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Recent Desymmetrization Reactions By CALB

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Abstract
Enzyme reactions are among the most environmentally friendly and important asymmetric reactions for organic synthesis. Candida Antarctica lipase B (CALB) is one of the most extensively utilized enzymes for various asymmetric reactions. It catalyzes a variety of asymmetric reactions, such as hydrolysis, esterification, and amidation. However, as the studies of desymmetrization reactions of symmetric compounds catalyzed by CALB is rather limited, this commentary focuses on some recent examples of desymmetrization reactions mediated by CALB.

Keywords — *enzyme, desymmetrization, CALB, building block, organic synthesis.*

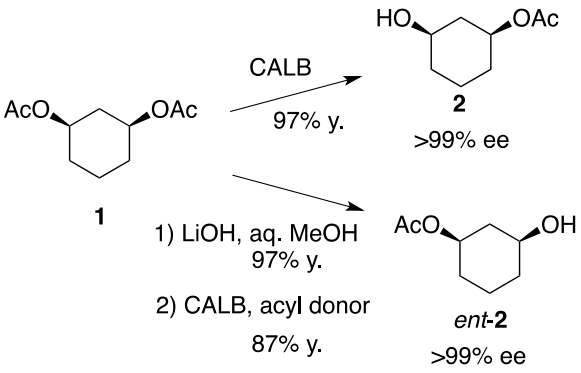
I. INTRODUCTION

Enzymes have been utilized extensively in organic synthesis. They are among the mildest and the most environmentally friendly chiral catalysts. Among these enzymes, *Candida Antarctica* lipase B (CALB) is robust and one of the most widely utilized enzymes in academia and industry. It has been applied to a wide range of important organic reactions such as hydrolysis, esterification, amidation, etc. Further applied to kinetic resolution of racemic compounds and desymmetrization of symmetric compounds. This commentary summarizes some recent examples of desymmetrization reactions catalyzed by CALB, which are rather limited compared to other types of conversions. While it has several other names such as Novozyme 435, SP 382, SP435, and Randozyme, CALB is used throughout this commentary.

II. Application of CALB to desymmetrization reactions

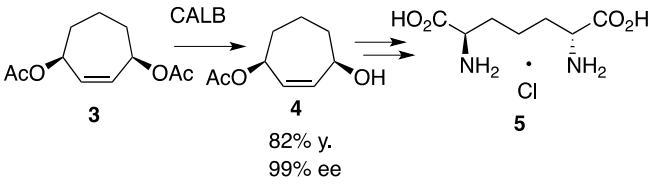
CALB exhibits actions similar to a serine protease like other lipases, with the Ser-His-Asp triad being responsible.[1] According to X-ray crystallographic studies, its active site pocket has portions hosting the acyl-moiety and the substrate's alcohol-moiety, with the former being more spacious. Due to this structural characteristic, CALB tends to show a wide specificity with acyl donors.

Among the most well-recognized desymmetrization reactions by CALB are monoacetylation of symmetric diols and monohydrolysis of symmetric diacetates. For example, a simple diacetate of *meso*-1,3-cyclohexane diol is reported to afford the corresponding monoacetate in 97% yield with >99% e.e. by Bäckvall et al.[2](Scheme 1) The antipodal monoacetate was also prepared by selective acylation of a *meso*-1,3-cyclohexane diol with a high chemical yield and optical purity.



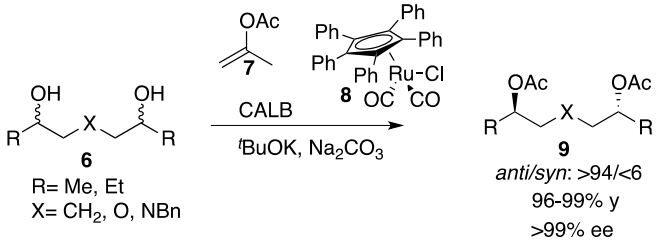
Scheme 1. Desymmetrization of a symmetric diacetate

Takahata et al. reported that a homochiral monoacetate was obtained with 99% e.e. by selective monohydrolysis of symmetric diacetate, which was further applied to the synthesis of (*S, S*) and (*R, R*)-2,6-diaminopimelic acid (**5**).[3]



Scheme 2. Desymmetrization of a symmetric diacetate in the synthetic study of 2,6-diaminopimelic acid

Combined with a Ruthenium catalyst (**8**), a dynamic kinetic asymmetric transformation (DYKAT) of several symmetric diols has also been reported by Bäckvall et al.[4](Scheme 3) In this study, two CALB-catalyzed acetylation reactions in the presence of the Ru-based catalyst, ^{t}BuOK and Na_2CO_3, yielded the corresponding diacetate in an enantio- and diastereoselective manner with high optical purity (>99% e.e.) and high chemical yields. The product diacetates were successfully converted to enantiopure pyrrolidine, piperidine, or morpholine derivatives.

