Highly efficient and practical monohydrolysis of symmetric diesters

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Project Title:
Highly efficient and practical monohydrolysis of symmetric diesters

The most recent milestone:
The nominated technology yielded a patent application (U.S. Serial No. 12/156,448 and PCT/US08/06907) on May 30, 2008, which was licensed by Kishida Chemical Co., Ltd. on August 21, 2008, and Wako Chemicals USA, Inc. on November 30, 2009. It also received a National Science Foundation-CAREER award (February 1, 2003), the Japanese Society for Process Chemistry Award for Excellence (July 21, 2006), and the ACS PROGRESS/Dreyfus Lectureship Award (July 12, 2007). It also yielded 13 publications, and an additional manuscript is in preparation.

Eligibility:
The nominated technology is eligible for the academic award, and for the small business award.

Focus Area:
The nominated technology primarily falls into focus area 2, the use of greener reaction conditions. Focus area 1, the use of greener synthetic pathways, may also be a suitable area.

Activities that took place within the United States:
All of the research in the nominated technology was conducted in the U.S. One of the two licensees for this technology, Wako Chemicals USA, Inc., is located in the U.S.

Abstract:

Water is the least expensive solvent and among the most environmentally friendly solvents because it generates no hazard during chemical conversion processes. Water-mediated organic reactions thus represent a typical "green chemistry." Among various synthetic conversions, desymmetrization of symmetric compounds is one of the most atom-economical and cost-effective reactions, because the starting symmetric compounds are typically obtained easily on a large scale from inexpensive sources, or are commercially available inexpensively. Therefore, water-mediated desymmetrization of symmetric organic compounds would be of tremendous synthetic value, and would make a significant contribution to creating greener reaction processes.

Dr. Niwayama pioneered water-mediated desymmetrization and has been developing monohydrolysis of symmetric diesters with remarkable success. Half-esters, which are produced by such monohydrolysis of symmetric diesters, are versatile building blocks in organic synthesis, frequently applied to synthesis of polymers, dendrimers, and hyperbranched polymers with various characteristics and applications to industrial products, and thus have a commercial value. However, since the two ester groups in the symmetric diesters are equivalent, the statistically expected yield of half-esters would be a maximum of only 50%. Classical saponification usually affords complex mixtures of dicarboxylic acids, half-esters, and the starting diesters, which are difficult to separate, yielding a large amount of undesirable dirty waste. Ring-opening reactions of cyclic acid anhydrides require hazardous organic solvents. However, Dr. Niwayama discovered a highly efficient and practical ester monohydrolysis of symmetric diesters. In this reaction, aqueous NaOH or KOH is added to a symmetric diester suspended in water that may or may not contain a small amount of a co-solvent such as THF at 0°C. With this reaction, pure

half-esters are obtained in high to near-quantitative yields without production of dirty waste and without use of hazardous organic solvents. This reaction, which is anticipated to significantly contribute to green chemistry useful in both industry and academia, has been licensed by two companies, and several half-esters produced by this reaction have been commercialized.

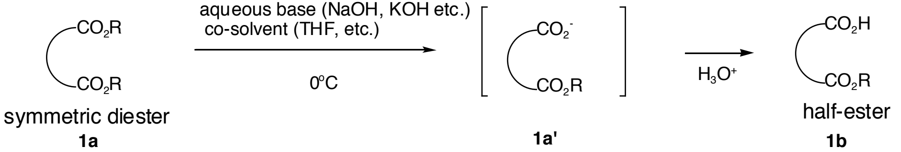
Description of nominated technology

Developing cost-effective and environmentally friendly organic synthetic methodologies has been of central importance in both academia and industry for synthesis of a variety of pharmaceuticals and biologically active compounds on a large scale. Water is among the most environmentally friendly and the least expensive solvents for such a purpose, and therefore water-mediated organic reactions represent a typical "green chemistry." Among the types of reactions, desymmetrization of symmetric compounds is one of the most atom-economical and cost-effective methods because the starting materials, symmetric compounds, are typically obtained easily on a large scale from inexpensive sources, or are commercially available at low cost. Therefore desymmetrization of symmetric compounds mediated by water would make a significant contribution to advancement of greener reaction conditions and/or greener synthetic pathways.

