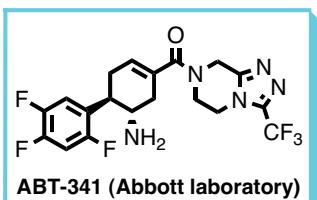
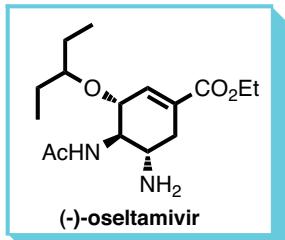
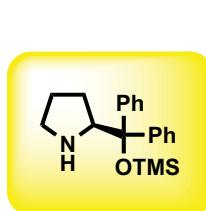


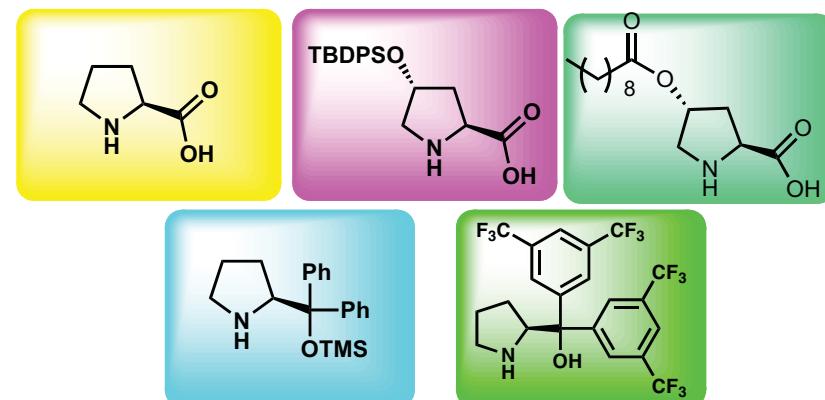
# Organocatalyst in Total Synthesis

Tohoku University  
Yujiro Hayashi

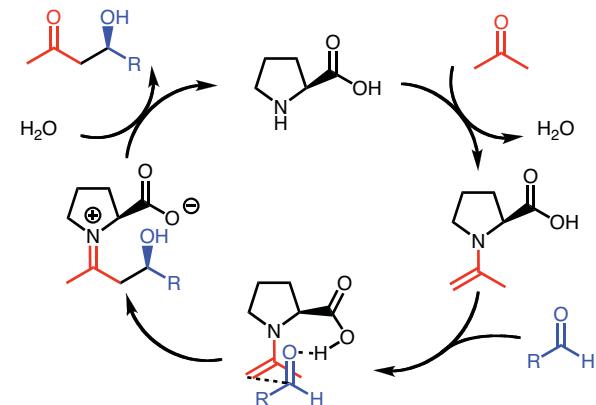
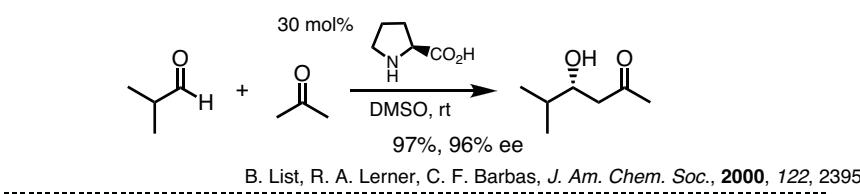


## Merit of organocatalysis

Product is free from the contamination of metal.  
Exclusion of water and air is not necessary.  
Most of the ligands are non-toxic.

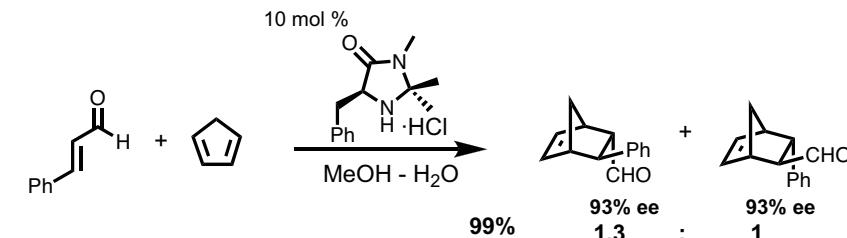


## Background: Enamine intermediate

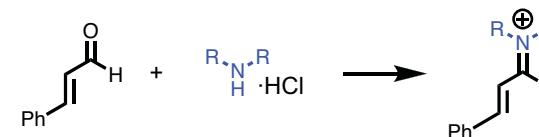


## Background: Iminium ion intermediate

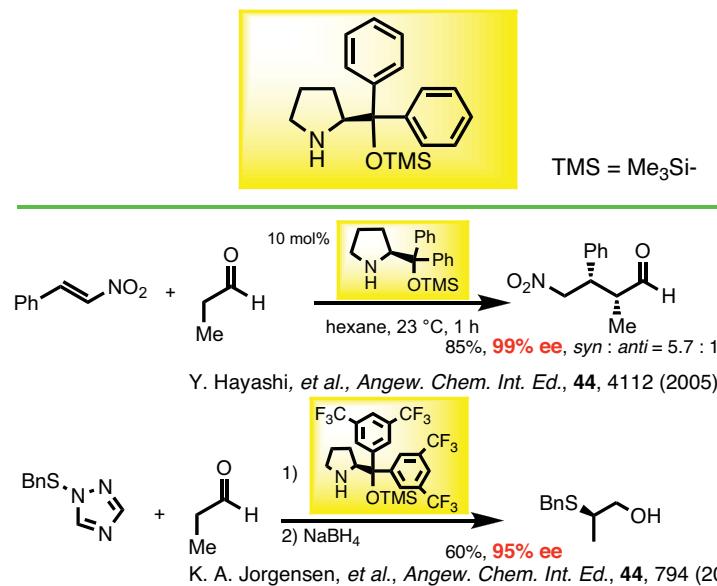
### Diels-Alder reaction



### LUMO-lowering activation

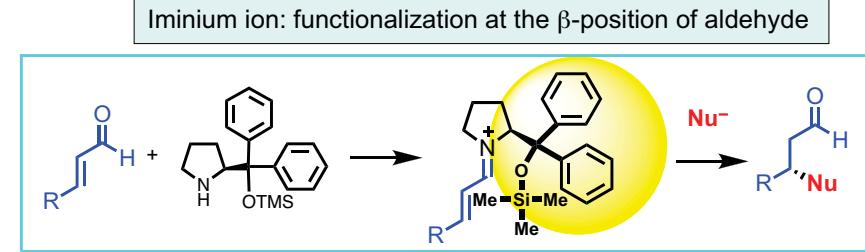
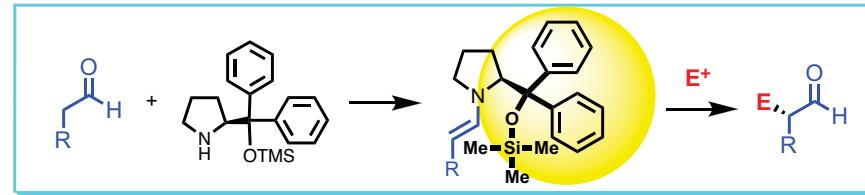


## Jorgensen-Hayashi Catalyst



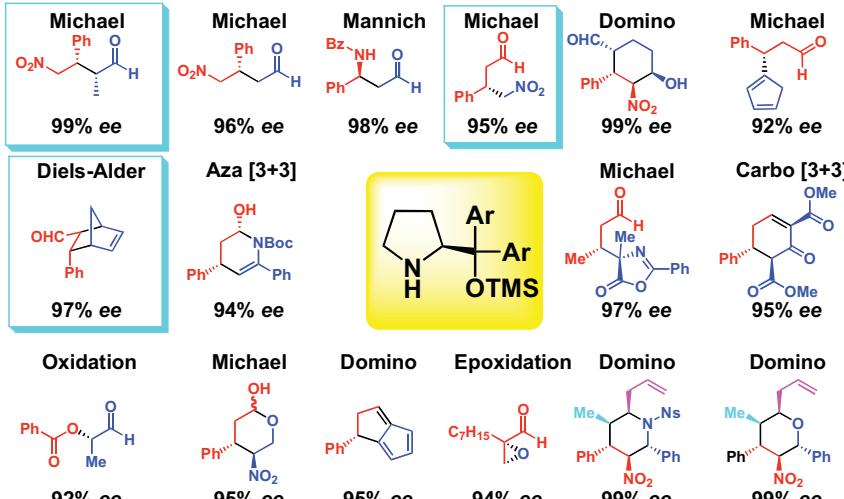
Effective for the both enamine and iminium ion intermediate

Enamine: functionalization at the  $\alpha$ -position of aldehyde



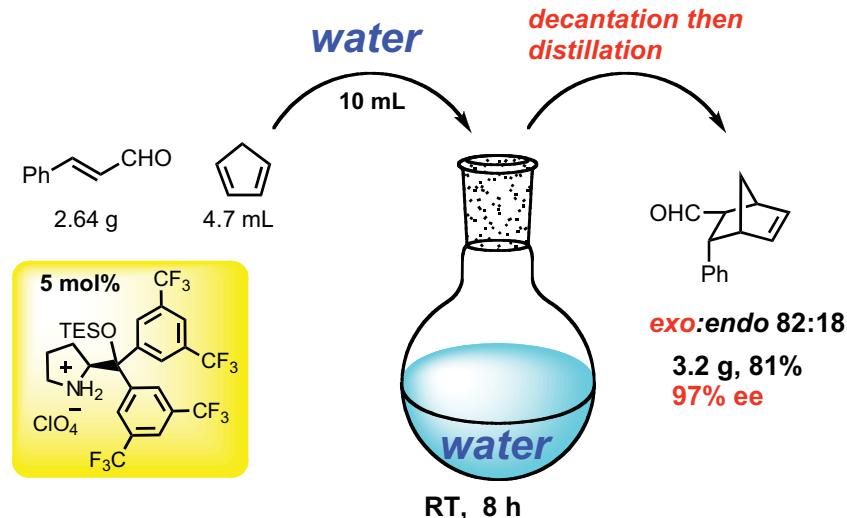
X-ray and *ab initio* calculation D. Seebach, Y. Hayashi, Uchimaru, et al., *Helv. Chim. Acta*, **2009**, 92, 1225.

