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Highly Stereoselective Hydroxy-Alkylation, Silylation and Alkylation Reactions of Lithium Derivatives of Chiral Phosphine Oxides

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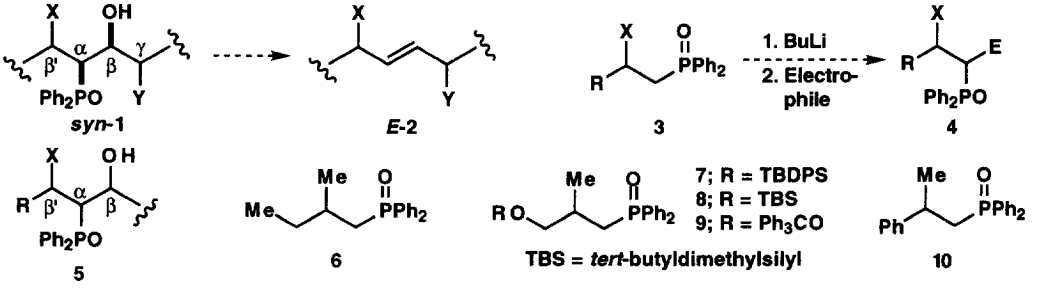
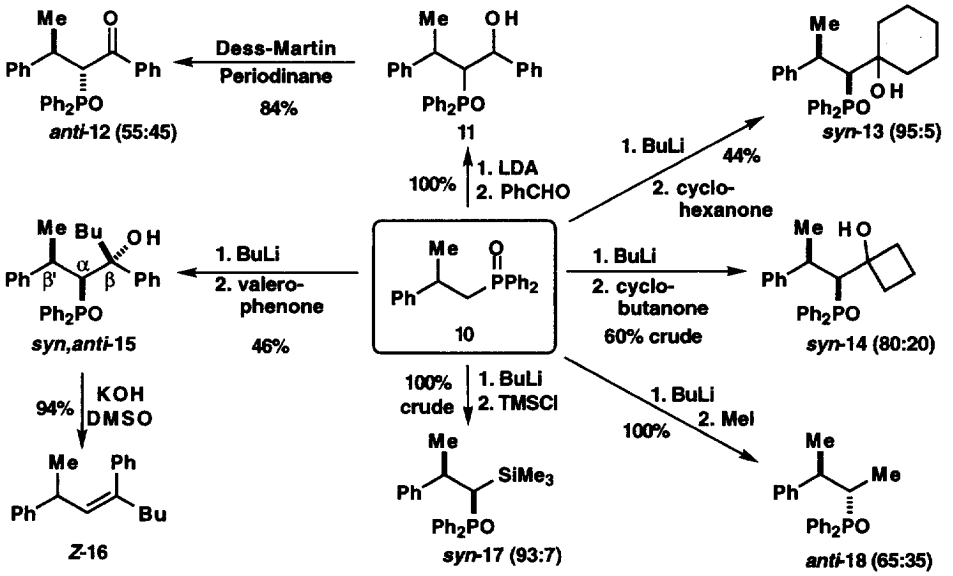
Abstract: Reactions of lithium derivatives of chiral phosphine oxides with ketones (e.g cyclohexanone, cyclobutanone, valerophenone) and Me_3SiCl proceed with excellent levels of *syn* selectivity. In contrast, reactions with methyl iodide are moderately *anti* selective and those with aldehydes show no selectivity whatsoever. Copyright © 1996 Elsevier Science Ltd

We have described three different synthetic approaches to alkenes (e.g. **2**) which possess 1,4 related chiral centres across a double bond of defined geometry.[1-3] Each one of these routes relies on the stereocontrolled synthesis of β-hydroxy phosphine oxides like **1**.[4] However, only one method[3] really addresses the issue of controlling the relative stereochemistry between the α and β' chiral centres in compounds such as **1**. In principle, it should be possible to use the stereogenic carbon of a chiral phosphine oxide such as **3** to control the formation of diastereomeric addition products **4** (which can be imagined as precursors to alcohols **1** with suitably chosen electrophiles). We now report that this approach does indeed work although as we shall see, the observed stereoselectivity depends as much on the nature of the electrophile as it does on the substituents R and X in **3**.



