JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Cite This: J. Am. Chem. Soc. 2017, 139, 17755–17758

pubs.acs.org/JACS

Total Synthesis of (−)-Himalensine A

Heyao Shi, Iacovos N. Michaelides,‡ Benjamin Darses, Pavol Jakubec, Quynh Nhu N. Nguyen, Robert S. Paton,* and Darren J. Dixon*

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K.

Robert S. Paton
Colorado State University

Darren J. Dixon
University of Oxford

J. Am. Chem. Soc. **2017,** *139,* 17755
Presented by: Chuan Pin Chen
CEM 852 Presentation
March 12, 2019

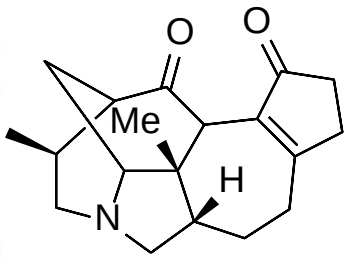
Introduction

- Daphniphyllum alkaloids

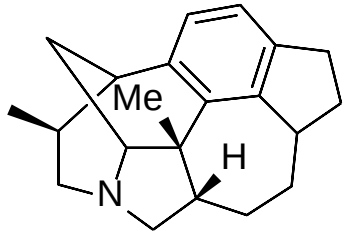
  Isolated from a genus of evergreen plants. >300 members

  anticancer, antioxidant, and vasorelaxation properties as well as elevation of nerve growth factor.

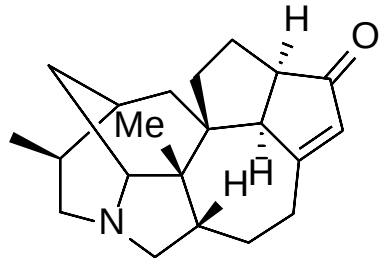
Chinese herbal medicine



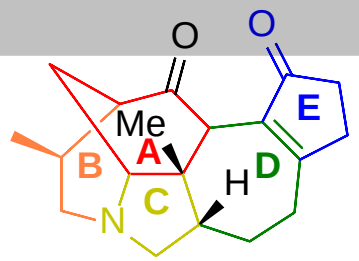
Himalensine A
2016



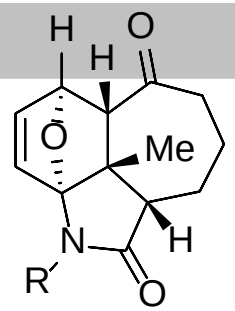
daphenylline
Nat. Chem., **2013**, *5*, 679.



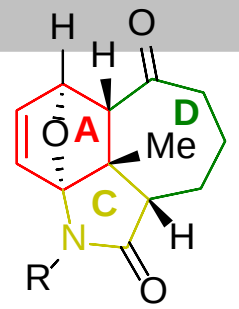
longeracinphyllin A
J. Am. Chem. Soc.' **2017**, *139*, 14893



Himalensine A

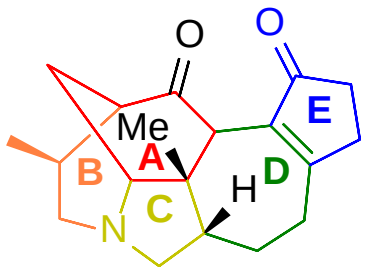


IMDAF core
Intramolecular Diels-alder furan reaction

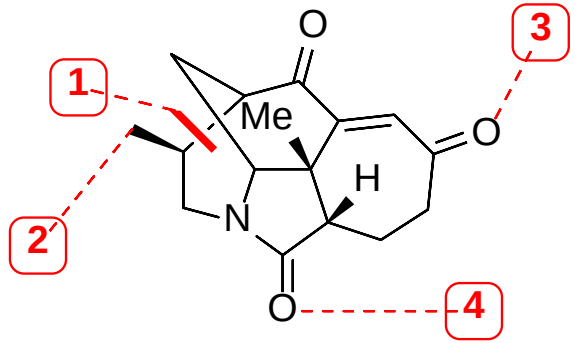


IMDAF core
J. Org. Chem., **1999**, *64*, 3595
Acta Chim. Slov., **2009**, *56*, 527

Retrosynthesis

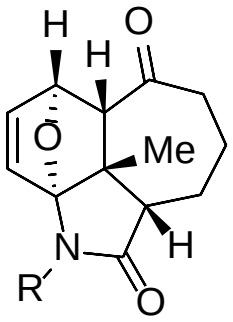


Himalensine A



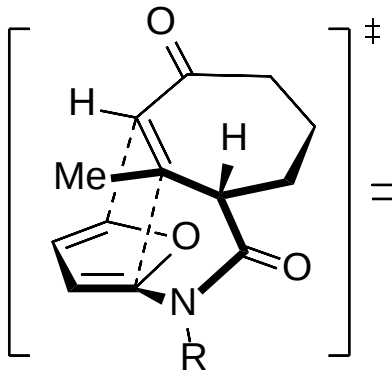
key disconnections:

1. radical cyclisation
2. disatereoselective hydrogenation
3. O_2 mediated C-H oxidation
4. chemoselective lactam reduction

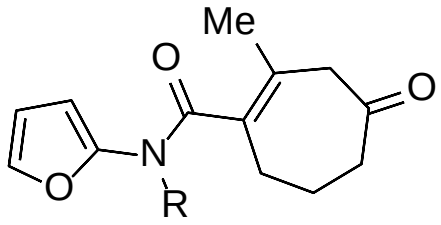


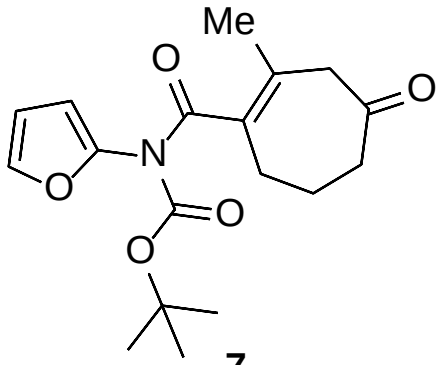
IMDAF

Diels-Alder



prototropic shift



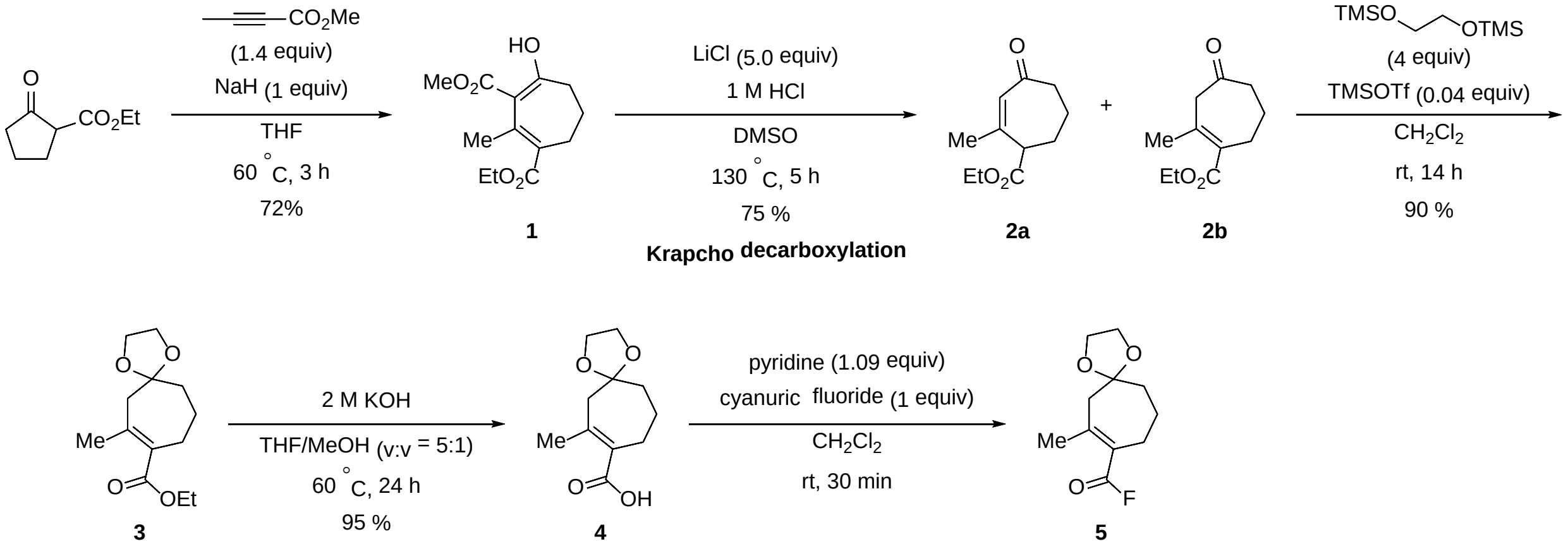


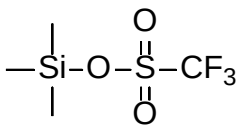
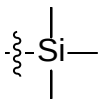
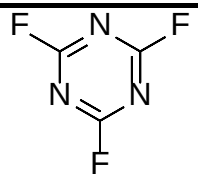
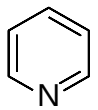
7

catalytic, enantioselective, 2 C-C bonds, 5 stereocenters
Tricyclic core construction

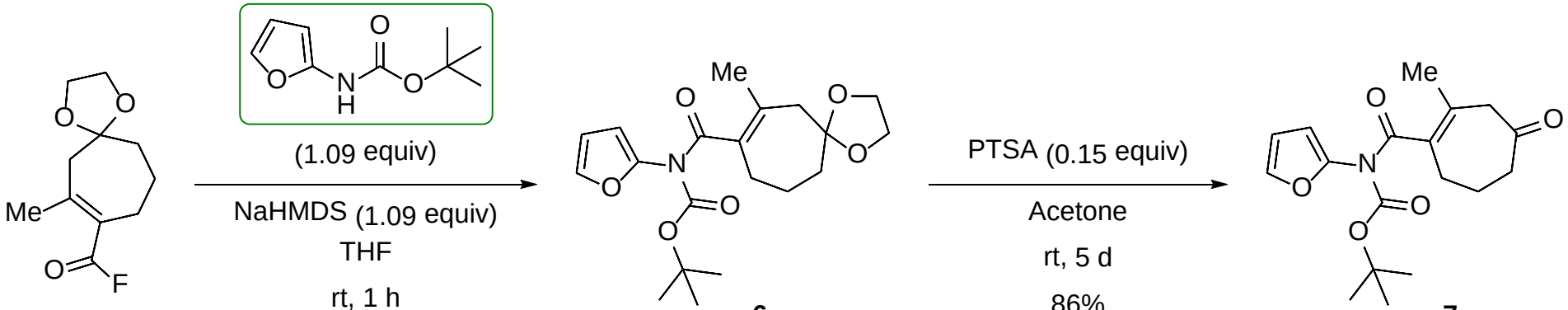
Note: label with bule color

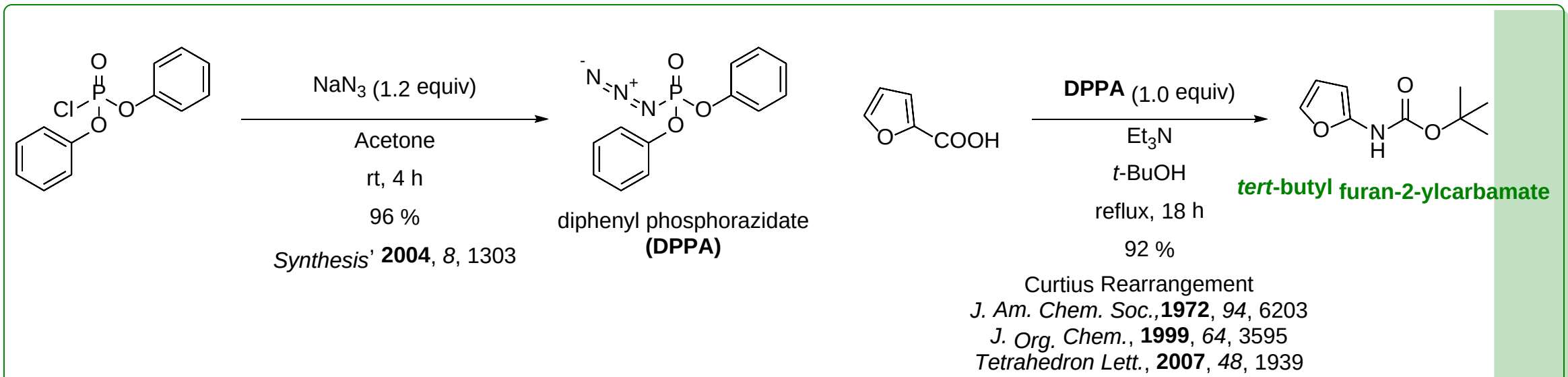
Synthesis of **(5)**



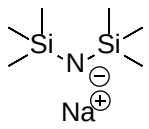
Trimethylsilyl trifluoromethanesulfonate **(TMSOTf)**	Trimethylsilyl **(TMS)**	2,4,6-trifluoro-1,3,5-triazine **(Cyanuric fluoride)**	pyridine
			

