H, RuNHNC(O)), 3.15 (vt, 8 H, NCH_2CH$_2$CH$_2$CH$_3$), 2.90 (m, 4 H, NHC(O)CH_2CH$_2$S), 2.70 (m, 4 H, NHC(O)CH$_2$CH_2S), 1.62 (m, 8 H, NCH$_2$CH_2CH$_2$CH$_3$), 1.45 (m, 8 H, NCH$_2$CH$_2$CH_2CH$_3$), 1.0 (t, 12 H, NCH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz, 18 °C) δ 180.5 (RuNHC(O)), 58.7 (NCH$_2$CH$_2$CH$_2$CH$_3$), 42.3 (NHC(O)CH$_2$CH$_2$S), 26.4 (NHC(O)CH$_2$CH$_2$S), 23.9 (NCH$_2$CH$_2$CH$_2$CH$_3$), 19.7 (NCH$_2$CH$_2$CH$_2$CH$_3$), 13.6 (NCH$_2$CH$_2$CH$_2$CH$_3$); IR (KBr, cm^{-1}) 3314 (ν_{N-H}), 2957, 2872, 1603 (ν_{CO}), 1368, 1269, 1173, 1094 (ν_{RuN}) 1048. Anal. Calcd for $RuC_{22}H_{46}O_2N_3$: C, 46.87; H, 8.12; N, 9.94. Found: C, 47.21; H, 8.30; N, 9.80.

[PPh$_4$][Ru(N)(HNC(O)CH$_2$CH$_2$S)$_2$] (7b) was prepared as above from 3-mercaptopropionamide and [PPh$_4$][Ru(N)(OSiMe$_3$)$_4$]: ^{1}H NMR ($CDCl_3$, 500 MHz, 18 °C) δ 7.90 (m, 4 H, p-(C$_6H_5$)$_4$P), 7.76 (m, 8 H, o-(C$_6H_5$)$_4$P), 7.58 (m, 8 H, m-(C$_6H_5$)$_4$P), 5.82 (s, 1 H, NHC(O)CH$_2$CH$_2$S), 3.03 (m, 1 H, NHC(O)CH$_2$CH$_2$S), 2.85 (m, 2 H, NHC(O)CH$_2$CH$_2$S), 2.71 (m, 1 H, NHC(O)CH$_2$CH$_2$S); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, 18 °C) δ 180.7 (OC(O)CH(NHC(O)CH$_3$)CH$_2$S), 135.9 (p-(C$_6$H$_5$)$_4$P), 134.3 (o-(C$_6$H$_5$)$_4$P), 130.8 (m-(C$_6$H$_5$)$_4$P), 117.7 (d, ipso-(C$_6$H$_5$)$_4$P), 117.0 (d, ipso-(C$_6$H$_5$)$_4$P), 42.4 (NHC(O)CH$_2$CH$_2$S), 26.4 (NHC(O)CH$_2$CH$_2$S).

Crystallization and Reduction of X-ray Diffraction Data. Yellow crystals of **2** suitable for X-ray crystallographic analysis were grown by vapor diffusion of hexane into a THF solution and stored in THF–hexane under dinitrogen. The data crystal was mounted with oil (Paratone-N, Exxon) on an Enraf-Nonius CAD4 automated κ-axis diffractometer equipped with a graphite crystal monochromator (λ(Mo Kα) = 0.71073 Å). Data were collected at −75 °C and corrected for absorption, anomalous dispersion, Lorentz, and polarization effects. The structure was solved by direct methods.[33] The Os and N1 atoms were disordered in two positions with a relative site occupancy 0.922 (2); a common variable was refined for the disordered Os–N distance.

(33) Sheldrick, G. M.; SHELXS-86. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press: London, 1985; pp 175–189.

Yellow crystals of **3** suitable for X-ray crystallographic analysis were grown by vapor diffusion of diethyl ether into a CH_2Cl_2 solution and stored in diethyl ether under dinitrogen. The data crystal was mounted with epoxy on an Enraf-Nonius CAD4 automated κ-axis diffractometer equipped with a graphite crystal monochromator (λ(Mo Kα) = 0.71073 Å). Data were collected at −75 °C and corrected for absorption, anomalous dispersion, Lorentz, and polarization effects. The mosaic spread was broad; typical ω-scan width at half-maximum was 0.5°. The structure was solved by Patterson methods.[30] Cation carbon atom C34 was disordered in two positions with relative site occupany 0.058 (5); amine hydrogen atoms did not surface in the final difference Fourier map.

Yellow crystals of **7b** suitable for X-ray crystallographic analysis were grown by slow crystallization from diethyl ether–hexane. The data crystal was mounted with epoxy on a Syntex P2$_1$ four-circle diffractometer equipped with Crystal Logic automation and a graphite crystal monochromator (λ(Mo Kα) = 0.71073 Å). Data were collected at 26 °C and the structure was solved by Patterson methods.[30] Positions for hydrogen atoms HN1 and HN2 were located and refined. Crystal and experimental data for all structures are summarized in the supplementary material.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (5 RO1 AI28851-02) and the National Science Foundation (CHE 88-07707) in support of this work. Spectra were obtained on NMR instruments purchased through grants from the National Institutes of Health and the National Science Foundation (NIH PHS 1532135, NIH 1531957, and NSF CHE 85-14500).

Supplementary Material Available: Tables of crystal and experimental data, atomic coordinates, thermal parameters, and selected distances and angles for **2**, **3**, and **7b** (18 pages); listings of observed and calculated structure factors (59 pages). Ordering information is given on any current masthead page.

Enantioselective Esterifications of Unsaturated Alcohols Mediated by a Lipase Prepared from *Pseudomonas* sp.

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Abstract: Competition experiments and measurements of enantioselectivities were used to develop a simple active-site model (Figure 1) for resolutions of β-hydroxy-α-methylene carbonyl compounds III via acyl transfers mediated by lipase from *Pseudomonas* sp. (AK). Further experiments were used to test and refine this model with respect to resolutions of allylic, propargylic, homopropargylic, and other alcohols (Tables I–IV, respectively). The model proved extremely reliable for predicting the sense of the asymmetric induction, and the combined data collected in this paper give an indication of what structural features of the substrates can be correlated with high enantioselectivities in these resolutions. Furthermore, the results account for the conspicuous reversal of enantioselectivity previously observed in resolutions of γ-hydroxy-α,β-unsaturated esters **35**. Kinetic resolutions of two substrates (allenol **14** and dienol **9**) via asymmetric epoxidations were performed for comparison with the methodology presented in this paper.

Three relatively recent developments have vastly expanded the scope of biocatalytic resolutions in organic chemistry: (i) the realization that enzymes can be used in organic solvents,[1-7] (ii) the emergence of enol esters[8-12] and similar reagents[13] for essentially irreversible transfer of carboxylates, and (iii) commercial availability of a range of lipase preparations at low cost. Consequently, many chiral alcohols can be conveniently resolved via "enantioselective esterifications" wherein an enzyme mediates acyl transfer to enantiomers of a given alcohol at different rates.

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(3) Cesti, P.; Zaks, A.; Klibanov, A. M. *Appl. Biochem. Biotechnol.* **1985**, *11*, 401.
(4) Zaks, A.; Klibanov, A. M. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 3192.
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(12) Laumen, K.; Breitgoff, D.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1459.
(13) Ghogare, A.; Kumar, G. S. *J. Chem. Soc., Chem. Commun.* **1989**, 1533.

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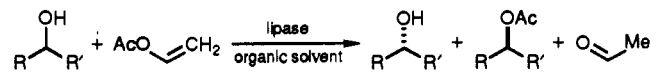
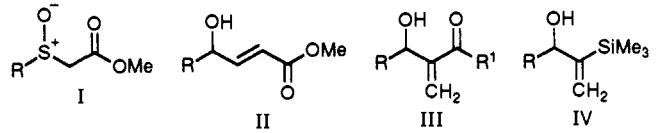


Such methodology is most readily applied when the selectivities of specific lipases can be correlated to structural features of the substrates they process; in the absence of such data one must rely upon abritrary screening to find a lipase suitable for a given resolution. Fortunately, some well-defined substrate–structure/enzyme–activity relationships are emerging. For instance, numerous resolutions of α-aryl alcohols mediated by the lipase SAM II have been reported, enough to establish that this is a good enzyme preparation for resolutions of these substrates, and that the *R* enantiomer of the alcohol is acylated preferentially in most cases.[14-18] Similarly, an active-site model for predicting the specificity of pig liver esterase has been developed.[19] Nevertheless, more studies to determine the behavior of a given enzyme toward a range of substrates are required if the synthetic organic community is to exploit biocatalytic resolutions to the full.

In previous studies we found sulfinylacetates I could be resolved via hydrolyses mediated by lipase from *Pseudomonas* sp. (Amano, K-10).[20] These sulfinylacetates react with aldehydes (RCH_2CHO) in the presence of pyridine (the SPAC reaction) to give γ-hydroxy-α,β-unsaturated esters II, products which could be resolved via irreversible acylations in hexane, *mediated by the same enzyme*.[21,22] Soon after, we demonstrated that crude lipases from *Pseudomonas* sp. also promote enantioselective esterifications of β-hydroxy-α-methylene esters and ketones III.[23]



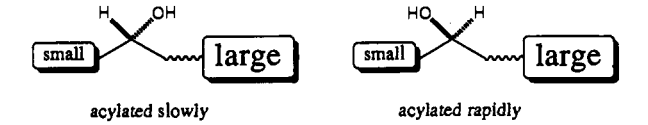
I II III IV

The observations outlined above led us to believe these simple biocatalytic resolutions could be widely applicable, and they could complement, or even supersede, some methods often used in contemporary asymmetric synthesis. Initially, we focussed on resolutions of substrates that, like compound types II and III, are not readily resolved via enantioselective epoxidation, and this work has been communicated.[24] The more extensive study reported here allows one to deduce the scope, and some limitations, of enantioselective esterification mediated by crude lipase from *Pseudomonas* sp.

Resolutions of Allylic Alcohols

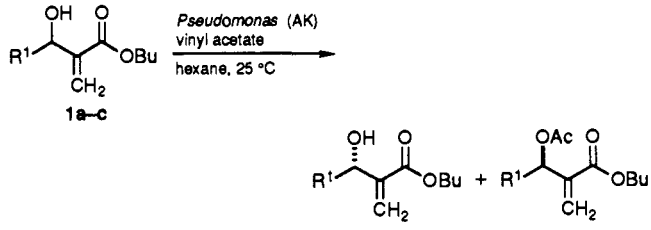
Competition experiments were performed to estimate *minimum* rate differences in biocatalytic resolutions of type III allylic alcohols; specifically product ratios were measured at less than 5% conversions (GC) for reactions of near-equimolar mixtures of starting materials. This data was correlated with measurements of enantioselectivity to determine how structural features affect these two parameters.

Acylations of butyl esters **1a–c** with progressively longer aliphatic chains attached to the hydroxymethine center were all enantioselective ($E > 20$),[25-27] but the initial rate of acylation of the methyl-substituted compound (R^1 = Me) is at least 15 times faster than that of the *n*-propyl-substituted substrate (R^1 = Pr).



acylated slowly acylated rapidly

Figure 1. Simple model for predicting which substrates will be resolved effectively via biocatalytic acylations mediated by crude lipase from *Pseudomonas* sp. (Amano AK), and the sense of the enantioselection.