Previously, we[1,2] and others[5] have reported spectacularly unselective reactions of chiral phosphine oxides with aldehydes. For example, reactions of **6** and **7** with acrolein and 2-butylpropenal respectively generated all four diastereomers of β-hydroxy phosphine oxides **5** – there was essentially no stereocontrol between the α and β' chiral centres. Slightly better levels of β' selectivity can be obtained if the chiral phosphine oxide contains functional groups capable of internal chelation.[6] However, by studying reactions of chiral phosphine oxides **8**, **9** and **10** with four different types of electrophile (benzaldehyde, cyclohexanone, Me_3SiCl and methyl iodide), the factors responsible for obtaining synthetically useful levels of β' selectivity have now been uncovered and are reported herein.

Our study began with an investigation of the reaction between the lithium derivative of **10** and benzaldehyde. All four alcohols **11** were obtained in a ratio of 33:26:24:17 and the β' selectivity of 55:45 was revealed by Dess-Martin periodinane oxididation to ketones **12**.[7] In stark contrast, complete β' stereocontrol was observed when we combined the same phosphine oxide **10** with cyclohexanone under identical reaction conditions (THF, –78 °C): only one diastereomer of alcohol **13** was obtained (albeit in a modest 44% yield). The remainder of the crude reaction mixture was starting material – presumably, with this hindered lithiated phosphine oxide, addition to cyclohexanone is accompanied with a significant amount of enolisation. The sole product of this reaction was identified as alcohol *syn*-**13** by X-ray crystallographic analysis of a derivative.[8,9]



Combination of phosphine oxide **10** with other ketones was also investigated. The reaction with cyclobutanone was less *syn* selective (80:20 of *syn*- and *anti*-**14**) but recrystallisation afforded a 40% yield of pure *syn*-**14**. The relative stereochemistry of the major product was assigned as *syn* by comparison with the cyclohexanone reaction and on the basis of a ^{13}C NMR coupling constant correlation.[11] In fact, we have used such a correlation to assign the β' stereochemistry of the compounds presented in the rest of this paper.

When we reacted **10** with the unsymmetrical ketone valerophenone, we were somewhat surprised to observe the formation of only one alcohol (46% isolated yield). This was assigned as *syn,anti*-**15** using our coupling constant rule[11] (for the β' stereochemistry) and NOE analysis of alkene *Z*-**16** obtained after Horner-Wittig elimination (for the relative stereochemistry between the α and β chiral centres).[12] Presumably, the β' selectivity is *syn* for the same reasons as with other ketones. We do not understand why the selectivity between the α and β chiral centres is also so high; with branched phosphine oxides it is usually low.[13] Indeed, we recall that all four alcohols **11** were obtained from the reaction with benzaldehyde: changing the electrophile from benzaldehyde to valerophenone clearly has a dramatic effect on the selectivity.

Silylation of phosphine oxide **10** with Me_3SiCl was also highly *syn* selective (93:7 of *syn*- and *anti*-**17** in quantitative yield) and by careful recrystallisation, a 57% yield of pure *syn*-**17** was isolated. Silyl

phosphine oxides (e.g. *syn*-**17**) are potentially useful compounds and we have recently demonstrated that they can be used successfully in cesium fluoride-mediated Horner-Wittig addition reactions.[14]

In contrast to the reactions described so far, methylation of phosphine oxide **10** with methyl iodide was much less selective and actually gave *anti*-**18** as the major product. There is precedent for the observed *anti* selectivity with methyl iodide: Fleming has previously reported *anti* selective methylations of β'-silyl chiral phosphine oxides using methyl iodide at 0 °C.[5]

The encouraging results obtained with phosphine oxide **10** paved the way for a more detailed study and we have now established the synthetic scope of these reactions. Reactions of phosphine oxides **8**, **9** and **10** with cyclohexanone, Me_3SiCl or methyl iodide are compared in Tables 1 and 2. We notice that essentially the same levels of *syn* selectivity were observed in reactions of **8**, **9** and **10** with each of the electrophiles cyclohexanone and Me_3SiCl. With R = Et, the *syn* selectivity does, however, drop. In contrast, reactions with methyl iodide are only moderately *anti* selective.

