Junzo Otera

Esterification

Methods, Reactions, and Applications

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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, extensive 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.

Contents

Part II Synthetic Applications

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 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.

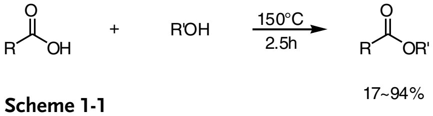
Part I
Methodology

1
Reaction of Alcohols with Carboxylic Acids and their Derivatives

1.1
Reaction with Carboxylic Acids

1.1.1
Without Activator

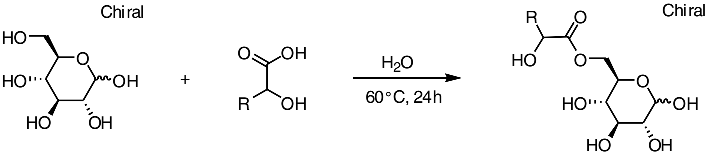
Although the direct reaction between alcohol and carboxylic acid is conventionally conducted under acid or base catalysis conditions, the catalyst-free reaction is more desirable. This requirement is satisfied when the reaction is carried out at high temperatures. A literature survey (refer to the database 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

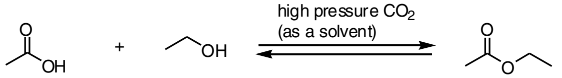
Interestingly, condensation between sugars and a-hydroxycarboxylic acids can be performed in water (Scheme 1-2) [99SC951]. The reaction takes place at 60 °C, regioselectively on the primary hydroxy groups of mannose, galactose, and glucose. The avoidance of any catalysts or additives allows the instant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



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.



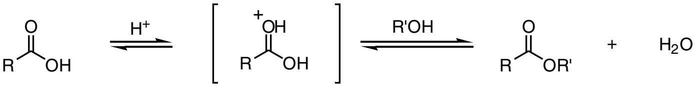
Scheme 1-3

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.

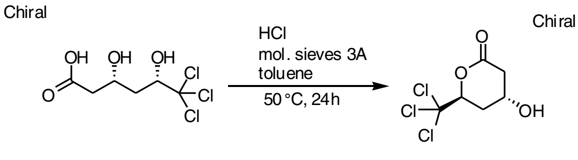
1.1.2
Acid Catalysts

1.1.2.1 Brønsted Acids

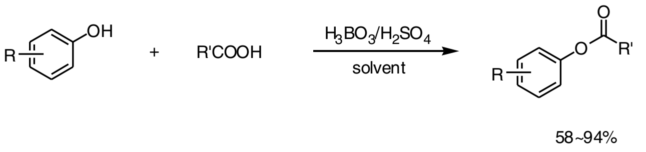
Since acid catalysis is one of the most popular methods for esterification, numerous papers are available (refer to the database disc). When the substrates are acid-resistant, the reaction is usually carried out in the presence of Brønsted acid such as HCl, HBr, H_2SO_4, $NaHSO_4$, $ClSO_3H$, NH_2SO_3H, 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

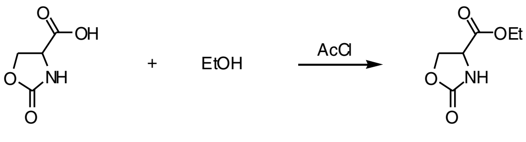
R'= aliphatic and aromatic

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].

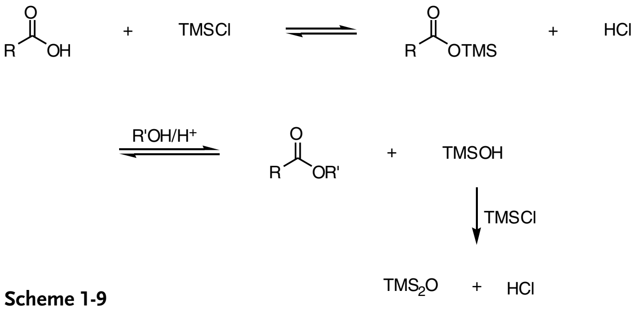
$$\mathrm{TMSCl} + \mathrm{R'OH} \longrightarrow \mathrm{TMSOR'} + \mathrm{HCl}$$

$$\mathrm{RCOOH} + \mathrm{TMSOR'} \xrightarrow{\mathrm{HCl}} \mathrm{RCOOR'} + \mathrm{TMSOH}$$

$$\mathrm{TMSOH} + \mathrm{R'OH} \xrightarrow{\mathrm{H^+}} \mathrm{TMSOR'} + \mathrm{H_2O}$$

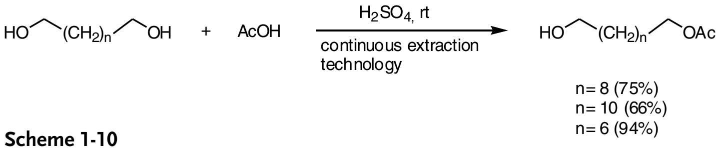
$$2\,\mathrm{TMSOH} \longrightarrow \mathrm{TMS_2O} + \mathrm{H_2O}$$

