Junzo Otera

Esterification

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ISBN: 3-527-30490-8

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Junzo Otera

Esterification

Methods, Reactions, and Applications

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Library of Congress Card No. applied for

British Library Cataloguing-in-Publication Data: A catalogue record for this book is available from the British Library.

Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

printed in the Federal Republic of Germany
printed on acid-free paper

Composition ProSatz Unger, Weinheim
Printing Strauss Offsetdruck GmbH
Bookbinding Grossbuchbinderei J. Schäffer GmbH & Co. KG, Grünstadt

ISBN 3-527-30490-8

Preface

Few would dispute that the synthesis of esters has played a most important role in organic synthesis from its infancy. This importance stemmed from its utility in diverse fields both in the laboratory and in industry. Ester moieties, irrespective of whether acyclic or cyclic, constitute major backbones, as well as functional groups of chemical significance, in numerous natural products and synthetic compounds. The essential feature of esterification that particularly distinguishes it from other reactions lies in its broad utilization in industry. Just a brief chronological look quickly reminds us of aspirin (acetyl salicylic acid), fatty acid esters, polyesters, macrolides, and so on. In addition to being essential molecular components in their own right, ester groups also play versatile temporary roles in organic synthesis for protection of carboxylic acids and hydroxy groups. The synthesis of natural products, especially macrolides, sugars, and peptides, depends heavily on acylation technology.

Being carboxylic acid derivatives, esters are largely produced from the reactions between the corresponding acids and alcohols. Transformation from one ester into another (transesterification) is also useful. On the other hand, since esters are also derivatives of alcohols, ester synthesis is also important from the standpoint of alcohol chemistry, such as acylation. A variety of routes to arrive at esters are therefore feasible, and numerous methods have been reported. Surprisingly, though, no book focussed solely on "esters" has been available up to now, esterification or transesterification usually being included in many books as a sub-class of functional group transformations. Obviously, this is not a fair treatment if the central position of (trans)esterification in organic synthesis is taken into account. Why did such biased circumstances arise? A number of reasons can be counted immediately, but only a few representatives among them are given here. Since (trans)esterification has such a long history and the reaction itself is simple, many people, especially in academia, take it for granted that little room is left for further scientific improvements. In industry, on the other hand, (trans)esterification still has permanent significance and so many new technologies remain undisclosed, as know-how. Since the utility of (trans)esterification has spread into diverse fields, it is indeed laborious to cover the whole. As such, even people involved in the (trans)esterification field, regardless of whether in academia or in industry, have rather limited knowledge about what is going on outside the very narrow disciplines close to them. Despite such undesirable circumstances, (trans)esterification has in fact been, and is still undergoing, exten-

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sive innovations. It is the aim of this book to inform a broad range of chemists and technicians on the state of the art relating both to fundamental ideas and to practical facets of (trans)esterification.

This book consists of two parts. The first thoroughly reviews the (trans)esterification reaction, from conventional approaches to the most up-to-date progress in terms of reaction patterns, catalysts, reaction media, etc., so that readers may acquire general, basic knowledge of the reaction. In addition, those wanting to survey suitable methods for a specific target will find great help from consulting this part. A number of "Experimental Procedures" given may help readers judge which reactions are suitable for their purposes.

Synthetic applications of (trans)esterification are the subjects of Part II. These reactions, many of which may already have appeared in Part I, are reorganized according to their respective synthetic purposes. Various aspects of interest to synthetic chemists are summarized, followed by an overview of industrial utilization.

Because of its long history, it has been impracticable to survey the literature of esterification completely from the beginning. A full survey on the literature since 1990 has therefore been made by use of commercial databases. Reference works appearing before 1990 have been selected arbitrarily depending on their importance. I believe that this treatment is fully acceptable to cover the literature that is basically significant and represents recent progress to meet the requirements for "modern esterification". As a result, we encountered more than 5,000 references, but for reasons of space not all of them could be accommodated in the text of this book. Only examples selected in terms of their fundamentality and generality have been taken, to provide a comprehensive view on the overall aspects as broadly as possible. All collected references are collected in a database library, a copy of which is provided on disc at the end of this book. Those who wish to obtain more detailed information will be able to consult this library through keyword access.

Last, but not least, I would like to express my sincere appreciation to Miss Masayo Kajitani, who contributed greatly in the literature survey and the illustrations. Without her collaboration and patience, this book might have not been completed.

Junzo Otera
Okayama, November 2002

Database

The database on the disk in the back of this book is accommodated in a FileMaker Developer 6 version for which both Windows and Macintosh operation systems are available. The database contains about 5,000 references, on which this book is based and the keyword access with schematic representation is feasible. Basically, the references are accessed according to the numbers of (sub)headings of the text. In addition, the following keywords are employable for more selective access.

KeyWords

For Chiral Compounds: Chiral Carboxylic Acids, Chiral Esters, Chiral Anhydrides, S-preference

For Selectivities: Primary/Primary, Primary/Primary and Secondary, Primary/Secondary, Primary/Secondary and Tertiary, Primary/Tertiary, Primary/Secondary and Phenol, Primary/Phenol, Secondary/Primary, Secondary/Primary and Secondary, Secondary/Primary and Tertiary and Phenol, Secondary/Secondary, Secondary/Secondary and Tertiary, Secondary/Secondary and Phenol, Secondary/Tertiary, Secondary/Phenol, Tertiary/Tertiary, Phenol/Secondary, Phenol/Secondary and Phenol, Phenol/Phenol, Secondary and Phenol/Secondary, Secondary and Phenol/Phenol, Primary and Secondary/Secondary, Secondary and Tertiary/Secondary, Identical hydroxyl-groups, Identical carboxylic-groups, Identical ester-groups, Identical acid chlorides

For Reaction Media: Ionic Liquids, Fluorous Biphasic Technology, Phase Transfer Catalysts, Surfactant-type Catalysts, Immobilization, Cyclodextrin, Supercritical Solvents

For Natural Products: The natural products which appear in **7.4** are accessed by their names as well.

Others: Yamaguchi method, Distannoxanes, TiTADDOLates, Al, B, Bi, Cu, Fe, Hf, I, Ni, Sc, Sn, Ti, Zn, Py, DMAP, NEt_3, NEt^iPr_2, NH^iPr_2, $PhNEt_2$, $PhNMe_2$, $EtNMe_2$, DBU, $NHMe_2$, $NHCy_2$, Cinchona Alkaloids, Guanidine, TMEDA, Imidazoles.

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Introduction

The biggest problem frequently encountered in (trans)esterification technology arises from equilibration. To bias the equilibrium to the product side, one of the reactants must be used in excess and/or one of the products must be removed constantly during the reaction. Use of a non-equilibrium reaction approach, with the aid of activated reactants such as acid anhydrides and halides or alkoxides, can be effective to bypass the problem on some occasions but is not always general. Ester synthesis reactions are usually conducted with the aid of acid or base catalysts, and so the employment of catalysts or promoters that are suitably active but also compatible with other functional groups is of great importance. Progress has been made to overcome these problems in (trans)esterification reactions.

Esterification can be regarded as the transformation of carboxylic acids or their derivatives into esters, as carried out in many natural products syntheses, in the protection or kinetic resolution of carboxylic acids, and in the fatty acids industry. However, its counterpart reaction – the transformation of alcohols into esters, as in protective acylation of hydroxy groups, kinetic resolution of alcohols, etc. – is equally important. The normal substrate/reagent relationship cannot therefore be straightforwardly applied to esterification. Moreover, in intramolecular cases (lactonization) and polycondensation, both functions as equal partners. In Chapter 1 the alcohol component is regarded as the substrate, because modifications of carboxylic acids are available in greater variety. Of course, such a classification is not strict: the carboxylic acid component might as well be taken as a substrate in, for instance, the direct reaction between neat alcohol and carboxylic acid. In any event, the chapter is subdivided into sections according to the means by which the carboxylic acid is modified. Each section is then further sub-classified according to the activation modes.

Tin alkoxides, together with some other metal alkoxides, are useful for selective acylation of polyols and, in particular, play an important role in sugar chemistry. This subject is grouped separately in Chapter 2.

In Chapter 3, the carboxylic acid component is treated as substrate, in reaction with various reagents other than alcohols. Chapter 4 deals with interconversion between different esters.

The first two chapters in Part II, Chapters 5 and 6, are both associated with chirality. In response to the increasing need for optically active compounds in modern synthetic chemistry, great progress has been achieved in ester technology, serving for

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the production of enantiomerically enriched or enantiomerically pure alcohols and carboxylic acids through kinetic resolution and desymmetrization.

Chapter 7 covers miscellaneous topics of great significance in terms of synthetic utility and various selectivities. Natural products syntheses in which esterification has played a crucial role are also described.

Finally, in Chapter 8, industrial uses of esterification technology are examined. Since many currently operational, especially state of the art, processes are veiled in darkness as know-how, it is not an easy task to delineate the real features. What can be done best is to sketch profiles that are either common knowledge or available from the literature. Despite such limitations, readers should acquire an idea of how and where esterification is utilized in practice.

Part I
Methodology

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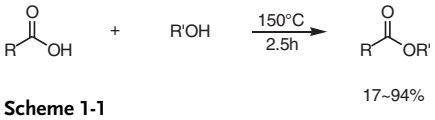
1
Reaction of Alcohols with Carboxylic Acids and their Derivatives

1.1
Reaction with Carboxylic Acids

1.1.1
Without Activator

Although the direct reaction between alcohol and carboxylic acid is conventionally conducted under acid or base catalysis conditions, the catalyst-free reaction is more desirable. This requirement is satisfied when the reaction is carried out at high temperatures. A literature survey (refer to the database disc) shows eight papers appearing in this category. For example, propanol or hexanol can be treated with various aliphatic carboxylic acids (1.35 equiv.) in an autoclave at 150 °C to furnish esters in poor to excellent yields (Scheme 1-1) [95ZPK(68)335]. The reaction is strongly influenced by the reaction temperature; the yield of propyl acetate is only 18% at 85 °C.



Scheme 1-1

Interestingly, condensation between sugars and α-hydroxycarboxylic acids can be performed in water (Scheme 1-2) [99SC951]. The reaction takes place at 60 °C, regioselectively on the primary hydroxy groups of mannose, galactose, and glucose. The avoidance of any catalysts or additives allows the instant application of the products in food technology and cosmetic formulation.

Experimental Procedure Scheme 1-2 [99SC951]
General procedure: A mixture of hydroxycarboxylic acid, carbohydrate, and water is heated to 60 °C in air for 24 h. To isolate the product as a pure compound for characterization the reaction mixture is extracted twice with diisopropyl ether, the solvent is removed in vacuo, and the residue is chromatographed on silica gel (CH_2Cl_2/MeOH 85 : 15).

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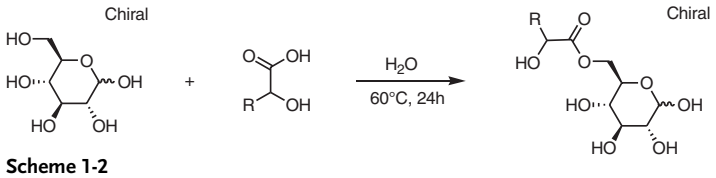
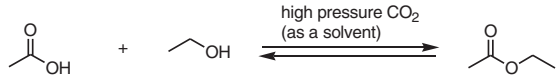


Scheme 1-2

The equilibrium in the reaction between ethanol and acetic acid can be shifted in favor of the ester by application of CO_2 pressure (Scheme 1-3) [2001GC17]. The ester yield is therefore increased from 63% in neat solution to 72% in CO_2 at 333 K/58.6 bar. This outcome is far from satisfactory, though the possibility does suggest itself that the equilibrium may be improved by changing the reaction conditions.



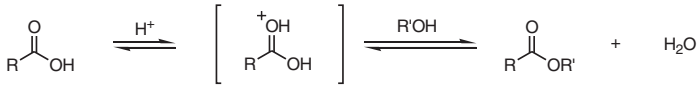
Scheme 1-3

On the whole, the catalyst-free reaction is ideal but difficult to achieve. Some special conditions are necessary, and employable reactants are rather limited. Nonetheless, it is obvious that this line of technology should be advanced more extensively in the context of green chemistry.

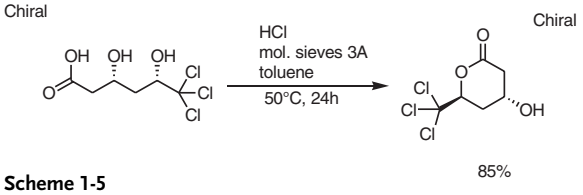
1.1.2 Acid Catalysts

1.1.2.1 Brønsted Acids

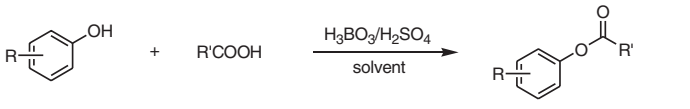
Since acid catalysis is one of the most popular methods for esterification, numerous papers are available (refer to the database disc). When the substrates are acid-resistant, the reaction is usually carried out in the presence of Brønsted acid such as HCl, HBr, H_2SO_4, $NaHSO_4$, $ClSO_3H$, NH_2SO_3H, H_3PO_4, HBF_4, AcOH, camphorsulfonic acid, etc. (Scheme 1-4). In cases in which the acidity is not high enough to trigger the desired reaction, the acid is combined with an activator. For example, the lactonization shown in Scheme 1-5 proceeds sluggishly with HCl only, but the reaction is effected smoothly in the presence of HCl and 3Å molecular sieves [97CL765]. The esterification of phenols with both aliphatic and aromatic carboxylic acids – difficult to achieve under normal conditions – can be catalyzed by a combination of H_3BO_3 and H_2SO_4 (Scheme 1-6) [71TL3453].



Scheme 1-4



Scheme 1-5



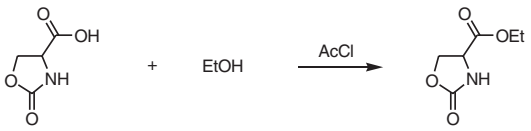
Scheme 1-6

Other ways to activate the acid catalysts are provided by the use of ultrasound and microwaves. H_2SO_4-catalyzed esterification, which usually requires a long reaction time under refluxing conditions, is complete at room temperature in several hours on exposure to ultrasonic waves [90SC2267]. Microwave irradiation accelerates *p*-toluenesulfonic acid-catalyzed esterification, the reaction finishing within 10 minutes [93CJC90].

Aqueous HCl is not employable for water-sensitive compounds. In such cases, dry HCl gas must be used, but generation of this is not operationally simple. Alternatively, generation of HCl under anhydrous conditions is conveniently feasible by addition of acetyl chloride to methanol or ethanol. Treatment of alcohol and carboxylic acid in the HCl solution obtained provides the desired ester (Scheme 1-7) [98SC471]. By this method, the concentration of HCl can readily be adjusted by changing the amount of acetyl chloride.

Experimental Procedure Scheme 1-7 [98SC471]

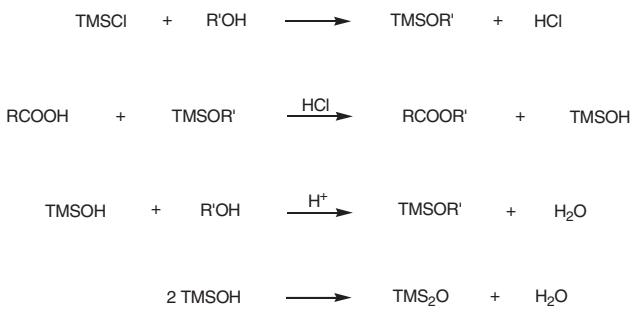
A typical experimental procedure involves the addition of a known amount of acetyl chloride, usually from a weighed syringe, to an ice-cold solution of an equivalent or excess amount of methanol (or ethanol) in an inert organic solvent, such as ethyl acetate, containing an equivalent amount of the compound to be treated. The acidic solution may also be prepared in the pure alcohol. Ice-cold solutions are used in order to increase the solubility of the HCl and to prevent its escape, the initial generation of the HCl being exothermic. In cases in which simple esterifications are to be carried out, excess acetyl chloride may be used without detrimental effects, since the



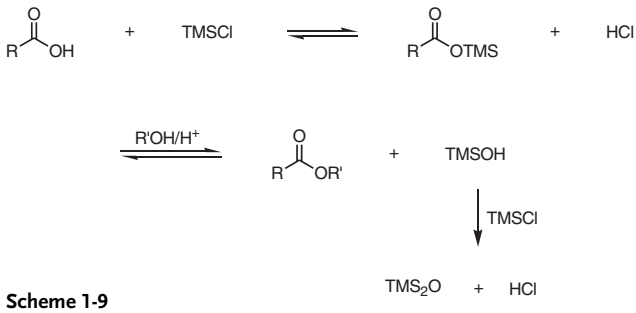
Scheme 1-7

workup involves simple evaporation of the solvent(s) and excess HCl. The solutions are allowed to warm to room temperature and the reactions are complete within 0.5–24 h.

A similar protocol is available with TMSCl (trimethylsilyl chloride) (Scheme 1-8) [81BCJ1267]. In this case, TMSCl is added to a mixture of alcohol and carboxylic acid. It has been suggested that the reactant alcohol works as a proton donor as well, while on the other hand the initial formation of the silyl ester is another proposed mechanism for a similar reaction (Scheme 1-9) [83S201].

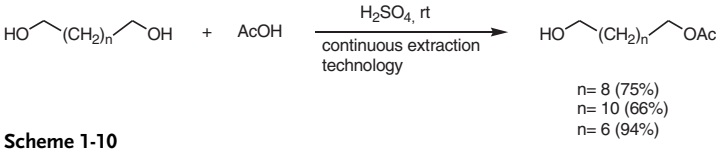


Scheme 1-8

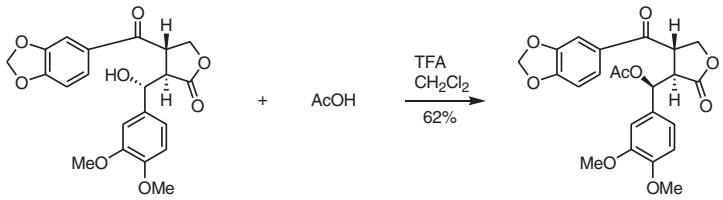


Scheme 1-9

Despite the rather harsh conditions, the Brønsted acid-catalyzed reaction sometimes enjoys selectivities. Continuous extraction technology enables selective monoacetylation in reasonable yields upon treatment of a 1,*n*-diol with acetic acid in the presence of H_2SO_4 (Scheme 1-10) [79TL1971]. Stereoselectivity is also attained in TFA-catalyzed esterification (TFA = trifluoroacetic acid), as shown in Scheme 1-11 [95JOC1148]. In this reaction, the inversion of the stereochemistry at C-4 proceeds effectively via the carbocation, the nucleophilic attack of an acetate anion on the carbocation taking place preferentially from the opposite side of the bulky 3,4-(methylenedioxy)benzoyl group in the Felkin-like model to afford the *anti* acetate.



Scheme 1-10

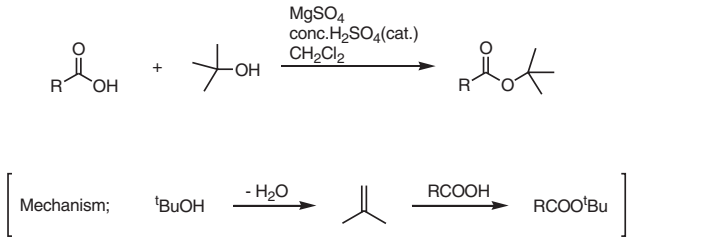


Scheme 1-11

A unique formation of *tert*-butyl esters is notable. When a mixture of carboxylic acid and *tert*-butanol is exposed to H_2SO_4 absorbed on $MgSO_4$, esterification takes place smoothly (Scheme 1-12) [97TL7345]. The reaction is successful for various aromatic, aliphatic, olefinic, heteroaromatic, and protected amino acids. No reaction occurs with the use of anhydrous $MgSO_4$ or H_2SO_4 alone. The reaction is initiated by dehydration of *tert*-butanol followed by addition of carboxylic acid to the resulting isobutylene.

Experimental Procedure Scheme 1-12 [97TL7345]

In a typical small-scale experiment, concentrated sulfuric acid (0.55 mL, 10 mmol) is added to a vigorously stirred suspension of anhydrous magnesium sulfate (4.81 g, 40 mmol) in 40 mL of solvent. The mixture is stirred for 15 minutes, after which the carboxylic acid (10 mmol) is added. Tertiary butanol (4.78 mL, 50 mmol) is added last. The mixture is stoppered tightly and stirred for 18 h at 25 °C, or until the reaction is complete by TLC analysis. The reaction mixture is then quenched with 75 mL of saturated sodium bicarbonate solution and stirred until all magnesium sulfate has dissolved. The solvent phase is separated, washed with brine, dried ($MgSO_4$), and concentrated to afford the crude *tert*-butyl ester, which is purified by chromatography, distillation, or recrystallization as appropriate.



Scheme 1-12

Hydrophobic polystyrene-supported sulfonic acids catalyze reactions between carboxylic acids and alcohols in water [2002ASC(343)270]. The catalysts are recovered and reused for further reactions.

1.1.2.2 Lewis Acids

Lewis acids are another important class of acid catalyst. In general, they are milder than Brønsted acids and, more importantly, template effects are to be expected as they are sterically bulkier than a proton. As such, the utilization of Lewis acids is rapidly increasing. They are classified as follows, according to elements:

B $BF_3 \cdot OEt_2$ [36JACS271, 69JPS1422, 70TL4011, 71S316, 72S628, 90ACH705, 91CE277, 95CC1391, 96JHC1171, 96TL1393]; BCl_3 [2001TL3959]; 3,4,5-$F_3C_6H_2B(OH)_2$ [96JOC4196]
Al $AlCl_3$ (immobilized) [73TL1823]
Zn ZnO [96IVY117]; $ZnCl_2$/microwave [2002TL45]
Sn Bu_2SnO [80JACS7578, 83JACS7130]; $(XR_2SnOSnR_2Y)_2$ [86TL4501; 91JOC5307; 96CL225]; $(XRf_2SnOSnRf_2X)_2$ 2002AGC(E)4117]; Ph_2SnCl_2 [87TL3713]
Fe $Fe(ClO_4)_3$ [94IJC(B)698, 92SC1087]; $Fe_2(SO_4)_3 \cdot H_2O$ [98SC1159]; $FeCl_3$ [99SL1200]
Ni $NiCl_2 \cdot 6H_2O$ [97T7335]
Cu $CuCl_2$ [89SC2897]; $Cu(NO)_3 \cdot 3H_2O$ [98SC1923]; $Cu(OTf)_3$ [99TL2611]
Hf $HfCl_4 \cdot 2THF$ [2000SCI(290)1140; 2001SL1117]
I I_2 [2002TL879]

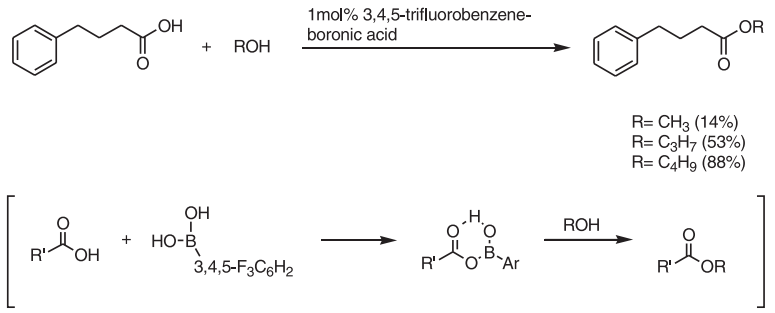
$BF_3 \cdot OEt_2$ is the oldest Lewis acid to have been employed as an esterification catalyst since the BF_3/CH_3OH complex had been known to be used for conversion of simple carboxylic acids to their methyl esters prior to GLC analysis. Although excess $BF_3 \cdot OEt_2$ (2–3 equiv.) and alcohol (>10 equiv.) for 1 equiv. of carboxylic acid should be used, esterification is feasible for 4-aminobenzoic acid, unsaturated organic acids, biphenyl-4,4′-dicarboxylic acid, 1,4-dihydrobenzoic acid, and heterocyclic carboxylic acids.

Experimental Procedure [71S316]

The reaction mixture comprising the acid (0.1 mol), boron trifluoride etherate (0.1 or 0.2 mol, depending on the number of carboxyl groups in the acid), and the appropriate alcohol (ten times in excess of the boron trifluoride etherate) is heated at reflux for a period of time not exceeding 24 h. The esters are precipitated by dilution with a 5% solution of sodium carbonate, followed by filtration or extraction with ether, and purified by crystallization from appropriate solvents or by distillation under reduced pressure.

BCl_3 is also useful for esterification with primary alcohols, but yields are not so high with secondary and tertiary alcohols. The disadvantage of this method is the cleavage of coexisting methyl ether functions.

3,4,5-Trifluorobenzeneboronic acid is claimed to be the most effective catalyst among the boronic acids (Scheme 1-13). Esterification takes place smoothly if heavy



Scheme 1-13

alcohols such as 1-butanol are employed. The reaction is presumed to proceed via a carboxylate intermediate.

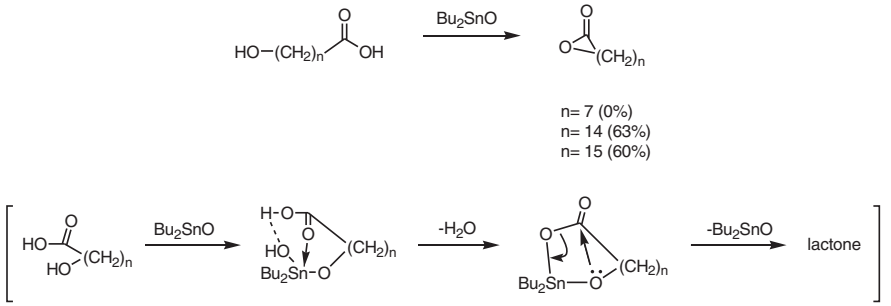
$AlCl_3$ is one of the most popular Lewis acids, but it is not employed in esterification because of its too strong acidity. However, polymer-supported $AlCl_3$ works as a milder catalyst for esterification although the yields are not always as high as those obtained by other methods. The advantage lies in the ease of separation of the catalyst by filtration.

Treatment of pentaerythritol with oleic acid in the presence of ZnO as catalyst provides a triester. Production of commercially important *p*-hydroxybenzoic acid ester (paraben) from *p*-hydroxybenzaldehyde and alcohol is catalyzed by $ZnCl_2$ under microwave irradiation conditions.

Another popular Lewis acid, $SnCl_4$, is also not usually employed in esterification. Organotin compounds work quite well, however, because the acidity is moderated by the replacement of chlorine with electron-donating alkyl groups. Bu_2SnO catalyzes lactonization of *seco* acids on continuous dehydration with a Dean–Stark apparatus (Scheme 1-14). This method is effective for large sized lactones but not for medium sized ones.

Experimental Procedure Scheme 1-14 [83JACS7130]

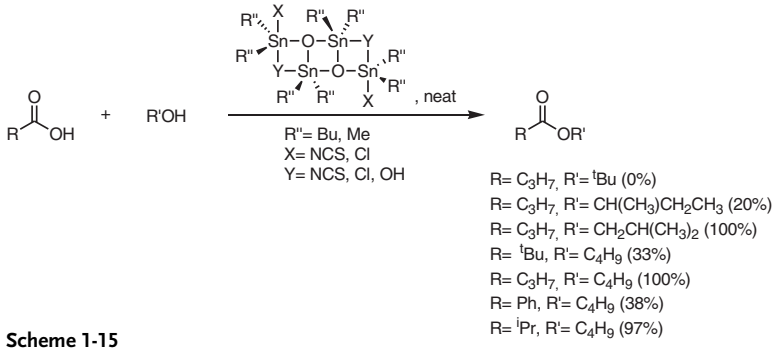
Preparation of hexadecanolide. A mixture of 16-hydroxyhexadecanoic acid (817.3 mg, 3.0 mmol) and dibutyltin oxide (74.7 mg, 0.3 mmol) is stirred in refluxing



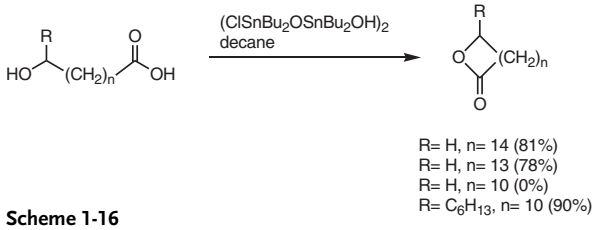
Scheme 1-14

mesitylene (100 mL) for 19 h with use of a Dean–Stark apparatus for the continuous removal of water. Removal of the solvent in vacuo (40 °C/0.2 mmHg) yields a yellow oily residue, which is Kugelrohr distilled (60 °C/0.2 mmHg) to give 457.9 mg (60%) of hexadecanolide.

Good yields of esters are obtained when carboxylic acids are treated with 1,3-disubstituted tetraalkyldistannoxanes, $(XR_2SnOSnR_2X)_2$, in alcohol solvent (Scheme 1-15). The catalysts are very mild, and the reaction is sensitive to the steric bulk of the reactants. The catalysts are also effective for lactonization (Scheme 1-16). The reaction proceeds simply on heating of a decane solution of *seco* acids. The convenience of operation is apparent from the lack of any need for dehydration apparatus and/or dehydration agents. Irreversible esterification apparently takes place because of the hydrophobicity of the surface alkyl groups surrounding the stannoxane core. Interestingly, alkyl side chains attached on the hydroxyl-bearing carbon of the ω-hydroxy acids exert a profound effect on lactonization. Lactone rings with fewer than 14 members are obtained in poor yields, while incorporation of R groups with more than four carbon atoms dramatically increases the yield.



Scheme 1-15



Scheme 1-16

Use of a fluoroalkyldistannoxane catalyst $(XRf_2SnOSnRf_2X)_2$ achieves a highly atom-efficient process in the context of fluorous biphasic technology (see Sections 7.2 and 7.3). Virtually 100% yields are available by the use of carboxylic acid and alcohol in a strict 1:1 ratio. The catalyst is recovered quantitatively and the catalyst solution in perfluoro-organic solvent is recycled repeatedly.

Experimental Procedure [2002AGC(E)4117]
A test tube (50 mL) is charged with 3-phenylpropanoic acid (300 mg, 2.0 mmol), benzyl alcohol (216 mg, 2.0 mmol), $(ClRf_2SnOSnRf_2Cl)_2$ (Rf = $C_6F_{13}C_2H_4$) (172 mg, 0.10 mmol, 5 mol %), and FC-72 (5.0 mL). The test tube is placed in a stainless steel pressure bottle and heated at 150 °C for 10 h. The pressure bottle is cooled, and toluene (5.0 mL) is added to the reaction mixture. The toluene and FC-72 layers are separated, and the latter layer is extracted with toluene (2.0 mL × 2). The combined organic layer is analyzed with GC to provide a quantitative yield of benzyl 3-phenylpropanoate.

Simple dimethyl- and diphenyltin dichlorides catalyze esterification of carboxylic acids in refluxing $C_1 \sim C_3$ alcohol.

Fe(III) salts are also effective. $Fe(ClO_4)_3 \cdot 9\,H_2O$ promotes esterification of carboxylic acids in alcohol. The reaction proceeds at room temperature, but a stoichiometric amount of the salt is needed. A catalytic version is available with $Fe_2(SO_4)_3 \cdot xH_2O$ (2 wt % cat. per acid) and $FeCl_3$ (5 mol % per acid). The reaction requires an excess amount of one reaction component in refluxing benzene or toluene. A similar outcome is obtained with $NiCl_2 \cdot 6\,H_2O$ catalyst.

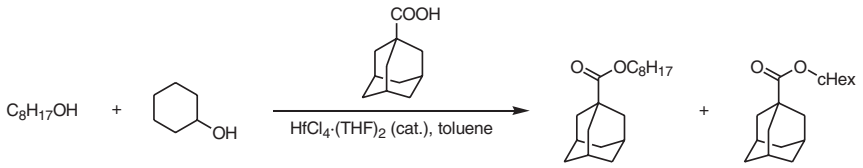
Experimental Procedure [98SC1159]
The Esterification of Adipic Acid with Ethanol in the presence of Ferric Sulfate: A mixture of adipic acid (14.5 g, 0.1 mol), absolute ethyl alcohol (18.5 g, 0.4 mol), dry benzene (35 mL), and commercial ferric sulfate (0.3 g) is placed in a flask equipped with an automatic water separator fitted with an efficient reflux condenser at its upper end. The mixture is heated at reflux on a steam bath for 3 h or until water no longer collects in appreciable amount in the water separator. The catalyst is filtered off and washed with two 20 mL portions of ether. The combined filtrate is washed with saturated sodium carbonate solution and then with cool water, and is dried with anhydrous magnesium sulfate. Most of the ether and benzene is removed by distillation under normal pressure, and the residue is then evaporated under reduced pressure to give the diethyl adipate at 116 ~117/9 mm. The yield is 19.4 g (96%).

Cupric salts are another class of species that work as catalyst. $CuCl_2 \cdot xH_2O$ catalyzes conversion of carboxylic acids in methanol solvent at 130 °C, while $Cu(NO_3)_2 \cdot 3\,H_2O$ effects acetylation of alcohols in refluxing acetic acid. $Cu(OTf)_2$ is used for acetylation of alcohols, but to a somewhat limited extent.

$HfCl_4 \cdot 2\,THF$ in the presence of 4 Å molecular sieves enables the use of equimolar amounts of alcohol and carboxylic acid to afford good to excellent yields of the desired esters (see Part II). This commercially available catalyst is highly active (usually 0.1 ~ 0.2 mol% loading) and hydrolytically stable. Polycondensations of ω-hydroxy acids or between dicarboxylic acids and diols to furnish polyesters are also feasible. The selective esterification of primary alcohols in the presence of secondary alcohols or phenol can be achieved with this catalyst (Scheme 1-17).

Experimental Procedure Scheme 1-17 [2000SCI1140]

The typical polycondensation procedure is as follows. A flame-dried, 5-mL, single-necked, round-bottomed flask fitted with a Teflon-coated magnetic stirring bar and a 5 mL pressure-equalized addition funnel [containing a cotton plug and 4 Å molecular sieves (~1.5 g)] surmounted by a reflux condenser is charged with ω-hydroxycarboxylic acid (10 mmol) or α,ω-dicarboxylic acid (10.0 mmol) and α,ω-diol (10.0 mmol) as substrates and $HfCl_4 \cdot 2THF$ (0.200 mmol) as a catalyst in *o*-xylene (2 mL). The mixture is brought to reflux with the removal of water. After 1 day, the resulting mixture is cooled to ambient temperature, dissolved in chloroform, and precipitated with acetone or methanol to furnish pure polyester as a white solid in quantitative yield.



Scheme 1-17

When a carboxylic acid is heated in alcohol with a catalytic amount of iodine, esterification takes place [2002TL879]. Primary, secondary, and even tertiary alcohols are employable, although the yields are rather low (56%) in the last case. The reaction is tolerant of high amounts of water. It is claimed that the iodine works as a Lewis acid.

Experimental Procedure [2002TL879]

Stearic acid (5 g, 17.6 mmol), methanol (10 mL), and iodine (50 mg,) are heated at reflux for the specified time, the progress of the reaction being monitored by TLC. After the reaction, excess alcohol is removed under reduced pressure and the residue is extracted with diethyl ether. The ether extract is washed with a solution of sodium thiosulfate and subsequently with distilled water, dried over anhydrous sodium sulfate, and concentrated in vacuo to yield the crude product, which is purified by column chromatography (hexane/ether, 9 : 1) to give the desired carboxylic ester (5.1 g, 98%).

1.1.2.3 Solid Acids

Various solid acids are utilized for esterification, although the substrates that can be employed suffer from considerable limitations due to the strong acidity. Nevertheless, solid acids have a great advantage in that they can be removed from the reaction mixture by filtration and thus applied to large-scale production.

Nafion-H

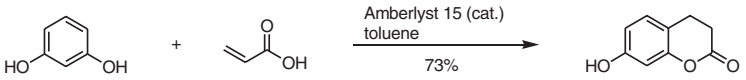
Nafion-H is the oldest solid acid to have been utilized as an esterification catalyst [78S929]. When a mixture of carboxylic acid and alcohol is allowed to flow over this catalyst at 95–125 °C, high yields of the corresponding esters are obtained with a contact time of ~5 sec. A batch reaction is also employable [91BKC9; 92BKC586].

Experimental Procedure [78S929]

Typical Esterification Procedure: The reactor is charged with activated Nafion-H catalyst (2.0 g). Carrier nitrogen gas is passed through the catalyst at a rate of 30 mL min^{-1}. A mixture of hexanoic (caproic) acid (2.6 g, 0.025 mol) and ethanol (2.9 g, 0.062 mol) is passed through the catalyst at 125 ° at a rate of 0.082 mL min^{-1}, corresponding to contact time of 5–7 sec. The two-phase product mixture is diluted with ether (30 mL) and washed with 5 % sodium hydrogen carbonate solution (2 × 20 mL), and then with water (2 × 20 mL). The organic layer is dried with magnesium sulfate and the solvent is evaporated. The residue is reasonably pure ethyl hexanoate, which may be distilled for further purification; yield: 3.5 g (98 %); b.p. 167°.

Amberlyst 15

α-Hydroxy esters [94SC2743] and α-amino acids [98SC1963] are successfully converted into the corresponding esters with this catalyst, while catechol undergoes esterification with acrylic acid to afford 7-hydroxycoumarin (Scheme 1-18) [95CC225].



Scheme 1-18

Experimental Procedure [94SC2743]

A solution of γ-butyrolactone (11.6 mmol) in anhydrous methanol (25 mL) is stored on Amberlyst-15 (25 g) with occasional shaking for 20 h. Methanol is decanted and the Amberlyst is washed with methanol (2 × 20 mL). The combined methanol fractions are evaporated and the residue is distilled to give methyl 4-hydroxybutanoate, b.p. 110–114/8–10 mm.

Amberlite IR120

Various substrates with hydroxy and related functions, such as sugars [93LA975; 95SC1099] and shikimic and quinic acids [91JCR(S)56], are esterified with this resin.

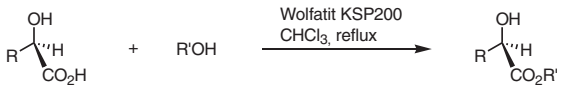
Experimental Procedure [93LA975]

5-*O*-(α-D-Glucopyranosyl)-D-arabinono-1,4-lactone: A solution of potassium 5-*O*-(α-D-glucopyranosyl)-D-arabinonate (7.7 g, 20 mmol) in water (20 mL) is passed through an ion-exchange column (Amberlite IR-120 H^+, 200 mL) and eluted with water (500 ml). Concentration of the eluent, followed by drying in vacuo (10^{-2} Torr), gives 5-*O*-(α-D-glucopyranosyl)-D-arabinono-1,4-lactone (3.2 g, 99 %) as an amorphous solid, softening around 88–90 °C.

Wolfatit KSP200

Esterification of chiral α-hydroxy carboxylic acids without racemization is feasible by heating in EtOH or MeOH/$CHCl_3$ in the presence of the ion-exchange resin Wolfatit

KSP200 (Scheme 1-19) [91CB1651]. The products are useful intermediates for synthesis of the corresponding α-hydroxy aldehydes.



Scheme 1-19

Zeolite

The rare earth-exchanged RE H-Y zeolite is the best of the various zeolite catalysts [96IJC(B)1174]. Heating of alcohol solutions of carboxylic acids in the presence of the freshly activated zeolite at 150 °C provides good to excellent yields of esters. The same type of zeolite is also useful for lactonization of *seco* acids [98TL293].

Experimental Procedure [96IJC(B)1174]

A mixture of phenylacetic acid (5 g, 0.036 mole) and ethanol (50 mL) is placed in a Parr reactor, and freshly activated zeolite (RE H-Y, 5 g) is slowly added. It is then heated at 150 °C under autogeneous pressure for 8 h. The reactor is allowed to cool to room temperature and the catalyst is filtered off and washed with ethanol (2 × 25 mL). The ethanol is removed from the filtrate by distillation. The residue is diluted with dichloromethane (50 mL) and washed with 5% aq. sodium carbonate solution (2 × 25mL) to remove the unreacted acid, then with water (2 × 25 mL), and finally with brine (20 mL), and dried over anhydrous sodium sulfate. Removal of the solvent provides pure ethyl phenylacetate (5.51 g, 91%).

$Nb_2O_5 \cdot nH_2O$

This catalyst is claimed to be more active than cation-exchange resin, $SiO_2 \cdot AlO_3$, and solid super acids [84CL1085].

$FeCl_3$ supported on salicylic resin

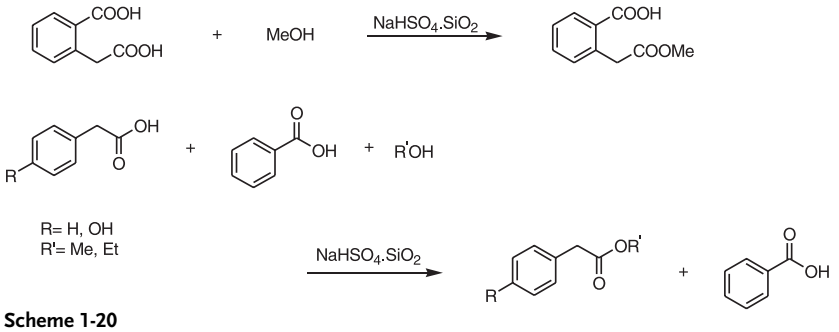
Azeotropic dehydration by heating of a mixture of carboxylic acid and alcohol (1 : 3 molar ratio) in benzene in the presence of the catalyst resin affords quantitative yields of esters [98SC1233]. The use of smaller amounts of alcohol gives rise to lower yields.

$Fe(ClO_4)_3(ROH)_6/SiO_2$

Grinding this "supported regent" with an equimolar amount of carboxylic acid provides esters [98SC2821]. This protocol is operationally simple, but requires a stoichiometric amount of the promoter.

$NaHSO_4/SiO_2$

Aliphatic carboxylic acids are esterified preferentially over aromatic ones at room temperature with the aid of $NaHSO_4$ supported on silica gel (Scheme 1-20) [2000SL59].



Scheme 1-20

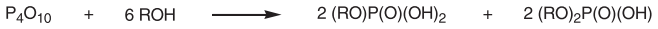
Phosphorus oxides

Phosphorus pentoxide can be used for dehydration between carboxylic acid and alcohol. Heating of a mixture of alcohol, carboxylic acid, and P_4O_{10} is the simplest treatment [83JOC3106]. In addition to intermolecular esterification, lactonization is also achievable [91T10129, 91H(32)669]. This procedure can be modified by initial treatment of P_4O_{10} with alcohol to furnish an equimolar mixture of mono- and dialkylphosphates (Scheme 1-21) [83T1475]. In practice, isolation of these compounds is not necessary, a carboxylic acid being added to the mixture to produce the ester.

Experimental Procedure Scheme 1-21 [83T1475]

Esterification of a Liquid Carboxylic Acid: Glacial acetic acid (0.6 mole, 36.0 g) is added to the alkyl phosphate reagent (0.1 mole equivalent), and the reaction mixture is heated at reflux on a water bath for 3 h, with ice-cold water being circulated through the condenser. The reaction mixture is allowed to come to room temperature and extracted with ether (2×100 mL), and the organic layer is washed (aq. $NaHCO_3$, 2×100mL) and dried (Na_2SO_4). After removal of the solvent, the residual liquid is distilled through a fractionating column to yield methyl acetate (39 g, 90%), b.p. 54–56°.

Esterification of Solid Acid: Phenylacetic acid (82.2 g, 0.6 mol) is added to the alkyl phosphate reagent. In this case, any required alkanol is added to ensure homogeneous solution. The reaction mixture is heated at reflux for 3 h. It is then diluted with water (100 mL) and extracted with ether (2×100 mL), and the organic layer is washed (aq. $NaHCO_3$, 2×100 mL) and dried (Na_2SO_4). After removal of solvent, the residual liquid is distilled off to yield ethyl phenylacetate (85 g, 86%), b.p. 224–226°.



Scheme 1-21

A flow system that uses a vertical column is available, although a mixture of $P_4O_{10}/CuSO_4/Na_2SO_4$ is better than simple P_4O_{10} for this purpose [83JOC3106]. $CuSO_4$ serves both as a water scavenger and, through its color change, as an indicator of the progress of the reaction and the duration of the reactivity of the column,

while Na_2SO_4 retains the desired porosity and is useful for sustained reactivity of the column with its water-absorbing property. This packing reagent is also used for a batch reaction [83JOC3106; 87JIC34].

Experimental Procedure [83JOC3106]
Mixtures of various organic acids (0.05 mol), freshly prepared packing reagent (2.5 g), and ethanol (50 mL) are taken in Erlenmeyer flasks and left at room temperature for 20 h with occasional shaking. Removal of the solvent (ca. 30 mL) on a steam bath (15–20 min) leaves a residue, which furnishes the ethyl esters on conventional workup.

Ph_3SbO/P_4S_{10}
The characteristic feature of this catalyst system is that the reaction temperature (25–85 °C) is lower than those used in other procedures [91AOMC513].

$H_3PO_{40}W_{12} \cdot xH_2O$
Various bromoacetates are obtained by treatment of bromoacetic acids (1.0 mol) with alcohol (1.1 mol) in the presence of 12-tungstophosphoric acid [91AOMC183].

Experimental Procedure [91AOMC183]
Bromoacetic acid (1.0 mol), alcohol (1.1 mol), benzene (70 mL), and $H_3PO_{40}W_{12} \cdot xH_2O$ (0.4 g) are placed in a 250 mL round-bottomed flask fitted with a Dean-Stark condenser and the mixture is heated at reflux for 3–4 h until 15–18 mL of water have been collected. The crude solution is separated, washed with water, twice with a saturated sodium bicarbonate solution, and finally again with water, and is then dried over magnesium sulfate and sodium sulfate (1 : 1), filtered, and distilled under normal pressure or under vacuum.

$H_4SiW_{12}O_{40}/C$
Heteropoly acids often leak out of catalyst supports, because these acids are extraordinary soluble in water and several organic solvents. Activated carbon can tightly immobilize or entrap a certain amount of the acids. With $H_4SiW_{12}O_{40}$ entrapped in carbon, vapor-phase esterification of acetic acid with ethanol can be conducted efficiently [81CL663].

$ZrO_2 \cdot nH_2O$ and Mo-ZrO_2
Hydrous ZrO_2, which catalyzes reactions between carboxylic acids and alcohols, exhibits the following advantages: (1) the catalyst is easily prepared and stable in air, and (2) the reaction does not require water-free conditions [89BCJ2353]. The catalytic activity is further improved by use of Mo-ZrO_2 mixed oxide, because electron-deficient sites are formed by introduction of Mo cations into the lattice of the solid ZrO_2 [98SC3183].

Experimental Procedure [89BCJ2353]
General Procedures for Vapor-Phase Reactions: The catalytic esterification is carried out in a glass-flow reactor (6.5 mm in diameter) with a fixed-bed catalyst: flow rate of

nitrogen gas = 60 mL min^{-1}; catalyst = 2.0 g, 24–60 mesh; reaction temperature = 135–280 °C. A mixture of a carboxylic acid, an alcohol, and a hydrocarbon as an internal standard is fed into the reactor (5 or 10 mL h^{-1}) with the aid of a microfeeder. In some cases benzene is also added, to dilute the reaction mixture. The activity and selectivity of the reaction are determined after a steady state has been reached. The products are then analyzed by gas chromatography (capillary column, PEG 20M 30 m). The products are identified by comparison of their retention times with those of authentic samples.

General Procedures for Liquid-Phase Reaction: The catalyst (2.0 g), a carboxylic acid, an alcohol, and a hydrocarbon as an internal standard are placed in a 25 mL round-bottomed flask fitted with a reflux condenser. The contents are then heated under gentle reflux. In some reactions toluene is added to the solution, in order to raise the reaction temperature. In some cases the reaction mixture is placed in an oil bath kept at 77.0 ± 0.1 °C. The reaction mixture is worked up after 5 hours, and the products are analyzed by gas chromatography.

Graphite bisulfate ($C_{24}^{+}HSO_4^{-} \cdot 2\,H_2SO_4$)

This intercalation compound, which can be prepared by electrolysis of 98% H_2SO_4 with a graphite anode, brings about reaction between alcohol and carboxylic acid in a 1 : 1 ratio at room temperature [74JACS8113]. The yields are usually over 90%.

Natural Montmorillonite

Another intercalation compound, natural montmorillonite is useful for selective acylation of various functionalized primary and secondary alcohols [2000GC67].

Experimental Procedure [2000GC67]

In a typical procedure, 1-phenylethanol (5 mmol) and glacial acetic acid (50 mmol, corresponding to a 1 : 10 molar ratio; 1 : 3 alcohol/carboxylic acid ratio for other solvent systems) are heated at reflux in the presence of Montmorillonite catalyst with stirring (100 mg) for 15 min. After completion of the reaction, monitored by TLC or GC, the reaction mixture is filtered and the filtrate is concentrated to obtain the pure product. The product is analyzed by ^1H NMR, while the catalyst is washed with ethyl acetate and dried in an oven at 120 °C for 1 h and then reused.

Solid acid with microwave irradiation

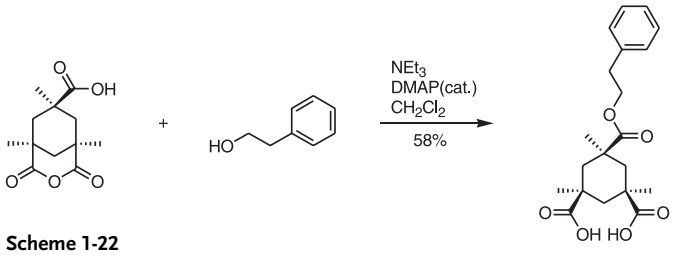
Esterification by solid acid catalysts is accelerated by microwave irradiation [99SL608]. Microwave irradiation in continuous flow systems is also feasible [2000JOC1210].

1.1.3 Base Activators

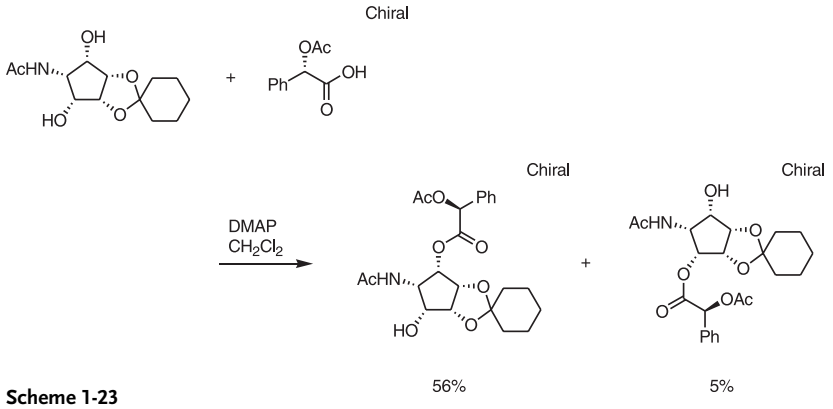
Base-mediated reactions to produce esters are catalytic on some occasions but noncatalytic on others, so both cases are dealt with together in this section. The basic catalysts are not suitable for esterification because esters are hydrolyzed when the reac-

tion mixture is subjected to aqueous workup. Nonetheless, a few non-aqueous methods are available for highly functionalized substrates. ω-Hydroxy acids undergo lactonization upon exposure to KOH/KOMe/glycerin [97SL600].

Another technique is provided by use of DMAP (4-dimethylaminopyridine). A Kemp's triacid derivative is transformed into a monoester by treatment with Et_3N/DMAP (cat.) (Scheme 1-22) [97BCJ1895]. The synthesis of deoxy derivatives of α-mannosidase inhibitor mannostatin A makes use of the DMAP methodology as a key step (Scheme 1-23) [99BMC1499].



Scheme 1-22



Scheme 1-23

Diphenylammonium triflate is an efficient catalyst for mediation of condensation between alcohol and carboxylic acid in a 1:1 ratio [2000TL5249]. The reaction usually affords greater than 90% yields of esters simply on treatment of the reactants with 1 mol % of the catalyst in refluxing toluene. After the reaction is complete, the solvent is evaporated, and column chromatography of the residue furnishes the esters.

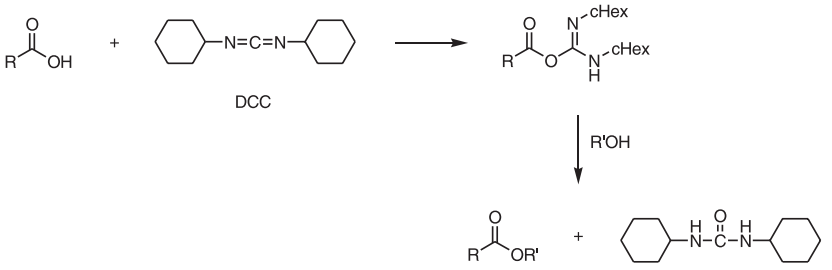
Experimental Procedure [2000TL5249]

3-Phenylpropionic acid (150 mg, 1.0 mmol), 1-octanol (130 mg, 1.0 mmol), and diphenylammonium triflate (3.2 mg, 0.01 mmol) are heated (80 °C) in toluene for 4 h. Evaporation of toluene (ca. 40 °C) under reduced pressure gives the crude material, which is purified by column chromatography (hexane/ether 10:1) to give the desired carboxylic ester (244 mg, 93%).

1.1.4
Carbodiimide Activators

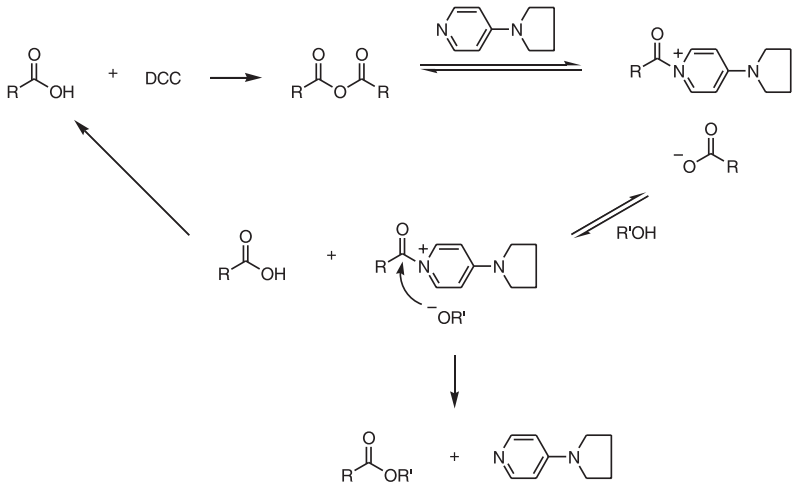
The use of DCC (dicyclohexylcarbodiimide) as a promoter represents one of the most versatile esterification methods. Although this reagent is irritant to skin and a stoichiometric dosage or more is necessary, this procedure enjoys various advantages. The reaction usually proceeds at room temperature, and the reaction conditions are so mild that substrates with various functional groups can be employed. The reaction is not sensitive to the steric bulk of the reactants, allowing production of esters of tertiary alcohols. As such, a wide range of applications has been achieved in the fields of natural products, peptides, nucleotides, etc., a literature survey finding about 400 references (see the database disc).

The application of the DCC method in pure organic synthesis dates back to 1967 [62CRA945]. The following mechanism for this reaction is suggested (Scheme 1-24).



Scheme 1-24

This original procedure, however, unfortunately suffers from some drawbacks: yields are not always high and undesirable *N*-acylureas are occasionally formed. These drawbacks can be overcome by addition of catalytic amounts of *p*-aminopyridines [78AG(E)522; 78TL4475]. As a result, methyl or *p*-nitrophenyl esters of pivalic and 2,4,6-trimethylbenzoic acids are obtainable. *tert*-Butyl esters of 3,5-dinitrobenzoic acid and glycerol tristearate can also be prepared: these esters are not accessible without the use of *p*-aminopyridines. However, combinations of *tert*-butyl alcohol and more sterically demanding acids such as adamantanecarboxylic acid or 1-phenylcyclohexane-1-carboxylic acid fail to afford the desired esters. The mechanism of the catalyzed reaction is depicted in Scheme 1-25 [78TL4475]. The carboxylic acid is first converted by DCC into an anhydride, which then forms an acylpyridinium species with DMAP. Nucleophilic attack on the acyl group by $R'O^-$ produces the ester concomitantly with regeneration of DMAP, together with a half quantity of RCOOH, which is again subjected to the reaction with DCC.

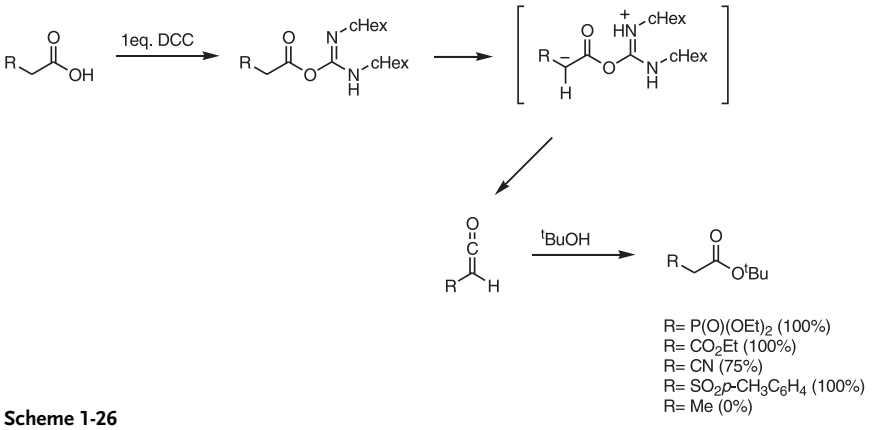


Scheme 1-25

Experimental Procedure [78AGC(E)522]

DMAP (30–110 mg) and alcohol or thiol (20–40 mmol; 10 mmol with alcohols or thiols that are not easily removable without significant loss; 3.4 mmol with glycerol) are added to a stirred solution of carboxylic acid (10 mmol) in anhydrous CH_2Cl_2 (10 mL; DMF in cases of sparingly soluble acids). DCC is added at 0°C to the reaction mixture, which is then stirred for 5 min at 0 °C and 3 h at 20°C. Precipitated urea is then filtered off and the filtrate is evaporated in vacuo. The residue is taken up in CH_2Cl_2 and, if necessary, filtered free of any further precipitated urea. The CH_2Cl_2 solution is washed twice with 0.5 N HCl and with saturated $NaHCO_3$ solution, and is then dried over $MgSO_4$. The solvent is removed by evaporation, and the ester is isolated by distillation or recrystallization.

When carboxylic acids carry a strongly electron-withdrawing group such as COOR, $P(O)(OEt)_2$, CN, or RSO_2 at the position α to the carboxyl group, sterically hindered alcohols, including tertiary alcohols, undergo smooth esterification (Scheme 1-26) [2001OL3733]. The reaction can be explained by the intermediacy of the corresponding ketene, which is highly electrophilic but relatively sterically undemanding.



Scheme 1-26

Addition of $Sc(OTf)_3$ to a mixture of DIPC (diisopropylcarbodiimide) or EDC (1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide/DMAP effects reaction between sterically bulkier reactants such as *tert*-butyl alcohol/*t*-Boc-(*S*)-(–)-Glu(OBz) or trimethylbenzoic acid and $Me_2C(OH)COOEt$/4-nitrobenzoic acid [98JOC7559].

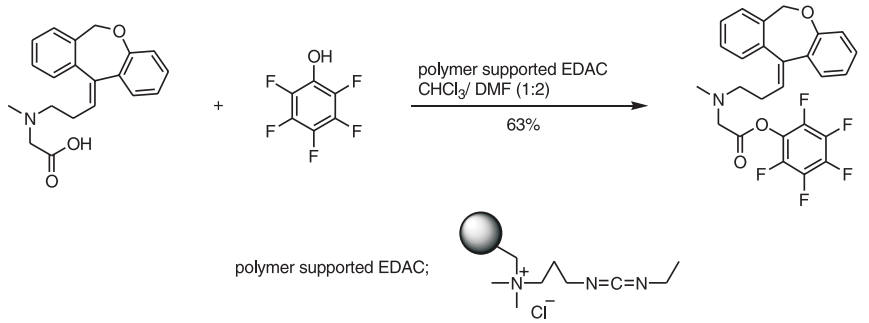
Experimental Procedure [98JOC7559]

Method A (acid in excess): A suspension of *tert*-butanol (0.094 mL, 1 mmol), scandium triflate (0.30 g, 0.6 mmol), $ClCH_2COOH$ (0.28 g, 3 mmol), and DMAP (0.37 g, 3 mmol) in anhydrous methylene chloride (10 mL) is cooled to –8 °C in an ice-salt bath for 30 min. DIPC (0.49 mL, 3.1 mmol) is added, and the reaction mixture is stirred at –8 °C for 30 min and then allowed to warm to room temperature over 2 h. The reaction mixture is filtered to remove any insoluble material, and the filtrate is washed with HCl (0.1 N, 2 × 20 mL), sodium bicarbonate (0.1 N, 2 × 20 mL), and distilled water (20 mL). The organic phase is dried ($MgSO_4$) and the solvent is removed under reduced pressure. Trace amounts of DIPU are precipitated with ether and removed by filtration. Evaporation of the ether gives the corresponding pure ester (0.14 g, 95%).

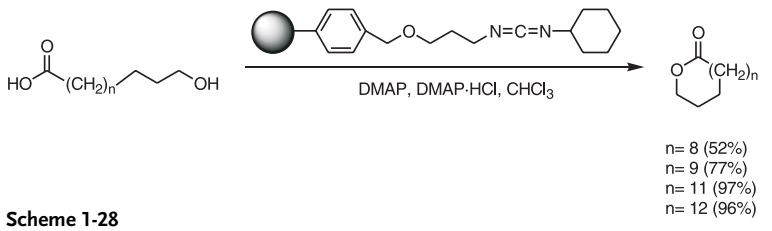
Method B (alcohol in excess): A suspension of *tert*-butanol (1.9 mL, 20 mmol), scandium triflate (0.3 g, 0.6 mmol), *t*-Boc-(*S*)-(–)-Glu(OBz) (0.34 g, 1 mmol), and DMAP (0.61 g, 5 mmol) in anhydrous methylene chloride (10 mL) is cooled to –8°C in an ice-salt bath for 30 min. EDC (0.38 g, 2 mmol) is added, and the reaction mixture is stirred at –8°C for 30 min and then allowed to warm to room temperature over 2 h. The reaction mixture is filtered to remove any insoluble material, and the filtrate is washed with HCl (0.1 N, 2 × 20 mL), sodium bicarbonate (0.1 N, 2 × 20 mL), and distilled water (20 mL). The organic layer is dried ($MgSO_4$), and the solvent is removed under reduced pressure. The product is further purified by chromatography on a silica gel column with 0–5% methanol in methylene chloride as the eluent to give the corresponding pure ester (0.32 g, 80%).

Since a stoichiometric amount of carbodiimide or more (sometimes 10 equivalents) must be used, immobilization of this reagent is highly convenient for separa-

tion from the reaction mixture. EDAC (ethyl dimethylaminopropylcarbodiimide) supported on polystyrene-divinylbenzene resin is effective for synthesis of esters for use in bioconjugation (Scheme 1-27) [95TL8345]. A variety of carboxylic acid haptens can be esterified with *N*-hydroxysuccinimide or pentafluorophenol. Of particular significance is the extension of this method to extremely water-soluble active esters that cannot be purified by conventional extraction methods. DCC analogues can be immobilized as well, and as such utilized for macrolactonization of *seco* acids (Scheme 1-28) [2000TL8673].



Scheme 1-27



Scheme 1-28

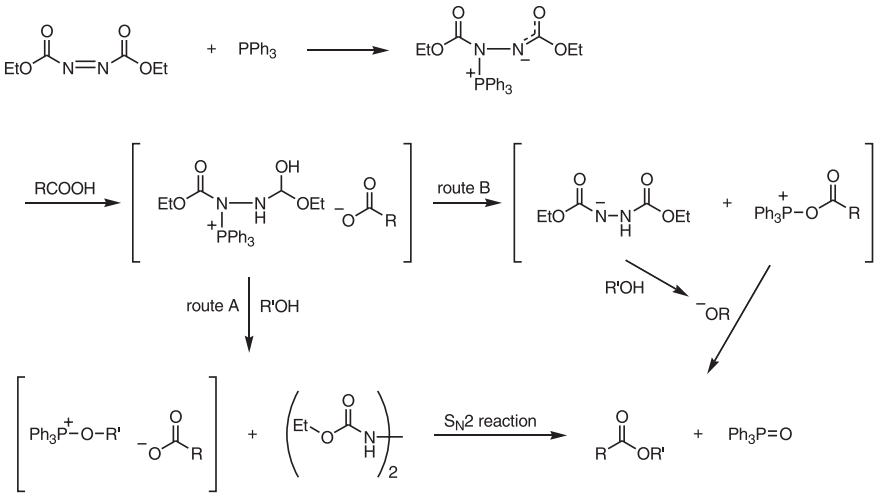
1.1.5 The Mitsunobu Reaction

The Mitsunobu reaction is another popular technique, although the employment of more than a stoichiometric amount of reagent is necessary [67BCJ2380; 81S1]. The reaction between alcohols and carboxylic acids proceeds smoothly under neutral conditions at or below room temperature. Of great significance are its high chemo-, stereo-, and regioselectivities. Typically, a mixture of alcohol and carboxylic acid is treated with DEAD (diethyl azodicarboxylate) and Ph_3P (Scheme 1-29) [88JACS6487]. The initial step is addition of Ph_3P to DEAD to give a zwitterion, which then reacts with carboxylic acid to afford a phosphonium carboxylate. Reaction of this intermediate with alcohol directly generates a key intermediate, alkoxyphosphonium salt (route A), which undergoes nucleophilic attack by the carboxylate ion to furnish the desired ester. Importantly, the high stereoselectivity arises from the complete inversion at the

alkoxy carbon center in the last S_N2 step. An alternative route is possible (route B) [96JOC2967]. After addition of a carboxylic acid to DEAD, an acyloxyphosphonium salt is formed, and this is attacked by an alkoxide ion generated by interaction between an alcohol and the hydrazide ion. With the use of primary-secondary diols, almost selective esterification at the primary position can be achieved in preference to the secondary one. The selectivity is explained by the steric hindrance of the three bulky phenyl groups attached to the phosphorus atom.

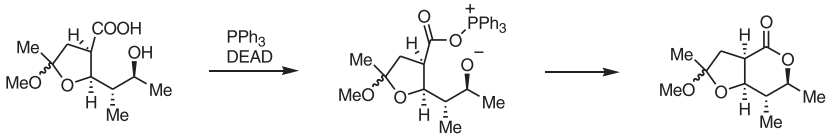
Experimental Procedure [67BCJ2380]

General Procedure for Mitsunobu Reaction. A solution of triphenylphosphine (0.01 mol) in ether (10 mL) is added drop by drop to a solution of diethyl azodicarboxylate (0.01 mol) and carboxylic acid (0.01 mol) in ether (10 mL), with vigorous stirring at room temperature. The reaction soon starts, and a white precipitate of triphenylphosphine oxide and diethyl hydrazodicarboxylate appears. After the solution has been kept standing overnight at room temperature, the precipitate is removed by filtration. The ether is removed from the filtrate, and the residue is filtered to remove a small amount of the remaining precipitates. The filtrate is then distilled to give the corresponding esters of the carboxylic acid.



Scheme 1-29

When the alcohol is sterically hindered, the acyloxyphosphonium intermediate in route B plays a key role. The acyloxy-alkoxy interchange is suppressed, and so the acyl carbon of the acyloxyphosphonium species is directly attacked by the alkoxy anion [2002JOC1751, 2002JOC1754]. In such cases the stereochemistry about the alkoxy carbon is retained, as shown in Scheme 1-30.



Scheme 1-30

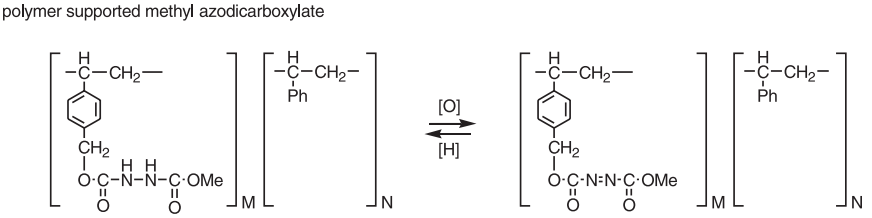
Despite its various advantages, the Mitsunobu process suffers from a serious problem due to the unavoidable use of large amounts of the reagents, the separation of by-products thus occasionally being tedious and problematic. Overcoming these problems is the biggest issue in this procedure. 1,2-Bis(diphenylphosphino)ethane is claimed to be a convenient replacement for Ph_3P because the resulting bis(phosphine oxide) is more readily removed, due to its more polar character [98TL7787]. Incorporation of an amino function in the phosphine, as in diphenyl(2-pyridyl)phosphine [88AJC1835] and (*p*-dimethylaminophenyl)diphenylphosphine [90SC2049] is the next strategy, as acidic workup can be used to remove phosphine oxides with an amino function. The use of di-*tert*-butyl azodicarboxylate coupled with diphenyl(2-pyridyl)phosphine is also more convenient, as the *tert*-butyloxycarbonyl group decomposes to isobutene and CO_2 upon acidic workup [99TL4497].

Experimental Procedure [88AJC1835]
Diisopropyl azodicarboxylate (1.97 ml, 10 mmol) is added dropwise with stirring to a cooled (0 °C) solution of diphenyl(2-pyridyl)phosphine (2.63 g, 10 mmol) and ethanol (0.69 g, 15 mmol) in ether (30 mL). Benzoic acid (1.16 g, 9.5 mmol) in the same solvent (10 mL) is then introduced. The reaction mixture is left to stir at room temperature overnight and cooled to –30 °C, and the by-products are removed by filtration. Residual amounts of the oxide remaining in solution are removed by washing with HCl (2 M, 2 × 25 ml). Distillation in a Kugelrohr apparatus affords the required ester (1.15 g, 80%).

Experimental Procedure [99TL4497]
A mixture of 3-chloro-5-methoxyphenol (79 mg, 0.5 mmol), diphenyl-2-pyridylphosphine (197 mg, 0.75 mmol), and benzyl alcohol (54 mg, 0.5 mmol) is dissolved in anhydrous THF under an atmosphere of nitrogen. Di-*tert*-butyl azodicarboxylate (172 mg, 0.75 mmol) is added to this solution in one portion, and the resulting mixture is stirred at room temperature for one day. GCMS analysis of an aliquot shows complete conversion of starting material into the desired product after 24 h. A solution of hydrogen chloride in dioxane (4 M, 2 ml) is added to the mixture, and after this has been stirred for one hour the excess solvent is evaporated. The residue is dissolved in ether or dichloromethane and shaken vigorously with magnesium sulfate, and the solvent is evaporated. Flash column chromatography (20% ethyl acetate in hexanes) gives the desired benzyl ester as a pale yellow oil (86 mg, 69%).

Polymer support of alkyl azodicarboxylates is also useful (Scheme 1-31) [89JACS3973]. Polystyrene-supported methyl azodicarboxylate obtained from 1%

cross-linked hydroxymethyl polystyrene resin can be used for various Mitsunobu reactions, with yields comparable to those obtained with soluble dialkyl diazodicarboxylates. Thanks to the lesser solubility of the polymer-supported reagent, purification of the resulting esters and recovery of the reagent are very easy. Also noteworthy is that the recovered reduced resin can be re-oxidized to the azodicarboxylate form and used again.



Scheme 1-31

The use of fluorous azodicarboxylate derivatives is another means by which the separation problem may be solved (see Part II). Bistridecafluorooctyl azodicarboxylate is one such reagent, readily recoverable from the reaction mixture simply by extraction with FC-72 (perfluorohexanes) [2002TL2807]. The combined use of fluorous azidocarboxylate and tertiary phosphine provides further elaboration of separation [2002T3855].

The activity of Mitsunobu reagents may be enhanced. Azodicarboxamides in place of esters can activate less reactive acids. 1,1′-(Azodicarbonyl)dipiperidine/Ph_3P [93TL1639] and *N,N,N′*,N′-teramethylazodicarboxamide/Bu_3P [95TL2529] effect acylation of various secondary alcohols, including steroids.

Experimental Procedure [93TL1639]

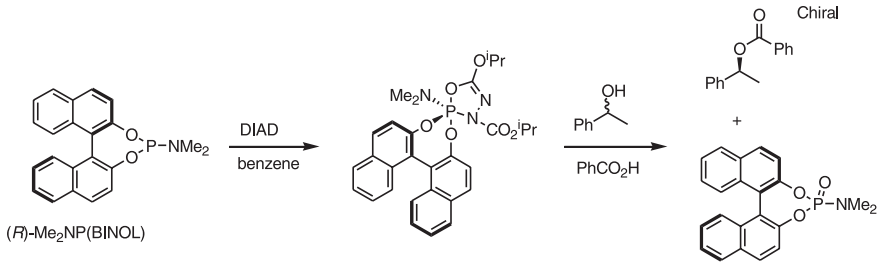
Under argon atmosphere, alcohol (1 mmol), tributylphosphine (1.5 mmol), and acid (1.5 mmol) are successively dissolved in dry benzene (3 mL) with stirring at 0 °C, and solid 1,1′-(azodicarbonyl)dipiperidine (ADDP, 1.5 mmol) is added to the solution. After 10 min, the reaction mixture is brought to room temperature and the stirring is continued for 24 h. Hexane is added to the reaction mixture, and precipitated dihydro-ADDP is filtered off. The product is purified by SiO_2 column chromatography after evaporation of the solvent in vacuo.

Experimental Procedure [95TL2529]

Under dry Ar atmosphere, solid *N,N,N′*,N′-tetramethylazodicarboxamide (TMAD) (1.5 mmol) is added in one portion, at 0 °C with stirring, to a dry benzene solution (3 mL) of an alcohol (1 mmol), tributylphosphine (1.5 mmol), and a carboxylic acid (1.5 mmol). After 10 min, the reaction mixture is heated to 60 °C and stirred at this

temperature for 24 h, during which time dihydro-TMAD crystallizes out. The epimeric mixture of esters obtained is analyzed as follows. The inversion ratios are determined by capillary GLC or ^{1}H NMR on the crude products obtained by the evaporation of the solvent in vacuo. The (combined) yields are obtained after product isolation by SiO_2 column chromatography.

As shown in Scheme 1-32, treatment of chiral trivalent alkoxyphosphorus compounds with DIAD results in cycloaddition rather than formation of a zwitterion [95JCS(P1)2961]. The newly formed adduct effects Mitsunobu-like esterification. Unfortunately, however, neither yields nor *ee*s of the esters are particularly high: ~50% yields and < 39% *ee*s.

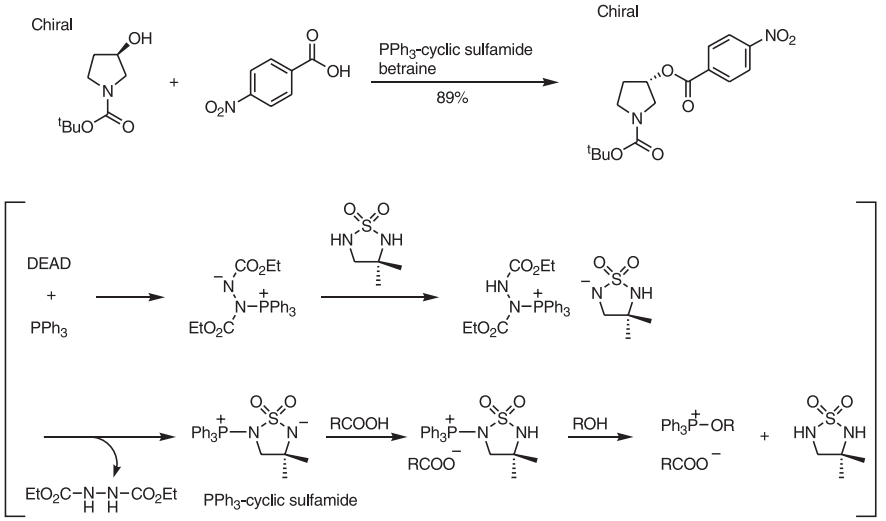


Scheme 1-32

Since the alkoxyphosphonium salt is the key intermediate in the standard Mitsunobu reaction, variants to generate this species through other routes have been investigated. Triphenylphosphine-cyclic sulfamide betaine, formed by treatment of cyclic sulfamide with DEAD/Ph_3P, is stable in the solid state for several months (Scheme 1-33) [94JOC2289]. This compound can be used for a Mitsunobu-like coupling between alcohol and carboxylic acid.

Experimental Procedure Scheme 1-33 [94JOC2289]

The adduct of triphenylphosphine and 3,3-dimethyl-1,2,5-thiadiazolidine 1,1-dioxide (5.0 mmol) is added portionwise over 10 min to a stirred mixture of the alcohol (3.32 mmol) and carboxylic acid (5.0 mmol) in anhydrous solvent (30 mL), and the resulting clear (milky) solution is stirred at rt under nitrogen for several hours. Et_2O (150 mL) is added, and the organic phase is washed with water (40 mL), dilute aqueous K_2CO_3 (40 mL), and brine (40 mL), and is then dried ($MgSO_4$) and concentrated. Products are purified by flash chromatography on silica gel (hexane/CH_2Cl_2 or hexane/EtOAc).

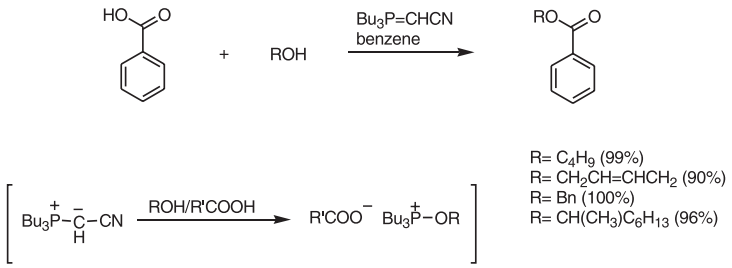


Scheme 1-33

Cyanomethylenetributylphosphorane mediates the direct condensation between alcohol and carboxylic acid through an alkoxy(tributyl)phosphonium salt intermediate (Scheme 1-34) [94TL5081]. This reagent is effective even for weak acids ($pK_a > 12$), which are not employable for the authentic Mitsunobu reaction.

Experimental Procedure Scheme 1-34 [94TL5081]

An alcohol (1 mmol) and a carboxylic acid (1.5 mmol) are successively dissolved in dry benzene (5 mL) with stirring under an argon atmosphere, and cyanomethylenetributylphosphorane (1.5 mmol) is added all at once, by syringe. The reaction mixture is heated with stirring in a sealed tube at 100 °C for 24 h. After evaporation of the solvent in vacuo, the product is purified by silica gel column chromatography.

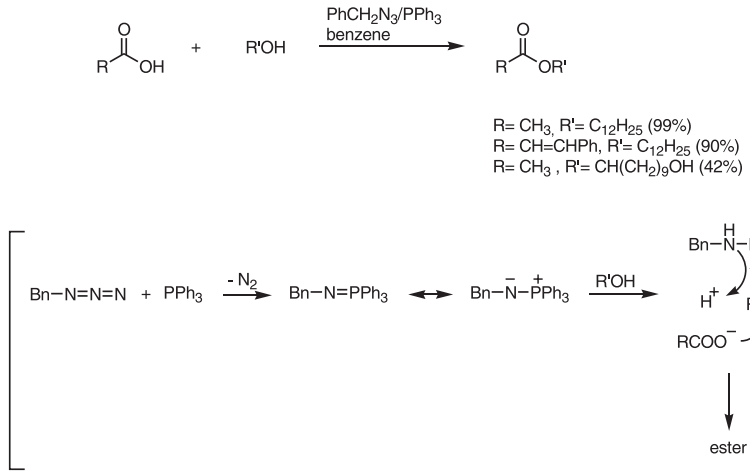


Scheme 1-34

Iminophosphorane functions as an alternative to the alkoxyphosphonium salt [92CE933]. Treatment of benzyl azide with triphenylphosphine (Staudinger reaction) affords an iminophosphorane, the positively charged phosphorus atom of which is

an activator of alcohol (Scheme 1-35). Heating of a mixture of alcohol, carboxylic acid, benzyl azide, and triphenylphosphine thus affords the desired esters in good to excellent yields.

Experimental Procedure Scheme 1-35 [92CE933]
A mixture of the alcohol, the carboxylic acid, benzyl azide (1.5 eq.), and triphenylphosphine (1.5 eq.) in THF is heated to reflux and concentrated to give a crude product, which is purified by column chromatography.



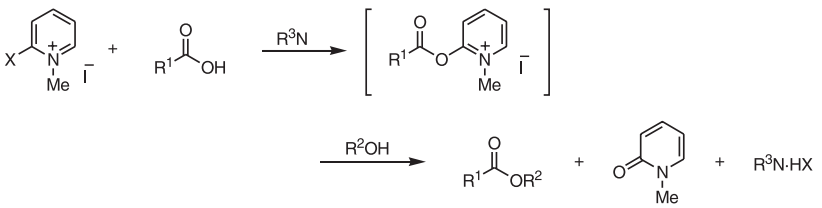
Scheme 1-35

1.1.6 Activation of Carboxylic Acids

2-Halo-1-methylpyridinium salts are another class of templates that induce condensation between alcohols and carboxylic acids (Scheme 1-36) [75CL1045, 80CL391]. Thus, treatment of equimolar quantities of alcohol and carboxylic acid with 1.2 moles of the salt in the presence of 2.4 moles of tertiary amine provides good to excellent yields of esters. This procedure is applicable to macrolide synthesis (Scheme 1-37) [76CL49]. Interestingly, the reaction proceeds in refluxing CH_3CN or CH_2Cl_2, at temperatures much lower than required with other techniques. Even medium-sized lactones (except for eight-membered rings) can be obtained in reasonable yields.

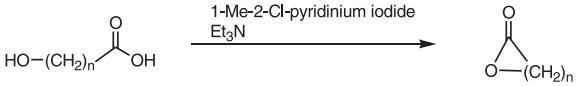
Experimental Procedure Scheme 1-36 [75CL1045]
A mixture of benzyl alcohol (216 mg, 2.0 mmol), phenylacetic acid (272 mg, 2.0 mmol), and tributylamine (888 mg, 4.8 mmol) in CH_2Cl_2 (2 mL) is added under an argon atmosphere to a CH_2Cl_2 (2 mL) suspension of 1-methyl-2-bromopyridinium iodide (720 mg, 2.4 mmol), and the resulting mixture is heated at reflux for

3 h. The dichloromethane-insoluble pyridinium salt is progressively dissolved as the reaction proceeds. After evaporation of the solvent under reduced pressure, the residue is separated by silica gel column or thin layer chromatography, and benzyl phenylacetate is isolated in 97% yield.



R^1= CH_3, R^2= Bn, X= Br (80%)
R^1= Ph, R^2= Bn, X= Br (80%)
R^1=R^2= Bn, X= Br (97%)
R^1= Bn, R^2= $CH(CH_3)$Ph, X= Cl (88%)

Scheme 1-36

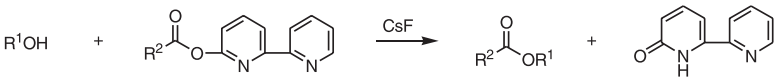


n= 5 (89%)
n= 6 (0%)
n= 7 (13%)
n= 10 (61%)
n= 11 (69%)
n= 14 (84%)

Scheme 1-37

More efficient and selective acylation is achieved by the use of 2,2′-bipyridyl-6-yl carboxylates (Scheme 1-38) [80CL563]. The reaction is promoted by CsF. Selective acylation on the primary alcohol takes place for primary-secondary diols, as well as for aromatic amino alcohols.

Experimental Procedure Scheme 1-38 [80CL563]
A mixture of 2,2′-bipyridyl-6-yl hexanoate (0.5 mmol), benzyl alcohol (0.6 mmol), and cesium fluoride (2–2.5 mmol, dried well at 140 °C for 3 h in vacuo before use) in acetonitrile is stirred for 1 d at room temperature, and benzyl hexanoate is isolated in 90% yield after workup and purification.

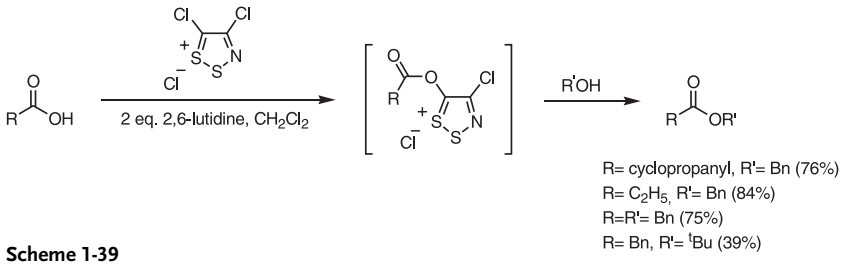


Scheme 1-38

It is claimed that 4,5-dichloro-1,2,3-dithiazolium chloride works at lower temperatures (–78 °C to room temperature) than the 2-halo-1-methylpyridinium chloride (Scheme 1-39) [93TL2737].

Experimental Procedure Scheme 1-39 [93TL2737]

A solution of the acid (0.87 mmol), the alcohol (0.87 mmol), and 2,6-lutidine (0.233 ml, 2.0 mmol) in dry CH_2Cl_2 (1 mL) is added at –78 °C, under an Ar atmosphere and over a period of 1 min, to a stirred slurry of the dithiazolium salt (0.207 g, 1.0 mmol) in dry CH_2Cl_2 (3 mL). The mixture is stirred at –78 °C for 2 h and allowed to warm to rt overnight (12 h). The reaction mixture is quenched with ice (5 g) and poured into CH_2Cl_2 (5 mL). The organic layer is washed with brine (2 × 10 ml), dried over $MgSO_4$, filtered through a plug of silica gel (CH_2Cl_2), and concentrated in vacuo. The residue is purified by silica gel chromatography.

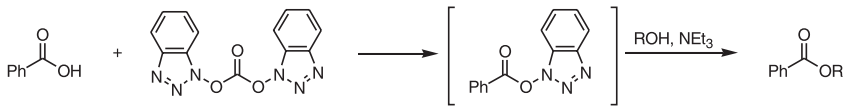


Scheme 1-39

Various carbonates such as 1,1′-[carbonyldioxy]dibenzotriazole (Scheme 1-40) [83S908] and di-2-pyridyl carbonate [84TL4943] are also useful.

