Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 4, pp. 989-992, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00099-7

Synthesis of Homochiral Dibenzo[*b,f*]phosphepin 5-Oxides Using a Double *Ortho*-lithiation Strategy

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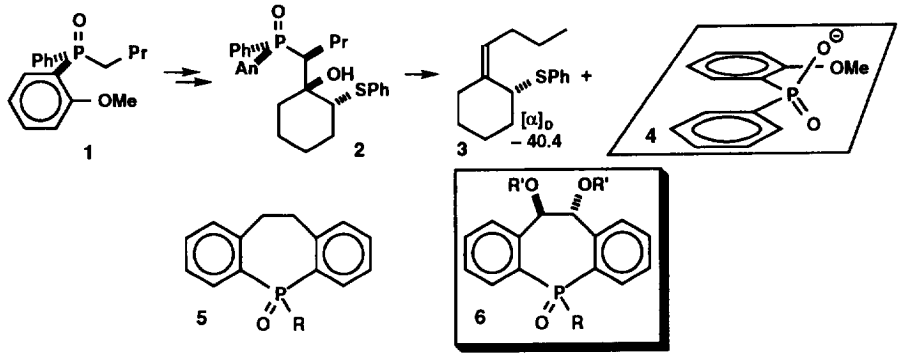
Abstract: Enantiomerically pure chiral seven membered phosphorus heterocycles – phosphepins – have been prepared by McMurry coupling, Sharpless dihydroxylation, *ortho*-lithiation and reaction with $PhPCl_2$ or $PrPCl_2$. Studies of the *ortho*-lithiation and of hydrolysis of phosphepinium salts are included.

The synthetic utility of the diphenylphosphinoyl group has been extensively demonstrated by our research group and used to make many achiral or racemic products.[1] Starting from achiral phosphine oxides, reagent based strategies like the Sharpless epoxidation and Sharpless osmylation have been used to make homochiral phosphine oxides and hence homochiral products such as oxazolidinones[2] and cyclopropyl ketones.[3] Homochiral phosphine oxides have been prepared by the combination of achiral phosphine oxides and homochiral electrophiles.[4] However, the use of the phosphine oxide *itself* as a chiral auxiliary – a substrate based strategy – is in its infancy.[5]



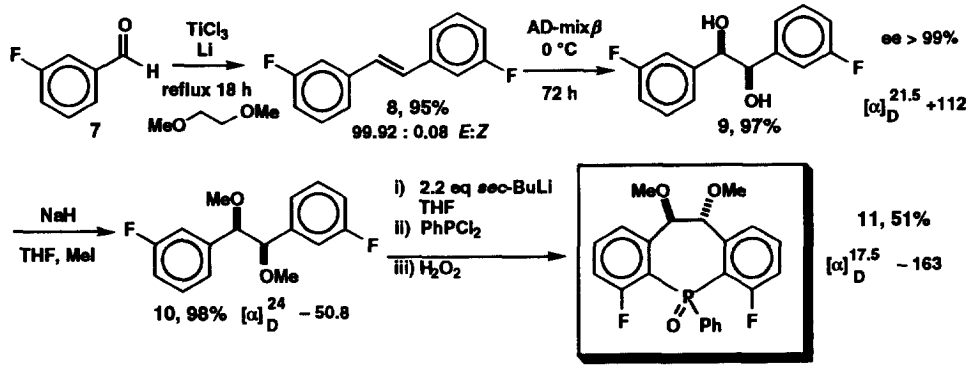
Homochiral phosphine oxides with a stereogenic phosphorus centre, such as **1**, have previously been prepared and used to synthesise[5] homochiral materials **3**. Although moderate selectivity was achieved with **1**, the ultimate removal of the diarylphosphinoyl group generates an achiral phosphinate anion **4** and so the carefully introduced chirality at phosphorus is lost and recycling of the precious auxiliary is precluded. An auxiliary which has its chirality securely cast in carbon is much more attractive. We chose to investigate the seven membered phosphorus heterocycles — phosphepins — for the reasons given below and report here the synthesis of homochiral phosphepin oxides such as **6** made with a view to their use in asymmetric synthesis.

It has been demonstrated that phosphepin **5** displays a twist between the two benzene rings attached to the heterocycle.[6] Phosphepin **5** has two enantiomeric conformations. We envisaged that stereogenic centres on the backbone would lock phosphepin **6** into one ring conformation. Such a twist could be utilised by

presenting a diastereotopic environment to the *exo*-cyclic R substituent on the phosphorus atom. The auxiliary **6** is C_2 derived and hence avoids chirality at phosphorus altogether.

