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

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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 diastereometric alcohols and then stereospecific elimination of Ph₂PO⁻ from pure *syn*-3 using a sodium or potassium base.² In contrast, reduction of ketones 2 using Luche's conditions³ can be highly *anti* selective allowing Z alkenes to be made.⁴



One method⁵ we have used to make the required β -keto phosphine oxides 2 is intermolecular acylation of alkyl phosphine oxides 1 with esters⁶ or lactones.⁷ However, we have never previously⁸ 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 Me₃SiCl in the intramolecular version⁹) 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 knew¹⁰ that reactions of 7 with other slow reacting electrophiles (e.g. ketones and Me₃SiCl) were *syn* selective and ³J_{PC} values in the ¹³C NMRs of alcohols 9 (obtained by reduction of ketone *syn*-8) were consistent with this assignment of stereochemistry¹¹ [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 énolate (equivalent to 6). Then, stereoselective protonation¹² 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 expected⁴ 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 epoxides¹⁴ with lithiated methyldiphenylphosphine oxide.¹⁵ Even though the chiral centre is one carbon further away, the reactions proceeded with moderate *anti* selectivity¹⁶ 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 ¹H NMR spectroscopy of the crude product mixtures. Both diastereomers of 15 had *syn* stereochemistry between the α and β chiral centres² 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.



^a Isolated yield of the mixture after chromatography; ^b By ¹H 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 NaBH₄ 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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