8
Gas–Liquid-phase Reactions: Substitution

Jun-ichi Yoshida and Aiichiro Nagaki

Microflow reactors serve as powerful tools for accomplishing gas–liquid-phase reactions in addition to liquid- and liquid–liquid-phase reactions. This chapter provides an overview of electrophilic and free-radical substitution under gas–liquid-phase conditions using microflow reactors.

8.1
Fluorination [1]

A new, effective method for the selective introduction of fluorine atoms into organic molecules is still keenly sought because the availability of suitable methods is still limited. Although many fluorinating agents have been developed [2], elemental fluorine (F_2) remains one of the most economically viable reagents for such purposes. However, because this reaction is a highly exothermic process ($\Delta H \approx -400\,\mathrm{kJ\,mol^{-1}}$), the safety issues regarding temperature control are of paramount importance, especially when performed on a large scale. Mixing of reagents may be also problematic for conducting direct fluorination. The use of microreactors for highly exothermic direct fluorination processes has attracted considerable attention because there is a small inventory of fluorine in the reaction zone. The opportunities for good mixing and temperature control are also advantageous.

The fluorination of organic compounds with elemental fluorine (F_2) by using a microflow system has been studied extensively [3]. Solution is injected by a syringe-pumping technique, whereas F_2 in nitrogen is introduced directly from a small cylinder by a mass-flow controller (Figure 8.1). By using this technique, all of the liquid–gas mixing proceeds by pipe flow rather than slug flow (Figure 8.2). The liquid forms an outer "pipe" coating the surface of the reaction channel with the gas flowing through the center. Pipe flow is the ideal situation for gas–liquid reactions because, in this case, mass transfer efficiency between the gas and liquid phases is maximized.

β-Dicarbonyl compounds can be converted to the corresponding fluorinated compounds in formic acid using 10% F_2 in N_2 in a microflow system by continuous

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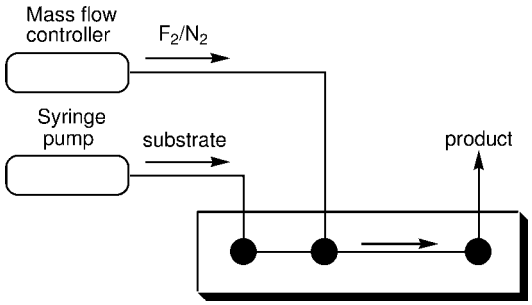


Figure 8.1 Schematic diagram of apparatus used for fluorination reactions.

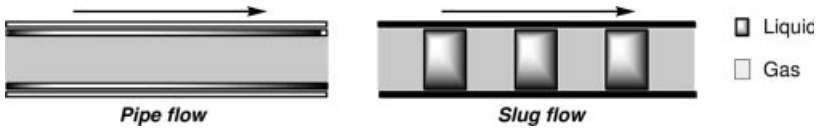
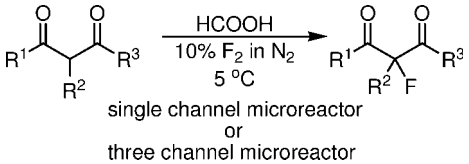


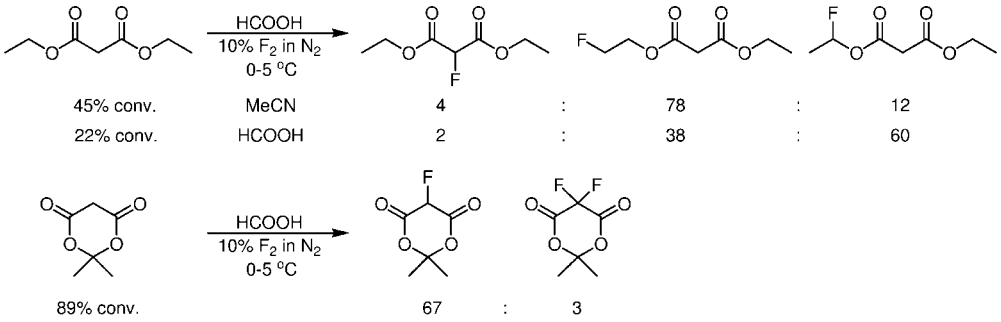
Figure 8.2 Pipe and slug flow.

operation [4–6]. The yields obtained in the microflow process are at least as high as those in macrobatch processes. For example, in the case of fluorination of ethyl 2-chloroacetoacetate, fluorination in a conventional batch system gives only low conversion and yield [7]. On the other hand, fluorination in the microflow reactor gives excellent results. The nickel surface of the microchannel may exhibit a catalytic effect through the favored formation of the enol form. Scale-out by the use of a three-channel reactor has been achieved by simple replication of the single-channel device (Table 8.1). Conversion and product composition are roughly similar to the results of the single-channel reactor experiments.

