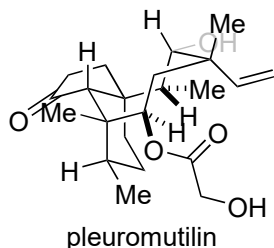


Problem Session (1) - Answer

2022/06/24 Wentao Wang

Topic: Synthesis of Pleuromutilin (Pronin et al. *J. Am. Chem. Soc.* **2022**, *144*, 10174.)

0. Introduction



Isolation: basidiomycetes from the genus *Clitopilus*

Biological activity: inhibitor of bacterial protein synthesis

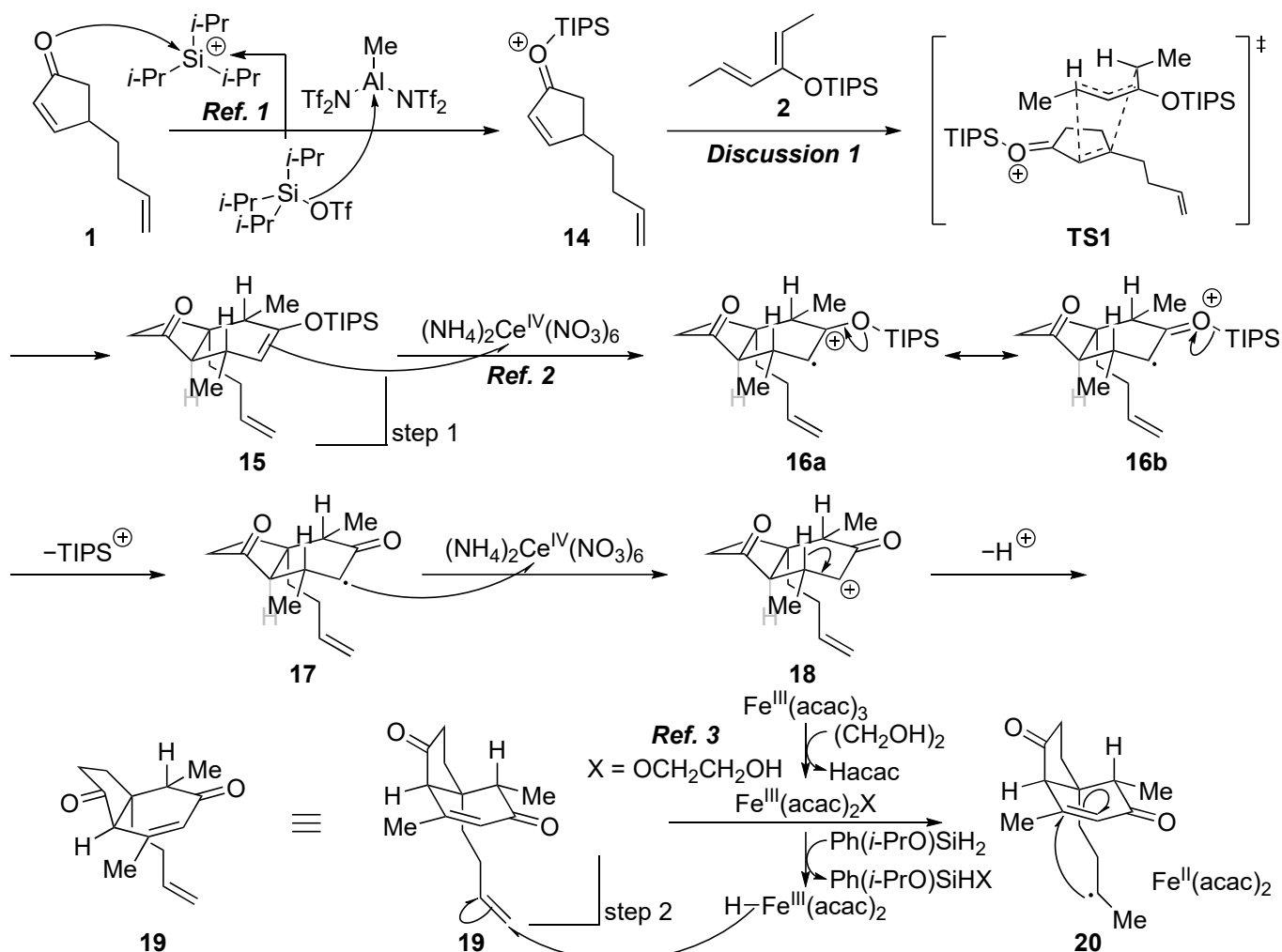
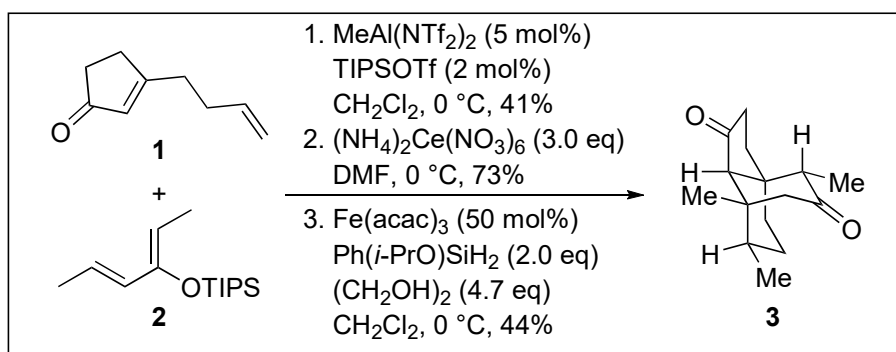
Structural features: 5,8,6-tricyclic skeleton, 8 chiral centers

Previous total syntheses:

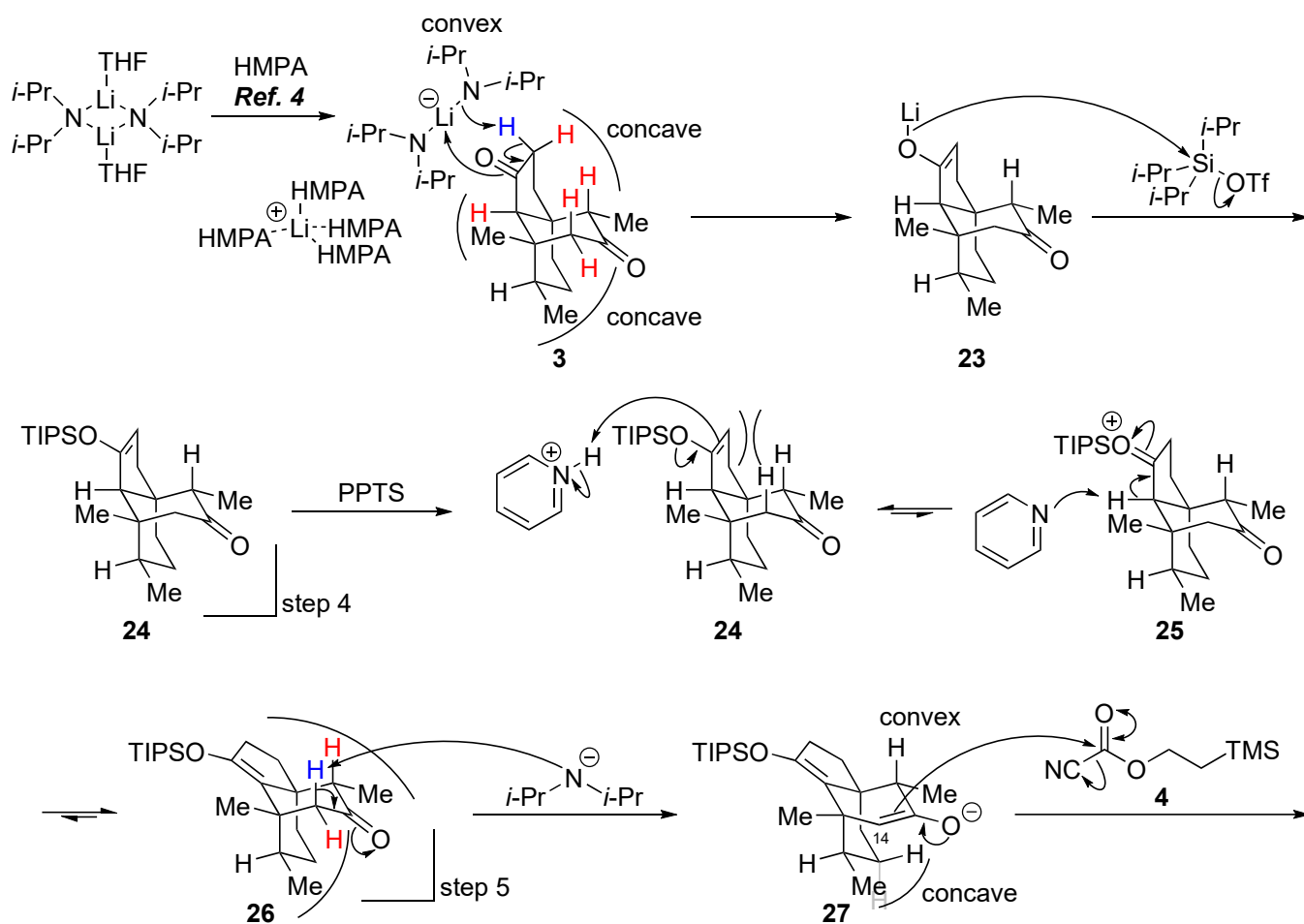
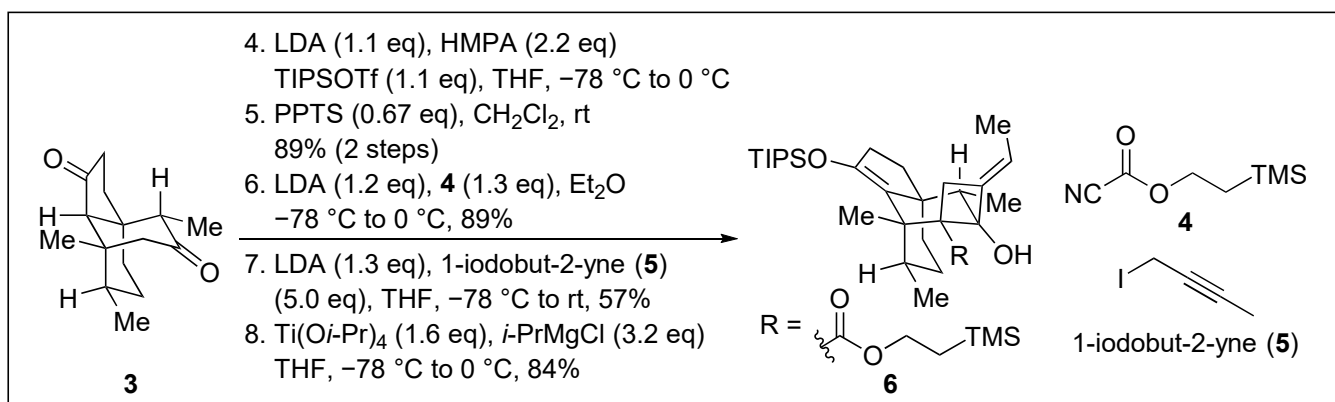
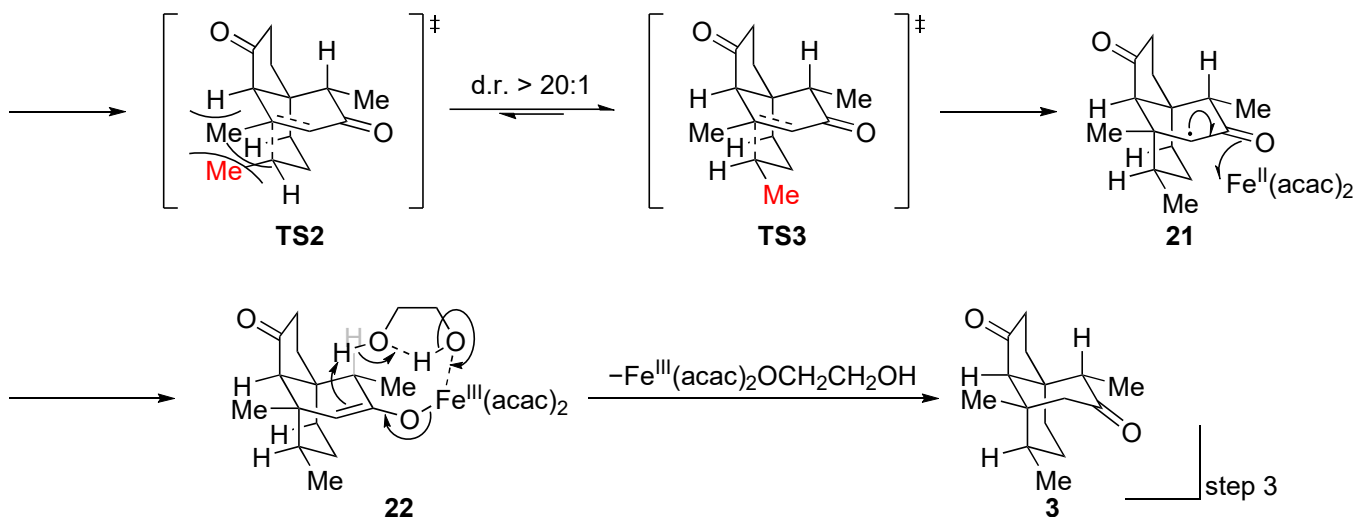
1. Gibbons. *J. Am. Chem. Soc.* **1982**, *104*, 1767. (racemic)
2. Boeckman et al. *J. Am. Chem. Soc.* **1989**, *111*, 8284. (racemic)
3. Procter et al. *Chem. Eur. J.* **2013**, *19*, 6718. (asymmetric)
4. Herzon et al. *Science* **2017**, *356*, 956. (asymmetric)
5. Herzon et al. *J. Am. Chem. Soc.* **2017**, *139*, 16377. (asymmetric)
6. Reisman et al. *J. Am. Chem. Soc.* **2018**, *140*, 1267. (asymmetric)