## Reactions developed by our group



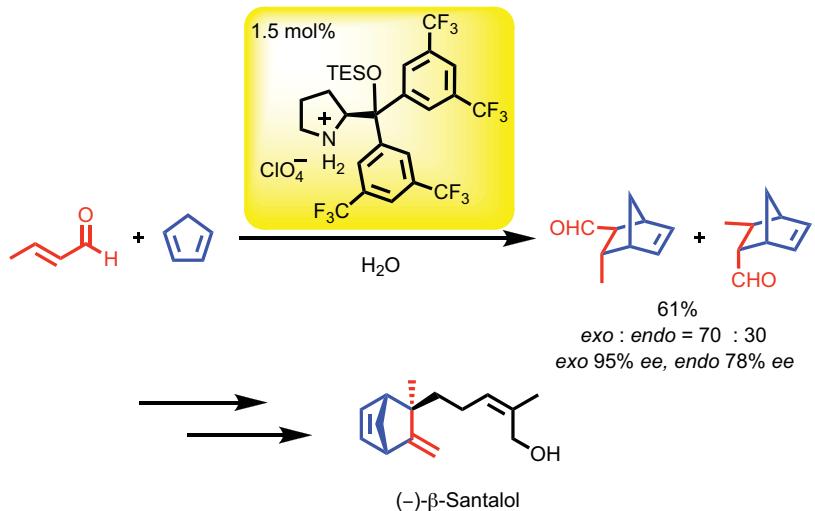
*Angew. Chem. Int. Ed.*, **44**, 4212 (2005). *Angew. Chem., Int. Ed.*, **45**, 6853 (2006). *Angew. Chem., Int. Ed.*, **46**, 4922 (2007). *Org. Lett.*, **9**, 5307 (2007). *Angew. Chem., Int. Ed.*, **47**, 4012 (2008). *Angew. Chem., Int. Ed.*, **47**, 4722 (2008). *Angew. Chem., Int. Ed.*, **47**, 9053 (2008). *Chem. Commun.*, 3083 (2009). *Chem. Asian. J.*, **4**, 246 (2009). *Org. Lett.*, **11**, 45 (2009). *Org. Lett.*, **11**, 4056 (2009). *Tetrahedron*, **66**, 4894 (2010). *Org. Lett.*, **12**, 4588 (2010). *Org. Lett.*, **12**, 5434 (2010).

## exo Selective Diels-Alder reaction in the presence of water

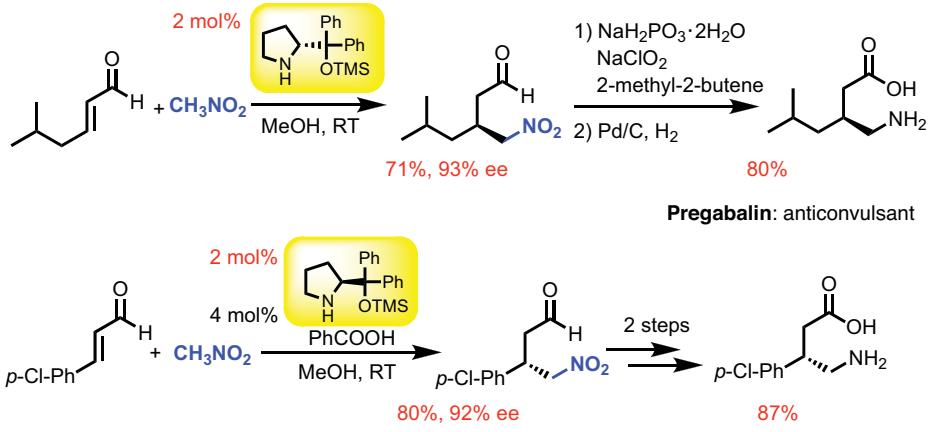


*Angew. Chem. Int. Ed.*, **47**, 6634 (2008).

### Synthesis of (-)- $\beta$ -Santalol by Firmenich

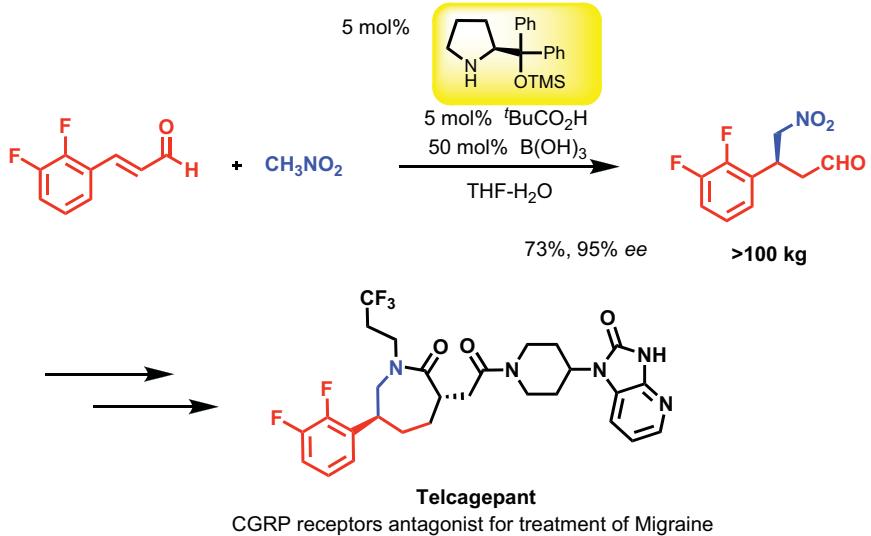


C. Fehr et al.,(Firmenich), *Angew. Chem., Int. Ed.*, **2009**, *48*, 7221.



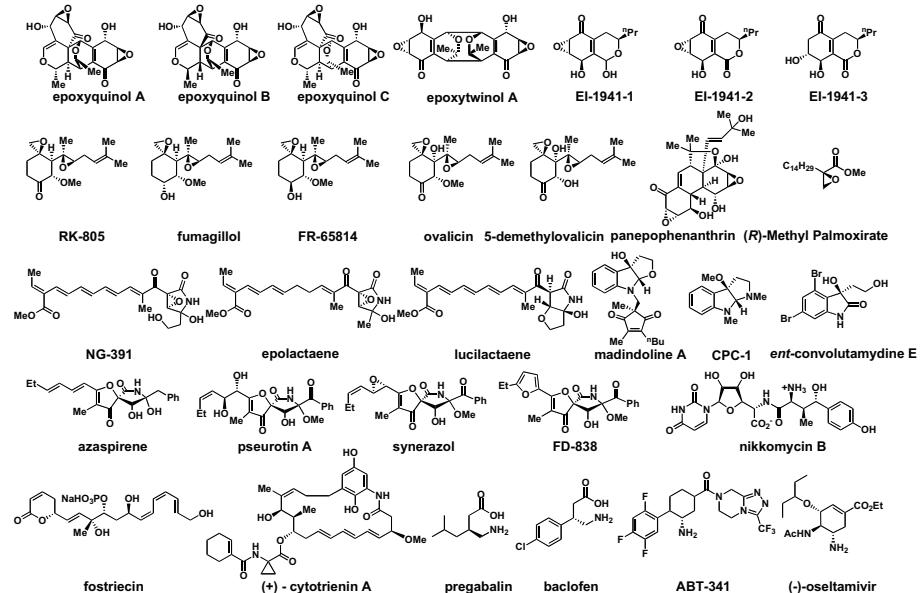
*Org. Lett.*, **9**, 5307 (2007).

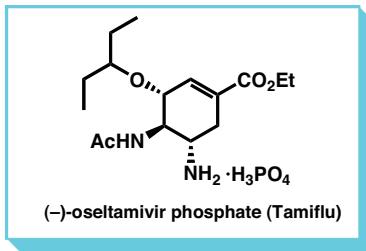
### Synthesis of Telcagepant by Merck



F. Xu et al.,(Merck), *J. Org. Chem.*, **75**, 7829 (2010).

### Total synthesis of biologically active compounds



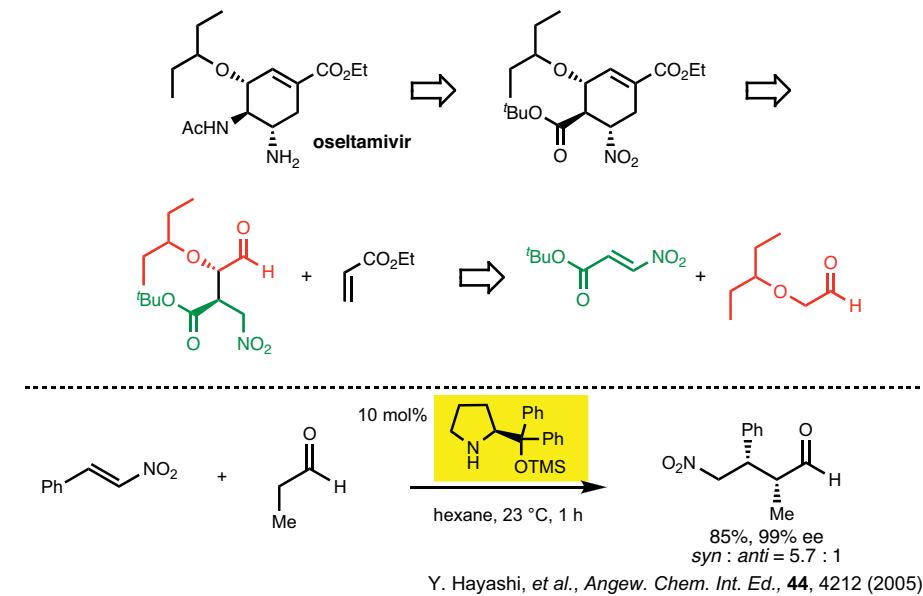


Tamiflu: Orally administrated anti-Influenza drug developed by Gilead Sciences, Inc. and Roche

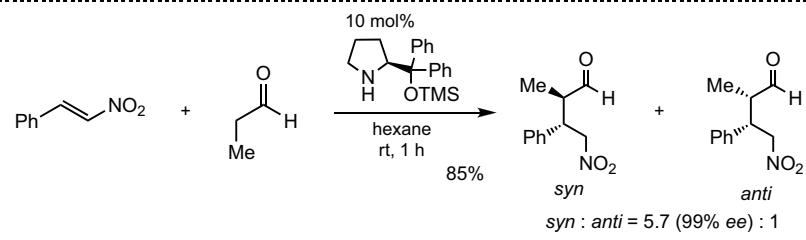
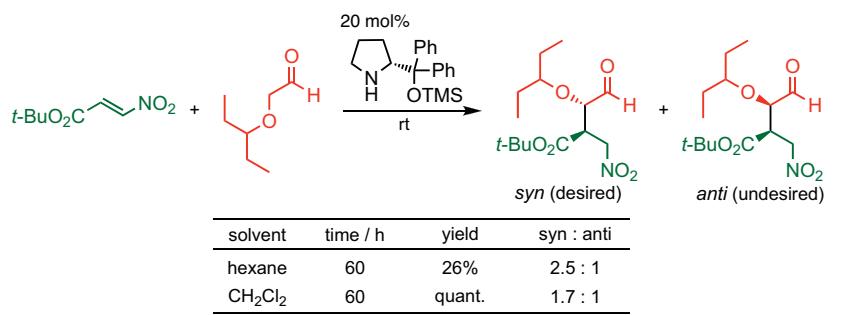
Total Synthesis: Corey (2006), Shibasaki (2006), Yao (2006), Wong (2007) Fukuyama (2007), Fang (2007), Kann (2007), Trost (2008) Banwell (2008), Mandai (2009), Hudlicky (2009) *et al.*, **53 total syntheses**

Synthetic Challenge: Control of three continuous chiral center Selectivity (enantio- and diastereo-)

