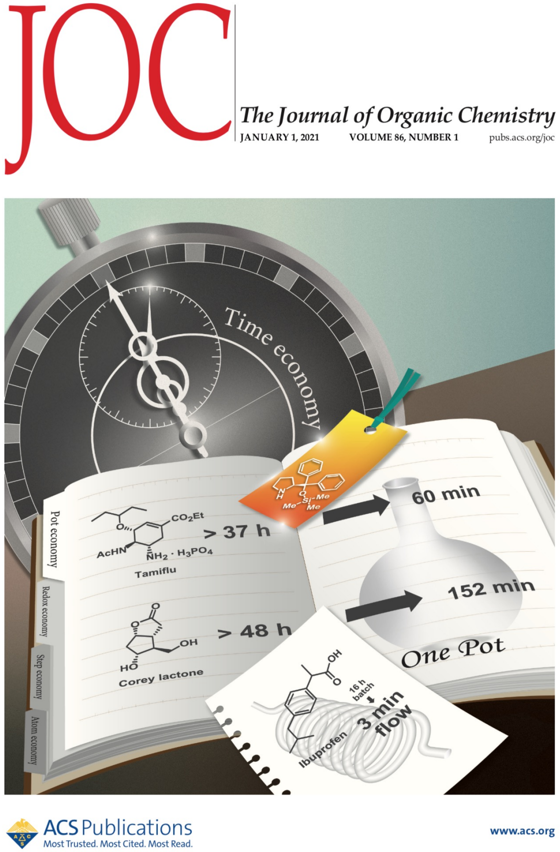
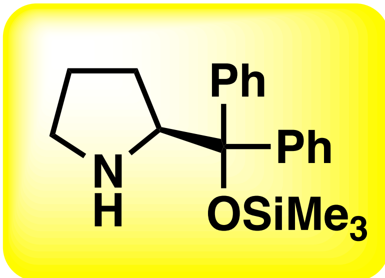
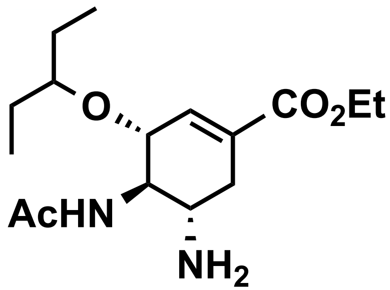
Time and Pot Economies in the Total Synthesis



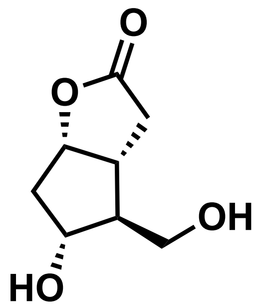
Tohoku University

Yujiro Hayashi

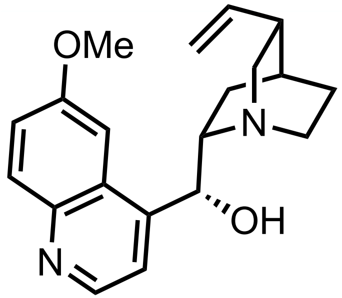




(–)-Oseltamivir



Corey lactone



(–)-quinine

Catalysis and Strategy

Target molecules : High valued, optically active molecules
Multi-step reactions are necessary.

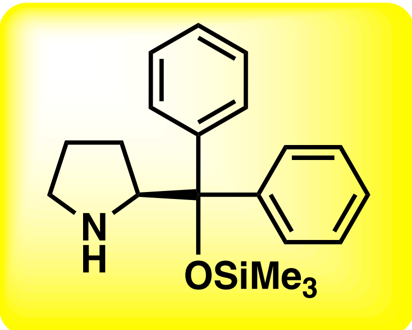
Reaction (Catalysis) and Strategy

Catalyst
Environmentally friendly reactions

Synthetic strategy
Environment-friendly
Efficient synthesis

Organocatalyst

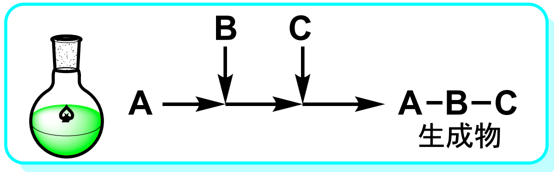
- Metal waste is not generated
- No metal residue in the product
- Stable in water, oxygen, etc.
- Safe and secure catalyst (low toxicity)
- Inexpensive

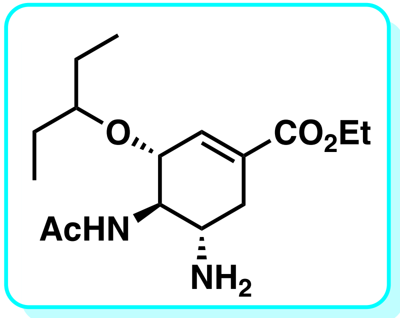


Hayashi-Jørgensen Catalyst

Pot Economy

One-pot reaction using organic catalysts





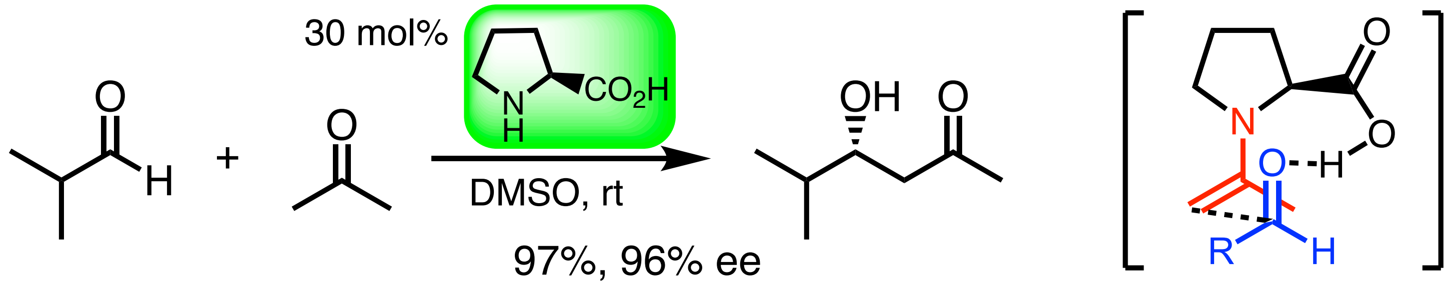
Tamiflu
One-pot synthesis

Asymmetric Catalysis

Metalcatalysis Nobel prize 2001

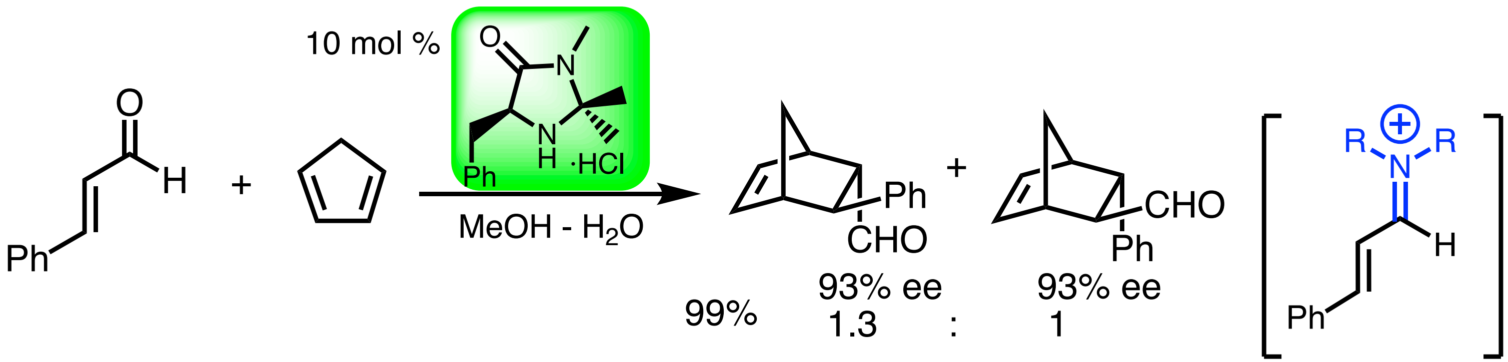
Organocatalysis Nobel prize 2021

Enamine as an intermediate : proline



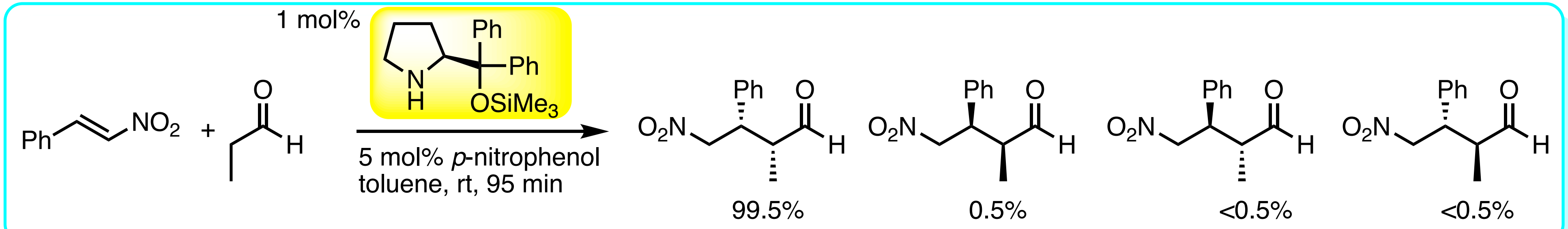
B. List, *et al.*, *J. Am. Chem. Soc.*, **2000**, *122*, 2395.

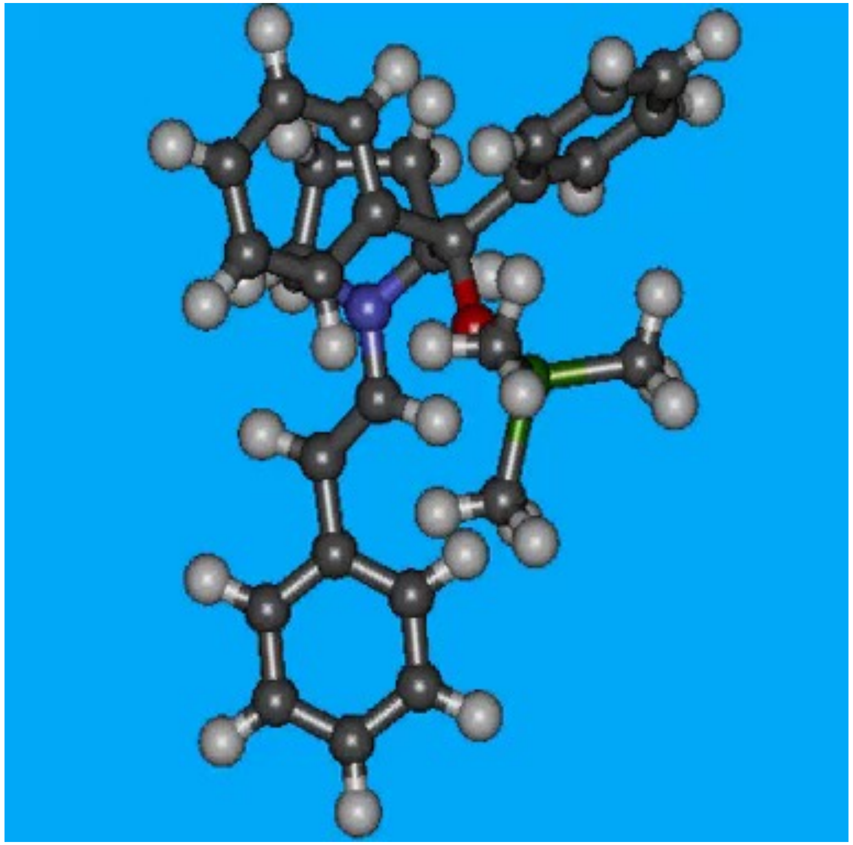
Iminium ion as an intermediate : MacMillan Catalyst



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

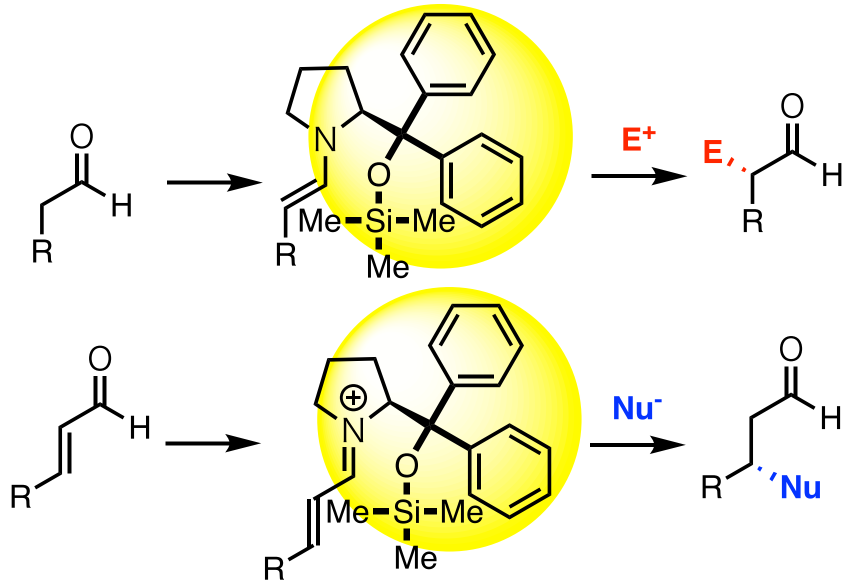
Hayashi—Jørgensen catalyst





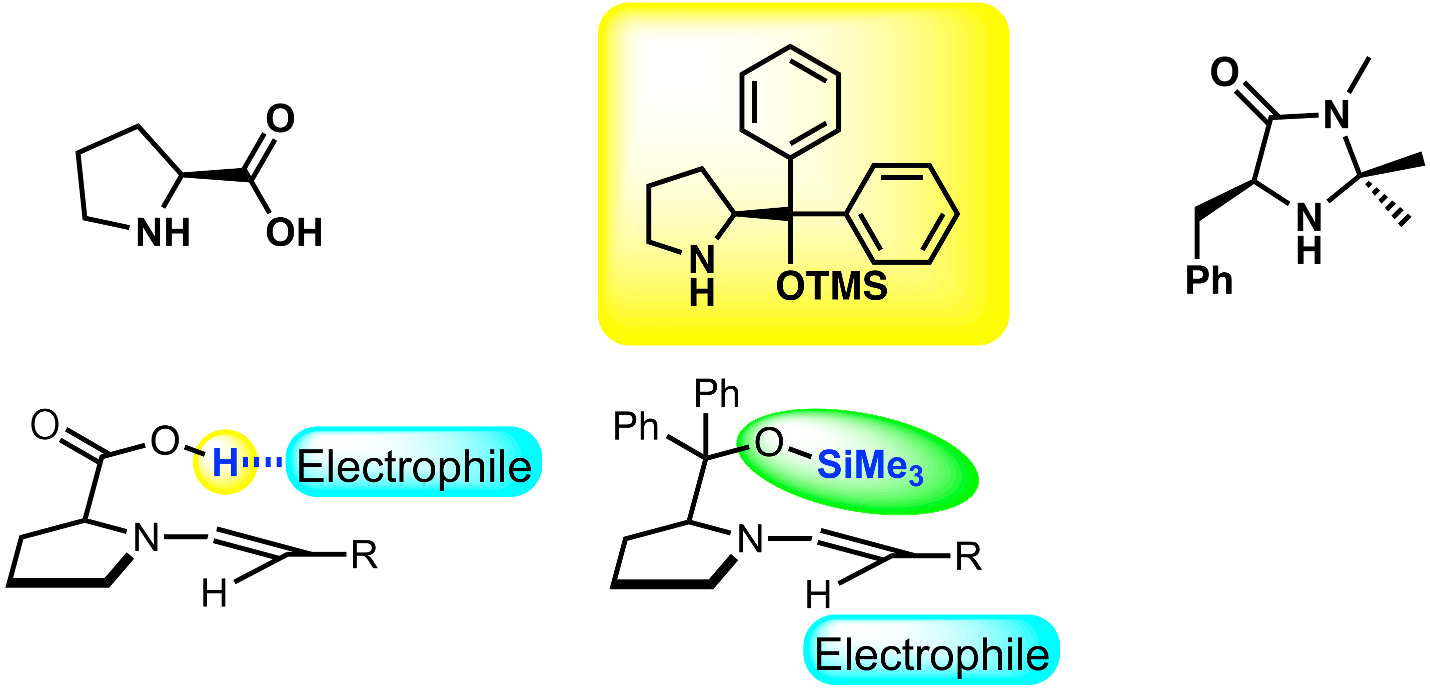
catalyst

- Easily synthesized from proline
- Both enantiomers are commercially available
- Inexpensive
- High asymmetric induction



Angew. Chem. Int. Ed. **2005**, *44*, 4112. *Chem. Eur. J.* **2014**, *20*, 17077.

Hayashi—Jørgensen catalyst



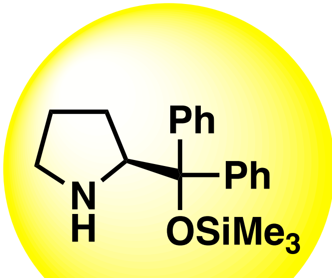
Effective both for enamine and iminium ion

Suitable nucleophilicity as enamine
Suitable electrophilicity as iminium ion

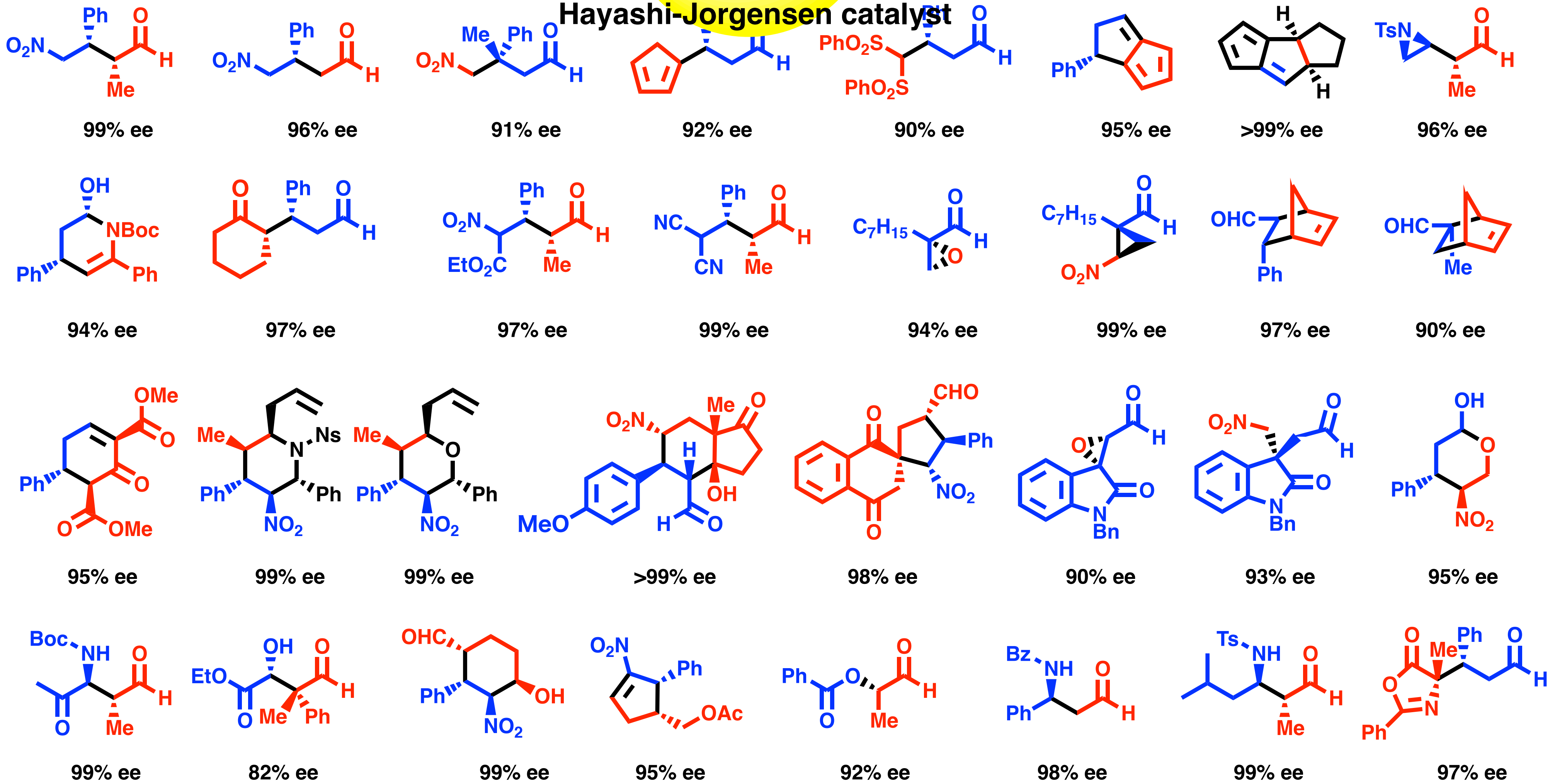
Suitable catalyst for one-pot reaction
Bulky secondary amine and weak base, which does not affect the other reactions

Hayashi—Jørgensen catalyst

- wide generality
- excellent enantioselectivity
- inexpensive



Hayashi-Jorgensen catalyst

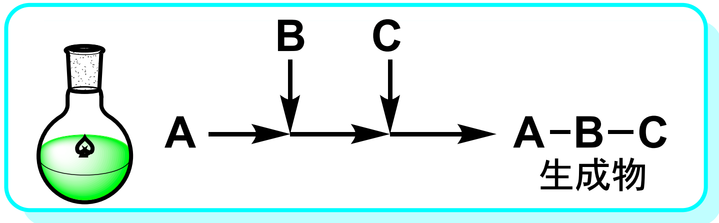


Efficient synthesis

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

Pot reaction

To conduct reactions in a single vessel.
To avoid the time-consuming operations.



Limitations of the pot reaction

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

Tedious operations

- quench
- separation of organic phase
- drying the organic phase
- filtration
- evaporation
- purification

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Pot economy and one-pot synthesis

Yujiro Hayashi

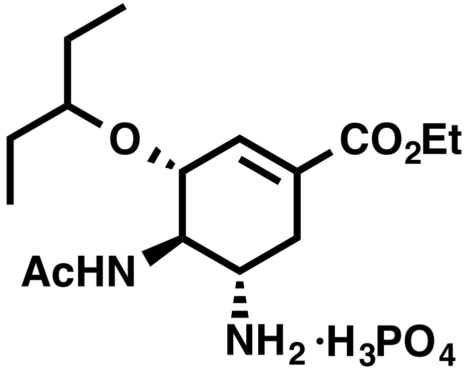
The one-pot synthesis of a target molecule in the same reaction vessel is widely considered to be an efficient approach in synthetic organic chemistry. In this review, the characteristics and limitations of various one-pot syntheses of biologically active molecules are explained, primarily involving organocatalytic methods as key tactics. Besides catalysis, the pot-economy concepts presented herein are also applicable to organometallic and organic reaction methods in general.

1. Introduction

Efficiency and environmental sustainability are central issues in contemporary organic chemistry. Both need to be addressed carefully when making a valuable target molecule over several distinct steps. When feasible, an effective approach is to synthesize the target in a single reaction vessel. This approach is often termed 'one-pot', and can apply to a multi-step reaction, method, or synthesis. It is effective because several synthetic transformations and bond-forming steps can be carried out in a single pot, while circumventing several purification procedures at the same time. A one-pot procedure can thus minimize chemical waste, save time, and simplify practical aspects. In fact, this approach has been used widely in synthetic organic chemistry for a long time. For instance, Robinson's one-pot synthesis of tropinone is a landmark achievement in organic chemistry, which was reported nearly 100 years ago (eqn (1)).[1]

Chem. Sci. **2016**, *7*, 866.

Tamiflu



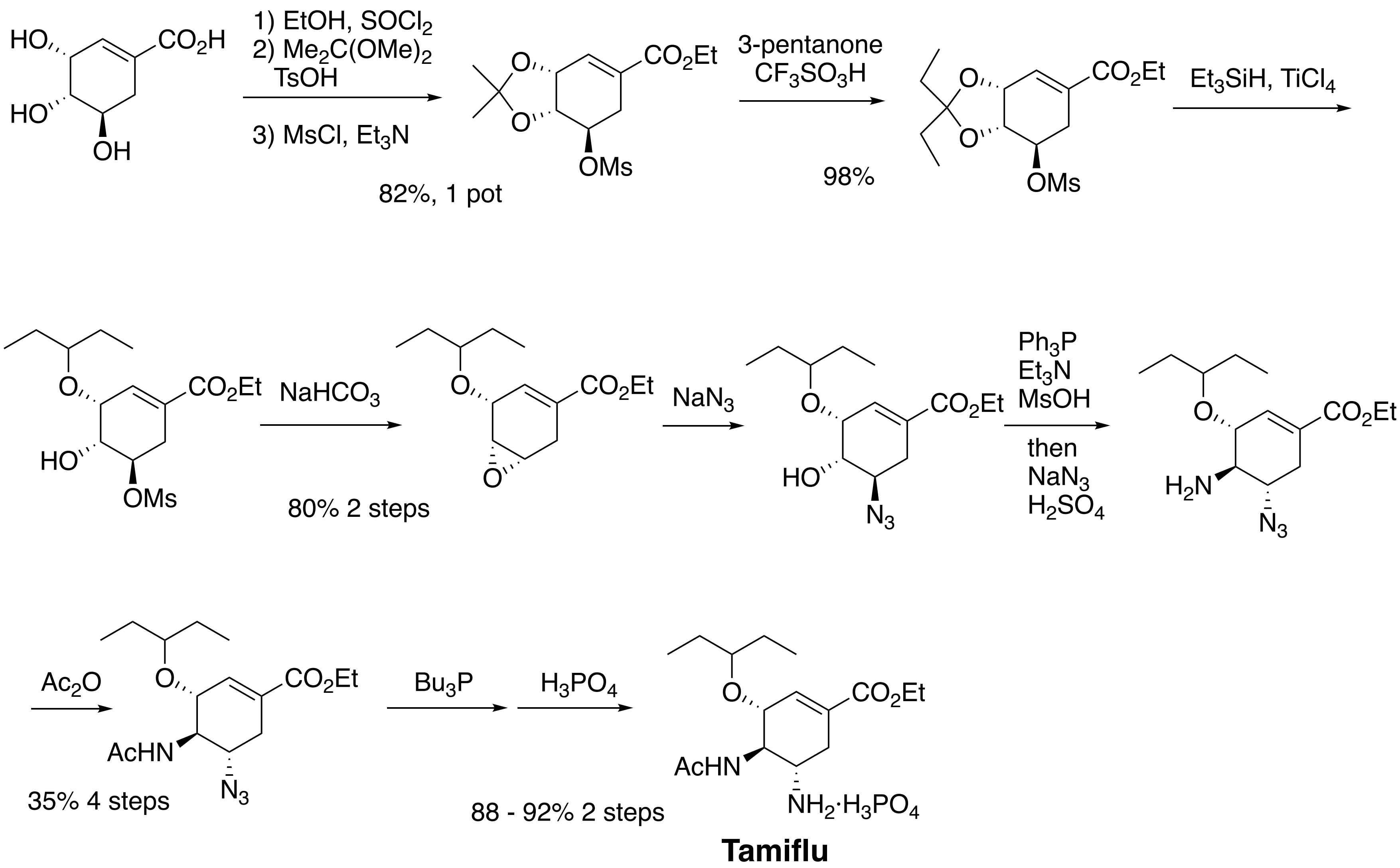
(–)-oseltamivir phosphate (Tamiflu)

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

Total Synthesis: Corey (2006), Shibasaki/Kanai (2006), Yao (2006), Wong (2007)
Fukuyama (2007), Fang (2007), Kann (2007), Trost (2008)
Banwell (2008), Mandai (2009), Ma (2010) *et al.*,
62 total syntheses

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

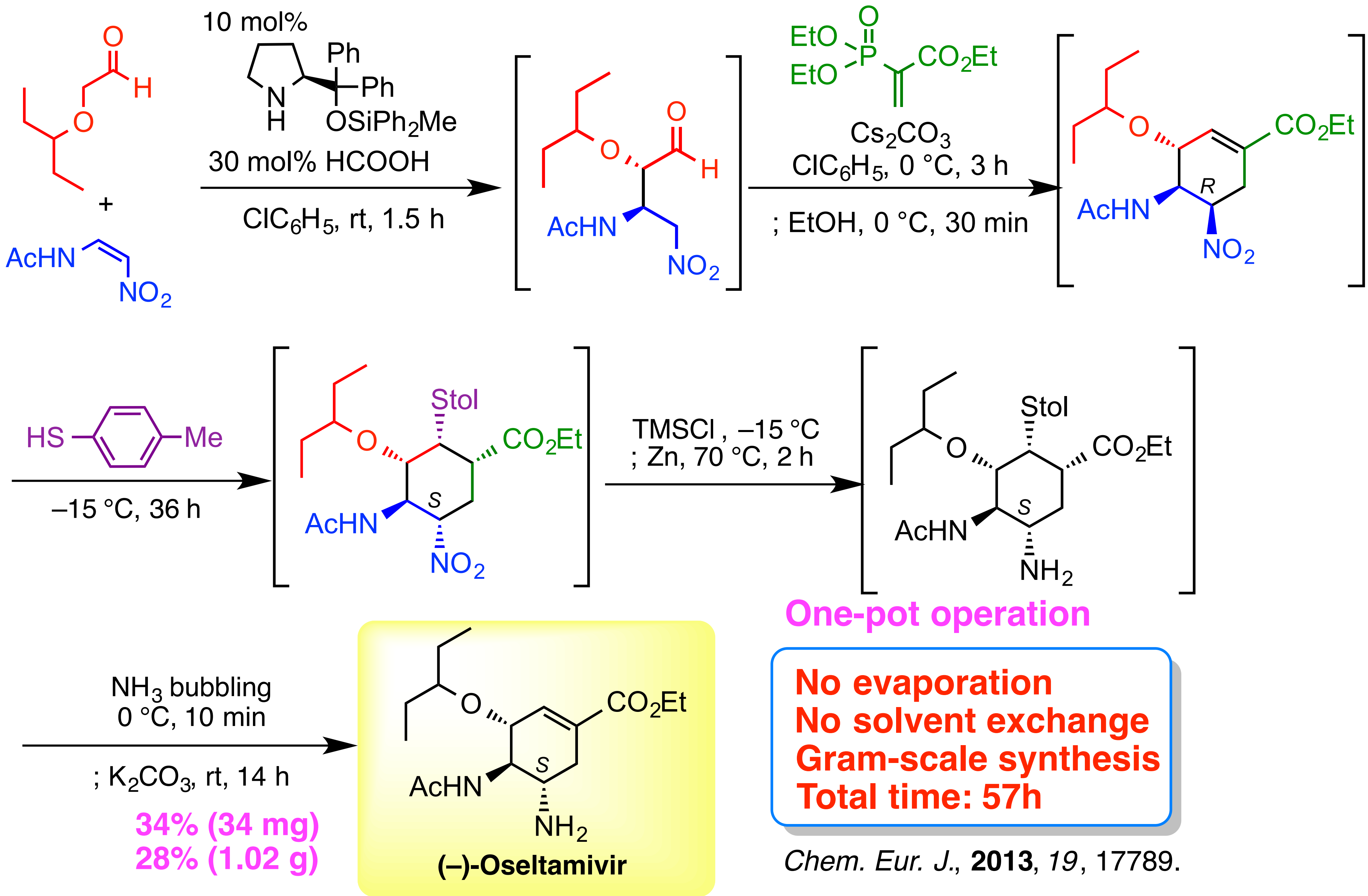
The synthesis of Tamiflu by Roche



Total reaction time: 43.5 h, total yield: 18%, total pots: 8

S. Albrecht, *et al.*, *Chimia*, **2007**, *61*, 93.

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



One-pot operation

No evaporation
No solvent exchange
Gram-scale synthesis
Total time: 57h

Chem. Eur. J., **2013**, *19*, 17789.

