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Dehydrative condensation catalyses

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Contents

1. Introduction

It is becoming increasingly attractive to replace current chemical processes with more environmentally benign alternatives.[1] The development of catalytic reactions that produce the desired products with higher atom efficiency[2] and a lower *E*-factor,[3] defined as the mass ratio of waste to the desired product, is needed. The stoichiometric use of condensing reagents and activators, and the excess use of substrates should be avoided if possible. This report focuses on recent progress in the catalytic dehydrative condensation reactions of carboxylic acids and phosphoric acids with alcohols and amines to give the corresponding esters and amides in excellent yields *without the activation of acids with stoichiometric condensing agents*.

2. Catalytic dehydrative condensation reactions

2.1. Synthesis of carboxylic esters

The ester condensation reaction is one of the most fundamental organic transformations, and more environmentally benign alternative approaches to those currently used by the chemical industry are in strong demand.[4] Conventional esterifications are conducted with excess carboxylic acids (or alcohols) against a counterpart in the presence of an acid catalyst, or with stoichiometric dehydrating reagents or activated carboxylic acid derivatives in the presence of a stoichiometric base. The use of excess substrates wastes these compounds, and the use of stoichiometric dehydrating reagents or activated carboxylic acid derivatives produces significant amounts of byproducts from the reagents. The contamination of crude products with excess substrates or byproducts requires substantial materials, energy and time for the purification of esters. In contrast, catalytic direct condensation between equimolar amounts of carboxylic acids and alcohols, in principle, lacks these drawbacks. Therefore, it is a desirable method for the synthesis of esters. Recently, several catalytic methods for the ester condensation

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reaction between equimolar amounts of carboxylic acids and alcohols have been published.[5–31]

2.1.1. Metal salt catalyses

In 2000, Yamamoto and co-worker reported a highly efficient and direct ester condensation of an equimolar mixture of carboxylic acids and alcohols catalyzed by Hf(IV) salts such as $HfCl_4$, $HfCl_4\cdot 2THF$, and $Hf(O\text{-}t\text{-}Bu)_4$ under azeotropic-reflux conditions in hydrocarbons with removal of the water produced.[5a] In 2002, they reported that Zr(IV) salts were also effective catalysts.[5c] Although Ti(IV) and Sn(IV) salts are well known to be good esterification catalysts, their catalytic activities are lower than those of Hf(IV) and Zr(IV) salts. Various other metal salts and organometallics such as $3,4,5\text{-}F_3C_6H_2B(OH)_2$, BCl_3, $AlCl_3$, $SiCl_4$, $ScCl_3$, $Sc(OTf)_3$, $FeCl_3$, $CoCl_2$, $NiCl_2$, $ZnCl_2$, $GaCl_3$, $GeCl_4$, $SbCl_3$, $LaCl_3$, and $PbCl_2$ are either less active or inert.

Hf(IV) and Zr(IV) compounds generally have low toxicity (LD_{50} [$HfCl_4$, oral, rat]=2400 mg kg^{-1}; LD_{50} [$ZrCl_4$, oral, rat]=1688 mg kg^{-1}), and are not considered particularly poisonous. The water tolerance of $HfCl_4$, $ZrCl_4$, and their THF complexes has been investigated by comparing their catalytic activities to those upon exposure to air (Table 1). $HfCl_4\cdot 2THF$ and $ZrCl_4\cdot 2THF$, which are less expensive than the corresponding metal(IV) alkoxides, are hydrolytically more stable than $HfCl_4$ and $ZrCl_4$ because the coordination of THF to $HfCl_4$ and $ZrCl_4$ effectively suppresses their hydrolysis. Furthermore, Hf(IV) salts are hydrolytically more stable than the corresponding Zr(IV) salts, although the former are more expensive than the latter. Thus, $HfCl_4\cdot 2THF$ is the most effective catalyst among the metal salts, which have been examined.[5a]

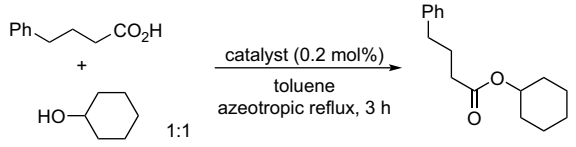
Dehydrative condensation proceeds more rapidly under azeotropic-reflux conditions in hydrocarbons than under heating without solvents. The efficiency of water removal is highly significant for the dehydrative esterification system because of the strong affinity of the metal salt catalysts with water and equilibration with the hydrolysis of esters.

Less than 0.2 mol % of $HfCl_4\cdot 2THF$ and $ZrCl_4\cdot 2THF$ are suitable for condensing various carboxylic acids with not only primary alcohols, but also sterically hindered secondary alcohols. However, esterification with tertiary alcohols does not proceed. Although aromatic substrates such as benzoic acid and phenol are less reactive than aliphatic substrates, their reactions proceed very well when *o*-xylene or mesitylene is used instead of toluene. α,β-Unsaturated alcohols, α,β-unsaturated carboxylic acids, and acid-sensitive substrates, such as a benzylic secondary alcohol, a tetrahydropyranyl (THP) ether, a *tert*-butyldimethylsilyl ether, a nitrile, and a tetrahydro-2-furoic acid, can all be used under these conditions. In particular, the resulting α,β-unsaturated esters are industrially important polymer materials. In addition to these examples, cyclopropanecarboxylic acid, 4-nitrophenylacetic acid, α-alkoxycarboxylic acids, and perfluorocarboxylic acid can also be used. Notably, direct thioesterifications proceed quantitatively in the presence of 5 mol % of $HfCl_4\cdot 2THF$ or $ZrCl_4\cdot 2THF$.

Kobayashi and co-workers reported that direct thioesterification from an equimolar mixture of carboxylic acids and alcohols proceeds in toluene in the presence of 1–10 mol % of trifluoromethanesulfonic acid (TfOH) under azeotropic-reflux conditions to afford the corresponding thioesters in high yields (Table 3).[6] In contrast, $HfCl_4$ and $ZrCl_4$ were much less active. These negative results may be caused by the concentration of substrates (0.1 M), which is 50-fold lower than the conditions (5 M) shown in Table 2.

Hf(IV) and Zr(IV) salts are effective catalysts for the polycondensation reaction of α,ω-hydroxycarboxylic acids or an equimolar mixture of aliphatic α,ω-dicarboxylic acids and aliphatic

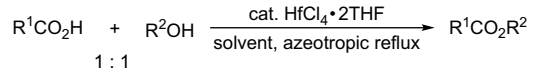
Table 1
Water tolerance of esterification catalysts

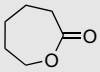
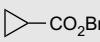
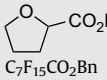


Dehydration (h) on exposure to air[a]	Conversion (%) into cyclohexyl 4-phenylbutyrate			
	$HfCl_4$	$HfCl_4\cdot 2THF$	$ZrCl_4$	$ZrCl_4\cdot 2THF$
0	74	71	71	69
40	—	70	65	75
47.5	63	71	49	—
60	31	68	8	—
65	—	67	5	65
96	—	65	5	62
137	—	61	—	48

[a] Catalysts exposed to air (ca. 50% humidity) at 20 °C.

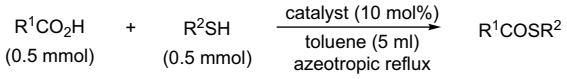
Table 2
Scope of the substrate for $HfCl_4\cdot 2THF$-catalyzed dehydrative esterification reaction



Entry	$R^1CO_2R^2$	$HfCl_4\cdot 2THF$ (mol %)	Time (h)	Yield (%)
1[a]	$Ph(CH_2)_3CO_2Bn$	0.1	18	>99
2[a]	$Ph(CH_2)_3CO_2Bn$	0.1[b]	18	99
3	$[Ph(CH_2)_3CO_2CH_2]_3CHEt$	0.2	24	>99
4	$Ph(CH_2)_3CO_2C_6H_{11}$-*c*	0.2	5	94
5	$Ph(CH_2)_3CO_2$-menthyl-*l*	0.2	36	>99
6	$Ph(CH_2)_3CO_2CEt_3$	1.0	24	0
7[c]	$Ph(CH_2)_3CO_2Ph$	0.2	36	91
8	$c\text{-}C_6H_{11}CO_2Bn$	0.2	7	96
9	Et_2CHCO_2Bn	0.2	60	98
10	$PhCO_2Bn$	0.2	15	92
11	1-Adamantane-CO_2Bn	0.2	10	92
12[d]	$PhCO_2C_6H_3Me_2$-3,5	1.0	24	95
13		0.2	10	96
14		0.2	10	94
15	$Ph(CH_2)_3CO_2CH_2C{\equiv}CPh$	0.2	6	97
16	$Ph(CH_2)_3CO_2CH_2C{=}CPh$-(*E*)	0.2	24	92
17	$Ph(CH_2)_3CO_2CHPhMe$	0.2	13	>99
18	$Ph(CH_2)_3CO_2(CH_2)_8OTHP$	0.2	18	95
19	$Ph(CH_2)_3CO_2(CH_2)_8OTBDMS$	0.2	24	93
20	$Ph(CH_2)_3CO_2(CH_2)_2CN$	0.2	24	94
21	$Ph(CH_2)_3COSBn$	5	24	97 (<2)[e]
22	$Ph(CH_2)_3COS(CH_2)_9Me$	5	17	>99
23	$Me(CH_2)_{10}COS(CH_2)_{11}Me$	5	24	>99 (93)[b]
24		0.2	17	95
25[f]	(*E*)-PhCH=$CHCO_2Bn$	0.2	10	92
26[f]	(*E*,*E*)-MeCH=CH-CH=$CHCO_2Bn$	1.0	38	>99
27[f]	MeCH=$CHCO_2Bn$	1.0	38	94
28[f]	$Me_2C{=}CHCO_2Bn$	1.0	38	>99
29[f]	(*E*)-MeCH=$CMeCO_2Bn$	1.0	45	>99
30[f]	$CH_2{=}CHCO_2Bn$	1.0	40	>99
31[f]	$CH_2{=}CMeCO_2Bn$	1.0	40	99
32	$p\text{-}NO_2C_6H_4CH_2CO_2Bn$	1.0	18	98
33[g]	(*S*)-PhCH(OMe)CO_2Bn	0.2	13	98
34		0.2	6	>99
35	$C_7F_{15}CO_2Bn$	0.2	11	82

[a] Toluene used.
[b] $ZrCl_4\cdot 2THF$ used instead of $HfCl_4\cdot 2THF$.
[c] *o*-Xylene used.
[d] 1,3,5-Mesitylene used.
[e] Data for the uncatalyzed reaction indicated.
[f] Benzene used instead of toluene.
[g] Enantiomerically pure carboxylic acid used. Enantiomeric purity of ester: 84%.

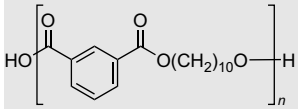
Table 3
TfOH-catalyzed dehydrative thioesterification



R^1,R^2=	Catalyst, yield (%)
n-$C_{11}H_{23}$, n-$C_{12}H_{25}$	TfOH, 97 $HfCl_4$, 0 (cf. Table 2, entry 23) $ZrCl_4$, 10 (cf. Table 2, entry 23)

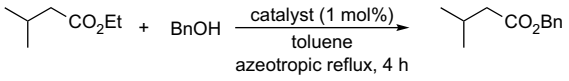
α,ω-diols.[5a,c] In most cases, the polycondensation proceeds quantitatively in the presence of 0.2 mol % of $HfCl_4\cdot 2THF$ in *o*-xylene with the removal of water for 1 day (Table 4). Although polycondensation between aromatic dicarboxylic acids and aromatic diols does not occur, due to the insolubility of aromatic carboxylic acids in *o*-xylene and the lower nucleophilicity of aromatic diols, polycondensation to semi-aromatic polyesters proceeds successfully.

Table 4
$HfCl_4\cdot 2THF$-catalyzed direct polycondensation[a]

Polyester	Yield[b] (%)	DP[c]	M_n[d] (/10^4)	M_w[d] (/10^4)
$HO[CO(CH_2)_8O]_nH$	95	>200	1.82	3.40
$HO[CO(CH_2)_{11}O]_nH$	97 (88)	>200	2.77	7.24
$HO[CO(CH_2)_2CO_2(CH_2)_6O]_nH$	98	>200	2.24	3.87
$HO[CO(CH_2)_7CO_2(CH_2)_{10}O]_nH$	97	>200	2.69	5.83
	96	>200	—	—

[a] Unless otherwise noted, polyesterification carried out in the presence of 0.2 mol % $HfCl_4\cdot 2THF$ for 1 day.
[b] Isolated yield.
[c] Average degree of polycondensation (DP) determined by ^1H NMR.
[d] Two linear TSK-gel-GMHXL GPC columns used.

Interestingly, Hf(IV) and Zr(IV) salts do not catalyze the transesterification of esters with alcohols. In contrast, Ti(IV) salts are known to be good catalysts for not only the dehydrative condensation of carboxylic acids with alcohols, but also transesterification (Eq. 1).[5b,c] Therefore, Hf(IV) and Zr(IV) salts are highly effective catalysts for the selective esterification reaction of primary alcohols in the presence of secondary alcohols, because they show no activation for transesterification.



(1)

Catalyst	Yield (%)
$TiCl_4$:	98
$HfCl_4$•2THF:	0
$ZrCl_4$•2THF:	<2

The distance between the two hydroxy groups in the diols strongly affects the reactivity: the reactivity reduces in the order 1,4-, 1,3-, and 1,2-diol, because of the tight chelation of diols with metal(IV) ions.[5b,c] The reaction of 1-adamantanecarboxylic acid with 1,5-hexanediol gives the primary monoester with >99% selectivity in 94% yield. In the reaction of cyclohexanecarboxylic acid with betulin, the primary monoester is obtained in 91% yield. In the reaction of 4-phenylbutyric acid with 3-(4-hydroxyphenyl)-1-propanol, the primary monoester is obtained in 93% yield (Fig. 1).

In 2004, Ishihara and co-workers reported that $HfOCl_2\cdot 8H_2O$ and $ZrOCl_2\cdot 8H_2O$ as well as $HfCl_4\cdot 2THF$ and $ZrCl_4\cdot 2THF$ are highly effective catalysts for the direct ester condensation reaction.[5d] The former are also commercially available and water tolerant. In contrast,

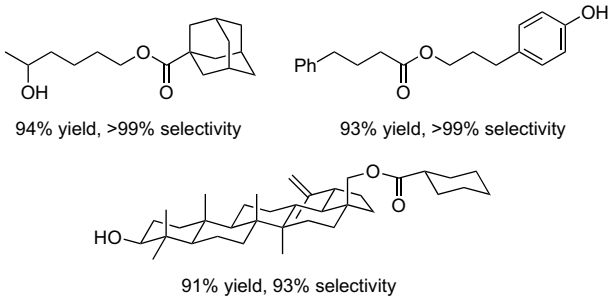


Figure 1. Selective esterification of primary hydroxy group of diols catalyzed by $HfCl_4\cdot 2THF$ (5 mol %).

$ZrOCl_2\cdot xH_2O$ ($x\leq 6$), which is transformed from anhydrous $ZrCl_4$ with exposure to air, is much less active and less soluble in the reaction solution than $ZrCl_4\cdot 2THF$ and $ZrOCl_2\cdot 8H_2O$. Furthermore, $Zr(OAc)_x(OH)_y$ ($x+y=4$) is also a practically useful catalyst, because it is very stable in air and less expensive than other active catalysts including Hf(IV) salts.

The hydration number (x) of $ZrOCl_2\cdot xH_2O$ and $HfOCl_2\cdot xH_2O$ is eight.[5d] The crystal structure of $ZrOCl_2\cdot 8H_2O$ is known to be an ionic cluster $[Zr_4(OH)_8(H_2O)_{16}]Cl_8\cdot 12H_2O$ (Fig. 2).[7] The

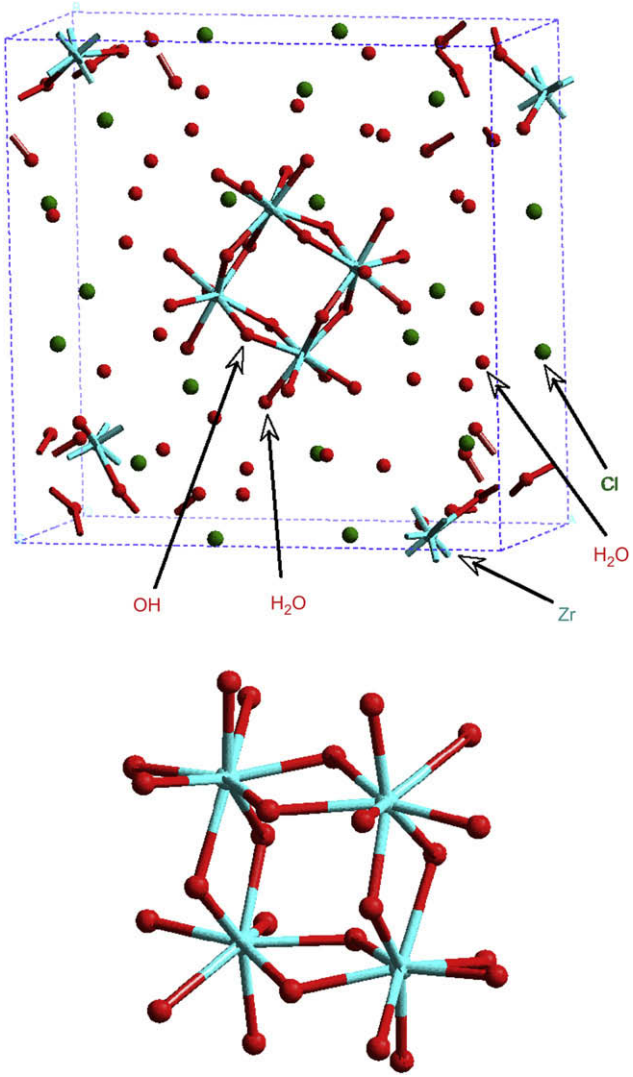


Figure 2. X-ray crystal structure of $[Zr_4(OH)_8\cdot 16H_2O]Cl_8\cdot 12H_2O$ (=$ZrOCl_2\cdot 8H_2O$) and the cationic cluster $[Zr_4(OH)_8\cdot 16H_2O]^{8+}$.[7]

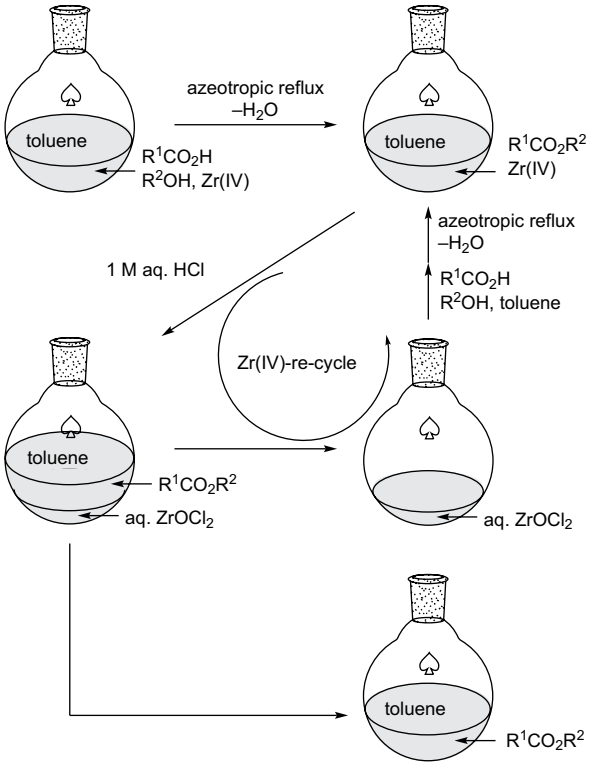


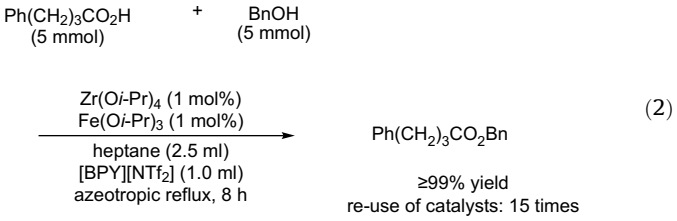
Figure 3. Simple recycling of Zr(IV) catalyst in esterification.

dehydration of $ZrOCl_2 \cdot 8H_2O$ lowers its catalytic activity and solubility in the reaction solution. Anhydrous $ZrOCl_2$ does not dissolve even in water, and the solid is amorphous, based on the results of XRD analysis. There are no zirconium–chlorine bonds in the cationic cluster structure. The ester condensation may proceed through a ligand-exchange reaction with carboxylic acids and/or alcohols on the cationic cluster. However, the mechanism is not clear.

