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Nanoflow system for perfect regiocontrol in the Baeyer–Villiger oxidation by aqueous hydrogen peroxide using lowest concentration of a fluorous lanthanide catalyst

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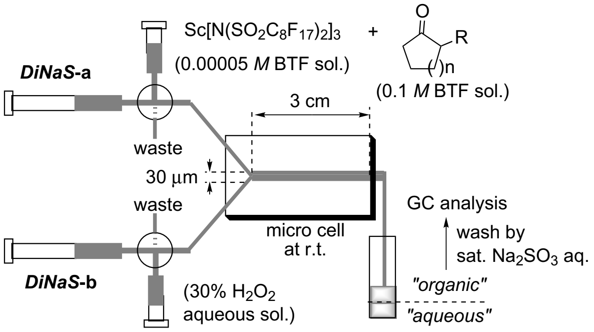
Abstract—The scandium bis(perfluorooctanesulfonyl)amide-catalyzed Baeyer–Villiger reaction significantly increased the regioselectivity as well as the reaction rate by nanoflow system continuously controlled by a nanofeeder even in the lowest concentration of the catalyst ($\ll 0.1$ mol %). The Baeyer–Villiger reaction completed within few seconds as a contact time in the microcell to afford the lactone products high regioselectively without hydrolysis.

The Baeyer–Villiger (B–V) reaction has been widely employed in organic synthesis by virtue of the unique transformation: an oxygen atom can be inserted into a carbon–carbon single bond.[1] Particularly, hydrogen peroxide is an environmentally friendly oxidant to waste only water. This environmental advantage can make hydrogen peroxide attractive for industrial operations. Hydrogen peroxide has, in turn, disadvantages: less reactivity, formation of the regioisomeric mixtures particularly from cyclopentenones, and hydrolysis of the lactone products in the presence of strong acids.[2] To overcome these disadvantages, a wide variety of homogeneous and heterogeneous metal catalysts have been explored for the B–V oxidation.[1b]

The miniaturization of chemical analytic device using the micro-total analysis system (μ-TAS) has demonstrated a new paradigm especially in biochemical field.[3] Recently, miniaturized chemical reactor, namely microreactor, has been attracting much attention of synthetic chemists to increase the reaction rate. However, strict control of the flow rates of the reaction media in nanolevel has been required to exploit the fully integrated microreaction system and further downsizing by three orders.[4] We herein report the significant increase not only in the reaction rate but also in the regioselectivity of the B–V oxidation with 30% H_2O_2 even by use of low concentration of a fluorous lanthanide complex[7,8] with bis(perfluorooctanesulfonyl)amide ponytail[9] (e.g., $Sc[N(SO_2C_8F_{17})_2]_3$) in our nanoflow system. This fluorous lanthanide catalyst can be fully employed through the microfabricated device strictly controlled by nanofeeder DiNaS[5,6] (Direct Nanoflow System) (Scheme 1).

When a substrate and $Sc[N(SO_2C_8F_{17})_2]_3$ in benzotrifluoride (BTF) as a fluorous–organic hybrid solvent[10]



Scheme 1. The Baeyer–Villiger reaction by nanoflow system.

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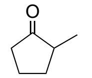
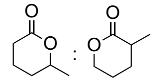
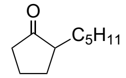
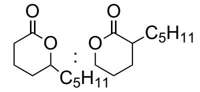
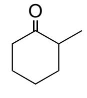
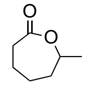
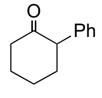
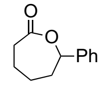
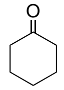
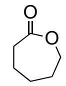
and 30% H_2O_2 were introduced through two microinlets separately, a very short diffusion of molecules at a large interfacial area between the two phases were achieved in the nanoflow system (Scheme 1). Significantly the B–V oxidation reactions of cyclic ketones were completed within seconds at rt even in very low concentration (0.00005 M) of $Sc[N(SO_2C_8F_{17})_2]_3$. The flow rate was continuously controlled by 100 nL/min for both phases and thus the reactions were examined for 8.1 s as biphasic contact time through 30 μm × 30 μm × 3 cm microchannel. Surprisingly high regioselectivity of the product as well as high chemical yield were obtained in sharp contrast to lower yield and regioselectivity obtained in the batch system (Table 1). It is noted that the complete regioselectivity was achieved with quantitative yield in the nanoflow system even employing cyclopentanone substrates. The lower yield and regioselectivity even after 5 h in the batch system is due to the heterogeneous conditions.

