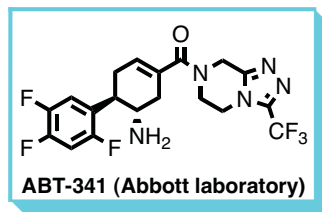
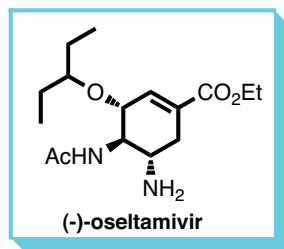
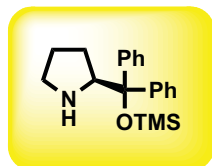


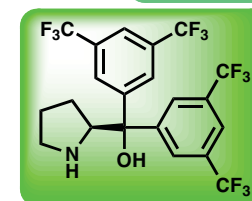
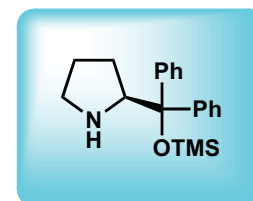
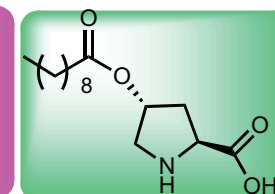
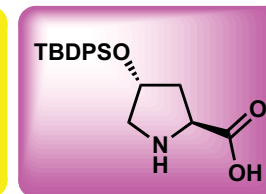
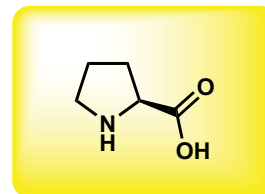
# Organocatalyst in Total Synthesis

Tohoku University  
Yujiro Hayashi

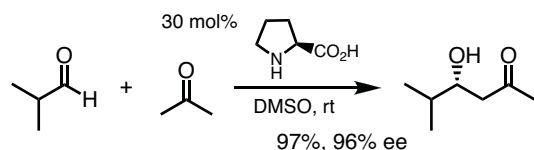


## Merit of organocatalysis

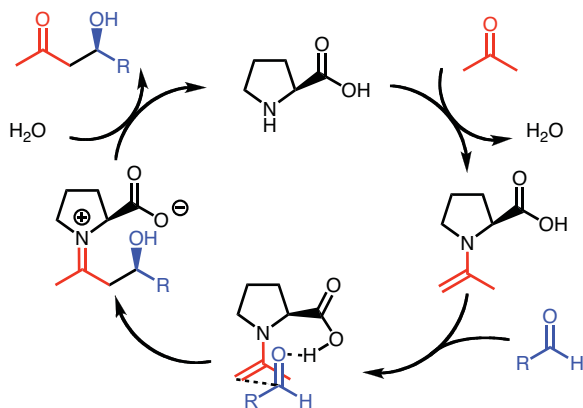
Product is free from the contamination of metal.  
Exclusion of water and air is not necessary.  
Most of the ligands are non-toxic.



## Background: Enamine intermediate

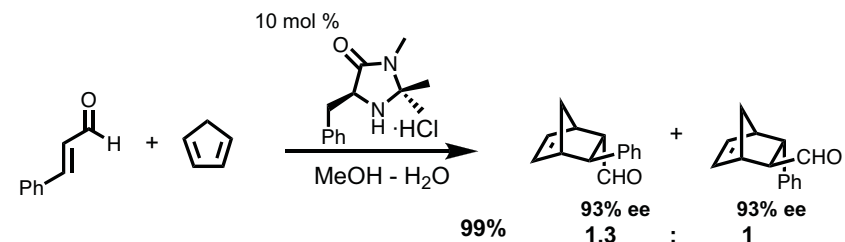


B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.*, **2000**, *122*, 2395.



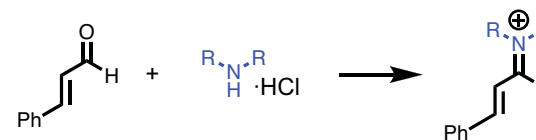
## Background: Iminium ion intermediate

### Diels-Alder reaction

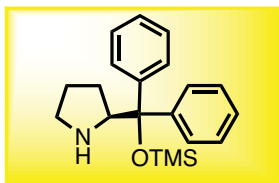


D. W. C. MacMillan, *et al.*, *J. Am. Chem. Soc.*, **122**, 4243 (2000).

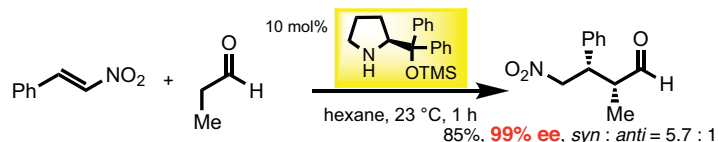
### LUMO-lowering activation



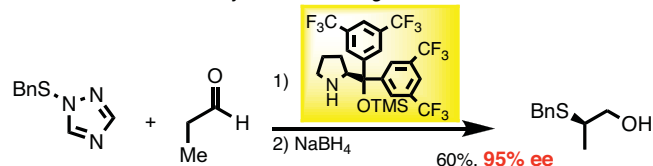
## Jorgensen-Hayashi Catalyst



TMS = Me<sub>3</sub>Si-



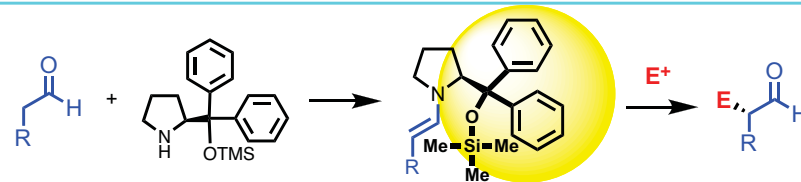
Y. Hayashi, *et al.*, *Angew. Chem. Int. Ed.*, **44**, 4112 (2005).



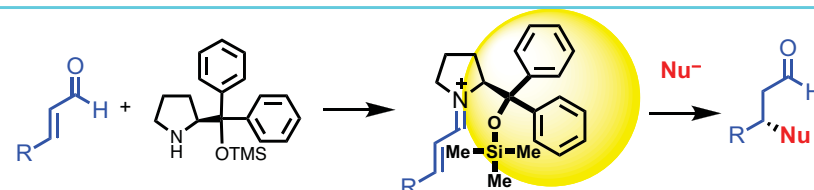
K. A. Jorgensen, *et al.*, *Angew. Chem. Int. Ed.*, **44**, 794 (2005).

