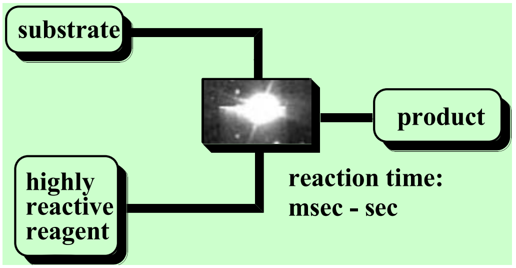
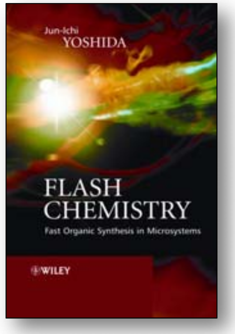
Flash Chemistry





- Flash chemistry is a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce desired compounds with high selectivity.
- The reaction time ranges from msec to sec.

How to achieve flash chemistry ?

- **fast reactions**
  - **highly reactive species**
    - **thermal generation**
    - **photochemical generation**
    - **electrochemical generation**
    - **generation by organometallic chemistry**

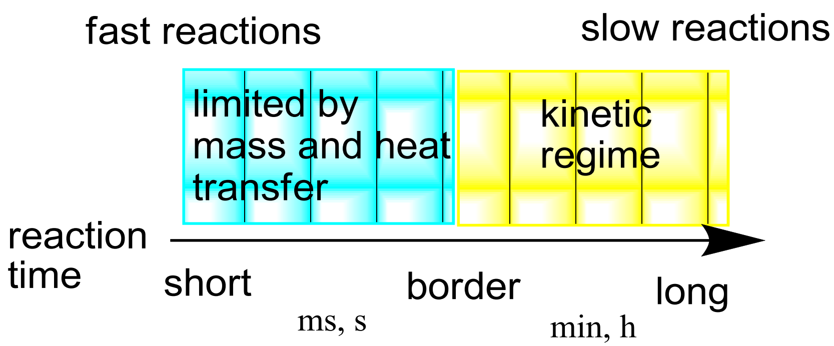
flow microreactor

Why micro ?
Problems inherent in conducting fast reactions in a preparative scale

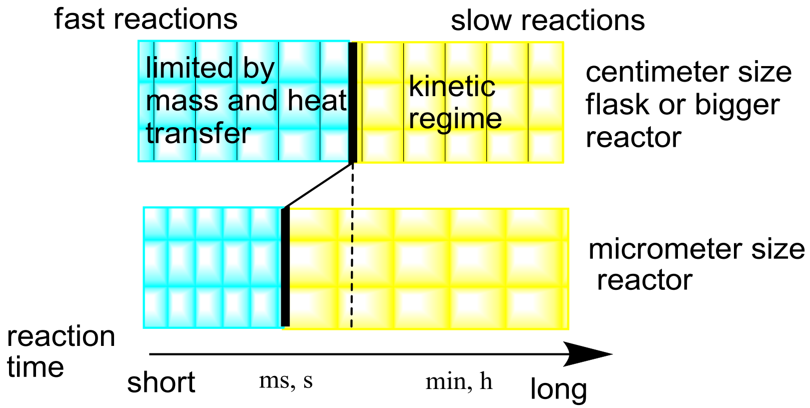
◆Fast reactions are usually highly exothermic.
◆Reactions are often faster than mass transfer.
◆Therefore, kinetics does not work!

explosion

Reaction Time and Reaction Regime



Reaction Time and Reaction Regime

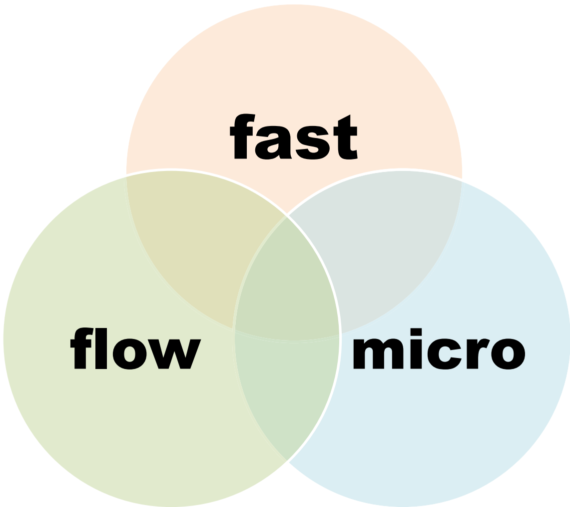


The border shifts with the size of a reactor, because mass and heat transfer strongly depend on diffusion.

Why flow microreactor?

- To conduct fast reactions in a controlled way, microreactors are essential.
- Productivity of batch microreactors are too small for synthesis.
- For synthesis, flow microreactors are essential.
- Especially, flow microreactors for fast reactions provide powerful tools for synthesis and production.

