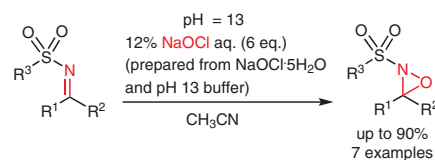


# A Concise, Catalyst-Free Synthesis of Davis' Oxaziridines using Sodium Hypochlorite

Saori Kitagawa<sup>a</sup>Hiromitsu Mori<sup>a</sup>Tatsuya Odagiri<sup>b</sup>Katsuya Suzuki<sup>a</sup>You Kikkawa<sup>a</sup>Rie Osugi<sup>a</sup>Shinobu Takizawa<sup>c</sup>Yoshikazu Kimura<sup>d</sup>Masayuki Kirihara<sup>\*a</sup>

Reactions were conducted in the absence of catalyst  
Environmentally benign oxidant NaOCl was used  
Simple method  
Mild reaction conditions (0 °C to r.t.; 30 min)

<sup>a</sup> Department of Materials and Life Science, Shizuoka Institute of Science and Technology, 2200-2 Toyosawa, Fukuroi, Shizuoka 437-8555, Japan  
kirihara.masayuki@sist.ac.jp

<sup>b</sup> R&D Department of Chemicals, Nippon Light Metal Company, Ltd., Kambara, Shimizu-ku, Shizuoka 421-3203, Japan

<sup>c</sup> The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki-shi, Osaka 567-0047, Japan

<sup>d</sup> Research and Development Department, Iharanikkei Chemical Industry Co. Ltd., Kambara, Shimizu-ku, Shizuoka 421-3203, Japan

Received: 15.12.2018

Accepted after revision: 23.01.2019

Published online: 19.02.2019

DOI: 10.1055/s-0037-1611722; Art ID: so-2018-d0064-op

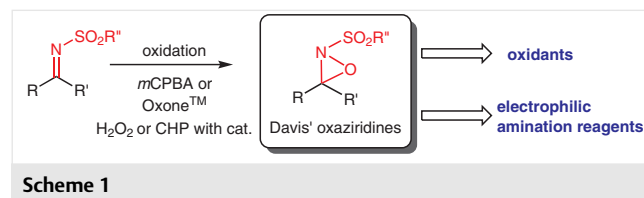
License terms:

**Abstract** *N*-Sulfonyloxaziridines (Davis' oxaziridines) can be synthesized by reacting the corresponding *N*-sulfonylimines with aqueous sodium hypochlorite in acetonitrile without any catalyst. The pH of the aqueous sodium hypochlorite is crucial to obtain the product in high yield. Optimized conditions are presented that allow synthetically useful Davis' oxaziridines to be easily obtained in up to 90% yields from the corresponding imines by using inexpensive, stable, environmentally friendly sodium hypochlorite pentahydrate crystals as the oxidant, with high reproducibility.

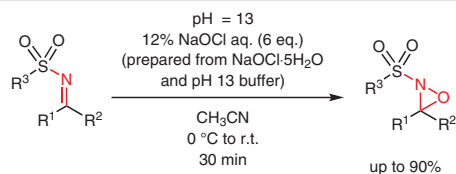
**Key words** oxaziridine, Davis' oxaziridine, sodium hypochlorite, sodium hypochlorite pentahydrate, *N*-sulfonylimine, oxidation

Oxaziridines contain a strained three-membered ring consisting of a carbon, nitrogen, and oxygen atom. They are interesting reagents in organic synthetic chemistry because they can be used both as oxidizing and electrophilic amination reagents.<sup>1</sup> Of the oxaziridines, *N*-sulfonyloxaziridines are the most extensively utilized in organic synthesis because of their stability. In the 1980s, Davis and co-workers developed the chemistry of *N*-sulfonyloxaziridines extensively, thus such compounds are commonly referred to as 'Davis' oxaziridines'.<sup>2</sup> They are generally prepared through oxidation of the corresponding imine, and several oxidants

(*m*-chloroperbenzoic acid,<sup>2a,3a-d</sup> Oxone<sup>TM</sup>,<sup>2b</sup> hydrogen peroxide or cumene hydroperoxide (CHP)<sup>3h</sup> with a catalyst<sup>3e-g</sup>) have been used for this purpose (Scheme 1).

