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Communication

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Total Synthesis of *Lycopodium* Alkaloids Palhinine A and Palhinine D

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Presented by: Chuan Pin Chen

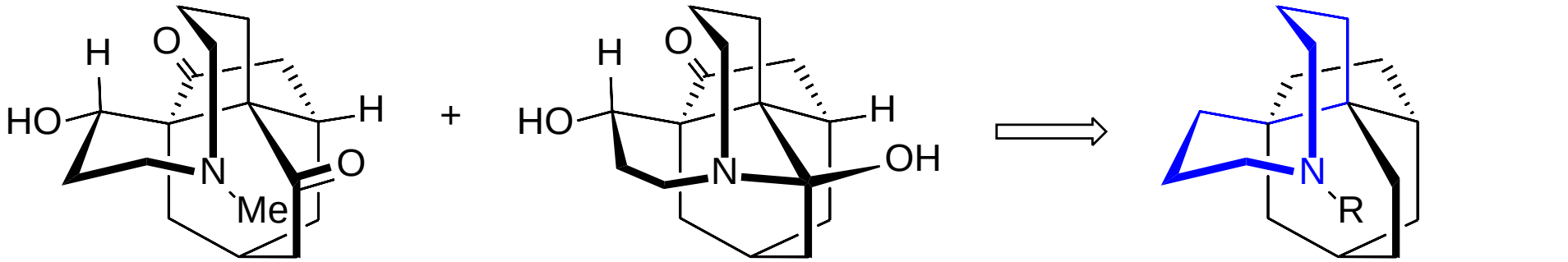
CEM 852 Presentation

February 9, 2019

Introduction

- Palhinine-type alkaloids, as members of the Lycopodium family

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



Palhinine A
2010 by Long *et al.*
Org. Lett. **2010,** *12,* 3922

Palhinine D
2013 by Yu *et al.*
Fitoterapia **2013,** *91,* **74**

Skeleton of Palhinine-type *Lycopodium* Alkaloids

Figure 1. Lycopodiaceae Plant and Known palhinine-type Lycopodium Alkaloids.

Although no activity was observed in preliminary studies, scarcity in nature precludes extensive biological evaluations of these alkaloids.

Challenge

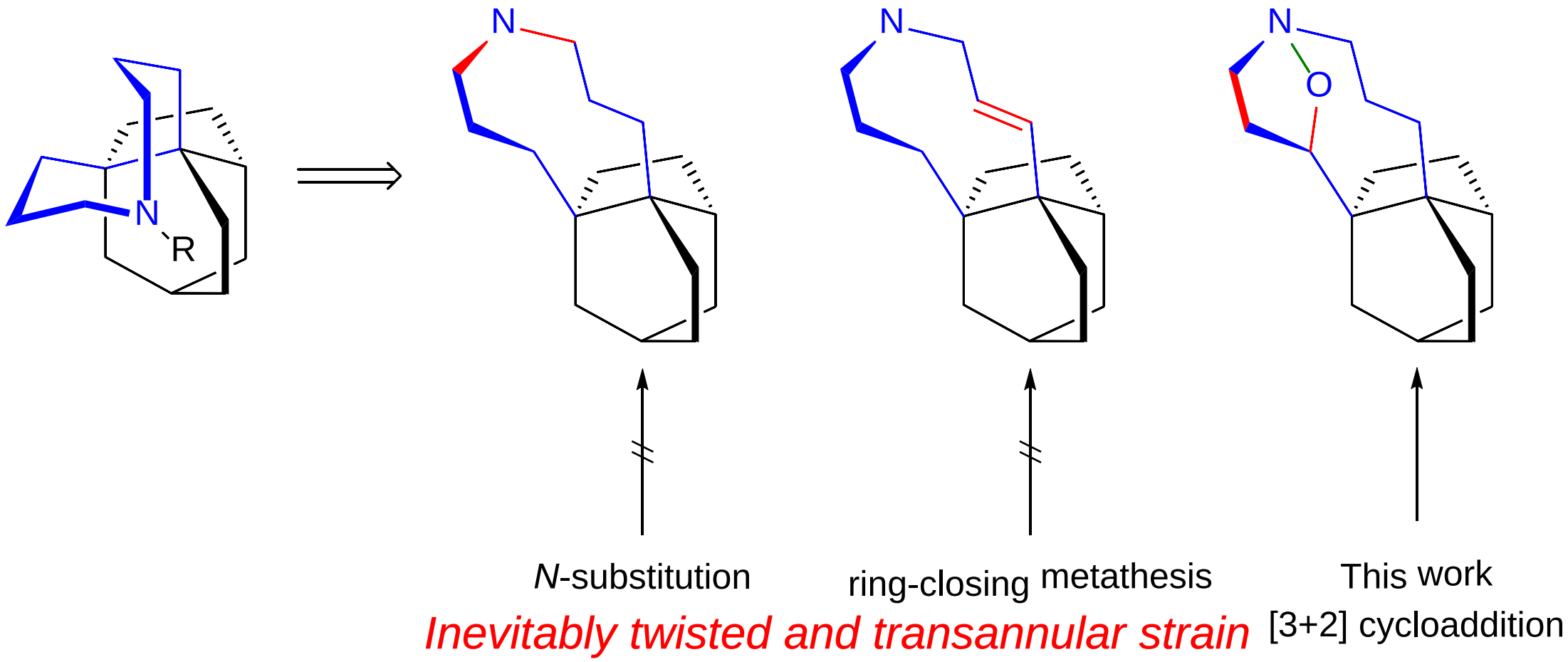
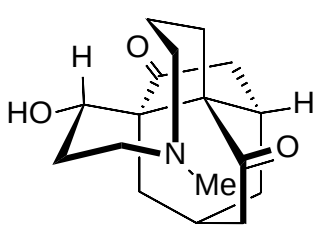


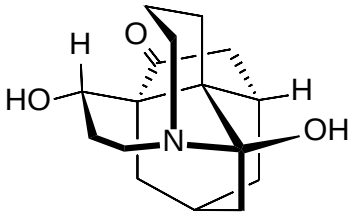
Figure 2. Designed Strategies for Assembly of the Nine-Membered Azonane Ring Embedded in the Framework of Palhinine-type Alkaloids

Retrosynthesis

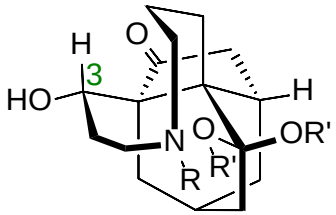


palhinine A

or

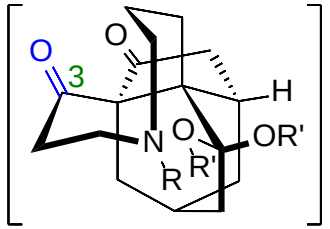


palhinine D

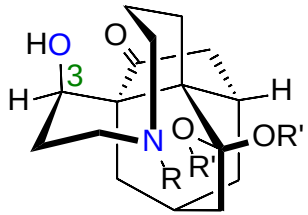


A

chemo- and stereoselective reduction

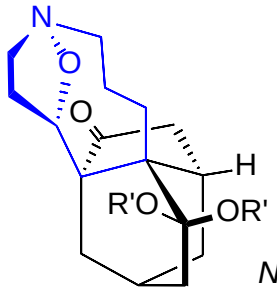


B



C

reductive cleavage of N-O bond



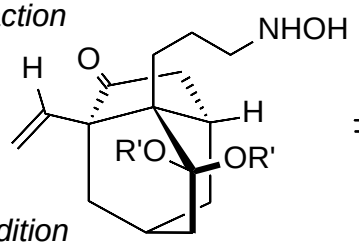
D

key step

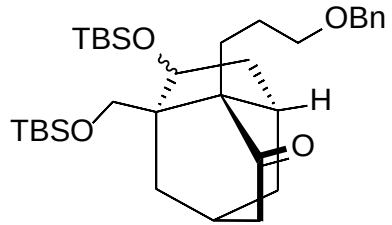
regio- and stereoselective Nitrone-olefin 3+2 cycloaddition 1,3 dipolar cycloaddition

