Synthetic Chemistry Group

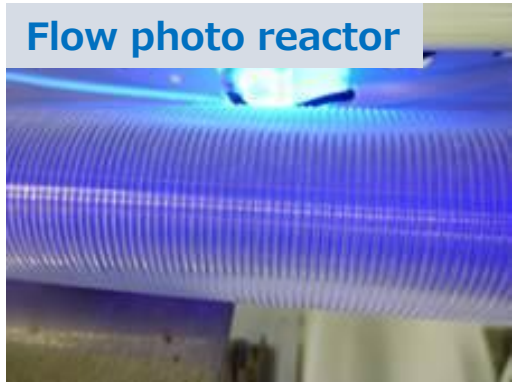
Services, technologies and facilities of Synthetic Chemistry Group

- **Development of efficient and practical synthetic route**
  - Retro synthesis design based on extensive experience, process shortening using advanced platform technology
- **Non-GLP bulk synthesis (～1 kg)**
  - High quality control (purity, residual solvent and metals, crystalline form etc.)
- **Synthesis of isotope labeled compounds**
  - Synthesis of stable isotope labeled compounds (^{2}H, ^{13}C, and ^{18}O etc)
  - Development of efficient synthetic route for radioisotope labeled compounds (^{3}H, ^{11}C, and ^{14}C) using cold compounds (Hot synthesis is outsourced)
- **Platform technologies**
  - Continuous flow chemistry, Photo redox cat. Reaction, Autoclaves etc.
- **Excellent facilities**
  - Automated sealed tube reactor, Jet-mill, Flow photo reactor, Autoclave etc.

