Development of Catalytic Ester Condensations and Hydrolysis of Esters toward Green Chemistry

Yoshiki Koshikari

Graduate School of Engineering, Nagoya University

Content

Chapter 1.
Introduction and General Summary

1.1 Ester

Esters are some of the most important substrates used in flavorings, cosmetics and materials like PET.[1] Many esters are currently synthesized on an industrial scale and used in our daily life (Figure 1). For example, butyl hexanoate is manufactured in Japan for use as a pineapple flavoring.

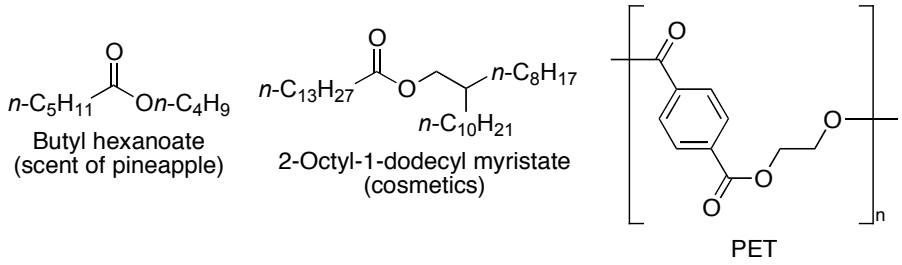
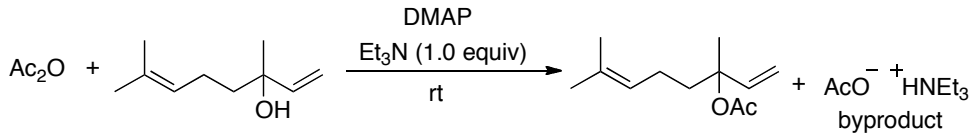


Figure 1. Useful esters in daily life

Since a variety of esters are synthesized on an industrial scale all over the world, large amounts of byproducts are also generated during synthetic processes. Therefore, the use of stoichiometric dehydrating reagents, activated carboxylic acid derivatives, excess amounts of substrates, or solvents can lead to considerable waste after ester condensation reactions. Furthermore, the use of additional energy for azeotropic reflux is not desirable. Thus, the catalytic dehydrative condensation between equimolar amounts of carboxylic acids and alcohols without the use of an additional dehydration procedure is the most ideal method for the synthesis of esters. Recently, some catalysts are reported toward this reaction but there are still some problems. Therefore, there is still strong demand for the development of the synthetic method.

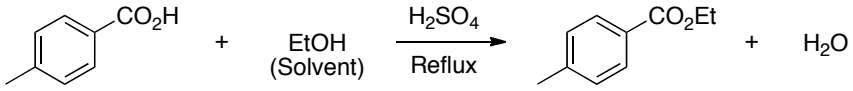
1.2 Development of Practical Methods for the Synthesis of Esters

The acylations of alcohols with carboxylic anhydrides or carboxylic chlorides are conventional methods for the synthesis of esters (Scheme 1).[2] These reactions are carried out under mild conditions and can be applied to the acylation of a variety of alcohols. However, these reactions produce one equivalent of carboxylic acid or hydrogen chloride as byproducts. Moreover, stoichiometric amounts of bases are needed to neutralize these acidic byproducts. Therefore, these methods are not desirable from the perspective of green chemistry.



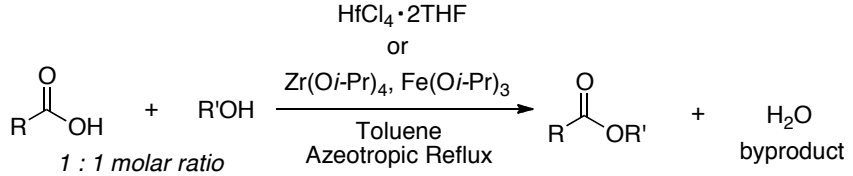
Scheme 1. Example of the conventional ester condensation method

The catalytic direct dehydrative condensation[3] of carboxylic acids with alcohols is an excellent alternative for the synthesis of esters with regard to atom economy[4] and E-factor[5] because a stoichiometric amount of condensation reagent is not used in this reaction. However, since the acid-catalyzed dehydrative ester condensation is an equilibrium reaction, it should be conducted with excess carboxylic acids (or alcohols) against a counterpart to obtain the esters in high yields (Scheme 2). The use of excess substrates is wasteful and is not desirable for green chemistry.



Scheme 2. Catalytic dehydrative ester condensation

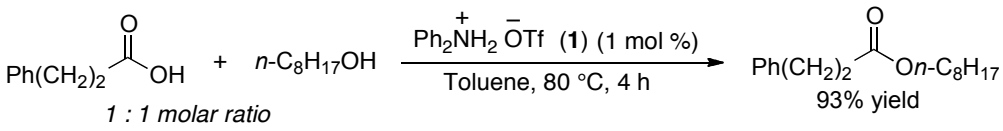
In 2000, Yamamoto and colleagues reported a Lewis acid-catalyzed ester condensation reaction between an equimolar mixture of carboxylic acids and alcohols (Scheme 3).[6] This is a more ideal method for green chemistry than the conventional approaches because one equivalent of water is the only byproduct of ester condensation processes. However, to give esters in high yields, water must be removed by azeotropic reflux, which requires additional energy.



Scheme 3. Lewis acid-catalyzed dehydrative ester condensation

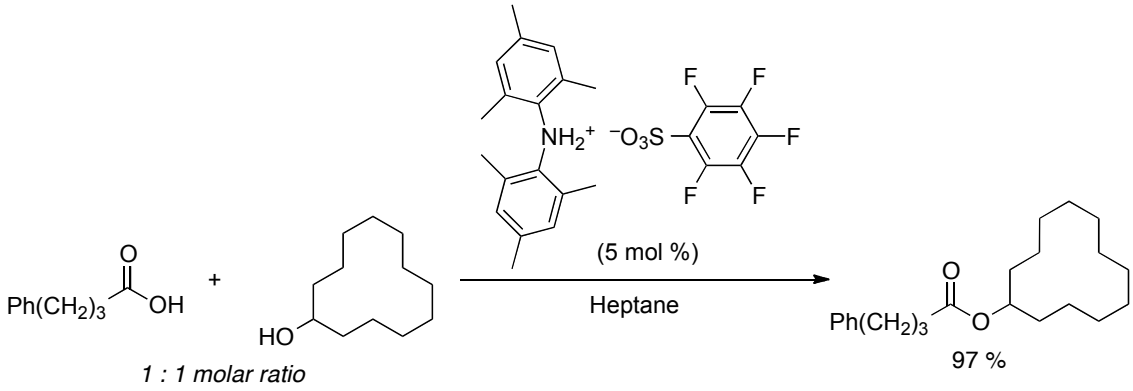
Tanabe and colleagues reported that *N*,*N*-diphenylammonium triflate (**1**) efficiently catalyzed the ester condensation reaction between an equimolar mixture of

carboxylic acids and alcohols under thermal conditions (Scheme 4).[7] Importantly, this method does not require any dehydration procedure such as azeotropic reflux. However, it does require the use of a less polar solvent for high reactivity. In addition, it is difficult to synthesize the esters of acid-sensitive alcohols because **1** is a rather strong Brønsted acid.



Scheme 4. *N*,*N*-Diphenylammonium triflate-catalyzed ester condensation

In 2005, Ishihara and colleagues reported that bulky *N*,*N*-diarylammonium pentafluorobenzenesulfonates were mild and highly efficient ester condensation catalysts (Scheme 5).[8] These catalysts promote the ester condensation of carboxylic acids with equimolar amounts of sterically demanding alcohols and acid-sensitive alcohols without the removal of water. However, this method also requires the use of a less polar solvent such as heptane or toluene for high reactivities.



Scheme 5. Bulky *N*,*N*-diarylammonium pentafluorobenzenesulfonate-catalyzed ester condensation

These two types of *N*,*N*-diarylammonium salts are good catalysts for the ester condensation between an equimolar amount of carboxylic acids and alcohols without dehydration procedures. Furthermore, they can promote the ester condensation of various substrates. However, these methods have five problems, as follows. First,

the reactions require long reaction time because the acidities of the *N*,*N*-diarylammonium salts are lower than various Brønsted acids which can promote the ester condensation. Therefore, the reactions use additional energy. Second, the catalysts are expensive. Third, the ester condensation reactions they catalyze require the use of less polar solvents to prevent water from deactivating the catalysts. These less polar solvents remove water from the active sites of the catalysts due to their hydrophobicity because the catalysts have not enough hydrophobicity to remove the generated water from active site. Since solvents are considered to be waste after the reaction, it is important to reduce the use of organic solvents. Fourth, the reactions do not run to completion since these catalysts also promote the hydrolysis of esters by a small amount of water dissolved in the organic phase. Finally, these methods require the use of column chromatography to separate the catalysts from the reaction mixture and to purify the esters.

Chapter 2 discusses the development of the ester condensation processes for greater practicality and higher reactivity than with the use of *N*,*N*-diarylammonium salt catalysts since less reaction time and energy is needed. Therefore, the author used sulfonic acids which are more acidic and have higher catalytic activities than *N*,*N*-diarylammonium salts as catalysts because the reaction time or energy can be reduced. Although sulfonic acid-catalyzed ester condensation may not be applied to the ester condensation of acid-sensitive substrates due to the high acidity of sulfonic acids, it is important to synthesize large amounts of esters of the simple substrates such as primary alcohols and benzoic acid at low price by simple procedure since the esters widely used. In addition, various sulfonic acids are less expensive than *N*,*N*-diarylammonium salts and are commercially available. Moreover, the purification method for ester condensation catalyzed by sulfonic acids might be easier than that with *N*,*N*-diarylammonium salts because sulfonic acids can be separated by washing the crude product with a small amount of water. However, sulfonic acids are easily deactivated by water since they have high hydrophlicity. Therefore, the author first considered that the solvent effect might play a key role in the high reactivity of ester condensation reactions catalyzed by sulfonic acids under the conditions without the removal of water.

The author examined the reactivity of 10-camphorsulfonic acid (CSA)-catalyzed ester condensation in various solvents (Figure 2). As expected, CSA showed high

catalytic activity in a less polar solvent such as heptane without the removal of water. Interestingly, the reaction proceeded the most rapidly under solvent-free conditions with little influence of water. However, the reaction was not completed because CSA also promoted the hydrolysis of esters under these reaction conditions. Thus, the author examined a simple dehydration procedure that did not require the use of additional equipment, procedures, or energy. The author was pleased to find that the reactivity of the ester condensation under open-air conditions was very high and the reaction was complete in 20 hours, since the generated water was gradually removed from the reaction mixture under thermal conditions. These results showed that the ester condensation under solvent-free and open-air conditions had high potential as a practical method for the synthesis of esters.

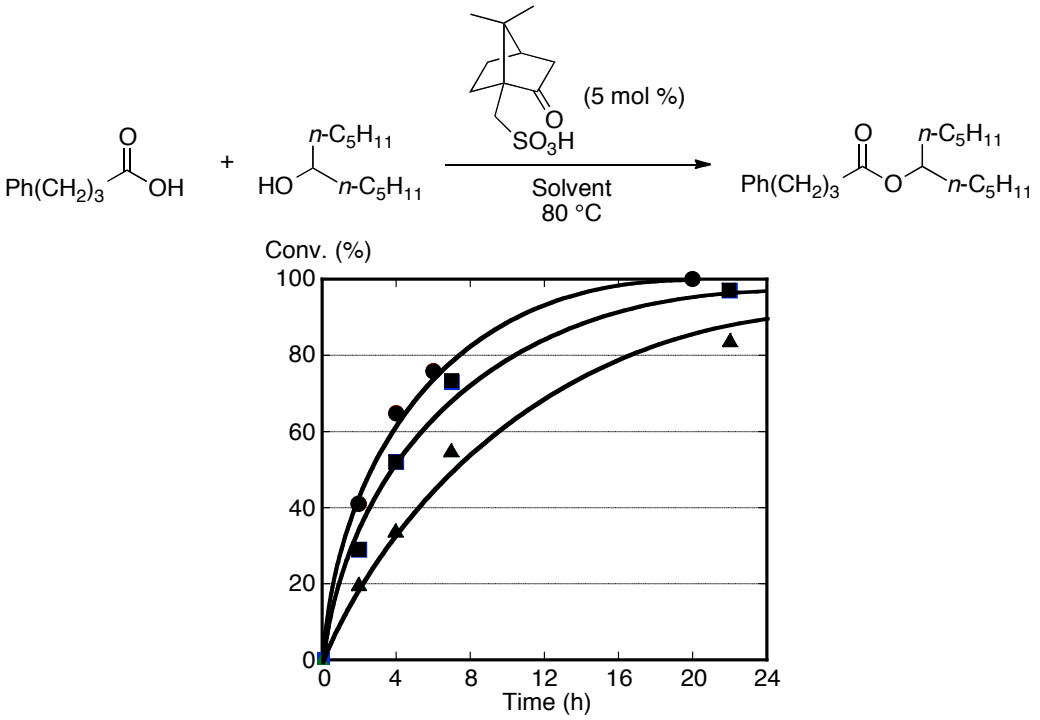


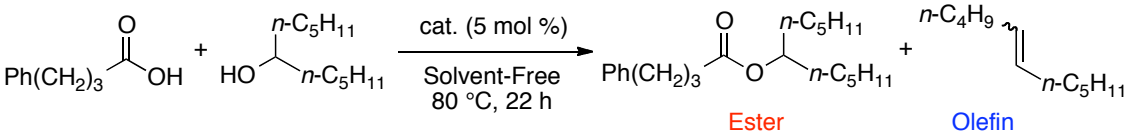
Figure 2. Solvent effect and the effect of dehydration

Circle, solvent-free and open-air; square, solvent-free; triangle, in heptane

Next, the author examined the catalytic activities of various sulfonic acids under solvent-free conditions (Table 1). The catalytic activities of the sulfonic acids depended on their pK_a values. For example, sulfuric acid (H_2SO_4) is highly acidic and showed high catalytic activity. However, when H_2SO_4 catalyzed the ester

condensation of secondary alcohols, significant amounts of olefins were produced as byproducts. On the other hand, *p*-toluenesulfonic acid (TsOH) and CSA, which are slightly less acidic than H_2SO_4, successfully promoted the ester condensation without the production of byproducts.

Table 1. Comparison of the Catalytic Activities of Various Sulfonic Acids



cat.	pK_a[a]	yield of ester (%)	yield of olefin (%)
H_2SO_4	7.0	93	7
TsOH	8.5	95	0
CSA	9.0	93	0

[a] pK_a values were measured in CD_3CO_2D

Dehydrative condensations between equimolar mixtures of various aliphatic alcohols and carboxylic acids were successfully promoted by sulfonic acid catalysts under solvent-free and open-air conditions. Sulfonic acid showed higher catalytic activities than *N*,*N*-diarylammonium salts. The present protocol could be easily applied to a large-scale process and could give the corresponding ester in almost quantitive yield by simple extraction. However, this method was not applied to the ester condensation of acid-sensitive alcohols and phenols because sulfonic acid catalysts also promoted decomposition of the acid-sensitive alcohols or hydrolysis of these phenyl esters.[9] Through the present protocols, a large amount of simple and useful esters can be synthesized in a rather simple method.

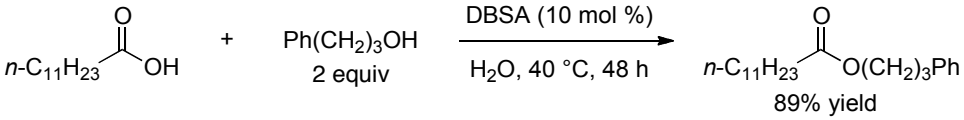
1.3 Ester Condensation Reactions under Aqueous Conditions

Water plays an important role in dehydrative ester condensation. Since water has unique physical and chemical properties, it may be possible to realize reactivity and selectivity that cannot be achieved in organic solvents under aqueous conditions.[10] Moreover, water is an inexpensive, safe and environmentally benign solvent compared to organic solvents. Therefore, the use of water as a reaction solvent has received

much attention in synthetic organic chemistry. Next, the author turned my attention to the development of ester condensation reactions under aqueous conditions.

Although various efficient catalytic systems under aqueous conditions have been developed so far, dehydrative ester condensation reactions under aqueous conditions are still difficult because these reactions are equilibrium reactions. The presence of water should have a detrimental effect on the equilibrium of dehydration reactions. Moreover, widely used Brønsted acid catalysts are highly hydrophilic. Under aqueous conditions, these Brønsted acids are dissolved in the aqueous phase and deactivated by water.

In 2001, Kobayashi and colleagues reported the dehydrative ester condensation between long-chain fatty acids and hydrophobic alcohols in water using *p*-dodecylbenzenesulfonic acid (DBSA) as a surfactant-type catalyst (Scheme 6).[11,12] They claimed that DBSA and long-chain substrates would form emulsion droplets in water to accelerate dehydration reactions (Figure 3).



Scheme 6. DBSA-catalyzed ester condensation in water

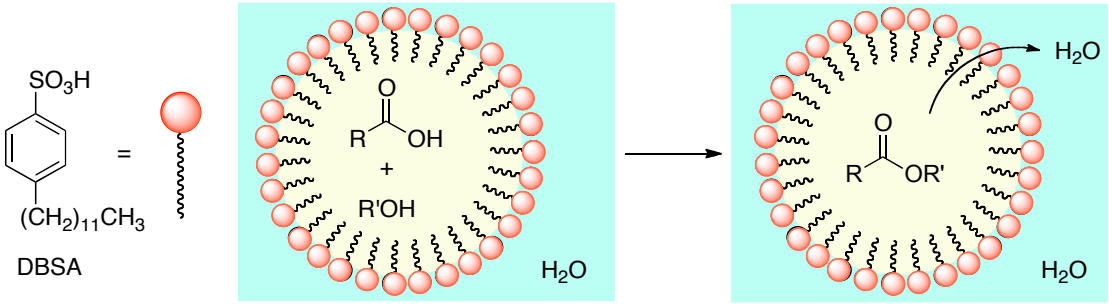


Figure 3. Illustration of ester condensation catalyzed by DBSA in water

Water is used as a reaction solvent in our bodies. For example, lipases successfully catalyze the ester condensation reactions under aqueous conditions. Lipases create a hydrophobic environment around the active site (Figure 4).[13] This hydrophobic wall prevents polar water molecules from gaining access to the active site of the lipase and thus inhibits the hydrolysis of esters. In contrast, less polar

substrates can approach the active site through the hydrophobic wall and be activated efficiently. Therefore, lipases promote ester condensation reactions and prevent the hydrolysis of esters.

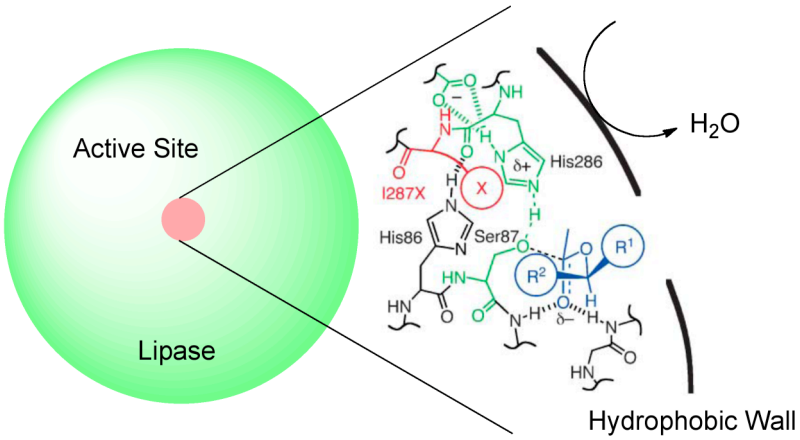


Figure 4. Illustration of the active site of lipase

In 2007, Ishihara and colleagues reported the X-ray crystallographic analysis of *N*-mesityl-[1,1':3',1''-terphenyl]-2'-ammonium pentafluorobenzenesulfonate **2** (Figure 5).[14] The bulky aryl groups of the *N*,*N*-diarylammonium salts create a hydrophobic environment around the catalytic center, as with the active site of lipase. Thus, **2** promotes dehydration reactions such as ester condensation and cyclization of 1,3,5-triketones in less polar solvents. Based on the design of this catalyst, the author considered dehydrative ester condensation might be promoted under aqueous conditions.

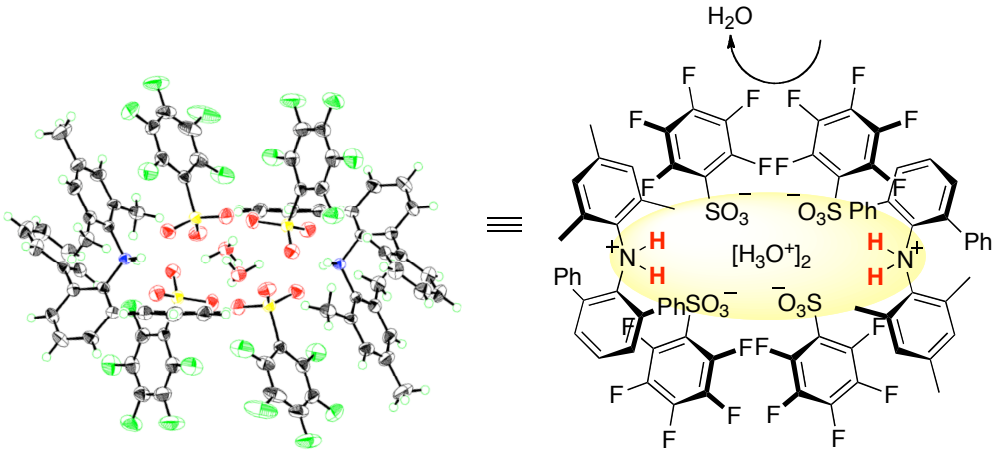
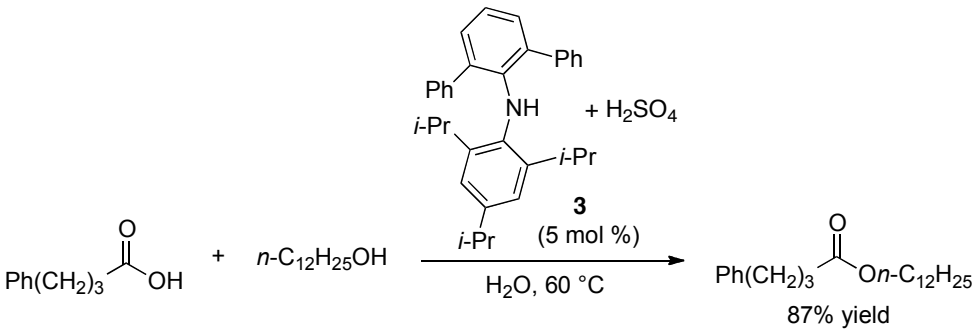


Figure 5. X-ray structure of **2**

In chapter 3, the author designed new Brønsted acid catalysts for dehydrative ester condensation under aqueous conditions. The author first examined various hydrophobic *N*,*N*-diarylammonium sulfonates that were prepared at ambient temperature. However, *N*,*N*-diarylammonium salts of various sulfonic acids were disappointingly inert because sulfonic acids were dissolved in the aqueous phase. After intensive studies, the author found that *N*,*N*-diarylammonium sulfate **3**, which was prepared at 80 °C for 0.5 h, surprisingly promoted ester condensations under aqueous conditions, although sulfuric acid is extremely hydrophilic (Scheme 7).