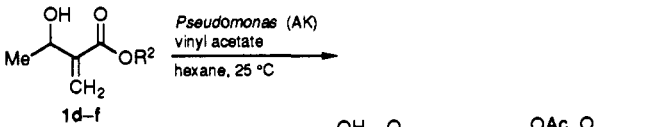


1a–c

R^1	Me (1a)	Et (1b)	Pr (1c)
rel rate	15	1.4	1.0
E	>20	>20	>20

These experiments show that acylations of alcohols **1a–c** mediated by *Pseudomonas* (AK) become progressively slower as the hydroxymethine substituent (R^1) increases in size.

Manipulation of the ester functionality for the methyl-substituted compounds **1d–f** had no significant influence on relative rates of acylation, but enantiodiscrimination for the methyl ester was appreciably less than for the ethyl and butyl esters.



1d–f

R^2	Me (1d)	Et (1e)	Bu (1f)
rel rate	1.2	1.0	1.1
E	8	>20	>20

These data indicate the enantioselectivity of the enzyme is low when the "large" group does not extend beyond approximately four atoms from the chiral center.

As a working hypothesis to identify substrates that could be resolved with high enantioselectivity via biocatalytic acylations mediated by lipase from *Pseudomonas* sp., we assumed that *the alcohols that are resolved most efficiently have one small and one relatively "large" group attached to the hydroxymethine functionality, where the latter group has a bulky functionality slightly removed from the asymmetric center* (Figure 1). In the context of this research, "large" groups are those that might have a significant effect on the extended three-dimensional structure of the enzyme, but they do not necessarily exert an appreciable steric presence immediately at the chiral center.

Data for biocatalytic acylations of other allylic alcohols mediated by *Pseudomonas* sp. are depicted in Table I. Our working hypothesis proved very reliable for predicting which enantiomer would be acylated preferentially; all but one of the recovered alcohols have the *S* configuration. Resolution of substrate **10** is the exception, but this is only a *formal* reversal of selectivity, arising from the fact that the smaller group (ethynyl) has a *higher* priority than the larger substituent. Indeed, the enantioselectivity

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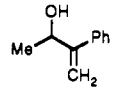
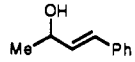
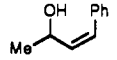
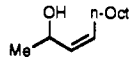
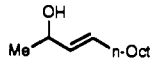
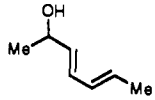
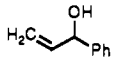
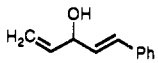
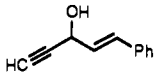
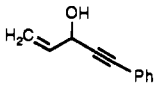
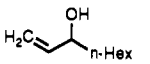
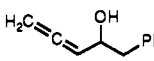
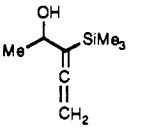
(27) Small errors in data used to calculate *E* values lead to large numerical differences due to the logarithmic nature of this relationship. Consequently *ranges* of *E* values are quoted in this paper to classify the resolutions as fair (E <10), good (E 10–20), and excellent (E >20).

Table I. Biocatalytic Resolutions of Allylic Alcohols[a]

compound structure	no.	time (h), conversion (%)[b]	recovered alcohol: yield (%),[c] ee (%)[d] (config)[e]	product acetate: yield (%), ee (%)	*E*[f]
	**2**	7.0, 52	32, >95 (*S*)	47, >95	>20
	**3**	3.0, 50	47, >95 (*S*)	50, >95	>20
	**4**	64, 57	26, 37[g]	26, –	3
	**5**	22, 63[h]	35, 56 (*S*)	46, 31	3
	**6**	3.0, 71	22, >95 (*S*)	63, 33	4
	**7**	3.0, 52	25, 71 (*S*)	25, –	5–10
	**8**	3.0, 60	33, >95 (*S*)[g]	32, 46	9
	**9**	2.5, 50[h]	41, >95 (*S*)	49, >95	>20
	**10**	6.0, 57	28, >95[g] (*R*)[i]	44, 68	>20
	**11**	3.5, 52	43, >95 (*S*)	42, >95	>20
	**12**	2.6, 62	20, 22	56, –	2
	**13**	4.0, 52[j]	38, >95[g]	47, 81	>20
	**14**	120, 45[j]	31, 81 (*S*)[k]	38, >95	>20

[a] The substrate at 0.1 M concentration in hexane was stirred with 0.5 mass equiv of enzyme (except where indicated), 4 equiv of vinyl acetate, and 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 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] Determined by ^{1}H NMR chiral shift experiments except where 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 by ^{1}H NMR and ^{19}F NMR analyses of Mosher's ester (MTPA) derivative. [h] Mass equivalents of enzyme = 2. [i] The *R* enantiomer is the slow-reacting enantiomer, but note the ethyne "small group" on the hydroxymethine center has higher priority; the absolute configuration of this compound was incorrectly reported to be *S* in the original communication of this work. [j] Mass equivalents of enzyme = 5. [k] The absolute configuration was determined by comparison of the sign of the optical rotation and the chiral lanthanide-reagent-shifted spectra to that of partially resolved *R* alcohol obtained from a Sharpless asymmetric epoxidation kinetic resolution using L-(+)-DIPT. [l] Mass equivalent of enzyme = 1.

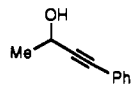
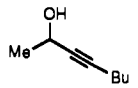
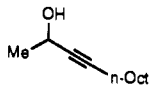
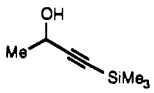
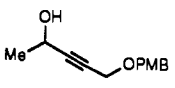
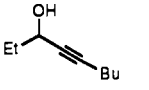
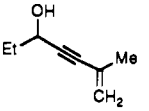
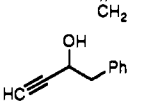
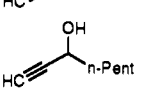
of lipase AK from *Pseudomonas* sp. is uniform for all the examples where absolute configuration was determined in this study; the enantiomer indicated in Figure 1 is acylated preferentially, regardless of whether it happens to be labelled *R* or *S*.

Results in Table I indicate there are restrictions on the nature of the "large" functionality that are not apparent from Figure 1. Aromatic groups seem to be particularly favorable (cf. resolutions of substrates **2**, **3**, **9**, **10**, **11**, and **13**), but the poor results obtained for (*Z*)-4-phenylbut-3-en-2-ol (**4**) and allylic alcohol **8** indicate constraints on the favored structural orientation of this group. Relatively subtle changes in structure can have appreciable effects in these experiments; for instance, low selectivity for the *Z*-alkene **4** is conspicuous when compared with the resolutions of its *E* isomer **3** and 4-phenylbutyn-2-ol (**17**, Table II, vide infra), both of which proceed with high enantiodiscrimination. Furthermore, alcohols **5** and **6** having aliphatic alkene substituents were not resolved efficiently, whereas results obtained for the (more rigid) dienol **7** are a little better.

Resolutions of Alkynols

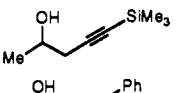
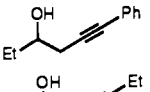
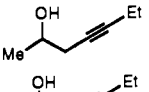
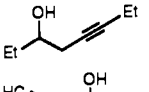
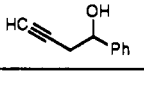
Enantioselective esterifications of nine propargylic alcohols were attempted and eight excellent enantioselectivities were obtained (Table II). Acylations of propargylic alcohols with butyl, octyl, trimethylsilyl, and [(*p*-methoxybenzyl)oxy]methylene alkyne substituents are all enantioselective, whereas allylic alcohols with aliphatic substituents are generally not resolved well by the lipase from *Pseudomonas* sp. (AK) (cf. resolutions of **18**–**22** compared with Table I, substrates **5** and **6**). The small group can be methyl, ethyl, or ethynyl, provided the large group is some acceptable structure. However, combination of an ethynyl substituent with a straight-chain aliphatic group (substrate **25**) is not favorable for resolution.

Table II. Biocatalytic Resolutions of Propargylic Alcohols[c]

compound structure	no.	time (h), conversion (%)	recovered alcohol: yield (%), ee % (config)	product acetate: yield (%), ee %	E
	**17**	3.5, 50	47, >95 (*S*)	48, >95	>20
	**18**	4.0, 52[a]	31, >95 (*S*)	41, 87	>20
	**19**	2.5, 50	30, >95 (*S*)	50, >95	>20
	**20**	48, 50	27, >95 (*S*)	49, >95	>20
	**21**	3.25, 52	46, >95 (*S*)	48, 78	>20
	**22**	3.0, 51[b]	46, >95 (*S*)	36, 82	>20
	**23**	3.5, 50	35, >95 (*S*)	44, >95	>20
	**24**	24, 53	31, 95 (*R*)	52, 77	>20
	**25**	3.0, 54	24, 23 (*R*)	49, –	2

[a] Mass equivalents of lipase used = 0.25. [b] Mass equivalents of lipase used = 1.0. [c] Conditions almost identical with those used in Table I except where noted.

Table III. Biocatalytic Resolutions of Homopropargylic Alcohols

compound structure	no.	time (h), conversion (%)	recovered alcohol: yield (%), ee % (config)	product acetate: yield (%), ee %	E
	**26**	24, 50	26, >95 (*S*)	20, >95	>20
	**27**	4.0, 66	33, >95	63, 50	10
	**28**	3.0, 55	21, 54 (*S*)	44, >95	4
	**29**	4.5, 61	27, 61 (*S*)	33, 38	4
	**30**	6.5, 64	34, >95 (*S*)	45, 72	>20

Resolutions of five homopropargylic alcohols were also examined (Table III). Of the four substrates for which the CH_2CCR group constitutes the "large" hydroxymethine substituent, the resolutions are highly enantioselective when the alkyne terminus is capped with a trimethylsilyl group (**26**), less so when this terminal substituent is phenyl (**27**), and they are ineffective when the alkyne has a terminal ethyl substituent (cf. esterification of **28** and **29**). Efficient resolution of alcohol **30** indicates the method can be useful when the small hydroxymethine substituent is propargyl and the "large" substituent is phenyl.

Resolutions of Other Alcohols

As one might anticipate, resolutions mediated by lipase from *Pseudomonas* sp. (AK) are not restricted to unsaturated alcohols; these substrates were chosen for this study simply because they are particularly useful for synthesis. Resolution of alcohols **31–33** are also effective, indicating the enzyme is sensitive to the phenyl group when it is up to three methylene units removed from the chiral center. However, the completely aliphatic alcohol **34** is acylated with very poor enantioselectivity.

