Dissolving Metal Reduction in Total Synthesis

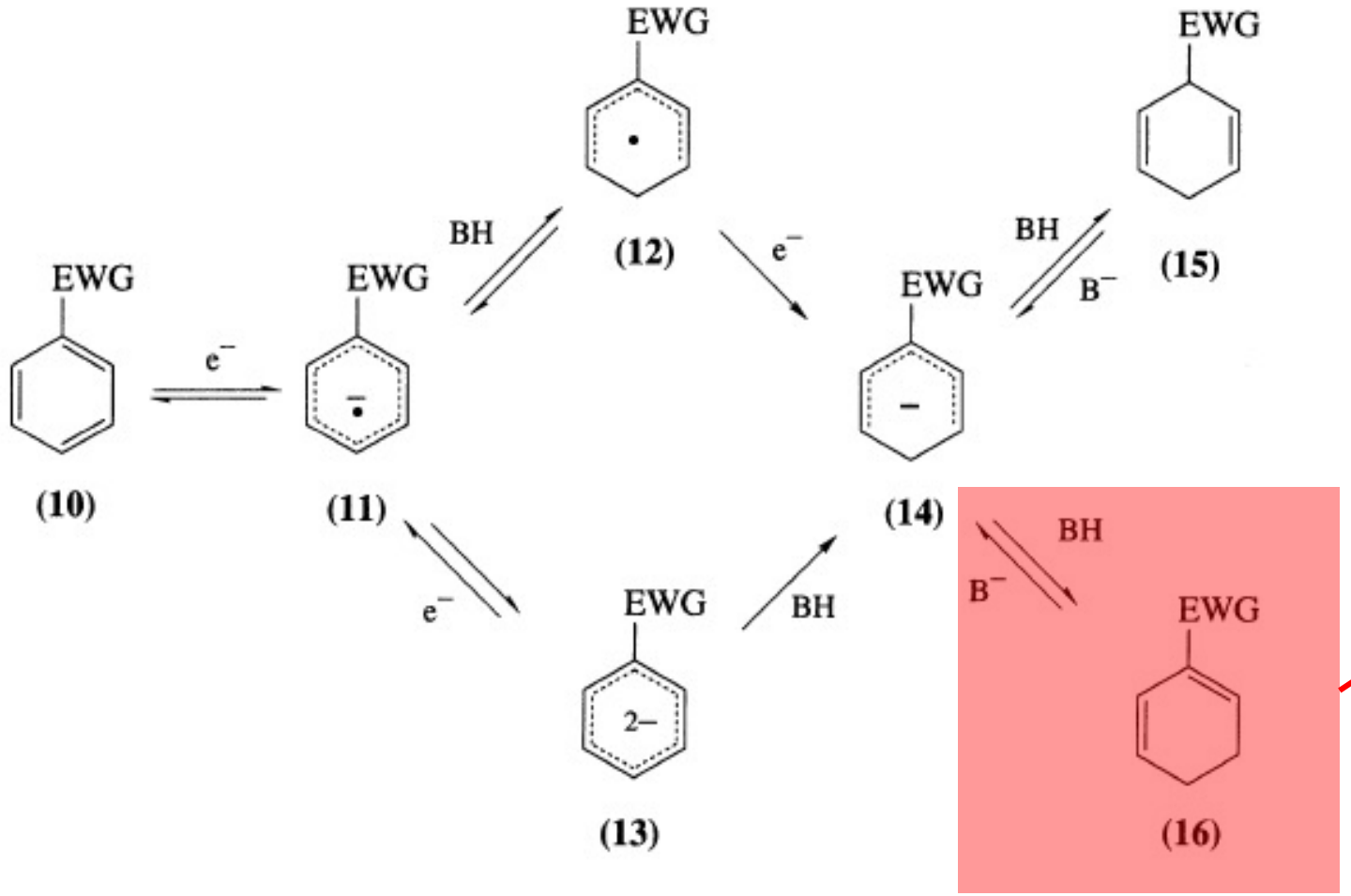
Date: Feb. 8, 2022 Speaker: Han-Hsiang Hsu

Birch Reduction

Conditions

- Metal: Li, Na, K, Ca…
- Solvent: NH_3
  (In R-NH_2: Benkeser Reduction)
- Proton source: alcohols (to prevent over-reduction).

Mechanism



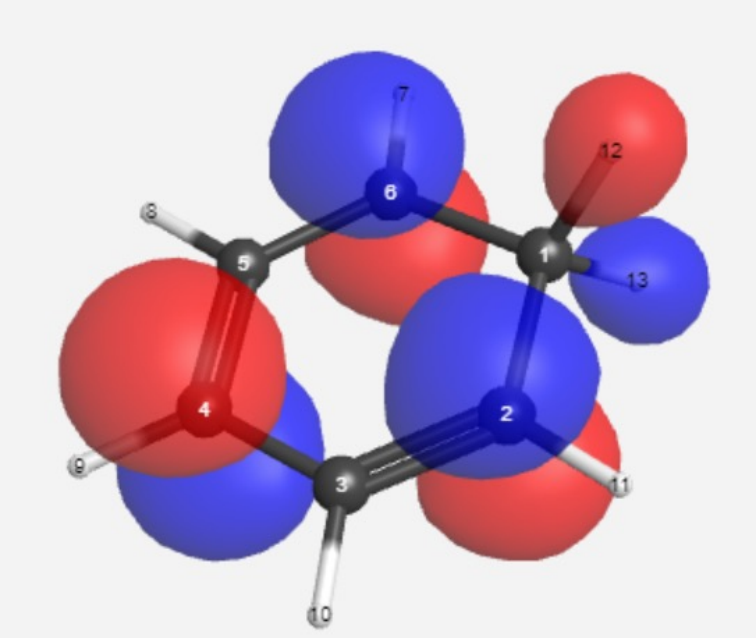
SIDE REACTION

Mander, L. N. Partial Reduction of Aromatic Rings by Dissolving Metals and by Other Methods. In *Comprehensive Organic Synthesis*, 1991; pp 489-521.

Frontier MO Analysis of Intermediate

- Charge Distribution*:
  C2: -0.20
  C4: -0.25
  (Same orbital coefficient from Huckel MO)

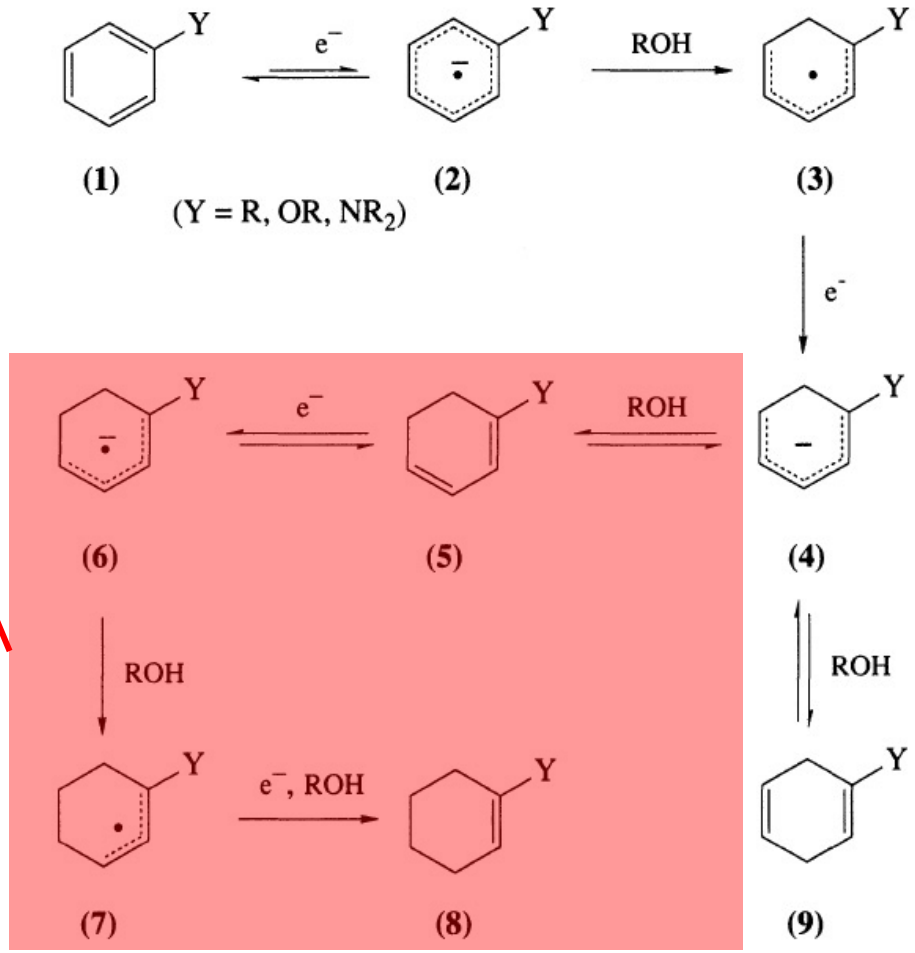
- Kinetic control to form non-conjugated product.