Effective for the both enamine and iminium ion intermediate

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

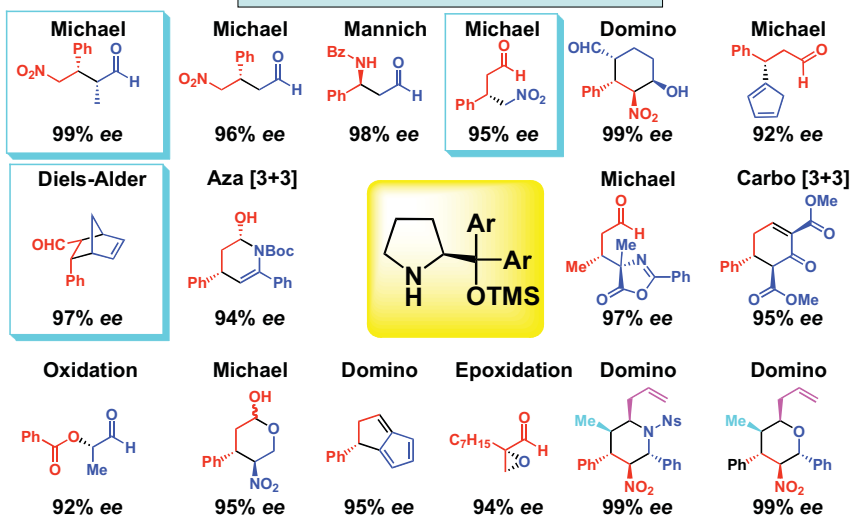


Iminium ion: functionalization at the  $\beta$ -position of aldehyde



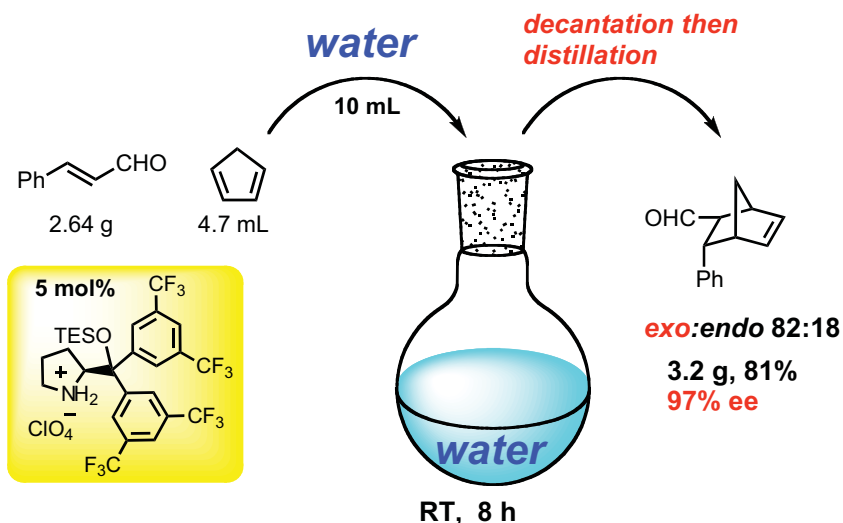
X-ray and *ab initio* calculation D. Seebach, Y. Hayashi, Uchimaru, *et al.*, *Helv. Chim. Acta*, **2009**, *92*, 1225.

## Reactions developed by our group



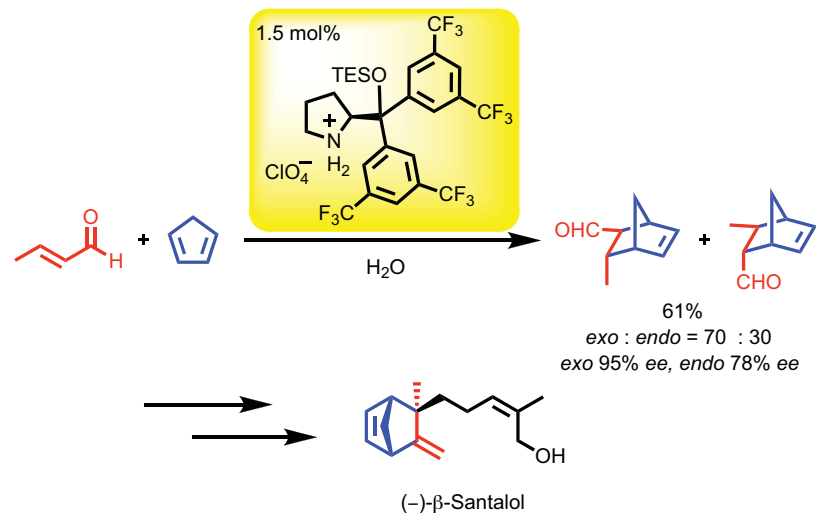
*Angew. Chem. Int. Ed.*, **44**, 4212 (2005). *Angew. Chem., Int. Ed.*, **45**, 6853 (2006). *Angew. Chem., Int. Ed.*, **46**, 4922 (2007). *Org. Lett.*, **9**, 5307 (2007). *Angew. Chem., Int. Ed.*, **47**, 4012 (2008). *Angew. Chem., Int. Ed.*, **47**, 4722 (2008). *Angew. Chem., Int. Ed.*, **47**, 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

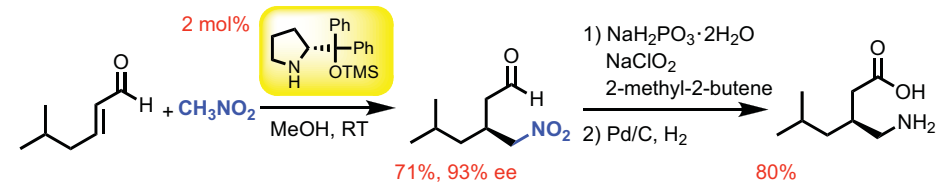


*Angew. Chem. Int. Ed.*, **47**, 6634 (2008).

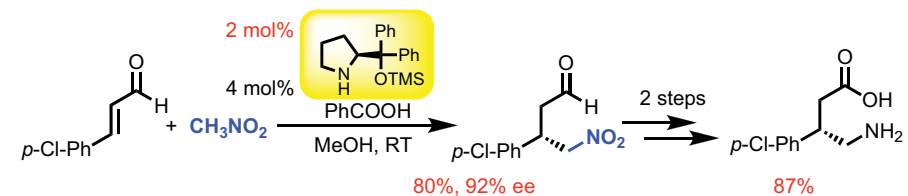
### Synthesis of (-)- $\beta$ -Santalol by Firmenich



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



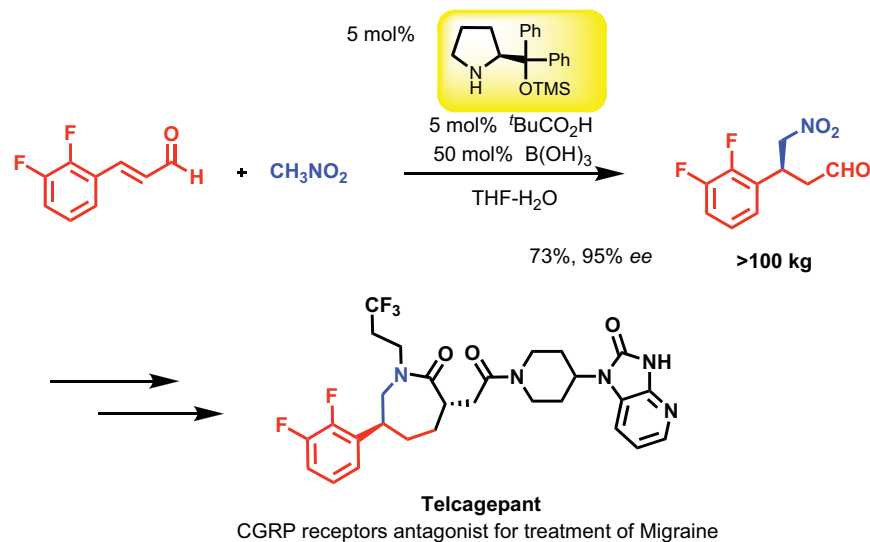
**Pregabalin:** anticonvulsant



**Baclofen:** GABA<sub>B</sub> receptor agonist

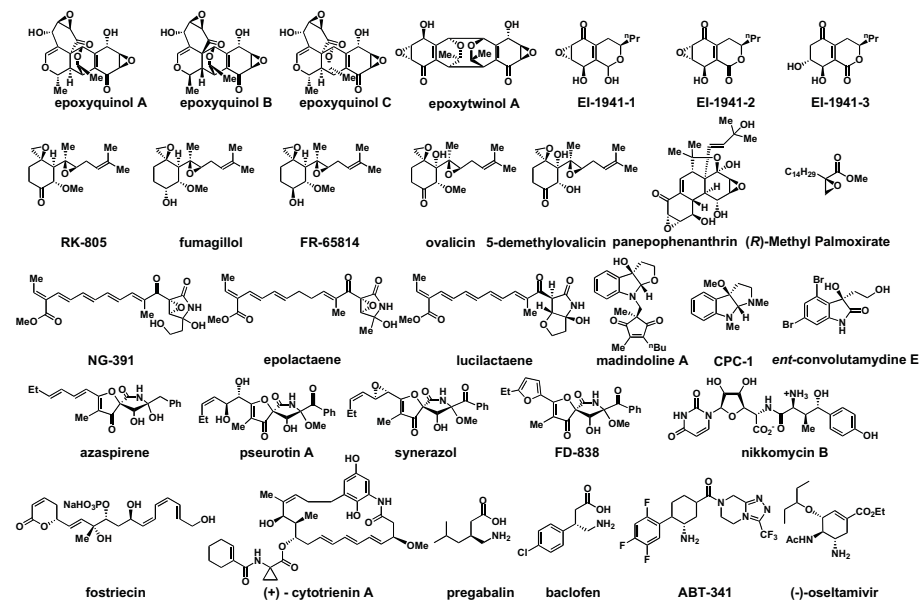
*Org. Lett.*, **9**, 5307 (2007).

