Kinetic Enzymatic Resolution of Cyclopropane Derivatives

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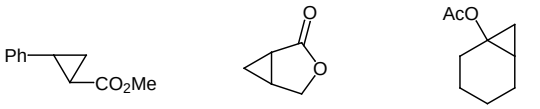
Abstract: The kinetic enzymatic resolution of cyclopropane acetates was systematically investigated utilizing 16 different hydrolases. Best results were obtained with hydrolyses in the presence of *Candida antarctica* B lipase.

Key words: enzymes, enantiomeric resolution, cyclopropanes, asymmetric synthesis, boron

Kinetic resolutions using hydrolases have been extensively investigated and applied in organic synthesis.[1] In view of the increasing interest in cyclopropane derivatives it is surprising that only a few successful examples are known in cyclopropane chemistry. In general, except for *meso*-configurated compounds, mediocre enantioselectivities are obtained when the cyclopropane moiety contains the only stereogenic unit in the molecule (e.g. compounds **1**-**3**).[2-4] We sought to optimize the kinetic resolution of **3** with various hydrolases (Table 1), solvents and reaction temperatures. The best results were obtained with *Mucor miehei* lipase (THF, phosphate buffer pH 7, 60 °C), but enantioselectivity enhancements were unacceptable.



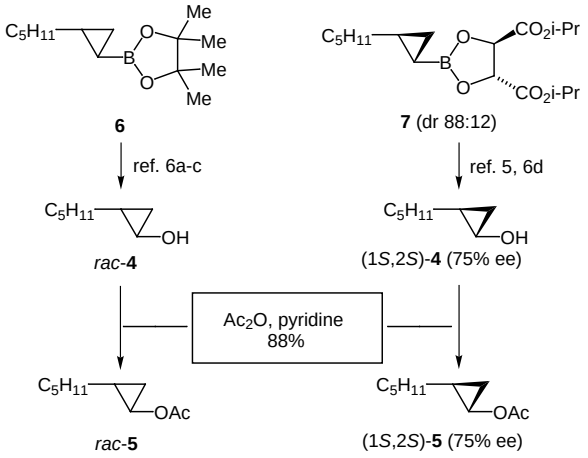
E = 20; ref. 4a — **1**
E = 36; ref. 4b — **2**
E = 23; ref. 4c — **3**

Figure 1

Table 1 Enzymes Used for Kinetic Resolutions

Enzyme (abbreviation)
Candida antarctica A lipase (CAL-A)
Candida antarctica B lipase (CAL-B)
Pseudomonas cepacia lipase (PCL)
Rhizomucor miehei lipase (RML)
Mucor miehei lipase (MML)
Candida rugosa lipase (CRL)
Aspergillus niger lipase (ANL)
Rhizopus arrhizus lipase (RAL)
Porcine liver esterase I (PLE I)
Porcine liver esterase II (PLE II)
Porcine pancrease lipase (PPL)
Rhizopus niveus lipase (RNL)
Horse liver esterase (HLE)
Acylase
Thermomyces lanuginosa lipase (TLL)
Alcaligines sp. lipase (ASL)

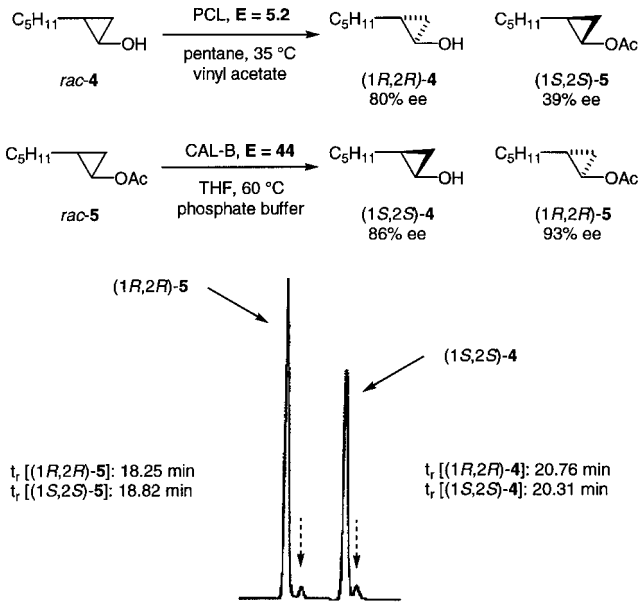
We then performed similar studies with racemic and enantiomerically enriched cyclopropanol *rac*-**4** and (1*S*,2*S*)-**4** (75% ee) and acetates *rac*-**5** and (1*S*,2*S*)-**5** (75% ee), obtained from cyclopropylboronic esters **6** and **7** (dr 88:12), respectively (Scheme 1).[5,6]



Scheme 1

All attempts to selectively acetylate cyclopropanol *rac*-**4** with vinyl acetate in the presence of an enzyme failed. At 67% (calculated) turnover, the enantiomeric excess of the cyclopropanol (1*R*,2*R*)-**4** was similar to that observed in the diastereoselective approach using cyclopropylboronic ester **7**, nevertheless this route was still impractical. Better results were obtained from hydrolysis, with CAL-B (E = 44; THF, phosphate buffer pH 7, 60 °C) superior to other enzymes (Scheme 2).[7] Although these findings were promising, it was obvious that by using this protocol enantiomerically pure cyclopropanols could not be obtained in just one cycle. However, since the enantiomerically enriched cyclopropanol (1*S*,2*S*)-**4** is synthesized from cyclopropylboronic ester **7** as conveniently as the racemic compound *rac*-**4** from the corresponding ester **6**, only one enzymatic purification step gave the enantiomerically pure product (1*S*,2*S*)-**4** (ee >98%; turnover 78%).

