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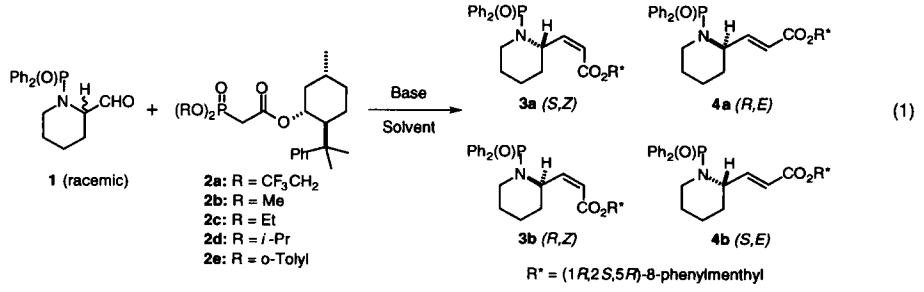
Versatile Stereocontrol in Kinetic Resolution of a Diphenylphosphinyl-Protected α-Amino Aldehyde by Reaction with Chiral Phosphonates

Reinhard Kreuder,[a,b] Tobias Rein,[b,*] and Oliver Reiser[c,*]

[a]Institut für Organische Chemie der Georg-August-Universität, Tammanstr. 2, D-37077 Göttingen, Germany
[b]Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark
[c]Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

Abstract: In kinetic resolutions of the racemic aldehyde **1** by reaction with chiral phosphonates of type **2**, all of which contain the same chiral auxiliary in the same enantiomeric form, any of the four diastereomers **3a**, **3b**, **4a** or **4b** can be obtained as the main product by an appropriate choice of reaction parameters (geometric selectivities from 66:34 to 98:2, diastereomer ratios between 93:7 and ≥99:1). The switch in stereoselectivity observed when KHMDS or NaHMDS is used as base instead of KHMDS/18-crown-6 is rationalized as resulting from a change in influence of the aldehyde α-stereocenter from Felkin-Anh-Eisenstein to chelation control. © 1997 Elsevier Science Ltd.

In recent years, the development of asymmetric versions of the synthetically very powerful Wittig reaction and its variants has received increased attention.[1] In many of the reactions of this type, the chiral reagent needs to distinguish both between enantiotopic carbonyl groups (either in a single bifunctional substrate molecule or in a racemic mixture) and between diastereotopic faces at the reacting carbonyl group. As a result, elements of substrate- and reagent-induced stereoselectivity[2] are both necessary for high product selectivities to be obtained. As part of our continuing studies in this area,[3] we have investigated asymmetric Horner-Wadsworth-Emmons (HWE) reactions of the *N*-diphenylphosphinyl[4] (DPP) aldehyde **1** with chiral phosphonates of type **2** (eq 1). Although well established in peptide chemistry,[4a] the DPP group has been used more seldom[4b-d] within the context of asymmetric synthesis. We wanted to investigate its utility as a substitute for a *N*-tosyl group, due to its being sterically and electronically similar but more easily removable. In addition, we have now discovered that the DPP group offers unique possibilities for stereocontrol: the product pattern in the asymmetric HWE reactions is highly dependent on the specific choice of reaction parameters, a fact which we preliminarily ascribe to an ability of the α-stereocenter in aldehyde **1** to influence the reaction stereochemistry differently under different conditions. As reported in this paper, we have been able to control the reaction outcome to obtain, at will, any of the four possible isomeric products as the main one, with modest to excellent geometric selectivities and in diastereomer ratios between 93:7 and ≥99:1. A tentative rationalization of the observed changes in stereoselectivity is also provided.



(1)

Selected results from kinetic resolutions of **1** by reaction[5] with **2a-e**[6] are summarized in the Table. As shown in entry 1, reaction with **2a** using our previously defined 'standard conditions' with a strongly dissociated counterion (KHMDS/18-crown-6) gave predominantly the (*S,Z*)-product **3a**,[7] with modest

geometric selectivity but excellent diastereomer ratio **3a:3b**. Changing the solvent to propionitrile (entry 2) resulted in an increased (*Z*)-selectivity, and complete preference for **3a** over **3b**.