Synthesis of **(7)**

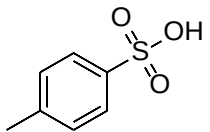




Sodium bis(trimethylsilyl)amide **(NaHMDS)**

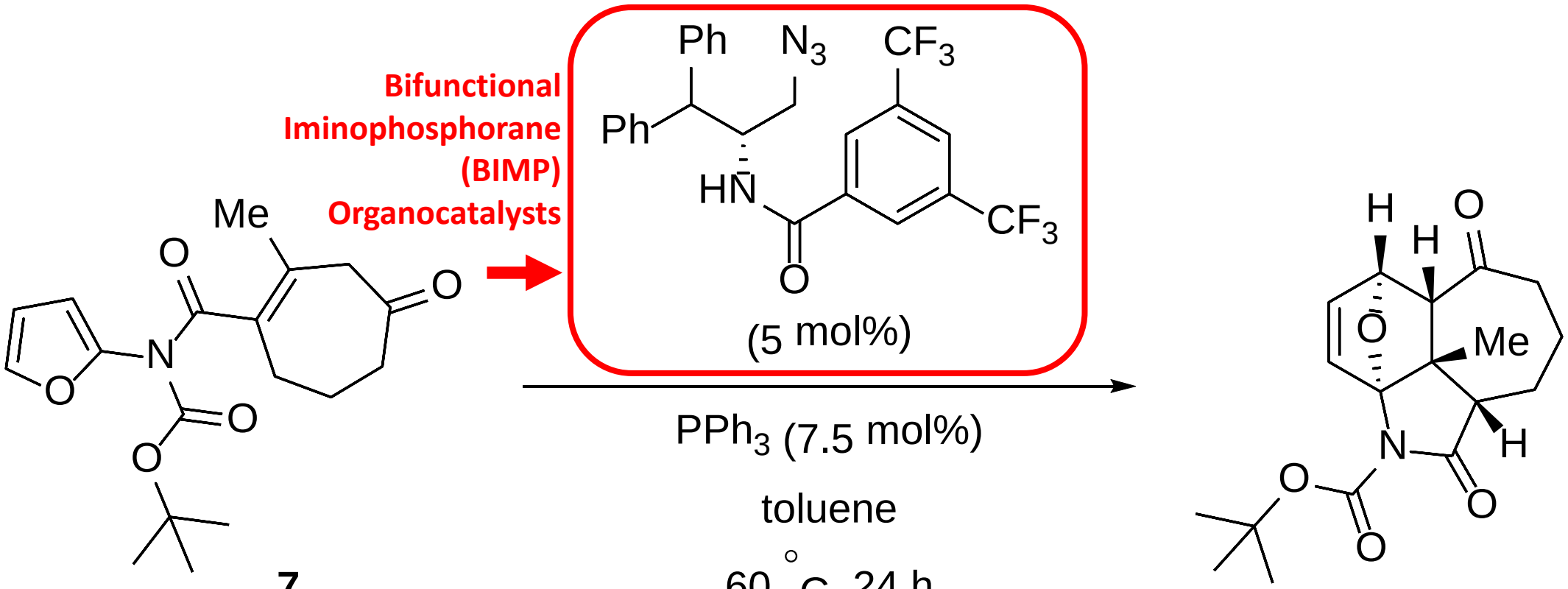


p-Toluenesulfonic acid **(*p*-TsOH)**



Synthesis of **(8)**

- Intramolecular Diels-Alder furan reaction (IMDAF) core



8

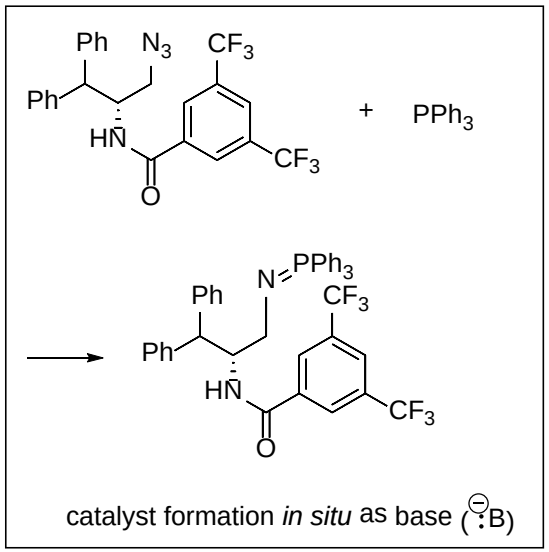
***(S)*-8-exo**

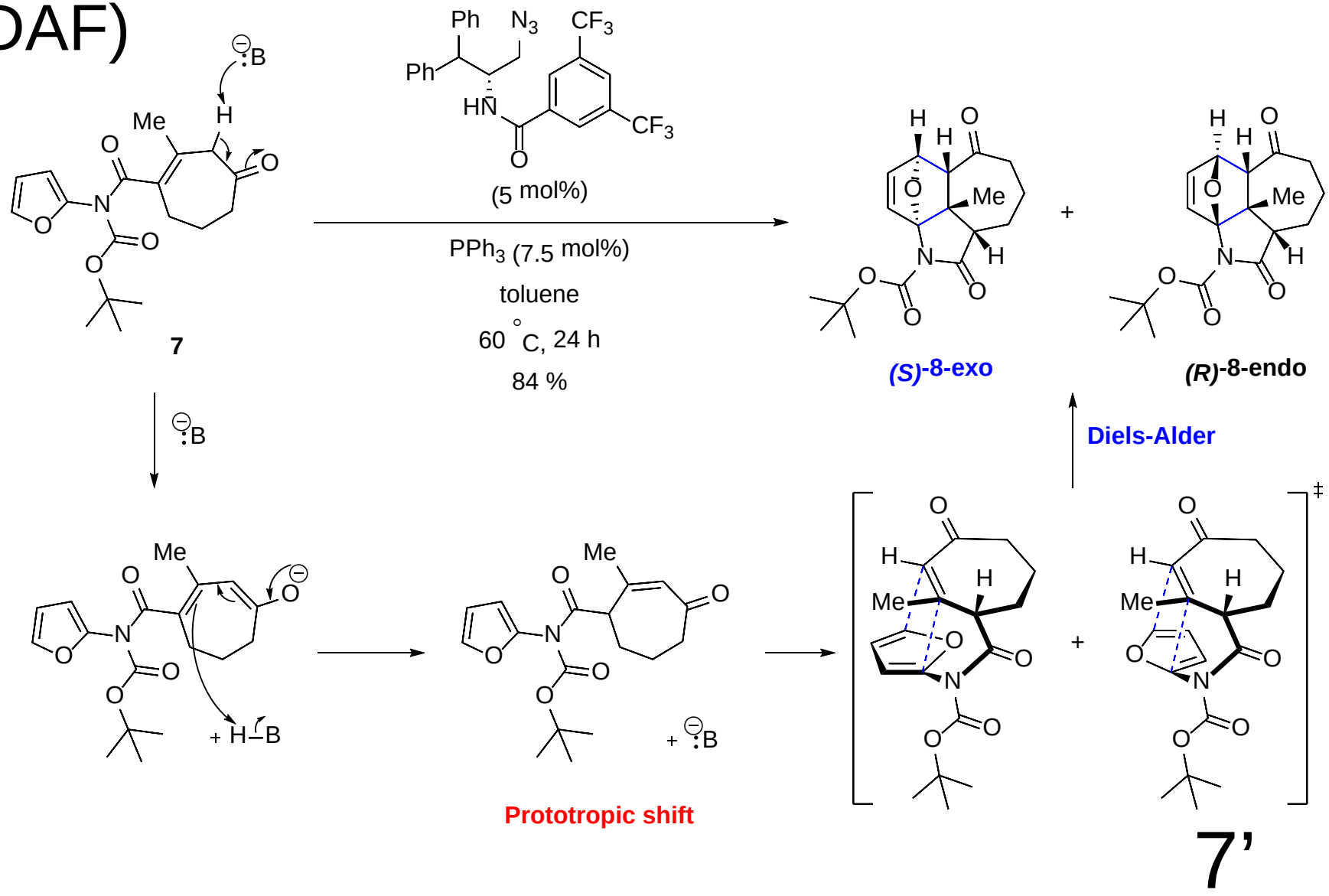
6 pages for details

Put prime for the page number

Mechanisms for Step **(7)** to **(8)**

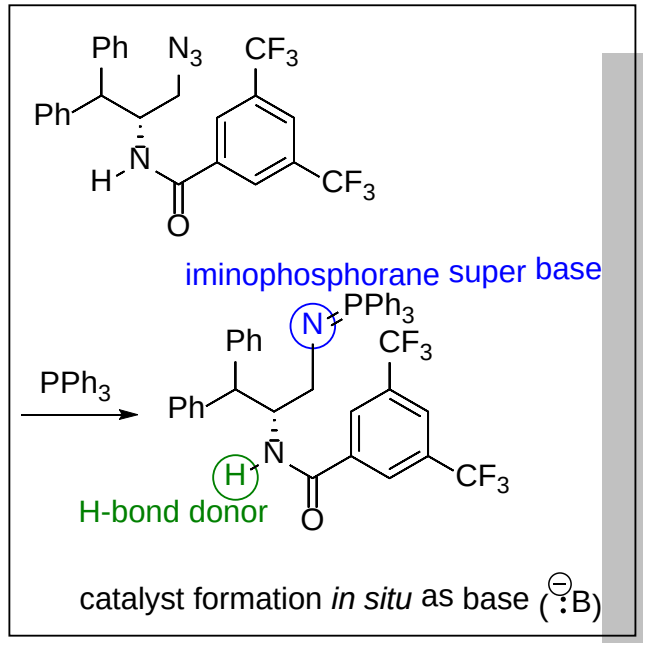
- Prototropic shift then Intramolecular Diels-Alder furan reaction (IMDAF)

