Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

### Electronic Supplementary Information

# Biphasic Nucleophilic Aromatic Substitution Using a Microreactor under Droplet Formation Conditions

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## 1. ***General information***

All commercially available reagents were used without further purification. Monolithic particles[S1] and non-monolithic resin were purchased from Emaus Kyoto Inc., Japan. The non-monolithic resins was crushed into particles by the Kitamura Co. Ltd., Japan. Both monolithic and non-monolithic particles (Figure S1) were composed of the TETRAD-C epoxy monomer (Mitsubishi Gas Chemical Co. Ltd., Japan.) and the245-S curing agent (Fujikasei Kogyo Co. Ltd., Japan). The $^{1}$H nuclear magnetic resonance (NMR) and $^{13}$C NMR spectra were recorded at 400 and 100 MHz (Avance Ⅲ 400 HD, Bruker Co. Ltd., USA), respectively, and the chemical shifts are given as δ-values relative to the internal standard, tetramethylsilane (TMS). The yields of 4-fluoronitrobenzene **1**, 4-nitrophenetol **2**, 4-(4-chlorophenoxy)-nitrobenzene **4**, and 2-(2-methoxy-4-methylphenoxy)-nitrobenzene **7** were calculated by NMR spectroscopy, based on the *t*-butyl benzene internal standard, unless otherwise noted. The microflow reaction was performed using an X-1 microreactor system manufactured by Nakamura Choukou Co., Ltd, Japan (Figure S2). A dual plunger pump (KP-22, Flom Co., Ltd., Japan) and a high-pressure syringe pump (PHD-2000, Harvard Co., Ltd., USA) were used for observation of the flow patterns and measurement of the pressure drop, respectively. Micro mixers of COMET X-01 (Techno Applications Co., Ltd., Japan, currently not available), T-shape mixer (Cat. No 6010-47210, GL Science Co. Ltd., Japan), static mixer (SM1-05A, GL Science Co. Ltd., Japan), and PEEK Mixing

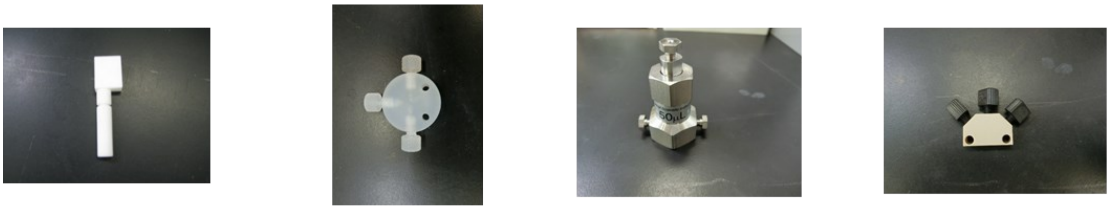
Monolithic particles Non-monolithic particles

**Figure S1**

Tee (Cat. No 6010-48650, GL Science Co., Ltd., Japan) were used for the study of the flow patterns, the pressure drop, and the reaction (Figure S3).

[S1] K. Furukawa, N. Ishizuka, D. Tokuda, N. Tsujioka, JP patent 2009-269948, 2009.

**Figure S2**



COMET X-01 T-Shaped mixer Static mixer PEEK Mixing Tee

**Figure S3**

## *2. Observation of flow patterns*

Toluene and water were separately flowed by a plunger pump and mixed in a mixer. The internal diameter of the PTFE tube was 0.25 mm for the front side of the mixer and 0.75 mm for the back side of the mixer. The flow rate was varied between 1 and 5 mL/min. The flow pattern was observed under a VCT-VBL-1e microscope (Shimazu-rika Co., Ltd., Japan) attached to a digital camera having a high-speed video mode (EXILIM EX-ZR1800, CASIO Co., Ltd., Japan) at room temperature. The flow patterns of the reaction solutions were observed at phase flow rates of 0.3 and 1 mL/min. As additional data to the main text, the flow patterns of various solvents are shown in Figures S4.

MIBK

Chlorobenzene

DIBK

AcO*t*Bu

**Figure S4** Photographic images of flow patterns (flow rate: toluene 1mL/ min, $H_2O$ 5mL/ min) .

### 3. Pressure drop measurements

The pressure drop of the mixer was measured using the apparatus shown in Figure S5.