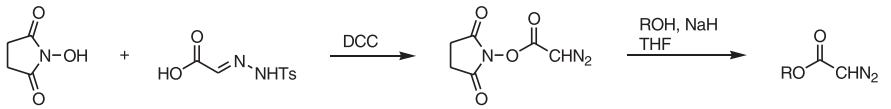
Experimental Procedure Scheme 1-40 [83S908]

A mixture of 1-hydroxybenzotriazole (41 g, 0.3 mol) and trichloromethyl carbonochloridate (18 mL, 0.15 mol) in benzene (200 mL) is heated at reflux with stirring for 2 h. The precipitate is filtered off, washed with benzene, and dried to give 1,1′-(carbonyldioxy)dibenzotriazole; yield: 31 g (70%); m.p. 150 °C (dec.; from benzene). A solution of 1,1′-[carbonyldioxy]dibenzotriazole (0.741 g, 2.5 mmol), benzoic acid (2.5 mmol), and pyridine (2.5 mmol) in *N*-methyl-2-pyrrolidone (4 mL) is stirred at room temperature for 1 h. The alcohol (2.5 mmol) and triethylamine (2.5 mmol) are then added. Stirring is continued two or three days, and the reaction mixture is subjected to conventional workup.



Scheme 1-40

A succinimidyl group is a good activator for carboxylic moieties, and so phenyl esters of diazoacetate can be obtained by treatment with succinimidyl diazoacetate, prepared from *N*-hydroxysuccinimide and glyoxylic acid tosylhydrazone (Scheme 1-41) [93JOC1641].

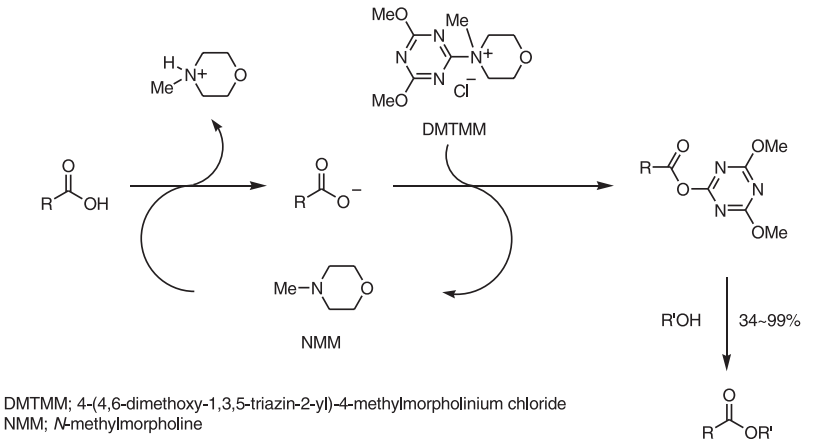


Scheme 1-41

Treatment of carboxylic acids with 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride in methanol, ethanol, or isopropyl alcohol in the presence of *N*-methylmorpholine affords the corresponding esters (Scheme 1-42) [99SL1255]. The amount of alcohol can be reduced to be nearly equimolar with the acid in THF as solvent.

Experimental Procedure Scheme 1-42 [99SL1255]

N-Methylmorpholine (0.24 mmol) is added at rt under nitrogen to a solution of carboxylic acid (0.20 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (0.40 mmol) in methanol (1 mL, dried over molecular sieves overnight). After the mixture has been stirred for 1.5 h, the solvent is evaporated, and the residue is extracted with ether. Purification by preparative TLC (hexane/AcOEt 2 : 1) affords methyl ester (0.186 mmol) in 93% yield.



DMTMM; 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
NMM; *N*-methylmorpholine

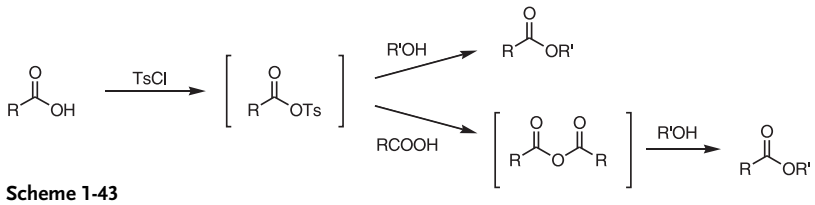
R= aromatic
R'= Me, Et, ^{i}Pr, Bn

Scheme 1-42

The use of sulfonyl halides for activation of carboxylic acids is a classical procedure. When carboxylic acid and alcohol are mixed in the presence of *p*-toluenesulfonyl chloride in pyridine, a variety of esters are produced [55JACS6214]. This technique is also employable for the synthesis of β-lactones from β-hydroxy acids [72JACS2000]. Two mechanisms are plausible, depending on the key intermediate actually reacting with the alcohol: (1) an acyl tosyl mixed anhydride, or (2) a symmetric acid anhydride resulting from further reaction of this mixed anhydride with carboxylic acid (Scheme 1-43). Methanesulfonyl chloride/Et_3N is also usable [82SC727], but yields are not always high because of a side reaction generating sulfene. This drawback can be overcome by use of Me_2NSO_2Cl, which has no α-hydrogen [2001TL7427]. Thus, treatment of an equimolar mixture of carboxylic acid and alcohol with the sulfamoyl chloride (2 equiv.) and DMAP (0.2 equiv.) provides esters in good yields. Sulfonyl chloride fluoride [81S790] and triflic anhydride [91JOC6488; 91JHC1581; 93SL119] also serve for the direct condensation.

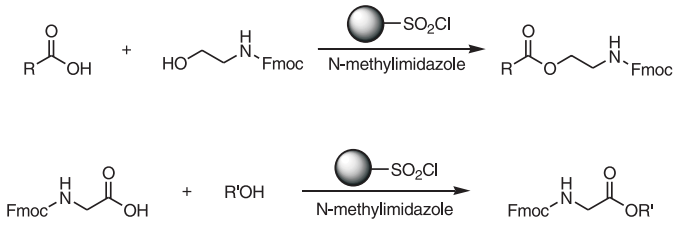
Experimental Procedure [55JACS6214]

The acid is dissolved in pyridine (20–50 parts, in some cases a salt separates), and benzenesulfonyl or toluenesulfonyl chloride (2 molecular equivalents) is added. The solution is chilled in ice, and the alcohol or phenol (1 molecular equivalent) is added. The solution is kept cold for about one hour and then poured into three or four volumes of an ice/water mixture. Solid esters are collected by filtration.



Scheme 1-43

Commercially available polystyrylsulfonyl chloride resin acts as a solid-supported ester condensation reagent (Scheme 1-44) [2001TL7783]. The purity of the esters is very good in the reaction between Fmoc-glycinol and carboxylic acids, but no reaction occurs with sterically hindered acids and electron-rich acids. On the other hand, Fmoc-glycine reacts more smoothly, except with *tert*-butanol.

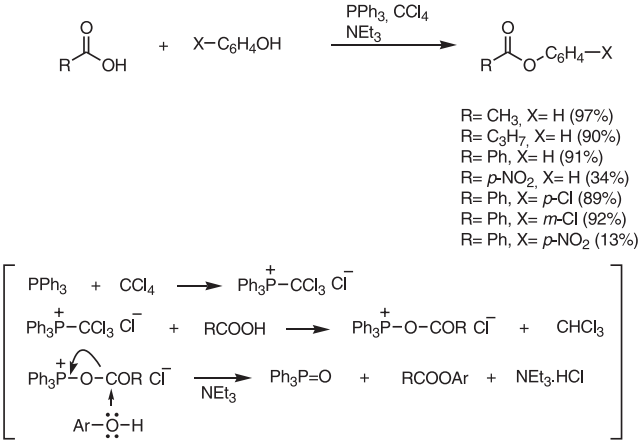


Scheme 1-44

The generation of acyloxy phosphorus intermediates, especially cationic species, is of great use for ester synthesis. Treatment of phenol and carboxylic acid with Ph_3P, CCl_4, and Et_3N provides phenyl carboxylates in reasonable yields, except in cases of reactants with strongly electron-withdrawing groups (Scheme 1-45) [81BCJ2227]. Similar acyloxy phosphonium intermediates are generated by treatment of triphenylphosphine with *N*-bromo- or -iodosuccinimide, further treatment of which with alcohol furnishes esters [94TL4415].

Experimental Procedure Scheme 1-45 [81BCJ2227]

A mixture of benzoic acid (24 mmol), phenol (20 mmol), carbon tetrachloride (24 mmol), triethylamine (24 mmol), and triphenylphosphine (24 mmol) in acetonitrile (30 mL) is stirred at room temperature for 4 h. After the acetonitrile has been evaporated, hexane is added to the residue. The hexane solution is filtered, removing the precipitated triphenylphosphine oxide and triethylamine hydrochloride, washed with an aqueous sodium hydroxide solution, and dried over anhydrous sodium sulfate, and then the hexane is removed. Subsequent distillation or recrystallization of the residual solid gives phenyl benzoate (3.6 g, 91%) as white crystals: mp 70–71 °C.



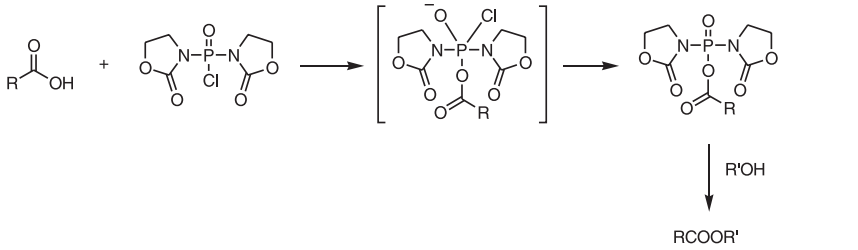
Scheme 1-45

Treatment of a tertiary ammonium salt of a carboxylic acid with *N,N*-bis(2-oxo-3-oxazolidinyl)phosphordiamidic chloride produces an acyloxy intermediate, which furnishes esters upon treatment with alcohol (Scheme 1-46) [84SC515].

Experimental Procedure Scheme 1-46 [84SC515]

Triethylamine (11 mmol) is added to a solution of the acid (5.5 mmol, or 10 mmol, via the anhydride) in 10 mL of solvent (acetonitrile, dichloromethane, dimethylacetamide). Complete dissolution of the mixture takes place easily, except in cases in which 5 mL of solvent are used. Subsequent addition of the alcohol (5 mmol or 20 mmol) and *N,N*-bis(2-oxo-3-oxazolidinyl)phosphordiamidic chloride (5.5 mmol)

yields a white precipitate of triethylammonium hydrochloride, which is insoluble under these conditions. All reaction mixtures in acetonitrile are heated at reflux (1 h ~ 1.5 h) and the triethylammonium salt is dissolved. Reaction mixtures in dichloromethane or dimethylacetamide are kept for 1 h at room temperature. When the reaction time is over, sodium bicarbonate solution (10%, 10 ~ 20 mL) is added. Solids are filtered, washed with water until neutral, dried, and identified as the corresponding ester. Some esters are recovered from the organic layer (addition of 10 mL of dichloromethane needed), which is dried with sodium sulfate, filtered, and evaporated to dryness.

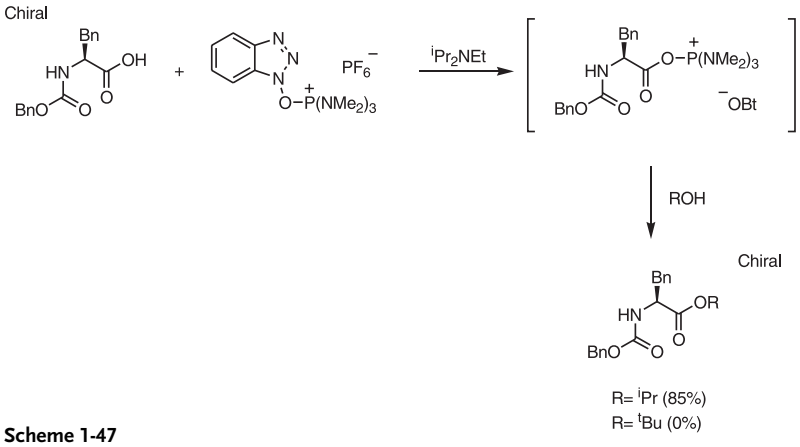


Scheme 1-46

Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate is a powerful reagent with which to generate an acyloxyphosphonium species (Scheme 1-47) [94TL5603]. Amino acids can thus be esterified with a nearly equal amount of alcohol (~1.1 equiv.), except in the case of *tert*-butanol. The acid- and base-sensitive protecting groups commonly used in peptide chemistry are tolerated in this procedure.

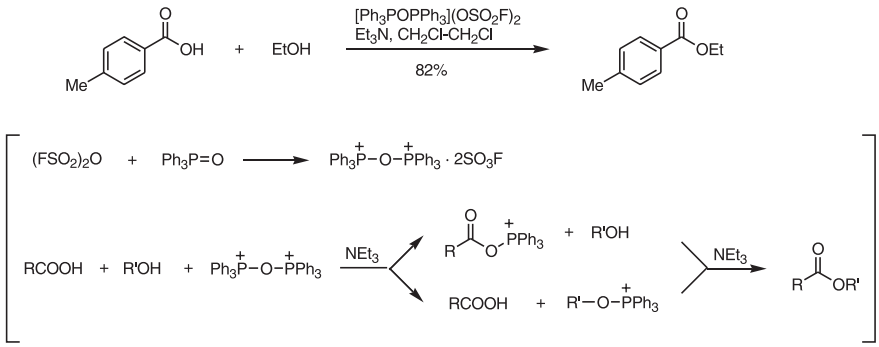
Experimental Procedure Scheme 1-47 [94TL5603]

An alcohol (1.1 mmol) is added at –20 °C (CCl_4/dry ice bath) under argon to a solution of an *N*-α-protected amino acid (1.0 mmol) and $^{i}Pr_2NEt$ (0.26 mL, 1.5 mmol) in CH_2Cl_2 (2 mL). After the mixture has been stirred at –20 °C for 15 min, benzotriazol-1-yloxytris(dimethylaminophosphonium hexafluorophosphate) (0.44 g, 1 mmol) is added, and the reaction mixture is left stirring overnight with gradual warming to rt. The next day (total reaction time = 10 to 14 h), the reaction mixture is suspended in CH_2Cl_2 and washed sequentially with buffer (pH 4, Aldrich), satd. aq. NaCl, satd. aq. $NaHCO_3$, and satd. aq. NaCl. Drying (Na_2SO_4) and concentration under vacuo affords the crude product, which is purified by silica gel flash chromatography.



Scheme 1-47

Diphosphonium fluorosulfonate effects dehydration between carboxylic acids and alcohols (Scheme 1-48) [94JFC(68)237]. This reagent has been prepared by mixing $Ph_3P{=}O$ and $(FSO_2)_2O$ and used in situ for esterification. It is assumed that the reaction proceeds through an acyloxy- or alkoxyphosphonium intermediate.



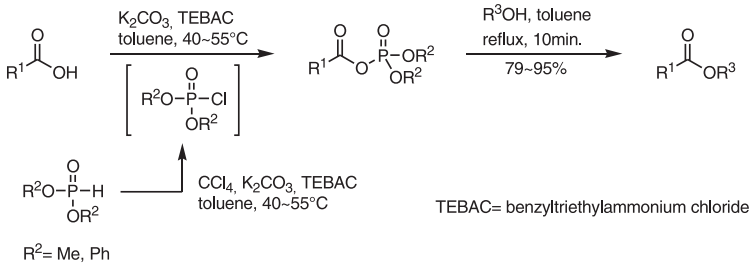
Scheme 1-48

Phase-transfer technology has been used to activate carboxylic acids with phosphoric acid diester chlorides generated in situ (Scheme 1-49) [98SC2761]. The reaction works even for hindered substrates such as pivalic acid, but is not applicable to phenylacetic acid and diphenylacetic acid.

Experimental Procedure Scheme 1-49 [98SC2761]

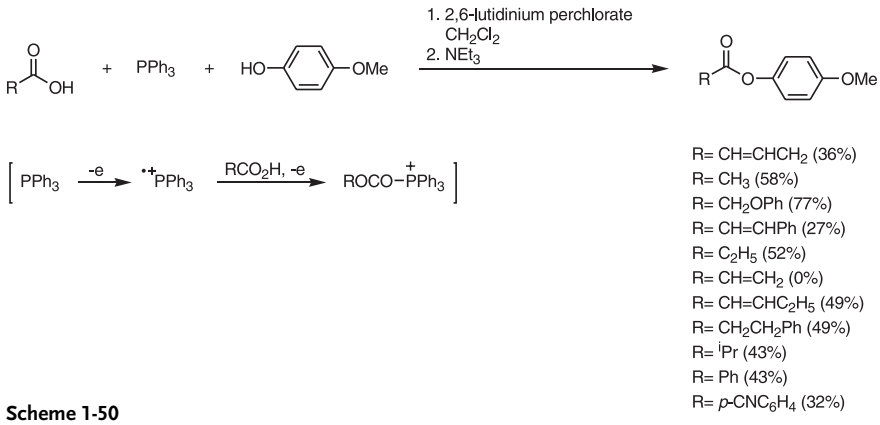
Phosphite (10–13 mmol) in toluene (15 mL) is added with stirring to a mixture of carboxylic acid (10 mmol), CCl_4 (100 mmol, 10 mL), K_2CO_3 (5.52 g, 40 mmol), and TEBAC (0.23 g, 1 mmol) in toluene (30 mL). The alcohol (10 mmol) is then added and stirring at reflux temperature is continued for 10 minutes. The esters obtained

are distilled under reduced pressure or purified by column chromatography on silica gel with benzene/acetone (9 : 1) as eluent.



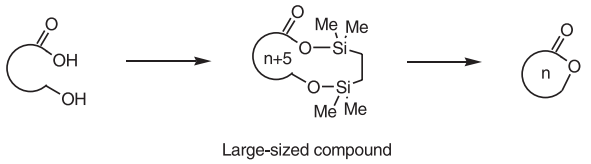
Scheme 1-49

Constant-current electrolysis, in an undivided cell, of Ph_3P in the presence of a carboxylic acid in CH_2Cl_2 containing 2,6-lutidinium perchlorate as a supporting electrode produces an acyloxyphosphonium ion, which is converted into the corresponding esters upon treatment with alcohol or phenol (Scheme 1-50) [91T767].

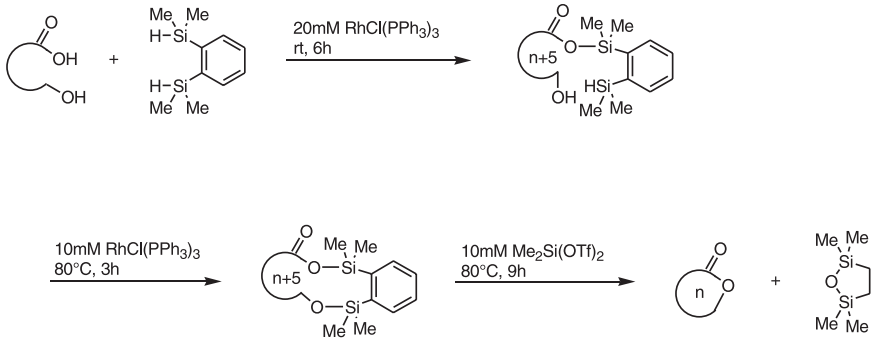


Scheme 1-50

Activation of carboxyl functions as silyl esters is also useful. Direct esterification of equimolar amounts of carboxylic acid and alcohol is achieved with catalysis by $TiCl(OTf)_3$ (0.1 mol%) in the presence of $(Me_2SiO)_4$ (2.0 equiv.) [95CL141]. A silyl carboxylate species is assumed to act as a key intermediate. Medium-sized lactones are accessible through a novel ring-contraction strategy (Scheme 1-51) [97CL187]. ω-Hydroxy acids are trapped by 1,2-bis(dimethylsilyl)benzene with $RhCl(PPh_3)_3$ catalysis, and the contraction of the resulting large-sized rings is achieved by treatment with $Me_2Si(OTf)_2$ (Scheme 1-52). Medium-sized lactones are obtained in high yields, except in the case of seven-membered rings.



Scheme 1-51

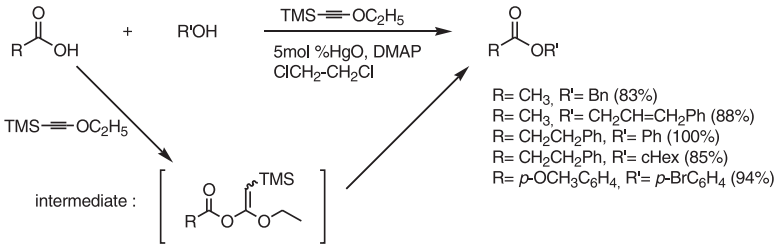


Scheme 1-52

Acyloxyketene acetals, obtainable from carboxylic acids and (trimethylsilyl)ethoxyacetylene by treatment with mercuric ion, afford esters upon treatment with alcohols (Scheme 1-53) [89S334]. Most conveniently, ketene acetals prepared in situ are straightforwardly converted into esters, lactones, and peptides.

Experimental Procedure Scheme 1-53 [89S334]

A solution of alcohol (1.0 mmol) and the ketene acetal (1.2 mmol) in an anhydrous solvent ($ClCH_2CH_2Cl$ or CH_2Cl_2, 2mL) is stirred under a nitrogen atmosphere for 25 min ~ 2 d. The mixture is concentrated by rotary evaporation and then by use of a high vacuum pump at 40 °C/0.4 mbar for 1 h to give the pure product.

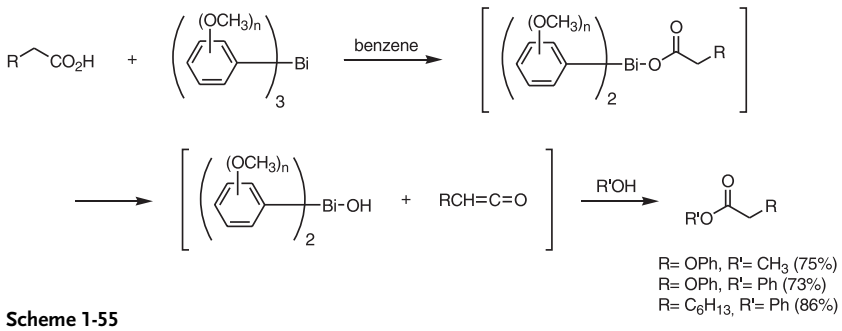


Scheme 1-53

Treatment of carboxylic acid with 1,1′-dimethylstannocene gives tin(II) carboxylates, which react with equimolar amounts of alcohols in refluxing xylene to afford the esters (Scheme 1-54) [83CL683].

Scheme 1-54

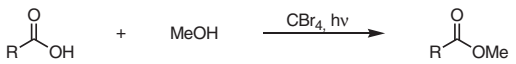
On heating with alcohols in the presence of tris(2-methoxyphenyl)- or tris(2,6-dimethoxyphenyl)bismuthines, carboxylic acids bearing α-hydrogens are readily converted into the corresponding esters in good yields (Scheme 1-55) [93CL815]. It is assumed that the reaction proceeds through ketene formation.



R= OPh, R'= CH_3 (75%)
R= OPh, R'= Ph (73%)
R= C_6H_{13}, R'= Ph (86%)

Scheme 1-55

Photoirradiation of carboxylic acids in methanol containing CBr_4 (0.05 equiv.) furnishes the corresponding methyl esters (Scheme 1-56) [2001TL301]. Interestingly, sp^3-tethered carboxylic acids undergo esterification smoothly under these conditions, while sp^2- and sp-tethered carboxylic acids are not esterified.



R= C_9H_{19} (90%)
R= $(CH_2)_7Br$ (98%)
R= CH_2CH_2cHex (96%)
R= cHex (40%)
R= Bn (96%)
R= $CH(CH_3)$Ph (95%)
R= Ph (14%)
R= $CH{=}CHCH{=}CHCH_2$ (99%)

Scheme 1-56

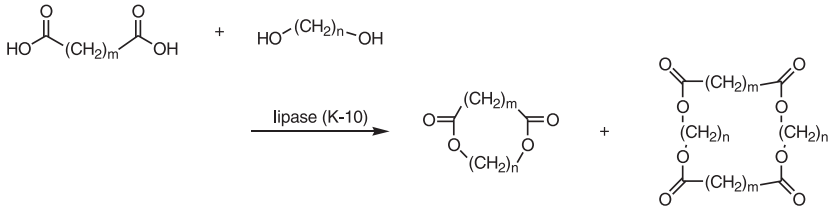
1.1.7 Enzymes

Enzymes play an important role in esterification technology. In particular, lipases have been widely used for the resolution of racemic alcohols and carboxylic acids through asymmetric hydrolysis of the corresponding esters. On the other hand, this technology is not straightforwardly applied to esterification because the esters are readily hydrolyzed in the presence of water. A new technology for use of enzymes in anhydrous organic solvent overcomes this difficulty. Yeast lipase (*Candida cylindracea*), for example, almost quantitatively converts a carboxylic acid and an alcohol into the corresponding ester in organic solvent, in a highly stereoselective manner when a chiral acid is employed [85JACS7072]. The advantages of this technique are that the stabilities of enzymes in organic solvents are much greater than in water, and that some substrates or products are unstable (e. g., toward racemization or other degradation reactions) in aqueous solution but stable in organic solvents. This technology has been extended to the intramolecular reaction of ω-hydroxy acids [87TL805]. Furthermore, the reaction between dicarboxylic acids and diols to arrive at macrolides is feasible through the use of lipase (K-10) (Scheme 1-57) [88JACS1999].

Experimental Procedure [85JACS7072]

Yeast Lipase-Catalyzed Production of Optically Active Esters: A solution of a racemic acid and an alcohol in a given solvent is treated with powdered lipase from *Candida cylindracea*. The suspension is placed in an Erlenmeyer flask and shaken on an orbit shaker at 250 rpm and at 30 °C to reach a certain degree of conversion. The enzyme is then removed by filtration, and the liquid phase is washed with three portions (each 80 mL) of aqueous $NaHCO_3$ (0.5 M). The obtained organic phase is dried with $MgSO_4$, and the solvent is evaporated in a rotary evaporator. To recover the ester, the remainder is distilled or chromatographed. The aqueous phase is acidified to pH 1 with HCl (6 N), and then the acids are extracted with three portions of CH_2Cl_2 (each 80 mL). The combined methylene chloride fractions are dried with $MgSO_4$, followed by evaporation of the solvent. The acids are isolated from the residue either by distillation or by liquid column chromatography.

Porcine Pancreatic Lipase-Catalyzed Production of Optically Active Esters: A solution of a racemic alcohol and 2,2,2-trichloroethyl butyrate (or 2,2,2-trichloroethyl heptanoate) in ether or heptane is dehydrated and then treated with powdered lipase from porcine pancreas. The suspension is placed in a round-bottomed flask and either shaken on an orbit shaker at 250 rpm or mechanically stirred at 300 rpm. When the degree of conversion reaches 45–50%, and the reaction virtually stops, the enzyme is removed by filtration. The liquid phase is dried with $MgSO_4$, followed by evaporation of the solvent in a rotary evaporator. The residue is subjected to liquid column chromatography; the esters are then separated from 2,2,2-trichloroethyl butyrate by distillation and the alcohols from 2,2,2-trichloroethanol by aqueous extraction of the latter. In another case, 2,2,2-trichloroethyl butyrate and trichloroethanol are first removed by distillation, and the alcohols are then separated from their butyric esters by liquid chromatography, or the remainder is separated by distillation.



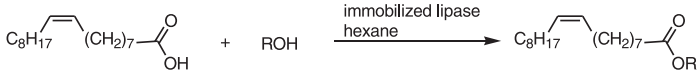
a; m= 12, n= 5 (18%)
b; m= 12, n= 16 (30%)
c; m= 10, n= 16 (56%)

a; 17%
b; 7%
c; 15%

Scheme 1-57

Supercritical carbon dioxide functions as an alternative to the organic solvent. Isoamyl acetate is obtained from isoamyl alcohol and ammonium acetate in the presence of lipase in supercritical carbon dioxide [97BMC259]. The ammonium salt is crucial because no ester is produced with acetic acid, indicative of delicate reaction conditions. However, isoamyl acetate is obtained in higher yields from the reaction in hexane, so it may consequently be concluded that the supercritical carbon dioxide methodology is not necessarily superior to that in organic solvent.

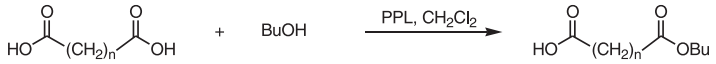
The simple use of enzymes in organic solvents is further improved by immobilization of the enzyme in microemulsion-base gels [92TL5891]. Through this technology, oleic acid can successfully be transformed into the corresponding esters (Scheme 1-58). Low, known concentrations of the catalyst may be immobilized in the water pool of a reverse micelle, which is frozen in a gel. It should be noted that small amounts of enzymes can be reused and the immobilization of enzymes in aqueous media is preferable because their solubility and activity are maximum.



R= $C_{12}H_{25}$ (62%)
R= Bn (52%)
R= C_2H_5 (61%)

Scheme 1-58

PPL-catalyzed esterification (PPL = porcine pancreatic lipase) allows selective formation of monoesters of α,ω-dicarboxylic acids (Scheme 1-59) [95BL939].



n= 4 (68%)
n= 6 (61%)
n= 7 (93%)
n= 8 (94%)
n= 14 (89%)

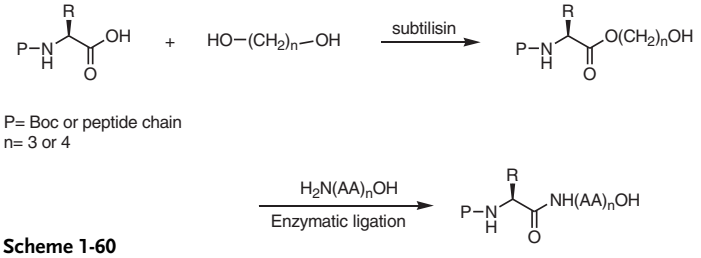
Scheme 1-59

Kinetic resolution of racemic alcohols is feasible. α-Substituted cyclohexanols [85TL1857] and various aliphatic alcohols [87JOC3477] are resolved through their reactions with alkanoic acids. Notably, the enantioselectivity of the lipase-catalyzed esterification of 2-(4-substituted phenoxy)propanoic acids is dramatically enhanced by addition of aqueous sodium dodecyl sulfate [2001CL912]. The effect of this additive is attributed to the increased conformational flexibility of lipase, which has a rigid conformation in organic solvent, preventing its active site from accepting a non-natural substrate with a structure significantly different from that of a natural product. The newly attained flexible conformation allows easier access of one of the enantiomers through induced fitting.

Experimental Procedure [87JOC3477]

The racemic alcohol (2.5 mmol), octanoic acid (8.0 mL, 50 mmol), and lipozyme (3.0 g) are swirled in either pentane or hexane (20 mL) at 30 °C for a period of 3–5 weeks. The progress of the resolution is monitored by derivatization of samples of the mixture directly with (*S*)-α-methylbenzyl isocyanate, followed by GLC analysis. The mixture is worked up by suction filtration; the resin is washed thoroughly with solvent and stored at 0–5 °C for future use. The combined organic phase is washed with NaOH (1.25 N) and then with H_2O. After drying ($MgSO_4$), the solvent is removed by careful distillation, and the concentrate is fractionally distilled to obtain the *S* alcohol and the *R* octanoate ester. The ester is saponified by heating with KOH (6 N, 25 mL) and methanol (20 mL) under reflux for 16 h. The resulting *R* alcohol is recovered from the saponification step in the usual manner and then distilled.

The synthesis of amino acid and peptide esters has been achieved. The serine protease substilisin Carlsberg efficiently catalyzes the specific formation of C^{α}-carboxyl 3-hydroxypropyl or 4-hydroxybutyl esters of certain Boc-amino acids and peptides in high-content 1,3-propanediol or 1,4-butanediol solution, with substrate specificity parallel to that of the normal hydrolytic reaction (Scheme 1-60). This approach can be coupled with kinetic-controlled reverse proteolysis in a two-step enzymatic peptide ligation scheme [2001OL4157].

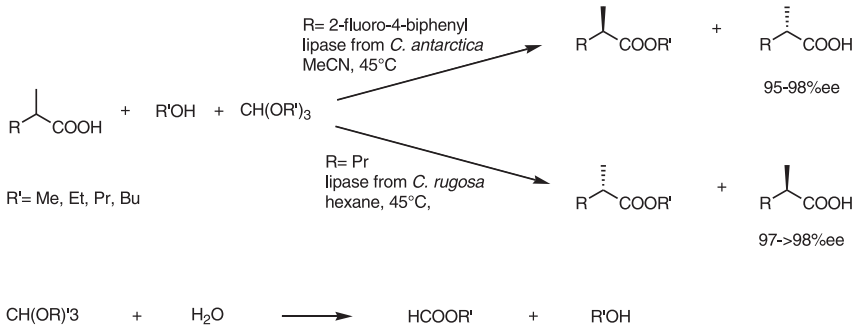


Scheme 1-60

The synthetic use of biocatalytic kinetic resolution is hampered by the reversible nature of the direct esterification of acids with alcohols. Addition of an orthoester

biases the equilibrium in favor of the ester side, due to the consumption of the water formed through hydrolysis of the orthoester (Scheme 1-61) [2001EJO1441].

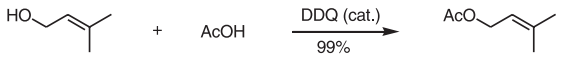
Experimental Procedure Scheme 1-61 [2001EJO1441]
Racemic flurbiprofen (41 mmol, 10 g) is added to a solution of CH_3CN (1 L) containing tripropyl orthoformate (123 mmol, 26.5 mL), 1-propanol (0.1 mL), and Novozym 435® (100 g). The mixture is incubated by shaking at 45 °C (300 rpm); the degree of conversion and the *ee* of unchanged flurbiprofen are followed by chiral HPLC analysis. After 6 days, conversion has reached 60% and the reaction is stopped by filtering off the enzyme. Removal of the solvent in vacuo leaves a residue that is partitioned between hexane and aq. $NaHCO_3$ (3 g in 200 mL of water). The organic phase is washed with water and dried over Na_2SO_4, and the solvent is removed to afford (*R*)-flurbiprofen propyl ester (6.8 g, yield 58%, *ee* 64%).



Scheme 1-61

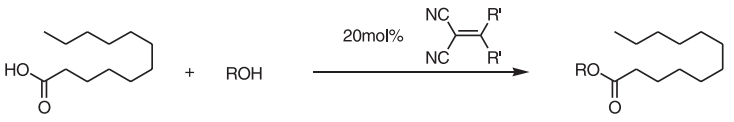
1.1.8
π-Acids

Treatment of allylic and tertiary benzylic alcohols with catalytic amounts of 2,3-dichloro-5,6-dicyanobenzoquinone in acetic acid affords the corresponding acetates (Scheme 1-62) [95SC2253]. It is believed that the reaction proceeds by initial oxidation of allylic alcohol to give a radical cation, which further undergoes carbon-oxygen bond cleavage to form a stable allylic cation species.



Scheme 1-62

Tetracyanoethylene and dicyanoketene dimethyl acetal are more versatile π-acids (Scheme 1-63) [97CL55]. Various aliphatic and aromatic carboxylic acids can be esterified.



R'= CN; TCNE (tetracyanoethylene)
R'= OMe; DCKDMA (dicyanoketene dimethyl acetal)

R= Me, Et, Pr, cHex, Bn, CH_2CH_2TMS

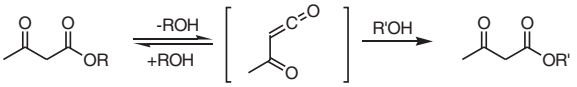
Scheme 1-63

1.2
Reaction with Esters: Transesterification

1.2.1
Without Activator

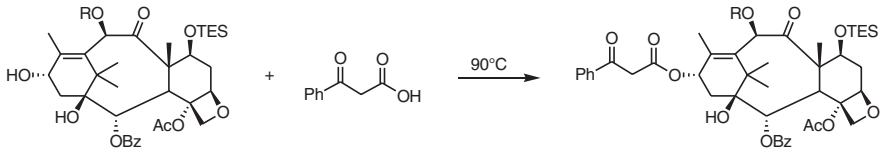
Ester-to-ester transformation through interchange of the alcohol components has been well known for a long time, as "transesterification". This reaction occupies a central position in organic synthesis, as important as direct esterification between carboxylic acid and alcohol. Both reactions are equilibrium processes, so what they have most deeply in common is the need to shift the reaction system to the product side to the greatest degree. In this respect, it may be generally said that esterification is more advantageous, because the water co-product is readily separable from the reaction medium, due to its incompatibility with organic solvents. This, on the other hand, is also an advantage for transesterification, in that water-sensitive materials are employable. Accordingly, once effective methods for removal of the produced alcohol from the reaction system are established, then transesterification is a better choice of reaction for ester production.

Although acid or base catalysts are usually necessary, transesterification without any promoters is ideal. β-Ketoesters are one such class of compounds, known for a long time to undergo thermal transesterification. Heating of alcohols such as alkanols, menthol, steroid alcohols, etc. in excess quantities of various β-ketoesters on a steam bath affords the new esters in yields better than 90% [51JACS4195]. The reaction can be explained as proceeding via an acylketene intermediate (Scheme 1-64) [90TL1401]. Accordingly, a more facile reaction takes place when *tert*-butyl acetoacetate is employed as a starting material, because of its high susceptibility to thermolysis [91JOC1713].



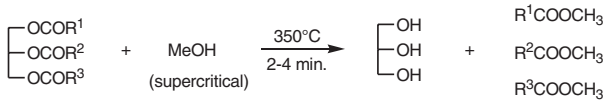
Scheme 1-64

This technique is utilized elegantly in the synthesis of baccatin III derivatives (Scheme 1-65) [2000TL239]. Heating of protected baccatin III derivatives in ethyl benzoylacetate (20 equiv.) allows smooth transesterification at the sterically hindered α-oriented 13-OH. The reaction is accelerated by continuous removal of the ethanol produced in vacuo.



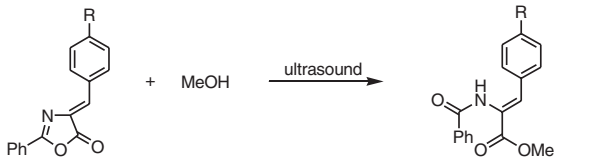
Scheme 1-65

Transformation of rapeseed oil, which consists of fatty acid esters of glycerin, into the methyl esters is of practical importance since these lighter esters are useful as biodiesel fuel. Subjection of rapeseed oil to supercritical methanol at 350 °C successfully provides the methyl esters (Scheme 1-66) [2001FU225, 2001FU693]. The supercritical state of methanol is believed to abolish the two-phase nature of the oil/methanol mixture to form a single phase, due to a decrease in the dielectric constant of methanol.



Scheme 1-66

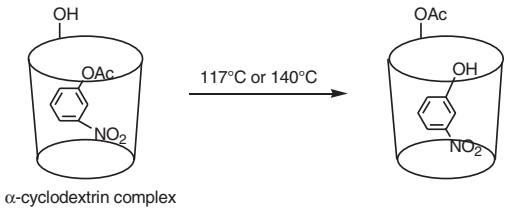
Ultrasound irradiation is effective for transesterification of an azalactone. A biologically active amino acid ester is thus accessible in methanol at room temperature (Scheme 1-67) [94IJC(B)3].



Scheme 1-67

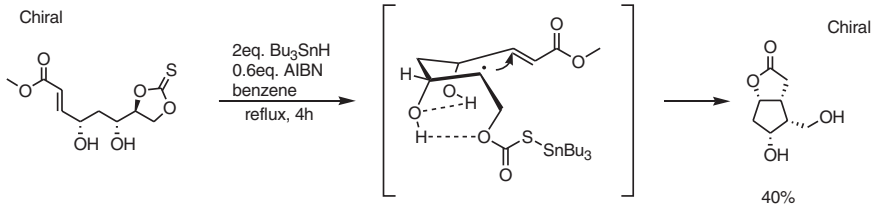
An α-cyclodextrin clathrate with *m*-nitrophenyl acetate undergoes ester transfer from the guest to the host in the solid state when heated at 117 ° or 140 °C (Scheme

1-68) [88JIP483]. No such transesterification occurs with *p*-nitrophenyl acetate complex.



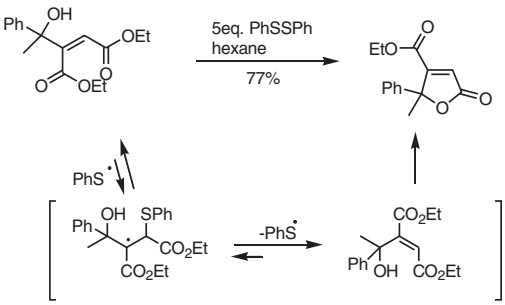
Scheme 1-68

When hydroxy ester intermediates are formed with appropriate conformations, intramolecular esterification takes place spontaneously. Two such examples taking advantage of radical reaction are available. As shown in Scheme 1-69, treatment of thionocarbonate diol with Bu_3SnH/AIBN affords an *all-syn* five-membered ring lactone as the major product in 40% yield [94JACS10829]. The product formed is best explained by a chair conformation in the radical intermediate. Hydrogen bonding of the type shown probably contributes in favoring this 1,3-diaxial arrangement of the two OH groups.



Scheme 1-69

When maleate esters with hydroxymethyl-based substituents on their β-carbons are isomerized to the corresponding fumarate esters by exposure to a thiyl radical, furanones are obtained in one-pot fashion (Scheme 1-70) [99T9341].



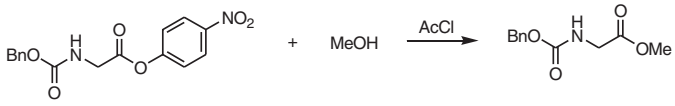
Scheme 1-70

1.2.2 Acid Catalysts

1.2.2.1 Brønsted Acids

Transesterification is most conveniently carried out with the aid of acid catalysts. Brønsted acids are classical but are still employed quite often; amongst the most popular are HCl, H_2SO_4, and *p*-toluenesulfonic acid, a literature survey from 1990 onwards hitting about 60, 40, and 75 references for them, respectively (refer to the database disc). Other acids utilized are HBr, HI, HF, AcOH, trifluoromethanesulfonic acid, camphorsulfonic acid, HBF_4, and $HClO_4$.

Transesterification must be carried out under anhydrous acidic conditions, because the ester is hydrolyzed otherwise. Accordingly, generation of HCl in a quantitative manner through the reaction between acetyl chloride and an alcohol as performed for esterification is feasible (see 1.1.2.1, Scheme 1-7). For example, a *p*-nitrophenyl ester has been transformed into the methyl ester without destruction of an *N*-Cbz protecting group (Scheme 1-71) [98SC471].

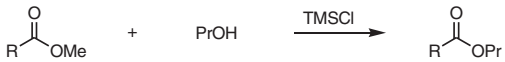


Scheme 1-71

The TMSCl/methanol technique is also applicable to transesterification. A variety of methyl esters are converted into propyl esters upon treatment with TMSCl in propanol (Scheme 1-72) [99SC1129].

Experimental Procedure [99SC1129] Scheme 1-72

$(CH_3)_3SiCl$ (1 mL) is placed in a round-bottomed glass flask loaded with a mixture of methyl ester (1.5 mmol) and 1-propanol (5 mL). The flask is closed with a glass stopper or fitted with a reflux condenser and a drying tube, and the reaction mixture is stirred either at 25 °C for 6 h or under gentle reflux for 2 h. The reaction mixture is then diluted with diethyl ether (5 mL), transferred to a separating funnel, and washed with saturated sodium bicarbonate solution (10 mL) followed by brine (10 mL). The organic solution is then dried with anhydrous magnesium sulfate and evaporated to dryness. The residue is weighed. After a standard workup, the residue



R= $(CH_2)_7(CH{=}CHCH_2)_3CH_3$ (97%)
R= $C_{17}H_{35}$ (95%)
R= cHex (89%)
R= C_3H_7 (52%)

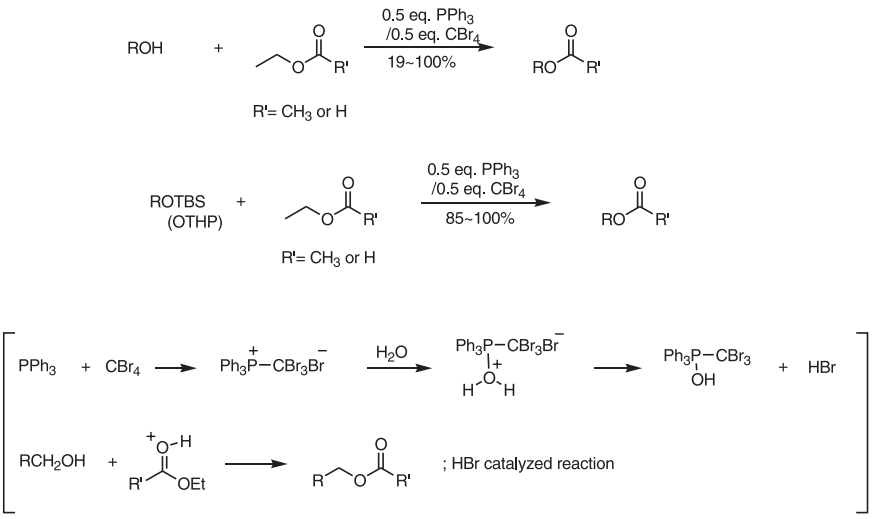
Scheme 1-72

is redissolved in hexane and the solution is analyzed by both GLC and GLC/MS to identify the product and to determine the degree of conversion.

In situ generation of HBr from the reaction between Ph_3P and CBr_4 in ester as a solvent has been claimed [98T5845]. Thus, stirring of a solution of alcohol, Ph_3P, and CBr_4 in 1 : 0.5 : 0.5 ratio in ethyl acetate solution at room temperature affords the corresponding acetates (Scheme 1-73). The use of methyl or ethyl formate provides the formates as well. Interestingly, TBS (*tert*-butyldimethylsilyl) and THP groups are directly transformed into the acetates or formates without the need for a deprotection procedure. A proposed mechanism is depicted in the Scheme. The key step is the hydrolysis of a phosphonium intermediate to generate HBr, which acts as an acid catalyst, but it is not clear where the water has come from. Although it is said that addition of 3 equiv. of H_2O is effective in promoting the reaction in some instances, no water is added in other cases.

Experimental Procedure [98T5845] Scheme 1-73

A solution of alcohol (1 mmol), triphenylphosphine (0.5 mmol), and carbon tetrabromide (0.5 mmol) in ethyl acetate (5 mL) is stirred at room temperature under nitrogen atmosphere and the reaction is monitored by TLC. Evaporation of ethyl acetate followed by flash column chromatography provides the acetate.

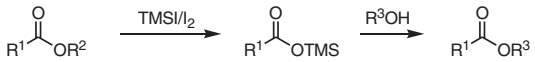


Scheme 1-73

A two-step procedure involving silyl ester formation followed by alcoholysis offers a one-pot esterification (Scheme 1-74) [81S142]. Treatment of ester with TMSI (1.0 equiv.)/I_2 in refluxing $CHCl_3$ furnished the silyl ester. Addition of alcohol (2.5 equiv.) to the reaction mixture, once more followed by heating, furnishes the new ester.

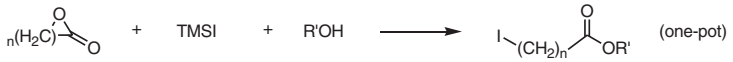
Experimental Procedure [81S142] Scheme 1-74

A solution of methyl benzoate (1.4 g, 10 mmol), iodotrimethylsilane (2.0 g, 10 mmol), and iodine (0.25 g, 1 mmol) in chloroform (20 mL) is heated at reflux under nitrogen for 3 h. The mixture is allowed to cool to ambient temperature and stirred with a drop of mercury until the color of the iodine disappears. A solution of ethanol (1.15 g, 25 mmol) in chloroform (2 mL) is then added, and the mixture is again heated under reflux overnight. The mixture is then allowed to cool to room temperature, quenched with aqueous sodium hydrogen carbonate solution (5%, 50 mL), and extracted with ether (2 × 50 mL). The ether extract is washed with water and dried with anhydrous sodium sulfate. Evaporation of the solvent and distillation of the residue gives ethyl benzoate.



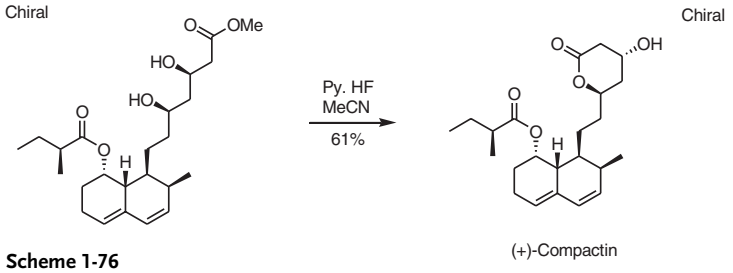
Scheme 1-74

Treatment of lactones with TMSI (1.5 equiv.) in the presence of an alcohol (2.5 equiv.) provides a short and convenient route to iodoalkyl esters (Scheme 1-75) [81SC763]. The reaction is effective for β-, γ-, δ-, and ε-lactones. Primary, secondary, and benzyl alcohols, as well as 2-trimethylsilylethanol, are employable. HI resulting from reaction between TMSI and alcohol is believed to act as a catalyst in this reaction.



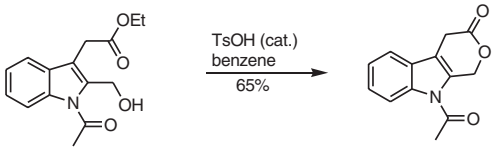
Scheme 1-75

The lactonization shown in Scheme 1-76 can be successfully run only when a HF/pyridine complex is employed [95JCS(P1)777]. (+)-Compactin and (+)-3,5-di-*epi*-compactin are accessible by this procedure.



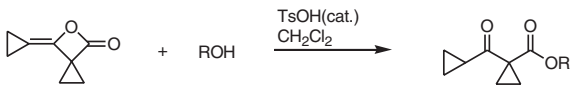
Scheme 1-76

TsOH (*p*-toluenesulfonic acid) is a useful catalyst for transesterification. As shown in Scheme 1-77, an indole lactone is formed when the depicted hydroxyl ester is heated in benzene in the presence of a catalytic amount of TsOH, N-O acyl transfer occurring under other conditions [97TL6541].



Scheme 1-77

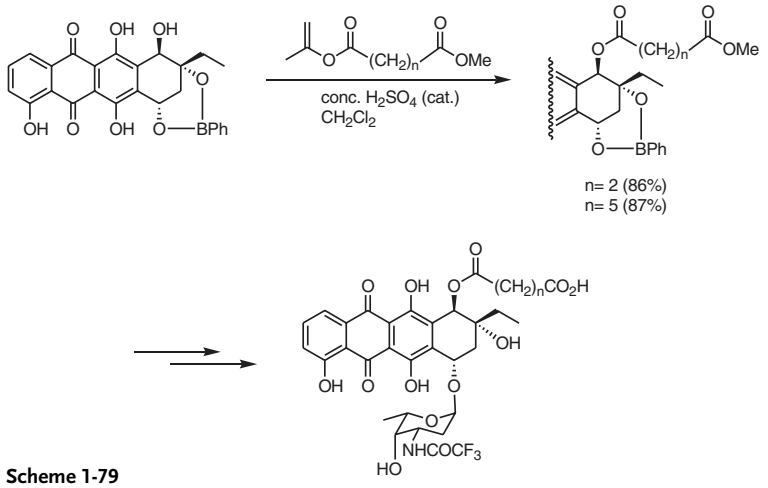
A tricyclic lactone undergoes alcoholysis under TsOH catalysis conditions to furnish unique dicyclopropyl β-ketoesters (Scheme 1-78) [94CB1275]. Even sterically hindered tertiary alcohols and phenols are employable, though the reaction is slower.



R= CH_3 (95%)
R= *p*-$OCH_3C_6H_4$ (83%)
R= ^{t}Bu (78%)
R= *p*-OCH_3 (83%)
R= *p*-$NO_2C_6H_4$ (45%)

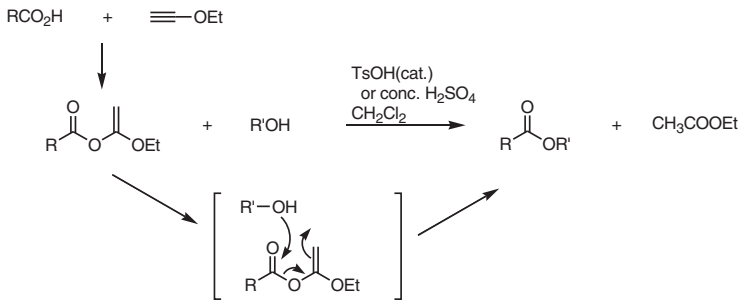
Scheme 1-78

Upon treatment with alcohols and phenols in the presence of catalytic amounts of TsOH or H_2SO_4, novel unsymmetrical diesters of dicarboxylic acids with an isopropenyl ester moiety on one terminal selectively undergo transesterification at this terminal to provide the monoesters (Scheme 1-79) [93CC410]. This procedure is utilized for synthesis of oxaunomycin derivatives.



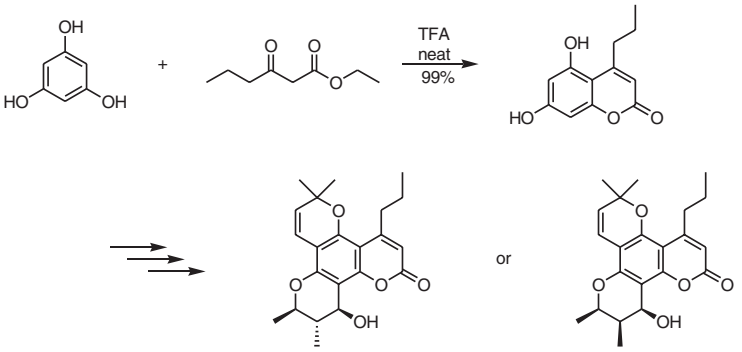
Scheme 1-79

1-Ethoxyvinyl esters derived from carboxylic acids and ethoxyacetylene function as efficient acylation reagents (Scheme 1-80) [93SL273]. The reaction is catalyzed by TsOH or H_2SO_4. Not only bulky alcohols, but also phenols, are acylated smoothly. Olefins and nitriles are tolerated under these conditions.



Scheme 1-80

The reaction between phenols and β-ketoesters furnishes coumarin lactones (Pechmann reaction). This reaction is effected by use of trifluoromethanesulfonic acid and utilized for the synthesis of (+)-calanolide A and C (Scheme 1-81) [93JOC5605].



(±)-Calanolide A (±)-Calanolide C

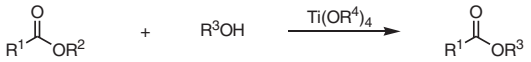
Scheme 1-81

1.2.2.2 **Lewis Acids**

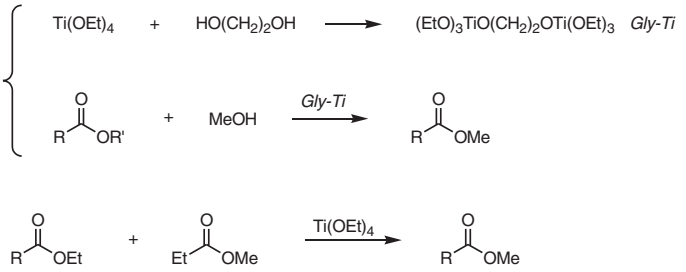
The most synthetically versatile methodology for transesterification is provided by Lewis acids, due to their mildness, simplicity in operation, catalytic capabilities, etc. In particular, titanium and tin compounds have long been used in both laboratories and industry. It may be said that those compounds, irrespective of whether they are organic or inorganic, possess more or less catalytic activity for transesterification. Among them, titanium tetraalkoxides are specifically useful in terms of their availability and readiness of handling, heating of an ester in alcohol solvent in the presence of $Ti(OR)_4$ smoothly effecting transesterification, although the titanate catalyst usually has to be employed in a rather large quantity (normally 0.2 ~ 0.6 mol per ester) (Scheme 1-82) [82S138]. Since the alcohol is used in excess, the alkoxy group in the titanate need not necessarily be identical with the alcohol component. A number of functional groups are tolerated, and the use of dried solvent is not necessary. It should be noted that methyl esters cannot be prepared, because of the low solubility of tetramethyl titanate. However, this drawback can be overcome by use of an ethylene glycol derivative that is soluble in methanol without formation of $Ti(OMe)_4$ (Scheme 1-83) [82HCA1197]. Alternatively, ester exchange with methyl propionate in the presence of $Ti(OEt)_4$ is also effective (Scheme 1-83). This procedure is utilized for synthesis of esters with sterically hindered alcohols, such as menthol, borneol, 2-adamantylmethanol, etc [98TL4223].

Experimental Procedure [82S138] Scheme 1-82

Ethyl 3-(*tert*-butyldimethylsiloxy)butanoate (2 g, 8.1 mmol) is dissolved in isopropanol (30 mL), tetraisopropyl titanate (1 g, 3.5 mmol) is added, and the mixture is heated at reflux temperature for 6 h. It is then cooled to ~45 °C, quenched with hydrochloric acid (1 N, 50 mL, temporary turbidity is observed), and extracted with pentane (2 × 150 mL). The organic extract is washed with saturated aqueous sodium hydrogen carbonate (30 mL), dried with magnesium sulfate, and evaporated under reduced pressure at 60 °C to remove solvent and residual isopropanol to give the isopropyl ester (2 g).

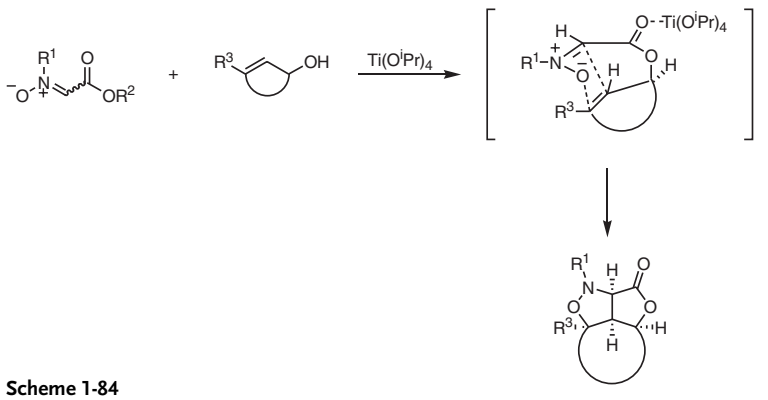


Scheme 1-82



Scheme 1-83

Tandem reactions of transesterification followed by intramolecular 1,3-dipolar cycloaddition of α-methoxycarbonylnitrones with allyl alcohols are promoted by titanium tetraisopropoxide (Scheme 1-84) [93TL4009]. Treatment of α-methoxycarbonylnitrone with allylic alcohol (5 equiv.) in the presence of $Ti(O^iPr)_4$ provides stereocontrolled polycyclic compounds in one-pot fashion.



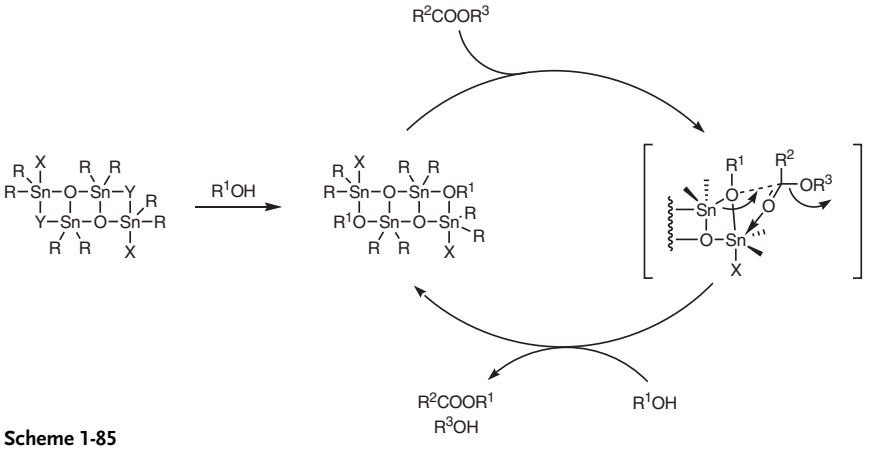
Scheme 1-84

Organotin compounds have long been known as transesterification catalysts [69BCF262, 79JOM(173)C7, 84PC187]. However, 1,3-disubstituted tetralkyldistannoxanes are amongst the most useful [86TL2383, 91JOC5307] (Scheme 1-85). The reaction is conducted by heating an ester in alcohol solvent with a catalytic amount of distannoxane. The catalyst activity is extremely high, so the reaction goes to completion even with a 0.05 mol % catalyst concentration. Thanks to the neutral conditions, various functional groups are tolerated and, remarkably, otherwise difficult-to-achieve transesterification of non-enolizable α,α-disubstituted β-keto esters smoothly takes place. An alkoxy distannoxane, on which the substrate ester coordinates, is be-

lieved to be a key intermediate. The entropy gain through cooperative *endo*- and *exo*-tins facilitates the alkoxy interchange on the template.

Experimental Procedure [91JOC5307] Scheme 1-85

Distannoxane-Catalyzed Transesterification: A toluene solution (25 mL) of ethyl 2,2-dimethylacetoacetate (791 mg, 5.00 mmol), BnOH (5.40 g, 50.0 mmol), and 1,3-dichlorotetrabutyldistannoxane (278 mg, 0.500 mmol) is heated at reflux for 24 h. The toluene and excess BnOH are evaporated in vacuo. The residue is purified by column chromatography on silica gel (hexane/EtOAc 95 : 5) to give benzyl 2,2-dimethylacetoacetate (968 mg, 88%).



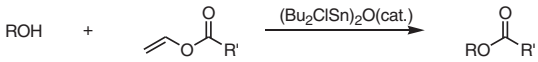
Scheme 1-85

The employment of vinyl or isopropenyl esters as ester components results in highly selective acylation of alcohols (Scheme 1-86) [98JOC2420, 99T2899] (see Section 7.1). This technique allows selective acylation of primary alcohols in the presence of secondary and tertiary alcohols, leaving various functional groups intact.

Experimental Procedure [99T2899]

Acetylation of Alcohol with Ethyl Acetate: An ethyl acetate solution (10 mL) of 2-phenylethanol (611 mg, 5.0 mmol) and distannoxane (138.2 mg, 0.25 mmol) is heated at reflux for 12 h. After evaporation, the residue is subjected to column chromatography on silica gel to give 2-phenethyl acetate (772 mg, 93%).

Acylation of Alcohol with Vinyl Acetate: A vinyl acetate solution (5 mL) of 2-phenylethanol (611 mg, 5.0 mmol) and distannoxane (138.2 mg, 0.25 mmol) is stirred at 30°C for 5 h. After evaporation, the residue is subjected to column chromatography on silica gel to give 2-phenethyl acetate (788 mg, 96%).



R= Ph, R'= CH_3 (0%)
R= CH_2Bn, R'= CH_3 (98%)
R= $CH(CH_3)Ph$, R'= CH_3 (99%)
R= C_8H_{17}, R'= CH_3 (99%)
R= $(CH_2)_4OCOCF_3$, R'= CH_3 (97%)
R= $(CH_2)S\text{-}S(CH_2)_2OH$, R'= CH_3 (98%)
R= $(CH_2)_4OTBS$, R'= CH_3 (98%)
R= *p*-$OHC_6H_4CH_2CH_2$, R'= CH_3 (99%)
R= $CH(CH_3)C_6H_{13}$, R'= CH_3 (97%)
R= C_6H_{11}, R'= CH_3 (0%)
R= $(CH_2)_4CH(OH)CH_3$, R'= Ph (96%)
R= C_8H_{17}, R'= Ph (98%)
R= C_8H_{17}, R'= ^{t}Bu (97%)
R= C_8H_{17}, R'= $CH{=}CH_2$ (98%)
R= $(CH_2)_4CH(OH)CH_3$, R'= $CH{=}CH_2$ (96%)
R= C_8H_{17}, R'= CH_2Cl (96%)

Scheme 1-86

Replacement of the alkyl groups on the distannoxane with fluoroalkyl groups gives fluorous distannoxanes, which are highly soluble in fluorocarbon solvents [2001AGC(E)3670, 2002ASC(344)84]. Fluorous biphasic transesterification with these catalysts gives 100% yields with use of a 1:1 reactant ratio (see Sections 7.2 and 7.3).

Experimental Procedure [2001AGC(E)3670]
Fluorous Biphasic Transesterification: A mixture of ethyl 3-phenylpropionate (356 mg, 2.0 mmol), 1-octanol (260 mg, 2.0 mmol), and the distannoxane catalyst (171 mg, 0.1 mmol) in FC-72 (4 mL) is placed in a test tube. The test tube is placed in a stainless steel pressure bottle and heated at 150 °C for 16 h. The reaction mixture is then allowed to cool to room temperature, and toluene (5 mL) is added. The FC-72 layer is washed with toluene (2 × 1 mL), and the combined toluene solution is evaporated to afford pure octyl 3-phenylpropionate (525 mg, 100%). The FC-72 solution can be reused in the next reaction.

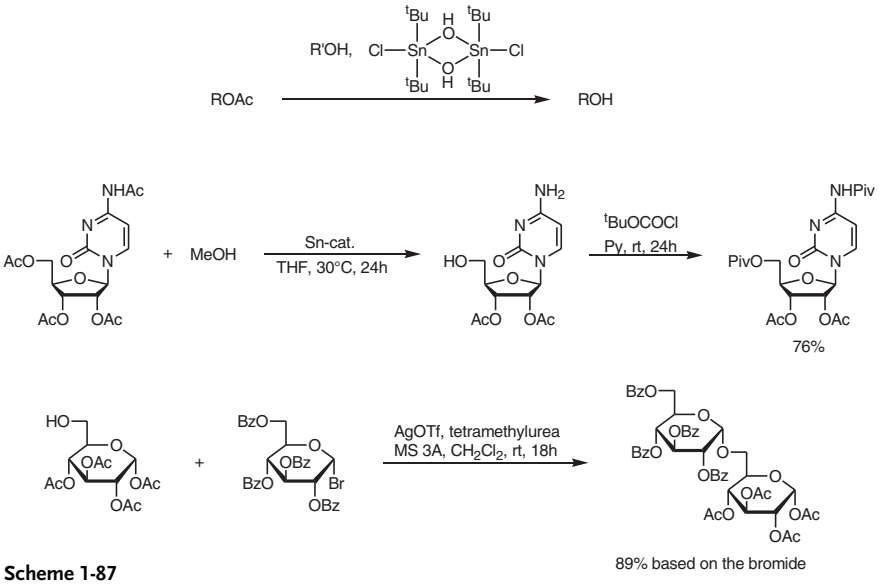
A neutral μ-hydroxy organotin dimer [*tert*-$Bu_2Sn(OH)Cl]_2$ is an efficient catalyst for deacetylation (Scheme 1-87) [2000SL140, 2001CEJ3321]. Various acetates undergo transesterification to afford the parent alcohols. High selectivities are attained for the combinations of primary > secondary, primary > tertiary, and secondary > tertiary. Notably, phenyl acetate is deacetylated more readily than the primary acetate. The same primary/secondary selectivity also holds for sugars and nucleosides. Since the reaction is so clean, the product may be used for further reaction without purification. For example, tetraacetylcytidine is deacetylated, and treatment of the crude product with pivaloyl chloride affords cytidine with primary and *N*-pivaloyl groups together with the secondary acetyl groups. Moreover, glycosidation with the crude deacetylation product is also feasible. Treatment of the crude glucose tetraacetate obtained by this procedure with tetra-*O*-benzoyl-α-D-glucopyranosyl bromide in the presence of AgOTf directly furnishes the corresponding dissacharide.

Experimental Procedure [2001CEJ3321] Scheme 1-87
Deacetylation of 2-Phenylethyl Acetate: 2-Phenylethyl acetate (82.1 mg, 0.5 mmol), [*tert*-$Bu_2Sn(OH)Cl]_2$ (28.6 mg, 0.05 mmol), methanol (5 mL), and THF (5 mL) are stir-

red at 30 °C for 3.5 h. After addition of ethyl acetate, the reaction mixture is filtered through a thin pad of silica gel, and the yield is determined to be 97% by GC analysis.

Deacetylation of Cytidine Tetraacetate and Subsequent Pivalation: Tetraacetylcytidine (411 mg, 1.0 mmol), [*tert*-$Bu_2Sn(OH)Cl]_2$ (28.5 mg, 0.05 mmol), methanol (5 mL), and THF (5 mL) are stirred at 30 °C for 24 h. After addition of CH_2Cl_2, the reaction mixture is filtered through a thin pad of silica gel, and the filtrate is concentrated to give crude 2,3-di-*O*-acetylcytidine. Pivaloyl chloride (4.0 mmol) and pyridine (5 mL) are added to this product, and the mixture is stirred at rt. for 24 h. After conventional aqueous workup (ethyl acetate/water), the organic layer is dried and evaporated to give a crude product, which is subjected to column chromatography on silica gel to give 2′,3′-di-*O*-acetyl-5′-*O,N*-dipivaloylcytidine in 76% yield.

Deacetylation of α-D-Glucose Pentaacetate and Subsequent Glucosylation: The pentaacetate (507 mg, 1.3 mmol), [*tert*-$Bu_2Sn(OH)Cl]_2$ (37.1 mg, 0.065 mmol), methanol (7 mL), and THF (7 mL) are stirred at 30 °C for 4 h. After addition of ethyl acetate, the reaction mixture is filtered through a thin pad of silica gel, and the filtrate is concentrated to give a crude product of the tetraacetate. A mixture of this crude product, tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (660 mg, 1.0 mmol), tetramethylurea (0.25 mL), and molecular sieves (3 Å) in CH_2Cl_2 (5 mL) is stirred at rt. for 15 min. AgOTf (452 mg, 1.3 mmol) is added. The mixture is stirred in the dark at rt. for 18 h. After addition of CH_2Cl_2, the reaction mixture is filtered. Conventional aqueous workup followed by column chromatography on silica gel provides the desired disaccharide in 89% yield.



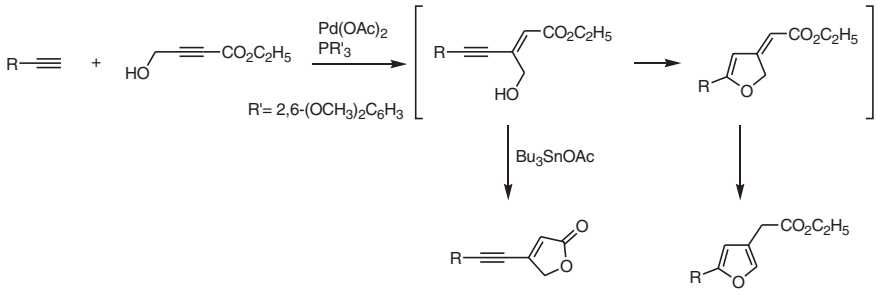
Scheme 1-87

Butylstannoic acid [BuSn(O)OH] mediates the transesterification of various substrates, although rather large amounts of the promoter (0.2~1.1 equiv. per substrate)

are required [98TL2257]. Dibutyltin oxide is useful as well [2001AGC(E)3672]. With this commercially available catalyst, a variety of substrates can be smoothly transesterified.

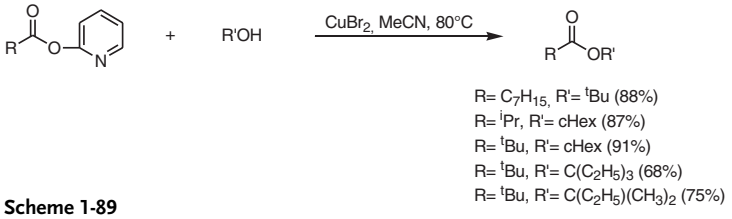
Experimental Procedure [2002AGC(E)3672]
The carboxylic ester (0.6 mmol) is dissolved in the desired alcohol (5 mL). After the addition of dibutyltin oxide (10 mol%, 15 mg, 0.06 mmol) the mixture is heated at reflux for 48–72 h. After completion of the reaction, the mixture is poured into a saturated sodium bicarbonate solution (20 mL) and extracted three times with ethyl acetate. The combined organic layers, which contain the dibutyltin oxide as a fine, white precipitate, are filtered through Celite and dried over sodium sulfate. After removal of the solvent in vacuo, the product is purified by flash chromatography.

Tributyltin acetate works for transesterification of a γ-hydroxy α,β-unsaturated ester generated in situ (Scheme 1-88) [95JACS7255]. Palladium coupling between terminal acetylene and γ-hydroxyalkynoate affords butenolide, although furan formation competes. Selective lactonization is achievable by addition of tributyltin acetate (10 ~ 40 mol %) to the reaction system to furnish the butenolide exclusively.



Scheme 1-88

Some of the Lewis acids used for esterification are effective for transesterification as well. $Fe(ClO_4)_3$ [93IJC(B)292] and iodine [2002TL879] are capable of catalyzing transesterification. Treatment of alcohols in refluxing ethyl acetate or formate in the presence of $Cu(NO_3)_2 \cdot 3H_2O$ provides the corresponding acetates or formates [98SC1923]. $CuBr_2$ (0.2 ~ 1.0 equiv.) catalyzes reactions between 2-pyridyl esters and alcohols (Scheme 1-89) [84JOC1712]. Despite the disadvantage of requiring a relatively large amount of the copper salt, this procedure is superior to other methods in terms of the rapidity of the reaction and its applicability to sterically hindered esters. It is notable that the corresponding thiopyridyl esters are more reactive.

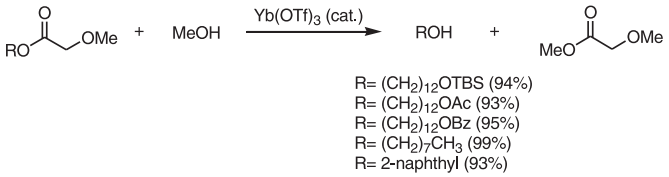


Scheme 1-89

Use of particular esters to activate transesterification is also possible with methoxyacetates (Scheme 1-90) [96JOC4491]. Treatment of these acetates with $Yb(OTf)_3$ in methanol delivers alcohols, and this approach thus also offers a facile deprotection method to recover alcohols.

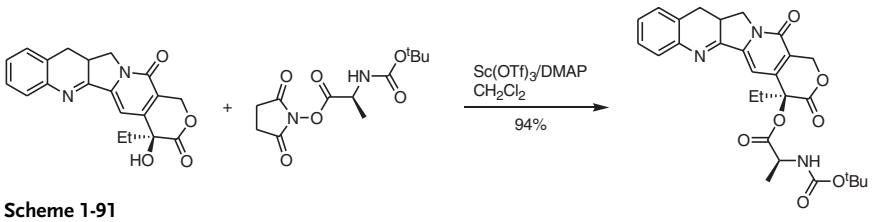
Experimental Procedure [96JOC4491] Scheme 1-90

A solution of $Yb(OTf)_3$ (9.5 mg, 30 mol%) in dry methanol (1 mL) is added to a solution of 1,2 : 3,4-di-*O*-isopropylidene-6-*O*-(methoxyacetyl)-α-D-galactopyranose (19.9 mg, 0.051 mmol) in dry methanol (0.5 mL), and the mixture is stirred for 12 min at 25 °C. A drop of water is added to the reaction mixture, and the solvent is then evaporated under vacuum. Purification of the crude product by preparative TLC on silica gel affords the desired alcohol (13.0 mg, 98%) as a colorless oil.

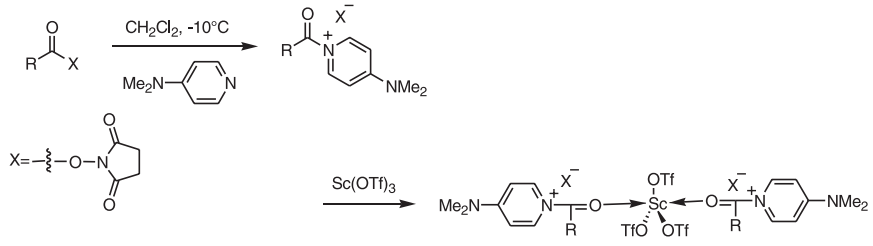


Scheme 1-90

Other activated esters, *N*-hydroxysuccinimidyl esters, are useful for obtaining highly sterically hindered esters (Scheme 1-91) [98JOC7559]. The reaction is promoted by the $Sc(OTf)_3$/DMAP reagent combination used for activation of the DCC procedure (see Section 1.1.4). DMAP is crucial for this reaction, and a scandium species coordinated by acylium ions is assumed to act as a powerful promoter (Scheme 1-92).



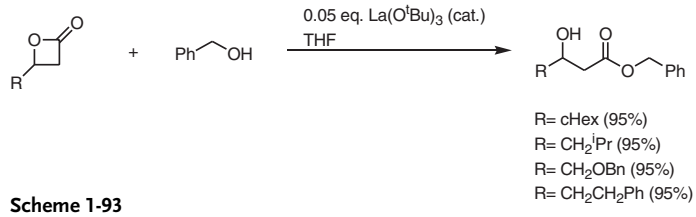
Scheme 1-91



Scheme 1-92

Mild $MgBr_2$ is employable for transesterification of activated esters. Transesterification of *N*-alkoxycarbonyl groups of chiral dimethylaminopyridine derivatives is effected by use of $MgBr_2$ or $ZnCl_2$ [96JACS1809]. The 4,6-dimethoxy-1,3,5-triazin-2-yl group serves as an active alkoxy group easily replaced by an alcohol in the presence of $MgBr_2$ [99S593].

Lanthanoid triisopropoxides catalyze transesterification efficiently [95CL246]. The reaction goes to completion on heating of esters in refluxing alcohol with 2 mol% of the catalyst. The catalytic activity is much higher than those of $Al(O^iPr)_3$ and $Ti(O^iPr)_4$, decreasing in the order La > Nd > Gd > Yb. $La(O^tBu)_3$ is an efficient catalyst for ring-opening of β-lactones with benzyl alcohol to afford β-hydroxy esters (Scheme 1-93) [99TL6535].

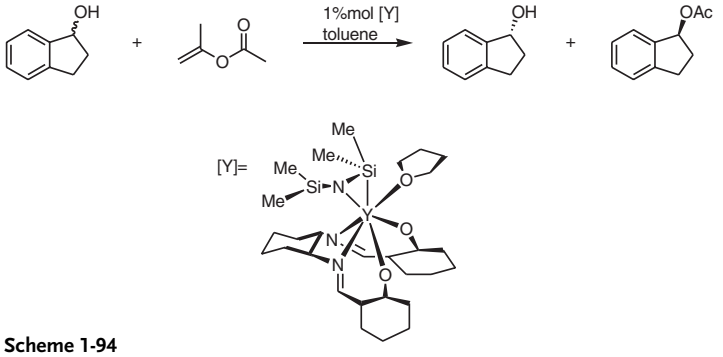


Scheme 1-93

Enol ester acylation is feasible with an yttrium aggregate [2000OL997]. Primary and secondary alcohols react with vinyl or isopropenyl acetate at room temperature in the presence of catalytic amounts (0.05~1 mol %) of $Y_5(O^iPr)_{13}O$ to give the corresponding esters. A chiral version of the yttrium procedure is available (Scheme 1-94) [2002OL1607]. Yttrium-salen complexes effect transesterification between enol esters and chiral secondary alcohols, resulting in varying degrees of kinetic resolution.

Experimental Procedure [2002OL1607] Scheme 1-94

A mixture of alcohol (1 mmol) and the Y catalyst in toluene (1.5 mL) under nitrogen is cooled to −3 to −25 °C, and the enol acetate (1.27 mmol) is added. When the reaction is complete, the cold solution is poured into water, and the products are extracted with ether. The ether solution is washed with saturated NaCl and dried, and the products are isolated by column chromatography. The *ee*s of the unreacted alcohols are determined by chiral HPLC.

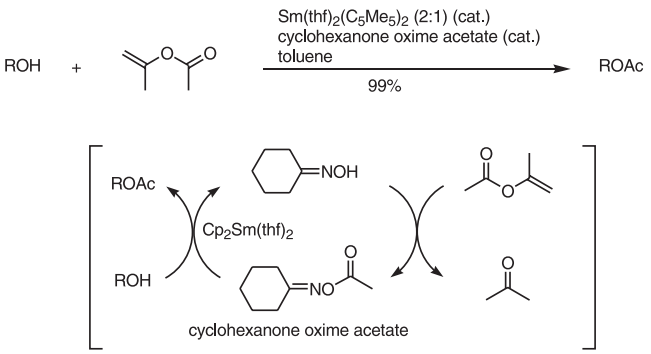


Scheme 1-94

$Cp^*_2Sm(THF)_2$ (Cp^* = pentamethylcyclopentadienyl) is an efficient catalyst for acylation of alcohols with vinyl esters [96JOC3088]. The acylation of primary alcohols is achievable in excellent yields, while secondary alcohols are acetylated with more difficulty. The deficient reactivity, however, is improved by the presence of cyclohexanone oxime acetate (Scheme 1-95) [97JOC8141]. Treatment of alcohol with isopropenyl acetate (2 equiv.) and the oxime acetate (0.2~2.0 equiv.) in the presence of $Cp^*_2Sm(THF)_2$ (10 mol %) allows transesterification to take place even for tertiary alcohols. A plausible reaction path involves reaction between alcohol and cyclohexanone oxime acetate, followed by acetylation of the oxime generated by isopropenyl acetate.

Experimental Procedure [97JOC8141] Scheme 1-95

Alcohol (1 mmol) is slowly added under argon to a toluene solution (1 mL) of $Cp^*_2Sm(thf)_2$ (0.1 mmol) in a Schlenk tube, followed by cyclohexanone oxime acetate (0.2–2.0 mmol) and isopropenyl acetate (2 mmol). When the reaction is complete, wet diisopropyl ether (10 mL) is added to the solution, and the catalyst is removed by filtration. Removal of the solvent under reduced pressure affords a yellow liquid, which is purified by column chromatography on silica gel with hexane/ethyl acetate (20 : 1 v/v) as eluent to give the corresponding acetates.



Scheme 1-95

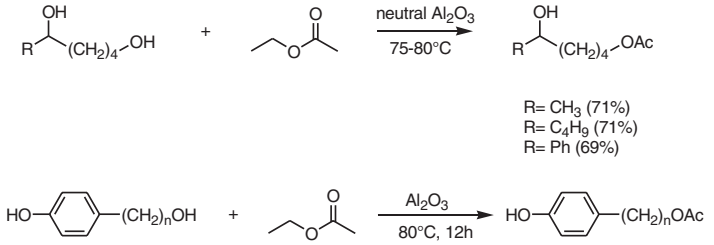
Commercially available methyl or ethyl (meth)acrylates are converted into higher homologues on treatment with alcohols with the aid of a nickel-containing complex reducing agent prepared from nickel acetate, NaH, and ^{t}BuONa [93JCR(S)418].

1.2.2.3 Solid Acids

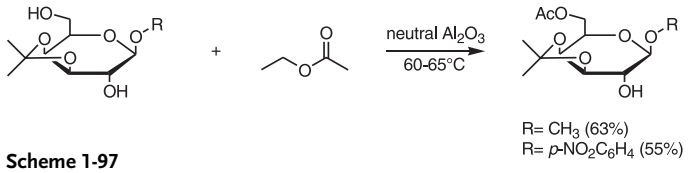
Solid acid catalysts are more important than any other acid catalysts in practical use, and so a number of techniques are available. Neutral alumina used for column chromatography can effect transesterification [81S789], stirring of an alcohol (100 mg) in ethyl acetate (10 mL) over commercially available alumina (10 g) at room temperature affording the corresponding acetate. This reaction is selective for primary alcohols, so primary-secondary diols undergo esterification on the primary alcohol almost exclusively (Scheme 1-96) [81TL5003]. Under the same reaction conditions phenol is also inert, allowing selective acetylation of the primary alcohol of *p*-(ω-hydroxyalkyl)phenol. Such selectivity holds with sugar diols as well (Scheme 1-97) [81TL5007]. Typically, a solution of the diol (1 mmol) in anhydrous ethyl acetate (100 mL) is heated at 60–65 °C in the presence of neutral alumina (10 g). Both mono- and disaccharides are smoothly acetylated on the primary alcohol.

Experimental Procedure [81S789]

Inside a nitrogen-filled glove bag, Woelm-200-N alumina (~100 g) is transferred from its commercial metal container into a 500 mL, three-necked, round-bottomed flask, which is then fitted with an overhead mechanical stirrer and a stirring rod. An ethyl acetate solution (~150 mL) containing cyclohexylmethanol (1.021 g) is poured into the flask. Rapid stirring is performed for 1 h at 25–30 °C. Ethyl acetate (~100 mL) is then added, and the reaction mixture is poured into sintered glass funnel containing a pad (~2 cm) of Celite. Slow gravity filtration and rinsing with additional ethyl acetate is followed by rotary evaporation to produce spectroscopically pure cyclohexylmethyl acetate.



Scheme 1-96

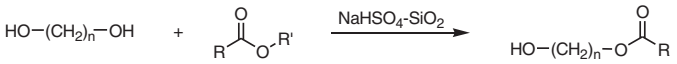


Scheme 1-97

Silica gel-supported $NaHSO_4$ mediates monoacylation of symmetrical diols upon treatment with various esters as solvent (Scheme 1-98) [89JACS9102, 92JOC312]. The selective acetylation of primary-secondary diols and also of primary aliphatic-aromatic diols, as shown in Scheme 1-98, is also feasible with this catalyst [97JOC8952]. Smaller amounts of the catalyst (typically 100 mg/1 mmol diol) are required than for the alumina procedure.

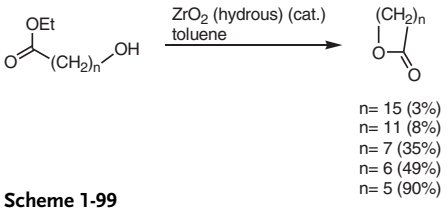
Experimental Procedure [92JOC312] Scheme 1-98

A stirred mixture of 1,4-butanediol (0.44 mL, 5 mmol), $NaHSO_4/SiO_2$ (189 mg, 0.42 mmol), and EtOAc/hexane (2 : 3 v/v, 16 mL) is warmed at 50 °C. The reaction is monitored by TLC (EtOAc/hexane 1 : 2) and GLC. After 5 h, 1,4-diacetoxybutane begins to appear, and the reaction mixture is then filtered. The separated catalyst is washed with CCl_4 (10 mL), and the filtrate and washings are combined and concentrated. Column chromatography of the residue on silica gel (EtOAc/hexane 1 : 4) gives 4-acetoxy-1-butanol (0.54 g, 82%).



