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A New Class of Chiral Phosphorus Catalyst for Asymmetric Palladium Catalysed Allylic Substitution Reactions.

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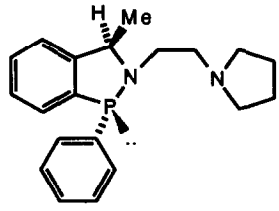
Abstract: Asymmetric inductions of up to 91.5% have been achieved in a palladium catalysed allylic substitution reaction using a new class of enantiomerically pure phosphorus ligand.

Palladium catalysed allylic substitution reactions[1] have recently been the subject of a great deal of interest from the synthetic community due to their wide synthetic scope, practical simplicity and potential for asymmetric synthesis through the use of chiral ligands. The most successful asymmetric ligands developed to date have been bidentate structures such as diphosphines,[2] diamines[3] or mixed donor ligands based on oxazolines.[4] Of these it is the latter category which have given the most impressive results, particularly those in which either a phosphine[4a,b,c] or a sulphide[4d,e] is employed as the non-directing auxiliary ligand. In this paper we report the results of our studies on a new class of mixed phosphorus/nitrogen donor ligands represented by **1** and **2** and a monodentate phosphorus-based ligand, **3**.[5]



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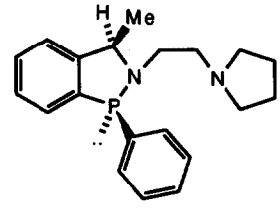

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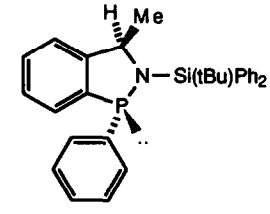

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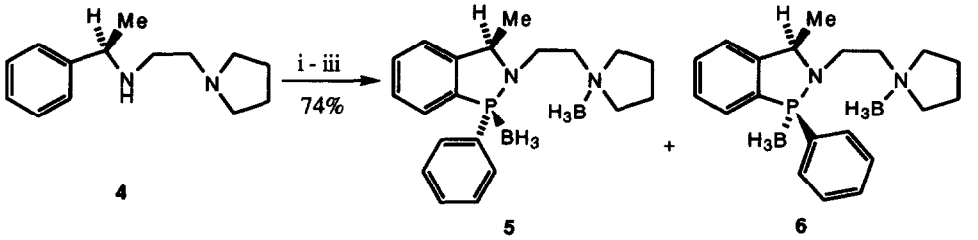
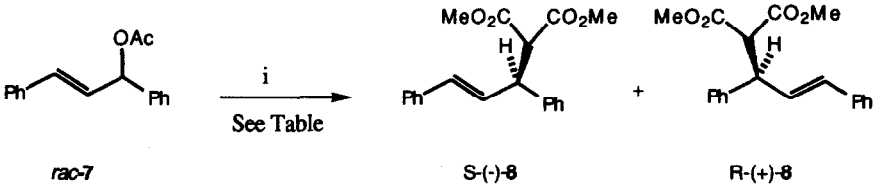
We wished to invesigate the applications to catalysis of a novel class of enantiomerically pure ligand designed in our laboratory which is chiral at phosphorus. The key structural unit, a dihydrobenzazaphosphole, contains an aromatic ring fused to a five membered ring containing a P-N bond. which ensures a high degree of conformational rigidity in the structure. Heterocycles of this type are known to bind to metals through the phosphorus, rather than nitrogen, atom.[6] Our initial targets were the bidentate ligands **1** and **2**, however in view of the susceptibility of the phosphorus atom in phosphines to oxidation we prepared the borane-protected derivatives **5** and **6** in the expectation that the free ligands could

be generated *in-situ* prior to the palladium catalysed reaction.[7] Compounds **5** and **6** were prepared from the enantiomerically pure diamine **4**[8] using an *ortho*- lithiation strategy[9] followed by trapping with dichlorophenylphosphine and then borane as a 1:1 mixture in 74% yield (Scheme 1). Resolution of this mixture was achieved by flash chromatography to yield the pure diastereoisomers. The more polar, **5**, was crystallised and found, by an X-ray crystal structure analysis, to contain a *trans*- relationship between the chiral centres in the heterocyclic ring.[10]



