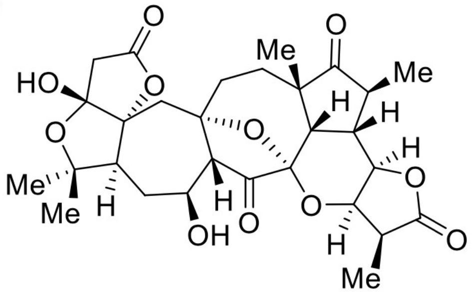
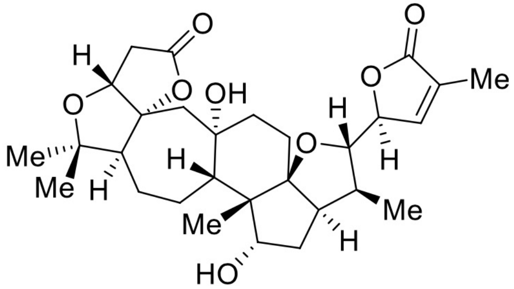
Total Synthesis of (±)-Rubriflordilactone A

Xudong Zheng, Xinlong Guo, Hongyu Wang, Pan-Pan Zhou, and Xiaoming Chen*

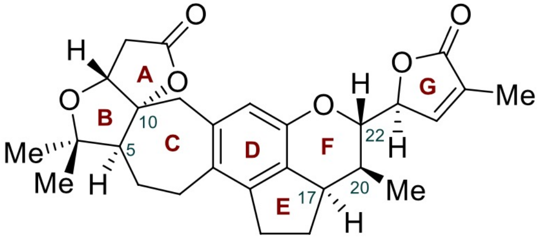
a



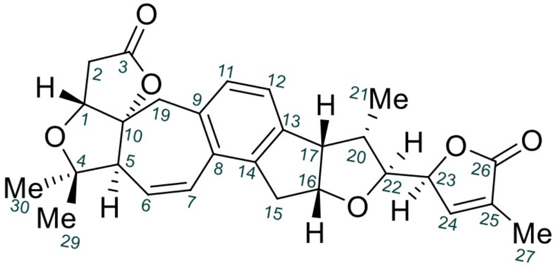
schindilactone A (**1**)



wuweizidilactone D (**2**)



rubriflordilactone A (**3**)



rubriflordilactone B (**4**)

rubriflordilactone A

Isolated from *Schisandra* plants, a subfamily of genus Schisandraceae

Has exhibited anti-HIV activities,

A range of bioactive natural products, especially structurally diverse, stereochemically dense, and highly oxygenated polycyclic triterpenoids have been isolated from these plants

Contain similar γ-lactone-containing A/B ring backbone

Hannah Robichaud
Liu Lab
July 24, 2024

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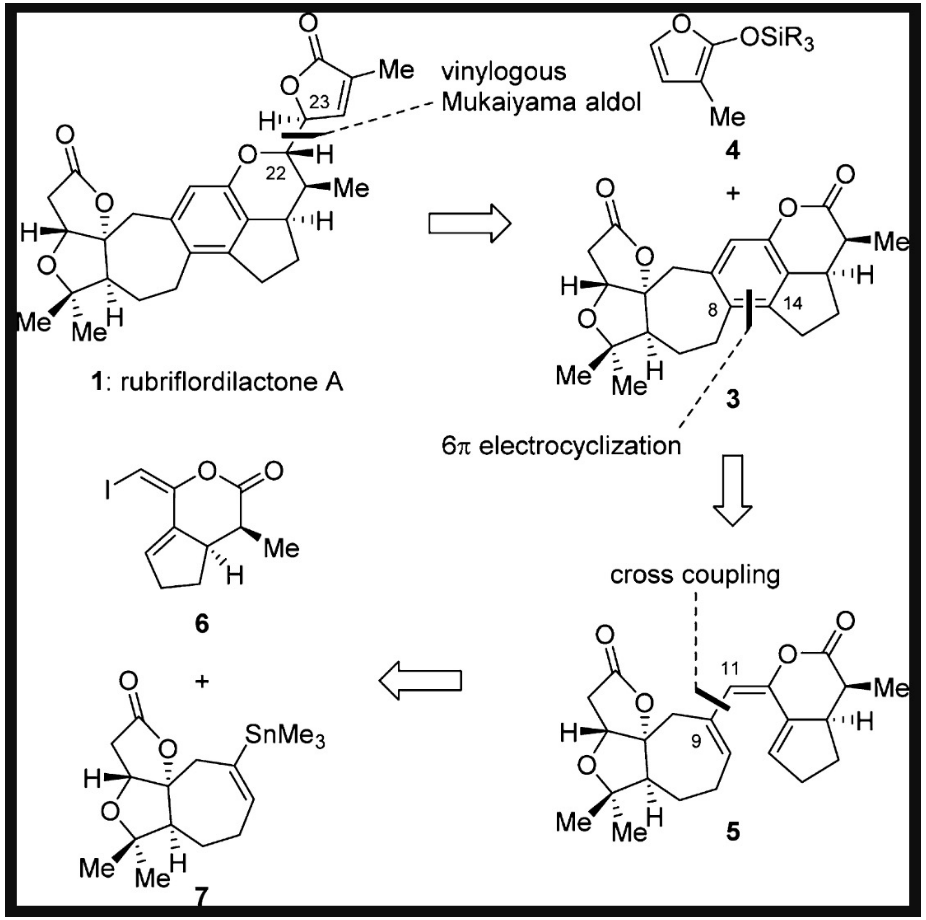
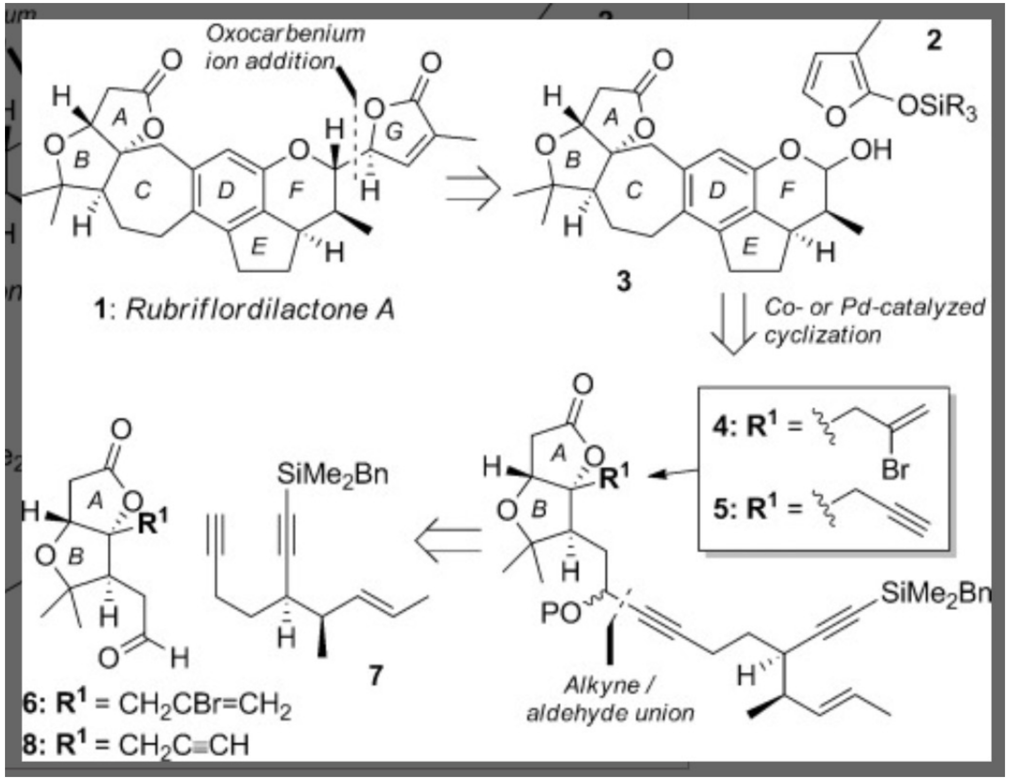
Previous Total syntheses



