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N,N-Diarylammonium Pyrosulfate as a Highly Effective Reverse Micelle-Type Catalyst for Hydrolysis of Esters

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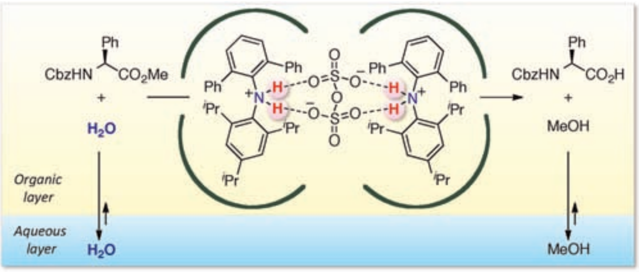
ABSTRACT



Reverse micelle-type *N,N*-diarylammonium pyrosulfate (3–5 mol %) efficiently catalyzes the hydrolysis of esters (up to 100 mmol scale) under organic solvent-free conditions. The present method is successfully applied to the hydrolysis of various esters without the decomposition of the base-sensitive moieties and without any loss of optical purity for α-heterosubstituted carboxylic acids.

The hydrolysis of esters is one of the most fundamental transformations in organic synthesis since esters are 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 irreversibly conducted using Brønsted bases such as LiOH and NaOH in a homogeneous solution.[2] Since the resulting carboxylic acids neutralize the Brønsted base, stoichiometric amounts of Brønsted bases are required to complete the reaction. In addition, after the reaction, stoichiometric amounts of strong Brønsted acids are required to acidify the resultant reaction mixture to obtain the carboxylic acids.

In sharp contrast, Brønsted acids catalytically promote the hydrolysis of esters.[3] Under organic/aqueous bilayer conditions, most Brønsted acid catalysts are ineffective because of their high solubility in water, while solid acids[4] such as Amberlite or zeolite can be used as catalysts.[5] When hydrophobic esters are hydrolyzed to hydrophobic carboxylic acids and hydrophilic alcohols or to hydrophilic carboxylic acids and hydrophobic alcohols, the reverse esterification should be suppressed under acidic organic/aqueous bilayer conditions, since the hydrophilic products are selectively removed to the aqueous layer. For this reaction system, oil-soluble hydrophobic small-molecule Brønsted acids would be more effective than these solid acid catalysts. Indeed, Okahata and colleagues reported that a lipid-coated lipase dissolved in the organic layer and showed 40- to 100-fold greater catalytic activity than the native lipase.[6]

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[§] CREST.

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(2) (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. (b) Theodorou, V.; Skobridis, K.; Tzakosb, A. G.; Ragoussis, V. *Tetrahedron Lett*. **2007**, *48*, 8230.

(3) For examples of the acid-catalyzed hydrolysis of esters under the homogeneous conditions, see: (a) Skeean, R. W.; Goel, O. P. *Synthesis* **1990**, 628. (b) Yamaguchi, S.; Mutoh, M.; Shimakura, M.; Tsuzuki, K.; Kawase, Y. *J. Heterocycl. Chem* **1991**, *28*, 119. (c) Hödl, C.; Raunegger, K.; Strommer, R.; Ecker, G.; Kunert, O.; Sturm, S.; Seger, C.; Haslinger, E.; Steiner, R.; Strauss, W. S. L.; Schramm, H.-W. *J. Med. Chem*. **2009**, *52*, 1268.

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(5) For examples of the solid acid-catalyzed hydrolysis of esters, see: (a) Ogawa, H.; Tensai, K.; Taya, K.; Chihara, T. *J. Chem. Soc., Chem. Commun*. **1990**, 1246. (b) Kimura, M.; Makato, T.; Okuhara, T. *Appl. Catal., A* **1997**, *165*, 227. (c) Iimura, S.; Manabe, K.; Kobayashi, S. *J. Org. Chem*. **2003**, *68*, 8723. (d) Delgado, P.; Sanz, M. T.; Beltrán, S. *Chem. Eng. J* **2007**, *126*, 111.

(6) Mori, T.; Kishimoto, S.; Ijiro, K.; Kobayashi, A.; Okahata, Y. *Biotechnol. Bioeng*. **2001**, *76*, 157.

