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Synthesis of Phenylalanine-derived β-Hydroxy and β-Keto Phosphine Oxides – Investigation of the Configurational Stability of Lithiated Phosphine Oxides Using the Hoffmann Test

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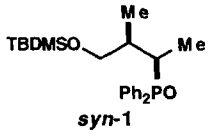
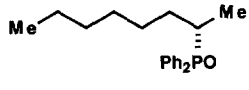
Abstract: Reaction between a phenylalanine-derived aldehyde and a lithiated phosphine oxide (the Hoffmann test) has been used to demonstrate that lithiated phosphine oxides are not configurationally stable in THF at –78 °C on the timescale of thier reaction with the aldehyde. Additionally, these reactions generate synthetically useful products. Copyright © 1996 Elsevier Science Ltd

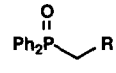
Recently, we suggested that organolithium derivatives of secondary phosphine oxides such as **1** and **2** did not maintain their configuration α to phosphorus even on the relatively short timescales of internal electrophilic quenches with Me_3SiCl or cyclobutanone.[1] In that study, "classical" methods such as relative (e.g. *syn*- and *anti*-**1**) and absolute [e.g. (*S*)- and (*R*)-**2**] stereochemistry were used to study configurational stability. However, two issues still remained: we had not obtained any information on lithium derivatives of primary phosphine oxides **3** and the timescale of our investigation could be shortened further.[2] In this paper, then, we provide a simple and synthetically useful solution to both of these issues using a "non-classical" method of investigating configurational stability – the "Hoffmann test".[3-5]



syn-**1**



(*S*)-**2**



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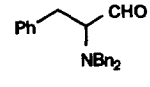

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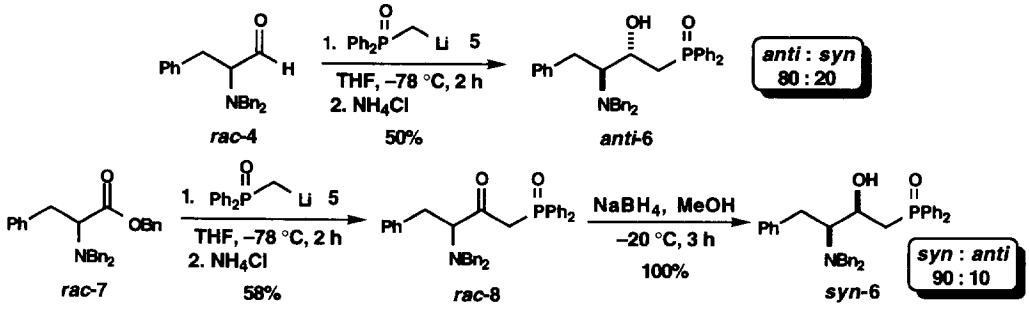
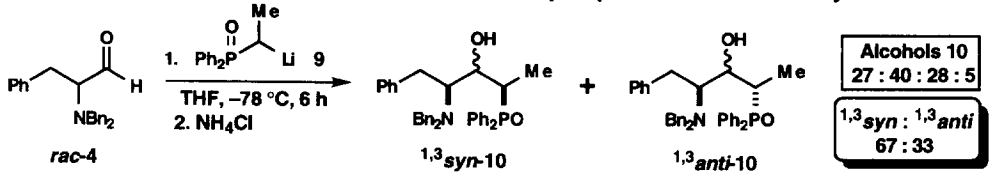
In the Hoffmann test, a *racemic* organolithium is reacted with a *racemic* electrophile (e.g. aldehyde **4**) and the ratio of the diastereomeric products so obtained is determined (experiment 1). A comparison of this ratio with that obtained from reaction between the same organolithium and an *enantiomerically enriched* electrophile (experiment 2) allows conclusions to be drawn about the configurational stability of the organolithium derivative. The theory behind the Hoffmann test has been discussed in detail elsewhere[4] and since its introduction in 1987 it has been used to investigate the configurational stability of organolithiums derived from sulfides,[3,6] selenides,[3] sulfones[6] and some benzyl-substituted compounds.[6-8] However, to date, the test has not been used to gain information on phosphorus-stabilised organolithiums.