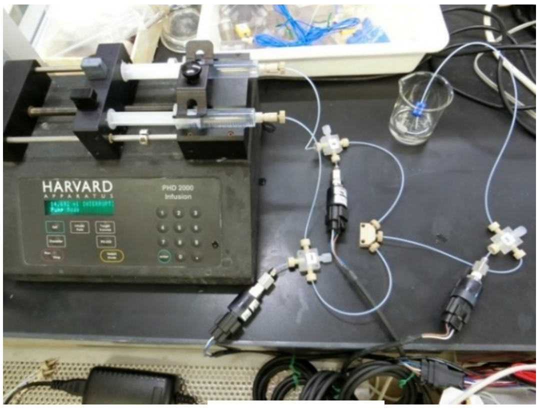


Figure S5

All parts were connected with 0.25 mm internal diameter PTFE tubing and water was flowed through the system using a high-pressure syringe pump at a flow rate of 0.5 mL/min. On-line pressure transducers (PA-750-352G-R1 and PA-750-103G-R1, COPAC Electronics Co., Ltd., Japan) were set at both the front and back sides of the mixer, and the data were collected using a data logger (Portable MULTI Logger ZR-RX40, OMRON Co., Ltd., Japan). The pressure drop was calculated from the difference between the front and back sides.

### 4. Typical reaction procedure

The microflow reaction was carried out using an X-1 microreactor system (Nakamura Choukou Co., Ltd, Japan). The organic solution (2 mM *p*-fluoronitrobenzene in an organic solvent) and the aqueous solution (50 mM tetrabutylammonium bromide in 30% ethanol/2N NaOH aq.) were separately flowed using dual-plunger pumps and mixed in a mixer. The flow rate was varied from 0.3 to 1 mL/min. The pumps and the mixer were connected to 0.25 mm internal diameter PTFE tubing, and the SUS tube was connected at the back side of the mixer as a reaction tube. The internal diameter of the reaction tube was 1 mm, and the length of the tube was 3 m. The reaction tube was introduced into the aluminum block, and the temperature was controlled regularly. The outlet flow was quenched using a 2N aqueous HCl solution. The solvent of the corrected organic phase was removed by evaporation, and the products were analyzed by NMR spectroscopy.

### *5. Reaction with phenol derivatives*

The reaction was performed according to the typical reaction procedure described above. The organic phase was composed of a DIBK solution containing 2 mM *p*-fluoronitrobenzene, while the aqueous phase was a 2N aqueous NaOH solution containing 2.2 mM of a phenol derivative and 50 mM tetrabutylammonium bromide. The obtained products were analyzed by NMR spectroscopy. The NMR signals of the reaction products were confirmed by comparison with the NMR spectra (shown below) of the compound separately synthesized via a batch process. The yield of the phenol derivative was calculated based on the internal standard (*t*-butyl benzene).

### *6. Analytical data of products (commercially unavailable)*

4-(4-Chlorophenoxy)-nitrobenzene **4**

$^1$H NMR ($CDCl_3$) δ:8.21(d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H) 7.02 (d, *J* = 9.2 Hz, 2H); $^{13}$C NMR ($CDCl_3$) δ:162.8, 153.2, 142.9, 130.6, 130.3, 126.0, 121.8, 117.2. Data obtained matched that previously reported.[S2]

[S2] *Bull. Fac. Sci. Tech. Hirosaki Univ*. **8**, 11－15 (2005)

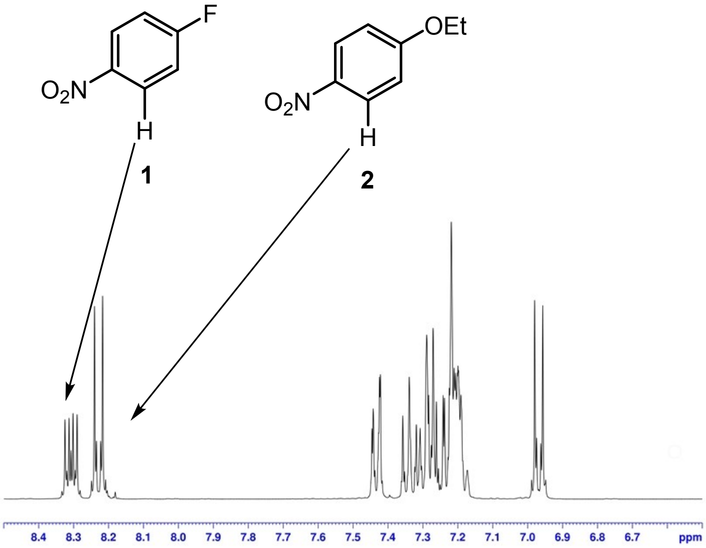
2-(2-Methoxy-4-methylphenoxy)-nitrobenzene **7**