*Calculation using resource on webmo.net
Basis set: DFT B3LYP 6-31G

Mechanism

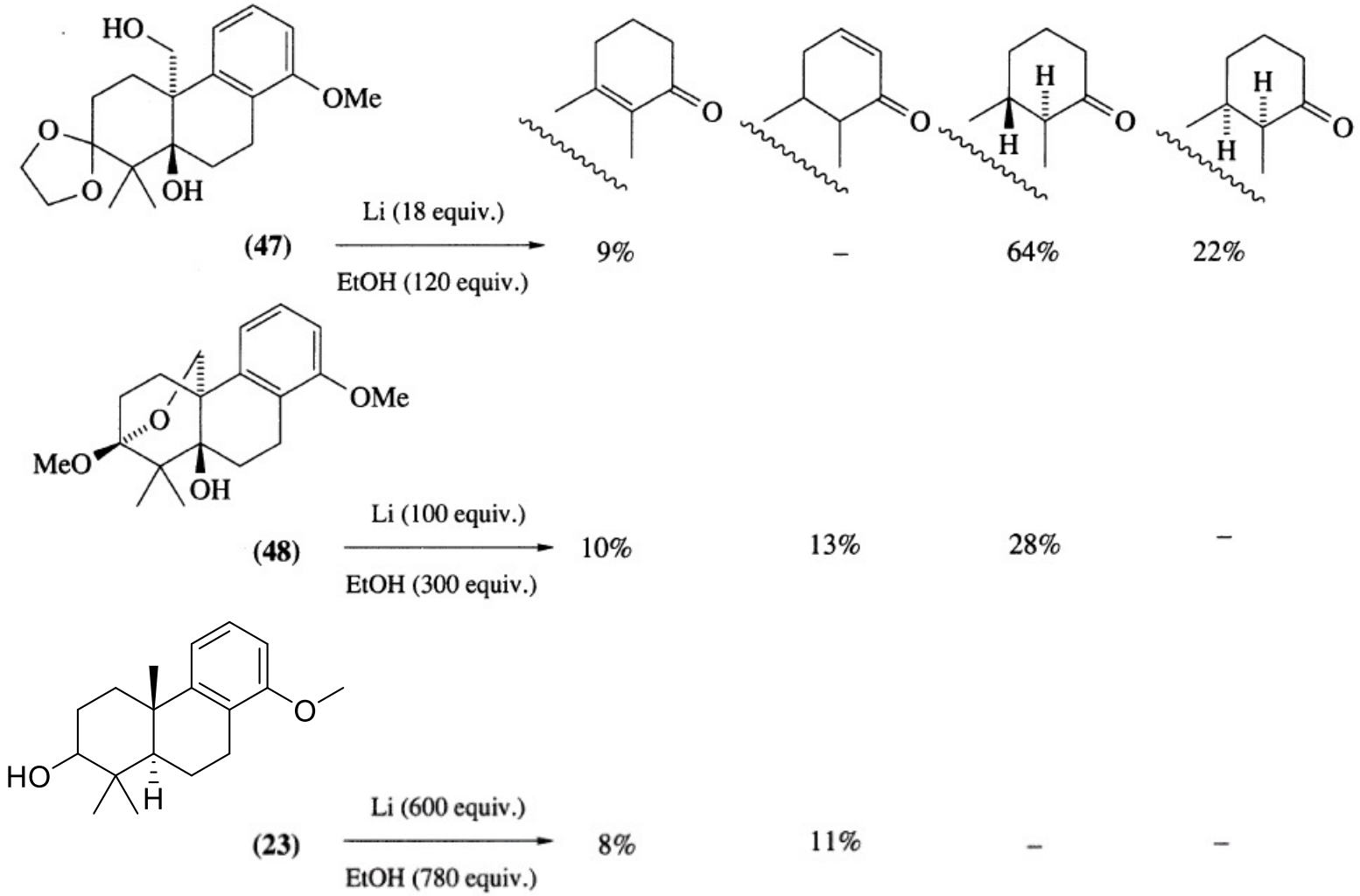
SIDE REACTION



- Need Alcohol to push reaction to completion.
- Rapid protonation prevents side reaction.

Mander, L. N. Partial Reduction of Aromatic Rings by Dissolving Metals and by Other Methods. In *Comprehensive Organic Synthesis*, 1991; pp 489-521.

Intramolecular Protonation

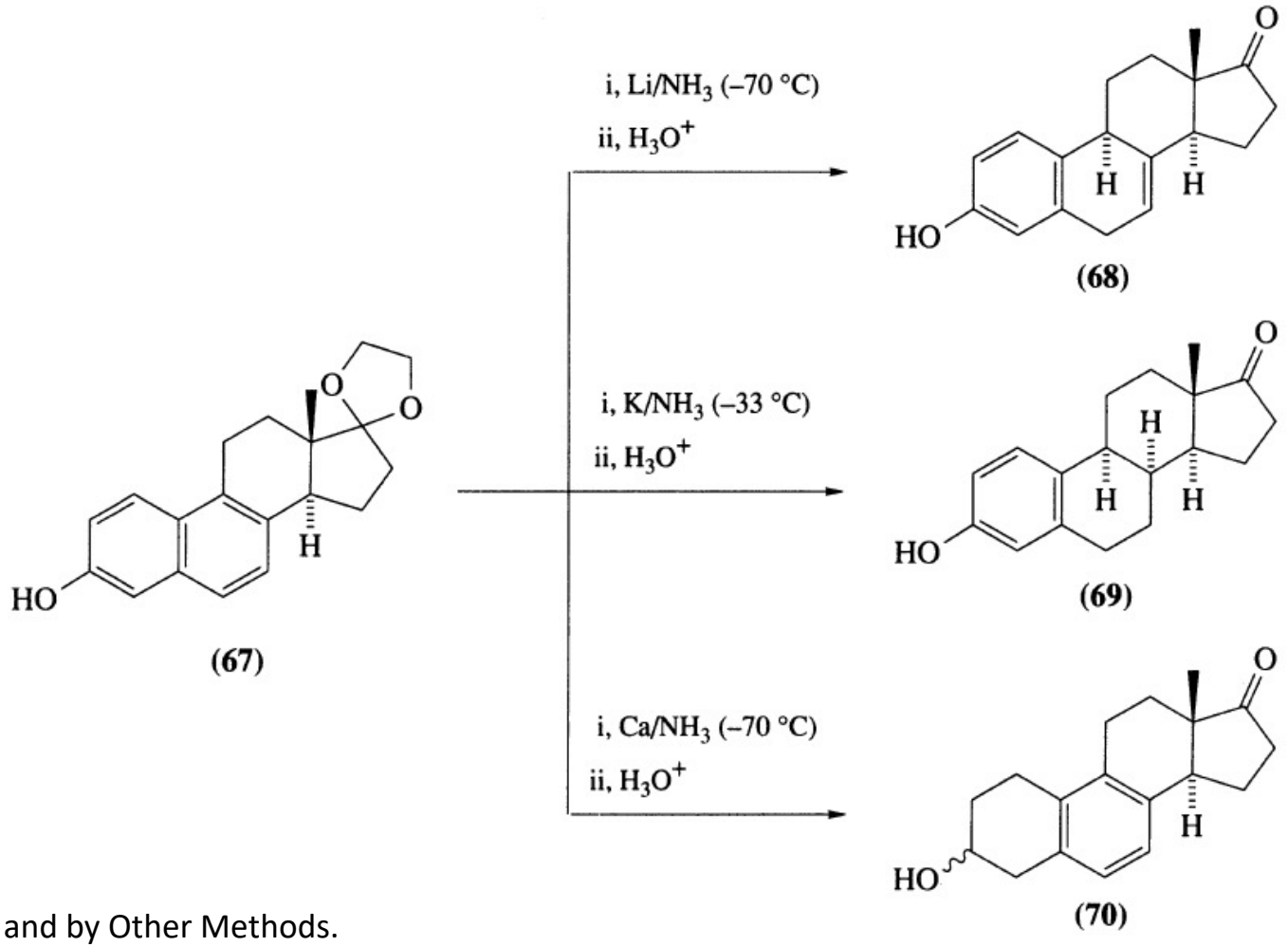


6-membered proton transfer

Mander, L. N. Partial Reduction of Aromatic Rings by Dissolving Metals and by Other Methods. In *Comprehensive Organic Synthesis*, 1991; pp 489-521.