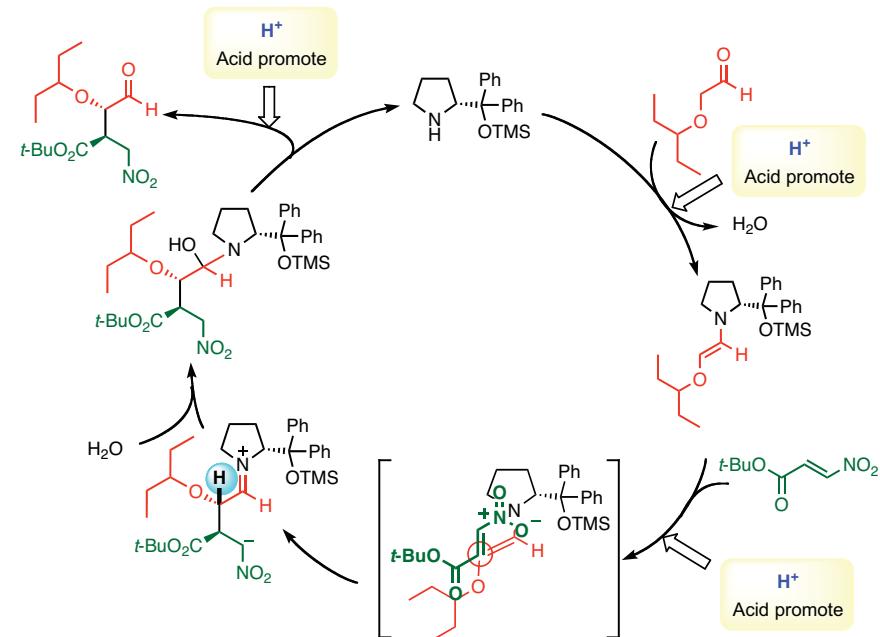
### First retro-synthetic analysis



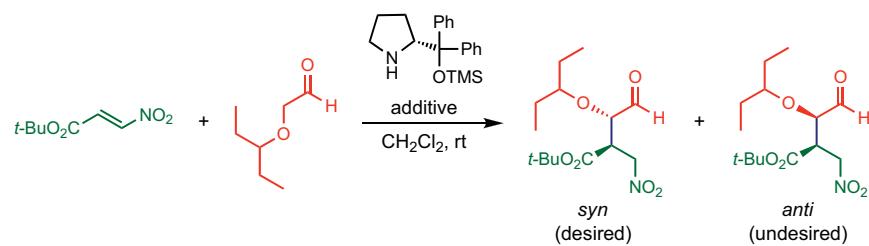
### Asymmetric Michael Reaction



### Proposed Reaction Mechanism

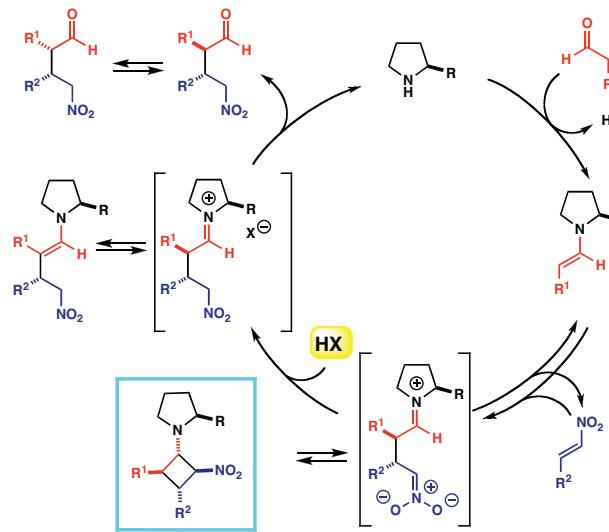


## Optimization for Key Michael Reaction



catalyst / mol%	additive (mol%)	pKa in H <sub>2</sub> O	time / h	yield	<i>syn : anti</i>	ee / % syn / anti
20	none	—	60	quant.	1.7 : 1	nd
20	CF <sub>3</sub> CH <sub>2</sub> OH (40)	12.5	24	50% (brsm 95%)	2.3 : 1	nd
20	<i>p</i> -nitrophenol (40)	7.1	24	quant.	1.7 : 1	nd
20	PhCO <sub>2</sub> H (40)	4.2	14	quant.	2.0 : 1	nd
5	HCO <sub>2</sub> H (20)	3.77	2	quant.	4.8 : 1	nd
<b>5</b>	<b>CICH<sub>2</sub>CO<sub>2</sub>H (20)</b>	<b>2.86</b>	<b>1</b>	<b>quant.</b>	<b>6.3 : 1</b>	<b>96 / 87</b>
5	Cl <sub>3</sub> CCO <sub>2</sub> H (20)	0.65	28	No Reaction	—	—

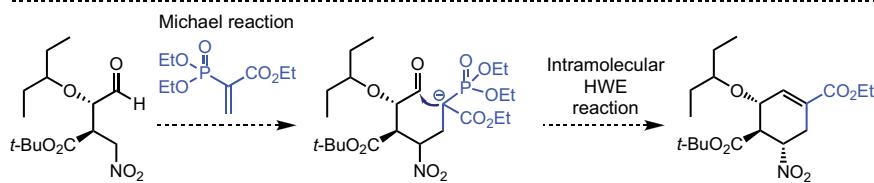
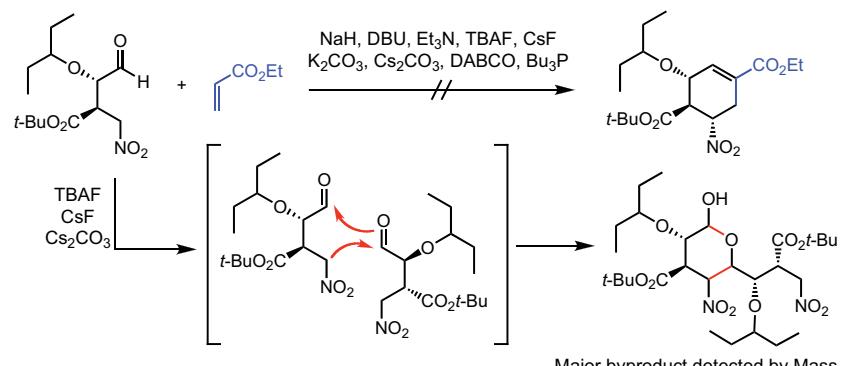
## Revised reaction mechanism



D. Seebach, Y. Hayashi, et al., *Helv. Chim. Acta*, **2011**, 94, 719.

Cf, D. Blackmond et al., *J. Am. Chem. Soc.*, **2011**, 133, 8822.

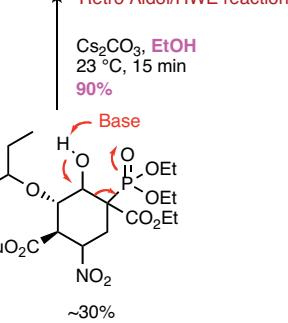
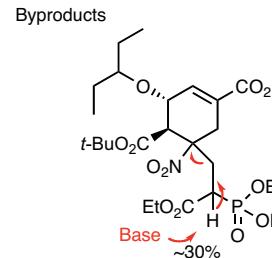
## Domino Michael / Intramolecular Aldol reaction



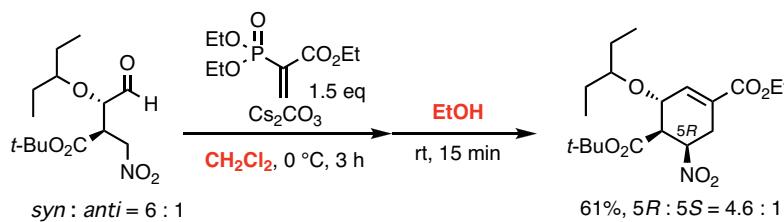
## Tandem Michael/HWE reaction



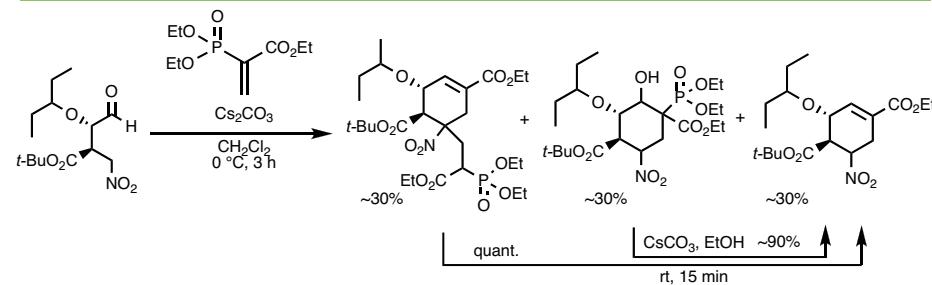
## Retro Michael reaction



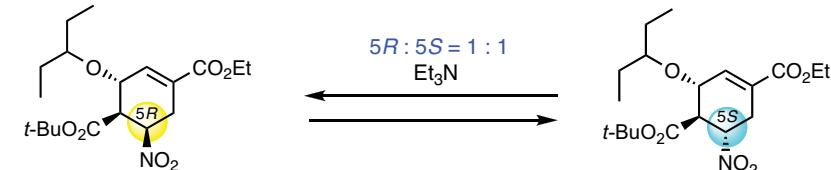
### Tandem Michael/HWE reaction



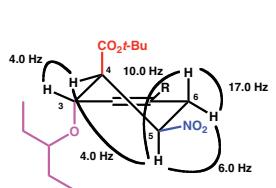
**One-pot Reaction:** purification economy, chemical waste economy, time economy increase yield



### Unsuccessful isomerization from 5*R* to 5*S*



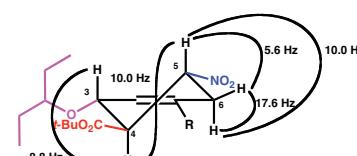
### 5*R* isomer



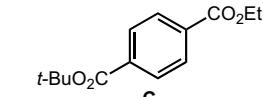
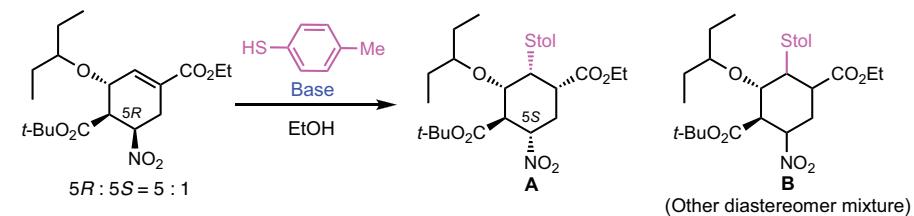
5*R*-isomer is stable than 5*S*-isomer in only 0.11 Kcal/mol by B3LYP/6-31G(d) calculation.

Calculation was performed by Dr.Uchimaru.

