerful approaches to introduce C–C/C–X bonds in target compounds. Many chiral ligands have been screened for 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, bisoxazolines, etc.) or heterobidentate nature (e.g., phosphinooxazolines etc.).[1] Unfortunately, in most cases these ligands are difficult to prepare and/or expensive, making the discovery of inexpensive alternatives or the re-employment of inexpensive and/or easily prepared known ligands that show high enantioselectivities and efficiencies in other asymmetric processes, an important endeavour.

In 1995, Berens et al.[2] reported the unexpected synthesis of the 1,4-dioxane based diphosphines **1a** and **1b**, which are analogues of DIOP **2**, a ligand strongly associated with Rh-catalysed hydrogenations.[3] These diphosphines have a more rigid back-bone than DIOP **2**, by virtue of the operation of a double anomeric effect, raising the possibility of achieving high enantioselectivities with **1a** and **1b**. Rh-catalysed hydrogenations of (*Z*)-2-*N*-acylaminoacrylates by Berens et al. with the Rh catalysts derived from **1a** and **1b** gave only moderate to good ee's (25–54%).[4] However, Zhang et al. managed to obtain remarkable ee's (94–99%) using ligand **1a** in the Rh(I) catalysed in situ hydrogenation of β-substituted enamides and MOM-protected β-hydroxyl enamides.[5] Despite the potential of this ligand for catalytic asymmetric synthesis, in addition to its application in catalytic asymmetric hydrogenation, as far as we are aware, there have been no other reports on the applications of this ligand system in catalytic asymmetric synthesis.

Herein, we report our preliminary results on the application of ligand **1a** in Pd(0) catalysed asymmetric allylic alkylations.



1a R = Me
1b R = Et



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2. Results and discussion

Ligand **1a** was screened in a number of asymmetric allylic alkylations of dimethyl malonate with both

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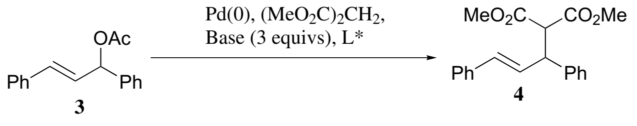
rac-1,3-diphenylpropenyl acetate **3** and *rac*-3-acetoxycyclohexene **5** using a variety of Pd pre-catalysts, solvents and other conditions (Tables 1 and 2) according to the procedure of Hilgraf and Pfaltz.[6] Generally, the enantioselectivities were moderate to good, with the (*R*)-isomer predominating[7] for the alkylated malonate **4**. However, ligand **1a** was inherently superior to DIOP **2** with regards to enantiofacial discrimination (DIOP gave a low ee of 6%, which is in agreement with the literature[8]). It can be seen from Table 1 that the ee's are generally moderate to good (max. 60%). There does appear to be a solvent effect, albeit weak. The relatively polar non-coordinating chlorinated solvents such as CH_2Cl_2 and $ClCH_2CH_2Cl$ give the highest ees (43–60%) (an observation previously made by Trost and Bunt[9a]) whilst apolar and polar coordinating solvents give lower ees (3–44%). There does not appear to be a solvent effect on reaction efficiency. One important factor that seems to have an important bearing on the product enantioselectivity is the temperature used in the reaction to form the chiral complex. When a higher temperature was used, it appeared that the conversion was somewhat better. In the case of the reaction in $ClCH_2CH_2Cl$, when under reflux, the conversion (100%) was double that obtained when a temperature of 40–50 °C was used. (Table 1, compare entry 10 with entry 12). The ee increased by almost 10%. This trend was the same for other solvents, such as THF, DME, DMF and MeCN. It was also observed that for both toluene and DMF, the ee also increased when the complexation temperature was reduced. Reactions carried out at 0 °C were consistently less efficient that those conducted at rt (Table 1, compare entry 1 with entry 2, entry 3 with 4 and entry 15 with 17). However, the ee's generally improved with the drop in temperature. Although increasing the loading of pre-catalyst to 2.5 mol % improved the reaction conversion, the ee dropped slightly (Table 1, compare entry 1 with entry 3). This would imply that the quantity of non-complexed non-chiral catalyst increased over that of complexed chiral catalyst.