$^1$H NMR ($CDCl_3$) δ: 7.92 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.39 (ddd, *J* = 1.6, 7.6, 8.0 Hz, 1H), 7.07 (ddd, 8.0 Hz, 7.6Hz, 1.2Hz, 1H), 6.96(d, 8.0Hz, 1H), 6.81 (s, 1H), 6.80 (d, 8.0Hz, 1H), 3.75 (s, 3H), 2.36 (s, 3H) ; $^{13}$C NMR ($CDCl_3$) δ:152.0, 151.0, 140.9, 139.8, 136.4, 133.9, 125.5, 121.6

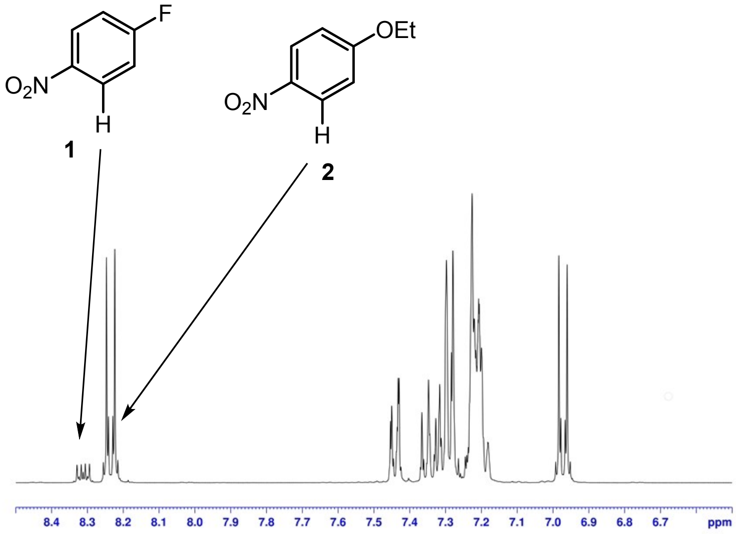
(containing three peaks), 117.8, 114.1, 55.9, 21.3. Data obtained matched that previously reported.[18a]

