Pergamon

Tetrahedron Letters, Vol. 35, No. 46, pp. 8671-8674, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01837-5

Mapping the Stereochemical Course of Carbonyl Phosphonylation *via* Chiral Phosphorodiamidites

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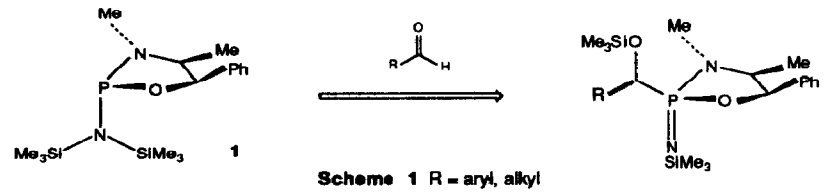
Abstract: *The asymmetric phosphonylation of aldehydes via chiral phosphorodiamidites has been examined as a function of the steric profile of the chiral auxiliary employed. Comparison of N-Me and N-^{i}Pr-(1R,2S)-ephedrine auxiliaries reveals that the latter results in a consistently stronger preference for ($S_P S_C$) product stereochemistry than the former.*

Phospho-transfer processes have long been recognised as being of fundamental importance in biological activity such as metabolism and cell biochemistry.[1] In particular, transfer of the phosphoro function, [$(RO)_2P(=O)O$] mediated by kinase and phosphatase enzymes has attracted significant interest.[2] However, some of the most desirable synthetic organophosphorus molecules are based on the phosphonate scaffold $(RO)_2P(=O)R$ (R = alkyl, aryl, H) where the substitution of a phosphoro oxygen atom by a carbon donor residue R imparts considerable hydrolytic stability to the resulting phosphorus compound thus making phosphonates extremely attractive mimics of phosphorylated biomolecules.[3] Furthermore, control over the steric, electronic, stereochemical and secondary binding capabilities of the R residue offers enormous flexibility to the phosphonate function, and has consequently stimulated rapidly growing interest in the development of stereoselective methodologies to functionalised phosphonate esters and acids.[4]

Two years ago we initiated a programme of research to develop stereoselective phospho-transfer processes and one of the most successful of these processes has been the asymmetric Abramov reaction which affords chiral α-functionalised phosphonate esters.[5]

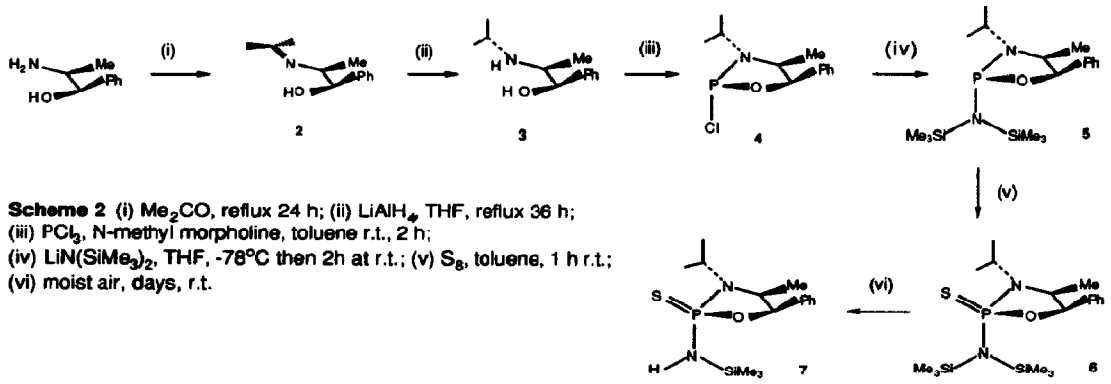


Scheme 1 R = aryl, alkyl

These studies suggest that stereocontrol at the phosphorus and α-carbon atoms of the phosphonate esters can be acheived by manipulation of the stereoelectronic properties of the phosphorus atom coordination sphere.[5f,h] In particular, exploitation of the [$N(SiMe_3)_2$] function ensures an almost exclusive (> 98%) S_P configuration in the imidophosphonate ester product whilst we envisage that the steric profile within the (1*R*,2*S*)-ephedrine auxilary strongly influences the stereochemistry at the α-carbon atom.

Herein we report our studies on a derivative of **1** in which (1*R*,2*S*)-N-^{i}Pr-ephedrine is used as the auxiliary and an examination of the influence that this structural modification has on the stereochemistry of the phosphonylation process.