The Essence of Flash Chemistry



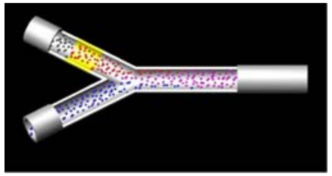
Examples of Flash Chemistry

- Organic Reactions
  - halogenation
  - nitration
  - oxidation
- Inorganic Reactions
  - inorganic particle synthesis
- Organometallic Reactions
  - organolithium reactions
  - Grignard reactions
- Polymerization Reactions
  - cationic polymerization
  - anionic polymerization
  - radical polymerization

Merit of Flash Chemistry

Flash chemistry enables use of short-lived highly reactive intermediates for synthesis

Residence time:
The length of time that the solution remains inside the reactor

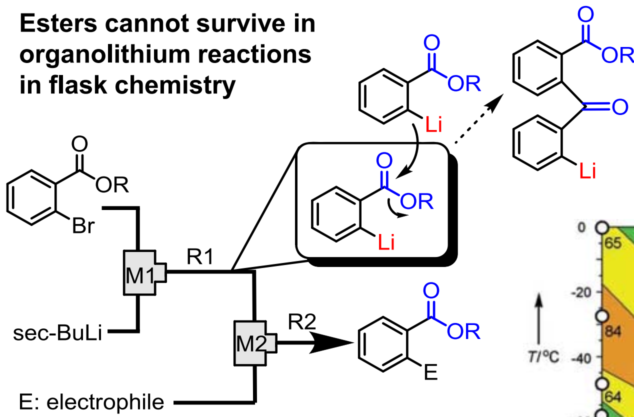


- **Highly reactive intermediates are unstable and are easy to decompose.**
- **If such intermediates are transported to the next reactor *within the lifetime*, we can use them for the reaction before decomposition.**
- **In flow microreactor systems, *residence time can be greatly reduced* by adjusting the length of micro channels and flow speed.**

Esters survive in organolithium reactions in flash chemistry.

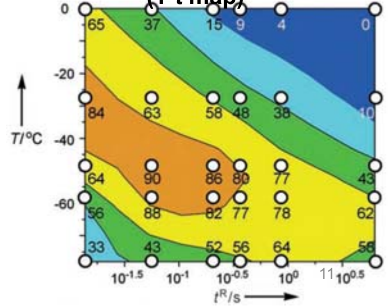
Nagaki, A.; Kim. H.; Yoshida, J. *Angew. Chem. Int. Ed.* 2008, 47, 7833.

Esters cannot survive in organolithium reactions in flask chemistry

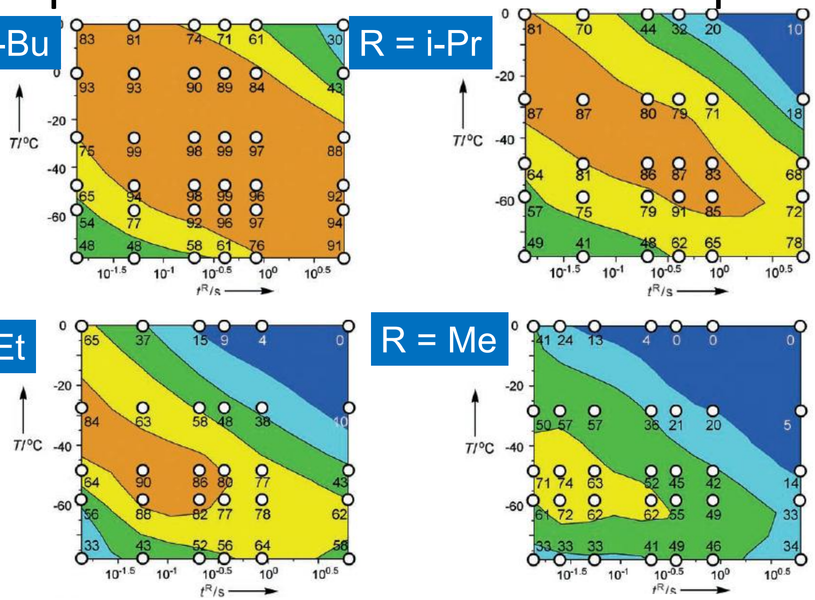


high time-solution analysis of reactions under preparative conditions

temperature-residence time map (T-*t* map)

