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Racemic auxiliaries: applications to asymmetric synthesis

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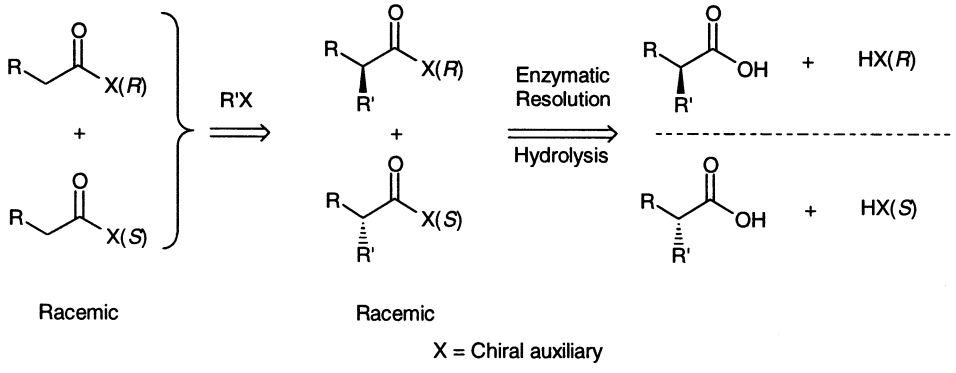
Abstract—Racemic auxiliaries have been successfully used to achieve asymmetric synthesis. Racemic Evans aldol products were obtained from racemic acyl oxazolidinones with good diastereocontrol. The enantiomers of the racemic aldol products were resolved by a lipase-catalysed acylation reaction. Hydrolysis afforded enantiomerically enriched oxazolidinones and enantiomerically enriched β-hydroxy acids. © 2002 Published by Elsevier Science Ltd.

The use of chiral auxiliaries is a widely used method for achieving asymmetric synthesis.[1] The reactions are often highly predictable and reliable and the auxiliary can often be recycled. Purification to high enantiomeric excess is easy in principle as the intermediate products are diastereoisomers, and removal of the chiral auxiliary produces enantiomerically pure material. However, stoichiometric quantities of chiral auxiliaries are required and, in turn, they need to be enantiomerically pure. In some cases chiral auxiliaries need to be prepared by resolution.

We have previously reported that racemic pantolactone can be converted into either enantiomerically enriched pantolactone acetate or pantolactone acrylate by an enzyme-catalysed kinetic resolution process.[2] This auxiliary was then used in subsequent chiral auxiliary-based chemistry. Herein we wish to report an unusual approach to asymmetric synthesis using racemic auxiliaries and an enzymatic resolution. The application of this methodology to obtain enantiomerically enriched auxiliary and enantiomerically enriched product is also reported (Scheme 1).

In order to achieve this goal, the auxiliary has to relay its stereochemistry to the substrate, which can then be resolved by the enzyme. The main priority was to employ auxiliaries which have already been used in asymmetric synthesis, and which are able to activate the substrate towards reaction. Evans auxiliaries were chosen because of the high chiral induction abilities of enantiomerically enriched 2-oxazolidinones. In addition, the aldol reaction was chosen because of the ability of Evans auxiliaries to effect asymmetric aldol reactions.[3]

Initially, racemic 4-benzyl-2-oxazolidinone **1** was prepared from the corresponding racemic amino acid



Scheme 1. General approach to asymmetric synthesis with a racemic auxiliary.

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phenylalanine. This was acylated to obtain the racemic 3-propionyl-4-benzyl-2-oxazolidinone **2**.[4] The subsequent diastereoselective aldol reaction with acetaldehyde in the presence of $TiCl_4$, (−)-sparteine and *N*-methyl-2-pyrrolidone[5] provided racemic *syn*-**3** in 99% diastereomeric excess[6] (Scheme 2).

Enzymatic resolution of the enantiomers of aldol adduct **3** via transesterification[7] catalysed by *Candida antarctica* lipase type B, afforded the acylated aldol adduct **4**[8] and the non-acylated aldol adduct **3** (Scheme 3). The choice of solvent is crucial to this process, and solvent effects are illustrated in Table 1.

The reaction rate of the lipase-catalysed transesterification was faster in non-polar solvents such as hexane and toluene (entries 1 and 3), whilst it was slower in polar solvents such as dichloromethane (entry 5).[9] However, the solvent had no affect upon the stereoselectivity of the reaction. The selectivity of *C. antarctica* lipase type B towards the aldol adduct enantiomers was in accordance with the reported stereoselectivity of this enzyme towards racemic secondary alcohols.[10]

The enantiomeric excess of the recovered **3** and of product **4** was monitored during the course of the reaction (Fig. 1). For hexane, the enantiomeric excess of the product was constant and at >99% during the course of the reaction. The enantiomeric excess of the starting material increased to 99% as the reaction approached 50% conversion.

