

Applications of liver acetone powders in enantioselective synthesis

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Dedicated to Prof. T. R. Govindachari on the occasion of his 85th birthday
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Abstract

Applications of liver acetone powders (crude enzymes) as possible substitutes for purified enzyme preparations, *hydrolases*, in enantioselective organic transformations have been systematically investigated. (1*R*, 2*R*)-2-(4-Alkylphenoxy)cyclohexan-1-ols, (1*R*, 2*R*)- & (1*S*, 2*S*)-2-nitroxycyclohexan-1-ols, (1*R*, 2*S*)-2-arylcyclohexan-1-ols, (3*R*, 4*R*)-6-methyl-3-phenylhept-1-en-4-ol, and (*R*)-1-(naphth-1-yl)ethanol have been synthesized in enantiomerically pure form *via* the enantioselective hydrolysis of the corresponding racemic acetates mediated by liver acetone powders.

Keywords: Liver acetone powders, enantioselective synthesis, enzymes

Introduction

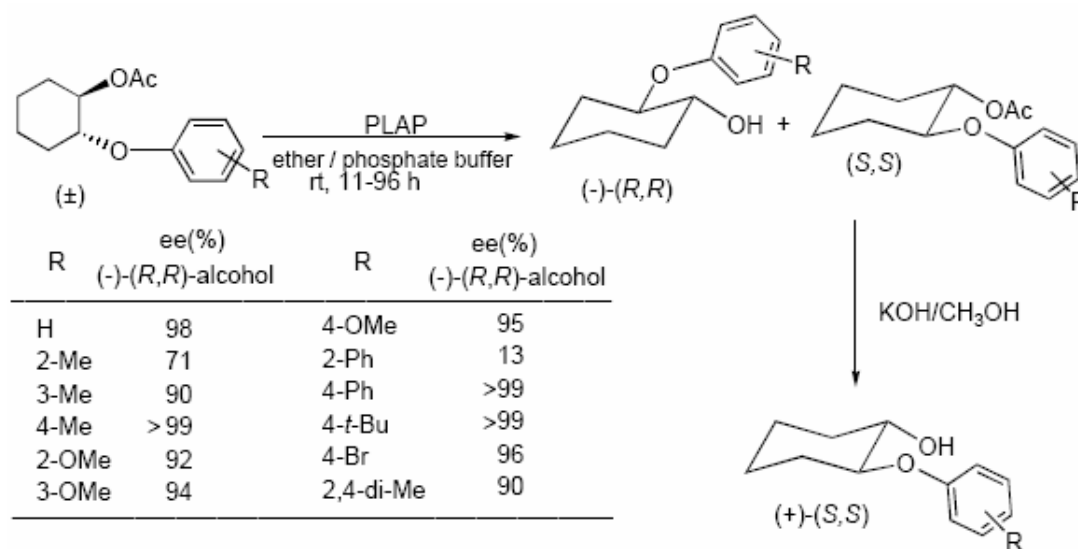
Enantiomerically pure molecules occupy a special place in the history of organic chemistry due to the key role of the enantiomer recognition in biological activity and hence development of convenient and simple methodologies for the synthesis of enantiomerically pure molecules has been and continues to be an interesting and challenging area in organic chemistry.¹⁻⁶ In recent years, biocatalytic methodology, once thought to be an esoteric area and largely confined to the laboratories with necessary expertise, has now become a primary activity of research in most of the leading research laboratories working in the areas of both organic, bioorganic and medicinal chemistry.⁷⁻¹⁴ Despite the very useful and attractive applications of chemico-enzymatic methodology in synthetic organic chemistry, there still exists some apprehension amongst organic chemists with respect to handling of the enzymes and experimental techniques. Also most of the commercially available enzymes are expensive.

We, therefore, have thought that these problems can possibly be solved to some extent using crude preparation of certain enzymes in projected reactions, if the other enzymes present in the crude preparations do not interfere. However, literature survey reveals that crude enzyme

preparations are relatively less explored compared to the purified enzymes.¹⁵⁻¹⁷ Therefore, we have undertaken a long range research program on this aspect and have successfully employed liver acetone powders such as *pig liver acetone powder* (PLAP), *goat liver acetone powder* (GLAP), *bovine liver acetone-powder* (BLAP) and *chicken liver acetone powder* [*crude chicken liver esterase* (CCLE)] (crude enzymes) as possible substitutes for purified enzyme preparations, *hydrolases*, in enantioselective organic synthesis. In fact, we have made some important contributions in enantioselective hydrolysis of various racemic organic acetates using these crude enzymes¹⁸. Though there are a few literature reports¹⁹⁻²³ from the other research laboratories in this area, this account will deal mostly with our work.