Changing the nature of the pre-catalyst from $[Pd(allyl)Cl]_2$ to others such as $PdCl_2(CH_3CN)_2$, $Pd(OAc)_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$ although leading to lower chemical conversions, led to no significant differences in ee. When the base was changed from BSA/KOAc to NaH, there was a decrease in chemical conversion, but the ee remained constant (Table 1, compare entry 1 with 9, 65–24%). Assuming that this was related to the poor solubility of the base (NaH) in the solvent (CH_2Cl_2), 18-crown-6 was added, but while the conversion increased slightly to 28%, the ee dropped from 46% to 10%, implying that this additive

Table 1. Asymmetric allylic alkylation of *rac*-1,3-diphenylpropenyl acetate **3** using ligands **1a** and **2**[a]



Entry	Pre-catalyst	Ligand	Solvent	Base(s)	Conver.[b] (%)	ee[c] (%)
1	$[Pd(allyl)Cl]_2$	**1a**	CH_2Cl_2	BSA/KOAc	65	49
2[d]	$[Pd(allyl)Cl]_2$	**1a**	CH_2Cl_2	BSA/KOAc	33	55
3[e]	$[Pd(allyl)Cl]_2$	**1a**	CH_2Cl_2	BSA/KOAc	87	34
4[d,e]	$[Pd(allyl)Cl]_2$	**1a**	CH_2Cl_2	BSA/KOAc	29	60
5	$[Pd(allyl)Cl]_2$	**2**	CH_2Cl_2	BSA/KOAc	71	6
6	$PdCl_2(CH_3CN)_2$	**1a**	CH_2Cl_2	BSA/KOAc	25	47
7	$Pd(OAc)_2$	**1a**	CH_2Cl_2	BSA/KOAc	11	43
8	$Pd_2(dba)_3{\cdot}CHCl_3$	**1a**	CH_2Cl_2	BSA/KOAc	31	49
9	$[Pd(allyl)Cl]_2$	**1a**	CH_2Cl_2	NaH	24	46
10	$[Pd(allyl)Cl]_2$	**1a**	$ClCH_2CH_2Cl$	BSA/KOAc	100	36
11[d,e]	$[Pd(allyl)Cl]_2$	**1a**	$ClCH_2CH_2Cl$	BSA/KOAc	92	49
12[f]	$[Pd(allyl)Cl]_2$	**1a**	$ClCH_2CH_2Cl$	BSA/KOAc	51	45
13	$[Pd(allyl)Cl]_2$	**1a**	Toluene	BSA/KOAc	19	3
14[f]	$[Pd(allyl)Cl]_2$	**1a**	Toluene	BSA/KOAc	24	42
15	$[Pd(allyl)Cl]_2$	**1a**	THF	BSA/KOAc	92	39
16[f]	$[Pd(allyl)Cl]_2$	**1a**	THF	BSA/KOAc	40	44
17[d,e]	$[Pd(allyl)Cl]_2$	**1a**	THF	BSA/KOAc	51	39
18	$[Pd(allyl)Cl]_2$	**1a**	DME	BSA/KOAc	37	35
19[f]	$[Pd(allyl)Cl]_2$	**1a**	DME	BSA/KOAc	83	31
20	$[Pd(allyl)Cl]_2$	**1a**	DMF	BSA/KOAc	2	21
21[f]	$[Pd(allyl)Cl]_2$	**1a**	DMF	BSA/KOAc	18	41
22	$[Pd(allyl)Cl]_2$	**1a**	MeCN	BSA/KOAc	18	27
23[f]	$[Pd(allyl)Cl]_2$	**1a**	MeCN	BSA/KOAc	63	33

[a] Reaction conditions: 2.5 mol % of ligand and pre-catalyst 1 mol % used, complexation conducted at reflux temperature and then rt for 20 h (when Base = BSA/KOAc, 1 mol % KOAc was used).