Table 8.1 Fluorination reaction of 1,3-dicarbonyl substrates.



R^1	R^2	R^3	Yield (%)	
			Single channel microreactor	Three channel microreactor
OEt	H	CH_3	71	82
OEt	CH_3	CH_3	49	38
-OCH_2CH_2-		CH_3	95	–
-$(CH_2)_4$-		CH_3	78	75
-$(CH_2)_4$-		OEt	76	–
OEt	Cl	CH_3	–	74



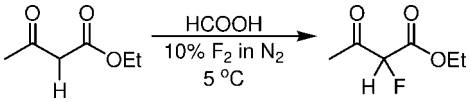
Scheme 8.1 The fluorination of diethyl malonates and Meldrum's acid.

The directed fluorination reaction of diethyl malonate can be performed in a three-channel microreactor (Scheme 8.1) [8]. The synthesis of fluoro- and difluoromalonate esters by the fluorination of Meldrum's acid is readily achieved in a microflow reactor without the use of added catalysts or malonate salts as substrates that are required in a conventional macrobatch reaction.

Reactors having either 9, 18 or 30 microchannels have also been developed for synthesis on the large scale (Scheme 8.2) [9] Direct fluorination of ethyl acetoacetate by fluorine gas is used as a model reaction to illustrate the successful numbering-up.

The fluorination of ethyl acetoacetate can be operated in a nine-channel microreactor device for many months (Figure 8.3). Scale-out to 30 channels can be also achieved by simply exchanging a nine-channel plate for 18-channel and 30-channel plates with no appreciable change in overall yield and conversion.

The very rapid optimization of the reaction conditions is a major advantage of the use of microreactor techniques. Direct fluorinations of various 1,3-keto esters and 1,3-diketo esters in formic acid can be accomplished by adjusting the gas and/or liquid flow rates using a nine-channel microreactor (Table 8.2) [6]. The efficiency of the fluorination depends on the rates of keto–enol exchange of the 1,3-dicarbonyl compounds. Substrates that have a high initial equilibrium enol concentration react rapidly and selectively with fluorine to give monofluorinated products in high yield and high conversion. High flow rates are used for such substrates and, therefore, the residence time of the substrates in the channels is short. In contrast, substrates that have low enol concentrations and slow exchange rates give low conversions and yields of the desired monofluorinated products. Lower flow rates and, therefore, longer residence times are used for such substrates.



9 channel microreactor	66%
18 channel microreactor	69%
30 channel microreactor	68%

Scheme 8.2 Fluorination of ethyl 3-oxobutanoate using 9-, 18-and 30-channel microreactors.

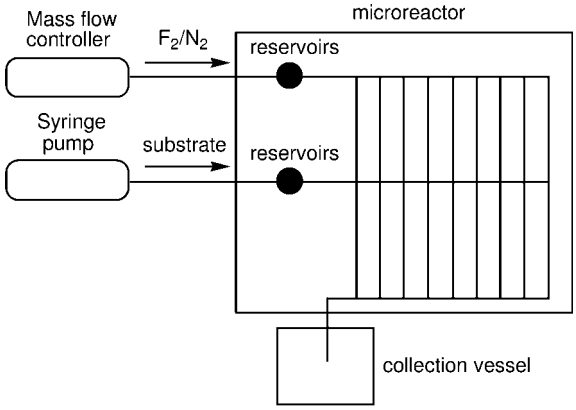


Figure 8.3 Schematic diagram of nine-channel microreactor.