Wittig reaction

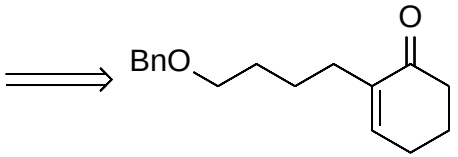
oxime formation and reduction



E

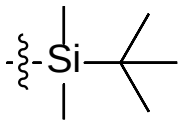


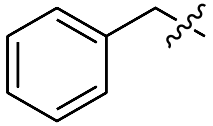
F-12

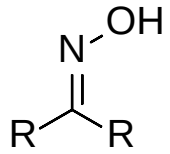


G-4

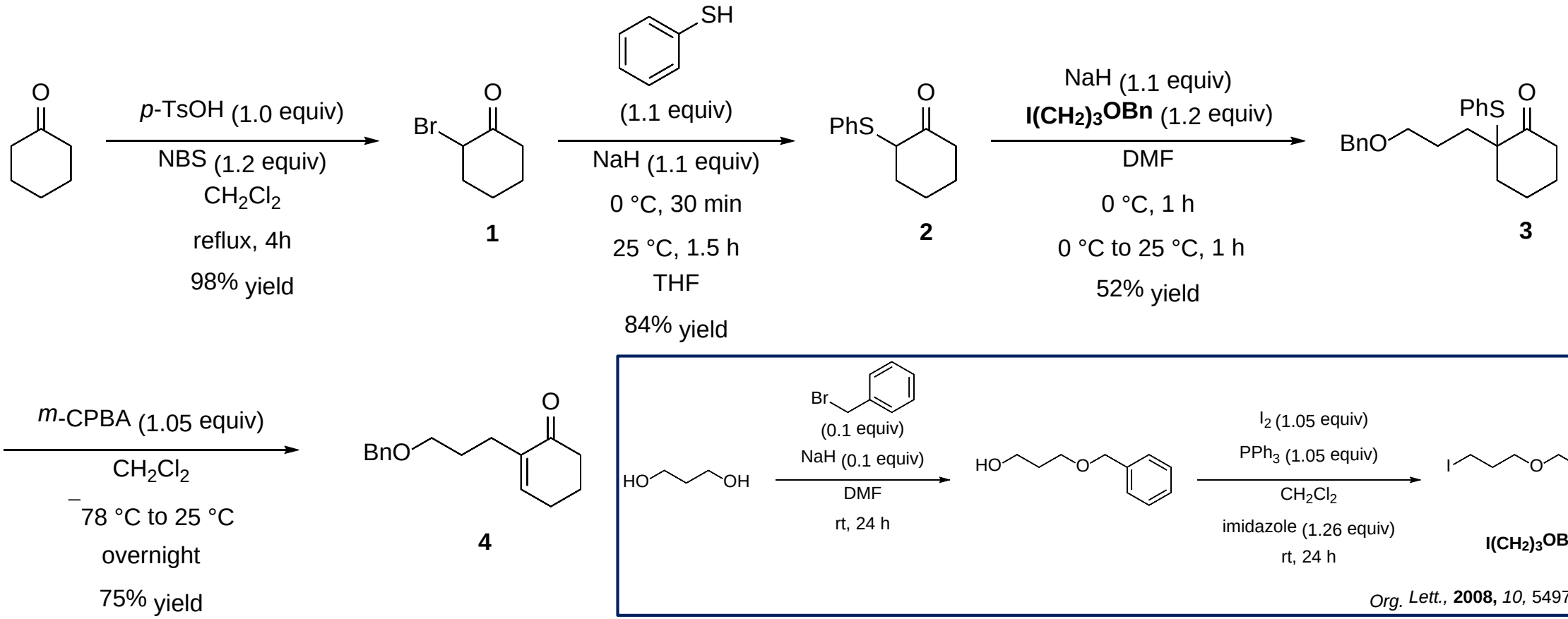
tert-Butyldimethylsilyl **(TBS)**	Benzyl **(Bn)**	Oxime



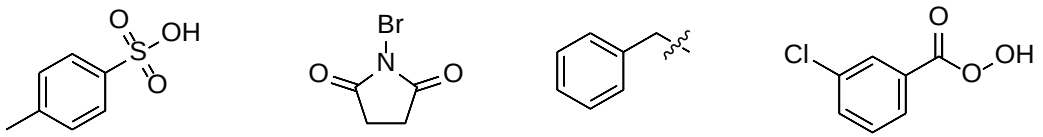




Synthesis of **4**

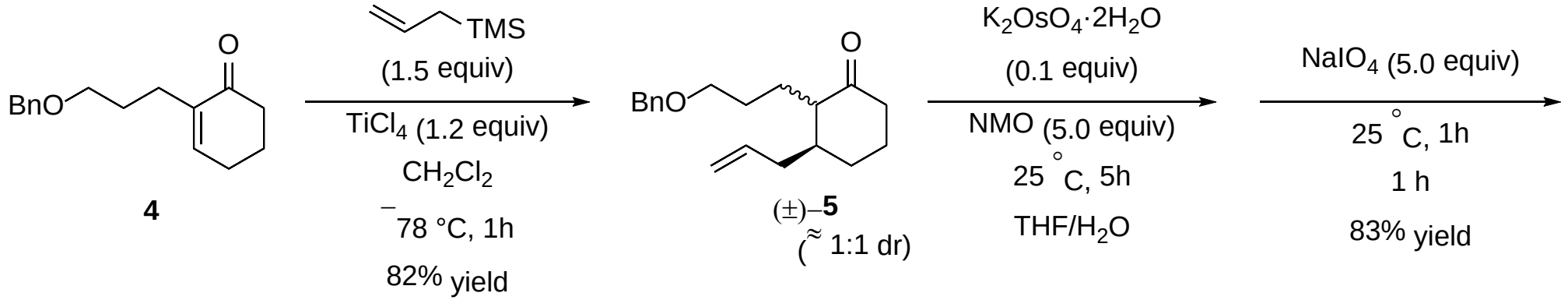


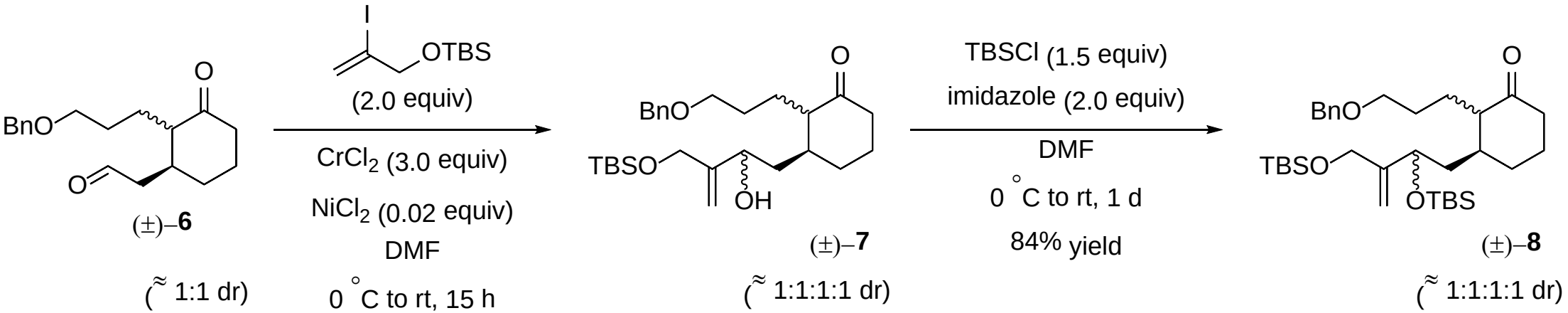
p-Toluenesulfonic acid ***(p*-TsOH)**	N-Bromosuccinimide **(NBS)**	Benzyl **Bn**	meta-Chloroperoxybenzoic acid **(*m*-CPBA)**