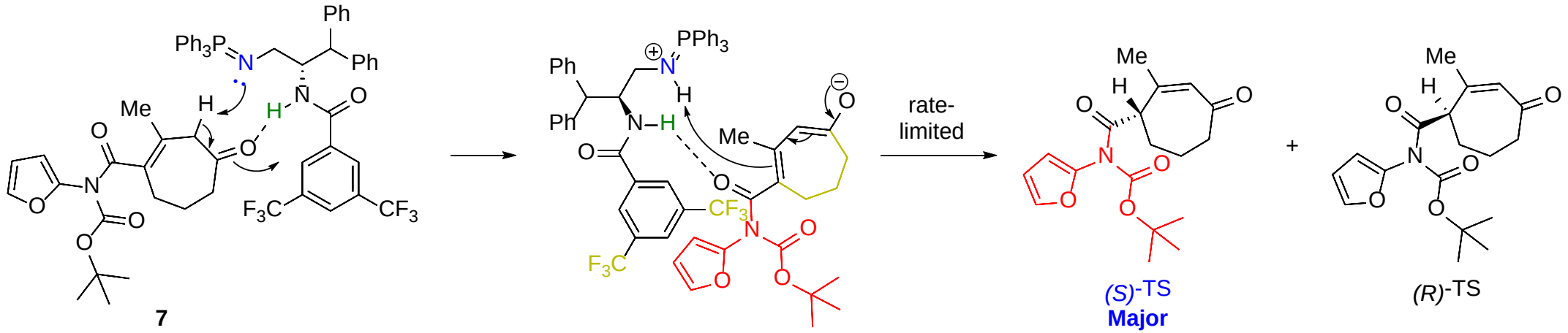




More details About Prototropic Shift/BIMP

Bifunctional Iminophosphorane Organocatalysts

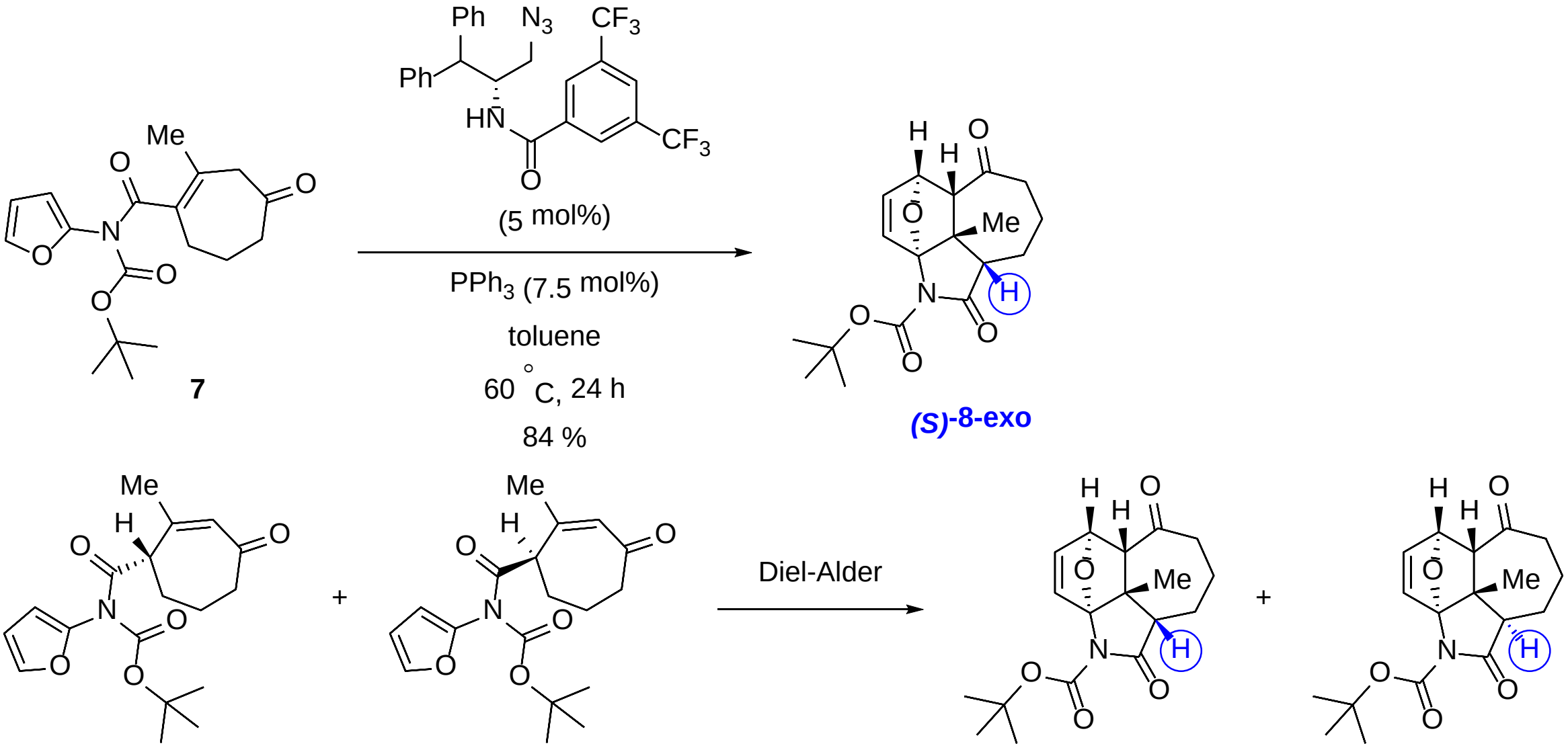




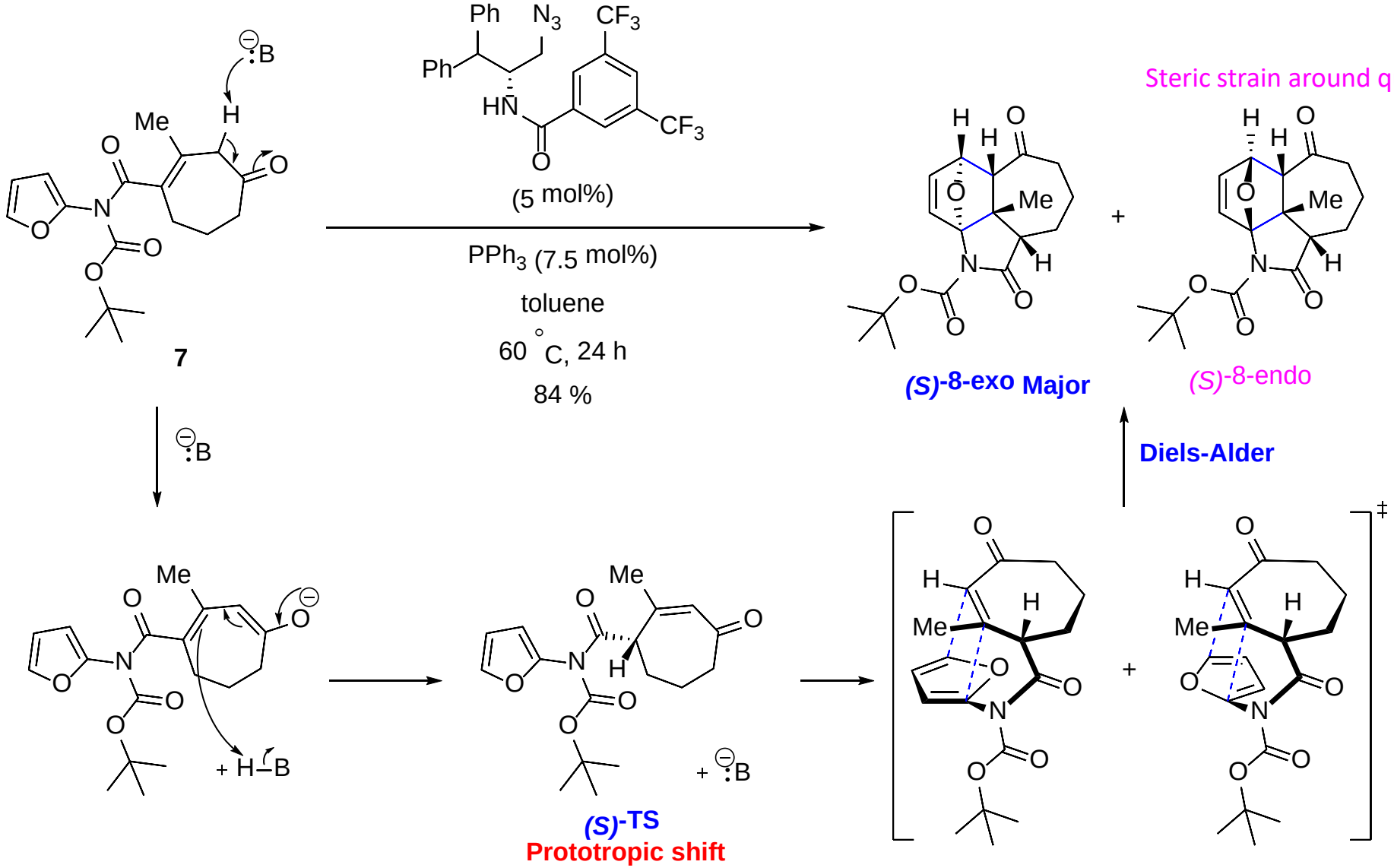
☺ 5 mol%, Good reactivity, Enantioselectivity, Easy and scalable, Metal free

8’

More details About Prototropic Shift/BIMP

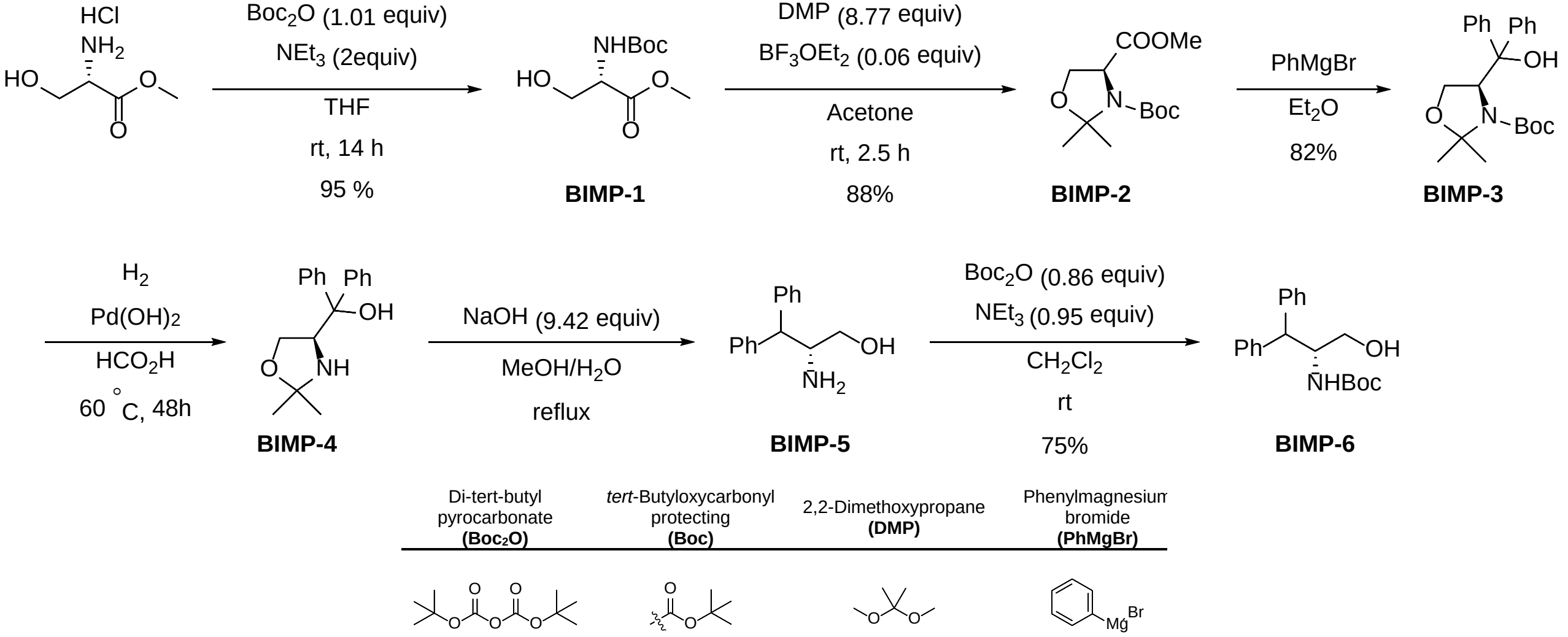


Intramolecular Diels-Alder furan reaction (IMDAF)



10’

Bifunctional Iminophosphorane Organocatalysts

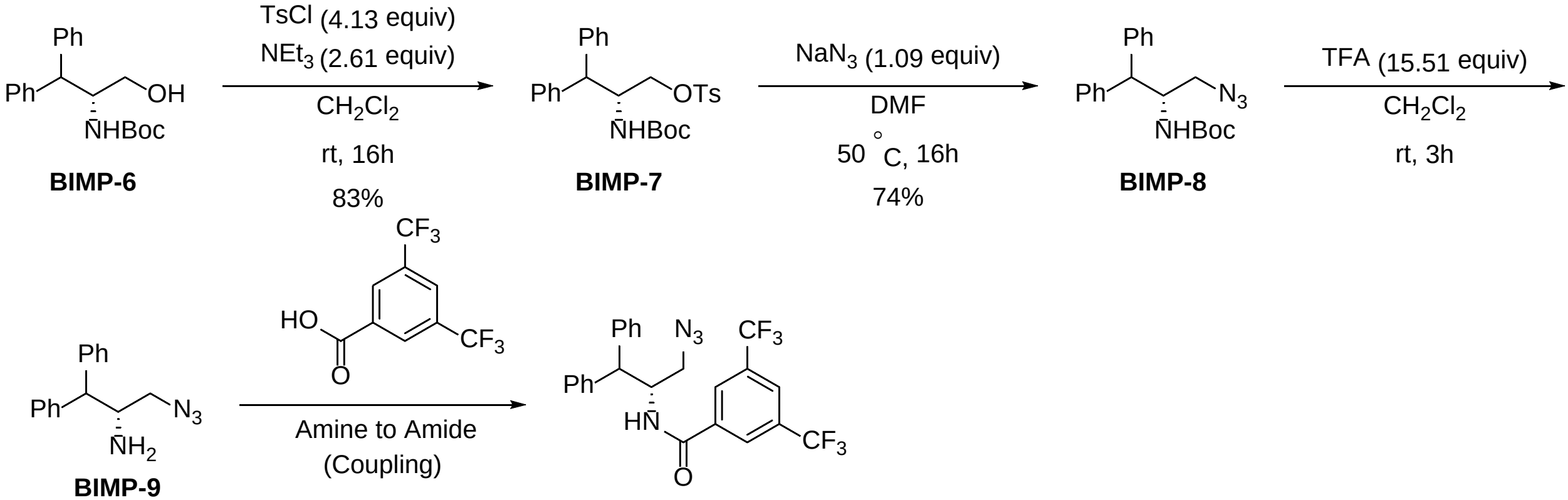


Di-tert-butyl pyrocarbonate **(Boc_2O)**	*tert*-Butyloxycarbonyl protecting **(Boc)**	2,2-Dimethoxypropane **(DMP)**	Phenylmagnesium bromide **(PhMgBr)**

(a) *Arkivoc,* **2010**, 108. Ollivier, A.; Goubert, M.; Tursun, A.; Canet, I.; Sinibaldi, M. E.
(b) *Org. Synth.,* **2000**, *77*, 64. Dondoni, A.; Perrone, D.
(c) *Tetrahedron: Asymmetry,* **2006**, *17*, 388. Dave, R.; Sasaki, N. A.
(d) *J. Am. Chem. Soc.,* **2013**, *135*, 16348. Núñez, M. G.; Farley, A. J.; Dixon, D. J.

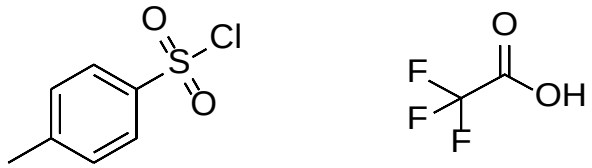
11’

Bifunctional Iminophosphorane Organocatalysts



BIMP Organocatalysts

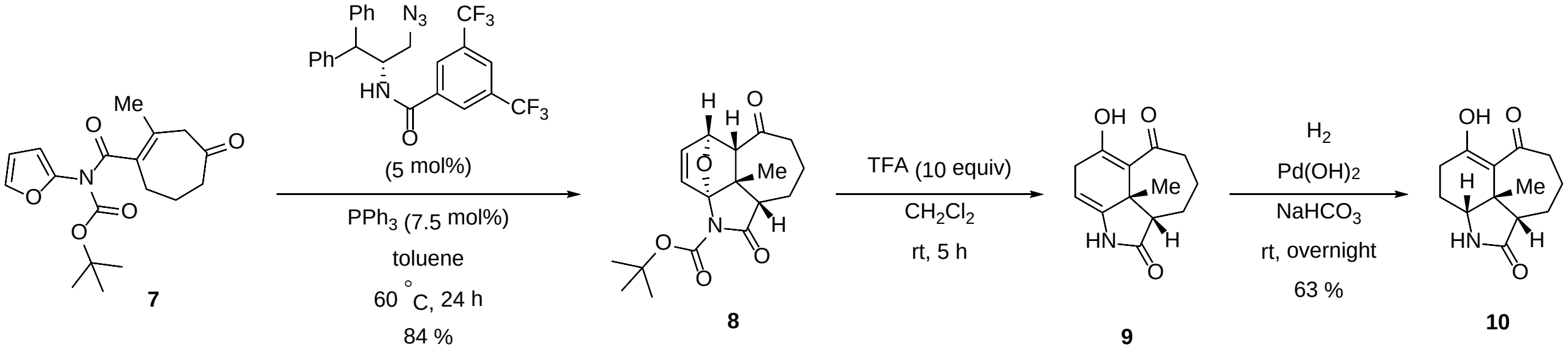
p-Toluenesulfonyl chloride **(TsCl)**	Trifluoroacetic acid **(TFA)**

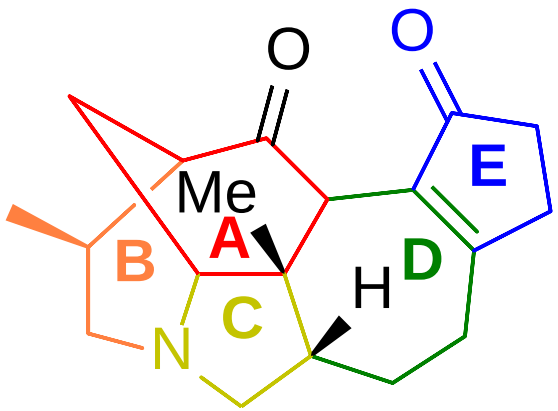


(d) *J. Am. Chem. Soc.*, **2013**, *135*, 16348. Núñez, M. G.; Farley, A. J.; Dixon, D. J.

