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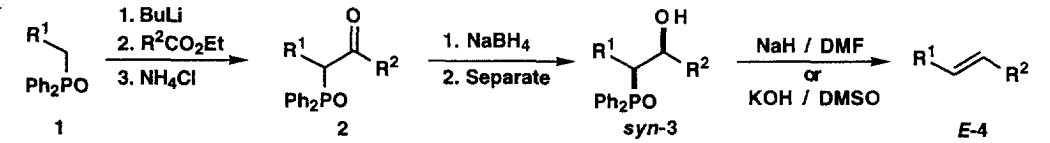
Chiral Phosphine Oxides and Chiral Esters in Stereoselective Intermolecular Acylation Reactions of Phosphine Oxides

David Cavalla, Catherine Guéguen, Adam Nelson, Peter O'Brien, Matthew G. Russell and Stuart Warren*

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW England

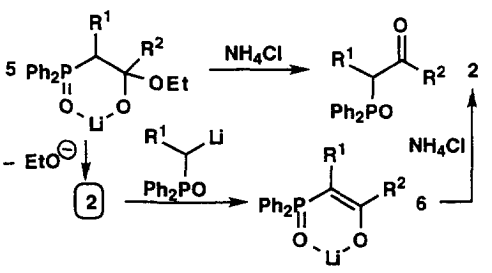
Abstract: Single diastereomers of β-keto phosphine oxides have been generated from intermolecular acylation of phosphine oxides using either chiral esters or chiral phoshine oxides. In most cases, reduction of the ketone products was not affected by the presence of extra chiral centres. Some mechanistic points of interest in the acylation reactions are discussed. Copyright © 1996 Elsevier Science Ltd

Our version of the Horner-Wittig reaction can be used to synthesise *E* or *Z* alkenes almost at will.[1] The best route to *E* alkenes involves *syn* selective sodium borohydride reduction of β-keto phosphine oxides **2**, separation of the resulting diastereomeric alcohols and then stereospecific elimination of Ph_2PO^- from pure *syn*-**3** using a sodium or potassium base.[2] In contrast, reduction of ketones **2** using Luche's conditions[3] can be highly *anti* selective allowing *Z* alkenes to be made.[4]

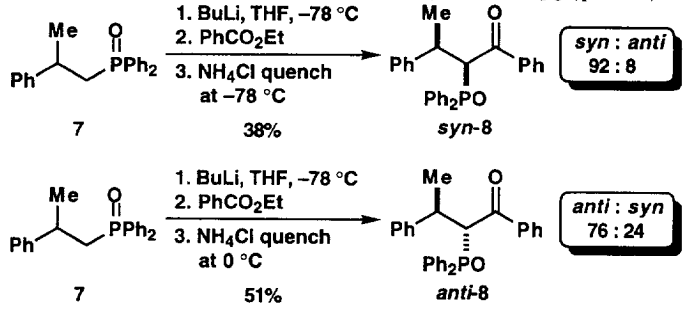


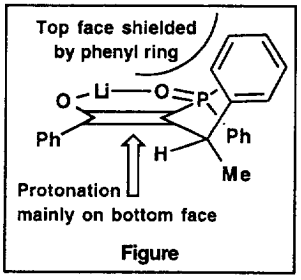
One method[5] we have used to make the required β-keto phosphine oxides **2** is intermolecular acylation of alkyl phosphine oxides **1** with esters[6] or lactones.[7] However, we have never previously[8] carried out such acylation reactions with either chiral phosphine oxides or chiral esters although the *intramolecular* acylation reaction of chiral phosphine oxides has already been described.[9] We now report that it is possible to carry out highly stereoselective *intermolecular* acylation reactions with chiral phosphine oxides or chiral esters. We have also found that, in most cases, these extra stereogenic centres do not interfere with the normal course of subsequent reduction.

As we shall see, the new results presented in this paper have allowed us to comment on some of the mechanistic aspects of acylations of phosphine oxides. Clearly, the first step involves generation of lithum alkoxide **5** . However, we were never sure whether alkoxide **5** (trapped by Me_3SiCl in the intramolecular version[9]) was the true product of the reaction or whether lithium enolate **6** was generated in solution via ethoxide elimination and subsequent enolisation.

