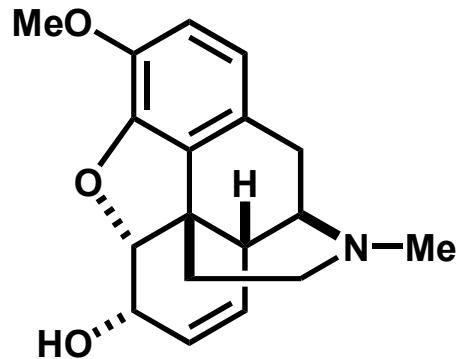


Total Synthesis of Morphine



2017/1/27 Takumi Fukuda

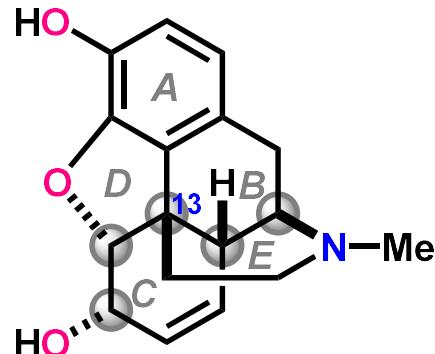
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Introduction of Morphine



Isolation

Papaver somniferum (Serturner, 1804)¹⁾

Structural determination (cf. 120908_PS_Masanori NAGATOMO)

proposed : Robinson (1925)²⁾

confirmed : Gates (1952, by total synthesis)³⁾, Hodgkin (1955, by X-ray crystallography)⁴⁾

Bioactivity

analgesic activity (activate the μ -opioid receptors)⁵⁾

Structural features

5 contiguous stereocenters

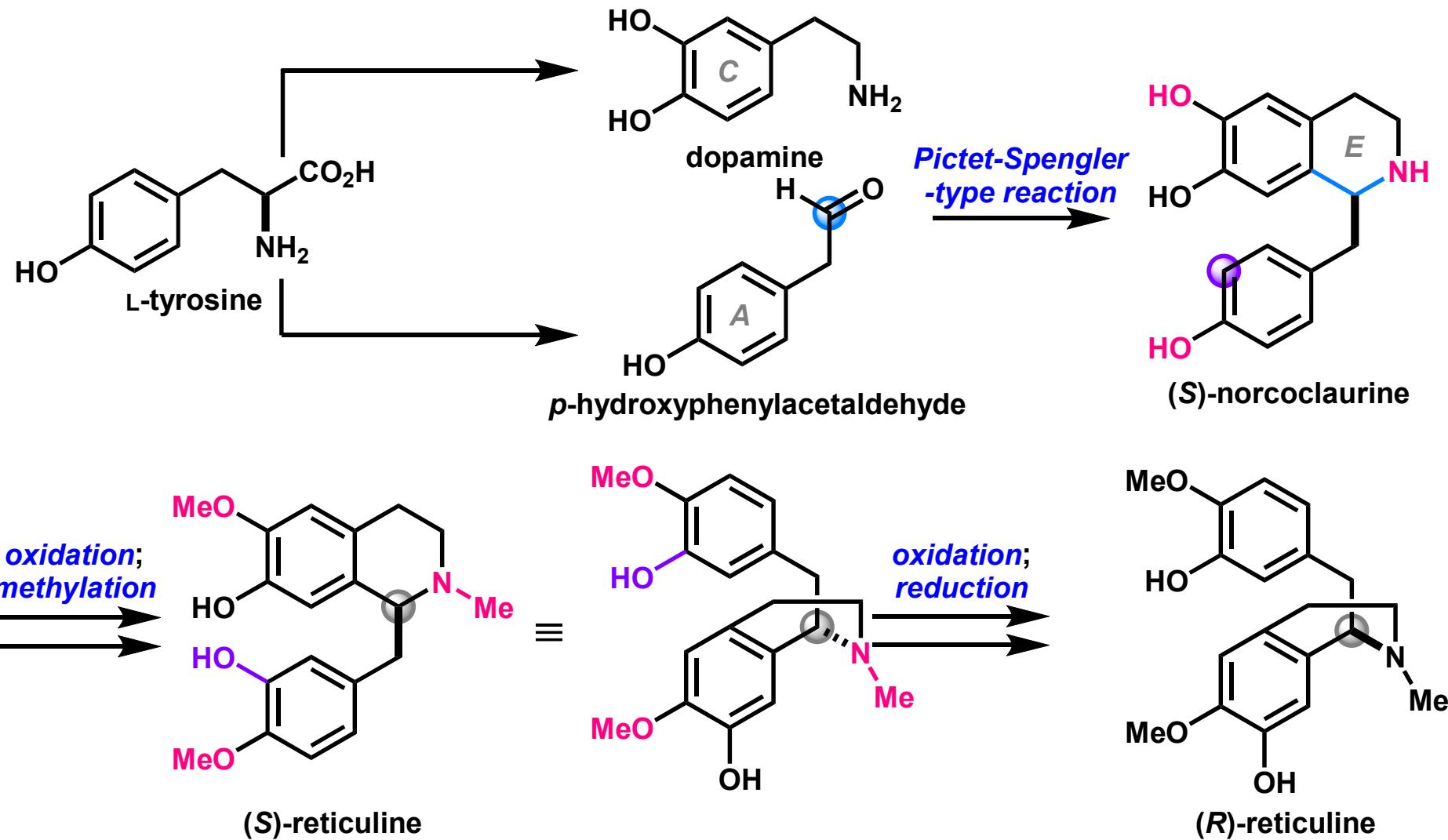
a quaternary carbon (C13)

Total and formal synthesis

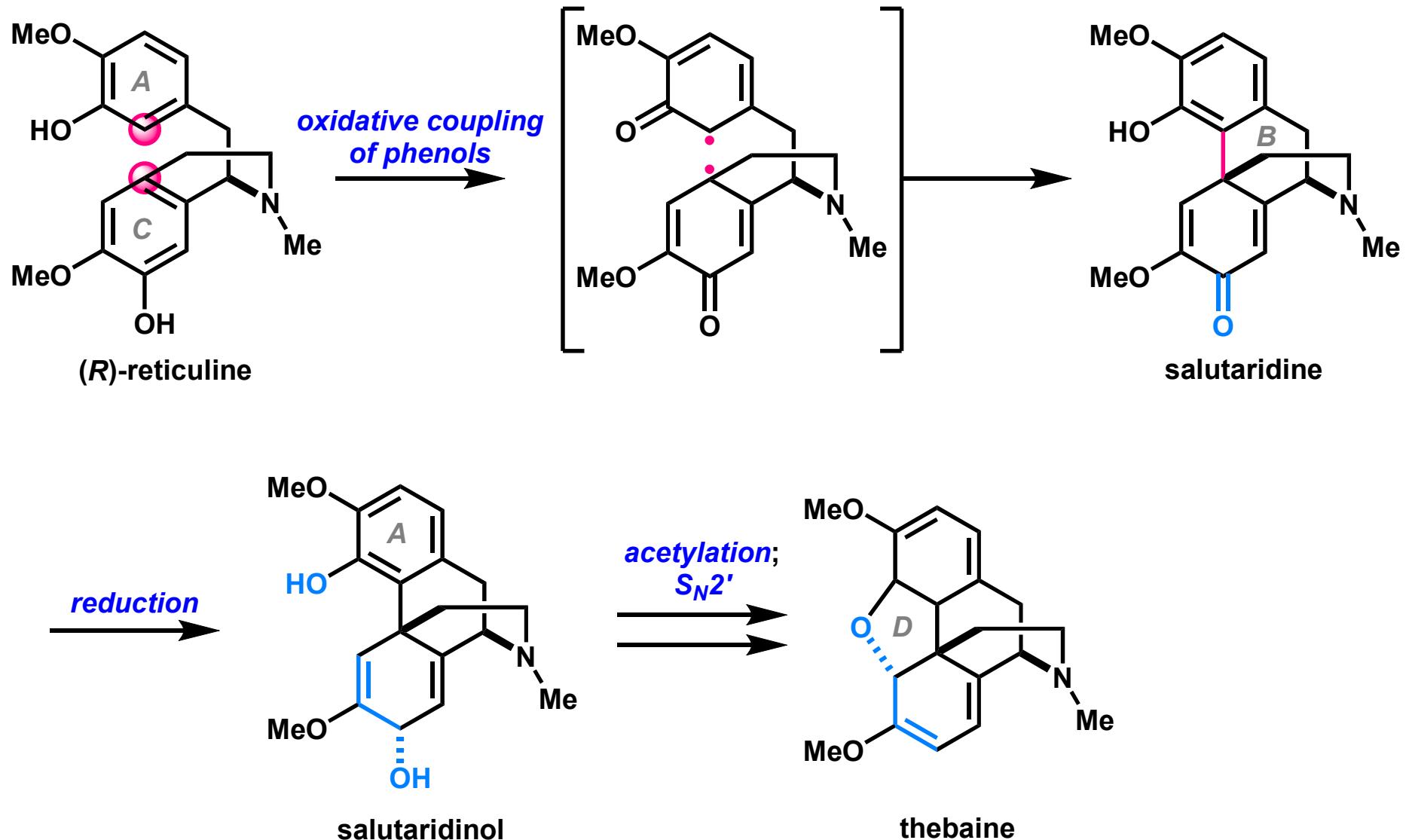
> 30 total or formal syntheses of morphine alkaloids

1) Serturner, F. W. Trommsdorffs *J. Pharm.* **1805**, 13, 234. 2) J. M. Gulland, R. Robinson, *Mem. Proc. Manchester Lit. Philos. Soc.* **1925**, 69, 79-86. 3) M. Gates, G. Tschudi, *J. Am. Chem. Soc.* **1952**, 74, 1109-1110. 4) M. Mackay, D. C. Hodgkin, *J. Chem. Soc.* **1955**, 3261-3267. 5) Waldhoer, M.; Bartlett, S. E.; Whistler, J. L. *Annu. Rev. Biochem.* **2004**, 73, 953.

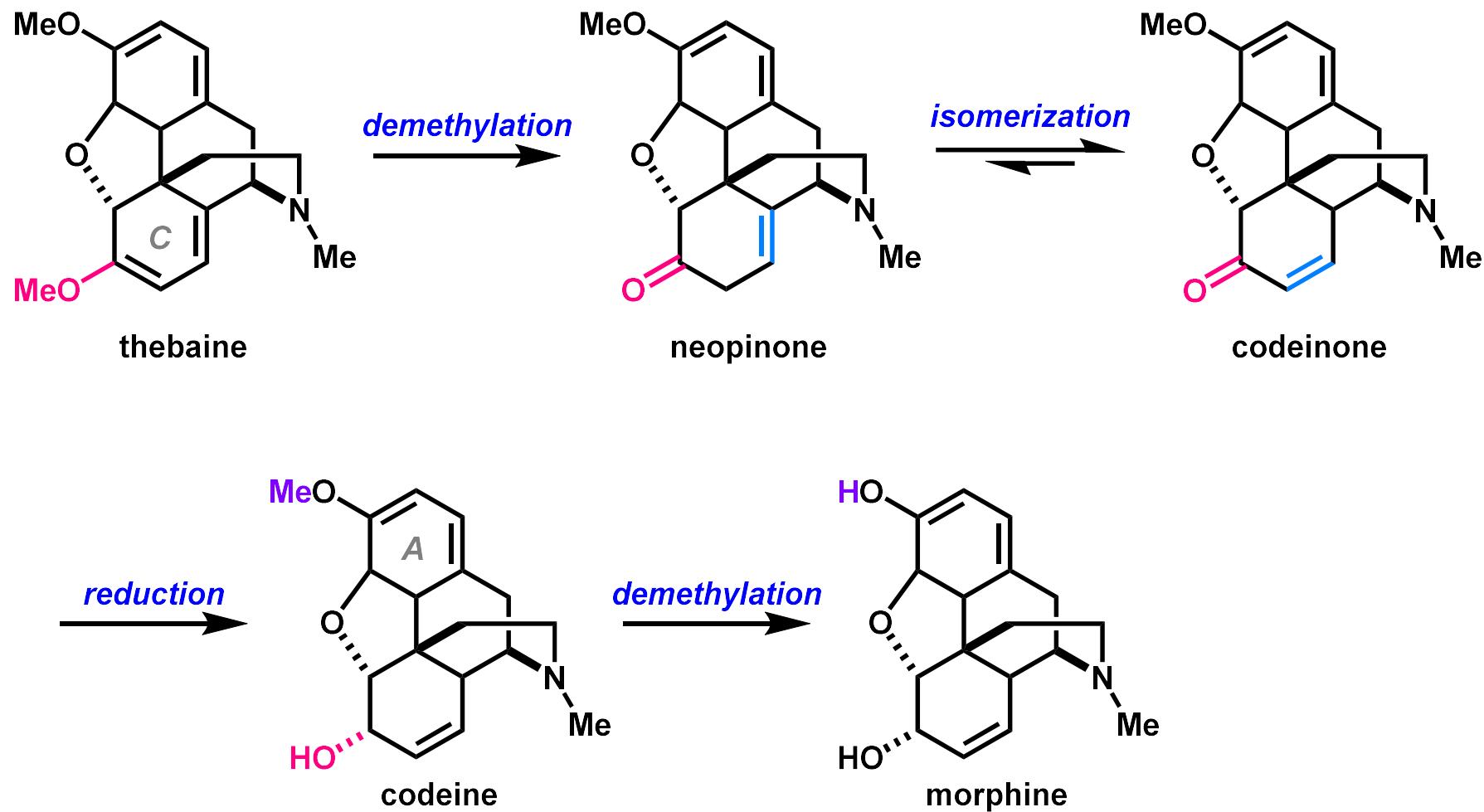
Biosynthesis of Morphine (1)



