Part One Methodology

Esterification. Methods, Reactions, and Applications. 2nd Ed. J. Otera and J. Nishikido

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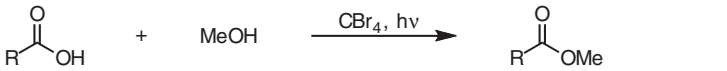
1
Reaction of Alcohols with Carboxylic Acids and their Derivatives

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. 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) [1]. The reaction is strongly influenced by the reaction temperature; the yield of propyl acetate is only 18% at 85 °C.



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= $CH{=}CHCH{=}CHCH_3$ (99%)

Scheme 1.1

Interestingly, condensation between sugars and α-hydroxycarboxylic acids can be performed in water (Scheme 1.2) [2]. 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.

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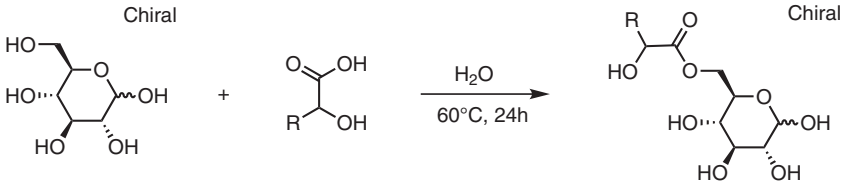
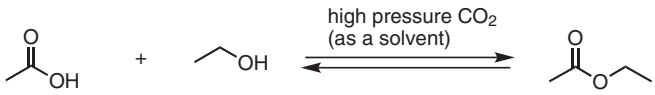
Experimental Procedure Scheme 1.2 [2] General procedure: A mixture of hydroxycarboxylic acid, carbohydrate, and water is heated to 60 °C in air for 24 h. To isolate the product as a pure compound for characterization, the reaction mixture is extracted twice with diisopropyl ether, the solvent is removed *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) [3]. The ester yield is 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.



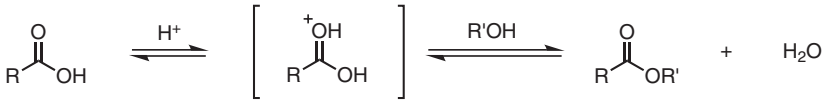
Scheme 1.3

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

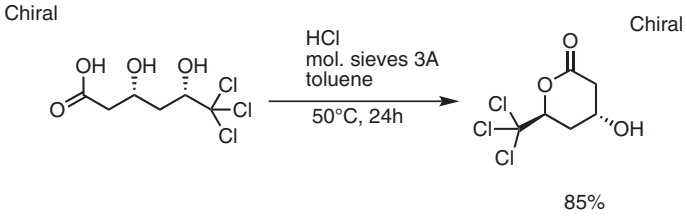
Since acid catalysis is one of the most popular methods for esterification, numerous papers are available. When the substrates are acid-resistant, the reaction is usually carried out in the presence of a Brønsted acid such as HCl, HBr, H_2SO_4, $NaHSO_4$, $ClSO_3H$, NH_2SO_3H, H_3PO_4, HBF_4, AcOH, camphorsulfonic acid, etc. (Scheme 1.4).



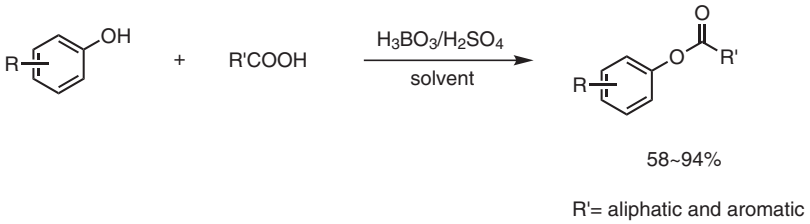
Scheme 1.4

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 3A molecular sieves [4]. 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) [5].



Scheme 1.5

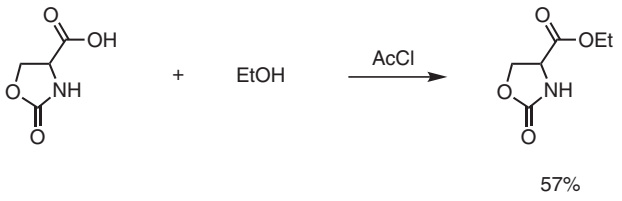


Scheme 1.6

Other ways to activate the acid catalysts are provided by the use of ultrasound and microwave. 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 [6]. Microwave irradiation accelerates the *p*-toluenesulfonic acid-catalyzed esterification, the reaction finishing within 10 min [7].

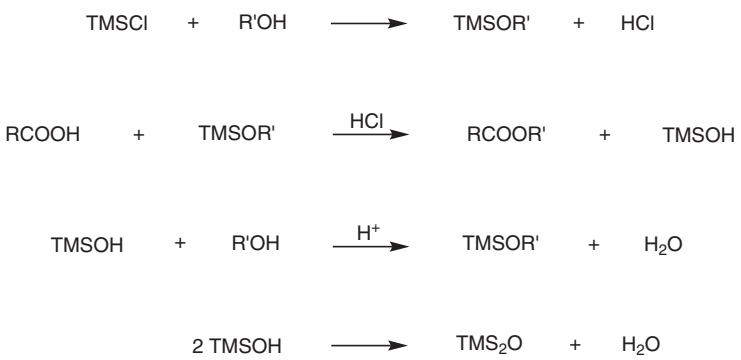
Aqueous HCl is not employable for water-sensitive compounds. In such cases, dry HCl gas must be used, but generation of this is not operationally simple. Alternatively, generation of HCl under anhydrous conditions is conveniently feasible by addition of acetyl chloride to methanol or ethanol. Treatment of alcohol and carboxylic acid in the HCl solution obtained provides the desired ester (Scheme 1.7) [8]. By this method, the concentration of HCl can be readily adjusted by changing the amount of acetyl chloride.

Experimental Procedure Scheme 1.7 [8] 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 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.

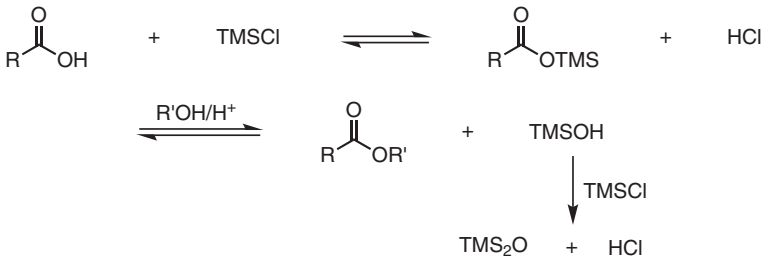


Scheme 1.7

A similar protocol is available with TMSCl (trimethylsilyl chloride) (Scheme 1.8) [9]. 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. On the other hand, the initial formation of the silyl ester is another proposed mechanism for a similar reaction (Scheme 1.9) [10]. Steroid-based alcohols also can be esterified by the use of TMSCl or TMSBr [11].



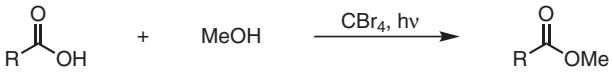
Scheme 1.8



Scheme 1.9

In situ generation of catalytic HCl is accessible photolytically. Photoirradiation of carboxylic acids in methanol containing CBr_4 (0.05 equiv.) furnishes the corresponding methyl esters (Scheme 1.10) [12]. Interestingly, sp^3 carbon-tethered

carboxylic acids undergo esterification smoothly under these conditions, while sp^2 or sp carbon-tethered carboxylic acids are not esterified. Similar photolytic esterification occurs in CCl_4 or $BrCCl_3$ in place of CBr_4 [13]. It has been proposed that HCl generated by abstraction of an α-hydrogen of alcohol by Cl radical is the real catalytic species in this reaction.



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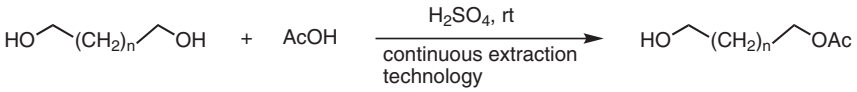
R= CH_2CH_2cHex (96%)
R= cHex (40%)
R= Bn (96%)
R= $CH(CH_3)Ph$ (95%)
R= Ph (14%)
R= $CH{=}CHCH{=}CHCH_3$ (99%)

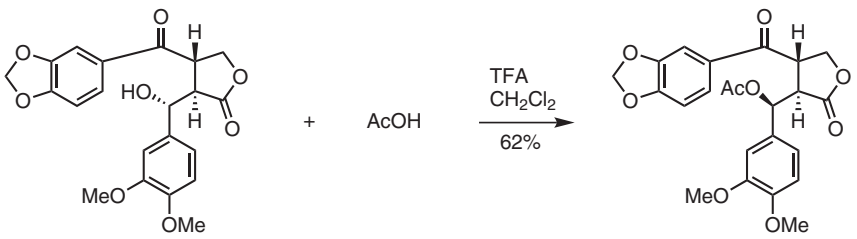
Scheme 1.10

Despite rather harsh conditions, the Brønsted acid-catalyzed reaction sometimes enjoys selectivities. Continuous extraction technology enables selective monoacetylation in reasonable yields upon treatment of 1,*n*-diol with acetic acid in the presence of H_2SO_4 (Scheme 1.11) [14]. Stereoselectivity is also attained in TFA-catalyzed esterification (TFA = trifluoroacetic acid), as shown in Scheme 1.12 [15]. 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.



n= 8 (75%)
n= 10 (66%)
n= 6 (94%)

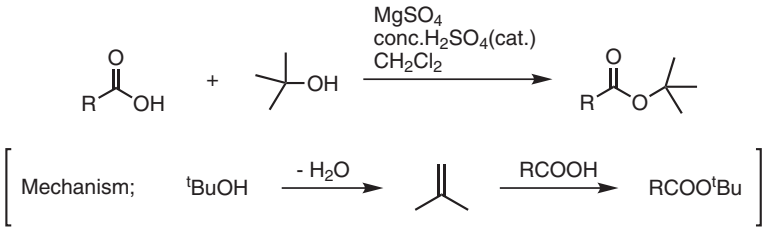
Scheme 1.11



Scheme 1.12

A unique formation of *tert*-butyl esters is notable. When a mixture of carboxylic acid and *tert*-butyl alcohol is exposed to H_2SO_4 absorbed on $MgSO_4$, esterification takes place smoothly (Scheme 1.13) [16]. 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*-butyl alcohol followed by addition of carboxylic acid to the resulting isobutylene.

Experimental Procedure Scheme 1.13 [16] 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 min, after which the carboxylic acid (10 mmol) is added. *tert*-Butyl alcohol (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 1.13

Hydrophobic polystyrene-supported sulfonic acids catalyze reaction between carboxylic acid and alcohol in water [17]. The catalysts are recovered and reused for further reactions.

The acidity of strong acids is moderated by forming the corresponding ammonium salts. Diphenylammonium triflate is an efficient catalyst for mediation of condensation between alcohol and carboxylic acid in a 1 : 1 ratio [18]. 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. When the reaction is performed in a fluorocarbon solvent such as perfluorohexane, the yield is increased [19]. Pentafluorophenylammonium triflate is also a good esterification catalyst [20]. The pentafluorophenyl group causes formation of a hydrophobic environment around the catalytic center, so

that dehydration techniques are required. Use of bulky ammonium groups together with arenesulfonyl anion results in highly efficient esterification [21]. Dimesitylammonium pentafluorobenzenesulfonate is one of the most useful catalysts, effecting condensation between carboxylic acid and alcohol in a 1:1 ratio without use of Dean-Stark apparatus.

Experimental Procedure [18] 3-Phenylpropanoic 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%).

Polyaniline salts with HCl, HNO_3, H_2SO_4, H_3PO_4, *p*-tolSO_3H, etc. catalyze reactions between carboxylic acids and alcohols, and can be separated easily from the reaction mixture by filtration [22, 23].

Brønsted acidic ionic liquids function as dual solvents/catalysts for condensation between carboxylic acid and alcohol (see Section 7.3) [24, 25]. Immobilized acidic ionic liquids can be recycled in catalysis for esterification [26]. Acidic ionic liquids can catalyze reactions of carboxylic acids with alcohols in water [27].