The first total synthesis by Li and co-workers
-6π-electro- cyclization/aromatization sequence to assemble the penta- substituted arene in 2014

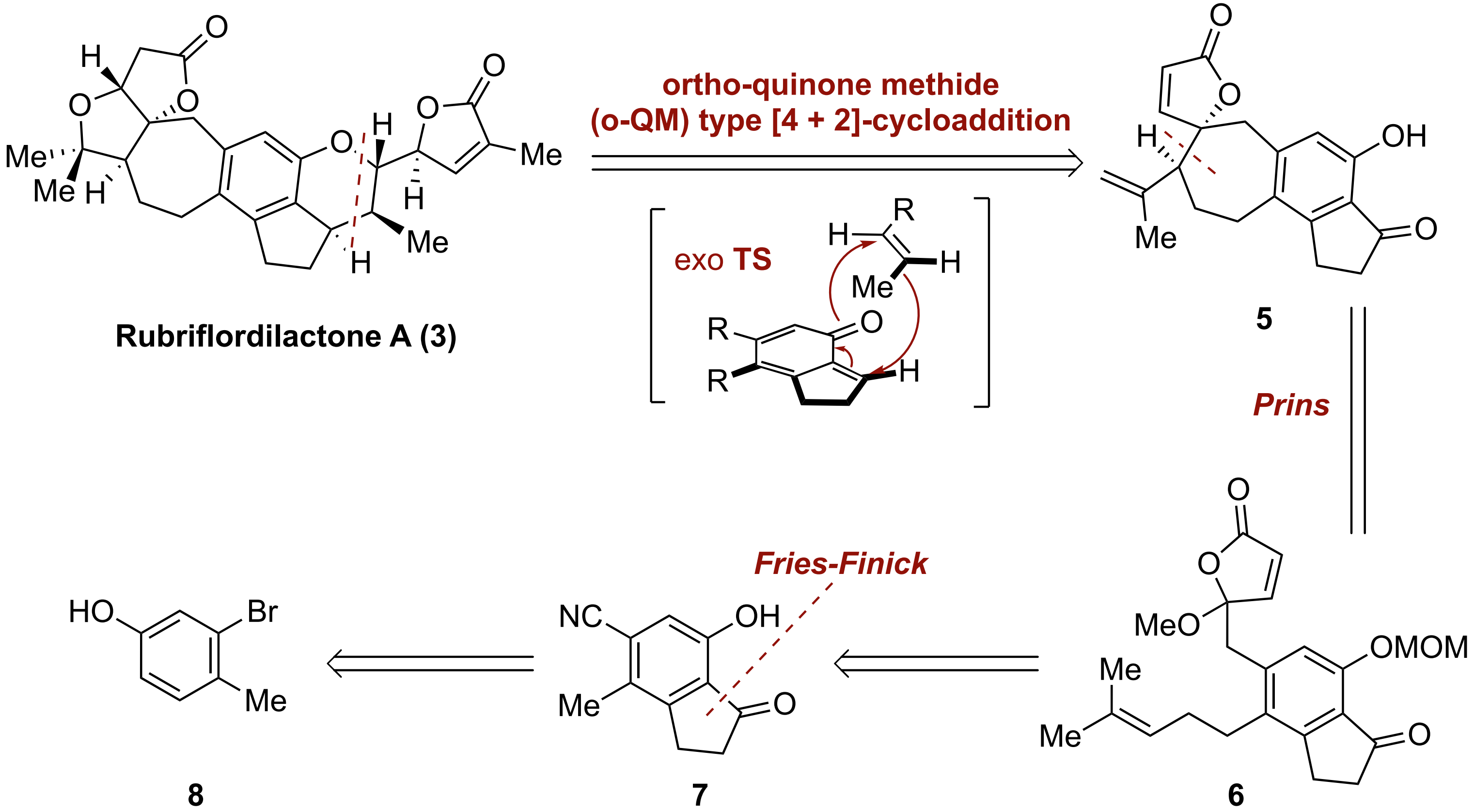


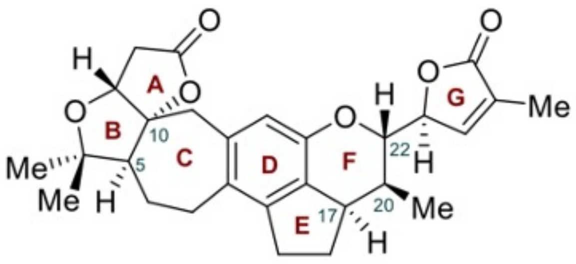
Anderson and co-workers in 2015
-a palladium- catalyzed bromoendiyne cyclization or a cobalt-catalyzed alkyne cyclotrimerization as the key transformation

Anderson, E. A. *et al. Angew. Chem., Int. Ed.* 2015, *54*, 12618–12621.

Ang Li*. *J. Am. Chem. Soc.* 2014, 136, 47, 16477-16480

Retrosynthetic Analysis





rubriflordilactone A (3)

- Intramolecular Prins cyclization to establish the seven-membered ring C containing two contiguous stereocenters
- a Mukaiyama hydration/oxa-Michael cascade to construct the B-ring
- Unprecedented stereocontrol intermolecular *o*-QM type [4 + 2]-cycloaddition to assemble ring F

