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Dramatic increase in the rate of the Mukaiyama aldol reaction by 'fluorous nano flow' system in the lowest concentration of a fluorous catalyst

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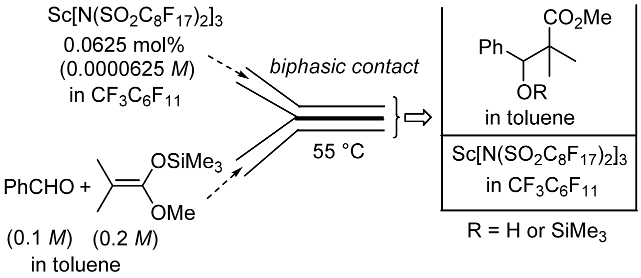
Abstract—The reactivity of the Mukaiyama aldol reaction is significantly increased by 'fluorous nano flow' system even in the low concentration (<0.0001 M) of a lanthanide fluorous catalyst and the reaction completes within seconds as a contact time in the micro cell.

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 in non-polar solvents.



Scheme 1. Mukaiyama aldol reaction by 'fluorous nano flow' system.

The Mukaiyama aldol reaction[5] is one of the most synthetically and biologically important carbon–carbon bond forming (CCF) reactions. 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.

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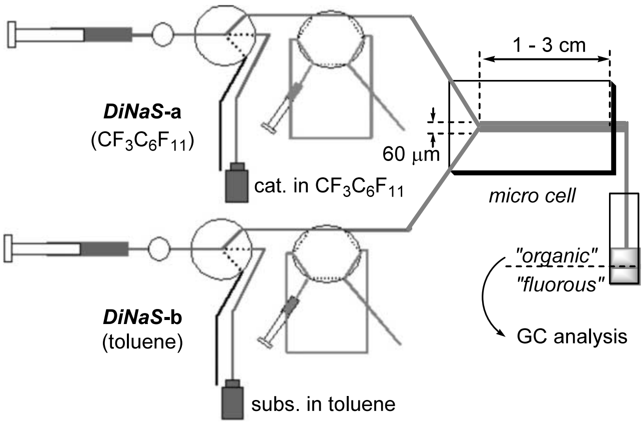
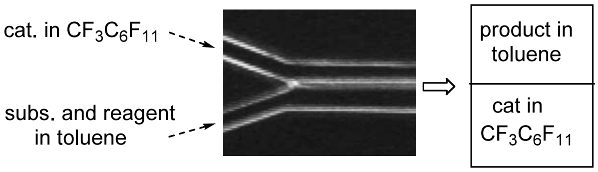
Herein, we report the dramatic increase in reactivity of the Mukaiyama aldol reaction in the fluorous media through the microfabricated device controlled by nano feeder *DiNaS* (Direct Nanoflow System) ('fluorous nano flow' system in Scheme 1).[8] Even by using low concentration (<0.0001 M) of Lewis 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 fluorocarbon solvents.[10] The significant increase in reactivity of the Mukaiyama aldol reaction by fluorous nano flow system is thus reported for the Ln fluorous complex-catalyzed CCF reaction (Scheme 1).

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. using a standard fabrication procedure.[11] Total experimental system of nano flow 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.

Due to the small characteristic dimensions and low flow rates (25 nl/min–200 nl/min), laminar flow conditions are sometimes encountered. 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 was obtained in the micro cell.



Scheme 2. The total experimental system of nano flow reactor.



Scheme 3. Biphasic laminar flow in micro cell.

The concentration of $Sc[N(SO_2C_8F_{17})_2]_3$ 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 μm 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 nano flow system. Surprisingly, a high yield was obtained, in spite of the very short reaction time and very low catalyst concentration, for silylated ($R=SiMe_3$) and de-silylated ($R=H$) aldol products (Scheme 1). As shown in Scheme 3, we sometimes observed the laminar flow separation in this reaction. The two phases were separated into the upper toluene and the lower fluorous perfluoromethylcyclohexane layers. The scandium catalyst should 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

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

Flow rate of both layers (nl/min)	Contact time in micro cell (s)	Micro cell length (cm)	Yield[b] (%)
200	16.2	3	88
200	10.8	2	67
200	5.4	1	50
100	10.8	1	76
50	43.2	2	94
50	21.6	1	82
25	43.2	1	97

[a] PhCHO (0.1 M), trimethysilyl ketene acetal (0.2 M) and cat. (0.0000625 M) were used.

