Synthesis and applications of a new class of phosphorus donor ligands for asymmetric catalysis

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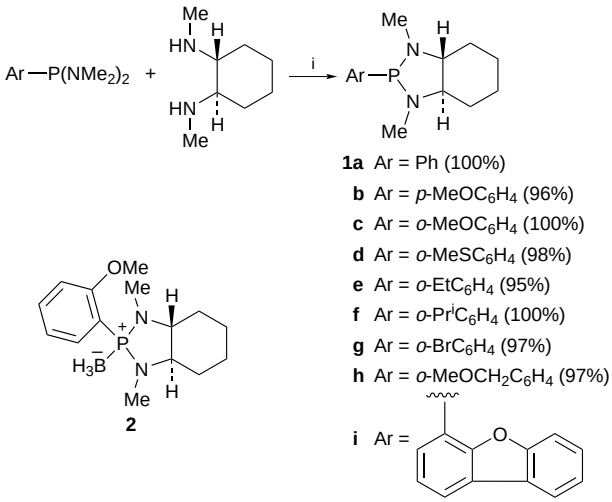
The synthesis and applications to allylic substitutions of a range of novel ligands based on diazaphospholidines is described; enantiomeric excesses of up to 89% were achieved in an allylic substitution reaction.

Recent years have seen dramatic developments in asymmetric catalysis.[1] Allylic substitution reactions in particular have been the subject of attention from a number of research groups and several excellent ligands have been developed for this particular application.[2] Of these, diphosphines and combined phosphine–amine donors have proven to be especially well suited to the required role.[2] As part of an ongoing programme[3] directed at the development of a range of phosphorus donor ligands with a wide range of applications to asymmetric synthesis, we wished to investigate diazaphospholidines **1** in this capacity. We anticipated that such ligands would benefit from a high level of conformational rigidity and would project a suitable chiral environment within organometallic complexes of which they may form a part. Furthermore we were aware of the facile synthesis of such materials from the corresponding C_2 symmetric chiral diamines.[4] Although similar compounds have been reported to act as effective chiral shift reagents, we were unaware of any catalytic asymmetric transformations to which they had been applied.[5]

The preparation of a series of ligands was achieved following literature precedents (Scheme 1).[4] The bis(dimethylamino)phosphine precursors to **1a**, **1b**, **1c**, **1e**, **1h** and **1i** were formed by the reaction of the corresponding lithiated aromatic compound with preformed $(Me_2N)_2PCl$. The corresponding precursors for **1d** and **1f** could not be prepared by this method. However lithiation and transmetallation with zinc dichloride, followed by reaction with phosphorus tirchloride and subsequently treatment with an excess of dimethylamine furnished the required intermediates. The precursor to compound **1g** was synthesised following the published procedure of Drewelies and Latscha.[6] Each intermediate bis(dimethylamino)phosphine was heated under reflux with (*R*,*R*)-*N*,*N*′-dimethyl-1,2-diaminocyclohexane until no further dimethylamine could be detected in the nitrogen stream from the reaction. At this point solvent removal provided the pure ligands **1**. Although always handled under an inert atmosphere when in solution, each of the ligands proved to be resistant to atmospheric oxidation when in solid form. Treatment of **1c** with $BH_3{\cdot}SMe_2$ complex resulted in formation of a highly stable borane complex **2** which could be purified by chromatography. We have in previous work demonstrated that related borane complexes could be used as a source of protected ligand[3] (borane may be removed by an amine), however in the case of **2** all attempts to remove the borane resulted in decomposition.

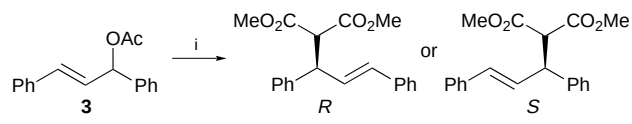


Scheme 1 *Reagents and conditions*: i, PhMe, heat, 8–24 h

We have applied the series of ligands thus produced to a number of asymmetric transformations. In particular the ligands appear to be particularly well disposed to the nucleophilic allylic substitution reaction of 1,3-diphenyl-3-acetoxyprop-1-ene **3**. In most cases the substitution reaction with dimethyl malonate (Scheme 2) gave good yields and, in the best cases, excellent asymmetric inductions (Table 1). A number of interesting trends become apparent upon analysis of the results. In particular a general improvement and reversal of selectivity is observed upon introduction of an *ortho* substituent. The level of electron density in the aromatic ring does not appear to influence the selectivity to any great extent (compare ligands **1a** and **1b**). Although the best results, 89 and 78% ee in favour of the *R* enantiomer, were achieved using the ligands **1c** and **1d**, the same product enantiomer was obtained using ligands which do not contain coordinating groups (*i.e.* **1e** and **1f**). This suggests that all may share a common mode for directing the asymmetric transformation. The importance of the size of the *ortho* substituent is also difficult to gauge since the ethyl and isopropyl substituted ligands **1e** and **1f** gave similar selectivities. We were unable to prepare the corresponding *tert*-butyl-substituted reagent.