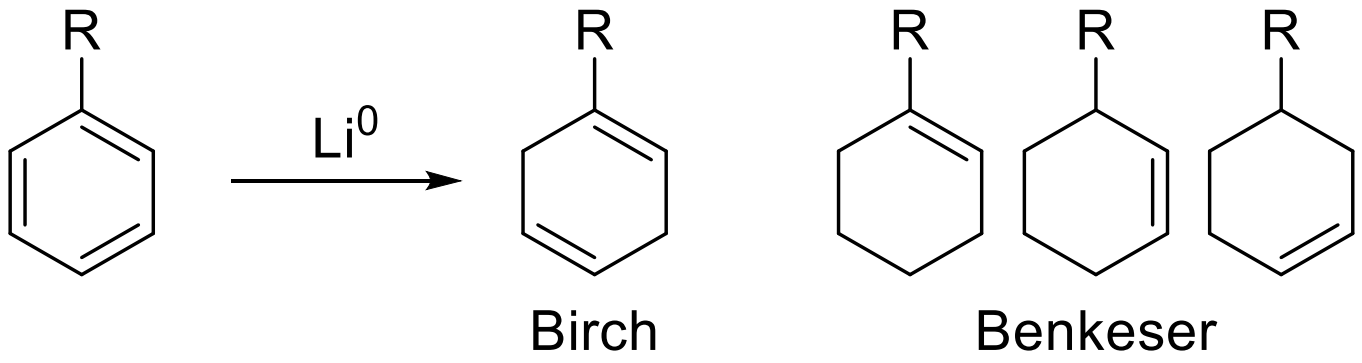
Metal Effect

- Reduction Potential:
  - Li : -2.99 V
  - Na: -2.59 V
  - K : -2.73 V
- Main difference:
  Aggregation / Coordination.



Mander, L. N. Partial Reduction of Aromatic Rings by Dissolving Metals and by Other Methods. In *Comprehensive Organic Synthesis*, 1991; pp 489-521.

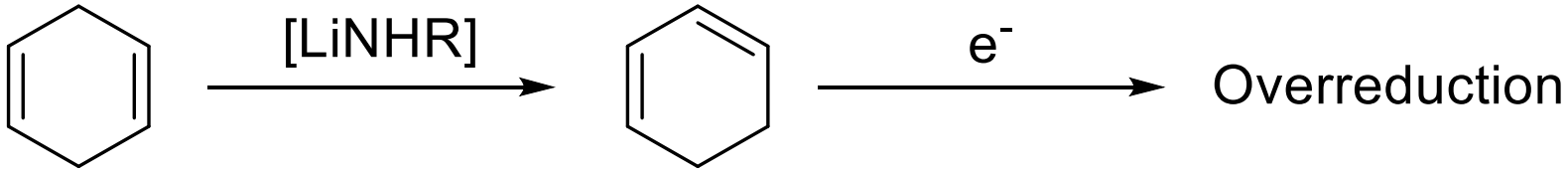
Solvent – Benkeser Reduction



- Electrolysis gives low conversion
- Direct reaction gives messy products

Kaiser, E. M. *Synthesis.* **1972,** *1972,* 08, 391-415.

Solvent – Benkeser Reduction

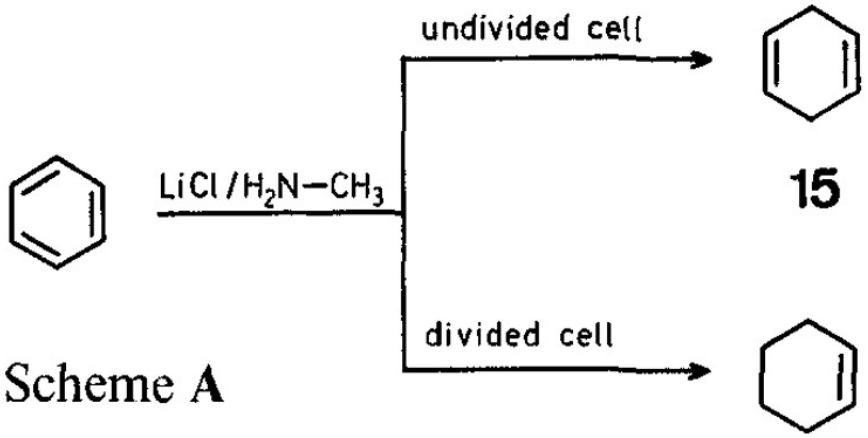


- LiNHR has a comparable basicity to 1,4-cyclohexadiene

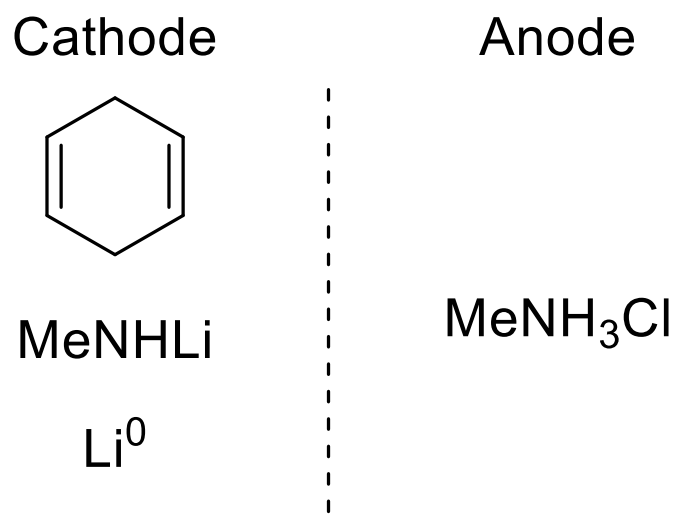
➢Isomerizes 1,4-cyclohexadiene to conjugated isomers, giving rise to over-reduced product.

Kaiser, E. M. *Synthesis.* **1972,** *08*, 391-415.

Solvent – Electrolysis Test



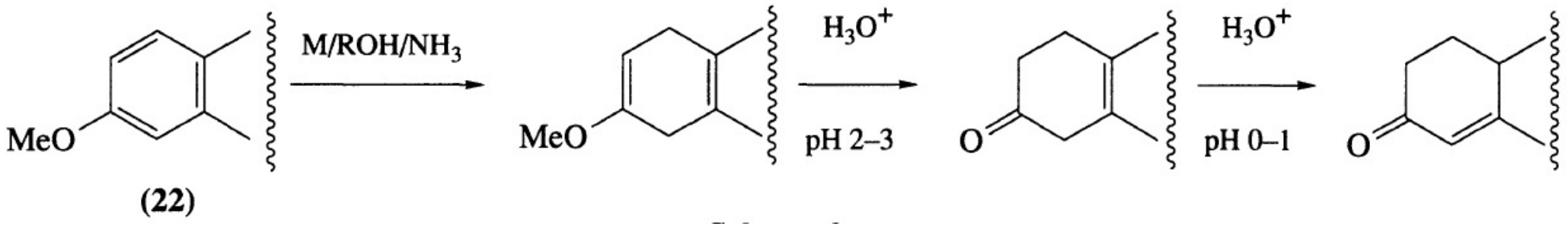
Scheme A



- Divided cell gives overreduction product.
- Divided cell prevents cathodic product $MeNH_3^+Cl^-$ from quenching alkyl amide.

