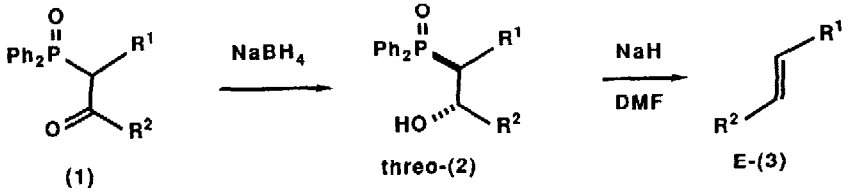
Tetrahedron Letters,Vol.30,No.34,pp4581-4584,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

EXTENSION OF THE HORNER-WITTIG REACTION TO THE SYNTHESIS OF E-ALKENES WITH CHIRAL SUBSTITUENTS: STEREOCHEMICAL CONTROL BY ACYL TRANSFER

Peter M. Ayrey and Stuart Warren*
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

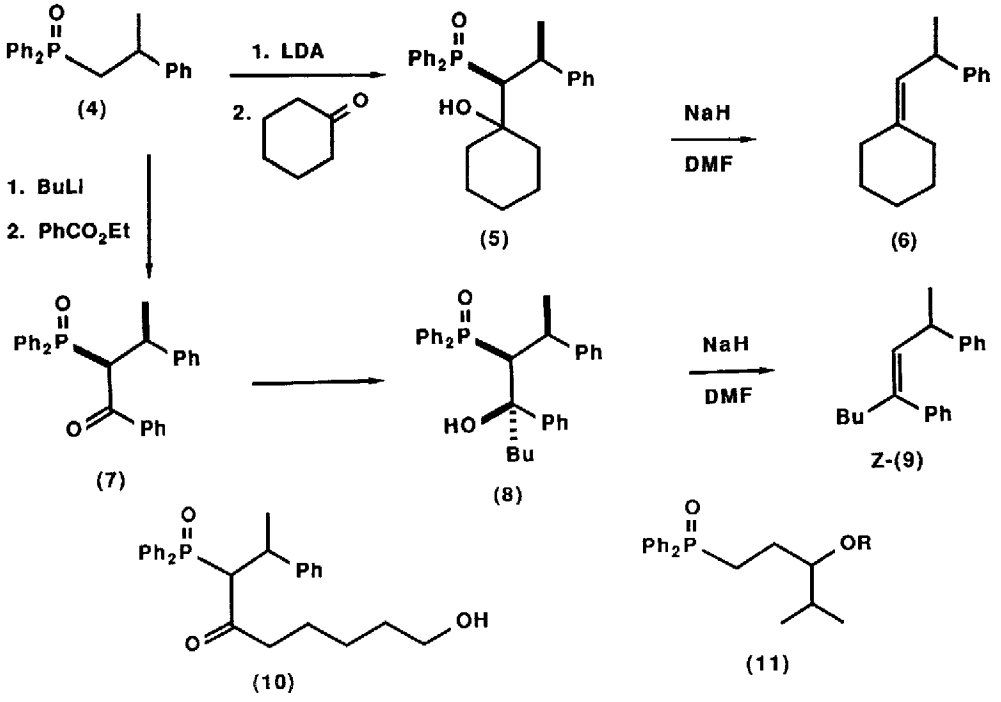
Single crystalline diastereoisomers of hydroxyalkyl phosphine oxides (and hence functionalised E-alkenes) can be isolated, even when other chiral centres are present in the molecule, if they are made by acyl transfer.

The isolation of intermediates (2) in our phosphine oxide variant[1,2] of the Horner-Wittig reaction is usually an advantage since stereoselective syntheses of either pure diastereoisomer are generally available and elimination of $Ph_2PO_2^-$ from either is stereospecific: thus pure threo-(2) from the reduction of the ketones (1) gives[2] pure E-alkene (3). We have now examined the more complicated situation where R^1 contains further chiral centres so that two or three diastereoisomers of (2) would give the E-alkene and an equal number the Z. More extended stereochemical control is clearly preferable to any method relying on the separation of diastereoisomers.[2]