Refinement of the Active-Site Model

Two referees suggested the data presented in this paper could be amenable to the cubic-space method recently used to formulate an active-site model for pig liver esterase.[19] Unfortunately, unlike many of the pig liver esterase substrates, the compounds examined in the current work are conformationally flexible; moreover, the enzyme(s) responsible for these acylations has not been characterized. Nevertheless, a model that accounts for the results is presented below, but it is simply a refinement of the working

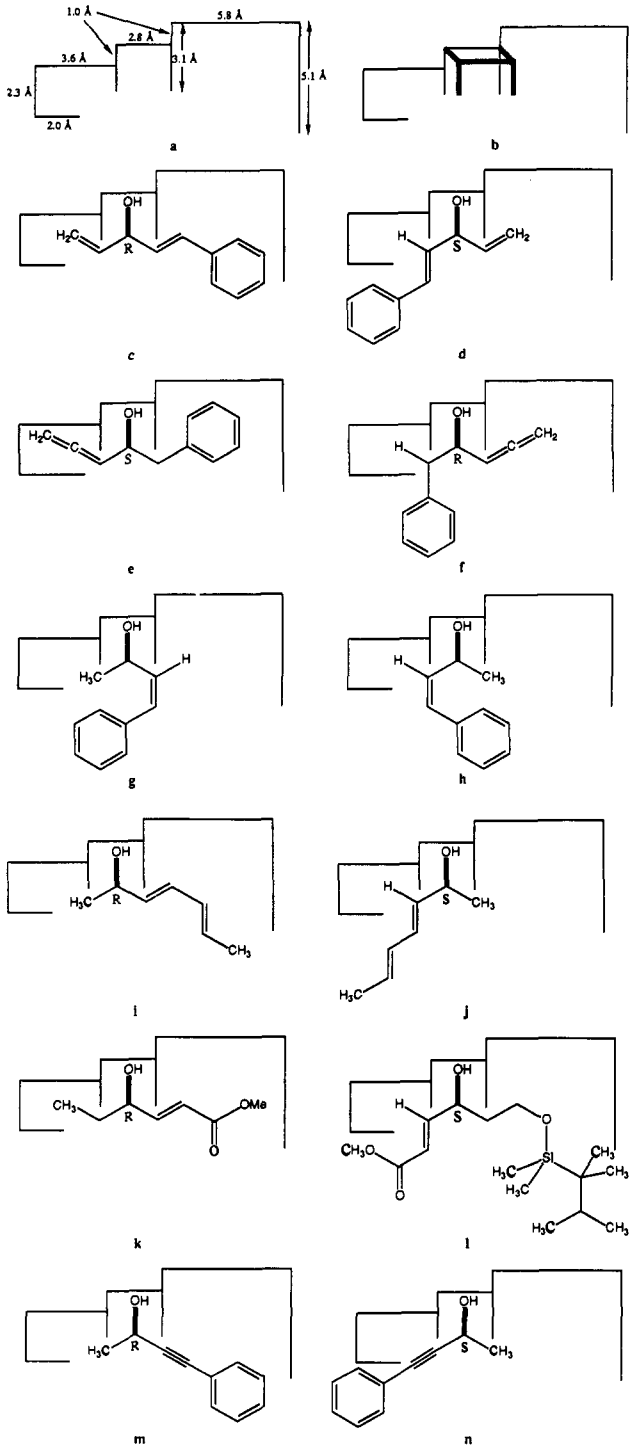


Figure 2. (a) Two-dimensional representation of the enzyme active site. (b) Representation of the enzyme active site with "canopy" for recognition of the hydroxyl functionality of the substrate indicated (this is omitted for clarity in subsequent diagrams. (c) Proposed fit of alkene *R*-**9** into this structure. (d) Poor fit of *S*-**9** into the proposed active-site model. (e) Excellent fit of *S*-**13** into this active-site model, predicting the enantioselectivity observed for this particular substrate. (f) Fit of *R*-**13** is less perfect than for its optical antipode. (g and h) Acylation of alkene **4** is nonselective because neither enantiomer fits well. (i and j) Moderately enantioselective acylation of diene **7** reflects reasonable fit of the *R* enantiomer in the active site area. (k and l) Enantioselective acylation of *R*-**35b** and of *S*-**35f** is consistent with the enzyme active-site model (the aliphatic chain of **35f** could be coiled into the eastern pocket). (m and n) Good and poor fit of *R*- and *S*-**17**.

hypothesis presented in Figure 1 rather than a proposal for the physical structure of the enzyme active site. Furthermore, the model presented here is not intended to imply anything about the overall rates of the acylation processes since these will depend upon

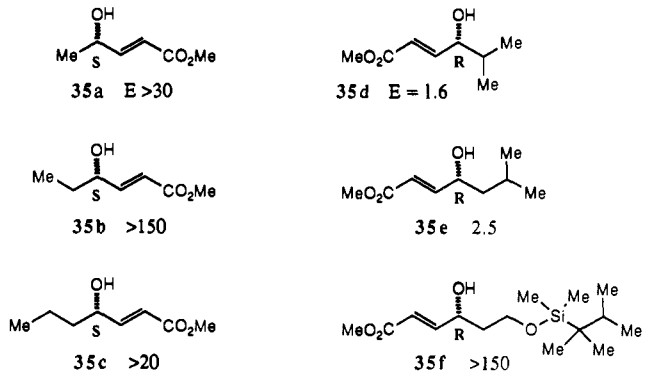


Figure 3. Apparent reversal of selectivity in biocatalytic acylations of SPAC reaction products (enantiomers shown are the slow-reacting optical isomers).

other factors, e.g. diffusion of the substrate to and from the active site.

Crude lipase preparations from *Pseudomonas* (AK) seem to be effective for resolutions of molecules with near-planar structures; it apparently is not suitable for resolutions of substrates with relatively bulky moieties close to the hydroxymethine center or those that are unable to form low-energy planar conformations around the hydroxyl group. Consequently, the active site is envisaged as a near-planar pocket (Figure 2a) with a hydrophilic canopy for the alcohol functionality projecting above the plane (Figure 2b). Substrates used in this work were constrained to fit this environment and minimized by use of the molecular mechanics package provided in SYBYL Molecular Modeling software (Tripos Associates, Inc.) to give the approximate dimensions shown in Figure 2a. The depth of this active site area is at least enough to accommodate the terminal methylene group of an allene (>1.8 Å), but no other information is available for more accurate estimates. Similarly, the eastern section of the active-site model is completely open on one face and the western section is partially open, but no other parameters are available to assess the dimensions of the undefined areas below these boundaries. Sih has previously commented on the importance of distal binding sites in enantioselective resolutions,[28] and we are unable to anticipate the likely effects of such influences.

Efficiencies of kinetic resolutions depend upon differential rates of reaction for two enantiomers. Here we assume these enzyme-mediated kinetic resolutions are a consequence of tight binding of the fast-reacting enantiomer relative to its optical isomer, *even though this may also be accommodated (but to a lesser extent) in the defined areas of the active-site model in Figure 2a.* In reality, enzyme kinetic resolution depends upon binding of the substrate to the enzyme (K_M terms) *and* the rate of the subsequent events (V_{max}), but the simplifying assumption defined above is intended as a basis for a working hypothesis rather than a factual statement.

Figure 2c depicts near perfect fit of *R*-**9**, whereas the enantiomer can only be accommodated by projecting the substrate into the undefined region (Figure 2d); this substrate is acylated with high enantioselectivity. One enantiomer of allene **13** fits well into the active-site model while the other is held much less efficiently (Figure 2e,f); racemic samples of this substrate are also resolved with high enantioselectivity, and the model predicts the *S* enantiomer reacts faster. By contrast, neither enantiomer of allyl alcohol **8** is accommodated well in the active-site model, and the acylation process is nonstereoselective (Figure 2g,h). Resolution of dienol **7** is also possible (though less efficient), as implied in Figure 2i,j.

In previous work we observed an apparent reversal of selectivity in lipase-mediated acylations of allylic alcohols **35** (Figure 3),[21] but this no longer seems surprising in the light of the model presented in Figures 1 and 2. The methyl, ethyl, and propyl

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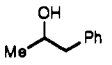
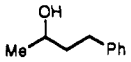
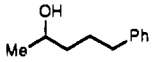
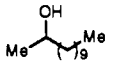
Table IV. Biocatalytic Resolutions of Other Alcohols

compound structure	no.	time (h), conversion (%)	recovered alcohol: yield (%), ee % (config)	product acetate: yield (%), ee %	E
	31	5.5, 50	43, >95 (S)	46, >95	>20
	32	8.0, 52	32, >95 (S)	40, >95	>20
	33	4.0, 57	32, >95 (S)[a]	50, 67	20
	34	2.0, 67[b]	13, 89 (S)	67, -	7

[a] Enantiomeric excess determined via ^{19}F NMR and MTPA ester. [b] Mass equivalents of lipase = 1.0.

substituents of alcohols **35a–c** constitute the "small" group on the chiral center; hence, *S* alcohols are recovered from the reaction (cf. Figure 2k). With substrate **36f**, however, the corresponding substituent [$(CH_2)_2OSiMe_2Thex$] is effectively "larger" than the α,β-unsaturated ester group; hence, *S* alcohol is acylated faster (Figure 2l). Alcohols **35d** and **35e** are intermediate between these extremes, and their resolutions are ineffective as a consequence.

Enantioselective acylations of the propargylic alcohols **17–24** are easily rationalized on the basis of the model given in Figure 2 (e.g. Figure 2m,n); typically the fast-reacting enantiomers have a variety of alkyne substituents that extend slightly into the undefined region of the active-site space, but their enantiomers have a relatively poor fit. Alcohol **25** (Table II) may be coiled in some conformation that is unfavorable for effective resolution. As the alkyne functionality is moved further along the chain (i.e. for substrates **26–30**, Table III), the structure of the acetylene "end group" apparently becomes more important, and distal binding sites may be more influential.

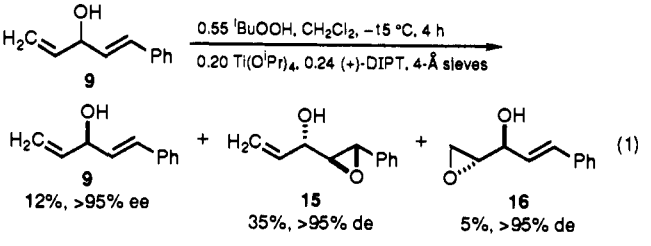
The model presented above might also be applicable to enantioselective hydrolyses of esters mediated by lipases from *Pseudomonas* sp.; we are unable to identify any examples where this model would clearly not be applicable amongst results published elsewhere,[28-44] but research with a series of closely related substrates is required to form more definite conclusions.

Conclusions

Resolutions promoted by *Pseudomonas* sp. (AK) are cheap and convenient. Acylations mediated by this lipase (available for around $1–2 per gram) are performed simply by stirring the substrate in hexane with half the mass of the enzyme and 4 equiv of vinyl acetate. The reactions are followed quantitatively by GC or NMR, and qualitatively by TLC. Scrupulously dry conditions are not required although significant quantities of water can retard these acylations; consequently, molecular sieves were routinely added to ensure the results would be easily reproduced. Workup of these reactions (filtration, rotary evaporation, and separation) is trivial, and the alcohol and ester components have significantly different R_f values, thus facilitating chromatographic separations. The enzyme recovered in the filtration step can be recycled without significant loss of activity, although for small-scale reactions this is unlikely to be necessary because the crude lipase preparation is cheap. Throughout this study, the sense of enantioselection by the enzyme is uniform; predictable behavior with respect to the sense induction in these kinetic resolutions increases the value of the methodology for asymmetric synthesis.

In comparison with Sharpless epoxidations for resolving chiral *allylic* alcohols,[45-47] the methodology here has more restrictions: it seems not to be applicable to substrates with aliphatic alkene substituents, and only to others with appropriate "small" and "large" groups at the hydroxymethine center. However, these biocatalytic resolutions are sometimes suitable where enantioselective epoxidations are not.[24] Furthermore, when both methods are applicable, we believe the enzyme-mediated route is experimentally superior. The reactions depicted below (i, ii, and iii) were performed to illustrate this point.