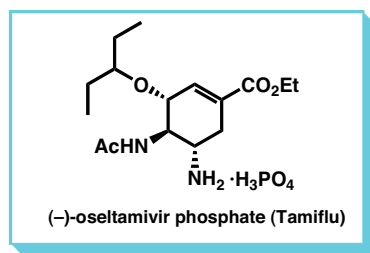
### Synthesis of Telcagepant by Merck



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

### Total synthesis of biologically active compounds



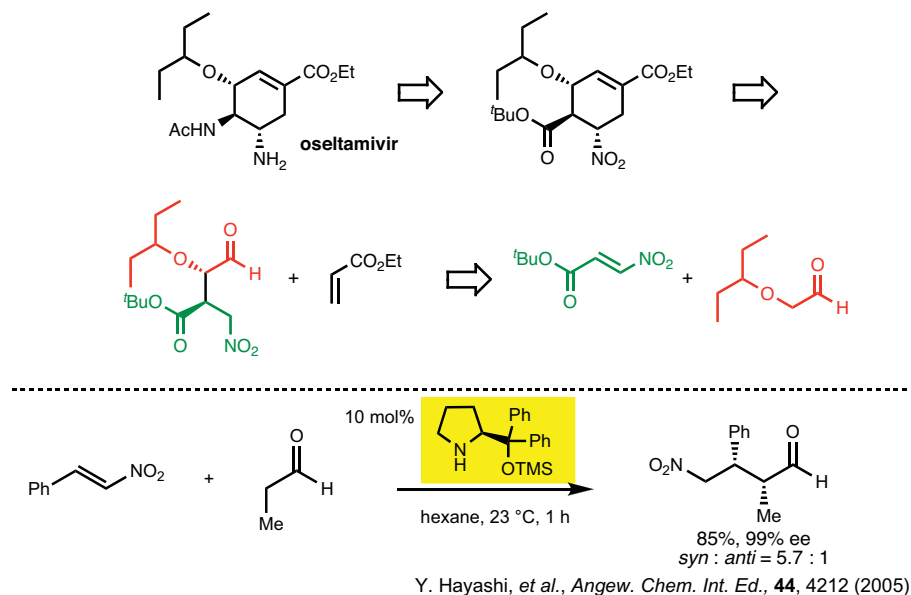


Tamiflu: Orally administered anti-Influenza drug developed by  
 Gilead Sciences, Inc. and Roche

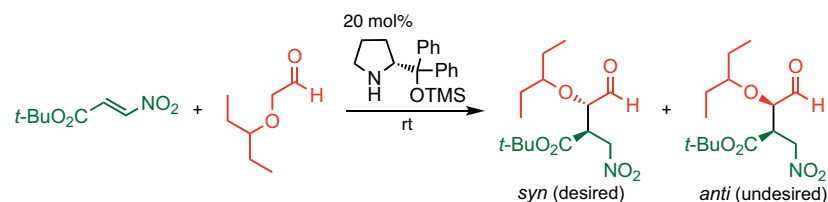
Total Synthesis: Corey (2006), Shibasaki (2006), Yao (2006), Wong (2007)  
 Fukuyama (2007), Fang (2007), Kann (2007), Trost (2008)  
 Banwell (2008), Mandai (2009), Hudlicky (2009) *et al.*,  
**53 total syntheses**

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

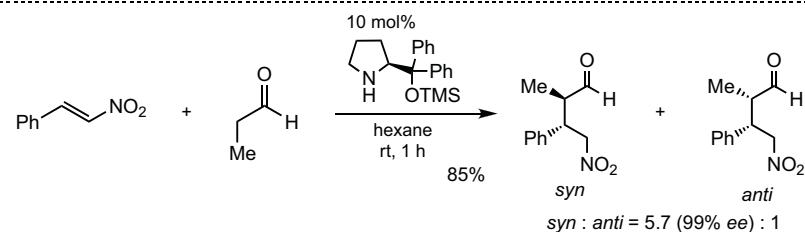
### First retro-synthetic analysis



### Asymmetric Michael Reaction

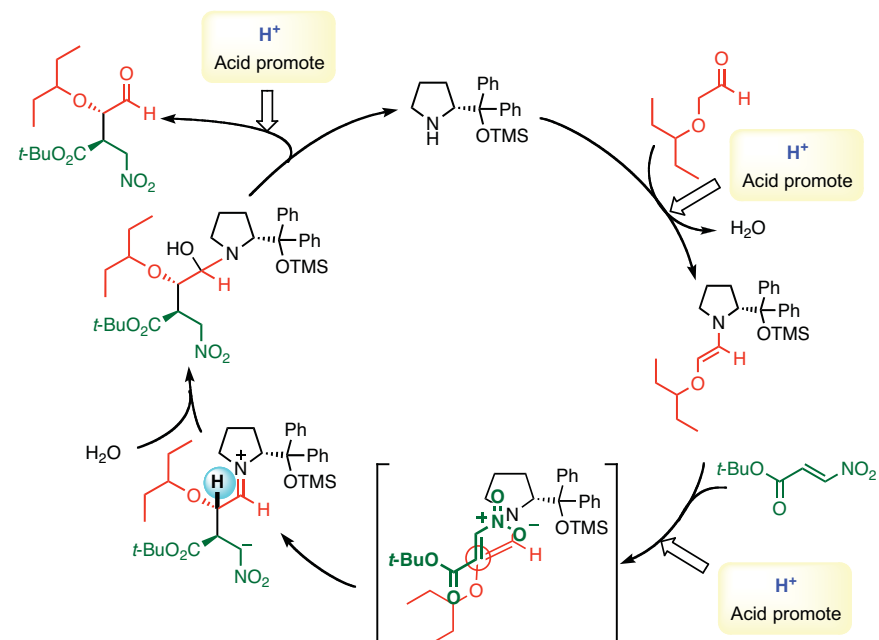


solvent	time / h	yield	syn : anti
hexane	60	26%	2.5 : 1
CH <sub>2</sub> Cl <sub>2</sub>	60	quant.	1.7 : 1

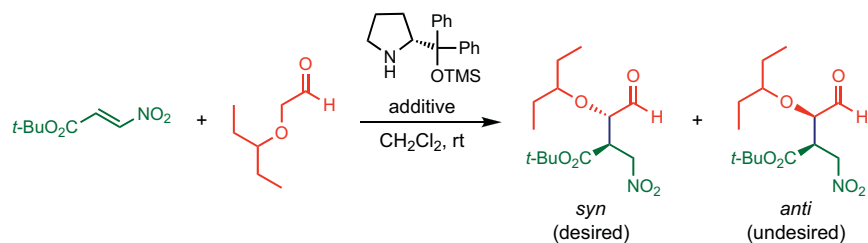


Y. Hayashi, *et al.*, *Angew. Chem., Int. Ed.* **2005**, **44**, 4212.

### Proposed Reaction Mechanism

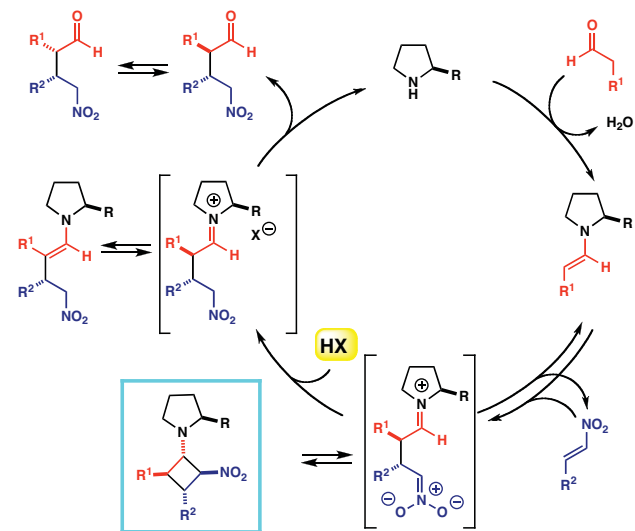


### Optimization for Key Michael Reaction



catalyst / mol%	additive (mol%)	pKa in H <sub>2</sub> O	time / h	yield	syn : anti	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>ClCH<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	–	