Multistep continuous - flow synthesis

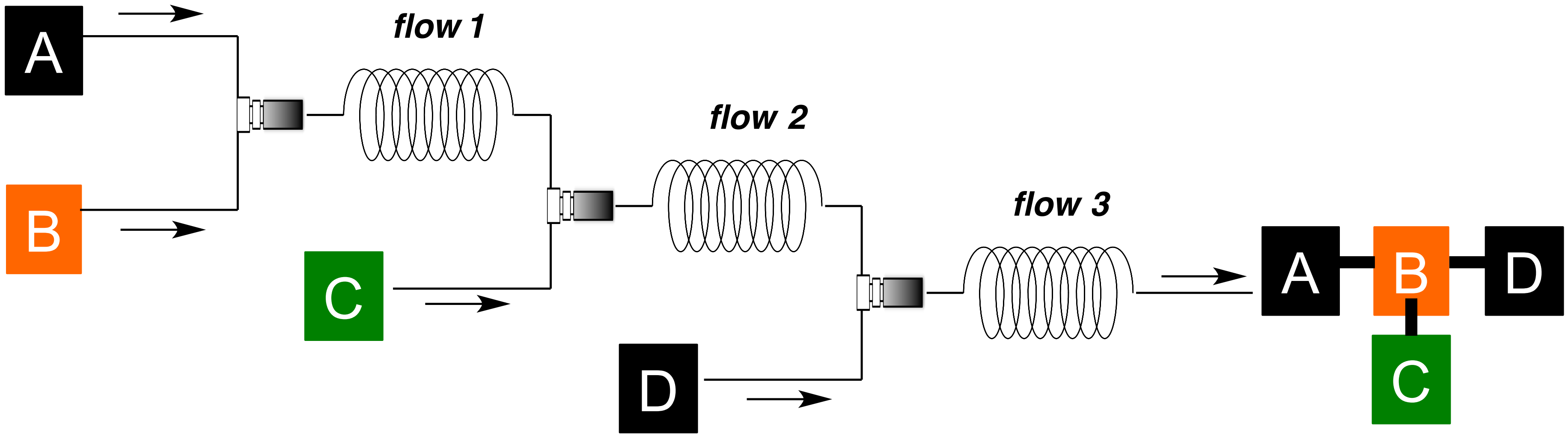
One-pot reaction

No evaporation
No solvent exchange

⇒

Flow synthesis

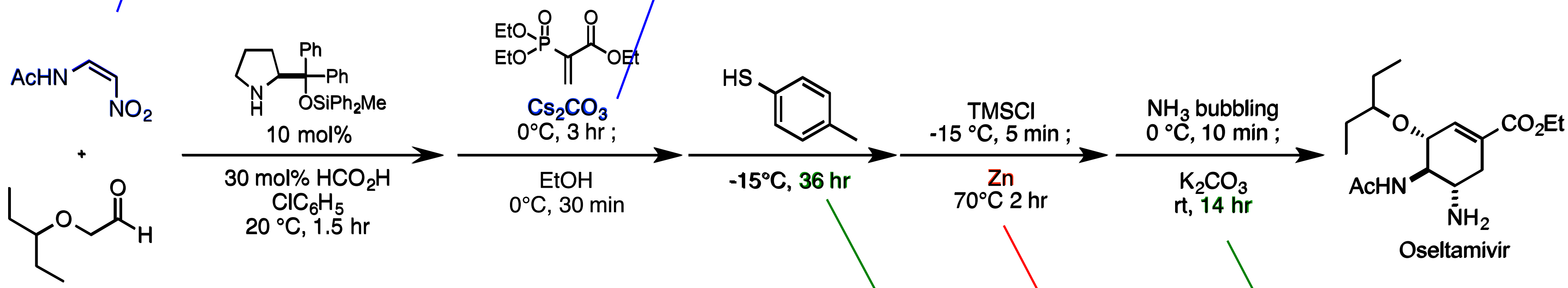
Efficiency
High reproducibility



Problems

Problem 1 : Nitroalkene was scarcely soluble in C_6H_5Cl.

Problem 2 : Cs_2CO_3 was difficult to dissolve in EtOH.

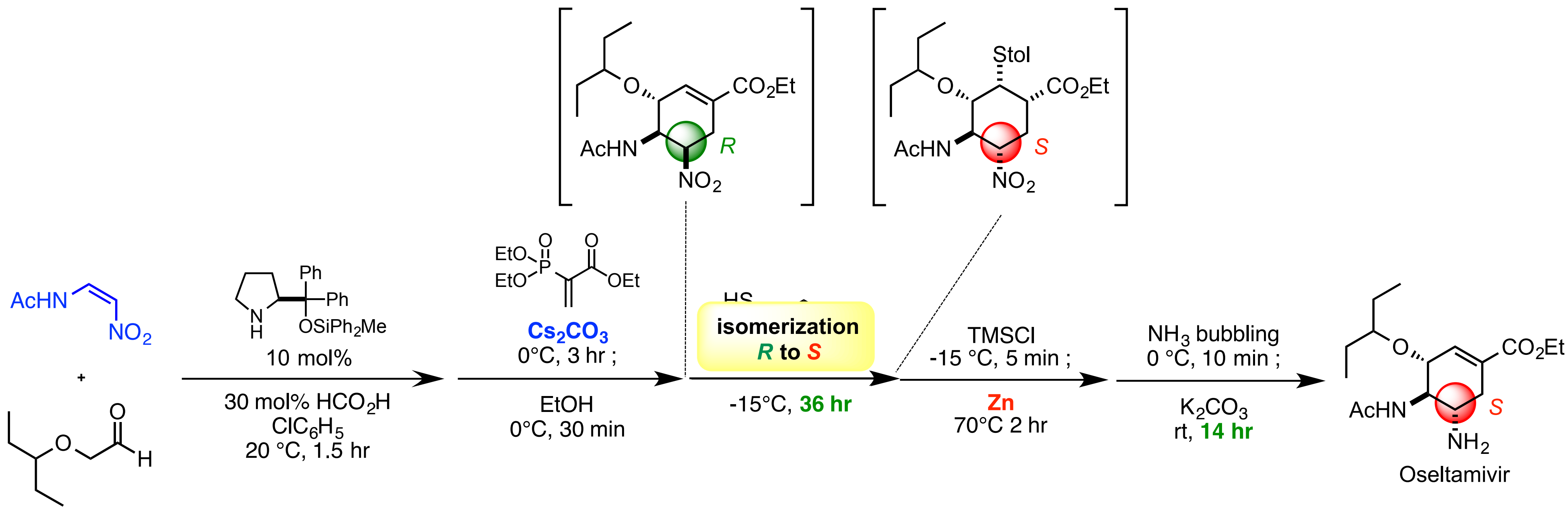


Problem 3 : Reaction time was too long.

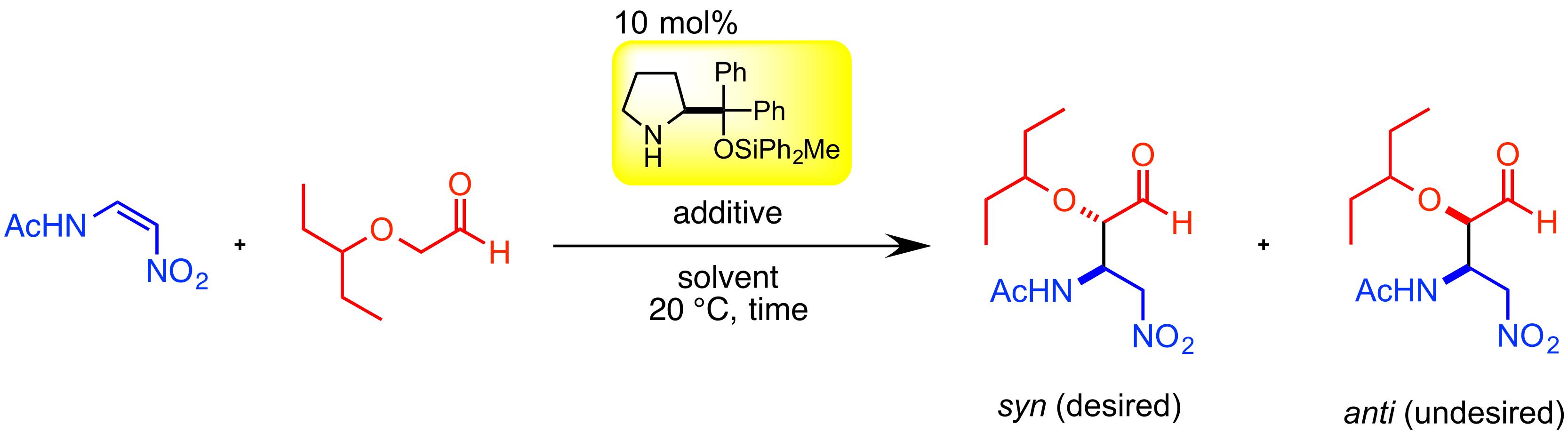
Problem 4 : How was Zn added in flow system?

Problem 5 : Reaction time was too long.

One-pot synthesis of (-)-oseltamivir



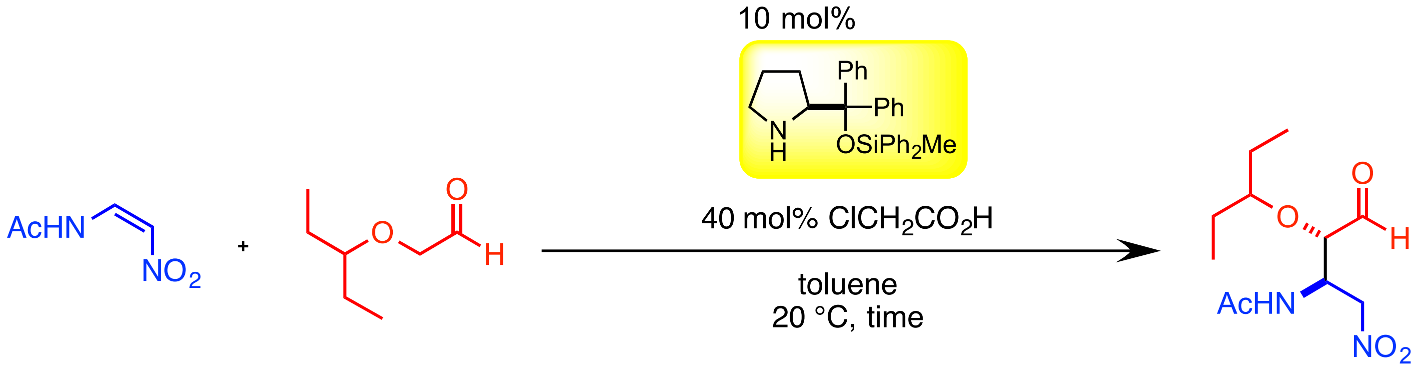
Asymmetric Michael reaction



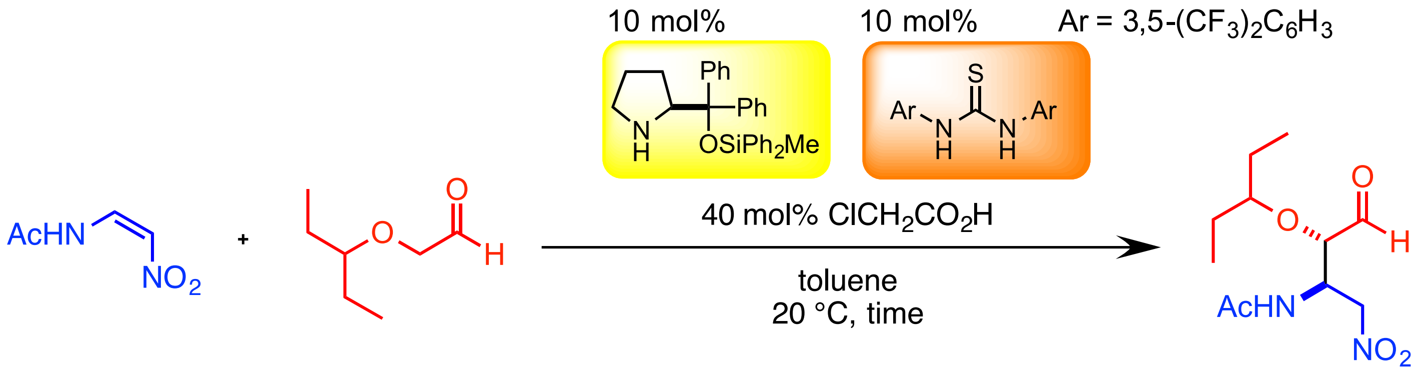
solvent	additive	time / h	conv. / %	*syn* / *anti*	*ee* / %
C_6H_5Cl (0.3 M) *	HCO_2H	1.5	80	7.1 : 1	99
C_6H_5Me (0.04 M)	$ClCH_2CO_2H$	6	39	>20 : 1	–
dioxane (0.3 M)	$PhCO_2H$	2	66	4.6 : 1	–
C_6H_5Me / dioxane (0.07 M)	$ClCH_2CO_2H$	1.5	52	5.9 : 1	–
C_6H_5Me (0.04 M)	**$ClCH_2CO_2H$ thiourea deriv.**	**1**	**91**	**10 : 1**	**97**

* This condition can not dissolve nitroalkene.

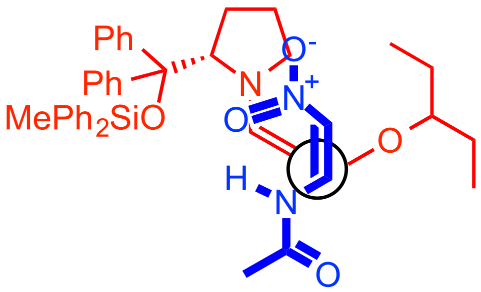
Michael reaction with or without thiourea derivative



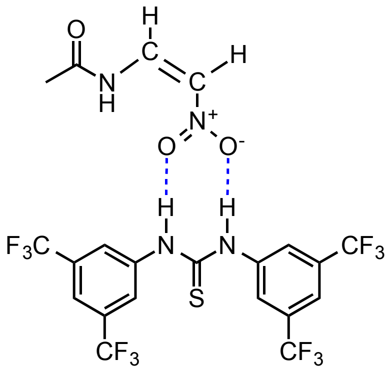
6 h
conv. 39%
dr = >20 : 1



1 h
conv. 91%
***dr* = 10 : 1 , 97%ee**

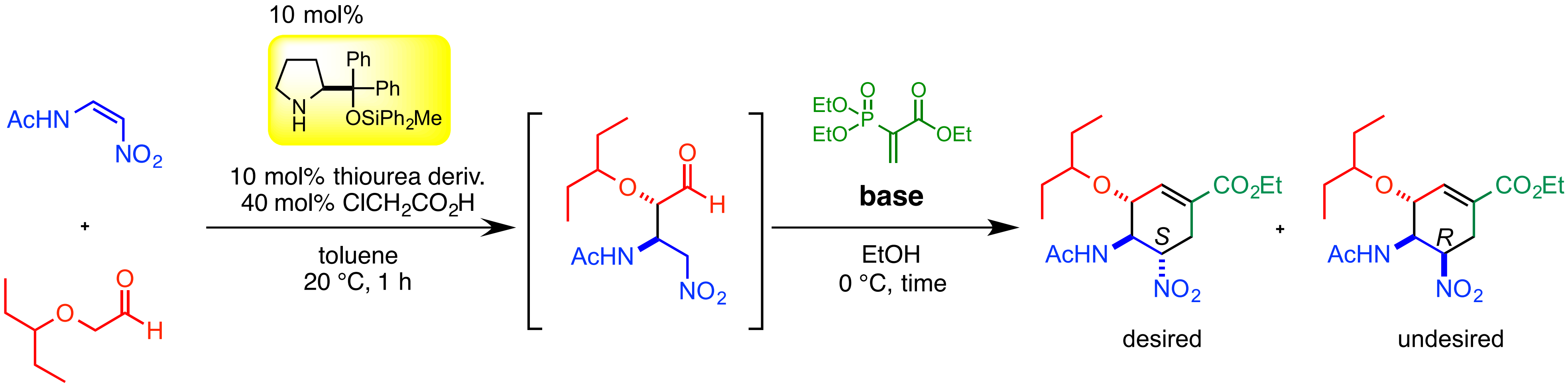


(*Z*)-enamine



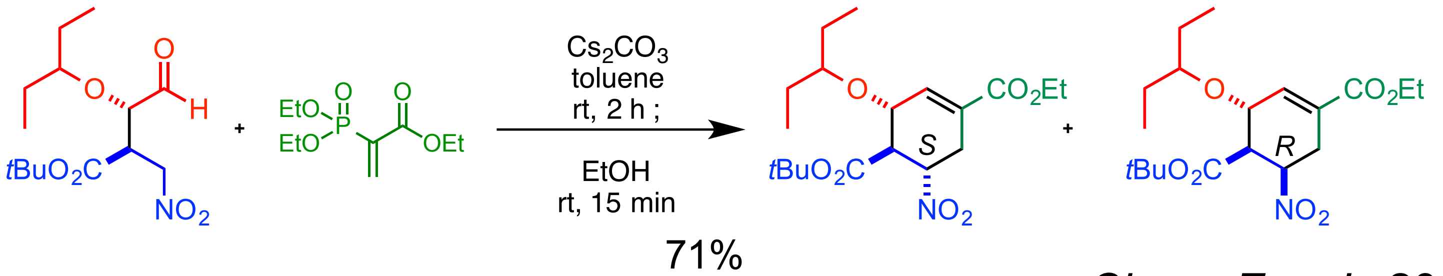
P. R. Schreiner *et al.*, *Org. Lett.*, **2002**, *4*, 217.

Screening of the soluble base instead of Cs_2CO_3



base	time / h	yield / % *	*S* / *R*
DBU	3	<10	–
TBAF	3	25	1 : 1.5
Triton B	3	47	1 : 8.0
***t*-BuOK**	**0.5**	**63**	**1 : 6.3**

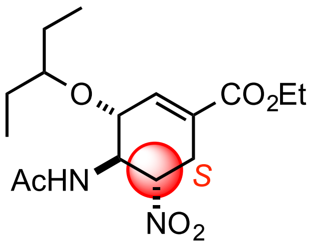
* from nitroalkene



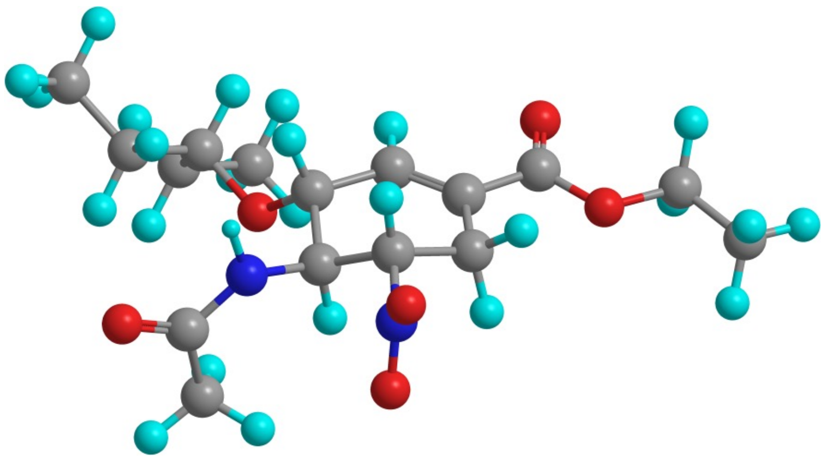
S / *R* = 1 : 4.6

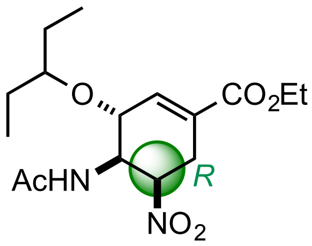
Chem. Eur. J., **2010**, *16*, 12616.

Stability of *R* and *S* isomers

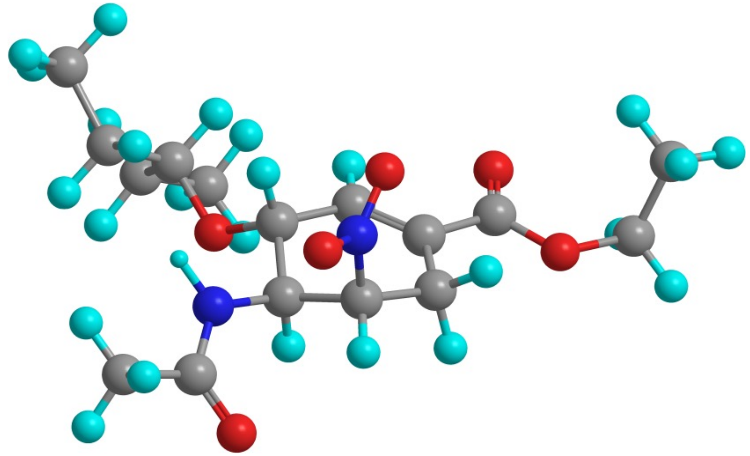


desired





undesired

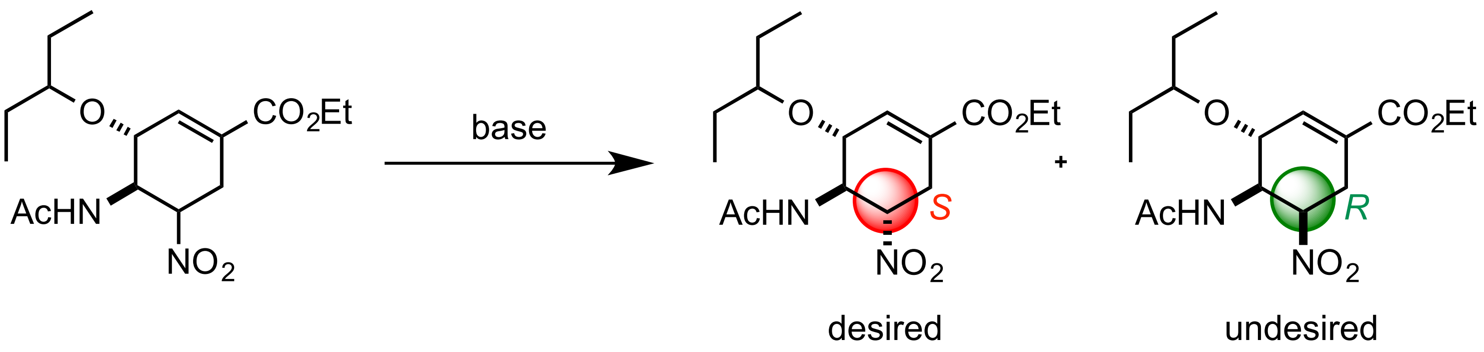


Substrate	Difference of energy / kcal/mol
5*S*	**0.46**
5*R*	0.00

calculated by M062X / 6-31+G (d,p)

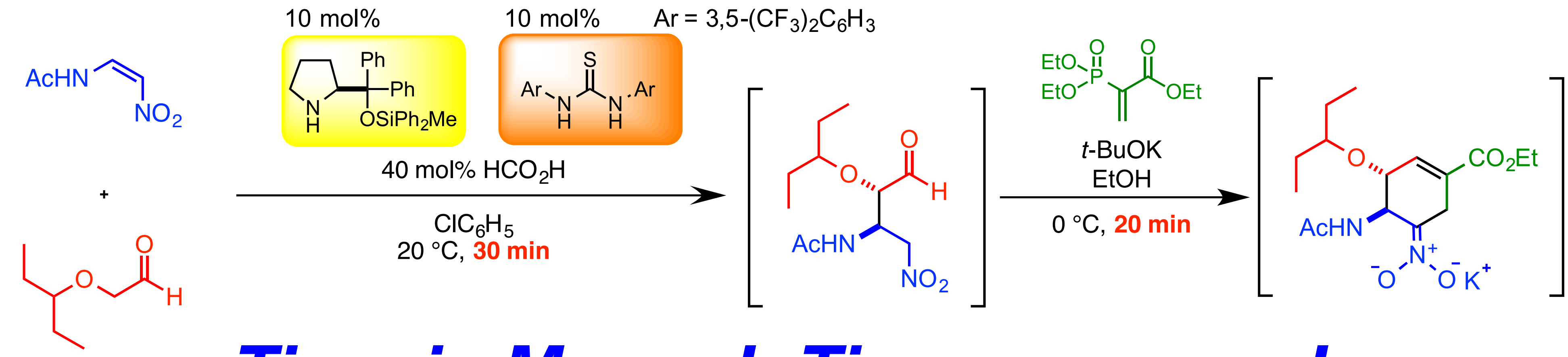
Dr. T. Uchimaru

Optimization of isomerization

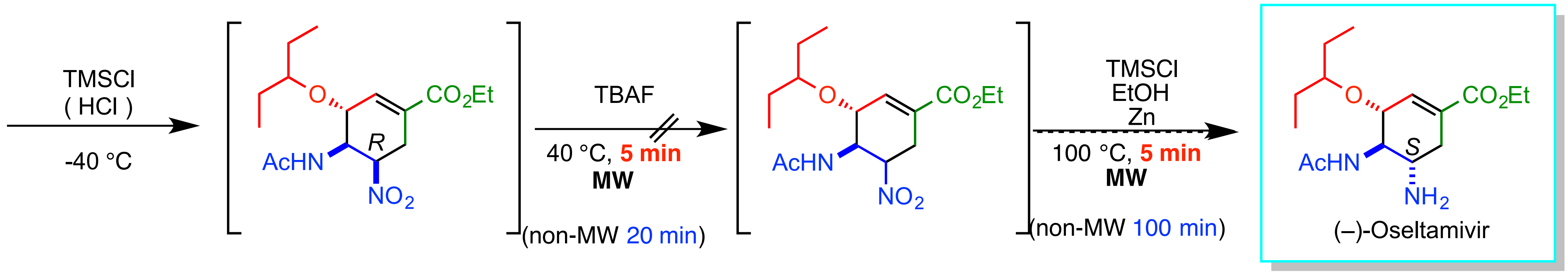


base	solvent	temp. / ℃	time / h	*S* / *R*
DABCO	C_6D_6	rt to 60	8	1 : 2.7
Bu_3P	$CDCl_3$	rt to 60	5	1 : 2.6
Et_3N	CD_3OD	60	1	1 : 1.5
i-Pr_2EtN	CD_3OD	60	1	1 : 1.5
_n_-Bu_4NF	**CD_3OD**	**0**	**1**	**1 : 1.0**

Rapid synthesis of (–)-Oseltamivir



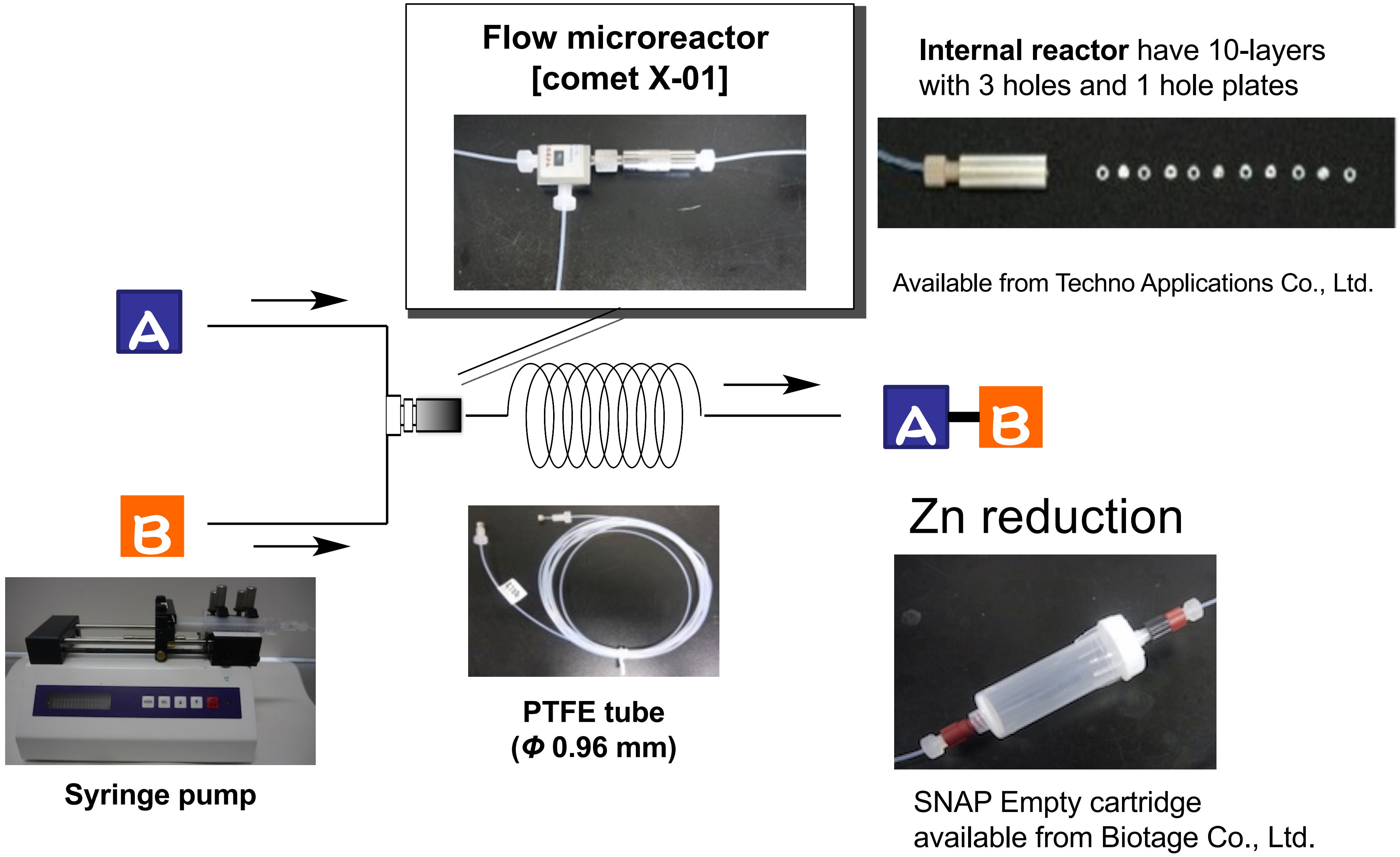
Time is Money! Time economy!