Table. Kinetic Resolution of Aldehyde **1** by Reaction with Chiral Phosphonate Reagents **2a-e**.[a]

Entry	Reagent	Base	Solvent	(*Z*):(*E*)[b]	**3a:3b**[b]	**4a:4b**[b]	Yield[c] [%]
1	**2a**	KHMDS/18C6	THF	68:32	99:1	88:12	92
2	**2a**	KHMDS/18C6	EtCN[d]	82:18	≥99:1	87:13	80
3	**2b**	KHMDS/18C6	THF	11:89	--[e]	51:49	90
4	**2c**	KHMDS/18C6	THF	2:98	--[e]	56:44	90
5	**2d**	KHMDS/18C6	THF	0:100	--[e]	72:28	84
6	**2e**	KHMDS/18C6	THF	2:98	--[e]	93:7	69
7	**2a**	KHMDS	THF	74:26	20:80	<5:95	95
8	**2b**	KHMDS	THF	9:91	--[e]	14:86	90
9	**2c**	KHMDS	THF	5:95	--[e]	21:79	90
10	**2d**	KHMDS	THF	12:88	10:90	28:72	98
11	**2a**	NaHMDS	THF	62:38	5:95	8:92	≥99
12	**2a**	LiHMDS	THF	20:80	72:28	12:88	60
13	**2a**	KHMDS	MeCN[f]	65:35	13:87	6:94	90
14	**2a**	NaHMDS	MeCN[f]	72:28	2:98	3:97	95
15	**2a**	KHMDS	CH_2Cl_2	34:66	6:94	3:97	97
16	**2a**	NaHMDS	CH_2Cl_2	29:71	0:100	7:93	98
17	**2e**	NaHMDS	MeCN[f]	51:49	≤1:99	9:91	81
18	**2e**	NaHMDS	CH_2Cl_2	18:82	≤1:99	20:80	66
19[g]	**2a**	KHMDS/18C6	THF	55:45	97:3	91:9	92

[a]General reaction conditions: 2.2-2.3 equivalents of **1**, 1.0-1.1 equivalents of phosphonate, 1.0 equivalent of base, 5.0 equivalents of 18-crown-6 (entries 1-6, 19), ca 0.02 M in the indicated solvent, -78 °C, 15-36 h. [b]Ratio in isolated product, determined by ^{1}H NMR (integrals of olefin protons). Ratios before and after chromatography generally differed very little (<2 %). The (*Z*):(*E*) ratio refers to the ratio of (**3a+3b**):(**4a+4b**). [c]Combined isolated yield of (*Z*) and (*E*) products (>95 % pure by NMR and TLC). See also footnote 4. [d]Reaction time 60 h. [e]Not determined. [f]Reaction temperature -40 °C. [g]Stoichiometry: 1.3 equivalents of **1**, 1.0 equivalent of **2a**, 1.1 equivalents of KHMDS, 5.0 equivalents of 18-crown-6.

Reagents **2b-d** gave good (*E*)-selectivities but only poor diastereocontrol under our standard conditions (entries 3-5). Changes of solvent had little influence on the outcome of the reactions with these reagents (results not included in the Table). Instead, the new chiral phosphonate **2e** turned out to be the reagent of choice for giving access to the (*R*,*E*)-product **4a**[7] (entry 6): in combination with KHMDS/18-crown-6, **2e** showed excellent (*E*)-preference and also gave a good **4a:4b** ratio. Very recently, it has been reported[8] that HWE reagents containing aryl substituents in the phosphoryl unit usually show high levels of (*Z*)-selectivity. Based on this precedence, the high (*E*)-selectivity in entry 6 is surprising; further studies will be needed before a detailed mechanistic explanation can be given.