The synthesis of the organic sulfur pentafluorides has also been studied in the case of *m*- and *p*-nitrophenylsulfur pentafluoride. *m*-Nitrophenylsulfur pentafluoride can be synthesized directly from di(*m*-nitrophenyl) disulfide in one step by using a single-channel microreactor (75% yield) and a three-channel microreactor (56% yield) (Scheme 8.3).

p-Nitrophenylsulfur has been synthesized from *p*-nitrophenylsulfur trifluoride in a single-channel thin-film microreactor (Scheme 8.4).

The fluorination reaction of *p*-nitrotoluene in formic acid can be carried out using 10% F_2 in N_2 in a three-channel microreactor to give fluorinated product in 78% yield (Table 8.3) [4, 5, 6]. Fluorination of 4-nitrotoluene is carried out in mixtures of acetonitrile and formic acid (3:2 v/v) because the formation of fluorinated *p*-nitrotoluene leads to blockage of the microchannel due to the low solubility of the substrate in formic acid.

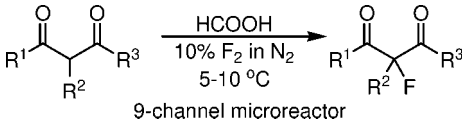
The fluorination reaction of *o,p*-dinitrotoluene in formic acid can also be carried out in a continuous three-channel microreactor using 10% F_2 in N_2 to give the corresponding fluorinated product in 70% conversion yield (Scheme 8.5).

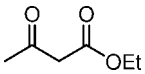
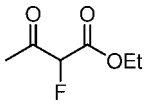
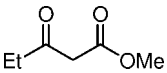
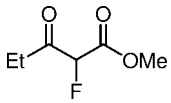
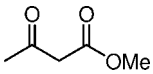
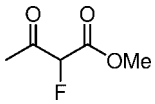
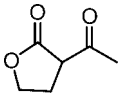
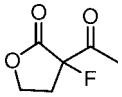
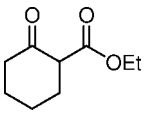
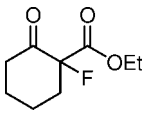
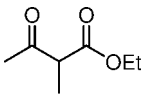
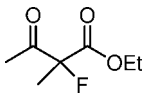
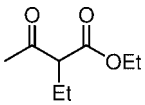
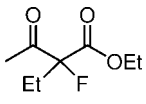
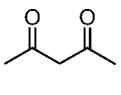
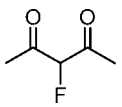
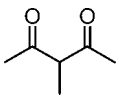
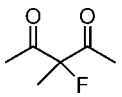
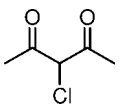
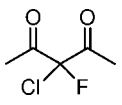
Direct fluorination reactions of *para*-disubstituted aromatic systems bearing an electron-withdrawing and -releasing group using a multichannel microreactor can proceed in either acetonitrile or formic acid reaction media to give a high selectivity and yield of monofluorinated products (Table 8.4) [10].

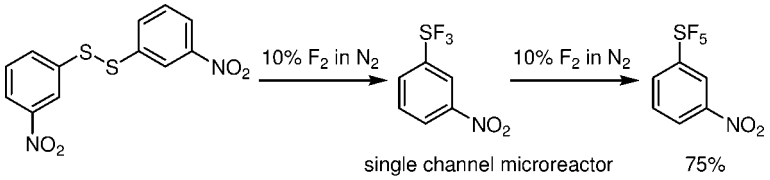
Although aromatic rings bearing two strong electron-withdrawing groups are relatively unreactive towards electrophilic attack, direct fluorination takes place smoothly to give fluorinated products with high selectivity (Table 8.5). The conversion of substrates can be increased by recycling the entire crude reaction mixture through the microreactor device several times.

Perfluorination of tetrahydrofuran and cyclohexane derivatives can be achieved to give the perfluorinated product in high yield (Scheme 8.6). These hazardous perfluorination processes can be carried out safely in single-channel microreactors with high yields.

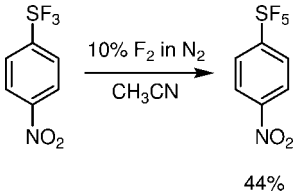
Table 8.2 Directed fluorinations of various 1,3-keto esters and 1,3-diketo esters in formic acid using a nine-channel microreactor.