As part of our studies into the configurational stability of lithiated phosphine oxides,[1] we proposed to carry out the two Hoffmann test reactions using ethyldiphenylphosphine oxide (**3**; R = Me) and aldehyde **4**. Before we actually did this, the inherent Felkin selectivity of aldehyde **4** (synthesised using Reetz's method[9,10]) in reactions with lithiated phosphine oxides was established: addition of lithiated phosphine oxide **5** to aldehyde *rac*-**4** afforded a 50% yield of an 80:20 ratio (by ^{1}H NMR) of alcohols *anti*- and *syn*-**6**. The *anti* stereochemistry of the major product was assigned from precedent[9] assuming that Felkin[11] non-chelation control predominates and on the basis of an alternative synthesis of alcohol *syn*-**6**: sodium borohydride reduction of β-keto phosphine oxide *rac*-**8** (synthesised using an acylation reaction with benzyl ester *rac*-**7**) generated a 90:10 ratio of alcohols *syn*- and *anti*-**6**. Once again, stereoselectivity was assigned from precedent[12] and is rationalised in terms of a Felkin[11] non-chelation controlled reduction.



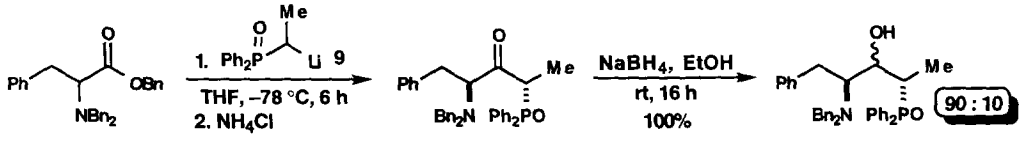
We were now ready to carry out the first of the Hoffmann test experiments. Addition of lithiated phosphine oxide **9** to aldehyde *rac*-**4** in THF at –78 °C (our usual reaction conditions[1]) and ^{1}H NMR analysis of the crude reaction mixture indicated that all of the four possible alcohol products **10** had been generated in a ratio of 27:40:28:5. Generally, in the Hoffmann test, only two out of the four possible alcohols are obtained because of the good Felkin selectivity usually exhibited by aldehyde **4** – in these cases, it is only necessary to measure this ratio without assigning the stereochemistry. However, when four alcohols are obtained,[13] those with the same 1,3 relative stereochemistry have to be identified. By repeated chromatography, we were fortunately able to isolate a pure sample of the major product which was shown to be alcohol *anti,anti*-**10** by X-ray crystal structure analysis[14] (Figure 1).

Hoffmann test experiment 1: Reaction of lithiated phosphine oxide 9 with aldehyde *rac*-4



Because we were unable to assign the stereochemistry of the other three alcohols **10**, we tried to synthesise the same alcohols using a reduction route. To our surprise, an acylation reaction between lithiated phosphine oxide **9** and benzyl ester **7** proceeded stereoselectively to give a 66% yield of a 90:10 ratio (by ^{1}H NMR) of β-keto phosphine oxides **11**. The major ketone, isolated by crystallisation, was identified as *anti*-**11** by X-ray crystallography[14] (Figure 2). We could have used this acylation reaction for our Hoffmann test experiments – indeed, such an experiment would not suffer from the complication of multiple diastereomeric products (unlike our reaction with aldehyde **4**). However, we believe[15] that the stereoselectivity of the acylation reaction is due to a thermodynamically driven equilibration of ketones *anti*- and *syn*-**11** by enolisation of the now quite acidic proton α to the diphenylphosphinoyl group. Sodium borohydride

reduction of β-keto phosphine oxide *anti*-**11** was also highly stereoselective[16] giving a mixture of the two alcohols ^{1,3}*anti*-**10**. Although we were unable to assign the stereochemistry of all four alcohols **10**, the reduction route did enable us to identify which alcohols had the same 1,3-relative stereochemistry. Thus, we assigned a 67:33 ^{1,3}*syn* : ^{1,3}*anti* ratio of alcohols **10** obtained from experiment 1 of our Hoffmann test experiments, a value which is in the optimum range[4] for carrying out the test.