Scheme 7. Dehydrative ester condensation catalyzed by *N*,*N*-diarylammonium sulfate **3**

The pretreatment of *N*,*N*-diarylammonium sulfate catalysts by heating was crucial for high catalytic activities. An alkaline titration experiment showed that large

amounts of preheated *N*,*N*-diarylammonium sulfates were included in the organic phase. Based on these results, ^{1}H NMR analysis of the active catalysts, and Halstead's report[15] of the thermal decomposition of ammonium sulfate, the author proposed that the active species of preheated *N*,*N*-diarylammonium sulfates would be the ammonium salts of pyrosulfuric acid. The *N*,*N*-diarylammonium pyrosulfates formed four hydrogen bondings in a bidentate fashion between two *N*,*N*-diarylammonium cations and a pyrosulfate anion (Figure 6). Thus, the structure of the *N*,*N*-diarylammonium salts of pyrosulfuric acid should be more stable than that of sulfuric acid. The high stabilities of *N*,*N*-diarylammonium pyrosulfates would increase the oil-solubilities and the catalytic activities for the dehydrative ester condensation under aqueous conditions.

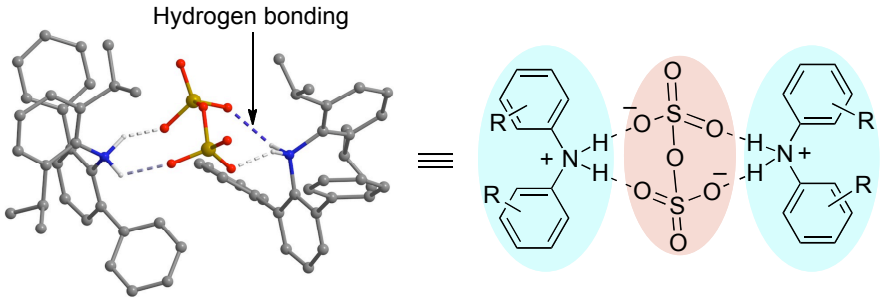
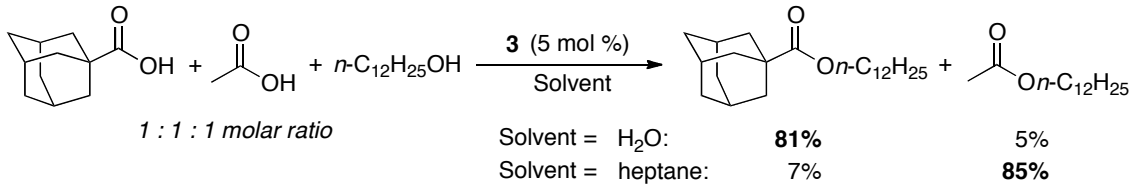


Figure 6. B3LYP/6-31G(d) optimized geometry of *N*,*N*-diarylammonium pyrosulfates

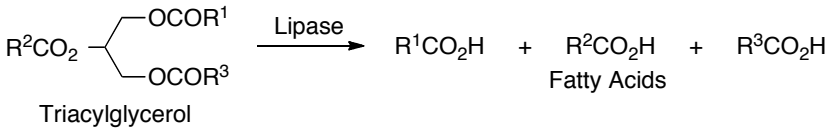
The use of **3** in water offered some additional advantages in unusual selective ester condensations. For example, when the reaction of a 1:1:1 molar mixture of 1-adamantanecarboxylic acid, acetic acid, and 1-dodecanol was conducted in water, the ester of hydrophobic 1-adamantanecarboxylic acid was predominantly obtained (81% yield) along with the ester of hydrophilic acetic acid in 5% yield (Scheme 8). In contrast, the same reaction in heptane preferentially gave the acetate (85% yield). This selectivity was based on the difference in hydrophobicity of the substrates.



Scheme 8. Unusual selective ester condensation

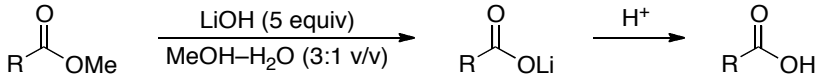
1.4 Hydrolysis of Esters without the Use of Any Organic Solvents

The hydrolysis of esters is also an important reaction because esters are often used not only as substrates for the synthesis of carboxylic acids but also as protecting groups of carboxylic acids or alcohols.[16] For example, in our bodies, triacylglycerols, which are triesters derived from glycerol and three fatty acids, are hydrolyzed by lipase to fatty acids and glycerol (Scheme 9).[17] The fatty acids are used as an energy source.



Scheme 9. Example of the hydrolysis of esters

In general, the hydrolysis of esters is performed under mild basic conditions (Scheme 9).[18] However, a stoichiometric amount of bases is required under these reaction conditions because the generated carboxylic acids form salts with the base catalysts. Thus, neutralization of the carboxylic acid salts with a strong acid is required to obtain the corresponding carboxylic acids. The alkaline hydrolysis is carried out in a mixture of organic solvents and water because both substrates and bases must be dissolved in a homogeneous solution to achieve high reactivities. Moreover, frequent problems encountered under these basic conditions include the epimerization of *N*-protected-α-amino acid esters and the decomposition of base-sensitive functional groups.[19]



Scheme 10. Conventional hydrolysis of esters under basic conditions

The hydrolysis of esters can also be promoted by the use of acid catalysts.[20] However, in general, acid-catalyzed hydrolysis also requires the use of organic solvents because both substrates and catalysts should be dissolved in a homogeneous solution. In a heterogeneous reaction mixture, Brønsted acid catalysts are dissolved in the aqueous phase and the reactivity of hydrolysis should be decreased.

In chapter 4, the author investigated the catalytic hydrolysis of esters under acidic conditions without the use of any organic solvents. In chapter 3, the author developed oil-soluble *N*,*N*-diarylammonium pyrosulfate catalysts for dehydrative ester condensation reactions under aqueous conditions. The author considered that these catalysts would promote the hydrolysis of esters without the use of any organic solvents based on the following hypothesis (Figure 7):[21] A small amount of water would be transferred into the organic phase as the substrate of hydrolysis. The hydrolysis of esters would proceed in the organic phase catalyzed by oil-soluble *N*,*N*-diarylammonium pyrosulfates. In the hydrolysis of methyl esters, the generated methanol would then move into the aqueous phase. Thus, the equilibrium of the reactions would favor the cleavage of esters.

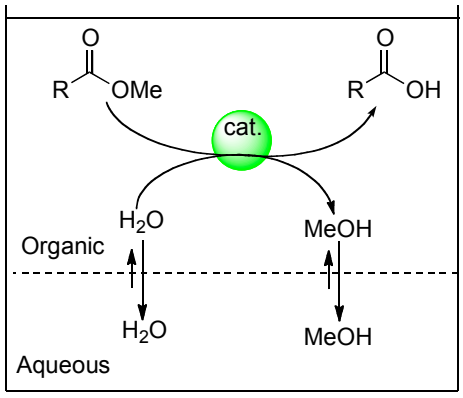
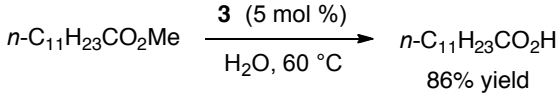
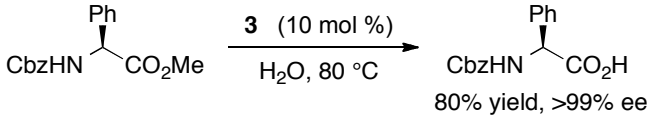


Figure 7. Working hypothesis for the hydrolysis of methyl esters under aqueous conditions catalyzed by *N*,*N*-diarylammonium pyrosulfate catalysts

Based on this hypothesis, the author found that **3** also promoted the hydrolysis of esters under aqueous conditions in the absence of any organic solvents (Scheme 11). The present method could be applied to various esters such as methyl, ethyl, and isopropyl esters. Especially, the hydrolysis of *N*-Cbz-L-phenylglycine methyl ester was successfully promoted by **3** without epimerization under aqueous conditions (Scheme 12). In contrast, conventional alkaline hydrolysis resulted in significant epimerization (93% yield, 15% ee).[22]



Scheme 11. *N*,*N*-Diarylammonium pyrosulfates promoted hydrolysis without the use of organic solvents



Scheme 12. Hydrolysis of *N*-Cbz-L-phenylglycine methyl ester

References

1. Otera, J.; Nishikido, J. *Esterification*; 2nd Ed., WILEY-VCH, Weinheim, 2010.
2. (a) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed.* **1978**, *17*, 569. (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. (c) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494. (d) Grondal, C. *Synlett* **2003**, 1568. (e) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436.
3. For a review, see: Ishihara, K. *Tetrahedron* **2009**, *65*, 1085.
4. Trost, B. M. *Science*, **1991**, *254*, 1471.
5. Sheldon, R. A. *Pure Appl. Chem*. **2000**, *72*, 1233.
6. (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *390*, 1140. (b) Ishihara, K.;Nakayama, M.; Ohara, S.; Yamamoto, H. *Synlett* **2001**, 1117. (c) Ishihara, K.;Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8179. (d) Nakayama, M.; Sato, A.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2004**, *346*, 1275. (e) Sato, A.; Nakamura, Y.; Maki, T.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2005**, *347*, 1337. (f) Nakamura, Y.; Maki, T.; Wang, X.; Ishihara, K.;Yamamoto, H. *Adv. Synth. Catal.* **2006**, *348*, 1505.
7. (a) Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249. (b) Funatomi, T.; Wakasugi, K.; Misaki, T.; Tanabe, Y. *Green Chem.* **2006**, *8*, 1022. (c) Gacem, B.; Jenner, G. *Tetrahedron Lett.* **2003**, *44*, 1391. (d) Mercs, L.; Pozzi, G.; Quici, S. *Tetrahedron Lett.* **2007**, *48*, 3053.
8. (a) Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, *127*, 4168. (b) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Tetrahedron* **2006**, *62*, 422. (c) Sakakura, A.; Ishihara, K. *Nature Protocols* **2007**, *2*, 1746.
9. Offenhauer, R. D. J. *Chem. Educ*. **1964**, *41*, 39.
10. (a) Lindström, U. M., Ed. *Organic Reactions in Water*; Blackwell, Oxford, 2007. (b) Li, C.-J.; Chen, L.; *Chem. Soc. Rev.* **2006**, *35*, 68. (c) Uozumi, Y.; Yamada, Y. M. A. *Chem. Rec.* **2009**, *9*, 51. (d) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687. (e) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.
11. (a) Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101. (b) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971.
12. For other reactions catalyzed by DBSA, see: (a) Kobayashi, S.; Iimura, S.; Manabe,

K. *Chem. Lett.* **2002**, *31*, 10. (b) Aoyama, N.; Kobayashi, S. *Chem. Lett.* **2006**, *35*, 238. (c) Shirakawa, S., Kobayashi, S. *Org. Lett.***2007**, *9*, 311.

13. Ema, T.; Fujii, T.; Ozaki, M.; Korenaga, T.; Sakai, T. *Chem. Commun.* **2005**, 4650.
14. Sakakura, A.; Watanabe, H.; Nakagawa, S.; Ishihara, K. *Chem.-Asian J.* **2007**, *2*, 477.
15. (a) Halstead, W. D. *J. Appl. Chem.* **1970**, *20*, 129. (b) Jariwala, M.; Crawford, J.; LeCaptain, D. J. *Ind. Eng. Chem. Res.* **2007**, *46*, 4900.
16. Haslam, E. *Tetrahedron* **1980**, *31*, 2409.
17. Bloor, W. R. *Chem. Rev*. **1925**, *2*, 243.
18. Wuts, P. G.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; 4th Ed., WILEY-VCH, Weinheim, 2006.
19. (a) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.*, **1977**, *42*, 918. (b) Kaestle, K. L.; Anwer, M. K.; Audhya, T. K.; Goldstein, G. *Tetrahedron Lett.* **1991**, 32, 327.
20. (a) Bamford, C. H.; Tipper, C. F. H.; Compton, R. G., Ed. *Ester Formation and Hydrolysis and Related Reactions*, Elsevier, 1972. (b) March, J. *Advanced Organic Chemistry*; 4th Ed., John Wiley & Sons, New York, 1992.
21. Mori, T.; Kishimoto, S.; Ijiro, K.; Kobayashi, A.; Okahata, Y. *Biotechnol. Bioeng.* **2001**, *76*, 157.
22. (a) Lovrić, M.; Cepanec, I.; Litvić, M.; Bartolinćić, A;Vinković, V. *Croat. Chem. Acta* **2007**, 80, 109. (b) Maegawa, Y.; Agura, K.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Synlett* **2012**, 137.

Chapter 2.
Development of Practical Ester Condensation Reactions

Abstract: Under solvent-free and drying agent-free conditions, catalytic amounts of sulfonic acids promote ester condensation between an equimolar mixture of carboxylic acids and alcohols. In particular, *p*-toluenesulfonic acid (TsOH) and 10-camphorsulfonic acid (CSA), which have appropriate acidities, efficiently catalyze the ester condensation of secondary alcohols without their decomposition. Since the present protocol does not require solvents under simple open-air conditions, a large amount of esters can be synthesized in a rather small apparatus.

Catalytic condensation between an equimolar mixture of carboxylic acids and alcohols is most desirable with regard to atom economy and E-factor.[1–4] Conventionally, the acid-catalyzed ester condensation is conducted under the azeotropic reflux conditions with the removal of water. For example, hafnium(IV) salts efficiently catalyze the ester condensation between an equimolar mixture of carboxylic acids and alcohols under the azeotropic reflux conditions in toluene.[3] However, catalytic activities of Hf(IV) salts significantly decrease when the reaction is conducted under the conditions without the removal of water due to the serious inactivation of the catalysts by water. Recently, Ishihara and colleagues reported bulky *N*,*N*-diarylammonium pentafluorobenzenesulfonates as mild and selective ester condensation catalysts.[5] These bulky *N*,*N*-diarylammonium salts efficiently catalyze ester condensation under heating conditions even without the removal of water. The use of non-polar solvent such as heptane is critical for high reactivities. In this chapter, the author found that the reaction of some alcohols with carboxylic acids was efficiently promoted by sulfonic acids under open-air and solvent-free conditions. This is a very simple and practical method for ester condensation catalyzed by sulfonic acids.

The author considered that the solvent effect might play a key role in ester condensation catalyzed by sulfonic acids under conditions without the removal of water. First, the solvent effect was examined in sulfonic acid-catalyzed ester condensation (Figure 1). 6-Undecanol (2 mmol) was reacted with 4-phenylbutyric acid (1.1 equiv) in the presence of 10-camphorsulfonic acid (CSA, 5 mol %) in several solvents (2 mL) at 80 °C without removal of the water produced. To reduce experimental errors, these reactions were performed in screw-capped vessels (ϕ16 mm × 100 mm). When the reaction was conducted in toluene, which is conventionally used as a solvent in Brønsted acid-catalyzed ester condensation, the reaction proceeded slowly and the corresponding ester was obtained in moderate yield (Figure 1, triangle). The water produced might decrease the catalytic activity of CSA in a relatively polar solvent such as toluene under these conditions without the removal of water. In contrast, the reaction proceeded more rapidly in heptane, a less polar solvent (Figure 1, square). Interestingly, the reaction proceeded most rapidly under solvent-free conditions with little influence of water (Figure 1, closed-circle). The finding that the reaction proceeded very well under solvent-free conditions without the removal of water is very important for the development of a practical ester condensation method. It is

conceivable that the use of a sulfonic acid catalyst is the key to the success of the solvent-free ester condensation. In contrast to Lewis acids such as Hf(IV) salts, the affinity of sulfonic acids with water might be weak. Therefore, sulfonic acids were unlikely to be inactivated under the solvent-free conditions. When CSA-catalyzed ester condensation was performed in a screw-capped vessel, the reaction did not proceed to completion, even though the reaction time was prolonged. It is conceivable that this result was due to hydrolysis of the product and/or the inactivation of CSA by the water produced. Therefore, we next performed ester condensation in an open-air vessel (ϕ16 mm × 100 mm) to remove water spontaneously. As a result, the reaction proceeded slightly more rapidly than in a screw-capped vessel, and was completed as expected (Figure 2A). The reactivity of ester condensation under solvent-free conditions in the open-air vessel was very high. In fact, the present ester condensation showed the same reactivity as that conducted under azeotropic reflux conditions in cyclohexane (bp 80.7 °C, bath temperature ~115 °C) with the removal of water (Figure 2B). When the ester condensation in solvents is conducted under the open-air conditions, solvents would be evaporated, which causes some trouble in the reaction. These results showed that the present ester condensation has high potential as a practical method for the synthesis of esters.

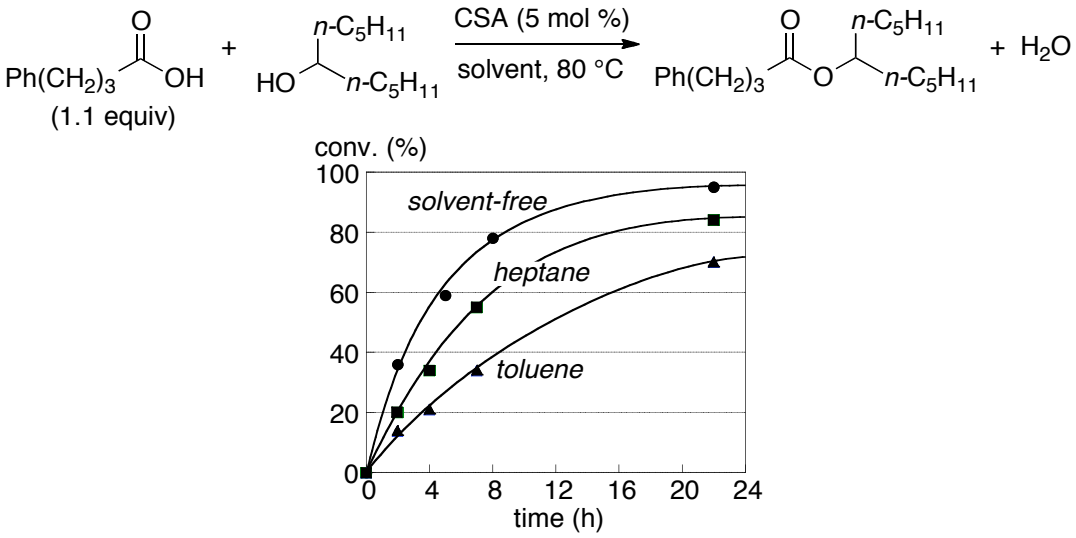


Figure 1. Solvent effect in CSA-catalyzed ester condensation.

6-Undecanol (2 mmol) was reacted with 4-phenylbutyric acid (1.1 equiv) in the presence of CSA (5 mol %) in solvent (2 mL) at 80 °C without the removal of water: closed-circle, solvent-free; square, heptane; triangle, toluene. Yield was determined by ^{1}H NMR analysis.

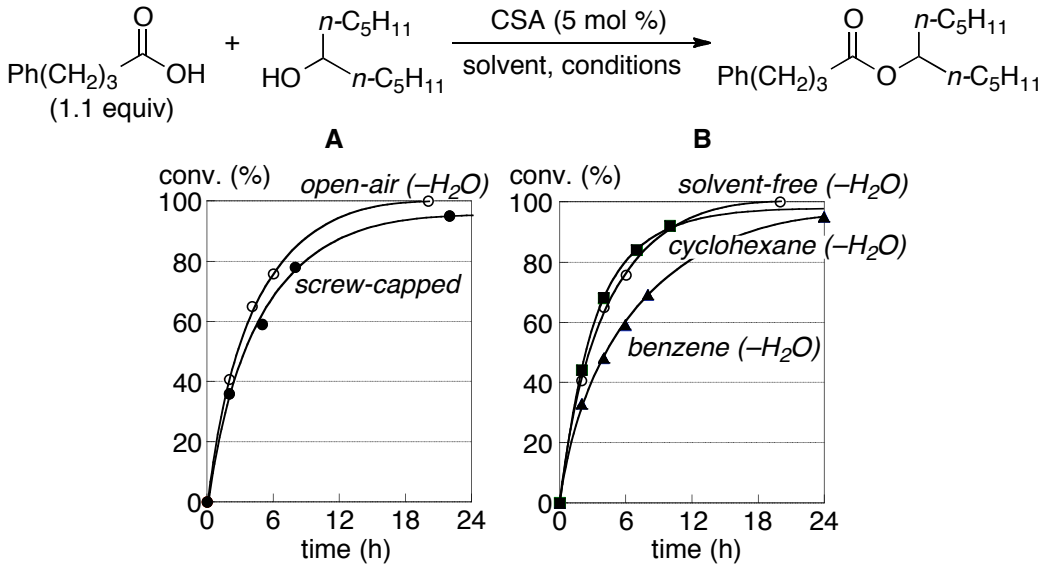
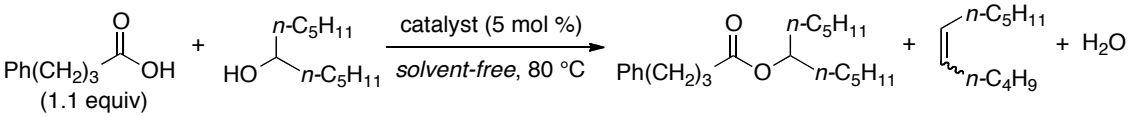


Figure 2. Effect of dehydration in CSA-catalyzed ester condensation. 6-Undecanol (2 mmol) was reacted with 4-phenylbutyric acid (1.1 equiv) in the presence of CSA (5 mol %) in solvent (2 mL) at 80 °C: open-circle, solvent-free conditions in an open-air vessel; closed-circle, solvent-free conditions in a screw-capped vessel; square, azeotropic reflux in cyclohexane (bp. 80.7 °C) with the removal of water; triangle, azeotropic reflux in benzene (bp. 80.1 °C) with the removal of water. The yield was determined by ^{1}H NMR analysis.