After dehydrative condensation is carried out in the presence of catalytic amounts of Zr(IV) or Hf(IV) salts such as $MOCl_2 \cdot xH_2O$, $MCl_4 \cdot 2THF$, $M(OH)_x(OAc)_y$, $M(OR)_4$, etc., metal species can be recovered as $MOCl_2 \cdot xH_2O$ from the aqueous layers by quenching with 1 M HCl aqueous solution. The recovered aqueous solution of $MOCl_2$ can be re-used repeatedly as a catalyst without any loss of activity for dehydrative condensation under azeotropic-reflux conditions (Fig. 3).

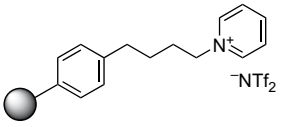
In 2005, Ishihara and co-workers found a synergism in catalytic activity with the combined use of Hf(O-*i*-Pr)$_4$ or Zr(O-*i*-Pr)$_4$ and Fe(O-*i*-Pr)$_3$ for direct esterification, and developed a very simple method for their extraction with ionic liquids for their recovery and re-use without any hazardous chemicals such as HCl.[5e]

A synergistic effect is observed in the combination of Zr(IV) or Hf(IV) with not only Fe(III) but also Al(III), Ga(III), and Sn(IV) salts. The 1:1 Zr(IV)–M(n) combined catalyst promotes the dehydrative esterification in biphasic solvents of hydrocarbons and *N*-butylpyridinium trifluoromethanesulfonimide ([BPY][NTf$_2$]). After esterification is complete, the produced ester and the Zr(IV)–Fe(III) combined catalyst are separated into hydrocarbon and [BPY][NTf$_2$] layers, respectively. Thus, a solution of Zr(IV)–M(n) combined catalyst in [BPY][NTf$_2$] can be recycled repeatedly without isolation (Eq. 2). When the esterification is carried out using Zr(O-*i*-Pr)$_4$ alone, most of the Zr(IV) species remains in the hydrocarbon layer. However, when 1 equiv of Fe(O-*i*-Pr)$_3$ is added per Zr(O-*i*-Pr)$_4$, the Zr(IV) species is easily transferred to a layer of [BPY][NTf$_2$] together with Fe(III).



(2)

In 2006, Ishihara and co-workers developed polystyrene resin-bound pyridinium triflylimide (**1**) to immobilize a Zr(IV)–Fe(III) combined salt catalyst (Fig. 4).[5f] Compound **1** is prepared by a coupling reaction of the commercially available 4-bromobutylpolystyrene with pyridine and a subsequent anion-exchange reaction with lithium triflylimide. Although Zr(O-*i*-Pr)$_4$ and Fe(O-*i*-Pr)$_3$ are not immobilized in **1** in the presence of carboxylic acids and alcohols, they are easily recovered as a **1**-immobilized binary metal complex by filtration after complete esterification, and can be re-used without any loss of activity. These phenomena demonstrate that the Zr(IV)–Fe(III) complex acts as a homogeneous catalyst, even in the presence of **1**. This is a unique example of a re-usable homogeneous catalyst that can be recovered by filtration. Zr(IV) and Fe(III) species are released from **1** by washing with a solution of acids such as carboxylic acids. In contrast, no Zr(IV) or Fe(III) species are released from **1**, even upon washing with not only less-polar solvents, but also polar solvents such as diethyl ether, ethyl acetate, and alcohols under neutral conditions.



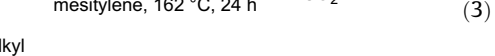
1

Figure 4. Polystyrene resin-bound pyridinium triflylimide **1**.

In general, homogeneous catalysts are more active than heterogeneous catalysts, due to the difference in the surface area of the active site. However, the latter can be more easily recovered and re-used by filtration than the former. This new method offers great advantages as both a homogeneous catalyst and a heterogeneous catalyst.

In 2005, Sugi and co-workers achieved direct condensation between equimolar amounts of long-chain carboxylic acids and long-chain alcohols, where the number of carbons is $\geq$10, by using unsupported and mesoporous silica-supported $ZrOCl_2 \cdot 8H_2O$ as catalysts.[8a,b] However, this is less active in combination with a branched acid and secondary alcohols to give the corresponding esters.

According to Sugi's report,[8c] some typical multivalent metal salts, such as chloride, sulfate, and acetate of Fe(III), Al(III), Ga(III), In(III), Zr(IV), Hf(IV), Zn(II), Co(II), Ni(II), Mn(III), Cr(III), and Cu(II), have catalytic activities for the esterification of saturated and unsaturated long-chain aliphatic carboxylic acids with long-chain aliphatic alcohols. In particular, Fe(III), Ga(III), In(III), and Zn(II) salts show very high catalytic activities. These catalysts are spontaneously separated from the reaction mixtures and can be recycled for use in further reactions. The catalytic activities in the esterification of palmitic acid using $FeCl_3 \cdot 6H_2O$ decrease with an increase in the number of carbons in the alcohols: $C_{12} \sim C_{14} > C_{16} \gg C_{18}$ (Eq. 3). A similar decrease in yield is observed in the case of $ZrOCl_2 \cdot 8H_2O$.[8a]



(3)

R^1, R^2 = long-chain alkyl

In 1998, Zhang reported that $Fe_2(SO_4)_3 \cdot xH_2O$ was an efficient catalyst for the esterification of not only aliphatic, but also aromatic carboxylic acids with primary alcohols (Eq. 4).[9a,b] In this catalytic reaction, excess amounts of substrate (2–4 equiv) are required to give the corresponding esters in good yields. In addition, large excess amounts of alcohols are required as solvents for the esterification of mandelic acid.[9c]

$$R^1CO_2H + R^2OH \xrightarrow[\text{benzene or toluene, azeotropic reflux}]{Fe_2(SO_4)_3 \cdot xH_2O\ (2\ mol\%)} R^1CO_2R^2 \quad \text{good yield} \qquad (4)$$

R^1CO_2H/R^2OH = 2 or 0.25~0.5

R^1 = primary alkyl or aryl groups, R^2 = primary alkyl groups

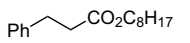
In 2008, Sugi and co-workers found that tungstophosphoric acid ($H_3PW_{12}O_{40} \cdot xH_2O$, HPW) and MCM-48-supported HPW were potential catalysts for the esterification of long-chain fatty acids with alcohols in a supercritical CO_2 (*sc*-CO_2) medium, even at low temperature (100 °C) and a short reaction period (6 h).[10] The high performances of HPW in the *sc*-CO_2 medium are due to the effective mass transfer of reactants and products for catalysis under these conditions. The yields of esters are enhanced with an increase in the chain length of acids and alcohols in the esterification in *sc*-CO_2. The MCM-48-supported HPW catalysts are active, even after several recycle experiments.

In 2005, Bartoli and co-workers reported $Zn(ClO_4)_2 \cdot 6H_2O$-catalyzed condensation between nearly equimolar amounts of carboxylic acids and alcohols without solvent under heating conditions (80–100 °C).[11] However, $MgSO_4$ (1 equiv) is required as a dehydrating agent to complete the reaction (Eq. 5). The catalyst and $MgSO_4$ can be recovered from the reaction mixture diluted in CH_2Cl_2 by filtration and heating in an oven at 60 °C overnight. The re-activated catalyst can be re-used without any appreciable loss of activity.

$$R^1CO_2H + HOR^2 \xrightarrow[MgSO_4\ (1\ equiv),\ 80\ °C]{Zn(ClO_4)_2 \cdot 6H_2O\ (5\ mol\%)} R^1CO_2R^2 \qquad (5)$$

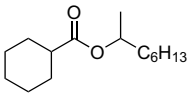
1.1 : 1.0

Examples


95% (8 h) [*cf.* 85% (8 h, withoout $MgSO_4$)]

$C_8H_{17}CO_2C_{22}H_{45}$ 95% (12 h)

$PhCO_2C_8H_{17}$ 89% (100 °C, 26 h)


70% (10 mol% cat., 40 h)

In 2002, Otera and co-workers reported the first fluorous biphasic condensation between carboxylic acids and alcohols in a 1:1 molar ratio.[12] As shown in Figure 5, an equimolar mixture of carboxylic acid and alcohol together with $[Cl(C_6F_{13}C_2H_4)_2SnOSn(C_2H_4C_6F_{13})_2Cl]_2$ (**2**, 5 mol %) in FC-72 (perfluorohexanes) is heated at 150 °C in a stainless pressure bottle to produce esters. After being cooled to room temperature, toluene is added to the mixture. The organic layer including esters is separated from the fluorous layer including the catalyst. The catalyst is recovered from the FC-72 layer without weight loss, but not in a pure form. A portion of the catalyst is converted into unidentifiable species, which are presumably organotin carboxylate derivatives. Nonetheless, the recovered material has a catalytic activity similar to that of the original, and the FC-72 solution that contained the organotin species can be recycled for repeated use. Since water is much less fluorophilic than alcohols, the condensation proceeds more efficiently in fluorous solvents. The reaction is sensitive to the steric bulk of the reactants. Secondary

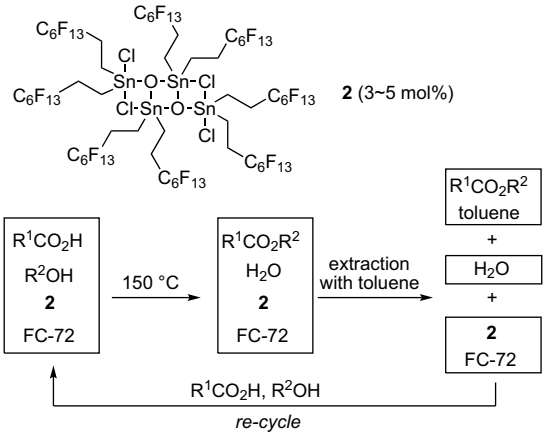
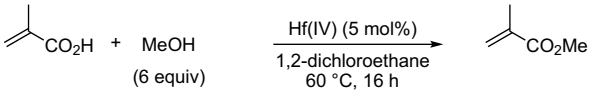


Figure 5. Esterification in biphasic system.

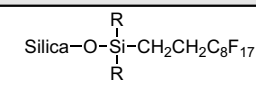
alcohols as well as carboxylic acids with a bulky group at the α position do not give satisfactory yields. Neither simple aromatic carboxylic acids nor α,β-unsaturated carboxylic acids give good yields.

In 2003, Nishikido and co-workers reported that fluorous reverse-phase silica gel (FRPSG)-supported $Hf[N(SO_2C_8F_{17})_2]_4$ acted as an effective catalyst for the direct esterification of methacrylic acid with 6 equiv of methanol in 1,2-dichloroethane.[13a] The FRPSG-supported catalyst can be recovered after the reaction by simple filtration. In contrast, $Hf[N(SO_2C_8F_{17})_2]_4$ without a support cannot be recovered, although $Hf[N(SO_2C_8F_{17})_2]_4$ is more active than the FRPSG-supported hafnium(IV) salt (Table 5).

Table 5
Reusability of Hf(IV) catalysts for esterification



Re-use	**1** (%)	**2** (%)	**3** (%)	**4** (%)
FRPSG-$Hf[N(SO_2C_8F_{17})_2]_4$	86	93	94	96
$Hf[N(SO_2C_8F_{17})_2]_4$	87	74	67	56

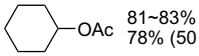
FRPSG:  (R = Me, EtO, Silica-O)

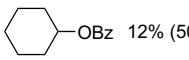
In 2004, Nishikido and co-workers reported that the use of tin(IV) and hafnium(IV) bis(perfluorooctanesulfonyl)imide complexes gave excellent yield and selectivity for transesterification and direct esterification (Eq. 6), respectively, with an equimolar ratio of the reactants in fluorous biphasic system (FBS).[13b,c] These metal complexes are selectively soluble in the lower fluorous phase, and can be recovered simply by phase separation without loss of their catalytic activities. With respect to the Hf(IV)-based catalysts, $Hf[N(SO_2C_8F_{17})_2]_4$ shows a significantly higher activity than $Hf(OTf)_4$, $HfCl_4$, and $HfCl_4 \cdot 2THF$ in FBS.

$$R^1CO_2H + R^2OH \xrightarrow[\text{perfluorodecalin/1,2-dichloroethane (1:1 v/v), 50–90 °C, 8–24 h}]{Hf[N(SO_2C_8F_{17})_2]_4 \text{ or } Sn[N(SO_2C_8F_{17})_2]_4\ (5\ mol\%)} R^1CO_2R^2 \quad \text{high yield} \qquad (6)$$

1 : 1

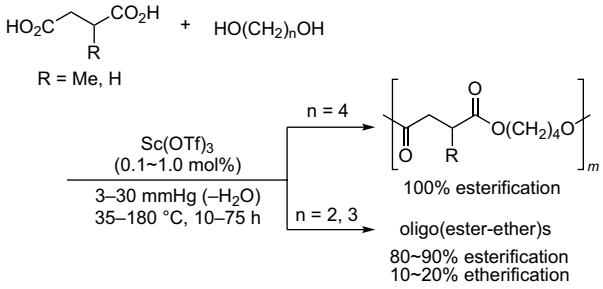
Examples


81~83% (50 °C, 8 h; Hf(IV) cat. was re-used 4 times.)
78% (50 °C, 8 h; Sn(IV) cat.)


12% (50 °C, 24 h; Hf(IV) cat.)

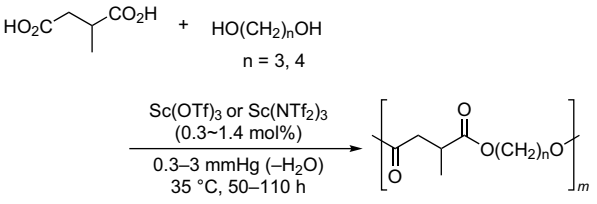
It is well known that $Sc(OTf)_3$ and $Sc(NTf_2)_3$ are extremely effective catalysts for the acylation of alcohols with carboxylic

anhydrides at low temperature.[14] In 2003, Takasu and co-workers reported that $Sc(OTf)_3$ catalyzed the direct esterification of ethanol with acetic acid (2 equiv) at room temperature.[15a] Furthermore, they applied this significant finding to the direct polycondensation of α,ω-dicarboxylic acids with α,ω-diols to synthesize polyesters (Scheme 1).[15a] $Sc(OTf)_3$ catalyzes not only polyesterification, but also etherification as a side reaction, which depends on the chain length (methylene number) of the diols. The catalyst makes it possible to prepare a biodegradable polyester, poly(butylene succinate) (PBS), with an M_n of $>1.0\times10^4$, even at 35 °C.



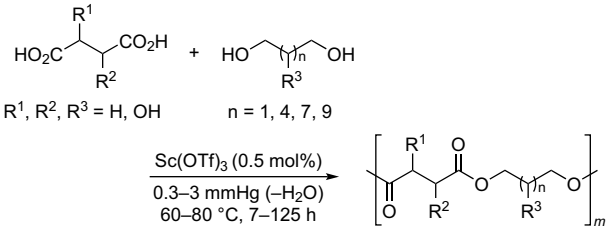
Scheme 1. Direct bulk (melt) polycondensation.

In 2005, Takasu and co-workers demonstrated the room-temperature direct polycondensation of α,ω-dicarboxylic acids with α,ω-diols catalyzed by $Sc(OTf)_3$ and $Sc(NTf_2)_3$, and reported that this breakthrough made it possible to synthesize aliphatic polyesters ($M_n>1.0\times10^4$) (Eq. 7).[15b] The catalysts used are easily recovered by solubilization in chloroform or chloroform–hexane (1:1 v/v) and successive extraction with water [95% for $Sc(OTf)_3$, 90% for $Sc(NTf_2)_3$]. The molecular weight distributions (M_w/M_n) are relatively narrow (1.4–1.7). The results support the notion that the polycondensation proceeds with the suppression of transesterification. This polycondensation system under mild conditions makes it possible to use thermally unstable monomers containing a carbon–carbon double bond and a bromo functionality.[15c] These Sc(III) catalysts are also effective for the direct polycondensation of L-lactic acid.[15d] Poly(L-lactic acid) (PLA) is obtained with an M_n of 1.1×10^4 in 90% yield by catalytic solution polycondensation in xylene at 135 °C for 48 h. In contrast, bulk polycondensation gives PLA in low yield.



