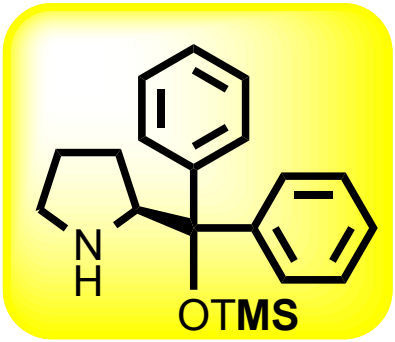
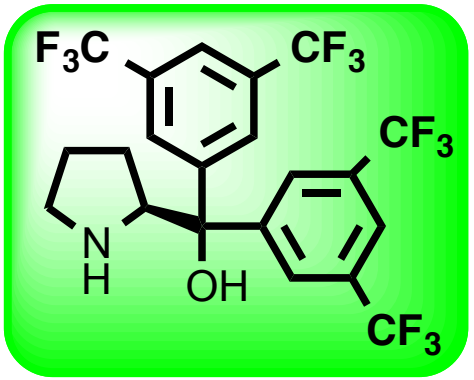
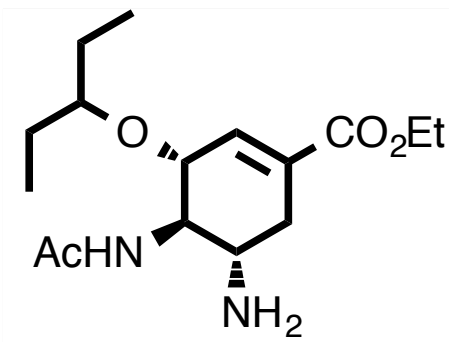
Pot-Economy in Total Synthesis

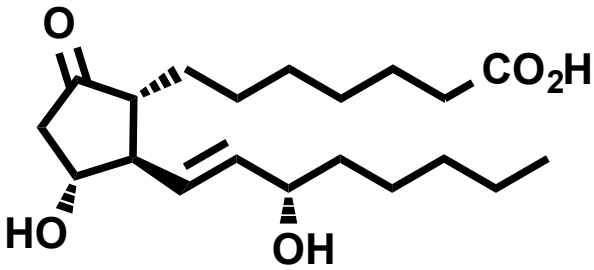


Tohoku University
Yujiro Hayashi





(-)-oseltamivir



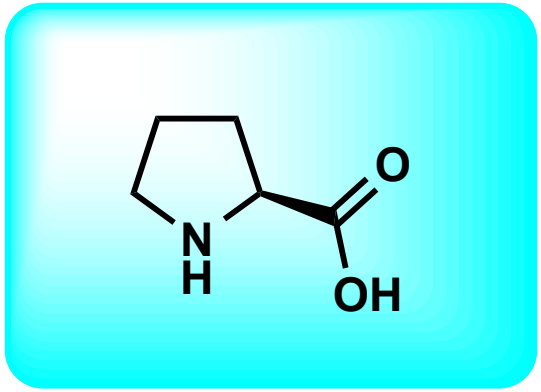
Prostaglandin E_1 (PGE_1)

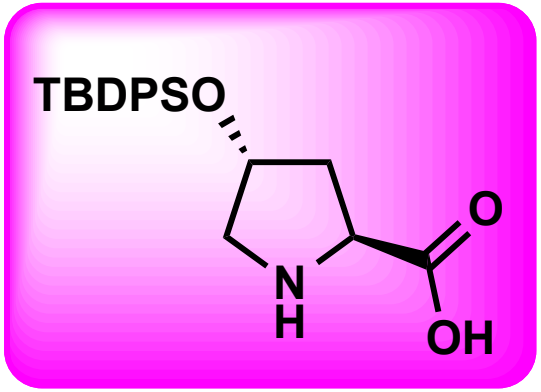
Organocatalysis

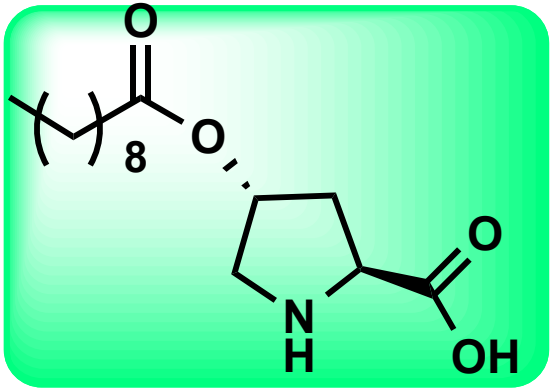
Product is free from the contamination of metal.

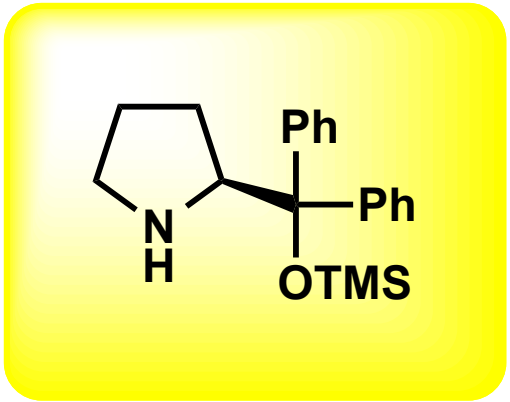
Exclusion of water and air is not necessary.

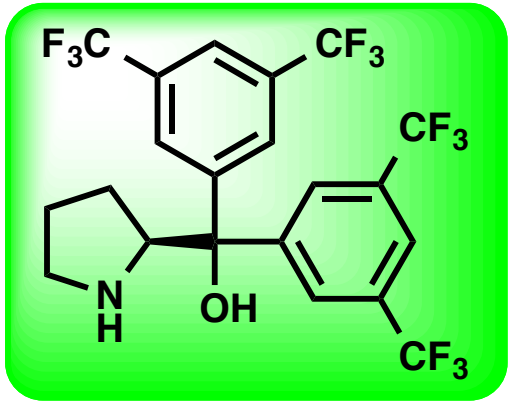
Most of the ligands are non-toxic.



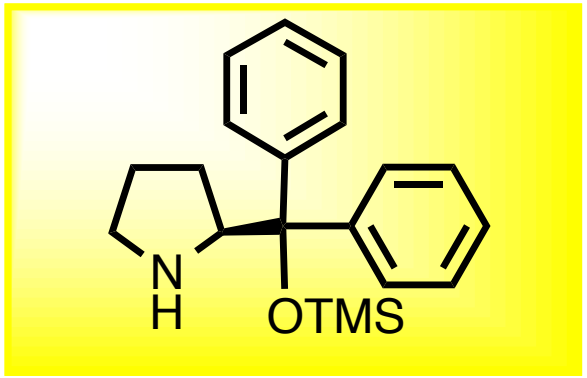




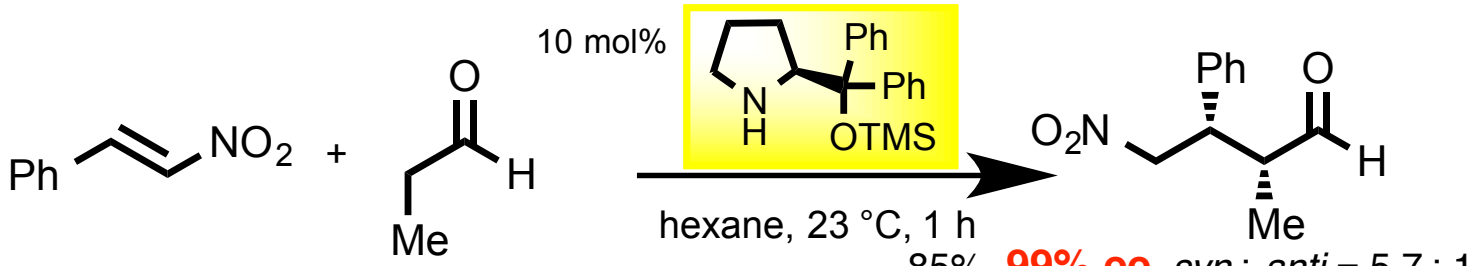




Jorgensen-Hayashi Catalyst

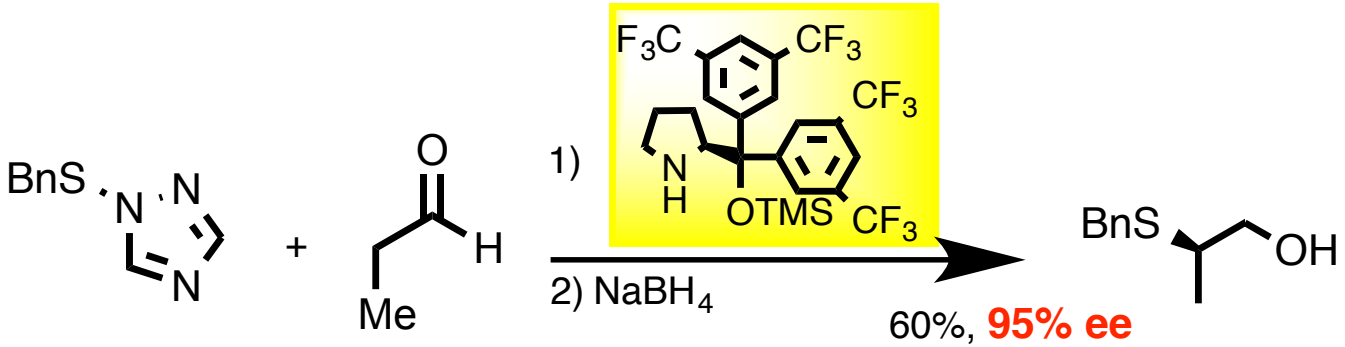


TMS = Me_3Si-



85%, **99% ee**, *syn* : *anti* = 5.7 : 1

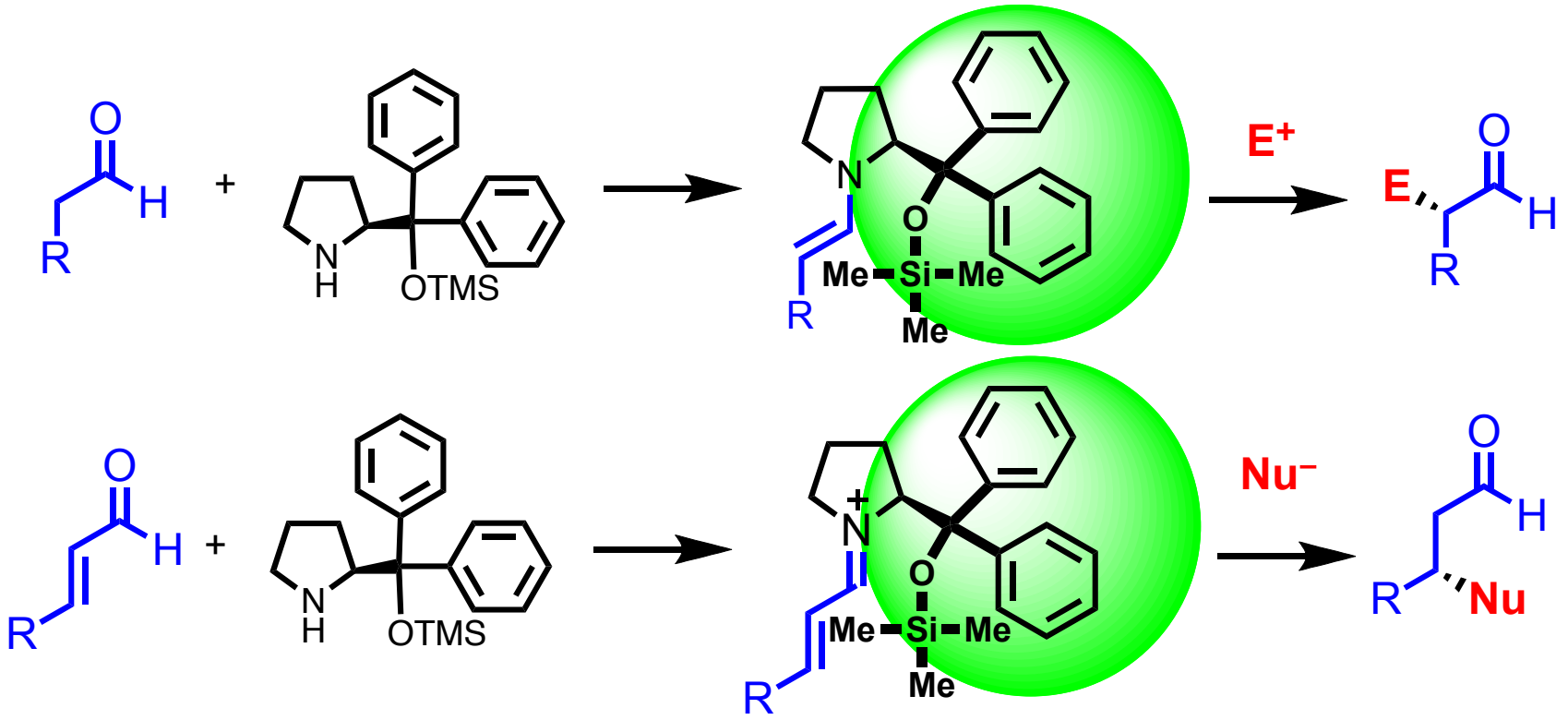
Y. Hayashi, *et al., Angew. Chem. Int. Ed.*, **44**, 4112 (2005).

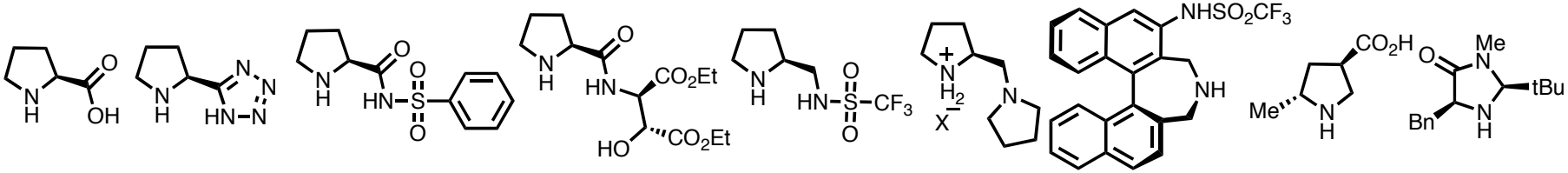


60%, **95% ee**

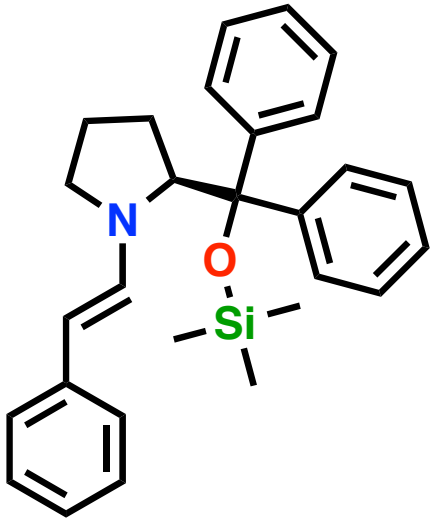
K. A. Jorgensen, *et al.*, *Angew. Chem. Int. Ed.*, **44**, 794 (2005).

