Hybrid P-chiral diphosphines for asymmetric hydrogenation

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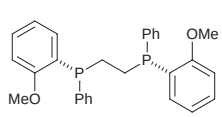
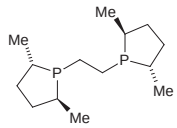
A family of diphosphine ligands has been prepared by Michael addition of *o*-anisylphenyl phosphide to diethyl vinylphosphonate and elaboration to phospholanes based on hexane-2,5-diol or mannitol; some preliminary results of Rh-complex catalysed hydrogenations are reported.

The scope of asymmetric hydrogenation of alkenes has been gradually extended both in reactant structure and catalyst efficiency over many years.[1] For rhodium catalysis, the early work of the Monsanto group using the P-chiral diphosphine DIPAMP has provided an enduring standard.[2] Only phospholane ligands in the DUPHOS and BPE series have exhibited superior enantioselectivity over a broad front.[3]



1 (*R*,*R*)-DIPAMP

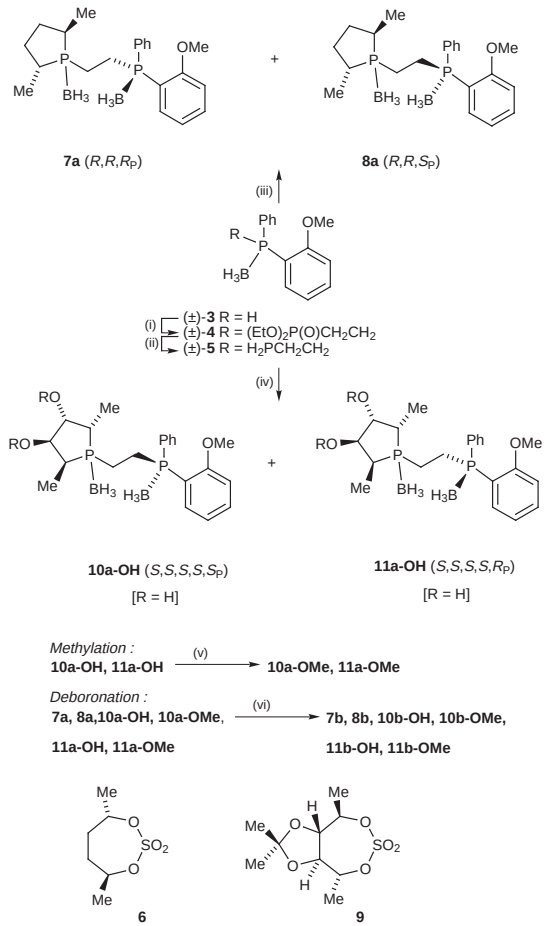


2 (*S*,*S*)-MeBPE

It is a commonly held belief that C_2 symmetric diphosphine (or diol or diamine) ligands are endowed with superior properties in catalysis, their attractiveness augmented by ease of synthesis.[4] An alternative view, stated most clearly by Achiwa and co-workers,[5] is that intermediates in a catalytic cycle lack the intrinsic symmetry of the ligand and consequently the two chelating atoms must fulfil different roles. The implication is that lack of symmetry may be a positive advantage in an appropriate case. In previous work we have endeavoured to separate the functions of the two chelating phosphorus atoms in asymmetric hydrogenation.[6] The synthesis of a new class of unsymmetrical ligands permits that approach to be extended further.

Our basic idea was to combine the phosphorus moieties of DIPAMP **1** and BPE **2** in a single ligand. The synthesis is based on conjugate addition of racemic phosphineborane **3**[7] to diethyl vinylphosphonate (Scheme 1).[8] Alane reduction of the product **4** gave the primary phosphineborane **5**. Following deboronation, stepwise double nucleophilic displacement on the cyclic sulfate **6**[9] *via* BuLi deprotonation permitted synthesis of the target compounds **7a** and **8a** as a diastereomeric mixture in good yield. These were separated by MPLC, with some difficulty (EtOAc–pentane). The analogous compounds **10a-OH** and **11a-OH**, prepared from the mannitol derivative **9**,[10] proved much more amenable to chromatographic separation, and subsequently afforded the pure methyl ethers **10a-OMe** and **11a-OMe**.[11] The absolute configuration of product boranes was established by CD in comparison with that of the diborane from *(S,S)*-DIPAMP, the phospholane part being essentially CD transparent in the 240-400 nm region. This set of procedures gives access to a family of unsymmetrical 1,2-phosphinoethane ligands as their stable diborane complexes.[12]

In most cases hydrogenation experiments were carried out by *in situ* deboronation[13] and reaction with $(COD)_2RhBF_4$ to generate the catalyst. In initial studies of the hydrogenation of simple dehydroamino acids and esters, two questions were posed: Is the enantioselectivity governed predominantly by one of the two phosphorus nuclei in the ligand? Does the alternative

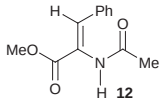
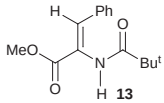
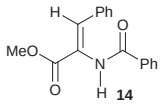


Scheme 1 *Reagents*: (i) CH_2=CHP(O)$(OEt)_2$, KOBu^t, THF, 95%; (ii) DABCO, C_7H_8; AlH_3, Et_2O; H_2O then CaH_2; (iii) BuLi, THF, −78 °C then **6** then further BuLi; Me_2S•BH_3, 45% overall; (iv) BuLi, −78 °C then **9**; then repeat; Me_2S•BH_3, 30% isolated overall for (ii), (iv); (v) NaH, MeI, THF, ⩾80%; (vi) HBF_4•OMe_2 then $NaHCO_3$.