[b] Pertains to the ratio of substrate to product.

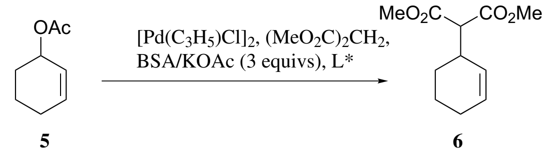
[c] Determined by HPLC using a Chiralcel OD–H column.

[d] The alkylation reaction was conducted at 0 °C.

[e] 2.5 mol % pre-catalyst.

[f] Complexation conducted at 40–50 °C.

Table 2. Asymmetric allylic alkylations of *rac*-3-acetoxycyclohexene **5** using ligands **1a** and **2**[a]



Entry	Ligand	Solvent	Conver.[b] (%)	ee[c] (%)
1	**1**	CH_2Cl_2	24	3
2[d]	**1**	$ClCH_2CH_2Cl$	11	9
3	**1**	Toluene	0	—
4[e]	**1**	THF	27	3
5[f]	**1**	$[bmim]PF_6$	1	55
6	**2**	CH_2Cl_2	41	1

[a] Reaction conditions: 2.5 mol % of ligand and pre-catalyst 1 mol % used and complexation conducted at reflux temperature and then rt for 20 h (1% KOAc was used).

[b] Pertains to the ratio of substrate to product.

[c] Determined by GC using a Cyclosil-beta column.

[d] Complexation conducted at 50–60 °C.

[e] Complexation conducted at 40–50 °C.

[f] Complexation conducted at 60–70 °C.

may interact unfavourably (by coordination or other means) with the chiral catalyst. When the ionic liquid $[bmim]PF_6$ was used with $[Pd(allyl)Cl]_2$, BSA/KOAc and dimethylmalonate in the same way for alkylation of **3**, a significant conversion of 76% was obtained, but with only a moderate ee of 18%, perhaps due to the negative counterion effect.[9b]

In the case of alkylation of *rac*-3-acetoxycyclohexene **5** (Table 2), the overall results were inferior to those using *rac*-1,3-diphenylpropenyl acetate **3**. The conversions were lower than those achieved with the former substrate, with a maximum conversion of 27% being obtained using THF (Table 2, entry 4). For this substrate, there was little difference in the enantiodiscrimination induced by either ligand **1** or DIOP **2** (Table 2, compare entry 1 with entry 6) but, it was DIOP **2**, which gave the best conversion (41%).

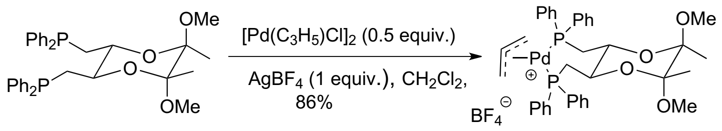
Surprisingly, ligand **1** gave a much higher ee (55%) using $[bmim]PF_6$ as a solvent than was achieved with acetate **3** (only 18% ee) (vide supra). Unfortunately, this good enantioselection came at the expense of a very poor chemical conversion.

We also successfully prepared, in good yield, the [allylPd-**1a**]BF_4 complex **7** by reacting ligand **1a** with $[Pd(allyl)Cl]_2$ according to the method of Brown and MacIntyre (Scheme 1).[8b] The isolation of this complex was confirmed by mass spectrometric analysis.

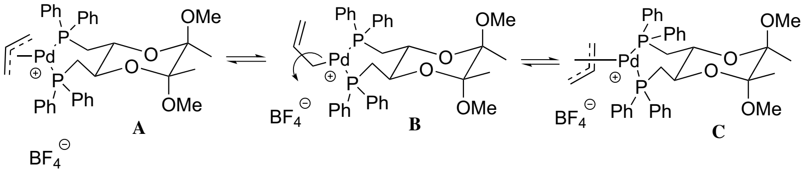
Unfortunately it was not possible to obtain crystals of this compound for X-ray crystallographic analysis and the ^1H NMR spectrum was very poorly resolved, most likely because of the possible fluxional behaviour of the [allylPd-**1a**]BF_4 complex **7** leading to the existence of two equivalent conformations **A** and **C** via an η^3–η^1–η^3 mechanism as suggested by Togni et al.[10a,b] and reported from other sources (Scheme 2).[1b] When this complex was employed in an asymmetric alkylation reaction with **3**, a conversion of 92% and an ee of 37% were obtained.