## *7. NMR spectra (aromatic region) of reaction mixtures*

Reaction mixtures of run 3 in Table 2

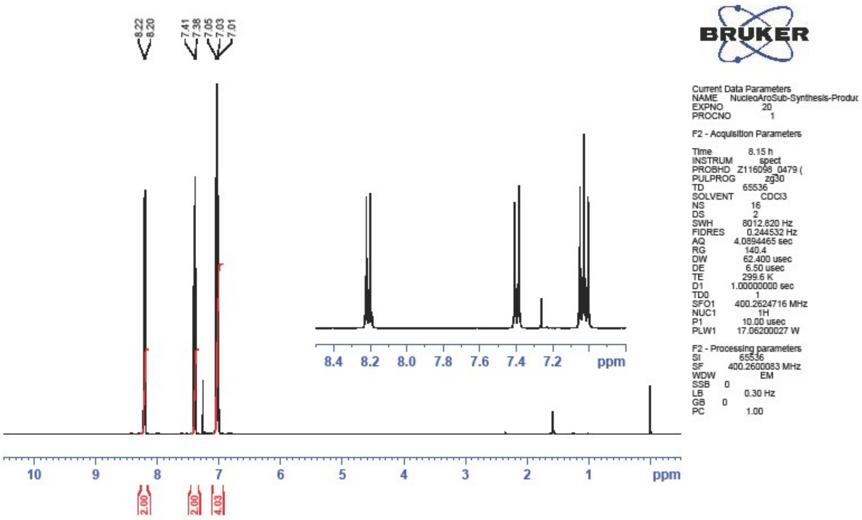


Reaction mixtures of run 5 in Table 2

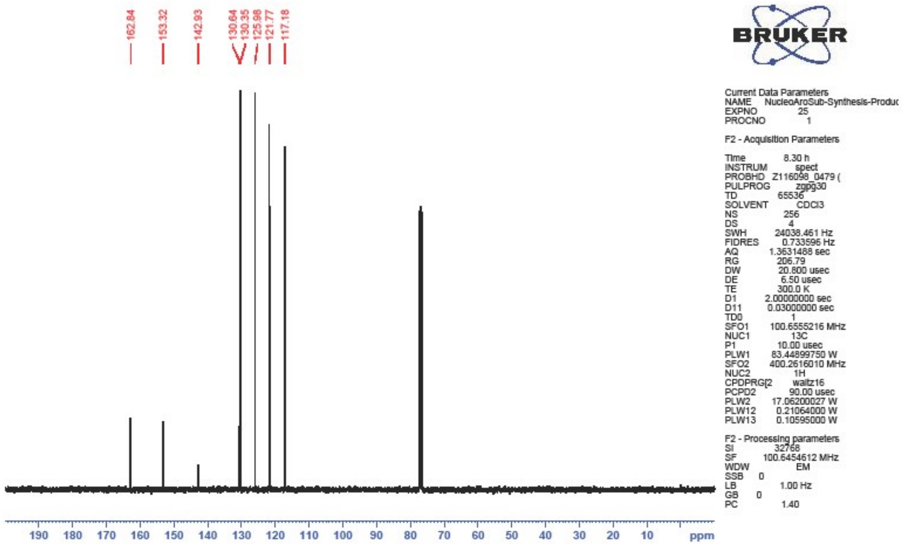


## *8. NMR spectra of the products*

4-(4-Chlorophenoxy)-nitrobenzene **4**

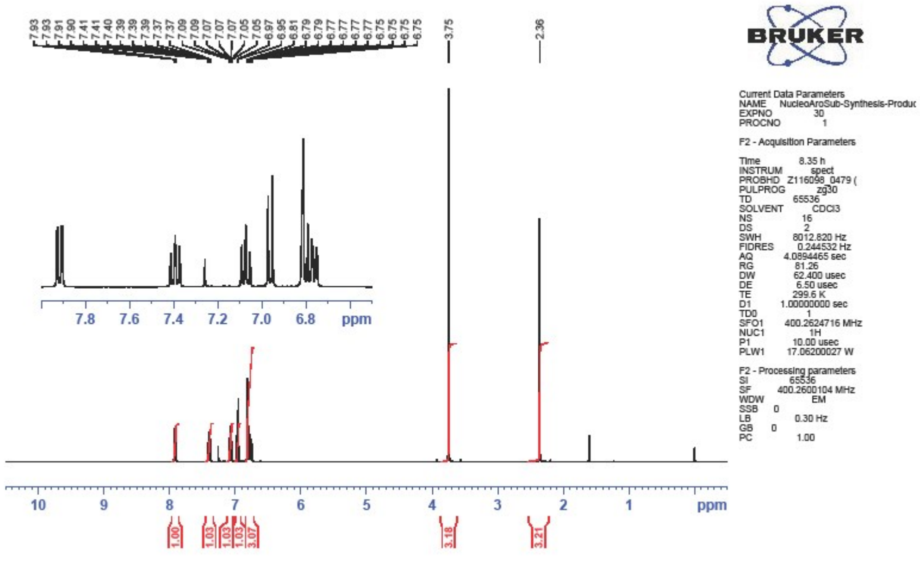


Sample 2 (4-FNB+p-Chlorophenol)

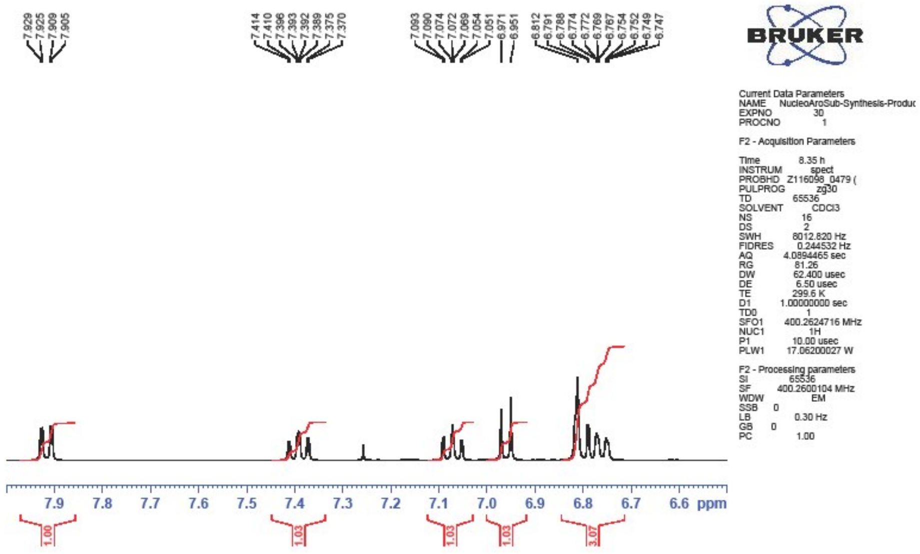


Sample 2 (4-FNB+p-Chlorophenol)

