Transesterification

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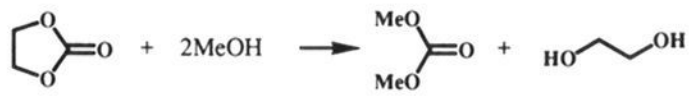
Contents

Junzo Otera received both a B.S. degree in 1966 and a Ph.D. degree in 1971 from Osaka University. He then became a research chemist at Central Research Laboratories of Kuraray Co. Ltd. He moved to Okayama University of Science as an associate professor in 1979 and has been a full professor since 1986. His research interests are synthetic applications of organometallic and organosulfur compounds. For these achievements, he won the Chemical Society of Japan awards twice: technical development of organotin catalyst for polymerization of oxiranes, in 1985, and divisional award of industrial organic chemistry for novel heteroatom chemistry, in 1991.

I. Introduction

Transesterification is one of the classic organic reactions that have enjoyed numerous laboratory uses and industrial applications. Organic chemists make use of this reaction quite often as a convenient means to prepared esters. On some occasions, transesterification is more advantageous than the ester synthesis from carboxylic acids and alcohols. For instance, some carboxylic acids are sparingly soluble in organic solvents and accordingly difficult to subject to homogeneous esterification whereas esters are commonly soluble in most of organic solvents. The ester-to-ester transformation is particularly useful when the parent carboxylic acids are labile and difficult to isolate. Some esters, especially methyl and ethyl esters, are readily or commercially available and thus they serve conveniently as starting materials in transesterification. This reaction can be conducted under anhydrous conditions to allow employment of moisture-sensitive materials. Transesterification is applicable not only to the pure organic synthesis but also to polymerization, i.e. ring opening of lactones. Besides the laboratory utilization, transesterification has a long history in industry as well. Production of esters of oils and fats is very important and transesterification processes were shown to have worked early in this century. Transesterification also plays a central role in the paint industry such as curing of alkyd resins. In the middle of this century, the reaction between dimethyl terephthalate and ethylene glycol became a crucial step for polyester production although the process has almost been replaced by direct esterification of terephthalic acid today. Notably, undimished potential of the transesterification process even in the modern industry has been exemplified by a recent *Chemical and Engineering News* article: cosynthesis of ethylene glycol and dimethyl carbonate from ethylene carbonate and methanol (eq 1).[1]



(1)

Transesterification is a process where an ester is transformed into another through interchange of the alkoxy moiety (eq 2). Since the reaction is an equi-

(2)

librium process, the transformation occurs essentially by simply mixing the two components. However, it has long been known that the reaction is accelerated by acid or base catalysts. Because of their versatility, the acid- or base-catalyzed reactions were the subjects of extensive investigation, and the fundamental features were almost brought to light during 1950s and 1960s. Two comprehensive review articles appeared in 1937[2] and 1974,[3] both of which thoroughly surveyed literatures available at those times. It is apparent, however, that the reaction under the acidic or basic conditions does not always meet requirements of modern synthetic chemistry which need to be highly efficient and selective. It is thus quite natural that efforts were made to discover new catalysts. As a consequence, various

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types of the catalysts were created since the late 1960s. More recently, utilization of enzymes has experienced explosive growth. Therefore, it is appropriate to review the recent progress in this field at this moment. In this article, the classical acid- or base-catalyzed transesterification is touched rather briefly so as simply to provide readers with the basic idea. Accordingly, only representative references among those which appeared before the 1974 review article will be cited together with newer ones. More emphasis is focused on the other catalysts which have enabled transesterification to be highly efficient and chemo-, stereo-, and regioselective. The enzymatic reaction is another topic, leading to various transformations which cannot be attained through chemical procedures. Finally, use of a catalytic antibody will be described.

This article is directed toward synthetic aspects. Some physicochemical studies on kinetics and mechanism involving gas-phase reactions have appeared, and acyl transfer is also important from the biochemical point of view. However, these subjects will not be included here on account of avoiding dispersion of the theme.[4]

II. Acid Catalysts

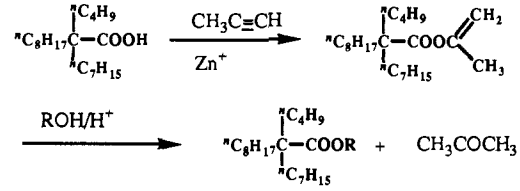
Transesterification has been carried out traditionally and most frequently by the use of acid catalysts such as sulfuric, sulfonic, phosphoric, and hydrochloric acids. This method is employable in various cases unless acid-sensitive components are involved. Most examples have been cited in the previous review articles. Among them described herein are some special applications of synthetic or industrial value together with literature which has appeared more recently. Acrylic esters are versatile materials for polymers. Methyl acrylate was successfully converted into higher homologs through transesterification with higher alcohols in the presence of sulfuric or *p*-toluenesulfonic acid.[5-8] Nitroalkyl acrylic esters were also prepared by the acid-catalyzed transesterification of the methyl esters.[9] Alkyl lactates and α-acetoxy lactates were obtained by analogous transesterification with methyl lactate.[10]

Biasing the transesterification equilibrium in favor of the desired ester is hampered by the alcohol partner produced (vide infra). Continuous removal of the alcohol is indispensable for good yield of the desired esters. Upon transesterification of enol esters, the initially resulting alkenyl alcohols are converted into carbonyls by the spontaneous tautomerization. The equilibrium, accordingly, is shifted to the target ester side. In fact, isopropenyl acetate proved to effect acetylation of alcohols (eq 3).[11] A mixture of the enol

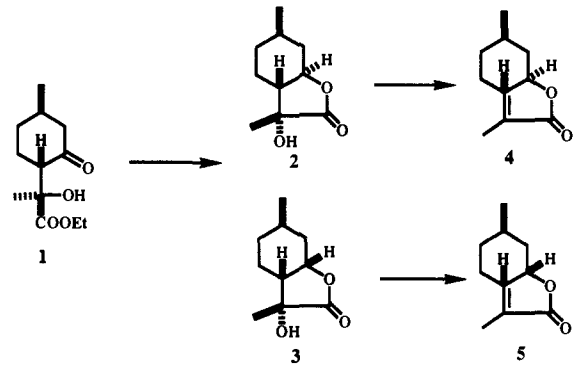
(3)

acetate and alcohol together with a catalytic amount of sulfuric acid was subjected to distillation. After complete distillation of the acetone, the desired esters were obtained in quantitative yields. Notably, the reaction is even applicable to sterically demanding alcohols such as *sec*-butyl and *tert*-amyl alcohols. Methyl α-acetoxypropionate and methyl α-acetoxyisobutyrate from methyl lactate and methyl α-hydroxyisobutyrate, respectively, ethylene glycol monoacetate and diacetate, and β-acetoxypropionitrile and α-acetoxyisobutyronitrile from ethylene cyanohydrin and acetone cyanohydrin were also prepared in better than 95% yields.

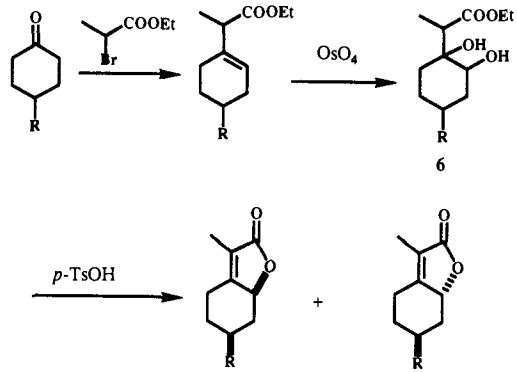
Scheme 1



Scheme 2



Scheme 3



Later, a bulky isopropenyl ester was found to serve for synthesis of highly hindered esters (Scheme 1).[12] Isopropenyl 2-butyl-2-heptyldecanoate was prepared from the corresponding carboxylic acid and propyne in the presence of ZnO. The isopropenyl ester thus obtained was exposed to alcohols in the presence of catalytic *p*-toluenesulfonic acid at 175 °C. The acylation completed in 5–10 min and the desired esters were produced in 75–95% yields. Needless to say, no acylation occurred even if the parent carboxylic acid had been employed.

Recently, acid-catalyzed lactonization leading to mintlactones was reported by two groups at nearly the same time. A Japanese group established an efficient route to (−)-mintlactone and (+)-isomintlactone as shown in Scheme 2.[13] Reduction of **1** with $MeN_4BH(OAc)_3$ followed by treatment with *p*-toluenesulfonic acid provided an easily separable mixture of **2** and **3** in a 30:1 ratio. Use of $Zn(BH_4)_2$–*p*-toluenesulfonic acid, on the other hand, provided **2** and **3** in a 1:6 ratio. Dehydration of **2** and **3** with $POCl_3$ afforded (−)-mintlactone (**4**) and (+)-isomintlactone (**5**), respectively. A strategy by an Indian group is depicted in Scheme 3.[14] Treatment of racemic diol **6** with *p*-toluenesulfonic acid afforded (±)-mintlactone and -isomintlactone in a 7:1 ratio. It should be noted that the reverse reaction, alcoholysis of γ-butyrolactone, was effected under

catalysis by sulfuric acid to give 4-hydroxybutyric acid esters.[15]

Ortho esters also were most conveniently accessible by acid-catalyzed transesterification.[16] Triethyl orthoformate was transformed to higher homologs by heating with the alcohol under continuous distillation of ethanol.[17] This process was accelerated by adding a small amount of sulfuric acid (eq 4).[18] Use of trimethyl

$$RC(OEt)_3 + 3ROH \xrightarrow{H^+} RC(OR)_3 + 3EtOH \qquad (4)$$

orthoformate in place of the ethyl analog was superior. Furthermore, the new method could afford triisopropyl and tri-*tert*-butyl orthoformates which the uncatalyzed reaction had failed to afford.

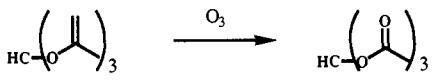
Treatment of ortho esters with β-chloroalkanol in the presence of catalytic hydrogen chloride followed by potassium *tert*-butoxide yielded otherwise difficult-to-obtain enol ortho esters (Scheme 4).[19] Ozonolysis of

Scheme 4

$$RC(OC_2H_5)_3 \xrightarrow{HOC(R')CH_2Cl/HCl} RC(OCH(R')CH_2Cl)_3$$

$$\xrightarrow{^tBuOK} RC(OC(R')=CH_2)_3$$

triisopropenyl orthoformate provided a novel class of compound, triacetoxymethane (eq 5).



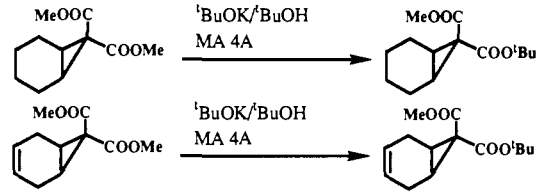
(5)

III. Base Catalysts

Base-catalyzed reaction is another conventional, popular transesterification. This reaction had been known since 1880s but it was not until 1920 and 1921 that systematic studies appeared in a comprehensive manner.[20,21] A wide variety of metal alkoxides are employable but the most popular are sodium and potassium alkoxides. Besides the alkoxides, metal acetate, oxides, and carbonates also work on occasion. The kinetics of this type of reaction was carried out for sodium methoxide-catalyzed methanolysis of methyl esters of ortho-, meta-, and para-substituted benzoates.[22] The results were compatible with the mechanism in terms of nucleophilic attack of alkoxide ion.

The reaction usually proceeds smoothly with primary alcohols while sluggishly with secondary and tertiary alcohols. Sodium ethoxide-catalyzed transesterification proved to be the best way to arrive at a variety of esters of γ-(diethylamino)-α-phenylbutyric acids starting from the methyl ester.[23] These esters were promising as anticonvulsants with low toxicity. Sodium methoxide successfully converted methyl acrylate and methacrylate to the corresponding 4-methyl-4-methoxypentyl esters which could not be obtained by the acid-catalyzed reaction.[24] Transesterification of glycerides is an important process both in laboratories and industry. 1,3-Di-*O*-stearoyl- or 1,3,-di-*O*-palmitoyl-2-benzylglycerol was prepared by exposing the corresponding 1,3-*O*-diacetate to 2 equiv of methyl stearate or palmitate in the presence of sodium methoxide in methanol.[25] Detailed conditions for transesterification in fat and oil technology were reported. Ethanolysis of glycerides in peanut oil[26] and conversion of monoesters of peanut oil fatty acids to triglycerides[27] were extensively discussed.

Scheme 5



Fatty acid esters of sucrose, cheap and nontoxic nonionic surfactants, were obtained by the reaction of sucrose with the methyl ester of a fatty acid in the presence of solid K_2CO_3 catalyst.[28-30] It was reported that more reproducible yields and reaction rates were gained when conditions for homogeneous catalysis were established.[31]

Employment of a stoichiometric amount of metal alkoxides is useful in some cases when catalytic reactions are not workable. Alkoxymagnesium bromides prepared from ethylmagnesium chloride and alcohols, were treated with methyl or ethyl acrylate, methacrylate, α-haloacrylates, carbonate, and malonate.[32] The corresponding esters and carbonates were obtained which were otherwise not easy to prepare: *l*-menthyl, *sec*-butyl, and cyclohexenyl derivatives were isolated. The *exo*-methoxycarbonyl group in 7,7-bis(methoxycarbonyl)norcarane and -norcar-3-ene was selectively replaced by a *tert*-butyl analog (Scheme 5).[33] An equimolar amount of potassium *tert*-butoxide together with molecular sieves 4A needed to be used in dry *tert*-butyl alcohol. Tertiary alcohol esters of substituted benzoic acids were accessible by treating phenyl benzoates with an equimolar or excess amount of potassium alkoxides in liquid ammonia (eq 6).[34] Two main factors were

$$ArCOOPh + ROK \xrightarrow[liq.NH_3]{} ArCOOR + PhOK \qquad (6)$$

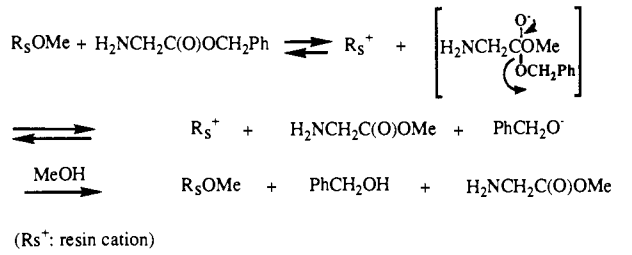
Ar = Ph, *o*-MeC_6H_5, 3,5-$(NO_2)_2C_6H_3$, *m*-ClC_6H_4

R = *tert*-Bu, *tert*-amyl, *iso*-Bu

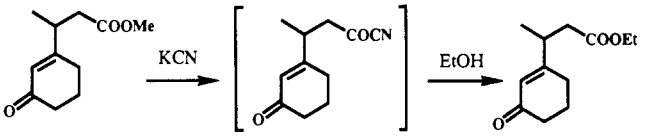
counted for biasing the reaction in the desired direction. First, the phenoxide ion is a better leaving group (lower pK_a) than any aliphatic alkoxides. Second, potassium phenoxide appears to be less soluble in the reaction medium. Recently, lithium alkoxides prepared from butyllithium and alcohols were disclosed to be powerful transesterifying reagents.[35] Methyl esters of aromatic and α,β-unsaturated acids, upon exposure to 1–3 molar equiv of lithium alkoxide, were converted to *tert*-butyl, allyl, menthyl, bornyl, choresteryl, and lanosteryl esters. Unfortunately, however, this method is not applicable to aliphatic esters.