This complex was immobilised on montmorillonite K-10 according to the procedure of Segarra et al.[11] Unfortunately the loading was quite poor at 0.06 mol **7**/g (as determined by ICP-OE). This was possibly due to weak non-covalent interactions between the BF_4^- ion and the support. The immobilised catalyst was employed at a low loading of ca. 1 mol % in an asymmetric alkylation reaction of **3** with dimethylmalonate using THF as a solvent and BSA/KOAc as a base. After a reaction time of 20 h at rt a disappointing conversion of 1% was obtained and an equally disappointing ee of 8%. To increase the reactivity and selectivity, we employed CH_2Cl_2 as a solvent, keeping everything else constant and increasing the reaction time to 138 h. This resulted in a conversion of 13% and an ee of 45%.

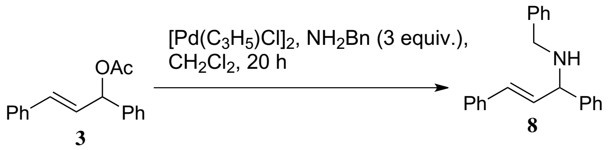
Some preliminary studies were conducted in order to access the outcome upon application of benzylamine in the reaction with **3**. The *N*-alkylated benzylamine **8** (Scheme 3) was obtained. In the first study, $[Pd(allyl)Cl]_2$ was used as the pre-catalyst at a loading of 1 mol % and the reaction performed in CH_2Cl_2 to give **8** with a conversion of 11% and an ee of 48% in favour of the (*R*)-enantiomer.[12] When



Scheme 1. Preparation of complex **7**.



Scheme 2. Postulated fluxional behaviour for **7**.



Scheme 3. Synthesis of *N*-alkylated benzylamine **8**.

the [Pd(allyl)Cl]$_2$ loading was increased to 2.5 mol %, the conversion was raised to 26%, but the ee remained constant. The lower conversions obtained here may be a consequence of the 'harder' nature of the nucleophile used (Scheme 3).

Many C$_2$ symmetric di-phosphine ligands have been tested in this particular reaction and have provided modest enantioselectivities.[13] This is presumably due to the fact that the enantiodiscrimination relies solely on the stereochemical properties of the enantiocontrolling catalytic species.[14]

The ees which were obtained from these studies are quite significant for C$_2$ symmetric di-phosphine ligands, as they generally give lower ee's than their heterobidentate P,N counterparts (even the highly rated di-phosphinamide ligand of Trost gave unsatisfactory results for the 1,3-diphenyl substrate **3**[9b] despite giving better ees for other acyclic systems[9b] and ee's of up to 98% with cyclic systems[9a,13a]). In the case of our active chiral catalyst, the asymmetric induction is solely dependent on the chiral rigid dioxane backbone. The poor results associated with *rac*-3-acetoxycyclohexene **5** could possibly be due to steric hindrance in forming the allyl–palladium complex.

3. Conclusions

Berens' C$_2$ symmetric di-phosphine ligands **1a**, which is an inexpensive chiral ligand, easily accessed from (+)-tartaric acid, was evaluated in a series of catalytic asymmetric alkylations. The ee's obtained were satisfactory and much better than those obtained using DIOP **2**. Further work is currently in progress in augmenting both the enantioselectivity, efficiency and also optimising the solid-phase version of the reaction.

4. Experimental

4.1. General information

All reagents were obtained from Aldrich, Fluka, Alfa Aesar or Acros. The ionic liquid [bmim]PF$_6$ was purchased from Solchemar and montmorillonite K-10 from Alfa-Aesar. 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 phosphomolybdic acid in ethanol.

