J|A|C|S
ARTICLES
Published on Web 09/13/2002

Dehydration Reactions in Water. Brønsted Acid−Surfactant-Combined Catalyst for Ester, Ether, Thioether, and Dithioacetal Formation in Water

Kei Manabe, Shinya Iimura, Xiang-Min Sun, and Shū Kobayashi*

Contribution from the Graduate School of Pharmaceutical Sciences, The University of Tokyo,
CREST, Japan Science and Technology Corporation (JST), Hongo,
Bunkyo-ku, Tokyo 113-0033, Japan

Received March 20, 2002

Abstract: Dehydration reactions in water have been realized by a surfactant-type catalyst, dodecylbenzenesulfonic acid (DBSA). These reactions include dehydrative esterification, etherification, thioetherification, and dithioacetalization. In these reactions, DBSA and substrates form emulsion droplets whose interior is hydrophobic enough to exclude water molecules generated during the reactions. Detailed studies on the esterification revealed that the yields of esters were affected by temperature, amounts of DBSA used, and the substrates. Esters were obtained in high yields for highly hydrophobic substrates. On the basis of the difference in hydrophobicity of the substrates, unique selective esterification and etherification in water were attained. Furthermore, chemospecific, three-component reactions under DBSA-catalyzed conditions were also found to proceed smoothly. This work not only may lead to environmentally benign systems but also will provide a new aspect of organic chemistry in water.

Introduction

Recently, use of water as a reaction solvent has received considerable attention in synthetic organic chemistry for several reasons.[1] First, water is a cheap, safe, and environmentally benign solvent when compared with organic solvents, which are normally used for organic reactions. Use of water will reduce the use of harmful organic solvents and is regarded as an important research topic in green chemistry.[2] Second, in aqueous reactions, it is unnecessary to dry solvents, substrates, and reagents before use. Thus, consumption of drying agents, energy, and time can be reduced. Third, water has unique physical and chemical properties, and by utilizing these it would be possible to realize reactivity or selectivity that cannot be attained in organic solvents.[3] In addition, because the “solvent” in living organisms is water, aqueous reaction systems may lead to development of artificial enzymes or molecular-level machines that work in biological systems.

Although various efficient catalytic systems in water have been developed so far,[4] there are still many types of reactions which are difficult to carry out in water. One such reaction is dehydration in which water molecules generated during the reaction must be removed to shift equilibrium to the dehydrated product side. A representative example is acid-catalyzed direct esterification of carboxylic acids with alcohols. Generally, direct esterification is carried out in organic solvents and requires either of two methods to shift the equilibrium to afford the product (ester) in good yields: continuous removal of water during the reaction (azeotropically or using dehydrating agents) and use of a large excess of one of the reactants.[5] In any case, the presence of large excess amounts of water as a solvent should have a detrimental effect on the equilibrium of the dehydration reaction.

Although water as a solvent impedes dehydration, there are some examples of dehydrative esterification in water.[6] Saam et al. reported direct polyesterification of 1,10-decanediol and nonanedioic acid in water in the presence of catalysts such as

---

* To whom correspondence should be addressed. E-mail: skobayas@mol.f.u-tokyo.ac.jp.

(1) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997.

(2) (a) Anastas, P.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998. (b) Tundo, P.; Anastas, P, Black, D. StC.; Breen, J.; Collins, T.; Memoli, S.; Miyamoto, J.; Polyakoff, M.; Tumas, W. *Pure Appl. Chem.* **2000**, *72*, 1207.

(3) For example: (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (c) Engberts, J. B. F. N.; Blandamer, M. J. *Chem. Commun.* **2001**, 1701.

(4) Reviews: (a) *Aqueous-Phase Organometallic Catalysis. Concepts and Applications*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim; 1998. (b) Engberts, J. B. F. N.; Feringa, B. L.; Keller, E.; Otto, S. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 457. (c) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439. (d) Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305. (e) Kobayashi, S.; Manabe, K. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; Wiley-VCH: Weinheim, 2000. (f) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209.

(5) (a) Larock, R. C. *Comprehensive Organic Transformations*; John Wiley & Sons: New York, 1999. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999. (c) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307. (d) Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, 141. (e) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196. (f) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140. (g) Masaki, Y.; Tanaka, N.; Miura, T. *Chem. Lett.* **1997**, 55. (h) Storck, S.; Maier, W. F.; Salvado, I. M. M.; Ferreira, J. M. F.; Guhl, D.; Souverijins, W.; Martens, J. A. *J. Catal.* **1997**, *172*, 414. (i) Zhang, G.-S. *Synth. Commun.* **1999**, *29*, 607. Esterification of carboxylic acids with equimolar amounts of alcohols without using dehydrating tools has been reported: (j) Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249.

(6) Esterification under water−toluene two-phase conditions has been reported, although the yields of esters are low: Okuhara, T.; Kimura, M.; Kawai, T.; Xu, Z.; Nakato, T. *Catal. Today* **1998**, *45*, 73.

10.1021/ja026241j CCC: $22.00

sulfuric acid, dodecylbenzenesulfonic acid, and sodium dodecylbenzenesulfonate.[7] The authors claimed that the reaction mechanism was not acid-catalyzed but alkylation of the carboxylate with sulfate or sulfonate esters generated in situ. Although the degrees of polymerization were modest, they exceeded those normally expected from dehydrative esterification in water.

Another example of dehydrative esterification in water is lipase-catalyzed ester or polyester formation in water. Okumura et al. reported that, in the presence of a lipase, esterification of oleic acid with various alcohols (1.8−14 equiv) proceeded to give the corresponding esters, in some cases, in high yields.[8] Later, Okumura et al.[9] and Matsumura et al.[10] applied the system to polyester formation in water, and Kobayashi et al. pointed out a unique feature of the lipase-catalyzed polyesterification where dehydrative ester formation proceeded in aqueous media.[11]

Although these examples realized dehydration reactions in water, the methodology is still limited in terms of substrate and reaction applicability and, further, lacks detailed mechanistic studies to explain how dehydration becomes feasible in water as a solvent. To address these issues, we initiated our investigations on dehydration reactions in water. Our strategy is based on previous work on surfactant-aided catalysis in water. We and others have developed surfactant-aided Lewis[12,13] or Brϕnsted acid[14,15] catalysis that mediates carbon−carbon bond-forming reactions in water. Under the reaction conditions, emulsion droplets were formed from catalytic amounts of these catalysts and reaction substrates.[12i,14c,16] These droplets, although dispersed in water, are hydrophobic enough for protecting water-labile substrates or intermediates from hydrolytic decomposition.[17] We expected that these reaction systems would be suitable to study acid-catalyzed dehydration reactions in water without using a large excess of one of the reactants.