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We recently reported that oil-soluble *N*,*N*-diarylammonium pyrosulfate **1** (Figure 1), which was prepared by mixing an equimolar amount of sulfuric acid and *N*-(2,4,6-triisopropylphenyl)-*N*-(2,6-diphenylphenyl)amine (**2**) at 80 °C for 0.5 h, was an efficient catalyst for ester condensation reactions between hydrophobic carboxylic acids and hydrophobic alcohols under aqueous conditions.[7,8] The high catalytic activity is attributed to the hydrophobic effect of the bulky aryl groups of the catalyst.[9,10] We report here a highly efficient hydrolysis of esters catalyzed by **1** under organic/aqueous bilayer conditions.

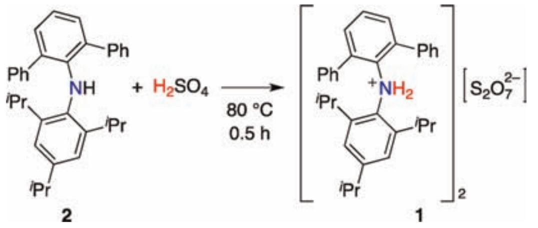
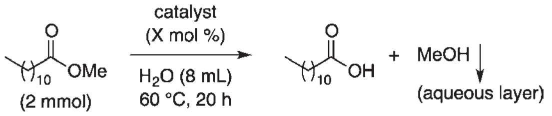


Figure 1. *N*,*N*-Diarylammonium pyrosulfate **1**.

We first examined the catalytic activity of **1** for the hydrolysis of methyl laurate under aqueous conditions (Table 1). When the reaction of methyl laurate (2 mmol) was conducted in the presence of **1** (5 mol %) and water (1 mL) at 60 °C for 20 h, lauric acid was obtained in 56% yield (entry 1). The yield was not improved by prolonging the reaction time. The low yield could be attributed to the rather low solubility of methanol in the aqueous layer. The use of 8 mL of water successfully improved the yield of lauric acid (86% yield, entry 2). Although the reaction mixture was an oil-in-water emulsion, the addition of NaOH (5 mol %) gave a clear separation of the organic substrate layer and the aqueous layer.[11] Thus, the crude lauric acid was easily obtained by simple decantation. When **1** was prepared under azeotropic reflux conditions in CH_3CN−hexane (1:1 v/v),[11] the catalytic activity increased (entry 3). Only 1 mol % of **1** was sufficient to give the lauric acid in 84% yield (entry 4).

Table 1. Catalytic Activities for the Hydrolysis of Methyl Laurate[a]



entry	catalyst	*X* (mol %)	yield[b] (%)
1[c]	**1**	5	56
2	**1**	5	86
3[d,e]	**1**	5	82
4[f]	**1**	1	84
5[g]	Amberlite IR 120-H	5	17
6	H_2SO_4	5	4
7	DBSA	5	77
8	LiOH	100	4 (6)[h]
9	Me_3SnOH	100	4

[a] The reaction of methyl laurate (2 mmol) was conducted with a catalyst (*X* mol %) in water (8 mL) at 60 °C for 20 h. [b] Determined by ^{1}H NMR analysis. [c] The reaction was conducted in water (1 mL). [d] Compound **1** was prepared by mixing an equimolar amount of sulfuric acid and **2** in CH_3CN−hexane (1:1 v/v) under azeotropic reflux conditions for 0.5 h. [e] For 8 h. [f] For 68 h. [g] The reaction was conducted under reflux conditions. [h] In the presence of Bu_4NBr (5 mol %).

On the other hand, Amberlite IR 120-H was ineffective even under reflux conditions (entry 5).[5] Hydrophilic sulfuric acid was almost inert under organic/aqueous bilayer conditions (entry 6). *p*-Dodecylbenzenesulfonic acid (DBSA)[12] catalyzed the hydrolysis of methyl laurate (entry 7). The reaction mixture catalyzed by DBSA also formed an oil-in-water emulsion. In contrast to the **1**-catalyzed reaction, the addition of NaOH (5 mol %) to the reaction mixture did not give a clear separation of the two layers,[11] since the sodium salt of DBSA might act as a surfactant. The initial rates of **1**-catalyzed hydrolysis were independent of the amounts of water (Figure 2A).[13] On the other hand, the initial rates of DBSA-catalyzed hydrolysis significantly depended on the amounts of water. The use of less amounts of water showed greater initial rates although yields of carboxylic acids were low because of the unfavorable equilibrium (Figure 2B). It is conceivable that catalyst **1** forms *reverse micelles in organic layer* to promote the hydrolysis.[7] In contrast, surfactant-type DBSA might promote the hydrolysis *on the surface of the oil-in-water emulsion*.[12] Since the use of larger amounts of water made the emulsion droplets smaller, the concentration of DBSA on the surface should decrease, which could result in lower reactivity in the DBSA-catalyzed hydrolysis.