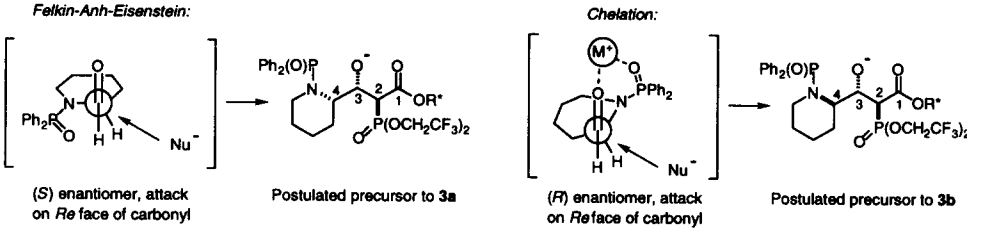
In our previous work on asymmetric HWE reactions, KHMDS/18-crown-6 has usually been the base system of choice; use of alternative bases have generally favored the same major products but with poorer selectivities. In the reactions with **1**, however, an unprecedented switch of selectivity occurred when the base was modified. As shown in entries 7-10, simply excluding the crown ether resulted in reversed diastereoselectivities for both the (*Z*)- and the (*E*)-products (compare with entries 1 and 3-5): the (*R*,*Z*)-isomer **3b**[7] was now the main product from **2a**, and reagents **2b-d** gave predominantly the (*S*,*E*)-product **4b**.[7] In order

to optimize the selectivities, the effects of varying the base and the solvent were investigated further. Although reagents **2b-d** generally did not give improved levels of selectivity (results not included in the Table), the outcome from reactions with **2a** was highly dependent on both base and solvent (compare entries 7 and 11-16). Use of KHMDS or NaHMDS as base enabled good selectivities to be obtained in some solvents, whereas LiHMDS gave poorer results[9] (entry 12). Furthermore, the geometric selectivity of **2a** varied significantly with the solvent. The combination of NaHMDS/acetonitrile gave optimal selectivity for **3b** (entry 14). In contrast, use of CH_2Cl_2 as solvent (entries 15-16) resulted in predominant formation of (*E*)-products[10] with KHMDS giving the highest diastereomer ratio in favor of **4b**.

A study of the performance of the new reagent **2e** under similarly modified conditions has also been initiated (entries 17-18). Although a reversal of the sense of diastereoselectivity was observed here as well (compare with entry 6), the levels of selectivity obtained with this reagent have so far been lower than with **2a**.

In previous work,[3b] we have found that suitably protected α-amino aldehydes can undergo dynamic resolution[11] under appropriate conditions. However, when similar conditions were applied to the reaction between **1** and **2a** (entry 19), the product ratios obtained indicate that aldehyde **1** does not epimerize fast enough to allow efficient dynamic resolution (compare with entry 1). Nevertheless, modification of the reaction conditions might enable dynamic resolution to operate, and this point is presently under investigation.

The dependence of the stereoselectivities on the choice of base and solvent is intriguing, and clearly warrants further investigation. In our 'working model' for the mechanism of these and similar asymmetric HWE reactions,[1a,12] we postulate that three separate factors influence the overall outcome: (i) the chiral auxiliary (determines the facial preference in the addition to the phosphonate enolate, and thus the absolute configuration at C2 in the formed oxyanion; *vide infra*); (ii) the R group in the $(RO)_2P(O)$ unit (determines the relative stereochemistry at C2 and C3, and thus ultimately the alkene geometry of the product); (iii) the substitution at the α-stereocenter in the substrate (determines the relative stereochemistry at C3 and C4).



The precursor of the main product isomer will be formed when all three of these control elements act in concert; as a consequence, the mechanism by which the substrate stereocenter exerts its influence will determine which of the substrate enantiomers will react faster. The major (*Z*)- and (*E*)-diastereomers obtained when KHMDS/18-crown-6 is used as the base are the ones predicted to be favored if the addition to the aldehyde carbonyl occurs according to the Felkin-Anh-Eisenstein (FAE) model.[13] If, on the other hand, the counter ion present can engage in chelation[14] between the carbonyl oxygen and the DPP protecting group,[15] a reversal of stereoselectivity would be expected. Although no definitive proof has been obtained yet, we postulate that the switch in selectivity observed when the base is altered is caused by a change in mechanism from FAE to chelation control in the addition to the aldehyde.

