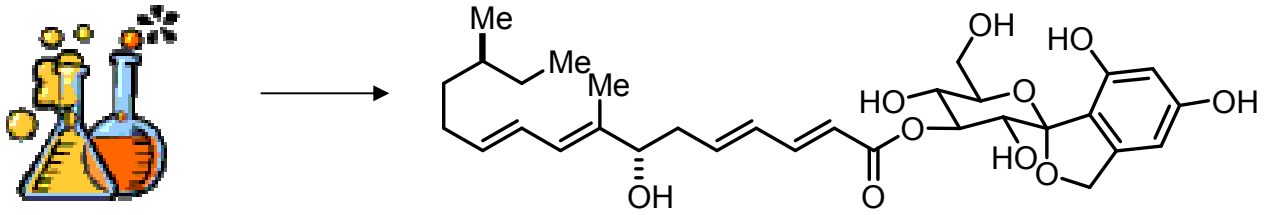
Total Synthesis of Papulacandin D

Scott E. Denmark, Christopher S. Regens and Tetsuya Kobayashi

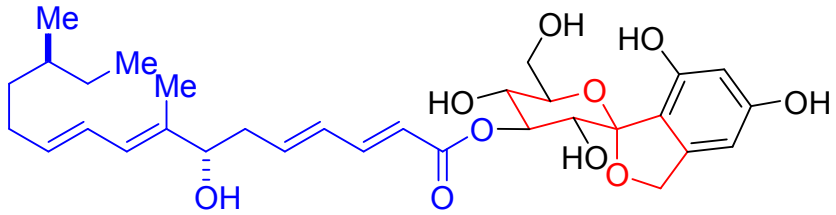


Journal Club Presentation

4/9/2007

Marija Manojlovic

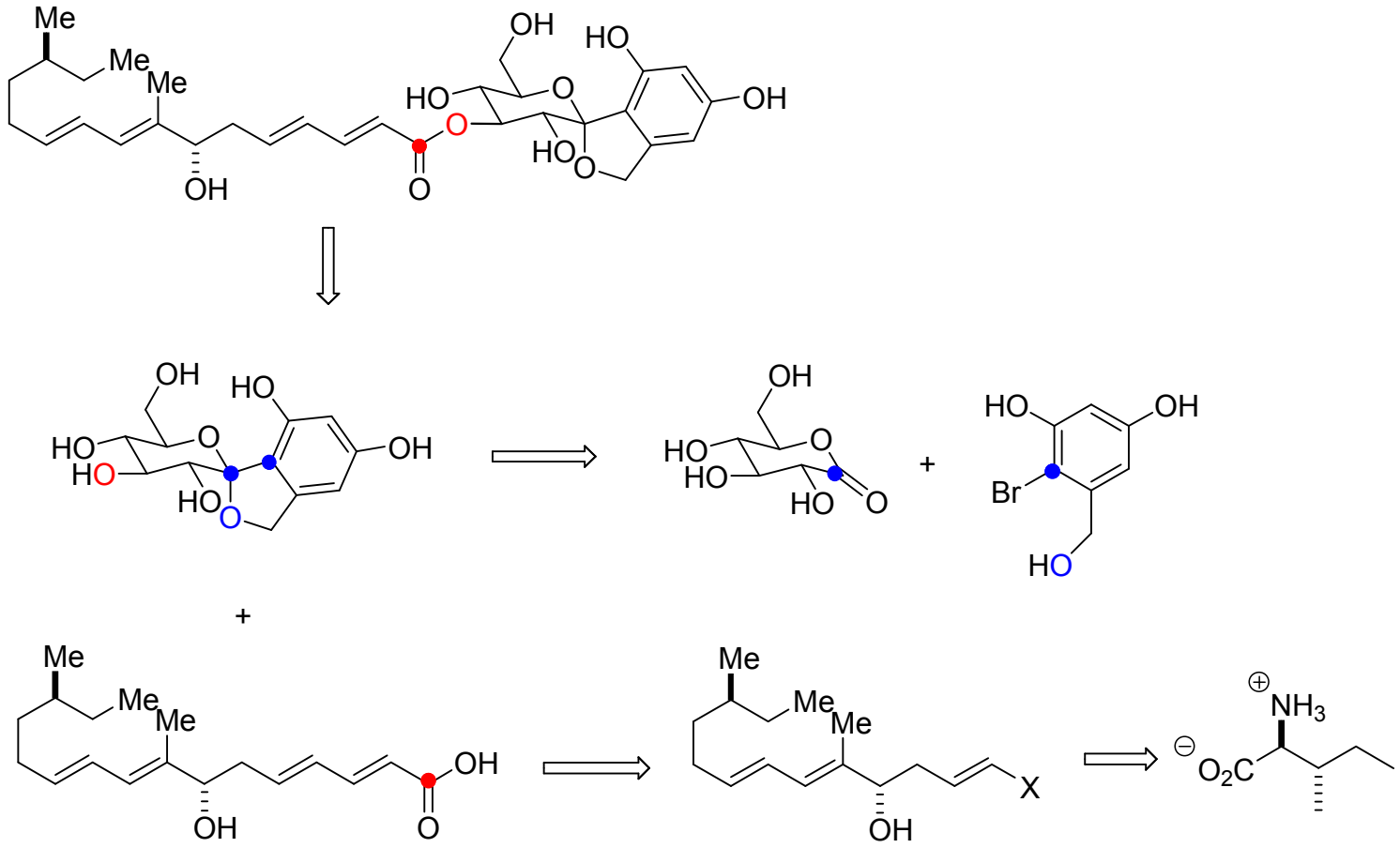
Papulacandin D



- Glycolipid isolated by Trexler in 1977 from the fermentation broth of *Papularia spherosperma*, together with papulacandins A, B, C and E
- Characteristic 1,7-dioxaspiro[5.4]decane skeleton with an aryl-β-D-C-glycopyranoside derived from 5-(hydroxymethyl)resorcinol
- Branched, 18-carbon unsaturated fatty acid ester
- Potent *in vitro* antifungal activity against *Candida albicanis, C. tropicalis, Pneumocystis carinii* and related microorganisms

Denmark, *JACS* **2007**, *129*, 2774.