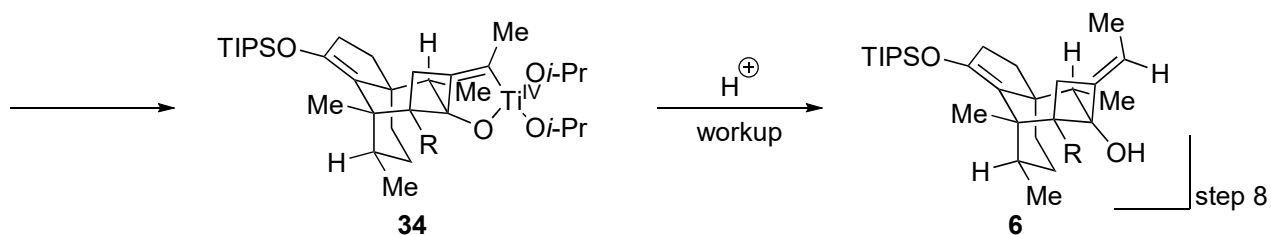
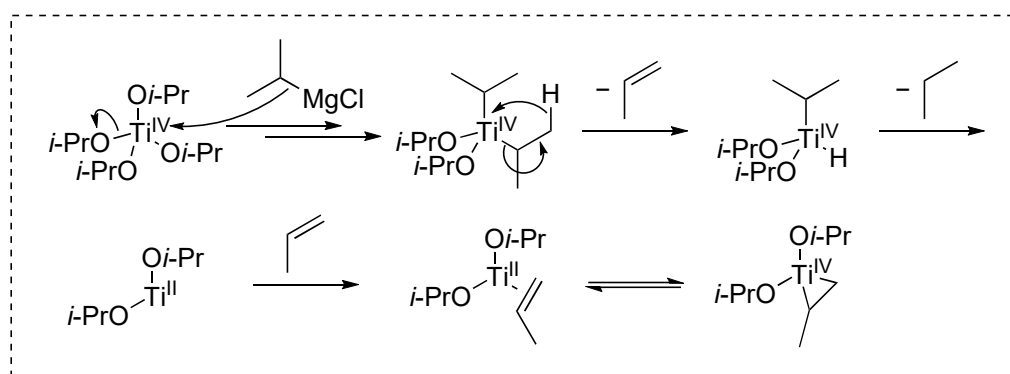
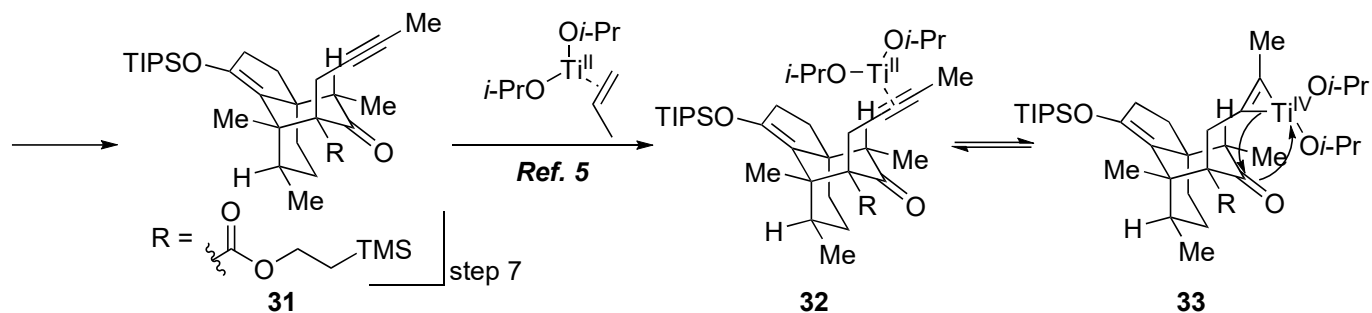
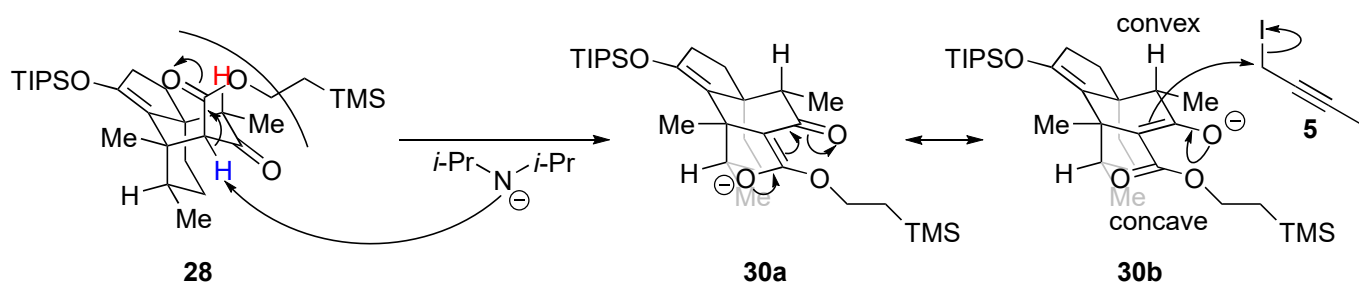
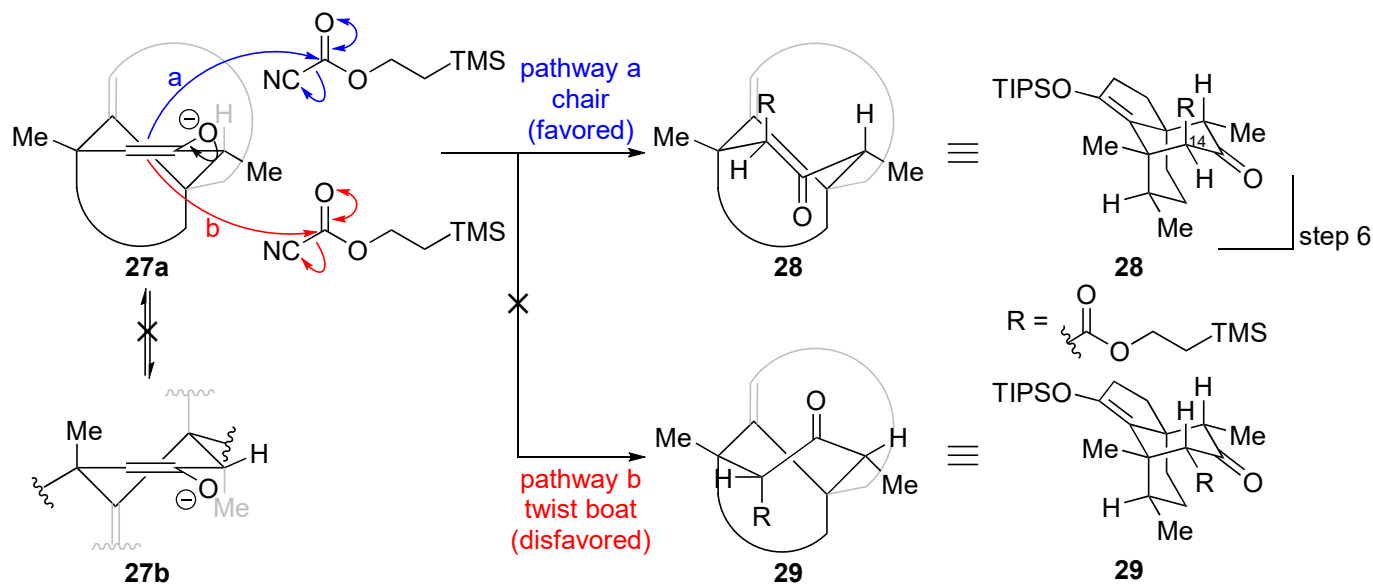
Refer to: 1&2: 130622_PS_Taro_Asaba; 1,4&5: 170617_LS_Hiroaki_Matoba
3&6: 180707_PS_Yuri_Takada