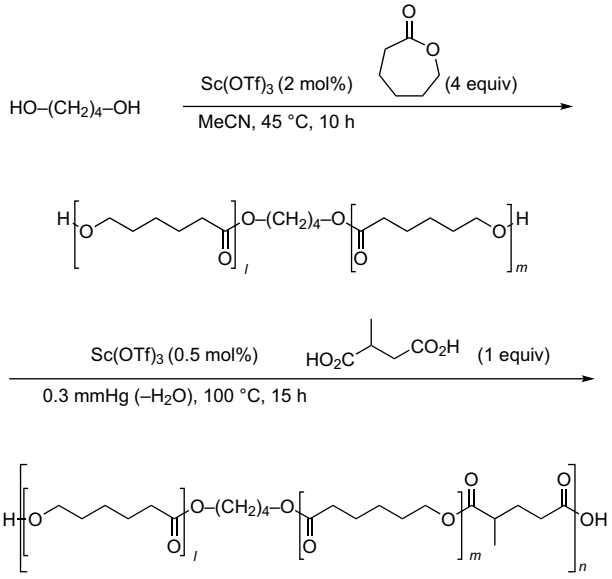
(7)

Furthermore, the one-step synthesis of polyester pendant hydroxy groups has been achieved by the chemoselective polycondensation of several primary diols with dicarboxylic acids having pendant secondary hydroxy groups including tartaric acid and malic acid using $Sc(OTf)_3$ under kinetic control (Eq. 8).[15e]



(8)

In 2007, Takasu and co-workers demonstrated a new system for the combination of chain and step polymerizations in which $Sc(OTf)_3$ catalyzes both polymerization modes.[15f,g] Ring-opening polymerization of ε-caprolactone initiated from 1,4-butanediol proceeds in acetonitrile at 45 °C ($M_n=1.2\times10^3$, $M_w/M_n=1.3$). After acetonitrile is removed under reduced pressure, bulk polycondensation with methylsuccinic acid is performed at 100 °C for 15 h to give the polyester in high yield: M_n and M_w/M_n are, respectively, 1.39×10^4 and 1.9 (Scheme 2). Transesterification does not occur during the two polymerizations. The chemoselective polycondensation of a dicarboxylic acid containing a hydroxy group and a diol and subsequent ring-opening copolymerization initiated from the pendant hydroxy groups have also been demonstrated using $Sc(OTf)_3$ as a dual catalyst.

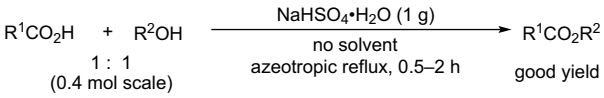


Scheme 2. Dual catalytic system for combination of ring-opening polymerization and subsequent direct polycondensation.

2.1.2. *Brønsted acid catalyses*

Conventionally, the ester condensation reaction of acid-resistant substrates is catalyzed by Brønsted acids such as HCl, H_2SO_4, *p*-toluenesulfonic acid (*p*-TsOH), etc. For acid-sensitive substrates, weak Brønsted acids such as pyridinium *p*-toluenesulfonate (PPTS) are often used. However, these have lower catalytic activities and a limited range of reactants.

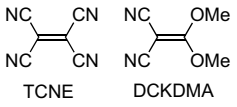
In 1999, Li succeeded in the rapid and convenient $NaHSO_4\cdot H_2O$-catalyzed synthesis of esters from an equimolar mixture of aliphatic carboxylic acids and primary or secondary alcohols under neat conditions (Eq. 9).[16] However, the substrates are limited to simple carboxylic acids such as acetic acid, propanoic acid, monochloroacetic acid, and trichloroacetic acid

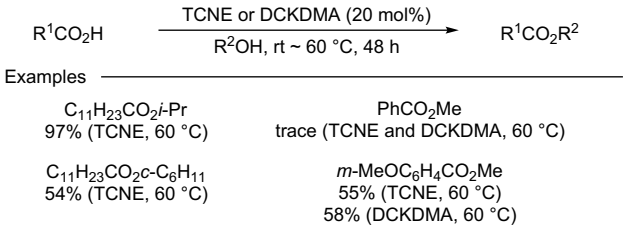


(9)

Metal-free organocatalytic methods are also desirable, especially for industrial processes. In 1997, Masaki and co-workers found that the π-acid tetracyanoethylene (TCNE) and its derivative, dicyanoketene dimethyl acetal (DCKMA), catalyzed the esterification of lauric acid with various types of alcohols (Eq. 10).[17] However, large excess amounts of alcohols are required as solvents. This method is effective for the methyl esterification of a variety of carboxylic acids including aromatic, α,β-unsaturated, α-hydroxy, and *N*-Cbz- and *N*-Boc-protected α-amino acids without racemization from room

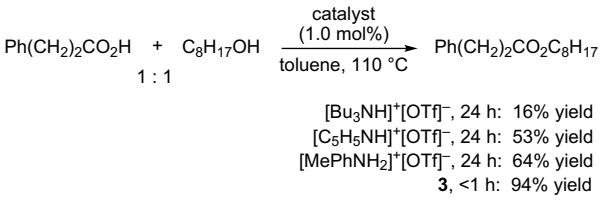
temperature to 60 °C. In addition, TCNE acts as a catalyst in the transesterification of methyl laurate.





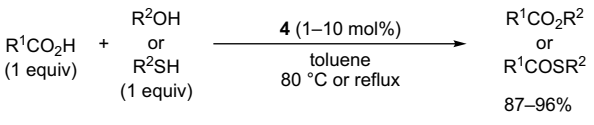
(10)

In 2000, Tanabe and co-workers reported that *N*,*N*-diphenylammonium triflate ($[Ph_2NH_2]^+[OTf]^-$, **3**) (1.0–10 mol %) efficiently catalyzed the ester condensation reaction under heating at 80 °C and without the removal of water.[18] Ester condensation processes that do not require dehydration are highly desirable, especially for large-scale industrial processes, since the dehydration process requires additional dehydrating reagents or energy for azeotropic reflux, as well as additional apparatus and time, which causes the production cost of the esters to increase. Since **3** is a strong Brønsted acid, which is characterized as an onium salt of a superacid with a weak base (Eq. 11), it is difficult to use in the reaction of sterically demanding and acid-sensitive alcohols.

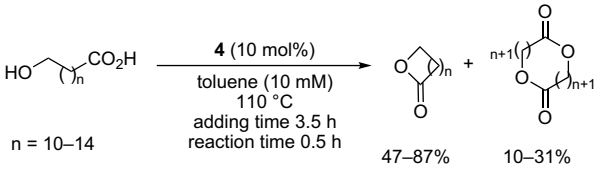


(11)

In 2006, Tanabe and co-workers reported that *N*-pentafluorophenylammonium triflate ($[C_6F_5NH_3]^+[OTf]^-$, **4**) (1–10 mol %) was superior to **3** as a catalyst for the dehydrative esterification (Eq. 12).[19] This catalyst is effective for thioesterification between a 1:1 mixture of carboxylic acids and thiols at 80 °C and the macrolactonization of ω-hydroxycarboxylic acids to give 13- to 17-membered macrolactones at 110 °C (Eq. 13).



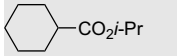
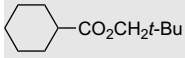
(12)



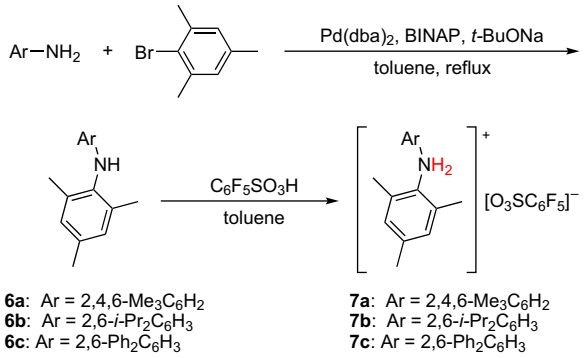
(13)

However, there are only a few successful examples of dehydrative esterification with secondary alcohols catalyzed by **3** or **4**,[18,19] probably due to their strong acidity. L-Menthol is a suitable substrate because it is more stable than non-substituted cyclic alcohols and acyclic secondary alcohols under acidic conditions. In contrast, conformationally flexible secondary alcohols are often dehydrated to alkenes under acidic conditions. Soon after the above paper[18] was published, **3** was reported by other researchers to be a good catalyst for ring-opening polymerization of lactide or ε-caprolactone.[20]

Table 6
Effect of medium in **3**-catalyzed esterification (80 °C, 24 h, **3** (2–10 mol %))

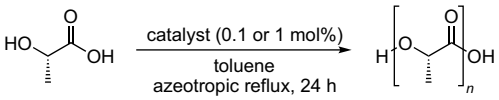
Ester	**3** (mol %)	Yield (%)		
		C_6F_{14}	Hexane	Toluene
	2	65	19	15
	10	84	40	50
i-$PrCO_2CH_2$-*t*-Bu	10	48	12	10

In 2003, Jenner and Gacem reported that the esterification of bulky acids with alcohols catalyzed by **3** proceeded more smoothly in perfluorohexane than in toluene and hexane (Table 6).[21] In sharp contrast, the esterification catalyzed by **3** (Scheme 3) proceeds more rapidly than Tanabe's catalytic system, the former regardless of the choice of hydrocarbons or fluorous hydrocarbons.[22c] The advantage of using fluorous hydrocarbons, in addition to enhancing reactivity, materializes in their environmental innocuity, full recovery by simply extracting the ester layer and re-using in subsequent runs.



Scheme 3. Synthesis of ammonium catalysts **7a–c**.

In 2008, Abiko and co-workers reported that triphenylphosphonium triflate ($[Ph_3PH]^+[OTf]^-$, **5**) was a superior catalyst to **3** and **4** in thermal stability and catalytic activity for the direct polycondensation of lactic acid and related hydroxy acids to polyesters (Eq. 14).[23] For example, poly(L-lactic acid) of $M_w=16\times10^4$ ($M_w/M_n=1.6$) is produced by direct polycondensation of water-containing L-lactic acid in xylene with 0.5 mol % of **5** for 72 h with a Dean–Stark apparatus.



catalyst	1 mol% cat.	0.1 mol% cat.
4	M_w = 33,000	M_w = 31,000
3	M_w = 17,000	M_w = 6,800
5	M_w = 16,000	M_w = 48,000

(14)

In 2005, Ishihara and co-workers reported that bulky *N*,*N*-diarylammonium pentafluorobenzenesulfonates **7a–c** were mild and selective ester condensation catalysts (Scheme 3).[22a] Bulky *N*-aryl-*N*-mesitylamine (**6**) is prepared from the corresponding arylamine by palladium-catalyzed cross-coupling with 2,4,6-mesityl bromide. The reaction of **6a–c** with an equimolar amount of pentafluorobenzenesulfonic acid ($C_6F_5SO_3H$) gives the ammonium salts **7a–c**. Catalyst **7a** is commercially available from TCI (Tokyo Chemical Industry Co., Ltd.) since January 2007.

It is known that $C_6F_5SO_3H$ [$pK_a(CD_3CO_2D)=11.1$, $H_0=-3.98$] is a weaker acid than TfOH [$pK_a(CD_3CO_2D)=-0.74$, $H_0=-14.00$],

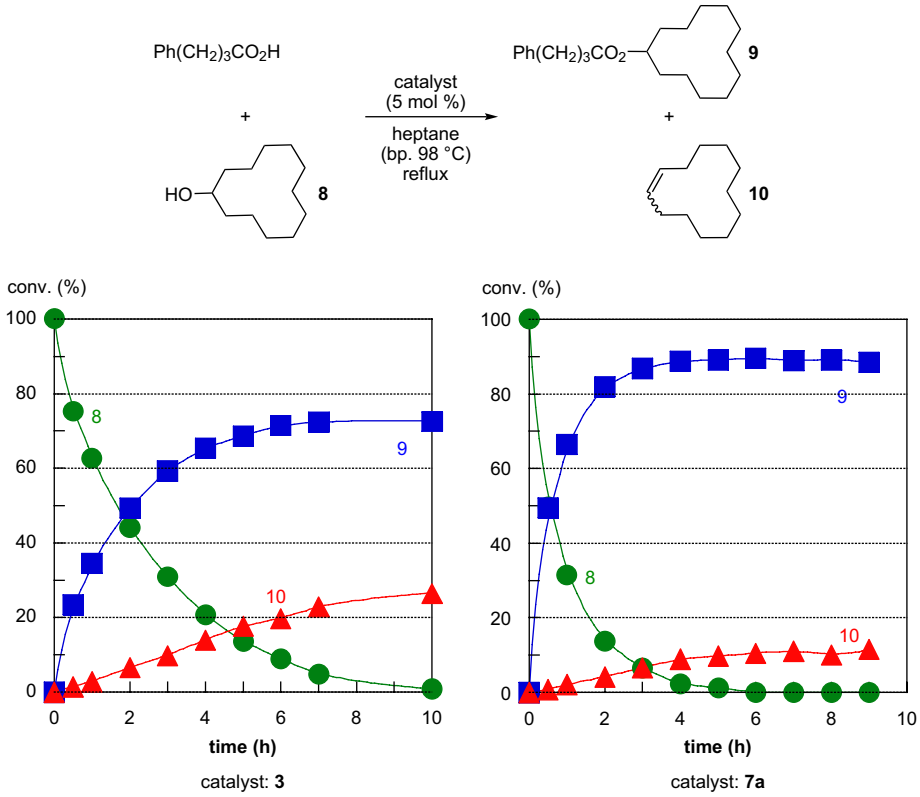


Figure 6. Ester condensation of 4-phenylbutyric acid with **9**. The proportions of **8** (green line), **9** (blue line), and **10** (red line) in the reaction mixture over time are shown.

concd H_2SO_4 [pK_a(CD_3CO_2D)=7.5, H_0=−11.93], and *p*-TsOH [pK_a(CD_3CO_2D)=8.5, H_0=−4.5]. This means that **7a–c** are milder acids than the corresponding ammonium triflates, sulfates, and tosylates. Nevertheless, **7a–c** have much higher catalytic activities than Tanabe's catalyst **3** (Fig. 6).

The use of less-polar solvents such as heptane is important. The catalytic activity of **7a** increases in such less-polar solvents to give the corresponding ester in good yield. One of the limitations of the present method arises from the requirement for less-polar solvents: it is difficult to perform ester condensations of hydrophilic substrates that cannot dissolve in less-polar solvents.

The single-crystal X-ray structures of **7a** and **3** are shown in Figure 7. The crystals obtained are dimeric cyclic ion pairs composed of two *N*,*N*-diarylammonium cations and two arenesulfonate anions. Interestingly, the dimeric cyclic ion pair of **7a** is stabilized by two intermolecular π–π interactions, as well as four hydrogen bonds, while there is no intermolecular π–π interaction in the ion pair of **3**. It is conceivable that a 'hydrophobic wall' prevents polar water molecules from gaining access to the active site of the catalysts and thus inhibits inactivation of the catalyst by water. Furthermore, the steric bulkiness of the mesityl and pentafluorophenyl groups in the catalyst suppresses the dehydrative elimination of secondary alcohols to produce alkenes.

Furthermore, a supramolecular complex **11** composed of two *N*,*N*-diarylammonium cations, four pentafluorobenzenesulfonate anions, and two oxonium cations has been obtained by the recrystallization of **3c**, which was a 1:1 molar mixture of **6c** and $C_6F_5SO_3H$ in $CHCl_3$–hexane (Scheme 4 and Fig. 8).[22c] Interestingly, two ammonium cations and two oxonium cations are surrounded by 12 hydrophobic aryl groups, like reverse micelles.[24] Cyclic ion pair **11** is thermodynamically and conformationally stabilized by not only four HN^+–H···O=SO_2^- and six H_2O^+–H···O=SO_2^- intermolecular hydrogen bonds, but also two intermolecular π–π interactions between *N*-mesityl groups and pentafluorophenyl groups, two intermolecular π–π interactions between phenyl groups and pentafluorophenyl groups, and two intramolecular π–π interactions between *N*-mesityl groups and phenyl groups. The extremely high catalytic activity of **7c** in ester condensation may be ascribed to the hydrophobic environment around the ammonium protons in **11**, which includes carboxylic acids in place of water.

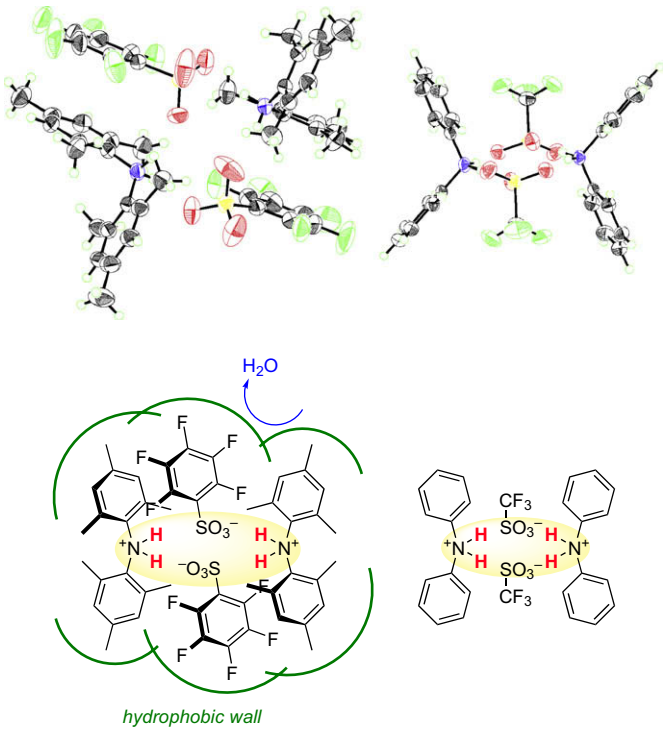
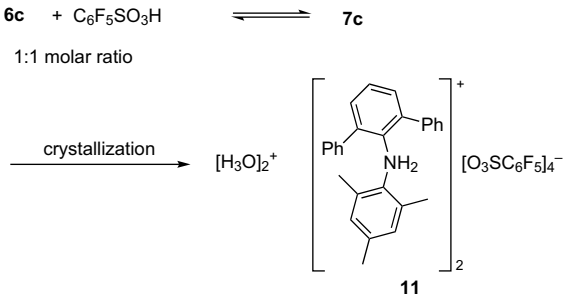


Figure 7. ORTEP diagrams of single-crystal X-ray structures of **7a** (*left*) and **3** (*right*). F=green, N=blue, O=red, S=yellow.



Scheme 4. Formation of **11** by crystallization of **7c**.

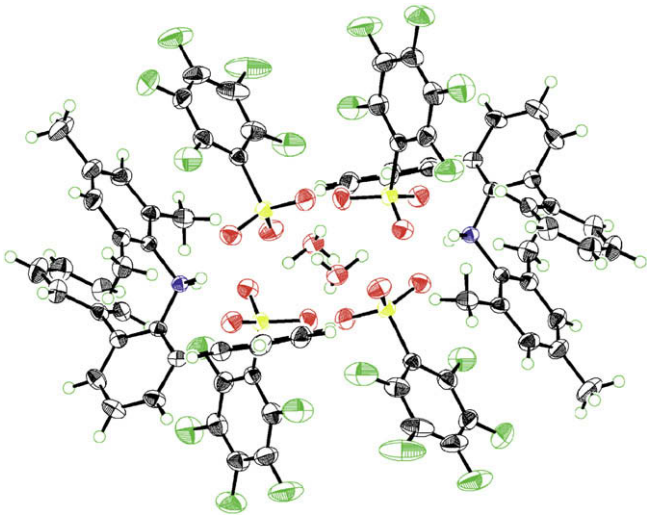


Figure 8. Single-crystal X-ray structure of **11**. Upper, ORTEP drawing; lower, space-filling drawing. F=green. N=blue, O=red, S=yellow.

