The Work of Prof. Jun-ichi Yoshida (1952-2019)

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Short Biography

- **Born** in Osaka, Japan on November 13, 1952.
- **Studied** chemistry at Kyoto University
- **PhD** at Kyoto University in 1982, under supervision of Prof. Makoto Kumada
- **Postdoc** at University of Wisconsin-Madison (USA) with Barry M. Trost

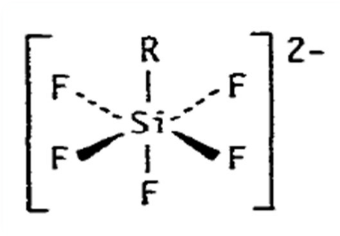
- **Assistant professor** at Kyoto Institute of Technology, until 1985.
- **Assistant professor** at Osaka City University, until 1992
- **Associate professor** at Osaka City University, until 1994
- **Full professor** at Kyoto University, from 1994-2018.

- Prof. Yoshida received several notable **awards**:
  - **1987:** Progress Award in Synthetic Organic Chemistry, Japan
  - **2001:** Chemical Society of Japan (CSJ) Award for Creative Work
  - **2006:** Nagoya Silver Medal
  - **2007:** Humboldt Research Award
  - **2013:** Chemical Society of Japan award
  - **2014:** Baizer Award
  - **2015:** Medal with Purple Ribbon
  - **2019:** Orders of the Sacred Treasure

PhD with Prof. Makoto Kumada

Makoto Kumada (1920-2007) : worldwide known as the father of polysilane chemistry and also as one of the discoverers of modern transition-metal-catalyzed cross-coupling reactions.

Yoshida's PhD Topic: *Synthetic applications of organopentafluorosilicates.*



Notable examples:

1. Anti-Markovnikoff hydrohalogenation of olefins via organopentafluorosilicate intermediates (Tamao, Yoshida, Takahashi, Yamamoto, Kakui, Matsumoto, Kurita, Kumada, *J. Am. Chem. Soc.* **1978**, *100*, 290-292,).

$$RCH{=}CH_2 + HSiCl_3 \xrightarrow{\text{catalyst}} RCH_2CH_2SiCl_3$$

$$\xrightarrow{KF} K_2[RCH_2CH_2SiF_5] \xrightarrow{XY} RCH_2CH_2X$$

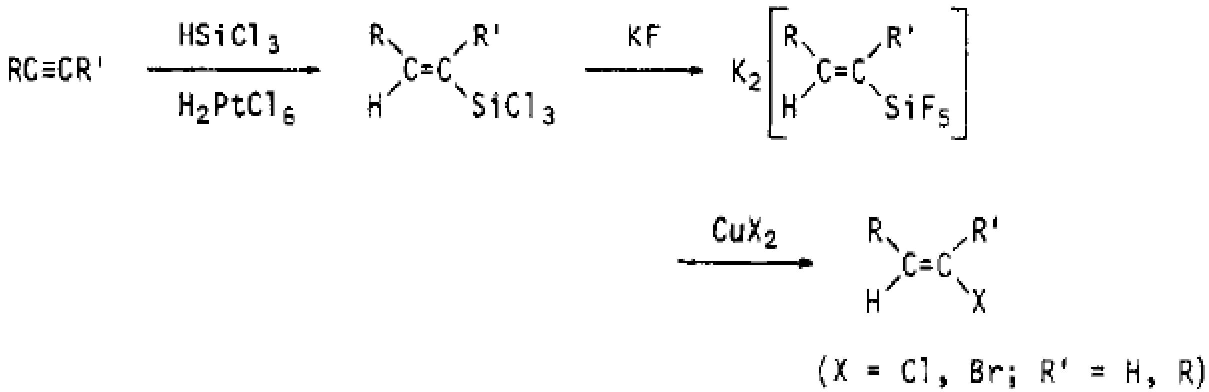
$(XY = Cl_2,\ Br_2,\ I_2,\ NBS)$

PhD with Prof. Makoto Kumada

Notable examples:

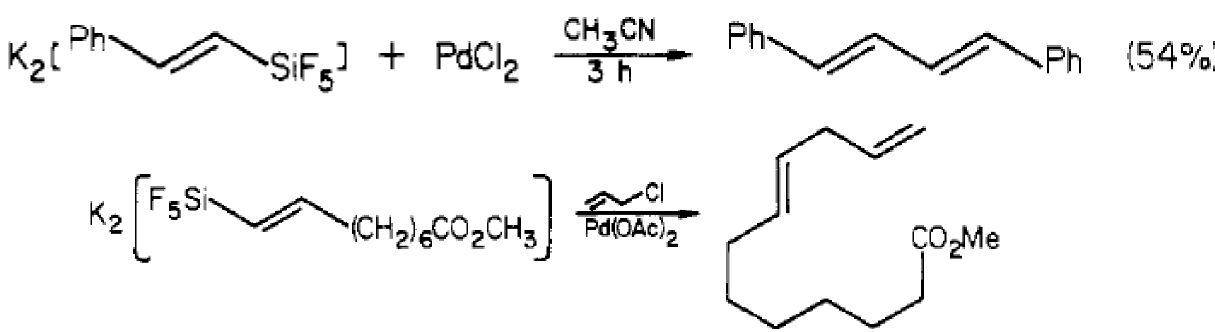
2. Cu(+II) oxidation of organopentafluorosilicate intermediates yielding organic halides

(Yoshida, Tamao, Kakui, Kurita, Murata, Yamada, Kumada, *Organometallics* **1982**, *1*, 369-380).



3. Pd-catalyzed C–C bond formation: homocoupling and cross coupling chemistry

(Yoshida, Tamao, Yamamoto, Kakui, Uchida, Yamada, Kumada, *Organometallics* **1982**, *1*, 542-549).

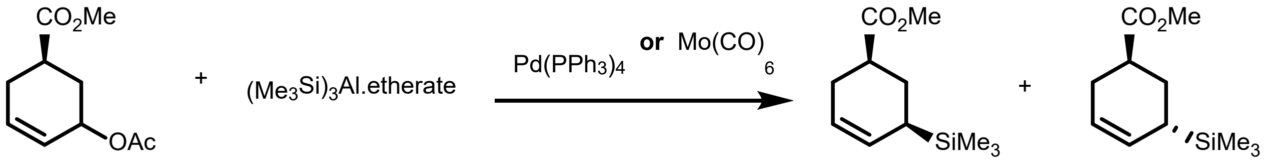


PostDoc with Prof. Barry Trost

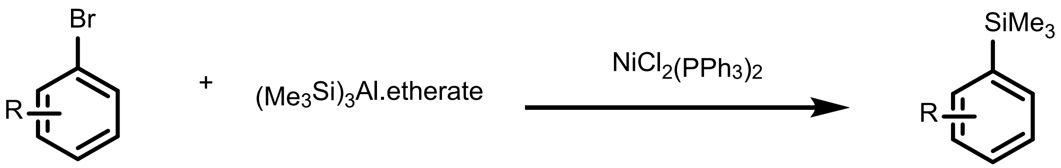
Barry Trost (1941) : worldwide known for his work in organic synthesis, particularly novel synthetic methodology.

Two papers emerged from his postdoc :

1. Silylation of allyl acetates (Trost, Yoshida, Lautens, *J. Am. Chem. Soc.* **1983**, *105*, 4494-4496).



2. Silylation of aryl and vinyl halides (Trost, Yoshida, *Tetrahedron Lett.* **1983**, *24*, 4895-4898)



PostDoc with Prof. Barry Trost

Lab Partner Prof. Mark Lautens (U Toronto): "Jin-ichi was a warm and nice guy, even when we first met. He and I jointly published work in JACS based on his knowledge of silicon chemistry (from his PhD with Kumada) and my work with molybdenum allylation. He tried Pd, I did Mo. "

"Also, I was invited to his house for dinners many times. I recall his wife once served mochi (not sure if correct spelling) and he said it was traditional at special events. I never tasted anything that was so chewy and easy to choke on. We laughed that it was what you served older senior professors when they were resistant to retire!"