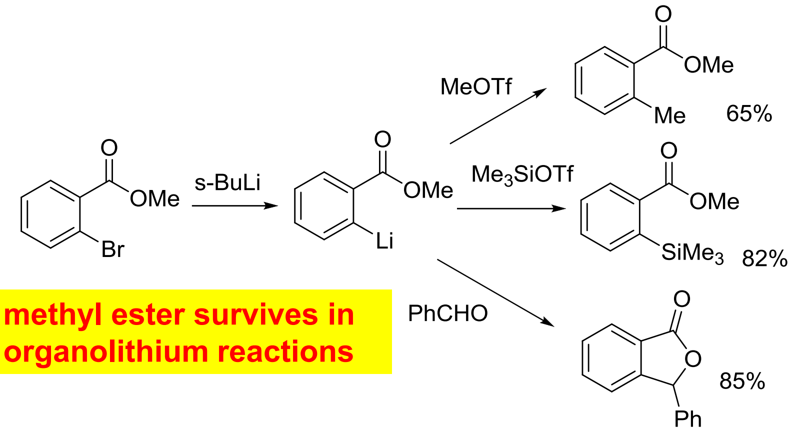


Temperature-Residence Time Map



Mission Impossible in Flask Chemistry!

Generation and Reactions of Aryllithium Bearing Methoxycarbonyl Group

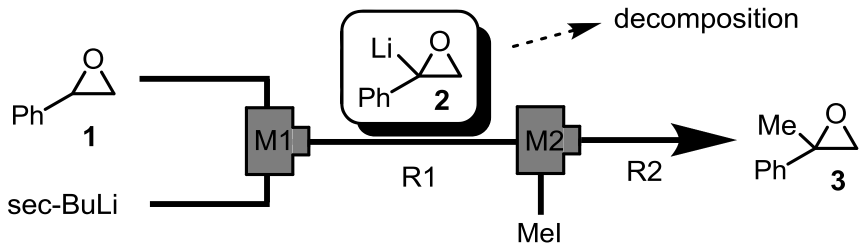


methyl ester survives in organolithium reactions

Example of Residence Time Control

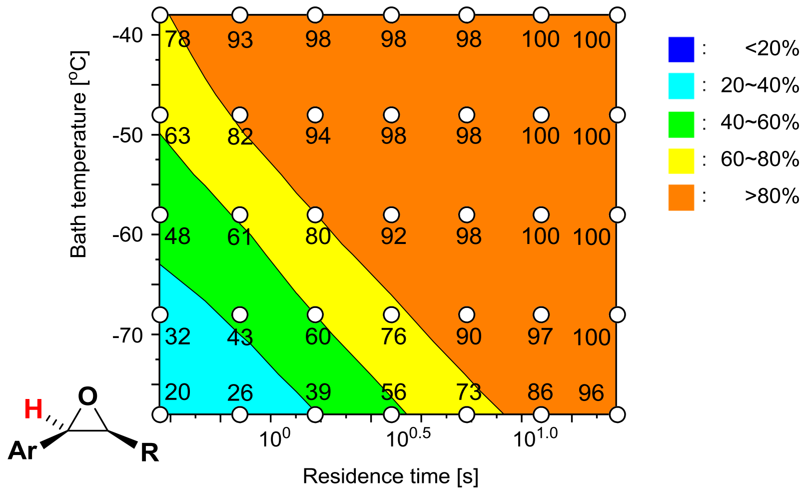
Lithiation of an Epoxide without Decomposition of the Oxyranyllithium Intermediate

