Literature Report V

Total Synthesis of (+/–)- and (+)-Euphohyrisnoid A

Reporter : Yu Yang
Checker : Xin-Yu Zhan

Ye, Z.-H.; Ao, Q.-Q.; Peng, Y.-C.; Liu, X.; Lin, X.; Li, C.-C.* *J. Am. Chem. Soc.* **2026**, *148*, 5940-5945

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CV of Prof. Chuang-Chuang Li (李闯创)

Background:

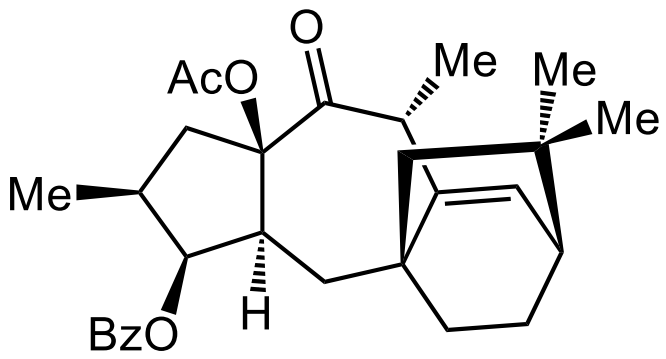
- 1997-2001 B.S., China Agricultural University
- 2001-2006 Ph.D., Peking University
- 2006-2008 Postdoc., The Scripps Research Institute
- 2008-2013 Associate Professor, Peking University Shenzhen Graduate School
- 2013-now Professor, Southern University of Science and Technology

Research:

- Total Synthesis of Complex Bioactive Natural Products
- Novel Synthetic Methodologies for Guided Natural Products
- Chemical Biology and Medicinal Chemistry of Natural Products

Contents

Introduction



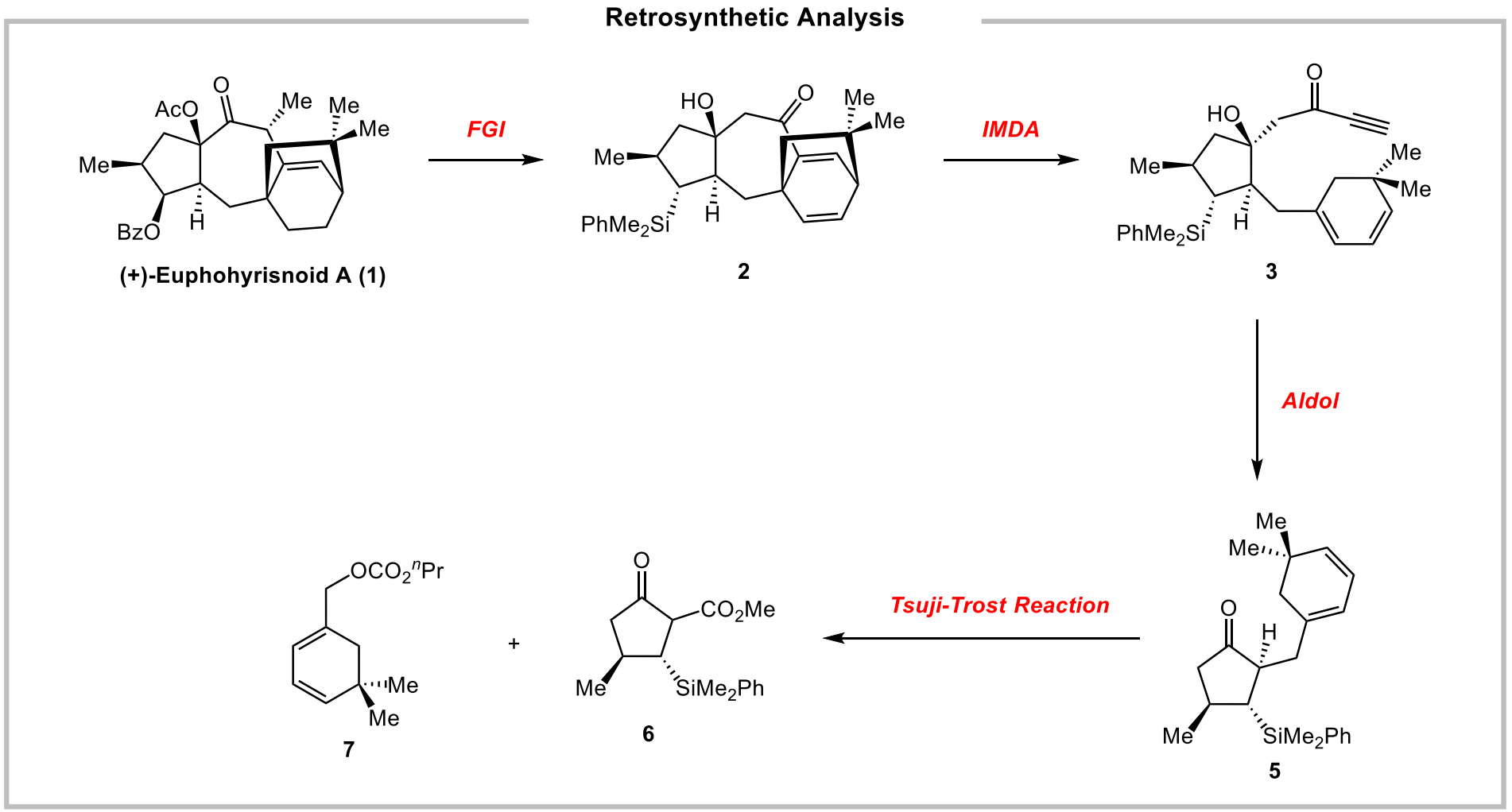
(+)-Euphohyrisnoid A

Euphorbia lathyris

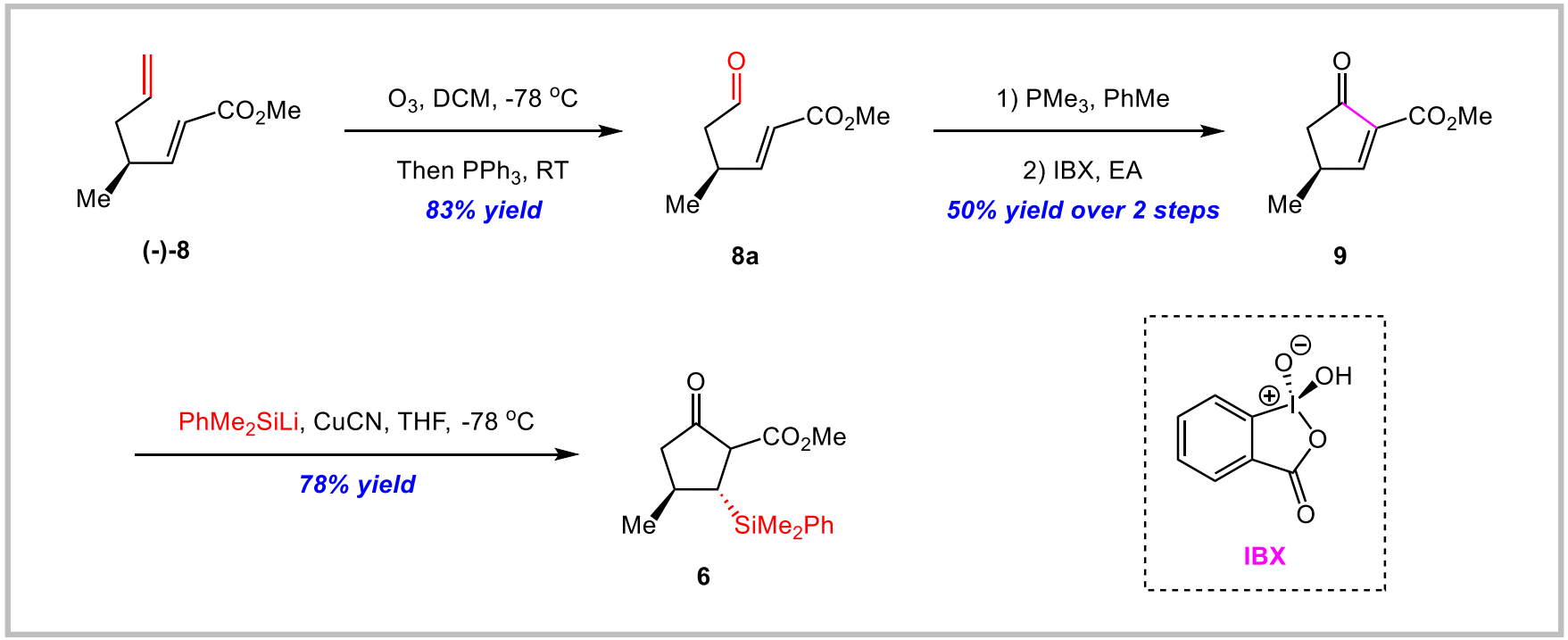
- It was isolated from *Euphorbia lathyris* in 2021;
- It has a new [5/7/6/6] tetracyclic core, with a unique bridged bicyclo[2.2.2] ring system;
- It demonstrated significant antiadipogenic activity.