The concept of dehydrative esterification in water using a surfactant-type acid catalyst is shown in Figure 1. The catalyst and organic substrates (carboxylic acids and alcohols) in water would form emulsion droplets, which have a hydrophobic interior, through hydrophobic interactions. The surfactant molecules would concentrate proton (for Brønsted acid catalysis) or metal cations (for Lewis acid catalysis) onto the surface of the droplets and then enhance the rate to reach equilibrium. For hydrophobic substrates, the equilibrium position between the substrates and the products (esters) would lie at the ester side, because water molecules generated during the reaction would be removed from the droplets due to the hydrophobic nature of their interior. As a result, the dehydration reactions would efficiently proceed even in the presence of a large amount of water as a solvent. Indeed, this type of thermodynamic preference of the ester formation based on the heterogeneous nature of the system has been regarded as one reason why dehydration reactions proceed in water.[7,11b]

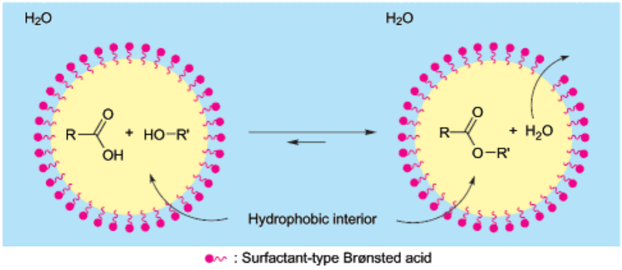


Figure 1. Illustration of direct esterification by dehydration in the presence of a surfactant-type catalyst in water.

The acid-catalyzed direct formation of simple esters with the aid of surfactants in water has not been reported as far as we know, although surfactants have been occasionally used to accelerate the reactions to the opposite direction, hydrolysis of esters.[18] Furthermore, this dehydration reaction system has several advantages when compared with the lipase-catalyzed reactions mentioned above. First, although enzymes often show severe substrate specificity based on highly efficient recognition processes, the acid catalysts with surfactants do not. Therefore, it should, in principle, be possible to apply these catalysts to various substrates, although they may be limited to highly hydrophobic ones. Second, the surfactant-aided catalysis can tolerate drastic reaction conditions such as high temperature. Third, the catalysts should be applicable to various types of acid-catalyzed reactions other than esterification. These advantages will enable us to study dehydration reactions in water in detail and to apply the reaction system to synthetically useful reactions. Herein we report detailed studies on the direct esterification of lipophilic substrates in water using a surfactant-type Brønsted acid and on the extension of the reaction system to other dehydration reactions including etherification, thioetherification, and dithioacetalization in water.[19]

Results and Discussion

1. Dehydrative Esterification in Water. Catalyst Screening. To study dehydrative esterification in water, we selected the esterification of lauric acid with 3-phenyl-1-propanol as simple model substrates and tested various catalysts including surfac-

---

(7) Baile, M.; Chou, Y. J.; Saam, J. C. *Polym. Bull.* **1990**, *23*, 251.
(8) Okumura, S.; Iwai, M.; Tsujisaka, Y. *Biochim. Biophys. Acta* **1979**, *575*, 156.
(9) Okumura, S.; Iwai, M.; Tominaga, Y. *Agric. Biol. Chem.* **1984**, *48*, 2805.
(10) Matsumura, S.; Takahashi, J. *Makromol. Chem., Rapid Commun.* **1986**, *7*, 369.
(11) (a) Kobayashi, S.; Uyama, H.; Suda, S.; Namekawa, S. *Chem. Lett.* **1997**, 105. (b) Suda, S.; Uyama, H.; Kobayashi, S. *Proc. Jpn. Acad.* **1999**, *75-(B)*, 201.
(12) (a) Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. *Tetrahedron Lett.* **1997**, *38*, 4559. (b) Kobayashi, S.; Wakabayashi, T. *Tetrahedron Lett.* **1998**, *39*, 5389. (c) Manabe, K.; Kobayashi, S. *Synlett* **1999**, 547. (d) Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3773. (e) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **1999**, *55*, 11203. (f) Kobayashi, S.; Mori, Y.; Nagayama, S.; Manabe, K. *Green Chem.* **1999**, *1*, 175. (g) Manabe, K.; Mori, Y.; Nagayama, S.; Odashima, K.; Kobayashi, S. *Inorg. Chim. Acta* **1999**, *296*, 158. (h) Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669. (i) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7202. (j) Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 3107. (k) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174.
(13) (a) Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517. (b) Rispens, T.; Engberts, J. B. F. N. *Org. Lett.* **2001**, *3*, 941.
(14) (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401. (b) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965. (c) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537.
(15) (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426. (b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 7831.
(16) Emulsion systems have been used for organic reactions. One successful example is emulsion polymerization. For example: Harkins, W. D. *J. Am. Chem. Soc.* **1947**, *69*, 1428.
(17) We have also reported that even boron enolates, which are highly water-labile, are produced and react with aldehydes in an emulsion system in water: Mori, Y.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2815.
(18) Feiters, M. C. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds; Elsevier Science: Oxford; 1996; Vol. 10.
(19) For preliminary reports, see: (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**, 10.

Table 1. Dehydrative Esterification in Water with Various Catalysts

$$\underset{(1:1)}{CH_3(CH_2)_{10}CO_2H + HO(CH_2)_3Ph} \xrightarrow[\substack{H_2O \\ 40\ °C,\ 24\ h}]{\substack{\text{catalyst} \\ (10\ \text{mol}\ \%)}} CH_3(CH_2)_{10}CO_2(CH_2)_3Ph$$

Entry	Catalyst	Yield (%)[a]
1	$Cu[O_3S(CH_2)_{11}CH_3]_2$	3
2	$Yb[O_3S(CH_2)_{11}CH_3]_3$	4
3	$Sc[O_3S(CH_2)_{11}CH_3]_3$	15
4	DBSA	60
5	H_2SO_4	1
6	TsOH	4
7	$NaO_3SC_6H_4C_{12}H_{25}$	2
8	OBSA	39
9	$HO_3S(CF_2)_3CF_3$	10
10	$HO_3S(CF_2)_7CF_3$	36

[a] Isolated yield.