Such successful results in the nanoflow system indicate that the faster dispersion of aqueous H_2O_2 into fluorous–organic hybrid BTF solution including the substrate and the Sc catalyst can be achieved. The origin of the perfect regioselectivity and remarkably increased chemical yield in the nanoflow system can be predicted to form the metal peroxo species,[11] which can increase the nucleophilicity of HO_2^-, by the faster dispersion of aqueous H_2O_2 into BTF solution. To find experimental support for the metal peroxo formation in the nanoflow system,[12] we then compared two experimental procedures in the batch system (round bottomed flasks) for 2-methylcyclopentanone (Table 2). In the first batch experiment (method a) under almost the same condition as the nanoflow system other than the high Sc catalyst concentration (otherwise, oxidation did not proceed within reasonable reaction times). The Sc catalyst was dissolved in BTF (0.001 M) and the substrate was added (0.1 M) followed by 30% aqueous H_2O_2. The low regioselectivity was observed throughout the reaction in the first batch experiment. In the second batch experiment (method b), the Sc catalyst was pre-mixed with aqueous H_2O_2 for about 30 min prior to substrate addition using the same concentrations of the substrate (0.1 M) and the Sc catalyst (0.001 M) as in method a. In contrast to the first experiment, the higher regioselectivity was achieved.

According to the above experimental observations in the batch system, the remarkably increased regioselectivity

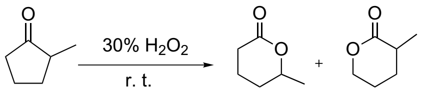
Table 1. The B–V reaction in the nanoflow and batch systems[a]

Substrate	Product	Contact time (s)	Yield (%)	Regioselectivity
		8.1	99	97:3
		(5 h	53	67:33)[b]
		8.1	92	99:1
		(5 h	55	70:30)[b]
		8.1	91	100:0
		(5 h	28	69:31)[b]
		8.1	74	100:0
		(5 h	17	100:0)[b]
		8.1	63	
		(5 h	22)[b]	

[a] Substrates (0.1 M), 30% H_2O_2 and a catalyst (0.05 mol%) were used in the nanoflow system and flow rates for both layer were maintained by 100 nL/min at rt.

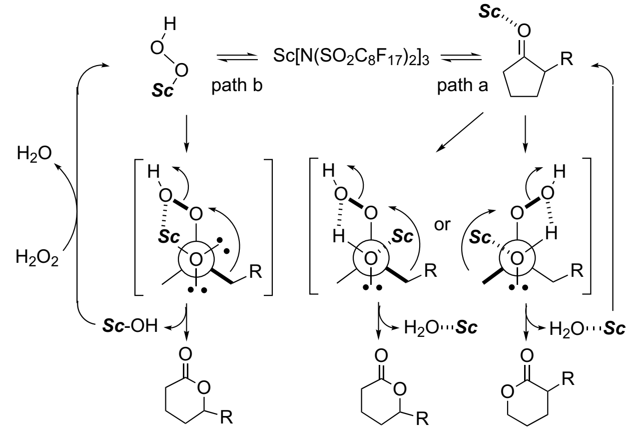
[b] Catalyst (1 mol%) was used in batch system.

Table 2. The experimental data for pre-complexation of the Sc peroxo species[a]



Time (h)	Method a		Method b	
	Regioselectivity	Yield (%)	Regioselectivity	Yield (%)
1	60:40	17	95:5	17
2	65:35	22	94:6	22
4	70:30	39	91:9	43

[a] Substrates (0.1 M) and catalyst (1 mol%) were used in batch system; yield and regioselectivity were determined by GC analysis.



Scheme 2. The mechanism of the metal peroxo formation followed by the regioselective oxygen atom insertion.

can be illustrated in terms of efficient metal peroxo formation in the nanoflow system as shown in Scheme 2. It is crucial step either the complexation of the Sc catalyst with H_2O_2 affording more nucleophilic Sc peroxo species (path b) or the coordination of the Sc catalyst on the ketone (path a). In path b, the intramolecular nucleophilic attack of the hydroperoxy moiety on the Sc-coordinated ketone can strictly control the direction of O–O bond *anti* to the migratory carbon bearing R group to afford highly regioselective product in contrast to path a, where the intermolecular H_2O_2 attack should be occurred. In the nanoflow system, the faster dispersion of aqueous H_2O_2 into BTF phase can predominantly re-form the Sc peroxo species by the complexation of the Sc hydroxide with H_2O_2.

In summary, we have envisioned that the Sc amide-catalyzed B–V reaction is significantly increased in the regioselectivity as well as the reaction rate by nanoflow system even in the low concentration of the catalyst (≪0.1 mol%). Further investigations to develop asymmetric Baeyer–Villiger reactions in nanoflow system are now under progress.