Kaiser, E. M. *Synthesis.* **1972,** *08*, 391-415.

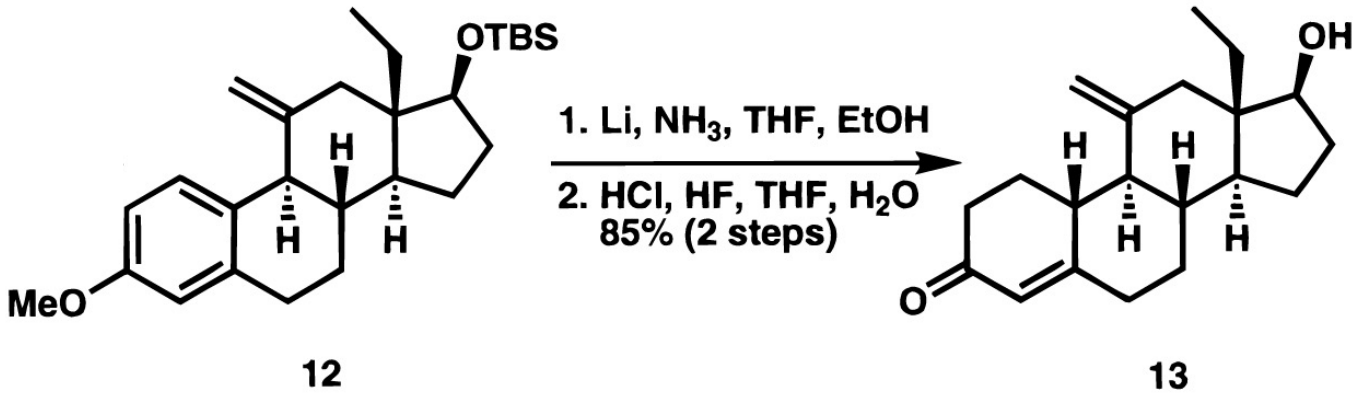
Application – Reduction of Anisoles



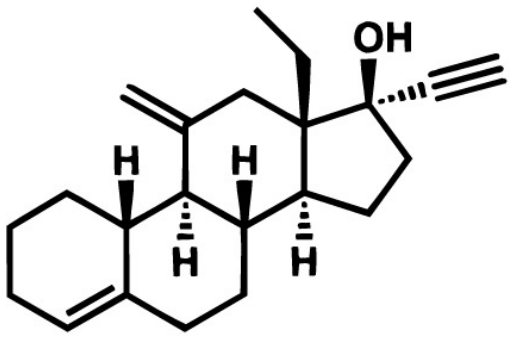
- Isomerizes to α,β-unsaturated ketone.
- Needs pH adjustment (prevents enolate formation).

Mander, L. N. Partial Reduction of Aromatic Rings by Dissolving Metals and by Other Methods.
In *Comprehensive Organic Synthesis*, 1991; pp 489-521.

Synthesis of Desogestrel (birth control drug)

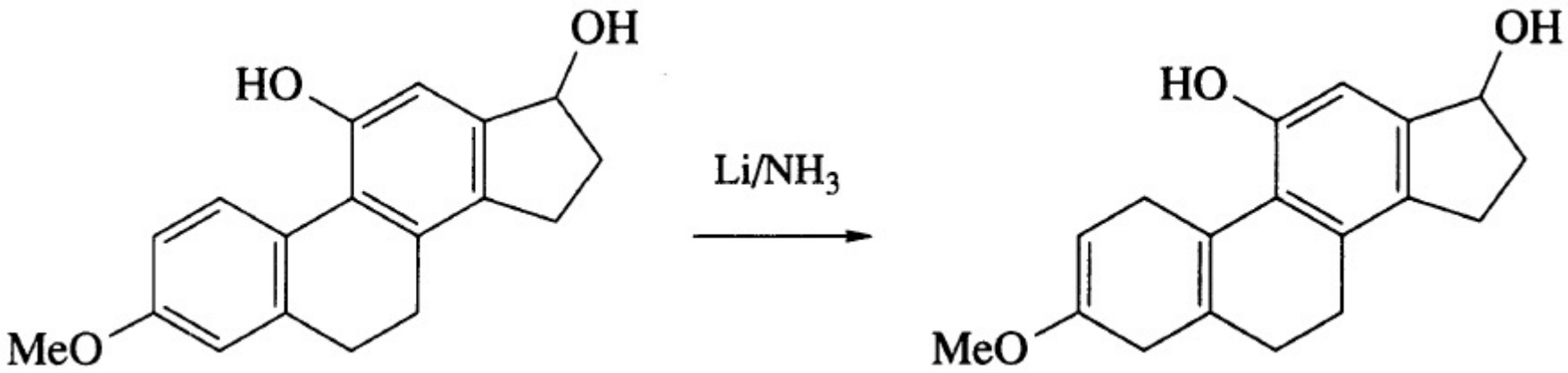


- Late-stage modification.
- Isolated double bond, silyl ether preserved.



Corey, E. J. *J. Am. Chem. Soc.* **1999,** *121*, 710-714.

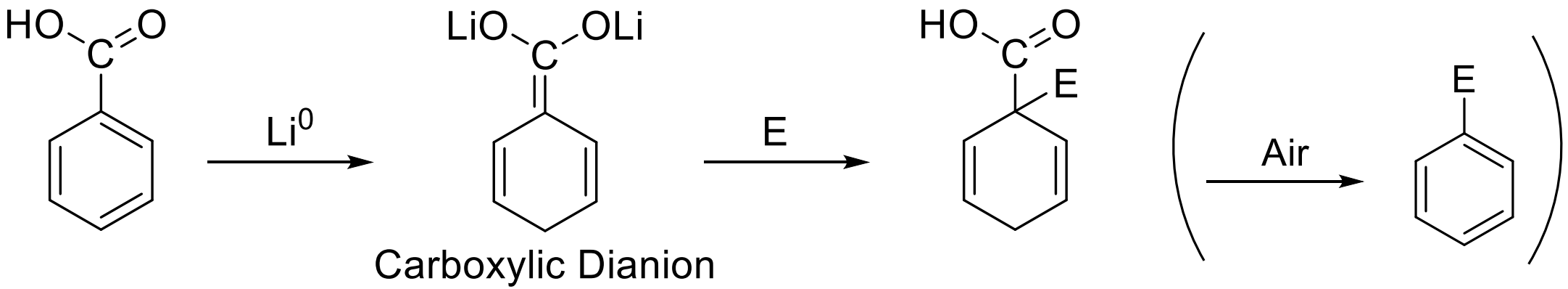
Application – Phenol



- Phenol not reduced due to formation of phenoxide.
- Strategic placement of hydroxyl group allows site selectivity.

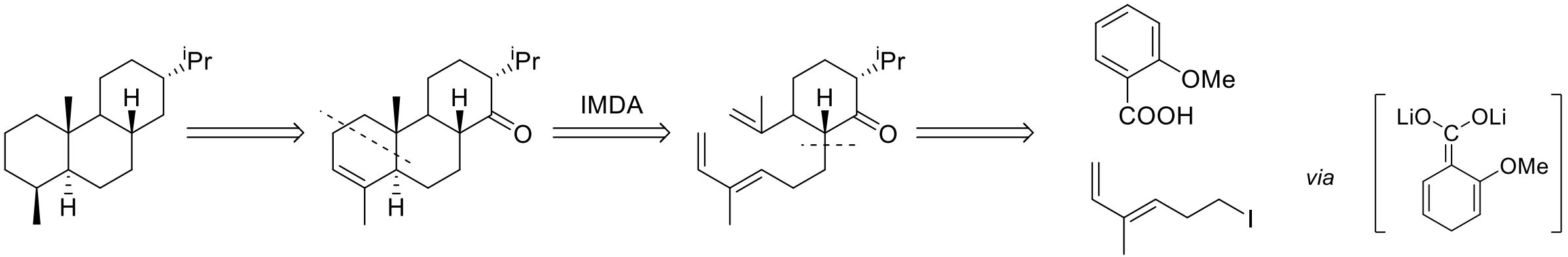
Mander, L. N. Partial Reduction of Aromatic Rings by Dissolving Metals and by Other Methods.
In *Comprehensive Organic Synthesis*, 1991; pp 489-521.