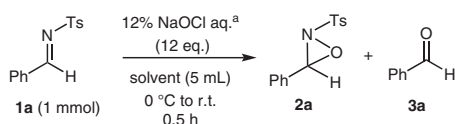


Sodium hypochlorite (NaOCl) is an ideal oxidant in organic synthesis,<sup>4</sup> because it produces only non-toxic sodium chloride (NaCl) as a by-product following oxidation, and commercial aqueous NaOCl is non-explosive and inexpensive. Recently, we found that stable, crystalline sodium hypochlorite pentahydrate (NaOCl·5H<sub>2</sub>O),<sup>5</sup> which is now commercially available from several companies, is a very useful oxidant for the nitroso radical-catalyzed oxidation of alcohols,<sup>5b,5c</sup> as well as the oxidation of organosulfur compounds.<sup>5d,5e</sup> However neither of these practical, environmentally friendly oxidants, aq. NaOCl or NaOCl·5H<sub>2</sub>O, have been used for the preparation of Davis' oxaziridines. In this paper, we report the concise, catalyst-free preparation of Davis' oxaziridines via reaction of *N*-sulfonyl imines in aqueous acetonitrile with NaOCl under basic conditions (Scheme 2).



Scheme 2

In initial optimization studies, *N*-tosylimine (**1a**) derived from benzaldehyde (**3a**) was chosen as a substrate, and treated with conventional 12% aqueous NaOCl in several solvents (Table 1). The desired oxaziridine **2a** was produced efficiently in acetonitrile (entry 1). On the other hand, hydrolysis of the imine **1a** predominated in other solvents, regenerating **3a** (entries 2–4).

Table 1 Solvent Effect for the reaction of **1a** with NaOCl

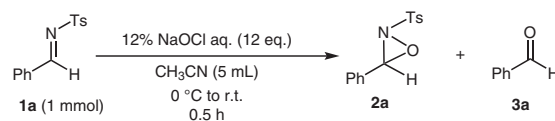
Entry	Solvent	Time (h)	<sup>1</sup> H NMR ratio		
			<b>1a</b>	<b>2a</b>	<b>3a</b> <sup>b</sup>
1	CH <sub>3</sub> CN	0.5	0	85	15
2	<i>t</i> -BuOH	5	1	5	94
3	CH <sub>2</sub> Cl <sub>2</sub>	24	8	57	35
4	toluene	24	0	3	97

<sup>a</sup> Conventional aqueous solution was used.

<sup>b</sup> *p*-Toluenesulfonylamide was produced as the side-product from hydration of **1a**.

In our effort to explore the use of environmentally benign oxidants, NaOCl·5H<sub>2</sub>O proved to be superior to conventional, commercial aqueous NaOCl in this type of reaction. Therefore, the reaction of **1a** with 12% aqueous NaOCl, freshly prepared from crystalline NaOCl·5H<sub>2</sub>O, was examined (Table 2). Contrary to our expectation, the desired oxaziridine **2a** was obtained in low yield, accompanied by a large amount of benzaldehyde **3a**, produced from the hydration of **1a** (entry 2) as with the alternative solvent above.

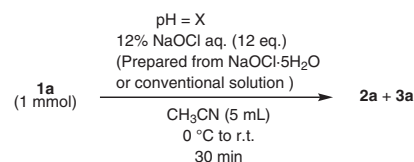
Table 2 Comparison of Conventional vs. Freshly Prepared 12% aq. NaOCl



Entry	12% NaOCl aq.	pH	<sup>1</sup> H NMR ratio	
			<b>2a</b>	<b>3a</b>
1	conventional aq. solution	13	85	15
2	prepared from NaOCl·5H <sub>2</sub> O	11	10	90

The main difference between conventional aqueous NaOCl and an aqueous solution prepared from NaOCl·5H<sub>2</sub>O crystals is the pH.<sup>5</sup> As shown in Table 2, the pH of the former was 13, and the pH of the latter was 11. In our previous work<sup>5b,5c</sup> on the nitroso radical-catalyzed oxidation of alcohols and the catalyst-free oxidation of sulfides to sulfoxides with NaOCl·5H<sub>2</sub>O, we observed that the pH of the aqueous NaOCl solutions dramatically influenced oxidation reactivity. Therefore, the reactivity of the 12% NaOCl aqueous solutions prepared from NaOCl·5H<sub>2</sub>O was evaluated while altering the pH with HCl or NaOH (Table 3).