Huang, D.; Pan, Y.-H.; Yuan, F.-Y.; Tang, G.-H.; Yin, S.* *Org. Lett.* **2021**, *23,* 9602-9605

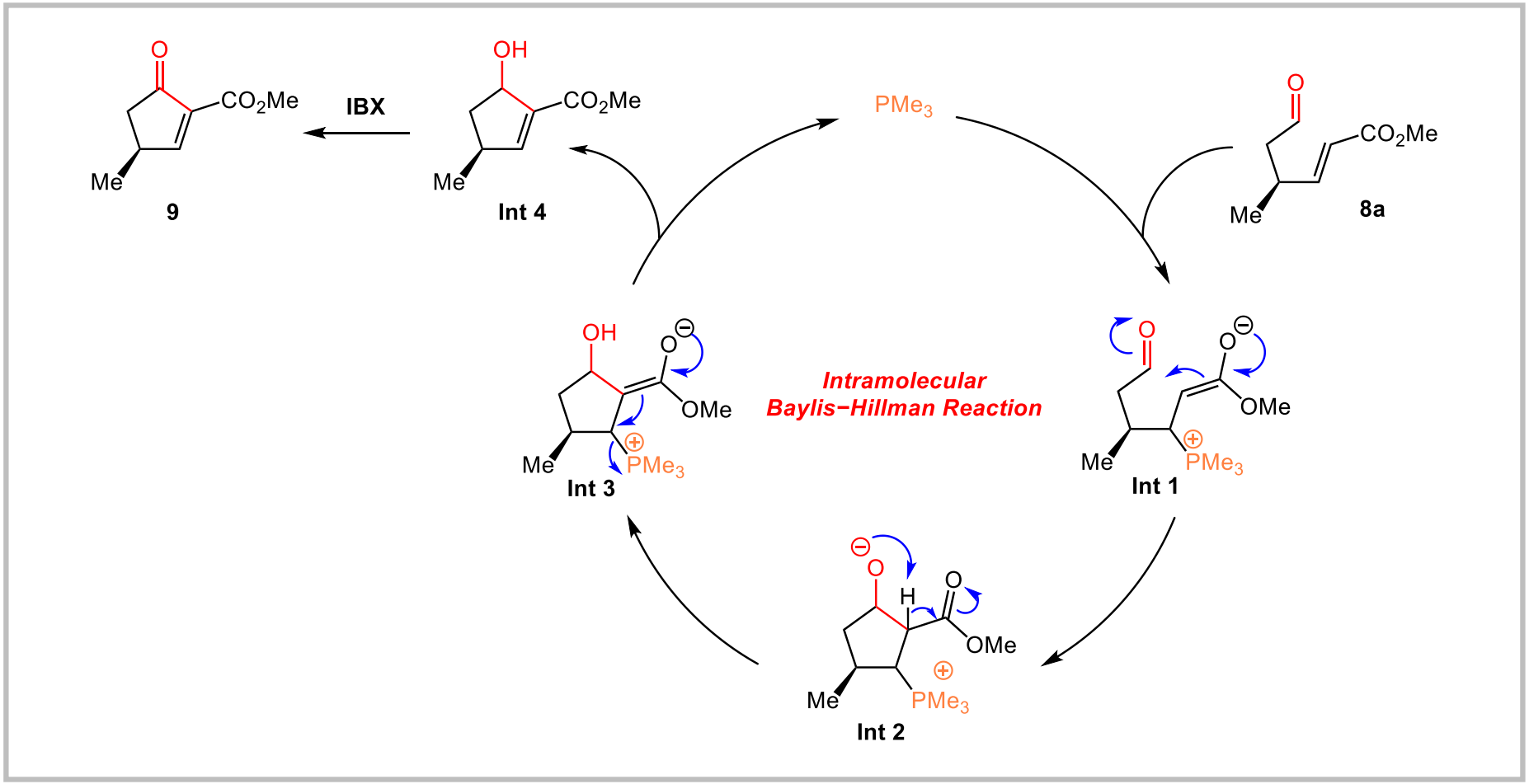
Retrosynthetic Analysis



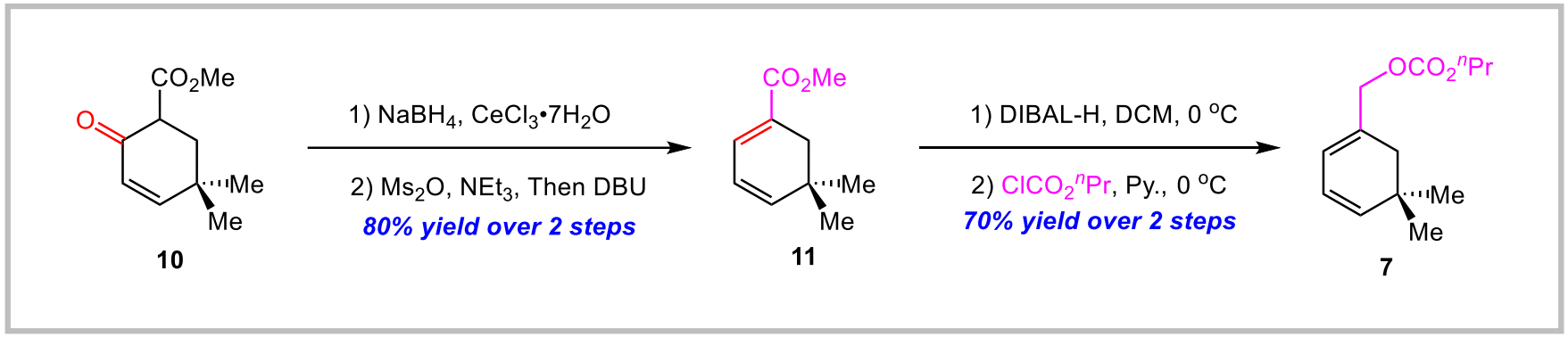
Synthesis of Critical Intermediate 6



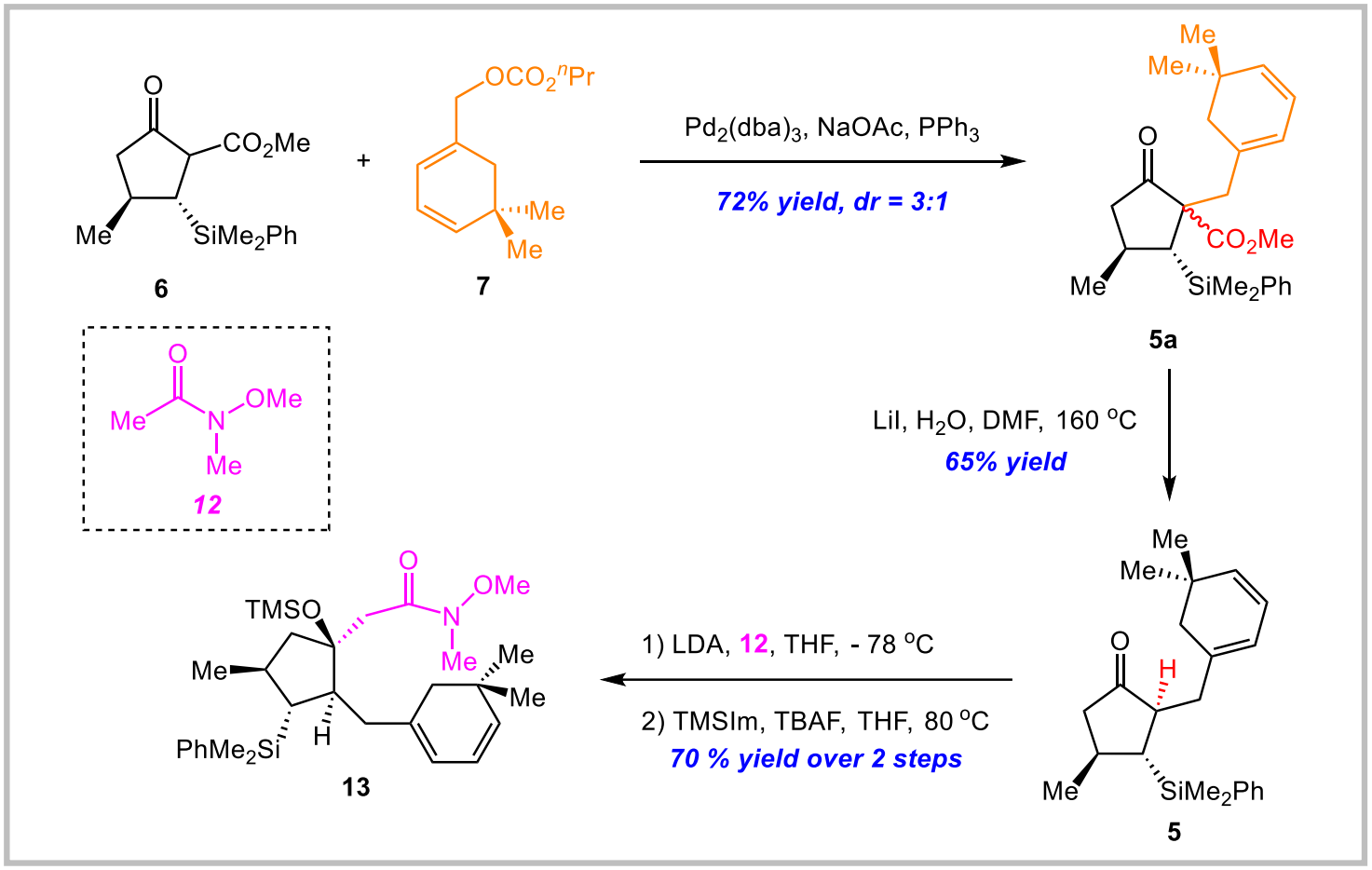
Intramolecular Baylis–Hillman Reaction



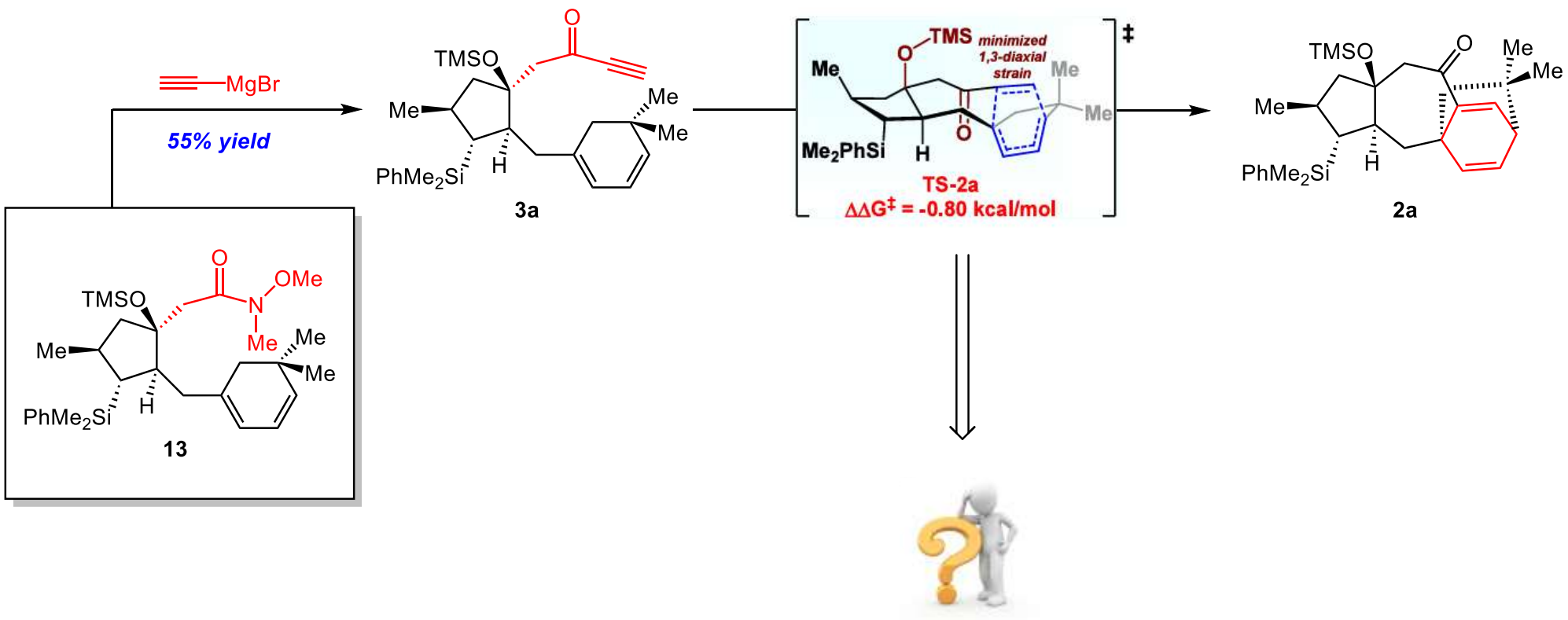
Synthesis of Critical Intermediate 7



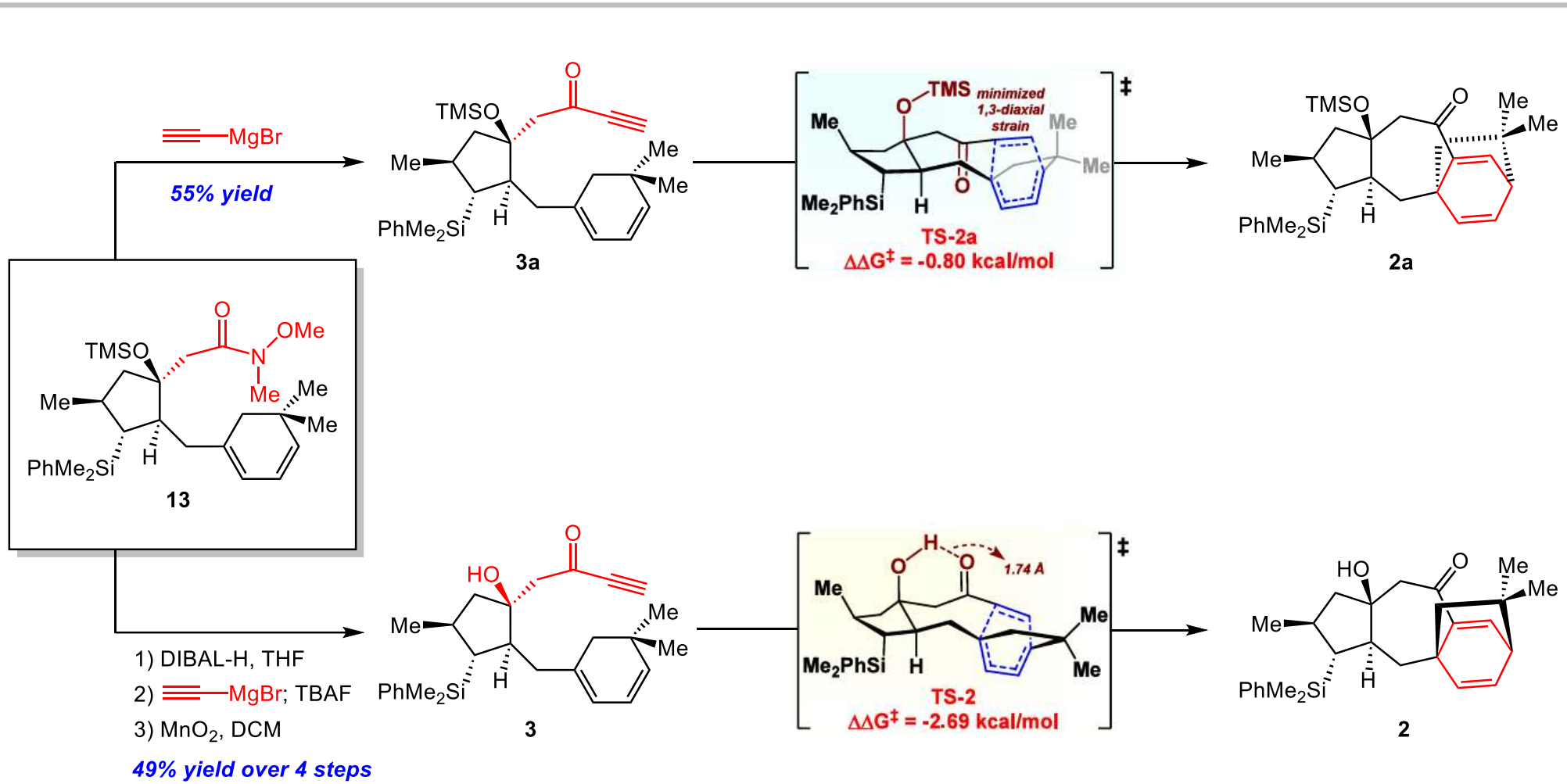
Synthesis of Compound 13



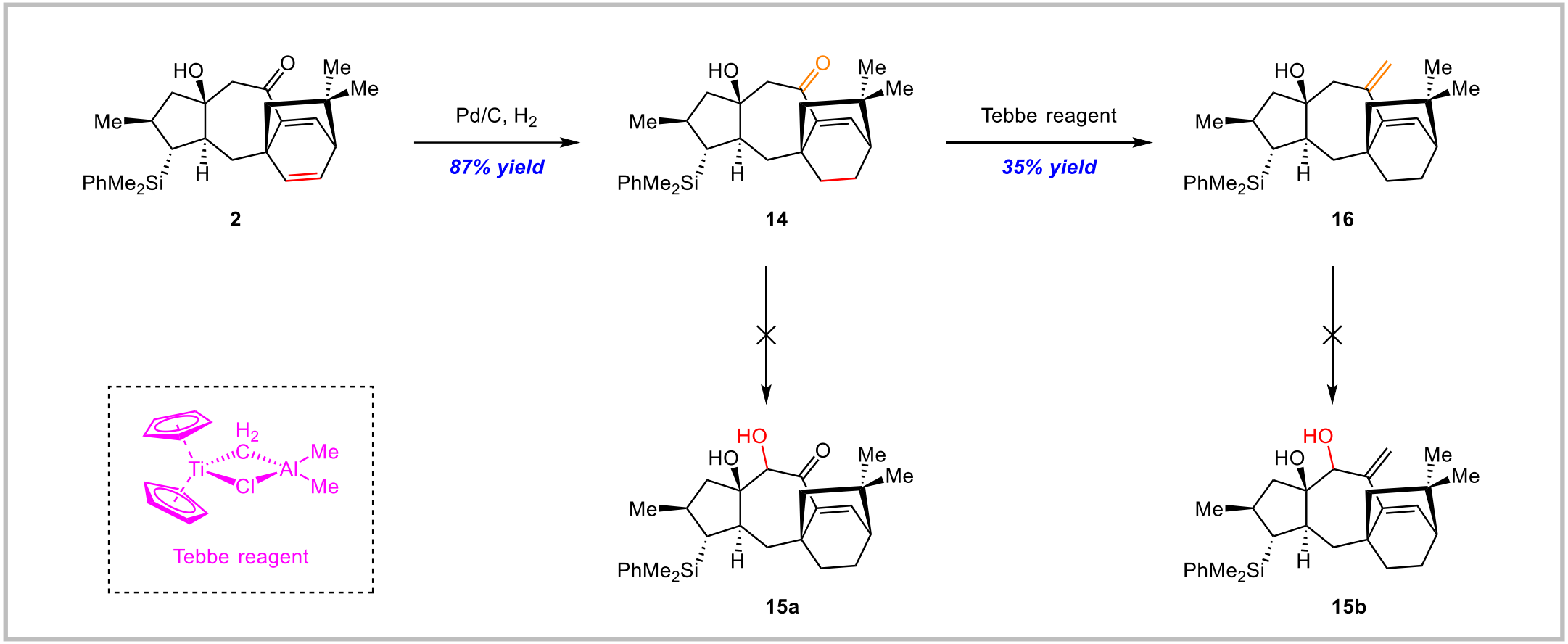
Synthesis of Compound 2



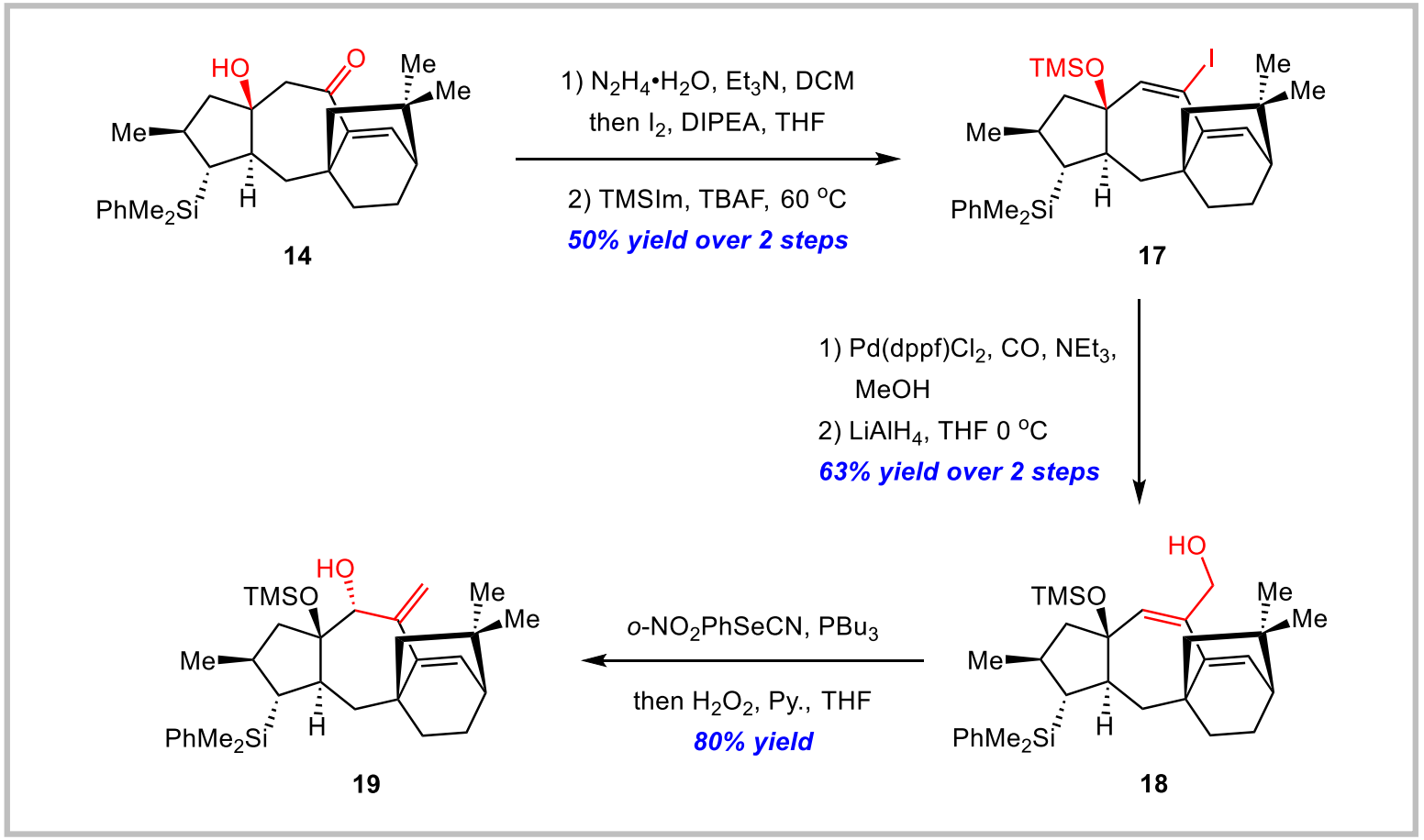
Synthesis of Compound 2



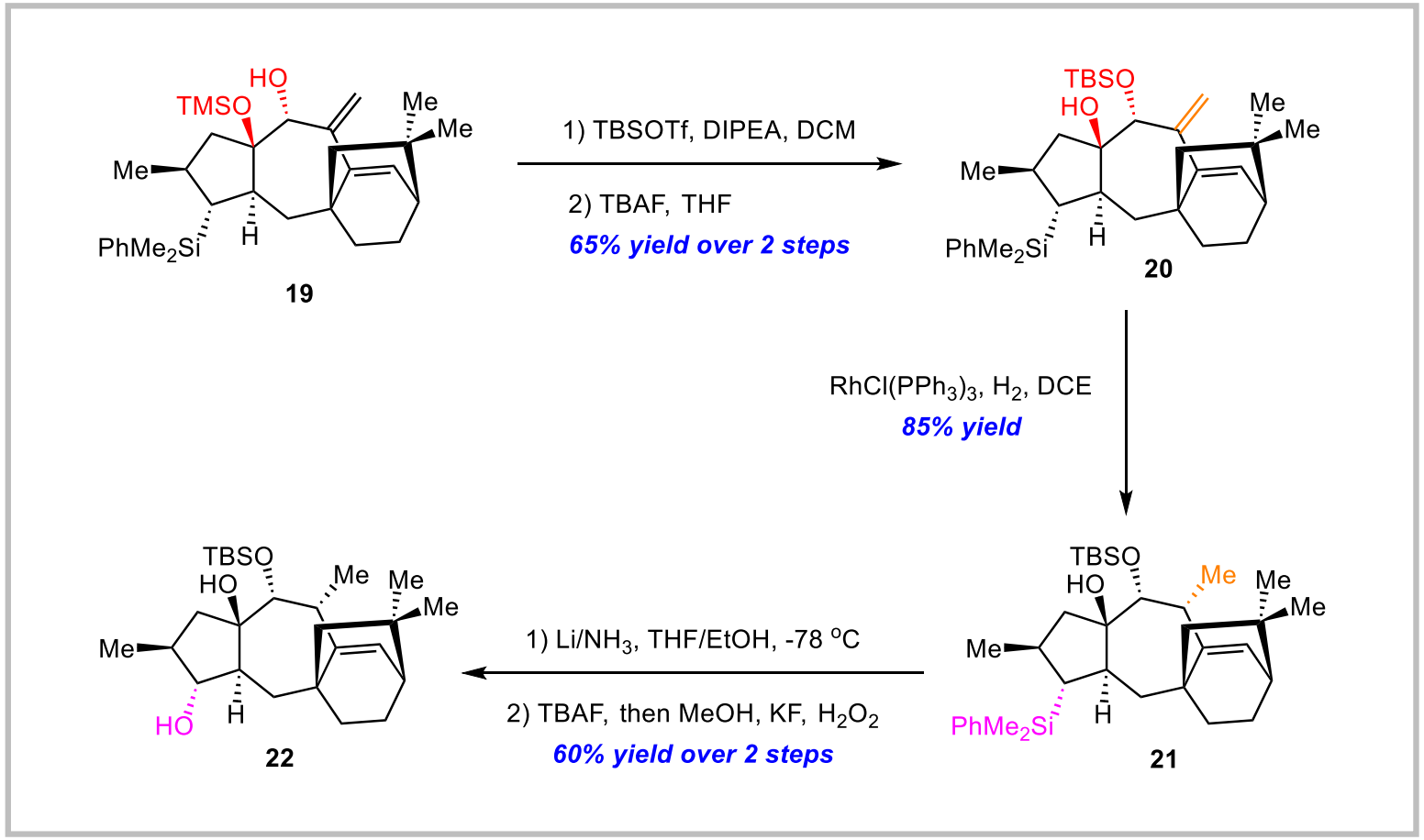
Synthesis of Compound 15



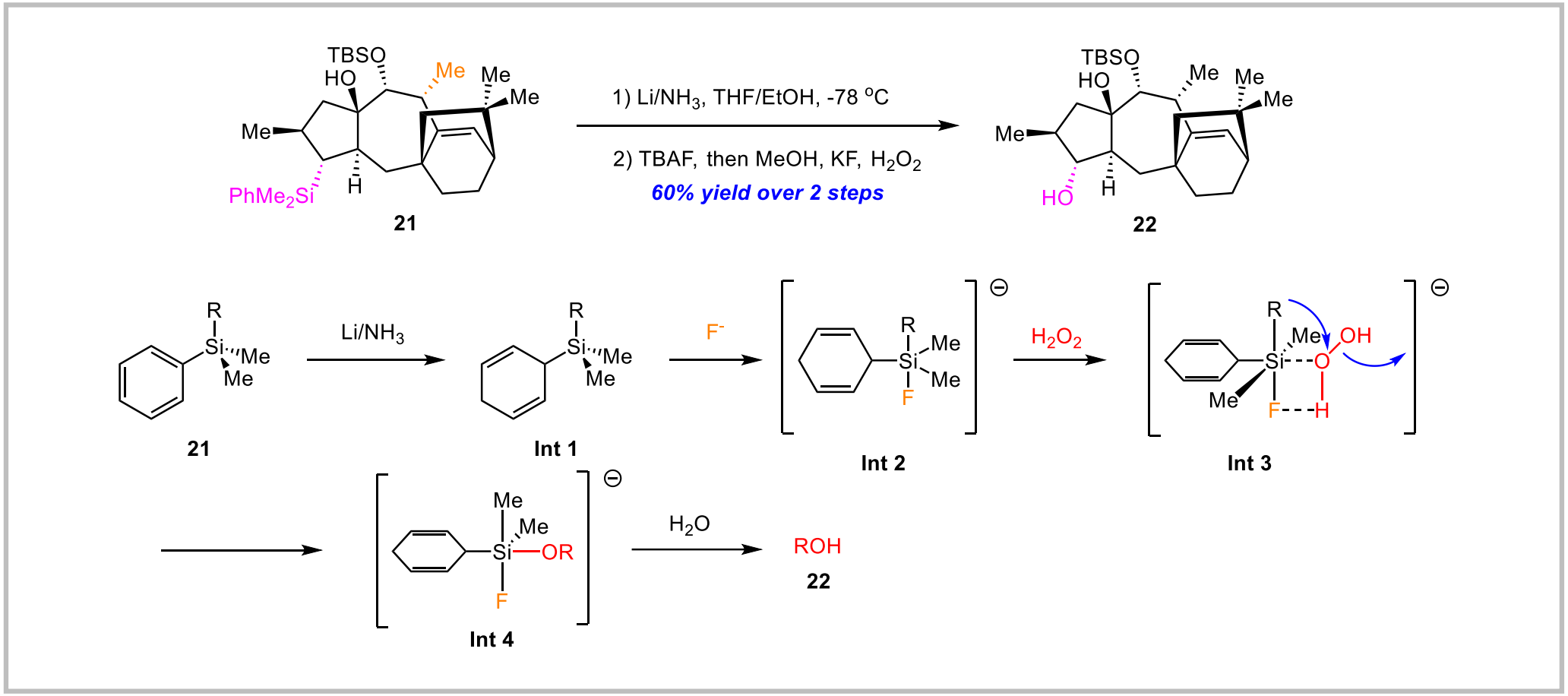
Synthesis of Compound 19



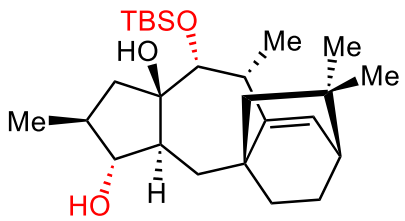
Synthesis of Compound 22



Synthesis of Compound 22



Synthesis of Compound 1

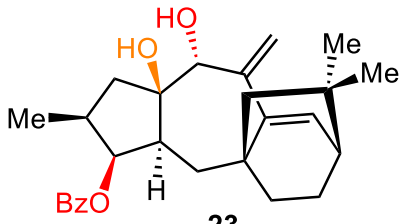


22

