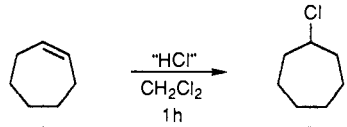
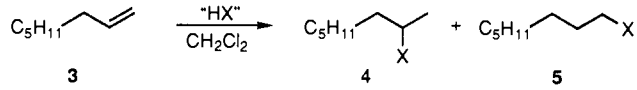


1 2

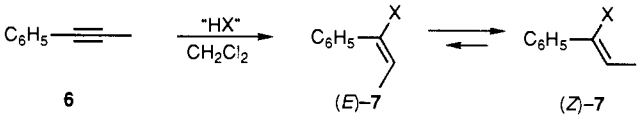
97%	HCl	0%
3%	HCl, SiO_2	62%
3%	$SOCl_2$, SiO_2	81%



3 4 5

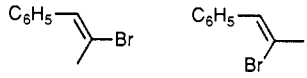
100%	HCl, 1 h	0%	
11%	HCl, Al_2O_3, 1h	60%	
6%	$(COCl)_2$, Al_2O_3	86%	
6%	HBr, 0.3 h	11%	83%
trace	HBr, SiO_2, 0.7 h	96%	0%
trace	$(COBr)_2$, Al_2O_3, 0.3 h	99%	0%
4%	PI_3, SiO_2, 0.3 h	78%	
9%	PI_3, Al_2O_3, 0.3 h	91%	

(*E*)-**7**, resulting from syn addition, was formed initially. In the presence of excess reagent, it rapidly equilibrated with the thermodynamically more stable *Z* isomer. Thus either isomer could be obtained in good yield by the proper choice of conditions.[8]



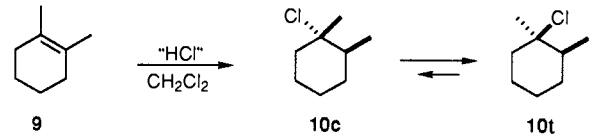
6 (*E*)-**7** (*Z*)-**7**

100%	HCl, 1 h	0%	0%
44%	HCl, SiO_2, 1 h	39%	11%
0%	$(COCl)_2$, Al_2O_3, 0.3 h	85%	14%
0%	3 h	3%	96%
0%	HBr, 3h	29%	8%
0%	HBr, Al_2O_3, 0.3 h	14%	79%
2%	PBr_3, Al_2O_3, 3 h	82%	10%
0%	PBr_3 (xs), Al_2O_3, 3 h	4%	80%
6%	HI, 24 h	74%	19%
trace	AcI, Al_2O_3, 0.3 h	92%	6%



(*E*)-**8** (*Z*)-**8**

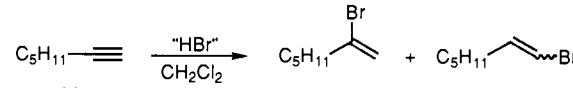
Alkenes also undergo preferential syn addition. Being tetrasubstituted, 1,2-dimethylcyclohexene (**9**) undergoes rapid addition of HCl in solution.[2b,c] However, treatment with $(COCl)_2$ in the presence of alumina afforded adducts even more rapidly. Initially chloride **10c** predominated. However, since addition is reversible under these conditions, ultimately the known thermodynamic ratio **10c**:**10t** = 0.3[2c] was reached.



9 **10c** **10t**

12%	HCl, 0.5 h	69%	14%
0%	$(COCl)_2$, Al_2O_3, 0.3 h	22%	73%

Simple treatment of 1-octene (**3**) or 1-phenylpropyne (**6**) with a saturated solution of HBr afforded, as expected, principally the radical addition product **5** (X = Br) or **8** (*E*, 18%; *Z*, 29%), respectively. However, similar treatment in the presence of silica gel or alumina resulted in almost *exclusive* formation of the ionic products **4** and **7** (X = Br).[9] Even more conveniently, treatment of alkene **3** or alkyne **6** with an HBr precursor such as $(COBr)_2$ or PBr_3 in the presence of alumina afforded the ionic product **4** or **7** (X = Br) in high yield. Once again, either the *E* or *Z* isomer of **7** could be obtained predominantly. Similar treatment with PI_3 or AcI readily afforded iodides **4** or **7** (X = I). The terminal alkyne **11**, which underwent only slow addition of HBr in solution, afforded bromide **12** in good yield on treatment with AcBr over alumina.