Organic compounds generally have limited solubility in water, and therefore successful organic reactions in aqueous media are still limited. Furthermore, these reported reactions do not necessarily show improvement of the reactivity and/or selectivity compared to those in organic solvents. Many of them also require many steps before the reactions are conducted in aqueous media.

However, the selective monohydrolysis reaction in the nominated technology is unique in that it enables a water-mediated desymmetrization with extremely high selectivity and reactivity hitherto impossible in the organic media, due to the fact that organic compounds are insoluble in water (Scheme 1). This is the first water-mediated reaction applied to desymmetrization.[1]

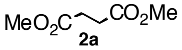
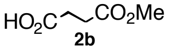
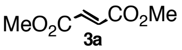
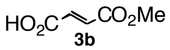
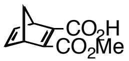
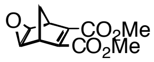
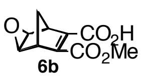
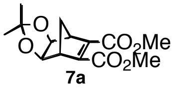
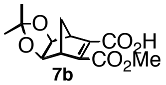
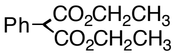
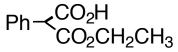
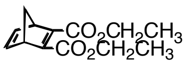
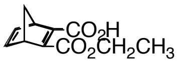
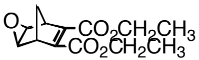
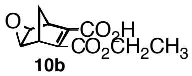
Scheme 1



This reaction employs an aqueous medium, in which aqueous NaOH or KOH is added to a symmetric diester that may be dissolved in a small amount (7% or less) of THF, CH_3CN, or another polar aprotic co-solvent diluted with ten times the volume of water at 0°C. As will be described below, this co-solvent is unnecessary in many cases. With this reaction, pure half-esters were obtained in high yields to near-quantitative yields, despite the fact that the statistically expected yield is a maximum of only 50%.

Half-esters, which are produced by such desymmetrization of symmetric diesters, are very versatile building blocks in organic synthesis, and their derivatives are also frequently applied to synthesis of polymers, dendrimers, and hyperbranched polymers with various characteristic and applications to industrial products such as films, adhesives, coatings, dental restoratives, and high loading solid-phase supports. Therefore they generally have tremendous commercial value. The starting symmetric diesters are also typically obtained easily on a large scale starting from inexpensive sources, or are commercially available at low cost. Table 1 summarizes the representative results of this reaction. These results were first published in *J. Org. Chem.*[1a] and were featured in an article about chemical process development in Chemical and Engineering News in 2001.[1b] Dr. Niwayama's invention of this reaction also yielded funding by the National Science Foundation-CAREER Award in 2003, and the American Chemical Society PROGRESS/Dreyfus Lectureship Award in 2007. From the international scientific community, her invention of this reaction was also recognized with the Banyu Award in Synthetic Organic Chemistry in 2002, and the Japanese Society for Process Chemistry Award for Excellence in 2006. Banyu is the Japanese branch of Merck. Furthermore, this reaction was licensed by Kishida Chemical Co., Ltd. in 2008, and Wako Chemicals, U.S.A. in 2009, and thus far, ten kinds of half-esters synthesized by the reaction have become commercially available.

Table 1 Monohydrolysis of Symmetric Diesters

entry	diester	product	yield (%)[a]
1	 **2a**	 **2b**	80%
2	 **3a**	 **3b**	79%
3	 **4a**	 **4b**	95%[b]
4	 **5a**	 **5b**	>99%
5	 **6a**	 **6b**	>99%
6	 **7a**	 **7b**	>99%
7	 **8a**	 **8b**	94%
8	 **9a**	 **9b**	>99%
9	 **10a**	 **10b**	>99%

[a] Yields are isolated yields from silica gel column chromatography based on the amounts of the diesters submitted to the reaction.