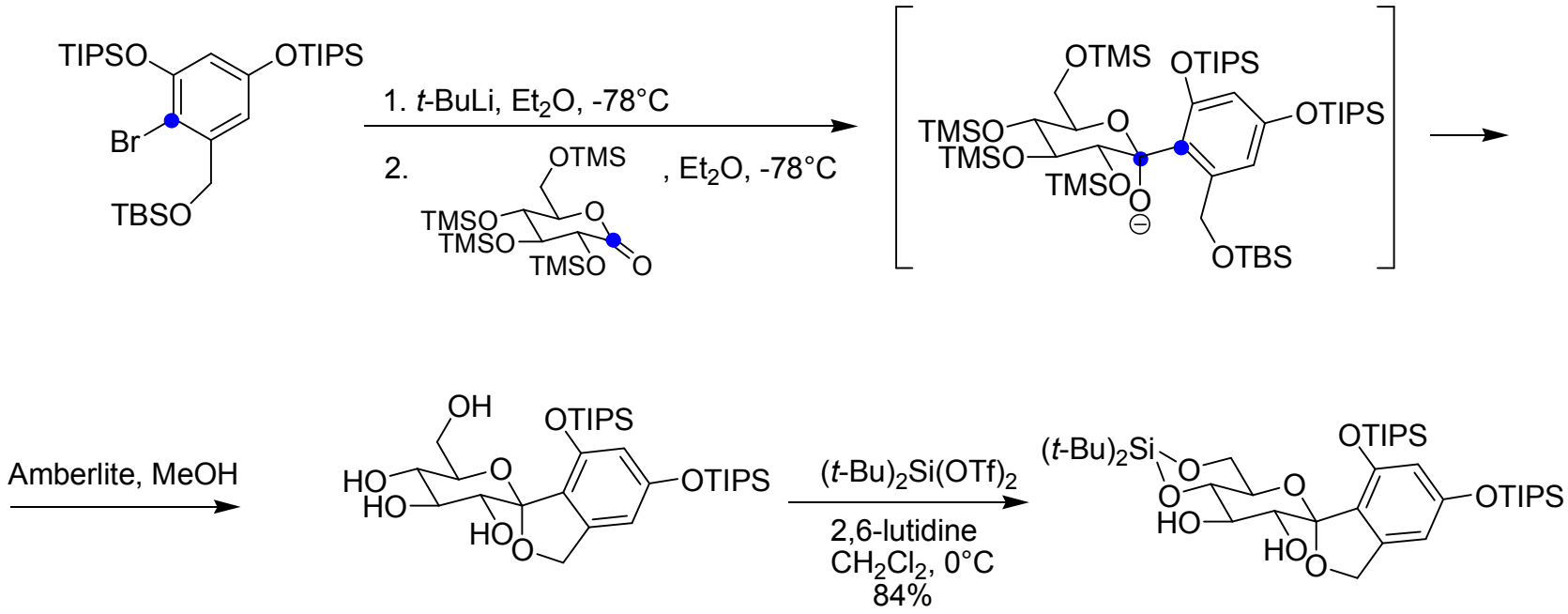
The First Total Synthesis of Papulacandin D - Barrett



Barrett, *JOC* **1996**, *61*, 1082.

The First Total Synthesis of Papulacandin D - Barrett

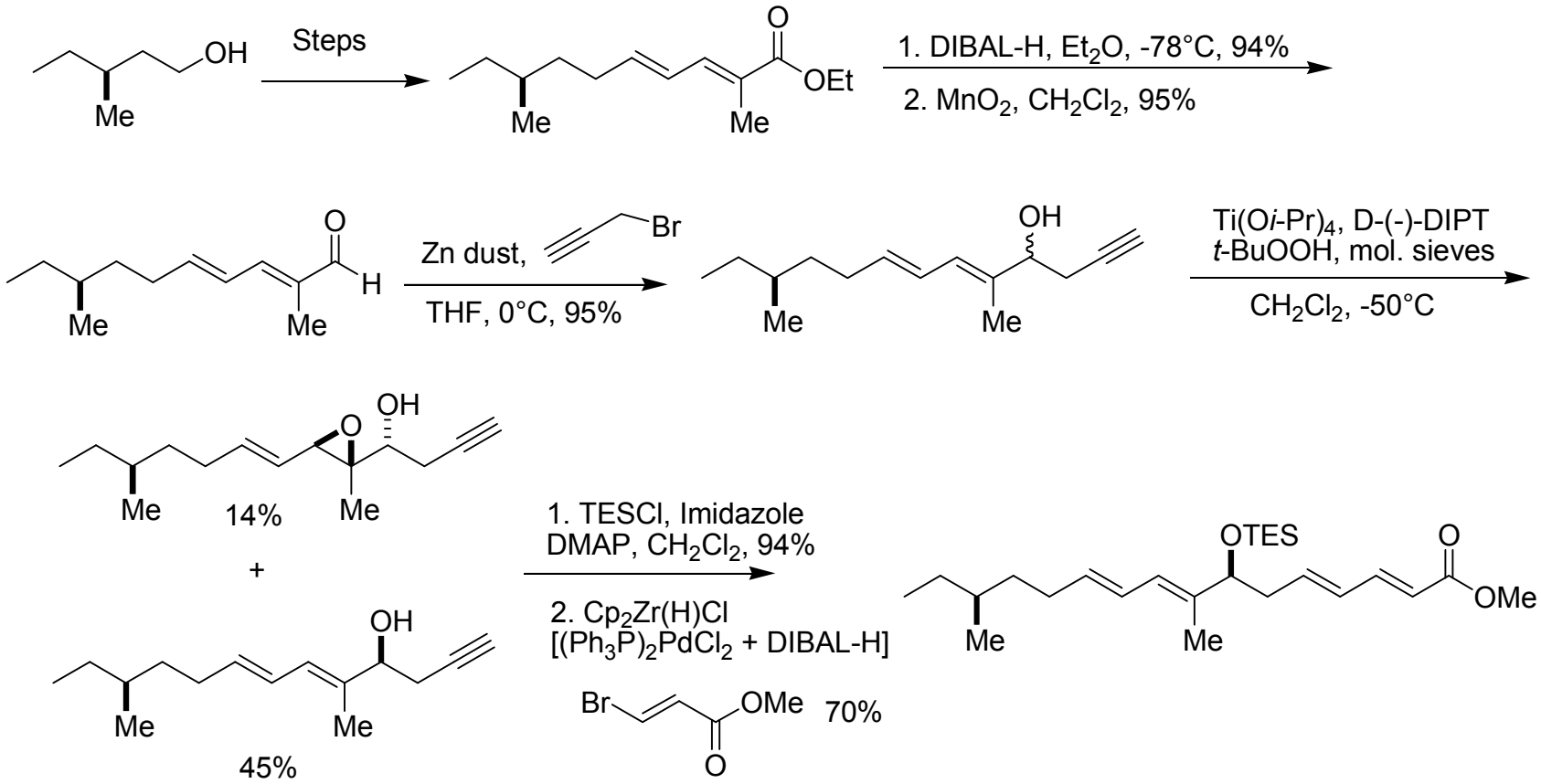
Synthesis of spiroketal



Barrett, *JOC* **1996**, *61*, 1082.