tant-type ones. The reaction was carried out in water with stirring (1400 rpm) using a magnetic stirring bar and quenched after 24 h with a 1:1 mixture of saturated aqueous $NaHCO_3$ and brine. The product was extracted with ethyl acetate easily even in the presence of a surfactant-type catalyst. One of keys in this reaction is use of a small amount of the surfactant. As shown in Table 1 (entries 1−3), when Lewis acid−surfactant-combined catalysts (LASCs), which were used in our previous work on aldol reactions in water,[12b−e,g,i] were used, 3-phenyl-1-propyl laurate was obtained in very low yields. On the other hand, dodecylbenzenesulfonic acid (DBSA),[20] which can act as a Brønsted acid−surfactant-combined catalyst (BASC),[14] was found to catalyze the reaction efficiently and afforded the ester in 60% yield in 24 h at 40 °C (entry 4). Simple Brϕnsted acids such as sulfuric acid and *p*-toluenesulfonic acid (TsOH) catalyzed the reaction very slowly (entries 5 and 6), and sodium dodecylbenzenesulfonic acid was also not effective (entry 7). These results contrast with those of polyesterification by Saam et al.,[7] indicating that the reaction mechanism is an acid-catalyzed one, not alkylation of the carboxylate as they claimed. Octylbenzenesulfonic acid (OBSA), which has a shorter alkyl chain than DBSA, was less active than DBSA (entry 8). Perfluoroalkanesulfonates were also inferior to DBSA (entries 9 and 10).

The difference between DBSA and OBSA or TsOH is noteworthy. According to a study on the initial rates of the esterification at 30 °C (Figure 2), DBSA was found to catalyze the reaction 2.3 times faster than OBSA and 59 times faster than TsOH (for DBSA, 5.4×10^{-3} M h^{-1}; for OBSA, 2.4×10^{-3} M h^{-1}; for TsOH, 9.1×10^{-5} M h^{-1}). These results clearly demonstrate that the long alkyl chain of DBSA is crucial for the efficient catalysis.

In the case using DBSA, the reaction mixture became a white turbid emulsion (Figure 3a), as in the case of the DBSA-catalyzed Mannich-type reactions, in which the formation of white turbid mixtures was important to attain good yields of the desired Mannich adducts.[14] Formation of emulsion droplets in the present reaction system was confirmed by optical microscopy (Figure 3b). The emulsion formation is attributed to the property of DBSA as a surfactant, and as shown in Figure 1, this property should be important to accelerate the rate of the esterification.[21]

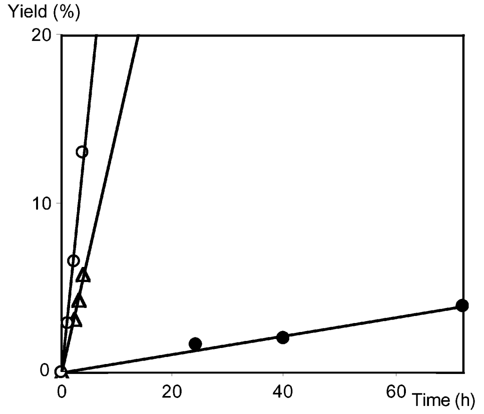


Figure 2. Initial rates of esterification in water. Conditions: lauric acid/3-phenyl-1-propanol = 1/1, at 30 °C in water (3 mL/0.5 mmol of lauric acid). Open circle: with 10 mol % of DBSA. Open triangle: with 10 mol % of OBSA. Closed circle: with 10 mol % of TsOH.

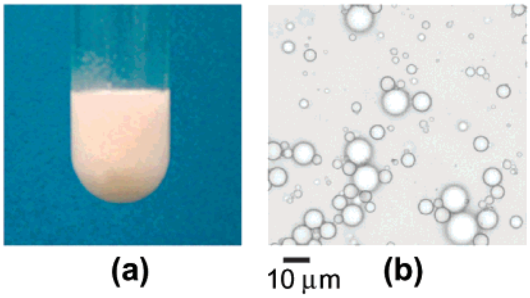


Figure 3. (a) Reaction mixture of the DBSA-catalyzed esterification of lauric acid with 3-phenyl-1-propanol in water. (b) Optical micrograph of the reaction mixture.

Equilibrium Position of Esterification in Water. Figure 4 shows the profiles of the DBSA-catalyzed reaction of lauric acid with 3-phenyl-1-propanol (1:1) at 40 °C in water (closed circle). The reaction reached its maximum yield of 84% in 170 h. We also conducted hydrolysis of the corresponding ester (open square). Both esterification and hydrolysis finally led to the same composition of the reaction mixture, indicating that the reaction reached its equilibrium position. The high yield at the equilibrium position should be attributed to the formation of a hydrophobic area in water as shown in Figure 1.

We next studied the effects of temperature on the equilibrium position. At the equilibrium position at 40 °C, the yield of the ester reached its maximum of 84% as mentioned above. Raising the temperature to 60 °C slightly decreased the maximum yield to 80%, although the reaction rate to reach the equilibrium became faster than that at 40 °C. Increase of the reaction temperature to 100 °C resulted in a further decrease of the ester yield at the equilibrium position to 60%, confirming that increasing the temperature has adverse effects on the maximum yields of the ester.

---

(20) Dodecylbenzenesulfonic acid (soft type) was purchased from Tokyo Kasei Kogyo Co., Ltd. This is a mixture of linear alkylbenzenesulfonic acids. Its molecular weight was regarded as 326.50.

(21) Stirring (usually 1400 rpm) of the reaction mixture was not very important to keep it an emulsion system. Without stirring, large, visible droplets were formed, but the aqueous phase was still a white turbid solution (the yield of 3-phenylpropyl laurate is 58% after 24 h at 40 °C without stirring). Cf. ref 12i.

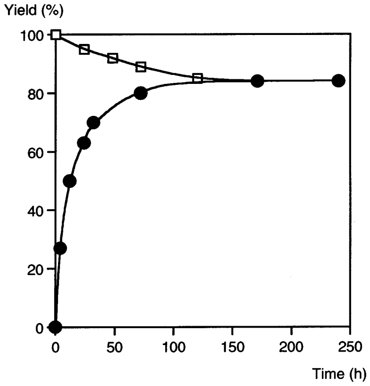


Figure 4. Reaction profiles for DBSA-catalyzed reactions in water. Closed circle: esterification of lauric acid with 3-phenyl-1-propanol (1:1). Open square: hydrolysis of 3-phenyl-1-propyl laurate.

