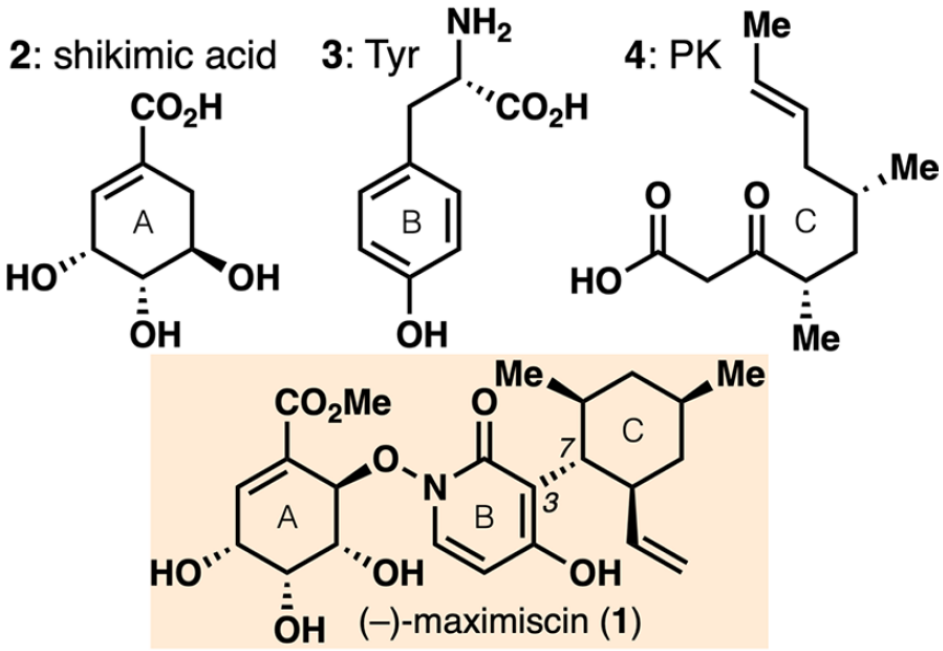
# Total Synthesis of (–)-Maximiscin

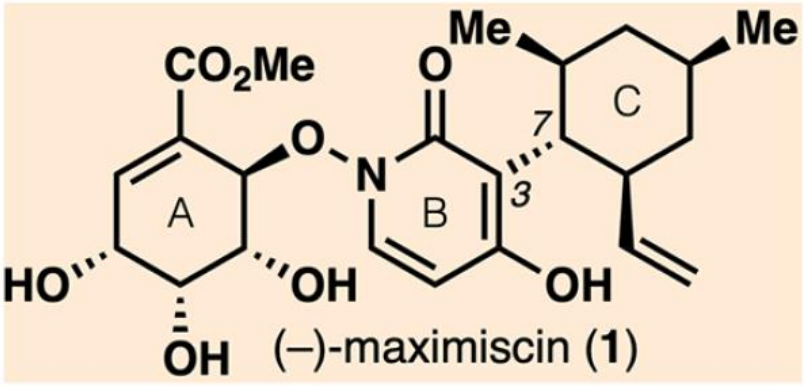
Kyle S. McClymont, Feng-Yuan Wang, Amin Minakar, Phil S. Baran*
*J. Am. Chem. Soc.* **2020**, *142*, 8608 - 8613.

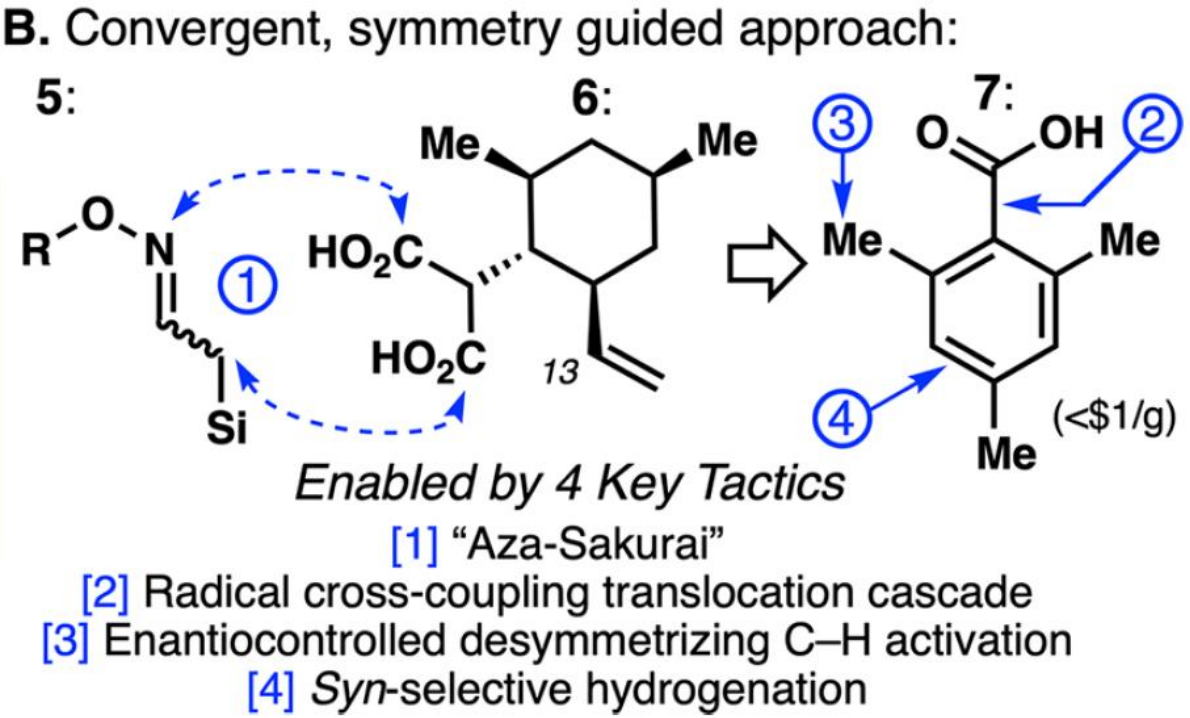
- (−)-Maximiscin (**1**) is a natural product derived from the rare union of three separate metabolic pathways.
- **1** has been shown to induce DNA damage (and DNA damage response pathways) in select triple-negative breast cancer cell lines.
- A central 1,4-dihydroxy-2-pyridone unit, a shikimate derivative, and a trisubstituted cyclohexyl fragment of polyketide origin.
- Exists as an equilibrating mixture of atropisomers (at C-3,7 bond).
- Documented instability – tends to fragment at the weak N-O bond.
- No synthesis of **1** has been reported, although similar variants without the shikimate subunit have been prepared.
- Convergent, enantioselective preparation of **1** – exploiting hidden symmetry, C–H functionalization, and radical retrosynthesis.