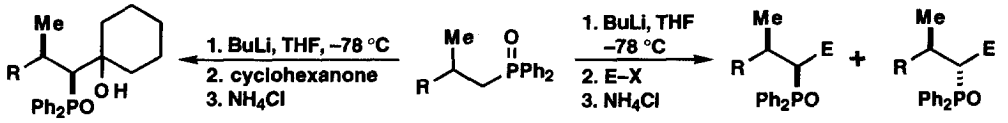


Table 1: Reactions with Cyclohexanone

R	Prod[a]	*syn* : *anti*	Yield
Ph	**13**	>95 : 5	44%
CH_2OTBS	**19**	80 : 20	76%
CH_2OCPh_3	**20**	96 : 4	65%

[a] Product

[b] Yield of *syn*-**17** after recrystallisation

Table 2: Reactions with Me_3SiCl and methyl iodide

R	E–X	Prod[a]	*syn* : *anti*	Yield
Ph	TMSCl	**17**	93 : 7	57%[b]
CH_2OTBS	TMSCl	**21**	85 : 15	79%
CH_2OCPh_3	TMSCl	**22**	96 : 4	89%
Et	TMSCl	**23**	56 : 44	85%
Ph	MeI	**18**	38 : 62	100%
CH_2OTBS	MeI	**24**	45 : 55	100%
CH_2OCPh_3	MeI	**25**	45 : 55	100%

Mechanisms used by Hoppe[15] (*directed lithiation and a configurationally stable organolithium*) and by McDougal[16] (*lithiation giving a thermodynamic mixture of organolithiums*) to rationalise stereoselective reactions of chiral carbamates and sulfides respectively cannot be used to explain our phosphine oxide reactions. The lithiation step may well be directed by the resident chiral centre in phosphine oxides such as **10** but this is irrelevant as lithiated phosphine oxides are not configurationally stable[17] and a thermodynamic mixture of lithiated phosphine oxides would not be expected to show such an electrophile-dependent selectivity. Therefore, we prefer to interpret our results in terms of a *dynamic kinetic resolution* of rapidly interconverting diastereomeric lithiated phosphine oxides. For efficient kinetic resolution and high levels of β' selectivity, slow reacting electrophiles such as ketones and Me_3SiCl are required. Benzaldehyde, a fast reacting electrophile, gives unselective reactions.

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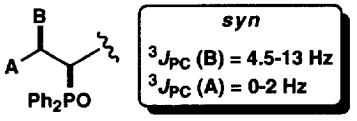
References and Notes

1. Hall, D.; Sévin, A-F.; Warren, S. *Tetrahedron Lett.*, **1991**, *32*, 7123-7126.
2. Clayden, J.; Collington, E. W.; Lamont. R. B.; Warren, S. *Tetrahedron Lett.*, **1993**, *34*, 2203-2206.

3. Mitchell, H.; Warren, S. *Tetrahedron Lett.*, **1996**, *37*, 2105-2108.
4. Clayden, J.; Warren, S. *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 241-270.
5. Fleming, I.; Gil, S.; Sarkar, A. K.; Schmidlin, T. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 3351-3361.
6. For some examples, see: Cavalla, D.; Cruse, W. B.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1883-1898; Clayden, J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1529-1539.
7. For an alternative and stereoselective synthesis of each of the ketones *anti-* and *syn*-**12**, see: Cavalla, D.; Guéguen, C.; Nelson, A.; O'Brien, P.; Russell, M. G.; Warren, S. *Tetrahedron Lett.*, **1996**, *37*, following paper.
8. We are grateful to Dr Paul Raithby for carrying out the X-ray crystal structure analysis.
9. Previously, we described the conversion of **10** into alcohol *anti*-**13** (ref 10). However, the *major product was incorrectly assigned* as *anti*-**13** on the basis of a ^{1}H NMR coupling constant correlation.
10. Ayrey, P. M.; Warren, S. *Tetrahedron Lett.*, **1989**, *30*, 4581-4584.
11. By comparing X-ray crystal structures of four β'-alkyl phosphine oxides with their ^{13}C NMR spectra, we have noticed that $^3J_{PC}$ coupling constants are consistently dependent on the β' relative stereochemistry: Compounds with *syn* relative stereochemistry (between the diphenylphosphinoyl group and the β' substituent) have $^3J_{PC}$ = 4.5-13 Hz and those with *anti* relative stereochemistry have $^3J_{PC}$ = 0-2 Hz.