### 5*S* isomer

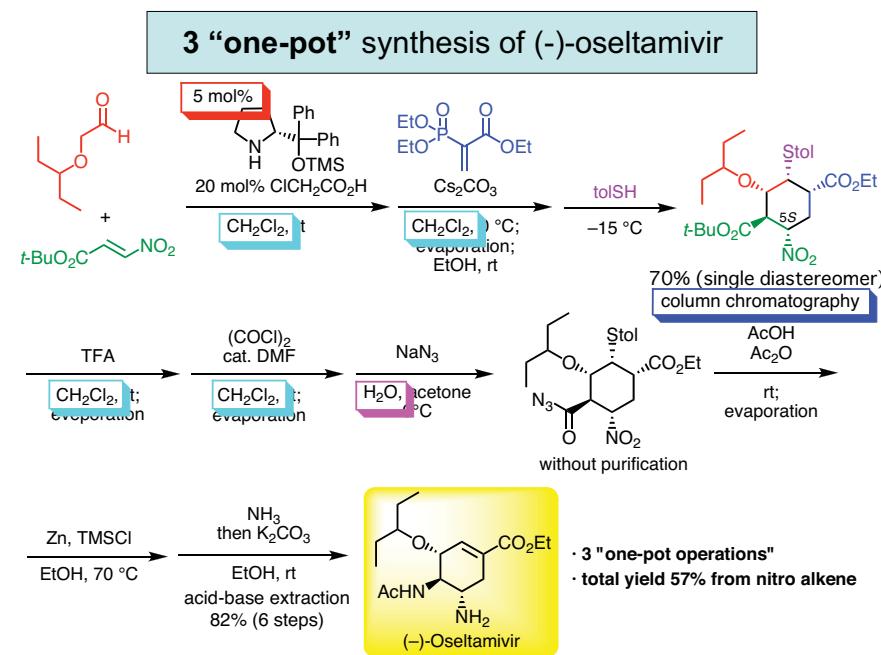
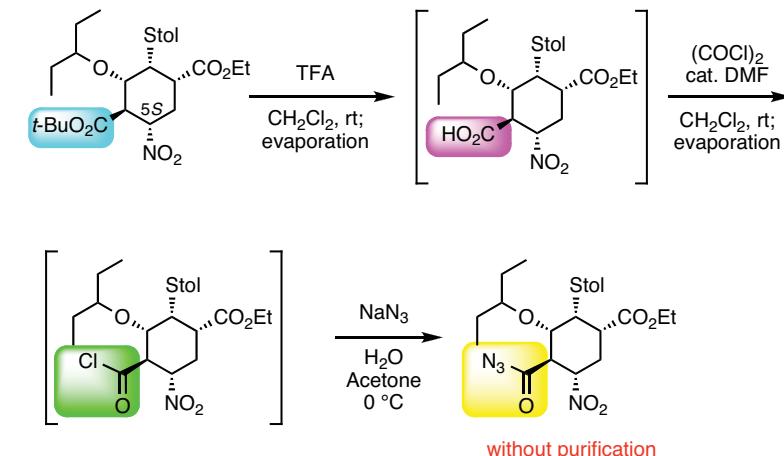
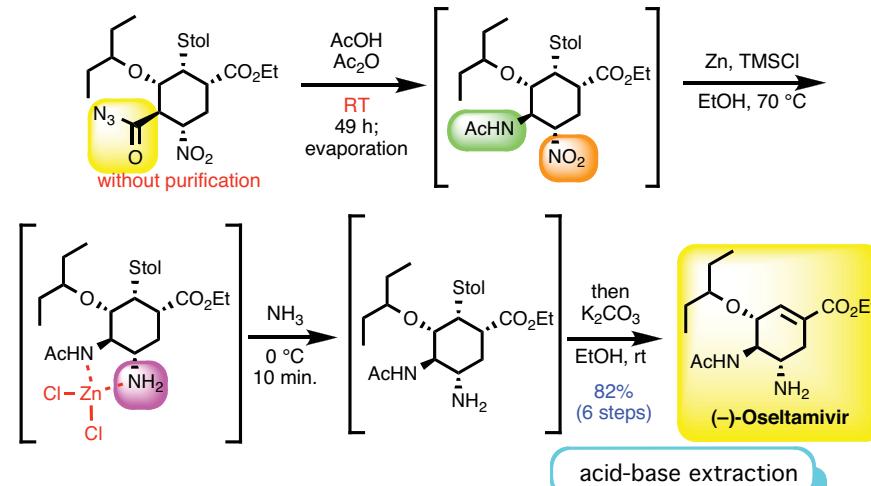
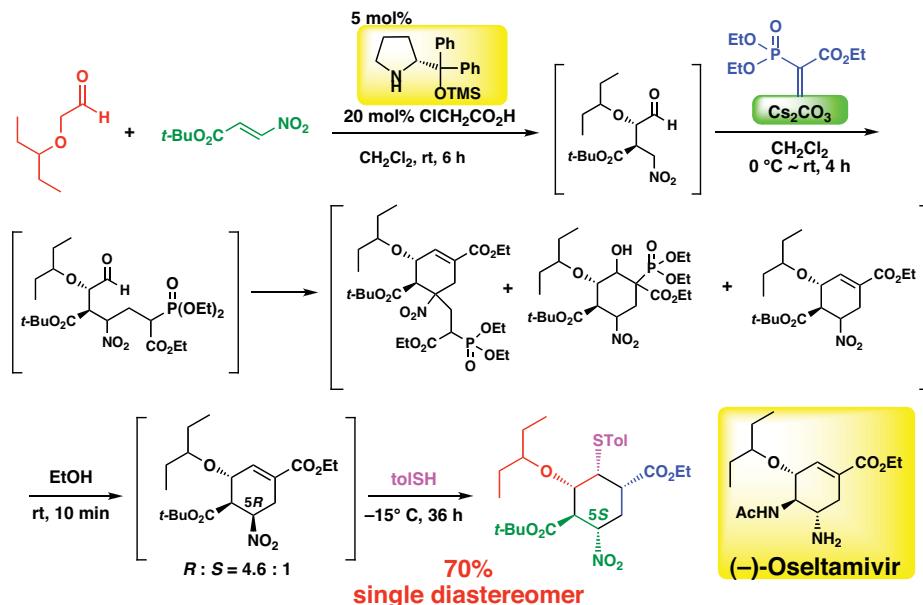


### Michael Reaction of Toluenethiol and Isomerization Reaction

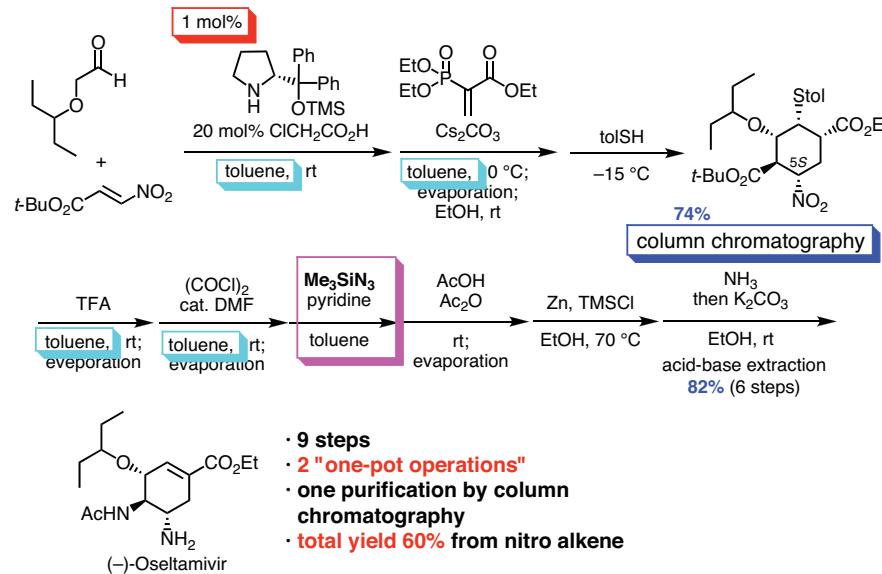


Base	temp. / °C	time / h	Yield/%		
			A	B	C
K <sub>2</sub> CO <sub>3</sub>	-5	24	85	15	-
Cs <sub>2</sub> CO <sub>3</sub>	-5	13	35	-	65
<b>Cs<sub>2</sub>CO<sub>3</sub></b>	<b>-15</b>	<b>36</b>	<b>90</b>	<b>&lt;5</b>	<b>-</b>

### Application to one-pot reaction



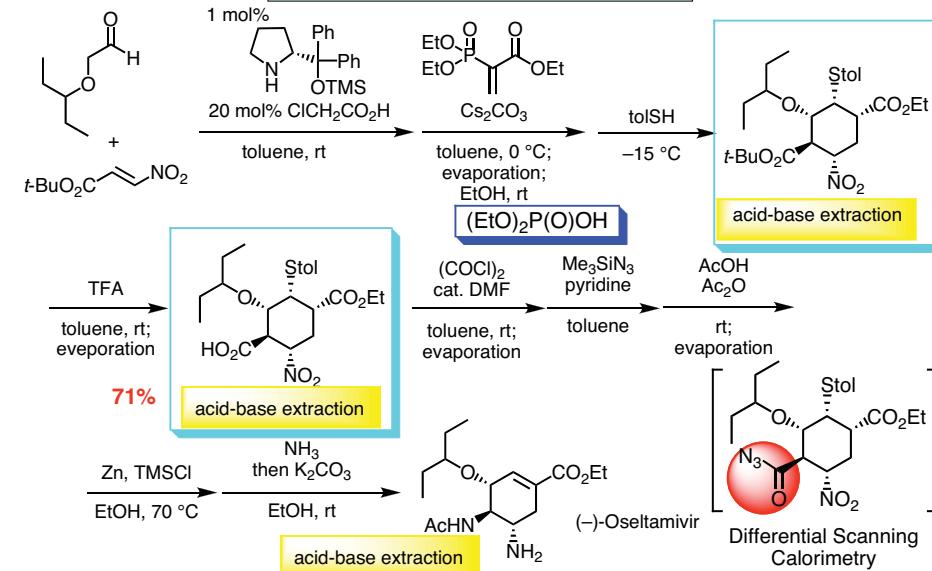
## 2 “one-pot” synthesis of (-)-oseltamivir



*Chem. Eur. J.*, **16**, 12616 (2010)

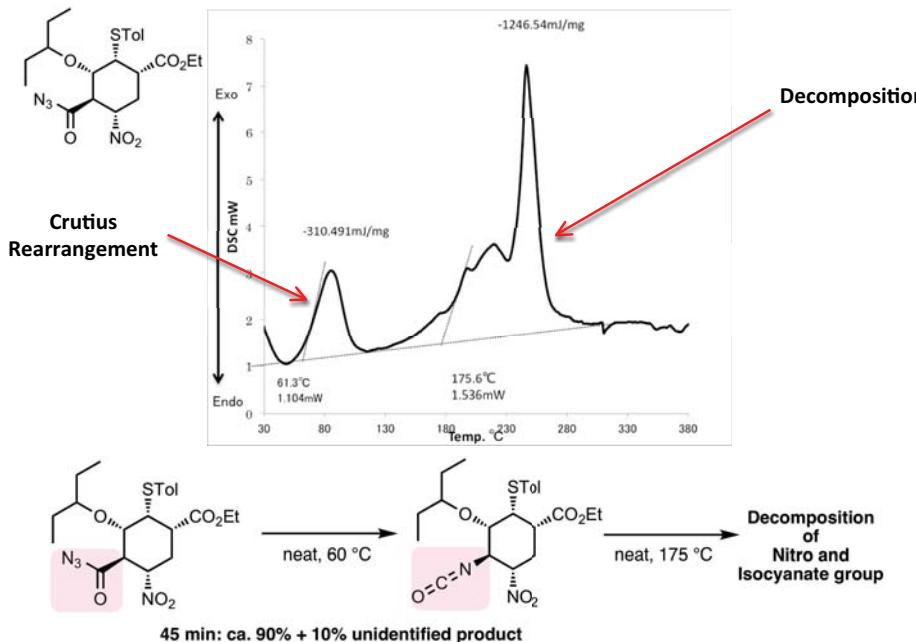
9 steps  
2 "one-pot operations"  
one purification by column chromatography  
total yield 60% from nitro alkene