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; the utilization of Lewis acids is therefore rapidly increasing. They are classified as follows, according to elements:

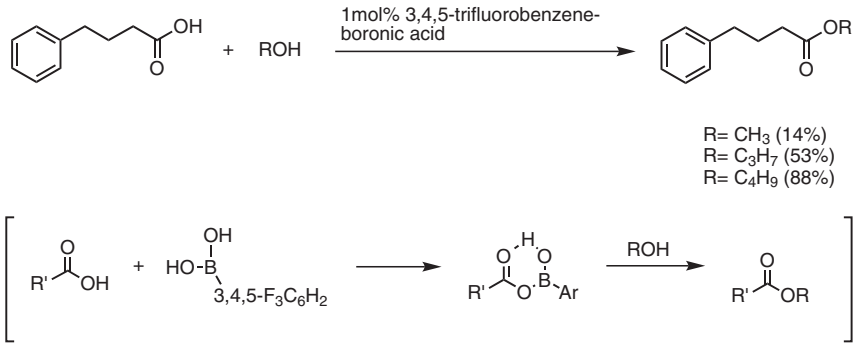
B	$BF_3 \cdot OEt_2$[28–37]; BCl_3[38]; 3,4,5-$F_3C_6H_2B(OH)_2$[39]
Al	$AlCl_3$ (immobilized) [40]; Al/NaI/CH_3CN [41]; $AlCl_3/ZnCl_2$[42]
Zn	ZnO [43]; $ZnCl_2$/microwave [44]; $Zn(OTf)_2$/microwave [45]; $Zn(ClO_4)_2 \cdot 6H_2O$ [46]
In	$InCl_3$[47]
Sn	$SnCl_2$[48]; Bu_2SnO [49, 50]; $(XR_2SnOSnR_2Y)_2$[51–53]; $(XRf_2SnOSnRf_2X)_2$[54]; Ph_2SnCl_2[55]
Ti	$TiO(acac)_2$[56]
Mn	$Mn(OAc)_3 \cdot 2H_2O$ [57]
Fe	$Fe(ClO_4)_3$[58–60]; $Fe_2(SO_4)_3 \cdot H_2O$ [61]; $Fe_2(SO_4)_3 \cdot nH_2O/H_2SO_4$[62]; $FeCl_3$[63, 64]
Ni	$NiCl_2 \cdot 6H_2O$ [65]
Cu	$CuCl_2$[66]; $Cu(NO)_3 \cdot 3H_2O$ [67]; $Cu(OTf)_3$[68]; $Cu(OMs)_2$[69]
Mo	$MoO(acac)_2$[70]
Sc	$Sc(OTf)_3$[71, 72]
Zr;Hf	$ZrCl_4 \cdot 2THF$ and $HfCl_4 \cdot 2THF$ [73–75]; $ZrOCl_2 \cdot 8H_2O$ and $HfOCl_2 \cdot 8H_2O$ [76, 77]; $Zr(O^iPr)_4$ or $Hf(O^iPr)_4$/ $Fe(O^iPr)_3$[78, 79]
I	I_2[80]

$BF_3 \cdot OEt_2$ 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 [31] 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 function.

3,4,5-Trifluorobenzeneboronic acid is claimed to be the most effective catalyst among boronic acids (Scheme 1.14). Esterification takes place smoothly if heavy alcohols such as 1-butanol are employed. The reaction is presumed to proceed via a carboxylate intermediate.



Scheme 1.14

$AlCl_3$ 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. The Lewis acidity can be moderated in combination with a soft nucleophile, NaI, in CH_3CN. An equimolar mixture of acid and alcohol is smoothly converted into the desired ester under reflux, but the yield is not high

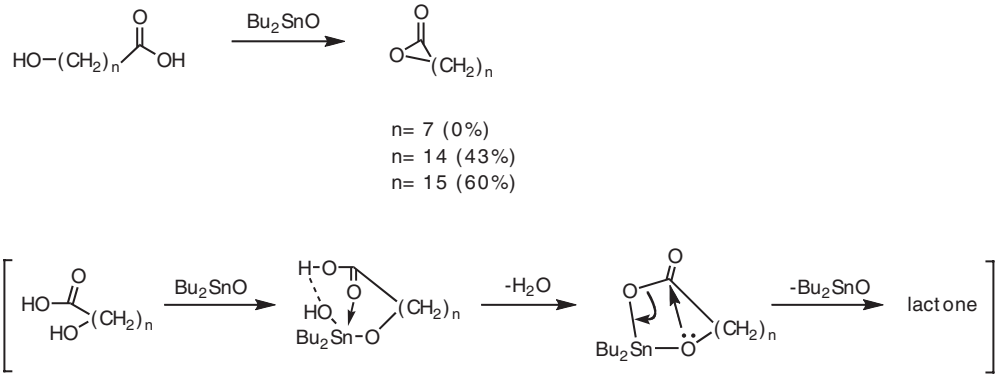
in general (77% at highest). Phenyl esters, which are otherwise rather difficult to prepare, can be obtained by reaction between aromatic or benzylic carboxylic acids with phenol in the presence of a catalytic amount of $AlCl_3$ and one equivalent of $ZnCl_2$. The strong acidity of $AlCl_3$ is responsible for efficient esterification, while $ZnCl_2$ serves for dehydration of the reaction mixture.

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. The microwave irradiation is effective for esterification catalyzed by $Zn(OTf)_2$. An equimolar mixture of carboxylic acid and alcohol is esterified, but yields are less than 90%. Smooth esterification is catalyzed by $Zn(ClO_4)_2 \cdot 6H_2O$ in the presence of $MgSO_4$ as a dehydrating agent.

Methyl esterification is feasible by heating a MeOH solution of carboxylic acid in the presence of $InCl_3$ (20 mol%). The reaction proceeds at room temperature under sonication as well.

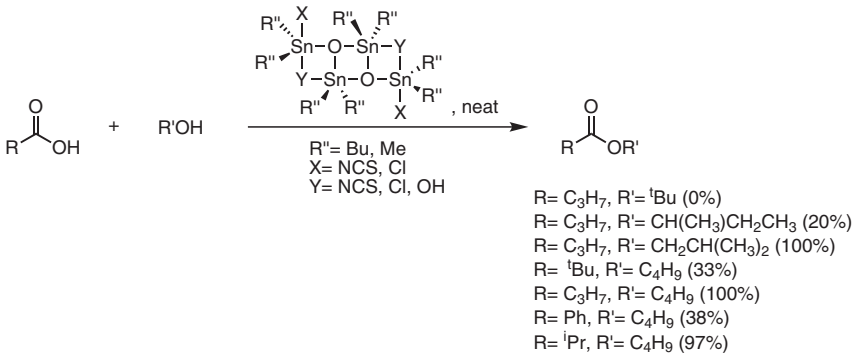
Another popular Lewis acid, $SnCl_4$, is also not usually employed in esterification, although the milder Lewis acid, $SnCl_2$, can catalyze reaction between carboxylic acids and solvent PrOH. Organotin compounds work quite well, however, because the acidity is moderated by the replacement of chlorine with electron-donating alkyl groups. Bu_2SnO catalyzes lactonization of *seco* acids on continuous dehydration with a Dean-Stark apparatus (Scheme 1.15). This method is effective for large-sized lactones but not for medium-sized ones.

Experimental Procedure Scheme 1.15 [50] 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 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.

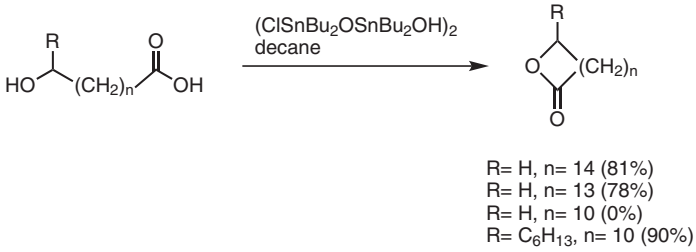


Scheme 1.15

Good yields of esters are obtained when carboxylic acids are treated with a catalytic amount of 1,3-disubstituted tetraalkyldistannoxanes, $(XR_2SnOSnR_2X)_2$, in alcohol solvent (Scheme 1.16). 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 1.17). 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 on the hydroxyl-carrying 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 1.16



Scheme 1.17

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 achievable 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 [54] A test tube (50 mL) is charged with 3-phenylpropanonic 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 by GC to provide a quantitative yield of benzyl 3-phenylpropanoate.

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

High-yielding ester synthesis from an equimolar mixture of carboxylic acid and alcohol is accessible by the use of $TiO(acac)_2$ (3 mol%). The catalyst is water-tolerant and neutral to leave various functional groups intact. Alcohols are acetylated by heating at reflux with $Mn(OAc)_3 \cdot 2H_2O$ (4 mol%) in acetic acid.

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 $Fe_2(SO_4)_3 \cdot nH_2O$ (2 wt% cat. per acid) and $FeCl_3$ (5 mol% per acid). Addition of a small amount of H_2SO_4 greatly increases the catalytic activity of $Fe_2(SO_4)_3 \cdot nH_2O$. Moreover, anhydrous $Fe_2(SO_4)_3$ is highly active for catalyzing acetylation of alcohols in acetic acid. $FeCl_3 \cdot 6H_2O$ (2 mol%) effects esterification of an equimolar mixture of long-chain acids and alcohols in high yields. 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 [61] 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 amounts 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 are 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%).

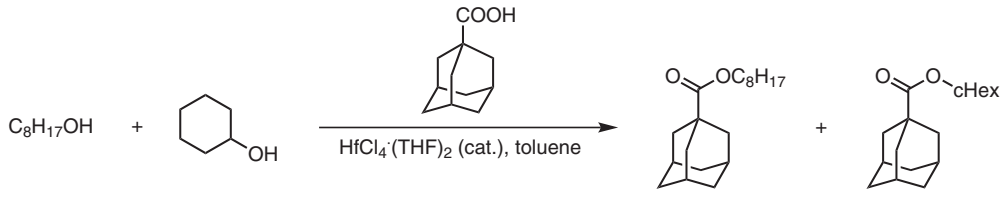
Cupric salts are another class of species that work as catalysts. $CuCl_2 \cdot nH_2O$ catalyzes conversion of carboxylic acids in methanol solvent at 130 °C, while $Cu(NO_3)_2 \cdot 3H_2O$ effects acetylation of alcohols in refluxing acetic acid. $Cu(OTf)_2$ is used for acetylation of alcohols but to a somewhat limited extent. Cupric

methanesulfonate ($Cu(OMs)_2$) is also effective. Treatment of carboxylic acid with alcohol (1.1 equiv.) in the presence of 1 mol% of the catalyst in refluxing cyclohexane affords the desired ester in excellent yield. $MoO(acac)_2$ also catalyzes transformation of propanoic acid into esters in refluxing alcohols.

$Sc(OTf)_3$ can be employed as a catalyst for acylation of high-molecular weight polyethylene glycols. Polycondensation between aliphatic dicarboxylic acids and diols is also achievable with this catalyst to furnish polyesters.

$HfCl_4 \cdot 2THF$ in the presence of 4A 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 Two). 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 1.18). Similar results are obtained with the zirconium analog. Unfortunately, however, these metal chlorides are moisture-sensitive. This drawback is overcome by the use of water-tolerant $ZrOCl_2 \cdot 8H_2O$ and $HfOCl_2 \cdot 8H_2O$. Combination of $Zr(O^iPr)_4$ with $Fe(O^iPr)_3$ exerts a synergistic effect, giving rise to increased catalytic activity as compared to the respective metal alkoxides alone. This combined catalyst is recovered by extraction with ionic liquid, so that recycling of the catalyst is feasible. Another method to recycle the catalyst is immobilization on *N*-(polystyrylbutyl)pyridinium triflylimide. The catalyst can be recycled at least 10 times with this technology.

Experimental Procedure Scheme 1.18 [73]
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 1.18

When a carboxylic acid is heated in alcohol with a catalytic amount of iodine, esterification takes place [80]. Primary, secondary, and even tertirary 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 [80]
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

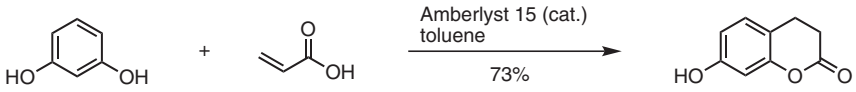
Various solid acids are utilized for esterification, although the substrates that can be employed suffer from considerable limitations due to the strong acidity. Nevertheless, solid acids have a great advantage in that they can be removed from the reaction mixture by filtration and thus applied to large-scale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

Nafion-H Nafion-H is the oldest solid acid to have been utilized as an esterification catalyst [81]. 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 s. A batch reaction is also employable [82, 83].