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

High performance liquid chromatographic (HPLC) analysis was performed on an Agilent 1100 series instrument. The following conditions were used: pmax = 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. In all cases, the acetate conversions were calculated by simply determining the ratio of the peak areas for the substrate and the alkylated product.

Melting points were recorded on a Barnstead Electothermal 9100 apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on 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. The % Pd contained in the montmorillonite K-10 was determined by inductively-coupled plasma optical emission spectrometry (ICP-OE) using a Perkin–Elmer Optima 4300-DV mass spectrometer.

4.2. Preparation and immobilisation of [allylPd-1a]BF$_4$ complex 7

4.2.1. Preparation of [allylPd-1a]BF$_4$ complex 7. Ligand **1a** (30 mg; 5.24×10^{-2} mmol) and [Pd(C$_3$H$_5$)Cl]$_2$ (9.6 mg; 2.62×10^{-2} mmol) were dissolved in dry CH$_2$Cl$_2$ (10 ml) and stirred at rt. After approximately 10 min AgBF$_4$ (10.2 mg; 5.24×10^{-2} mmol) was added and the AgCl$_2$ precipitate was removed by filtration. The solvent was evaporated and the solid washed with pentane to give the title complex **7** as an orange solid (39 mg, 86%). Mp 119.6 °C (decomp.), IR (KBr). ν_{max} 3052, 2989, 1436, 1120, 1034, 747, 695, 505 cm^{-1}; FAB-MS *m*/*z*: 720.17 [M+H−CH$_3$].

4.2.2. Immobilisation of [allylPd-1a]BF$_4$ complex 7 on montmorillonite K10. Montmorillonite K-10 (0.2 g) was added to a solution of [allylPd-**1a**]BF$_4$ complex **7** (16.1 mg, 0.02 mmol) in dry THF (5 ml). After stirring at rt for 24 h, the suspension was filtered and the solid washed with THF and dried under vacuum. % Pd = 0.64% (ICP-OE).

4.3. Catalytic reactions

4.3.1. General procedure for the homogeneous catalytic asymmetric allylic alkylation reactions. [Pd(C$_3$H$_5$)Cl]$_2$ (2.9 mg; 7.93×10^{-3} mmol) and the chiral ligand (0.011 g; 1.982×10^{-2} mmol) were placed in a flask with a dry solvent (1.0 ml) under a nitrogen atmosphere and refluxed (or heated within a fixed temperature range) for 2 h. The temperature was reduced to rt after which the substrate (0.2 g; 0.79 mmol) dissolved in a dry solvent (3.2 ml) was added. Dimethylmalonate (0.27 ml; 2.38 mmol), BSA (0.58 ml; 2.38 mmol) and potassium acetate (0.0008 g; 1 mol %) or alternatively benzylamine (0.26 g, 2.38 mmol) were added. The mixture was maintained at rt (or in certain cases at 0 °C) for 20 h after which it was filtered using a pad of silica gel, using a mixture of hexane/EtOAc (2:1) for washing. The solvent was evaporated and the resulting mixture analysed by HPLC.

4.3.2. General procedure for the catalytic asymmetric allylic alkylation reaction using [allylPd-1a]BF_4 complex 7 on montmorillonite K-10 support. *rac*-1,3-Diphenylpropenyl acetate **3** (0.2 g; 0.79 mmol) dissolved in dry CH_2Cl_2 (3.2 ml) was added to a suspension of immobilised [allyl-Pd-**1a**]BF_4 complex **7** on montmorillonite K-10 support (112.10 mg; 1 mol %) in dry CH_2Cl_2 (1.0 ml) under a nitrogen atmosphere. Dimethylmalonate (0.27 ml; 2.38 mmol), BSA (0.58 ml; 2.38 mmol) and potassium acetate (0.0008 g; 1 mol %) were added. The mixture was maintained at rt for 20 h and the solids removed by filtration using a pad of silica gel and a mixture of hexane/EtOAc (2:1) for washing. The solvent was evaporated and the resulting mixture analysed by HPLC.

Acknowledgements

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