Ricky Alvarado
May 26th, 2020
Liu Group

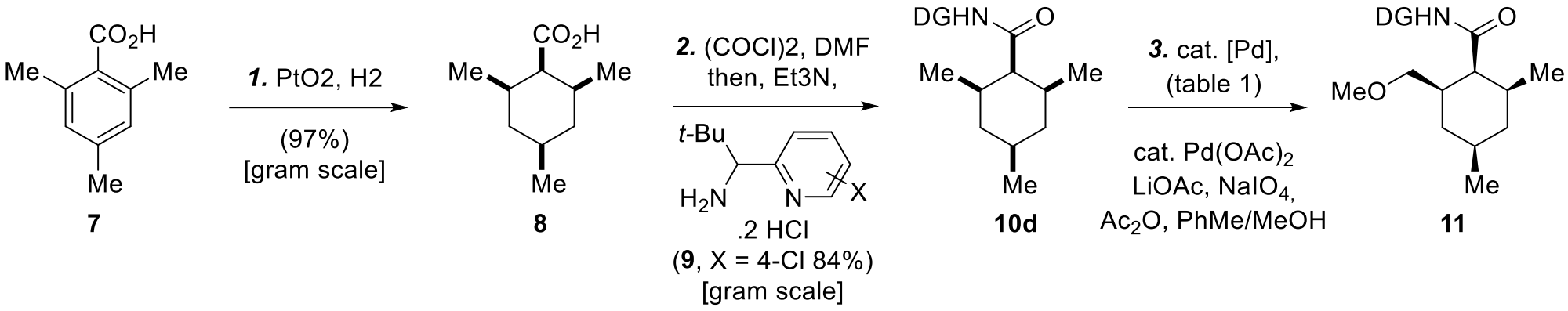
# Retrosynthesis



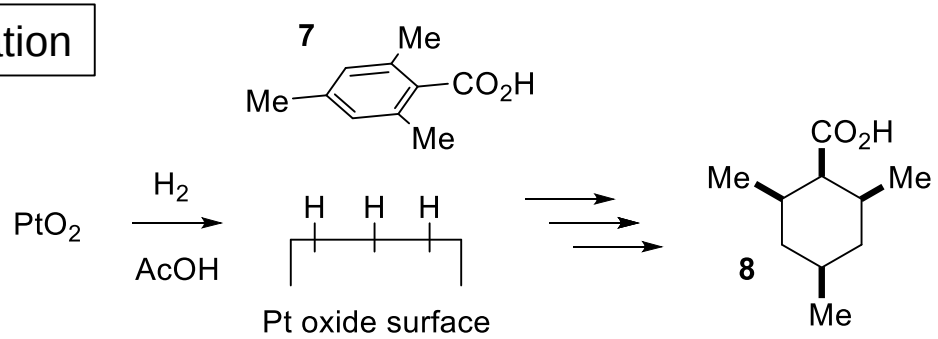




To maximize convergency, **1** is split down the middle at the pyridone ring, yielding fragment **5** derived from shikimic acid in previous reports, and fragment **6** which could be accessed through hydrogenation and desymmetrization of a mesitylene-derived carboxylic acid.

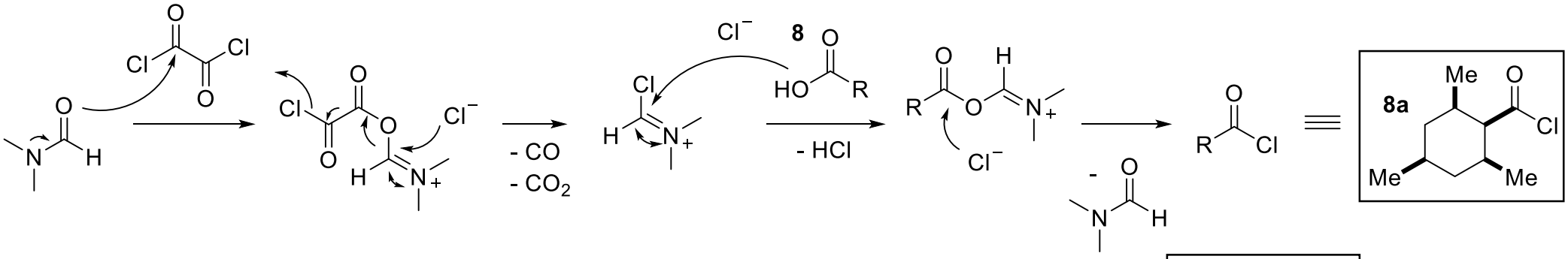
Mizuki, K.; Iwahashi, K.; Murata, N.; Ikeda, M.; Nakai, Y.; Yoneyama, H.; Harusawa, S.; Usami, Y. Synthesis of Marine Natural Product (−)-Pericosine E. *Org. Lett.* **2014**, *16*, 3760–3763