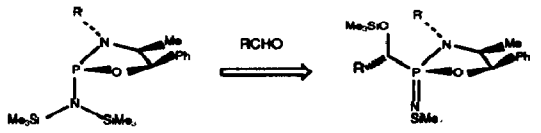
The new, chiral phosphordiamidite S_P-{(1*R*,2*S*)-N-^{i}Pr-ephedrine}$PN(SiMe_3)_2$ **5** is synthesised as outlined in Scheme 2 and isolated as a single diastereoisomer (>98%).[6] Assignment of the stereochemistry at phosphorus has been facilitated by conversion of **5** to the sulfide **6** which, on the basis of ^{1}H NMR spectroscopy appears to have the R_P configuration.[7] Upon exposure to moist air, **6** is converted to **7** quantitatively with retention of configuration at phosphorus.[5h] Subsequently, the configuration of **7** has been confirmed by a single crystal X-ray diffraction study.[8]



Scheme 2 (i) Me_2CO, reflux 24 h; (ii) $LiAlH_4$, THF, reflux 36 h; (iii) PCl_3, N-methyl morpholine, toluene r.t., 2 h; (iv) $LiN(SiMe_3)_2$, THF, -78°C then 2h at r.t.; (v) S_8, toluene, 1 h r.t.; (vi) moist air, days, r.t.

Phosphordiamidite **5** phosphonylates aldehydes stereoselectively as illustrated in Table 1. In each case the product α-siloxoimidophosphonate esters[9] are produced as two epimers with differing configurations at the α-carbon atom. ^{1}H NMR spectroscopy is consistent with both epimers having the S_P configuration. However, **5** is a less facile phosphonylating agent than **1**, presumably due to the increased steric congestion in the primary coordination sphere of the phosphorus atom resulting from replacement of a methyl group by an isopropyl group on the ephedrine nitrogen atom. Consistently, an assessment of the relative reactivities of **5** and **1** towards o-bromobenzaldehyde under standard conditions[10] reveals that the former is the less facile phosphonylating agent by a factor of at least .

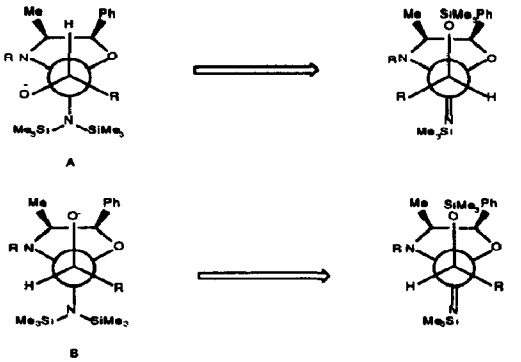
Our prime concern is how substitution of an N-Me group by an N-^{i}Pr function affects stereocontrol at the α-carbon atom. Diastereoselectivities (d.s.) in the phosphonylation of selected aldehydes *via* both **1** and **5** are reproduced in Table 1 along with the ^{31}P NMR resonances of both diastereoisomers of the products using N-^{i}Pr-(1*R*,2*S*)-ephedrine. It can be seen that, of the two phosphonylating agents, **5** has a similar diastereoselectivity profile with all benaldehyde derivatives except those containing *ortho* substituents, for which higher selectivities are obtained. We have found previously that **1** will phosphonylate *meta* and *para* substituted benzaldehydes to afford α-siloxoimidophosphonate esters in which the (S_P,S_C) epimer dominates and furthermore that the (S_P,S_C) epimer consistently displays the higher frequency ^{31}P NMR resonance.[5h] Consequently, when ΔP [δ(major) - δ(minor)] is *positive* the (S_P,S_C) epimer dominates. The d.s. values quoted in columns 2 and 3 of Table 1 reflect the proportion of this high frequency (S_P,S_C) isomer in the crude product mixture. Analysis of the ^{31}P chemical shifts for the α-siloxoimidophosphonate esters produced from **5** reveals consistently possess positive ΔP parameters and consequently we assign the dominant isomers as having the (S_P,S_C) configuration.



B	R' = Me[a]	R' = ^{i}Pr[a]	^{31}P NMR (R' = ^{i}Pr; ppm) Major	Minor	ΔP[c]
p-CNC$_6$H$_4$ **8**	91[b]	90	19.1	18.2	+0.9
p-O$_2$NC$_6$H$_4$ **9**	90[b]	90	18.9	18.0	+0.9
o-PPh$_2$C$_6$H$_4$ **10**	20[b]	85	21.4[d]	20.4[d]	+1.0
o-O$_2$NC$_6$H$_4$ **11**	47[b]	83	20.6	18.3	+2.3
2-C$_{10}$H$_7$ **12**	91[b]	92	20.3	19.4	+0.9
o-BrC$_6$H$_4$ **13**	54[b]	94	18.0	16.7	+1.3
m-BrC$_6$H$_4$ **14**	90	86	19.4	18.5	+0.9
p-BrC$_6$H$_4$ **15**	89	92	19.9	18.9	+1.0

Table 1 [a] Percentage of high frequency product (^{31}P NMR) in the crude phosphonylation mixture as determined by integration of appropriate resonances in the ^{31}P and ^{1}H NMR. [b] Reference 5h. [c] ΔP = δ(major) - δ(minor). [d] Phosphonate phosphorus only, $^{4}J_{PP}$ 3.

