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Synthesis of Achiral and Homochiral Dibenzo[*b,f*]phosphepin 5-Oxides Using Bromine/Lithium Exchange. X-Ray Structure of (10*R*, 11*R*)-10,11-Dihydroxy-10,11-dihydro-5-phenyl-5H-dibenzo[*b,f*]phosphepin 5-Oxide

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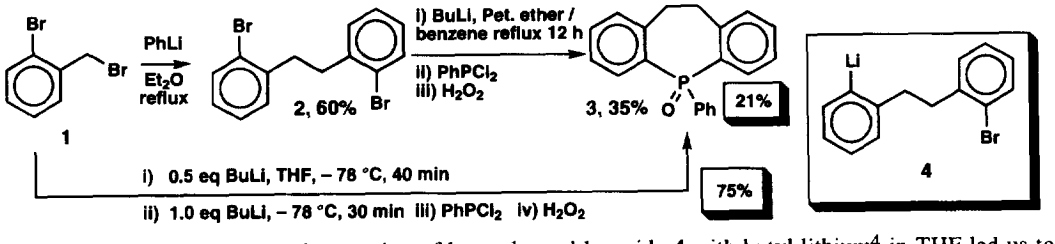
Abstract: An improved synthesis of 5-phenyldibenzo[*b,f*]phosphepin 5-oxide by a seven step one-pot procedure and the synthesis of enantiomerically pure 5-phenyl- and 5-propyldibenzo[*b,f*]phosphepin 5-oxides by use of McMurry coupling, Sharpless dihydroxylation and a bromine-lithium exchange strategy is described. Copyright © 1996 Elsevier Science Ltd

We recently described the synthesis of homochiral dibenzo[*b,f*]phosphepin-5-oxides[1] such as **6** and **7** by a route that included a McMurry coupling, Sharpless osmylation and double *ortho*-lithiation. We report here a wide range of phosphepins synthesised by a similar route but using bromine-lithium exchange instead of *ortho*-lithiation and the X-ray crystal structure of one of them. We also report the synthesis of achiral phosphepins using a seven step synthesis in one pot which includes three successive lithiation reactions.

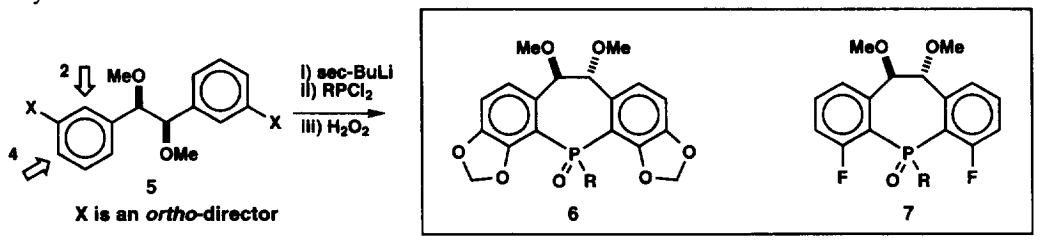
Achiral Phosphepins – We have developed an improved synthesis of the achiral phosphepin **3**. It had previously been prepared by Granoth *et al.* in a 35% yield,[2] from the dibromobibenzyl precursor **2** which in turn was synthesised in a 60% yield[3] from **1**. We reasoned that side products in the first lithiation, such as **4**, which would be quenched and purified away when **2** is isolated, could be intermediates in the subsequent lithiation of **2**. Hence telescoping the two lithiations into one pot could enhance the yield.