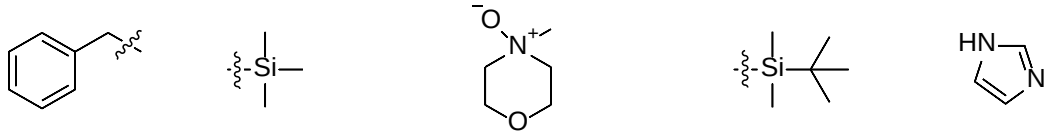
Org. Lett. **2012,** *14,* 3696.

Synthesis of **8**



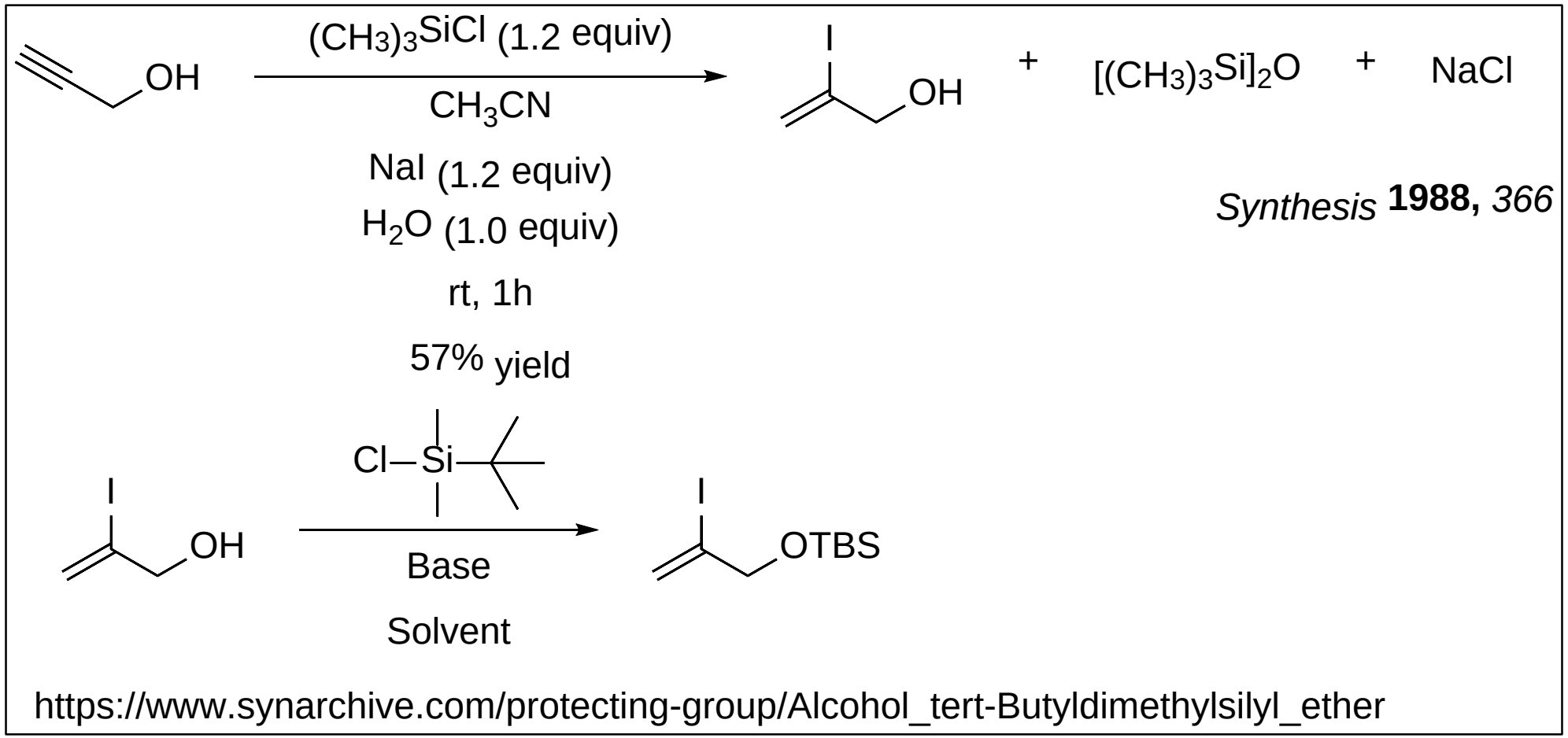


Benzyl **(Bn)**	Trimethylsilyl **(TMS)**	4-methylmorpholine 4-oxide **(NMO)**	*tert*-Butyldimethylsilyl **(TBS)**	imidazole



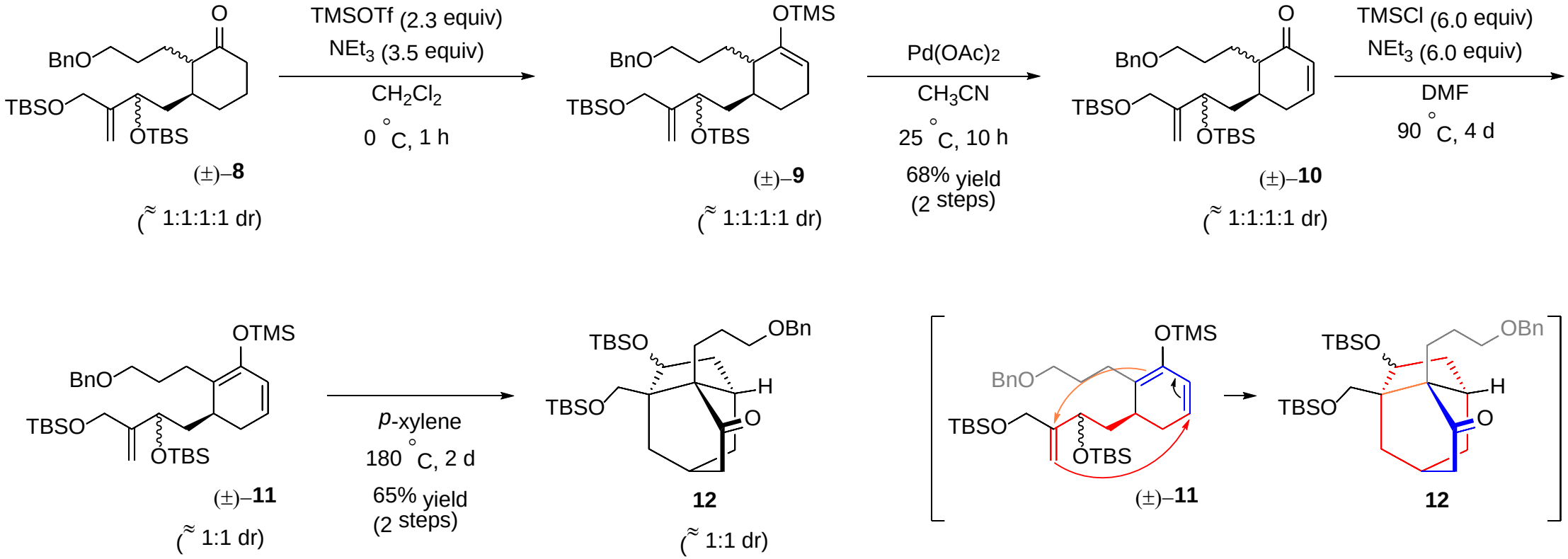
Org. Lett. **2012,** *14,* 3696.