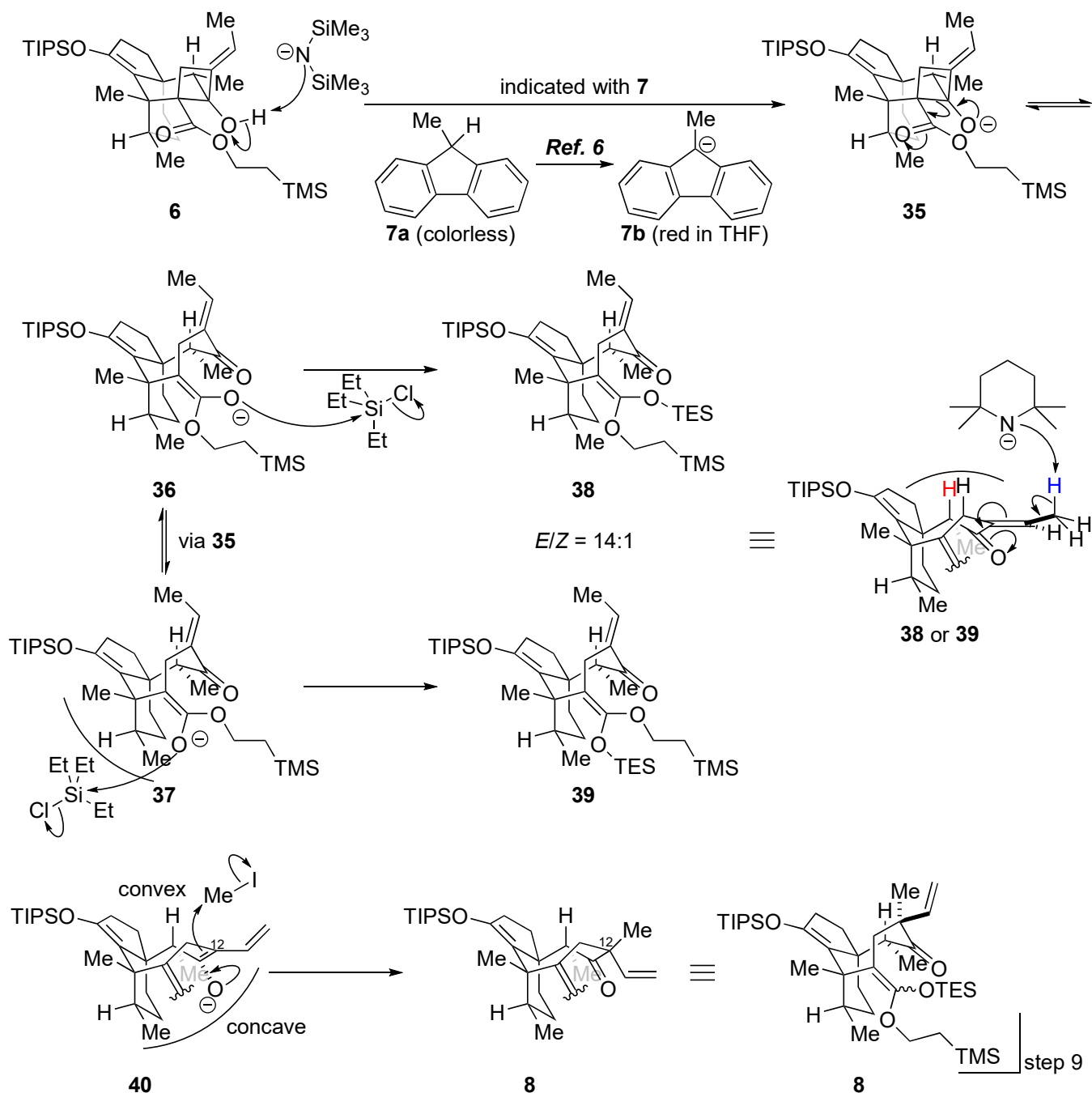
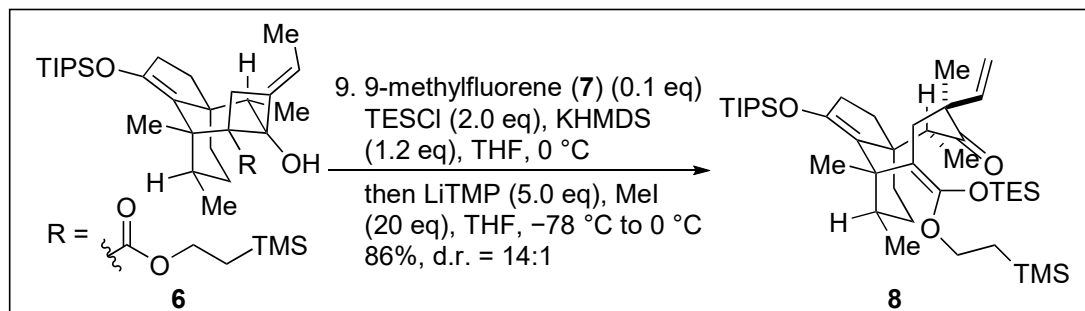
1. Answer



