Tetrahedron Letters, Vol 32, No 33, pp 4171-4174, 1991
Printed in Great Britain

0040-4039/91 $3 00
Pergamon Press plc

Stereocontrolled Synthesis of Homoallylic Amines using Phosphine Oxides and Isoxazolines

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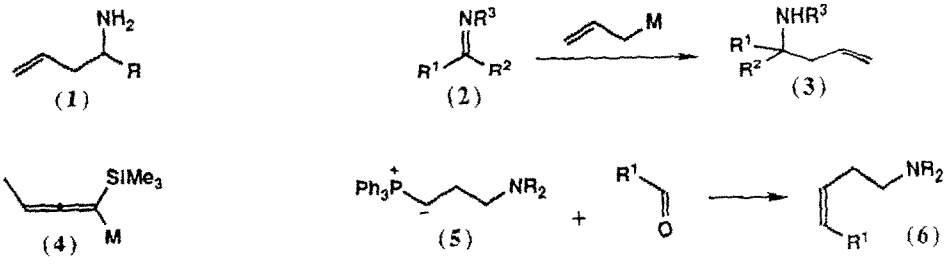
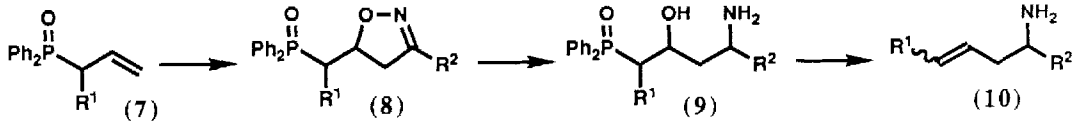
Abstract: Allylic diphenylphosphine oxides (7) undergo stereoselective 1,3-dipolar cycloadditions with nitrile oxides to give Δ^2-isoxazolines (8) These may be reduced, also stereoselectively, to δ-amino-β-hydroxyalkyl-diphenylphosphine oxides (9) Stereospecific Wittig-Horner type elimination of $Ph_2PO_2^-$ from amino alcohols (9) gives homoallylic amines (10) with controlled double bond geometry

Homoallylic amines have been made by several strategies. For simple compounds such as (**1**, R = H or Me) azide displacement of an arene sulphonate and subsequent reduction are successful [1] More recently, attack of an allyl metal on imines (**2**) has been used to make homoallylic amines (**3**).[2] This approach can be very stereoselective when one of R^1, R^2, or R^3 is chiral, but gives no control over double bond geometry. A related approach is the attack of allenyl metals (**4**) on imines (**2**),[3] which has the same drawback A third strategy is to react a 3-aminopropyl phosphonium ylid (**5**) with an aldehyde.[4] This method gives mixtures of geometric isomers of homoallylic amines (**6**) in which the *Z*-isomer predominates.



We used this Wittig strategy[5] when making allylic amines from 2-aminoethyldiphenylphosphine oxides. The double bond was created by standard Wittig-Horner chemistry. the attack of a diphenylphosphinoyl-stabilised anion on a symmetrical ketone and elimination of $Ph_2PO_2^-$. The present work creates the necessary P-C-C-O unit in a different way. The oxygen is introduced in a masked form, as the isoxazoline (**8**) Reduction then reveals the OH group in the amino alcohol (**9**), and $Ph_2PO_2^-$ elimination gives the homoallylic amines

(**10**). Sakurai and co-workers have used a similar cycloadditive approach, based on 1,3-dipolar cycloaddition to allylic silanes.[6]



Allylic diphenylphosphine oxides (**7**) are readily available from allylic alcohols (R^1 = alkyl)[7] or acetals (R^1 = alkoxy).[8] They undergo 1,3-dipolar cycloadditions with nitrile oxides in the expected regiochemical sense[9] to give 3,5-disubstituted Δ^2-isoxazolines (**8**). The reaction is slow, needing days or weeks to reach completion, but is dramatically accelerated by ultrasound: the reaction may then be complete within a few hours.[10] When R^1 was H, primary alkyl or alkoxy, yields were moderate to excellent (see Table 1). The best nitrile oxide was benzonitrile oxide, i.e. R^2 = Ph. Alkyl nitrile oxides did not react with hindered alkenes (**7**; R^1 = Pr^n or Bu^i), and very hindered alkenes (**7**, R^1 = Pr^i or cyclopentyl) did not react even with benzonitrile oxide. The reaction was stereoselective, with diastereomer ratios ranging from 3.0:1 to 5.1:1. *Anti*-**8** was the major product,[11] which is consistent with Houk's transition state model for nitrile oxide cycloadditions[12] when Ph_2PO is in the least sterically demanding 'anti' position. In almost every case, the diastereomers were readily separable by column chromatography.