The ester condensation reaction of 4-phenylbutyric acid with 6-undecanol in hexane has been compared using reflux conditions without the removal of water and azeotropic-reflux conditions with the removal of water (Fig. 9). The reaction catalyzed by **3** is slightly decelerated under reflux conditions without removal of the water produced. In contrast, the reaction catalyzed by the more bulky catalyst **7b** proceeds very well without the influence of water.

The generality and scope of the esterification catalyzed by **7a** are shown in Table 7. 2-Unsubstituted carboxylic acids, 2-monosubstituted carboxylic acids, and sterically demanding 2,2-disubstituted carboxylic acids are smoothly condensed to produce the corresponding esters (entries 1–6 and 15). α,β-Unsaturated carboxylic acids and benzoic acids are also transformed into the corresponding esters (entries 7–11 and 22). 2-Alkoxycarboxylic acids and 3-hydroxycarboxylic acids are very reactive substrates, probably due to favorable chelation between the substrates and **7a** (entries 12, 13, 16, 24, and 29–31). 4-Oxopentanoic acid is selectively esterified without a protecting ketone moiety (entries 14 and 23), and **7a** can be used for acid-sensitive alcohols such as benzyl alcohol, allylic alcohols, propargylic alcohols, and secondary alcohols (entries 17–28). In particular, esterification with a sterically demanding alcohol such as 6-undecanol gives the desired esters in good yield with less than 5% of alkenes (entries 20–24). Although Lewis-acidic metal salts such as Hf(IV) and Zr(IV) are not adapted to 1,2-diols, due to tight chelation of the diols with metal ions,[5c] these diols are also esterified in high yield by **7a** (entries 26–28). Less-reactive aryl alcohols and 1-adamantanol are also esterified in high yields (entries 29–31).

Ester condensation reactions with more reactive primary alcohols proceed even at ambient temperature (22 °C) without solvents (Table 8). For example, when condensation between

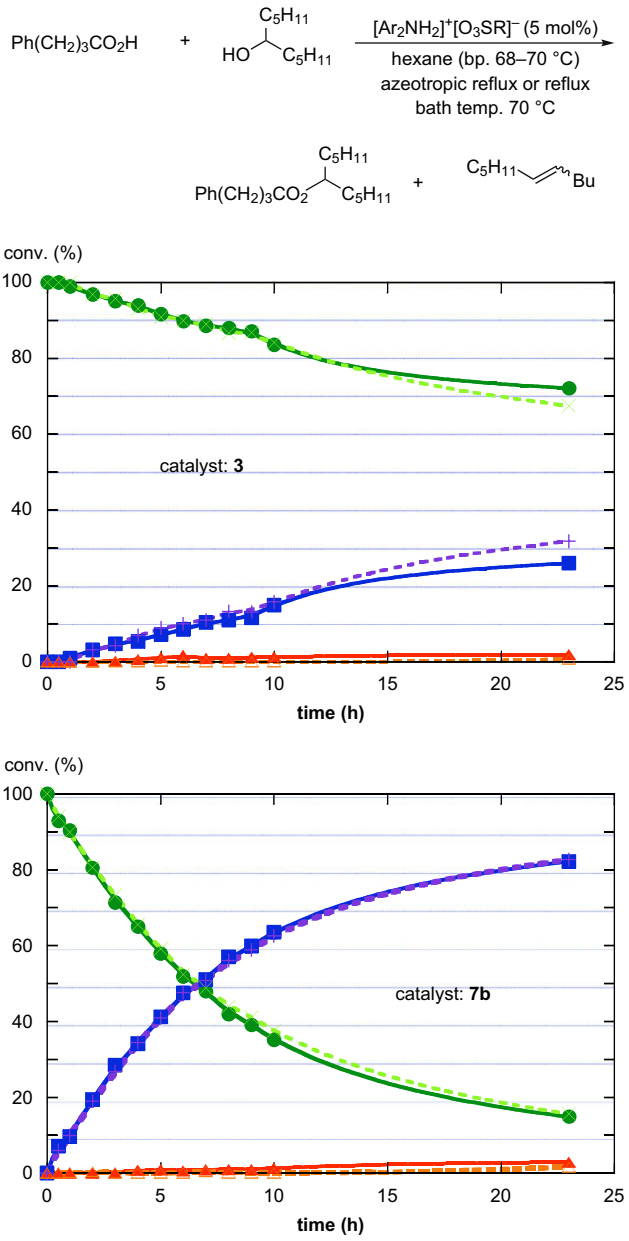


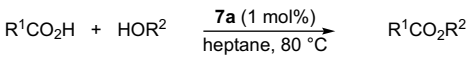
Figure 9. Ester condensation of 4-phenylbutyric acid with 6-undecanol. The catalytic activities of **3** and **7b** under reflux conditions without the removal of water (solid lines) and azeotropic-reflux conditions (broken lines) were compared. The proportions of 6-undecanol (green line), 6-undecyl 4-phenylbutyrate (blue line), and 5-undecene (red line) in the reaction mixture over time were evaluated by ^{1}H NMR analysis.

4-phenylbutyric acid and methanol (1.1 equiv) is carried out in the presence of **7a** (1 mol %) without the removal of water for 24 h, the corresponding ester is obtained in 95% yield. 1-Octanol is also reactive, albeit slightly less reactive than methanol.[22]

One major problem associated with the use of soluble catalysts lies in the recovery of the catalyst from the reaction medium. A simple solution is to immobilize the catalyst on a polymeric matrix. The bulky *N,N*-diarylammonium pentafluorobenzenesulfonate catalyst **12** immobilized on a polystyrene support can be recovered and re-used more than 10-fold without any loss of catalytic activity (Fig. 10). *In contrast, a polystyrene-supported diarylammonium triflate cannot be prepared, since the polymer support decomposes with superacidic TfOH.*

Although bulky *N,N*-diarylammonium pentafluorobenzenesulfonates efficiently catalyze ester condensation under heating

Table 7
Esterification reactions between equimolar mixtures of carboxylic acids and alcohols catalyzed by **7a**



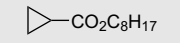
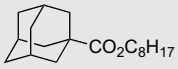
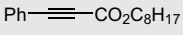
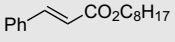
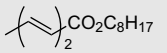
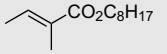
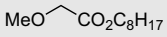
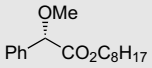
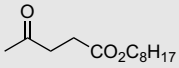
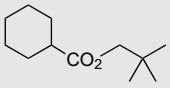
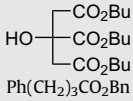
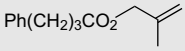
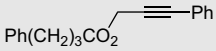
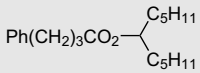
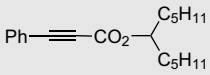
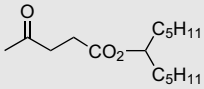
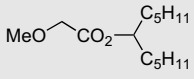
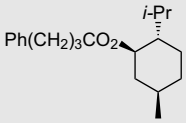
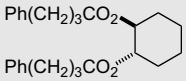
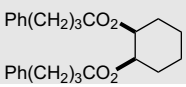
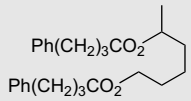
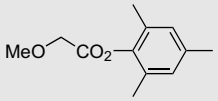
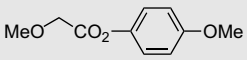
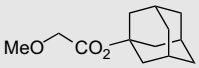
Entry	$R^1CO_2R^2$	Time (h)	Yield[a] (%)
1	$Ph(CH_2)_3CO_2C_8H_{17}$	1	99
2		8	94
3	$c\text{-}C_6H_{11}CO_2C_8H_{17}$	5	98
4	$Et_2CHCO_2C_8H_{17}$	24	94
5	$t\text{-}BuCO_2C_8H_{17}$	6	93
6		7	91
7		5	96
8		24	96
9		24	91
10		24	90
11	$PhCO_2C_8H_{17}$	24	91
12		1	99
13		3	>99
14		3	98
15		2	71
16		24	97
17	$Ph(CH_2)_3CO_2Bn$	2	95
18		3	>99
19		24	88
20[b]		23	83 (3)
21[c]		24	85 (0)
22[c]		30	88 (0)
23		24	82 (5)
24		4	95 (0)
25		10	93 (0)
26[c]		48	90 (0)
27[d]		48	90 (0)

Table 7 (*continued*)

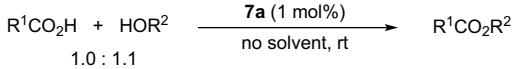
Entry	$R^1CO_2R^2$	Time (h)	Yield[a] (%)
28		24	97 (0)
29[e]		24	73
30[e]		24	99
31		72	92

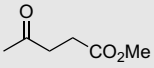
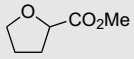
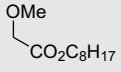
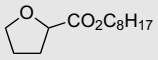
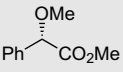
[a] Yield of alkenes shown in parentheses.
[b] Compound **7b** (5 mol %) used in hexane at 70 °C.
[c] Compound **7b** (1 mol %) used.
[d] Compound **7a** (5 mol %) used.
[e] Compound **7a** (10 mol %) used at 115 °C.

conditions, even without the removal of water, the use of a non-polar solvent such as heptane is critical for high reactivities. In the course of their continuing study on ester condensation, Ishihara and co-workers found that the reaction of some alcohols with carboxylic acids was efficiently promoted by sulfonic acids under open-air and solvent-free conditions.[25]

The solvent effect plays a key role in sulfonic acid-catalyzed ester condensation under conditions without the removal of water (Fig. 11, graph A). When the reaction of 6-undecanol with 4-

Table 8
Ester condensation reaction at room temperature without solvents



Entry	$R^1CO_2R^2$	Time (h)	Yield (%)
1	$Ph(CH_2)_3CO_2Me$	24	95
2		48	90
3		11	91
5[a]		48	69
6		24	74
7		42	69

[a] Compound **7c** (1 mol %) used.

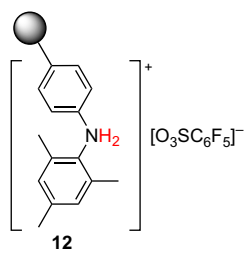


Figure 10. Preparation of polymer-supported catalyst **12**.

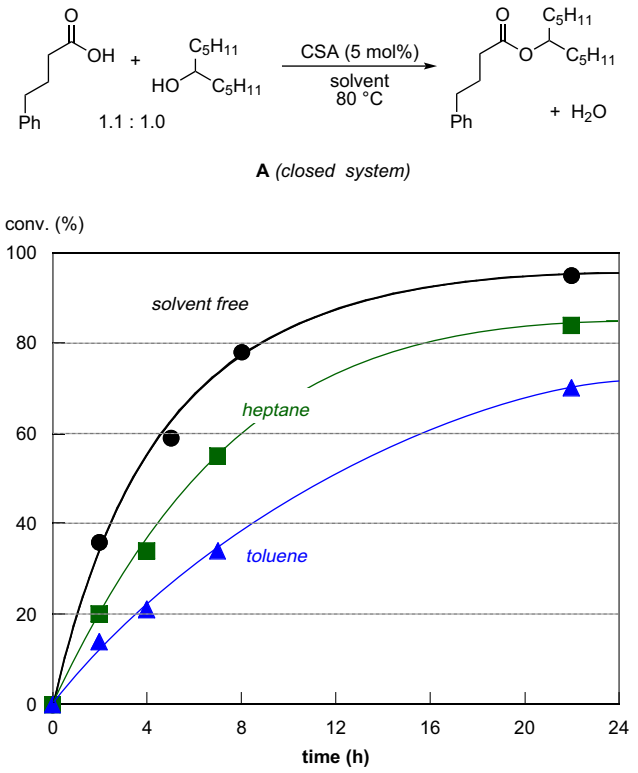


Figure 11. Solvent effect in CSA-catalyzed ester condensation: black line, solvent free; green line, heptane; blue line, toluene.

phenylbutyric acid is conducted in toluene in the presence of 10-camphorsulfonic acid (CSA, 5 mol%) without removal of the water produced, the reaction proceeds slowly and the corresponding ester is obtained in moderate yield (blue line). In contrast, the reaction proceeds more rapidly in heptane, a less-polar solvent (green line). Interestingly, the reaction proceeds more rapidly under solvent-free conditions with little influence of water (black line). To reduce experimental errors, these reactions were performed in screw-capped vessels. In contrast to Lewis acids such as Hf(IV) salts, sulfonic acids show weak affinity with water.

As shown in Figure 11, when CSA-catalyzed ester condensation is performed in a screw-capped vessel, the reaction does not proceed to completion, even though the reaction time is prolonged, due to hydrolysis of the product and/or inactivation of the CSA by the water produced. In contrast, when the condensation is performed in an open-air vessel to remove water spontaneously, the reaction proceeds slightly more rapidly than in a screw-capped vessel and proceeds to completion (Fig. 12, graph B). The condensation under solvent-free conditions in the open-air vessel shows the same reactivity as that conducted under azeotropic-reflux conditions in cyclohexane (bp 80.7 °C, bath temperature ~115 °C) (Fig. 12, graph C).

Sulfonic acid (1–5 mol%)-catalyzed ester condensation with an equimolar mixture of various alcohols and carboxylic acids has been examined under solvent-free conditions in an open-air vessel (Table 9). The ester condensation of primary alcohols proceeds very well, even with sterically hindered carboxylic acids (entries 1–6). The present protocol is a highly practical and atom-economical esterification method, since it does not require any solvent or additional equipment, materials, or energy for dehydration. Through the present protocols, a large amount of esters can be synthesized in a rather small apparatus. For example, 49 g of 2-octyldodecyl palmitate was synthesized in a 100-ml round-bottomed flask (entry 3). Esters derived from secondary alcohols are also obtained in good yields (entries 7–16). Ester condensation of *trans*-1,2-cyclohexanediol gives the corresponding diester in high yields (entries 7–9), while Lewis-acidic metal salts, such as $HfCl_4 \cdot 2THF$, are not suitable for use with these diols, due to tight chelation with metal ions.[5] In general, the catalytic activities of Brønsted acids depend on

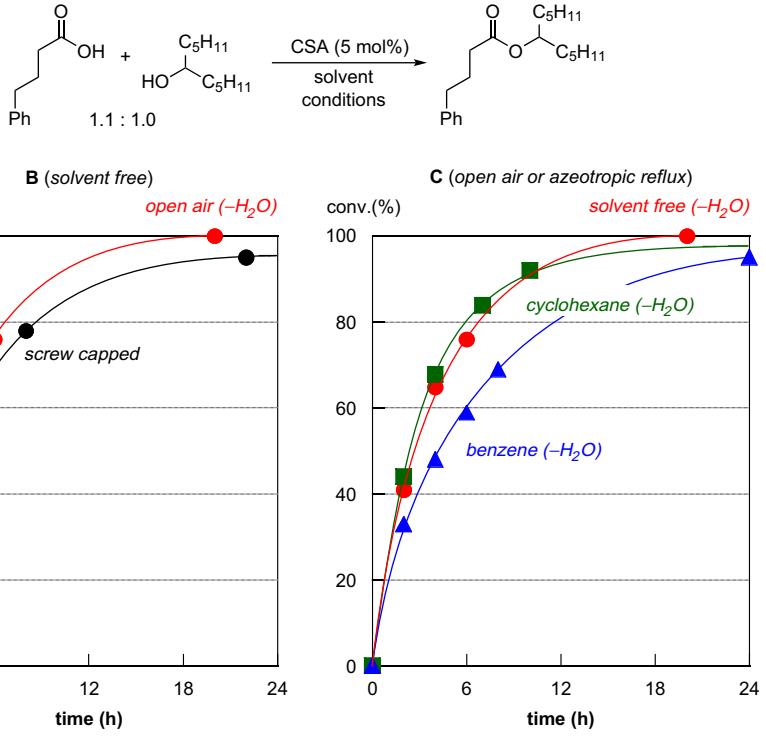
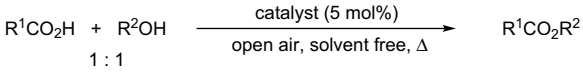
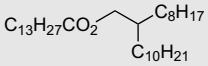
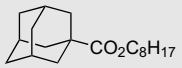
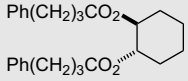
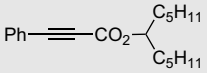
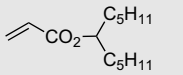
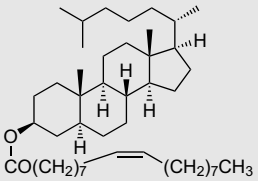
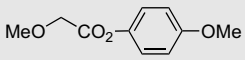
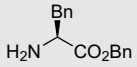


Figure 12. Effect of dehydration in CSA-catalyzed ester condensation. Red line, solvent-free conditions in an open-air vessel; black line, solvent-free conditions in a screw-capped vessel; green line, azeotropic reflux in cyclohexane (bp 80.7 °C); blue line, azeotropic reflux in benzene (bp 80.1 °C).