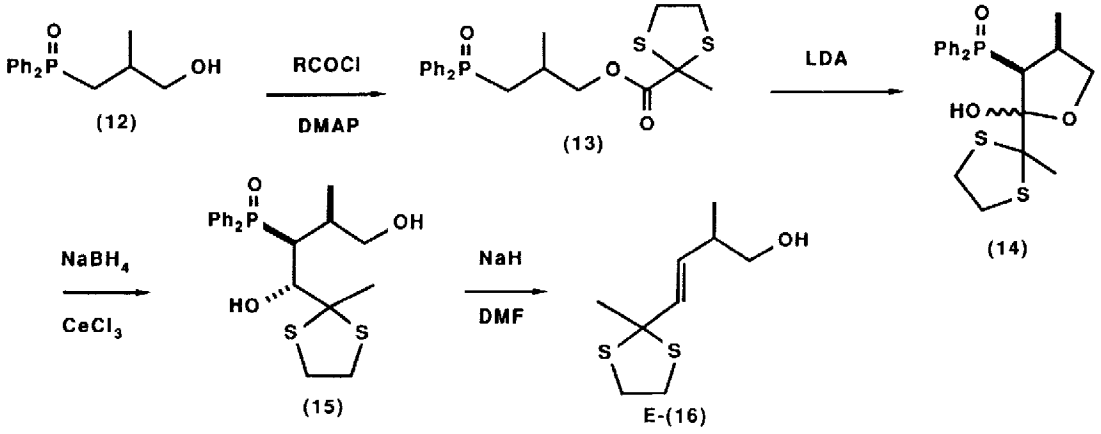


(1) threo-(2) E-(3)

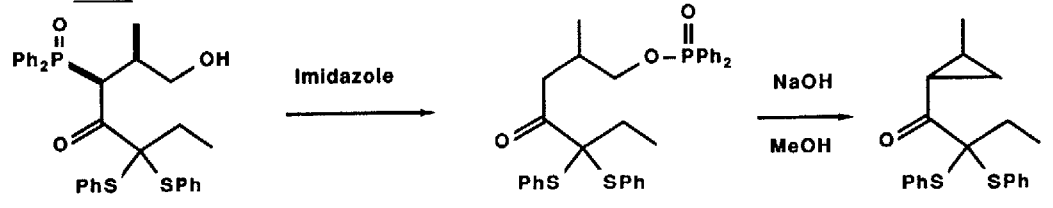
In one simple case, trisubstituted alkenes can be made with excellent control. The classical regioselectivity problem - putting a double bond exo to a ring - is easily solved by combining the racemic phosphine oxide (4) with cyclohexanone to give, without purification, a single diastereoisomer[4] of the alcohol (5) in quantitative yield, and hence the exo alkene (6) in 77% overall yield from (4). Acylation[5] of the same phosphine oxide (4) gave one diastereoisomer[4] of the ketone (7) and addition of butyllithium gave one diastereoisomer of the alcohol (8) [76% from (4) in one pot] and hence Z-(9).[6] Other reactions were less successful: the phosphine oxide (4) gave a good yield (LDA then lactone, 81%) of the ketone (10) but poor (3:1) stereoselectivity and the phosphine oxide (11; R=Me) gave a 1:1 mixture of adducts with cyclohexanone.



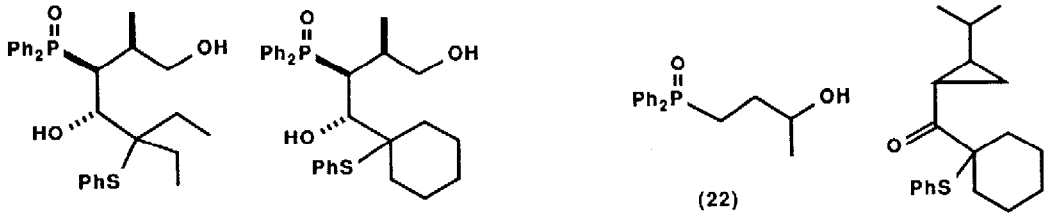
A more reliable approach to functionalised compounds uses acyl transfer.[7] The propionate of the alcohol[8] (12) rearranged with LDA to an intractable mixture of starting material and open and closed (hemiacetal) forms of the product. Blocking the site of ester enolisation with sulphur (PhS groups or a dithiolan) (13) encouraged a faster, cleaner reaction to give the hemiacetal (14), apparently as a single diastereoisomer. Threo-selective reduction ($NaBH_4/CeCl_3$)[11] undoubtedly gave a single diastereoisomer[4] of the diol (15) and hence E-(16) in good yield.



The same alcohol (12) combined with branched α-PhS acids to give single diastereoisomers[4] of two more threo-alcohols (17) and (18) and with a bis-PhS-acid to give one isomer[4] of (19). The attempted silylation of the keto-alcohol (19; R=H, a mixture with hemiacetals) revealed that treatment with imidazole in DMF initiated Ph_2PO transfer[7] to give the rearranged ester (20) and hence the cyclopropyl ketone (21) with NaOH. Stereoselectivity was equally good when the chiral centre was at the alternative position (C-1). The secondary alcohols (11; R=H) and (22) transferred similar α-PhS acyl groups with high stereoselectivity (in an unknown sense) giving an alternative route to cyclopropyl ketones such as (23) [c.f. (21)].