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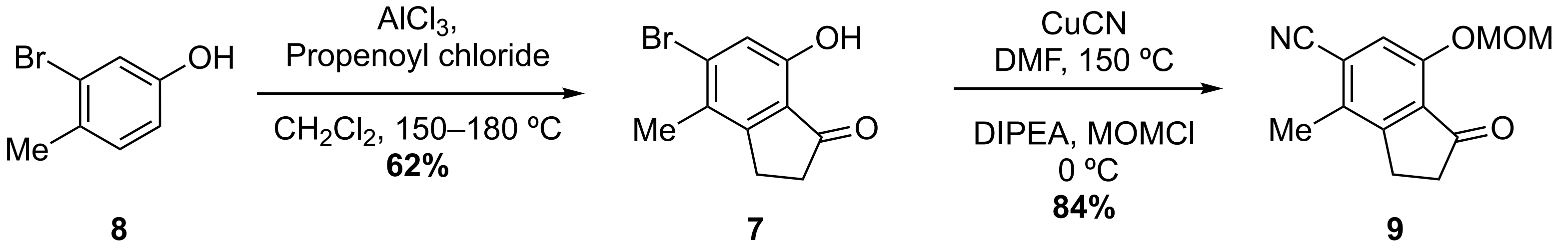
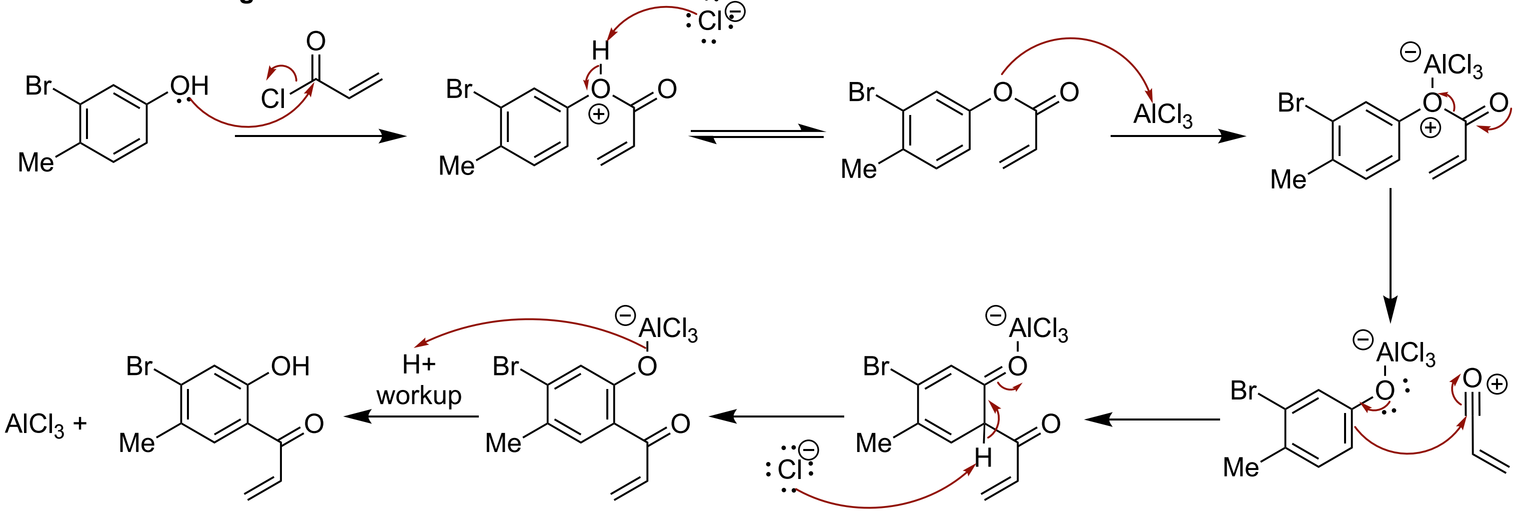
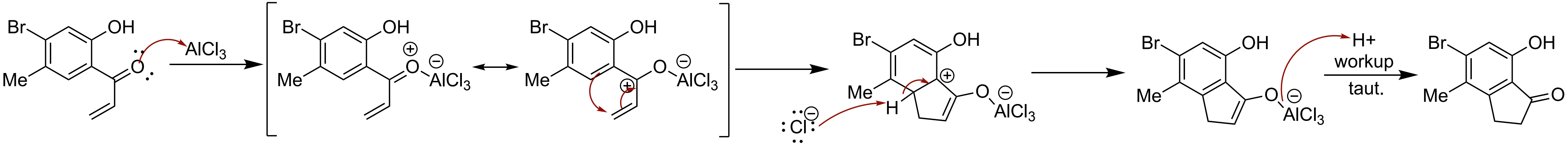


Fries-Finick rearrangement



Nazarov cyclization



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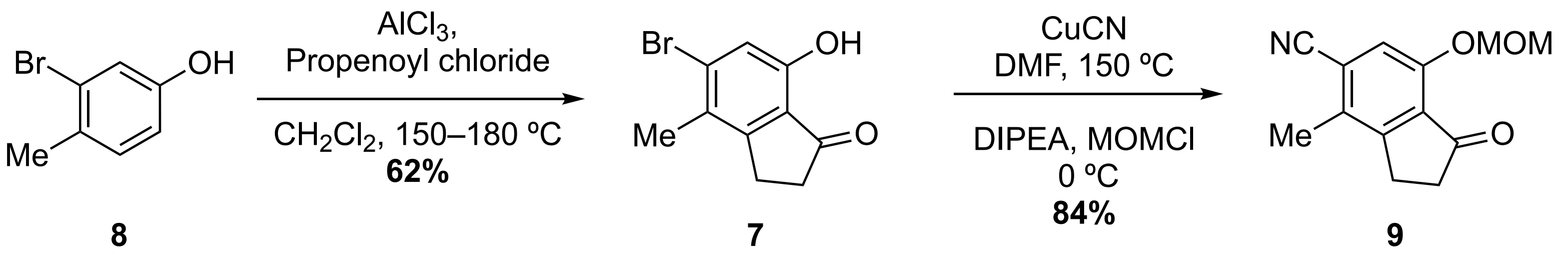
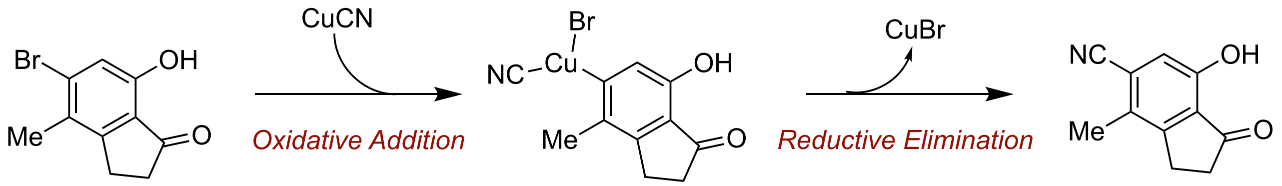
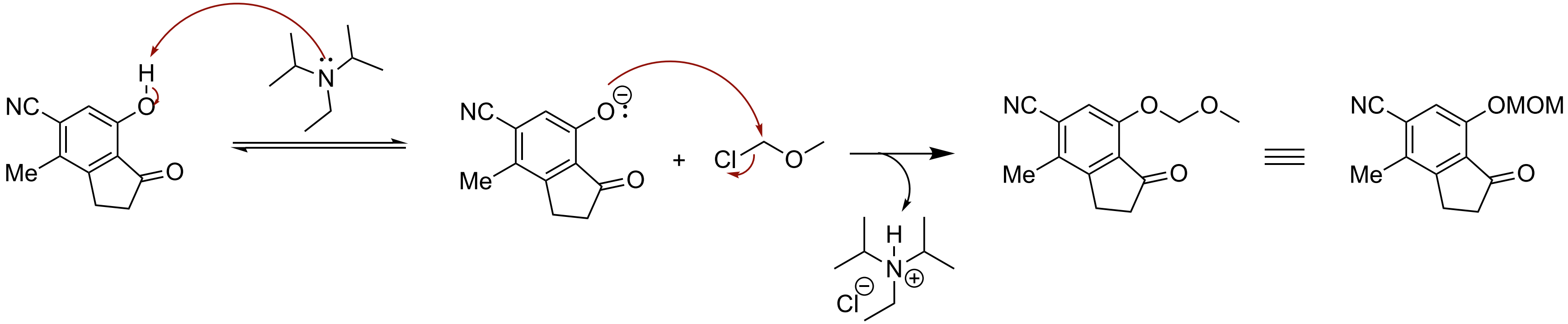