Scheme 1-98

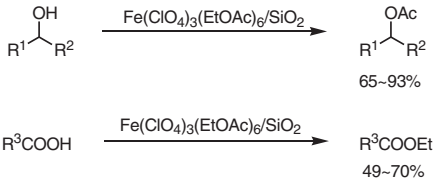
Hydrous tin oxide, obtainable from tin metal and conc. HNO_3, can be used for vapor-phase transesterification at 170 ~ 210 °C [99SC513]. The catalyst can be recycled for at least 50 runs. Hydrous zirconium oxide mediates transesterification in the vapor phase by use of a glass flow-reactor with a fixed-bed catalyst, in the liquid phase, and in an autoclave [89BCJ2353]. Remarkably, this catalyst is effective for lactonization to furnish medium-sized macrolides (Scheme 1-99) [92CL571]. In the vapor-phase reaction at 275 °C, ω-hydroxy esters are converted into the corresponding lactones. Otherwise difficult-to-obtain heptanolide and octanolide are accessible in reasonable yields. The catalytic activity is enhanced by modification with trimethylsilyl chloride [93BCJ1305], the yields of heptanolide and octanolide increasing from 49% to 77% and from 35% to 67%, respectively.



Scheme 1-99

β-Keto esters are transesterified by solid acids such as zeolite [96CC707], sulfated SnO_2 [96TL233], natural kaolinitic clay [98JOC1058], Mo-ZrO_2 [99SC1235], and yttria-zirconia [2000SL251]. The reaction presumably proceeds via an acylketene intermediate.

$Fe(ClO_4)_3(EtOAc)_6/SiO_2$ is prepared by adsorption of $Fe(ClO_4)_3(H_2O)_6$ onto chromatographic grade silica gel in the presence of ethyl acetate. Grinding of equimolar amounts of this complex with alcohols under solvent-free conditions produces the corresponding acetates (Scheme 1-100) [99SC139]. The supported reagent also reacts with carboxylic acids to afford the corresponding ethyl esters.



Scheme 1-100

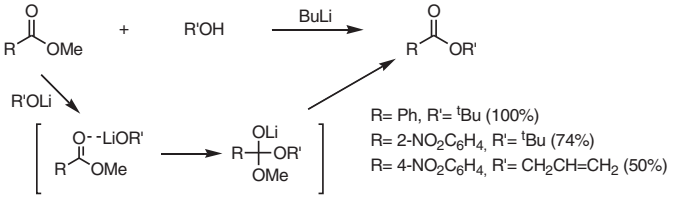
1.2.3 Base Activators

1.2.3.1 Metal Salts

As well as acid catalysts, basic reagents also serve for transesterification, and some inorganic metal bases are successfully used. A thorough investigation into the effectiveness of lithium alkoxides is available (Scheme 1-101) [86CC695]. The lithium alkoxide is generated in situ by addition of an equivalent amount of BuLi to a THF solution of an alcohol, and treatment of the resulting alkoxide with an ester (mostly methyl esters) results in transesterification. The reaction proceeds at or below ambient temperature, electron-deficient esters generally reacting within minutes. For secondary and tertiary alcohols, equimolar amounts of the ester and alcohol suffice for good yields. Although roughly one molar equivalent of BuLi per mole of alcohol is generally employed, use of smaller amounts suffices, but lengthens reaction times. Alcohols that are insoluble in THF frequently dissolve on addition of BuLi. With primary alcohols, an excess of the alcohol (~3 equiv.) is necessary for good yields. Ethyl esters undergo alcoholysis but with poorer equilibration shifts in the desired direction and lower reaction rates. Phenyl esters appear to offer no advantage, being slower and less effective in the transesterification. Commercial alcohols can be directly employable without drying. Aromatic esters react without problems, α,β-unsaturated esters behave normally, without isomerization, and asymmetric alcohols react without loss of chiral integrity. A major limitation of the method concerns alcohols that complex strongly with the lithium intramolecularly, such as sugar derivatives. Polymerizable compounds such as methyl acrylate are best used in excess. Also, if the alcohol is precious or difficult to separate from the product ester, this problem can be solved by use of an excess of the methyl esters. The reaction is presumably initiated by strong complexation of the lithium alkoxide to the ester carbonyl group. The lower p*K*a of methanol than of higher homologous alcohols encourages efficient equilibration to produce esters.

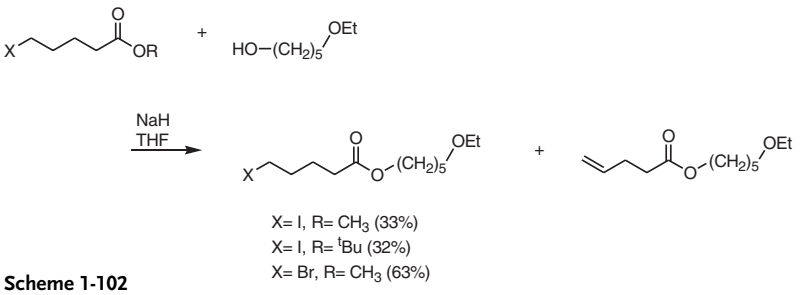
Experimental Procedure [86CC695] Scheme 1-101

Butyllithium in hexane (1.6 M; ~0.01 mol) and methyl *p*-methoxybenzoate (0.01 mol) are added under nitrogen to (–)-menthol (0.01 mol) in dry stirred THF (20 mL) in an ice bath. The reaction is monitored by TLC (20% diethyl ether/light petroleum; ~50% in 1 h; 70% in 6 h). After 18 h, water and ether are added and the organic layer is dried, evaporated, and flash chromatographed (20% diethyl ether/light petroleum). The product is further distilled in a Kugelrohr apparatus (215 °C at ~0.5 mmHg) to give menthyl *p*-methoxybenzoate (92%) as a colorless liquid.



Scheme 1-101

NaH mediates the reaction between 5-ethoxypentan-1-ol and alkyl 5-halovalerates to furnish transesterification products, no Williamson-type reaction taking place (Scheme 1-102) [91JOC731]. Yields of up to 66% are thus obtained from bromovalerates, but considerable amounts of elimination products are formed from the iodo derivatives.



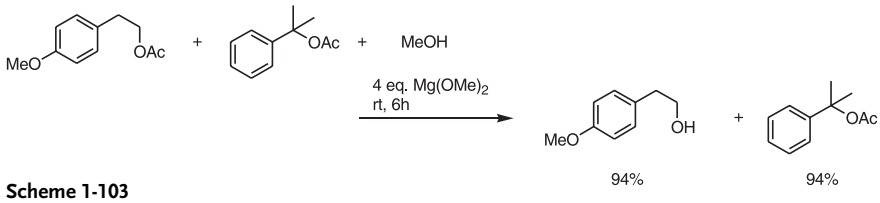
Scheme 1-102

Alcoholysis of esters, particularly acetates, offers a convenient deprotection method. It is possible to cleave primary alcohol acetates selectively in the presence of secondary or tertiary alcohol acetates, and also to cleave secondary alcohol acetates in the presence of tertiary alcohol acetates, with the aid of $Mg(OMe)_2$ (Scheme 1-103) [96JOC9086]. High selectivities between primary acetates can also be obtained if the β-positions of the acetates offer different degree of steric bulkiness. This mild reagent is applicable to the selective deprotection of many naturally occurring molecules, including hydroxycitronellol diacetate, *trans*-sobrerol diacetate, betulin diacetate, and baccatin III. Both aromatic and 4-acetoxycoumarin acetates undergo deacetylation with zinc-copper couple or activated zinc (Scheme 1-104) [81TL335]. Com-

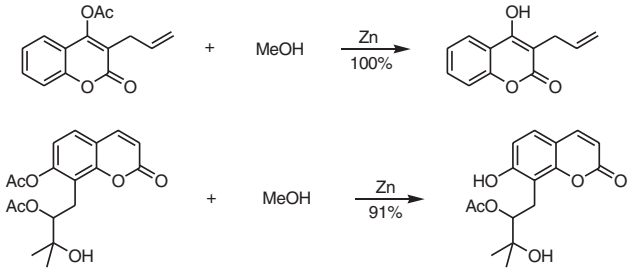
mercial zinc is completely ineffective, and the reaction is hindered by the addition of water.

Experimental Procedure [96JOC9086] Scheme 1-104

Magnesium methoxide solution in methanol (10.3%, 0.973 N, 4.1 mL, 4.0 mmol) is added dropwise under nitrogen at rt. to a stirred solution of 4-methoxyphenethyl acetate (194.0 mg, 1.0 mmol) and 2-phenyl-2-propyl acetate (187.0 g, 1.0 mmol) in anhydrous methanol (20 mL). The progress of the reaction is monitored by TLC. After the mixture has been stirred at rt. for 6 h, 4-methoxyphenethyl acetate is all consumed. HCl solution (0.2 N) is added until the pH of the mixture is 4 to 5. Some of the methanol is removed under reduced pressure, and the product is extracted with dichloromethane (30 mL × 5). The combined organic layer is dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the crude residue with hexanes and ethyl acetate (7 : 3) gives 4-methoxyphenethyl alcohol (144.0 mg, 0.94 mmol) in 94% yield, along with recovered starting material (176.0 mg, 0.94 mmol) in 94% yield. No 2-phenyl-2-propanol is detected.



Scheme 1-103

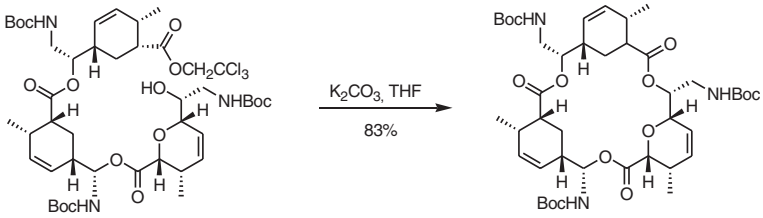


Scheme 1-104

Solid potassium carbonate coated with a phase-transfer catalyst (Carbowax 6000 or 18-crown-6) can be utilized as a catalytic bed for continuous transesterification under gas-liquid phase-transfer conditions [83JOC4106].

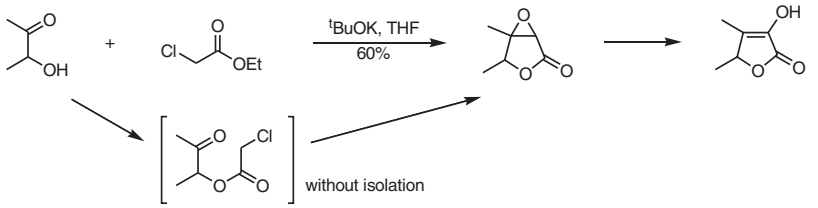
The effect of alkali metal salts on lactonization of ω-hydroxy esters is the subject of extensive investigation (Scheme 1-105) [98JOC2715]. The use of K_2CO_3 in THF gives amongst the highest yields of the desired macrolide. The rate-determining step is the addition of the alcohol or alkoxide fragment to the carbonyl carbon, followed by the fast breakdown of the resulting tetrahedral intermediate. The conversion of

the hydroxy ester into the macrolide is a M^+-templated cyclization in which the slow step is the collapse of the tetrahedral intermediate. With the proximity of the hydroxy and ester moieties enforced and the associated entropic costs met by the template effect, the formation of the tetrahedral intermediates is facilitated. The rate of the productive collapse of this intermediate is dependent on the departing alkoxide nucleofuge; hence the superiority of trichloroethyl esters.



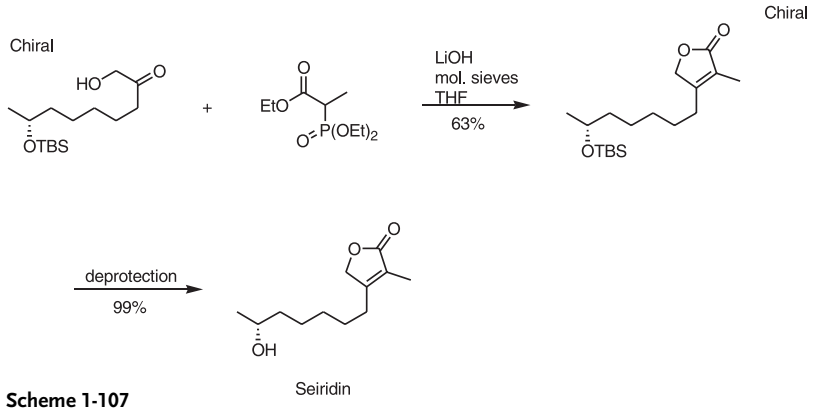
Scheme 1-105

Treatment of β-hydroxy ketones with α-chloro esters in the presence of *tert*-BuOK affords α,β-epoxy-γ-lactones through transesterification followed by Darzens reaction (Scheme 1-106) [93TL2753]. Under acidic conditions, the epoxy butenolide is transformed into 3-hydroxy-4,5-dimethyl-2(5H)-furanone, an extremely powerful and very important flavor ingredient.



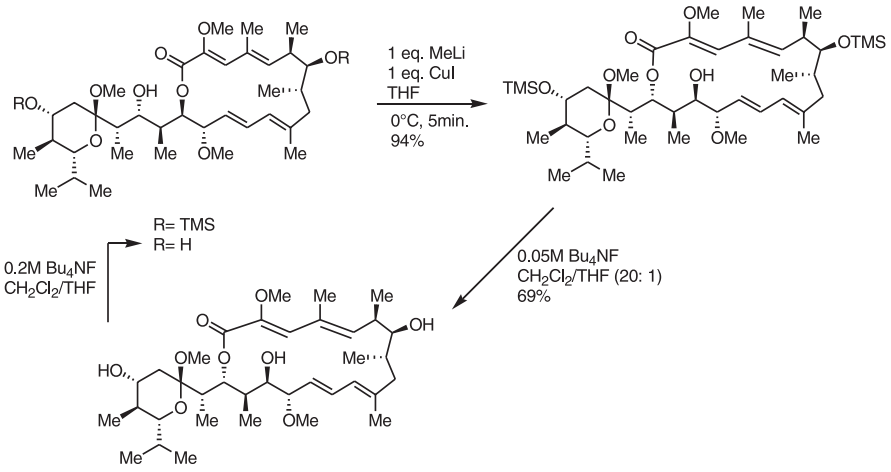
Scheme 1-106

Another phytotoxic butenolide, seiridin – a fungal cypress pathogen produced by three Seiridium species is accessible through successive Wittig-type olefination and lactonization (Scheme 1-107) [95TL7285]. Both reactions are promoted by LiOH with molecular sieves.

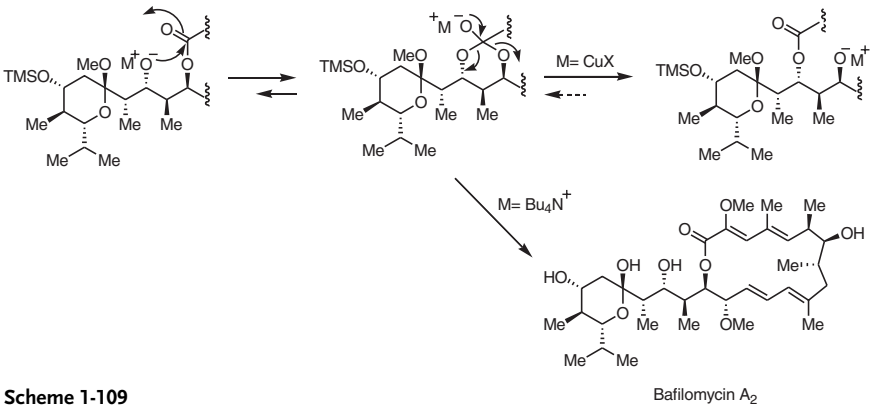


Scheme 1-107

Interesting ring-expansions and -contractions of macrolides can take place, depending on the base (Scheme 1-108) [94TL5393]. Treatment of the 16-membered lactone 7,21-di-*O*-trimethylsilyl bafilomycin A_2 with an organocopper reagent prepared from equimolar quantities of methyllithium and cuprous iodide results in ring-expansion. A further surprising event occurs when the resulting 18-membered lactone is treated with highly concentrated Bu_4NF, which regenerates bafilomycin A_2, although the use of smaller amounts of the fluoride results in simple desilylation. A plausible explanation is given in Scheme 1-109. The initial step is the formation of alkoxycopper species suitably situated to undergo a potentially reversible rearrangement involving a copper(I) orthoacetate intermediate. Evidently a kinetically controlled and presumably stereoelectronically allowed process produces the ring-expansion product as the preponderant if not exclusive product. The behavior of this product towards fluoride ion can be explained as follows. In dilute dichloromethane, the effective concentration of Bu_4NF is not high enough to allow reversion to the 16-membered lactone, thus providing just a desilylation product. In a more concentrated solution of Bu_4NF, the ring-contraction presumably takes place via the same orthoacetate, with the tetrabutylammonium species as the cation.

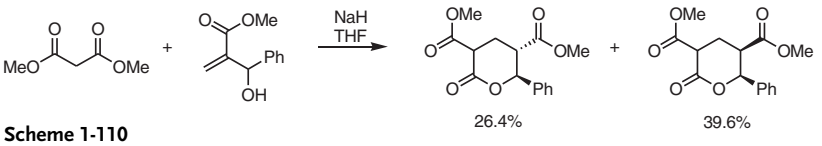


Scheme 1-108



Scheme 1-109

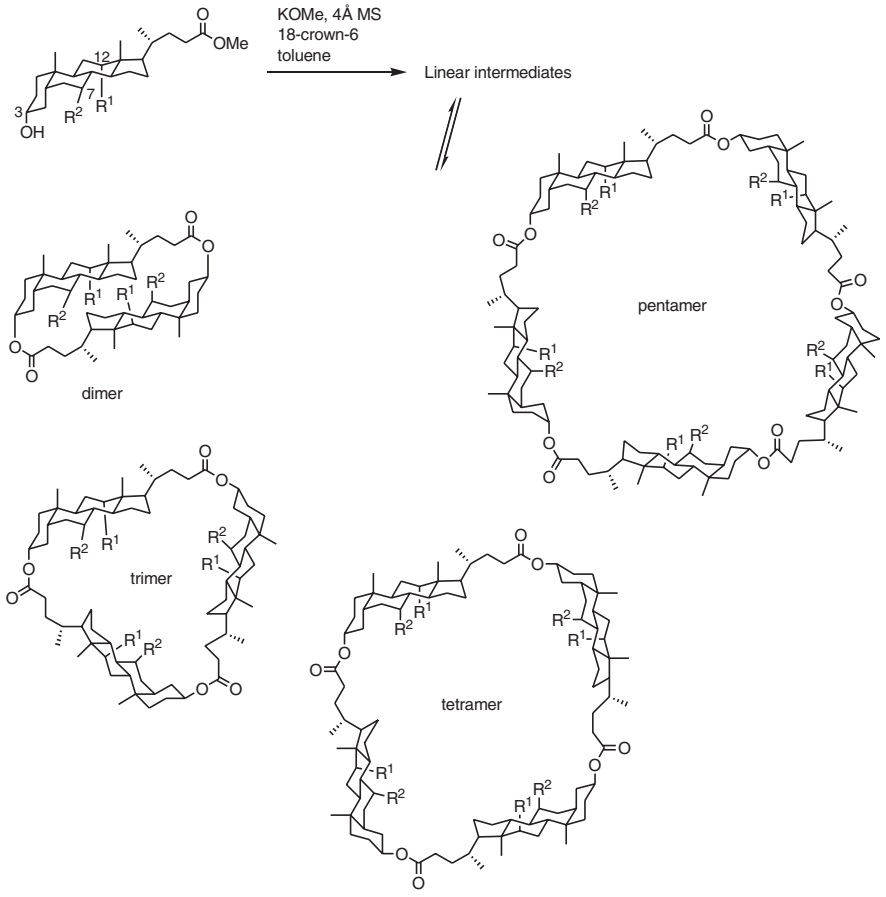
Consecutive Michael addition and lactonization provides useful intermediates for carbapenem (Scheme 1-110) [92CL305]. Treatment of dimethyl malonate with alkyl 2-(1-hydroxyalkyl)propenoates in the presence of NaH furnishes lactones as pairs of diastereomers.



Scheme 1-110

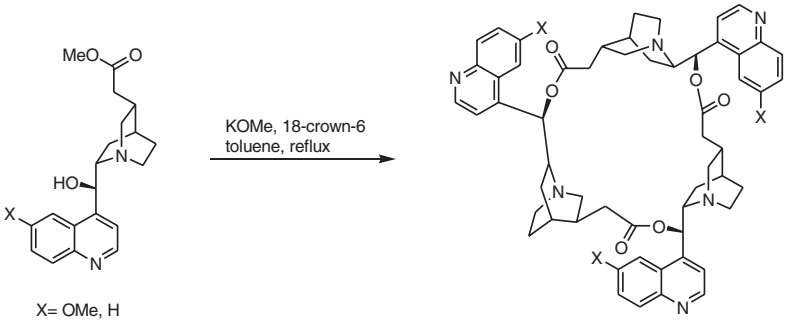
A thermodynamically controlled macrolactonization procedure is feasible with cholic acid derivatives (Scheme 1-111) [96CC319]. The product distribution, from di-

mer to pentamer, is basically the same for the substrates employed, but dependent to some extent on the substituents on C7 and C12. The distinct difference is that a dimer is produced only for the substrate without substituents at C7. The thermodynamic and reversible nature of the obtained distribution is apparent from the fact that exposure of the pure cyclic oligomers to the reaction conditions gives the same ratio of products irrespective of the starting materials.



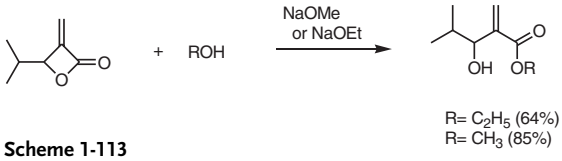
Scheme 1-111

Trimerization of hydroxy esters derived from cinchonidine is catalyzed by KOMe/[18]crown-6 (Scheme 1-112) [96AGC(E)2143, 97JACS2578].

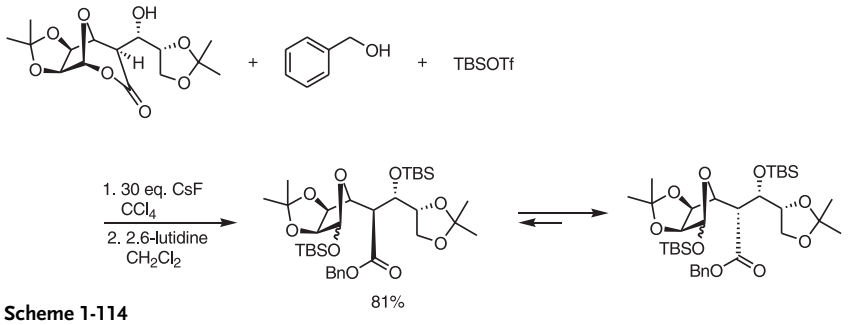


Scheme 1-112

Transesterification is useful for ring-opening of lactones. Treatment of an α-methylene-β-lactone with sodium methoxide or ethoxide provides β-hydroxy α,β-unsaturated esters (Scheme 1-113) [91JOC5782]. Alcoholysis of uronolactone with benzyl alcohol in the presence of various bases such as K_2CO_3 and CsF produces a mixture of the desired benzyl ester and its epimer (Scheme 1-114) [94JOC2487]. The highest ratio (12 : 1) is achieved when 30 equiv. of CsF are employed.



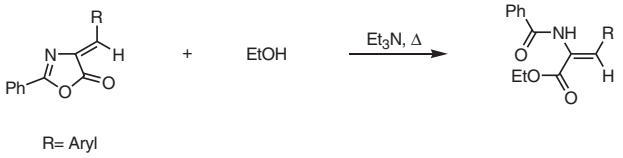
Scheme 1-113



Scheme 1-114

1.2.3.2 **Amines**

Amines are not normally strong enough bases to effect transesterification, but they are employable if the substrates or reagents are reactive. The most common amine, Et_3N (1.5 equiv.), induces ring-opening of 4-arylmethylene-2-phenyl-2-oxazolin-5-ones in refluxing ethanol (Scheme 1-115) [91H(32)1317]



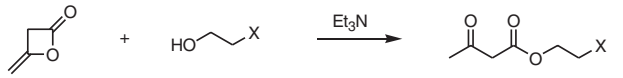
R= Aryl

Scheme 1-115

Ring-opening of diketene is effected by Et_3N. Treatment of diketene and 2-azidoethanol (1 equiv.) or ethylene glycol (4 equiv.) in the presence of Et_3N furnishes the corresponding 2-azido- or 2-hydroxyethyl acetoacetate, respectively (Scheme 1-116) [96JHC157, 96JMEC4576]. The β-aminoethyl acetoacetate obtained by this procedure can be further transformed into the diazoacetate (Scheme 1-117) [94JOC6051].

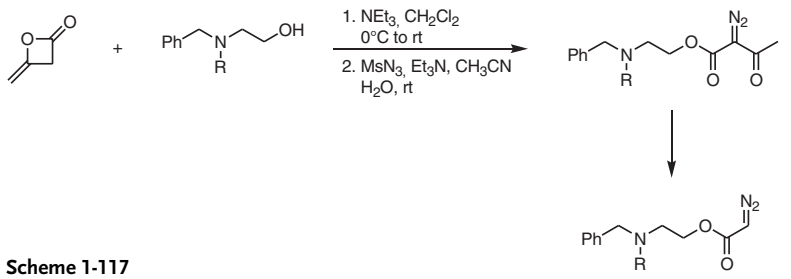
Experimental Procedure [96JHC157]

Diketene (4.2 g, 50 mmol) is added dropwise with stirring to preheated (60 °) 2-azidoethanol (4.35 g, 50 mmol) containing a catalytic amount of triethylamine (4–5 drops). Diketene is added at such a rate that the temperature of the reaction mixture does not exceed 80 °, and the reaction is allowed to proceed at 80 ° for one additional hour. Removal of the solvent in vacuo gives a residue that is purified by silica gel column chromatography with ethyl acetate/hexane (1 : 1 v/v) as eluent to afford 2-azidoethyl acetoacetate as an oil (5.2 g, 60 %).



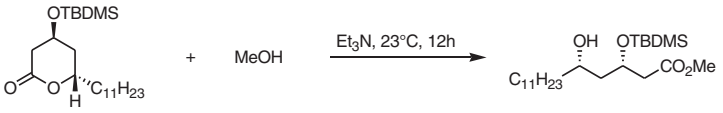
X= N_3, OH

Scheme 1-116

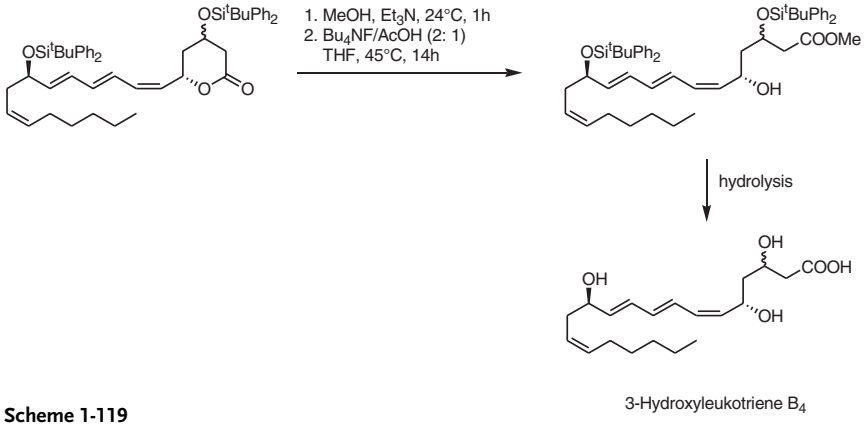


Scheme 1-117

δ-Lactones also undergo ring-opening by alcohol. Treatment of the lactone shown in Scheme 1-118 with methanol in the presence of Et_3N at 23 °C affords the methyl ester [99CC1743]. Similarly, methanolysis of a δ-lactone in the presence of Et_3N constitutes the final key step in the synthesis of methyl ester of 3-hydroxyleukotriene B_4 (Scheme 1-119) [94JACS5050].

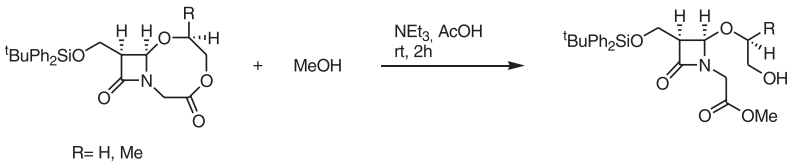


Scheme 1-118



Scheme 1-119

Larger rings are quantitatively opened as well (Scheme 1-120) [97T14153].



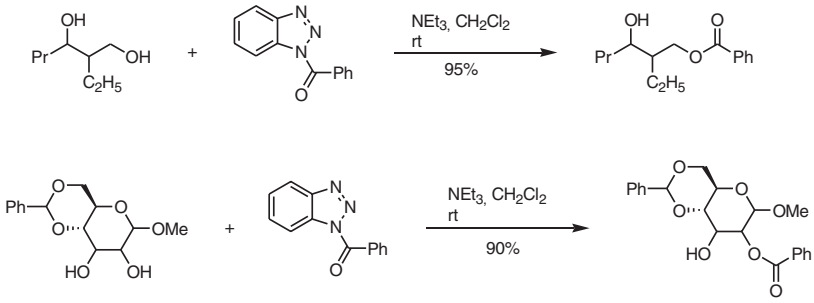
Scheme 1-120

1-(Benzoyloxy)benzotriazole is a reactive acylation reagent. Selective benzoylation of a primary alcohol over a secondary one in a glycol is feasible in the presence of Et_3N in CH_2Cl_2 at room temperature, while the 2-hydroxy groups in glucopyranoside and altropyranoside are selectively benzoylated under the same conditions (Scheme 1-121) [85JOC1751]. The benzoates obtained are applicable to the synthesis of methyl mono- and di-*O*-α-L-rhamnopyranosyl-α-D-glucopyranosiduronic acids [99JCC69].

Experimental Procedure [85JOC1751] Scheme 1-121

Triethylamine (305 μL, 2.2 mmol) is added at room temperature to a stirred solution of 1-phenyl-1,2-ethanediol (280 mg, 2.0 mmol) and 1-(benzoyloxy)benzotriazole (503 mg, 2.1 mmol) in methylene chloride (8 mL). The reaction mixture is stirred at room temperature for 24 h, diluted with methylene chloride (30 mL), washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product is subjected to silica gel col-

umn chromatography with a hexane/ethyl acetate (6:1) mixture as an eluent to afford the dibenzoate (34 mg, 5%), the primary monobenzoate (390 mg, 83%), and the secondary monobenzoate (42 mg, 9%).

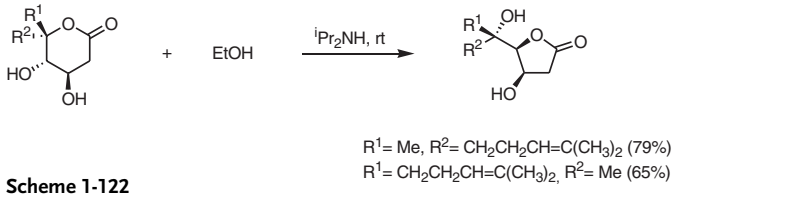


Scheme 1-121

Diisopropylamine is useful for ring-contraction from δ-lactones to γ-lactones (Scheme 1-122) [97T659]. The reaction is conducted in the presence of 2 equiv. of the amine at room temperature to afford γ-lactones, which are converted into 5-methylated 2-deoxysugars.

Experimental Procedure [97T659] Scheme 1-122

Dry $ZnCl_2$ (4 equiv.) is added at rt. and under nitrogen atmosphere to a stirred solution of epoxy ester in anhydrous CH_2Cl_2 (15 mL $mmol^{-1}$). When the reaction is complete (20 min), quenching is performed by addition of a saturated solution of $NaHCO_3$, and the mixture is extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated to give the crude product.



Scheme 1-122

Strongly basic amines find broader applications. DMAP (4-dimethylaminopyridine) is one such. Methyl β-ketoesters are successfully transformed into the corresponding esters with higher alcohol components [85JOC3618]. This reaction is versatile because it is workable for a variety of alcohols. Tertiary alcohols and non-enolizable β-keto esters are not employable, however, and a large excess (10 equiv.) of β-keto ester usually has to be used. This drawback can be offset by conducting the reaction in the presence of molecular sieves [88JOC449]. This new technique provides good yields of the desired esters from the use of β-keto ester, allylic alcohol, and DMAP in 1:1:1 ratio. It should be noted, though, that non-enolizable α,α-disubsti-

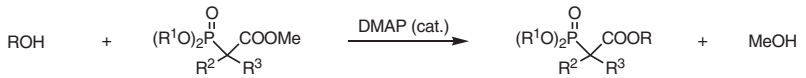
tuted keto esters are not employable (see 1.2.2.2). The DMAP procedure is applicable to synthesis of phosphonoacetates (Scheme 1-123) [87TL2713]. The ester exchange reaction takes place selectively at a carboxylic acid ester moiety rather than at a phosphonic acid ester moiety, and only enolizable phosphonoacetates react effectively with primary and secondary alcohols, but not with tertiary alcohols. This reaction is utilized for a synthesis of (–)-pyrenophorin (Scheme 1-124) [87TL2717]. Subjection of a lactol to transesterification with phosphonoacetate followed by Horner-Emmons-Wadsworth olefination affords the desired macrolide.

Experimental Procedure [85JOC3618]

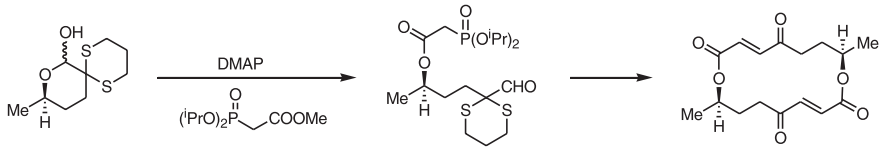
A flame-dried, two-necked, 50 mL, round-bottomed flask fitted with a reflux condenser and a nitrogen purge is flushed with N_2 and charged with *l*-menthol (300 mg, 1.92 mmol), DMAP (70 mg, 0.577 mmol), and toluene (6 mL). The mixture is magnetically stirred until the *l*-menthol and DMAP are dissolved, and methyl acetoacetate (0.62 mL, 5.77 mmol, 3.0 equiv.) is then added. The mixture is warmed at reflux for 42 h. The reaction mixture is cooled in an ice/water bath and quenched with saturated ammonium chloride solution (20 mL). Extracting solvent (20 mL) is added, and the two layers are separated. The aqueous layer is extracted three times with extracting solvent (25 mL portions). The combined organic layers are dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue is bulb-to-bulb distilled to remove excess methyl acetoacetate (bp_{50} 70°C). The pot residue is then chromatographed on silica gel (10 g) with EtOAc/petroleum ether (3.0%). The first 30 mL is discarded. The next 60 mL is concentrated in vacuo to give *l*-menthyl acetoacetate (385 mg, 1.6 mmol, 83%) as a clear oil.

Experimental Procedure [88JOC449]

A mixture of β-keto ester (5 mmol), allylic alcohol (5 mmol), and DMAP (5 mmol) is dissolved in sufficient toluene (ca. 200 mL) to ensure wetting of 25 g of oven-dried molecular sieves (4 Å). The mixture is then heated at reflux until no starting material is detectable by ^1H NMR spectroscopy; this typically requires 12–36 h. After being allowed to cool to room temperature, the solution is washed with saturated ammonium chloride (2 × 25 mL) and dried ($MgSO_4$). The toluene is removed by rotary evaporation, and the products are isolated by HPLC (1.5% EtOAc–98.5% Skelly B).



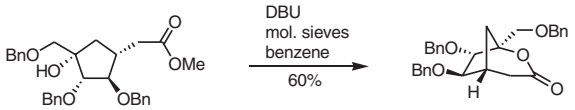
Scheme 1-123



Scheme 1-124

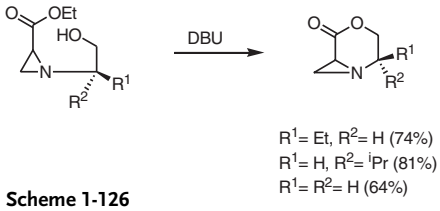
Selective acetylation of a primary alcohol over a secondary alcohol or a phenol is achievable by use of vinyl acetate in the presence of DMAP, although the yields are modest [94TL3583].

DBU (diazabicyclo[5.4.0]undec-7-ene) is another amine that serves for these purposes. Stirring of 4-hydroxycyclopentanylacetate in the presence of a catalytic amount of DBU and molecular sieves (4 Å) in refluxing benzene furnishes a bicyclic lactone (Scheme 1-125) [90CAR(206)233].



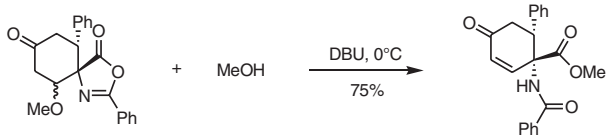
Scheme 1-125

Lactonization of 1-β-hydroxyalkylaziridine-2-carboxylic esters is effected by DBU to furnish 4-oxa-1-azabicyclo[4.1.0]heptane-5-ones (Scheme 1-126) [90T6741].



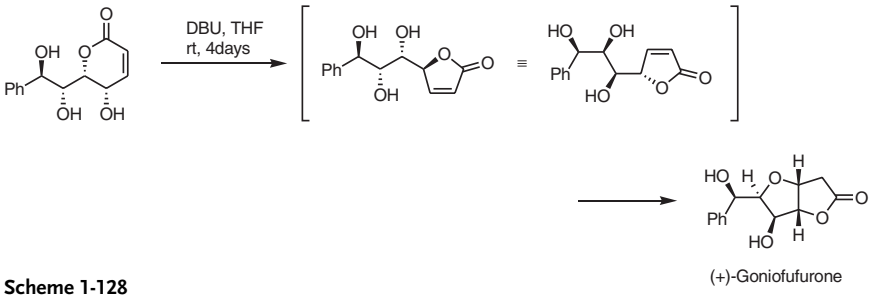
Scheme 1-126

When stereoisomers of the spirooxazolone shown in Scheme 1-127 are treated with Et_3N in MeOH, only the *endo* cycloadduct undergoes methanolysis of the oxazolone ring and elimination, the *exo* isomer remaining unaltered. The use of DBU instead results in a clean reaction for both isomers [94T12989].



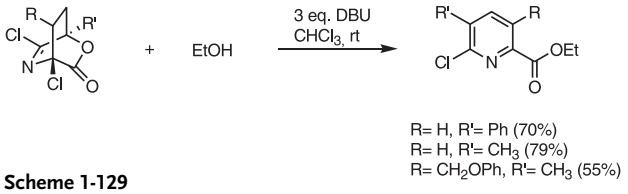
Scheme 1-127

Treatment of triol lactone with DBU results in ring-contraction to give (+)-goniofufurone (Scheme 1-128) [95T1429].



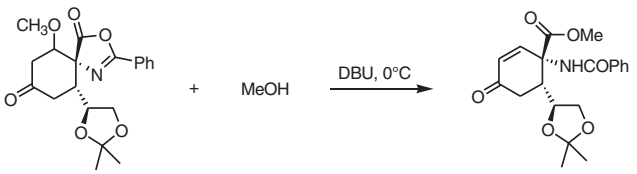
Scheme 1-128

Concomitant lactone alcoholysis and dehydrochlorination is effected by treatment of 3,5-dichloro-2H-1,4-oxazin-2-ones with alcohols in the presence of DBU, affording 6-chloro-2-pyridinecarboxylic acid esters (Scheme 1-129) [96T6997, 96T12529].

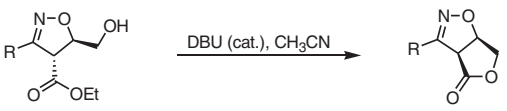


Scheme 1-129

Treatment of oxazolones with methanol/DBU results in ring-opening (Scheme 1-130) [96TA1431]. Lactonization is induced by treatment of hydroxy ester derivatives of 4,5-*trans*-isoxazoline with DBU (Scheme 1-131) [98CL1023]. The 4,5-*trans*-isoxaziline substrate initially undergoes facile isomerization to the *cis* isomer, thus offering a convenient way to arrive at *cis*-isoxazoline compounds.



Scheme 1-130

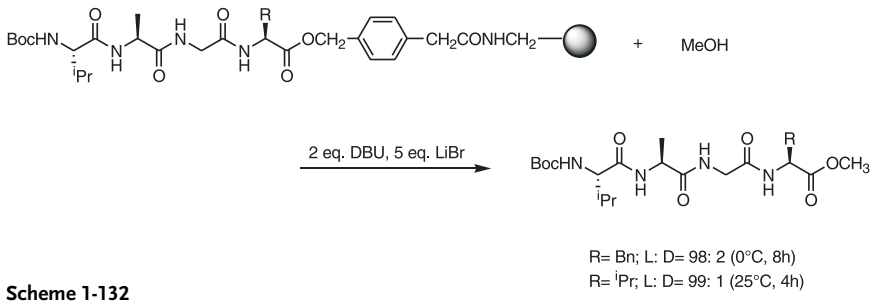


Scheme 1-131

As seen above, DBU is not always active enough to be used as a promoter for transesterification in a general manner. The basicity, and hence activity, are improved by combining it with LiBr [91HCA1102]. Typically, the use of 0.5 equiv. of DBU together with 2~5 equiv. of LiBr in neat alcohol mediates transesterification of enolizable esters in high yields, except in the case of tertiary butanol. Peptide esters are also employable, although elaboration to make the reaction conditions as mild as possible is needed; otherwise epimerization cannot be avoided. This technology is successfully applicable to detach peptides from PAM and Wang resins (Scheme 1-132).

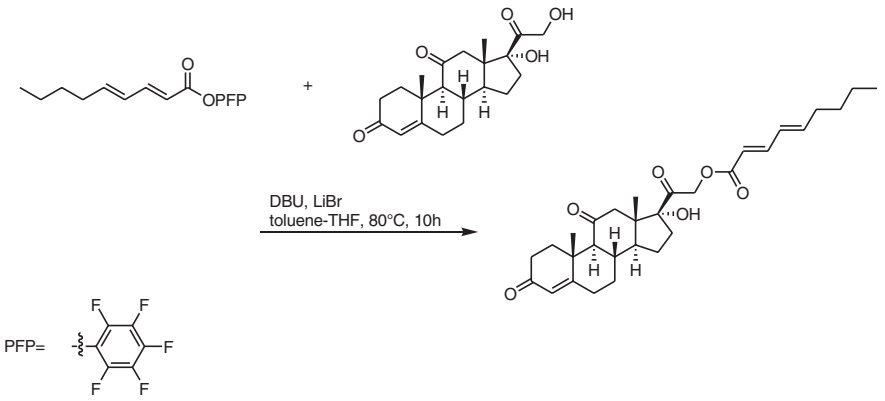
Experimental Procedure [91HCA1102] Scheme 1-132

LiBr (5 equiv.) and the starting carboxylate ester (1 equiv.) are dissolved under dry Ar in the appropriate quantity of the desired absolute alcohol, so that a 0.2–0.3 M concentration of substrate is obtained. Freshly distilled DBU (0.5 equiv.) is then added to this solution, and stirring is continued at rt., the course of the reaction being monitored by TLC or GC. When transesterification is complete, the mixture is evaporated and hydrolyzed with a sat. aq. NH_4Cl solution, or HCl (1 N). The product is extracted twice with Et_2O, the combined organic fractions are washed to neutrality with brine, dried (Na_2SO_4), and evaporated, and the crude product is purified by distillation or flash chromatography.



Scheme 1-132

This technique is also applicable to transesterification of the pentafluorophenyl dienoate shown in Scheme 1-133 [97CC2305].

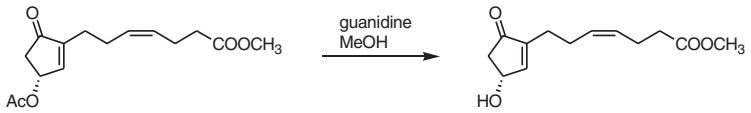


Scheme 1-133

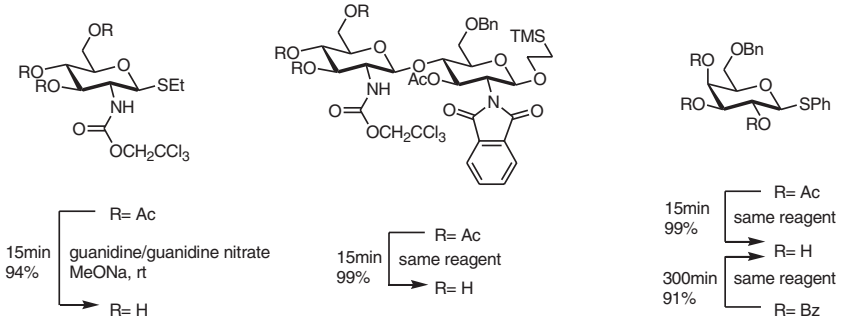
Guanidine-mediated transesterification between acetylated carbohydrates and phenols with alcohol effects deprotection of these substrates [87TL3569]. This technique is applied to deacetylation of 3-acetoxycyclopentenone (Scheme 1-134) [90JOC3377]. However, straightforward application of this procedure to 2-deoxy-2-aminosugars with 2,2,2-trichloroethoxycarbonyl groups results in decomposition of this group to the corresponding carbamate. The use of guanidine/guanidine nitrate in methanol, on the other hand, brings about the desired deacetylation (Scheme 1-135) [97TL1627].

Experimental Procedure [90JOC3377] Scheme 1-134

A stock solution of 0.5 M guanidine in CH_3OH is prepared by addition, under argon atmosphere, of hexane-washed (3 ×) sodium spheres (1.78 g, 77.4 mmol) to ice-cooled CH_3OH (154 mL). When all the sodium has reacted, guanidine carbonate (14.2 g, 79.0 mmol) is added. This solution is stirred at room temperature for 25 min, and the mixture is allowed to stand, to settle out precipitated salts. Methyl 7-[3-(*R*)-(acetyloxy)-5-oxo-1-cyclopenten-1-yl]-4(*Z*)-heptanoate (93 : 7 *R*/*S* ratio, 12.8 g, 45.6 mmol) in absolute CH_3OH (50 mL) is placed under argon in a separate flask. This is cooled to 0 °C in an ice bath, and the guanidine in CH_3OH prepared above (0.5 M, 100 mL) is added to it by syringe over ~5 min. This mixture is stirred at ~10 °C for 5 min. TLC (80% ethyl acetate in hexane on silica gel) shows complete consumption of acetate. Glacial acetic acid (2.86 mL, 3.0 g, 50.0 mmol) is then added to the reaction mixture to neutralize the guanidine. After the mixture has been stirred for 5 min, solvent is removed at reduced pressure to give a thick slurry. The residue is partitioned between water (100 mL) and toluene/ethyl acetate (1 : 1 v/v, 100 mL). The aqueous layer is further extracted with ethyl acetate). The combined organic layers are washed with water (2 × 50 mL) and brine (50 mL) and dried over sodium sulfate. Removal of solvent at reduced pressure gives a deep amber oil, which is purified by flash chromatography on silica gel with 50% ethyl acetate in hexane to give methyl 7-(3(*R*)-hydroxy-5-oxo-1-cyclopenten-1-yl)-4(*Z*)-heptenoate (8.06 g, 77%) after exhaustive removal of solvent.

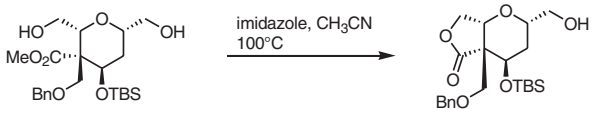


Scheme 1-134

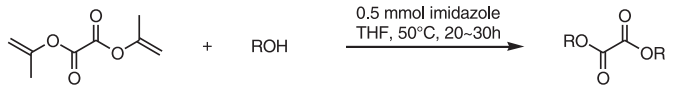


Scheme 1-135

Imidazole is employable as a promoter for lactonization, as shown in Scheme 1-136 [97TL1001]. The reaction in CH_3OH at 100 °C allows complete differentiation between the two hydroxy groups. Diisopropenyl oxalate, obtained by addition of oxalic acid to propyne, is transformed into various oxalate esters upon treatment with alcohol in the presence of imidazole (Scheme 1-137) [93T2629].



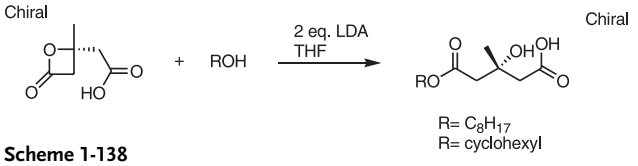
Scheme 1-136



Scheme 1-137

1.2.3.3 **Others**

Treatment of a chiral β-lactone with alcohols in the presence of LDA provides chiral half-esters (Scheme 1-138) [96TL2275]. Octanol, cyclohexanol, 3-pentanol, farnesol, and gymnoprenol are successfully incorporated by use of 2 equiv. of LDA.



Scheme 1-138

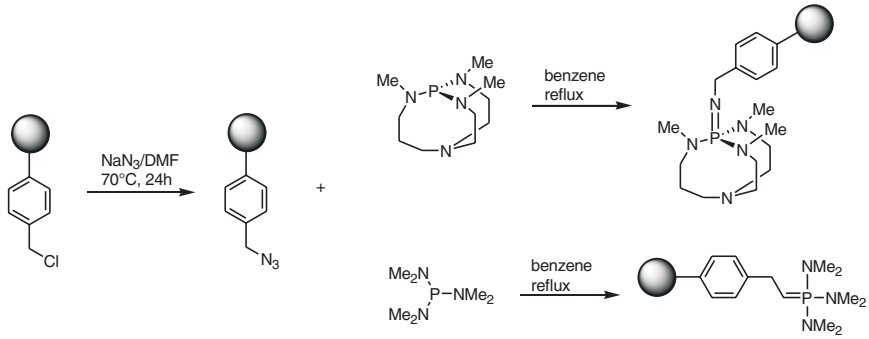
Strongly basic phosphorus compounds are also useful. For example, non-ionic superbases of the type $P(RNCH_2CH_2)_3N$ catalyze transesterification of various carboxylic acids with primary, secondary, and allylic alcohols [99JOC3086]. Acylation of alcohols with enol esters is also feasible. A broad range of substituents – such as epoxide, carbamate, acetal, oxazoline, nitro, and alkynyl groups – are tolerated. *N*-Protected peptides undergo clean transesterification without significant racemization. The iminophosphorane bases $PhCH_2N{=}P(MeNCH_2CH_2)_3N$ and $PhCH_2N{=}P(NMe_2)_3$ catalyze acylation of primary alcohols with enol esters as well [99JOC9063]. Since these catalysts are not effective for secondary alcohols, these alcohols can be discriminated from primary ones. Immobilization of these catalysts does not give rise to any decrease in catalytic activity (Scheme 1-139). The new catalysts can be used three times without significant loss of product yield, although the catalyst beads become a fine powder that is more difficult to isolate.

Experimental Procedure [99JOC3086]

Ester (1 mmol) is added at room temperature to a stirred solution of $P(RNCH_2CH_2)_3N$ (R = Me or *i*-Pr, 10–15 mol%) in the alcohol (5 mL). The mixture is stirred for 4–24 h and the alcohol is then evaporated in vacuo. The residue is dissolved in diethyl ether and passed through a pad of silica. Solvent evaporation under vacuum gives the product, which is found to be pure by ^1H NMR analysis.

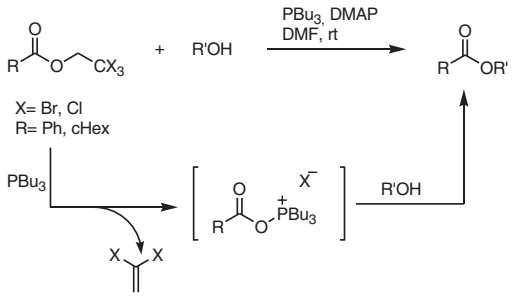
Experimental Procedure [99JOC9063] Scheme 1-139

Enol ester (5 mmol) is added at room temperature to a stirred solution of iminophosphorane base (10 mol %) and alcohol (1 mmol) in THF (0.5 mL). The mixture is stirred at room temperature for 14–38 h, and the solvent and excess enol ester are evaporated in vacuo. The residue is purified by column chromatography on a small pad of silica gel, with 0–20 % ethyl acetate in hexane as eluent. When polymer-supported catalyst is employed, the polymer is filtered off after the completion of the reaction and washed with ether. The solvent is then evaporated in vacuo, and the residue is purified by column chromatography on a small pad of silica gel with 0–20 % ethyl acetate in hexane as eluent.



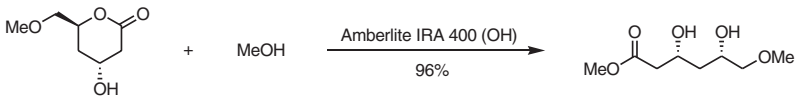
Scheme 1-139

Tris(2,4,6-trimethoxyphenyl)phosphine is utilized for deacetylation [2001CL934]. Peracetylated sugars and glucals are deacetylated completely upon treatment with the phosphine in methanol. 2,2,2-Trihaloethylesters are transesterified by action of Bu_3P/DMAP (Scheme 1-140) [99JOC1430]; no reaction takes place in the absence of phosphine. The reaction proceeds via an acyloxyphosphonium intermediate, so transesterification does not involve Mitsunobu-type inversion.



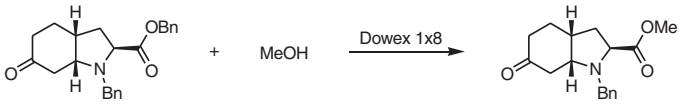
Scheme 1-140

Amberlite IRA 400 (OH) mediates methanolysis of a lactone to give a quantitative yield of *syn*-1,3-diol (Scheme 1-141) [94JACS8422].



Scheme 1-141

A benzyl to methyl ester transformation of *cis*-octahydroindolone is performed efficiently with the aid of DOWEX 1x8, a strongly basic anion exchange resin (Scheme 1-142) [96TA1899].



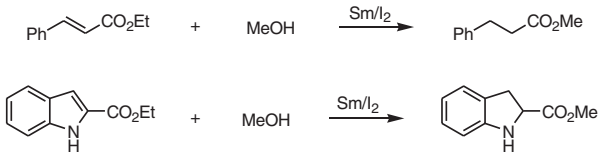
Scheme 1-142

Diphenylammonium triflate, an excellent catalyst for esterification between carboxylic acids and alcohols (see Section 1.1.3), also catalyzes transesterification where 1.5 equiv. of alcohol being necessary [2000TL5249]. Addition of 0.1 equiv. of TMSCl improves catalytic activity.

1.2.4
Other Activators

Transesterification takes place when mixtures of β-keto esters and alcohols are heated in toluene in the presence of NBS (*N*-bromosuccinimide), [2001SL1715]. NBS is only effective for β-keto esters, no reaction occurring with other esters.

Samarium iodine is frequently used in reduction of various functionalities. During these reactions, coexisting esters occasionally undergo transesterification. When conjugate reduction of α,β-unsaturated esters is performed with these reagent in methanol, the ethyl esters are transformed into the corresponding methyl esters (Scheme 1-143) [95SL443]. Reduction of azides [97TL1065] and aromatic nitro compounds [98TL7243] to the corresponding amines is accompanied by transesterification of coexisting ester functions.

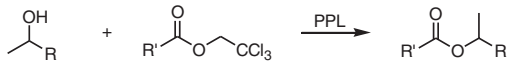


Scheme 1-143

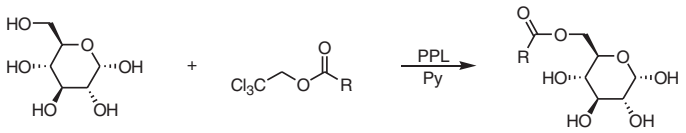
1.2.5
Enzymes

Transesterification is one of the reactions for which enzymes are utilized most effectively. This technology has experienced explosive expansion for the last decade. According to the literature survey, in fact, more than 600 papers have appeared since 1990. This figure constitutes 10% of all the references hit by our literature survey on esterification, and nearly 550 of these papers are related to lipases, an indication of

the pivotal position of these enzymes (refer to the database disc). As in the case of esterification, their utilization was boosted by the development of enzyme reactions in organic solvents. The enzymatic reaction is highly specific to individual reactions and enzymes. In contrast to yeast lipase (see Section 1.1.7), PPL (porcine pancreatic lipase) is not effective for esterification. However, kinetic resolution of secondary alcohols with this lipase by transesterification with 2,2,2-trichloroethyl esters is feasible (Scheme 1-144) [85JACS7072]. PPL is quite flexible with respect to experimental conditions. The enzymatic process can be carried out in a variety of solvents such as paraffins, toluene, carbon tetrachloride, ether, acetone, acetonitrile, dioxane, etc. In all instances the presence of even a small amount of water severely suppresses the enzymatic transesterification. The lipase can be used as a catalyst over a wide temperature range: the enzymatic transesterification accelerates more than sevenfold upon a temperature increase from 25 to 60 °C. The enzyme loses virtually no catalytic activity after each transesterification performed at 25 °C and less than a quarter of its initial activity if the reaction is carried out at 60 °C. The PPL/2,2,2-trichloroethyl ester technique is applicable for the preparation of monoacylated sugars [86JACS5638]. Only the primary hydroxy group can be acylated in pyridine at 45 °C (Scheme 1-145).



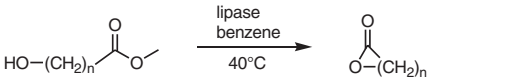
Scheme 1-144



R= C_4H_9 (50%)
R= CH_3 (76%)
R= C_8H_{17} (57%)
R= $C_{11}H_{23}$ (91%)

Scheme 1-145

As well as PPL, lipase P from *Pseudomonas* sp. can also be used for lactonization of methyl esters of ω-hydroxycarboxylic acids (Scheme 1-146) [87TL805]. Subjection of chiral methyl 10-hydroxyundecanoate to the same reaction conditions produces no monolide but a small amount of diolide. However, γ-methyl- and γ-phenylbutyrolactones are obtainable in optically pure form with PPL (Scheme 1-147) [87TL3861]. The efficiency of lactone formation from methyl ω-hydroxy carboxylates with lipase Amano P is enhanced by addition of molecular sieves (4 Å), which serve for removal of the methanol formed [89CL1775].



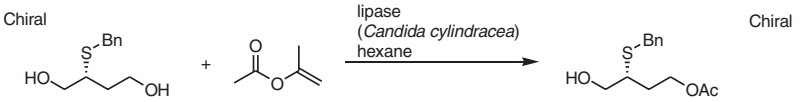
lipase= *P. sp.* (78%)
PPL (73%)
C. cylindracea (0%)

Scheme 1-146

R=R'= H
R= CH_3, R'= H
R= H, R'= CH_3
R= Ph, R'= H
R= H, R'= Ph

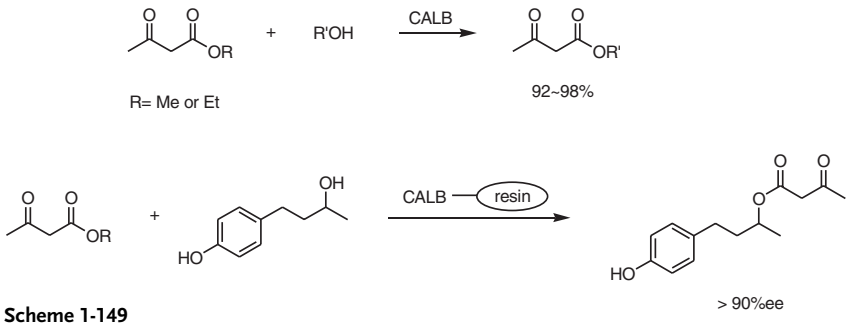
Scheme 1-147

There is a unique regioselectivity between primary alcohols [90CL1137]. The 4-hydroxy group of the diol depicted in Scheme 1-148 undergoes exclusive esterification by isopropenyl acetate with the aid of *Candidia cylindracea* lipase.



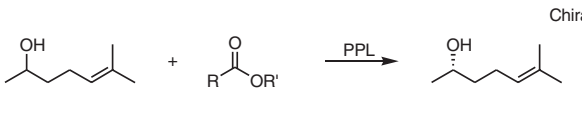
Scheme 1-148

Immobilization of lipase is possible. Thus, CALB (*Candida antarctica* lipase B) attached to a macroporous resin effects transesterification of β-keto esters (Scheme 1-149) [2001JOC1906]. Primary, secondary, allylic, and propargylic alcohols are employable. The kinetic resolution of secondary alcohols gives rise to esters with > 90% *ee*.



Scheme 1-149

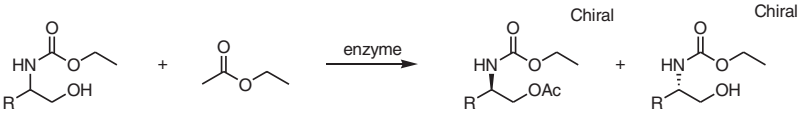
The enantioselectivity in the kinetic resolution of racemic sulcatol by PPL in ether is increased tenfold by dehydration of the enzyme and use of 2,2,2-trifluoroethyl laurate as the ester (Scheme 1-150) [87TL2091].



R	R'	E
C_3H_7	-$CHClCHCl_2$	24
	-$CHFCHF_2$	22
C_7H_{15}	-$CHClCHCl_2$	24
	-$CHFCHF_2$	19
$C_{11}H_{23}$	-$CHClCHCl_2$	27
	-$CHFCHF_2$	100

Scheme 1-150

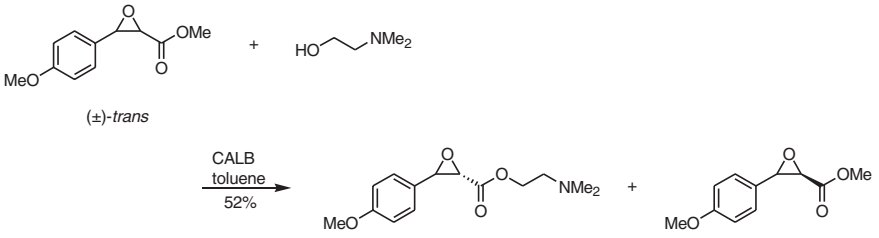
2-Amino alcohols are transesterified successfully, *N*-alkoxycarbonyl derivatives of 2-amino alcohols undergoing kinetic resolution by mammalian lipases in ethyl acetate (Scheme 1-151) [87JOC5079]. 2-Halo-1-arylethanols are also substrates that can be successfully kinetic resolved by lipase Amano P from *Pseudomonas fluorescens* [88JOC6130].



R= Et
R= Me
enzyme= steapsin/Celite or steapsin or pancreatin etc.

Scheme 1-151

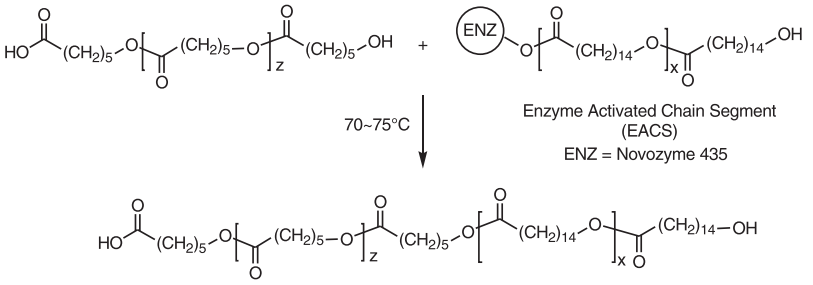
The use of amino alcohols in enzyme-catalyzed transesterification is occasionally convenient when the presence of other alcohols results in difficulties in workup operations. Kinetic resolution of racemic methyl *trans*-3-(4-methoxyphenyl)glycidate (a key intermediate for the synthesis of the well known drug diltiazem hydrochloride) is accomplished with suitable amino alcohols and catalysis by CALB in organic solvents (Scheme 1-152) [2001ASC(343)721]. The use of normal alcohols in this procedure encounters difficulty in the separation, due to insolubility of the products.



Scheme 1-152

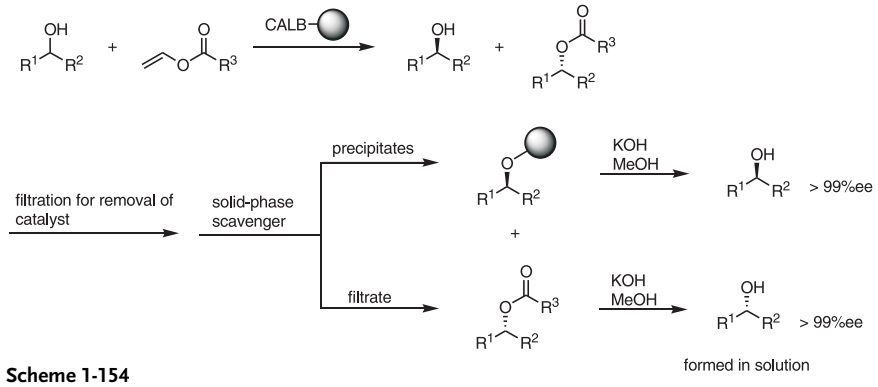
Protein engineering is useful for improving the activity of lipase. Although 1-halo-2-alkanols are poorly resolved by CALB, mutants display high efficiency for kinetic resolution with vinyl ester [2001CBC766].

Transesterification reactions between polyesters can be used to prepare copolymers [2000JACS11767]. Transacylation reactions between polyesters are believed to involve intrachain cleavage by the lipase to form an enzyme-activated chain segment, followed by reaction of this activated segment with the terminal hydroxyl unit of another chain (Scheme 1-153).



Scheme 1-153

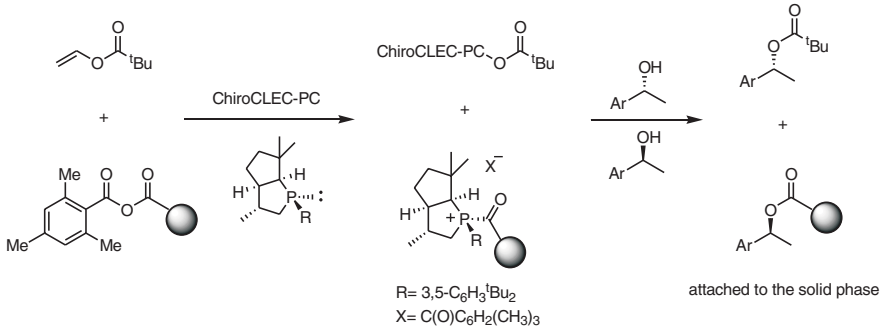
A sequential application of a polymer-supported catalyst for kinetic resolution and a scavenging reagent provides a convenient method for the isolation of chiral secondary alcohols (Scheme 1-154) [2001JOC5645]. After the standard kinetic resolution of a racemic secondary alcohol with polymer-supported CALB, the lipase is filtered off. The filtrate containing the ester and unreacted alcohol is then treated with polymer-supported benzoyl chloride as a scavenger. Upon filtration, the ester is obtained from the filtrate while hydrolysis of the resin releases the alcohol.



Scheme 1-154

Lipase-catalyzed transesterification in ionic liquids proceeds with markedly enhanced enantioselectivity: lipases such as CALB and *Pseudomonas cepacia* lipase are up to 25 times more enantioselective in ionic liquids than in conventional organic solvents [2001OL1507]. Extraction of the CALB-promoted reaction mixture with supercritical carbon dioxide enables facile separation of the products and the lipase/ionic liquid mixture [2002CC992].

A combination of enzyme and phosphine catalyst allows parallel kinetic resolution [2001JACS2428]. A three-phase system consists of ChiroCLEC-PC (a commercial cross-linked lipase acylation catalyst), polymer-bound mesitoyl anhydride as an insoluble acyl donor, and a soluble chiral phosphine catalyst, together with vinyl pivalate as a soluble acyl donor (Scheme 1-155). Such phase separation provides one way to control which reagent is activated by a given catalyst.

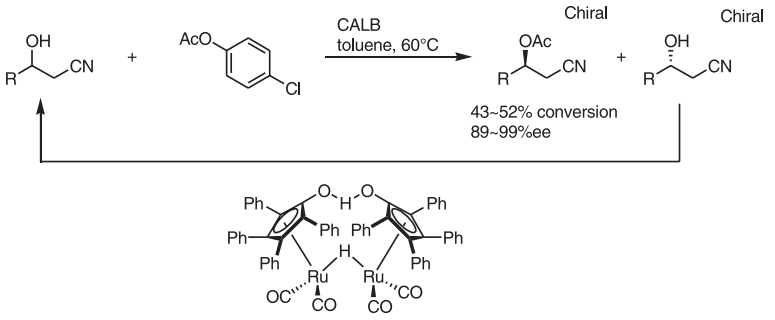


Scheme 1-155

The combination of lipase and artificial catalysts can also provide dynamic kinetic resolution [2001ASC(343)726]. Treatment of racemic β-hydroxy nitriles with CALB (Novozym-435) and a ruthenium catalyst affords the corresponding *S* acetates in 85% yield with >94% *ee* (Scheme 1-156). The isomerization of the alcohol is catalyzed by the ruthenium catalyst without deterioration in the lipase activity.

Experimental Procedure

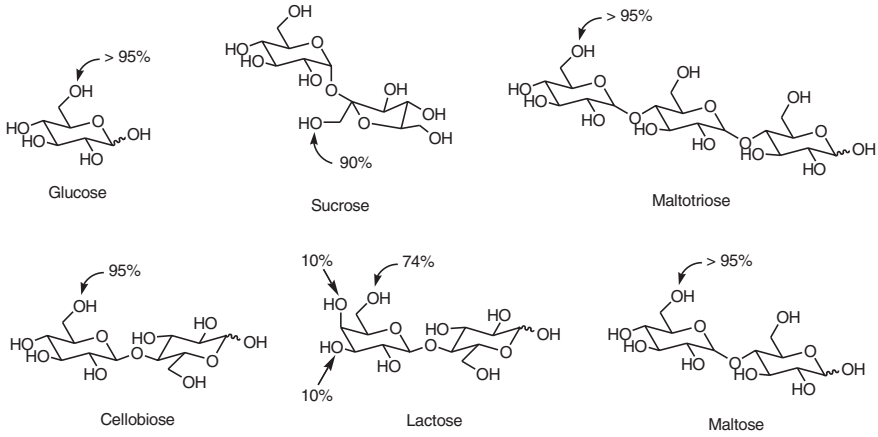
The ruthenium catalyst (10.8 mg, 4 mol%) and Novozym-435 (20 mg) are placed under argon in a Schlenk flask. A solution of 3-hydroxy-3-phenylpropionitrile (112 mg, 0.6 mmol) in dry toluene (2 mL) is added under argon. The reaction mixture is stirred at 100 °C for 36 h. The enzyme is filtered off and washed with toluene (3 × 5 mL). The organic layer is evaporated to leave the desired product.



Scheme 1-156

Esterase catalyzes transesterifications carried out in biphasic aqueous/organic mixtures [84JACS2687]. Water-insoluble substrates occupy the organic phase, while the enzyme is situated in the aqueous phase. By use of porous supports (Sepharose or Chromosorb) filled with aqueous solutions of hog liver carboxyl esterase as a stereoselective catalyst and methyl propionate as a matrix ester, the optically active alcohols and their propionic esters can be produced on a preparative scale. Kinetic resolution of 2-arylpropanoic acid ester is effected by rabbit liver esterase [92TL5901].

The proteolytic enzyme subtilisin is catalytically active in anhydrous dimethylformamide. A number of carbohydrates and other sugar-containing compounds can be regioselectively acylated by enzymatic transesterification through taking advantage of the unique dissolving potency and broad substrate specificity of subtilisin, (Scheme 1-157) [88JACS584]. Monobutyryl esters of the disaccharides maltose, cellobiose, lactose, and sucrose are readily prepared on a gram scale. The presence of a bulky aglycon moiety does not substantially reduce the catalytic efficiency of subtilisin in dimethylformamide, thus permitting preparative-scale enzyme esterification of natural compounds such as riboflavin, salicin, and the nucleosides adenosine and uridine. In addition to the butyryl group, various *N*-acetylamino acid residues can also be introduced onto sugars.



Scheme 1-157

A subtilisin mutant derived from subtilisin BPN′ is 100 times more stable than the wild-type enzyme in aqueous solution at room temperature and 50 times more stable than the wild types in anhydrous dimethylformamide [90JACS945]. The mutant enzyme can be applied to regioselective acylation of nucleosides in anhydrous dimethylformamide with 65–100 % regioselectivity.

The use of pyridine in place of dimethylformamide allows regioselective esterification of the primary hydroxy groups of ribonucleosides [94TL1353]. By this procedure, 5'-*O*-acylribobucleosides are obtained in high yields with crude subtilisin and even with the cheaper crude protease Proleather.

Cross-linked enzyme crystals of subtilisin, prepared by cross-linking of the crystallized enzyme with gultaraldehyde, are more stable than the original in both aqueous and mixed aqueous/organic solutions [97JOC3488]. This enzyme is used for transesterification.

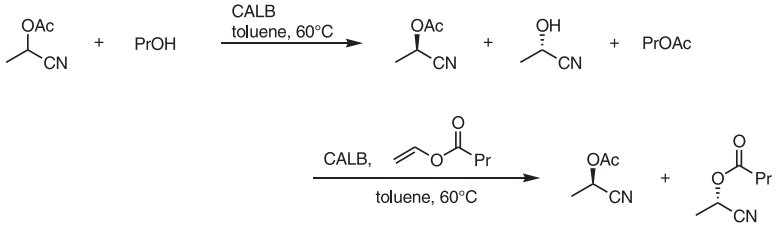
The acylase from *Aspergillus* species catalyzes acylation of alcohols with vinyl acetate [95SL599]. This technique can be applied to highly enantioselective kinetic resolutions of secondary alcohols [97SL367].

Consecutive enzymatic reactions in one pot are feasible for chemically labile cyanohydrin derivatives (Scheme 1-158) [2002EJO1516]. Racemic *O*-acetylcyanohydrins are resolved by treatment with propanol in the presence of CALB, but isolation of deprotected *S* cyanohydrins as their THP or TBS ethers results in decreases in % *ee*. This problem can be solved by esterification in situ. After the kinetic resolution, addition of vinyl butyrate to the reaction mixture affords the butyrate of the *S* cyanohydrin without any decrease in % *ee*.

Experimental Procedure

Immobilized Lipase B from *Candida Antarctica* CAL-B (368 mg) is added under nitrogen at 25 °C to a solution of *O*-acetylcyanohydrin (3.68 mmol) in dry toluene (36 mL). The reaction mixture is heated to 60 °C and 1-propanol (0.54 mL,

7.36 mmol) is then added. After the mixture has been stirred for 3 h, vinyl butyrate (2.8 mL, 18.4 mmol) is added. The mixture is stirred overnight and filtered. The organic layer is washed with sat. $NaHCO_3$ (25 mL) and dried. Evaporation followed by column chromatography affords the corresponding acetate and butyrate.

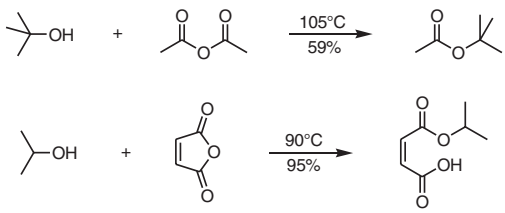


Scheme 1-158

1.3 Reaction with Acid Anhydrides

1.3.1 Without Activator

The acylation of alcohols is most frequently conducted by treatment with acid anhydrides. The use of bases such as amines is a common way to promote the reaction, but acid-based procedures are also available. The reaction without recourse to any activators is more desirable if possible. Many examples have demonstrated that the reaction does indeed proceed, in particular for acetylation (refer to the database disc). The reaction is best performed by heating an alcohol in acetic anhydride, even secondary and tertiary alcohols successfully undergoing acetylation (Scheme 1-159) [97SC2777]. It should be noted that this technique is also useful in terms of conversion of acid anhydrides into half esters.

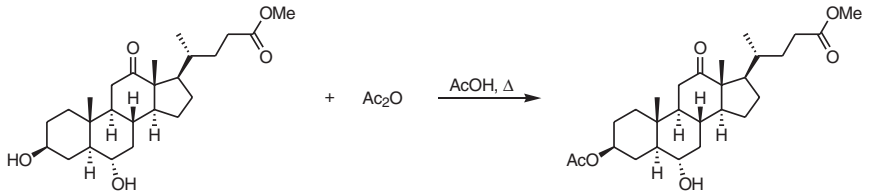


Scheme 1-159

In the synthesis of des-*N*-methyl-*N*-acetylerythromycin derivatives, acetylation at the 2′-position can be best performed simply by treating with Ac_2O in EtOAc at room temperature (Scheme 1-160) [97BMC1203], addition of amines such as Et_3N,

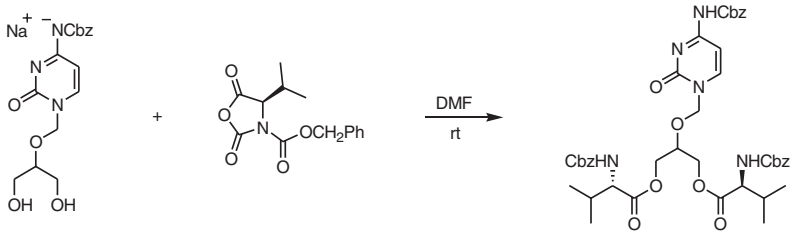
pyridine, or DMAP resulting in the formation of complex mixtures. A steroid derivative is also acetylated smoothly by Ac_2O in acetic acid without activator (Scheme 1-161) [98TL1145].

Scheme 1-160



Scheme 1-161

The preparation of valinate esters is successfully achieved by stirring the alcohol with *N*-CBZ-L-Val-*N*-carboxy anhydride at room temperature (Scheme 1-162) [95NN1591]. This is a clean reaction because CO_2 is the sole by-product.



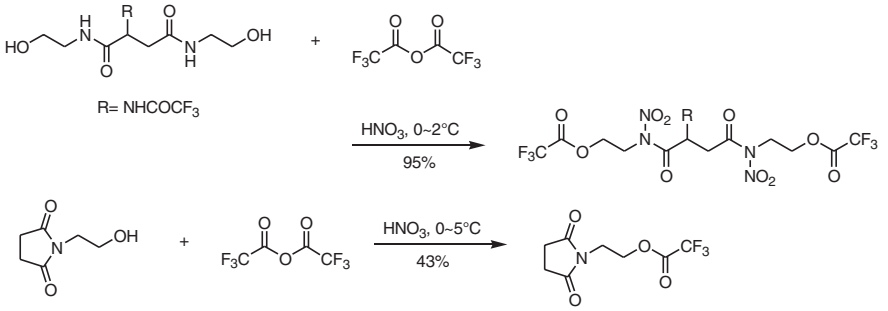
Scheme 1-162

1.3.2 Acid Catalysts

1.3.2.1 Brønsted Acids

Brønsted acids commonly employed for reaction between alcohols and acid anhydrides are sulfonic acids, sulfuric acid, and perchloric acid. There is nothing special to note on the use of these acids, although a number of examples are available (refer

to the database disc). For instance, ethanolysis of *cis*-Δ^4-tetrahydrophthalic anhydride is carried out by the action of catalytic *p*-toluenesulfonic acid [63OS304]. Sulfuric acid effects acetylation of sugars [90CJC2055] and quinols with acetic anhydride [91BCJ842]. Sulfamic acid H_2NSO_3H is also employable [98SC3173]. Perchloric acid is useful for acetylation of lactones with acetic anhydride [92CC1775]. When *N,N*-bis(2-hydroxyethyl)trifluoroacetaminosuccinodiamide is treated with a mixture of trifluoroacetic anhydride and nitric acid, both *O*-acylation and *N*-nitration take place (Scheme 1-163) [96IZV1321]. When the amine is tertiary, no nitration occurs.



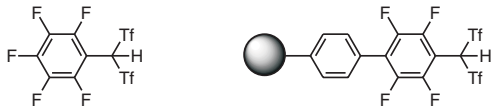
Scheme 1-163

Pentafluorophenylbis(triflyl)methane is a new, strong, organic Brønsted acid that catalyzes benzoylation of menthol with benzoic anhydride (Scheme 1-164) [2001AGC(E)4077]. Polystyrene-bound tetrafluorophenylbis(triflyl)methane also works similarly as an organic-solvent-swellable catalyst.

Experimental Procedure [2001AGC(E)4077] Scheme 1-164

Synthesis of Polystyrene-Bound 2,3,5,6-Tetrafluorophenylbis(triflyl)methane: BuLi (1.6 M solution in hexanes, 1.9 mL, 3.0 mmol) is added at room temperature to a mixture of poly(4-bromostyrene) [0.37 g, 1 mmol, 2.71 mmol Br/g resin, 2% divinylbenzene (DVB) cross-linked, 200–400 mesh] and benzene (5 mL). The reaction mixture is stirred at 60 °C for 3 h. After the mixture has cooled to ambient temperature, the solvents – together with excess BuLi – are removed by decantation. Benzene (1 mL), THF (1 mL), and lithium pentafluorophenylbis(triflyl)methide (1.36 g, 3 mmol) are added at 0 °C to the residual lithiated resin. The reaction mixture is stirred at room temperature for 0.5 h and further at 70 °C for 6 h. After the mixture has cooled to ambient temperature, water (0.5 mL) and HCl (4 M, 0.5 mL) are added in that order at 0 °C. The polystyrene-bound 2,3,5,6-tetrafluorophenylbis(triflyl)methane resin is filtered off, washed with water (5 mL), a 50% aqueous solution of THF (5 mL), THF (5 mL), and Et_2O (5 mL) in that order, and dried at 80 °C under vacuum (ca. 1 Torr) for 12 h to afford the polystyrene-bound 2,3,5,6-tetrafluorophenylbis(triflyl)methane (0.46 g). The loading of pentafluorophenylbis(triflyl)methane on the resin polystyrene-bound 2,3,5,6-tetrafluorophenylbis(triflyl)methane is estimated to be 1.01 mmol $Tf_2CHC_6F_4$ unit/g resin, based on fluorine content as determined by elemental analysis.

General Procedure for the Acylation of *l*-Menthol with Carboxylic Anhydride: A mixture of *l*-menthol (0.47 g, 3 mmol) and acetic anhydride (0.42 mL, 4.5 mmol) or benzoic anhydride (1.02 g, 4.5 mmol) in acetonitrile (7 mL) is stirred at 27 °C in the presence of the Brønsted acid catalyst. After the mixture has been stirred at 27 °C for 1–17 h, polystyrene-bound 2,3,5,6-tetrafluorophenylbis(triflyl)methane resin is filtered off, washed with HCl (4 M, 5 mL), water (5 mL), aqueous THF (50%, 5 mL), THF (5 mL), and Et_2O (5 mL) in that order, and dried at 80 °C under vacuum (ca. 1 Torr) for 12 h to be reused. The filtrate is extracted twice with hexane, and the organic layers are dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude oil is purified by column chromatography on silica gel (hexane/EtOAc) to afford the corresponding ester.



Scheme 1-164

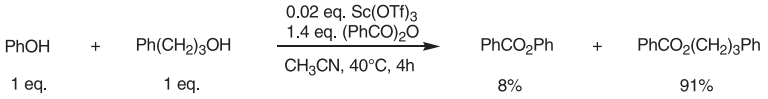
1.3.2.2 **Lewis Acids**

The last decade has witnessed dramatic progress in the utilization of Lewis acids in the acid anhydride procedure, particularly thanks to the development of metal triflates. Commercially available $Sc(OTf)_3$ is a versatile catalyst for this purpose [95JACS4413, 96JOC4560]. The high catalytic activity is apparent from catalyst loadings as low as 0.1 mol %. Besides acetylation, pivaloylation and benzoylation are also feasible. Not only primary alcohols but also sterically hindered secondary or tertiary alcohols are acylated. In contrast to the well known selectivity under basic conditions, aromatic alcohols are less reactive than their aliphatic counterparts in competition reactions with this catalyst (Scheme 1-165). In cases in which the reaction rate is slow, mixed anhydrides generated in situ serve for improvements. This methodology is elegantly applied to lactonization of ω-hydroxy carboxylic acids (Scheme 1-166). Even medium-sized lactones are obtainable in reasonable yields with contamination with only small amounts of the diolides. Chelation by the acid anhydride moiety with concurrent intramolecular coordination by the terminal hydroxyl is believed to be responsible for the efficient lactonization.

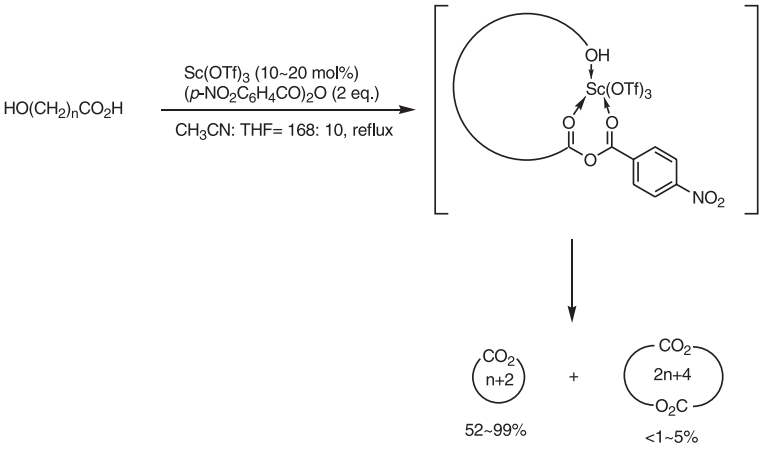
Experimental Procedure [96JOC4560] Scheme 1-166

p-Nitrobenzoic anhydride (253 mg, 0.8 mmol) is dissolved in dry acetonitrile (169 mL), and a cloudy solution of scandium triflate (0.1 M, 0.8 mL, 0.08 mmol) in acetonitrile is added to the solution at room temperature under argon. A solution of ω-hydroxy carboxylic acid (0.04 M, 10 mL, 0.4 mmol) in THF is added slowly (from a mechanically driven syringe over 15 h) to the mixed solution at reflux under argon, and the reaction mixture is further stirred at reflux for 5 h. After being cooled to room temperature, the solution is quenched with aqueous saturated sodium hydrogen carbonate (4 mL). The resulting mixture is concentrated under reduced pressure

and extracted twice with ether. The organic layers are dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification is done by column chromatography on silica gel (eluent: hexane/ethyl acetate system) to give the desired lactone in good yield. In some cases, diolide is also afforded as minor product.