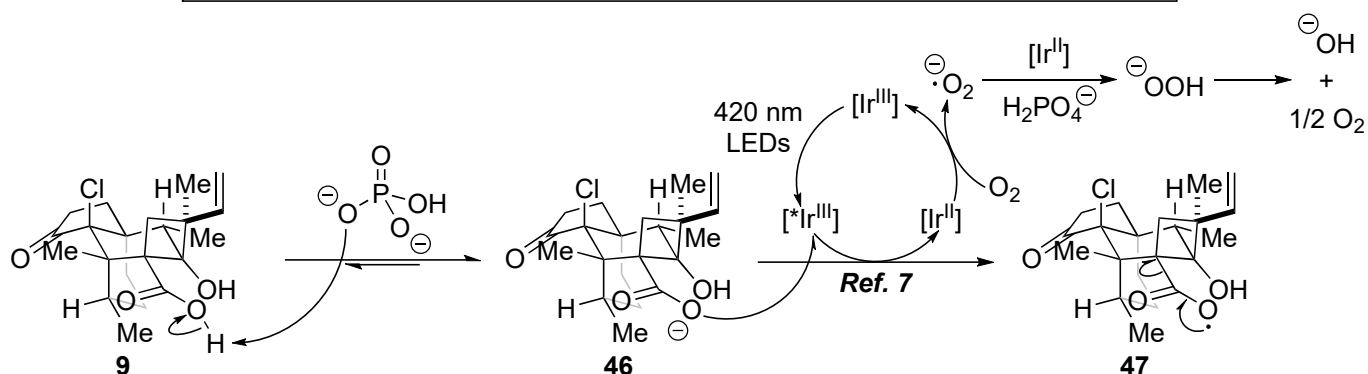
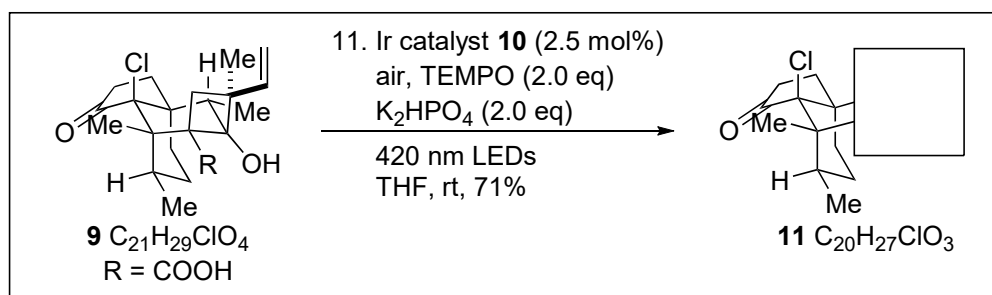
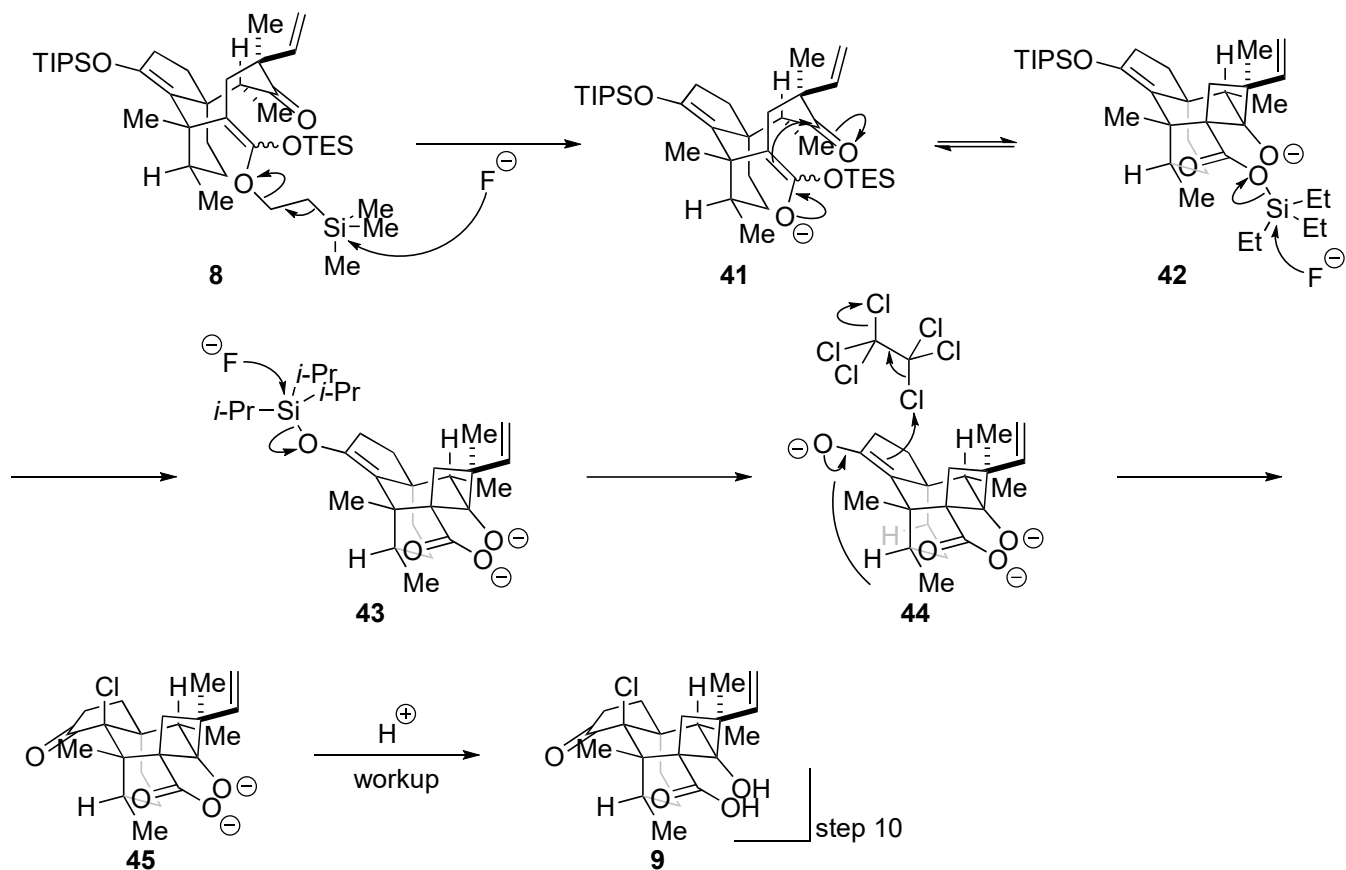
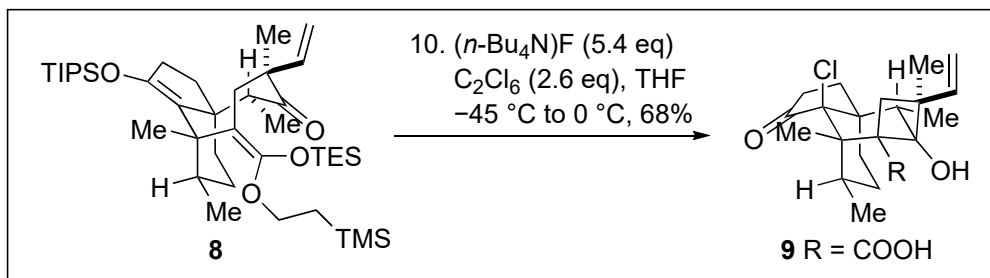
Reference(s): 1. Bosnich et al. *J. Am. Chem. Soc.* **1998**, *120*, 8271. 2. Evans et al. *Tetrahedron Lett.* **1995**, *36*, 3985. 3. Holland et al. *J. Am. Chem. Soc.* **2019**, *141*, 7473.

