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Parallel Kinetic Resolution of Racemic Aldehydes by Use of Asymmetric Horner–Wadsworth–Emmons Reactions

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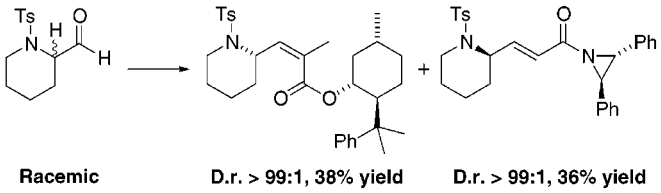
ABSTRACT



A racemic aldehyde can undergo parallel kinetic resolution (PKR) by simultaneous reaction with two different chiral phosphonates, differing either in the structure of the chiral auxiliary or in the structure of the phosphoryl group (i.e., one (*E*)- and one (*Z*)-selective reagent). This strategy allows conversion of a racemic aldehyde to two different, synthetically useful chiral products with essentially doubled material throughput and similar or improved selectivities as compared to conventional kinetic resolution.

Development of new methodology for asymmetric synthesis is presently an area of great importance in organic chemistry, and in this context kinetic resolution[1] has proved to be a useful strategy. However, the major drawback with this approach is that a maximum of only half of the racemic starting material is converted into nonracemic product. To make the process truly efficient with respect to material throughput, it would thus be required that both the unreacted starting enantiomer and the product are obtained in high isomeric purity and furthermore that they both are of use for the particular application at hand. Parallel kinetic resolution (PKR), an interesting strategy by which both enantiomers of a racemate can be converted to useful products via simultaneous reaction with two different chiral reagents, was recently introduced by Vedejs and Chen.[2] Asymmetric Wittig-type reactions have previously been studied by several groups including ours,[3] and in previous work, we have shown that racemic, α-substituted aldehydes are good substrates for asymmetric Horner−Wadsworth−Emmons (HWE) reactions.[4] We have demonstrated that α-amino aldehydes can even undergo dynamic kinetic

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(1) For a review, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(2) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584.

(3) For a review, see: (a) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369. Selected recent examples: (b) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1077. (c) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753. (d) Dai, W.-M.; Wu, J.; Huang, X. *Tetrahedron: Asymmetry* **1997**, *8*, 1979. (e) Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem.* **1998**, *110*, 525; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 515. (f) Vaulont, I.; Gais, H.-J.; Reuter, N.; Schmitz, E.; Ossenkamp, R. K. L. *Eur. J. Org. Chem.* **1998**, 805. (g) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284. (h) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997. (i) Tanaka, K.; Watanabe, T.; Shimamoto, K.-Y.; Sahakitpichan, P.; Fuji, K. *Tetrahedron Lett.* **1999**, *40*, 6599.

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resolution under appropriate reaction conditions,[4b] but for aldehydes not containing α-amino substituents, we have not yet been able to develop conditions that permit dynamic resolution. Therefore, PKR constitutes a useful complementary strategy by which both enantiomers of the racemic aldehyde could conceivably be converted into chiral products of high isomeric purity and in high combined yield. In this paper, we report the first examples of PKR by use of asymmetric HWE reactions.

We have investigated two alternative approaches by which the overall goal could be achieved. In the first case, the racemic substrate is reacted with two phosphonate reagents containing different chiral auxiliaries. The products obtained from the individual substrate enantiomers are then separated on the basis of some difference in physical properties (e.g., chromatographic behavior) imparted by the characteristic properties of the respective chiral auxiliaries. In the second approach, we have taken advantage of the observation[5] that (*E*)- and (*Z*)-selective phosphonates containing the exact same chiral auxiliary generally react with opposite enantiotopic group preference. Thus, reaction of a racemic substrate with one (*E*)-selective and one (*Z*)-selective reagent could in principle afford one (*E*)- and one (*Z*)-product with opposite absolute configuration at the allylic stereocenter, each one in high diastereomeric purity. If the products are separable on the basis of their different alkene geometry (e.g., by chromatography), even though they contain an identical auxiliary, efficient PKR would be feasible.

As an initial demonstration of how the first approach could be turned into practice, we have studied PKR of aldehyde **1**[4b] by reaction with chiral phosphonates **2**[4c] and **3a**,**b**[6] to form alkene products **4**[4c] and **5a**,**b**,[6] respectively (Scheme 1, Table 1). Reagents **3a**,**b** were readily prepared from the respective enantiomer of the chiral aziridine[7] and diethylphosphonoacetic acid. Our choice of these specific reagents was based on our previous experience of asymmetric HWE reactions with the 8-phenylmenthyl reagents on one hand and of similar asymmetric transformations of chiral carboxamides containing the aziridine auxiliary on the other. Furthermore, we expected the respective alkene products to be readily separable as a result of the difference in polarity between the two auxiliaries.