## Column free synthesis

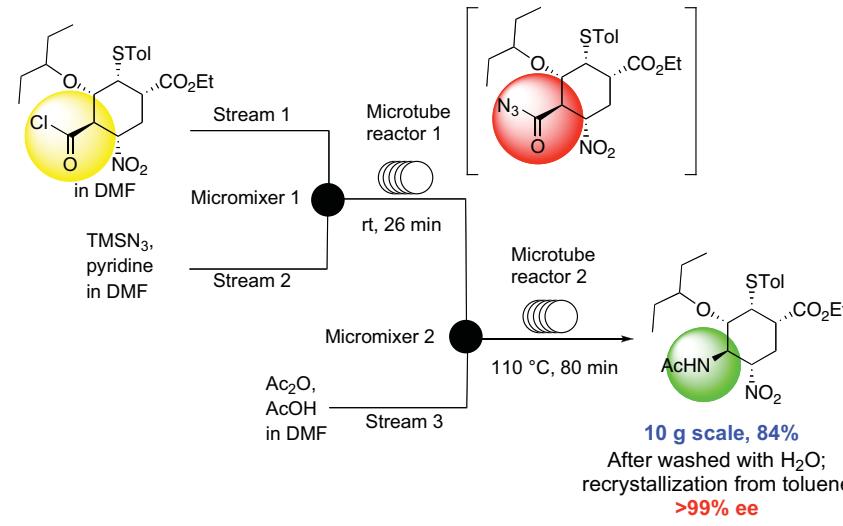


*Chem. Eur. J.*, **16**, 12616 (2010)

## Differential Scanning Calorimetry (DSC) Experiment



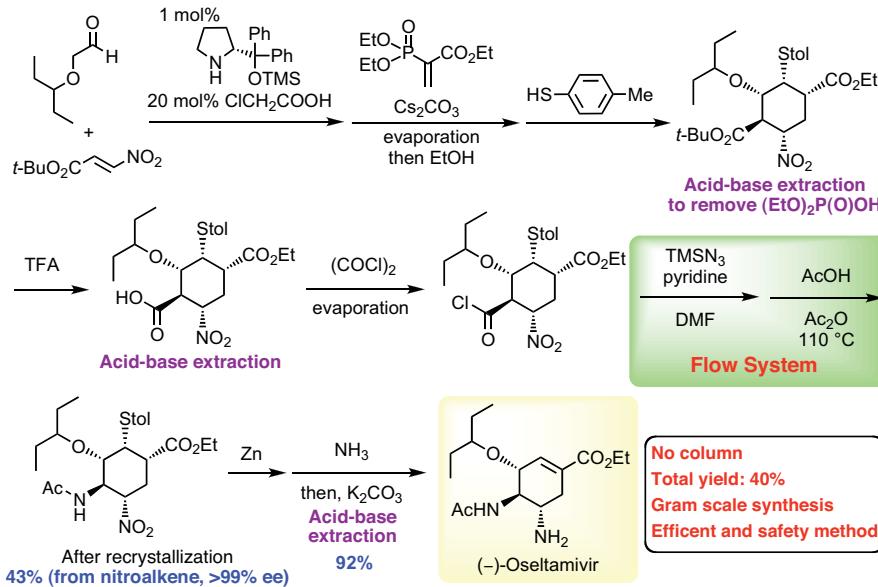
## Microreactor in the Curtius Rearrangement



**10 g scale, 84%**  
After washed with H<sub>2</sub>O;  
recrystallization from toluene  
**>99% ee**

Eur. J. Org. Chem., 2011, 6020.

### Practical synthesis of (-)-oseltamivir



### Green Reaction

- Atom economy (Trost)
- Step economy (Wender)
- Redox economy (Baran & Hoffmann)

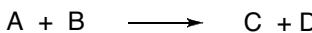
### Operational Economy

- Purification step economy
- Chemical waste economy
- Time economy
- Solvent economy

One pot reaction is not a simple combination of each optimized reaction.

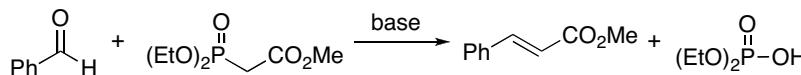
### One-Pot Reaction

- High yield in each step (spot to spot reaction)
- Restriction on the amount of the reagent (1:1 molar ratio)
- Restriction on the solvent (Solvent of high boiling point is not suitable)
- Restriction on the reaction



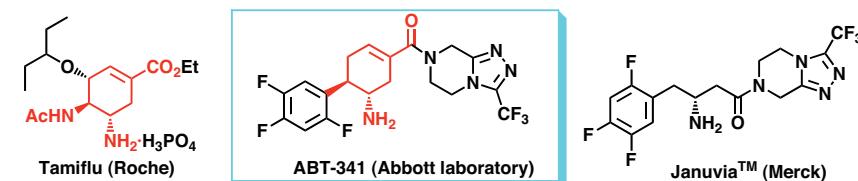
C is the desired product:

Next reaction has to be performed in the presence of D.

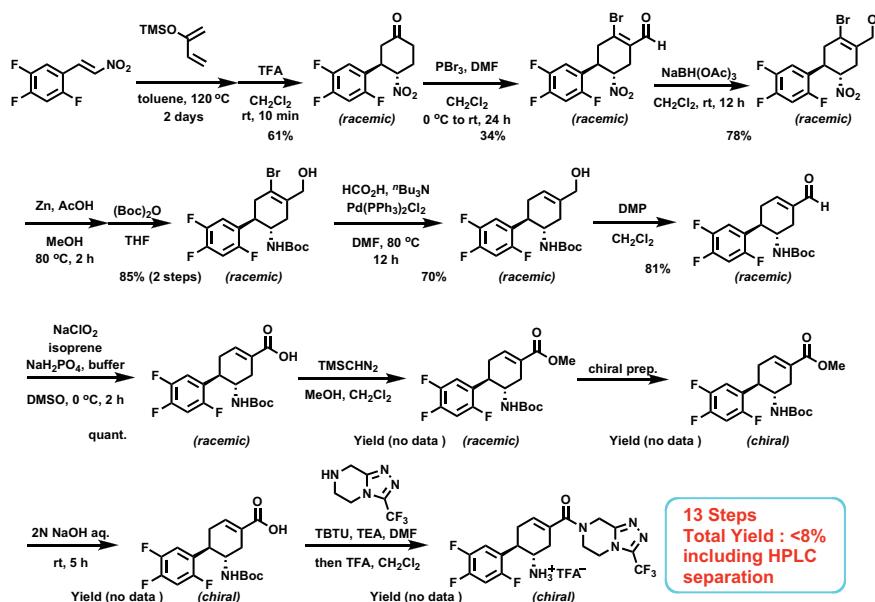


### Non-insulin dependant diabetes

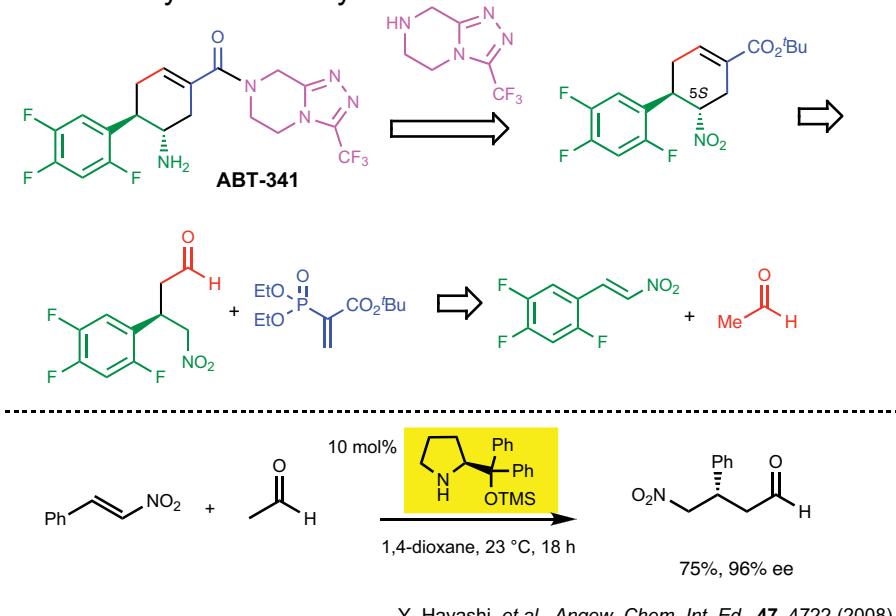
Dipeptidyl peptidase-4 (DPP-4) inhibitor



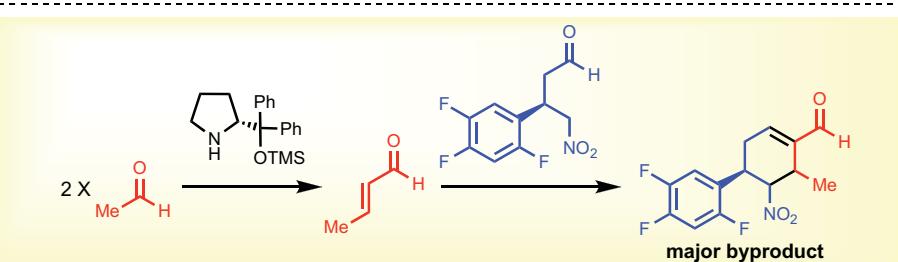
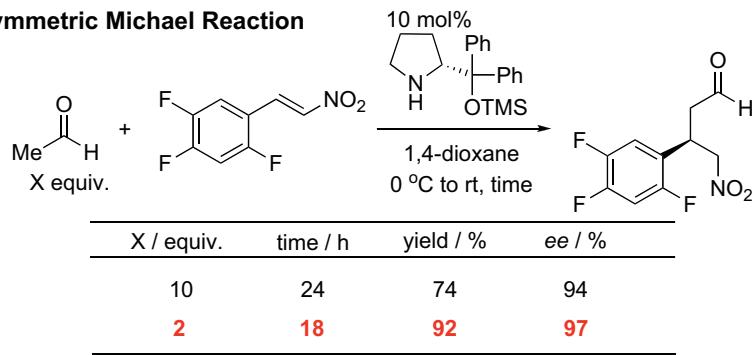
### Synthesis of ABT-341 by Abbott (J. Med. Chem., 2006, 49, 6439)