Anion-exchange resin was used for transesterification of peptide alkyl esters.[36] Benzyl esters of L-amino acids or LL dipeptide derivatives were stirred with anion-exchange resin in methanol at room temperature for 30–80 min. The methyl esters were obtained in 80–90% yields. Conversions from ethyl esters to methyl esters and from methyl esters to ethyl esters proceeded analogously but methyl esters were converted to benzyl esters in less than 50% yields. Under the experimental conditions used, the carbobenzoxy, the *tert*-butyloxycarbonyl, and the *O*-benzyl, *S*-benzyl and imidazolylbenzyl protecting groups remained intact. No racemization was detected. The presence of the resin is essential for the transesterification to proceed. The probable mechanism for the benzyl-to-methyl ester transformation is depicted in Scheme 6.

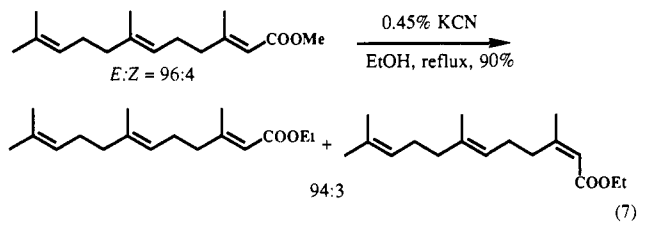
Scheme 6



Scheme 7



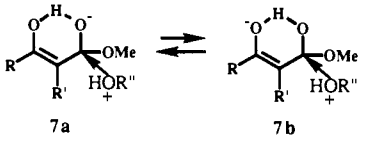
Potassium cyanide was found to be of use for compounds sensitive to the strongly acidic or basic conditions.[37] Reaction of an ethanolic solution of a methyl ester with an equimolar KCN at 25 °C led after 3 h to the ethyl derivative (Scheme 7). The reaction presumably occurs through an acyl cyanide intermediate, which reacts with the large excess of ethanol present. Later, this method was applied to transesterification of methyl farnesoate (eq 7).[33] Upon treatment of this compound (96% trans, trans) with KCN in refluxing ethanol, the ethyl ester formed as a mixture of 2-trans (94%) and 2-cis (3%) isomers. Use of propanol, however, caused the serious isomerization of the 2-double bond because of the higher refluxing temperature under analogous conditions. Methyl palmitate was converted to the ethyl and propyl esters in 90% yields but methyl benzoate gave only 50–65% yields.



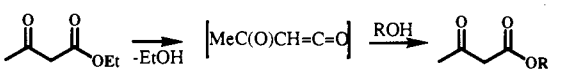
(7)

IV. Amine Catalysts

Strongly basic amines have found extensive use as transesterification catalysts recently. Taber discovered the effectiveness of 4-(dimethylamino)pyridine (DMAP), which was employed for β-keto esters.[39] This class of compounds acts somewhat differently from others in transesterification and, therefore, deserves detailed comments about its history here. Carroll[40] and Bader et al.[41] independently found that β-keto esters were transesterified by heating the esters and alcohols in the absence of catalysts. Malonates and oxalates reacted analogously.[42] Metal chelates of acetoacetates also underwent uncatalyzed transesterification but more slowly.[43] The dialkylation at the 2-position of acetoacetates retarded the reaction with *l*-methanol while the reaction occurred with the monoalkylated acetoacetate, implicating an active hydrogen to be a prerequisite for the reaction. These criteria led Bader et al. to propose cyclic enolate intermediates, **7a** and **7b**.[41] However, recent kinetic studies revealed the inadequacy of the bimolecular mechanism, judging from the independence of reaction rate on alcohol concentration and a high enthalpy of activation together with a comparatively small negative entropy of activation.[44] The results were interpreted in terms of the acyl ketene intermediate (Scheme 8). This mechanism was given further support on the basis of kinetics and matrix IR spectroscopy by Witzeman.[45] It was also disclosed that *tert*-butyl and *tert*-amyl acetoacetates reacted 15–20-fold faster than other less sterically hindered esters. These findings allowed the same researchers to utilize commercially available *tert*-butyl acetoacetate as a versatile acetoacetylating reagent.[46] The ester and an equimolar amount of alcohol were heated at 100–150 °C in toluene or xylene in the absence of any catalyst to yield a variety of acetoacetates. The development of this process is of practical significance in producing acetoacetates, useful chemical intermediates, from storable and readily available materials. It is to be noted that the alternate process is alcoholysis of ketenes, the use of which should be avoided due to their lachrymatory and toxic properties as well as the shipping problem.



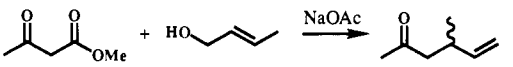
Scheme 8



Despite these extensive studies, Taber et al. found that methyl acetoacetates were more smoothly transesterified under the influence of DMAP.[39] The reaction is workable for a variety of alcohols but an unenolizable β-keto acetoacetate was inert (Table 1).

With recourse to this method as a key step, Taber formed a route to (−)-5-hexadecanolide, a pheromone of the wasp *Vespa orientlis* (Scheme 9).[47] Methyl ester **8**, prepared from lauroyl chloride and methyl acetate, was subjected to transesterification with **9**. Reduction of the resulting ester **10** with DIBAH/BHT gave 3-(*S*)-hydroxytetradecanoate **11** selectively. The reaction is stereochemically controlled by the naphthyl group and reaction with $ZnCl_2/Zn(BH_4)_2$ occurs in the opposite sense. $LiAlH_4$ reduction of **11** followed by tosylation afforded **12**. Allylation with allylmagnesium chloride, reductive ozonolysis, and PCC oxidation provided the desired lactone.

Allylic acetoacetates are rather difficult to prepare because of facile decarboxylated rearrangement (Carroll rearrangement) (eq 8). The modified DMAP method



(8)

was successfully applied to this end.[48] The original Taber's recipe resulted in slow reaction but as shown in Table 2, the reaction in the presence of molecular sieves proved to be effective (the effect of molecular sieves will be discussed later). The ethanol formed is removed by molecular sieves 4A and the equilibrium

Scheme 9

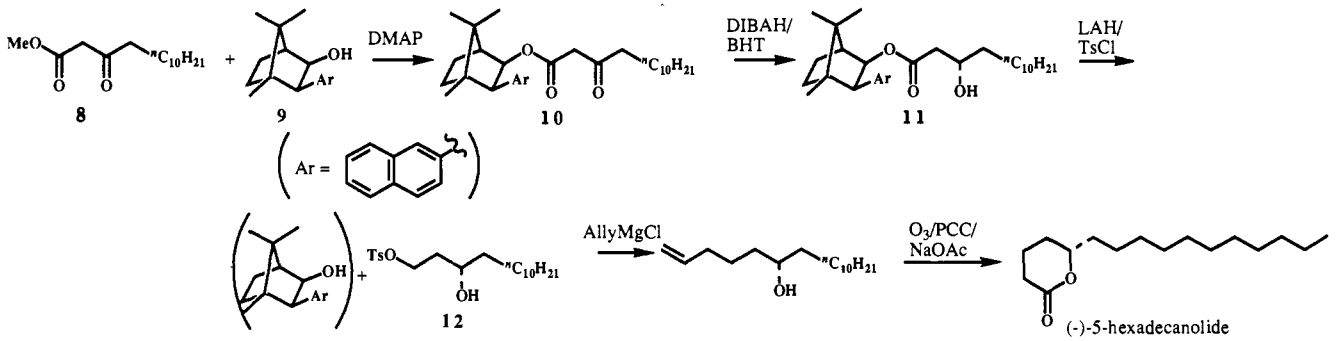
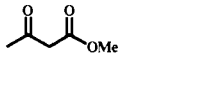
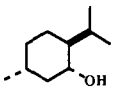
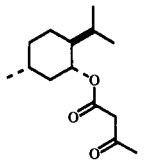
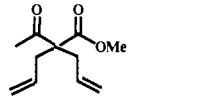
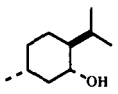
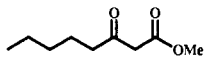
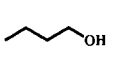
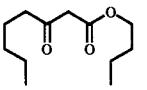
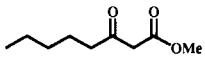
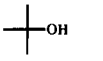
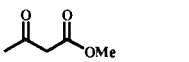
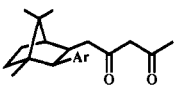
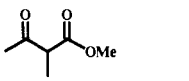
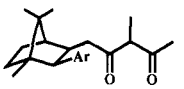
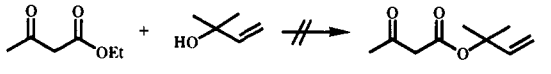


Table 1. DMAP-Promoted Transesterification

acetoacetate	alcohol	ester	yield, %
			83
		no reaction	
			74
		no reaction	
			71
			55

is shifted in favor of the allylic esters. Allyl alcohol itself did not react well probably because it was small enough to be absorbed by the molecular sieves. However, this problem was overcome by using the methyl β-keto ester and molecular sieves 3A. Secondary and tertiary alcohols were unreactive (eq 9) and a nonenolizable keto ester failed to react (eq 10) as was observed in the uncatalyzed reactions.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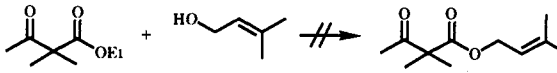
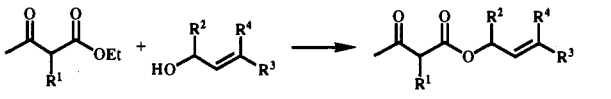

(10)

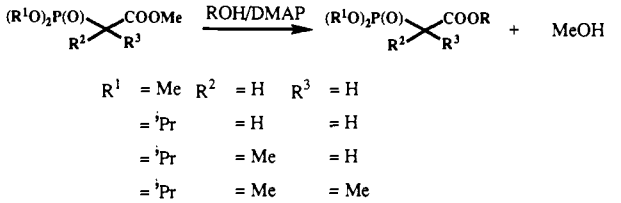
DMAP was successfully employed to catalyze transesterification of phosphonoacetates by Takano et al. (Scheme 10).[49] Typically, alcohol (2 mmol), phosphonoacetate (6 mmol), and DMAP (0.6 mmol) in toluene (5 mL) were heated under reflux to give otherwise difficult-to-obtain compounds in 70–95% yields. It should be noted, however, that trimethyl phosphonoacetate (R^1 = Me) reacted less satisfactorily than diisopropyl methoxycarbonyl phosphonate (R^1 = ^{i}Pr). Presumably, the ester exchange of a phosphonic ester

Table 2. Synthesis of Allylic β-Keto Esters by Modified DMAP-Promoted Transesterification

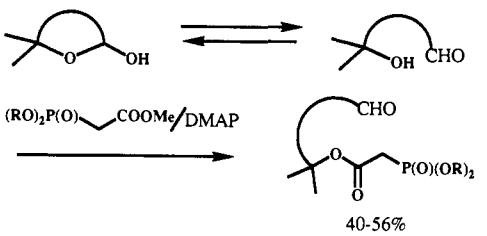


R^1	R^2	R^3	R^4	yield, %
H	H	H	H	96
H	H	Me	H	94
H	H	Me	Me	86
H	Me	H	H	84
Me	H	H	H	32
Me	H	Me	H	83
Me	H	Me	Me	84
Me	Me	H	H	54

Scheme 10

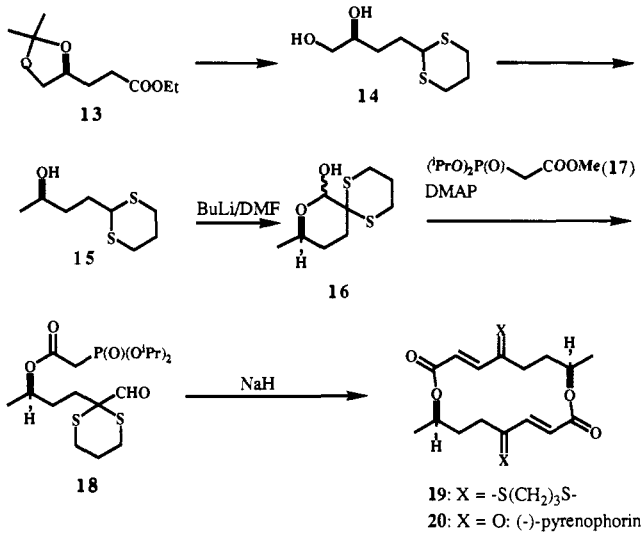


Scheme 11

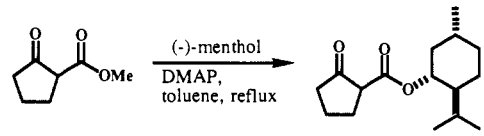


moiety competed with the desired transesterification in the former case. DMAP was further utilized to catalyze direct conversion of lactols into (ω-formylalkoxy)carbonyl phosphonates (Scheme 11).[50] Despite moderate yields, this method is attractive in offering a straightforward route to synthetically useful intermediates without protection–deprotection manipulations. The synthetic potentiality was demonstrated by the synthesis of (−)-pyrenophorin as illustrated in Scheme 12. Ethyl *O*-isopropylidene-(*S*)-4,5-dihydroxypentanoate (**13**), easily prepared from D-mannitol, was successively subjected to reduction (LAH), oxidation (PCC), and thioacetalization ($HS(CH_2)_3SH/BF_3{\cdot}OEt_2$) to give diol **14**. Tosylation followed by reduction (LAH) gave alcohol **15**, which was then converted into lactol **16** (BuLi/DMF). Reaction of the lactol **16** with **17** afforded the key aldehyde phosphonoacetate **18**. Upon treatment of **18** with 1.1 equiv of NaH provided diolide **19**. Finally, hydrolysis of the dithiane group accom-

Scheme 12

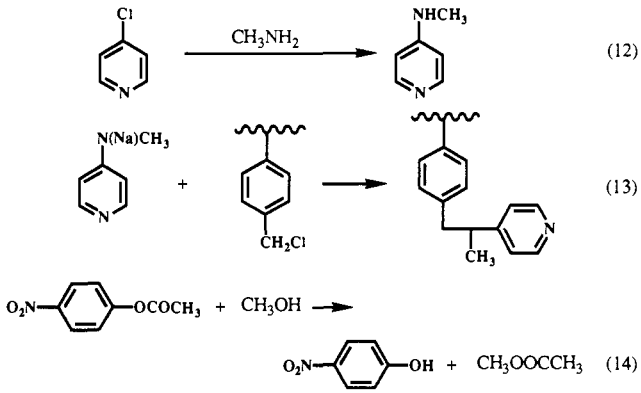


plished the total synthesis of (−)-pyrenophorin (**20**). More recently, (1*R*,2*S*,5*R*)-(−)-menthyl 2-oxoalkanecarboxylates were prepared by the DMAP method (eq 11).[51]



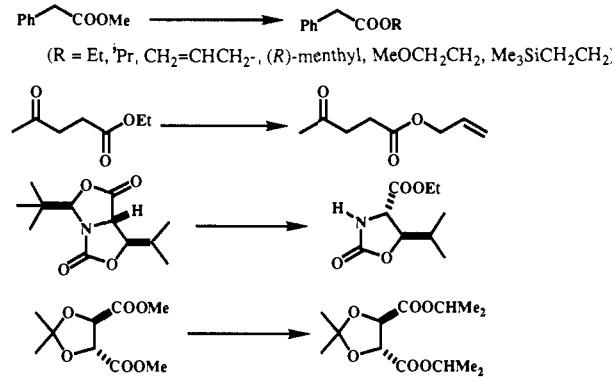
(11)

DMAP was immobilized by attaching 4-(methylamino)pyridine, which had been prepared according to eq 12, to commercial poly(vinylbenzyl chloride) (eq 13).[52] The product which contains one nitrogen per repeat unit exhibited catalytic activities for various base-catalyzed reactions. Among them, methyl *p*-nitrobenzoate was transformed to methyl acetate in 100% yield (eq 14).