Encouraged by these results, we next examined the catalytic activities of various sulfonic acids under the present reaction conditions. 6-Undecanol (2 mmol) was reacted with 4-phenylbutyric acid (1.1 equiv) in the presence of 5 mol % of concentrated sulfuric acid (H_2SO_4), *p*-toluenesulfonic acid (TsOH), methanesulfonic acid (MsOH), 2-propanesulfonic acid (*i*-$PrSO_3H$), and CSA in a screw-capped vessel (Table 1). The catalytic activities of the sulfonic acids depended on their pK_a values, and H_2SO_4 [pK_a (CD_3CO_2D) = 7.0][6] showed the highest reactivities among the catalysts examined (entry 1). However, the high acidity of H_2SO_4 resulted in the production of 5-undecene as a byproduct (7%), and the yield of the desired ester decreased (93%). In contrast to the results with H_2SO_4, other sulfonic acids such as TsOH [pK_a (CD_3CO_2D) = 8.5], MsOH [pK_a (CD_3CO_2D) = 8.6], CSA [pK_a (CD_3CO_2D) = 9.0], and *i*-$PrSO_3H$ [pK_a (CD_3CO_2D) = 9.6] did not cause the production of 5-undecene, and gave the ester in good yields (93–97%). In general, sterically hindered secondary alcohols

are easily dehydrated to give alkenes under acidic conditions. However, the results described above showed that sulfonic acids with appropriate acidities successfully promoted the ester condensation of secondary alcohols without the production of alkenes.

Table 1. Comparison of the Catalytic Activities of Sulfonic Acids for Ester Condensation between 6-Undecanol and 4-Phenylbutyric Acid[a]



Entry	Catalyst	pK_a[b]	Conv. (%)[c]	
			2 h	22 h
1	H_2SO_4	7.0	60	93 [7][d]
2	TsOH	8.5	45	97 [0][d]
3	MsOH	8.6	45	97 [0][d]
4	CSA	9.0	36	95 [0][d]
5	*i*-$PrSO_3H$	9.6	22	93 [0][d]

[a]The reaction was conducted in the presence of a sulfonic acid (5 mol %) under solvent-free conditions at 80 °C in a screw-capped vessel. [b]pK_a values were measured in CD_3CO_2D. [c]Determined by ^1H NMR analysis. [d]Yield of 5-undecene is shown in brackets.

Next, we examined the catalytic activities of sulfonic acids in ester condensation between 6-undecanol and benzoic acid (Figure 3). The reaction was conducted at 100 °C, since the reactivity of benzoic acid was rather low. This high reaction temperature caused the generation of an increased amount of 5-undecene. Especially, the reaction catalyzed by H_2SO_4 produced a significant amount of 5-undecene, and the yield of the desired ester was poor (graph A). Lower catalyst loading (1 mol % of H_2SO_4) did not suppress the generation of 5-undecene, and merely decreased the reactivity (ester: 63% yield, 5-undecene: 20% yield for 47 h reaction). In contrast, TsOH and CSA efficiently promoted the ester condensation with little production of 5-undecene, and a 50 h reaction gave the desired ester in 90% yield (graphs B and C). In the ester condensation catalyzed by TsOH, however, a prolonged reaction time

caused the generation of a significant amount of 5-undecene (graph B). The catalytic activity of *i*-$PrSO_3H$ was much lower than those of TsOH and CSA, due to its lower acidity (graph D).

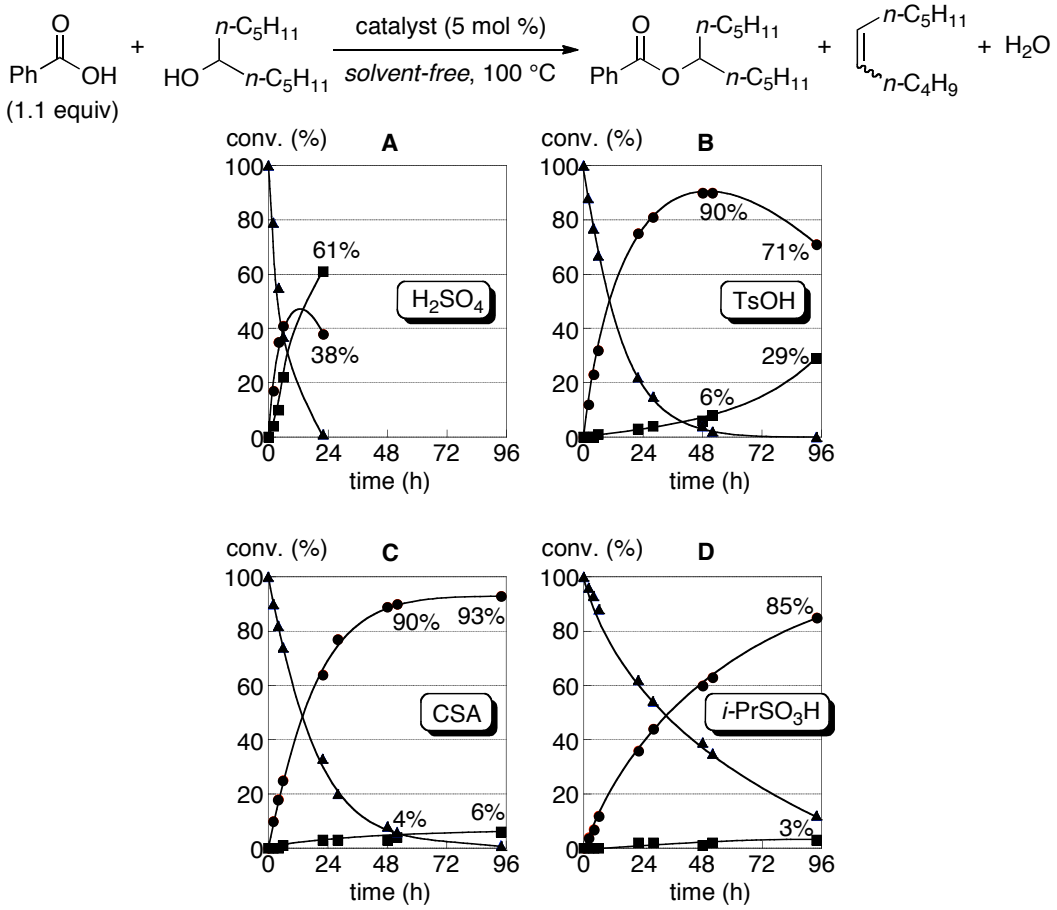


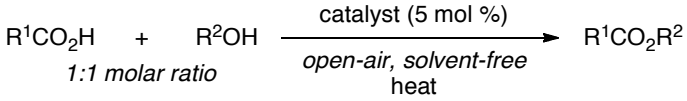
Figure 3. Ester condensation with benzoic acid catalyzed by sulfonic acid. 6-Undecanol (2 mmol) was reacted with benzoic acid (1.1 equiv) in the presence of a sulfonic acid (5 mol %) under solvent-free conditions at 100 °C in a screw-capped vessel. The proportions of 6-undecanol (triangle), 6-undecyl benzoate (circle) and 5-undecene (square) over time were evaluated by ^{1}H NMR analysis.

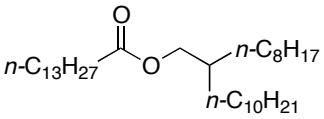
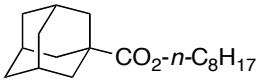
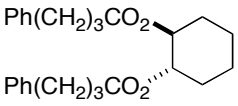
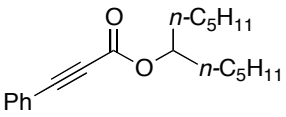
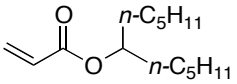
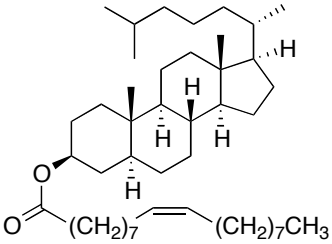
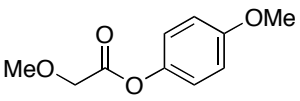
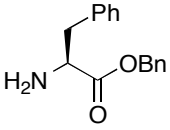
To explore the generality and scope of the present ester condensation catalyzed by sulfonic acids, the reaction was examined with an equimolar mixture of various alcohols and carboxylic acids under solvent-free conditions in an open-air vessel (Table 2). The ester condensation of primary alcohols proceeded very well even with sterically hindered carboxylic acids such as 1-adamantanecarboxylic acid, and the

corresponding esters were obtained in excellent yields (entries 1–6). The present protocol could be easily applied to a large-scale process. The ester condensation of an equimolar mixture of 2-octyldodecanol and myristic acid catalyzed by CSA (1 mol %) gave the corresponding ester in 97% yield, just after simple extraction with the minimal use of organic solvents (entry 3). Esters derived from secondary alcohols were also obtained in good yields (entries 7–16), although the reactivities of secondary alcohols were lower than those of primary alcohols. Ester condensation of *trans*-1,2-cyclohexanediol gave the corresponding diester in high yields (entries 7–9), while Lewis acidic metal salts, such as $HfCl_4$•2THF, were not suitable for use with these diols due to tight chelation with metal ions.[3c] The reactions catalyzed by TsOH and CSA gave particularly excellent results (entries 8 and 9), although the use of H_2SO_4 led to isomerization of the product (*trans*: *cis* = 93:7) (entry 7). When the reaction of 6-undecanol with 3-phenylpropionic acid was conducted with a catalytic amount of H_2SO_4, a significant amount of 5-undecene was generated (12%) and the yield of the desired ester was decreased (78%) (entry 10). In contrast, neither TsOH nor CSA promoted the generation of 5-undecene and the ester was obtained in good yields (entries 11 and 12). Ester condensation of acrylic acid was also successfully conducted without promoting undesired conjugate addition (entries 13–15). When substrates and/or products were solid, they were effectively dissolved by the addition of a small amount of octane. For example, the reaction of β-cholestanol (solid, 2 mmol) with oleic acid proceeded well in the presence of octane (1 mL), and gave the corresponding ester (solid) in 98% yield (entry 16). Tertiary alcohols are generally much less reactive than secondary alcohols and decompose much more easily to give alkenes under acidic conditions. In fact, the reaction of 2-methyl-4-phenyl-2-butanol with 4-phenylbutyric acid resulted in the generation of alkenes in ca. 85% yields under the present reaction conditions. In contrast to the ester condensation of aliphatic alcohols, the reaction of 4-methoxyphenol with methoxyacetic acid gave poor results (entries 17–19), while bulky *N*,*N*-diarylammonium salt-catalyzed esterification gave the corresponding ester in 99% yield.[5] It is conceivable that the hydrophilic nature of sulfonic acids promoted hydrolysis of the product to decrease its yield without the removal water.[8] Amino acid esters could be prepared through the present ester condensation by using 1 equiv of an additional sulfonic acid. When L-phenylalanine and benzyl alcohol (2 equiv) were reacted with CSA (1.05 equiv), the corresponding

benzyl ester was obtained in good yield and with complete retention of its chiral center (entry 20).

Table 2. 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 [97][d]
4[e]		H_2SO_4	80, 3	93
5[e]		TsOH	80, 3	95
6[e]		CSA	80, 3	92
7[e]		H_2SO_4	80, 22	89 [93:7][f]
8[e]		TsOH	80, 22	95
9[e]		CSA	80, 22	95
10		H_2SO_4	80, 19	78 [12][g]
11		TsOH	80, 29	95
12		CSA	80, 29	90
13[e]		H_2SO_4	80, 48	81
14[e]		TsOH	80, 48	87
15[e]		CSA	80, 48	91
16[h]		TsOH	60, 35	98
17		H_2SO_4	80, 20	34
18		TsOH	80, 26	39
19		CSA	80, 26	35
20[i]		CSA	60, 36	89 [>99][j]

[a]Unless otherwise noted, a mixture of alcohol (2 mmol) and carboxylic acid (2 mmol)

was heated with sulfonic acid (5 mol %) in an open-air vessel (ϕ16 mm × 100 mm). [b]The reaction was conducted with sulfonic acid (1 mol %). [c]The reaction of alcohol (100 mmol) and carboxylic acid (100 mmol) was conducted in a 100-mL round-bottomed flask. [d]The purity of the product is shown in brackets. [e]The reaction was conducted with 1.1 equiv of carboxylic acid. [f]The ratio of *trans* isomer:*cis* isomer is shown in brackets. [g]The yield of alkenes is shown in brackets. [h]The reaction was conducted with octane (1 mL). [i]The reaction was conducted with 2 equivalents of benzyl alcohol. [j]The optical purity of the product is shown in brackets.

In conclusion, we have demonstrated that 1–5 mol % of sulfonic acids could efficiently catalyze the ester condensation of alcohols with carboxylic acids (1.0–1.1 equiv) under open-air and solvent-free conditions. This is a highly practical and atom-economical esterification method, since it does not require any solvent as well as additional equipment or additional amounts of materials and 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 (Table 2, entry 3).

References and notes

1. Otera, J.; Nishikido, J. *Esterification*; 2nd Ed., WILEY-VCH, Weinheim, 2010.
2. Otera, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 2044. (b) Ishihara, K. *Tetrahedron* **2009**, *65*, 1085
3. For Hf(IV)- or Zr(IV)-catalyzed ester condensation, see: (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *390*, 1140. (b) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Synlett* **2001**, 1117. (c) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8179. (d) Nakayama, M.; Sato, A.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2004**, *346*, 1275. (e) Sato, A.; Nakamura, Y.; Maki, T.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2005**, *347*, 1337. (f) Nakamura, Y.; Maki, T.; Wang, X.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2006**, *348*, 1505.
4. For recent studies on catalytic ester condensation, see: (a) Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249. (b) Xiang, J.; Toyoshima, S.; Orita, A.; Otera, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 3670. (c) Gacem, B.; Jenner, G. *Tetrahedron Lett.* **2003**, *44*, 1391. (d) Funatomi, T.; Wakasugi, K.; Misaki, T. Tanabe, Y. *Green Chem.* **2006**, *8*, 1022.
5. (a) Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, *127*, 4168; (b) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Tetrahedron* **2006**, *62*, 422; (c) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Nat. Protoc.* **2007**, *2*, 1746. (d) Sakakura, A.; Watanabe, H.; Nakagawa, S.; Ishihara, K. *Chem. Asian J.* **2007**, *2*, 477.
6. For the measurement of pK_a in CD_3CO_2D, see: Rode, B. M.; Engelbrecht, A.; Schantl, J. *Z. Physik. Chem. (Leipzig)* **1973**, *253* (1–2), 17.
7. See Supporting Information for experimental details.
8. Offenhauer, R. D. *J. Chem. Educ.* **1964**, *41*, 39.

Experimental Section

General Methods.

IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) or INOVA spectrometer (500 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on an INOVA spectrometer (125 MHz) at ambient temparature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). High performance liquid chromatography (HPLC) was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-M10A and chiral column of Daicel Chiralcel OD-H (ϕ4.6 mm × 250 mm). For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm) were used. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) were used. High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University on a JEOL JMS-700 spectromemer.

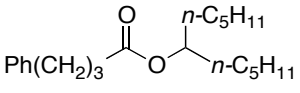
Conc. H_2SO_4 (Nacalai Tesque), TsOH (Wako Pure Chemical Industries, Ltd.), CSA (Wako Pure Chemical Industries, Ltd.), MsOH (TCI) and other materials were obtained commercially and used without further purification. *i*-$PrSO_3H$ was prepared by passing its sodium salt (purchased from Fluka) through cation-exchange resin (Amberlite® IR-120H, H^+ form).

General Procedure

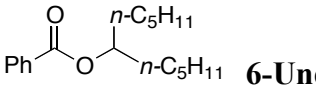
An open-air vessel (ϕ16 mm × 100 mm) was charged with the alcohol (2 mmol), the carboxylic acid (2 mmol) and the sulfonic acid (0.10 mmol), and the mixture was heated at 60–80 °C for several hours. After the substrate had been consumed, the mixture was cooled to ambient temperature, and purified by column chromatography on silica gel (ca. 10 g) to give the corresponding ester.

Procedure for Ester Condensation under Azeotropic Reflux Conditions (Figure 2B)

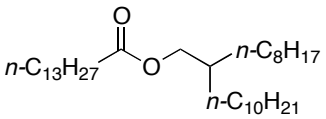
A flask (ϕ18 mm × 85 mm), equipped with a 5 mL pressure-equalized addition funnel containing a cotton plug and ca. 2 g of molecular sieves 4Å and a reflux condenser, was charged with 6-undecanol (2 mmol), 4-phenylbutyric acid (2.2 mmol) and CSA (0.10 mmol) in solvent (2 mL). The mixture was heated under azeotropic reflux with the removal of water (bath temperature: ca. 115 °C). The yields were determined by ^{1}H NMR analysis.



6-Undecyl 4-phenylbutyrate:[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 6H), 1.19–1.36 (m, 12H), 1.45–1.56 (m, 4H), 1.95 (quint, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 4.89 (tt, *J* = 6.5, 6.0 Hz, 1H), 7.16–7.21 (m, 3H), 7.28 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 25.0, 26.7, 31.7, 34.0, 34.1, 35.2, 74.3, 125.9, 128.4, 128.5, 141.5, 173.3.



6-Undecyl benzoate: IR (neat) 1718, 1603, 1585, 1451, 1378, 1313, 1273, 1175, 1110, 1069, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 6H), 1.23–1.44 (m, 10H), 1.58–1.73 (m, 4H), 5.13 (tt, *J* = 7.5, 5.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.55 (tt, *J* = 8.0, 1.5 Hz, 1H), 8.05 (dd, *J* = 8.0, 1.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 25.0, 31.7, 34.2, 75.1, 128.3, 129.5, 130.9, 132.6, 166.4; HRMS (FAB) calcd for $C_{18}H_{29}O_2$ [$(M + H)^+$] 277.2168, found 277.2151.

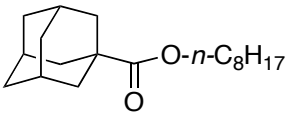


2-Octyl-1-dodecyl myristate: A 100-mL round-bottomed flask was charged with 2-octyl-1-dodecanol (100 mmol), myristic acid (100 mmol) and CSA (1 mmol). The mixture was stirred at 60 °C for 24 h, and then the reaction was quenched by the addition of $NaHCO_3$ (1 mmol) and water (30 mL). After the mixture was stirred for 5 min, the resulting aqueous mixture was extracted with hexane (10 + 20 mL), and the organic layer was concentrated *in vacuo*, to give the product (49.3 g, 97%

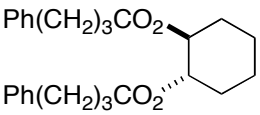
yield, 97% purity). IR (neat) 1739, 1466, 1171 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 9H), 1.20–1.34 (m, 51H), 1.62 (tt, *J* = 7.5, 7.0 Hz, 4H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.97 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.1, 26.7, 29.2, 29.30, 29.32, 29.4, 29.5, 29.56, 29.60, 29.62, 29.65, 29.67, 29.68, 30.0, 31.3, 31.90, 31.92, 34.5, 37.3, 67.0, 174.1; HRMS (FAB) calcd for $C_{34}H_{69}O_2$ [$(M + H)^+$] 509.5298, found 509.5301.

Procedure of large-scale process (Table2, entry 3)

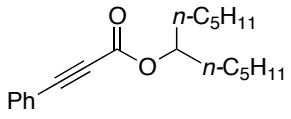
A 100-mL round-bottomed flask was charged with 2-octyl-1-dodecanol (100 mmol), myristic acid (100 mmol) and CSA (1 mmol). The mixture was stirred at 60 °C for 24 h, and then the reaction was quenched by the addition of $NaHCO_3$ (1 mmol) and water (30 mL). After the mixture was stirred for 5 min, the resulting aqueous mixture was extracted with hexane (10 + 20 mL), and the organic layer was concentrated *in vacuo* to give the product (49.3 g, 97% yield, 97% purity).



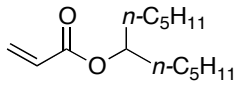
Octyl 1-adamantancarboxylate:[2] ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.22–1.38 (m, 8H), 1.61 (quint, *J* = 7.0 Hz, 2H), 1.71 (tt, *J* = 15.0, 3.0 Hz, 6H), 1.89 (d, *J* = 3.0 Hz, 6H), 2.01 (br s, 3H), 4.03 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 25.9, 28.0, 28.6, 29.16, 29.18, 31.8, 36.5, 38.9, 40.7, 64.2, 177.8.



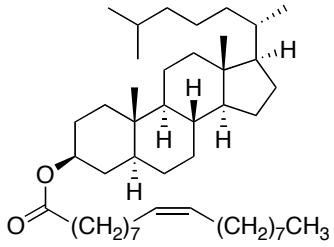
***trans*-1,2-Di(4-phenylbutyroxy)cyclohexane**:[1] ^1H NMR (300 MHz, $CDCl_3$) δ 1.26–1.47 (m, 2H), 1.55–1.63 (m, 2H), 1.65–1.78 (m, 2H), 1.88 (quint, *J* = 7.5 Hz, 4H), 1.98–2.09 (m, 2H), 2.26 (t, *J* = 7.5 Hz, 4H), 2.59 (t, *J* = 7.5 Hz, 4H), 4.77–4.90 (m, 2H), 7.11–7.22 (m, 6H), 7.23–7.31 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 26.6, 30.2, 33.8, 35.1, 73.5, 126.0, 128.38, 128.43, 141.3, 172.8.



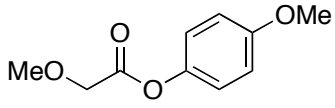
6-Undecyl propiolate:[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 6H), 1.22–1.44 (m, 12H), 1.54–1.68 (m, 4H), 5.04 (tt, J = 7.5, 5.0 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.44 (dd, J = 7.5, 7.0 Hz, 1H), 7.60 (d, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 25.0, 31.7, 34.0, 76.9, 81.0, 85.8, 119.8, 128.5, 130.5, 133.0, 154.1.



6-Undecyl acrylate: IR (neat) 1724, 1637, 1620, 1467, 1405, 1296, 1272, 1196, 1123, 1047 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.5 Hz, 6H), 1.22–1.36 (m, 12H), 1.50–1.61 (m, 4H), 4.95 (quint, J = 6.0 Hz, 1H), 5.80 (dt, J = 10.5, 1.5 Hz, 1H), 6.12 (ddt, J = 17.0, 10.5, 0.5 Hz, 1H), 6.39 (dt, J = 17.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 24.9, 31.7, 34.1, 74.6, 129.0, 130.1, 166.1; HRMS (FAB) calcd for $C_{14}H_{27}O_2$ [$(M + H)^+$] 227.2011, found 227.1987.

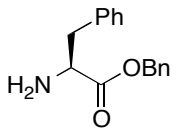


β-Cholestanyl oleate:[4] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60–0.67 (m, 1H) 0.64 (s, 3H), 0.82 (s, 3H), 0.859 (d, J = 6.5, 3H), 0.864 (d, J = 6.5, 3H), 0.88 (t, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.93–1.40 (m, 40H), 1.42–1.68 (m, 8H), 1.72 (dt, J = 13.0, 3.5 Hz, 1H), 1.75–1.85 (m, 2H), 1.96 (dt, J = 12.5, 3.0 Hz, 2H), 1.93–2.08 (m, 3H), 2.25 (t, J = 7.5 Hz, 2H), 4.69 (tt, J = 11.0, 5.0 Hz, 1H), 5.29–5.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1, 12.2, 14.1, 18.7, 21.2, 22.5, 22.7, 22.8, 23.8, 24.2, 25.1, 27.15, 27.20, 27.5, 28.0, 28.2, 28.6, 29.1, 29.2, 29.3, 29.5, 29.7, 29.8, 31.9, 32.0, 34.1, 34.8, 35.46, 35.47, 35.8, 36.2, 36.8, 39.5, 40.0, 42.6, 44.7, 54.2, 56.3, 56.4, 73.4, 129.8, 130.0, 173.4.