Table 3 Reactivity of aq 12% NaOCl with Varying pH



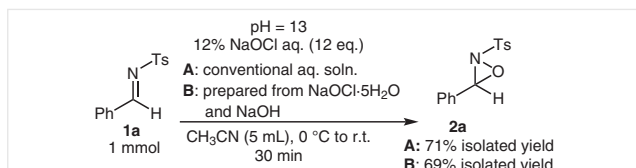
Entry	pH	12% NaOCl aq.	<sup>1</sup> H NMR ratio	
			<b>2a</b>	<b>3a</b>
1	14 <sup>a</sup>	Prepared from NaOCl·5H <sub>2</sub> O	68	32
2	14 <sup>a</sup>	Conventional solution	81	19
3	13 <sup>a</sup>	Prepared from NaOCl·5H <sub>2</sub> O	87	13
4	13 <sup>a</sup>	Conventional solution	85	15
5	12 <sup>a</sup>	Prepared from NaOCl·5H <sub>2</sub> O	26	74
6	12 <sup>b</sup>	Conventional solution	30	70 <sup>c</sup>
7	10 <sup>b</sup>	Prepared from NaOCl·5H <sub>2</sub> O	0	100 <sup>c</sup>
8	10 <sup>b</sup>	Conventional solution	0	0 <sup>c</sup>

<sup>a</sup> pH was adjusted using 12.5 M aqueous NaOH.

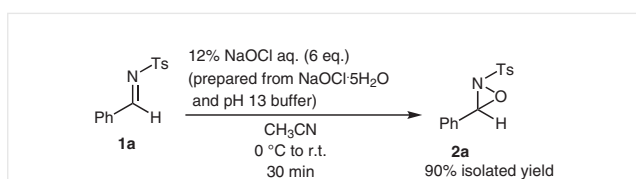
<sup>b</sup> pH was adjusted using conc. HCl.

<sup>c</sup> Formation of benzoic acid was detected.

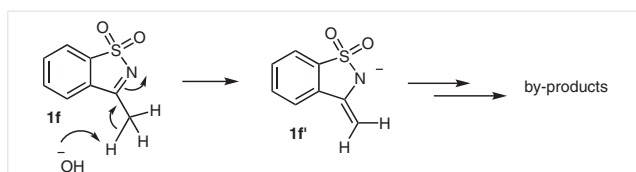
As we had proposed, the reactivity of **1a** toward NaOCl depended on the pH of the reaction mixture. A pH of 13 optimized the outcome (entries 3 and 4), and **2a** was obtained in good isolated yields (71% and 69%) as shown in Scheme 3.



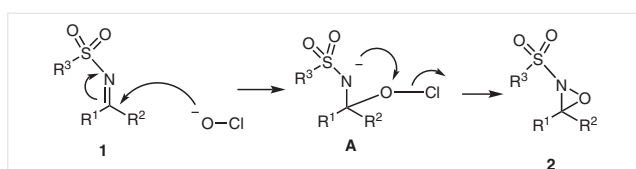
Further screening of the reaction conditions revealed that 6 equivalents of 12% aqueous NaOCl solution, prepared from NaOCl·5H<sub>2</sub>O with commercial pH 13 buffer (KCl-NaOH) in acetonitrile, afforded **1a** in 90% isolated yield (Scheme 4).



Several sulfonylimines **1** were then treated with aqueous NaOCl under the optimized conditions using CH<sub>3</sub>CN as the solvent, including the optically active substrate **1g** (Table 4). In most cases, the corresponding oxaziridine **2** was obtained in moderate to high yield. In the case of **1f**, the desired **2f** was obtained in only 4% yield accompanied by several unidentified by-products. Since the reaction conditions were basic, the acidic methyl proton of **1f** might be removed, and the resulting anion **1f<sup>-</sup>** converted into several by-products (Scheme 5).



A plausible reaction mechanism for the formation of **2** is depicted in Scheme 6. A hypochlorite anion attacks the imine carbon of **1** to produce intermediate **A** and then the amide anion attacks the oxygen atom to produce the oxaziridine **2**. Strongly basic conditions are required to prevent the hydrolysis of **1** to the corresponding aldehyde.