Automated sealed tube reactor

Jet-mill

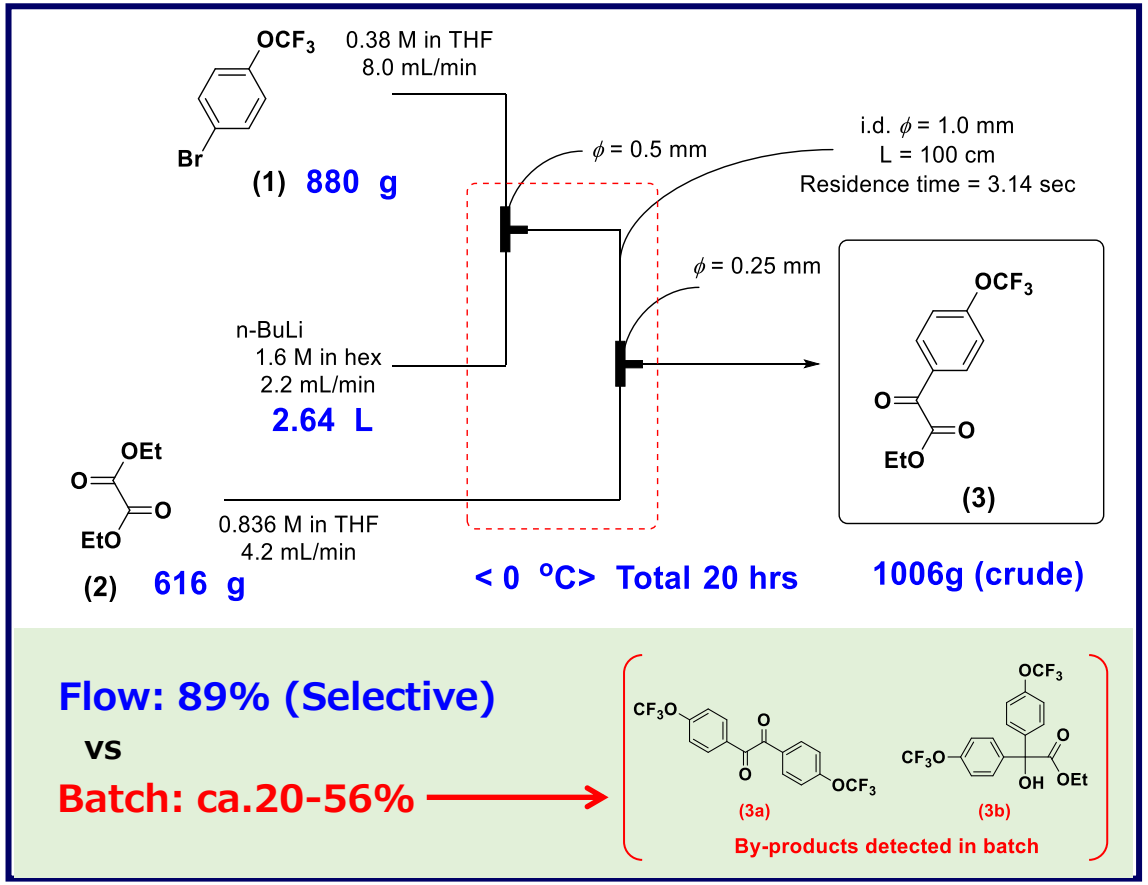
Flow photo reactor



Autoclave

Flow Chemistry

■ Kilogram-scale synthesis by continuous flow microreactor system



Set up of flow reaction system

A. Flow microreactor

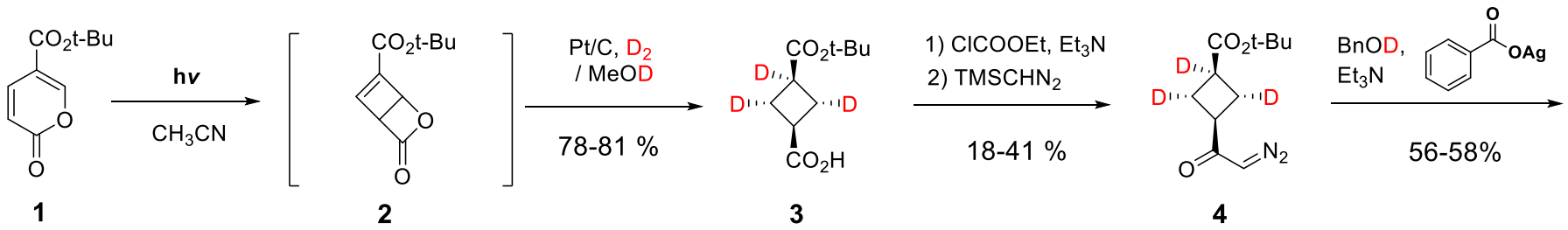
B. Multi-gram scale synthesis

C. Kilo-gram scale synthesis

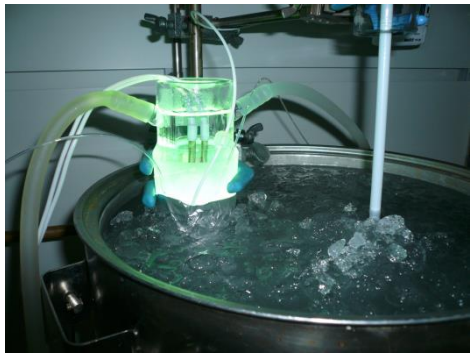
Flow chemistry enables reactions that have difficulties in batch system!

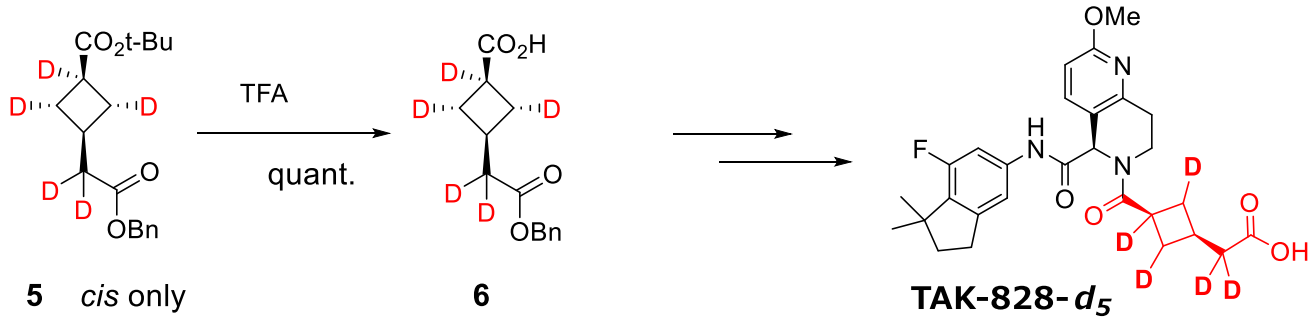
Synthesis of deuterated compounds by flow photo reaction