1) TBAF, THF, 100 °C

2) TMAD, PBu_3, $PhCO_2H$

63% yield over 2 steps

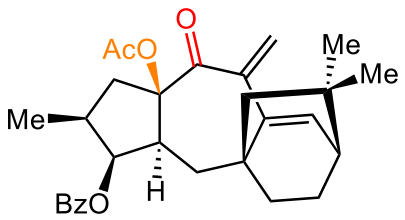


23

1) DMP, $NaHCO_3$, DCM

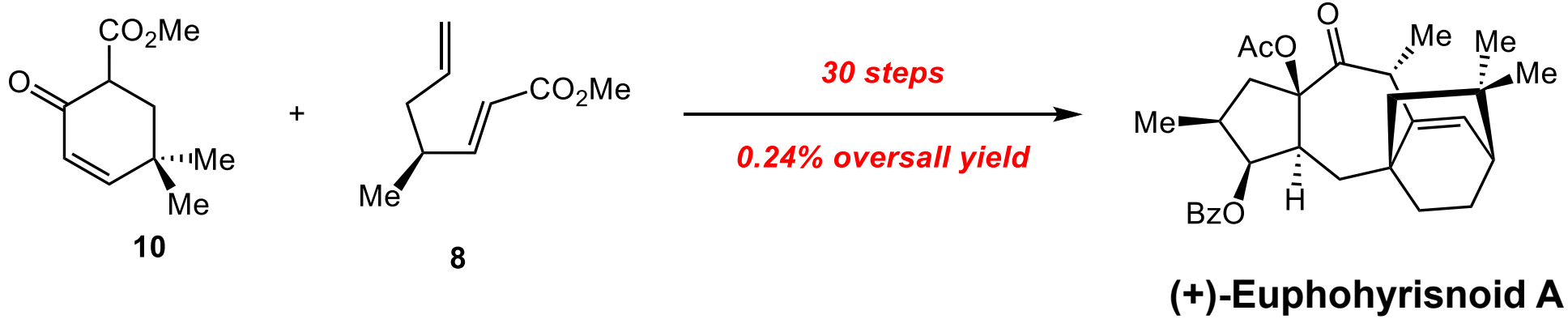
2) Ac_2O, TMSOTf, DCM

71% yield over 2 steps



Euphohyrisnoid A(1)

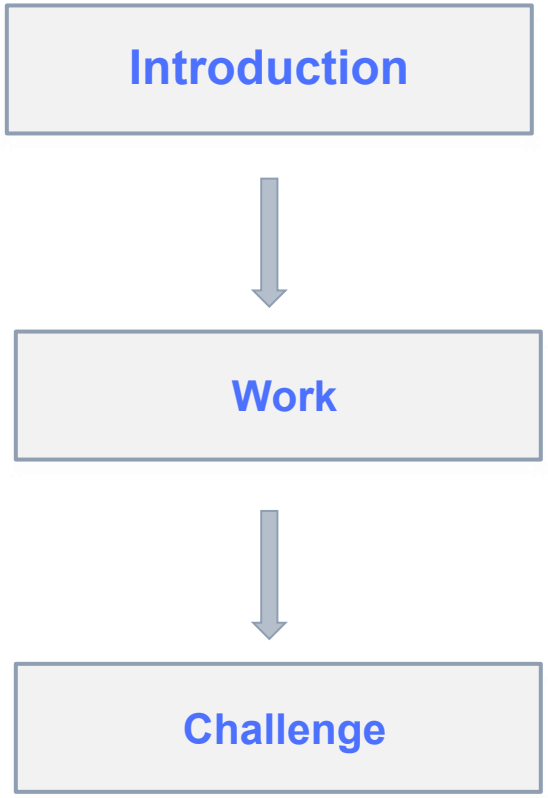
Summary



- The bicyclo[2.2.2] ring system was constructed efficiently by mild IMDA reaction;
- The IMDA reaction precursor was installed efficiently *via* a Tsuji-Trost reaction;
- Benzoyl group was introduced *via* modified Tamao-Fleming oxidation and Mitsunobu reaction

Writing Strategy

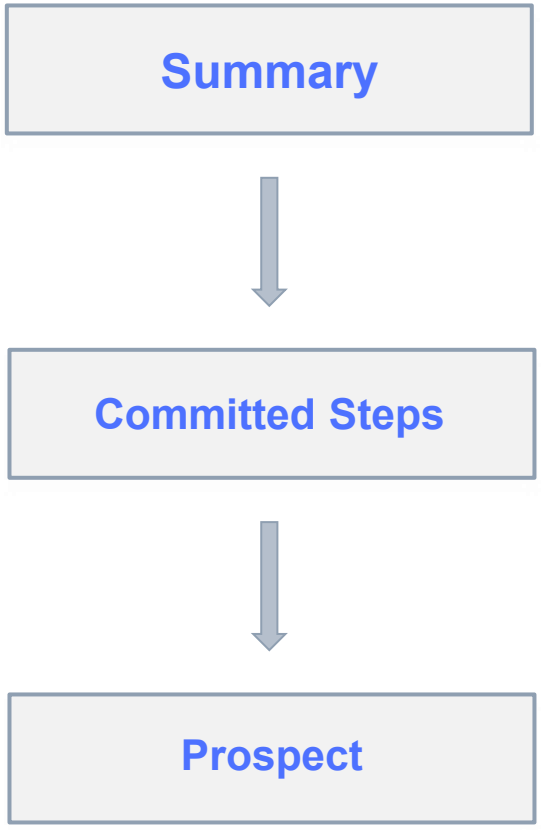
First paragraph



- Euphorbia diterpenoids, comprising ~40 subfamilies and over 1,400 members, have attracted significant interest in synthetic chemistry owing to their structural diversity, complexity, and intriguing biological activities.
