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Development of a Continuous-Flow Microreactor for Asymmetric Sulfoxidation Using a Biomimetic Manganese Catalyst

Wen Dai,[+a] Yuan Mi,[+a] Ying Lv,[a] Bo Chen,[a] Guosong Li,[a] Guangwen Chen,[a,*] and Shuang Gao[a,*]

[a] Dalian Institute of Chemical Physics, the Chinese Academy of Sciences and Dalian National Laboratory for Clean Energy, Dalian 116023, People's Republic of China
Fax: (+86)-411-8437-9248 or (+86)-411-84379327; phone: (+86)-411-8437-9248 or (+86)-411-84379031;
e-mail: gwchen@dicp.ac.cn or sgao@dicp.ac.cn

[+] These authors contributed equally to this work.

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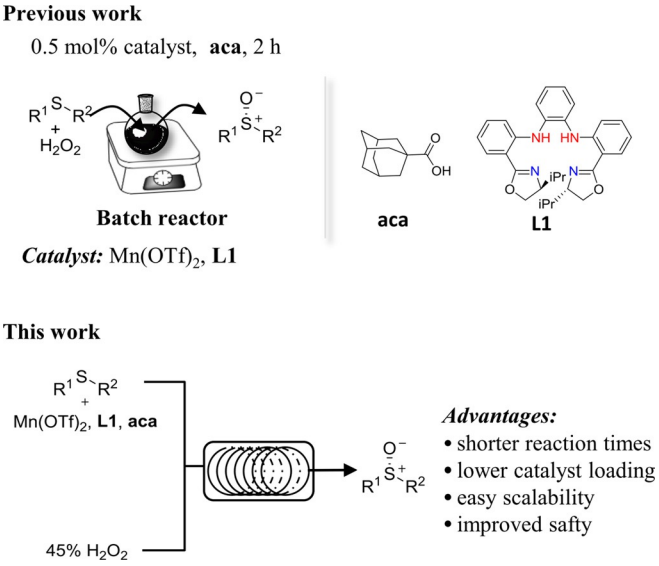
Abstract: Asymmetric sulfoxidation catalyzed by a biomimetic manganese complex under continuous-flow microreactor is described. The reaction is conducted in microreactor, it can rapidly (<4 min) oxidize a wide scope of sulfides with high yield (up to 91%) and excellent enantioselectivity (up to 99% *ee*), and allows shorter reaction times, easier scale-up and lower catalyst loadings than its batchwise counterpart. Additionally, a convenient numbering-up strategy for the scale-up of asymmetric sulfoxidation has been developed which enables a direct scaling of the reaction to 5 g affording the corresponding sulfoxides within 20 min.

Keywords: asymmetric sulfoxidation; biomimetic process; continuous flow conditions; microreactor; porphyrin-inspired catalyst

Optically active sulfoxides are extremely useful and versatile building blocks, chiral auxiliaries and organocatalysts in organic synthesis.[1] They have also been extensively applied in the manufacture of pharmaceuticals such as modafinil and esomeprazole.[2] In view of the importance of optically pure sulfoxides, intensive effort has been devoted to expand the methods towards sulfoxides with high enantiomeric purity.[3] Among the available approaches, it is widely appreciated that the asymmetric sulfoxidation is the most straightforward and reliable route. Nevertheless, despite the general success story of this approach, some problems such as long reaction times, high catalyst loading and/or difficult scale-up still remain that can rarely be addressed by conventional batch approaches. Consequently, the pursuit of new methods for the synthesis of enantiopure sulfoxides is desirable.