Application – Reductive Alkylation of Carboxylic Acid



- Ipso-alkylation
- COOH group assists reaction
  (as little as 2.2 eq of Li can be achieved).
- Easily removed.

Synthesis of Fichtelite (Related to Resin acid)



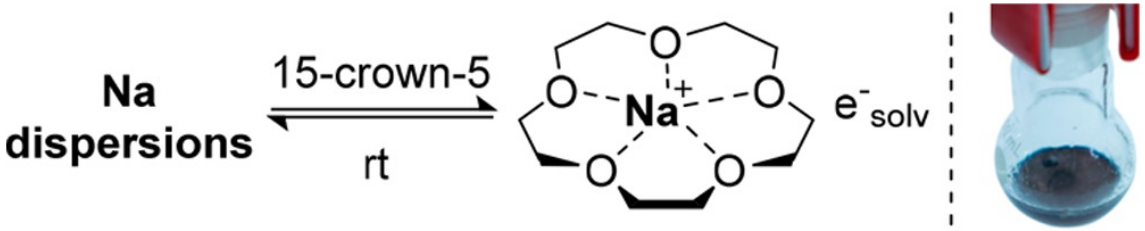
- Early-stage scaffold construction.
- Decarboxylation assisted by 3-keto group.

Taber, D. F. *J. Am. Chem. Soc.* **2002,** *102*, 5085-5088.

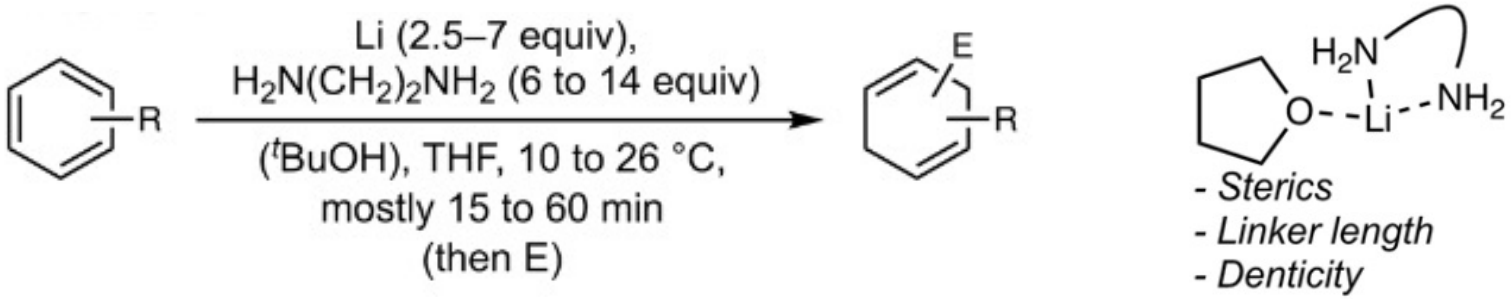
Variant: Ammonia-Free Birch Reduction

<u>"Other ways to make solvated electron"</u>

- Crown-Ether



- THF-ethylenediamine



Lei, P. *Org Lett* **2018,** *20*, 12, 3439-3442.
Burrows, J. *Science* **2021,** *374* (6568), 741-746.

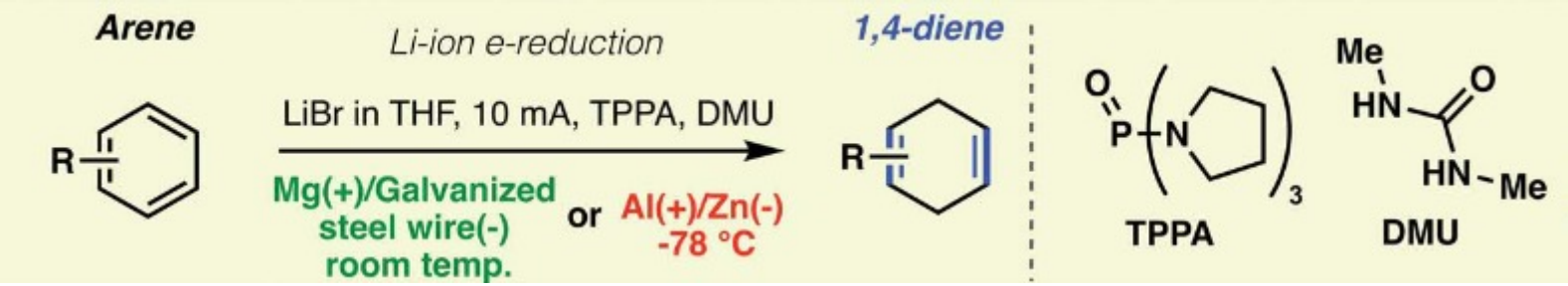
Variant: Catalytic Birch Reduction

“Other Source of energy”

- Electrochemical Birch

Overcharge Protection

Proton source



sacrificial anode

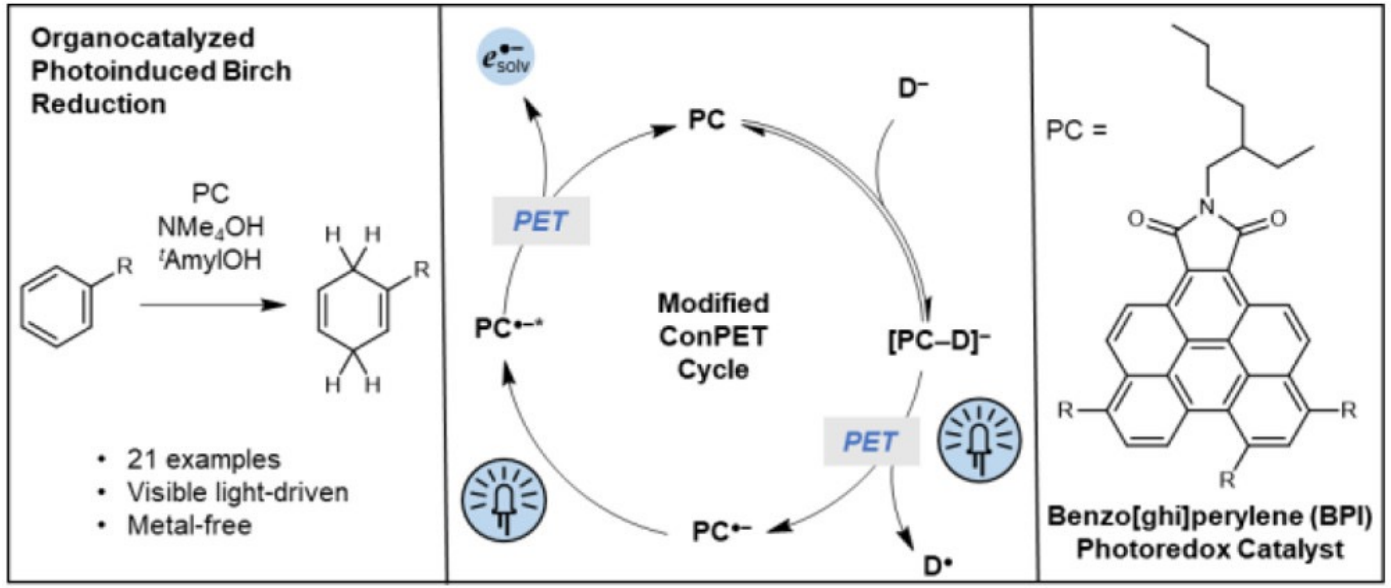
- Solvated electron pathway ruled out.
  (no Pinacol coupling observed in standard condition)
- Inspired by Li-ion battery.

Peters, B. K. *Science* **2019,** *363* (6429), 838-845.
Cole, J. P. *J Am Chem Soc* **2020,** *142* (31), 13573-13581.