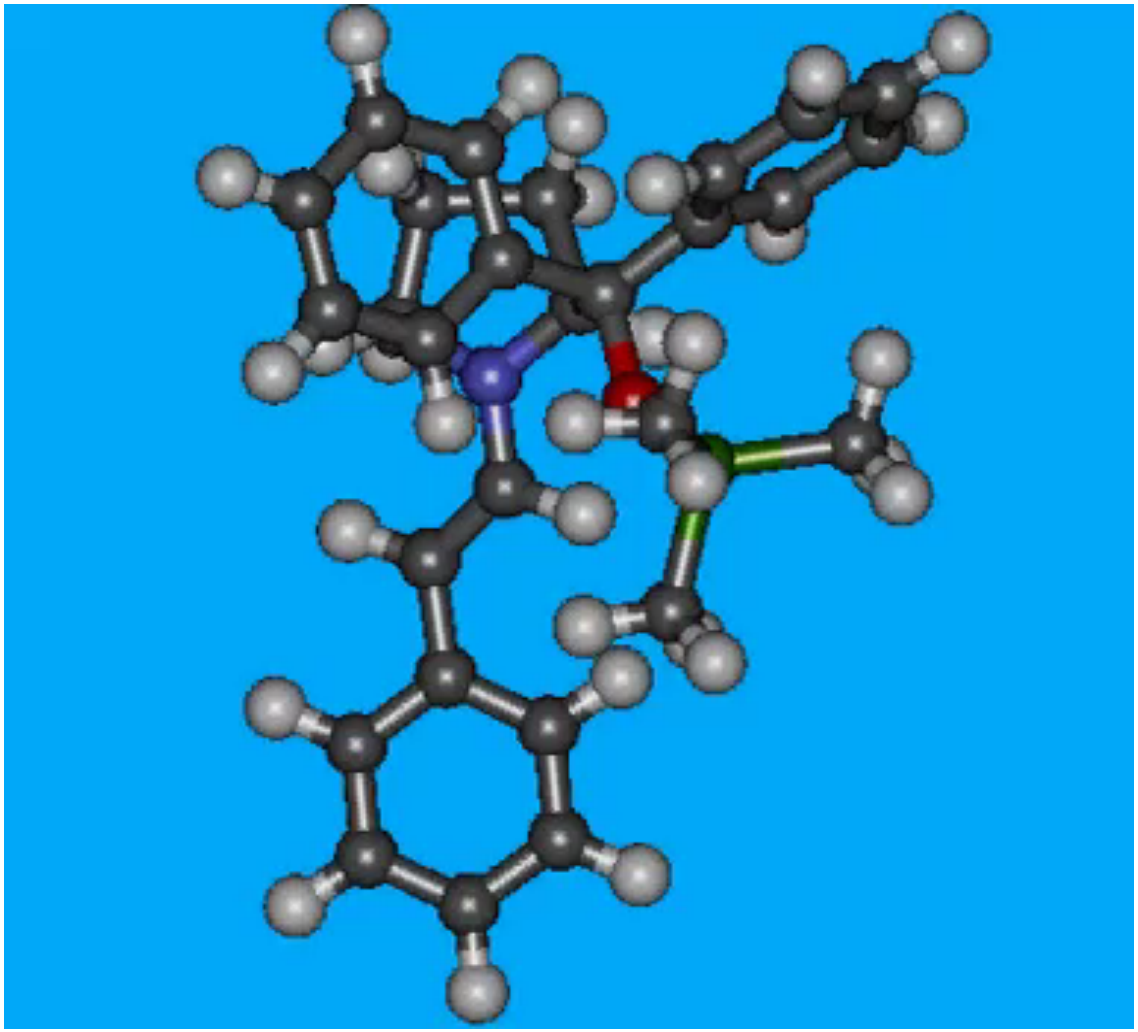
Jorgensen-Hayashi Catalyst





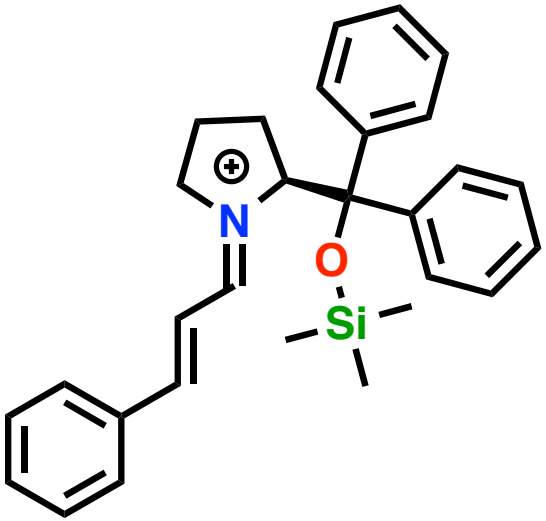
Conformation of Enamine

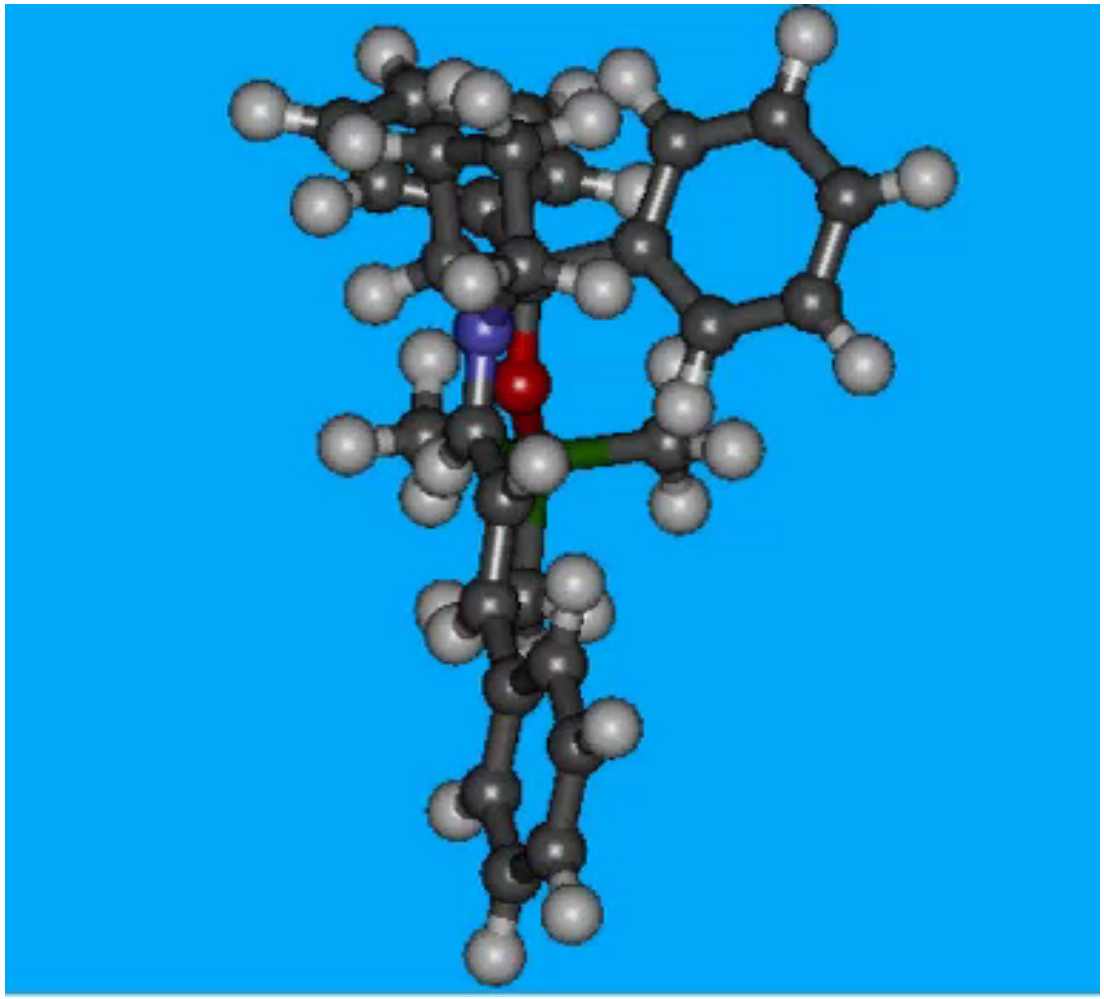




Y. Hayashi, D. Seebach, T. Uchimaru; *Chem. Eur. J.,* ASAP.

Conformation of Iminium ion

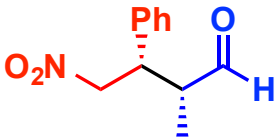




Y. Hayashi, D. Seebach, T. Uchimaru; *Chem. Eur. J.*, ASAP.

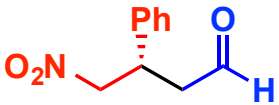
Reactions developed by our group

Michael



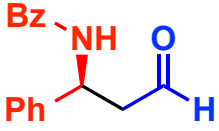
99% *ee*

Michael



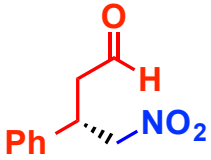
96% *ee*

Mannich



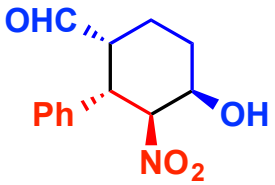
98% *ee*

Michael



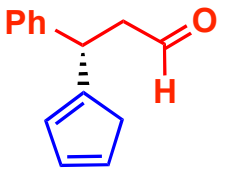
95% *ee*

Domino



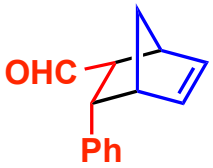
99% *ee*

Michael



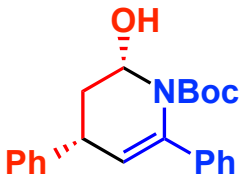
92% *ee*

Diels-Alder

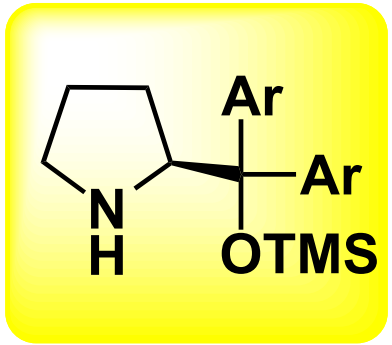


97% *ee*

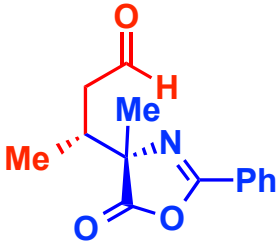
Aza [3+3]



94% *ee*

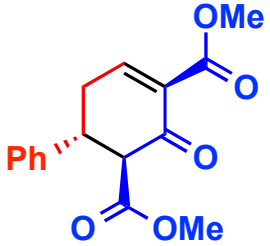


Michael



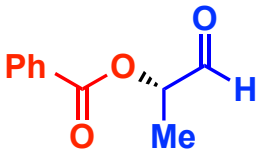
97% *ee*

Carbo [3+3]



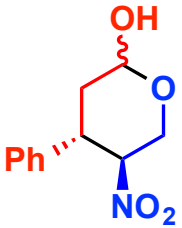
95% *ee*

Oxidation



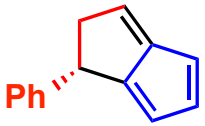
92% *ee*

Michael



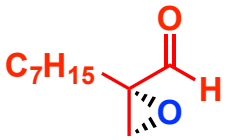
95% *ee*

Domino



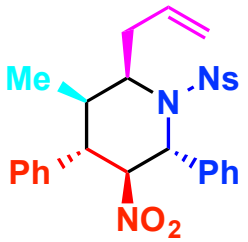
95% *ee*

Epoxidation



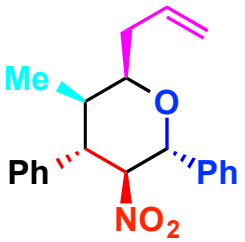
94% *ee*

Domino



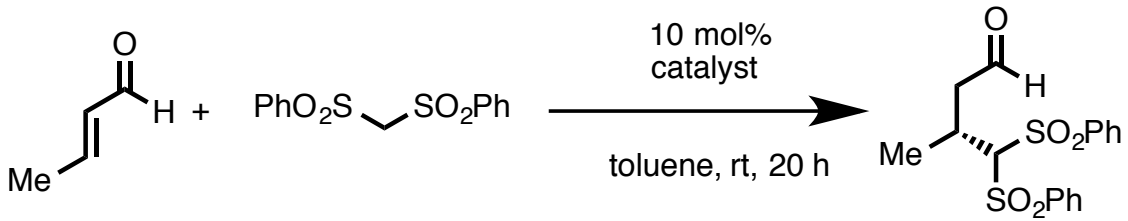
99% *ee*

Domino

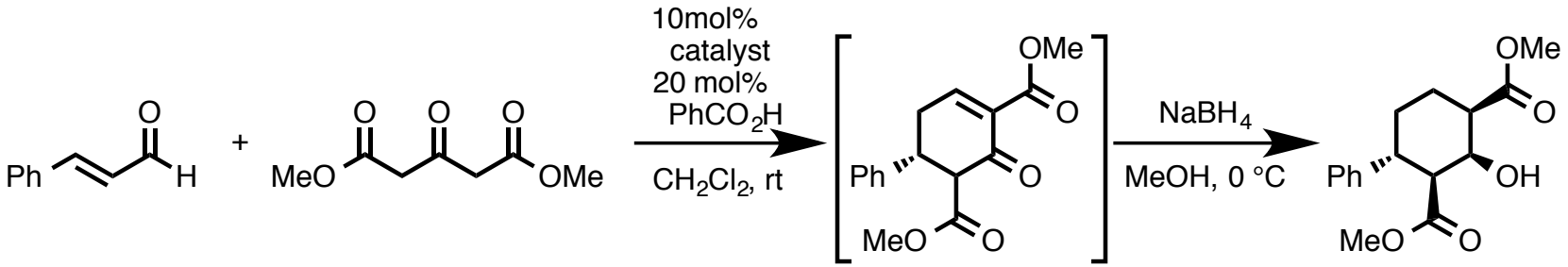


99% *ee*

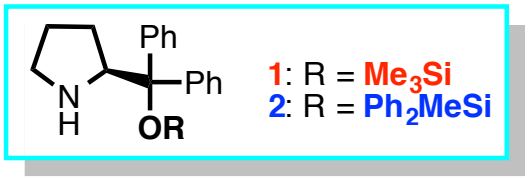
Type A: Iminium ion as an intermediate/ Michael type reaction

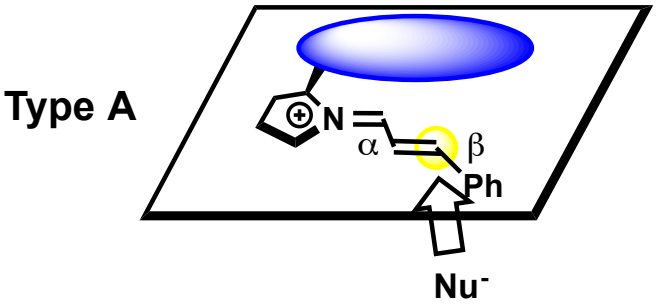


Catalyst	Temperature/ °C	Yield/%	ee/%
1	23	90	71
2	23	88	83
2	0	94	90



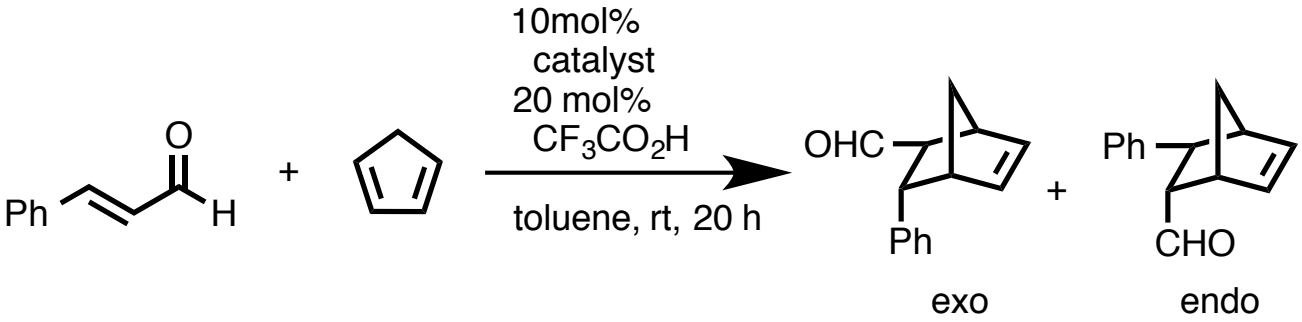
Catalyst	Time/min	Yield/%	ee/%
1	50	79	91
2	80	76	95



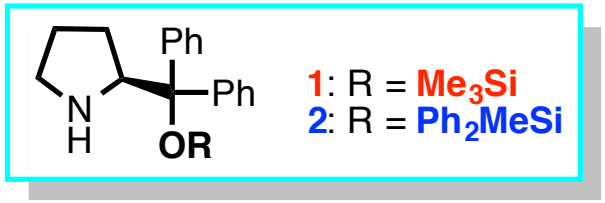


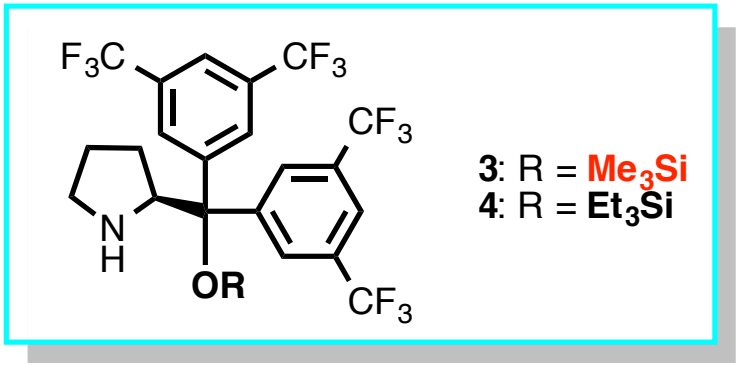
There is a large effect of the substituent of silyl group on the enantioselectivity.

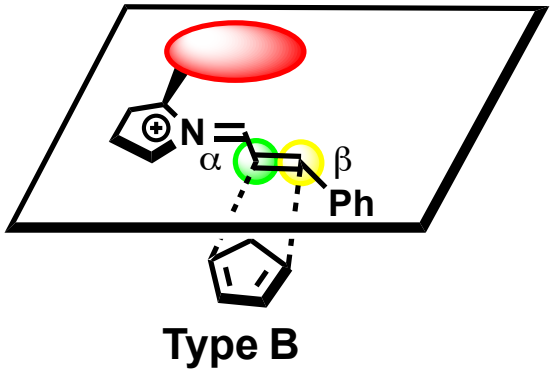
Type B: Iminium ion intermediate/ Diels-Alder reaction



Catalyst	Yield/%	exo:endo	ee/%
1	14	80:20	83
2	16	77:23	83
3	86	84:16	95
4	80	85:15	97

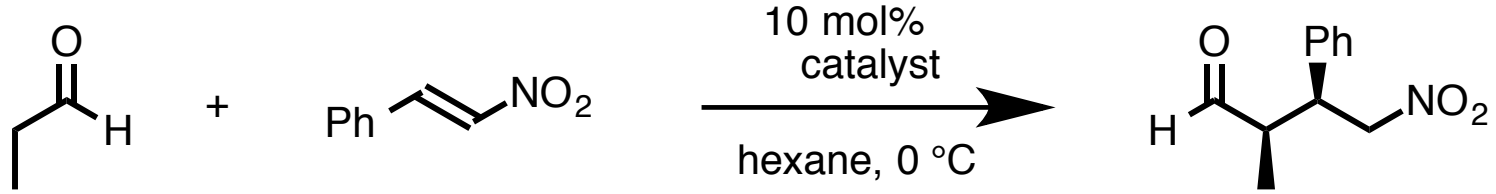




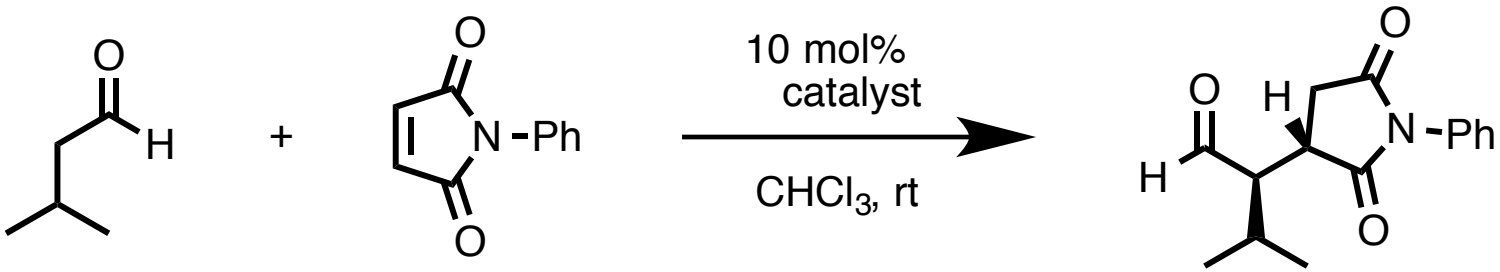


There is small effect of the substituent of silyl group on the enantioselectivity.

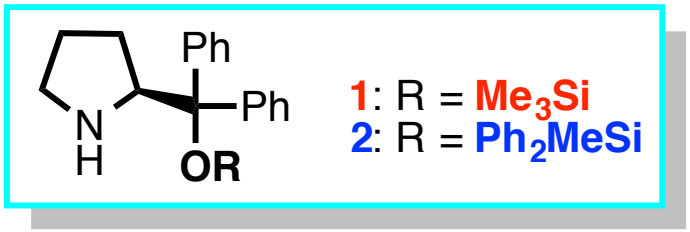
Type C: Enamine intermediate



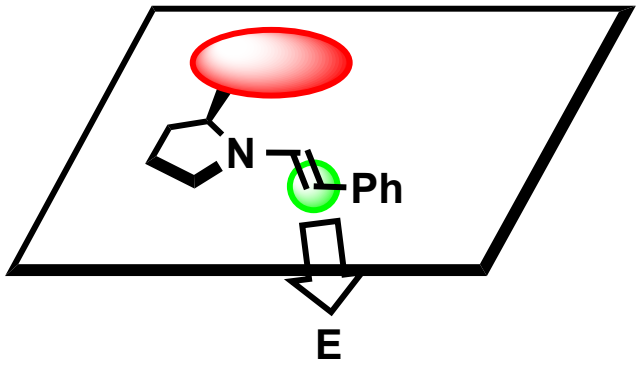
cat **1**	5 h	syn:anti = 16:1	85%	99% ee
cat **2**	24 h	syn:anti = >20:1	89%	99% ee



cat **1**	24 h	anti:syn = 8:1	70%	99% ee
cat **2**	24 h	syn:anti = 5:1	38%	99% ee

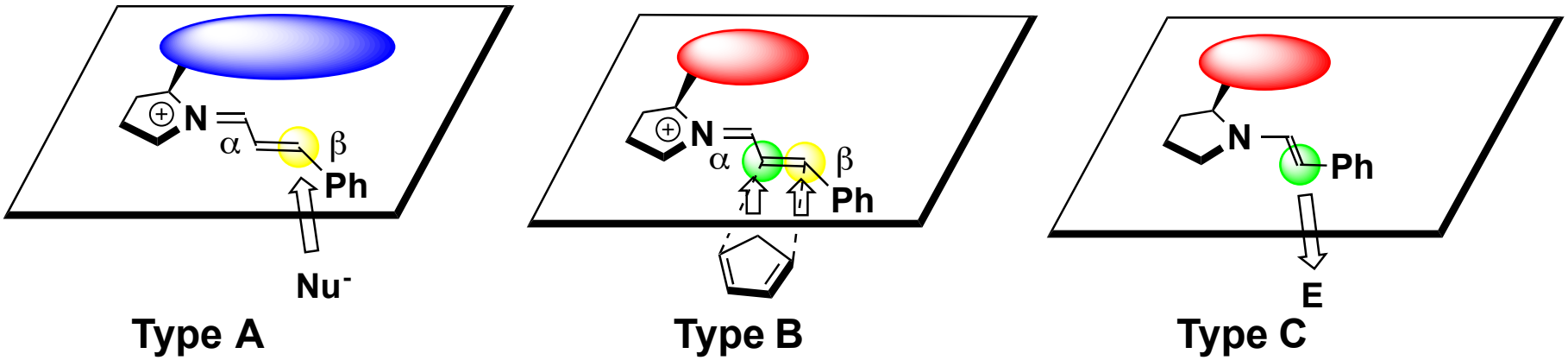


Type C



There is no effect of the substituent of silyl group on the enantioselectivity.

Three types of the reaction

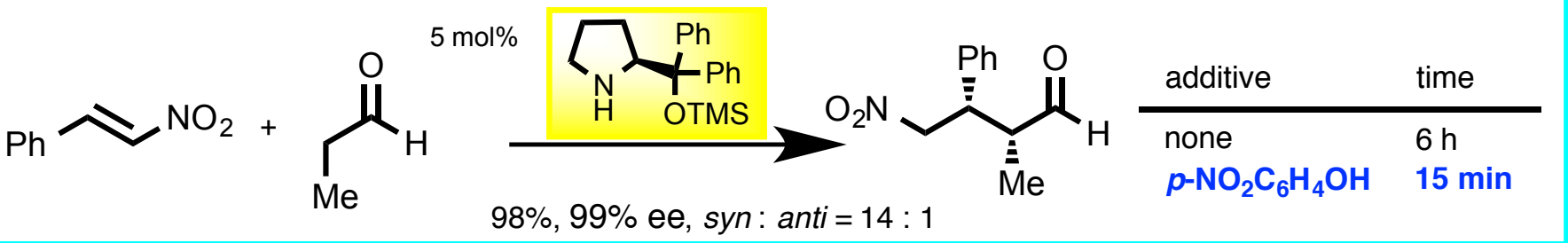


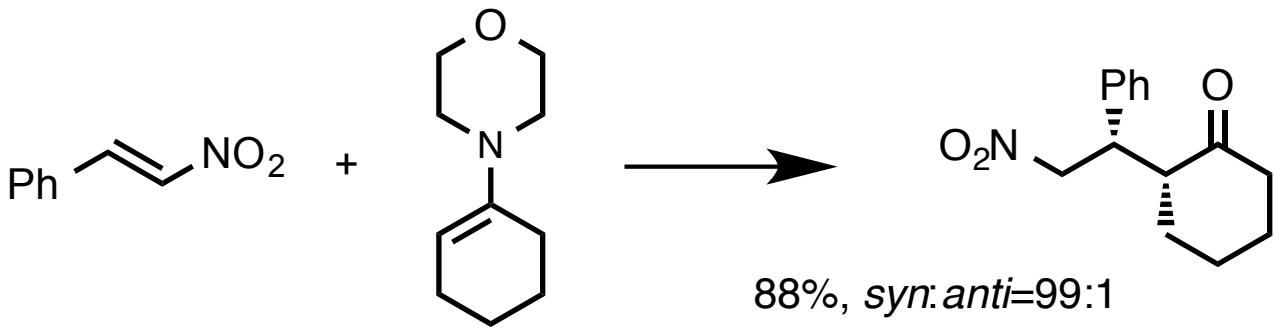
Type A: Bulkier silyl substituent affords higher enantioselectivity.
Type B and **C**: Small TMS affords excellent enantioselectivity.