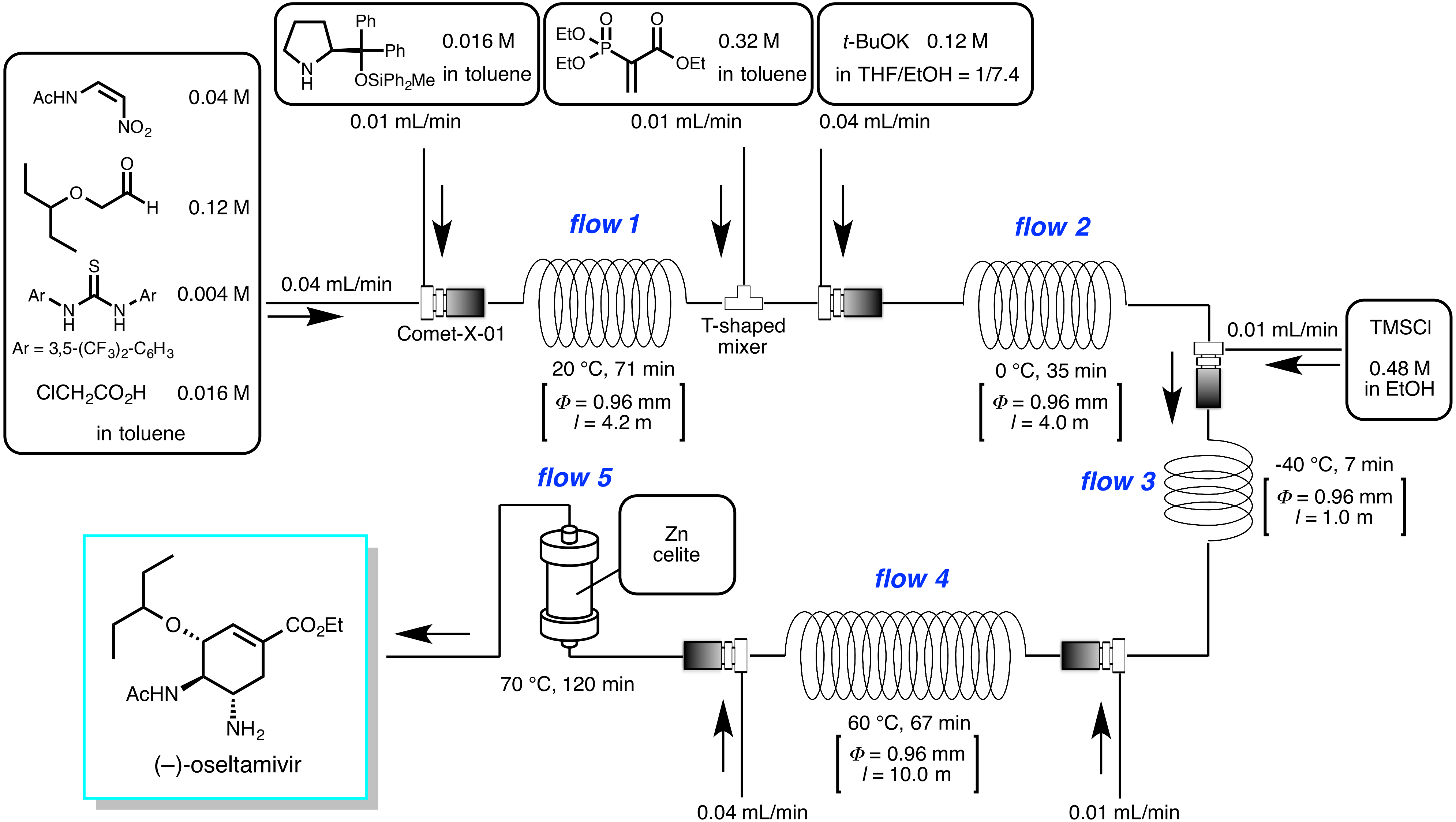
	MW	non-MW
Total yield :	15% (46 mg)	14% (1.12 g)
Total reaction time :	60 min	170 min

Org. Lett., **2016**, *18*, 3426.

Flow synthesis device



Multistep flow synthesis



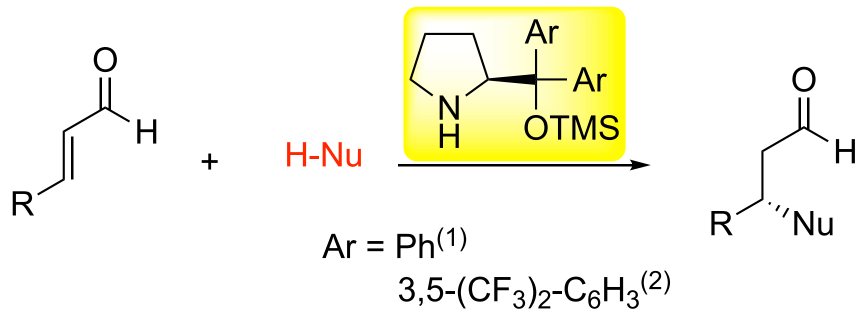
Total residence time: 310 min

Total yield 13%

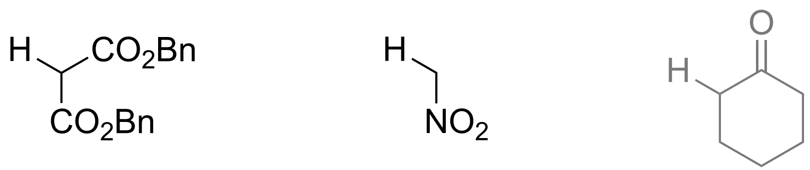
Synthesis, **2017**, *49*, 424

Michael reaction of α,β-unsaturated aldehyde and ketone catalyzed by diphenylprolinol silyl ether

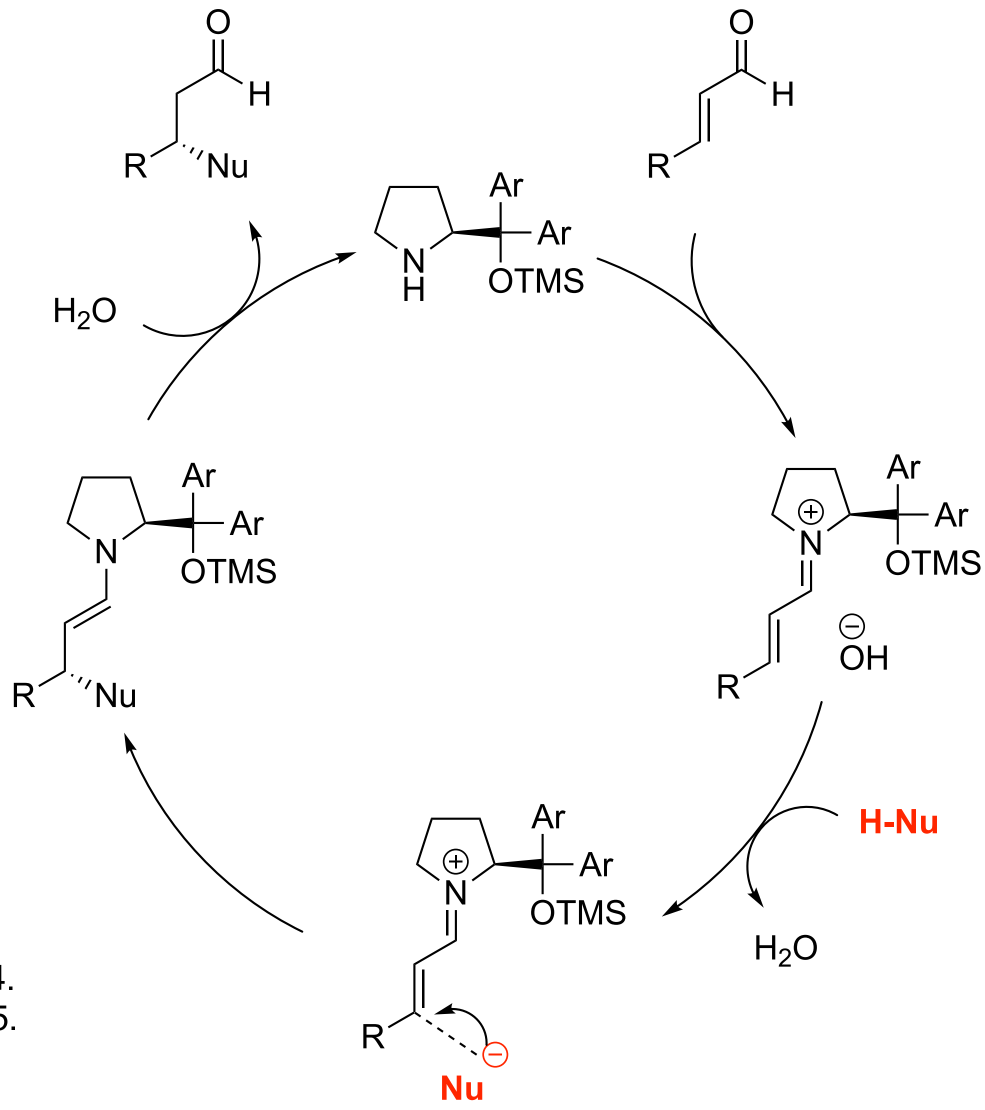
Michael donor is limited to active methylene compounds.



H-Nu =



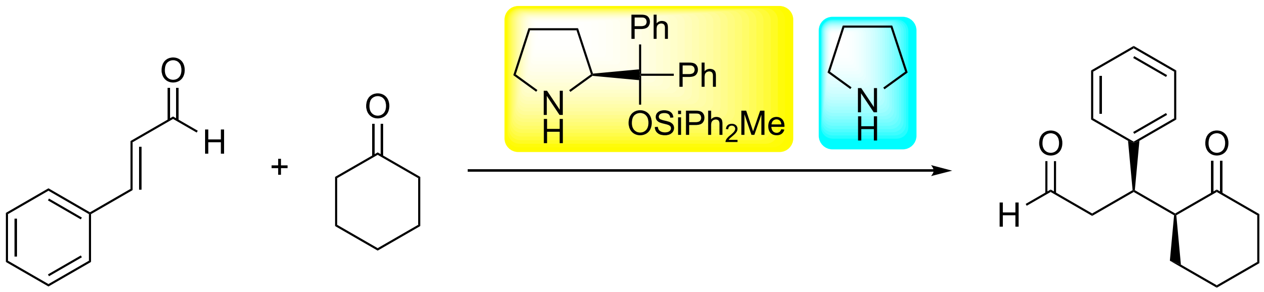
Dibenzyl malonate[3]	Nitromethane[4]	Cyclohexanone
pKa ca.15.7	**pKa 17.2**	**pKa 26.4**
(in DMSO)	(in DMSO)	(in DMSO)

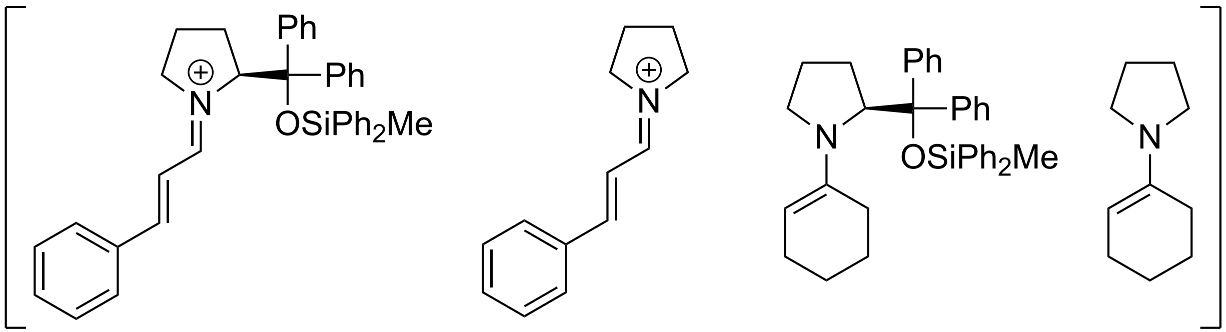


(1) Y. Hayashi, *et al.*, *Angew. Chem. Int. Ed.* **2005**, *117*, 4284.
(2) K. A. Jørgensen, *et al.*, *Angew. Chem. Int. Ed.* **2005**, *117*, 804.
(3) K. A. Jørgensen, *et al.*, *Angew. Chem. Int. Ed.* **2006**, *45*, 4305.
(4) Y. Hayashi,*et al.*, *Org. Lett.* **2007,** *9*, 5307.

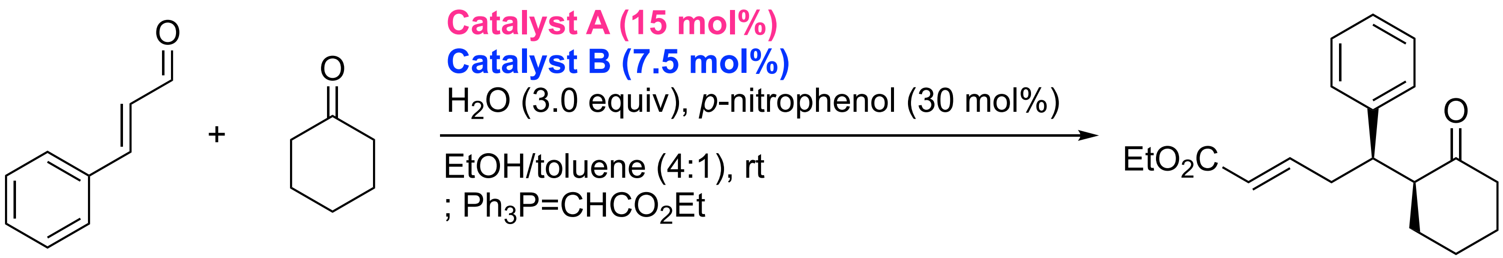
Design of asymmetric Michael reaction using hybrid catalyst system

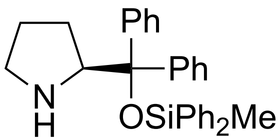
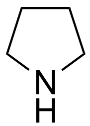
An idea of a student



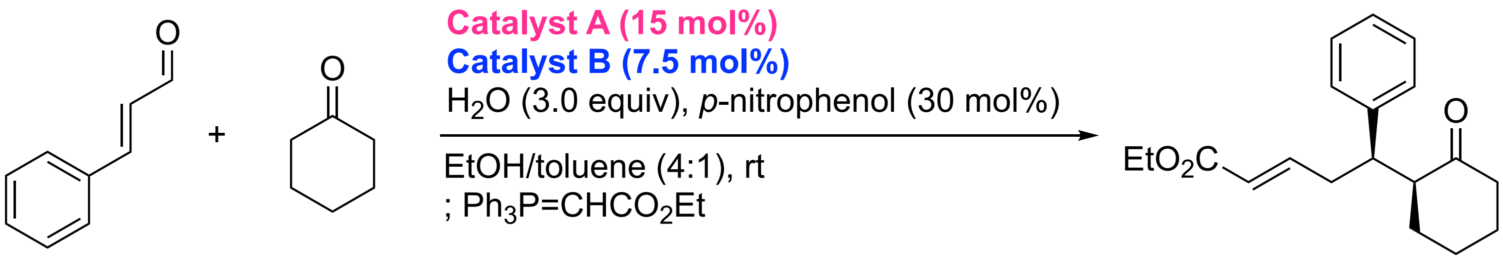


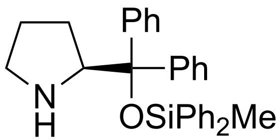
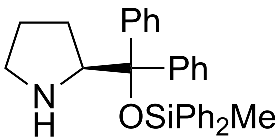
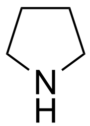
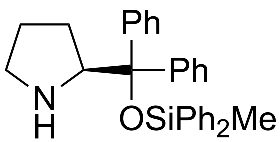
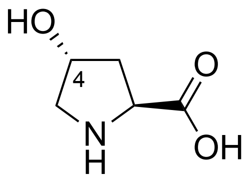
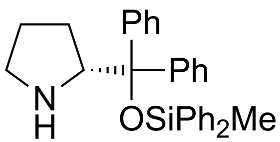
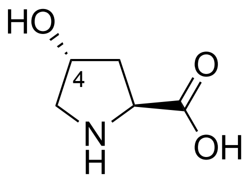
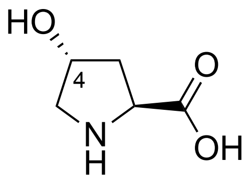
Asymmetric Michael reaction using hybrid catalyst system



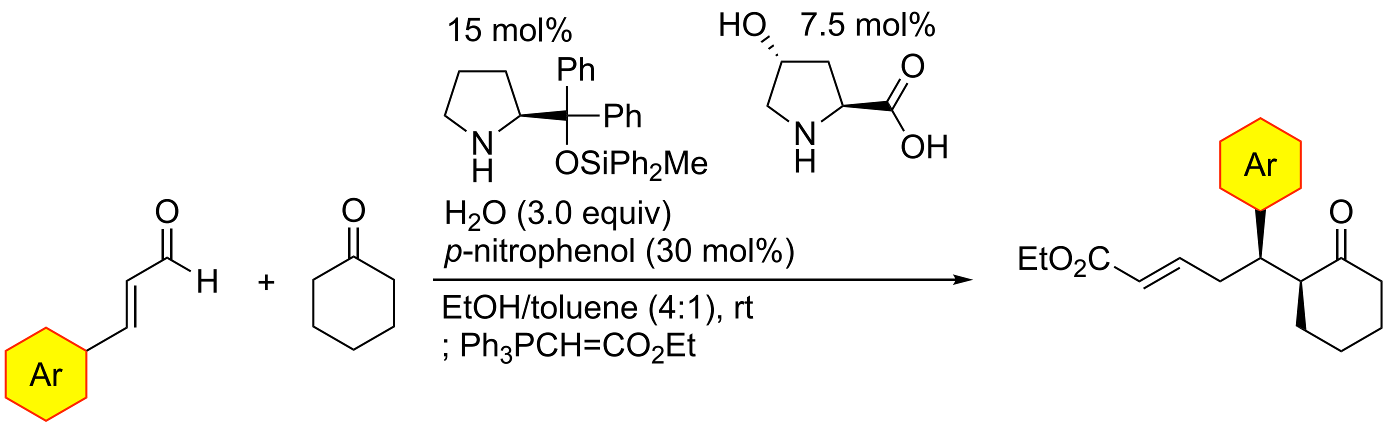
Catalyst A	Catalyst B	*t* [h]	yield [%]	*syn:anti*	*ee* [%]
		24	74	5:1	91

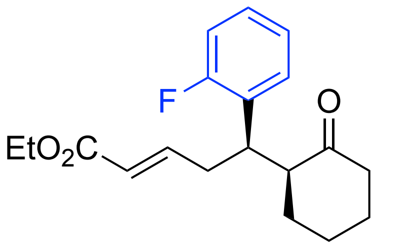
Asymmetric Michael reaction using hybrid catalyst system



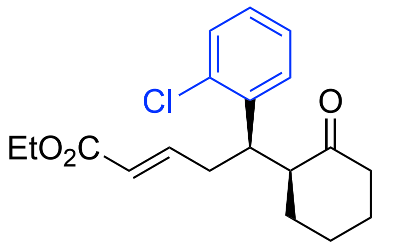
Catalyst A	Catalyst B	*t* [h]	yield [%]	*syn:anti*	*ee* [%]
	none	72	no reaction	n.d.	n.d.
		24	74	5:1	91
		40	74	15:1	96
		40	70	10:1	-95
none		72	no reaction	n.d.	n.d.

Substrate scope

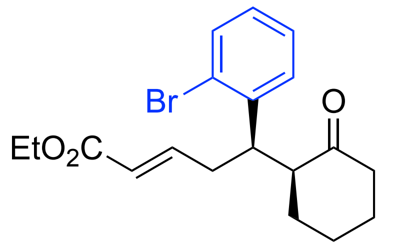




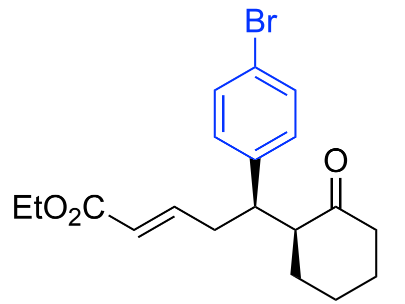
67%, *syn:anti* = 7:1, 82% *ee*



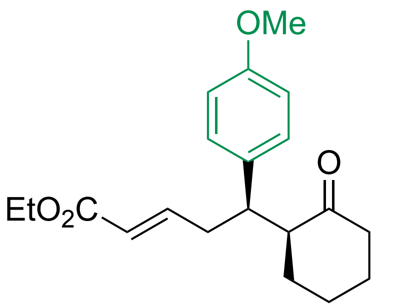
71%, *syn:anti* = 5:1, 89% *ee*



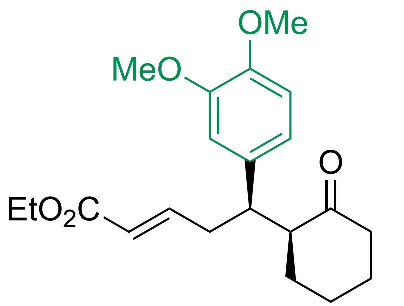
72%, *syn:anti* = 5:1, 92% *ee*



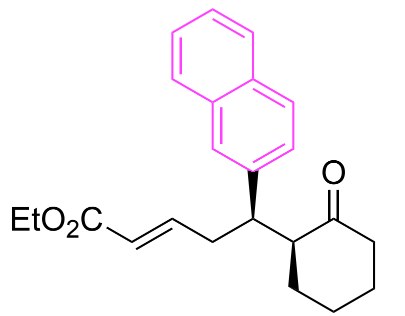
71%, *syn:anti* = 8:1, >99% *ee*



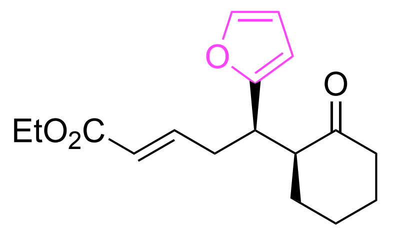
78%, *syn:anti* = 14:1, 96% *ee*



81%, *syn:anti* = 9:1, 96% *ee*

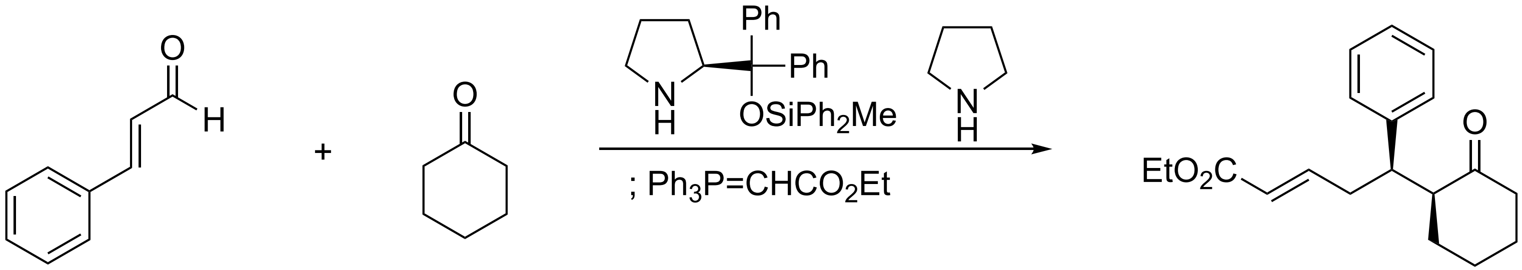


88%, *syn:anti* = 13:1, 96% *ee*

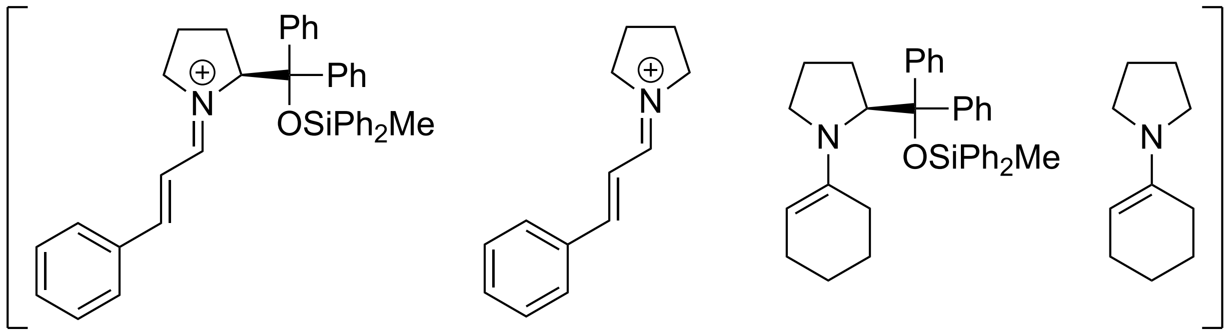


61%, *syn:anti* = 6:1, 89% *ee*

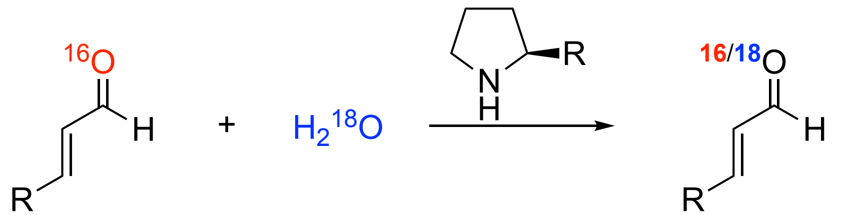
What is an active species in this reaction?

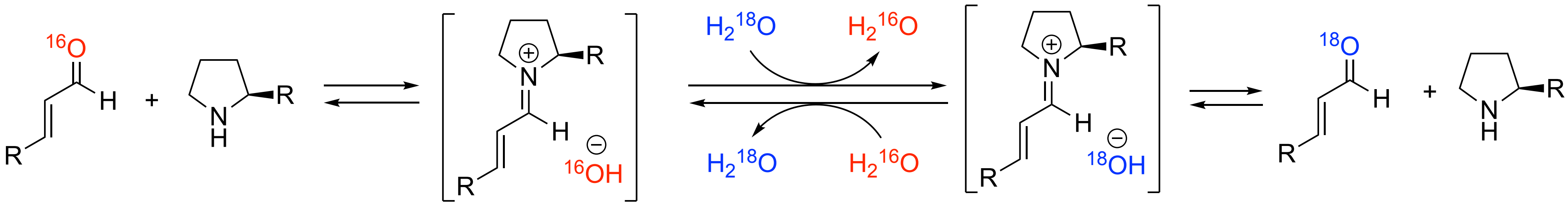


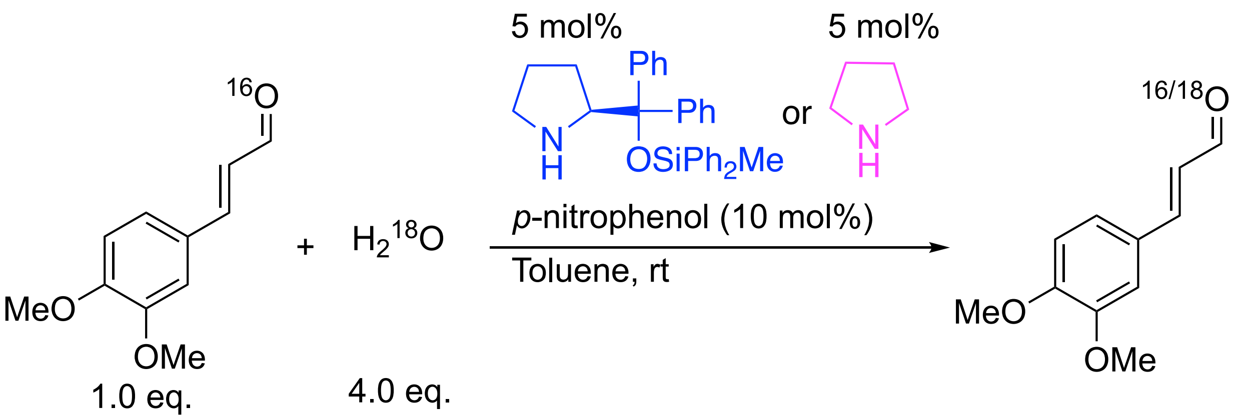
74%, **91% ee**

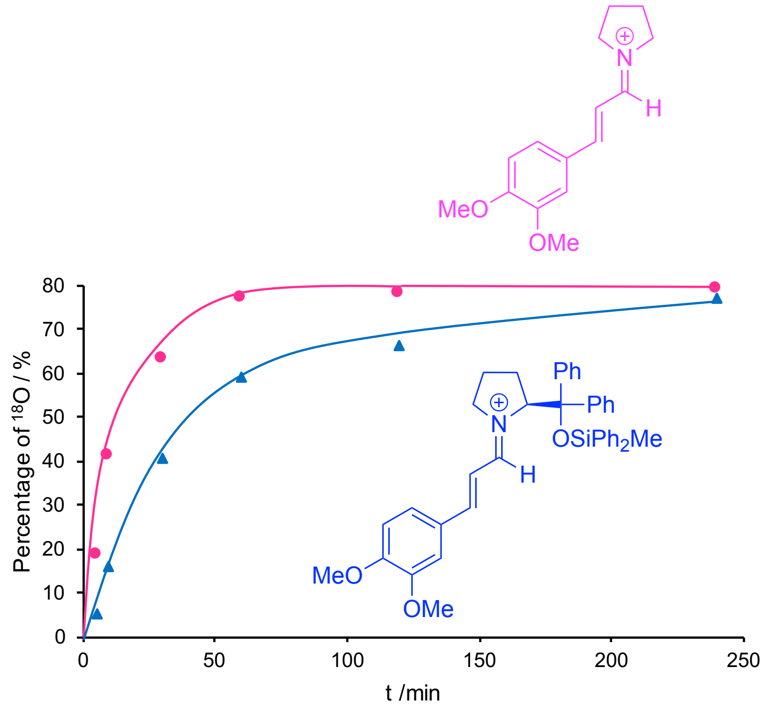


Generating reaction rate of iminium ions using $H_2^{18}O$ (1)



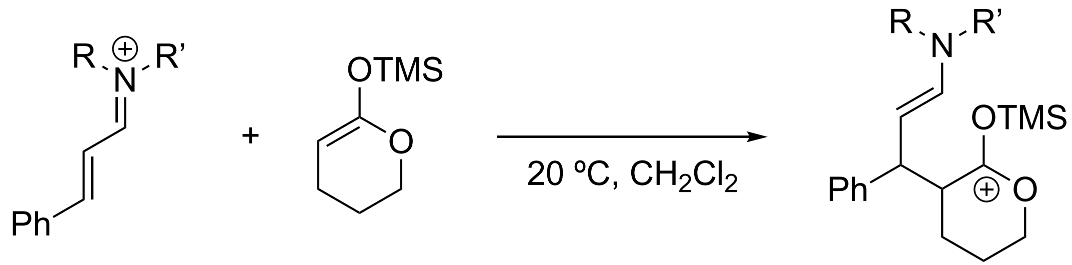




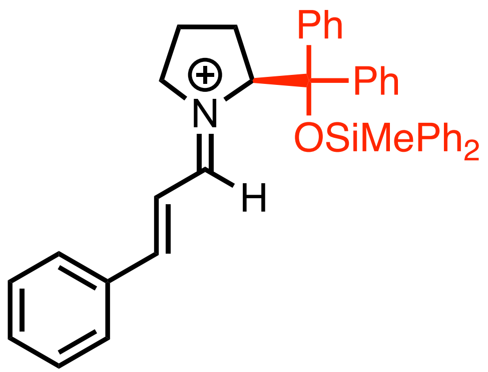


(1) Y. Hayashi, *et al.*, *Chem. Eur. J.* **2016**, *22*, 5868.