11 12 13

48%	HBr	8%	1%
14%	AcBr, Al_2O_3 (in C_5H_{12})	82%	3%

Silica gel and alumina surfaces presumably promote ionic addition through hydrogen-bonding interactions, which both polarize the HX bond and reduce entropy effects by bringing the two reactants together. Studies continue to delineate the mechanistic features of this highly useful procedure and extend it to additional unsaturated substrates and other electrophilic reagents.

Acknowledgment. Generous financial support by the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of North Carolina Research Council is gratefully acknowledged.

(7) In a typical experiment, 2 equiv of reagent was added to a stirred suspension of 2.5 g of Merck grade 40 silica gel or Fisher A540 alumina, which had been equilibrated with the atmosphere at 120 °C for at least 48 h, in 5 mL of CH_2Cl_2 containing 1.0 mmol of the substrate. Yields were determined gas chromatographically. Comparable results were obtained on a preparative scale by adding the reagent as a 1.0 M solution to a stirred suspension of 25 g of adsorbent in 50 mL of CH_2Cl_2 containing 20 mmol of the substrate. Products were isolated by distillation or preparative gas chromatography and identified by IR and ^1H NMR spectroscopy.

(8) By contrast, alkyne **6** undergoes slow Lewis acid catalyzed addition of HCl or HBr in CH_2Cl_2 to give adducts (*E*)-**7** and (*Z*)-**7** in a ratio of 2.3 or 3.0, respectively: Marcuzzi, F.; Melloni, G. *J. Am. Chem. Soc.* **1976**, *98*, 3295-3300; *Gazz. Chim. Ital.* **1975**, *105*, 495-507.

(9) Similarly, the ratio of heterolytic to homolytic decomposition of peroxides is much greater on the highly polar surface of silica gel than in solution: (a) Leffler, J. E.; Barbas, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 7768-7773. (b) Lindley, S. M.; Flowers, G. C.; Leffler, J. E. *J. Org. Chem.* **1985**, *50*, 607-610.

Kinetic Resolutions of Chiral Unsaturated Alcohols That Cannot Be Resolved Efficiently via Enantioselective Epoxidation

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Received June 19, 1990

Katsuki/Sharpless epoxidations of allylic alcohols[1,2] perhaps constitute the single most important development in asymmetric induction during the last decade; certainly, they are among the most useful reactions for contemporary organic syntheses.[3,4] Protocols based upon asymmetric epoxidations also include some extremely valuable kinetic resolutions,[5] but there are restrictions that limit this approach. Specifically: (i) they do not work well for some allyl alcohol derivatives; (ii) they are not generally applicable to substrates other than allylic alcohols; and (iii) experimental procedures involved are moderately tedious because,

(1) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(2) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 247.

(3) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 193.

(4) Pfenninger, A. *Synthesis* **1986**, 89.

(5) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (b) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Taktani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589. (c) Carlier, P. R.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978. (d) Dai, L.; Lou, B.; Zhang, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5195.

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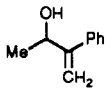
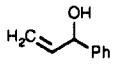
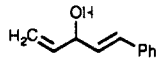
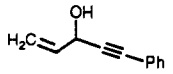
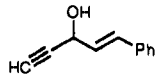
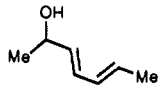
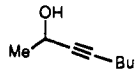
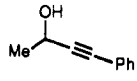
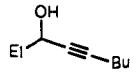
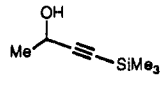
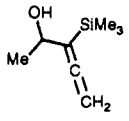
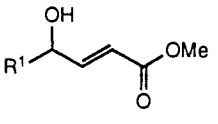
Table I. Biocatalytic Resolutions of Unsaturated Alcohols **1–11**[a]