(i) Two epoxides were isolated from a Sharpless epoxidation[48,49] of racemic diene **9** (eq 1). Yields after chromatographic separation are shown below; GC analysis of the crude reaction mixture indicates **9**, **15**, and **16** are formed in a ratio of approximately 45:50:5. Resolution of substrate **9** via enantioselective epoxidation



is viable; however, the lipase-mediated biocatalytic resolution depicted is experimentally simpler, and allows more facile recovery of unreacted starting material (see Table I, and the Experimental Section).

(ii) Sharpless' studies on asymmetric epoxidations of allenols[50] focussed on those that have axial chirality (due to two nonidentical 1,3-substituents on the 1,2-diene functionality); alcohols **13** and **14** are fundamentally different insofar as these materials are only

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(34) Hamaguchi, S.; Ohashi, T.; Watanabe, K. *Agric. Biol. Chem.* **1986**, *50*, 375.
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(47) Pfenninger, A. *Synthesis* **1986**, 89.
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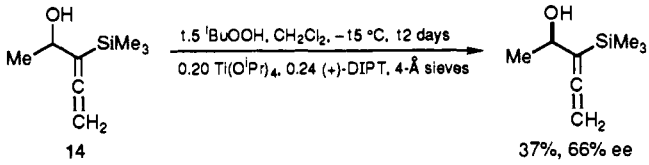
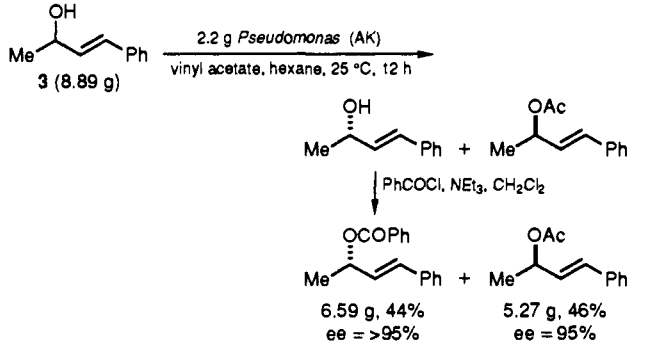
chiral at the hydroxymethine group. Furthermore, one might expect high selectivities for asymmetric epoxidation of substrate **14** because enantioselective epoxidations of allylic alcohols IV are very effective.[51] In fact, this material reacted slowly under the standard conditions, and the starting material was recovered with only moderate optical purity at 43% conversion. The biocatalytic



14 37%, 66% ee

resolution of substrate **9** depicted in Table I is superior to enantioselective epoxidation of this substrate in every respect.

(iii) Sharpless epoxidations on large amounts of material are extremely inconvenient and purification of products can be difficult. The biocatalytic resolutions outlined here are easy to perform on a multigram scale, and one may devise conditions for separating the alcohol and acetate derivatives without chromatography. To illustrate a practical approach, a pilot reaction was performed with approximately 9 g of racemic alcohol **3**. This material was acylated to 50% conversion (GC) with 0.25 mass equiv of the lipase; the enzyme was removed by filtration and the solvent/excess vinyl acetate was evaporated in vacuo. The mixture then was dissolved in dichloromethane and the residual alcohol was benzoylated, giving two esters that were conveniently separated by fractional distillation. If one of the components was thermally



products separated via fractional distillation

unstable, separation might be achieved by converting the alcohol into a polar ester (e.g. 3,5-dinitrobenzoyl) and exploiting the differential solubilities of the two substances in polar and apolar solvents. Details of the such protocols depend on the physical properties of the substrates; no one procedure is likely to be general, hence no example is given here.

The most notable success of this methodology, however, is with alkynols and allenic alcohols; biocatalytic resolutions of these substrates are widely applicable and extremely convenient in comparison with other methods.[24,52-62] We advocate use of this biocatalytic methodology for novel syntheses and large-scale preparations.

Optically active unsaturated alcohols have been employed as starting materials for numerous syntheses, and they will undoubtedly be used in many more. The resolutions depicted here are a complete list of all the substrates we tested; none were attempted and not reported. Consequently, it is evident that similar resolutions could be performed on other synthons, e.g. stannanes, silanes, and other heterosubstituted substrates might be tested for specific applications. Resolutions of unsaturated alcohols mediated by lipase from *Pseudomonas* sp. increase the depth of the chiral pool from which synthetic chemists can draw optically active building blocks.

Experimental Section

General Procedures. Melting points are uncorrected. NMR spectra were recorded on IBM 300-MHz, 250-MHz Bruker, or 90-MHz JEOL instruments with $CDCl_3$ solvent. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FTIR. Low-resolution (EI) and high-resolution (EI) mass spectra were recorded on a Finnigan 3300 mass spectrometer and a CAC 21/110 C high-resolution mass spectrometer, respectively. Gas chromatograph (GC) analyses of crude reaction mixtures were performed on a Shimadzu GC-9A using a Quadrex Corp. 50-m fused silica glass capillary column, type 007 MPS5. Integrals were corrected with mixtures of known amounts of compound. Unless otherwise indicated, the purity of all products was assessed via ^1H and ^{13}C NMR analyses, and optical purities were measured via ^1H NMR analyses of samples with added (+)-Eu(hfc)$_3$. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from Whatman. Flash chromatography[63] was performed on SP silica gel 60 (230–400 mesh ASTM). Tetrahydrofuran (THF) was distilled immediately before use from sodium benzophenone ketyl; hexane was dried over sodium before use. The resolution procedures are more reliable with freshly distilled vinyl acetate.

Throughout the following experimental section the term "lipase" refers to crude lipase AK from *Pseudomonas* sp. obtained from Amano Enzyme Co. (Troy, VA). The absolute configurations of the products of asymmetric epoxidations were inferred from the model for predicting the stereochemical outcome of asymmetric epoxidations of secondary allylic alcohols.[49]

Standard Procedure for Enzymatic Resolution of Alcohols: (*S*)-(+)-3-Phenyl-3-buten-2-ol (2). The racemic alcohol was prepared by reacting the Grignard reagent prepared from 1-phenylvinyl bromide in THF with acetaldehyde at 0 °C. The product was distilled to give an oil, bp 140 °C (15 mmHg).[64] To 0.3 g of ground, activated 4-Å molecular sieves and 0.15 g (0.5 mass equiv) of the lipase were added 20 mL of hexane, 0.69 g of distilled vinyl acetate, and 0.296 g (2 mmol) of the substrate. The solution was stirred at 25 °C and the course of the reaction was followed by either ^1H NMR or GC. After 7 h, ^1H NMR indicated 52% conversion. The solution was filtered and volatiles were removed by reduced pressure. The crude product was chromatographed, eluting with 5–15% acetone/hexane to afford the acetate (R_f 0.3, 5% acetone/hexane) 0.18 g (47%), ee >95%, and the alcohol (R_f 0.3, 10% acetone/hexane) 0.094 g (32%), ee >95%: $[\alpha]^{25}_D$ +34.2° (*c* 1.77, $CHCl_3$); ^1H NMR (250 MHz) δ 7.5–7.1 (m, 5 H), 5.36 (s, 1 H), 5.27 (s, 1 H), 4.28 (m, 1 H), 1.68 (d, J = 5 Hz, 1 H), 1.32 (d, J = 5 Hz, 3 H). The absolute configuration of the resolved alcohol was deduced from the ^1H NMR spectra of the diastereotopic (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetate (MTPA) derivatives of the racemic and resolved alcohols;[65] chemical shifts of the methyl protons of the MTPA derivative of the resolved alcohol (*R,S*) were downfield [δ 1.47 (d, J = 6.5 Hz)] relative to the (*R,R*) diastereomer [δ 1.42 (d, J = 6.5 Hz)].

Competitive Acylations of Type III Allylic Alcohols. Reactions were carried out according to the standard procedure with exactly 1 mmol of each of two alcohols; small portions were taken out at regular intervals (usually 5 min or so), filtered, silated (pyridine, hexamethyldisilazane, and trimethylsilyl chloride), and analyzed by GC. Minimum rate differences were determined by measuring the relative amounts of products formed by integration at up to, but not exceeding, 3% conversion.

Large Enzymatic Resolution and Derivitization of (*E*)-4-Phenylbut-3-en-2-ol (3). The racemic alcohol was prepared from (*Z*)-cinnamaldehyde and methyllithium. The product was distilled, bp 86 °C (2 mmHg), to afford a colorless solid. The alcohol (8.89 g, 60 mmol) was added to a stirred suspension of 3.0 g of ground activated 4-Å molecular sieves, 2.22 g (0.25 mass equiv) of the lipase, and 20.66 g (240 mmol) of vinyl acetate (dried over $MgSO_4$) in 500 mL of hexane. The suspension was stirred at 25 °C for 12 h, upon which time GC analysis

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indicated 54% conversion. The solution was filtered and concentrated under reduced pressure, and the crude product was dissolved in 200 mL of dry, distilled CH_2Cl_2. To this solution at 0 °C were added 3.44 g (34 mmol) of triethylamine (dried over KOH) and 4.49 g (32 mmol) of distilled benozyl chloride. The solution was stirred for 15 h at 25 °C and then diluted with 600 mL of ether and washed with 2 × 200 mL of 2 N HCl and 6 × 100 mL of aqueous $NaHCO_3$. The organic fractions were dried (Na_2SO_4 and $MgSO_4$) and concentrated. The crude mixture was fractionally distilled under vacuum (0.3 mmHg) to afford the acetate as an oil (5.27 g, 46% yield) [bp 75–77 °C, $[\alpha]^{27}_D$ +93.2° (*c* 2.37, $CHCl_3$)], and the benzoate as a colorless solid (6.59 g, 44% yield) [bp 135–137 °C, $[\alpha]^{27}_D$ +0.42° (*c* 8.16, $CHCl_3$)]. The benzoate was deprotected (1% NaOH, MeOH) to afford the resolved alcohol of ee >95%, determined by ^{19}F NMR of an (*R*)-MTPA derivative.

The substrate **3** was also resolved according to the standard procedure given for alcohol **2** above (2-mmol scale, 54% conversion by ^1H NMR). The crude product was chromatographed with 5–10% acetone/hexane, affording the acetate (R_f 0.3, 5% acetone/hexane) as an oil (0.187 g, 50%, ee >95%) and the alcohol (R_f 0.3, 10% acetone/hexane) as colorless crystals (0.132 g, 47%, ee >95%): $[\alpha]^{25}_D$ −29.2° (*c* 2.00, $CHCl_3$) [lit. $[\alpha]^{25}_D$ −24.5° (*c* 5.16, $CHCl_3$), ee 98%];[66] ^1H NMR (250 MHz) δ 7.60–7.20 (m, 5 H), 6.56 (d, *J* = 16.5 Hz, 1 H), 6.25 (dd, *J* = 16.5 Hz, 8.2 Hz, 1 H), 4.49 (m, 1 H), 1.60 (s, 1 H), 1.37 (d, *J* = 5.5, Hz, 3 H).