In the bulky silyl substituent, the reactivity decreases because of the slow formation of iminium ion, which is accelerated by acid.

Y. Hayashi, D. Seebach, T. Uchimaru; *Chem. Eur. J.,* ASAP.

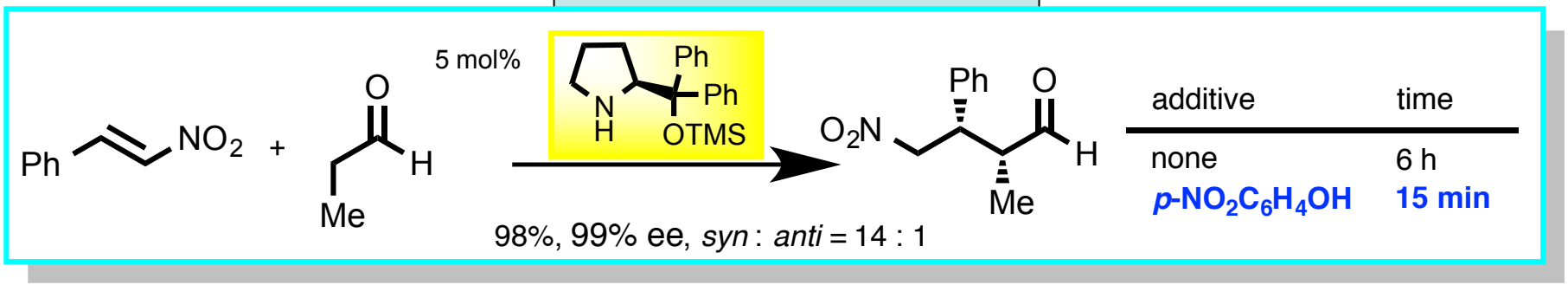
Michael reaction ?

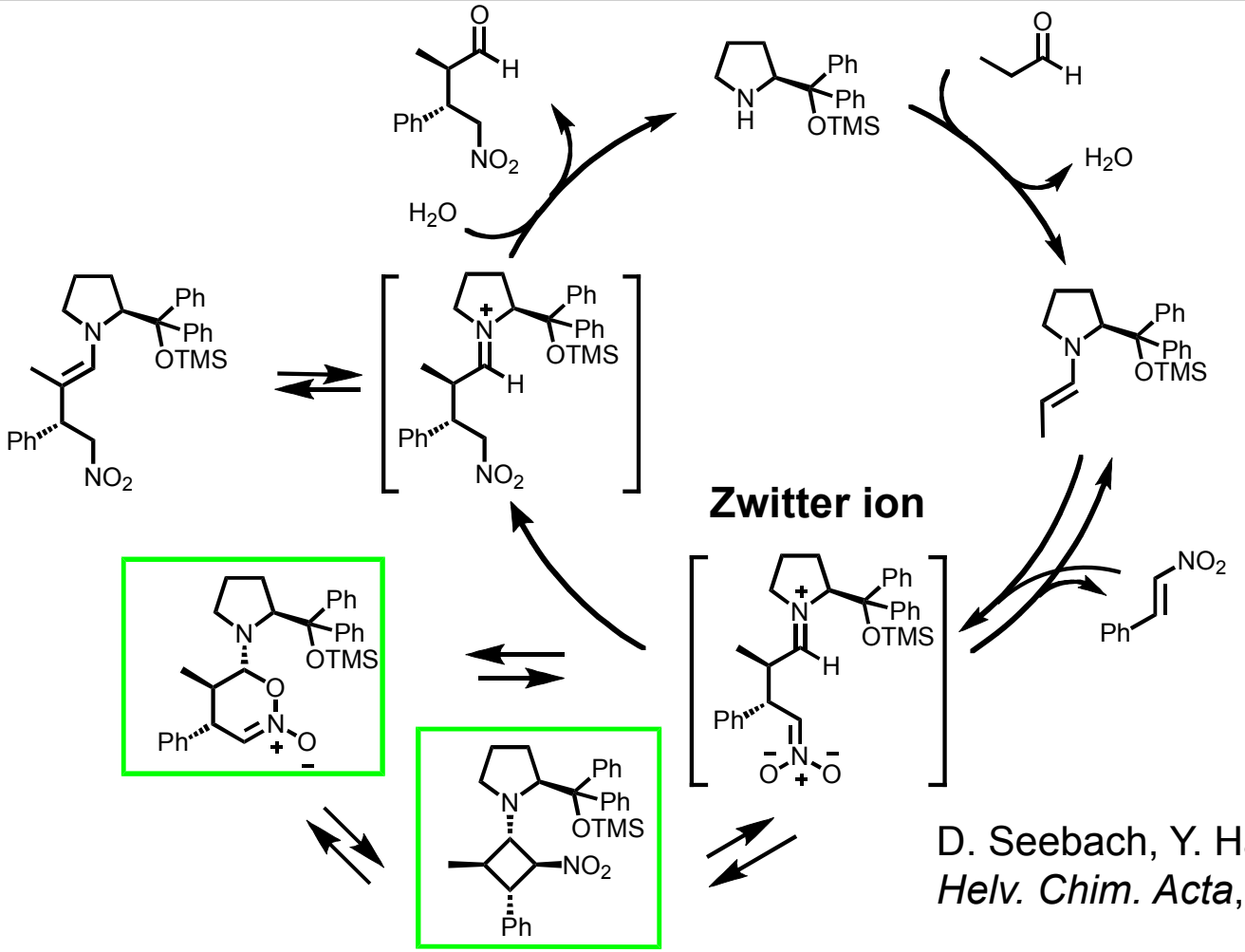




D. Seebach, *et al.*, *Helv. Chim. Acta.*, **64**, 1413 (1981).

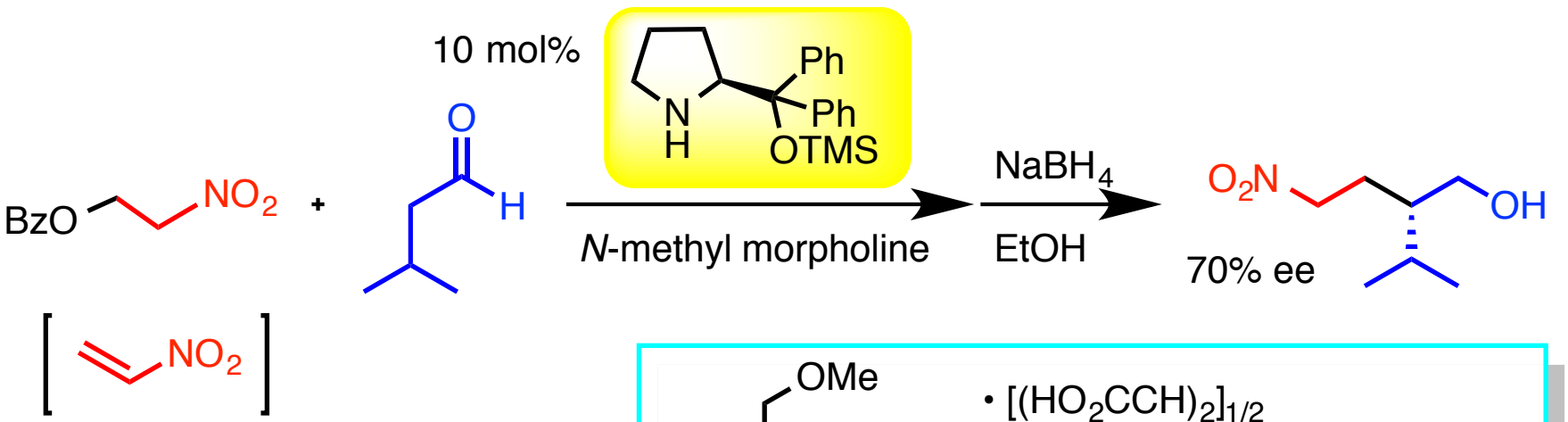
Michael reaction ?





D. Seebach, Y. Hayashi, *et al.*,
Helv. Chim. Acta, **2013**, *96*, 799.

Novartis' synthesis of Aliskiren



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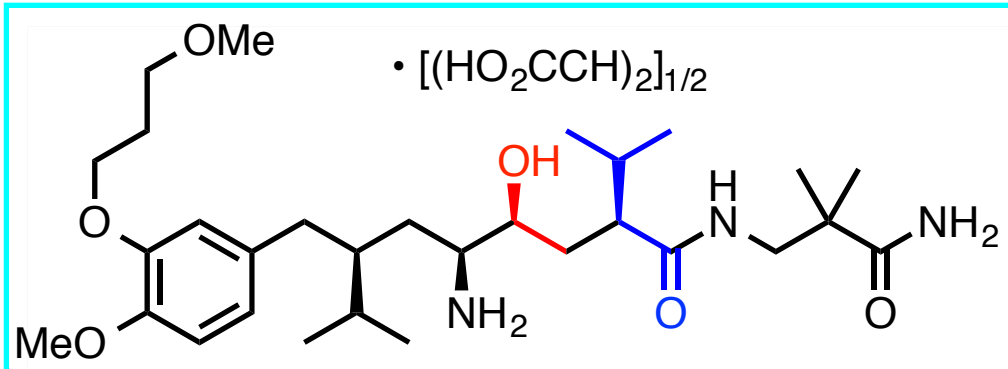
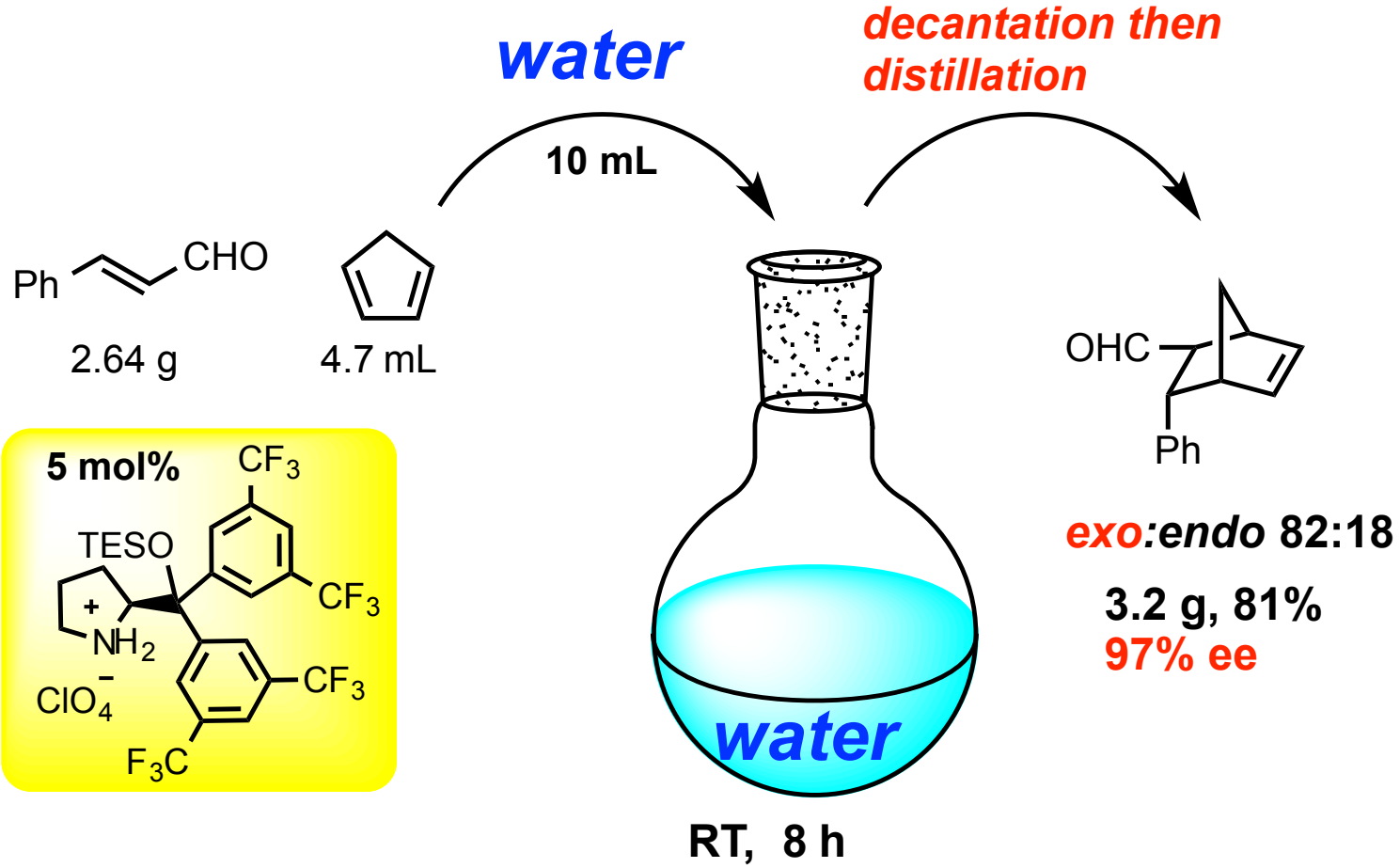


Aliskiren / Tektuma®

Novartis / hypertention medication

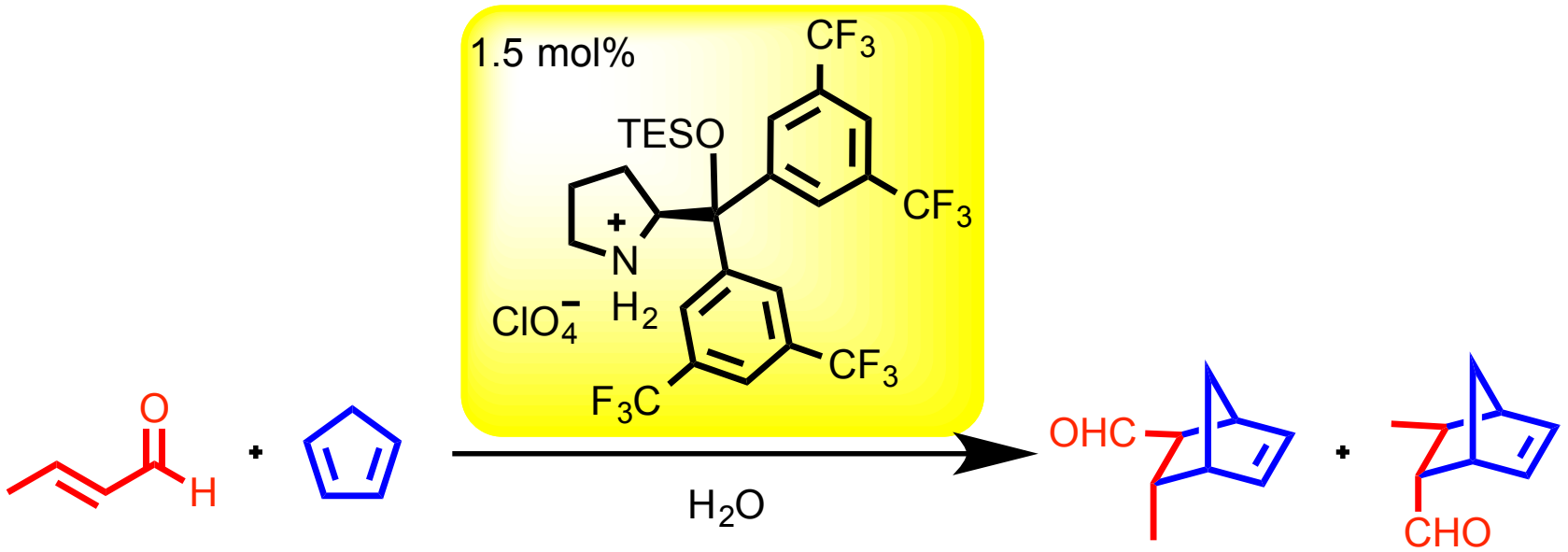
exo Selective Diels-Alder reaction in the presence of water



No organic solvent = Green chemistry
Unusual exo-selectivity
Low temperature is not necessary

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

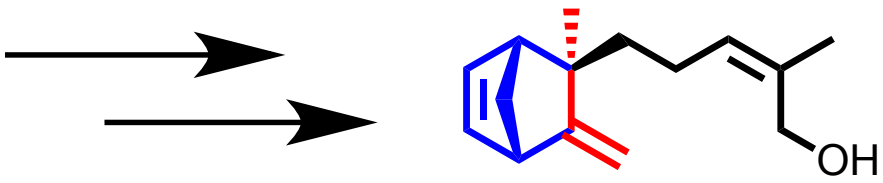
Synthesis of (-)-β-Santalol by Firmenich



61%

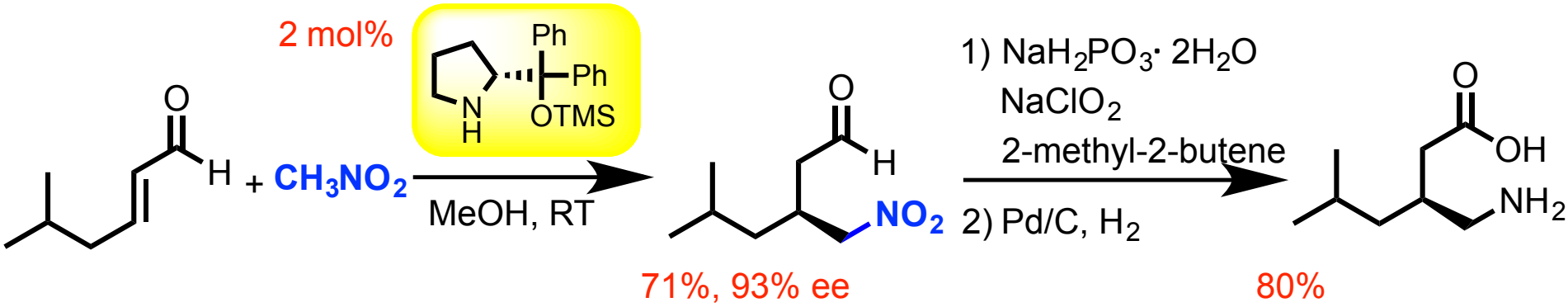
exo : *endo* = 70 : 30

exo 95% *ee*, *endo* 78% *ee*

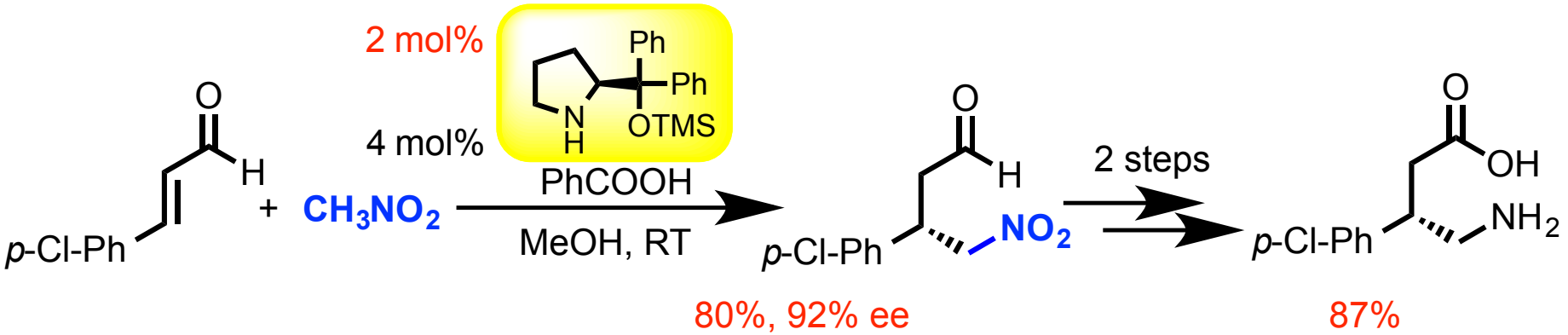


(–)-β-Santalol

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



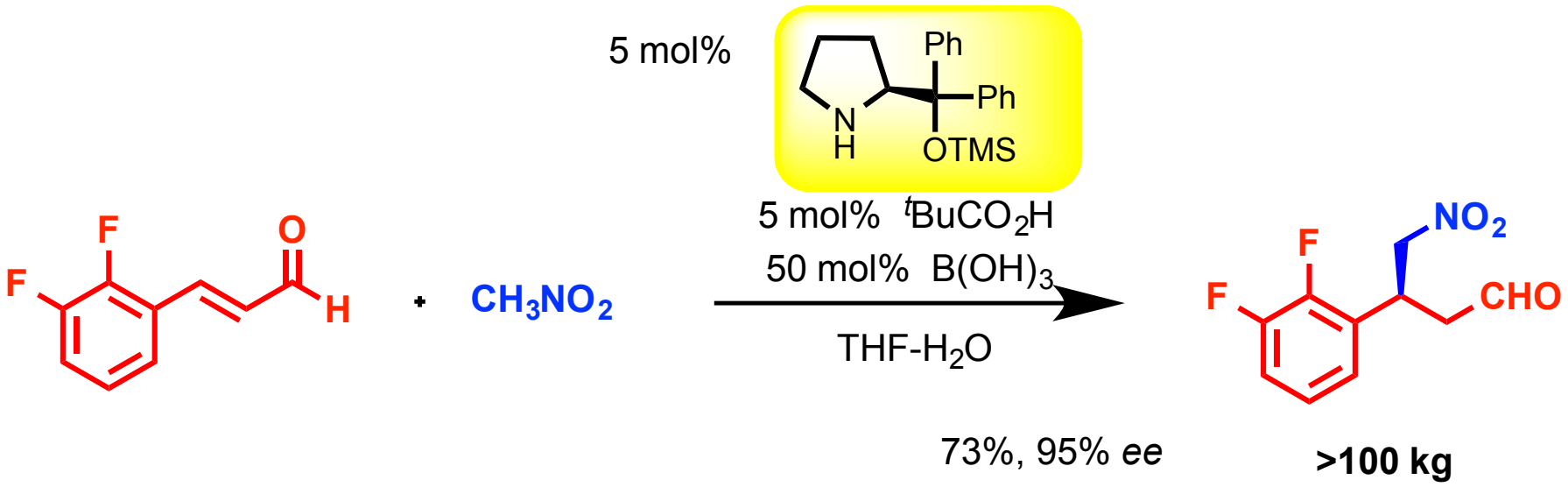
Pregabalin: anticonvulsant



Baclofen: $GABA_B$ receptor agonist

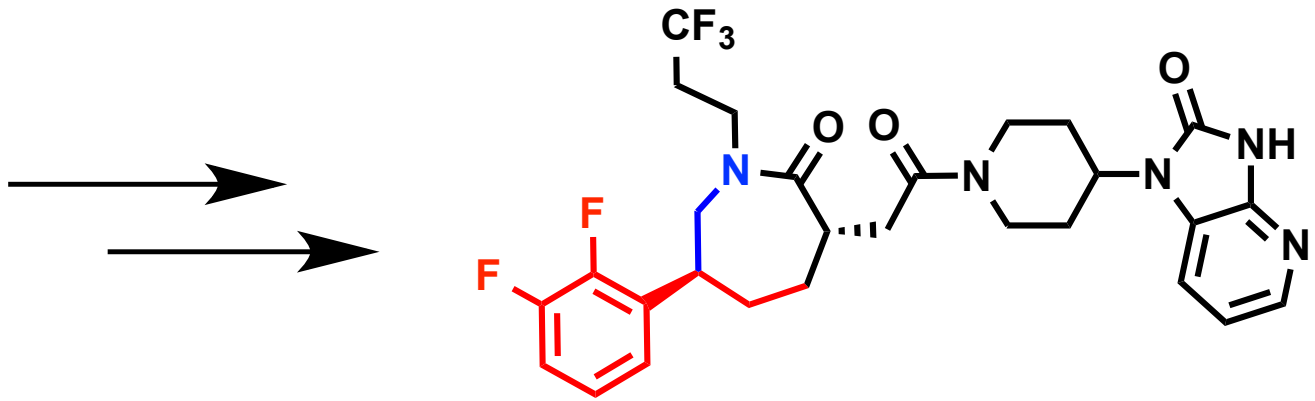
Org. Lett., **9**, 5307 (2007).