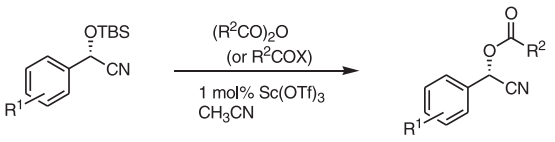


Scheme 1-165



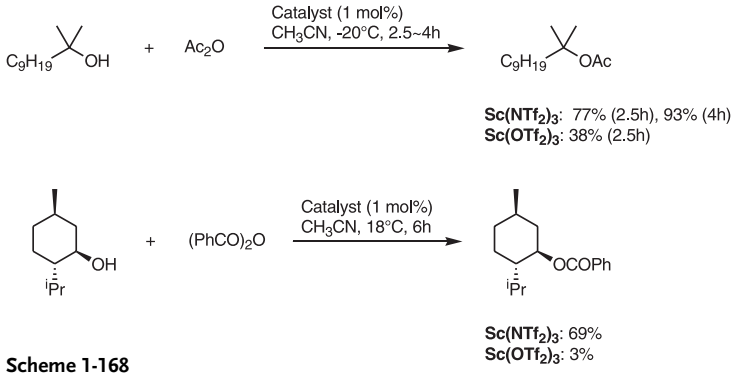
Scheme 1-166

The direct transformation of chiral *O*-trimethylsilyl cyanohydrins into the corresponding *O*-acyl cyanohydrins is feasible with acid anhydrides or acid halides with $Sc(OTf)_3$ catalysis (Scheme 1-167) [2002TL5715]. The reaction occurs with full retention of stereochemistry.



Scheme 1-167

The slow acylation rate occasionally encountered with $Sc(OTf)_3$ is accelerated by use of $Sc(NTf_2)_3$, which is believed to result from $Sc(OAc)_3$ and Tf_2NH [96SL265]. Acetylation of a tertiary alcohol and benzoylation of menthol, for example, proceed much more rapidly (Scheme 1-168).

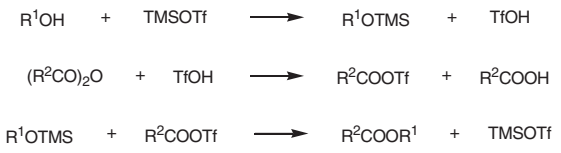


Scheme 1-168

TMSOTf is also a useful catalyst for acylation of alcohols and phenols [96CC2625, 98JOC2342]. It is claimed that this catalyst is more powerful and cheaper than $Sc(OTf)_3$. The reaction is extremely fast, selective, and mild. The following functional groups are tolerated: acetylene, allylic ester, aromatic ring, carbamate, diene, enone, ester, α,β-unsaturated ester, ether, halide, ketal, ketone, nitrile, sulfonate ester, thioester, and triene. A plausible mechanism is shown in Scheme 1-169. The alcohol reacts with TMSOTf to form the TMS ether and TfOH. The latter reacts with the anhydride to form the active acylating species, which could be a mixed anhydride or an acylium ion. This species then reacts with the TMS ether to form the ester and regenerate TMSOTf, which reenters the catalytic cycle. It may be said that TMSOTf is not a genuine Lewis acid catalyst if this mechanism is valid. The more popular TMSCl also catalyzes acetylation, but to a somewhat limited extent [97SC277].

Experimental Procedure [98JOC2342] Scheme 1-169

A solution of the alcohol (1 mmol) in CH_2Cl_2 (2 mL) is treated at 0 °C with the acid anhydride (1.5 mmol), followed by a CH_2Cl_2 solution of TMSOTf (1 M, 20 μL). Upon completion (TLC or HPLC), the reaction is treated with saturated aqueous $NaHCO_3$, and the two phases are separated. In cases in which an excess of acid anhydride has been used, the reaction is quenched with stoichiometric quantities of methanol, followed by washing with $NaHCO_3$. The organic extracts are washed with water and dried, and the solvent is evaporated. The products are generally very clean and do not require any further purification.



Scheme 1-169

$Bi(OTf)_3$, which can conveniently be prepared from Ph_3Bi (Scheme 1-170), is more synthetically useful than $Sc(OTf)_3$ and TMSOTf [2000AG(E)2877, 2001JOC8926]. The catalytic activity is so high that the catalyst concentration can be lowered to a 0.005 mol % level for practical uses. The lack of a need for anhydrous reaction conditions is a great operational advantage. Less reactive acylation reagents such as benzoic and pivalic anhydrides are employable. The elimination reaction of tertiary alcohols is virtually suppressed and, more remarkably, acid-labile THP- or TBS-protected alcohols, furfuryl alcohol, geraniol, and linalool can be acylated, as well as base-labile alcohols. Although a slight excess amount of acylating reagent should be used for complete conversion of the alcohol in question, this sometimes causes tedious problems in separation of the acylation product from the remaining acylating reagent. The methanolysis technique is useful to overcome such an obstacle. Addition of methanol after completion of acylation transforms the remaining acylating reagent into the methyl ester, which is separable from the desired acylation products. This technique is particularly useful for the $Bi(OTf)_3$/anhydride technique, while addition of methanol induces decomposition of the acylated product in the cases of $Sc(OTf)_3$ and TMSOTf. Other bismuth(III) salts such as $BiCl_3$ and $Bi(OCOCF_3)_3$ also effect acylation, but not so usefully as the triflate [2001T5851].

Experimental Procedure [2001JOC8926]

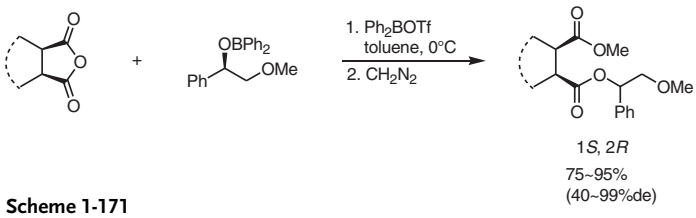
$Bi(OTf)_3$-Catalyzed Acetylation in Ac_2O: Acetic anhydride (8.4 mL, 89 mmol), 2-phenethyl alcohol (1.22 g, 10.0 mmol), and an acetic anhydride solution (1.0 mL) of $Bi(OTf)_3$ – prepared from $Bi(OTf)_3$ (7.3 mg, 0.01 mmol, calculated as the tetrahydrate) and Ac_2O (10 mL) – are placed in a round-bottomed flask, and the mixture is stirred at 25 °C for 10 min. After ethyl acetate and aqueous $NaHCO_3$ have been added, the organic and aqueous layers are separated. The aqueous layer is extracted three times with ethyl acetate, and the organic layers are combined and dried over $MgSO_4$. GC analysis of the crude mixture shows the formation of 2-phenethyl acetate in 98% yield.

$Bi(OTf)_3$-Catalyzed Acetylation in THF: THF (0.5 mL), furfuryl alcohol (98.1 mg, 1.0 mmol), Ac_2O (0.94 mL, 10.0 mmol), and $Bi(OTf)_3$ (0.36 mg, 0.05 mol %, calculated as the tetrahydrate) are placed in a flame-dried, round-bottomed flask. The mixture is stirred at 25 °C for 4 h. After ethyl acetate and aqueous $NaHCO_3$ have been added, the organic and aqueous layers are separated. The aqueous layer is extracted three times with ethyl acetate, and the organic layers are combined and dried over $MgSO_4$. GC analysis of the crude mixture shows the formation of furfuryl acetate in 93% yield.

$Bi(OTf)_3$-Catalyzed Pivalation of Menthol with $(t\text{-BuCO})_2O$: A CH_2Cl_2 solution (3 mL, not purified, wet) of menthol (156.3 mg, 1.0 mmol) and $(t\text{-BuCO})_2O$ (279.5 mg, 1.5 mmol) is stirred at 25 °C in the presence of $Bi(OTf)_3$ (21.8 mg, 3.0 mol %, calculated as the tetrahydrate) for 4 h. MeOH (10 mL, unpurified, wet) is added, and the mixture is passed through a pad of silica gel with hexane, and the filtrate is evaporated. Ethyl acetate (30 mL) is added to the crude product, and this organic layer is washed three times with aqueous $NaHCO_3$ and dried ($MgSO_4$). Evaporation furnishes the pure pivalate ester (98% yield, 235.6 mg).

Scheme 1-170

In the presence of a catalytic amount of Ph_2BOTf, cyclic *meso*-dicarboxylic anhydrides are esterified stereoselectively with the diphenylboric ester of (*R*)-2-methoxy-1-phenylethanol to afford chiral diesters (Scheme 1-171) [87CL377].



Scheme 1-171

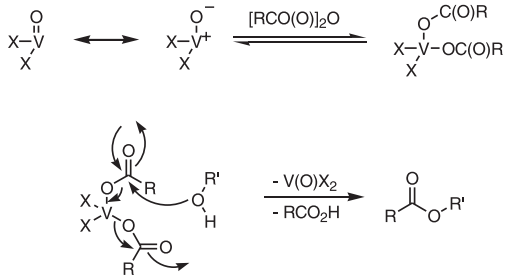
Vanadyl triflate promotes acylation to a considerable degree in terms of catalytic activity and chemoselectivity, although neither benzoic anhydride nor tertiary alcohols are employable [2001OL3729]. Since VCl_3 and $V(OTf)_3$ are catalytically inactive, the amphoteric character of the V=O bond is responsible for the catalysis (Scheme 1-172). The positively charged vanadium acts as an acidic center, while the oxygen, as a nucleophile, attacks the carbonyl carbon of the anhydride. $In(OTf)_3$ [99SL1743] and $Cu(OTf)_2$ [99TL2611] serve equally well for acylation.

Experimental Procedure [2001OL3729] Scheme 1-172

General Procedure for the Preparation of Vanadyl Triflate, $V(O)(OTf)_2 \cdot x(H_2O)$: Vanadyl sulfate trihydrate (342 mg, 2.1 mmol) is placed in a dry, 50 mL, two-necked, round-bottomed flask, and methanol (2 mL) is then added. A solution of $Ba(OTf)_2$ (872 mg, 2 mmol) in methanol (2 mL) is then added at ambient temperature. After 30 min stirring, precipitation of barium sulfate is observed; this is filtered off over a short pad of dry Celite. The filtrate is concentrated and dried in vacuo at 120 °C for 4 h to furnish vanadyl triflate (622 mg, 85 % yield) as a faint blue solid, which is used directly for the acylation reactions.

General Procedure for Acylation Reactions: Vanadyl triflate (3.7 mg, 0.01 mmol) in anhydrous CH_2Cl_2 (3 mL) is placed in a dry, 50 mL, two-necked, round-bottomed flask. The acyl anhydride (1.5 mmol) is slowly added to the above solution at ambient temperature. After 10 min, a solution of the nucleophile (1.0 mmol in CH_2Cl_2, 2 mL) is slowly added to the dark green solution, and the reaction mixture is stirred for the required period. After completion of the reaction as monitored by TLC, the reaction mixture is quenched with cold, saturated aqueous $NaHCO_3$ solution (5 mL). For the acylation of β-hydroxy ketones or esters, ice-cold water is used to quench the reaction, to prevent β-elimination. The separated organic layer is washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude product is purified by column

chromatography on silica gel if required (in most of the acetylation reactions essentially pure material is obtained without further purification).



Scheme 1-172

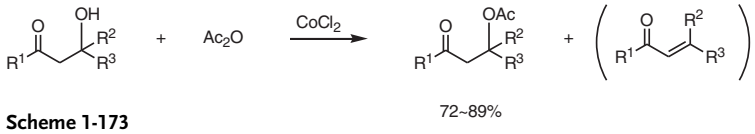
Metal bis(trifluoromethylsulfonyl)amides such as $(^{i}PrO)_2Ti(NTf_2)_2$ and $Yb(NTf_2)_3$ are powerful acylation catalysts [96SL171], and $Yb[N(SO_2C_4F_9)_2]_3$ is more active than $Yb(OTf)_3$ for the reaction between ethanol and benzoic anhydride [98SL1347]. $M[C(SO_2C_8F_{17})_3]_3$ (M = Sc and Yb) work as catalysts for acetylation with acetic anhydride both in mono- and in biphase systems containing fluorocarbon and non-fluorous organic solvents [2001TL289, 2002T4015]. $M[N(SO_3CH(CF_3)_2)_2]_3$ (M = La, Sm, Ga, Yb) also act as catalysts for acylation of alcohols and phenols [99JCR(S)160].

Experimental Procedure [2002T4015]

Cyclohexanol (0.21 mL, 0.20 g, 2 mmol) and acetic anhydride (0.19 mL, 0.20 g, 2 mmol) are added to a mixture of perfluoromethylcyclohexane (5 mL) and toluene (5 mL). Scandium tris(perfluorooctanesulfonyl)methide (1 mol%, 89 mg, 0.02 mmol) is added to the resultant mixture. The solution is stirred at 30 °C for 20 min, and the resultant mixture is then allowed to stand at room temperature (20 °C), so that the reaction mixture separates into the upper phase of toluene and the lower phase of perfluoromethylcyclohexane. Each of the upper phase and the lower phase is individually analyzed by GC. Cyclohexyl acetate is obtained from the upper phase after evaporation under reduced pressure and silica gel chromatography (0.279 g, 98% isolated yield).

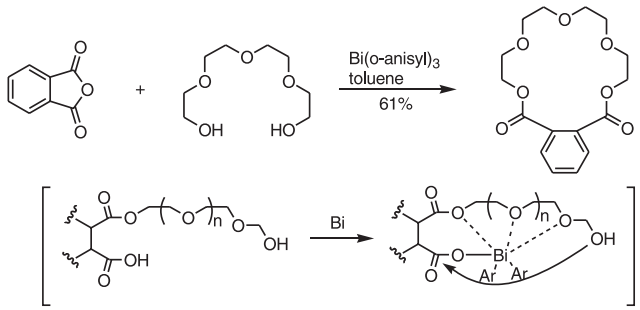
To the lower phase, containing the catalyst, toluene (5 mL), cyclohexanol (0.21 mL, 0.20 g, 2 mmol), and acetic anhydride (0.19 mL, 0.20 g, 2 mmol) are again added, followed by stirring at 30 °C for 20 min. The resultant mixture is again allowed to stand at room temperature (20 °C), so that the reaction mixture separates into the upper toluene phase and the lower perfluoromethylcyclohexane phase. Each phase is once more individually analyzed by GC. The overall yield of cyclohexyl acetate in the upper phase and lower phase is 100%. Essentially, the same procedure can be repeated a further three times. The overall yields of cyclohexyl acetate in the three repeated reactions are 99, 99, and 100%, respectively.

$CoCl_2$ catalyzes acylation with aliphatic acid anhydride [87CC114]. With this catalyst, β-hydroxy carbonyl compounds do not undergo elimination to afford α,β-unsaturated carbonyl compounds (Scheme 1-173).



Scheme 1-173

Tris(2-methoxyphenyl)bismuthane acts as a good template for macrocyclic ester synthesis [95CC1407]. Treatment of an anhydride (1 equiv.), a polyethylene glycol (1 equiv.), and the bismuthane (0.4 equiv.) in refluxing toluene furnishes the macrocyclic diester as the major product (Scheme 1-174). A small amount of tetraester is also formed. A unique template effect of Bi(III) is proposed.

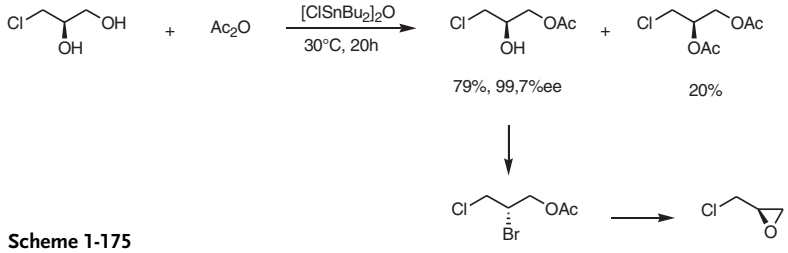


Scheme 1-174

Various organotin Lewis acids are useful catalysts. Treatment of an alcohol with acetic anhydride (1.1 ~ 3.0 equiv.) in the presence of 1,3-dichlorotetrabutyldistannoxane results in quantitative formation of the corresponding acetates [99T2899]. The mildness of this reaction is apparent from the successful use of THP- or TBS-containing substrates. The selectivity between primary and secondary alcohols is high, and this technique is applied to monoacetylation of chiral 3-chloropropane-1,2-diol at the primary position (Scheme 1-175) [99SL1927]. The resulting monoacetate is transformed into optically pure epichlorohydrin via the 2-bromide.

Experimental Procedure [99T2899]

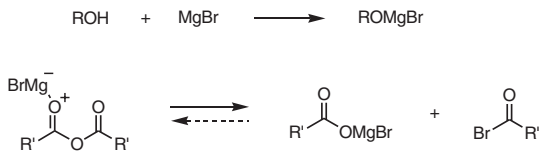
An acetic anhydride solution (1.4 mL, 15 mmol) of 2-phenylethanol (611 mg, 5.0 mmol) and 1,3-dichlorotetrabutyldistannoxane (27.6 mg, 0.25 mmol) is stirred at 30 °C for 24 h. After conventional workup with aqueous sodium hydrogen carbonate solution and ethyl acetate, the organic layer is dried over magnesium sulfate and evaporated. The crude mixture is subjected to column chromatography to give phenethyl acetate (788 mg, 96%).



Scheme 1-175

The catalytic activity of organotin Lewis acids is dependent on the amount of positive charge on the tin [99OM3555, 2000OM3220]. Thus, the activity for acid anhydride acetylation decreases in the order: $[Bu_2Sn(OH)(H_2O)]_2^{2+} \cdot 2OTf^- > [(BuSn)_{12}O_{14}(OH)_6]^{2+} \cdot 2\,Cl^- > (ClBu_2SnOSnBu_2Cl)_2$. The dicationic character is shared by the two tin atoms in the first compound but by the 12 tin atoms in the second, while the third compound is neutral.

LiCl [99SC2311], $LiClO_4$ [2001SL1584], and $MgBr_2$ [2000SC2587] are other Lewis acids effective for acylation. Notably, addition of a tertiary amine dramatically enhances the activity [96JOC5702], so the combination of $MgBr_2$ (2 equiv.), acid anhydride (2 equiv.), and tertiary amine (1.5 ~ 3 equiv.) effects benzoylation or pivaloylation very quickly. The high reactivity is explained on the basis of dual activation arising from magnesium alkoxide formation and the formation of $MgBr_2$-anhydride complex, which may fragment into acyl bromide and magnesium carboxylate (Scheme 1-176). MgI_2 also acts as a promoter [93JCR(S)338].



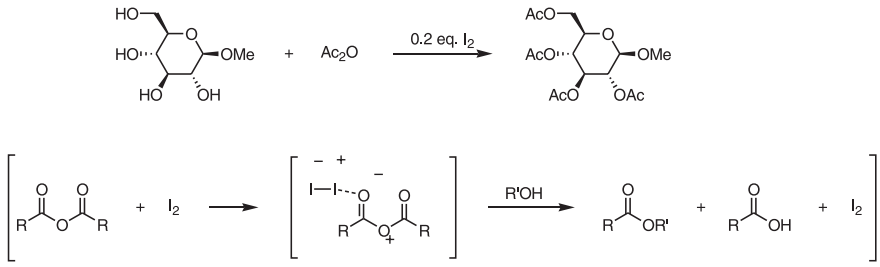
Scheme 1-176

Iodine mediates acetylation of sugars [97T11753]. Addition of I_2 to a suspension of sugars in Ac_2O followed by stirring affords the corresponding per-*O*-acetates (Scheme 1-177). It is postulated that iodine acts as a Lewis acid that activates the carbonyl group of the anhydride.

Experimental Procedure [97T11753] Scheme 1-177

The sugar is suspended in acetic anhydride (5 mL per g of sugar for acetylation, 10 mL per g of sugar for acetolysis) and stirred. Iodine (10 to 500 mg per g sugar) is added, and stirring is continued until TLC shows the reaction to be complete. In small-scale reactions the reaction mixture is diluted with CH_2Cl_2 and washed successively with dilute aqueous sodium thiosulfate and aqueous sodium carbonate solutions. The organic layer is then dried (Na_2SO_4) and concentrated to give the product.

The products obtained are in most cases pure enough for use elsewhere directly, or they are otherwise purified by column chromatography. In large-scale acetylations the reaction mixture is poured with stirring into ice-cold, dilute sodium thiosulfate solution. The products are allowed to crystallize in the refrigerator, and are separated by filtration.



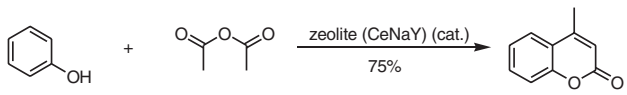
Scheme 1-177

1.3.2.3 Solid Acids

Various types of zeolites are employable for acylation. With zeolite HSZ-360, alcohols and phenols are acetylated at 60 °C [98TL6049]. Chiral alcohols are acetylated with complete retention of optical purity, and β-nitroalcohols experience no dehydration to nitroolefins. Mono- and disaccharides undergo per-*O*-acetylation on stirring in acetic anhydride in the presence of H-beta zeolite at room temperature [99SL129]. This zeolite is better than HY, H-EMT, H-ZSM-5, H-ZSM-12, and H-ZSM-22. A novel acylative cyclization reaction between phenol and acetic anhydride occurs over CeNaY zeolite to give 4-methylcoumarin (>70 %) (Scheme 1-178) [93CC1456]. Mesoporous molecular sieves HMCM-41 effect acetylation of linalool [98G811].

Experimental Procedure [98TL6049]

In a typical procedure, the alcohol or phenol (10 mmol) and acetic anhydride (20 mmol) are placed with stirring in a two-necked flask. After 5 min, zeolite HSZ-360 (0.2 g) is added, and the mixture is heated at 60 °C for the appropriate time. After cooling, the mixture is extracted with Et_2O and the catalyst is filtered off. After evaporation of the solvent, the acetate is purified by distillation or flash chromatography.



Scheme 1-178

Montmorillonite K-10 and KSF are efficient catalysts for acylation of alcohols [97CC1389, 98JCS(P1)1913]. No selectivity between primary and secondary alcohols is observed, while tertiary alcohols are not employable. In general, K-10 is better

than KSF in terms of reaction time, temperature, and/or yield. Per-*O*-acetylation of mono-, di-, and trisaccharides is feasible with Montmorillonite K-10 [98TL2215]. Formation of α,β-furanose per-*O*-acetates takes place mostly in monosaccharide cases, partial anomerization and acetolysis occurring under these conditions. Most disaccharides are smoothly converted into mixtures of pyranose per-*O*-acetates.

Experimental Procedure [98JCS(P1)1913]
Acetic anhydride (10.0 mmol) is added to a mixture of the alcohol (1.94 g, 5.00 mmol), K-10 (100 mg), and CH_2Cl_2 (10 mL). After the mixture has been stirred at room temperature for 2 h, the catalyst is removed by filtration and washed with CH_2Cl_2 (10 mL). The solvent is evaporated under reduced pressure. The residue is pure enough for general purposes, while further purification may be achieved by column chromatography on silica gel, to give acetate in 98% yield.

Acidic resins such as Nafion H [2000SL1652] and Amberlyst-15 [92SC2703] are also useful. In particular, the former resin effects acylation of a variety of alcohols, such as primary, secondary, and allylic alcohols, as well as monosaccharides. Interestingly, acid-sensitive groups (ketals, acetals, THP ethers, cyclopropanes, etc.) are tolerated.

Experimental Procedure [2000SL1652]
Nafion H (30 mg) is added to a solution of acetic anhydride (4 mmol) and an alcohol (2 mmol) in CH_2Cl_2 (3 mL). The resulting heterogeneous mixture is stirred at room temperature for 3–20 h. The CH_2Cl_2 layer is decanted into another flask, and the residual Nafion H is washed with CH_2Cl_2 (2 × 2 mL). Evaporation of the solvent, followed by purification, affords pure acetates.

Yttria-zirconia-based Lewis acid efficiently catalyzes acylation of structurally diverse alcohols [2001SL206]. The catalytic activity of $TaCl_5$ is enhanced when it is supported on silica gel [98TL3263]. Primary, secondary, allylic, and benzyl alcohols, and also phenols, are smoothly acetylated, but tertiary alcohols are not employable.

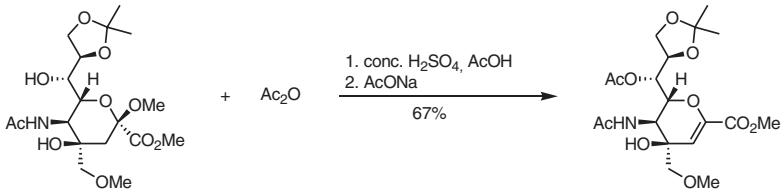
Zirconium sulfophenyl phosphonate (of formula α-$Zr(O_3PCH_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$) is an efficient heterogeneous catalyst for acylation of primary, secondary, tertiary, allylic, benzylic, and acetylenic alcohols, and also phenols [2000SC1319]. Good selectivity between primary and secondary alcohols is attained (pri > sec), but phenols cannot be discriminated from alcohols.

1.3.3 Base Activators

1.3.3.1 Metal Salts

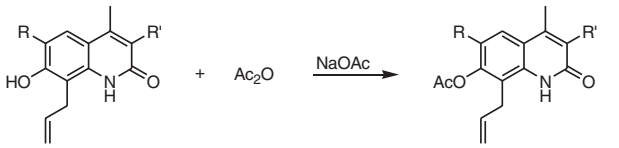
Acetylation with acetic anhydride is often accelerated by addition of sodium acetate. Acetolysis of methyl glycosides of *N*-acetylneuraminic acid is effected by treatment with acetic anhydride and sulfuric acid in glacial acetic acid (Scheme 1-179) [99JCS(P1)2109]. The yields of the corresponding 2,3-unsaturated derivatives are im-

proved by increasing the pH of the reaction mixture to 5 during workup by addition of sodium acetate.



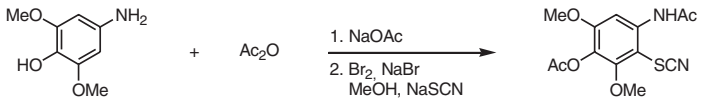
Scheme 1-179

Acetylation of phenols with acetic anhydride is smoothly conducted in the presence of sodium acetate (Schemes 1-180, 1-181, 1-182, 1-183) [91JOC980, 93JOC5855, 95ZN(B)1257, 93IJC(B)817]. Similarly, enols are converted into vinyl esters (Scheme 1-184) [92SC3013, 96SC4023, 98SC2907].



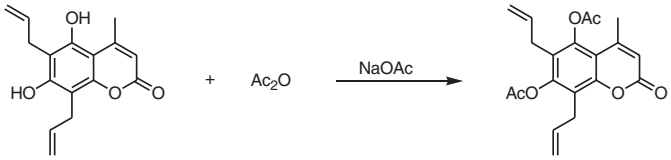
R= CH_3, R'= H (96%)
R=R'= H (90%)
R= H, R'= CH_3 (83%)

Scheme 1-180

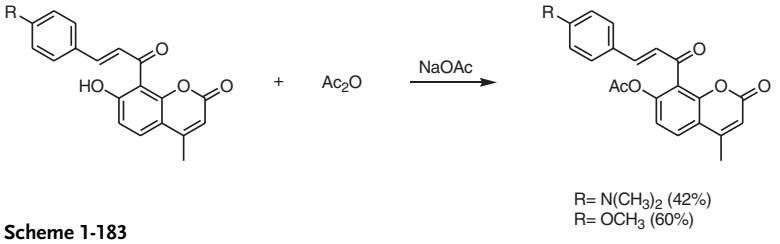


46%

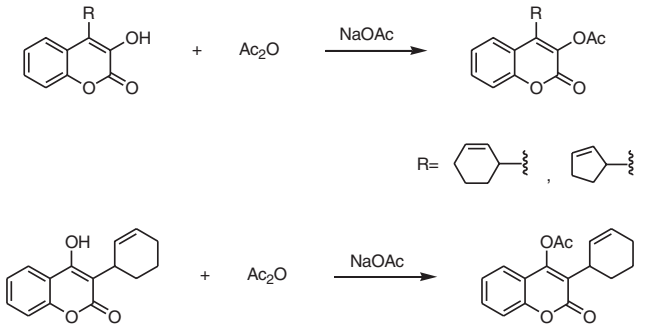
Scheme 1-181



Scheme 1-182



Scheme 1-183

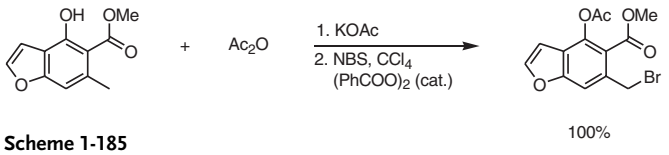


Scheme 1-184

Potassium acetate works as well for acetylation of phenol (Scheme 1-185) [94JOC4735] and benzyl alcohol (Scheme 1-186) [97JOC5627].

Experimental Procedure [94JOC4735] Scheme 1-185

KOAc (0.55 g, 5.57 mmol) is added to methyl 4-hydroxy-6-methylbenzofuran-5-carboxylate (0.750 g, 5.06 mmol) in Ac_2O (20 mL). The mixture is stirred at 120 °C for 12 h, cooled to rt., diluted with NaOH (2 N, 50 mL), and extracted with ether (3 × 60 mL). The organic layer is dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel flash chromatography with hexane/ethyl acetate (10 : 1) to give the acetate of methyl 4-hydroxy-6-methylbenzofuran-5-carboxylate (1.24 g, 100 % yield).

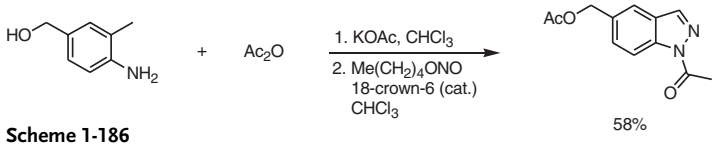


Scheme 1-185

Experimental Procedure [97JOC5627] Scheme 1-186

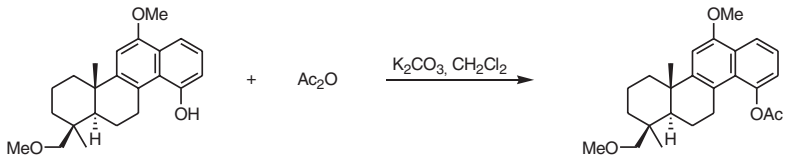
A mixture of 4-(hydroxymethyl)-2-methylaniline (16.58 g, 0.12 mol), acetic anhydride (34.0 mL, 0.36 mol), and potassium acetate (23.71 g, 0.24 mol) in $CHCl_3$ (240 mL) is stirred at rt. for 3 h, heated at reflux for 2 h, and stirred at rt. overnight. *n*-Amyl nitrite (32 g, 0.27 mol) and 18-crown-6 (1.59 g, 6.0 mmol) are then added, and the mix-

ture is heated at reflux for 28 h. After being cooled to rt., the reaction mixture is added to acetic anhydride (10 mL) and stirred at rt. overnight. The reaction mixture is diluted with CH_2Cl_2 (400 mL), washed with saturated $NaHCO_3$ (200 mL), water, and brine, and dried (Na_2SO_4), and the solvent is evaporated to give a dark brown solid. Chromatography (silica gel, 15% EtOAc/hexane) gives 1-acetyl-5-(acetoxymethyl)indazole as a yellow solid (16.98 g, 58%).

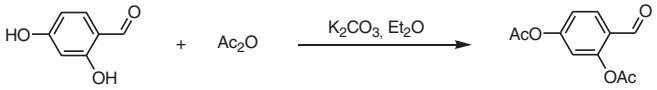


Scheme 1-186

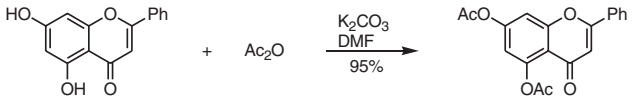
Acetylations of phenols are also effected by use of suspensions of potassium carbonate (Schemes 1-187, 1-188, 1-189) [94AJC1815, 98JCS(P1)3453, 99BMC869].



Scheme 1-187

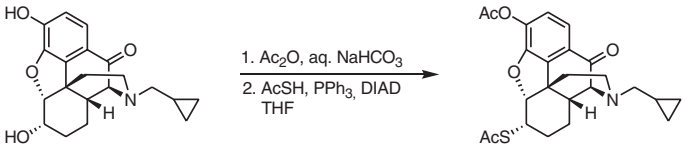


Scheme 1-188

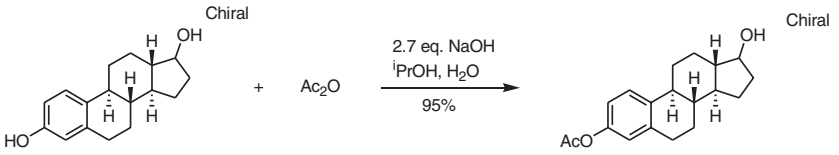


Scheme 1-189

In contrast to the above reactions in suspension, use of an aqueous solution of sodium bicarbonate allows selective acetylation of phenol, leaving aliphatic alcohols intact (Scheme 1-190) [95BMC1505]. The analogous selective acetylation is also feasible in a liquid-liquid two-phase system consisting of aqueous sodium hydroxide and isopropanol (Scheme 1-191) [92SC2703].

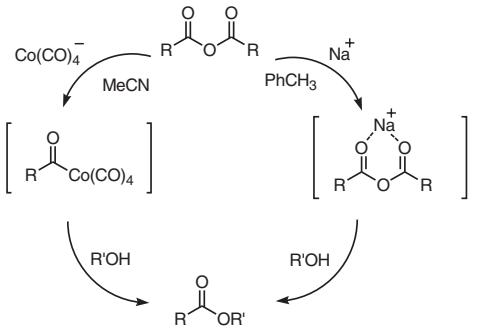


Scheme 1-190



Scheme 1-191

A unique mechanistic switch is seen with $NaCo(CO)_4$ catalyst (Scheme 1-192) [99OL1985]. The reaction between the alcohol and acetic anhydride proceeds via an acylcobalt intermediate in acetonitrile, since ionization of the catalyst is induced in polar solvent, while in non-polar toluene the sodium cation acts as a Lewis acid.



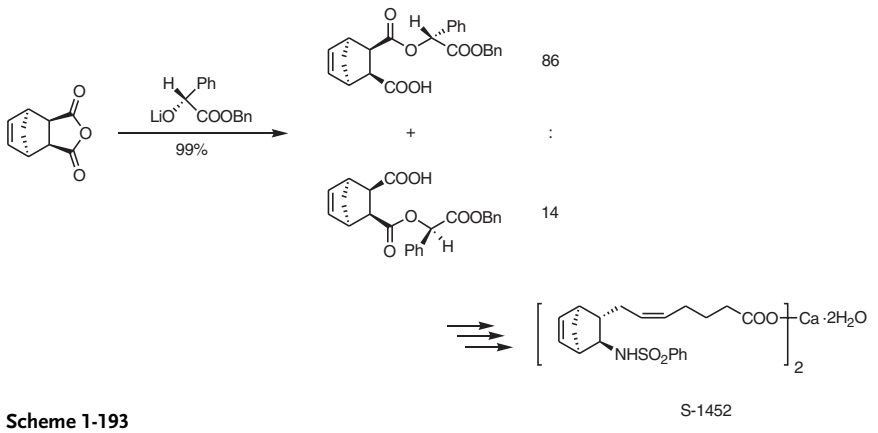
Scheme 1-192

In addition to acylation of alcohols, the acid anhydride technique also serves for the synthesis of half esters of dicarboxylic acids. Enantioselective cleavage of cyclic *meso* anhydrides is achievable by treatment with the lithium salt of a chiral mandelate ester (Scheme 1-193) [91JOC2122]. The obtained half ester can be used as a starting material for the synthesis of S-1452, an orally active potent thromboxane A_2 receptor antagonist.

Experimental Procedure [91JOC2122] Scheme 1-193

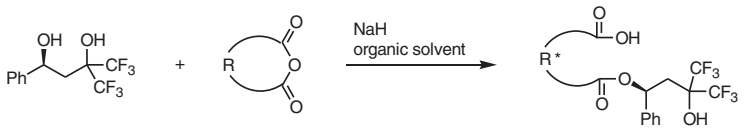
A solution of benzyl (*R*)-mandelate (5.33 g, 22.0 mmol) in THF (50 mL) is cooled to –78 °C, butyllithium in hexane (1.6 M 13.13 mL, 21.0 mmol) is added dropwise, and the mixture is stirred for 15 min. A solution of bicyclo[2.2.1]hept-5-ene-2,3-*endo*-dicarboxylic anhydride (3.32 g, 20.0 mmol) in THF (20 mL) is added to the reaction

mixture, and the resulting mixture is stirred at –78 °C for 1 h. The reaction mixture is acidified with HCl (2 N), and the product is extracted with ethyl acetate. The organic layer is washed with water and an aqueous solution of sodium chloride and then concentrated to yield a mixture of (1*S*,2*R*,3*S*,4*R*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid 2-(benzyl (*R*)-mandelate) and its diastereomer (9.33 g, 99%).



Scheme 1-193

Highly diastereoselective alcoholysis of σ-symmetric dicarboxylic acid anhydrides can be performed by use of a sodium salt of 1-phenyl-3,3-bis(trifluoromethyl)propane-1,3-diol (Scheme 1-194) [92CL389].

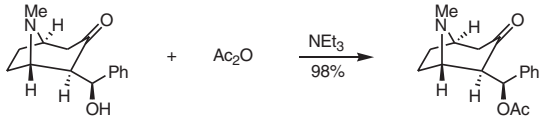


Scheme 1-194

1.3.3.2 **Amines**

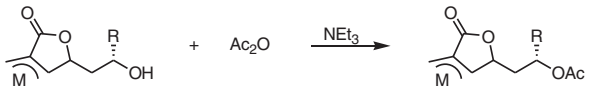
The acylation of alcohols by acid anhydrides can most conveniently be carried out with the aid of amines. Although simple amines are not always employable, because of their relatively low basicity, they are the reagents of choice when the alcohol function is reactive enough, the substrates are too labile towards strong bases, or the acid anhydrides are reactive. The following are some representative examples.

Acetylation of azabicyclo[3.2.1]octanonone is achieved by stirring with Ac_2O in Et_3N at room temperature (Scheme 1-195) [95JOC5825].



Scheme 1-195

π-Allyltungsten complexes undergo acetylation by Ac_2O/Et_3N in high yields (Scheme 1-196) [92CC45].

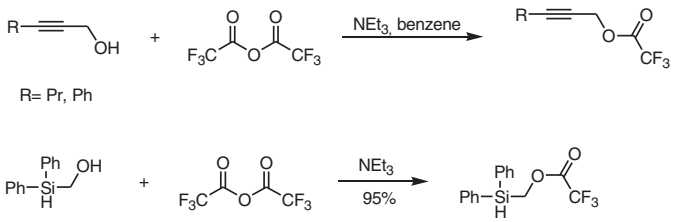


M= $WC_5H_5(CO)_2$

R= Ph (88%)
R= ^{i}Pr (90%)

Scheme 1-196

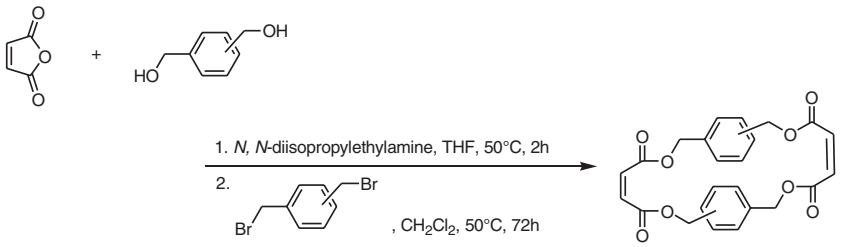
Trifluoroacetylation can normally be carried out by use of triethylamine. Propargylic alcohols [98SC1201] and silylmethanols [92CB591] are smoothly converted into the corresponding trifluoroactates (Scheme 1-197).



R= Pr, Ph

Scheme 1-197

The reaction between two equivalents of maleic anhydride and a benzenedimethanol in the presence of *N,N*-diisopropylethylamine affords dicarboxylic acid salts, which are further converted into cyclophanes upon treatment with α,α-dibromoxylenes (Scheme 1-198) [98TL1857].

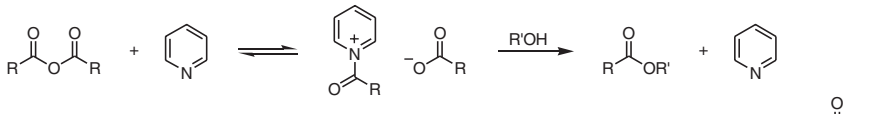


Scheme 1-198

The limitations frequently encountered in the simple amine protocol can be overcome to a considerable degree by use of 4-dialkylaminopyridines, usually DMAP or PPY (4-pyrrolidinopyridine) [69AGC(E)981, 71CB3229, 72S619]. The use of these reagents in either stoichiometric or catalytic amounts is effective: in the latter case, excess triethylamine or pyridine should be added to trap the acid formed. A wide range of alcohols, including highly sterically demanding tertiary alcohols and phenols, are acylated. It is postulated that *N*-acylpyridinium carboxylates are key intermediates, undergoing nucleophilic attack by alcohols (Scheme 1-199) [78AGC(E)569].

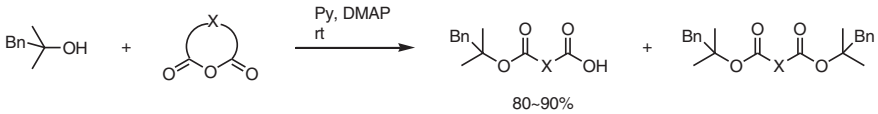
Experimental Procedure [69AGC(E)981]

A mixture of 1-chloro-1-methylhexanol (11.4 g, 0.1 mole), acetic anhydride (20 mL, 0.21 mole), triethylamine (20 mL, 0.15 mol), and DMAP (0.5 g, 4.1 mmol) is stirred at rt. After 14 h at room temperature, an 86% yield of the corresponding acetate is obtained. The amounts of acetate produced by use of pyridine and/or triethylamine only are less than 5%.



Scheme 1-199

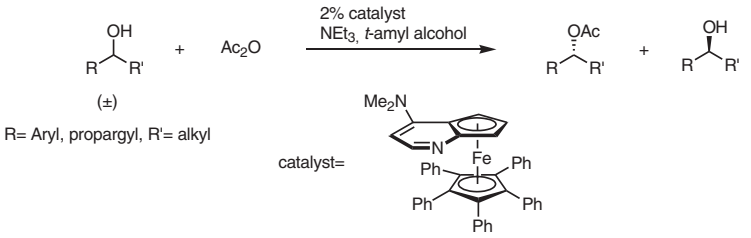
The DMAP/pyridine technique can be further elaborated by use of high pressures (1.5 GPa) to effect acylation of cyclic anhydrides with sterically demanding alcohols (Scheme 1-200) [95SL650]. The monoesters are obtained selectively in 80–90% yields.



X= CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH(Me)CH_2$, CH_2OCH_2, 1,2-C_6H_4

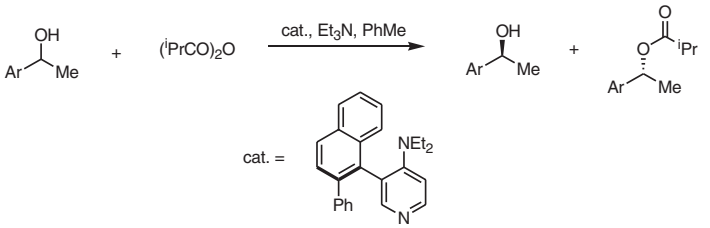
Scheme 1-200

A planar-chiral DMAP derivative catalyzes kinetic resolution of arylalkylcarbinols [98JOC2794] and secondary propargylic alcohols (Scheme 1-201) [99JACS5091]. The use of *tert*-amyl alcohol as solvent is crucial for attaining high selectivity.



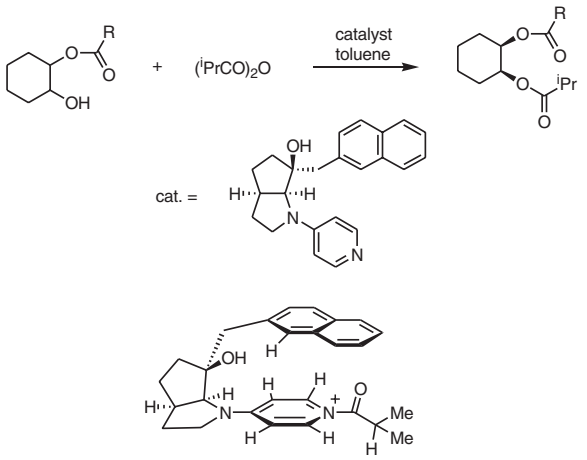
Scheme 1-201

Another chiral analogue of DMAP is also effective for kinetic resolution of arylalkylcarbinols (Scheme 1-202) [2000JOC3154].



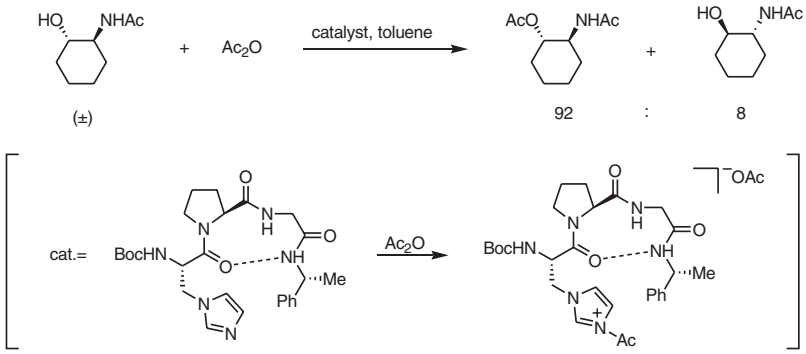
Scheme 1-202

A chiral catalyst derived from PPY is also available (Scheme 1-203) [97JACS3169]. Kinetic resolution of various half-esters of cyclic 1,2-diols can be achieved. An acyliminium ion is proposed as a key species responsible for asymmetric induction.

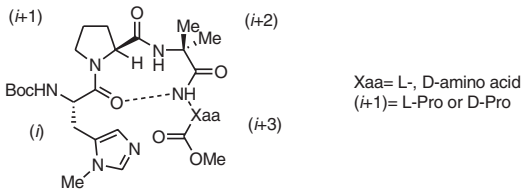


Scheme 1-203

A peptide bearing 3-(1-imidazoyl)-(*S*)-alanine as the *N*-terminal amino acid catalyzes the kinetic resolution of *trans*-2-(*N*-acetylamino)cyclohexan-1-ol (Scheme 1-204) [98JACS1629]. An acyl imidazolium intermediate is postulated. This catalyst exhibits catalyst specificity, no resolution being feasible with methylnaphthylcarbinol. The second generation catalysts involve variation of the amino acids at the (i + 1) and (i + 3) positions (Scheme 1-205) [98JOC6784]. Alteration of the amino acid unit at the (i + 3) position has little influence on the selectivity of *trans*-2-(*N*-acetylamino)cyclohexan-1-ol in kinetic resolution, while substitution of L-proline at the (i + 1) site with D-proline results in a tenfold increase in the selectivity.

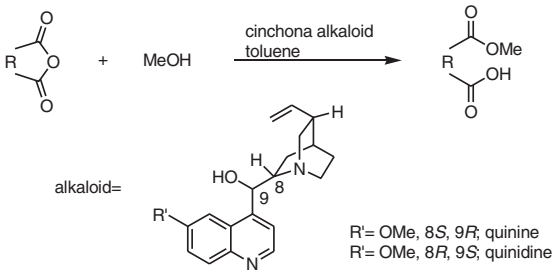


Scheme 1-204



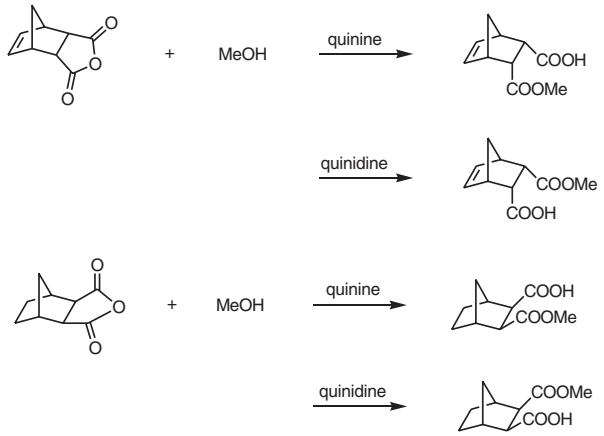
Scheme 1-205

Asymmetric ring-opening of prochiral cyclic acid anhydrides is a useful method for obtaining optically active compounds. Naturally occurring cinchona alkaloids mediate the ring-opening of *meso* cyclic anhydrides with methanol to furnish the corresponding half-esters, which can be transformed into lactones with up to 70% *ee* (Scheme 1-206) [85CC1717, 87JCS(P1)1053]. Interestingly, the diastereomers obtained by inversion of the C-9 hydroxy group exhibit low activity as well as % *ee*s.



Scheme 1-206

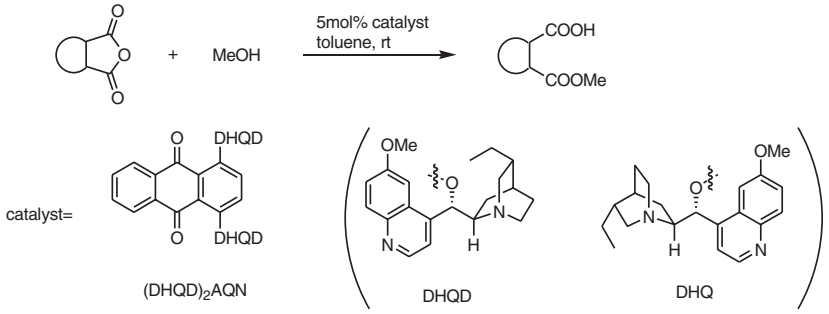
Cinchona alkaloids are also effective for ring-opening of tri- and tetracyclic anhydrides to afford the corresponding half-esters with 35–67% *ee*s (Scheme 1-207) [90TA517, 88CC632]. The absolute configurations of the products are tunable by selection of quinine and quinidine.



Scheme 1-207

Optimization of the cinchona alkaloid procedure improves the selectivity up to 99% *ee* in the presence of a stoichiometric amount of the promoter [2000JOC6984]. The catalytic version (0. 1 equiv.) is feasible with co-use of pempidine (1.0 equiv.), resulting in a 100 yield with 90% *ee*.

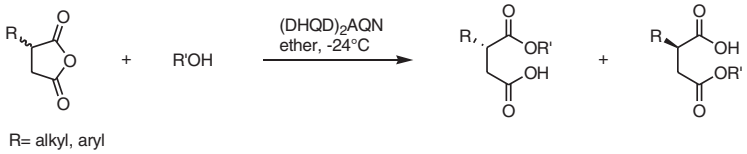
Ethers of cinchona alkaloids – $(DHQD)_2AQN$ and $(DHQ)_2AQN$ – are more efficient catalysts (Scheme 1-208) [2000JACS9542]. High yields (77–90%) and % *ee*s (82–98) are attained in desymmetrization of cyclic carboxylic anhydrides with methanol, while the absolute configurations can be switched by the selection of the two catalysts above (Scheme 1-209).



Scheme 1-208

Scheme 1-209

These ethers are also useful for parallel kinetic resolution with a single catalyst (Scheme 1-210) [2001JACS11302]. Alcoholysis of 2-alkyl or 2-aryl succinic anhydrides in the presence of $(DHQD)_2AQN$ provides the two corresponding stereoisomers. The stereocenters at the C-2 position of the substrates are fully recognized, followed by regioselective alcoholysis. Quite naturally, $(DHQ)_2AQN$ induces the opposite selectivities.



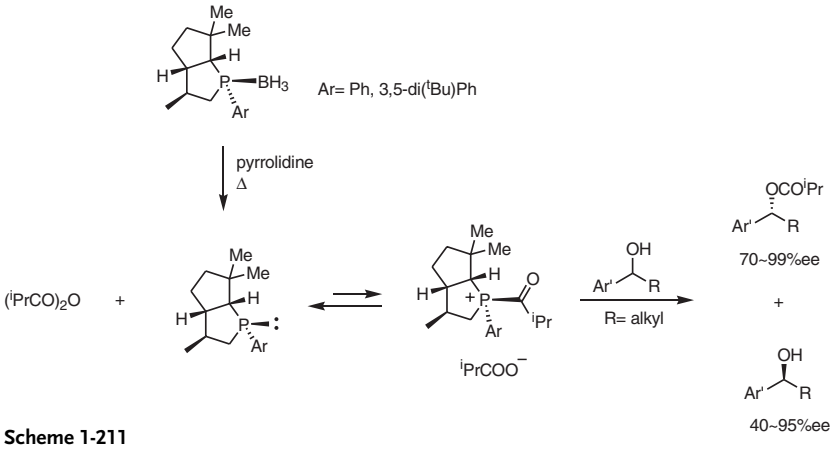
Scheme 1-210

Diethyzinc complexes with amino alcohols such as ephedrine, cinchonine, cinchonidine, and quinidine also effect desymmetrization of cyclic carboxylic anhydrides [93BCJ2128].

1.3.3.3 Phosphines

Phosphines possess a considerable degree of basicity and so can be used for promoting acylation. Bu_3P is a weak base in organic solvent but exhibits activities nearly comparable to those of DMAP [93JACS3358, 93JOC7286]. For benzoylation, the Bu_3P-catalyzed reaction is faster than its DMAP counterpart. DMAP is more versatile though, since it shows catalytic activity in reactions between alcohols and a larger variety of elec-

trophiles than Bu_3P does. The phosphine also appears to be somewhat more sensitive than DMAP to counter-ion effects. Nevertheless, use of Bu_3P is advantageous in that it is cheaper and less toxic than DMAP, is not easily deactivated by the carboxylic acid generated in reactions using acid anhydride, and can be used under nearly neutral conditions. Enantiopure 2,3-dialkyl-1-phenylphosphapentane is employable for desymmetrization of racemic 1,2-diols and kinetic resolution of secondary alcohols through acid anhydride acylation [96JOC430], but the *ee*s of the products are modest. The enantioselectivity is improved by the use of 2-aryl-4,4,8-trimethyl-2-phosphabicyclo[3,3,0]octanes (Scheme 1-211) [99JACS5813]. These phosphines can be stored as borane adducts and released by warming with pyrrolidine. Aryl alkyl carbinols are resolved with isobutyric anhydride, an acylphosphonium intermediate being postulated.

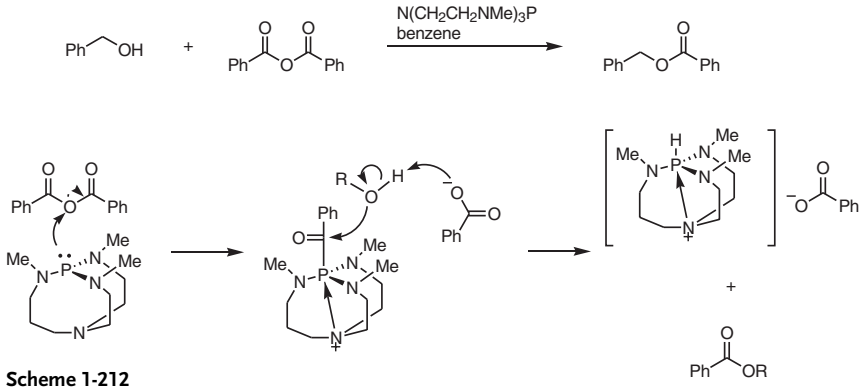


Scheme 1-211

The non-ionic superbase $P[MeNCH_2CH_2]_3N$ acts as a catalyst for acylation with acid anhydrides for hindered alcohols and also for acid-sensitive alcohols [96JOC2963]. The reaction is likely to proceed with assistance of transannular coordination, as shown in Scheme 1-212.

Experimental Procedure [96JOC2963] Scheme 1-212

After the superbase $P[MeNCH_2CH_2]_3N$ (1.1 g, 5.1 mmol) has been dissolved in solvent (30 mL) at 24 °C under N_2, the appropriate acid anhydride (5.1 mmol) is added and the mixture is stirred for 5 min. The alcohol (4.8 mmol) is then added with continued stirring. After ~1.5 h, water (0.05 mL) is added with stirring. This is followed by the addition of ether (80 mL), and stirring is continued for 5 min more. (When acetonitrile or benzene is used as the solvent, ~95% of the solvent is evaporated before addition of the ether.) The mixture is then filtered, and the residue is washed with ether (20 mL). The organic layer is dried with anhydrous sodium sulfate, followed by concentration under vacuum, to afford the crude ester, which is purified by chromatography on silica gel. The residue obtained from the reaction is treated with KO-*t*-Bu to recover $P[MeNCH_2CH_2]_3N$.



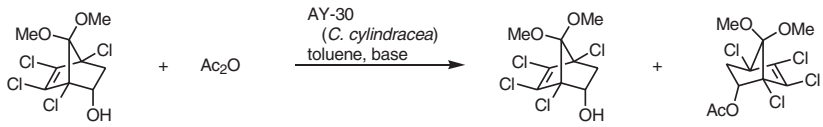
Scheme 1-212

1.3.4 Enzymes

The acid anhydride technique with enzymes is in some respects more advantageous than esterification and transesterification. Since no water is formed, the enzyme is protected from hydrolysis, and undesired side reactions requiring water (such as racemization) are avoided. The equilibrium is more readily shifted to the product ester side than transesterification, because the acid formed is completely removed from the equilibrium system. Lipase Amano P from *Pseudomonas fluorescens* adsorbed on Celite 577 can be used for kinetic resolution of primary and secondary alcohols [88JOC5531]. Analogously, lipase AY-30 from *Candida cylindacea* adsorbed on Celite can bring about kinetic resolution of highly lipophilic substrates (Scheme 1-213) [90TA541]. The adsorption or the addition of organic base 2,6-lutidine or the inorganic base $KHCO_3$ improve the selectivity.

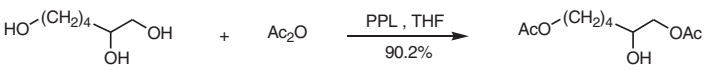
Experimental Procedure [88JOC5531]

Amano P lipase (0.12 g, 3600 units) supported on Celite 577 (0.48 g) is added to a magnetically stirred solution of racemic 1-phenylethanol (2 g, 16.3 mmol) and acetic anhydride (1.66 g, 16.3 mmol) in benzene (40 mL), and the reaction mixture is stirred at room temperature. Periodically, 1 μL aliquots of the liquid phase are withdrawn and analyzed by GC. After 24 h, approximately 50% conversion has been reached, and the reaction is stopped. The solid enzyme preparation is filtered off, and the filtrate is washed with aqueous Na_2CO_3 (5%, 40 mL), dried over sodium sulfate, and evaporated to dryness. Chromatography on silica gel with hexane/ether (95 : 5) as eluent affords (*S*)-(–)-1-phenylethanol (0.86 g, 43%).



Scheme 1-213

Selective acylation of primary alcohols in preference to secondary ones in diols and triols is achieved by use of PPL in organic solvents (Scheme 1-214) [90TL3405]. Propionic anhydride gives better outcomes than acetic anhydride.



Scheme 1-214

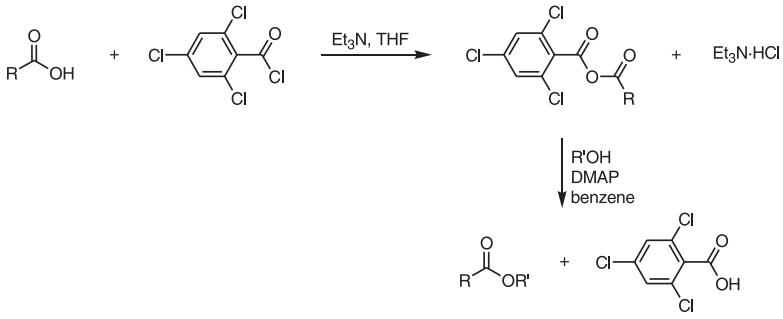
1.3.5 Mixed Anhydrides

The reactivities of anhydrides towards nucleophiles can be enhanced by combining different carboxylic acid partners. Benzoic acid derivatives with electron-withdrawing groups are most commonly employed to activate the counterpart. Mixed anhydrides with a 2,4,6-trichlorobenzoic acid moiety (Yamaguchi procedure) are also extremely versatile (Scheme 1-215) [79BCJ1989]. The mixed anhydride is prepared by treatment of a carboxylic acid with trichlorobenzoyl chloride (1 equiv.) in the presence of Et_3N (1 equiv.) and then treated with alcohol (1–2 equiv.) in the presence of DMAP (2–4 equiv.) to provide the desired esters. Both secondary and tertiary alcohols are smoothly esterified at room temperature. Of great significance is the applicability to lactonization of ω-hydroxy acids. This procedure is now recognized as the most versatile means in macrolactone synthesis.

Experimental Procedure [79BCJ1989] Scheme 1-215

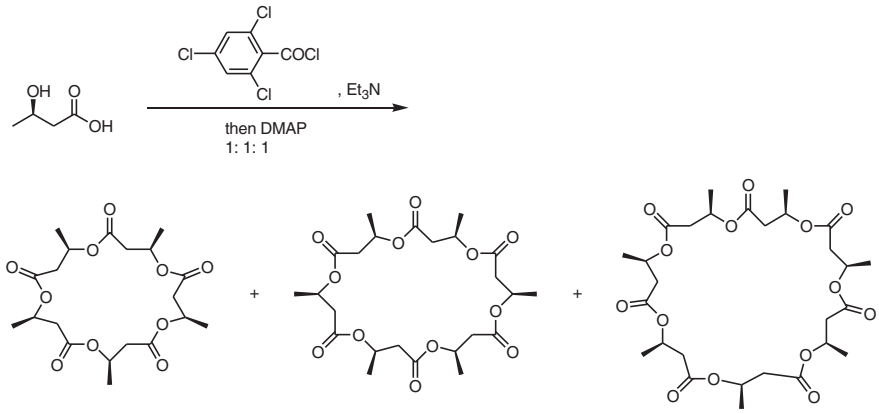
Relative Rates of Alcoholysis of Mixed Anhydrides: The acid chloride to be examined (0.3 mmol) is added to a mixture of 2-methylpentanoic acid (37 μL, 0.3 mmol) and triethylamine (42 μL, 0.3 mmol) in THF (2 mL), after which the mixture is stirred at room temperature for 20 min. After the removal of triethylamine hydrochloride by filtration, the filtrate is evaporated under nitrogen and the residue is dissolved in dichloromethane (1 mL). To this solution is added a mixture of 2-methyl-2-propanol (56 μL, 0.6 mmol) and 4-dimethylaminopyridine (73 mg, 0.6 mmol) in dichloromethane (1 mL), and the resulting mixture is stirred at room temperature. The formation of the ester is followed by GLC by addition of bromobenzene (50 μL) as an internal standard.

Preparation of Lactones: 2,4,6-Trichlorobenzoyl (or 2,3,6-trimethyl-4,5-dinitrobenzoyl) chloride (1.0 mmol) is added to a mixture of a hydroxy acid (1.0 mmol) and triethylamine (1.1 mmol) in THF (10 mL), after which the mixture is stirred at room temperature for 1–2 h (12 h in the case of 2,3,6-trimethyl-4,5-dinitrobenzoyl chloride). After removal of triethylamine hydrochloride, the filtrate is diluted with toluene (500 mL) and added under high-dilution conditions, over a period of 1.5–8 h, to a refluxing solution of DMAP (3–6 mmol) in toluene (100 mL). The reaction mixture is worked up and purified by preparative TLC (silica gel G, Merck). The crude products are purified by distillation or recrystallization.



Scheme 1-215

Subjection of enantiopure 3-hydroxybutanoic acid to the Yamaguchi procedure gives three cyclic oligomers (Scheme 1-216) [88HCA155]. Only the pentamer, hexamer, and heptamer are formed, with no tetramer.



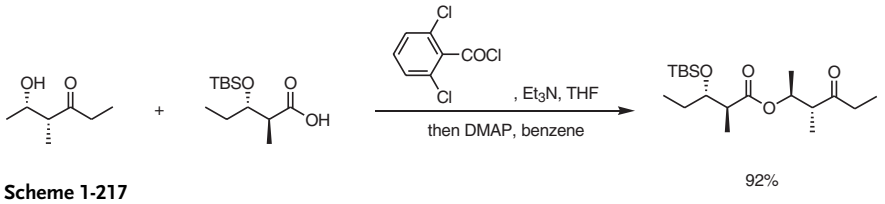
Scheme 1-216

A modified Yamaguchi procedure, with use of 2,6-dichlorobenzoyl chloride, also serves for both inter- and intramolecular esterification (Schemes 1-217, 1-218) [86T4685, 98S386, 93JOC7170].

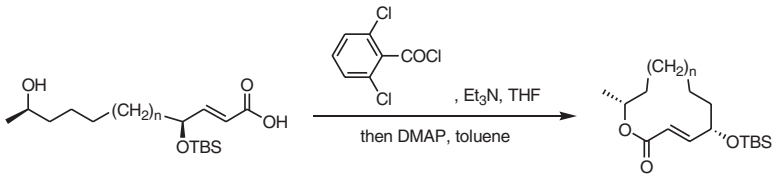
Experimental Procedure [86T4685] Scheme 1-217

2,6-Dichlorobenzoyl chloride (577 mg, 2.76 mmol) is added under Ar to a mixture of (2*S*,3*S*)-3-*tert*-butyldimethylsilyloxy-2-methylpentanoic acid (678 mg, 2.76 mmol) and Et_3N (306 mg, 3.03 mmol) in dry THF (14 mL). The mixture is stirred overnight at room temperature. After the removal of $Et_3N \cdot HCl$ by filtration, the filtrate is concentrated under N_2, and the residue is dissolved in dry C_6H_6 (10 mL). Solutions of hydroxy ketone (358 mg, 2.76 mmol) in dry C_6H_6 (3 mL) and DMAP (370 mg, 3.03 mmol) in dry C_6H_6 (3 ml) are added to this solution at 0° under Ar. The result-

ing mixture is stirred for 5 h at 0°. It is then diluted with ether (15 mL), washed with HCl (1 N), water, sat. aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue is purified by chromatography over SiO_2 (Fuji Davison BW-820 MH, 30 g). Elution with hexane/ether (20 : 1) gives (1′*S*,2′*R*)-1′,2′-dimethyl-3′-oxopentyl (2*S*,3*S*)-3-*tert*-butyldimethylsilyloxy-2-methylpentanoate (906 mg, 91.9%).



Scheme 1-217



E

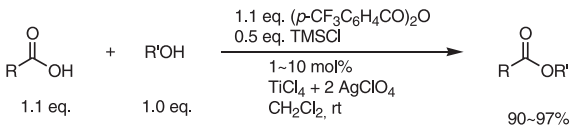
E (n= 2~4; 28~67%)

Scheme 1-218

4-Trifluoromethylbenzoic acid anhydrides, when activated by $TiCl_4/AgClO_4$, enable nearly equimolar amounts of free carboxylic acids and alcohols to be employed, affording quantitative yields of the desired esters (Scheme 1-219) [94CL515].

Experimental Procedure [94CL515] Scheme 1-219

A mixture of 4-(trifluoromethyl)benzoic anhydride (740 mg, 2.04 mmol) and 3-phenylpropionic acid (307 mg, 2.04 mmol) in dichloromethane (7.5 mL) and a solution of 1-methyl-3-phenylpropanol (278 mg, 1.85 mmol) in dichloromethane (2.5 mL) are added successively to a suspension of $AgClO_4$ (7.7 mg, 0.037 mmol), $TiCl_4$ (3.5 mg, 0.0185 mmol), and chlorotrimethylsilane (101 mg, 0.93 mmol) in dichloromethane (10 mL). The reaction mixture is kept stirring for 13 h at rt., and is then quenched with sat. aq. $NaHCO_3$. After conventional workup, the crude product is purified by preparative TLC on silica gel to afford 1-methyl-3-phenylpropyl 3-phenylpropionate (518 mg, 1.83 mmol) in 99% yield.

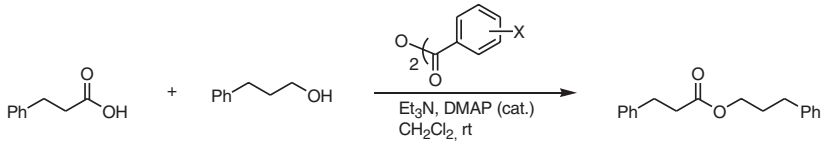


Scheme 1-219

The employment of nearly equimolar quantities of reactants is also feasible with 2-methyl-6-nitrobenzoic anhydride (Scheme 1-220) [2002CL286]. The utility of 4-nitrobenzoic anhydride in the presence of scandium catalysts was described in Section 1.3.2.2.

Experimental Procedure [2002CL286] Scheme 1-220

DMAP (2.5 mg, 0.020 mmol), 2-methyl-6-nitrobenzoic anhydride (82.9 mg, 0.24 mmol), and 3-phenylpropanoic acid (36.3 mg, 0.24 mmol) are added to a solution of triethylamine (66.1 mg, 0.65 mmol) in dichloromethane (1.5 mL). After the mixture has been stirred for 10 min, a solution of 4-phenyl-2-butanol (30.1 mg, 0.20 mmol) in dichloromethane (2.0 mL) is added. The reaction mixture is stirred for 20 h at room temperature, and saturated aqueous ammonium chloride is then added. Conventional workup and purification of the mixture by TLC on silica gel afford 1-methyl-3-phenylpropyl 3-phenylpropanoate (53.9 mg, 95%).



Scheme 1-220

The trifluoroacetic acid moiety acts as an activating group for acid anhydrides. Treatment of acid and alcohol in the presence of trifluoroacetic acid provides various sterically demanding esters [65JOC927].

Experimental Procedure [65JOC927]

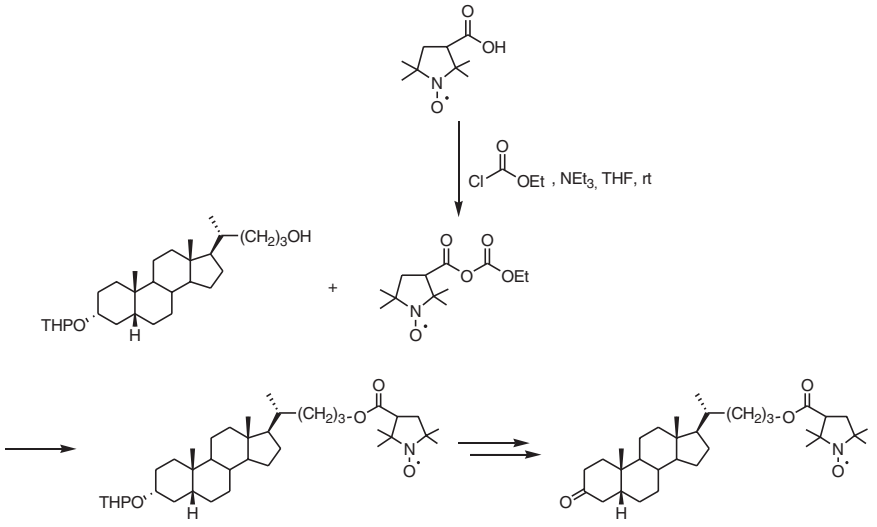
Method A: 9-Anthroic acid (2.00 g, 9.0 mmol) is suspended in benzene (40 mL), and trifluoroacetic anhydride (5.0 mL, 36 mmol) is added. The acid dissolves on gentle warming after 10 min. Methanol (5 mL) is then added. After a short period, aqueous sodium hydroxide (10%) is added to extract the acids. The benzene layer is washed with water and dried. Methyl 9-anthroate is isolated by removal of the solvent in vacuo and by recrystallization from ethanol or hexane.

Method B: Mesitoic acid (1.00 g, 6.1 mmol) and mesitol (0.83 g, 6.1 mmol) are treated with trifluoroacetic anhydride (5.0 mL, 36 mmol). The resulting solution is stirred at room temperature for 20 min. Benzene (20 mL) is added, and mesityl mesitoate is isolated as in method A.

Mixed carboxylic carbonic anhydrides are another useful type of acyl transfer reagent. Treatment of carboxylic acids with alkyl chloroformate affords alkoxycarbonyl esters, which can undergo facile transesterification. An ethoxycarbonyl derivative is employable for a key coupling process in the synthesis of a steroidal spin label compound (Scheme 1-221) [92T9939].

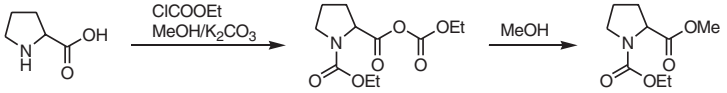
Experimental Procedure [92T9939] Scheme 1-221

1-Carboxy-2,2,5,5-tetramethylpyrrolidine-N-oxyl (0.17 g, 0.9 mmol) is dissolved in dry tetrahydrofuran (3.5 mL), and a solution of freshly distilled ethyl chloroformate (0.08 mL, 0.9 mmol) and triethylamine (0.14 mL, 1.0 mmol) is added to it. The resultant mixture is stirred for one hour, during which precipitation is observed. A solution of the protected alcohol (0.26 g, 0.6 mmol) in THF (5.0 mL) is added to this mixture, which is stirred at room temperature for 48 h. The solution is then filtered to remove the precipitated salt and the filtrate is concentrated in vacuo to give a yellow, viscous product. The crude product shows two close spots on TLC. Repeated column chromatographic purification on silica gel with ethyl acetate in petroleum ether as eluent affords the unreacted mixed anhydride (0.012 g, 5%) and the nitroxide ester as a yellow, viscous liquid (0.13 g, 37%).



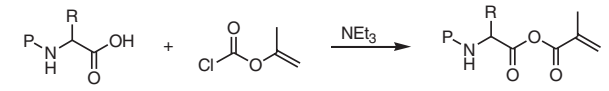
Scheme 1-221

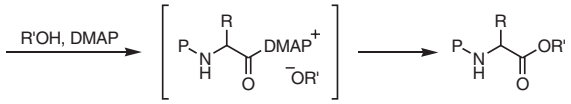
This procedure is effective for simultaneous *O*-esterification and *N*-carbalkoxylation (Scheme 1-222) [95SC1523].



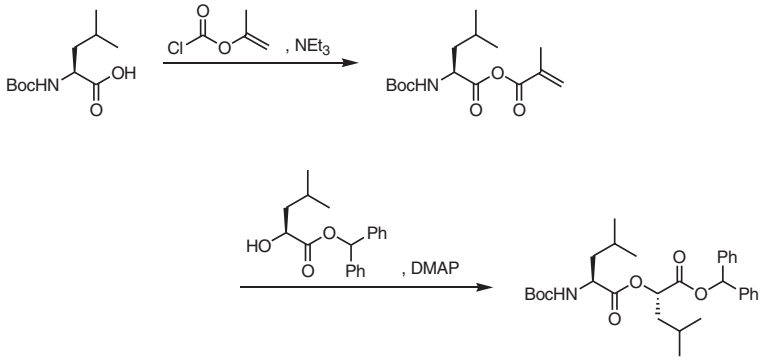
Scheme 1-222

Isopropenyl chloroformate is a more versatile reagent and is employable for esterification of various *N*-protected amino acids (Scheme 1-223) [87TL1661]. This methodology is applied to the synthesis of cyclic depsipeptide leualacin (Scheme 1-224) [95JOC6082].



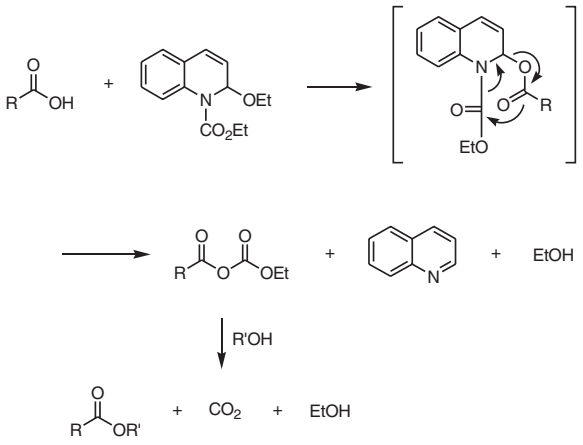


Scheme 1-223



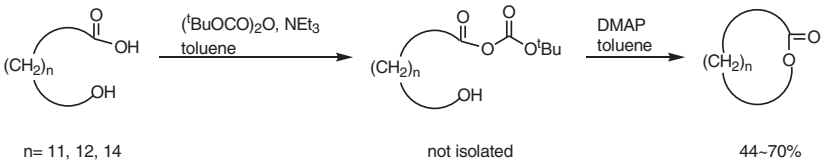
Scheme 1-224

Treatment of acid with 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline in alcohol affords the ethoxycarbonyl ester, which is spontaneously transformed into the corresponding ester (Scheme 1-225) [95JOC7072].



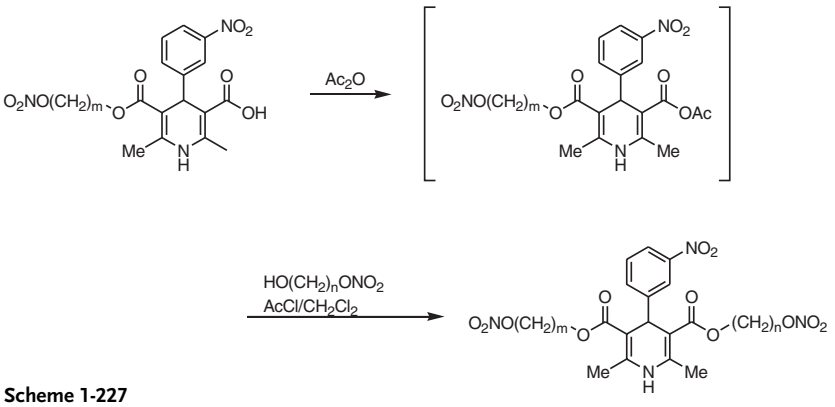
Scheme 1-225

Di-*tert*-butyl pyrocarbonate is used for the synthesis of *tert*-butyloxycarbonyl esters. Lactonization of ω-hydroxy carboxylic acids is achieved as shown in Scheme 1-226 [97TL5835].



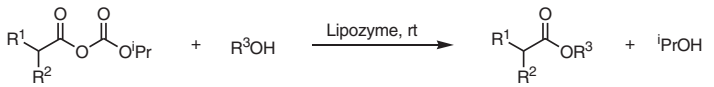
Scheme 1-226

Esterification of 1,4-dihydropyridine carboxylic acids is induced by formation of mixed acetic acid anhydrides (Scheme 1-227) [93CPB1049].



Scheme 1-227

Carboxylic carbonic anhydrides can be employed in lipase-catalyzed kinetic resolution of chiral α-substituted carboxylic acids (Scheme 1-228) [94TL421].



R^1= Ph, R^2= Me
R^1= *p*-^{s}BuC$_6$H$_4$, R^2= Me
R^1= Ph, R^2= OMe
R^1= Pr, R^2= Me

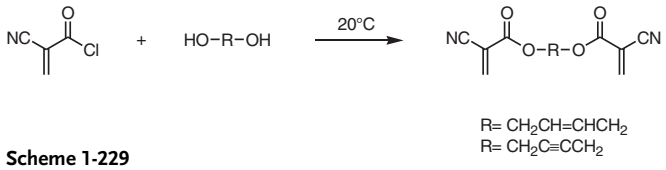
R^3= Pr, Bu, Oct

Scheme 1-228

1.4
Reaction with Acid Halides and Other Acyl Derivatives

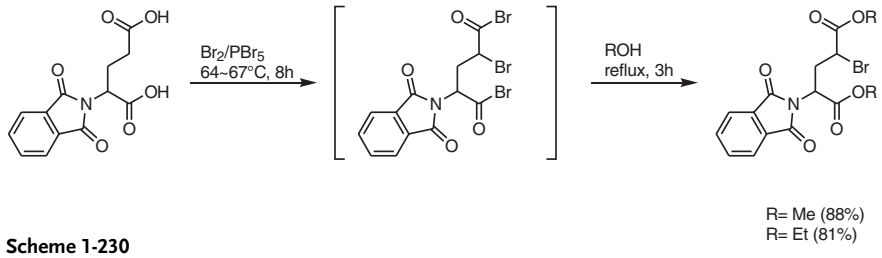
1.4.1
Without Activator

Acid halides are acylating reagents just as classical as acid anhydrides. Acid halides are more reactive than acid anhydrides, so reactions with alcohols usually proceed spontaneously at room temperature. Sterically demanding alcohols require higher reaction temperatures. Despite such high reactivity, acid halides are less popular than acid anhydrides, due to their labile nature. It is also not convenient that their reactions with alcohols produce hydrogen halides. Nevertheless, if the vigorousness of the reaction is controlled and the hydrogen halides are trapped effectively, a useful acylation methodology is attainable. One such example can be seen in the synthesis of bis(2-cyanoacrylates), used as cross-linking agents for cold-setting glues (Scheme 1-229) [95IZV779]. Treatment of 2-cyanoacryloyl chloride with 2-butene- or 2-butyne-1,4-diol at 20 °C provides unsaturated bis(2-cyanoacrylates). It should be noted that direct esterification with 2-cyanoacrylic acid and *p*-toluenesulfonic acid catalysis does not work for unsaturated diols.



Scheme 1-229

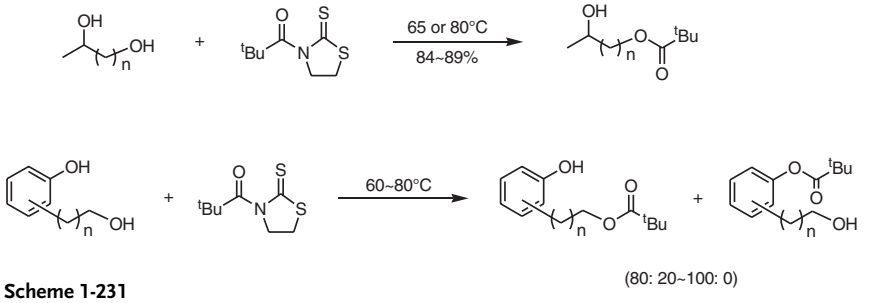
N-Phthaloylglutamic acid is transformed into the corresponding 4-brominated methyl or ethyl ester by treatment with bromine in the presence of PBr_5 under irradiation, followed by direct alcoholysis (Scheme 1-230) [94S961].



Scheme 1-230

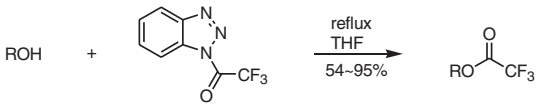
Other acyl derivatives such as amides and thioesters are stable but less reactive, and so are not easily transformed into esters unless activated in some manner. The inertness of amides is attributable to the resonance of the nitrogen lone pair electrons with the carbonyl group. Twisted amides, which lose their resonance energy

through their non-planarity, function as acylating reagents without activator [96JOC5932]. 3-Pivaloyl-1,3-thiazolidine-2-thione, for example, selectively pivaloylates primary alcohols in preference to secondary ones and phenols (Scheme 1-231), the bulky pivaloyl group not allowing the substrates to adopt a planar conformation. This situation brings about a unique reversal of reactivity in terms of steric bulk: less bulky acetyl and benzoyl analogues, normally more reactive than the pivalates, exhibit no acylation ability.



Scheme 1-231

Trifluoroacetylations that cannot usually be readily done are feasible with great ease through the use of (trifluoroacetyl)benzotriazole, prepared from trifluoroacetic anhydride and benzotriazole (Scheme 1-232) [97JOC726]. A variety of trifluoroacetates are obtained simply by heating with alcohol and phenol. Notably, *p*-nitrophenol, which is difficult to trifluoroacetylate by other means, undergoes the desired transformation smoothly.

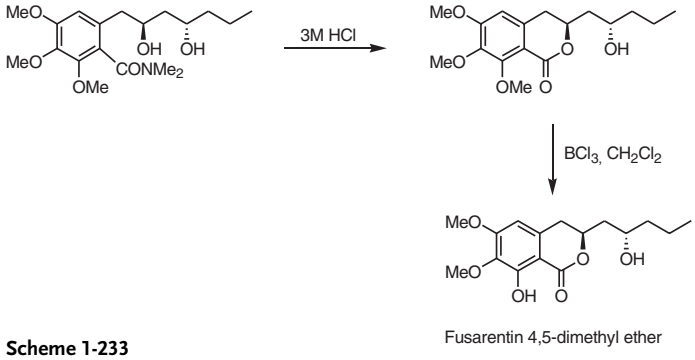


Scheme 1-232

1.4.2 Acid Catalysts

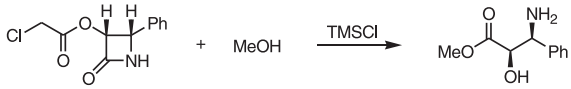
1.4.2.1 Brønsted Acids

While acid catalysts are useless for reactions between acid halides and alcohols, amides can be transformed into esters with catalysis by various acids. Some Brønsted acids serve for this purpose. Lactonization of a hydroxy amide by aqueous HCl is utilized for the penultimate step in the synthesis of fusarentin methyl ethers (Scheme 1-233) [96TL8053].



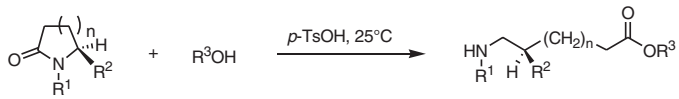
Scheme 1-233

Alcoholysis of lactams, which is of great synthetic use for the synthesis of amino acid esters, can be achieved with Brønsted acids. α-Hydroxy β-lactams undergo methanolysis by the action of dry HCl produced in situ from TMSCl and methanol (Scheme 1-234) [90TL6429]. The α-hydroxy β-amino acid moiety occurs in taxol and bestatin.



Scheme 1-234

Alkoxide ions cannot be employed for alcoholysis of lactams bearing *N*-alkoxycarbonyl or -arylsulfonyl groups, because the nucleophilic attack may occur on the *N*-substituent as well as on the desired lactam carbonyl. Lewis acid-mediated reactions avoid such problems. *p*-Toluenesulfonic acid catalyzes alcoholysis of lactams possessing *N*-COOMe, -CSSMe, or -SO_2Ar groups without cleavage of these groups (Scheme 1-235) [94TL6133].