tert-butyldimethylsilyl 2-iodoallyl ether



https://www.synarchive.com/protecting-group/Alcohol_tert-Butyldimethylsilyl_ether

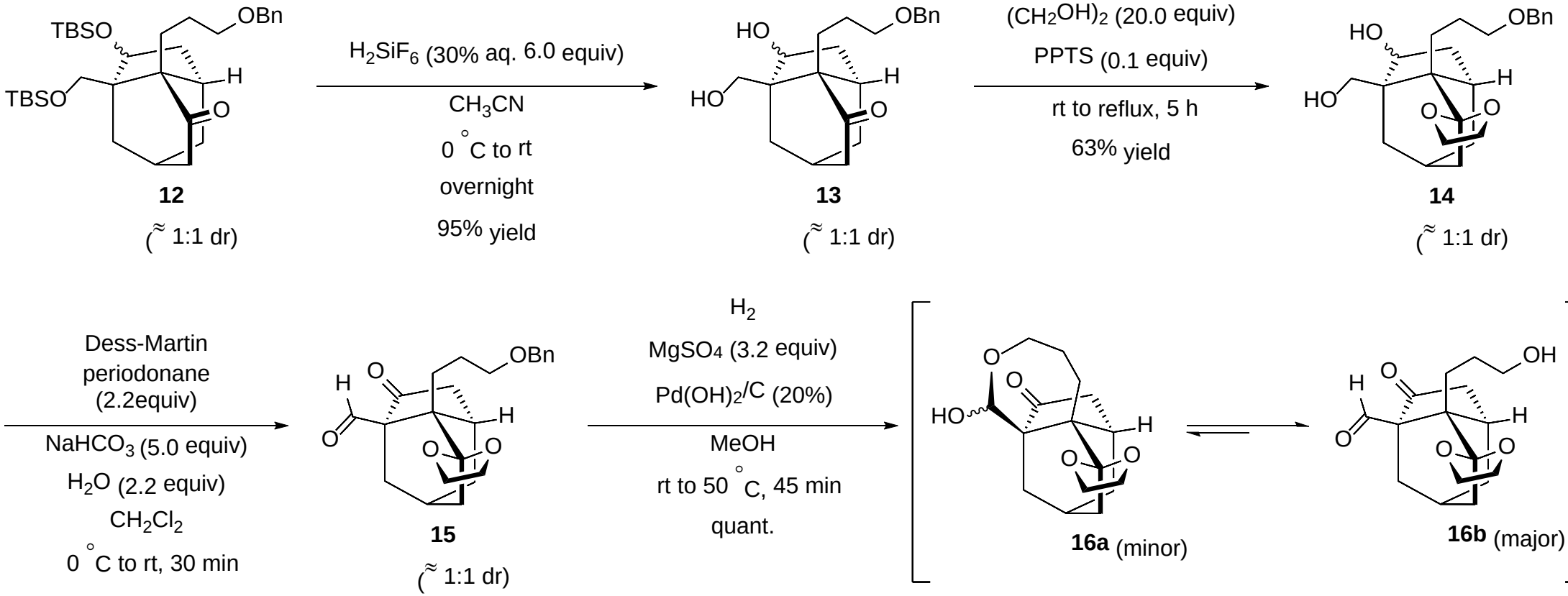
Synthesis of **12**



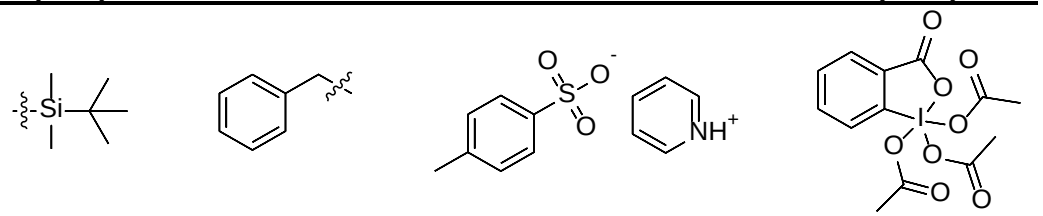
Benzyl **(Bn)**	*tert*-Butyldimethylsilyl **(TBS)**	Trimethylsilyl trifluoromethanesulfonate **(TMSOTf)**	Palladium(II) acetate **($Pd(OAc)_2$)**	Trimethylsilyl **(TMS)**	*p*-xylene

Org. Lett. **2012,** *14,* 3696.

Synthesis of **16**



tert-Butyldimethylsilyl **(TBS)**	Benzyl **(Bn)**	Pyridinium p-toluenesulfonate **(PPTS)**	Dess–Martin periodinane **(DMP)**



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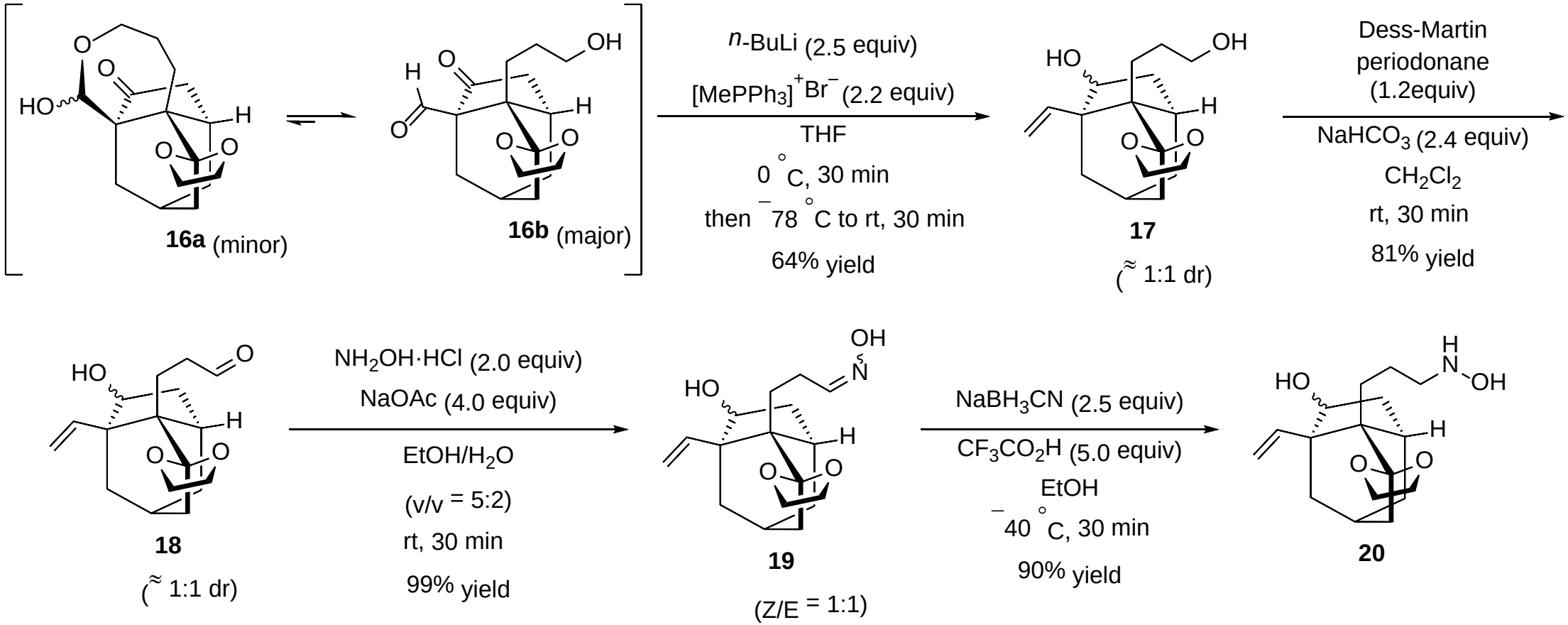
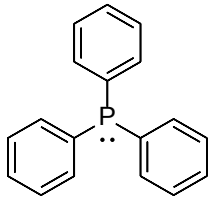
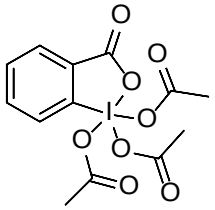
Synthesis of **20**



