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Double and triple asymmetric induction in phosphaaldol reactions

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Dedicated in honour of Professor Przemyslaw Mastalerz on the occasion of his 80th birthday

Abstract—A multiple asymmetric induction synthesis was applied to increase the stereoselectivity of the phosphaaldol reaction. The double stereoselectivity was achieved in the reaction of chiral di(1*R*,2*S*,5*R*)-menthyl phosphite **3** with chiral 2,3-D-isopropyliden-(*R*)-glyceraldehyde **2**. The reaction of aldehyde **2** with phosphite **1** in the presence of chiral (*R*)-ALB catalyst proceeding under stereochemical control of three chiral auxiliaries was the most stereoselective to support the conception of multiplicativity of facial selectivities of chiral reactants involved into the reaction. The stereochemistry of the phosphaaldol reaction was in agreement with Cram's rule. The absolute configuration of the new chiral compounds was established on the basis of NMR and X-ray analysis.

Stereoselectivity and stereoselective methods in organic synthesis are a problem of fundamental importance.[1] One of the more effective methods for increasing the stereoselectivity of reactions is multiple stereoselectivity, when the stereochemical process proceeds under the control of more than one chiral auxiliary.[2] Proceeding with these studies, we have applied multiple asymmetric induction to increase the stereoselectivity of a phosphaaldol reaction.[3] Initially we were interested in the additivity of several chiral inductors participating in the asymmetric synthesis. With this in mind we studied the stereoselectivity of the reaction of 2,3-D-isopropylidene-(*R*)-glyceraldehyde **2** with dialkyl phosphites. It has previously been reported, that the reaction of dimethyl phosphite with aldehyde **2** in the presence of sodium hydroxide as catalyst, proceeded with low stereoselectivity (~5–10% de), to give an inseparable mixture of (2*R*)-glycerol diastereomers.[4–6]

We studied the reaction of achiral diethyl- and diisopropyl phosphites **1a** and **b** with the chiral 2,3-D-isopropylidene-(*R*)-glyceraldehyde **2** in the presence of diazabicycloundecene (DBU) and found that this reaction proceeded with very low stereoselectivity to furnish an inseparable mixture of diastereomers (1*R*,2*R*)-**3a**,**b**/(1*S*,2*R*)-**3a**,**b** in a 45:55 ratio (Table 1). As a result we introduced additional asymmetric centres into the reacting system to increase the stereoselectivity of the reaction. The chiral di(1*R*,2*S*,5*R*)-menthyl phosphite **1c** reacted with the chiral aldehyde **2** in the presence of DBU with the double asymmetric induction increasing the stereoselectivity of reaction up to de 60%. The diastereomers (*R*,*R*)-**3c**/(*S*,*R*)-**3c** were easily separated by crystallisation or column chromatography with silica gel; a mixture of hexane–ethyl acetate in a 3:1 ratio served as eluent. The stereoselectivity of the reaction depended on the solvent, nature of the base and temperature (Table 1).

The reaction of chiral phosphite **1c** with chiral aldehyde **2** in the presence of the chiral (*S*)-ALB catalyst [aluminium–lithium bis(binaphthoxide)][7] involving three chiral auxiliaries proceeded with high stereoselectivity (85% de). At the same time the (*R*)-ALB catalyst did not increase the stereoselectivity (55% de). Hence the highest stereoselectivity in the phosphaaldol reaction was achieved in the reaction involving three chiral auxiliaries, which reinforced one another in matched asymmetric induction as in the case of (*R*)-glyceraldehyde/(1*R*,2*S*,5*R*)-menthyl/(*S*)-binol. The stereoselectivity did not increase, if the absolute configurations of chiral auxiliaries were mismatched as in the case of (*R*)-glyceraldehyde/(1*R*,2*S*,5*R*)-menthyl/(*R*)-binol.

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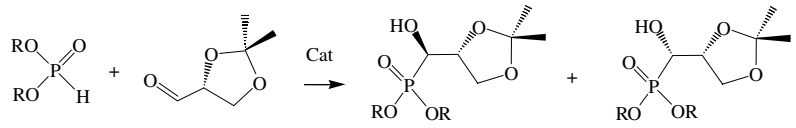
Table 1. Single, double and triple asymmetric induction in the phosphaaldol reaction



1a-c **2** (1*R*,2*R*)-**3a-c** (1*S*,2*R*)-**3a-c**

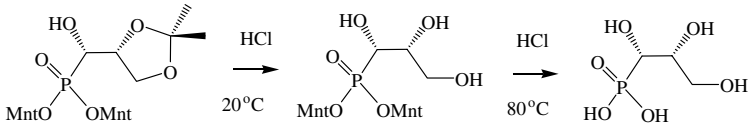
(a) R = Et, (b) *i*-Pr, (c) Mnt = (1*R*,2*S*,5*R*)-Menthyl