4-Methoxyphenyl methoxyacetate:[1] ^{1}H NMR (500 MHz,

$CDCl_3$) δ 3.53 (s, 3H), 3.79 (s, 3H), 4.27 (s, 2H), 6.89 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.5, 59.4, 69.7, 114.5, 122.1, 143.5, 157.3, 169.1.



L-Phenylalanine benzyl ester: A mixture of L-phenylalanine (2.0 mmol), benzyl alcohol (4.0 mmol) and CSA (2.1 mmol) was heated at 60 °C for 36 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL), and the mixture was extracted with EtOAc (3 × 20mL). The combined extracts were washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (15 g, hexane–EtOAc 5:1 → 1:1 → 1:2 → 1:4) to give the ester (454 mg, 89%). The optical purity of the product was analyzed by HPLC analysis (Daicel Chiralcel OD-H column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min, UV 254 nm): t_R = 11.9 min [L-(*S*)-isomer] and 13.3 min [D-(*R*)-isomer]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (dd, J = 14.0, 5.5 Hz, 1H), 3.08 (dd, J = 14.0, 8.0 Hz, 1H), 3.77 (dd, J = 8.0, 5.5 Hz, 1H), 5.13 (s, 2H), 7.12–7.16 (m, 2H), 7.20–7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.0, 55.8, 66.7, 126.8, 128.3, 128.4, 128.5, 128.6, 129.3, 135.5, 137.0, 174.9.

References

1. Sakakura, A.; Nakagawa, S.; Ishihara, K. *Tetrahedron* **2006**, *62*, 422.
2. Barret, A. G. M.; Prokopion, P. A.; Barton, D. H. R.; Boar, R. B.; McGhie, J. F. *J. Chem. Soc., Chem. Commun.* **1979**, 1173.
3. (a) Ralitsch, M.; Ciccio, J.; Calzada, J. *Rev. Latinoam. Quim.* 1982, *13*, 16. (b) Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc.* **2007**, *129*, 14775.
4. Roden, A.; Williams, J. L.; Bruce, R.; Detrano, F.; Boyer, M. H.; Higgins, J. D., III. US Patent, 6184397, 2001 (*Chem. Abstr.* **2001**, *134*, 131709)

Chapter 3.
Design of Hydrophobic *N*,*N*-Diarylammonium Pyrosulfates Catalysts for Dehydrative Ester Condensation under Aqueous Conditions

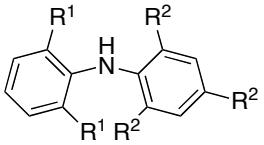
Abstract: Oil-soluble *N*,*N*-diarylammonium pyrosulfates as nonsurfactant-type catalysts for the dehydrative ester condensation under aqueous conditions are described. Preheat treatment of dibasic sulfuric acid with bulky *N*,*N*-diarylamines generates water-tolerant salts of pyrosulfuric acid as active catalyst species. The present catalysts in the presence of water can also widely be applied to unusual selective esterifications, dehydrative glycosylation.

Water has unique physical and chemical properties, which allow us to realize reactivities that cannot be attained in organic solvents. In addition, water is a cheap, safe and environmentally benign solvent when compared with organic solvents. Use of water will reduce the use of harmful organic solvents and is regarded as an important subject in green chemistry. Therefore, the use of water as a reaction solvent has received much attention in synthetic organic chemistry.[1] Although several efficient catalysts have been exploited for the direct dehydrative ester condensation of an equimolar mixture of carboxylic acids and alcohols,[2] it is still difficult to conduct the dehydrative condensation under aqueous conditions, since the presence of water should have a detrimental effect on the equilibrium of dehydration reactions. Moreover, widely used Brønsted acid catalysts are highly hydrophilic. Under aqueous conditions, these Brønsted acids are dissolved in aqueous phase and deactivated by water.

In 2001, Kobayashi and colleagues reported the dehydrative ester condensation between long-chain fatty acids and hydrophobic alcohols in water using *p*-dodecylbenzenesulfonic acid (DBSA) as a surfactant-type catalyst.[3] They claimed that DBSA and long-chain substrates would form emulsion droplets in water to accelerate the dehydration reactions. In 2005, Ishihara and colleagues reported bulky *N,N*-diarylammonium pentafluorobenzenesulfonates as mild and highly active dehydrative ester condensation catalysts.[4,5] The high catalytic activity is attributed to the hydrophobic effect of bulky aryl groups of the catalysts.[4c] However, these bulky *N,N*-diarylammonium salt catalysts are almost inert under aqueous conditions. Herein, the author report the dehydrative ester condensation reactions catalyzed by *N,N*-diarylammonium pyrosulfates under aqueous conditions.

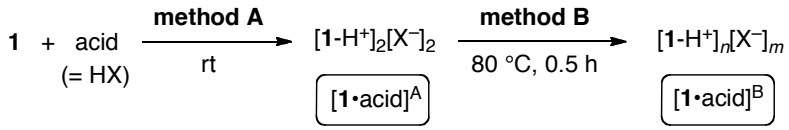
The author first examined the catalytic activities of various Brønsted acids and their ammonium salts with bulky *N,N*-diarylamine **1d**[4] (Figure 1) under aqueous conditions. The reaction of 4-phenylbutyric acid (1.1 equiv) with 1-dodecanol (4 mmol) was conducted in the presence of water (2 mL) at 60 °C for 6 h (Table 1). As a result, hydrophilic Brønsted acids such as trifluoromethanesulfonic acid (TfOH), sulfuric acid (H_2SO_4), *p*-toluenesulfonic acid (TsOH), 10-camphorsulfonic acid (CSA), and pentafluorobenzenesulfonic acid ($C_6F_5SO_3H$) were almost inert under aqueous conditions,[6] although they can catalyze the same reaction in less polar solvents,[4] ionic liquids,[7] and solvent-free conditions. *N,N*-Diarylammonium salts, which were represented as [**1d**•acid]^A, were prepared by mixing an equimolar amount of **1d** and an acid in a homogeneous solution at ambient temperature and then evaporation of the solvent (method A) (Scheme 1). Disappointingly, [**1d**•acid]^A also gave similar results with the corresponding acids (Table 1). Next, [**1d**•acid]^A were heated at 80 °C for 0.5

h (method B) before being used as catalysts for the dehydrative condensation reaction. *N,N*-Diarylammonium salts prepared by method B are represented as [**1d**•acid]^{B}. Very surprisingly, [**1d**•H_2SO_4]^{B}, which was a salt of extremely hydrophilic H_2SO_4, showed excellent catalytic activity under aqueous conditions and gave 1-dodecyl 4-phenylbutyrate in 85% yield. In contrast, *N,N*-diarylammonium salts of sulfonic acids [**1d**•RSO_3H]^{B} were almost inert.



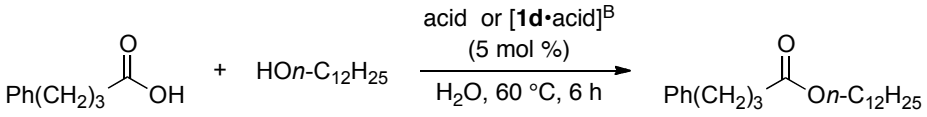
1a (R^1, R^2 = H) **1d** (R^1 = *i*-Pr, R^2 = Me)
1b (R^1 = Me, R^2 = H) **1e** (R^1, R^2 = *i*-Pr)
1c (R^1, R^2 = Me) **1f** (R^1= Ph, R^2 = *i*-Pr)

Figure 1. *N,N*-Diarylamines **1**



Scheme 1. Preparation of *N,N*-diarylammonium salts (methods A and B).

Table 1. Catalytic Activities of Brønsted Acids and Their Ammonium Salts with **1d** under Aqueous Conditions[a]



acid or [**1d**•acid]^B	pK_a [b]	yield of ester (%)[c]
TfOH	–0.74	6
H_2SO_4	7.0	15
TsOH	8.5	23
CSA	9.0	9
$C_6F_5SO_3H$	9.2	11
[**1d**•TfOH]^B		9 [6][d]
[**1d**•H_2SO_4]^B		**85** [10][d]
[**1d**•TsOH]^B		11 [15][d]
[**1d**•CSA]^B		7 [6][d]
[**1d**• $C_6F_5SO_3H$]^B		13 [15][d]

[a]Conditions: 4-phenylbutyric acid (1.1 equiv), 1-dodecanol (4 mmol), and catalyst (5 mol %) in the presence of water (2 mL) at 60 °C for 6 h. [b]pK_a values were measured in CD_3CO_2D.[11] [c]Determined by ^{1}H NMR analysis. [d]Yield of ester catalyzed by [**1d**•acid]^A is shown in brackets

The catalytic activities of [**1**•H_2SO_4]^B, which were assessed by their initial rates (v_i) of the dehydrative ester condensation under aqueous conditions, significantly depended on the steric bulkiness around ammonium protons (Figure 2).[4b] The use of *N,N*-diarylamines **1c–f** bearing substituents at each *ortho*-positions successfully accelerated the reaction. The most sterically hindered [**1f**•H_2SO_4]^B showed the highest catalytic activities. The catalytic activity of [**1f**•H_2SO_4]^B (v_i = 0.13 Mh^{-1}) was almost the same as that of DBSA (v_i = 0.13 Mh^{-1}), and was ca. 60 times higher than that of [**1a**•H_2SO_4]^B (v_i = 0.0023 Mh^{-1}) under aqueous conditions.[8,9]

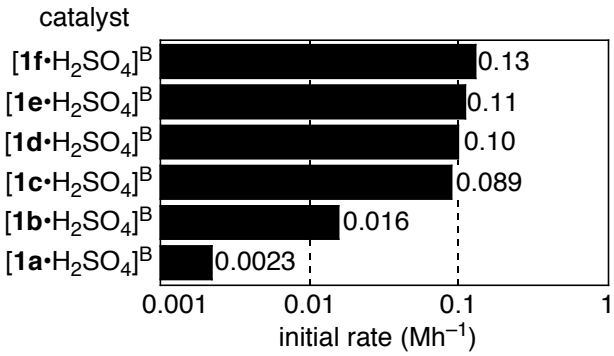


Figure 2. Initial rates [Mh^{-1}] of ester condensation under aqueous conditions using [**1**•H_2SO_4]^B (5 mol %). Conditions: 4-phenylbutyric acid (1.1 equiv) and 1-dodecanol (4 mmol) in the presence of water (2 mL) at 40 °C.

Next, [**1**•H_2SO_4]^A and [**1**•H_2SO_4]^B were compared by ^{1}H NMR in CD_3CN (Table 2). Based on chemical shifts of the ammonium protons, the active catalyst [**1f**•H_2SO_4]^B prepared by the heat treatment (method B) was a species different from [**1f**•H_2SO_4]^A, a simple salt of **1f** and H_2SO_4. In the case of [**1a**•H_2SO_4]^A and [**1a**•H_2SO_4]^B, both of which were almost inert under aqueous conditions, chemical shift of the ammonium protons also shifted downfield by the heat treatment (7.19 → 8.34 ppm). However, [**1a**•H_2SO_4]^B was labile and gradually decomposed to [**1a**•H_2SO_4]^A in CD_3CN at 60 °C for 6 h (8.34 → 7.29 ppm), while [**1f**•H_2SO_4]^B was stable under the same conditions.[9] In addition, the alkaline titration experiment showed that in the case of [**1f**•H_2SO_4]^B, only 29% of H_2SO_4 was leaked to the aqueous phase, while large amounts of H_2SO_4 were included in the aqueous phase in the cases of [**1f**•H_2SO_4]^A and [**1a**•H_2SO_4]^B.[9]

Table 2. Comparison of *N,N*-Diarylammonium Salt Catalysts Prepared by Methods A and B

catalyst	yield of ester (%)[a]	chemical shift of N***H***$_2$ in CD_3CN (ppm)	content of H_2SO_4 in aq phase (%)
[**1f**•H_2SO_4]^A	10	7.59	75
[**1f**•H_2SO_4]^B	85	9.01	29
[**1f**•$H_2SO_4(SO_3)_X$]^A	82	9.18	34
[**1a**•H_2SO_4]^A	9	7.19	81
[**1a**•H_2SO_4]^B	15	8.34 (→ 7.29)[b]	82
[**1a**•$H_2SO_4(SO_3)_X$]^A	13	7.17	84

[a]The reaction of 4-phenylbutyric acid (1.1 equiv) with 1-dodecanol (4 mmol) in the presence of catalyst (5 mol %) was conducted in the presence of water (2 mL) at 60 °C for 6 h. Yields were determined by ^{1}H NMR analysis. [b]Chemical shift of ammonium protons changed at 60 °C during 6 h.

[**1**• H_2SO_4]^A would be dimeric complexes composed of two *N,N*-diarylammonium cations and two sulfonate anions: $[ArNH_2^+]_2[X^-]_2$, based on X-ray crystallographic analysis of [**1a**•H_2SO_4]^A (Figure 3A).[4c] While, these results showed that the heat treatment of [**1f**•H_2SO_4]^A generated some water-tolerant salts as active catalyst species. According to Halstead's report that thermal decomposition of ammonium sulfate or ammonium hydrogen sulfate generates ammonium pyrosulfate[10], the author expected that the active species [**1f**•H_2SO_4]^B might be ammonium salts of pyrosulfuric acid ($H_2S_2O_7$). In fact, [**1f**•$H_2SO_4(SO_3)_X$]^A, the ammonium salt of **1f** with oleum (containing ca. 30% SO_3), also showed high catalytic activity (82% yield) even without the heat treatment before use. In addition, chemical shift of ammonium protons of [**1f**•$H_2SO_4(SO_3)_X$]^A was almost identical to that of [**1f**•H_2SO_4]^B. Theoretical calculation of dissociation free energy showed that $H_2S_2O_7$ is more acidic than H_2SO_4.[9] In the optimized geometry, the salt of **1f** and $H_2S_2O_7$ formed four hydrogen bondings in bidentate fashion between two ammonium cations ($Ar_2NH_2^+$) and a pyrosulfate anion ($S_2O_7^{2-}$) (Figure 3B). These results suggested that the ammonium salts of $H_2S_2O_7$ should be more stable than those of H_2SO_4. This stability would increase the water-tolerance of the active catalyst [**1f**•H_2SO_4]^B. The fact that *N,N*-diarylammonium salts of dibasic sulfonic acids[9] were inert also implied that the formation of pyrosulfates was crucial for the high catalytic activity.

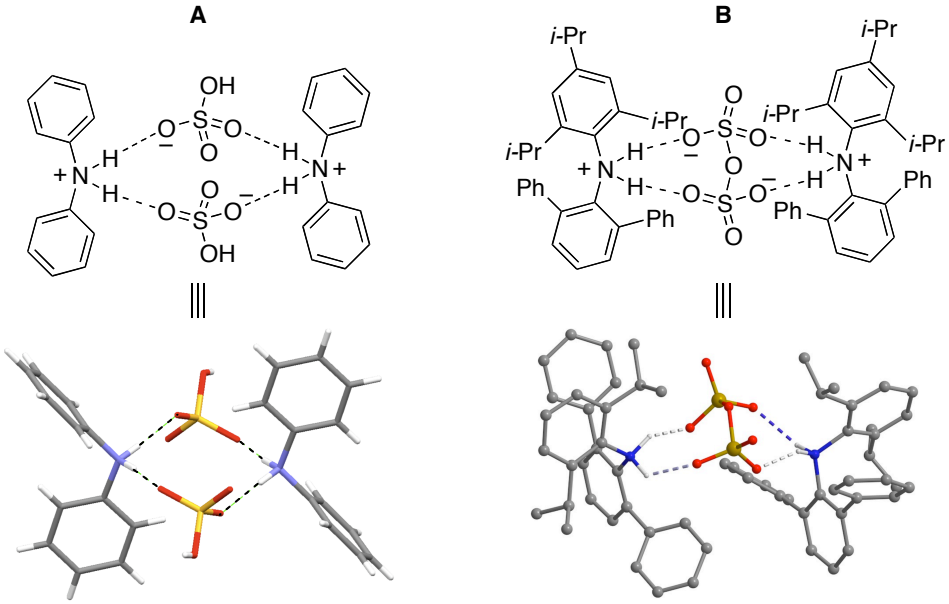
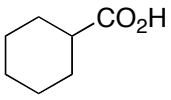
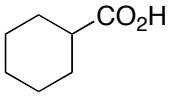
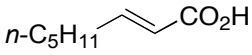
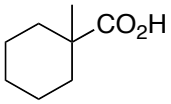


Figure 3. Structures of *N,N*-diarylammonium sulfates

A: X-ray single-crystal structure of [**1a**-H^+]$_2$[HSO_4^-]$_2$. B: B3LYP/6-31G(d) optimized geometry of [**1f**-H^+]$_2$[$S_2O_7^{2-}$]. Hydrogen atoms, except for ammonium protons, are omitted for clarity.

The present hydrophobic *N,N*-diarylammonium pyrosulfate-catalyzed dehydrative ester condensation could be applied to the reactions of a variety of substrates (Table 3). Significantly, [**1f**•H_2SO_4]^B showed higher catalytic activity than DBSA for the esterification of rather hydrophilic substrates (entries 1–6). For example, the reaction of hexanoic acid with 1-butanol successfully catalyzed by [**1f**•H_2SO_4]^B to give 1-butyl hexanoate in 80% yield (6 h), while the use of DBSA gave 47% yield of the ester in the same reaction time. It is noteworthy that for the ammonium salt-catalyzed esterification of hexanoic acid with 1-butanol, the addition of NaOH (10 mol %) to the reaction mixture gave clear separation between the organic and aqueous phases, and the crude product could be easily obtained by simple decantation.[9] In contrast, the addition of NaOH (5 mol %) to the reaction mixture of the DBSA-catalyzed esterification did not give clear separation between the two phases, which was probably because DBSA acted as a surfactant. The esterification of α,β-unsaturated carboxylic acids and sterically bulky carboxylic acids could also be catalyzed by [**1f**•H_2SO_4]^B to give the corresponding esters in good yields (entries 7 and 8).

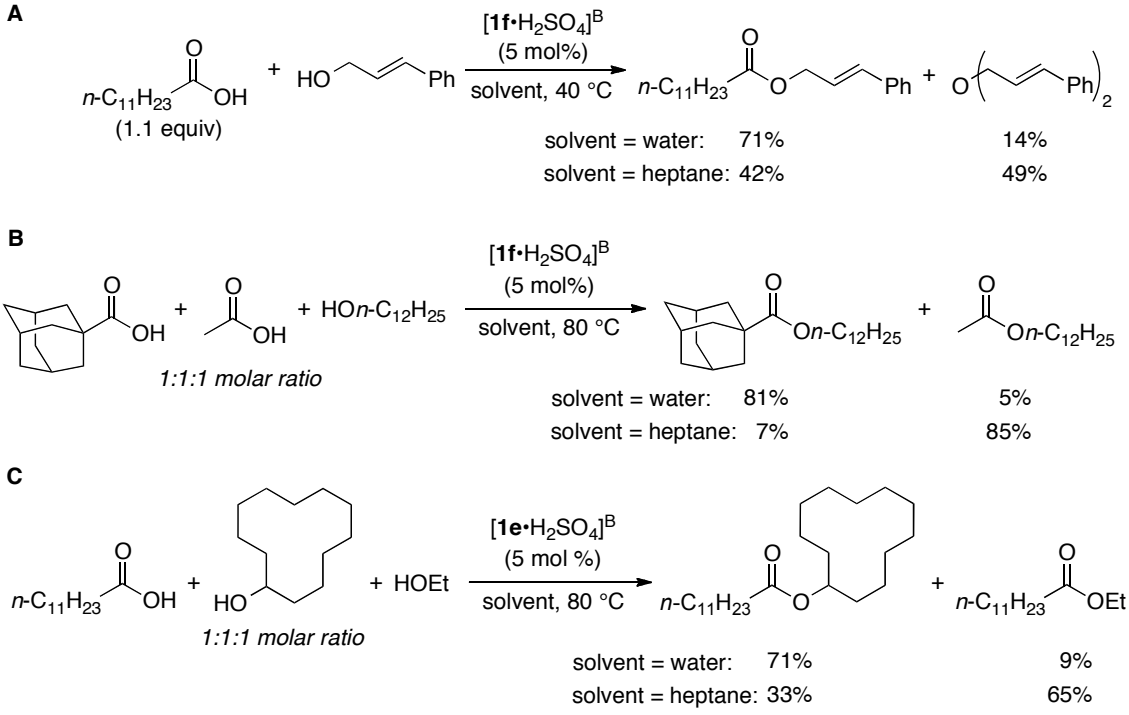
Table 3. [**1**•H_2SO_4]^B-Catalyzed Dehydrative Ester Condensation of Various Substrates under Aqueous Conditions[a]

entry	carboxylic acid	alcohol	temp (°C)	time (h)	yield (%)[b]
1	*n*-$PrCO_2H$	HO*n*-Bu	60	8	74 [60]
2	*n*-$C_5H_{11}CO_2H$	HO*n*-Bu	60	6	80 [47]
3		HO*n*-Pr	70	8	76 [48]
4		HO*n*-Bu	70	6	85 [65]
5	*n*-$C_5H_{11}CO_2H$	$HO(CH_2)_3OBn$	60	8	75 [53]
6	*n*-$C_5H_{11}CO_2H$	$HO(CH_2)_6SH$	60	8	86 [66]
7		HO*n*-C_8H_{17}	80	19	81
8		HO*n*-C_8H_{17}	80	47	81

[a]Conditions: carboxylic acid (1.1 equiv), alcohol (4 mmol), and [**1f**•H_2SO_4]^B (5 mol %) in the presence of water (2 mL) at 60–80 °C. [b]Data in brackets refer to yield when DBSA (5 mol %) was used as a catalyst.

