Kyushu University 100th 2011
知の新世紀を拓く

Acid-catalyzed Rapid Nazarov Cyclization and its Asymmetric Conversion

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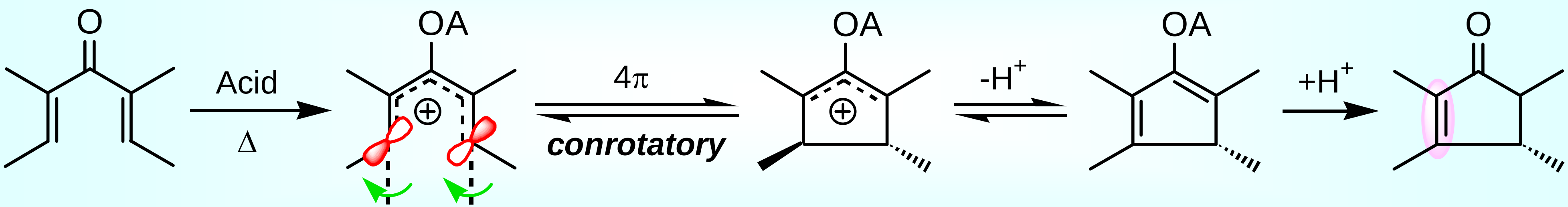
(Shindo Group)

Feb. 17. 2009, University of Illinois at Urbana-Champaign

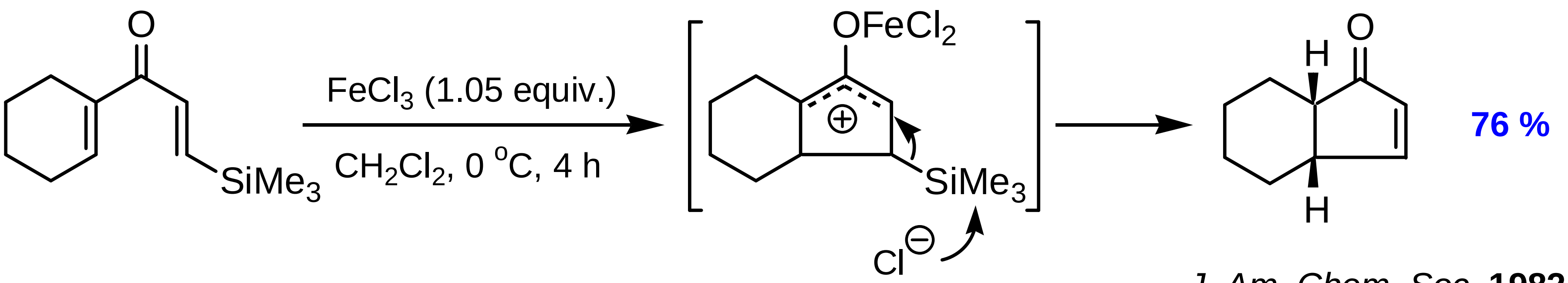
KYUSHU UNIVERSITY

Nazarov Cyclization



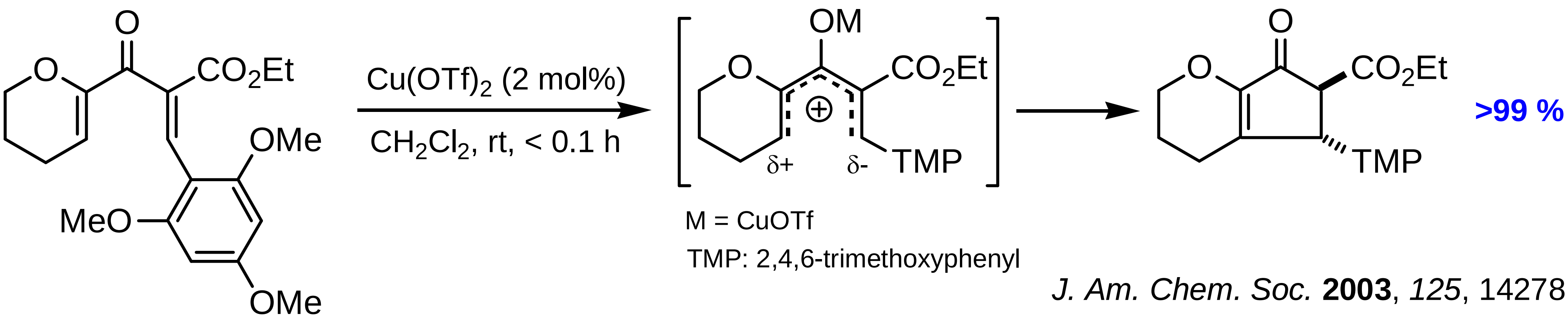
Nazarov, I. N. *Izv. Akad. Nauk. SSSR, Ser. Khim*. **1941**, 211-224.

S. E. Denmark (1982) ~ Silicon-direct Nazarov cyclization ~



J. Am. Chem. Soc. **1982**, *104*, 2642.

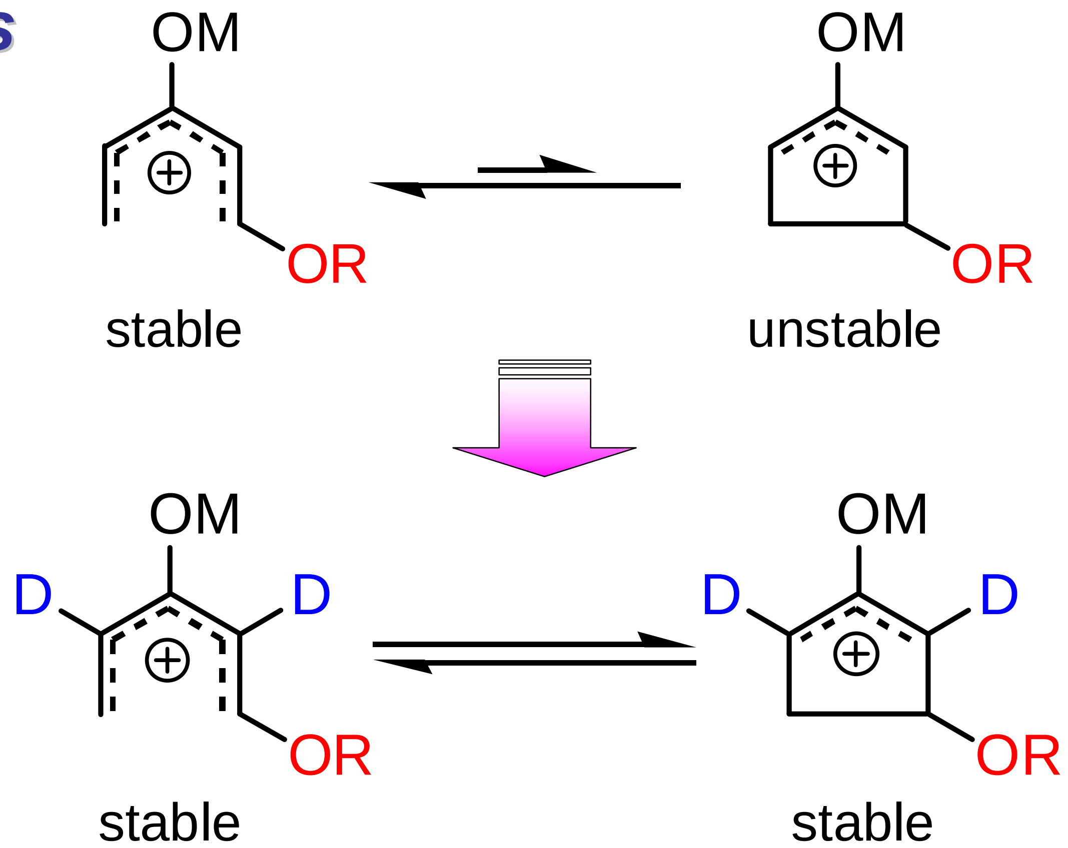
A. J. Frontier (2003) ~ Polarizing Nazarov cyclization ~



J. Am. Chem. Soc. **2003**, *125*, 14278.

Novel effect of electron-donating β-substituents

Concepts



☞ **Retro-Nazarov**

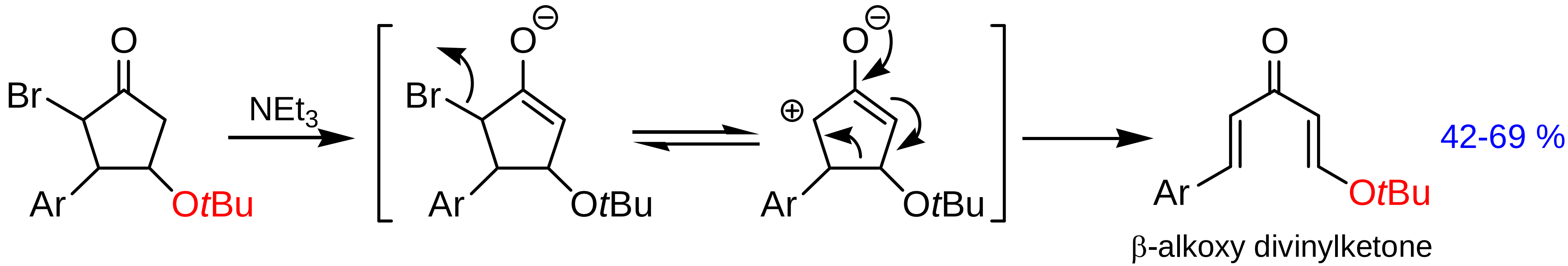
☞ **New Nazarov**

D: electon-donating group

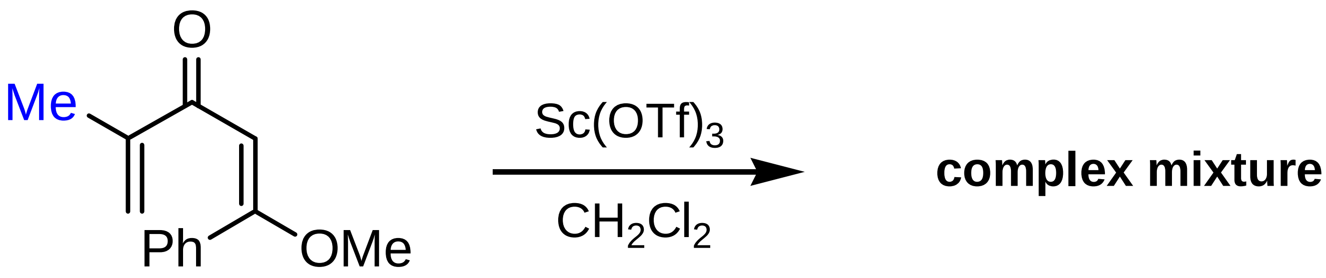
☞ **Elimination of β-alkoxide** induced the **rapid** and **regioselective** reaction.