- Following Wender's groundbreaking work, the total syntheses of Euphorbia diterpenoids have been successfully accomplished by several groups. Notable examples include the contributions from the laboratories of Cha, Inoue, Baran, Dai, Li, Liu, Maimone, Jia, and Luo.
- These synthesized Euphorbia diterpenoids all contain a common [5/7/6] tricyclic motif, imparting a consistent set of synthetic challenges. Particularly, the lathyrane diterpenoids, defined by their unique [5/11/3] fused carbocyclic core represent one of the largest subfamilies of Euphorbia diterpenoids ……

Writing Strategy

Last paragraph



- In summary, we have achieved the first total synthesis of (+/–)- and (+)-euphohyrisnoid A, a highly rearranged lathyrane diterpenoid with a new [5/7/6/6] tetracyclic core.
- A mild IMDA reaction enabled the diastereoselective and efficient synthesis of the desired bicyclo[2.2.2] ring system. This outcome experimentally validated the prior quantum mechanical calculations. The IMDA precursor was installed efficiently via a Tsuji–Trost reaction……
- This approach could be applied to diversified synthesis of euphohyrisnoid's analogs, enabling further biological research. This work is ongoing and will be described in the near future

Representative Examples

- The ozonolysis of terminal alkene in the known compound **8** gave the corresponding aldehyde, which underwent intramolecular Baylis-Hillman reaction catalyzed by PMe_3 (30 mol %) followed by IBX oxidation to provide **9**. (corresponding *adj.* 相应的，相关的)

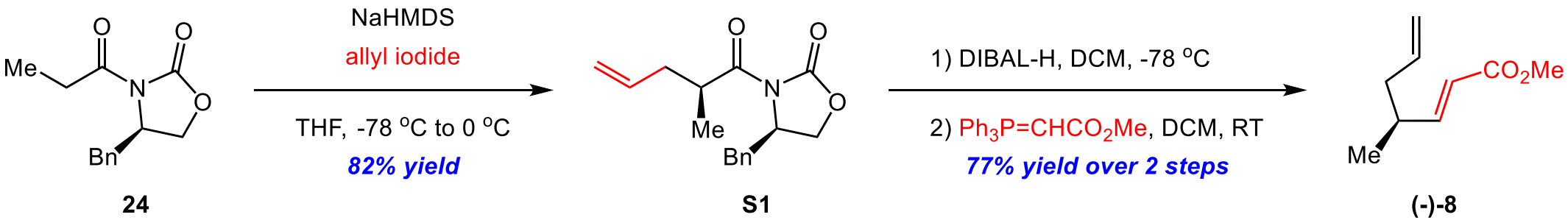
- This transformation proved challenging due to the inherent instability of the *β*-hydroxy ketone moiety in **14**. (inherent *adj. adj.* 固有的，内在的; 天生)

- Initially, we attempted to advance **21** to **22** *via* Tamao-Fleming oxidation to unmask the latent hydroxy group at C3. (unmask *v.* 揭露，揭示真相，脱保护)

Acknowledgment

Thanks for your attention!