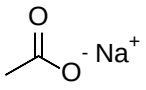
Triphenylphosphine **(PPh_3)**



Dess–Martin periodinane **(DMP)**



Sodium acetate **(NaOAc)**



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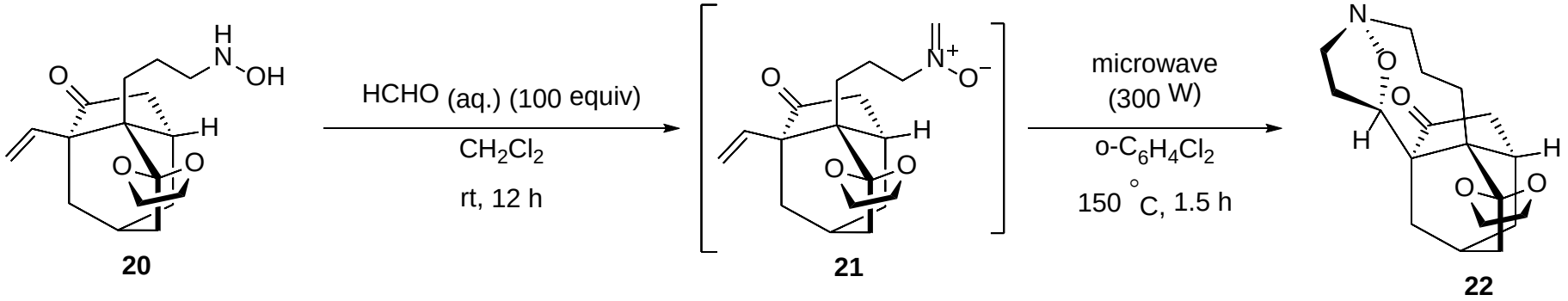
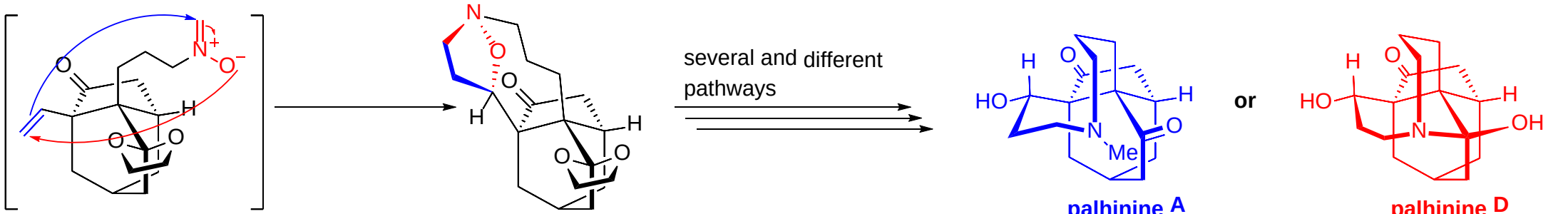
Synthesis of **22 Building Block**



20 **21** **22**

Nitrone-olefin 3+2 cycloaddition
1,3 dipolar cycloaddition



21 **22**

palhinine A
from 22, 23...to 26

palhinine D
from 22, 27 to 31

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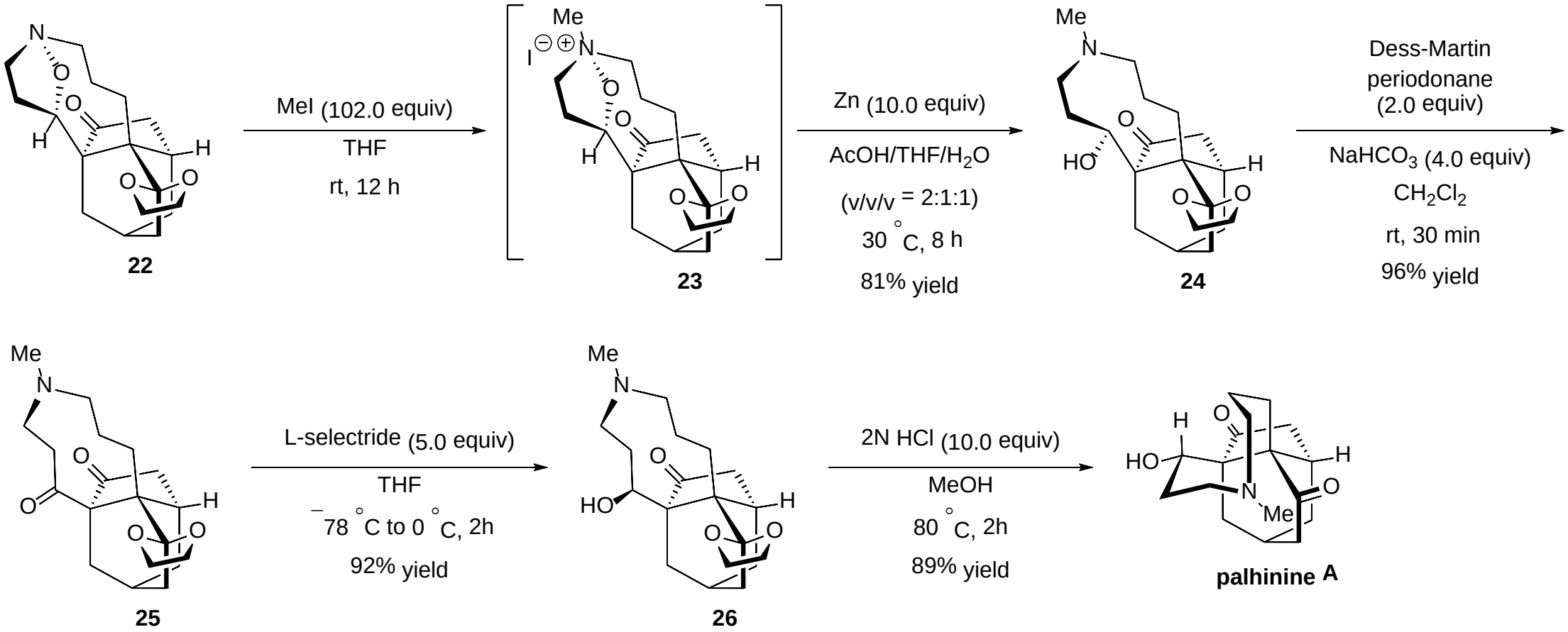
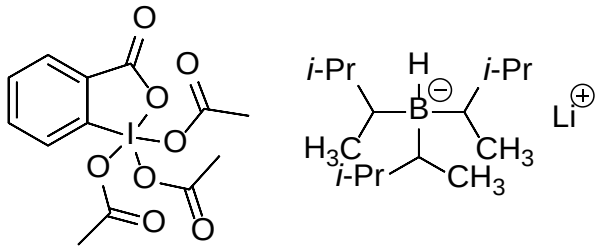
Palhinine A (the Blue Pathway)