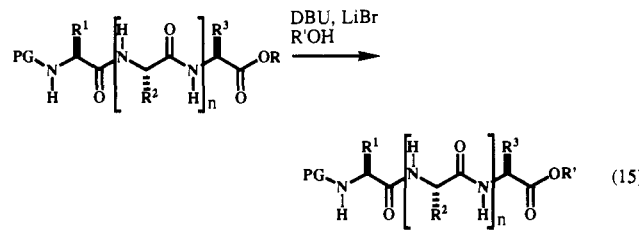


1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is another amine which proved to be an effective catalyst when coupled with LiBr. Seebach et al. recently reported a full account on this issue.[53] Methyl phenylacetate was converted quantitatively to various esters on exposure to a mixture of 0.5 equiv of DBU and 5 equiv of LiBr in alcohol solvent at room temperature or in refluxing THF/CH_2Cl_2 (3:1) containing 1–2 equiv of alcohol and molecular sieves 5A (Scheme 13). 4-Oxopentanoate, a bicyclic urethane, and tartrate acetonide were transesterified as well. In the latter case, however, extensive racemization took place under these conditions (optical activity of the isopropyl esters: ca. 25%). Limitations

Scheme 13



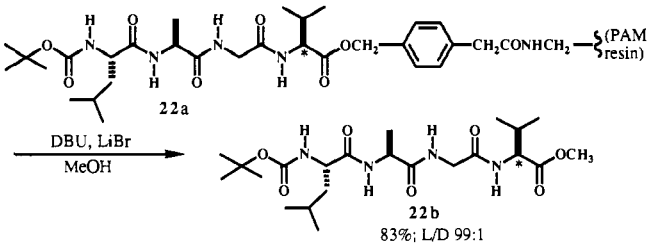
of this method were revealed: methyl acetoacetate and bromoacetate could not be transesterified in EtOH or ^{i}PrOH; methyl phenylacetate could not be converted to the *tert*-butyl ester. More importantly, however, the present method was applied to transesterification of peptide esters (eq 15). Long reaction times and/or



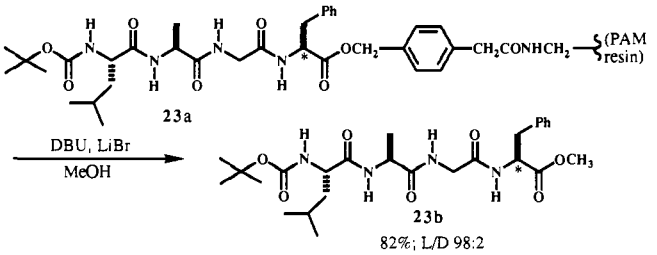
(15)

high temperatures led to extensive epimerizations, not only of the C-terminal amino acid in Boc-Phe-Ala-OR (**21**) but also of the N-terminal one. On the other hand, use of the mildest possible conditions led to rapid transesterification with practically no epimerization when going from methyl to ethyl, isopropyl, or allyl esters. LiCl and $LiClO_4$ worked equally well. Neither DBU in the absence of LiBr, nor Et_3N or $^i Pr_2NEt$ in the presence of LiBr, nor LiBr alone caused transesterification. From experiments on epimerization-free transesterification of the dipeptide ester **21** were drawn the following conclusions: (1) Both Boc- and Z-protected groups may be at the N-terminus, with the latter being somewhat less stable. (2) Ester groups in the sidechain of aspartate units also undergo RO exchange. (3) The method is especially well applicable when going from methyl to ethyl or vice versa and from benzyl to methyl esters. (4) Benzyl esters of peptides cannot be prepared in this way without appreciable epimerization. (5) Allyl ester may or may not be formed without epimerization. Detachment of peptides from the solid-phase matrix is an important technology in the peptide synthesis. In the most commonly used procedure for the peptide-(polystyrene resin) cleavage leading to the peptide acids, strong acids such as HF are used. The effectiveness of the DBU/LiBr-promoted transesterification was assessed with Boc-Leu-Ala-Gly-Val-(PAM resin) (**22a**) and Boc-Leu-Ala-Gly-Phe-(PAM resin) (**23a**) [PAM resin:poly(styrene/1% divinylbenzene)]. From **22a**, the methyl ester **22b** was set free within 4 h in 83% yield without any epimerization (Scheme 14). This result is comparable with those obtained by HF-promoted hydrolysis or $Ti(OEt)_4$-promoted transesterification (this transesterification method will be discussed later). Cleavage of the more epimerization-

Scheme 14



Scheme 15



prone Phe-containing peptide-resin **23a** to the methyl ester **23b** led to a considerable level of epimerization (14%) at room temperature, but carrying out the reaction at 0 °C resulted in no detectable epimerization (Scheme 15).

V. Equilibrium and Use of Molecular Sieves

As transesterification is an equilibrium process, the ease with which a target ester is formed is dependent upon the combination of alcohol and ester reactants. It is important, therefore, to determine the relative reactivities of the alcohol component. Substantial understanding has been gained on this issue and it is of great help to summarize available date at this stage. Various alcohols were compared in water- or $Al(OEt)_3$-catalyzed alcoholysis of acetates by Adkins et al. (eq 16).[54,55] The conclusions drawn from these studies are

$$\text{RCOOR'} + \text{R''OH} \longrightarrow \text{RCOOR''} + \text{R'OH} \qquad (16)$$

R' = $^n C_{12}H_{25}$, $^n C_7H_{15}$, benzyl, cyclohexyl, 2-octyl, 2- or 3-phenylpropyl
R'' = Me, Et, ^{n}Pr, ^{i}Pr, allyl, ^{n}Bu, ^{i}Bu, ^{s}Bu

as follows. (1) Methanol has the strongest replacing power: formation of methyl acetate is thermodynamically most favored. (2) The replacing power of alcohols with a longer alkyl chain is lower. (3) Branching of the chain causes the decrease in the reactivity. In these experiments, the quantities of the reactants and products were determined by isolation through distillation. Later, more accurate GLC method was invoked.[56]

To shift the equilibrium in favor of the desired ester, the liberated alcohol must be removed as an azeotrope with the reactant ester or with entraining materials like aliphatic hydrocarbons, cyclohexane, benzene, xylene, and *trans*-1,2-dichloroethane. The process of removing methanol or ethanol as an azeotrope is, however, difficult to control since the reaction rate increases with increasing reaction temperature, but increasing temperature results in greater reactant ester content at the stillhead owing to the relatively low boiling point of the methyl or ethyl ester. Use of molecular sieves was recommended alternatively. The alcohol to be removed is absorbed. Roelofsen et al. disclosed the effectiveness of molecular sieves in the alkoxide-catalyzed transesterification.[57,58] Reaction of methyl or ethyl esters with *tert*-butyl and isopropyl alcohols, cyclohexanol, and phenol proceeded smoothly. In addition, they investigated rate constants k_1 in eq 17 and equilibrium constants K_i in eq 18. On the basis

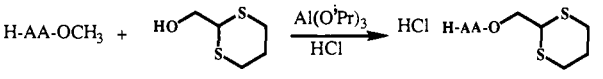
$$\text{RCOOR}^1 + \text{R}^2\text{O}^- \underset{}{\overset{k_1}{\rightleftharpoons}} \text{RCOOR}^2 + \text{R}^1\text{O}^- \qquad (17)$$

$$\text{R}^1\text{O}^- + \text{R}^2\text{OH} \overset{K_i}{\rightleftharpoons} \text{R}^1\text{OH} + \text{R}^2\text{O}^- \qquad (18)$$

of these results, discussion was made on the optimal conditions under which the reaction was carried out. In some experiments, the concentration of alkoxide catalyst decreased, eventually becoming zero. This was attributed to absorption of the alkoxide ion on the molecular sieves. Cation exchange between metal alkoxide and molecular sieves was also observed. These phenomena were fully discussed in terms of different pore sizes of molecular sieves. Haken reported acid-catalyzed transesterification in the presence of molecular sieves.[59] Methacrylate esters were obtained in good yields without polymerization. The improvement by molecular sieves in the DMAP process has already been described.

VI. Lewis Acid and Metal Alkoxide Catalysts

Lewis acids, instead of Brønstead acids, serve as catalysts as well. Acid catalysts failed to transesterify methyl methacrylate with olefinic alcohols such as allylic, cinnamyl, and furfuryl alcohols. Polymerization, isomerization, or decomposition of the olefinic alcohols or their esters could occur. Aluminum isopropoxide was found to smoothly catalyze the reaction.[60] Methyl cyanoacetate was also transesterified with this catalyst.[61] Aluminum isopropoxide catalyzed conversion of methyl esters of α-amino acids without racemization.[62] Use of sodium alkoxides as catalysts resulted in complete or partial racemization. More recently, aluminum isopropoxide was a catalyst of choice for conversion of methyl esters of amino acids to 1,3-dithian-2-ylmethyl derivatives (eq 19).[63,64] The reaction



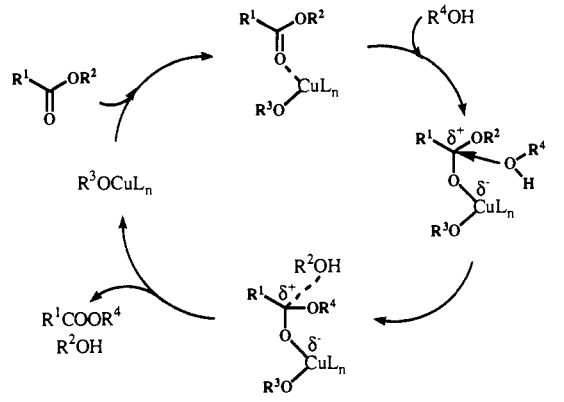
(19)

proceeded with Boc-procted amino acids as well as unprotected amino acids such as glycine, alanine, phenylalanine, valine, leucine, and isoleucine. The esters thus obtained were utilized for synthesis of *N*-glycopeptides.

Some alkoxides of transition metal complexes, although usually they are not categorized as Lewis acids, were found to be effective catalysts by Yamamoto et al. $(RO)Cu(PPh_3)_n$ (R = Me, Et, ^{i}Pr, and Ph; n = 1 or 2) served for transesterification.[65] The catalytic activity of ^{i}PrOCuPPh$_3$ is superior to $Al(O^iPr)_3$ and $Ti(O^iPr)_4$ and comparable to NaO^{i}Pr at the level of the catalytic concentration of 1.6 mol % relative to the ester. It was proposed that the copper-catalyzed reaction proceeded through nucleophilic attack of alcohol toward the ester carbonyl coordinated on the copper (Scheme 16).

The reaction between phenyl acetate (10 equiv/Pd) and 2,2,2-trifluoro-1-phenylethanol (200 equiv/Pd) was catalyzed by PdMe(OCH(CF$_3$)Ph(dpe)) (eq 20).[66] The

Scheme 16

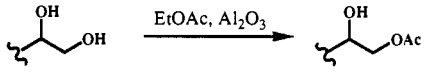


driving force of this reaction was attributed to the morethermodynamic stability of the phenoxypalladium complex.

$$\text{MeCOOPh} + \text{HOCH(CF}_3\text{)Ph} \xrightarrow[\text{Pd: PdMe(OCH(CF}_3\text{)Ph)(dpe)}]{\text{Pd}} \text{MeCOO(CF}_3\text{)Ph} + \text{PhOH} \quad (20)$$

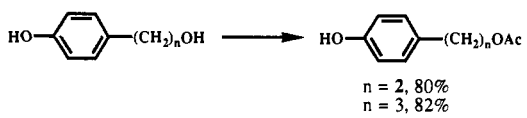
Two examples of transesterification promoted by boron tribromide were demonstrated.[67] Anhydrous aluminum trichloride embedded in polystyrene–divinylbeznene copolymer was used as a catalyst for transesterification between butyl propionate and 1-hexanol.[68] The yield of hexyl propionate was 57% after 43 h at 95 °C.

As part of his program on organic reactions at alumina surface, Posner investigated transesterification, too. Woelm-200-neutral chromatographic alumina, which they used, was so mild that base-sensitive functional groups such as chlorohydrin and β-mercaptoethanol and acid-sensitive moieties such as a pyridyl ring and carbon–carbon double bonds remained intact in the transesterification employing primary alcohols.[69] The primary alcohol moiety was selectively acetylated when primary–secondary diols were subjected to the alumina-promoted reaction (eq 21).[70] Ethyl acetate was the only



(21)

practically workable ester and virtually no diacetates were observed in the crude reaction products. As Table 3 shows representatively, some unsaturated and polyether carbohydrates were effectively monoacetylated without disturbing the sugar structure or the ether linkage. Despite their large size and therefore their inability to fit inside the narrow pores of the most porous solids, some steroidal diols and a triol were conveniently monoacetylated. Phenols were not acetylated and thus chemospecific acetylation of the aliphatic hydroxyl of primary (hydroxyalkyl)phenols was realized (eq 22). The selective acetylation of the primary hydroxyl was further extended to various carbohydrates.[71] Com-

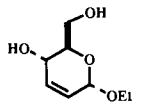
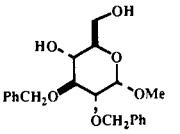
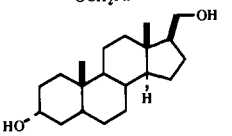
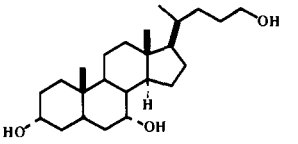


n = 2, 80%
n = 3, 82%

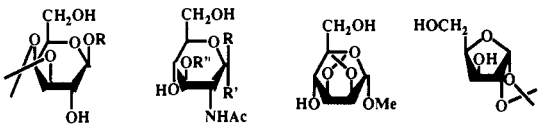
(22)

pounds **24–27** were acetylated at their primary hydroxyl

Table 3. Selective Acylation of the Primary Hydroxy Group of Primary–Secondary Diols by Alumina

diol	yield of primary monoacetate, %
	69
	97
	55
	92

exclusively to provide suitable intermediates for oligosaccharide synthesis.