Biosynthesis of Morphine (2)



Biosynthesis of Morphine (3)



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Syntheses of Morphine Alkaloids

Principal author	Year	Target	Steps	Yield (%)
Gates ¹⁾	1952	morphine	31	0.06
Rice ¹⁾	1980	<i>rac</i> -dihydrocodeinone	14	29.7
Parker ¹⁾	1992	<i>rac</i> -dihydrocodeinone	11	11.1
Overman ¹⁾	1993	dihydrocoddeinone	14	1.9
Trost ¹⁾	2002	codeine	15	6.8
Chida ¹⁾	2008	<i>rac</i> -dihydroisocodeine	24	3.8
Magnus ¹⁾	2009	<i>rac</i> -codeine	13	20.1
Fukuyama ¹⁾	2010	morphine	17	4.8
Hudlicky ²⁾	2014	<i>ent</i> -hydromorphone	12	2
Smith	2016	<i>rac</i> -morphine	9	6.6

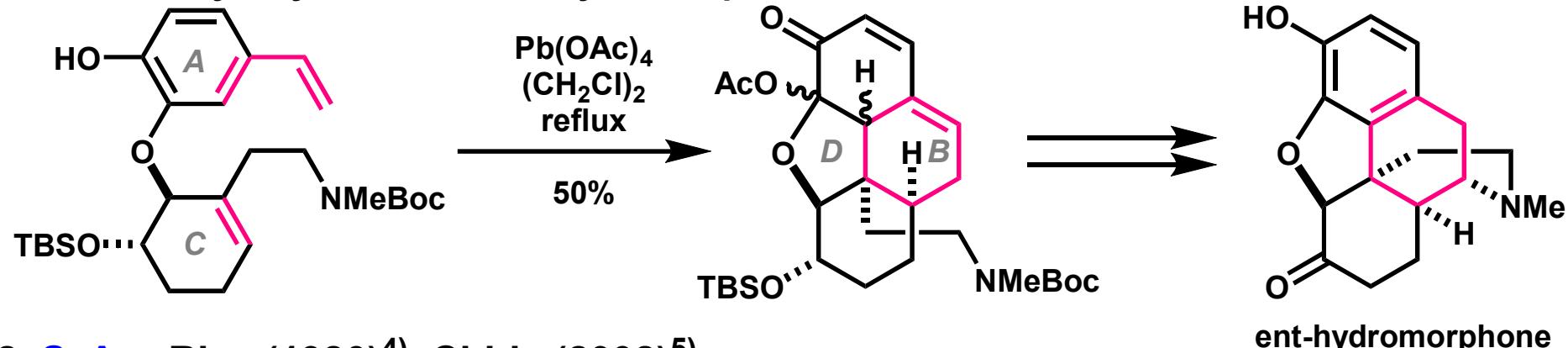
1) Rinner, U.; Hudlicky, T. *Top Curr Chem* **2012**, 309, 33–66.

2) Varghese, V.; Hudlicky, T. *Angew. Chem., Int. Ed.* **2014**, 53, 4355.

Strategy Overview

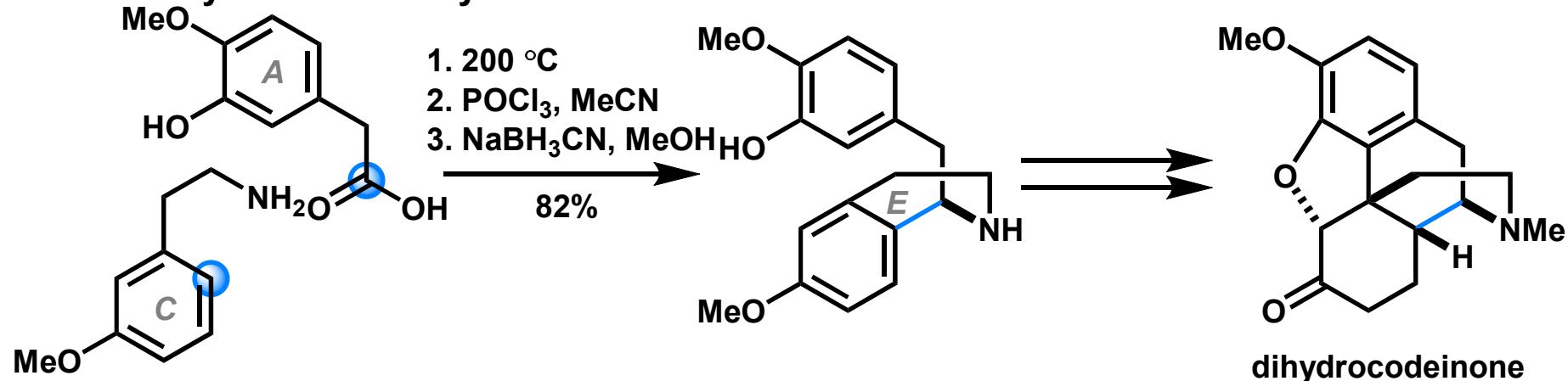
1. Diels-Alder - Gates (1952)¹⁾, Stork (2009)²⁾, Hudlicky (2014)³⁾

Ex. Hudlicky's synthesis of *ent*-hydromorphone



2. S_EAr - Rice (1980)⁴⁾, Chida (2008)⁵⁾

Ex. Rice's synthesis of dihydrocodeinone

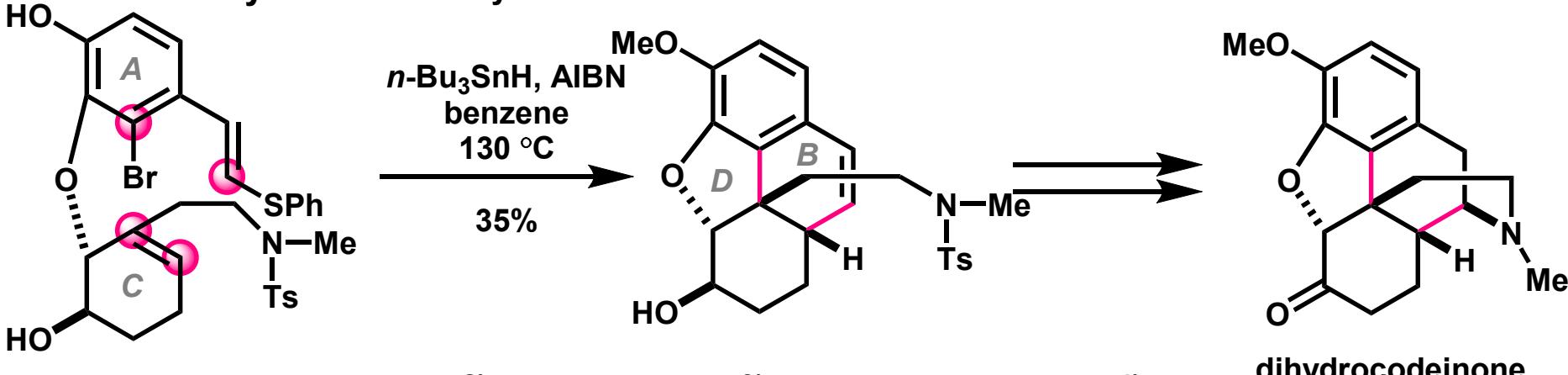


1) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, 74, 1109. 2) Stork, G.; Yamashita, A.; Adams, J.; Schulte, G. R.; Chesworth, R.; Miyazaki, Y.; Farmer, J. *J. Am. Chem. Soc.* **2009**, 131, 11402. 3) Varghese, V.; Hudlicky, T. *Angew. Chem., Int. Ed.* **2014**, 53, 4355. 4) Rice, K. C. *J. Org. Chem.* **1980**, 45, 3135. 5) Tanimoto, H.; Saito, R.; Chida, N. *Tetrahedron Lett.* **2008**, 49, 358.

Strategy Overview

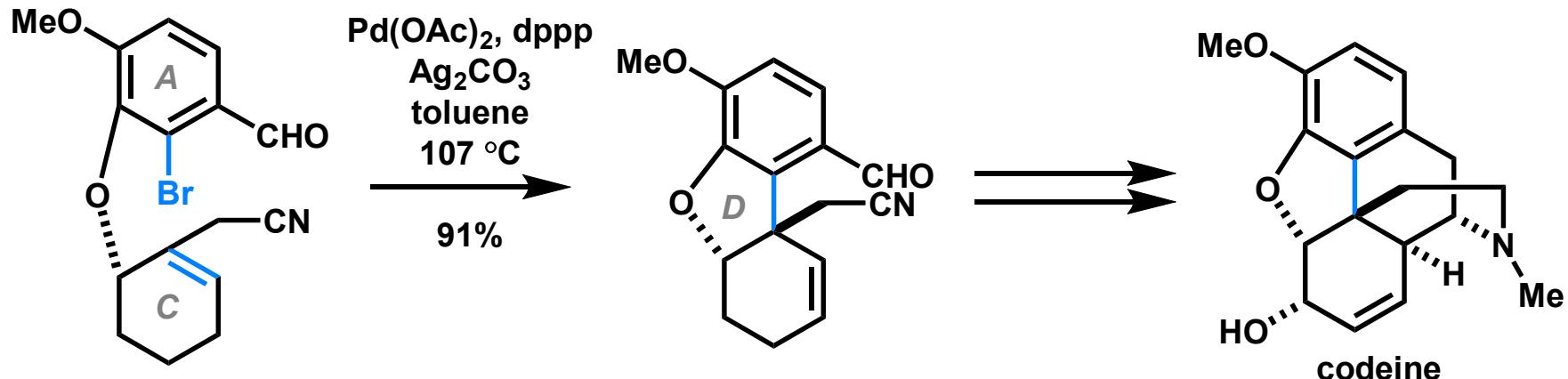
3. Radical cyclization - Parker (1992)¹⁾

Ex. Parker's synthesis of dihydrocodeinone¹⁾



4. Heck - Overman (1993)²⁾, Trost (2002)³⁾, Fukuyama (2010)⁴⁾

Ex. Trost's synthesis of codeine³⁾



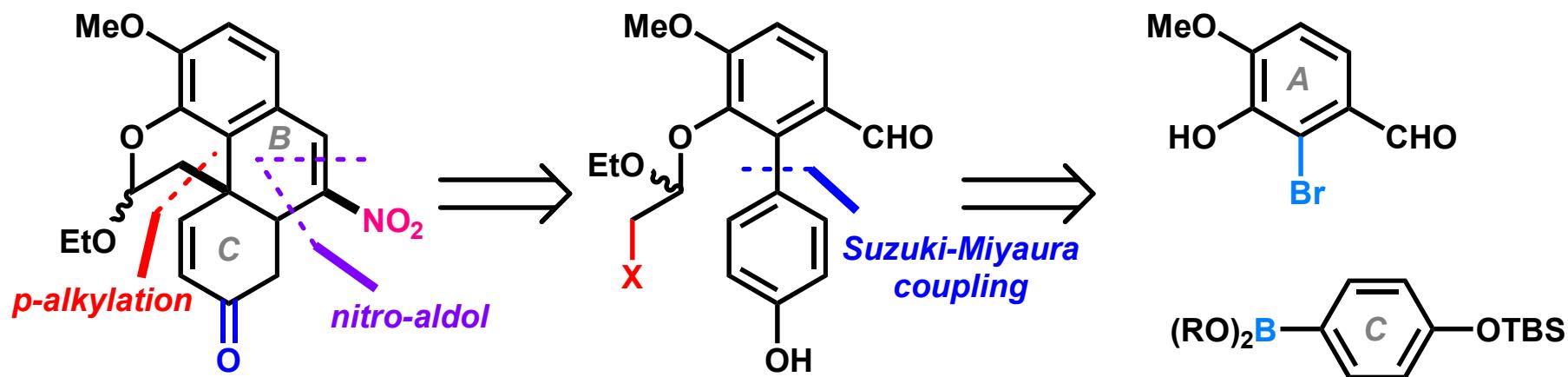
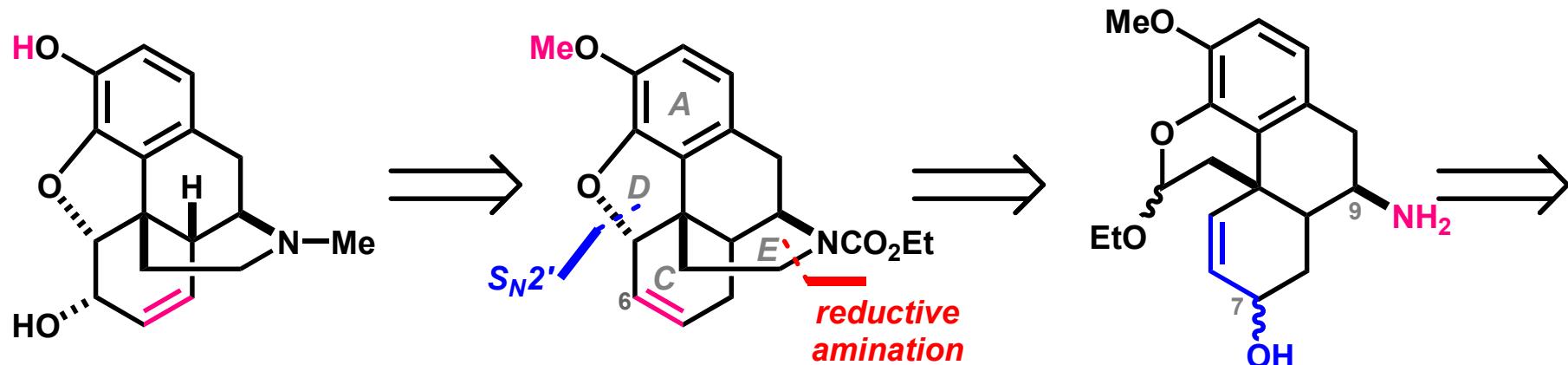
1) Parker, K. A.; Fokas, D. J. *Am. Chem. Soc.* **1992**, 114, 9688. 2) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, 115, 11028. 3) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2002**, 124, 14542.