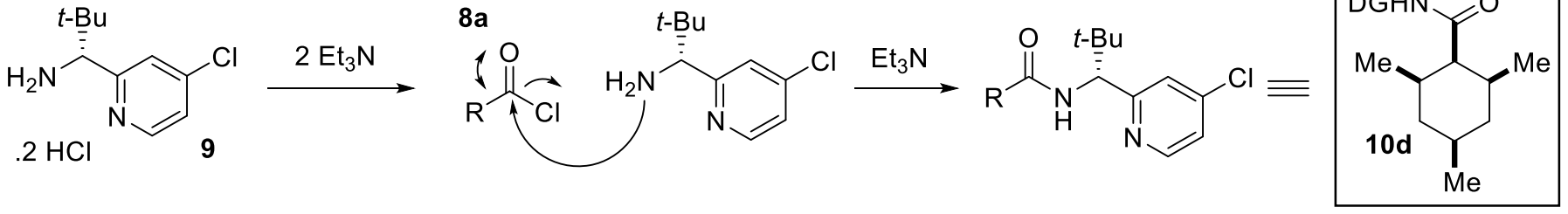


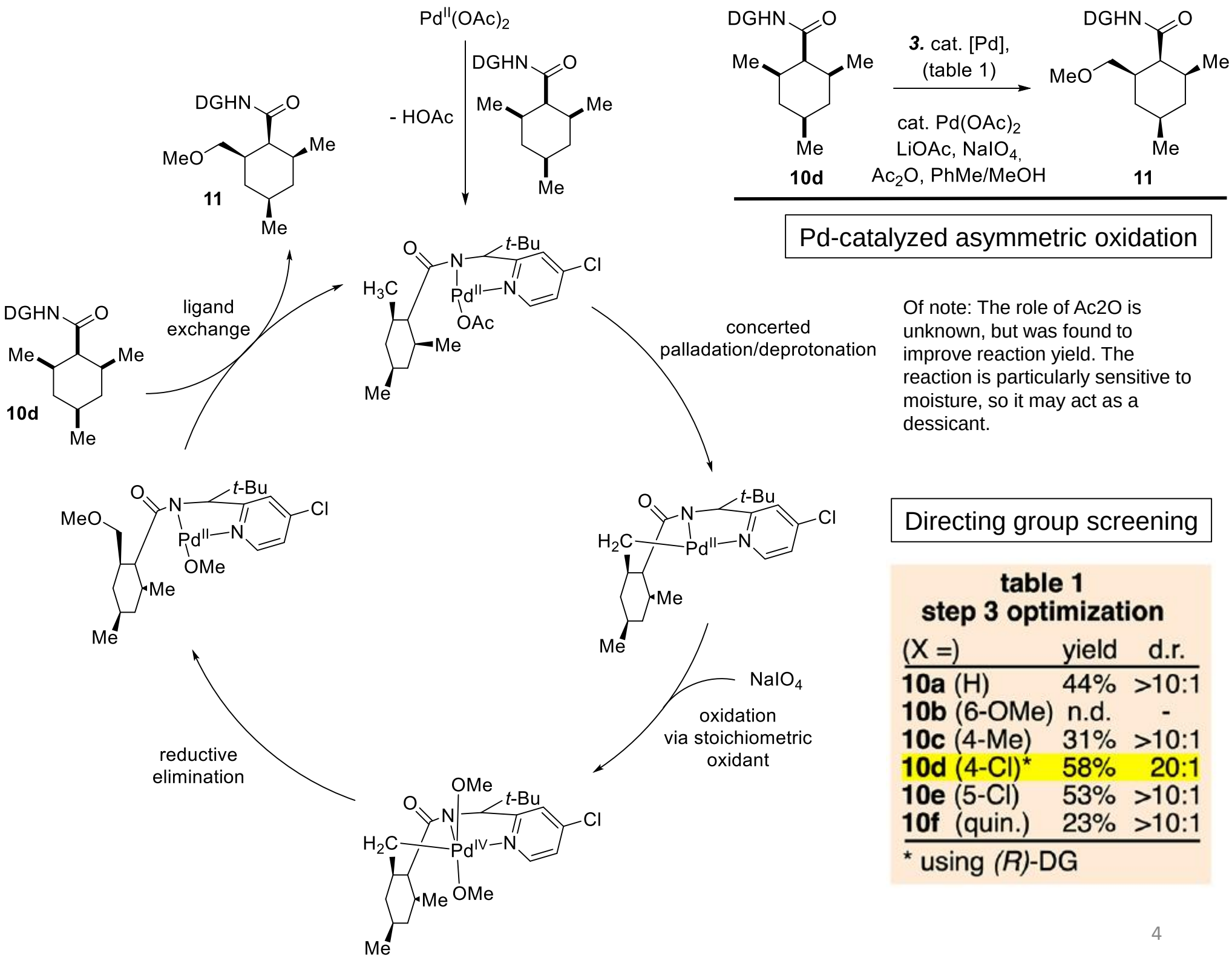

## Stereoselective Hydrogenation




## Amidation – Preparation of directing group









## Pd-catalyzed asymmetric oxidation

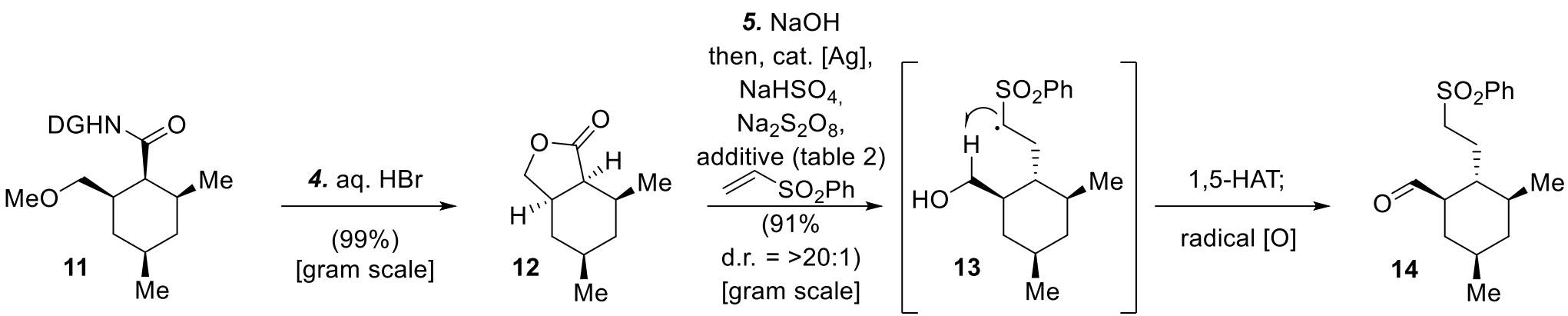
Of note: The role of Ac2O is unknown, but was found to improve reaction yield. The reaction is particularly sensitive to moisture, so it may act as a dessicant.

