A Novel Enantioselective Access to Enantiomerically Pure Phospholanes Using the Chiral Lithium Amide Base Approach

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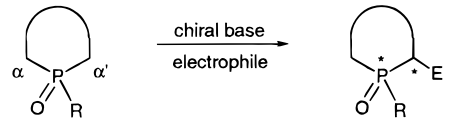
Introduction

Enantiomerically pure phosphines are without doubt the most powerful and versatile ligands for use in asymmetric catalysis involving transition metals.[1] The C_2-symmetric bis-phosphines, such as BINAP and DuPHOS, have been most widely applied,[2] although unsymmetric chiral phosphines, usually incorporating additional metal-coordinating groups, have also been shown to have important applications, Hayashi's ferrocene derivatives being prime examples.[3] Although many chiral phosphines and bis-phosphines have been prepared, there remains a need for novel and easily accessible examples, with the potential for structural fine-tuning, which may give improved results in processes that at present give only modest selectivities.[4]

We became interested in the development of a novel access to chiral phosphines, incorporating an alicyclic backbone (*cf.* the phospholane unit of DuPHOS), involving a symmetry-breaking chiral base reaction, exemplified in its simplest form by the conversion of **1** into **2**.[5,6]



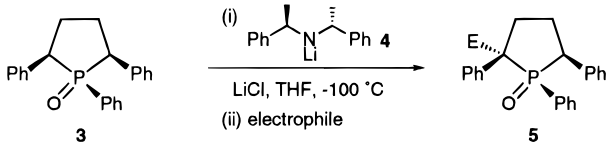
1 **2**

As in the analogous reactions of cyclic sulfoxides,[7] kinetically controlled discrimination between the two acidic sites (α and α′) should result in a chiral metalated intermediate, which on electrophilic quenching would give a phosphine oxide product having at least two asymmetric centers. Bearing in mind structural features that might be desirable in the final chiral phosphine, we realized this plan using the readily available 1,2,5-triphenylphospholane oxide (**3**),[8] by reaction with the chiral base **4** in THF at −100 °C, Table 1.

Table 1. Enantioselective Deprotonation of Phosphine Oxide 3

electrophile	product	yield (%)	ee[a] (%)	$[\alpha]_D$[b]
MeI	5a	87	85	36
EtI	5b	89	90	55
BnBr	5c	62	*c*	117
allylBr	5d	72	87	92
MeCOMe	5e	85	87	100
PhCHO	5f	82[d]	92[e]	97
cyclohex-CHO	5g	74	82[f]	
$PhSSO_2Ph$	5h	60	82	100

[a] Measured by HPLC using a Chiralcel OD column, with 30% ^{i}PrOH in hexane as eluant (1 mL/min) and UV detection at 256 nm. [b] All positive in sign, measured in $CHCl_3$ (c = *ca.* 0.8−1.1). [c] The ee could not be determined by HPLC. [d] Yield of 7:1 mixture of diastereomers. [e] The ee shown is for the major diastereomer. [f] Determined using the inseparable 1:1 mixture of diastereomers ($[\alpha]_D$ values not measured for this mixture).



3 **5**

As can be seen, useful levels of asymmetric induction of around 90% ee were achieved, it being possible to further enrich several of the products to at least 97% ee by simple recrystallization.[9]

Limited literature precedent suggested that the relative configuration of the alkylated phosphine oxides should be as shown for **5**.[10,11] Using enriched samples, X-ray crystallography allowed both the relative and absolute configurations to be assigned for **5e** and for the major adduct **5f** from reaction with PhCHO (as shown);[12] the other products are assumed to belong to the same diastereo- and enantiomeric series. Evidence that the anion alkylations had indeed occurred in the same diastereomeric sense as the carbonyl addition reactions (i.e., *syn* to the P═O bond) was obtained from NOE studies of **5a**, **5b**, and **5d** (see structure).

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(1) For recent reviews, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994. (b) *Advanced Asymmetric Synthesis*; Stephenson, R., Ed.; Blackie Academic and Professional: London, 1996. (c) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers Inc.: New York, 1993. For more complete listings, see the bibliographies in ref 4a−d.

(2) BINAP: Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. DuPHOS: Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.

(3) See, for example: Hayashi, T.; Ohno, A.; Lu, S.; Matsumoto, Y.; Fukuyo, E.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 4221 and previous papers in the series.

(4) For recent examples of C_2-symmetric bis-phosphine syntheses, see: (a) Longmire, J. M.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 1725. (b) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799. (c) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. See also: (d) Langer, F.; Püntener, K.; Stürmer, R.; Knochel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 715.

(5) (a) The enantioselective deprotonation of phosphine−boranes, using ^{s}BuLi−sparteine, has been described; see: Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075. (b) Chiral lithium amides have been shown to be ineffective with acyclic phosphine oxides; see: O'Brien, P.; Warren, S. *Synlett* **1996**, 579.