Experimental Procedure [81] 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 °C at a rate of 0.082 mL min^{-1}, corresponding to contact time of 5–7 s. 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 [84] and α-amino acids [85] are successfully converted into the corresponding esters with this catalyst, while catechol undergoes esterification with acrylic acid to afford 7-hydroxy coumarin (Scheme 1.19) [86]. A detailed kinetic study on esterification of acetic acid with 1-butanol with Amberlyst 15 has appeared more recently [87].

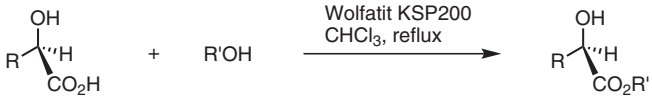
Experimental Procedure [84] A solution of γ-butyrolactone (11.6 mmol) in anhydrous methanol (25 mL) is stored on Amberlyst-15 (25 g) with occasional shaking for 20 h. Methanol is decanted and the Amberlyst is washed with methanol (2 × 20 mL). The combined methanol fractions are evaporated and the residue is distilled to give methyl 4-hydroxybutanoate, b.p. 110–114 °C/ 8–10 mm.



Scheme 1.19

Amberlite IR120 Various substrates with hydroxy and related functions, such as sugars [88, 89] and shikimic and quinic acids [90], are esterified with this resin.

Experimental Procedure [88] 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.



Scheme 1.20

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 1.20) [91]. The products are useful intermediates for synthesis of the corresponding α-hydroxy aldehydes.

Zeolite The rare earth-exchanged RE H-Y zeolite is the best of the various zeolite catalysts [92]. 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 [93]. Zeolite catalysts for petroleum cracking are employable for synthesis of α-amino acid esters [94] and phenyl benzoates [95]. Reactions between acetic acid and C_2–C_4 alcohols with Hβ, HY and ZSM-5 zeolites are the subject of extensive studies [96–98].

Experimental Procedure [92] A mixture of phenylacetic acid (5 g, 0.036 mol) 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 × 25 mL) 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%).

Mesoporous Silica Mesoporous silica has received extensive attention recently. Al-MCM-41 molecular sieves effect reactions between various acids and alcohols in the vapor phase: acetic acid/amyl alcohol [99]; acetic acid/butyl alcohols [100, 101]; terephthalic acid/methanol [102]; butyric acid/1-pentanol [103]. Microporous titanosilicate ETS-10 molecular sieves are also effective for esterification of long-chain carboxylic acids with alcohols [104]. Sulfonic acid-functionalized mesoporous silicas are utilized for esterification of fatty acids with methanol and glycerol [105–107]. Hydrophobic sulfonic acid-functionalized mesoporous benzene/silica is more active than Nafion-H for esterification of acetic acid with ethanol [108]. A similar hydrophobic SO_3H-modified catalyst is accessible from mesoporous ethylene/silica [109]. Mesoporous MCM-41 and SBA-15 functionalized with perfluoroalkanesulfonic acid are more active for esterification of long-chain fatty acids with alcohols than Nafion/silica composite [110, 111].

Comparison of commercial solid acid catalysts is now available in some reports [112–114].

Modification of Silica and Alumina Treatment of silica or alumina with $ClSO_3H$ results in immobilization of sulfuric acid on the surface of silica or alumina, which catalyzes esterification of aryloxyacetic acid or aromatic carboxylic acid [115, 116]. Silica chloride obtained from silica and thionyl chloride effects esterification of amino acids [117]. Sulfate-, phosphate-, and borate-modified silica, alumina, and zirconia furnish benzyl acetate from acetic acid and benzyl alcohol concomitant with only a small amount of dibenzyl ether [118].

$Nb_2O_5 \cdot nH_2O$ This catalyst is claimed to be more active than cation-exchange resin, $SiO_2 \cdot AlO_3$, and solid super acids [119]. Interestingly, supermicroporous niobium oxide, synthesized using a nonionic block copolymer as a structural directing reagent, is employable for gas-phase esterification of acetic acid with ethanol [120].

$ZrO_2 \cdot nH_2O$ and Mo–ZrO_2 Hydrous ZrO_2, which catalyzes reactions between carboxylic acids and alcohols, exhibits the following advantages: (i) the catalyst is easily prepared and stable in air, and (ii) the reaction does not require water-free conditions [121]. 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. [122].

Experimental Procedure [121] 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 (a capillary column, PEG 20 M 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 h, and the products are analyzed by gas chromatography.

Strongly Acidic Carbon Materials Graphite bisulfate ($C^{+}_{24}HSO^{-}_{4}2H_2SO_4$), 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 [123]. The yields are usually over 90%. Sulfonation of incompletely carbonized D-glucose results in amorphous carbon consisting of small polycyclic carbon sheets with high density of SO_3H groups [124]. This carbon material exhibits remarkable catalytic performance for esterification of higher fatty acids. Poly(vinyl alcohol) membranes crosslinked with sulfosuccinic acid catalyze esterification of acetic acid with isoamyl alcohol [125].

Natural Montmorillonite Another intercalation compound, natural montmorillonite, is useful for selective acylation of various functionalized primary and secondary alcohols [126].

Experimental Procedure [126] 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 (100 mg) with stirring 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.

Metal-Exchanged Montmorillonite and Bentonite Montmorillonites enwrapped with various metal cations such as Na^+, Al^{3+}, Fe^{3+}, Cr^{3+}, Zn^{2+}, Mn^{2+}, Ni^{2+}, Ti^{4+} are active catalysts for esterification [127–131]. Acid-activated bentonite catalyzes reactions between various carboxylic acids and alcohols [132]. A superacid SO_4^{2-}/TiO_2 catalyst on Al^{3+}-modified bentonite brings about esterification of benzoic acid with 1-pentanol [133].

Phosphorus Oxides Phosphorus pentoxide can be used for dehydration between carboxylic acid and alcohol. Heating a mixture of alcohol, carboxylic acid, and P_4O_{10} is the simplest treatment [134]. In addition to intermolecular esterification, lactonization is also achievable [135, 136]. This procedure is modified by initial treatment of P_4O_{10} with alcohol to furnish an equimolar mixture of mono- and dialkylphosphates (Scheme 1.21) [137]. 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 [137] Esterification of a Liquid Carboxylic Acid: Glacial acetic acid (0.6 mol, 36.0 g) is added to the alkyl phosphate reagent (0.1 mol 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 × 100 mL) 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 (86%, 85 g), 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 [134]. $CuSO_4$ serves both as a water scavenger and, through its color change, as an indicator for 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 [134, 138].

Experimental Procedure [134] Mixtures of various organic acids (0.05 mol), freshly prepared packing reagent (2.5 g), and ethanol (50 mL) are placed 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 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 in other procedures [139].

Inorganic Sn- or Ti-Based Solid Acids Amorphous M(IV) tungstates (M = Sn, Ti) are useful for synthesis of dioctyl phthalate [140]. Methyl ester synthesis from octanoic acid is feasible with a ceramic acid obtained by impregnating $SnO_2 \cdot H_2O$ and $(NH_4)_6(H_2W_{12}O_{40})$ followed by calcination [141]. Solid superacid of sulfated tin oxide, SO_4^{2-}/SnO_2, is a highly active catalyst for condensation between acids and alcohols [142, 143]. Similarly, titanium superacid, SO_4^{2-}/TiO_2, is capable of esterifying chemically labile mandelic acid [144].

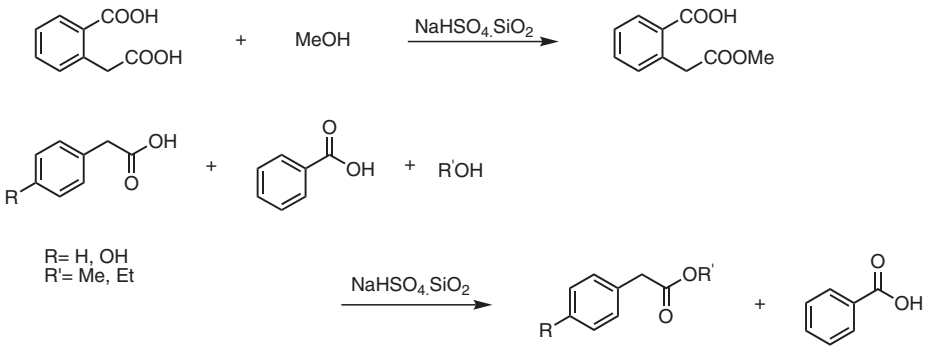
Heteropolyacids Various bromoacetates are obtained by treatment of bromoacetic acids (1.0 mol) with alcohols (1.1 mol) in the presence of 12-tungstophosphoric acid, $H_3PO_{40}W_{12} \cdot H_2O$, [145]. Its partially substituted Cs and K salts are also useful catalysts for esterification [146]. The corresponding ammonium salt catalyzes selective reactions between aliphatic carboxylic acids and alcohols in the presence of aromatic carboxylic acids [147, 148]. $H_{14}[NaP_5W_{30}O_{110}]$ can be employed for esterification of salicylic acid with aliphatic and benzylic alcohols [149]. Cobalt-containing polyoxometalate, $K_5CoW_{12}O_{40} \cdot 3H_2O$, is suitable for esterification of mandelic acid [150].

Experimental Procedure [145] Bromoacetic acid (1.0 mol), alcohol (1.1 mol), benzene (70 mL), and $H_3PO_{40}W_{12} \cdot nH_2O$ (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 once 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.

Acid Catalysts on Inorganic Solid Support Heteropoly acids often leak out of catalyst supports, because these acids are extraordinary soluble in water and several organic solvents. $H_3PW_{12}O_{40}$ can be immobilized by hydrous zirconia, which catalyzes reactions between glacial acetic acid and cyclohexanol [151] and between acetic acid and isoamyl alcohol [152]. $H_4SiW_{12}O_{40}$ on hydrous zirconia brings about esterification of primary and secondary alcohols with C_1—C_3 carboxylic acids [153]. Zirconia is also employable to support WO_3, which catalyzes esterification of pal-

mitic acid with methanol [154]. Porous zirconium phosphate is also employable to support WO_3 [155].

Silica gel is employable for supporting various acid catalysts: P_2O_5 [156]; $H_3PMo_{12}O_{40}$ [157]; $H_3PW_{12}O_{40}$ [158, 159]. All of these supported catalysts are effective for esterification. Grinding $Fe(ClO_4)_3(ROH)_6/SiO_2$ with an equimolar amount of carboxylic acid provides esters [160]. This protocol is operationally simple, but requires a stoichiometric amount of the promoter. Aliphatic carboxylic acids are esterified preferentially over aromatic ones at room temperature with the aid of $NaHSO_4$ supported on silica gel (Scheme 1.22) [161]. $Hf[N(SO_2C_8F_{17})_4]$ supported on fluorous reverse-phase silica gel efficiently catalyzes esterification of methacrylic acid with methanol [162].



Scheme 1.22

Supporting $ZrOCl_2 \cdot 8H_2O$ on mesoporous silica MCM-41 enhances the catalytic activity for esterification of C_{10}–C_{18} normal acid with alcohols [163]. 12-Phosphotungstic acid and its cesium salts supported on a dealuminated Y zeolite catalyze reaction between 1-butanol and acetic acid in high yield [164].

$H_3PW_{12}O_{40}$ can be supported on neutral alumina, catalyzing esterification of aliphatic carboxylic acids with primary and secondary alcohols [165].

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 [166]. Zirconium sulfate supported on activated carbon exhibits higher activity for esterification of oleic acid with 1-butanol [167].

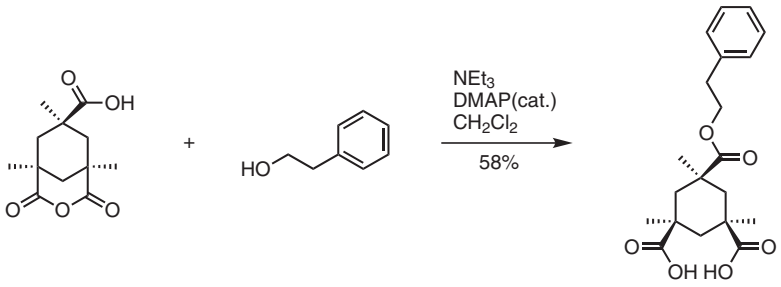
Acid Catalysts on Organic Solid Support Heteropolyacids supported on ion-exchange resin accelerate the rates of reaction between lactic acid and ethanol [168]. Polyaniline-supported acid catalysts are effective for esterification of carboxylic acids with alcohols [169, 170]. Triphenylphosphine ditriflate anchored onto cross-linked polystyrene is useful for ester synthesis from functionally substituted carboxylic acids and alcohols [171]. Esterification of amino acids takes place smoothly with polystyrylsulfonyl-3-nitro-1*H*-1,2,4-triazolide resin [172].