24 25 26 27

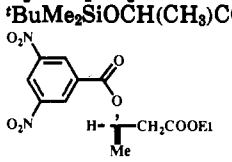
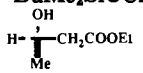
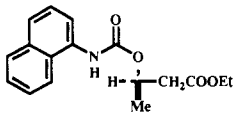
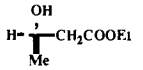
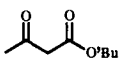
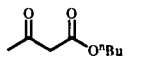
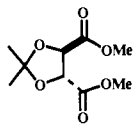
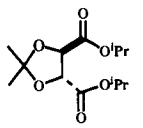
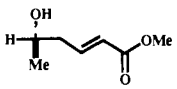
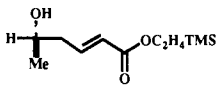
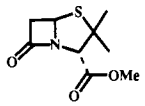
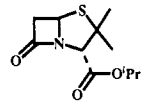
1,*n*-Alkanediols were selectively converted to the monoacetates by treating with ethyl acetate in the presence of metallic sulfates supported on silica gel.[72] The selectivity was explained by the following assumptions: (1) only the alcohols adsorbed on the catalyst surface reacted; (2) as long as the diol, which is more polar and more apt to be adsorbed than the monoester, remained, it reacted preferentially; (3) the monoester was adsorbed and reacted after most of the diol had been consumed; and (4) the reactivity per hydroxy group is alike both in the diol and in the monoester as long as these compounds are adsorbed.

Titanium tetraalkoxides and organotin compounds are also classified into Lewis acids which have been utilized for transesterification. These catalysts, nevertheless, will be described separately in the sections that follow because of their importance and versatility.

VII. Titanium Tetraalkoxide Catalysts

Titanium alkoxides, $Ti(OR)_4$, were used extensively as transesterification catalysts in industry for a long time. Yet the technology remained within industrial circles as know-how and little information was open to public.[73] Seebach was the first who called attention of researchers in the academic fields to the titanium method.[74] Some results are summarized in Table 4. Apparently, this transesterification is extremely mild and compatible with a large variety of functional groups. Chiral centers are not affected. However, *tert*-butyl esters can be obtained only in poor yields (<20%) and attempts to prepare an allyl ester from an ethyl ester have been unsuccessful. The surprising selectivity and

Table 4. $Ti(OR)_4$-Mediated Transesterification

ester	alcohol	product	yield, %
$PhCH_2COOEt$	$PhCH_2OH$	$PhCH_2COOCH_2Ph$	85
$NCCH_2COOCH_2CH_2OMe$	^iPrOH	$NCCH_2COO^iPr$	77
$O_2NCH_2CH_2COOMe$	^iPrOH	$O_2NCH_2CH_2COO^iPr$	50
$^tBuMe_2SiOCH(CH_3)COOEt$	^iPrOH	$^tBuMe_2SiOCH(CH_3)COO^iPr$	83
	EtOH		90
	EtOH		35–45
	^nBuOH		78
	^iPrOH		91
	$TMSH_2CH_2OH$		74
	^iPrOH		91

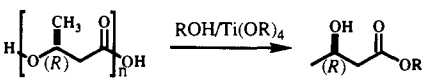
mildness is undoubtedly due to the essentially neutral conditions during the reaction and also during aqueous workup when the titanate is hydrolyzed to give $(TiO_2)_{aq}$ and ROH. Due to its poor solubility in organic solvents, titanium tetramethoxide could not be used under standard conditions. The problem was circumvented by two methods:[75] (1) Esters were exposed to $Ti(OEt)_4$ in methyl propionate solvent (eq 23). $Ti(OEt)_{4-n}(OMe)_n$

$$RCOOC_2H_5 + \underset{\text{(solvent)}}{CH_3CH_2COOCH_3} \xrightarrow{TiCl_4} RCOOCH_3 \qquad (23)$$

arising from the Ti–OEt addition to the propionate carbonyl was supposed to be an active species. (2) $Ti(OEt)_4$ was treated with a 0.5 equiv of ethylene glycol to give a mixed alkoxide (eq 24). Exposure of esters to

$$2Ti(OC_2H_5)_4 + HO(CH_2)_2OH \xrightarrow[-2C_2H_5OH]{} (C_2H_5O)_3TiO(CH_2)_2OTi(OC_2H_5)_3 \qquad (24)$$

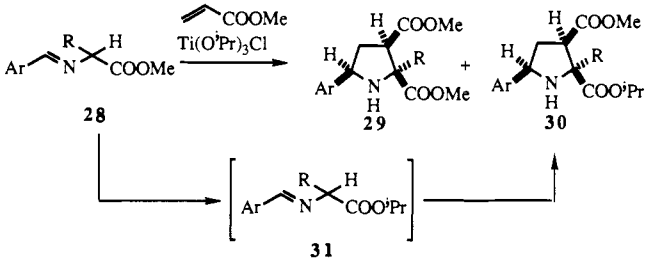
this alkoxide in methanol afforded the desired methyl esters. Degradation of poly-(*R*)-3-hydroxybutanoic acid was effected by the transesterification (eq 25).[76] Con-



(25)

sequently, versatile chiral building blocks, methyl, ethyl, butyl, and β-methoxyethyl (*R*)-3-hydroxybutanoates were obtained from the readily accessible material. The titanium method was applied to conversion of Boc-dipeptide methyl esters to the isopropyl and benzyl esters.[77] Boc-glycine moiety connected to the Merrifield resin via benzyl ester bonding was detached by $Ti(OEt)_4$.

Scheme 17



Recently, $Ti(O^iPr)_3Cl$ and $Ti(O^iPr)_2Cl_2$ were shown to transesterify α-imino ester **28** (Scheme 17).[78] When **28** was treated with methyl acrylate in the presence of $Ti(O^iPr)_3Cl$ and triethylamine, two cycloadducts **29** and **30** were formed. The prior transesterification of **28** gave **31**, reaction of which with methyl acrylate afforded **30**. The validity of the former step was confirmed by a separate reaction of $Ti(O^iPr)_3Cl$ with **28** to give **31**. Subjection of pyrrolidine **29** to the same reaction conditions underwent no transesterification. $Ti(O^iPr)_2Cl_2$ gave similar results.

VIII. Organotin Catalysts

Pereyre et al. disclosed that tributyltin alkoxides were able to catalyze transesterification (eq 26).[79] A mixture of ester (0.05 mol), alcohol (0.5 mol), and Bu_3SnOR' (0.003 mol) was heated at 120 °C for 40–100 h. Although

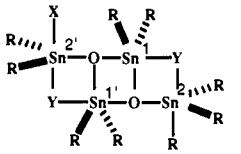
$$RCOOR' + R''OH \xrightarrow{Bu_3SnOR''} RCOOR'' + R'OH \qquad (26)$$

the yields were modest (30–70%), it is to be noted that acrylic esters were smoothly transesterified. Later, Poller et al. investigated relative catalytic activity of a variety of organotin compounds for the reaction between

propyl acetate and methanol.[80] The activity decreases in the order $R_2Sn(OAc)_2 > R_2SnO > R_2SnCl_2 > R_2SnS$, R_4Sn. For the R_2SnO series, the activity is in the order R = *p*-$MeOC_6H_4$ > $PhCH_2CH_2$ > *o*-$MeOC_6H_4$ > Ph > Bu > Me > $^nC_8H_{17}$. These results are consistent with the ease with which the organotin alkoxides are formed from the respective compounds. In their studies on catalytic effects in polyester formation, Pilati compared organotin compounds with the titanium compound.[81] It was concluded that dibutyltin dilaurate, diphenoxide, and oxide along with tetraphenyltin were less active than $Ti(OBu)_4$ in the transesterification of 4-hydroxybutyl benzoate (eq 27).

$$2PhCOO(CH_2)_4OH \longrightarrow PhCOO(CH_2)_4OCOPh + HO(CH_2)_4OH \quad (27)$$

As can be seen from the above results, organotin compounds were, in general, regarded not so practical as other catalysts. This recognition, however, would be completely changed by distannoxane catalysts. Distannoxanes **32** are air-stable crystalline compounds



32a, R = Bu, X = Y = NCS; **32b**, R = Bu, X = NCS, Y = OH; **32c**, R = Bu, X = Y = Cl; **32d**, R = Bu, X = Cl, Y = OH; **32e**, R = Me, X = Y = NCS

which can be readily prepared from the corresponding organotin oxide and dihalide (eqs 28 and 29).[82] These

$$R_2SnO + R_2SnX_2 \longrightarrow XR_2SnOSnR_2X \quad (28)$$

$$3R_2SnO + R_2SnX_2 + H_2O \longrightarrow 2XR_2SnOSnR_2OH \quad (29)$$

compounds have high melting points and thus virtually no toxicity in handling. Unique features emerge from the ladder structure induced by molecular association both in the solid state and in solution. As a result of the proximate location of two different tin atoms, Sn-(1) and Sn(2), reactants bonded to, or coordinated on, these atoms can directly interact with one another. Despite involving a large metalloxane core, the distannoxanes are soluble in most organic solvents even in hydrocarbons since the eight surface alkyl chains prevent the inorganic core from exposure to the ambient solvent phase. Otera et al., by making use of the above features, devised a mild transesterification method.[83] The effects of the substituents, X and Y, and of the catalyst concentration were screened for the reaction between methyl butyrate and benzyl alcohol (Table 5). All the distannoxanes screened exhibited remarkably high catalytic activity irrespective of the substituents. (Note that the catalytic concentration of 0.05 mol % was sufficient.) Since the reaction proceeded under nearly neutral conditions, various functional groups were tolerated and β-keto esters were smoothly transesterified. Particularly noteworthy is the first successful transesterification of the dialkylated acetoacetate which is very inert under other conditions. The probable mechanism are illustrated in Scheme 18. The initial step is formation of the alkoxydistannoxane **32f**, which then undergoes coordination of the ester. Subsequent

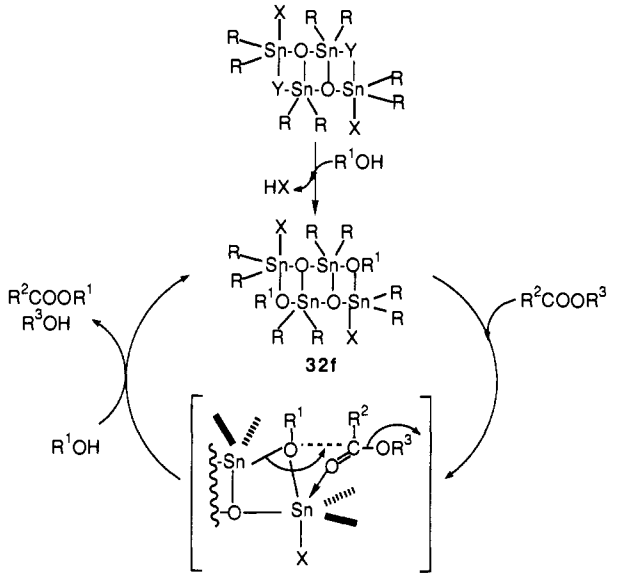
Table 5. Effects of the Structure and Concentration of the Distannoxane Catalyst 1 on Transesterification[a]

$$^nC_3H_7COOMe + PhCH_2OH \xrightarrow{32} {}^nC_3H_7COOCH_2Ph + MeOH$$

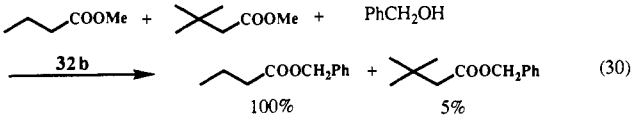
1 (concentration)[b]	reactn time (h)	yield of $^nC_3H_7COOCH_2Ph$ (%)[c]
32a (0.005)	3	100
32b (0.005)	4	100
32c (0.005)	3	100
32e (0.005)	10	100
32b (0.0005)	20	77
32c (0.0005)	20	100
32d (0.0005)	20	100
32e (0.0005)	20	83

[a] Reaction conditions: $^nC_3H_7COOMe:PhCH_2OH$ = 1:2, toluene, reflux. [b] Molar ratio of catalyst relative to $^nC_3H_7COOMe$.

Scheme 18



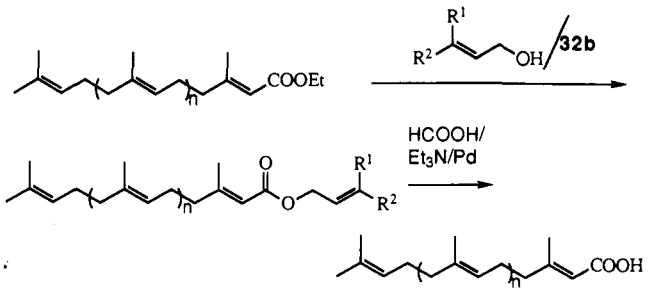
alcoholysis provides the transesterified product and regenerates the alkoxydistannoxane. This mechanism involves no enolization of esters and, hence, explains why the dialkylated acetoacetate is employable. If this mechanism is valid, the approaching ester experieneces steric hindrance from the distannoxane template. This is indeed the case. Bulky esters failed to react while no such retardation was observed with the alcohol component. Accordingly, the competition reaction between methyl butyrate and methyl 3,3-dimethylbutyrate resulted in preferential consumption of the less hindered ester (eq 30). The synthetic potential of the



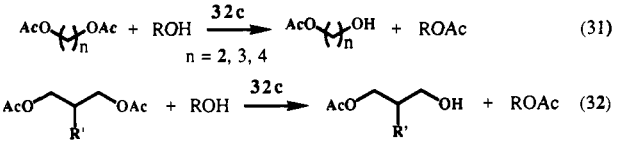
(30)

distannoxane method was exemplified by stereospecific synthesis of β,β-disubstituted enoic acids (Scheme 19).[83a] Stereochemically pure ethyl esters were converted to allylic esters which were, then, transformed to the desired acids through palladium-catalyzed reductive deprotection. The yields were constantly high and no isomerization was detected. In the scheme are illustrated the *E* isomers only but, of course, the *Z* counterparts gave the same outcome. The distannoxane-catalyzed transesterification takes place more smoothly in nonpolar solvents than in polar ones.[84] This

Scheme 19



was interpreted on the bases of the unique dimeric structure. Exposure of 1,*n*-diol diacetates to **32c** in ROH led to selective conversion of one of the chemically equivalent acetate groups (eqs 31 and 32).[85] The



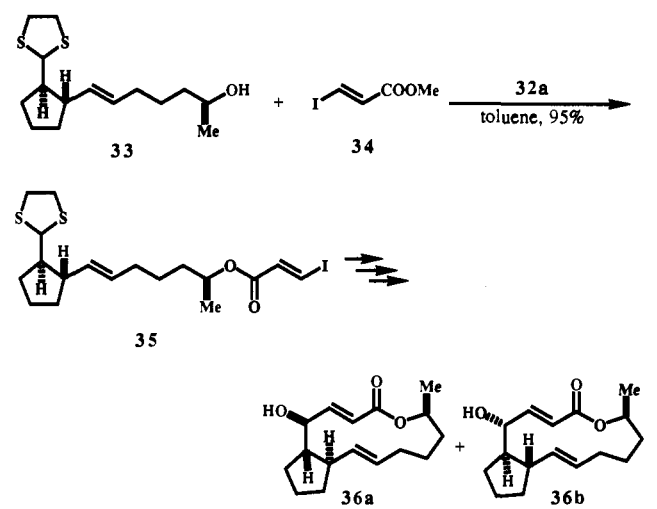
(31)

(32)

unusual selectivity was ascribed to suppression of conversion of the resulting monoacetates to the diols when the diacetates coexisted.