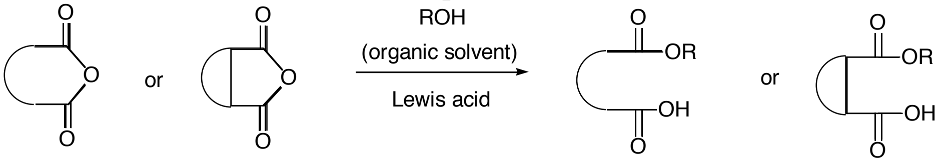
[b] The yield was diminished due to the slight volatility of **4b**.

The typical reaction procedures are as follows: A diester (1.20 mmol) is suspended in 20 mL of water. The diester may be dissolved in less than 7% volume of a co-solvent. The reaction mixture is cooled to 0 °C in an ice-water bath. To this mixture is added approximately 1-2 equivalents of 0.25 M aqueous NaOH or KOH solution dropwise with stirring. The reaction mixture is stirred until the starting diester is consumed, acidified with 1M HCl at 0 °C, saturated with NaCl, extracted with ethyl acetate (X4), and dried over Na_2SO_4. This extract is concentrated *in vacuo* and purified by silica gel column chromatography. For a larger scale, instead of extraction of the products with ethyl acetate, the products can be salted out.

The procedures are simple, and the reaction mixtures were quite clean unlike the mixtures that result from classical saponification, and therefore the isolation and purification of the resultant half-esters after the routine procedure was straightforward in all the cases thus far tried. In most cases, the silica gel column chromatography was practically unnecessary for further use, making this reaction feasible for industrial processes. Under these conditions, a base-labile functional group (epoxy group) remained intact as well. Even for the cases in which the yields of the corresponding half-esters are not quantitative, the only by-products are a small amount of the corresponding diacids, which can be re-submitted to the monohydrolysis reaction after the simple conversion of them to the starting diesters. Therefore this selective monohydrolysis reaction produces no waste, unlike classical saponification, which typically yields a large amount of undesirable solid and/or liquid waste, polluting the environment.

Another common approach for synthesis of half-esters has been the ring opening of cyclic acid anhydrides with alcohols and an organic solvent such as toluene, benzene, ethers, or chloroform, etc., and Lewis acids (Scheme 2).[2] However, these ring-opening reactions require anhydrous conditions with a dry organic solvent, many of which are classified as hazardous. These ring-opening reactions also require the stereochemistry of the formed cyclic half-esters to be *cis*, while the water-mediated selective monohydrolysis reaction Dr. Niwayama reported can produce any kind of half-esters with far lesser impact on human health and the environment.

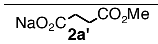
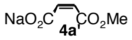
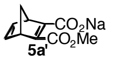
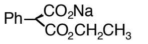
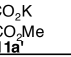
Scheme 2

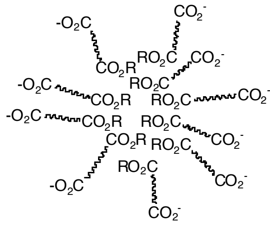


Although in theory a half-ester may be prepared by selective monoesterification starting from a symmetric diacid, organic diacids are usually very difficult to isolate by routine methods such as column chromatography because of limited solubilities in organic solvents and in aqueous media, and therefore preparation of diacids tends to require unusually large amounts of organic solvents. Overall, compared to other existing methods for synthesis of half-esters, the nominated technology of selective monohydrolysis is the most cost effective, the greenest, and productive of the most diverse range of half-esters with among the highest yields.

The reason for the high selectivity remains uncertain. However, Dr. Niwayama has hypothesized that once one of the carboalkoxy groups is converted to a carboxylate anion, it may form micelle-like aggregates in which the hydrophobic carboalkoxy group is pointed inside and the hydrophilic COO$^-$ is pointed outside. This aggregate is expected to prohibit further hydrolysis by the aqueous base solution. Dr. Niwayama recently observed such aggregations for several kinds of the intermediate carboxylate anions by dynamic light-scattering experiments.[3] The Zeta potential and particle diameter in Table 2 shows that several kinds of carboxylates form micelle-like aggregates with minus charges under the reaction conditions.