Synthesis of Compound 8

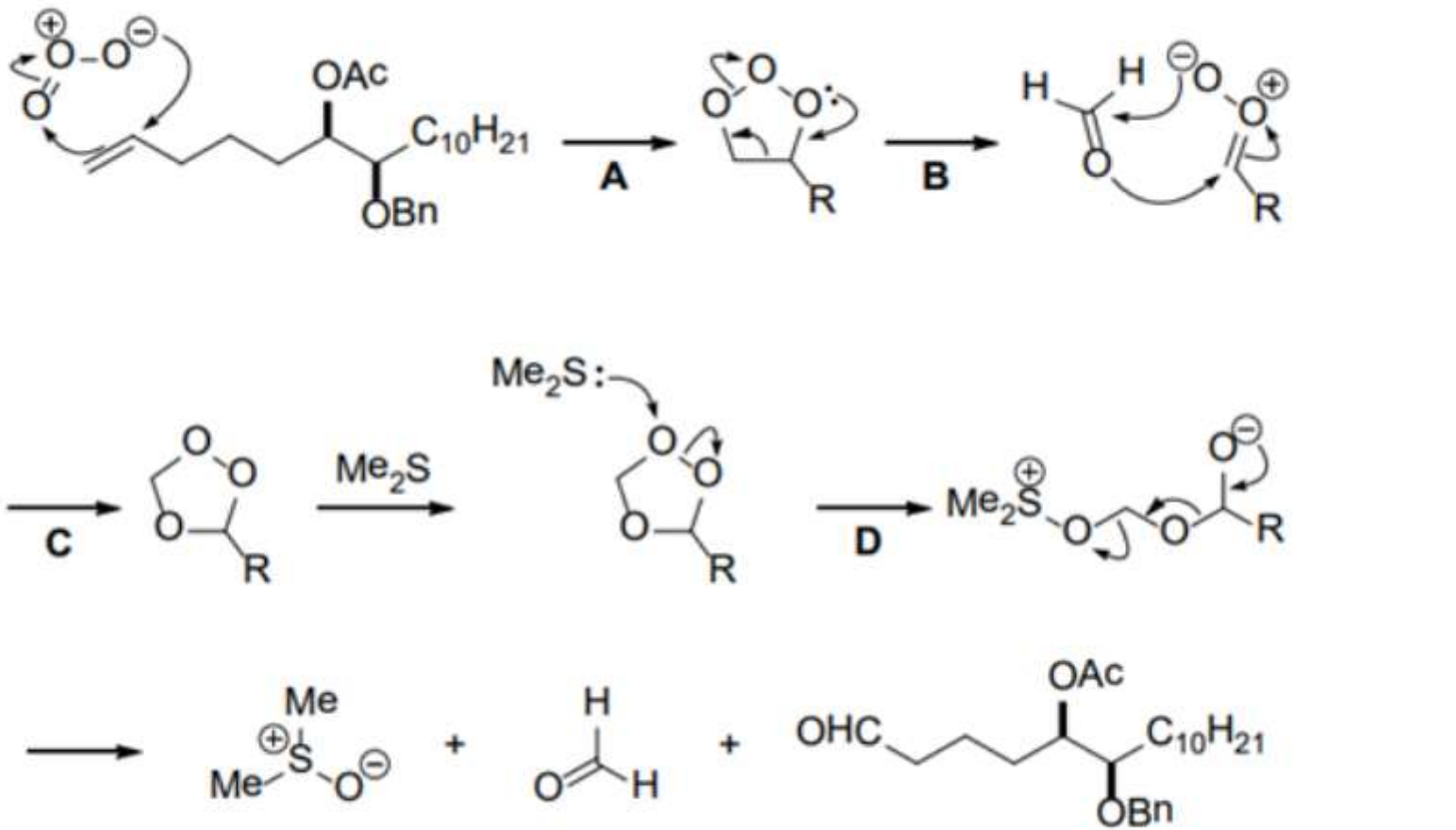


24 **S1** **(-)-8**

Serendipitous	意外且幸运的发现	非常积极	**全新、无人研究**的领域
Incidental	作为副产品的发现	中性	**研究很少**的次要现象
Fluke	纯粹的侥幸	中性/略消极	**极罕见、未被研究**的事件
Adventitious	来自外部的、非固有的	中性	**新兴、刚开始被研究**的特性
Unlooked-for	完全未预料到的	中性/积极	**计划外、可能开启新方向**
Contingent	依赖不确定因素的	中性	在**已知模型**中的偶然性
Aleatory	完全随机的	中性	**随机性本身已被充分研究**
Fortuitous	偶然且幸运的	积极	不特指研究状态，泛指好运气
Inadvertent	因疏忽造成的	消极	实验中的**失误**，非发现

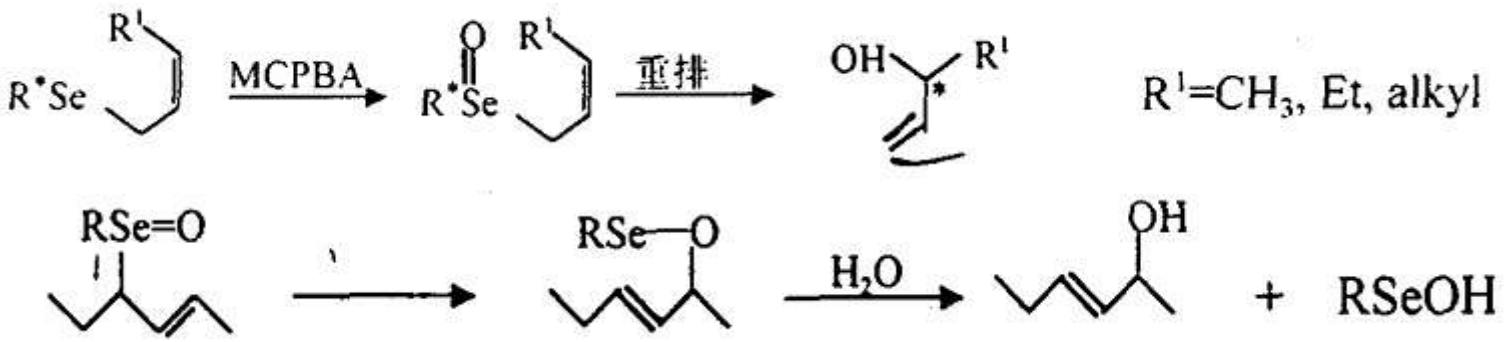
Note

A029



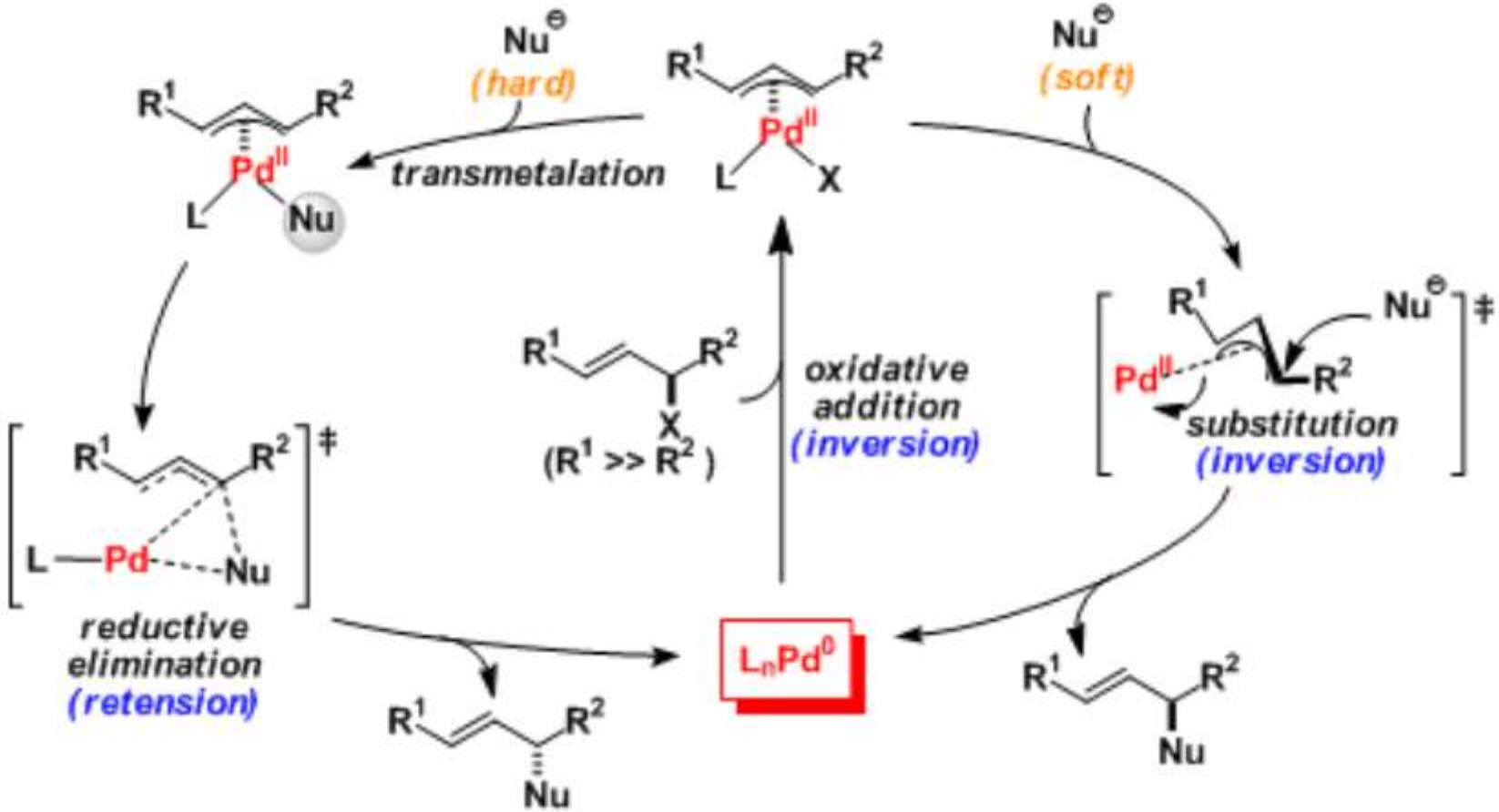
Ko, K.-Y.; Eliel, E. L. *J Org. Chem.* **1986**, 51, 5353