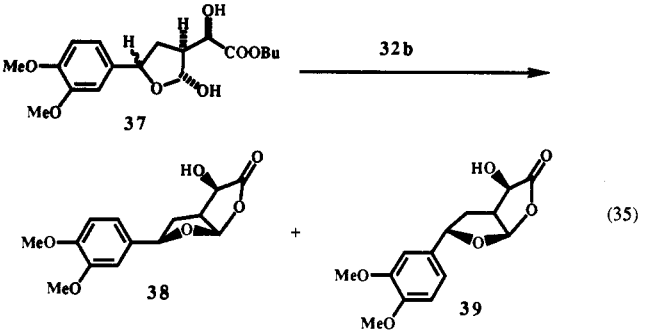
Synthetic applications were made also by other workers. Schreiber et al. applied the present method in the brefeldin synthesis.[86] They attempted transesterification between **33** and **34** but failed with conventional promotors due to the sensitivity of the β-iodoacrylate (Scheme 20). However, the desired ester **35**

Scheme 20



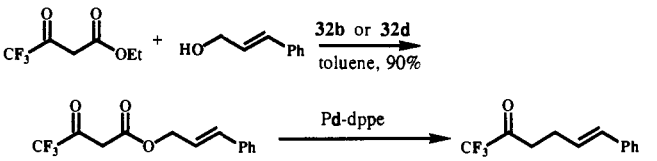
was obtained in 95% yield by the use of **32a**. From this key intermediate, a 4:1 mixture of 4-*epi*-brefeldin C (**36a**) and (+)-brefeldin C (**36b**) was obtained. Schreiber's group also disclosed the effectiveness of a distannoxane for cyclization of lactol **37** in the synthesis of a kadsurenone–ginkgolide hybrid (Scheme 21).[87] Both acid- and base-catalyzed reactions gave only cyclization of the lactol ring oxygen (in the open form of **37**) to afford six-membered ring lactone products. On the other hand, the distannoxane method provided, as expected, a 1:1 mixture of readily separable bicyclic compounds **38** and **39** that were isomeric at the benzylic carbon. Shimizu et al. revealed that allyl esters of β-ketoacetates were obtained in high yields (Scheme 22).[88] By the catalysis of **32b** or **32d**, ethyl 4,4,4-

Scheme 21



(35)

Scheme 22

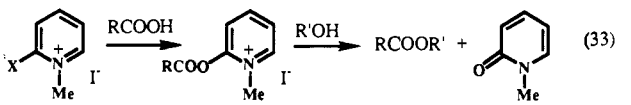


trifluoroacetoacetate was converted to the allyl esters, which were utilized to the synthesis of trifluoromethyl ketones by palladium-catalyzed Carroll rearrangement.

More recently, Smith et al. reported that monoalkyltin(IV) compounds also work as transesterification catalysts.[89]

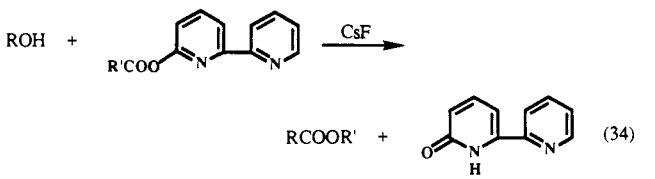
IX. Use of 2-Pyridyl Esters

Activation of the ester component is promising for smooth transesterification. Mukaiyama et al. devised reaction of carboxylic acids and alcohols promoted by 1-methyl-2-halopyridinium salt (eq 33).[90-92] Tertiary



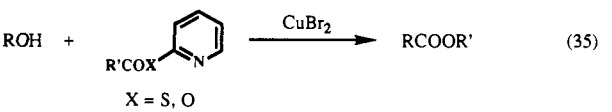
(33)

amine or 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one was used as a scavenger of hydrogen halide. This reaction is regarded to proceed via 2-pyridinium ester, which subsequently reacts with alcohol, a transesterification process. Use of 1-ethyl-2-fluoropyridinium tetrafluoroborate coupled with cesium fluoride was also effective.[93] Later, reaction of 2,2′-bipyridyl-6-yl carboxylates and alcohol in the presence of cesium fluoride was reported (eq 34).[94] When primary–secondary diols



(34)

were subjected to the reaction, the primary hydroxyl was selectively acylated. Amino alcohols underwent acylation on the hydroxy group selectively. More recently, 2-pyridyl esters were employed for ester synthesis (eq 35).[95] In the presence of $CuBr_2$ (1 equiv),



(35)

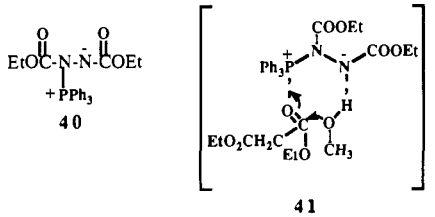
the pyridyl ester was treated with alcohol (1.2 equiv)

at room temperature or 80 °C in acetonitrile. Otherwise difficult-to-obtain esters were produced in good yields. 2-Pyridyl esters of sterically hindered aliphatic acids such as pivalic acid and triethylacetic acid, upon treatment with sterically hindered alcohols, such as *tert*-butyl alcohol, *tert*-amyl alcohol, and mesitol at 80 °C, were converted to the corresponding esters within 5 h. Reaction of 2-pyridyl mesitoate proceeded more rapidly than that of 2-pyridyl esters of sterically hindered aliphatic acids. Thus, reaction of 2-pyridyl mesitoate with sterically hindered alcohols such as *tert*-butyl alcohol and *tert*-amyl alcohol afforded the corresponding esters in high yields within 24 h at room temperature.

X. Miscellaneous Methods under Mild Conditions

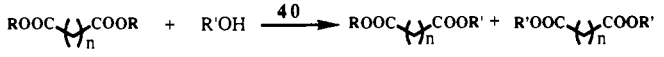
Mitsunobu reagent **40** prepared from diethyl azodicarboxylate and triphenylphosphine proved to catalyze transesterification of 1,*n*-dicarboxylates with alcohol solvent (Scheme 23).[96] The rate of conversion followed

Scheme 23



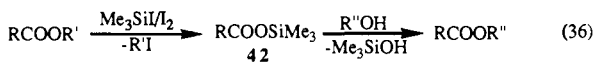
40

41



the order $n = 0 > 1 > 2 > 3$. Monocarboxylic acid esters reacted somewhat more slowly. The 1:1:1 associated intermediated **41** was proposed.

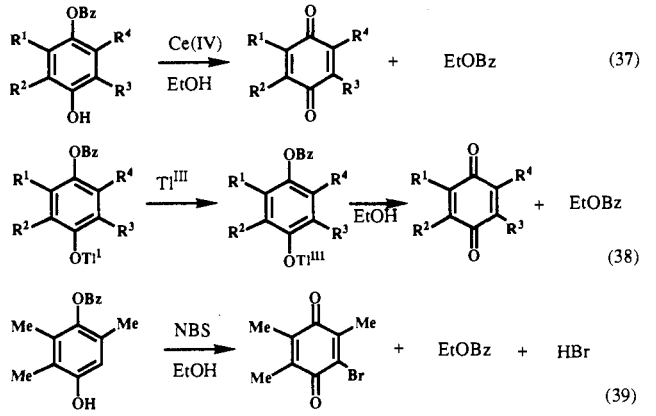
A two-step but one-pot reaction was put forth by use of iodotrimethylsilane (eq 36).[97] Treatment of ester



(36)

with an equimolar amount of the silane and 0.1 equiv of I_2 furnished silyl ester **42**, which was combined with 2.5 equiv of alcohol to give the ester. This method is effective for aryl, alkyl, and α,β-unsaturated carboxylic acid esters. Even hindered esters such as methyl pivalate underwent transesterification in good yields.

Upon treatment with cerium(IV) ion (eq 37), thallic ion (eq 38), and *N*-bromsuccinimide (eq 39), hydroquinone benzoate in alcohol was oxidized to result in acyl transfer.[98] This protocol was further modified on



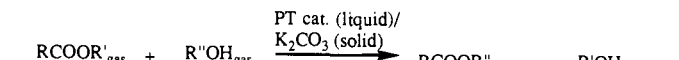
(37)

(38)

(39)

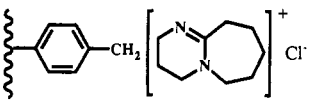
the basis of electrochemical technology for the synthetic purpose.[99] Thus, electrochemical oxidation of hydroquinone esters in the presence of alcohol provided the corresponding exchanged esters. Notably, highly sterically demanding esters such as *tert*-butyl pivalate were obtained.

Phase transfer (PT) catalysts were employed successfully. Tundo et al. reported the gas-phase transesterification over solid K_2CO_3 covered with liquid PT catalysts like Carbowax 6000 or 18-crown-6 (eq 40).[100]



(40)

A 1:2 molar solution of ester and alcohol was passed through the column packed with the catalyst at 170 °C. The phase transfer catalysts are crucial because no reaction occurred with K_2CO_3 alone. K_2CO_3 mixed with quaternary ammonium salt ($(n\text{-}C_8H_{17})_3MeN^+Cl^-$ or $Bu_4N^+HSO_4^-$) was also reported to effect liquid-phase transesterification.[101] DBU was immobilized as a quaternary salt by treating chloromethylated polystyrene **43**.[102] In transesterification of benzyl phenylacetate with methanol, this resin showed higher catalytic activity than those anchoring trimethyl- or triethylammonium salt.

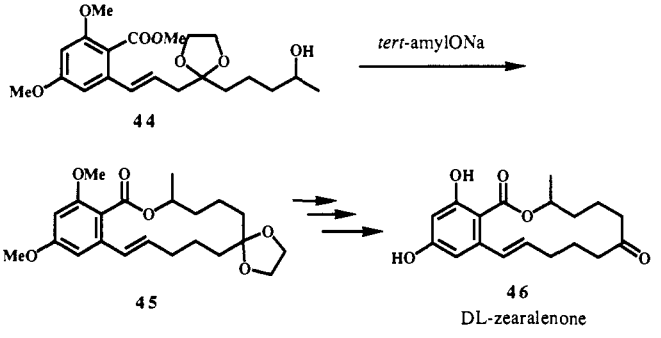


43

XI. Macrolactonization

Synthesis of macrolides has been one of the central targets in natural product chemistry.[103] Intramolecular transesterification of ω-hydroxy esters is a promising route to this end. Base-catalyzed lactonization of ω-hydroxy ester **44** was employed in DL-zearalenone (**46**) synthesis (Scheme 24).[104] The ester **44** was heated

Scheme 24



44

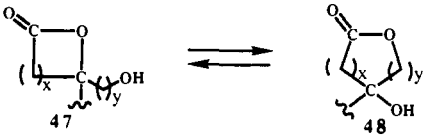
45

46

DL-zearalenone

with sodium *tert*-amyl oxide in refluxing toluene. However, the yield of **45** was only 8%.

Corey et al. devised an elegant translactonization strategy.[105] Upon exposure to acid or base catalyst, ω-hydroxyalkyl lactone **47** should equilibrate with the ring-expanded one **48** (eq 41). If thermodynamically



47 48

(41)

unstable medium-ring lactones are employed, the equilibrium would shift to the right-hand side. This proved to be true, indeed. They concluded that the reaction was workable only for y = 1, 2, or 3 and not for y = 4 in eq 41. In the case where y = 4, the ring expansion necessitates an 8-membered cyclic transition state which is evidently much more difficulty attained than the smaller membered cyclic structure. Based on relative stabilities of various lactone ring sizes and the constraint that y = 1, 2, or 3 in eq 41, the following ring expansion can be most favorable:

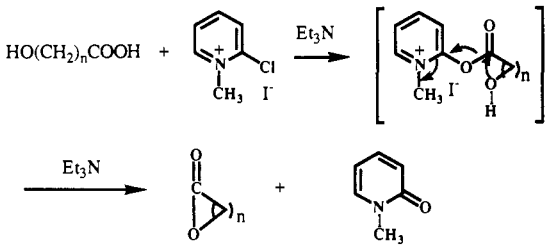
8 ——> 11 ——> 13 or 14

9 ——> 12 ——> 14 or 15

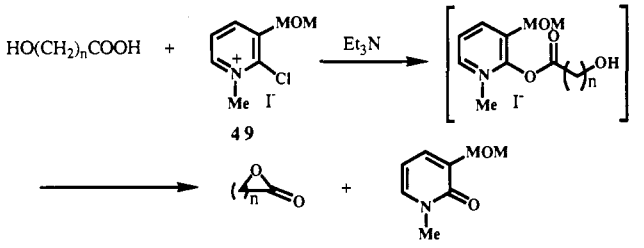
10 ——> 13

Mukaiyama et al. applied their intermolecular transesterification methodology to an intramolecular version (Scheme 25).[106] The lactones with a 12-, 13-, or 16-membered ring were obtained in 60–85% yields, but diolides also formed in 3–24% yields. Improvement of this drawback was investigated in consideration of activating the intermediate in Scheme 26.[107] Since hydrolysis of esters is, in general, accelerated by introduction of a heteroatom near the ester group, the 3-methoxymethyl (MOM) pyridinium salt (**49**) was employed. The reaction proceeded under milder conditions. This methodology was applied to total synthesis of brefeldin A (Scheme 27).[108]

Scheme 25



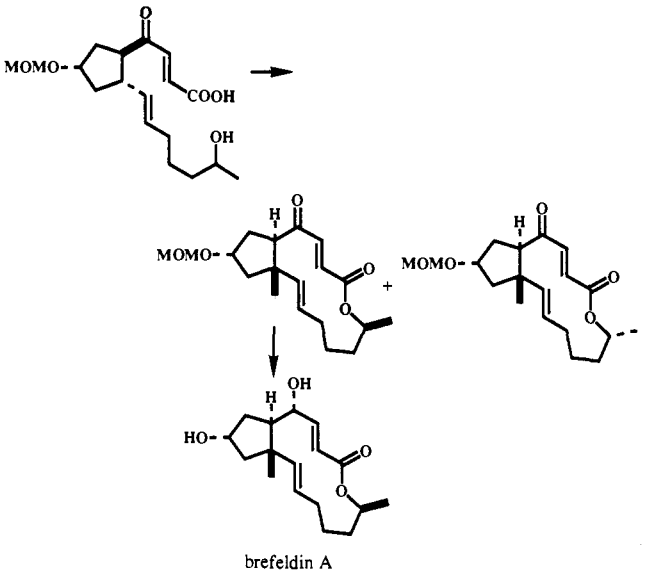
Scheme 26



ω-Hydroxy carboxylic acids were quantitatively converted to 6-phenyl-2-pyridyl esters by treatment with 6-phenyl-2-pyridone and 2-chloro-1-methylpyridinium iodide in the presence of triethylamine (Scheme 28).[109] The pyridyl esters were cyclized through intramolecular transesterification with *p*-toluenesulfonic acid in high yields. This method was utilized for total syntheses of (±)-recifeiolide (Scheme 29) and (*R*)-(+)-ricinelaidic acid lactone (Scheme 30).[110]

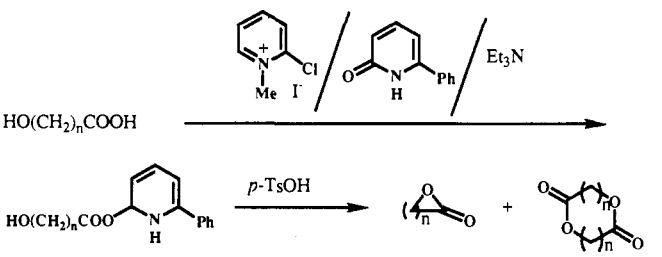
In the study on total synthesis of (±)-integerrimine, Narasaka et al. disclosed that a sulfonylmethyl ester was a nice leaving group in the intramolecular transesterification (Scheme 31).[111] Treatment of **50** with butyllithium or (triphenylmethyl)lithium yielded the desired bislactonic product in 40% yield.