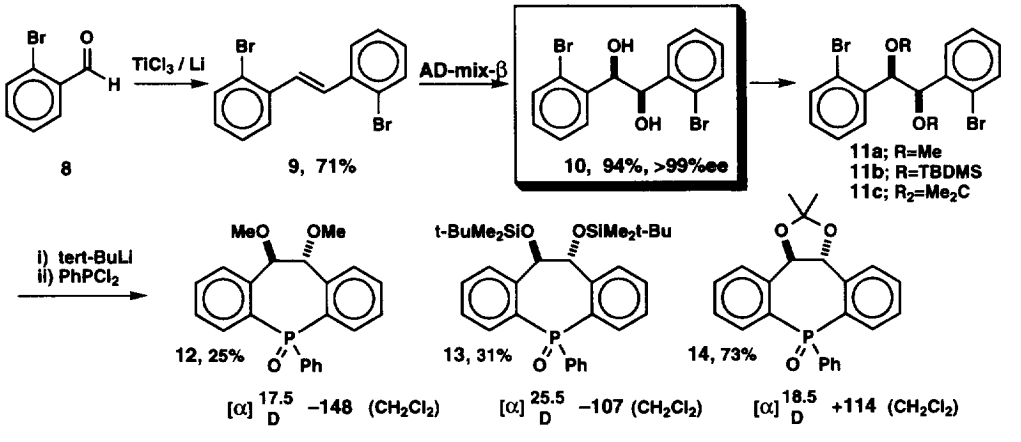
Parham's observations on the reaction of bromobenzyl bromide **4** with butyl lithium[4] in THF led us to believe that the reaction conditions might also be modernised and Granoth's boiling benzene replaced with THF at –78 °C. The resulting dilithiated species was reacted with $PhPCl_2$ to form the phosphepin which, without isolation, was oxidised to **3** with H_2O_2. These improvements worked and phosphepin oxide **3** was synthesised from **1** in 75% yield in a one pot process formally involving seven steps (three lithiations, three nucleophilic displacements and an oxidation). This contrasts with an overall yield of 21% from **1** using Granoth's preparation. Attempts to improve the yield further by using $PhPOCl_2$ as the electrophile were not successful. The same procedure using $PrPCl_2$ instead of $PhPCl_2$ yielded 66% of the *P*-propyl phosphepin.

Chiral Phosphepins – Phenyl derivatives

The synthesis of phosphepin oxides **6** and **7** utilised the acetal oxygen atoms or fluorine atoms respectively to direct an *ortho*-lithiation so that a phosphorus atom might be introduced and ring closure effected. These lithiations required, in addition to such powerful *ortho* activating groups, a benzylic oxygen atom to control the regioselectivity (position 2 rather than 4).[5] Lithiation achieved by bromine-lithium exchange allows for the synthesis of phosphepins without potent *ortho*-directors and without constraint on the benzylic substituent.



The syntheses of compounds **12-14** started with 2-bromobenzaldehyde **8**. Two molecules were coupled to give **9** by McMurry coupling. The conditions of the coupling involve refluxing DME at 85 °C which contains, in addition to low valent titanium, excess lithium metal. Such conditions might appear to be incompatible with an aromatic bromide which might be lithiated. McMurry does state that organohalides are not reduced with low-valent titanium.[6] Indeed, we isolated dibromostilbene in a yield of 71% after a shortened reaction time (6 hours) but found that the full reaction time[7] (18 hours) led to extensive debromination and a yield of only 44%. Sharpless osmylation converted the dibromostilbene **9** to the corresponding diol **10** in high yield and excellent enantiomeric excess.



The diol **10** represents the nexus of the various syntheses because different protecting groups on this diol will lead to different phosphepins. We tried a variety of protecting groups. The dimethyl ether **11a** is readily made by the action of NaH followed by MeI. We found TBDMS triflate to be an excellent reagent for protection of the secondary alcohol, giving **11b** in good yield.[8] And the formation of acetal **11c** was effected using catalytic TsOH and excess dimethoxypropane in excellent yield (98%). It was not necessary to remove the methanol by-product to drive the reaction to completion.