References and notes

1. Comprehensive reviews: (a) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737; (b) Strukul, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1198; (c) Krow, G. R. *Org. React.* **1993**, *43*, 251; (d) Krow, G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, p 671; (e) Vogel, P. *Chimie Organique*; De Boek-Universit: Paris, Bruxelles, 1997.
2. Silbert, L. S.; Siegel, E.; Swern, D. *J. Org. Chem.* **1962**, *27*, 1336, and references cited therein.
3. (a) Ache, H.-J. In *Micro Total Analytical Systems*; van den Berg, A., Bergveld, P., Eds.; Kluwer: Dordrecht, 1995; (b) *Microsystem Technology in Chemistry and Life Sciences*; Manz, A., Becker, H., Eds.; Springer: Berlin, 1998; (c) Manz, A.; Graber, N.; Widmer, H. M. *Sens. Actuators B* **1990**, *1*, 244; (d) Freemantle, M. *Chem. Eng. News* **1999**, *77*, 27; (e) Sato, K.; Hibara, A.; Tokeshi, M.; Hisamoto, H.; Kitamori, T. *Adv. Drug Deliver. Rev.* **2003**, *55*, 379; (f) Sato, K.; Hibara, A.; Tokeshi, M.; Hisamoto, H.; Kitamori, T. *Anal. Sci.* **2003**, *19*, 15.
4. Usual flow rate in the recent micropumping systems are in the range of 10–500 μL/min, see: (a) Ehrfeld, W.; Hessel, V.; Lehr, H. *Top. Curr. Chem.* **1998**, *194*, 233; (b) Jensen, K. F. *Chem. Eng. Sci.* **2001**, *56*, 293; (c) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors: New Technology for Modern Chemistry*; Wiley-VCH: Weinheim, Germany, 2000; (d) Haswell, S. J.; Middleton, R. J.; O'Sullivan, B.; Skelton, V.; Watts, P.; Styring, P. *Chem. Commun.* **2001**, 391; (e) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. *Tetrahedron* **2002**, *58*, 4735.
5. DiNaS can be now supplied from KYA TECH Corp. as a high pressure (up to 20.0 MPa) syringe delivery system controlling the tunable flow of solution from 1 to 200,000 nL/min.
6. Our primary communication of the aldol reaction in DiNaS; Mikami, K.; Yamanaka, M.; Islam, M. N.; Kudo, K.; Seino, N.; Shinoda, M. *Tetrahedron Lett.* **2003**, *44*, 7545.
7. Reviews on lanthanide complexes: (a) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573; (b) Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon, 1991; p 231; (c) Molander, G. A. *Chem. Rev.* p 29; (d) Imamoto, T. *Lanthanide in Organic Synthesis*; Academic: London, 1994; 92; (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307; (f) *Lanthanides, Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: Berlin, 1999; (g) Mikami, K.; Terada, M.; Matsuzawa, H. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3554.
8. Kotsuki, H. and co-workers have reported the use of Sc(OTf)$_3$ in the Baeyer–Villiger oxidation of methylcyclohexanone by commercial grade *m*-CPBA provided high regioselectivity (96:4) for 12 min: *Synlett* **1999**, 462.
9. (a) Mikami, K.; Mikami, Y.; Matsuzawa, H.; Matsumoto, Y.; Nishikido, J.; Yamamoto, F.; Nakajima, H. *Tetrahedron* **2002**, *58*, 4015; (b) Barret, A. G. M.; Bouloc, N.; Braddock, D. C.; Catterick, D.; Chadwick, D.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2002**, *58*, 3835.
10. (a) Maul, J. J.; Ostrowske, P. J.; Ublackes, G. A.; Linclan, B.; Curran, D. P. *Top. Curr. Chem.* **1999**, *206*, 80; (b) Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450; (c) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
11. (a) B–V reaction catalyzed by other metal peroxo species generated from H_2O_2, and references therein. Pt: Todesco, M. D.; Pinna, F.; Strukul, G. *Organometallics* **1993**, *12*, 148; (b) Strukul, G.; Varagnolo, A.; Pinna, F. *J. Mol. Catal. A* **1997**, *117*, 413; (c) Roberta, G.; Maurizio, C.; Francesco, P.; Strukul, G. *Organometallics* **1998**, *17*, 661; Re: (d) Herrmann, W. A.; Fischer, R. W. *J. Mol. Catal.* **1994**, *94*, 213; (e) Huston, P.; Espenson, J. H.; Bakac, A. *Inorg. Chem.* **1993**, *32*, 4517; (f) Yamazaki, S. *Chem. Lett.* **1995**, 127; Mo: (g) Jacobson, S. E.; Tang, R.; Mares, F. *J. Chem. Soc., Chem. Commun.* **1978**, 888; (h) Jacobson, S. E.; Tang, R.; Mares, F. *Inorg. Chem.* **1978**, *17*, 3055.
12. The mechanistic issue of the B–V reaction in terms of the metal peroxo formation has been studied in details, particularly in the transition metal–H_2O_2 systems based on Pt, by the kinetic study under various conditions. See Refs. 11a–c.