Scheme 27

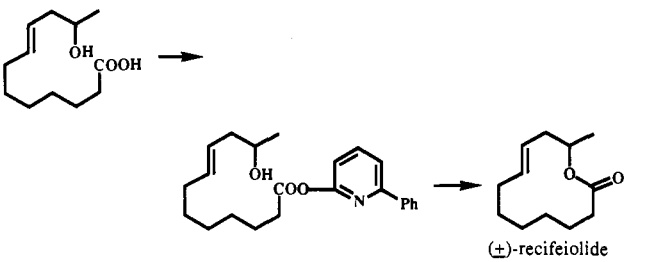


brefeldin A

Scheme 28

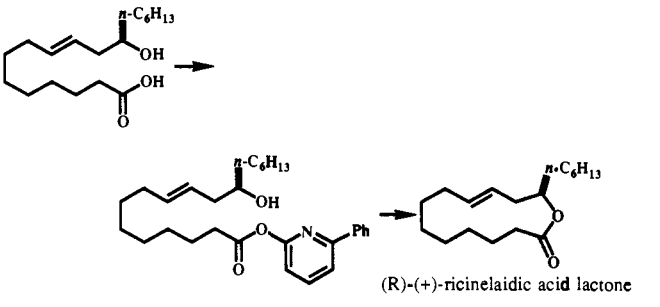


Scheme 29



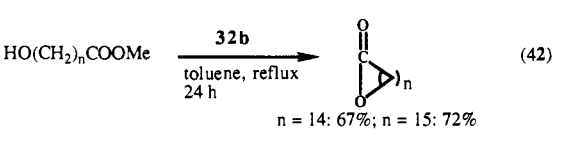
(±)-recifeiolide

Scheme 30



(R)-(+)-ricinelaidic acid lactone

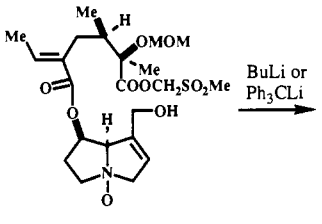
The distannoxane catalysts were also able to catalyze the intramolecular transesterification.[112] Thus, simply heating ω-hydroxy carboxylic acid esters in refluxing toluene provided the corresponding lactones in high yields (eq 42). This protocol was employed for the



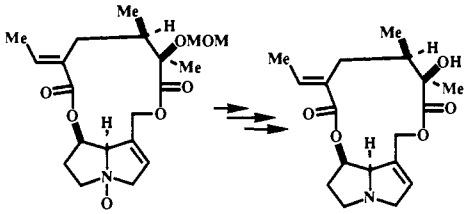
(42)

n = 14: 67%; n = 15: 72%

Scheme 31



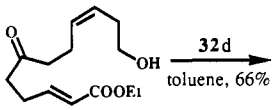
50

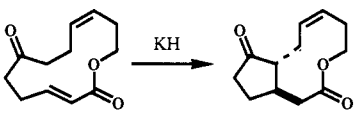


(±)-integerrimine

synthesis of 13-membered lactone **51**, which was further converted to (±)-jasmine ketolactone (Scheme 32).[113]

Scheme 32





51 (±)-jasmineketolactone

Hydrous zirconium(IV) oxide proved to catalyze the cyclization of ω-hydroxy esters (eq 43).[114] The reaction was carried out in a glass flow reactor with a fixed-bed catalyst at 275 °C. Notably, heptanolide and octanolide which are difficult to prepare by other means were obtained in 49% and 36% yields, respectively.

$$HO(CH_2)_nCOOEt \xrightarrow[275\ ^\circ C]{ZrO_2 \cdot nH_2O} \text{cyclic ketone}_n \quad (43)$$

n = 5: 90% n = 7: 48%
n = 6: 49% n > 11: 90-100%

XII. Enzymes

A. General Features

Transesterification catalyzed by enzymes has met with explosive expansion recently. This subject was boosted by successful employment of dry enzymes in organic solvents which was initiated by Klibanov and his co-workers.[115] Although the enzymatic procedures are not always familiar with synthetic organic chemists yet and sometimes not suitable for the large scale preparation, they no doubt have some advantages over the chemical ones. In particular, enzymatic transesterification is attractive in terms of specificity. Since the transesterification is an equilibrium process, no stereo- and enatioselectivities are usually expected. However, the highly specific character of enzymes enables one to satisfy such needs. Several review articles are available dealing with general aspects of the enzyme utilization in organic solvents[116] and some of them briefly referred to the transesterification. In 1990, Klibanov delivered an account which was directed toward asymmetric transesterification.[117] In addition, a review article by Santaniello et al. appeared in 1992 under the title of "The Biocatalytic Approach to the Preparation of Enantiomerically Pure Chiral Building Blocks", a part of which was allotted for transesterification.[118] Herein, scrutinies will be given into the fundamental features from the viewpoint of transesterification and into references which were not covered in the previous articles as well as those which have appeared more recently.

Now it is generally accepted that the enzymatic transesterification is carried out by use of powdered dry enzymes in organic solvents. It might be noted, however, that the Klibanov's establishment of this method was preceded by an immobilized enzyme method, where enzymes entrapped in the porous supports (Sepharose or Chromosorb) worked in biphasic aqueous–organic solvent mixtures.[119] The reactions of various racemic alcohols with methyl propionate catalyzed by hog liver carboxylesterase (eq 44) and with glyceryl tributyrate (tributyrin) catalyzed by yeast lipase (eq 45) resulted in clean kinetic resolutions. The

$$CH_3CH_2C(O)OCH_3 + RCH_2CH_2OH \longrightarrow CH_3CH_2C(O)OCH_2CH_2R + CH_3OH \quad (44)$$

R = $CH_3CH(OCH_3)$-, $CH_3CH(CH_3)$-, $(CH_3)_2CH(CH_2)_3CH(CH_3)$-, $(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)$-

$$\text{tributyrin} + R^1R^2CHOH \longrightarrow CH_3CH_2CH_2C(O)CHR^1R^2 + \text{dibutyrin} \quad (45)$$

R^1	= Me	R^2	= Et
	= Me		= ^{n}Hex
	= Me		= Ph
	= Me		= $(CH_3)_2C{=}CHCH_2CH_2$-
	= Me		= $ClCH_2$-
	= H		= $ClCH_2CHCl$-
	= H		= $CH_3CH_2CH(OH)$-

optical purities of unreacted alcohols and of reactive alcohols which were recovered from the new esters were over 94% ee's. This transesterification was compared with ester hydrolysis and esterification between carboxylic acid and alcohol.[120] It was concluded that the transesterification method was the best among them for kinetic resolution of a secondary alcohol.

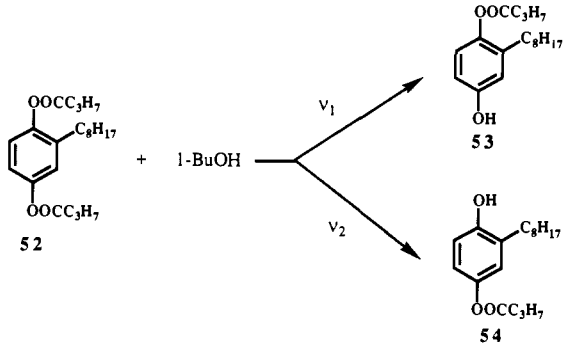
The successful use of the dry pig pancreatic lipase (PPL) that contained 0.48% water was demonstrated for the first time in the reaction of tributyrin with a variety of alcohols in dry organic solvents with 0.015% water.[115] It was further disclosed that the dry lipase even withstood heating at 100 °C for many hours when placed in the dry organic environment. Two other lipases (yeast and mold) also behaved analogously.[121] The transesterification proceeded smoothly in different solvents such as hexane, acetone, THF, ether, pyridine, and toluene except DMSO and DMF. The catalytic power of each lipase in the transesterification reaction compared to that in the hydrolysis reaction in water was of the same order. That is, the enzymes seem to display their full inherent catalytic power in organic solvents. Needless to say, however, the reaction is substantially affected by the reaction media. For example, the substrate specificity of enzymes in organic solvents is reversed from that in water.[122] Hydrolysis of hydrophilic *N*-Ac-Ser-OMe catalyzed by α-chymo-

tripsin is slower by 5×10^4-fold than that of hydrophobic *N*-Ac-Phe-OEt while the rate of trasnesterification reaction of the former substrate catalyzed by the same enzyme in octane is 3 times higher than that of the latter. Similar data were obtained for subtilisin and porcine liver carboxyl esterase.

Solvent effects on enantioselectivity were investigated in detail with two series of reactions. Upon increasing hydrophobicity of the solvent, transesterification of 2-chloroethyl esters of *N*-acetyl-L-amino acid with 1-propanol by use of subtilisin Carlsberg proceeded more slowly than that of the D-amino acid derivatives: the enzyme enantioselectivity decreased.[123] The driving force of the enzyme–substrate interaction is release of water from the hydrophobic binding pocket of the protease. The release of water molecules into the reaction medium will become less thermodynamically favorable with more hydrophobic solvents. Thus, the reactivity of the more reactive L enantiomer might be diminished to a greater extent. On the other hand, the enantioselectivity of the reaction between *sec*-phenethyl alcohol and vinyl butyrate in the presence of subtilisin Carlsberg was shown to be dependent on the dielectric constant and dipole moment of the solvent but much less so with its hydrophobicity.[124] The greater the dielectric constants of the solvents were, the poorer the enantioselectivities. In solvents with larger dielectric constants, the enzyme structure is more flexible allowing for a greater reactivity of the innately less reactive *R* enantiomer.

Regioselectivity was also found to be controlled by solvents. Exposure of disester **52** to 1-BuOH in anhydrous organic solvents provided **53** preferentially over **54** under the catalysis of a variety of enzymes (Scheme 33).[125] The ratio of the initial reaction rates

Scheme 33



for **53** and **54** (v_1/v_2) ranged from 1 to 10. However, surprising results were obtained with *Pseudomonas cepacia* lipase and *Pseudomonas* lipoprotein lipase: while in toluene v_1/v_2 was in agreement with the aforementioned data, 2.0 and 2.4, respectively, in acetonitrile the rate ratios were 0.5 and 0.8, respectively. Thus the regioselectivity of these two enzymes reversed upon a transition from toluene to acetonitrile as the reaction medium. It was hypothesized that the enzyme has a hydrophobic cleft in the vicinity of the catalytic site and that **52** can bind to the enzyme in two distinct modes. In the first one, the octyl moiety does not occupy the putative hydrophobic cleft, thus placing the distal butyryl group in the catalytic site, leading to formation of **53**. In the second mode, the octyl moiety fills the cleft and places the proximal butyryl moiety in the catalytic site, thus leading to formation of **54**. In hydrophobic toluene, transfer of the octyl moiety from the solvent to the cleft offers no thermodynamic advantage and therefore, the first binding mode, yielding **53**, prevails. Conversely, in hydrophilic acetonitrile the free-energy partitioning of the octyl moiety from the solvent in the hydrophobic cleft is favorable; consequently, the second binding mode, yielding **54**, is preferred.

It is important in the enzymatic transesterification as well to bais the equilibrium in favor of the desired ester side. Klivanov et al. disclosed that 2,2,2-trichloroethyl esters afforded the highest rates of the lipase-catalyzed reaction (eq 46).[126] The driving force is the less nucleophilic character of the liberated 2,2,2-trichloroethanol, suppressing the reverse reaction. In line with this idea, 2,2,2-trifluoroethyl laurate was shown to work well for the PPL-catalyzed resolution of (±)-sulcatol.[127]

$$RCOOCH_2CCl_3 + R'OH \rightleftharpoons RCOOR' + Cl_3CCH_2OH \quad (46)$$

As described in the acid-catalyzed transesterification, enol esters proved to be quite effective in the enzymatic procedures, too. De Jeso et al. reported the effectiveness of vinyl esters in PPL-catalyzed acylation of alcohols.[128] Wong et al. investigated in a comprehensive manner on this issue and revealed that isopropenyl and vinyl esters were useful in lipase-catalyzed stereoselective acylation of a number of hydroxy compounds including glycerol and serinol derivatives, ferrocenylethanol, sugars, and other alcohols.[129] Oda et al. revealed that enol esters were better acylating reagents than 2,2,2-trichloroethyl acetate in resolution of 2-halo-1-arylethanols.[130] Achiwa et al. also demonstrated that the utility of vinyl esters in acylation of 1-decanol,[131] 2-octanol, and 1-phenethyl alcohol.[132] In addition, phenyl acetate was found to be more effective in acetylation of 1-dodecanol.[131]

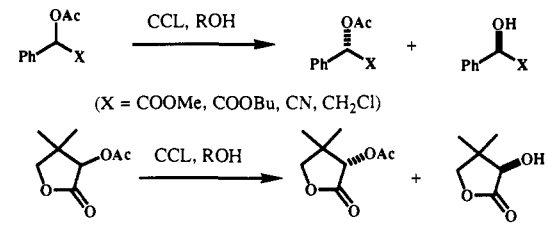
Oxime esters displayed an overwhelming preference toward various alcohols over alkyl or enol esters in lipase-catalyzed reaction (eq 47).[133] The liberated oxime does not participate in the reverse reaction and thus otherwise difficult-to-obtain esters are accessible.

$$RCOO\text{-}N{=}R'_2 + R''OH \xrightarrow{PPL} RCOOR'' + HO\text{-}N{=}CR'_2 \quad (47)$$

(R = Me, $CH_2{=}CH$-; R'' = ^{n}Bu, *cyclo*-hexyl)

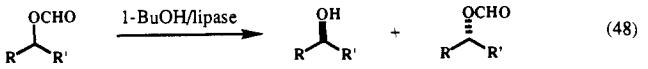
Suppression of the reverse reaction was also achieved by employing bulky secondary alcohol esters (Scheme 34).[134]

Scheme 34



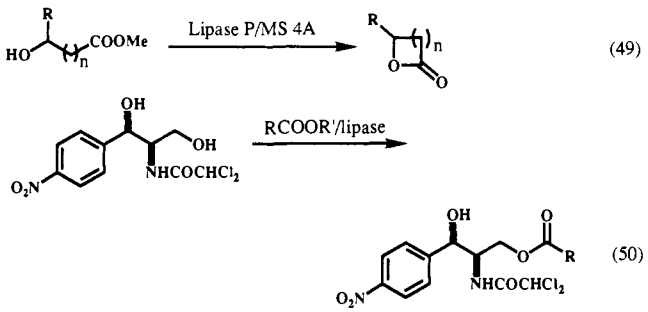
Dependency on the steric bulk of the ester and alcohol components in lipase-catalyzed transesterification led to Bevinakatti et al. to employ formates of secondary alcohols rather than the acetates (eq 48).[135] Less

sterically hindered formates served as better substrates to enhance the reaction rates.