Under organic/aqueous bilayer conditions, a conventional Brønsted base such as lithium hydroxide (100 mol %) was almost inert (entry 8). The addition of Bu_4NBr, a

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(8) Igarashi, T.; Yagyu, D.; Naito, T.; Okumura, Y.; Nakajo, T.; Mori, Y.; Kobayashi, S. *Appl. Catal., B* **2012**, *119–120*, 304.

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(13) In contrast to the hydrolysis of esters, the reactivity of **1**-catalyzed ester condensation in water became lower as the amounts of water increased.[7] The carboxylic acid used as a substrate might act as a surfactant in the early stage of the ester condensation to decrease the reactivity when larger amounts of water were used.

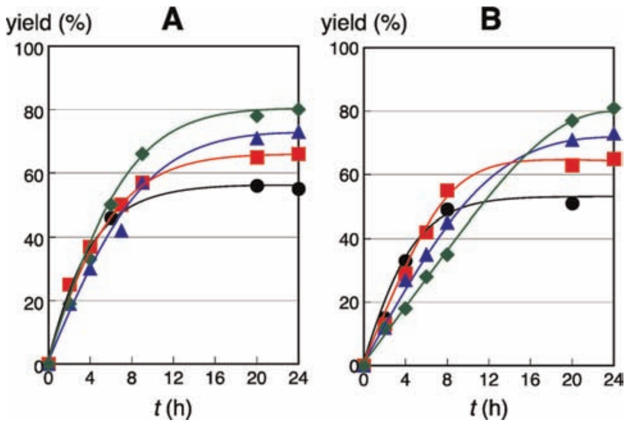
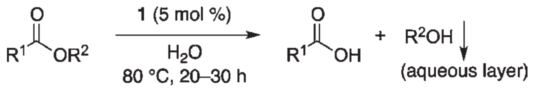
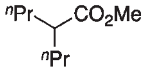
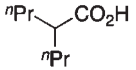
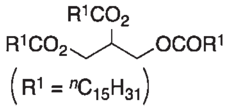
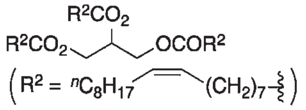
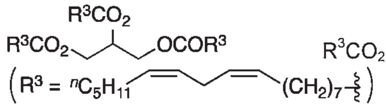


Figure 2. Plot of conversion versus time for the hydrolysis of methyl laurate: (A) catalyzed by **1**; (B) catalyzed by DBSA. Key: green, H_2O (8 mL); blue, H_2O (4 mL); red, H_2O (2 mL); black, H_2O (1 mL).

Table 2. **1**-Catalyzed Hydrolysis of Esters Composed of Hydrophobic Carboxylic Acids and Hydrophilic Alcohols[a]



entry	ester	carboxylic acid	yield (%)[b]
1[c]	${}^nC_{11}H_{23}CO_2Et$	${}^nC_{11}H_{23}CO_2H$	83
2			80
3[c]	$({}^nC_{11}H_{23}CO_2CH_2)_2$	${}^nC_{11}H_{23}CO_2H$	92
4[d]	${}^nC_{11}H_{23}CO_2{}^iPr$	${}^nC_{11}H_{23}CO_2H$	85
5		R^1CO_2H	95
6		R^2CO_2H	86
7[e]			82
8		R^3CO_2H	90

[a] The reaction of ester (1 mmol) was conducted with **1** (5 mol %) in water (4 mL) at 60 °C. [b] Determined by ^1H NMR analysis. [c] At 80 °C. [d] The reaction was conducted in water (8 mL/mmol). [e] The reaction of triolein (100 mmol) was conducted with **1** (3 mol %) in water (400 mL) at 80 °C for 56 h.

phase-transfer catalyst,[14] did not improve the reactivity. Trimethyltin hydroxide (100 mol %), a mild and effective promoter for the hydrolysis of esters in organic solvent,[15] was also inert (entry 9). The low activities of these alkaline catalysts might be attributed to their low solubilities in the organic substrate layer.