Scheme 1

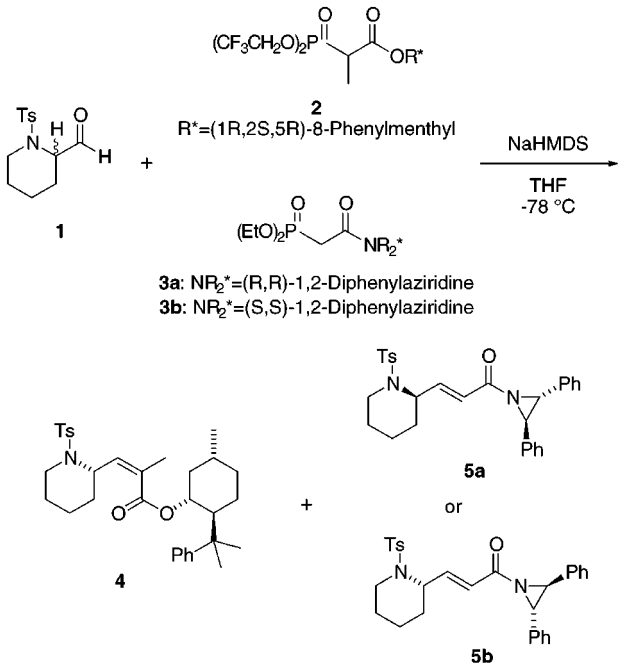


Table 1. Parallel Kinetic Resolution of Aldehyde **1** by Reaction with Phosphonates **2** and **3**[a]

entry	equiv of **2**	equiv of **3**	dr, **4**[b]	yield[c] of **4** (%)	dr, **5**[b]	yield[c] of **5** (%)
1	0.5		>99:1	43		
2		0.5 (**3a**)			80:20 (**5a**)	27
3	0.5	0.5 (**3a**)	>99:1	38	>99:1 (**5a**)[d]	36
4	0.5	0.5 (**3b**)	99:1	30	55:45 (**5b**)	41

[a] General reaction conditions: 1.0 equiv aldehyde, 0.50−0.55 equiv of each indicated phosphonate, 0.50 equiv (entries 1, 2) or 1.0 equiv (entries 3, 4) of NaHMDS, −78 °C, ca. 0.02 M in THF, 2−6 h. [b] Diastereomeric ratio in isolated product; if not otherwise indicated, the ratio in the crude was identical. The ratios refer to isomers with identical alkene geometry but opposite configuration at the allylic stereocenter. The major product isomers have the absolute configurations shown in Scheme 2. For all entries, at most trace amounts of (*Z*)-products were formed. [c] Yield of isolated product, judged as >95% pure by TLC and NMR. See also footnote 11. [d] See footnote 10.

In individual reactions with aldehyde **1**, reagent **3** displayed only modest selectivity (entry 2), whereas reagent **2** gave excellent selectivity (entry 1).[8] When the two reagents were combined in PKR experiments, the outcome very clearly illustrated the possibility for matched or mismatched combinations. In the matched case (entry 3), products **4** and **5a** were both formed with excellent stereoselectivity, with respect to both the allylic stereocenter and the alkene geometry.[9] Thus, out of the eight theoretically possible products essentially only two were formed.[10] In dramatic contrast, the mismatched case (entry 4) afforded **5b** as an almost 1:1 epimeric mixture with respect to the allylic stereocenter, while **4** was still obtained with high selectivity (although in lower yield).[11]

(5) Norrby, P.-O.; Brandt, P.; Rein, T. *J. Org. Chem.* **1999**, *64*, 5845 and references therein.

(6) All new compounds gave spectroscopic and analytical data in accordance with the proposed structures. For details regarding experimental procedures and compound characterization, see the Supporting Information.

(7) (a) Tanner, D.; Wyatt, P.; Johansson, F.; Bertilsson, S.; Andersson, P. G. *Acta Chem. Scand.* **1999**, *53*, 263. (b) Tanner, D.; Harden, A.; Johansson, F.; Wyatt, P.; Andersson, P. G. *Acta Chem. Scand.* **1996**, *50*, 361.

(8) Control experiments with various reaction stoichiometries showed that aldehyde **1** does not epimerize fast enough to undergo efficient dynamic kinetic resolution[4b] under these reaction conditions. As pointed out by a reviewer, it would be advantageous to compare the enantiomeric purity and chemical yield of the recovered **1** for each entry listed in Table 1; however, due to the relative lability of the aldehyde, this has not been performed. The same reasoning applies to aldehydes **6** and **9**, Table 2.