Consequently, it appears that an N-^{i}Pr for N-Me substitution on ephedrine leads to a consistently high level of stereocontrol at both the phosphorus and α-carbon sites with a strong, consistent preference for the (S_P,S_C) product stereochemistry. Thus, with *meta*- and *para*-substituted benzaldehydes the stereoselectivity is not significantly different between **5** and **1**,[11] whereas with *ortho*-substituted derivatives the (S_P,S_C) epimers are distinctly favoured over the (S_P,R_C) isomers. Since the product composition appears to be controlled by both the stability of and rate of silyl transfer in the important intermediate adducts A and B,[5h] we envisage that dominance of the (S_P,S_C) product isomers may reflect a decrease in stability of A over B as the stereoelectronic demands of the ephedrine nitrogen substituent increases from methyl to isopropyl (Scheme 3).



Scheme 3 Perspective view of the approach and interaction of an aldehyde with **1** or **5**. R = Me, ^{i}Pr.

Currently, our efforts are being directed towards delineating the source of stereoselectivity in the Abramov reaction and the development of catalytic, enantioselective hydrophosphonylation processes which couple the stoichiometric results reported here and earlier[5] with new approaches from metallo-organic and biological chemistries.[12]

Aknowledgements

We thank the EPSRC for for their continued support of our programmes in organophosphorus chemistry and an Earmarked studentship (to M.J.C.). We are most grateful to Dr Mark Thornton-Pett for the crystallographic analysis of **7**.

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6. Selected NMR data for **2-7** ($CDCl_3$ or C_6D_6 solvents, 298K): **2** δ_H 7.4-7.1 (m, 5H, Ph), 5.04 (d, 1H, $^3J_{HH}$ 7.6, PhC*H*O), 3.86 (dq, 1H, $^3J_{HH}$ 6.8, MeC*H*N), 2.08 (br s, 1H, NH), 1.65 (s, 3H, NCMe), 1.43 (s, 3H, NCMe), 0.72 (d, 3H, $^3J_{HH}$ 6.6, MeCHN). **3** δ_H 7.4-7.2 (m, 5H, Ph), 4.67 (d, $^3J_{HH}$ 4.0, PhC*H*O), 3.9 (br s, 1H, OH), 3.04 (dq, 1H, $^3J_{HH}$ 6.5, 4.0, MeC*H*N), 2.96 (sept, 1H, $^3J_{HH}$ 6.2, Me_2CH), 1.10 (d, 3H, $^3J_{HH}$ 6.1, Me_2CH), 1.08 (d, 3H, $^3J_{HH}$ 6.1, Me_2CH), 0.79 (d, 3H, $^3J_{HH}$ 6.6, *Me*CHN). **4** δ_H 7.2-7.1 (m, 5H, Ph-H), 5.77 (dd, 1H, $^3J_{HH}$ 9, $^3J_{PH}$ 1, PhC*H*O), 3.85 (m, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.3, MeC*H*N), 3.53 (m, 1H, $^3J_{HH}$ 6.6, $^3J_{PH}$ 15.6, C*H*Me$_2$), 1.46 (dd, 3H, $^3J_{HH}$ 6.9, $^4J_{PH}$ 2.7, CH*Me*$_2$), 1.25 (d, 3H, $^3J_{HH}$ 6.4, CH*Me*$_2$), 0.63 (d, 3H, $^3J_{HH}$ 6.3, *Me*CHN). δ_P 170.8 (s). **5** δ_H 7.3-7.0 (m, 5H, Ph-H), 5.65 (d, 1H, $^3J_{HH}$ 5.1, PhC*H*O), 3.58 (dqd, 1H, $^3J_{HH}$ = 6.6, $^3J_{PH}$ 5.2, MeC*H*N), 3.37 (dqq, 1H, $^3J_{HH}$ 6.4, 6.3, $^3J_{PH}$ 3.3, C*H*Me$_2$), 1.30 (d, 3H, $^3J_{HH}$ 6.5, CH*Me*$_2$), 1.08 (d, 3H, $^3J_{HH}$ 6.4, CH*Me*$_2$), 0.55 (d, 3H, $^3J_{HH}$ 6.4, *Me*CHN), 0.37 (s, 18H, $SiMe_3$). δ_P 147.6 (s). **6** δ_H 7.6-7.0 (m, 5H, Ph), 5.51 (dd, 1H, $^3J_{HH}$ 7.3, $^3J_{PH}$ 3.7, PhC*H*O), 3.60 (dqd, 1H, $^3J_{HH}$ 7.0, $^3J_{PH}$ 24.4, MeC*H*N), 3.52 (dsept, $^3J_{HH}$ 6.5, $^3J_{PH}$ 4.4, C*H*Me$_2$), 1.25 (d, 3H, $^3J_{HH}$ 6.6, CH*Me*$_2$), 1.12 (d, 3H, $^3J_{HH}$ 6.5, CH*Me*$_2$), 0.93 (d, 3H, $^3J_{HH}$ 6.8, *Me*CHN), 0.49 (s, 18H, $SiMe_3$). δ_P 78.9 (s). **7** δ_H 7.5-7.0 (m, 5H, Ph), 5.11 (d, 1H, $^3J_{HH}$ 5.3, PhC*H*O), 3.63 (oct, 1H, $^3J_{HH}$ 6.0, MeC*H*N), 3.34 (ddq, $^3J_{HH}$ 5.4, $^3J_{PH}$ 24.6, C*H*Me$_2$), 1.34 (d, 3H, $^3J_{HH}$ 6.5, CH*Me*$_2$), 1.01 (d, 3H, $^3J_{HH}$ 6.6, CH*Me*$_2$), 0.82 (d, 3H, $^3J_{HH}$ 6.6, *Me*CHN), 0.28 (s, 9H, $SiMe_3$). δ_P 76.1 (s).