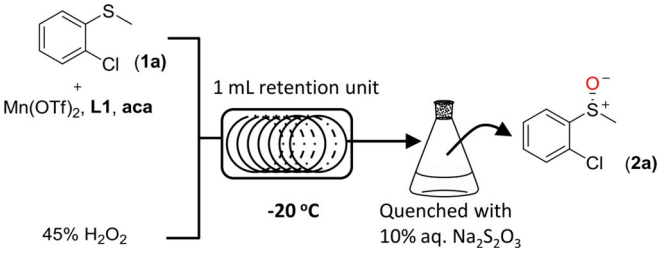
Over the past decade, interest has grown in continuous-flow microreactors due to their potential in accelerating reactions, facilitating scale-up and allowing safe handling of hazardous reactions.[4] Owing to these attributes, the microreactors are becoming an ideal alternative to traditional batch reactors for synthetic chemistry and have been applied to many standard transformations in organic synthesis. However, only a few examples on homogeneous enantioselective catalysis performed in microreactors have been described to date.[4a–d,o,5] In addition, we recently developed a new type of porphyrin-inspired N_4 ligands which fulfilled the structural requirements of the porphyrin ligand in some way.[6] The biomimetic ligands possessing excellent tolerance have been successfully applied in the asymmetric sulfoxidation.[6e,f] With this background in mind, it was envisioned that we could develop an asymmetric sulfoxidation method conducted in continuous-flow microreactor exploiting the porphyrin-inspired manganese catalyst which could allow shorter reaction times, easier scale-up and lower catalyst loading than its batchwise counterpart (Scheme 1). Herein we present the, to the best of our knowledge, first example of homogeneous asymmetric sulfoxidation conducted in a microreactor which can rapidly (<4 min) oxidize a wide range of sulfides with low catalyst loading (0.35 mol%) using environmentally friendly hydrogen peroxide which provides a valuable approach to circumvent the known drawbacks of asymmetric sulfoxidation in traditional batch reactors. Moreover, direct scaling of the reaction to 5 g afforded the corresponding sulfoxides in good yield and enantioselectivity within 20 min.



Scheme 1. Strategy for the development of asymmetric sulfoxidation under continuous-flow microreactor conditions.

A microfluidic system was initially assembled as shown in Scheme 1. The asymmetric sulfoxidation was carried out in a 1-mL reactor made of PTFE (polytetrafluoroethylene) tubing (0.8 mm inner diameter, 1989 mm length). Homogeneous solutions of **1a** (0.4 mmol), 0.08 mmol adamantinecarboxylic acid (**aca**) and 0.5 mol% of catalyst which was generated from $Mn(OTf)_2$ (0.5 mol%) and **L1** (0.5 mol%) as well as 45% H_2O_2 (1.5 equiv.) in the mixed solvent CH_3CN and isopropyl alcohol (IPA) were loaded into syringes and introduced into microfluidic systems through syringe pumps. First, to obtain an insight into the features of the reaction, reactions with varying residence times were carried out. We found that sulfides could be converted into their corresponding sulfoxides in the microreactor within shorter times than in batch reactions while maintaining yield and enantioselectivity (Table 1). The result is probably attributed to the improved mass transfer as well as mixing. Interestingly, almost identical *ee* values could be obtained when the residence time was shortened from 8 min to 4 min (entries 1–4). Further shortening the residence time to 2 min resulted in an obvious decrease in enantioselectivity, albeit with no obvious decrease of yield (entry 5). Subsequently, the oxidant loading was examined (entry 6). The enantioselectivity was significantly increased when the oxidant loading was raised to 2 equiv. which might be attributed to the oxidative kinetic resolution. Eventually, the catalyst loading was investigated. It is noteworthy that the catalyst loading was successfully lowered to 0.35 mol% without erosion of yield and enantioselectivity, and even a catalyst loading of 0.25 mol% gave a good result (entries 7 and 8).

Table 1. Optimization of the asymmetric sulfoxidation under continuous-flow conditions.[a]



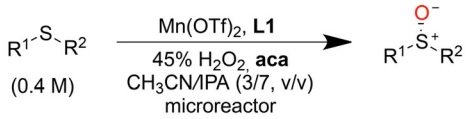
Entry	*t* [min][b]	Yield [%][c]	*ee* [%][d]
1	8	94	89
2	6	93	88
3	5	95	88
4	4	96	86
5	2	95	82
6[e]	4	92	90
7[f]	4	91	90
8[g]	4	93	88