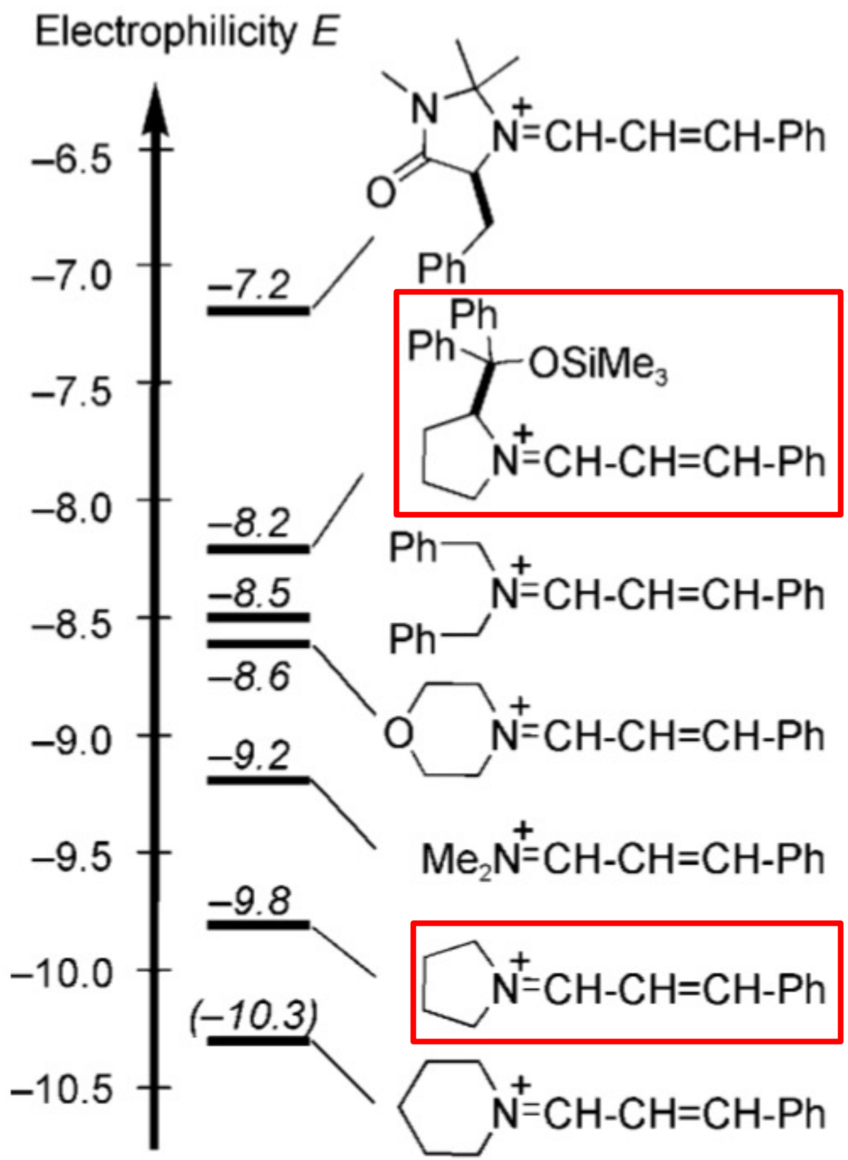
Reactivity of iminium ions



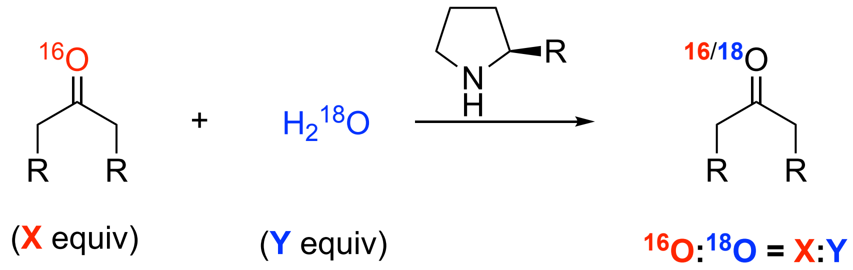
H. Mayr, *et al.*, *Angew. Chem. Int. Ed.* **2008**, *47*, 8723.

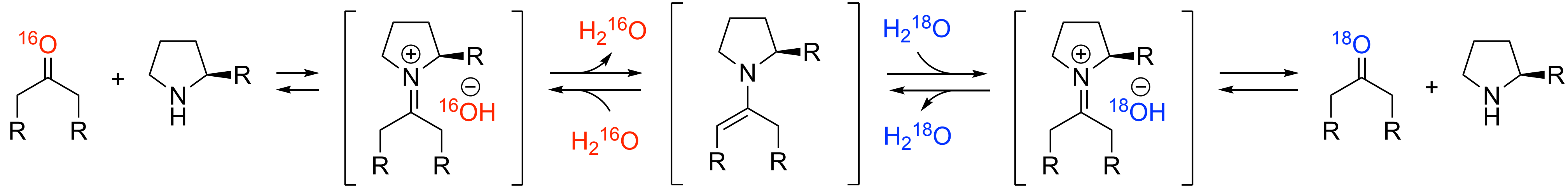


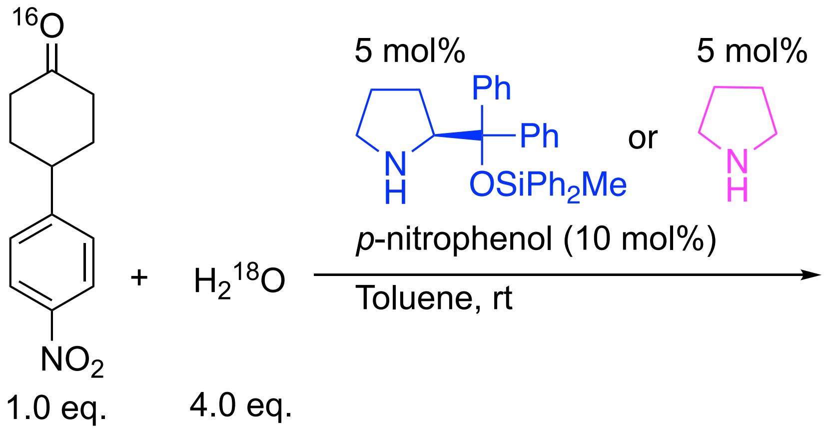
more electrophilic
lower LUMO
higher reactivity

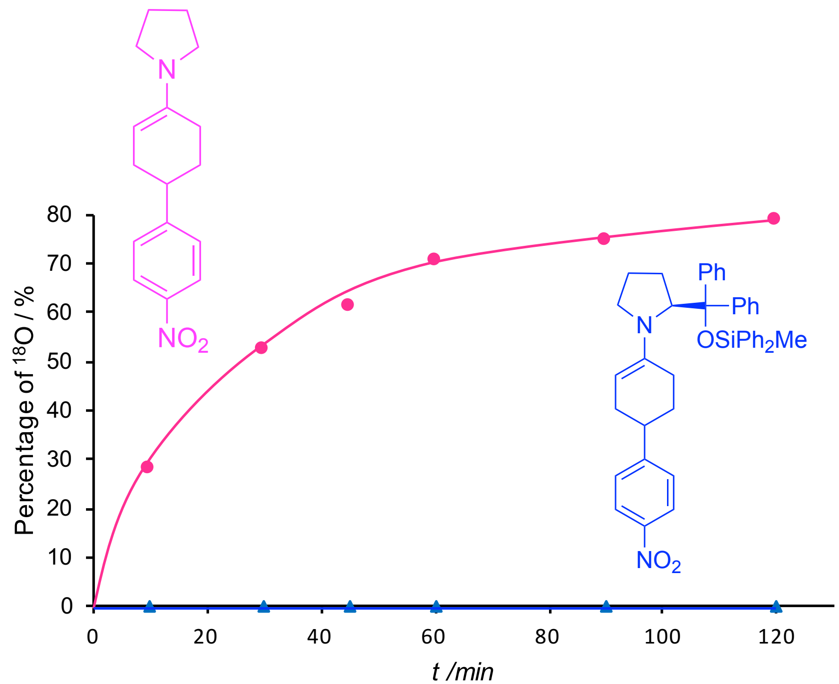


Generating reaction rate of enamines using $H_2{}^{18}O$ (1)



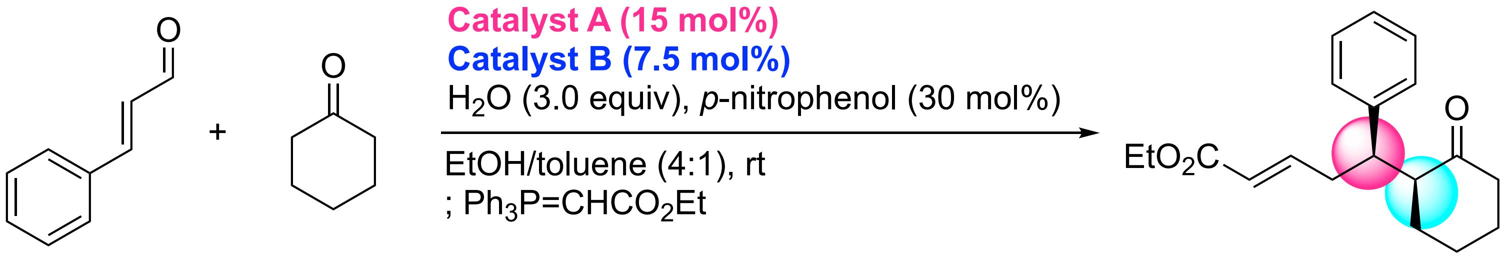


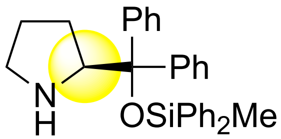
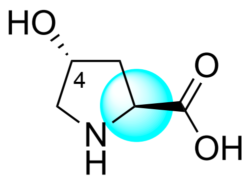
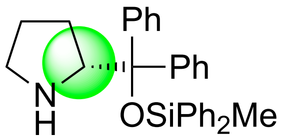
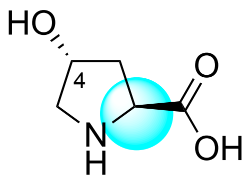




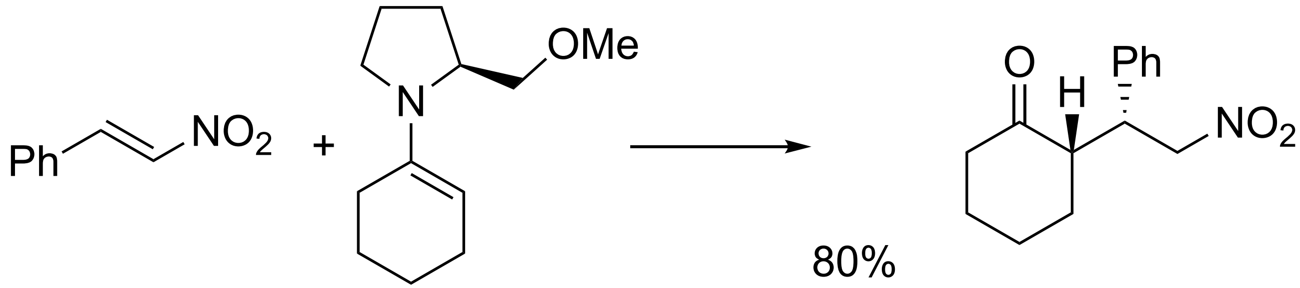
(1) Y. Hayashi, *et al.*, *Chem. Eur. J.* **2016**, *22*, 5868.

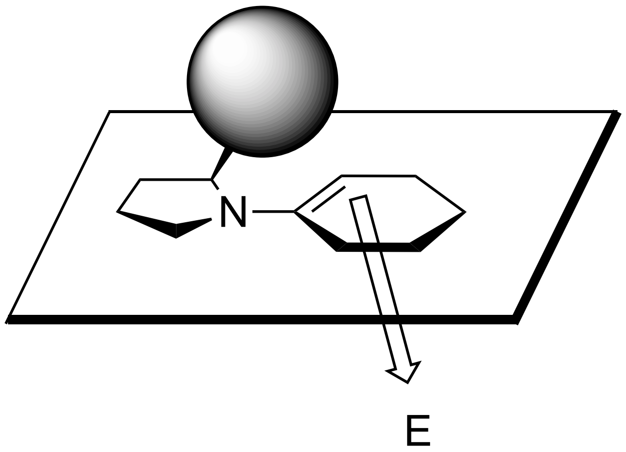
Asymmetric Michael reaction using hybrid catalyst system



Catalyst A	Catalyst B	*t* [h]	yield [%]	*syn:anti*	*ee* [%]
		40	74	**15:1**	**96**
		40	70	**10:1**	**–95**

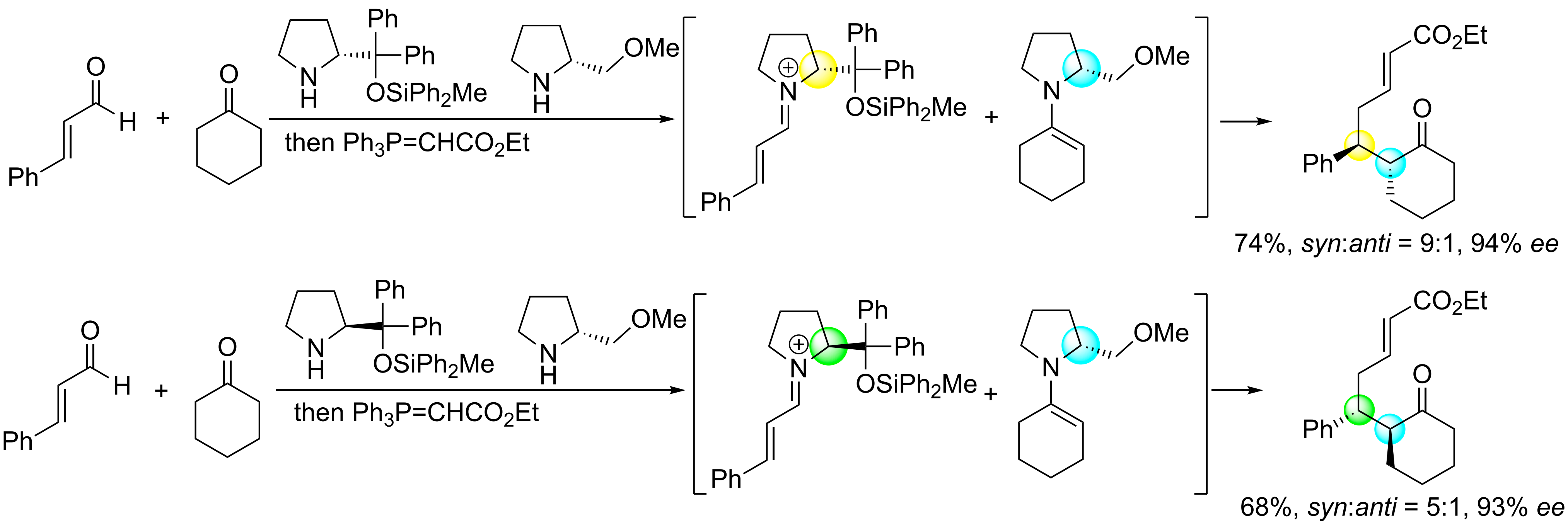
Seebach's chiral enamine

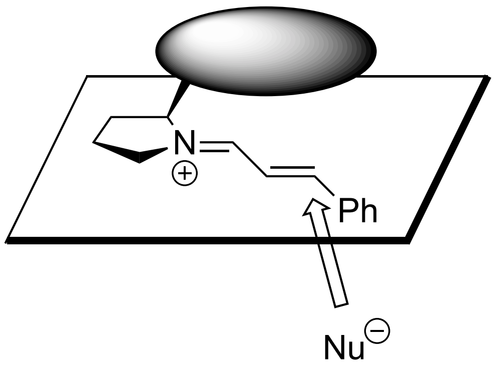


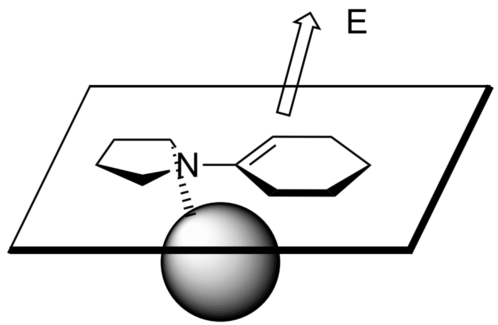


D. Seebach, *et al., Helv. Chim. Acta*, **1982**, *65*, 1637.

What is an active species in this reaction?



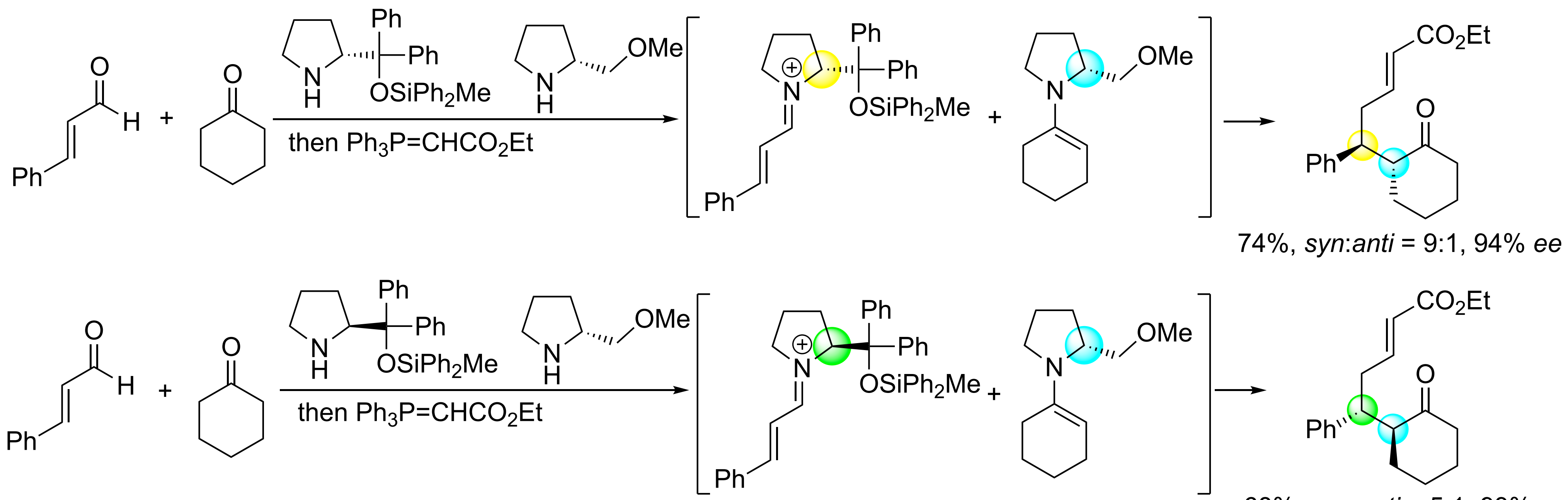




Y. Hayashi, et al., *Chem. Eur. J.*, **2015**, *21*, 1233.

D. Seebach, *et al.*, *Helv. Chim. Acta*, **1982**, *65*, 1637

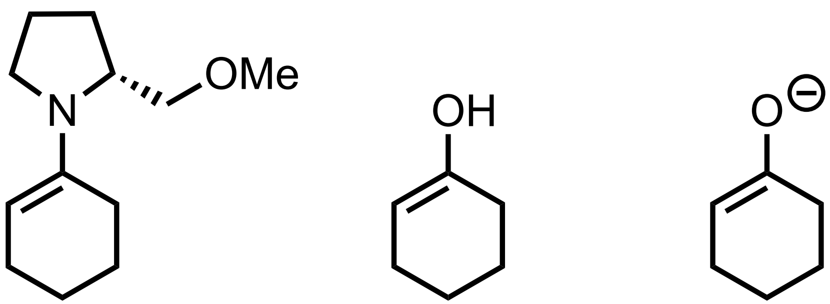
What is an active species in this reaction?



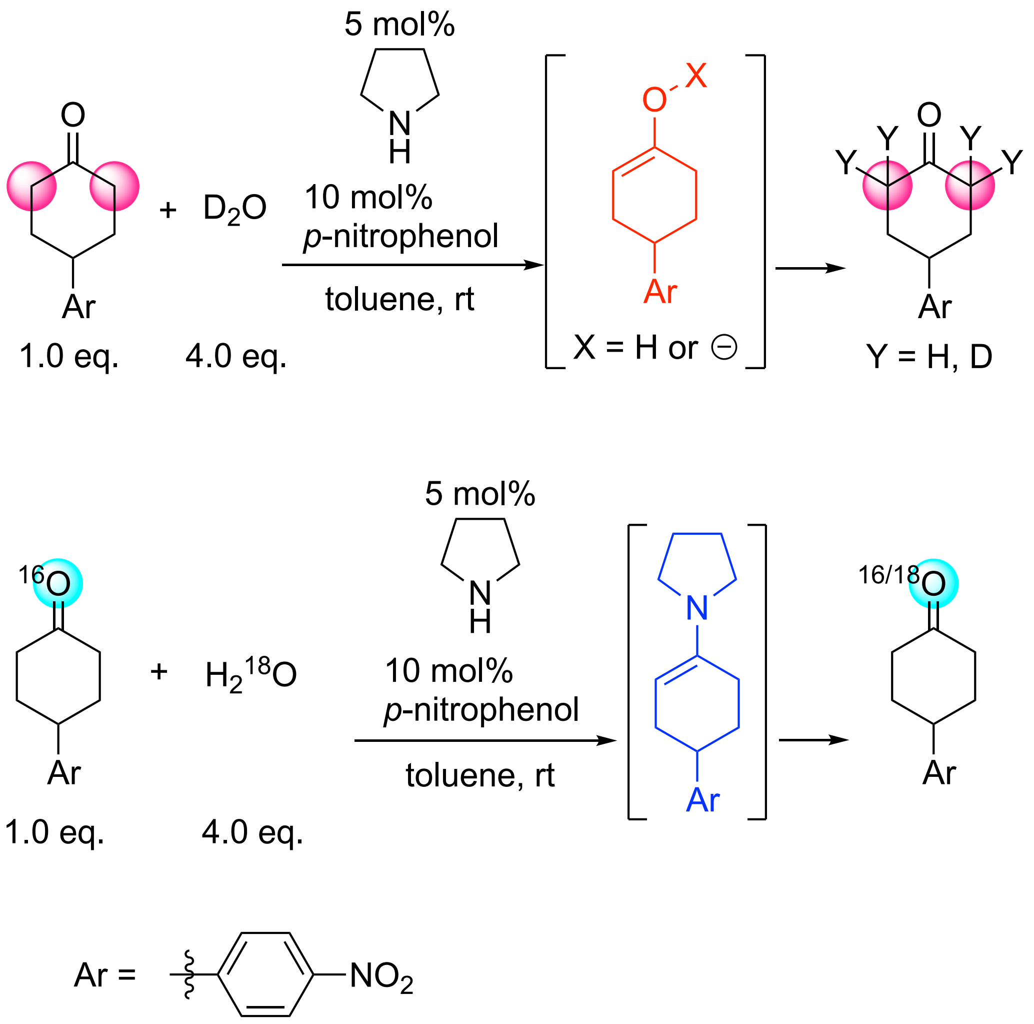
74%, *syn*:*anti* = 9:1, 94% *ee*

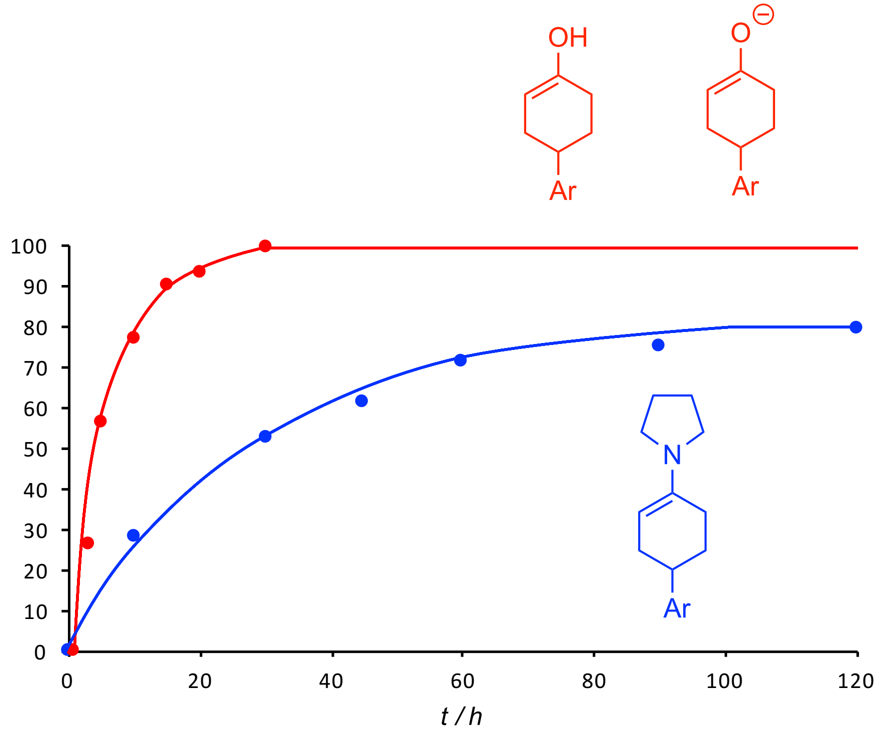
68%, *syn*:*anti* = 5:1, 93% *ee*

Possible nucleophile

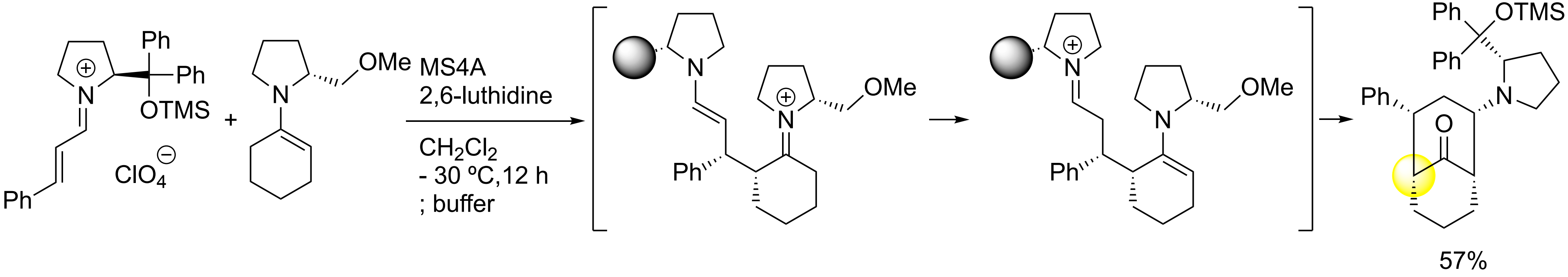


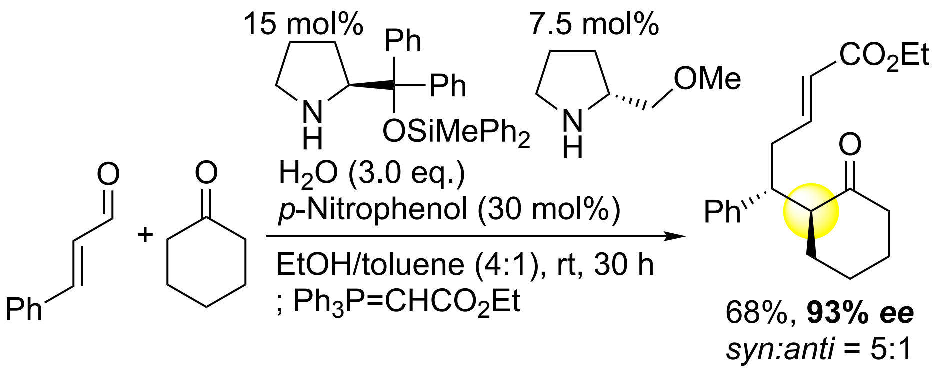
Study of generating speed of enamine, enol, and enolate