Nagaki, A.; Takizawa, E.; Yoshida, J. *J. Am. Chem. Soc.* **2009**, *131*, 1654



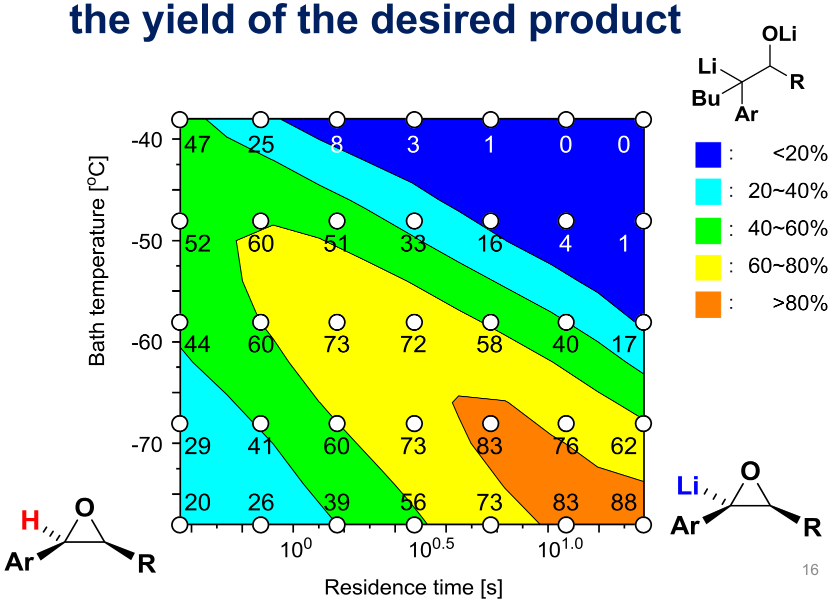
Temperature – Residence Time Map

conversion of the starting material

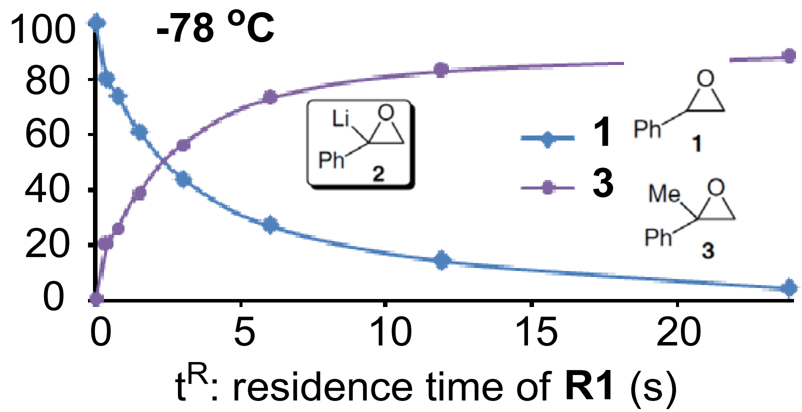


Temperature – Residence Time Map

the yield of the desired product

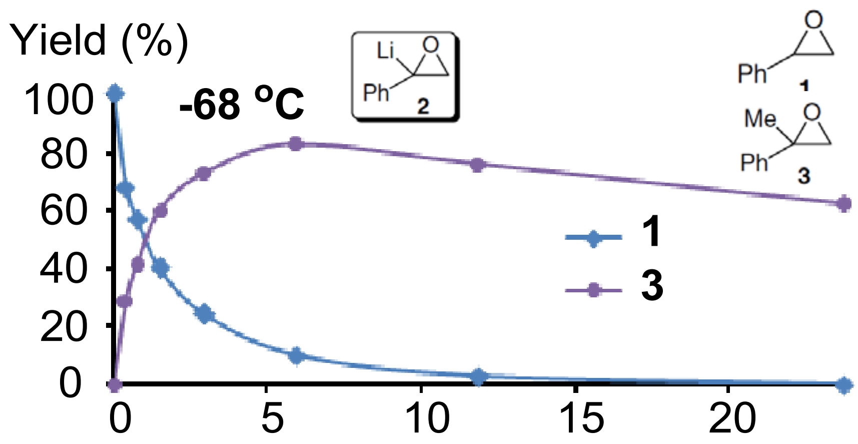


How does the reaction take place at -78 °C?

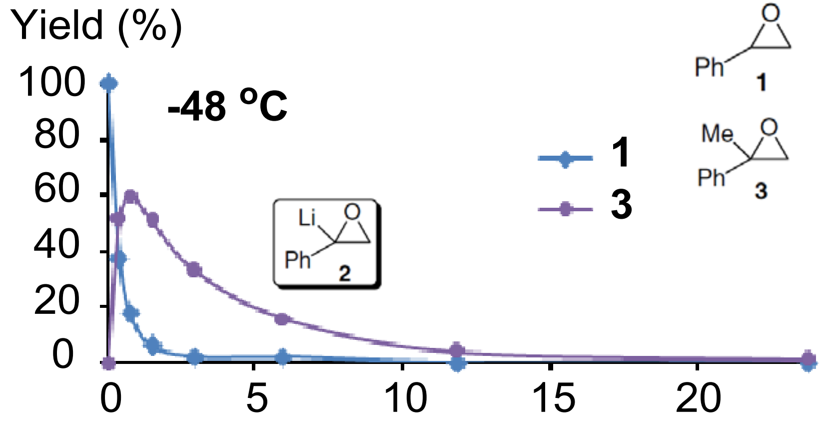


Lithiation takes 20 sec.

If we increase the temperature,



Further increase in the temperature



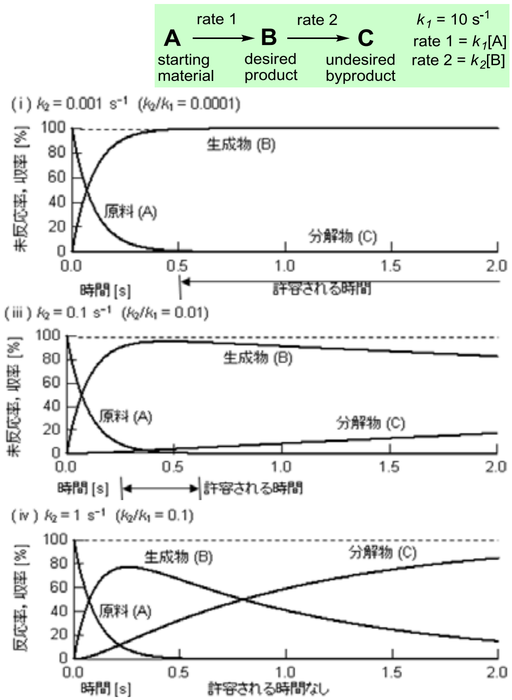
Lithiation finishes within 1 sec at -48 °C, but the oxyranyllithium decomposes very quickly.