12’

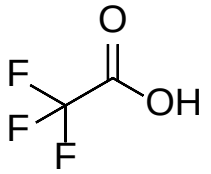
Synthesis of **(10)**



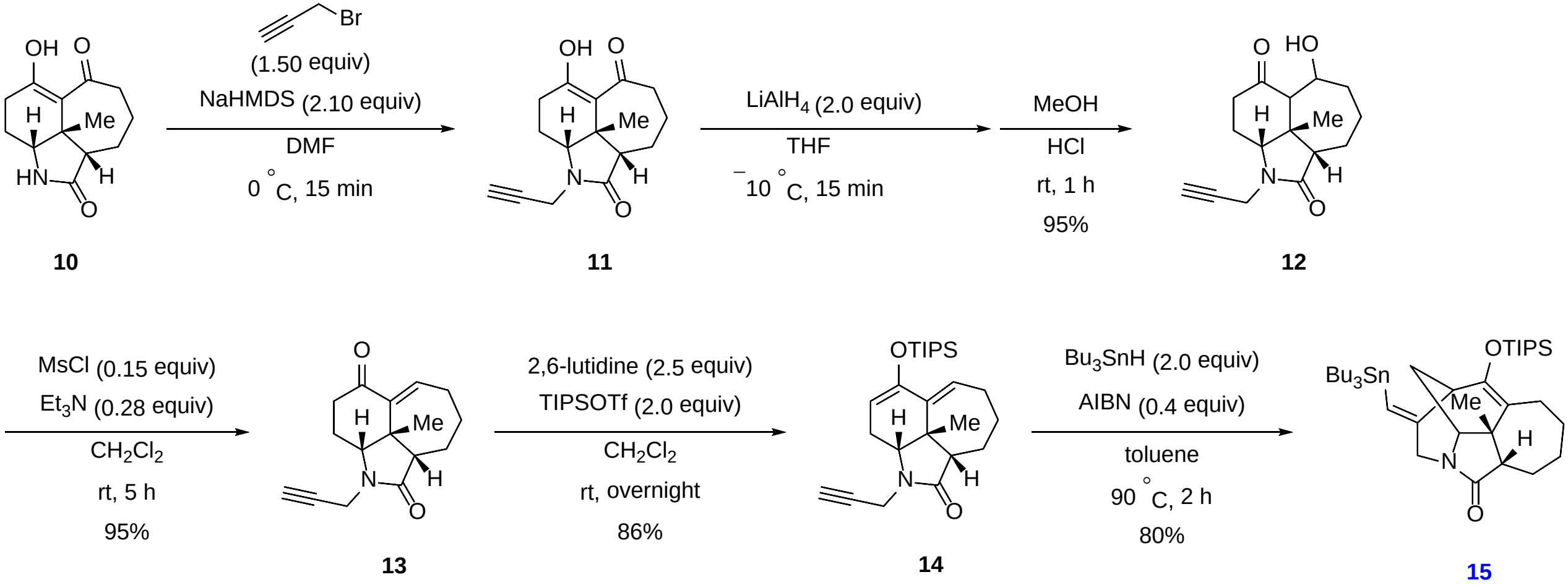


Himalensine A

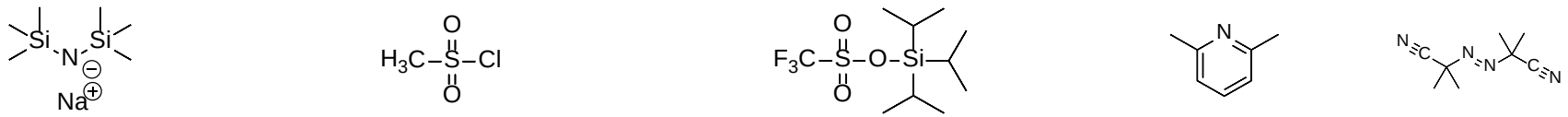
Trifluoroacetic acid
(TFA)



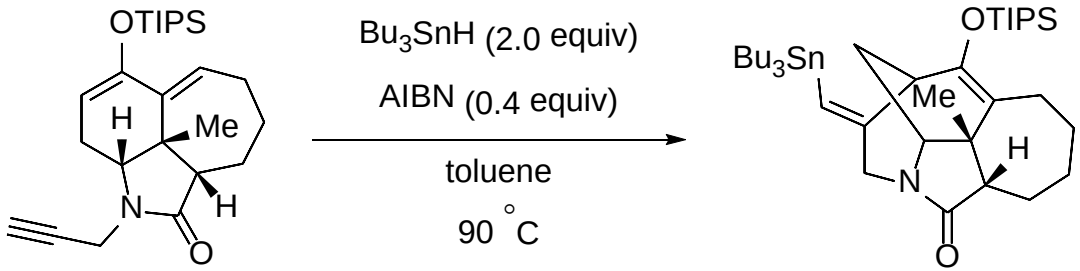
Synthesis of **(15)**



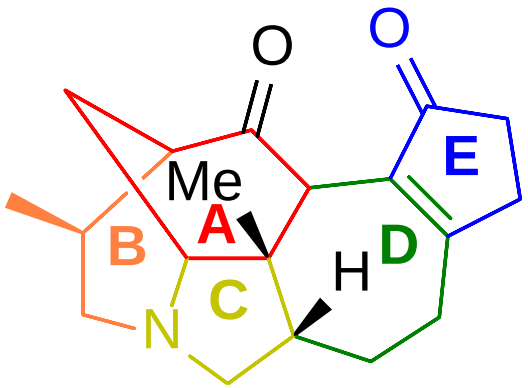
Sodium bis(trimethylsilyl)amide **(NaHMDS)**	Methanesulfonyl chloride **(MsCl)**	Triisopropylsilyl trifluoromethanesulfonate **(TIPSOTf)**	2,6-Lutidine	2,2'-Azoisobutyronitrile **(AIBN)**



Mechanisms for Step **(14)** to **(15)**

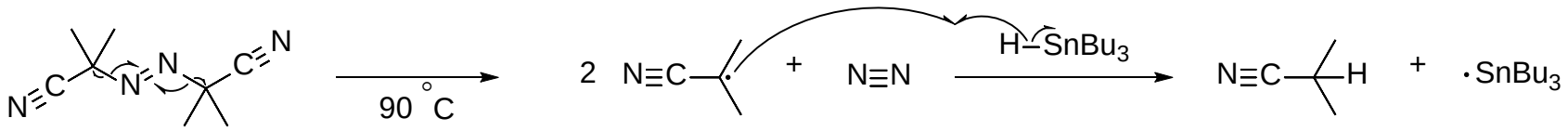


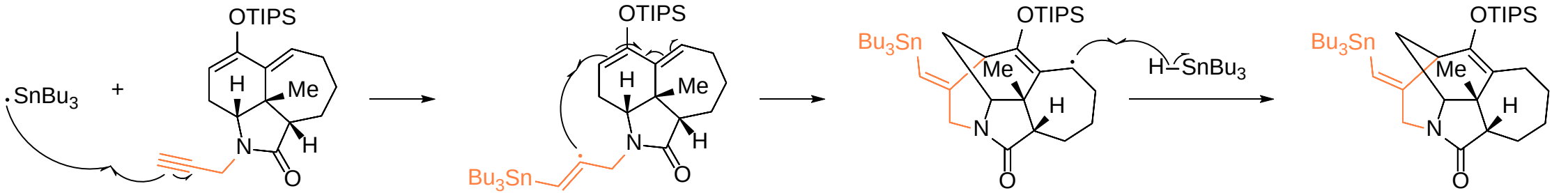
14 **15**



Himalensine A

Mechanism:

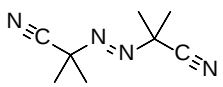


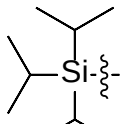


14 **TS** **TS** **15**

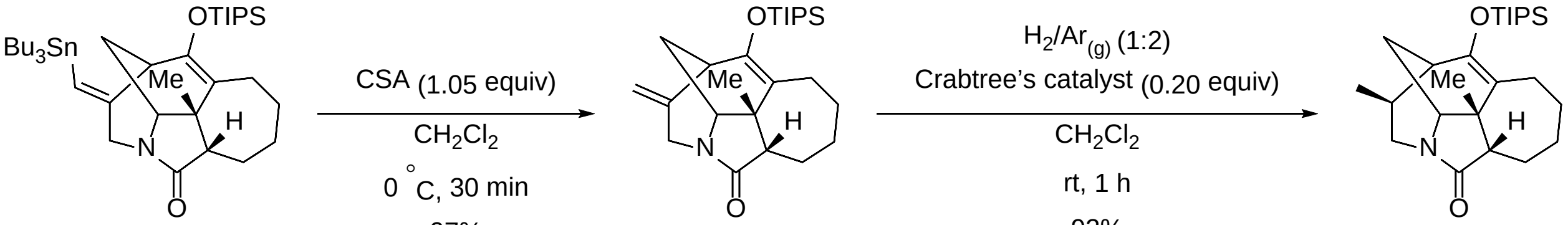
2,2'-Azoisobutyronitrile **(AIBN)**

Triisopropylsilyl **(TIPS)**





Synthesis of **(17)**

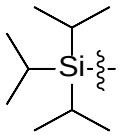
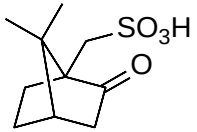
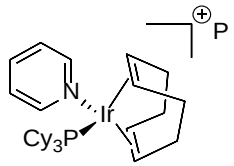
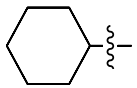


15

Protometalation
Protodestannylation

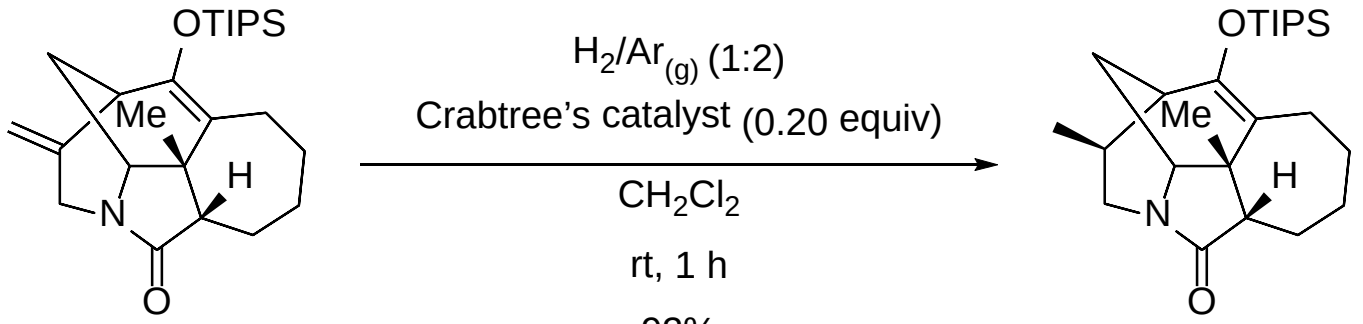
16

17

Triisopropylsilyl **(TIPS)**	Camphor-10-sulfonic acid (β) **(CSA)**	Crabtree catalyst[1]	Cyclohexyl **(Cy)**
			

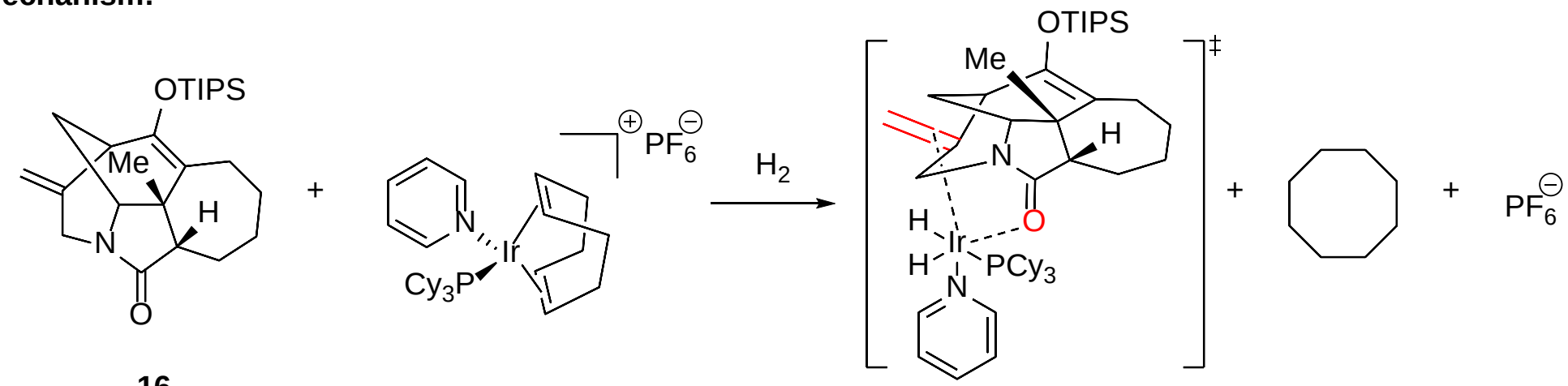
1. (1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)-iridium(I) hexafluorophosphate

Mechanisms for Step **(16)** to **(17)**



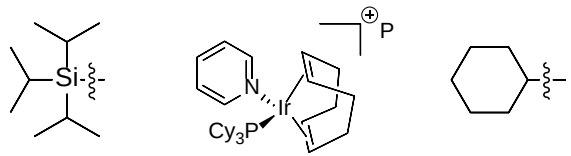
16 **17**

Mechanism:

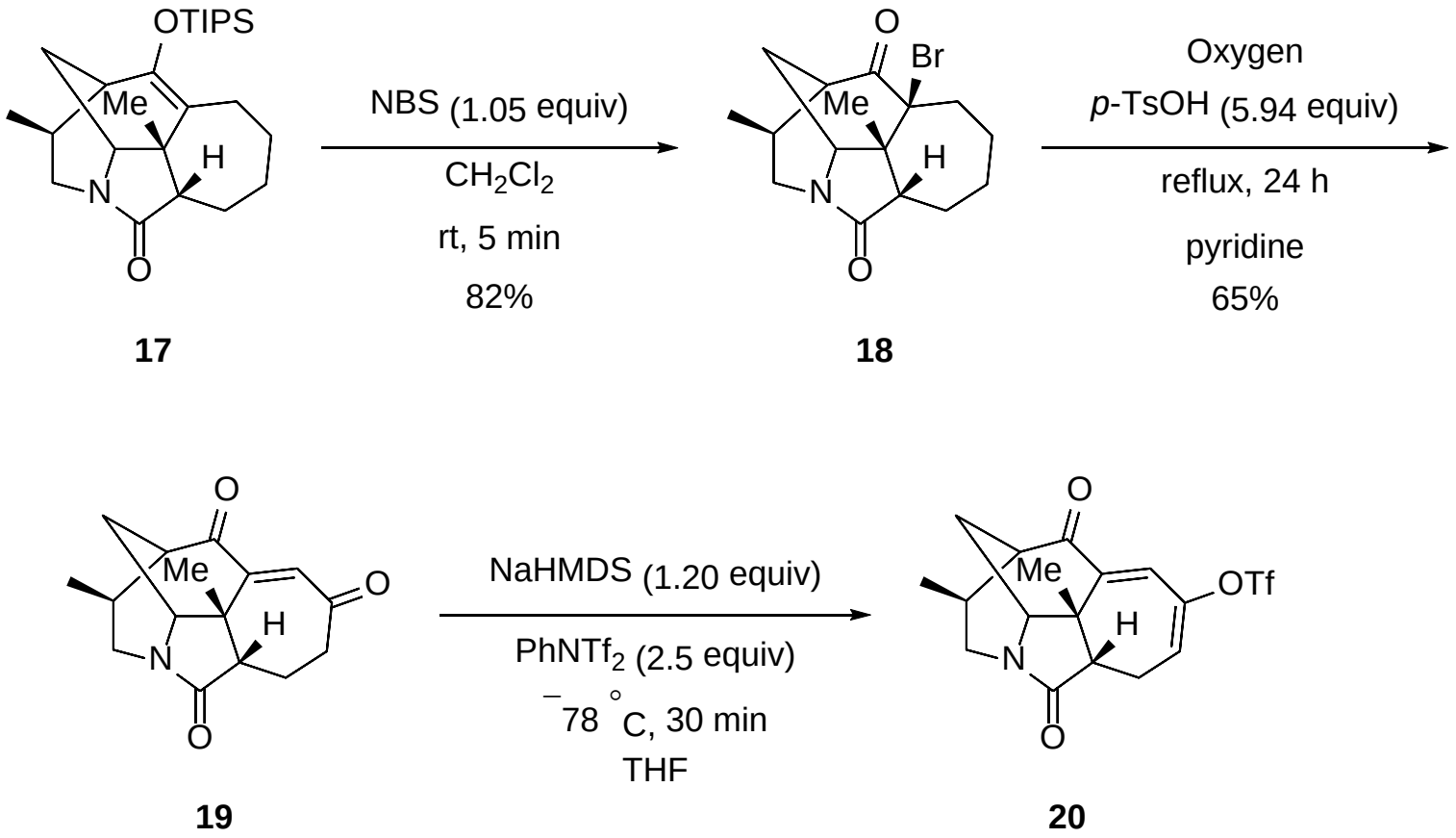


16

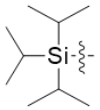
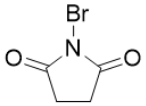
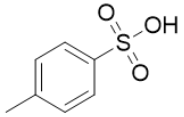
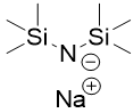
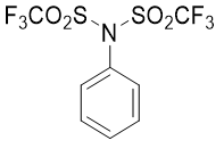
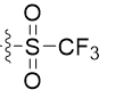
Triisopropylsilyl **(TIPS)**	Crabtree catalyst[1]	Cyclohexyl **(Cy)**



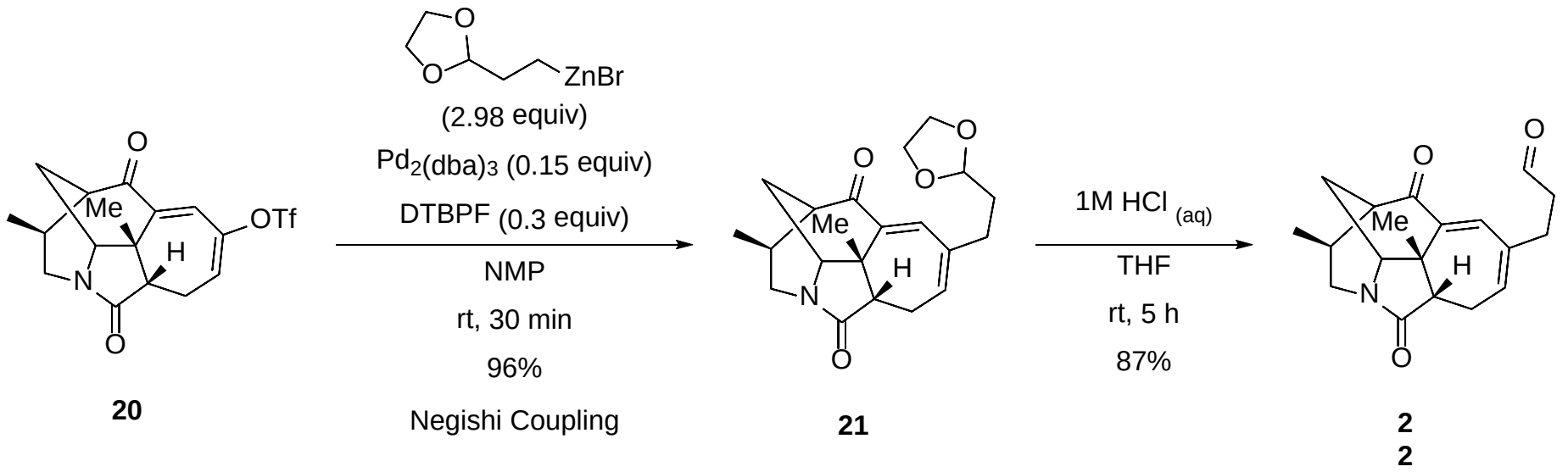
Synthesis of **(20)**

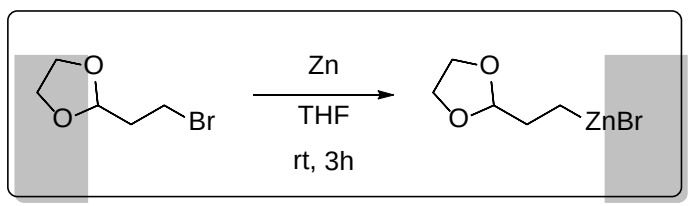


17 **18** **19** **20**

Triisopropylsilyl **(TIPS)**	N-Bromosuccinimide **(NBS)**	*p*-Toluenesulfonic acid **(*p*-TsOH)**	Sodium bis(trimethylsilyl)amide **(NaHMDS)**	N-Phenyl-bis(trifluoromethanesulfonimide) **($PhNTf_2$)**	Trifluoromethylsulfonyl **(OTf)**
					

Synthesis of **(24)**





Tris(dibenzylideneacetone)dipalladium(0) (**$Pd_2(dba)_3$**)

1,1'-Bis(di-tert-butylphosphino)ferrocene (**DTBDF**)

tert-butyl (**t-Bu**)

N-Methyl-2-Pyrrolidone (**NMP**)

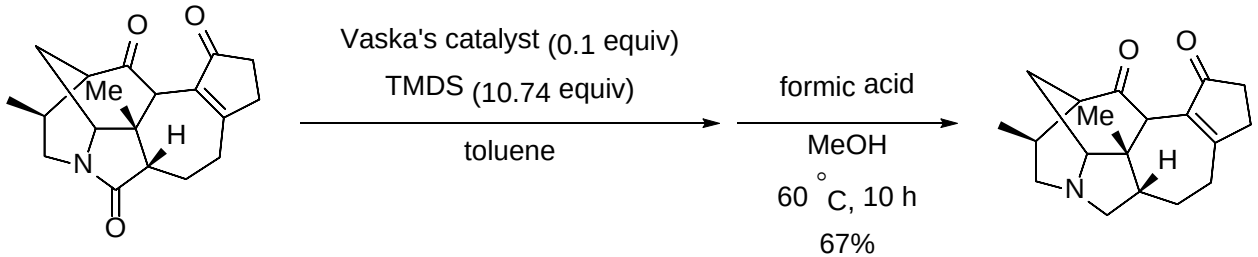
Vaska's catalyst[2]

1,1,3,3-Tetramethyldisiloxane (**TMDS**)

Formic acid

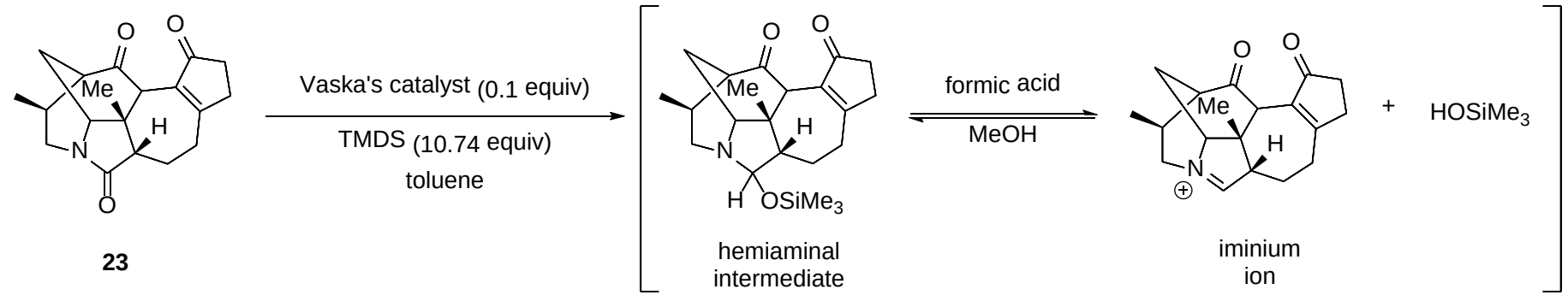
2. Bis(triphenylphosphine)iridium(I) carbonyl chloride

Mechanisms for Step **(23)** to **(24)**



23 **24**

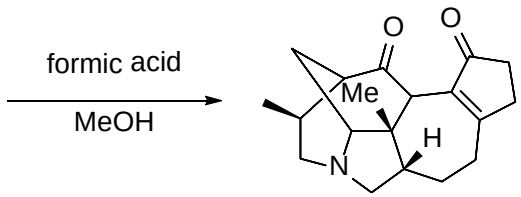
Mechamism:



23

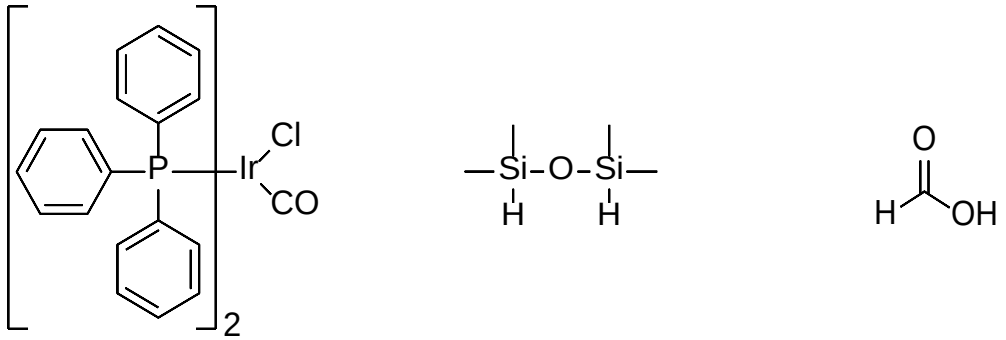
hemiaminal intermediate

iminium ion



24

Vaska's catalyst[2]	1,1,3,3-Tetramethyldisiloxane **(TMDS)**	Formic acid

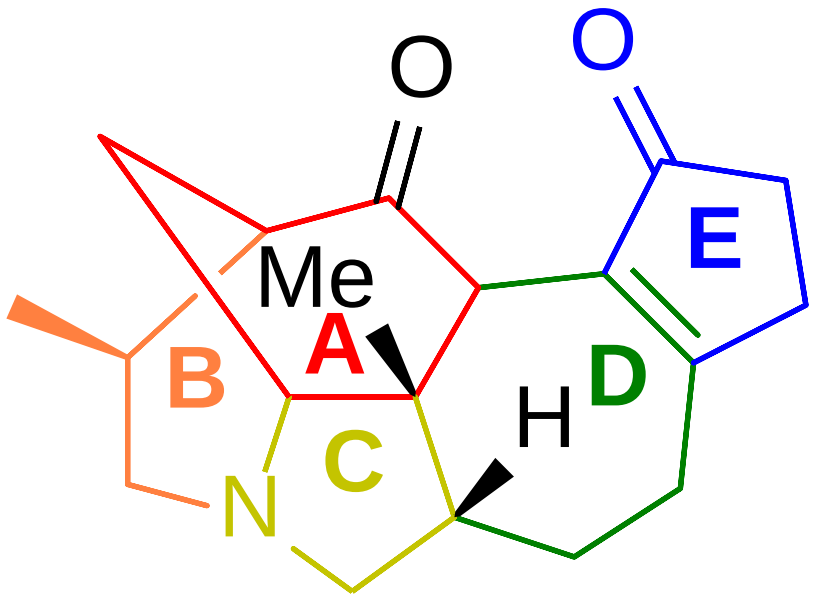


2. Bis(triphenylphosphine)iridium(I) carbonyl chloride

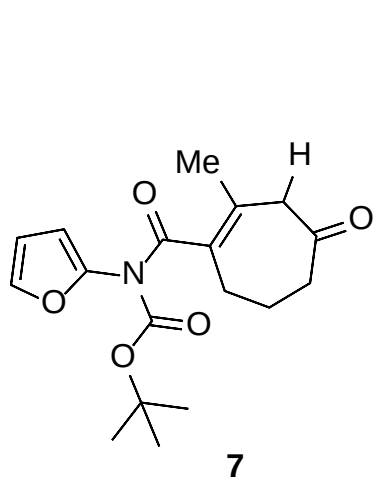
Conclusion

- First total synthesis of (−)-Himalensine A in 23 steps. (Highly efficient and scalable steps)

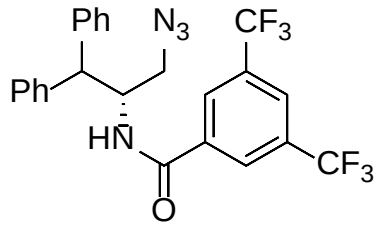
- First enantioselective IMDAF reaction.