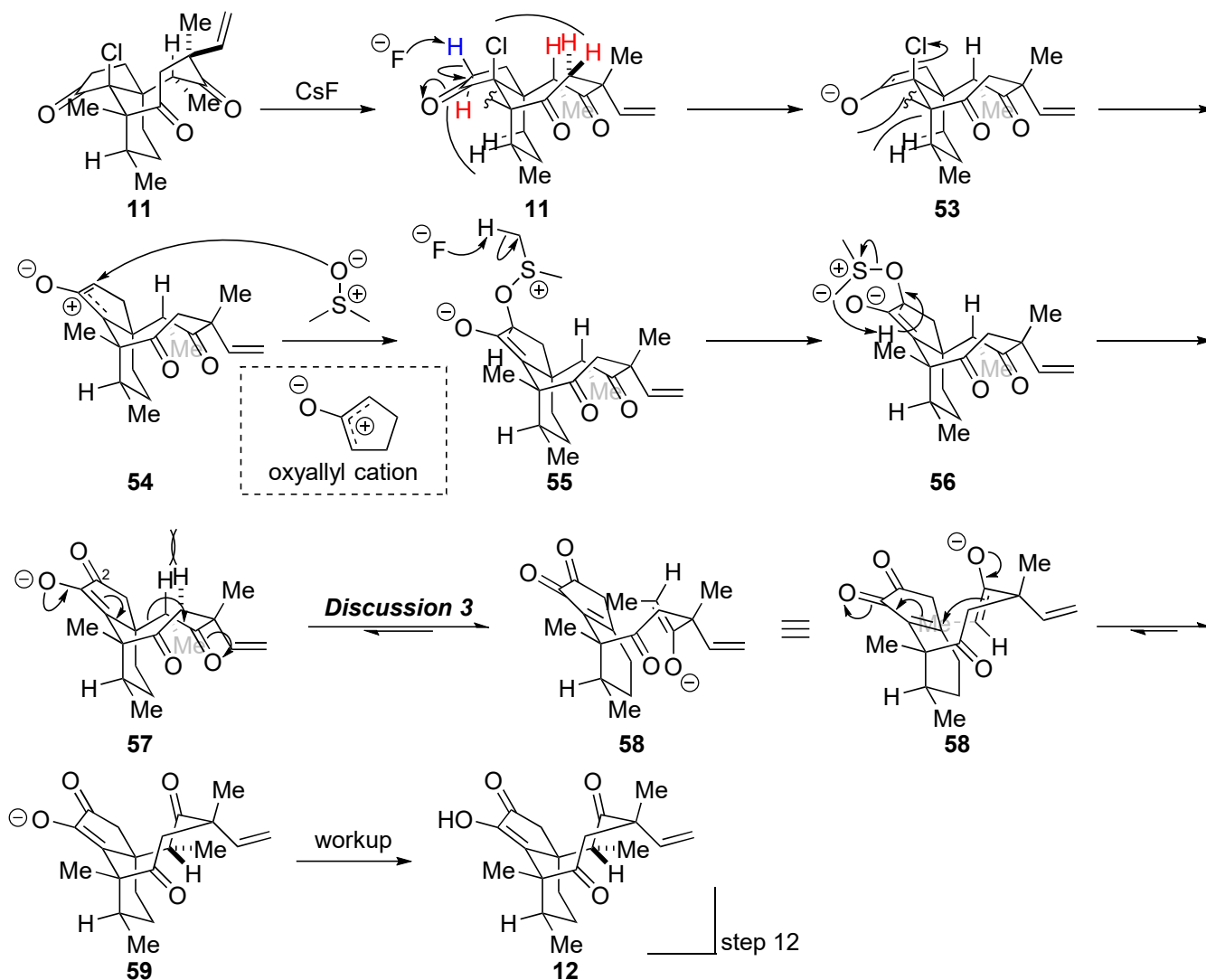
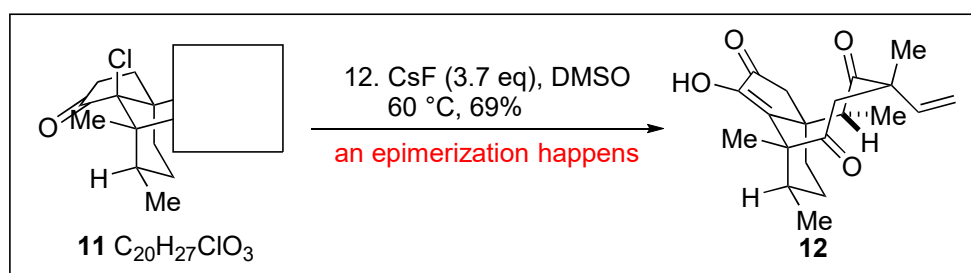
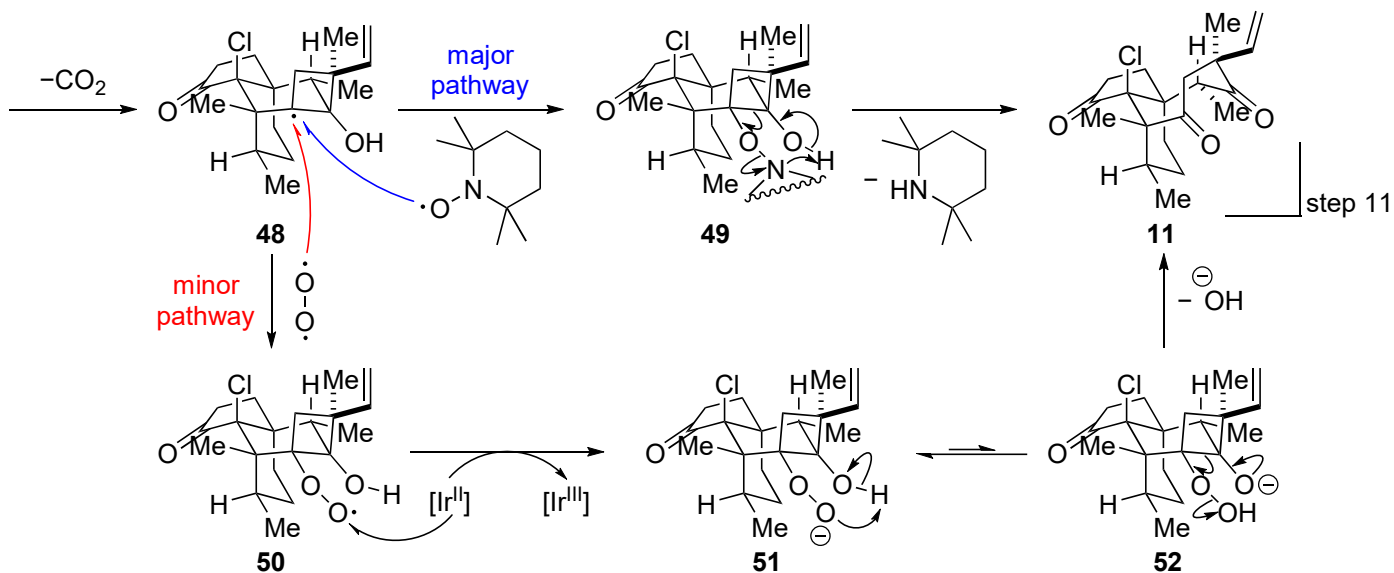