The predominant formation of (*E*)-products from **2a** in CH_2Cl_2 is unexpected and, if possible to generalize to reactions with other substrates, will enhance the synthetic value of reagent **2a** even further. This change in selectivity presumably reflects a change in the kinetic diastereoselectivity of the initial addition step.[12]

To summarize, we have shown that in kinetic resolutions of aldehyde **1** with a chiral phosphonate of type **2**, a judicious choice of reaction parameters (base, solvent, and the R group in the phosphonate) enables any of the four possible isomeric products to be obtained as the predominant one. It deserves emphasizing that this flexibility is possible even though all the reagents **2a-e** utilized in this study contain the same enantiomer of the chiral 8-phenylmenthol auxiliary. We are presently investigating possible extensions of the underlying concept to reactions with other substrate types, as well as the opportunities for obtaining dynamic resolution of **1** and

similar DPP-protected substrates. Furthermore, a general study of the possibilities for substrate-induced stereoselectivity in nucleophilic additions to DPP-protected amino aldehydes seems worthy of consideration.

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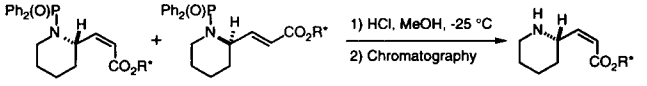
5. For a general experimental procedure for the kinetic resolutions, see reference 3c. The initially obtained (*Z*)- and (*E*)-products could not be separated by chromatography. However, the free amines obtained after cleavage of the DPP group were cleanly separable (hexanes:EtOAc:Et_3N 50:50:1 as eluent) to give geometrically pure compounds (see example below). Diastereomer ratios for each alkene isomer were unchanged after chromatography.



3 *(S,Z)*:*(R,Z)*=99:1 **4** *(R,E)*:*(S,E)*=88:12 **3**:**4**=68:32 — **5** *(S,Z)*:*(R,Z)*=99:1, 56% yield

6. For the preparation of **2a-d**, see reference 3c. The new reagent **2e**[7] was obtained (in ≥95% yield) from the corresponding methyl phosphonoacetate,[8a] in analogy with the method used for **2a-d**.
7. Spectral and analytical data in accordance with the assigned structure were obtained for this compound. The alkene geometries of **3a-b** and **4a-b** were determined by ^1H NMR. For **3a** and **4a**, the absolute configurations at the allylic stereocenter were assigned by conversion to the corresponding *N*-tosyl-protected amines.[3b] Assignments of absolute configurations for **3b** and **4b** follow by analogy.
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9. In entry 12, both alkene isomers were obtained predominantly with (*S*)-configuration at the allylic stereocenter. This fact indicates that the mechanistic details (eg., rate-determining step of the reaction) might differ between reactions using Li bases on the one hand and K or Na bases on the other.
10. For another example of the preparation of (*E*)-alkenes from a bis(trifluoroethyl) phosphonate, see: Sano, S.; Yokoyama, K.; Fukushima, M.; Yagi, T.; Nagao, Y. *Chem. Commun.* **1997**, 559-560.
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12. Our mechanistic model is based on the assumption that the initial addition of the phosphonate enolate to the aldehyde is irreversible. This assumption is likely to be correct for reagents containing a relatively electron-deficient phosphoryl unit (eg., **2a** and **2e**), at least in the absence of strongly coordinating counterions such as Li; for other reagents, however, the reaction mechanism might well depend on the specific conditions. For an excellent review which includes mechanistic discussions, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.
13. For a review, see: Gung, B. W. *Tetrahedron* **1996**, *52*, 5263-5301.
14. For a review, see: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462-468.
15. For a postulated similar effect, see reference 4c.

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