Scheme 1-8

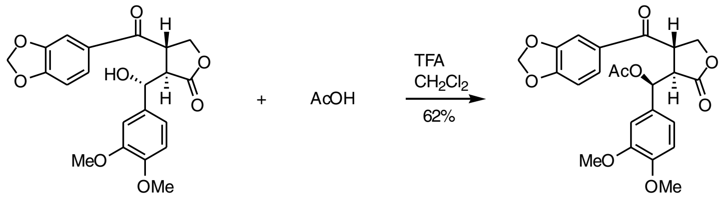


Scheme 1-9

Despite the rather harsh conditions, the Brùnsted 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

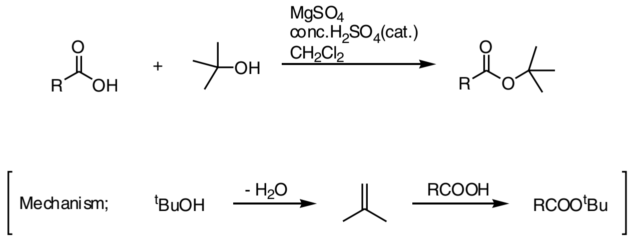


Scheme 1-11

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]

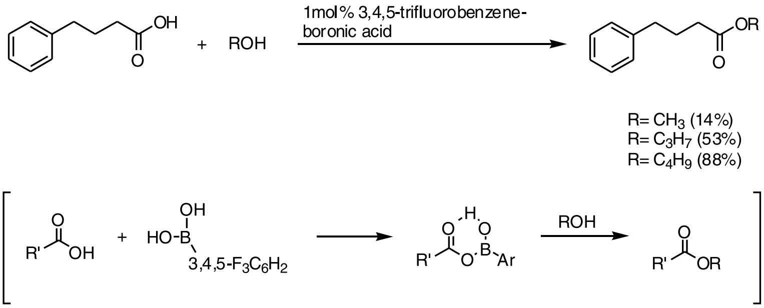
$BF_3\cdot OEt_2$ is the oldest Lewis acid to have been employed as an esterification catalyst since the BF_3/CH_3OH complex had been known to be used for conversion of simple carboxylic acids to their methyl esters prior to GLC analysis. Although excess $BF_3\cdot OEt_2$ (2–3 equiv.) and alcohol (>10 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.

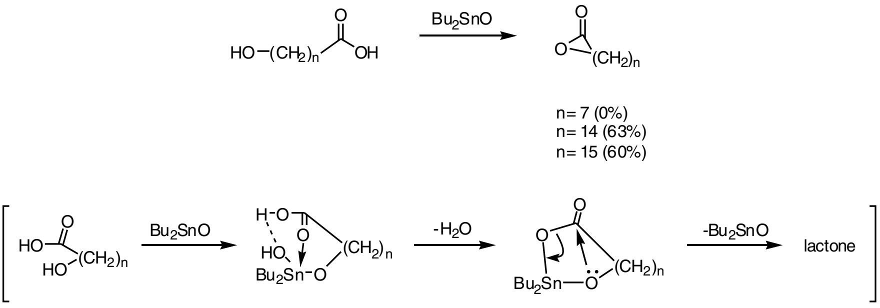
$AlCl_3$ is one of the most popular Lewis acids, but it is not employed in esterification because of its too strong acidity. However, polymer-supported $AlCl_3$ works as a milder catalyst for esterification although the yields are not always as high as those obtained by other methods. The advantage lies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

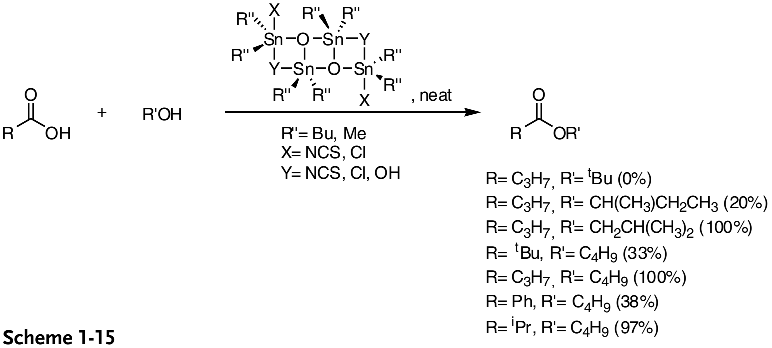
Preparation of hexadecanolide. A mixture of 16-hydroxyhexadecanoic acid (817.3 mg, 3.0 mmol) and dibutyltin oxide (74.7 mg, 0.3 mmol) is stirred in refluxing



Scheme 1-14

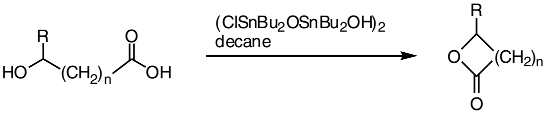
mesitylene (100 mL) for 19 h with use of a Dean–Stark apparatus for the continuous removal of water. Removal of the solvent in vacuo (40 °C/0.2 mmHg) yields a yellow oily residue, which is Kugelrohr distilled (60 °C/0.2 mmHg) to give 457.9 mg (60 %) of hexadecanolide.