Rosenmund−von Braun Cyanation



MOM protection of phenol



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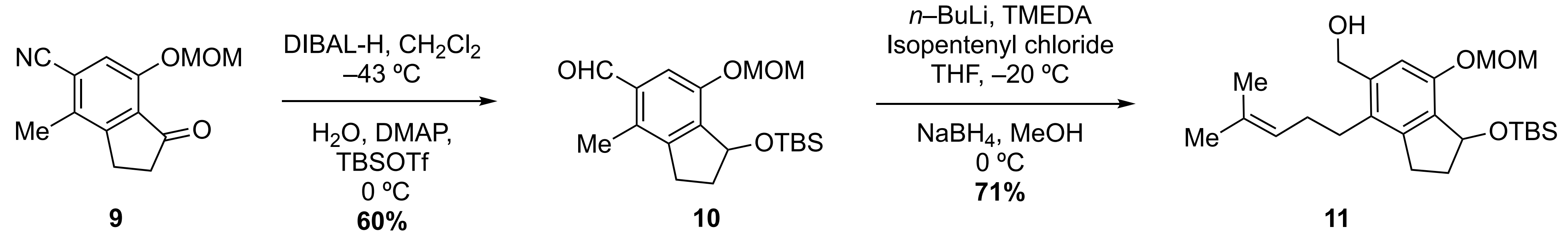