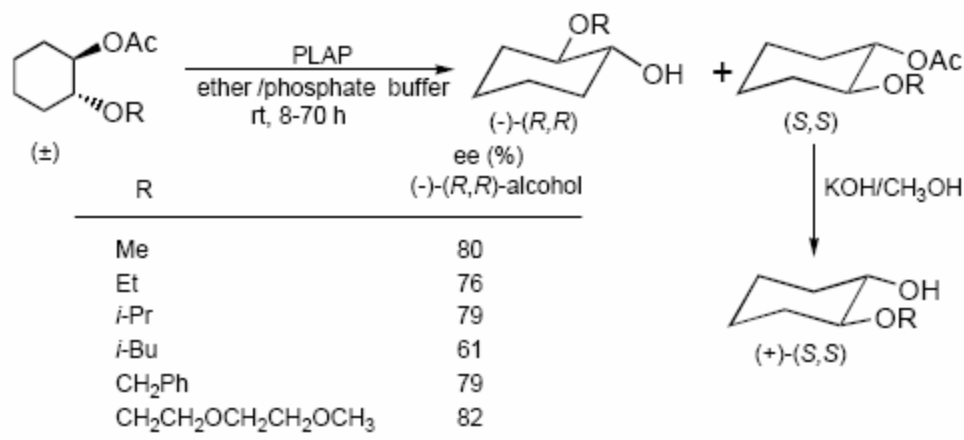
Applications of liver acetone powders

Cyclohexyl based chiral auxiliaries play an important role in enantioselective organic synthesis.²⁴ With a view that chiral *trans*-2-aryloxycyclohexan-1-ols will offer promise as useful chiral auxiliaries, we have successfully used *pig liver acetone powder* (PLAP) as chiral source for enantioselective hydrolysis of racemic *trans*-1-acetoxy-2-aryloxycyclohexanes to provide the resulting (-)-(*R,R*)-2-aryloxycyclohexan-1-ols in very high enantiomeric purities²⁵⁻²⁶ (13- >99%) and in 24-47% isolated yields²⁷ (Scheme 1). The (*R,R*)-selectivity in the hydrolysis of racemic *trans*-1-acetoxy-2-aryloxy-cyclohexanes can be possibly explained on the basis of the Jones three dimensional active site model.²⁸⁻³¹



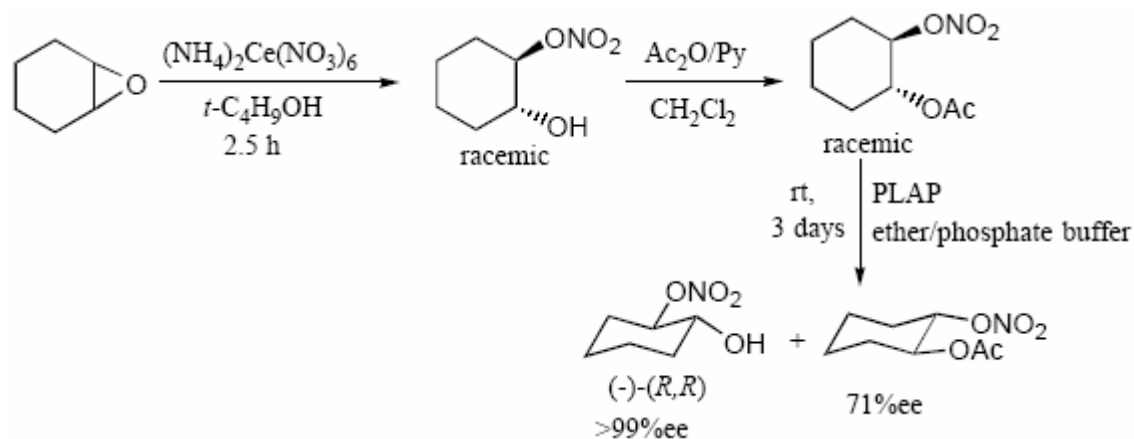
Scheme 1

We have next examined the enantioselective hydrolysis of racemic *trans*-1-acetoxy-2-alkoxycyclohexanes using PLAP, with a view to understand the levels of enantioselectivity that aliphatic groups can offer. The resulting *trans*-2-alkoxycyclohexan-1-ols were obtained with (*R,R*)-configuration in 61-82% enantioselectivities³² and in 22-40% isolated yields³³ (Scheme 2).