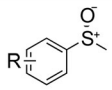
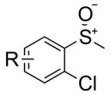
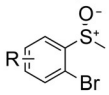
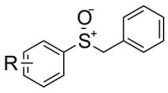
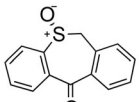
[a] *Reaction conditions:* **1a** (0.4 mmol), **L1** (0.5 mol%), $Mn(OTf)_2$ (0.5 mol%), **aca** (0.08 mmol), 45% H_2O_2 (0.6 mmol), microreactor: 0.8 mm inner diameter, 1989 mm length.
[b] Residence time.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.
[e] 45% H_2O_2 (2.0 equiv.).
[f] **L1** (0.35 mol%), $Mn(OTf)_2$ (0.35 mol%), 45% H_2O_2 (2.0 equiv.).
[g] **L1** (0.25 mol%), $Mn(OTf)_2$ (0.25 mol%), 45% H_2O_2 (2.0 equiv.).

With the optimal conditions in hand, exploration of the substrate scope was carried out under flow conditions, and the results are summarized in Table 2. A wide variety of aryl methyl sulfides could be efficiently oxidized within short reaction times, providing the corresponding sulfoxides in high yields with excellent enantioselectivities regardless of the position of the substituent on the aromatic ring (entries 1–5). Good yields and excellent enantioselectivities were preserved even when extending the alkyl chain linearly from methyl to pentyl (entries 6–10).

Presumably as result of electronic effects, use of substrates containing electron-withdrawing halogen substituents at the *meta*-position of the phenyl groups could significantly shorten the residence time when compared with *ortho*- and *para*- positions. This situation is largely attributed to the transition state of the reaction being electron-demanding and the active oxidant being electrophilic.[6] Encouraged by these results, we next turned our attention to the aryl benzyl sulfides. High yields and excellent enantioselectivities could also be achieved (entries 11–16). In order to extend the substrate scope further, a cyclic sulfide was subjected to the continuous-flow reactor. Gratify-

Table 2. Substrate scope.



Entry	Product	*t* [min][b]	Yield [%][c]	*ee* [%][d]
				
1	R = 2-Cl (**2a**)	4	91	90
2	R = 4-Cl (**2b**)	4	87	90
3	R = 2-Br (**2c**)	4	90	96
4[e]	R = 3-Br (**2d**)	1	90	96
5	R = 4-Br (**2e**)	4	89	92
				
6	R = *n*-Bu (**2f**)	4	82	94
7	R = *n*-pentyl (**2g**)	4	85	96
				
8	R = Et (**2h**)	4	89	94
9	R = n-Bu (**2i**)	4	89	92
10	R = n-pentyl (**2j**)	4	86	93
				
11[e]	R = H (**2K**)	1	85	91
12[e]	R = 3-Me (**2l**)	1	89	98
13[e]	R = 4-Me (**2m**)	1	87	95
14	R = 2-Cl (**2n**)	4	86	99
15	R = 3-Cl (**2o**)	1	90	99
16	R = 2-Br (**2p**)	4	90	96
17[e]	 (**2q**)	1	85	94

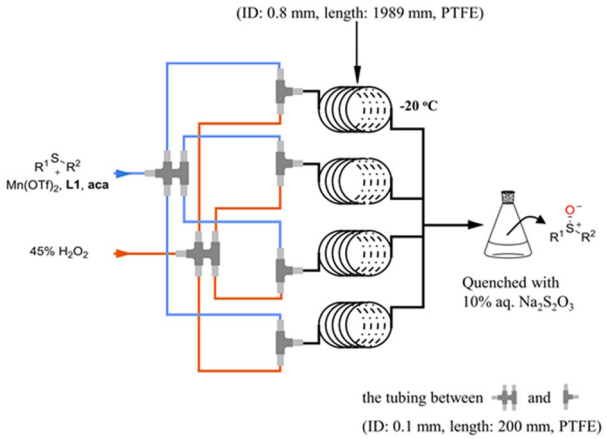
[a] *Reaction conditions:* substrate (0.4 mmol), **L1** (0.35 mol%), $Mn(OTf)_2$ (0.35 mol%), **aca** (20 mmol%), 45% H_2O_2 (1.5 equiv.).
[b] Residence time.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.
[e] 45% H_2O_2 (0.6 mmol).