Entry	R	Cat	Solvent	*T* (°C)	(1*R*,2*R*)-**3**/(1*S*,2*R*)-**3**
1	Et	DBU[b]	[a]	20	45:55
2	*i*-Pr	DBU	[a]	20	45:55
3	Mnt	DBU	[a]	20	20:80
4	Mnt	DBU	Toluene	20	25:75
5	Mnt	DBU	Toluene	−10	20:80
6	Mnt	DBU	Benzene	20	26:74
7	Mnt	DBU	THF	20	28:72
8	Mnt	DBU	CH_2Cl_2	20	35:65
9	Mnt	NaOH	THF	20	30:70
10	Mnt	(*S*)-ALB[c]	THF	20	5:95
11	Mnt	(*R*)-ALB	THF	20	22:78

[a] Without solvent.
[b] DBU = diazabicycloundecene.
[c] ALB = Al–Li-bis(binaphthoxide).

The hydrolysis of compound **3c** with dilute hydrochloric acid at room temperature followed by deacetonisation produced triol **4**, whereas subsequent hydrolysis of **4** with concentrated hydrochloric acid in dioxane with heating resulted in the formation of the phosphorus analogue of threonic acid **5**, representing an important metabolite of ascorbic acid (Scheme 1).[8]

The absolute configurations of compounds **3**–**5** were established on the basis of NMR and X-ray analysis.[9–12]



(1*S*,2*R*)-(-)-**3c** (1*S*,2*R*)-(-)-**4** (1*S*,2*R*)-(+)-**5**

Scheme 1. Synthesis of phosphorus analogue of threonic acid.

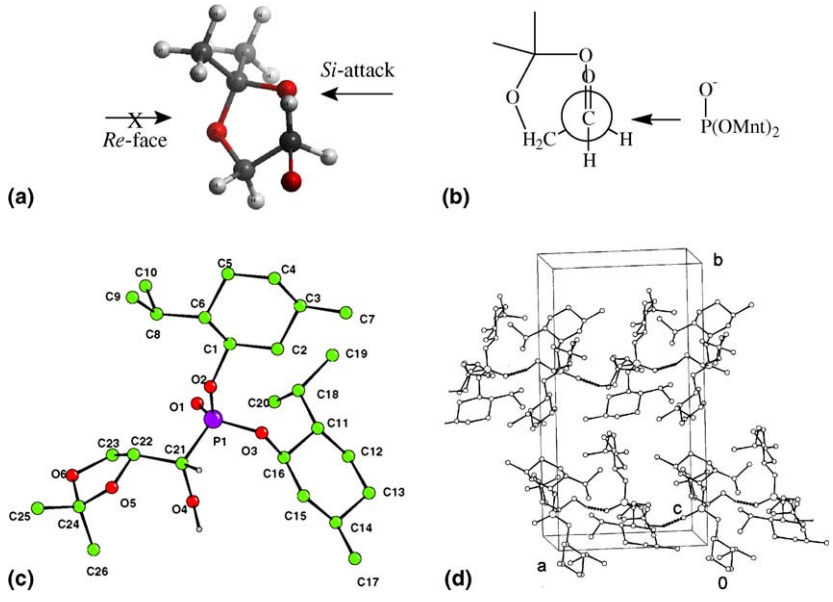


Figure 1. (a) MOPAC-8 modelling of aldehyde **2**; (b) Cram modelling of the reacting system; (c) a perspective view and labelling scheme for the independent molecule **a** of compound **3c**; (d) a perspective view and labelling scheme for the independent molecule **b** of the compound **3c**.

The MOPAC-8 modelling of the reaction between the initial compounds **1** and **2** showed, that the *Re*-side is strongly shielded and the *Si*-side is open (Fig. 1a). Therefore the phosphaaldol reaction should lead preferentially to the formation of the (*S*)-diastereomer, corresponding to the *anti*-aldol product. Consideration of the models of the formed products showed, that the stereochemistry of the phosphaaldol reaction is in the agreement with Cram's rule (Fig. 1b).[13]

X-ray analysis confirmed the (1*S*,2*R*)-configuration of product **3c**. It was found also that in its solid state there are two symmetrically independent molecules **a** and **b** connected in the chains by the O(4)–H···O(7) and O(10)–H···O(1) hydrogen bonds (Fig. 1c and d).