Retirement 2018

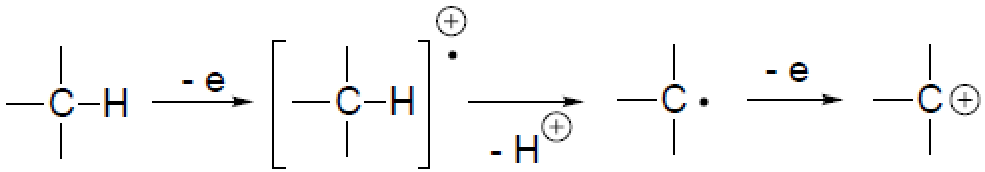
Mentorship:
Prof. Seiji Suga (Okayama University)

Relevant topics:

- Cation pool method
- Electrochemistry in flow

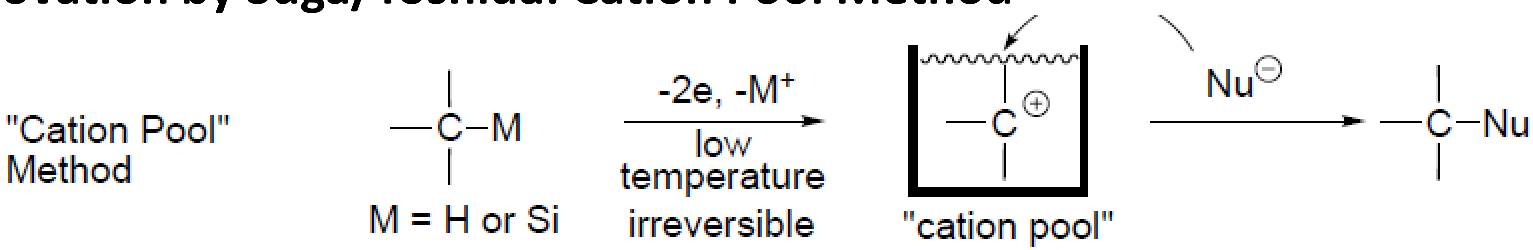
Cation Pool Flow Method

Oxidative generation of unstable carbocations:



Only possible with nucleophiles which are compatible under the carbocation generation conditions.

Innovation by Suga/Yoshida: Cation Pool Method



Generation and accumulation of highly reactive cations can be done at low temperatures (-78 ^{o}C).

For a review: Yoshida, Suga, *Chem. Eur. J.* **2002**, *8*, 2650-2658.

Cation Pool Method

Notable examples:

1. Generation of iminium cation pools and reaction with carbon nucleophiles

(Yoshida, Suga, Suzuki, Kinomura, Yamamoto, Fujiwara, *J. Am. Chem. Soc.* **1999**, *121*, 9546-9549).

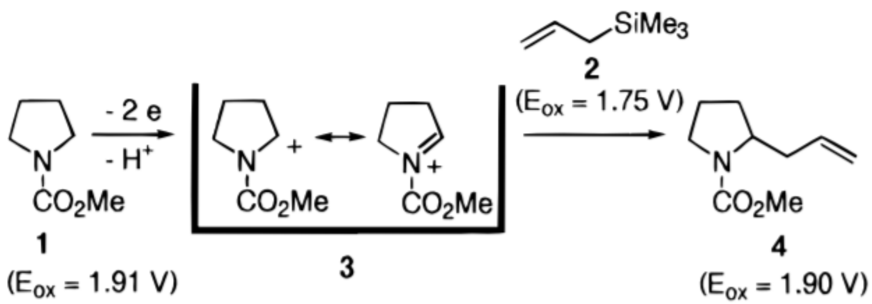


Table 1. Effect of the Temperature on the Electrolysis of **1**[a]

temp (°C)	conversion (%)	yield[b] (%)
−72	100	82
−47	100	78
−25	84	31
0	77	10
20	61	5

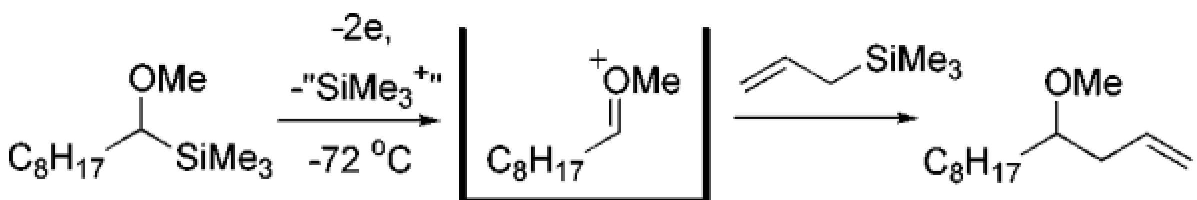
For a review: Yoshida, Suga, *Chem. Eur. J.* **2002**, *8*, 2650-2658.

Cation Pool Method

Notable examples:

2. Generation of alkoxycarbenium ion pools and reaction with carbon nucleophiles

(Suga, Suzuki, Yamamoto, Yoshida, *J. Am. Chem. Soc.* **2000**, *122*, 10244-10245).



1

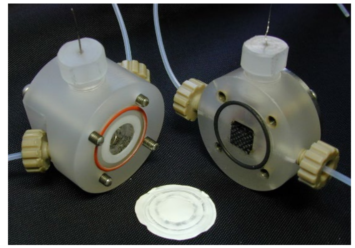
2
cation pool

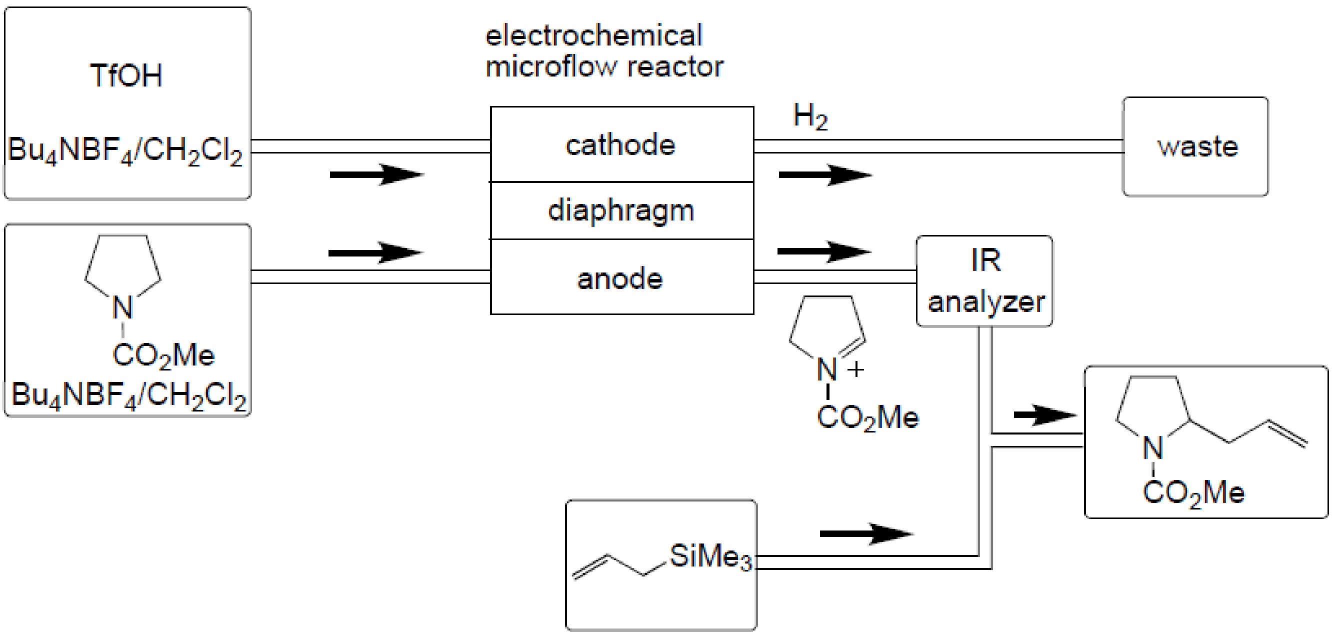
3

For a review: Yoshida, Suga, *Chem. Eur. J.* **2002**, *8*, 2650-2658.

Cation Pool Flow Method

Cation Pool Flow method:

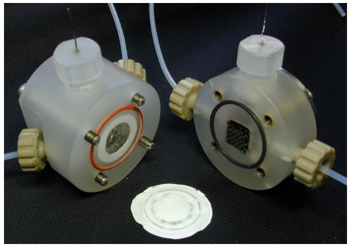


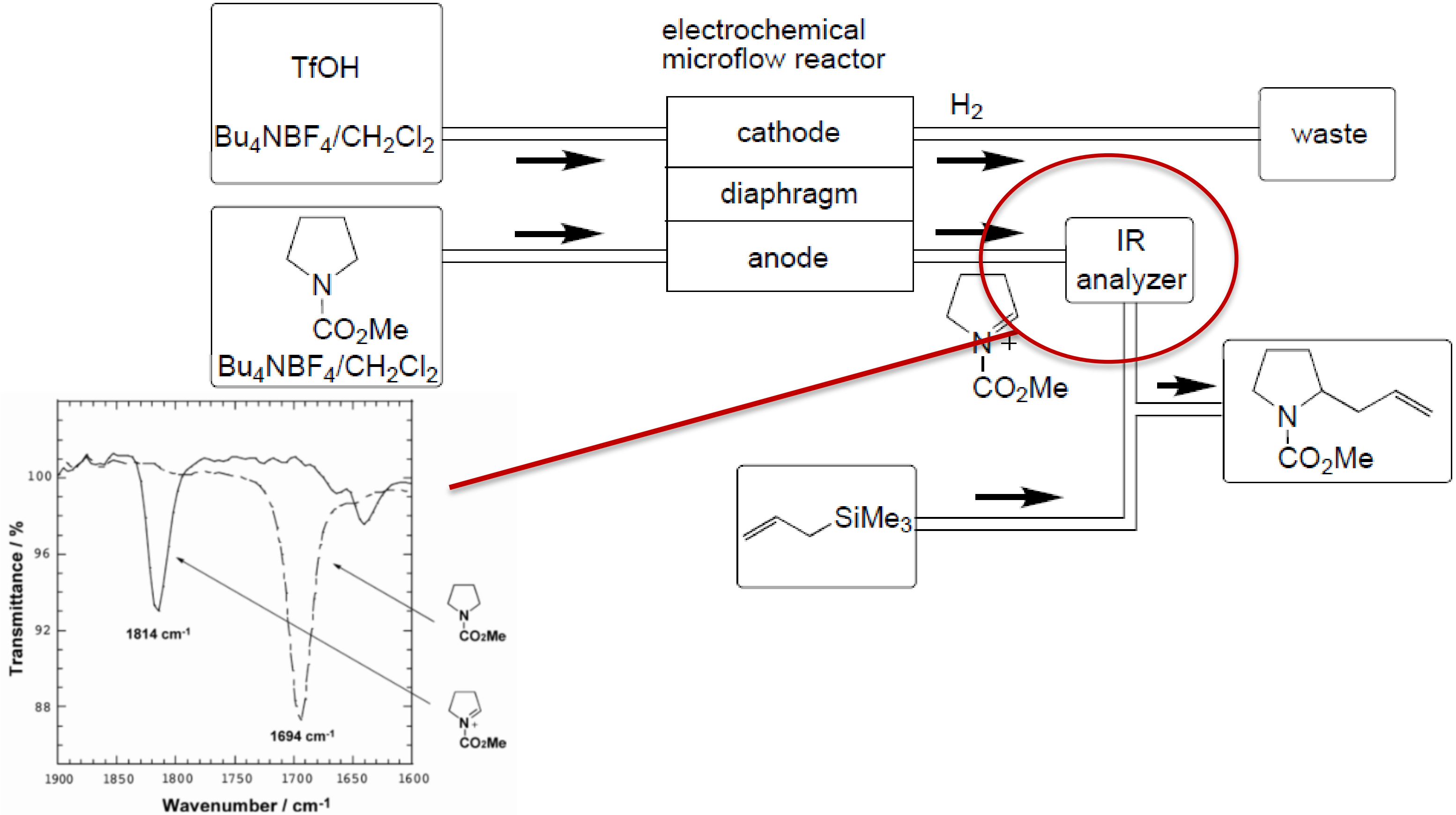


Suga, Okajima, Fujiwara, Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 7941-7942.

Cation Pool Flow Method

Cation Pool Flow method:

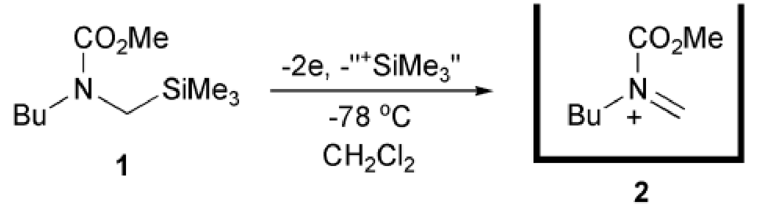




Suga, Okajima, Fujiwara, Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 7941-7942.

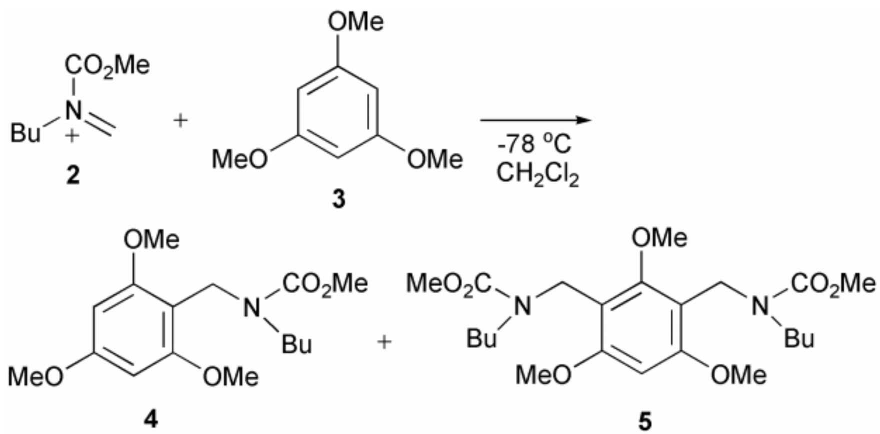
Importance of mixing

Cation Pool Flow method:

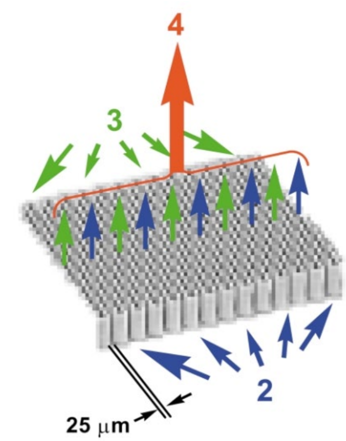


N-acyliminium ion pool

Follow-up step: Friedel-Crafts monoalkylation



reactor	**4** (%)	**5** (%)	**4** : **5**
batch	37	32	54 : 46
T-shaped tube (ϕ = 500 μm)	36	31	54 : 46
micromixer (channel width = 25 μm)	92	4	96 : 4



Suga, Nagaki, Yoshida, *Chem. Commun.* **2003**, 354-355.

Overcoming the Ohmic Drop

- **Ohmic drop:** voltage drop between the two electrodes

This voltage drop is influenced by:

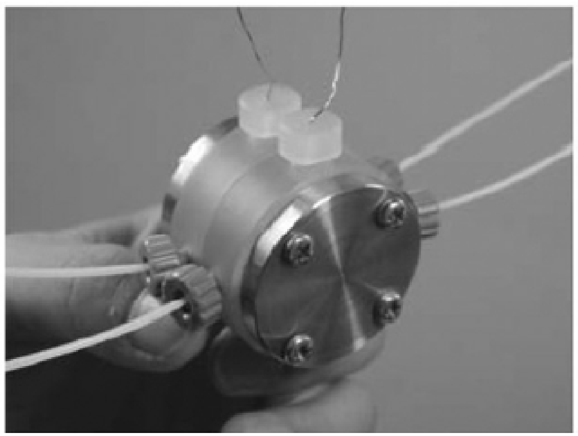
1. the conductivity of the solution
2. the relative distance between the two electrodes.
3. the magnitude of the current

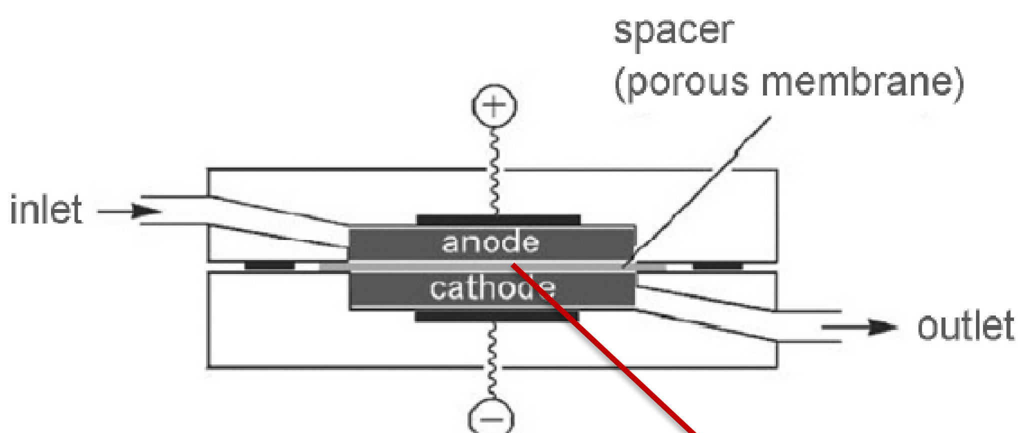
Ohmic drops are typically controlled by adding **supporting electrolytes**.

Overcoming the Ohmic Drop

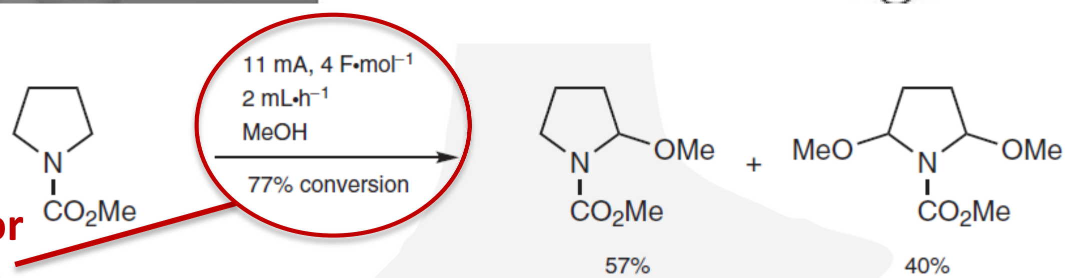
The shorter the distance between two electrodes, the lower the Ohmic drop will be.

Consequently, lower amounts of electrolyte or even none needs be used compared to larger scale reactors.