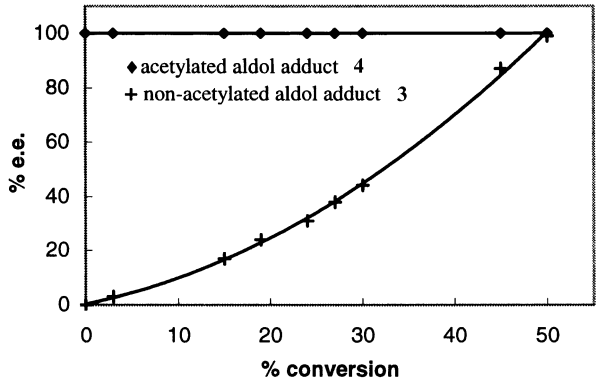
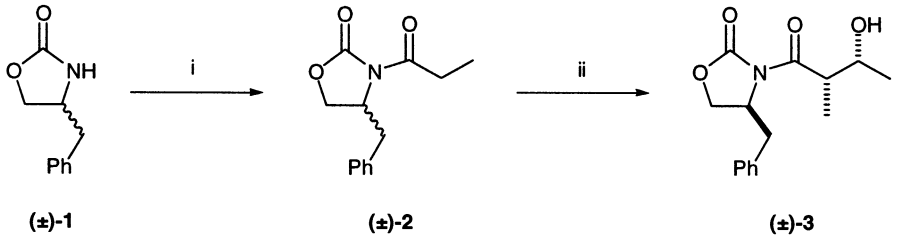
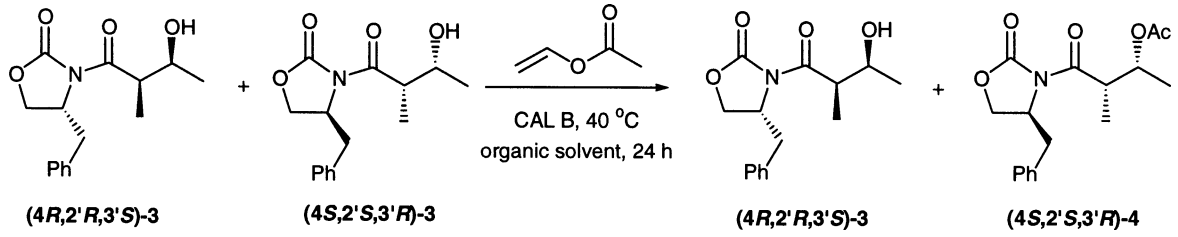


Figure 1. Kinetic study of enantiomeric excess versus conversion in hexane.



Scheme 2. Acylation and aldol reaction of (±)-4-benzyl-2-oxazolidinone **1**. *Reagents and conditions*: (i) *n*-BuLi, EtCOCl/THF, −78°C (88%); (ii) $TiCl_4$, (−)-sparteine, *N*-methyl-2-pyrrolidone, CH_3CHO/CH_2Cl_2, 0→−78°C (54%).



Scheme 3. Lipase-catalysed aldol adduct resolution.

Table 1. Influence of solvent on conversion and enantiomeric excess[a,b]

Entry	Solvent	Conversion (%)	(4*R*,2′*R*,3′*S*)-**3** e.e. (%)	(4*S*,2′*S*,3′*R*)-**4** e.e. (%)
1	Hexane	50	>99	>99
2	iPr_2O	45	>95	>99
3	Toluene	42	89	>99
4	Vinyl acetate	34	85	>99
5	CH_2Cl_2	6	17	>99

[a] 30 $mg_{enzyme}/mmol_{substrate}$ in 5 mL solvent using 1 mmol of racemic aldol and 2 mmol vinyl acetate; CAL B was Chirazyme® L-2, carrier-fixed, Carrier 3, lyophilizate from Boehringer Mannheim.

[b] Conversion and enantiomeric excess were determined by HPLC analysis (Chiralcel® OD column, hexane/*iso*-propanol 80:20, 1 mL min^{-1}, $\lambda = 254$ nm).

Finally, hydrolysis[4b] of the enzymatically resolved aldol **3** and ester **4** afforded the enantiomerically enriched 3-hydroxy-2-methylbutanoic acids (2*R*,3*S*)-**5** and (2*S*,3*R*)-**5** and the enantiomerically enriched 2-oxazolidinones (*R*)-**1** and (*S*)-**1**[11] (Scheme 4).