Table 2. Yield at the Equilibrium Position in the Esterification in the Presence of Various Amounts of DBSA in Water[a]

entry	amount of DBSA (mol %)	yield (%)
1	10	84
2	50	71
3	100	58
4	200	32

[a] Conditions: lauric acid/3-phenyl-1-propanol = 1/1, at 40 °C in water (3 mL/0.5 mmol of lauric acid). The yields were determined by ^{1}H NMR.

The amounts of DBSA used were also found to affect the equilibrium position (Table 2). Each equilibrium position was confirmed by conducting both esterification of the carboxylic acid with the alcohol and hydrolysis of the ester. The times required to reach the equilibrium positions became shorter as the amount of DBSA increased (ca. 120 h for 10 mol % of DBSA, 96 h (at longest) for 50 mol % of DBSA, 72 h (at longest) for 100 and 200 mol % of DBSA; we have not carried out the reaction with less than 10 mol % of DBSA because of the very long reaction time required to reach the equilibrium position). Table 2 clearly shows that an increase of the amount of DBSA resulted in a decrease of the yield of the ester at the equilibrium position. This result may be attributable to the size difference of the emulsion droplets which were formed by the hydrophobic substrates and the surfactant in water. As the amount of the surfactant-type catalyst increases, the size of each droplet may decrease, because the emulsion system may become a microemulsion system where the substrates are solubilized in water by a large amount of the surfactant.[22] In fact, while 10 mol % of DBSA gave the white turbid mixture (Figure 3a), the reaction mixture was almost clear in the presence of 200 mol % of DBSA (Figure 5), indicating that the size of the droplets became smaller. The smaller the droplets, the larger the sum of the surface area of the droplets. As a result, the organic phase and water can contact each other, and the hydrolysis of the ester becomes a favorable process. These results suggest that a large hydrophobic area inside the emulsion droplets is important to attain high yields at the equilibrium position.

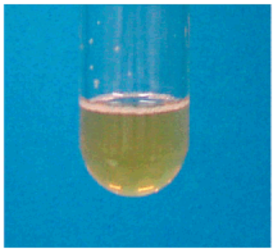


Figure 5. Reaction mixture of esterification in water in the presence of 200 mol % of DBSA.

Table 3. Yield at the Equilibrium Position in the Reaction of $CH_3(CH_2)_nCO_2H$ with 3-Phenyl-1-propanol in Water[a]

entry	*n*	yield (%)
1	0	5
2	2	39
3	4	72
4	6	78
5	8	81
6	10	84
7[b]	10	15

[a] Conditions: $CH_3(CH_2)_nCO_2H$/3-phenyl-1-propanol = 1/1, DBSA (10 mol %), at 40 °C in water (3 mL/0.5 mmol of the carboxylic acid). [b] Ethanol was used instead of 3-phenyl-1-propanol. The yields were determined by ^{1}H NMR.

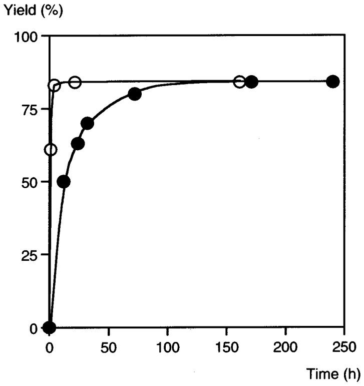


Figure 6. Reaction profiles for esterification of lauric acid with 3-phenyl-1-propanol in the presence of 10 mol % of DBSA. Closed circle: in water. Open circle: under neat conditions.

Effects of substrates on the equilibrium position were next studied (Table 3). As expected, when various alkanecarboxylic acids were used for the DBSA-catalyzed esterification in water, carboxylic acids with a longer alkyl chain afforded the corresponding esters in higher yields at the equilibrium position (entries 1−6). In addition, use of a water-soluble alcohol such as ethanol resulted in lower yield of the ester (entry 7). These results emphasize the importance of hydrophobicity of substrates in the dehydration reactions in water. Hydrophobic substrates themselves form a hydrophobic area dispersed in water and facilitate the ester formation. Although these effects are the cause of substrate limitation in the present reaction system, they also enable selective esterification and transesterification as mentioned later.

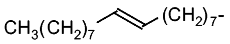
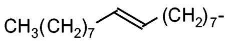
Comparison with Neat Conditions. To compare the esterification in water with that under neat conditions, the esterification of lauric acid with 3-phenyl-1-propanol in the presence of DBSA was carried out without any solvents (Figure 6). Since DBSA is soluble in organic substrates, the reaction mixture was homogeneous at the beginning. Therefore, the reaction system is regarded to be similar to that with conventional dry conditions but in high concentration without dehydrating agents. It is noteworthy that, although the reaction under neat conditions was faster than that in water probably because of the absence of competitive protonation between the substrate and a large number of water molecules under the neat conditions, the yield of the ester at the equilibrium position was unchanged. Under

---

(22) Jönsson, B.; Lindman, B.; Holmberg, K.; Kronberg, B. *Surfactants and Polymers in Aqueous Solutions*; John Wiley & Sons: West Sussex, 1998.

Table 4. DBSA-Catalyzed Esterification of Various Substrates in Water

$$\underset{(1:2)}{RCO_2H + HOR'} \xrightarrow[\substack{H_2O \\ 40\ °C,\ 48\ h}]{\text{DBSA (10 mol \%)}} RCO_2R'$$

Entry	R	R'	Yield (%)[a]
1	$CH_3(CH_2)_{10}$-	-$(CH_2)_3Ph$	89
2	$CH_3(CH_2)_{10}$-	-CH_2Ph	82
3	$CH_3(CH_2)_{10}$-	-$(CH_2)_{11}CH_3$	97
4	$CH_3(CH_2)_{10}$-	-$(CH_2)_{13}CH_3$	>99
5	$CH_3(CH_2)_{10}$-	*c*-Hex	46[b], 70[c]
6	$CH_3(CH_2)_{10}$-	-$CH(CH_3)CH_2Ph$	53[b], 69[c]
7	$CH_3(CH_2)_{16}$-	-$(CH_2)_{11}CH_3$	98
8	$PhCH_2$-	-$(CH_2)_{11}CH_3$	92
9	$Ph(CH_2)_2$-	-$(CH_2)_{11}CH_3$	90
10	$Ph(CH_2)_4$-	-$(CH_2)_{11}CH_3$	91
11	$Ph(CH_2)_4$-	-$(CH_2)_{13}CH_3$	97
12	$Ph(CH_2)_4$-	-$(CH_2)_{12}Br$	91
13		-$(CH_2)_{11}CH_3$	95
14		-$(CH_2)_{13}CH_3$	97
15	*c*-Hex	-$(CH_2)_{11}CH_3$	90
16	*c*-Hex	-$(CH_2)_{13}CH_3$	95
17	1-adamantyl	-$(CH_2)_{11}CH_3$	93[d]

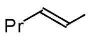
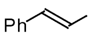
[a] Isolated yield. [b] For 96 h. [c] For 288 h. [d] At 60 °C.

neat conditions, the amount of water in the reaction mixture must be less than 1 equiv to the substrates. On the other hand, a large excess of water is present in the reaction in water. The result that these two sets of conditions gave the same yield at the equilibrium position is surprising and is a characteristic feature of the present system.