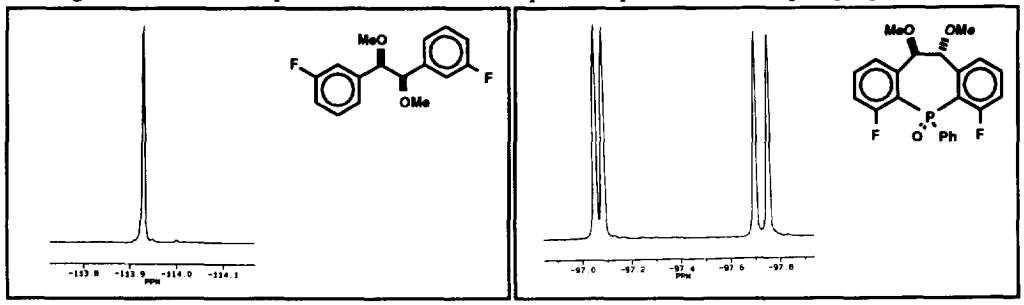
One of the key steps in the synthesis of our phosphepins is the ring closure which requires lithiation at the *ortho* position. This may be achieved by *ortho*-lithiation (hydrogen-lithium exchange) or by halogen-lithium exchange. Synthesis of phosphepin **11** was achieved in four steps invoking the former strategy. 3-Fluorobenzaldehyde **7** was reacted with low valent titanium in a McMurry coupling[7, 8] to give the stilbene **8** in a 95% yield. The reaction was highly stereoselective with an *E*:*Z* ratio of 99.92:0.08 (isolated material) and the difluorostilbene **8** was dihydroxylated using Sharpless methodology and the commercially available AD-β-mix.[9] Stilbenes are the best substrates for the asymmetric dihydroxylation and diol **9** was formed in a 97% yield and >99% ee.[10] The ee was determined using Pirkle reagent[11] in conjunction with racemic diol.[12] Protection of the diol as the dimethyl ether **10** was achieved in a 98% yield using NaH followed by MeI.[13]

The final operation involved the dilithiation of diether **10** and we used *sec*-BuLi to do it (see below). Reaction of the dilithiated species with $PhPCl_2$ followed by oxidation with H_2O_2 yielded the desired phosphepin oxide **11** in a 51% yield.[14]

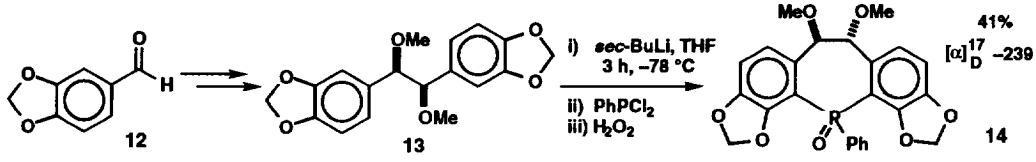


The phosphepin precursor **10** is clearly C_2 symmetric. However, the C_2 axis is destroyed upon ring closure to form the product **11**. The ^1H decoupled ^{19}F NMR of the two compounds give a striking illustration of this loss of symmetry (Figure 1). Precursor **10** displays a singlet because the two fluorine nuclei are homotopic. After ring closure we see two doublets in the ^{19}F NMR of phosphepin **11**. Each doublet corresponds to one of the, now diastereotopic, fluorine atoms. They are each doublets because they couple to phosphorus. The coupling constants are $^3J_{FP}$ 7.5 and $^3J_{FP}$ 12.7. The phosphorus atom lies not on a C_2 axis but, for want of a better term, on a pseudo-C_2 axis. It is not a stereogenic centre and may be described as being nonstereogenic and chirotopic.[15]

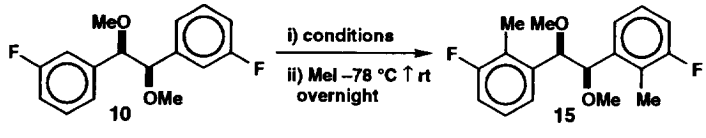
Figure 1; Proton decoupled 235 MHz ^{19}F NMR spectra of precursor **10** and phosphepin **11**.

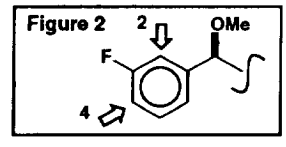


The strategy involved in the synthesis of phosphepin **11** is appropriate for other substrates that will support *ortho*-lithiation. Hence phosphepin **14** was also synthesised by the same sequence.[13] Two pairs of acetal protons are diastereotopic in precursor **13** and appear as 2 × 2 H doublets ($^2J_{HH}$ 1.4 Hz) in the ^{1}H NMR.[13] Obviously C_2 symmetry is destroyed upon ring closure. In phosphepin **14** the four acetal protons are all diastereotopic and appear as 4 × 1 H well separated fine doublets (*J* 1.3 Hz).[14]



The lowest yielding step in both reaction sequences is the last one which involves double lithiation followed by nucleophilic attack on $PhPCl_2$. The *ortho*-lithiation of substrates **10** and **13** was investigated (Table 1) using methyl iodide as a probe for the degree of lithiation achieved with n-BuLi and *sec*-BuLi.