4) Koizumi, H.; Yokoshima, S.; Fukuyama, T. *Chem. Asian J.* **2010**, 5, 2192.

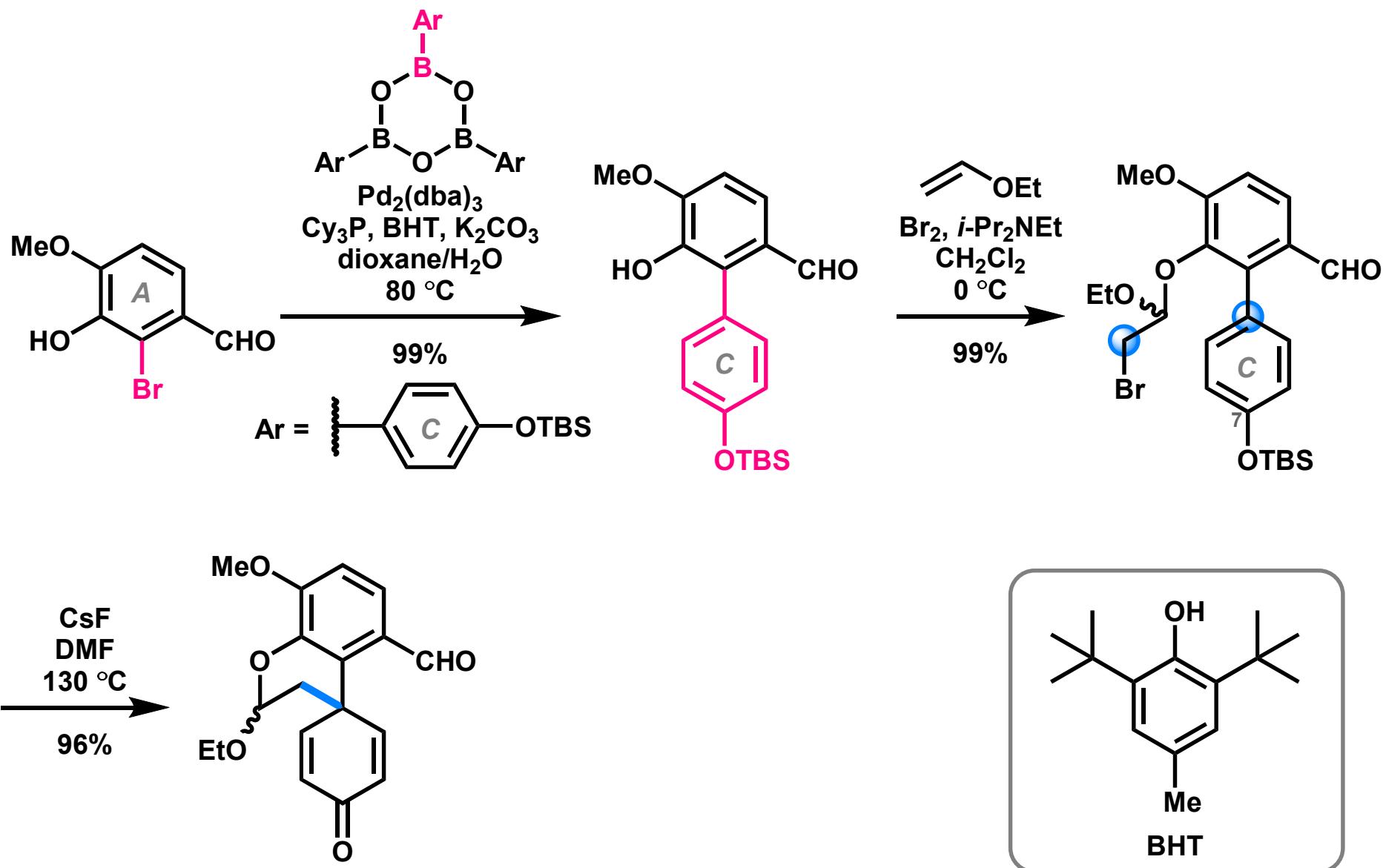
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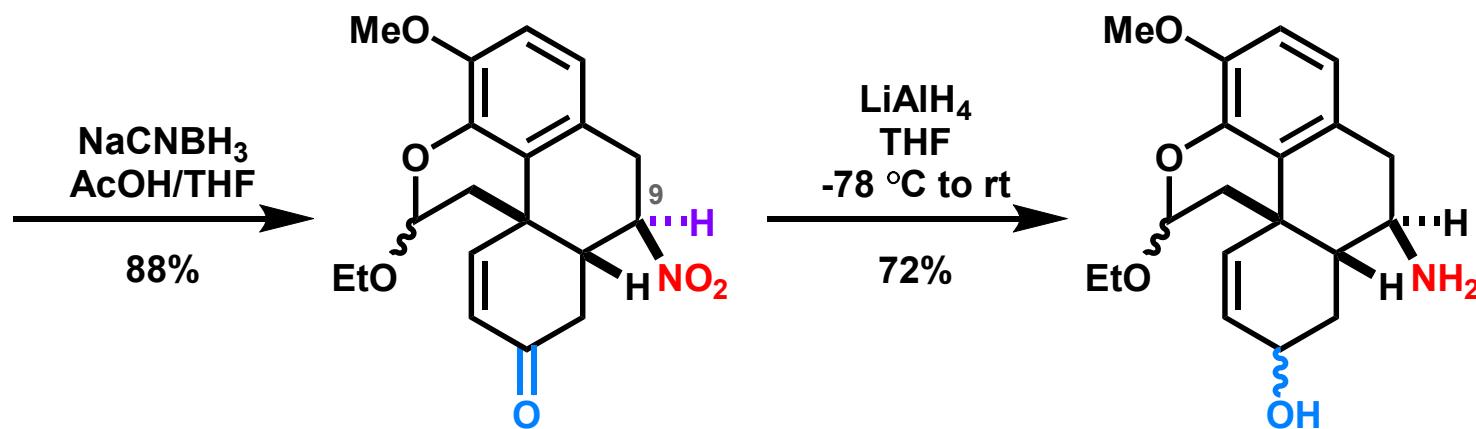
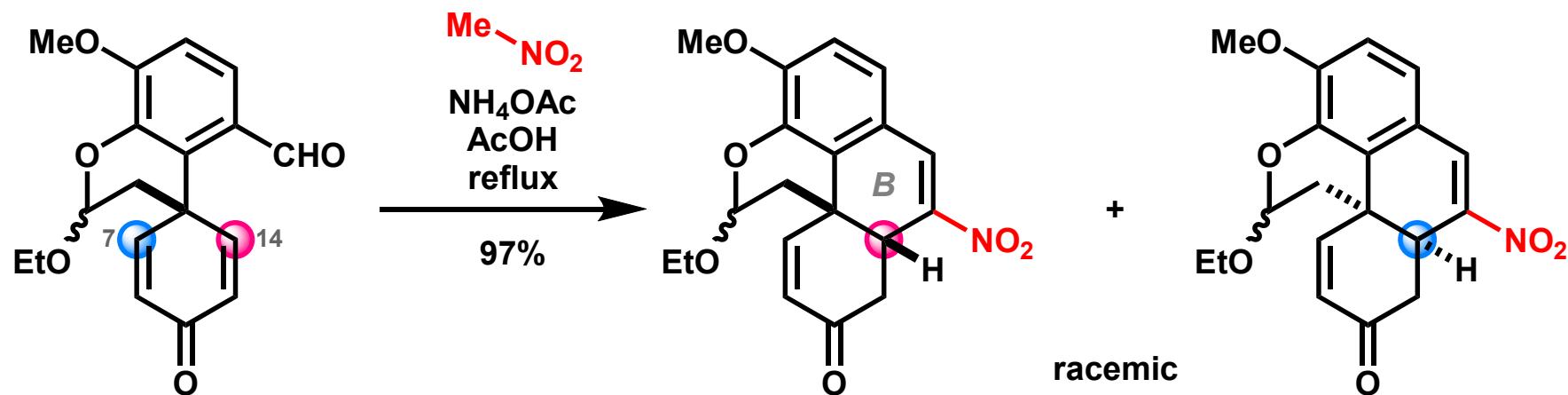
Retro Synthesis



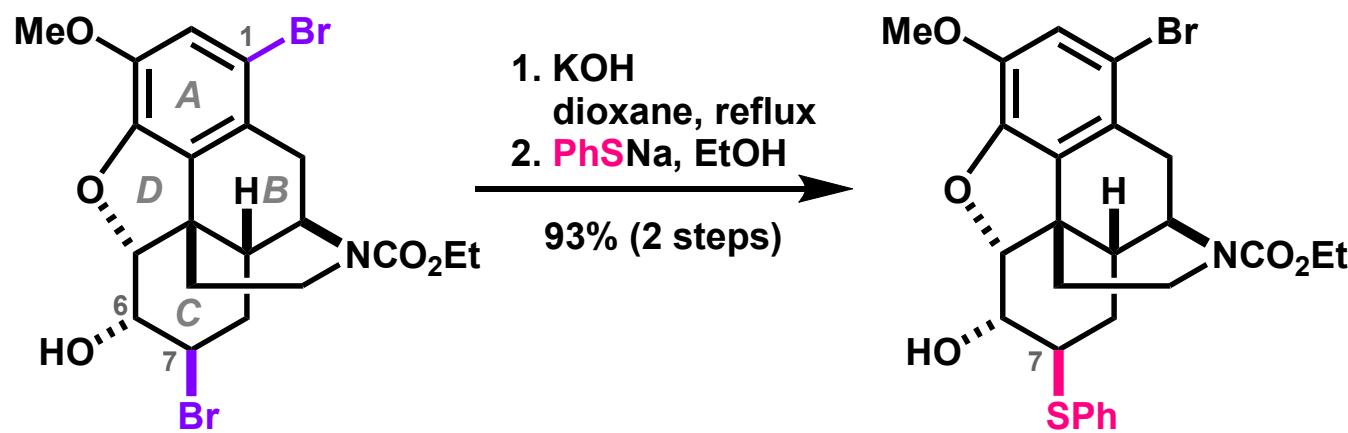
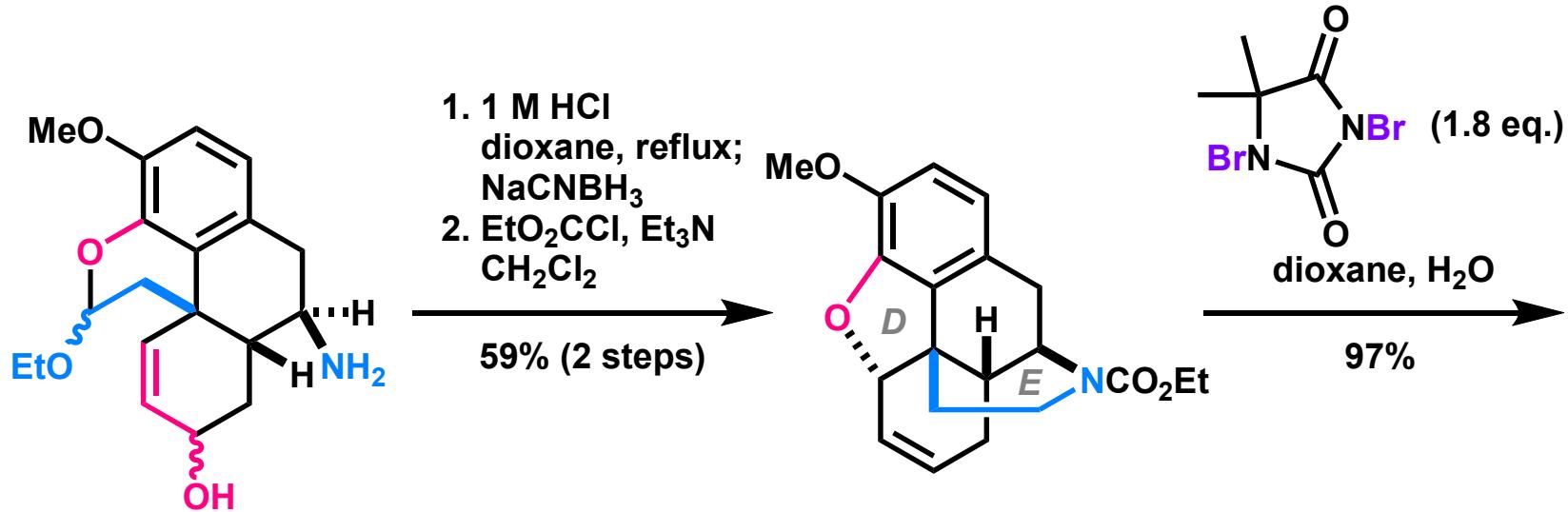
p-Alkylation of Phenol