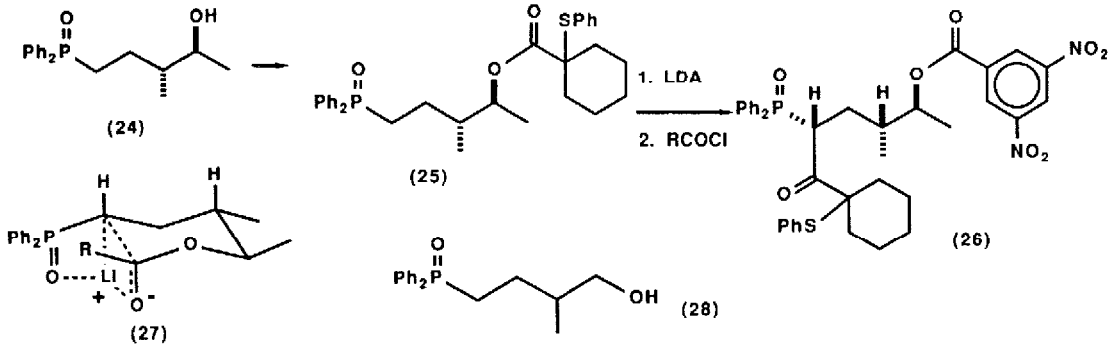


(19) (20) (21)



(17) (18) (22) (23)

The alcohol[8] (24) allowed us to explore the effect of two chiral centres in the R^1 side chain and the stereoselectivity of acyl transfer[7] through a six-membered cyclic transition state. The ester (25) rearranged to a hydroxyketone (as a mixture with hemiacetals) revealed as a single diastereoisomer of the 3,5-dinitrobenzoate (26). We suggest that this

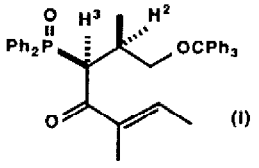


(24) (25) (26) (27) (28)

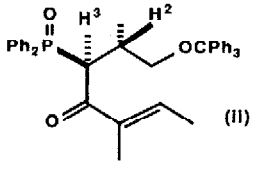
rearrangement goes through the chair transition state (**27**) and hence that the product (**26**) has the stereochemistry shown, but this is not proved. One chiral centre is not enough to make such an acyl transfer stereoselective: esters of the alcohols (**28**) gave mixtures of diastereoisomers on treatment with LDA.

References and Notes

1. A.D. Buss and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1985, 2307.
2. A.D. Buss, N. Greeves, R. Mason, and S. Warren, Ibid., 1977, 2569.
3. We have published a synthesis of Z-α-bisabolene via the separation of one diastereoisomer of an alcohol (**2**) in which R^2 contains a third chiral centre in inevitably modest (53%) yield.[2]
4. The stereochemistry of these intermediates was deduced by ^1H n.m.r. correlation with an X-ray crystal structure of the enone (**i**): M. Doyle, D. Hall, P.R. Raithby, N. Skelton, and S. Warren, in the press. Typical $J_{2,3}$ (Hz): (i) 10.5 (ii) 5.5-7.0 Ketones in this study: 4.3-6.9.

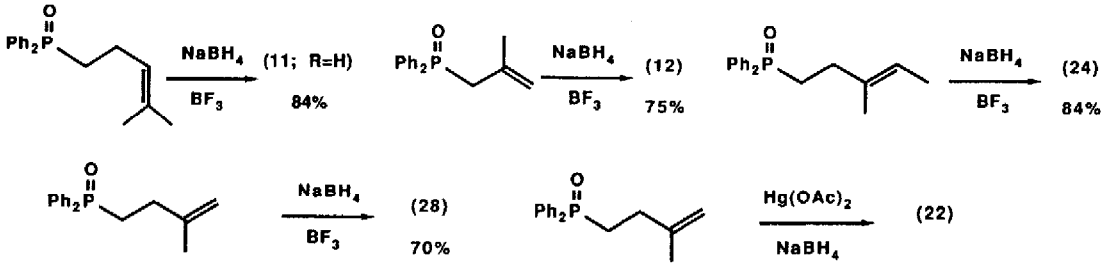


(I)



(II)

5. A.D. Buss, W.B. Cruse, O. Kennard, and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1984, 243.
6. The stereochemistry of Z-(**9**) was determined by n.O.e. experiments.
7. P.N. Wallace and S. Warren, Tetrahedron Lett., 1985, **26**, 5713; J. Chem. Soc., Perkin Trans. 1, 1988, 2971.
8. The hydroxyalkyl phosphine oxides were made by the hydroboration ($NaBH_4/BF_3$, Et_2O)[9] or mercuration-reduction[10] (for **22**) of the following alkenyl phosphine oxides:



9. G. Zweifel and H.C. Brown, Org. React. (N.Y.), 1963, **13**, 1.
10. H.C. Brown and P.J. Geoghegan, J. Org. Chem., 1970, **35**, 1844.
11. The threo-selectivity of this reduction is a consequence of chelation of Ce^{3+} by OH, C=O, and P=O, see N. Greeves and S. Warren, Tetrahedron Lett., 1986, **27**, 259 and J. Elliott, D. Hall, and S. Warren, Ibid., 1989, **30**, 601.

(Received in UK 12 June 1989)