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‘Fluorous nanoflow’ system for the Mukaiyama aldol reaction catalyzed by the lowest concentration of the lanthanide complex with bis(perfluorooctanesulfonyl)amide ponytail

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Abstract—‘Fluorous nanoflow’ system is extremely effective for the lanthanide bis(perfluorooctanesulfonyl)amide-catalyzed Mukaiyama aldol reaction with dramatic increase in the reaction rate by the continuously controlled nano feeder. Thus, the acceleration of the aldol reaction was achieved even in the lowest concentration (<0.0001 M) of the lanthanide fluorous catalyst and, hence, the reaction completed within seconds as a bi-phase contact time in the micro cell.

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1. Introduction

The miniaturization of chemical analytic device using the micro total analysis system (μ-TAS) has demonstrated a new paradigm especially in biochemical field.[1] Recently, miniaturized chemical reactor, namely micro reactor, has been attracting much attention of synthetic chemists.[2] The inherent benefits of micro reactors, those are rapid generation of small but detectable quantities of reaction products, efficient heat transfer, fluidic control and short molecular diffusion distance can be applied in organic synthesis,[3] wherein strict control of the flow rates of the reaction media is the key to exploit the fully integrated microreaction system. Usual flow rate in the recent micro pumping systems are in the range of 10–500 μL/min.[2] The development of high-performance nano-scale flow pumping system (‘nanoflow system’) has been required for further down sizing of the micro reactors (by three orders). Electro osmotic flow (EOF) and hydrodynamic pumping technique are often employed in micro reactors.[4] However, the flow rate is simply proportional to the polarity of the solvent in EOF, and hence, non-polar solvents cannot be used. By contrast, our nanoflow system can be employed through strict fluidic control in nano-ordered level using non-polar solvents.

The Mukaiyama aldol reaction is one of the most synthetically and biologically important carbon–carbon bond forming (CCF) reactions.[5] Therefore, a wide variety of Lewis acid catalysts[6] have been developed for this CCF reaction involving silyl enol ether as a storable enolate component in batch system (round-bottomed flask) using 1–10 mol% of catalyst for several hours under the standard conditions on the basis of the Lewis acid–base complexation usually in polar aprotic solvents. To date, fluorous biphasic catalysis (FBC)[7] has attracted a great deal of attention in view of environmentally friendly chemical process, however, only in batch systems, and hence been overlooked in micro reactors.

Herein, we are pleased to report the dramatic increase in reactivity of the Mukaiyama aldol reaction in the fluorous media through the microfabricated device controlled by nano feeder Direct Nanoflow System (DiNaS) (‘fluorous nanoflow’ system in Scheme 1).[8] Even by using low concentration (<0.0001 M) of Lewis acid catalyst in the non-polar fluorous solvents, the reaction completes within seconds as a biphasic contact time. Particularly, lanthanide (Ln) complexes with fluorous bis(perfluorooctanesulfonyl)-amide (e.g. $Sc[N(SO_2C_8F_{17})_2]_3$) ponytails[9,10] effectively form immobilized Lewis acid catalysts in the fluorous phase, since this catalysts are virtually insoluble in usual hydrocarbon solvents at ambient temperature and soluble in

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Keywords: Mukaiyama aldol reaction; environmental benignity; fluorous phase; lanthanide; Lewis acid catalysis; bis(perfluoroalkanesulfonyl)amide; nanoflow; micro reactor.

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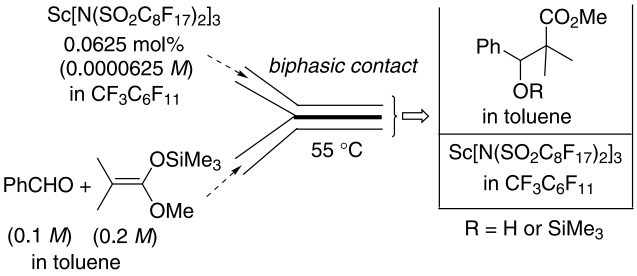