## Directing group screening

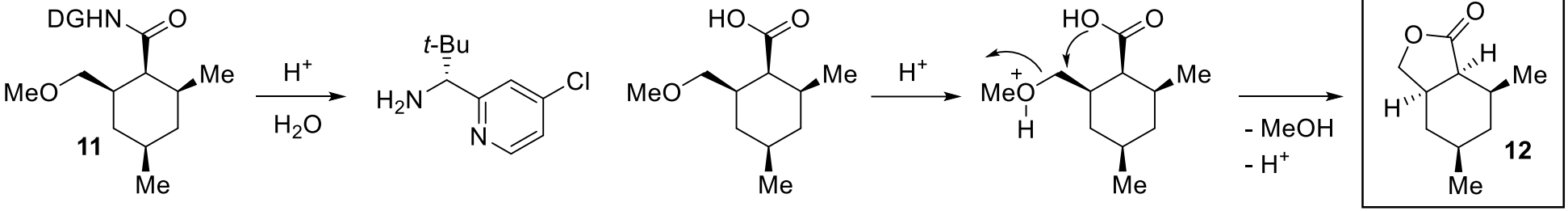
**table 1**
**step 3 optimization**

| (X =) | yield | d.r. |
|---|---|---|
| **10a** (H) | 44% | >10:1 |
| **10b** (6-OMe) | n.d. | - |
| **10c** (4-Me) | 31% | >10:1 |
| **10d** (4-Cl)* | 58% | 20:1 |
| **10e** (5-Cl) | 53% | >10:1 |
| **10f** (quin.) | 23% | >10:1 |