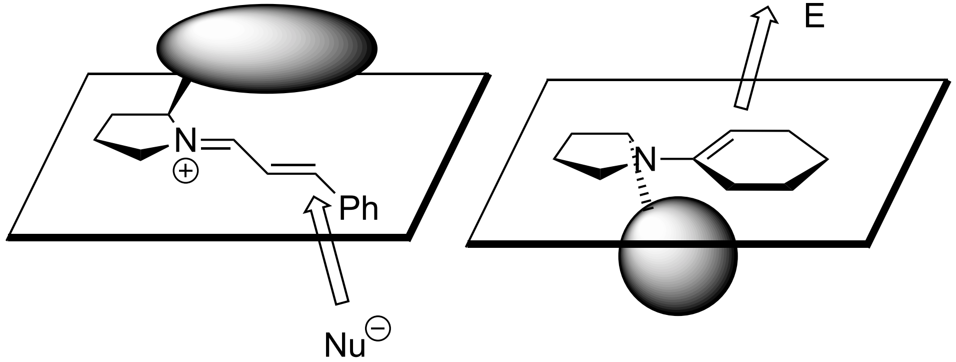


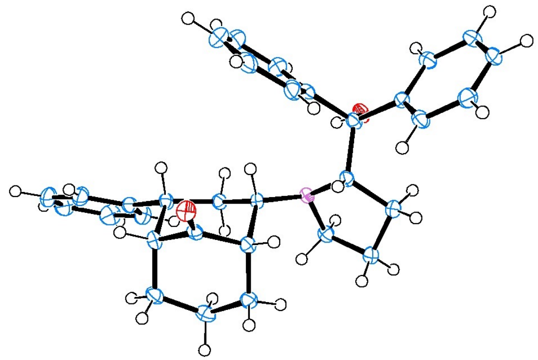


Reaction between isolated iminium salt and nucleophiles

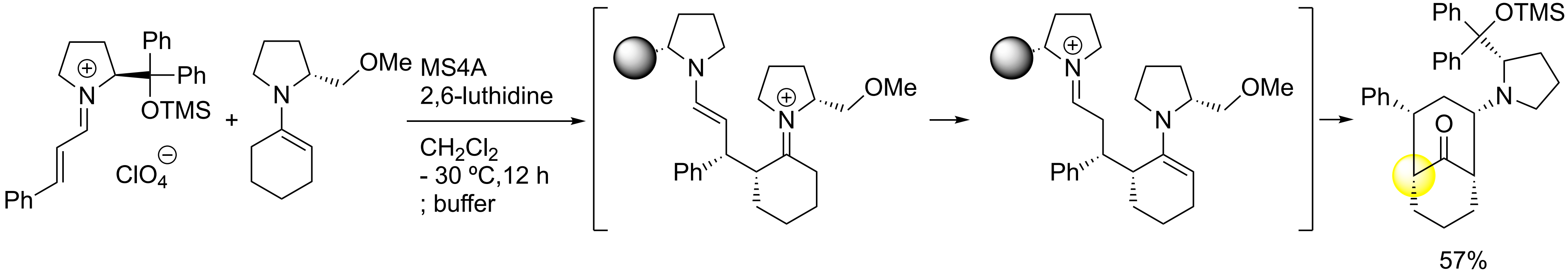


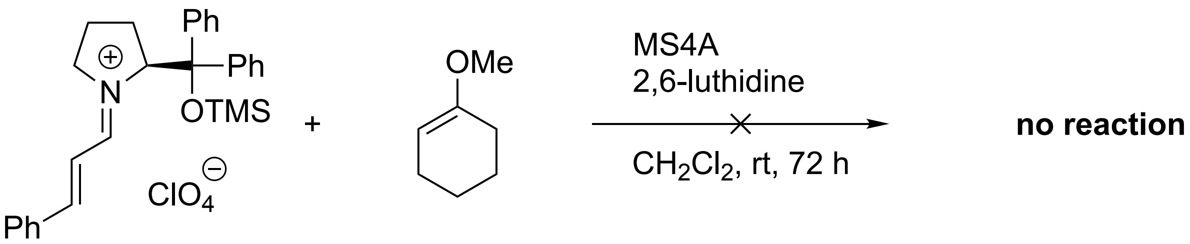


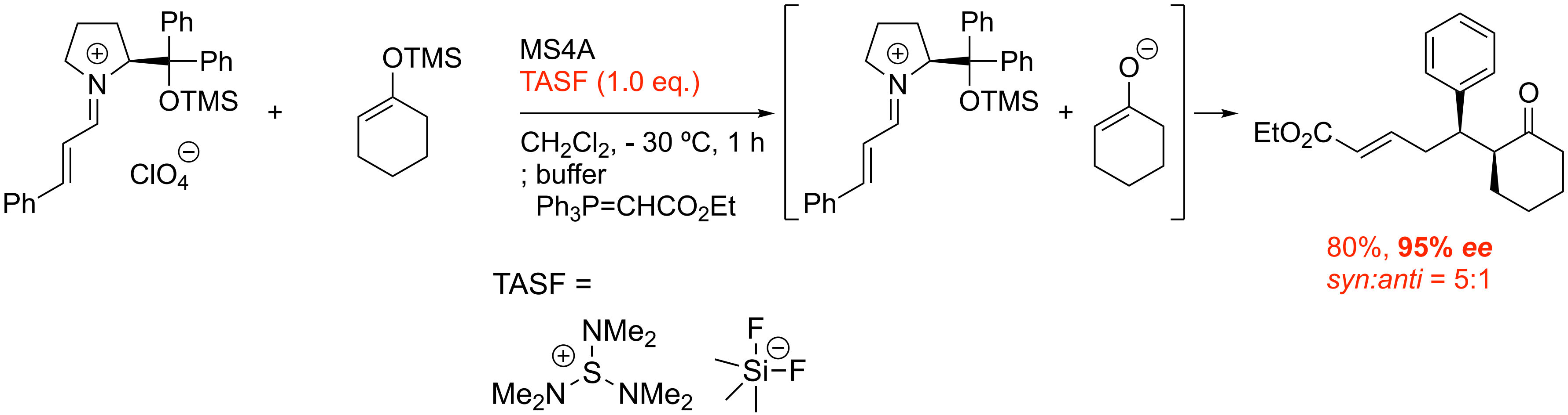




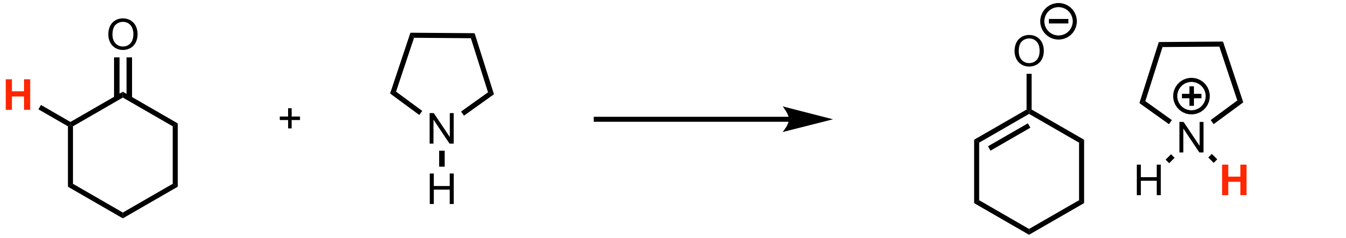
Reaction between isolated iminium salt and nucleophiles





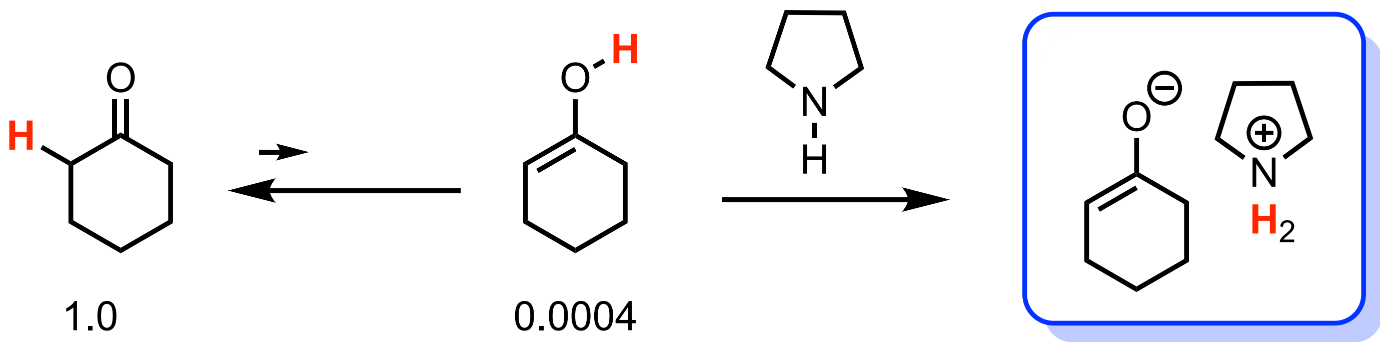


Is an enolate generated by the secondary amine?



pKa = **16.7** [1)]
(in water)

pKa = **11.2**[2)]
(in water)

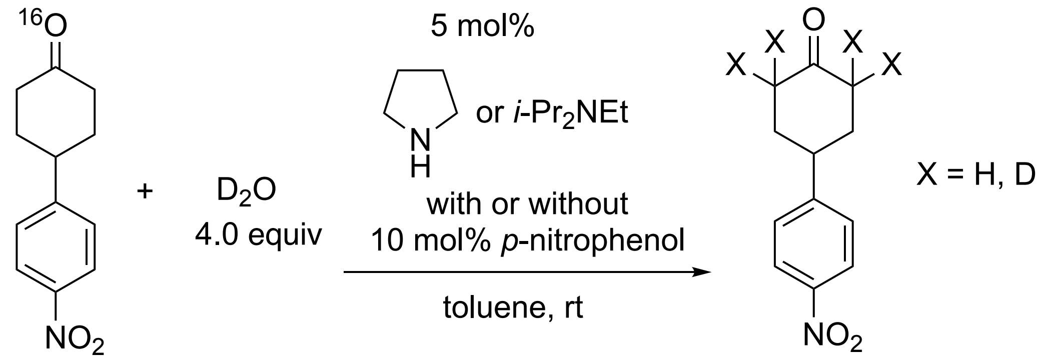


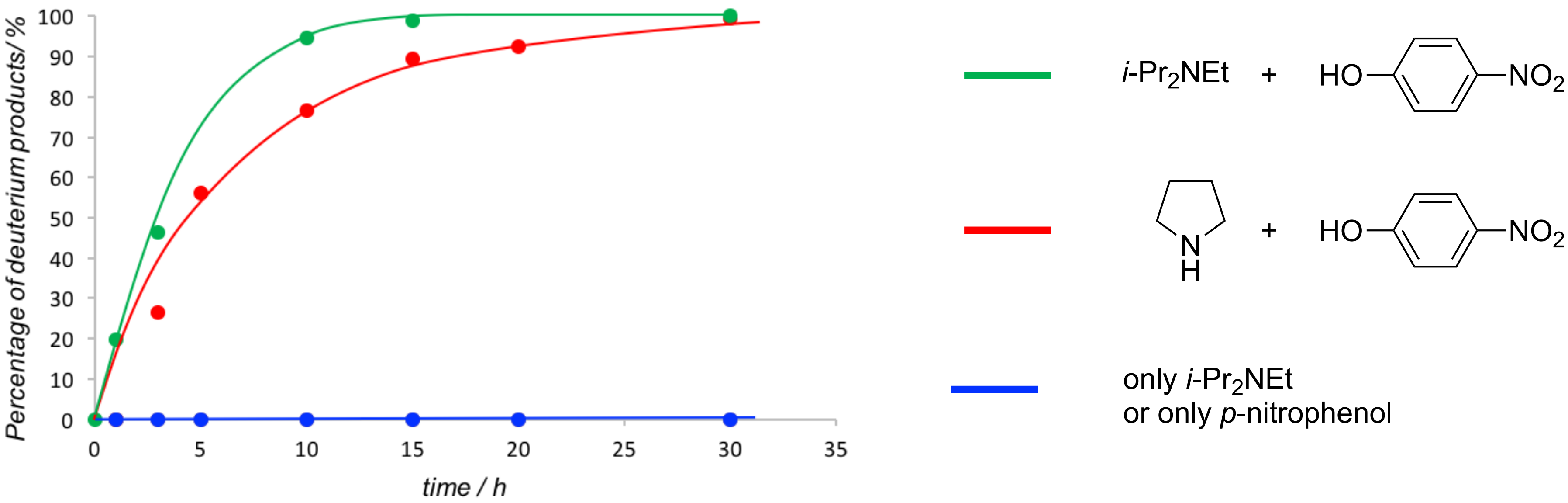
existance ratio 1.0 0.0004

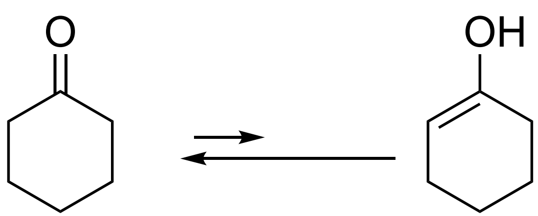
pKa **16.7** [1)] (in water) **12.1**[1)] (in water) **11.2**[2)] (in water)

1) J. P. Guthrie, *Can. J. Chem.* **1979**, *57*, 1177. 2) H. K. Hall Jr., *J. Am. Chem. Soc*, **1957**, *79*, 5441.

The generation speed of an enolate



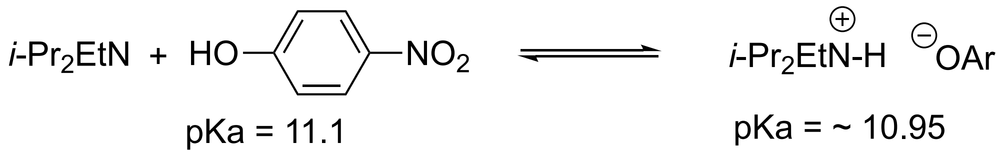


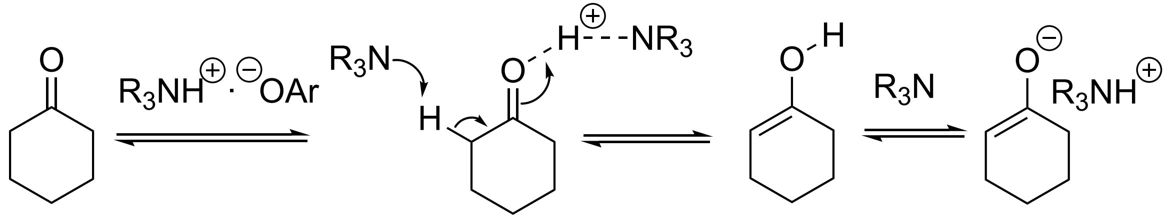


This equilibrium is very slow with amines alone or with acids alone.
A combination of weak amines and weak acids is essential for enolization.

Rapid generation of an enolate

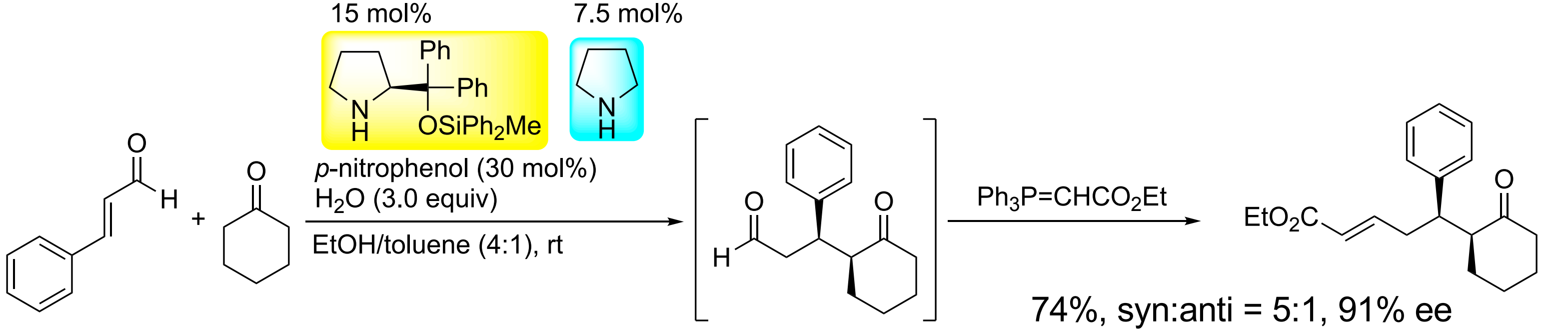
Free amine and free acid are required for the fast enolization

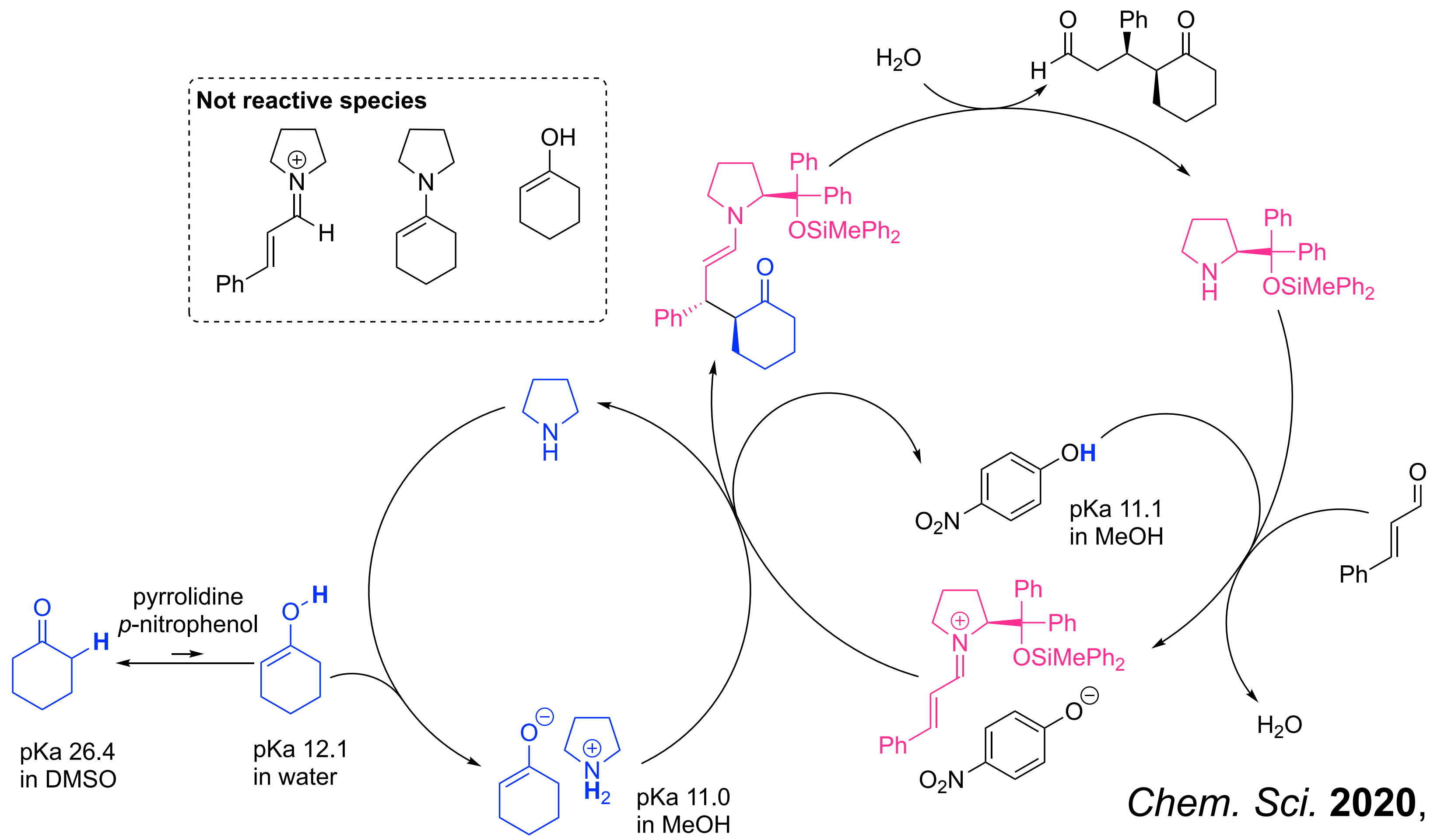




R_3N = *i*-Pr_2EtN
HOAr = *p*-$HOC_6H_4NO_2$

Mechanism of the Michael reaction

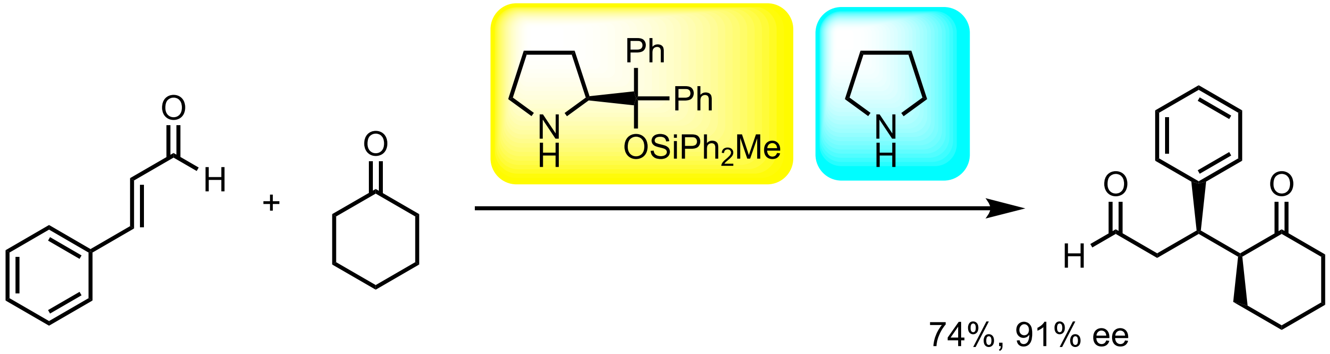




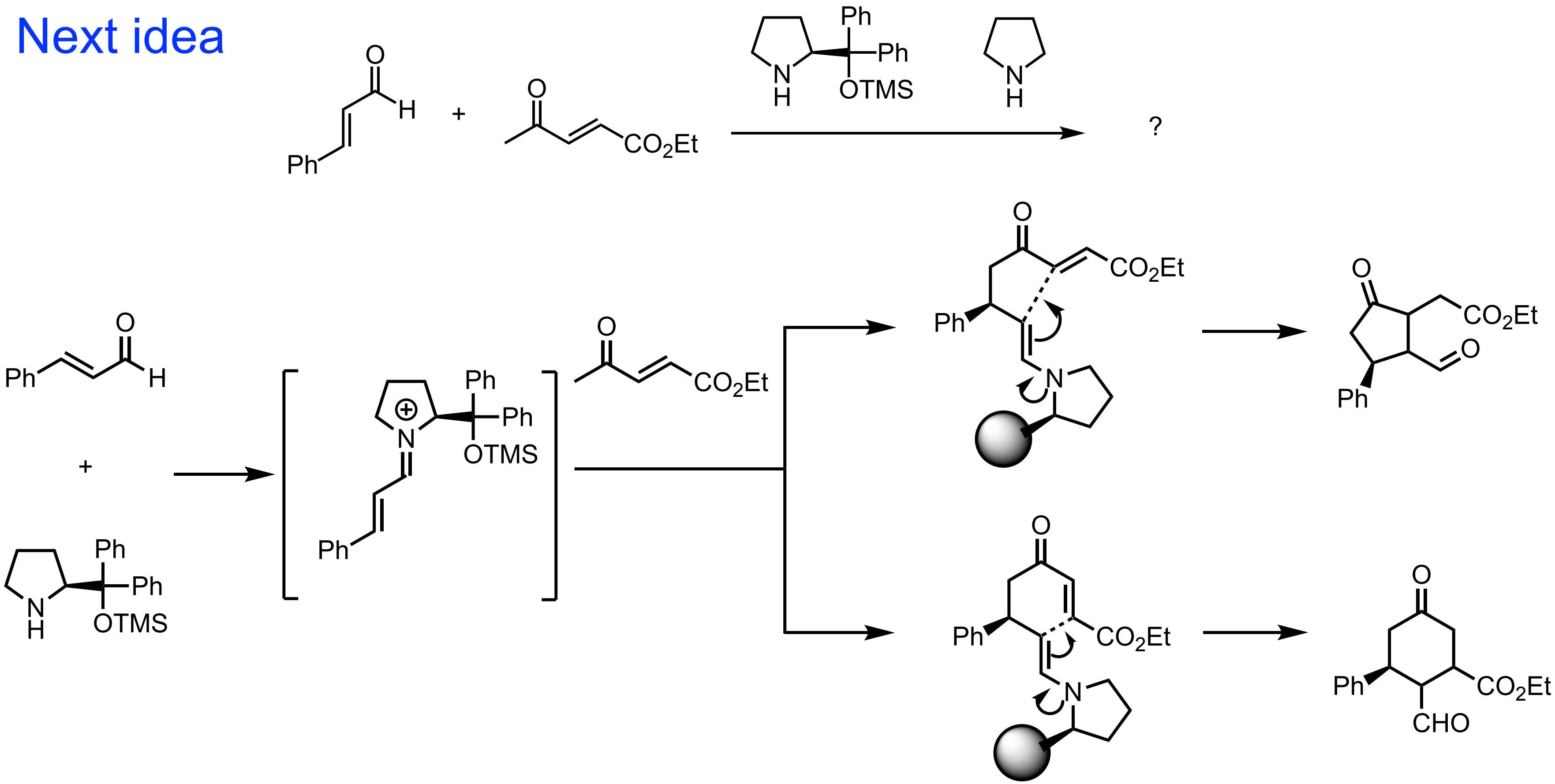
Chem. Sci. **2020**, *11*, 11293.

Design of the domino reaction

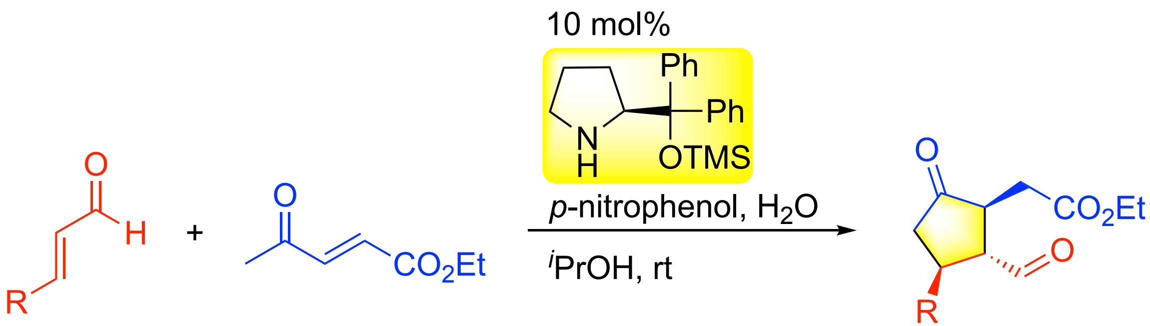
Ketone can be used as a nucleophile.



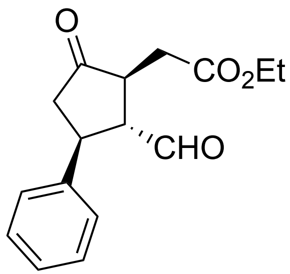
Next idea



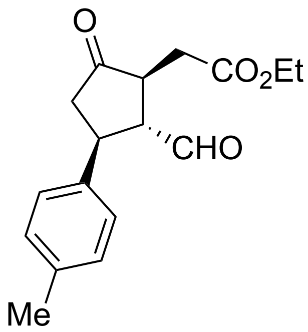
Generality of the formal 3+2 cycloaddition reaction