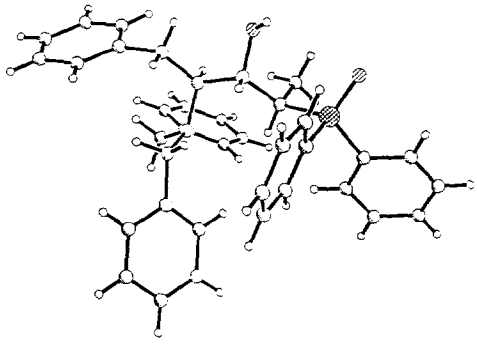


Figure 1: X-ray crystal structure of *anti,anti*-10

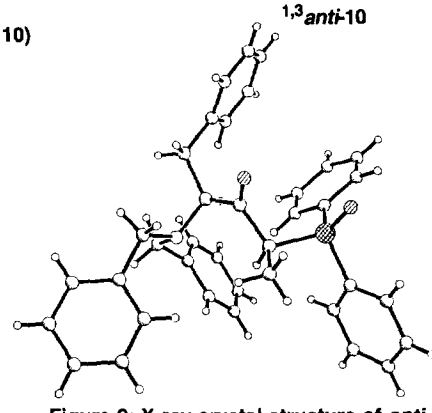
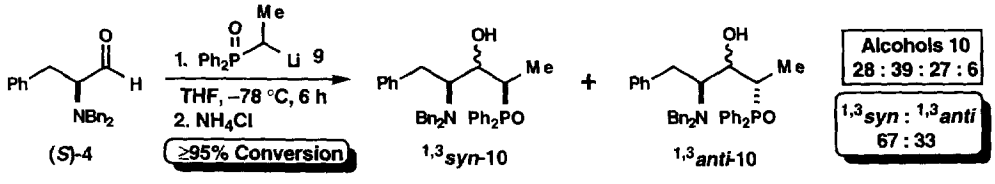


Figure 2: X-ray crystal structure of *anti*-11.

When carrying out experiment 2 of the Hoffmann test, there are two important practical points. Firstly, inverse addition of pre-cooled organolithium to the electrophile ensures that the timescale of the test is indeed the rate of reaction with the electrophile[4] and, secondly, a ten-fold excess of the electrophile is used to ensure that the reaction goes to completion. In this way, reaction of lithiated phosphine oxide **9** with 10 equivalents of aldehyde (*S*)-**4** generated a 28:39:27:6 ratio of alcohols **10** at ≥95% completion as judged by ^{1}H NMR of the crude reaction mixture. The ^{1,3}*syn* : ^{1,3}*anti* ratio of alcohols **10** was 67:33 which is identical to that obtained from experiment 1. Purification by chromatography gave a 93% isolated yield of essentially the same ratio of alcohols **10**.

Hoffmann test experiment 2: Reaction of lithiated phosphine oxide 9 with aldehyde (*S*)-4



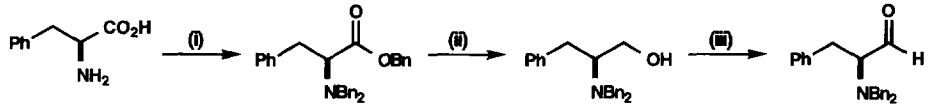
Since the conversion of ethyldiphenylphosphine oxide into alcohols **10** is complete using aldehyde (*S*)-**4** (chemical yield, 93%) and since the ^{1,3}*syn* : ^{1,3}*anti* ratios are the same in experiments 1 and 2,[4] we can conclude that organolithium derivatives of primary phosphine oxides such as **3** are not configurationally stable in THF at –78 °C even on the timescale of their reaction with aldehyde **4**. A configurationally stable lithiated phosphine oxide would have generated a 50:50 mixture of ^{1,3}*syn*- and ^{1,3}*anti*-**10** in experiment 2.[4] The results of the Hoffmann test reactions are completely consistent with our earlier findings.[1] Furthermore, these reactions are synthetically useful: the β-hydroxy functionality in alcohols (e.g. **10**) is a masked alkene