The First Total Synthesis of Papulacandin D - Barrett

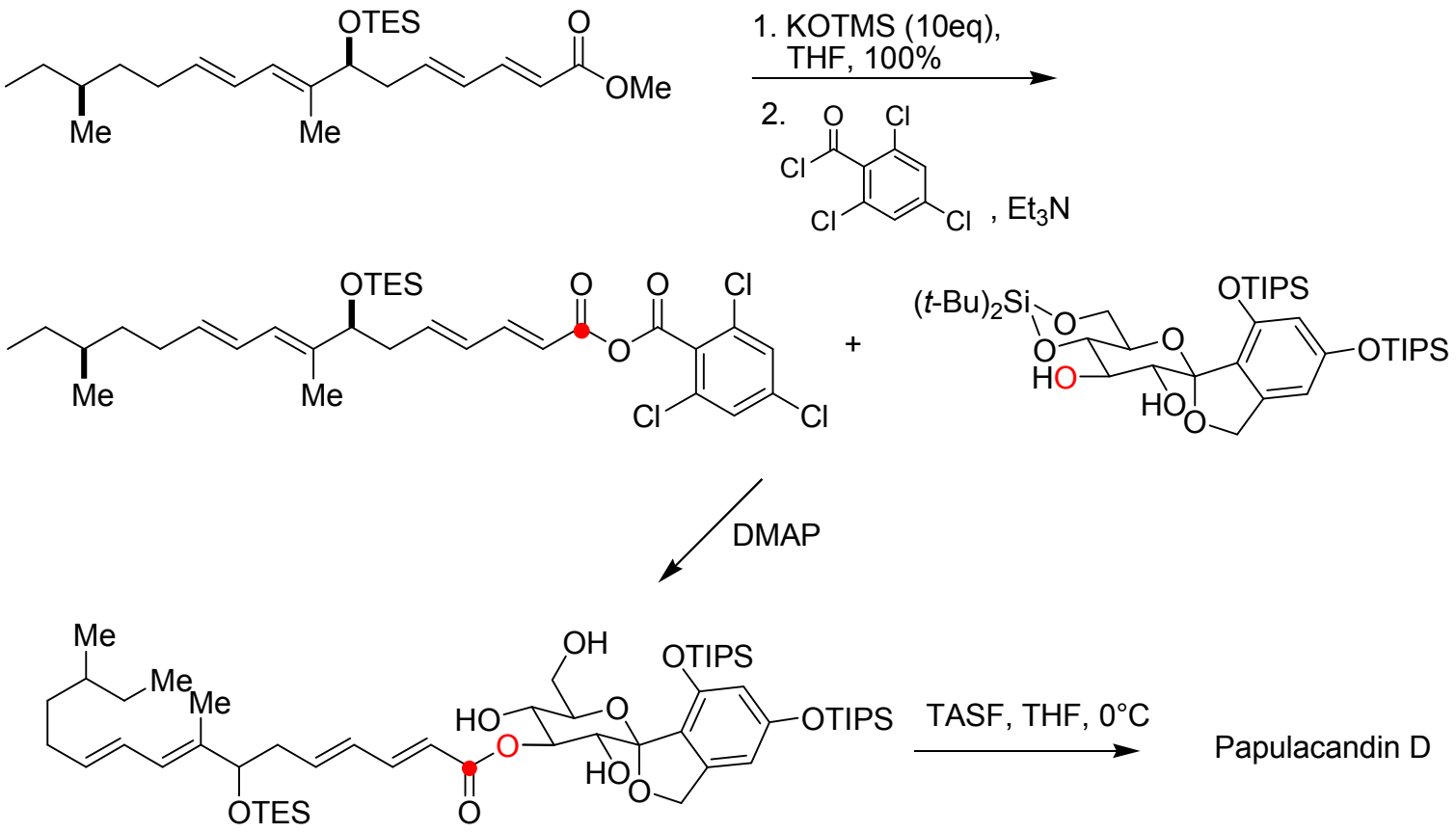
Synthesis of the side chain



Barrett, *JOC* **1996**, *61*, 1082.