Note

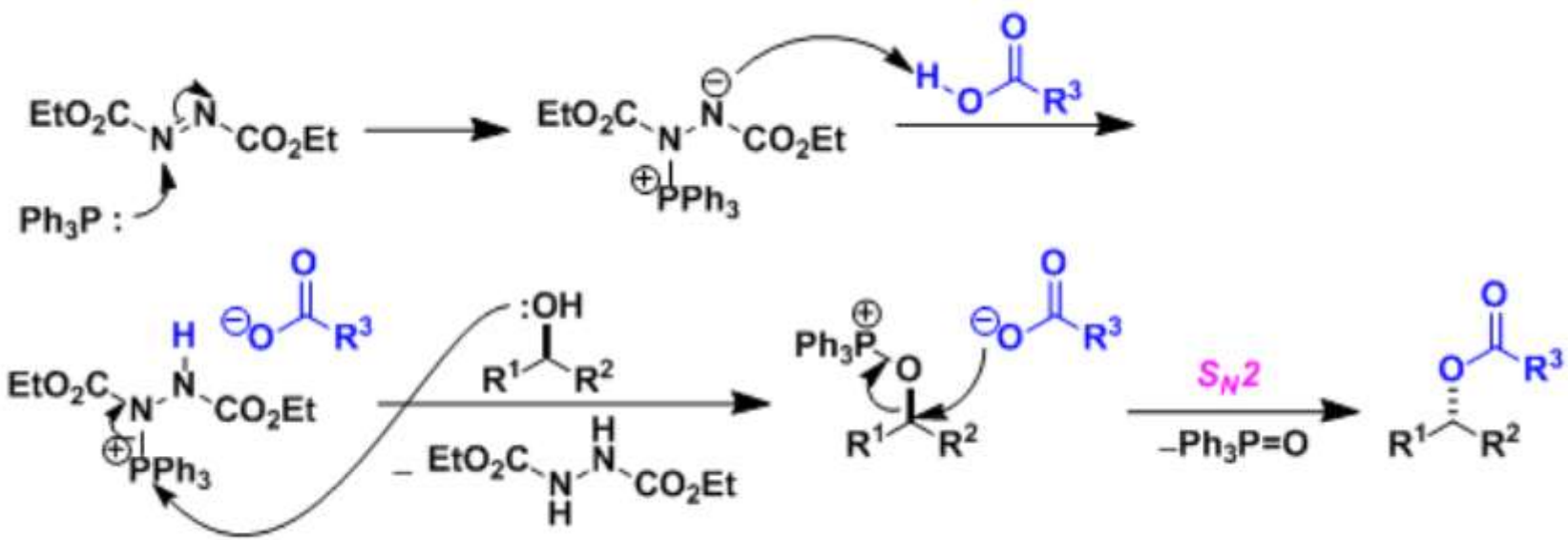


烯丙基硒氧化合物可发生 σ－[2,3]重排反立生成烯丙基醇化合物[19,20]，重排反立在同一侧面进行，得到的 OH 基在同一侧面，OH 基的立体构型保持不变。

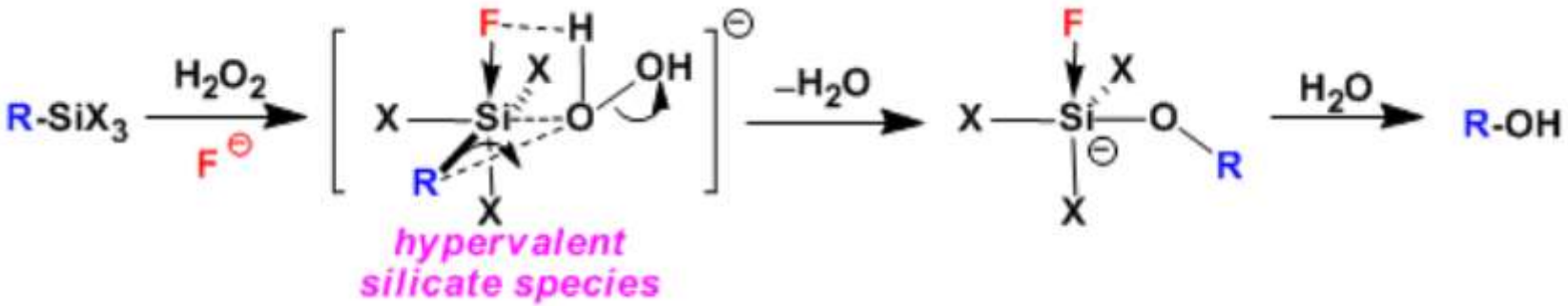
Note


Nu⊖
(hard)
transmetalation
Nu⊖
(soft)
oxidative
addition
(inversion)
(R1 >> R2)
substitution
(inversion)
reductive
elimination
(retension)
LnPd0
Nu

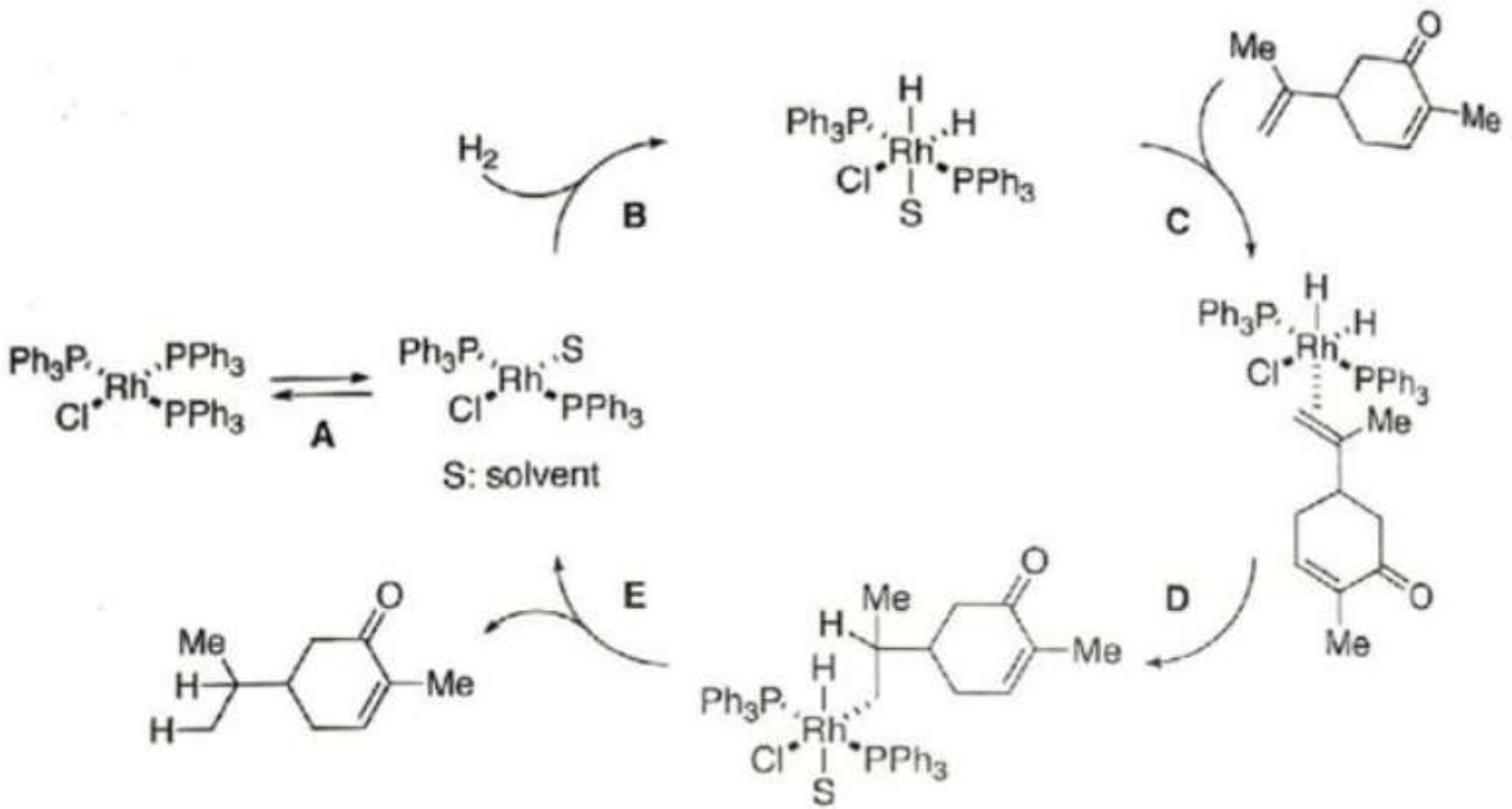
Note



Note


R-SiX3
H2O2
F⊖
F
H
X
OH
Si
O
R
X
hypervalent
silicate species
–H2O
F
X
Si
O
R
X
H2O
R-OH