Scheme 1 Reagents: i) 2.2 eq. nBuLi, 1.1 eq. TMEDA, Et_2O, rt, 16 hr, ii) 1.5 eq.$PhPCl_2$, -70°C, 1 hr then rt, 2 hrs, iii) 4.2 eq. $H_3B{:}SMe_2$, rt, 1 hr.

In common with other researchers we chose the reaction of *rac*-(E)-1,3-diphenylprop-2-enyl-1-acetate **7** with dimethyl malonate, to give **8**, as a convenient model reaction for the evaluation of our catalysts (Scheme 2). Removal of the borane immediately prior to the allylic substitution reaction could be achieved using either morpholine or DABCO.[7,11] A dichloromethane solution of $[(C_3H_5)PdCl]_2$ was then transferred to the deprotected catalyst and heated at 50°C for two hours.[3] The reaction was cooled to room temperature prior to addition of **7** and the other reagents then degassed using three freeze/thaw cycles.[3] In all the cases we employed the bis(trimethylsilyl)acetamide method[12] for the activation of the dimethyl malonate. The enantiomeric excess (e.e.) of the product **8** was assessed by 400 MHz ^{1}H-NMR spectroscopy using the chiral shift reagent Eu(hfc)$_3$ and the absolute configuration was determined by comparison of its sign of rotation with that reported for authentic material (Table).[3]



Scheme 2 Reagents: i) 1.1 eq. Dimethylmalonate, X mol% $[(C_3H_5)PdCl]_2$, Y mol% **1**, **2** or **3**, 1. eq. (TMS)NCO(TMS)Me, cat. KOAc, CH_2Cl_2, r.t.

As expected, use of the non-crystalline ligand **2** gave a low yield of **8** and an e.e. significantly lower than that achieved using the crystalline ligand **1**, which underlines the importance of ligand purity in these reactions. Significantly, using morpholine to remove the borane, ligands **1** and **2** gave compounds of opposite configuration, which would be expected if it is the configuration at the phosphorus atom which determines the absolute configuration in the product **8**. More remarkable however was the observation that when DABCO was used to remove borane from **5**, the configuration of the major enantiomer of **8** was

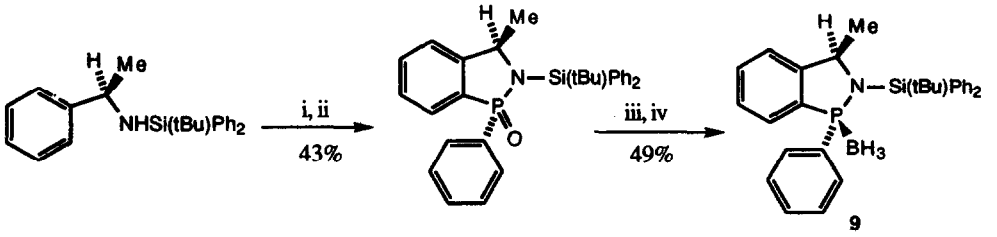
reversed. Since either amine would have been expected to give a common bidentate ligand, the stereochemical outcome should also be the same.

Table Conversion of **7** into **8** by palladium catalysed allylic substitution.

Ligand	X [1]	Y	Deboration method [2]	Time [3]	Yield	R/S	Enantiomeric Excess
1	4	10	M	50 min.	86%	R	60%
2	4	10	M	3 hr	35%	S	33%
1	4	10	D	2 hr	99%	S	62%
3	4	20	M	o/n	56%	S	91.5%
3	4	20	D	o/n	31%	S	89%
3	1	5	M	48 hr	85%	S	66%
3	1	5	M	o/n	84%	S	84% [4]
3	1	5	D	o/n	56%	S	85% [4]

[1] X refers to mol% Pd, i.e. if X=4, 2 mol% of $[(C_3H_5)PdCl]_2$ was used.
[2] M=morpholine, D=DABCO. [3] Time required for full consumption of **7** by tlc.
[4] = No freeze/thaw cycle used in preparation of catalyst.