The First Total Synthesis of Papulacandin D - Barrett

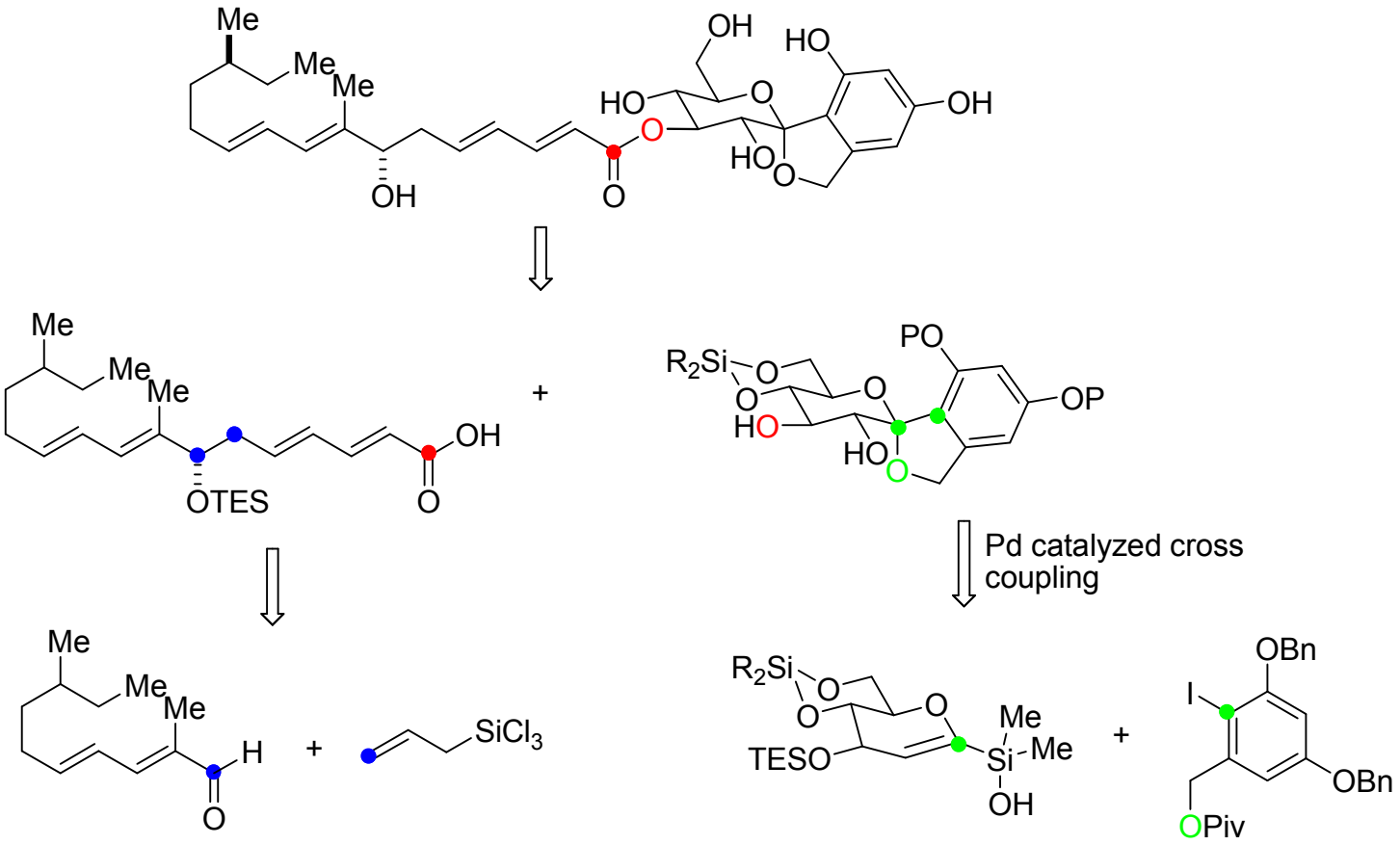
Completion of the synthesis



Barrett, *JOC* **1996**, *61*, 1082.

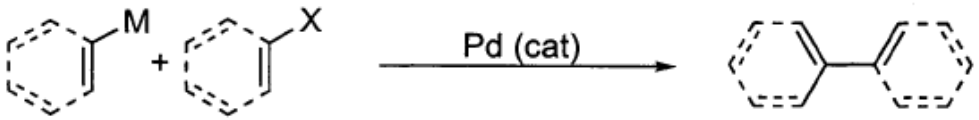
Denmark's Synthesis of Papulacandin D

Retrosynthetic analysis



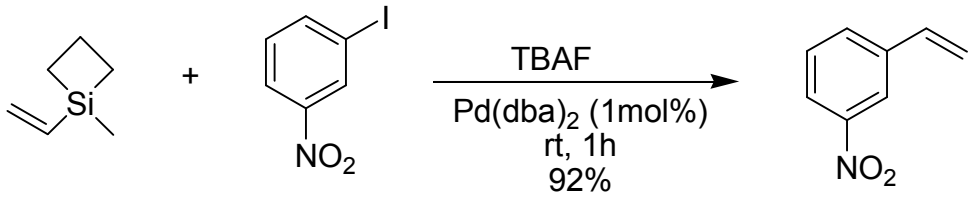
Denmark, *JACS* **2007**, *129*, 2774.

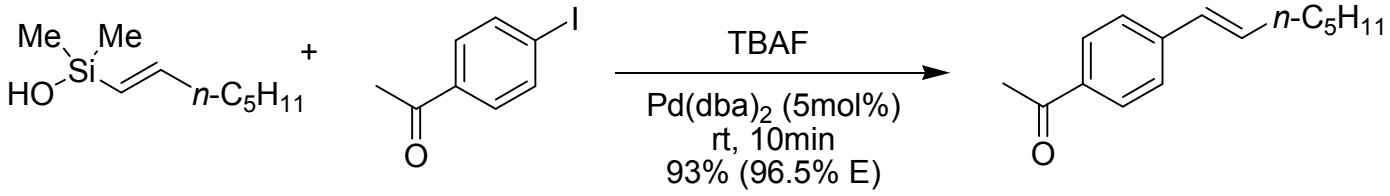
Silicon-Based Pd Catalyzed Cross-Couplings



M = SnR_3 (*Stille-Migita-Kosugi*)
BR_2 or $B(OR)_2$ (*Suzuki-Miyaura*)
$SiR_{(3-n)}F_n$ (*Hiyama*)
$Si(OR)_3$ (*Tamao-Ito*)

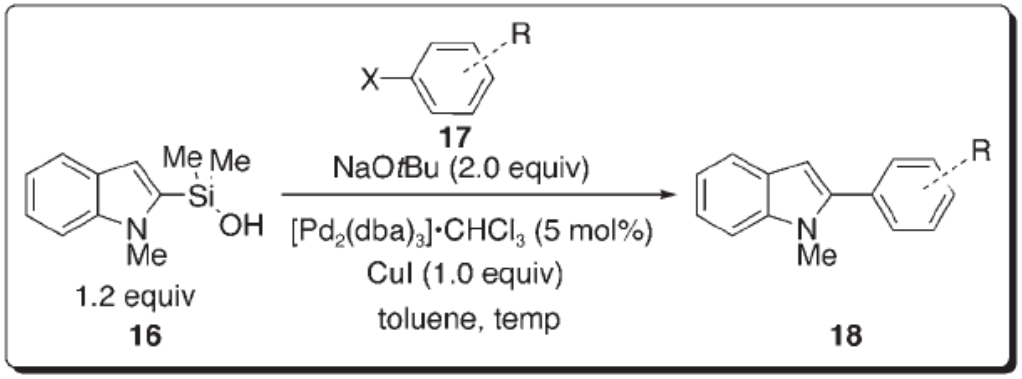
X = I, Br, Cl, OTf

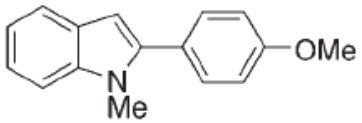




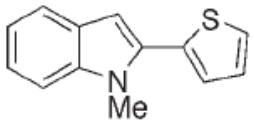
Denmark, *Acc. Chem. Res*. **2002**, *35*, 835.