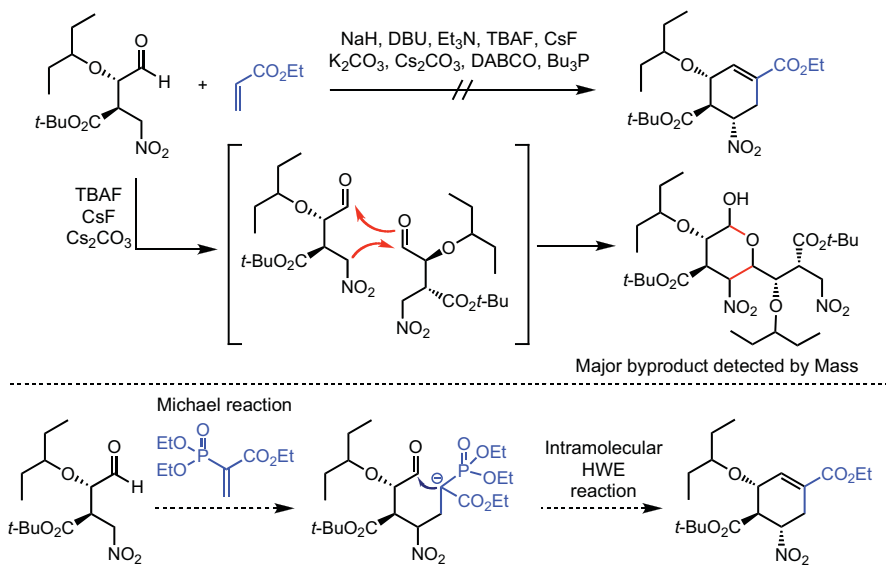
### Revised reaction mechanism



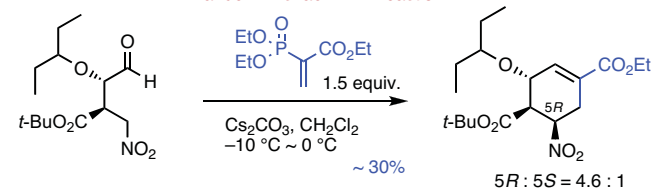
D. Seebach, Y. Hayashi, *et al.*, *Helv. Chim. Acta*, **2011**, *94*, 719.

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

### Domino Michael / Intramolecular Aldol reaction



### Tandem Michael/HWE reaction



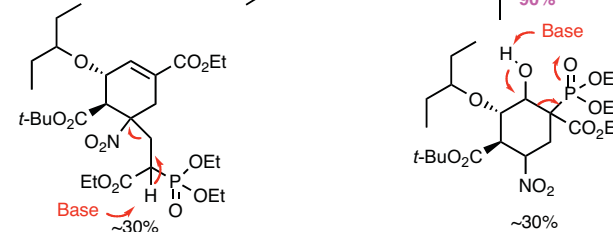
### Retro Michael reaction

Cs<sub>2</sub>CO<sub>3</sub>, EtOH  
23 °C, 15 min  
quant.

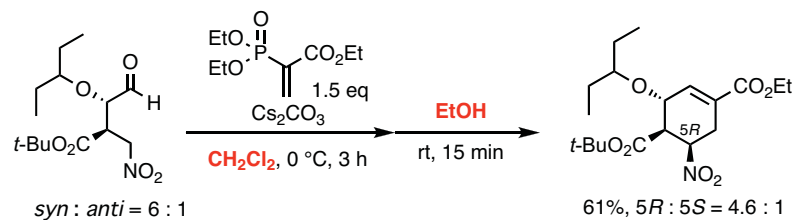
### Retro Aldol/HWE reaction

Cs<sub>2</sub>CO<sub>3</sub>, EtOH  
23 °C, 15 min  
90%

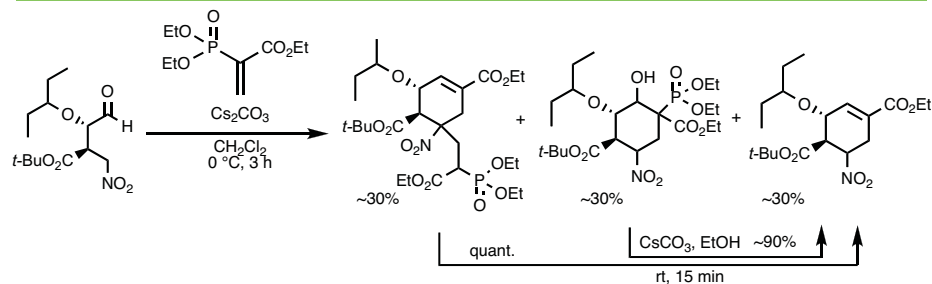
Byproducts



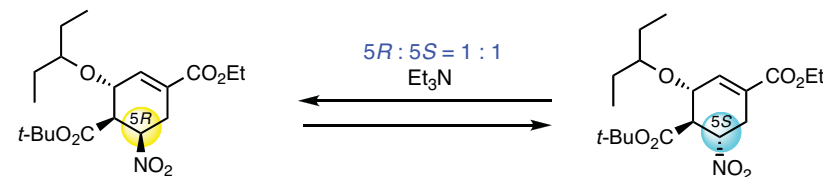
### Tandem Michael/HWE reaction



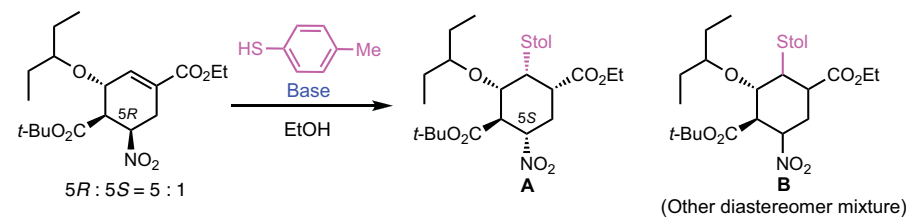
**One-pot Reaction:** purification economy, chemical waste economy, time economy increase yield



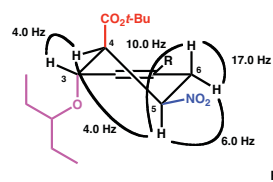
### Unsuccessful isomerization from 5*R* to 5*S*



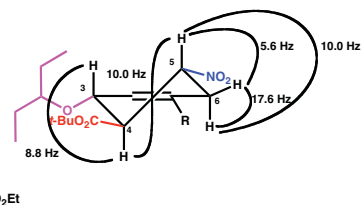
### Michael Reaction of Toluenethiol and Isomerization Reaction