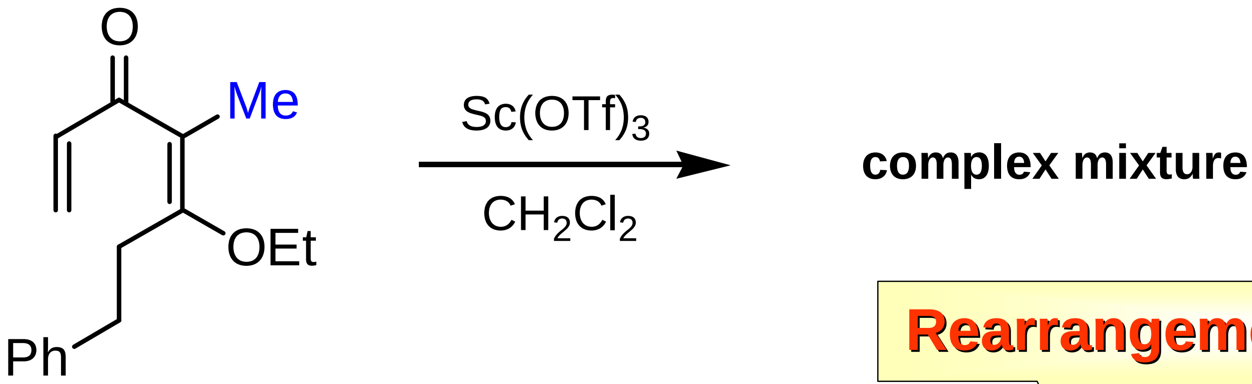
Retro-Nazarov cyclization

Harmata. M. *et al.* *J. Am. Chem. Soc.* **2002**, *124*, 14328; **2004**, *126*, 10954.



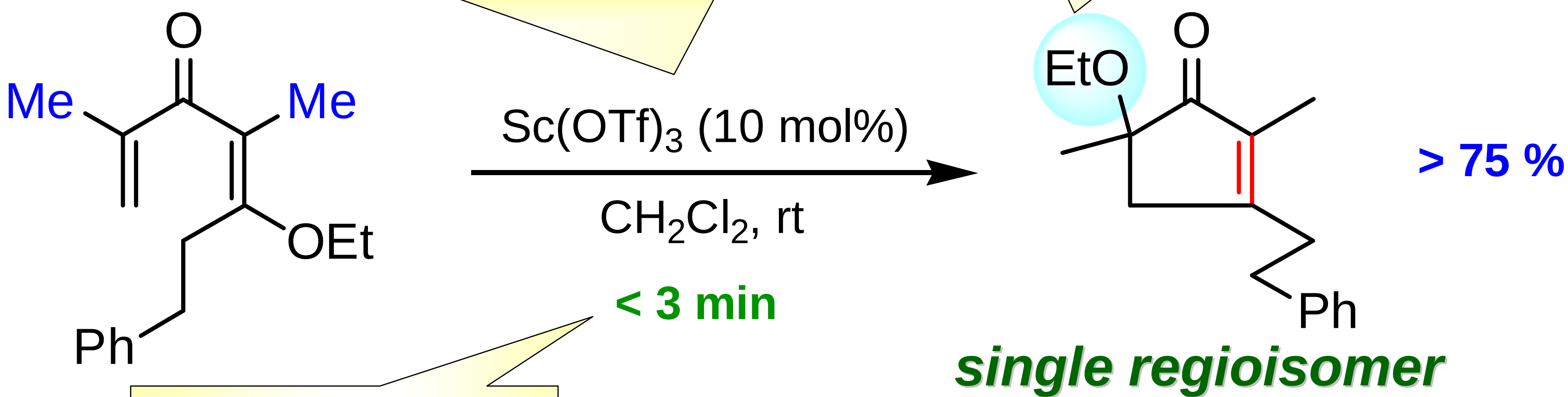
Acid-catalyzed rapid Nazarov cyclization





Rearrangement of alkoxyl group

Highly efficient acid-catalyzed reaction

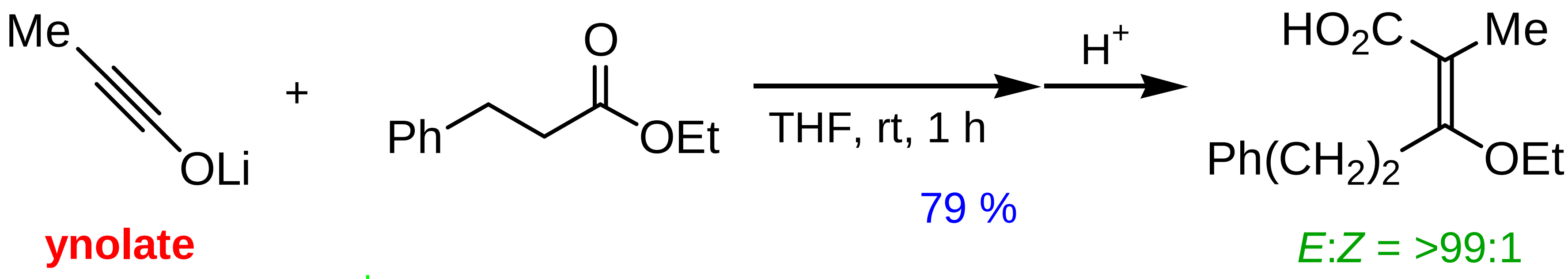


Quick reaction

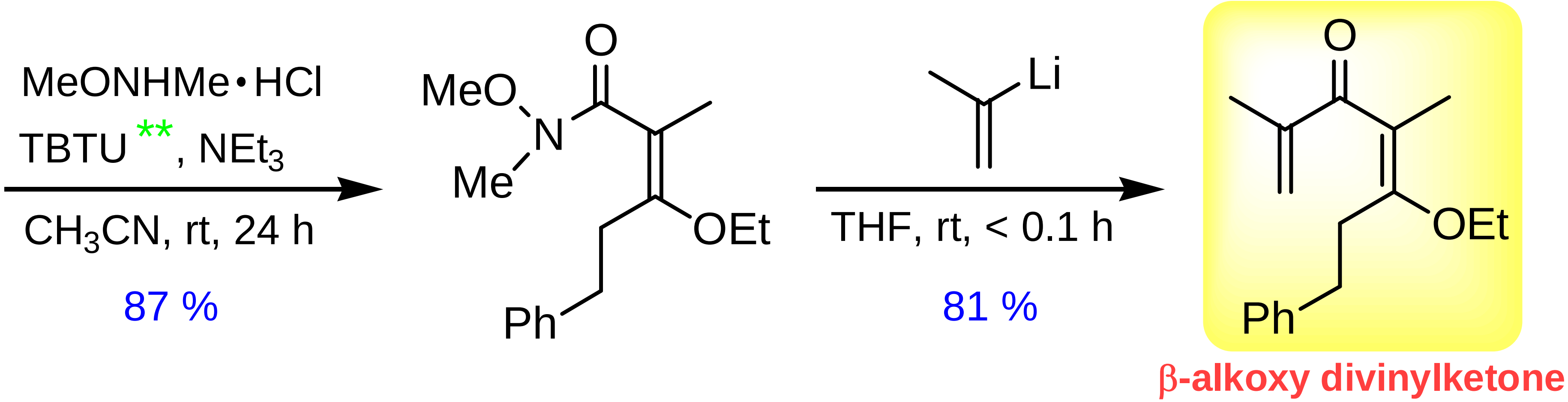
Regioselective formation

Synthesis of β-alkoxy divinylketones

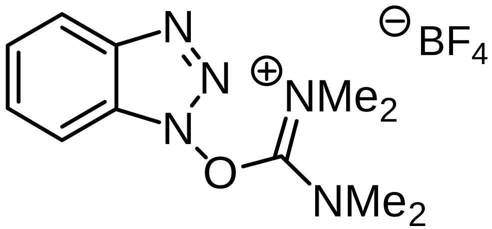
Torquoselective Olefination*



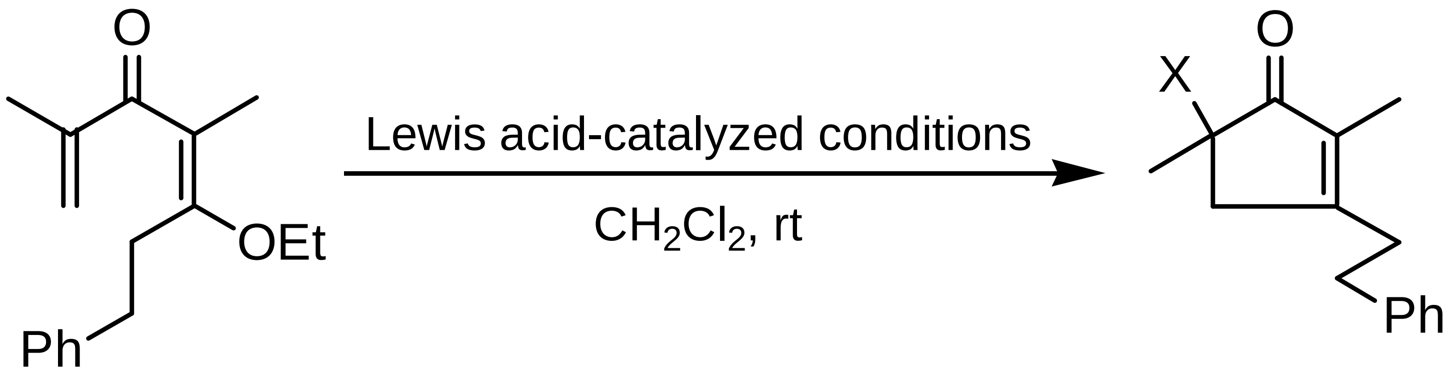
*Shindo, M. *et al. J. Am. Chem. Soc.* **2006**, *128*, 1062.