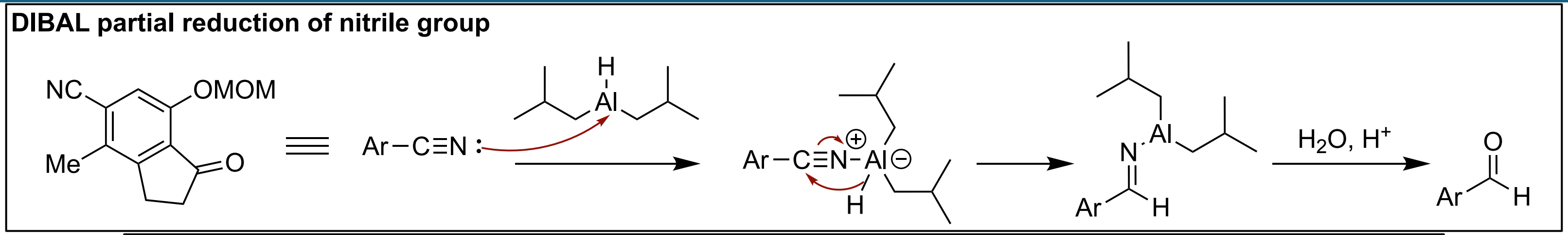

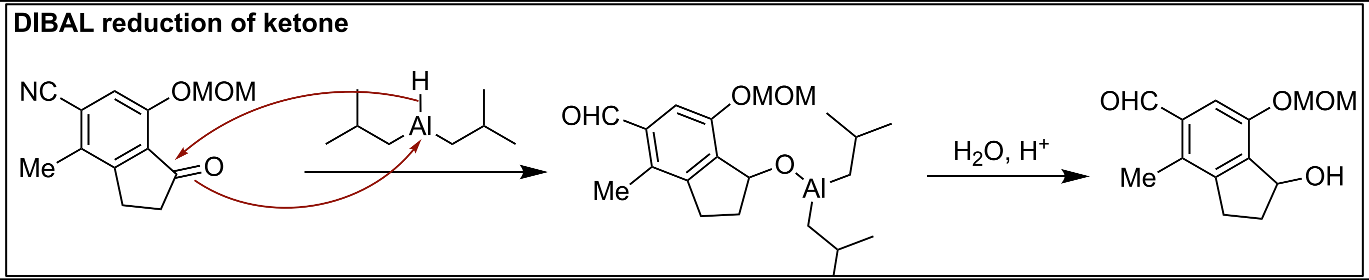

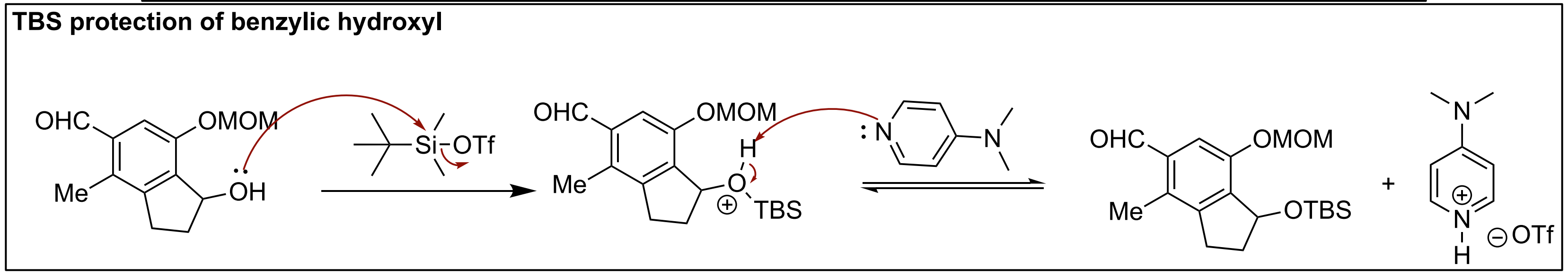

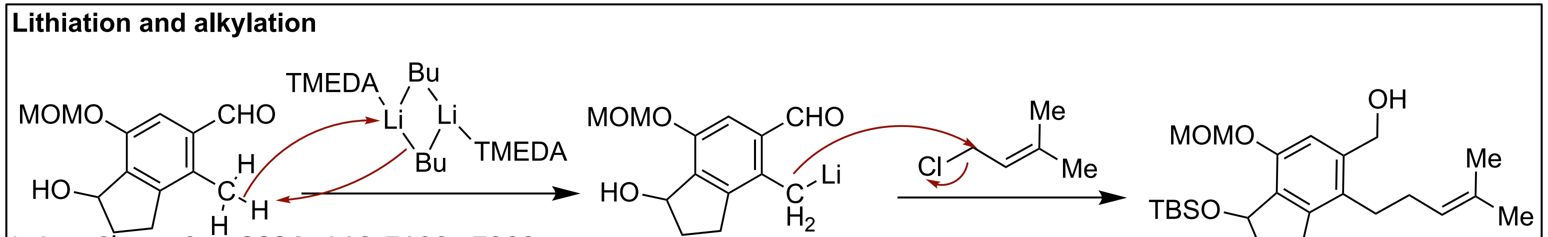

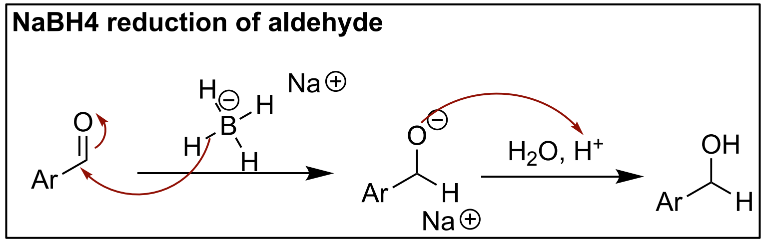

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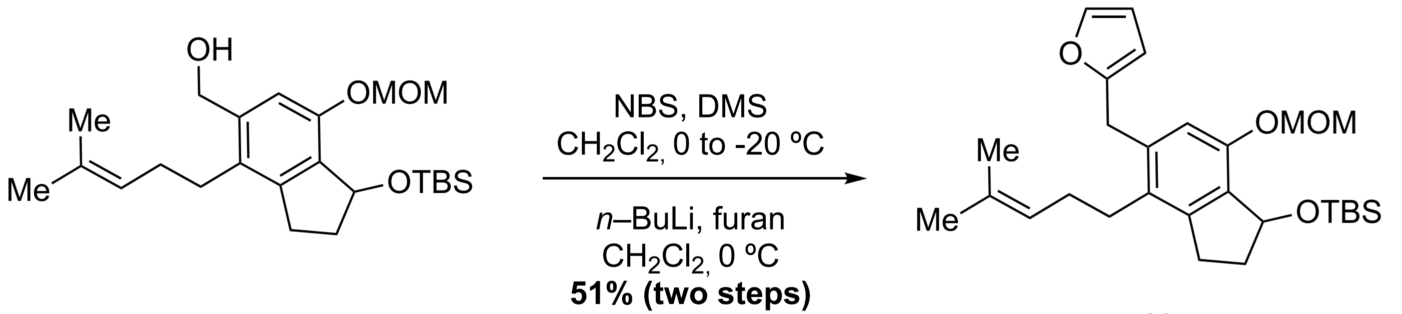
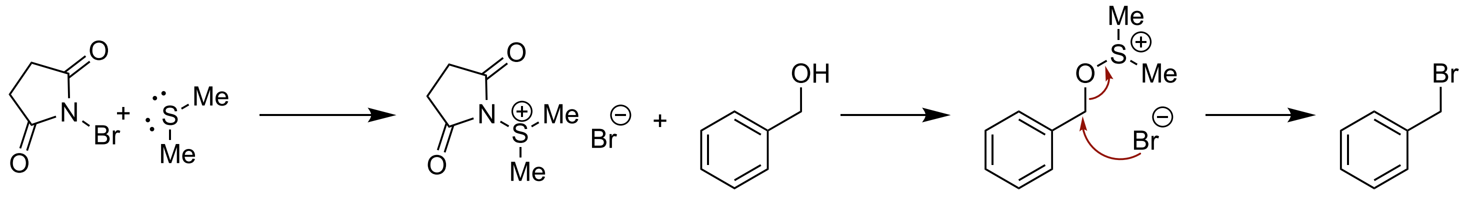
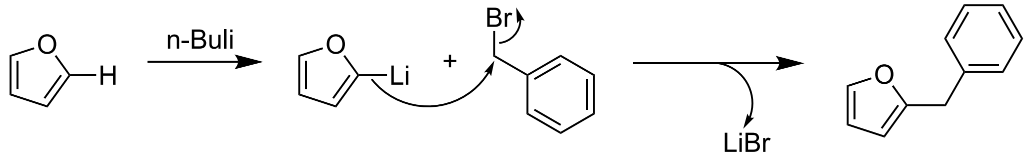


11 **12**

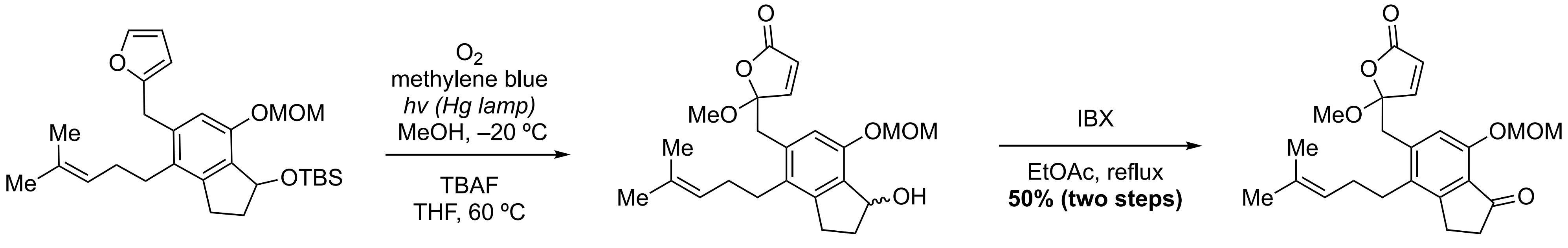
NBS, DMS borylation of benzylic alcohol (Corey)