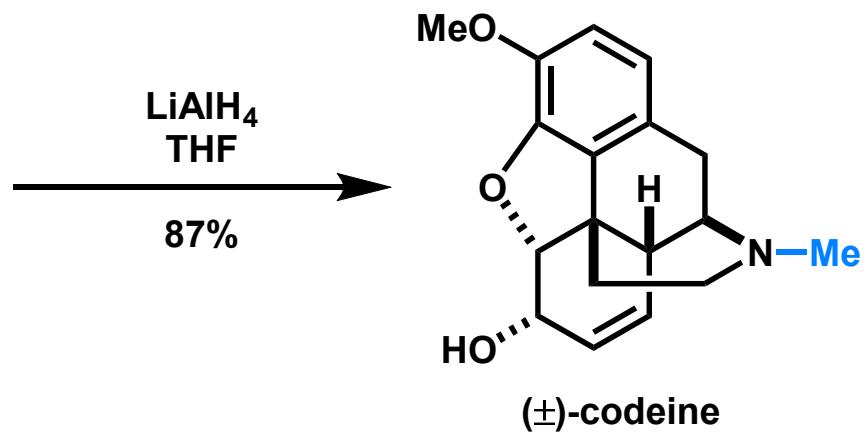
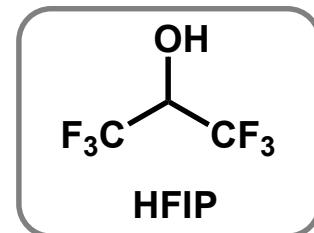
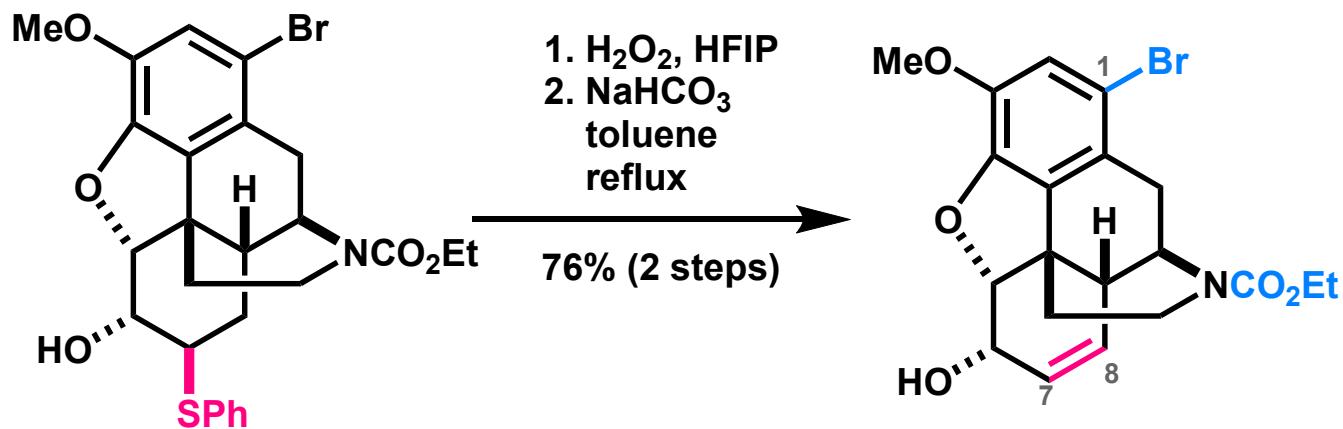
Nitro-Aldol Reaction



S_N2' Reaction and Reductive Amination



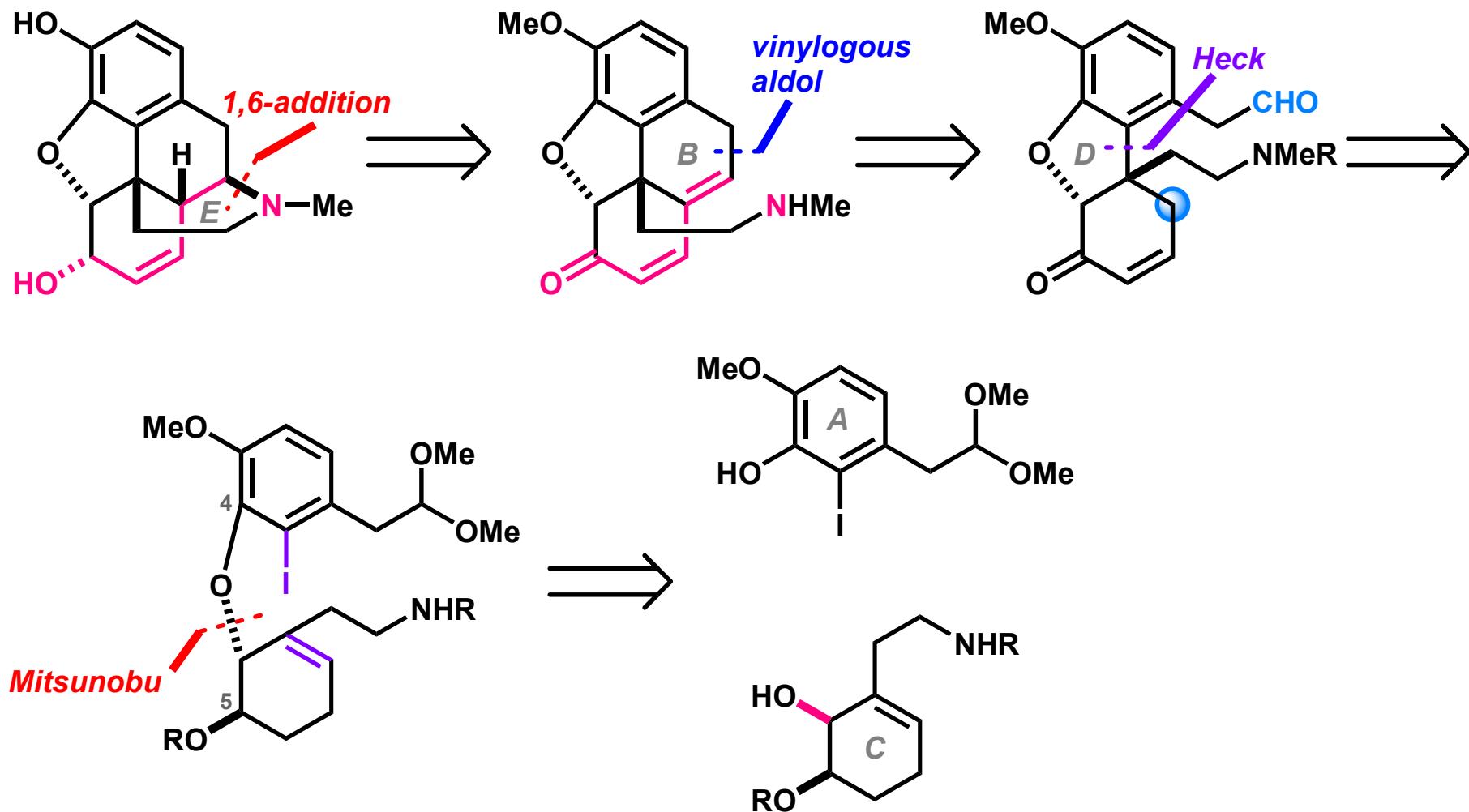
End Game



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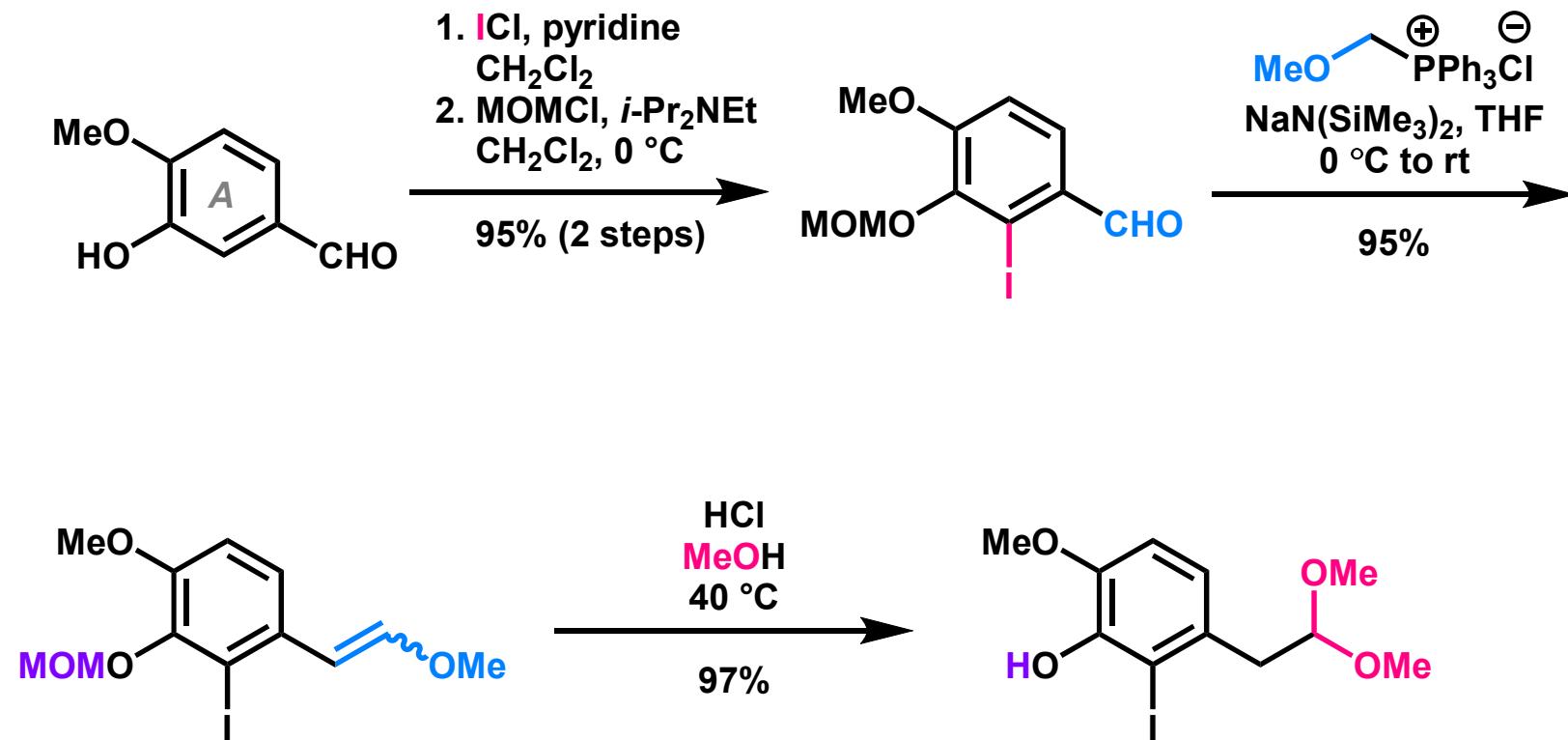
Retro Synthesis



Koizumi, H.; Yokoshima, S.; Fukuyama, T. *Chem. Asian J.* **2010**, 5, 2192.