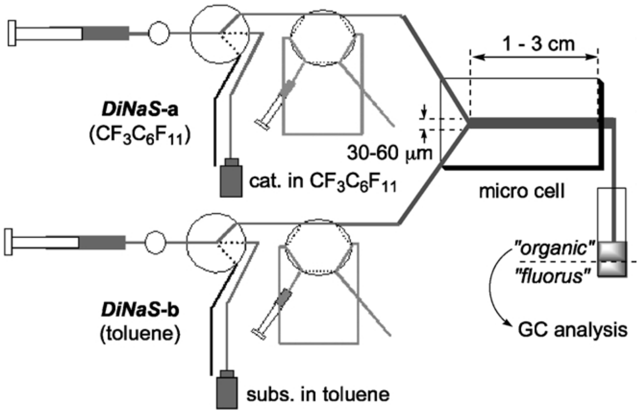
Scheme 1. Mukaiyama aldol reaction by 'fluorous nanoflow' system.

fluorocarbon solvents.[10] The significant increase in reactivity of the Mukaiyama aldol reaction by fluorous nanoflow system is thus reported for the Ln fluorous complex-catalyzed CCF reaction (Scheme 1).

2. Results and discussion

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 nL/min to 200,000 nL/min. The borosilicate micro reactors are delivered from Fuji Electric Co. and fabricated by using a standard fabrication procedure.[11] The total experimental system of nanoflow reactor is illustrated in Scheme 2. The reaction path dimension are 1, 2, and 3 cm lengths×30 μm depth×60 μm width, respectively, for different runs. We also conducted the experiments in a narrow (half-sized) cell of 30 μm width (1 cm length×30 μm depth) for examining the effect on reaction rates. With decreasing cell dimensions the surface area to volume ratio increases, thereby arising the most striking property of the micro cell. Fick's second law of diffusion tells us that the time of transportation T is reduced by shortening the width as shown in the diffusion equation: $T - L^2/D$ (L: width, D: diffusion coefficient).[12]

The nature of fluid flow is of great influence on the mixing in the cell. Under laminar flow condition, molecular diffusion is the only mechanism for exchange of molecules. In turbulent flow, however, a fluid portion does not stay within a certain layer but moves in a random manner across the flow path. As compared to the length of molecular diffusion for mixing fluid in laminar flow, the distance travelled by small volume elements in the turbulent flow is much higher, leading to fast and continuous mixing.[13] Due to low flow rates (25–200 nL/min) and small characteristic dimensions, laminar flow conditions are sometimes encountered. Figure 1 shows the introduction of two solutions into a micro cell at constant flow rates for different runs; parallel side by side laminar flow is formed. When the substrates in hydrocarbon solvent and the catalyst in fluorocarbon solvent were introduced through two inlets of the nano feeders separately, a very short diffusion of molecules at a large interfacial area between the two phases were obtained in the micro cell. Diffusion between the adjacent domains leads to a homogeneous mixing at molecular level and larger interfacial areas lead to enhance mass and heat transfer as well as promotion of chemical reactions.[13]



Scheme 2. The total experimental system of nanoflow reactor.

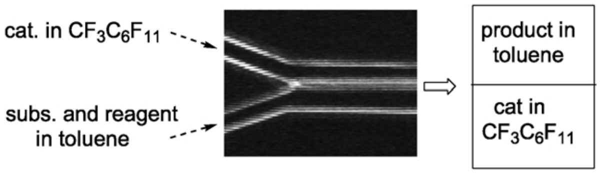


Figure 1. Biphasic laminar flow in micro cell.

The concentration of Sc bis(perfluorooctanesulfonyl)amide ($Sc[N(SO_2C_8F_{17})_2]_3$) in fluorous solvent could be controlled to be low enough [0.0000625 M (0.0625 mol%)] and therefore economically interesting. The flow rates were continuously controlled by 25–200 nL/min; the length of the cell was 1, 2 and 3 cm along with 30 and 60 μm widths, and 30 μm depth in different experiments. The Mukaiyama aldol reactions were thus examined for 5.4–43.2 s as biphasic contact times at 55°C in the micro cell by nanoflow system. Surprisingly, a high yield was obtained, in spite of the very short reaction time and very low catalyst concentration, as calculated by GC analysis on the basis of the calibration curves for silylated and de-silylated aldol products using n-decane as an internal standard. Then, the heterogeneous two phases were separated into the upper toluene and the lower fluorous perfluomethylcyclohexane layers. The scandium catalyst could be recovered and reused in the fluorous phase without isolation.

