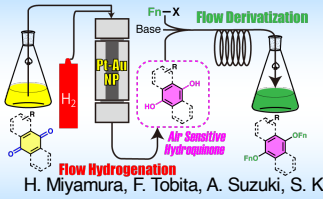
A03班 不均一系触媒による連続フロー合成系の開発とその空間的，時間的反応集積化による精密有機合成

（東大院理）宮村浩之

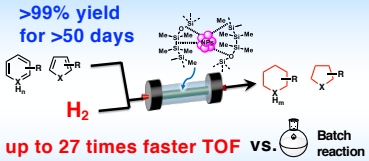


Unique Points of Continuous-flow Systems

- ✓ Controlling selectivity by residence time
- ✓ Suppression of over-reduction
- ✓ Use of air-sensitive intermediates
- ✓ Extreme robustness (> 1 months)
- ✓ Wide scope of derivatization
- ✓ Compatible to various solvent systems

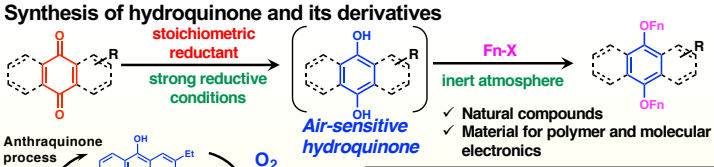
H. Miyamura, F. Tobita, A. Suzuki, S. Kobayashi, *Angew. Chem., Int. Ed.* **2019,** *58,* 9220.

- ✓ Reaction acceleration (up to x27) in flow
- ✓ Heterogeneous catalyst as mixer
- ✓ Extreme robustness (> 50 days)
- ✓ Site selective arene hydrogenation
- ✓ Wide scope

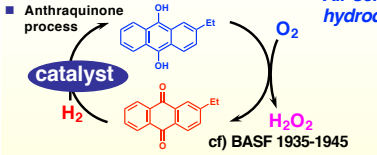


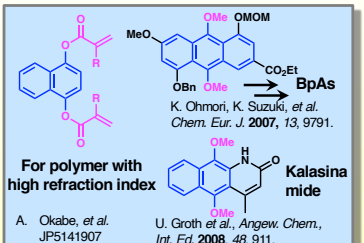
H. Miyamura, A. Suzuki, T. Yasukawa, S. Kobayashi, *J. Am. Chem. Soc.* **2018**, *140*, 11325.

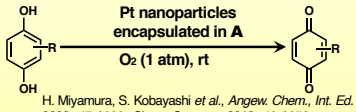
Synthesis of hydroquinone and its derivatives



- ✓ Natural compounds
- ✓ Material for polymer and molecular electronics

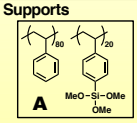


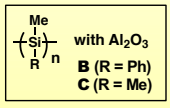




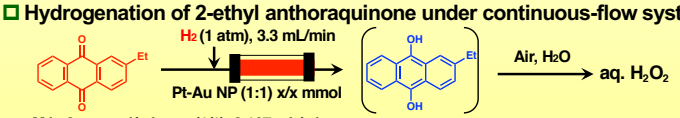
H. Miyamura, S. Kobayashi *et al.*, *Angew. Chem., Int. Ed.* **2008**, *47*, 8093; *Chem. Commun.* **2010**, *46*, 8052.

Supports





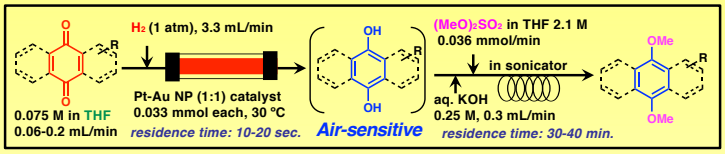
Hydrogenation of 2-ethyl anthoraquinone under continuous-flow system

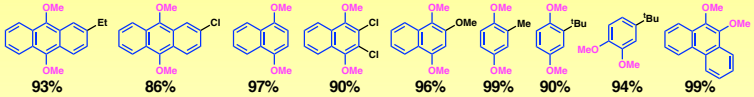


entry	support	x [mmol]	quinone (y M)	(H_2O_2) yield (%)
1	A	0.05	fresh (0.05)	81
2	A	0.05	reuse of entry 1	75
3	B	0.028	fresh (0.075)	76
4	B	0.028[a]	reuse of entry 3	67 (69[b], 61[c])
5	C	0.045	fresh (0.075)	91
6	C	0.045[a]	reuse of entry 5	91 (95[b], 95[c])