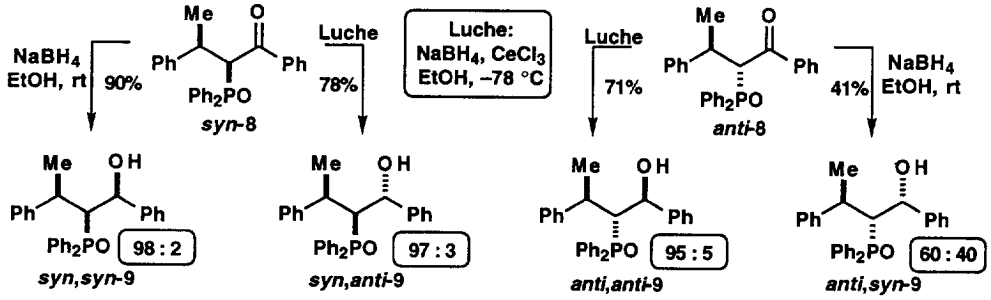


In the preceding paper,[10] we described some stereoselective reactions of chiral phosphine oxides with a variety of electrophiles. As a continuation of that study, the lithium derivative of phosphine oxide **7** was reacted with ethyl benzoate and quenched at –78 °C to give a 38% yield of a 92:8 mixture of diastereomeric ketones **8** which could be recrystallised to a single compound. We identified the major product as ketone *syn*-**8** since we knew[10] that reactions of **7** with other slow reacting electrophiles (e.g. ketones and Me_3SiCl) were *syn* selective and $^3J_{PC}$ values in the ^{13}C NMRs of alcohols **9** (obtained by reduction of ketone *syn*-**8**) were consistent with this assignment of stereochemistry[11] [e.g. alcohol *syn,syn*-**9**: $^3J_{PC}$ (Me) 4.7 Hz, $^3J_{PC}$ (*ipso*-Ph) 0 Hz; alcohol *syn,anti*-**9**: $^3J_{PC}$ (Me) 6.0 Hz, $^3J_{PC}$ (*ipso*-Ph) 0 Hz].





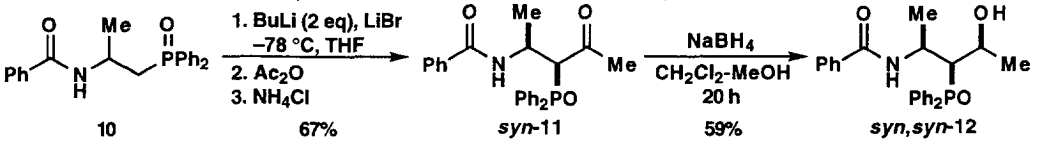
To our surprise, if we allowed the reaction of phosphine oxide **7** with ethyl benzoate to warm up to 0 °C *before* quenching, we isolated an improved 51% yield of a mixture of ketones **8** enriched in the other diastereomer (76:24). Once again, recrystallisation afforded a pure compound. We suggest that at this higher temperature the *syn* lithium alkoxide (equivalent to **5**) which is initially formed decomposes to a lithium enolate (equivalent to **6**). Then, stereoselective protonation[12] on the bottom face of the enolate in a Houk conformation (see Figure) generates *anti*-**8** as the major product.



With these complementary routes to quantities of pure ketones *syn*- and *anti*-**8** in place, we could now study what effect these stereogenic centres would have on the reduction reactions. Using Luche's conditions, there was actually no effect: as expected[4] for branched β-keto phosphine oxides, both *syn*- and *anti*-**8** were reduced with high levels of *anti* selectivity. However, there was a pronounced match/mismatch effect with the sodium borohydride reductions. Ketone *syn*-**8** was reduced to essentially a single alcohol of **9** (90% isolated yield) whereas ketone *anti*-**8** was reduced with virtually no selectivity at all (60:40); despite this, we isolated *anti,syn*-**9** in 41% yield after chromatography. Thus, by a combination of stereoselective acylations and reductions, we have synthesised each one of the four diastereomers of alcohols **9**. Direct reaction of lithiated **7** with benzaldehyde generated all four alcohols **9** with no selectivity at all.[10]

Stereoselective hydroxy-alkylation reactions of dilithiated phosphine oxide **10** with aldehydes and

ketones have previously been used by us to synthesise some *E*-allylic amides.[13] We now report that acylation of dilithiated **10** with acetic anhydride is also stereoselective giving ketone *syn*-**11** in a good 67% yield. Its stereochemistry was elucidated by X-ray crystallography of alcohol *syn,syn*-**12** which was the only product obtained when ketone *syn*-**11** was reduced with sodium borohydride.



Next, we investigated acylation of enantiomerically enriched phosphine oxides **13** which were synthesised by opening terminal epoxides[14] with lithiated methyldiphenylphosphine oxide.[15] Even though the chiral centre is one carbon further away, the reactions proceeded with moderate *anti* selectivity[16] and good yields of the ketone mixtures were isolated after chromatography (Table). The mixtures of the diastereomers of **14** were directly reduced with sodium borohydride to give only two diastereomers of alcohols **15** as judged by ^{1}H NMR spectroscopy of the crude product mixtures. Both diastereomers of **15** had *syn* stereochemistry between the α and β chiral centres[2] and the obtained ratio of alcohols **15** merely reflects the ratio of starting ketones **14**. In other words, the reductions were all completely *syn* selective.