At present there is insufficient evidence to determine the exact means by which asymmetric induction by the ligand is achieved. It would appear that whilst the introduction of an *ortho* substituent in the ligand is crucial to their success, the observation of similar results from coordinating and non-coordinating groups suggests that the ligand is probably only appended to the palladium through the phosphorus atom. If this is the case then their mechanism of action may have a parallel with the phosphine ligand MOP, which has been demonstrated to be effective for this application through the formation of a 1 : 1 phosphine–metal complex.[7]

Of significance is the *pseudo*-C_2 symmetry of the ligand and potential participation of a conformational rigidity conferred to



Scheme 2 *Reagents and conditions*: i, **1a–i**, $[Pd(\eta\text{-}C_3H_5)Cl]_2$, dimethyl malonate, $(Me_3Si)N{:}CMe(OSiMe_3)$, NaOAc, CH_2Cl_2

Table 1 Asymmetric addition of dimethyl malonate to **3** catalysed by **1a–i**

Ligand	Pd (mol%)	Ligand (mol%)	*t*/h	Yield (%)	ee (%)[a] (config.)
1a	10	20	16	97	28 (*S*)
1b	10	20	16	71	23 (*S*)
1c	10	20	16	97	89 (*R*)
1c	10	10	20	89	83 (*R*)
1c	5	10	12	85	85 (*R*)
1c	2	4	20	94	82 (*R*)
1d	10	20	24	90	78 (*R*)
1e	10	20	16	84	59 (*R*)
1f	10	20	16	91	56 (*R*)
1g	10	20	24	85	66 (*R*)
1h	10	20	24	84	51 (*R*)
1i	10	20	20	92	35 (*R*)

[a] Enantiomeric excess determined by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as a chiral shift reagent.

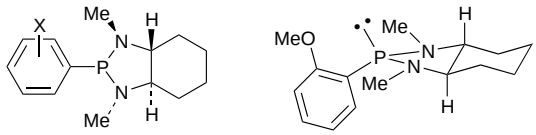
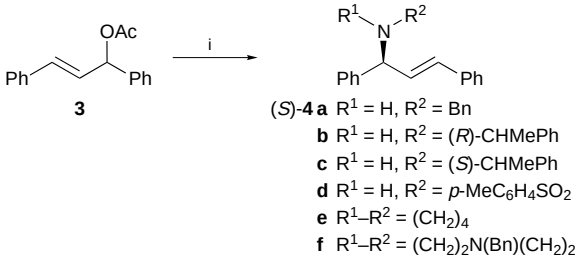


Fig. 1



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(*S*)-**4a** R^1 = H, R^2 = Bn
b R^1 = H, R^2 = (*R*)-CHMePh
c R^1 = H, R^2 = (*S*)-CHMePh
d R^1 = H, R^2 = *p*-MeC$_6$H$_4$SO$_2$
e R^1–R^2 = (CH$_2$)$_4$
f R^1–R^2 = (CH$_2$)$_2$N(Bn)(CH$_2$)$_2$

Scheme 3 *Reagents and conditions*: i, **1c**, [Pd(η-C$_3$H$_5$)Cl]$_2$, R^{1}R^{2}NH, NaOAc, THF or CH$_2$Cl$_2$

the nitrogen methyl groups by the adjacent chiral centre. Studies by others,[4,8] and our own X-ray crystal structure of the borane complex **2**[9] indicate that the nitrogen atoms are partially tetrahedral, the result of the methyl groups avoiding eclipsing interactions with the adjacent C–C bonds (Fig. 1). The X-ray crystal structure also reveals that the *ortho* substituent favours a position away from the heterocyclic ring (Fig. 1). This suggests that steric interactions may prevent a 180° rotation about the P–C(aryl) bond. This proposition is supported by our observation that 2,6-disubstituted aromatic ring diazaphospholidines failed to be formed using our general method (Scheme 1). If this conformational preference is maintained in the palladium complex then clearly this *ortho* group may be projected into the region of the appended allylic group, and thus provide a means to influence the reaction selectivity. Precisely how this effect is transferred to the asymmetric reaction, however, is at present unclear.

In an attempt to increase the observed selectivity we attempted some studies of diazaphospholidines bearing larger groups on the nitrogen atoms. The dibenzyl derivative of **1c** gave a product of 64% ee in 78% yield for the reaction depicted in Scheme 2. The diisopropyl ligand failed to form using our standard procedure, possibly due to steric hindrance.

Having identified **1c** as the best of the series of ligands, we have examined the use of nitrogen nucleophiles in the substitution reaction (Scheme 3, Table 2). The results obtained using benzylamine and sodium toluene-*p*-sulfonamide compared favourably to those previously reported using other ligands,[2,10] but were significantly lower (although in the same sense) than the selectivity achieved using dimethyl malonate as nucleophile. The presence of a chiral centre in the nucleophile

Table 2 Asymmetric addition of nitrogen nucleophiles catalysed by **1c**

Product	Solvent	*t*/h	Yield (%)	ee[a] (%) (config.)
4a	CH_2Cl_2	42	68	78 (*S*)
4a	THF	20	49	73 (*S*)
4a	THF	5	77	68 (*S*)
4b	CH_2Cl_2	168	67	78 (*S*)
4b	THF	8	51	61 (*S*)
4c	THF	8	67	61 (*S*)
4d	CH_2Cl_2	64	45	76 (*S*)
4e	CH_2Cl_2	41	48	68 (*S*)
4f	CH_2Cl_2	16	63	58 (*S*)

[a] Enantiomeric excess determined by chiral HPLC using a chiralcel OD column.

(α-methylbenzylamine of either configuration) appeared to have no effect on the enantioselectivity of the reaction or the sense of induction. Use of the cyclic amines pyrrolidine and *N*-benzylpiperazine as nucleophiles resulted in the formation of novel allylic amines **4e** and **4f** respectively, in excellent yields but reduced enantioselectivities.

In conclusion a novel class of diazaphospholidine ligands has been synthesised and their application to palladium-catalysed allylic substitution has been demonstrated. Ongoing work is directed towards the synthesis of improved ligands based on this class for a variety of transition metal-catalysed asymmetric transformations.

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Footnote

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