Solid Acid under Microwave Irradiation Esterfication by solid acid catalysts is accelerated by microwave irradiation [173]. Microwave irradiation in a continuous flow system is also feasible [174]. More detailed description of microwave irradiation is given in Section 7.4.

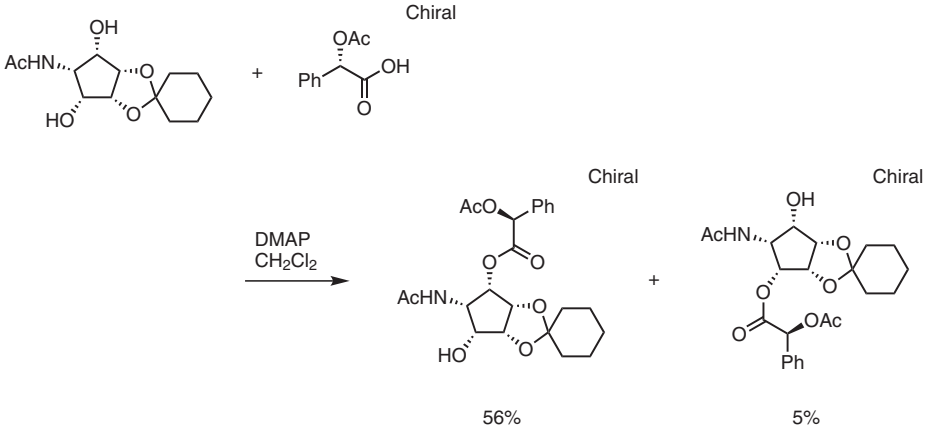
1.1.3 Base Activators

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 reaction mixture is subjected to aqueous workup. Nonetheless, a few nonaqueous methods are available for highly functionalized substrates. ω-Hydroxy acids undergo lactonization upon exposure to KOH/KOMe/glycerin [175].

Another technique is the use of DMAP (4-dimethylaminopyridine). A Kemp's triacid derivative is transformed into a monoester by treatment with Et_3N/DMAP (cat.) (Scheme 1.23) [176]. The synthesis of deoxy derivatives of α-mannosidase inhibitor mannostatin A makes use of the DMAP-methodology as a key step (Scheme 1.24) [177].



Scheme 1.23

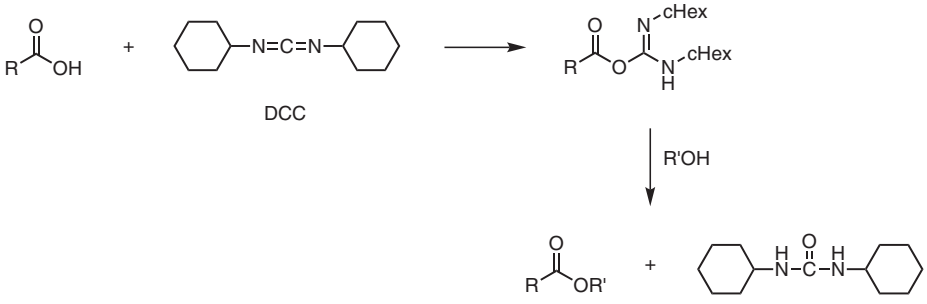


Scheme 1.24

1.1.4
Carbodiimide Activators

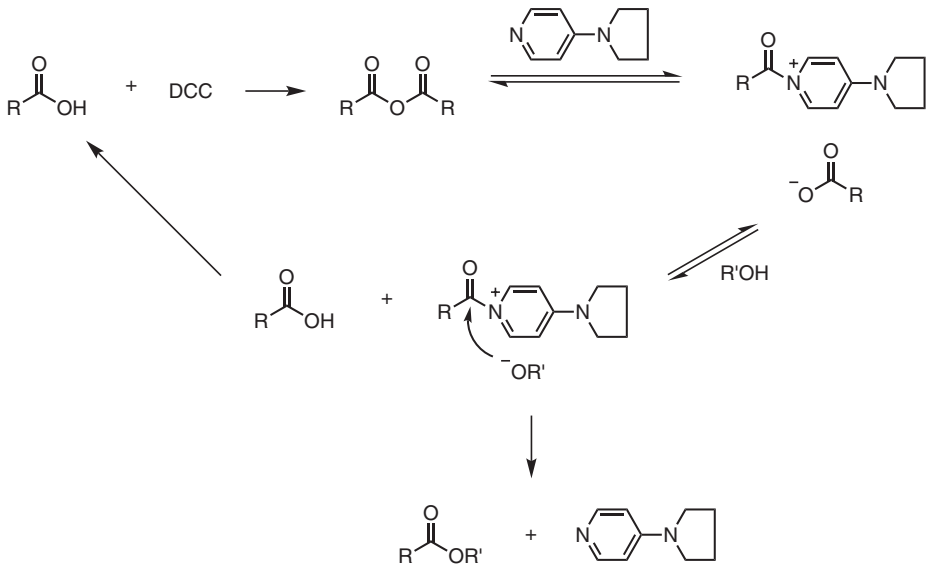
The use of DCC (dicyclohexylcarbodiimide) as a promoter represents one of the most versatile esterification methods. Although this reagent is irritant to skin and a stoichiometric dosage or more is necessary, this procedure enjoys various advantages. The reaction usually proceeds at room temperature,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

The application of the DCC method in pure organic synthesis dates back to 1967 [178]. The following mechanism for this reason is suggested (Scheme 1.25).



Scheme 1.25

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 strong acid such as *p*-toluenesulfonic acid [179, 180]. Alternatively, addition of a catalytic amount of *p*-aminopyridines is more effective [181, 182]. 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 between *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 1.26 [182]. The carboxylic acid is first converted by DCC to the anhydride, which then forms an acylpyridinium species with DMAP. Nucleophilic attack on the acyl



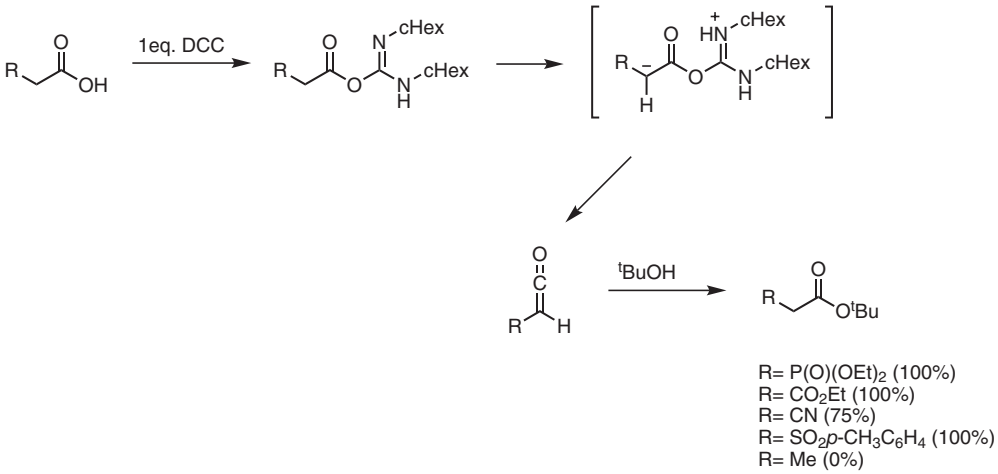
Scheme 1.26

group by $R'O^-$ produces the ester concomitantly with regeneration of DMAP, together with a half quantity of RCOOH, which can be again used for the reaction with DCC. This technique is employable for high-yielding synthesis of anthranilate esters from sterically hindered alcohols [183]. The reaction under high pressure (1.5 GP) effects smooth esterification of monomethylsuccinates with tertiary alcohols [184]. 4-(Pyrrolidin-1-yl)pyridine is also a useful base for deconjugative coupling of 2-cyclohexylideneacetic acid [185].

Experimental Procedure [181] A mixture of 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) is added to a stirred solution of carboxylic acid (10 mmol) in anhydrous CH_2Cl_2 (10 mL, DMF in case 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 1.27) [186–188]. The reaction can be explained by the intermediacy of the corresponding ketene, which is highly electrophilic but relatively sterically undemanding.



Scheme 1.27

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 [189].

Experimental Procedure [189] Method A (acid in excess): A suspension of *tert*-butyl alcohol (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%).

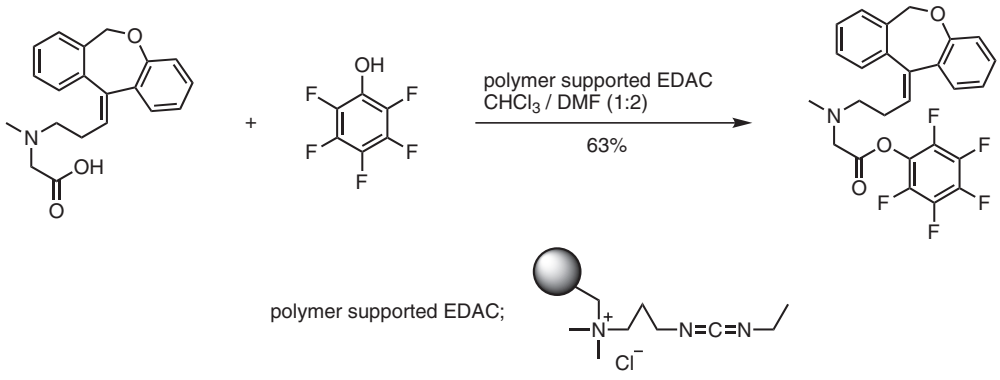
Method B (alcohol in excess): A suspension of *tert*-butyl alcohol (1.9 mL, 20 mmol), scandium triflate (0.3 g, 0.6 mmol), *t*-Boc(*s*)-(-)-Glu(OBz) (0.34 g, 1 mmol), and DMAP (0.61 g, 5 mmol) in anhydrous methylene chloride (10 mL) is cooled to –8 °C in an ice-salt bath for 30 min. EDC (0.38 g, 2 mmol) 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 corresponding pure ester (0.32 g, 80%).

Tributylphosphine is an additive of choice when the reactants are base-sensitive [190], even when the use of DMAP results in poor yield.

The conventional DCC/base esterification of carboxylic acids containing α-halogen atom(s) in a solvent induces complex side reactions due to *N*-acylation. Remarkably, a high yield of the desired ester is obtained when the reaction is conducted in the absence of solvent and base [191].

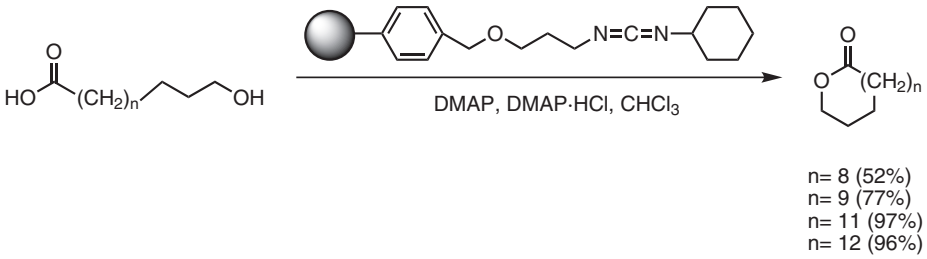
Since a stoichiometric amount of carbodiimide or more (sometimes 10 equivalents) must be used, immobilization of this reagent is highly convenient for separation from the reaction mixture. EDAC (ethyl dimethylaminopropylcarbodiimide) supported on polystyrene-divinylbenzene resin is effective for synthesis of esters for use in bioconjugation (Scheme 1.28) [192]. 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 analogs can be immobilized as well, and as such utilized for macrolactonization of *seco* acids (Scheme 1.29) [193].