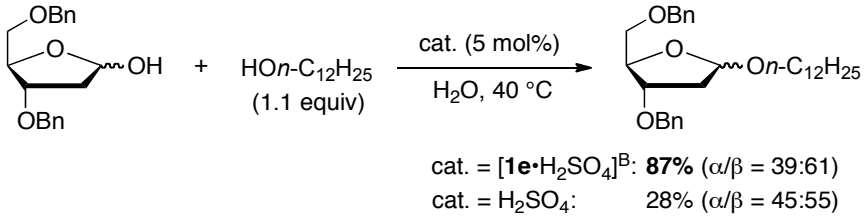
The use of *N,N*-diarylammonium sulfate catalysts under aqueous conditions has an additional advantage in the ester condensations of acid-sensitive alcohols. For example, the esterification of cinnamyl alcohol with lauric acid (1.1 equiv) using [**1f**•H_2SO_4]^B (5 mol %) under aqueous conditions predominantly improved the yield of the ester (74%) (Scheme 1A).[9] The use of water as a solvent also allowed us to achieve unusual selective ester condensations of two substrates based on the difference in hydrophobicity of the substrates. For example, when the reaction of a 1:1:1 molar mixture of 1-adamantanecarboxylic acid, acetic acid and 1-dodecanol was conducted under aqueous conditions, the ester of hydrophobic 1-adamantanecarboxylic acid was predominantly obtained in 81% yield along with the ester of hydrophilic acetic acid in 5% yield (Scheme 1B).[9] On the other hand, the same reaction in heptane preferentially gave the acetate in 85%. The selective esterification of cyclododecanol (71%) over ethanol could also be achieved under aqueous conditions (Scheme 1C).[9]

Scheme 1. Unusual Selective Ester Condensations under Aqueous Conditions



In addition, the [**1e**•H_2SO_4]^B-catalyzed dehydrative glycosylation of 3,5-*O*-dibenzyl-2-deoxy-D-ribose with 1-dodecanol under aqueous conditions gave the corresponding acetal in 87% yield, while the use of H_2SO_4 as a catalyst decreased the yield (28%) (Scheme 2).

Scheme 2. Dehydrative Glycosylation



In conclusion, oil-soluble complexes of hydrophobic *N,N*-diarylamines with sulfuric acid successfully catalyzed dehydrative ester condensation reactions under aqueous conditions. The pre-heat treatment of dibasic sulfuric acid with bulky *N,N*-diarylamines was crucial for the generation of water-tolerant aggregated complexes of pyrosulfuric acid as active catalyst species. Further studies to elucidate the detailed aggregated structure of the *N,N*-diarylammonium pyrosulfate catalysts and their

applications to other reactions under aqueous conditions are now underway. Water is still not commonly used as a solvent for organic synthesis despite the distinctive properties. The present non-surfactant-type Brønsted acid catalysis will provide a new aspect of organic synthesis under aqueous conditions.

References and notes

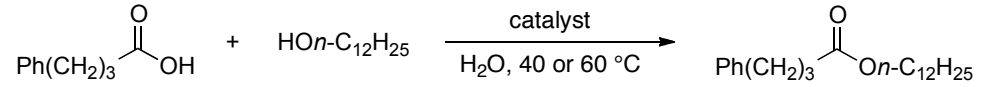
1. Lindström, U. M., Ed. *Organic Reactions in Water*; Blackwell, Oxford, 2007. (b) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* 2006, 35, 68. (c) Uozumi, Y.; Yamada, Y. M. A. *Chem. Rec.* **2009**, *9*, 51. (d) Raj, M.; Singh, V. K. *Chem. Commun*. **2009**, 6687. (e) Chanda, A.; Fokin, V. V. *Chem. Rev*. **2009**, *109*, 725.
2. (a) Ishihara, K. *Tetrahedron* **2009**, *65*, 1085. (b) Otera, J.; Nishikido, J. *Esterification*, 2nd ed.; WILEY-VCH, Weinheim, 2010.
3. (a) Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101. (b) Kobayashi, S.; Iimura, S.; Manabe, K. *Chem. Lett*. **2002**, *31*, 10. (c) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc*. **2002**, *124*, 11971. (d) Aoyama, N.; Kobayashi, S. *Chem. Lett*. **2006**, *35*, 238. (e) Shirakawa, S., Kobayashi, S. *Org. Lett*. **2007**, *9*, 311.
4. (a) Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, *127*, 4168. (b) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Tetrahedron* **2006**, *62*, 422. (c) Sakakura, A.; Watanabe, H.; Nakagawa, S.; Ishihara, K. *Chem. Asian J.* **2007**, *2*, 477. (d) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Nat. Protoc*. **2007**, *2*, 1746.
5. (a) Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett*. **2000**, *41*, 5249. (b) Funatomi, T.; Wakasugi, K.; Misaki, T.; Tanabe, Y. *Green Chem*. **2006**, *8*, 1022. (c) Gacem, B.; Jenner, G. *Tetrahedron Lett*. **2003**, *44*, 1391. (d) Mercs, L.; Pozzi, G.; Quici, S. *Tetrahedron Lett*. **2007**, *48*, 3053.
6. Liu, Y.; Lotero, E.; Goodwin, J. G., Jr. *J. Mol. Catal. A: Chemical* **2006**, *245*, 132.
7. (a) Wells, T. P.; Hallett, J. P.; Williams, C. K.; Welton, T. *J. Org. Chem*. **2008**, *73*, 5585. (b) Jiang, T.; Chang, Y.; Zhao, G.; Han, B.; Yang, G. *Synth. Commun*. **2004**, *34*, 225.
8. The ammonium salts $[\mathbf{1}\bullet H_2SO_4]^B$ of **1a–f** contained ca. 10–15% of the corresponding 4-(arylamino)benzenesulfonic acids, which were generated during the catalyst preparation procedure B. The real active catalyst species should be the ammonium salts $[\mathbf{1}\bullet H_2SO_4]^B$, not the sulfonic acids. See Supporting Information for details.
9. See Supporting Information for details.
10. (a) Halstead, W. D. *J. Appl. Chem*. **1970**, *20*, 129. (b) Jariwala, M.; Crawford, J.; LeCaptain, D. J. *Ind. Eng. Chem. Res*. **2007**, *46*, 4900.
11. Rode, B. M.; Engelbrecht, A.; Schantl, J. *Z. Phys. Chem. (Leipig)* **1973**, *253*, 17.

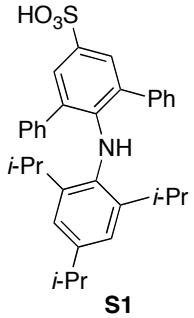
Supporting Information

Real active catalyst species

During the catalyst preparation procedure B, 10–15% of **1f** was converted to the corresponding 4-(arylamino)sulfonic acid **S1**; i.e. the reaction mixture contained 4.3–4.5 mol % of diarylammonium salt $[\mathbf{1f}\bullet H_2SO_4]^B$ and 0.5–0.7 mol % of **S1**. On the other hand, $[\mathbf{1g}\bullet H_2SO_4(SO_3)_X]^A$, ammonium salt of **1g** (Figure 1, R^1 = Ph, R^2 = I, R^3 = *i*-Pr) bearing a 4-iodo substituent, included only less than 1% of the **S1**; i.e. the reaction mixture contained less than 0.05 mol % of **S1**. As shown in Table S1, $[\mathbf{1g}\bullet H_2SO_4(SO_3)_X]^A$ showed same catalytic activity (v_i = 0.13 Mh^{-1}) as $[\mathbf{1f}\bullet H_2SO_4]^B$ and $[\mathbf{1f}\bullet H_2SO_4(SO_3)_X]^A$, while the sulfonic acid **S1** showed low catalytic activity. Therefore, the real active catalyst species should be the ammonium salts $[\mathbf{1}\bullet H_2SO_4]^B$, not the sulfonic acids.

Table S1.



catalyst [mol %]	Content of **S1** (mol %) in the reaction mixture	yield of ester (%) (at 60 °C for 6 h)	v_i (Mh^{-1}) (at 40 °C)
$[\mathbf{1f}\bullet H_2SO_4]^B$ [5]	0.5–0.7	88	0.13
$[\mathbf{1f}\bullet H_2SO_4(SO_3)_X]^A$ [5]	0.5	85	0.12
$[\mathbf{1g}\bullet H_2SO_4(SO_3)_X]^A$ [5]	<0.05	82	0.13
 **S1** [1]	—	39	0.036

Examination of the catalytic activities of various *N,N*-diarylammonium sulfates [1•H_2SO_4]^B

The same reaction as in Table 1 was conducted at 40 °C in the presence of 5 mol % of [**1**•H_2SO_4]^B in the presence of water or hexane, and the initial rates (v_i) were investigated (Figure S1). As a result, the initial rates significantly depended on the steric bulkiness around ammonium protons in water (Figure 2).[4b] In contrast, the use of hexane as a solvent resulted in slight dependence of the catalytic activities on the steric bulkiness of **1** (Graph A). Thus, the catalytic activity of [**1f**•H_2SO_4]^B (v_i = 0.66 Mh^{-1}) was just twice as that of [**1a**•H_2SO_4]^B (v_i = 0.33 Mh^{-1}) in hexane. Interestingly, the initial rates of [**1a**•H_2SO_4]^B-catalyzed ester condensation dramatically decrease as the amount of water increased (Graph C): the reaction in the presence of 2 mL of water was 28 times slower than that in the presence of 0.072 mL (1 equivalent) of water. On the other hand, the catalytic activity of [**1f**•H_2SO_4]^B did not highly depend on the amount of water (Graph B): the reaction in the presence of 2 mL of water was only 3.7 times slower than that in the presence of 0.072 mL of water.

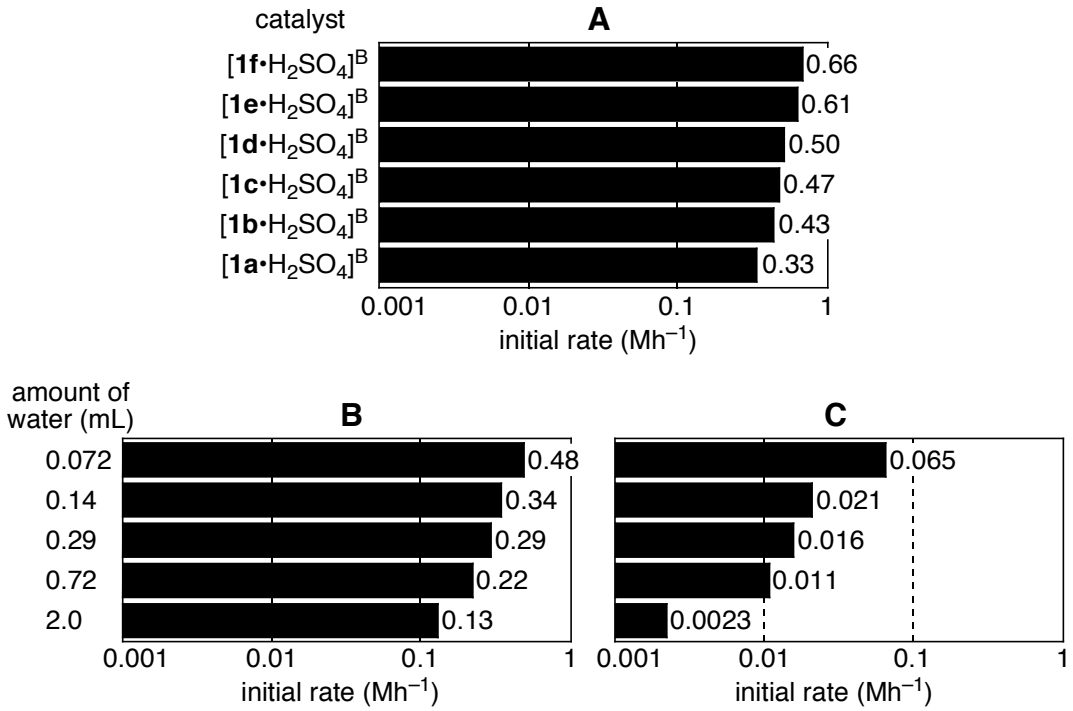


Figure S1. Initial rates (Mh^{-1}) of esterification using [**1**•H_2SO_4]^B. Conditions: 4-phenylbutyric acid (1.1 equiv), 1-dodecanol (4 mmol), catalyst (5 mol%) at 40 °C. Graph A: [**1**•H_2SO_4]^B were used as catalysts in hexane (2 mL). Graph B: [**1f**•H_2SO_4]^B was used as a catalyst in the presence of water (0.072–2 mL). Graph C: [**1a**•H_2SO_4]^B was used as a catalyst in the presence of water (0.072–2 mL).

^{1}H NMR Analysis of [1f·H_2SO_4]^B and [1a·H_2SO_4]^B

Chemical shifts of ammonium protons of [**1a**•H_2SO_4]^B gradually moved upfield (8.34 → 7.29 ppm) in CD_3CN (0.14 M) at 60 °C for 6 hours, while those of [**1f**•H_2SO_4]^B did not change (Figure S2A). In addition, chemical shifts of ammonium protons of [**1a**•H_2SO_4]^B significantly moved upfield (8.34 → 5.39 ppm) as the concentration of [**1a**•H_2SO_4]^B was decreased (0.14 → 0.014 M), while that of [**1f**•H_2SO_4]^B slightly moved upfield (9.01 → 7.32 ppm) (Figure S2B). These ^{1}H NMR experiment also shows that [**1a**•H_2SO_4]^B is much less stable than [**1f**•H_2SO_4]^B.

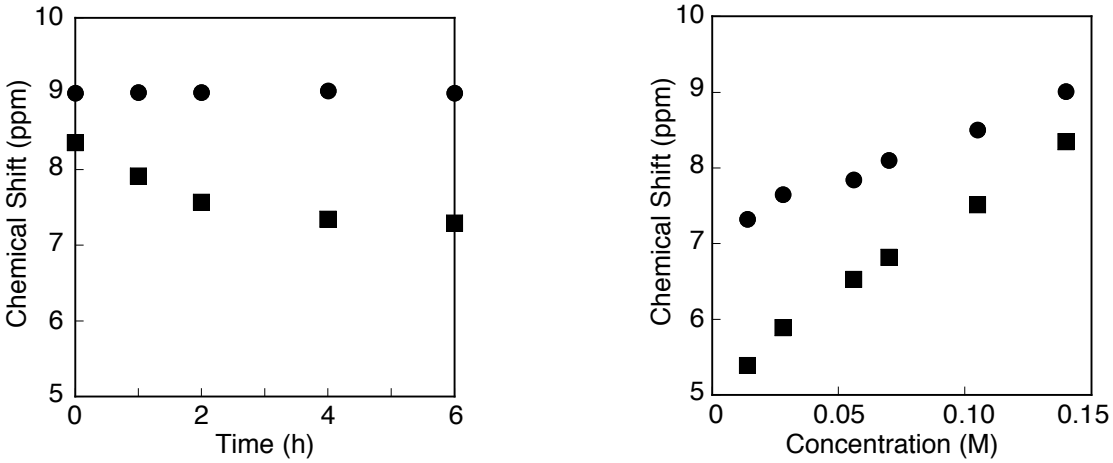


Figure S2. ^{1}H NMR chemical shifts of ammonium protons versus time (**A**) or concentration (**B**) in CD_3CN. Circles: [**1f**•H_2SO_4]^B; squares: [**1a**•H_2SO_4]^B.

Alkaline Titration of Brønsted Acids in Aqueous Phase

The distribution of Brønsted acids was examined under the biphasic reaction conditions by alkaline titration (Table S2). As a result, in the case of [**1d**•H_2SO_4]^B, 38% of H_2SO_4 was included in the aqueous phase. On the other hand, more than 70% of sulfonic acids were leaked into the aqueous phase when ammonium salts of **1d** with sulfonic acids were used as catalysts. Furthermore, in the case of [**1f**•H_2SO_4]^B, the most active catalyst, only 29% of H_2SO_4 was leaked into the aqueous phase. In contrast, in the case of [**1f**•H_2SO_4]^A, 75% of H_2SO_4 was leaked into the aqueous phase. These results indicated that [**1**•H_2SO_4]^B catalyzed the dehydrative ester condensation in the organic substrate phase, and that the heat treatment (method B) was important for the formation of active catalyst species in the organic substrate phase.

Table S2. Content of Brønsted Acid in Aqueous Phase

Catalyst	Content (%)	Catalyst	Content (%)
H_2SO_4	80	TfOH	77
[**1a**•H_2SO_4]^B	82	[**1d**•TfOH]^B	80
[**1b**•H_2SO_4]^B	63	TsOH	77
[**1c**•H_2SO_4]^B	42	[**1d**•TsOH]^B	83
[**1d**•H_2SO_4]^B	38	CSA	73
[**1e**•H_2SO_4]^B	42	[**1d**•CSA]^B	72
[**1f**•H_2SO_4]^B	29 [75]^a	$C_6F_5SO_3H$	70
[**1f**•$H_2SO_4(SO_3)_X$]^A	34	[**1d**•$C_6F_5SO_3H$]^B	72

^{a}[**1f**•H_2SO_4]^A was used in place of [**1f**•H_2SO_4]^B.

Theoretical Calculation of Free Energy of Dissociation of H_2SO_4 and $H_2S_2O_7$

Theoretical calculations were performed at B3LYP/6-31++G(3df,2pd) level (Figure S1). The calculations at MP2/6-311++G(3df,2pd) level were also carried out for confirmation of the values of B3LYP levels. These results showed that pyrosulfuric acid is more acidic than sulfuric acid.

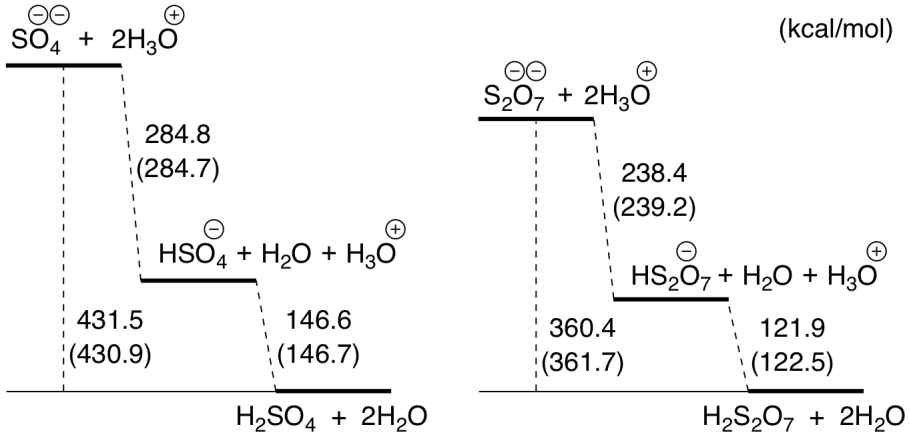
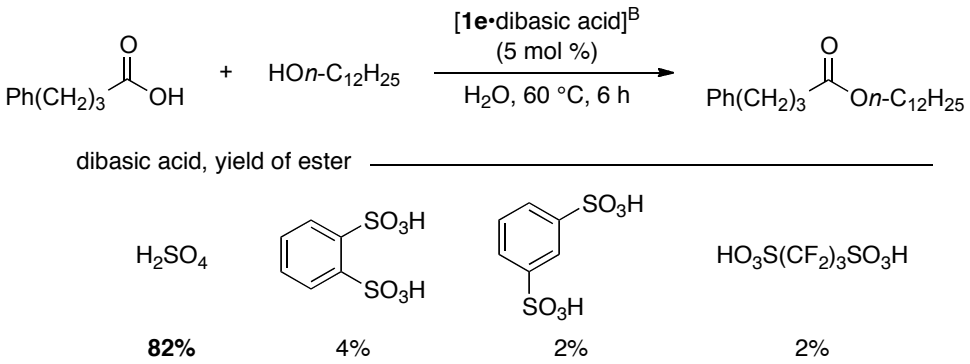


Figure S1. Free energy of dissociation of H_2SO_4 and $H_2S_2O_7$ in kcal mol^{-1}. The values of MP2 levels are in parentheses

Catalytic Activities of *N,N*-Diarylammonium Salts of Dibasic Sulfonic Acids

The catalytic activities of *N,N*-diarylammonium salts of various dibasic sulfonic acids [**1e**•dibasic acid]^{B} were low (Table S3).

Table S3.



Separation of Ester from the Reaction Mixture

When the reaction of hexanoic acid with 1-butanol was conducted in the presence of [1f•$H_2SO_4(SO_3)_X$]^{A} (5 mol %), the reaction mixture became a turbid emulsion (Figure S2A), as in the case of DBSA-catalyzed ester condensation reactions (Figure S2B). The formation of turbid mixtures was important to attain high yields of esters. The addition of aqueous NaOH (10 mol %) to the reaction mixture catalyzed by [1f•$H_2SO_4(SO_3)_X$]^{A} gave a clear separation between the organic substrate layer and the aqueous layer (Figure S2C). So, the crude butyl hexanoate was easily obtained by simple decantation. In contrast, even when aqueous NaOH (5 mol %) was added to the reaction mixture catalyzed by DBSA, the two layers did not separate clearly (Figure S2B → S2D).