entry no.	compd	time (h), conversn[b] (%)	recovered alcohol: yield[c] (%), ee[d] (%) (confign)[e]	product acetate: yield (%), ee (%)	E[f]
1		7.0, 52	32, >95 (*S*)	47, >95	>20
2		3.0, 67	39, >95 (*S*)[g]	32, 46	<10
3		2.5, 50[h]	41, >95 (*S*)	49, >95	>20
4		3.5, 52	43, >95 (*S*)	42, >95	>20
5		3.0, 57	28, >95 (*S*)[g]	44, 68	>20
6		3.0, 46	26, 69 (*S*)	37, 79	10–20
7		4.0, 52	31, >95 (*S*)	41, 87	>20
8		3.5, 50	47, >95 (*S*)	48, >95	>20
9		3.0, 54[i]	48, >95 (*S*)	36, 82	>20
10		48, 50	27, >95 (*S*)	45, >95	>20
11		120, 45	31, 81[j]	45, >95	>20

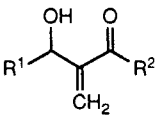
[a] The substrate (×g) at 0.1 M concentration in hexane was stirred with the enzyme (0.5 × g, an alternative number of "mass equivalents" is indicated), 4 equiv of vinyl acetate, and 0.5 g of ground molecular sieves, for the indicated time at 25 °C. [b] As monitored by capillary GC (corrected by using mixtures of known composition) and by ^{1}H NMR integrals. [c] GC studies show that these reactions are very clean; some of the isolated yields expressed here reflect the usual difficulties encountered with separation and purification of volatile compounds. [d] Enantiomeric excess determined via ^{1}H NMR/chiral shift experiments unless otherwise indicated. [e] Assigned by conversion to compounds of known absolute configuration and/or comparison of optical rotations. [f] Values determined from the extent of conversion and the enantiomeric excess of the recovered substrate as described and checked via values determined from the ee of the product. [g] Enantiomeric excess determined via ^{1}H NMR analysis of the Mosher ester (MPTA) derivative. [h] Number of mass equivalents of enzyme = 2.0. [i] Number of mass equivalents of enzyme = 1.0. [j] Absolute configuration not determined. In another run of this experiment, the reaction was left to proceed to 50% conversion and starting material of >95% ee was isolated.

for instance, products and substrates must be isolated from significant amounts (10–20 mol %) of catalyst residues and then separated from each other.

Recent studies in our laboratories[6] demonstrated that irreversible, enzyme-mediated acylations[7] in organic solvents[8] could be used to resolve compound types I and II. Data collected from



I



II

those resolutions indicate that enantioselectivity is high when the substituent R^1 is relatively small, and, for such substrates, the *R* enantiomer is acylated faster than its *S* antipode.

Subsequently, it occurred to us that the *only* restriction on these resolutions might be that the alcohol must have one small and one relatively large substituent at the hydroxymethine center for good enantioselection. Preliminary findings based on this working hypothesis are presented here.

Eleven substrates were subjected to vinyl acetate and a crude preparation of *Pseudomonas* AK in hexane, and nine were resolved with high enantioselectivity (i.e., E values >20,[9] Table I). The other two resolutions (entries 2 and 6) were only moderately selective; nevertheless, starting material of over 95% ee was isolated by letting one of these reactions run to 67% conversion (entry 2). All the alcohols in Table I have one small and one relatively large substituent attached to the hydroxymethine center, and the resolutions can be effective when the small group is methyl (entries 1, 6–8, 10, and 11), ethenyl (entries 2–4), ethynyl (entry 5), or ethyl (entry 9). None of the substrates in the present study have electron-withdrawing groups attached to the alkene, hence, such functionality is not a prerequisite for effective resolution. The

(6) (a) Burgess, K.; Henderson, I. *Tetrahedron Asymmetry* **1990**, *1*, 57. (b) Burgess, K.; Jennings, L. *J. Org. Chem.* **1990**, *55*, 1138.