(*R*)-(+)-(*Z*)-4-Phenylbut-3-en-2-ol (4). The racemic alcohol was prepared according to the literature procedure from 4-phenylbut-3-yn-2-ol[67] and resolved according to standard procedure on a 1.2-mmol scale (57% conversion by ^1H NMR). The crude product was chromatographed with 5–10% acetone/hexane to afford the acetate (R_f 0.3, 5% acetone/hexane) as an oil (0.061 g, 26%) and the alcohol (R_f 0.27, 10% acetone/hexane) as an oil (0.045 g, 26%, ee 37% by ^1H NMR of MTPA ester derivative): $[\alpha]^{25}_D$ +1.8° (*c* 0.54, $CHCl_3$) [lit. $[\alpha]^{20}_D$ +9.7° (*c* 1.0, $CHCl_3$)];[68] ^1H NMR (90 MHz) δ 7.25 (m, 5 H), 6.48 (d, *J* = 11.5 Hz, 1 H), 5.68 (dd, *J* = 11.5 Hz, 9.0 Hz, 1 H), 4.76 (m, 1 H), 1.55 (s, 1 H), 1.35 (d, *J* = 6.4 Hz, 3 H).

(*S*)-(−)-(*Z*)-3-Dodecen-2-ol (5). The racemic alcohol[69] was prepared from 3-dodecyn-2-ol according to the literature procedure,[70] and was resolved according to standard procedure on a 2-mmol scale with conversion (63%) determined by GC. The crude product was chromatographed with 2–6% acetone/hexane to afford the acetate (R_f 0.3, 5% acetone/hexane) as an oil (0.21 g, 46%, ee 31%) and the alcohol (R_f 0.10, 5% acetone/hexane) as an oil (0.13 g, 35%, ee 56%): $[\alpha]^{25}_D$ −0.2° (*c* 2.00, $CHCl_3$); ^1H NMR (250 MHz) δ 5.41 (m, 2 H), 4.64 (m, 1 H), 2.05 (m, 2 H), 1.4–1.1 (m, 16 H), 0.87 (m, 3 H). The absolute configuration of this material was determined by hydrogenation (5% Pd/C, MeOH) to afford (*S*)-(+)-2-dodecanol, $[\alpha]^{25}_D$ +0.2° (*c* 0.95, EtOH) [lit. for (*R*)-(−)-2-dodecanol $[\alpha]^{25}_D$ −7.9° (*c* 8.7, EtOH),[71] $[\alpha]^{25}_D$ −4.8° (*c* 5, EtOH)[72]].

(*S*)-(−)-(*E*)-3-Dodecen-2-ol (6). The racemic alcohol[69] was prepared by lithium aluminum hydride reduction of 3-dodecyn-2-ol and was resolved according to the standard procedure (2-mmol scale, 71% conversion by GC). The crude product was chromatographed with 2–6% acetone/hexane to afford the acetate (R_f 0.3, 5% acetone/hexane) as an oil (0.29 g, 63%, ee 33%) and the alcohol (R_f 0.10, 5% acetone/hexane) as an oil (0.081 g, 22%, ee >95%): $[\alpha]^{25}_D$ −9.0° (*c* 2.35, $CHCl_3$); ^1H NMR (250 MHz) δ 5.55 (m, 2 H), 4.25 (m, 1 H), 2.00 (m, 2 H), 1.5–1.1 (m, 16 H), 0.85 (m, 3 H). The absolute configuration was determined by hydrogenation (Pd/C, MeOH) to afford (*S*)-(+)-2-dodecanol, $[\alpha]^{25}_D$ +5.6° (*c* 2.29, EtOH) [lit. for (*R*)-(−)-2-dodecanol $[\alpha]^{25}_D$ −7.9° (*c* 8.7, EtOH),[71] $[\alpha]^{25}_D$ −4.8° (*c* 5, EtOH)[72]].

(*S*)-(+)-(*E*,*E*)-Hepta-3,5-dien-2-ol (7). The racemic alcohol was prepared from methyllithium and (*E*,*E*)-hexadienal,[73] and was resolved according to the standard procedure (1.7-mmol scale, 52% conversion by GC). The crude product was chromatographed with 8–13% acetone/hexane to afford the acetate (R_f 0.3, 5% acetone/hexane) as an oil (0.066 g, 25%) and the alcohol (R_f 0.23, 10% acetone/hexane) also as an oil (0.049 g, 25%, ee 71%): $[\alpha]^{25}_D$ +8.8° (*c* 0.725, $CHCl_3$); ^1H NMR (90 MHz) δ 6.20–5.40 (m, 4 H), 4.30 (m, 1 H), 1.74 (d, *J* = 7.7 Hz, 3 H), 1.40 (d, *J* = 3.8 Hz, 1 H), 1.26 (d, *J* = 6.4 Hz, 3 H). The absolute configuration was determined by hydrogenation (5% Pd/C, MeOH) of the resolved alcohol to afford the known (*S*)-(+)-2-heptanol, $[\alpha]^{25}_D$ +7.2° (*c* 1.3, EtOH) [lit.[74] $[\alpha]_D$ +7.8° (*c* 12.0, EtOH)].

(*S*)-(−)-1-Phenylallyl Alcohol (8). The racemic alcohol was prepared from vinylmagnesium bromide and benzaldehyde and was distilled to give an oil, bp 130 °C (15 mmHg). The alcohol was resolved according to the standard procedure on a 2-mmol scale. The crude product was chromatographed with 10–20% acetone/hexane to afford the acetate (R_f 0.5, 20% acetone/hexane) as an oil (0.11 g, 32%, ee 46%) and the alcohol (R_f 0.3, 20% acetone/hexane) also as an oil (0.106 g, 39%, ee >95%): $[\alpha]^{25}_D$ −1.3° (*c* 1.74, $CHCl_3$) [lit.[75] $[\alpha]^{25}_D$ +3.0° (*c* 5.17, $CHCl_3$, *R* enantiomer)]; ^1H NMR (250 MHz) δ 7.5–7.2 (m, 5 H), 6.12 (m, 1 H), 5.98 (m, 1 H), 5.35, (d, 15 Hz, 1 H), 5.19 (m, 1 H), 1.94 (s, 1 H).

(*S*)-(+)-(*E*)-1-Phenylpenta-1,4-dien-3-ol (9). The racemic alcohol was prepared from vinylmagnesium bromide and (*Z*)-cinnamaldehyde,[76] and was resolved according to the standard procedure (2-mmol scale, with 2 mass equiv of the lipase, 50% conversion by ^1H NMR). The crude product was chromatographed with 5–15% acetone/hexane to afford the acetate (R_f 0.4, 10% acetone/hexane) as an oil (0.198 g, 49%, ee >95%) and the alcohol (R_f 0.2, 10% acetone/hexane) also as an oil (0.131 g, 41%, ee >95%): $[\alpha]^{25}_D$ +38.5° (*c* 1.90, $CHCl_3$); ^1H NMR (250 MHz) δ 7.60–7.16 (m, 5 H), 6.62 (d, *J* = 16.5 Hz, 1 H), 6.22 (dd, *J* = 16.5 Hz, 5.5 Hz, 1 H), 5.98 (m, 1 H), 5.34 (d, *J* = 16.5 Hz, 1 H), 5.19 (d, *J* = 11.0 Hz, 1 H), 4.81 (m, 1 H), 1.79 (s, 1 H). The absolute configuration was determined by hydrogenation over 5% Pd/C at 1 atm to obtain the known (*S*)-(+)-1-phenyl-3-pentanol, $[\alpha]^{25}_D$ +18.8° (*c* 0.975, EtOH) [lit.[77] $[\alpha]^{25}_D$ +22.2° (*c* 0.9, EtOH)].

(*R*)-(+)-1-Phenyl-1-penten-4-yn-3-ol (10). The racemic alcohol was prepared according to literature procedure,[78] and was resolved according to the standard procedure (1.5-mmol scale, 57% conversion by ^1H NMR). The crude product was chromatographed with 8–20% acetone/hexane to provide the acetate (R_f 0.35, 10% acetone/hexane) as an oil (0.13 g, 44%, ee 68%) and the alcohol (R_f 0.10, 10% acetone/hexane) as a colorless solid (0.066 g, 28%, ee >95% by ^1H NMR of MTPA derivative): mp 64–65 °C (lit. mp 65–66 °C); $[\alpha]^{25}_D$ +6.8° (*c* 2.35, $CHCl_3$); ^1H NMR (250 MHz) δ 7.5–7.2 (m, 5 H), 6.80 (d, *J* = 15 Hz, 1 H), 6.30 (dd, *J* = 17.5 Hz, 5 Hz, 1 H), 5.06 (m, 1 H), 2.64 (d, *J* = 2 Hz, 1 H), 1.96 (d, *J* = 6.2 Hz, 1 H). The absolute configuration was determined by hydrogenation (Pd/C, MeOH) to afford the known (*S*)-(+)-1-phenyl-3-pentanol, $[\alpha]^{25}_D$ +21.4° (*c* 0.29, EtOH) [lit.[77] $[\alpha]^{20}_D$ +22.2° (*c* 0.9, EtOH)].

(*S*)-(+)-1-Phenyl-4-penten-1-yn-3-ol (11). The racemic alcohol[79] was prepared by reacting lithium phenylacetylide with propenal and was purified by distillation, bp 88 °C (1 mmHg). The alcohol was resolved according to the standard procedure (2-mmol scale, 52% conversion by ^1H NMR). The crude product was chromatographed with 8–15% acetone/hexane to yield the acetate (R_f 0.3, 10% acetone/hexane) as an oil (0.171 g, 42%, ee >95%) and the alcohol (R_f 0.13, 10% acetone/hexane) as an oil (0.134 g, 43%, ee >95%): $[\alpha]^{25}_D$ +51.6° (*c* 2.00, $CHCl_3$); ^1H NMR (250 MHz) δ 7.5–7.2 (m, 5 H), 6.15–6.0 (m, 1 H), 5.54 (dd, *J* = 17.5 Hz, 1 Hz, 1 H), 5.27 (dd, *J* = 7.5 Hz, 1 Hz, 1 H), 5.11 (m, 1 H), 2.11 (s, 1 H). The absolute configuration was determined by lithium aluminum hydride reduction to (*S*)-(+)-1-phenylpenta-1,4-dien-3-ol (**9**) and comparison of optical rotations.

1-Nonen-3-ol (12). The racemic alcohol[80] was resolved according to the standard procedure (2-mmol scale, 62% conversion by GC). The crude product was chromatographed with 6–15% acetone/hexane to afford the acetate (R_f 0.4, 10% acetone/hexane) as an oil (0.208 g, 56%) and the alcohol (R_f 0.22 10% acetone/hexane) as an oil (0.0567 g, 20%, ee 22%): ^1H NMR (250 MHz) δ 5.86 (m, 1 H), 5.20 (dd, *J* = 17 Hz, 1 Hz, 1 H), 5.09 (dd, *J* = 10 Hz, 1 Hz, 1 H), 4.08 (m, 1 H), 1.55–1.27 (m, 11 H), 0.87 (m, 3 H).