1,3-Dicarbonyl	Major product	Conversion (%)	Yield (%)
		100	69
		100	68
		100	82
		100	83
		100	74
		92	49
		32	22
		100	76
		100	91
		100	86

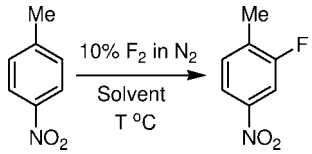


Scheme 8.3 Fluorination reaction of di(*m*-nitrophenyl) disulfide.

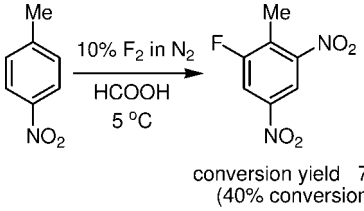


Scheme 8.4 Fluorination reaction of *p*-nitrophenylsulfur trifluoride.

Table 8.3 Fluorination reaction of 4-nitrotoluene.

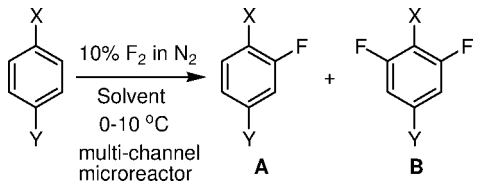


Solvent	T (°C)	Conversion (%)	Conversion yield (%)
MeCN	r.t.	15	71
MeCN:HCOOH (3:2)	5	44	78
MeCN:HCOOH (3:3)	0	66	71



Scheme 8.5 Fluorination reaction of *m*,*p*-dinitrotoluene.

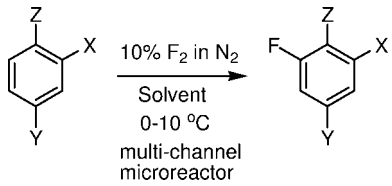
Table 8.4 Fluorination of 1,4-disubstituted aromatic derivatives.



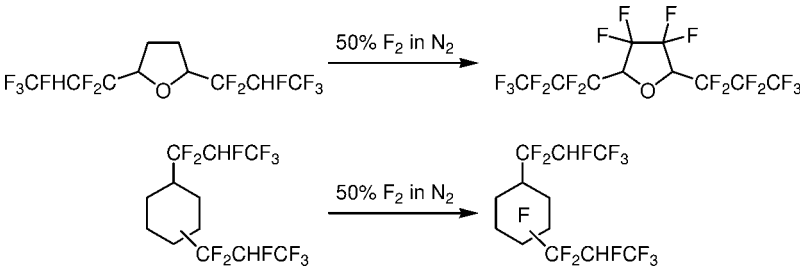
X	Y	Solvent	A (%)	B (%)
OCH_3	NO_2	CH_3CN	77	11
OCH_3	NO_2	CH_3CN/HCOOH	78	4
OCH_3	CN	CH_3CN	74	12
OH	NO_2	HCOOH	71	18
CH_3	CN	CH_3CN	75	7
OCH_3	CHO	CH_3CN	82	9

The fluorination of toluene with 10% F_2 in N_2 by using the falling-film microreactor and the microbubble column has also been studied (Scheme 8.7) [11, 12]. Both the falling-film microreactor and the microbubble column offer advantages over conventional reactors in fluorination reactions. The selectivity of the formation of monofluorinated toluene in a falling-film microreactor is significantly higher than

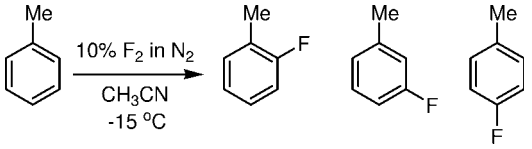
Table 8.5 Fluorination of 1,3-disubstituted aromatic derivatives.



X	Y	Z	Solvent	Conversion (%)	Conversion yield (%)
NO_2	NO_2	CH_3	CH_3CN	38	98
NO_2	NO_2	OCH_3	CH_3CN/HCOOH	86	79
NO_2	NO_2	F	CH_3CN	16	96
NO_2	NO_2	F	HCOOH	34	94
NO_2	NO_2	Cl	HCOOH	53	97
NO_2	CN	H	CH_3CN	18	95
NO_2	NO_2	H	HCOOH	19	96
NO_2	NO_2	H	CH_3CN	27	94
CN	CN	H	CH_3CN	28	85



Scheme 8.6 Perfluorination of tetrahydrofuran and cyclohexane derivatives.