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 [194, 195]. The reaction between alcohols and carboxylic acids proceeds smoothly under neutral

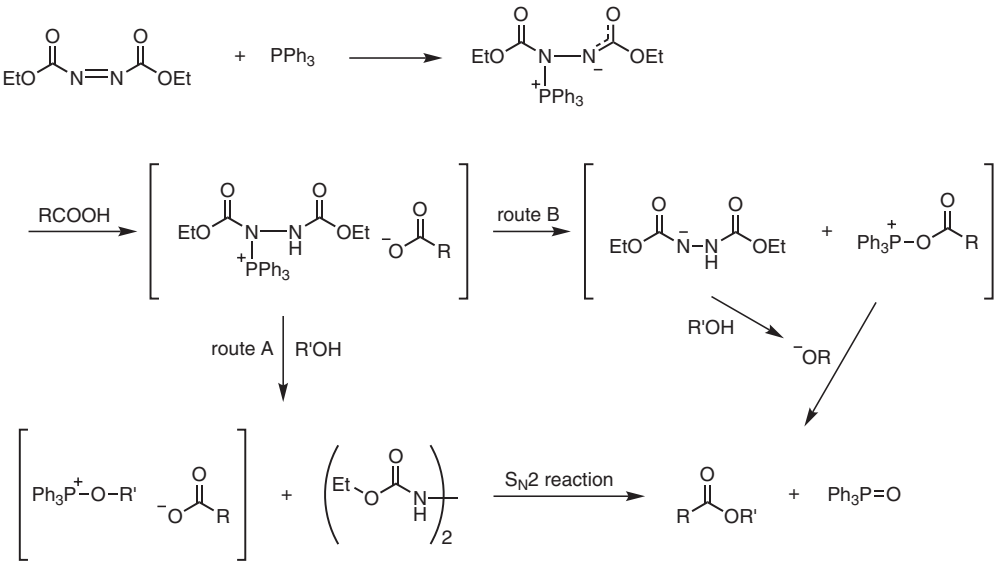


Scheme 1.29

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 1.30) [196]. 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. The phosphonium carboxylate intermediate is isolable with cyclodiphosphazane [197]. An alternative route is possible (route B) [198]. 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 three bulky phenyl groups attached to the phosphorus atom.

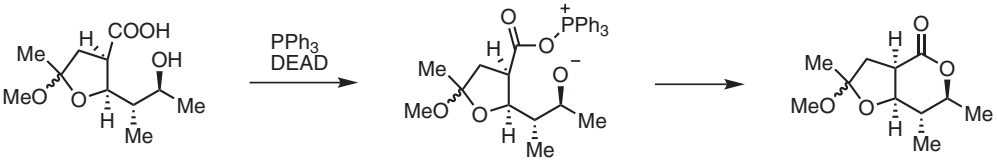
Experimental Procedure [194] General Procedure for Mitsunobu Reaction. A solution of triphenylphosphine (0.01 mol) in ether (10 mL) is added drop by drop into a solution of diethyl azodicarboxylate (0.01 mol) and carboxylic acid (0.01 mol) in ether (10 mL), with vigorous stirring at room temperature. 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.

The Mitsunobu reaction has found numerous applications. For instance, benzylic and styryl alcohols are esterified selectively in the presence of (poly)phenolics [199]. Otherwise difficult-to-achieve esterification of benzoic acids with phenols is feasible [200]. Inversion of sterically hindered 17-hydroxy steroids [201] and regioselective esterification of sucrose [202] are feasible.



Scheme 1.30

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 [203, 204]. In such a case the stereochemistry about the alkoxy carbon is retained, as shown in Scheme 1.31.



Scheme 1.31

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 because of its more polar character [205]. Incorporation of an amino function in the phosphine, as in dipheny(2-pyridyl)phosphine [206] and (*p*-dimethylaminophenyl)diphenylphosphine [207] is the next strategy, as acidic workup can be used to remove the phosphine oxides with an amino function. The use of di-*tert*-butyl azodicarboxylate coupled with

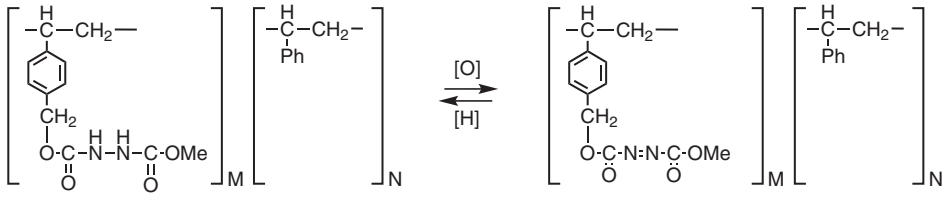
dipheny(2-pyridyl)phosphine is also more convenient, as the *tert*-butyloxycarbonyl group decomposes to isobutene and CO_2 upon acidic workup [208].

Experimental Procedure [206] 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 [208] 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 1 h 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 azodicaboxylates is also useful (Scheme 1.32) [209]. 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.

polymer supported methyl azodicarboxylate



Scheme 1.32

Thanks to the lower 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.

The use of fluorous azodicarboxylate derivatives is another means by which the separation problem may be solved (see Part Two). Bistridecafluorooctyl azodicarboxylate is one such reagent, readily recovered from the reaction mixture simply by extraction with FC-72 (perfluorohexanes) [210]. The combined use of fluorous azidocarboxylate and tertiary phosphine provides further elaboration of separation [211].

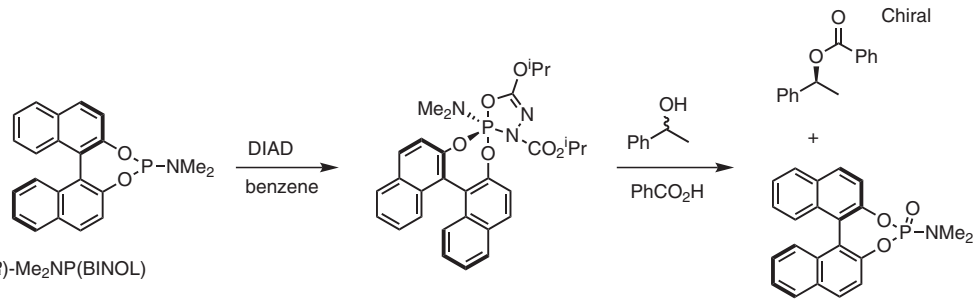
The activity of the Mitsunobu reagent may be enhanced. Azodicarboxamides in place of esters can activate less reactive acids. 1,1′- (Azodicarbonyl)dipiperidine/Ph_3P [212] and *N, N, N′, N′*-teramethylazodicarboxamide/Bu_3P [213] effect acylation of various secondary alcohols, including steroids.

Experimental Procedure [212] 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 [213] 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 at 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 the product isolation by SiO_2 column chromatography.

As shown in Scheme 1.33, treatment of chiral trivalent alkoxyphosphorus compounds with DIAD results in cycloaddition rather than formation of a zwitterion [214]. The newly formed adduct effects the Mitsunobu-like esterification. Unfortunately however, neither yields nor *ee*s of the esters are particularly high: ~50% yields and <39% *ee*s.

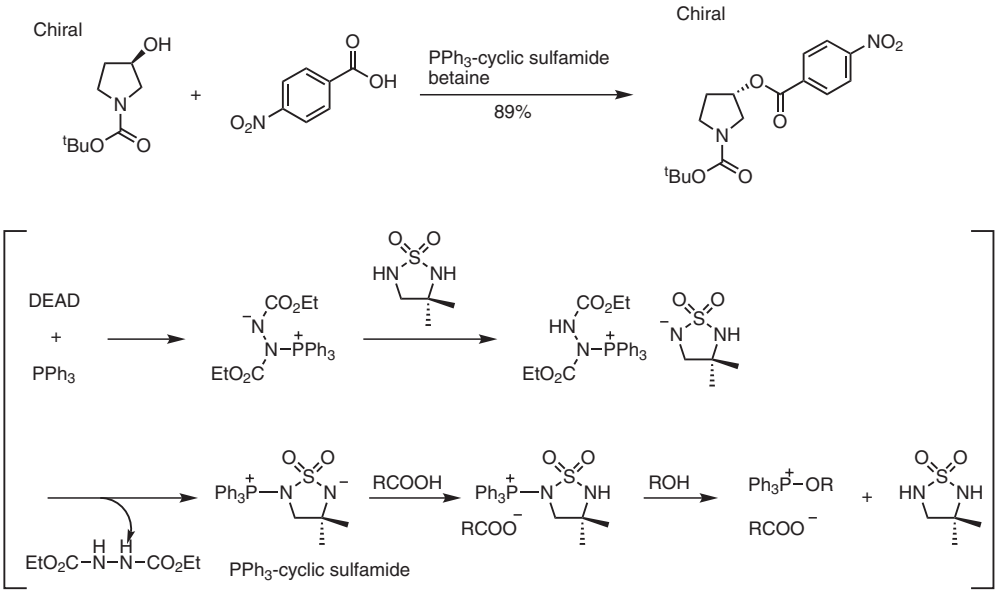
Since the alkoxyphosphonium salt is the key intermediate in the standard Mitsunobu reaction, variants to generate this species through other routes have been investigated. Triphenylphosphine-cyclic sulfamide betaine, formed by treating cyclic sulfamide with DEAD/Ph_3P, is stable in the solid state for several months



Scheme 1.33

(Scheme 1.34) [215]. This compound can be used for a Mitsunobu-like coupling between alcohol and carboxylic acid.

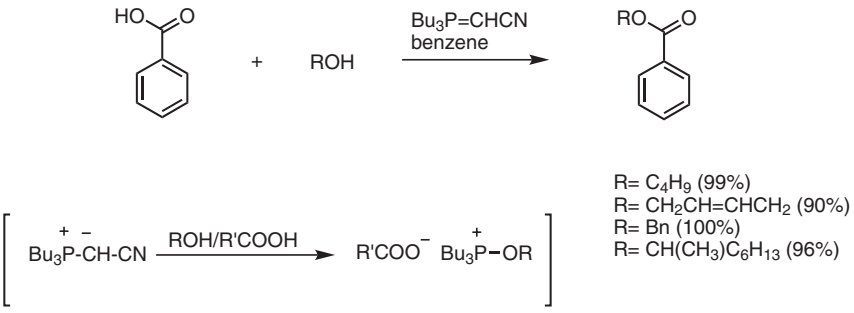
Experimental Procedure Scheme 1.34 [215] The adduct of triphenylphosphine and 3,3-dimethyl-1,2,5-thiadiazolidine 1,1-dioxide (5.0 mmol) is added portionwise over 10 min to a stirred mixture of the alcohol (3.32 mmol) and carboxylic acid (5.0 mmol) in anhydrous solvent (30 mL), and the resulting clear (milky) solution is stirred at room temperature 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 1.34

Cyanomethylenetributylphosphorane mediates the direct condensation between alcohol and carboxylic acid through an alkoxy(tributyl)phosphonium salt intermediate (Scheme 1.35) [216]. This reagent is effective even for weak acids ($pK_a > 12$), which are not employable for the authentic Mitsunobu reaction. $Bu_3P{=}C(CO_2Me)_2$ acts similarly [217]. The inversion product prevails in toluene, while the retention is favored in DMF.

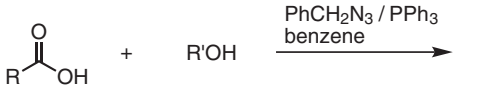
Experimental Procedure Scheme 1.35 [216] An alcohol (1 mmol) and a carboxylic acid (1.5 mmol) are successively dissolved in dry benzene (5 mL) with stirring under an argon atmosphere, and cyanomethylenetributylphosphorane (1.5 mmol) is added all at once, by syringe. The reaction mixture is heated with 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.



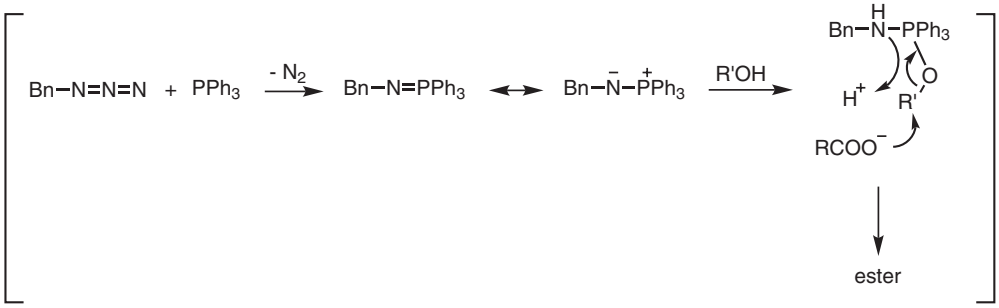
Scheme 1.35

Iminophosphorane functions as an alternative to the alkoxyphosphonium salt [218]. Treatment of benzyl azide with triphenylphosphine (Staudinger reaction) affords an iminophosphorane, the positively charged phosphorus atom of which is an activator of alcohol (Scheme 1.36). 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 1.36 [218]
A mixture of the alcohol, the carboxylic acid, benzyl azide (1.5 equiv.), and triphenylphosphine (1.5 equiv.) in THF is heated to reflux and concentrated to give a crude product, which is purified by column chromatography.