■ Establishment of efficient synthetic method for TAK-828-d_5 by using flow photo reaction



Flow : 3.6 g/10 hrs
Batch: 0.48 g/68 hrs





5 *cis* only **6**

TAK-828-d_5

$d_0 : d_1 : d_2 : d_3 : d_4 : d_5$ =
n.d. : n.d. : 0.7 : 9 : 47 : 100

ROR inverse agonist (WO 2016002968)

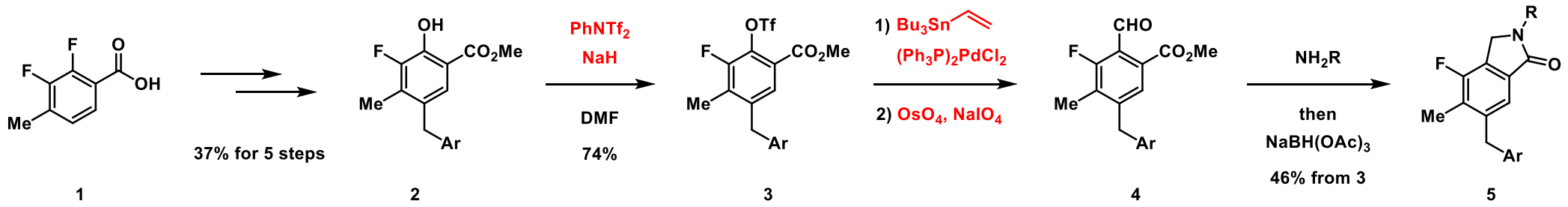
- **Cyclobutane derivative 3 labeled with deuterium at 3-positions was synthesized by [2+2]cycloaddition of compound 1 followed by hydrogenation with deuterium.**
- **Synthetic route of TAK-828-d_5 has been established by introducing additional two deuterium via Wolff rearrangement.**

T. Yamashita, *4th International Symposium for Medicinal Sciences* (**2018**).

Application of flow chemistry to establish efficient synthetic route

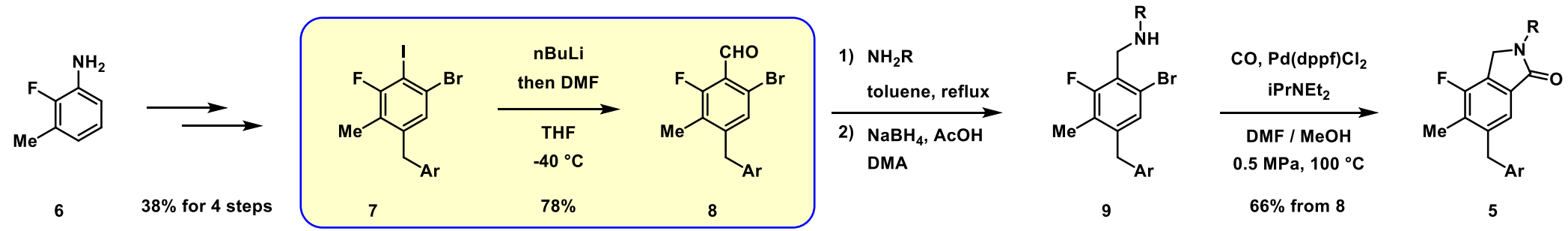
■ Averting toxic metal reagents

Original Route



Axcelead's Route

Flow Chemistry



747 g → **343 g** → **198 g**

- **Averting problematic reagents for scale-up synthesis has been achieved by taking advantage of flow chemistry.**
- **Efficient synthetic route of isoindolinone ring has been established.**

Org. Biomol. Chem., 2019, **17**, 8166.