Fluoride-free Conditions

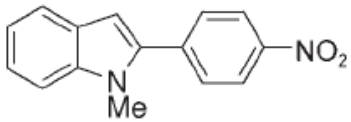




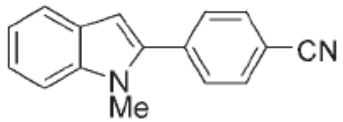
19
3 h, RT, 80%
X = I



20
6 h, RT, 73%
X = I



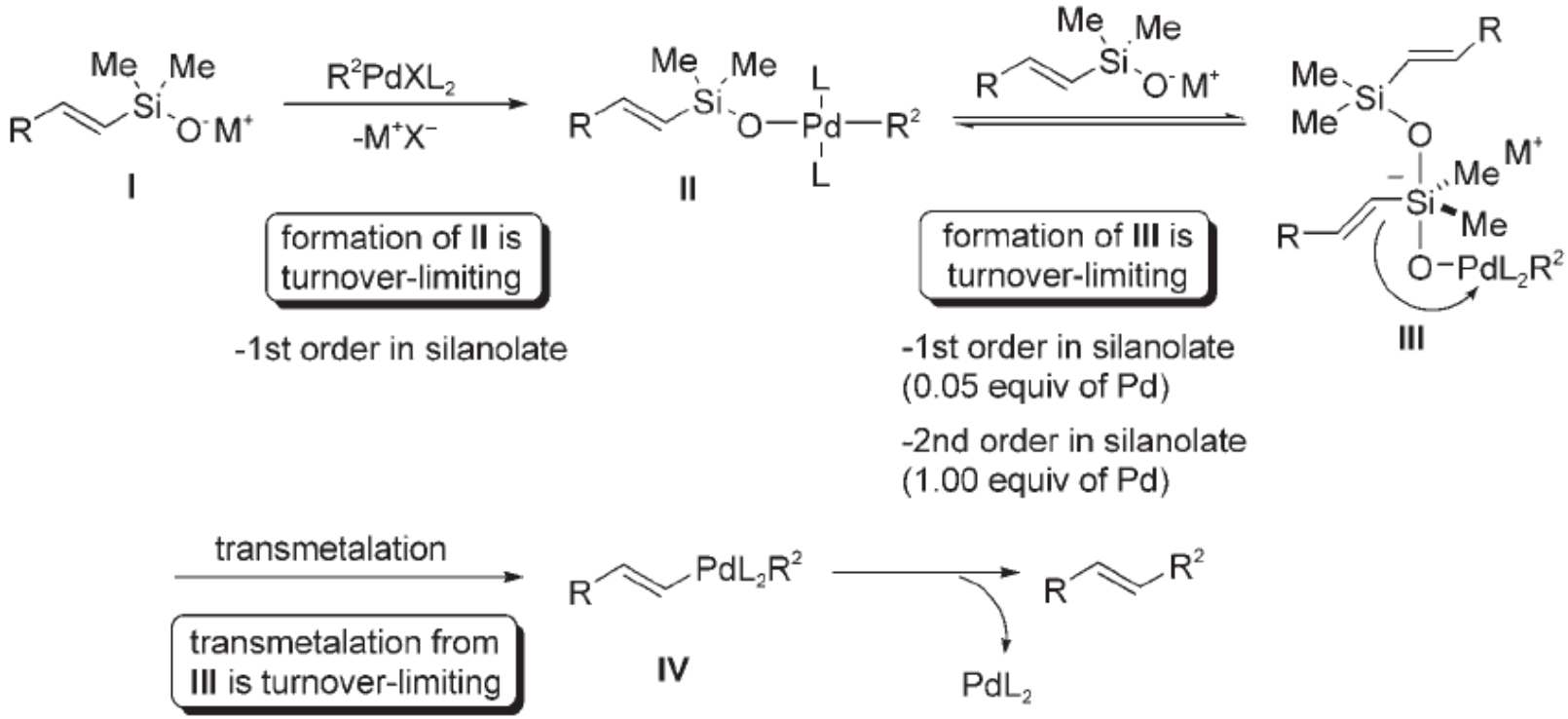
21
20 h, 55 °C, 84%
X = Br



22
20 h, 55 °C, 80%
X = Br

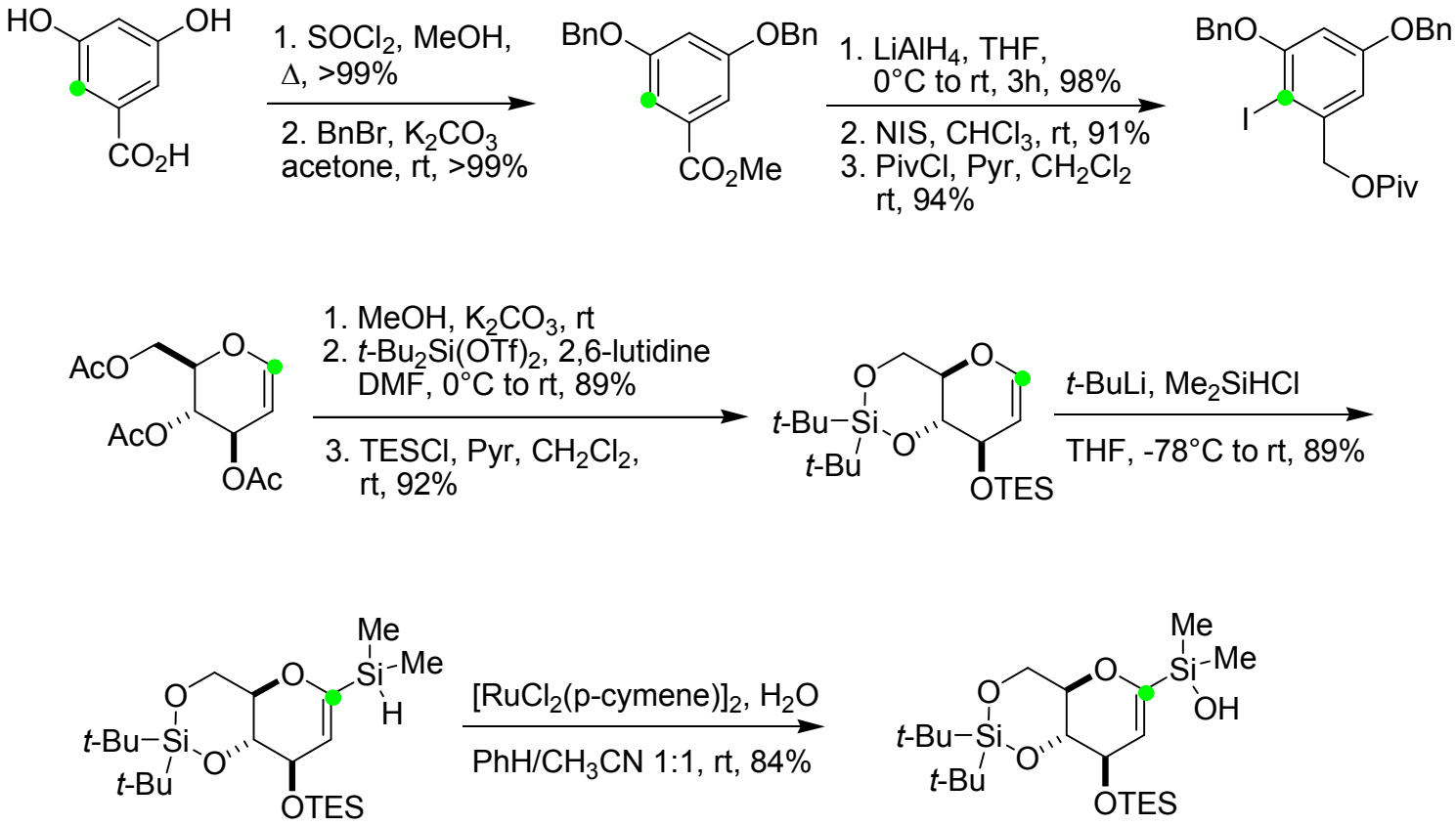
Denmark, *Chem. Eur. J.* **2006**, *12*, 4954.