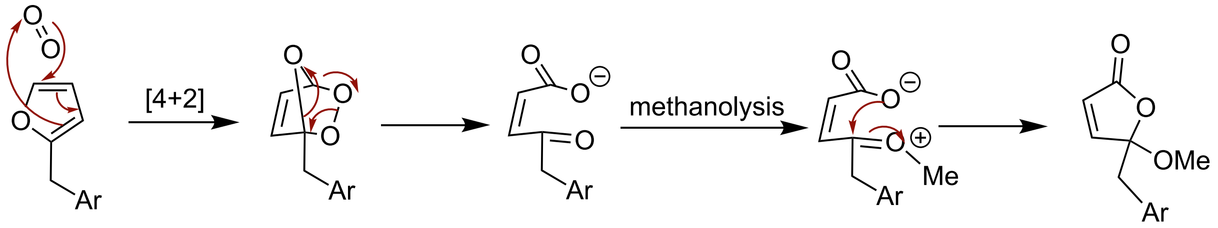
Furan Lithiation and Benzyl installment

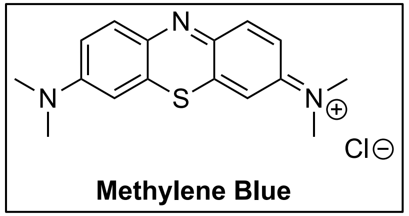


J. Am. Chem. Soc. **2024**, *146*, 7198–7203.
Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339–4342.

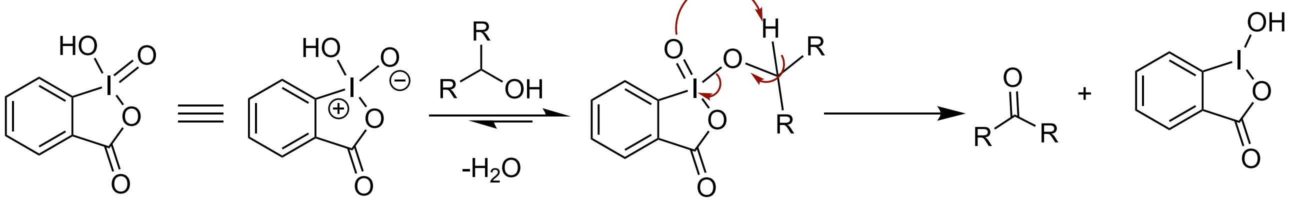


Oxidation with singlet oxygen

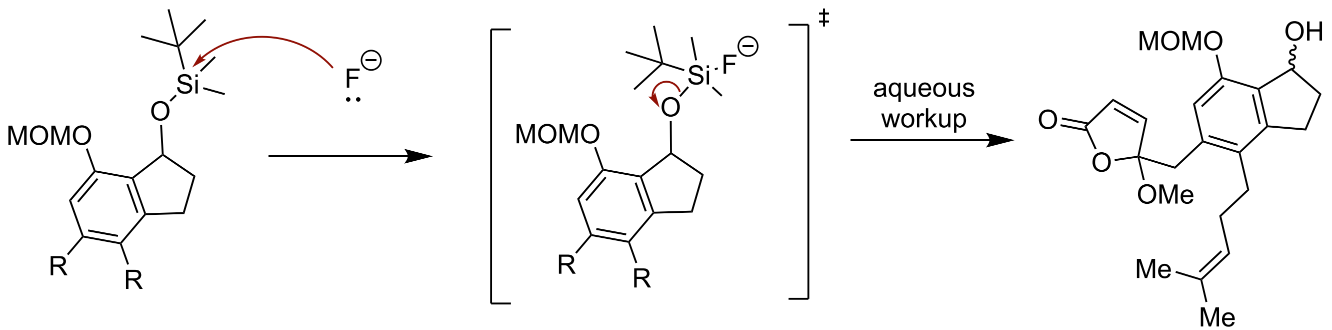




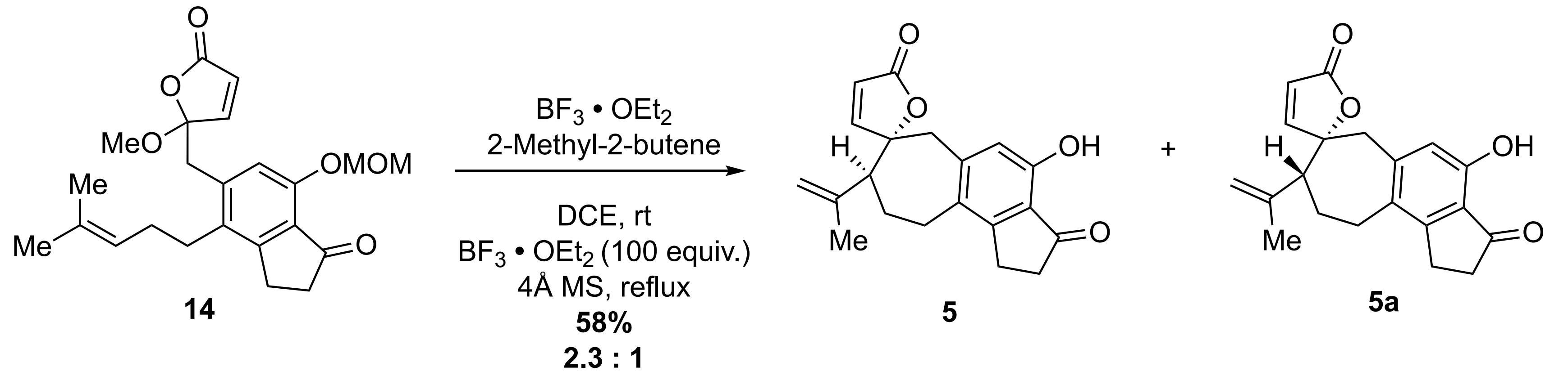
IBX oxidation



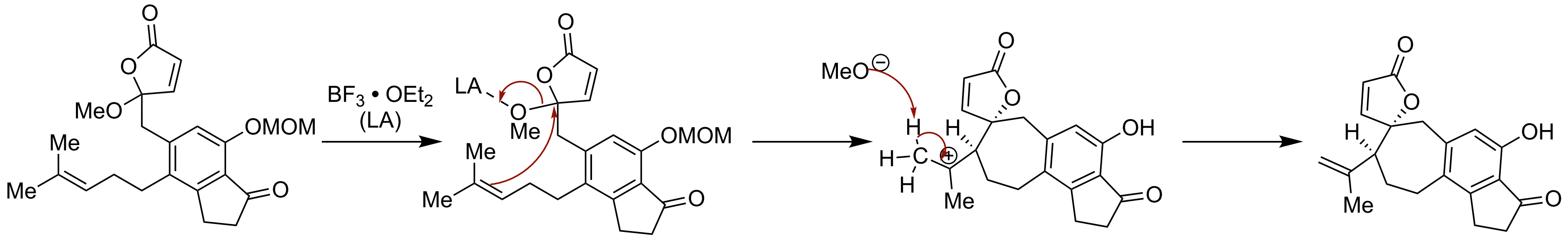
Deprotection with TBAF



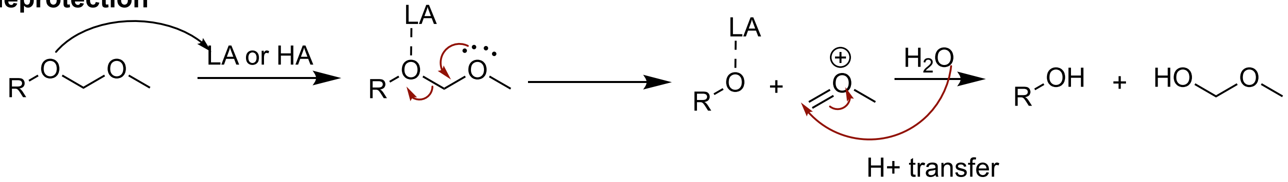
J. Am. Chem. Soc. **2024**, *146*, 7198–7203.
Acc. Chem. Res. **2008**, *41*, 1001–1011.



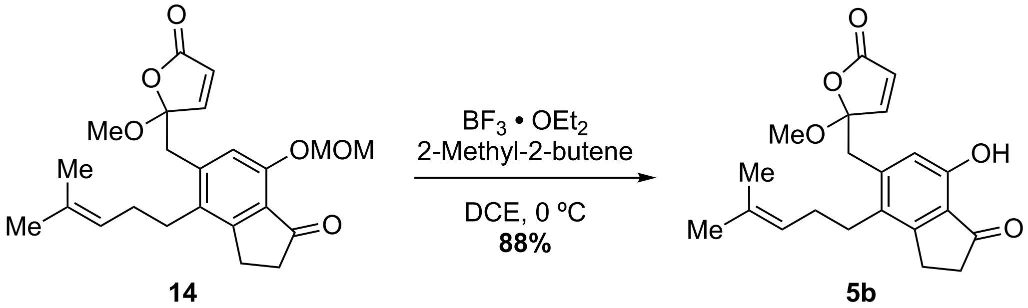
Prins Cyclization



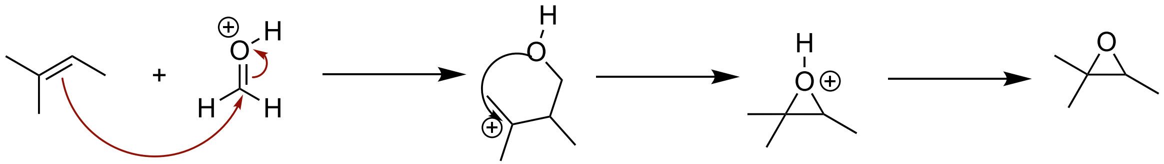
MOM deprotection



Observed byproduct:



2-methyl-2-butene prins reaction with formaldehyde generated from MOM deptrotection