Synthesis of Telcagepant by Merck



73%, 95% *ee*

>100 kg

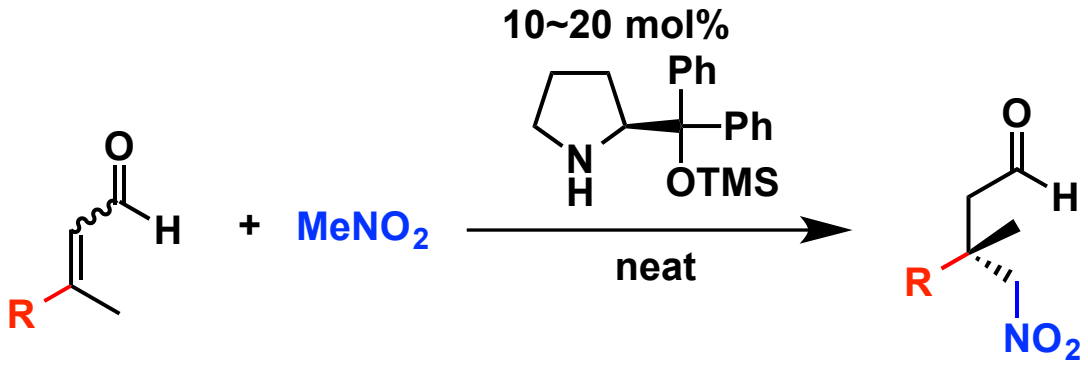


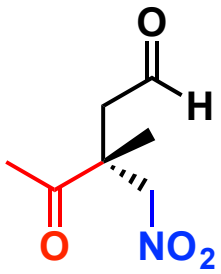
Telcagepant

CGRP receptors antagonist for treatment of Migraine

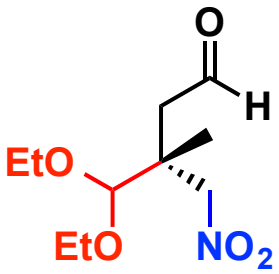
F. Xu *et al.*,(Merck), *J. Org. Chem.*, **75**, 7829 (2010).

Generation of quaternary stereocenters

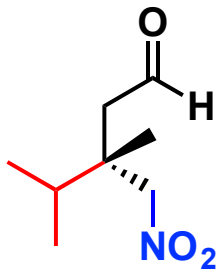




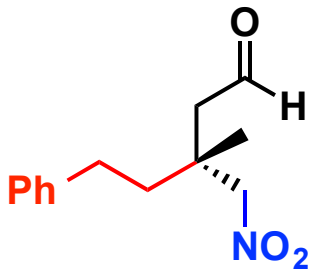
88%, 89% *ee*
E : *Z* = 90 : 10 (SM)



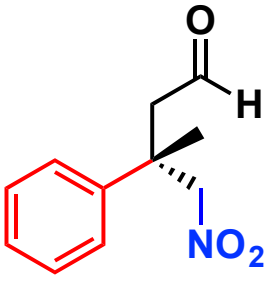
76%, 91% *ee*
E : *Z* = 68 : 32 (SM)



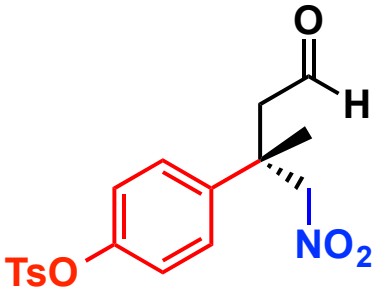
63%, 87% *ee*
E : *Z* = 89 : 11 (SM)



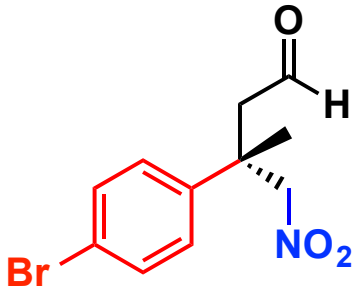
74%, 72% *ee*
E : *Z* = 80 : 20 (SM)



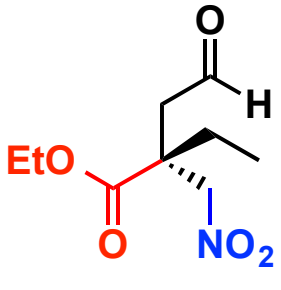
49%, 88% *ee*
E : *Z* = > 99 : 1 (SM)



89%, 90% *ee*
E : *Z* = > 99 : 1 (SM)



81%, 88% *ee*
E : *Z* = > 99 : 1 (SM)

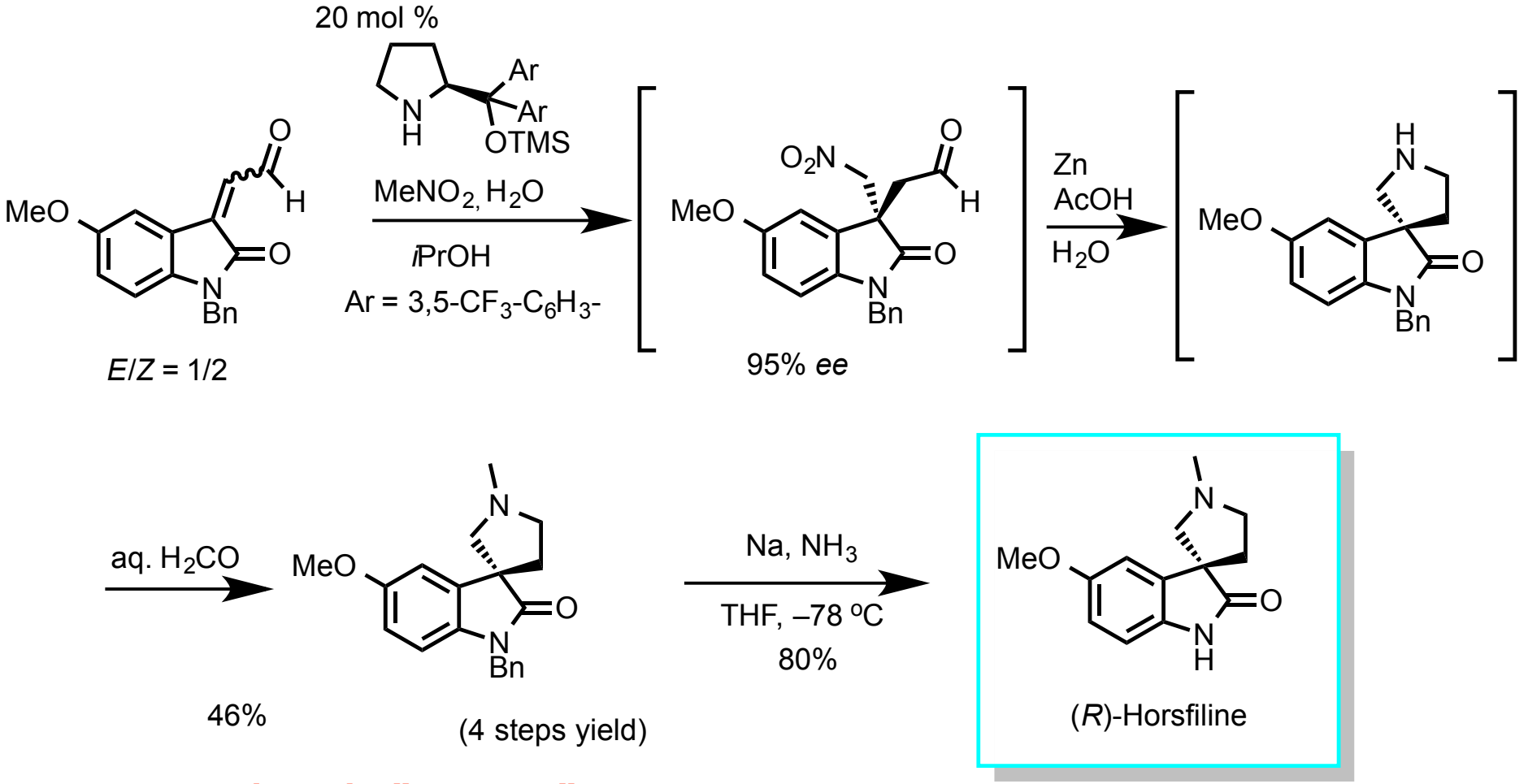


67%, 80% *ee*
E : *Z* = > 99 : 1 (SM)

SM : Starting Material

Chem. Eur. J., **2014**, *20*, 12072.

Total synthesis of (*R*)-Horsfiline



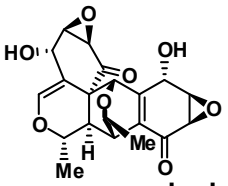
4 reactions in "one-pot"

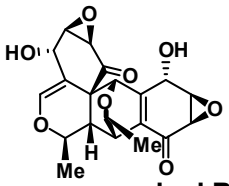
Total yield, 33%

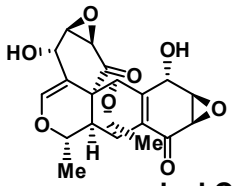
Isolation from *Horsfieldia superba:*
B. Bode *et al.*, *J. Org. Chem.*, **1991**, *56*, 6527.

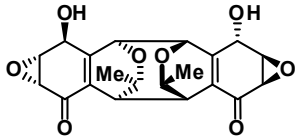
Chem. Eur. J., **2014**, *20*, 13583.

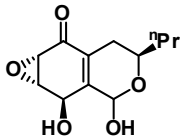
Total synthesis of biologically active compounds

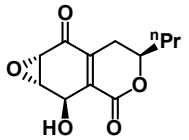

epoxyquinol A

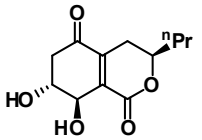

epoxyquinol B

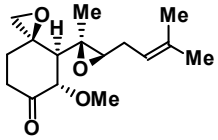

epoxyquinol C

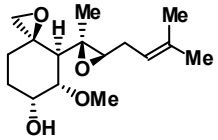

epoxytwinol A

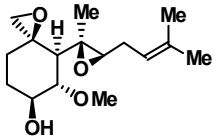

EI-1941-1

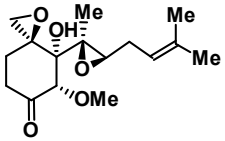

EI-1941-2

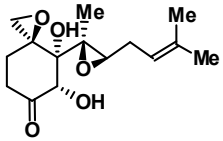

EI-1941-3

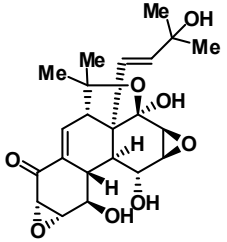

RK-805

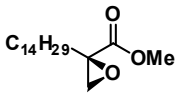

fumagillol

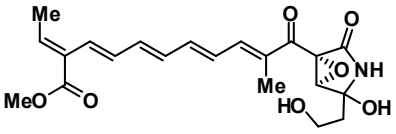

FR-65814

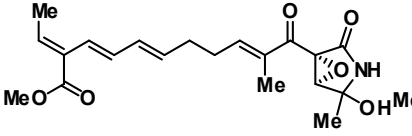

ovalicin

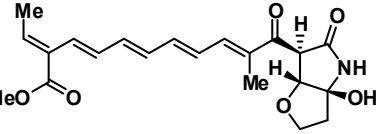

5-demethylovalicin

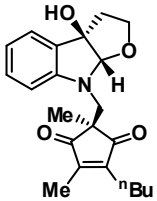

panepophenanthrin

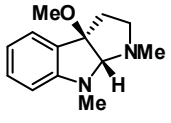

(*R*)-Methyl Palmoxirate

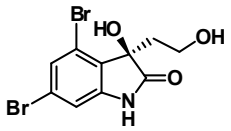

NG-391

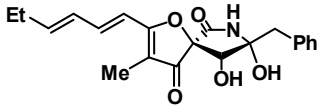

epolactaene

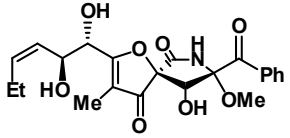

lucilactaene

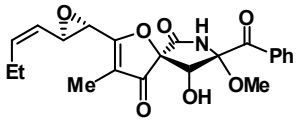

madindoline A

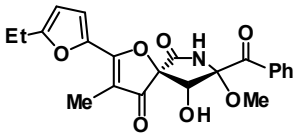

CPC-1

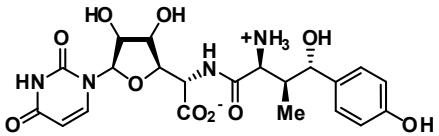

ent-convolutamydine E

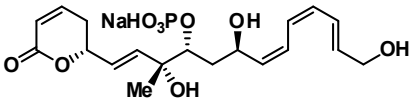

azaspirene

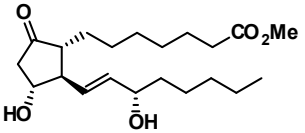

pseurotin A

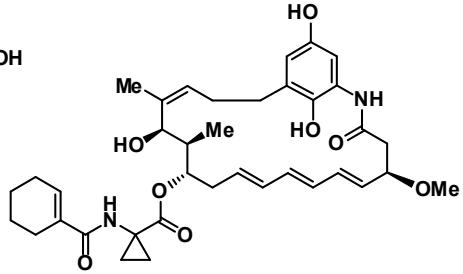

synerazol

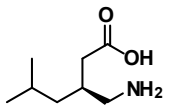

FD-838

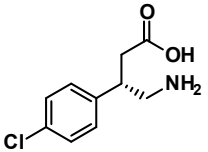

nikkomycin B

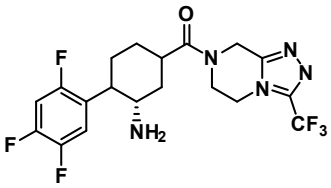

fostriecin

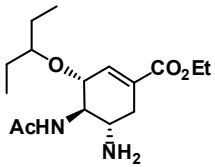

Prostaglandin E_1 methyl ester

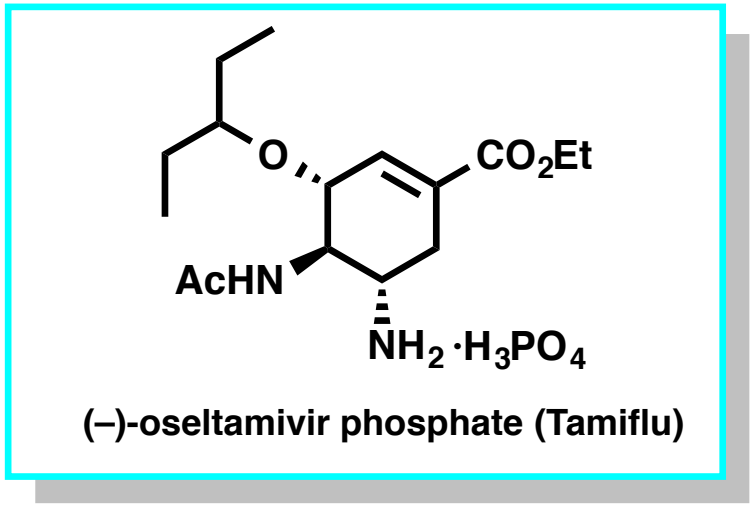

(+) - cytotrienin A


pregabalin


baclofen


ABT-341


(-)-oseltamivir



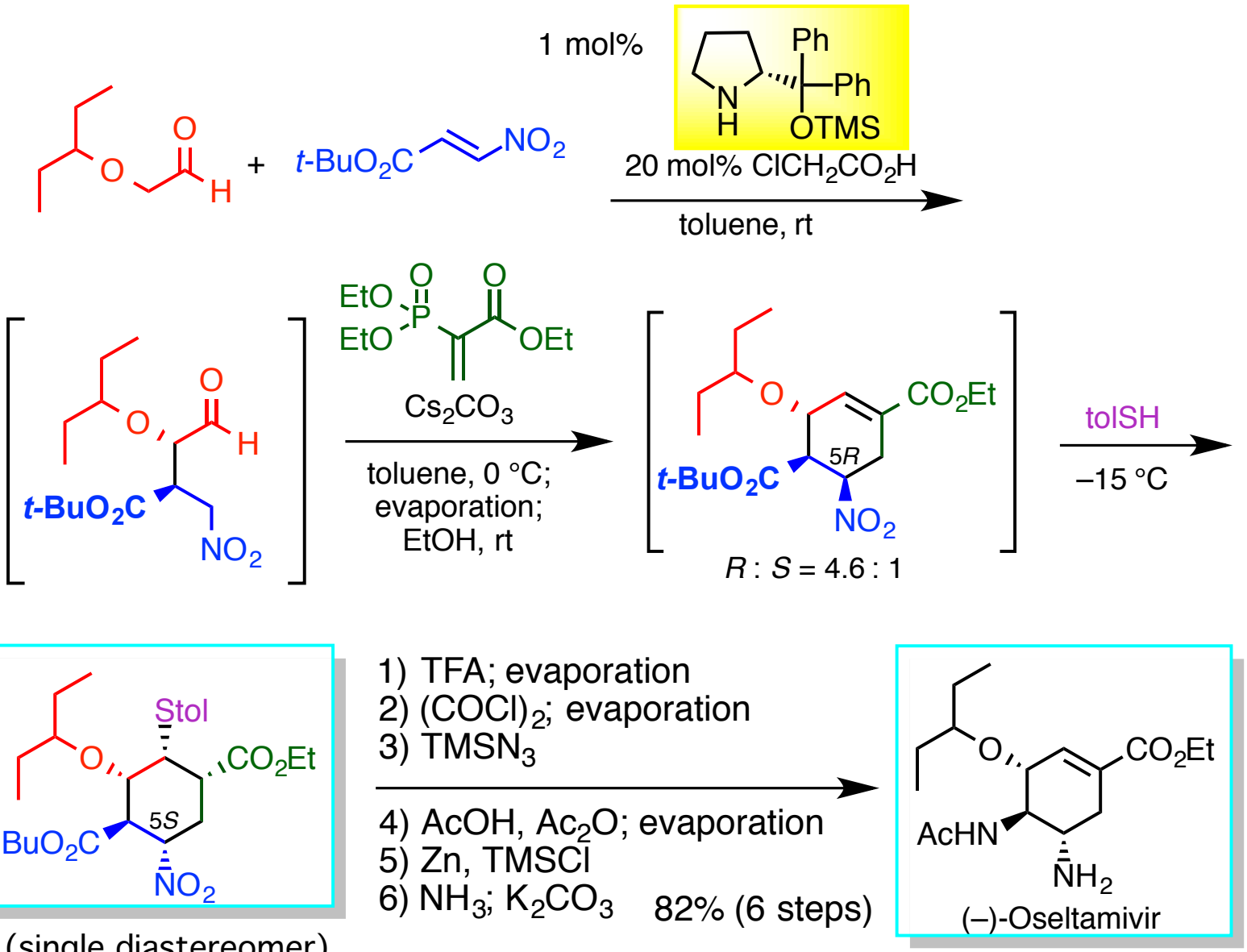
(–)-oseltamivir phosphate (Tamiflu)