### 5*R* isomer



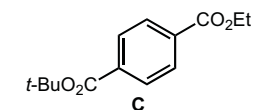
### 5*S* isomer



R = CO<sub>2</sub>Et

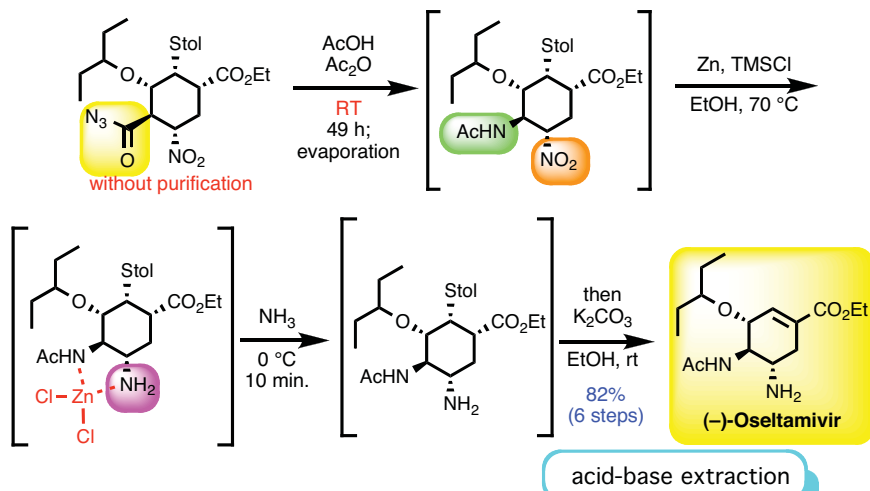
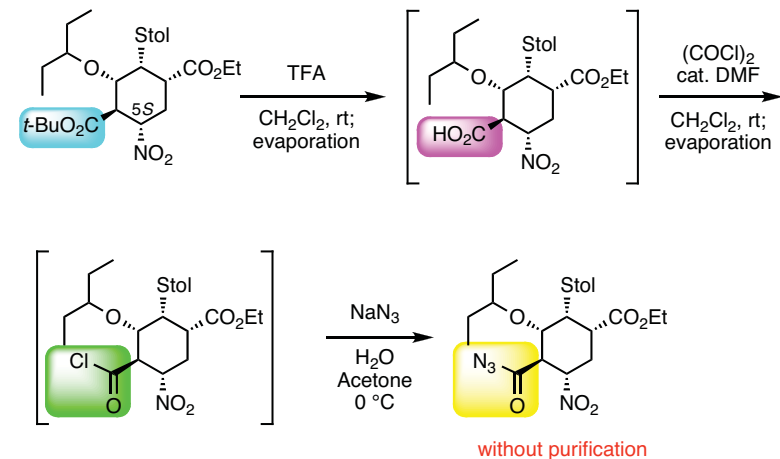
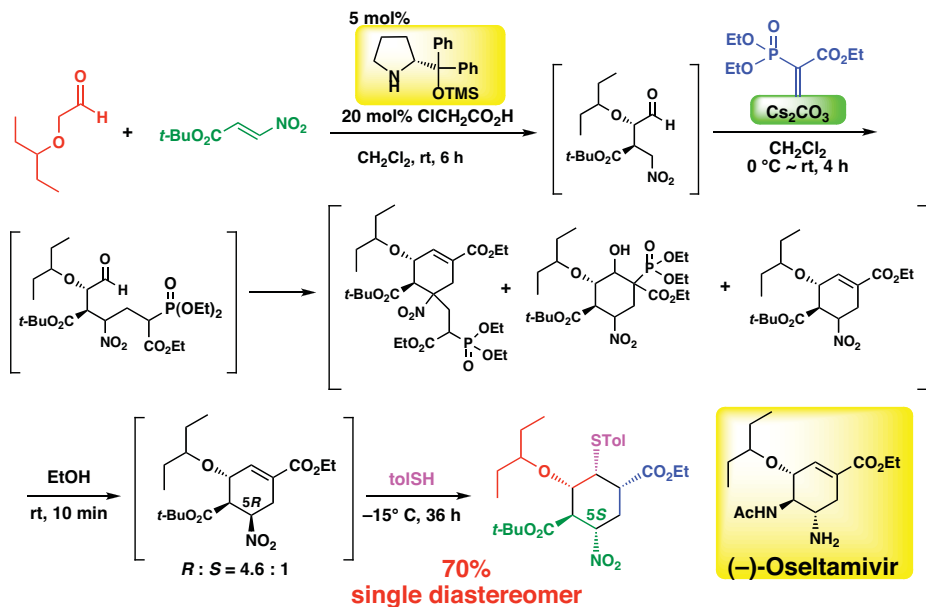
5*R* - isomer is stable than 5*S* - isomer in only 0.11 Kcal/mol by B3LYP/6-31G(d) calculation.

Calculation was performed by Dr.Uchimaru.

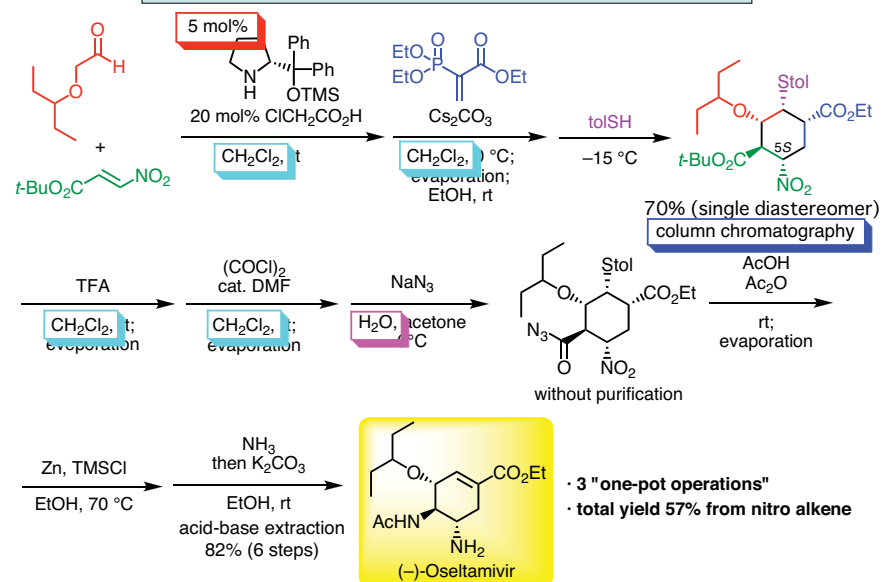


Base	temp. / °C	time / h	Yield/%		
			A	B	C
K <sub>2</sub> CO <sub>3</sub>	-5	24	85	15	-
Cs <sub>2</sub> CO <sub>3</sub>	-5	13	35	-	65
<b>Cs<sub>2</sub>CO<sub>3</sub></b>	<b>-15</b>	<b>36</b>	<b>90</b>	<b>&lt;5</b>	<b>-</b>