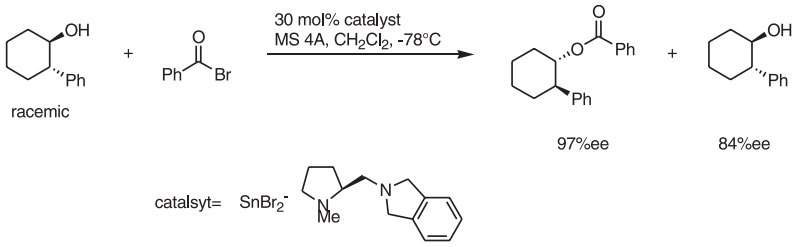


R^1= COOMe, CSSMe, Ts

Scheme 1-235

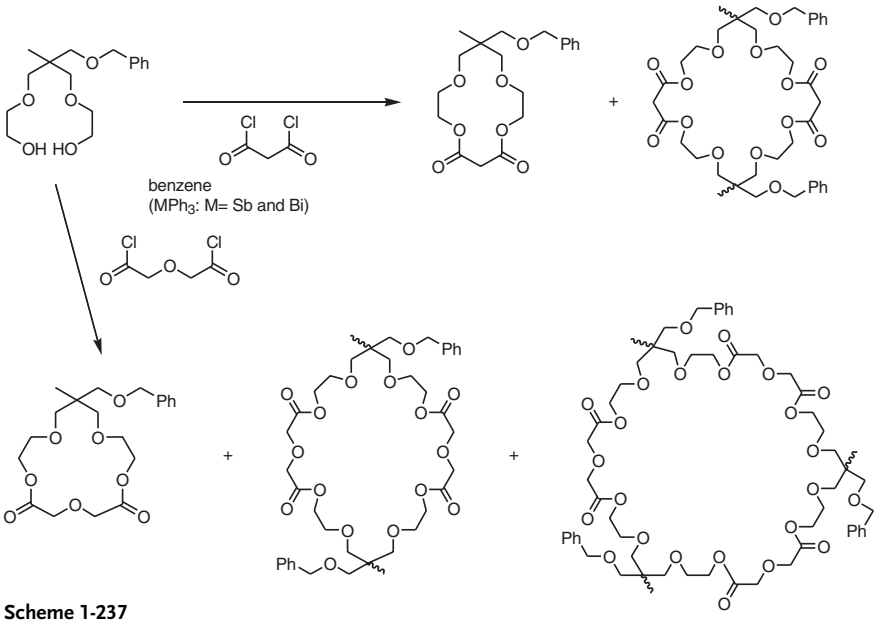
1.4.2.2 **Lewis Acids**

Reaction between alcohols and acid halides on chiral templates can result in kinetic resolution of racemic secondary alcohols. Racemic secondary alcohols are resolved by their reaction with benzoyl halides in the presence of tin(II) dihalide/chiral diamine/molecular sieves (Scheme 1-236) [96TL8543].

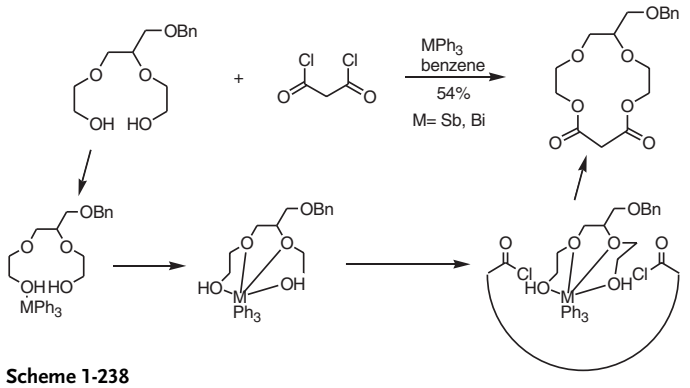


Scheme 1-236

Crown ether esters are obtained by the acid halide approach when polyether diols are treated with dicarboxylic acid dichlorides in the presence of Ph_3M (M = Sb, Bi) (Scheme 1-237) [96JCS(P1)953]. A unique template effect is responsible for this reaction (Scheme 1-238).

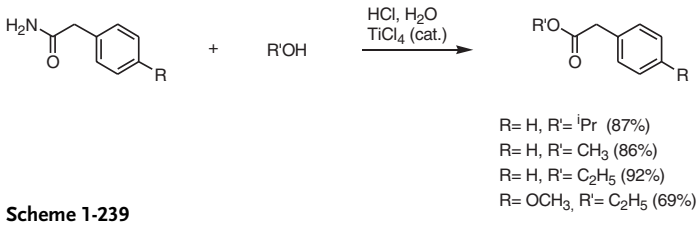


Scheme 1-237



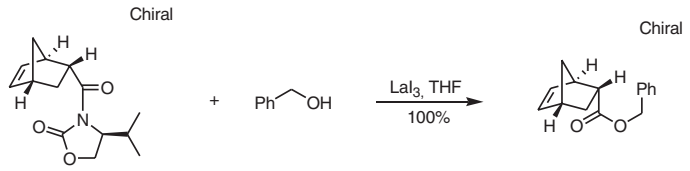
Scheme 1-238

Alcoholysis of *N*-unsubstituted amides and *O*-methylhydroxamates proceeds smoothly with a catalytic amount of $TiCl_4$ and one equivalent of aqueous HCl in alcohol solvent (Scheme 1-239) [94CJC142]. However, *N*-alkyl and *N,N*-dialkyl carboxamides are not affected under these conditions. Although the reaction also occurs in the absence of HCl, addition of one molar equivalent of aqueous HCl increases the rate considerably. $Ti(OR)_4$ species also catalyze the reaction under similar conditions. These results suggest that the Ti(IV) species involved in the alcoholysis reaction is not $TiCl_4$, but rather some intermediate $TiCl_x(OR)_{4-x}$ complex. Boron trifluoride etherate, tin tetrachloride, and silicon tetrachloride also catalyze the reaction, but with less efficiency.



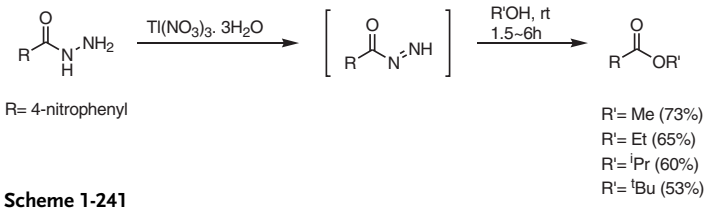
Scheme 1-239

Conversion of acyloxazolidinones into the corresponding methyl or benzyl esters is feasible with LaI_3 catalyst (Scheme 1-240) [98TL3521].



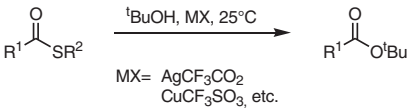
Scheme 1-240

Hydrazides are transformed into the corresponding esters upon treatment with thallium(III) nitrate trihydrate (2 equiv.) in alcohol (Scheme 1-241) [95JOC1466]. The reaction is triggered by oxidation of the hydrazides to acyl diimides.



Scheme 1-241

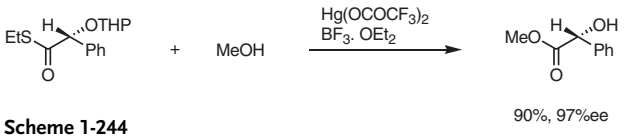
Thioesters, though stable, can be converted to the corresponding esters. Reaction between thioesters and alcohols is activated by thiophilic metal cations (Scheme 1-242) [75JACS3515, 77JACS6756]. Various sterically demanding thioesters and alcohols, even tertiary alcohols, can be employed. Soft metal salts of Hg(II), Ag(I), Cu(I), and Cu(II) are effective. The synthetic utility of this procedure is apparent from the successful lactonization shown in Scheme 1-243.



Scheme 1-242

Scheme 1-243

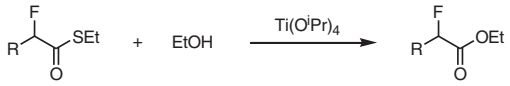
The combined use of $Hg(OCOCF_3)_2$ and $BF_3 \cdot OEt_2$ brings about the S O ester conversion (Scheme 1-244) [94CC1653].



Scheme 1-244

A thioethyl ester of 2-hydroperfluoropropionic acid is transformed into the corresponding ethyl ester by use of $Ti(O^iPr)_4$ (Scheme 1-245) [93JOC29]. It should be noted that the acidic procedure is crucial for this transformation, since base-induced

transesterification is not available, due to the acidic α-proton. However, this procedure is employable only with the thioethyl ester, the volatility of the ethanethiol being able to favor the equilibrium toward the *O*-ester.

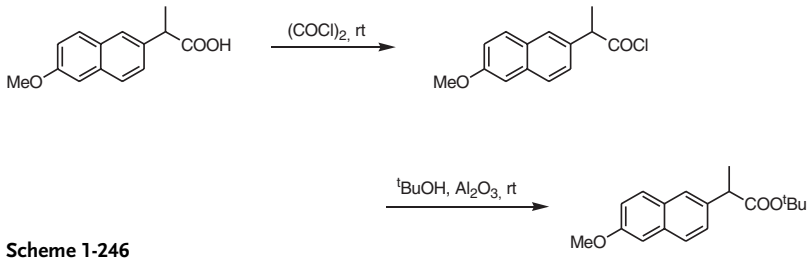


R= CF_3 (60%)
R= Et (61%)

Scheme 1-245

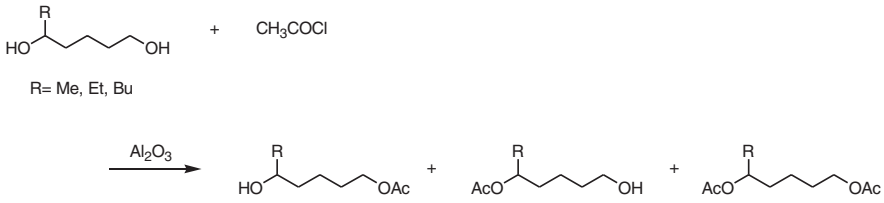
1.4.2.3 **Solid Acids**

Montmorillonite K-10 and KSF are efficient catalysts for acylation of alcohols with acid chlorides [98JCS(P1)1913]. Microwave irradiation of a mixture of naphthol, acyl bromide, and a copper/cupric chloride composite induces solventless reaction. Both α- and β-naphthols undergo acylation [98SC4495]. Reactions between acyl chlorides and *tert*-butanol to afford *tert*-butyl esters are promoted by activated alumina [90SC2033]. Notably, the reaction does not involve a ketene intermediate, often encountered in the chemistry of acid halides, and so optically active Naproxen, which is quite susceptible to ketene formation from its acid chloride, can be transformed into the corresponding *tert*-butyl ester without racemization (Scheme 1-246).



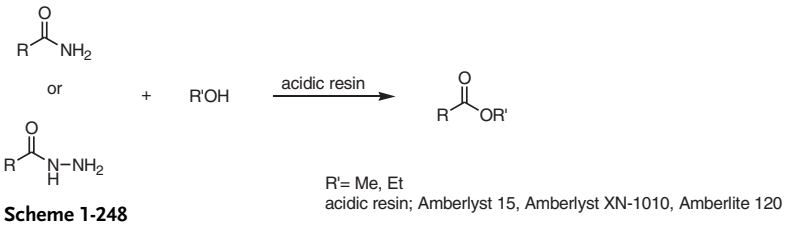
Scheme 1-246

Alumina is also used for selective acetylation of unsymmetrical diols [97TL3825]. The primary alcohol moieties in 2-substituted 1,5-diols are selectively acetylated over the secondary alcohols upon treatment with acetyl chloride, although the selectivity is not particularly high (monoacetate:diacetate < 60 : 20) (Scheme 1-247).



Scheme 1-247

A mild and selective conversion of carboxamides and carboxylic acid hydrazides into the corresponding esters is brought about by the use of acidic resins (Scheme 1-248) [81JOC5351]. Heating of the substrates with Amberlyst 15 or XN-10101 or Amberlite 120 in refluxing methanol or ethanol provides the corresponding esters. The process is specific for unsubstituted carboxamides, with even an *N*-methyl substituent preventing the reaction from proceeding.

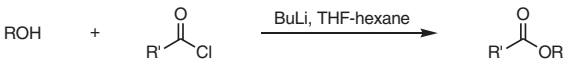


Scheme 1-248

1.4.3 Base Activators

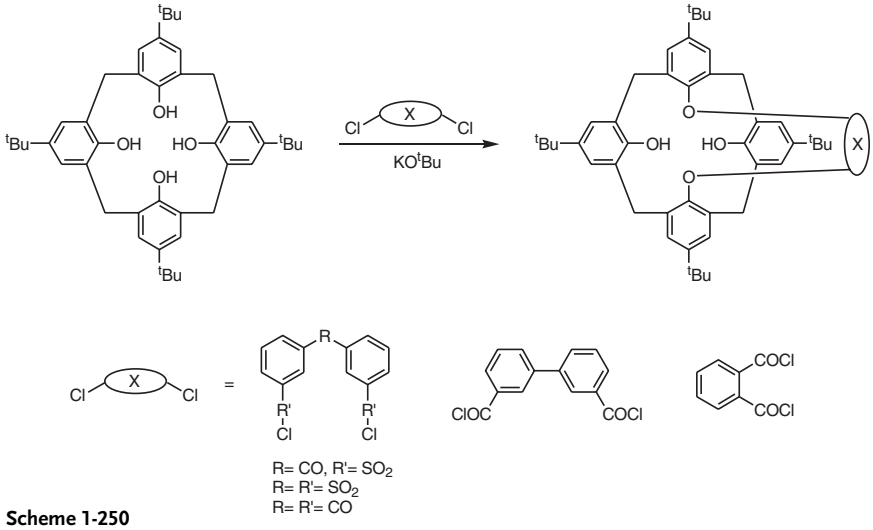
1.4.3.1 Metal Salts

Treatment of alkoxide ions with acid halides and other acyl derivatives is a common way to arrive at esters. Treatment of acid chlorides with lithium alkoxides prepared from BuLi and alcohols affords esters (Scheme 1-249) [70JOC1198]. This reaction allows the use of sterically demanding alcohols, such as tertiary alcohols, as well as acid-sensitive alcohols but is limited to acid chlorides that do not possess labile α-hydrogens or at least to those halides that produce ketenes that either are not volatile or do not dimerize.



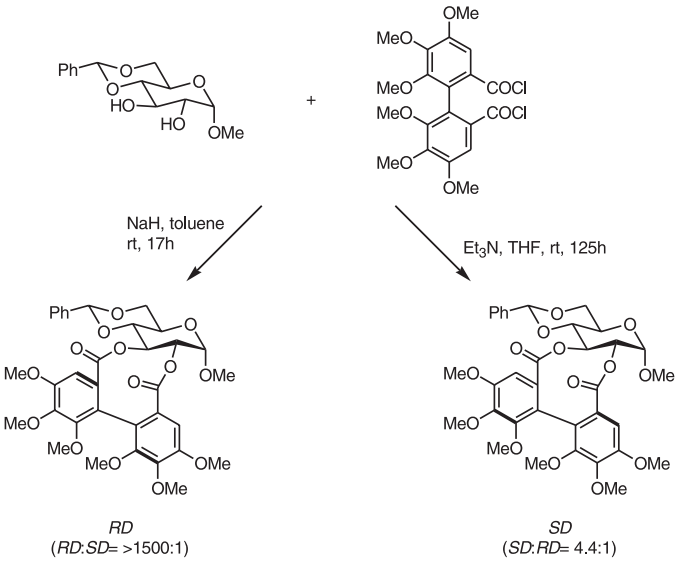
Scheme 1-249

Treatment of the dipotassium salt of *p-tert*-butylcalix[4]arene with diacid halides results in bridging at the lower rim (Scheme 1-250) [90JOC5176]. The reaction is dependent on the shape of the bridging unit: ring-closure reaction takes place only when fitting occurs between the calix[4]arene and the capping reagent.



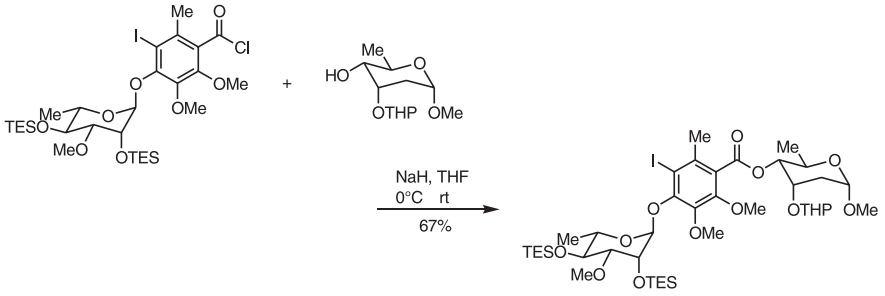
Scheme 1-250

The dialkoxide/diacid halide procedure is applicable to kinetic resolution. Treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with hexamethoxydiphenic acid dichloride provides only the *RD* cyclic diester (Scheme 1-251) [95JOC4968]. The reaction is highly stereoselective, and so the *R* isomer is obtained in 38% yield (76% theoretical yield) and the *RD*/*SD* ratio of the isomers is >1500:1. The *SD* isomer-selective reaction is best performed with Et_3N, but the selectivity is only 4.4:1. The enantiopure diphenic acid is used for the synthesis of trideca-*O*-methyl-α-pedunculagin [96JOC3700] and ferrocenyl allagitannins [98CL979].



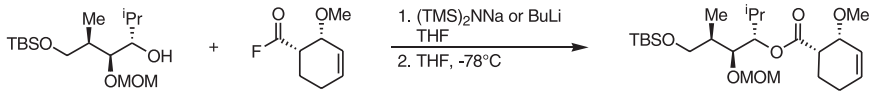
Scheme 1-251

In the synthesis of the BCD carbohydrate domain of calicheamicin, the coupling between acyl chloride and a cyclohexanol unit shown in Scheme 1-252 is best performed by use of NaH [98TL9667]. Use of Et_3N/DMAP or BuLi results in poor yields.



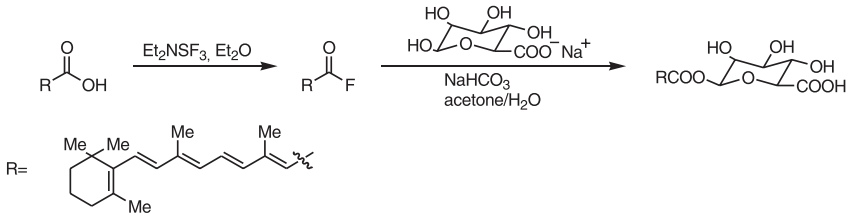
Scheme 1-252

Acyl fluorides are more reactive than the chlorides, and so the acylation of a sterically demanding alcohol is achievable, as shown in Scheme 1-253 [96JOC1655]. A 70% yield of the desired ester is obtained by use of sodium hexamethylsilazane or BuLi.



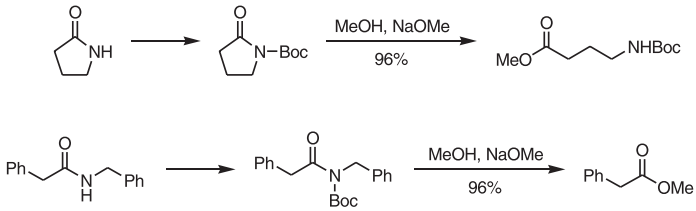
Scheme 1-253

This method is successfully applied to the synthesis of glucuronide conjugates of retinoid carboxylic acids [96SC1355]. Retinoic acid is converted into the corresponding acyl fluoride upon treatment with diethylaminosulfur trifluoride (Scheme 1-257). This product, after purification, is treated with the sodium salt of glucuronic acid in the presence of $NaHCO_3$ in acetone/water to provide the desired ester.



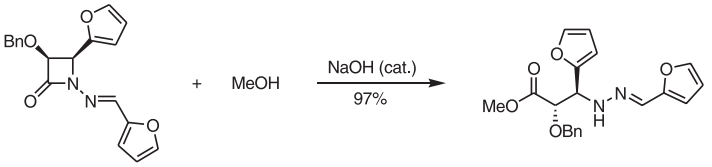
Scheme 1-254

Ring-opening of lactams is frequently required in organic synthesis. *N*-Boc-Lactams can be converted into amino esters by treatment with sodium methoxide in methanol (Scheme 1-255) [83JOC2424]. This methodology is also applied to secondary amide substrates.



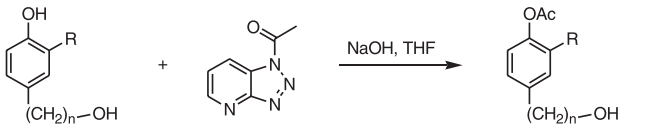
Scheme 1-255

The 2-azetidinone ring undergoes alcoholysis by catalytic NaOH (Scheme 1-256) [94JOC8003]. The facile reactivity is attributable to the presence of the imino group attached to N1, which labilizes the 2-azetidinone ring towards nucleophiles, probably reducing the amide resonance and hence the strength of the N1-C2 bond.



Scheme 1-256

1-Acetyl-*v*-triazolo[4,5-*b*]pyridine works for selective acetylation of phenol over primary alcohol (Scheme 1-257) [86TL5029]. ω-Hydroxyalkylphenols undergo monoacetylation on the phenolic alcohol when treated with this reagent in aqueous NaOH/THF.



R= H, n= 1 (80%)
R= OCH_3, n= 1 (89%)
R= H, n= 2 (90%)
R= H, n= 3 (88%)

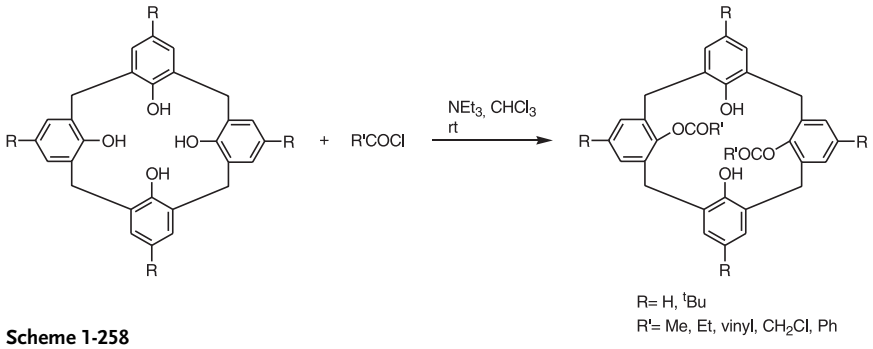
Scheme 1-257

Silver cyanide works as a more active promoter than the conventional alternatives for reactions between acid chlorides and alcohols [76BCJ2335]. Various sterically hindered acid chlorides such as pivaloyl, 2,2-diethylbutyryl, mesitoyl, and 2-methylpentanoyl chlorides are therefore employable.

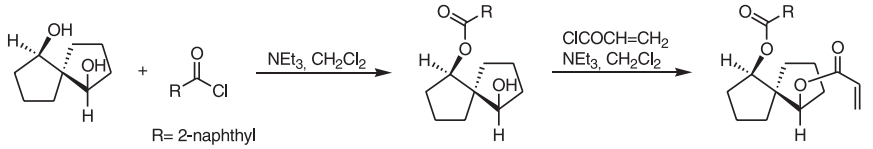
1.4.3.2 **Amines**

Acylation of alcohols by acid halides is most conveniently achieved in the presence of amine(s). Pyridine is amongst the most popular; nearly 400 references since 1990 were hit by our survey. Triethylamine is the second most popular, amounting to ca. 150 papers. DMAP follows the above amines, but is much less common (about 25 citations) because the *N*-acylpyridinium halide intermediate emerging from interaction between DMAP and acid halides is a very tightly bound ion pair and so its reactivity is low [78AGC(E)569]. Nevertheless, the combined use of catalytic DMAP/tertiary amine is very powerful: there are about 60 papers for DMAP/pyridine and 70 for DMAP/triethylamine. Since these procedures are now well known, the standard procedures are not taken up in this section but more specialized examples are the subjects of choice.

The tertiary amine/acid halide procedure is relatively mild, so selective acylation can be performed. Treatment of calix[4]arenes with various acid halides in the presence of Et_3N affords only the distal isomers of the diesters, no proximal counterparts being detected (Scheme 1-258) [94SC11]. Spiro[4,4]nonane-1,6-diol undergoes stepwise acylation on subjection to 2-naphthoyl chloride and methacroyl chloride in succession in the presence of Et_3N (Scheme 1-259) [96TA3521].

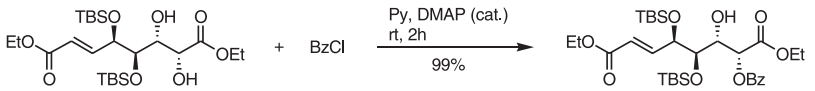


Scheme 1-258



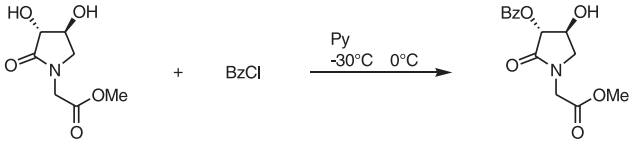
Scheme 1-259

An α,β-dihydroxy ester is selectively acylated at the α-position upon treatment with benzoyl chloride in pyridine (Scheme 1-260) [96T7861]. The β-hydroxy group is much less reactive, particularly when a bulky substituent is present at the γ-position. Benzoylation of the diol shown in Scheme 1-261 with benzoyl chloride/DMAP gives selective reaction at the C2 site [94TL4959]. The regioselective acylation of unsymmetrical diol is also seen in Scheme 1-262 [93TA2483].



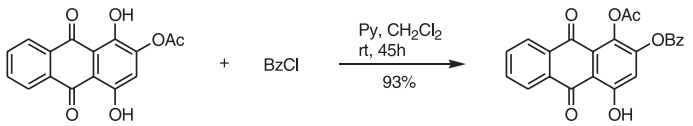
Scheme 1-260

Scheme 1-261



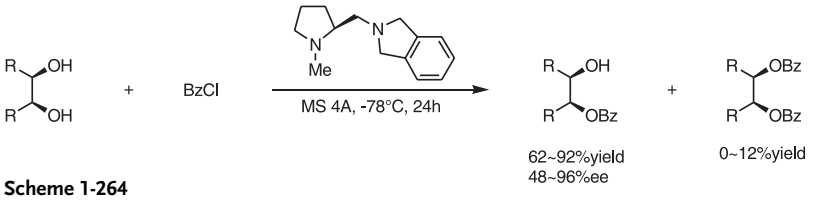
Scheme 1-262

When 2-acetoxypurpurin is treated with benzoyl chloride/pyridine, the 1-acetoxy-2-benzoyloxy derivative is obtained (Scheme 1-263) [91S438]. Migration of the acetyl group from position 2 to position 1 occurs, probably under the influence of pyridine, and the benzoyl group enters in place of the acetate.



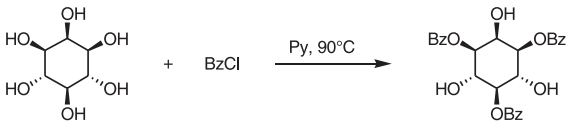
Scheme 1-263

Asymmetric acylations of *meso* diols are feasible with benzoyl chloride in the presence of a chiral diamine derived from (*S*)-proline to give monobenzoates in high optical yield (Scheme 1-264) [98TL397].

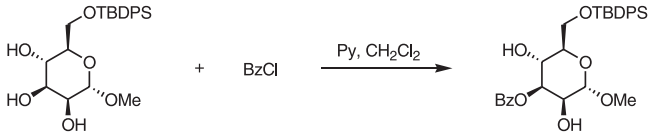


Scheme 1-264

myo-Inositol undergoes selective benzoylation upon treatment with benzoyl chloride, to give the symmetrical 1,3,5-tri-*O*-benzoyl-*myo*-inositol (Scheme 1-265) [91CC428]. Methyl 6-*O*-(*tert*-butyldiphenyl)silyl-α-D-mannopyranoside is benzoylated selectively at the 3-position (Scheme 1-266) [96BMC1461]. The use of 1.0 equiv. of benzoyl chloride is crucial for monobenzoylation; when more than 1 equiv. of this reagent is used, a considerable amount of 2,3-dibenzoate is produced.

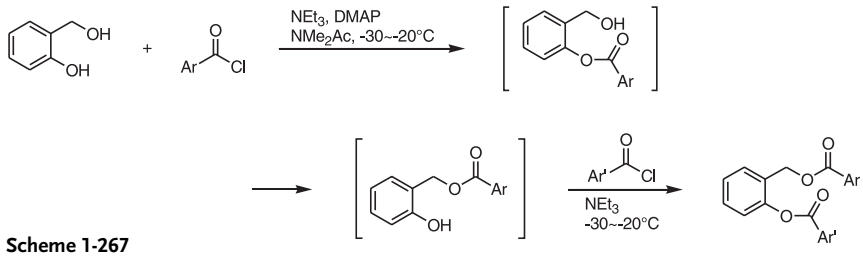


Scheme 1-265



Scheme 1-266

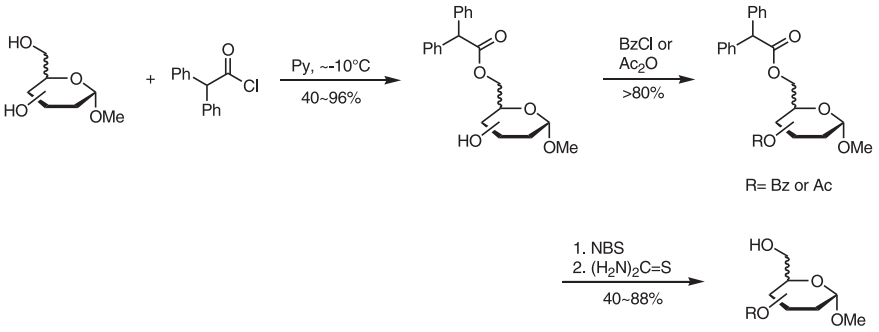
As illustrated in Scheme 1-267, when salicyl alcohol is treated with a substituted benzoyl chloride in the presence of Et_3N/DMAP at –20 to –30 °C, the phenolic hydroxy group reacts first [91TL6919, 92H(34)2061]. Upon warming of the reaction mixture to room temperature, the monoester thus formed rearranges completely to the benzyl ester. Without isolation of this intermediate, a second acylation by addition of another aroyl chloride to the reaction mixture at –20 to –30 °C is feasible, to provide the diester in good yield.



Scheme 1-267

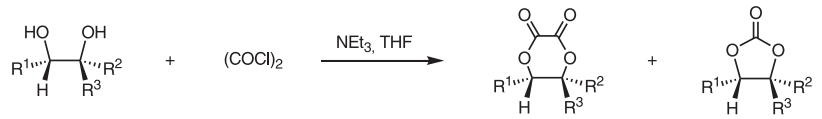
Discrimination between primary and secondary alcohols can be achieved by this procedure. A high preference for the primary alcohol is obtained by use of 2,4,6-collidine, *N,N*-diisopropylethylamine, or 1,2,2,6,6-pentamethylpiperidine [93JOC3791]. Quite naturally, too many examples of selective acylation of primary hydroxy groups over secondary ones in sugar chemistry are available to accommodate here. A summary is given in Section 7.1.

The diphenylacetoxy group is a useful protecting group because high selectivity for primary hydroxyl groups is to be expected due to its steric bulk and, moreover, they can be deprotected under neutral conditions by free-radical bromination with *N*-bromosuccinimide on the benzylic position, followed by treatment of the resulting bromo esters with thiourea or hydrazinedithiocarbonate (Scheme 1-268) [94S97]. The acylation is carried out at low temperature (~ –10 °C) by addition of diphenylacetyl chloride in anhydrous pyridine to the corresponding sugar in anhydrous pyridine.



Scheme 1-268

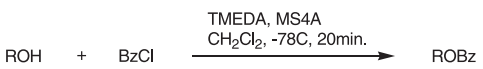
Oxalyl chloride reacts with a wide range of acyclic 1,2-glycols in the presence of Et_3N to produce 1,3-dioxolan-2-ones, together with 1,4-dioxolane-2,3-diones (Scheme 1-269) [93T10511, 94JCS(P1)1671]. Ethylene glycol, monosubstituted ethylene glycols, and *erythro*-1,2-disubstituted ethylene glycols provide the cyclic carbonates, while *threo*-1,2-disubstituted ethylene glycols afford the 1,4-dioxane-2,3-diones.



R^1= Me, Ph, CH_2Br
R^2= H, Me
R^3= H, Me, CH_2Br

Scheme 1-269

Reactions between alcohols and benzoyl chloride are accelerated by TMEDA (*N,N,N′,N′*-tetramethylethylenediamine) (Scheme 1-270) [99S1141]. Even secondary alcohols are normally acylated at –78 °C within 20 minutes.

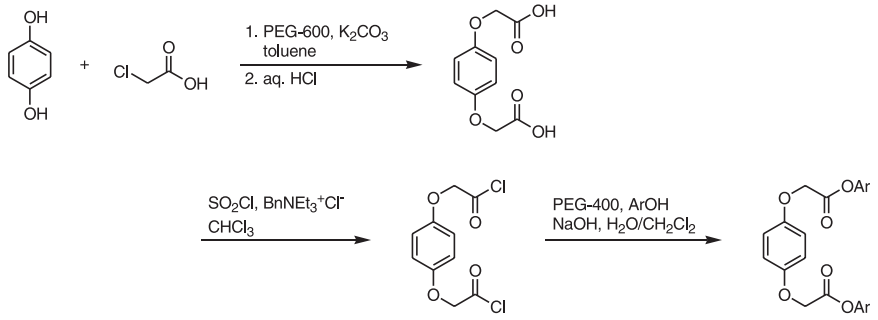


Scheme 1-270

1.4.3.3 **Phase-Transfer Catalysts**

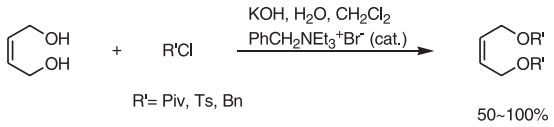
Phase-transfer technology is successfully employed in a variety of alkali-catalyzed reactions. However, it should be taken into account that this technology cannot be invoked for esterification with acid halides because these compounds are readily hydrolyzed upon contact with the aqueous phase. The use of a solid/liquid two-phase system overcomes this predisposition. Stirring of a mixture of alcohol, $Bu_4N^+HSO_4^-$, powdered NaOH, and acetyl chloride provides the desired esters in good yield [79TL2431]. More interestingly, even aqueous NaOH is employable. Phenyl acetate is

obtained in 84% yield by treatment of phenol and acetyl chloride in a two-phase system consisting of CH_2Cl_2 and aqueous NaOH containing $Bu_4N^+Cl^-$ [93CE445]. In the absence of the ammonium salt, the yield is only 15%. The use of NaOH is crucial for a good yield, but the use of this reagent in high concentrations (over 30%) decreases the yield, probably due to hydrolysis of the resulting ester. Both variants of this technology are applied to the synthesis of diaryl 1,4-phenylene dioxydiacetate (Scheme 1-271) [96SC1447]. Hydroquinone is acylated with chloroacetic acid in the presence of PEG-600 (polyethylene glycol-600) and KI with powdered K_2CO_3 in toluene to give dipotassium 1,4-phenylenedioxydiacetate, which is converted into the diacid by treatment with aqueous HCl. The diacid is transformed into the acyl chloride, which is then converted into the final products by treatment with phenols under liquid-liquid phase-transfer catalysis conditions with 3% PEG-400 as phase-transfer catalyst and NaOH in H_2O/CH_2Cl_2.



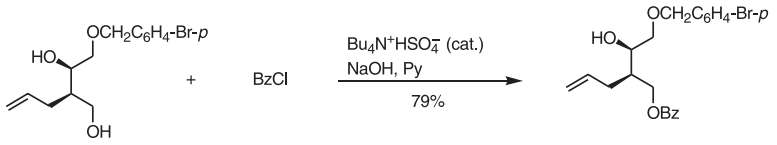
Scheme 1-271

Esters of (*Z*)-1,4-but-2-enediols are obtainable only under phase-transfer conditions (Scheme 1-272) [90SC2821]. Treatment of the diol with acyl chlorides in the presence of benzyltriethylammonium bromide in H_2O/CH_2Cl_2 at –5 °C furnishes the desired esters. No other conventional acylation methods give satisfactory yields.



Scheme 1-272

Phase-transfer technology is the method of choice in the acylation shown in Scheme 1-273 [94JOC1783]. Attempted regioselective benzoylation of the primary alcohol by use of benzoyl chloride in pyridine results in only 45% yield. On the other hand, phase-transfer catalysis with $Bu_4^+HSO_4^-$ in aqueous $NaOH/CH_2Cl_2$ gives the desired mono-*O*-benzoylated compound in 79% yield.

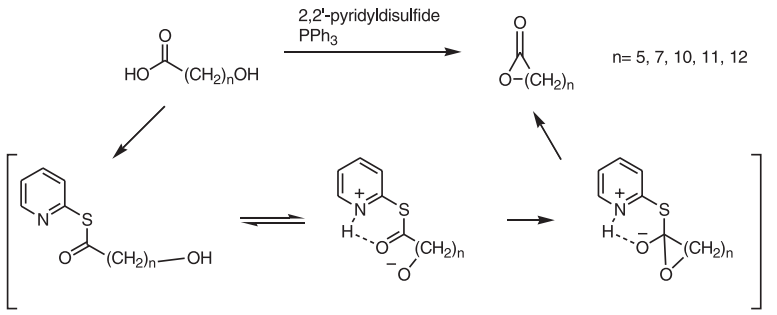


Scheme 1-273

1.4.4 Other Activators

Template effects of heterocyclic compounds are often invoked for activation of carboxylic acids. 2-Pyridinethiol esters of ω-hydroxy carboxylic acids, which can be prepared from 2,2′-pyridyldisulfide and the acids, undergo lactonization upon heating in refluxing xylene under high-dilution conditions (Scheme 1-274) [74JACS5614]. Various macrolides, including medium-sized ones, are obtained, although with the exception of nine-membered rings.

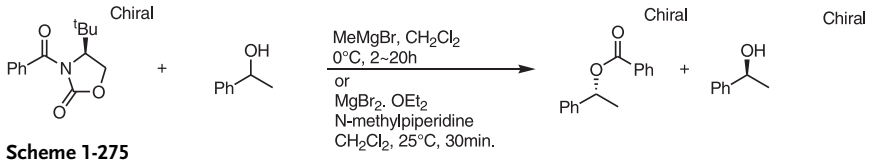
Experimental Procedure [74JACS5614] Scheme 1-274
The hydroxy acid (0.5 mmol), 2,2'-dipyridyl disulfide (165 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) are dissolved under argon in dry, oxygen-free xylene and stirred at 25° for 5 h. The reaction mixture containing the 2-pyridinethiol ester is diluted with dry, oxygen-free xylene (10 mL), and the resulting solution is added slowly from a mechanically driven syringe, over 15 h, to dry xylene (100 mL) at reflux under argon. Refluxing is continued for an additional 10 h. Quantitative GLC analysis is performed directly on the obtained solution of product (10 ft, 10% silicone SE-30 column), by using the next higher homologous lactone as standard. The solvent is removed under reduced pressure and the ether-soluble part of the residue is subjected to preparative thin layer chromatography on silica gel (10% ether in pentane for development) to afford pure lactones and diolides.



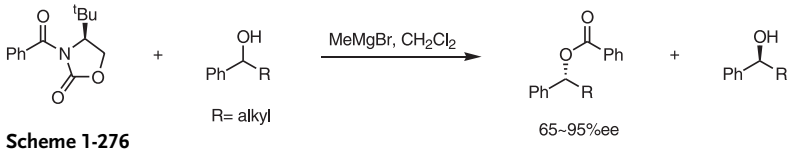
Scheme 1-274

N-Acyl oxazolidinones are useful chiral building blocks, but are not easy to convert into esters or carboxylic acids. Esters are produced by treatment with magnesium

alkoxides, obtainable either by alcohol deprotonation with MeMgBr or through deprotonation with the Lewis acid-base combination of $MgBr_2/R_3N$ (Scheme 1-275) [93TL5563]. Selective benzoylation of racemic carbinols with kinetic selectivities of 20–30 : 1 for the *R* enantiomer can be attained. This method is also applied to enantioselective acylation of aryl alkyl carbinols with *N*-benzoyl-4(*S*)-*tert*-butyl-2-oxazolidinone (Scheme 1-276) [96TL6777, 99JOC9365]. Lewis acids are also effective for methyl ester synthesis from 4-substituted and unsubstituted *N*-acyl oxazolidinones [2001SL637].

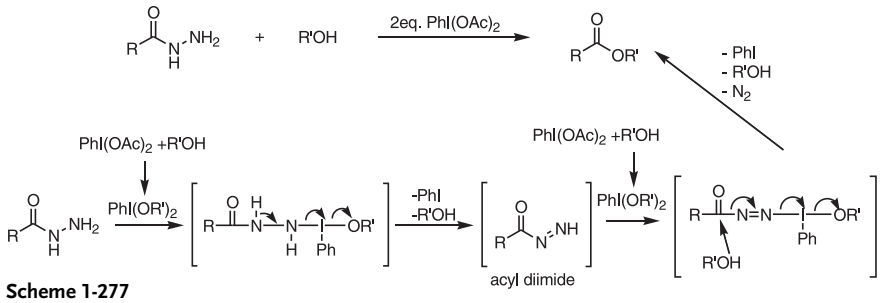


Scheme 1-275



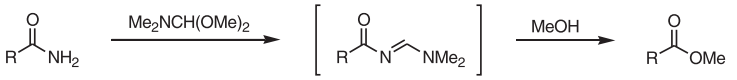
Scheme 1-276

Hydrazides readily undergo alcoholysis through the action of iodobenzene diacetate [96JCR(S)100]. The reaction proceeds via a key acyldiimide intermediate (Scheme 1-277). A similar oxidative process is feasible with CAN (ceric(IV) ammonium nitrate) [99TL4429].



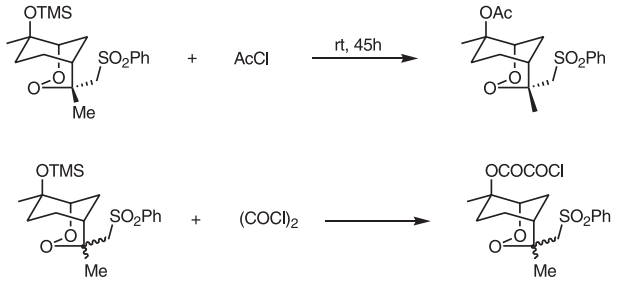
Scheme 1-277

Primary carboxamides are converted into the corresponding esters by treatment with dimethylformamide dimethylacetal (2 equiv.) in methanol (Scheme 1-278) [97TL2367]. The hydroxy group is tolerated in this reaction, but some functional groups such as NH_2, NHR, and COOH are not employable. The transient *N*-acylformamidine can be observed by monitoring of the reaction course by HPLC or GC.



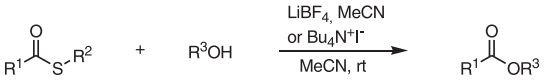
Scheme 1-278

Direct conversion of silyl ethers into esters is feasible (Scheme 1-279) [98BMC903]. Treatment of silyl ethers with acid chlorides at room temperature affords the corresponding esters.



Scheme 1-279

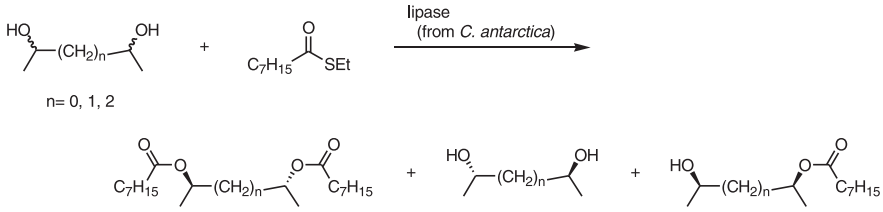
Thioesters are usually more stable than normal esters. Nevertheless, conversion into the corresponding esters can be effected by electrochemical means (Scheme 1-280) [90CL1223]. The reaction requires an electrolyte: $Bu_4N^+I^-$ or $Li^+BF_4^-$ in acetonitrile. The reaction proceeds differently depending on the electrolyte, and a wider range of substrates are employable with use of $Bu_4N^+I^-$.



Scheme 1-280

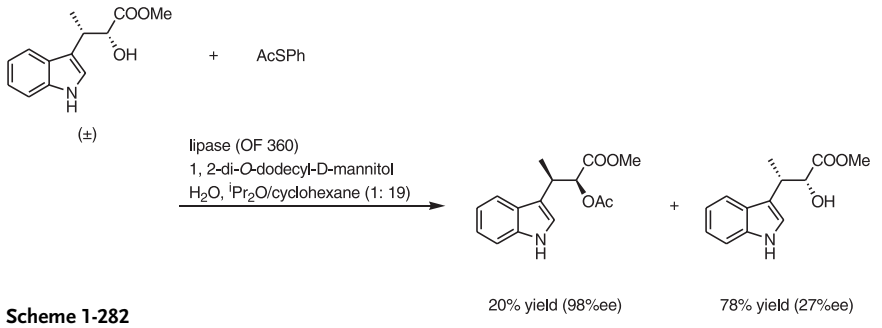
1.4.5 Enzymes

Thiol esters function as acyl donors in enzymatic acylation. 2,3-Butanediol, 2,4-pentenediol, and 2,5-hexanediol are resolved by a lipase derived from *Candida Antarctica* (Scheme 1-281) [93TA925]. The (*R,R*) isomers react more rapidly than their (*S,S*) counterparts, both enantiomers being available with >99%*ee*s for the hexane- and pentanediols, but the selectivity being lower for the butanediol derivative.



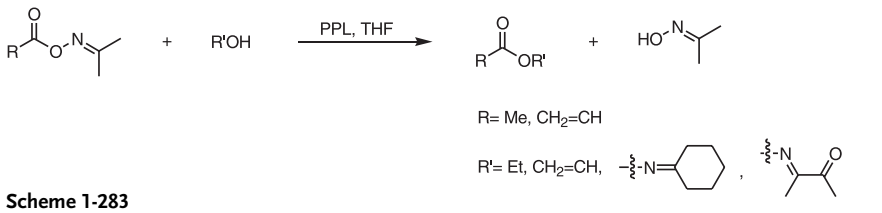
Scheme 1-281

Racemic indolemycenic ester is acetylated with lipase OF-360 (Scheme 1-282) [97CPB2085]. Phenyl thioacetate is a better acyl donor than isopropyl acetate and nitrophenyl acetate in terms of chemical yield.



Scheme 1-282

Oxime acetates and acrylates are efficient irreversible acyl transfer agents for lipase-catalyzed transesterification in organic media (Scheme 1-283) [89CC1533].



Scheme 1-283

N-Pivaloyl imidazole serves as an acyl donor in pivaloylation of monosaccharides and lactose [98S1787]. The primary hydroxy group is selectively acylated over the secondary hydroxy groups but the selectivity is not always high.

2
Use of Tin and Other Metal Alkoxides

The oxygen atom of a metal alkoxide exhibits enhanced nucleophilicity due to the electropositive character of the metal. If the metal-oxygen bond is chemically labile, then the alkoxide should function well as a nucleophile. Tin alkoxides, especially organotin(IV) alkoxides, are extremely useful because the tin-oxygen bond is readily formed, thanks to its thermodynamic stability, while this bond is reactive enough to attack electrophiles. Because of its mildness and high selectivity, this procedure has found a wide range of applications, particularly in sugar chemistry, and so this subject is discussed in this chapter.

Bu_3SnOMe undergoes exothermic reaction with acid anhydrides and halides to give the corresponding esters [62CRA3693]. This reactivity of Bu_2SnO is utilized for the selective acylation of nucleosides (Scheme 2-1) [74JOC24]. The 2′,3′-*O*-(dibutylstannylene) nucleosides are obtained by heating a methanolic suspension of the nucleosides and an equimolar amount of Bu_2SnO. It is postulated that $Bu_2Sn(OMe)_2$ is initially formed under these conditions. Treatment of the stannylene nucleosides with acetic or benzoic anhydride or chloride results in selective acylation at the 3′-position, no acylation taking place on the primary alcohol. The stannylene intermediate does not need to be isolated, resulting in a one-pot acylation: the addition of 5–10 equiv. of Ac_2O and Et_3N to a solution of the stannylene prepared in methanol effects selective monoacetylation.

Experimental Procedure [74JOC24] Scheme 2-1

2′,3′-*O*-(Dibutylstannylene)uridine: A suspension of uridine (488 mg, 2 mmol) and dibutyltin oxide (500 mg, 2 mmol) in methanol (100 mL) is heated under reflux for 30 min, and the resulting clear solution is then evaporated to dryness and dried in vacuo. The resulting crystalline residue (915 mg, 96%) is analytically pure and has m.p. 232–234°.

3′-*O*-Benzoyluridine: A solution of 2′,3′-*O*-(dibutylstannylene)uridine (2 mmol) in methanol (100 mL) is prepared in situ as above. Triethylamine (1.4 mL, 10 mmol) and benzoyl chloride (1.2 mL, 10 mmol) are added, and the mixture is stirred at room temperature for 10 min, at which point TLC (ethyl acetate/acetone 1 : 1) shows no remaining uridine. The solvent is evaporated in vacuo and the residue is partitioned between ether (100 mL) and water and filtered. The aqueous phase is concentrated to about 30 mL and allowed to crystallize. Recrystallization from aqueous ethanol gives pure (NMR and TLC) 3′-*O*-benzoyluridine (570 mg, 78%) as the dihydrate.

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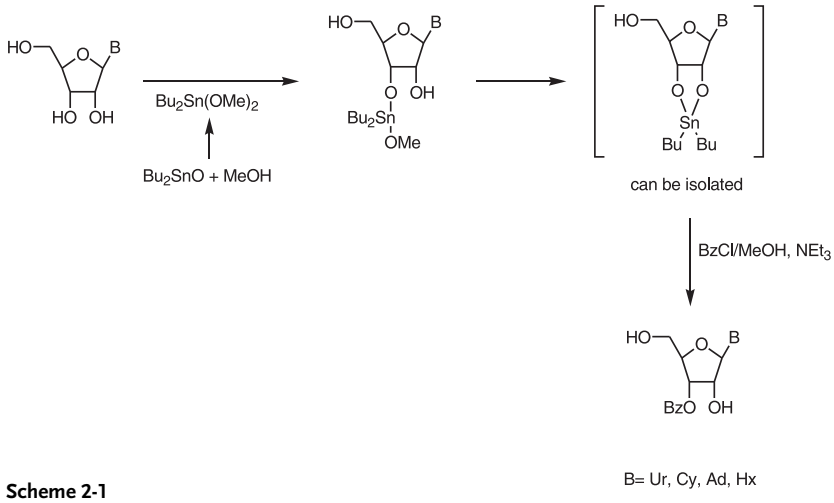


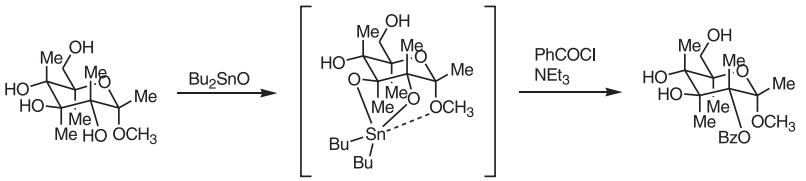
Scheme 2-1

Methyl α-D-hexopyranosides undergo selective acylation at the 2-position by the stannylene method [76JOC1832]. While 4,6-*O*-benzylidene D-hexopyranosides are converted into the corresponding stannylene derivatives, which undergo acylation at the 2-position upon treatment with acyl halides in dioxane in the presence of Et_3N, the unprotected sugars are also successfully transformed into the C2 monoesters in one-pot fashion without isolation of the stannylene intermediates (Scheme 2-2). The C2 esters of methyl α-D-gluco-, α-D-allo-, and α-D-galactopyranosides are obtained by this procedure.

Experimental Procedure [76JOC1832] Scheme 2-2

Methyl 2,3-*O*-Dibutylstannylene-α-D-glucopyranoside: Dibutyltin oxide (12.50 g, 50 mmol) is added to a solution of methyl α-D-glucopyranoside (9.7 g, 50 mmol) in methanol (200 mL), and the resulting milky solution is heated at reflux until it becomes homogeneous and clear (45 min). After further heating at reflux for an additional 0.5 h, the solvents are evaporated in vacuo to leave a white solid, m.p. range 105–115 °C.

Methyl 2-*O*-Benzoyl-α-D-glucopyranoside: Triethylamine (1.54 mL, 11 mmol) is added to a magnetically stirred, slightly cloudy solution of methyl 2,3-*O*-dibutylstannylene-α-D-glucopyranoside (4.25 g, 10 mmol) in dioxane (75 mL), followed by slow addition of benzoyl chloride (1.32 mL, 11 mmol). The solution becomes clear upon addition of the benzoyl chloride, but a white precipitate starts to form ~2 min later. TLC examination of the solution (ethyl acetate, silica gel G) after 1 h shows the presence of a major spot at R_f 0.50 and a minor spot at R_f 0.70. The salts are filtered off and washed with dioxane (20 mL), and the combined filtrates are evaporated in vacuo to leave a syrup. This is fractionated on a column of silica gel G (120 g) with ethyl acetate as eluent. The first compound eluted from the column is methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside (0.08 g, ~2%). The second compound eluted from the column is the desired material (2.05 g, 70%).

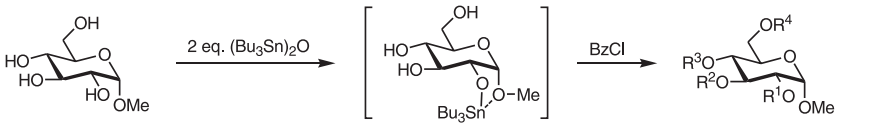


Scheme 2-2

Regioselective acylation of sugars through the use of $(Bu_3Sn)_2O$ is also feasible [81T2363]. In this case the selectivity is governed by a monoalkoxytin intermediate coordinated by the proximate hydroxy group. For example, stannylation of methyl α-D-glucopyranoside with two equiv. of $(Bu_3Sn)_2O$, followed by treatment with benzoyl chloride at 20 °C provides the 2,6-di-*O*-benzoyl ester (81%) and the 2,3,6-tri-*O*-benzoyl ester (18%) (Scheme 2-3). When the reaction is conducted at –10 ° to –5 °C, the dibenzoate is obtained in 95% yield.

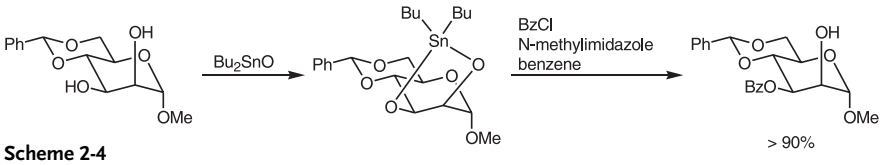
Experimental Procedure [81T2363] Scheme 2-3

Methyl α-D-glucopyranoside (283 mg, 1.46 mmol) is stannylated with $(Bu_3Sn)_2O$ (1.3 g, 2.19 mmol) in toluene (23 mL). A solution of benzoyl chloride (600 mg, 4.4 mmol) in toluene (5 mL) is added then dropwise to the cooled solution, over 5 min at –10 °C. The mixture is stirred for 4 h at –10 °C and then left for 17 h at –5 °C. Acetic acid (0.2 mL) is added and the solvent is evaporated in vacuo to give an oily residue, which is triturated with diisopropyl ether to afford the crystalline product (588 mg, 95%).



Scheme 2-3

The regioselectivity in the monoacylation of secondary hydroxy groups in monosaccharides can be controlled by the stannylene technique (Scheme 2-4) [84SAC19]. Use of one equiv. of strong base such as *N*-methylimidazole results in the formation of the equatorial 3-benzoate in a yield of more than 90%.

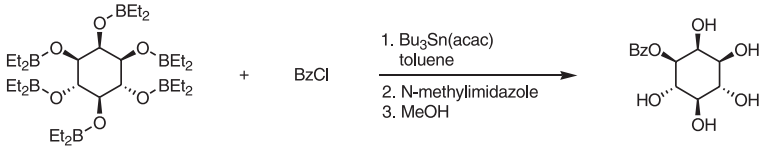


Scheme 2-4

Borylated carbohydrates are quantitatively *O*-stannylated by transmetalation with tributyltin acetylacetonate. This methodology is applicable to *O*-acylation of *myo*-inositol (Scheme 2-5) [91JOC444]. The standard stannylene procedure is not effective for acylation, due to the poor solubility of the stannylene intermediate, whereas the hexa-*O*-diethylboryl derivative prepared by treatment with excess Et_3B is soluble in hexane and treatment of this compound with tributyltin acetylacetonate furnishes a partially borylated-stannylated intermediate. Treatment of this compound with benzoyl chloride in the presence of *N*-methylimidazole affords 1-*O*-benzoyl-*myo*-inositol.

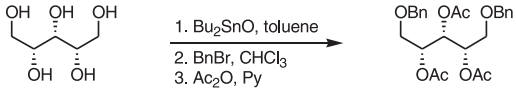
Experimental Procedure [91JOC444] Scheme 2-5

A solution of the hexa-*O*-diethylboryl derivative (234 mg, 0.4 mmol) in toluene is treated with tributyltin acetylacetonate (0.5 mmol), and N-methylimidazole (0.25 mmol) and benzoyl chloride (0.625 mmol) are then added at –5 °C. The reaction mixture is stirred at 5 °C for 10 h. After conventional workup the mixture is purified by column chromatography on silica gel (chloroform/methanol 3 : 1).

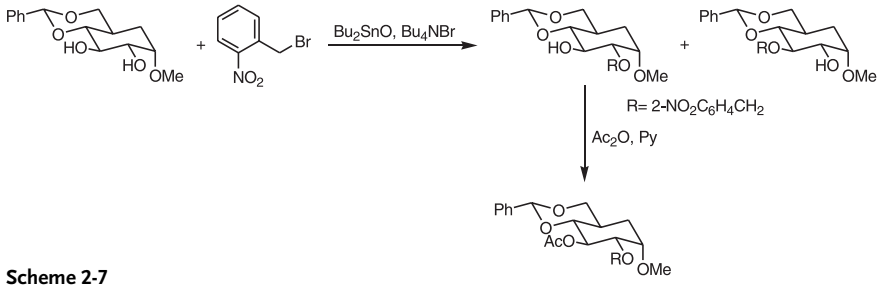


Scheme 2-5

Selective *O*-acylation and -alkylation are feasible, as shown in Scheme 2-6 [98CAR(307)355] and Scheme 2-7 [93JCS(P1)2161].



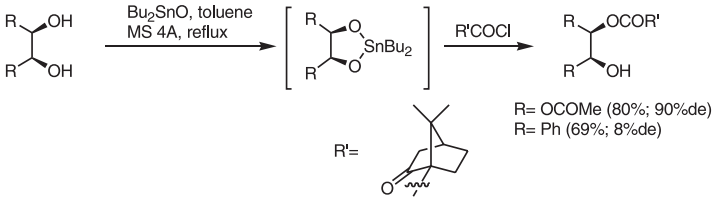
Scheme 2-6



Scheme 2-7

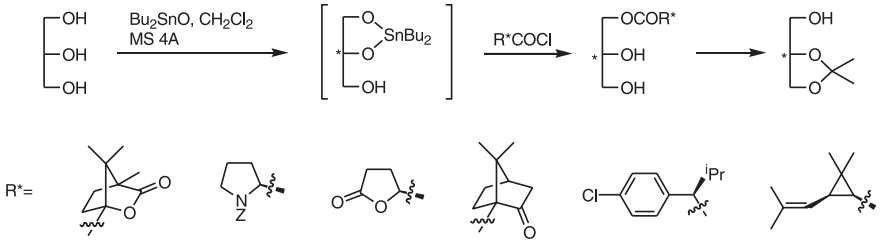
The use of chiral acid halides in the stannylene approach allows asymmetric acylation of *meso*-1,2-diols. Thus, treatment of *meso*-dimethyl tartrate with Bu_2SnO fol-

lowed by (1*S*)-ketopinic acid chloride exclusively affords the monoacylation product, in high yield and with high diastereoselectivity (Scheme 2-8) [84CL49].



Scheme 2-8

Optically active glycerol acetonide can be prepared analogously from achiral glycerol (Scheme 2-9) [84CL401].

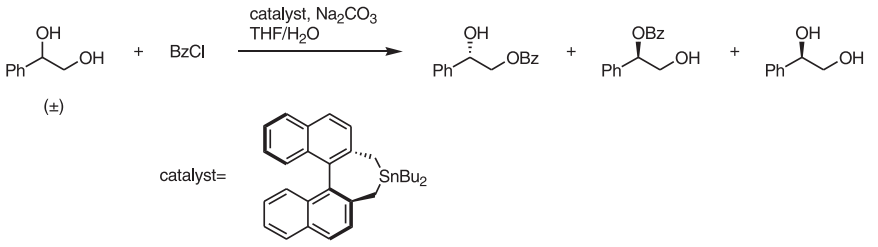


Scheme 2-9

Kinetic resolution of chiral 1,2-diols is effected by use of an organotin catalyst with a binaphthyl moiety as a chiral source (Scheme 2-10) [99OL969]. Addition of sodium carbonate and a small amount of water improves the selectivity.

Experimental Procedure [99OL969] Scheme 2-10

Sodium carbonate (1.5 mmol) base is suspended in HF (5 mL) containing racemic alcohol (1 mmol), water (100 μL, 5.5 mmol), and organotin catalyst (0.25 mol%). Benzoyl chloride (0.5 mmol) is then added to the suspension at –10 °C, and the re-



Scheme 2-10

sulting solution is stirred at that temperature for 14 h. After conventional workup, a mixture of primary monobenzoate (86% *ee*, 38% yield) and recovered racemic alcohol (46% *ee*, 58% yield) is obtained, with a trace amount of secondary monobenzoate.

When the treatment of unsymmetrical diols by the stannylene procedure is accompanied by in situ quenching with chlorosilane or oxalic acid, acylation takes place on the more substituted hydroxy group (Scheme 2-11) [85CC1457, 90JOC5132]. This method can be applied to 1,2-, 1,3-, and 1,4-diols of primary-secondary, primary-tertiary, and secondary-tertiary natures. Benzoyl chloride and other acid chlorides are employable, but acid anhydrides are of no use.

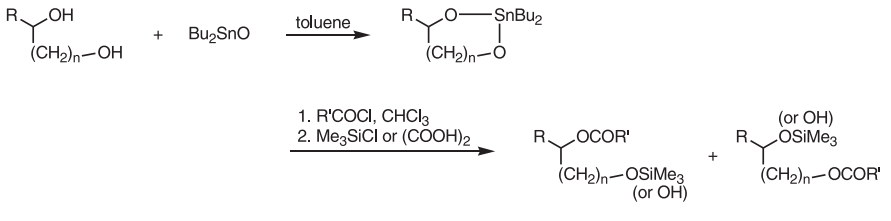
Experimental Procedure [90JOC5132] Scheme 2-11

General Acylation Procedure: A portion of the diol (1.5 mmol) is dissolved or suspended in toluene (30 mL) and, after the addition of dibutyltin oxide in 5% molar excess, water is separated by azeotropic distillation in a Dean-Stark apparatus for a variable length of time, depending on the substrate. After evaporation of the solvent, the residue is dried under vacuum, dissolved under nitrogen in anhydrous $CHCl_3$ (1.5 mL), and cooled to 0–5 °C. An equimolar amount of the appropriate acylating reagent in the same solvent (1 mL) is added dropwise to the stirred solution by syringe through a septum cap, and the reaction mixture is allowed to react at room temperature for 1 h and then quenched by one of two different methods.

Method A. Quenching with Trialkylsilyl Chlorides: A solution of the appropriate silyl chloride (5% molar excess) in anhydrous $CHCl_3$ (1 mL) is added dropwise by syringe to the cooled solution (0–5 °C), and the mixture is then allowed to react at room temperature for 1–2 h. The mixture obtained is then analyzed by ^{1}H NMR spectroscopy.

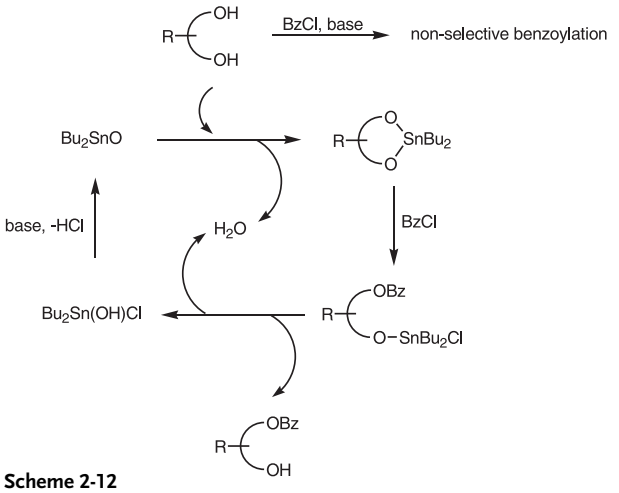
Method B. Quenching with Oxalic Acid: The solvent is evaporated under vacuum, and the residue is dissolved in anhydrous CH_3CN (8 mL). The solution is cooled to 0–5 °C, oxalic acid (0.75 mmol) in CH_3CN (3.5 mL) is added, and the mixture is stirred at room temperature for 20 h. The resulting suspension is filtered under nitrogen, and the solid is washed several times with CH_3CN. The residue obtained after evaporation of the solvent under vacuum is dissolved in $CDCl_3$ and the mixture is analyzed by ^{1}H NMR spectroscopy.

Microwave irradiation is useful not only for shortening the time required to prepare the stannylene intermediates but also for rendering the procedure catalytic. As



Scheme 2-11

shown in Scheme 2-12, if $Bu_2Sn(OH)Cl$ is successfully transformed into Bu_2SnO in the presence of a base, the organotin species can be recycled. Under normal conditions, however, in which heating is necessary to prepare stannylate diols, the base promotes reaction between benzoyl chloride and diols. No such direct reaction occurs under microwave conditions though, thus allowing the catalytic cycle to complete.

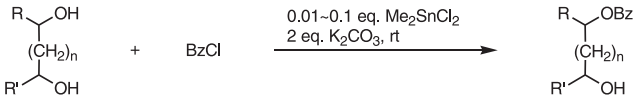


Scheme 2-12

The catalytic process is also achievable through the use of Me_2SnCl_2 in the presence of K_2CO_3, although the mechanism is not clear (Scheme 2-13) [98TL5601]. A variety of cyclic and acyclic diols, 1,2-diols in particular, are selectively monobenzoylated in good yield.

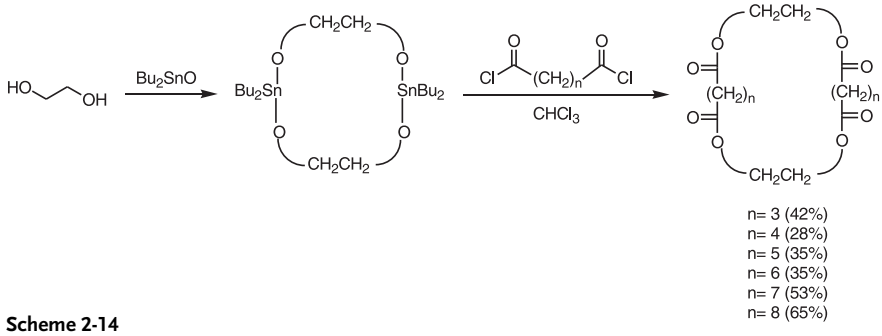
Experimental Procedure [98TL5601] Scheme 2-13

A catalytic amount of dimethyltin dichloride (0.01 mmol), solid K_2CO_3 (2.0 mmol), and benzoyl chloride (1.2 mmol) are successively added at room temperature to a THF (5 mL) solution of *trans*-1,2-cyclohexanediol (1 mmol). After the mixture has been stirred at room temperature until the *trans*-1,2-cyclohexanediol has disappeared (checked by thin layer chromatography), the mixture is poured into water and the organic portion is extracted with CH_2Cl_2. After evaporation of the solvent, a residue is obtained, and this is confirmed by NMR to be pure monobenzoylated product (>99%).

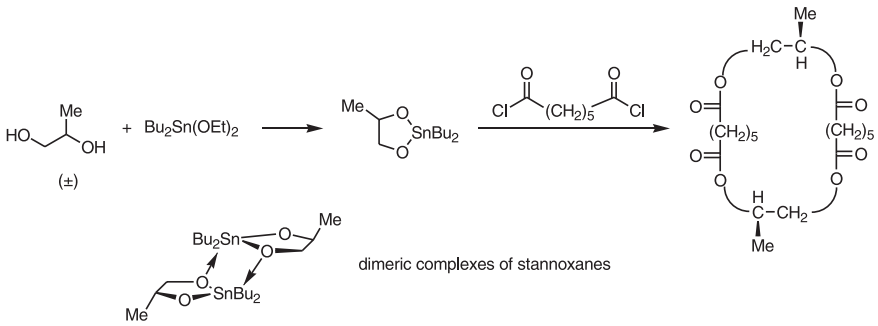


Scheme 2-13

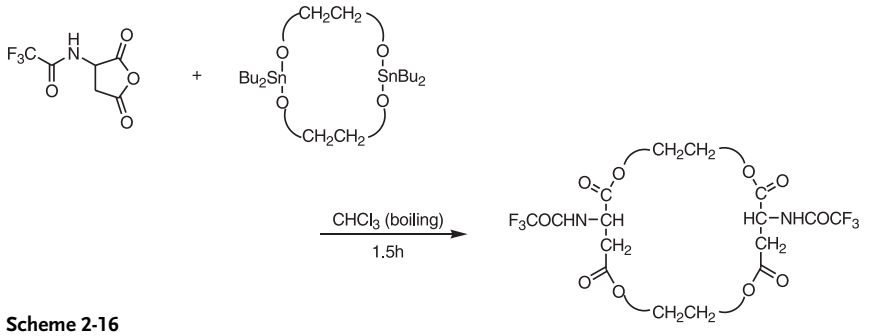
Cyclic stannoxanes made up of dibutylstannylene and 1,*n*-dialkoxy units function as covalent templates in reactions with acid dihalides to give macrocycles (Scheme 2-14) [80CC176, 81JOC4662]. Acid anhydrides are also employable, and the use of chiral tin templates affords diastereomeric macrocycles (Scheme 2-15) [80CC259, 82JACS4220]. *N*-(Trifluoroacetyl)-glutamic and -aspartic anhydrides provide macrocycles with amino residues on the rings (Scheme 2-16). Treatment of the distannoxane with a cyclic carboxy-carbonate derived from glycolic acid or isatoic anhydride results in ring-opening (Scheme 2-17) [82JOM(239)301].



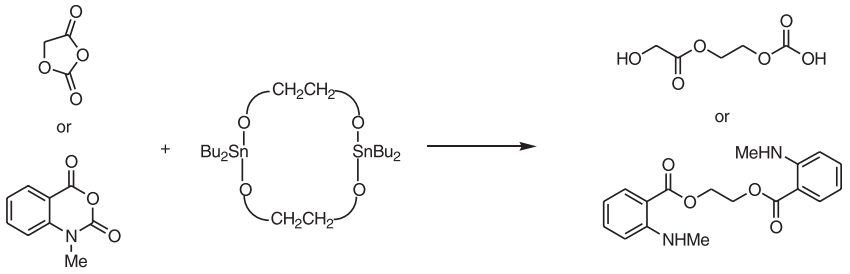
Scheme 2-14



Scheme 2-15



Scheme 2-16

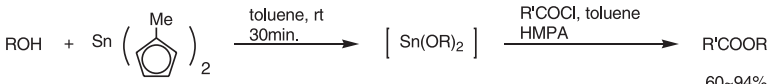


Scheme 2-17

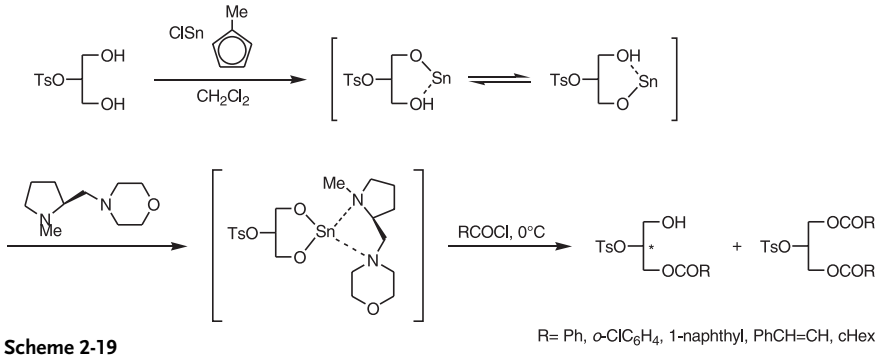
Tin(II) alkoxides are also effective. Reactions between 1,1′-dimethylstannocene and alcohols readily occur at room temperature and the resulting tin(II) alkoxides provide esters upon treatment with acid halides (Scheme 2-18) [83CL293]. When this reaction is carried out in the presence of a chiral amine ligand, asymmetric desymmetrization of 2-*O*-protected glycerols is feasible, furnishing monoesters with up to 84% *ee* (Scheme 2-19) [84CL949].

Experimental Procedure [83CL293] Scheme 2-18

3-Phenylpropanol (125 mg, 0.921 mmol) in toluene (1.5 mL) is added at room temperature, under an argon atmosphere, to a toluene solution (2 mL) of 1,1′-dimethylstannocene (153 mg, 0.552 mmol). After the mixture has been stirred for 30 min, hexamethylphosphoric triamide (1 mL) and benzoyl chloride (155 mg, 1.11 mmol) in toluene (1.5 mL) are successively added. The mixture is kept stirring at room temperature for 2 h and quenched with pH 7 phosphate buffer. The aqueous phase is extracted three times with ether and the combined extracts are washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the resulting crude product is purified by silica gel thin layer chromatography to afford 3-phenylpropyl benzoate (200 mg, 90%).

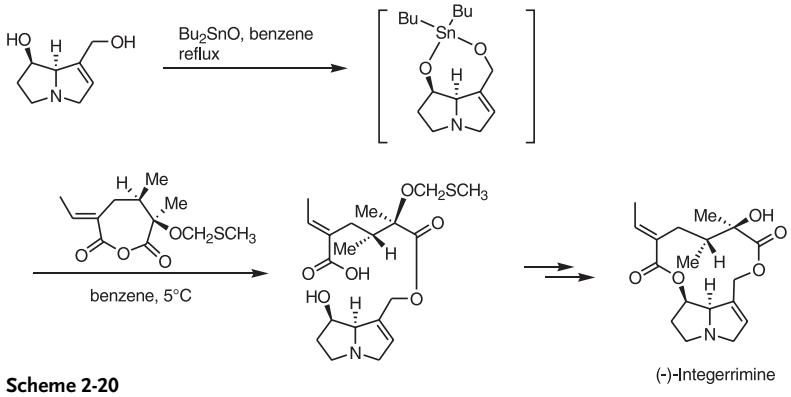


Scheme 2-18

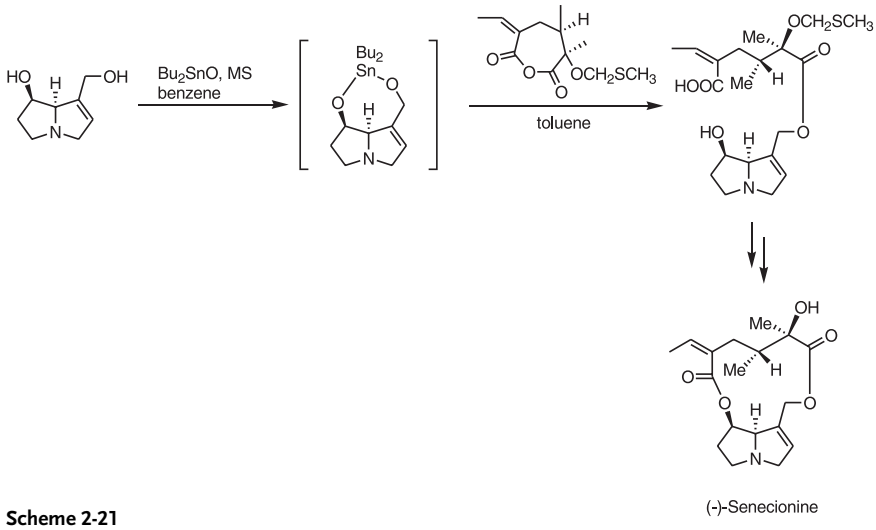


Scheme 2-19

The stannylene technique has been successfully applied to the synthesis of (–)-integerrimine (Scheme 2-20) [92T393] and (–)-senecionine (Scheme 2-21) [94BCJ1990].

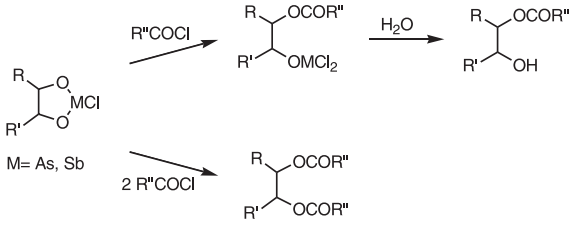


Scheme 2-20

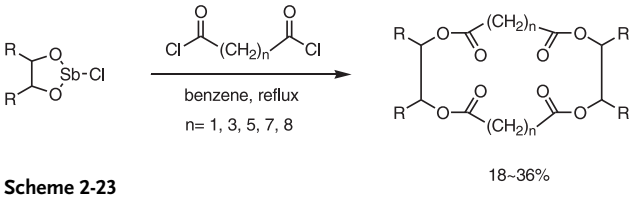


Scheme 2-21

Metalacycles with metals other than tin also react with acid halides. When an arsole or a stibole is treated with one equiv. of acid halide with subsequent hydrolysis, a monoester is produced (Scheme 2-22) [82JHC141]. On the other hand, treatment with two equiv. of acid halides affords the corresponding diester. Macrocycles can be obtained by treatment of stiboles with diacid dihalides (Scheme 2-23) [84JHC577].

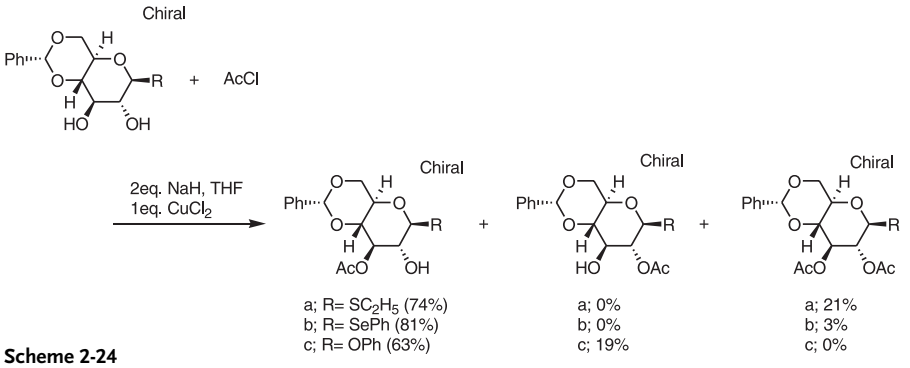


Scheme 2-22



Scheme 2-23

Copper(II) also functions as a template. Regioselective C3 *O*-acylation is achieved by treatment of sodium salts of 4,6-*O*-benzylidene-glucopyranosides (prepared by addition of NaH) with $CuCl_2$ followed by acid halides (Scheme 2-24) [99TL6991].

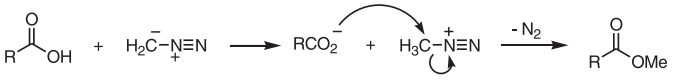


Scheme 2-24

3
Conversion of Carboxylic Acids into Esters without Use of Alcohols

3.1
Treatment with Diazomethane

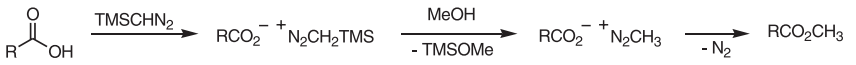
Diazomethane chemistry was pioneered by von Pechmann [1894CB1888, 1895CB855]. Since then, the use of this reagent – despite its explosive and toxic nature – has proven to be one of the most convenient ways by which to convert carboxylic acids into their methyl esters (Scheme 3-1) [67ROS191]. The reaction proceeds at room temperature under mild conditions, and even sterically hindered carboxylic acids are employable. Thanks to the simplicity of the preparation of the reagent and its operation in esterification, numerous papers on the use of this reagent are available (refer to the database disc). Notwithstanding, since no special technique is involved, there is no need to describe this method in more detail here, save for the following special cases.



Scheme 3-1

The hazards associated with diazomethane can be circumvented by the use of trimethylsilyldiazomethane, which is stable, non-explosive, and non-toxic (Scheme 3-2) [81CPB1475]. Various carboxylic acids, including aromatic, heteroaromatic, alicyclic and aliphatic ones, smoothly undergo methylation.

Experimental Procedure [81CPB1475] Scheme 3-2
$TMSCHN_2$ (1.3 mmol) in benzene (1 mL) is added at room temperature to a stirred carboxylic acid (1 mmol) in methanol (2 mL)/benzene (7 mL). The mixture is stirred at room temperature for 30 min and concentrated to give the corresponding methyl ester.

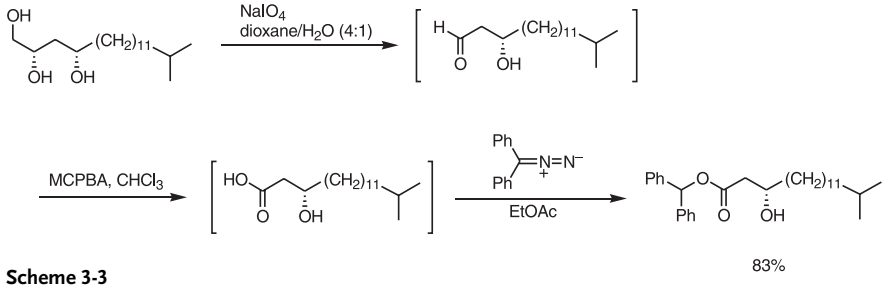


Scheme 3-2

Esterification. Junzo Otera

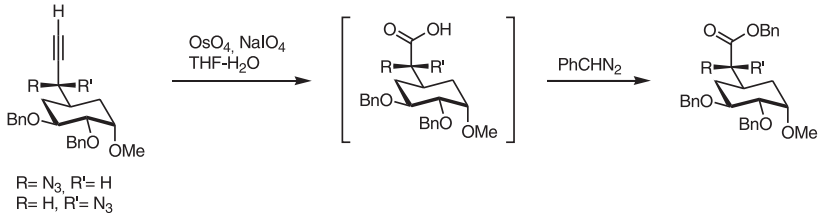
ISBN: 3-527-30490-8

Diphenyldiazomethane is employed to transform a carboxylic acid into the corresponding diphenylacetate (Scheme 3-3) [96TL3875]. After oxidation of a terminal diol to the carboxylic acid via the aldehyde, treatment of the carboxylic acid with diphenyldiazomethane provides the desired ester.



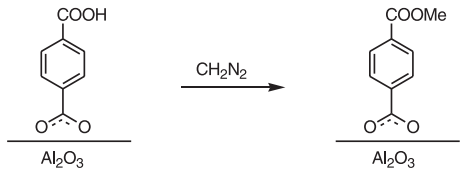
Scheme 3-3

A terminal acetylene moiety is converted into a benzyl ester by use of phenyldiazoacetate (Scheme 3-4) [96BCJ1347]. After conversion of the acetylene into the carboxylic acid, the crude product is treated with phenyldiazomethane to furnish the benzyl ester.



Scheme 3-4

Selective monomethylation of dicarboxylic acids with diazomethane is effected with the aid of alumina (Scheme 3-5) [85JACS1365]. Adsorption of one of the carboxylic acids permits selective esterification of the remaining free carboxylic acid function. High selectivities for monoesters can be achieved.

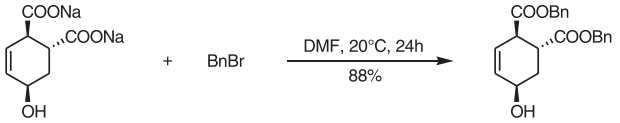


Scheme 3-5

3.2
Reaction with Alkyl Halides

The reaction between carboxylic anions and alkyl halides is a simple way to arrive at esters, but not particularly easy to achieve because of the weak nucleophilicity of the anion. The most classical way is to use silver salts of carboxylic acids, taking advantage of the insolubility of the silver halides formed. However, use of silver halides may be impractical because of the expense involved. More common alkali metal salts react with alkyl halides in polar solvents [76JOC1373]. The use of HMPA (hexamethylphosphoramide) as solvent or co-solvent is useful to promote the alkylation [72TL4063, 73TL689].

Benzylation of the sodium salts of dicarboxylic acids is smoothly carried out by treatment with benzyl bromide in DMF (Scheme 3-6) [92TL5649]. Z-Protected L-amino acids react smoothly with alkyl halides at room temperature in DMF in the presence of sodium hydrogen carbonate [79S961].

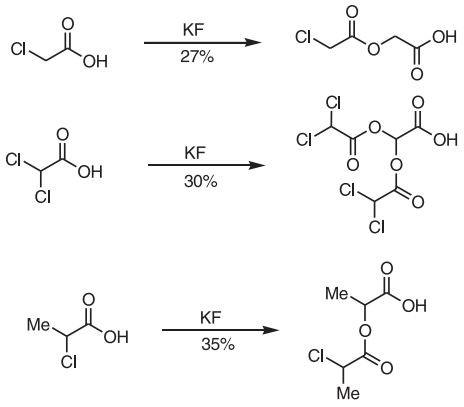


Scheme 3-6

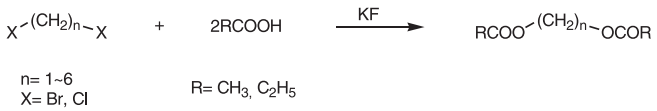
Another feasible mode of activation of carboxylic acids is by use of KF, which promotes the reaction through hydrogen bonding between the hydroxyl and the fluorine, resulting in increased nucleophilicity of the hydroxy oxygen [77JACS498]. Since KF is very soluble in acetic acid, heating of chloroacetic acids or benzyl chloroacetate in the presence of KF in acetic acid provides the corresponding alkylation products (Scheme 3-7) [75JCS(D)2129]. Similar treatment of dichloro- and dibromoalkanes in carboxylic acids affords the corresponding diesters (Scheme 3-8) [77JCS(P1)1091]. It should be noted that no such reaction occurs in the absence of KF. Phenacyl esters that are difficult to prepare by other conventional methods are readily obtained by treatment of α-bromoacetophenone and carboxylic acid with KF in DMF [77TL599].

Experimental Procedure [75JCS(D)2129] Scheme 3-7

Potassium fluoride (58 g, 1.0 mol) and $ClCH_2CO_2H$ (47 g, 0.5 mol) are heated at 150 °C and the reaction is monitored by ^1H NMR spectroscopy. This shows the disappearance of $ClCH_2CO_2H$ and the appearance of (chloroacetoxy)acetic acid, $ClCH_2CO_2CH_2CO_2H$, and later the formation of higher polymers. These appear before the complete disappearance of the starting material. At no time are there any resonances attributable to fluoroacetic acid present in the spectrum. After 7 h the reaction mixture is cooled, extracted with diethyl ether, filtered, dried, and evaporated. The product is distilled and (chloroacetoxy)acetic acid (10.2 g, 0.066 mol, 27%) is obtained.