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), Ma (2010) *et al.*,
62 total syntheses

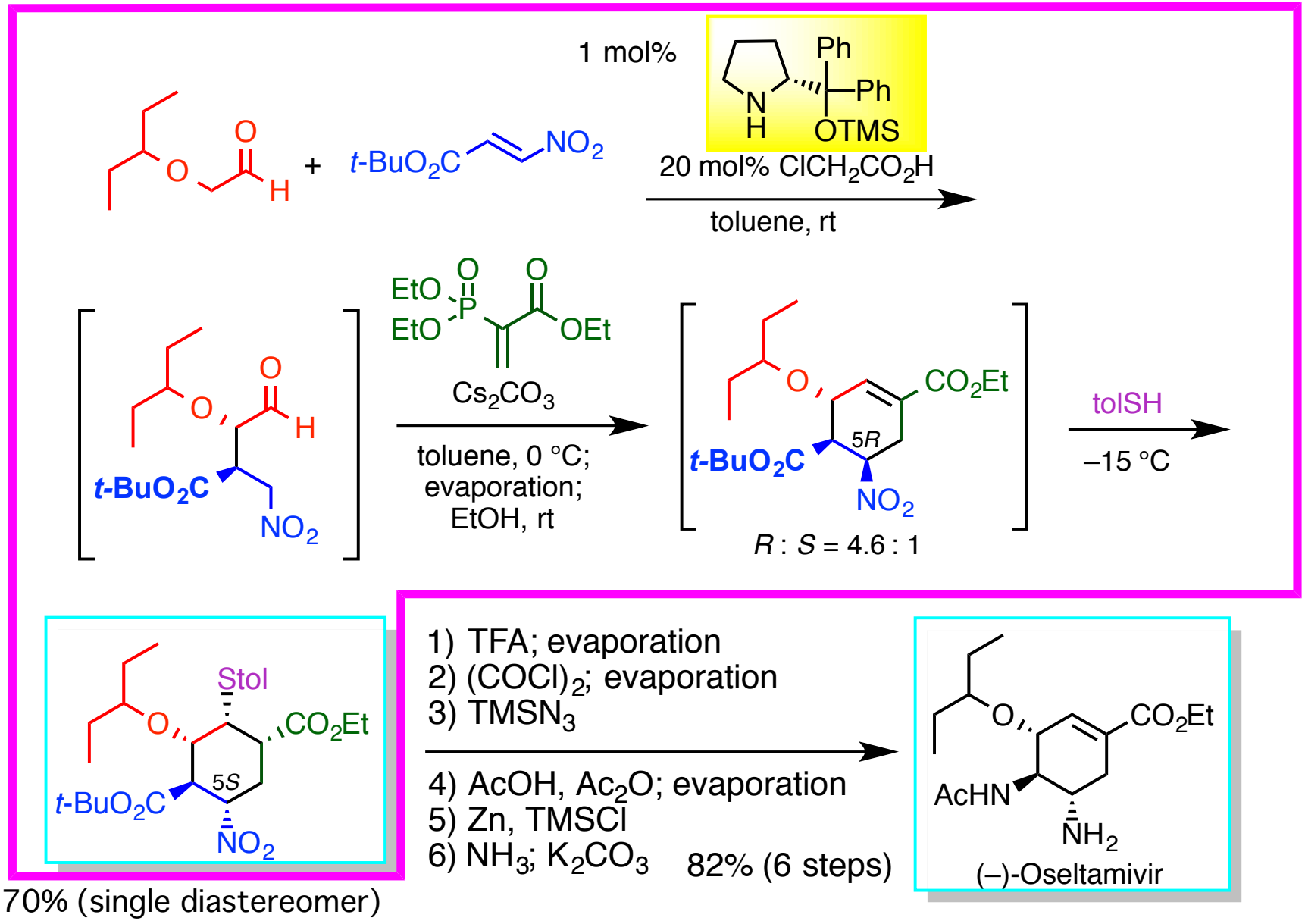
Synthetic Challenge: Control of three continuous chiral center
Selectivity (enantio- and diastereo-)

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



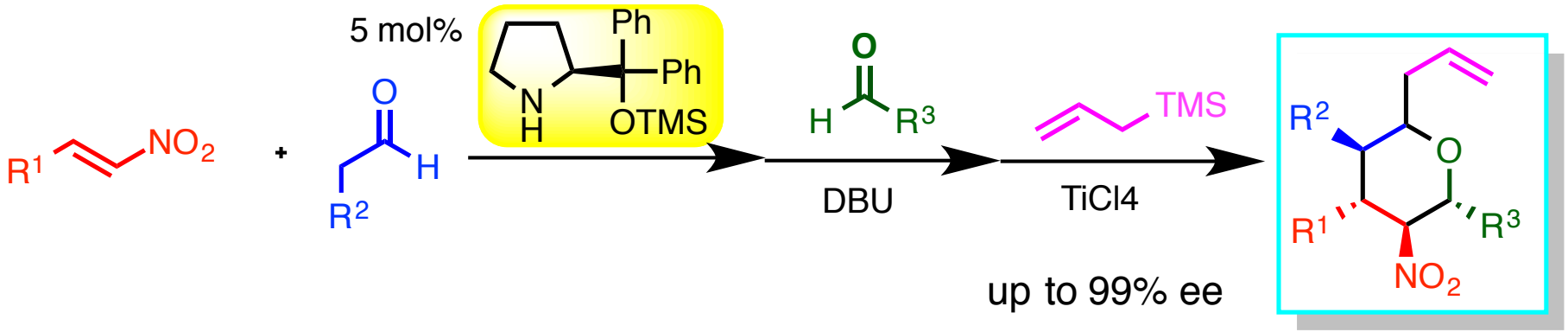
Angew. Chem. Int. Ed., **2009**, *48*, 1304; *Chem. Eur. J.*, **2010**, *16*, 12616.

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

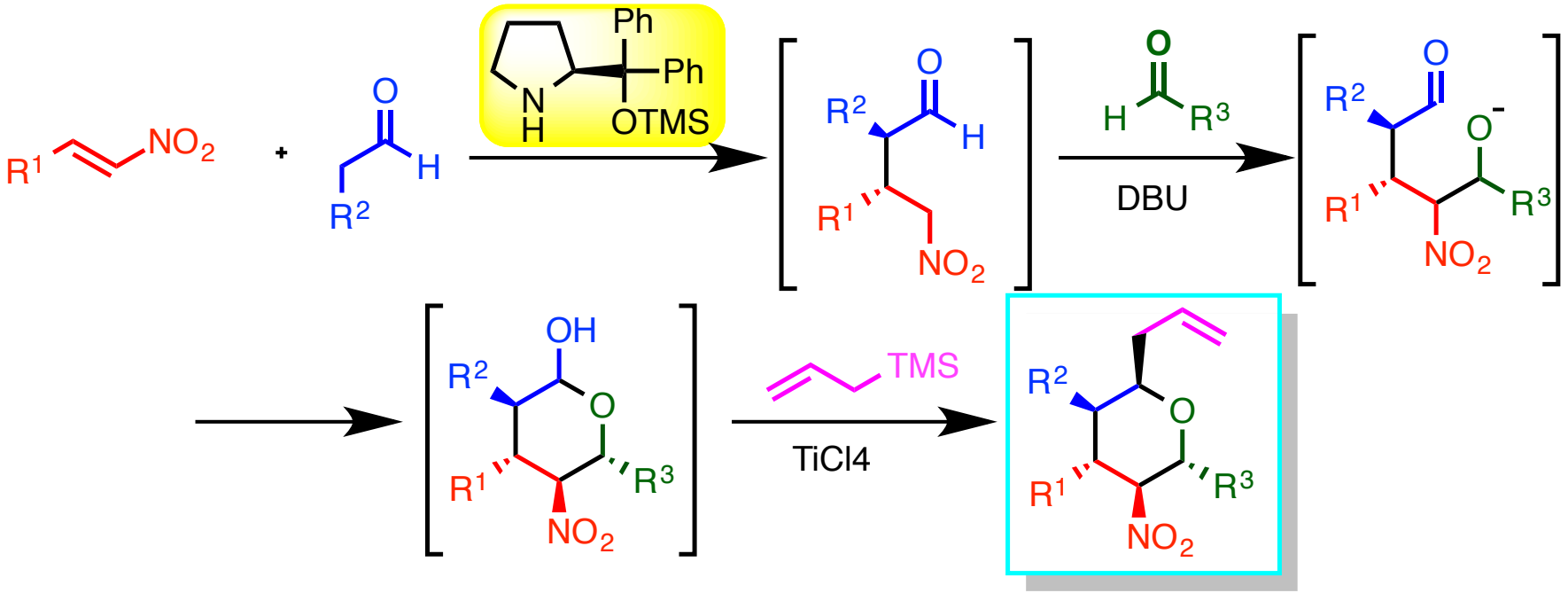


Angew. Chem. Int. Ed., **2009**, *48*, 1304; *Chem. Eur. J.*, **2010**, *16*, 12616.

One-pot and cascade synthesis of substituted chiral pyran

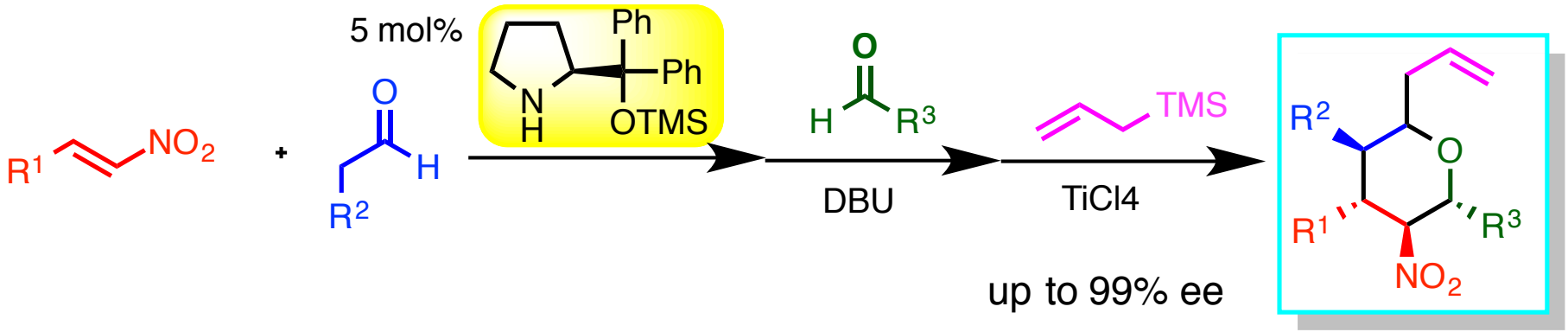


Y. Hayashi et al., *Angew. Chem. Int. Ed.*, **2011**, *50*, 3774.



Highly diastereo- and enantio-selective

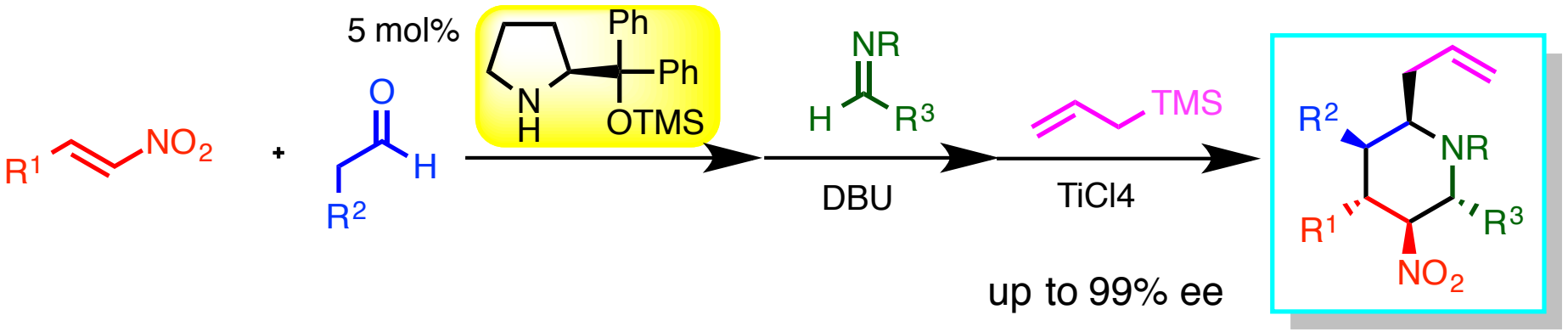
One-pot and cascade synthesis of substituted chiral pyran



up to 99% ee

Y. Hayashi et al., *Angew. Chem. Int. Ed.*, **2011**, *50*, 3774.

One-pot and cascade synthesis of substituted chiral pyperidine

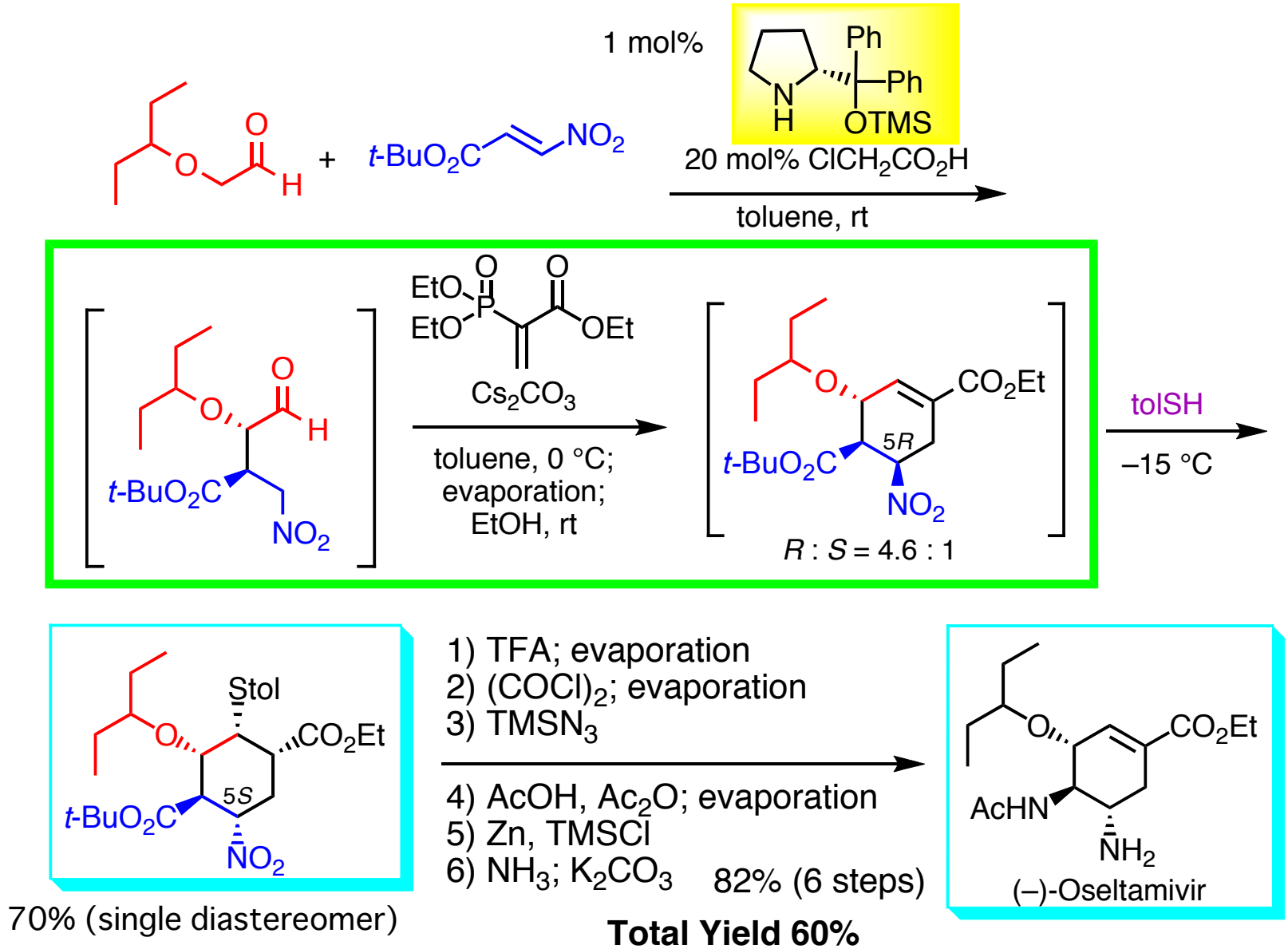


up to 99% ee

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

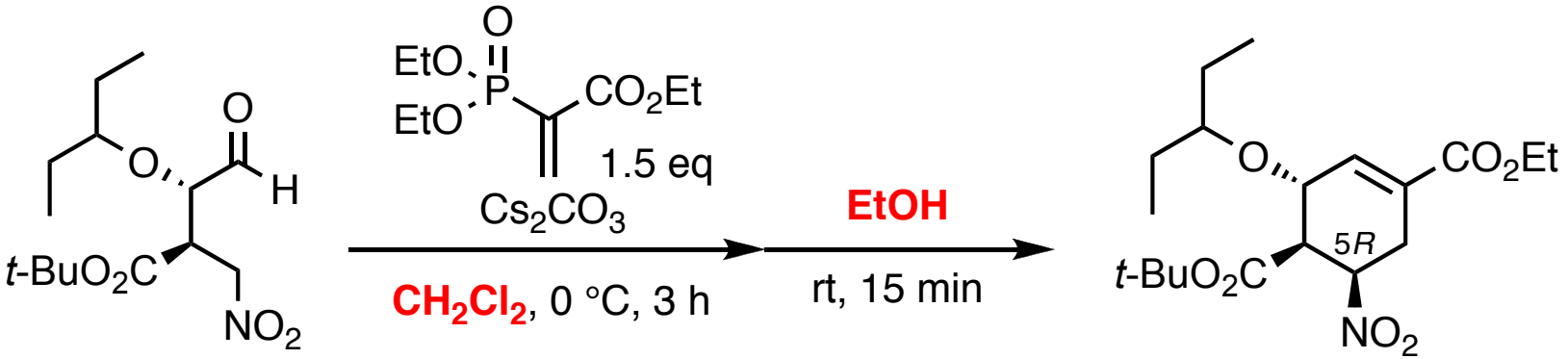
One-pot reaction is powerful for the library synthesis.
One-pot reaction is useful ***for the medicinal chemistry***.

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



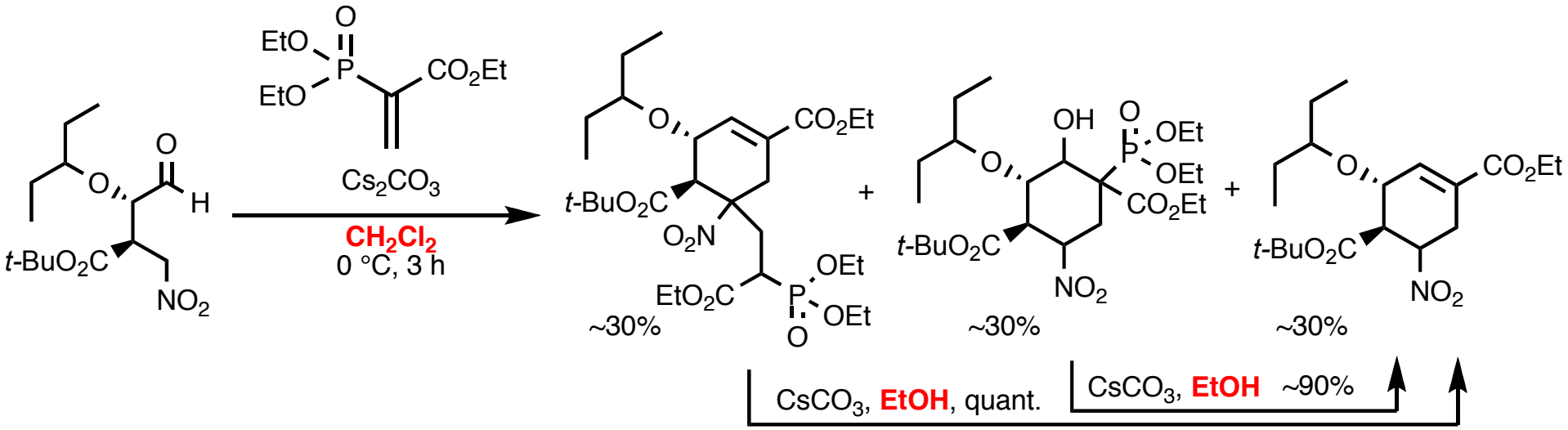
Angew. Chem. Int. Ed., **2009**, *48*, 1304; *Chem. Eur. J.*, **2010**, *16*, 12616.