Dess–Martin periodinane **(DMP)**	Lithium trisiamylborohydride **(L-Selectride)**



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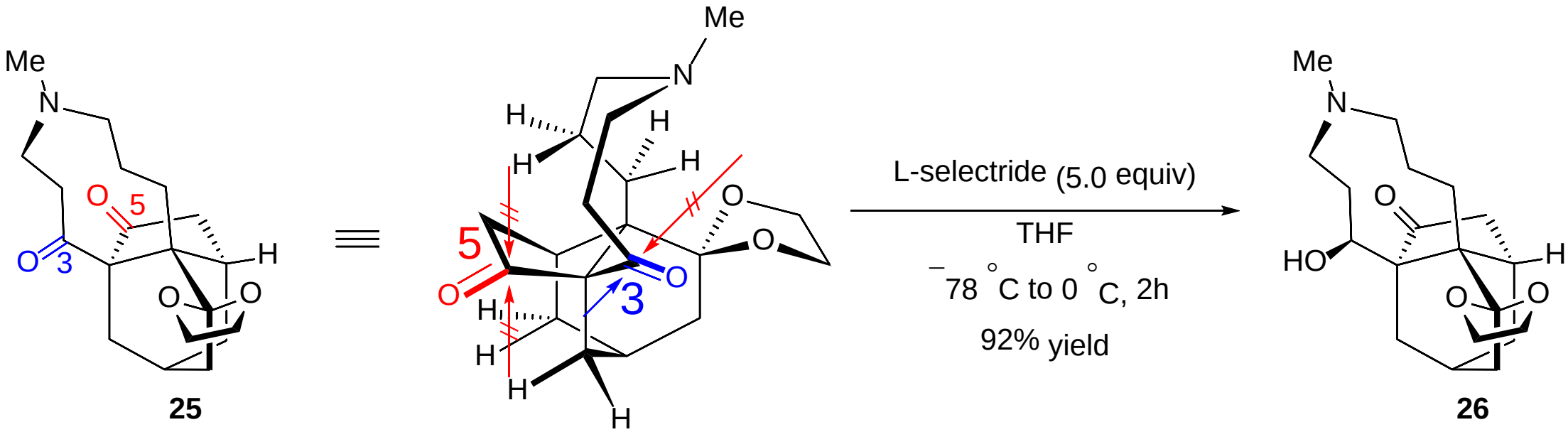
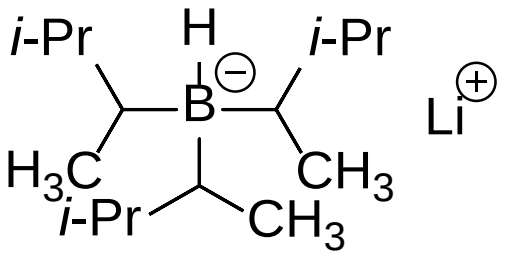
Chemo- and Stereoselective Reduction



Lithium trisiamylborohydride
(L-Selectride)



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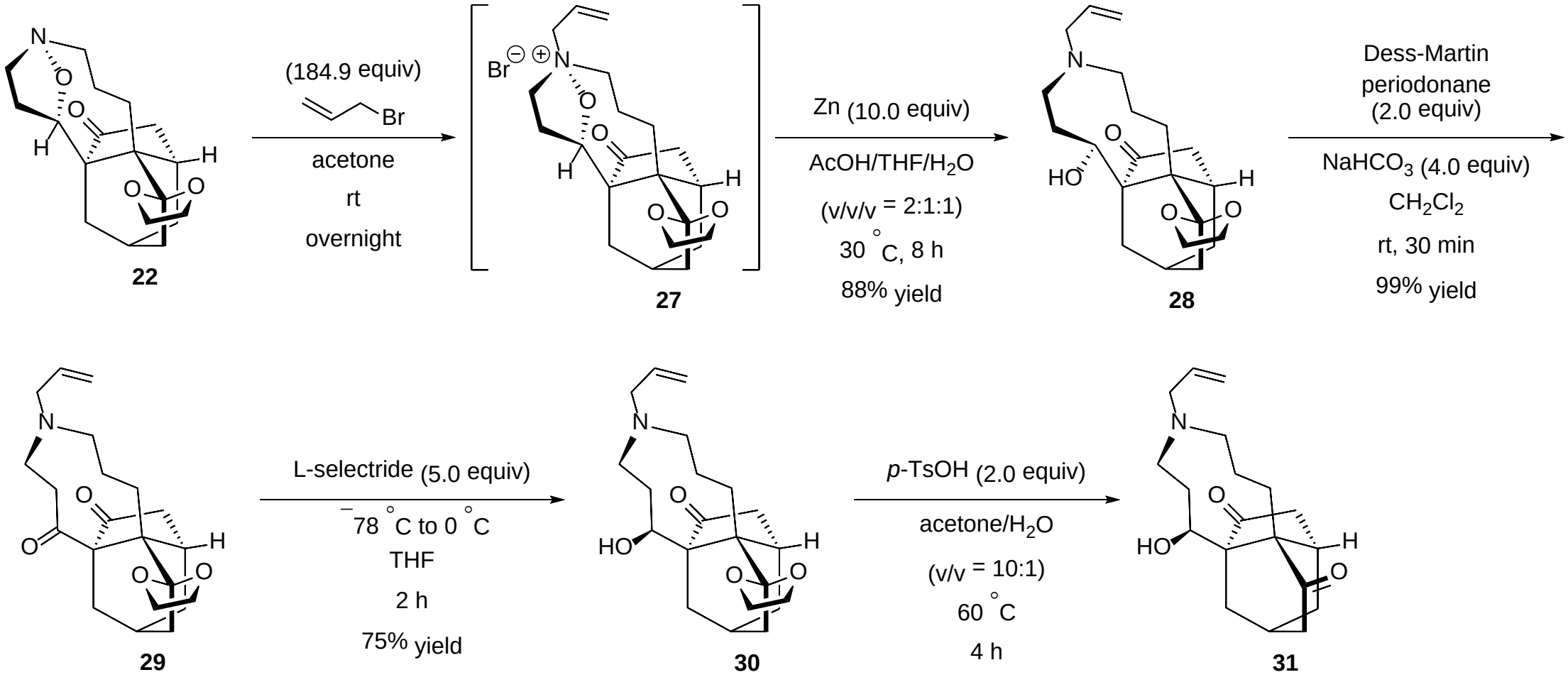
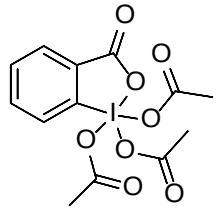
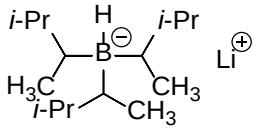
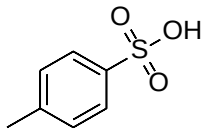
Synthesis of **31** (the Red Pathway)



Dess–Martin periodinane **(DMP)**	Lithium trisiamylborohydride **(L-Selectride)**	*p*-Toluenesulfonic acid **(*p*-TsOH)**
		