**Table 4** Reaction of **1** with NaOCl in CH<sub>3</sub>CN

1	2	Time (min)	Yield (%)
		30	90 <sup>a</sup>
		30	67 <sup>b</sup>
		20	73 <sup>a</sup>
		28	81 <sup>a</sup>
		24	69 <sup>a</sup>
		18	4 <sup>b</sup>
		30	66 <sup>a</sup>

<sup>a</sup> Isolated yield.

<sup>b</sup> <sup>1</sup>H NMR yield using an internal standard (dimethyl sulfone).

Oxaziridines **2**, prepared from the reaction of **1** with NaOCl, can be used as oxidants. We confirmed that the  $\alpha$ -hydroxylation of 2-methyl-1-tetralone using **2a** or **2g** as the oxidant provided results that tallied with those reported in the literature.<sup>2</sup>

In conclusion, synthetically useful *N*-sulfonyloxaziridines (Davis' oxaziridines) **2** can be synthesized from reaction of the corresponding *N*-sulfonylimine **1** with aqueous NaOCl in acetonitrile without need for a catalyst. Strongly basic conditions (pH 13) are required to obtain the products in high yields.<sup>6</sup> Although both NaOCl·5H<sub>2</sub>O and conventional aq. NaOCl can be used as the oxidant, NaOCl·5H<sub>2</sub>O is recommended because, due to the instability of conventional aq. NaOCl, we observed that the target compounds are not always obtained in high yields.

All reagents were purchased from Nacalai Tesque, Wako Pure Chemicals Industries, Kanto Kagaku, Kishida Reagents Chemical Co., Tokyo Chemical Industry, or Aldrich, and used without further purification. Melting points were measured with a Yanaco micro melting point apparatus (MP-J3) and are uncorrected. NMR spectra were recorded with a JEOL (JNM-EX400) spectrometer as solutions in CDCl<sub>3</sub> using TMS or the residual CHCl<sub>3</sub> peak as an internal standard. IR spectra were recorded with a JASCO IR-8300 FT-IR spectrophotometer. Mass spectra were recorded with a Shimadzu GCMS-QP1100EX spectrometer. Specific rotations were measured with a JASCO DIP-370 polarimeter. All of the sulfonyl imines **1** were prepared according to reported methods (**1a**,<sup>2a</sup> **1b**,<sup>3a</sup> **1c**,<sup>3a</sup> **1d**,<sup>3a</sup> **1e**,<sup>3a</sup> **1f**,<sup>3a</sup> **1g**<sup>2c</sup>). NMR yields were determined using dimethyl sulfone as an internal standard. All of the products **2** and **5** are known compounds, and <sup>1</sup>H and <sup>13</sup>C NMR data of the products obtained in this study are identical to those reported.

### Preparation of **2**; Typical Procedure

An aqueous NaOCl solution prepared from NaOCl·5H<sub>2</sub>O (987 mg, 6.0 mmol) and pH 13 buffer solution (KCl-NaOH) (50 mL) was added to a stirred solution of **1a** (260 mg, 1.0 mmol) in acetonitrile (10 mL) at 0 °C. The resulting mixture was stirred at r.t. for 30 min. Water (30 mL) was added to the reaction mixture, and the mixture was extracted with EtOAc (3 × 30 mL). The extract was washed with brine, dried with anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by silica-gel column chromatography using hexane/EtOAc (20:1) as an eluent to obtain pure **2a** (250 mg, 90%) as colorless crystals.

### 3-Phenyl-2-tosyl-1,2-oxaziridine (**2a**)<sup>2a</sup>

Colorless crystals: mp 87–92 °C (lit.<sup>2a</sup> 87 °C).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.86 (d, *J* = 8.4 Hz, 2 H), 7.33–7.42 (m, 7 H), 5.38 (s, 1 H), 2.43 (s, 3 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 145.39, 130.37, 129.51, 129.03, 128.39, 127.70, 127.20, 75.30, 28.68, 20.81.

MS: *m/z* = 259 (M<sup>+</sup> – O), 155 (M<sup>+</sup> – C<sub>7</sub>H<sub>6</sub>ON), 91 (M<sup>+</sup> – C<sub>7</sub>H<sub>6</sub>O<sub>3</sub>NS).

IR (neat): 2924, 2856, 1596, 1351, 1170, 1087, 807, 712, 569, 543, 421 cm<sup>-1</sup>.