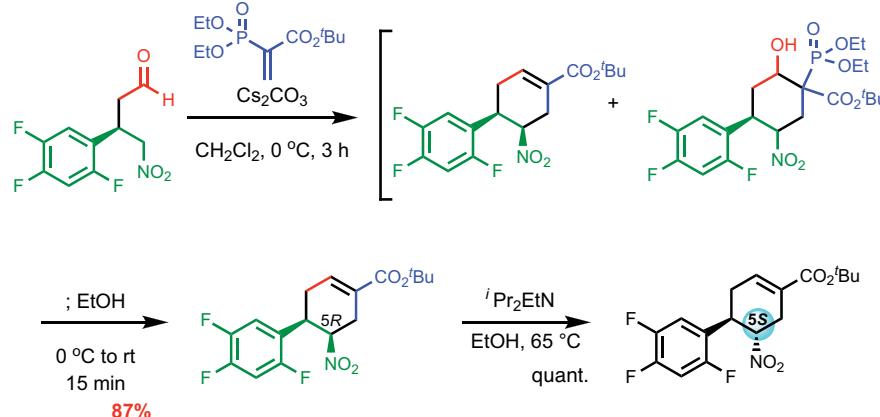
### Retro-synthetic analysis



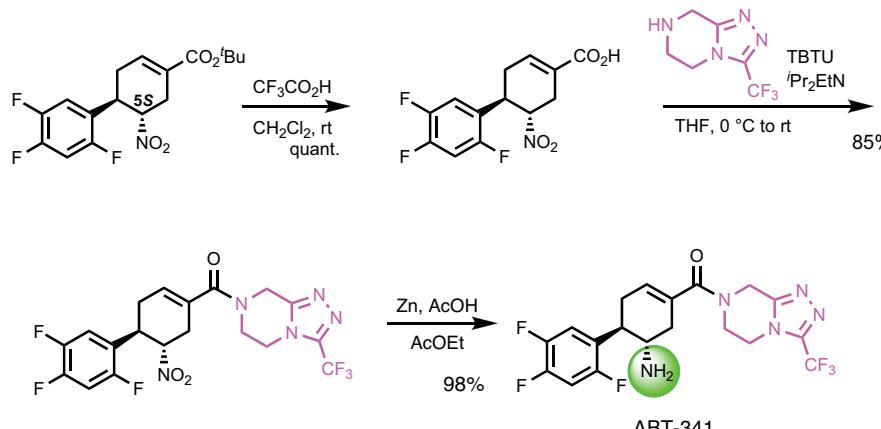
### Asymmetric Michael Reaction



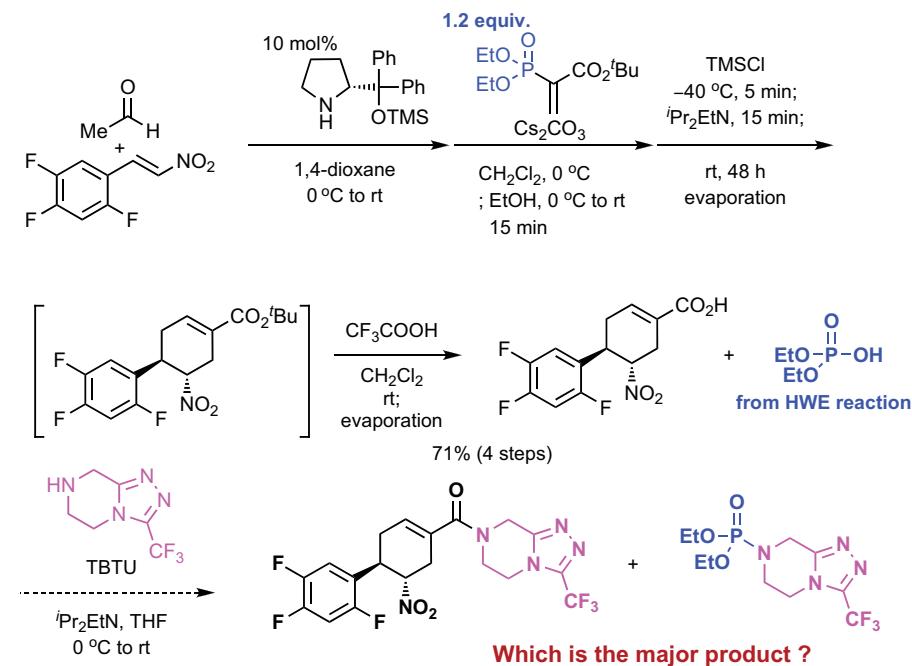
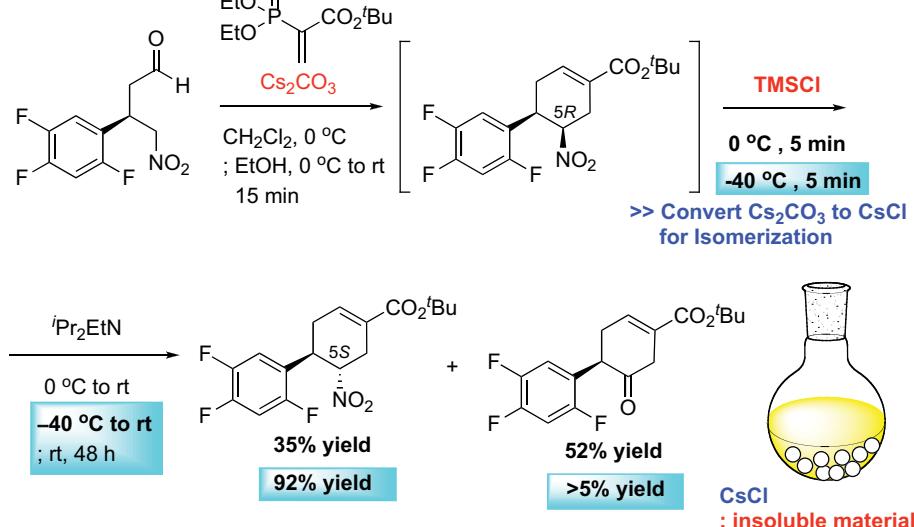
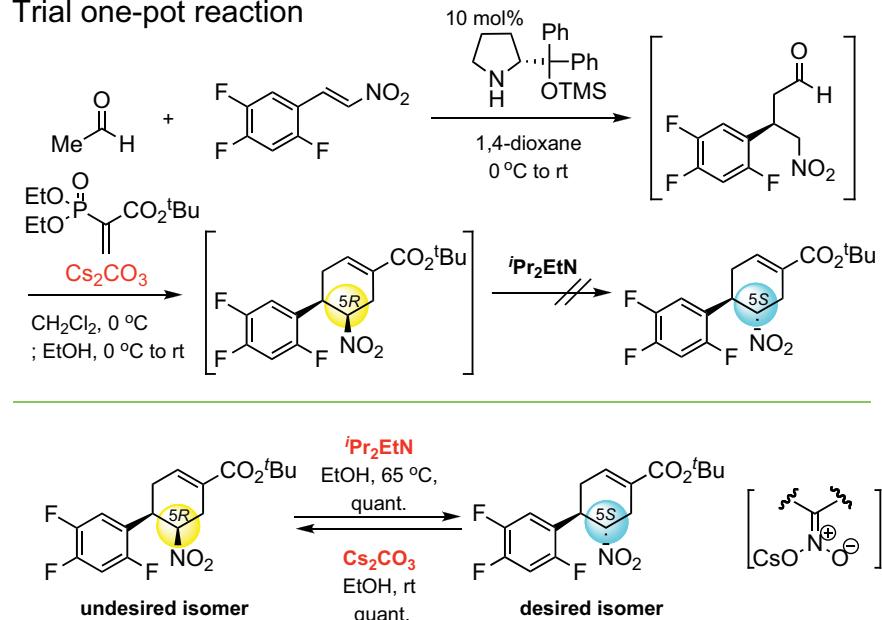
### Chiral cyclohexene formation

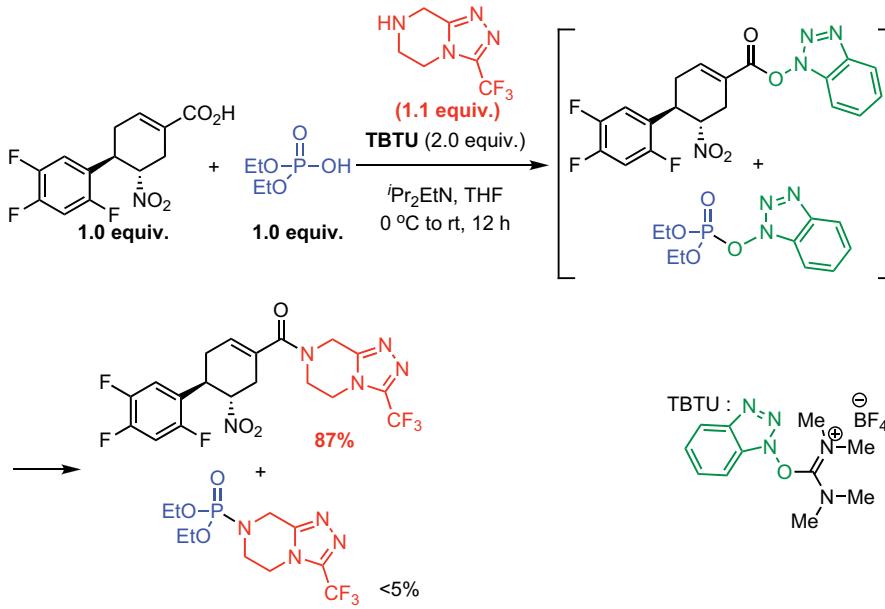


## Synthesis of ABT-341

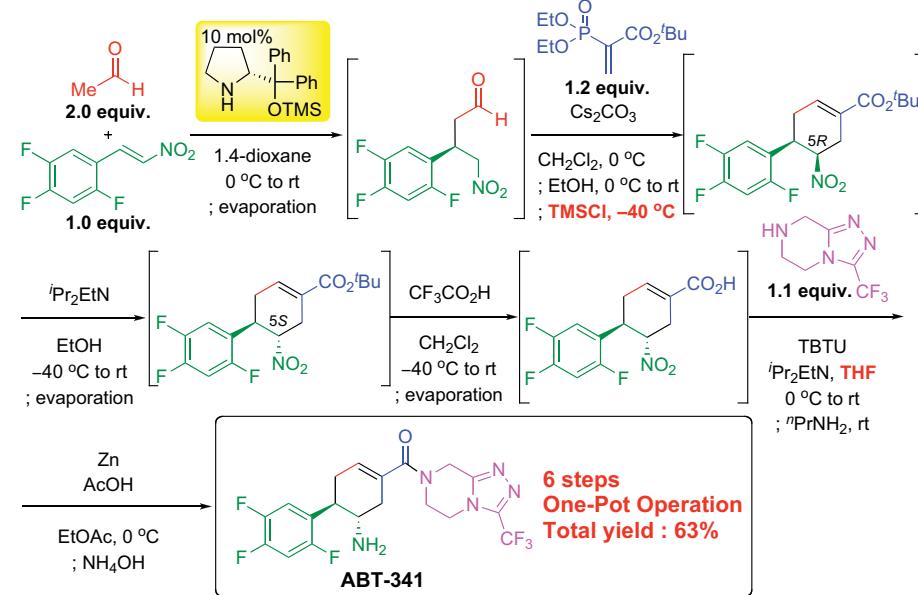


## Trial one-pot reaction





### One-Pot Total Synthesis of ABT-341



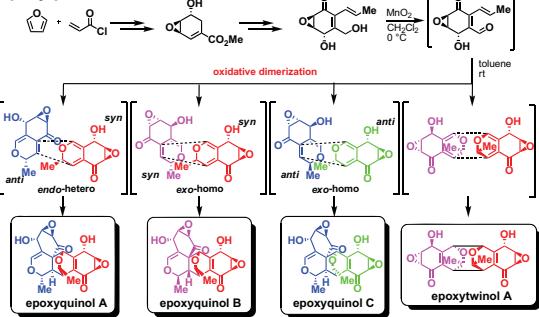
Angew. Chem. Int. Ed. **2011**, *50*, 2824.