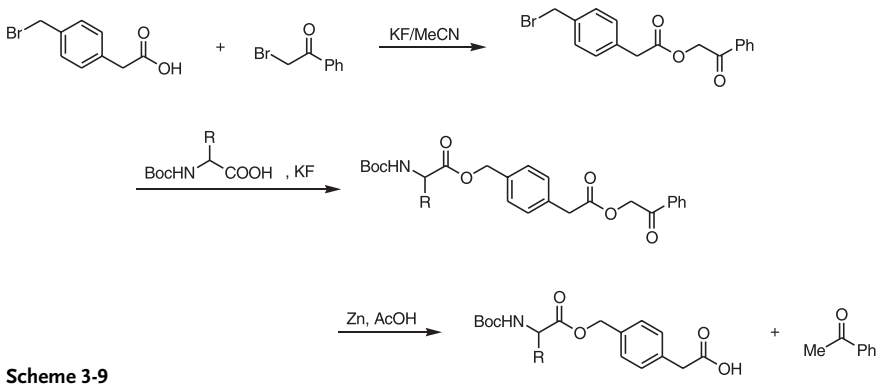


Scheme 3-7



Scheme 3-8

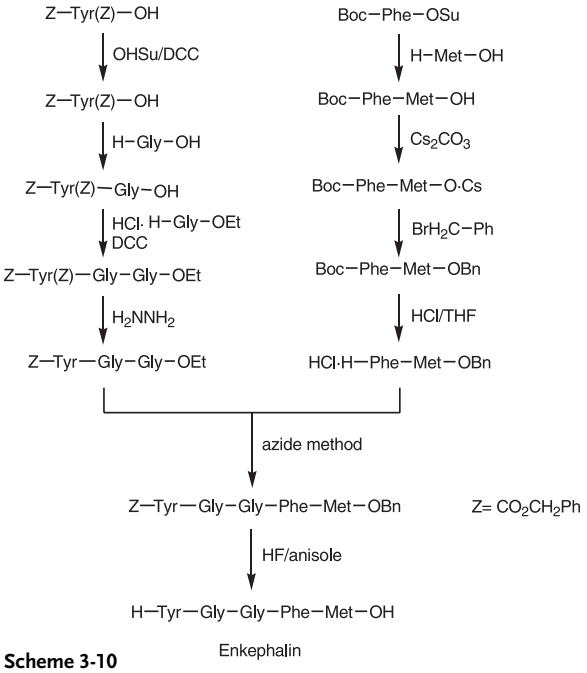
KF-promoted alkylation has been applied to the synthesis of Boc-aminoacyloxymethylphenylacetic acid, useful in solid-phase peptide synthesis (Scheme 3-9) [79S955]. The yields of the first and second reactions are larger than those obtained from reactions with amine as base because the competing reaction between the bromomethyl group and the amine base is avoided.



Scheme 3-9

Tetrabutylammonium fluoride is a good fluoride anion source, but its utility is limited by its hygroscopic nature. This drawback can be circumvented by the use of a silica gel support. Silica gel-supported Bu_4NF effects reaction between α-bromoacetophenone and acetic acid to give phenacyl acetate [78CC789].

Cesium salts also promote the alkylation of carboxylic acids. Merrifield resins are prepared without side reactions by treatment of chloromethylated polystyrene/1% divinylbenzene resin with cesium salts of *N*-protected amino acids [73HCA1476]. A similar method is utilized for the synthesis of a wide variety of esters derived from protected amino acids and peptides [77JOC1286]. The carboxylic acid to be esterified is first titrated to pH 7 with cesium carbonate or cesium bicarbonate, and the obtained neutral salt is then allowed to react with different alkyl halides to form the corresponding esters. The reaction is simple, easily scaled up, and proceeds without observable racemization. Many amino acid and peptide esters that might be difficult to prepare by other methods are obtainable. The synthesis of enkephalin is illustrated in Scheme 3-10 as a representative example.

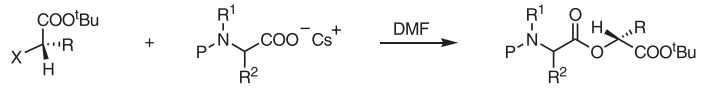


Scheme 3-10

Experimental Procedure [77JOC1286]

Boc-Asn-OBzl: Boc-Asn-OH (11.0 g, 47.5 mmol) is dissolved in MeOH (200 mL), and water (20 mL) is added. The solution is titrated to pH 7.0 (pH paper) with a 20% aqueous solution of Cs_2CO_3 (~55 mL). The mixture is evaporated to dryness and the residue is re-evaporated twice from DMF (120 mL, 45 °C). The obtained white, solid cesium salt is stirred with benzyl bromide (8.9 g, 52 mmol) in DMF (120 mL) for 6 h. On evaporation to dryness and treatment with a large volume of water (500 mL) the product solidifies. It is taken into ethyl acetate, washed with water, dried over Na_2SO_4, evaporated to a solid mass, and crystallized from ethyl acetate with petroleum ether: yield 13.8 g (90.3%); mp 120–122 °C; $[\alpha]_D^{25}$ –17.29° (c = 1, DMF).

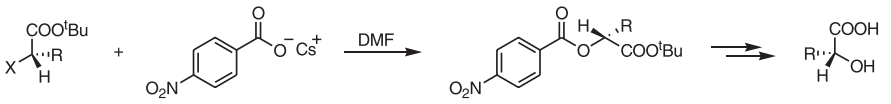
Depsipeptides containing D-α-hydroxycarboxylic acids are efficiently synthesized in an analogous manner (Scheme 3-11) [85TL5257]. Moreover, optically active D-α-hydroxy carboxylic acids are obtained from L-amino acids via L-α-halocarboxylic acids and their stereoselective reaction with cesium *p*-nitrobenzoate (Scheme 3-12) [87TL1873].



X= Br, Cl
R= Me, ^{i}Pr

R^1= H, Me
R^2= Me, ^{i}Pr, ^{i}Bu

Scheme 3-11



X= Cl, Br
R= Me, Bn, ^{i}Pr, ^{i}Bu

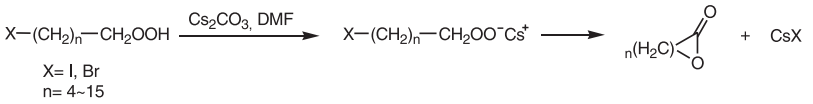
Scheme 3-12

Treatment of ω-halo carboxylic acids with an equivalent amount of dry Cs_2CO_3 in DMF affords the corresponding lactones (Scheme 3-13) [81JACS5183]. The reaction proceeds through intramolecular nucleophilic attack of cesium carboxylate. Cesium carboxylates undergo ring-closure more readily and in far better yield than the carboxylates of lithium, sodium, potassium, rubidium, silver, thallium, magnesium, strontium, or barium.

Experimental Procedure [81JACS5183] Scheme 3-13

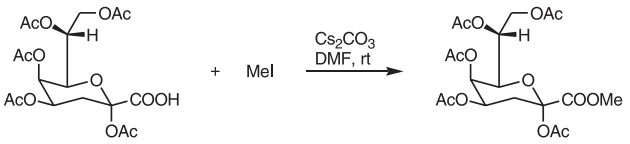
Cs_2CO_3 (180 mg, 1.1 equiv.) is added to 16-iodohexadecanoic acid (190 mg, 0.5 mmol) dissolved in dry DMF (50 mL) in a single-necked flask containing a magnetic stirring bar. The reaction mixture is stirred magnetically at 40 °C for 24 h, during which time all the solid Cs_2CO_3 goes into solution. A precipitate of cesium halide usually forms slowly during the course of the reaction. The DMF is removed under vacuum (2–3 Torr) on a rotary evaporator. A saturated aqueous NaCl solution is added to the residue, and extraction with diethyl ether is carried out (three times). A mixture of macrolide and diolide (127 mg, 0.5 mmol in total) is obtained; GLC with use of an internal standard shows this to consist of at least 99% of macrolide and diolide, present in yields of 85% and 15%, respectively.

In a reaction carried out with 16-iodohexadecanoic acid (1 mmol), the cyclization products are isolated by preparative layer chromatography on silica gel, with a 9:1 light petroleum (40–60 °C)/ether eluent. The macrolide is isolated pure in 68% yield and the diolide in 4% yield. Both are identified from their mass spectra and by comparison with authentic materials.



Scheme 3-13

The cesium carboxylate technique can also be used for alkylation of carboxylic acids on sugars, as shown in Scheme 3-14 [87JOC3777]. The pentaacetate is converted into the corresponding methyl ester by treatment with cesium carbonate and iodomethane in DMF.



Scheme 3-14

Cesium fluoride is another reagent of choice for reactions between carboxylic acids and alkyl halides [92JOC2166]. Alkyl bromides and iodides (except for *tert*-BuI) are employable and a wide range of functional groups are tolerated since CsF is a good scavenger of hydrogen halides (Scheme 3-15). As a result, this technique is able to replace diazomethane-based esterification in many cases. Organotin carboxylates are protected carboxylic acids frequently used in peptide synthesis, and these compounds also undergo alkylation with RX/CsF. No epimerization occurs with α-amino acids. The DMF solvent is crucial in the above procedure, but CH_3CN is employable when the CsF is supported [98SC2021].

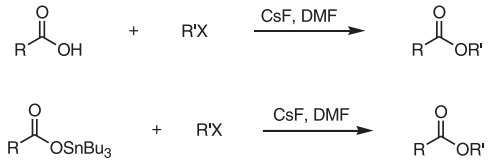
Experimental Procedure [92JOC2166] Scheme 3-15

A mixture of (*S*)-*N*-acetylphenylalanine (207 mg, 1 mmol), CsF (227 mg, 1.5 mmol), EtI (234 mg, 1.5 mmol), and DMF (3 mL) is stirred at 15 °C for 24 h. The reaction mixture is combined with aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (100 mL). The organic layer is dried (Na_2SO_4) and evaporated. Column chromatography on silica gel (50 : 50 hexane/EtOAc) gives ethyl (*S*)-*N*-acetylphenylalanine (211 mg, 90%, 98% ee).

Large-Scale Preparation of Methyl 7-(Tetrahydropyranyloxy)-5-heptynoate from 7-(Tetrahydropyranyloxy)-5-heptynoic Acid and Methyl Iodide: A mixture of 7-(tetrahydropyranyloxy)-5-heptynoic acid (6.0 g, 26.4 mmol), CsF (8.8 g, 58 mmol), MeI (8.2 g, 58 mmol), and DMF (100 mL) is stirred at 30 °C for 18 h. The reaction mixture is extracted with EtOAc and washed with saturated aqueous $NaHCO_3$ (100 mL × 3). The organic layer is dried (Na_2SO_4) and evaporated to give an oil. Column chromatography on silica gel (95 : 5 hexane/EtOAc) provides methyl 7-(tetrahydropyranyloxy)-5-heptynoate (5.0 g, 79%).

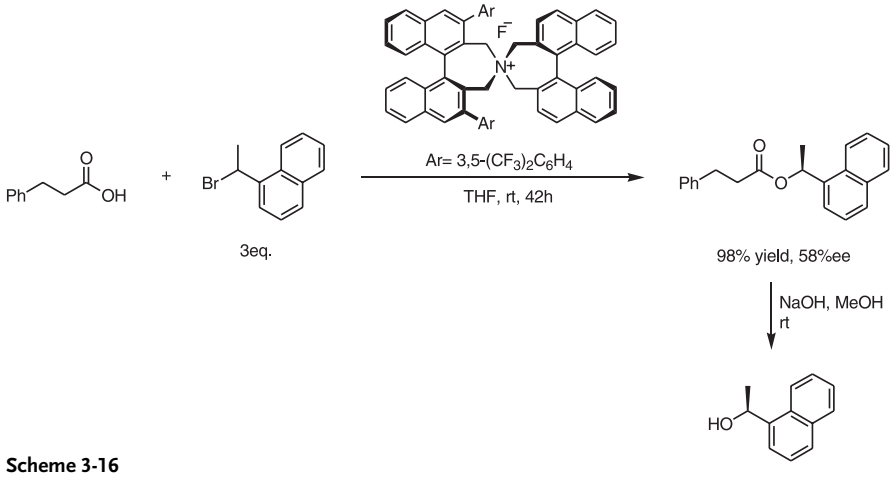
General Procedure for the Preparation of Esters from Tributyltin Carboxylates and Alkyl Halides in the Presence of Cesium Fluoride: A mixture of hexabutyldistannox-

ane (656 mg, 1.1 mmol), (*S*)-*N*-acetylphenylalanine (414 mg, 2 mmol), and benzene (30 mL) is heated at reflux in a Dean-Stark apparatus for 3 h. The benzene is removed under reduced pressure, and DMF (6 mL) is added. CsF (456 mg, 3 mmol) and EtI (468 mg, 3 mmol) are added to this solution, and the reaction mixture is stirred at 30°C for 30 h. Aqueous workup as described for the reaction between (*S*)-*N*-acetylphenylalanine and ethyl iodide and column chromatography on silica gel (50:50 benzene/EtOAc) affords ethyl (*S*)-*N*-acetylphenylalanine (430 mg, 91%, 98% *ee* determined by ^{1}H NMR in the presence of Eu(hfc)$_3$.



Scheme 3-15

Tetraalkylammonium fluorides are also effective for the alkylation of carboxylic acids [2001TL9245]. Bu_4NF generated in situ from Bu_4NHSO_4 and KF promotes alkylation even of sterically demanding carboxylic acids such as adamantanecarboxylic acid and triphenylacetic acid. Use of a chiral ammonium fluoride derivative can effect kinetic resolution of *sec*-alkyl halides (Scheme 3-16).



Scheme 3-16

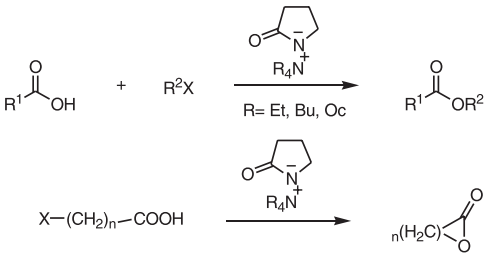
Experimental Procedure [2001TL9245]

Tetrabutylammonium hydrogensulfate (8.7 mg, 0.025 mmol) and potassium fluoride dihydrate (240 mg, 2.5 mmol) are placed under argon in a two-neck flask fitted with a stirring bar and dried in vacuo (0.6 mmHg) for 10 min. After replacement of the argon atmosphere, freshly distilled THF (1 mL) is introduced. 3-Phenylpropionic

acid (76.6 mg, 0.5 mmol) and benzyl bromide (66.8 μL, 0.55 mmol) are then added sequentially at room temperature. After having been stirred for 3 h at room temperature, the resulting reaction mixture is poured into water (5 mL) and extracted with ether (10 mL × 2). The combined organic extracts are washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (hexane/ether = 10 : 1 as eluent) gives pure benzyl ester (120 mg, 99% yield) as a colorless oil.

Strongly basic amines also serve for esterification. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) is one such amine, in the presence of which a variety of carboxylic acids including simple acids, sterically hindered acids, thermally unstable acids, and *N*-protected amino acids react with alkyl halides [78BCJ2401]. A novel base can be prepared by electroreduction of 2-pyrrolidone in the presence of a tetraalkylammonium salt in DMF. By use of this base, sterically demanding acids and amino acids can be alkylated to give the corresponding esters (Scheme 3-17) [86JOC546]. In addition, ω-bromo carboxylic acids are transformed into lactones.

Experimental Procedure [78BCJ2401]
A solution of ethyl iodide (1.56 g, 0.01 mol) in benzene (5 mL) is added to a solution of 2,4,6-trimethylbenzoic acid (1.64 g, 0.01 mol) and DBU (1.52 g, 0.01 mol) in benzene (15 mL) and the mixture is stirred at room temperature for 2 h. The reaction mixture is then washed with water, dried over anhydrous magnesium sulfate, and distilled. Ethyl 2,4,6-trimethylbenzoate is obtained (1.53 g, 80% yield).

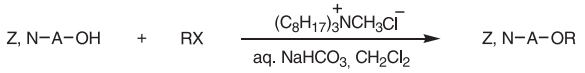


Scheme 3-17

A wide variety of suitably protected amino acids and peptides are alkylated with alkyl halides under phase-transfer conditions (Scheme 3-18) [79S957, 93IJC(B)793]. The method is particularly convenient for acid-sensitive amino acids.

Experimental Procedure [79SC957] Scheme 3-18
A mixture of trioctylmethylammonium chloride (Adogen-464; 0.404 g, 1 mmol) and organic halide (1.2 mmol) in dichloromethane (1 mL) is added at room temperature to a solution of Cbz- or Boc-*N*-protected L-amino acid or dipeptide (1 mmol) in saturated aqueous sodium hydrogen carbonate solution (1 mL). After the reaction is complete (3–24 h) the mixture is extracted twice with dichloromethane. The organic

phase is washed with water, dried with sodium sulfate, and concentrated to a small volume under vacuum at room temperature. The residue is purified by percolation on a silica gel column by elution with hexane/ethyl acetate (8 : 2).



Z= CO_2CH_2Ph
A=amino acid or peptide
R= Bn, Et, 4-$NO_2C_6H_4$

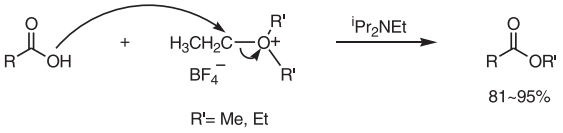
Scheme 3-18

3.3 Treatment with Other Electrophiles

An alkyl group on an onium center undergoes facile attack even by weak electrophiles such as carboxylate ions. Trialkyloxonium tetrafluoroborates are onium centers of this kind, and they react with carboxylic acids in the presence of diisopropylethylamine to furnish ethyl esters (Scheme 3-19) [71TL4741, 79JOC1149]. A broad series of sterically hindered and polyfunctional carboxylic acids are employable.

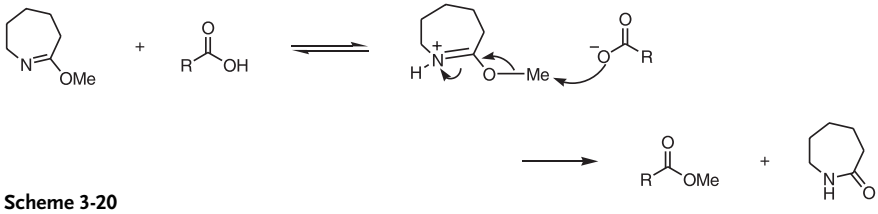
Experimental Procedure [79JOC1149] Scheme 3-19

Carboxylic acid (0.010 mol) is added to a suspension of trimethyloxonium tetrafluoroborate (1.63 g, 0.011 mol) in dichloromethane (75 mL). The resulting suspension is stirred magnetically while *N*,*N*-diisopropylethylamine (1.42 g, 0.011 mol) is introduced by syringe. For di- and triprotic acids, a corresponding increase in the number of equivalents of oxonium salt and amine is used. During the addition of the amine, warming of the reaction mixture is observed; larger scale reactions require a dropping funnel and a reflux condenser. The flask is stoppered after the addition of the amine, and the suspension is allowed to stir for 1–24 h. After approximately 1 h virtually all of the originally undissolved oxonium salt has gone into solution. After the end of the reaction time, the organic solution is extracted with hydrochloric acid (1 N, 3×50 mL), potassium bicarbonate (1 N, 3×50 mL), and saturated sodium chloride. With maleic acid, fumaric acid, 3-butenoic acid, and citric acid, the HCl and the $KHCO_3$ solutions are back-extracted, due to the water solubility of the corresponding esters. The organic solution is then dried over anhydrous sodium sulfate and the solvent is removed by evaporation under reduced pressure. The residue is purified by short-path (Kugelrohr) distillation or by recrystallization to afford 70–97% of the desired esters with purities of 95% or greater.



Scheme 3-19

Sulfonium salts are also powerful alkylating agents. Heating of a mixture of trimethylsulfonium hydroxide and carboxylic acids affords the corresponding methyl esters [79JOC638]. In the presence of copper(I) salts, reactions of allyl sulfonium salts are highly accelerated [83T3111]. Trimethylselenonium hydroxide works similarly [79TL1787]. Pentamethylphosphorane $(CH_3O)_5P$ reacts with carboxylic acids such as benzoic acid and salicylic acid to afford the corresponding methyl esters [78JOC4672]. *O*-Methylcaprolactam effects methylation of carboxylic acids just on being heated with one equivalent of the acids (Scheme 3-20) [82SC453].



Scheme 3-20

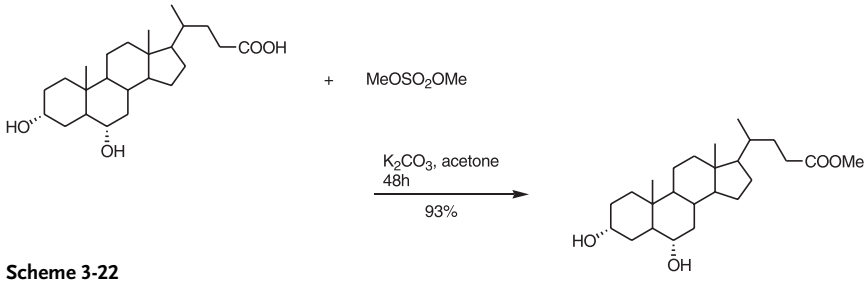
Experimental Procedure [78JOC4672]
$(CH_3O)_5P$ (4.0 g, 0.0215 mol) is added dropwise over a period of 10 min and under an atmosphere of nitrogen to a solution of benzoic acid (2.44 g, 0.02 mol) in methylene chloride (20 mL). After the addition, the methylene chloride solution is washed with water to remove trimethyl phosphate. The methylene chloride solution is evaporated to give essentially pure methyl benzoate (2.48 g, 90%).

Dimethyl sulfate is used for various *O*-methylations. The reaction takes place with carboxylic acids in the presence of a base (Scheme 3-21) [72TL757]. This technique has been applied to the preparation of bile acid methyl esters (Scheme 3-22) [83SC1197]. In these reactions though, the use of aqueous alkali induces side reactions such as hydrolysis of dimethyl sulfate and the ester formed. This drawback can be overcome by employing lithium carboxylates (Scheme 3-23) [99JOC8014].

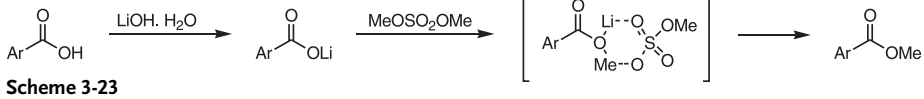
Experimental Procedure [99JOC8014] Scheme 3-23
2-Hydroxy-1-naphthoic acid (470.5 mg, 2.5 mmol) in dry THF (2.5 mL) is treated with $LiOH \cdot H_2O$ (104.9 mg, 2.5 mmol) at room temperature for 30 min. Me_2SO_4 (0.12 mL, 1.25 mmol) is then added, and the mixture is heated under reflux for 3 h. Solvent is distilled off, and the mixture is diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O to afford the ester (white solid, 404.3 mg, 80%).

The yield may be improved to 96% by the use of 2.5 mmol of Me_2SO_4.

Scheme 3-21



Scheme 3-22

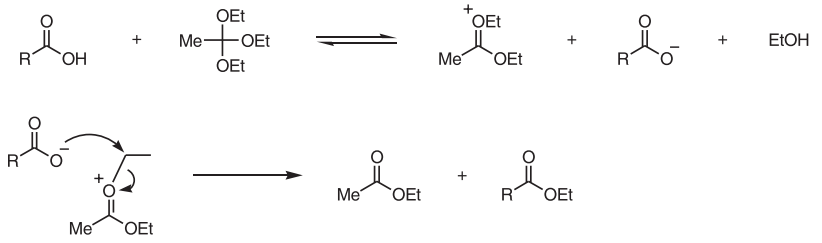


Scheme 3-23

Orthoesters are reagents long used for alkylation of carboxylic acids; alkyl orthoformates are most popular. The reaction is catalyzed by ammonium chloride or nitrate, ferric chloride, and acidic ion-exchange resins. Reactions between triethyl orthoacetate and carboxylic acids proceed without catalyst in refluxing toluene or in the absence of solvent (Scheme 3-24) [93TL7355]. The *O*-alkylation mechanism is suggested by the fact that no significant rate difference is observed in the esterifications of 2,6-dimethylbenzoic acid and of benzoic acid. The enhanced rate of esterification observed for the orthoacetate over the orthoformate is ascribed to the higher stability of the cationic intermediate. This method is employable for ethyl ester formation from amino acids (Scheme 3-25) [96JOC6033].

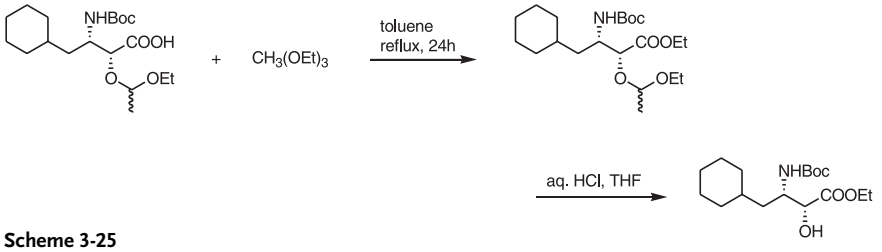
Experimental Procedure [93TL7355] Scheme 3-24

Triethyl orthoacetate (16.0 mL, 87 mmol, 3 equiv.) is added dropwise to a solution of 1-naphthoic acid (5.0 g, 29 mmol) in toluene (35 mL). The reaction mixture is heated at reflux for 24 h. After the mixture has cooled, HCl (2 M, 30 mL) is added. The organic extract is washed with saturated $NaHCO_3$ (1×30 mL) and brine (1×30 mL) and dried with $MgSO_4$. The solvent and excess reagent are removed in vacuo to give a brown oil. Kugelrohr distillation of the product at 100°C (0.45 Torr) gives the ethyl ester (5.15 g, 89%) as a colorless liquid.



R= 1-naphthoic, 1-naphthylacetic, nicotinic, adipic, 2,6-dimethylbenzoic

Scheme 3-24

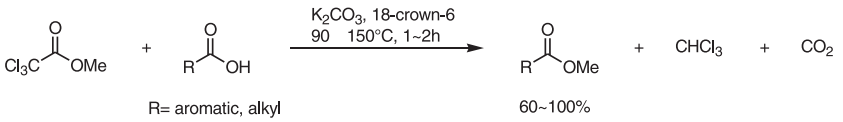


Scheme 3-25

Methyl trichloroacetate is a unique methyl donor, releasing chloroform and carbon dioxide upon treatment with carboxylic acids (Scheme 3-26) [84SC77]. The reaction is catalyzed by potassium carbonate and 18-crown-6.

Experimental Procedure [84SC77] Scheme 3-26

A mixture of methyl trichloroacetate (12.5 mmol), carboxylic acid (12.5 mmol), potassium carbonate (0.035 g, 0.25 mmol), and 18-crown-6 (0.066 g, 0.25 mmol) is placed in a 25 mL round-bottomed flask fitted with a distillation head and a dry ice-cooled receiver and trap. The stirred reaction mixture is gradually warmed to 90 °C, whereupon the evolution of carbon dioxide begins. The temperature is gradually raised to 150 °C and maintained there until the evolution of carbon dioxide and the distillation of chloroform (1.3–1.4 g) cease (1–2 h). The product is isolated by distillation or crystallization.



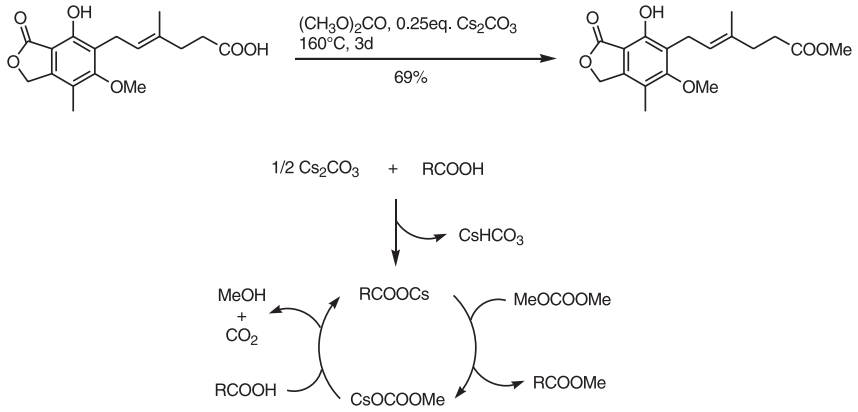
Scheme 3-26

Dimethyl carbonate reacts both with carboxylic acids and with phenols in the presence of Cs_2CO_3 (Scheme 3-27) [98SL1063]. DBU is also an effective catalyst (Scheme 3-28) [2002JOC2188]. A mechanism involving a carbamate intermediate

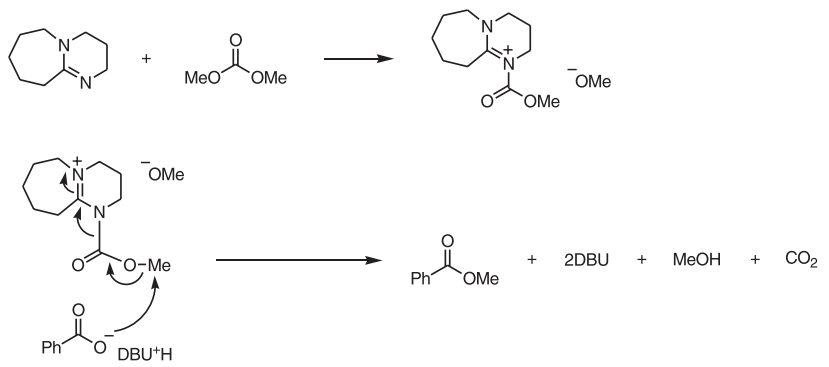
has been proposed on the basis of an ^{18}O-labeling study. The dimethyl carbonate/DBU technique can be upgraded by conducting the reaction in a continuous-flow reactor under microwave irradiation conditions [2002TL5607].

Experimental Procedure [2002JOC2188] Scheme 3-28

DBU (1 equiv.) is added to a 10% solution of carboxylic acid in dimethyl carbonate, and the resulting mixture is heated to reflux. Upon completion of reaction, the mixture is allowed to cool to room temperature and diluted with either CH_2Cl_2 or EtOAc and H_2O. The aqueous layer is removed, and the organic layer is washed once with H_2O, twice with HCl (2 M) or aqueous citric acid (10%), twice with saturated aqueous $NaHCO_3$, and twice with H_2O. The organic layer is dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the ester.



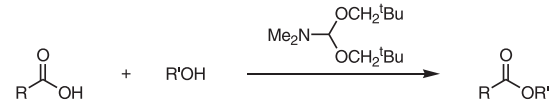
Scheme 3-27



Scheme 3-28

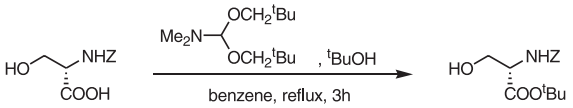
N,N-Dimethylformamide acetals are another class of reagents used to alkylate carboxylic acids. Treatment of carboxylic acids with the diethyl or dibenzyl acetal in re-

fluxing CH_2Cl_2 or $ClCH_2CH_2Cl$ furnishes the corresponding esters [63AGC296]. A variety of acetals are useful for the preparation of esters of sterically demanding carboxylic acids [65HCA1746]. The sterically bulky dineopentyl acetal can be employed for reactions between carboxylic acids and *p*-dodecylbenzyl alcohol or *p*-methoxybenzyl alcohol (Scheme 3-29) [64AGC(E)62]. The reaction involves alkylation of the carboxylate anion with an alkoxyimmonium ion. The use of *tert*-butyl acetal affords the corresponding *tert*-butyl esters [83S135]. The *tert*-butyl ester formation is achieved by slow addition of the dineopentyl acetal to a solution of amino acid in benzene/*tert*-butanol (2 : 1) (Scheme 3-30) [96TL3761]



R'= *p*-dodecylbenzyl, *p*-methoxybenzyl

Scheme 3-29



Scheme 3-30

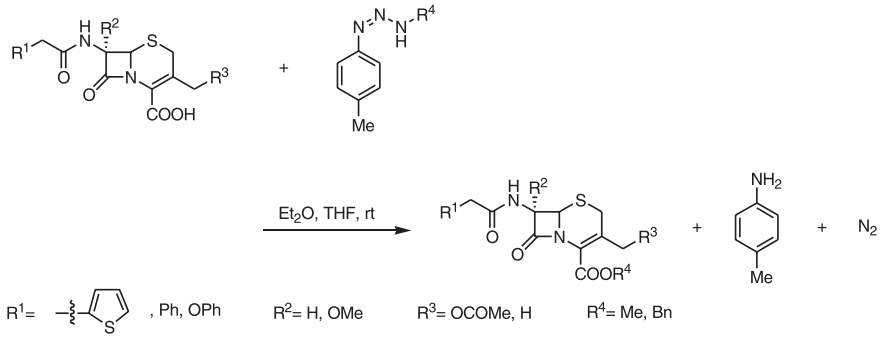
3-Alkyl-1-*p*-tolyltriazenes (2.1–2.5 equiv.) can be used for alkylation of cephalosporanic acids in ether/THF (Scheme 3-31) [78TL5219]. The reaction proceeds at room temperature. O-Alkylisoureas effect *O*-alkylation of carboxylic acids under microwave irradiation conditions (Scheme 3-32) [2002OL2961]. The reaction is normally complete in 5 minutes. An immobilized *O*-alkylisourea is also available.

Experimental Procedure [78TL5219] Scheme 3-31

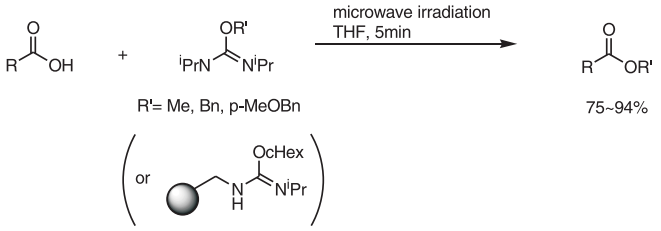
1-Alkyl-1-*p*-tolyltriazene in diethyl ether (2.1–2.5 equiv.) is added to a solution of cephalosporanic acid in THF, and the mixture is stirred under nitrogen at room temperature for 6 h (R_4 = Me) or overnight (R_4 = Bn). Conventional workup gives the desired Δ^3 ester in a crude state, and the product is confirmed free of the Δ^2 ester by NMR (no peak due to the vinylic proton of the Δ^2 isomer in the δ = 6.4 region is observed). Recrystallization or column chromatography affords analytically pure samples.

Experimental Procedure [2002OL2961] Scheme 3-32

A microwave vial is charged with the carboxylic acid (1.0 mmol) and *O*-alkylisourea, followed by addition of THF (2 mL). The vial is heated at the required temperature in a Smith Synthesizer for 5 min. The white solid is filtered off, and the solvent is evaporated under vacuum. The residue is then further purified by column chromatography.



Scheme 3-31

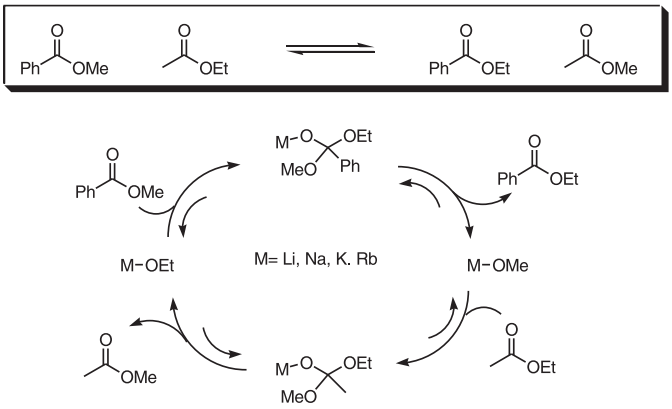


Scheme 3-32

4
Ester-Interchange Reactions

Reactions between two different esters result in exchange of the alkoxy components, but it is not easy to bias the reaction in favor of the one side, because of equilibration. Tributyltin alkoxides catalyze reactions between methyl and ethyl esters, for example, but these unfortunately reach equilibrium at 30–60% conversions [69BCF262]. A similar situation applies with $[La(O^iPr)_3]_n$ [93BCJ1863].

These reactions are dramatically accelerated, however, by catalytic alkali metal alkoxides (Scheme 4-1) [97JACS5075, 98JACS5981].



Scheme 4-1

Reactivities increase in the order: $Li^+ < Na^+ < K^+ < Rb^+ < Cs^+$. When methyl or ethyl esters are treated with *tert*-butyl acetate under reduced pressure (to remove the methyl or ethyl acetate formed), the *tert*-butyl esters are formed quantitatively [97JOC8240]. These reactions proceed by stepwise exchange of the *tert*-butoxy group with the methoxy group in the tetrameric cluster (Scheme 4-2). When the third substitution is completed, the resulting mixed alkoxide precipitates, and so no further ester exchange takes place. The catalyst turnovers are increased by use of a mixed alkoxide composed of NaO^tBu and $NaOC_6H_4$-4-^{t}Bu in a 1:3 ratio (Scheme 4-3)

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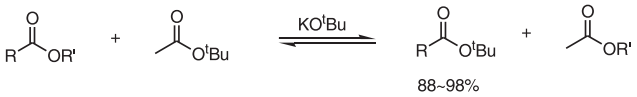
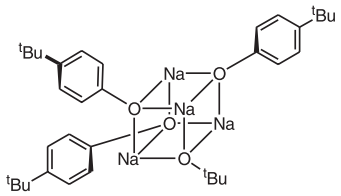
[2000OL4209, 2001JOC9005]. The aryloxy groups are never substituted by other alkoxy group and are longer-lived than the simple metal alkoxides.



R= aromatic, aliphatic, alkyl
R' =Me, Et

Scheme 4-2



Scheme 4-3

Experimental Procedure [98JACS5981]

A typical kinetic measurement is run as follows: methyl benzoate (5 mmol, 0.63 mL) and *tert*-butyl acetate (5 mmol, 0.67 mL) are mixed in a round-bottomed flask and diluted with the desired solvent (2.5 mL). In a separate flask, M*Ot*Bu (0.025 mmol) is also dissolved in the desired solvent (2.5 mL). The esters (0.8 M in each ester) are transferred to the catalyst solution by syringe. Aliquots are withdrawn by syringe, quenched in saturated aqueous NH_4Cl solution, diluted with ethyl acetate, and analyzed by GC to monitor the conversion of methyl benzoate into *tert*-butyl benzoate. Integration percentages are corrected for response factor differences between *tert*-butyl benzoate and methyl benzoate [%$PhCO_2Me$ (GC)/%$PhCO_2{}^tBu$ (GC) = 1.46 × %$PhCO_2Me$ (actual)/%$PhCO_2{}^tBu$ (actual)].

As already described in Section 1.2.2.2, the exchange reaction between an ethyl ester and methyl propionate in the presence of $Ti(OEt)_4$ is an effective means to prepare the corresponding methyl ester without recourse to the use of insoluble $Ti(OMe)_4$ [82HCA1197].

Part II
Synthetic Applications

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ISBN: 3-527-30490-8

5
Kinetic Resolution

5.1
Enzymatic Resolution

Racemic substrates can be resolved when one of the enantiomers reacts more rapidly than the other with a reagent. Esterification serves well for this end, racemic alcohols, carboxylic acids, esters, thioesters, and anhydrides successfully undergoing resolution. In this procedure, one of the enantiomers is selectively consumed while the other remains unchanged. Accordingly, the effectiveness of the reaction cannot be evaluated simply from the optical purity of the product or the remaining substrate, but the degree of conversion also has to be taken into account. In an ideal case, both product and remaining substrate are obtained in 50% yield, each with 100% *ee*. Such a degree of conversion/%*ee* relationship is measured by the stereoselectivity factor **s**, which is the relative ratio of the reaction rates of the two enantiomers [88TS249]. For enzymatic reactions, the biochemical stereoselectivity factor E (which is virtually the same as **s** under steady-state conditions) is employed [82JACS7294]. To obtain a 99% *ee* in the recovered material, for example, 72.1% conversion is required for **s** = 10, 52.3% conversion for **s** = 100, 51.1% conversion for **s** = 200, and 50.0% conversion for **s** = 1000.

Kinetic resolution with alcohol substrates is most frequently performed through enzymatic acylation, and more than 400 papers on this subject are available. Representative examples for various enzymes are shown in Table 5-1. Lipases are most popular, and acetylation with enol acetates is invoked most frequently, whereas acid anhydrides, trihaloethyl esters, and simple carboxylic acids as well as esters are employable as acyl donors. Esterases, acylase, hydrolase, and protease are also effective. The stereoselectivity factor is usually higher than that of the chemical process, as described later. Because of the specificity characteristic of eynzymatic reactions, the E value is dependent on substrates, acylating reagents, and reaction conditions. The acylation in most cases takes place on the *R* alcohols, although *S* secondary alcohols are acylated in a few cases. The use of additives such as amines often increases E values. The reaction is run in organic solvent, but water is occasionally added. Improved enantioselectivity may be achieved by immobilization of enzymes or by use of an ionic liquid solvent. The enzymes can be separated from reaction mixture by filtration. As well as these advantages, there are also some disadvantages: a relatively large amount of solvent is necessary and the reaction time tends to be long.

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Tab. 5-1 Enzymatic kinetic resolution of racemic alcohols

Enzyme	*Acylating agent*	*Medium*	*E*	*Remarks*	*Reference*
Porcine pancreatic lipase and yeast lipase	1,1,1-Trichloroethyl-alkylate	Organic solvent		PPL catalyzes transesterification. Yeast lipase catalyzes esterification. Stability of enzyme is much greater in organic solvents than in water.	85JACS7072
Lipase from *M. miehei* (lipozyme)	*n*-Alkanoic acid	Hexane	1~50	Kinetic resolution of aliphatic alcohols by esterification.	87JOC3477
Rabbit gastric lipase	Isopropenyl acetate	Organic solvent	1.1~500	Kinetic resolution of secondary benzylic and allylic alcohols with RGL.	97TL1915
Lipase AK-20 (unspecified *P. species*)	Vinyl acetate	Benzene		Resolution of neopentyl alcohols produced from protected α-vinyl amine acids.	94TL8743
Lipase from *P. sp.*	Vinyl acetate	Organic solvent ($^{i}Pr_2O$, acetone)	1057	Kinetic resolution of 3-hydroxy-3-(penta-fluorophenyl)propionitrile. *R* and *S* optically active products can be obtained.	97TL1987
	Diketene	Toluene, $^{i}Pr_2O$	4~12	Diketene can be used as a new reagent for irreversible and enantioselective acylation of secondary alcohols.	95TL6663
	Ac_2O	Et_2O	2~13	Resolution of sterically hindered *myo*-inositol derivatives. Racemic 3,4,5,6-*O*-tetrabenzyl-*myo*-inositol is resolved by this method.	95BCJ1200
Lipase from *P. cepacia*	Vinyl acetate	Organic solvent (hexane/THF, $^{i}Pr_2O$, etc.)	2~645	Resolution of 2-acylamino-1-arylethanol. *S* specificity is obtained.	93BCJ1216
	Vinyl acetate	Organic solvent ($^{i}Pr_2O$, THF, pentane)	8~97	Kinetic resolution of *N*-hydroxymethyl γ-butyrolactams: access to optically active γ-butyrolactams.	93TL2307
	Vinyl acetate	CH_2Cl_2		Kinetic resolution of 5-hydroxy-4-oxa-*endo*-tricyclo[5.2.0]dec-8-en-3-ones is described. This reaction produces a homochiral D-ring synthon for strigolactones.	96JOC6931

Tab. 5-1 (continued)

Enzyme	*Acylating agent*	*Medium*	*E*	*Remarks*	*Reference*
	Various vinyl esters	$^{i}Pr_2O$	4~1057	Kinetic resolution of 2-substituted 3-cyclopenten-1-ols and the effect of the acyl group of acylating agent are studied.	96JOC8610
	Vinyl acetate	Organic solvent and crown ether (cat. amount)	5~1200	Thiacrown ether additive enhances enantioselectivity in transesterification of allyl alcohols	96TL4991 97CL1247
	1-Ethoxyvinyl acetate	$^{i}Pr_2O$ or BuOMe	640	1-Ethoxyvinyl acetate can be used as acyl donor in resolution of secondary alcohols.	96TL7369 (see also 97TL387)
	Vinyl acetate	Et_2O, −40 °C	17~99	(*S*)-(+)-Phenyl-2H-azirine-2-methanol is obtained by lipase-catalyzed kinetic resolution at −40 °C.	97JOC4906
	Vinyl acetate	Hexane, 30 °C	5.3~52	Resolution of *N*-aryl methylated *trans*-2,5-disubstituted pyrrolidines. The enantioselectivity depends on the structure of the aryl ring.	98CL1231
	Vinyl acetate			Transesterification of *syn*-2,3-dihydroxy esters, resulting in the synthesis of the taxol side chain.	98TL2163
	Vinyl acetate	$^{i}Pr_2O$, 30 °C	298	The first kinetic resolution of large secondary alcohols having tetraphenylporphyrin. Lipases from *C. antarctica, R. miehei, P. aeruginosa* also give good selectivities (E >104).	98TL6311
	2,2,2-Trifluoroethyl butanoate	$^{i}Pr_2O$	5~58	Resolution of 2-(1-hydroxyalkyl)-triazoles, important synthetic equivalents of 2-hydroxy aldehydes.	96JOC4144
	Vinyl 3-phenyl-butanoate	Hexane	98	*S* preference. 2-Phenyl-1-propanol is resolved by use of a racemic mixture of vinyl 3-phenylbutanoate with improvement of enantioselectivity. This reaction is performed by lipase from *Alcaligenes sp.* giving rise to moderate E values.	2000TA1199

Tab. 5-1 (continued)

Enzyme	*Acylating agent*	*Medium*	*E*	*Remarks*	*Reference*
	Vinyl acetate	Ionic liquid	1000	Ionic liquids can serve as solvents for enantioselective transesterification with markedly enhanced enantioselectivity. Immobilized lipase from *C. antarctica* also gives good selectivities (E = >172).	2001OL1507
Lipase from *P. fluorescens*	Enol ester	$^{i}Pr_2O$		Irreversible enantioselective acylation of 2-halo-1-arylethanols.	88JOC6130
	Vinyl acetate	Organic solvent	4.5~44	Kinetic resolution of (±)-*cis*-hydroxy-methyl-2-phenyl-1,3-dioxane, an inter-mediate in the synthesis of pheromones and branched-chain sugars.	93SL108
Lipase from *C. antractica*	Isopropyl acetate	Hexane, 50 °C		Five-to seven-membered 2-iodo-2-cycloalken-1-ols are resolved by transesterification.	92SL813
	Vinyl acetate	Organic solvent (hexane, THF, etc.)	2~280	Resolution of 1,1,1-trifluoro-2-alkanols. *S* preference.	96JOC2332
	Vinyl acetate	MeCN and amine	38~43	Kinetic resolution of (±)-phenylbutan-1-ol and study on the role of the amine and acetanilide in the resolution is documented. The use of amine in the reaction enhances the enantiomeric ratio.	2001ACS(343)646
	Vinyl acetate	$^{i}Pr_2O$	30	Resolution of racemic 2-hydroxymethyl-1-methylthioferrocene. Lipozyme also gives good selectivity (E = 20).	96TL127
	Isopropenyl acetate		81	Resolution of *endo*-bicyclo[4.1.0]heptan-2-ols.	97TL8503
Mutant lipase	Vinyl butyrate	Hexane	12~30	Efficient resolution of halohydrins by rational protein engineering to procedure CALB mutants.	2001CBC766
Polymer-supported lipase	Methyl acetoacetate	Solvent-free	70~226	β-Keto esters are prepared by a polymer-supported lipase-catalyzed reaction.	2001JOC1906

Tab. 5-1 (continued)

Enzyme	*Acylating agent*	*Medium*	*E*	*Remarks*	*Reference*
Lipase from *C. cylindracea*	Fatty acid	Apolar organic solvent, 40 °C		The resolution of α-substituted cyclohexanols by esterification.	85TL1857
Lipase from *C. rugosa*	Vinyl acetate	$^{i}Pr_2O$	72	Resolution of 3,3,8a-trimethyl- octahydro-1-naphthol, a key intermediate in the total synthesis of lactaranes and marasmanes.	99TA2729
Lipase from *Alcaligenes* sp.	Vinyl acetate	$^{i}Pr_2O$		Enantioselective acetylation of albicanol, resulting in the synthesis of several natural products ((–)-3,4-dihydroxycinnamate, etc.).	2000TA1375
Porcine pancreatic lipase (PPL)	Vinyl acetate	$^{i}Pr_2O$		Kinetic resolution of aliphatic 2-alkanols of varying chain length. A gradual decline both in the reaction rate and in the enantioselectivity with increasing chain length is observed.	96SC19
	Vinyl acetate, palmitic acid, etc.	Benzene, microwave irradiation	117~196	1,2,3,4-Tetrahydro-1-naphthol, 1-inda-nol, and menthol are resolved by microwave irradiation with enhancement of reaction rates and enantioselectivities.	98TL4333
Lipase and polymer-supported scavenger	Vinyl acetate	Toluene	3~500	This strategy features a simple two-step procedure that combines both kinetic resolution and separation of the products by solid-phase scavenging of the remaining alcohol.	2001JOC5645
Carboxylic esterase	Methyl propionate	Biphasic aqueous/ organic mixture			84JACS2687
Pig liver esterase on MPEG (methoxypoly-ethylene glycol)	Vinyl acetate	Wet toluene	~100	PLE/MPEG is more effective than PLE.	97TA3657

Tab. 5-1 (continued)

Enzyme	*Acylating agent*	*Medium*	*E*	*Remarks*	*Reference*
Acylase (from *Aspergillus* sp.)	Vinyl acetate or vinyl butyrate	Organic (toluene, acetone, etc)	31~100	Several secondary alcohols, especially aryl alkanols, are resolved with high selectivities on using acylase.	97SL367 96SL449 2000TA1801
Hydrolase (papain)	5-Phenylpentanoic acid	Isooctane, H_2O	2~28	Esterification of ethylmethylphenyl-silyl-methanol.	94TA73
Protease (subtilisin)	Vinyl acetate	$^{i}Pr_2O$, 30 °C	8~15	*S* preference.	99TL4367

P.; Pseudomonas, C.; Candida, M.; Mucor , R; Rhizomucor

Tab. 5-2 Enzymatic resolution of carboxylic acids, esters, anhydrides or thioesters by reaction with alcohols.

Substrate	*Enzyme*	*Medium*	*E*	*Remarks*	*Reference*
Carboxylic acids					
2-Methylalkanoic acid	Lipase from *C. cylindracea*	Heptane	1.4~70		91TA165
	Lipase from *C. rugosa*		3~130	*S* preference. Study of alcohol chain length and enantio-selectivity.	93TA1869
2-Methylvaleric acid fluorobiprofen	Lipase from *C. rugosa*	Organic solvents orthoformates		Use of orthoesters precludes accumulation of water in the reaction mixture.	2001EJO1441
Fluorobiprofen	Lipase from *C. antarctica*	MeCN	1.0~22.2		95TA1773
α-Lipoic acid	Lipase from *C. rugosa*	Hexane	1.3~7.5	*S* preference.	97TA337
3,7-Dimethyl-6-octanoic acid	Lipase from *C. rugosa*	Cyclohexane H_2O	3.6–53		99TA1821

Tab. 5-2 (continued)

Substrate	*Enzyme*	*Medium*	*E*	*Remarks*	*Reference*
2-(4-Substituted phenoxy)-propanoic acid	Lipase from *C. rugosa*	$^{i}Pr_2O$ and SDSaq.	3.8~72	SDS enhances the enantioselective lipase-catalyzed esterification of 2-(4-substituted phenoxy)propanoic acids with BuOH.	2001CL912
2- to 8-Methyl decanoic acid	Lipase from *C. rugosa*		2.8~68	Racemic substrates with 1-hexadecan-ol. The lipase shows enantiopreference for the *S* enantiomer when the methyl group is located on even-numbered carbons.	2002TA835
Esters					
Methyl 3-phenyl-glycidate	Lipase from *C. antarctica*	Toluene	6.5~16.2	Kinetic resolution of 3-phenylglycidate with amino alcohols.	2001ACS(343)721
Vinyl esters of arylaliphatic carboxylic esters	Lipase from *C. antarctica*	Toluene hexanol	3.5~100	Resolution of vinyl esters.	99JOC1709
α-Methylene β-lactones	Lipase from *C. antarctica*	^{t}BuOMe	>200	Substituent on the substrate influences the absolute configuration of the desired lactone. Lipase *from C. antarctica* gives the best result.	97TA833
Ketrolac	Lipase from *C. antarctica*	Chlorinated solvent		The resolving efficiency is very high in octanol.	2001TA1865
Cyanohydrin acetate	Lipase from *C. antarctica*	Toluene		Optically active protected cyanohydrins, important building blocks for the synthesis of drugs and agrochemicals, are prepared through enzymatic kinetic resolution.	2002EJO1516
Anhydrides Carboxylic-carbonic anhydride	Lipase from *M. miehei*	Organic solvent (Et_2O, ^{t}BuOMe)	7~200	Resolution of mixed carboxylic-carbonic anhydrides. This can be used for the resolution of chiral carboxylic acids.	94TL421 96T4397
1,4-Dihydropyridine-3,5-dicarboxylates	Protease	Phosphate buffer (also aqueous solution)			93TL5915

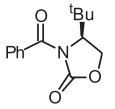
M.; Mucor, P.; Pseudomonas, C.; Candida

Substrates other than alcohols are also amenable to kinetic resolution. Again, lipases are the most important enzymes. As shown in Table 5-2, carboxylic acids, esters, lactones, and acid anhydrides are resolved. As in the case of alcohols, the *R* isomer is selectively consumed in many cases. Exceptions to this trend are referred to as "*S* preference" in this table.

5.2 Nonenzymatic Resolution

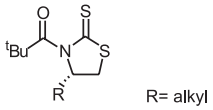
Kinetic resolution by non-enzymatic procedures is feasible as well. Although the stereoselectivity factor is not generally so high as for the enzymatic procedures (**s** < 370 thus far), there are several synthetic merits. A variety of chemical reactions can be utilized, depending on the chiral catalysts or acyl donors. Any type of substrate is theoretically employable, thanks to the lack of the substrate specificity inevitably encountered with enzymes. The substrates to be resolved are usually alcohols, although one example of diacid dichloride resolution is available. Acid anhydrides or chlorides are most popular as acyl donors. The absolute configuration can be controlled by changing the chirality of catalysts or acyl donors. The reaction time is shorter and the required amount of solvent smaller than in the enzymatic reactions. The following list covers representative non-enzymatic kinetic resolution procedures available up to September 2002.

(a) Alcohol: secondary alcohols in general
(b) Acylating agent: *N*-benzoyl-*tert*-butyl-2-oxazolidinone



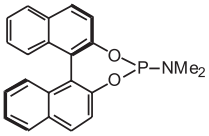
(c) Promoter: MeMgBr or $MgBr/NEt_3$
(d) Conditions: 1~1.1 equiv. promoter, CH_2Cl_2
(e) 65~95%*ee*
(f) Reference: 93TL5563
Remarks: The acylation process is promoted by the formation of the derived Mg alkoxides, which may be obtained either from alcohol deprotonation with MeMgBr or through deprotonation with the Lewis acid-base combination of $MgBr_2/NEt_3$.

(a) Alcohol: secondary alcohols in general
(b) Acylating agent: (*S*)-4-alkyl-3-pivaloyl-1,3-thiazolidine-2-thiones



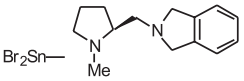
(c) Promoter: MeMgBr
(d) Conditions: organic solvent (toluene, hexane, etc.)
(e) References: 96TL6777, 99JOC9365
Remarks: The *R* esters are produced as major products in the presence of MeMgBr. On the other hand, the *S* isomers are selectively produced under neutral conditions.

(a) Alcohol: secondary alcohols in general
(b) Acylating agent: arylcarboxylic acids
(c) Promoter: Chiral, non-racemic 1,3,2-dioxaphosphepanes



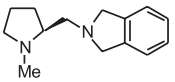
(d) Conditions: benzene, rt.
(e) 14~73% conversion, 11~39%*ee*
(f) Reference: 95JCS(P1)2961
Remarks: The reactions are run under Mitsunobu conditions. The alcohols can be obtained in >99%*ee*.

(a) Alcohol: cyclic and acyclic secondary alcohols
(b) Acylating agent: benzoyl bromide
(c) Catalyst: $SnBr_2$-chiral diamine derived from (*S*)-proline complex



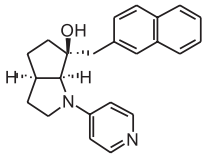
(d) Conditions: 30mol% catalyst, CH_2Cl_2, –78°C
(e) **E**: 4.5~100
(f) Reference: 96TL8543
Remarks: Acyclic racemic alcohols give lower E values than cyclic ones.

(a) Alcohol: cyclic and acyclic alcohols
(b) Acylating agent: benzoyl chloride
(c) Catalyst: chiral diamine derived from (*S*)-proline



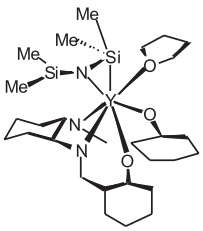
(d) Conditions: 0.3 mol% catalyst, CH_2Cl_2, NEt_3, –78 °C
(e) **s**: 4.5~170
(f) Reference: 99CL265
Remarks: Acyclic racemic alcohols give lower **s** values than cyclic ones.

(a) Alcohol: cyclic secondary alcohols
(b) Acylating agent: $(^{i}PrCO)_2O$
(c) Catalyst: chiral diamine derived from PPY (4-pyrrolidinopyridine)



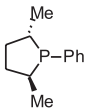
(d) Conditions: 5mol% catalyst, toluene, rt.
(e) **s**: 4.3~12.3
(f) Reference: 97JACS3169
Remarks: The catalyst acts as though through an induced fit mechanism, like a natural enzyme.

(a) Alcohol: secondary alcohols in general
(b) Acylating agent: isopropenyl acetate
(c) Catalyst: Yttrium-salen complex



(d) Conditions: 1~2mol% catalyst, toluene, −10 to −3 °C
(e) **s**: 1.5~4.8
(f) Reference: 2002OL1607
Remarks: This is first example of a transition metal-catalyzed acyl transfer reaction.

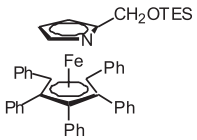
(a) Alcohol: cyclic and acyclic secondary alcohols and PhCH(OH)R
(b) Acylating agent: Ac_2O or $(m\text{-}ClC_6H_5CO)_2O$
(c) Catalyst: chiral phosphine



(d) Conditions: CH_2Cl_2 or CD_2Cl_2
(e) **s**: 3~15
(f) Reference: 96JOC430
Remarks: better selectivity is obtained in the case of R = ^{t}Bu.

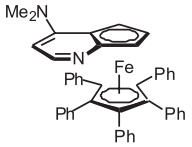
(a) Alcohol: aromatic and allylic alcohols
(b) Acylating agent: $(^{i}PrCO)_2O$
(c) Catalyst: 2-aryl-4,4,8-trimethyl-2-phosphabicyclo[3.3.0]octane
(d) Conditions: 2.5~6mol% catalyst, heptane, –40 °C
(e) **s**: 15~369
(f) References: 99JACS5813, 2001OL535

(a) Alcohol: arylalkylcarbinols
(b) Acylating agent: diketene
(c) Catalyst: azaferrocene derivative



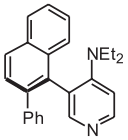
(d) Conditions: 10mol% catalyst, benzene, rt.
(e) **s**: 3.7~6.5
(f) Reference: 96JOC7230

(a) Alcohol: propargylic and arylalkylcarbinols
(b) Acylating agent: Ac_2O
(c) Catalyst: planer chiral DMAP derivative



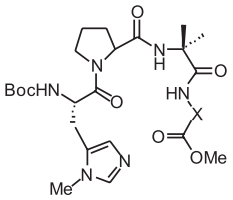
(d) Conditions: 1~2mol% catalyst, *t*-amyl alcohol, 0 °C
(e) **s**: 3.8~20
(f) References; 99JACS5091, 97JACS1492, 98JACS7479, 98JOC2794, 2000ACR412

(a) Alcohol: 1-arylethanols
(b) Acylating agent: Ac_2O
(c) Catalyst: diethyl[3-(2-phenylnaphthyl)(4-pyridyl)]amine



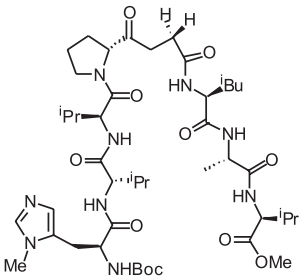
(d) Conditions: 0.01mol% catalyst, organic solvent, –78 °C
(e) s: 8.9~29
(f) Reference: 2000JOC3154

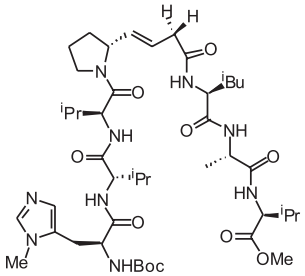
(a) Alcohol: (±)-*trans*-2-*N*-acetamidocyclohexanol
(b) Acylating agent: Ac_2O
(c) Catalyst: chiral oligopeptide



(d) Conditions: 2~5mol% or 0.25 equiv. catalyst, toluene, 25 °C
(e) s: 3.0~28
(f) References: 98JOC6784, 98JACS1629

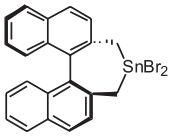
(a) Alcohol: (±)-*trans*-2-*N*-acetamidocyclohexanol
(b) Acylating agent: Ac_2O
(c) Catalyst: chiral oligopeptide





(d) Conditions: 1~2mol% catalyst, toluene, 25 °C
(e) s: 15~51
(f) References: 99JACS11638, 2001AGC(E)2824

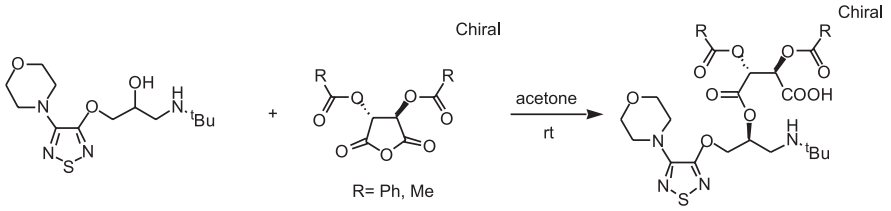
(a) Alcohol: 1,2-diols
(b) Acylating agent: benzoyl chloride
(c) Catalyst: (*S*,*S*)-4,4-dibromo-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′2-*e*]stannepine



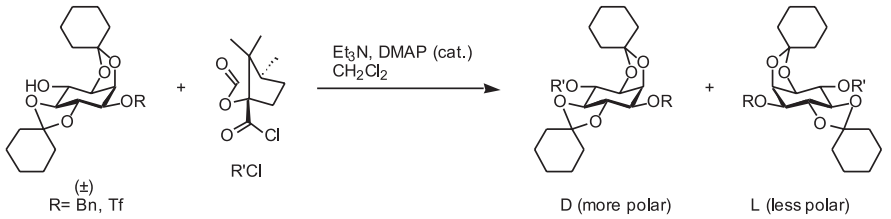
(d) Conditions: 0.25mol% catalyst, H_2O, Na_2CO_3, THF, –10 °C
(e) s: 3.2~10.0

(f) Reference: 99OL969
Remarks: Primary hydroxy group is selectively benzoylated in the presence of a secondary alcohol.

(a) Alcohol: racemic timolol
(b) Acylating agent: (*R,R*)-*O,O*-diacetyl or -dibenzoyl-tartaric acid anhydride
(c) Conditions: acetone, rt., 2 ~ 20 h
(d) Reference: 97JHC1065
(e) Reaction:



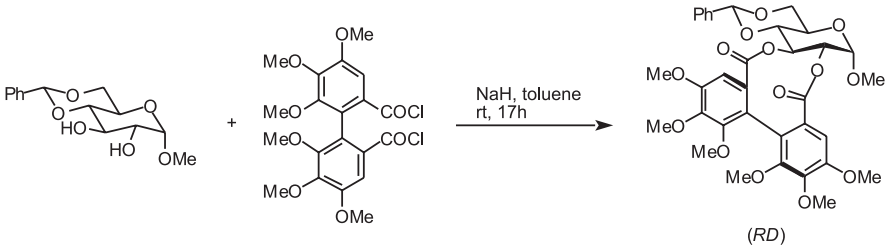
(a) Alcohol: 1,2-:4,5-di-*O*-protected *myo*-inositols
(b) Acylating agent: camphanoyl chloride
(c) Promoter: NEt_3, DMAP (cat.)
(d) Conditions: CH_2Cl_2, 25 °C
(e) References: 91T1, 89T5679
(f) Reaction:



Remarks: The treatment of racemic alcohols with camphanic chloride gives the diastereomeric camphanate esters. The more polar diastereomer is obtained by three crystallizations. The second diastereomer is recovered from the mother liquors by MPLC.

(a) Alcohol: methyl 4,6-*O*-benzylidene-α-D-glucopyranoside
(b) Acylating agent: racemic hexamethoxydiphenoyl chloride
(c) Promoter: NaH or NEt_3
(d) Conditions: NaH in toluene, NEt_3 in CH_2Cl_2
(e) References: 95JOC4968, 96JOC3700, 98CL979

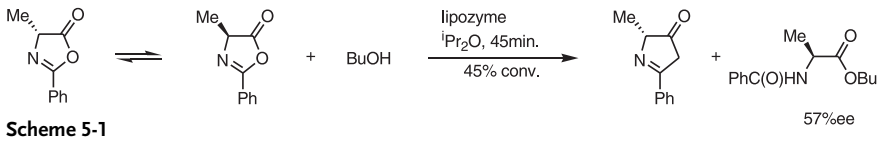
(f) Reaction:



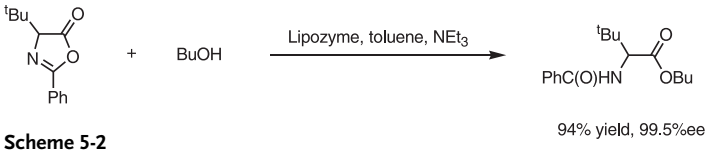
Remarks: the *R* isomer is obtained when the reaction is performed in the presence of NaH, while the *S* isomer is produced in the case of NEt_3.

5.3 Dynamic Kinetic Resolution

Kinetic resolution suffers from the intrinsic limitation that the yield of the desired enantiomer can never exceed 50% except at the cost of inclusion of the enantiomeric counterpart. This drawback can be overcome by dynamic kinetic resolution. If the substrate undergoes racemization much more rapidly than it undergoes the enzyme-catalyzed reaction or if the unreacted substrate remaining in the reaction mixture is racemized in situ, then the racemic substrate can be completely transformed into one enantiomer. One such case is the lipase-catalyzed methanolysis of 4-substituted oxazolin-5-ones. Treatment of 4-methyl-2-phenyloxazolin-5-one with BuOH in the presence of lipozyme affords the corresponding amino acid ester in 57% *ee* at 45% conversion (Scheme 5-1) [90CC1091]. The recovered substrate exhibits no optical rotation, suggestive of in situ racemization. Better outcomes in terms both of yield and of optical purity are obtainable with various 4-substituted 2-phenyloxazolin-5-ones by use of *Pseudomonas cepacia* lipase [93JOC3252]. The *tert*-butyl derivative is transformed into (*S*)-*N*-benzoyl-*tert*-leucine butyl ester in 94% yield with 99.5% *ee* in the presence of lipozyme. The use of toluene containing BuOH as solvent together with a catalytic amount of Et_3N is crucial (Scheme 5-2). The enantioselectivity and catalytic activity in the formation of the butyl ester in the presence of *Candida Antarctica* Lipase B in organic solvent is improved by addition of Et_3N [98CC2247].

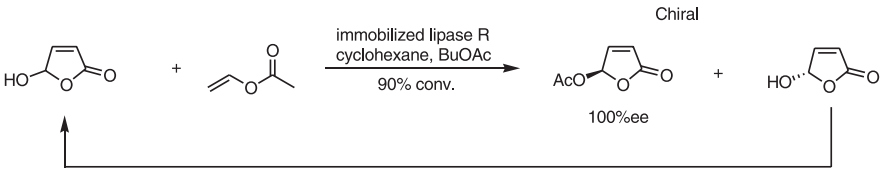


Scheme 5-1



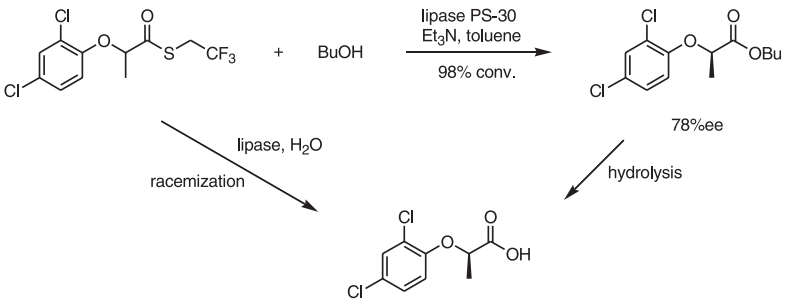
Scheme 5-2

5-Hydroxy-5*H*-furan-2-one undergoes dynamic kinetic resolution on acylation with vinyl acetate (Scheme 5-3) [96TL4759, 96JACS3801]. With the aid of lipase R immobilized on Hyflo Super Cell, 100% enantiomeric excess is feasible at 90% conversion.



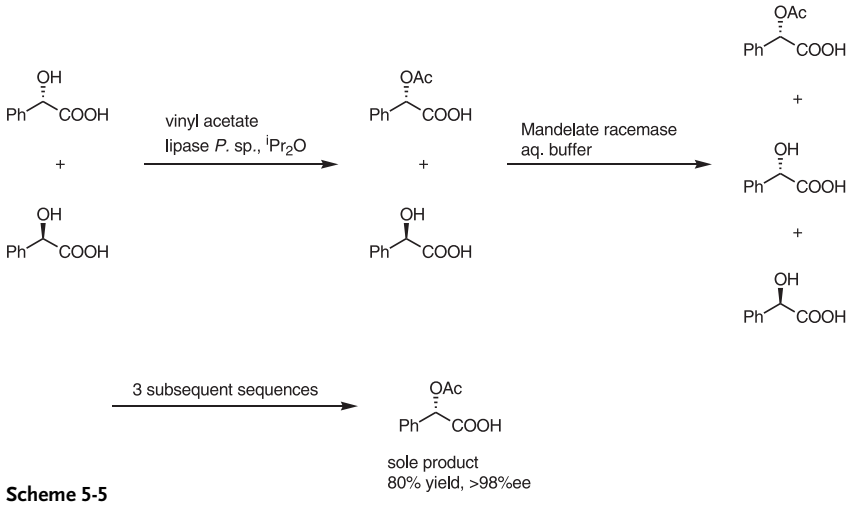
Scheme 5-3

Enzymatic hydrolysis of the trifluoroethyl thioester of 2,4-dichlorophenoxypropionic acid is accompanied by non-enzymatic hydrolysis, resulting in racemization. On the other hand, lipase PS-30-catalyzed transesterification with BuOH furnishes the corresponding butyl ester in 75% *ee* at 98% conversion. The resulting ester is then successfully hydrolyzed to the carboxylic acid in 93% *ee* (Scheme 5-4) [98JACS5605].



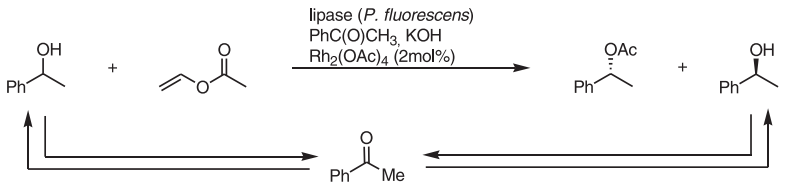
Scheme 5-4

Mandelic acid is prone to racemization, so kinetic resolution with high conversion is feasible (Scheme 5-5) [99TA4079]. Racemic mandelic acid is resolved by acylation with vinyl acetate in the presence of *Pseudomonas* sp. lipase with excellent enantioselectivity (E >200). The resulting 1:1 mixture of (*S*)-*O*-acetylmandelic acid and (*R*)-mandelic acid, after filtration of the lipase, is treated with immobilized mandelate racemate to racemize the mandelic acid. Repetition of this procedure three more times provides (*S*)-*O*-acetylmandelic acid in 80% yield and with >98% *ee*.



Scheme 5-5

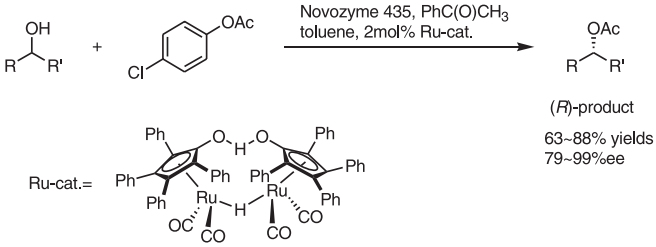
Integration of enzymatic kinetic resolution and transition metal-catalyzed racemization results in dynamic kinetic resolution [97AGC(E)1173]. Hydrogen-transfer reactions between secondary alcohols and ketones are useful for racemization of the alcohols. Thus, subjection of racemic 2-phenethyl alcohol to kinetic resolution with vinyl acetate in the presence of *Pseudomonas fluorescence* lipase with concurrent hydrogen-transfer reaction with acetophenone in the presence of $Rh_2(OAc)_4$ affords (*R*)-phenethyl acetate in 98% *ee* at 60% conversion (Scheme 5-6) [96TL7623].



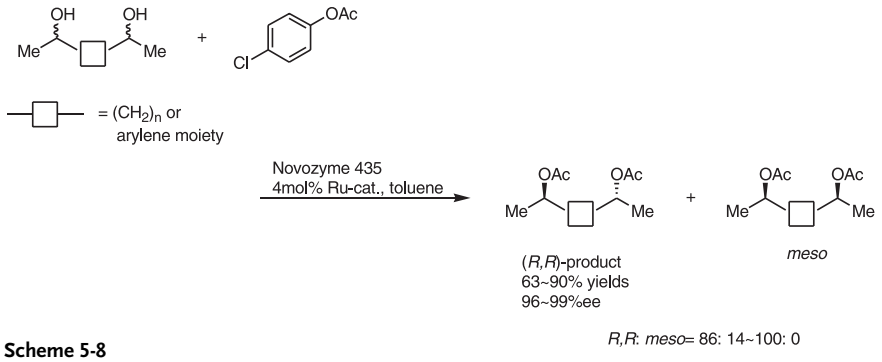
Scheme 5-6

The ruthenium catalyst illustrated in Scheme 5-7 is another efficient catalyst for hydrogen transfer [99JACS1645]. Various secondary alcohols are converted into the corresponding *R* acetates by use of Novozyme 435 and the ruthenium catalyst. *p*-Chlorophenyl acetate is a better acyl donor than enol acetates. The procedure is also effective even in the absence of ketone to furnish secondary alcohol acetates in reasonably high yields (~88%) and with high *ee*s (~99%). In this case, the ruthenium catalyst serves for hydrogen abstraction from the alcohol, followed by rehydrogenation of the resulting ketone. Diols are also transformed into (*R,R*) diacetates and *meso* diacetates in ratios of 74 : 26~100 : 0 under similar conditions (Scheme 5-8) [99JOC5237]. This technique can be further applied to substrates such as α-hydroxy

acids [2000OL1037, 2001JOC4736], α-hydroxy nitriles [2001ASC(343)726], β-azido alcohols [2001JOC4022], and γ-hydroxy acid derivatives [2002TL2983].

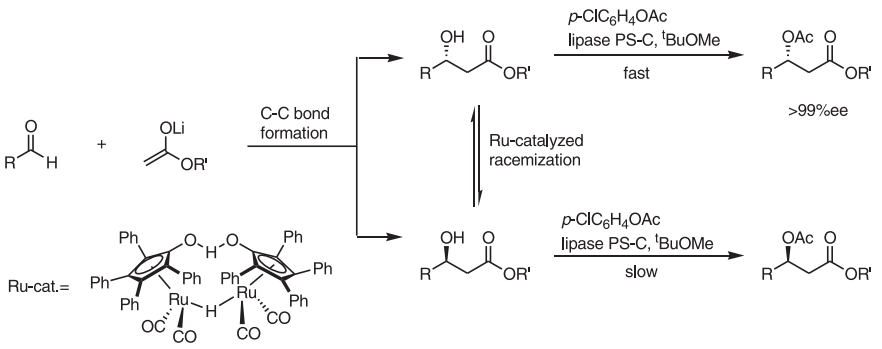


Scheme 5-7



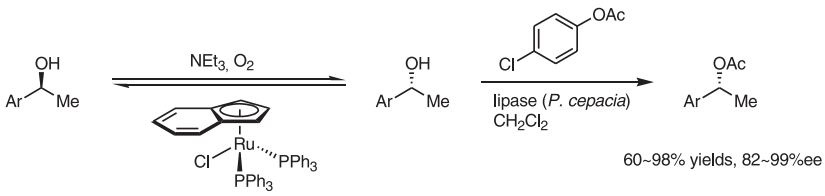
Scheme 5-8

Integration of aldol reaction and kinetic resolution gives rise to an alternative to the asymmetric aldol reaction (Scheme 5-9) [2001OL1209]. In this procedure, a key role is played by racemization of the aldols by the above ruthenium catalyst. The aldol products are obtained in ca. 70% yield, and mostly with >95% *ee*.



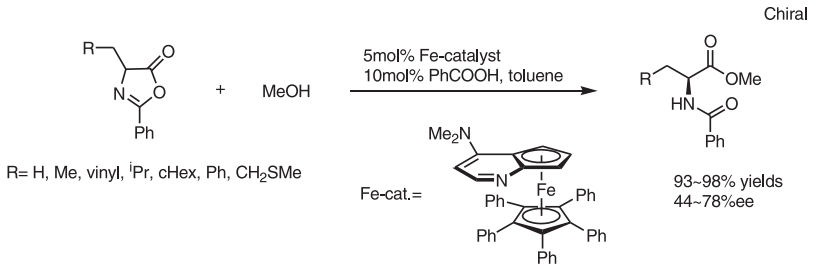
Scheme 5-9

Another ruthenium catalyst, illustrated in Scheme 5-10, is also an effective catalyst for dynamic kinetic resolution [99TL6281]. This procedure results in none of the ketone formation frequently encountered in the above technique. Various secondary alcohols including hydroxy acids, diols, and hydroxy aldehydes are successfully transformed into the corresponding esters.



Scheme 5-10

Non-enzymatic dynamic kinetic resolution is feasible with TiTADDOLate [97T7539] and a planar-chiral derivative of DMAP (Scheme 5-11) [98JOC3154]. 4-Substituted 2-phenyloxazolin-5-ones undergo alcoholysis under catalysis by these catalysts to provide quantitative yields of α-amino acid esters with up to 78% *ee*.



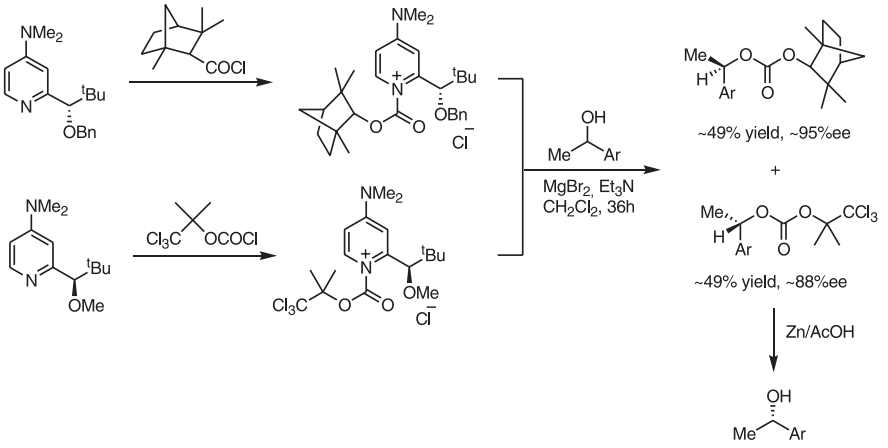
Scheme 5-11

5.4
Parallel Kinetic Resolution

In kinetic resolution, one enantiomer is consumed preferentially as the reaction proceeds, so the relative concentrations of the remaining substrate enantiomers deviate from the original 1 : 1 ratio with the progress of the reaction. As a result, the reaction rate of the more reactive enantiomer decreases with its lower concentration, resulting in decreasing enantioselectivity. Such drawbacks can be offset if the both enantiomers are consumed in parallel in separate reactions, their concentrations decreasing at a comparable rate or – under ideal conditions – at the same rate.

Although a carbonation rather than an esterification, the following is a nice example with which to show the effectiveness of parallel kinetic resolution. Two chiral DMAP derivatives react selectively with each of a pair of secondary alcohol enantio-

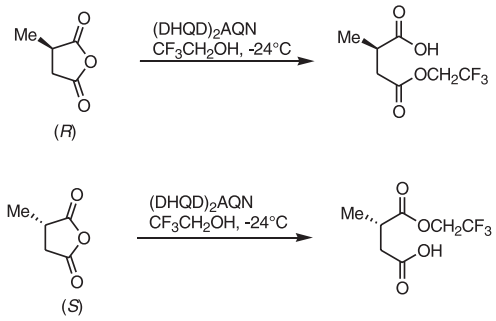
mers (Scheme 5-12) [97JACS2584]. Treatment of a secondary alcohol with the 1:1 mixture of these DMAP derivatives results in preferential reaction of the trichlorobutyloxycarbonyl derivative with the *S* isomer and of the fenchyloxycarbonyl derivative with the *R* counterpart. The *R* alcohols are recovered in ~50% yields with up to 88% *ee* and the fenchyl carbonates in ~49% yields with up to 95% *ee*.



Scheme 5-12

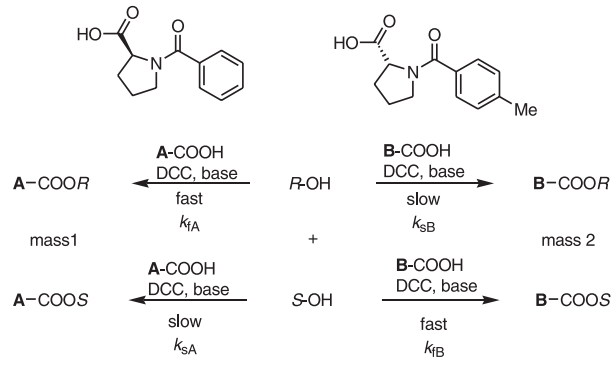
A three-phase system is useful for upgrading the selectivity (Section 1.2.5; Scheme 1–154) [2001JACS2428]. The system is composed of: (1) insoluble cross-linked lipase acylation catalyst (ChiroCLEC), (2) insoluble polymer-bound acyl donor, and (3) soluble phosphine catalyst and soluble acyl donor (vinyl pivalate). The interaction between ChiroCLEC and vinyl pivalate produces the acylated lipase intermediate, which reacts with the *R* enantiomer of a secondary alcohol. On the other hand, reaction between the polymer-bound acyl donor and the chiral phosphine catalyst generates the acyl phosphonium salt, which preferentially affords the *S* isomer of an ester. Satisfactory results in terms of conversion (~50%) and enantioselectivity (~98% *ee*) are obtained.

A modified cinchona alkaloid catalyzes ring-opening of methylsuccinic anhydride in which the *R* and *S* isomers undergo alcoholysis at different sites (Scheme 5-13) [2001JACS11302]. Thus, subjection of 2-alkyl-substituted succinic anhydrides to kinetic resolution with 1,1,1-trifluoroethanol in the presence of $(DHQD)_2AQN$ provides two regioisomers of different absolute configuration at the chiral center, giving rise to a reagent-controlled parallel kinetic resolution.



Scheme 5-13

Parallel kinetic resolution is utilized in the determination of enantiomeric excesses by mass spectrometry (Scheme 5-14) [1999AGC(E)1755]. The technique employs an equimolar mixture of pseudo-enantiomeric mass-tagged chiral acylating reagents possessing different substituents remote from the chiral center, so that the mass of the molecule can be correlated with its absolute configuration. A twentyfold excess of an equimolar mixture of the mass-tagged *N*-acylprolines is treated with racemic alcohols in the presence of DCC and DMAP. The relative amounts of the enantiomers of the resulting esters are determined by mass spectrometry.



$$\frac{I_{\text{mass 1}}}{I_{\text{mass 2}}} = \boldsymbol{y \cdot q} \qquad \%\text{ee} = \left[\frac{(y\text{-}1)(s\text{+}1)}{(y\text{+}1)(s\text{-}1)}\right] \cdot 100 \qquad \text{where} \quad s = \frac{k_f}{k_s}$$

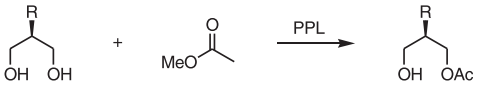
y = corrected intensity ratio
q = ionization correction factor

Scheme 5-14

6
Asymmetric Desymmetrization

Asymmetric desymmetrization is a method that allows many stereocenters to be established by enantioselective esterification of *meso* or prochiral compounds through breaking of symmetry. The substrates that can be employed are symmetric diols and polyols, and also dicarboxylic acids and their anhydrides. The desymmetrization is performed either by enzymatic or by chemical means.

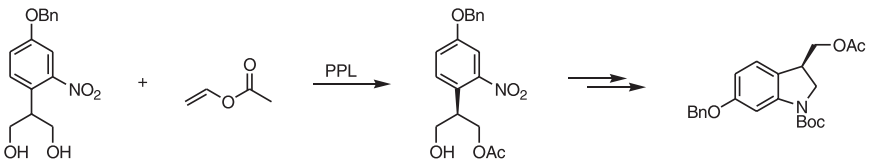
PPL catalyzes desymmetrization of 2-substituted 1,3-propanediols in methyl acetate (Scheme 6-1) [86TL5707]. The enantiomeric excesses of the resulting monoacetates are dependent on the substituents at the 2-position, and range from 10% to 90%.



Scheme 6-1

Isopropenyl and vinyl esters are more efficient acyl donors than alkyl esters in lipase-catalyzed desymmetrization of 2-substituted 1,3-diols such as glycerol and serinol derivatives, ferrocenylethanol, sugars, and other alcohols [88JACS7200].

Similar treatment of 2-[4-(benzyloxy)-2-nitrophenyl]propane-1,3-diol with vinyl acetate as an acyl donor furnishes the corresponding monoacetate, which can be transformed into an indoline (Scheme 6-2) [97CL11].