[b] GC yield.

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 for 2 h by using the same catalyst and substrate concentrations. In contrast, virtually quantitative yield was obtained using nano flow system within seconds of contact time. It is noted that a much higher yield was obtained within much shorter time in the micro cell using nano flow system than the standard batch system.

Next, we demonstrated the effect of the lengths of the cell (Fig. 1) and the effect of the contact time therein (Fig. 2) on the product% yield. In nano flow reactors with longer cell length and contact time, higher chemical yields of the aldol product were obtained up to quantitatively by continuous flow of organic and fluorous phase layers. The longer length of the micro cell and longer contact time provided the larger interfacial area in the low concentration of the catalyst, and hence the rate of Mukaiyama aldol reaction is significantly increased (>90% yield) by the present fluorous nano flow system as compared with the batch system.

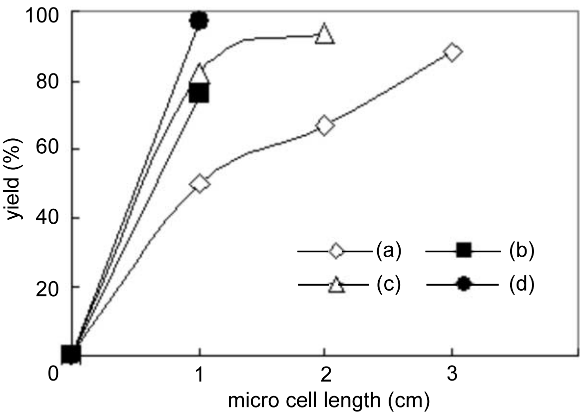


Figure 1. The effect of the lengths of the micro cell. For flow rates for both layers: (a) 200 nl/min, (b) 100 nl/min, (c) 50 nl/min, (d) 25 nl/min.

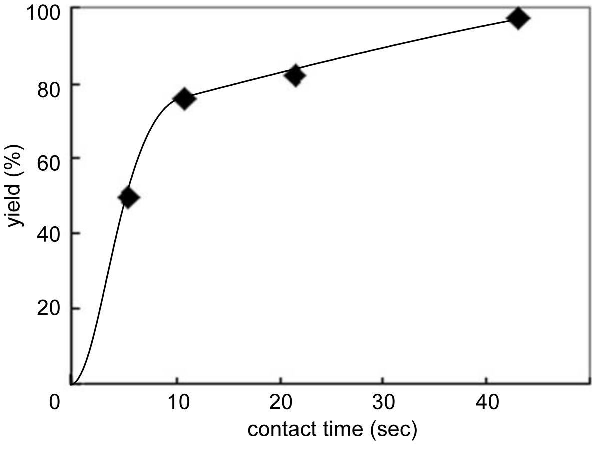


Figure 2. The effect of the contact time in the micro cell.

In summary, we have envisioned that Ln amide-catalyzed Mukaiyama aldol reaction is significantly accelerated by fluorous nano flow system even in the low concentration of the catalyst. 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[12] ponytails without any hydrocarbon spacer.[13]