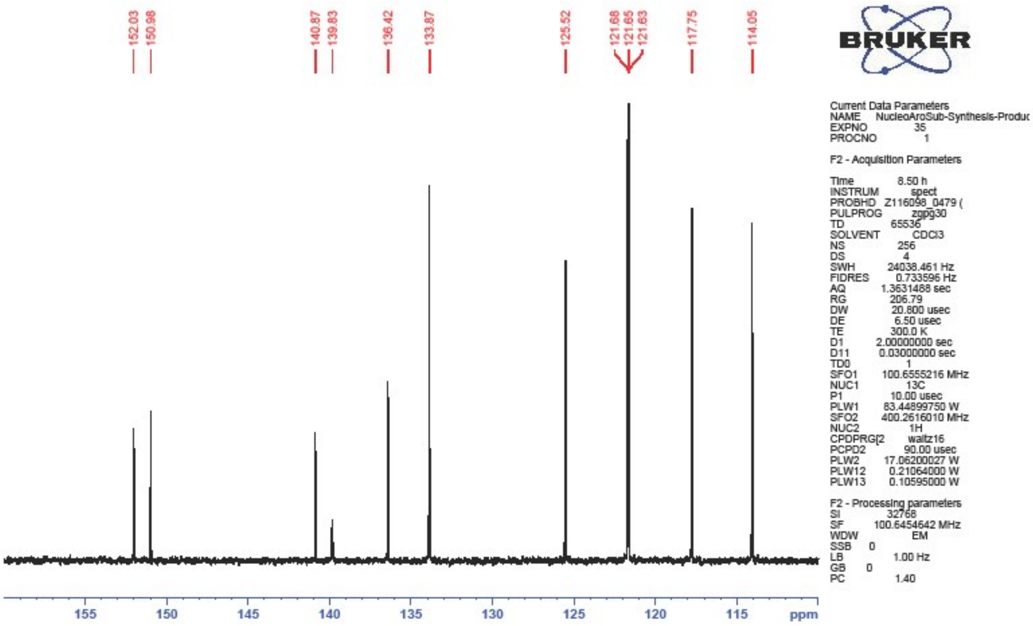
2-(2-Methoxy-4-methylphenoxy)-nitrobenzene **7**



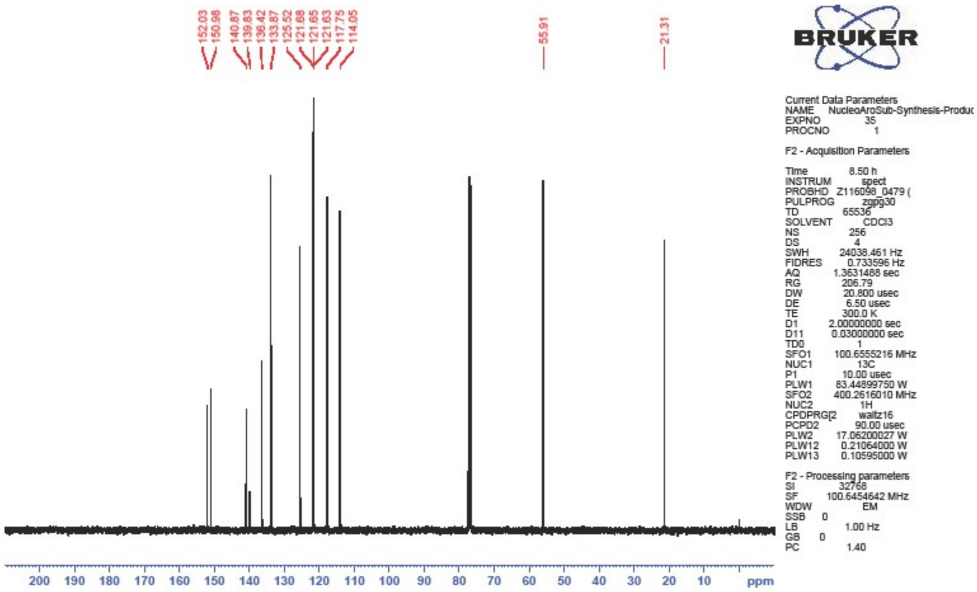
Sample 3 (o-Fluoronitrobenzene + o-Methoxy-p-methylphenol)



Sample 3 (o-Fluoronitrobenzene + o-Methoxy-p-methylphenol)



Sample 3 (o-Fluoronitrobenzene + o-Methoxy-p-methylphenol)



Sample 3 (o-Fluoronitrobenzene + o-Methoxy-p-methylphenol)