Table 2 Zeta potentials and particle diameters of various half-esters in THF/H_2O at 4°C.

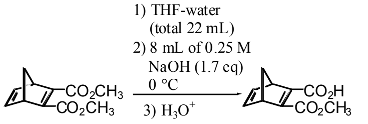
Intermediate half-ester	concentration (mM)	Zeta potential (mV)	particle diameter (nm)
 **2a'**	40 100	-37.0±0.7 -26.4±0.6	250±50 400±100
 **4a'**	40 100	-29.6±1.8 -16.3±0.7	550±100 350±50
 **5a'**	40 100	-29.0±2.6 -22.3±0.9	250±50 400±100
 **8a'**	40 100	-39.8±0.9 -28.4±0.9	200±50 150±50
 **11a'**	40 100	-45.3±2.0 -24.0±3.5	350±50 600±100



potential intermediate

According to this reaction mechanism, the reaction media (solvent) should play an important role. Dr. Niwayama conducted kinetic studies on this monohydrolysis reaction by measuring the reaction rate of monohydrolysis of a diester, **5a**, changing the proportion of water and a typical co-solvent, THF, and also varying the co-solvents from THF.[4] It has been found that using only a small amount (7% or less) of a polar aprotic solvent that is water-miscible such as THF and CH_3CN increases the reaction rates and selectivity. Therefore, in the reaction mixture, the small amount of THF is dissolved in the larger amount of water, making one aqueous phase, and the diester participates in the reaction as the second phase, which is an organic phase, and the monohydrolysis occurs at the interface between the aqueous phase and the diester. Therefore, the monohydrolysis occurs even without a co-solvent, and the co-solvent helps dissolve and disperse the starting diesters effectively. The aggregates are expected to form more tightly by maximizing hydrophobic attractive interactions in this mainly aqueous media as in the hypothesis. An alcohol was observed to be a less effective co-solvent because it interferes with the aggregates formed by the hydrophobic attractive interaction of the intermediary carboxylate, which is also consistent with the hypothesis. This role of co-solvent is particularly advantageous when the starting diester is a solid, while the conditions free from an organic solvent are also anticipated to offer another practical advantage as a green reaction.

Table 3 Effect of volume of THF



5a (1.2 mmol) **5b**

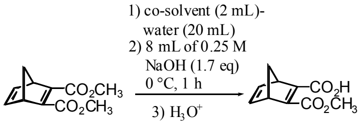
Volume (mL) of THF[a]	Time	Yield (%)[b]	Reaction rate constant ($L \cdot mol^{-1} \cdot s^{-1}$)
22 (73%)	8 h	88 (0)	$3.26 \pm 0.02 \times 10^{-3}$
18 (60%)	6 h 30 min	81 (1.2)	$6.06 \pm 0.12 \times 10^{-3}$
14 (47%)	5 h 20 min	84 (0.4)	$1.10 \pm 0.02 \times 10^{-2}$
10 (33%)	3 h	90 (1.6)	$2.06 \pm 0.23 \times 10^{-2}$
6 (20%)	70 min	94 (1.2)	$2.56 \pm 0.06 \times 10^{-2}$
2 (7%)c	70 min	>99 (0)	$4.70 \pm 0.02 \times 10^{-2}$
1 (3%)	70 min	>99 (0)	$4.81 \pm 0.10 \times 10^{-2}$
0 (0%)	70 min	>99 (0)	$4.59 \pm 0.07 \times 10^{-2}$

[a] Percentage of THF(v/v) is shown in parenthesis.

[b] Isolated yield of **5b**. Recovered **5a** is shown in parenthesis.