Fluoride-free Conditions - Mechanism



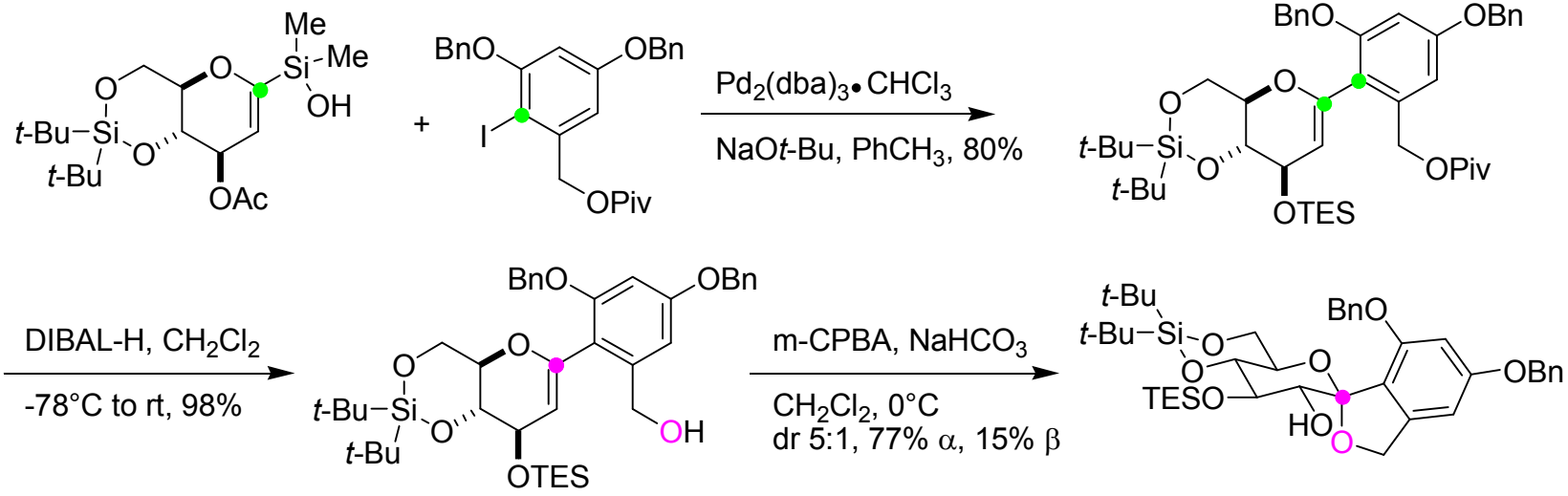
Denmark, *Chem. Eur. J.* **2006**, *12*, 4954.

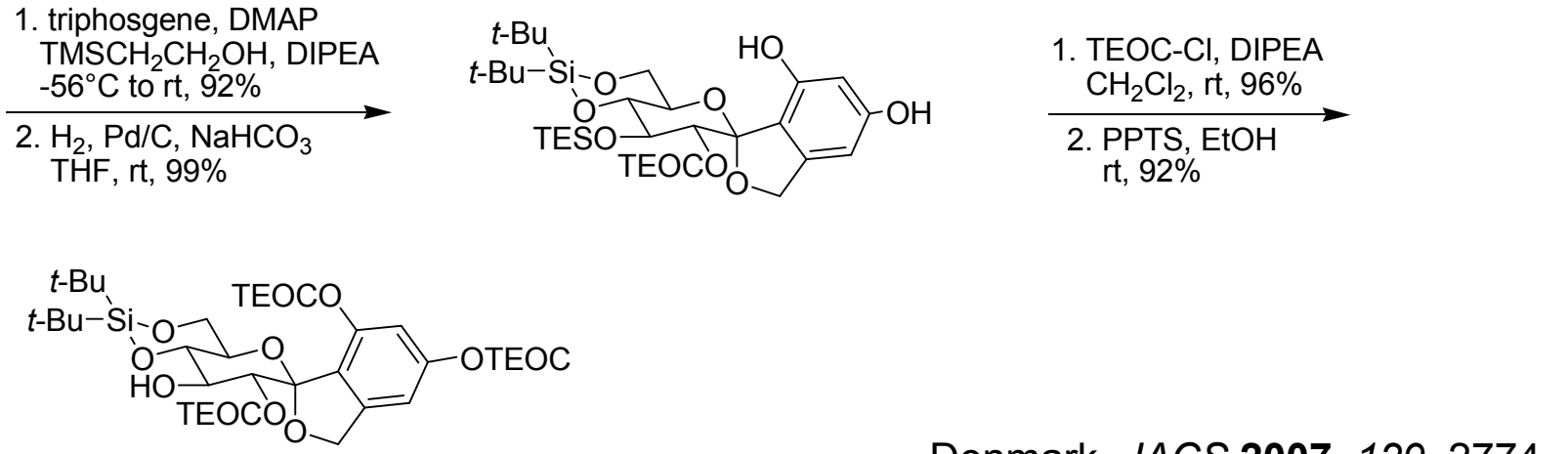
Synthesis of Coupling Partners



Denmark, *JACS* **2007**, *129*, 2774.