Variant: Catalytic Birch Reduction

<u>"Other Source of energy"</u>

- Photocatalyzed Birch (Metal-Free)

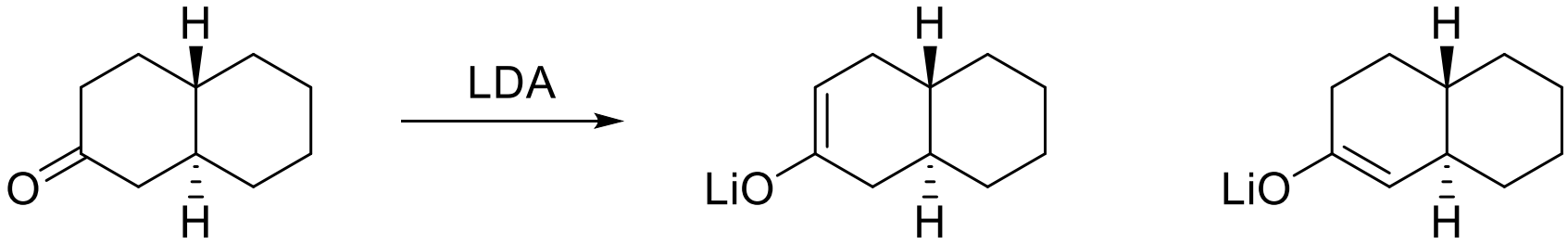


- OH^- (or F^-) as true reducing agent.

Peters, B. K. *Science* **2019,** *363* (6429), 838-845.
Cole, J. P. *J Am Chem Soc* **2020,** *142* (31), 13573-13581.

Dissolving metal in enolates

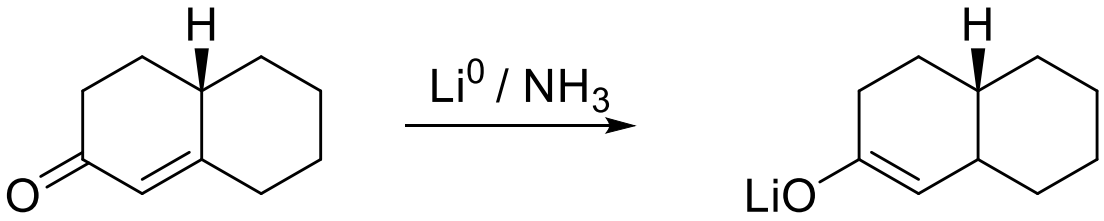
Stereospecific Enolate Generation



kinetic

Thormodynamic

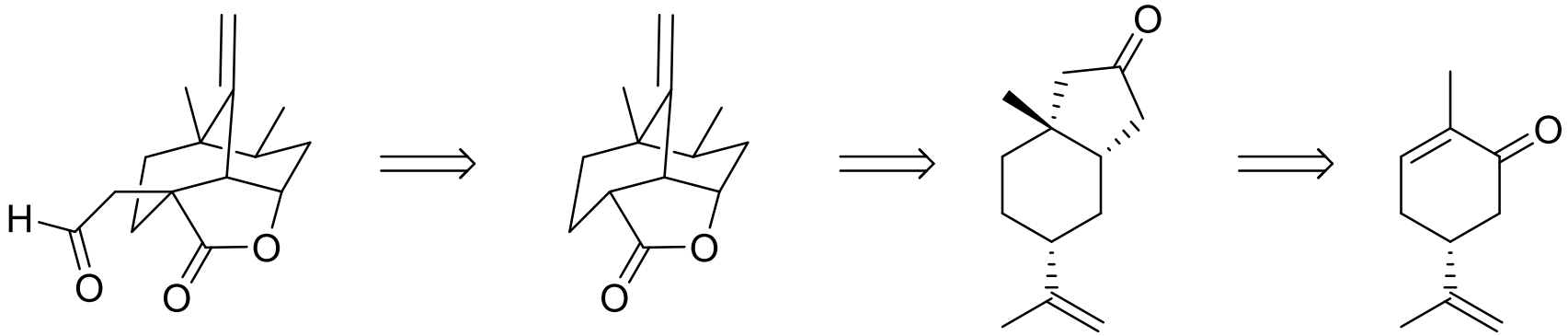
Can't be cleanly obtained

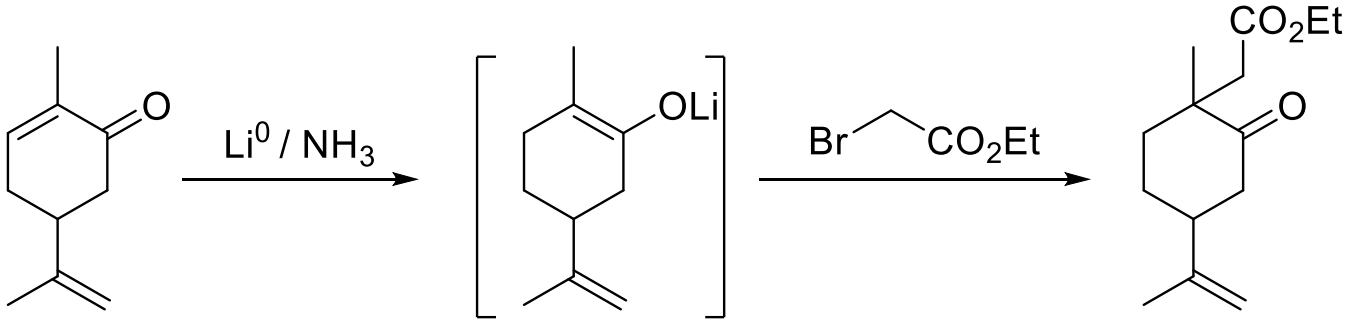


Site-specific

Crabtree, S. R. *Org. Synth.* **1992,** *70*.
Huffman, J.W. *J. Org. Chem.* **2002,** *53* (16), 3828-3831.

Synthesis of (-) – Upial

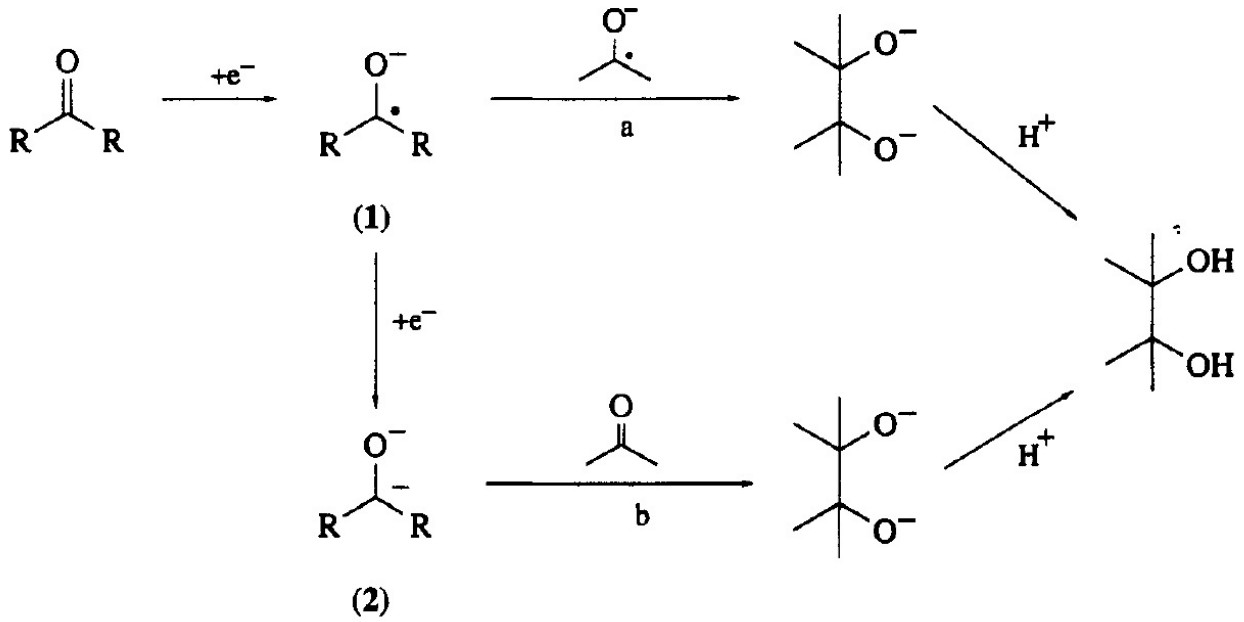




Taschner, M. J. *J. Am. Chem. Soc.* **2002,** *107* (19), 5570-5572.