Scheme 2

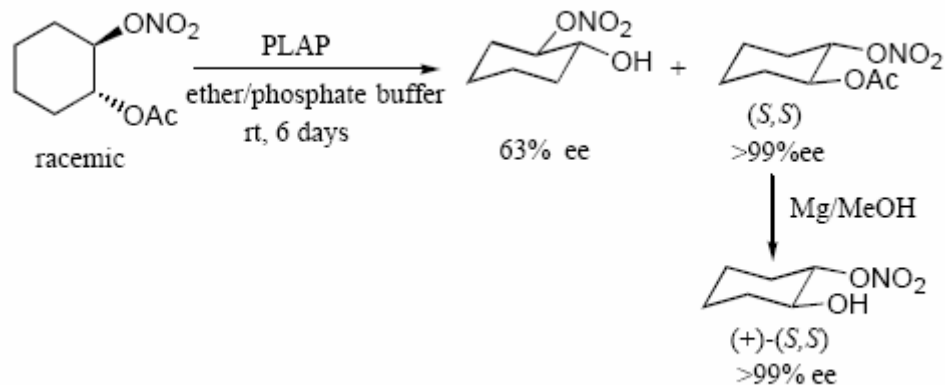
Nitrate esters find widespread therapeutical importance as drugs for treatment of heart and vascular diseases.^{34,35} *trans*-2-Nitroxycyclohexan-1-ol is one such molecule, which has attracted our attention. We have enantioselectively hydrolyzed racemic *trans*-1-acetoxy-2-nitroxycyclohexane with PLAP to produce homochiral (-)-(*R,R*)-2-nitroxycyclohexan-1-ol in 35% isolated yield²⁷ (Scheme 3) and homochiral (*S,S*)-acetate in 36% isolated yield²⁷ (Scheme 4) which was subsequently transformed into (+)-(*S,S*)-2-nitroxycyclohexan-1-ol by treatment with Mg/MeOH in 55% yield, thus developing the first enantioselective synthesis of both (*R,R*)-& (*S,S*)-2-nitroxycyclohexan-1-ols.³⁶



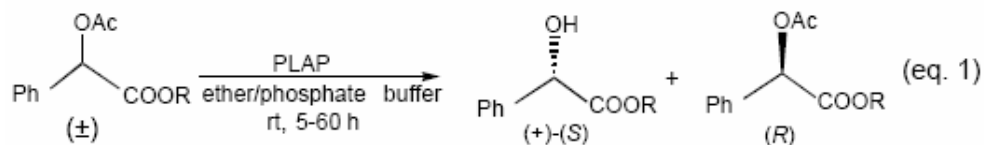
Scheme 3

Optically pure α -hydroxy acids are important synthons that have been extensively utilized in a number of stereoselective processes.^{37,38} *Pig liver acetone powder* (PLAP) catalyzed hydrolysis of alkyl α -acetoxy- α -phenylacetates produces alkyl (*S*)- α -phenyl- α -hydroxyacetates in 23-80% enantiomeric purities,³⁹ and in 22-40% isolated yields.³³ Enantioselectivity is dependent on the

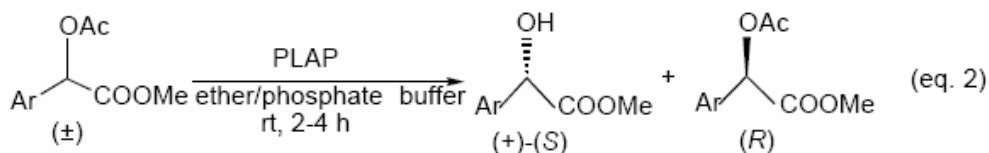
ester group of O-acetylmandelates, methyl ester (75% ee, eq. 1) and *tert.* butyl ester (80% ee, eq.1) offer better selectivities.³⁹ Substitution on the aromatic ring provides desired α -hydroxy acids in low selectivities (26-57% ee) though the chemical yields are satisfactory (29-36% isolated yields).³³ Only acetate group is hydrolyzed by PLAP while the ester functionality is found to be completely intact (eq. 1 & eq. 2).³⁹