**TBTU : *O*-(Benzotiazol-1-yl)-
N,*N*,*N*',*N*'-tetramethyluronium
tetrafluoroborate



Lewis-acid catalyzed Nazarov cyclization



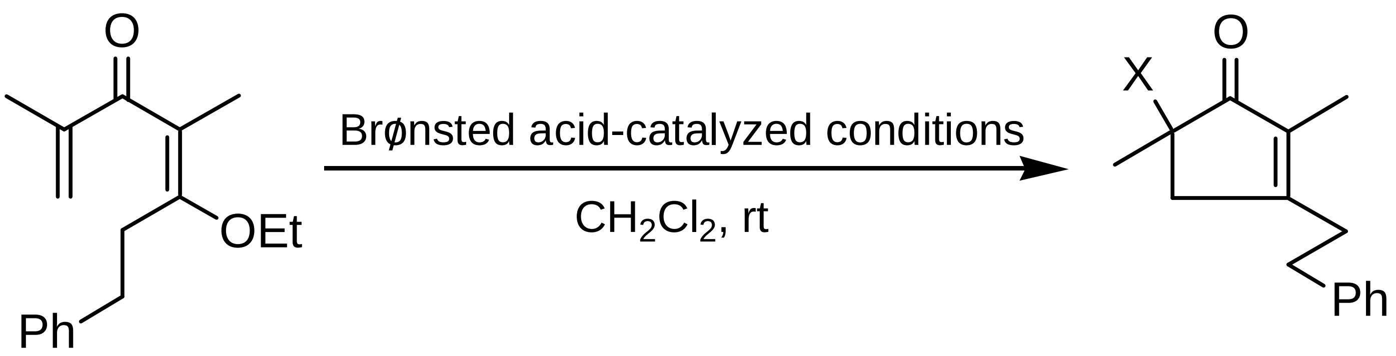
1: X = OEt
2: X = OMe
3: X = OH
4: X = Cl

Entry [a]	Lewis acid	mol %	Time (min)	Additive	Product	Yield (%)
1	$FeCl_3$	10	< 3		**1**	62
2 [b]	$Sc(OTf)_3$	10	< 3		**1**	92
3	$Sc(OTf)_3$	1	10		**1**	76
4	$Sc(OTf)_3$	10	< 3	MeOH (10 equiv.)	**2**	72
5 [c]	$Sc(OTf)_3$	10	20	H_2O (1 equiv.)	**3**	94
6	$TiCl_4$	100	< 3		**4**	73

[a] 0.025 M, unless otherwise noted. [b] 0.25 M. [c] The reaction was carried out at 0 ^oC in MeCN.

Shindo, M., Yaji, K., Kita, T., Shishido, K. *Synlett* , **2007**, 1096.

Brønsted-acid catalyzed Nazarov cyclization



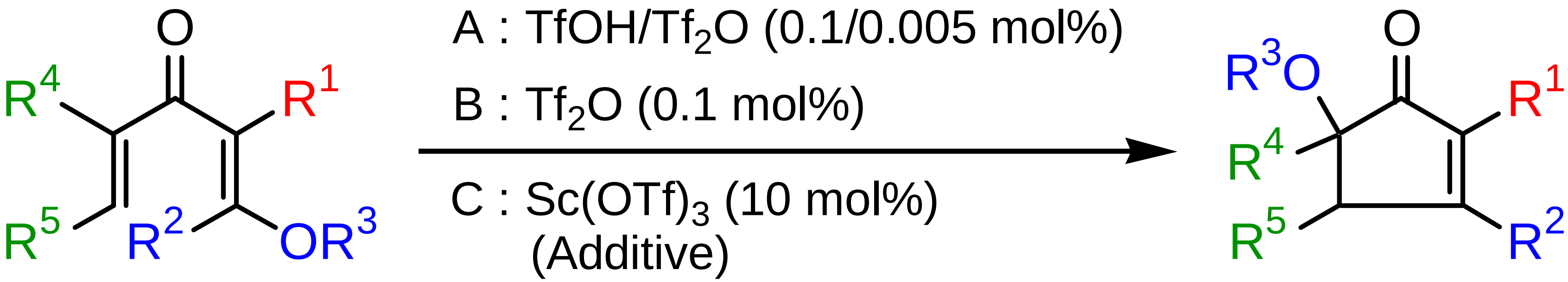
1: X = OEt
4: X = Cl

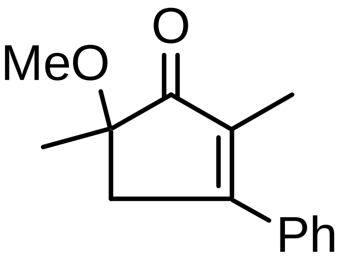
Entry [a]	Brønsted acid	pKa [b]	mol %	Time (min)	Product	Yield (%)
1	AcOH	4.8	100	no reaction		
2	TsOH	-2.8	10	10	**1**	40
3	TFA	-0.25	200	240	**1**	39
4	HCl	-8	300	< 3	**4**	83
5	TfOH	-14	0.1	< 3	**1**	74
6	TfOH/Tf_2O	—	0.1/0.005	< 3	**1**	91
7	Tf_2O	—	0.001	< 3	**1**	80
8	Tf_2NH	< -14	0.1	< 3	**1**	76

[a] 0.25 M. [b] pKa value in H_2O.

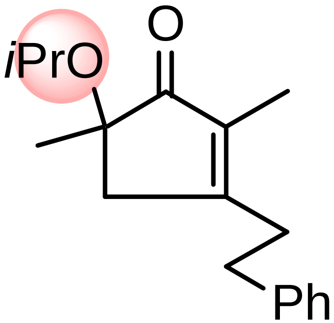
Shindo, M., Yaji, K., Kita, T., Shishido, K. *Synlett* , **2007**, 1096.

Synthesis of multi-substituted cyclopentenones

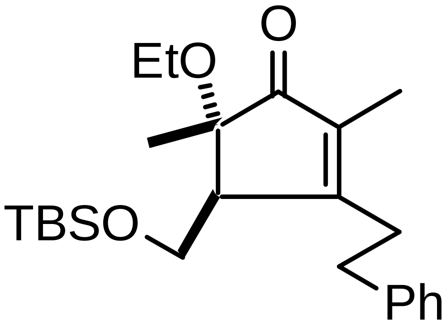




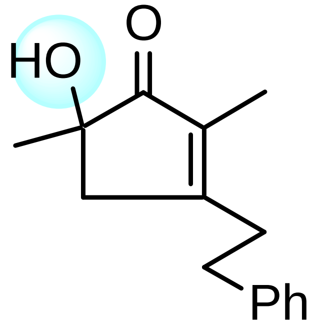
96 % (A)



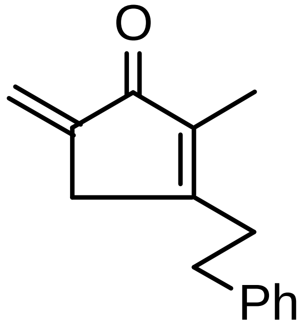
73 % (B)



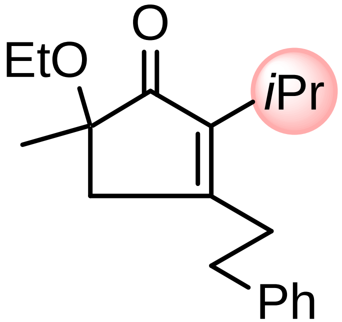
60 % (C)
>99% de



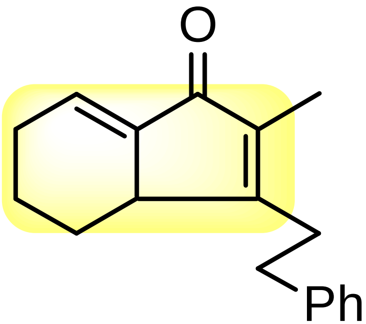
94 % (C)
(H_2O)



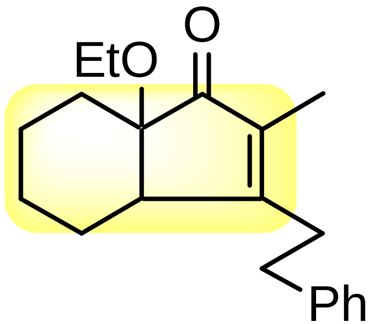
64 % (C)
(*t*BuOH)



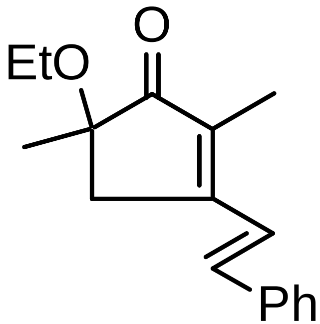
82 % (A)