Table 9
Ester condensation under solvent-free conditions[a]



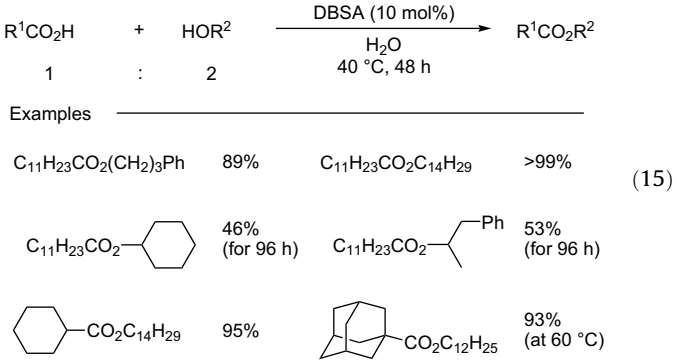
Entry	Product ($R^1CO_2R^2$)	Catalyst	Conditions (°C, h)	Isolated yield (%)
1[b]		H_2SO_4	60, 39	97
2[b]		CSA	60, 39	92
3[b,c]		CSA	60, 24	97
4[d]		H_2SO_4	80, 3	93
5[d]		TsOH	80, 3	95
6[d]		CSA	80, 3	92
7[d]		H_2SO_4	80, 22	89 [93:7][e]
8[d]		TsOH	80, 22	95
9[d]		CSA	80, 22	95
10		H_2SO_4	80, 19	78 [12][f]
11		TsOH	80, 29	95
12		CSA	80, 29	90
13[d]		H_2SO_4	80, 48	81
14[d]		TsOH	80, 48	87
15[d]		CSA	80, 48	91
16[g]		TsOH	60, 35	98
17		H_2SO_4	80, 20	34
18		TsOH	80, 26	39
19		CSA	80, 26	35
20[h]		CSA	60, 36	89 [>99][i]

[a] Unless otherwise noted, reaction conducted on 2-mmol scale.
[b] Reaction conducted with sulfonic acid (1 mol %).
[c] Reaction conducted on 100-mmol scale in 100-ml round-bottomed flask.
[d] Reaction conducted with 1.1 equiv carboxylic acid.
[e] Ratio of trans–cis isomer shown in brackets.
[f] Yield of alkenes shown in brackets.
[g] Reaction conducted with octane.
[h] Reaction conducted with 2 equiv benzyl alcohol.
[i] Optical purity of the product shown in brackets.

their pK_a values. However, sterically hindered secondary alcohols (entries 10–12) are easily dehydrated to give alkenes under acidic conditions, including catalytic amounts of H_2SO_4. Aliphatic sulfonic acids such as CSA successfully promote the ester condensation of secondary alcohols without the production of alkenes. Ester condensation of acrylic acid also proceeds without promoting the undesired conjugate addition (entries 13–15). When the substrates and/or products are solid, they are effectively dissolved by the addition of a small amount of octane (entry 16).

In contrast to the ester condensation of aliphatic alcohols, the reaction of 4-methoxyphenol with methoxyacetic acid gives poor results (entries 17–19), while bulky ammonium salt-catalyzed esterification gives the corresponding ester in 99% yield (see entry 30 in Table 7).[22] Amino acid esters can be prepared through the present ester condensation by using 1 equiv of an additional sulfonic acid with complete retention of its chiral center (entry 20).

In 2001, Kobayashi and co-workers realized dehydration reactions including esterification, etherification, thioetherification, and dithioacetalization in water by a surfactant-type catalyst, dodecylbenzenesulfonic acid (DBSA, p-$C_{12}H_{25}C_6H_4SO_3H$).[26a,b,27] In these reactions, the DBSA and substrates formed emulsion droplets with interiors that were hydrophobic enough to exclude water molecules generated during the reactions. Detailed studies on the esterification revealed that the yields of esters are affected by temperature, the amount of DBSA used, and the substrates (Eq. 15).



(15)

To compare the esterification in water with that under neat conditions, the esterification of lauric acid with 3-phenyl-1-propanol in the presence of DBSA has been carried out without any solvents (Fig. 13). Since DBSA is soluble in organic substrates, the reaction mixture is homogeneous at the beginning. Therefore, the reaction system is regarded as being similar to that with conventional dry conditions, but in high concentration without dehydrating agents. Although the reaction under neat conditions is faster than that in water, probably because of the absence of competitive protonation between the substrate and a large number of water molecules under the neat conditions, the yield of the ester at equilibrium is changed. Under neat conditions, the amount of water in the reaction mixture must be less than 1 equiv with respect to the substrate. On the other hand, a large excess of water is present in the reaction in water.

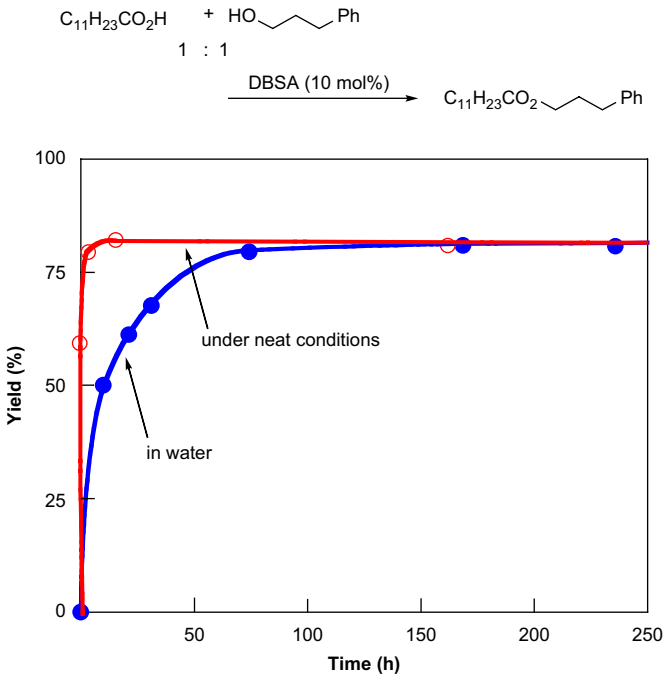
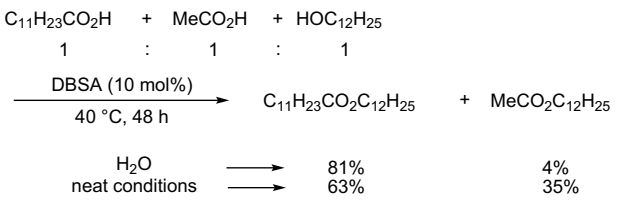


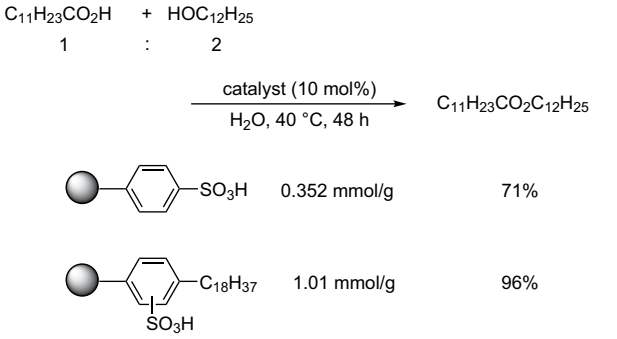
Figure 13. Reaction profiles for DBSA-catalyzed direct esterification. Closed circle: in water; open circle: under neat conditions.

Based on the differences in the hydrophobicity of the substrates, unique selective esterification and etherification in water have been attained (Eq. 16).[26b]



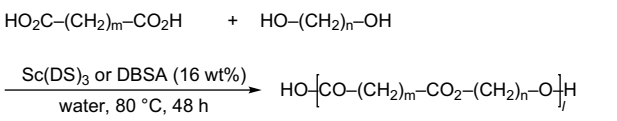
(16)

In 2002, Manabe and Kobayashi developed hydrophobic polystyrene-supported sulfonic acids as recoverable and re-usable catalysts for the dehydrative esterification of carboxylic acids with alcohols in water.[26c] In these reactions, esters are obtained in high yields without the use of any dehydrating agents or apparatus. The sulfonic acid contents of the catalysts and the presence of long alkyl chains on the benzene rings of the polystyrene significantly affect the catalytic activity (Eq. 17).



(17)

In 2006, Takasu and co-workers demonstrated that direct polycondensation of dicarboxylic acids with alcohols proceeds with a surfactant-combined Brønsted acid such as DBSA[26a,b] and a Lewis acid such as scandium tris(dodecyl sulfate) [Sc(DS)$_3$],[28] which were developed by Kobayashi and co-workers, without the removal of water, since esterification occurs at the interface of the emulsion in water (Eq. 18).[29] Emulsion polycondensation of 1,9-nonanediol with dodecanedioic acid proceeds at 80 °C for 48 h in the presence of 16 wt % DBSA, and the corresponding polyester (M_w=10.1×10^3, M_w/M_n=2.0) is obtained in 95% yield.

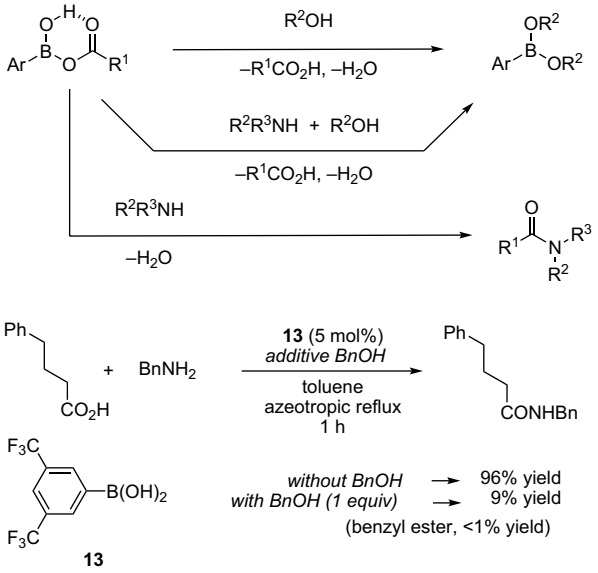


(18)

2.1.3. Boron(III) catalyses

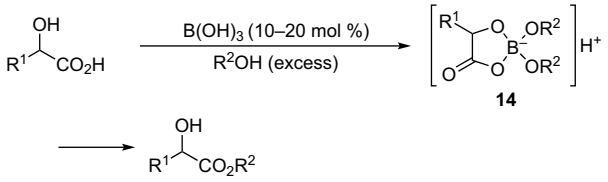
Generally, boron(III) compounds such as 3,5-bis(trifluoromethyl)benzeneboronic acid (**13**) promote the amide condensation of carboxylic acids with amines via the corresponding acyloxyborane intermediates (see Section 2.2), but are less effective for the esterification of carboxylic acids with alcohols, because an alkoxyborane species is preferentially produced rather than the desired acyloxyborane species (Scheme 5).[30a]

In 2004, Houston and co-workers reported that boric acid [B(OH)$_3$, 10–20 mol %] was effective as a catalyst for the chemoselective esterification of α-hydroxycarboxylic acids with excess alcohol as a solvent, even at ambient temperature (Scheme 6).[31]



Scheme 5. Amide versus ester condensation.

This unexpected reactivity of α-hydroxycarboxylic acids with alcohols can be understood by considering that a thermally stable 2,2-dialkoxy-4-oxo-1,3,2-dioxaborolan-2-uide (**14**) is preferentially produced as an anionic active intermediate, even in the presence of excess alcohol.



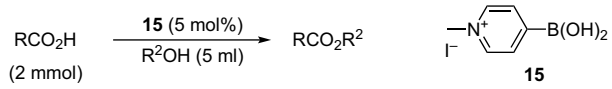
Scheme 6. Houston's boric acid-catalyzed esterification.

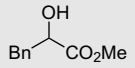
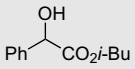
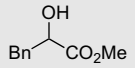
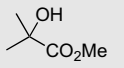
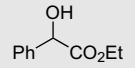
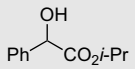
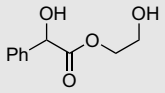
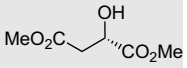
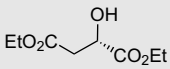
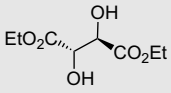
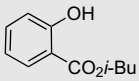
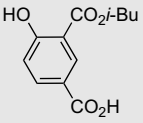
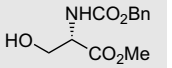
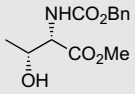
In 2005, Yamamoto and co-worker reported that 4-borono-*N*-methylpyridinium iodide (**15**) is a more effective catalyst than boric acid for the esterification of α-hydroxycarboxylic acids in excess alcohol solvents (Houston's conditions), probably because **15** is a tolerant cationic Lewis acid catalyst in polar alcohols.[30] On the other hand, boric acid is a more effective esterification catalyst for equimolar mixtures of α-hydroxycarboxylic acids and alcohols. Representative results are shown in Table 10. Not only α-hydroxycarboxylic acids (entries 1–10), but also β-hydroxycarboxylic acids (entries 11–14) are condensed. In the esterification of 4-hydroxyisophthalic acid, the 3-hydroxycarbonyl group is selectively reacted (entry 12). The esterification condensation of less-reactive secondary alcohols and aromatic carboxylic acids proceeds well with the use of 10 mol % of **15** (entries 6, 11, and 12). β-Hydroxycarboxylic acids bearing a benzyloxycarbonylamino group at the α-position also reacted (entries 13 and 14). Although ethylene glycol is known to react with boronic acid, leading to the corresponding cyclic boronic ester, esterification with mandelic acid is unexpectedly preferred (entry 7).

N-Polystyrene-bound 4-boronopyridinium chlorides (**16a–d**) are effective as heterogeneous catalysts. Compounds **16a–d** can be recovered by filtration and re-used 10-fold without any loss of activity for the esterification of mandelic acid in excess isobutanol under reflux conditions (Fig. 14).[30]

Figure 15 shows the correlation between the catalytic activity of boron(III) compounds and the molar ratio of mandelic acid and butanol for esterifications catalyzed by 2 mol % of boric acid, **13**, and **15**.

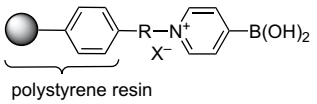
Table 10
Esterification of hydroxycarboxylic acids in alcohols catalyzed by **11**



Entry	Temp, time, yield	Product
1	rt, 10 h, 93%	
2	Reflux, 6 h, 99%	
3	rt, 10 h, 96%	
4	Reflux, 15 h, 92%	
5	Reflux, 4 h, 95%	
6[a]	Reflux, 21 h, 81%	
7	80 °C, 5 h, 97%	
8[a]	Reflux, 15 h, 95%	
9[a]	Reflux, 23 h, 86%	
10[a]	Reflux, 18 h, 92%	
11	Reflux, 17 h, 85%	
12[b,c]	Reflux, 20 h, 84%	
13	Reflux, 20 h, 93%	
14	Reflux, 22 h, 89%	

[a] Dicarboxylic acid used as substrate.
[b] Compound **15** (10 mol %) used.
[c] Diisobutyl 4-hydroxyisophthalate and 2-hydroxy-5-(isobutoxycarbonyl)benzoic acid produced in respective yields of 5 and 2%.

The conversion into butyl mandelate after heating under reflux conditions in toluene for 1 h is plotted in terms of the molar ratio of mandelic acid to butanol. Boric acid is the most active catalyst for a molar ratio of mandelic acid–butanol of >1:2. On the other hand, **15** is the most active catalyst for a molar ratio of mandelic acid–butanol of <1:3. In contrast, **13** is less active than boric acid and **15**, regardless of the molar ratio of mandelic acid–butanol. These three catalyses share two common phenomena: (1) excess mandelic acid accelerates



16a (R = CH_2, X = Cl)
16b (R = $(CH_2)_2$, X = Br)
16c (R = $(CH_2)_2$, X = NTf_2)
16d (R = $(CH_2)_4$, X = Br)

Figure 14. Heterogeneous catalysts **16**.

the esterification and (2) excess butanol suppresses the esterification, probably because excess butanol dilutes the concentration of mandelic acid and the Lewis basicity of excess butanol weakens the Lewis acidity of catalysts. However, **15** is still active in the presence of excess butanol, because of its ability to tolerate polar compounds.

The generality and scope of the esterification of equimolar mixtures of α-hydroxycarboxylic acids and alcohols catalyzed by boric acid are shown in Table 11 (entries 1–6).[30] Not only α-hydroxy-

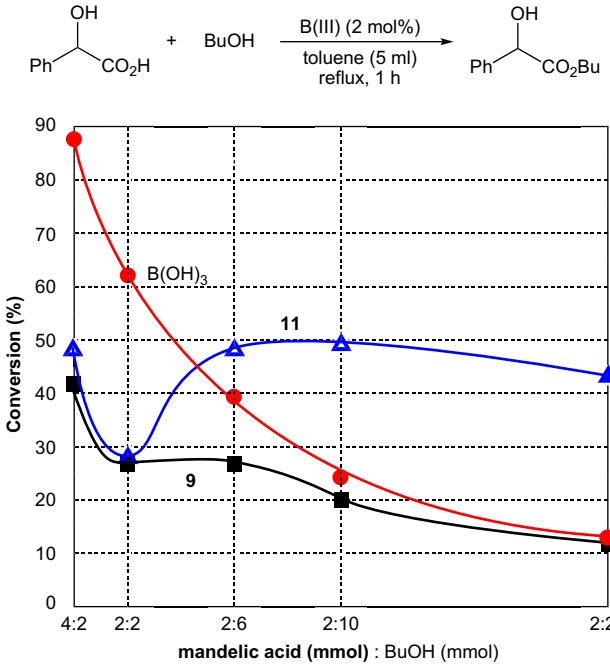
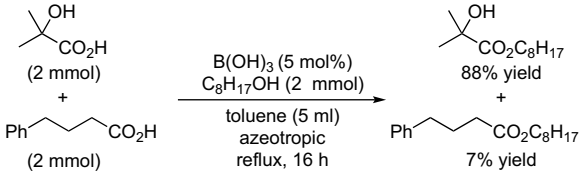


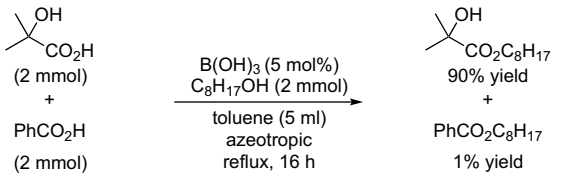
Figure 15. Correlation between catalytic activity of boron(III) compounds and molar ratio of mandelic acid and butanol.

carboxylic acids and primary alcohols, but also β-hydroxycarboxylic acids and secondary alcohols are applicable.

The boric acid-catalyzed chemoselective esterification of α-hydroxy-α-methylpropanoic acid proceeds in the presence of 4-phenylbutyric acid or benzoic acid (Eqs. 19 and 20).



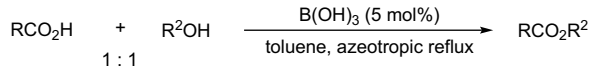
(19)

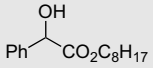
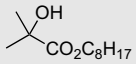
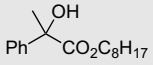
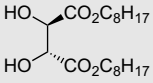
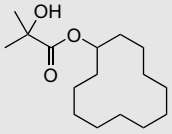
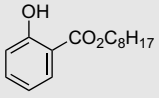


(20)

Boric acid is known to react with 2 equiv of α-hydroxycarboxylic acids to give dimeric **18**, which is more active than monomeric **17** (Scheme 7). However, an equilibrium is observed between **17** and

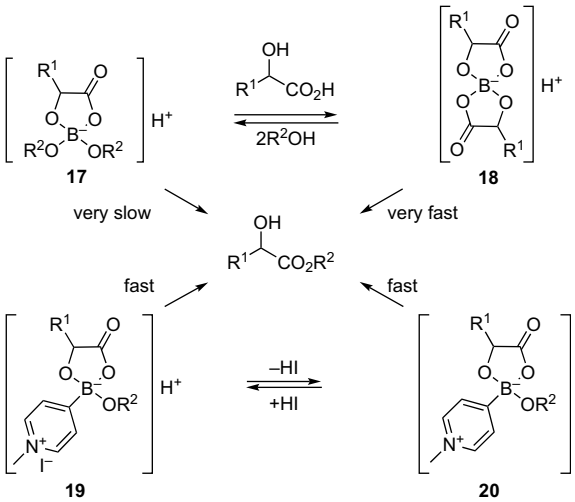
Table 11
Esterification of equimolar mixture of hydroxycarboxylic acids and alcohols catalyzed by boric acid



Entry	Time (h)	Product	Yield (%)
1	4		93
2	21		99
3	21		90
4[a]	21		87
5[a]	20		82
6[a,b]	21		86

[a] Boric acid (10 mol %) used.
[b] *o*-Xylene used in place of toluene.