Scheme 4

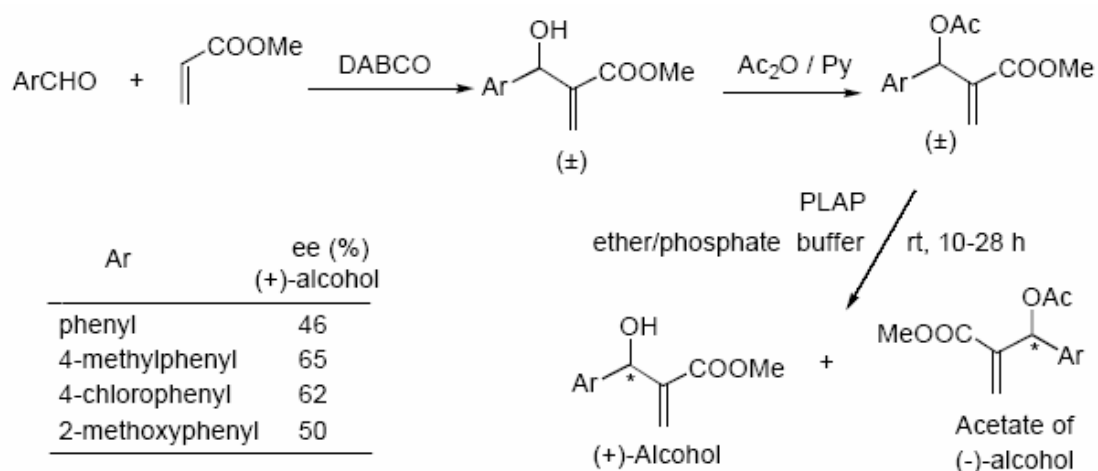


R	ee (%) (+)-(S)-alcohol
Me	75
Et	47
<i>i</i> -Pr	55
<i>t</i> -Bu	80
cyclohexyl	23

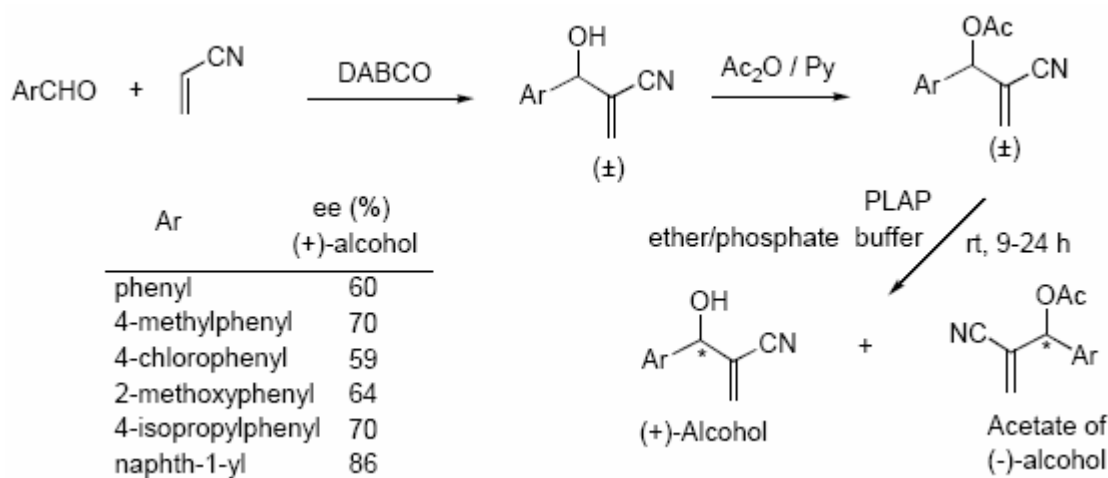


Ar	ee (%) (+)-(S)-alcohol
2-methoxyphenyl	55
4-methylphenyl	26
4-methoxyphenyl	57
naphth-1-yl	30

The Baylis-Hillman reaction is an emerging and atom economy carbon-carbon bond forming reaction between the α -position of activated alkenes and carbon electrophiles under the influence of tertiary amine catalyst (usually DABCO) providing molecules with unique structural features *i.e.* containing a minimum of three functional groups (hydroxy group, alkene, and electron withdrawing group) and one chiral center.⁴⁰⁻⁴³ We have employed *pig liver acetone powder* (PLAP) for the enzymatic hydrolysis of acetates of the racemic Baylis-Hillman adducts (alcohols) to provide the corresponding optically active alcohols in 46-86% enantioselectivities and in 19-37% isolated yields³³ (Schemes 5 & 6).⁴⁴