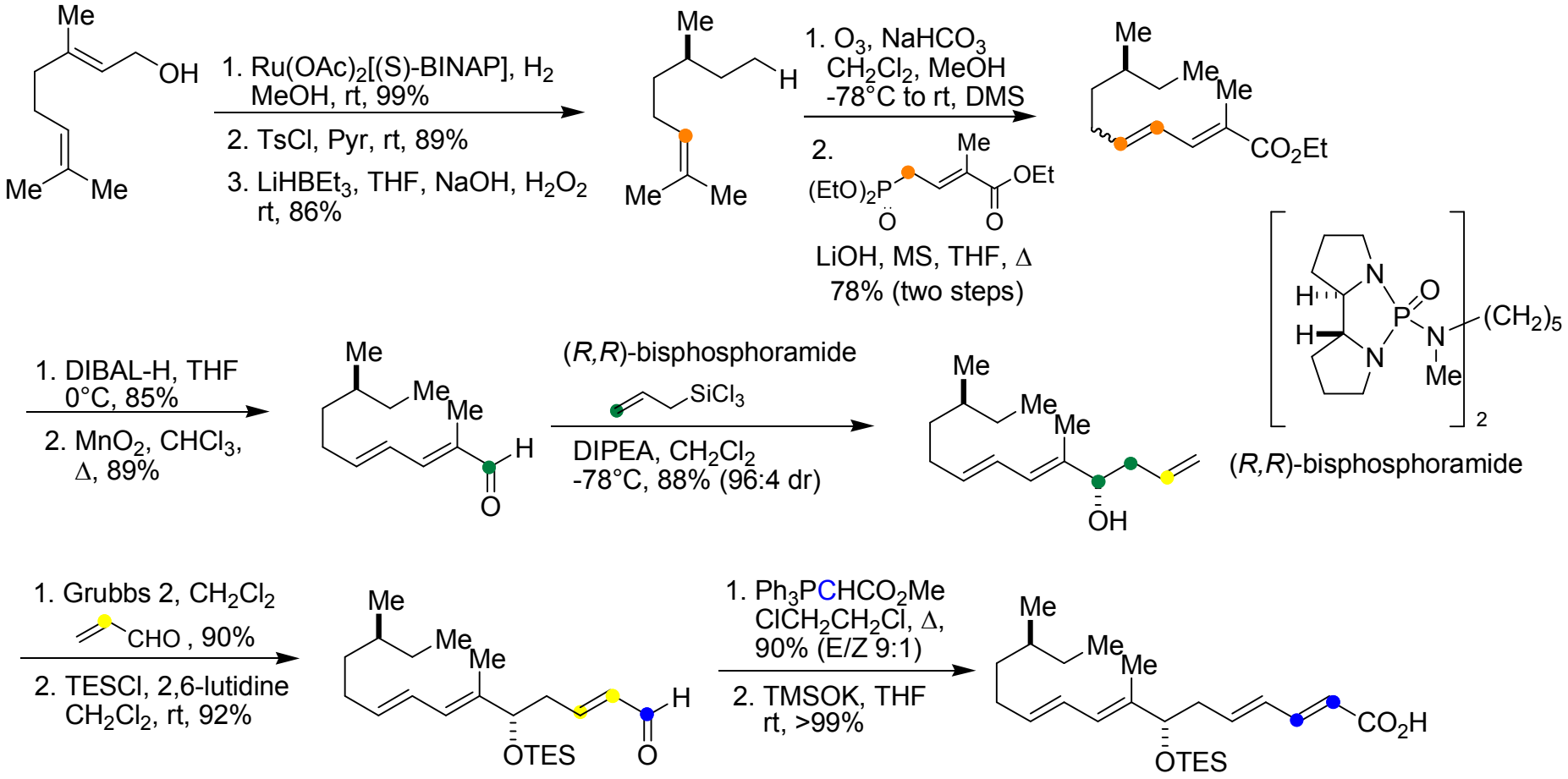
Silicon-Based Cross-Coupling





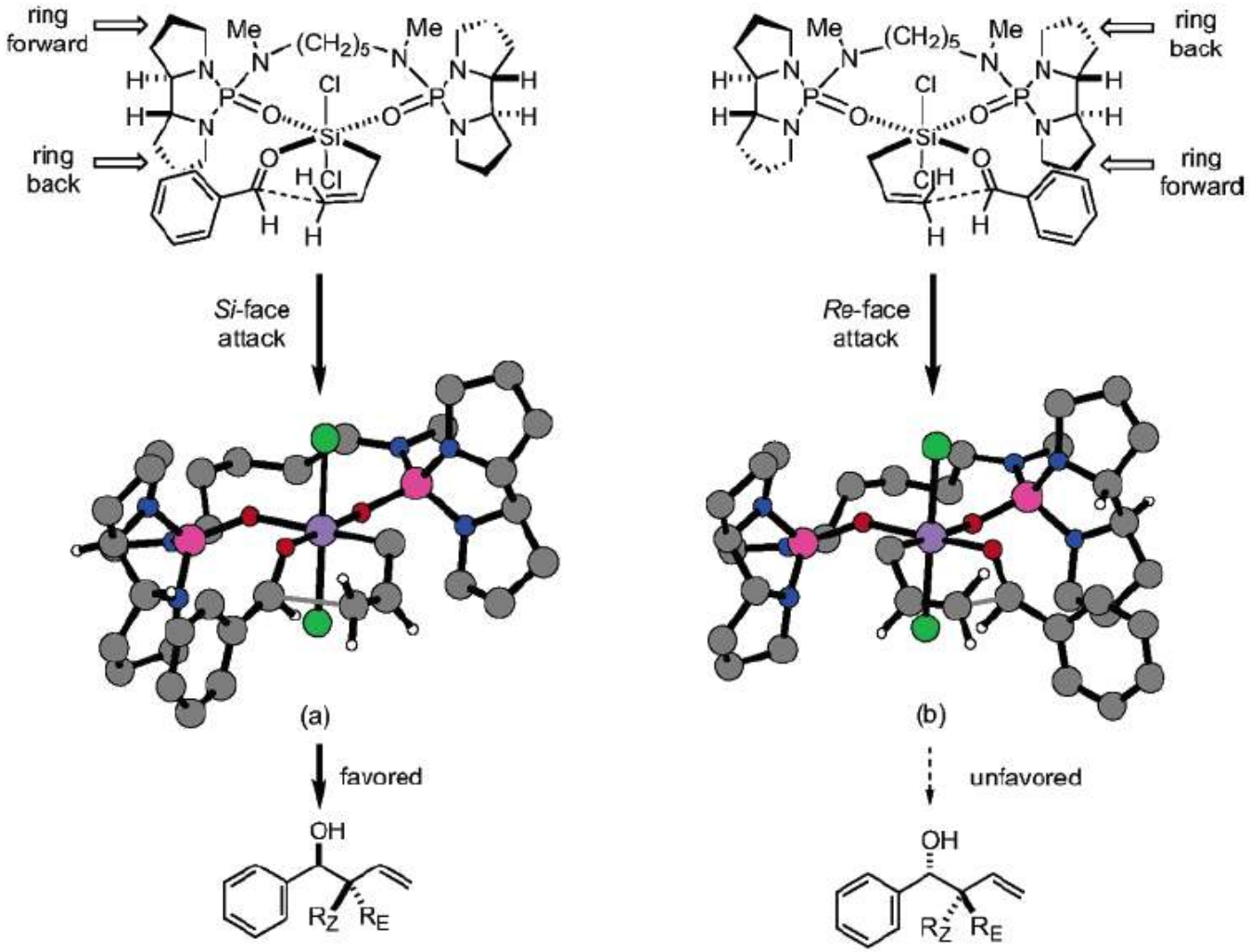
Denmark, *JACS* **2007**, *129*, 2774.