18. The more active species **18** exists as a major intermediate in an esterification reaction solution with a higher molar ratio of α-hydroxycarboxylic acid, while the less active species **17** is a major intermediate in excess alcohol. Based on the experimental results

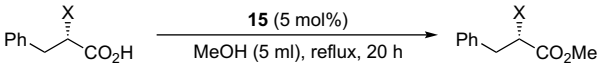


Scheme 7. Proposed reaction mechanism.

shown in Figure 14, the reactivity of the intermediates with alcohols increases in the order: **17**<**19** and **20**<**18**.

Compound **15** is effective for the esterification of L-phenylalanine and its *N*-protected derivatives in methanol (Table 12, entries 1–8). In particular, *N*-tosyl-L-phenylalanine (entry 1) and methoxyphenylacetic acid (entry 7) are much more reactive than L-phenylalanine and its *N*-carboxyl derivatives. In contrast, α-phenylpropionic acid is much less reactive (entry 8). The good results (entries 1 and 7) can be

Table 12
Methyl esterification of α-functionalized carboxylic acids



Entry	X	Yield (%)
1	TsNH	76
2	CbzNH	61
3	BzNH	45
4	AcNH	28
5	TfNH	24
6	NH_2[a]	N.R.
7	OMe[b]	71
8	Me[c]	28

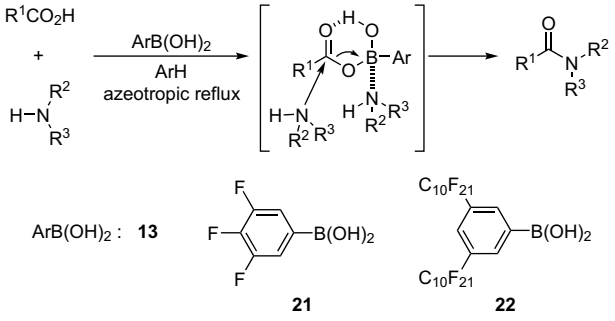
[a] L-Phenylalanine not dissolved.
[b] α-Methoxyphenylacetic acid used as substrate.
[c] α-Phenylpropanoic acid used as substrate.

understood in terms of the weak coordination of α-tosylamino and α-methoxy groups to the boron(III) atom.

2.2. Synthesis of carboxamides

The most desirable method for preparing carboxamides is a catalytic direct condensation between carboxylic acids and amines, which is generally understood to be impossible, due to the formation of an unreactive carboxylate–ammonium salt. Although the direct formation of amide bonds by heating without catalysts has been known since 1858,[32] this process has found little synthetic utility, with a few exceptions. In 2002, Loupy and co-workers reported that carboxamides could be efficiently obtained by mixing neat carboxylic acids and primary amines under microwave irradiation.[33] However, this method is not effective for aromatic substrates such as benzoic acids and anilines.

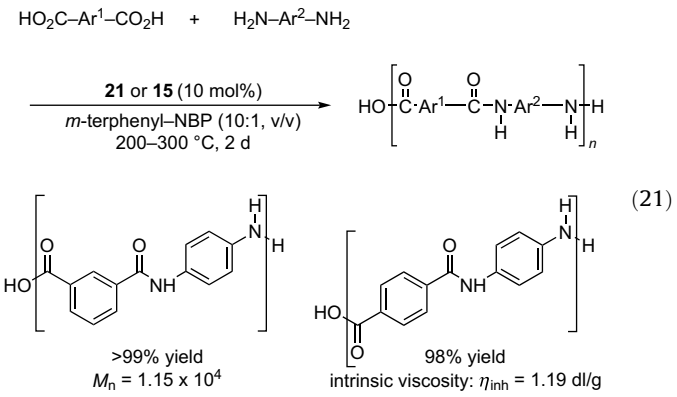
In 1996, Yamamoto and co-workers found that the dehydrative condensation of equimolar mixtures of carboxylic acids and amines or ureas proceeds under azeotropic-reflux conditions with the removal of water in less-polar solvents such as toluene or xylene in the presence of benzeneboronic acids bearing electron-withdrawing groups at the *meta*- or *para*-position, such as **13**,[34–36] 3,4,5-trifluorobenzeneboronic acid (**21**),[34,35] and 3,5-bis(perfluorodecyl)benzeneboronic acid (**22**),[37] which is re-usable in fluorous biphasic system (FBS) (Scheme 8).



Scheme 8. Boronic acid-catalyzed dehydrative amide condensation reaction.

However, the scope of suitable substrates has been limited, because the catalytic activities of these neutral boronic acids are greatly reduced in polar solvents and for sterically demanding substrates. In 2000, Ishihara and co-workers found that **15** was effective as a polar-solvent-tolerable catalyst for amide condensation.[38] Cationic boronic acid **15** is much more active than neutral boronic acids in polar solvents, such as anisole, acetonitrile, and *N*-methylpyrrolidinone (NMP), because the boron atom in **15** shows greater Lewis acidity in polar solvents. Thus, **15** is useful as

a catalyst for the direct polycondensation of arenedicarboxylic acids with diaminoarenes in a mixed solvent of terphenyl and *N*-butylpyrrolidinone (NBP) (Eq. 21).[35,38a,b]



(21)

When **15** is heated in DMF at 120 °C, **15** is completely changed to a yellow precipitate, which is a dodecamer of **15**, $[\mathbf{15}]_{12}$, within 1 h, and then gradually undergoes hydrolytic protodeboration (Fig. 16).[38c] Interestingly, $[\mathbf{15}]_{12}$ is dissolved and stable, even in water, because the 12 hydrophilic pyridinium ion moieties are oriented on the outside of $[\mathbf{15}]_{12}$.

The catalytic activities of **15** and $[\mathbf{15}]_{12}$ (5 mol % for B atom) were compared in the amide condensation of 4-phenylbutyric acid with benzylamine under azeotropic-reflux conditions in toluene with the removal of water (entries 1 and 2, Table 13). The catalytic activity of $[\mathbf{15}]_{12}$ is much lower than that of **15**. However, the catalytic activities of **15** and $[\mathbf{15}]_{12}$ are dramatically improved in the biphasic solvents of toluene and [emim][OTf] (entries 3 and 4). These results can be understood in terms of the good stability of **15** and the good solubility of **15** and $[\mathbf{15}]_{12}$ in the presence of [emim][OTf]. In contrast, **15** is partially soluble in toluene while $[\mathbf{15}]_{12}$ is insoluble. It is likely that **15** is regenerated from $[\mathbf{15}]_{12}$ by hydrolysis in the presence of [emim][OTf]. Furthermore, [emim][OTf] plays an important role in suppressing the condensation of **15** to $[\mathbf{15}]_{12}$. Thus, the amide condensation proceeds to completion in the presence of 5 mol % of **15** in toluene–[emim][OTf] (5:1 (v/v)) within 5 h (entry 5). After amide condensation, the desired amide is obtained in quantitative yield by repeated extraction with Et_2O from an [emim][OTf] layer. Compound **15** remains in the [emim][OTf] layer. Thus, a solution of **15** in [emim][OTf] can be repeatedly re-used for the same amide condensation reaction without any loss of catalytic activity.

The generality and scope of the amide condensation catalyzed by **15** in the presence of [emim][OTf] are shown in Table 14 (entries 1–9). Not only aliphatic, but also aromatic substrates are condensed in the presence of 5 mol % of **15**. The amide condensation of less-reactive substrates proceeds well under azeotropic-reflux conditions in *o*-xylene in place of toluene. Functionalized substrates such as conjugated carboxylic acids, α-hydroxycarboxylic acids, α-alkoxycarboxylic acids, and cyanobenzoic acids are also applicable. Furthermore, a solution of **15** in [emim][OTf] is repeatedly re-used without any loss of activity.

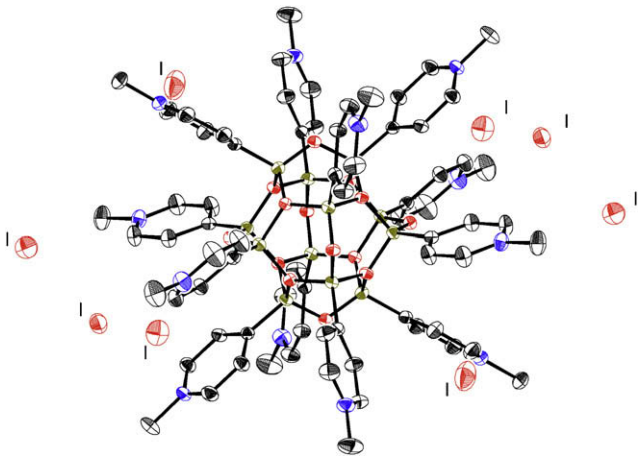


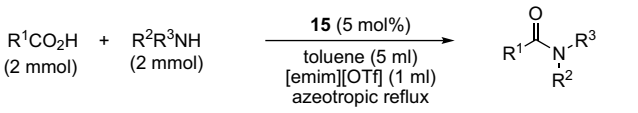
Figure 16. X-ray crystal structure of dodecamer $[\mathbf{15}]_{12}$, $[CH_3NC_5H_4BO_{14/12}]_{12}I_8 \cdot 10H_2O$. Water is omitted for clarity.

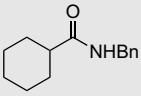
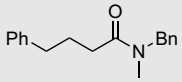
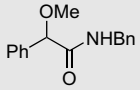
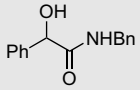
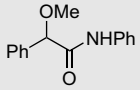
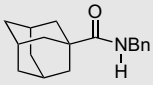
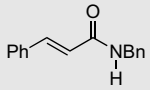
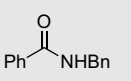
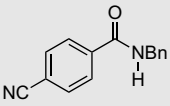
Table 13
Catalytic activities of **15** and $[\mathbf{15}]_{12}$ for amide condensation

Entry	Catalyst (mol %)	Time (h)	Yield (%)
1[a]	**15** (5)	1	41
2[a]	$[\mathbf{15}]_{12}$ (10)[b]	1	15
3	**15** (5)	1	74
4	$[\mathbf{15}]_{12}$ (5)[c]	1	75
5	**15** (5)	5	>99

[a] Only toluene was used as solvent.
[b] Compound $[\mathbf{15}]_{12}$ (10 mol % for B atom) used.
[c] Compound $[\mathbf{15}]_{12}$ (5 mol % for B atom) used.

Table 14
Direct amide condensation reaction catalyzed by **15**



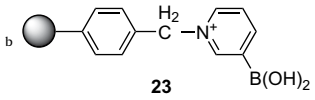
Entry	Time (h)	Product	Yield (%)
1	6		92
2	18		95
3[a]	5 (first), 5 (second), 5 (third)		98 (first), 93 (second), 95 (third)
4[b]	18		91
5[b]	18		80
6[b]	10		91
7[b]	3		90
8[b]	6		98
9[a,b]	5 (first), 5 (second), 5 (third)		99 (first), 98 (second), 99 (third)

[a] Solution of **15** in [emim][OTf] re-used threefold.
[b] *o*-Xylene used as solvent in place of toluene.

Table 15
Recovery and re-use of **23** and **16a**[a,b]

Run	Conversion (%)					
	Catalyst **23**			Catalyst **16a**		
	1 h	3 h	5 h	1 h	3 h	5 h
1	64	93	98	68	94	98
2	53	90	98	67	94	98
3	50	85	94	69	93	98
4	40	76	88	69	93	98
5	28	60	74	70	92	96

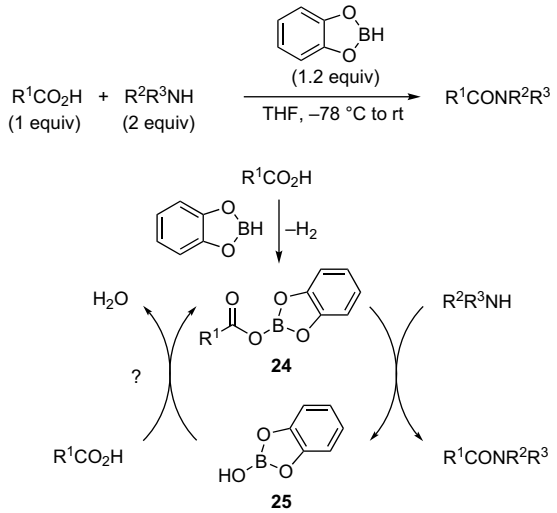
[a] See the equation in Table 13.

b 

23

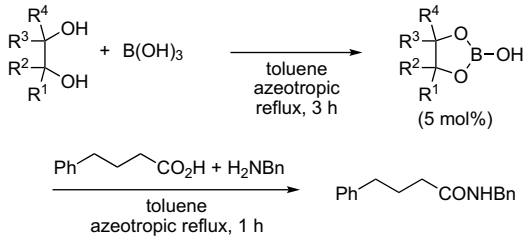
N-Polystyrene-bound 4-boronopyridinium chloride (**16a**) and *N*-polystyrene-bound 3-boronopyridinium chloride (**23**) were developed by Ishihara[38] and Wang,[39] respectively, to recover and re-use *N*-alkyl-4-boronopyridinium halides without any ionic liquids (Table 15). Compound **23** is gradually decomposed to *N*-polystyrene-bound pyridinium chloride and boric acid by hydrolytic protodeboration. In contrast, **16a** can be re-used repeatedly. The high catalytic activity of **16a**, which is observed even in the absence of [emim][OTf], can be understood by assuming that the polymer support may prevent dodecamerization of the 4-boronopyridinium chloride moiety in **16a**. After the amide condensation reaction, **16a** is repeatedly washed with 1 M HCl aqueous solution and ethyl acetate to be re-used in the next reaction. When the treatment of **16a** with 1 M HCl aqueous solution is omitted, the catalytic activity is reduced, since the chloride anions of **16a** are partially exchanged to carboxylate anions through the amide condensation. Therefore, the treatment of **16a** with acid is significant for re-activating **16a**.

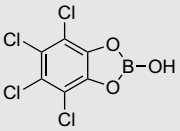
In 1970, Levitt and co-workers reported that several boron reagents such as $X_nB(OR)_{3-n}$ (X=H, Cl, etc.), $B(NR^2R^3)_3$, and BR_3 were effective for synthesizing carboxamides.[40] In 1978, Ganem and co-workers reported that carboxylic acids condensed with amines via a 2-acyloxy-1,3,2-benzodioxaborolane (**24**) in the presence of stoichiometric amounts of catecholborane under mild conditions (THF, −78 °C to rt).[41,42] As shown in Scheme 9, 2 equiv of amine is required, because the reaction proceeds via nucleophilic attack of amine to [**24**·amine]. Catecholborane is converted into benzo[*d*][1,3,2]dioxaborol-2-ol (**25**), which is inert throughout the condensation.



Scheme 9. Ganem's amide condensation of carboxylic acids with amines using catecholborane as condensing agent and possible catalytic pathway.

Table 16
Catalytic activities of 1,3,2-dioxaborolan-2-ol derivatives for amide condensation of 4-phenylbutyric acid with benzylamine



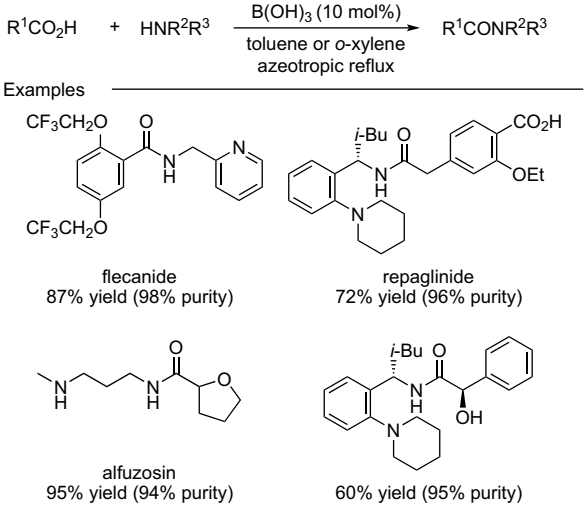
Entry	Catalyst	Conv. (%)
1	**25**	61
2		93
3[a]	$B(OH)_3$	31
4[a]	**13**	96

[a] Boric acid and **13** used instead of 1,3,2-dioxaborolan-2-ol derivatives.

Nevertheless, 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]dioxaborol-2-ol (**26**), which is prepared in situ from tetrachlorocatechol and boric acid, is sufficiently active as a catalyst for the dehydrative condensation of equimolar mixtures of carboxylic acids and amines (Table 16, entries 1–4).[43] The catalytic activity of **26** is almost the same as that of **13**. According to the *Chemicals* price catalog[58] **13** is 40-fold more expensive than tetrachlorocatechol. Since boric acid[44] is also available at a rather low price, **26**, which can be prepared from this in situ, is very economical and practical.

Catalyst **26** is greatly superior to **13** for the amide condensation of not only sterically bulky aliphatic and aromatic carboxylic acids, but also functionalized carboxylic acids such as Boc–L-Ala–OH (Table 17, entries 1–10). In contrast, **26** and **13** show a similar trend in catalytic activity with regard to the steric bulk of amines. The less-hindered **26** has an advantage over **13** at the regeneration step from hydroxyboron compounds to acyloxyboron species.