General Consideration

Possible in a flask

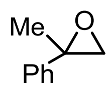
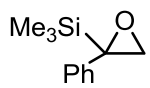
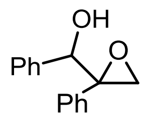
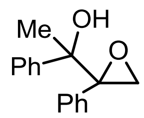
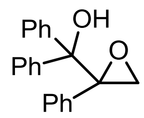
Possible only in a flow microreactor (residence time = 0.3∼0.6 s)

Impossible even in a flow microreactor



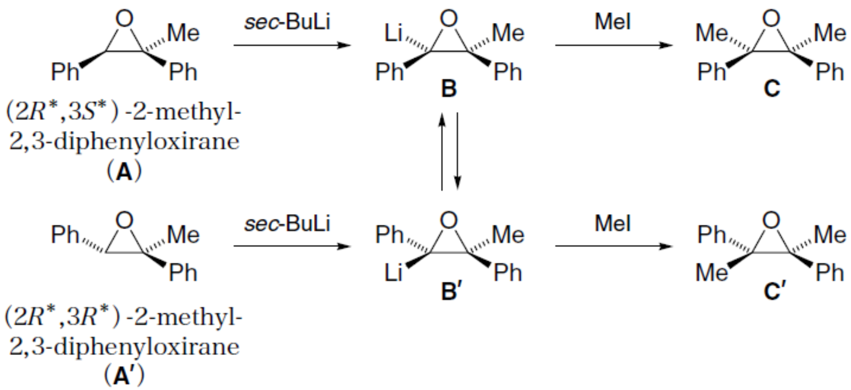
Reactions with Various Electrophiles

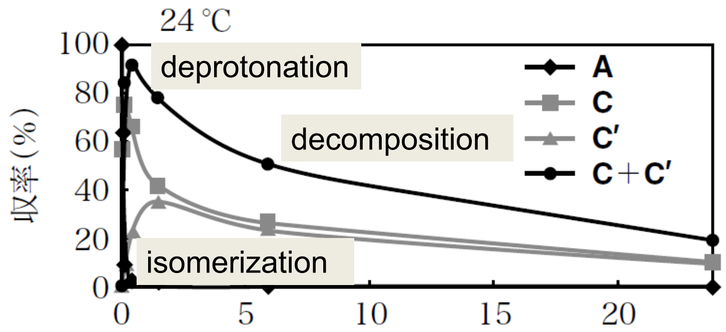
Temperature： -78 oC、 residence time 23.8 s

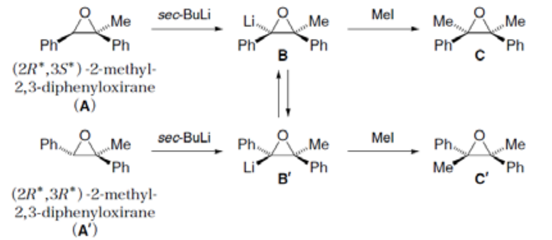
electrophile	MeI	Me_3SiCl	PhCHO	$PhCOCH_3$	PhCOPh
product					
% yield	88	72	84^b	70^c	82
productivity g/h	4.2	5.0	6.8	6.1	9.0