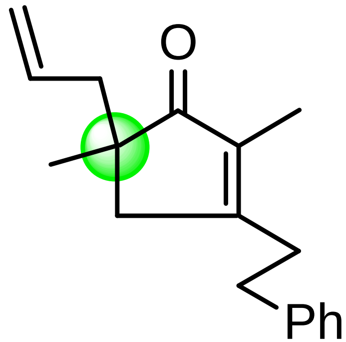
89 % (C)



58 % (C)
(EtOH)

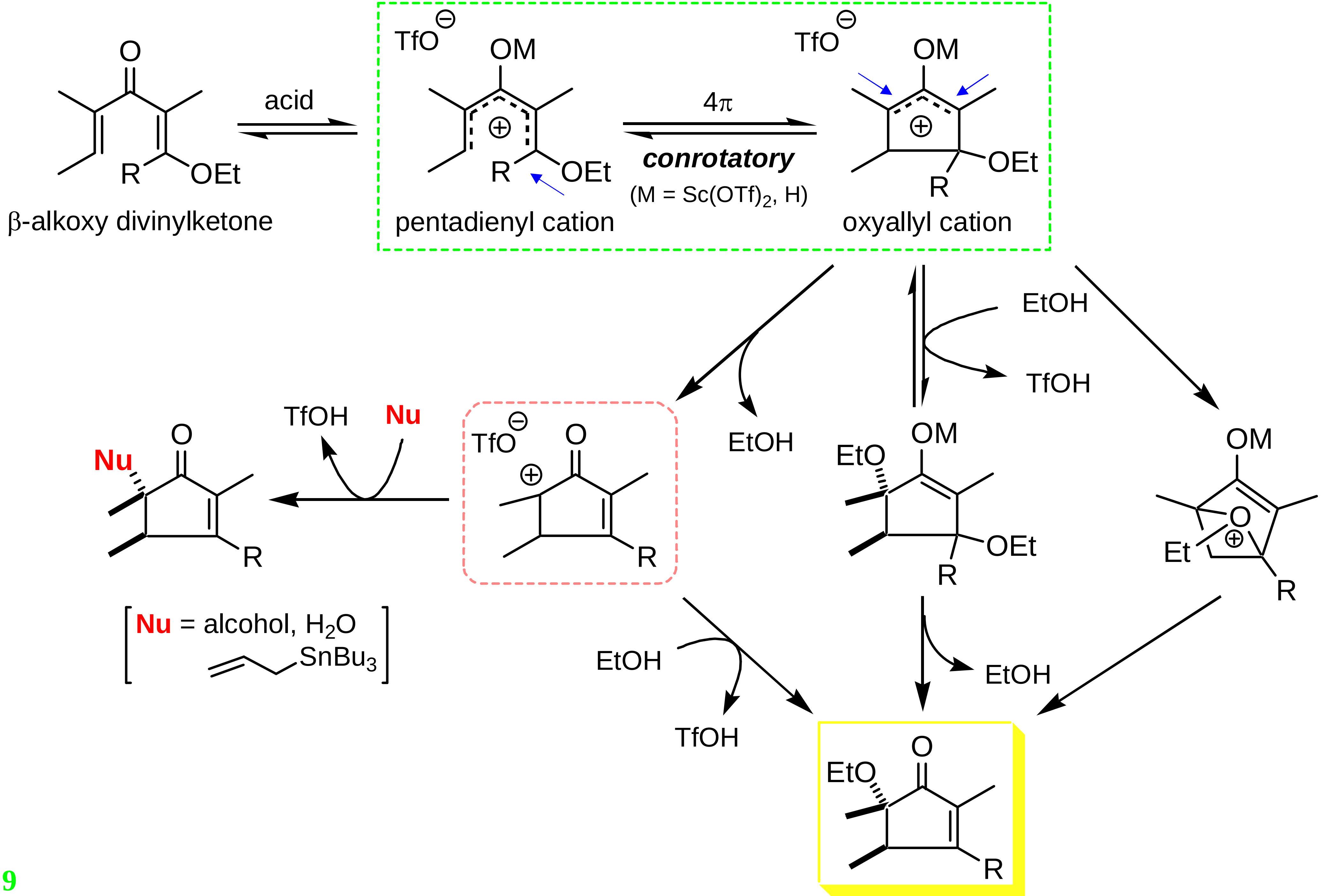


92 % (B)

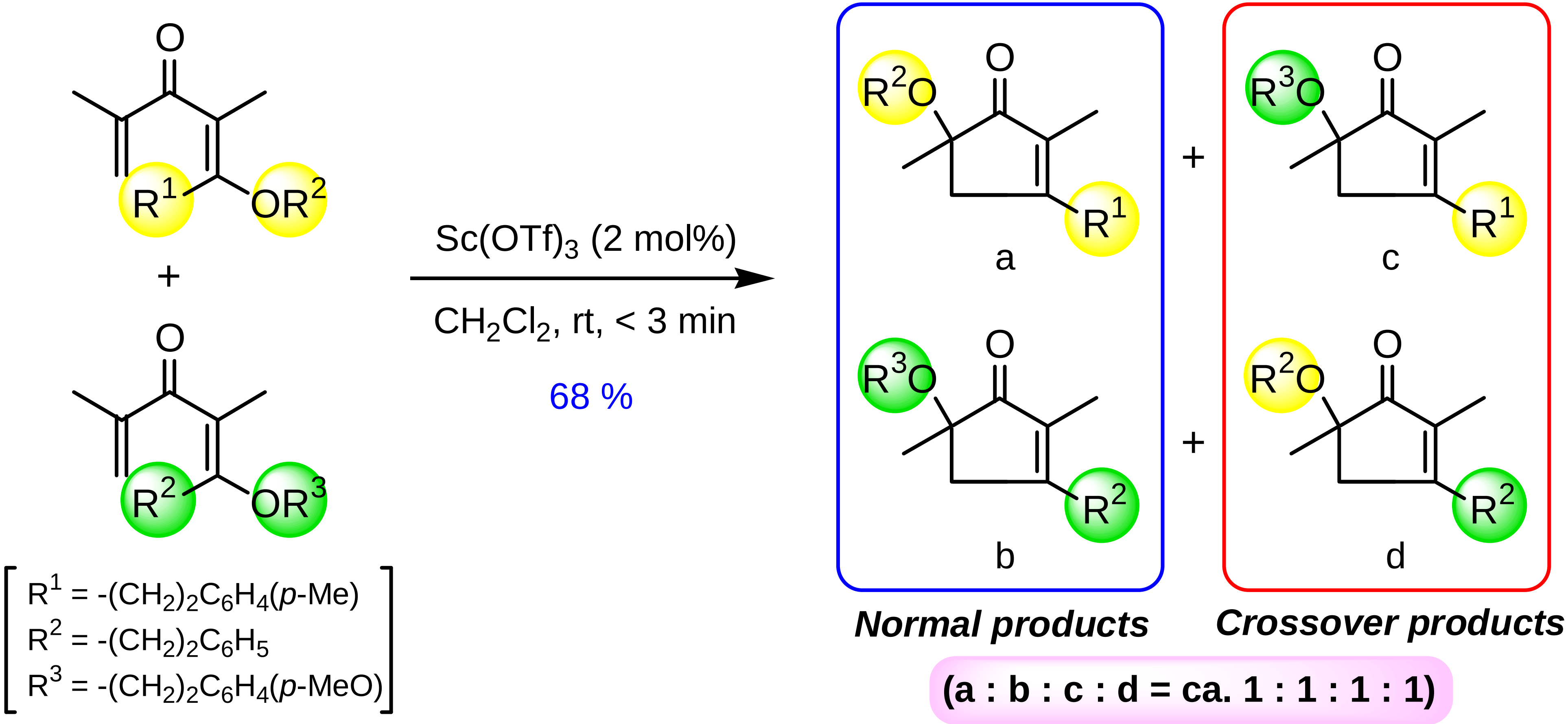


50 % (C)
(allylBu_3Sn)

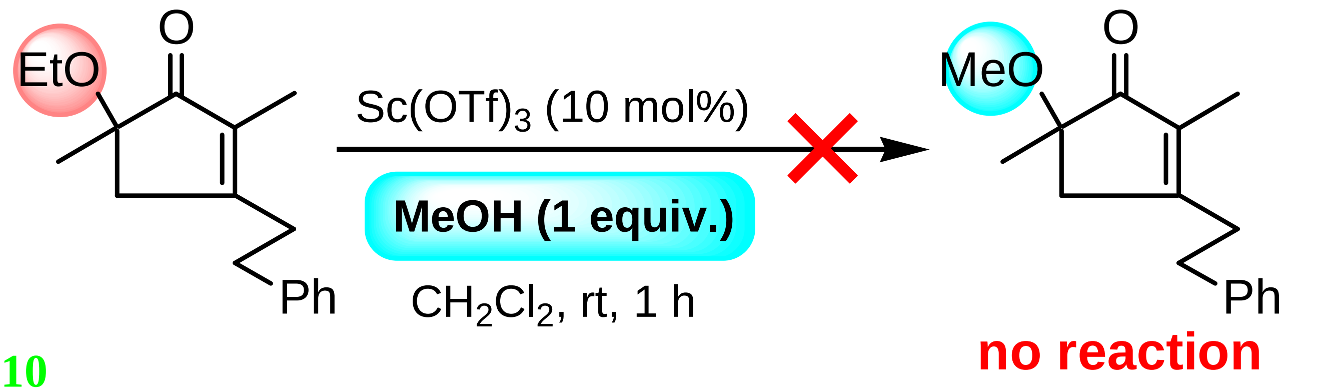
Proposed mechanism



Crossover experiments



R^1 = -$(CH_2)_2C_6H_4$(*p*-Me)
R^2 = -$(CH_2)_2C_6H_5$
R^3 = -$(CH_2)_2C_6H_4$(*p*-MeO)