Himalensine A



7



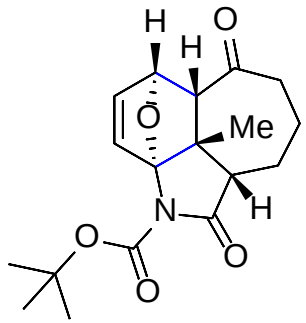
(5 mol%)

PPh_3 (7.5 mol%)

toluene

60 °C, 24 h

84 %



8-exo

Thank You For Listening

https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&ved=2ahUKEwiw6sGdk6vgAhUOUt8KHYC6DLkQjxx6BAgBEAI&url=https%3A%2F%2Fdepositphotos.com%2F41441791%2Fstock-illustration-cartoon-chemist.html&psig=AOvVaw21koLy1qu0x5EKHaDb_W1s&ust=1549677893534548

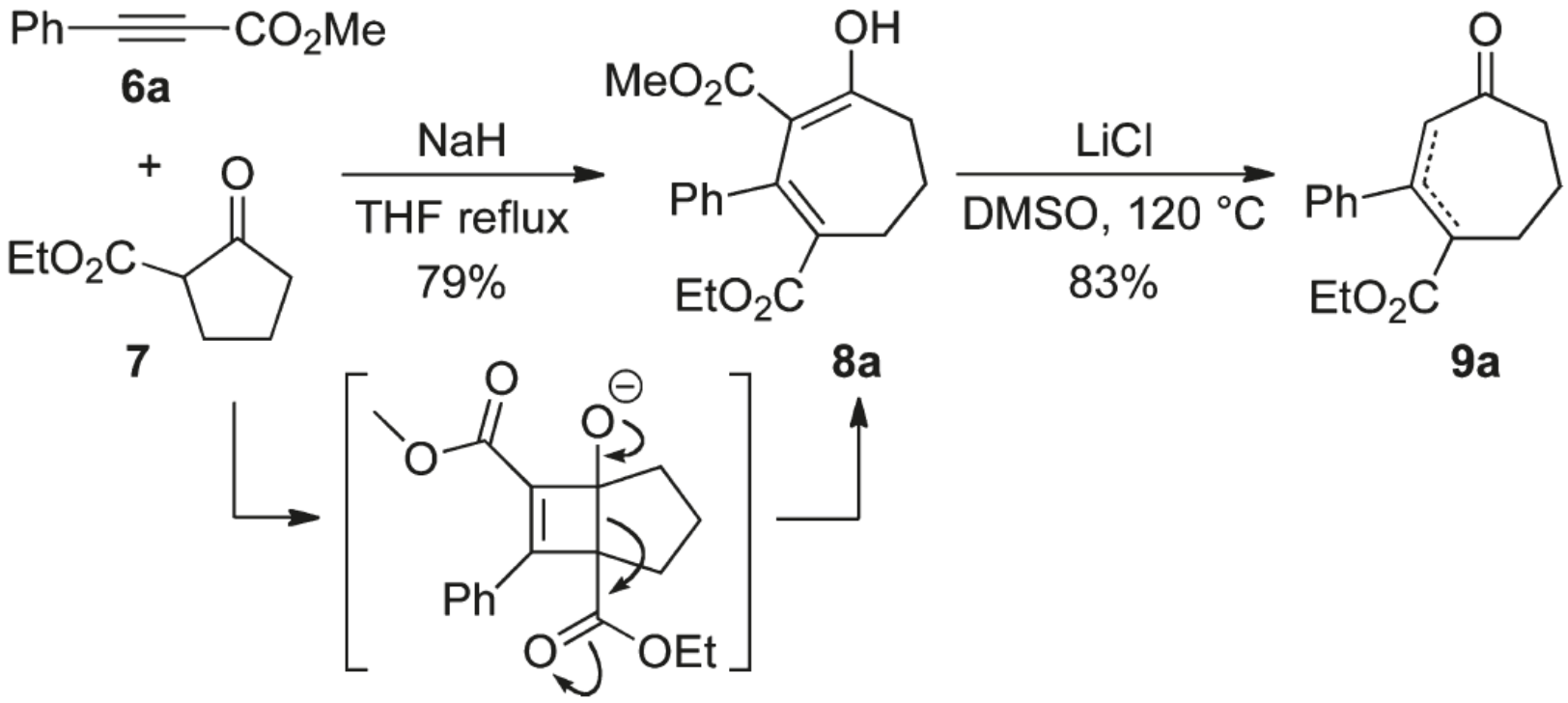
- ~~

- ~~

Mechanism for **(1)**

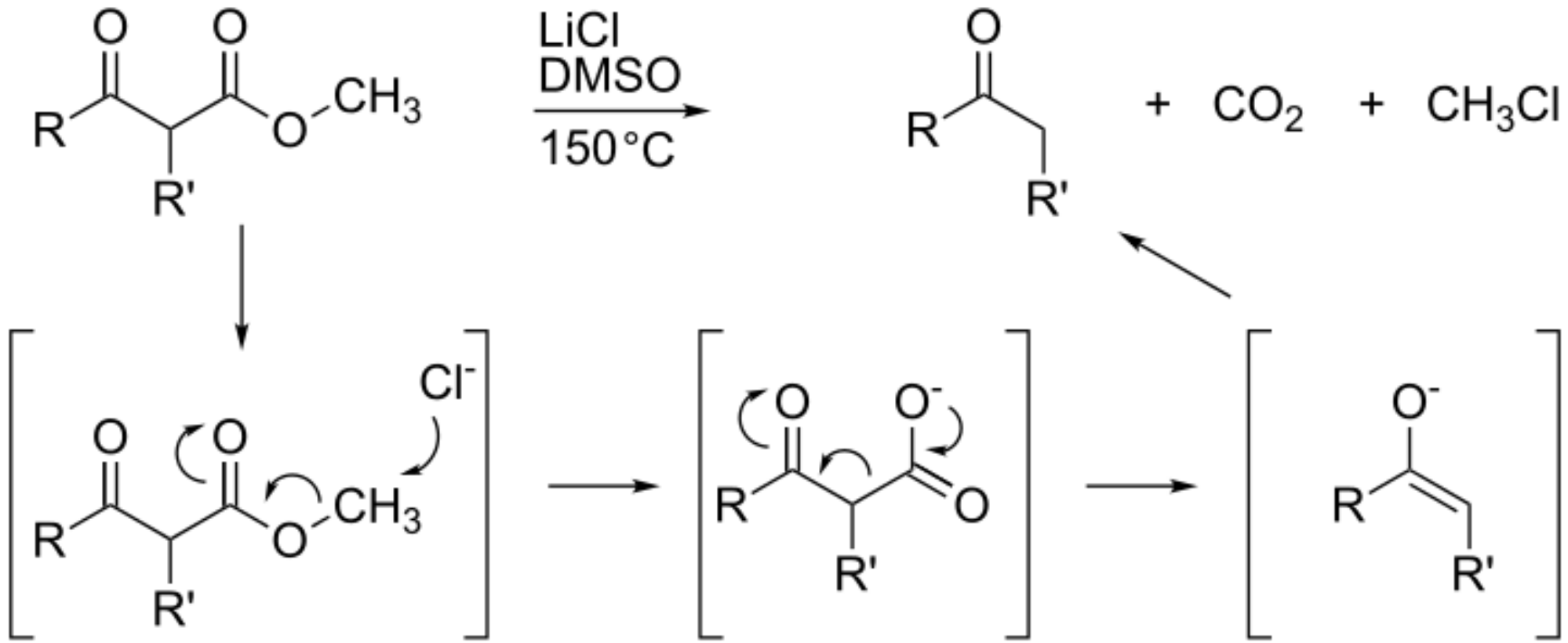
- An acid-catalyzed Dieckmann-type reaction

Scheme 2. Preparation of the Model Substrate **9a**



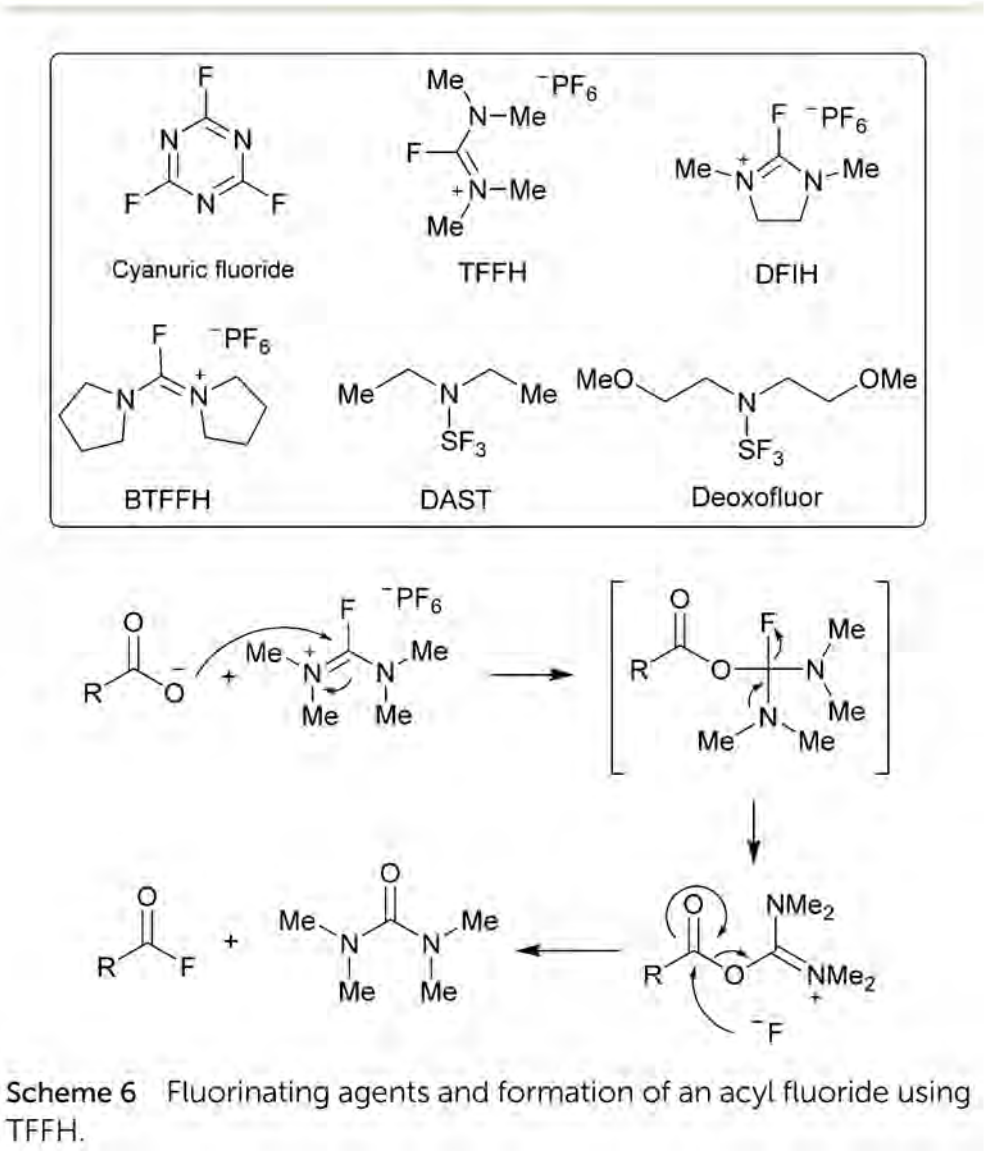
Mechanism for **(2)**

- Krapcho decarboxylation



https://en.wikipedia.org/wiki/Krapcho_decarboxylation

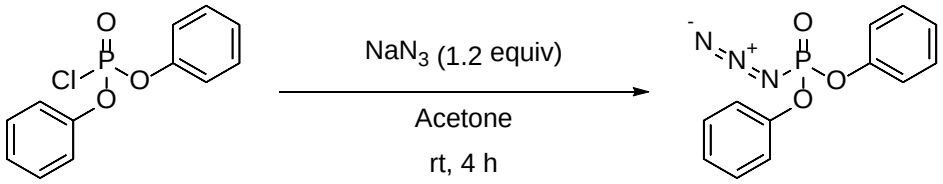
Mechanism for **(5)**



Scheme 6 Fluorinating agents and formation of an acyl fluoride using TFFH.

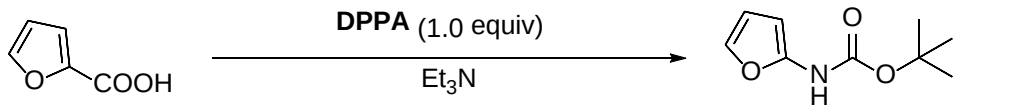
Nat. Prod. Rep., **2015**, *32*, 605
https://en.wikipedia.org/wiki/Cyanuric_chloride

DPPA and Curtius Rearrangement



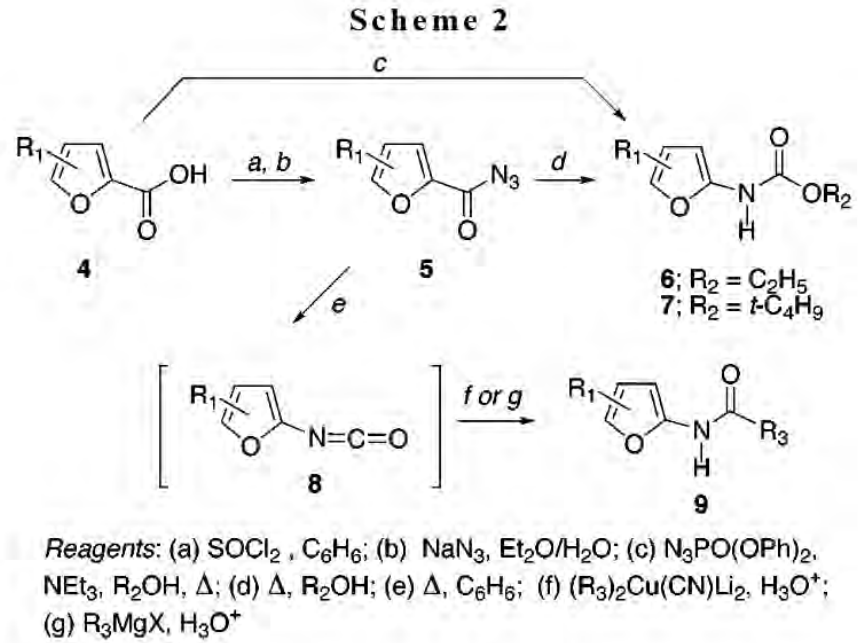
Synthesis' **2004**, *8*, 1303

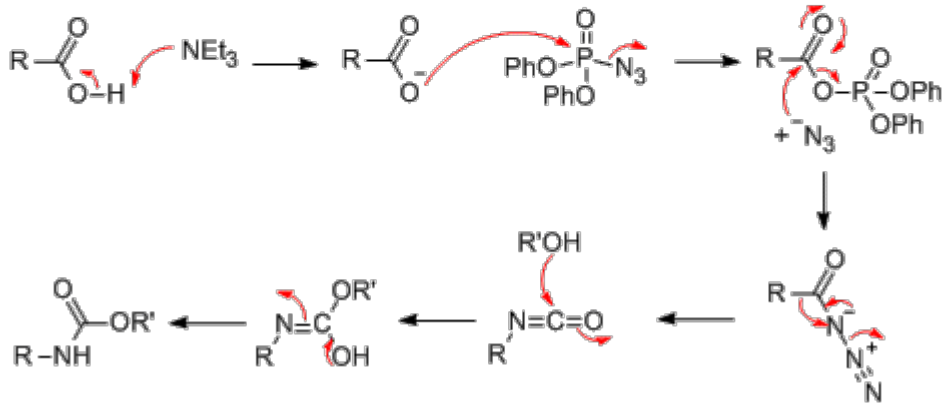
diphenyl phosphorazidate
(DPPA)