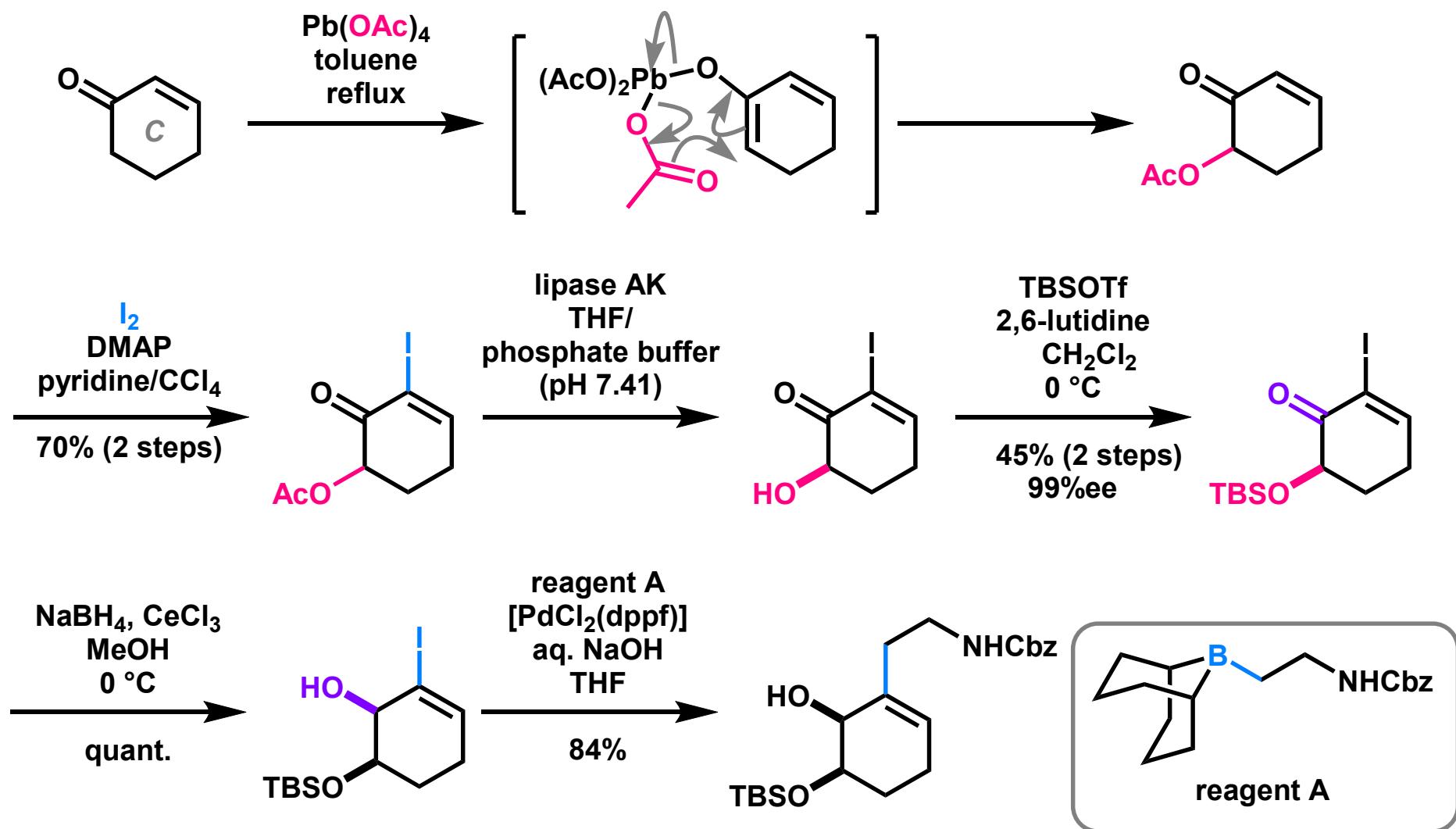
Synthesis of Mitsunobu Reaction Precursor (1)

(1) Preparation of phenol unit

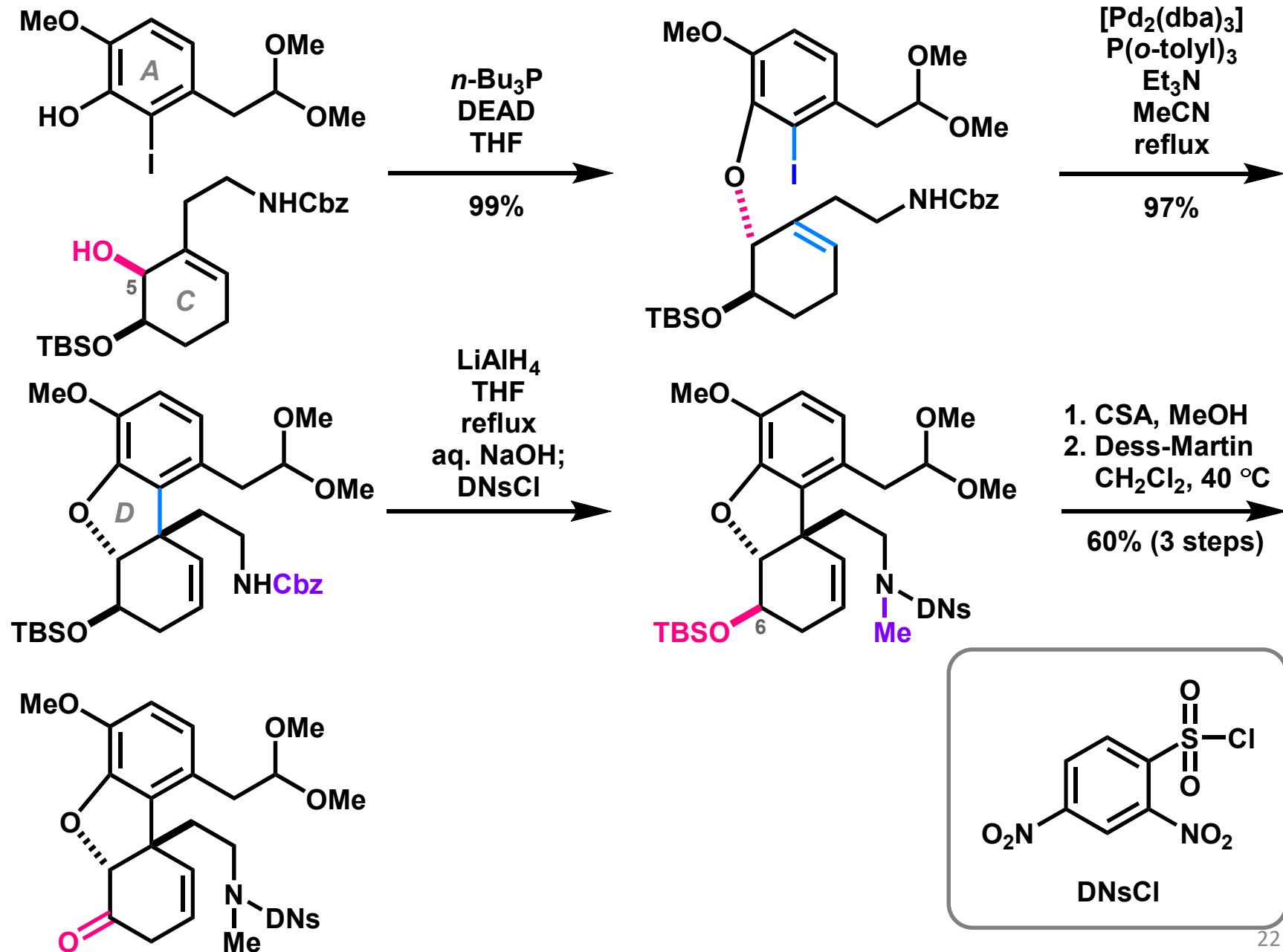


Synthesis of Mitsunobu Reaction Precursor (2)

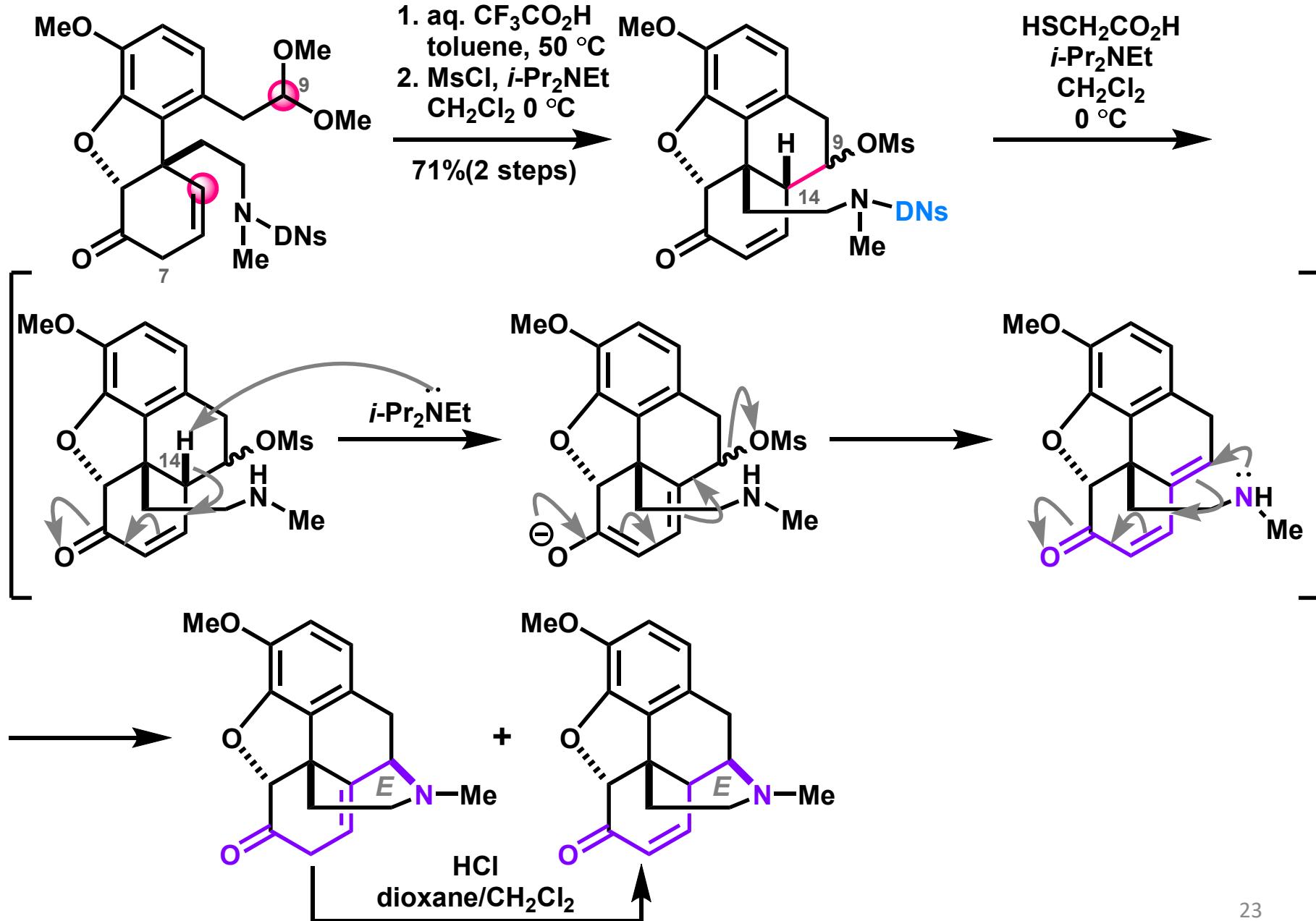
(2) Preparation of cyclohexenol



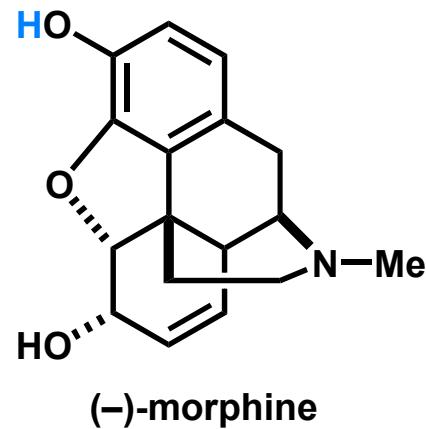
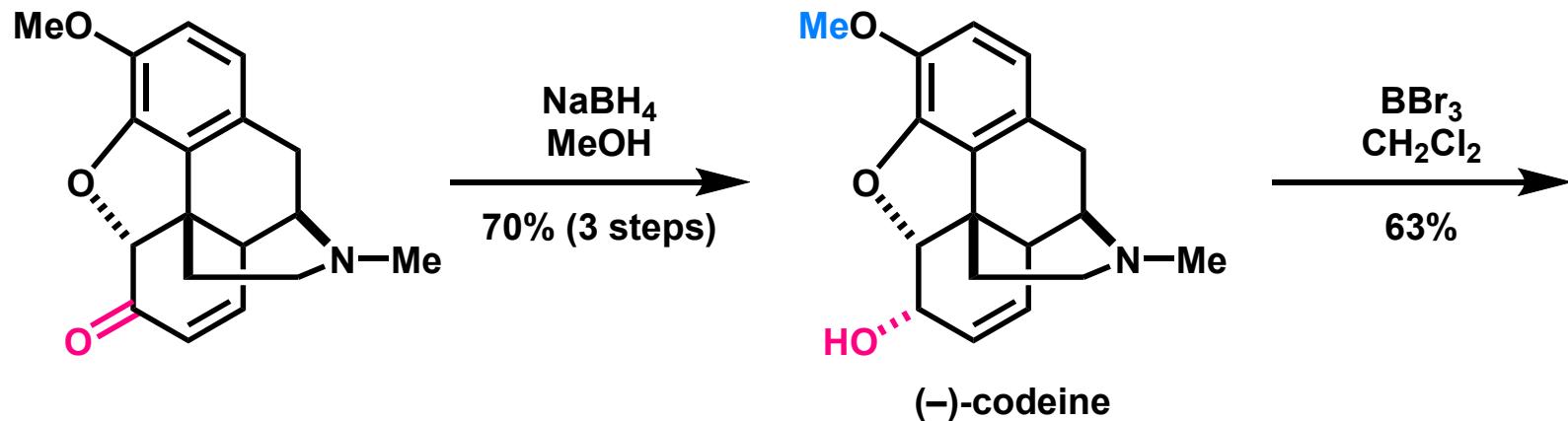
Mitsunobu Reaction and Heck Reaction