To explore the generality and scope of the present **1**-catalyzed method, the hydrolysis of various esters, composed of hydrophobic carboxylic acids and hydrophilic alcohols, were examined (Table 2). In these reactions, the hydrophilic alcohols were removed to the aqueous layer and the hydrophobic carboxylic acids remained as the organic substrate layer. The solubility of the generated alcohol in water was important for obtaining the corresponding carboxylic acid in high yield. Methyl, ethyl, and ethylene glyceryl esters (1 mmol) were smoothly hydrolyzed in the presence of water (4 mL) and gave the corresponding carboxylic acids in good yields (entries 1–3). A larger amount of water (8 mL) was required for the efficient hydrolysis of isopropyl laurate (1 mmol), since isopropyl alcohol is less soluble in water than methanol (entry 4). The present method could also be applied to the hydrolysis of triacylglycerols[16] in high yields without the isomerization of carbon–carbon double bonds (entries 5–8). The present protocol could be applied to a gram-scale reaction. The hydrolysis of triolein (89 g, 100 mmol) catalyzed by **1** (3 mol %) gave oleic acid in 82% yield (entry 7).

Next, we examined the hydrolysis of chiral α-heterosubstituted esters (Table 3). These esters are unstable under basic conditions and easily racemized.[17] For example, the conventional alkaline hydrolysis (method B) of (*S*)-methyl *O*-methylmandelate (entry 2), *N*-Cbz-L-phenylglycine methyl ester (entry 4),[18] and *N*-Cbz-*O*-benzyl-L-serine methyl ester (entry 6) resulted in epimerization, although the corresponding carboxylic acids were obtained in high yields. In contrast, **1**-catalyzed hydrolysis of these esters (method A) gave the corresponding carboxylic acids without any loss of optical purity (entries 1, 3, and 6). The present protocol could be conducted on a gram scale: 25 g of *N*-Cbz-L-phenylglycine was obtained in a single reaction (entry 4).

The present method could also be applied to esters bearing a base-sensitive group. For example, *N*-Fmoc-protected L-phenylalanine methyl ester was successfully hydrolyzed without cleavage of the Fmoc group by method A (entry 8). In contrast, under alkaline conditions (method B), the Fmoc group was completely removed and unprotected L-phenylalanine was generated (entry 9).[2] When the substrates and/or products were solid under the reaction conditions, the addition of a small amount of organic solvent

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(14) Crouch, R. D.; Burger, J. S.; Zietek, K. A.; Cadwallader, A. B.; Bedison, J. E. *Synlett* **2003**, 991.

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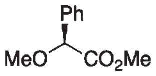
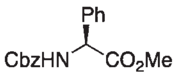
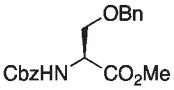
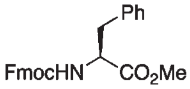
(19) (a) Orita, A.; Hamada, Y.; Nakano, T.; Toyoshima, S.; Otera, J. *Chem.—Eur. J.* **2001**, *7*, 3321. (b) Iwasaki, T.; Agura, K.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Chem.—Eur. J.* **2010**, *16*, 11567.

(20) Otera, J. *Acc. Chem. Res.* **2004**, *37*, 288.

Table 3. Hydrolysis of Base-Sensitive Optically Active Methyl Esters

entry	ester	conditions[a]	yield (%)[b]	*ee* (%)
1[c]		A	83	>99
2		B	94	97
3		A	80	>99
4[d]		A	86	>99
5		B	93	15
6		A	83	>99
7		B	94	65
8[e]		A	82	>99
9		B	0	nd