### 3-(Naphthalene-2-yl)-2-tosyl-1,2-oxaziridine (**2b**)<sup>3a</sup>

According to the typical procedure, **1b** (312.5 mg, 1.01 mmol) was treated with aq. NaOCl to provide a crude product (277.6 mg) containing **2b** (67%, <sup>1</sup>H NMR yield using dimethyl sulfone as an internal standard). All the peaks shown below appeared in the <sup>1</sup>H and <sup>13</sup>C NMR spectra of the crude product.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 8.03 (brs, 1 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 7.89–7.84 (m, 3 H), 7.57–7.52 (m, 2 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.40 (dd, *J* = 8.8, 2.0 Hz, 1 H), 5.61 (s, 1 H), 2.50 (s, 3 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 146.43, 142.20, 134.72, 132.57, 131.50, 130.07, 129.75, 129.45, 128.86, 128.33, 127.92, 127.88, 127.64, 126.82, 123.45, 21.86.

### 7b-Phenyl-7bH-benzo[d][1,2]oxazireno[2,3-b]isothiazol-2,3-dioxide (**2c**)<sup>3a</sup>

According to the representative procedure, **2c** (190 mg, 73%) was obtained from **1c** (242 mg, 1.00 mmol).

Colorless crystals: mp 97–99 °C (lit.<sup>2i</sup> 105–106 °C).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.88 (dd, *J* = 6.8, 1.2 Hz, 1 H), 7.79–7.71 (m, 2 H), 7.65–7.50 (m, 6 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 134.57, 134.44, 133.84, 132.79, 131.34, 129.00, 128.07, 128.04, 127.87, 124.13, 85.25.

### 7b-(4-Chlorophenyl)-7bH-benzo[d][1,2]oxazireno[2,3-b]isothiazol-2,3-dioxide (**2d**)<sup>3a</sup>

According to the representative procedure, **2d** (237 mg, 81%) was obtained from **1d** (276 mg, 1.00 mmol).

White solid; mp 140–143 °C (lit.<sup>3a</sup> 144–145 °C).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.88 (dd, *J* = 6.4, 1.6 Hz, 1 H), 7.81–7.73 (m, 2 H), 7.63–7.61 (dd, *J* = 6.8, 0.8 Hz, 1 H), 7.57–7.49 (m, 4 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 137.75, 134.41, 133.98, 133.95, 133.00, 129.51, 129.36, 127.82, 126.42, 124.24, 84.68.

### 7b-(3-Chlorophenyl)-7bH-benzo[d][1,2]oxazireno[2,3-b]isothiazol-2,3-dioxide (**2e**)<sup>3a</sup>

According to the representative procedure, **2e** (237 mg, 81%) was obtained from **1d** (276 mg, 1.00 mmol).

Pale-orange solid; mp 124–126 °C (lit.<sup>3a</sup> 125–126 °C).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.90–7.87 (m, 1 H), 7.82–7.74 (m, 2 H), 7.64–7.59 (m, 2 H), 7.56 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.52–7.45 (m, 2 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 135.22, 134.35, 134.06, 133.76, 133.06, 131.61, 130.40, 129.93, 128.15, 127.86, 126.29, 124.24, 84.38.

### 7b-Methyl-7bH-benzo[d][1,2]oxazireno[2,3-b]isothiazol-2,3-dioxide (**2f**)<sup>3a</sup>

According to the representative procedure, **1f** (181.5 mg, 1.00 mmol) was treated with aq. NaOCl to provide a crude product (28.0 mg) containing **2f** (4%, <sup>1</sup>H NMR yield using dimethyl sulfone as an internal standard). All the peaks shown below appeared in the <sup>1</sup>H and <sup>13</sup>C NMR spectra of the crude product.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.80–7.71 (m, 4 H), 2.14 (s, 3 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 135.09, 134.06, 133.29, 132.56, 125.57, 123.84, 83.91, 15.57.

### (+)-(4aR,7R)-9,9-Dimethyltetrahydro-4H-4a,7-methanobenzo[c][1,2]oxazireno[2,3-b]isothiazole 3,3-Dioxide (**2g**)<sup>2c</sup>

According to the representative procedure, **2g** (151 mg, 66%) was obtained from **1g** (210 mg, 1.00 mmol).