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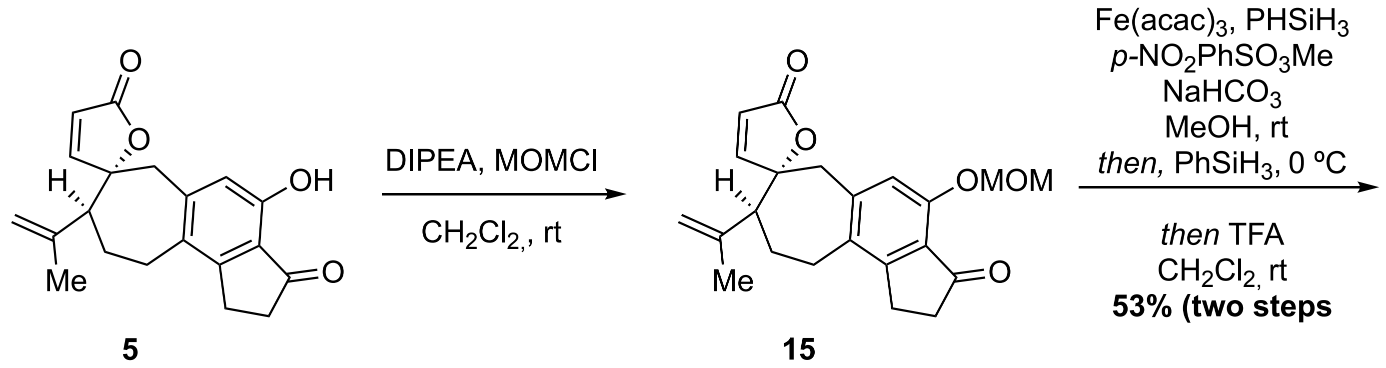
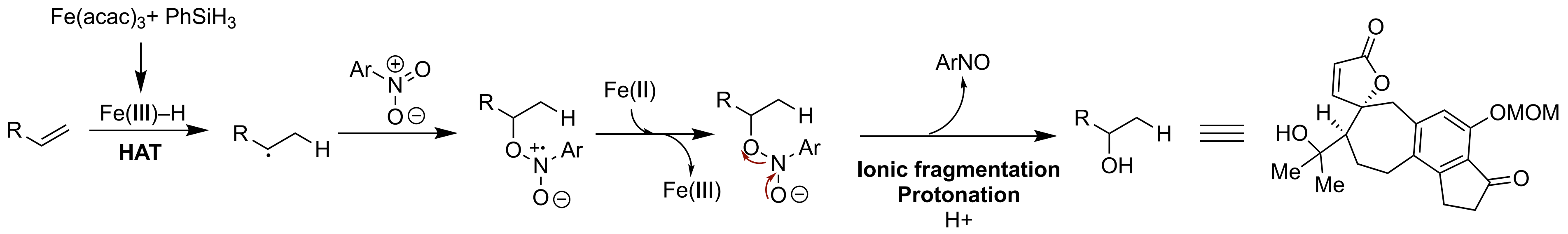
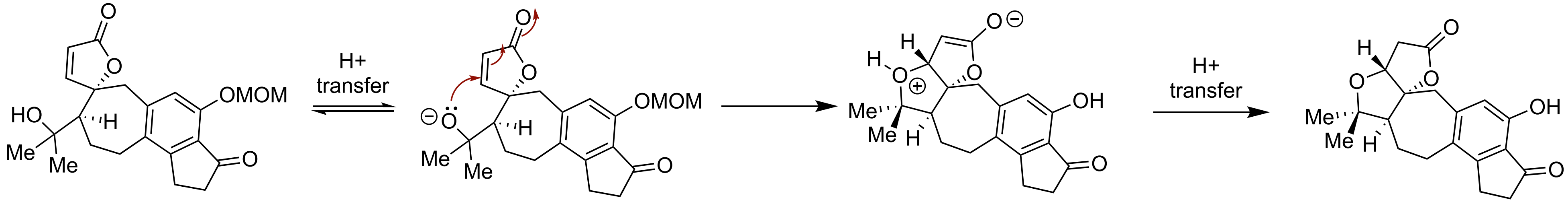


Mukaiyama hydration with Nitroarene



Oxa-michael addition



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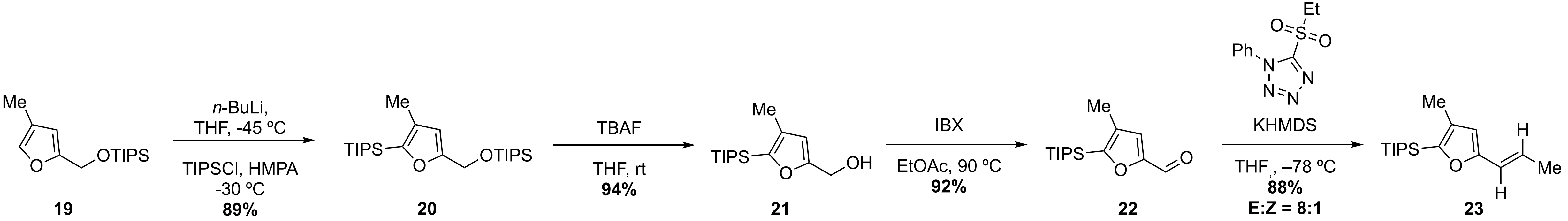
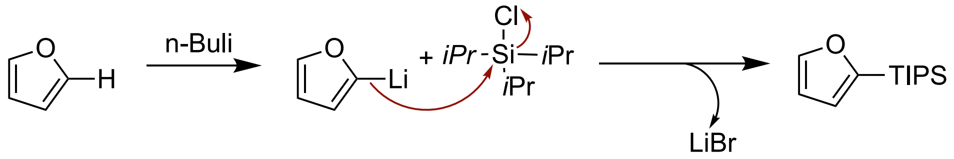
Angew. Chem., Int. Ed. 2021, *60*, 8313–8320.

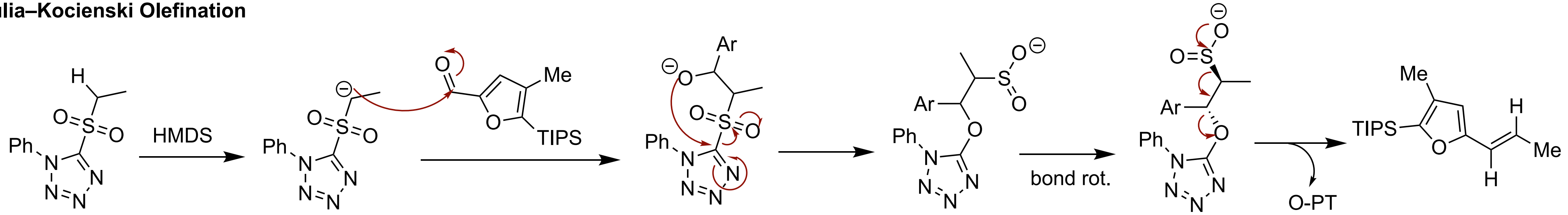


Chem. Eur. J. 2009, 15, 6626-6644.