* using *(R)*-DG




## Deamidation and lactone cyclization




## Metal-mediated radical cascade

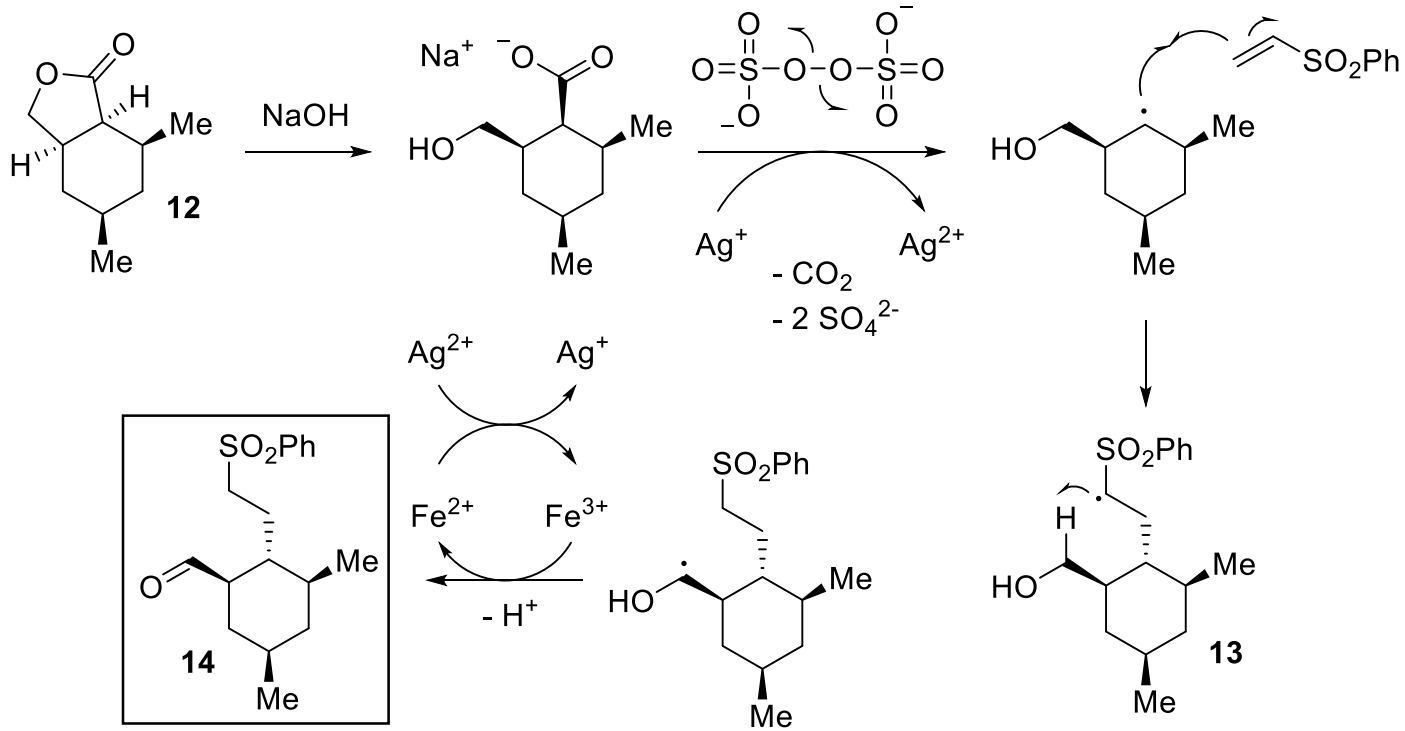
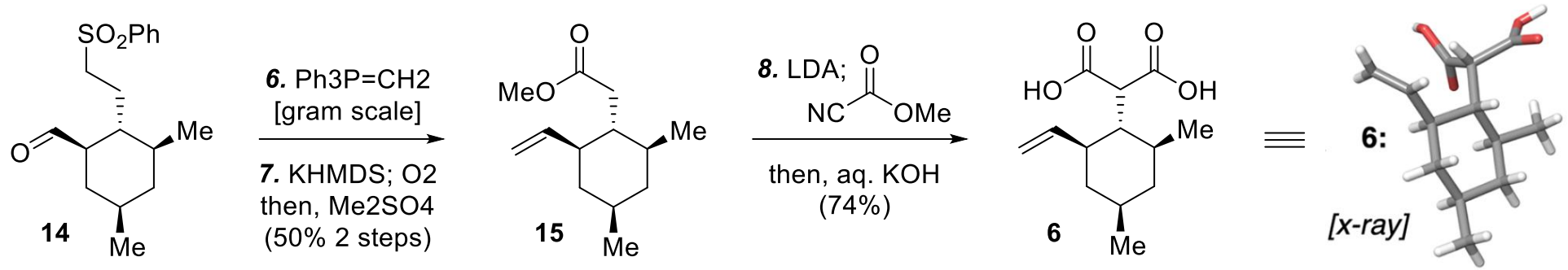


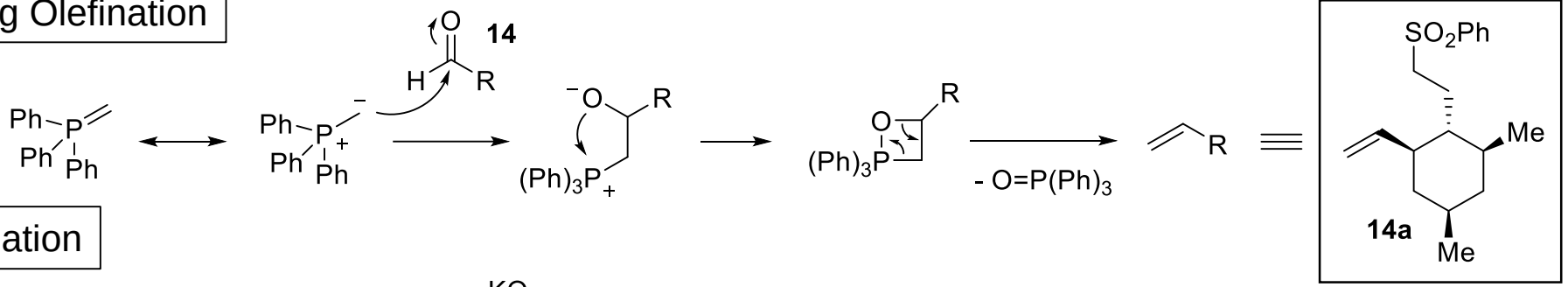

**table 2**
**step 5 optimization**

| cocatalyst | yield |
|---|---|
| none | 6% |
| $Cu(OAc)_2$ | 22% |
| $Co(ClO_4)_2$ | 28% |
| $Fe(OAc)_2$ | 48% |
| $Fe_2(SO_4)_3$ | 71% |
| $Fe_2(SO_4)_3$ | 91%* |