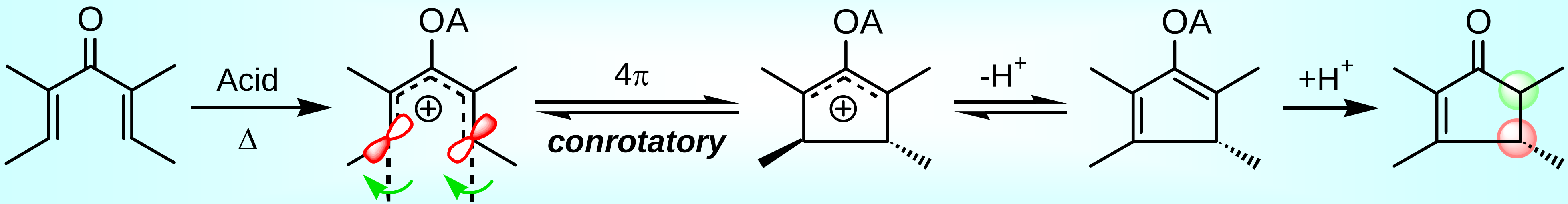


Inter-molecular Alkoxide Trapping

~~Intra-molecular Alkoxide Trapping~~

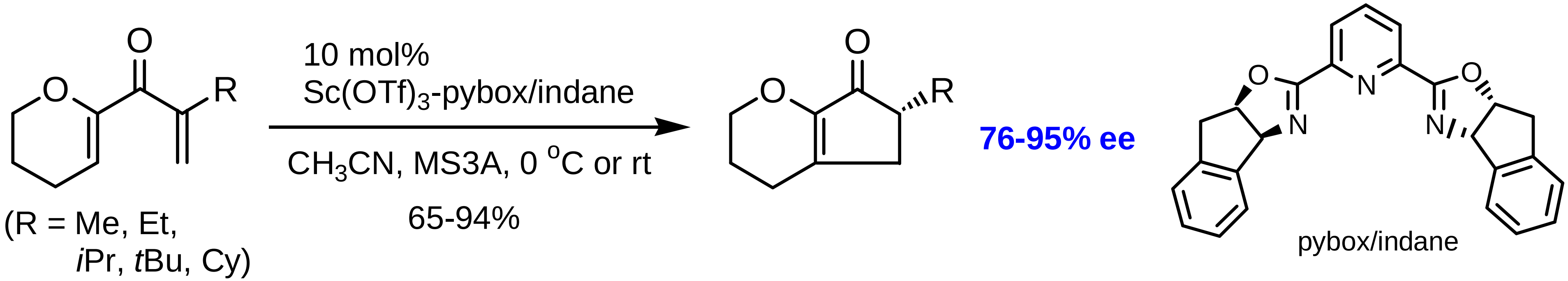
Asymmetric Nazarov cyclization

Nazarov Cyclization



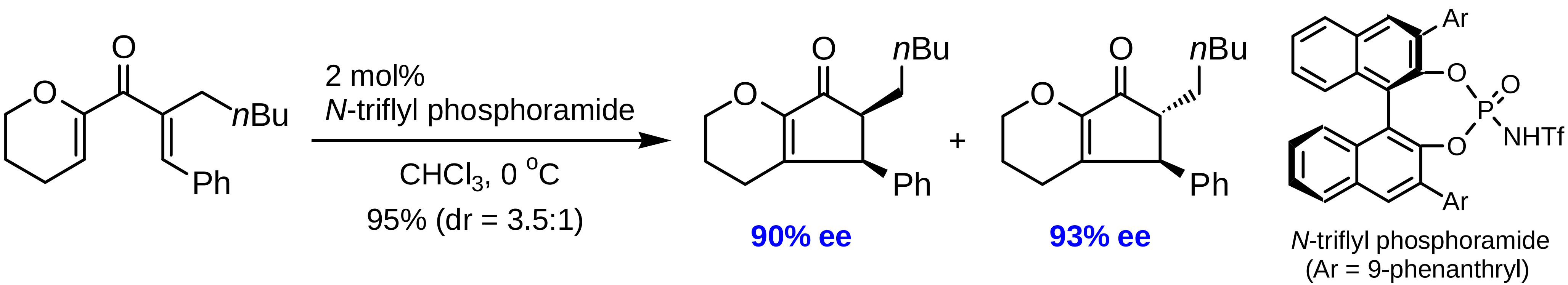
Nazarov, I. N. *Izv. Akad. Nauk. SSSR, Ser. Khim*. **1941**, 211-224.

D. Trauner (2004) ~ Catalytic Asymmetric Proton Transfer ~



J. Am. Chem. Soc. **2004**, *126*, 9544.

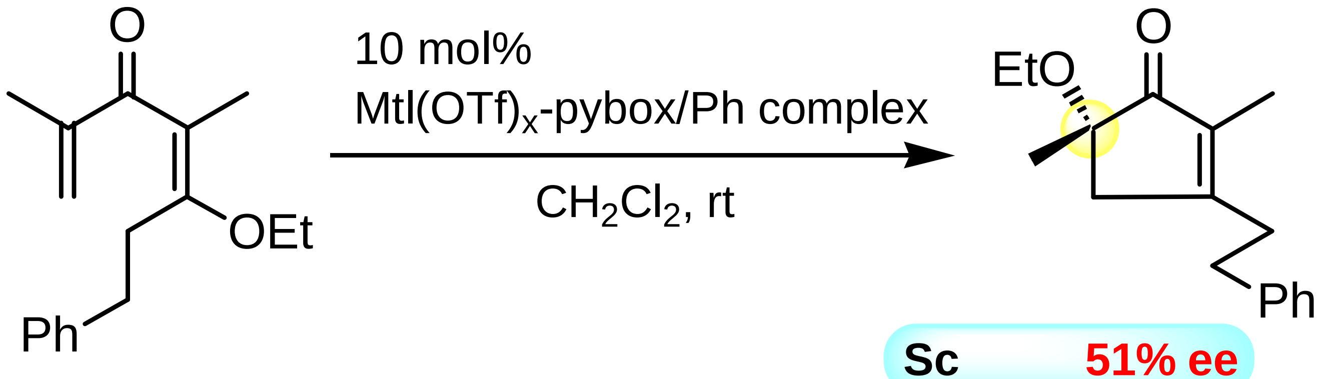
M. Rueping (2007) ~ The First Enantioselective Organocatalytic Electrocyclic Reaction ~



Angew. Chem. Int. Ed. **2007**, *46*, 2097.

Chiral bisoxazoline-type Lewis acids

<MtI(OTf)$_x$- pybox/Ph complexes>

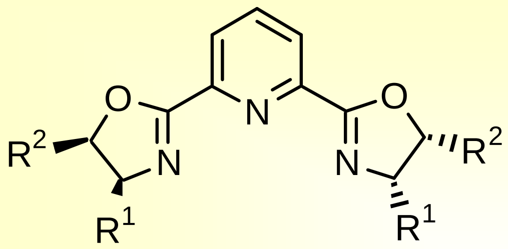


Sc **51% ee**

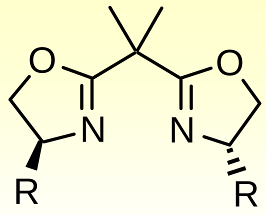
Cu, Zn, Fe, In, Sn, Yb, La, Pr, Eu   0 ~ 4% ee

<Sc(OTf)$_3$ - Ligand complexes>

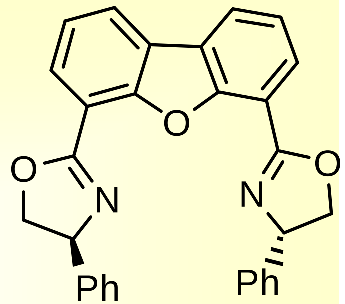
Entry	Ligand	Time (h)	Yield (%)	ee (%)
1	pybox/Ph	3	65	**51**
2	pybox/*p*-MeO-Ph	2	56	46
3	pybox/Ph, Me	0.5	69	8
4	pybox/indane	5	59	3
5	pybox/*i*-Pr	12	37	9
6	pybox/Bn	24	46	3
7	box/Ph (Cu)	1	74	0
8	box/*t*-Bu (Cu)		no reaction	
9	DBFOX/Ph (Ni)	0.5	90	0



pybox/Ph: R^1 = Ph, R^2 = H
pybox/*p*-MeOPh:
R^1 = *p*-MeO-Ph, R^2 = H
pybox/*i*-Pr: R^1 = *i*-Pr, R^2 = H
pybox/Ph, Me: R^1 = Ph, R^2 = Me
pybox/indane: R^1, R^2 = indanyl
pybox/Bn: R^1 = Bn, R^2 = H

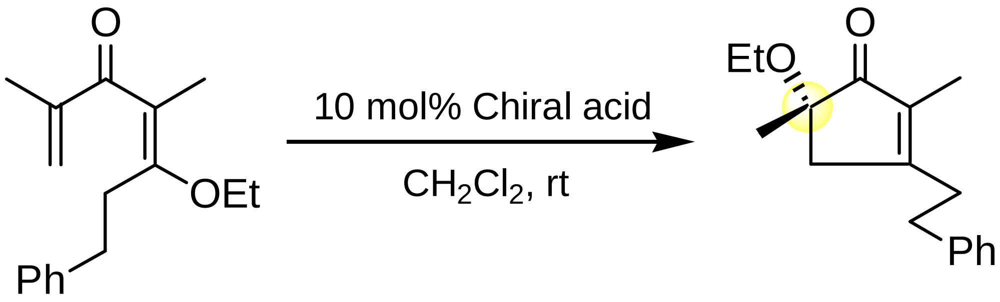


box/Ph: R = Ph
box/*t*-Bu: R = *t*-Bu

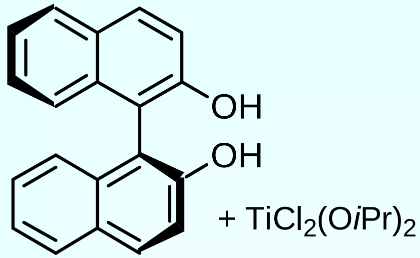


DBFOX/Ph

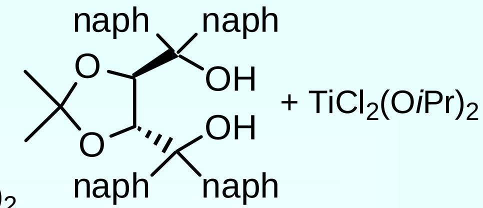
Screening of chiral Lewis or Brønsted acids