Significantly, the aldol reaction of benzaldehyde (0.1 M) with trimethylsilyl enol ether (0.2 M) derived from methyl 2-methylpropanoate was completed within seconds even in the presence of only <0.1 mol% of the lanthanide complex, particularly $Sc[N(SO_2C_8F_{17})_2]_3$ in perfluoromethylcyclohexane. The aldol product was obtained in up to quantitative yield (Table 1). We then conducted macro-scale experiment using normal batch (round-bottomed flask) system for comparison. The product was obtained in only 11% yield after vigorous stirring at 55°C even for 2 h by using the same catalyst and substrate concentrations. In sharp contrast, virtually quantitative yield was obtained within much shorter time (seconds of contact time) in the micro cell using nanoflow system than the standard batch system.

We also conducted our experiments in a narrower (half-sized) micro cell of 30 μm width separately for examining the effect of widths of micro cells (vide supra) in separate runs (Table 2). The reaction rates were dramatically

Table 1. The experimental data of the nanoflow system[a]

Flow rate of both layers (nL/min)	Contact time in micro cell (s)	Micro cell length (cm)	Yield[b] (%)	Ratio R=H:SiMe$_3$
200	16.2	3	88	1.9:1
200	10.8	2	67	1.1:1
200	5.4	1	50	1.5:1
100	10.8	1	76	2.6:1
50	43.2	2	94	1.3:1
50	21.6	1	82	1.5:1
20	43.2	1	97	1.1:1

[a] PhCHO (0.1 M), trimethysilyl ketene acetal (0.2 M) and cat. (0.0000625 M) was used.
[b] GC yield.

Table 2. The comparative experimental data of the micro cell[a]

Flow rate of both layers (nL/min)	Contact time in micro cell (s)	Micro cell width (μm)	Yield[b] (%)	Ratio R=H:SiMe$_3$
200	5.4	60	50	1.5:1
100	5.4	30	71	2.5:1
100	10.8	60	76	2.6:1
50	10.8	30	92	2.2:1

[a] PhCHO (0.1 M), trimethysilyl ketene acetal (0.2 M) and cat. (0.0000625 M) was used.
[b] GC yield.

increased in the narrower cell as the surface area to volume ratio increases with decreasing cell dimension and thereby higher diffusion rate and much interfacial contact between the two phases were achieved.

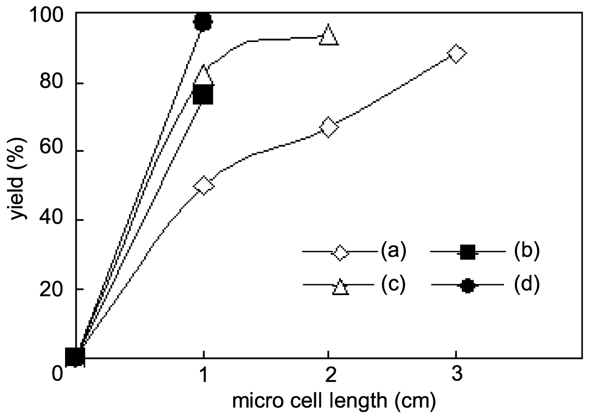


Figure 2. The effect of the lengths on reaction rate of the micro cell. Flow rates for both layers: (a) 200 nL/min, (b) 100 nL/min, (c) 50 nL/min, (d) 25 nL/min.

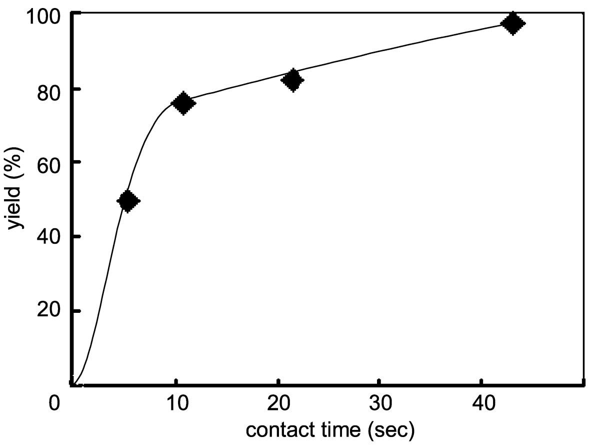


Figure 3. The effect of the contact time in the micro cell.

It can be shown that the yield of the reaction depends on the contact time in micro cell. Next, we demonstrated the effect of the lengths of the cell (Fig. 2) and the effect of the contact time therein (Fig. 3) on the product (%) yield. In nanoflow reactors with longer cell length and longer biphasic contact time, higher chemical yields of the aldol product were obtained up to quantitatively by continuous flow of organic and fluorous phase layers.