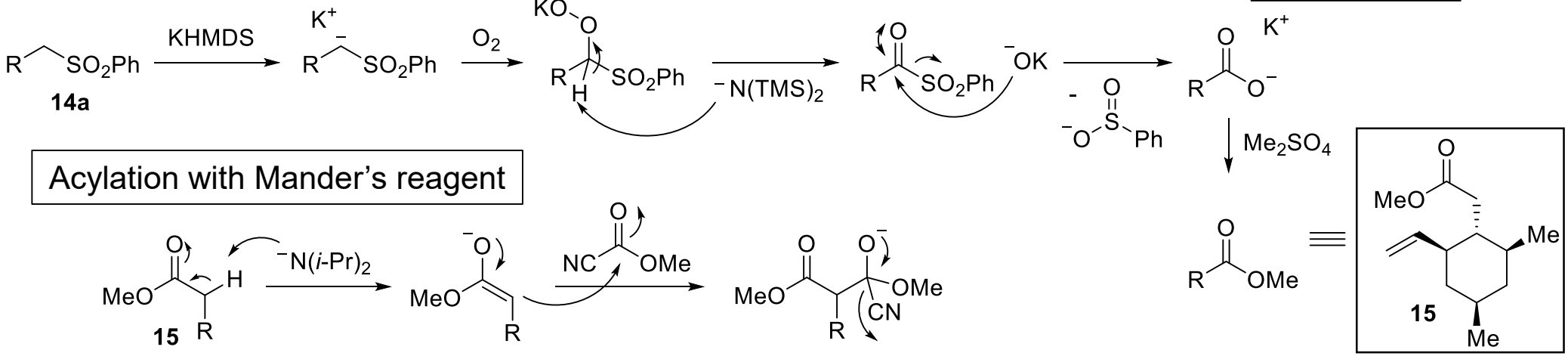
* gram scale



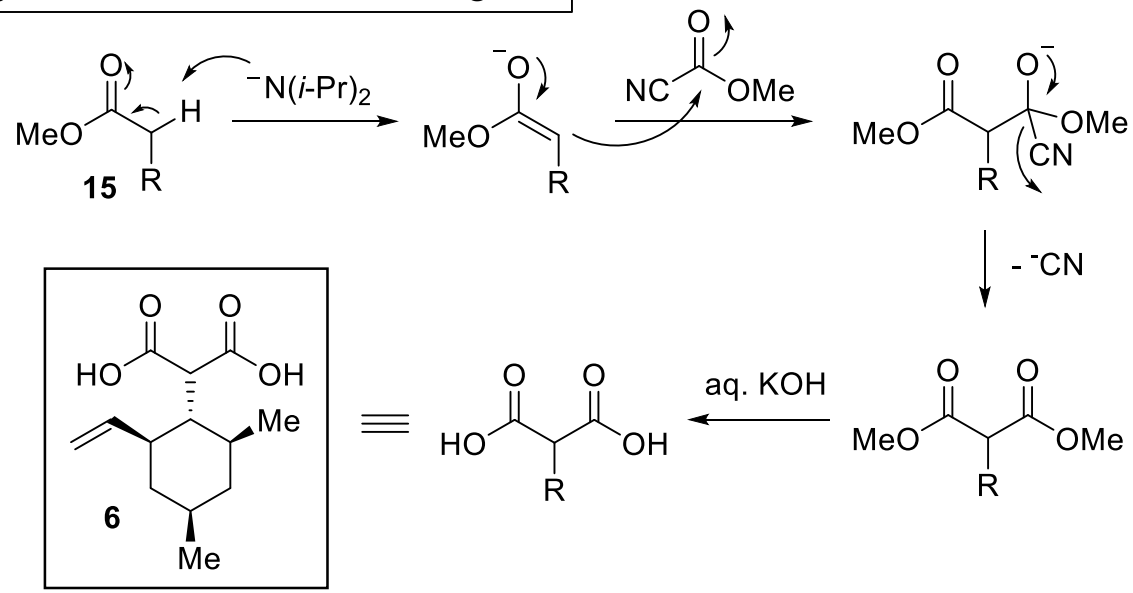

## Wittig Olefination

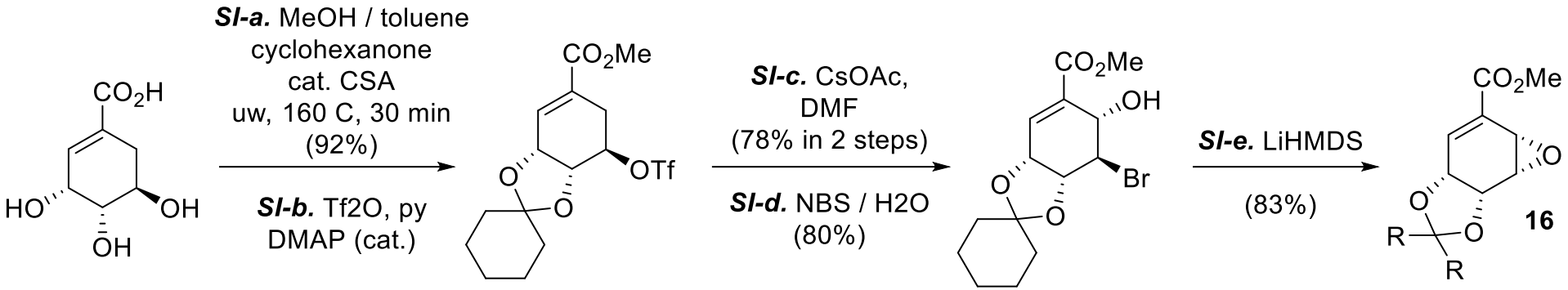



## Oxidation

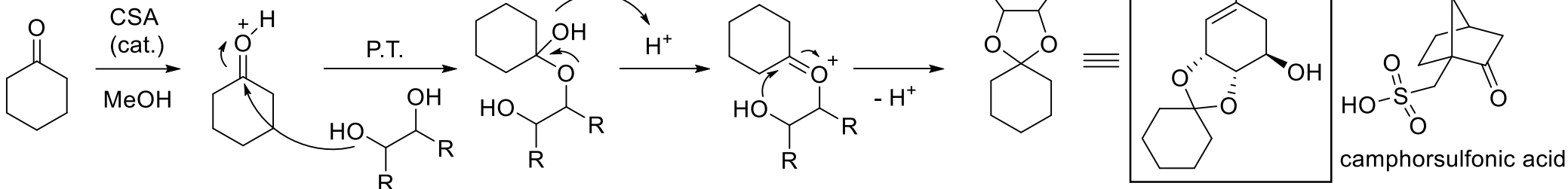



## Acylation with Mander's reagent

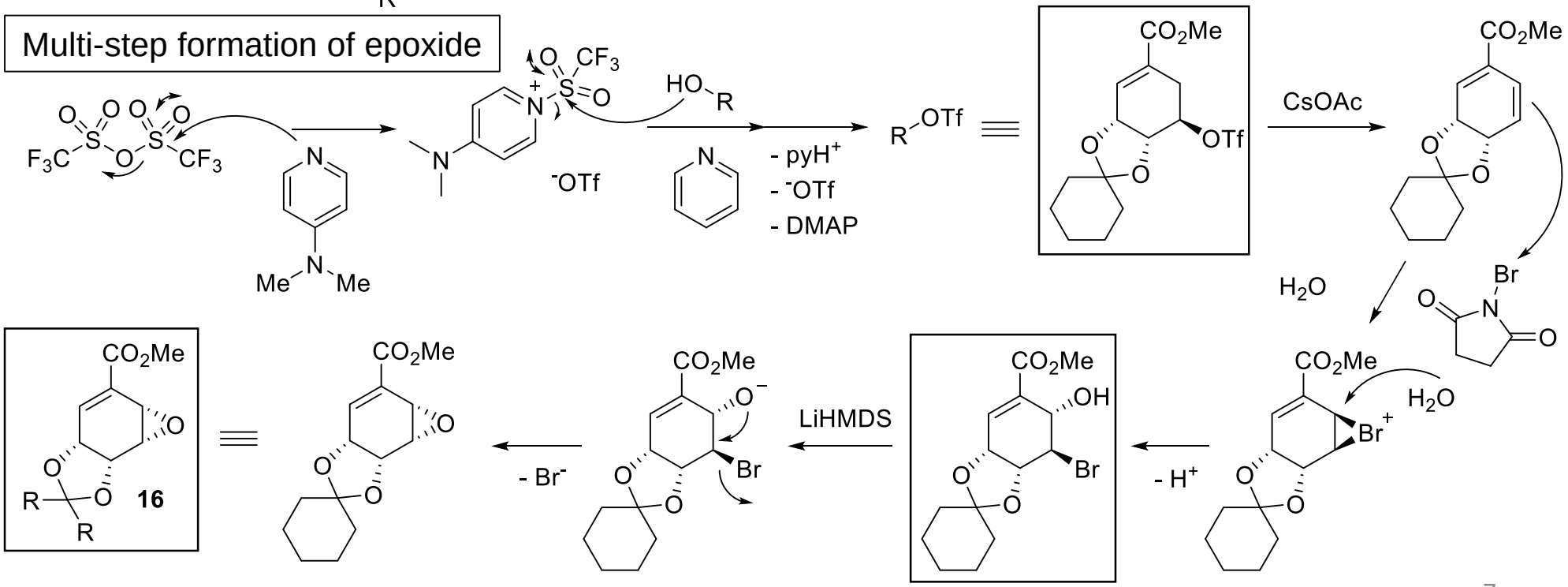




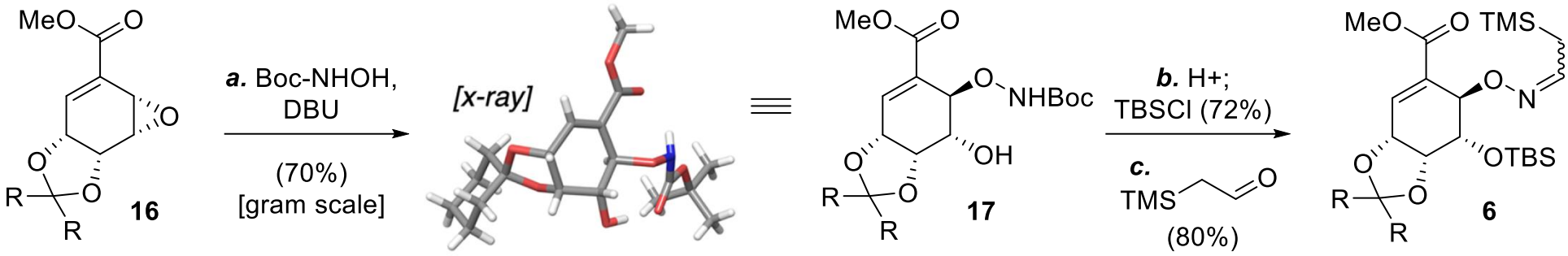