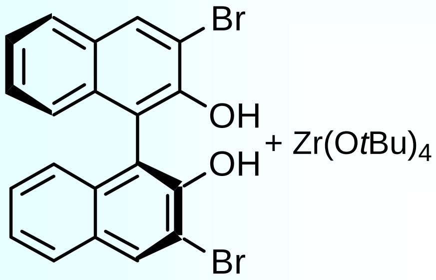
Entry	Chiral acid	Time (h)	Yield (%)	ee (%)
(chiral Lewis acid)				
1	BINOL / Ti (**1**)	2.5	61	65
2	TADDOL / Ti (**2**)		0	—
3	BINOL / Zr (**3**)		no reaction	
4	BINOL / $Sc(OTf)_3$/ TMP (**4**)	48	30	0
(chiral Brønsted acid)				
5	phosphoric acid / Ph (**5**)		0	—
6	*N*-triflyl phosphoramide / Ph (**6**)	< 0.1	44	14
7	TADDOL		no reaction	



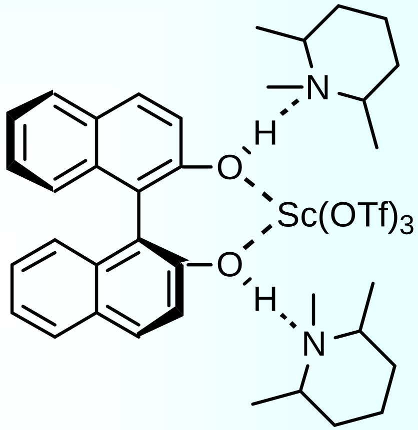
Mikami
BINOL/Ti (**1**)



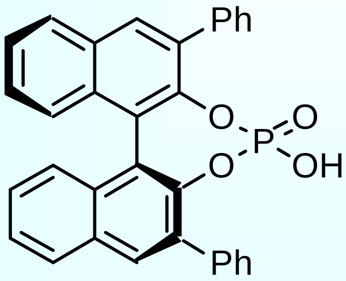
Narasaka
TADDOL/Ti (**2**)



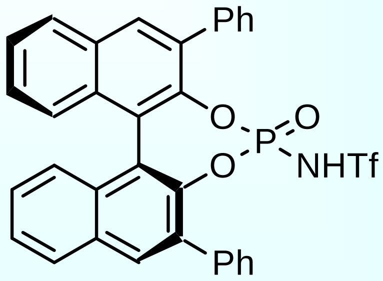
J. R. Pedro
BINOL/Zr (**3**)



S. Kobayashi
BINOL/$Sc(OTf)_3$/TMP (**4**)



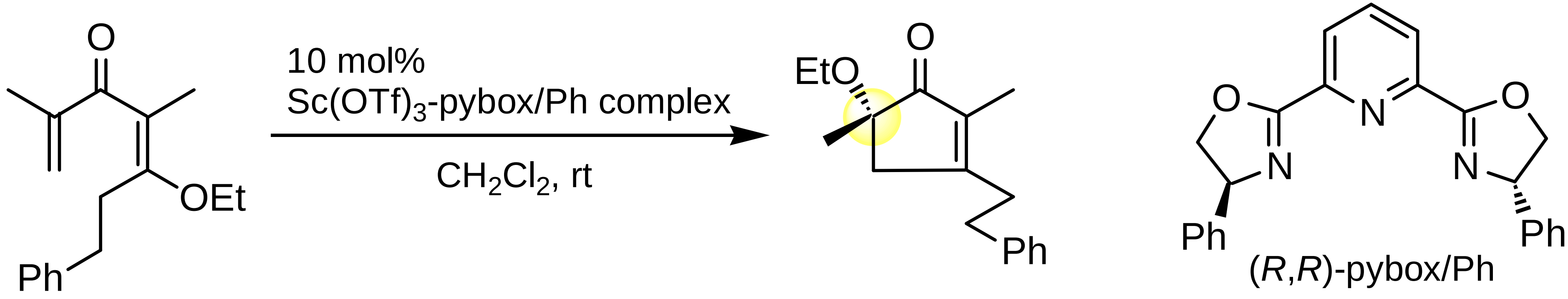
Terada, Akiyama
phosphoric acid / Ph (**5**)



H. Yamamoto
N-triflyl phosphoramide / Ph (**6**)

Capture of TfOH

The ratio of $Sc(OTf)_3$: pybox/Ph



Entry	$Sc(OTf)_3$: pybox	Additive (ratio) [b]	Time (h)	Yield (%)	ee (%)
1	1 : 1.1	—	1	71	0
2	1 : 1.5	—	1	64	21
3	1 : 1.8	—	3	65	**51**
4	1 : 2.0	—	5	72	40
5	1 : 1.1	NEt_3 (0.7)	3	71	**54**
6 [a]	1 : 1.1	NEt_3 (0.9)	20	55	56
7	1 : 1.1	pyridine (0.7)	20	30	54
8	1 : 1.1	Hünig base (0.7)	1.5	69	46
9	1 : 1.1	K_2CO_3 (0.7)	2	58	25

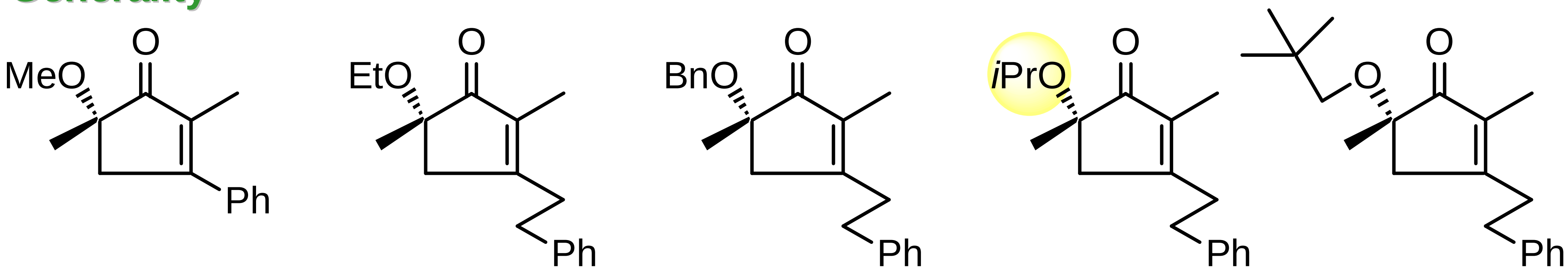
← Condition (A) (entry 3)

← Condition (B) (entry 5)

a) The starting material remained. b) The ratio based on $Sc(OTf)_3$.

Asymmetric Nazarov cyclization

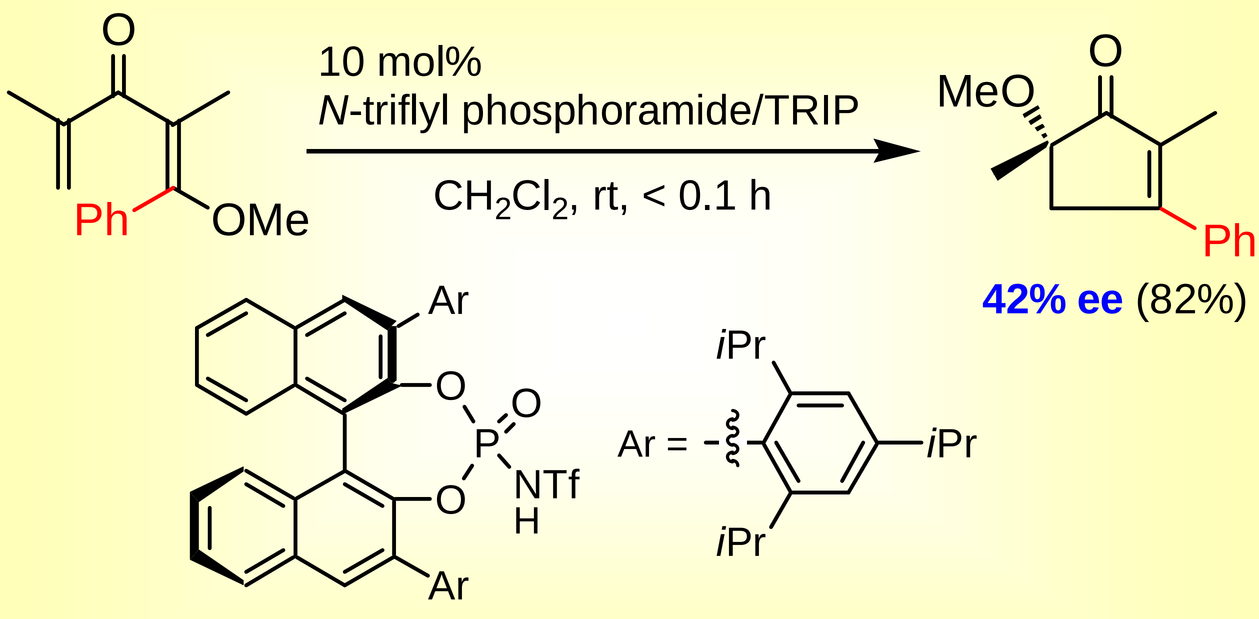
Generality



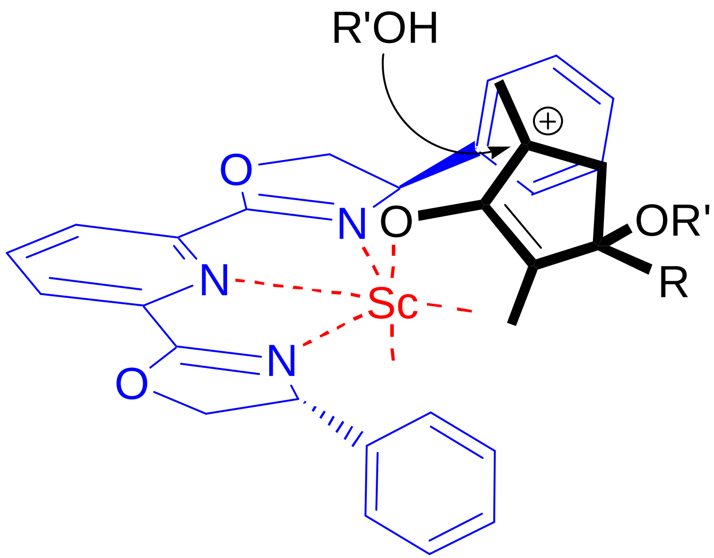
40% (12% ee) | 71% (54% ee) | 53% (67% ee) | 38% (**84% ee**) | 34% (0% ee)

☞ Sterically hindered β-alkoxy groups improved the stereoselectivity.