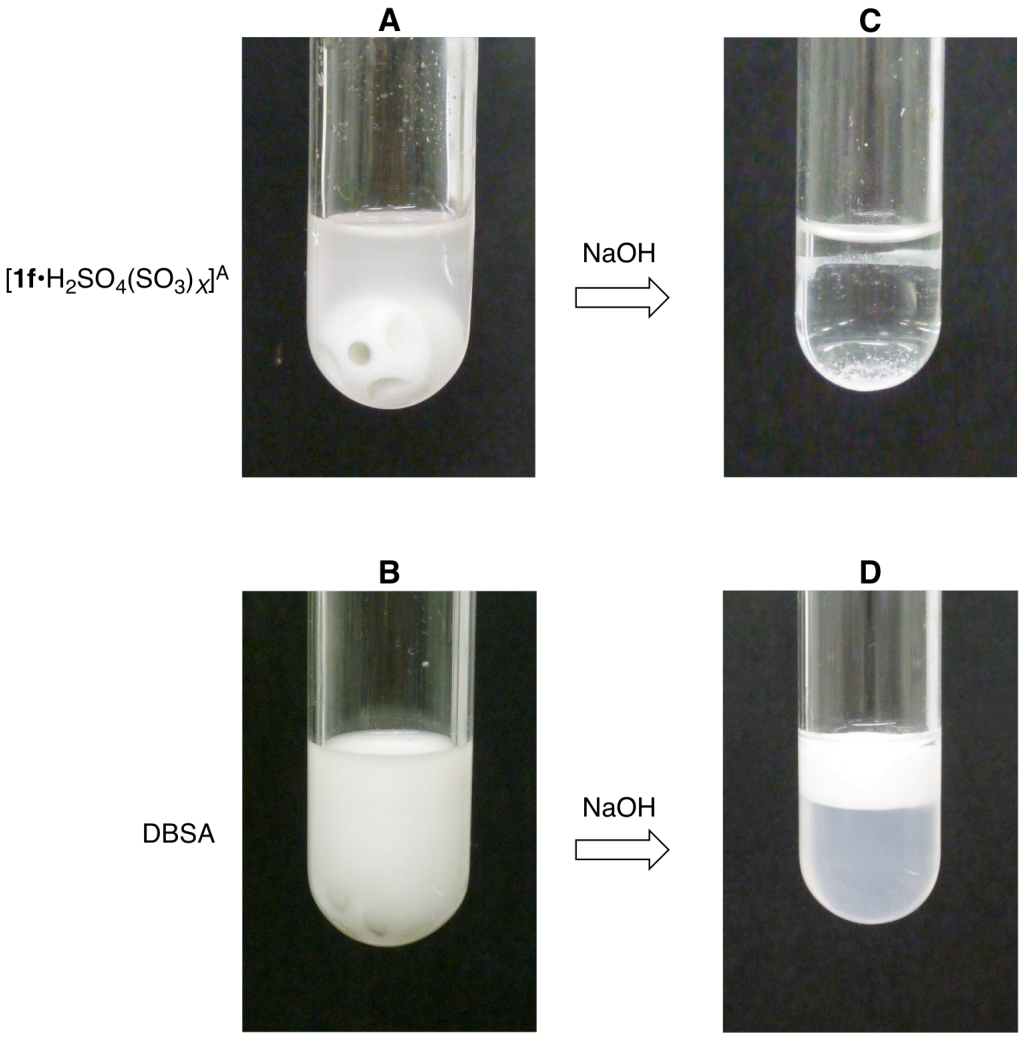
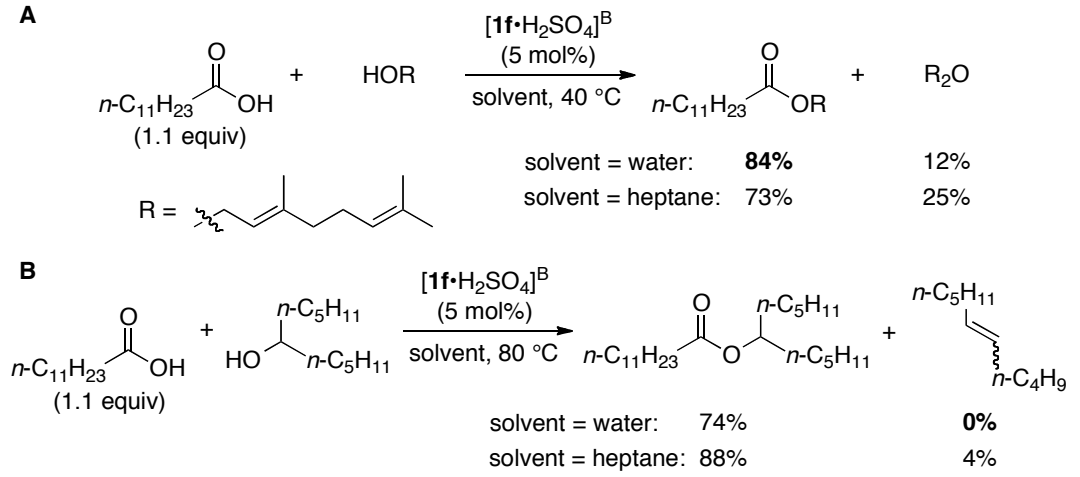


Figure S2

Other Examples of Dehydrative Ester Condensation of Acid-Sensitive Alcohols

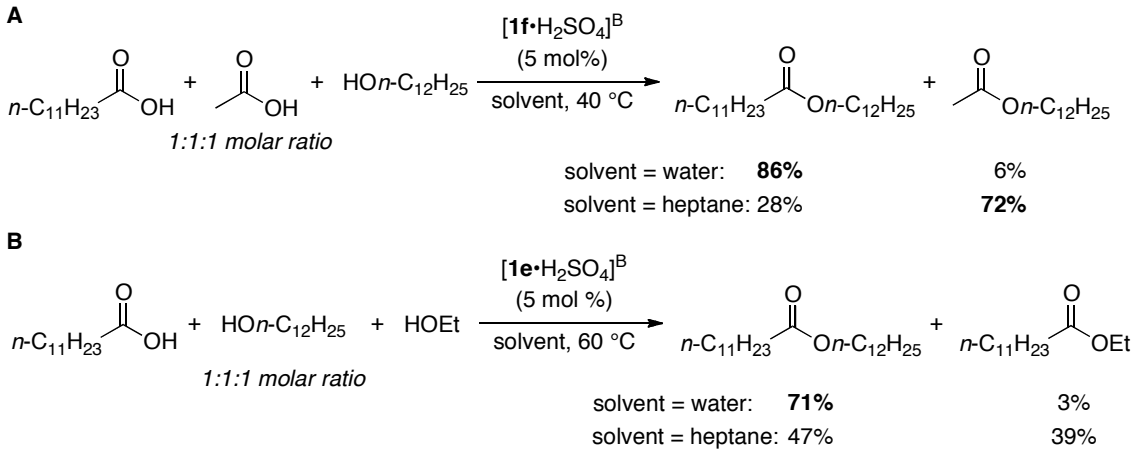
The esterification of geraniol also predominantly gave the desired ester (84%) under aqueous conditions (Scheme S1A). In addition, dehydrative ester condensation of 6-undecanol under aqueous conditions gave the corresponding ester in 74% yield without any generation of alkenes, despite the fact that open-chain secondary alcohols are sometimes dehydrated to the corresponding alkenes under acidic conditions (Scheme S1B).



Scheme S1. Dehydrative Ester Condensation of A: geraniol; B: 6-undecanol

Other Examples of Selective Ester Condensation

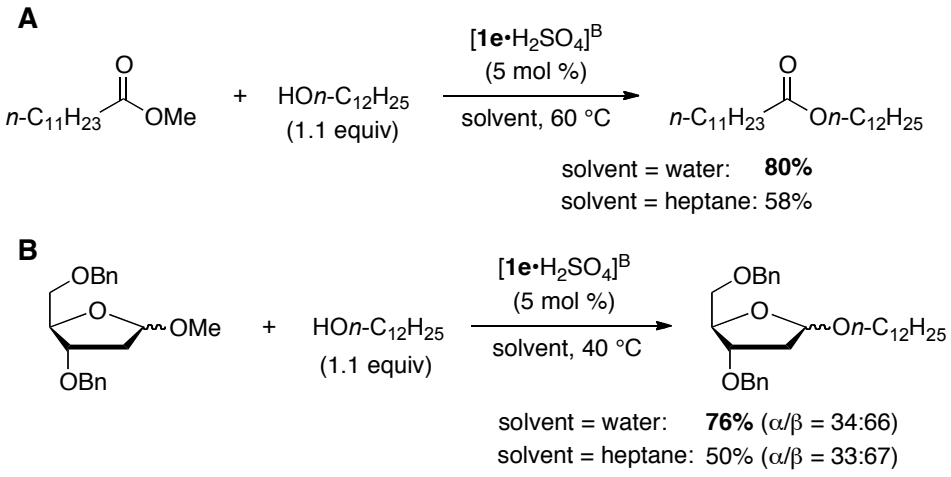
The selective esterification of lauric acid (86%) over acetic acid could also be achieved under aqueous conditions (Scheme S2A). Moreover, the selective esterification of 1-dodecanol (71%) over ethanol could be achieved (Scheme S2B).



Scheme S2.

Transesterification and Transglycosylation

The present catalytic system in water could also be applied to. The **1e**•H_2SO_4-catalyzed transesterification[1] of methyl laurate (Scheme 5A) and transglycosylation of methyl 2-deoxy-L-ribofuranoside in water gave better results than those in heptane (Scheme 5B), due that methanol produced was transferred into aqueous layer in the former case.



Scheme S3.

Reference

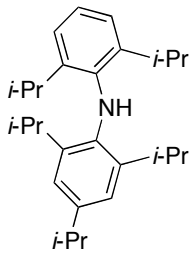
1. (a) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971. (b) Hoydonckx, H. E.; De Vos, D. E.; Chavan, S. A.; Jacobs, P. A. Top. Catal. 2004, 27, 83. (c) Otera, J. *Chem. Rev*. **1993**, *93*, 1449. (d) Maegawa, Y.; Ohshima, T.; Hayashi, Y.; Agura, K.; Iwasaki, T.; Mashima, K. *ACS Catalysis* **2011**, *1*, 1178.

Experimental Section

General Methods.

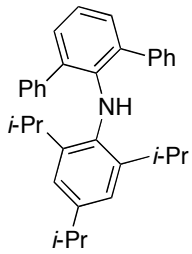
IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR spectra were measured on an INOVA spectrometer (500 MHz) or a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on an INOVA spectrometer spectrometer (125 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm) were used. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. High resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on a JEOL JMS-700 spectrometer. X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å) and the structure was solved by direct methods and expanded using Fourier techniques (Sir97 and SHELXL[1]). Conc. H_2SO_4 (Nacalai Tesque or Aldrich), oleum (containing ca. 30% SO_3, Nacalai Tesque), diphenylamine (**1a**, Nacalai Tesque) and other materials were obtained commercially and used without further purification.

Synthesis of *N,N*-Diarylamines 1

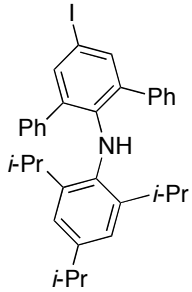


***N*-(2,6-diisopropylphenyl)-2,4,6-triisopropylaniline (1e).** **1e** was prepared according to the reported method.[2] A mixture of 2,6-diisopropylaniline (4.7 mL, 25 mmol), 2,4,6-triisopropylbromobenzene (7.6 mL, 30 mmol), $Pd(dba)_2$ (719 mg, 1.3 mmol), BINAP (934 mg, 1.5 mmol) and *t*-BuONa (7.2 g, 75 mmol) in toluene (30 mL) was heated under reflux for 24 h. After cooling the mixture to ambient temperature, 3 M aqueous HCl (30 mL) was added, and the mixture was extracted with Et_2O (50 mL × 3). The combined organic phase was washed with saturated aqueous solution of $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel using hexane and recrystallization from hexane to give **1e** (4.83 g, 51% yield). Colorless solid; R_f = 0.48 (hexane); IR (KBr) 3450, 1491, 1467, 1456, 1382, 1362, 1344, 1320, 1287, 1251, 1106, 1057 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (d, J = 7.0 Hz, 24H),

1.24 (d, J = 7.0 Hz, 6H), 2.86 (septet, J = 7.0 Hz, 1H), 3.05 (septet, J = 7.0 Hz, 2H), 3.11 (septet, J = 7.0 Hz, 2H), 4.77 (s, 1H), 6.93 (s, 2H), 6.96 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5 (4C), 23.6 (4C), 24.2 (2C), 27.6 (2C), 27.9 (2C), 33.9, 121.6 (2C), 121.8, 123.8 (2C), 138.0 (2C), 139.8 (2C), 140.9, 141.7, 143.6; HRMS (FAB) calcd for $C_{27}H_{42}N$ $[M+H]^+$ 380.3317, found 380.3292.

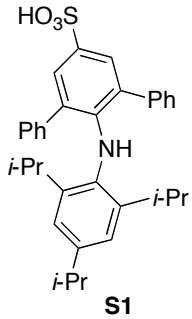


***N*-(2,4,6-triisopropylphenyl)-[1,1':3',1''-terphenyl]-2'-amine (1f).** **1f** was prepared according to the method for the preparation of **1e**. 49% yield. Colorless solid; R_f = 0.39 (hexane); IR (KBr) 3412, 1491, 1457, 1410, 1317, 1234, 1069 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, J = 7.0 Hz, 12H), 1.07 (d, J = 7.0 Hz, 6H), 2.62 (septet, J = 7.0 Hz, 1H), 2.97 (septet, J = 7.0 Hz, 2H), 5.34 (s, 1H), 6.50 (s, 2H), 6.84 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 2H), 7.09 (tt, J = 1.5, 7.5 Hz, 2H), 7.15 (m, 4H), 7.21 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0 (4C), 24.1 (2C), 28.3 (2C), 34.2, 117.0 (2C), 120.2 (2C), 126.5 (2C), 127.7, 128.8 (4C), 129.2 (4C), 130.9 (2C), 134.8 (2C), 140.1 (2C), 140.9, 144.0, 145.6; HRMS (FAB) calcd for $C_{33}H_{38}N$ $[M+H]^+$ 448.3004, found 448.3004.



5'-iodo-*N*-(2,4,6-triisopropylphenyl)-[1,1':3',1''-terphenyl]-2'-amine (1g). **1g** was prepared according to the reported method.[3] To a solution of **1f** (447 mg, 1.0 mmol) and $CaCO_3$ (150 mg, 1.5 mmol) in CH_2Cl_2–MeOH (8:3 v/v, 11 mL) was added $BnMe_3N^+ICl_2^-$ (418 mg, 1.2 mmol) at ambient temperature, and the mixture was stirred for 3 h. Insoluble materials in the reaction mixture were removed by filtration. The filtrate was diluted with saturated aqueous solution of $NaHSO_3$ (20 mL) and the mixture was extracted with Et_2O (20 mL × 3). The combined organic extracts were dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 1:0 → 40:1) to give **1g** (361 mg, 63% yield). Colorless solid; R_f = 0.38 (hexane); IR (KBr) 3405, 1468, 1415, 1381, 1361, 1316, 1298, 1237, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, J = 7.0 Hz, 12H), 1.06 (d, J = 7.0 Hz, 6H), 2.62 (septet, J = 7.0 Hz, 1H), 2.92 (septet, J = 7.0 Hz, 2H), 5.31 (s, 1H), 6.49 (s, 2H), 7.09–7.20 (m, 10H), 7.36 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9 (4C), 24.1 (2C), 28.4 (2C), 34.2, 77.8, 120.3 (2C), 127.0 (2C), 127.9 (4C), 129.0 (4C), 130.8 (2C), 134.1 (2C), 138.6 (2C), 138.9 (2C), 140.9, 144.1, 146.1; HRMS (FAB) calcd for $C_{33}H_{37}IN$ $[M+H]^+$ 574.1971, found 574.1989.

N,N-Diarylamines **1b**,[4] **1c**,[5] **1d**[6] were reported previously.



S1

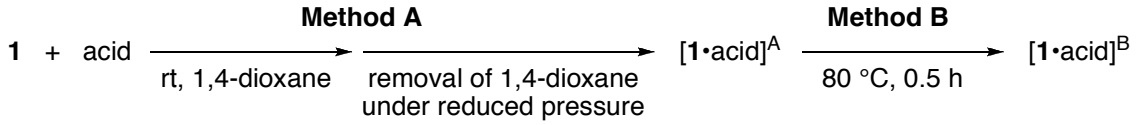
2'-((2,4,6-Triisopropylphenyl)amino)-[1,1':3',1''-terphenyl]-5'-sulfonic acid (S1): Purification: column chromatography on silica gel (hexane–EtOAc–MeOH 2:1:0 → 1:1:1) and ion exchange column (amberlite IR-120H, MeOH); IR (KBr) 3402, 1602, 1586, 1489, 1426, 1397, 1362, 1325, 1179, 1125, 1060, 1035, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 6.9 Hz, 12H), 1.07 (d, J = 6.9 Hz, 6H), 2.62 (septet, J = 6.9 Hz, 1H), 2.88 (septet, J = 6.9 Hz, 2H), 3.10 (br s, 1H), 5.47 (s, 1H), 6.46 (s, 2H), 6.89–7.01 (m, 6H), 7.11 (d, J = 6.4 Hz, 4H), 7.50 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8 (4C), 24.1 (2C), 28.4 (2C), 34.2, 120.2 (2C), 126.7 (2C), 127.5 (2C), 127.6 (4C), 128.9 (2C), 129.3 (4C), 130.8, 134.0 (2C), 138.9 (2C), 142.7, 144.1, 146.0; HRMS (FAB) calcd for $C_{33}H_{38}NO_3S$ $[M+H]^+$ 528.2572, found 528.2574.

Crystal Data for *N,N*-Diphenylammonium Hydrogen Sulfate ($[1a \cdot H_2SO_4]^A$)

Bruker SMART APEX diffractometer with CCD detector (graphite monochromator, MoKα radiation, λ = 0.71073 Å). The structure was solved by direct methods and expanded using Fourier techniques. Formula $C_{24}H_{26}N_2O_8S_2$, colorless, crystal dimensions 0.50 × 0.40 × 0.30 mm^3, triclinic, space group *P-1*, a = 9.4437(18) Å, b = 9.5965(18) Å, c = 15.477(4) Å, β = 82.583(3)°, V = 1217.5(4) $Å^3$, Z = 2, and D_{calc} = 1.458 g cm^{-3}, F(000) = 560, μ = 0.272 mm^{-1}, T = 173(2) K. 5942 reflections collected, 2900 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 28.36°), and 333 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0630 and *wR2* = 0.1677, GOF = 1.091. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk]. Supplementary publication no. CCDC-787065.

Comparison of Diarylammonium Salt Catalysts Prepared by Methods A and B (Table 1)

Preparation of Diarylmmonium Salt Catalysts



Method A: For the preparation of a homogeneous salt, a Brønsted acid (0.20 mmol) and 1 (0.20 mmol) were dissolved in 1,4-dioxane (0.4 mL) in a 10 mL flask at ambient temperature. After stirring at ambient temperature for several minutes, 1,4-dioxane was removed under reduced pressure to give a solid ammonium salt [**1**•acid]^{A}.

Method B: A solid salt [**1**•acid]^{A} (prepared by method A) was heated at 80 °C for 0.5 h to give a solid ammonium salt [**1**•acid]^{B}.

Analysis of Diarylammonium Salts Catalysts

^{1}H NMR Analysis: Diarylammonium salts [**1**•acid]^{A} and [**1**•acid]^{B} were analyzed by ^{1}H NMR in CD_3CN (0.14 M). Chemical shifts of ammonium protons are shown in Table 2.

Catalytic Activity: Catalytic activities of diarylammonium salts [**1**•acid]^{A} and [**1**•acid]^{B} (5 mol %) were investigated for the ester condensation reaction of 4-phenylbutyric acid (722 mg, 4.4 mmol) and 1-dodecanol (895 μL, 4.0 mmol) in the presence of water (2.0 mL) at 60 °C for 6 h. Yields of 1-dodecyl 4-phenylbutyrate were shown in Table 1.

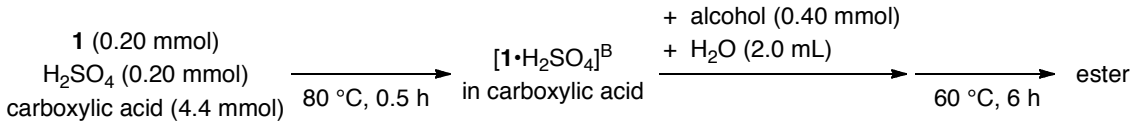
Computational Methods

All the ground state computations have been performed with the Gaussian 03 and 09 suite of programs[7,8]. At first, dissociation free energies of H_2SO_4 and $H_2S_2O_7$ in gas phase were calculated at B3LYP/6-311++G(3df,2pd) level[9]. Harmonic frequency calculations were performed to calculate vibrational zero point energy and thermal corrections. The unscaled frequencies were used for calculating Gibbs free energies of the species (at 298 K and 1 atm). Second-order Mϕller-Plesset perturbation theory (MP2)[10] was used to confirm the relative energy difference calculated at B3LYP level. Next, we performed the optimized structures of bulky *N,N*-diarylammonium pyrosulfate [**1f**-H^{+}]$_2$[$S_2O_7^{2-}$] at B3LYP/6-31G(d) level in gas phase and followed harmonic frequency calculations at same level.

Alkaline Titration of Brønsted Acids in Aqueous Phase

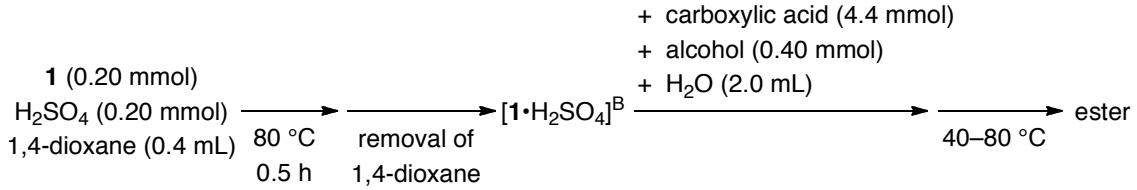
A mixture of Brønsted acid (0.20 mmol), **1** (0–0.20 mmol) and 4-phenylbutyric acid (4.4 mmol) was stirred at 80 °C for 30 min. After cooling the mixture to ambient temperature, 1-dodecanol (4.0 mmol) and water (2.0 mL) was added successively. The mixture was stirred vigorously at 40 °C for 30 min, and then, the organic substrate phase and the aqueous phase were separated by centrifugation (4000 rpm, 3 min). The aqueous phase was washed with hexane (3 mL × 2), and the amount of Brønsted acid in the aqueous phase was established by titration with 0.025 M aqueous NaOH (Tables 1 and S2).

Typical Procedure for *N,N*-Diarylammonium Pyrosulfate-Catalyzed Ester Condensation under Aqueous Conditions (Method B)



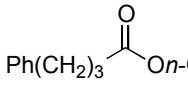
As a practical procedure, the *active* catalyst $[\mathbf{1}\bullet H_2SO_4]^B$ can be prepared in a carboxylic acid *in situ*. A 10 mL flask with a Teflon-coated magnetic stirrer bar was charged with 4-phenylbutyric acid (722 mg, 4.4 mmol), sulfuric acid (10.6 μL, 0.20 mmol), and 1d (59 mg, 0.20 mmol) and the mixture was heated at 80 °C for 30 min. After cooling the mixture to ambient temperature, 1-dodecanol (895 μL, 4.0 mmol) and water (2.0 mL) were added successively, and the mixture was stirred vigorously at 60 °C for 6 h. The yields were determined by ^{1}H NMR analysis of the reaction mixture.

The representative isolation procedure is as follows: After the reaction mixture was cooled to ambient temperature, saturated aqueous $NaHCO_3$ (2 mL) was added, and the mixture was extracted with EtOAc (5 mL × 2). The combined organic phases were dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (10 g, eluent: hexane–EtOAc 15:1 → 6:1) to give 1-dodecyl 4-phenylbutyrate (1.14g, 86%).

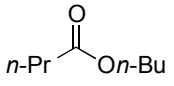


When it is difficult to prepare the *active* catalyst $[\mathbf{1}\bullet H_2SO_4]^B$ in a carboxylic acid, the following procedure is recommended. A 10 mL flask with a Teflon-coated

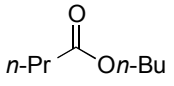
magnetic stirrer bar was charged with sulfuric acid (10.6 μL, 0.20 mmol), 1 (0.20 mmol) and 1,4-dioxane (0.4 mL), and the mixture was heated at 80 °C for 30 min. After cooling the mixture to ambient temperature, 1,4-dioxane was removed under reduced pressure to give the *active* catalyst [**1**•H_2SO_4]^B. To this flask, a carboxylic acid (4.4 mmol), an alcohol (4.0 mmol) and water (2.0 mL) were added successively, and the mixture was stirred vigorously at 40–80 °C.



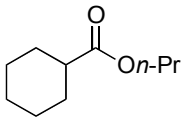
1-Dodecyl 4-phenylbutyrate. IR (neat) 1737, 1496, 1455, 1243, 1199, 1172, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.19–1.42 (m, 18H), 1.61 (quint, *J* = 6.9 Hz, 2H), 1.96 (quint, *J* = 7.8 Hz, 2H), 2.32 (t, *J* = 7.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H), 4.06 (t, *J* = 6.9 Hz, 2H), 7.16–7.22 (m, 3H), 7.24–7.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.9, 26.6, 28.6, 29.2, 29.3, 29.5, 29.56, 29.63 (2C), 31.9, 33.7, 35.1, 64.5, 125.9, 128.4, 128.5, 141.4, 173.6; HRMS (FAB) calcd for $C_{22}H_{37}O_2$ [$(M+H)^+$] 333.2794, found 333.2778.