R= CH_3, R'= $C_{12}H_{25}$ (99%)
R= CH=CHPh, R'= $C_{12}H_{25}$ (90%)
R= CH_3 , R'= $CH(CH_2)_9OH$ (42%)

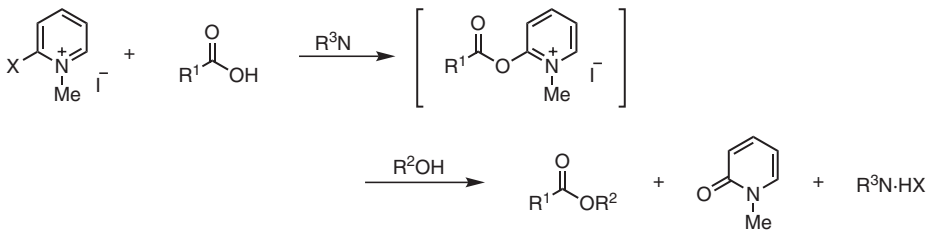


Scheme 1.36

1.1.6
Activation of Carboxylic Acids

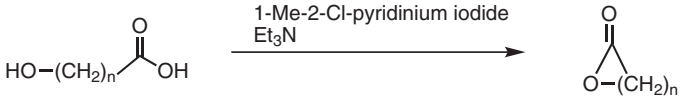
2-Halo-1-methylpyridinium salts are another class of templates that induce condensation between alcohols and carboxylic acids (Scheme 1.37) [219, 220]. Thus, treatment of equimolar quantities of alcohol and carboxylic acid with 1.2 moles of the salt in the presence of 2.4 moles of tertiary amine provides good to excellent yields of esters. This procedure is applicable to macrolide synthesis (Scheme 1.38) [221]. 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 1.37 [219] 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 1.37

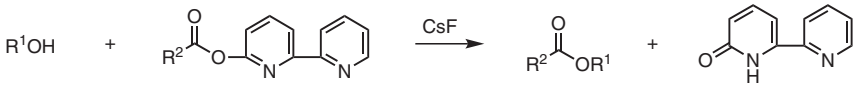


n= 5 (89%)
n= 6 (0%)
n= 7 (13%)
n= 10 (61%)
n= 11 (69%)
n= 14 (84%)

Scheme 1.38

More efficient and selective acylation is achieved by the use of 2,2′-bipyridyl-6-yl carboxylates (Scheme 1.39) [222]. 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.

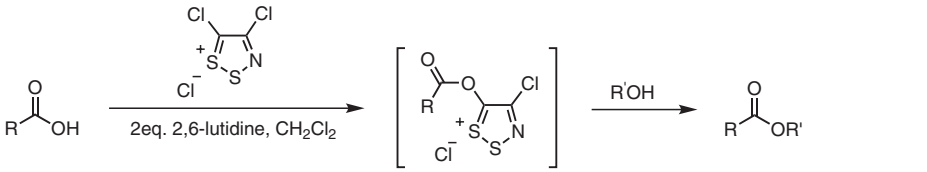
Experimental Procedure Scheme 1.39 [222]
A mixture of 2,2′-bipyridyl-6-yl hexanoate (0.5 mmol), benzyl alcohol (0.6 mmol), and cesium fluoride (2–2.5 mmol, dried well at 140 °C for 3 h *in vacuo* before use) in acetonitrile is stirred for 1 d at room temperature, and benzyl hexanoate is isolated in 90% yield after workup and purification.



Scheme 1.39

It is claimed that 4,5-dichloro-1,2,3-dithiazolium chloride works at a lower temperature (–78 °C to room temperature) than the 2-halo-1-methylpyridinium chloride (Scheme 1.40) [223].

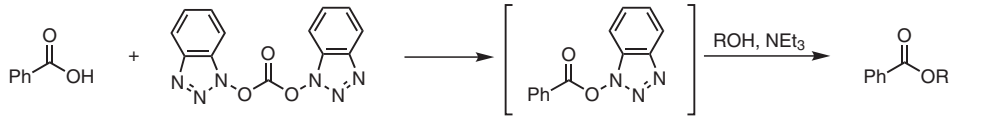
Experimental Procedure Scheme 1.40 [223] A solution of the acid (0.87 mmol), the alcohol (0.87 mmol), and 2,6-lutidine (0.233 mL, 2.0 mmol) in dry CH_2Cl_2 (1 mL) is added at –78 °C, under an Ar atmosphere and over a period of 1 min, to a stirred slurry of the dithiazolium salt (0.207 g, 1.0 mmol) in dry CH_2Cl_2 (3 mL). The mixture is stirred at –78 °C for 2 h and allowed to warm to room temperature 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 1.40

Various carbonates such as 1,1′-[carbonyldioxy]dibenzotriazole (Scheme 1.41) [224] and di-2-pyridyl carbonate [225] are also useful.

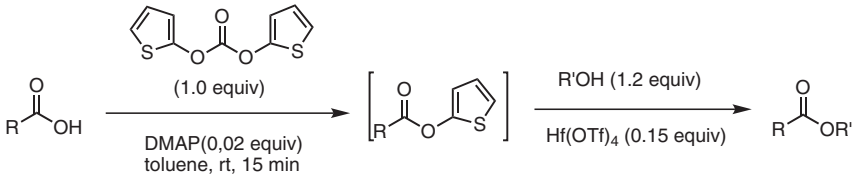
Experimental Procedure Scheme 1.41 [224] A mixture of 1-hydroxybenzotriazole (41 g, 0.3 mol) and trichloromethyl carbonochloridate (18 mL, 0.15 mol) in benzene (200 mL) is heated at reflux with stirring for 2 h. The precipitate is filtered off, washed with benzene, and dried to give 1,1′-(carbonyldioxy)dibenzotriazole; 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 for two or three days and the reaction mixture is subjected to conventional workup.



1.1'-[carbonyldioxy]dibenzotriazole

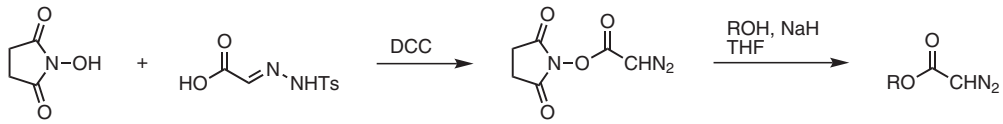
Scheme 1.41

Treatment of carboxylic acids with 2-dithienyl carbonate in the presence of DMAP followed by addition of alcohols with $Hf(OTf)_4$ furnishes the corresponding esters (Scheme 1.42) [226, 227].



Scheme 1.42

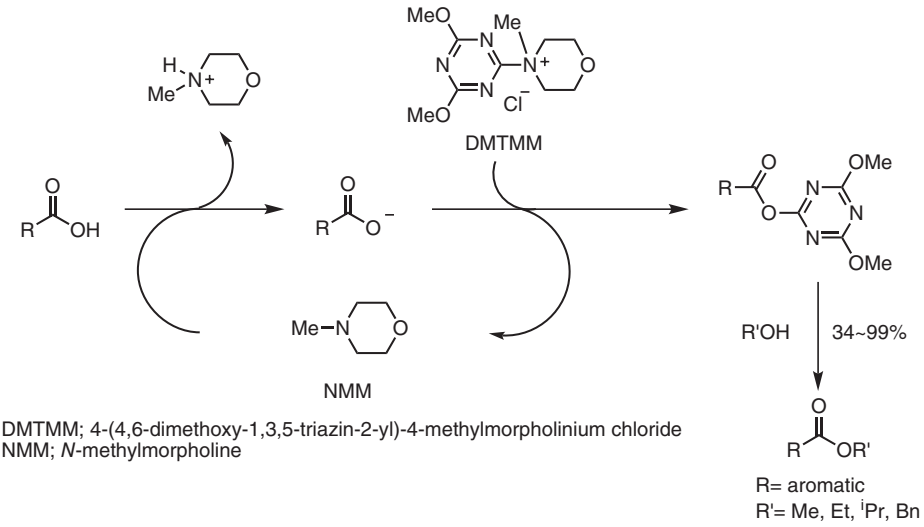
A succinimidyl group is a good activator for carboxylic moieties, and so phenyl esters of diazoacetate can be obtained by treatment with succinimidyl diazoacetate, prepared from *N*-hydroxysuccinimide and glyoxylic acid tosylhydrazone (Scheme 1.43) [228].



Scheme 1.43

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 1.44) [229]. The amount of alcohol can be reduced to be nearly equimolar with the acid in THF as solvent.

Experimental Procedure Scheme 1.44 [229] *N*-methylmorpholine (0.24 mmol) is added at room temperature 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.



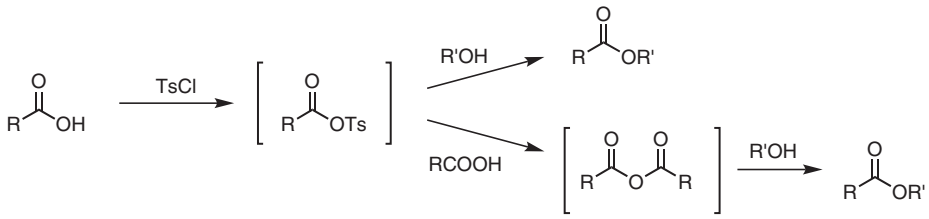
DMTMM; 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
NMM; *N*-methylmorpholine

Scheme 1.44

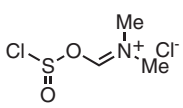
The use of sulfonyl halides for activation of carboxylic acids is a classical procedure. When carboxylic acid and alcohol are mixed in the presence of *p*-toluenesulfonyl chloride (TsCl) in pyridine, a variety of esters are produced [230]. This technique is also employable for the synthesis of β-lactones from β-hydroxy acids [231]. Two mechanisms are plausible, depending on the key intermediate actually reacting with alcohol: (i) an acyl tosyl mixed anhydride or (ii) a symmetric acid anhydride resulting from further reaction of this mixed anhydride with carboxylic acid (Scheme 1.45). The use of TsCl (1.2 equiv.) in the presence of *N*-methylimidazole is effective for reaction between carboxylic acids and alcohols in a 1 : 1 ratio [232]. 1-Tosylimidazole (1.2 equiv.) activates reaction between alcohol (1.0 equiv.) and RCOONa (2 equiv.) in the presence of Et_3N (1.5 equiv.) and Bu_4NI (cat) to give the structurally diverse esters [233]. Methanesulfonyl chloride/Et_3N (or pyridine) is also usable [234, 235], but yields are not always high because of a side reaction generating sulfene. This drawback can be overcome by use of Me_2N-SO_2Cl, which has no α-hydrogen [236, 237]. 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 [238] and triflic anhydride [239–241] also serve for the direct condensation. *N,N*-Dimethylchlorosulfitemethaniminium chloride [242] and 4,5-dichloro-2-[(4-nitrophenyl) sulfonyl]pyridazin-3(*2H*)-one [243] are other modified activators for esterification (Scheme 1.46).

Experimental Procedure [230] 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

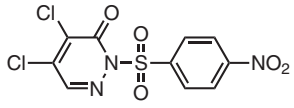
or phenol (1 molecular equivalent) is added. The solution is kept cold for about 1 h and then poured into three or four volumes of an ice/water mixture. Solid esters are collected by filtration.