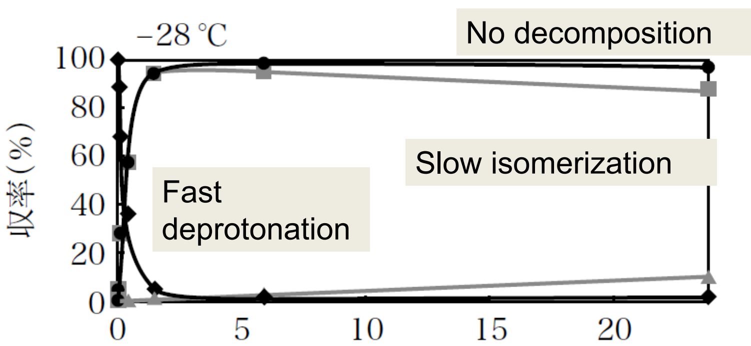
Good productivity

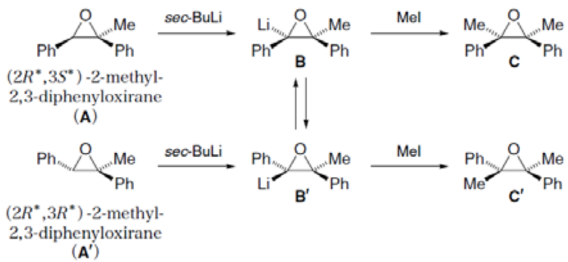
More Complex Reaction System

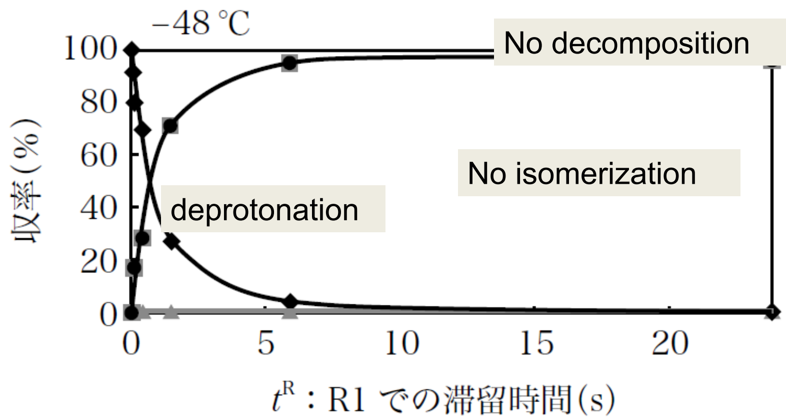


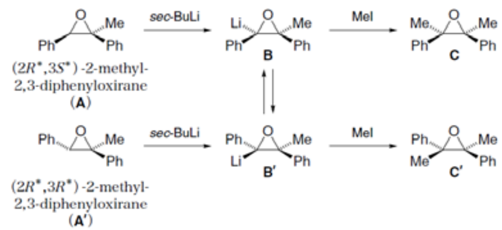












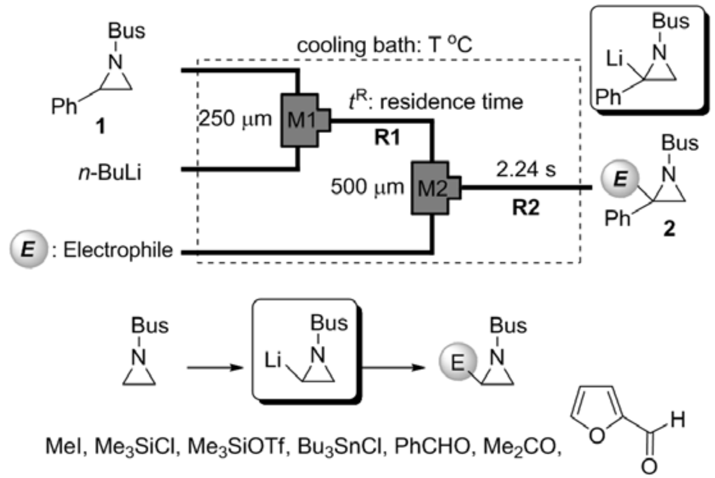
Reactions with Various Electrophiles

Temperature -48 oC, Residence Time: 23.8 s

epoxide	oxyranyllithium	electrophile	yield (%) (c/t ratio)	productivity g/h
c-8[a]	*c*-9	MeI	*c*-10 / *t*-10: 96 (> 99 : 1)[c]	7.8
t-8[b]	*t*-9	MeI	82 (2 : 98)[c]	3.3 [e]
c-8[a]	*c*-9	Me_3SiCl	*c*-11 / *t*-11: 97 (> 99 : 1)[c]	9.9
t-8[b]	*t*-9	Me_3SiCl	79 (4 : 96)[c]	4.0 [e]
c-8[a]	*c*-9	PhCOPh	*c*-12 / *t*-12: 92 (> 99 : 1)[d]	13
t-8[b]	*t*-9	PhCOPh	72 (4 : 96)[d]	5.1[e]

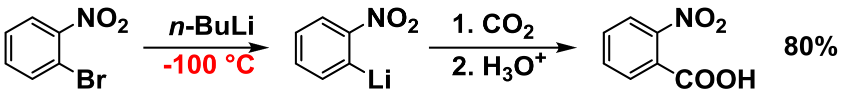
N-tert-Butylsulfonyl(Bus)-a-phenylaziridinyllithium

A. Nagaki, E. Takizawa, J. Yoshida, *Chem. Lett. In press.*

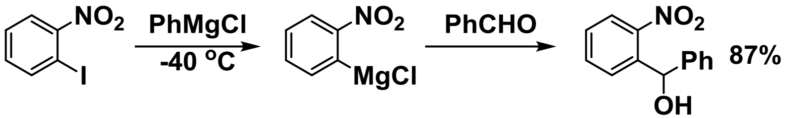


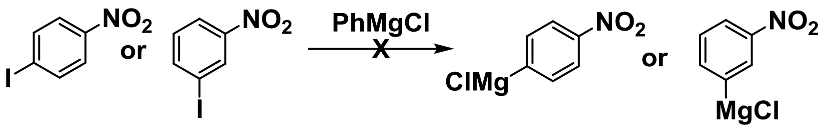
Generation and Reactions of Aryllithiums Bearing a Nitro Group

There is no literature about the generation and reaction of aryllithium bearing a nitro group at *m*- or *p*-position.