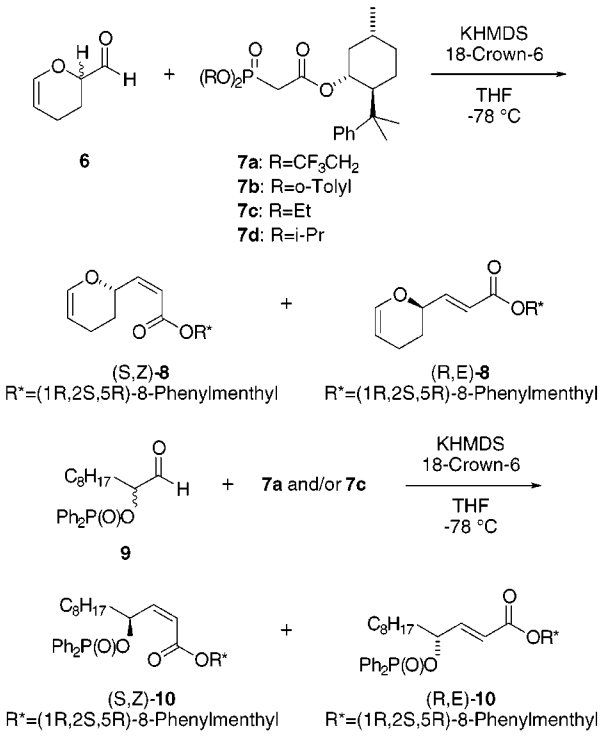
(9) At most, trace amounts of (*Z*)-products were detected in the crude products. Compounds **4** and **5a**/**5b** were readily separated and isolated in pure form by standard flash chromatography.

(10) In the crude product, the ratio (*R*,*E*)-**5a**/(*S*,*E*)-**5a** was 97:3. After chromatography, (*R*,*E*)-**5a** was obtained as a single detected diastereomer in the indicated yield.

The outcome of these PKR experiments is nicely explained by assuming that in the matched case the two chiral reagents show similar reaction rates as well as opposite enantiomer preference, which results in the ratio of the substrate enantiomers being roughly constant throughout the reaction. In the mismatched case, however, the two reagents compete for the same substrate enantiomer, leading to inferior selectivities and/or yields.

The alternative approach for PKR using asymmetric HWE reactions, in which one (*E*)- and one (*Z*)-selective reagent containing the exact same auxiliary are used in combination, has been tested in reactions between phosphonates **7a**−**d**[3g,4e] and aldehydes **6**[4a] and **9**[6] (Scheme 2, Table 2). These

Scheme 2



reactions differ from the PKR examples described in the previous section in that a maximum of four different products can be formed since the two reagents contain the exact same chiral auxiliary. Furthermore, there is a possibility for "crossover" in that the (*Z*)-selective reagent might form small amounts of (*E*)-product and vice versa.

As demonstrated by the results obtained with acrolein dimer (**6**), PKR using a combination of either one of the (*Z*)-selective reagents **7a** or **7b** with an (*E*)-selective reagent (**7c** or **7d**) afforded both (*S*,*Z*)-**8**[4a] and (*R*,*E*)-**8**[4a] in synthetically useful diastereoselectivities and good combined yields (Table 2, entries 5−8).[8,12] A comparison with the individual

(11) The yields in the HWE reactions are calculated on the amount of base used, since this is the limiting reagent. It should be noted that the yields based on the amount of aldehyde substrate in general are almost twice as high in the PKR experiments as in the individual kinetic resolutions using a single phosphonate reagent.

Table 2. Parallel Kinetic Resolution of Aldehydes **6** and **9** by Reaction with Phosphonates **7**[a]

entry	ald	equiv of **7a/7b**	equiv of **7c/7d**	prod	dr, (*Z*)[b]	yield,[c] (*Z*) (%)	dr, (*E*)[b]	yield,[c] (*E*) (%)
1[d]	**6**	0.5 (**7a**)		**8**	98:2	38	96:4	10
2	**6**	0.5 (**7b**)		**8**	94:6	33	98:2	12
3[d]	**6**		0.5 (**7c**)	**8**	81:19	12	92:8	35
4[d]	**6**		0.5 (**7d**)	**8**	69:31	1	87:13	44
5	**6**	0.5 (**7a**)	0.5 (**7c**)	**8**	94:6	38	94:6	34
6	**6**	0.5 (**7a**)	0.5 (**7d**)	**8**	96:4	42	93:7	50
7	**6**	0.5 (**7b**)	0.5 (**7c**)	**8**	92:8	36	96:4	37
8	**6**	0.5 (**7b**)	0.5 (**7d**)	**8**	95:5	40	92:8	42
9[e]	**9**	0.5 (**7a**)		**10**	79:21	39	95:5	7
10[e]	**9**		0.5 (**7c**)	**10**	59:41	4	80:20	29
11[e]	**9**	0.5 (**7a**)	0.5 (**7c**)	**10**	90:10	33	94:6	30