PTFE membrane (75 µm thick, 3 µm pores)



No electrolyte for Anodic methoxylation

Horcajada, Okajima, Suga, Yoshida, *Chem. Commun.* **2005**, 1303-1305.

Mentorship:
Prof. Seiji Suga (Okayama University)

Prof. Seiji Suga: *"It is very sad for me to accept his passing away. I learned a lot from Prof. Yoshida. We discussed much about organic chemistry, electroorganic chemistry, and flow chemistry. I have to carry out my research with the intention of my great former mentor."*

M. Baizer Award ceremony, ECS meeting Orlando, 2014

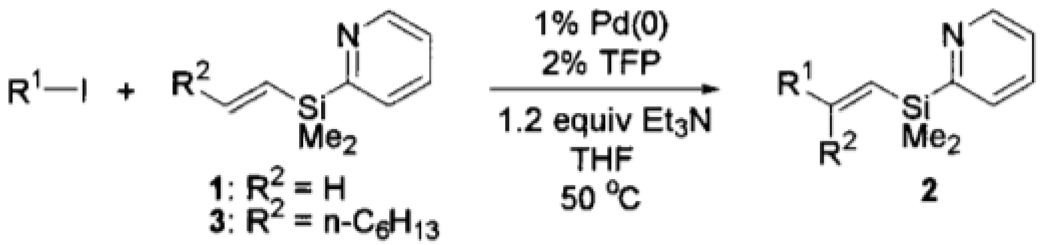
Mentorship:
Prof. Kenichiro Itami (Nagoya U)

Relevant topics:

- Cross Coupling chemistry

Cross-Coupling Chemistry

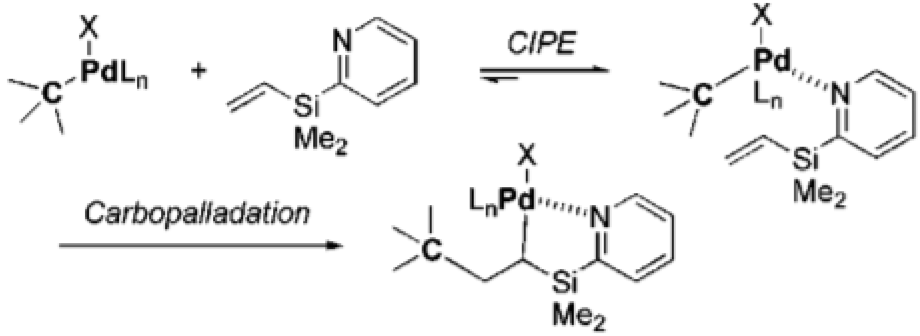
Palladium-Catalyzed Heck-type Coupling of Pyridyl-Substituted Vinylsilanes:



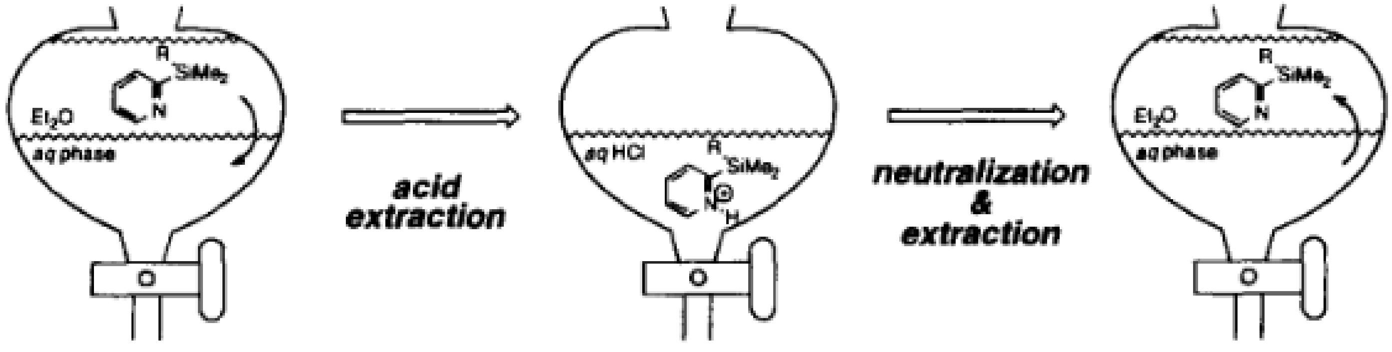
Itami, Mitsudo, Kamei, Koike, Nokami, Yoshida, *J. Am. Chem. Soc.* **2000**, 122, 12013-12014.
For a review: Itami, Mitsudo, Nokami, Kamei, Koike, Yoshida, *J. Organomet. Chem.* **2002**, *653*, 105-113.

Cross-Coupling Chemistry

*a 2-pyridyldimethylsilyl (2-PyMe$_2$Si) group functions as a directing group (*complex induced proximity effect (CIPE)*)*



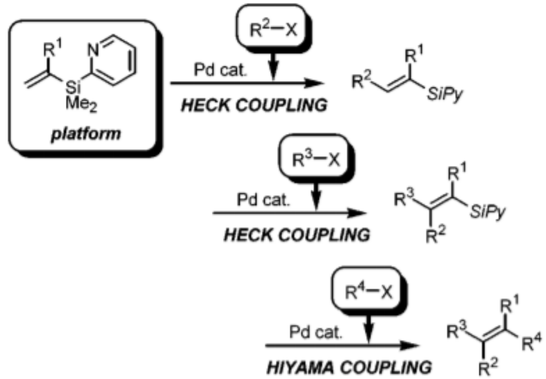
+ as a phase tag for acid-base extraction of the product.:



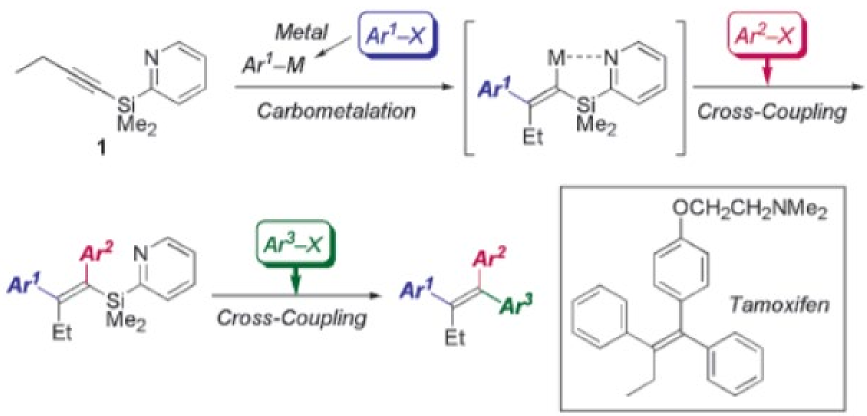
Itami, Mitsudo, Kamei, Koike, Nokami, Yoshida, *J. Am. Chem. Soc.* **2000**, 122, 12013-12014.

Cross-Coupling Chemistry

2-Pyridyl-Substituted Vinylsilanes as template for sequential cross coupling reactions:



Utility: *Expedient synthesis of Tamoxifen and analogues*



Itami, Nokami, Ishimura, Mitsudo, Kamei, Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 11577-11585.
Itami, Kamei, Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670-14671.

Mentorship:
Prof. Kenichiro Itami (Nagoya U)

Prof. Ken Itami: *"Prof. Yoshida was very unique in everything. He is unparalleled. I learned many things from him."*

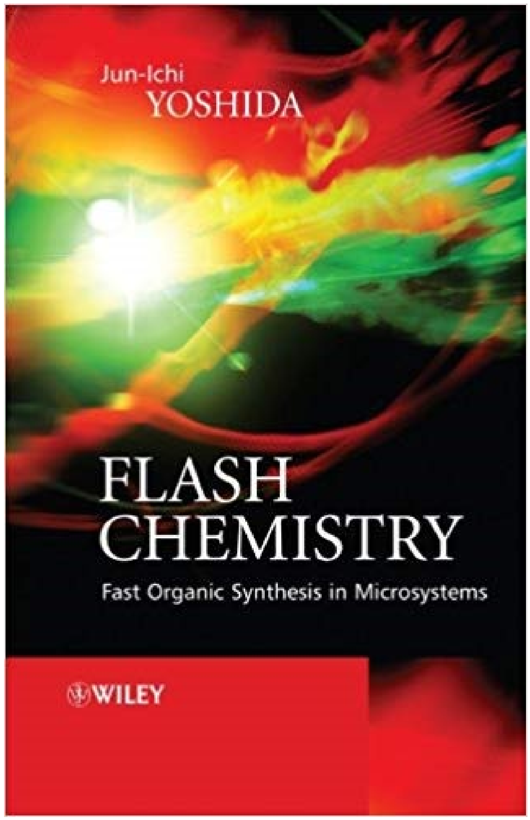
Yoshida Lab group photo (2002)

Mentorship:
Prof. Aiichiro Nagaki (Kyoto U)

Relevant topics:

- Flow Chemistry
- Flash Chemistry

Flash Chemistry



Jun-ichi
YOSHIDA
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Japan

FLASH CHEMISTRY
Fast Organic Synthesis in Microsystems

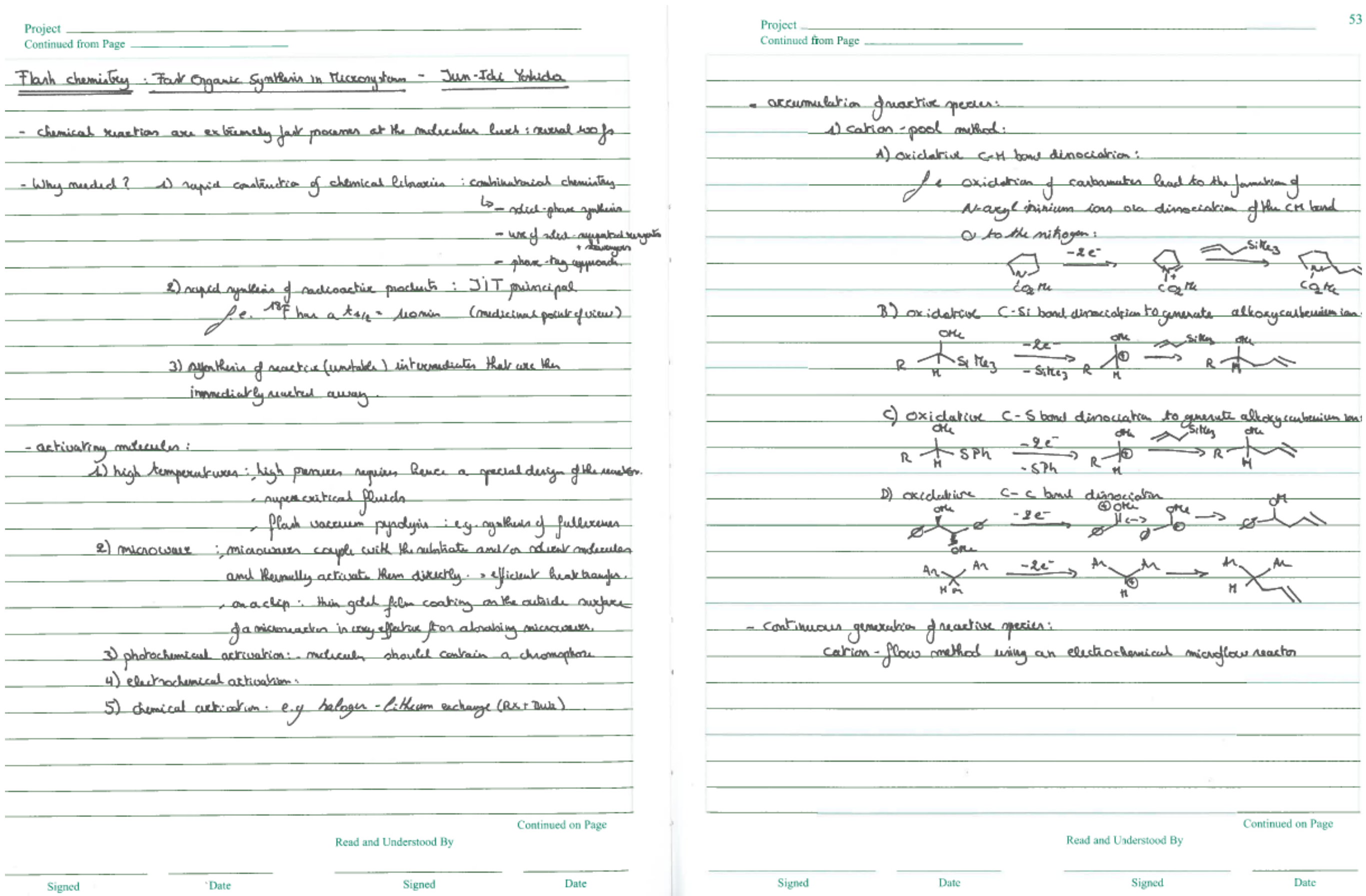
Have you ever wished you could speed up your organic syntheses without losing control of the reaction? Flash Chemistry is a new concept which offers an integrated scheme for fast, controlled organic synthesis. It brings together the generation of highly reactive species and their reactions in microsystems to enable highly controlled organic syntheses on a preparative scale in timescales of a few seconds or less.

Flash chemistry is defined as a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce desired compounds with high selectivity. Reaction times range from milliseconds to seconds.

For a review: (i) Yoshida, Kim, Nagaki, *Chem. Eur. J.* **2008**, *14*, 7450-7459. (ii) Yoshida, Takahashi, Nagaki, *Chem. Commun.* **2013**, *49*, 9896-9904.

Flash Chemistry

For me, it all started with the Flash Chemistry book:



Project
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Flash chemistry : Fast Organic Synthesis in Microsystems - Jun-Ichi Yoshida

- chemical reactions are extremely fast processes at the molecular level : several 100 fs

- Why needed? 1) rapid construction of chemical libraries : combinatorial chemistry
  - solid-phase synthesis
  - use of solid-supported reagents + scavengers
  - phase-tag approach.

2) rapid synthesis of radioactive products : JIT principal
i.e. ^{18}F has a $t_{1/2}$ = 110 min (medicinal point of view)

3) synthesis of reactive (unstable) intermediates that are then immediately reacted away.

- activating molecules :
1) high temperatures : high pressures requires hence a special design of the reactor.
  - supercritical fluids
  - flash vacuum pyrolysis : e.g. synthesis of fullerenes
2) microwave : microwaves couple with the substrate and/or solvent molecules and thermally activate them directly. > efficient heat transfer.
  - on a chip : thin gold film coating on the outside surface of a microreactor is very effective for absorbing microwaves.
3) photochemical activation : molecules should contain a chromophore
4) electrochemical activation.
5) chemical activation : e.g. halogen - lithium exchange (RX + BuLi).

Read and Understood By
Signed Date Signed Date
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- accumulation of reactive species:
1) cation - pool method:
A) oxidative C-H bond dissociation:
i.e. oxidation of carbamates lead to the formation of N-acyl iminium ions via dissociation of the CH bond α to the nitrogen:
B) oxidative C-Si bond dissociation to generate alkoxycarbenium ions
C) oxidative C-S bond dissociation to generate alkoxycarbenium ions
D) oxidative C-C bond dissociation

- continuous generation of reactive species:
cation - flow method using an electrochemical microflow reactor

Read and Understood By
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Notes from May 2010 (Postdoc MIT, Buchwald Research Group)

Disguised Chemical Selectivity

Reaction rate > mixing rate

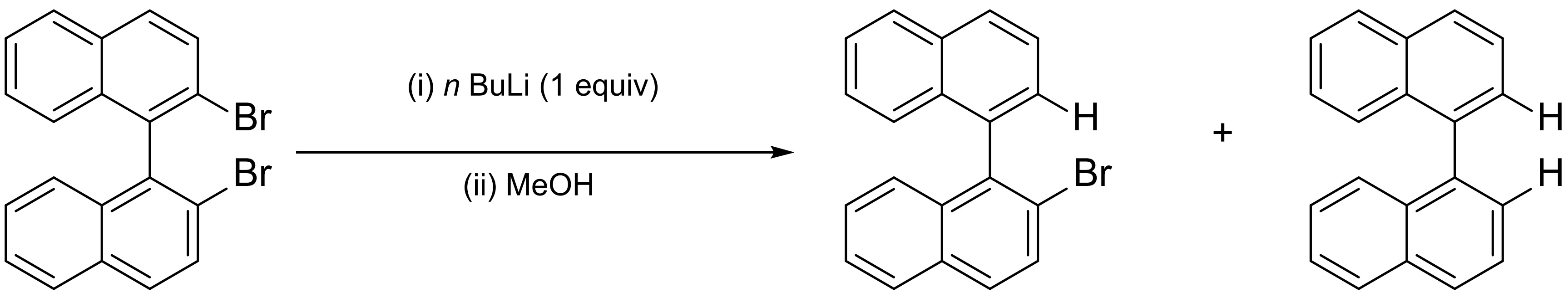
- Product selectivity is not determined by kinetics but by the mixing efficiency

$$A + B \xrightarrow{k1} P1 + A \xrightarrow{k2} P2$$

- If k1 > k2 and reaction is faster than mixing, both P1 and P2 are formed = *disguised chemical selectivity (Da_{II} > 1).*
- ***Possible solutions**:*
  - ***Lower reaction temperature***: decreases reaction rate and makes the reaction rate slower than the mixing rate
  - ***Diluted reaction conditions**:* lower concentration results in lower reaction rates; consequently, faster mixing and slower reaction rate
  - ***Micromixing**:* speed up the mixing rate through shortening of the diffusion path length (diffusion time is strongly dependent of the diffusion length)
    - ***Active mixing =*** external energy is used to induce mixing
    - ***Passive mixing =*** flow energy is used to restructure the flow

For a review: (i) Yoshida, Nagaki, Iwasaki, Suga, *Chem. Eng. Technol.* **2005**, *28*, 259-266.