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9. Representative characterising data for major isomers of α-siloxoimidophosphonate esters. **8** (Found: C, 60.7; H, 7.8; N, 7.95. $C_{26}H_{40}N_3O_2PSi_2$ requires C, 60.78; H, 7.85; N, 8.18). (Found: M^+, 513.241 287. Calc. for $C_{26}H_{40}N_3O_2PSi_2$: M, 513.239 673). δ_H 7.5-6.8 (m, 9H, Ph-H), 5.31 (d, 1H, $^3J_{HH}$ 5.6, PhC*H*O), 5.03 (d, 1H, $^2J_{PH}$ 14.8, PC*H*Ar), 3.41 (dqd, 1H, $^3J_{PH}$ 15.1, $^3J_{HH}$ 6.4, MeC*H*N), 2.96 (m, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.8, C*H*Me$_2$), 1.01 (d, 3H, $^3J_{HH}$ 6.5, CH*Me*$_2$), 0.75 (d, 3H, $^3J_{HH}$ 6.7, CH*Me*$_2$), 0.69 (d, 3H, $^3J_{HH}$ 6.8, *Me*CHN) 0.29 (s, 9H, $SiMe_3$), 0.01 (s, 9H, $SiMe_3$). δ_C 145.11 (s, CH-C_6H_4CN-$C_{ipso-CH}$), 137.59 (d, $^3J_{PC}$ 10.6, Ph-C_{ipso}), 131-126 (several, Ar-C), 118.60 (d, $^6J_{PC}$ 2.6, Ar-*C*N), 111.52 (d, $^5J_{PC}$ 4.1, CH-C_6H_4CN-$C_{ipso-CN}$), 80.38 (d, $^2J_{PC}$ 2.2, PhCHO), 74.42 (d, $^1J_{PC}$ 159.2, PCHAr), 53.04 (d, $^2J_{PC}$ 8.0, MeCHN), 46.72 (d, $^2J_{PC}$ 4.0, CHMe$_2$), 23.11 (d, $^3J_{PC}$ 7.4, CH*Me*$_2$), 18.37 (s, *Me*CHN), 4.02 (d, $^3J_{PC}$ 3.6, $NSiMe_3$), 1.41 (s, $OSiMe_3$).

10. Relative reactivities were assessed from the percentage reaction in a 1:5 mixture of the organophosphorus ester and aldehyde (0.17 mmol scale) in 2 cm^3 toluene solvent after 5 minutes at 25°C, as determined by ^{31}P NMR spectroscopy.[5g]

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(*Received in UK* 9 *August* 1994; *revised* 8 *September* 1994; *accepted* 16 *September* 1994)