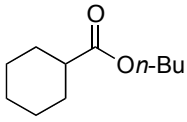
1-Butyl butyrate.[11]



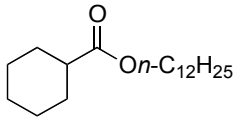
1-Butyl hexanoate.[12]



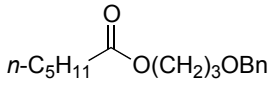
1-Propyl cyclohexanecarboxylate. Colorless oil; IR (neat) 1734, 1452, 1391, 1313, 1247, 1196, 1172, 1133, 1062, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.17–1.33 (m, 3H), 1.44 (dddd, *J* = 3.5, 11.0, 12.0, 13.0 Hz, 2H), 1.61–1.67 (m, 1H), 1.64 (tq, *J* = 7.0, 7.5 Hz, 2H), 1.75 (m, 2H), 1.90 (m, 2H), 2.29 (tt, *J* = 3.5, 11.0 Hz, 1H), 4.02 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.4, 22.0, 25.4 (2C), 25.8, 29.0 (2C), 43.3, 65.6, 176.2; HRMS (FAB) calcd for $C_{10}H_{19}O_2$ [$(M+H)^+$] 171.1385, found 171.1409.



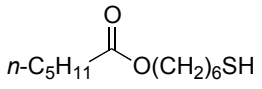
1-Butyl cyclohexanecarboxylate.[13]



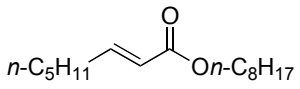
1-Dodecyl cyclohexanecarboxylate.[14,15]



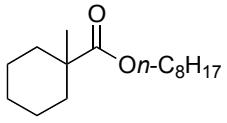
3-(Benzyloxy)propyl hexanoate. Colorless oil; IR (neat) 1736, 1456, 1363, 1246, 1173, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.25–1.36 (m, 4H), 1.57–1.64 (m, 2H), 1.94 (tt, *J* = 6.5, 6.5 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 3.55 (t, *J* = 6.5 Hz, 2H), 4.19 (t, *J* = 6.5 Hz, 2H), 4.51 (s, 2H), 7.26–7.30 (m, 1H), 7.30–7.37 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.3, 24.6, 29.1, 31.3, 34.3, 61.4, 66.7, 73.0, 127.59, 127.60 (2C), 128.4 (2C), 138.3, 173.9; HRMS (FAB) calcd for $C_{16}H_{25}O_3$ [$(M+H)^+$] 265.1804, found 265.1801.



6-Mercaptohexyl hexanoate. Colorless oil; IR (neat) 1736, 1458, 1246, 1173, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.5 Hz, 3H), 1.25–1.40 (m, 9H), 1.57–1.68 (m, 6H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.53 (dt, *J* = 7.5, 7.5 Hz, 2H), 4.06 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.3, 24.5, 24.7, 25.4, 27.9, 28.5, 31.3, 33.8, 34.3, 64.1, 174.0; HRMS (FAB) calcd for $C_{12}H_{25}O_2S$ [$(M+H)^+$] 233.1575, found 233.1568.



(*E*)-Octyl oct-2-enoate. Colorless oil; IR (neat) 1723, 1655, 1466, 1458, 1311, 1265, 1202, 1171, 1125 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H), 1.22–1.40 (m, 14H), 1.46 (quint, *J* = 7.0 Hz, 2H), 1.65 (quint, *J* = 7.0 Hz, 2H), 2.19 (tdd, *J* = 7.0, 7.0, 1.5 Hz, 2H), 4.11 (t, *J* = 7.0 Hz, 2H), 5.81 (td, *J* = 1.5, 15.5 Hz, 1H), 6.96 (td, *J* = 7.0, 15.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.1, 22.4, 22.6, 25.9, 27.7, 28.7, 29.17, 29.22, 31.3, 31.8, 32.1, 64.4, 121.2, 149.4, 166.9; HRMS (FAB) calcd for $C_{16}H_{31}O_2$ [$(M+H)^+$] 255.2324, found 255.2342.

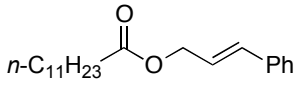


Octyl 1-methylcyclohexanecarboxylate. Colorless oil; IR (neat) 1729, 1458, 1310, 1207, 1162, 1135, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.5 Hz, 3H), 1.14 (s, 3H), 1.18–1.40 (m, 15H), 1.47–1.59 (m, 3H), 1.62 (tt, *J* = 6.5,

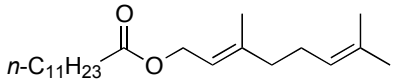
6.5 Hz, 2H), 2.03 (m, 2H), 4.06 (t, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 23.2 (2C), 25.7, 26.0, 26.5, 28.7, 29.2 (2C), 31.8, 35.5 (2C), 43.1, 64.3, 177.9; HRMS (FAB) calcd for $C_{16}H_{31}O_2$ [$(M+H)^+$] 255.2324, found 255.2346.

Dehydrative Ester Condensation of Acid-Sensitive Alcohols

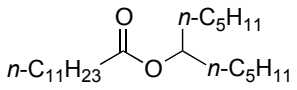
According to the typical procedure (method B), the reaction of acid-sensitive alcohols such as cinnamyl alcohol, geranyl alcohol and 6-undecanol (4.0 mmol) was conducted in the presence of [**1f**•H_2SO_4]^B (5 mol%) in the presence of water (2 mL) (Scheme 2). As a result, the use of water successfully suppressed the generation of the corresponding ethers or alkene, and gave the ester in high yields.



Cinnamyl laurate. Colorless oil; IR (neat) 1738, 1496, 1465, 1379, 1352, 1164, 1113 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.20–1.36 (m, 16H), 1.65 (quint, J = 7.5 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 4.73 (dd, J = 1.0, 6.5 Hz, 2H), 6.29 (td, J = 6.5, 16.0 Hz, 1H), 6.65 (d, J = 16.0 Hz, 1H), 7.26 (tt, J = 1.5, 7.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.39 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.0, 29.15, 29.26, 29.32, 29.4, 29.6 (2C), 31.9, 34.3, 64.8, 123.3, 126.6, 128.0, 128.6, 134.0, 136.2, 173.7; HRMS (FAB) calcd for $C_{21}H_{33}O_2$ [$(M+H)^+$] 317.2481, found 317.2480.



Geranyl laurate. Colorless oil; IR (neat) 1736, 1456, 1378, 1168, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.20–1.37 (m, 16H), 1.57–1.66 (m. 2H), 1.60 (s, 3H), 1.68 (s, 3H), 1.70 (s, 3H), 2.04 (dt, J = 1.5, 7.0 Hz, 2H), 2.11 (td, J = 7.0, 7.0 Hz, 2H), 2.23 (t, J = 7.5 Hz, 2H), 4.59 (d, J = 7.0 Hz, 2H), 5.08 (tt, J = 1.5, 7.0 Hz, 1H), 5.34 (qt, J = 1.5, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 16.4, 17.6, 22.7, 25.0, 25.6, 26.3, 29.1, 29.2, 29.3, 29.4, 29.6, 31.9, 34.4, 39.5, 61.1, 118.4, 123.7, 131.7, 142.0, 173.9; HRMS (FAB) calcd for $C_{22}H_{41}O_2$ [$(M+H)^+$] 337.3107, found 337.3101.

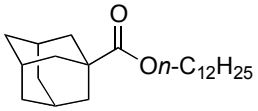


6-Undecyl laurate. Colorless oil; IR (neat) 1735, 1466, 1378, 1178, 1119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 9H), 1.20–1.34 (m, 28H), 1.46–1.54 (m, 4H), 1.62 (quint, J = 7.5 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 4.87

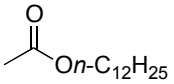
(quint, J = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 14.1, 22.5 (2C), 22.7, 25.0 (2C), 25.2, 29.2, 29.30, 29.32, 29.5, 29.6 (2C), 31.7 (2C), 31.9, 34.1 (2C), 34.7, 74.1, 173.7; HRMS (FAB) calcd for $C_{23}H_{47}O_2$ [$(M+H)^+$] 355.3576, found 355.3571.

Selective Ester Condensation on the Bases of Hydrophobicity of the Substrates

The reaction of a 1:1:1 mixture of 1-adamantanecarboxylic acid, acetic acid and 1-dodecanol (4.0 mmol each) was conducted in the presence of water or heptane (24 mL) in the presence of [**1f**•H_2SO_4]^B (5 mol %). The yields were determined by ^{1}H NMR analysis (Scheme 3A).

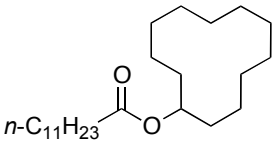


1-Dodecyl 1-adamantanecarboxylate.[15]

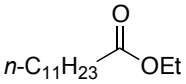


1-Dodecyl acetate.[16]

The reaction of a 1:1:1 mixture of lauric acid, cyclododecanol and ethanol (4.0 mmol each) was conducted in the presence of water or heptane (24 mL) in the presence of [1e•H_2SO_4]^B (5 mol %). The yields were determined by ^{1}H NMR analysis (Scheme 3B).



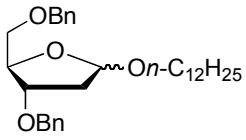
Cyclododecyl laurate. Colorless oil; IR (neat) 1731, 1469, 1446, 1256, 1184, 1151, 1111 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.20–1.53 (m, 36H), 1.61 (quint, J = 7.0 Hz, 2H), 1.65–1.74 (m, 2H), 2.26 (t, J = 7.5 Hz, 2H), 5.01 (tt, J = 5.0, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 20.9 (2C), 22.7, 23.2 (2C), 23.3 (2C), 23.8 (2C), 24.0 (2C), 25.1, 29.08, 29.12, 29.26, 29.32, 29.5, 29.6 (2C), 31.9, 34.7, 71.8, 173.6; HRMS (FAB) calcd for $C_{24}H_{47}O_2$ [$(M+H)^+$] 367.3576, found 367.3569.



Ethyl laurate.[17]

Dehydrative Glycosylation

In a 10 mL flask with a Teflon-coated magnetic stirrer bar, [**1e**•H_2SO_4]^B (0.10 mmol) was prepared according to the typical procedure (method B). To this flask, 3,5-*O*-Dibenzyl-2-deoxy-D-ribose (629 mg, 2.0 mmol) and 1-dodecanol (492 μL, 2.2 mmol) and water (1.0 mL) were added successively, and the mixture was stirred vigorously at 40 °C. The conversion yields were determined by ^{1}H NMR analysis (Scheme 4). As a result, 1-dodecyl 3,5-*O*-dibenzyl-2-deoxy-L-ribofuranoside was obtained in 87% yield (α/β = 39:61). In contrast, the use of H_2SO_4 (5 mol %) as a catalyst gave the product in 28% yield (α/β = 45:55).



1-Dodecyl 3,5-O-dibenzyl-2-deoxy-L-ribofuranoside. Colorless oil; IR (neat) 1496, 1454, 1362, 1203, 1117, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t *J* = 7.0 Hz, 3H), 1.20–1.37 (m, 18H), 1.44–1.53 (m, 1.4H), 1.59 (m, 0.6H), 2.01 (ddd, *J* = 1.5, 3.5, 14.0 Hz, 0.4H), 2.13 (ddd, *J* = 5.5, 6.0, 13.5 Hz, 0.6H), 2.23 (ddd, *J* = 2.0, 6.5, 13.5 Hz, 0.6H), 2.26 (ddd, *J* = 6.0, 8.0, 14.0 Hz, 0.4H), 3.32 (td, *J* = 7.0, 9.5 Hz, 0.6H), 3.41 (td, *J* = 6.5, 9.5 Hz, 0.4H), 3.50 (dd, *J* = 6.0, 9.5 Hz, 0.6H), 3.52 (dd, *J* = 4.5, 10.5 Hz, 0.4H), 3.54 (dd, *J* = 6.0, 9.5 Hz, 0.6H), 3.58 (dd, *J* = 4.5, 10.5 Hz, 0.4H), 3.64 (td, *J* = 7.0, 9.5 Hz, 0.6H), 3.73 (td, *J* = 6.5, 9.5 Hz, 0.4H), 3.99 (ddd, *J* = 3.5, 5.0, 8.0 Hz, 0.4H), 4.15 (ddd, J = 3.5, 6.0, 6.5 Hz, 0.6H), 4.22 (ddd, *J* = 4.5, 4.5, 5.0 Hz, 0.4H), 4.26 (ddd, *J* = 3.5, 6.0, 6.0 Hz, 0.6H), 4.46 (d, *J* = 12.0 Hz, 0.4H), 4.48 (d, *J* = 12.0 Hz, 0.6H), 4.52 (d, *J* = 12.0 Hz, 0.6H), 4.52 (d, *J* = 12.0 Hz, 0.4H), 4.54 (d, *J* = 12.0 Hz, 0.4H), 4.55 (d, *J* = 12.0 Hz, 0.6H), 4.57 (d, *J* = 12.0 Hz, 0.4H), 4.59 (d, *J* = 12.0 Hz, 0.6H), 5.17 (dd, *J* = 1.5, 6.0 Hz, 0.4H), 5.19 (dd, *J* = 2.0, 5.5 Hz, 0.6H), 7.24–7.36 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.2, 29.3, 29.43, 29.44, 29.58, 29.61, 29.62, 29.65, 31.9, 38.8, 39.4, 67.81, 67.82, 70.0, 71.5, 72.1, 73.3, 73.4, 78.5, 80.2, 81.5, 82.7, 103.7, 104.3, 127.52, 127.57, 127.60, 127.63, 127.64, 127.66, 127.68, 128.28, 128.31, 128.34, 138.0, 138.10, 138.19, 138.24; HRMS (FAB) calcd for $C_{31}H_{47}O_4$ [$(M+H)^+$] 483.3474, found 483.3464.

Transesterification of Methyl Esters

A 10 mL flask with a Teflon-coated magnetic stirring bar, [**1e**•H_2SO_4]^B (0.10 mmol) was prepared according to the typical procedure (method B). To this flask, methyl laurate (985 μL, 4.0 mmol), 1-dodecanol (984 μL, 4.4 mmol) and a solvent (2.0

mL) were added successively, and the mixture was stirred vigorously at 60 °C. The yields were determined by ^{1}H NMR analysis (Scheme 5A).

Transglycosylation of Methyl Acetals

The reaction of methyl 2-deoxy-L-ribofuranoside (657 mg, 2.0 mmol) and 1-dodecanol (492 μL, 2.2 mmol) was conducted in a solvent (1.0 mL) at 40 °C in the presence of [**1e**•H_2SO_4]^B (5 mol%) according to the procedure for the transesterification of methyl esters (Scheme 5B).

References

1. Sheldrick, G. M. SHELXL-97, *Program for Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, **1997**.
2. Vyskocil, S.; Jaracz, S.; Smrcina, M.; Stícha, M.; Hanus, V.; Polásek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7727.
3. Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600.
4. Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479.
5. Ackermann, L.; Spatz, J. H.; Gschrei, C. J.; Born, R.; Althammer, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7627.
6. Sakakura, A.; Nakagawa, S.; Ishihara, K. *Tetrahedron* **2006**, *62*, 422.
7. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A. Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapp,rich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.;

Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03 revision E.01*, Gaussian Inc., Wallingford, CT, **2004**.

8. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ã.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09 Revision B.01*, Gaussian Inc., Wallingford, CT, **2009**.
9. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Stephens, P. J.; Devlin, J. F., Chablowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.
10. (a) Mϕller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. (b) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503. (c) Frisch, M. J., Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 275. (d) Frisch, M. J., Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 281. (e) Head-Gordon, M; Head-Gordon, T. *Chem. Phys. Lett.* **1994**, *220*, 122.
11. Morita, K.-I.; Nishiyama, Y.; Ishii, Y. *Organometallics* **1993**, *12*, 3748.
12. Guo, Q.; Miyaji, T.; Hara, R.; Shen, B.; Takahashi, T. *Tetrahedron* **2002**, *58*, 7327.
13. Iwasaki, T.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *J. Org. Chem.* **2008**, *73*, 5147.
14. Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101.
15. Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971.
16. Zeng, T.; Song G.; Li, C.-J. *Chem. Commun.* **2009**, 6249.
17. Brenstrum, T.; Gerristma, D. A.; Adjabeng, G. M.; Frampton, C. S.; Britten, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 7635.

Chapter 4.
N,*N*-Diarylammonium Pyrosulfate-catalyzed Hydrolysis of Esters without the Use of Any Organic Solvents

Abstract: Oil-soluble *N*,*N*-diarylammonium pyrosulfates effectively promote the catalytic hydrolysis of esters under aqueous conditions without the use of any organic solvents. The present method can be applied to the reaction of various esters composed of hydrophobic carboxylic acids and hydrophilic alcohols to give carboxylic acids in high yields. Especially, the hydrolysis of *N*-protected α-amino acid esters is successfully promoted without epimerization under acidic aqueous conditions. Esters composed of hydrophobic alcohols and hydrophilic carboxylic acids are also hydrolyzed to give alcohols in high yields. This study may lead to a new perspective in green chemistry since the present method does not require any organic solvents.

The hydrolysis of esters is one of the most widely used transformations in organic synthesis because esters are often used not only as substrates for the synthesis of carboxylic acids but also as protecting groups for carboxylic acids or alcohols.[1] In general, the hydrolysis of esters is performed in a homogeneous mixture of organic solvents and water under mild basic conditions.[2–4] However, stoichiometric amounts of bases are needed under these conditions because the generated carboxylic acids form salts with the base catalysts. Thus, neutralization of the carboxylic acid salts with a strong acid is required to obtain the desired carboxylic acids. Moreover, problems that are frequently encountered under these basic conditions include the epimerization of *N*-protected α-amino acid esters and the decomposition of base-sensitive functional groups.[5]

The hydrolysis of esters can also be promoted with acid catalysts.[6] However, organic solvents are required as co-solvents to make the reaction mixture homogeneous. Under heterogeneous conditions, Brønsted acid catalysts are dissolved in the aqueous phase and the reactivity of the hydrolysis decreases. Since the organic solvents are considered waste after the reaction, these methods are not desirable for green chemistry. In 2003, Kobayashi and colleagues reported that a polystyrene-supported sulfonic acid catalyzed the hydrolysis of dodecyl acetate.[7] This is the only example of the hydrolysis of esters without the use of organic solvents.

In chapter 3, the author reported that *N*,*N*-diarylammonium pyrosulfates catalyzed ester condensation reactions under aqueous conditions. These catalysts are dissolved in the organic phase and promote dehydrative condensation reactions. Next, the author considered that *N*,*N*-diarylammonium pyrosulfates would promote the hydrolysis of esters without the use of any organic solvents based on the following hypothesis (Figure 1).[8] A small amount of water would be transferred into the organic phase as the substrate of hydrolysis. In the hydrolysis of methyl esters, the generated methanol would move into the aqueous phase. Thus, the equilibrium of the reaction would favor the cleavage of esters. Herein, the author report that *N*,*N*-diarylammonium pyrosulfates promote the hydrolysis of esters without the use of any organic solvents.

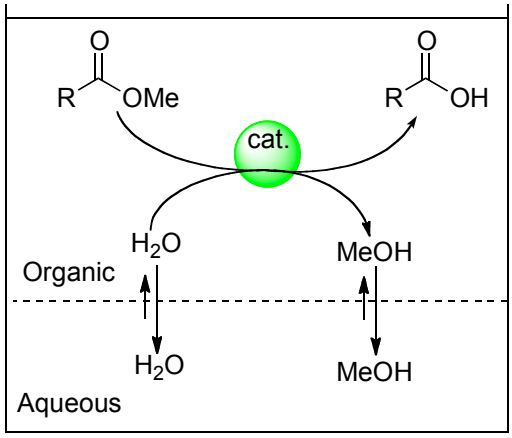
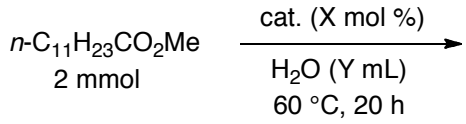
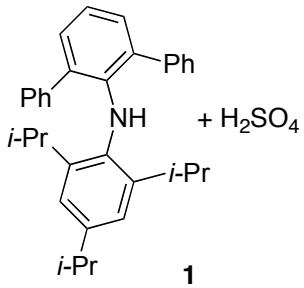


Figure 1. Working hypothesis for the *N*,*N*-diarylammonium pyrosulfate-catalyzed hydrolysis of hydrophobic methyl esters under aqueous conditions

The author first examined the catalytic activity of *N*-(2,4,6-triisopropylphenyl)-[1,1':3',1''-terphenyl]-2'-ammonium pyrosulfate **1** for the hydrolysis of esters under aqueous conditions in the absence of any organic solvents. When the reaction of methyl laurate (2 mmol) was conducted in the presence of water (1 mL) at 60 °C for 20 h, in the presence of **1** (5 mol %), lauric acid was obtained in 56% yield. (Table 1, entry 1). The low reactivity could be attributed to the rather low solubility of methanol in the aqueous phase. The yield of lauric acid was improved by the use of more water (entries 2–4). The use of 8 mL of water for the hydrolysis of methyl laurate (2 mmol) gave the best result (86% yield) (entry 4). On the other hand, as in the case of dehydrative ester condensation, sulfuric acid (H_2SO_4) and the *N*,*N*-diarylammonium sulfate that was prepared at room temperature were almost inert under aqueous conditions (entries 4 and 5). *p*-Dodecylbenzenesulfonic acid (DBSA)[7] also promoted the hydrolysis of methyl laurate, although the reactivity was slightly lower than that with **1** (entry 6). This might be because DBSA prevented water from transferring to the organic phase by forming emulsion droplets. In contrast, the conventional alkaline catalyst LiOH was inert in the absence of organic solvents (entry 7). LiOH-catalyzed hydrolysis was also not promoted in the presence of a phase transfer catalyst Bu_4NBr (entry 8).[4] Trimethyltinhydroxide (Me_3SnOH) is an effective and mild catalyst in organic solvent.[9] However, Me_3SnOH was inert under aqueous conditions, and may be dissolved in water (entry 9).