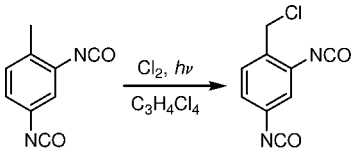
Scheme 8.7 Fluorination of toluene.

that in a conventional bubble column. Analysis of the reaction mixture confirmed the substitution pattern to be 3:2:1 *o*-:*m*-:*p*-fluorinated toluene [13].

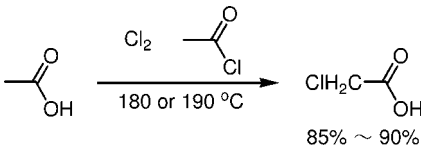
8.2 Chlorination

Thermally induced radical chlorination of alkanes using a hybrid system consisting of two micro heat-transfer modules and a conventional tube reactor has been reported [1, 5]. The exact nature of the alkanes and products, however, has not been disclosed for confidentiality reasons.

The photochemical chlorination of toluene-2,4-diisocyanate (Scheme 8.8) has been reported [14]. By employing a falling film microreactor (channel dimensions: 600 µm wide × 300 µm deep × 6.6 cm long) consisting of 32 parallel microchannels, gaseous chlorine is irradiated through a quartz window to generate chlorine radicals *in situ*. The effect of varying the flow rate of chlorine (from 14.0 to 56.0 mL min^{-1}) and that of toluene-2,4-diisocyanate (from 0.1 to 0.6 mL min^{-1}) on the proportion of benzyl chloride-2,4-diisocyanate produced has been investigated. At a reactor temperature of 130 °C, the optimal residence time is 9 s and benzyl chloride-2,4-diisocyanate is produced in 81.0% conversion. The space–time yield is 401.0 mol L^{-1} hr^{-1}, which is much higher than that obtained with a conventional reactor (1.3 mol L^{-1} hr^{-1}).



Scheme 8.8 Photochemical chlorination of toluene-2,4-diisocyanate.

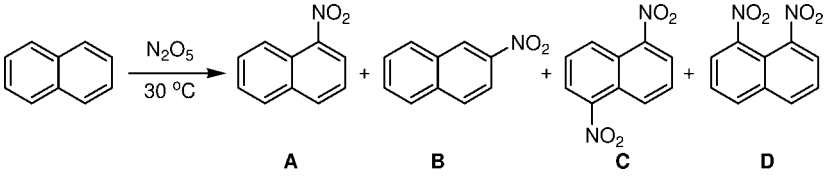


Scheme 8.9 Chlorination of acetic acid.

An industrial development was performed to increase the selectivity for monochlorination of acetic acid to give chloroacetic acid (Scheme 8.9) [1, 5]. This product is amenable under the reaction conditions by further chlorination to give dichloroacetic acid by consecutive reaction. Chloroacetic acid was obtained in 85% yield by using a falling film microreactor. The selectivity was much better and only less than 0.05% of dichloroacetic acid was formed, whereas typical conventional processing gives 3.5%. Increasing both temperature and pressure slightly resulted in an increase in the yield from 85 to 90%.

8.3 Nitration

Because liquid–liquid nitration reactions are described in another chapter [15–19], this section deals with nitration reactions involving the gas phase. The nitration of naphthalene using N_2O_5 in both the gas phase (*in situ* production from N_2O_4 and O_3) and the liquid phase has been carried out in microflow reactors under continuous flow conditions at 30 °C (Scheme 8.10) [20, 21]. The residence time is 3 s. The same reactions in conventional macrobatch operation require temperatures from −50 to −20 °C to avoid undesired side-reactions. The isomer ratio of the dinitration products (**C**:**D**) in a macrobatch process (1:3.6) is different from that for the microflow process (1:2.8). The isomer ratio of mononitration products (**A**:**B**) can also be changed; it is 20:1 for the macrobatch process and 32:1 for the microflow process.



Scheme 8.10 Nitration of naphthalene in a microflow reactor.

8.4 Conclusion

Substitution reactions in the gas-liquid phase such as fluorination with F_2, chlorination with $Cl_2/h\nu$, and nitration with N_2O_5 can be carried out in microflow reactors.

Fast heart transfer in microflow reactors is responsible for the control of such highly exothermic reactions.

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