Chiral Brønsted acid catalyst

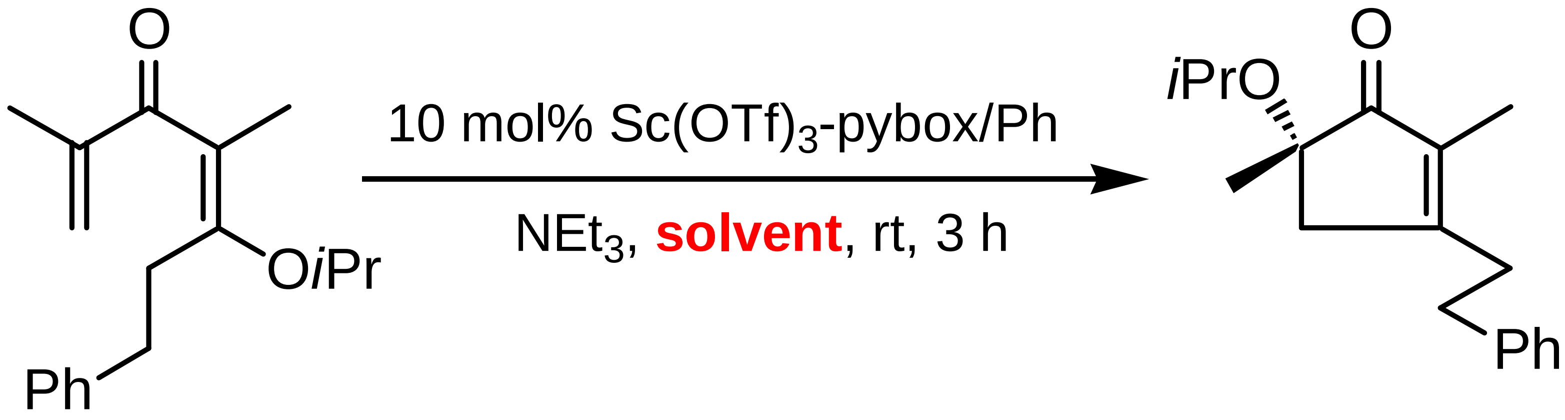


N-triflyl phosphoramide/TRIP
(TRIP: 2,4,6-triisopropyl phenyl)



Proposed model for asymmetric induction

Solvent effects

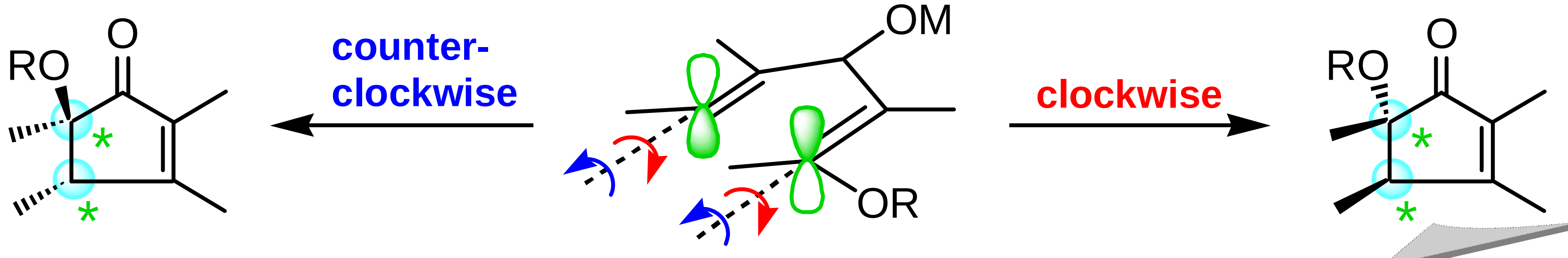


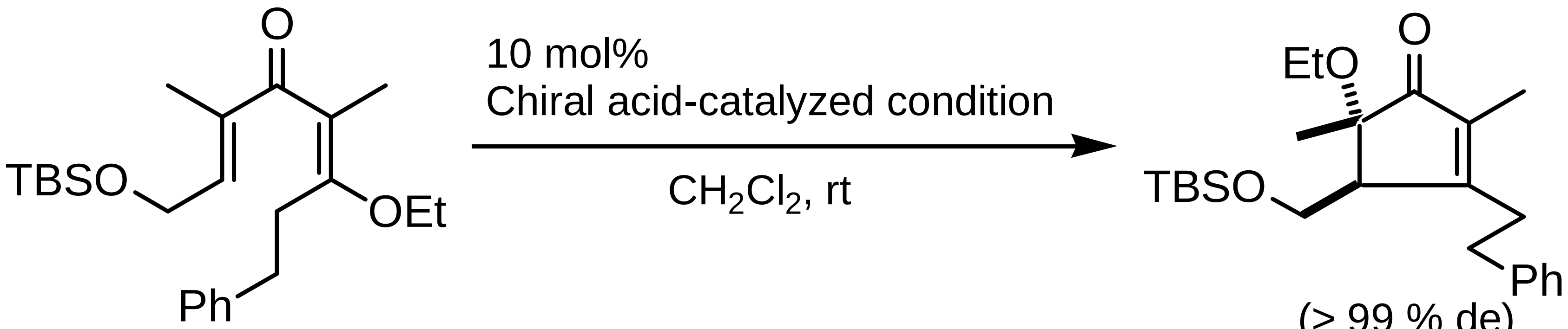
Entry	**Solvent**	Yield	ee (%)
1	CH_2Cl_2	41	80
2	MeOH	no reaction	
3	EtOH	no reaction	
4	*i*PrOH	55	91
5	*i*PrOH + CH_2Cl_2 (1:1)	56	90
6	*t*BuOH	no reaction	

☞ Using *i*PrOH as a solvent, stereoselectivity was improved.

Torquoselective Nazarov cyclization

Concept: Torquoselective Nazarov cyclization

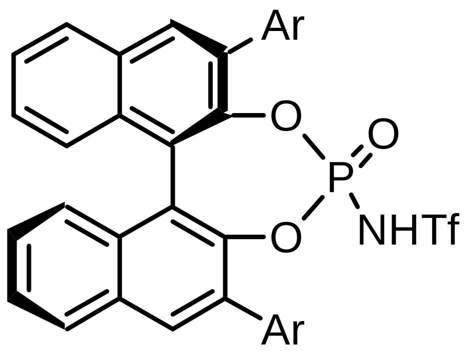




(> 99 % de)

Entry	Chiral acid	Time (h)	Yield (%)	ee (%)
1 [a]	Sc(OTf)$_3$-pybox/Ph	5	34	25
2 [a]	chiral phosphoramide / Ph	4	55	15
3	chiral phosphoramide / TRIP [b]	3	68	35

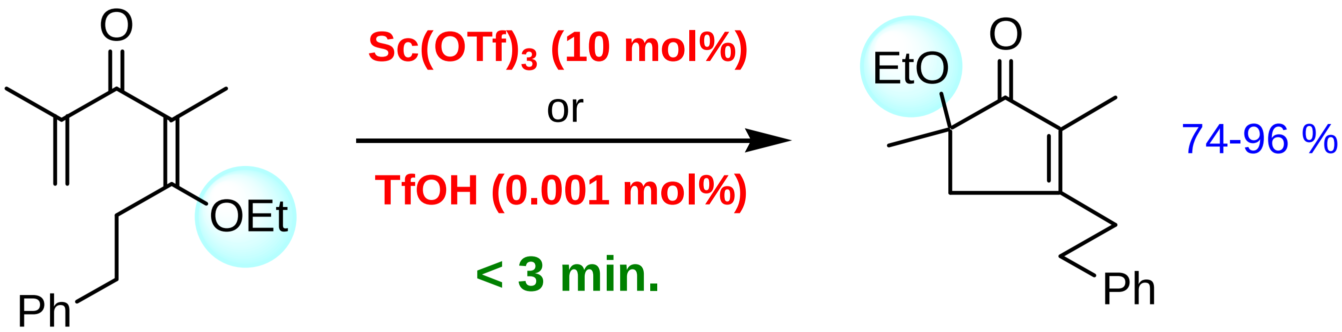
[a] Starting material was not consumed. [b] TRIP: 1,3,5-triisopropylbenzene



chiral phosphoramide
(Ar = Ph, TRIP)