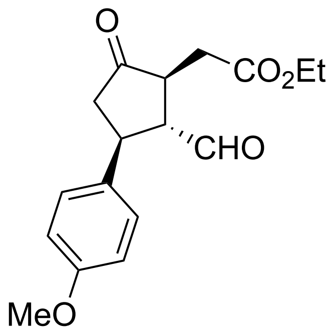
single isomer



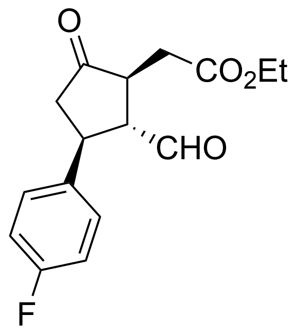
90%, **>99% ee**



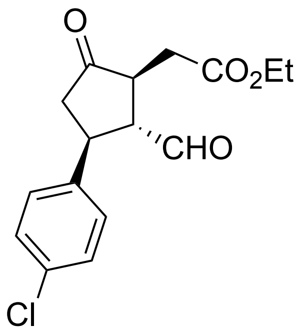
91%, **>99% ee**



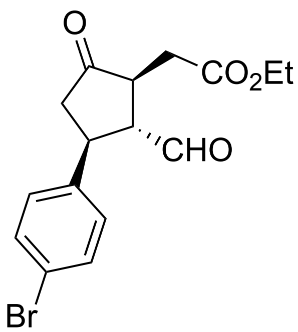
88%, **>99% ee**



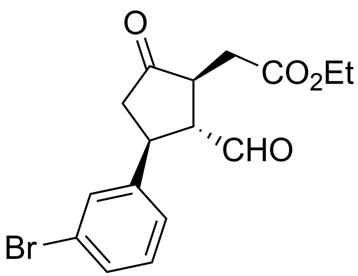
81%, **>99% ee**



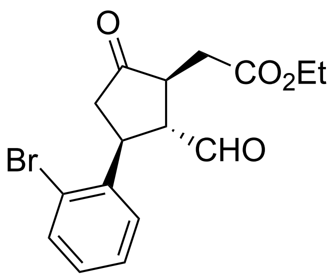
85%, **>99% ee**



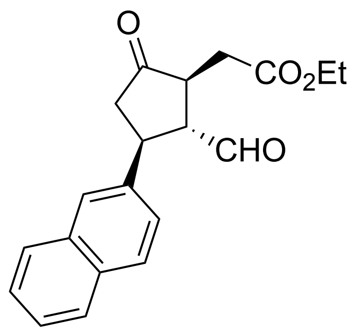
83%, **>99% ee**



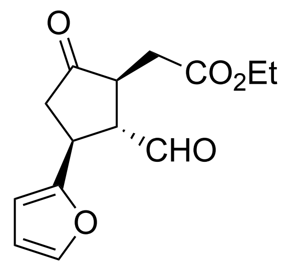
74%, **>99% ee**



82%, **96% ee**

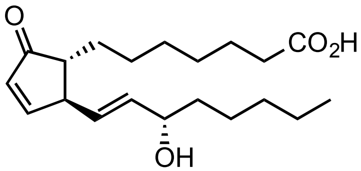


84%, **>99% ee**

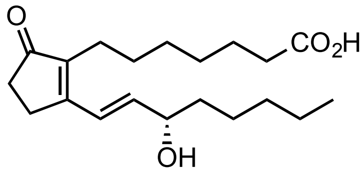


80%, **96% ee**

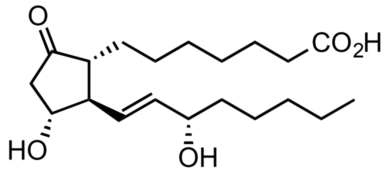
Prostaglandins



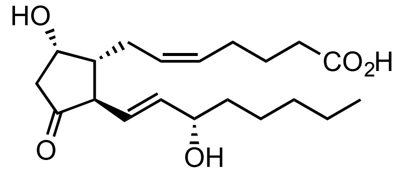
PGA$_1$



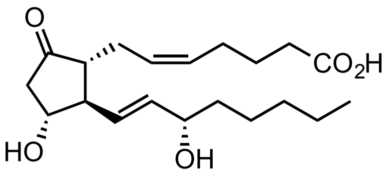
PGB$_1$



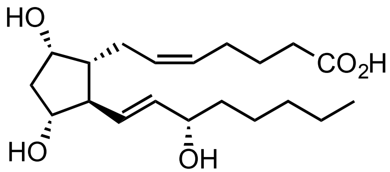
PGE$_1$



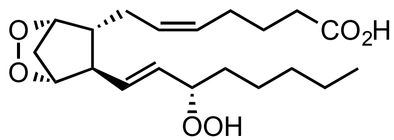
PGD$_2$



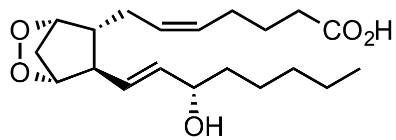
PGE$_2$



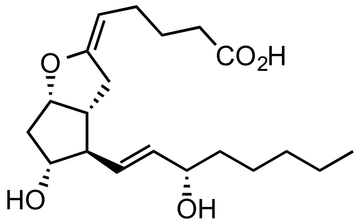
PGF$_{2\alpha}$



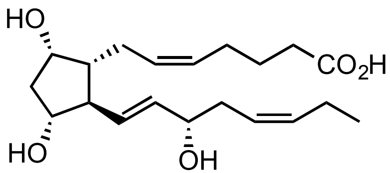
PGG$_2$



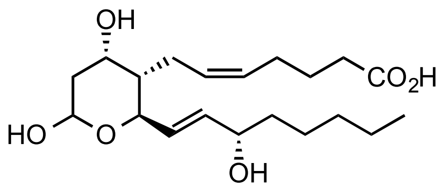
PGH$_2$



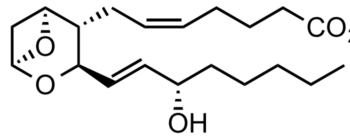
PGI$_2$



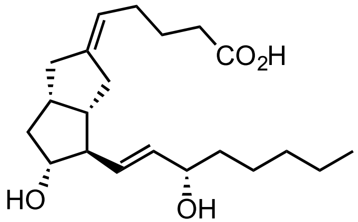
PGF$_{3\alpha}$



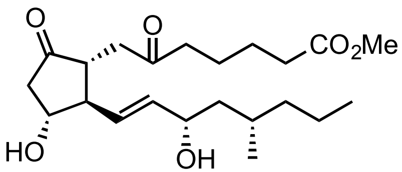
TXB$_2$



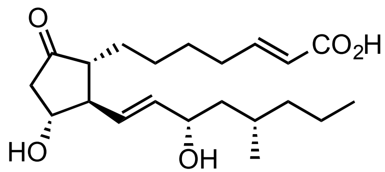
TXA$_2$



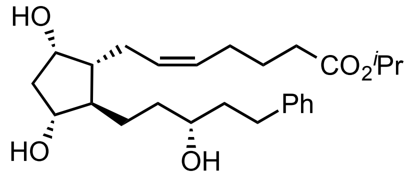
Carbacyclin



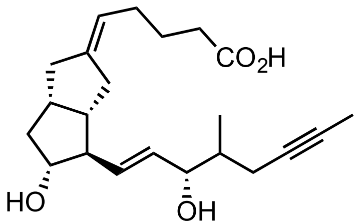
ornoprost



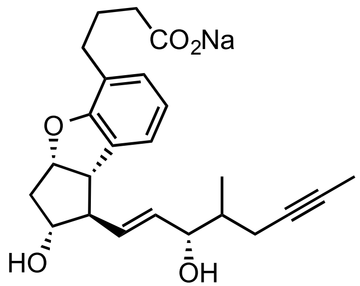
limaprost



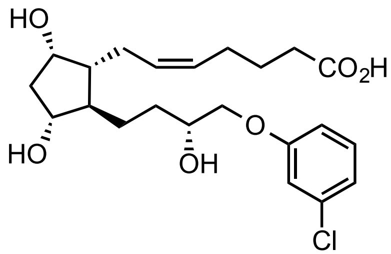
latanoprost



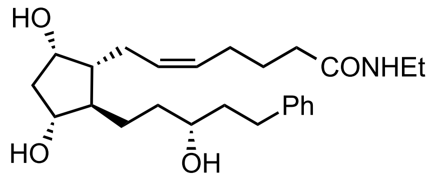
iloprost



beraprost



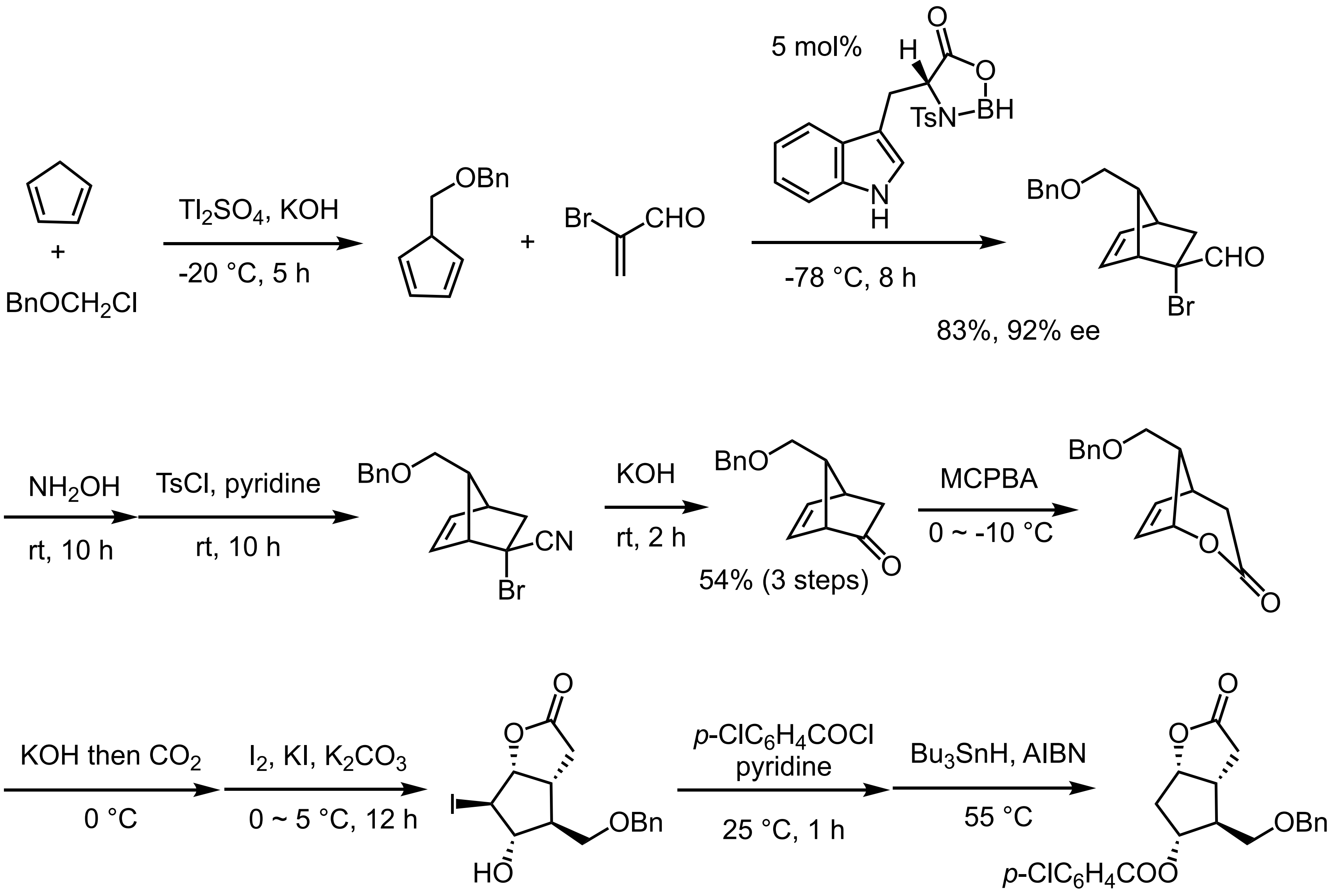
cloprostenol



bimatoprost

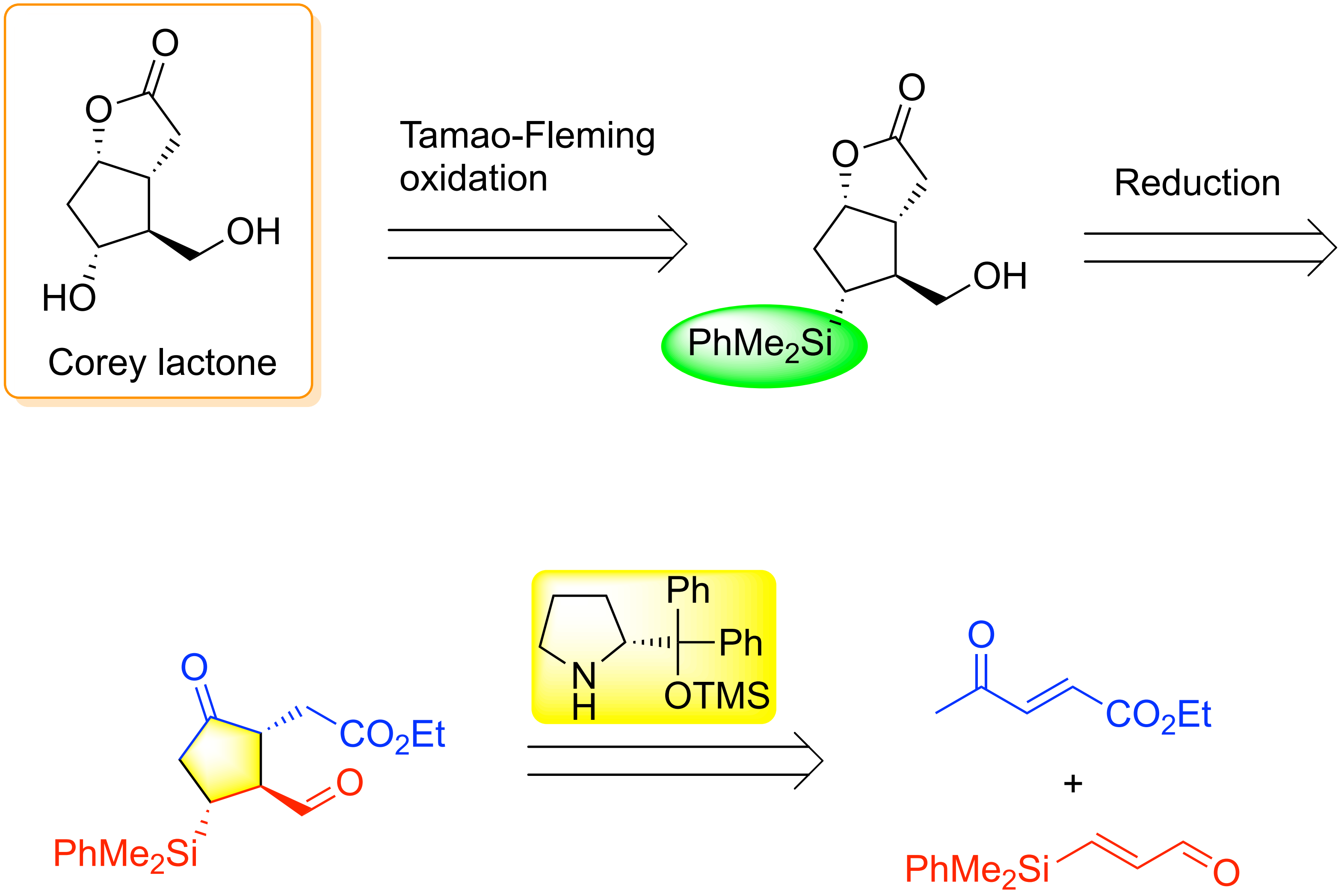
Total syntheses: Corey, Stork, Woodward, Noyori, Danishefsky etc.

Corey's synthesis of Corey lactone

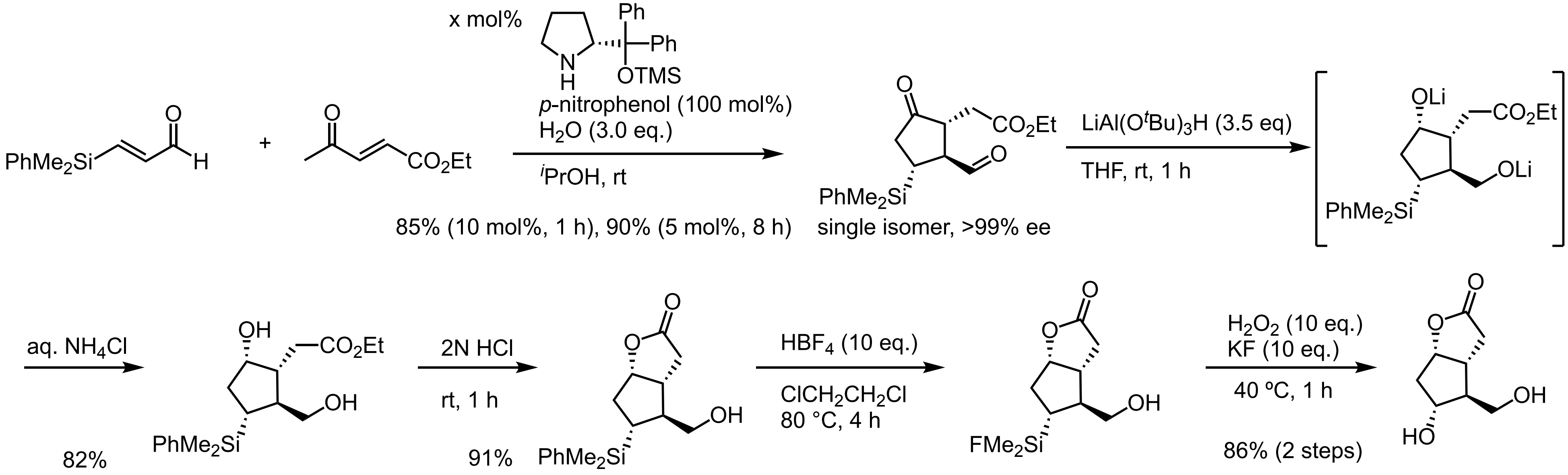


48 h + unreported time for 2 steps

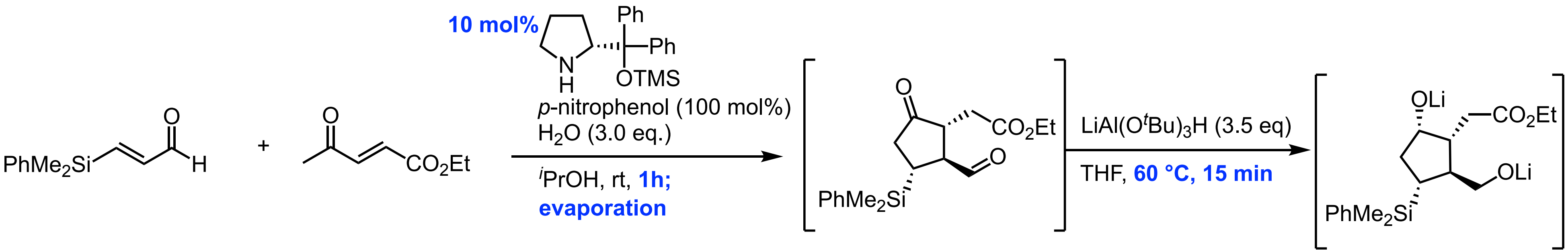
Retro-synthesis of Corey Lactone



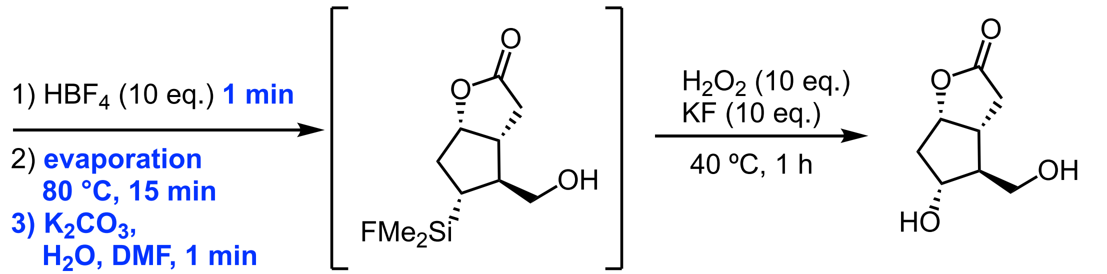
Synthesis of Corey lactone



Total yield: 58%, 5 pots

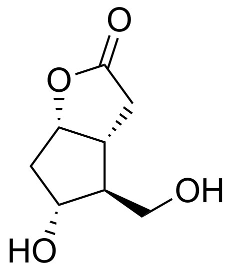


Total reaction time: 152 min

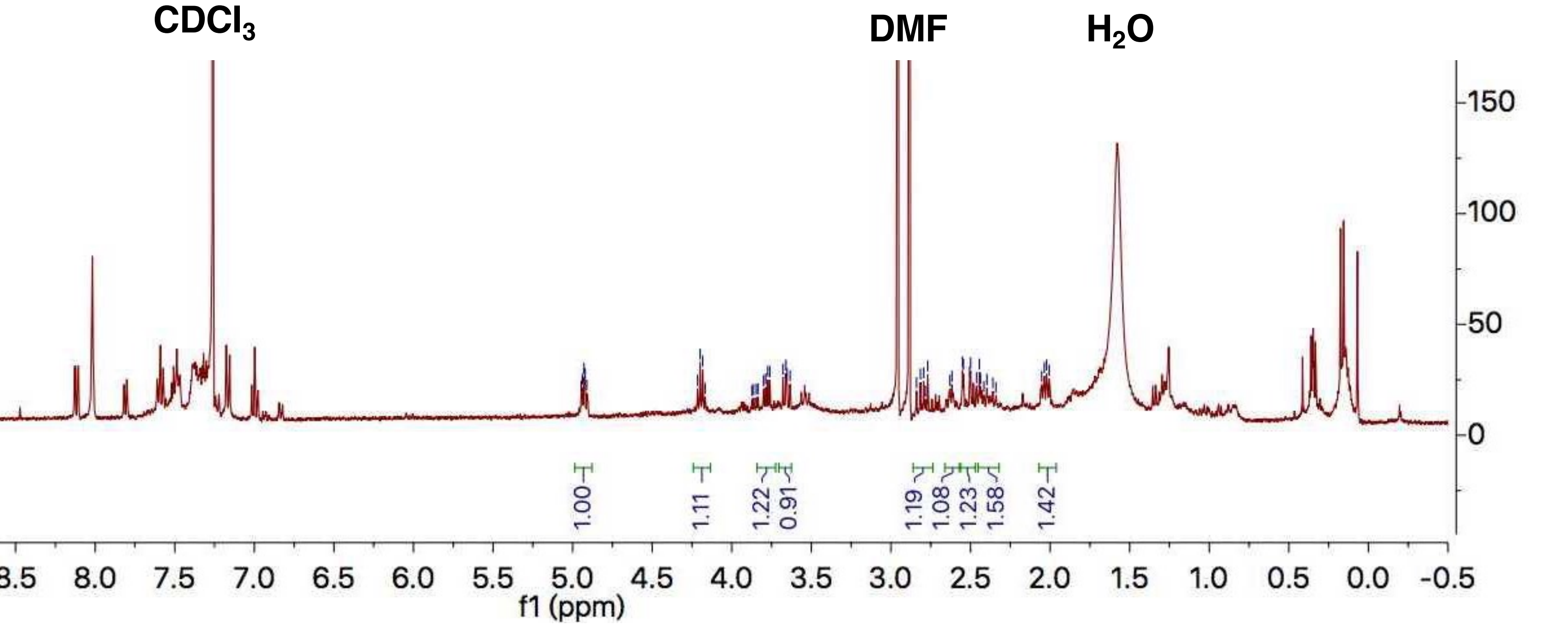


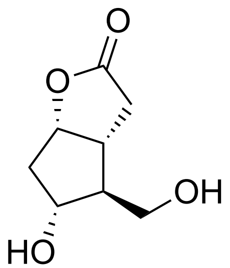
Total yield: 50%, one pot

Corey lactone のNMR

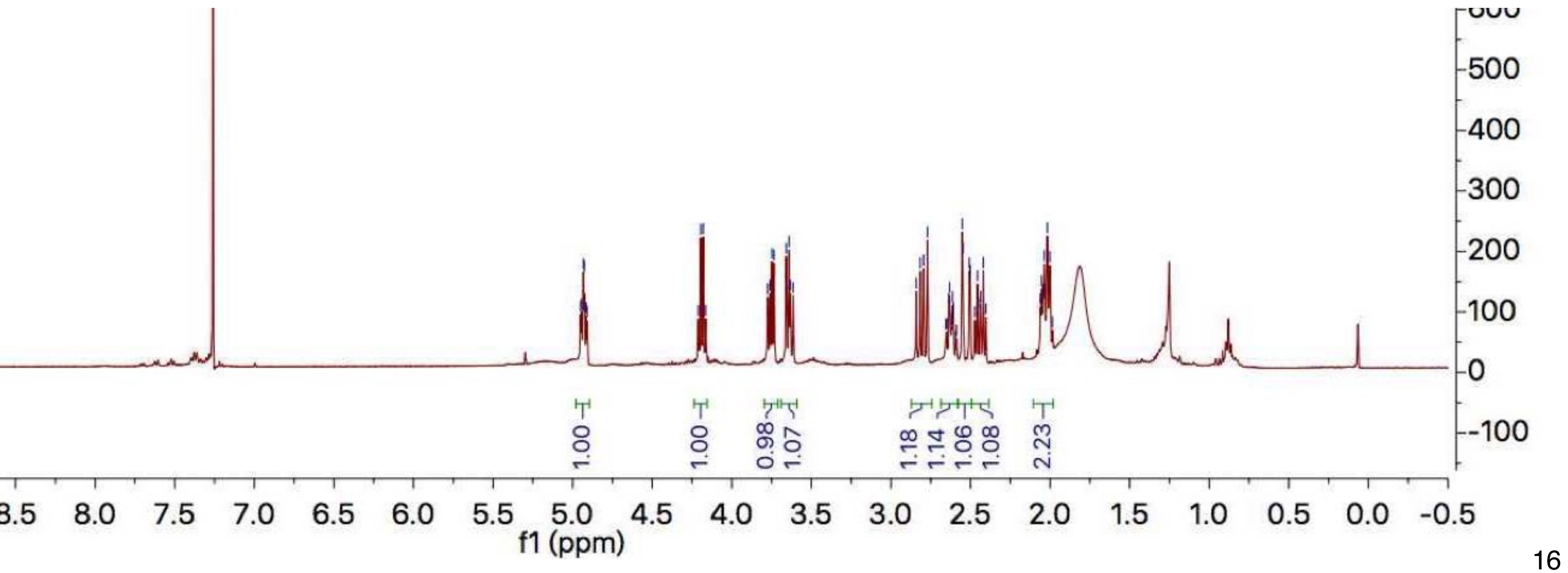


Corey lactone
(crude ^{1}H-NMR)

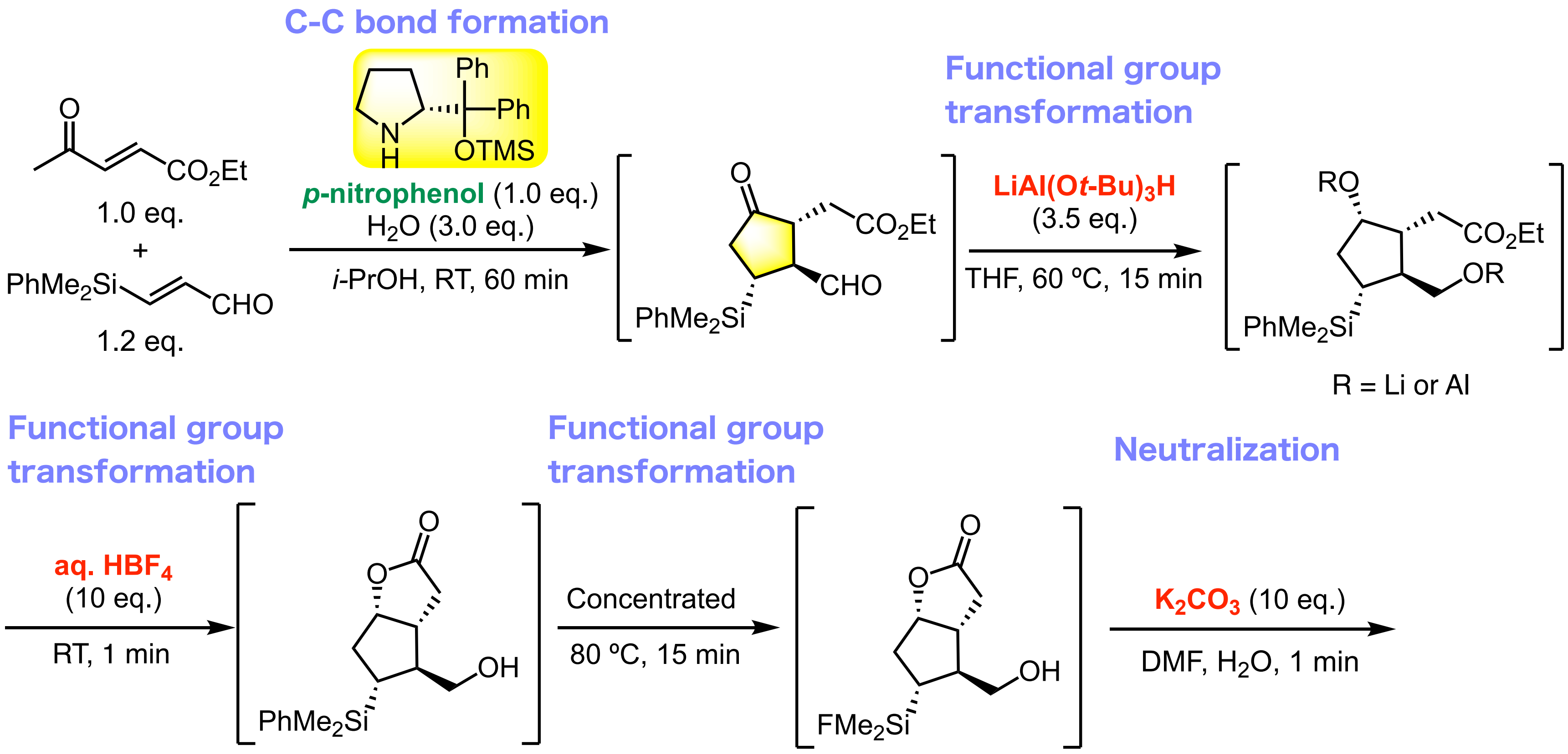


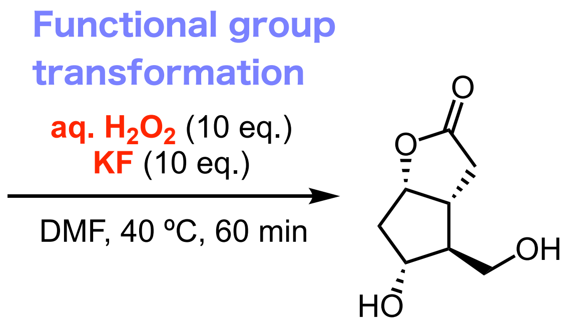


Corey lactone
(pure ^{1}H-NMR)



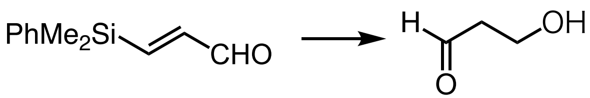
The reason of the success of one-pot reaction of Corey lactone





One catalyst catalyzes two reaction (Michael/Michael)

Total yield 50% (5 steps): average **87%/steps**
***p*-Nitrophenol** was removed by acid/base separation.
All the reagents are inorganic, which go to water phase.
Excess starting material was removed by following reaction.



Chem. Sci., **2020**, *11*, 1205.

A guide toward the rapid multi-step synthesis of molecules

Consideration of reaction method

1. Employ rapid reactions as frequently as possible.
2. Employ reactions that are easy to handle and fast to purify.
3. Employ a domino (cascade, tandem) reactions.

Consideration of reaction scheme (retrosynthesis)

4. Design the synthesis based on step economy and redox economy.

Consideration of optimal conditions in a one pot

5. Find reaction conditions under which the reaction can proceed rapidly.
6. Design the synthesis based on pot economy.

Is making a molecule in a short time important?

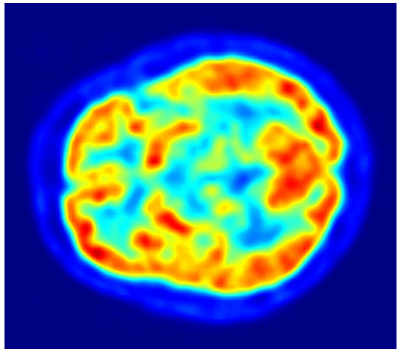
Save time

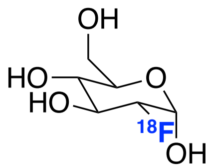
When we make a molecule rapidly, we can examine the function of the molecule.

Unstable molecule

Rapid reaction is necessary.

PET (Positron emission tomography)





Fluorodexoyglucose (^{18}F)

PET scan of the human brain

Half time

^{11}C: 20 min, ^{13}N: 10 min, ^{15}O: 2 min, ^{18}F: 110 min

A case study of ^{11}C

Isotope production: 10 min, radiotracer synthesis and purification: 40 min, PET imaging: up to 90 min

Is making a molecule in a short time important?

In the Production Process

Save labor cost

Save energy cost

Save equipment cost: We can use expensive equipments efficiently.

On demand synthesis is possible:
We can make molecules when and where we need them.
There is no need to stockpile the molecule.

Time economy

Time Economy in Total Synthesis

JOC The Journal of Organic Chemistry

pubs.acs.org/joc Perspective

Time Economy in Total Synthesis

Yujiro Hayashi*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c01581 Read Online

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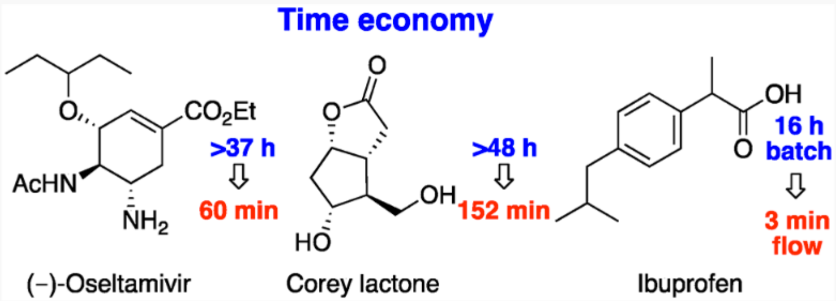
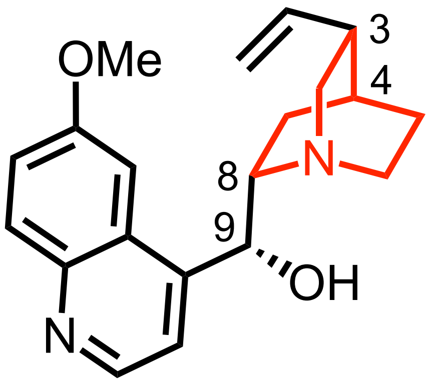


ABSTRACT: It is often said that "time is money". This is certainly true in a multistep synthesis when a high-valued product or set of products is needed urgently. Fulfilling this need requires the sensible balancing of atom economy, step economy, and redox economy with the time taken to make the product. In this age of flu-based pandemics, the need for rapid provision of effective therapeutic agents makes the importance of "time economy" particularly clear. In this Perspective, the importance of time economy in total synthesis is described, as well as the general considerations underlining the timely production of desired molecules. As case studies, the syntheses of Tamiflu, Corey lactone, and ibuprofen are discussed, with emphasis on comparing classical and contemporary approaches to a rapid total synthesis. By using modern tactics such as one-pot reaction procedures and versatile synthetic methodologies such as organocatalyst mediated domino reactions coupled with strict-control technologies such as flow chemistry, Tamiflu and Corey lactone can now be synthesized within 60 and 152 min, respectively, using one vessel via a batch system. Tamiflu and ibuprofen can be prepared via flow system, and their total residence times are 11.5 and 3 min, respectively.