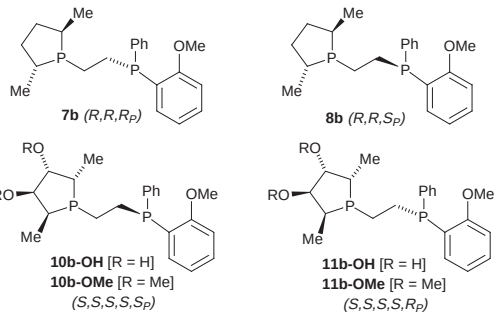
match or mismatch of arylphosphine and phospholane chirality have a significant effect on enantioselectivity? The results recorded in Table 1 provide answers to these points but also some surprises. A broad conclusion from these and parallel results is that the 'matched' ligand[14] gives significantly higher ees than the 'mismatched' ligand, and also that the phospholane configuration is dominant in defining the stereochemical course of hydrogenation, but to an extent that depends on the substrate. In the case of the bulkier pivalamide **13** and benzamide **14**, the configuration of the arylphosphine part plays a very minor role. In comparison to the mannitol derived ligands **11**, the simple phospholanes **7b** and **8b** gave significantly inferior results in these and related cases and were thus investigated in less detail.

Further results of interest came from a study of the itaconate esters and half-esters recorded in Table 2. Here the mismatched diastereomers of ligand **10b** gave poor ees and are not included. For the 1-substituted monoester **15**, the hydroxy ligand **11b-OH** gives a superior ee to its methyl ether. The reverse is true for the 3-substituted monoester **16**, where the methyl ether **11b-OMe**

Table 1

Substrate	Catalyst precursor	Ee (%)
 **12**	**10b-OMe**	19 *S*
	11b-OMe	85 *S*
	10b-OH	43 *S*
	11b-OH	**92** *S*
	7b	38 *S*
	8b	60 *R*
 **13**	**10b-OMe**	58 *S*
	11b-OMe	67 *S*
	10b-OH	82 *S*
	11b-OH	**88** *S*
	7b	5 *R*
	8b	36 *R*
 **14**	**11b-OMe**	77 *S*
	10b-OH	72 *S*
	11b-OH	**90** *S*[a]

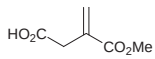
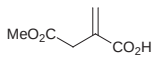
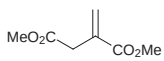
Conditions: substrate : catalyst 100 : 1, $(COD)_2RhBF_4$ as precursor ($HBF_4{\cdot}OMe_2$ deboronation *in situ*), 1.3 bar, MeOH, 1–3 h. [a] TfO^- instead of BF_4^-.



provides the product of higher enantioselectivity. Changing the solvent from MeOH to CH_2Cl_2 led to inferior rates and selectivities in both these cases.

These preliminary results indicate that, contrary to expectation, the enantioselectivity is sensitive to remote oxygen substituents in the phospholane ring. Inspection of molecular models indicates that the MeO- or HO- groups are axial in the 5-membered ring of the phospholane, and in the vicinity of substituents on the coordinated alkene. Hence the opportunity exists for cooperative association through H-bonding between ligand and coordinated reactant.[15] The combination of good enantioselectivities in simple unoptimised reactions make this an attractive series of ligands for further investigation with the potential for rational structural alteration, and the impetus of additional synthetic power and mechanistic information arising from the distinct role of the two ligating atoms. The results nicely complement those of Börner and co-workers on asymmetric hydrogenation with mannitol-derived diphospholanes.[16]

Table 2

Substrate	Catalyst precursor	Ee (%)
 **15**	**11b-OMe**	85 *R*
	11b-OH	**95** *R*
 **16**	**11b-OMe**	**93** *R*[a]
	11b-OH	87 *R*
 **17**	**11b-OMe**	**85** *R*
	11b-OH	80 *R*[a]

Conditions: substrate : catalyst 100 : 1, $(COD)_2RhBF_4$ as precursor, ($HBF_4{\cdot}OMe_2$ deboronation *in situ*), 1.3 bar, MeOH, 1–3 h. [a] 94% ee for **16** with TfO^- instead of BF_4^-.

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Notes and references

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8 *C.f.* K. Bourumeau, A.-C. Gaumont and J.-M. Denis, *Tetrahedron Lett.*, 1997, **38**, 1923.

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10 In 90% yield from the corresponding diol, L. F. Wiggins and D. J. C. Wood, *J. Chem. Soc*., 1950, 1566; Y. Le Merrer, A Dureeault, C. Greck, D. Micas-Languin, G. Gravier and J. C. Depezay, *Heterocycles*, 1983, **25**, 541.

11 The absolute configuration of all product boranes was established by CD in comparison with that of the diborane from (*S,S*)-DIPAMP, the phospholane part being essentially CD transparent in the 240–400 nm region. We warmly thank Dr Guiliano Siligardi, KCL, for this data.

12 Full details of the synthesis will be published separately; D. Carmichael and J. M. Brown *Tetrahedron: Asymmetry*, in preparation.

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14 (*R,R*)-DIPAMP (ref. 2) and the (*S,S*)-phospholane MeBPE (ref. 8) both give *S*-amino acids on Rh asymmetric hydrogenation, hence **8b** and **11b** constitute the configurationally matched ligands and **7b**, **10b** the mismatched ligands.

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