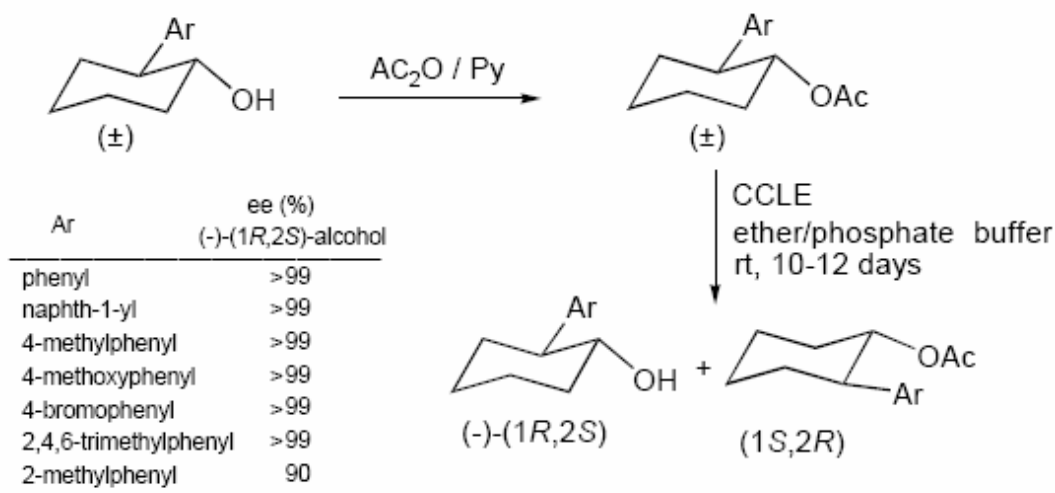
Scheme 5



Scheme 6

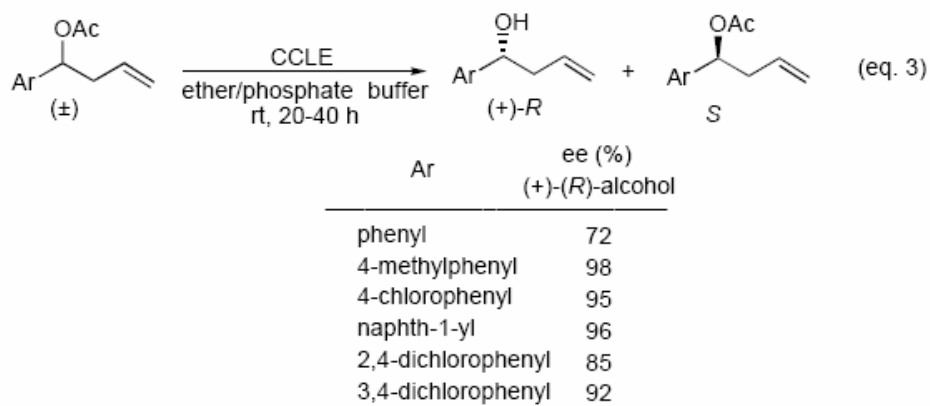
Recent work of Whitesell on the applications of *trans*-2-phenylcyclohexan-1-ol as a chiral auxiliary has attracted our attention.^{24,45} It occurred to us that if we have sterically more

demanding aromatic groups in the cyclohexane ring, the resulting *trans*-2-arylcyclohexan-1-ols might offer better enantioselectivities in chiral auxiliary mediated asymmetric reactions. Accordingly, we planned to prepare various *trans*-2-arylcyclohexan-1-ols in enantiomerically pure form *via* the hydrolysis of the corresponding racemic acetates with PLAP. Unfortunately all our attempts to hydrolyze racemic *trans*-1-acetoxy-2-arylcyclohexanes (except *trans*-1-acetoxy-2-phenylcyclohexane) with PLAP were unsuccessful. However, we have successfully prepared homochiral (-)-*trans*-(1*R*,2*S*)-2-arylcyclohexan-1-ols in satisfactory yields (21-33% isolated yields)²⁷ *via* the *crude chicken liver esterase* (CCLE) mediated enantioselective hydrolysis of the corresponding racemic acetates (Scheme 7).⁴⁶