Scheme 6-2

Esterification. Junzo Otera

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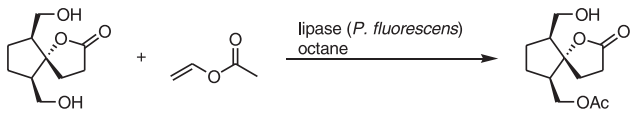
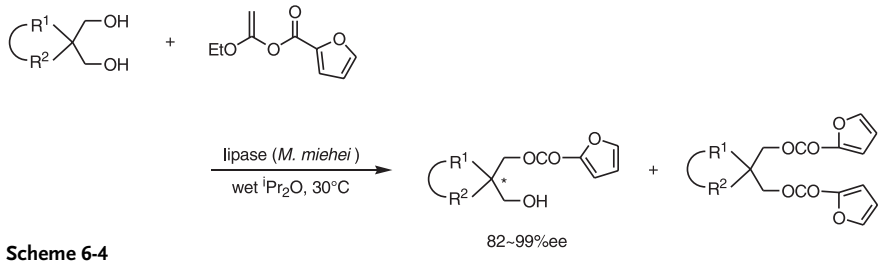
A *meso* spirodiol undergoes monoacetylation on transesterification with vinyl acetate/*Pseudomonas fluorescens* lipase in octane to afford the enantiomerically pure monoacetate in 56% yield (Scheme 6-3) [97JOC3824].



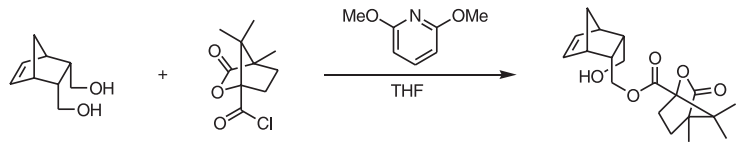
Scheme 6-3

2,2-Disubstituted 1,3-propanediols are rather reluctant to undergo efficient desymmetrization, due to their steric bulk and the facile racemization of the resulting monoacetate. The use of 1-ethoxyvinyl 2-furoate as an acyl donor results in successful formation of the corresponding monoesters possessing asymmetric quaternary centers with 82–99% *ee* (Scheme 6-4) [2002JOC411].



Scheme 6-4

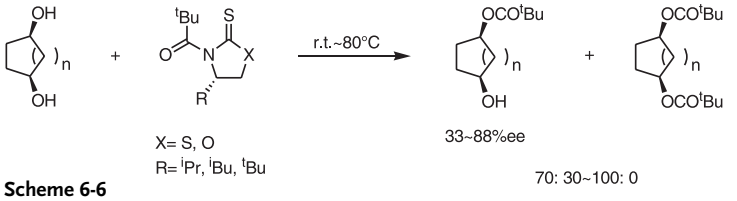
Asymmetric desymmetrization by chemical means is also useful. As already described in Chapter 2, treatment of stannylenes derived from *meso*-1,2-diols with (1*S*)-ketopinic acid chloride affords the monoacylation product with high diastereoselectivity (Scheme 2-8) [84CL49]. A similar tin(II) alkoxide derived from 2-*O*-protected glycerols coordinated with a chiral ligand catalyzes asymmetric desymmetrization (Scheme 2-19) [84CL949]. *meso*-1,2-Diols are esterified with (1*S*,4*R*)-(–)-camphanoyl iodide in the presence of 2 equiv. of 2,6-dimethoxypyridine (Scheme 6-5) [94SL611].



Scheme 6-5

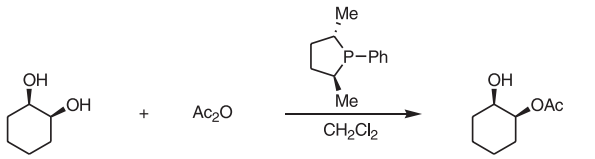
Axially chiral twisted amides effect desymmetrization of *meso*-1,2-, -1,3-, and -1,4-diols (Scheme 6-6) [98CL995]. The corresponding monoesters are obtained, occasion-

ally together with diester, in 33–88%*ee* by treatment of the diols with the amide at 80 °C.



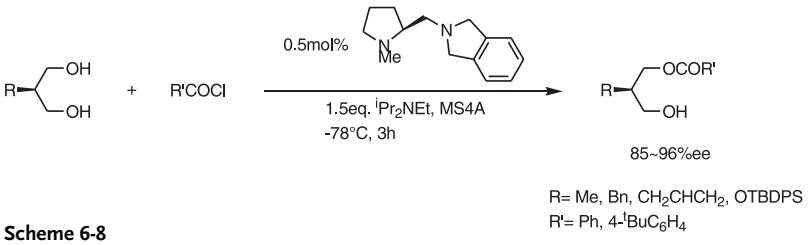
Scheme 6-6

meso-Cyclohexane-1,2-diol and *meso*-1,2-diphenylethylene glycol are transformed into the corresponding monoesters by treatment with acetic or benzoic anhydride with catalysis by a chiral phosphine, although the **s** values are modest (1.2–5.5) (Scheme 6-7) [96JOC430].



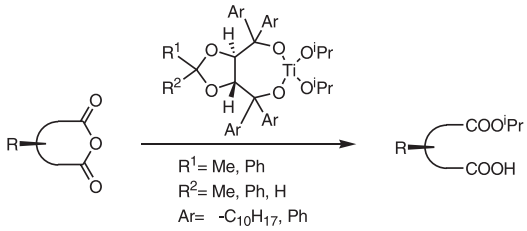
Scheme 6-7

Highly enantioselective desymmetrization through the use of a chiral 1,2-diamine catalyst is feasible (Scheme 6-8) [2002CL26]. The reaction proceeds at –78 °C in the presence of the chiral amine catalyst (0.5 mol %) and diisopropylethylamine (1.5 equiv.) to furnish the corresponding monoesters in 85–96% *ee*.



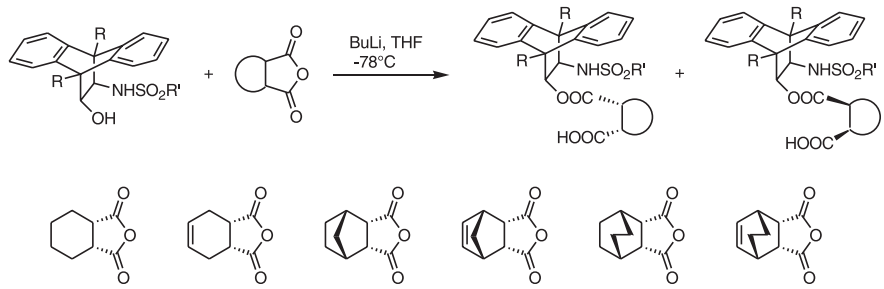
Scheme 6-8

Asymmetric desymmetrization of *meso* dicarboxylic acid anhydrides is a useful means to provide chiral half-esters. The combined use of Ph_2BOTf and (*R*)-2-methoxy-1-phenylethanol was described in Section 1.3.2.2 (Scheme 1-171) [87CL377]. The employment of a chiral 1,3-diol has also been mentioned in Section 1.3.3.1 (Scheme 1-194) [92CL389]. TiTADDOLates mediate mediates ring-opening of various cyclic *meso* anhydrides with isopropanol to afford the corresponding half-esters in up to 98% *ee* (Scheme 6-9) [95AGC(E)2395, 98JOC1190].



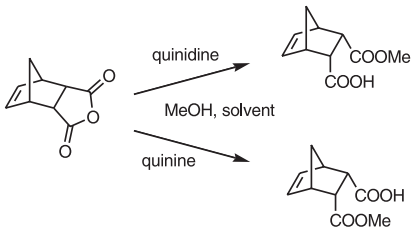
Scheme 6-9

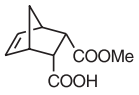
Some chiral amino alcohols such as ephedrine, cinchonine, cinchonidine, quinine, and quinidine are effective for the desymmetrization of 1,2-cyclohexanedicarboxylic acid anhydride [93BCJ2128]. Lithium salts of sterically congested chiral *N*-sulfonylaminoalcohols mediate the ring-opening of *meso* dicarboxylic acid anhydrides in a highly diastereoselective manner (up to >500:1 diastereomer ratio; Scheme 6-10) [95TL931].



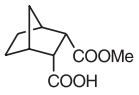
Scheme 6-10

As described in Section 1.3.3.2, cinchona alkaloids efficiently catalyze methanolysis of *meso* dicarboxylic acid anhydrides to give half-esters (Scheme 1-206) [85CC1717, 87JCS(P1)1053, 90TA517, 88CC632, 2000JACS9542]. The enantioselectivity can be improved up to 98% *ee* by conduction of the reaction at low temperature (~ −50 °C) (Scheme 6-11) [99SL195].

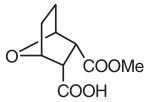




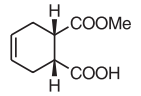
83%yield, 98%ee



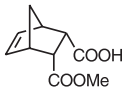
84%yield, 94%ee



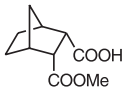
69%yield, 94%ee



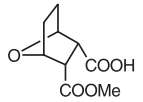
93%yield, 95%ee



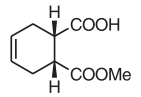
85%yield, 98%ee



86%yield, 98%ee



79%yield, 93%ee



99%yield, 93%ee

Scheme 6-11

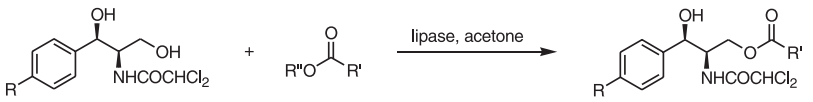
7
Miscellaneous Topics

7.1
Selective Esterification

7.1.1
Differentiation between Primary, Secondary, and Tertiary Alcohols and Phenols

The selective modification of one of a set of coexisting hydroxy functions is an important manipulation in organic synthesis, some examples already having been described in Part I. This chapter focuses on this subject by adding new procedures to provide an overview.

Most frequently encountered in the synthetic process is the need to discriminate between primary and secondary alcohols. Basically, a preference for a primary alcohol is generally attainable to some extent due to its innate superior reactivity, irrespective of acylating reagents. This is reflected to a degree in the simple thermal reaction of sugars (see Section 1.1.1) [99SC951]. However, enzymes improve the selectively in a more general manner, as discussed in Sections 1.2.5 (Scheme 1-145) [86JACS5638] and 1.3.4 (Scheme 1-214) [90TL3405]. The following examples constitute further addenda. Regioselective esterification on the primary alcohol moieties in chloramphenicol and thiamphenicol is successfully catalyzed by lipases (Scheme 7-1) [90JOC2366]. Analogous selectivity is obtained with *Pseudomonas fluorescens* lipase (Scheme 7-2) [97LA211]. The melanoma-associated disialoganlioside 9-*O*-acetyl GD3 can be obtained through regioselective enzymatic acetylation of GD3 with subtilisin as biocatalyst and vinyl acetate as acetyl donor (Scheme 7-3) [96TL9271].

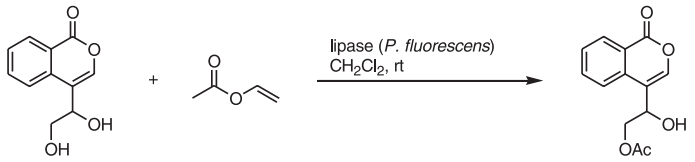


R= NO_2, SO_2CH_3
R'= $CH_2CH_2CH_3$, $(CH_2)_{14}CH_3$, CH=CHPh, CH_2CH_2COOH

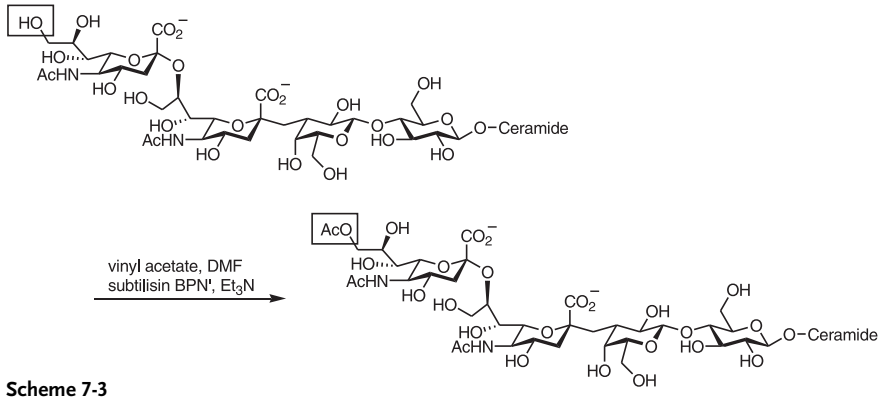
Scheme 7-1

Esterification. Junzo Otera

ISBN: 3-527-30490-8

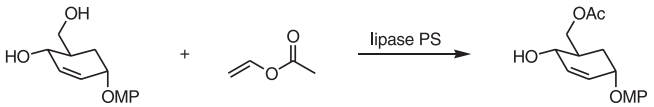


Scheme 7-2



Scheme 7-3

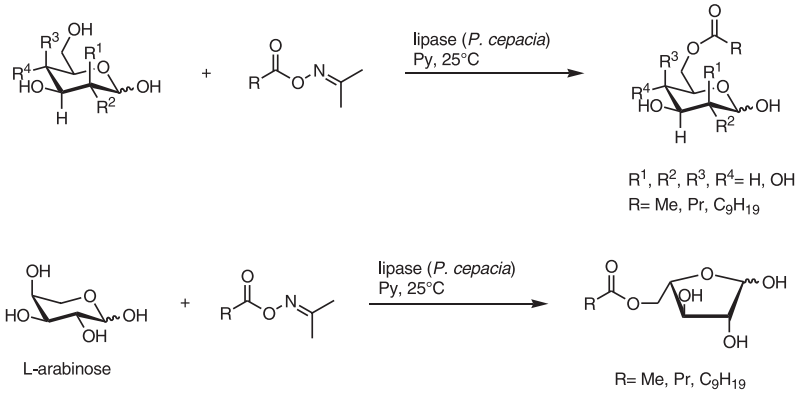
Primary/secondary alcohol differentiation finds its most important utilization in sugar and nucleoside chemistry. Selective acetylation on the 6-position of a glucal derivative with vinyl acetate occurs in high yield (>90%) with catalysis by lipase PS (Scheme 7-4) [97BCJ2535].



MP= *p*-$MeOC_6H_4$

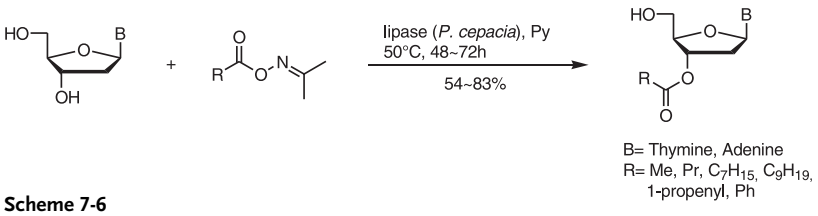
Scheme 7-4

The use of oxime esters as acyl donors in lipase-catalyzed acylation of sugars effects selective acylation (Scheme 7-5) [91JCS(P1)491, 92JCS(P1)2891]. The regioselectivity is dependent on the substrates, high regioselectivity on the primary alcohol being attained for hexoses such as D-galactose and D-mannose with lipase from *Pseudomonas cepacia*. Among pentoses, L-arabinose and D-ribose exhibit good selectivity, while D-xylose and D-lyxose yield complex mixtures. Notably, free pentoses are employable in this procedure.

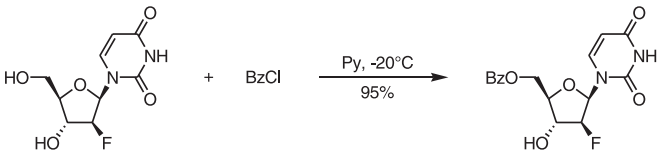


Scheme 7-5

Subjection of nucleosides to the same reaction conditions also results in preference for the primary alcohol [93JOC653]. Some 2′-deoxynucleosides, however, undergo selective acylation on the 3′-position (Scheme 7-6) [92S626]. On the other hand, the 2'-fluoro derivative is benzoylated on the primary hydroxy group simply on treatment with benzoyl chloride in pyridine at –20 °C (Scheme 7-7) [95JOC4276].

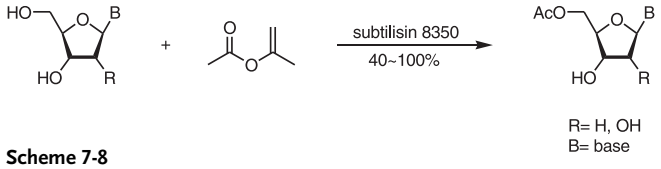


Scheme 7-6



Scheme 7-7

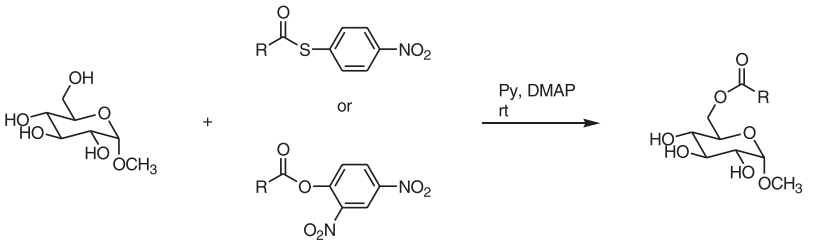
A subtilisin mutant (subtilisin 8350) derived from subtilisin BPN′ through six site-specific mutations (Met50Phe, Gly169Ala, Asn76Asp, Gln206Cys, Tyr217Lys, and Asn218Ser) effects regioselective acetylation of uridine, adenosine, and cytidine with isopropenyl acetate in DMF (Scheme 7-8) [90JACS945]. "Solvent engineering" points to pyridine as a better solvent for primary acetylation of ribonucleosides [94TL1353].



Scheme 7-8

These successful examples by use of enzymes notwithstanding, much more attention has been paid to the use of non-enzymatic reactions. In particular, recent progress in Lewis acid chemistry has revealed that control over Lewis acidity can enable efficient discrimination. In the $HfCl_4 \cdot 2THF$-catalyzed reaction between carboxylic acids and alcohols, primary alcohols react preferentially over secondary ones (see Section 1.1.2.2; Scheme 1-17) [2001SL1117]. TMSOTf is useful for selective acylation of primary alcohols (see Section 1.3.2.2) [96CC2625, 98JOC2342]. Organotin Lewis acids are extremely mild, resulting in high selectivity. 1,3-Disubstituted tetraalkyldistannoxanes $(XBu_2SnOSnBu_2Y)_2$ catalyze transesterification of primary alcohols over secondary ones with various esters, including enol esters (see Section 1.2.2.2; Scheme 1-86 and Section 1.3.2.2) [86TL2383, 91JOC5307, 98JOC2420, 99T2899]. This technique can be applied to the synthesis of enantiopure epichlorohydrin (see Section 1.3.2.2; Scheme 1-175) [99SL1927]. The neutral μ-hydroxy organotin dimer $[tert\text{-}Bu_2SnOH(Cl)]_2$ is particularly useful for deacetylation through transesterification, the primary alcohol being predominantly cleaved over the secondary one in a wide range of substrates including sugars and nucleosides (see Section 1.2.2.2; Scheme 1-87) [2000SL140, 2001CEJ3321]. It should further be noted that solid acids are also employable. Thus, a primary alcohol is selectively consumed in competition with a secondary alcohol in alumina-catalyzed transesterification (see Section 1.2.2.3; Scheme 1-96) [81TL5003] and zirconium sulfophenyl phosphonate-catalyzed acylation with acetic anhydride (see Section 1.3.2.3) [2000SC1319].

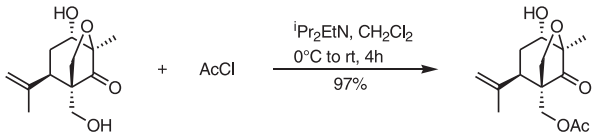
Differentiation under basic conditions is also feasible. As described in Section 1.1.5, the Mitsunobu reaction usually provides high primary/secondary alcohol selectivity. Amines such as 2,4,6-collidine, *N,N*-diisopropylethylamine, and 1,2,2,6,6-pentamethylpiperidine effect preferential acylation of primary alcohols with acid halides (see Section 1.4.3.2) [93JOC3791]. Diphenylacetyl chloride is used for selective acylation of primary alcohols in sugars, this reaction being promoted by pyridine (see Section 1.4.3.2; Scheme 1-268) [94S97]. Various esters of *p*-nitrothiophenol or 2,4-dinitrophenol effect regioselective acylation on the 6-positions of non-protected glycopyranosides catalyzed by DMAP in pyridine (Scheme 7-9) [95SC2235].



Scheme 7-9

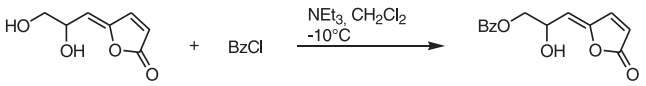
The use of activated esters occasionally gives high selectivity. Bipyridyl esters exhibit high preferences for primary alcohols over secondary ones in the presence of a CsF promoter (see Section 1.1.6; Scheme 1-38) [80CL563]. Benzoylation with 1-(benzoyloxy)benzotriazole in the presence of Et_3N takes place on primary alcohols in preference to secondary ones (see Section 1.2.3.2; Scheme 1-121) [85JOC1751]. A phase-transfer reaction with benzoyl chloride affords the primary benzoate (see Section 1.4.3.3; Scheme 1-273) [94JOC1783]. *N*-Pivaloylimidazole is employable for pivaloylation of monosaccharides on primary hydroxy groups in preference over secondary ones (see Section 1.4.5) [98S1787].

Differentiation between primary and secondary alcohols is quite easily achieved in some cases of practical natural products synthesis, probably due to the steric bulk of the substrates. Thus, simple treatment with acid halides in the presence of a base results in satisfactory selective primary alcohol acylation, as shown in Schemes 7-10 ~ 7-14 [96TA673, 97BMC181, 97TA3067, 97T8129, 94T10491].

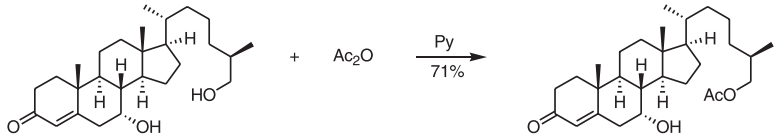


Scheme 7-10

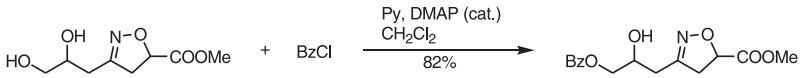
Scheme 7-11



Scheme 7-12

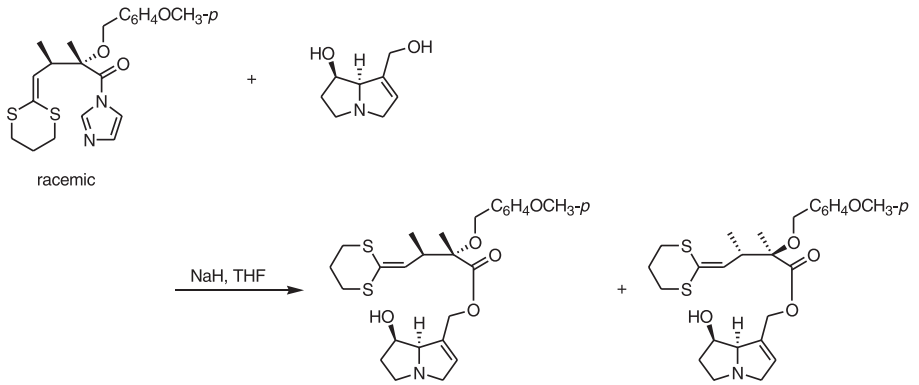


Scheme 7-13

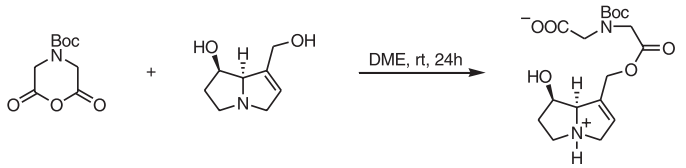


Scheme 7-14

It was described in Chapter 2 that the primary alcohol in (+)-retronecine is selectively acylated via the stannylene intermediate (Schemes 2–20 and 2–21). As shown in Scheme 7-15, the sodium salt of (+)-retronecine reacts with a racemic imidazolide to afford the primary alcohol ester (1 : 1 diastereomer ratio) [96JOC1473]. Treatment of (+)-retronecine with a highly reactive anhydride results in spontaneous ring-opening (Scheme 7-16) [92T1407].



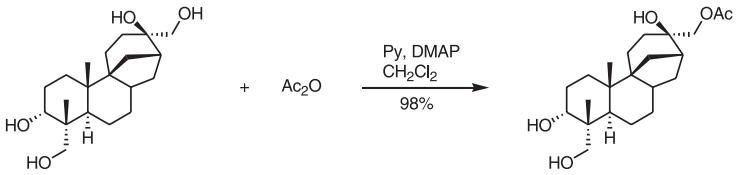
Scheme 7-15



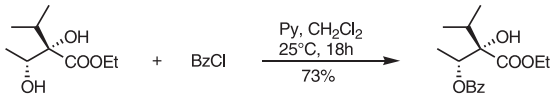
Scheme 7-16

Discrimination of primary and secondary alcohols from tertiary ones is very easily accomplishable: the conventional acid anhydride or halide techniques provide satisfactory outcomes, as demonstrated in Schemes 7-17 and 7-18 [91JCS(P1)969,

96CC1619]. Primary acetates preferentially undergo methanolysis in the presence of secondary and tertiary acetates (see Section 1.2.3.1; Scheme 1-103) [96JOC9086].

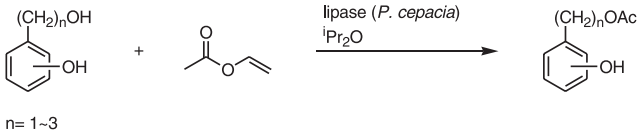


Scheme 7-17



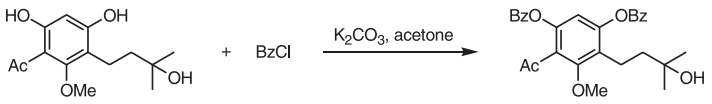
Scheme 7-18

Differentiation between aliphatic alcohols and phenols is also important in organic synthesis. Lipase catalysis induces selective acylation of the aliphatic alcohol. *Pseudomonas cepacia* PS lipase adsorbed on Celite mediates selective acetylation of the aliphatic alcohol with vinyl acetate (Scheme 7-19) [98TA2915]. The same selectivity holds with immobilized lipase, even a secondary alcohol being preferentially acylated over a phenol (see Section 1.2.5; Scheme 1-149) [2001JOC1906].



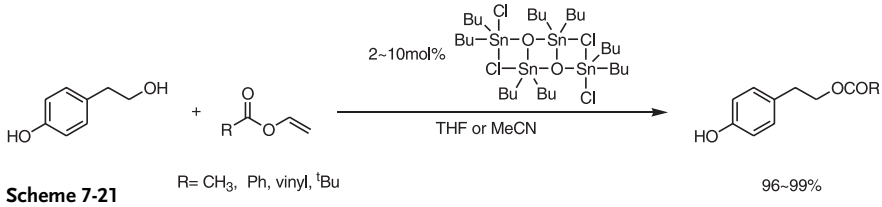
Scheme 7-19

In non-enzymatic treatments, differentiation between aliphatic and aromatic alcohols is dependent on the reaction conditions. Phenols are preferentially acylated over aliphatic alcohols under basic conditions. An example was described in the NaOH-promoted acetylation with 1-acetyl-ν-triazolo[4,5-*b*]pyridine (see Section 1.4.3.1; Scheme 1-257) [86TL5029]. In addition, ω-hydroxyalkylphenol undergoes selective benzoylation of the phenol moiety on treatment with benzoyl chloride in the presence of K_2CO_3 in acetone (Scheme 7-20) [93CL1895, 98BCJ2673]. On the other hand, the reverse is true under acidic conditions.

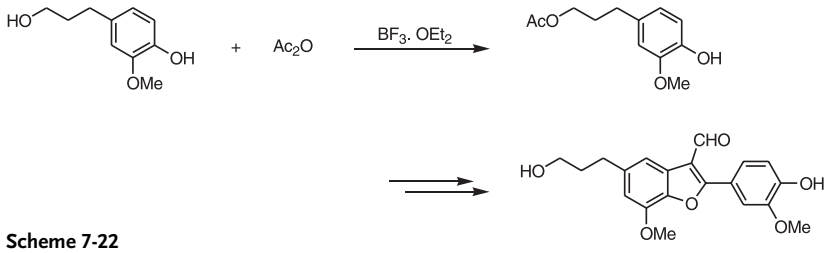


Scheme 7-20

Primary alcohols are typically acylated with acetic anhydride with catalysis by $Sc(OTf)_3$ (see Section 1.3.2.2) [96JOC4560] or TMSOTf (see Section 1.3.2.2) [98JOC2342]. Distannoxane-catalyzed acylation with vinyl esters takes place completely on the aliphatic alcohol, with no acylation on the phenol (Scheme 7-21) [99T2899]. An acid-based technique is utilized in the synthesis of benzofuran adenosine antagonist XH-14 (Scheme 7-22) [97BMC3081], while solid acids such as alumina (see Section 1.2.2.3; Scheme 1-96) and $NaHSO_4/SiO_2$ (see Section 1.1.2.3; Scheme 1-20) [2000SL59] produce aliphatic carboxylic esters in competition with aromatic carboxylic acids in transesterification or esterification.



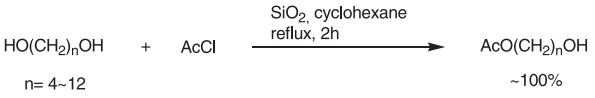
Scheme 7-21



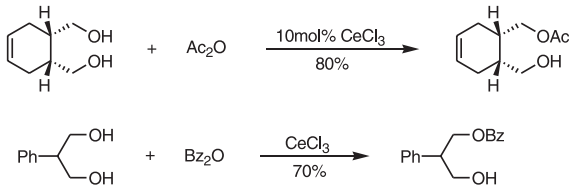
Scheme 7-22

7.1.2
Differentiation between Identical or Similar Functions

The selective transformation of one of two or more identical hydroxy groups is not easy to achieve. Subjection of an α,ω-diol to acylation, for instance, usually provides a mixture of monoester, diester, and unreacted diol even with the use of one equivalent of acylating reagent. This notwithstanding, treatment of diols adsorbed on silica gel with acetyl chloride in refluxing cyclohexane affords >99% yields of the corresponding monoacetate (Scheme 7-23) [98CC495]. Monoacylation of *meso* and C_2-symmetric 1,2- and 1,3-diols can be achieved by the use of acid anhydrides and catalytic amounts of $CeCl_3$ (Scheme 7-24) [2002TL4761]. Other lanthanide chlorides such as $DyCl_3$, $YbCl_3$, etc. are also effective for monoacylation of symmetrical diols [2002JOC5226].

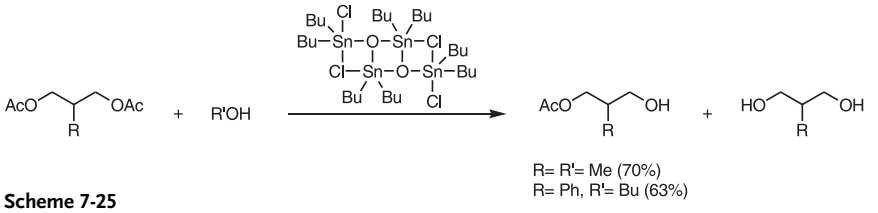


Scheme 7-23



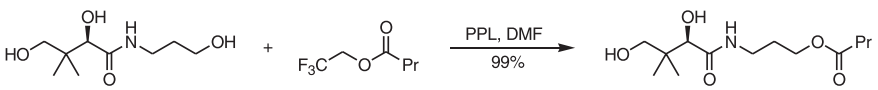
Scheme 7-24

Under distannoxane catalysis conditions, α,ω-diesters with fewer than four carbons are transformed into the corresponding monoesters on treatment with alcohol (Scheme 7-25) [91CC1742]. 2-Substituted propylene glycols also exhibit a considerable level of selectivity.

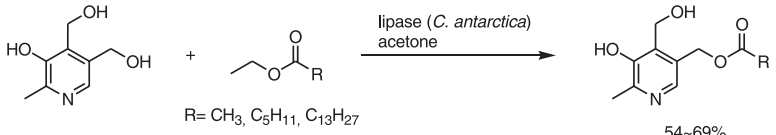


Scheme 7-25

Although very similar difficulties arise with unsymmetrical substrates bearing different primary hydroxy groups at non-equivalent positions, because of the close reactivities involved, lipases act to overcome such problems. *Candidia cylindracea* lipase selectively induces transesterification with isopropenyl acetate on the less sterically hindered sites in 2-alkylthio- and 2-dialkylamino-substituted 1,4- or 1,5-diols (see Section 1.2.5; Scheme 1-148) [90CL1137, 92JCS(P1)1029]. Both PPL and CCL mediate acylation at the less hindered site with 2,2,2-trifluoroethyl butyrate (Scheme 7-26) [93T4107]. Analogously, one of two hydroxymethyl groups on a pyridine ring may undergo acylation, as shown in Scheme 7-27 [98HCA2407].

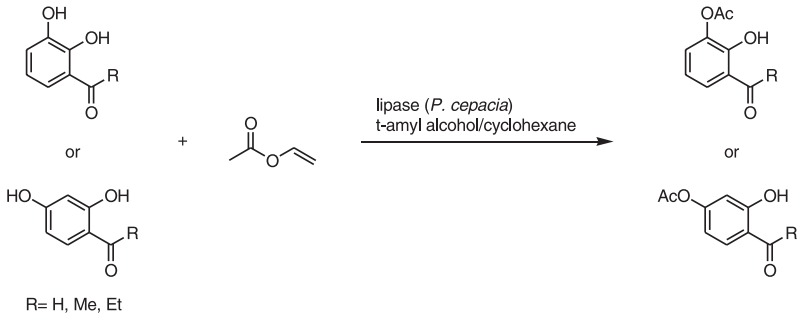


Scheme 7-26

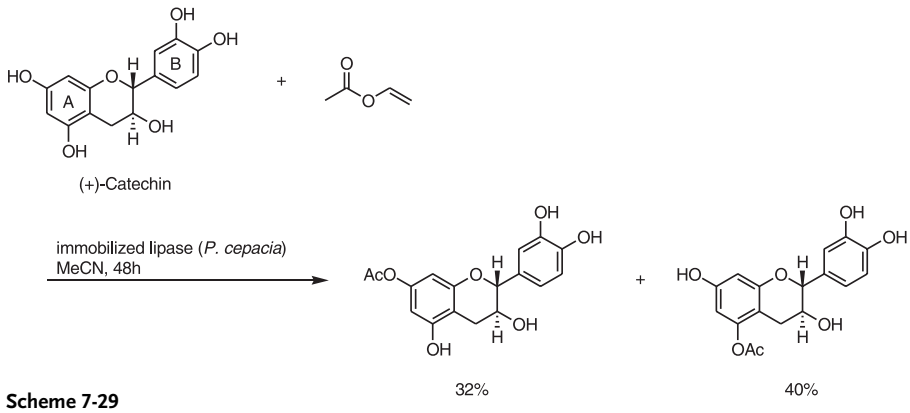


Scheme 7-27

Regioselective acetylation takes place even with dihydroxy derivatives of phenyl ketones and benzaldehyde (Scheme 7-28) [93T3143]. Treatment of these substrates with vinyl acetate in the presence of PCL results in selective acetylation of the *meta*- or *para*-hydroxy group, the *ortho*-hydroxy moiety being untouched. Treatment of (+)-catechin with vinyl acetate in the presence of immobilized PSL results in acetylation of the hydroxy groups on the A ring only, with neither diacetylation nor acetylation on the B ring occurring (Scheme 7-29) [93S1155].



Scheme 7-28



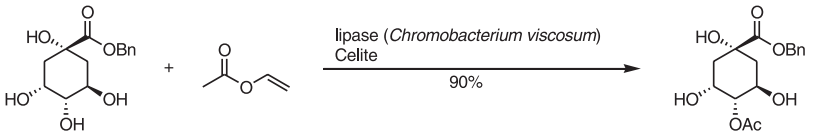
Scheme 7-29

Efficient differentiation between secondary hydroxy groups situated on different sites is required in a broad spectrum of organic syntheses. In particular, selective protection and deprotection of the hydroxy functions on the cyclohexane ring are

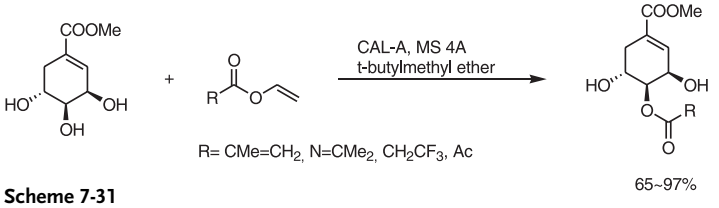
amongst the most important themes in sugar, nucleoside, and steroid chemistry. As described in Chapter 2, the organotin procedure serves quite well to this end. The stannylene intermediate derived from 1,2-diol and dialkyltin oxide or dialkoxide undergoes regioselective acylation on one of the alkoxide sites upon treatment with acid halide or anhydride.

Benzoyl chloride in pyridine mediates selective benzoylation. Thus, *myo*-inositol is converted into the symmetrical 1,3,5-tri-*O*-benzoyl derivative (see Section 1.4.3.2; Scheme 1-265) [91CC428]. Similarly, methyl 6-*O*-(*tert*-butyldiphenyl)silyl-α-D-mannopyranoside undergoes selective benzoylation at the 3-position (see Section 1.4.3.2; Scheme 1-266) [96BMC1461]. One of two hydroxy groups on a pyrrolidinone ring is benzoylated under similar conditions (see Section 1.4.3.2; Scheme 1-262) [93TA2483].

Quinic and shikimic acid esters demand similar selectivity, because three hydroxy groups are present on the cyclohexane ring. *Chromobacterium viscosum* lipase allows selective acetylation of quinate esters at the 4-position by use of vinyl acetate (Scheme 7-30) [92HCA1297]. Methyl shikimate is also selectively acetylated at the 4-position by use of *Candida Antarctica* lipase A (Scheme 7-31) [2002JOC4978]. Vinyl esters with longer chains give better results.

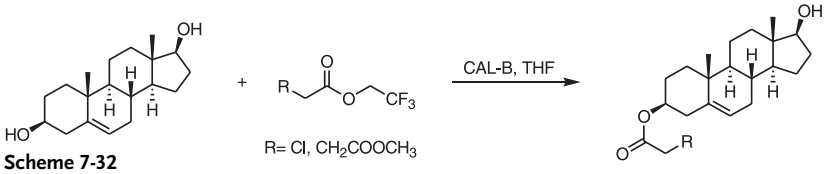


Scheme 7-30

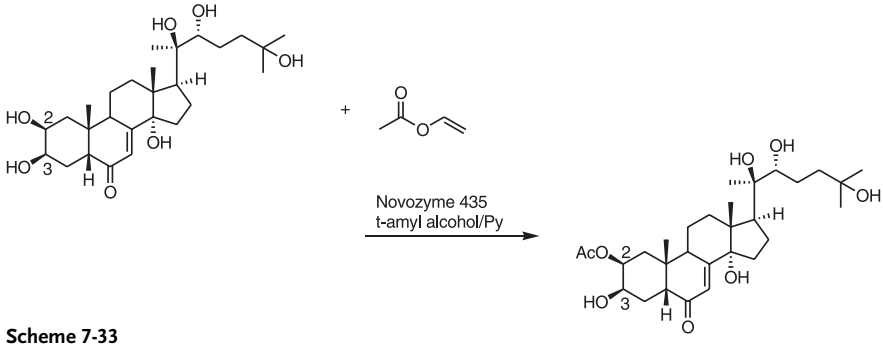


Scheme 7-31

Steroids are another class of compounds that frequently require selective acylation. *Candida Antarctica* lipase B and 2,2,2-trifluoroethyl esters, for example, showed a marked preference for the alcoholic moiety on the A ring of the steroid skeleton (Scheme 7-32) [94T13165]. Immobilized enzyme (Novozym 435) catalyzes the regioselective acylation of (20*R*)-hydroxyecdysone at the C-2 OH (Scheme 7-33) [97T5855].

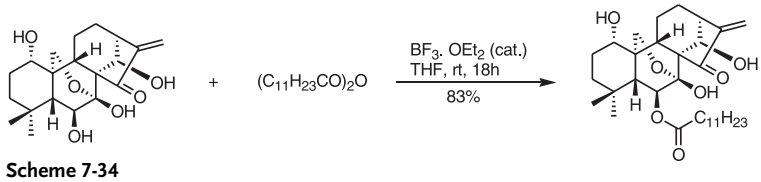


Scheme 7-32

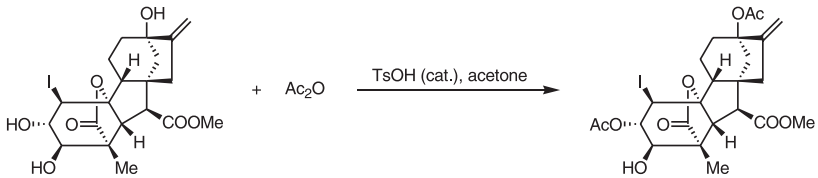


Scheme 7-33

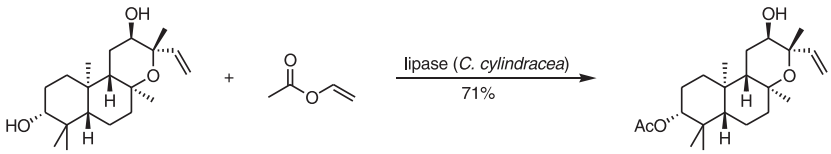
Polycyclic compounds fairly easily undergo selective acylation at the least sterically demanding position, due to their steric congestion, through both enzymatic and non-enzymatic means. Some examples are given in Schemes 7-34 to 7-37 [81CPB3202, 91JCS(P1)1191, 99T8567, 2002JOC4623].



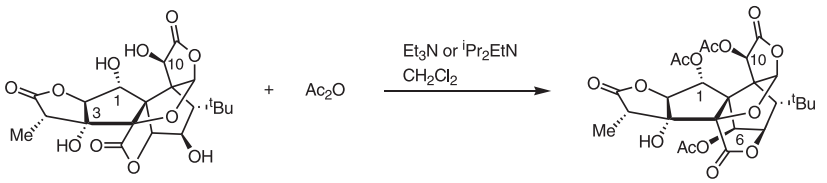
Scheme 7-34



Scheme 7-35



Scheme 7-36



Scheme 7-37

7.2
Use of Theoretical Amounts of Reactants

The esterification reaction between carboxylic acid and alcohol and the transesterification reaction between ester and alcohol are both equilibrium processes, so it is common to use one of the reactants in excess and/or to remove the resulting alcohol or water constantly during the reaction to shift the equilibrium in favor of the product side. From the viewpoint of green chemistry, it is highly desirable to improve on such an inconvenient situation in esterification technology in order to save resources and energy. The use of the reactants in a strict 1:1 ratio is a first step towards this goal [2001AGC(E)2044]. The reaction between carboxylic acid and alcohol is promoted by graphite bisulfate (see Section 1.1.2.3) [74JACS8113], an equimolar mixture of carboxylic acid and alcohol being stirred in the presence of graphite bisulfate in dry cyclohexane. The yield of the ester is more than 94% with simple reactants, but lower with secondary alcohols or cyclopropanecarboxylic acid (50–70%). Tertiary alcohols and phenol are not employable. $NaHSO_4 \cdot H_2O$ mediates reaction between acetic and propanoic acids and primary and secondary alcohols if the neat mixture is heated at reflux with an automatic water separator [99SC3901]. The yields of esters are 85–96%. Microwave irradiation increases the yields of esters from *p*-toluenesulfonic acid-catalyzed esterification between equimolar amounts of carboxylic acid and alcohol, ranging from 82–97% [93CJC90]. $HfCl_4 \cdot 2THF$ is a versatile catalyst with which to effect esterification of an equimolar mixture of a carboxylic acid and an alcohol, although the use of a Soxhlet extractor with molecular sieves (4Å) is needed (see Section 1.1.2.2) [2000SCI1140]. Aliphatic, aromatic, α,β-unsaturated, and sterically demanding carboxylic acids are employable, as are primary, secondary, allylic, and propargylic alcohols. The yields of esters are more than 90%, and greater than 99% in the reactions between 4-phenylbutyric acid and benzyl and 1-phenethyl alcohols. This reaction is applicable to polycondensation of ω-hydroxycarboxylic acids to afford polyesters with Mn = $\sim 10^4$. Diphenylammonium triflate also catalyzes esterification with equimolar amounts of reactants (see Section 1.1.3) [2000TL5249]. Heating of the reactants in toluene at 80–110 °C in the presence of 1 mol% of the catalyst furnishes the corresponding esters in 78–96% yield.

It should be noted that the above procedures successfully achieve the use of reactants in 1:1 ratios, but that the yield of the ester is not 100% except in the two cases of $HfCl_4 \cdot 2THF$-catalyzed reactions. Importantly, the 1:1 stoichiometry is truly effec-

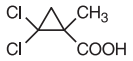
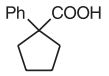
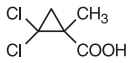
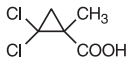
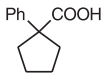
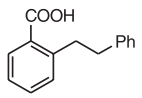
tive only if 100% conversion is reached, since the two starting materials (recovered carboxylic acid and alcohol) otherwise have to be separated from the product mixture, which is a less favorable situation than that in which one of the reactants has been employed in excess. In this case the recovery of only one reactant is necessary, on account of the more facile feasibility of 100% conversion. As such, a 100% yield with use of equimolar amounts of the reactants is ideal because of the lack of a need for a purification process. Such conditions come close to fulfillment through the use of fluorous biphase technology. Heating of a mixture of a methyl or ethyl ester and an alcohol in a 1:1 molar ratio in the presence of $[(ClRf_2SnOSnRf_2Cl)_2$: (Rf = $C_6F_{13}C_2H_4)]$ catalyst in FC-72 solvent at 150 °C provides the corresponding esters in 100% yields (see Section 1.1.2.2) [2002AGC(E)4117]. Some representative results are given in Table 7-1. The perfect conversion is apparent from GLC analysis, which shows no reactants remaining at all. In addition, the tolerance of various functional groups is of great synthetic promise. The perfect conversion is attributable to the poor solubility of the liberated water in FC-72, so the equilibrium is shifted to the ester side. Sterically bulky carboxylic acids are reluctant to react under these conditions. This can result in complete discrimination in competition between carboxylic acids of different steric bulk (Table 7-2). When a 1:1 mixture of two carboxylic acids of different size is treated with one equivalent of alcohol, only the smaller carboxylic acid reacts, to give a 100% yield of the corresponding ester, while no reaction at all takes place with the larger carboxylic acid. Similar perfect differentiation is also observed between aliphatic and aromatic carboxylic acids (Scheme 7-38). The unique features of this technology are described in further detail in the next section.

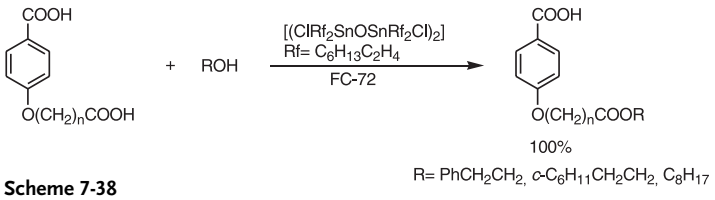
Tab. 7-1 Fluorous biphasic esterification.

Entry	RCOOH	R'OH	Yield of RCOOR' [%]	
			GLC	Isolated
1	$Ph(CH_2)_2COOH$	$PhCH_2OH$	>99.9	100
2	$Ph(CH_2)_2COOH$	$C_8H_{17}OH$	>99	100
3	$Ph(CH_2)_2COOH$	$TBSO(CH_2)_8OH$	>99	98
4	$Ph(CH_2)_2COOH$	$THPO(CH_2)_8OH$	>99	98
5	$Ph(CH_2)_2COOH$	geraniol	>99	100
6	$Ph(CH_2)_2COOH$	$PhCH{=}CHCH_2OH$	>99	99
7	$Ph(CH_2)_2COOH$	$PhC{\equiv}CCH_2OH$	>99	99
8	*p*-$NO_2C_6H_4COOH$	$PhCH_2OH$	>99.9	100
9	C_6F_5COOH	$PhCH_2OH$	>99.9	99
10	*p*-$CF_3C_6H_4COOH$	$PhCH_2OH$	>99.9	99
11	$CH_2{=}CH(CH_2)_8COOH$	$PhCH_2OH$	>99.9	98
12	2-(4-$ClC_6H_4O)OC(CH_3)_2COOH$	$PhCH_2OH$	>99.9	98

Tab. 7-2 Competition between carboxylic acids in fluorous biphasic esterification.

$$R^1COOH + R^2COOH + R^3OH \xrightarrow[Rf= C_6H_{13}C_2H_4]{[(ClRf_2SnOSnRf_2Cl)_2]} R^1COOR^3 + R^2COOR^3$$

Entry	R^1COOH	R^2COOH	R^3OH	Yield[%] R^1COOR^2 GLC	Yield[%] R^1COOR^2 Isolated	Yield[%] R^1COOR^3 GLC
1	$Ph(CH_2)_2COOH$	$PhC(CH_3)COOH$	$C_8H_{17}OH$	>99.9	98	<0.1
2	$Ph(CH_2)_2COOH$		$C_8H_{17}OH$	>99.9	100	<0.1
3	$Ph(CH_2)_2COOH$		$C_8H_{17}OH$	>99.9	100	<0.1
4	$C_7H_{15}COOH$	$PhC(CH_3)COOH$	$C_8H_{17}OH$	>99.9	97	<0.1
5	p-$CF_3C_6H_4COOH$		$C_8H_{17}OH$	>99.9	99	<0.1
6	p-$CF_3C_6H_4COOH$		$PhCH_2OH$	>99.9	98	<0.1
7	p-$CF_3C_6H_4COOH$		$C_8H_{17}OH$	>99.9	100	<0.1
8	p-$CF_3C_6H_4COOH$		$C_8H_{17}OH$	>99.9	99	<0.1



Scheme 7-38

As well as the above catalytic processes, activation of carboxylic acids by stoichiometric amounts of promoters is also available (see Section 1.1.6). Treatment of carboxylic acid with dimethylstannocene affords a tin(II) dicarboxylate intermediate, which is converted into the corresponding ester by treatment with one equivalent of

alcohol (Scheme 1-54) [83CL683]. The yield of the esters ranges from 74–86%. Addition of $(Me_2SiO)_4$ effects esterification with equimolar amounts of carboxylic acid and alcohol [95CL141]. The yield of the ester is 77–99% and the silyl carboxylates are believed to be intermediates. Dimethylsulfamoyl chloride (2 equiv.) mediates the reaction between one equivalent each of carboxylic acid and alcohol in the presence of Et_3N (3 equiv.)/DMAP (0.1 equiv.) [2001TL7427]. The yield is generally high (~95%).

High levels of conversion in transesterification are more difficult to achieve than with esterification, because the alcohol formed is more difficult to remove from the reaction mixture than the water, due to its better compatibility with organic solvents. Nevertheless, the fluorous biphase approach with the fluoroalkyldistannoxane catalyst (see Section 1.2.2.2) allows perfect transesterification [2001AGC(E)3670, 2002ASC(344)84]. Upon treatment of methyl or ethyl esters with one equivalent of an alcohol heavier than ethanol in the presence of the fluoroalkyldistannoxane, the new esters are obtained in 100% yields (Table 7-3). The equilibrium is forced com-

Tab. 7-3 Transesterification in single fluorous phase system.

RCOOR' + R"OH $\xrightarrow[\text{Rf= } C_6F_{13}C_2H_4\text{, FC-72}]{[(ClRf_2SnOSnRf_2Cl)_2]}$ RCOOR" + R'OH

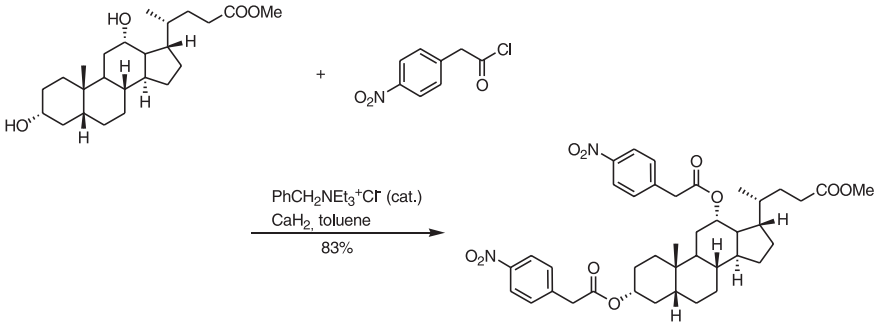
			yield (%)	
entry	RCOOR'	R"OH	GLC	isolated
1	$Ph(CH_2)_2COOEt$	$C_8H_{17}OH$	>99	100
2		$PhCH{=}CHCH_2OH$	>99	100
3	$Ph(CH_2)_2COOMe$	$PhCH{=}CHCH_2OH$	>99	100
4		geraniol	>99	98
5		$PhC\equiv CCH_2OH$	>99	100
6		$THPO(CH_2)_8OH$	>99	99
7		$TBSO(CH_2)_8OH$	>99	100
8		2-octanol	>99	100
9		cyclohexanol	>99	99
10		menthol	>99	
11		borneol	>99	
12	PhCH=CHCOOEt	$PhCH{=}CHCH_2OH$	>99	99
13	PhCOOEt	$PhCH{=}CHCH_2OH$	>99	100
14	PhCOOMe	$PhCH{=}CHCH_2OH$	>99	100

pletely to one side because the methanol or ethanol produced are much less soluble in FC-72 than the heavier alcohols, so it is crucial to use esters with low-alcohol components. This technology is described in more detail in the next section.

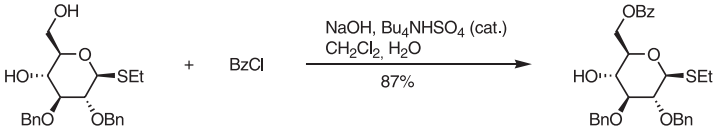
Finally, it should be noted that β-keto esters are unique substrates capable of undergoing facile transesterification with one equivalent of an alcohol (see Sections 1.2.2.3 and 1.2.4) [96CC707, 2000SL251, 2001SL1715].

7.3
New Reaction Media

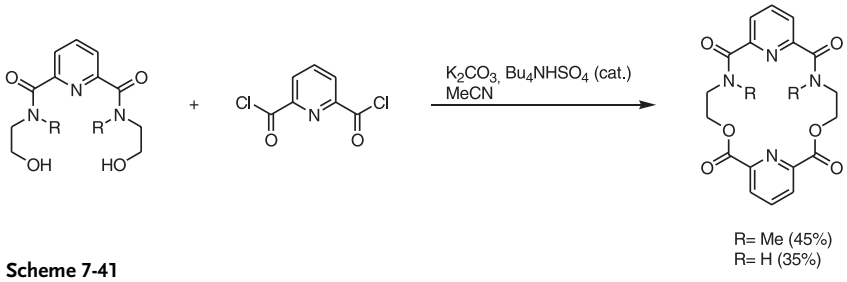
(Trans)esterification reactions are usually conducted in organic solvents, but use of other reaction media occasionally gives better outcomes. As described in Section 1.4.3.3, acylation with acid halides can readily be conducted under phase-transfer conditions [79TL2431, 93CE445, 96SC1447, 90SC2821, 94JOC1783]. Other examples include acylation of steroids (Scheme 7-39) [92JOC6979], benzoylation of a thiosugar (Scheme 7-40) [93JCC933], formation of azacrown ethers (Scheme 7-41) [93BMC363], and benzoylation followed by condensation (Scheme 7-42 and 7-43) [96OPI325 and 97SC3181].



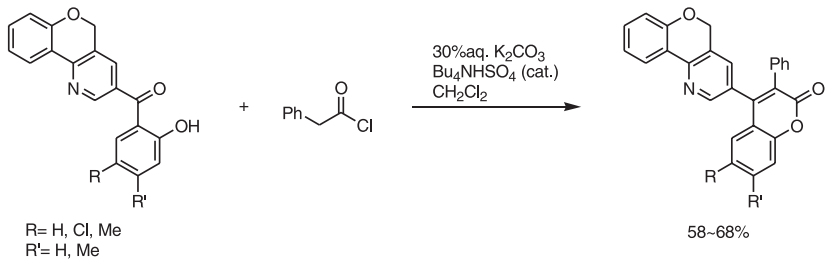
Scheme 7-39



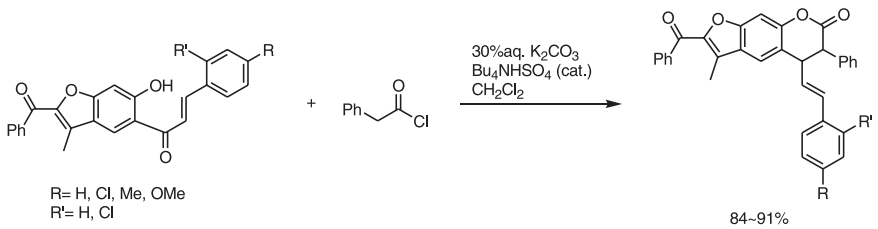
Scheme 7-40



Scheme 7-41

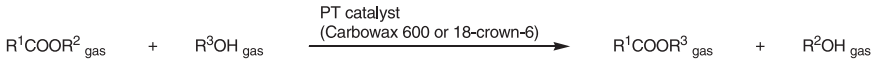


Scheme 7-42

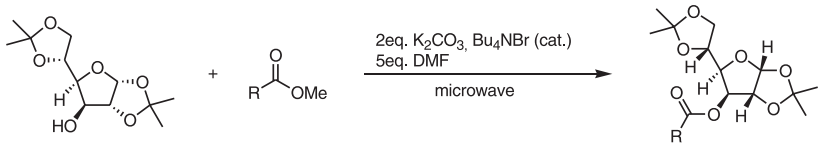


Scheme 7-43

This technology is applicable to transesterification as well. Introduction of a gaseous mixture of the reactant ester and an alcohol into a column packed with solid potassium carbonate coated with a phase-transfer catalyst (Carbowax 6000 or 18-crown-6) induces transesterification (Scheme 7-44) [83JOC4106]. The yield of the esters, however, is modest (up to 65%). Transesterification of sugars under phase-transfer conditions is assisted by microwave irradiation (Scheme 7-45) [98T13567]. The primary and secondary hydroxy groups undergo acylation with methyl benzoate or laurate.

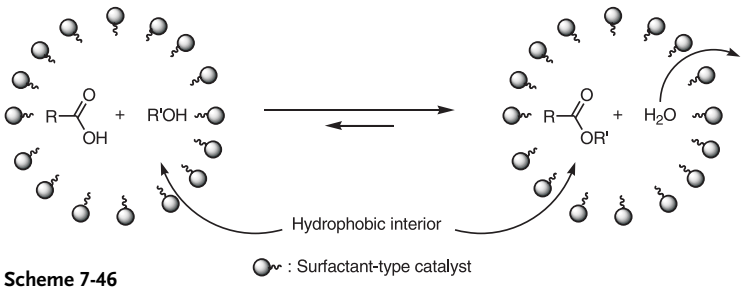


Scheme 7-44



Scheme 7-45

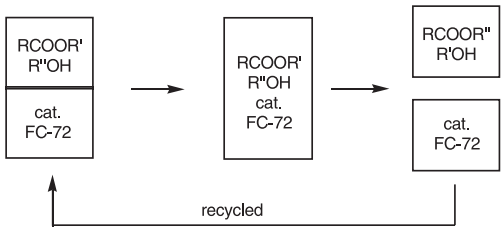
p-Dodecylbenzenesulfonic acid acts as a surfactant-type Brønsted acid catalyst to permit direct esterification in water (Scheme 7-46) [2001JACS10101]. In water, the surfactant-type catalyst and organic substrates form droplets with hydrophobic interiors. The surfactants concentrate the catalytic species (such as a proton) onto the droplets' surfaces, where the reaction takes place, and then enhance the rate to reach equilibrium. For lipophilic substrates, the equilibrium position between the substrates and the products (esters) lies on the ester side, because water molecules are expelled out of the droplets due to the hydrophobic nature of their interiors. As a result, quantitative yields of esters are obtained.



Scheme 7-46

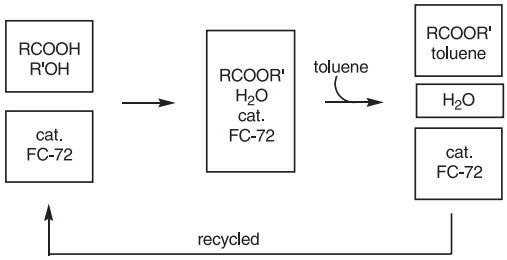
Fluorous biphase technology is useful for (trans)esterification. It has already been mentioned that fluoroalkyldistannoxanes are effective catalysts for both esterification and transesterification in various aspects, yet some further characteristic features in terms of fluorous chemistry deserve to be noted here. Transesterification is most conveniently performed simply by heating the ester and alcohol reactants in the presence of the catalyst in FC-72 (Scheme 7-47) [2001AGC(E)3670, 2002ASC(344)84]. Reaction at 150 °C is crucial, to make the reaction mixture homogenous. Usually, the products are extracted into toluene after the reaction, but it is also possible instead, when the reaction is conducted on a large scale, to separate the products directly from the surface of the FC-72 layer. The yield is always quantitative. Although the catalyst can be recovered from the FC-72 solution, the solution itself can also be used straightforwardly for the next reaction without isolation of the catalyst, no deterioration in the catalytic activity being observed after 20 recycles. Of course, FC-72/toluene or/alcohol binary solvent systems are employable. In the former case, use of a slight excess (~1.3 equiv.) of alcohol is required for > 99% yield, while the reaction

proceeds rapidly in the latter case. Reaction in toluene is also feasible, since the catalyst is soluble in hot toluene. The catalyst can be recovered by extraction with FC-72.



Scheme 7-47

Esterification is carried out similarly (Scheme 7-48) [2002AGC(E)4117]. After the reaction, easily separable organic, aqueous, and fluorous phases result. The recovered catalyst is not the same as the original one, but somehow modified (probably carboxylated). However, this new form is also sufficiently active and so the catalyst solution in FC-72 can be reused repeatedly.



Scheme 7-48

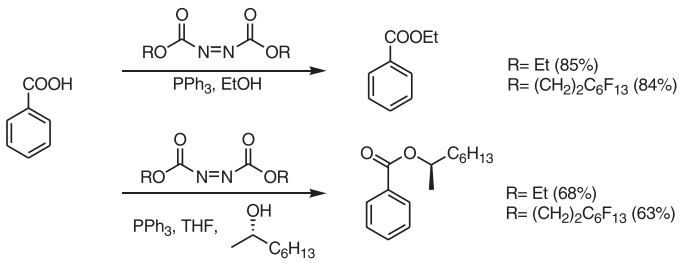
Scandium and ytterbium tris(perfluoromethanesulfonyl)methide complexes $M[C(SO_2C_8F_{17})_3]_3$ (M = Sc, Yb) can be used for acetylation of cyclohexanol both in homogeneous and heterogeneous phases [2001TL289, 2002T4015]. A 1:1 mixture of cyclohexanol and acetic anhydride, together with the catalyst (1 mol%) in perfluoromethylcyclohexane (5 parts), toluene (5 parts), and perfluorobenzene (3 parts), constitutes a homogeneous phase at 40 °C. The reaction is complete in 15 minutes and the reaction mixture then turns into two layers upon standing at 15 °C. Cyclohexyl acetate is obtained in quantitative yield from the upper layer (19.9% $CF_3C_6H_{11}$, 52.5% toluene, 27.6% C_6F_6), while the catalyst is completely recovered from the lower layer (69.9% $CF_3C_6H_{11}$, 13.8% toluene, 16.3% C_6F_6). The same reaction is feasible in the heterogeneous two-phase system made up of perfluoromethylcyclohexane and toluene in a 1:1 ratio.

The temperature-dependent solubility of a fluorous super Brønsted acid is utilized in acylation and esterification without fluorous solvents (Scheme 7-49) [2002SL1299]. 4-(1*H*,1*H*-Perfluorotetradecanoxy)-2,3,5,6-tetrafluorophenylbis(trifluoromethanesul-

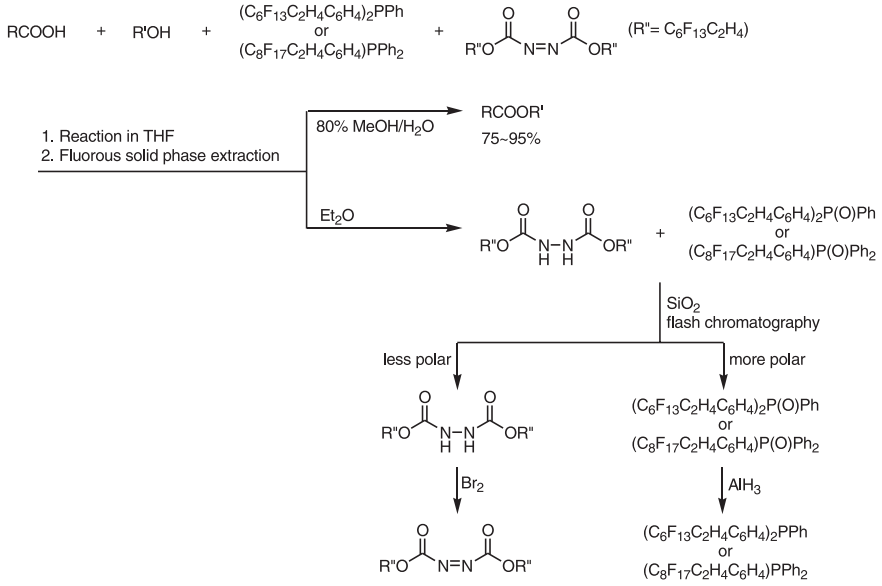
fonyl)-methane is soluble in toluene at 70 °C but not soluble at room temperature. Thus, when a mixture of the reactants and catalyst in toluene is heated, a homogeneous solution is produced, in which the reaction takes place. After completion of the reaction, cooling of the reaction mixture to room temperature causes precipitation of the catalyst, which is separated by filtration. With the aid of this technology it is possible to conduct the benzoylation of methanol with benzoic anhydride and the esterification of 3-phenylpropionic acid in methanol to produce the esters quantitatively.

Scheme 7-49

The Mitsunobu reaction can be carried out under fluorous conditions. Bisfluoroalkyl azodicarboxylate effects esterification of benzoic acid (Scheme 7-50) [2002TL2807]. After the reaction, solvent is evaporated and the residue is partitioned between dichloromethane and FC-72. The fluorous hydrazine co-product is not detected in the organic layer, thus leaving only triphenylphosphine oxide to be separated from the desired product. The combined use of the fluorous phosphines $(C_6F_{13}C_2H_4C_6H_4)_2PPh$ or $C_8F_{17}C_2H_4C_6H_4PPh_2$ and fluorous azodicarboxylate allows easier separation of the product ester (Scheme 7-51) [2002T3855]. After the reaction, the solvent is evaporated, and the residue is taken up in MeOH and loaded onto fluorous silica. Elution with 80% MeOH gives the Mitsunobu adduct in 75–95% yield, free of any impurities. Further elution with ether gives a mixture of the fluorous phosphine oxide and fluorous hydrazine. This fluorous mixture can readily be separated on normal silica gel. These recovered fluorous reagents can be reconverted into the original fluorous phosphine and fluorous azocarboxylate pure enough to be reused. Also importantly, this technique can be applied in parallel reactions.

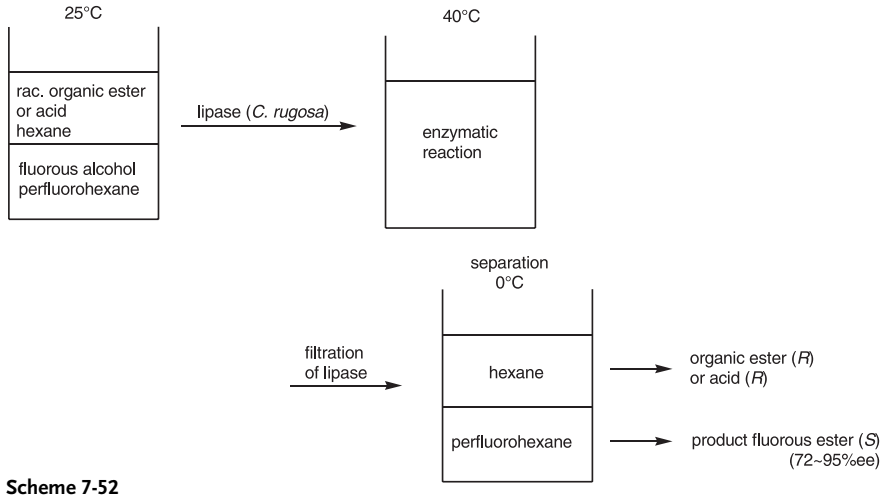


Scheme 7-50



Scheme 7-51

Kinetic resolution of racemic esters or carboxylic acids is conveniently achieved with the aid of fluorous biphase technology (Scheme 7-52) [2002CC1680]. A mixture of a hexane solution containing racemic ester or carboxylic acid and a perfluorohexane solution containing a highly fluorinated decanol is heated at 40 °C with lipase from *Candida rugosa*. The reaction mixture is homogeneous at this stage. After removal of the lipase by filtration, the liquid phases are cooled to 0 °C, resulting in separation of the two solutions. From the fluorous solution, the *S* fluoroalkyl esters are



Scheme 7-52

recovered in ca. 50% conversion with 72–95% *ee*. The unreacted esters or carboxylic acids recovered from the organic layer show 44–95% *ee*.

Ionic liquids are attracting growing interest as alternative reaction media for a wide variety of synthetic processes, because they are involatile, thermally stable, and environmentally benign. The *O*-acetylation of alcohols and carbohydrates with acetic anhydride takes place smoothly in the ethylmethyl- and butylmethylimidazolium dicyanamides shown below [2002CC714]. All hydroxy groups in saccharides such as glucoses, sucrose, etc. are acetylated. Notably, the dicyanamides function both as solvent and as catalyst. The DCC/DMAP technique for esterification between ferrocenemonocarboxylic acid and benzoic acid derivatives can be conducted in butylmethylimidazolium terafluoroborate or hexafluorophosphate [2002GC159].

Enzymatic reactions in ionic liquids are also feasible. Lipase-catalyzed kinetic resolution of secondary alcohols in ethylmethyl- or butylmethylimidazoles can be up to 25 times more enantioselective than in organic solvents [2001OL1507]. Lipases in ionic liquids exhibit catalytic activities comparable with those in organic solvents for acetylation of 2-hydroxymethyl-1,4-benzodioxane with vinyl acetate [2002TL2979]. In these reactions, the reaction mixture is usually worked up with organic solvents for purification of the products, although this defeats the original purpose of the use of ionic liquids. To bypass this problem, an extraction technique with supercritical carbon dioxide is available, both in batchwise and in continuous flow processes [2002CC992].

The supercritical methanol is used for transesterification of rapeseed oil (Scheme 1-66) [2001FU225, 2001FU693]. Methyl esters are obtained without use of catalyst.

Finally, immobilization of catalyst, though not categorizable as a modification of reaction media in a strict sense, should be briefly mentioned. This technology can offset many drawbacks encountered in homogeneous reactions and is discussed in Part I, but in a number of different places. The studies relevant to immobilization of catalysts are therefore complied here.

Brønsted acid: [2002ASC(344)270] (see Section 1.1.2.1); [2001AGC(E)4077] (see Section 1.3.2.1).

Carbodiimide: [95TL8345] (see Section 1.1.4); [2000TL8673] (see Section 1.1.4).

Sulfonyl chloride: [2001TL7783] (see Section 1.1.6).

Lipase: [2001JOC1906] (see Section 1.2.5); [2000JACS11767] (see Section 1.2.5); [2001JOC5645] (see Section 1.2.5); [2001JACS2428] (see Section 1.2.5)

7.4
Application to Natural Products Synthesis

There are numerous reports of natural products synthesis involving esterification. The literature survey hit more than 300 studies in which esterification plays a key role in natural products synthesis; these are listed in Table 7-4 in the order of the sections in this book. Since it is not possible to describe all of them here, only representative examples are given.

Tab. 7-4 Natural products synthesis involving esterification.

Method	*Reference*	*Conditions*	*Target or related products*
Reaction between alcohols and carboxylic acids			
1.1.1	91JACS3533	At 190 °C	Quadrone
	92TL4931	Reflux	Whisky lactone, eldanolide
1.1.2.1	90TL5575	TsOH	Parasorbic acid, tridecanol acetate
	94TA1979	HCl	(–)-Horsfiline
	95SL735	H_2SO_4	Pachylactone
	96TL7553	TsOH	Anthridic acid
	97JOC465	TsOH	(–)-Reserpine
1.1.4[a]	86JACS4586		Dihydromevinolin
	91AGC(E)412		Taxol
	91T9929		(–)-Valilactone
	92CL49		Antrimycin
	92JACS9673		Byssochlamic acid
	92T10531		Pyrrolizidine alkaloid
	92TL5185		Taxol
	93T1571		Pyrrolizidine alkaloid
	93TL6049		Taxol
	94BCJ2345		Pyrrolizidine alkaloid
	94BCJ3094		Pyrrolizidine alkaloid
	94CC2591		Taxol
	94JACS11213		(±)-Myrocin
	94JOC1238		Taxol
	94TL105		Taxol
	94TL2349		Taxol
	94TL3063		Taxol
	94TL4483		Taxol
	94TL4707		Taxol
	94TL6839		Taxol
	94TL7893		Taxol
	94TL9709		Taxol
	94TL9713		Taxol
	94TL9717		Taxol
	95JCS(P1)3073		Enterochelin
	95JOC4774		Dolabellin
	95T8809		(–)-Sypringolides
	95TL8933		Taxol

Tab. 7-4 (continued)

Method	*Reference*	*Conditions*	*Target or related products*
	96JACS919		Taxol
	96JACS3301		(–)-Virginiamycin
	96JACS10335		Maitotoxin
	96JOC6893		Cryptophycin
	96TA2371		Tarchonanthuslactone
	96TL1777		Taxol
	96TL5049	EDC	Octalactin
	97JACS11769		Atractyligenin
	97JACS7960	EDC	Epothilone
	97JOC4428		Aerothionin
	98BMC427		Taxol
	98CC1745		Taxol
	98JOC9624	DIC	Taurospongin
	98TL2223	EDC	Diazonamide A
	99BMC1189	EDC	Taxol
	99TL1631	EDC	2-Ara-Gl (2-arachidonylglycerol)
1.1.5[b]	91JCS(P1)1825		Samanine
	91TL5781		Combretastatin D
	92JACS2567	PBu_3, DEAD	Echinosporin
	92JACS2995		Latrunclin A and B
	92TL4931		Whisky lactone, eldanolide
	93JCS(P1)1549		Lipstatin
	94BCJ3327		Paniculide A
	94CL1083		Pyrenophorin
	94JOC4853		Suspensolide
	94JOC5414		Combretastatin D
	94TL591		Geodiamolide A
	94TL4409		Combretastatin D
	94TL8237		(–)-Vermiculine
	95BCJ3151		Nosiheptide
	95JOC7334		(–)-Lipstatin
	96TL1461		Deoxymannojirimycin
	97JOC4	PPh_3, DIAD	Panclicin D
	97CC1647	PPh_3, DIAD	(+)-Acetylphomalactone
	97JOC6619		Styllactone
	97SL577		Hastanecine
	97TL6055		10-Oxo-11(E)-octadecen-13-olide
	98CEJ33		Combretastatin D
	98JACS3935		Macrolactins
	98T10029		Actinomycin Z_1
	98TL143		Lipoxin A
	98TL779		Dideemnin M
	98TL1075		Solandelactones
	98TL2765		Pyrrolizidine alkaloid
	98TL4363	PPh_3, DIAD	UK-2A
	99SC399		Patulolide C

Tab. 7-4 (continued)

Method	*Reference*	*Conditions*	*Target or related products*
1.1.6	77CL959	2-Cl-1-Me-Pyridinium iodide	(±)-Recifeiolide
	88JACS5917	Di(2-Py)carbonate	Taxol
	92JCS(P1)553	*N*-Me-2-Cl-Pyridinium iodide	(–)-α-Kainic acid
	93SL333	*N*-Me-2-Cl-Pyridinium iodide	Murrayaquinone A
	94JOC3347	$PhSO_2Cl$	Bourgeanic acid
	94JOC3642	*p*-Br-Benzene-sulfonyl-chloride	Obafluorin
	95CEJ454	*N*-Me-2-Cl-Pyridinium iodide	Balanol
	96TL2141	*N*-Me-2-Cl-Pyridinium iodide	9-Propyl-10-azacyclododecan-12-olide
	97CPB1793	Di(2-Py)carbonate	Taxol
	97SL580	*N*-Me-2-Cl Pyridinium iodide	Balanol
	97T4857	*N*-Me-2-Cl-Pyridinium iodide	Balanol
	98CL3	Di(2-pyridyl)thio-carbonate	Taxol
	98JOC4397	*N*-Me-2-Cl-Pyridinium iodide	Balanol
1.1.7	96TA2639	Lipase from *C. rugosa*	(4*E*,7*S*)-7-Methoxytetradec-4-enoic acid
Reaction with Esters			
1.2.1	90JACS8907	At 0 °C	Chorismic acid
	95JHC395	Heat	Unnamed natural product
	95JOC5785	At 210 °C	(–)-Oblongolide
	96TA1281	light	(*R*)-(+)-Umbelactone
	97M281	At 130 °C	(+)-Heptelidic acid
	2000TL239	At 90 °C	Taxol
1.2.2.1	92T5667	MesOH	(+)-Eldanolide
	92TA533	HCl	(6*R*)-(–)-Massoialactone, (4*R*,6*R*)-(+)-4-Hydroxy-6-pentyl-valerolactone
	92TL4605	TsOH	(±)-Mint lactone
	93JOC6915	TsOH	(±)-(1β,6α,9β,10α)-9-Chloro-10-hydroxy-8-(methoxycarbonyl)-4-methylene-2,5-dioxabicyclo[4.4.0]-dec-7-en-3-one
	94CPB2161	Camphorsulfonic acid	Cryptocaryalactone
	94JOC4122	HF	(±)-Muricatacin
	94T8209	H_2SO_4	(±)-Cuanzine
	94TL2217	TsOH	Taxol
	95JCS(P1)777	HF	(+)-Compactin

Tab. 7-4 (continued)

Method	*Reference*	*Conditions*	*Target or related products*
	95SL505	HCl	Tetrodotoxin
	95TL5475	H_2SO_4	Calanolide A
	96JACS9992	TsOH	9-Acetoxyfukinanolide
	96SC4005	TFA	(±)-Calanolide A
	96TL2335	TsOH	*cis*-Hydrindane
	96TL6503	TFA	(+)-Dihydrokawain
	98JOC1102	HCl	(3α*S*,6α*S*)-Ethisolide, whisky lactone, (–)-avenacioide
1.2.2.2	88JACS5198	$(SCNBu_2SnOSnBu_2OH)_2$	Brefeldin
	88TL6689	$(SCNBu_2SnOSnBu_2OH)_2$	Kadsurenone-ginkgolide hybrid
	99JACS9073	$(SCNBu_2Sn)_2O$	Library of polycyclic small molecules for use in chemical genetic assays
	99OL957	$BF_3 \cdot OEt_2$	Mycalamide
	2000TL243	$(Bu_2SnCl)_2O$	Taxol
1.2.2.3	97JOC4550	Al_2O_3	Clavepictines A and B
	98JCS(P1)2563	Dowex 50Wx4	Naphthylisoquinoline alkaloid
1.2.3.1	93JACS4891	K_2CO_3	Acetogenins (solamin, reficulatacin)
	94TL5393	MeLi/CuI	Bafilomycin A
	95TL7285	LiOH	Seiridin
	98JACS1914	K_2CO_3	Harringtonolide
	98T3693	KI	Methyl picrotoxate
1.2.3.2	92JCS(P1)1907	DBU	Goniotriol, 8-acetylgoniotriol
	95JACS2657	DMAP	(–)-Ptilomycalin A
	95TL7233	DMAP	(±)-Heptelidic acid
1.2.5	92TA29	PPL	(–)-Massoialactone, 3-hydroxy-5-icosanolide, 3-hydroxy-5-decanolide
	93JOC7535	PPL	(3*Z*,6*Z*)-Dodecanolide
	94AJC1661	Lipase from *C. cylindracea*	(*Z*,*Z*)-2-Hydroxy-4-oxohenicosa-12,15-dien-1-yl acetate
	94TL6975	Lipase from *C. antarctica*	(2*S*,3*R*)-3-Hydroxyproline
	95TA2219	PPL	(3*Z*)-Dodecen-12-olide, (2*E*)-9-Hydroxydecenoic acid
	96JOC1814	Lipase from *C. rugosa*	(*R*)-Patulolide A
	96JOC6931	Lipase PS	(+)-Strigol
	96SL163	Lipase PS	(+)-Crooksidine
	96SL925	Lipae PS	Nitraria alkaloid
	97CL11	PPL	CC-1065, duocarmycin
	97 JACS11554	Lipase from *C. antarctica*	Taxol

Tab. 7-4 (continued)

Method	*Reference*	*Conditions*	*Target or related products*
	97JOC3824	Lipase from *P. fluorescens*	(–)-Curcumanolide A
	97LA211	Lipase from *P. fluorescens*	Oosponol
	97SL580	Lipase from *P. sp.*	Balanol
	97T5855	Lipase from *C. antarctica*	Ecdysteriods
	97TL4121	Lipase from *C. antarctica*	Triptoquinone B and C
	98JOC4397	Lipase from *P. sp.*	Balanol
	98JOC920	Lipase PS	(±)-(3aα,8aα)-Ethyl 8β-hydroxy-6β-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate
	98SL1001	Lipase LIP	Rengyoxide
	98TL2163	Lipase PS	Taxol
	98TL4677	Lipase LIP	(–)-Neplanocin A
	98TL7747	Lipase PS	Sceletium alkaloid
	99TA2729	Lipase from *C. rugosa*	Lactaranes, marasmanes
	99TL1207	Lipase from *C. rugosa*	Macrolide antibiotic A26771B
	99TL4965	Novozyme 435	(±)-Azamacrolide
	2000TA1375	Lipase OF-360	(+)-Albocanol, etc.
Treatment with Acid Anhydrides			
1.3.2.1	91JCS(P1)1191	TsOH	Gibberellin, A81
	92CJC1375	H_2SO_4	Longifolene
	98TL1145	AcOH	Secosterol
1.3.2.2	97BMC3081	$BF_3 \cdot OEt_2$	XH-14 (5-(3-hydroxypropyl)-7-methoxy-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde)
	98TL2883	$ZnCl_2$	Taxol
	98TL6081	$Ln(OTf)_3$	Taxol
1.3.3.1	84JOC1909	BuLi	Lasubine I , Subcosine I
	93JOC5855	NaOAc	BMY40662 (benzothiazinone)
	94JOC4735	KOAc	Coriandrin
1.3.3.2	85JACS3731	DMAP, NEt_3	(+)-Compactin
	90JACS9001	DMAP	(–)-Anisatin
	91HCA941	Py	Bretonin
	91T7937	Py	3β,6α-Dihydroxy-9-oxo-9,11-seco-5α-cholest-7-en-11-al
	92AJC2025	Py	Ventilagone
	92JCS(P1)1907	Py	Goniotriol, 8-acetylgoniotriol
	92JOC5807	Py, DMAP	Myrtine, lasubinem, subcosine
	92T1407	DME	Pyrrolizidine alkaloid
	93BCJ3053	Py	Salvinolone

Tab. 7-4 (continued)

Method	*Reference*	*Conditions*	*Target or related products*
	93JCS(P1)633	Py, DMAP	Gephyrotoxin
	93T5225	DMAP	Epoxypolyynes
	94CC295	DMAP	Taxol
	94JACS1591	DMAP, NEt_3	Taxol
	94JCS(P1)61	NEt_3	Specionin
	94LA1065	DMAP, NEt_3	(*Z*)-6,8-Nonadien-2-ol
	94SL343	Py	(±)-Epibatidine
	94T10083	Py, DMAP	Drimane sesquiterpene
	94T10597	Py, DMAP	Kjellmanianone
	94TL3201	Py	Azamacrolide
	94TL3489	Py	6,7-Diepicastanospermine
	94TL4145	DMAP	Tautomycin
	95CC743	Py	Goniodiol-8-monoacetate
	95CC1369	DMAP	Batzelladin A
	95JOC4184	DMAP	Carabrone
	95JOC5726	DMAP, NEt_3	GERI-BP001
	95JOC5825	NEt_3	Tropane alkaloid
	95T1663	DMAP	(–)-(5*R*,6*S*)-6-Acetoxy-5-hexadecanolide
	95TL6345	Py	Paraconic acid
	96BCJ1033	Py	Naturally occurring flavones
	96CL223	Py, DMAP	Taxol
	96JACS1309	Py	Acetoxycrenulide
	96JACS7094	Py, DMAP	(–)-Galbonolide B
	96JOC4882	Py	Clavepictine A and B
	96JOC8698	Py	Biopterin
	96T14877	Py	(+)-Goniodiol
	96TA3141	Py	Melodorinol, acetylmelodorinol
	96TL893	Py, DMAP	Tonghaosu
	96TL4047	DMAP, NEt_3	Conagenin
	97BCJ427	Py	Nagastatin
	97JCS(P1)317	Py, DMAP	(+)-Asperlin, (+)-acetylphomalactone, (+)-(5*S*,6*S*,7*R*,8*S*)-asperlin
	97JOC3824	Py, DMAP	Curcumanolide A
	97JOC5542	Py	Microcolin B
	97JOC8095	DMAP, NEt_3	Secosyrin, syributin
	97JOC8155	Py	Salsolene oxide
	97T16435	DMAP, NEt_3	Monensin
	97TA633	Py	(5*R*,6*S*)-6-Acetoxy-5-hexadecanolide
	97TA3067	Py	Melodorinol
	98CPB559	Py	Duocarmycin SA
	98CPB1199	DMAP, NEt_3	Halichondrin B
	98JOC6281	Py, DMAP	(±)-Swainsonine
	98SL259	Py, DMAP	Coniochaetone A and B
	99TL1257	DMAP, NEt_3	(+)-Phomalactone, (+)-acetylphomalactone, asperlin

Tab. 7-4 (continued)

Method	*Reference*	*Conditions*	*Target or related products*
	99TL1963	Py, DMAP	Prevercynamin
	2000TL243	Py, DMAP	Taxol
1.3.5[c]	92T393		Pyrrolizidine alkaloid
	93JACS11446		Rutamycin B
	94TL3201		Epliachnene
	94TL3613	ClCOOEt	Camptothecin
	95JOC6082	$ClCOOCMe{=}CH_2$	Leualacin
	95S1007		Luffariolide E
	95SL893		Luffariolide E
	95TA2219		(3*Z*)-Dodecen-12-olide, (2*E*)-9-hydroxydecenoic acid
	95TL4117		(–)-Colletol
	96JACS1229		Dolabellatrienone
	96TL8065		(+)-Ikarugamycin
	97JACS7483		(+)-Laurencin
	97JACS7974		Epothilone A and B
	97JOC3271		Bafilomycin A_1
	97TL53		6-Deoxyerythromolide B
	98JOC642		Halicholactone, Neohalicholactone
	98T7127		Epothilone
Treatment with acid halides and related compounds			
1.4.1	91CC1438	Reflux	(*R*)-(–)-Muscone
	96JOC5697	Reflux	Cyclo-2,3-diphospho-D-glycerate
	97JOC960	At rt.	Myriceric acid A
1.4.2.1	92TL7355	AcOH	Cerpegin
	93TL6049	HCl	Taxol
	94CL543	TsOH	(–)-Isoiridomyrmecin
	95ACS8258	MesOH	Lankacidin C
	96TL8053	HCl	Fusarentin methyl ethers
	98JOC8045	HCl	Taspine
1.4.3.1	92T6985	NaH	Taxol
	93JOC5028	BuLi	Taxol
	93TL3205	BuLi	Taxol
	93TL4149	$NNa(TMS)_2$	Taxol
	93TL6845	$NLi(TMS)_2$	Taxol
	94BMC335	NaH	Taxol
	94BMC487	NaH	Taxol
	94BMC1571	$NNa(TMS)_2$	Taxol
	94JACS1591	$NNa(TMS)_2$	Taxol
	94JOC515	$NNa(TMS)_2$	Taxol
	94JOC5147	KOtBu	Balanol
	94JOC6156	$NLi(TMS)_2$	Taxol
	94TL1665	$NLi(TMS)_2$	Taxol
	94TL5543	BuLi, $NLi(TMS)_2$	Taxol
	95JCS(P1)2849	$AgOCOCF_3$	(+)-Bengamide E

Tab. 7-4 (continued)

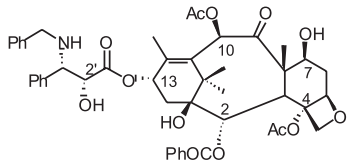
Method	*Reference*	*Conditions*	*Target or related products*
	95JACS624	$NNa(TMS)_2$	Taxol
	95JACS2409	$NNa(TMS)_2$	Taxol
	95JACS5228	$NNa(TMS)_2$	Taxol
	95JOC5910	$AgOCOCF_3$	(+)-Bengamide E
	96JOC1473	NaH and $AgOCOCF_3$	Pyrrolizidine alkaloid
	96JOC2664	NaH	Taxol
	96TL6495	$NLi(TMS)_2$	Taxol
	97BMC1941	$NNa(TMS)_2$	Taxol
	97JOC4746	$NLi(TMS)_2$	Taxol
	98BCJ2673	K_2CO_3	Prenylisoflavones
	98BKC1027	$NLi(TMS)_2$	Taxol
	98BMC273	$NLi(TMS)_2$	Taxol
	98BMC2977	$NLi(TMS)_2$	Taxol
	99BMC1189	$NLi(TMS)_2$	Taxol
1.4.3.2	88JACS5917	Py	Taxol
	91HCA941	Py	Bretonin
	92CL1417	Py	PAF (platelet-activating factor)
	92JMEC4230	Py, DMAP	Taxol
	93JACS8873	Py, DMAP	Oleanolic acid, erythrodiol, β-amyrin
	93JOC2931	Py	Taxol
	93TL4751	DMAP, NEt_3	Pancratistatin
	94BMC487	DMAP	Taxol
	94JOC5147	NEt_3	Balanol
	94T10491	Py, DMAP	Melodienone, 7-Hydroxy-6-hydromelodienone
	94TL4959	Py, DMAP	Taxol
	95CPB1617	NEt_3	Lycoperdic acid
	95JHC195	NEt_3	Galanthamine
	95TL5861	NEt_3	*m*-Hydroxycocaine, *m*-Hydroxybenzoylecgonine
	95 TL6515	Py	Bryostatin
	96CPB627	Py	Mitotoxin
	96LA271	Py, DMAP	Alkanonic acid
	97JACS8391	Py, DMAP	Cladantholide, estafiatin
	97SC4003	NEt_3	Cocaine metabolite
	97SL1387	Py	Anistatin
	97TA3067	NEt_3	Melodorinol
	98TL7747	DMAP, NEt_3	Scletium alkaloid ((–)-mesembrine, (+)-sceleium A-4, (+)-tortuosamine, (+)-*N*-formyltortusamine)
Use of Tin Alkoxides			
2	92T393	Bu_2SnO	Pyrrolizidine alkaloid
	94BCJ1990	Bu_2SnO	Pyrrolizidine alkaloid
	94BCJ2345	Bu_3SnOMe	Pyrrolizidine alkaloid

Tab. 7-4 (continued)

Method	*Reference*	*Conditions*	*Target or related products*
Treatment with Diazomethane			
3.1	99 CL141		Zoanthamine alkaloid
Treatment with alkyl halides			
3.2	94JOC2773		Kainic acid
	97TL4697		Differanisole A
	98JOC2385		Phaseolinic acid

[a] DCC is employed if no other conditions are noted.
[b] The standard Mitsunobu reaction if no other conditions are noted.
[c] 2,4,6-Trichlorobenzoyl chloride is employed if no other conditions are noted.