[c] The same conditions reported before.[1a]

Table 4 Effects of co-solvents



5a (1.2 mmol) **5b**

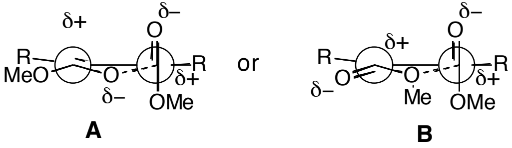
Co-solvent	Yield (%)[a]	Reaction rate constant ($L \cdot mol^{-1} \cdot s^{-1}$)
THF[b]	>99 (0)	$4.70 \pm 0.02 \times 10^{-2}$
CH_3CN	>99 (0)	$4.85 \pm 0.40 \times 10^{-2}$
methanol	90 (0.8)	$3.73 \pm 0.50 \times 10^{-2}$
ethanol	86 (0)	$3.48 \pm 0.06 \times 10^{-2}$
2-propanol	88 (0.8)	$3.29 \pm 0.02 \times 10^{-2}$
CH_2Cl_2	9 (89)	$8.60 \pm 0.27 \times 10^{-4}$
None	>99 (0)	$4.59 \pm 0.07 \times 10^{-2}$

[a] Isolated yield of **5b**. Recovered **5a** is shown in parenthesis.

[b] The same conditions reported before.[1a]

Another factor likely to contribute to the selectivity *before* formation of the mono-carboxylate is some conformational effect, as particularly high selectivity was observed for diesters with two ester groups in close proximity, as in **4a**-**10a** in Table 1. Therefore, there may be some conformational bias, as in A or B, due to electrostatic interactions between the two closely located carboalkoxy groups in these diesters, which might facilitate the hydrolysis of a carboalkoxy group from one particular direction.

Scheme 3

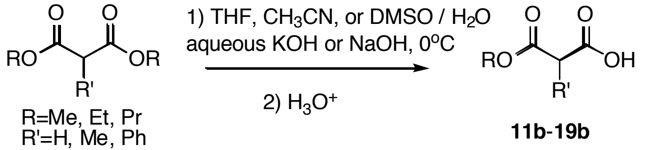


Dr. Niwayama and her students conducted theoretical studies on the conformational search of several symmetric diesters, and found several symmetric diesters, including linear diesters such as dimethyl succinate, possessing the conformations close to A or B to be the most stable.[5] A bonding interaction has also been found between the lone pair of a carbonyl oxygen and the antibonding orbital of the other C=O according to the natural bond orbital (NBO) analysis. The same interaction, referred to as the n->π* interaction, has also been proposed to explain amide carbonyl-carbonyl interactions in protein folding.[6] It is natural that the same concept can be extended to other organic molecules to explain various reactivities, and Dr. Niwayama's finding in this particular confirmation and interaction is among the first examples that demonstrates the n->π* interaction. This conformation has been proven by X-ray analysis of a similar symmetric diester, **7a**, above, which showed conformations similar to A or B above.[7]

Dr. Niwayama also obtained an additional piece of information regarding this geometrical trend. When the base was switched from NaOH to LiOH, KOH, and CsOH in the selective monohydrolysis of an acyclic dimethyl glutarate, the highest selectivity was observed with the use of KOH, despite the fact that KOH has higher reactivity than LiOH or NaOH. This selectivity was roughly correlated with the electropositive character of the counter cations, and therefore the more electropositive counter cation (K^+) more effectively coordinates on the carbonyl groups. Dr. Niwayama thus hypothesized that K^+ showed higher selectivity by more effectively bringing the two ester groups into close proximity for the discrimination to occur.[8]

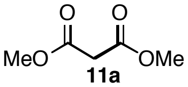
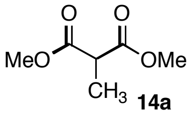
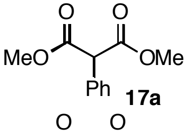
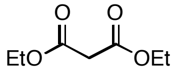
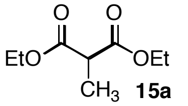
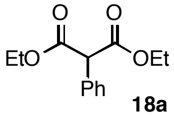
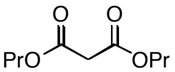
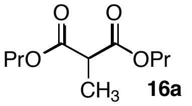
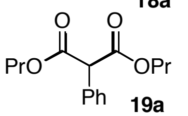
Based on the information from the above studies, Dr. Niwayama and her students have been successful in finding reaction conditions sufficiently improved to maximize the yield of monohydrolysis of acyclic symmetric diesters such as dialkyl malonates as well, by modification of the amounts and types of bases and co-solvents. Table 5 below shows some examples.