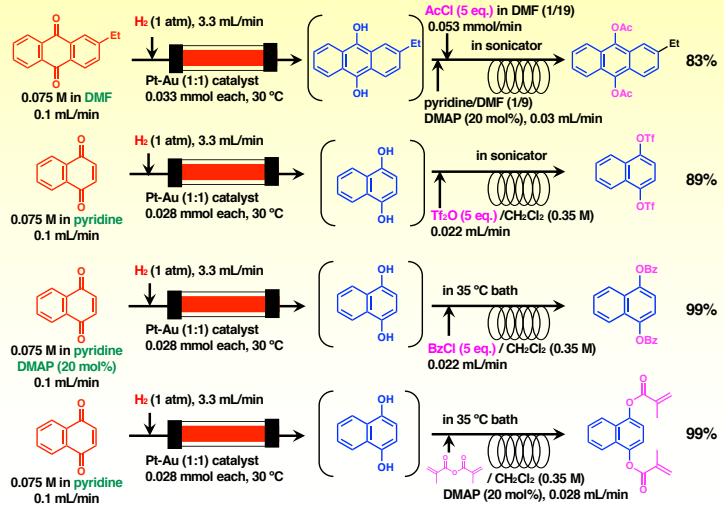
[a] The same catalyst column was used. [b] 2nd reuse. [c] 3rd reuse

Hydrogenation-derivatization reaction through space-integration

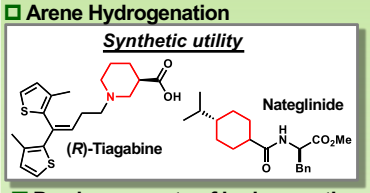




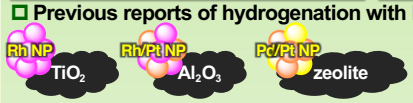
Scope of functionalizations of hydroquinone through space-integration



Arene Hydrogenation



Previous reports of hydrogenation with heterogeneous catalysts

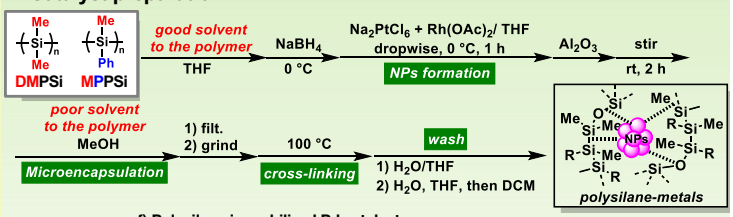


MeOH as solvent ⁱPrOH as solvent 150 °C

high temperature & pressure

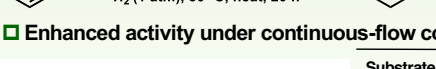
S. U. Son *et al., Angew. Chem., Int .Ed.* **2007**, *46*, 1152.
J. M. Buriak *et al., Inorg. Chem.* **2010**, *49*, 2706.
J. Wittayakun *et al., J. Ind. Eng. Chem.* **2009**, *15*, 819.

Catalyst preparation



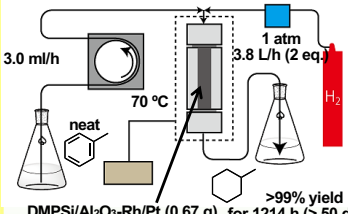
cf) Polysilane immobilized Pd catalysts: S. Kobayashi *et al.*,*Org. Biomol. Chem.* **2008**, *6*, 4297.
S. Kobayashi *et al., ChemCatChem* **2015**, *7*, 4025.

Metal screening



- Rh: 40%, Pt: 2%, Pd: N. R.
- Rh/Pt: 76%, >99% (50 °C)
- MPPSi/Al2O3-Rh/Pt: 77% (50 °C)

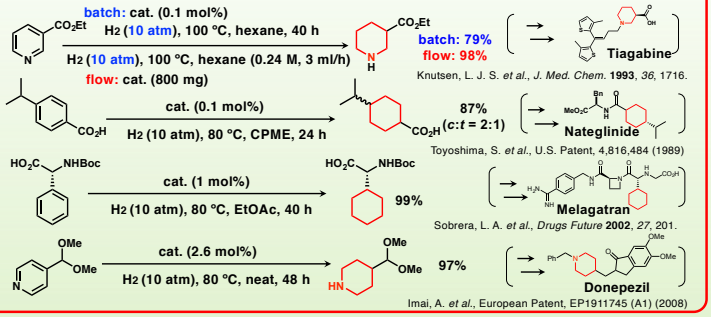
Enhanced activity under continuous-flow conditions



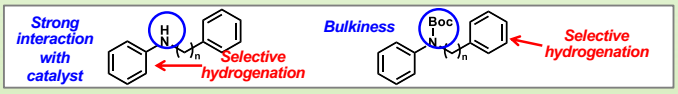
Substrate Product	TOF (Batch)	TOF (Flow)	TOF (Flow) /TOF (Batch)
	604 h^{-1}	3390 h^{-1}	5.6
	90 h^{-1}	681 h^{-1}	7.6
	41 h^{-1}	1118 h^{-1}	27
	43 h^{-1}	1507 h^{-1}	25

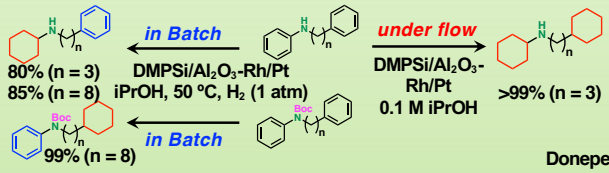
TON: reacted H_2/Rh (mol/mol)
TOF: TON/time (/h)

Application to drug precursor synthesis



Selective arene hydrogenation





Synthesis of Donepezil through time-integration

Donepezil (API) one-pot 2 steps 87%