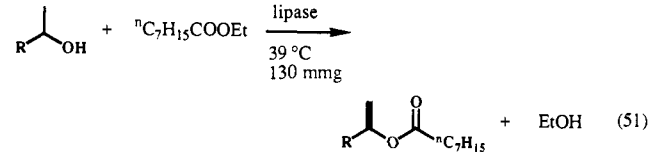
(48)

Removal of the liberated alcohol component from the reaction medium is another means to shift the equilibrium. Molecular sieves were added to the reaction mixture to absorb the liberated alcohol. Thus, lipase-catalyzed macrolactonization of ω-hydroxy esters was effected in the presence of MS 4A (eq 49).[136] In the regioselective acylation of chloramphenicol, the conversion was increased almost up to 100% by the use of molecular sieves (eq 50).[137] It was also revealed that both conversion and enantioselectivity of resolution of secondary alcohol were improved.[138]



(49)
(50)

A Swedish team recently reported a practical procedure (eq 51).[139] Secondary alcohols were exposed to ethyl octanoate in the presence of immobilized lipase under reduced pressure (100–130 mmHg). Under these

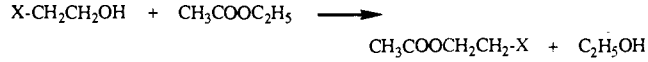


(51)

conditions, the ethanol was evaporated efficiently and thus the reaction was driven to 54% conversion in 24 h whereas the conversion stayed ca. 25% under normal pressure. Concomitantly, the optical yields of the remaining alcohols were increased.

Effect of alcohol components was also screened.[140] The reaction of ethyl acetate with XCH_2CH_2OH in the presence of PPL was monitored (Scheme 35). If steric

Scheme 35

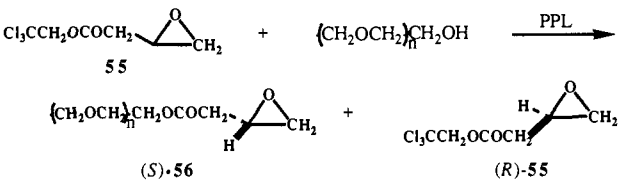


X	
group 'a' aclcohl	group 'b' alcohol
Cl	Br
MeO	BuO
Me_2N	Et_2N

factors play a major role in governing the rate of reaction, then the "a" alcohols should react faster than the "b" alcohols of the same class. On the other hand, if electronic factors play a more important role, then the observed results should be quite opposite. Actually, the "a" alcohols reacted much faster than the "b" alcohols and there were no significant differences between 2-chloroethanol, 2-methoxyethanol, and *N,N*-dimethylethanolamine. It follows that steric factors in the alcohol moiety play a bigger role than the electronic factors in governing the lipase-catalyzed transesterification.

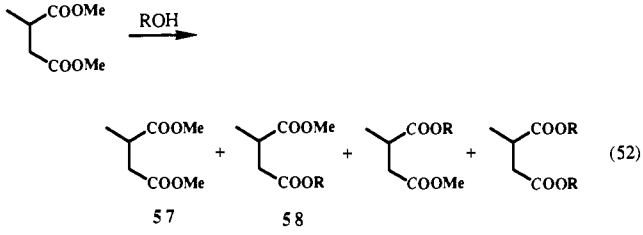
For the practical use of the enzymatic process in organic solvents, an easy separation of the alcohol and ester components is required. Resolution of 2,2,2-trichloroethyl (*R,S*)-3,4-epoxybutanoate (**55**) was selectively transesterified by low molecular weight (~1500) poly(ethylene glycols) (PEG) (Scheme 36).[141]

Scheme 36



The PEG ester **56** is insoluble in the reaction medium (diisopropyl ether) at 0 °C and accordingly easily separated from the unchanged (*R*)-**55**.

Recently, improvements have been undertaken by modifications of enzymes themselves. Immobilization has led to significant improvements. Transesterification of dimethyl methylsuccinate was conducted by using immobilized enzymes without added solvent (eq 52).[142] Among the various combinations of enzymes



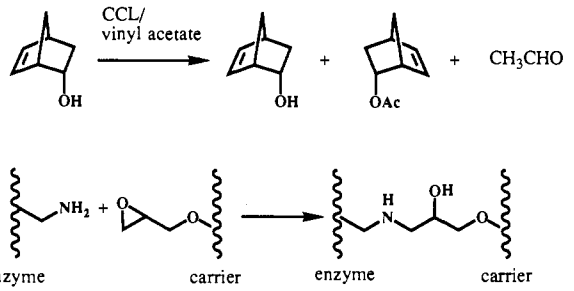
(52)

[PPL, *Candida cylindracea* (CCL), α-chymotrypsin, and Horse liver esterase] and supports (alumina, silica gel, and florisil), PPL on florisil in 1-propanol gave the best outcome: (*R*)-**57** (52% yield; 95% ee) and (*S*)-**58** (45% yield; 95% ee).

Wang et al. disclosed that resolution of secondary alcohols catalyzed by XAD-8 immobilized lipoprotein lipase was accelerated by >200 times faster than that with unimmobilized enzyme.[143]

Immobilization also changes the character of enzyme. Lipase P immobilized on florisil improved the enantiomeric excess in the lactonization of methyl 5-hydroxyhexadecanoate.[144] The improvement was ascribed to deactivation of the active site of the enzyme which caused nonspecific lactonization. Acetylation of *endo*-bicyclo[2.2.1]hept-5-en-2-ol by vinyl acetate in the presence of CCL resulted in low enantioselectivity (50–70% ee of the acetate) (Scheme 37).[145] The coproduct acetaldehyde is the cause for the enzyme's deactivation since acetaldehyde is known to act as an alkylating agent on enzymes by forming Schiff's base in a Maillard-type reaction, particularly on the terminal amino residue of lysine. Then, the reactive groups in the enzyme was blocked by treating with epoxy-activated macroscopic carriers. By using the immobilized enzyme thus obtained, the optical purity of the acetate was increased up to ca. 92% ee. Furthermore, this increased selectivity could be entirely preserved in repetitive use over three consecutive runs.

Scheme 37



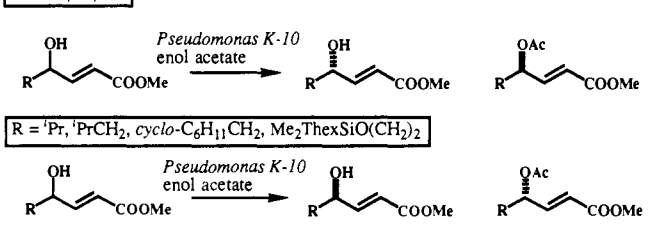
Wong et al. created a subtilisin mutant to enhance the stability of the enzyme in unnatural environments.[148] The mutant derived from subtilisin BPN' via six site-specific mutations was found to be 100 times more stable than the wild-type enzyme in aqueous solution at room temperature and 50 times more stable than the wild type in anhydrous dimethylformamide. By the use of this mutant, synthesis of peptides and various enantioselective synthesis were conducted.

B. Resolution of Racemates

The enzymatic transesterification has been most frequently used for kinetic resolution of racemic secondary alcohols which was first put forth by Klibanov et al.[119,126] and is still expanding its scope. A comprehensive study was reported by Zwanenburg et al. recently.[138] Oehlschlager et al. investigated the effect of various branched and straight alkyl chains on resolution of 2-alkanols catalyzed by PPL as an enzyme with 2,2,2-trifluoroethyl esters as acyl donors.[147] In the series of linear 2-alkanols studied there is a rapid increase in the degree of enantioselectivity as the alkyl group is changed from Et to ^{n}Bu. Further chain extension has little effect on the degree of enantioselectivity. The presence of branch methyls in alcohols that possess longer alkyl chains exerted only weak influence on enantioselectivity.

Burgess et al. investigated lipase-catalyzed transesterification of γ-hydroxy-α,β-unsaturated esters and disclosed that the sense of enantioselection was dependent on the substituent R (Scheme 38).[146] That is,

Scheme 38



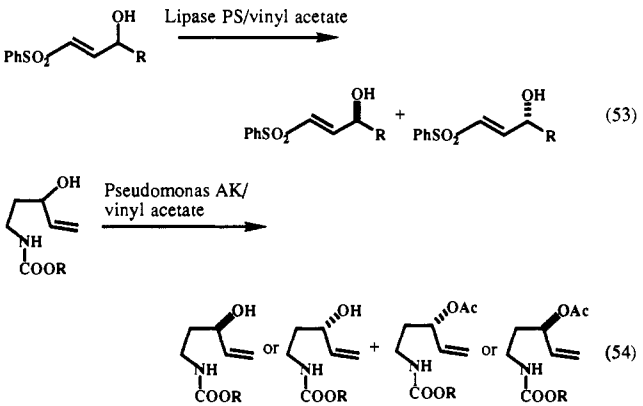
when R is a straight chain like methyl, ethyl, and *n*-propyl, the *R* isomers are more reactive while the reactivity is completely reversed when R is a branched chain. An alcohol thus obtained was utilized for the synthesis of statine analogue (92% ee).[146b] Burgess et al. further developed an effective method for kinetic resolution of unsaturated secondary alcohols that cannot be resolved by Sharpless epoxidation.[149] Various allyl alcohols with high optical purity were obtained by transesterification process using *Pseudomonas* sp. (AK) and vinyl acetate. They concluded that "the alcohols

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.

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). Satisfactory results were obtained with proprgylic alcohols and other relevant alcohols as well.

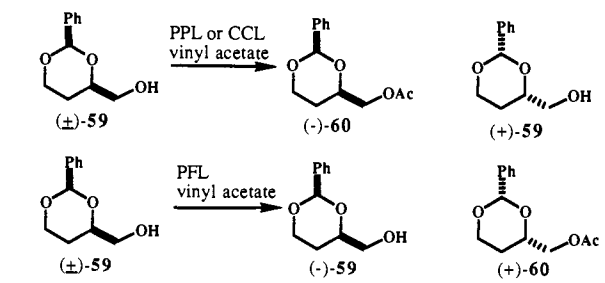
γ-Hydroxy-α,β-unsaturated sulfones (eq 53)[150] and 3-hydroxy-4-pentenylurethanes (eq 54)[151] were also resolved successfully.



The effect of adjacent unsaturation on the PPL-catalyzed kinetic resolution of secondary alcohols was studied for a series of allylic, homoallylic, propargylic, homopropargylic, and phenyl-substituted 2-alkanols in anhydrous ether.[152] Excellent enantioselectivity was observed for α-phenethyl alcohol, propargylic alcohols, and (*E*)-allylic alcohols, but (*Z*)-allylic alcohols showed poor selectivity. Enantioselectivity was also low for both (*E*)- and (*Z*)-homoallylic alcohols, homopropargylic alcohol, 1-phenyl-2-propanol, and 4-phenyl-2-butanol.

Resolution of (±)-*cis*-4-(hydroxymethyl)-2-phenyl-1,3-dioxane [(±)-**59**] was attempted (Scheme 39).[153]

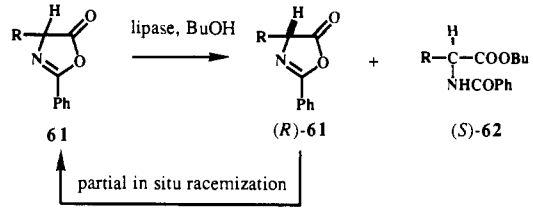
Scheme 39



PPL and CCL afforded (−)-**60** and (+)-**59** while the sense of the enantioselectivity is reversed by use of the lipase from *Pseudomonas fluorescens* (PFL). This enzyme gave the best results with regard to the optical purity of the alcohol (>99% ee).

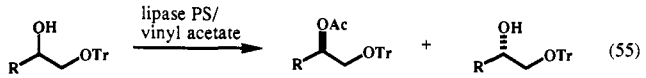
Enantioselective ring opening of oxazol-5(4*H*)-ones were investigated (Scheme 40).[154] These compounds, commonly known as azlactones, form a class of highly

Scheme 40



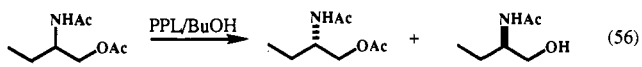
versatile intermediates for the synthesis of α-amino acids and peptides. However, hydrolysis of these compounds in an enantioselective manner met with little success. Lipase from *Mucor miehei* effected transesterification of **61** with 1-butanol in diisopropyl ether. After 45% conversion, (*S*)-**62** was obtained in 57% ee while no optical rotation was found for the isolated unreacted azlactone. This suggests in situ racemization of the unreacted azlactone under the reaction conditions. This was confirmed by driving the reaction to 100% conversion when (*S*)-**62** was obtained with 34% ee.

Selective modification of a certain functional group in polyfunctionalized compounds is a quite useful manipulation in organic synthesis. In particular, acylation of hydroxy groups or deacylation of ester groups in a selective manner is often required. 2-Substituted 1-*O*-tritylethylene glycols were resolved by use of lipase PS from *Pseudomonas* sp. (eq 55).[155] The acetates obtained exhibited satisfactory ee's (>99%) except for the compounds with R = Pr. Recently, Holla[156] and Danishefsky et al.[157] reported resolution of racemic glycals.



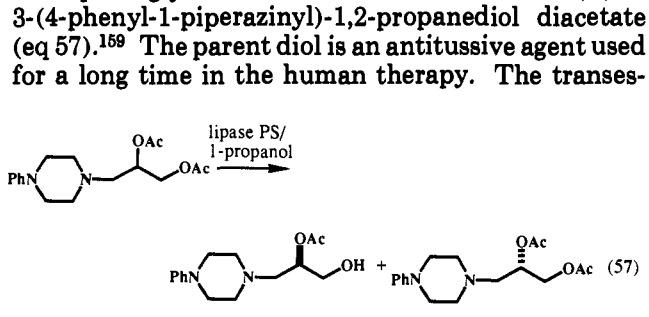
(55)

Bevinakatti reported that PPL-catalyzed transesterification of *N*,*O*-diacetyl-2-amino-1-butanol led to resolution with modest selectivity: 66% ee for the unreacted (*S*)-diacetate (eq 56).[158]



(56)

Surprisingly clean resolution was achieved for (*R*,*S*)-3-(4-phenyl-1-piperazinyl)-1,2-propanediol diacetate (eq 57).[159] The parent diol is an antitussive agent used for a long time in the human therapy. The transes-

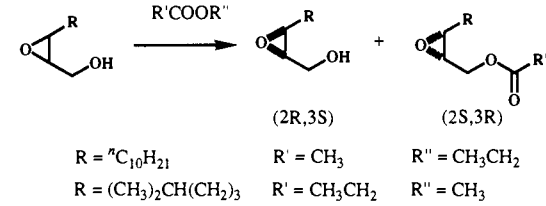


(57)

terification reaction in the presence of lipase PS spontaneously stopped after the stereoselective cleavage of the primary ester group, affording 50% of (*S*)-diacetate (95% ee) and 47% of (*R*)-monoacetate (95% ee). Only small traces of the regioisomer of the monoacetate (less than 4%) were detected.

2,3-Epoxy alcohols were subjected to enzyme-catalyzed resolution (Scheme 41).[160] Use of PPL as enzyme and ethyl acetate as acyl donor provided the (2*R*,3*S*)-alcohol with >95% ee.