Scheme 1.45



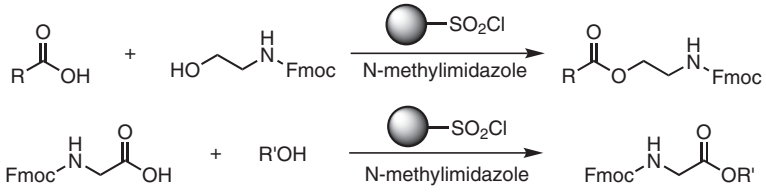
N,N-dimethylchlorosulfitemethanimium chloride



4,5-dichloro-2-[(4-nitrophenyl)sulfonyl]pyridazin-3(2*H*)-one

Scheme 1.46

Commercially available polystyrylsulfonyl chloride resin acts as a solid-supported ester condensation reagent (Scheme 1.47) [244]. 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*-butyl alcohol.

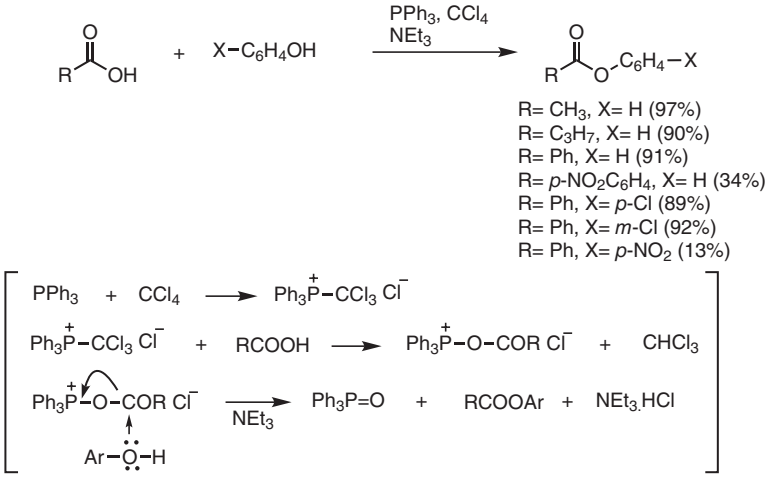


Scheme 1.47

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 a strongly electron-withdrawing groups (Scheme 1.48) [245]. Ph_3P/CCl_3CN/DMAP also acts similarly [246]. Similar acyloxy phosphonium

intermediates are generated by reaction of triphenylphosphine with *N*-bromo or iodo succinimide, treatment of which with alcohol furnishes esters [247].

Experimental Procedure Scheme 1.48 [245] 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% yield) as white crystals: mp 70–71 °C.

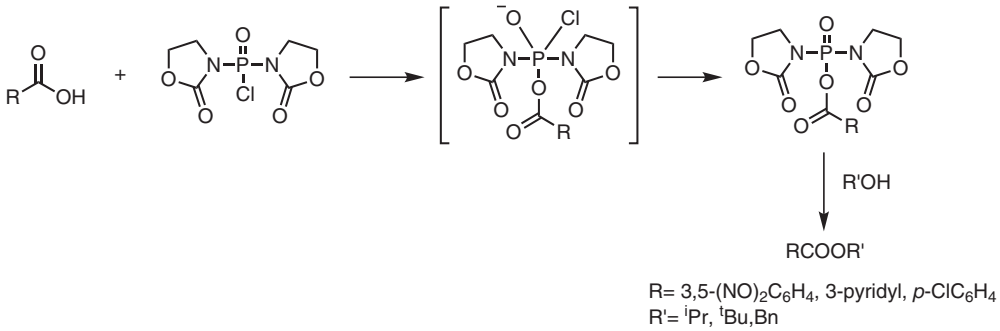


Scheme 1.48

Treatment of tertiary ammonium salt of carboxylic acid with *N, N*-bis(2-oxo-3-oxazolidinyl)phosphordiamidic chloride produces an acyloxy intermediate which furnishes esters upon treatment with alcohol (Scheme 1.49) [248].

Experimental Procedure Scheme 1.49 [248] 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

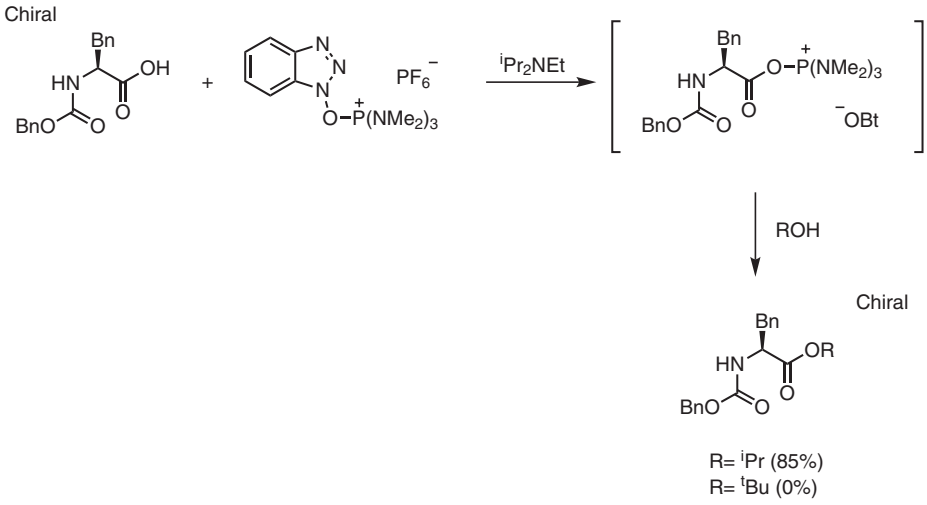
conditions. All reaction mixtures made in acetonitrile are heated at reflux (1 h~1.5 h) and the triethylammonium salt is dissolved. Reaction mixtures in dichloromethane or dimethylacetamide are kept for 1 h at room temperature. When the reaction time is over, sodium bicarbonate solution (10%, 10–20 mL) 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 1.49

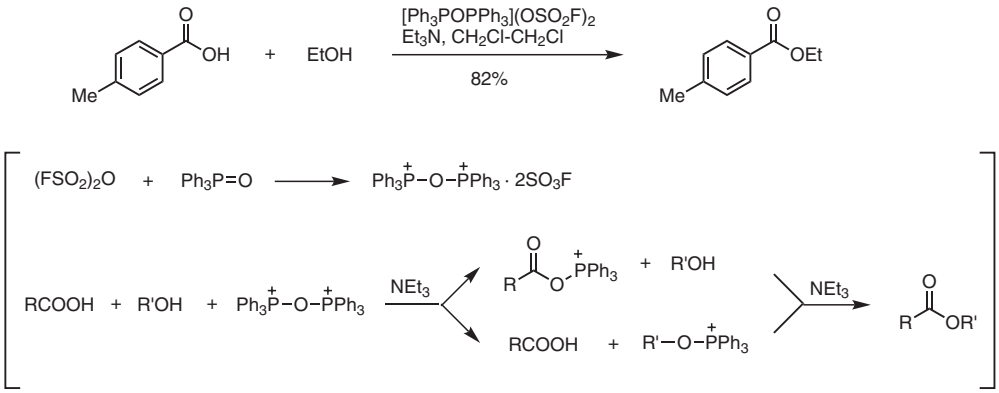
Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate is a powerful reagent with which to generate an acyloxyphosphonium species (Scheme 1.50) [249]. Amino acids can thus be esterified with a nearly equal amount of alcohol (~1.1 equiv.) except in the case of *tert*-butyl alcohol. The acid- and base-sensitive protecting groups commonly used in peptide chemistry are tolerated in this protocol.

Experimental Procedure Scheme 1.50 [249] 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(dimethy laminophosphonium hexafluorophosphate) (0.44 g, 1 mmol) is added, and the reaction mixture is left stirring overnight with gradual warming to room temperature. 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 *in vacuo* affords the crude product, which is purified by silica gel flash chromatography.



Scheme 1.50

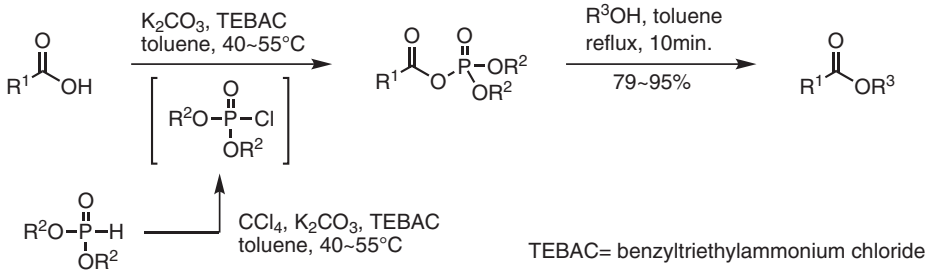
Diphosphonium fluorosulfonate effects dehydration between carboxylic acids and alcohols (Scheme 1.51) [250]. This reagent has been prepared by mixing $Ph_3P{=}O$ and $(FSO_2)O$ and used *in situ* for esterification. It is assumed that the reaction proceeds through an acyloxy- or alkoxyphosphonium intermediate.



Scheme 1.51

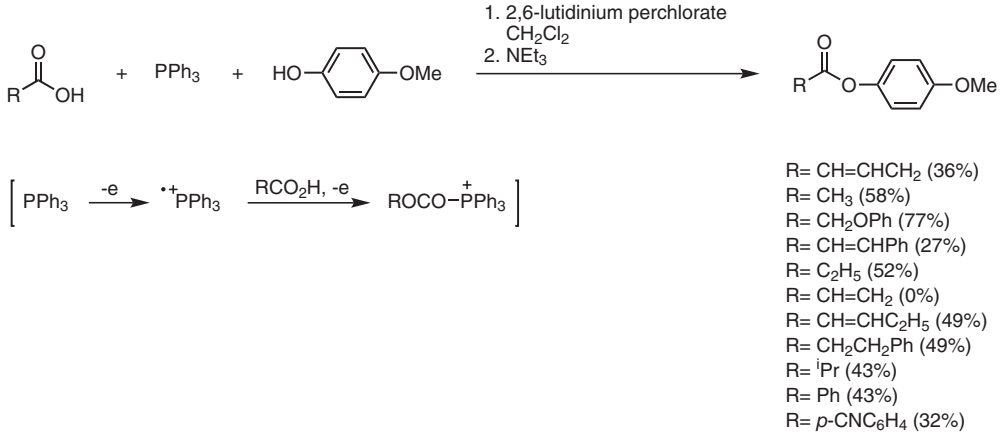
Phase transfer technology has been used to activate carboxylic acids with phosphoric acid diester chlorides generated *in situ* (Scheme 1.52) [251]. The reaction works even for hindered substrates such as pivalic acid, but is not applicable to phenylacetic acid or diphenylacetic acid.

Experimental Procedure Scheme 1.52 [251] 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 min. The esters obtained are distilled under reduced pressure or purified by column chromatography on silica gel with benzene/acetone (9 : 1) as eluent.



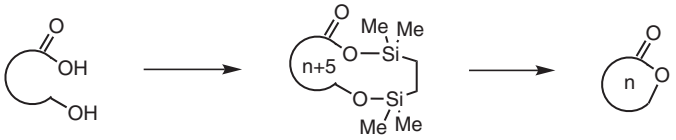
Scheme 1.52

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 1.53) [252].

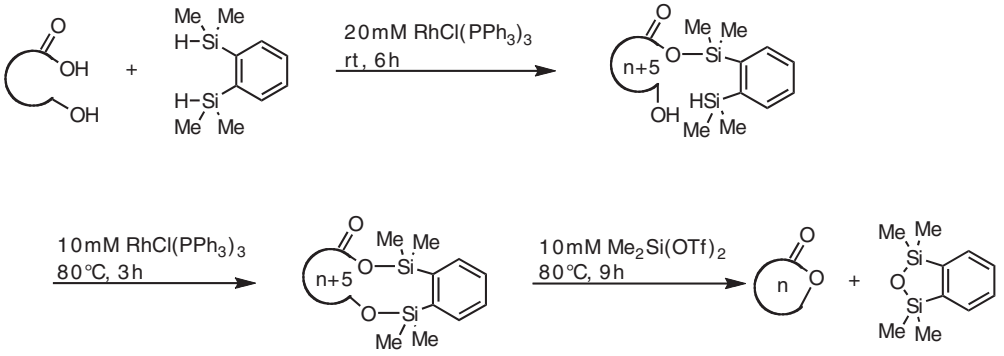


Scheme 1.53

Activation of carboxylic function as a silyl ester 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.) [253]. A silyl carboxylate species is assumed to act as a key intermediate. Medium-sized lactones are accessible through a novel ring-contraction strategy (Scheme 1.54) [254]. 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 1.55). Medium-sized lactones are obtained in high yields, except the seven-membered rings.