References

1. (a) Ache, H.-J. *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*, Feb. 22, 27; (e) Sato, K.; Hibara, A.; Tokeshi, M.; Hisamoto, H.; Kitamori, T. *Advanced Drug Delivery Rev.* **2003**, *55*, 379; (f) Sato, K.; Hibara, A.; Tokeshi, M.; Hisamoto, H.; Kitamori, T. *Anal. Sci.* **2003**, *19*, 15.
2. (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.
3. (a) Honicke, D. *Stud. Sur. Sci. Cat.* **1999**, *122*, 47; (b) 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; (c) Mello, A. D.; Wootten, R. *Lab Chip* **2002**, *2*, 7N; (d) Skelton, V.; Watts, P.; Styring, P. *Chem. Commun.* **2001**, 391.
4. (a) Fletcher, P. D. I.; Haswell, S. J.; Paunov, V. N. *Analyst* **1999**, *124*, 1273; (b) Manz, A.; Effenhauser, C. S.; Burggraf, N.; Harrison, D. J.; Seiler, K.; Fluri, K. *J. Micromech. Microeng.* **1994**, *4*, 257; (c) Graveson, P.; Branebjerg, J.; Jensen, O. S. *J. Micromech. Microeng.* **1994**, *4*, 157.
5. Reviews on Mukaiyama aldol Reactions: (a) Carreira, E. M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, p. 997; (b) Nelson, G. *Tetrahedron: Asymmetry* **1998**, *9*, 357; (c) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417; (d) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
6. Reviews on Lewis acid catalysis: (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vols. 1 and 2; (b) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289; (c) Santelli, M.; Pons, J. M. *Lewis Acid and Selectivity in Organic Synthesis*; CRC Press: New York, 1996; (d) Mikami, K.; Nakai, T. *Asymmetric Lewis Acid Catalysts*; Kagaku Zoukan, Kagaku Dojin: Tokyo, 1995; Vol. 124, p. 177; (e) Oh, T.; Reilly, M. *Org. Prep. Proced. Int.* **1994**, *26*, 129; (f) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763; (g) Narasaka, K. *Synthesis* **1991**, 1; (h) Shanbayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p. 283; (i) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986.

7. (a) Horvath, I. T. *Acc. Chem. Res.* **1998**, *31*, 641; (b) Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1174; (c) Gladysz, J. A. *Science* **1994**, *266*, 55; (d) Fish, R. H. *Chem. Eur. J.* **1999**, *5*, 1677; (e) Cornils, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2057; (f) Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72; (g) Vogt, M. *The Application of Perfluorinated Polyethers for Immobilization of Homogeneous Catalysts*, PhD Thesis, Rheinisch-Wesfakischen Technischen Hochschule, Aachen, Germany, 1991. (h) For historical view and definitions of fluorous chemistry, also see: Gladysz, J.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3823.
8. The aldol reaction of silyl enol ethers using TBAF in the micro reactor by electro osmotic flow (EOF) has been recently reported: Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab on a Chip* **2001**, 100.
9. Reviews on lanthanide complexes: (a) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573; (b) Imamoto, T. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press, 1991; Vol. 1, p. 231; (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29; (d) Imamoto, T. *Lanthanide in Organic Synthesis*; Academic Press: London, 1994; (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.
10. (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.
11. (a) *Fundamentals of Microfabrication*; Madou, M., Ed.; CRC Press: Boca Raton, 2000; (b) *Jaeger, R. C. Modular Series on Solid State Devices*; Neudeck, G. W.; Pierret, R. F., Eds.; Addison-Wesley, 1993; (c) McCreedy, T. *Anal. Chim. Acta* **2001**, *427*, 39.
12. Koppel and Taft et al. have reported the gas phase acidities of a variety of super acids: Bis(trifluoromethanesulfonyl)amine is stronger than trifluofomethanesulfonic acid by $\Delta G = 7.7$ kcal/mol and tris(trifluoromethanesulfonyl)methane is stronger than bis(trifluoromethanesulfonyl)amine by $\Delta G = 2.8$ kcal/mol. They have also reported that bis(perfluorobutanesulfonyl)amine is stronger than bis(trifluoromethanesulfonyl)amine by $\Delta G = 7.7$ kcal/mol: *J. Am. Chem. Soc.* **1994**, *116*, 3047.
13. Unfortunately, tris(trifluorometanesulfonyl)methide is of too short hair to render the complexes in fluorous media. Earliest contributions on the lanthanide complex preparation: (a) $La(NTf_2)_3$: Kobayashi, H.; Nie, J.; Sonoda, T. *Chem. Lett.* **1995**, 307; (b) $Yb(NTf_2)_3$: Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H.; Maruta, M. *Synlett* **1996**, 171; (c) $Sc(NTf_2)_3 \cdot 1.5\ CH_3CO_2H$: Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265.