Pinacol Coupling Reactions

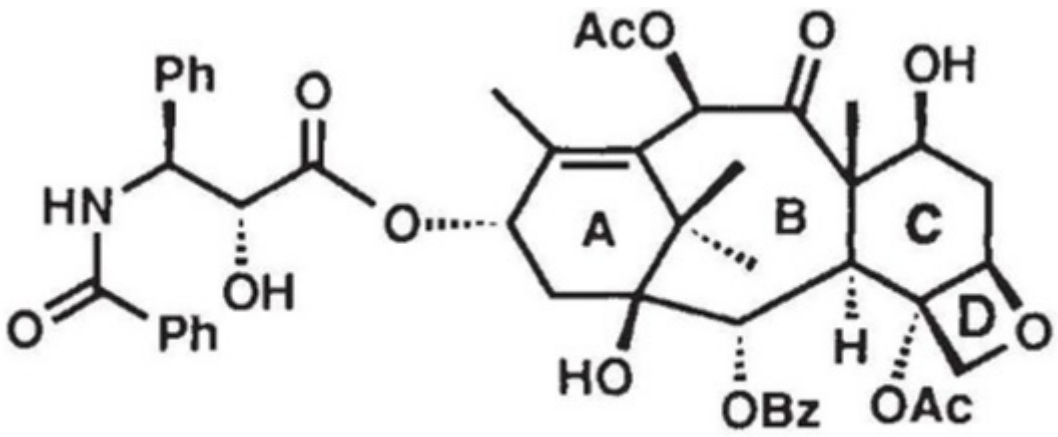
Pinacol Coupling Reactions



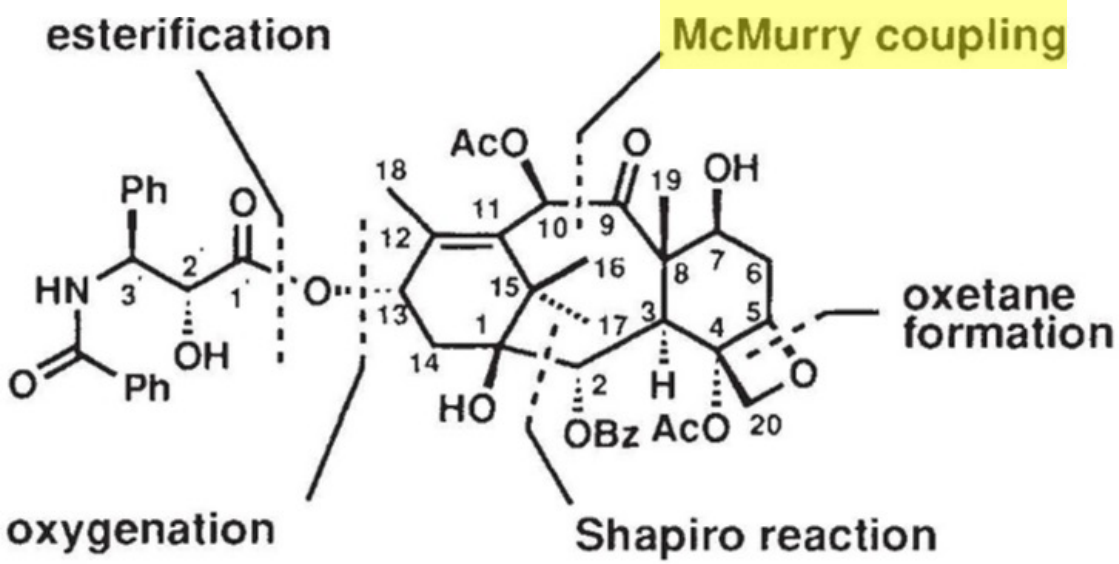
- Usually radical pathway (a), but using TMSCl promotes anionic pathway (b).
- Coordination nature ⇒ best for intramolecular coupling.

Trost, B. M. Fleming, I. Pinacol Coupling Reactions. In *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry, Vol. 1 - 9* , pp 563 – 591.

Total Synthesis of Taxol



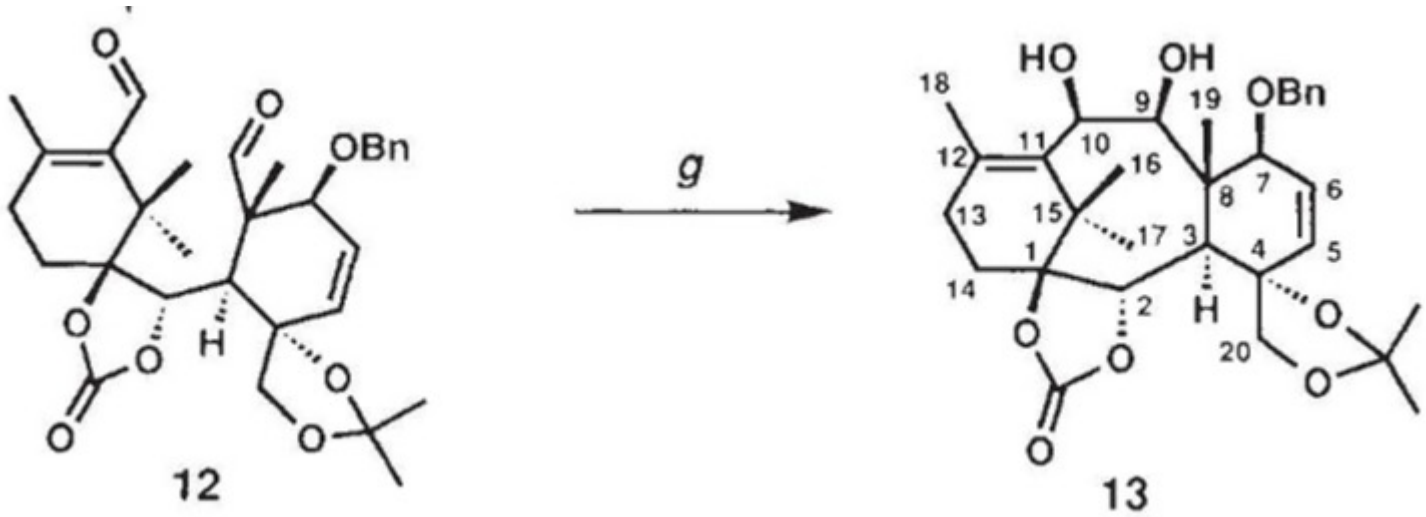
1: Taxol



- Challenging 8-membered ring closure

Nicolaou, K. C. *Nature* **1994,** *367* (6464), 630-4.

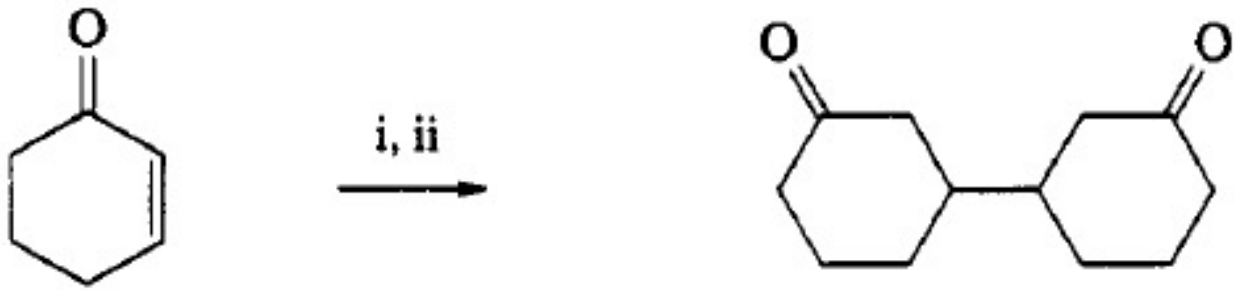
Total Synthesis of Taxol



- $(TiCl_3)_2$-$(DME)_3$ (10 eq.), Zn-Cu (20 eq.), DME, 70 °C, 1 h,

Nicolaou, K. C. *Nature* **1994,** *367* (6464), 630-4.