# Hayashi Laboratory (Tokyo University of Science, TUS)

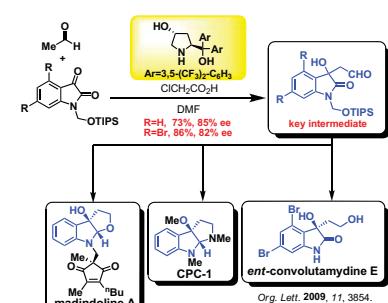
Hayashi Lab. Homepage: <http://www.ci.kagu.tus.ac.jp/lab/org-chem1/>

## Total Synthesis of Bioactive Compounds

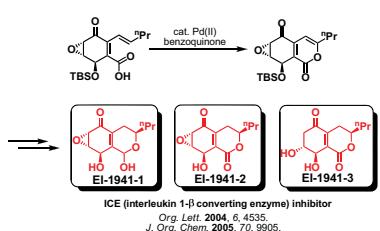
### epoxyquinols



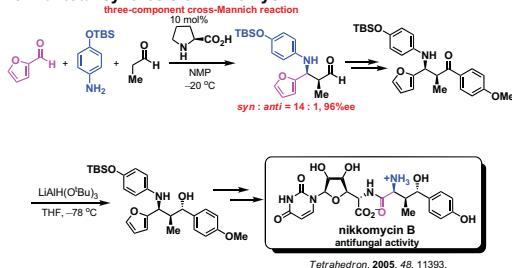
### CPC-1, ent-convolutamidine E, and half segment of madindoline A



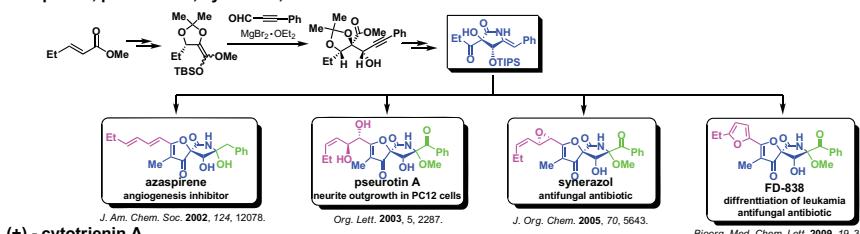
### EI-1941-1, EI-1941-2, EI-1941-3



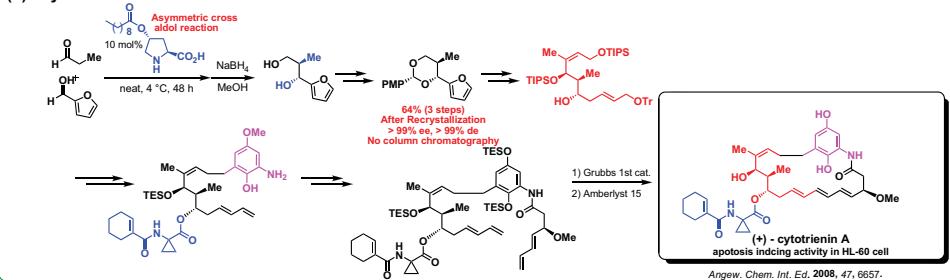
### formal total synthesis of nikkomycin B



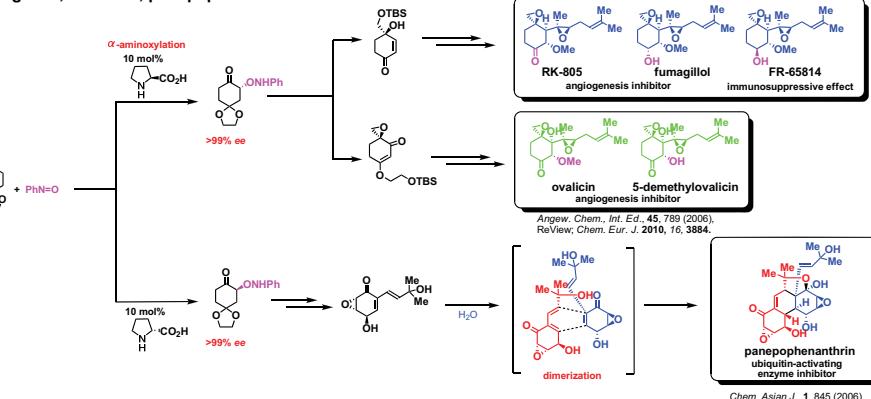
### azaspirene, pseurotin A, synerazol, FD-838



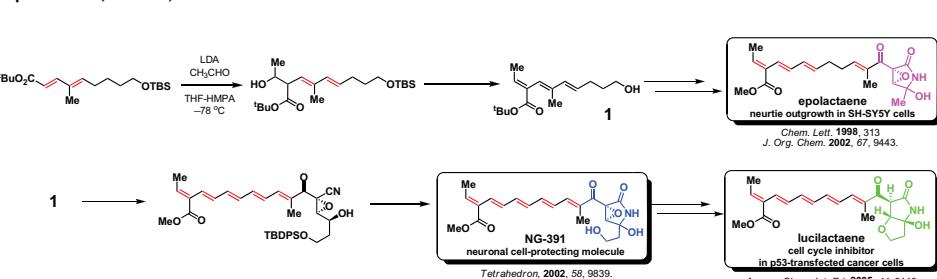
### (+)-cytotoxin A



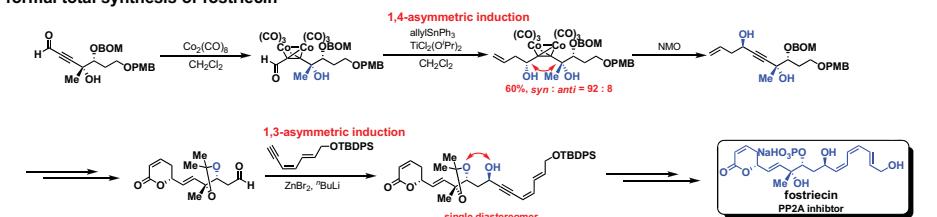
### fumagillins, ovalicins, paneppophenanthrin



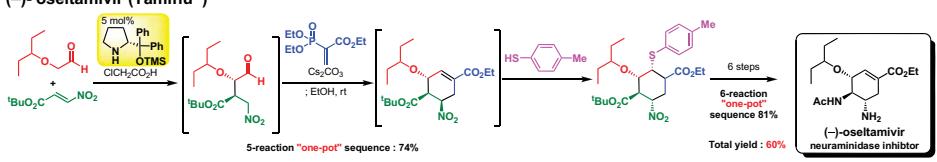
### epolactaene, NG-391, lucilactaene



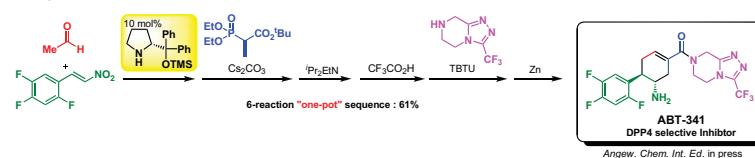
### formal total synthesis of fostriecin