(6) Complementary studies of enantioselective *protonation* of metalated phosphine oxides have appeared; see: (a) Vedejs, E.; Garcia-Rivas, J. A. *J. Org. Chem.* **1994**, *59*, 6517. (b) Guillen, F.; Moinet, C.; Fiaud, J-C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 371 (this report concerns the phospholane system employed in our work). See also ref 5b.

(7) (a) Armer, R.; Begley, M. J.; Cox, P. J.; Persad, A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3099. (b) Blake, A. J.; Westaway, S. M.; Simpkins, N. S. *Synlett* **1997**, 919.

(8) Fiaud, J-C.; Legros, J-Y. *Tetrahedron Lett.* **1991**, *32*, 5089.

(9) Recrystallization: **5a** from MeOH-H_2O (×3), ≥99% ee, 30% recovery (or from EtOH-H_2O 96% ee, 69% recovery); **5d** from EtOAc, ≥99% ee, 59% recovery; **5e** from EtOH-H_2O, 97% ee, 69% recovery; **5h** from EtOH-H_2O, ≥99% ee, 40% recovery.

(10) (a) Marinetti, A.; Kruger, V.; Le Menn, C.; Ricard, L. *J. Organomet. Chem.* **1996**, *522*, 223 and references therein. For related results involving phospholanic acid derivatives, see: (b) Polniaszek, R. P. *J. Org. Chem.* **1992**, *57*, 5189. In some cases the stereochemical outcome seems not to have been assigned; see: Mathey, F.; Muller, G.; Bonnard, H. *Bull. Soc. Chim. Fr.* **1972**, 4021.

(11) The intermediate lithiated phosphine oxide would be expected to be configurationally unstable, on the basis of previous studies; see O'Brien, P.; Warren, S. *Tetrahedron Lett.* **1995**, *36*, 8473. Our results can be interpreted as a highly diastereoselective electrophilic quench of the intermediate, leading to substitution with overall retention. Only in the case of anion protonation have we seen substitution with inversion, in accord with the observations of Fiaud and co-workers (see ref 5b).

(12) The absolute configurations for **5e** and **5f** were established by the collection of low-temperature data, including Friedel equivalents, and by refinement of a Flack parameter (values 0.05(8) and 0.0(3), respectively); see: Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876. We thank Drs. W-S. Li and A. J. Blake of this department for these determinations; full details will be published elsewhere.

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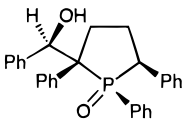
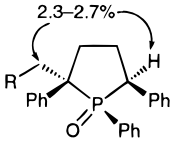
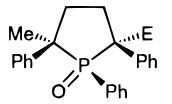


5f

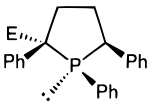


5a, **5b** and **5d**

In order to allow access to additional types of product, especially those having a functional group "handle", we briefly examined further metalation−electrophilic quench sequences using enantiomerically pure **5a** as the starting material. For example, reaction with ^{n}BuLi in THF, followed by addition of either PhCHO or Ac_2O, gave **6a** and **6b** in 87% and 53% yields, respectively.[13]



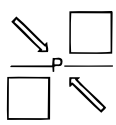
6a E = CH(OH)Ph
6b E = COMe



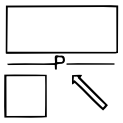
7a E = Me (80%)
7b E = Et (70%)
7c E = SPh (67%)

Finally, we have shown that reduction of such phosphine oxides can be carried out employing a mixture of Cl_3SiH and pyridine,[14] for example, to give **7a**−**c** in the yields indicated.[15]

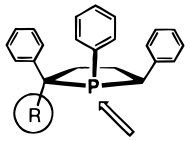
Many recent syntheses of phosphines and bis-phosphines have focused on the C_2-symmetry element as a key design feature,[16] *cf.* **8**, in which access to the reactive center is possible via two equivalent open quadrants.



8



9



10

Although these systems have been very successful, the requirement for C_2-symmetry poses quite a serious limitation on the structures available. We considered that a design in which one of the quadrants is closed to give a situation such as **9** where only one carefully tailored "open site" is available may offer some advantages, particularly with respect to steric fine-tuning. The product phosphines available from our new chiral base chemistry, described above, appear to conform to this design, as indicated by **10**, and give substantial flexibility in the choice of R. The ability to prepare simple phosphines and bifunctional systems, of either absolute configuration, starting with a readily available phospholane is clearly attractive. Further studies of the asymmetric deprotonation, along with application of the product ligands in asymmetric catalysis, are ongoing.

Acknowledgment. We thank the EPSRC for a studentship in support of S.C.H. and for the provision of a four-circle diffractometer.

Supporting Information Available: Selected data for **5a**,**c**−**f**,**h** and **6b**, including HPLC determination of ee and a typical experimental procedure (23 pages).

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(13) Compound **6a** was formed as a 15:1 mixture of diastereomers at the new carbinol center.

(14) Naumann, L.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012.

(15) At present we have not proved that the phosphine oxide reduction has occurred with retention of configuration.

(16) For a review of C_2-symmetry and asymmetric induction, see: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.