J. Org. Chem. **2021**, *86*, 1.

(−)-Quinine



Quinine

Medicinal effect
Specific drug for malaria

Utility
Organocatalyst
Food additive

Structural features
Quinuclidine skeleton
4 stereocenters: C3, C4, C8, C9

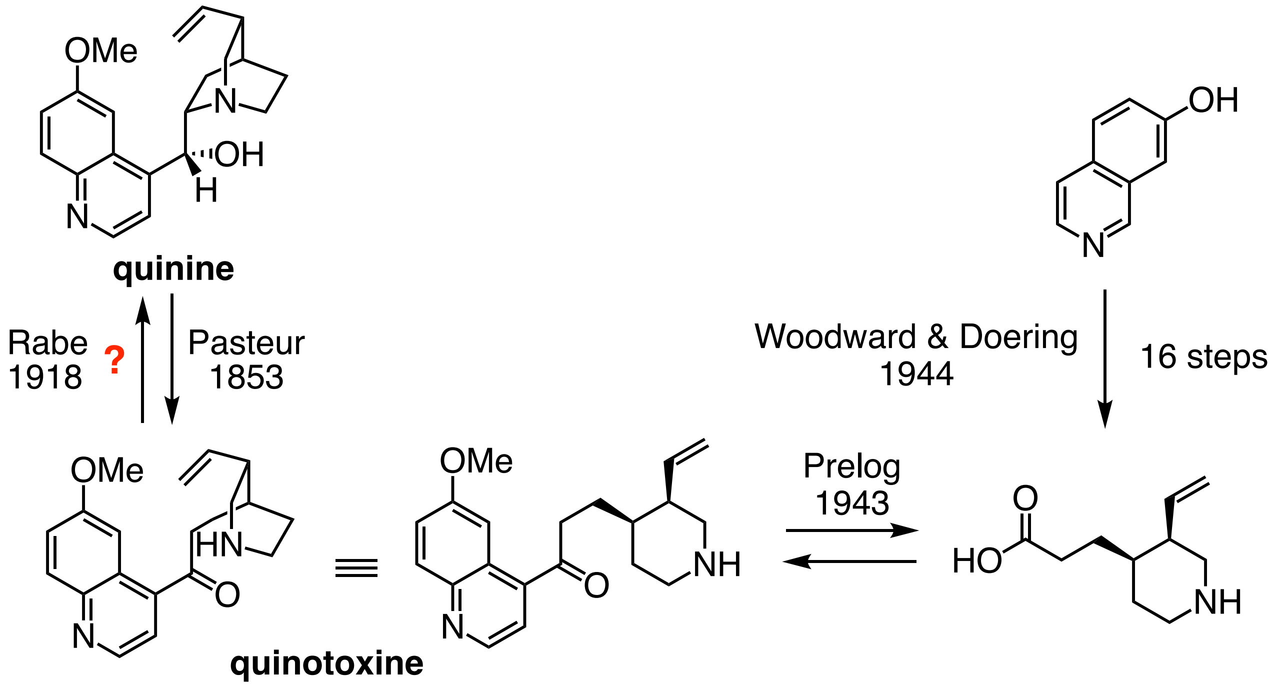
Formal synthesis
R. B. Woodward, M. J. Krische

Asymmetric total synthesis
G. Stork (13 pots), E. N. Jacobsen (15 pots)
Y. Kobayashi (21 pots), S. Hatakeyama (23 pots)
Y. -K. Chen (14 pots), N. Maulide (10 steps)
H. Ishikawa (15 pots), A. Córdova (16 pots)

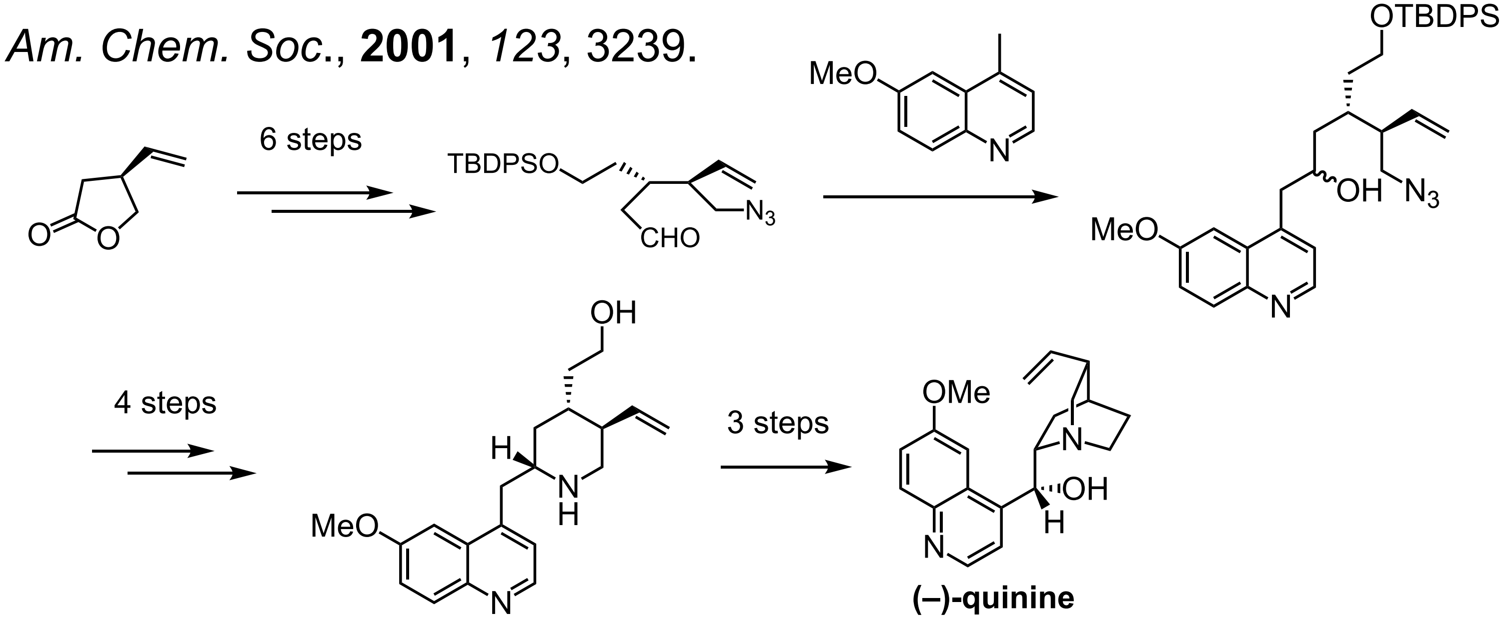
Problem

· Many steps (10~20 pots)
· Control of 4 stereocenters
· Application to analogs syntheses

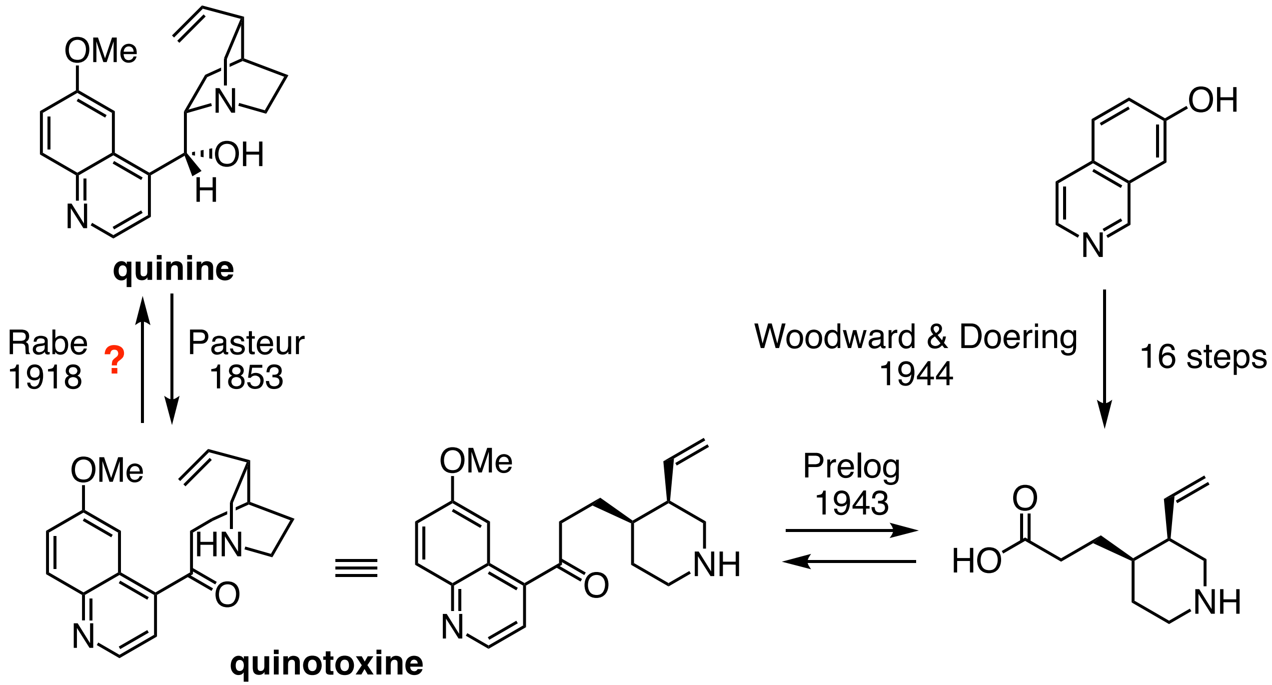
(−)-Quinine



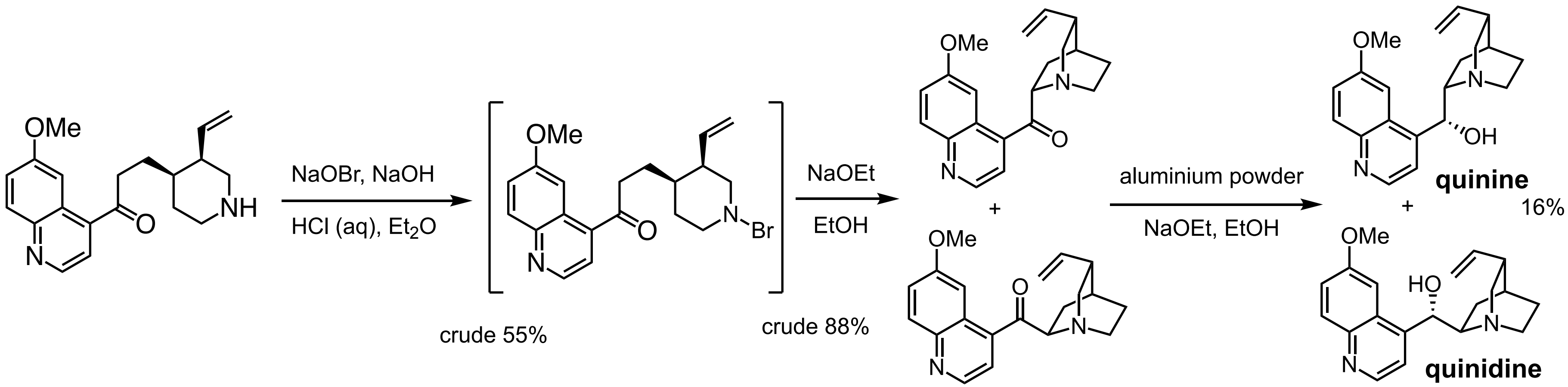
G. Stork, *J. Am. Chem. Soc.*, **2001**, *123*, 3239.



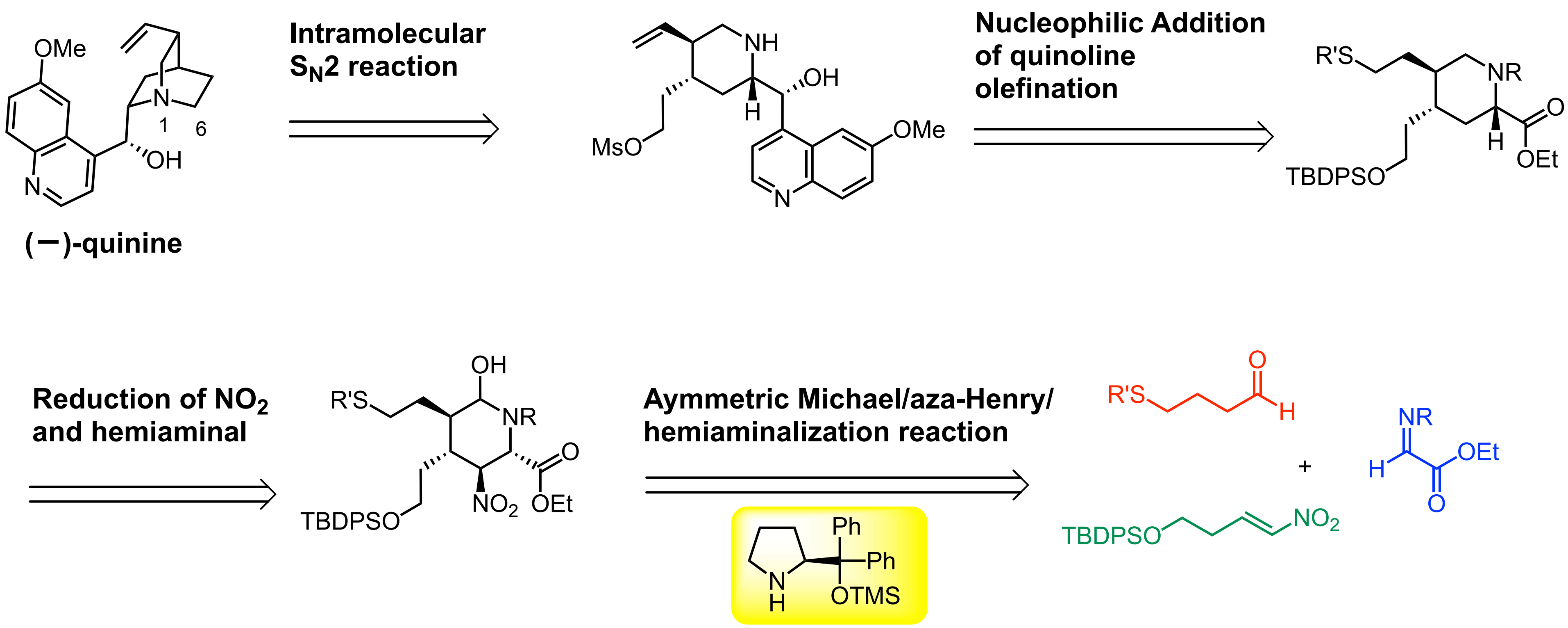
(−)-Quinine

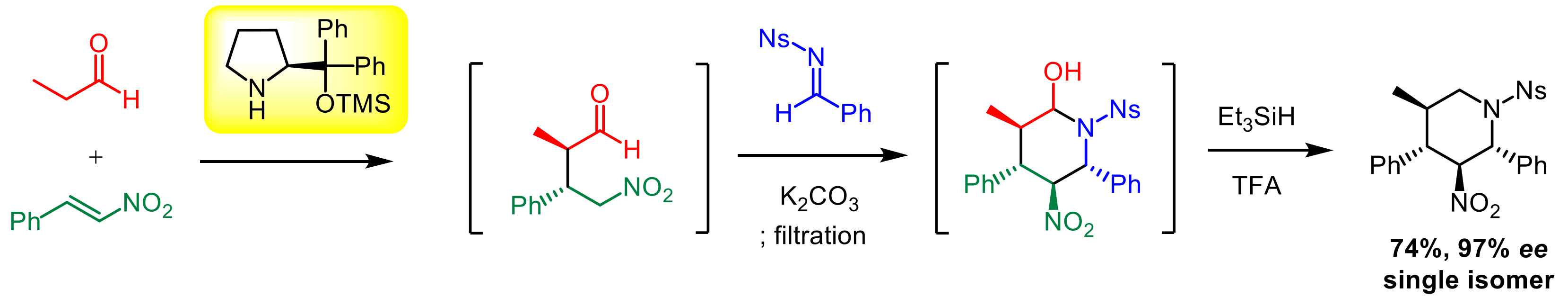


R. M. Williams, *Angew. Chem. Int. Ed.*, **2008**, *47*, 1736.



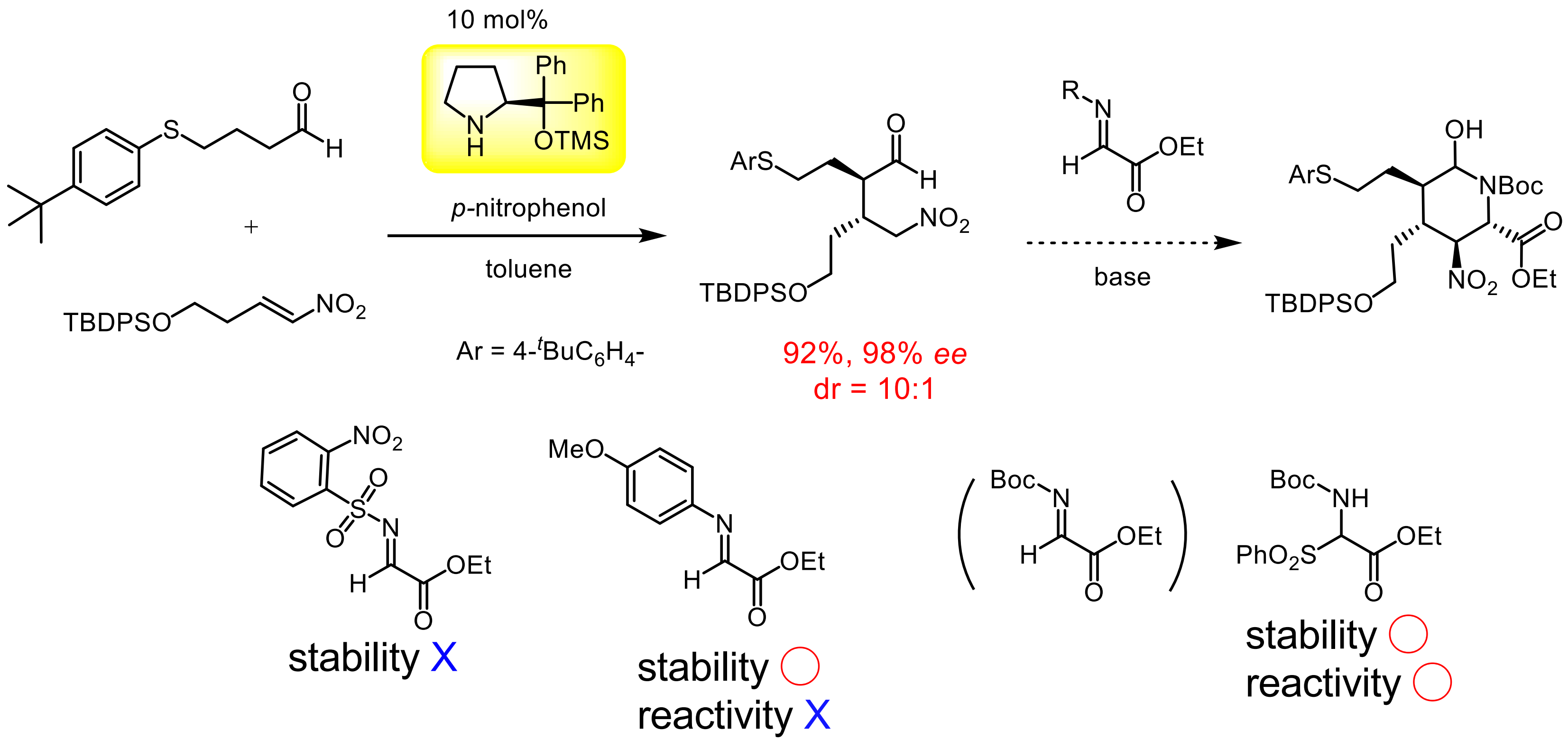
Retrosynthetic analysis

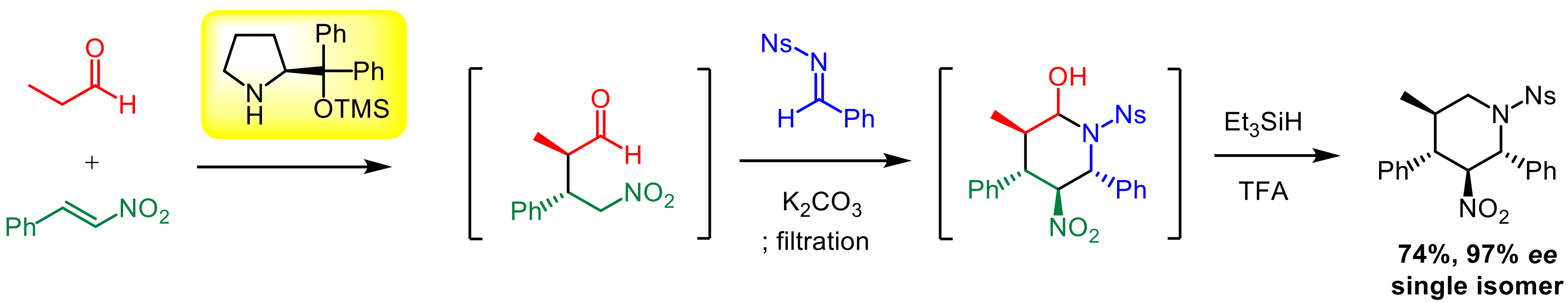




Y. Hayashi *et al.*, *Org. Lett.*, **2010**, *12*, 4588.

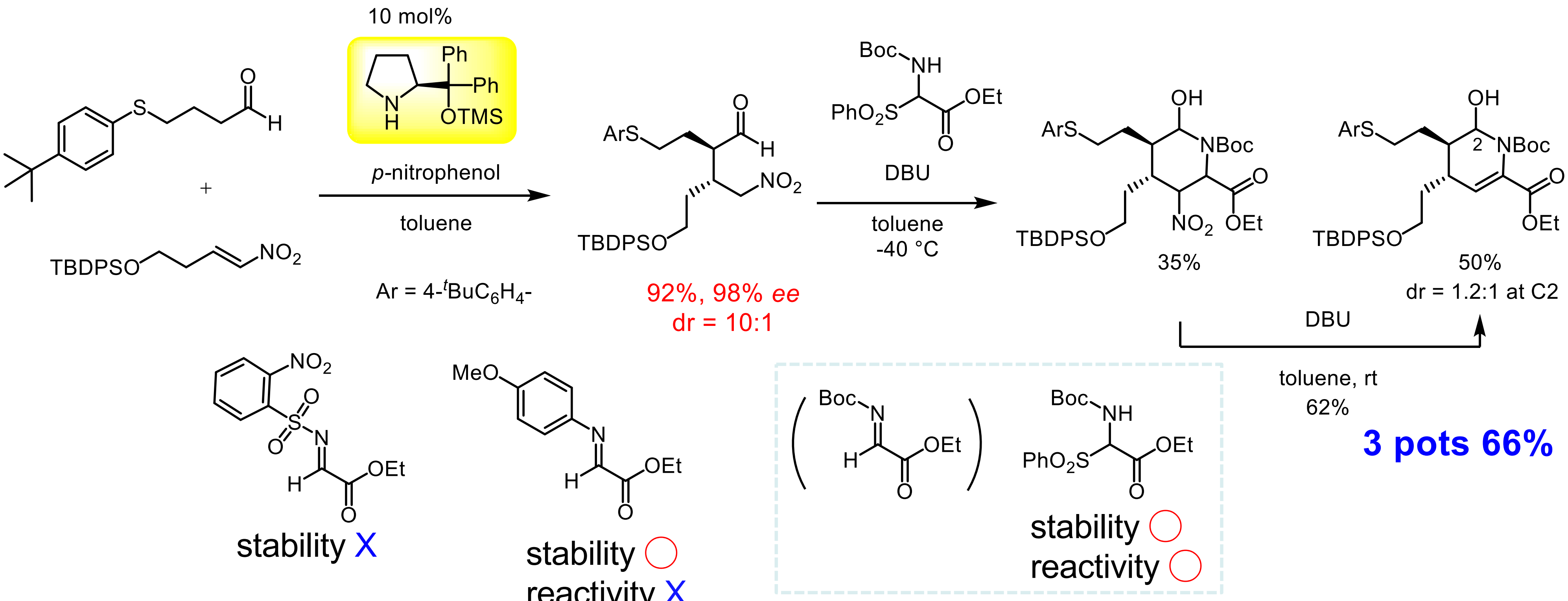
Asymmetric Michael/Aza-Henry/Hemiaminalization Reaction

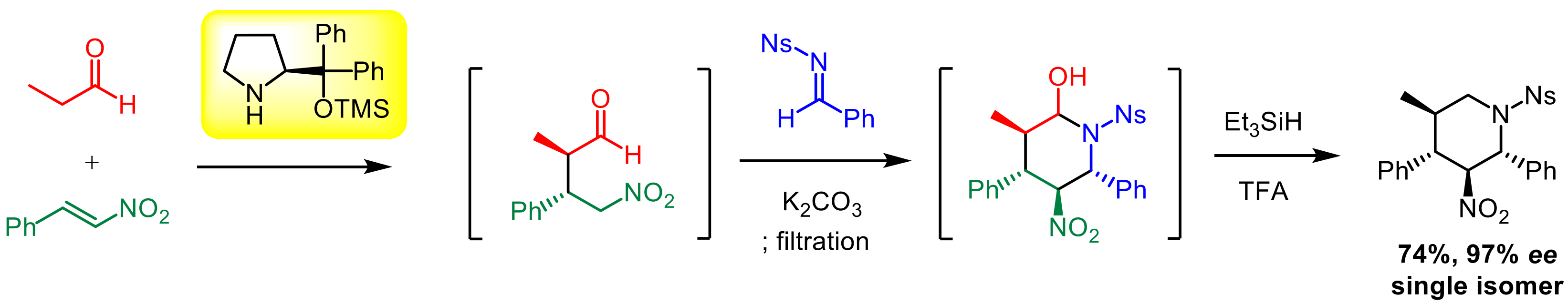




Y. Hayashi *et al.*, *Org. Lett.*, **2010**, *12*, 4588.

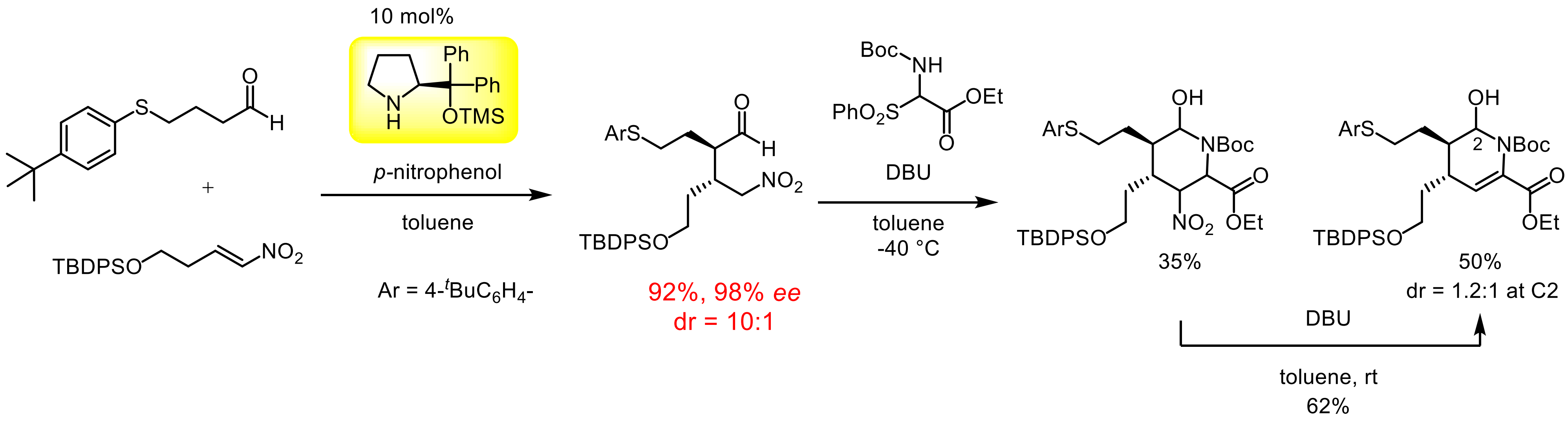
Asymmetric Michael/Aza-Henry/Hemiaminalization Reaction