Tandem Michael/HWE reaction

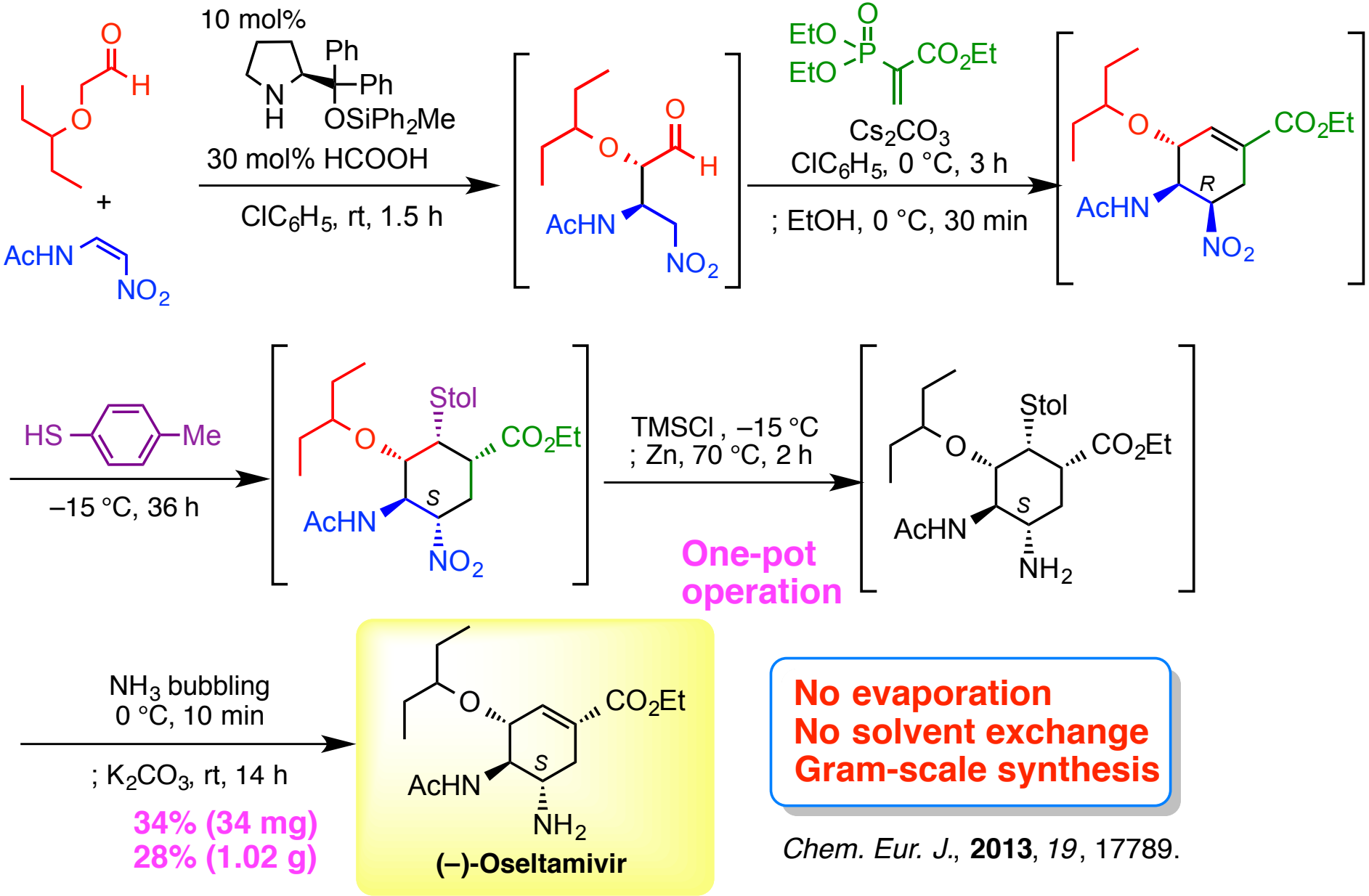


~80%, 5*R* : 5*S* = 4.6 : 1

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



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



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

D. Ma, *Angew. Chem. Int. Ed.*, **2010**, *49*, 4656. R. Sebesta, *Synthesis*, **2012**, *44*, 2424. G. Lu, *ChemCatChem*, **2012**, *4*, 1007.

Green Reaction

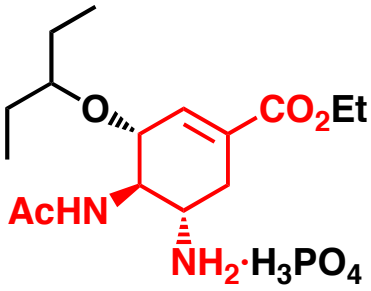
- Atom economy (Trost)
- Step economy (Wender)
- Redox economy (Baran & Hoffmann)

Pot economy Operational Economy

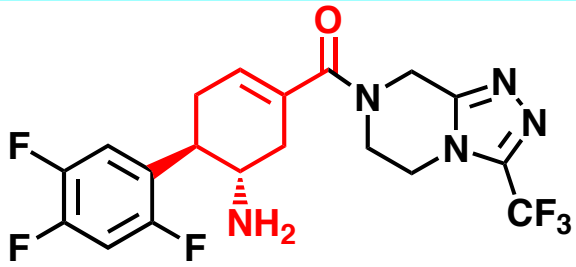
- Purification step economy
- Chemical waste economy
- Time economy
- Solvent economy

Non-insulin dependant diabetes

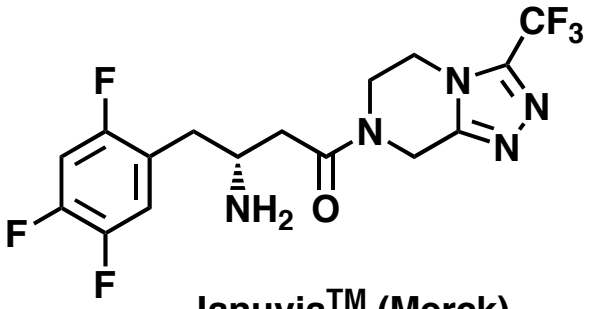
Dipeptidyl peptidase-4 (DPP-4) inhibitor



Tamiflu (Roche)

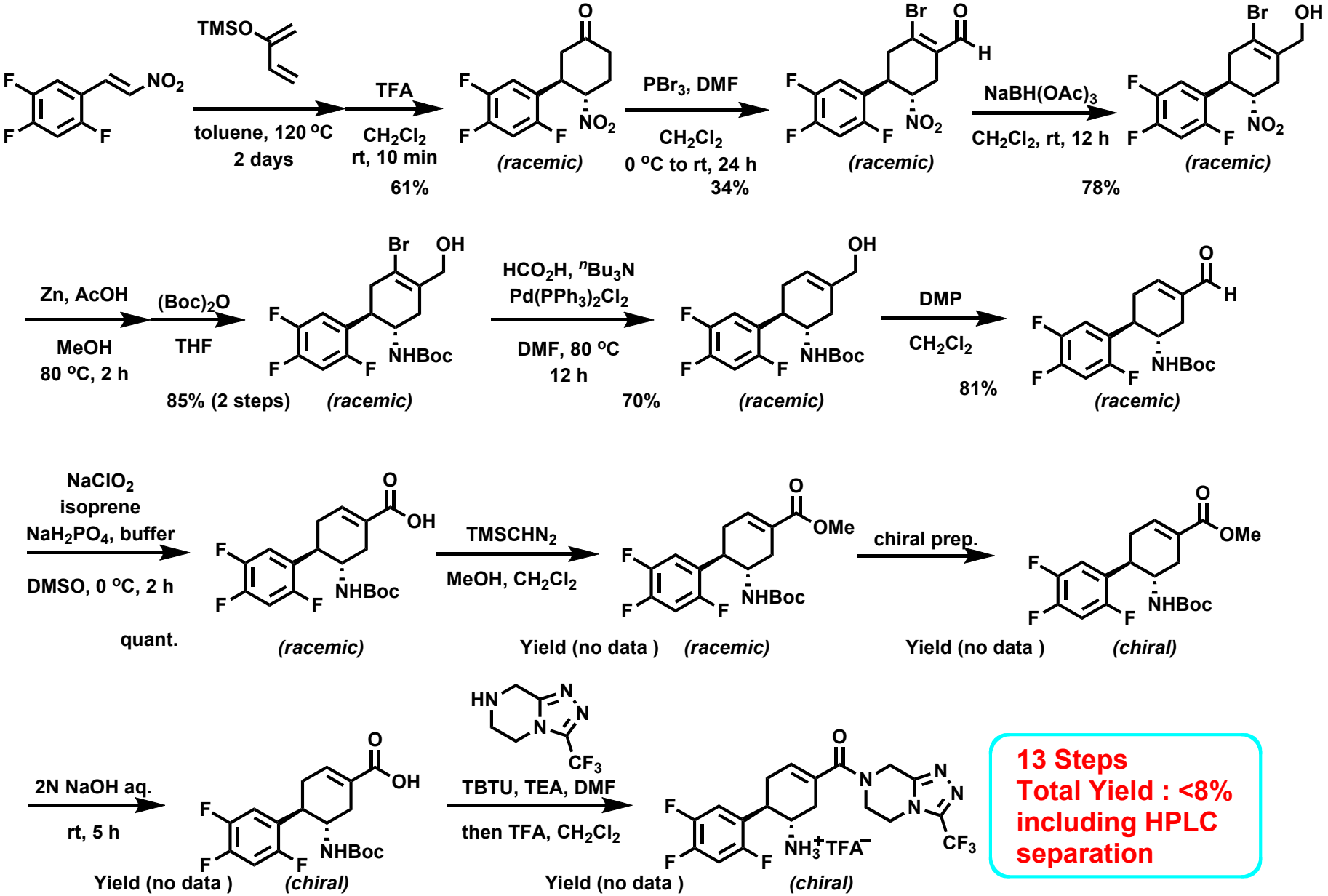


ABT-341 (Abbott laboratory)

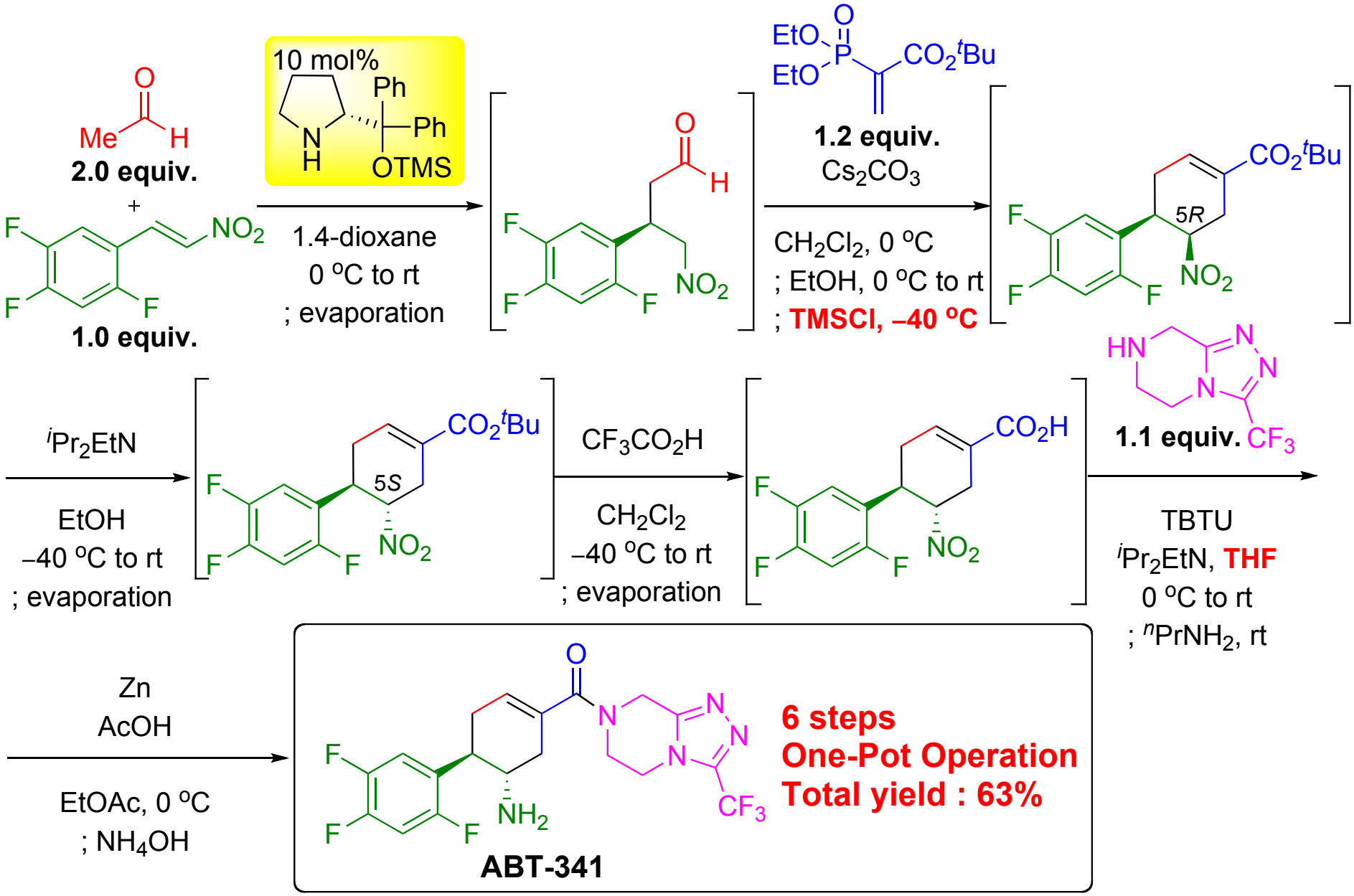


Januvia™ (Merck)

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

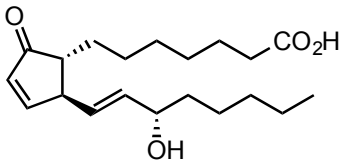


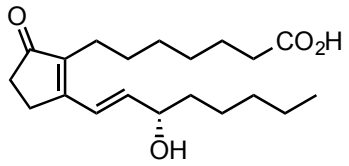
One-Pot Total Synthesis of ABT-341

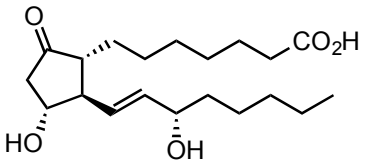


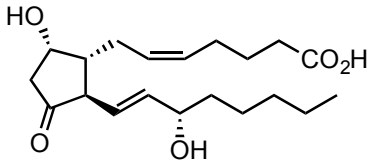
Angew. Chem. Int. Ed. **2011**, *50*, 2824.

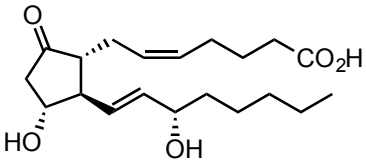
Prostaglandins


PGA$_1$


PGB$_1$


PGE$_1$


PGD$_2$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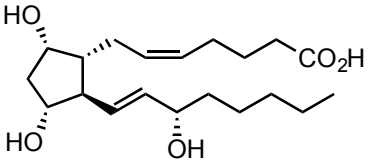
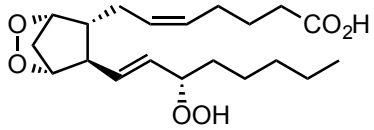

PGF$_{2\alpha}$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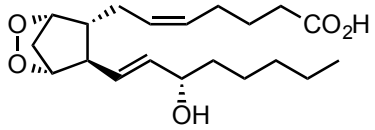
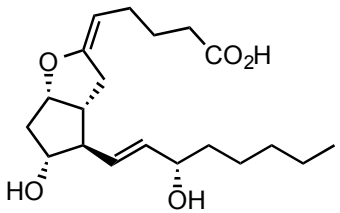
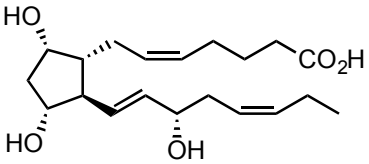
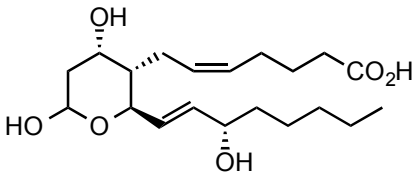
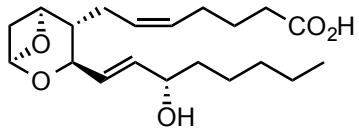
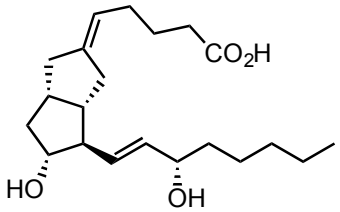