Furan Lithiation and Silylation



Julia–Kocienski Olefination



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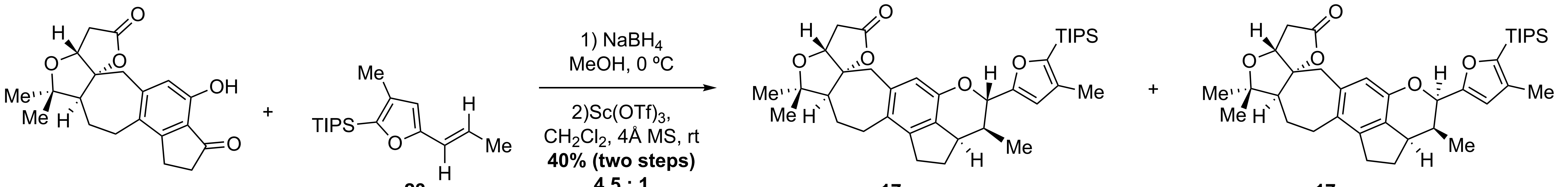
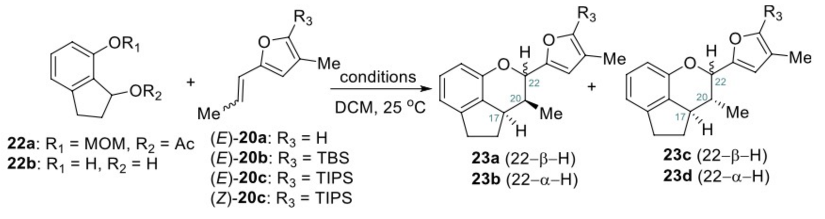
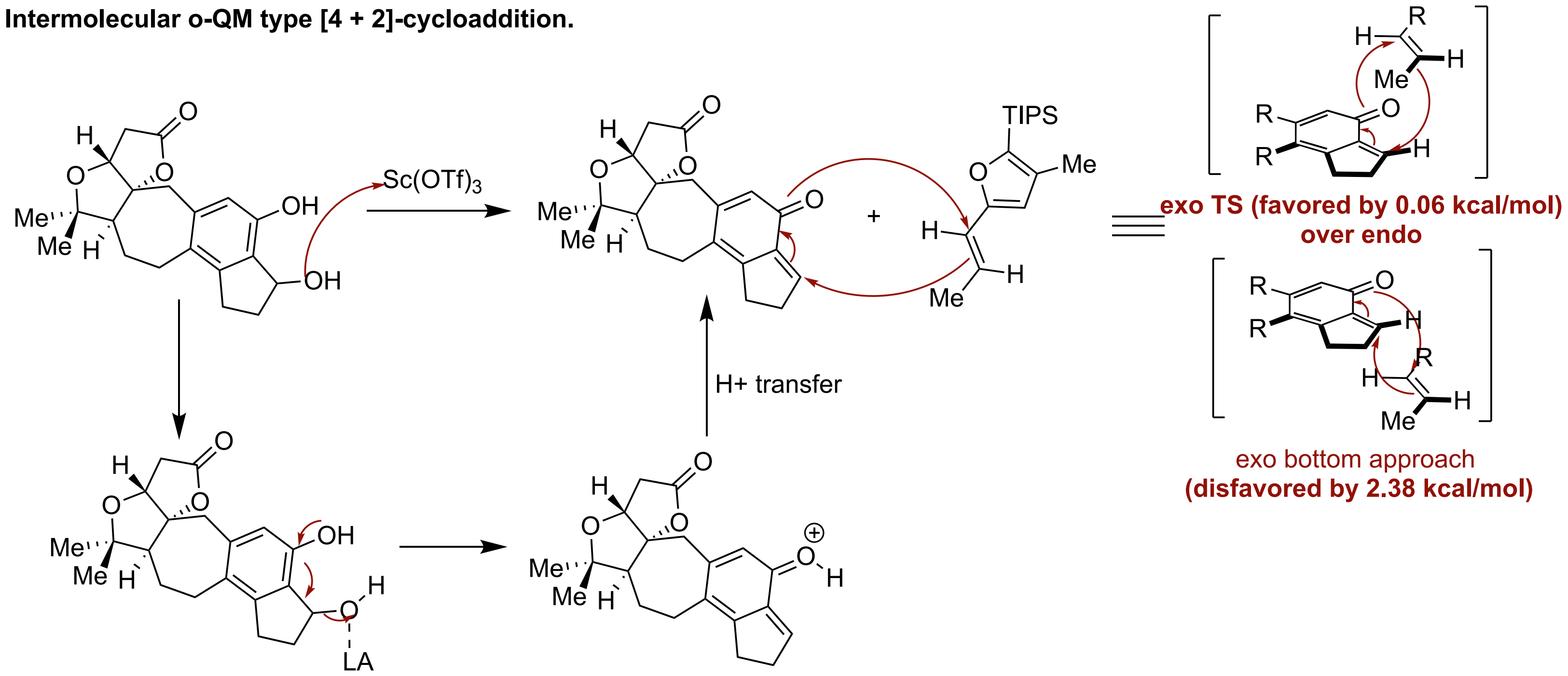


Table 1. Optimization of the *o*-QM Type [4 + 2]-Cycloaddition[a]



Entry	Substrates	Cat.	Yield (%)[b] (23a:23b:23c:23d)
1	**22a**, (*E*)-**20a**	$PtCl_4$	NA
2	**22a**, (*E*)-**20b**	$PtCl_4$	NA
3	**22a**, (*E*)-**20c**	$PtCl_4$	3 (1.5:1.0:0:0.8)
4	**22b**, (*E*)-**20c**	$PtCl_4$	6 (1.5:1.0:0:0.8)
5[c]	**22b**, (*E*)-**20c**	$PtCl_4$	14 (1.5:1.0:0:0.8)
6[c]	**22b**, (*E*)-**20c**	CSA	23 (3.7:1.0:0:0.3)
7[c]	**22b**, (*E*)-**20c**	$Zn(OTf)_2$	28 (3.2:1.0:0:0.6)
8[c]	**22b**, (*E*)-**20c**	$In(OTf)_3$	31 (2.2:1.0:0:0.5)
9[c]	**22b**, (*E*)-**20c**	$Sc(OTf)_3$	33 (1.1:1.0:0:0.4)
10[c]	**22b**, (*E*)-**20c**	$Bi(OTf)_3$	57 (3.0:1.0:0:0.4)
11[c]	**22b**, (*Z*)-**20c**	$Sc(OTf)_3$	63 (2.1:1.0:1.0:7.0)
12[c,d]	**22b**, **20c**	$Sc(OTf)_3$	30 (1.5:1.0:0.2:1.0)

[a]Reaction conditions: **22** (0.07 mmol), **20** (0.2 mmol), Cat. (10 mol %), DCM (5 mL), 25 °C. [b]Isolated yield. [c]4 Å MS (50 mg) was added. [d]**20c:** *E*:*Z* = 1:1.



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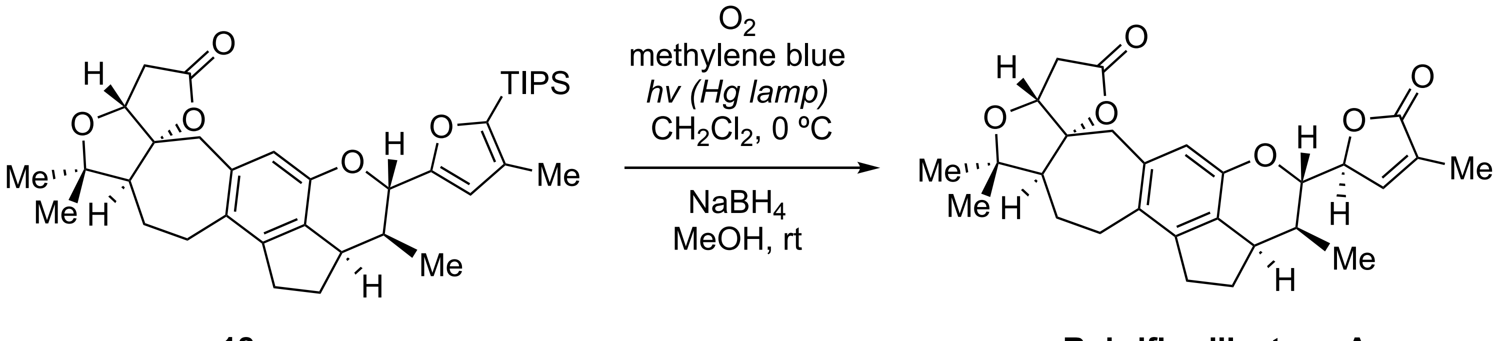
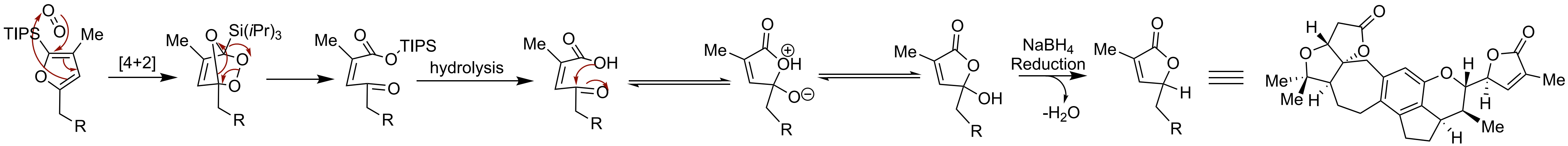


Oxidation with singlet oxygen and reduction with sodium borohydride



Rubriflordilactone A

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Acc. Chem. Res. **2008**, *41*, 1001−1011.