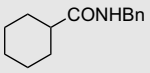
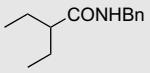
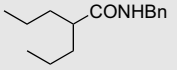
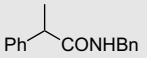
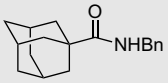
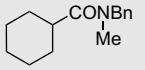
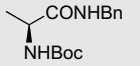
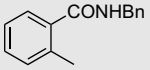
In 2005, Tang reported that the cheap, readily available, nontoxic, and eco-friendly boric acid, $B(OH)_3$, was also usable as a catalyst for the dehydrative amidation process.[44a] This amidation procedure has been applied in the synthesis of several active pharmaceutical ingredients (APIs) by Bandichhor and co-workers (Eq. 22).[44b]



(22)

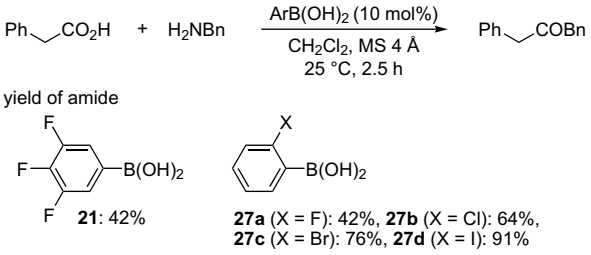
Table 17
Amide condensation of various carboxylic acids with amines catalyzed by **13** or **26**

R^1CO_2H (2 mmol) + R^2R^3NH (2 mmol) —**13** or **26** (5 mol%), solvent, azeotropic reflux→ $R^1CONR^2R^3$

Entry	Product	Solvent	Time (h)	Yield (%)	
				13	**26**
1		Toluene	1	32	62
		Toluene	**5**	—	**94**
2		**Toluene**	**24**	8	**93**
3		Toluene	19	11	55
		***o*-Xylene**	**24**	—	**99**
4	*t*-BuCONHBn	Toluene	20	5	55
		***o*-Xylene**	**15**	—	**94**
5		Toluene	2	25	77
		Toluene	**5**	—	**95**
6		Toluene	24	15	22
		***o*-Xylene**	**20**	20	**99**
7	$Ph_2CHCONHBn$	Toluene	2	30	32
		Toluene	**11**	—	**93**
8		*o*-Xylene	5	47	53
		***o*-Xylene**	**19**	—	**93**
9		Toluene	5	35	42
		Toluene	**20**	—	**91**[a]
10		*o*-Xylene	1	32	62
		***o*-Xylene**	**9**	—	**92**

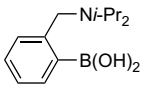
[a] Optical purity of amide reduced from >99 to 86% ee through amide condensation.

In 2008, Hall and co-workers reported that a 2-halobenzeneboronic acid (**27**) was much superior to **21** as an amide condensation catalyst in the presence of MS 4 Å at 25 °C (Eq. 23).[45] In particular, 2-iodobenzeneboronic acid (**27d**) gives amides in higher yields. However, the substrates are limited to sterically less-hindered compounds such as phenylacetic acids, primary amines, and pyrrolidine.



(23)

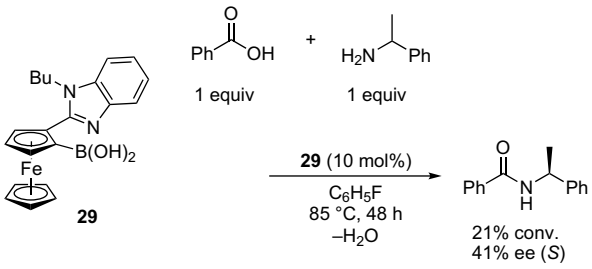
According to kinetic studies on the direct formation of amides from amines and carboxylic acids with/without boron(III) catalysts by Whiting and co-workers,[46a] the efficiency of amide formation under thermal and catalyzed conditions is highly substrate dependent. For alkyl carboxylic acids such as 4-phenylbutyric acid, the addition of boron-based catalysts improves the reaction rate and the yield of amide, despite the competing thermal reaction. However, there is an even greater improvement with aryl carboxylic acids such as benzoic acid, where the thermal reaction is truly nonexistent. Interestingly, the use of an amino-boronate catalyst **28** clearly improves amide formation, particularly for aryl carboxylic acids and at lower reaction temperatures. This catalyst has also been shown to act through a bifunctional mechanism, the exact nature of which has not yet been fully elucidated. However, **28** is superior to other monofunctional boronic acid catalysts for more difficult amidations (Fig. 17).



28

Figure 17. Amino-boronate catalyst **28**.

In 2008, Whiting and co-workers reported that (*pS*)-2-(2-boronoferrocenyl)-*N*-*n*-butylbenzimidazole (**29**) could induce the kinetic resolution of racemic α-substituted benzylamines through direct amide condensation with achiral carboxylic acids (Eq. 24).[46b]



(24)

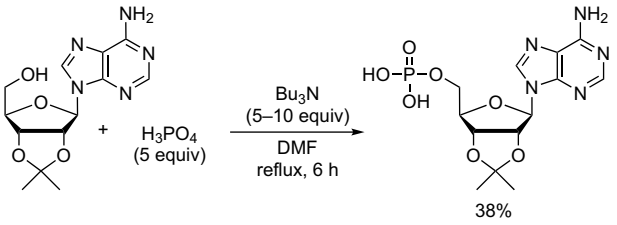
In 2008, Sugi and co-workers reported multivalent metal salts, such as ferric chloride and sulfate, were active and versatile catalysts for the dehydrative condensation between an equivalent mixture of aliphatic fatty acids and long-chain aliphatic amines in mesitylene under azeotropic-reflux conditions.[47] The catalytic activity of multivalent metal chlorides decreases in the order: $FeCl_3\cdot 6H_2O > ZnCl_2 > NiCl_2\cdot 6H_2O \approx MnCl_3\cdot 6H_2O > CoCl_2\cdot 6H_2O > CrCl_3\cdot 6H_2O \geq ZrOCl_2\cdot 8H_2O \geq CuCl_2\cdot 4H_2O \geq InCl_3 > AlCl_3\cdot 6H_2O$. Metal sulfates, nitrates, and acetates are active for the reaction as well as chlorides, although the yields of the amides vary with the salt used. These results show that the active center for the amidation is on the metal cation and that the anionic part does not significantly influence the catalysis.

2.3. Synthesis of phosphoric esters

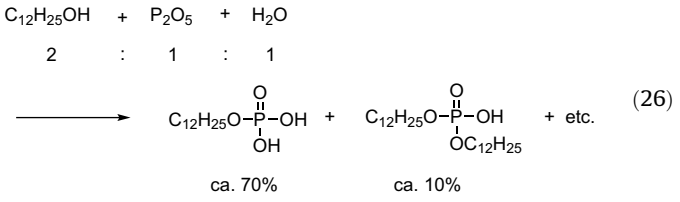
2.3.1. Synthesis of monoalkyl phosphates

Monoalkyl phosphates are among the most important substances in materials chemistry, medicinal chemistry, and so on. Monoalkyl phosphates have been synthesized on an industrial scale and are used as necessities in daily life. From the perspective of green chemistry, the direct catalytic condensation of equimolar amounts of phosphoric acid and alcohols is attractive for the synthesis of monoalkyl phosphates, especially for industrial-scale synthesis, since the reaction produces only water as a byproduct. Although many methods for preparing monoalkyl phosphates using condensing reagents have been reported, there are few

examples on the dehydrative condensation of phosphoric acid with alcohols (Eqs. 25[48] and 26[49]).[50]

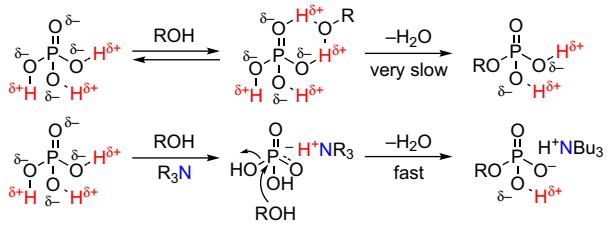


(25)



(26)

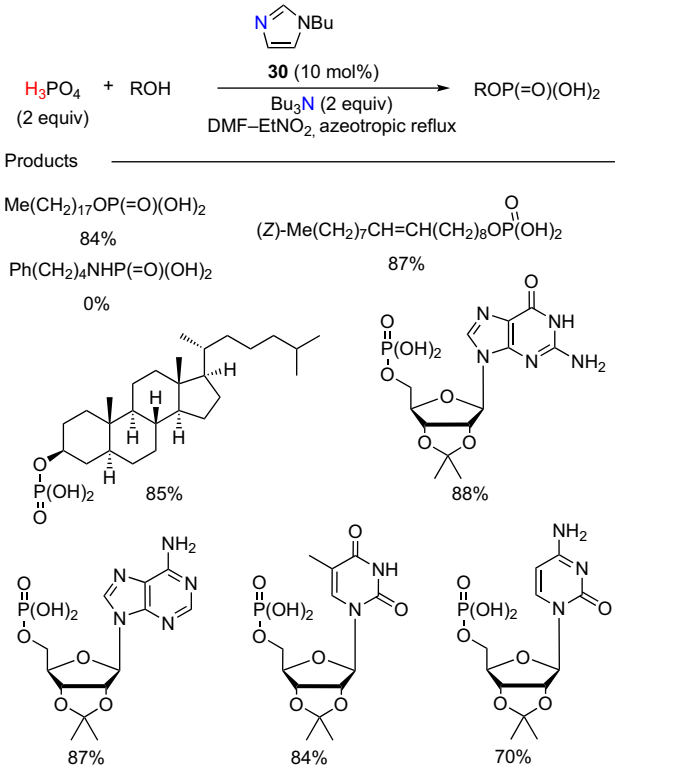
In general, the esterification of phosphoric acid (pK_{a1}=2.15, pK_{a2}=7.20, pK_{a3}=12.35) is more difficult than that of carboxylic acids (pK_a=4.76 for acetic acid), due to the stronger acidity of phosphoric acid. Phosphoric acid reduces the nucleophilicity of alcohols by protonation (Scheme 10). Furthermore, the three P–OH bonds of phosphoric acid have a partial double-bond character, due to charge delocalization. Therefore, in general, the reaction of phosphoric acid with alcohols gives monoalkyl phosphates in poor yield. Monoalkyl phosphates and dialkyl phosphates are known to be stronger acids than phosphoric acid. In fact, the pK_a values of $MeOPO(OH)_2$ and $(MeO)_2PO(OH)$ are 1.54 and 1.29, respectively. The reactivity of esterification is further reduced in the order mono-, di-, and triesterification. However, if 1 equiv of a trialkylamine as a Brønsted base is added to an equimolar mixture of phosphoric acid and alcohols, neutral ammonium phosphonate



Scheme 10. Dehydrative condensation of phosphoric acid with alcohols under acidic or basic conditions.

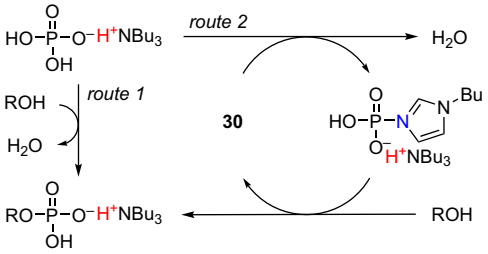
should be generated. The single P–OH bond of ammonium phosphonate should be more easily cleaved by the nucleophilic attack of alcohols, because of its neutral and single-bond character.

In 2005, based on acid–base combination chemistry,[51] Ishihara and co-workers succeeded in the selective synthesis of monoalkyl phosphates from a mixture of phosphoric acid (2 equiv) and alcohols (1 equiv) in the presence of tributylamine (2 equiv) under azeotropic-reflux conditions with the removal of water in DMF–$EtNO_2$ (1:1 v/v) (Eq. 27).[52] The reaction is promoted by nucleophilic bases (10 mol %) such as *N*-butylimidazole (**30**) and 4-(*N*,*N*-dibutylamino)pyridine. Not only primary alcohols, such as stearyl alcohol and oleyl alcohol, but also β-cholestanol are converted into monoalkyl phosphates in respective yields of 84, 87, and 85%. In this method, phosphoric acid does not react with primary or secondary amines to provide the corresponding phosphoramidates. 2′,3′-*O*-Isopropylidene ribonucleosides derived from guanosine, adenosine, uridine, and cytidine are also selectively condensed with phosphoric acid to give 5′-monoalkyl phosphates in good yield without protection of the amino groups of the nucleobases.



(27)

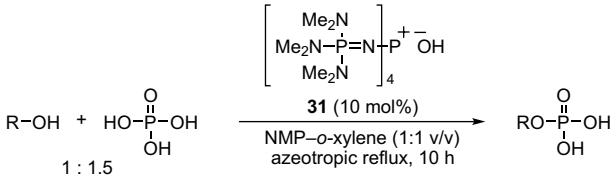
A possible mechanism is shown in Scheme 11. In the presence of an equimolar amount of a tertiary amine such as tributylamine, phosphoric acid and the tertiary amine produce ammonium phosphate, which does not protonate alcohols, because of its low acidity. Ammonium phosphate still has two hydroxy groups that can be eliminated and reacts with alcohols to give the monoalkyl phosphates in moderate yield (*route 1*). Nucleophilic bases such as **30** probably react with ammonium phosphate to give active species, such as phosphorimidazolidate, which reacts with alcohols to more effectively give monoalkyl phosphates (*route 2*).

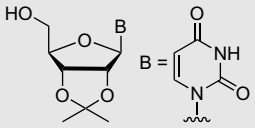


Scheme 11. Proposed mechanism for catalysis of phosphorylation.

From the perspective of green chemistry, a metal-free catalytic method is more desirable for the preparation of monoalkyl phosphates. In 2007, Ishihara and co-workers reported a phosphazenium salt as a metal-free catalyst for dehydrative condensation between phosphoric acid and alcohols.[53] In their previous work,[52] 100 mol % of Bu_3N was required to dissolve phosphoric acid and promote the reaction, since phosphoric acid cannot be dissolved in a 1:1 (v/v) mixture of DMF and $EtNO_2$ as a solvent. Later, they found that phosphoric acid dissolves well in NMP–*o*-xylene (1:1 v/v), and tetrakis[tris(dimethylamino)phosphoranilidenamino]-phosphonium

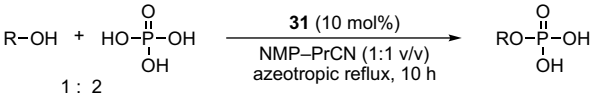
Table 18
Synthesis of monoalkyl phosphates[a]

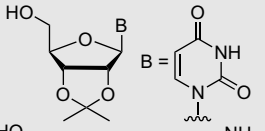
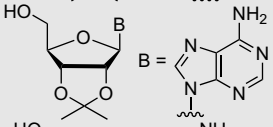
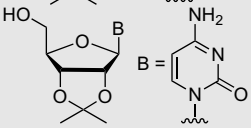
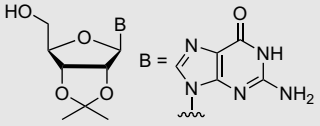


Entry	Alcohol	Isolated yield (%)[b] [Purity (%)[c]]
1	$C_{18}H_{37}$–OH	92 [97]
2[d]	$C_{18}H_{37}$–OH	93 [91]
3	(*Z*)-$C_8H_{17}CH{=}CH(CH_2)_8$–OH	87 [96]
4	$C_{12}H_{25}(OCH_2CH_2)_2$–OH	95 [98]
5	β-cholestanol	90 [93]
6[e]		62 [–]

[a] Unless otherwise noted, reaction conducted on 3-mmol scale.
[b] Product contains dialkyl phosphate and pyrophosphoric acid esters as well as monoalkyl phosphate.
[c] Ratio of monoalkyl phosphate in product.
[d] Reaction conducted on 100-mmol scale for 12 h.
[e] Reaction conducted with 2 equiv H_3PO_4.

Table 19
Direct condensation of phosphoric acid with alcohols catalyzed by **31** in NMP–PrCN (1:1 v/v)



Entry	Alcohol	Method[a]	Yield (%)	
			Conv.	Isolated
1	$C_{18}H_{37}$–OH	A	81 (18)[b]	ND
2	$C_{18}H_{37}$–OH	B	94 (5)[b]	ND
3		B	85	83
4		B	82	72
5		B	82	70
6		B	77	73

[a] Method A: alcohol added to the reaction mixture in one portion. Method B: alcohol added to the reaction mixture in four portions during the reaction.
[b] Yields of stearyl butyrate shown in parentheses.

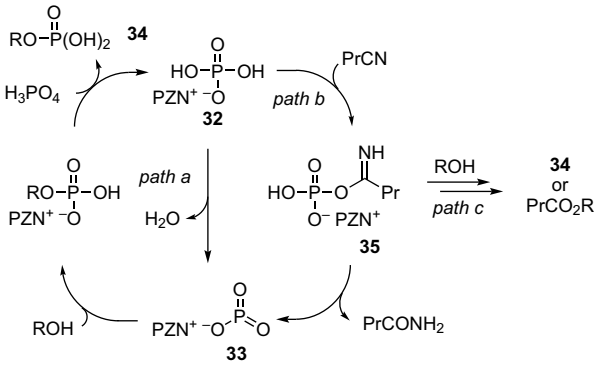
hydroxide (**31**) has good catalytic activity (10 mol %) for the dehydrative condensation between phosphoric acid (1.5 equiv) and alcohols (1.0 equiv) in NMP–*o*-xylene (1:1 v/v), even in the absence of any auxiliary base. After the reaction is completed, the monoalkyl phosphates are purified as follows: **31** is removed by purification using a cation-exchange resin (DOWEX® 50WX2-200, H^+ form) and excess phosphoric acid is then removed by extraction using 1 M aqueous HCl and diethyl ether.

The generality and scope of the phosphazenium cation-catalyzed condensation are shown in Table 18. Saturated and unsaturated primary alcohols such as stearyl alcohol and oleyl alcohol can be easily converted into the corresponding monoalkyl phosphates in excellent isolated yields (92 and 87%, entries 1 and 3). The geometry of the C–C double bond in oleyl alcohol is maintained during the reaction. The present protocol can be easily applied to a large-scale process, and the condensation of phosphoric acid (1.5 equiv) with oleyl alcohol (100 mmol) gives oleyl phosphate in 93% yield (entry 2). Diethylene glycol dodecyl ether also shows high reactivity (95% yield, entry 4). Monoalkyl phosphates of diethylene glycol dodecyl ether are useful as surfactants in detergents. A secondary alcohol such as β-cholestanol is also converted into the corresponding monoalkyl phosphate in 92% yield without decomposition, even though the reaction conditions are significantly acidic (entry 5). The reaction of acid-sensitive 2′,3′-*O*-isopropylidene uridine gives the corresponding phosphate in 62% yield (entry 6).

When the condensation between phosphoric acid (2 equiv) and stearyl alcohol is conducted in NMP–butyronitrile (PrCN) (1:1 v/v), the reaction proceeds more smoothly than that in NMP–*o*-xylene (1:1 v/v), despite the fact that PrCN has a much lower boiling point (116 °C) than *o*-xylene (144 °C) (Table 19). However, stearyl butyrate is produced as a byproduct in 18% yield, along with stearyl phosphate (81% yield), which must be produced by the reaction between stearyl alcohol and PrCN (entry 1, method A). To reduce the production of stearyl butyrate, the slow addition of stearyl alcohol (method B) is effective. Thus, the production of stearyl butyrate is reduced to 5% and stearyl phosphate is obtained in 94% conversion yield (entry 2). Since the reaction in NMP–PrCN can be conducted at a lower temperature than that in NMP–*o*-xylene, it is suitable for the synthesis of monoalkyl phosphates derived from alcohols that are sensitive to heat such as 2′,3′-*O*-isopropylidene ribonucleosides. The phosphorylation of 2′,3′-*O*-isopropylidene uridine proceeds well without significant decomposition of the alcohol (entry 3). Phosphorylation of three other ribonucleosides can also be carried out under the same reaction conditions to give the corresponding 5′-*O*-monophosphates in isolated yields of 70–73% (entries 4–6). No phosphorylation of the nucleobases is detected, even without any protection.