(7) Degueil-Castaing, M.; Jeso, B. D.; Drouillard, S.; Maillard, B. *Tetrahedron Lett.* **1987**, *28*, 953.

(8) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114.

(9) (a) Chen, C.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294. (b) Sih, C. J.; Wu, S.-H. *Top. Stereochem.* **1989**, *19*, 63. Small errors in measurements of E values lead to large numerical differences due to the logarithmic nature of this mathematic relationship. Consequently, ranges of E value are quoted in this paper to classify the resolution procedures as fair (E < 10), good (E = 10–20), and excellent (E > 20).

R enantiomer is acylated faster than the *S* antipode in the experiments depicted in the first 10 entries of Table I (the sense of the enantioselectivity for the resolution depicted in entry 11 has not yet been established).

Crude preparations of *Pseudomonas* AK are currently available for around $1 per gram, and approximately equal masses of the substrate and enzyme preparation are used; consequently, these resolutions are extremely economical. Furthermore, the experimental procedure for these resolutions is exceedingly simple (see Table I).

Substrates resolved in this study were chosen because the corresponding asymmetric epoxidations do not work well. For instance, the allylic alcohol shown in entry 1 is unlikely to be resolved smoothly under the metal-catalyzed conditions due to decomposition of the product (as observed for epoxidation of 2-phenylallyl alcohol).[2] Similarly, 1-phenylallyl alcohol reacts slowly under metal-catalyzed conditions and with poor enantiodiscrimination[2] (cf. entry 2), and Sharpless epoxidations of 2,4-dienols, while possible,[10] generally are complicated by decomposition products[11] (cf. entry 6).

The resolutions depicted in entries 3–6 are particularly notable for two reasons. Firstly, good yields of recovered starting materials and acetate products were isolated, demonstrating that the method can be applied to such sensitive substrates. Secondly, it would be extremely difficult to obtain optically active 3-hydroxy-1-phenylpenta-1,4-diene (**3**), for instance, via the Sharpless epoxidation. The Sharpless selection rules for kinetic resolution via asymmetric epoxidation[3] imply that each enantiomer of this diene (**3**) has one reactive stereotopic face no matter what enantiomer of dialkyl tartrate is used in the catalyst; hence, epoxidations that leave unreacted starting material are possible only if one of the alkene groups reacts much faster.[12] Biocatalytic resolutions, however, provide an excellent route to optically active 1,4-dien-3-ol (**3**) and related compounds.

Entries 5 and 7–10 (Table I) indicate that acylations mediated by *Pseudomonas* AK also provide access to optically active *propargylic* alcohols. Asymmetric reductions of the corresponding ketones with Alpine-Borane (B-isopinocampheyl-9-borabicyclo-[3.3.1]nonane),[13] probably the most useful of the literature procedures[14] for preparation of such materials, are *least* enantioselective when a small group is attached to the ketone functionality. The lipase-catalyzed process is nicely complementary insofar as resolutions of alkynyl alcohols with a small substituent at the hydroxymethine center proceed with high enantiodiscrimination.

Finally, while asymmetric epoxidations of allenic alcohols are generally disappointing,[2] the biocatalytic resolution depicted in entry 11 of Table I is highly enantioselective. In fact, the main restriction on this resolution is decomposition of the product and starting material during the chromatographic separation used to purify them.