Note



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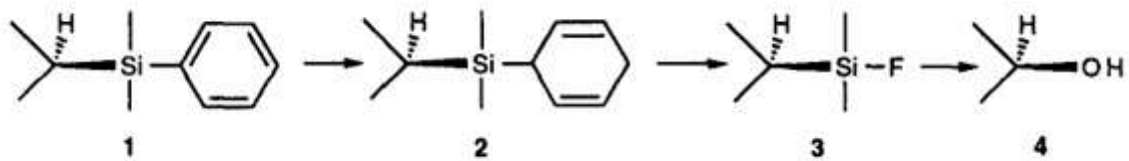


1 2 3 4

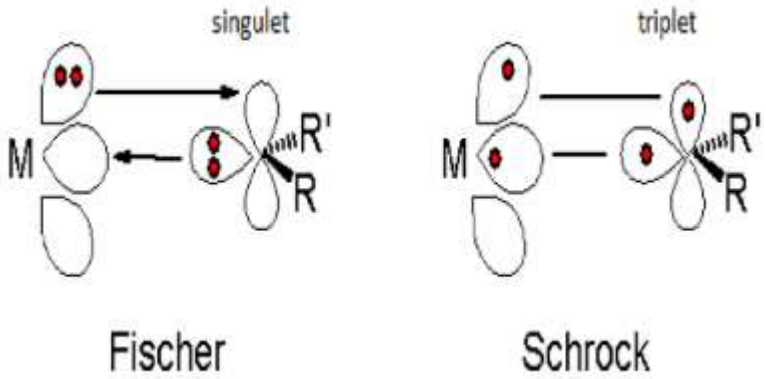
Note

Fischer卡宾通常有以下特征：

- 低氧化态的金属中心[2]
- 中后部过渡金属，如Fe(0), Mo(0), Cr(0)
- 能接受π电子的配体
- 卡宾碳上有提供π电子的取代基，如烷氧基和烷基化氨基

Schrock卡宾通常有以下特征：

- 高氧化态的金属中心
- 前过渡金属，如Ti(IV), Ta(V)
- 能提供π电子的金属配体
- 卡宾碳上的取代基通常只有氢和烷基



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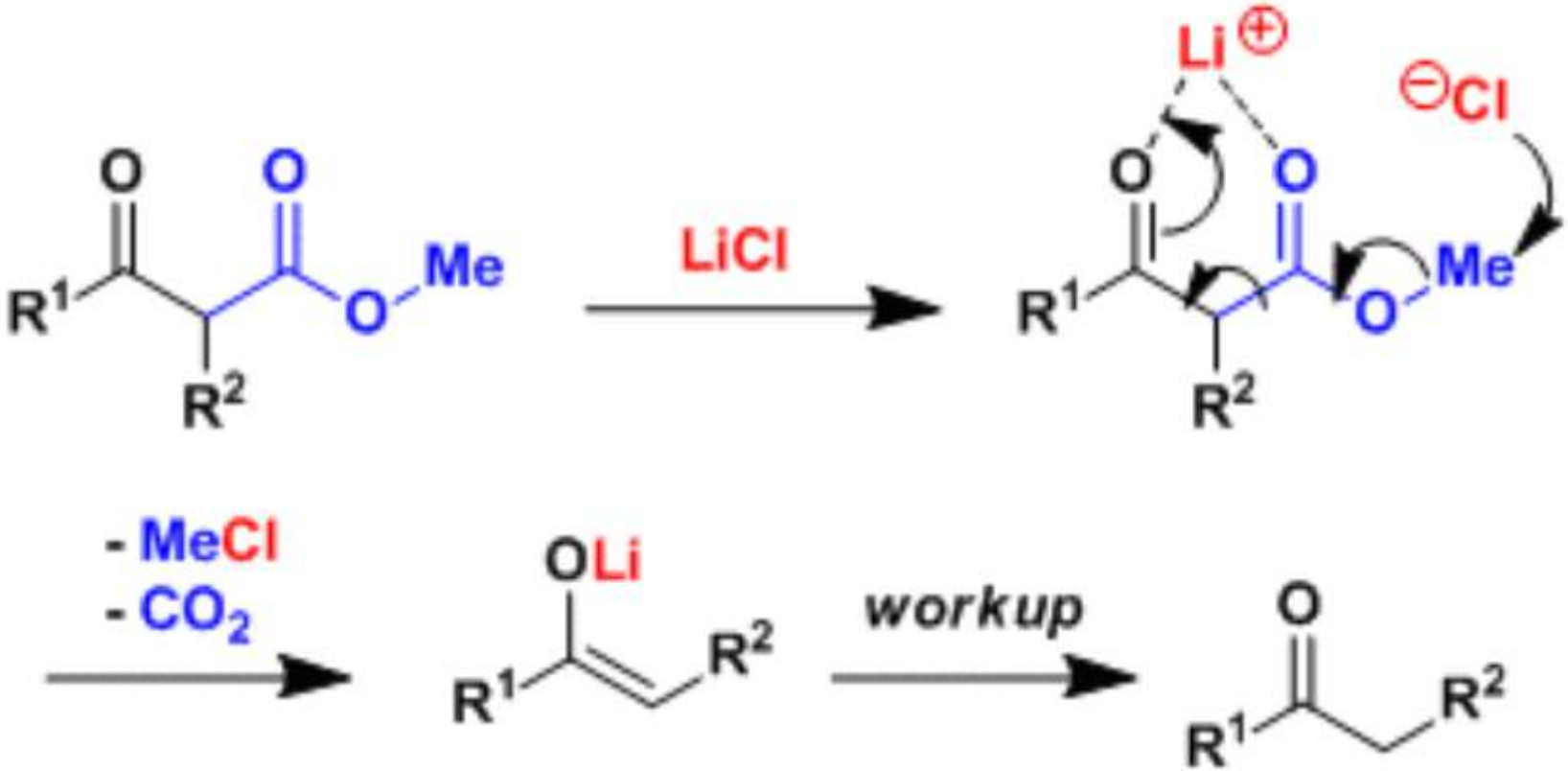
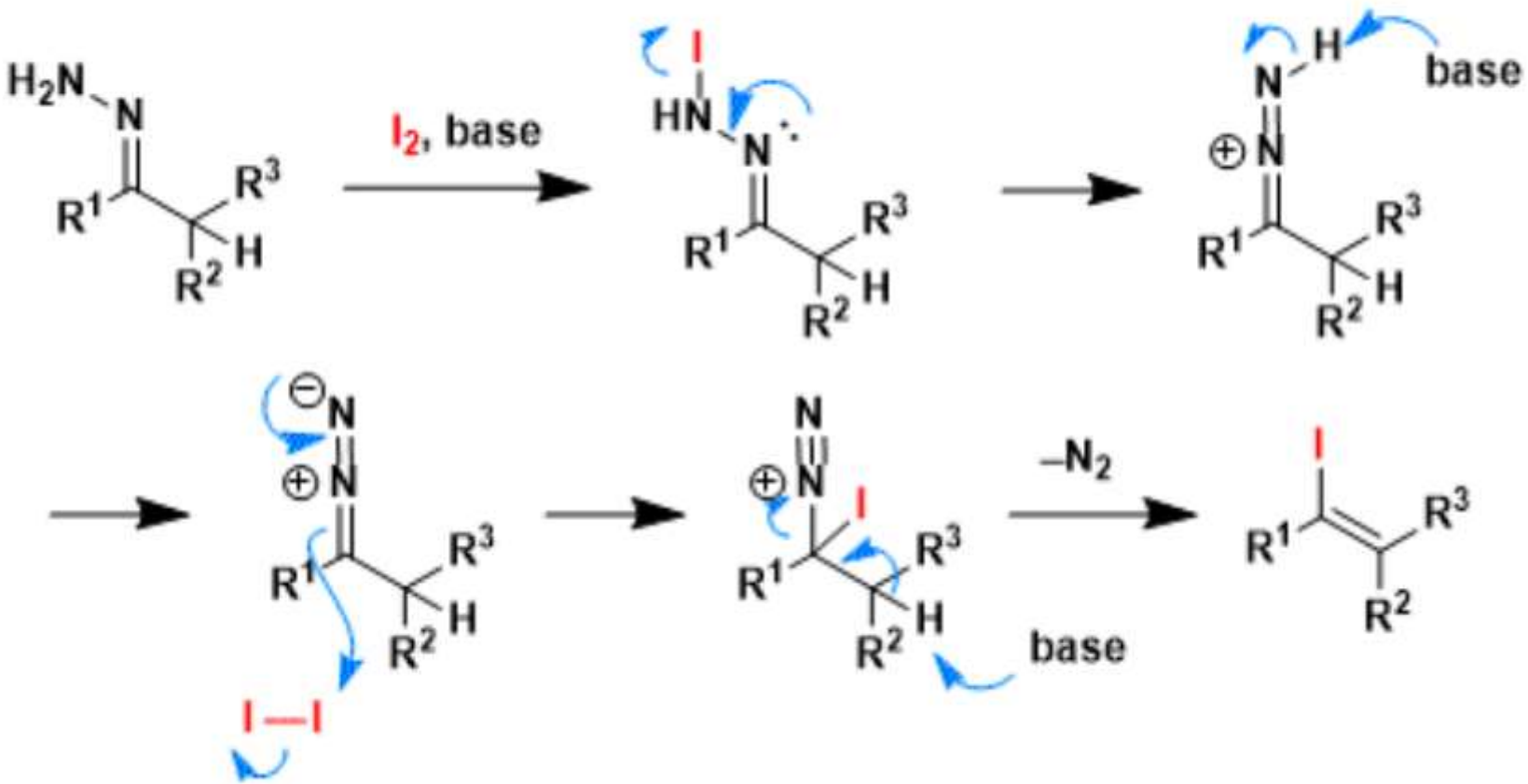


Note

- 反应机理



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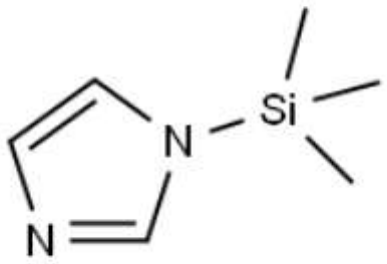

TMSIm