Side Chain Synthesis



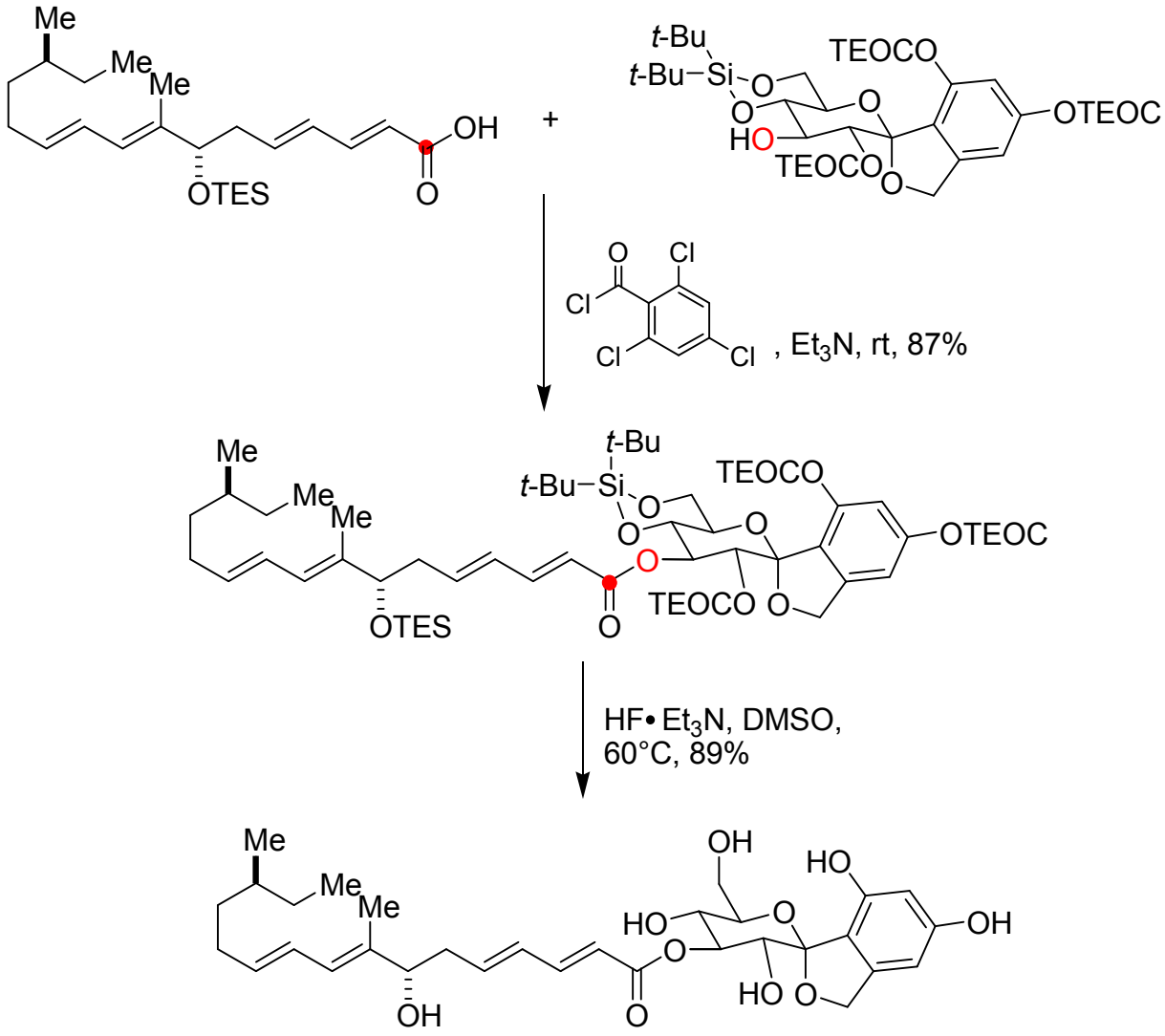
Denmark, *JACS* **2007**, *129*, 2774.

Allylation Selectivity



Denmark, *JOC* **2006**, *61*, 1523.

End Game



(+)-papulacandin D

Denmark, *JACS* **2007**, *129*, 2774.

Conclusion

- Asymmetric synthesis of Papulacandine D was achieved
- The Denmark group synthesis is longer than the previous one, but the overall yield is significantly improved (31 steps, 5.6% vs. 24 steps, 0.6%)
- Fluoride-free silicon-based cross-coupling and enantioselective silyl-allylation methodologies developed in the Denmark group are applied in a natural product synthesis