The choice of Evans auxiliary can be limited by the availability of an appropriate enantiomerically pure amino acid or alcohol. Aside from the (*S*)-substituted 2-oxazolidinones readily available from naturally occurring α-amino acids such as L-valine and L-phenylalanine,[12] their configurational antipodes are less accessible. The sterically constrained, designed chiral 2-oxazolidinones, such as 4,5-disubstituted-2-oxazolidinones conformationally fixed by bicyclo [2.2.1] and bicyclo [2.2.2] systems,[13] are also less easily available. However, this methodology allows the use of racemic amino alcohols to access the otherwise difficult to prepare antipodes. For example, racemic 2-amino-1-butanol is readily available at low cost.[14] Using racemic 2-amino-1-butanol to synthesise racemic (2′,3′)-*syn*-**6**, the application of the methodology herein described produced resolved (4*R*,2′*R*,3′*S*)-**6** and (4*S*,2′*S*,3′*R*)-**7**.[15] Oxidative cleavage afforded enantiomerically enriched (2*R*,3*S*)-**5** and (2*S*,3*R*)-**5** and the enantiomerically enriched 4-ethyl-2-oxazolidinones (*R*)-**8** and (*S*)-**8**[16] (Scheme 5).

In summary, starting from racemic Evans auxiliary, using a diastereoselective aldol reaction coupled to a lipase-catalysed resolution, two goals can be achieved: the preparation of enantiomerically enriched β-hydroxy acids and the indirect resolution of racemic Evans auxiliaries.

Acknowledgements

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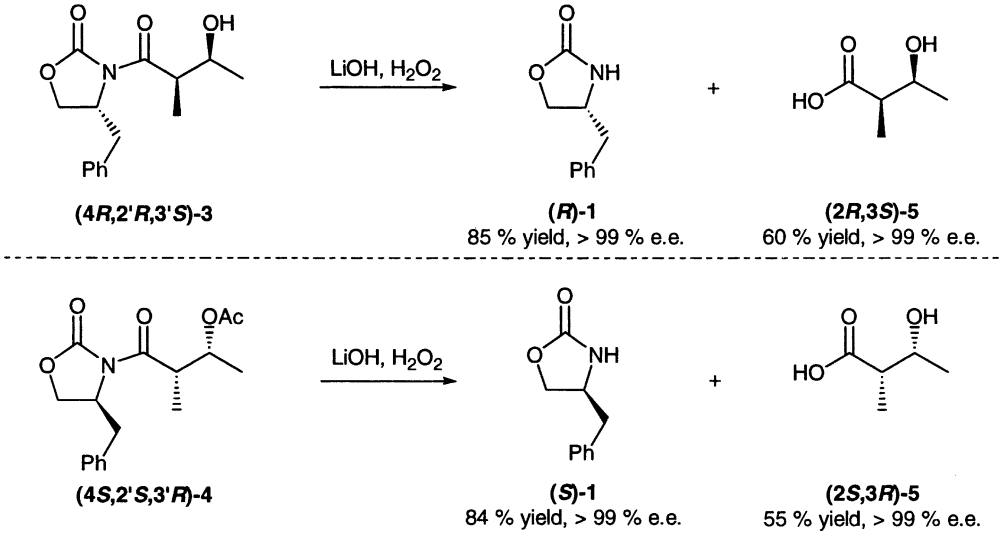
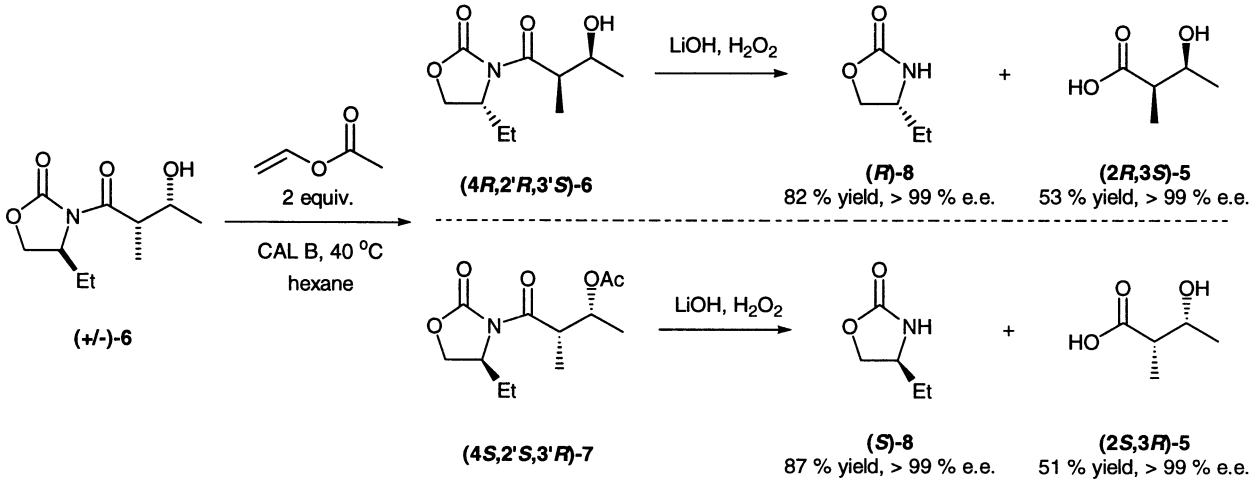


Scheme 4. Hydrolysis of products from enzymatic resolution.