A possible explanation for this observation was that a small amount of excess DABCO carried through from the deboration reaction was replacing the amine part of the ligand in the complex, which was therefore acting as a *monodentate* phosphorus ligand. Since this suggested that the heterocyclic part of the catalyst could act as an effective ligand in its own right we prepared the N-*t*-butyldiphenylsilyl protected heterocycle **9** as a single diastereoisomer by the route shown in Scheme 3, which we have previously reported.[13] The *trans*- stereochemistry in **9** was confirmed by a single crystal X-ray structure analysis[10] and this represents a correction to our previously reported assignment.[13] The use of **9** in the model reaction resulted in the formation of **8** in much higher enantiomeric excess than had been achieved using either **1** or **2**. In both cases S-(-)-**8** was formed in excess, which matched the result when **1** was used as a ligand following DABCO deboration.



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Scheme 3 Reagents: i) 2.2 eq. nBuLi, 1.1 eq. TMEDA, Et_2O, rt, 16 hr, ii) $PhP(O)Cl_2$, -78°C, 1hr; rt, 1.5 hr, iii) 6 eq. Et_3N, 5 eq. $HSiCl_3$, toluene, 70°C, 3 hr, iv) 7 eq. $BH_3.SMe_2$, rt, 16 hr.

The yields in the above cases were low due to the formation of a significant amount of 1,3-diphenylpropene, which presumably arises due to reduction of the allyl palladium complex by residual amine/borane complex.[7] The yields could be improved significantly without loss of asymmetric induction by lowering the amount of ligand and palladium source to 5 and 1 mol% respectively (Table). To our

surprise we found that the fastest reaction rates and highest e.e.s were achieved at the lower levels of ligand if the freeze-thaw cycles were omitted.

In conclusion, we have reported three new ligands which have application to the asymmetric catalysis of palladium catalysed allylation reactions. Most significant of these is **3**, which to our knowledge generates the highest reported asymmetric induction for a monodentate ligand in the model reaction studied.

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6) Use of a similar ligand in Ni chemistry: G. Wilke, *Angew. Chem., Int. Edn. Engl.*, **1988**, *27*, 566.

7) H. Brisset, Y. Gourdel, P. Pellon and M. LeCorre, *Tetrahedron Lett.*, **1993**, *34*, 4523. Conditions: excess morpholine, 70°C, 2hrs, excess removed under vacuum or DABCO 1 (with **9**) or 2 (with **5** and **6**) equivalents, toluene, 40°C, 2 hrs. Small amounts of amine-borane complex will inevitably by transferred into the palladium catalysed reaction however at the lower level (5 mol%) of catalyst they do not appear to cause any appreciably side-reactions such as allylic reduction.

8) Diamine **4** was prepared from the reaction between R-(+)-α-methyl benzylamine and bromo acetyl bromide, followed by addition of pyrrolidine and reduction with lithium aluminium hydride.

9) D. Barr, R. Snaith, D. S. Wright, R. E. Mulvey, K. Jeffrey and D. Reed, *J. Organomet. Chem.*, **1987**, *325*, C1.

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11) In order to prove that no epimerisation at the phosphorus atom was taking place a sample of **5** was deborated using morpholine under the standard conditions, recooled to r.t. and treated with excess borane-dimethylsulphide complex. Pure **5** was recovered, uncontaminated by its diastereoisomer **6**.

12) B. M. Trost and D. J. Murphy, *Organometallics*, **1985**, *4*, 1143. Preliminary experiments in our group showed this method to be superior to the use of the sodio-anion.

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