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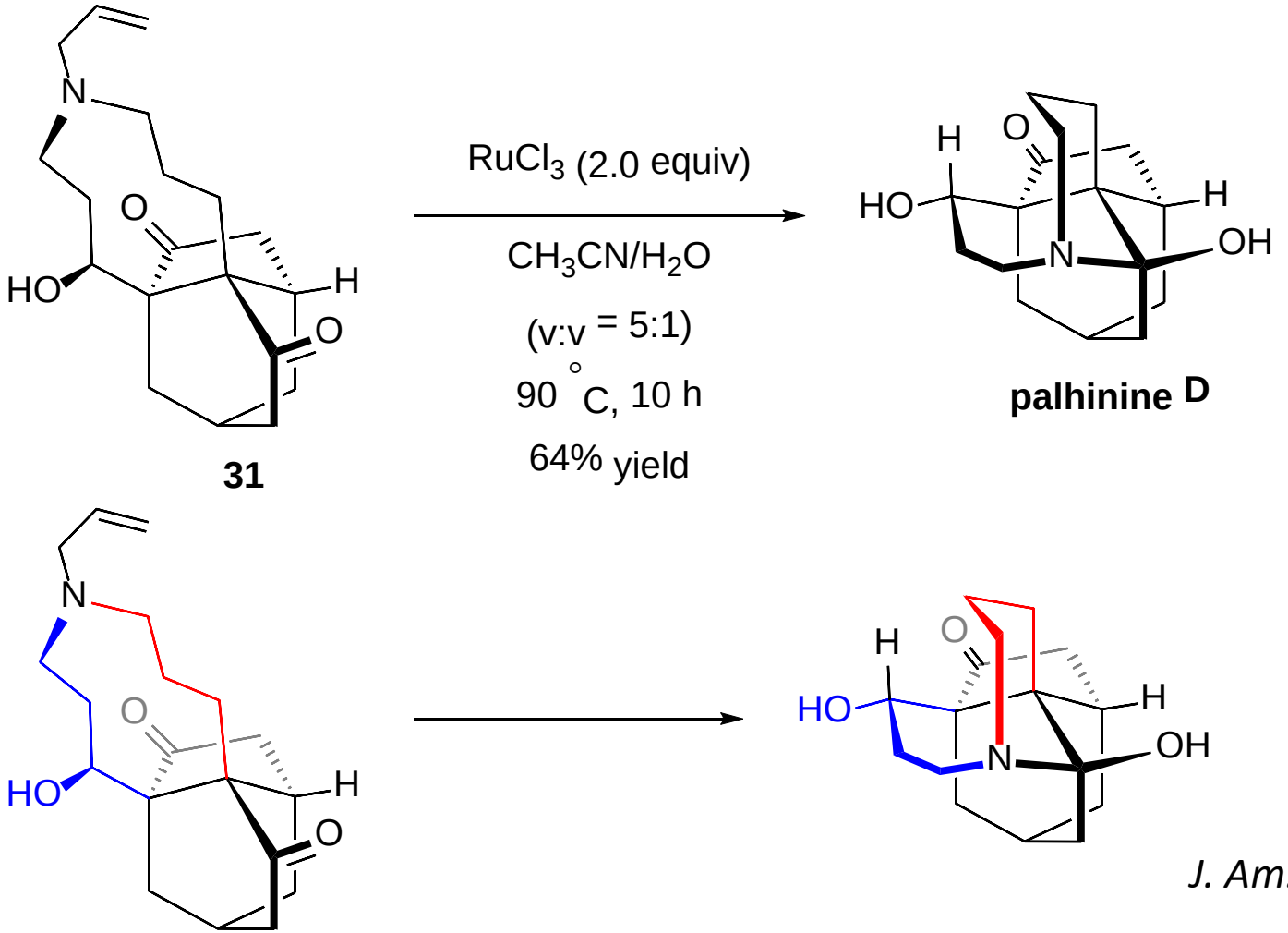
Palhinine D (the Red Pathway)



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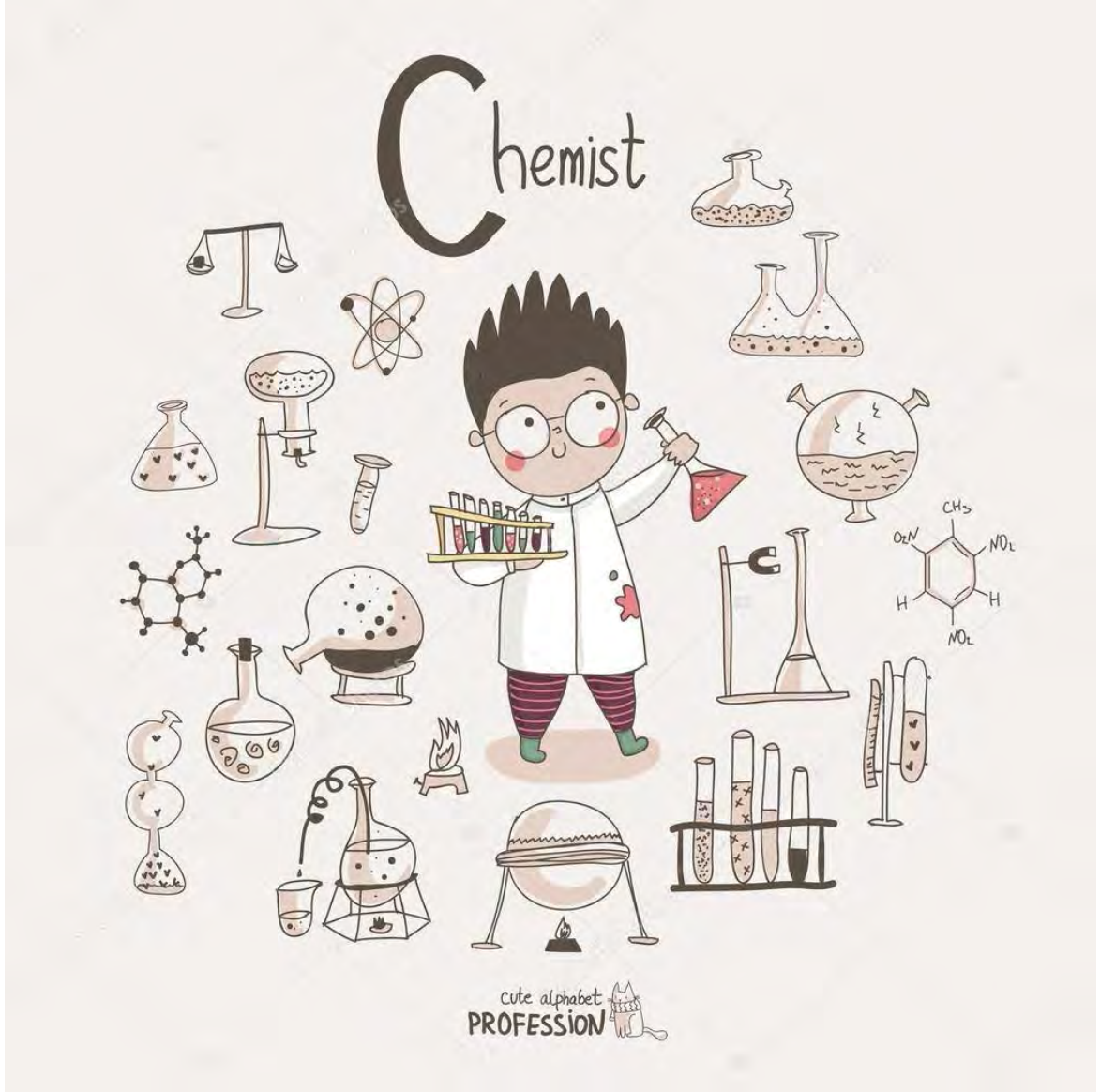
Conclusion

