Stereodivergent Synthesis of Two Diastereoisomeric Enoates by Asymmetric Horner–Wadsworth–Emmons Reaction using a Single Chiral Auxiliary

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Stereodivergent synthesis of both diastereoisomeric enoates, including vinylogous amino acids, is achieved in the kinetic resolution of branched aldehydes and asymmetrization of prochiral cyclic ketone by chiral phosphorus reagents derived from (−)-8-phenylmenthol.

α,β-Unsaturated esters having γ-chirality are versatile building blocks in synthetic organic chemistry. We are interested in the construction of such structures, especially γ-amino enoates (vinylogous amino acids), with regard to peptide mimetic chemistry.[1] Very recently, Rein *et al.* reported the highly diastereoselective synthesis of γ-substituted α,β-enoates by the asymmetrization of *meso* dialdehydes with homochiral phosphonoacetates.[2] We applied this reaction to the asymmetric synthesis of γ-amino enoates from racemic aldehyde having an α stereogenic centre and found that the sense of chiral induction is dependent on the nature of the substituents on the phosphorus atom.[3] (The synthesis of both enantiomers from the same chiral auxiliary is an attractive concept from economic and mechanistic viewpoints). In this paper, we report our study on the influence of the phosphonate structure on the diastereoselection in the asymmetric alkenation reaction.

First, we investigated the kinetic resolution of (±)-2-phenylpropanal **2** by a homochiral dimethylphosphonoacetate **1a**,[4] which was made from (−)-8-phenylmenthol, to examine the effect of bases on both *E*/*Z*- and diastereo-selectivity. The results are presented in Table 1.

Both *E* and *Z* α,β-enoates were produced. The *E*/*Z* selectivity was sensitive to the reaction conditions. High *E* selectivity (*E*:*Z* = 95:5) was observed using lithium chloride and *N*,*N*-diisopropylethylamine (entry 1), while use of potassium hexamethyldisilazide (KHMDS) and 18-crown-6 resulted in high *Z* selectivity (entry 5, *E*:*Z* = 10:90). The diastereoselectivities were modest regardless of the reaction conditions. Highest selectivity was observed when either NaH or KHMDS–18-crown-6 was used, giving (2*E*)-**4** (48% de) and (2*Z*)-**6** (60% de), respectively. To determine the sense of chiral induction, (2*E*)-**4** and (2*Z*)-**6** were transformed to 2-phenylpropanal by ozonolysis followed by treatment with Zn/AcOH. The absolute stereochemistry of both products was determined to be 4*S* by comparison of the optical rotation with the literature value.[5]

In order to investigate whether the sizes of the substituents on the phosphorus atom affect the diastereoselectivity, two phosphonoacetate reagents, diisopropylphosphonoacetate **1b**

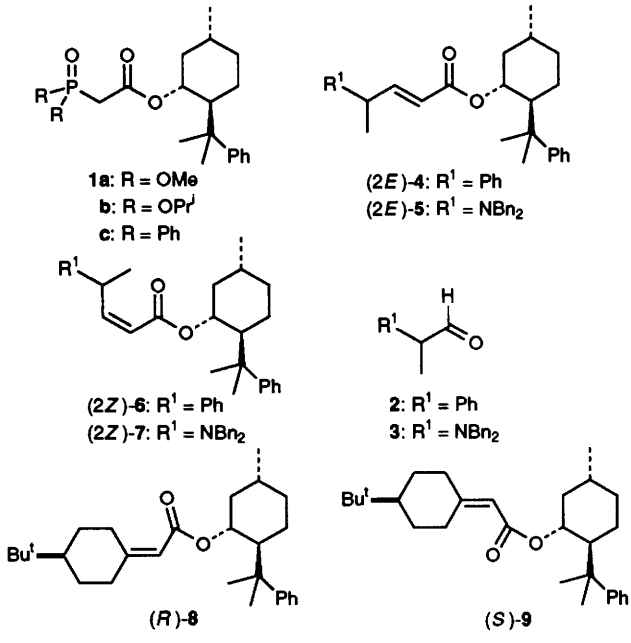

Table 1 Reaction of **1a** and (±)-2-phenylpropanal in the presence of various bases[a]