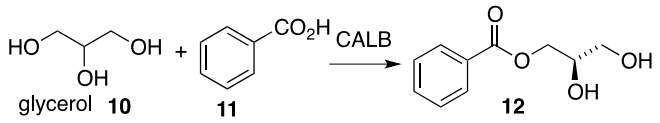


Scheme 3. Dynamic kinetic asymmetric transformation (DYKAT) of diols

Kolodziejska et al. studied CALB-catalyzed asymmetric monoacetylation reactions of symmetric diols in a pyrimidine acyclonucleioside structure ionic liquid. They found increased optical purities compared to those with conventional organic solvents.[5]

Hult et al. studied monoacetylation of several symmetric diols with CALB and found that single point mutation can enhance monoacetylation's selectivity.[6]

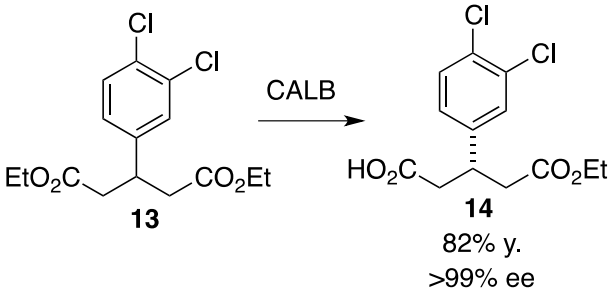
Cabrera et al. reported that CALB could catalyze monobenzoylation of symmetric diols using glycerol, producing (*R*)-□-monobenzoate glycerol (**12**) with up to 99% e.e., although the chemical yields were low.[7](Scheme 4)



Scheme 4. Desymmetrization of glycerol

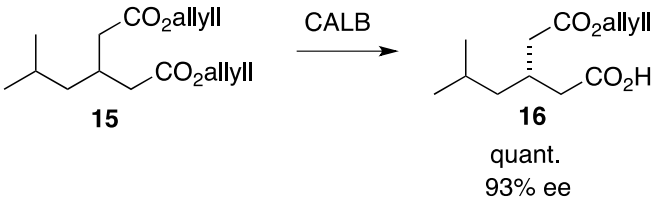
It is also reported that CALB can catalyze acetylation of one of two symmetrical diols or deacetylation of one of the two symmetrical diols in the synthesis of various nucleosides.[1(a)]

Although more limited, CALB can also desymmetrize dicarboalkoxy esters in which the alcohol functional groups are far smaller, such as dicarbomethoxy and dicarboethoxy esters. Glutarate derivatives, important starting materials for various biologically significant compounds, are among the most extensively studied substrates for this purpose. For example, diethyl 3-[3',4'-dichlorophenyl]-glutarate was successfully monohydrolyzed with CALB with >99% e.e. even on a pilot scale. [8]



Scheme 5. Desymmetrization of diethyl 3-[3',4'-dichlorophenyl]-glutarate

Lee and Ha et al. studied monohydrolysis of a variety of 3-alkyl glutamic acid diesters using CALB with the best optical purity being 93% e.e. with 100% conversion.[9] (Scheme 6) They found an "olefin effect," as the best result was obtained with the diallyl esters, which is potentially suggestive of remote interactions between the substrate and the enzyme active site. They further applied the result to the synthesis of pregabalin.

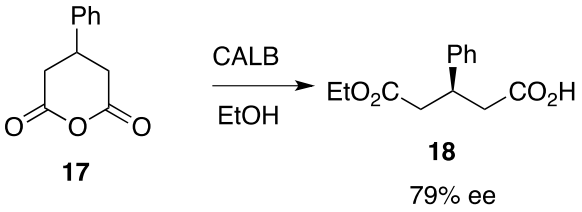


Scheme 6. Desymmetrization of 3-alkyl glutaric acid diesters

Guisan and Palomo et al. reported that depending on the immobilization style of CALB, the asymmetric selective monohydrolysis of dimethyl 3-phenyl glutaric acid can show different outcomes in the optical purities and chemical yields. [10]

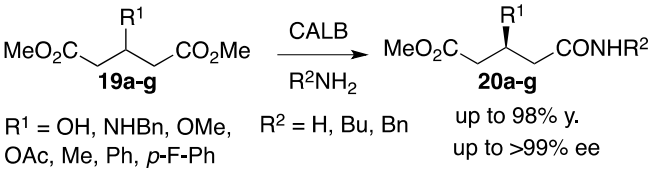
Liu et al. reported that mutation of CALB combined with *in silico* studies could improve the production of (*R*)-3-TBDMSO glutaric acid monomethyl ester by asymmetric selective monohydrolysis of the corresponding diester. [11]

Asymmetric alcoholysis reactions of 3-substituted anhydrides by CALB still appear to be challenging. For example, Liu et al. reported the preparation of (*R*)-3-TBDMS glutaric acid methyl ester from 3-TBDMSO-substituted glutaric anhydride; the optical purity is only 22% e.e. and the yield is also 59%.[12] A similar alcoholysis was attempted from 3-phenylglutaric anhydride by Ostaszewski et al.. Still, the best optical purity by CALB also showed 79% e.e., while Amano PS immobilized showed 99% e.e. for the 3-(4-methoxyphenyl)-glutaric anhydride.[13] (Scheme 7)



Scheme 7. Desymmetrization of 3-substituted anhydrides

Gotor et al. reported successful CALB-catalyzed aminolysis and ammonolysis reactions of several dimethyl 3-substituted glutarates, although studies of enzymatic enantioselective amidation by desymmetrization are limited in general.[14](Scheme 8) They further combined such desymmetrization with the resolution, yielding optically active compounds with several chiral centers with high e.e. They also applied the products of these desymmetrization reactions synthesis of enantiopure unnatural amino acids. [15]



Scheme 8. Desymmetrization of 3-alkyl glutaric acid diesters by aminolysis and ammonolysis

Symmetric compounds are typically obtained inexpensively on a large scale. Enzymatic desymmetrization can allow the production of enantiomerically enriched compounds in quantitative yields. Therefore, further development of enzymatic desymmetrization will be of significance in the field of synthetic organic chemistry.

Acknowledgments

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