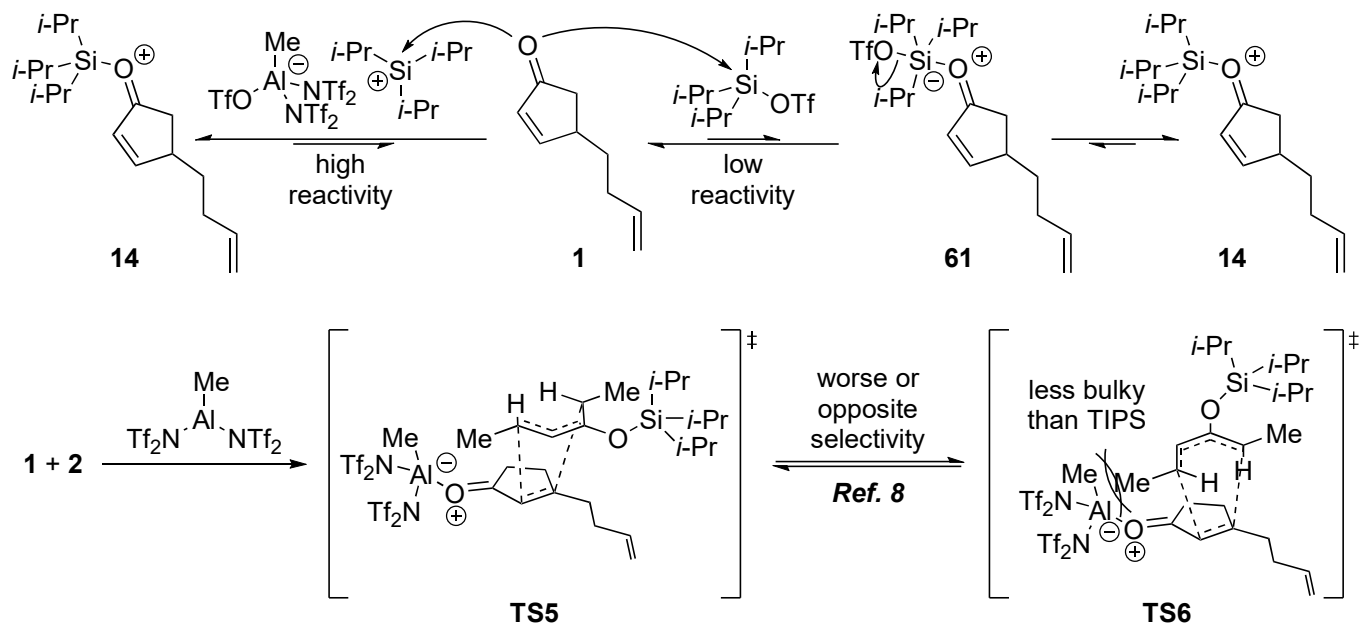
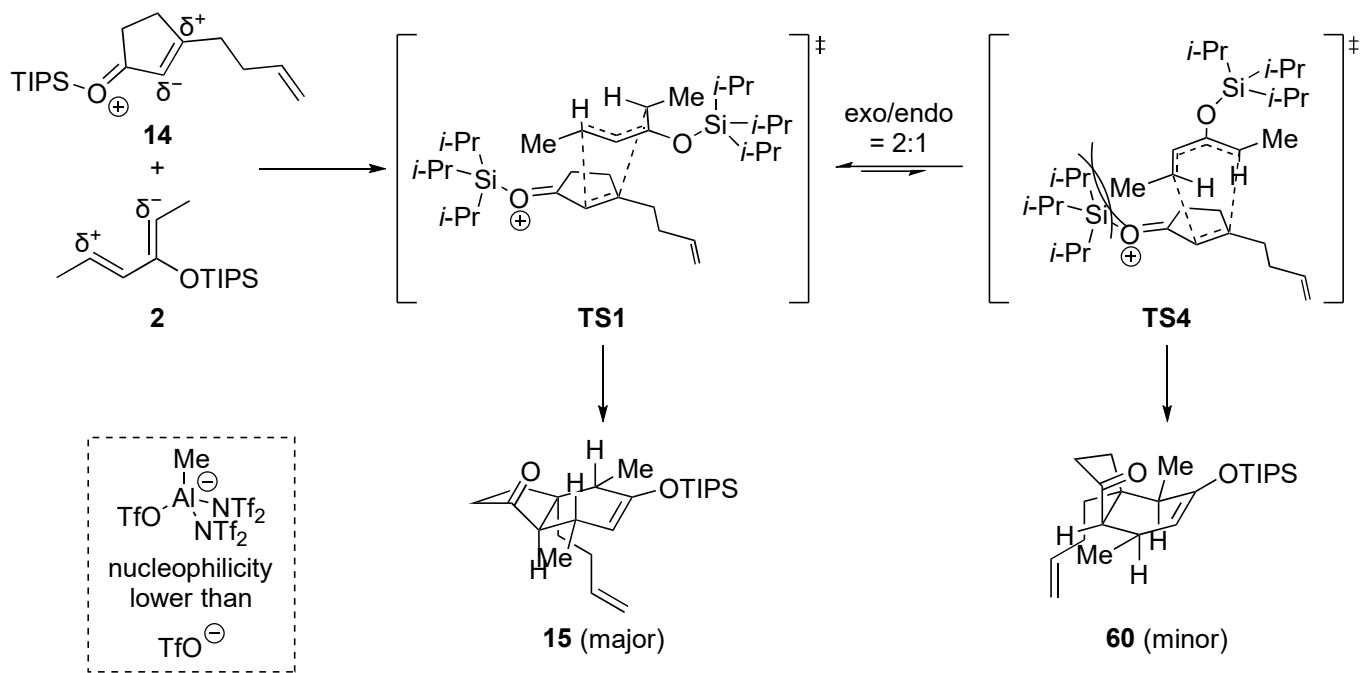
See **Discussion 2** for more details.





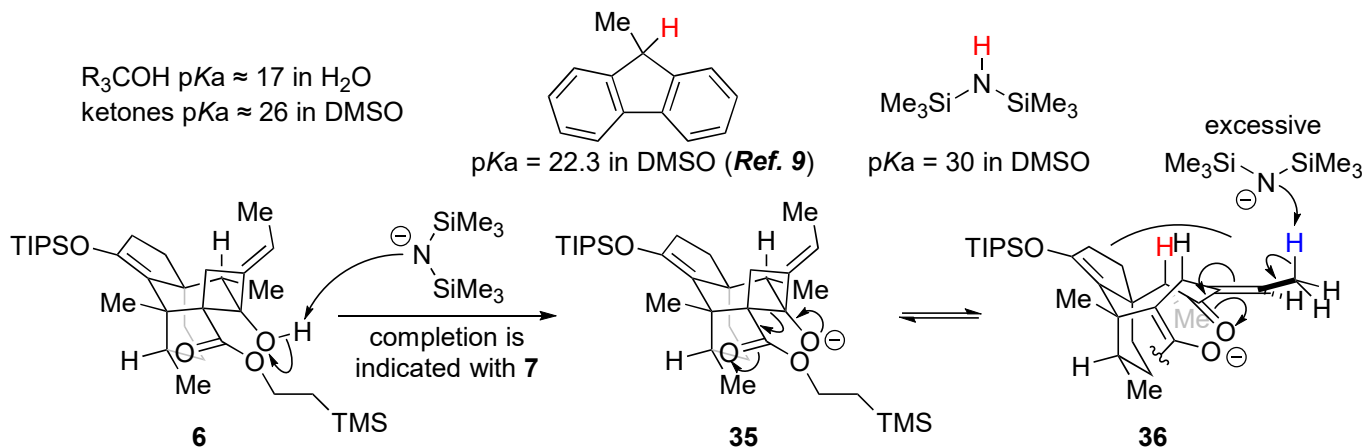
2. Discussion

2-1. Discussion 1: Stereoselectivity of Diels-Alder reaction



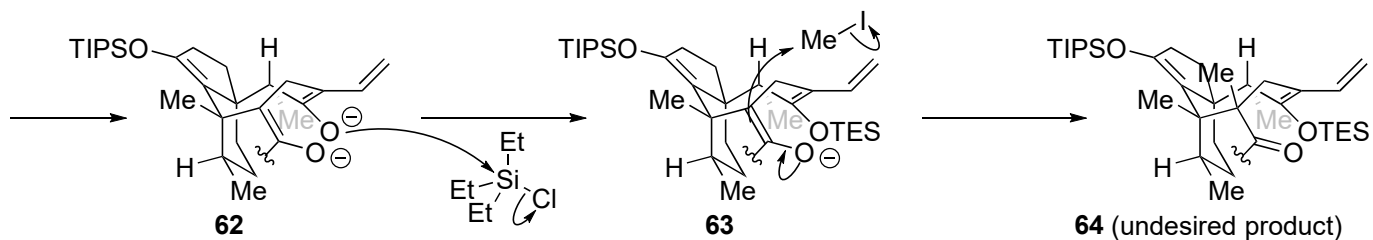
2-2. Discussion 2

2-2-1. Role of 9-methylfluorene (**7**)