On the other hand, the reaction rate was significantly increased in narrow cell, although the contact time was the same as in the previous one (Fig. 4). These results indicated that the narrow width and longer length of the micro cell, and therefore longer contact time provided the larger interfacial area in the low concentration of the catalyst, although the rate of Mukaiyama aldol reaction is significantly increased by the present fluorous nano flow system as compared with the batch system.

It is, therefore, concluded that the product formation in a micro cell are governed by several factors, such as the cell

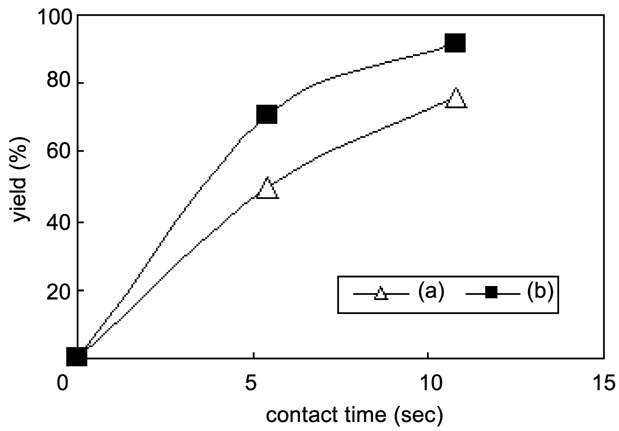


Figure 4. The effect of the width of the micro cell. For widths: (a) 60 μm, (b) 30 μm.

dimension, the cell geometries and bi-phasic contact time. In summary, we have envisioned that Ln amide-catalyzed Mukaiyama aldol reaction is significantly accelerated by fluorous nanoflow system even in the lowest concentration of the catalyst within much shorter bi-phasic contact time in the micro cell. We have also disclosed the Ln amide complex as an efficient Lewis acid catalyst in the non-polar fluorous nano flow system by virtue of the electron-withdrawing effect of the bis(perfluorooctanesulfonyl)amide ponytails[14] without any hydrocarbon spacer.[15] Further investigations to develop other useful synthetic processes in nano flow systems are now under progress.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were measured on a Varian GEMINI 300 (300 MHz), a JEOL GSX-500 (500 MHz) and a JEOL EX-270 (270 MHz) spectrometers. Chemical shifts of ^{1}H NMR were expressed in parts per million relative to chloroform (δ 7.26) or tetramethylsilane (δ 0.00) as an internal standard in chloroform-*d*. Chemical shifts of ^{13}C NMR were expressed in parts per million relative to chloroform-*d* (δ 77.0) as an internal standard. IR spectra were measured on a JASCO FT/IR-5000 spectrometer. GC analysis was carried out in SHIMADZU GC-1700. DiNaS was supplied from KYA TECH Corp. as a high pressure (up to 20.0 MPa) syringe delivery system controlling the continuous and tunable flow of solution from 1 to 200,000 nL/min. The borosilicate micro reactors used in this nano flow reaction system were prepared by Fuji Electric Co. using a standard fabrication procedure.

3.2. The Mukaiyama-aldol reaction of benzaldehyde with trimethylsilyl enol ether of methyl 2-methylpropanoate

For batch system. Benzaldehyde (0.1 mmol) and trimethylsilyl enol ether (0.2 mmol) derived from methyl 2-methylpropanoate were added to a mixture of perfluoromethylcyclohexane (1 mL) and toluene (1 mL). To the resultant mixture was added [0.0000625 M (0.0625 mol%)] of scandium bis(perfluorooctanesulfonyl)amide. The solution was stirred at 55°C for 2 h. The resultant mixture was allowed to stand still at room temperature (20°C), so that the reaction mixture separated into the upper phase of toluene and the lower phase of perfluoromethylcyclohexane. The product was collected from the upper layer and the yield was determined by GC analysis.

For nano flow system. The reaction was performed by introducing a toluene solution containing benzaldehyde (0.1 M), trimethysilyl ketene acetal (0.2 M) and *n*-decane (0.1 M) as an internal standard, and a fluorous solution containing Sc bis(perfluorooctanesulfonyl)amide [0.0000625 M (0.0625 mol%)] through the two inlets of the nano feeder respectively and the reaction temperature was maintained by heating the micro cell by 55°C. Contact time of the starting materials and the catalyst in the micro cell was determined by total volume of the cell path and volume flow rates of the two phases. The yield was determined by GC analysis.

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