				Product ratio (diastereoselectivity)			
Entry	Base	*T*/°C	Yield/%	**4** (% de)	Config.	**6** (% de)	Config.
1[b]	LiCl–$NEtPr^i_2$	20	84	95 (32)	4*S*	5 (20)	4*S*
2	$KOBu^t$	−75	64	58 (38)	4*S*	42 (36)	4*S*
3	NaH	−75	92	45 (48)	4*S*	55 (54)	4*S*
4	$LiBu^n$	−75	80	39 (44)	4*S*	61 (58)	4*S*
5	KHMDS–18-crown-6	−75	70	10 (0)	—	90 (60)	4*S*

[a] All reactions were performed in THF with the following ratio unless otherwise noted; **1a**: base:aldehyde = 1:1:2. [b] MeCN was used instead of THF.

Table 2 Effect of the substituent on the phosphorus atom on diastereoselectivity[a]

					Products					
Entry	Phosphonate	Aldehyde	Yield/%	2*E*:2*Z*		% de	Config.		% de	Config.
1	**1a**	**2**	92	45:55	**4**	48	4*S*	**6**	54	4*S*
2	**1b**	**2**	64	>99:<1	**4**	26	4*S*	**6**	—	
3	**1c**	**2**	51	>99:<1	**4**	46	4*R*	**6**	—	
4	**1a**	**3**	43	>99:<1	**5**	60	4*R*	**7**	—	
5	**1c**	**3**	55	>99:<1	**5**	40	4*S*	**7**	—	

[a] All reactions were performed in THF using NaH as a base. The molar ratio phosphonate:base:aldehyde = 1:1:2

and diphenylphosphinoacetate **1c** were employed and their reactivity in the reaction with (±)-2-phenylpropanal were compared. The results are summarized in Table 2. The reaction of the diisopropyl derivative **1b** gave (2*E*, 4*S*)-**4** with higher *E*:*Z* ratio (>99:<1) and lower diastereoselectivity (26% de) compared with the reaction of **1a**. When the diphenylphosphinate derivative **1c** was used, the major product was (2*E*, 4*R*)-**4** with high *E*:*Z* ratio (>99:<1) and modest diastereoselectivity (46% de). Although the *E*:*Z* ratio is known to be more or less controlled by the size of the substituents on phosphorus atom,[6] it is surprising that the reversal of chiral induction was also observed in the reaction of **1c**.

The observed divergence was applicable to other types of carbonyl compounds and similar results were obtained in the resolution of (±)-*N*,*N*-dibenzylalaninal **3**. A vinylogue of D-alanine, (2*E*,4*R*)-**5**, was obtained as a major product with 60% de by the use of **1a**, while a major diastereoisomer by **1c** was (2*E*, 4*S*)-**5** (40% de), an L-alanine vinylogue. These results indicate that we can synthesize diastereoisomeric vinylogous amino acids using the same chiral auxiliary.

Interestingly, we observe the same reversibility in the reaction with a prochiral carbonyl compound. The reaction of 4-*tert*-butylcyclohexanone and **1a** produced a 36:64 mixture of (*R*)-**8** and (*S*)-**9**.† Use of **1c** instead of **1a** gave a 68:32 mixture of (*R*)-**8** and (*S*)-**9**.

We have elucidated for the first time that not only the *E*:*Z* ratio but also the sense of chiral induction can be controlled by tuning the nature of the substituents on the phosphorus atom in homochiral phosphonate mediated asymmetric Wittig type alkenations. Although the diastereoselectivity is as yet modest, the observed stereodivergence clearly shows the usefulness of this type of reaction.

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Footnote

† Although the absolute stereochemistry of these products has not been determined, the major product is assigned to have (*S*) stereochemistry since the reaction of antipode of **1a** and bicyclo[3.3.0]-octane-3,7-dione monoethylene ketal gave the *E*-alkene as a major product.[4a]

References

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