***tert*-butyl furan-2-ylcarbamate**

Curtius Rearrangement
*J. Am. Chem. Soc.,***1972**, *94*, 6203
J. Org. Chem., **1999**, *64*, 3595
Tetrahedron Lett., **2007**, *48*, 1939

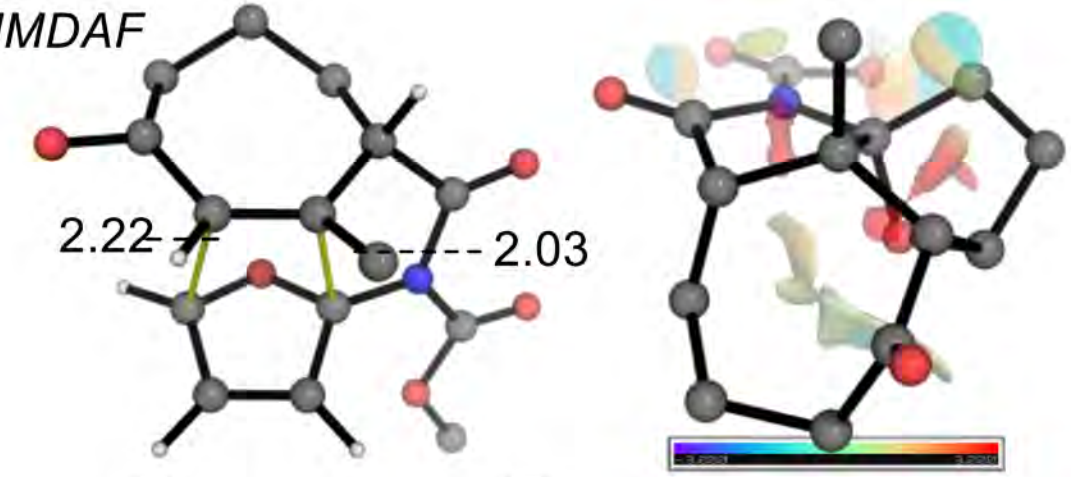


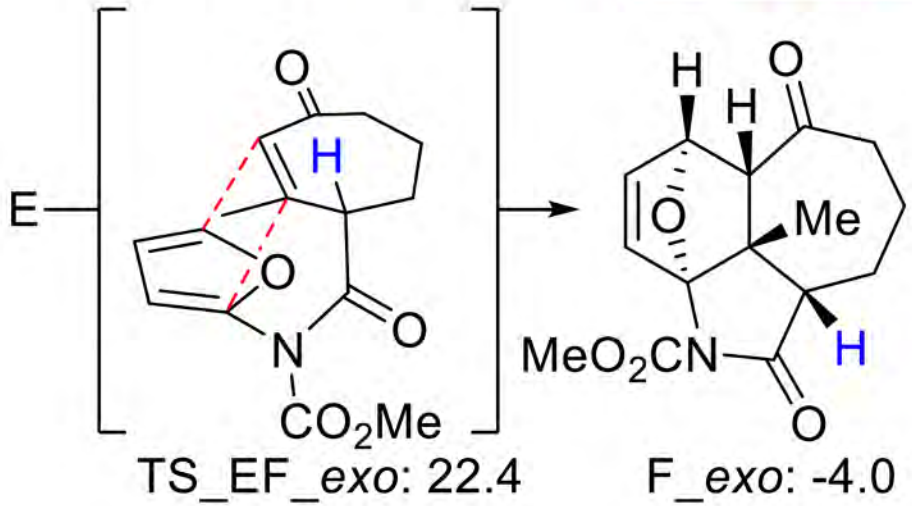


https://blogs.yahoo.co.jp/organicchem12/1373185.html

Details about Mechanisms for Step **(7)** to **(8)**

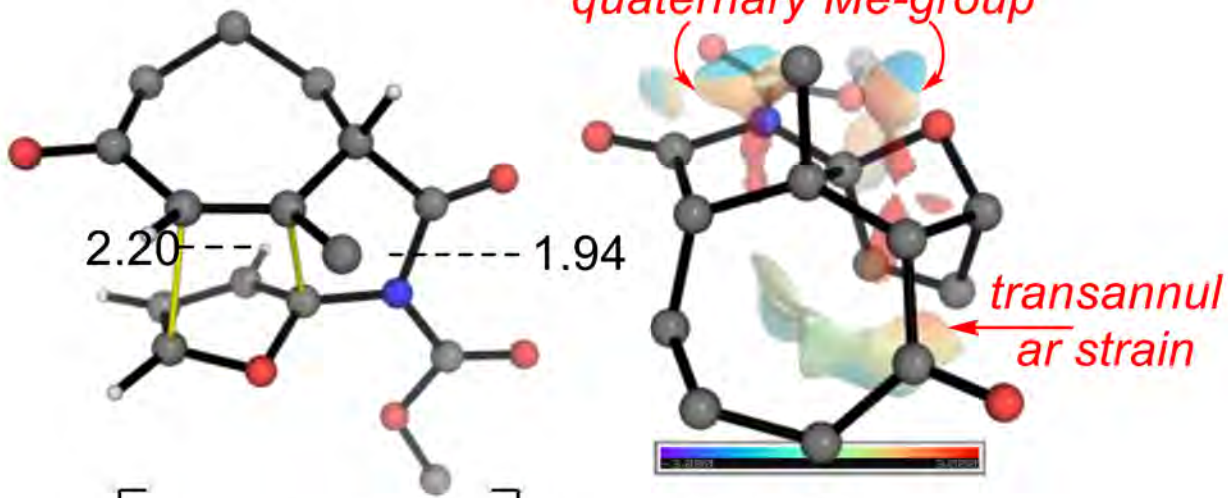
ii) *IMDAF*

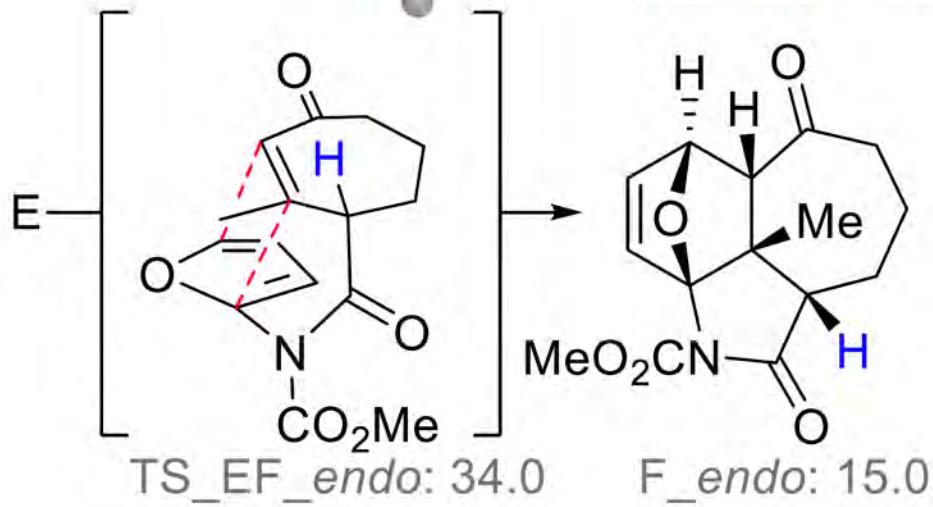




TS_EF_*exo*: 22.4 F_*exo*: -4.0

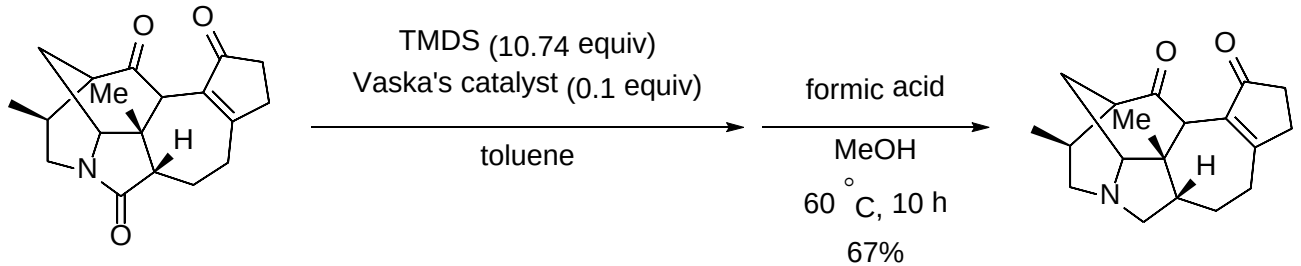
vs.





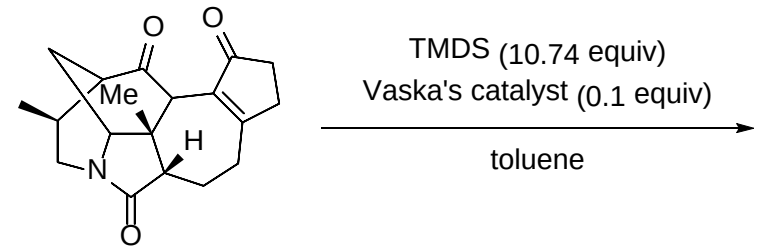
TS_EF_*endo*: 34.0 F_*endo*: 15.0

Iridium-catalyzed

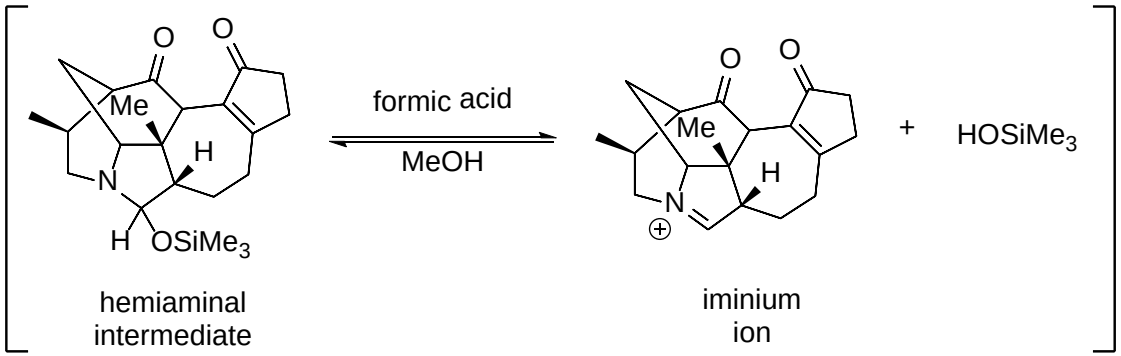


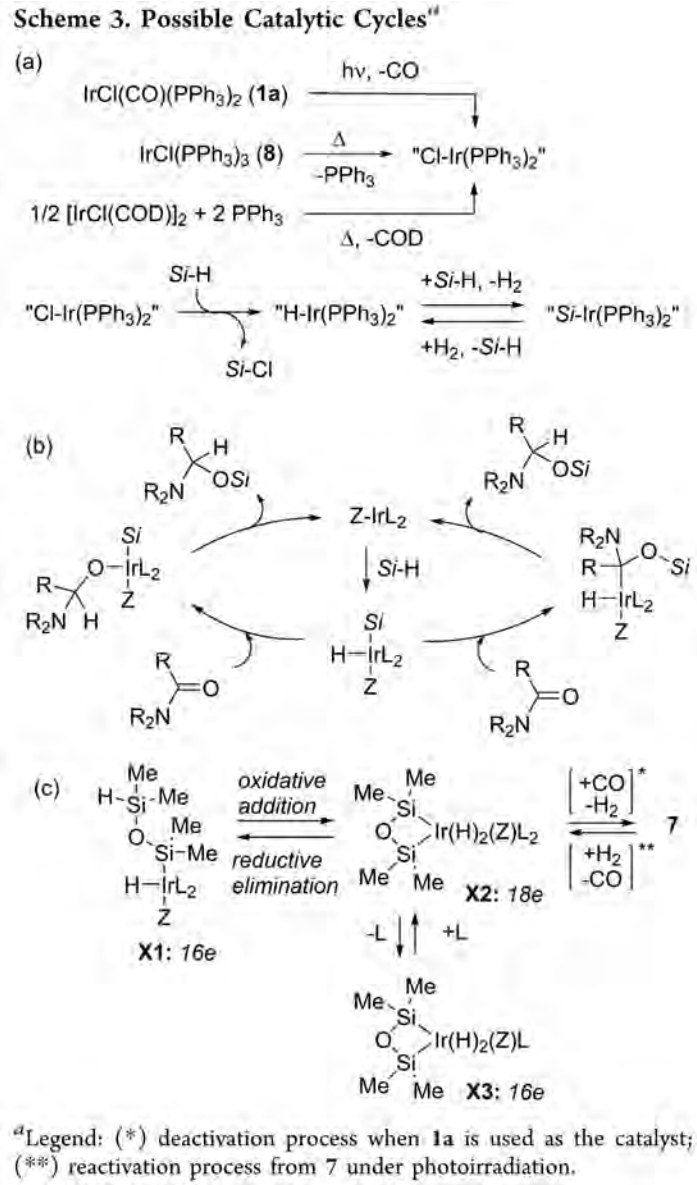
23 **24**

Mechamism:



23

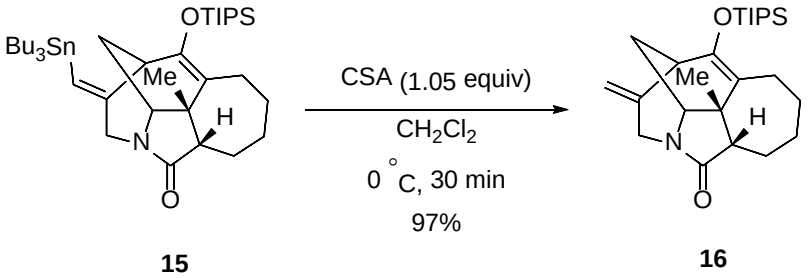




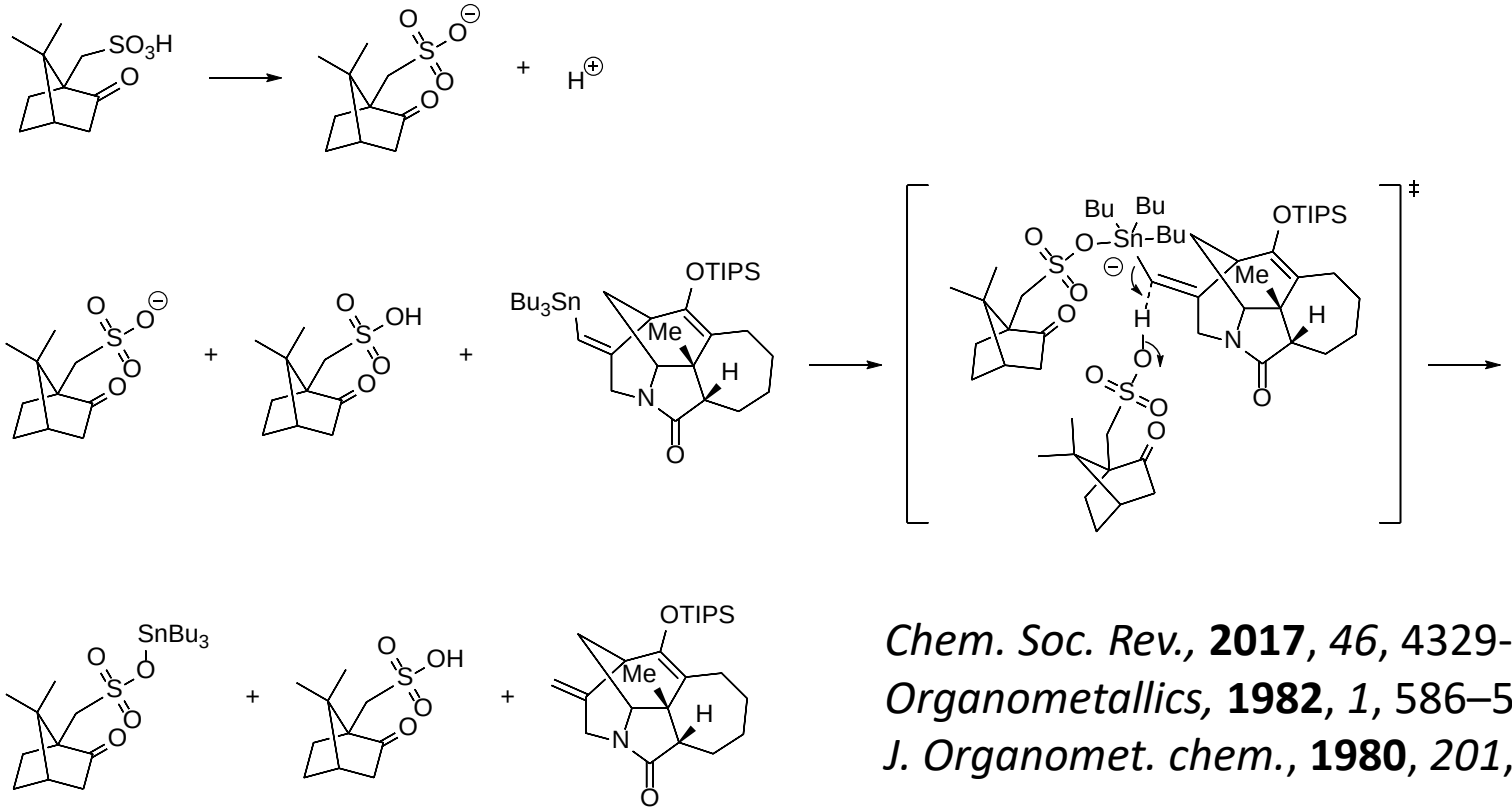
[a]Legend: (*) deactivation process when **1a** is used as the catalyst; (**) reactivation process from 7 under photoirradiation.

Organometallics **2019**, *38*, 852

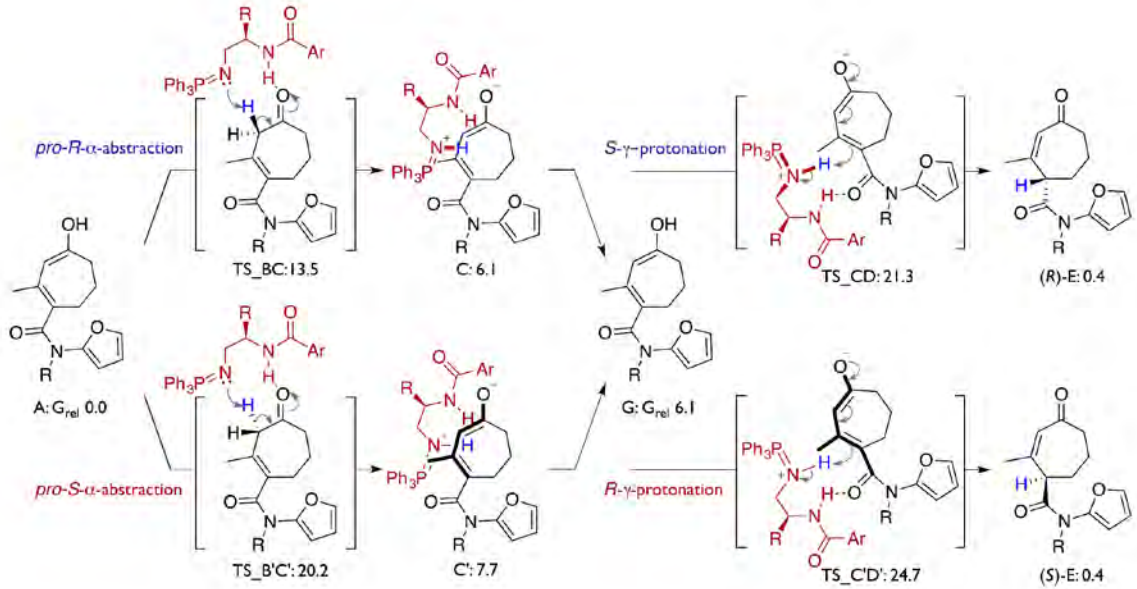
Protodestannylation



15 **16**



Chem. Soc. Rev., **2017**, *46*, 4329-4346
Organometallics, **1982**, *1*, 586–590
J. Organomet. chem., **1980**, *201*, 233.



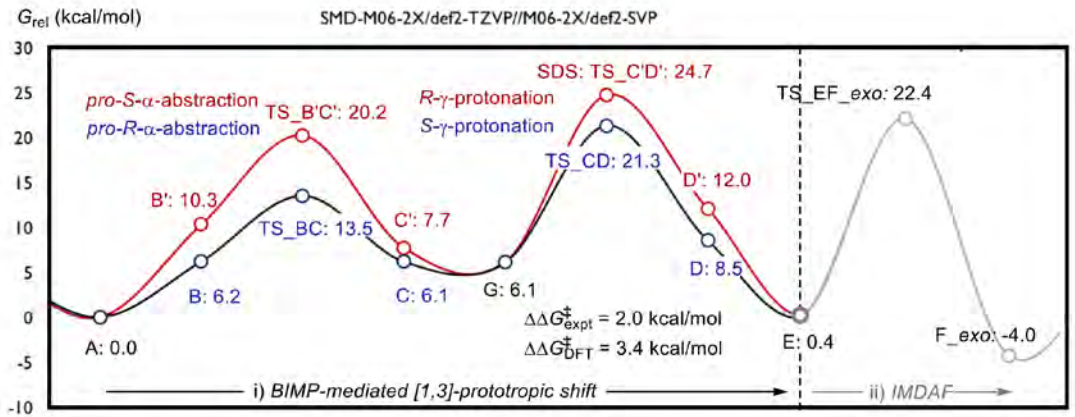
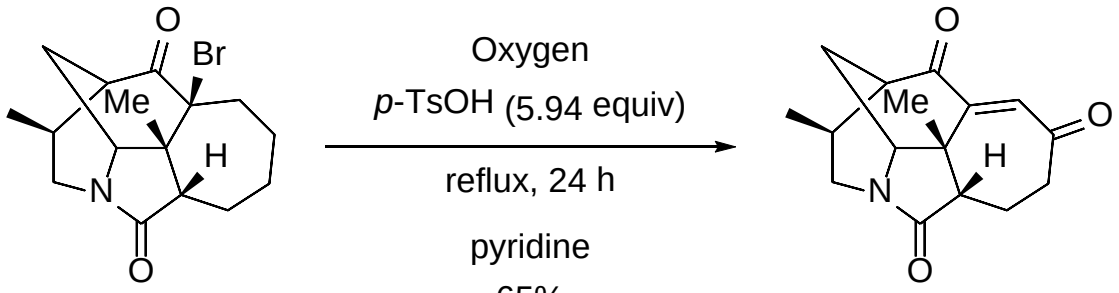
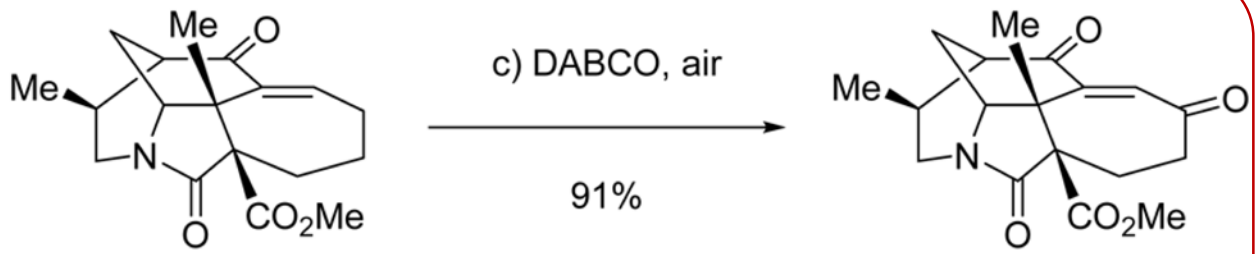


Figure S6. BIMP Catalyst **11a**-promoted [1,3]-prototropic shift, followed by the IMDAF cycloaddition. M06-2X/def2-TZVP(SMD=toluene)//M06-2X/def2-SVP quasi-harmonic Gibbs energy profile in kcal/mol.

Mechanisms for Step **(18)** to **(19)**



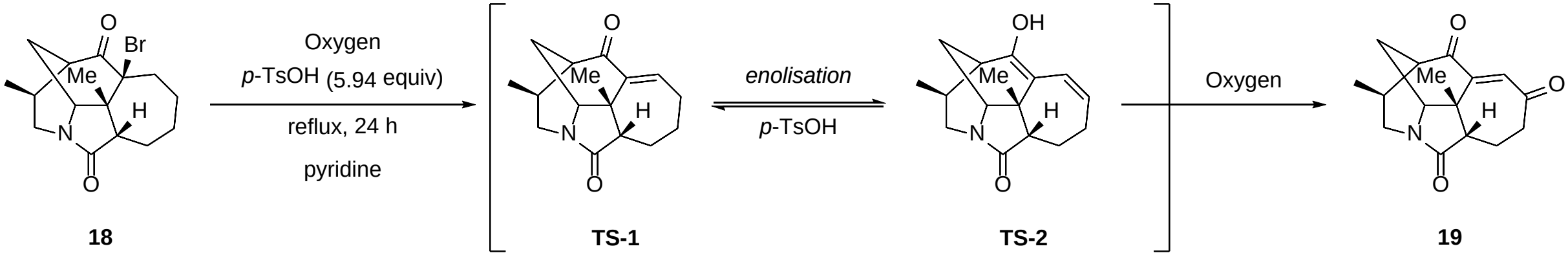
18 **19**



J. Am. Chem. Soc. **2017**, *139*, 14893. Li, J.; Zhang, W.; Zhang, F.; Chen, Y.; Li, A.

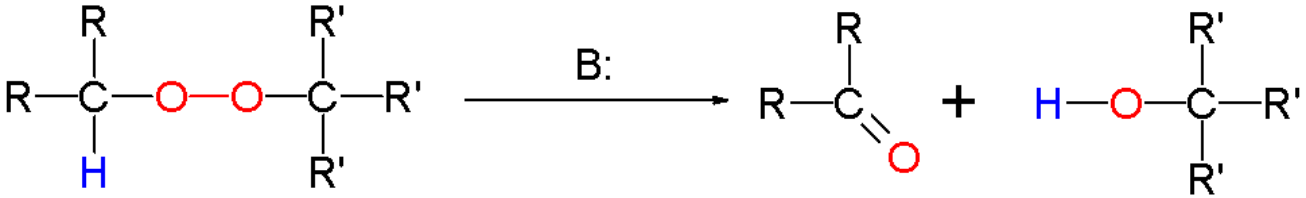
Plausible Mechanism:

γ-radical combination with oxygen and Kornblum DeLaMare rearrangement



18 **TS-1** **TS-2** **19**

DeLaMare rearrangement



https://en.wikipedia.org/wiki/Kornblum%E2%80%93DeLaMare_rearrangement

p-Toluenesulfonic acid (***p*-TsOH**)	1,4-diazabicyclo[2.2.2]octane (**DABOC**)