- First report on total synthesis of palhinines A and D

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

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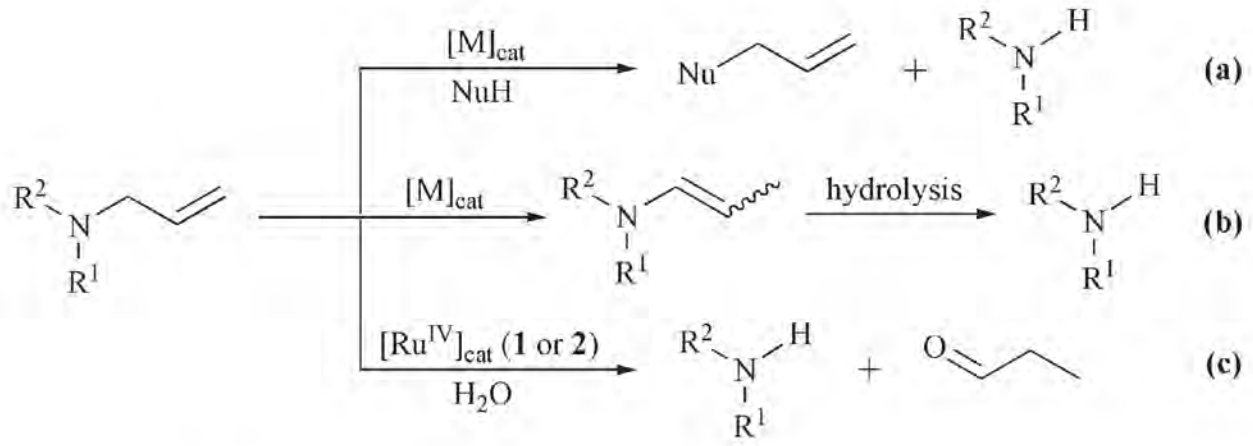
Details About Deprotection of *N*-allylamines



Scheme 1 Strategies used for the catalytic deprotection of *N*-allylamines.

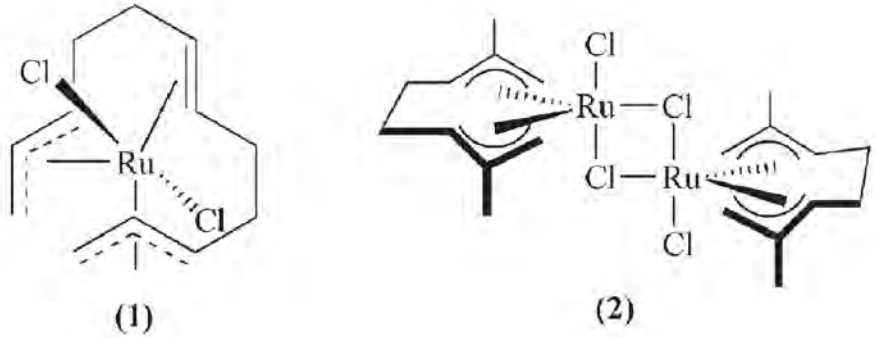
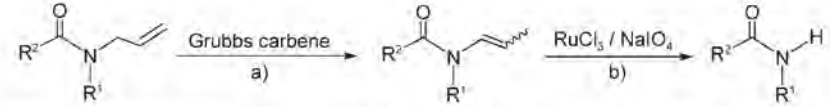


Fig. 1 Structure of the bis(allyl)-ruthenium(IV) complexes **1** and **2**.

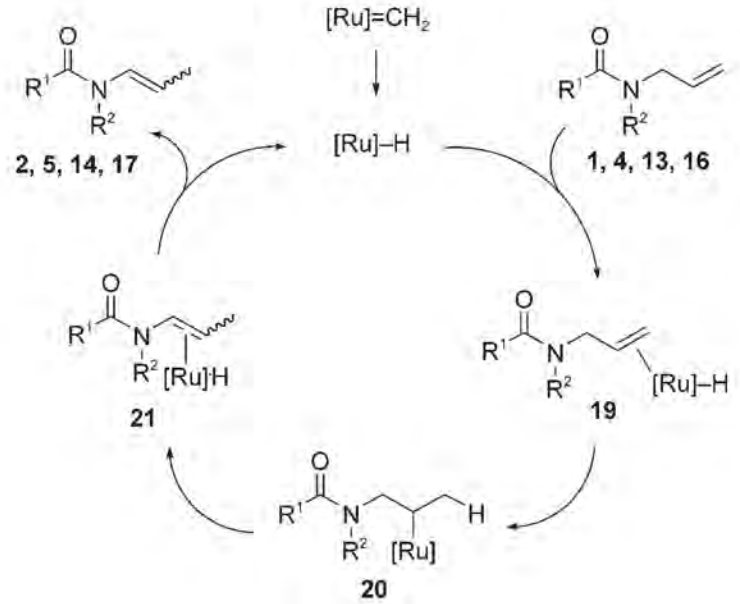
Chem. Commun. **2005,** *4086*



Scheme 3. General procedure for the (CO)N–allyl cleavage. Conditions: a) 5 mol% [Ru(=CHPh)Cl$_2$(PCy$_3$)$_2$], toluene, reflux; b) 3.5 mol% $RuCl_3$, $NaIO_4$ (2 equiv), 1,2-dichloroethane/water (1:1 v/v), RT, aqueous workup under basic conditions, see reference [8].

To promote C=C migrations in water

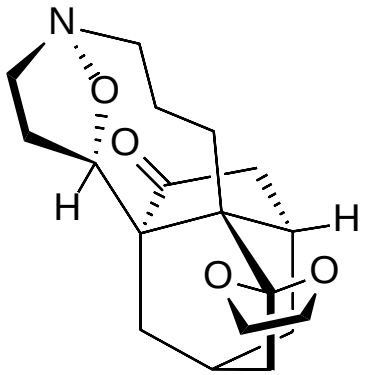
Chem. Eur. J. **2007,** *13,* 6590



Scheme 6. Mechanistic explanation for the ruthenium Grubbs' carbene-catalyzed amide-enamide isomerization.

Tetrahedron Lett. **2003,** *44,* 8693

Palhinine Related Products



22

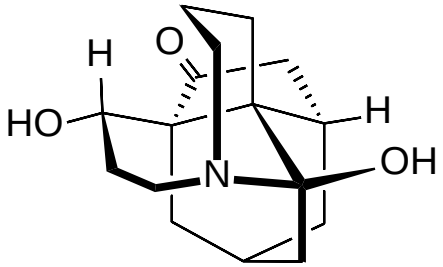
$Mo(CO)_6$ (5.0 equiv)

CH_3CN/H_2O

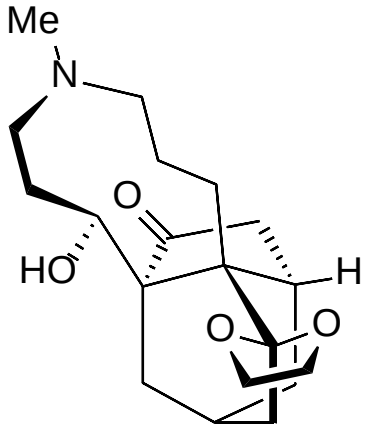
(v/v = 9:1)

85 °C

75% yield



3-*epi*-palhinine D



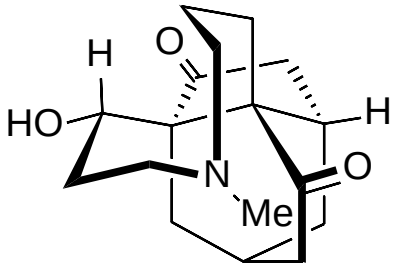
24

p-TsOH (2.0 equiv)

acetone/H_2O

(v/v = 10:1)

98% yield



3-*epi*-palhinine A

p-Toluenesulfonic acid

(p*-TsOH*)