PGH$_2$

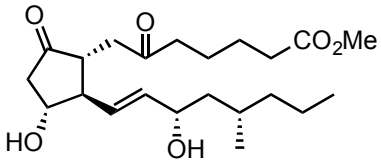

PGI$_2$

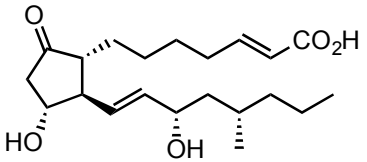

PGF$_{3\alpha}$

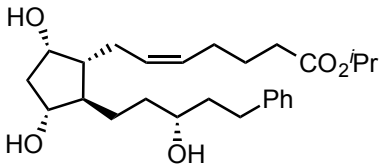

TXB$_2$

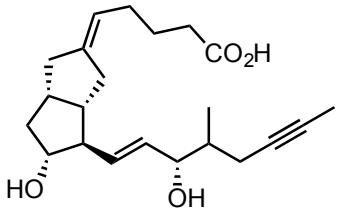

TXA$_2$

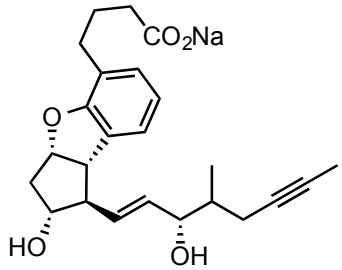

Carbacyclin

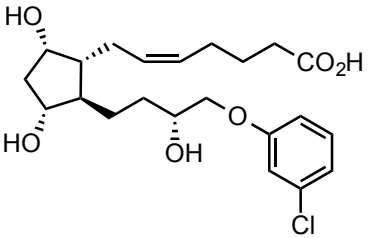

ornoprost

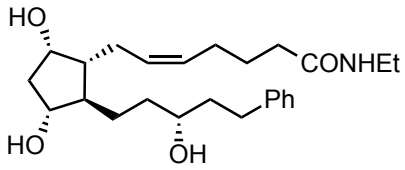

limaprost


latanoprost


iloprost

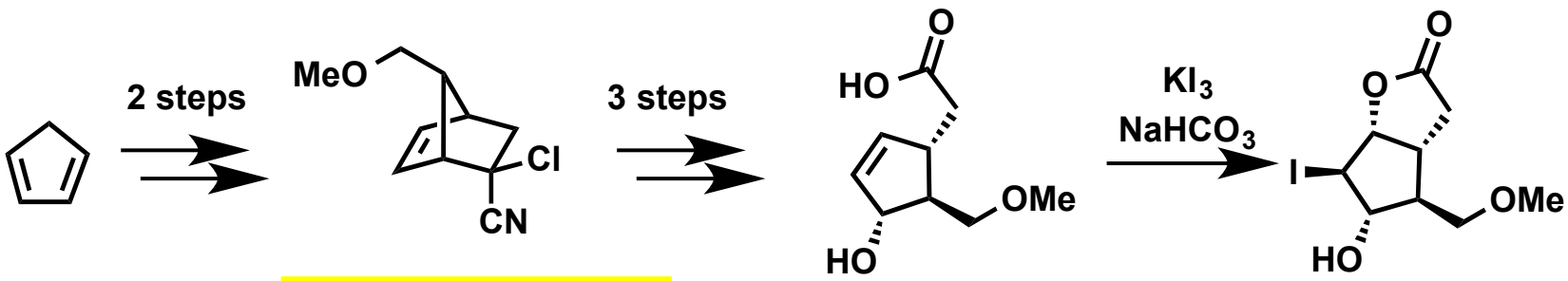

beraprost

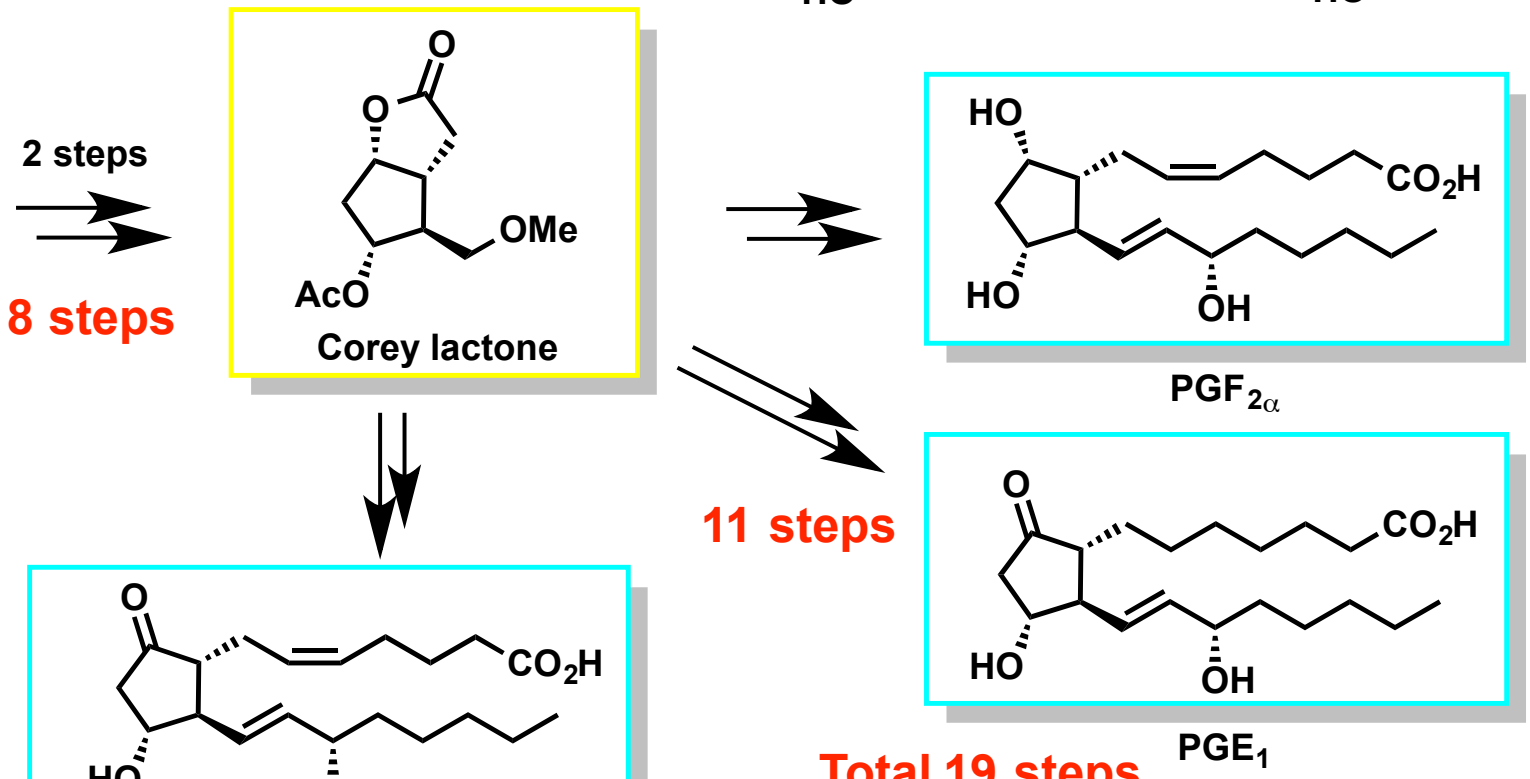

cloprostenol


bimatoprost

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

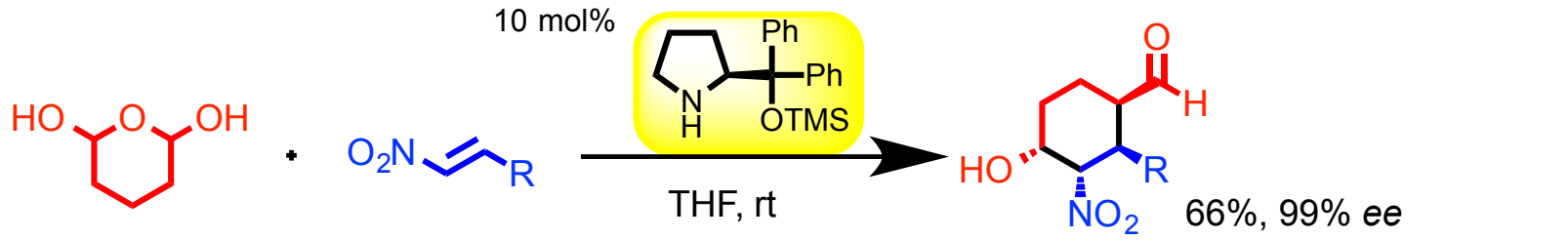
Corey's Total Synthesis



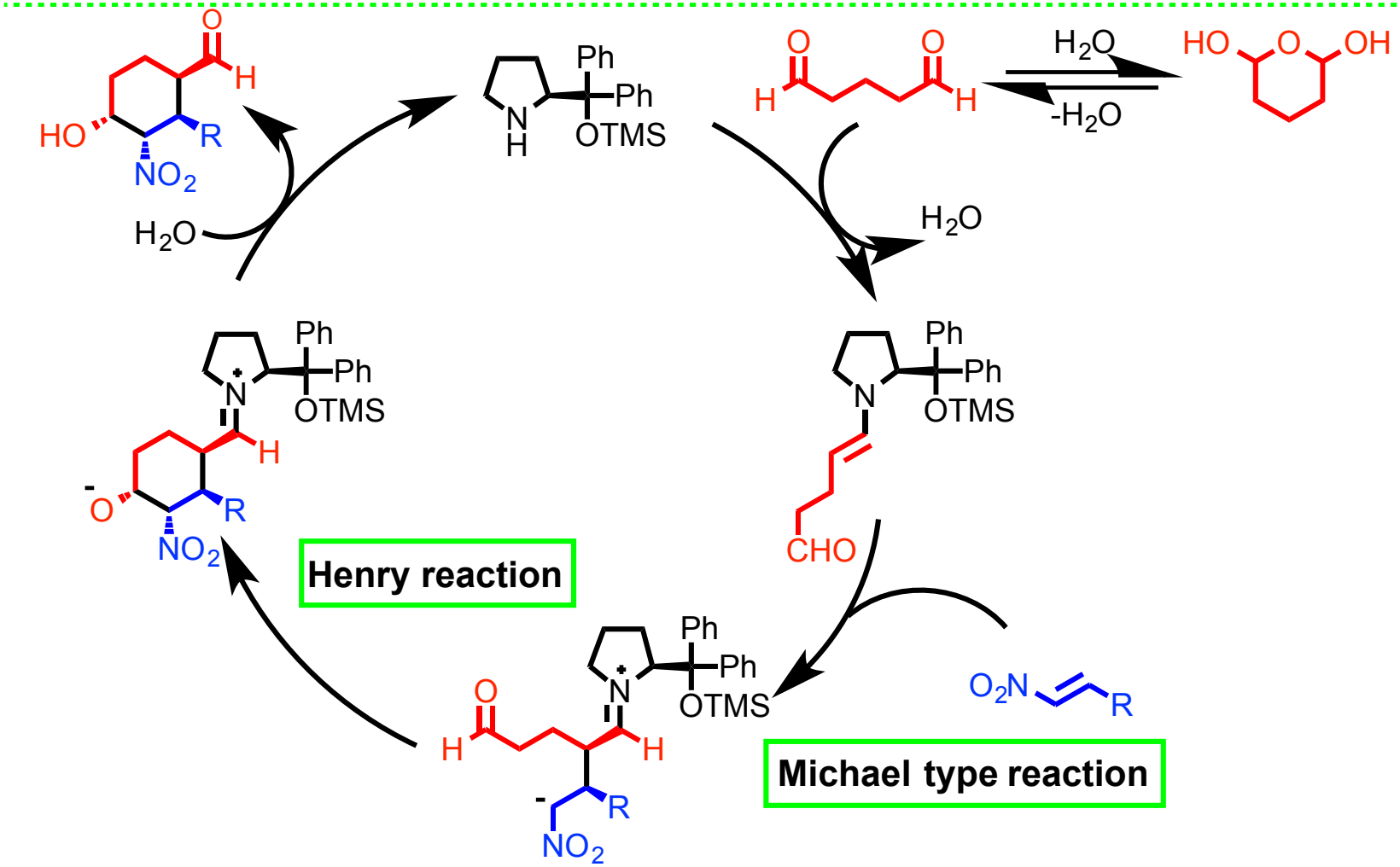


E. J. Corey *et al.*, *J. Am. Chem. Soc.*, **91**, 5675 (1969).
E. J. Corey *et al.*, *J. Am. Chem. Soc.*, **92**, 2586 (1970).
Cf. V. K. Aggarwal *et al.*, *Nature*, **489**, 278 (2012).

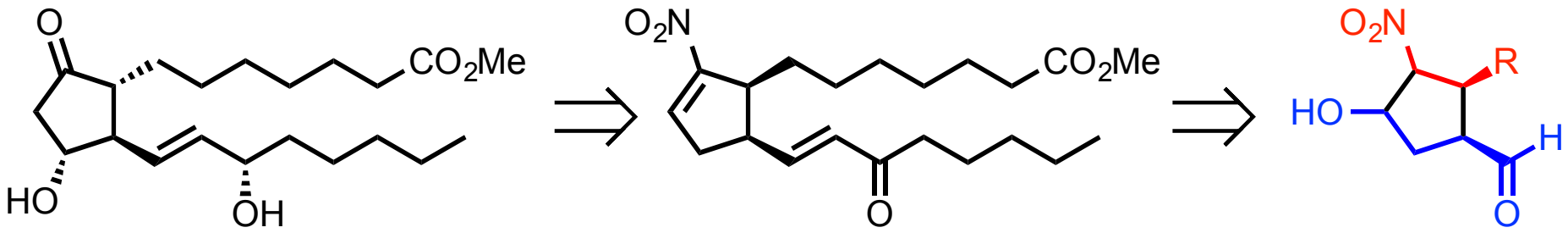
Our background: Formal 4+2 cycloaddition reaction



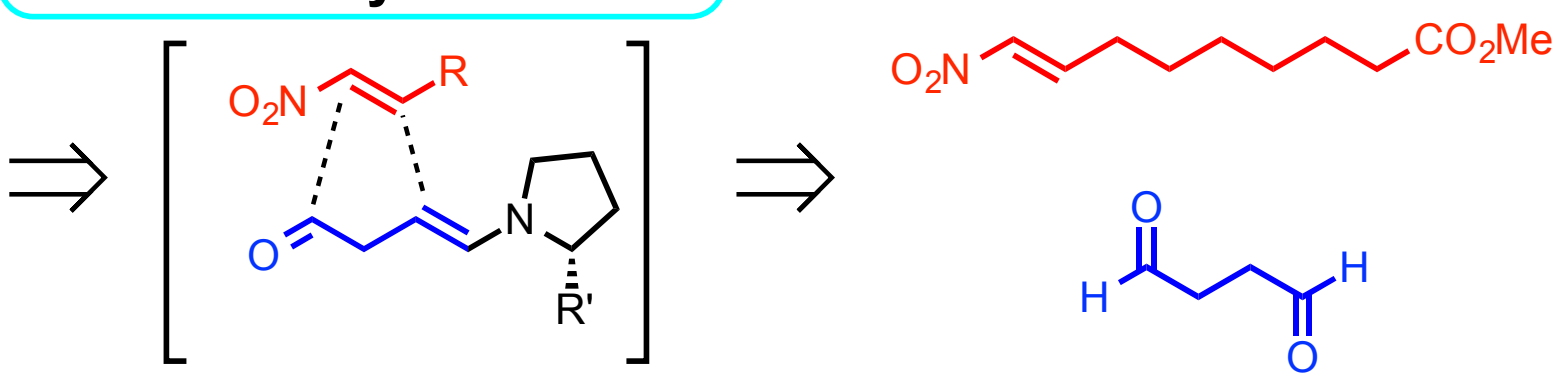
Y. Hayashi *et al.*, *Angew. Chem. Int. Ed.*, **46**, 4922 (2007).

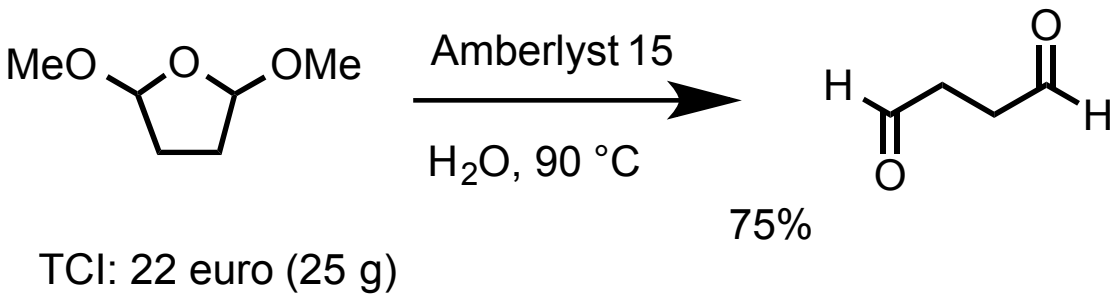


Retrosynthetic analysis 1

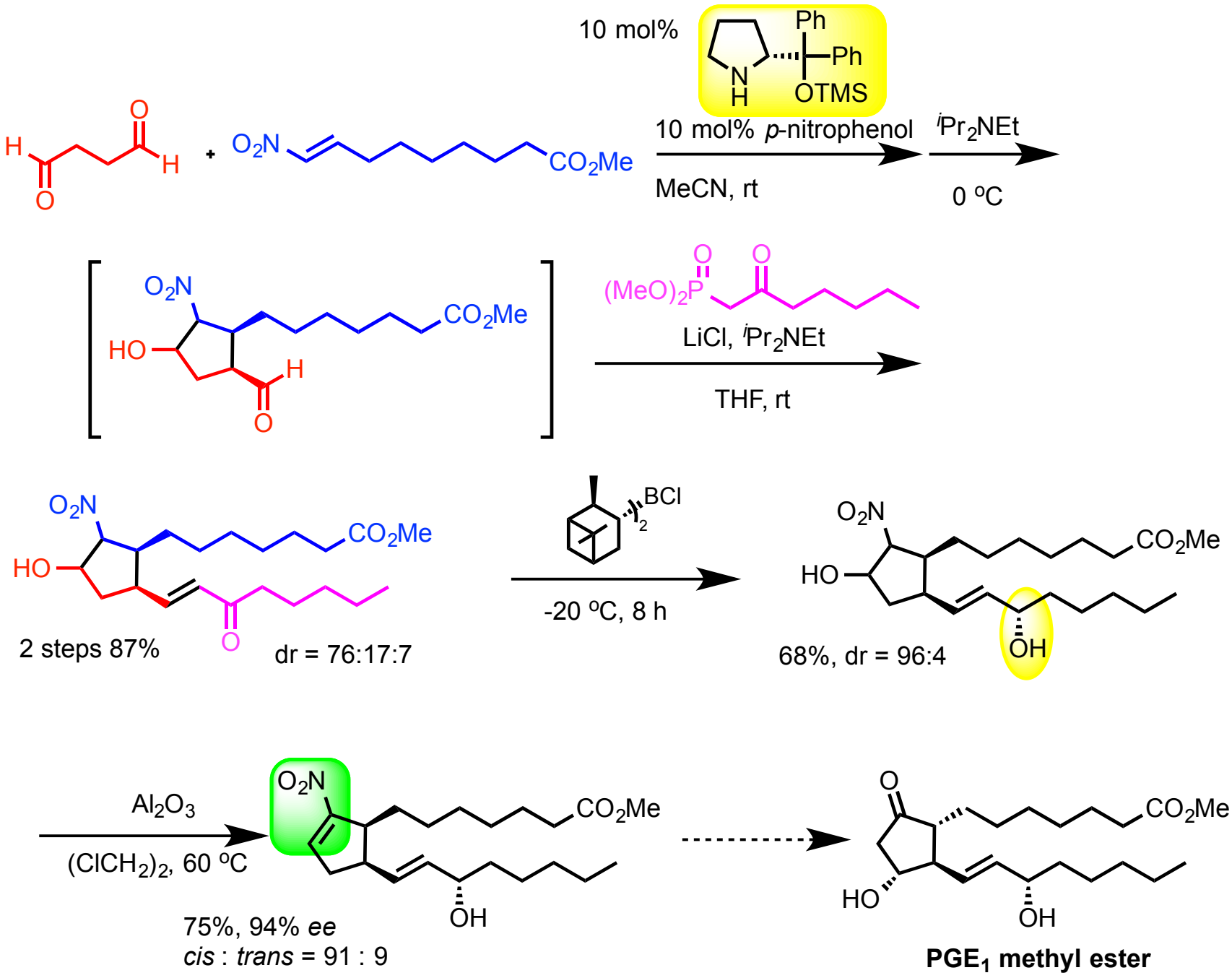


Formal 3+2 cycloaddition

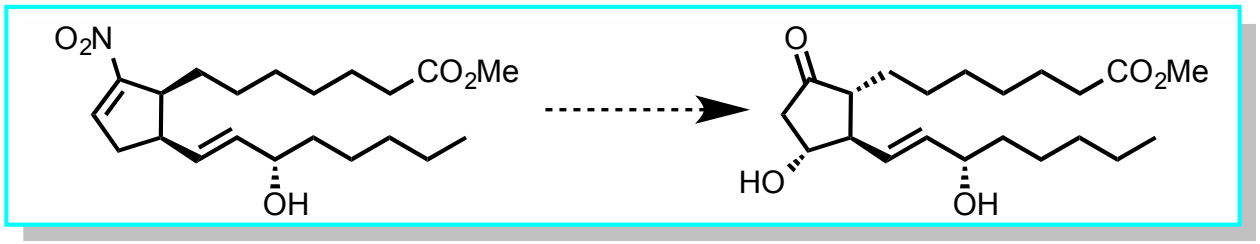


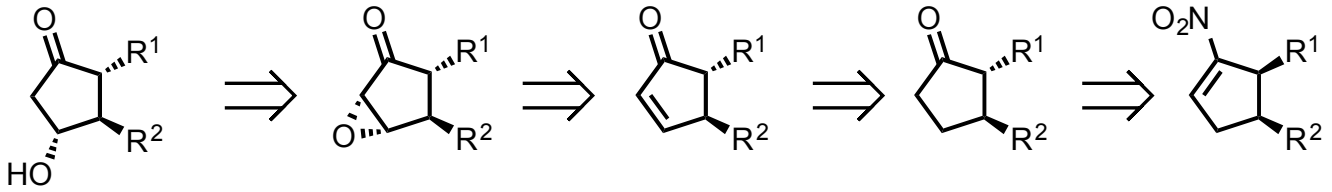


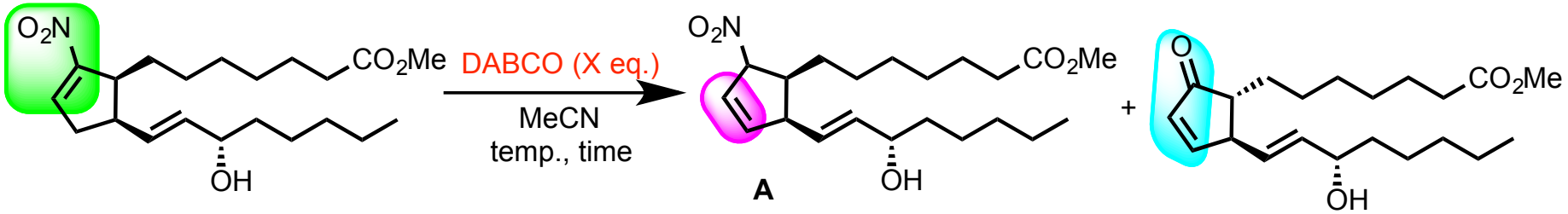
TCI: 22 euro (25 g)


10 mol%
Ph
Ph
N
H
OTMS
10 mol% p-nitrophenol
MeCN, rt
iPr2NEt
0 °C
LiCl, iPr2NEt
THF, rt
2 steps 87%
dr = 76:17:7
BCl2
-20 °C, 8 h
68%, dr = 96:4
Al2O3
(ClCH2)2, 60 °C
75%, 94% ee
cis : trans = 91 : 9
PGE1 methyl ester