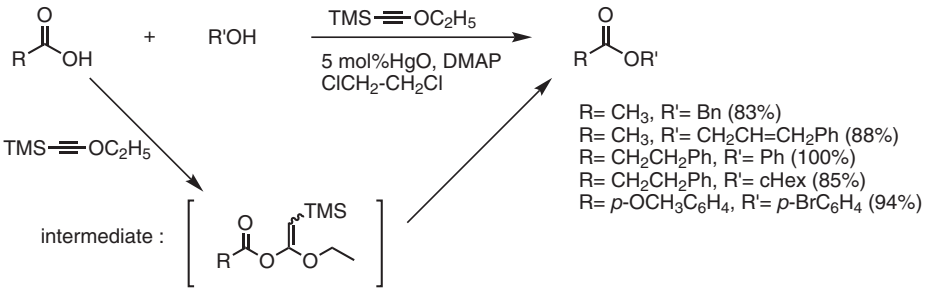
Scheme 1.54



Scheme 1.55

Acyloxyketene acetals, obtainable from carboxylic acids and (trimethylsilyl) ethoxyacetylene by treatment with mercuric ion, afford esters upon treatment with alcohols (Scheme 1.56) [255]. Most conveniently, ketene acetals prepared *in situ* are straightforwardly converted into esters, lactones, and peptides.

Experimental Procedure Scheme 1.56 [255] 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, 2 mL) is stirred under a nitrogen atmosphere for 25 min ~ 2 days. The mixture is concentrated by rotary evaporator and then by use of a high-vacuum pump at 40 °C/0.4 mbar for 1 h to give the pure product.

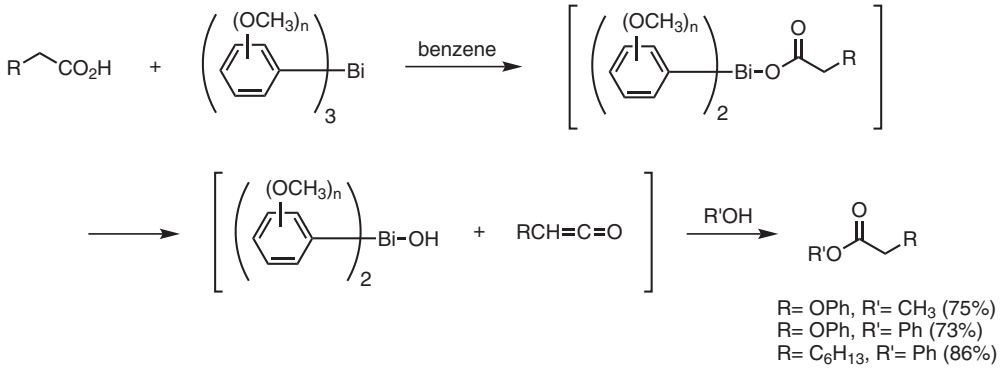


Scheme 1.56

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 1.57) [256].

Scheme 1.57

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 1.58) [257]. It is assumed that the reaction proceeds through ketene formation.



Scheme 1.58

Carboxylic acids are activated by treating with BCl_3 [38], benzeneboronic acids [258], or borane/THF (or Me_2S) [259]. The resulting acyloxyboranes are transformed into esters upon treatment with alcohols. Bismuth (III) carboxylates obtained from Ph_3Bi and carboxylic acids react similarly to give esters [260]. Cerium ammonium nitrate effects reaction between carboxylic acids and alcohols, although the mechanism is not clear [261–263].

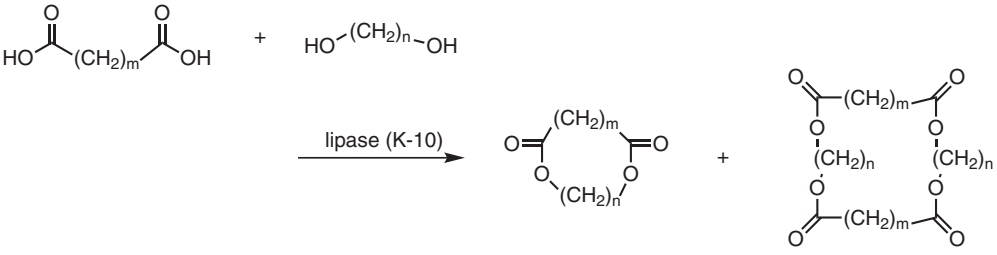
1.1.7 Enzymes

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 [264]. 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 [265]. Furthermore, the reaction between dicarboxylic acids and diols to arrive at macrolides is feasible through the use of lipase (K-10) (Scheme 1.59) [266].

Experimental Procedure [264] 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 letter. 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.



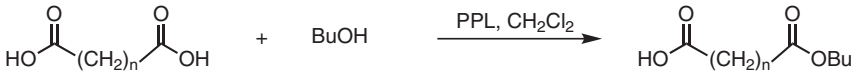
a: m= 12, n= 5 (18%)
b: m= 12, n= 16 (30%)
c: m= 10, n= 16 (56%)

a: 17%
b: 7%
c: 15%

Scheme 1.59

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 [267]. 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 be consequently concluded that the supercritical carbon dioxide methodology is not necessarily superior to that in organic solvent. More detailed description of the use of supercritical carbon dioxide is given in Section 7.3.

The enzymatic esterification is applicable to a variety of synthetic uses, for example, selective acylation of a cyclohexane-3,5-diol derivative in *trans*-(+)sobrerol synthesis [268], esterification of sterols with fatty acids [269], esterification of phenylacetic and 2-phenylpropanoic acids [270], and esterification of glycosides with lactic acid [271]. PPL-catalyzed esterification (PPL = porcine pancreatic lipase) allows selective formation of monoester of α, ω-dicarboxylic acids (Scheme 1.60) [272].

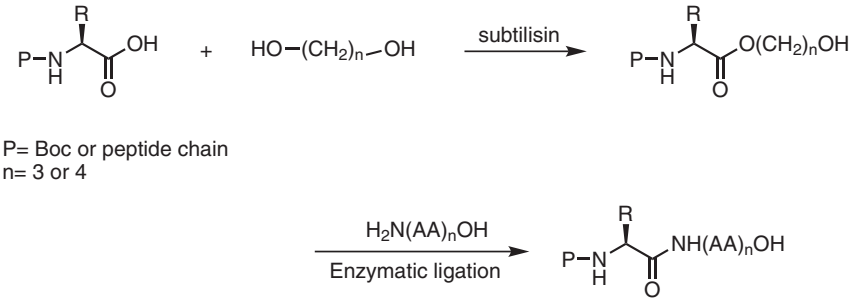


n= 4 (68%)
n= 6 (61%)
n= 7 (93%)
n= 8 (94%)
n= 14 (89%)

Scheme 1.60

The synthesis of amino acids 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 1.61). This approach can be coupled with kinetic-controlled reverse proteolysis in a two-step enzymatic peptide ligation scheme [273].



Scheme 1.61

Enzymatic esterification is accelerated by continuous azeotropic removal of water [274, 275]. Removal of water is also achievable by adsorptive control with molecular sieves [276]. On the other hand, when a small amount of water is added to a polar solvent, esterification by *Candida rugosa* exhibits better enantioselectivity and/or yield in esterification of *R*- and *S*-ketoprofen [277]. Modification of enzymes by surfactants improves the esterification process [278–281].

Esterification without solvent is another choice [282–287].

In addition to an advantage of facile separation of the enzyme, higher enantioselectivity and/or higher catalytic activity are also attainable by immobilization of enzymes. Chitosan immobilizes microbial lipases from *Candida rugosa*, *Pseudomonas fluorescens*, and *Candida antarctica* B to allow repeated uses in esterification of carboxylic acids with various alcohols [288, 289]. Poly(*N*-vinyl-2-pyrrolidone-*co*-styrene) can also immobilize *Candida rugosa*, resulting in enantioselective esterification of (*R, S*)-2-(4-chlorophenoxy)propanoic acid with *n*-tetradecanol [290]. Polypropylene is another immobilizer employable for synthesis of ethyl oleate [291–293].

Various inorganic supports are available for immobilizing enzymes. Silica gels are some of the most popular ones by which to increase the activity and to allow the repeated use of enzymes [294–296]. The stability of *Candida rugosa* can be enhanced when entrapped in hybrid organic-inorganic sol-gel powder prepared by acid-catalyzed polymerization of tetramethoxysilane and alkyltrimethoxysilanes [297]. Gas-phase esterification between acetic acid and ethanol is feasible with lipases immobilized in MCM molecular sieves [298]. Zeolite NaA can be a supporter of Novozyme, catalyzing esterification of geraniol with acetic acid [299]. The layered double hydroxides of Zn/Al—NO_3 hydrotalcite, Zn/Al-dioctyl sodium sulfosuccinate, Ni/Al-sodium dodecyl sulfonate, and Mg/Al-sodium dodecyl sulfate immobilize *Candida rugosa* effectively [300–302]. All immobilized enzymes exhibit higher activities and storage stability. $CaCO_3$ is a good adsorbent for *Rhizopus oryzae* and *Staphylococcus*, increasing the stability of the enzymes for esterification

of oleic acid [303, 304]. Continuous esterification is feasible with a packed-bed bioreactor [305, 306].

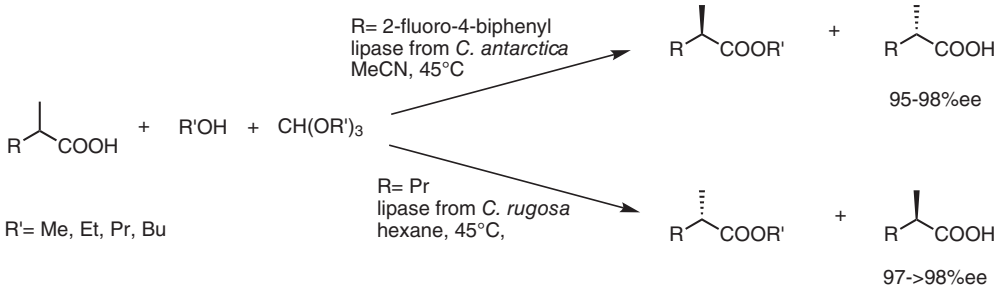
As seen above, immobilization of enzymes has become popular, and many immobilized enzymes are commercially available. Use of such enzymes is quite common now [307–311].

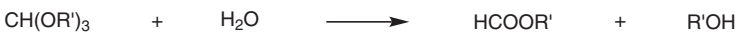
Kinetic resolution of racemic alcohols is feasible. α-Substituted cyclohexanols [312] and various aliphatic alcohols [313] are resolved through their reactions with alkanoic acids. Notably, the enantioselectivity of the lipase-catalyzed esterification of 2-(4-substituted phenoxy)propanoic acids is dramatically enhanced by addition of aqueous sodium dodecyl sulfate [314]. 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 the one of the enantiomers through induced fitting.

Experimental Procedure [313] 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 (3.0 g) 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 *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 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 because of the consumption of the water formed through hydrolysis of the orthoester (Scheme 1.62) [315].

Experimental Procedure [315] Scheme 1.62 Racemic fluorbiprofen (41 mmol, 10 g) is added to a solution of CH_3CN (1 l) containing tripropyl orthoformate (123 mmol, 26.5 mL), 1-propanol (20 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 fluorbiprofen 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*)-fluorbiprofen propyl ester (6.8 g, yield 58%, *ee* 64%).

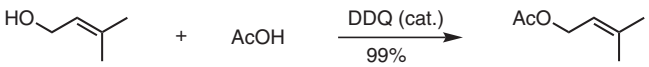




Scheme 1.62

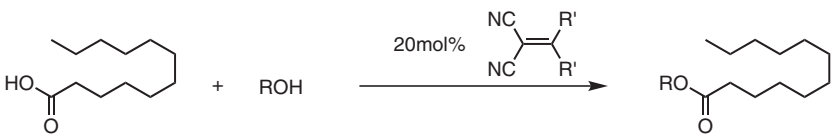
1.1.8 π-Acids

Treatment of allylic and tertiary benzylic alcohols with a catalytic amount of 2,3-dichloro-5,6-dicyanobenzoquinone in acetic acid affords the corresponding acetates (Scheme 1.63) [316]. 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 1.63

Tetracyanoethylene and dicyanoketene dimethyl acetal are more versatile π-acids (Scheme 1.64) [317]. 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 1.64