Disguised Chemical Selectivity example



Batch (20 mL flask):	T = 0 °C	86%	13%
Batch (20 mL flask):	T = -78 °C	90%	10%
Flow (500 μm ID):	T = 0 °C	**97%**	**1%**

Nagaki, Takabayashi, Tomida, Yoshida, *Org. Lett.* **2008**, *10*, 3937-3940.

Importance of heating

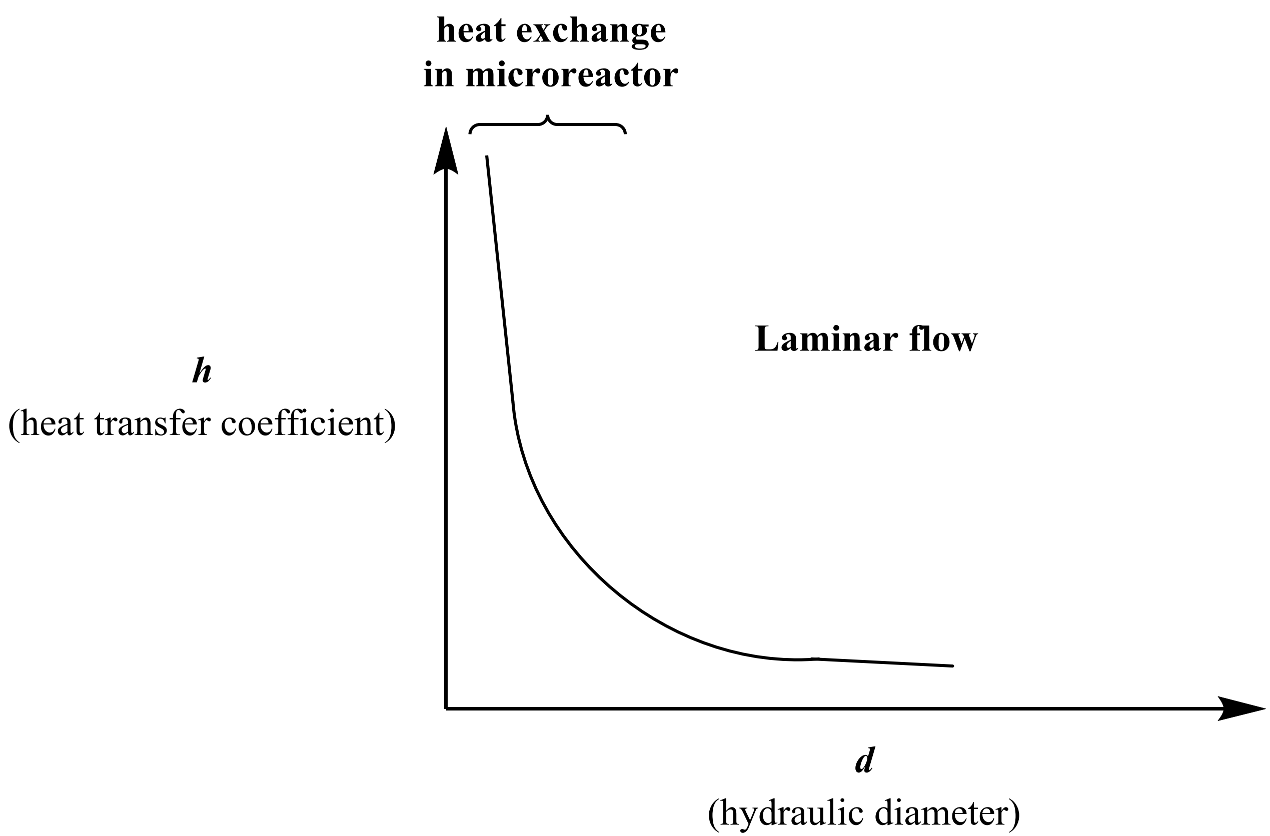
- **In microreactors**
  - Heat transfer in the solution happens via conduction and convection
  - Heat transfer though the reactor wall is also important (Teflon, stainless steel, silicon carbide)

Material	Thermal Conductivity [W m^{-1} K^{-1}]
PFA	0.195
FEP	0.19-0.24
Glass	1
Stainless Steel	12–45
Silicon	149
Aluminum	237 (pure) 120–180 (alloy)
Silicon Carbide	120-490
Copper	401

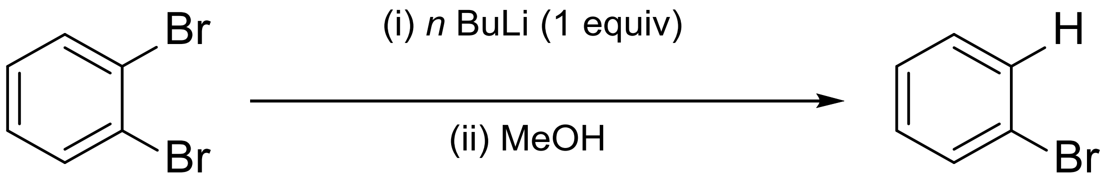
  - High surface to volume ratio = very fast heat transfer in microsystems.
    - The reactor walls become a strong influential part of the reaction or process

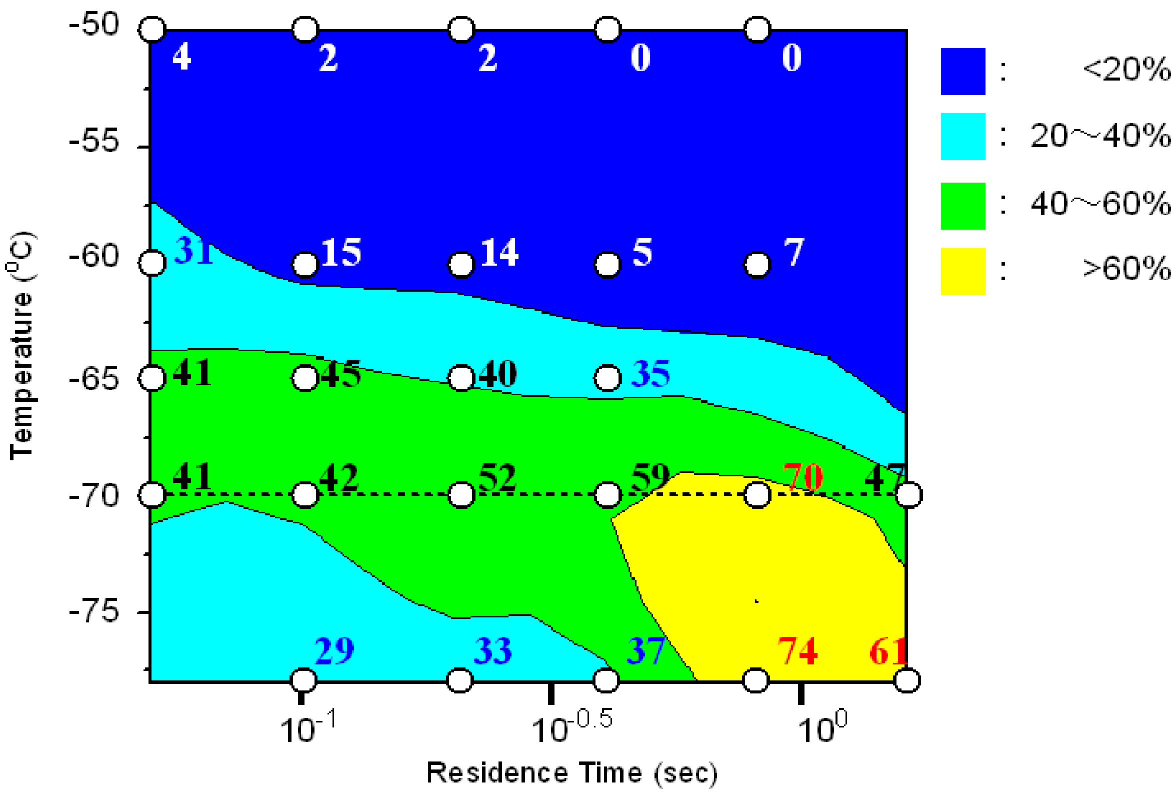
Importance of heating

Nusselt-number	Use to characterize relative importance of convective heat transfer over conductive heat transfer	$Nu = \frac{h \cdot d_h}{\lambda}$