Table 1. Catalytic Activities of Various Catalysts under Aqueous Conditions

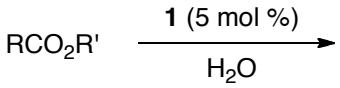


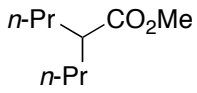
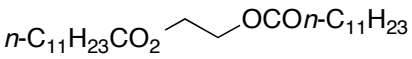
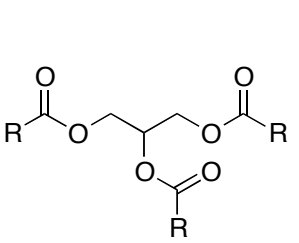
entry	cat.	X (mol %)	Y (mL)	yield (%)[a]
1	 **1**	5	1	56
2		5	2	65
3		5	4	71
4		5	8	86 [3][b]
5	H_2SO_4	5	8	4
6	DBSA	5	8	70
7	LiOH	100	8	4
8[c]	LiOH	100	8	6
9	Me_3SnOH	100	8	4

[a]Determined by ^{1}H NMR analysis. [b]Data in bracket refer to the yield of lauric acid when *N*,*N*-diarylammonium sulfate (5 mol %) prepared at rt was used as a catalyst. [c]The reaction was conducted in the presence of Bu_4NBr (5 mol %).

The present **1**-catalyzed method could be applied to the hydrolysis of various esters of hydrophilic alcohols (Table 2). The solubilities of the generated alcohols in water were important to give the corresponding carboxylic acids in high yields because the equilibrium of the reaction favored the cleavage of esters when the alcohols were dissolved in the aqueous phase. Methyl, ethyl, and ethylene glyceryl esters were smoothly hydrolyzed and gave the corresponding carboxylic acids in good yields (entries 1–3). More water was required for the hydrolysis of isopropyl laurate since isopropyl alcohol is less soluble in water than methanol (entry 4). This method could also be applied to the hydrolysis of triacylglycerols in high yields under aqueous conditions without the isomerization of carbon–carbon double bonds (entries 5–7).[10]

Table 2. **1**-catalyzed Hydrolysis of Esters under Aqueous Conditions[a]



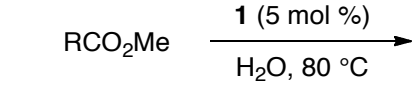
entry	ester	temp (°C)	time (h)	yield (%)[b]
1	*n*-$C_{11}H_{23}CO_2Et$	60	20	83
2		80	30	80
3		60	24	92
4[c]	*n*-$C_{11}H_{23}CO_2$*i*-Pr	80	30	85
5	 R = *n*-$C_{15}H_{31}$	80	24	95
6	R = *n*-C_8H_{17} C_7H_{14}	80	30	86
7	R = C_7H_{14} *n*-C_5H_{11}	80	24	90

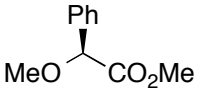
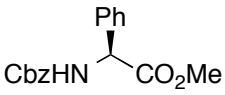
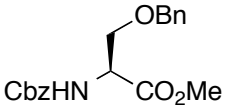
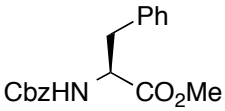
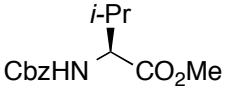
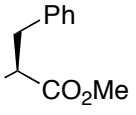
[a]Unless otherwise noted, the reaction of ester (1 mmol) was conducted with **1** (5 mol %) in water (4 mL). [b]Determined by ^{1}H NMR analysis. [c]Water (8 mL) was used.

Next, the author examined the hydrolysis of α-hetero-substituted esters (Table 3). The esters of α-hetero-substituted carboxylic acids are easily racemized under basic conditions.[5b] For example, the conventional alkaline hydrolysis of (*S*)-methyl *O*-methylmandelate (entry 2), *N*-Cbz-L-phenylglycine methyl ester (entry 4),[11] and *N*-Cbz-*O*-benzyl-L-serine methyl ester (entry 6) resulted in epimerization, although carboxylic acids were obtained in high yields. In contrast, **1**-catalyzed hydrolysis of these esters gave the corresponding carboxylic acids without any loss of chirality (entries 1, 3, and 5). Moreover, other *N*-Cbz-α-amino acid methyl esters such as *N*-Cbz-L-phenylalanine methyl ester and *N*-Cbz-L-valine methyl ester were successfully hydrolyzed without epimerization (entries 7 and 8). The present method was also applied to base-sensitive esters. For example, *N*-9-fluorenylmethyloxycarbonyl (Fmoc)-protected L-phenylalanine methyl ester was successfully hydrolyzed without cleavage of the Fmoc group (entry 9). In contrast, under conventional alkaline conditions, the Fmoc group was completely removed although the ester were hydrolyzed (entry 10).[2,10b] When the substrates and/or products were solid under the

reaction conditions, the addition of a small amount of organic solvent such as nitroethane ($EtNO_2$) was effective for dissolving the ester and promoting the hydrolysis (entry 9).

Table 3. **1**-catalyzed Hydrolysis of α-Hetero-substituted Methyl Esters under Aqueous Conditions[a]

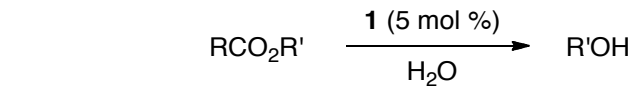


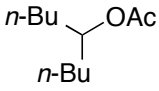
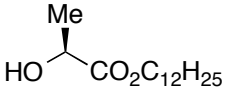
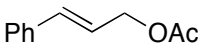
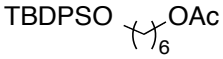
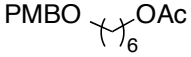
entry	ester	time (h)	yield (%)[b]	ee (%)
1		20	83	>99
2[c]		2	94	97
3		9	80	>99
4[c]		2	93	15
5		9	83	>99
6[c]		4	94	65
7		9	84	>99
8		9	86	>99
9[d]		9	82	>99
10[c]		2	—	

[a]Unless otherwise noted, the reaction of ester (1 mmol, >99% ee) was conducted with **1** (5 mol %) in water (4 mL) at 80 °C. [b]Isolated yield. [c]LiOH (100 mol %) was used in THF–MeOH–water (1:2:2 v/v, 2.5 mL) at rt. [d]$EtNO_2$–water (1:3 v/v, 1.3 mL) was used as a solvent.

Next, the author examined the hydrolysis of various esters of hydrophilic carboxylic acids such as acetic acid (Table 4).[4,12] In this case, the solubilities of the generated carboxylic acids in water were also important to give the corresponding alcohols in high yields. A variety of acetates, propionates and lactates were successfully converted to the corresponding alcohols (entries 1–4). In the hydrolysis of 1-dodecyl lactate, L-lactic acid was also obtained from the aqueous phase in 88% yield along with 1-dodecanol (87% yield) (entry 4). However, dodecyl isobutyrate gave 1-dodecanol in 38% yield (entry 5). This is because isobutyric acid is not sufficiently soluble in water to move into the aqueous phase. In general, when the hydrolysis of acid-sensitive allylic esters is carried out under acidic conditions, a significant amount of diallylic ether is produced as a byproduct. In fact, the hydrolysis of cinnamyl acetate[13] at 60 °C gave dicinnamyl ether in 15% yield (entry 6). When the same reaction was conducted at 40 °C, the yield of dicinnamyl ether was reduced to 2% and the desired cinnamyl alcohol was obtained in 92% yield (entry 7). The hydrolysis of acetates bearing *tert*-butyldiphenylsilyl (TBDPS) (entry 8) and *p*-methoxybenzyl (PMB) (entry 9) groups afforded the corresponding alcohols without cleavage of these protecting groups.[2,7]

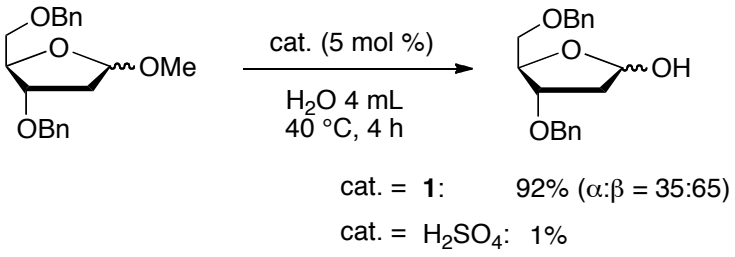
Table 4. **1**-catalyzed Deacylation without the Use of Any Organic Solvents[a]



entry	ester	temp (°C)	time (h)	yield (%)[b]
1	*n*-$C_{12}H_{25}$OAc	60	6	86
2		80	24	89
3[c]	$EtCO_2C_{12}H_{25}$	60	30	74
4		80	4	87[d] [88][e]
5	*i*-$PrCO_2$*n*-$C_{12}H_{25}$	80	24	38
6		60	6	82 [15][f]
7		40	24	92 [2][f]
8[c]		40	30	88
9		40	30	86

[a]Unless otherwise noted, the reaction of ester (1 mmol) was conducted with catalyst (5 mol %) in water (4 mL). [b]Determined by ^{1}H NMR analysis. [c]Water (8 mL) was used. [d]Isolated yield. [e]Isolated yield of L-lactic acid is shown in brackets. [f]Yield of dicinnamyl ether is shown in brackets.

Next, the author examined the hydrolysis of acetals.[2,14] The **1**-catalyzed hydrolysis of methyl 3,5-*O*-dibenzyl-2-deoxy-D-ribose under aqueous conditions gave the corresponding hemiacetal in 92% yield, while the use of H_2SO_4 as a catalyst decreased the yield (1%) (Scheme 2).



Scheme 2. **1**-catalyzed hydrolysis of methyl 3,5-*O*-dibenzyl-2-deoxy-D-ribose

In conclusion, *N*,*N*-diarylammonium pyrosulfate **1** successfully catalyzed the hydrolysis of various esters under aqueous conditions. Especially, *N*-protected α-amino acid methyl esters, which were easily racemized under basic conditions, were hydrolyzed by **1** without epimerization. This method did not require any organic solvents. The hydrolysis of esters is one of the most fundamental organic reactions. The ability to avoid using organic solvents should help to promote green chemistry.

References

1. Haslam, E. *Tetrahedron* **1980**, *31*, 2409.
2. Wuts, P. G.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; 4th Ed., WILEY-VCH, Weinheim, 2006.
3. Dehmlow E. W.; Barahona-Naranjo, S. *J. Chem. Res. Synopses* **1979**, 238.
4. Crouch, R. D.; Burger, J. S.; Zietek, K. A.; Cadwallader, A. B.; Bedison, J. E. *Synlett* **2003**, 991.
5. (a) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.*, **1977**, *42*, 918. (b) Kaestle, K. L.; Anwer, M. K.; Audhya, T. K.; Goldstein, G. *Tetrahedron Lett.* **1991**, 32, 327.
6. (a) Bamford, C. H.; Tipper, C. F. H.; Compton, R. G., Ed. *Ester Formation and Hydrolysis and Related Reactions*, Elsevier, 1972. (b) March, J. *Advanced Organic Chemistry*; 4th Ed., John Wiley & Sons, New York, 1992.
7. (a) Iimura, S.; Manabe, M.; Kobayashi, S. *J. Org. Chem.*, **2003**, *68*, 8723. (b) Iimura, S.; Manabe, M.; Kobayashi, S. *Org. Lett.*, **2003**, *5*, 101.
8. Mori, T.; Kishimoto, S.; Ijiro, K.; Kobayashi, A.; Okahata, Y. *Biotechnol. Bioeng.* **2001**, *76*, 157.
9. (a) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *J. Chem. Soc. Perkin Trans. 1* **1998**, 355. (b) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A.; Pena, C.; Coba, M. P.; *Tetrahedron* **1998**, *54*, 13023. (c) Furlan, R. L. E.; Mascaretti, O. A. *Aldrichimica Acta* **1997**, *30*, 55. (d) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1996**, *37*, 5229. (e) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 1378.
10. (a) Beal, G. D. *Organic Syntheses* **1926**, *6*. (b) Theodorou,V.; Skobridis, K.; Tzakosb A. G.; Ragoussis, V. *Tetrahedron Lett.* **2007**, *48*, 8230.
11. (a) Lovrić, M.; Cepanec, I.; Litvić, M.; Bartolinćić, A;Vinković, V. *Croat. Chem. Acta* **2007**, 80, 109. (b) Maegawa, Y.; Agura, K.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Synlett* **2012**, 137.
12. (a) Orita, A.; Hamada, Y.; Nakano, T.; Toyoshima, S.; Otera, J. *Chem. Eur. J.* **2001**, *7,* 3321. (b) Iwasaki, T.; Agura, K.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Chem. Eur. J.* **2010**, *16,* 11567.
13. Otera, J. *Acc. Chem. Res*. **2004**, *37*, 288.
14. (a) Colvin, E. W.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Chem. Commun.* **1971**, 858. (b) Coppola, G. M. *Synthesis* **1984**, 1021. (c) Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett*. **1975**, 499. (d) Kametani, T.; Kondoh, H.; Honda, T.; Ishizone H.; Suzuki, Y.; Mori, W. *Chem. Lett*. **1989**, 901.

(e) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun*. **1982**, *12*, 267. (f) Eash, K. J.; Pulia, M. S.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2000,** *65,* 8399. (g) Krishnaveni, N. S.; Surendra, K.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2018.

Experimental Section

General Methods.

IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR spectra were measured on an INOVA spectrometer (500 MHz) or a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from tetramethysilane as an internal standard on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on an INOVA spectrometer (125 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the resonance of the solvent used as an internal standard ($CDCl_3$ at 77.0 ppm). For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm) were used. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. High resolution mass spectral analysis (HRMS) was performed at the Chemical Instrumentation Facility, Nagoya University on a JEOL JMS-700 spectrometer. High performance liquid chromatography (HPLC) analysis was conducted using a Shimadzu LC-20A coupled diode array-detector SPD-M20A and a chiral column of Daicel CHIRALCEL OD-H (4.6 mm Å~ 25 cm), Daicel CHIRALCEL OJ-H (4.6 mm Å~ 25 cm) or Daicel CHIRALPAK AS-H (4.6 mm Å~ 25 cm). Conc. H_2SO_4 (Aldrich) and other materials were obtained commercially and used without further purification.

Typical Procedure for the *N,N*-Diarylammonium Pyrosulfate-Catalyzed Hydrolysis of Esters under Aqueous Conditions

A 10 mL flask with a Teflon-coated magnetic stirrer bar was charged with sulfuric acid (2.5 μL, 0.05 mmol), *N*-(2,4,6-triisopropylphenyl)-[1,1':3',1''-terphenyl]-2'-amine (22 mg, 0.05 mmol) and 1,4-dioxane (0.1 mL), and the mixture was heated at 80 °C for 30 min. After the mixture was cooled to ambient temperature, 1,4-dioxane was removed under reduced pressure. To this flask were added successively an ester (1.0 mmol) and water (4.0 mL), and the mixture was stirred vigorously at 40–80 °C. The yields were determined by ^{1}H NMR analysis of the reaction mixture.

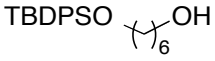
A representative isolation procedure is as follows: After the reaction mixture was cooled to ambient temperature, the mixture was extracted with EtOAc (4 mL× 2). The combined organic layers were dried over Na_2SO_4, and concentrated. The crude

product was purified by column chromatography on silica gel to give the product. The ee value was determined by HPLC analysis.

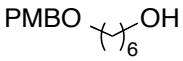
Typical Procedure for the LiOH-Catalyzed Hydrolysis of Esters

Ester (1.0 mmol) was added to a mixture of LiOH•H_2O (126 mg, 3 mmol), THF (0.5 mL), MeOH (1.0 mL) and water (1.0 mL) with a Teflon-coated magnetic stirrer bar, and the mixture was stirred at ambient temperature. The reaction was quenched with 1 M HClaq (4 mL), and the mixture was extracted with EtOAc (5 mL× 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel to give the product. The ee value was determined by HPLC analysis.

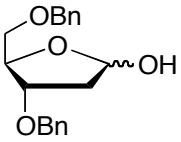
The following obtained carboxylic acids and alcohols were obtained commercially: lauric acid, 2-propyl valeric acid, palmitic acid, oleic acid, linoleic acid, L-*O*-methylmandelic acid, *N*-benzyloxycarbonyl L-phenylglycine, *N*-benzyloxycarbonyl-*O*-benzyl L-serine, *N*-benzyloxycarbonyl L-phenylalanine, *N*-benzyloxycarbonyl L-valine, *N*-9-fluorenyl ethyloxycarbonyl L-phenylalanine, 1-dodecanol, 5-nonanol, L-lactic acid, and cinnamyl alcohol.



6-(*tert*-butyldiphenylsilyloxy)-1-hexanol.[1]



6-(*p*-methoxybenzyl)-1-hexanol.[2]



3,5-*O*-dibenzyl-2-deoxy-D-ribose.[3]

References

1. Yeom, C.-E.; Kim, Y. J.; Lee, S. Y.; Shin, Y. J.; Kim, B. M. *Tetrahedron* **2005**, *61*, 12227.
2. Hu, T.-S.; Yu, Q.; Wu, Y.-L.; Wu, Y. *J. Org. Chem.* **2001**, *66*, 853.
3. Vandenriessche, F.; Snoeck, R.; Janssen, G.; Hoogmartens, J.; Aerschot, A. V.; Clercq, E. D.; Herdewijn, P. *J. Med. Chem.* **1992**, *35*, 1458.

Research Achievement

Paper

"Open-air and solvent-free ester condensation catalyzed by sulfonic acids"
Akira Sakakura, Yoshiki Koshikari, and Kazuaki Ishihara
Tetrahedron Lett. **2008**, *49*(34), 5017–5020.

"Hydrophobic *N*,*N*-Diarylammonium Pyrosulfates as Dehydrative Condensation Catalysts under Aqueous Conditions "
Akira Sakakura, Yoshiki Koshikari, Matsujiro Akakura, and Kazuaki Ishihara
Org. Lett. **2012**, *14*(1), 30-3.

"*N*,*N*-Diarylammonium Pyrosulfates Catalyzed Hydrolysis of Esters without the Use of Any Organic Solvents "
Akira Sakakura, Yoshiki Koshikari, and Kazuaki Ishihara
In preparation

Patent

「エステルの加水分解によるカルボン酸及びアルコールの製造方法」
発明者:石原　一彰、坂倉　彰、越仮　良樹; 権利者:国立大学法人名古屋大学
特願 2011-289040、2011 年 12 月 28 日

Award

第 5 回 GSC Student Travel Grant Awards
「水中エステル脱水縮合に有効な硫酸アンモニウム超分子塩触媒の開発」
2011 年 6 月、GSC ネットワーク

Newspaper

「水中で働く新触媒　名大教授ら　酵素ヒントに開発」
中日新聞朝刊、2011 年 12 月 15 日 29 面
(*Org. Lett.* **2012**, *14*(1), 30-3.に関する記事)

Poster or Oral Presentation

International Conference

"Design of hydrophobic *N*,*N*-diarylammonium pyrosulfate catalysts for dehydrative esterification reactions under aqueous conditions"
Yoshiki Koshikari, Akira Sakakura, Matsujiro Akakura, Kazuaki Ishihara
Nagoya University Global COE International Symposium on Elucidation and Design of Materials and Molecular Functions & 7th and 8th Yoshimasa Hirata Memorial Lectures, P-18, Nagoya, Nov 2011, Poster

"Development of Dehydrative Ester Condensation under Aqueous Conditions Catalyzed by Hydrophobic *N*,*N*-Diarylammonium Sulfates"
Yoshiki Koshikari, Akira Sakakura, Matsujiro Akakura, Kazuaki Ishihara
The 3rd Asia-Oceania Conference on Green and Sustainable Chemistry, Melbourne, Australia, Dec 2011, Poster

Domestic Conference

題名：エステル脱水縮合反応におけるスルホン酸触媒の活性と構造の相関関係
越仮　良樹、坂倉　彰、石原　一彰
日本化学会第 88 春季年会、3J3-04、東京、平成 20 年 3 月、口頭発表

題名：水中でのエステル脱水縮合に有効な疎水性硫酸アンモニウム塩触媒の設計
越仮　良樹、坂倉　彰、石原　一彰
日本化学会第 89 春季年会、4G1-12、千葉、平成 21 年 3 月、口頭発表

題名：嵩高い硫酸ジアリールアンモニウム塩触媒による水溶媒の特性を利用した選択的エステル脱水縮合法の開発
越仮　良樹、坂倉　彰、石原　一彰
日本化学会第 90 春季年会、3F5-35、大阪、平成 22 年 3 月、口頭発表

題目：水中でのエステル脱水縮合に有効なカプセル型ブレンステッド酸触媒の開発
越仮　良樹、坂倉　彰、石原　一彰
第 41 回中部化学関係学協会支部連合秋季大会、2E06、愛知、平成 22 年 11 月、口頭発表

題名：硫酸 *N,N*-ジアリールアンモニウム塩超分子錯体触媒を用いる水中エステル脱水縮合反応
越仮　良樹、坂倉　彰、石原　一彰
日本化学会第 91 春季年会(2011)講演予稿集、2C1-28、平成 23 年 3 月

題目：水中エステル脱水縮合に有効な硫酸アンモニウム超分子塩触媒の開発
越仮　良樹、坂倉　彰、石原　一彰
第 11 回ＧＳＣシンポジウム、A-16、東京、平成 23 年 6 月、ポスター発表

題目：超分子硫酸アンモニウム塩触媒を用いた水中エステル縮合法の開発
越仮　良樹、坂倉　彰、赤倉　松次郎、石原　一彰
第 5 回物質科学フロンティアセミナー、P-6、名古屋、平成 23 年 10 月、ポスター発表

題名：水中エステル脱水縮合反応に有効なピロ硫酸 *N,N*-ジアリールアンモニウム塩触媒とその応用
越仮　良樹、坂倉　彰、赤倉　松次郎、石原　一彰
日本化学会第 92 春季年会、1K7-16、東京、平成 24 年 3 月、発表予定

Acknowledgement

I would like to express my grateful acknowledgment to my supervisors, Professor Kazuaki Ishihara and Associate Professor Akira Sakakura, whose encouragement and helpful suggestions have been indispensable in the completion of the present thesis. The excitement with which they approach synthesis and their dedication to the goal of producing good science is inspiring. Their teaching style in the laboratory and positive attitude for the research work motivated me to be engaged in chemistry. It has been a privilege to work under their tutelage.

I am indebted to Associate Professor Manabu Hatano and Assistant Professor Muhammet Uyanik for their practical and fruitful discussions. I am also very grateful to Associate Professor Matsujiro Akakura (Aichi University of Education) for collaborative research. It is pleasant to express my appreciation to the former and present colleagues in Ishihara's group, especially Drs. Yoshiro Furuya, Yuji Kosugi, Takashi Miyamoto, Makoto Fushimi, Toshikatsu Maki, Kazuhiko Nakano, Takafumi Asai, Mikimoto Katsukawa, Rei Kondo, Atsushi Ukai, Shinji Suzuki, Shuhei Umemura, Katsuhiko Moriyama, Atsuto Izumiseki, and Hidefumi Nakatsuji, Ms. Shoko Nakagawa, and Mr. Hitoshi Watanabe.

I would like to thank Professors Hiroyuki Asanuma, Toshio Nishikawa, and Takashi Ooi for serving on my discussion committee.

I am very grateful to the Fellowships from the Global COE Program.

Finally, I would like to thank my father and mother.

January 2012
Yoshiki Koshikari