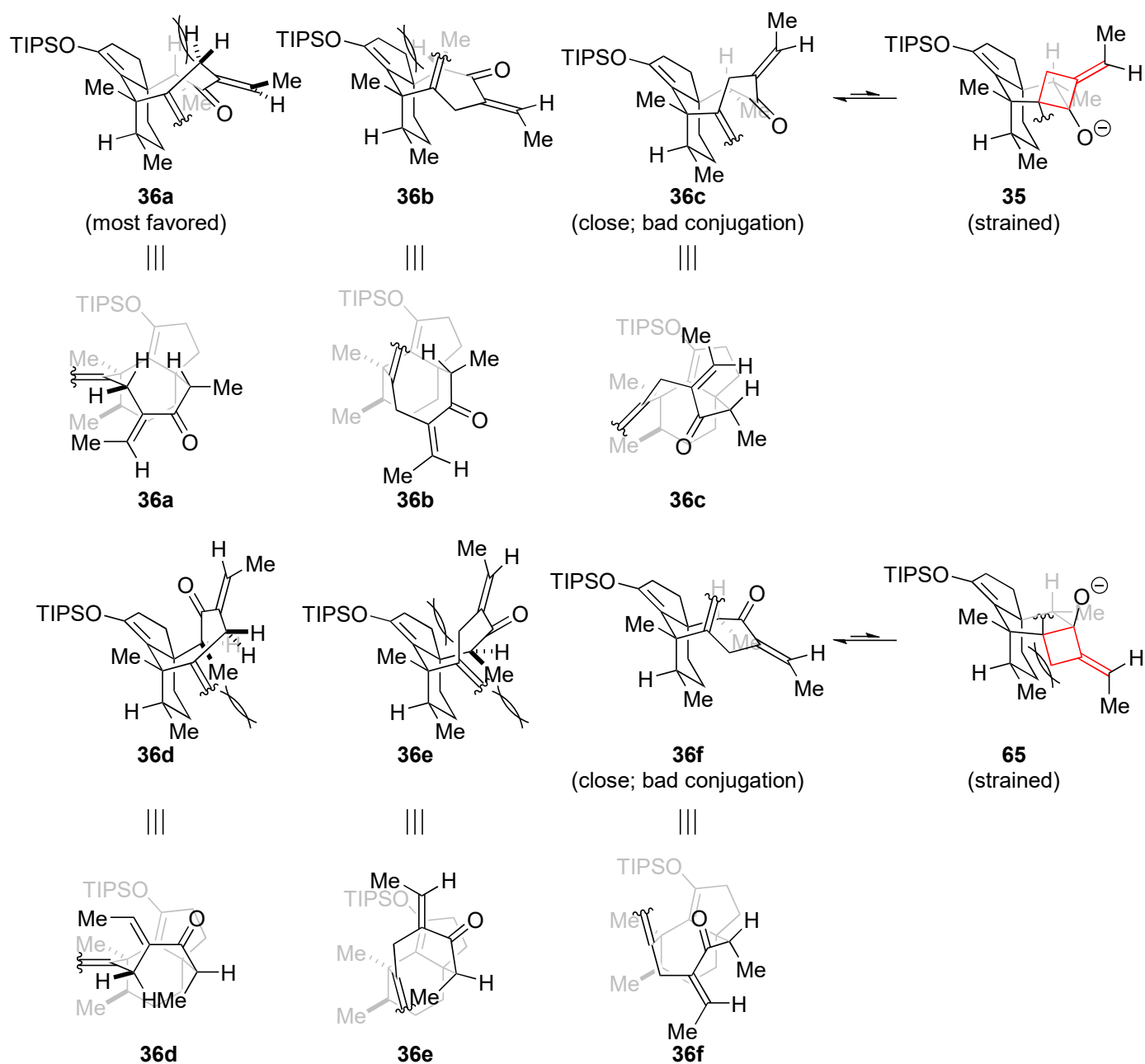
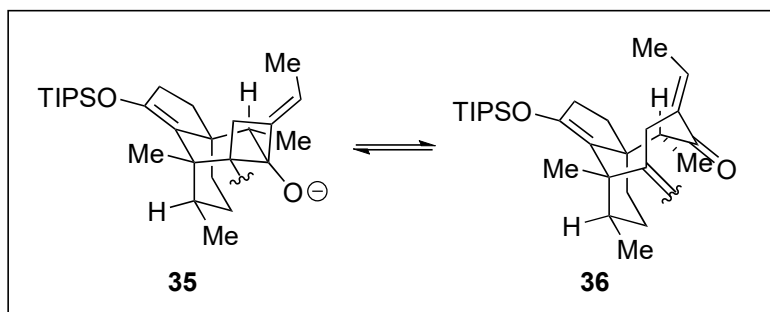
Reference(s): 8. Jung et al. *Org. Lett.* **2012**, *14*, 5169.

9. Bordwell et al. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

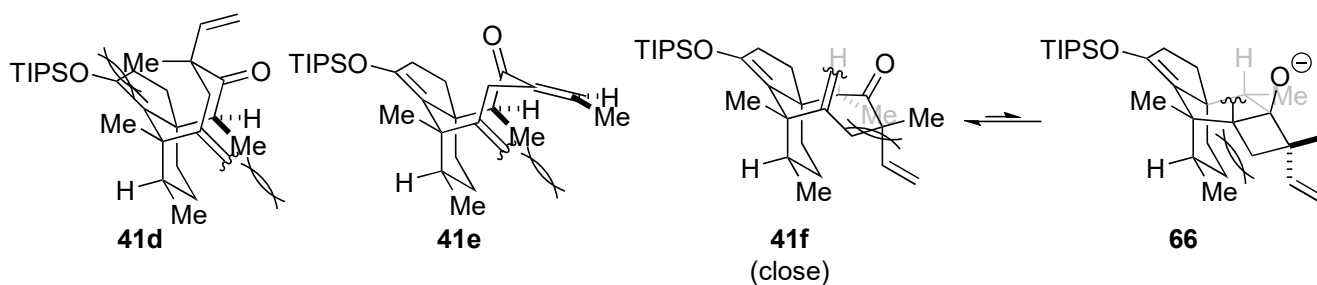
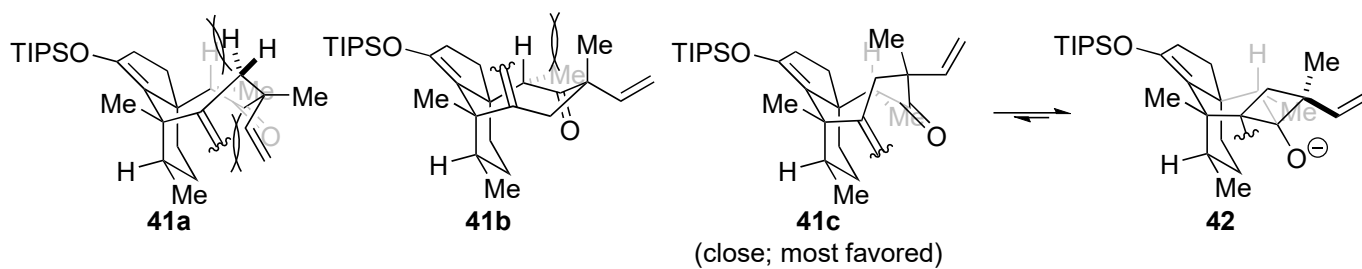
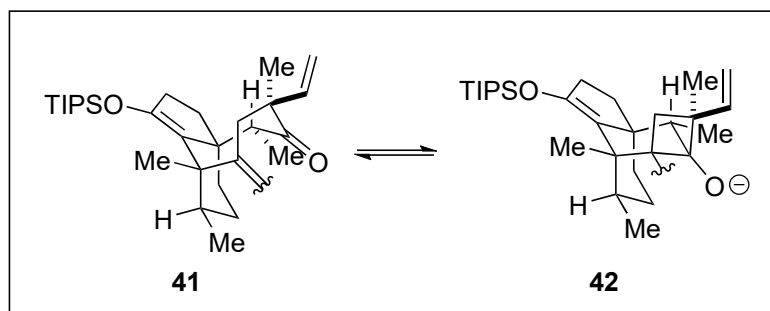


2-2-2. 4-membered ring opening and closing

Before methylation:



After methylation:



2-3. Discussion 3: Retro-Michael fragmentation / Michael addition