Acknowledgements

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9. (1*S*,2*R*)-**3**: Yield 50%, mp 98 °C (prisms from acetonitrile), $[\alpha]_D^{20} = -65$ (*c* 2, $CHCl_3$). ^1H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 0.76 (d, *J* 7.0, 6H, CH_3–Mnt); 0.87 (d, *J* 6.6, 12H, (CH_3)$_2$CH–Mnt); 1.1–2.2 (m, CH_2+CH–Mnt); 1.33 (c); 1.40 (c, 6H, (CH_3)$_2$C), 1.62 (d, *J* 11.1, 2H, CH–Mnt); 2.1–2.27 (m, CH–Mnt, 2H); 2.65 (br, *J* 12, 1H, OH); 4.05 (dt, *J* 6.6, *J* 10.5, OCHCH_2+PCH); 4.23 (dt, *J* 7, J_{AB} 6, 2H, CH_2); 4.39 (m, 2H, CH_2). ^{31}P NMR ($CDCl_3$), δ_P, 20.9 ppm.
(1*R*,2*R*)-**3** contains small quantity of the (1*S*,2*R*)-diastereomer: Yield 5–15%. ^{31}P NMR ($CDCl_3$), δ_P, 20.0 ppm.
(1*S*,2*R*)-**4**. Yield 90%, mp 108–109 °C (needles). $[\alpha]_D^{20} = -60$ (*c* 2, $CHCl_3$). ^1H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 0.78 (d, *J* 6.9, 3H, (CH_3)$_2$C); 0.78 (d, *J* 6.6, 3H, (CH_3)$_2$C); 0.89 (d, *J* 6.0, 6H, CH_3–Mnt); 0.89 (d, *J* 6.6, 6H, CH_3–Mnt); 1.00–1.50 (m, CH_2+CH–Mnt); 1.63 (m, 2H, *H*–Mnt); 1.66 (m, 2H, *H*–Mnt); 2.13 (m, 2H, H–Mnt); 2.23 (m, 2H, H–Mnt); 2.74 (br, 3H, OH); 3.83 (m, 2H, POCH); 3.90 (m, 1H, PCH); 4.23 (m, 2H, CH_2). ^{31}P NMR ($CDCl_3$), δ_P 22.51 ppm.
Cyclohexylammonium salt of (1*S*,2*R*)-**5**: Yield 65%. Mp >200 °C (dec.). ^1H NMR (CD_3OD), δ, ppm (*J*, Hz): 0.90–1.20 (m, 2H, CH_2); 1.60 (m, 4H, CH_2); 1.75 (m, 4H, CH_2); 2.70 (m, 2H, CH_2); 3.10 (s, 4H, OH); 3.40–3.60 (m, 2H, NH+CH). ^{31}P NMR (CD_3OD), δ_P 18.10 ppm. Cyclohexylammonium salt of (1*S*,2*R*+1*R*,2*R*)-**5**: ^{31}P NMR (CD_3OD), δ_P 18.1; 17.8 ppm.
10. All new compounds gave satisfactory microanalytical data. Compound **3c**: Anal. Calcd for $C_{26}H_{49}O_6P$: C, 63.91; H, 10.11; P, 6.34. Found: C, 63.80; H, 10.13; P, 6.20. Compound **4**: Anal. Calcd for $C_{23}H_{45}O_6P$: P, 6.90. Found: P, 6.71. Compound **5**: Anal. Calcd for $C_9H_{22}NO_6P$: N, 5.16; P, 11.42. Found: N, 5.00; P, 11.03.
11. Crystal data for (*SR*)-**3c**: $C_{26}H_{49}O_6P$, colourless prism $0.22\times0.37\times0.49$ mm from acetonitrile, monoclinic, space group $P2_1$, *a* 10.954(3), *b* 20.801(6), *c* 12.880(9) Å, β 94.78(8), *V* 2924 A^3, *M* 977.3, *Z* 4, $d_{calcd} = 1.11$ g/cm^3, $\mu = 11.1$ cm^{-1}, *F*(000) 977.3. Data collection: Enraf-Nonius CAD-4 diffractometer. Measured reflections 9112 (θ_{max} 68°), 5484 independent (R_{int} 0.024). Structure solution: direct method, anisotropic refinement on *F* (CRYSTALS program). The structure was refined over 4021 reflections with $I > 3\sigma(I)$ (595 refined parameters with 6.8 reflections on parameter). The absolute configuration of the compound was determined according to Flack method. The Flack parameter[12] was refined to 0.04(2) over 6563 reflections with unaveraged Friedel equivalents. Full details (excluding the structure factors) for the structure have been deposited at the Cambridge Crystallographic Data Centre, as supplementary publication no. CCDC-235073 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.ul].
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