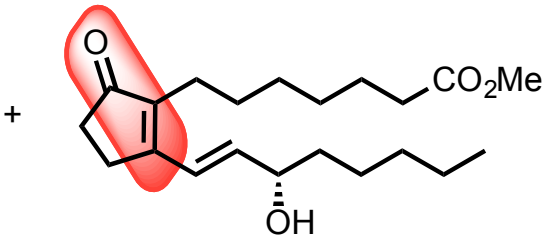
Retrosynthetic analysis 2



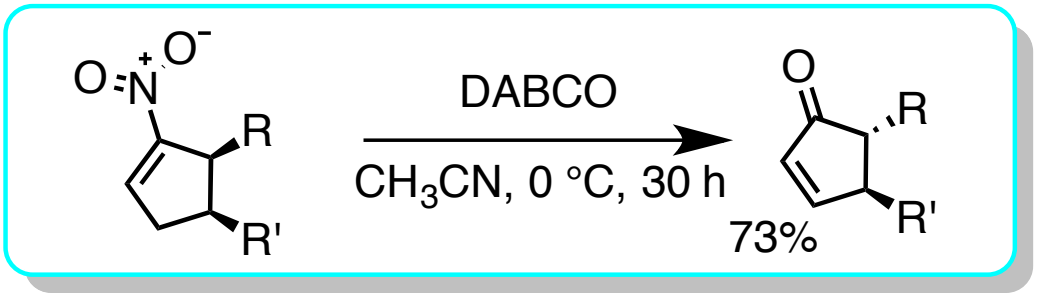


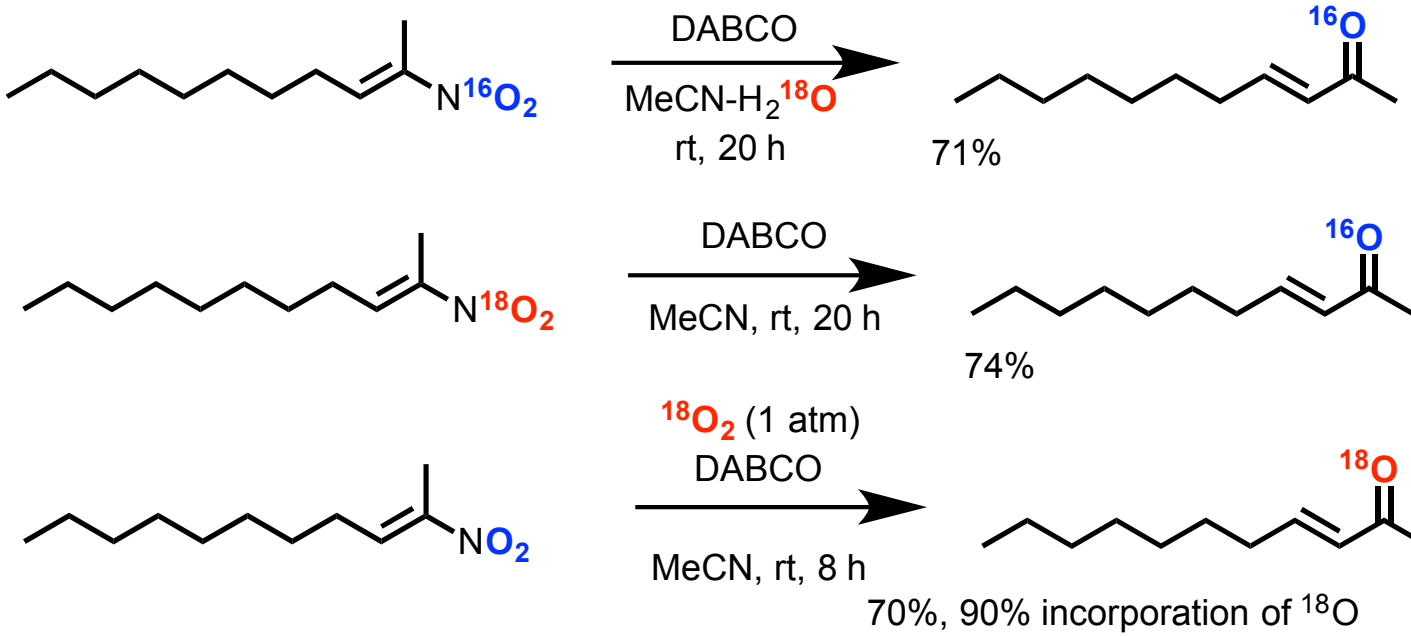


X eq.	temp. / °C	time / h	yield / %		
			A	B	C
1	0	16	60	11	trace
1	23	12	0	42	19
1.5	0	30	0	73	trace

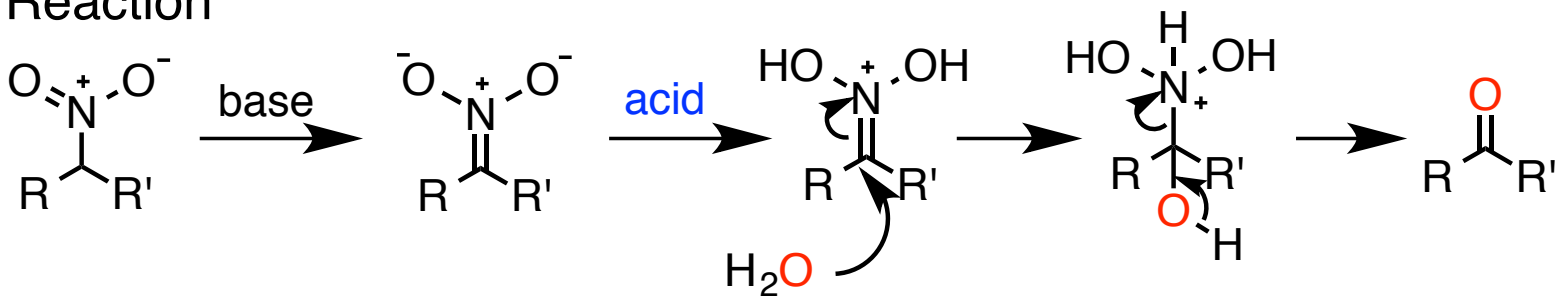


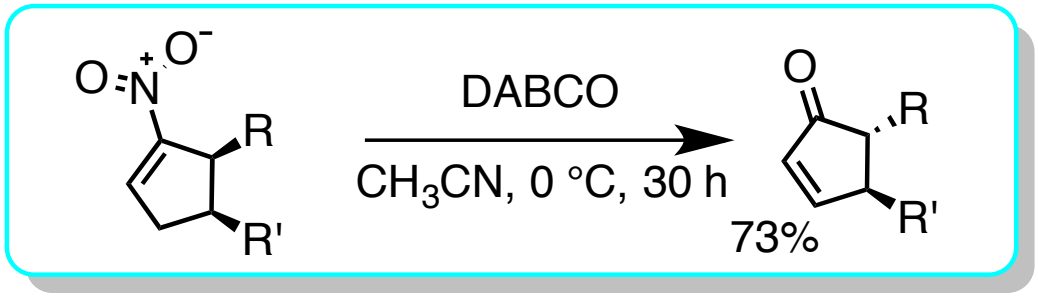
C

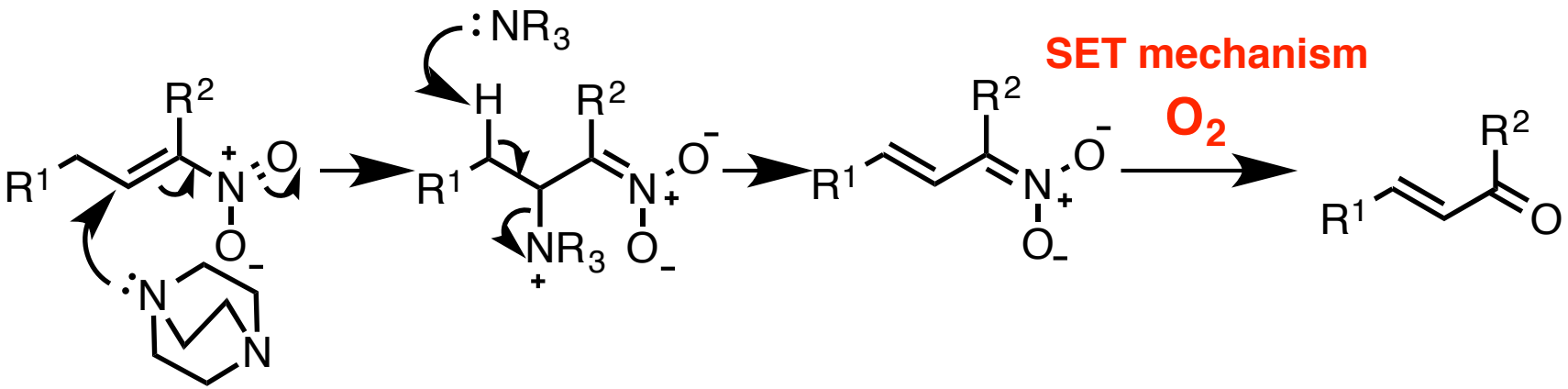




Nef Reaction

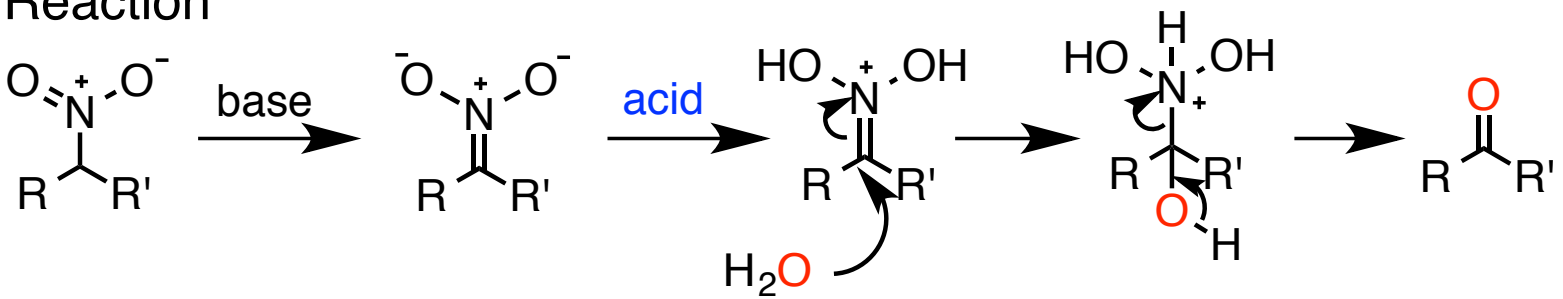


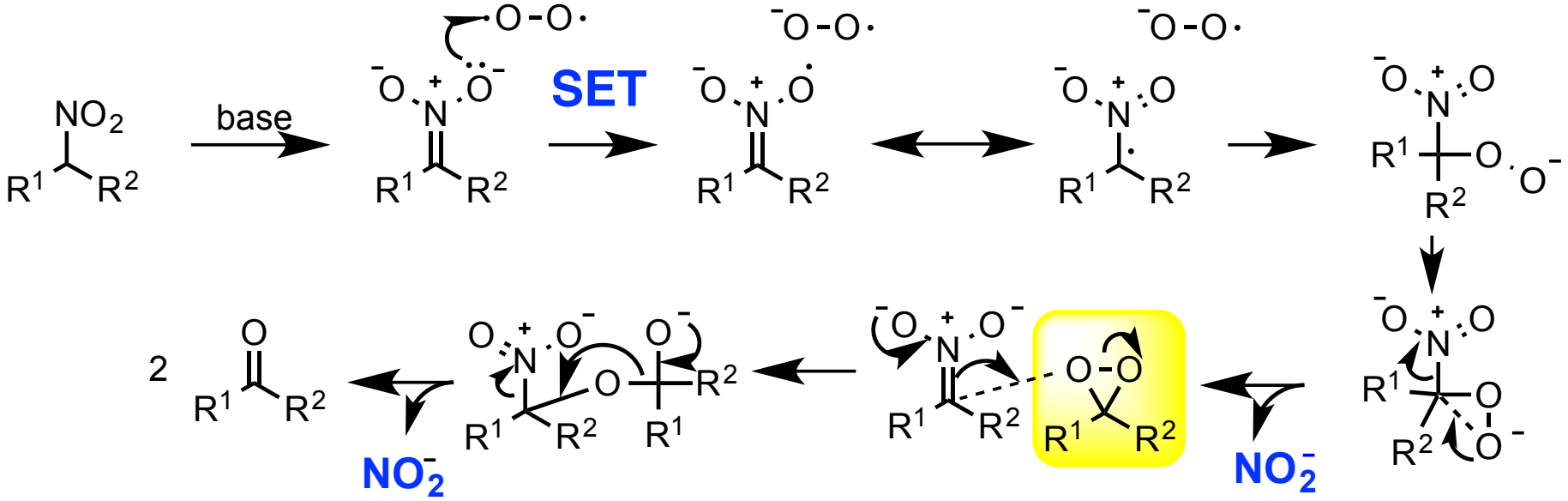




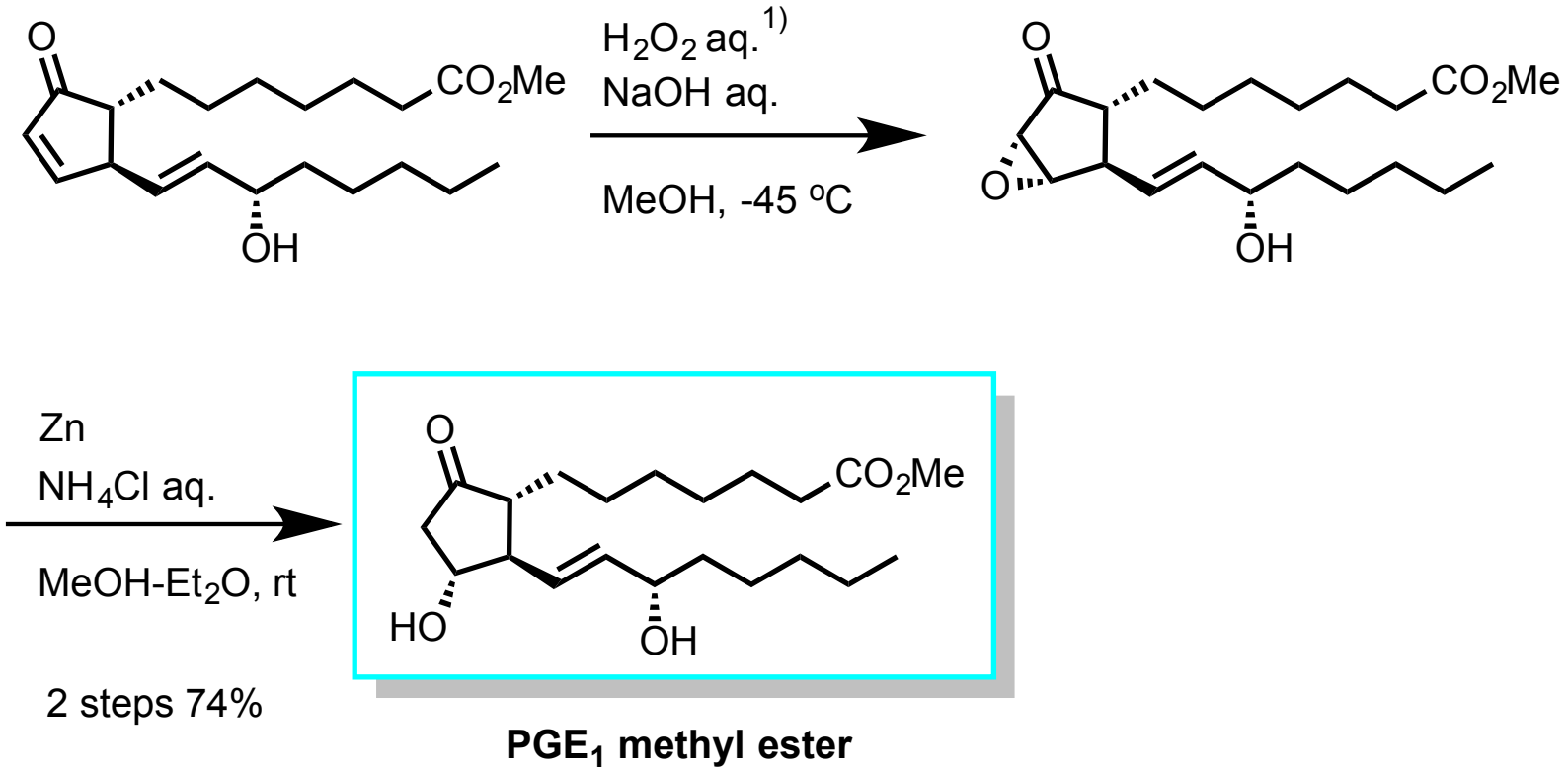
Chem. Eur. J. ASAP.

Nef Reaction





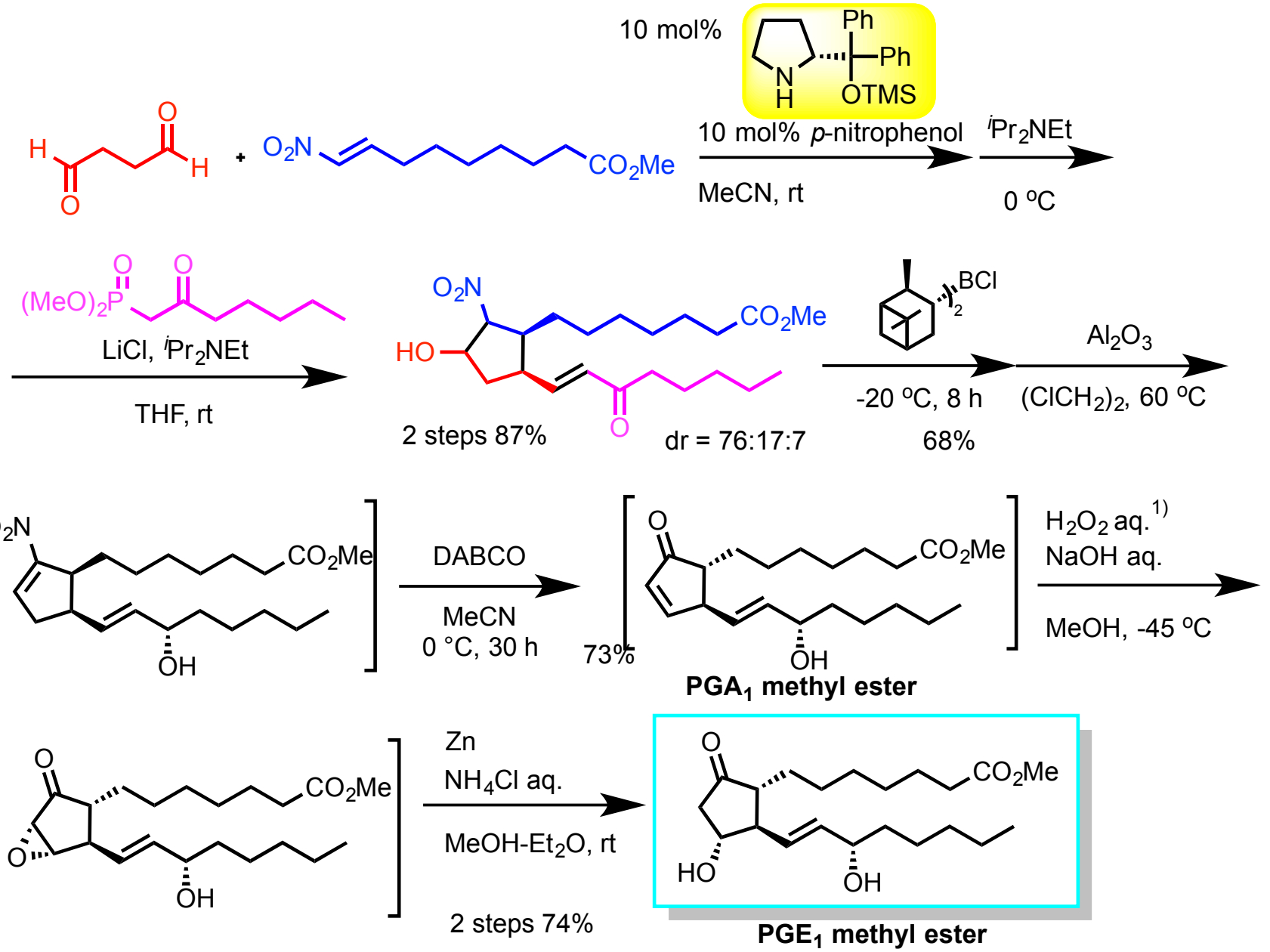
Chem. Eur. J. ASAP.



PGE_1 methyl ester

1) E. J. Corey *et al.*, *J. Org. Chem.*, **38**, 3187 (1973).

3 “One-pot” synthesis of PGE_1 methyl ester



3 pot, Total yield 14% Y. Hayashi, S. Umemiya, *Angew. Chem. Int. Ed.*, **2013**, *52*, 3450.

Angewandte Communications

Pot Economy in the Synthesis of Prostaglandin A_1 and E_1 Methyl Esters**

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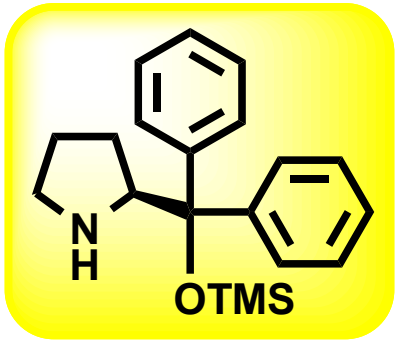
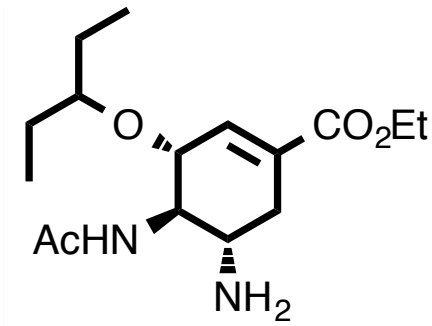
Dedicated to Professor E. J. Corey

Angew. Chem. Int. Ed., **2013**, *52*, 3450.

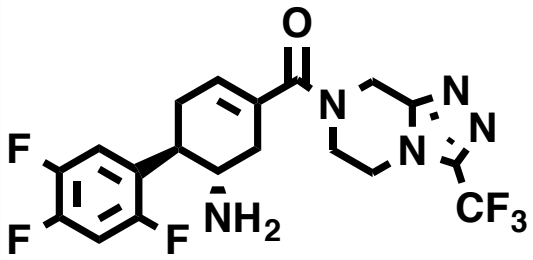
2013, July

Summary

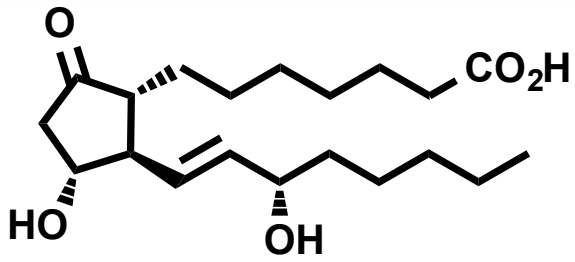




(-)-oseltamivir



ABT-341 (Abbott laboratory)



Prostaglandin E_1 (PGE_1)

One catalyst can change the synthesis.