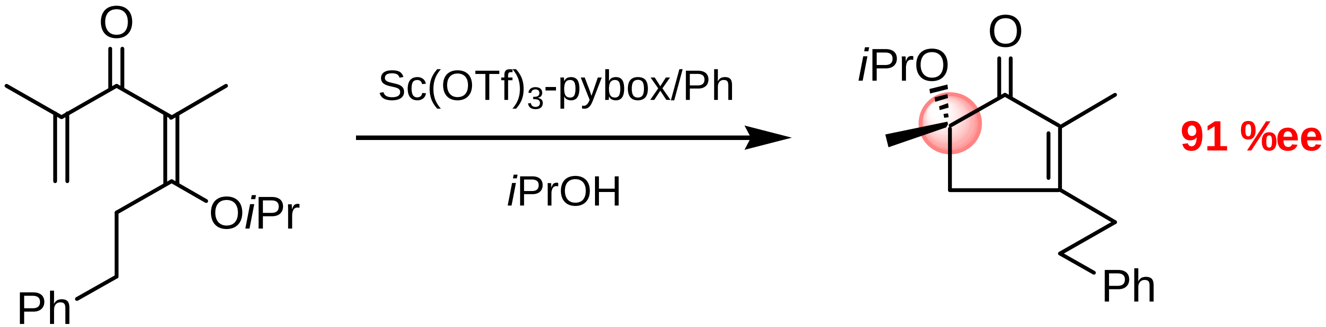
Conclusion

1. Acid-catalyzed Rapid Nazarov Cyclization



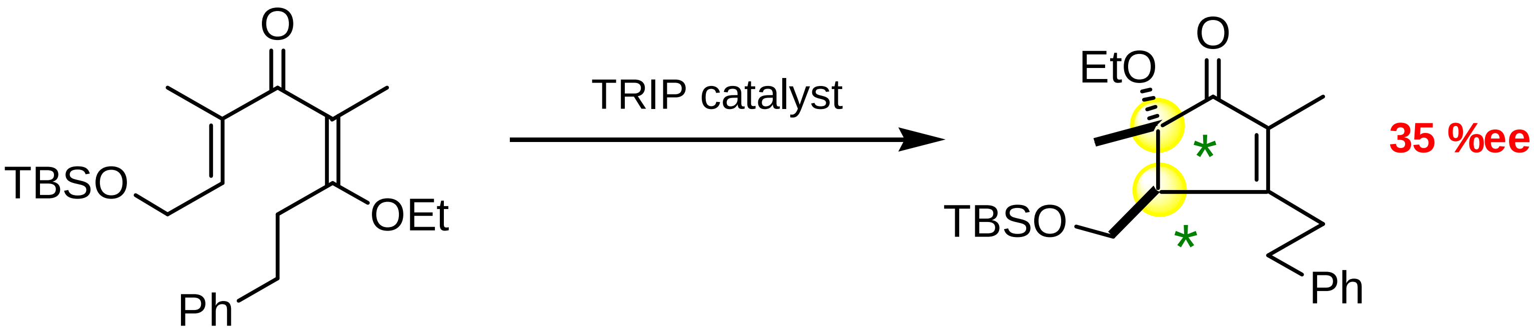
Shindo, M.; Yaji, K.; Kita, T.; Shishido, K. *Synlett* **2007**, *7*, 1096.

2. Catalytic Asymmetric Nazarov Cyclization



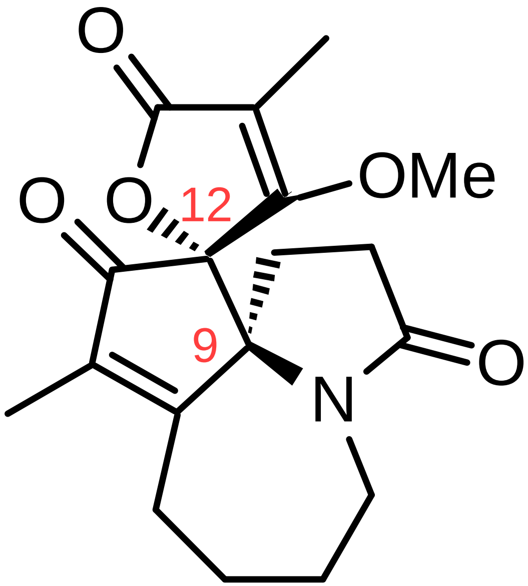
The 128th Annual Meeting of the Pharmaceutical Society of Japan Highlight Selected Title.

3. Asymmetric Torquoselective Nazarov Cyclization

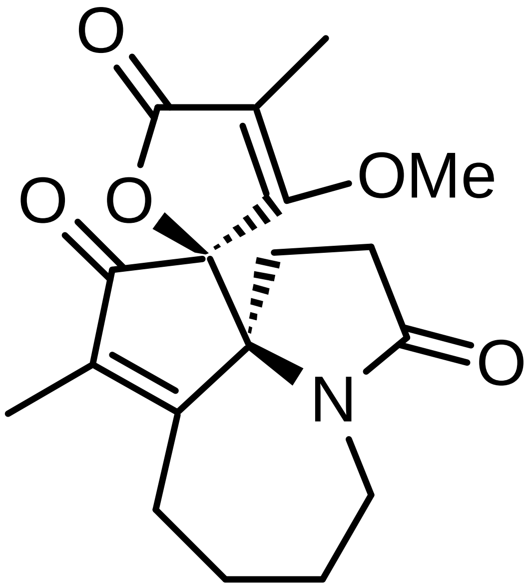


The current project

Total Synthesis of Stemonamide & Isostemonamide



stemonamide



isostemonamide

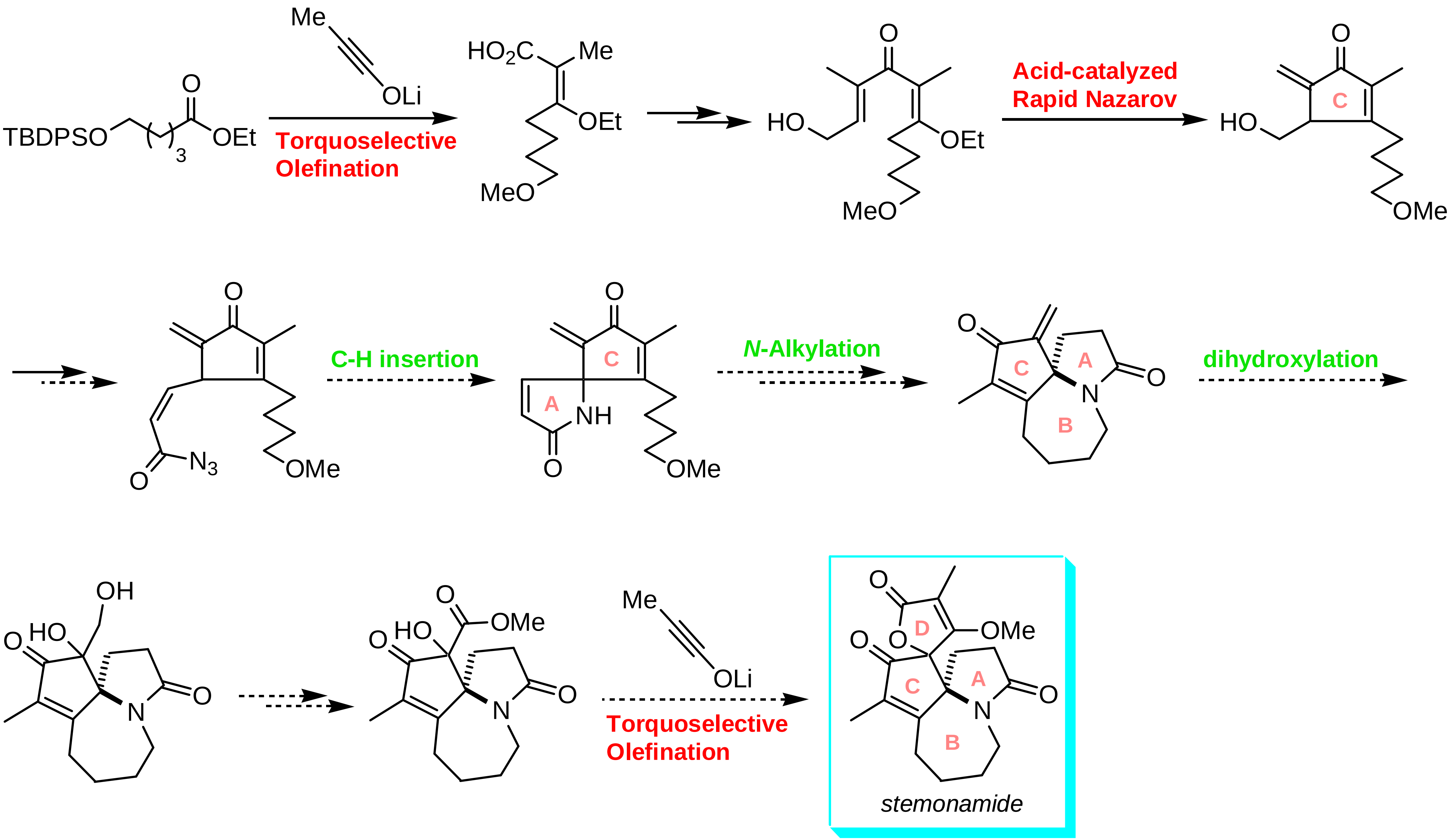
From the roots of *Stemona japonica*

stemona japonica Miq.

- Alkaloids from *Stemona* plants have been used in Chinese and Japanese folk medicine as cough-relief agents and insecticides.
- The biological activities of stemonamide & isostemonamide has not been reported.

Structure: Xu, R-S. *et al. J. Nat. Prod*. **1994**, *57*, 665.
The 1st Total Synthesis: (racemic) Kende, A. S. *et al. Org. Lett.* **2001**, *3*, 2505.;*Tetrahedron.* **2002**, *58*, 61.
The 2nd Total Synthesis: (racemic) Ishibashi, H. *et al. Org. Lett*. **2008**, *10*, 197.

Synthetic strategy for Stemonamide



Kyushu University (Shindo Lab.)

Prof. M. Shindo