Application to Various Substrates. This catalytic esterification in water was applied to various substrates as shown in Table 4.[23] Many hydrophobic substrates were successfully esterified by DBSA in water, and the use of 2 equiv of the alcohols improved the yields to greater than 90% in most cases. Not only α-monosubstituted carboxylic acids (entries 1−14) but also α-disubstituted (entries 15 and 16) and α-trisubstituted acids (entry 17) gave the corresponding products in high yields. Primary alcohols reacted smoothly, but the reactions were very slow in the case of secondary alcohols (entries 5 and 6). Functional groups such as a bromide (entry 12) and a double bond (entries 13 and 14) survived under the reaction conditions.

Table 5. DBSA-Catalyzed Selective Esterification in Water

$$\underset{(1:1:x)}{R^1CO_2H + R^2CO_2H + HOR} \xrightarrow[\substack{H_2O \\ 40\ °C,\ 48\ h}]{\text{DBSA (10 mol \%)}} \begin{array}{c} R^1CO_2R\ (\mathbf{A}) \\ + \\ R^2CO_2R\ (\mathbf{B}) \end{array}$$

Entry	R¹	R²	R (x equiv)	Yield (%)[a]	
				A	**B**
1[b]	$CH_3(CH_2)_{10}$-	CH_3-	-$(CH_2)_{11}CH_3$ (1)	63	35
2	$CH_3(CH_2)_{10}$-	CH_3-	-$(CH_2)_{11}CH_3$ (1)	81	4
3	$CH_3(CH_2)_{10}$-	CH_3-	-$(CH_2)_{11}CH_3$ (2)	>99	16
4[c]	$CH_3(CH_2)_{10}$-	CH_3-	-$(CH_2)_3Ph$ (1)	78	trace
5	*c*-Hex	CH_3-	-$(CH_2)_{11}CH_3$ (1)	65	5
6	*c*-Hex	CH_3-	-$(CH_2)_{11}CH_3$ (2)	90	13
7	*c*-Hex	Ph	-$(CH_2)_{11}CH_3$ (2)	83	5
8	*c*-Hex		-$(CH_2)_{11}CH_3$ (2)	84	14
9	$Ph(CH_2)_2$-		-$(CH_2)_{11}CH_3$ (1)	78	trace

[a] NMR yield. [b] Under neat conditions. [c] 120 h.

$$\underset{(1:1:1)}{CH_3(CH_2)_{10}CO_2H + HO(CH_2)_3Ph + HOCH_2CH_3} \xrightarrow[\substack{H_2O \\ 40\ °C,\ 136\ h}]{\substack{\text{DBSA} \\ \text{(10 mol \%)}}} \begin{array}{ll} CH_3(CH_2)_{10}CO_2(CH_2)_3Ph & 76\% \\ + & \\ CH_3(CH_2)_{10}CO_2CH_2CH_3 & 9\% \end{array} \quad (1)$$

In the workup procedure for the esterification, the crude products were extracted with ethyl acetate after quenching the reactions with a saturated aqueous solution of $NaHCO_3$ and brine. According to this procedure, the organic phase can be easily separated from the aqueous phase even in the presence of the surfactant.

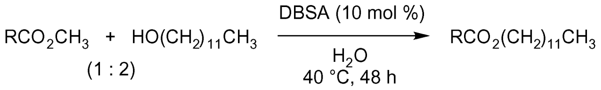
Selective Esterification. We next carried out selective esterification of two substrates in this reaction system. When a 1:1 mixture of lauric acid and acetic acid was esterified with dodecanol in the presence of DBSA under neat conditions at 40 °C for 48 h, the laurate ester and the acetate ester were obtained in 63% and 35% yields, respectively (Table 5, entry 1). On the other hand, when the same reaction was conducted in water, the laurate ester was predominantly obtained in 81% yield, and the yield of the acetate was only 4% (entry 2). Similar selective esterification of lauric acid over acetic acid was also observed in the reaction of another alcohol (entry 4). Furthermore, even cyclohexanecarboxylic acid, which is an α-disubstituted acid, was preferentially esterified in the presence of acetic acid (entries 5 and 6). These selectivities are attributed to the hydrophobic nature of lauric acid and cyclohexanecarboxylic acid and to the high hydrophilicity of acetic acid.[24] These unique selectivities became possible by using water as a solvent. Selective esterification based on the difference in hydrophobicity was also attained in the reaction of two alcohols, one of which is hydrophobic and the other is water-soluble (eq 1).[24]

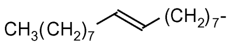
Table 5 also lists examples of selective esterification of nonconjugated carboxylic acids over aromatic or conjugated carboxylic acids[25] (entries 7−9). These selectivities are due to the difference in reactivity between these acids. In fact, the esterification of benzoic acid or cinnamic acid with 3-phenyl-1-propanol in the presence of DBSA (10 mol %) in water (40

---

(23) For a typical experimental procedure, see the Supporting Information.

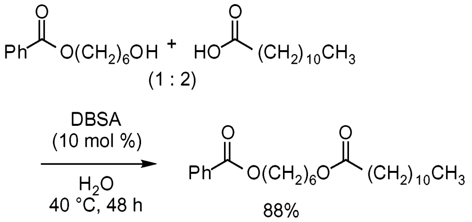
Table 6. Transesterification of Methyl Esters in Water



Entry	R	Yield (%)[a]
1	$CH_3(CH_2)_{10}$-	90
2	$PhCH_2$-	84
3		88

[a] Isolated yield.