Colorless crystals; mp 167–172 °C (lit.<sup>2c</sup> 165–167 °C); [α]<sub>D</sub> +44.6 (CHCl<sub>3</sub>, c 1.9) (lit.<sup>2c</sup> [α]<sub>D</sub> +44.6 (CHCl<sub>3</sub>, c 1.8)).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 3.10 and 3.27 (AB quartet, *J* = 14 Hz, 2 H, CH<sub>2</sub>-SO<sub>2</sub>), 2.64 (m, 1 H), 1.50–2.13 (m, 6 H), 1.18 (s, 3 H), 1.03 (s, 3 H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 98.77, 54.06, 48.32, 45.80, 33.64, 28.39, 26.56, 20.55, 19.50.

## Funding Information

This work was performed under the Cooperative Research Program of the 'Network Joint Research Center for Materials and Devices'.

## References and Notes

- (1) For recent reviews, see: (a) Williamson, K. S.; Michaelis, D. J.; Yoon, T. P. *Chem. Rev.* **2014**, *114*, 8016. (b) Sala, G. D.; Lattanzi, A. *ACS Catal.* **2014**, *4*, 1234.
- (2) (a) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774. (b) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087. (c) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477. (d) Davis, F. A.; Sheppard, A. C.; Chen, B.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679. (e) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715. (f) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. (g) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919. (h) Petrov, V. A.; Resnati, G. *Chem. Rev.* **1996**, *96*, 1809. (i) Narasaka, K.; Ukaji, Y.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1987**, *96*, 1457.
- (3) Asymmetric syntheses of oxaziridines: (a) Takizawa, S.; Kishi, K.; Abozeid, M. A.; Murai, K.; Fujioka, H.; Sasaia, H. *Org. Biomol. Chem.* **2016**, *14*, 761. (b) Lykke, L.; Rodríguez-Esrich, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 14932. (c) Zhang, T.; He, W.; Zhao, X.; Jin, Y. *Tetrahedron* **2013**, *69*, 7416. (d) Jin, Y.; Zhang, T.; Zhang, W.; Chang, S.; Feng, B. *Chirality* **2014**, *26*, 150. (e) Uraguchi, D.; Tsutsumi, R.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 8161. (f) Tsutsumi, R.; Kim, S.; Uraguchi, D.; Ooi, T. *Synthesis* **2014**, 871. (g) Uraguchi, D.; Tsutsumi, R.; Ooi, T. *Tetrahedron* **2014**, *70*, 1691. (h) Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 5440.
- (4) Galvin, J. M.; Jacobsen, E. N.; Palucki, M.; Frederick, M. O. *e-EROS* **2013**, DOI: 10.1002/047084289X.rs084.pub3 ; and references cited therein.
- (5) (a) Kirihara, M.; Okada, T.; Sugiyama, Y.; Akiyoshi, M.; Matsunaga, T.; Kimura, Y. *Org. Process Res. Dev.* **2017**, *21*, 1925. (b) Okada, T.; Asawa, T.; Sugiyama, Y.; Kirihara, M.; Iwai, T.; Kimura, Y. *Synlett* **2014**, *25*, 596. (c) Okada, T.; Asawa, T.; Sugiyama, Y.; Iwai, T.; Kirihara, M.; Kimura, Y. *Tetrahedron* **2016**, *72*, 2818. (d) Okada, T.; Matsumuro, H.; Kitagawa, S.; Iwai, T.; Yamazaki, K.; Kinoshita, Y.; Kimura, Y.; Kirihara, M. *Synlett* **2015**, *26*, 2547. (e) Okada, T.; Matsumuro, H.; Iwai, T.; Kitagawa, S.; Yamazaki, K.; Akiyama, T.; Asawa, T.; Sugiyama, Y.; Kimura, Y.; Kirihara, M. *Chem. Lett.* **2015**, *44*, 185.
- (6) Given that addition of 10 mol% tetrabutylammonium hydroxide ( $\text{Bu}_4\text{NOH}$ ) accelerated the oxidation reaction in a biphasic solvent system using trifluoromethylbenzene (benzotrifluoride, BTF), the reaction might proceed enantioselectively if an optically pure alkylammonium salt was employed. As a preliminary result, the desired product **2a** was obtained with 7% ee when the reaction was conducted using *N*-benzylcinchonidinium chloride.