(−)-1-Phenyl-3,4-pentadien-2-ol (13). The racemic alcohol was prepared by a modification of the reported procedure for the homologation of the acetylenic alcohols.[81] Thus, to a suspension of 1.11 g (37.5 mmol) of paraformaldehyde and 1.43 g (7.5 mmol) of CuI in 30 mL of dioxane was added 2.78 g (27.5 mmol) of diisopropylamine and 2.19 g (15 mmol) of 1-phenyl-3-butyn-2-ol. The suspension was refluxed for 4 h, cooled,

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filtered, concentrated, and diluted with 75 mL of water and 150 mL of ether. The aqueous phase was acidified (pH 2) with 6 N HCl, the two phases were separated, and the aqueous phase was extracted with ether three times. The combined organic fractions were washed with water and dried over Na_2SO_4, and the solvent was evaporated. The product was distilled twice to afford an oil (1.17 g, 49%), bp 56–57 °C (0.3 mmHg). The alcohol was resolved according to the standard procedure (2-mmol scale, 1 mass equiv of the lipase, 52% conversion by GC). The crude product was chromatographed with 6–12% acetone/hexane to afford the acetate (R_f 0.45, 10% acetone/hexane) as an oil (0.19 g, 47%, ee 81% by ^{1}H NMR of MTPA ester derivative) and the alcohol (R_f 0.16, 10% acetone/hexane, 0.123 g, 38%, ee >95% by ^{1}H and ^{19}F NMR of MTPA ester derivative): $[\alpha]^{27}_D$ −16.25° (*c* 2.375, $CHCl_3$); ^{1}H NMR (250 MHz) δ 7.25 (m, 5 H), 5.28 (m, 1 H), 4.84 (dd, *J* = 6.75 Hz, 2.5 Hz, 2 H), 4.41 (m, 1 H), 2.88 (m, 2 H), 1.75 (d, *J* = 4.25 Hz, 1 H); ^{13}C NMR (62.87 MHz) δ 206.9 (C) 137.6 (C), 129.5 (CH), 128.4 (CH), 126.5 (CH), 94.1 (CH), 77.7 (CH_2), 70.1 (CH), 43.8 (CH_2); IR (neat) 3380, 1960, 1610, 1500, 1460, 1040, 860, 750, 710, 300 cm^{-1}; MS (EI 50 eV) *m/e* 159 (3, M − 1), 142 (18, m − 18), 92 (60), 91 (100), 69 (27); HRMS calcd for $C_{11}H_{12}O$ 160.088 81, found 160.088 80. Hydrogenation of the deprotected acetate over 5% Pd/C afforded (−)-1-phenylpentan-2-ol, $[\alpha]^{27}_D$ −14.8° (*c* 2.22, $CHCl_3$).

(*S*)-(−)-3-(Trimethylsilyl)-3,4-pentadien-2-ol (14). The racemic alcohol was prepared by a modification of the literature procedure for preparation of allenic alcohols.[82] Thus 8 mmol of *tert*-butyllithium were added to a solution of 0.898 g (8 mmol) of 1-(trimethylsilyl)-1-propyne in 20 mL of THF at 0 °C. The solution was stirred at 0 °C for 30 min and cooled to −78 °C; 2.27 g (8 mmol) of Ti(O-*i*-Pr)$_4$ was added and the solution was stirred for 10 min. Distilled acetaldehyde (0.35 g, 8 mmol) was added and the solution was allowed to gradually warm to −30 °C over 1 h. The reaction was quenched by pouring it into ice-cold 1 N HCl, and it was then extracted with ether. The organic phases were dried over Na_2SO_4 and concentrated to afford a colorless liquid (0.99 g, 63%). The alcohol was resolved according to the standard procedure on a 5-mmol scale with 3.75 g (5 mass equiv) of the lipase. The course of the reaction was monitored by GC. The crude product was chromatographed with 5–15% acetone/hexane to afford the acetate (R_f 0.3, 5% acetone/hexane) as an oil (0.375 g, 38%, ee 95%) and the alcohol (R_f 0.3, 10% acetone/hexane, 0.246 g, 31%, ee 81%): $[\alpha]^{25}_D$ −11.1° (*c* 2.5, $CHCl_3$); ^{1}H NMR (90 MHz) δ 4.55 (d, *J* = 1.7 Hz, 2 H), 2.34 (m, 1 H), 1.60 (d, *J* = 6.4 Hz, 1 H), 1.32 (d, *J* = 6.4 Hz, 3 H), 0.26 (s, 9 H); ^{13}C NMR (62.89 MHz) δ 206.7, 101.8, 71.9, 66.6, 24.2, −0.97; IR (neat) 3401 (m), 2966 (m), 1924 (m), 1719 (m), 1678 (m), 1372 (w), 1249 (s), 1078 (w), 843 (s) cm^{-1}; MS (EI 30 eV) *m/e* 157 (50), 155 (4), 147 (83), 143 (73), 75 (98), 73 (100), 28 (72). The absolute configuration was determined by comparison of the optical rotation to that of the *R* alcohol obtained by kinetic resolution of the racemic alcohol by Sharpless asymmetric epoxidation using L-(+)-DIPT, $[\alpha]^{27}_D$ +3.4° (*c* 5.75, $CHCl_3$).

Kinetic Resolution of 1-Phenylpenta-1,4-dien-3-ol (9). The racemic alcohol was resolved according to Sharpless' standard procedure[49] on a 2-mmol scale with 0.112 g (0.24 equiv) of L-(+)-diisopropyl tartrate, 0.113 g (0.2 equiv) of Ti(O-*i*-Pr)$_4$, and 0.55 equiv of *tert*-butyl hydroperoxide (TBHP) at −18 °C for 6 h. Analysis of the crude reaction mixture indicated 55% conversion (GC). The crude product was chromatographed with 10–20% acetone/hexane to afford the following products: resolved alcohol **9** (0.04 g, 12%, ee >95%, $[\alpha]^{27}_D$ −40.9° (*c* 1.45, $CHCl_3$)); (1*S*,2*S*,3*S*)-1,2-epoxy-1-phenylpent-4-en-3-ol (**15**) (0.124 g, 35%, ee 90% by ^{1}H NMR); and a third fraction containing (2*R*,3*R*)-1,2-epoxy-5-phenyl-4-penten-3-ol (**16**) (single diastereomer by ^{13}C NMR analysis) contaminated with an unidentified impurity (0.52 g total). **(1*S*,2*S*,3*S*)-1,2-Epoxy-1-phenyl-4-penten-3-ol (15):** ^{1}H NMR (250 MHz) δ 7.4–7.2 (m, 5 H), 6.0–5.84 (m, 1 H), 5.45 (d, *J* = 15 Hz, 1 H), 5.28 (d, *J* = 8.2 Hz, 1 H), 4.46 (m, 1 H), 3.95 (d, *J* = 2 Hz, 1 H), 3.17 (m, 1 H), 2.09 (s, 1 H); ^{13}C NMR (62.89 MHz) δ 136.5 (C), 135.3 (CH), 128.4 (CH), 128.2 (CH), 125.7 (CH), 117.7 (CH_2), 70.2 (CH), 63.9 (CH), 54.7 (CH); IR (neat) 3421 (s), 2925 (m), 2359 (w), 1723 (s), 1026 (s), 756 (s), 700 (s) cm^{-1}; MS (EI 50 eV) *m/e* 176 (1, M$^+$), 120 (30), 107 (95), 91 (100), 90 (40), 89 (40); HRMS calcd for $C_{11}H_{12}O_2$ 176.083 72, found 176.083 73. **(2*R*,3*R*)-1,2-Epoxy-5-phenyl-4-penten-3-ol (16):** ^{1}H NMR (250 MHz) δ 7.4–7.25 (m, 5 H), 6.72 (d, *J* = 16 Hz, 1 H), 6.17 (dd, *J* = 16 Hz, 7.5 Hz, 1 H), 4.52 (m, 1 H), 3.17 (m, 1 H), 2.87 (m, 1 H), 2.77 (m, 1 H), 2.00 (d, *J* = 2.5 Hz, 1 H); ^{13}C NMR (62.87 MHz) δ 136.1, 132.8, 128.5, 128.0, 126.5, 125.6, 69.9, 54.0, 43.6; MS (EI 30 eV) *m/e* 176 (7, M$^+$), 133 (100), 115 (72), 104 (94), 91 (30), 77 (32); HRMS calcd for $C_{11}H_{12}O_2$ 176.08372, found 176.08373.

Kinetic Resolution of 3-(Trimethylsilyl)penta-3,4-dien-2-ol (14). The racemic alcohol was resolved according to Sharpless' standard procedure[49] on a 2-mmol scale with 0.112 g (0.24 equiv) of L-(+)-diisopropyl tartrate, 0.113 g (0.2 equiv) of Ti(O-*i*-Pr)$_4$, and 1.5 equiv of TBHP at −18 °C. Analysis (GC) after 12 days indicated 43% conversion. The crude product was chromatographed with 8–15% acetone/hexane, affording the resolved alcohol (0.115 g, 37% yield, ee 66%), $[\alpha]^{27}_D$ +3.4° (*c* 5.75, $CHCl_3$).

(*S*)-(−)-4-Phenyl-3-butyn-2-ol (17). The racemic alcohol[83] was prepared from lithium phenylacetylide and acetaldehyde, and was purified by distillation, bp 80 °C (2 mmHg). The alcohol was resolved according to the standard procedure (2-mmol scale, 50% conversion by ^{1}H NMR). The crude product was chromatographed with 10–20% EtOAc/hexane, giving the acetate (R_f 0.3, 10% EtOAc) as an oil (0.18 g, 48%, ee >95%) and the alcohol (R_f 0.13, 10% EtOAc) as an oil (0.14 g, 47%, ee >95%): $[\alpha]^{25}_D$ −50.6° (*c* 1.475, ether) [lit. for (*R*)-(+)-4-phenyl-3-butyn-2-ol[84] [α] +51.8° (no solvent reported)]; ^{1}H NMR (250 MHz) δ 7.42 (m, 2 H), 7.30 (m, 3 H), 4.75 (m, 1 H), 1.85 (d, *J* = 5.5 Hz, 1 H), 1.54 (d, *J* = 5.5 Hz, 3 H).

(*S*)-(−)-3-Octyn-2-ol (18). The racemic alcohol was prepared by the reaction of the lithium anion of 1-hexyne with acetaldehyde, bp 115 °C (15 mmHg), an oil. This alcohol was resolved according to the standard procedure (5-mmol scale). The crude product was chromatographed with 5–8% EtOAc/hexane to afford the acetate (R_f 0.42, 5% EtOAc/hexane) as an oil (0.344 g, 41%, ee 87%) and the alcohol (R_f 0.19, 5% EtOAc/hexane, 0.20 g, 31%, ee >95%): $[\alpha]^{25}_D$ −26.3° (*c* 2.03, $CHCl_3$) −37.0° (*c* 1.58, ether) [lit.[85] [α] −14.5° (ee 36%), lit. for (*R*)-(+)-3-octyn-2-ol[58] [α] +39.1° (*c* 1.63, ether)]; ^{1}H NMR (250 MHz) δ 4.50 (m, 1 H), 2.18 (m, 2 H), 1.84 (s, 1 H), 1.42 (m, 4 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

(*S*)-(−)-3-Dodecyn-2-ol (19). The racemic alcohol was prepared by reacting the lithium anion of 1-decyne with acetaldehyde, and was resolved following the standard procedure (2-mmol scale, 50% conversion by ^{1}H NMR). The crude product was chromatographed with 2–20% acetone/hexane, giving the acetate (R_f 0.57, 5% acetone/hexane) as an oil (0.225 g, 50%, ee >95% by ^{1}H NMR chiral shift experiment after hydrolysis back to alcohol **19**) and the alcohol (R_f 0.25, 5% acetone/hexane) as an oil (0.109 g, 30%, ee >95%): $[\alpha]^{25}_D$ −21.8° (*c* 3.01, $CHCl_3$); ^{1}H NMR (250 MHz) δ 4.50 (m, 1 H), 2.18 (m, 2 H), 1.68 (d, *J* = 5 Hz, 1 H), 1.55–1.26 (m, 12 H), 0.84 (m, 6 H).