°C, 24 h) afforded the corresponding esters in very low yields (2% for benzoic acid, 6% for cinnamic acid). Furthermore, hydrolysis of 3-phenyl-1-propyl benzoate (DBSA: 10 mol %, 40 °C, 24 h) gave a trace amount of the hydrolyzed product. On the basis of this difference in reactivity, esterification of an alcohol having a benzoyloxy group was possible under the DBSA-catalyzed conditions as shown in eq 2. It should be noted that the benzoate group remained intact and that the reaction system differentiated two kinds of ester groups.



(2)

Transesterification. The results of the selective esterification based on the difference in hydrophobicity of substrates prompted us to study transesterification, in which esters and alcohols were used as substrates.[26] First, we tested the reactions of methyl esters with hydrophobic alcohols in the presence of DBSA in water. As shown in Table 6, the reactions proceeded smoothly to give the desired esters in high yields. In these cases, methanol, which is generated during the reactions, dissolved mostly in the aqueous phase, and thus, the equilibrium of the reactions favors the formation of the transesterified products.

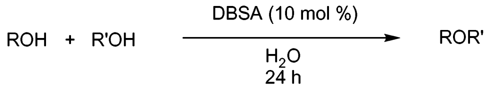
Transesterification of a triglyceride was also realized by the DBSA-catalyzed reactions in water (Table 7). This system will provide a useful method to convert natural triglycerides into other hydrophobic esters directly without using excess alcohols.

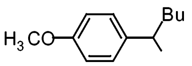
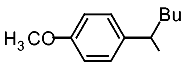
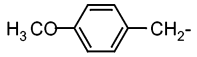
Table 7. Transesterification of a Triglyceride in Water

Entry	R	Time (h)	Yield (%)[a]
1	$-(CH_2)_{11}CH_3$	91	90
2	$-(CH_2)_{13}CH_3$	168	87
3[b]	$-(CH_2)_3Ph$	120	94

[a] Isolated yield. [b] Triglyceride:HOR = 1:6.

Table 8. DBSA-Catalyzed Etherification in Water



Entry	R	R'	Yield (%)[a]
1[b]			90
2[c]	Ph_2CH-	Ph_2CH-	91
3[c,d]	$CH_3(CH_2)_{11}$-	Ph_2CH-	89
4[d,e]	$CH_3(CH_2)_{11}$-	$Ph(CH_3)_2C$-	83
5[c,d]	$CH_3(CH_2)_{11}$-		77

[a] Isolated yield. [b] For 7 h at 30 °C. [c] At 80 °C. [d] 2 equiv of R′OH was used. [e] At 50 °C.

2. Other Dehydration Reactions in Water. Etherification. Although the Williamson ether synthesis is probably one of the most common methods for preparation of ethers,[27] the method required strongly basic conditions and initial conversion of alcohols to halides or tosylates. On the other hand, acid-promoted dehydration of alcohols provides an alternative important method of preparing ethers.[28] As an extension of the DBSA-catalyzed reactions, we next investigated dehydrative ether formation from two alcohols in water.

First, we tried formation of symmetric ethers from benzylic alcohols in water using 10 mol % of DBSA as a catalyst. The reactions were found to proceed smoothly in water to afford the corresponding symmetric ethers in high yields (Table 8, entries 1 and 2). It should be noted that the etherification of the substrate shown in entry 1 in the presence of TsOH instead of DBSA gave only a trace amount of the product. This result indicates that the long alkyl chain of DBSA, which leads to the formation of emulsion droplets, is essential for the efficient catalysis as in the case of the dehydrative esterification. We then carried out unsymmetrical etherification of two alcohols, a primary alcohol and a benzylic alcohol (2 equiv). The reactions

---

(24) Water−octanol partition coefficients, log P_{oct}, have been used to indicate hydrophobicity of organic compounds (log P_{oct} for lauric acid: 4.6, acetic acid: −0.17, 3-phenyl-1-propanol: 1.88, ethanol: −0.30): Sangster, J. *J. Phys. Chem. Ref. Data* **1989**, *18*, 1111.

(25) For examples of selective esterification of nonconjugated carboxylic acids over aromatic or conjugated carboxylic acids, see: (a) Blossey, E. C.: Turner, L. M.; Neekers, D. C. *Tetrahedron Lett.* **1973**, 1823. (b) Bertin, J.; Kagan, H. B.; Luche, J.-L.; Setton, R. *J. Am. Chem. Soc.* **1974**, *96*, 8113. (c) Rehn, D.; Ugi, I. *J. Chem. Res. Synop.* **1977**, 119. (d) Banerjee, A.; Sengupta, S.; Adak, M. M.; Banerjee, G. C. *J. Org. Chem.* **1983**, *48*, 3106. (e) Matsumoto, I. *Jpn. Kokai Tokkyo Koho* JP 59 152,347 [84 152,347] (Cl. C07C67/08), *Chem. Abstr.* **1985**, *102*, 5952w. (f) Ogawa, T.; Hikasa, T.; Ikegami, T.; Ono, N.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3473. (g) Ram, R. N.; Charles, I. *Tetrahedron* **1997**, *53*, 7335. (h) Rodríguez, A.; Nomen, M.; Spur, B. W. *Tetrahedron Lett.* **1998**, *39*, 8563. (i) Lee, A. S.-Y.; Yang, H.-C.; Su, F.-Y. *Tetrahedron Lett.* **2001**, *42*, 301.

(26) Recently, excellent methods of transesterification have been reported: (a) Xiang, J.; Toyoshima, S.; Orita, A.; Otera, J. *Angew, Chem, Int. Ed.* **2001**, *40*, 3670. (b) Xiang, J.; Orita, A.; Otera, J. *Adv. Synth. Catal.* **2002**, *344*, 84. (c) Baumhof, P.; Mazitschek, R.; Giannis, A. *Angew, Chem, Int. Ed.* **2001**, *40*, 3672. See also ref 5j.

(27) (a) Williamson, A. W. *J. Chem. Soc.* **1852**, *4*, 229. (b) Baggett, N. In *Comprehensive Organic Synthesis*; Barton D., Ollins, W. D., Eds.; Pergaman: Oxford, 1979; Vol. 1.

(28) For recent examples of acid-catalyzed etherification, see: (a) Sharma, G. V. M.; Mahalingam, A. K. *J. Org. Chem.* **1999**, *64*, 8943. (b) Ooi, T.; Ichikawa, H.; Itagaki, Y.; Maruoka, K. *Heterocycles* **2000**, *52*, 575. (c) Sharma, G. V. M.; Prasad, T. R.; Mahalingam, A. K. *Tetrahedron Lett.* **2001**, *42*, 759. (d) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1996**, *61*, 324.