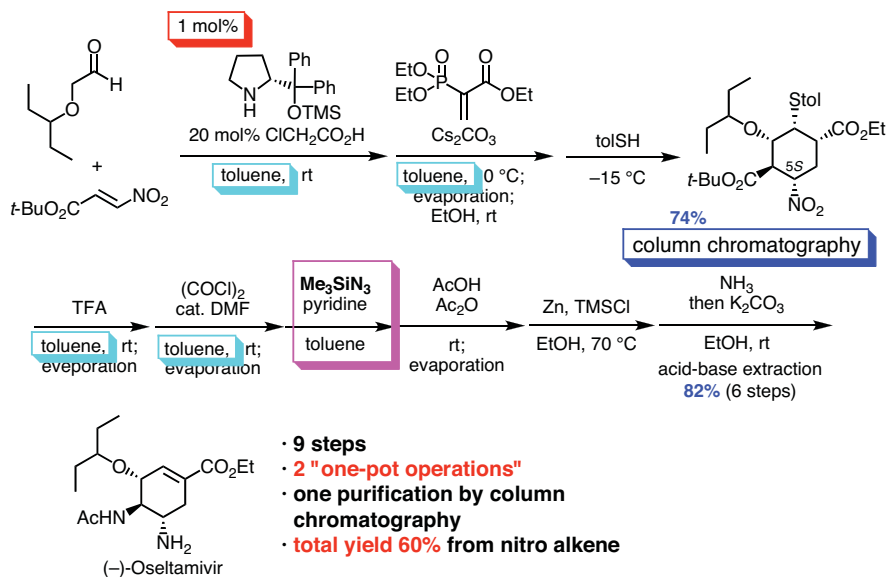
## Application to one-pot reaction



## 3 "one-pot" synthesis of (-)-oseltamivir

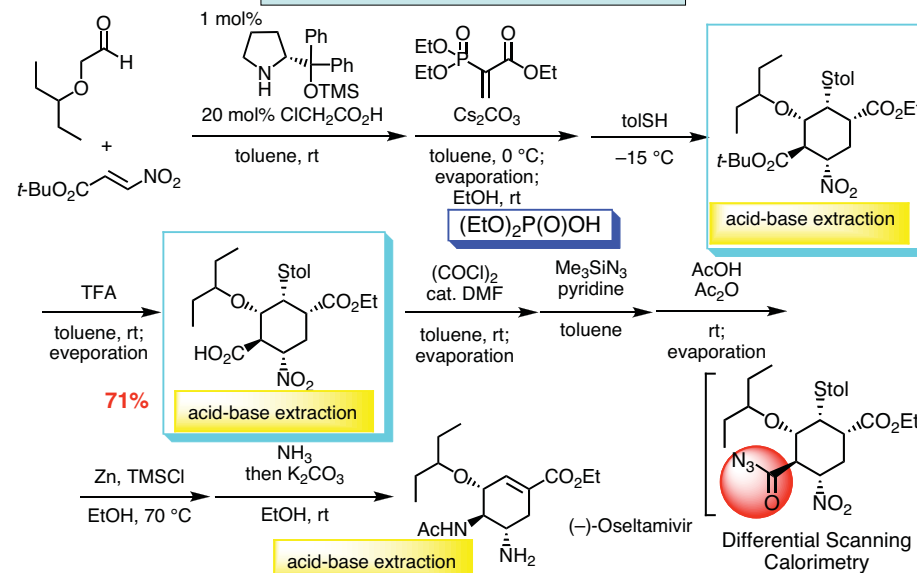


## 2 "one-pot" synthesis of (-)-oseltamivir



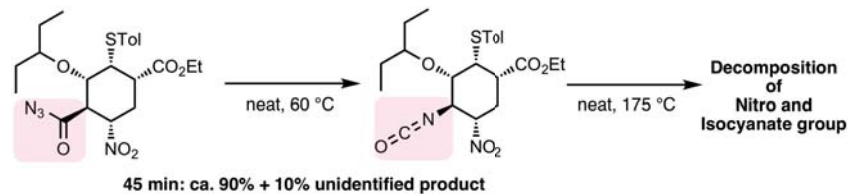
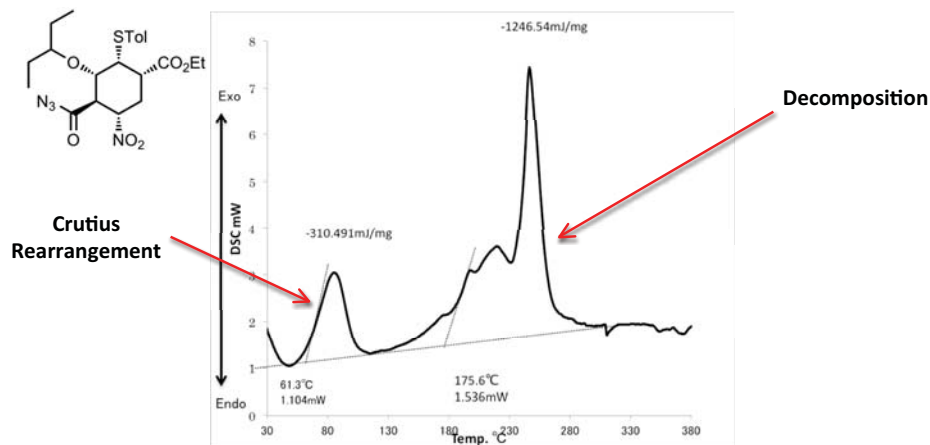
*Chem. Eur. J.*, **16**, 12616 (2010).

## Column free synthesis

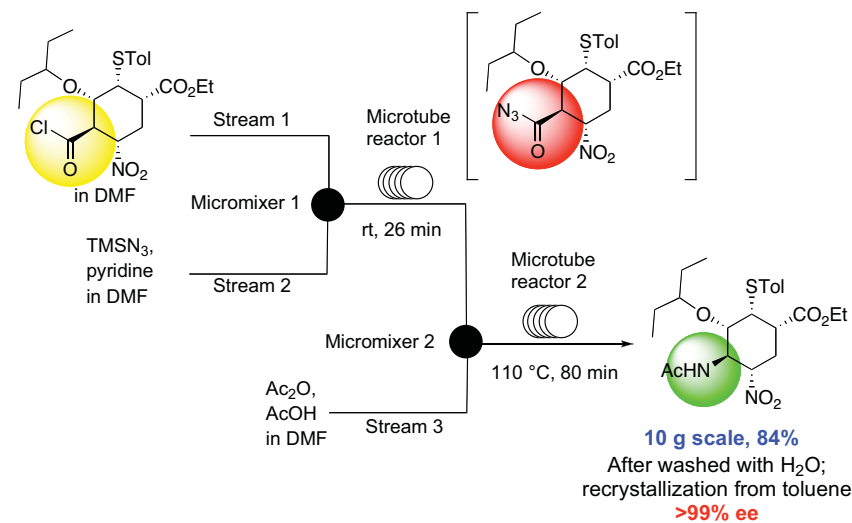


*Chem. Eur. J.*, **16**, 12616 (2010).

## Differential Scanning Calorimetry (DSC) Experiment



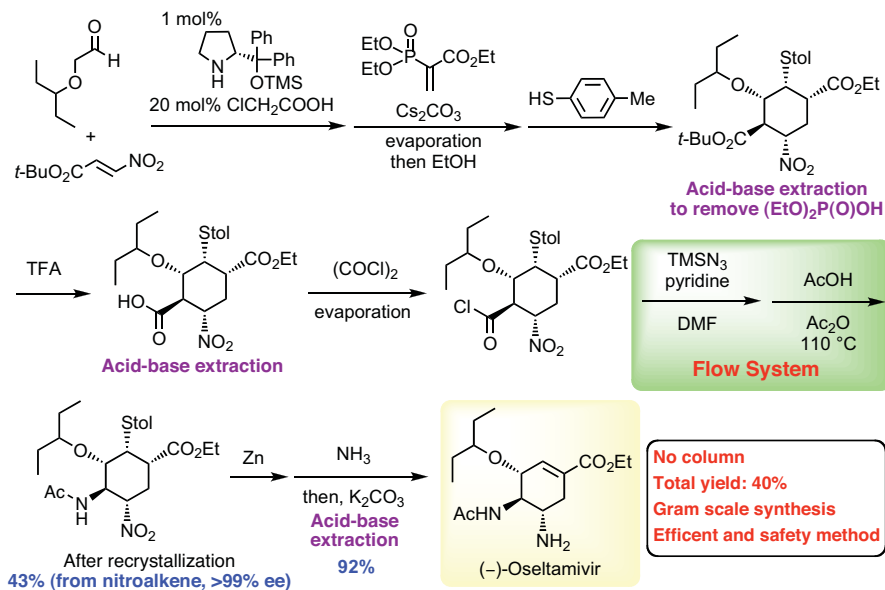
## Microreactor in the Curtius Rearrangement



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



### Practical synthesis of (-)-oseltamivir



### Green Reaction

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

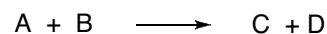
### Operational Economy

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

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

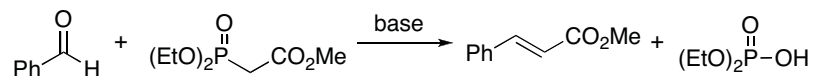
### One-Pot Reaction

- 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



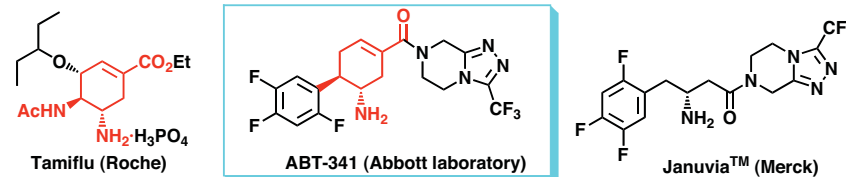
C is the desired product:

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

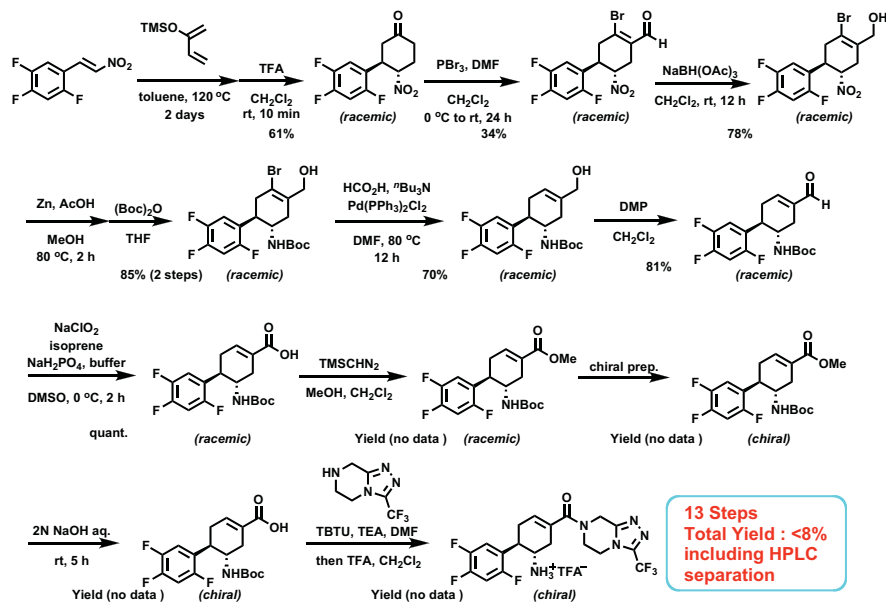


### Non-insulin dependant diabetes

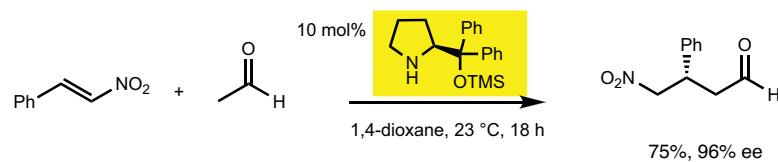
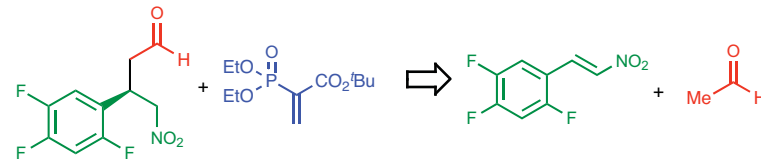
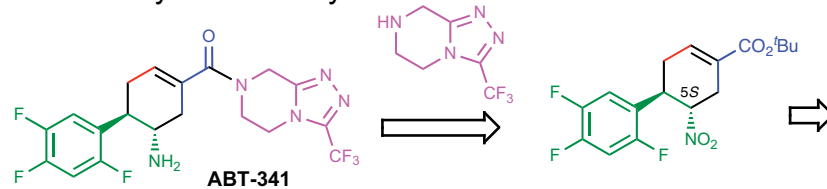
Dipeptidyl peptidase-4 (DPP-4) inhibitor



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

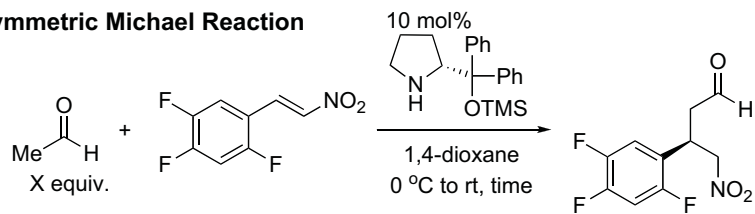


### Retro-synthetic analysis

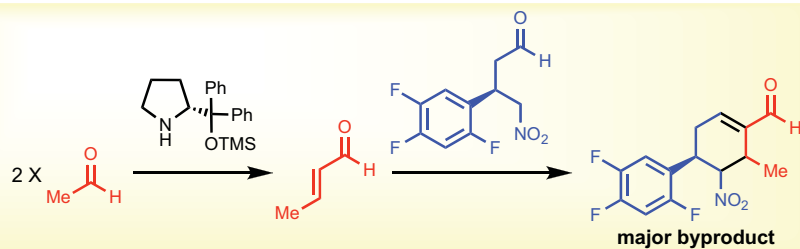


Y. Hayashi, *et al.*, *Angew. Chem. Int. Ed.*, **47**, 4722 (2008).

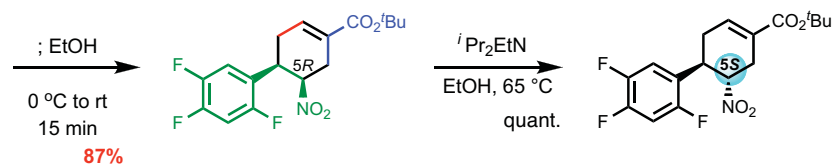
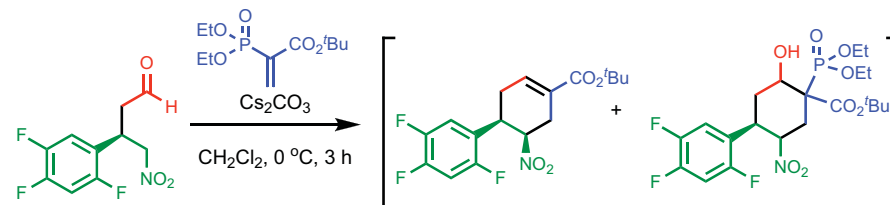
### Asymmetric Michael Reaction



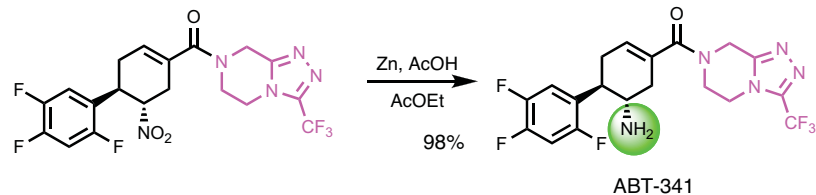
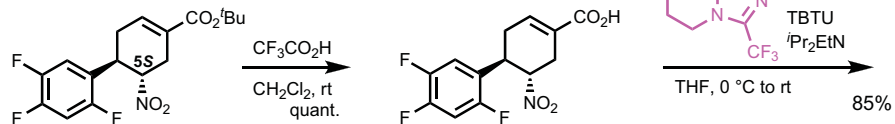
X / equiv.	time / h	yield / %	ee / %
10	24	74	94
<b>2</b>	<b>18</b>	<b>92</b>	<b>97</b>