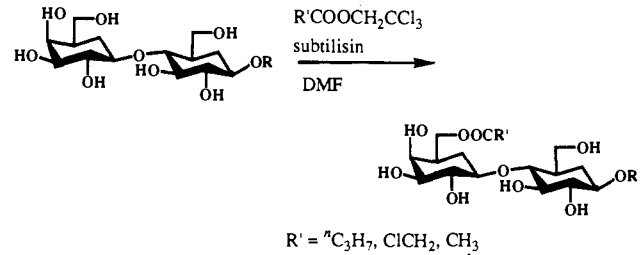
Scheme 41



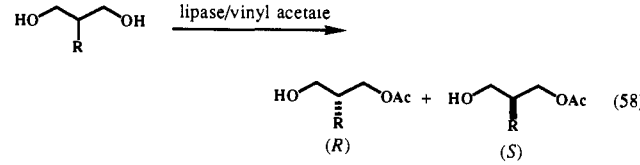
C. Acylation of Polyol Derivatives

Klibanov et al. disclosed that the primary hydroxy group of primary–secondary glycol was exclusively acylated upon exposure to PPL in ethyl carboxylate solvents.[161] Subsequently, direct monoacylation of sugars was studied.[162] Treatment of sugars with trichloroethyl carboxylates in the presence of PPL in pyridine resulted in regioselective acylation: the C-6 position of glucose, galactose, and mannose was predominantly acylated (selectivity ranging from 82 to 100%). Two primary hydroxyls in fructose displayed comparable reactivities. Since then, a number of studies on the regioselective acylation followed which were cited in the Klibanov's account. Most recently, subtilisin-catalyzed esterification of methyl 4-*O*-β-D-galactopyranosyl-β-glucopyranoside with 2,2,2-trichloroethyl butyrate in dimethylformamide distinguished between the two primary hydroxyl groups, yielding exclusively the 6′-*O*-monobutyl derivative (Scheme 42).[163]

Scheme 42



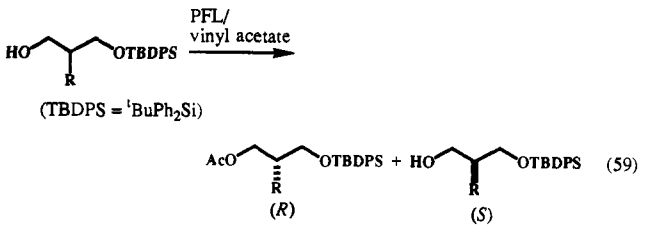
Diols bearing a chiral center serve as versatile building blocks in organic synthesis. In particular, enzymatic preparation of 2-substituted propanediols which constitute one of the most fundamental prototypes in this field has received extensive attention since the pioneering work by Ramos Tombo et al.[164] Achiwa conducted analogous reaction employing PFL and *Pseudomonas fragi* lipase as enzymes and vinyl acetate as an acyl donor as well as solvent (eq 58).[165] PFL afforded better results with 60–98% ee's. The same



(58)

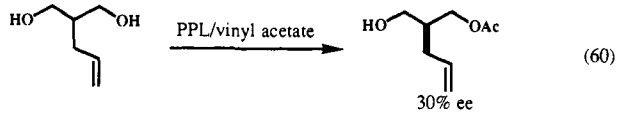
reaction using PFL was reported independently in the synthetic program for a renin inhibitor, BW-175.[166] The *R* configuration of the resulting monoacetates was put forth from both studies. Conversely, Santaniello et al. assigned the methyl-substituted derivative as an *S* isomer which was obtained from the reaction in $CHCl_3$.[167] They also displayed that the PFL-catalyzed

reaction was effective for resolution of a racemic monosilyl ether (eq 59).



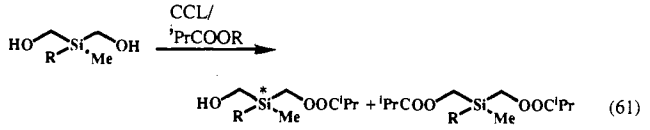
(59)

Mori et al. attempted transformation of a prochiral diol to the corresponding monoacetate but with poor optical purity (30% ee) (eq 60).[168]



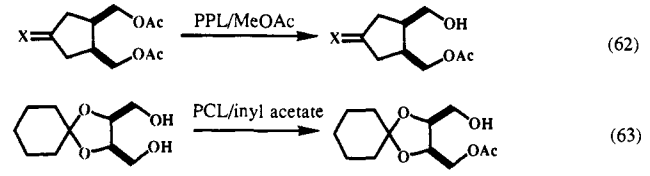
(60)

Achiwa et al. also reported acetylation of 2-*O*-substituted glycerols with the aid of PFL.[169] The same reaction was conducted using long chain fatty acid 2,2,2-trifluoroethyl esters.[170] It was found that optically active 2-sila-1,3-propanediols were accessible by enzymatic transesterification (eq 61).[171] CCL and lipase from *Chromobacterium viscosum* were employed and the ee values for the monoacetates were 70–76%.



(61)

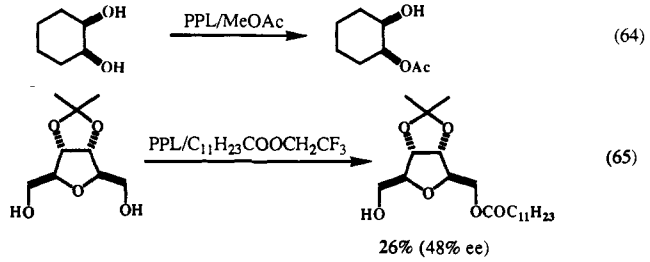
Asymmetric modification of meso compounds is an attractive means to arrive at chiral building blocks of great synthetic use. Gais et al. investigated monoacetylation of cyclopentane and cyclopentanone derivatives (eq 62)[172] and 2,3-*O*-cyclohexylidene erythritol (eq 63).[173]



(62)

(63)

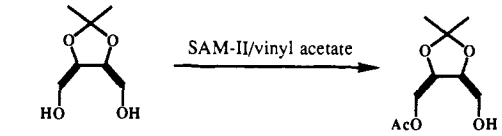
PPL and *Pseudomonas cepacia* lipase (PCL) were the enzymes of choice and the optical purity of the monoacetate ranged from 26–94% ee. 1,2-Hexanediol was also acetylated with 84% ee (eq 64). Jones et al. disclosed that PPL-promoted transesterification of 2,5-bis(hydroxymethyl)-3,4-(isopropylidenedioxy)tetrahydrofuran resulted in modest enantioselectivity (48% ee) as well as chemical yield (eq 65).[174]



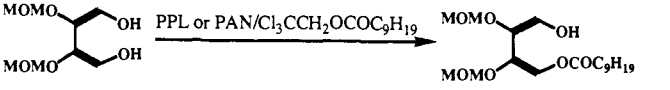
(64)

(65)

meso-Erithritol derivatives underwent monoacylation with high enantioselectivity. Vandewalle et al. employed an acetonide under catalysis by PFL coupled with vinyl acetate (eq 66)[175] while Bestmann et al. subjected a MOM ether to PPL or pancreatin from porcine pancreas (PAN)-2,2,2-trichloroethyl decononylate (eq 67).[176] The ee values of both monoesters were 95%.



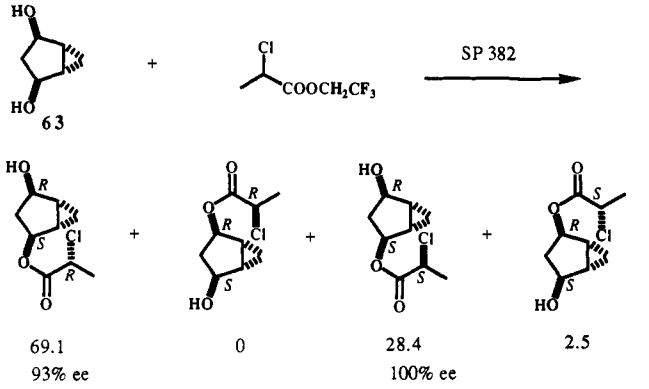
(66)



(67)

The first example of lipase-catalyzed doubly enantioselective transesterification was put forth by Thiel et al. (Scheme 43).[177] *meso*-Diol **63** was exposed to a

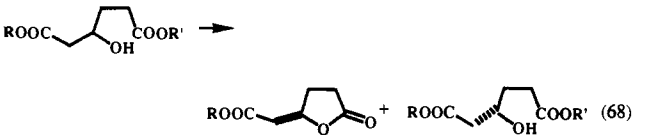
Scheme 43



variety of lipases. Among them the lipase from *Candida* sp 382 and pancreatin gave the highest selectivities.

D. Lactonization and Polycondensation

The first intramolecular transesterification of ω-hydroxy esters was reported by Yamada et al.[178] and Gutman et al.[179] independently in 1987. Since then, a considerable number of studies have appeared on the relevant subject. Most of them are cited in the Klibanov's account. A few papers appeared since then. Ohta et al. reported enantioselective macrolactonization of 12-hydroxydodecanoate (>99% ee)[136] and 5-hexadecanoate (80% ee)[144] with recourse to the molecular sieve acceleration and the immobilized enzyme method, respectively. Synthesis of 5-substituted-2-furanones was attempted (eq 68).[180] Disappointingly, however, the PPL-catalyzed reaction resulted in up to 49% ee of the furanones.

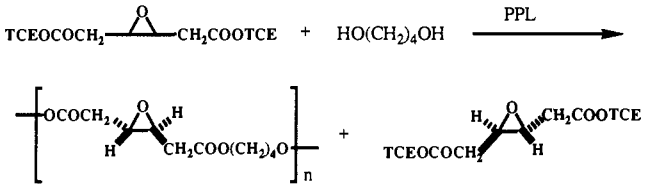


(68)

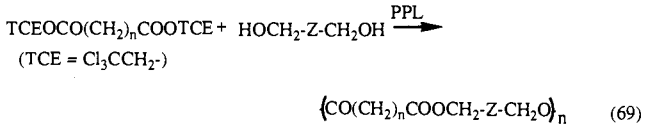
Synthesis of high polymers by condensation was carried out by Morrow et al. The enantioselective polycondensation between bis(2,2,2-trichloroethyl) *trans*-3,4-epoxyadipate and 1,4-butanediol using PPL as a catalyst provided a polymer whose M_n = 5300 Da

(on the basis of end group analysis) or M_w = 7900 Da (on the basis of GPC) (Scheme 44).[181] The optical

Scheme 44



purities of the (−)-polymer and the unchanged diester were found to be >96% and >95%, respectively. The general trend of condensation between bis(2,2,2-trichloroethyl) alkanedioates and diols was investigated using PPL as a catalyst (eq 69).[182] While the molecular weights of the polymers (1300–8200 Da based on end-group analysis or 2800–14900 Da based on GPC) were not as high as was desirable, the improvements would be promising by modifying the reaction conditions.

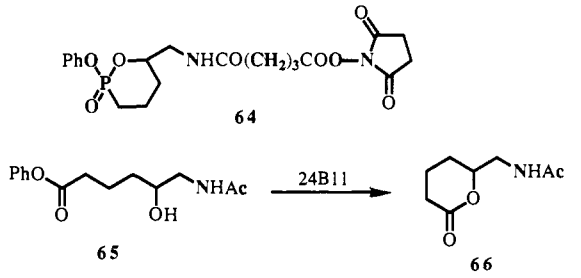


(69)

XIII. Catalytic Antibody

A monoclonal antibody (24B11) to a cyclic phosphonate **64** was employed for lactonization of racemic δ-hydroxy ester **65** (Scheme 45).[183] The reaction was

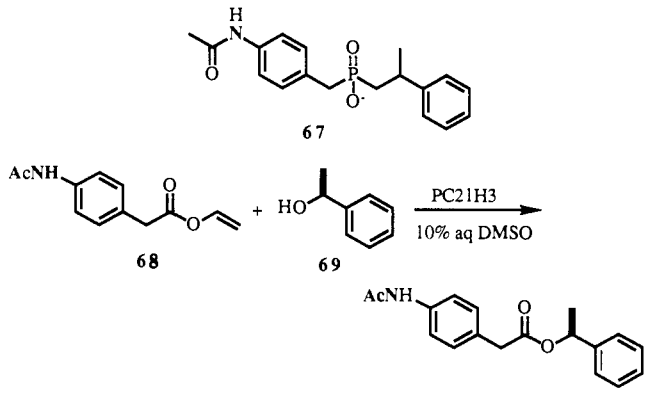
Scheme 45



accelerated by the antibody by a factor of 170. The enantiomeric excess of the lactone **66** thus obtained was found to be 94%.

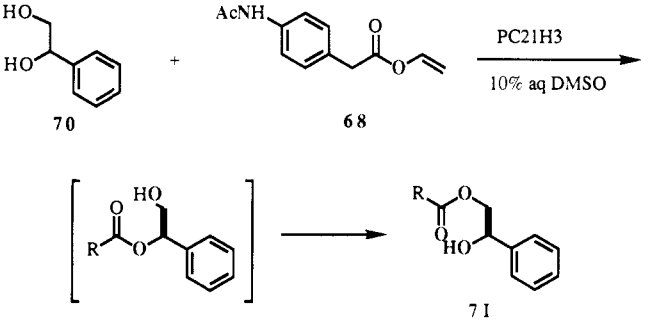
Lerner et al. screened antibodies to phosphonate **67** as catalysts for transesterification and found that one antibody, monoclonal PC21H3, catalyzed the reaction between **68** and **69** (Scheme 46).[184] The reaction

Scheme 46



proceeded in a mixture of water and 10% DMSO, reflecting characteristic features of this process. Transesterification is a difficult bimolecular reaction to run in water because water itself is present in vast excess and is preserved as a reactant. However, the antibody activates substrates which match an induced fit mechanism and thus water cannot be involved in the reaction. The scope and limitations of this reaction was investigated.[185] It was revealed that the antibody accepted 6-membered-ring aromatic alcohols, but furan or cyclohexyl derivatives were poorly accepted. When the diol **70** was subjected, primary alcoholic acetate **71** was obtained (Scheme 47). This is surprising because if

Scheme 47



the diol is placed in the active site as is **69**, the ester bond should be formed at the secondary alcohol group. It was suggested that the secondary alcohol ester is formed first followed by an acyl migration to the primary position. The reaction is best performed with enol esters as acyl donors. This is a disadvantage since the enol ester is not stable in aqueous solution and must be added in several portions to the reaction mixture.

XIV. Concluding Remarks

The chemical approach in transesterification has almost matured. However, efforts may be continued to make the reaction milder and more selective. One of the ultimate goals is to devise enantioselective reactions. Since transesterification is an equilibrium process, this goal cannot be accessible by simple extention of the conventional methodologies. Conceptually novel ideas need to be invoked to suppress the equilibration.

The enzyme processes have overcome this proposition to a considerable degree. Yet there still remain some problems to be solved for satisfying synthetic chemists' requirements. The guidelines for employment of enzymes in organic synthesis must be established more clearly. (1) What kind of enzyme can be used for a certain reaction? (2) Are the conditions common in all reactions using the same enzyme or should they be specified? (3) Is the reaction applicable to the large scale preparation? Hopefully, rapid accumulation of experimental data in recent years will give answers to these questions in the near future.

In summary, chemical means will, no doubt, continue to play a pivotal role in transesterification but innovation is strongly desired for broadening the scope, especially in terms of selectivity. It should be recognized, on the other hand, that enzyme methods are getting close to the stage where they can be utilized

practically for a variety of synthetic purposes. Synthetic chemists will be urged to pay more attention to this field.

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