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.



R= C_3H_7, R'= ^tBu (0%)
R= C_3H_7, R'= $CH(CH_3)CH_2CH_3$ (20%)
R= C_3H_7, R'= $CH_2CH(CH_3)_2$ (100%)
R= ^tBu, R'= C_4H_9 (33%)
R= C_3H_7, R'= C_4H_9 (100%)
R= Ph, R'= C_4H_9 (38%)
R= ^iPr, R'= C_4H_9 (97%)

Scheme 1-15



R= H, n= 14 (81%)
R= H, n= 13 (78%)
R= H, n= 10 (0%)
R= C_6H_{13}, n= 10 (90%)

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. $Fe(ClO_4)_3 \cdot 9H_2O$ 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 $NiCl_2 \cdot 6H_2O$ catalyst.

Experimental Procedure [98SC1159]

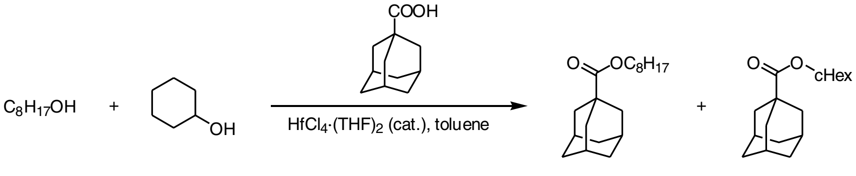
The Esterification of Adipic Acid with Ethanol in the presence of Ferric Sulfate: A mixture of adipic acid (14.5 g, 0.1 mol), absolute ethyl alcohol (18.5 g, 0.4 mol), dry benzene (35 mL), and commercial ferric sulfate (0.3 g) is placed in a flask equipped with an automatic water separator fitted with 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 $Cu(NO_3)_2 \cdot 3H_2O$ effects acetylation of alcohols in refluxing acetic acid. $Cu(OTf)_2$ is used for acetylation of alcohols, but to a somewhat limited extent.

$HfCl_4 \cdot 2THF$ 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

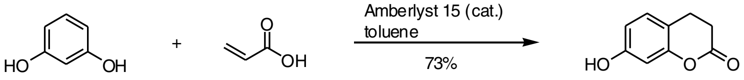
Nafion-H is the oldest solid acid to have been utilized as an esterification catalyst [78S929]. When a mixture of carboxylic acid and alcohol is allowed to flow over this catalyst at 95–125 °C, high yields of the corresponding esters are obtained with a contact time of ~5 sec. A batch reaction is also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

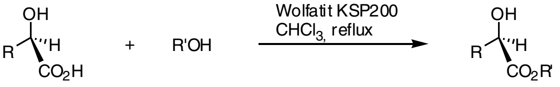
Experimental Procedure [93LA975]

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–AlO_3, and solid super acids [84CL1085].

$FeCl_3$ supported on salicylic resin

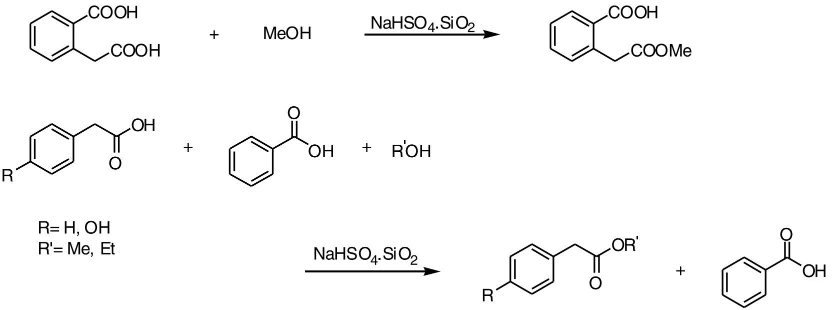
Azeotropic dehydration by heating of a mixture of carboxylic acid and alcohol (1 : 3 molar ratio) in benzene in the presence of the catalyst resin affords quantitative yields of esters [98SC1233]. The use of smaller amounts of alcohol gives rise to lower yields.

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

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°C.

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°C.

$$P_4O_{10} \quad + \quad 6\ ROH \longrightarrow 2\ (RO)P(O)(OH)_2 \quad + \quad 2\ (RO)_2P(O)(OH)$$

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