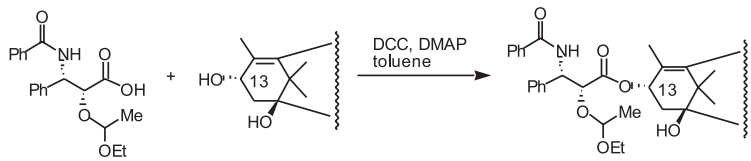
The synthesis of taxol and its analogues exemplifies how profoundly esterification contributes to this field. Although several total syntheses of taxol have been reported, the semi-synthesis starting from 10-deacetyl baccatin III is really practical.



Taxol

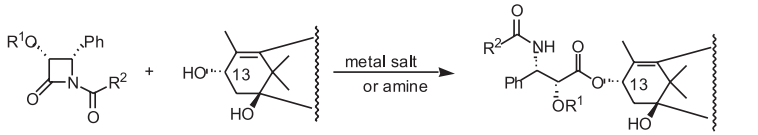
A key step in this strategy is the incorporation of the (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine side chain onto the highly sterically hindered 13-position, and the following methods have been reported.

(i) Direct coupling between 10-deacetyl baccatin III and (2*R*,3*S*)-*N*-benzoyl-*O*-(1-ethoxyethyl)-3-phenylisoserine [88JACS5917, 92TL5185, 94CC2591, 94TL105]. The condensation of 7-triethylsilyl baccatin III is effected by use of di-2-pyridyl carbonate and DMAP, in 80% yield at 50% conversion or 60% yield at 85% conversion [88JACS5917]. In addition to the unsatisfactory yields, this approach suffers from epimerization at carbon 2′.



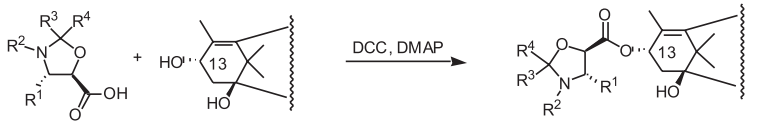
(ii) Use of β-lactam [91CA164568p, 92T6985, 92JMEC4230, 93JOC5028, 93TL3205, 93TL4149, 93TL6845, 94BMC335, 94BMC487, 94BMC1571, 94JACS1591, 94JOC6156, 94TL1665, 94NA(367)630, 94TL5543, 95AGC(E)1723, 95JACS624,

95JACS2409, 95JACS5228, 96JOC2664, 96TL6495, 97BMC1941, 98BMC273, 98BMC2977, 99BMC1189]. The drawbacks encountered in the above direct coupling technique are tackled by use of (3*R*,4*S*)-3-(1-ethoxy)ethoxy-4-phenyl-2-azetidinone [91CA(114)164568p, 92T6985]. The ring-opening is promoted by DMAP/pyridine or more efficiently by use of sodium salt of the baccatin III.



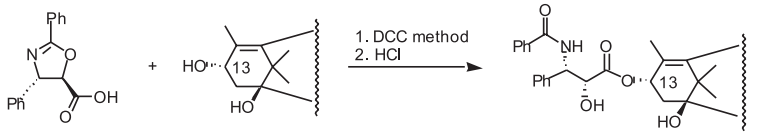
R^1= $CH(CH_3)OC_2H_5$, TBS, TES, EE
R^2= Ph, OCH_2Ph, O^tBu, *p*-ClC_6H_4, *p*-$N_3C_6H_4$

(iii) Use of 1,3-oxazolidine carboxylic acids [92TL5185, 93TL6049, 94CC2591, 94JOC1238, 94TL2349, 94TL3063, 94TL6839, 94TL4707, 94TL7893, 94TL9709, 94TL9713, 94TL9717, 95JOC2918, 96JACS919, 96TL1777, 98BMC427, 98CC1745, 98CL3]. Treatment of 2-substituted-1,3-oxazoline carboxylic acid with the C-7 triethylsilyl derivative of baccatin III in the presence of DCC/DMAP affords a 94% yield of the condensation product, which is transformed into taxol upon hydrolysis [94CC2591].

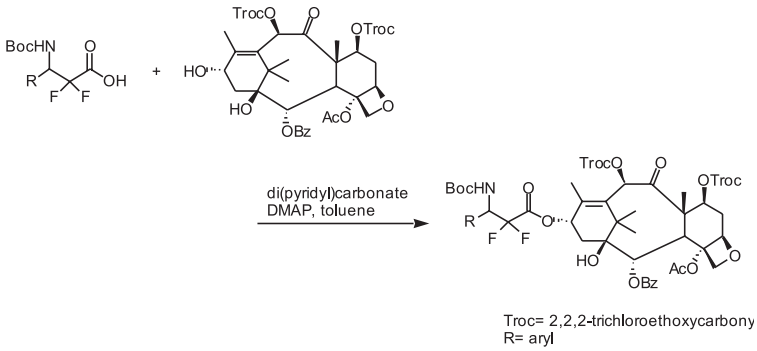


R^1= aryl
R^2= H, Boc, Bz
R^3=H, CH_3
R^4= CH_3, Ph, CCl_3, PMP, OPMP

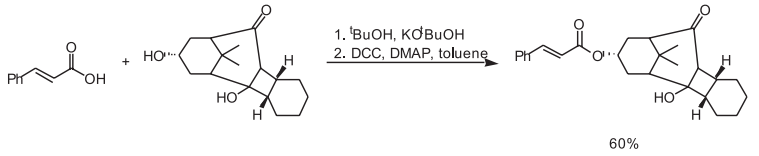
(iv) Use of oxazoline [94TL4483, 95TL8933, 97JOC4746]. 2-Substituted oxazolines are also useful protected side chains. Coupling between (4*S*,5*R*)-2,4-diphenyloxazoline-5-carboxylic acid and 7-(triethylsilyl)baccatin III in the presence of DCC/4-pyrrolidinopyridine provides the desired condensation product in 95% yield, and subsequent hydrolysis furnishes taxol in 75% yield [94TL4483]. The thioesters of the oxazolidine and oxazoline are attached to the baccatin nucleus through promotion with lithium bis(trimethylsilyl)amide [97JOC4746].



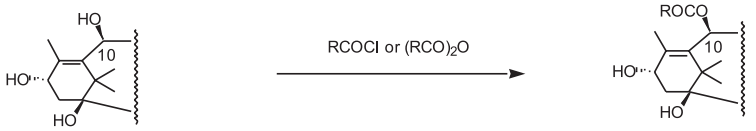
(v) Use of other side chain equivalents. Transesterification of ethyl benzoylacetate with protected baccatin III is carried out simply by heating at 90 °C (see Section 1.2.1; Scheme 1-65) [2000TL239], and the resulting ester is successfully transformed into taxol [2000TL243]. 2′,2′-Difluoro derivatives of docetaxel are obtained by use of 3-amino-2,2-difluoropropionic acids in the presence of dipyridyl carbonate/DMAP [97CPB1793].



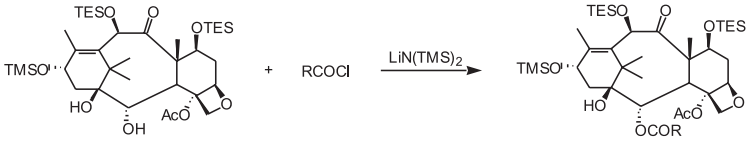
The less sterically demanding cinnamic acid is readily incorporated at the 13-position of a taxol analogue [91AGC(E)412].



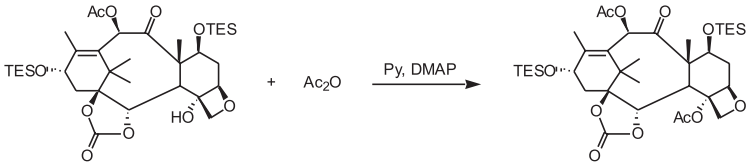
When 1-deacetyl baccatin III is utilized, it is necessary to discriminate the C-13 OH from the three other hydroxy groups. The selective acylation of C-10 OH is achieved by the following methods: with acid chloride [94TL5543, 93JOC2931], or with acid anhydride [98TL2883, 94CC295, 98TL6081, 2000TL243].



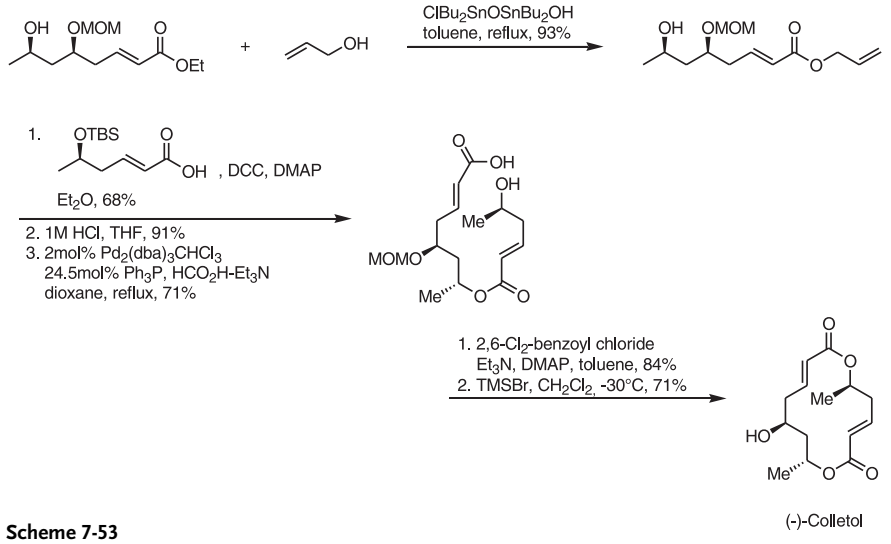
The C-2 hydroxy group is acylated through the action of acid halides in the presence of bis(trimethylsilyl)amide [98BKC1027].



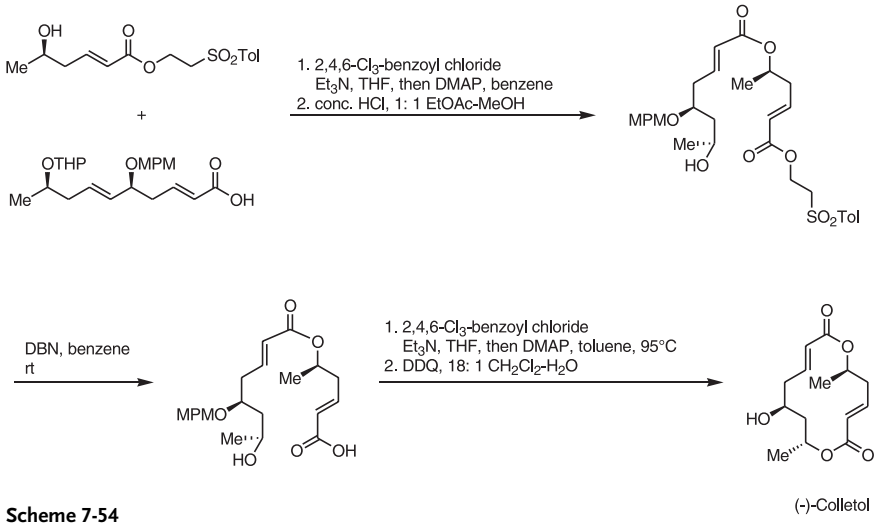
The tertiary alcohol at the C-4 position is acetylated with acetic anhydride in pyridine [96CL223].



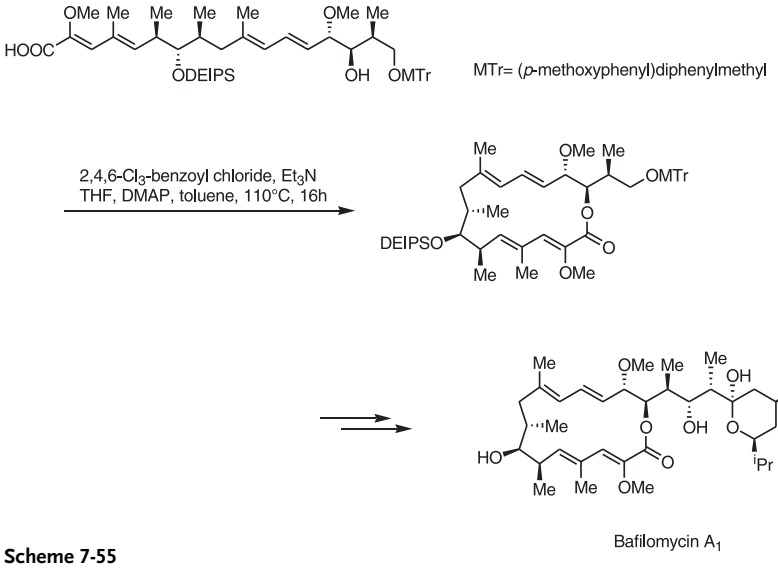
The next important application is seen in the synthesis of macrolides, because this is heavily dependent on esterification technology. The Yamaguchi technique (Section 1.3.5) serves quite well to this end. Two strategies are available for the final ring-closure in the synthesis of (–)-colletol. The first makes subtle use of various types of esterification technology (Scheme 7-53)[93CL1759]: (1) distannoxane-catalyzed transesterification, (2) DCC/DMAP condensation, and (3) the Yamaguchi technique with 2,6-dichlorobenzoyl chloride/Et_3N/DMAP. The final lactonization proceeds in 84% yield. The second strategy employs the Yamaguchi reaction twice for the ester formation (Scheme 7-54) [95TL4117]. The yield is 70% in the first esterification and 60% in the second. Total syntheses of bafilomycin A_1 (Scheme 7-55) [97JOC3271] and of epothilones A and B (Scheme 7-56) [97JACS7974] succeed through taking advantage of this approach.



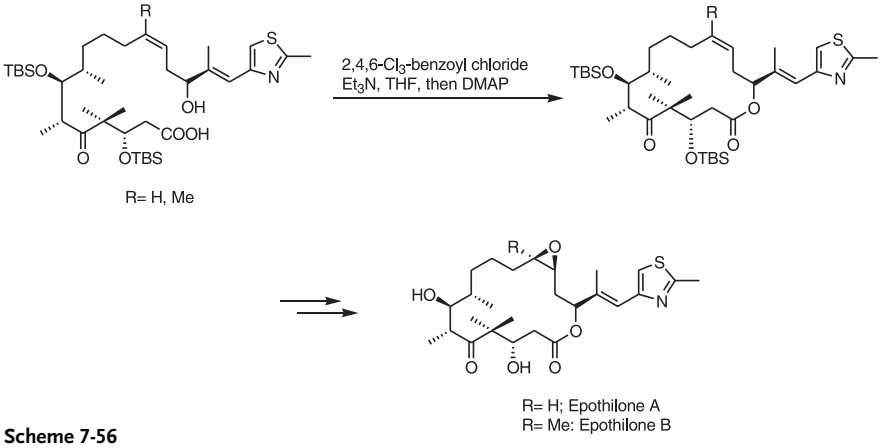
Scheme 7-53



Scheme 7-54

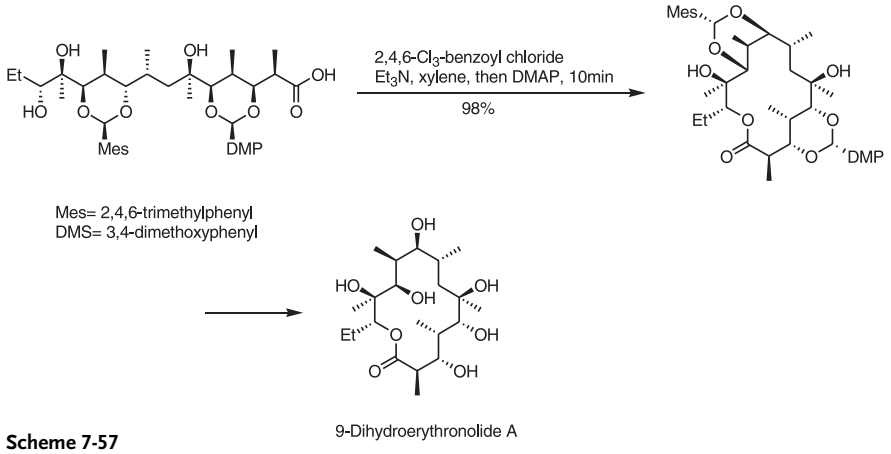


Scheme 7-55

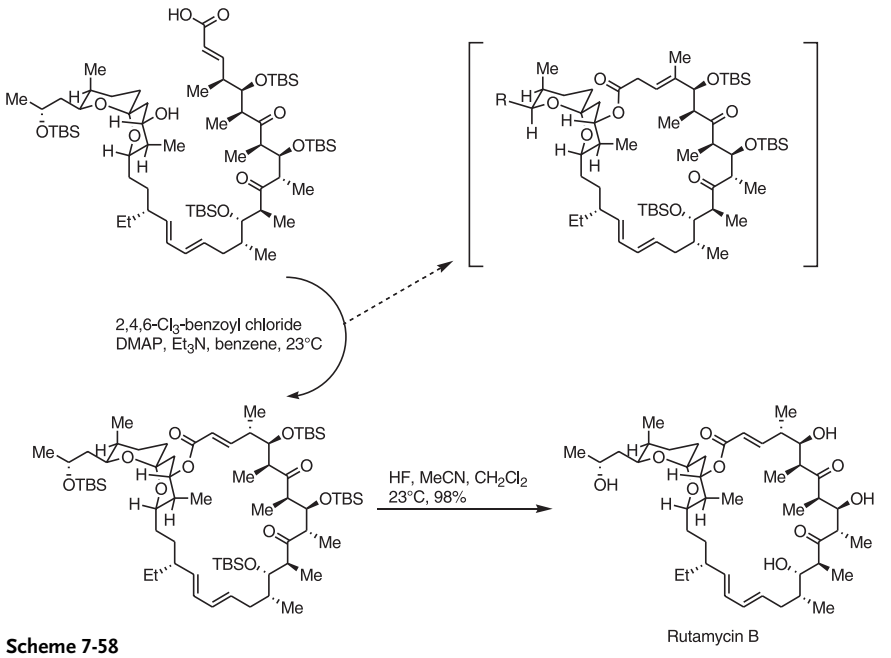


Scheme 7-56

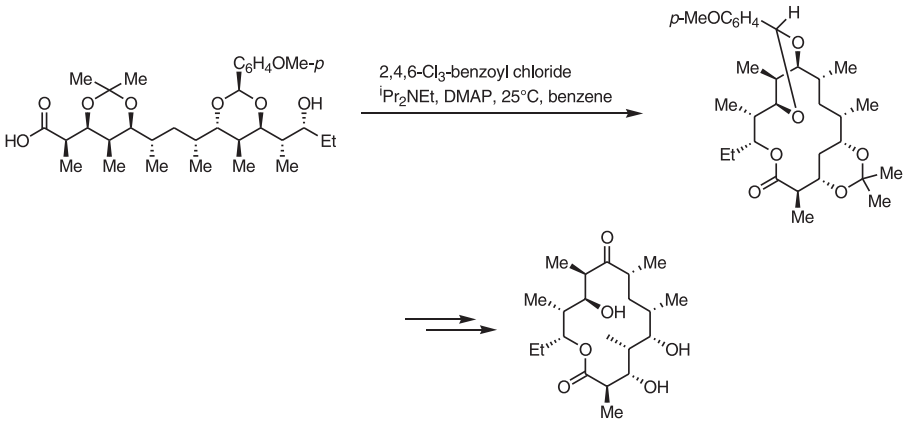
The Yamaguchi reaction is made easier when the substrates have a suitable conformation (Yonemitsu modification). Thus, protection of 1,3-diol units as sterically demanding benzylidene acetals, coupled with DMAP activation, allows lactonization at room temperature in quantitative yield in the synthesis of 9-dihydroerythronolide (Scheme 7-57) [90JOC7]. This new version finds successful applications in the synthesis of macrolide antibiotics. The rutamycin B skeleton is constructed in 86% yield (Scheme 7-58) [93JACS11446]. Notably, the deconjugated macrolide inevitably forms in other methods. *p*-Methoxybenzylidene acetalization results in smooth lactonization in the synthesis of 6-deoxyerythronolide B (Scheme 7-59) [97TL53].



Scheme 7-57

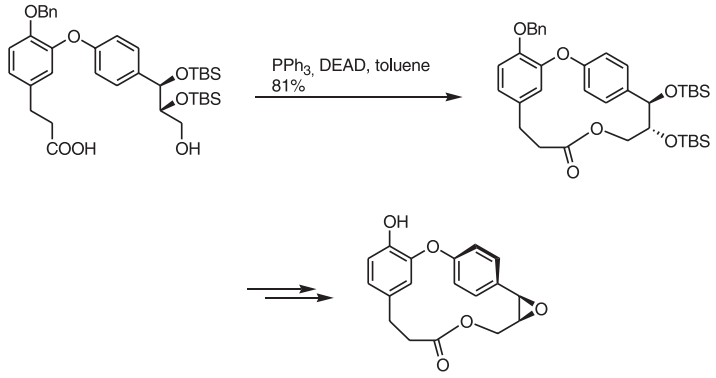


Scheme 7-58



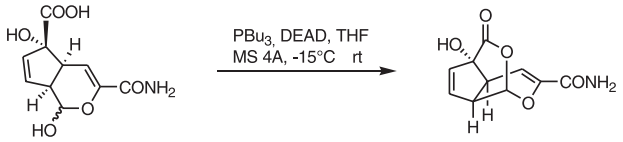
Scheme 7-59

The Mitsunobu reaction (Section 1.1.5) is useful for macrolide synthesis as well. The key intermediate for combresstatins D is constructed under the standard Mitsunobu conditions (Scheme 7-60) [94TL4409, 98CEJ33]. The synthesis of (–)-echinosporin requires modified conditions (Scheme 7-61) [92JACS2567]. Of various phosphines, tributylphosphine is the best when coupled with diethyl azodicarboxylate at –15 °C. Dimerization of hydroxy acid is utilized for the synthesis of (–)-pyrenophorin (Scheme 7-62) [94CL1083]. In this route, the Mitsunobu reaction is employed twice, for the synthesis of secondary acetate and for the final lactonization. In contrast, the analogous direct dimerization strategy furnishes only an 11% yield of (–)-vermiculine, owing to the concomitant formation of the trimer and tetramer. Use of the stepwise method instead gives rise to a better outcome (Scheme 7-63) [94TL8237]. Under the Mitsunobu conditions, the first coupling is between hydroxy ester and silyloxy carboxylic acid, while the second lactonization, after protection of the masked functions, provides the diolide in 62% yield.



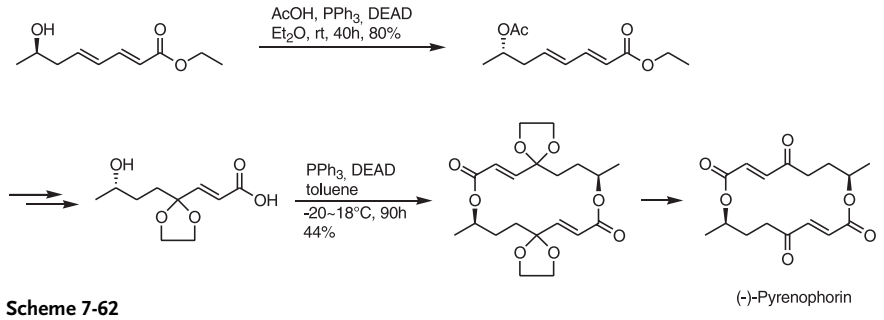
Combretastin D-1

Scheme 7-60



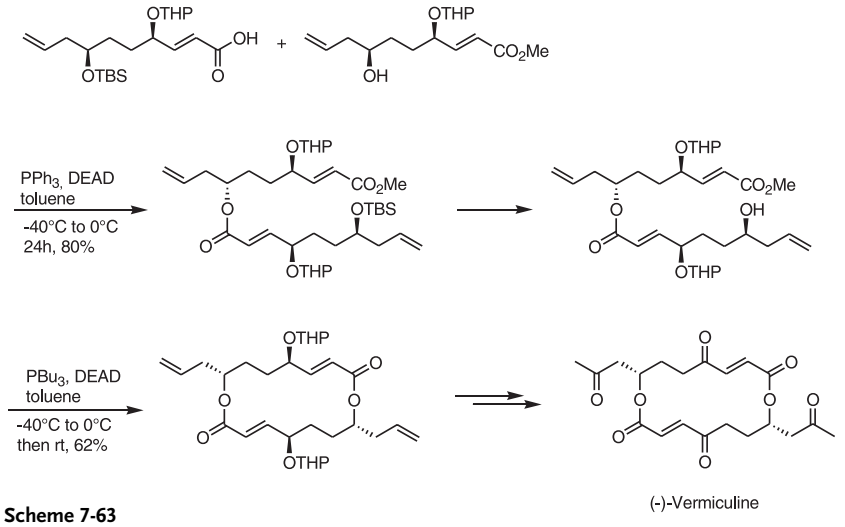
(-)-Echinosporin (XK-213)

Scheme 7-61



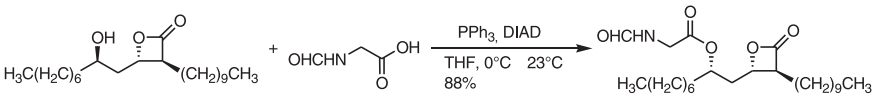
(-)-Pyrenophorin

Scheme 7-62



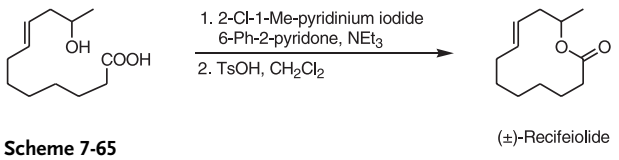
Scheme 7-63

Needless to say, the Mitsunobu procedure is also applicable to intermolecular esterification. One example is provided in the synthesis of (–)-panclicin D (Scheme 7-64) [97JOC4].

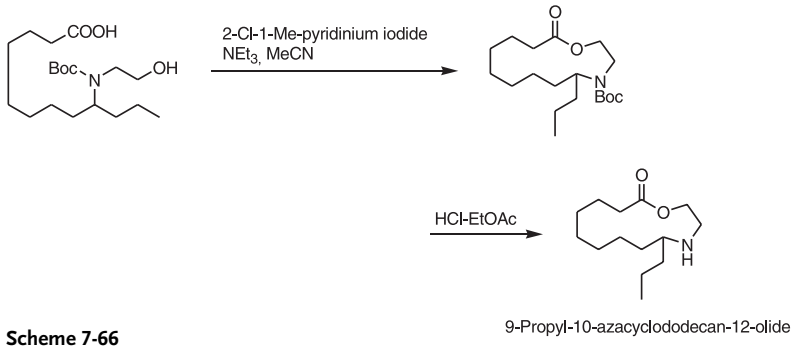


Scheme 7-64

Lactonization is effected by the Mukaiyama technique with 2-chloro-1-methylpyridinium iodide (Section 1.1.6). (+)-Recifeiolide is obtained in high yield when 6-phenyl-2-pyridone and Et_3N are used as activators (Scheme 7-65) [77CL959]. 9-Propyl-10-azacyclododecan-12-olide, a minor component of the defensive secretion of the Mexican bean, is synthesized from the corresponding hydroxy acid (Scheme 7-66) [96TL2141].

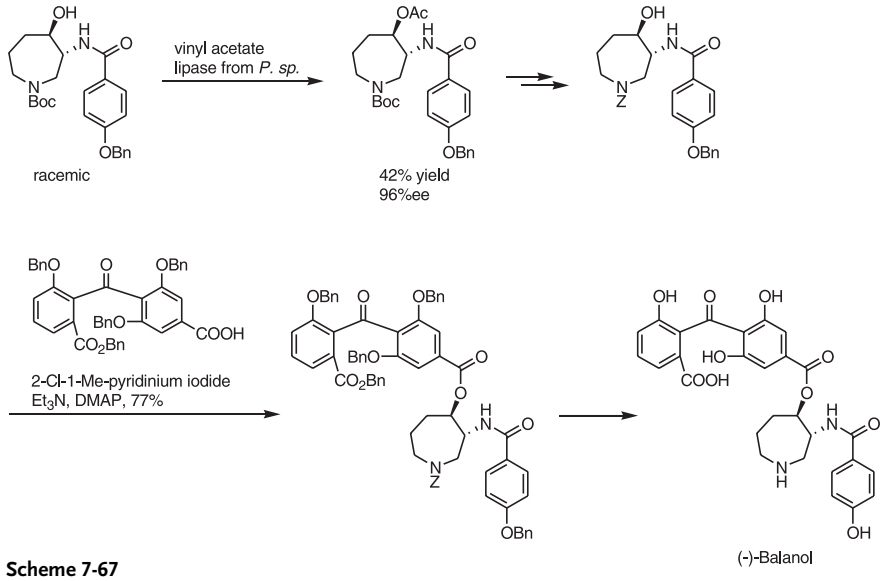


Scheme 7-65



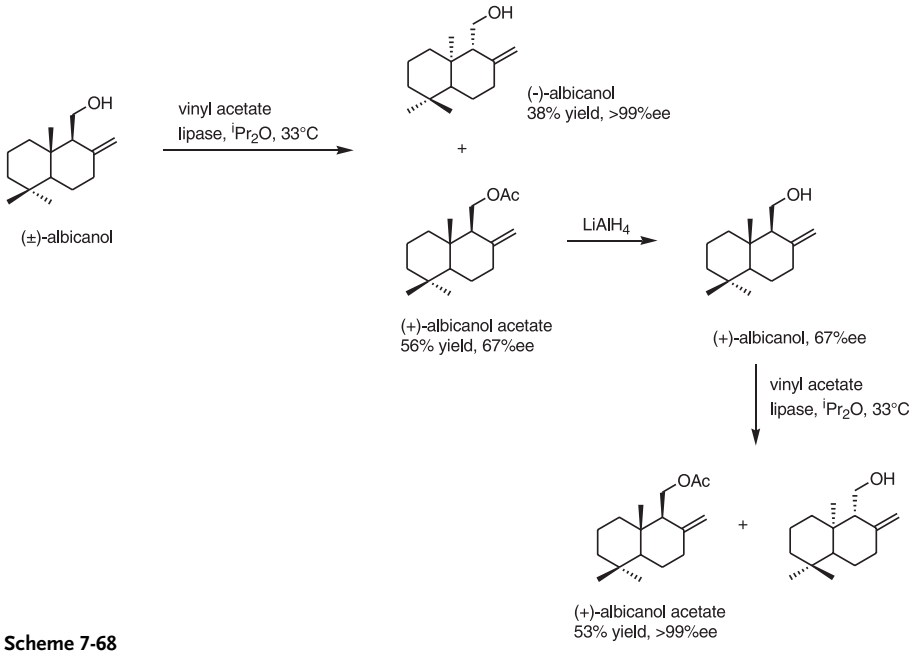
Scheme 7-66

The intermolecular version is utilized for the synthesis of (–)-balanol (Scheme 7-67) [98JOC4397].



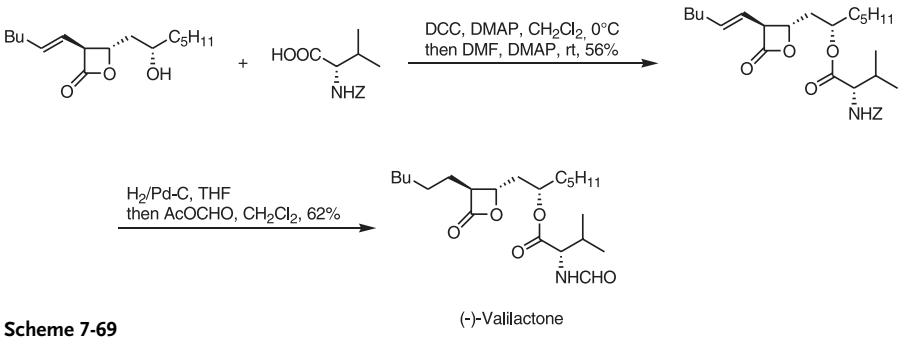
Scheme 7-67

In the above process, enzymatic kinetic resolution is invoked for preparation of the enantiopure hydroazepine. Another example of enzymatic kinetic resolution in natural product synthesis is illustrated in Scheme 7-68 [2000TA1375]. Racemic albicanol is transformed into enantiopure form. In addition, (–)-drimenol, (–)-drimenin, and (–)-ambrox are obtained by similar procedures.

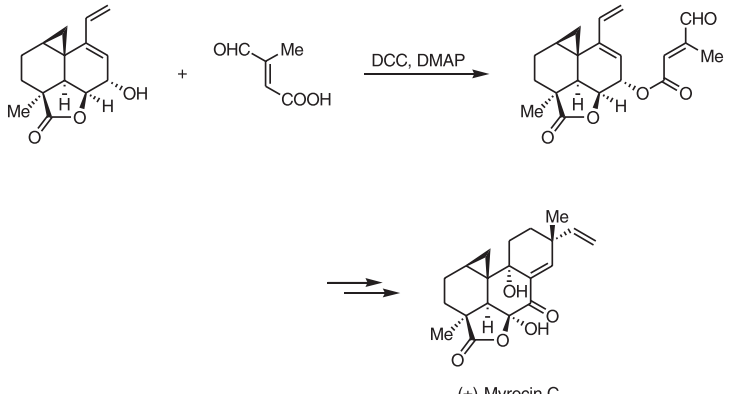


Scheme 7-68

DCC-promoted condensation (Section 1.1.4) is used in the synthesis of (–)-valilactone (Scheme 7-69) [91T9929] and (+)-myrocin C (Scheme 7-70) [94JACS11213]. EDC is the reagent of choice for preparation of a precursor for an olefin metathesis approach to epothilone A and its analogues (Scheme 7-71) [97JACS7960].

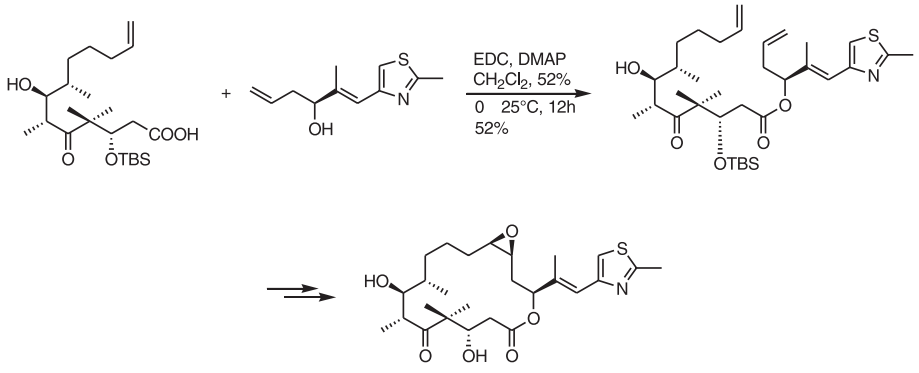


Scheme 7-69



(±)-Myrocin C

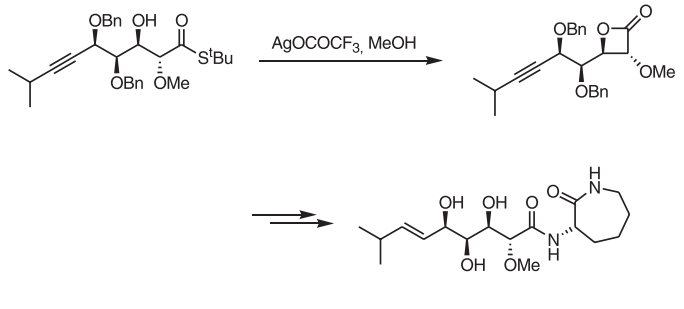
Scheme 7-70



Epothilone A

Scheme 7-71

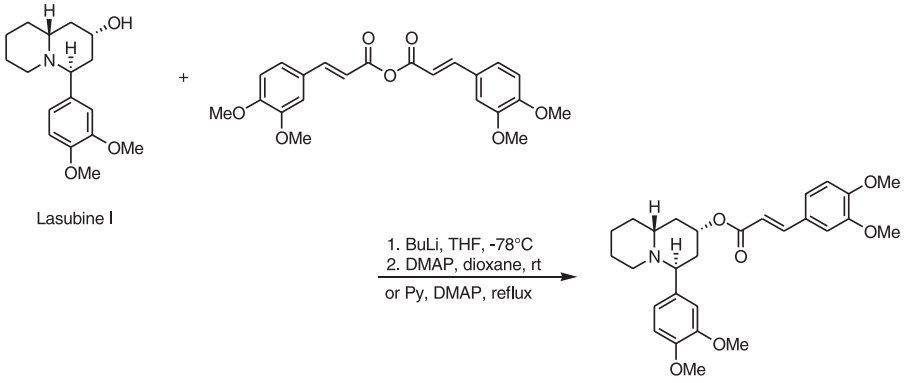
Masamune's thioester procedure (Section 1.4.2.2) effects β-lactone formation, which constitutes a key step in the total synthesis of (+)-bengamide E (Scheme 7-72) [95JCS(P1)2849].



(+)-Bengamide E

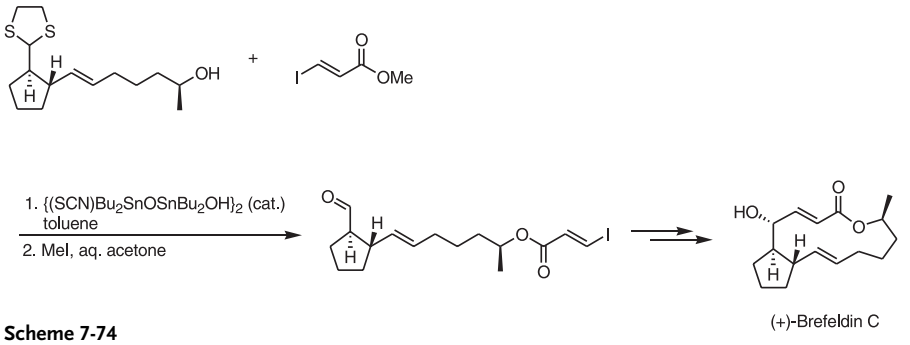
Scheme 7-72

3,4-Dimethoxycinnamic anhydride is a useful acylating agent in the synthesis of (+)- and (+)-subcosine I (Scheme 7-73) [4JOC1909, 92JOC5807].

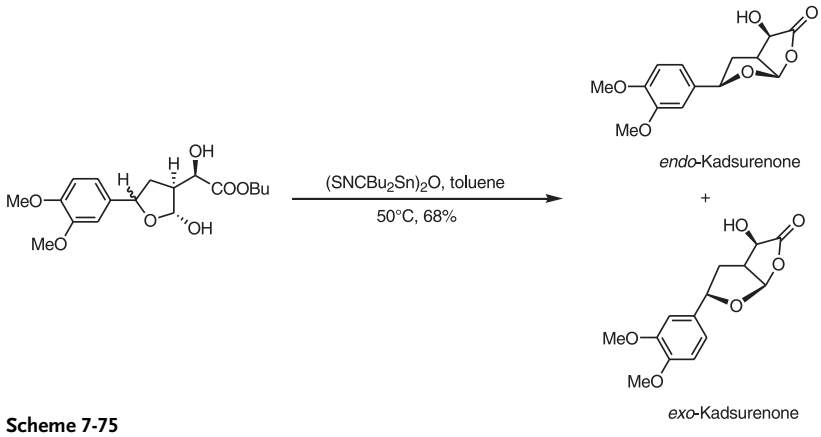


Scheme 7-73

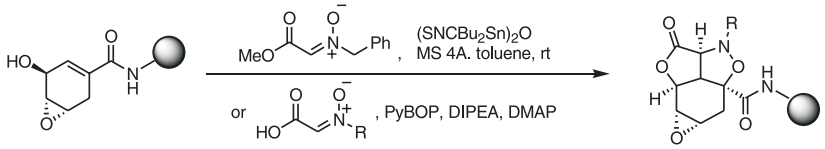
Distannoxanes are extremely mild catalysts, with the aid of which transesterification can proceed under neutral conditions to enable the use of labile substrates. Highly sensitive methyl β-iodoacrylate successfully underwent distannoxane-catalyzed transesterification in synthetic studies relating to the brefeldin series (Scheme 7-74) [88JACS5198], while no satisfactory results were obtained with other coupling agents. In the final step of the synthesis of kadsurenone, coupling between the lactol moiety and the butyl ester was achieved only with a distannoxane catalyst, to give a 1:1 mixture of readily separable bicyclic compounds isomeric at the benzylic carbon (Scheme 7-75) [88TL6689]. A tetracylic template for a library of small polycyclic molecules for use in chemical genetic assays is obtained by a tandem transesterification-cycloaddition reaction of nitrone and expoxycyclohexanol (Scheme 7-76) [99JACS9073]. The transesterification is catalyzed by distannoxane in solution, but the solid-phase reaction proceeds sluggishly. In this case, the use of *N,N*-diisopropylamine/DMAP affords satisfactory results.



Scheme 7-74



Scheme 7-75



PyBOP= benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
DIPEA= *N,N*-diisopropylethylamine

Scheme 7-76

8
Industrial Uses

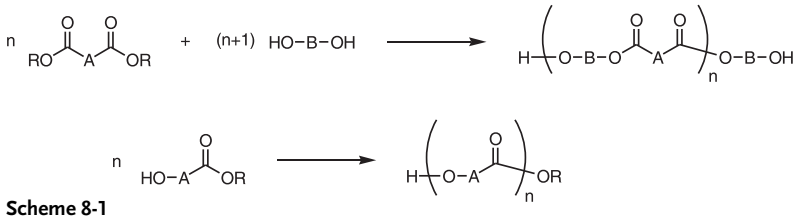
Esterification technology is utilized in a wide range of chemical industry and so it is not possible to cover all of them here. Moreover, many of the industrial processes are not fully disclosed and it is therefore not possible to delineate actual features precisely and correctly. Consequently, only representative examples among them are described in this chapter, so that the readers may obtain a brief overview on the practical utilization of esterification.

8.1
Polyesters

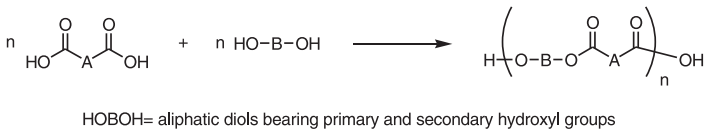
Polyesters have a long history, since the 19th century, and experienced extensive development in the 1920s. As the fundamental production technology is fully established and well known, just a brief sketch is given here. Polyesters can be prepared through an exchange reaction between ester and hydroxy groups, usually called alcoholysis (Scheme 8-1). Alcoholysis proceeds very slowly in the absence of catalysts, even at high temperatures. Of the many catalysts, the most effective are acetates of Pb(II), Pb(IV), Zn, Mg, Ca, Co, and Cd, oxides such as Sb_2O_3 and GeO_2, and Ti alkoxides. This process used to be of great commercial importance, but – on account of higher costs resulting from more expensive raw materials, higher energy consumption, and more expensive plants – the process actually employed at present is direct esterification. Most high-molecular-weight polyesters can be obtained by this process, from dicarboxylic acids and diols or from hydroxy acids at high temperature (Scheme 8-2). Reactions can take place at high temperatures (180~230 °C) even in the absence of added catalysts. Small amounts (0.1~0.5 wt%) of catalyst are necessary in order to increase the reaction rate significantly. Many catalysts are reported: strong Brønsted acids (H_2SO_4, TsOH are most popular), oxides or salts of heavy metal ions (acetates are often preferred because of their higher solubility), and organometallic compounds of Ti, Sn, Zr and Pb.

Esterification. Junzo Otera

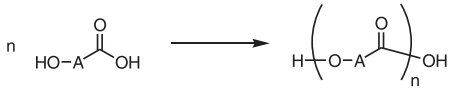
ISBN: 3-527-30490-8



Scheme 8-1

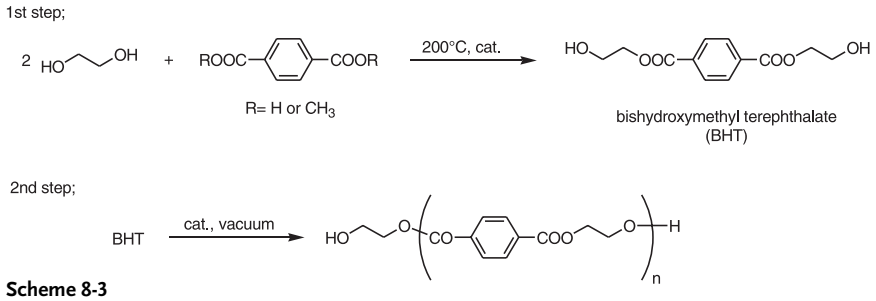


HOBOH= aliphatic diols bearing primary and secondary hydroxyl groups



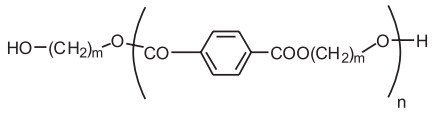
Scheme 8-2

Polyesters are used in a variety of fields: textile fibers, films, bottles, resins, plastics, etc. Notably, polyester fibers have since 1971 been the major material in synthetic fibers. The main component of polyester fibers is the condensation polymer between ethylene glycol and terephthalic acid (PET). This is synthesized in two steps: esterification or transesterification with terephthalic acid or dimethyl terephthalate followed by polycondensation conducted under high temperature and vacuum conditions (Scheme 8-3).



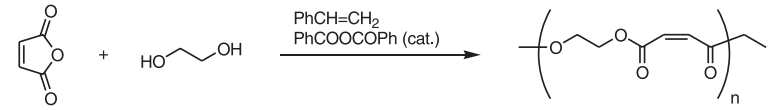
Scheme 8-3

Some other polyesters are also used as fibers; these include polytrimethylene terephthalate (PTT) and polybutylene terephthalate (PBT), in which the ethylene glycol in PET is replaced by 1,3-propanediol and 1,4-butanediol, respectively. PTT fibers are very attractive, because the raw material (1,3-propanediol) is cheap and they have shape-stability, softness, and elongation-recovery. PBT fibers are easy to dye and have good elasticity.



m= 3; PTT
m= 4; PBT

Polyesters are used as materials in plastics as well. Unsaturated polyesters are produced from diacids such as maleic acid or fumaric acid and diols such as ethylene glycol. Styrene as a vinyl monomer and benzoyl peroxide as catalyst are added. Cross-linking and hardening occur at room temperature or above (Scheme 8-4). Unsaturated polyesters reinforced by glass fibers are used for pipes, helmets, car bodies, chairs, etc. Saturated polyesters such as PET and PBT are also used as plastics in electronics devices, bumpers, etc.



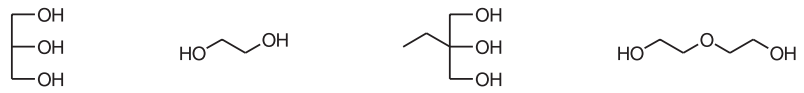
maleic acid

Scheme 8-4

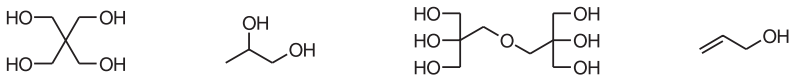
Polycondensates between polyhydric alcohols and polybasic carboxylic acids are known as alkyd resins. A variety of alcohols and acids, as shown below, are combined and the resulting polycondensates are further treated with other oils or fatty acids. The properties of the resins are modified by this post-treatment. Drying oil resins, which are obtained by treatment with soybean oil at temperatures higher than 200 °C, are used for baking paint and air-drying coatings. Non-drying oil resins are obtained by treatment with castor oil or other non-drying fatty acids. These resins do not dry at room temperature and are used as components of thermosetting paints.

Another important facet of polyesters is their potential for biodegradable polymers, and some of these have already been brought onto the market. These polymers find a wide spectrum of applications. Medical uses are most popular: prosthetic de-

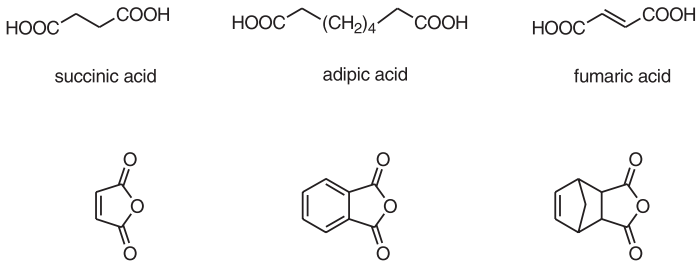
[Alcohols]



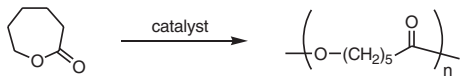
glycerol | ethylene glycol | trimethylol propane | diethylene glycol



[Acids]



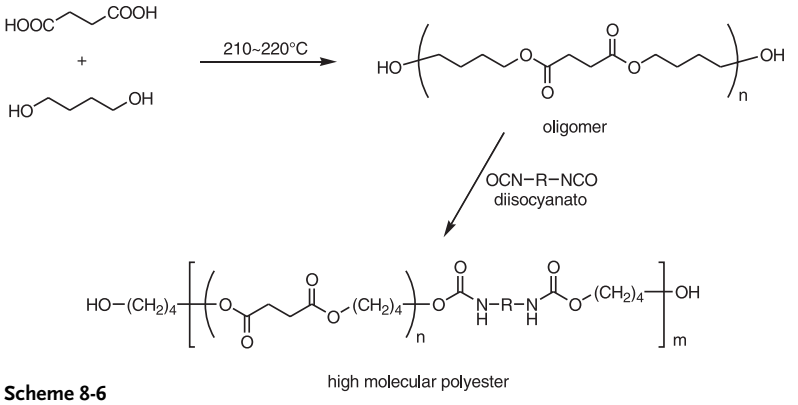
vices such as bone plates and orthopedic pins and screws, artificial blood vessels, intravascular stents, nerve guides, surgical suture, and drug delivery systems for controlled release. In addition to such specialist applications, biodegradable polymers are also of great promise for disposable plastics in general use, and their market should grow rapidly with the increasing demand for ecomaterials. The physical or mechanical properties of these polymers therefore need to be improved as soon as possible to satisfy the requirements for commodity thermoplastics used in packaging and consumer goods. The first biopolymer to be commercialized was poly(3-hydroxybutyrate), while a copolymer with 3-hydroxyvalerate is also produced (Zeneca). Polycaprolactone, obtained by ring-opening of ε-caprolactone, is available both from UCC and from Daicel (Scheme 8-5). This polymer is used in the form of film or fiber, and its melting point is fairly low (60 °C). This is a fault in terms of physical properties but an advantage in terms of processability, since it is easily molded with hot water.



ε-caprolactone polycaprolactone

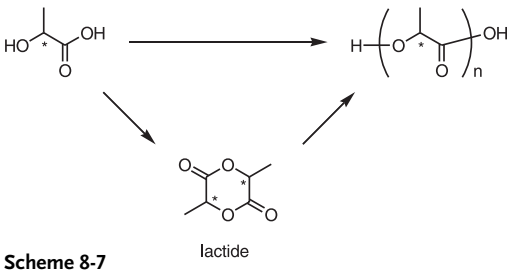
Scheme 8-5

The condensation polymer of succinic acid and 1,4-butenediol cured with diisocyanate (Showa High Polymer) is also biodegradable (Scheme 8-6). This polymer possesses a high melting point (110 °C) as well as impact strength.



Scheme 8-6

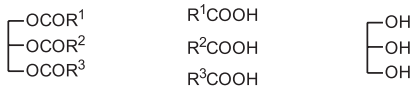
Despite these precedents, the material that has recently received the more intensive attention is poly(lactic acid). Several companies (Cargill Dow Polymers, Mitsui Chemical, Shimatdzu, etc.) are setting out to commercialize this polymer. Poly(L-lactic acid) exhibits high biodegradability, and the L-lactic acid monomer is produced in large quantity by fermentation of starch from corn or sugar beet. Polyesters do not exhibit satisfactory physical properties until the molecular weight is at least 25,000, but it is not easy to exceed this requirement by direct condensation of the monomer as the removal of the water formed in the last stages of the condensation is difficult due to the increased viscosity, preventing further increase in the molecular weight. The polymer is thus usually produced by ring-opening of the lactide, which is crystalline and easy to free from water (Scheme 8-7). This method is not straightforward, however, and the costs are rather high. More economical direct condensation has been achieved by the Mitsui Chemical group. In order to improve the physical properties, various copolymers with glycolide, β-propiolactone, γ-butyrolactone, δ-valerolactone, and ε-caprolactone are available.



Scheme 8-7

8.2
Oils and Fats

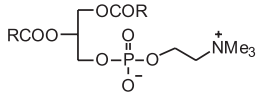
Oils and fats are triglycerides: triesters of glycerin with fatty acids. They are obtained from plants and animal products and are used in vast fields such as shortening, margarine, lard, plasticizers, materials for toilet and laundry soap, lubricating oil, and so on. Although natural oils and fats are very useful in their original forms, chemical modifications such as ester exchange and hydrogenation increase their utility further. Fatty acid esters, obtained by transesterification of oils and fats with alcohols, are also particularly important as surfactants for soaps, as food emulsifiers including foaming agents and antifoamers, and as dispersing agents.



oils and fats | fatty acids | glycerol

8.2.1
Food Emulsifiers

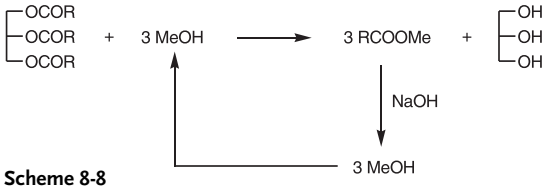
Acylglycerols, mixtures of mono- and diacylglycerols, are produced by transesterification of glycerol and fatty acids or oils. They are used as oil-in-water or water-in-oil emulsions, and as antifoamers in bread and tofu. Fatty acid esters of polyglycerols are produced by transesterification of polyglycerol of a degree of polymerization of less than 10 with fatty acids, and give rise to emulsification at high salt levels or low pH values. Organic acid esters of monoacylglycerols are produced by esterification of the remaining hydroxyls in monoacylglycerols with organic acids such as acetic, lactic, citric, tartaric, and succinic acids. They are used in chewing gums and bread. Sucrose esters of fatty acids (sugar esters) are used in milk products and beverages. Sorbitan fatty acid esters, which are non-ionic surfactants, are produced by treatment of solbitol with fatty acids such as lauric, palmitic, stearic, or oleic acids. Propylene glycol esters serve for improvement of properties of oils and fats. Lecithin (1,2-diacyl-*sn*-glycerol 3-phosphocholine) is a phospholipid present in plants, animals, and yeast. Lecithin from soybeans is mainly used for emulsification of milk products and reduction of viscosity in chocolates.



Lecithin

8.2.2
Soaps

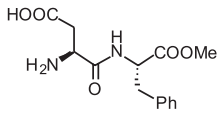
Soaps are alkali salts of fatty acids, which are known and used as anionic surfactants. They are produced by several methods, one of which includes transesterification. Oils and fats are first transesterified to provide methyl esters of fatty acids, and these are then subjected to saponification to afford alkali salts of fatty acids and methanol (Scheme 8-8). Base catalysts such as NaOMe and NaOH (0.2~2.0%) are used at relatively low temperatures (50 °C~90 °C); methanol can be recycled. This method has the following advantages: 1) purification is possible through transesterification, 2) the oils and fats deteriorate less, because the reaction is performed at low temperature, and 3) glycerol can be recovered in high concentrations.



Scheme 8-8

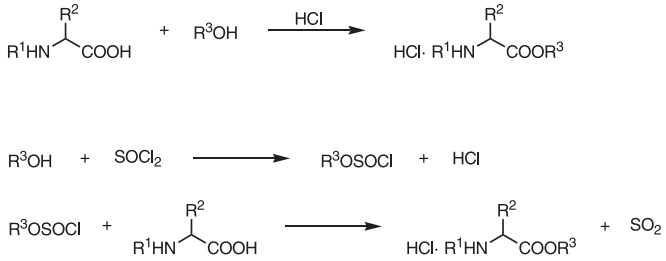
8.3
Amino Acid Esters

Amino acid esters are utilized in various fields such as cosmetics, toiletries, flavor substances, surfactants, fungicides, etc. Of particular importance is α-L-aspartyl-L-phenylalanine methyl ester, a sweetener known as Aspartame.



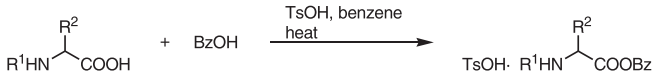
Aspartame

Methyl or ethyl esters are produced by treatment of a suspension of amino acids in methanol or ethanol with HCl or $SOCl_2$ (Scheme 8-9). The latter approach is advantageous in that the reaction proceeds at lower temperatures and does not require the use of HCl gas. The product esters are isolated as HCl salts, the free esters being unstable. In cases in which the HCl salts are hygroscopic and crystallization is difficult, *p*-toluenesulfonic acid is frequently employed instead.



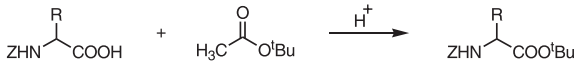
Scheme 8-9

The corresponding benzyl and *p*-nitrobenzyl esters are obtained as *p*-toluenesulfonic acid salts by heating of mixtures of amino acid, the benzyl alcohol, and *p*-toluenesulfonic acid in benzene (Scheme 8-10), while DCC-assisted coupling between Z-protected amino acids and *p*-methoxybenzyl alcohol is used for *p*-methoxybenzyl esters.



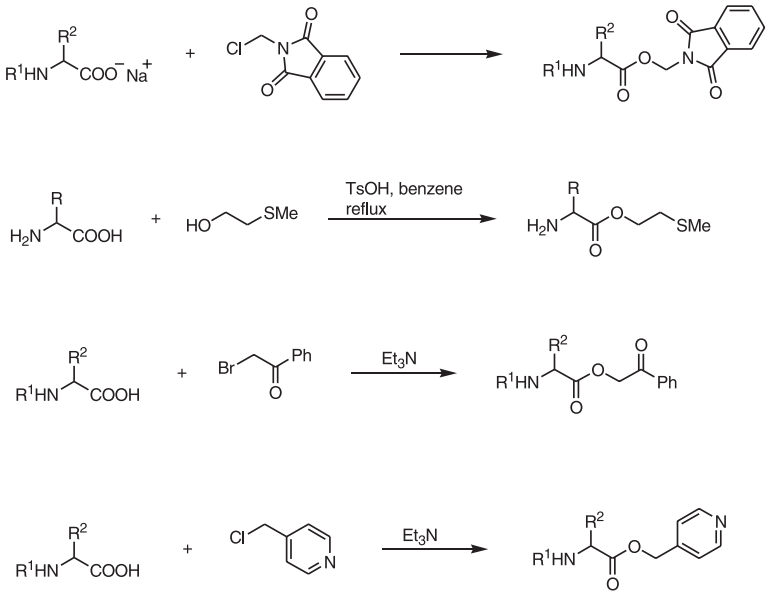
Scheme 8-10

The general way to produce *tert*-butyl esters is by treatment of *N*-protected amino acids with isobutene in the presence of H_2SO_4. Alternatively, the ester-interchange reaction between amino acid and *tert*-butyl acetate with H_2SO_4 or $HClO_4$ catalysis is also employed (Scheme 8-11).



Scheme 8-11

Other methods, as shown in Scheme 8-12, are also feasible for practical production of amino acid esters.

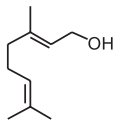


Scheme 8-12

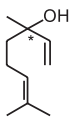
8.4
Flavoring Agents and Fragrances

Flavoring agents are used in perfumes, cosmetics, soaps, toothpastes, mouthwashes, medical products, bath products, air fresheners, confectionery, chewing gums, beverages, alcohol drinks, general foods, milk products, meat products, seasonings, aerosol products, insecticides, deodorants, paints, adhesive agents, rubbers, plastics, leather, printing inks, textile products, etc. Most are synthetic, and a great number of compounds are available.

Flavoring agents are classified into acyclic and cyclic compounds, depending on their structures, and also into another group: terpenes. Terpenes have a common $(C_5H_8)_n$ unit and are very important for flavoring. Monoterpenes $(C_5H_{10})_2$ and sesquiterpenes $(C_5H_{10})_3$ especially are present as odoriferous components in several plants, and useful materials for various synthetic flavoring agents. Geraniol, with a rose-like odor, is a useful material for the synthesis of citral or other esters. Linalool is also important for the synthesis of ester fragrances, which have different odors depending on the absolute structure of the linalool.



(*trans*)(*E*)-Geraniol



(-)(3*S*)- or (+)(3*R*)-Linalool

These esters are prepared by the methods demonstrated in previous sections (1.1, 1.2, 1.3, 1.4, and 3.1). The most popular processes are direct esterification between carboxylic acid and alcohol, or acylation of the alcohol with acid anhydride in the presence of a small amount of H_2SO_4 or TsOH at high temperature, toluene usually being used as solvent. If the reactants or the product esters are acid-sensitive, the esterification is conducted at higher temperatures without use of catalysts. Representative esters produced commercially in substantial amounts are listed as follows.

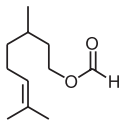
Ethyl formate (ethyl methanoate)

1) Uses: fruity flavor (peach, pineapple) for foods and butter, brandy and whisky (9.4~11ppm); insecticide.
2) Synthesis: usually prepared by esterification of ethyl alcohol and formic acid or by distillation of ethyl acetate and formic acid in the presence of concentrated H_2SO_4.
3) Organic/physical characteristics: colorless, mobile, flammable liquid; ether-like sweet odor.

Butyl formate (butyl methanoate)

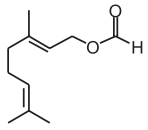
1) Uses: top note of flowery flavors; fruity flavor (2.9~11ppm); leathers.
2) Synthesis: esterification of 1-butanol with formic acid in the presence of concentrated H_2SO_4.
3) Organic/physical characteristics: colorless liquid; present in several natural products; ether- and rum-like odor, miscible in organic solvents.

Citronellyl formate (3,7-dimethyl-6-octen-1-yl formate)



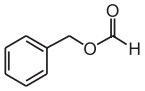
1) Uses: geranium, bergamot, citrus, lavender flavors for soap; fruity, honey flavor for foods (14~32ppm).
2) Synthesis: prepared from citronellol and formic acid.
3) Organic/physical characteristics: colorless oily liquid; present in geranium essential oil; strong, fruity, rose-like odor with a sweet, fruity taste; soluble in alcohol, diethyl phthalate, oils, insoluble in water, glycerol.

Geranyl formate



1) Uses: top note of rose, tuberose, neroli, citrus, lavender flavors; apple, apricot, peach flavor for foods (0.8~7.5ppm).
2) Synthesis: esterification of geraniol with formic acid.
3) Organic/physical characteristics: colorless to pale yellow liquid with rose-like odor; present in oil of geranium; insoluble in water.

Benzyl formate (benzyl methanoate)



1) Uses: flowery flavor (jasmine); cherry, apple, nut, strawberry flavor for foods (2.4~12ppm).
2) Synthesis: by heating a mixture of formic acetic anhydride and benzyl alcohol to 50°C; by passing a mixture of formic acid and excess benzyl alcohol over a catalyst at high temperature.
3) Organic/physical characteristics: colorless liquid; intense, pleasant, floral-fruity odor.

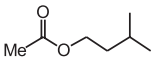
Ethyl acetate

1) Uses: berry, fruits flavor of foods and butter, mint (~1500ppm); industrial use (paints, etc.).
2) Synthesis: esterification of 50% ethanol with 10% acetic acid; or catalytic oxidation of acetaldehyde.
3) Organic/physical characteristics: colorless, mobile liquid; soluble in most organic solvents.

Isopropyl acetate

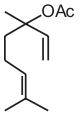
1) Uses: top note of citrus flavor.
2) Synthesis: by direct acetylation of isopropyl alcohol in the presence of various catalysts (concentrated H_2SO_4, diethyl sulfate, chlorosulfonic acid, BF_3).
3) Organic/physical characteristics: colorless liquid.

Isoamyl acetate (isopentyl acetate, 3-methyl-1-butyl acetate)



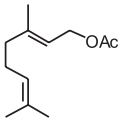
1) Uses: fruits (banana, pear, apple, berry) flavor for foods, candy, butter, coconut, cola, rum (28~2700ppm); flavor for paint and insecticide
2) Synthesis: by esterification of commercial isoamyl alcohol with acetic acid in the presence of H_2SO_4 at high temperature
3) Organic/physical characteristics: colorless liquid with banana-like odor; almost insoluble in water, soluble in ether and most common organic solvents.

Linalyl acetate (3,7-dimethyl-1,6-octadien-3-yl acetate)



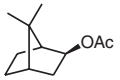
1) Uses: bergamot, lavender, clay sage, jasmine flavor.
2) Synthesis: almost direct acetylation of linalool with acetic anhydride.
3) Organic/physical characteristics: colorless liquid with bergamot-lavender odor; soluble in essential oils and most common organic solvents.

Geranyl acetate (*trans*-3,7-dimethyl-2,6-octadien-1-yl acetate)



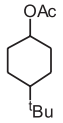
1) Uses: fragrance in soap; apple, apricot, banana, lemon, peach flavor for foods.
1) Synthesis: esterification of geraniol with acetic acid.
2) Organic/physical characteristics: colorless to pale yellow liquid; present in essential oils of lemongrass, neroli, Ceylon; pleasant, flowery odor; soluble in organic solvents.

Isobornyl acetate (*exo*-1,7,7-trimethylbicyclo[2.2.1]heptane-2-yl acetate)

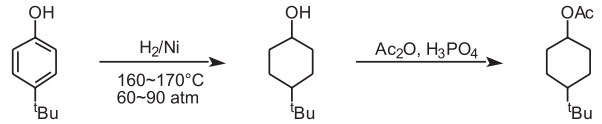


1) Uses: soap, eau de cologne, shampoo, bath product, air care; woody and herbal flavor for aromatherapy.
2) Synthesis: treatment of camphene with acetic acid, usually in the presence of catalyst; also by acetylation of isoborneol.
3) Organic/physical characteristics: clear, colorless liquid, tends to yellow slightly on aging; readily soluble in organic solvents.

***p-tert*-Butyl cyclohexyl acetate**

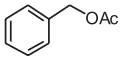


1) Uses: soap, shampoo, toiletries, because of cheapness and stability.
2) Synthesis:



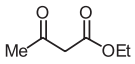
3) Organic/physical characteristics: colorless liquid with orris and woody odor.

Benzyl acetate (phenylmethyl acetate)



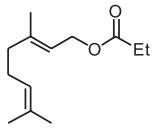
1) Uses: industrial uses such as anesthetics, printing inks, lacquers; 5600t produced annually worldwide.
2) Synthesis: prepared from benzyl chloride and sodium acetate in the presence of a small amount of Ac_2O and pyridine at 160~170 °C; treatment of benzyl chloride with excess acetic acid in the presence of NaOH at 85~145 °C.
3) Organic/physical characteristics: colorless liquid with flowery odor; present in jasmine, gardenia, hyacinth, apple, strawberry.

Ethyl acetoacetate



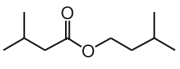
1) Uses: pesticide, medicine, chelate crosslinking agent, etc.
2) Synthesis: condensation of two molecules of ethyl acetate in the presence of sodium alkoxide; treatment of diketene with ethanol in the presence of acid or base catalyst.
3) Organic/physical characteristics: colorless liquid with ether-like odor.

Geranyl propionate (*trans*-3,7-dimethyl-2,6-octadien-1-yl propionate)



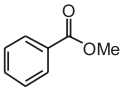
1) Uses: essential for geranium and rose flavors, also used for gardenia, bergamot flavor.
2) Synthesis: esterification of geraniol with propionic acid in the presence of catalyst.
3) Organic/physical characteristics: colorless liquid with fruity, rose-like odor.

Isoamyl isovalerate (isopentyl isovalerate, 3-methylbutyl 3-methylbutyrate)



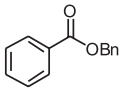
1) Uses: essential for apple flavor; flavor of wine, honey, walnut.
2) Synthesis: esterification of isoamyl alcohol with isovaleric acid.
3) Organic/physical characteristics: colorless liquid; sweet, apple flavor.

Methyl benzoate



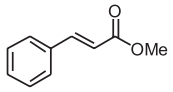
1) Uses: base flavor of floral fragrance such as ylang-ylang; soap, industrial flavoring agent.
2) Synthesis: direct esterification of methanol with benzoic acid.
3) Organic/physical characteristics: colorless liquid; present in essential oil of ylang-ylang; insoluble in water, miscible with alcohol and ether.

Benzyl benzoate



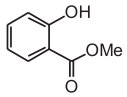
1) Uses: floral fragrance such as tuberose, ylang-ylang; solvent, medicinal agents, plasticizer.
2) Synthesis: treatment of benzyl chloride with sodium acetate in the presence of NEt_3; esterification of benzyl alcohol with benzoic acid; Cannizaro reaction of benzaldehyde in the presence of alkali.
3) Organic/physical characteristics: colorless liquid with light balsamic odor; present in oil of Tolu balsam and Peru balsam; insoluble in water or glycerol, soluble in alcohol, $CHCl_3$, and ether.

Methyl cinnamate (methyl 3-phenylpropanoate)



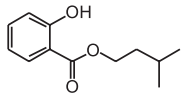
1) Uses: applied in carnation fragrance; soap, mouthwash.
2) Synthesis: direct esterification of ethanol with cinnamic acid in the presence of HCl; carboxymethylation of styrene.
3) Organic/physical characteristics: white to slightly yellow, crystalline solid; soluble in propylene glycol, mineral oils; insoluble in water.

Methyl salicylate (methyl 2-hydroxybenzoate)



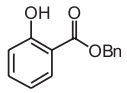
1) Uses: toothpastes, mouthwashes, medicinal agents.
2) Synthesis: direct esterification of methanol with salicylic acid.
3) Organic/physical characteristics: colorless liquid; found in oil of wintergreen

Isoamyl salicylate (Isopentyl salicylate)



1) Uses: clover, carnation fragrance; cosmetics, perfumes, soaps.
2) Synthesis: direct esterification of isoamyl alcohol with salicylic acid in the presence of catalyst.
3) Organic/physical characteristics: colorless liquid; strong herbaceous, persistent odor.

Benzyl salicylate (benzyl *o*-hydroxybenzoate)

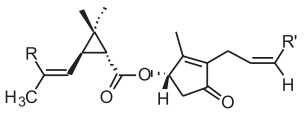


1) Uses: flowery fragrance (jasmine, carnation); solvent of musk ambrette flavor.
2) Synthesis; prepared from benzyl chloride and sodium salicylate; transesterification between methyl salicylate and benzyl alcohol (better yield).
3) Organic/physical characteristics: colorless, oily liquid; faint, sweet odor.

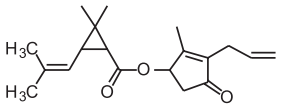
8.5 Pyrethroids

Pyrethroid esters, extracted from *Crysanthemum cinerariaefolium*, are natural insecticides with six congeners (pyrethrin I and II, cinerin I and II, jasmolin I and II). It is expensive to extract these esters from their natural sources, so many synthetic pyrethroid esters have been developed, as shown below. NRDC-156, NRDC-149, and fenvalerate, which have strong insecticidal properties and are used as pesticides, are also produced.

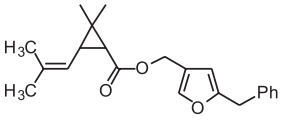
Pyrethroid ester components are produced in various ways. Some representative examples are described here. Classical methods are the azeotropic esterification of free acids and the reaction between acid chlorides and simple alcohols, but transes-



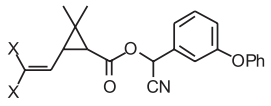
Pyrethrin I R= CH_3, R'= $CH{=}CH_2$
Pyrethrin II R= $COOCH_3$, R'= $CH{=}CH_2$
Cinerin I R= CH_3, R'= CH_3
Cinerin II R= $COOCH_3$, R'= CH_3
Jasmolin I R= CH_3, R'= CH_2CH_3
Jasmolin II R= CH_3, R'= CH_2CH_3



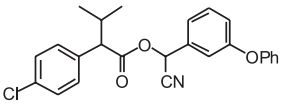
Allethrin



Resmethrin

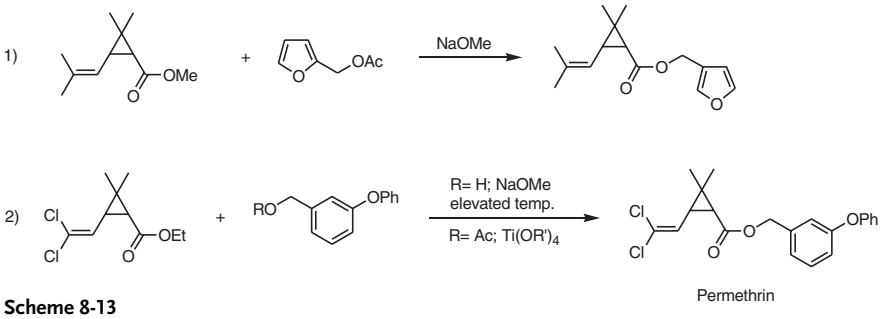


NRDC-156 X= Br
NRDC-149 X= Cl



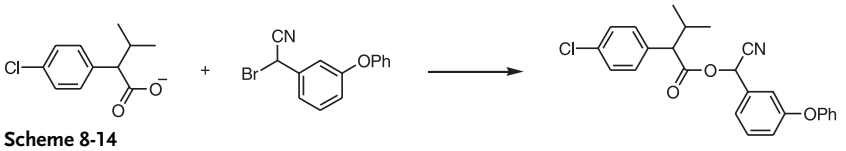
Fenvalerate

terification or ester interchange is also employable. Examples are: 1) treatment of methyl chrysanthemates with furfuryl acetate in the presence of NaOMe, and 2) treatment of permethric acid ethyl ester with *meta*-phenoxybenzyl alcohol in the presence of NaOMe at elevated temperatures or the ester-interchange of the acetate of the latter alcohol in the presence of titanium tetraalkoxide to give permethrin (Scheme 8-13).



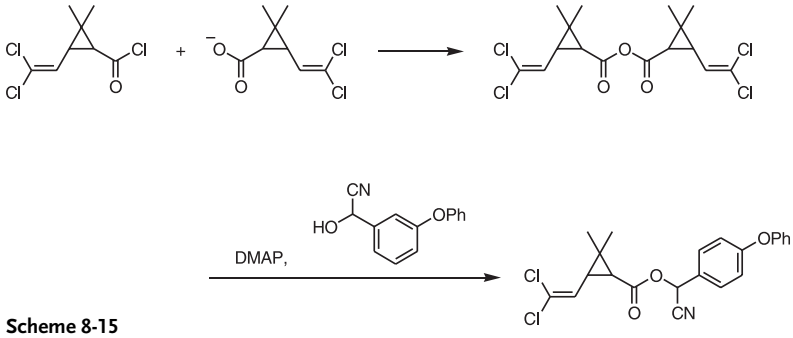
Scheme 8-13

Alkylation of acid salts is also usable (Scheme 8-14).

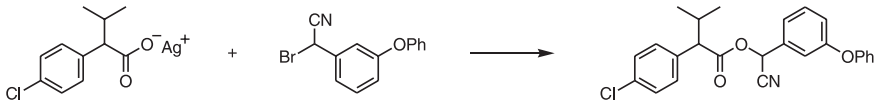


Scheme 8-14

NRDC-149 can be prepared by use of anhydride (Scheme 8-15) and active fenvalerate can be prepared by making use of the silver salt of the carboxylic acid (Scheme 8-16).



Scheme 8-15



Scheme 8-16

Epilogue

Esterification will no doubt continue to play important roles both in organic synthesis and in the chemical industry. However, further innovations need to be pursued in response to the demands arising from the continuing progress in organic synthesis. Selectivity in acylation is one such technology in need of advancement to higher levels. Chemoselective acylation of the hydroxy group in the presence of other functional groups is now achievable to a considerable degree, especially through the use of mild Lewis acid catalysis. On the other hand, selective acylation of one of a number of coexisting hydroxy groups, a highly useful manipulation in sugar and natural products chemistries, needs further improvement. At the current state of the art, it is not difficult to acylate less sterically demanding hydroxy groups selectively in the presence of bulkier groups but few effective methods for reversal of the selectivity are available. Differentiation between identical primary or secondary hydroxy groups at different sites is also a problem that has not been fully cleared up.

Enantioselectivity also needs further improvement. Enzymatic procedures are at present superior to non-enzymatic ones with regard both to kinetic resolution and to desymmetrization. However, screening of the best enzyme for a given target reaction is not so straightforward and so it is highly desirable to develop synthetic methods that can be used in a more general way to give better outcomes than the enzymatic procedures.

Not only esterification, but all chemical processes, should be as "green" as possible. Since the materials involved in esterification – esters, carboxylic acids, and alcohols – are mostly non-toxic, attention here usually has to be devoted solely to solvents. There are already some processes that do not use solvent, and it would be highly desirable to develop these lines further. The use of the theoretical amounts of reactants is also important. In most existing procedures, the equilibrium is shifted to the desired product side either by employment of one of the reactants in excess or by removal of one of the products. It is true that virtually no significant technical problems are encountered in these processes, but a lot of energy is wasted in these operations. It should be remembered that post-treatment processes such as separation, isolation, and purification of the products and recovery of catalysts in practical processes often take more time and energy than the reaction itself. Achievement of 100 % yields with equimolar amounts of reactants simplifies the separation steps and reduces redundancy. For this purpose, new reaction media are of great promise.

Esterification. Junzo Otera

ISBN: 3-527-30490-8

From the viewpoint of green chemistry, it also should be mentioned that polyesters appear destined to occupy key positions in plastics production, due to the biodegradability. If their mechanical properties were improved to satisfy demands for general uses, then polyesters should find a broad range of application. In particular, poly(L-lactic acid) is potentially the most attractive plastics commodity, as the monomer is available from biomass resources and biodegradation of the polymer completes recycling of the natural resources. It can reasonably be said that esterification technology has the potential to contribute a great deal to green chemistry.

Reference Code Index

ACH	*Acta Chim. Hung.*
ACR	*Acc. Chem. Res.*
ASC	*Adv. Synth. Catal.*
AGC	*Angew. Chem.*
AGC(E)	*Angew. Chem., Int. Ed. Engl.*
AJC	*Aust. J. Chem.*
AOMC	*Appl. Organomet. Chem.*
BCF	*Bull. Soc. Chim. Fr.*
BCJ	*Bull. Chem. Soc. Jpn.*
BKC	*Bull. Korean. Chem. Soc.*
BL	*Biotech. Lett.*
BMC	*Bioorg. Med. Chem. Lett.*
CA	*Chem. Abst.*
CAR	*Carbohydr. Res.*
CB	*Chem. Ber.*
CBC	*Chembiochem.*
CC	*J. Chem. Soc., Chem. Commun.*
CE	*Chem. Express*
CEJ	*Chem. Eur. J.*
CJC	*Can. J. Chem.*
CL	*Chem. Lett.*
CPB	*Chem. Pharm. Bull.*
CRA	*C. R. Acad. Sci.*
EJO	*Eur. J. Org. Chem.*
FU	*Fuel*
G	*Gazz. Chim. Ital.*
GC	*Green. Chem.*
H	*Heterocycles*
HCA	*Helv. Chim. Acta.*
IJC(B)	*Indian J. Chem., Sect. B*
IVY	*Izv. Vyssh. U. Zaked, Khim. Khim. Tekhnol.*
IZV	*Izv. Akad. Nauk. SSSR, Ser. Khim.*
JACS	*J. Am. Chem. Soc.*

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JCC	*J. Carbohydr. Chem.*
JCR(S)	*J. Chem. Res., Synop.*
JCS(D)	*J. Chem. Soc., Dalton Trans.*
JCS(P1)	*J. Chem. Soc., Perkin Trans. 1*
JFC	*J. Fluorine Chem.*
JHC	*J. Heterocycl. Chem.*
JIC	*J. Indian Chem. Soc.*
JIP	*J. Incl. Phenom.*
JMEC	*J. Med. Chem.*
JOC	*J. Org. Chem.*
JOM	*J. Organomet. Chem.*
JPS	*J. Pharm. Sci.*
LA	*Liebigs Ann. Chem.*
M	*Monatsh. Chem.*
NA	*Nature*
NN	*Nucleosides Nucleotides*
OL	*Org. Lett.*
OM	*Organometallics*
OPI	*Org. Prep. Proced. Int.*
OS	*Org. Synth.*
PC	*Polymer Commun.*
ROS	*Reagents for Org. Synth.*
S	*Synthesis*
SAC	*S. Afr. J. Chem.*
SC	*Synth. Commun.*
SCI	*Science*
SL	*Synlett*
T	*Tetrahedron*
TA	*Tetrahedron: Asymmetry*
TL	*Tetrahedron Lett.*
TS	*Top. Stereochem.*
ZN(B)	*Z. Naturforsch, B: Chem. Sci.*
ZPK	*Zh. Prikl. Khim. (St.-Peterburg)*

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Esterification. Junzo Otera

ISBN: 3-527-30490-8

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