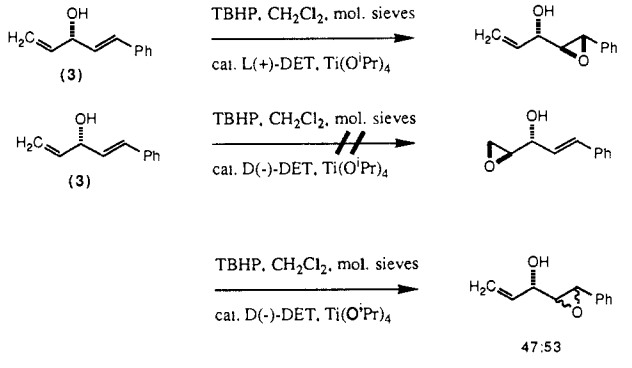
Unlike the Sharpless methodology, the resolutions described here are limited to alcohols with one relatively large and one small substituent attached to the hydroxymethine center; however, our procedure can be used to resolve substrates that are not amenable to asymmetric epoxidation. Furthermore, acylations of *R* enantiomers mediated by *Pseudomonas* AK consistently proceed faster than those of the other enantiomer, a trend that will be valuable in the planning of synthetic schemes based on this methodology. Other data, to be described in the full account of this work, indicates that *Pseudomonas* AK also mediates enantioselective acylations of some allylic alcohols that *can* be resolved via the Sharpless methodology. We believe that where both techniques are applicable, the enzyme-mediated approach is usually superior and will usurp the role of many epoxidation-based kinetic resolutions in organic synthesis.[15]

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support. We also thank Amano Company, and Mr. Tominaga and Mr. Watanabe in particular, for assistance with the lipase enzymes.

(10) Falck, J. R.; Mana, S.; Siddhanta, A. K.; Capevila, J.; Bunyak, J. D. *Tetrahedron Lett.* **1983**, *24*, 5715.

(11) Bernat, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491.

(12) Results presented below prove that the aryl-substituted alkene group is indeed more reactive than the monosubstituted alkene; epoxidation occurs on the aryl-substituted alkene for catalysts based both on L-(+)-diethyl tartrate (DET) *and* on D-(−)-DET. *Clean* epoxidation of the aryl-substituted alkene



(**3**) to one epoxide stereoisomer with the catalyst from L-(+)-DET, and epoxidation to a mixture of diastereomers with D-(−)-DET, implies the *S* configuration at the hydroxymethine center, an assertion that was confirmed via other means.

(13) Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553.

(14) (a) Mori, K.; Akao, H. *Tetrahedron Lett.* **1978**, 4127. (b) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. (c) Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854. (d) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717. (e) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. S. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (f) Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron Lett* **1986**, *27*, 983. (g) Ito, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1989**, *30*, 7083. (h) Pappo, R.; Collins, P.; Jung, C. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 64. (i) Soai, K.; Niwa, S. *Chem. Lett.* **1989**, 481. (j) Yadav, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455.

(15) Lipase-mediated *hydrolyses* of some unsaturated compounds containing $CF_3CH(OH)$ functionality have been reported, but the enantioselectivities observed are inferior to the results reported here. See: Lin, J. T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1987**, *52*, 3211.

Enantio-DNA Recognizes Complementary RNA but Not Complementary DNA

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Antisense oligonucleotides provide an attractive strategy for designing chemotherapeutic agents and biochemical tools,[1] but the biological applicability is quite limited because of the existence in cells of large amounts of nucleases. To overcome this problem, efforts to increase resistance to nucleases as well as to improve the stability of duplex (or triplex) formation have been made.[1] As oligonucleotides with a modified nucleoside unit, oligomers with an α-deoxyribose backbone instead of a natural β-deoxyribose backbone have been prepared and characterized.[2]

(1) For reviews, see: (a) Miller, P. S.; Ts'O, P. O. P. *Annu. Rep. Med. Chem.* **1988**, *23*, 295. (b) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543.

(2) (a) Morvan, F.; Rayner, B.; Imbach, J.-L.; Lee, M.; Hartley, J. A.; Chang, D.-K.; Lown, J. W. *Nucleic Acids Res.* **1987**, *15*, 7027. (b) Bloch, E.; Lavignon, M.; Bertrand, J.-R.; Pognan, F.; Morvan, F.; Malvy, C.; Rayner, B.; Imbach, J.-L.; Paoletti, C. *Gene* **1988**, *72*, 349. (c) Imbach, J.-L.; Rayner, B.; Morvan, F. *Nucleosides Nucleotides* **1989**, *8*, 627.

0002-7863/90/1512-7436$02.50/0