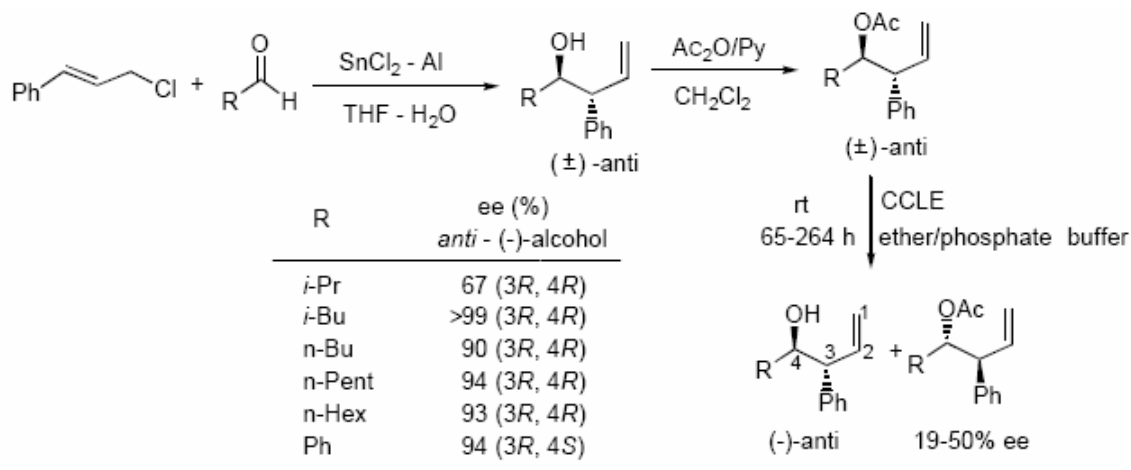


Scheme 7

Enantiomerically pure homoallyl alcohols are important intermediates for the synthesis of many naturally occurring and pharmacologically useful molecules.⁴⁷⁻⁴⁹ Acetates of racemic homoallyl alcohols have been enantioselectively hydrolyzed by *crude chicken liver esterase* (CCLE) (*chicken liver acetone powder*) to provide homoallyl alcohols in 72-98% optical purities with (*R*)-configuration⁵⁰ and in 24-39% isolated yields³³ (eq. 3).⁵⁰ We have also noticed that similar enantioselective hydrolysis using PLAP provides the desired (+)-(*R*)-homoallyl alcohols with inferior enantiomeric purities (56-72% ee).⁵¹



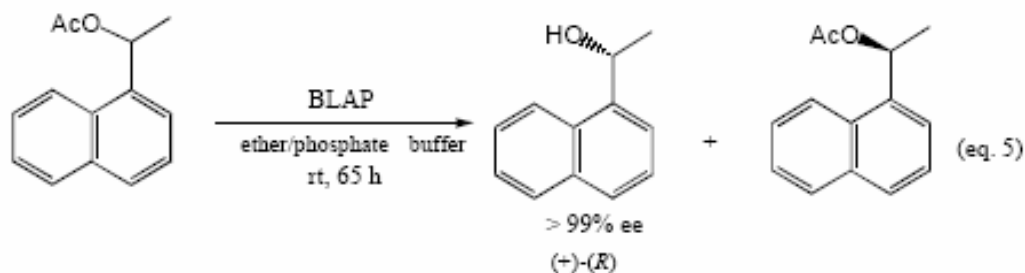
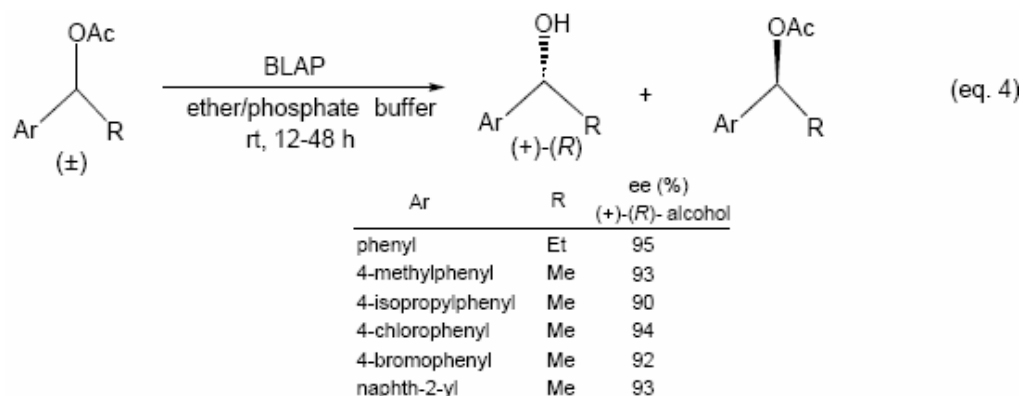
Diastereomerically and enantiomerically pure homoallylic alcohols are invaluable surrogates in the synthesis of various molecules of biological importance containing several stereogenic centers.^{52,53} *Crude chicken liver esterase* (CCLE) has been conveniently employed for enantioselective hydrolysis of the corresponding racemic acetates to obtain the desired enantiomerically enriched *anti*-homoallyl alcohols in 67->99% enantiomeric purities and in 20-31% isolated yields²⁷ (Scheme 8).⁵⁴