Scheme 5. Preparation of enantiomerically enriched 4-ethyl-2-oxazolidinones and 3-hydroxy-2-methylbutanoic acids.

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8. **(4*S*,2′*S*,3′*R*)-*N*-(3-Acetoxy-2-methylbutanoyl)-4-benzyl-2-oxazolidinone 4**: yellow needles; mp 79–80°C; $[\alpha]_D^{30}=+77.7$ (0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta_H=1.22$ (d, $J=6.9$ Hz, 3H), 1.28 (d, $J=6.5$ Hz, 3H), 2.05 (s, 3H), 2.76 (dd, $J=9.7$ and 13.3 Hz, 1H), 3.27 (dd, $J=3.1$ and 13.2 Hz, 1H), 3.95 (dq, $J=4.3$ and 6.9 Hz, 1H), 4.08–4.28 (m, 2H), 4.56–4.64 (m, 1H), 5.30 (dq, $J_1=4.3$ and 6.4 Hz, 1H), 7.19–7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta_C=8.9$, 16.2, 19.3 36.1, 40.5, 54.0, 64.5, 68.4, 125.5, 127.1 (2C), 127.6 (2C), 133.5, 151.7, 168.8, 172.2; IR (CH_2Cl_2): ν_{max} 2975, 1780, 1735, 1695, 1450, 1370, 1225, 1110 cm^{-1}. MS (70 eV): m/z (%): 319 Da ($M^{\bullet+}$, 10%), 259 (57), 244 (46), 178 (30), 83 (95), 43 (100). Acc. mass EI+: 319.1420 Da, calcd for $C_{17}H_{21}NO_5$ 319.1417 Da. Anal. calcd for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.62; N, 4.38. Found: C, 63.54; H, 6.59; N, 4.22%.
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11. Spectroscopic data were in agreement with those reported by Harris, R. C.; Cutter, A. L.; Weissman, K. J.; Hanefeld, U.; Timoney, M. C.; Staunton, J. *J. Chem. Res. (M)* **1998**, 1228. (2*R*,3*S*)-**5**: $[\alpha]_D^{30}=+6.9$ (*c* 1.02, $CHCl_3$); (2*S*,3*R*)-**5**: $[\alpha]_D^{30}=-6.8$ (1.02, $CHCl_3$). (*R*)-**1a** and (*S*)-**1b** presented the same spectroscopic data and specific rotations of the commercial enantiomers.
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14. Commercial product from Aldrich.
15. **(4*S*,2′*S*,3′*R*)-*N*-(3-Acetoxy-2-methylbutanoyl)-4-ethyl-2-oxazolidinone 7**: yellow oil; $[\alpha]_D^{30}=-86.6$ (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.92 (t, $J=7.5$ Hz, 3H), 1.19 (d, $J=6.9$ Hz, 3H), 1.26 (d, $J=6.4$ Hz, 3H), 1.72–1.82 (m, 2H), 2.02 (s, 3H), 3.96 (dq, $J=3.4$ and 6.9 Hz, 1H), 4.13 (dd, $J=1.8$ and 8.0 Hz, 1H), 4.35–4.44 (m, 2H), 5.27 (dq, $J=3.2$ and 6.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta_C=8.2$, 11.0, 18.1, 21.1, 25.1, 42.1, 55.6, 66.8, 70.3, 153.8, 170.6, 174.0; IR (neat): ν_{max} 1780, 1735, 1700, 1385, 1370, 1240, 1210 cm^{-1}; MS (70 eV): m/z (%): 258 Da ($M^{\bullet+}$+1, 55%), 198 (100), 143 (21), 83 (40). Anal. calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.60; H, 7.47; N, 5.38%.
16. Spectroscopic data were in agreement with those reported by Iwama, S.; Katsamura, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3363; (*R*)-**8**: $[\alpha]_D^{30}=+5.7$ (0.30, $CHCl_3$); (*S*)-**8b**: $[\alpha]_D^{30}=-5.5$ (0.30, $CHCl_3$).