Table 5 Selective monohydrolysis dialkyl malonate derivatives



R=Me, Et, Pr
R'=H, Me, Ph
11a-19a

11b-19b

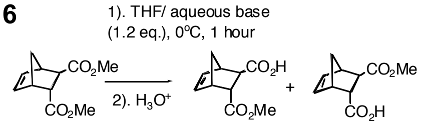
diester	time	half-ester (%)^a	diester	time	half-ester (%)^a	diester	time	half-ester (%)^a
 **11a**	1 h	84	 **14a**	1.5 h	94 (2)	 **17a**	1 h	95 (5)
 **12a**	1 h	86 (3)	 **15a**	1.5 h	96 (4)	 **18a**	5 h	94 (4)
 **13a**	1 h	92 (8)	 **16a**	1.75 h	98 (2)	 **19a**	33 h	80 (20)

^{a}Isolated yield of the half-ester. The recovered diester is shown in the parentheses (%).

Although half-esters of malonic acid derivatives are difficult to synthesize because of potential decarboxylation and therefore a limited number of examples have been reported,[9a-c] Dr. Niwayama has been able to obtain nearly quantitative yields of half-esters of several alkyl malonates and their derivatives as a pure form by this highly practical reaction.[10] The reaction conditions are also effective even on a mole scale.[11]

In addition, while studying the structural effects of the reaction, we found a unique feature in the selectivities of desymmetrization of symmetric and semi-symmetric diesters that are norbornene/norbornane derivatives.[12] We found that the relative reaction rates of the *exo*-ester groups are faster than those of the *endo*-ester groups. Although *exo*/*endo* facial selectivities of electrophilic, nucleophilic or cyclic additions to norbornene or 2-norbornanone derivatives have been studied extensively, and known to show high *exo*-selectivity, no study had previously been reported for reactions that occur on the carbon that is one covalent bond away from the norbornene/norbornane ring, as the difference in the steric environment between the *exo* and the *endo* direction is considered insignificant. These diesters also have "*trans*" stereochemistry, but we found the yields for monohydrolysis were near-quantitative. Tables 6 and 7 below are some examples.

Table 6

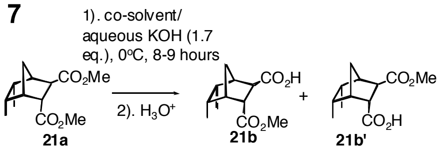


20a **20b** **20b'**

entry	base	half-ester 20b+20b'(%)^a	ratio 20b:20b'
1	LiOH	77 (22)	79:21
2	NaOH	93 (4)	78:22
3	KOH	97 (2)	80:20

^{a}Isolated yield of the half-ester. The recovered diester is shown in parentheses (%).

Table 7



21a **21b** **21b'**

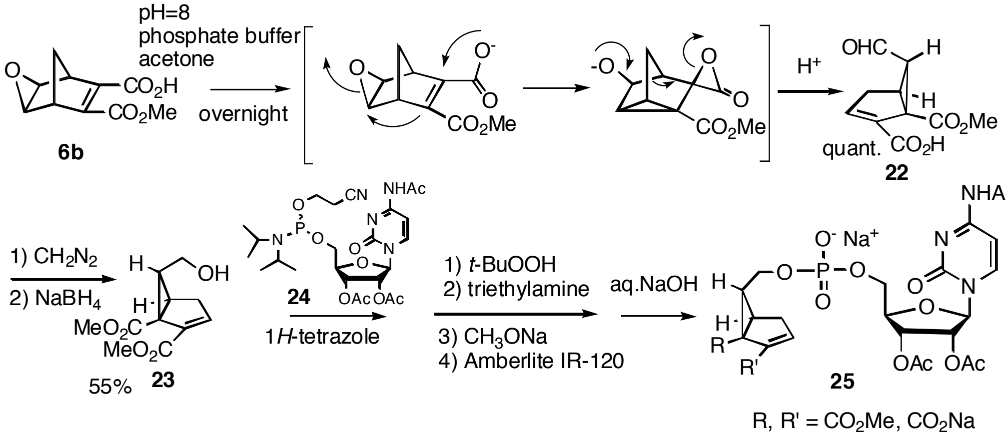
entry	co-solvent	half-ester 21b+21b"(%)^a	ratio 21b:21b'
1	CH$_3$CN	99	100:0
2	DMSO	99	100:0