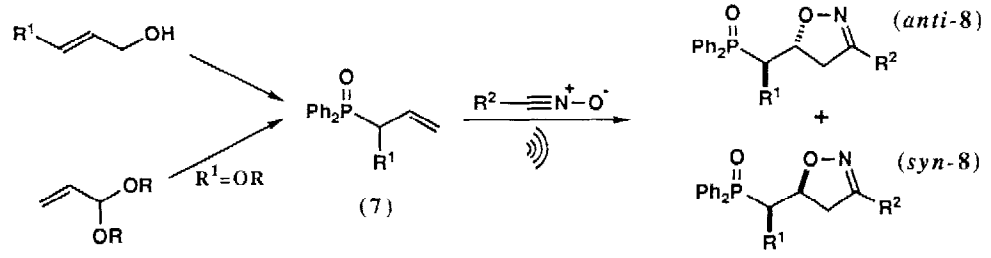


Table 1: Nitrile Oxide Cycloadditions to Allylic Phosphine Oxides (7)

R^1	H	H	Me	Me	Me	Me	Me	Pr^n	Bu^i	MeO	EtO	EtO
R^2	Pr^n	Ph	Me	Pr^n	n-Hx[a]	Ph	COEt	Ph	Ph	Ph	Pr^n	Ph
Yield/%	96	59	10	86	95	93	44[b]	73	55	66	63	63
Recovered **7**		18	88				63[c]	8	32			
Ratio[d]	-	-	≥5:1	4:1	3:1	4.3:1	4:1	5.1:1	5:1	3.3:1	2.5:1	4:1

[a]n-Hexyl [b]Diastereomers could not be separated [c]Not recrystallised [d]*anti*-**8**:*syn*-**8**

Careful choice of reducing agent is necessary for the reduction of isoxazolines (**8**) to amino alcohols (**9**). We found that the nickel chloride/sodium borohydride system of Annunziata *et al*[13] worked well, the reduction being very soon complete even at –30°C. Yields were good to excellent (see Tables 2 and 3). The two stereocentres already present in isoxazoline (**8**) are not affected by the reduction, but the stereoselectivity in the creation of the third centre is sometimes low. A variety of metals, including Ti, Co, Pd, Pt, and Ce, was tried in

an effort to improve the stereoselectivity of the reduction, but none worked better than Ni. The stereochemistry of the new centre relative to the other two has been determined in only one case,[14] as the diastereomers of (**9a**), and also of (**9s**), are often hard to separate by colum chromatography This is not important, however, as the two pre-existing chiral centres are sacrificed in a stereoselective manner to make the double bond, and the final product (**10**) has only one chiral centre

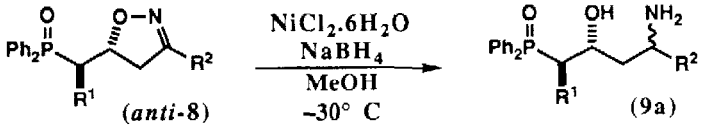


Table 2: Reduction of the Isoxazolines *Anti-8*

R^1	Me	Me	Pr^n	Bu^t	EtO	EtO
R^2	Pr^n	Ph	Ph	Ph	Pr^n	Ph
Yield/%	79	84	94	68	97	98
Ratio	4.5.1	1 2.1	5.1	3·1	3 5:1	1 1