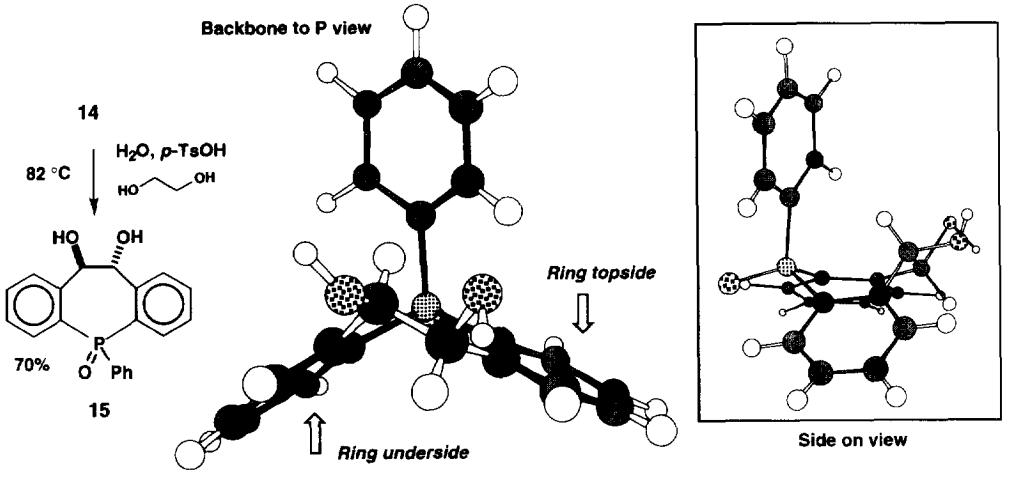
Although n-BuLi is well known as a reagent for the lithiation of aromatic bromides,[9] we found it unsuitable for our phosphepin precursors **11a-c**. The precursors were not lithiated smoothly and attempts to probe the lithiation of **11a** with methyl iodide demonstrated that although some of the dilithiated species was produced, so were numerous other products. This result is in contrast to the reaction of benzylically unsubstituted analogue **2** which lithiates very cleanly under similar reaction conditions.

We found *tert*-BuLi to be far superior to n-BuLi for our application. Using 4.1 equivalents[10] of *tert*-BuLi and quenching with MeI we found 96% of **11a** had been lithiated. However, phosphepin **14** was synthesised in its highest yield (73%) using only 2.4 equivalents of *tert*-BuLi in THF whereas the best conditions for **13** (31%) were 2.3 equivalents in Et_2O and for **12** (25%) were 4.1 equivalents in Et_2O. Phosphepins **12-14** have the same aromatic substitution and different backbone substituents whereas the reverse is true for **6** and **7**.

*X-Ray of (10*R*, 11*R*)-10,11-Dihydroxy-10,11-dihydro-5-phenyl-5H-dibenzo*[b,f]*phosphepin 5-Oxide*

The acetal function of phosphepin **14** was hydrolysed in aqueous ethylene glycol to yield the diol **15** which was crystallised from chloroform and the structure determined by X-ray. We can view the twisted relationship between the two benzene rings fused to the seven membered ring as being composed of two features. Firstly the rings are bent, from an imaginary plane, into a 'butterfly' arrangement. Secondly they are twisted relative to one another about another axis – inspection of the structure shows that we see the *underside* of the left ring but the *top* side of the right ring.

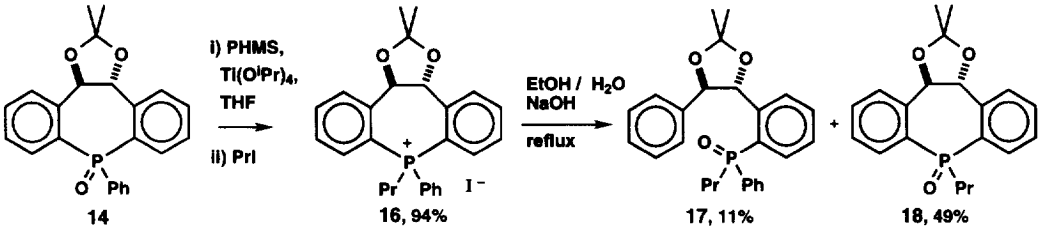
The side-on view from one benzene ring to the other (box) clearly shows that the *exo*-cyclic phenyl group is in a pseudoaxial position and that the two benzylic protons are antiperiplanar to one another. There is no evidence for any hydrogen bonding The seven membered ring itself has adopted a twist boat arrangement with the twist influenced by the backbone substituents.