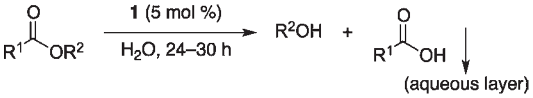
[a] Conditions A: The reaction of methyl ester (1 mmol, > 99% ee) was conducted with **1** (5 mol %) in water (4 mL) at 80 °C for 9 h. Conditions B: The reaction of methyl ester (1 mmol, > 99% ee) was conducted with LiOH (100 mol %) in water–MeOH–THF (2:2:1 v/v, 2.5 mL) at rt for 2–4 h. [b] Isolated yield. [c] For 20 h. [d] The reaction of *N*-Cbz-L-phenylglycine methyl ester (100 mmol) was conducted in the presence of **1** (1 mol %) in water (400 mL) at 80 °C for 9 h. [e] Water–$EtNO_2$ (13:1 v/v, 4.3 mL) was used as a solvent.

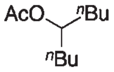
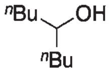
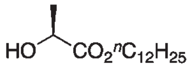
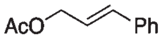
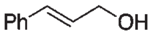
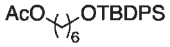
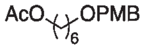
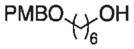
such as nitroethane was effective for dissolving the ester and promoting the hydrolysis (entry 8).

Next, the **1**-catalyzed hydrolysis of esters composed of hydrophobic alcohols and hydrophilic carboxylic acids was examined (Table 4).[19] In this case, the hydrophilic carboxylic acids were removed to the aqueous layer and the hydrophobic alcohols remained as the organic substrate layer. A variety of acetates and propionates were successfully converted to the corresponding alcohols (entries 1–3). The **1**-catalyzed hydrolysis of dodecyl isobutyrate gave 1-dodecanol in only 38% yield (entry 4). This is because isobutyric acid is not sufficiently soluble in water to transfer to the aqueous layer. The hydrolysis of 1-dodecyl L-lactate gave 1-dodecanol in 87% yield as the organic layer, while L-lactic acid was obtained from the aqueous layer after purification by ion-exchange chromatography (entry 5).[11]

In general, allylic esters and allylic alcohols are acid-sensitive, and the acid-catalyzed hydrolysis of allylic esters generates a significant amount of diallylic ethers as byproducts. In fact, the **1**-catalyzed hydrolysis of cinnamyl acetate[20] at 60 °C gave dicinnamyl ether in 15% yield along with cinnamyl alcohol (82%). 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 6). The hydrolysis of acetates bearing *tert*-butyldiphenylsilyl (TBDPS) (entry 7) or *p*-methoxybenzyl (PMB) (entry 8) groups afforded the corresponding alcohols without cleavage of these protecting groups.[2] However, highly acid-sensitive protecting groups such as *tert*-butyldimethylsilyloxy (TBSO) and tetrahydropyranyloxy (THPO) groups hydrolyzed more rapidly than an acetoxy group under the present reaction conditions.[11]

Table 4. 1-Catalyzed Hydrolysis of Esters Composed of Hydrophobic Alcohols and Hydrophilic Carboxylic Acids[a]



entry	ester	temp (°C)	alcohol	yield (%)[b]
1[c]	$AcO^nC_{12}H_{25}$	60	$^nC_{12}H_{25}OH$	86
2		80		89
3	$EtCO_2{}^nC_{12}H_{25}$	60	$^nC_{12}H_{25}OH$	74
4	$^iPrCO_2{}^nC_{12}H_{25}$	80	$^nC_{12}H_{25}OH$	38
5[d]		80	$^nC_{12}H_{25}OH$	87 [80][e]
6		40		92 [2][f]
7		40		88
8		40		86

[a] The reaction of ester (1 mmol) was conducted with **1** (5 mol %) in water (4 mL). [b] Determined by ^1H NMR analysis. [c] For 6 h. [d] For 4 h. [e] Isolated yield of L-lactic acid. [f] Yield of dicinnamyl ether.

In conclusion, reverse micelle-type *N*,*N*-diarylammonium pyrosulfate **1** highly efficiently catalyzed the hydrolysis of various esters under organic/aqueous bilayer conditions to give the corresponding carboxylic acids and/or alcohols in good yields. The present method was successfully applied to the hydrolysis of base-sensitive esters to give the corresponding carboxylic acids without decomposition of the base-sensitive moieties and without any loss of optical purity for α-heterosubstituted carboxylic acids.

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Supporting Information Available. Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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