[a] General reaction conditions: 1.1 equiv of aldehyde, 0.50−0.55 equiv of each indicated phosphonate, 0.50 equiv (entries 1−4, 9, 10) or 1.0 equiv (entries 5−8, 11) of KHMDS, 2.5 equiv (entries 1−4, 9, 10) or 5.0 equiv (entries 5−8, 11) of 18-crown-6, −78 °C, ca. 0.02 M in THF, 2−5 h. [b] Diastereomeric ratio in isolated product; if not otherwise indicated, the ratio in the crude was identical. The ratios refer to isomers with identical alkene geometry but opposite configuration at the allylic stereocenter. The major product isomers have the absolute configurations shown in Scheme 2. [c] Yield of isolated product, judged as >95% pure by TLC and NMR. See also ref 11. [d] See ref 4a. [e] In this experiment, the (*Z*)- and (*E*)-products were not separated; the yields given are calculated on the basis of ^{1}H NMR of the mixture.

kinetic resolutions (Table 2, entries 1−4) shows that the diastereoselectivity for the (*E*)-product has increased substantially in the PKR, whereas the diastereoselectivity for the (*Z*)-product in some cases is slightly lower but generally still very good. Formation of a small amount of (*Z*)-product, with low diastereoselectivity, from the (*E*)-selective reagent (**7c** or **7d**) can explain why the diastereoselectivity in favor of (*S*,*Z*)-**8** has not increased in the PKR reactions in entries 5−7. With respect to material throughput, it is important to note that on the basis of the amount of racemic aldehyde substrate, the yield of chiral alkene product is almost *doubled* in the PKR.[11] This will be an important factor in cases where the aldehyde substrate is not very readily available.

The reactions with aldehyde **9** (Scheme 2, Table 2) demonstrate that in favorable cases both products of the PKR might be obtained in increased selectivities as compared to the individual reactions. In separate reactions of **9** with reagents **7a** and **7c**, products (*S*,*Z*)-**10**[6] and (*R*,*E*)-**10**[6] were both obtained with only modest diastereoselectivity (Table 2, entries 9−10). In contrast, PKR afforded both compounds in substantially improved selectivities (Table 2, entry 11).[11,12] The products of this and analogous PKR reactions are interesting synthetic building blocks, since further conversion, via a Pd-catalyzed allylic nucleophilic substitution,[13] to

(12) With the exception of (*Z*)-**10** and (*E*)-**10**, which are only partially separable, products differing in alkene geometry could be readily separated by flash chromatography. For compounds **8** and **10**, isomers having identical alkene geometry but opposite configuration at the allylic stereocenter are at best partially separable by chromatography.

(13) (a) Tanikaga, R.; Jun, T. X.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1185, and references therein. (b) Gatti, R. G. P.; Larsson, A. L. E.; Bäckvall, J.-E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 577 and references therein.

various chiral γ-substituted α,β-unsaturated ester derivatives can be envisioned. This possibility is presently under active investigation, and preliminary results are very promising.[14]

To conclude, we have demonstrated that by applying the strategy of PKR to asymmetric HWE reactions, efficient conversion of a racemic aldehyde to two different chiral products of high isomeric purity is feasible. This can be accomplished either by using two chiral phosphonate reagents containing different chiral auxiliaries or by using one (*Z*)-selective and one (*E*)-selective reagent containing the same auxiliary. In both cases, increased material throughput is observed since both aldehyde enantiomers are converted to product(s). Furthermore, the PKR reactions can in favorable cases afford increased selectivities compared to the individual kinetic resolutions. We believe that PKR will prove particularly useful for synthetic applications in which *both* the obtained products can be of further utility *in the same context*, either as building blocks for *two different subunits* of the same overall synthetic target or for providing access to *both enantiomeric series of the same subunit* of a given target (e.g., for natural products of unknown absolute configuration). We are presently investigating several such applications, as well as further developments of the PKR reactions, and the results of these studies will be the subject of future reports.

(14) Pedersen, T. M.; Hansen, E. L.; Jensen, J. F.; Rein, T.; Tanner, D.; Helquist, P. Manuscript in preparation.

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Supporting Information Available: Experimental procedures and characterization data for compounds **3**, **4**, **5a**, **8**−**10**, and precursors. This material is available free of charge via the Internet at *http://pubs.acs.org.*

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