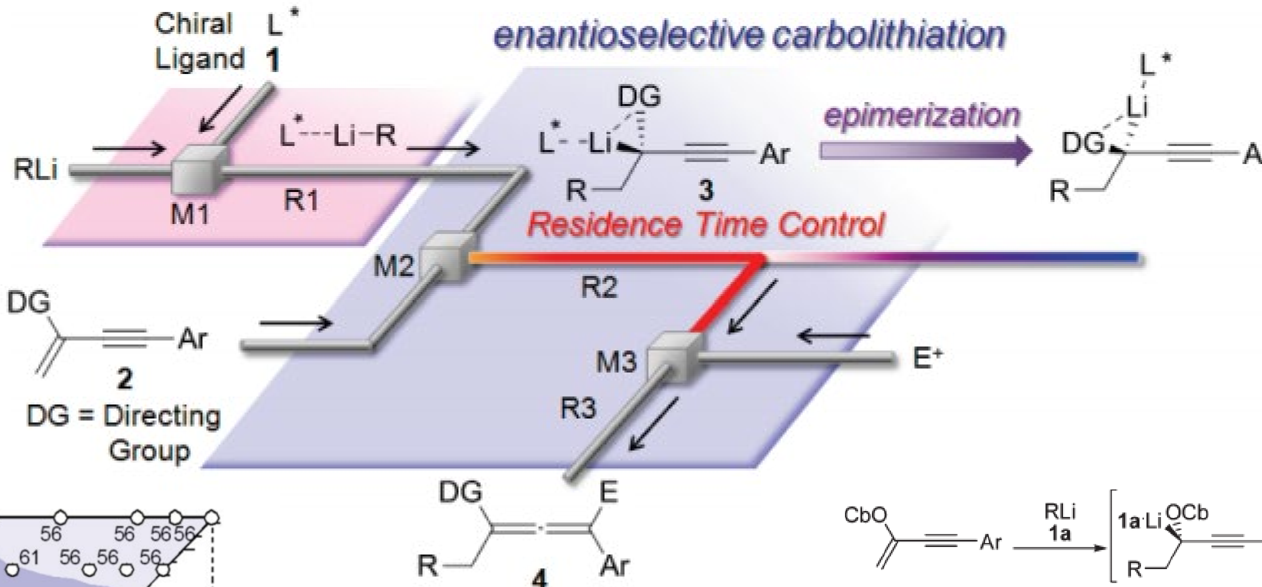
Halogen-Lithium Exchange

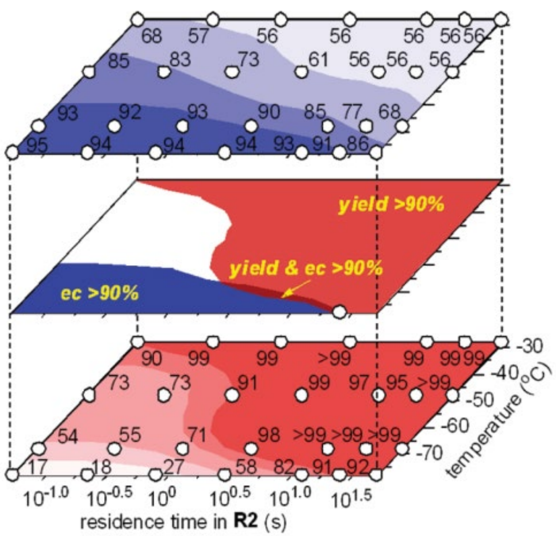




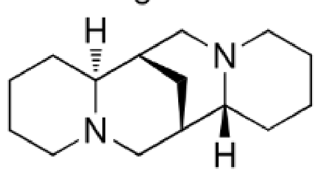
Usutani, Tomida, Nagaki, Okamoto, Nokami, Yoshida, *J. Am. Chem. Soc.*, **2007**, *129*, 3046-3047.

Asymmetric Carbolithiation

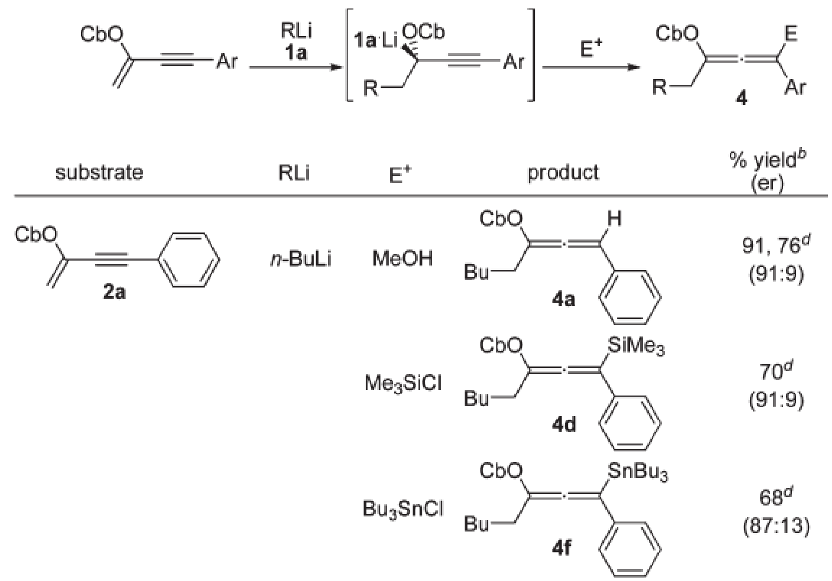




Chiral Ligand 1



1a (-)-sparteine



Tomida, Nagaki, Yoshida, *J. Am. Chem. Soc.*, **2011**, *133*, 3744-3747.

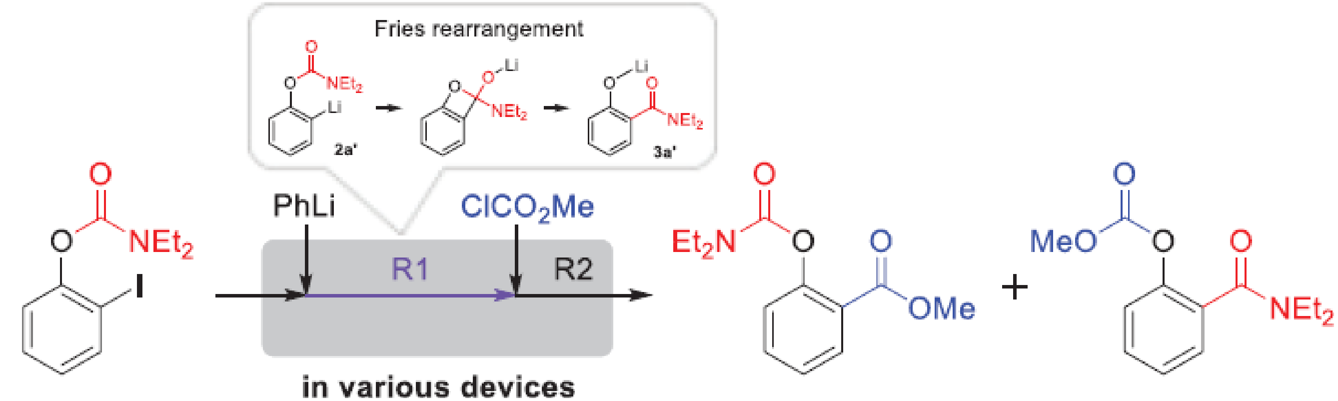
Mentorship:
Prof. Aiichiro Nagaki (Kyoto U)

Prof. Aiichioro Nagaki: “*Prof. Yoshida was always passionate about flow research, and looking ahead to the future of it. He often said, even on his sickbed, “Don’t look back to how far we’ve come because so much more needs to be done. The most exciting part has yet to come for this field.””*

