SYNLETT
Spotlight 324

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Alcohol Dehydrogenase

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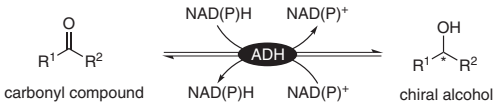
Introduction

Alcohol dehydrogenases (ADHs) can catalyze the reduction of carbonyl compounds, also referred to as carbony reductases,[1] as well as the reverse reaction – the oxidation of the corresponding alcohols.[2] The most promising feature of ADHs is the strict recognition of the substrate which leads to very high chemo-, regio- and enantioselectivity. Although the demand for a stoichiometric amount of the expensive and unstable nicotinamide coenzyme NAD(P)H involved in ADHs catalyzing oxidoreductions is the major challenge for ADHs' industrial application, many efficient coenzyme regeneration systems have been developed,[3] and the most common methods are known as enzyme-coupled and substrate-coupled approaches. ADHs are versatile biocatalysts in asymmetric synthesis of highly enantiomerical products, e.g. chiral alcohols, which are very important chiral building blocks for production of drugs, agrochemicals, and fine chemicals in chemical and pharmaceutical industry.[4]

ADHs from different species have been isolated and are commercially available in different preparations including purified enzymes, crude powders, and enzyme-involving whole cells, and have been largely applied in the preparation of chiral alcohols and chiral hydroxyl compounds through asymmetric reactions.[5a,b]

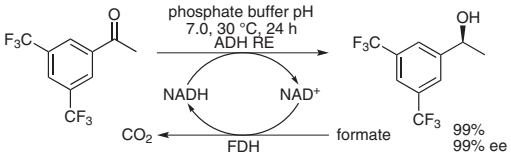
ADHs catalyze the carbonyl reduction or the hydroxyl oxidation through hydride transfer between coenzyme and substrate (Scheme 1). Typically, the chiral products from ADHs catalyzing asymmetric reaction are optically active alcohols and corresponding chiral hydroxyl derivatives. Therefore, the applications of ADHs in organic synthesis mainly include asymmetric reduction of prochiral ketones, stereospecific oxidation of alcohols, resolution of racemic alcohols, and stereoinversion of chiral alcohol enantiomers.



Scheme 1 Principal reactions catalyzed by alcohol dehydrogenases

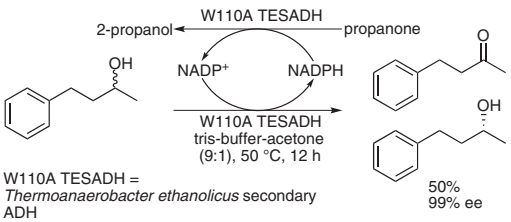
Abstracts

(A) *Asymmetric Reduction of Ketones:*
Asymmetric reduction of prochiral carbonyl compounds to produce chiral alcohols is the most important application of ADHs. To date, a large number of ADHs can be used to prepare a broad spectrum of chiral compounds at lab-scale and large-scale.[6a,b] (*S*)-3,5-Bistrifluoromethylphenyl ethanol was enantioselectively synthesized with excellent enantiomeric excess and yield by Pollard et al. using ADH from *Rhodococcus erythropolis*.[7]



ADH RE = *Rhodococcus erythropolis* ADH
FDH = formate dehydrogenase

(B) *Kinetic Resolution of Racemic Alcohols:*
Although the asymmetric reduction of ketones for chiral alcohols is the major application of ADHs, optical pure compounds can be also achieved by oxidation, for example, kinetic resolution (KR) of racemic alcohols by a suitable enantioselective ADH. One of the enantiomers in the racemate is enantioselectively oxidized by ADH while the other remains untouched throughout the process. However, the maximum yield of each enantiomer cannot exceed 50%. Musa et al. employed an enantioselective ADH from *Thermoanaerobacter ethanolicus* to separate racemic alcohols.[8]



W110A TESADH =
Thermoanaerobacter ethanolicus secondary ADH

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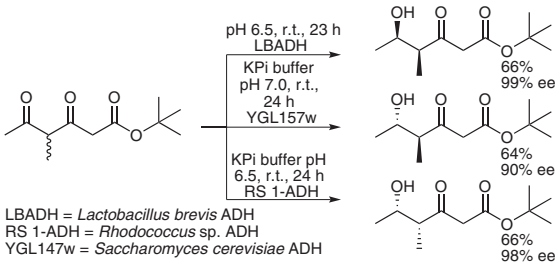
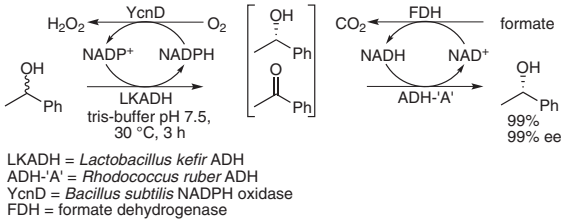
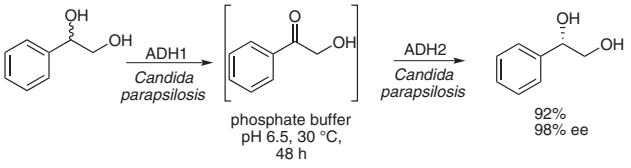
(C) *Dynamic Kinetic Resolution of Racemic Alcohols:*
In view of the maximum theoretical yield of 50% of KR which will be a great waste when it comes to industrial application, dynamic kinetic resolution (DKR), which combines resolution and in situ racemization of the unreacted enantiomer shows its advantages by complete transformation of both enantiomers into a single enantiopure product in 100% theoretical yield.[9] Lüdeke et al. reported an efficient DKR to synthesize three isomers of the substrate.[10]



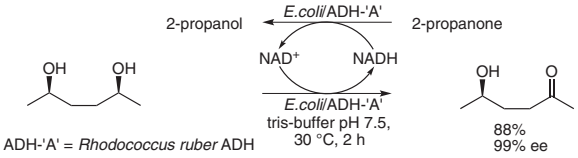
(D) *Stereoinversion of Racemic Alcohols via Multiple Catalysis:*
In recent years, deracemization of racemic substrates to obtain high enantiomerical products in a one-pot process though multiple catalysis has gained increasing attentions.[11a,b] Since ADHs can catalyze the interconversion of a carbonyl compound into the corresponding alcohol and vice versa, the one-pot stereoinversion can be achieved by ADHs through an oxidation of an alcohol followed by a reduction of the carbonyl intermediates. Voss et al. proposed a concurrent tandem oxidation and reduction cycle for stereoinversion of secondary alcohols employing two ADHs with opposite stereoselectivity and cofactor preference.[12]



(E) *Stereoinversion of Racemic Alcohols by a Whole Cell:*
Although stereoinversion has been achieved via multiple catalysis, the reduction and oxidation cycle requires extra enzymes and substrates for coenzyme regeneration, which makes the cycle complicated and hard to control. Therefore, employing a whole cell as catalyst is a good option for stereoinversion of racemic alcohols for its internal cofactor regeneration. Nie et al. employed *Candida parapsilosis*, which contains ADHs with different coenzyme preference to stereoinverse racemic substrates with high enantiomeric excess and yield.[13]



(F) *Regio- and Enantioselective Oxidation of Alcohols:*
To date, the most important application of ADHs is to prepare chiral alcohols by asymmetric reduction, while oxidation of alcohols also shows advantages in some cases. Enantiopure compounds can also be obtained. For example, ADHs can oxidize one specific hydroxy group of a chiral carbon out of all other chemically equivalent hydroxy groups without any protection strategies when the chiral substrate has more than one chiral center.[14]



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