Aldol Reaction and 1,6-Addition



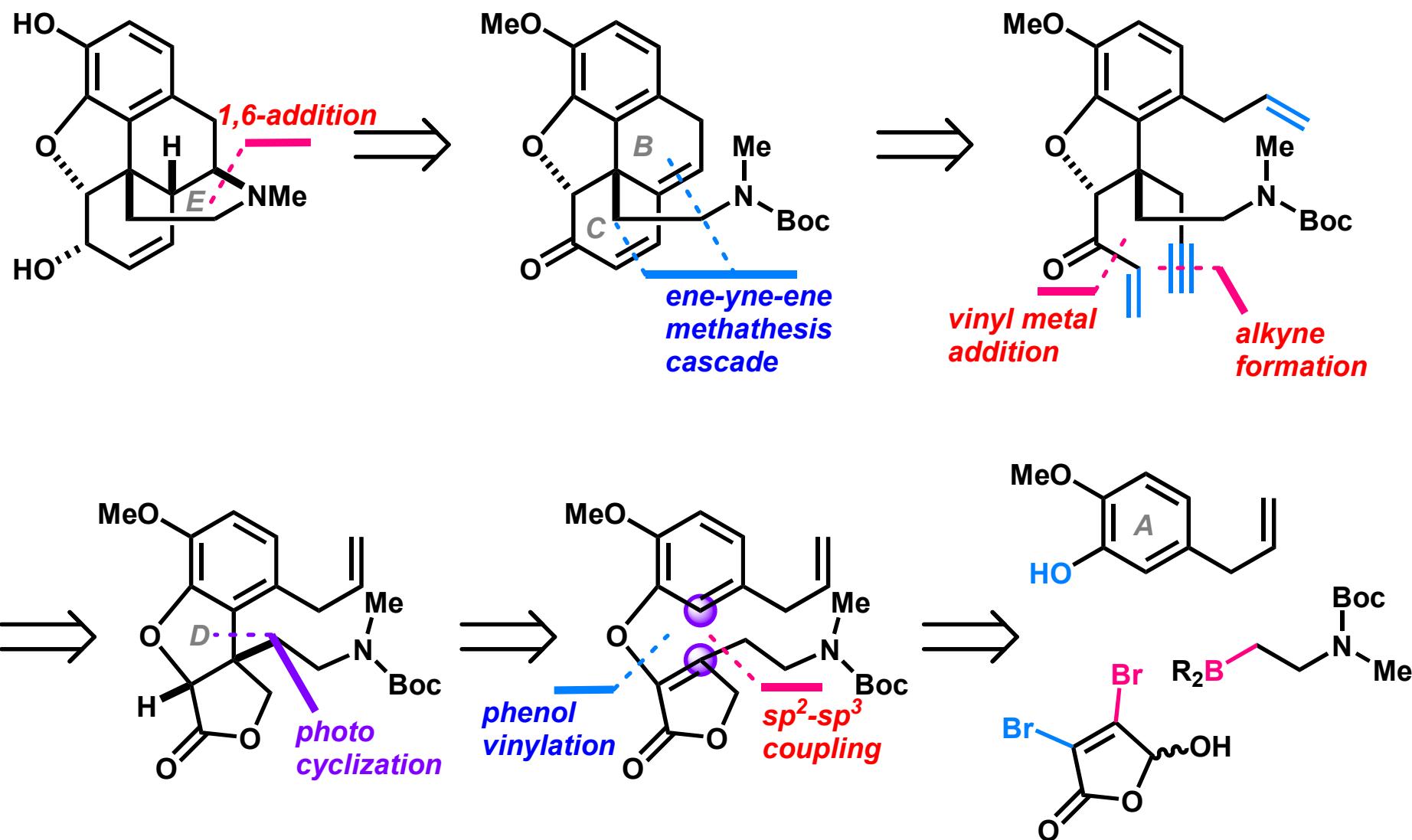
End Game



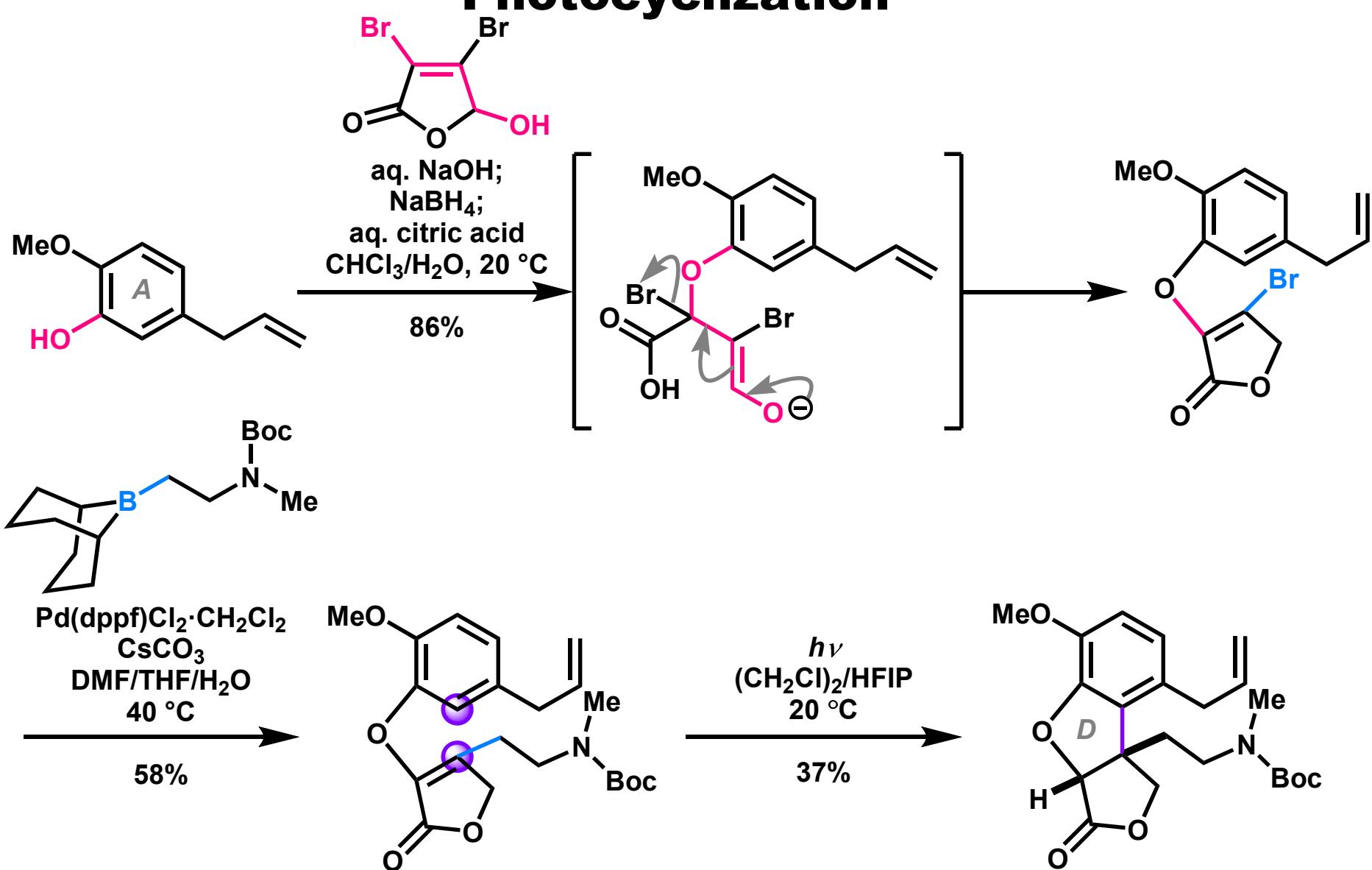
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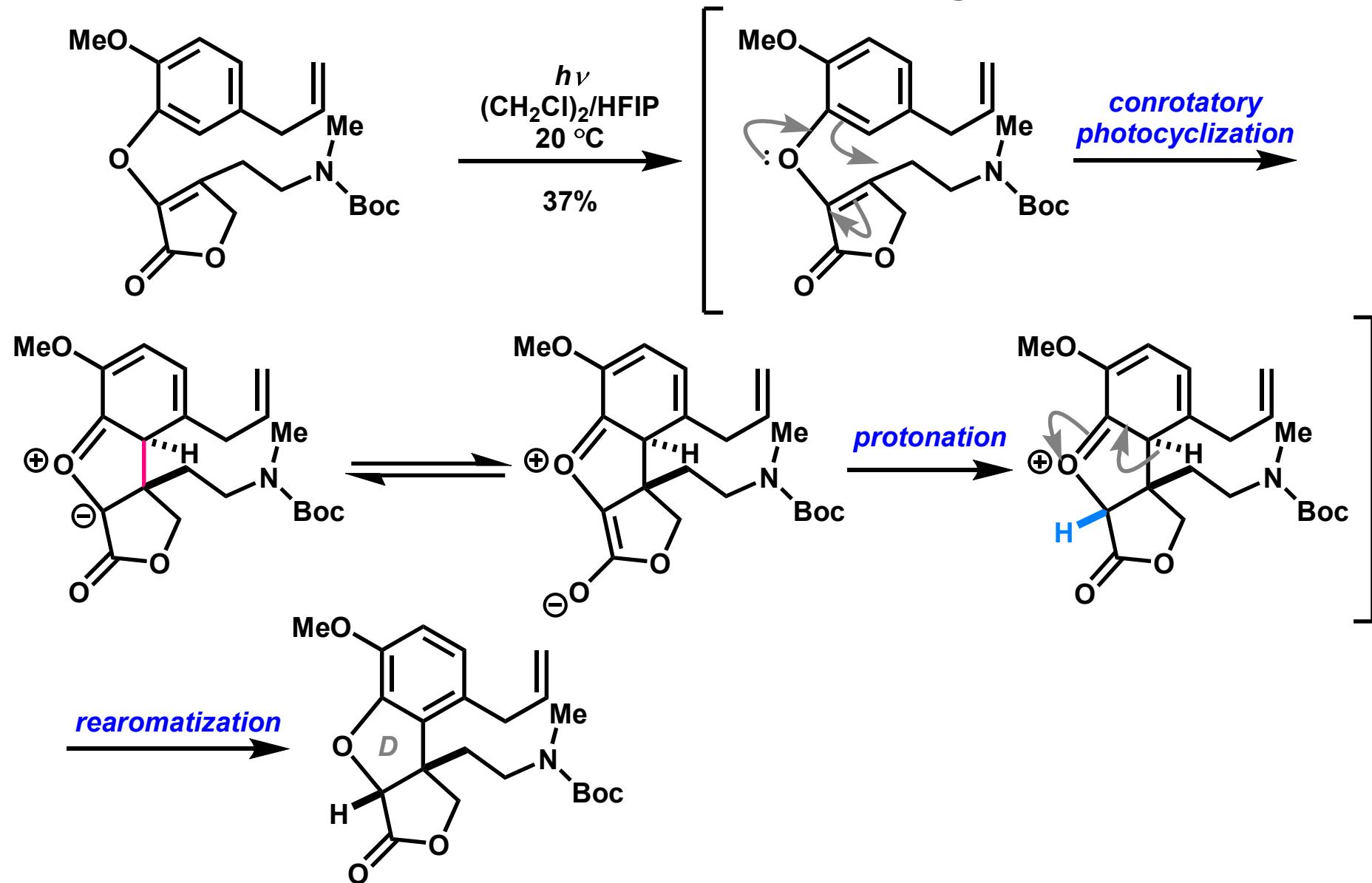
Retro Synthesis