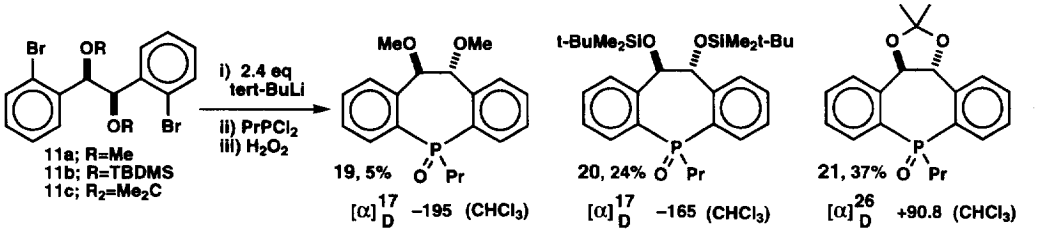
Chiral Phosphepins – Propyl derivatives

We wished to replace the phenyl substituent on the phosphorus atom in phosphepins **12-14** with an alkyl substituent to give compounds with potential in asymmetric synthesis. We converted phosphepin **14** to phosphepinium salt **16** by first reducing the P=O bond with PHMS[11] and then alkylating with PrI. The phosphepinium salts were formed in high yield under these conditions. However, we have previously reported[1] that *endo*-cyclic cleavage dominates with phosphepinium salts derived from **2** despite the

observations of Allen *et al.*[12] Although phosphepinium salt **16** has no fluorine atoms to encourage *endo*-cyclic cleavage, its hydrolysis also met with limited success. Acetal **14** formed a substantial amount of *endo*-cyclic cleavage product **17** in addition to the desired product **18** by *exo*-cyclic cleavage. The salt derived from **13** failed to yield any detectable hydrolysis products at all.



We had to alter our strategy for the introduction of a propyl group and use $PrPCl_2$ as the electrophile instead of $PhPCl_2$ in the ring closure step.[13, 14] Yields were lower using $PrPCl_2$ but usable quantities of the propyl compounds **17**, **20**, and **21** could be made. Ether was used for **19** and **20** and THF for **21**.



Studies in asymmetric synthesis with these and related compounds continue and we are determining the X-ray structures of other phosphepins. These homochiral dilithiated C_2 symmetric species have considerable synthetic potential with other electrophiles including those which could be captured to form similar seven membered ring compounds. This is currently being investigated.

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References and Notes

1. Warren, S.; Wyatt, P., *Tetrahedron: Asymmetry*, **1996**, *7*, 989-992.
2. Segall, Y.; Shirin, E.; Granoth, I., *Phosphorus and Sulfur*, **1980**, *8*, 243-254.
3. Letsing, R. L.; Skoog, I. H., *J. Am. Chem. Soc.*, **1955**, *77*, 5176-5177.
4. Parham, W. E.; Jones, L. D.; Sayed, Y. A., *J. Org. Chem.*, **1976**, *41*, 1184-1186.
5. Or position 5 in the case of the acetal.
6. McMurry, J. E., *Chem. Rev.*, **1989**, *89*, 1513-1524.
7. McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R., *J. Org. Chem.*, **1978**, *43*, 3255-3266.
8. Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H., *Tetrahedron Lett.*, **1981**, *22*, 3455-3458.
9. Parham, W. E.; Bradsher, C. K., *Acc. Chem. Res.*, **1982**, *15*, 300.
10. Neuman, H.; Seebach, D., *Tetrahedron Lett.*, **1976**, 4839-4842.
11. Coumbe, T.; Lawrence, N. J.; Muhammad, F., *Tetrahedron Lett.*, **1994**, *35*, 625-628.
12. Allen, D. W.; Hutley, B. G.; Oades, A. C., *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2326-2328.
13. Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M., *Tetrahedron Lett.*, **1994**, *35*, 433-436.
14. Reuman, M.; Meyers, A. I., *Tetrahedron*, **1985**, *41*, 837-860.

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