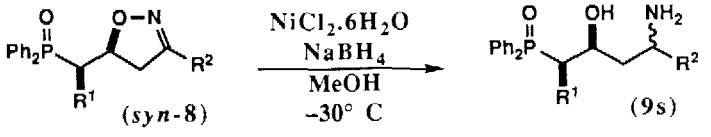
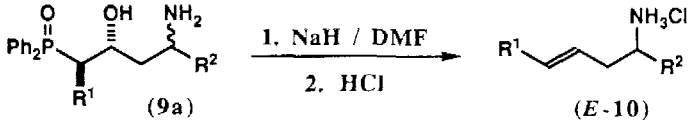


Table 3: Reduction of the Isoxazolines *Syn-8*

R^1	Me	Me	Bu^t	H	H
R^2	Pr^n	Ph	Ph	Pr^n	Ph
Yield/%	95	86	89	90	76
Ratio	2·1	2:1	2·1	1.5.1	2.5 1

The δ-amino-β-hydroxydiphenylphosphine oxides (**9**) may be converted into homoallylic amines (**10**) of known double bond geometry by our standard conditions of NaH in DMF.[5,15] The stereospecific elimination means that the double bond geometry is controlled by the stereochemistry of the original cycloaddition Thus alcohols (**9a**) give *E*-alkenes and alcohols (**9s**) give Z-alkenes The amines were isolated as their hydrochlorides, in yields of 45 to 84%, e.g , (*E*-**10**, R^1=Me. R^2=Ph) 81%; (*Z*-**10**,R^1=Me, R^2=Ph) 74%



In summary, we have developed a short, moderately stereoselective route to homoallylic amines (**10**) of defined double bond geometry, the two isomers being formed quite separately. The *E* isomer is the major product by this route, which therefore complements that of De Castro Dantas, Laval, and Lattes [4]

Acknowledgement

S.K. Armstrong is grateful to Glaxo Group Research Limited for funding the project, and to Dr. R.B. Lamont of G.G.R. for performing the X-ray analysis (see footnote 10).

References and Footnotes

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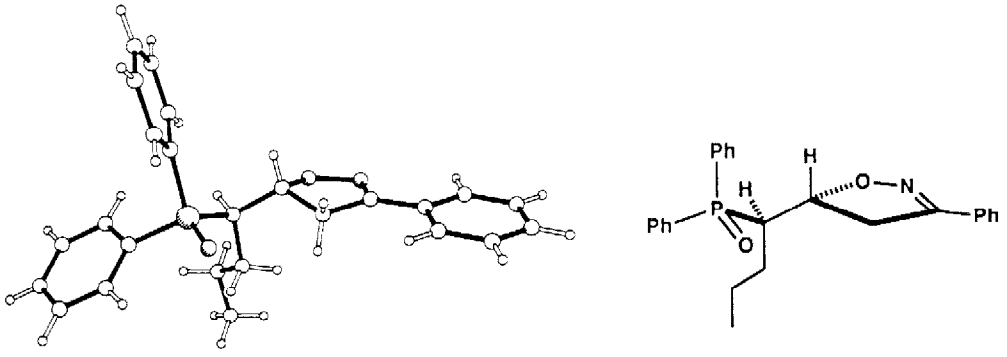
10. cf D. R. Borthakur and J. S. Sandhu, *J. Chem. Soc. Chem. Commun.*, 1988, 1444, who used ultrasound to accelerate nitrone cycloadditions.
11. Single crystal X-ray diffraction on the major isomer of (**8**, $R^1 = Pr^n$, R^2 = Ph) showed that this was the *anti* isomer, whose conformation closely resembles the proposed transition state for the cycloaddition, cf. ref. 12.:



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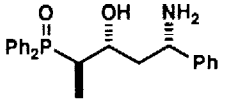
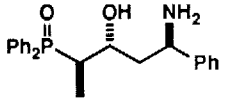
14. The diastereomers of (**9a**, R^1 = Me, R^2 = Ph) were separately submitted for NOE experiments. These suggested that the major isomer was *anti,anti*-**9** and the minor isomer was *anti,syn*-**9**. Similar NOE experiments on (**9a**, $R^1 = Bu^i$, R^2 = Ph) did not allow such assignments to be made, and NMR comparisons between different amino alcohols (**9**) were not reliable.



(*anti,syn*-**9**)



(*anti,anti*-**9**)

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(Received in UK 3 May 1991)