^{a}Isolated yield of the half-ester. The recovered diester is shown in parentheses (%).

In these studies, we applied the effects of the co-solvent and type of bases described above, which contributed substantially to maximizing the reactivity and selectivity, as a relatively polar aprotic solvent such as DMSO or acetonitrile improved the selectivity and reactivity significantly, especially for **21**.

Dr. Niwayama also applied this selective monohydrolysis reaction to synthesis of a library of cytidine monophosphate *N*-acetylneuraminic acid (CMP-Neu5Ac) analogues, **25** (Scheme 4).[13] These analogues are expected to serve as inhibitors of sialyltransferases, enzymes for transfer of sialic acids from CMP-Neu5Ac to growing oligosaccharides, the processes of which are implicated in various diseases like cancer.

Scheme 4



Dr. Niwayama pioneered the invention of water-mediated desymmetrization reactions, combining fundamental knowledge of basic science and a practical aspect of process chemistry that is environmentally benign. Therefore, her invention of the selective monohydrolysis of symmetric diesters is expected to continue to advance the field of green chemistry.

References:

1. (a) Niwayama, S. *J. Org. Chem.* **2000**, *65*, 5834-5836. (b) Chemical and Engineering News, January 22, **2001**, p92-94. (c) Niwayama, S. *J. Synth. Org. Chem., Jpn.* **2008**, *66*, 983-994.
2. For example, (a) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc. Perkin Trans. I*, **1987**, 1053-1058. (b) Sabitha, G.; Srividya, R.; Yadav, J. S. *Tetrahedron* **1999**, *55*, 4055-4018. (c) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542-9543. (d) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, *2*, 195-195.
3. Niwayama, S.; Hiraga, Y. Manuscript in preparation.
4. Niwayama, S.; Wang, H.; Hiraga, Y.; Clayton, J. C. *Tetrahedron Lett.*, **2007**, *48*, 8508-8510.
5. Cho, H.; Alexander, R. B.; Niwayama, S. Manuscript submitted for publication.
6. Hodges, J. A.; Raines, R. T. *Org. Lett.* **2006**, *8*, 4695-4697.
7. Niwayama, S.; Inouye, Y.; Eastman, M. *Tetrahedron Lett.* **1999**, *40*, 5961-5965.
8. Niwayama, S.; Rimkus, A. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 498-500.
9. For example, (a) Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 5897-5905. (b) Grakauskas, V.; Guest, A. M. *J. Org. Chem.* **1978**, *43*, 3485-3488. (c) Strube, R. E. *Org. Synth.* **1963**, Col. Vol. IV, 417-419.
10. Niwayama, S.; Cho, H.; Lin, C. *Tetrahedron Lett.* **2008**, *49*, 4434-4436.
11. Niwayama, S.; Cho, H. *Chem. Pharm. Bull.* **2009**, *57*, 508-510.
12. (a) Niwayama, S.; Cho, H.; Zabet-Moghaddam, M.; Whittlesey, B. R. *J. Org. Chem.* **2010**, *75,* 3775-3780. (b) Niwayama, S.; Hiraga, Y. *Tetrahedron Lett.*, **2003**, *44*, 8567-8670.
13. Niwayama, S.; Kandula, V. S.; Wang, H.; Chen, X. *Tetrahedron Lett.* **2007**, *48*, 8757-8760.