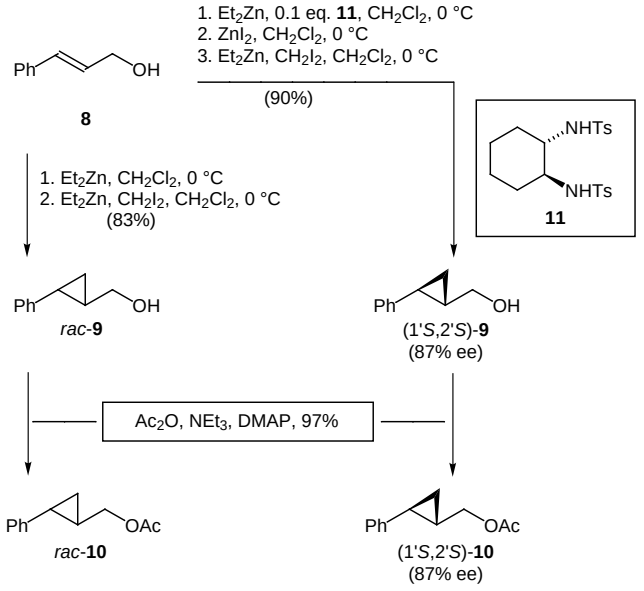
Similar results could be obtained with the cyclopropanes **9** and **10**, respectively. Again, racemic and enantiomerically enriched compounds were both readily synthesized from cinnamyl alcohol (**8**) (Scheme 3). In this case the *Simmons-Smith* reaction was used,[8] following the *Furukawa* protocol to get *rac*-**9** (83%),[9] and utilizing the



Glc trace for the enantioseparation of cyclopropanol **4** and acetate **5** (dotted arrows: minor enantiomers). Conditions: 0.5 bar H_2, 3 min at 60 °C then 2 °C/min. Stationary phase: Bondex β (25 m glass capillary).

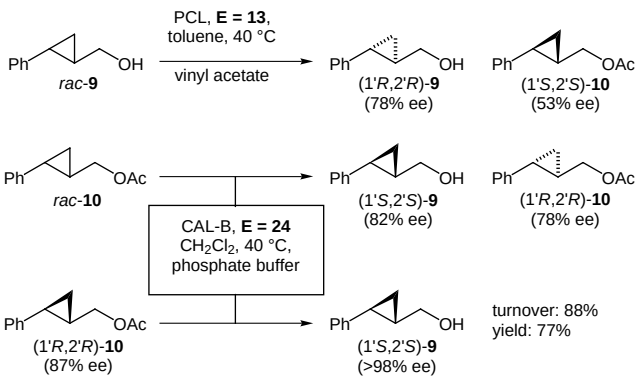
Scheme 2

Denmark conditions[10] to furnish (1'*S*,2'*S*)-**9** (90%, 87% ee) in the presence of ligand **11**.[11,12] The enantiomeric excess for these compounds was determined by hplc (Chiracel OD, hexane:isopropanol 99.6:0.4 to 95:5).



Scheme 3

Although the enzymatic conversion of alcohol *rac*-**9** gave slightly better selectivities (up to E = 13; PCL, toluene, 40 °C) than for cyclopropanol *rac*-**4**, these results were inferior to the catalytic asymmetric cyclopropanation reaction. Hydrolysis of *rac*-**10** was achieved best in the presence of CAL-B. In this case the selectivity could be increased by changing the solvent from THF (E = 5.3), pentane (E = 7.3) and toluene (E = 13) to dichloromethane (E = 24). Again, the enantiomeric excess obtained was not sufficient to get the enantiomerically pure compound, but starting from the enantiomerically enriched (1'*S*,2'*S*)-**10** (87% ee from the enantioselective catalytic reaction) did efficiently yield the pure enantiomer (ee >98%, 88% turnover, 77% yield).[13]



Scheme 4

Given that the maximum yield of a kinetic enzymatic resolution is <50% (exception: *meso*-compounds), *versus* an enantioselective catalysis that does not yield enantiomerically pure cyclopropanes, the herein reported combination of both would be the most efficient protocol. In conclusion, we did not only get high *E*-values (for cyclopropanes) for the lipase-catalyzed transformation, but could also propose a practical route to pure compounds. The evaluation of the generality of this approach is currently under investigation in our laboratories.

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(13) Experimental Procedure: CAL-B (1.20 g; 'Chirazyme L 2') was suspended in 40 mL phosphate buffer (pH 7) and 3.40 g (17.5 mmol) (1'*S*,2'*S*)-**10** (87% ee) in 20 mL CH_2Cl_2 was added. After 22 h at 40 °C (monitored by hplc) the organic layer was separated, the aqueous layer extracted with CH_2Cl_2, and the combined layer dried over $MgSO_4$. Chromatographic separation (petroleum ether 40-60:EtOAc 9:1 to 3:1) followed by Kugelrohr destillation (80 °C/0.5 torr) yielded 2.00 g (13.5 mmol, 77%) of the pure (3-phenylcyclopropyl)methanol (1'*S*,2'*S*)-**9** (>98% ee). The spectroscopic data were in full agreement with those published previously; $[\alpha]^{20}_D$ = +86 (*c* 1.0, EtOH), $C_{10}H_{12}O$ (148.20): calcd. C 81.04, H 8.16; found C 81.03, H 8.21.

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