Photocyclization

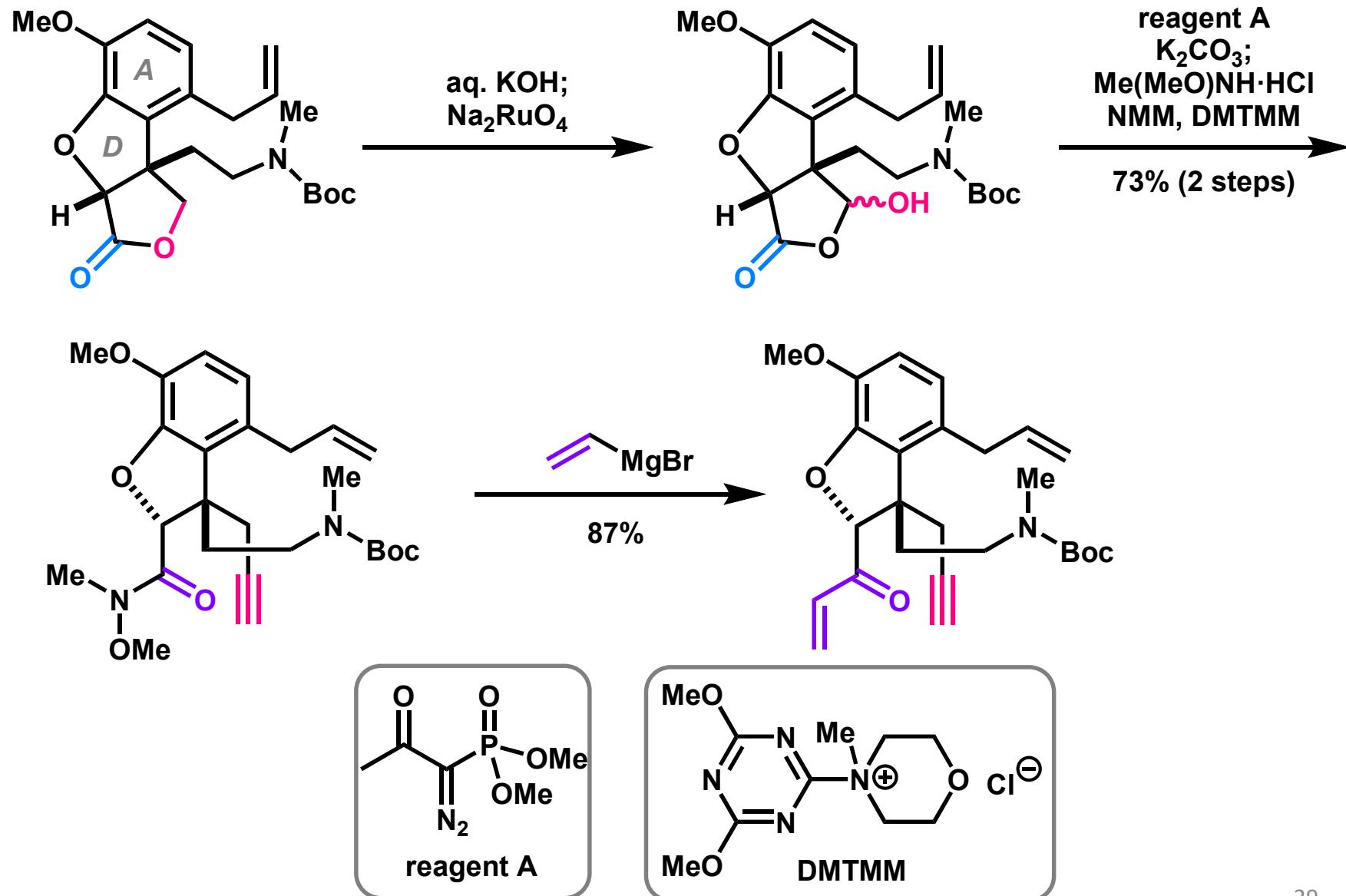


Proposed Mechanism of Photocyclization

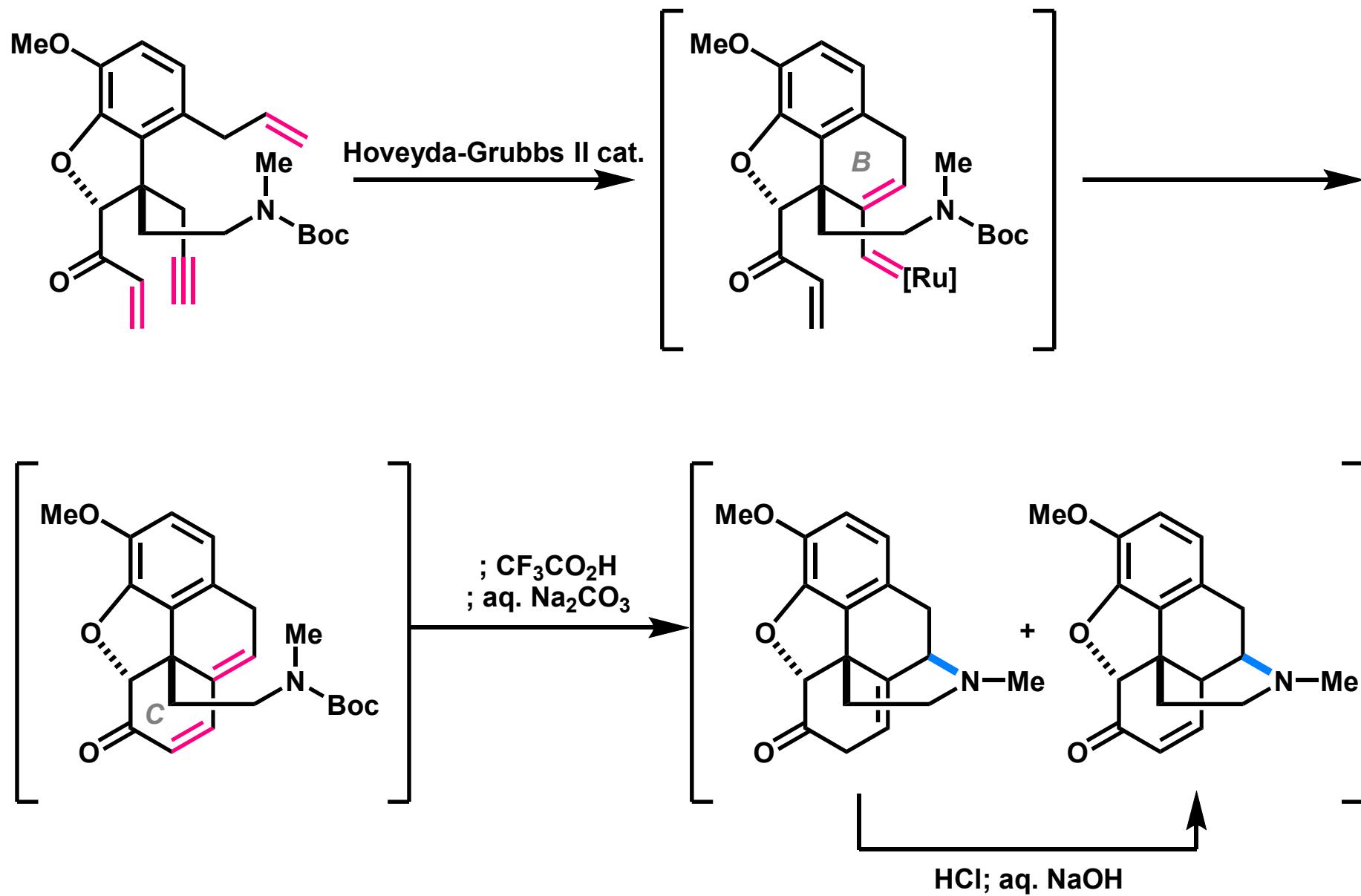


Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 2150-2162.

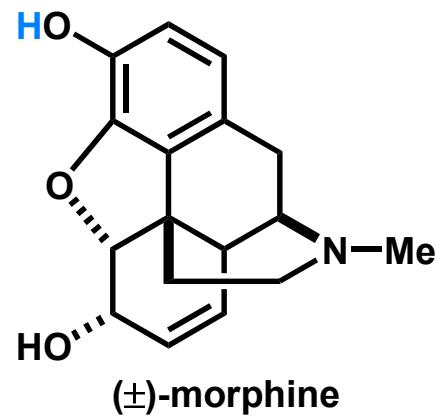
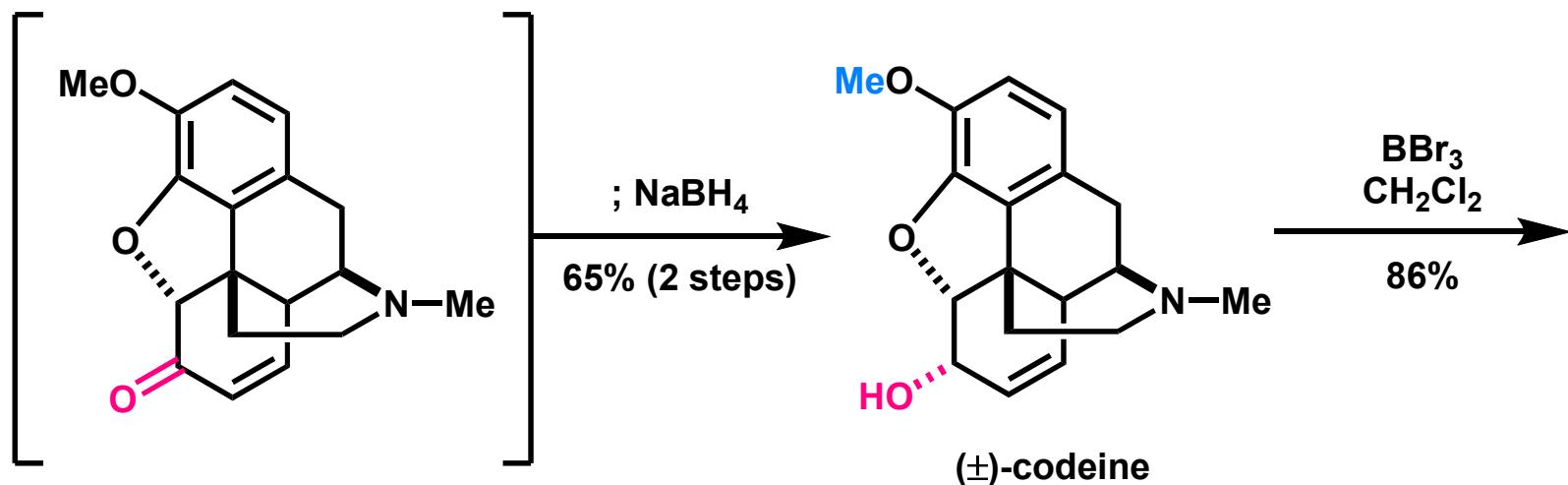
Synthesis of Ene-yne-ene Metathesis Precursor



Ene-yne-ene Metathesis Cascade

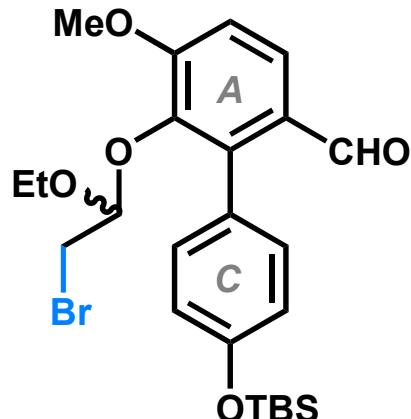


End Game

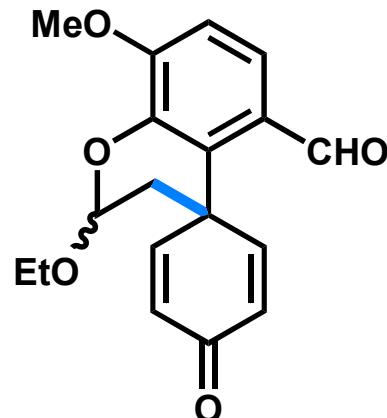


Summary

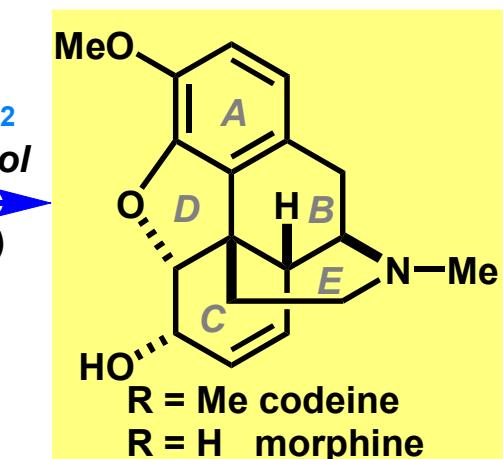
Magnus (2009)
 (\pm) -codeine: 20 % (13 steps)



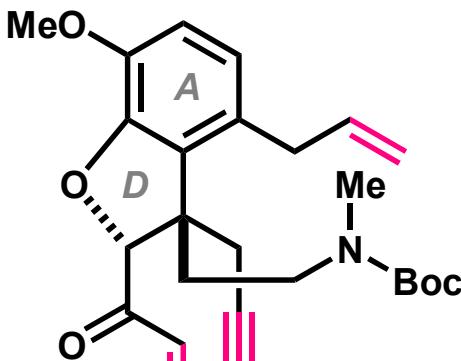
p-alkylation



$\text{Me}-\text{NO}_2$
nitro-aldo
(B ring)

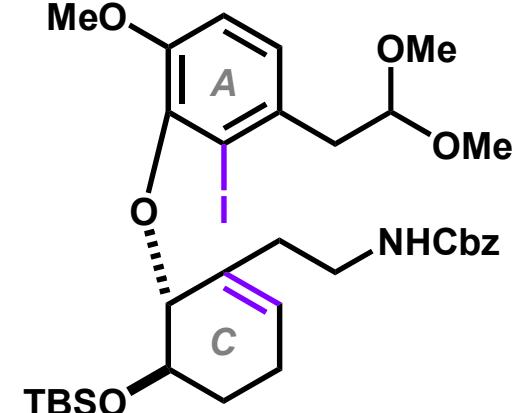


Smith (2016)
 (\pm) -morphine: 6.6 % (9 steps)

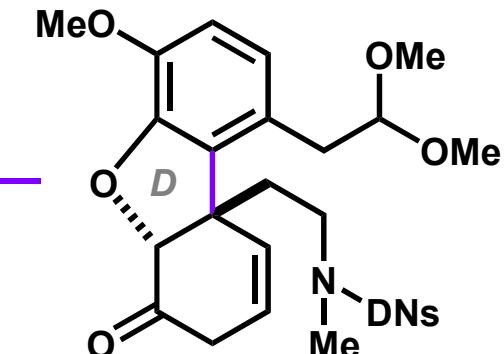


ene-yne-ene
metathesis
(BC ring)

Fukuyama (2010)
 $(-)$ -morphine: 4.8 % (17 steps)