Variant: α,β-unsaturated ketone

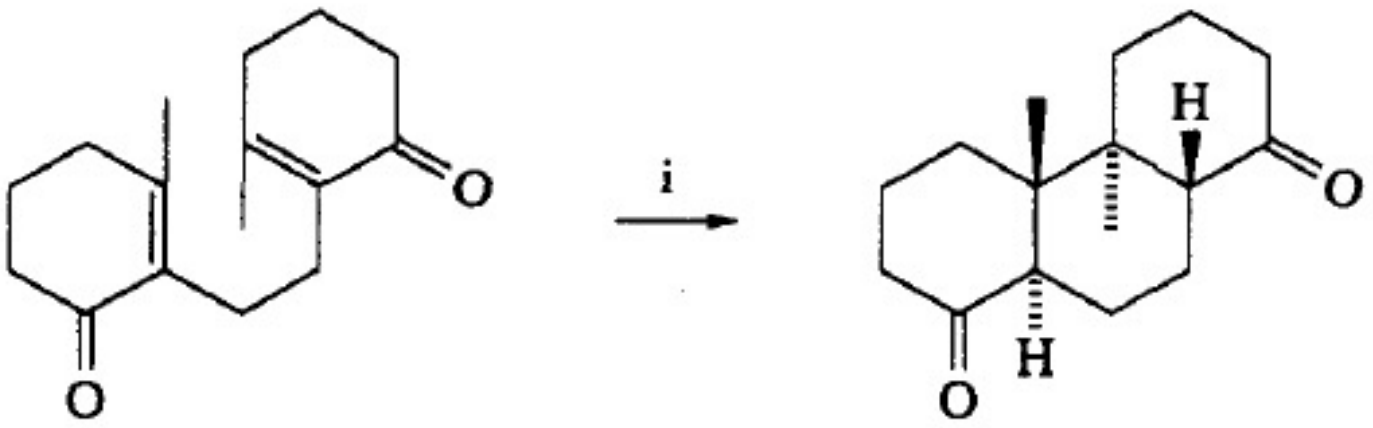


i, Me_3SiCl, Mg, $TiCl_4$, HMPA, 80 °C; ii, HCl, aq. EtOH, 65%

- Strong coordination favors 1,4-coupling

Trost, B. M. Fleming, I. Pinacol Coupling Reactions. In *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry, Vol. 1 - 9* , pp 563 – 591.

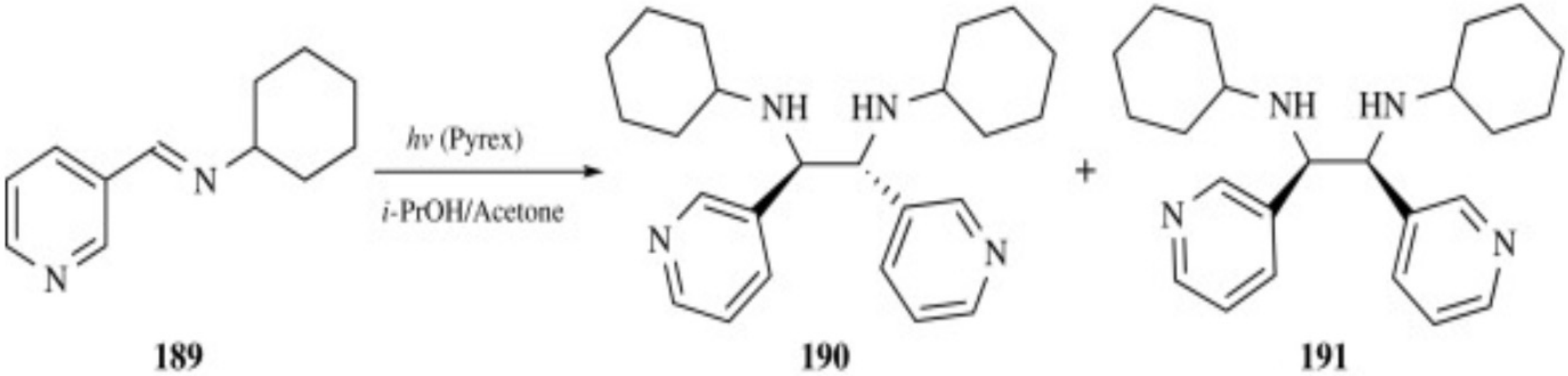
Application: Steroidal Scaffold



i, Hg, Et_4NCl, aq. MeCN, –1.80 V, 81%

Trost, B. M. Fleming, I. Pinacol Coupling Reactions. In *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry, Vol. 1 - 9* , pp 563 – 591.

Variant: Imines



Trost, B. M. Fleming, I. Pinacol Coupling Reactions. In *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry, Vol. 1 - 9* , pp 563 – 591.

Variant: McMurry Reaction

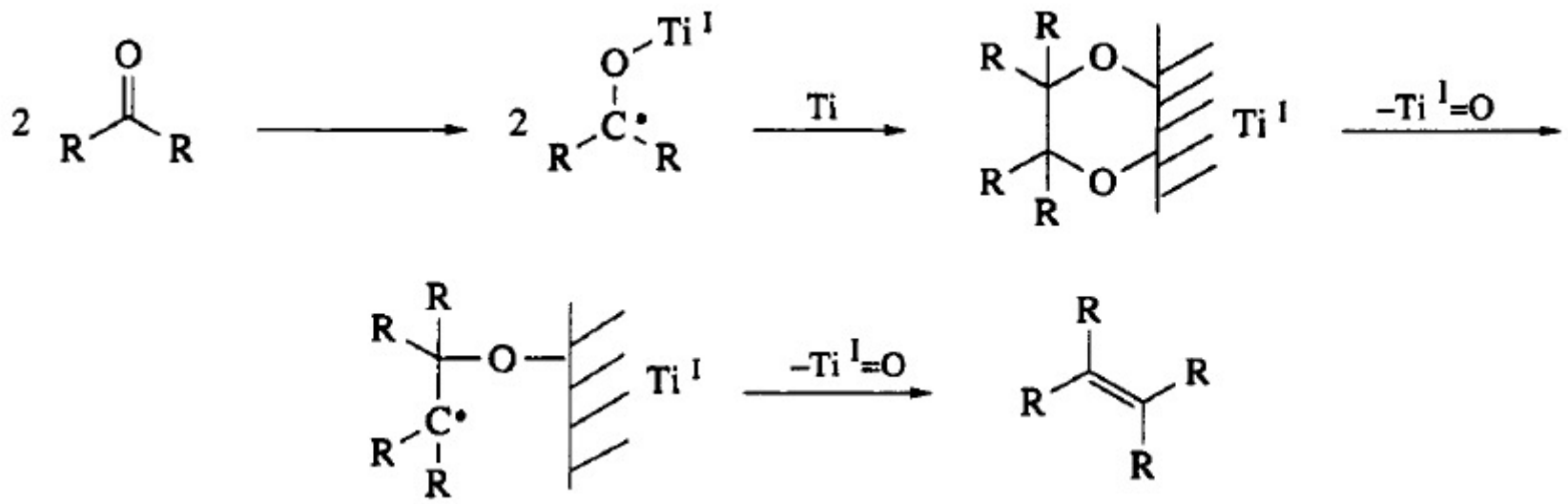
(E):*(Z)* =13:1 to 31:1

i, WCl_6, $LiAlH_4$, THF, r.t., 60–80%

- Oxophilic metal (**Ti**, W) to promote deoxygenation.
- Reducing agent: Mg, Zn, Li, KC_8, **Zn/Cu**, LAH, Mg(Hg).

Trost, Barry M. Fleming, Ian. (1991). *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry, Volumes 1 - 9 - 2.6*

McMurry Reaction - Mechanism



- Subsequent deoxygenation after pinacol coupling.
- Thermodynamic control on E/Z selectivity.

Trost, Barry M. Fleming, Ian. (1991). *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry, Volumes 1 - 9 - 2.6*

Thank You!