Kobrich, B.; Buck, P. *Chem. Ber*. **1970**, *103*, 1412.



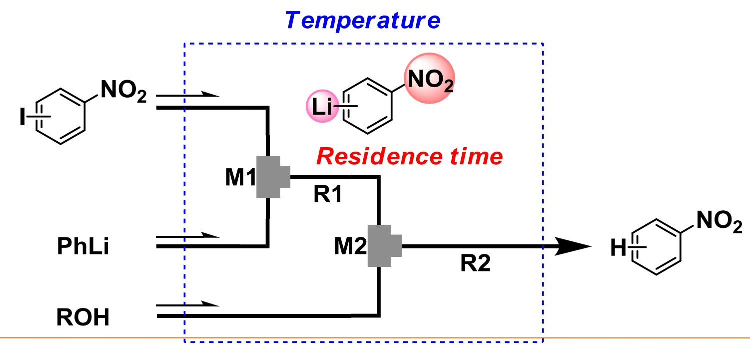


Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed*. **2002**, *41*, 1610.

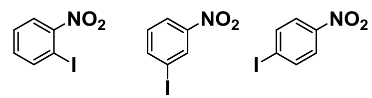
Sapountzis, I.; Dube, H.; Lewis, R.; Gommermann, N.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2445.

Generation and Reaction of Nitrophenyllithiums Using Microflow Systems

A. Nagaki, H. Kim, and J. Yoshida, *Angew. Chem. Int. Ed.* 2009, *48*, 8063 **.**



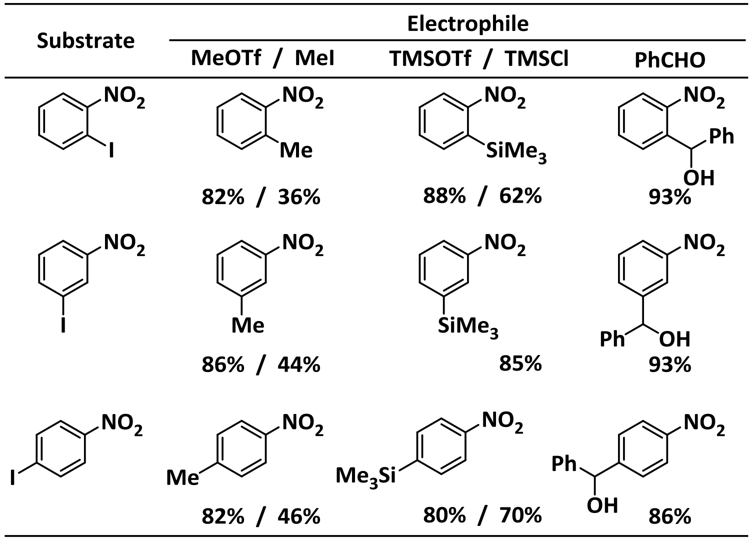
Substrates :