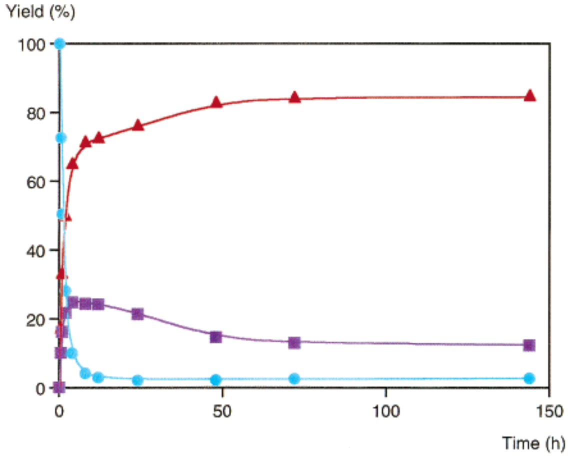


Figure 7. Reaction profiles for DBSA-catalyzed etherification of dodecanol with benzhydrol in water. Red triangle: for benzhydryl dodecyl ether. Purple square: for dibenzhydryl ether (the yield is based on the benzhydryl group used). Blue circle: for benzhydrol.

also proceeded smoothly to give the desired ethers in high yields (entries 3−5).

Figure 7 shows the reaction profile of the etherification of dodecanol with benzhydrol (1 equiv) in the presence of 10 mol % of DBSA in water at 80 °C. The formation of the unsymmetrical ether (benzhydryl dodecyl ether) was found to reach the equilibrium position in 72 h (red triangle). In this reaction, dibenzhydryl ether derived from two benzhydrol molecules was generated, and the formation is also plotted in Figure 7 (purple square). The yield of the symmetrical ether went up to its maximum (25%) in 4 h and then slowly decreased to reach the equilibrium position, indicating that dibenzhydryl ether once formed also acted as a benzhydryl group source.

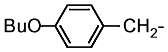
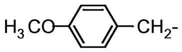
Selective etherification based on the difference in hydrophobicity of two alcohols was also possible in the present reaction system (eq 3). When an equimolar mixture of dodecanol and propanol was etherified with benzhydrol in the presence of DBSA in water, benzhydryl dodecyl ether was selectively obtained. On the other hand, the ratio of benzhydryl dodecyl ether to benzhydryl propyl ether decreased significantly under neat conditions (58% yield and 25% yield, respectively). This result of the selective reaction based on the difference in hydrophobicity[29] again emphasizes a characteristic feature of the present dehydration system.

$$\underset{(1:1:1)}{CH_3(CH_2)_{11}OH + CH_3(CH_2)_2OH + Ph_2CHOH} \xrightarrow[\substack{H_2O \\ 80\ °C,\ 72\ h}]{\substack{DBSA \\ (10\ mol\ \%)}} \begin{array}{lr} CH_3(CH_2)_{11}OCHPh_2 & 70\% \\ + & \\ CH_3(CH_2)_2OCHPh_2 & 6\% \end{array} \quad (3)$$

Thioetherification. Thioethers are, in general, synthesized from halides and thiolates.[5b] However, a drawback to this method is that aerobic oxidation to disulfides is prone to occur. An alternative route to thioethers is acid-promoted condensation of thiols and activated alcohols such as benzylic alcohols.[30] Along this line, we expected that the DBSA-catalyzed dehydration in water would be applicable to thioetherification. Indeed, the reaction of dodecanethiol with trityl alcohol proceeded smoothly in the presence of DBSA in water (Table 9, entry 1).

Table 9. DBSA-Catalyzed Thioetherification in Water

$$RSH + R'OH \xrightarrow[\substack{H_2O \\ 80\ °C,\ 24\ h}]{DBSA\ (10\ mol\ \%)} RSR'$$

Entry	R	R'	Yield (%)[a]
1	$CH_3(CH_2)_{11}$-	Ph_3C-	97
2[b]	$CH_3(CH_2)_{11}$-	Ph_2CH-	93
3[b,c]	$CH_3(CH_2)_{11}$-		87
4	$CH_3(CH_2)_{11}$-		82
5[d]	$PhCH_2$-	Ph_3C-	96
6[e]	Ph	Ph_3C-	76

[a] Isolated yield. [b] 2 equiv of R′OH was used. [c] At 50 °C. [d] For 12 h. [e] For 16 h.

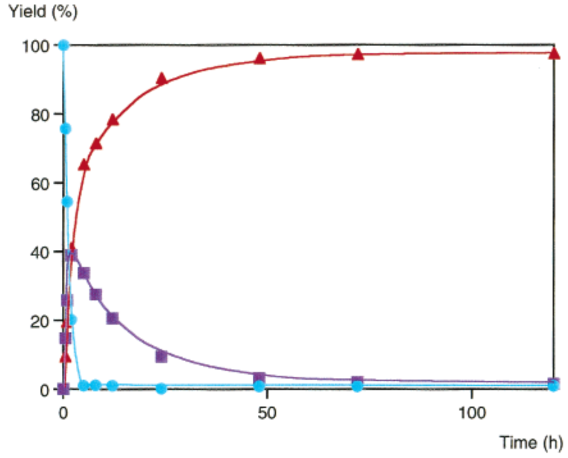


Figure 8. Reaction profiles for DBSA-catalyzed thioetherification of dodecanethiol with benzhydrol in water. Red triangle: for benzhydryl dodecyl sulfide. Purple square: for dibenzhydryl ether (the yield is based on the benzhydryl group used). Blue circle: for benzhydrol.

Not only the trityl thioether but also benzhydryl, 4-butoxybenzyl, and 4-methoxybenzyl thioethers were obtained in high yields (entries 2−4). Tritylation of other thiols such as benzyl thiol and thiophenol in water also gave the desired thioethers (entries 5 and 6). These results demonstrate that this direct thioetherification in water provides a useful method to protect thiols.

The reaction profile of the thioetherification of dodecanethiol with benzhydrol (1 equiv) is shown in Figure 8. In contrast to the etherification shown in Figure 7, the equilibrium positionof the thioetherification largely lies to the thioether side, affording the thioether in excellent yield. Although dibenzhydryl ether was generated in maximum yield of around 40% in 2 h, the yield declined and finally diminished at the equilibrium position. This result indicates that the formation of dibenzhydryl ether is kinetically comparable to the thioether formation but thermodynamically unfavorable under these conditions.