## Esterification and 1,2-diol protection



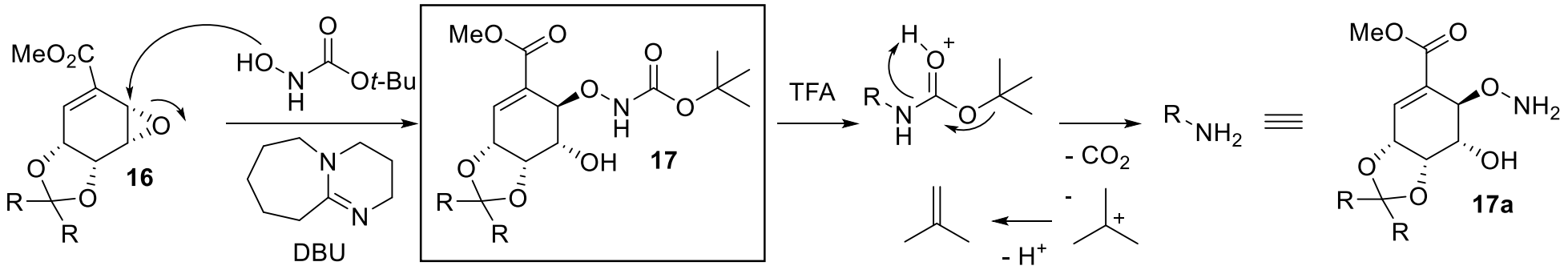

## Multi-step formation of epoxide



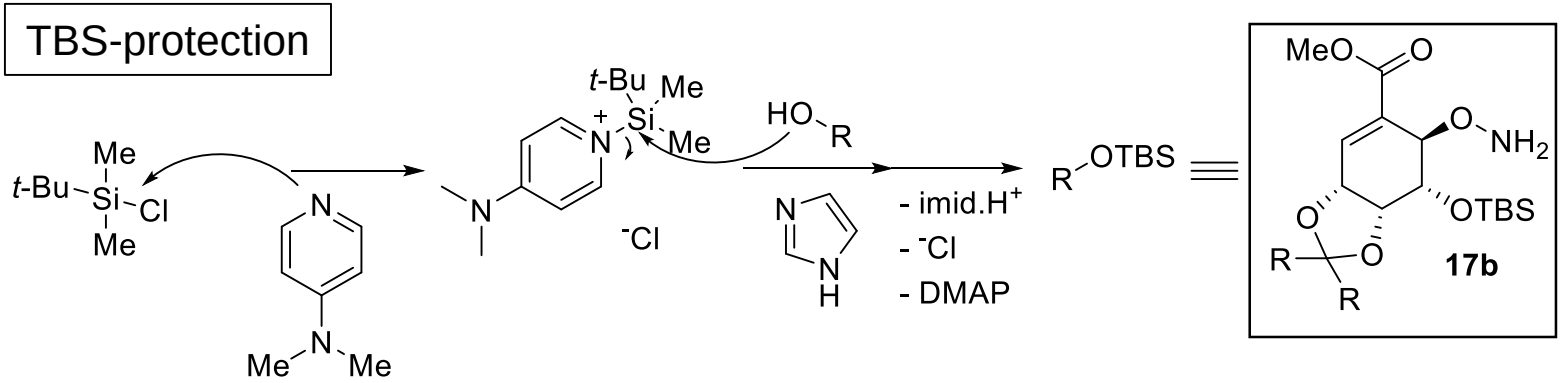

Mizuki, K.; Iwahashi, K.; Murata, N.; Ikeda, M.; Nakai, Y.; Yoneyama, H.; Harusawa, S.; Usami, Y. Synthesis of Marine Natural Product (−)-Pericosine E. *Org. Lett.