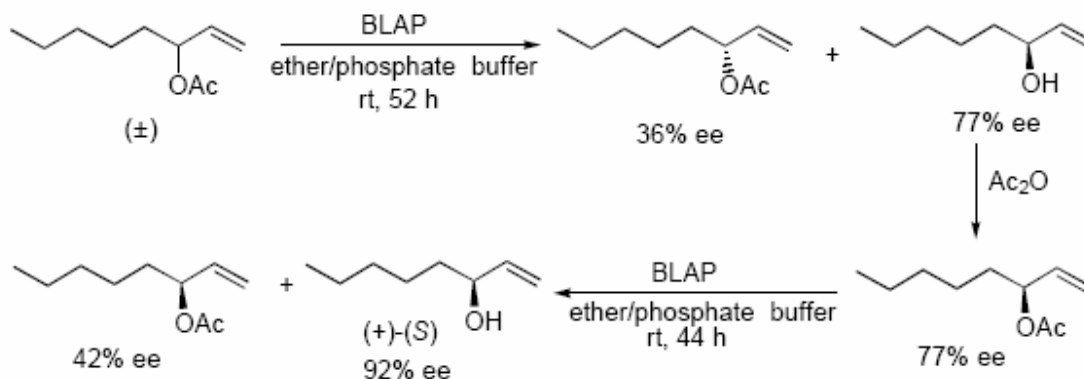
Scheme 8

We have successfully employed *bovine liver acetone powder* (BLAP) in the hydrolysis of racemic 1-acetoxy-1-arylalkanes to provide the corresponding (+)-(*R*)-1-aryl-1-alkanols in high (90-95%) optical purities and in 27-34% isolated yields³³ (eq. 4).⁵⁵ We have also utilized this methodology for the homochiral synthesis of (*R*)-1-(naphth-1-yl)ethan-1-ol (eq. 5) in 31% isolated yield³³, an important reagent for enantioselective opening of prochiral meso anhydrides.⁵⁶ It is interesting to mention that similar enantioselective hydrolysis of racemic 1-acetoxy-1-arylalkanes using PLAP and GLAP provided the required (+)-(*R*)-1-arylalkan-1-ols