(*S*)-(−)-4-(Trimethylsilyl)-3-butyn-2-ol (20). The alcohol[86] was resolved according to the standard procedure (18-mmol scale, 50% conversion by ^{1}H NMR). The crude product was chromatographed with 4–10% acetone/hexane to afford the acetate (R_f 0.55, 5% acetone/hexane) as an oil (1.75 g, 45%, ee >95%) and the alcohol (R_f 0.2, 5% acetone/hexane, 0.71 g, 27%, ee >95%): $[\alpha]^{25}_D$ −25.9° (*c* 3.12, $CHCl_3$); ^{1}H NMR (90 MHz) δ 4.50 (m, 1 H), 1.85 (d, *J* = 3.8 Hz, 1 H), 1.42 (d, *J* = 4.6 Hz, 3 H), 0.15 (s, 9 H). The absolute configuration was determined to be *S* by conversion to (*S*)-(−)-3-(2-tetrahydropyranyloxy)-1-butyne by sequentially forming the tetrahydropyranyl ether (dihydropyran, catalytic *p*-toluenesulfonic acid, CH_2Cl_2) and hydrolyzing the (trimethylsilyl)acetylene (K_2CO_3, MeOH). The crude product was chromatographed with 2–8% EtOAc/hexane to give the product (R_f 0.26, 4% EtOAc/hexane) as an oil: $[\alpha]^{25}_D$ −187.5° (*c* 2.3, MeOH) [lit.[87] $[\alpha]^{25}_D$ −122.3° (*c* 10.8, MeOH)]; ^{1}H NMR (90 MHz) δ 4.92 (m, 1 H), 4.56 (dd, *J* = 6.4 Hz, 3.6 Hz, 1 H), 3.80 (m, 1 H), 3.52 (m, 1 H), 2.38 (d, *J* = 3.6 Hz, 1 H), 2.0–1.2 (m, 6 H), 2.5 (d, *J* = 6.4 Hz, 1 H).

(*S*)-(−)-4-[(4-Methoxybenzyl)oxy]-3-butyn-2-ol (21). The racemic alcohol was prepared as an oil by the reaction of [3-[(4-methoxybenzyl)oxy]-1-propynyl]lithium with acetaldehyde, bp 118 °C (0.3 mmHg). It was resolved according to the standard procedure (4-mmol scale, 52% conversion by GC). The crude product was chromatographed with 12–25% acetone/hexane to afford the acetate (R_f 0.28, 10% acetone/hexane) as an oil (0.501 g, 48%, ee 78%), $[\alpha]^{27}_D$ +67.35° (*c* 2.04, $CHCl_3$) [lit. for (*R*)-4-[(4-methoxybenzyl)oxy]-3-butyn-2-ol acetate[55] $[\alpha]_D$ +73.5 (ee 73%)], and the alcohol (R_f 0.09, 10% acetone/hexane, 0.399 g, 46%, ee >95%): $[\alpha]^{27}_D$ −15.4° (*c* 2.23, $CHCl_3$) [lit. for (*R*)-4-[(4-methoxybenzyl)oxy]-3-butyn-2-ol[55] $[\alpha]_D$ +15.0° (ee 73%)]; ^{1}H NMR (250 MHz) δ 7.27 (d, *J* = 10 Hz, 2 H), 6.87 (d, *J* = 7.5 Hz, 2 H), 4.57 (m, 1 H), 4.51 (s, 2 H), 4.15 (s, 2 H), 3.80 (s, 3 H), 1.78 (d, *J* = 5 Hz, 1 H), 1.46 (d, *J* = 6.5 Hz, 3 H).

(*S*)-(−)-4-Nonyn-3-ol (22). The racemic alcohol was prepared from 1-hexyne and propionaldehyde, bp 116 °C (15 mmHg). The alcohol was resolved according to the standard procedure (0.76-mmol scale, 54% conversion by ^{1}H NMR). The crude product was chromatographed with

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2–6% EtOAc/hexane to provide the acetate (R_f 0.38, 2% EtOAc/hexane) as an oil (0.05 g, 36%, ee 82%) and the alcohol (R_f 0.25, 4% EtOAc) also as an oil (0.05 g, 48%, ee >95%): $[\alpha]^{25}_D$ −4.67° (*c* 1.07, $CHCl_3$), −19.7° (*c* 0.63, ether), [lit. for (*R*)-(+)-4-nonyn-3-ol[58] $[\alpha]_D$ +21.6° (ether)]: ^{1}H NMR (300 Hz) δ 4.25 (m, 1 H), 2.33 (s, 1 H), 2.16 (m, 2 H), 1.63 (m, 2 H), 1.42 (m, 4 H), 0.89 (m, 6 H); ^{13}C NMR (62.89 MHz) 85.0, 80.8, 63.5, 30.7, 30.5, 21.6, 16.0, 13.3, 9.2.

(*S*)-(−)-6-Methyl-6-hepten-4-yn-3-ol (23). The racemic alcohol (Farchan Laboratories) was resolved according to the standard procedure (2-mmol scale). The crude product was chromatographed with 3–20% acetone/hexane to afford the acetate (R_f 0.4, 5% acetone/hexane) as an oil (0.146 g, 44%, ee >95%) and the alcohol (R_f 0.1, 5% acetone/hexane, 0.083 g, 33%, ee >95%): $[\alpha]^{25}_D$ −2.3° (*c* 2.43, $CHCl_3$); ^{1}H NMR (250 MHz) δ 5.25 (d, *J* = 15 Hz, 2 H), 4.43 (m, 1 H), 1.87 (s, 3 H), 1.73 (m, 3 H), 1.01 (t, *J* = 5 Hz, 3 H). The absolute configuration was determined by hydrogenation (Pd/C, MeOH) to afford the known (*S*)-(+)-6-methylheptan-3-ol, $[\alpha]^{25}_D$ +3.8° (*c* 0.18, EtOH) [lit.[77] $[\alpha]^{20}_D$ +7.2° (*c* 0.45, EtOH)].

(*R*)-(+)-1-Phenyl-3-butyn-2-ol (24). The racemic alcohol[88] was prepared by the reaction of ethynylmagnesium bromide with phenylacetaldehyde, and was distilled, bp 59 °C (0.3 mmHg), to afford the product as an oil. The alcohol was resolved according to the standard procedure (2-mmol scale, 53% conversion by GC). The crude product was chromatographed with 6–16% acetone/hexane to afford the acetate (R_f 0.45, 10% acetone/hexane) as an oil (0.195 g, 52%, ee 77%) and the alcohol (R_f 0.20, 10% acetone/hexane, 0.092 g, 31%, ee >95%): $[\alpha]^{25}_D$ +11.1° (*c* 2.05, $CHCl_3$); ^{1}H NMR (250 MHz) δ 7.28 (m, 1 H), 4.57 (m, 1 H), 3.02 (dd, *J* = 6 Hz, 1.25 Hz, 2 H), 2.48 (d, *J* = 2.25 Hz, 1 H), 1.85 (d, *J* = 5 Hz, 1 H). The absolute configuration was determined by hydrogenation over 5% Pd/C to afford (*S*)-(+)-1-phenyl-2-butanol, $[\alpha]^{27}_D$ +25.5° (*c* 2.11, $CHCl_3$) [lit. for (*R*)-(−)-1-phenyl-2-butanol[89] $[\alpha]_D$ −20.2° (*c* 7.16, $CHCl_3$)].

(*R*)-(+)-1-Octyn-2-ol (25). The racemic alcohol[78] was resolved according to the standard procedure (2-mmol scale, 54% conversion by ^{1}H NMR). The crude product was chromatographed with 7–18% acetone/hexane to afford the acetate (R_f 0.30, 10% acetone/hexane) as an oil (0.17 g, 49%) and the alcohol (R_f 0.27, 15% acetone/hexane, 0.061 g, 24%, ee 23%): $[\alpha]^{25}_D$ +4.4° (*c* 1.82, ether) [lit. for (*S*)-(−)-1-octyn-3-ol[90] $[\alpha]^{25}_D$ −18.8° (*c* 1.30, ether)]; ^{1}H NMR (250 MHz) δ 4.36 (m, 1 H), 2.45 (d, *J* = 2 Hz, 1 H), 1.8–1.2 (m, 8 H), 0.88 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR (62.89 MHz) δ 85.0, 72.6, 62.0, 37.4, 31.2, 24.0, 22.4, 13.9.

(*S*)-(+)-5-(Trimethylsilyl)-4-pentyn-2-ol (26). The racemic alcohol was prepared by the following procedure: 10 mmol of *tert*-butyllithium (1.7 M solution in pentane) was added to a solution of 1.12 g (10 mmol) of 1-(trimethylsilyl)-1-propyne in 24 mL of THF at −78 °C.[82] The solution was stirred at −78 °C for 40 min, upon which time 2.84 g (10 mmol) of Ti(O-*i*-Pr)$_4$ was added and the solution was stirred for 10 min; 0.44 g (10 mmol) of acetaldehyde was added, and the solution was stirred at −78 °C for 30 min and then allowed to warm to −20 °C over 20 min. The resulting mixture was poured into an aqueous NH_4Cl/ice slurry and was extracted with ether (^{1}H NMR indicated the crude reaction mixture contained 3-(trimethylsilyl)-3,4-pentadien-2-ol and 5-(trimethylsilyl)-4-pentyn-2-ol, in near-equal amounts). The crude product was chromatographed, eluting with 5–9% acetone/hexane containing ~0.2% NEt_3 to afford the alkynol (R_f 0.3, 7% acetone/hexane) as an oil (0.42 g, 27%). The alcohol was resolved according to the standard procedure (2-mmol scale), and chromatographed with 4–10% acetone/hexane to afford the acetate (R_f 0.3, 4% acetone/hexane) as an oil (0.08 g, 20%, ee >95%) and the alcohol (0.08 g, 26%, ee >95%): $[\alpha]^{25}_D$ +9.35° (*c* 2.00, $CHCl_3$) [lit.[91] $[\alpha]^{23}_D$ +13.5° (*c* 3.0, $CHCl_3$)]; ^{1}H NMR (250 MHz) δ 3.93 (m, 1 H), 2.38 (m, 2 H), 1.97 (d, *J* = 4.7 Hz, 1 H), 1.26 (d, *J* = 6.2 Hz, 3 H), 0.15 (s, 9 H).

(+)-6-Phenyl-5-hexyn-3-ol (27). The racemic alcohol (Farchan) was resolved according to the standard procedure (2-mmol scale, 55% conversion by GC), and chromatographed with 3–10% acetone/hexane to afford the acetate (R_f 0.37, 5% acetone/hexane) as an oil (0.27 g, 63%, ee 50%) and alcohol **27** (R_f 0.12, 5% acetone/hexane, 0.12 g, 33%, ee >95%): $[\alpha]^{25}_D$ +12.8° (*c* 2.6, $CHCl_3$); ^{1}H NMR (250 MHz) δ 7.39 (m, 2 H), 7.28 (m, 3 H), 3.77 (m, 1 H), 2.58 (m, 2 H), 1.94 (d, *J* = 5 Hz, 1 H), 1.62 (m, 2 H), 0.99 (t, *J* = 7.5 Hz, 3 H).