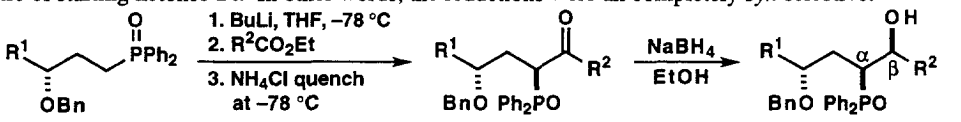
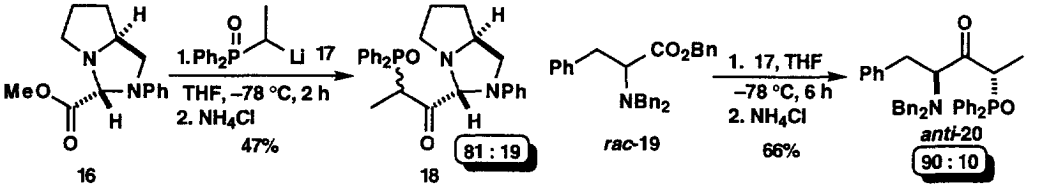


Table: Intermolecular acylation of phosphine oxides **13** and subsequent reduction.

R^1	R^2	**14**, Yield (%)[a]	^{1,3}*anti* : *syn*[b]	**15**, Yield (%)[a]	^{1,3}*anti* : *syn*[b]
n-Bu	Ph	74	65 : 35	46	70 : 30
n-Bu	Furan	60	63 : 37	97	63 : 37
Ph	Ph	82	80 : 20	93	72 : 28
c-C_6H_{11}	Furan	78	69 : 31	71	71 : 29

[a] Isolated yield of the mixture after chromatography; [b] By ^{1}H NMR.

Acylation reactions of prochiral phosphine oxides with chiral esters have also been studied. For example, reaction of proline-derived methyl ester **16** with lithiated phosphine oxide **17** generated a 47% yield of an 81:19 mixture of ketones **18**. Recrystallisation afforded a single unidentified ketone which readily epimerised to the same 81:19 mixture if left in wet deuterochloroform for a few hours. Thus, we surmise that the 81:19 mixture of ketones **18** isolated from the reaction mixture is the thermodynamic ratio.

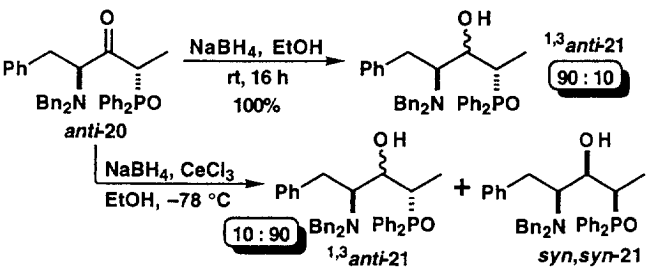


Another stereoselective acylation reaction was observed when we reacted lithiated phosphine oxide **17** with phenylalanine-derived benzyl ester **19**: a 66% yield of a 90:10 mixture of ketones **20** was obtained. The major ketone *anti*-**20** was isolated pure by crystallisation and identified by X-ray crystallography.[17] As in the preceding example, we believe that the observed stereoselectivity is due to an equilibration of ketones *anti*- and *syn*-**20** by enolisation of the now quite acidic proton α to the diphenylphosphinoyl group. In other words, the 90:10 mixture of ketones **20** is a thermodynamic ratio. We suggest this because Dess-Martin

periodinane oxidation of a 44:56 ratio of alcohols ^{1,3}*syn*- and *anti*-**21** generated the same 90:10 mixture of ketones *anti*- and *syn*-**20**. Even with these mild oxidation conditions, epimerisation has occurred.

Sodium borohydride reduction of pure ketone *anti*-**20** proceeded uneventfully to give a 90:10 mixture of alcohols **21**. In this case, we have not identified the major product and do not know which one of the two stereogenic centres in ketone *anti*-**20** determines the stereoselectivity.

The susceptibility of ketone *anti*-**20** to enolisation was again revealed when we carried out the reduction using Luche's conditions: we obtained *three* alcohols in a ratio of 63:31:6. The most abundant ^{1,3}*anti* alcohol was the minor product from the $NaBH_4$ reduction. The next most abundant alcohol was identified as *syn,syn*-**21** and must have been formed via epimerisation of ketone *anti*-**20** followed by highly stereoselective reduction. Such epimerisation during Luche reductions is unprecedented.



In summary, we have demonstrated that *intermolecular* acylation reactions with chiral phosphine oxides or chiral esters are synthetically viable and can be highly stereoselective. This selectivity can arise from (i) formation of kinetic products (e.g. *syn*-**8**, *syn*-**11** and *anti*-**14**), (ii) stereoselective protonation of an enolate generated in situ (e.g. *anti*-**8**) or (iii) equilibration of the ketone products (e.g. **18** and *anti*-**20**). In addition, stereoselective reduction of the ketones generates alcohols such as **9**, **12**, **15** and **21** in which the relative stereochemistry between all three chiral centres is set up in a controlled manner.

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