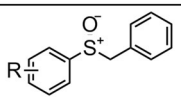
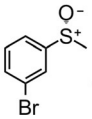
ingly, good yield and high enantioselectivity were also obtained (entry 17).

To further evaluate the practical utility of the current microreactor system, the application of the protocol towards scale-up was investigated. The volume output per unit time from a single microreactor element is small, but high-throughput rates can be realized by having many microreactors working in parallel.[4t] Therefore, we developed a novel continuous-flow microreactor system containing 4 microreactors in parallel (see the Supporting Information Figure 2). This change corresponds to an approximately 4 times enlargement of the reactor volume when compared to the set-up used in Scheme 1. First the reaction using aryl benzyl sulfides as the substrate was tested. Direct scaling of the reaction to 5 g, and collecting for 20 min, afforded the corresponding sulfoxides in 84–86% yield and 92–98% *ee* (Table 3, entries 1–3). Then the scope of the scale-up reaction was further extended to aryl methyl sulfides. Good yield and excellent enantioselectivity were also achieved (Table 3, entry 4).

Moreover, it is well-known that the primary difficulty in the use of hydrogen peroxide as the oxidant is the extremely explosive nature of the compound. Due to the microreactor possessing superior heat and

Table 3. Scale-up of asymmetric sulfoxidation under continuous-flow microreactor conditions.



Entry	Product	*t* [min][b]	Yield[%][c]/ run time [min]	*ee* [%][d]
				
1	R = H (**2K**)	1	84/20	92
2	R = 3-Me (**2l**)	1	83/20	99
3	R = 4-Me (**2m**)	1	86/20	98
4	 (**2d**)	1	80/20	92

[a] *Reaction conditions:* substrate (5.0 g), **L1** (0.35 mol%), $Mn(OTf)_2$ (0.35 mol%), **aca** (20 mmol%), 45% H_2O_2 (1.5 equiv.).
[b] Residence time.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.

mass transfer rates, this hazard can be minimized or prevented effectively which makes the procedure safe.

In summary, it was first determined that a continuous-flow microreactor could be used for the asymmetric sulfoxidation catalyzed by a biomimetic manganese complex to afford the corresponding sulfoxides with almost the same level in yield and enantioselectivity as the batch system. Additionally, the asymmetric sulfoxidation conducted in a continuous-flow microreactor could allow shorter reaction times and lower catalyst loading than its batchwise counterpart. Finally, scale-up of the asymmetric sulfoxidation under the current microreactor system is facilitated. The current continuous-flow microreactor system is being extended to other enantioselective reactions.

Experimental Section

General Procedure

The asymmetric sulfoxidation was conducted in a 1-mL reactor made of PTFE (polytetrafluoroethylene) tubing (0.8 mm inner diameter, 1989 mm length).The **L1** (0.0014 mmol, 0.67 mg) and $Mn(OTf)_2$ (0.0014 mmol, 0.50 mg) were added to 0.3 mL mixed solvent of CH_3CN and *i*-PrOH (3:7, v/v) and the mixture was stirred at room temperature for 8 h. To the solution of manganese complex was directly added substrate (0.4 mmol) and 0.7 mL mixed solvent of CH_3CN and *i*-PrOH (3:7, v/v) and the solution was introduced at one inlet at a flow rate of 125 $\mu L \cdot min^{-1}$, while 45% H_2O_2 (60.4 mg, 0.8 mmol) which was diluted with 1 mL mixed solvent of CH_3CN and *i*-PrOH (3:7, v/v) was introduced from other inlet at the same flow rate. Total output was 250 $\mu L \cdot min^{-1}$ (4 min of residence time). Then the two solutions were combined in a T-mixer. The T-mixer and microreactor were cooled to −20 °C in a refrigerator. The reaction mixture was collected, quenched with 10% aqueous $Na_2S_2O_3$ (4 mL) and extracted with EtOAc (10 mL × 3). The organic layer was combined and washed with a saturated aqueous solution of $NaHCO_3$ (8 mL) and brine, dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by silica gel column chromatography to afford the corresponding sulfoxide.

Acknowledgements

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