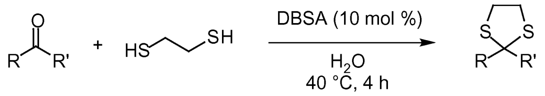
Dithioacetalization. Dithioacetals are useful in organic synthesis as protective groups for carbonyl compounds,[5b] as pre-

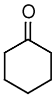
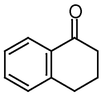
---

(29) log P_{oct} for dodecanol: 5.13, propanol: 0.25.[24]

(30) For examples of acid-catalyzed thioetherification in the presence of water, see: (a) Pastuszak, J. J.; Chimiak, A. *J. Org. Chem.* **1981**, *46*, 1868. (b) Breitschuh, R.; Seebach, D. *Synthesis* **1992**, 83. (c) Stewart, A. S.; Drey, C. N. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1753.

Table 10. DBSA-Catalyzed Dithioacetalization in Water

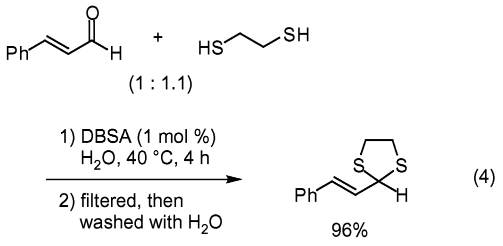


Entry	Carbonyl compound	Yield (%)[a]
1	PhCHO	94
2[b]	PhCHO	88
3	$CH_3(CH_2)_4CHO$	92
4[c]		82
5[c,d]		74

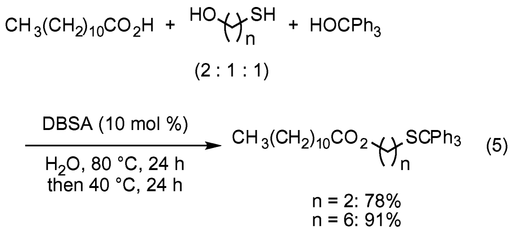
[a] Isolated yield. [b] 1,3-Propanedithiol was used instead of 1,2-ethanedithiol. [c] For 24 h. [d] At 80 °C.

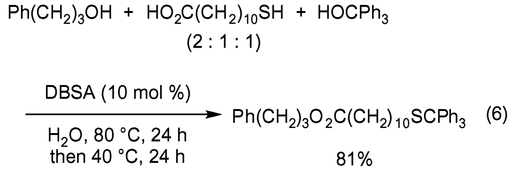
cursors of acyl carbanion equivalents,[31] or as electrophiles under Lewis acidic conditions.[32] The DBSA-catalyzed system was found to be also applicable to dithioacetalization in water[33] (Table 10). The reactions proceeded smoothly not only for aldehydes (entries 1−3) but also for ketones (entries 4 and 5) under mild conditions.

In addition, easy workup has been realized without the use of organic solvents when the products are solid and insoluble in water. In fact, the dithioacetalization of cinnamaldehyde on a 10 mmol scale with 1 mol % of DBSA proceeded smoothly to deposit crystals. The pure product was obtained in excellent yield after the crystals were filtered and washed with water (eq 4). This simple procedure is one of the advantages of the present reaction system.



Chemospecific Dehydration of Two Functional Groups. With several types of DBSA-catalyzed dehydration in hand, we tried chemospecific reactions of substrates having two reactive functional groups. As shown in eq 5, mercaptoalcohols such as 2-mercaptoethanol and 6-mercapto-1-hexanol were subjected to reactions in the presence of both triphenylmethanol and lauric acid in an aqueous solution of DBSA. These three-component reactions predominantly gave tritylthioalkyl laurates in high yields, accompanied with small amounts of tritylthioalcohols. It is noteworthy that the thiol parts of the mercaptoalcohols were selectively transformed to the thioethers and the alcohol parts to the esters. A chemospecific reaction of a mercaptocarboxylic acid was also possible as shown in eq 6. Under these conditions, thioester formation is thermodynamically unfavorable.[34] Thus, these chemospecificities are attributed to thermodynamic stability of the products and are controlled under equilibrium conditions.[35]





Conclusion

We have described dehydration reactions in water in the presence of DBSA as a Brønsted acid−surfactant-combined catalyst (BASC). This reaction system was found to be applicable to various reactions including esterification, etherification, thioetherification, and dithioacetalization. In addition, unique selective esterification and etherification have successfully been carried out, and interesting chemospecific reactions have also been realized. Detailed studies on the reactions have revealed the importance of the hydrophobic nature of DBSA and substrates. The reactions need neither dehydrating agents nor azeotropic removal of water. Instead, the catalyst and substrates in the present system assemble together through hydrophobic interactions to form emulsion droplets whose interior is hydrophobic enough to exclude water molecules. Furthermore, since both the sole byproduct and the solvent in the reactions are water, the reactions may lead to a method which solves some environmental problems. This work will not only lead to reaction systems which work in water but also provide a new aspect of organic chemistry in water.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Science.

Supporting Information Available: Experimental section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA026241J

---

(31) (a) Seebach, D. *Synthesis* **1969**, 17. (b) Ager, D. J. In *Umpoled Synthons. A Survey of Sources and Uses in Synthesis*; Hase, T. A. Ed.; John Wiley & Sons: New York; 1987.

(32) (a) Reetz, M. T.; Giannis, A. *Synth. Commun.* **1981**, *11*, 315. (b) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. (c) Ohshima, M.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1871. (d) Saigo, K.; Hashimoto, Y.; Kihara, N.; Hara, K.; Hasegawa, M. *Chem. Lett.* **1990**, 1097.

(33) For an example of dithioacetalization in water, see: Ceschi, M. A.; Felix, L. A.; Peppe, C. *Tetrahedron Lett.* **2000**, *41*, 9695.

(34) Thioester formation in the presence of water is thermodynamically unfavorable compared with ester formation: (a) Bruice, T. C. In *Organic Sulfur Compounds*; Kharasch, N., Ed.; Pergamon Press: New York; 1961. Formation of thioesters is also a kinetically unfavorable process under acidic conditions compared with ester formation. See: (b) Iimura, S.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2002**, 94.

(35) For examples of a similar type of reactions, see: (a) Scholl, T.; Roth, H. J. *Arch. Pharm. (Weinheim)* **1985**, *318*, 624. (b) Siedlecka, R.; Skarzewski, J. *Polish J. Chem.* **2000**, *74*, 1369.