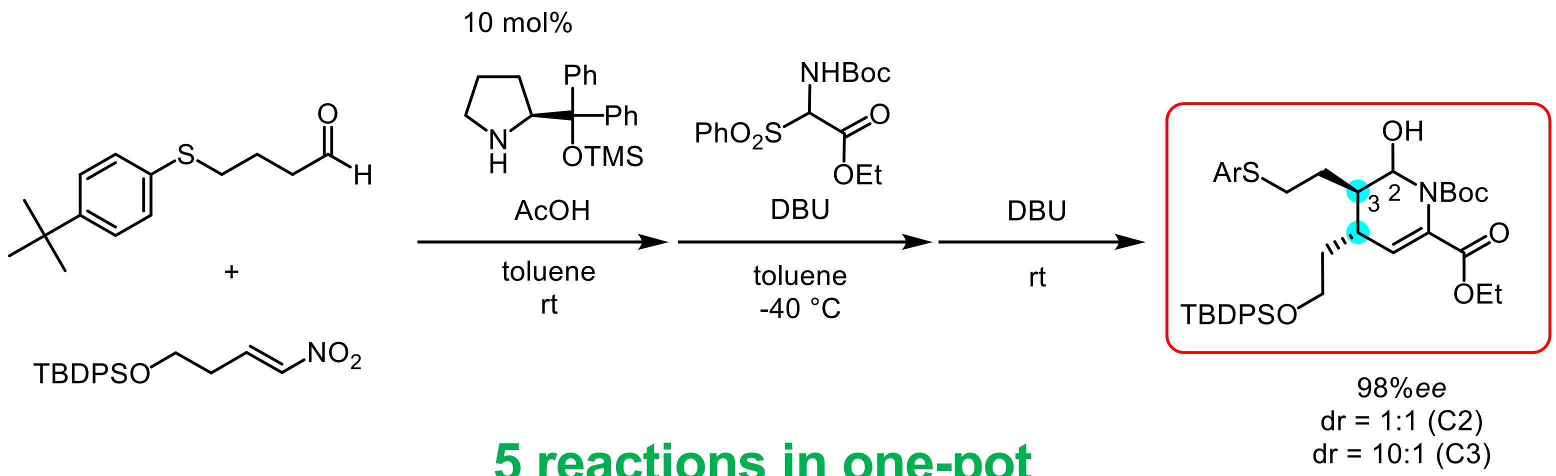


Y. Hayashi *et al.*, *Org. Lett.*, **2010**, *12*, 4588.

One-Pot Reaction of Key Reaction



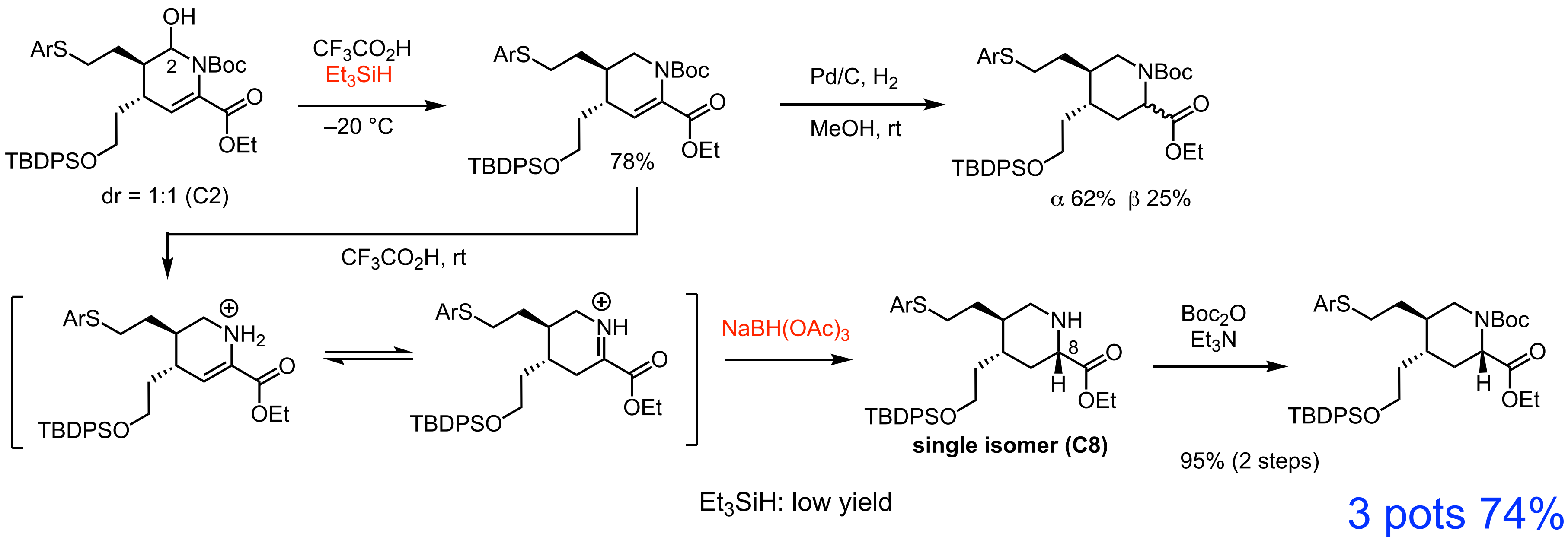
3 pots 66%



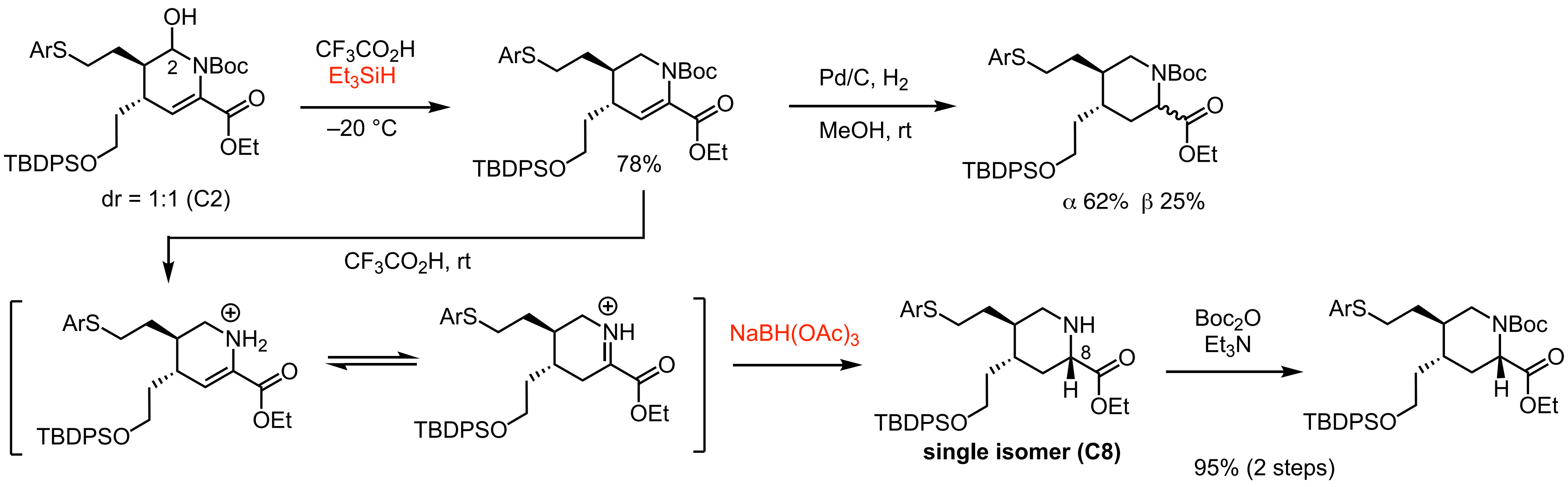
1 pot 70%

5 reactions in one-pot sequence

One-Pot Optimization of Reduction Sequence

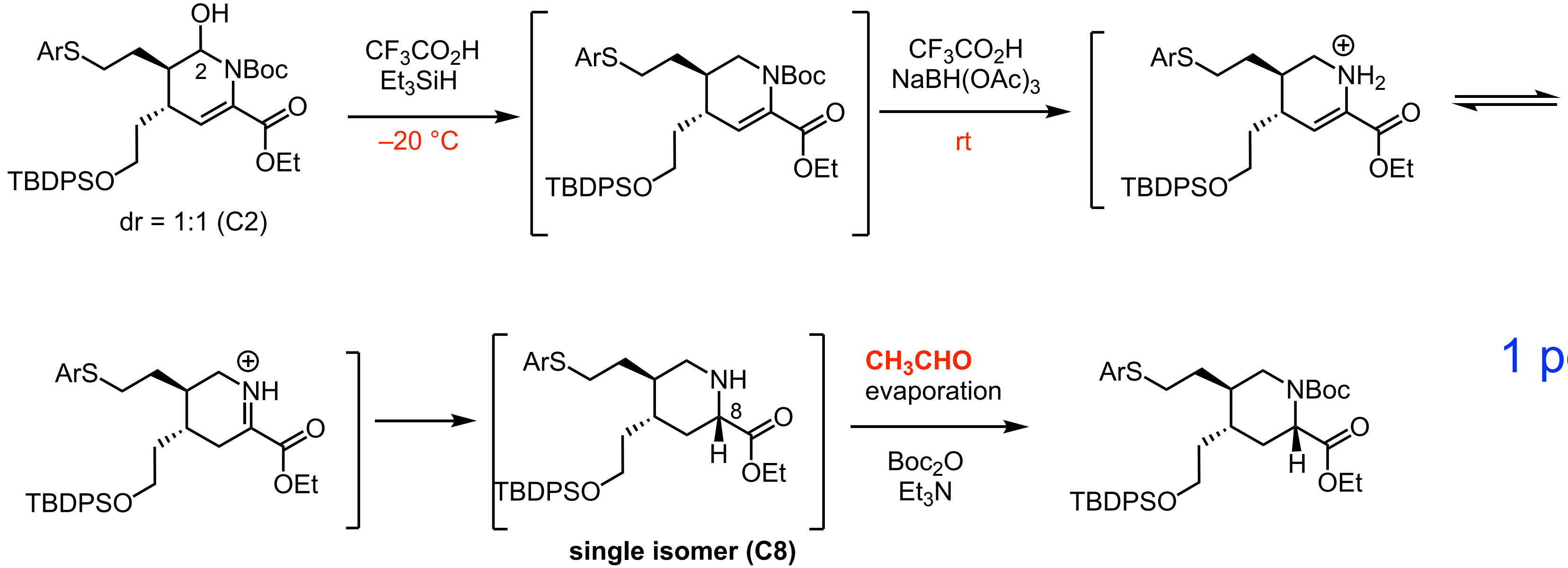


One-Pot Optimization of Reduction Sequence



Et_3SiH: low yield

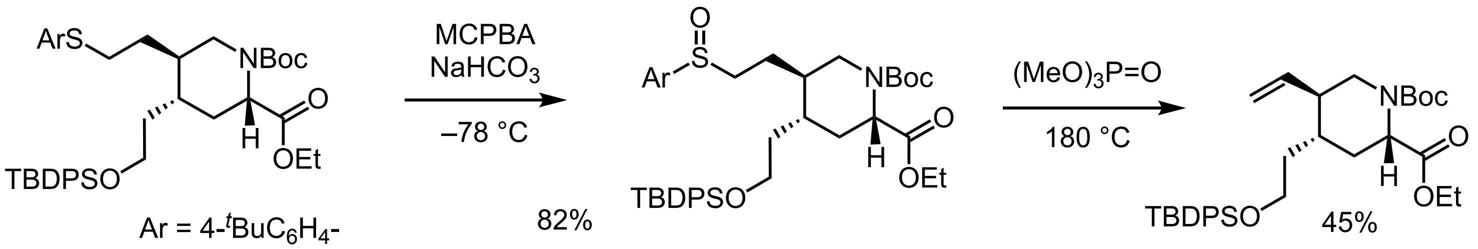
3 pots 74%

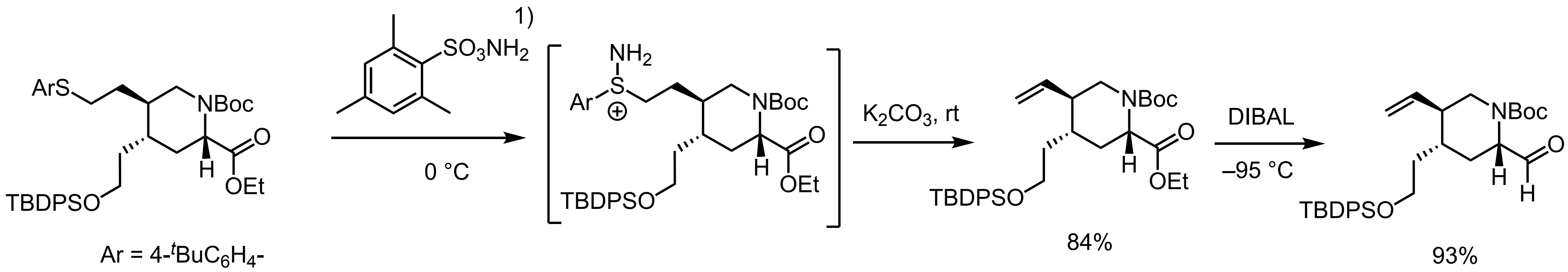


1 pot 86%

5 reactions in one-pot sequence

One-Pot Optimization of Olefination and Reduction

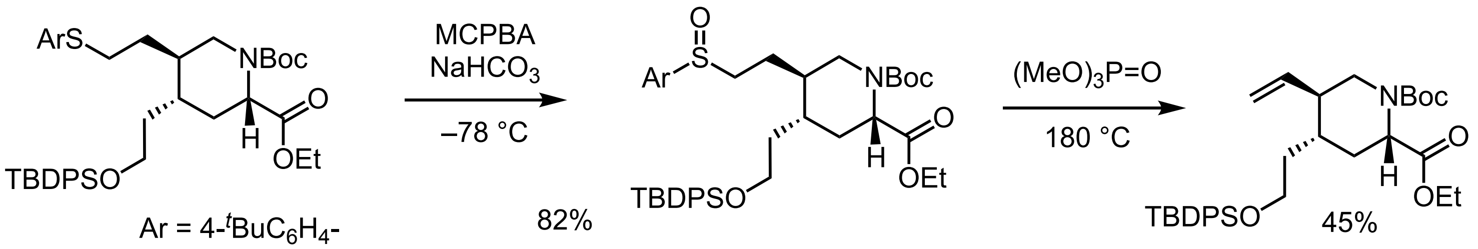


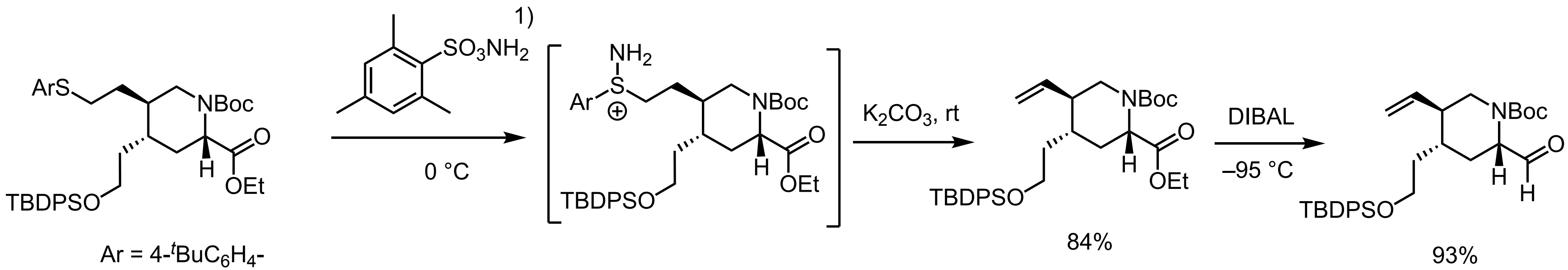


2 pots 78%

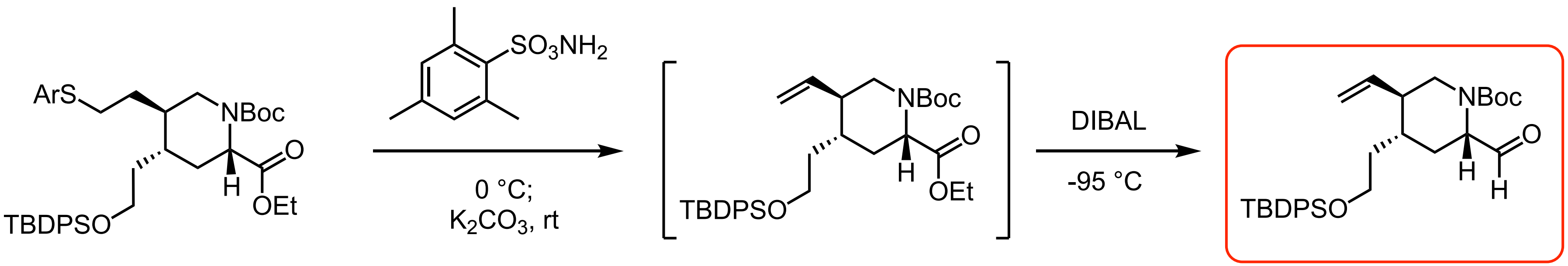
1) J. Matsuo *et al.*, *Org. Lett.* **2006**, *8*, 6095.

One-Pot Optimization of Olefination and Reduction





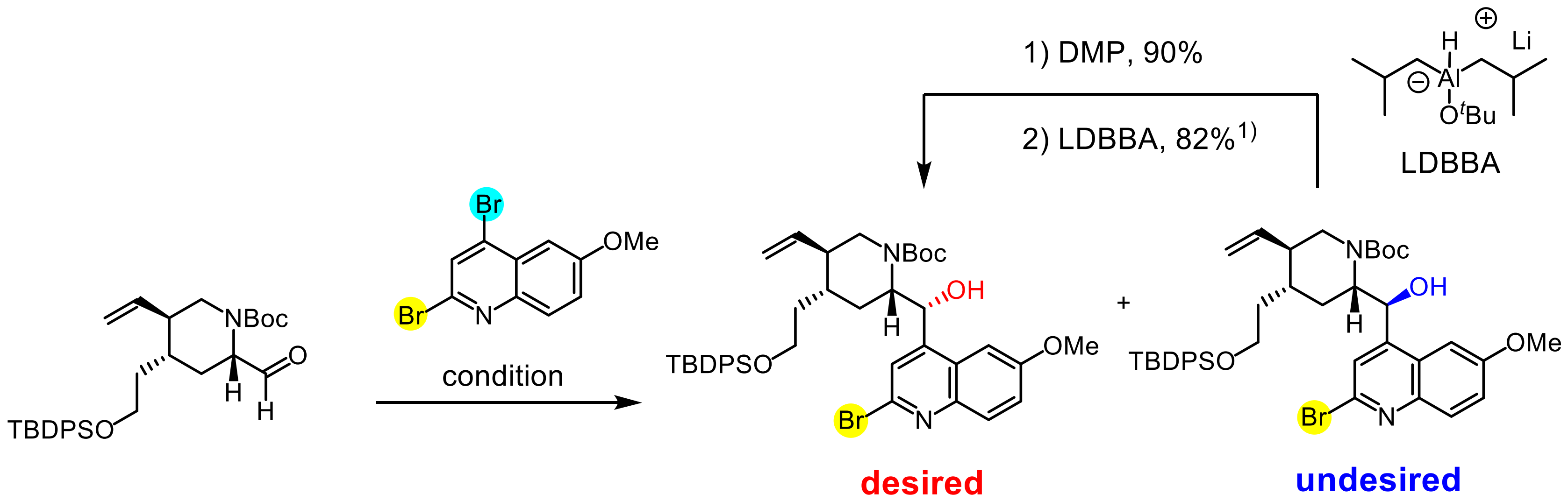
2 pots 78%



1 pot 75%

1) J. Matsuo *et al.*, *Org. Lett.* **2006**, *8*, 6095.

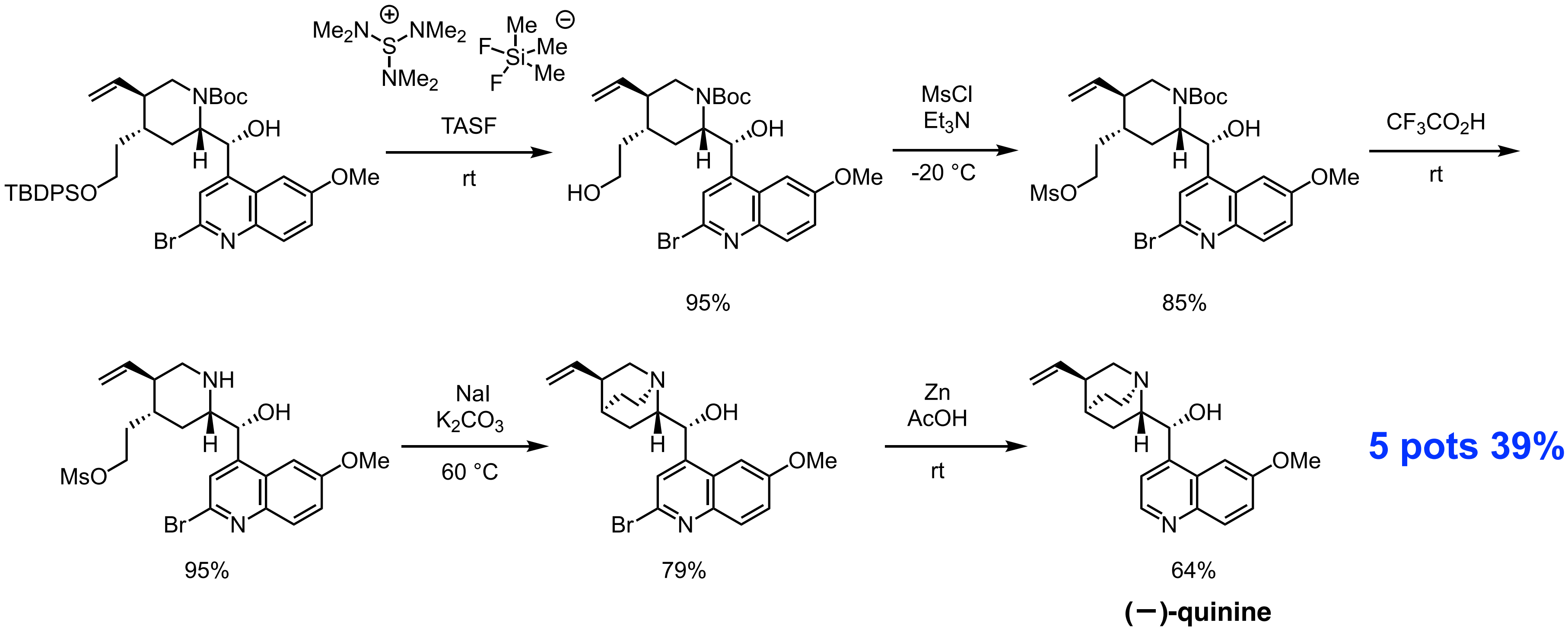
Nucleophilic Addition of Quinoline

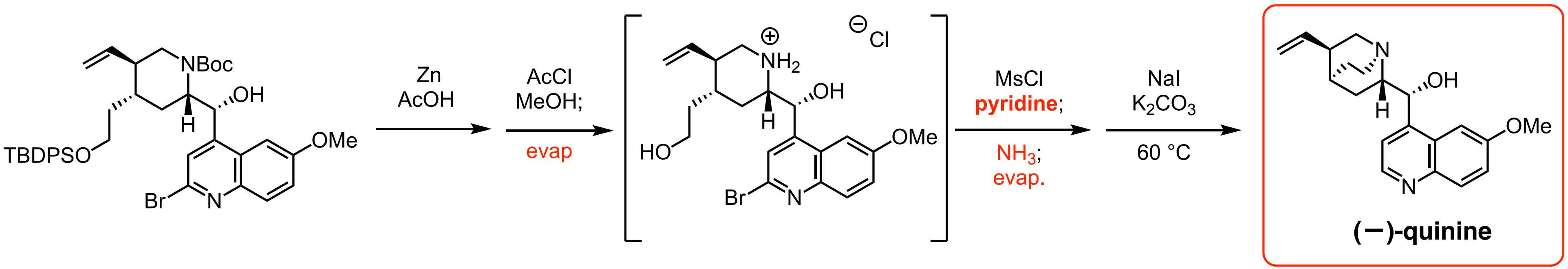


condition	yield	
	desired	undesired
^{i}PrMgCl•LiCl, THF, -20 °C	<5%	<5%
^{i}PrMgCl•LiCl, $CeCl_3$, THF, -20 °C	27%	26%
^{i}PrMgCl•LiCl, $LaCl_3$•2LiCl, THF, -20 °C	41%	44%

1) Y. Qin *et al.*, *Angew. Chem. Int. Ed.* **2018**, *57*, 12299.

Completion of Pot-Economical Synthesis of (−)-Quinine

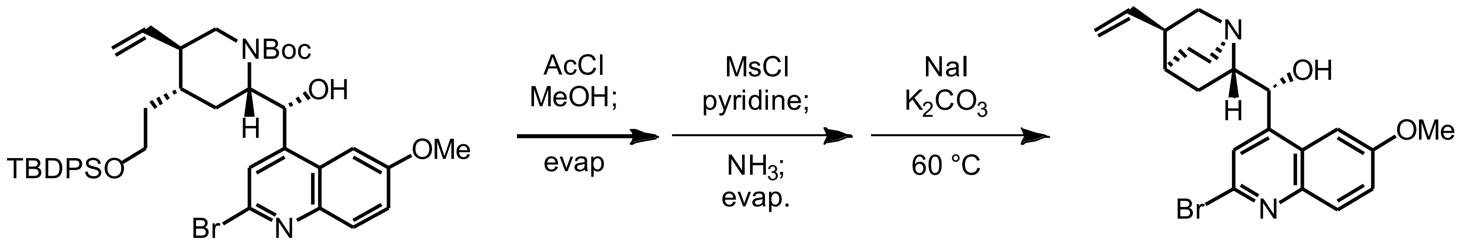




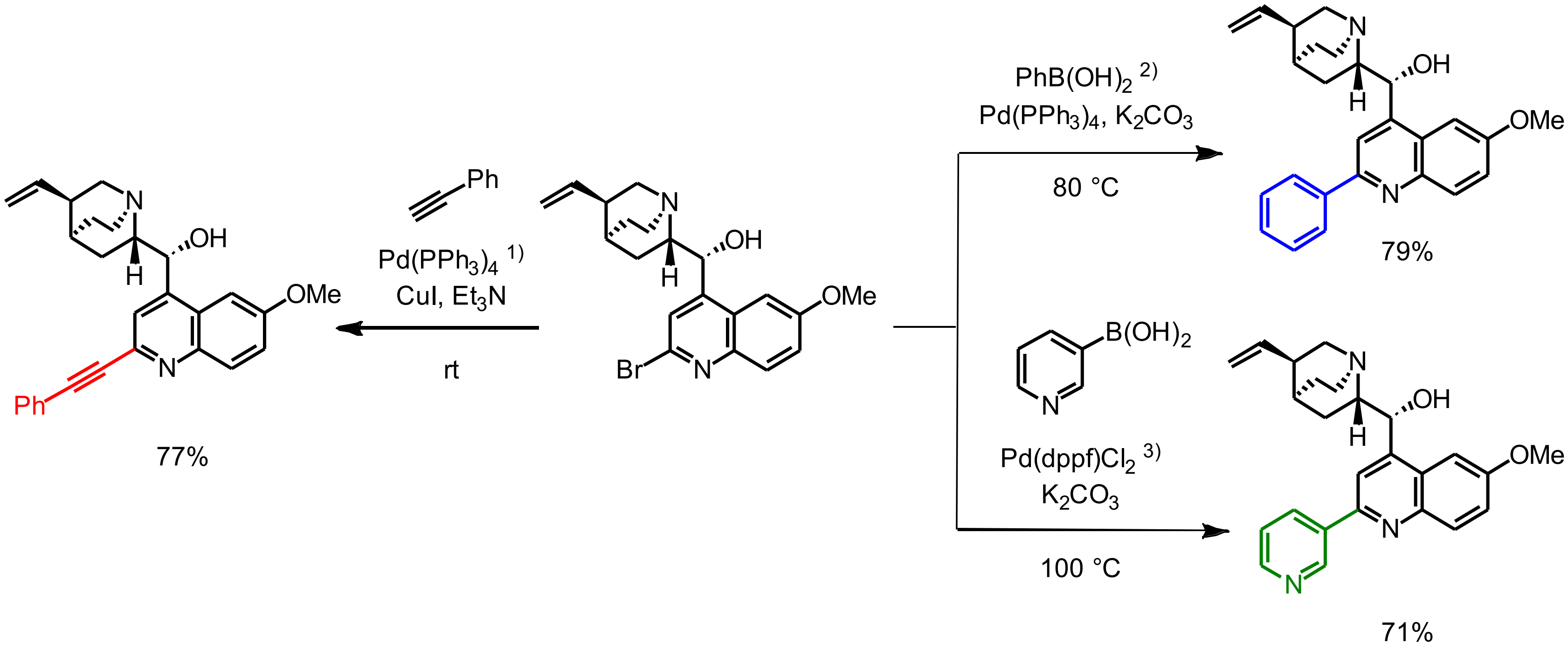
5 reactions in one-pot sequence

1 pot 50%

Synthesis of (−)-Quinine Derivatives

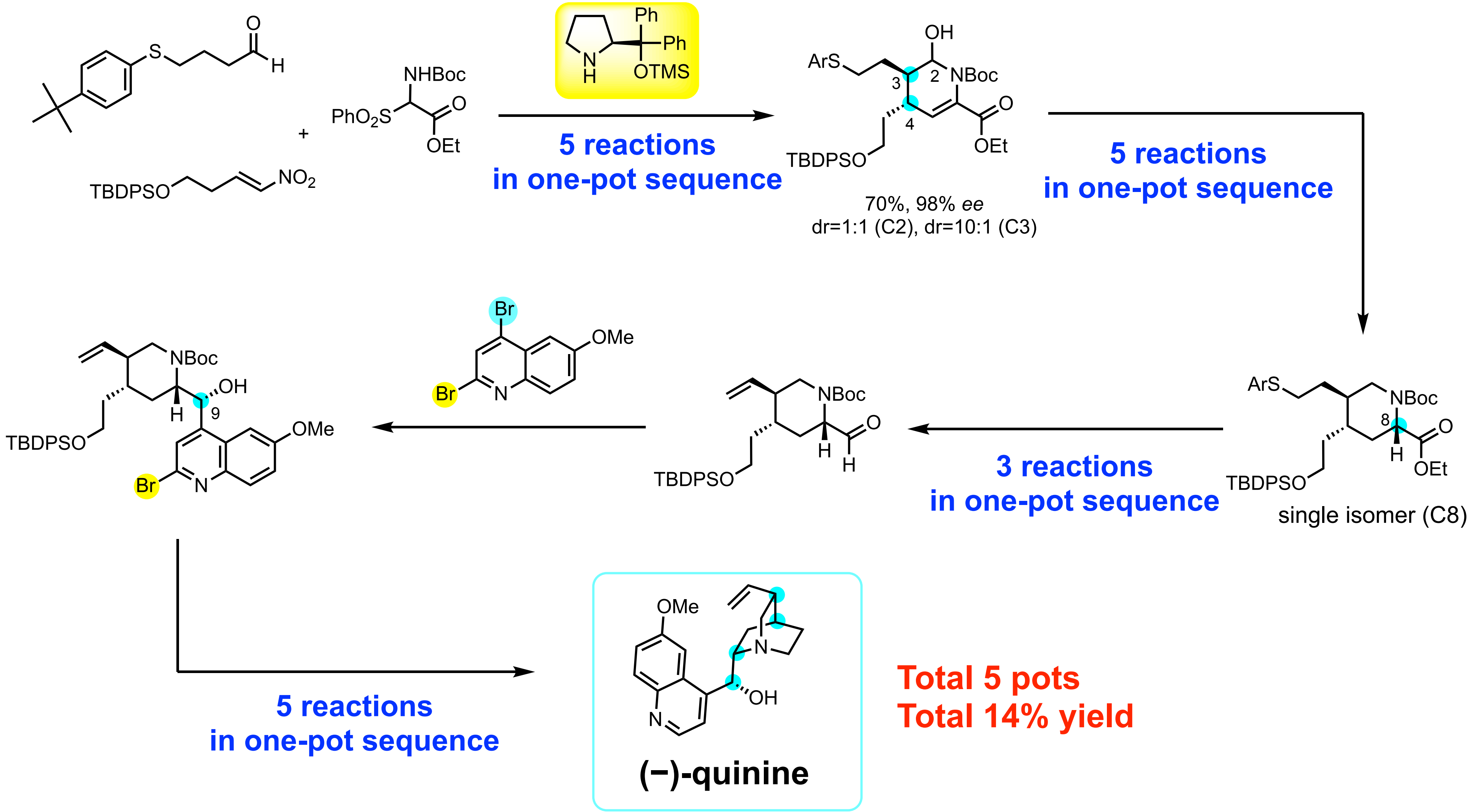


4 reactions in one-pot sequence, 77%



1) P. J. Boratynsky *et al*., *ChemistrySelect*, **2018**, *3*, 936.
2) Q.-W. Meng *et al*., *Org. Biomol. Chem*., **2019**, *17*, 7938. 3) S. Cocklin *et al* *Molecules* **2019**, *24*, 1581.

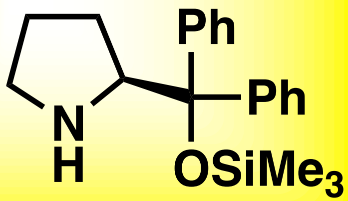
Summary of (–)-quinine

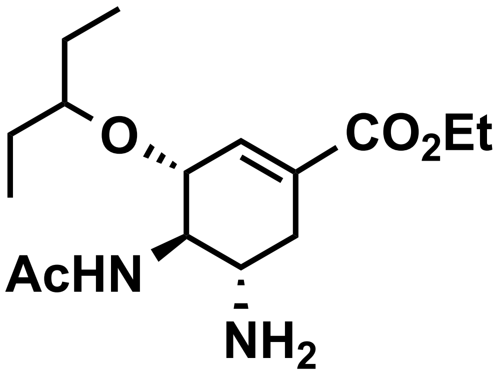


Shortest pot synthesis of (−)-quinine with controlling 4 stereocenters

submitted.

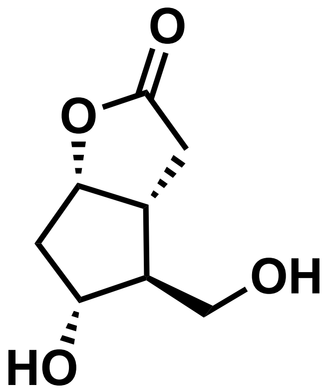
Summary: Pot Economy and Time Economy





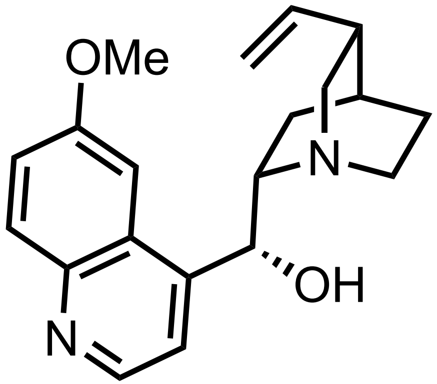
(–)-Oseltamivir

60 minutes



Corey lactone

152 minutes



(–)-quinine