Examples:
syn-**13**: $^3J_{PC}$ (Me) 4.5 Hz, $^3J_{PC}$ (*ipso*-Ph) 0 Hz; *syn*-**14**: $^3J_{PC}$ (Me) 6.4 Hz, $^3J_{PC}$ (*ipso*-Ph) 0 Hz; *syn,anti*-**15**: $^3J_{PC}$ (Me) 5.9 Hz, $^3J_{PC}$ (*ipso*-Ph) 0 Hz; *syn*-**17**: $^3J_{PC}$ (Me) 7.4 Hz, $^3J_{PC}$ (*ipso*-Ph) 0 Hz; *anti*-**18**: $^3J_{PC}$ (Me) 0 Hz, $^3J_{PC}$ (*ipso*-Ph) 14.4 Hz; *syn*-**19**: $^3J_{PC}$ (Me) 8.15 Hz, $^3J_{PC}$ (CH_2) 0 Hz; *anti*-**19**: $^3J_{PC}$ (Me) 0 Hz, $^3J_{PC}$ (CH_2) 14.9 Hz; *syn*-**20**: $^3J_{PC}$ (Me) 8.15 Hz, $^3J_{PC}$ (CH_2) 0 Hz; *syn*-**21**: $^3J_{PC}$ (Me) 9.1 Hz, $^3J_{PC}$ (CH_2) 0 Hz; *anti*-**21**: $^3J_{PC}$ (Me) 0 Hz, $^3J_{PC}$ (CH_2) 14.9 Hz; *syn*-**22**: $^3J_{PC}$ (Me) 10.2 Hz, $^3J_{PC}$ (CH_2) 0 Hz; *syn*-**23**: $^3J_{PC}$ (Me) 13.3 Hz, $^3J_{PC}$ (CH_2) 0 Hz; *anti*-**23**: $^3J_{PC}$ (Me) 0 Hz, $^3J_{PC}$ (CH_2)14.2 Hz; *syn*-**24**: $^3J_{PC}$ (Me) 11.5 Hz, $^3J_{PC}$ (CH_2) 0 Hz; *anti*-**24**: $^3J_{PC}$ (Me) 1.8 Hz, $^3J_{PC}$ (CH_2) 14.0 Hz; *syn*-**25**: $^3J_{PC}$ (Me) 10.6 Hz, $^3J_{PC}$ (CH_2) 0 Hz; *anti*-**25**: $^3J_{PC}$ (Me) 0 Hz, $^3J_{PC}$ (CH_2) 13.5 Hz.
12. We have already described a synthesis of a single diastereomer of alcohol **15** starting from excess n-butyllithium, phosphine oxide **10** and ethyl benzoate (ref 10). In that paper, the *major product was incorrectly assigned*. Additionally, in light of the results presented in this paper, we are certain that valerophenone is an intermediate in this reaction i.e. the reaction does not proceed via ethyl benzoate acylation of **10** with subsequent addition of n-butyllithium as we had originally suggested (ref 10). To confirm this, we have repeated the reaction: phosphine oxide **10** was reacted with 5 equivalents of n-butyllithium and 2 equivalents of ethyl benzoate to give only the same alcohol *syn,anti*-**15** (40% yield).
13. Hutton, G.; Jolliff, T.; Mitchell, H.; Warren, S. *Tetrahedron Lett.*, **1995**, *36*, 7905-7908.
14. O'Brien, P.; Warren, S. *Synlett*, **1996**, 579-581.
15. Schwerdtfeger, J.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.*, **1992**, *31*, 1505-1507.
16. McDougal, P. G.; Condon, B. D.; Lafosse Jr, M. D.; Lauro, A. M.; VanDerveer, D. *Tetrahedron Lett.*, **1988**, *29*, 2547-2550.
17. O'Brien, P.; Warren, S. *Tetrahedron Lett.*, **1995**, *36*, 8473-8476; O'Brien, P.; Warren, S. *Tetrahedron Lett.*, **1996**, *37*, 4271-4274.

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