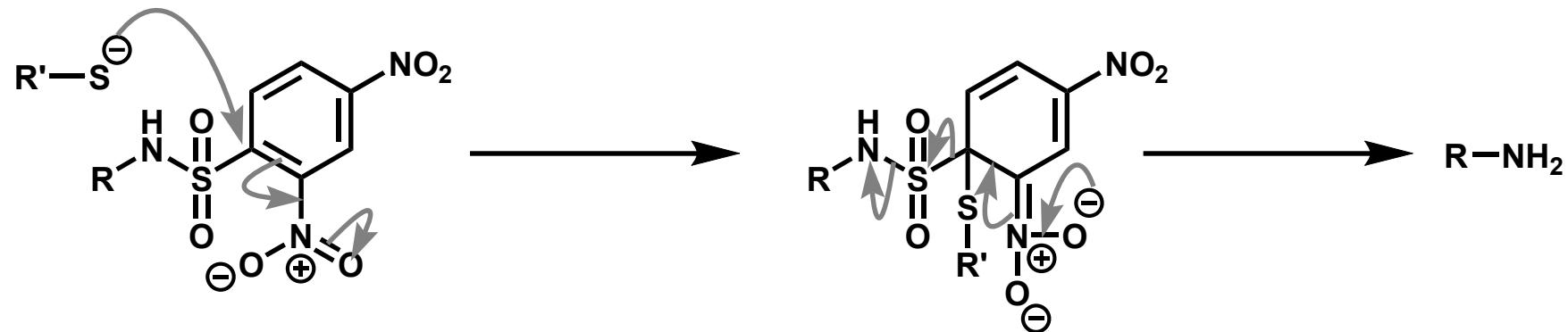
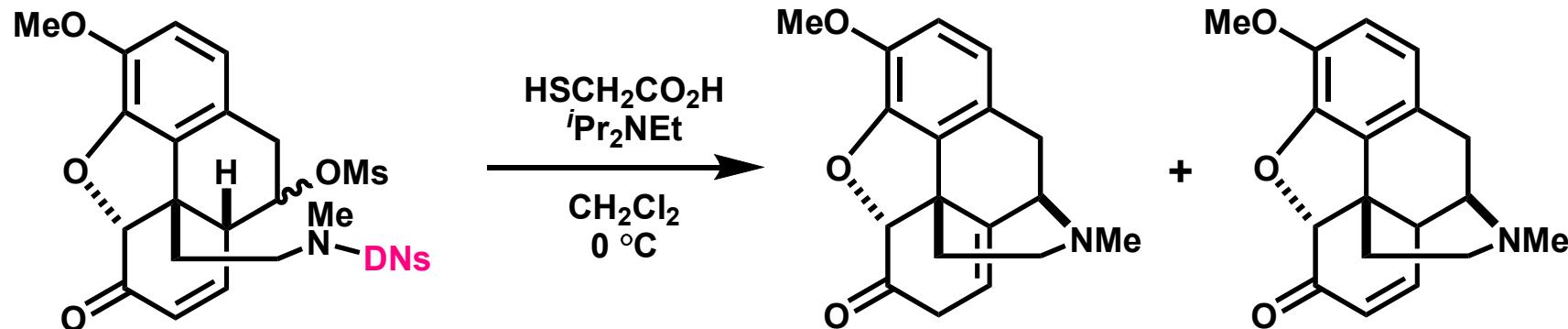
Heck
(D ring)



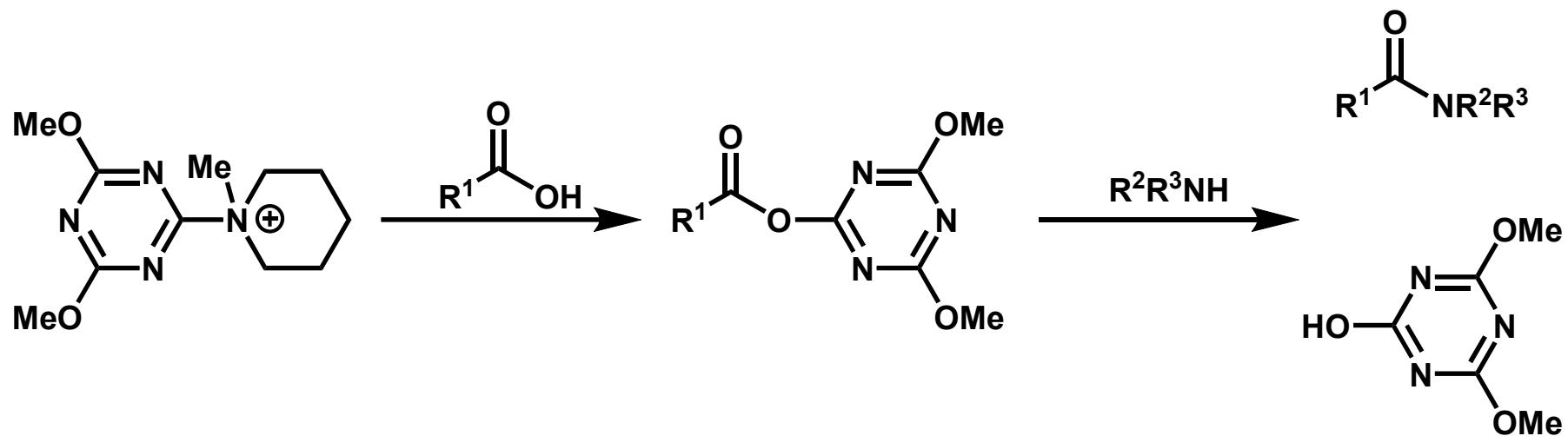
aldol
(B ring)

Appendix

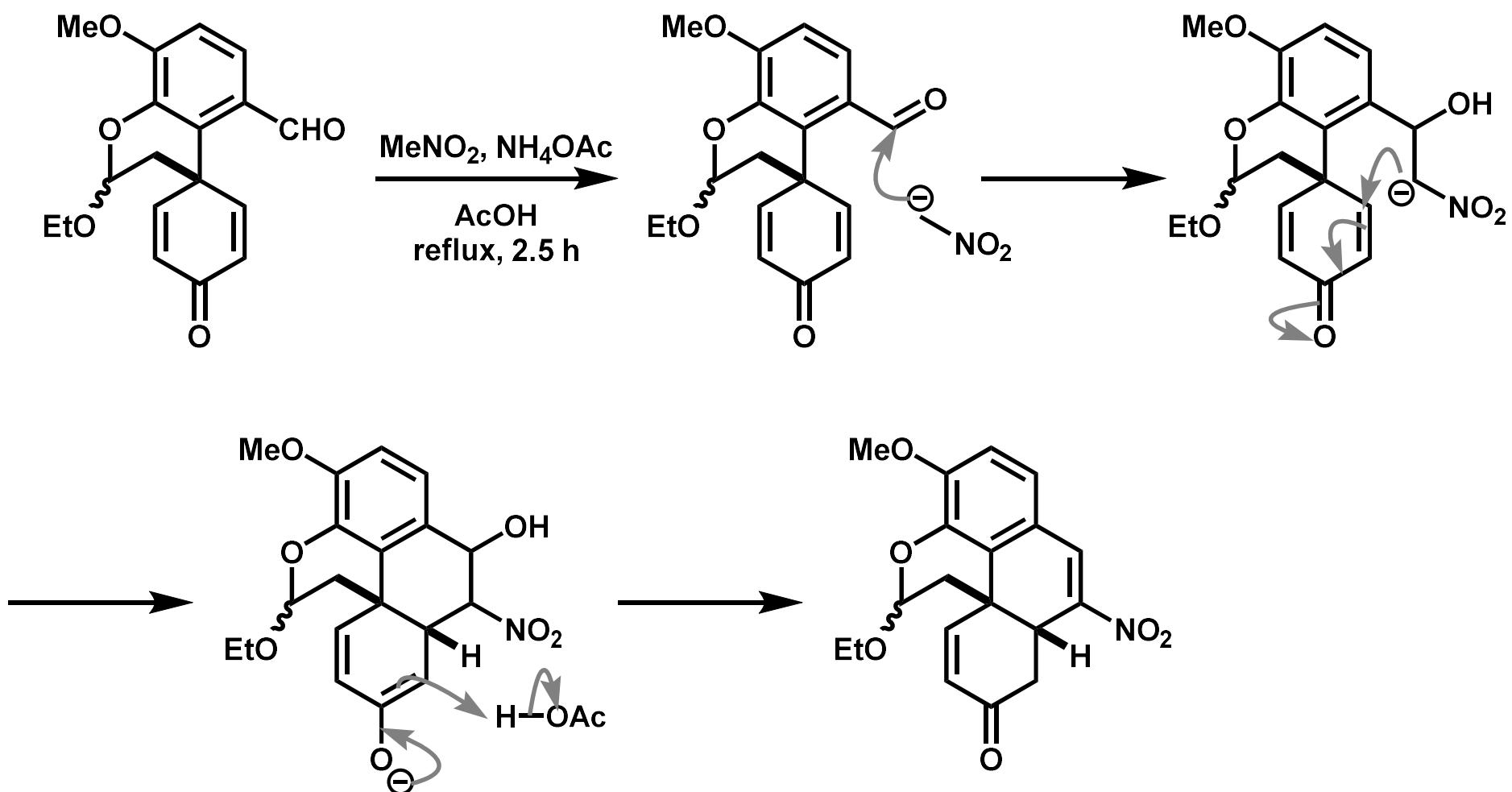
DNs deprotection



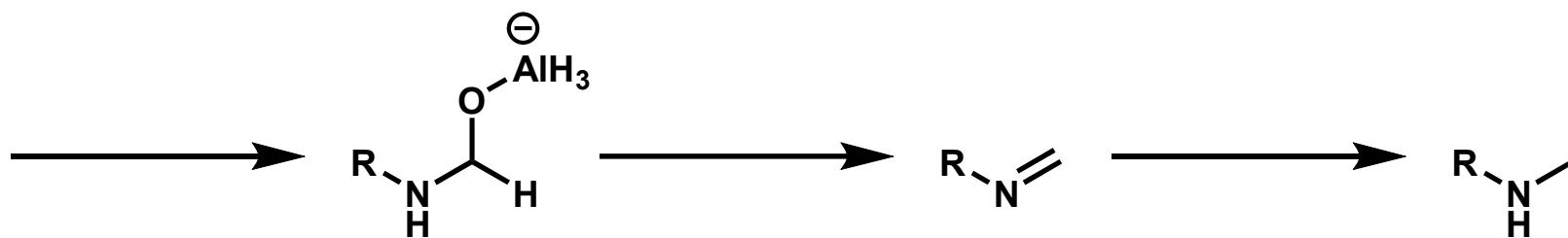
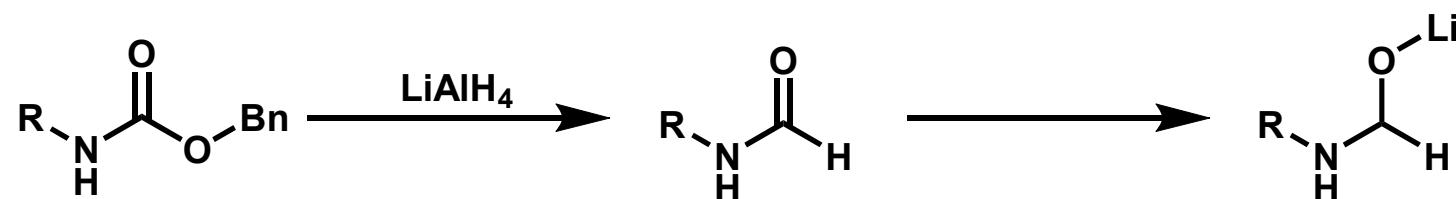
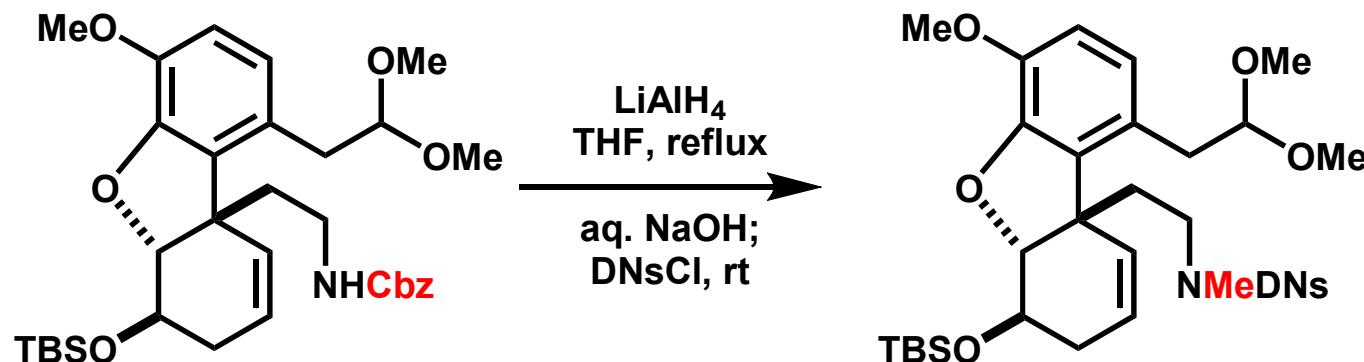
Condensation



Nitoro-Aldol



LiAlH₄ reduction



Reaction Mechanism