(*S*)-(+)-4-Heptyn-2-ol (28). The racemic alcohol (Farchan) was resolved according to the standard procedure (2-mmol scale, 55% conversion by GC). The crude product was chromatographed with 2–20% acetone/hexane to afford the acetate (R_f 0.4, 5% acetone/hexane, 0.135 g, 44%, ee 42%) and the alcohol (R_f 0.15, 5% acetone/hexane, 0.048 g, 21%, ee 54%): $[\alpha]^{25}_D$ +10.0° (*c* 1.80, $CHCl_3$) [lit.[92] $[\alpha]^{25}_D$ +17.7° (*c* 1.60, $CHCl_3$)]; ^{1}H NMR (250 MHz) δ 3.89 (m, 1 H), 2.4–2.1 (m, 4 H), 1.94 (d, *J* = 5 Hz, 1 H), 1.23 (d, *J* = 6.25, 3 H), 1.12 (t, *J* = 7.7 Hz, 3 H).

(*S*)-(+)-5-Octyn-3-ol (29). The racemic alcohol (Farchan) was resolved according to the standard procedure (2-mmol scale, 61% conversion by GC). The crude product was chromatographed with 2–20% acetone/hexane to afford the acetate (R_f 0.7, 20% acetone/hexane, 0.16 g, 33%, ee 38%) and alcohol **29** (R_f 0.5, 20% acetone/hexane, 0.068 g, 27%, ee 61%): $[\alpha]^{25}_D$ +7.3° (*c* 2.00, $CHCl_3$); ^{1}H NMR (250 MHz) δ 3.62 (m, 1 H), 2.5–2.1 (m, 4 H), 1.93 (d, *J* = 5 Hz, 1 H), 1.55 (m, 2 H), 1.11 (t, *J* = 7.5 Hz, 3 H), 0.94 (t, *J* = 7.5 Hz, 3 H). The absolute configuration was determined by hydrogenation (Pd/C, MeOH) to afford (*S*)-(+)-3-octanol, $[\alpha]^{25}_D$ +6.9° (*c* 1.13, ether) [lit. for (*R*)-(−)-3-octanol[72] $[\alpha]^{25}_D$ −9.0° (*c* 6, ether)].

(*S*)-(−)-1-Phenyl-3-butyn-1-ol (30). The racemic alcohol (Farchan) was resolved according to the standard procedure (2-mmol scale, 64% conversion by ^{1}H NMR). The crude product was chromatographed with 5–10% acetone/hexane to afford the acetate (R_f 0.3, 5% acetone/hexane, 0.17 g, 45%, ee 72%) and the alcohol (R_f 0.16, 5% acetone/hexane, 0.10 g, 34%, ee >95%): $[\alpha]^{25}_D$ −48.8° (*c* 2.50, $CHCl_3$) [lit.[93] $[\alpha]$ −9.21° (*c* 3.5, MeOH, ee 79%)]; ^{1}H NMR (250 MHz) δ 7.37 (m, 5 H), 4.88 (m, 1 H), 2.65 (m, 2 H), 2.34 (d, *J* = 2.5 Hz, 1 H), 2.07 (t, *J* = 2.5 Hz, 1 H).

(*S*)-(+)-1-Phenylpropan-2-ol (31). The racemic alcohol (Aldrich Chemical Co.) was resolved according to the standard procedure (2-mmol scale, 50% conversion by GC). The crude product was chromatographed with 10–18% acetone/hexane to afford the acetate (R_f 0.66, 20% acetone/hexane) as an oil (0.165 g, 46%, ee >95% by ^{19}F NMR of MTPA derivative) and the alcohol (R_f 0.36, 20% acetone/hexane, 0.117 g, 43%, ee >95% by ^{19}F NMR of MTPA derivative): $[\alpha]^{27}_D$ +41.8° (*c* 2.15, $CHCl_3$) [lit.[94] $[\alpha]^{25}_D$ +5.0° (*c* 4.00, $CHCl_3$, ee 14.8%)].

(*S*)-(+)-4-Phenylbutan-2-ol (32). The racemic alcohol (prepared by hydrogenation of 4-phenylbut-3-en-2-ol over 5% Pd/C in MeOH) was resolved according to the standard procedure (2-mmol scale, 52% conversion by GC). The crude product was chromatographed with 8–20% acetone/hexane to afford the acetate (R_f 0.3, 10% acetone/hexane) as an oil (0.113 g, 40%, ee >95% by ^{19}F NMR of the MTPA derivative) and the alcohol (R_f 0.13, 10% acetone/hexane) as an oil (0.074 g, 32%, ee >95% by ^{19}F NMR of MTPA derivative): $[\alpha]^{27}_D$ +17.45° (*c* 2.04, $CHCl_3$) [lit.[95] $[\alpha]^{20}_D$ +13.5° (*c* 2.1, $CHCl_3$, ee 73%)]; ^{1}H NMR (250 MHz) δ 7.23 (m, 5 H), 3.83 (m, 1 H), 2.70 (m, 2 H), 1.75 (m, 3 H), 1.22 (d, *J* = 5 Hz, 3 H).

(*S*)-(+)-5-Phenyl-2-pentanol (33). The racemic alcohol[96] (prepared by the reaction of (3-phenylpropyl)magnesium bromide with acetaldehyde) was resolved according to the standard procedure (2-mmol scale, 57% conversion by GC). The crude product was chromatographed with 8–12% acetone/hexane to afford the acetate (R_f 0.6 10% acetone/hexane) as an oil (0.208 g, 50%, ee 67% by ^{19}F NMR of the MTPA derivative) and the alcohol (R_f 0.21, 10% acetone/hexane) also as an oil (0.106 g, 32%, ee >95% by ^{19}F NMR of the MTPA derivative): $[\alpha]^{27}_D$ +8.47° (*c* 3.00, $CHCl_3$) [lit.[97] $[\alpha]^{25}_D$ +8.63° ($CHCl_3$)]; ^{1}H NMR (250 MHz) δ 7.20 (m, 5 H), 3.80 (m, 1 H), 2.63 (t, *J* = 7.25 Hz, 2 H), 1.80–1.43 (m, 5 H), 1.18 (d, *J* = 6.25 Hz, 3 H).

(*S*)-(+)-2-Dodecanol (34). The racemic alcohol was prepared by hydrogenation of 3-dodecyn-2-ol over 5% Pd/C, and resolved according to the standard procedure (1.4-mmol scale with 1 mass equiv lipase, 67% conversion by GC). The crude product was chromatographed with 5–12% acetone/hexane to afford the acetate (R_f 0.45, 5% acetone/hexane) as an oil (0.243 g, 77%) and the alcohol (R_f 0.32 10% acetone/hexane) as an oil (0.034 g, 13%, ee 89% by ^{1}H NMR of MTPA derivative): $[\alpha]^{25}_D$ +6.2° (*c* 0.97, EtOH) [lit. for (*R*)-2-dodecanol[71] $[\alpha]$ −7.94° (*c* 8.7, EtOH), $[\alpha]^{25}_D$ −4.8° (*c* 5, EtOH)];[72] ^{1}H NMR (90 MHz) δ 3.75 (m, 1 H), 1.5–1.0 (m, 18 H), 0.85 (m, 6 H).

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Further Evidence for the Role of $d\pi$-$p\pi$ Bonding in Rhodium-Mediated Hydroborations

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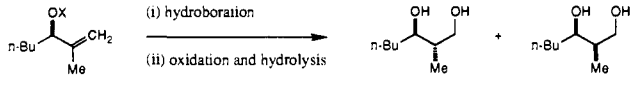
Abstract: Stereoelectronic effects governing coordination of the alkene functionality to rhodium have been postulated to account for diastereofacial selectivities in catalyzed hydroborations of allylic alcohol derivatives **1**; this paper describes two sets of experiments to test this controversial hypothesis. The first one involves competition experiments between related allylic alcohol derivatives, and shows that allylic trifluoroacetates react at least 160–210 times faster than allylic acetates under the catalyzed conditions. Similar competition experiments with uncatalyzed hydroborations reveal rate differences of less than 5-fold in the opposite sense (i.e. allylic acetates react faster). The second set of experiments show that catalyzed and uncatalyzed hydroborations of 5-substituted 2-methyleneadamantanes **5** proceed with opposite diastereofacial selectivities. Results from the competition experiments and the stereoselectivity studies are consistent with the original postulate for stereoelectronic effects in catalyzed hydroborations, and provide pointers to some of the mechanistic features that characterize the process. Experiments to probe the reversibility of mechanistic steps in rhodium-catalyzed hydroborations are presented. Finally, selectivities observed in the catalyzed hydroborations of 5-substituted 2-methyleneadamantanes **5** are discussed with reference to the "Cieplak postulate", a hypothesis that is shown to be inappropriate for predicting the stereochemical outcome of catalyzed hydroborations.

Introduction

One of the most significant observations to emerge from recent studies of rhodium-mediated hydroboration reactions is that catalyzed hydroborations of the allyl alcohol derivatives **1** give syn products **2** selectively, whereas uncatalyzed reactions preferentially give the anti isomers.[1-3] Similarly, catalyzed and uncatalyzed hydroborations of allylamine derivatives tend to be syn and anti selective, respectively.[4,5]



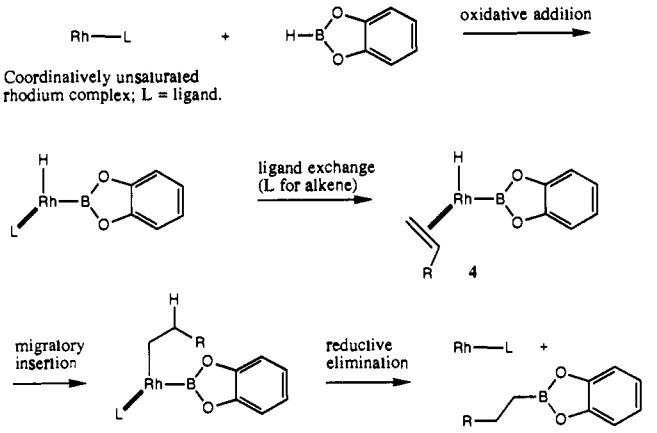
1 *anti*-**2** *syn*-**2**

X	$HBO_2C_6H_4$, Rh-cat *syn:anti*	9-BBN *syn:anti*
$COCH_3$	2.7:1.0	1.0:7.5
$COCF_3$	7.5:1.0	1.0:14
CO^tBu	6.5:1.0	1.0:15

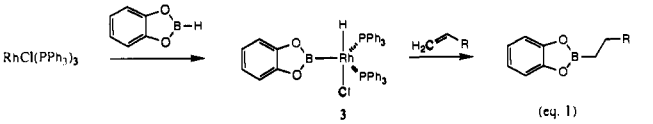
The origin of this "stereocomplementary" behavior is an enigma in contemporary organic chemistry, and one that is difficult to address because the details of the mechanism of catalyzed hydroborations are unknown. However, the generalized reaction pathway shown in Scheme I seems reasonable,[6] particularly when compared with the related, and much better understood, rhodium-promoted *hydrogenation* reactions.[7,8]

Further support for the mechanism postulated in Scheme I is derived from some stoichiometric reactions of transition-metal

Scheme I. Generalized Mechanism for Catalyzed Hydroborations



complexes, which resemble steps in the proposed catalytic cycle. For instance, catecholborane oxidatively adds to $RhCl(PPh_3)_3$ giving complex **3**, which combines with alkenes to give hydroboration products (eq 1).[6,9] Furthermore, migratory insertion



3 (eq. 1)

of alkynes into the iridium–hydride bond of a borylhydridoiridium complex has been observed,[10,11] and reductive elimination of vinyl

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