A possible mechanism for the phosphazenium cation-catalyzed condensation of phosphoric acid with alcohols is shown in Scheme 12. When **31** (PZN^+OH^-) is mixed with phosphoric acid, the phosphazenium phosphate **32** is formed immediately. Since the bulky phosphazenium cation (PZN^+), in which the positive charge is highly delocalized, frees the phosphate anion, **32** is dehydrated to give the monometaphosphate **33** as an active species under heating in NMP–*o*-xylene (*path a*). Compound **33** reacts rapidly with alcohols to give the monoalkyl phosphates **34**. In NMP–PrCN, **32** initially reacts with PrCN to produce an active intermediate **35** (*path b*), which easily decomposes to give **33**, even at a lower reaction temperature. Compound **35** also reacts directly with alcohols to give **34** or butyric acid esters ($PrCO_2R$) (*path c*). It is conceivable that *path c* is suppressed when the alcohol is added slowly.

In 2007, Ishihara and co-workers reported that the use of oxorhenium(VII) complexes as extremely active catalysts for the direct condensation of phosphoric acid with nearly equimolar amounts of alcohols gave the corresponding monoalkyl phosphates.[54] Since the present reaction can be easily expanded to a large scale and



Scheme 12. Proposed mechanism for phosphazenium cation-catalyzed condensation of phosphoric acid with alcohols.

rhenium(VII) salts are believed to exhibit low toxicity, it is a useful method for the environmentally and industrially important synthesis of monoalkyl phosphates. This is the first direct catalytic condensation of a nearly equimolar mixture of phosphoric acid and alcohols for the selective synthesis of monoalkyl phosphates.

Rhenium(VII) oxo complexes gradually decompose to dark insoluble species (probably oligomeric low-valent rhenium oxides) to be inactivated under heating conditions. When the reaction is conducted in the presence of 1 mol % of perrhenic acid at azeotropic reflux in NMP–*o*-xylene (1:1 v/v) for 12 h, stearyl phosphate is obtained in 16% yield (Fig. 18, red solid circles). The same reactivity is observed, even in the absence of perrhenic acid (black open squares), while 10–20 mol % of sterically less-hindered secondary and tertiary amines, such as dibutylamine (Bu_2NH) and dimethyloctylamine, can stabilize perrhenic acid to promote the condensation. In the presence of 20 mol % of Bu_2NH, the reaction catalyzed by 1 mol % of perrhenic acid gives stearyl phosphate in 98% yield (green open circles). The reaction mixture is a clear dark-brown solution when the reaction is conducted in the presence of Bu_2NH.

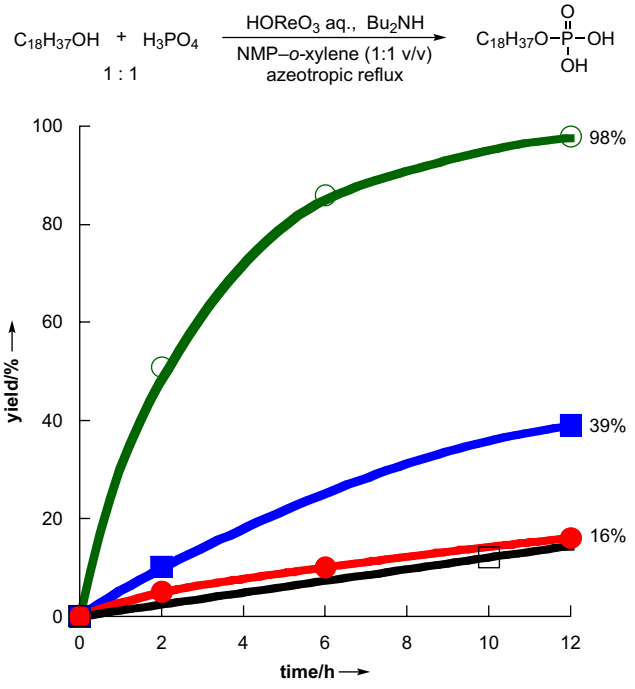
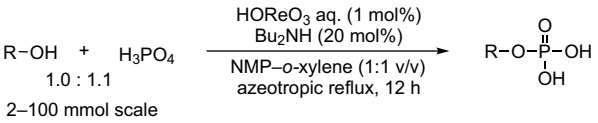
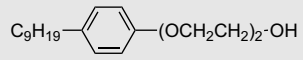
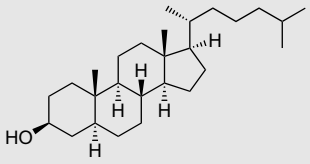


Figure 18. Conversion versus time for the dehydrative condensation of phosphoric acid with stearyl alcohol catalyzed by perrhenic acid. Green open circles, $HOReO_3$ (1 mol %) and Bu_2NH (20 mol %); blue closed squares, Bu_2NH (20 mol %); red closed circles, $HOReO_3$ (1 mol %); black open squares, without $HOReO_3$ and Bu_2NH.

Table 20
Direct condensation of phosphoric acid with alcohols catalyzed by perrhenic acid and dibutylamine



Entry[a]	Substrate	Yield[b] (%)
1	$C_{18}H_{37}$–OH	98
2	(*Z*)-$C_8H_{17}CH{=}CH(CH_2)_8$–OH	100
3[c]	(*Z*)-$C_8H_{17}CH{=}CH(CH_2)_8$–OH	96
4	(*E*)-$C_8H_{17}CH{=}CH(CH_2)_8$–OH	100
5	$C_{12}H_{25}(OCH_2CH_2)_2$–OH	100
6		100
7		95[d]

[a] Unless otherwise noted, reaction carried out on 2-mmol scale.
[b] Isolated yield.
[c] Reaction on 100-mmol scale performed with $HOReO_3$ aq (0.5 mol %) and Bu_2NH (20 mol %).
[d] Reaction conducted for 10 h.

When the reaction is conducted with Bu_2NH (20 mol %) in the absence of perrhenic acid, stearyl phosphate is obtained in only 39% yield (blue solid squares).

The generality and scope of the dehydrative condensation of phosphoric acid (1.1 equiv) with alcohols catalyzed by perrhenic acid are shown in Table 20 (entries 1–7). Monoalkyl phosphates are isolated by purification using ion-exchange resins. Unsaturated primary alcohols such as (*Z*)-oleyl alcohol and its (*E*)-isomer can be easily converted into the corresponding monoalkyl phosphates in excellent yields (100%, entries 2 and 4). The geometries of the C–C double bonds in oleyl alcohol and its (*E*)-isomer are maintained during the reaction. The present protocol can be easily applied to a large-scale process, and the condensation of phosphoric acid (1.1 equiv) with oleyl alcohol (100 mmol) catalyzed by $HOReO_3$ (0.5 mol %) gives oleyl phosphate in 96% yield (entry 3). Ethylene glycol dodecyl ether and ethylene glycol *p*-nonylphenyl ether (Igepal® CO-210) also show high reactivities (100%, entries 5 and 6). Monoalkyl phosphates of ethylene glycol dodecyl ether and ethylene glycol *p*-nonylphenyl ether are useful surfactant ingredients in detergents. A secondary alcohol such as β-cholestanol is also converted into the corresponding monoalkyl phosphate in 95% yield (entry 7), while the product is completely decomposed when the reaction is conducted in the absence of Bu_2NH, because of the high acidity of the reaction media, Bu_2NH contributing to the stabilization of acid-sensitive substrates as well as perrhenic acid.

The catalytic cycle of perrhenic acid is shown in Figure 19. In the presence of alcohols, dibutylammonium perrhenate **36** may be converted into its alkyl perrhenate **37** under azeotropic-reflux conditions. Phosphoric acid then reacts with compound **36** or **37** to give a plausible intermediate such as a mixed anhydride **38**. Since perrhenic acid has a higher acidity (pK_a=−1.25) than phosphoric acid (pK_{a1}=2.1), nucleophilic substitution of **33** by alcohols occurs preferentially on the phosphine atom to produce the monoalkyl phosphate **34**. Mono- and dialkyl phosphates are stronger acids than phosphoric acid. For example, the pK_a values of $MeOPO(OH)_2$ and $(MeO)_2PO(OH)$ are 1.54 and 1.29,

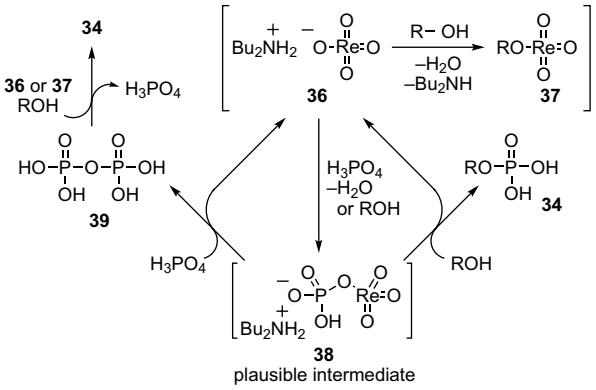
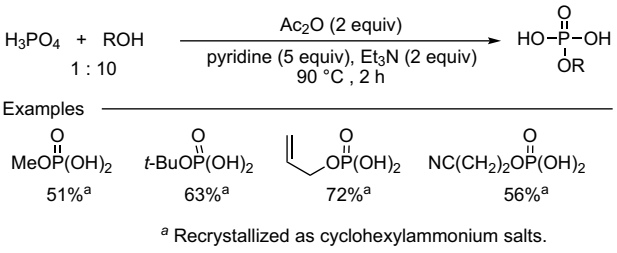


Figure 19. Proposed mechanism for dehydrative condensation of phosphoric acid with alcohols catalyzed by perrhenic acid.

respectively. Therefore, the nucleophilic substitution of **36** or **37** with monoalkyl phosphates **34** is slower than that with phosphoric acid. Thus, monoalkyl phosphates are selectively produced by the present condensation. Alternatively, the active species **38** may react with phosphoric acid to produce pyrophosphoric acid **39**, which could easily react with alcohols to give **34**.

In 2008, Pascal and co-workers reported that simple aliphatic alcohols could be selectively converted into the monoalkyl phosphates on a laboratory scale using the acetic anhydride-mediated activation of phosphoric acid in the presence of pyridine (Eq. 28).[55] Although this procedure requires excess amounts of alcohols, condensing agents, and bases,[56] several monoalkyl phosphates including protecting groups that can be removed by various procedures can be prepared in convenient yields.

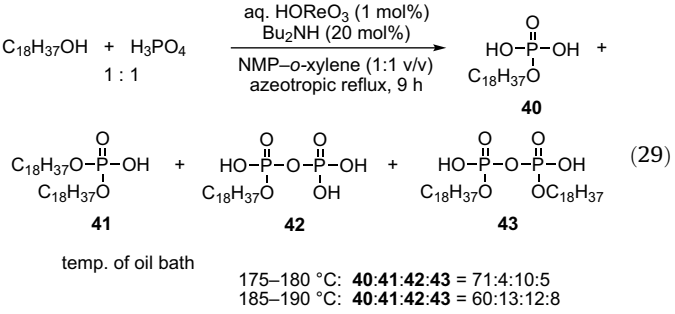


(28)

2.3.2. Synthesis of dialkyl phosphates

Dialkyl phosphates are important substances that have been used as liquid ion exchangers for the recovery of valuable metals from waste liquors. In particular, cyclic dialkyl phosphates have recently been widely used in the fields of organic synthesis, materials chemistry, and so on. For example, cyclic dialkyl phosphates of BINOL derivatives are useful chiral Brønsted acid catalysts for asymmetric synthesis. Amphiphilic dialkyl phosphates are useful surfactants with biological activities.

The perrhenic acid-catalyzed dehydrative condensation reaction is usually conducted at 175–180 °C (temp of oil bath) under azeotropic-reflux conditions, and selectively gives the monoalkyl phosphates in excellent yields.[53] However, the yield of the dialkyl phosphate **41** increases when the reaction of phosphoric acid with stearyl alcohol (1 equiv) is conducted at a higher reaction temperature (185–190 °C (temp of oil bath)) (Eq. 29).[57] Mixed anhydrides **42** and **43** are hydrolyzed to the monoester **40** through the usual work-up. Dialkyl phosphates can also be selectively obtained when the oxorhenium(VII)-catalyzed condensation of phosphoric acid is conducted with 2 equiv of alcohols under appropriate reaction conditions.



(29)

When the reaction of phosphoric acid with stearyl alcohol (2 equiv) is conducted with perrhenic acid (1 mol %) and BnNHMe (20 mol %) in NMP–*o*-xylene (1:1 v/v) at azeotropic reflux with the removal of water in the range of 0.05–0.2 M, a lower concentration effectively increases the efficiency of dehydration (Fig. 20). However, the reaction with 0.02 M of phosphoric acid gives a rather poor result (black line). The best result is obtained with 0.05 M of phosphoric acid (red line).

With the optimized conditions, several dialkyl phosphates have been synthesized (Table 21). Primary and secondary alcohols are converted into the corresponding dialkyl phosphates in moderate-to-good yields (entries 1 and 2). In contrast, the present reaction conditions work very well for the synthesis of cyclic dialkyl phosphates. The condensation of phosphoric acid with equimolar amounts of diols gives the cyclic dialkyl phosphates in almost quantitative yields (entries 3–7). Catechol is smoothly converted into the corresponding five-membered cyclic dialkyl phosphate **36**, which cannot be isolated, since it is very labile and decomposes during purification (entry 4). A 1,3-diol such as 9,9-bis(hydroxymethyl)heptadecane is also converted into the corresponding six-membered cyclic diester in 93% isolated yield (entry 5). This double-tailed cyclic phosphate is in a novel class of phosphate

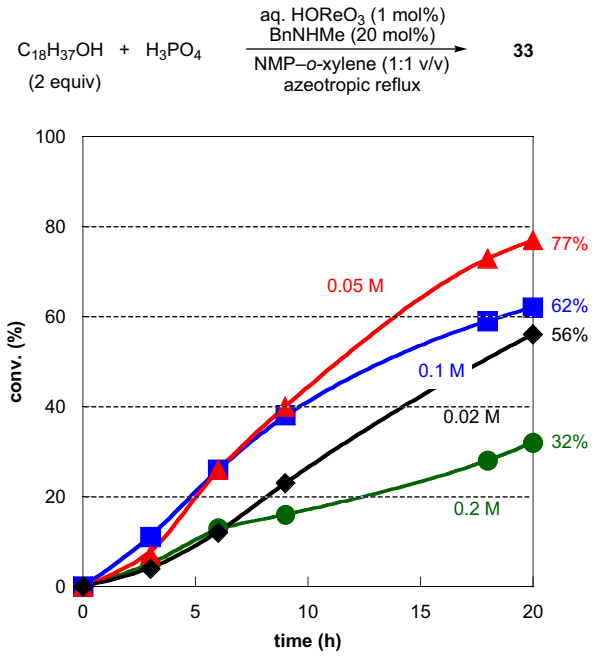
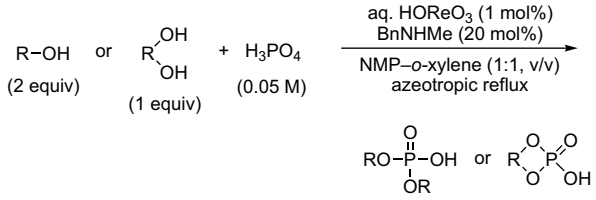
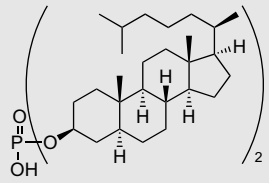
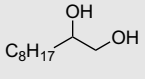
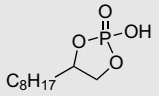
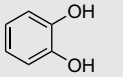
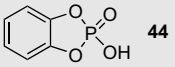
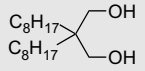
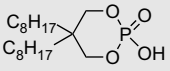
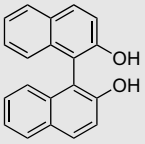
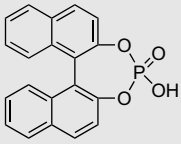


Figure 20. Plot of conversion versus time for dehydrative condensation of phosphoric acid. Green line: 0.2 M phosphoric acid; blue line: 0.1 M; red line: 0.05 M; black line: 0.02 M.

Table 21
Synthesis of phosphoric acid diesters



Entry	Alcohol	Product	Time (h)	Yield (%)
1	$C_{12}H_{25}(OC_2H_4)_2OH$	$C_{12}H_{25}(OC_2H_4)_2O-P(=O)(OH)-OC_2H_4)_2C_{12}H_{25}$	96	72
2	β-Cholestanol		30	66
3			8	>99[a]
4		 **44**	20	>99
5			50	93
6[b]			75	84
7[b,c]			48	90

[a] Isolated as *N*-benzyl-*N*-methylammonium salt.
[b] Reaction conducted with 40 mol % BnNHMe.
[c] Reaction conducted in the presence of 10 mol % catechol.

surfactants. Since BINOL is slightly less reactive than aliphatic alcohols, the condensation of BINOL was conducted with 40 mol % of BnNHMe (entry 6). Interestingly, when the reaction of phosphoric acid with BINOL is conducted in the presence of catechol (10 mol %) and BnNHMe (40 mol %), the reaction proceeded more smoothly (entry 7). Compound **44** may be generated in situ as an active intermediate.

3. Conclusions

This review clearly demonstrates the recent progress in methods for the synthesis of carboxylic esters, carboxamides, monoalkyl phosphates, and dialkyl phosphates, from classical methods with stoichiometric condensing agents to dehydrative condensation methods with re-usable catalysts directed toward green and sustainable chemistry. Catalytic dehydrative condensation processes have recently matured with an impressive and steadily increasing number of reports regarding the synthesis of carboxylic esters. In contrast, there are only a few successful examples of catalytic methods for the synthesis of carboxamides and phosphoric esters. For the synthesis of carboxylic esters, several catalytic dehydrative condensation reactions have been realized without removal of the water produced. The application of organocatalysts has permitted the preparation of several valuable products, while excluding the use of hazardous metals and offering several economic and environmental advantages. These contributions from many academic groups have led to dramatic improvements in dehydrative condensation catalyses. By improvements in practicality and environmental safety, these groups will undoubtedly continue to advance this field in a direction that benefits academic chemists, process chemists, material chemists, natural product chemists, and medicinal chemists alike.

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Biographical sketch

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