Development of practical synthetic route

■ Optical resolution via diastereomeric salt formation

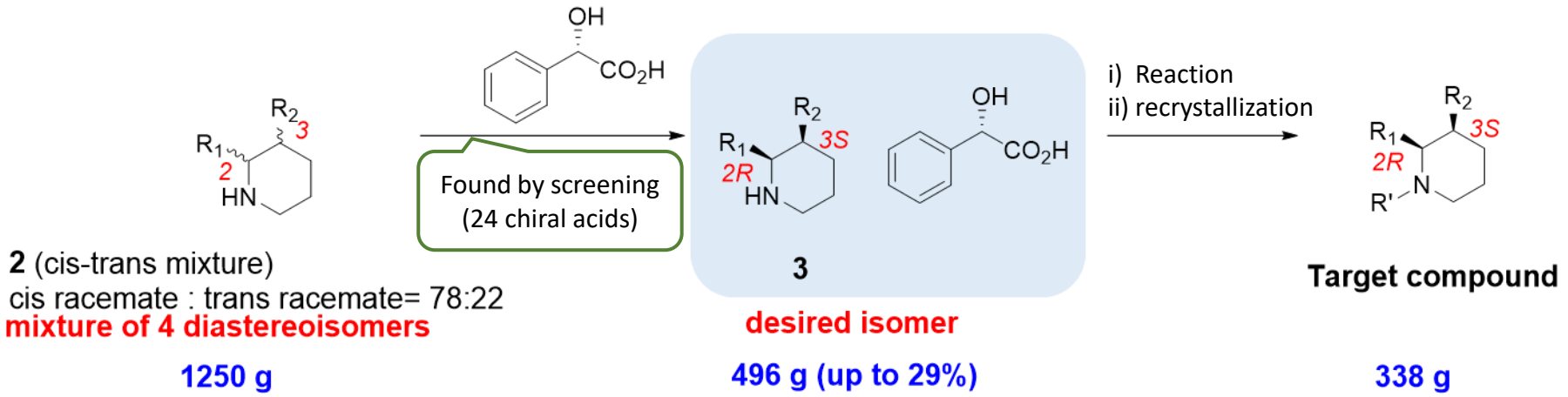
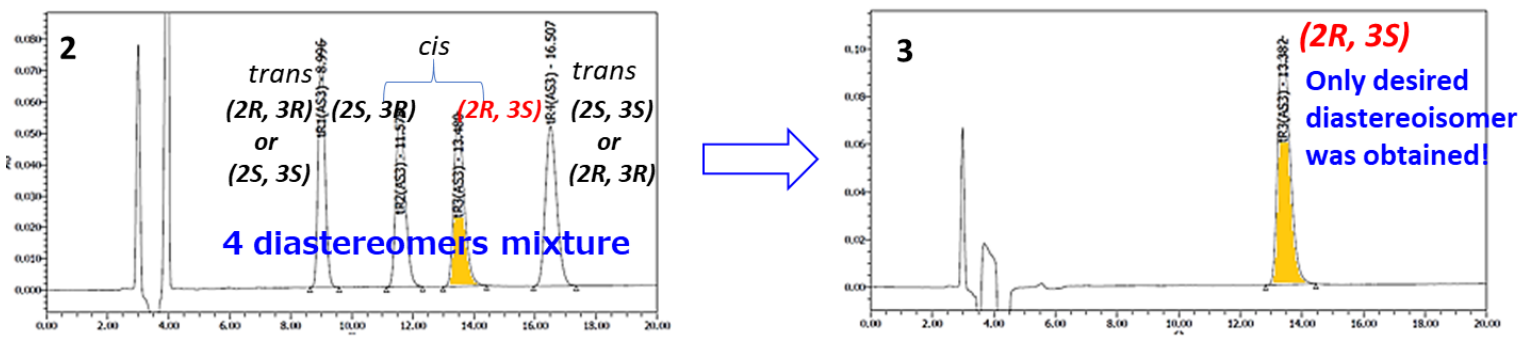


image of HPLC chart



- **The method to obtain single isomer from the mixture of 4 isomers without preparative HPLC purification has been established by diastereomeric salt formation.**
- **The absolute configuration of target compound has been determined by single crystal X-ray structure analysis of diastereomeric salt.**