Yoshida group picture 2006

Outpacing Anionic Fries Rearrangement

A

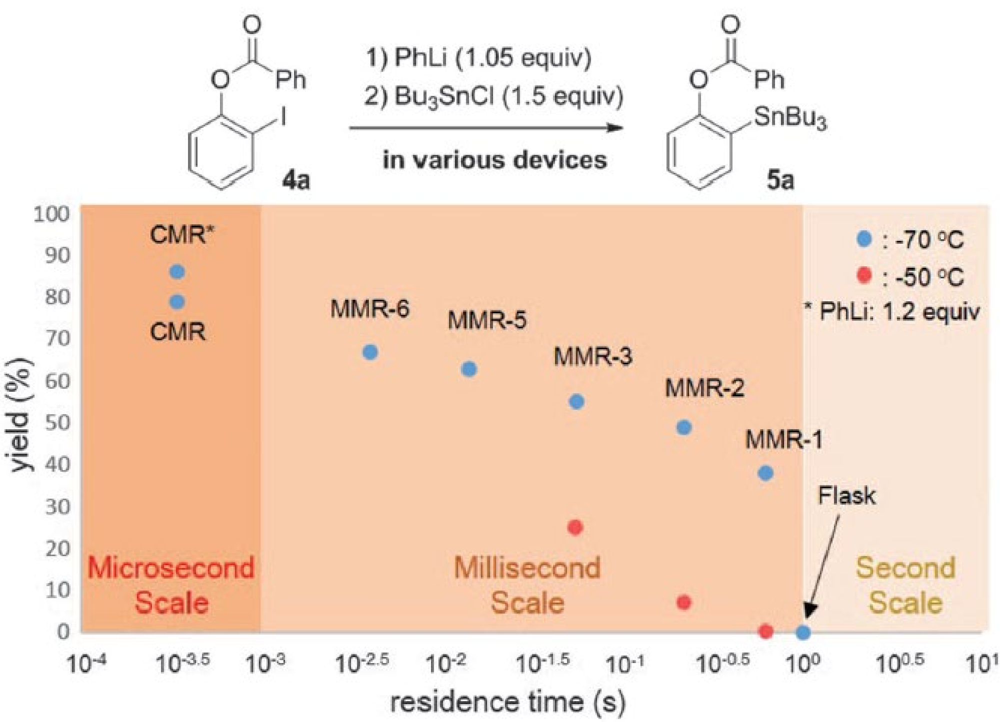


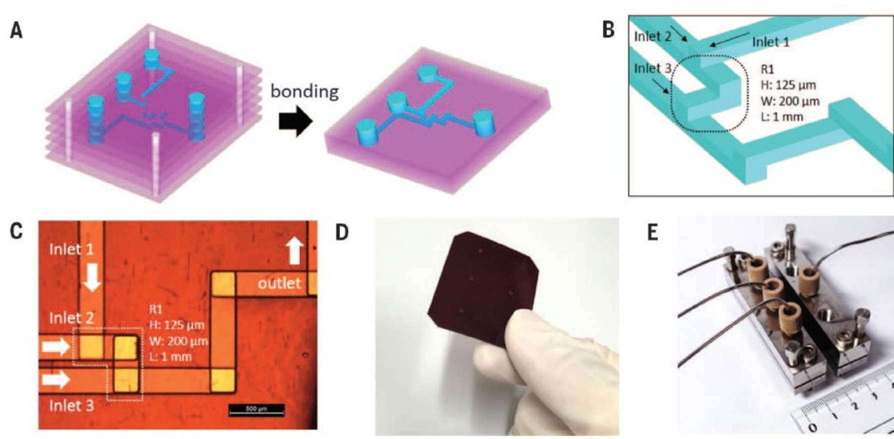
entry	microfluidic device	inner volume of R1 (μL)	residence time in R1 (ms)	yield of **2a** (%)	yield of **3a** (%)
1	**MMR-1**	**79**	**628**	**0**	**91**
2	MMR-2	39	377	20	74
3	MMR-3	27	220	45	51
4	MMR-4	7	55	73	21
5	MMR-5	2	14	79	15
6	MMR-6	0.49	4	87	4
7*	CMR	0.025	0.33	74	0
8†	**CMR**	0.025	**0.33**	**91**	**0**

Kim, Min, Inoue, Im, Kim, Yoshida, *Science*, **2016**, *352*, 691-694.

Outpacing Anionic Fries Rearrangement

Fast mixing is key in this transformation:

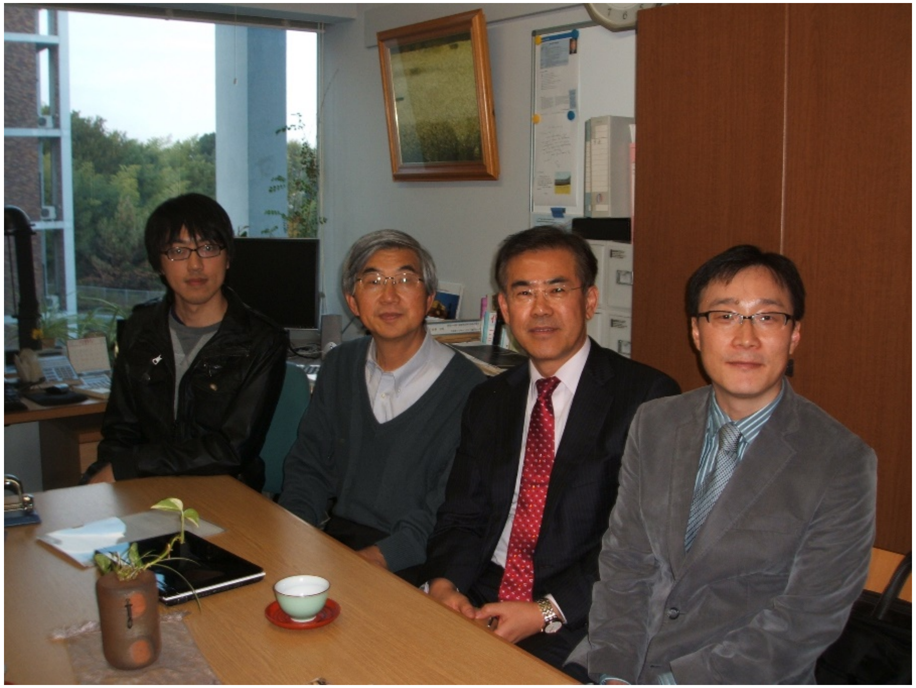




Kim, Min, Inoue, Im, Kim, Yoshida, *Science*, **2016**, *352*, 691-694.

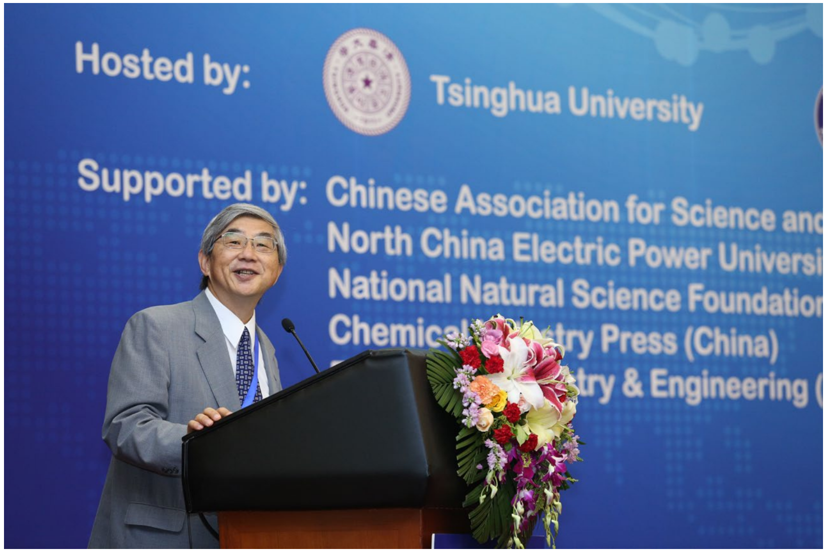
Science paper

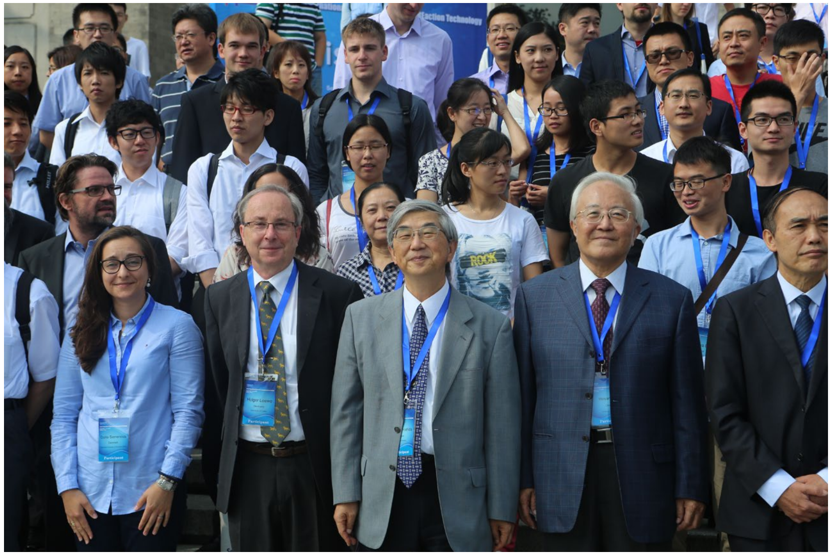
Collaborator Prof. Dong-Pyo Kim (POSTECH): “I feel a pure happiness that comes from scientific collaboration with the balanced and kind attitude of a sincere scientist like Prof. Yoshida. This collaboration confirmed again that science is a tool for good communication in friendship, irrespective of age, language, or culture. ”



Visit Kyoto, July 2010

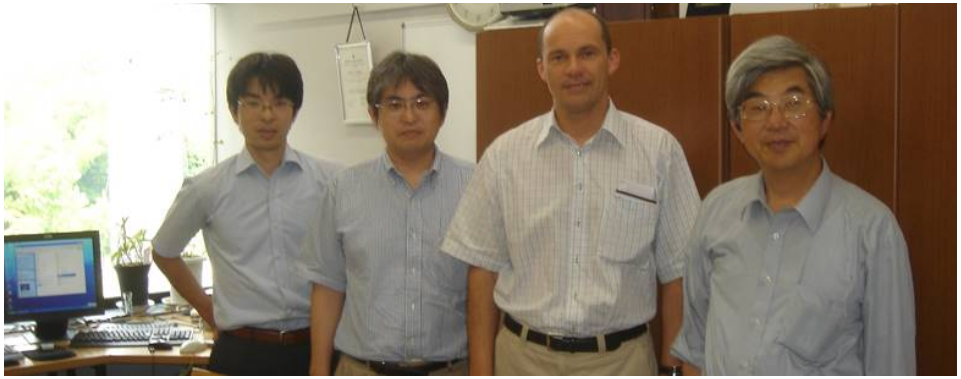
IMRET 2016, Beijing, P.R. China





Cardiff, February 2012

Office of Prof. Yoshida, Kyoto, 2008



First Symposium on Microreaction Technology in 1998 (Osaka)

Prof Yoshida with Prof Ilhyong Ryu (199)

Lab trip, 2006

Lab alumni party, 2001

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- Anna Maria Lozza and Antimo Gioiello (University of Perugia)