* **2014**, *16*, 3760–3763.



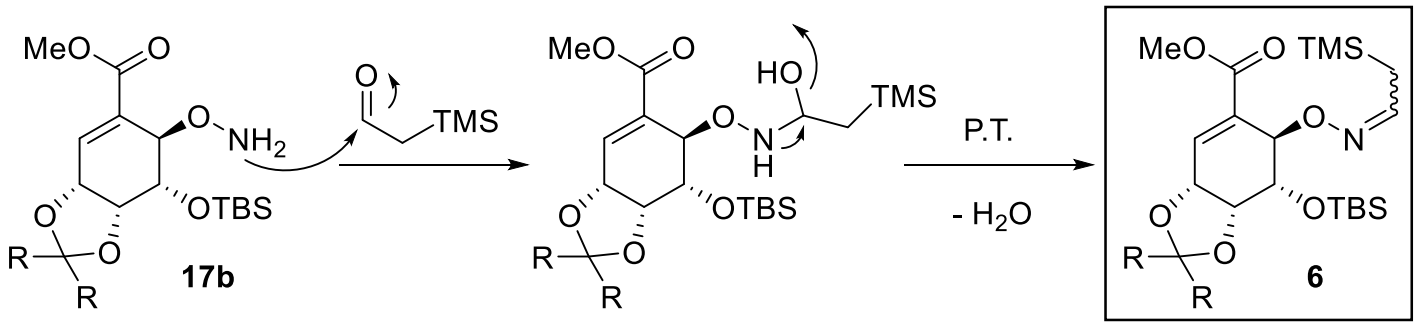

## Regioselective nucleophilic ring-opening of epoxide and Boc deprotection

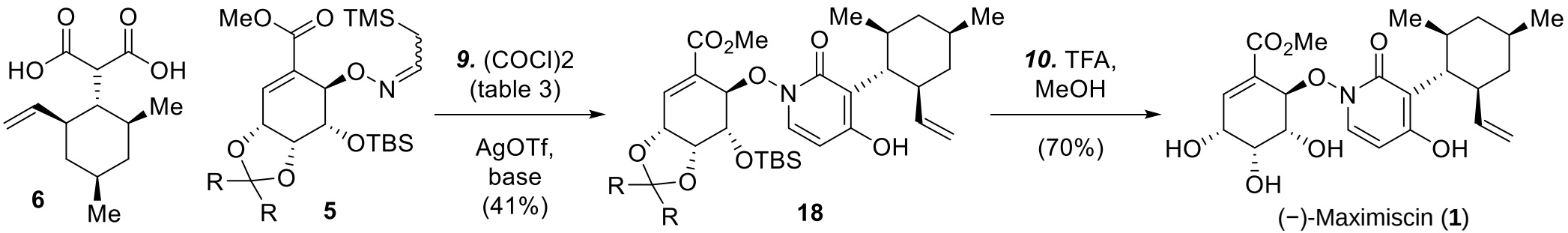



## TBS-protection




## Imination






## Di-acid activation, “Aza-Sakurai” cyclization, and final deprotection