We found that the degree of lithiation was greater with *sec*-BuLi than with n-BuLi. Substrate **10** did not tolerate *tert*-BuLi. Although TMEDA increased the extent of methylation when used with n-BuLi, it *decreased* the extent of methylation with *sec*-BuLi. The degree of lithiation must be *at least* as good as that indicated by the high yields of methylated products such as **15** (Table 1). Hence lithiation is not the yield limiting process.

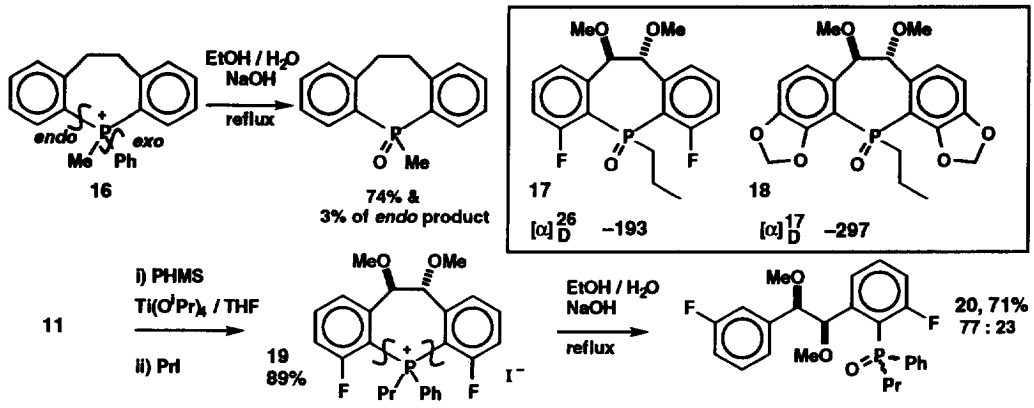
It is interesting to note the complete regioselectivity between positions 2 and 4 of **10** (Figure 2). We would expect the fluorine atom to acidify both its *ortho* protons by the same amount,[16, 17] and yet only deprotonation at position 2 was detected. Although benzylic oxygen atoms are poor directors of lithiation on their own, the methoxy group collaborates with the fluorine atom to direct this complete regioselectivity.[18]

Table 1. Lithiation of 10 and 13

Substrate[a]	Base	Temp. (°C)	Time	Starting Material[b]	Mono-Methylated Product[b]	Di-Methylated Product[b]
10	n-BuLi / TMEDA	–78	1 hr 40 min	8%	52%	39%
10	n-BuLi	–78	4 hr	21%	60%	19%
10	*sec*-BuLi / TMEDA	–78	3 hr	20%	34%	46%
10	***sec*-BuLi**	**–78**	**3 hr**	**0%**	**16%**	**84%**
13	n-BuLi	–78 - 0	55 min	60%	25%	15%
13	***sec*-BuLi**	**–78**	**1 hr 20 min**	**2%**	**14%**	**84%**

[a]reactions were performed in THF. [b]By ^{1}H NMR

The *exo*-cyclic P-phenyl substituent in phosphepins **11** and **14** precludes lithiation by α-deprotonation and so we need to replace it with an alkyl substituent as in phosphepins **17** and **18**. Our research group routinely makes diphenylphosphinoyl compounds by hydrolysing phosphonium salts.[1] It is known that when phosphepinium salt **16** is subjected to such hydrolysis conditions it is the *exo*-cyclic phosphorus-aryl bond that is selectively cleaved.[19] We converted phosphepin **11** to phosphepinium salt **19** in 89% yield by first reducing the P=O bond using the procedure of Lawrence *et al.*[20] and then alkylating with propyl iodide.



The hydrolysis of phosphepinium salt **19** led to two products but *both* were from *endo*-cyclic cleavage. It seems that the fluorine atoms encourage *endo*-cyclic cleavage by stabilising the anionic intermediate and, of course, since the two sides of the phosphepinium salt are diastereotopic, the two products must be diastereoisomers. However, using $PrPCl_2$ with **10** and **13**, instead of $PhPCl_2$, we were able to synthesise phosphepins **17** and **18** in 30% and 8% yield respectively. The lower yields obtained when $PrPCl_2$ is used instead of $PhPCl_2$ could be due to some α-deprotonation of the electrophile.

The efficiency of the first three steps makes our synthesis of the homochiral phosphepin oxides a viable preparative route despite the lower yielding ring closure step. Studies into different backbone substituents on the phosphepin precursors and into using a bromine/lithium exchange strategy in the ring closure step are in progress.

Acknowledgements We thank EPSRC and ZENECA fine chemicals for a CASE award to Paul Wyatt.

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(*Received in UK* 19 *February* 1996)