with inferior enantiomeric purities (50-95% ee).⁵⁷

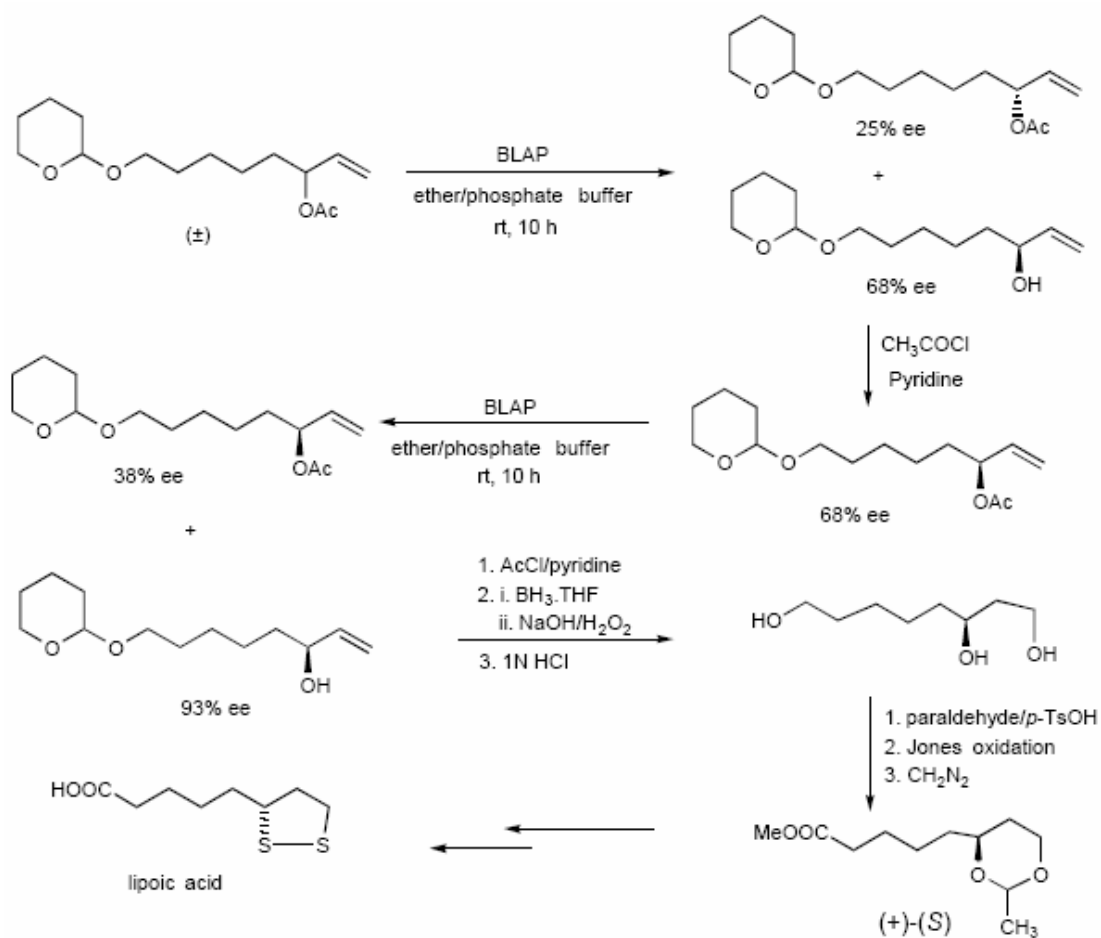


We have successfully synthesized (*S*)-oct-1-en-3-ol, a well known pheromone matsutake alcohol,⁵⁸ a flavor component of the mushroom *Tricholoma matsutake*, in 92% enantiomeric purity *via* the enzymatic hydrolysis of racemic 3-acetoxyoct-1-ene using *bovine liver acetone powder* (BLAP) according to Scheme 9.⁵⁹ Racemic 8-(tetrahydro-pyran-2-yloxy)-3-acetoxyoct-1-ene was enantioselectively hydrolyzed with BLAP to provide (3*S*)-8-(tetrahydropyran-2-yloxy)oct-1-en-3-ol, in 93% enantiomeric purity which was subsequently transformed into (3*S*)-1,3,8-octanetriol, an important synthon, for synthesis of lipoic acid, a co-enzyme associated with α -keto acid dehydrogenases,^{60,61} following the reaction sequence as described in the Scheme 10.⁵⁹

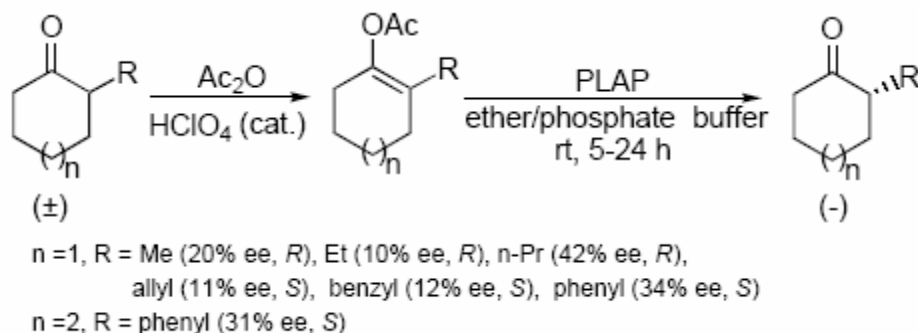


Scheme 9

Synthesis of enantiomerically enriched cyclic ketones continues to attract the attention of organic chemists because of the utility of these molecules as chiral building blocks in the synthesis of natural products.⁶²⁻⁶⁶ With a view to further expand the scope of *pig liver acetone powder* (PLAP) as biocatalyst in organic synthesis, we have examined hydrolysis of prochiral cyclic enol acetates with PLAP to provide the resulting (-)-2-substituted cyclic ketones in 10-42% ee, in high (69-88%) isolated yields (Scheme 11).^{67\}



Scheme 10



Scheme 11

In conclusion, we have systematically utilized the crude enzymes (liver acetone powders), which are inexpensive and easily accessible, as possible substitutes for pure enzyme preparations, *hydrolases*, in enantioselective hydrolysis of acetates of racemic secondary alcohols to provide operationally simple and convenient methodology for synthesis of enantiomerically enriched secondary alcohols. These studies also clearly demonstrate that liver acetone powders enantioselectively hydrolyze a variety of substrates with different substitution pattern, such as acetates of racemic 2-aryloxy-cyclohexan-1-ols, 2-nitroxycyclohexan-1-ol, Baylis-Hillman alcohols, 2-arylcyclohexan-1-ols, homoallyl alcohols, 1-arylalkan-1-ols, and C-8 allyl alcohols. From these studies, to some extent, it is also clear that liver acetone powders from different liver sources have different levels of reactivities and show different levels of selectivities though they exhibit similar direction of stereoselection. These studies and work from other research groups^{15-17,19-23} clearly demonstrate the enormous potential of liver acetone powders as biocatalysts in enantioselective organic synthesis and also give enough indication that these crude enzymes will probably offer promise in other biotransformations which were not explored so far.

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percentage hydrolysis. To have uniformity we have converted them into actual isolated yields and mentioned the same in this account.

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