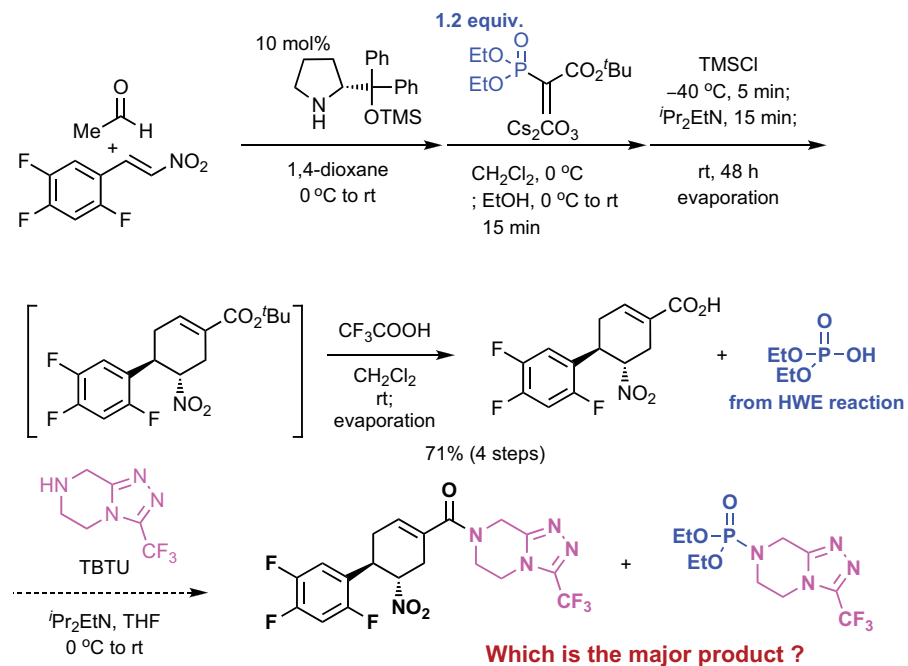
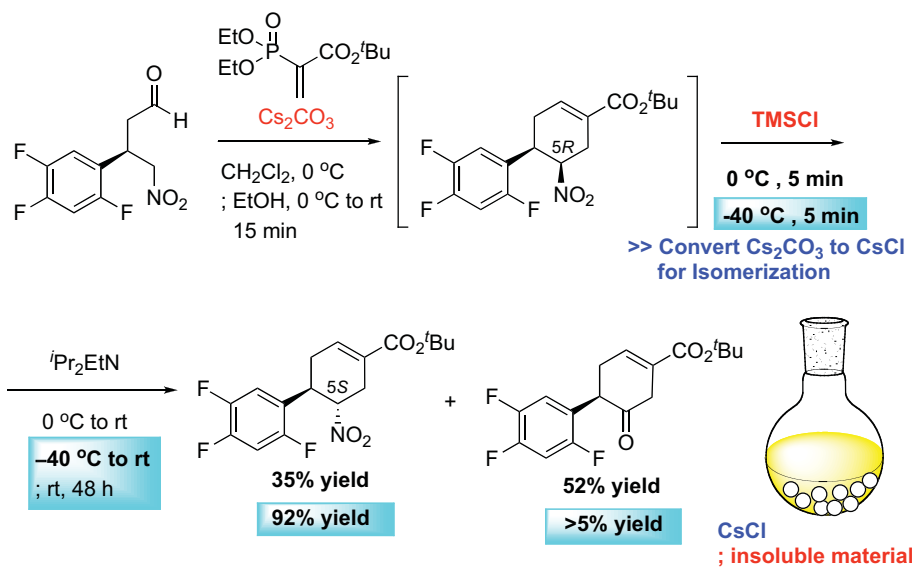
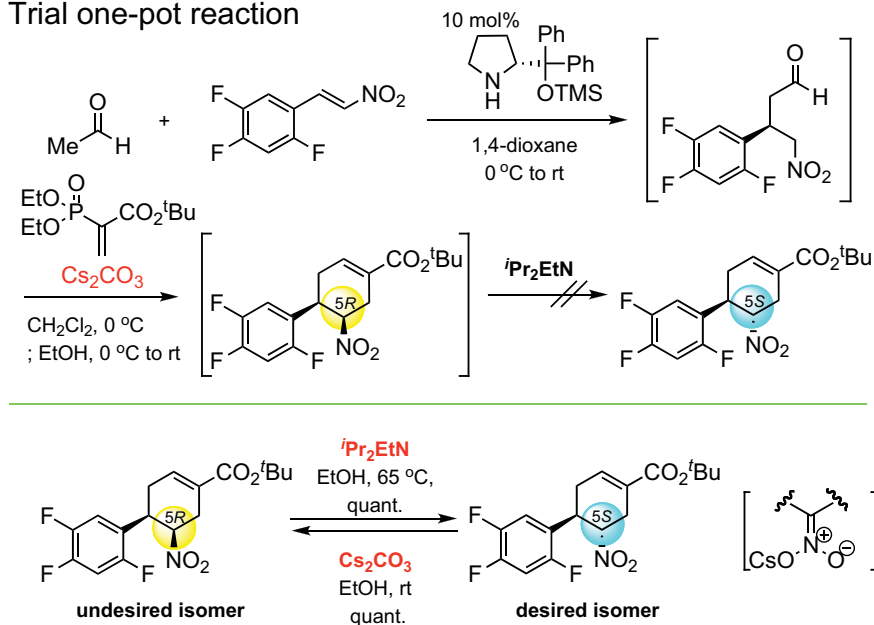
### Chiral cyclohexene formation

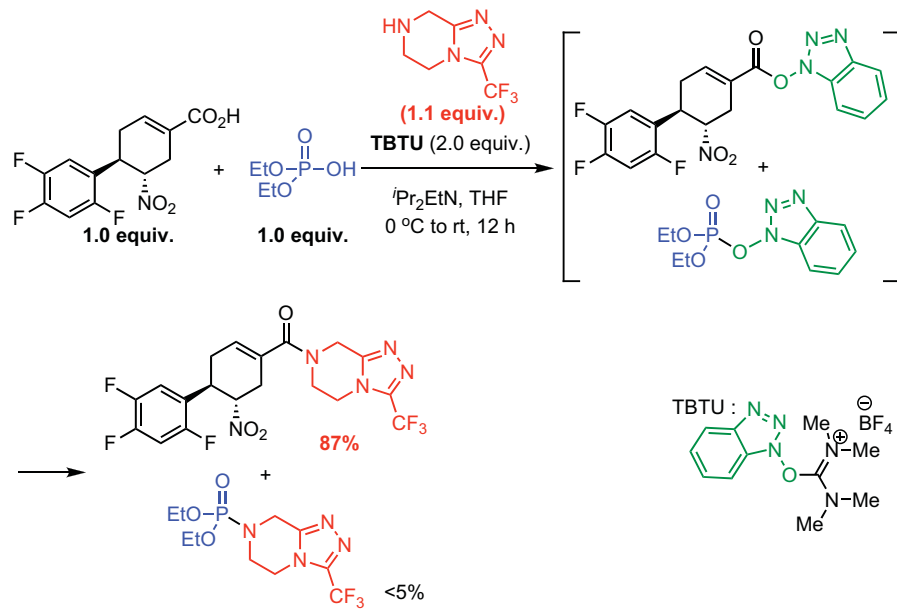


## Synthesis of ABT-341

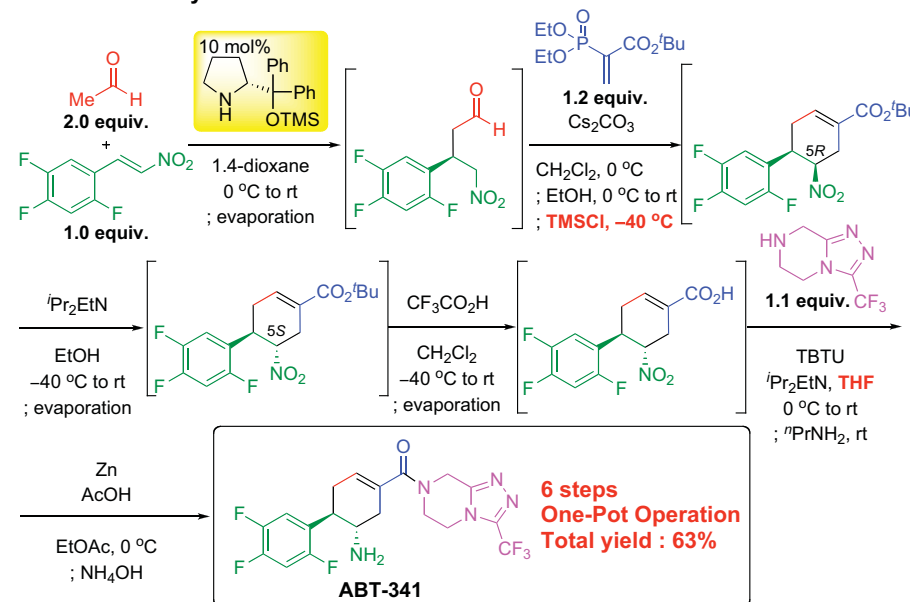


## Trial one-pot reaction





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



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