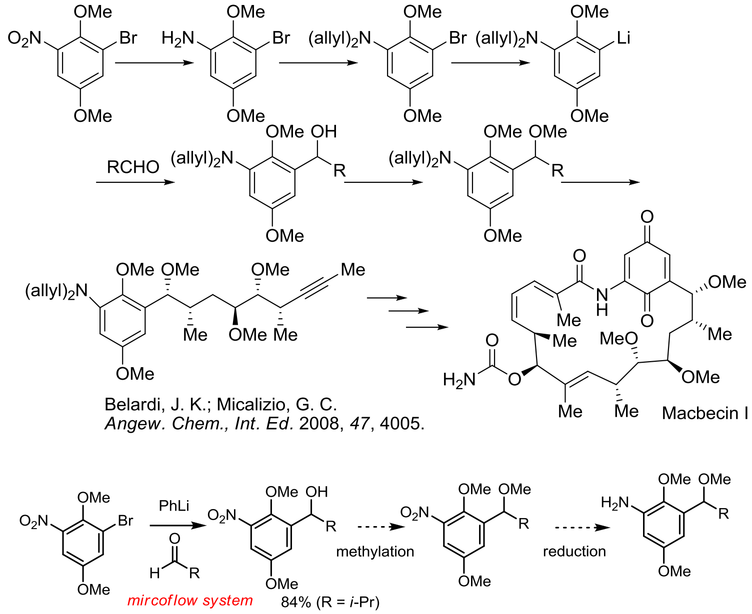
Residence time: 0.014 s to 6.3 s

Temperature : -78 °C to 0 °C

Reactions with Electrophiles

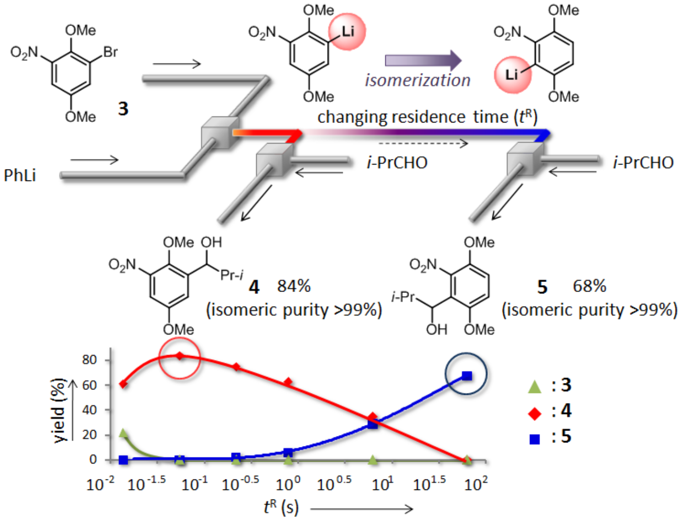


Applications to Synthesis of Complex Molecules



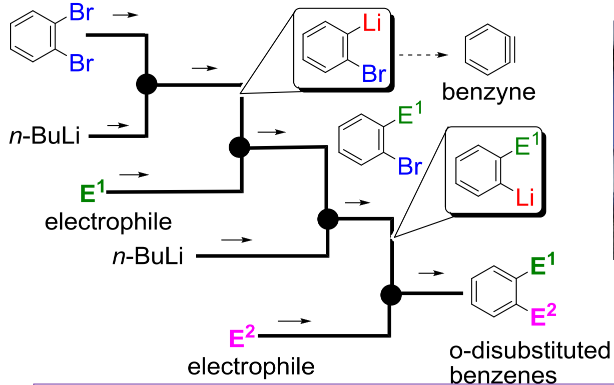
ArylLi bearing NO_2 Isomerization or Not Isomerization

Nagaki, A.; Kim, H.; Yoshida, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 8063



Integrated Synthesis of *o*-Disubstituted Benzenes

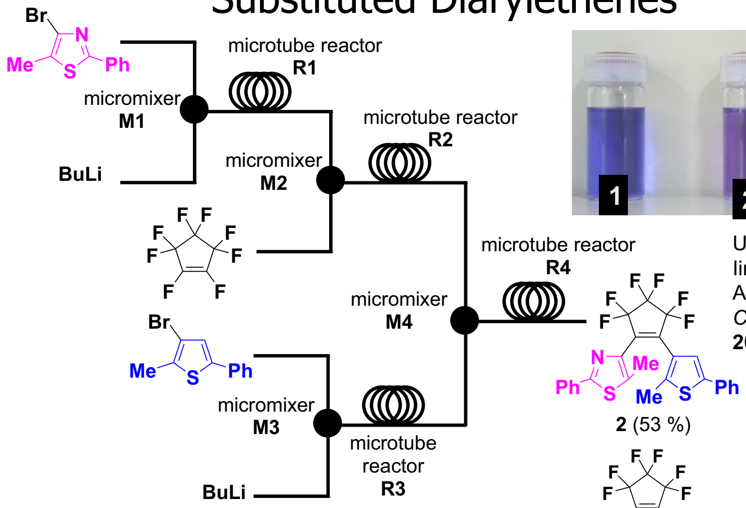
Usutani, H.; Tomida, T.; Nagaki, A.; Okamoto, H.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 3046



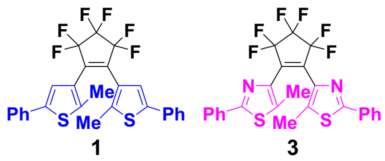
Integrated Flow Microreactor System

Integrated flow microreactor system enables a straightforward transformation that is difficult to achieve by conventional method

Integrated Synthesis of Unsymmetrically-Substituted Diarylethenes



Ushiogi, Y.; Hase, T.; Iinuma, Y.; Takata, A.; Yoshida, J. *Chem. Commun.* **2007**, 2947-2949.



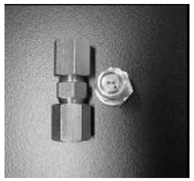
Effective way of making new functional materials

Can flash chemistry be applied to industrial production ?

Yes !

A Pilot Plant Grignard Exchange Reaction

Wakami, H.; Yoshida, J. *Org. Process Res. Dev.* **2005**, *9*, 787-791



Toray Hi-mixer

continuous operation
20 °C
residence time 5 sec
14.7 kg/24 h

Conclusion

Synthetic reactions can be much faster if they are released from the constraints of a flask.

Reactions can be conducted at natural rates in a highly controlled manner without deceleration by virtue of characteristic features of microflow systems.

New synthetic transformations which are difficult to achieve using conventional flask chemistry can be achieved (straightforward synthesis without protecting groups).

Flash chemistry will make paradigm shift in laboratory chemical synthesis and industrial production