### (-) oseltamivir (Tamiflu®)



### ABT-341



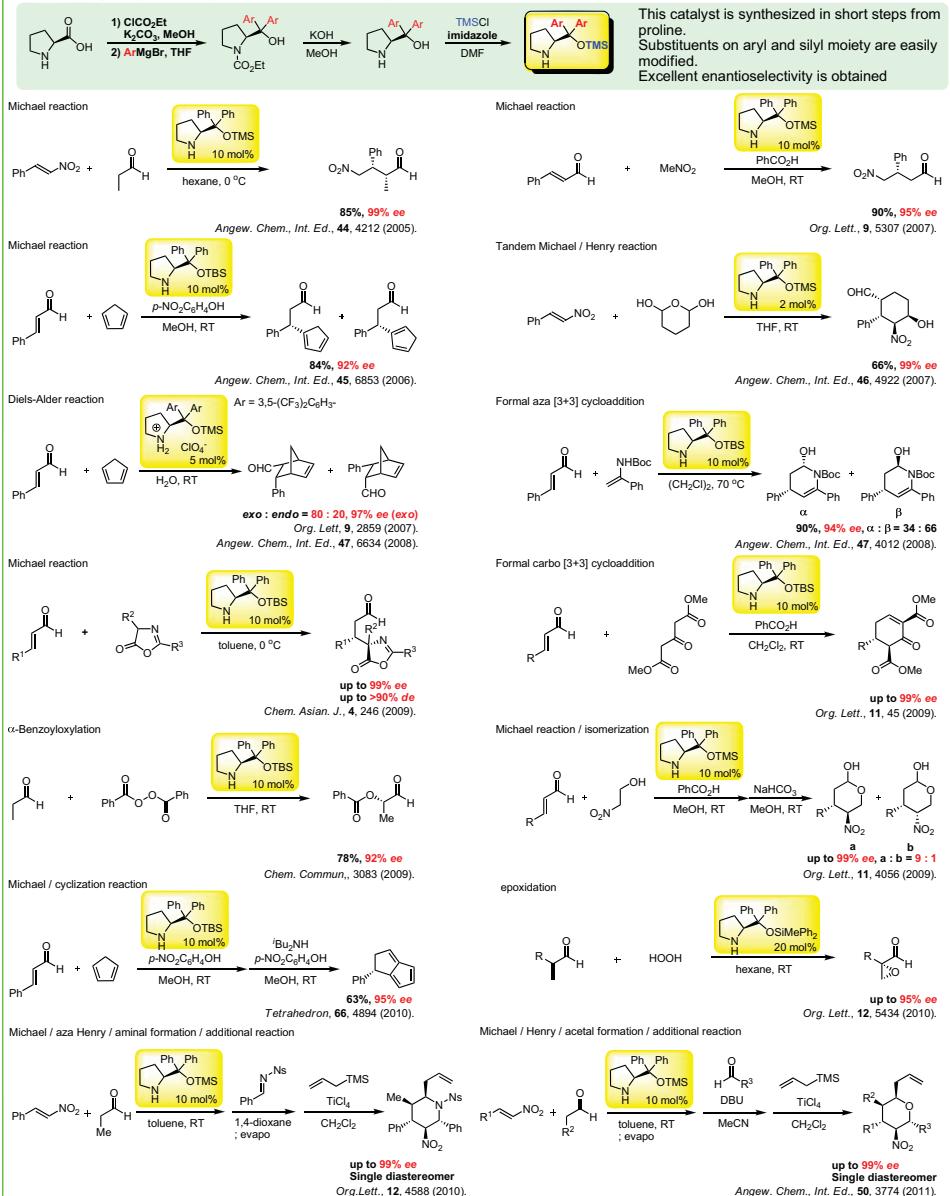
# Hayashi Laboratory

Hayashi Lab. Homepage <http://www.ykbsc.chem.tohoku.ac.jp/>

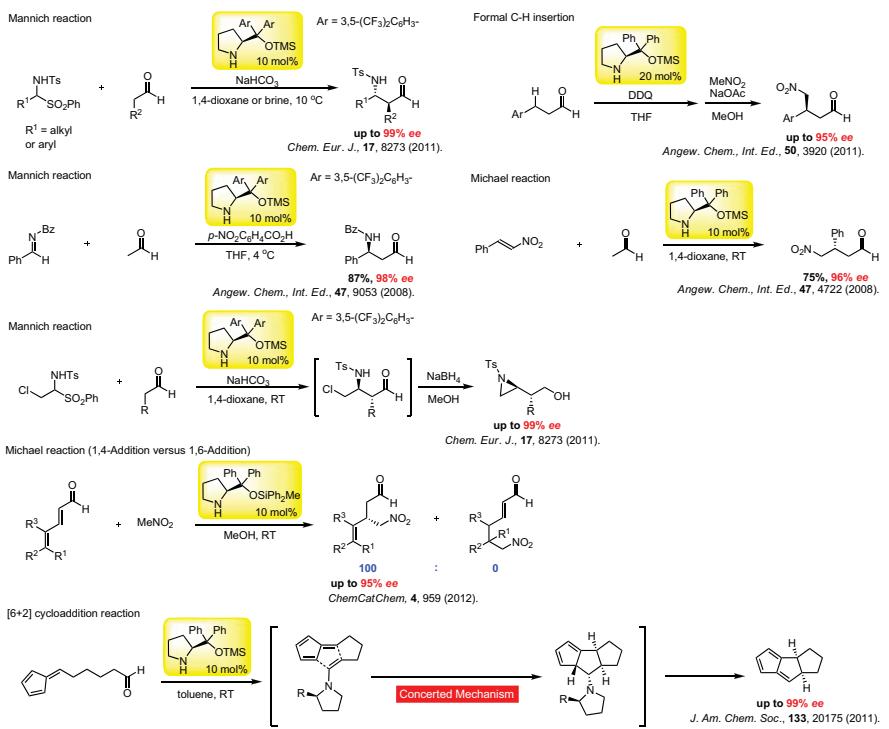
## Development of new reactions

Asymmetric reaction using amino acid or their derivatives as a catalyst,  
environmental conscious asymmetric reaction using water as a solvent, and research about origin of chirality

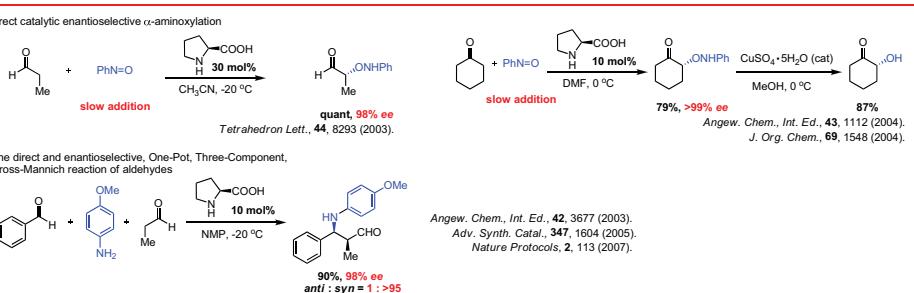
### Reaction using diarylprolinol silyl ether derivatives as catalyst



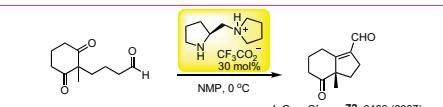
### Reaction using diarylprolinol silyl ether derivatives as catalyst



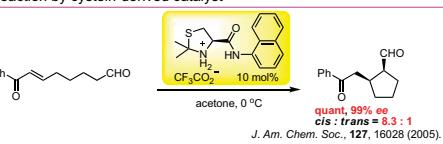
### Reaction catalyzed by proline



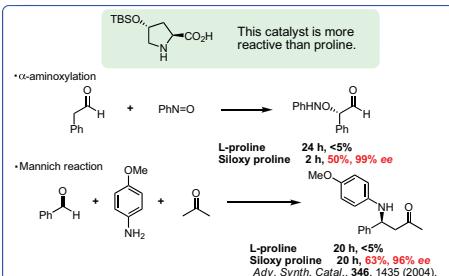
### Reaction by proline-derived catalyst



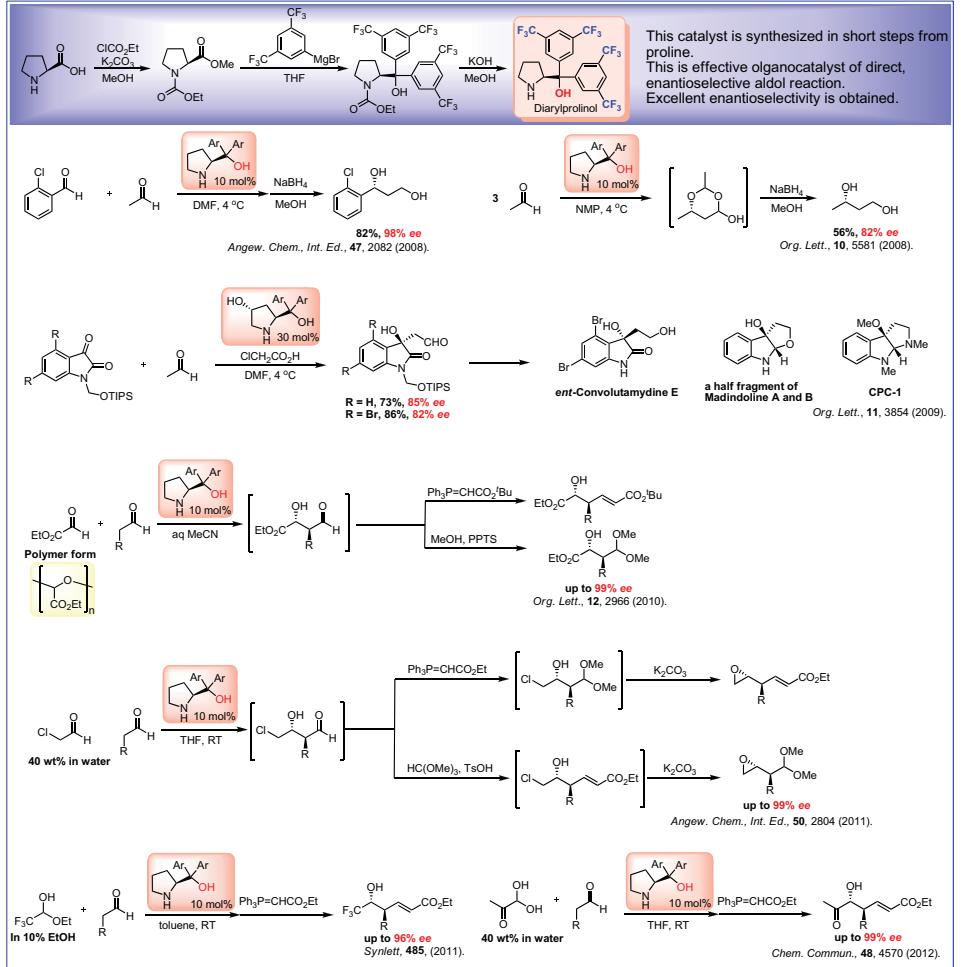
### Reaction by cysteine-derived catalyst



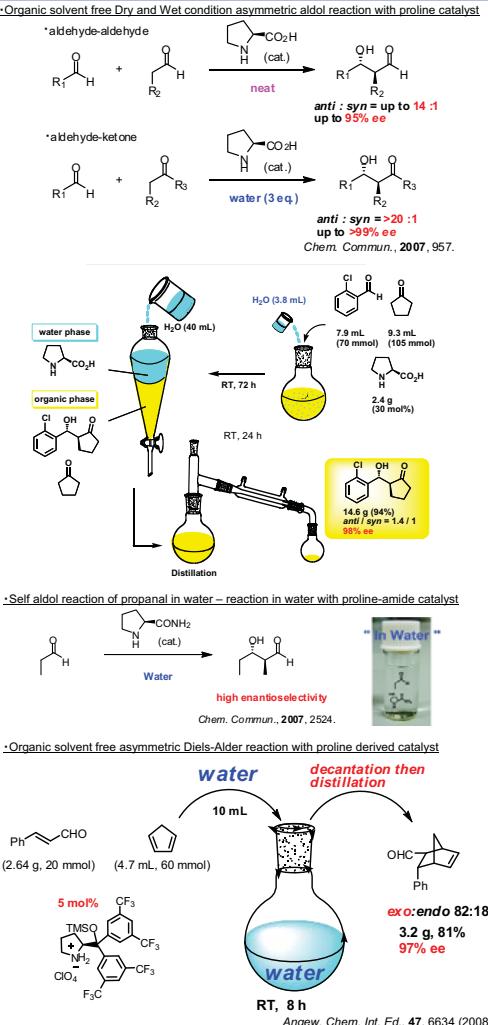
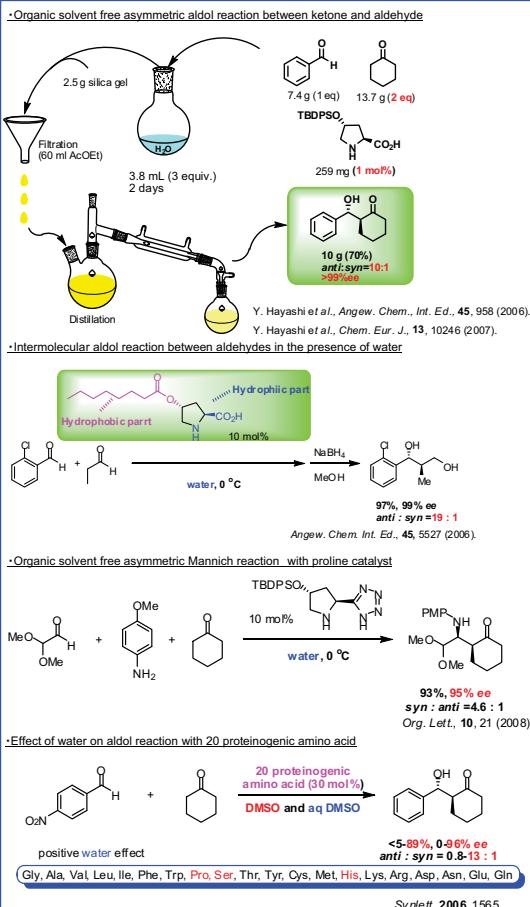
### Reaction by siloxyproline catalyst



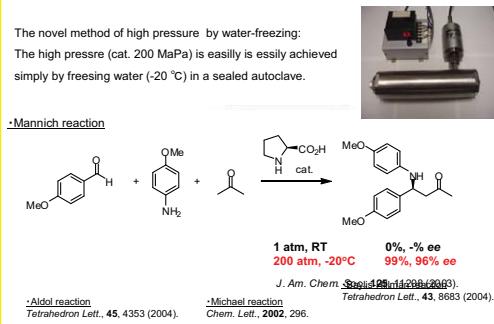
### Aldol reaction by diarylprolinol as a catalyst



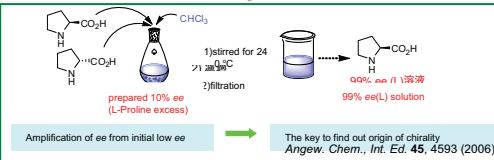
### Organic solvent free reaction



### Application of High Pressure Induced by Water-Freezing to the direct catalytic asymmetric reaction



### Research about of chirality



### Proposed mechanistic cycle