and so the synthetic sequence benzyl ester **7** → β-keto phosphine oxide **11** → alcohol **10** actually represents a stereocontrolled route to amino acid-derived allylic amines of defined double bond geometry.[17]

Acknowledgements: We thank EPSRC for a grant (to P. O'B.).

References and Notes

1. O'Brien, P.; Warren, S. *Tetrahedron Lett.*, **1995**, *36*, 8473-8476.
2. The timescale of investigation could be shortened using faster reacting electrophiles under *in situ* quench conditions. For example, Seebach has successfully used benzaldehyde as an internal electrophile to trap a lithium enolate derived from an amino acid: Seebach, D.; Weber, T. *Tetrahedron Lett.*, **1983**, *24*, 3315-3318. In contrast, we did not see any addition product when we reacted a simple phosphine oxide (**3**; R = n-Pr) using a similar procedure (LDA added to a solution of the phosphine oxide and benzaldehyde).
3. Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron*, **1994**, *50*, 6049-6060.
4. Hirsch, R.; Hoffmann, R. W. *Chem. Ber.*, **1992**, *125*, 975-982.
5. Hoffmann, R. W.; Lanz, J.; Metternich, R.; Tarara, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.*, **1987**, *26*, 1145-1146.
6. Hoffmann, R. W.; Rühl, T.; Harbach, J. *Liebigs Ann. Chem.*, **1992**, 725-730.
7. Hoffmann, R. W.; Rühl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.*, **1992**, 719-724.
8. Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.*, **1994**, *116*, 9755-9756.
9. Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.*, **1987**, *26*, 1141-1143.
10. Details of the synthesis of aldehyde **4** have not been published (ref 9). Our synthesis is outlined below.



Reagents: (i) 3.5 eq BnBr, 3 eq K_2CO_3, EtOH–water (5:1), reflux, 12 h, 83%
(ii) $LiAlH_4$, THF, 0 °C, 1 h, 80%
(iii) $(COCl)_2$, DMSO, –78 °C, CH_2Cl_2 then Et_3N → 0 °C, 93%

(*S*)-**4**

Aldehyde **4** cannot be purified by chromatography on silica without decomposition. However, we found that washing the crude product quickly with 3 M HCl during the Swern work up generated essentially pure material. Aldehyde **4** prepared using Dess-Martin periodinane oxidation was of lower purity.

11. Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.*, **1968**, 2199-2204.
12. Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymmetry*, **1990**, *1*, 375-378.
13. Hoffmann encountered the same problem when he described the first use of the test (see ref 5).
14. We are grateful to H. R. Powell and P. R. Raithby for carrying out the X-ray crystal structure analyses depicted in this paper. Full details of the crystal sructure investigation of alcohol *anti,anti*-**10** and ketone *anti*-**11** have been deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, UK.
15. Evidence for this is provided by the fact that Dess-Martin periodinane oxidation of a 44:56 ratio of alcohols ^{1,3}*syn*- and *anti*-**10** generated a 90:10 ratio of β-keto phosphine oxides *anti*- and *syn*-**11**. This clearly demostrates that epimerisation had occurred even under these mild oxidising conditions.
16. We have not been able to identify the major alcohol **10** obtained from this reduction reaction.
17. A related example: Clayden, J.; Collington, E. W.; Warren, S. *Tetrahedron Lett.*, **1993**, *34*, 1327-1330.

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