The Morita-Baylis-Hillman Reaction

Stephen Goble

Organic Super-Group Meeting
Literature Presentation

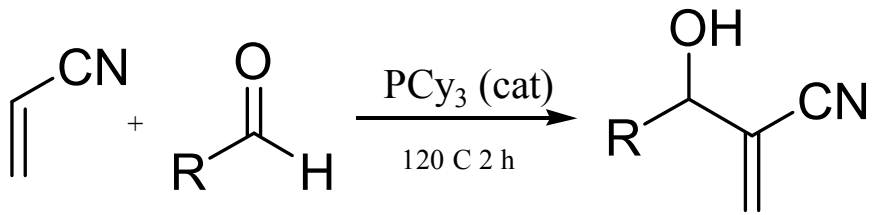
November 19, 2003

Leading References: Drewes, S. E. *et. al.* **1988**. *Tetrahedron*. 4653-4670.
Basavaiah, D. *et. al.* **1996**. *Tetrahedron*. 8001-8062.
Langer, P. **2000**. *Angew. Chem. Int. Ed.* 39(17) 3049-3052.

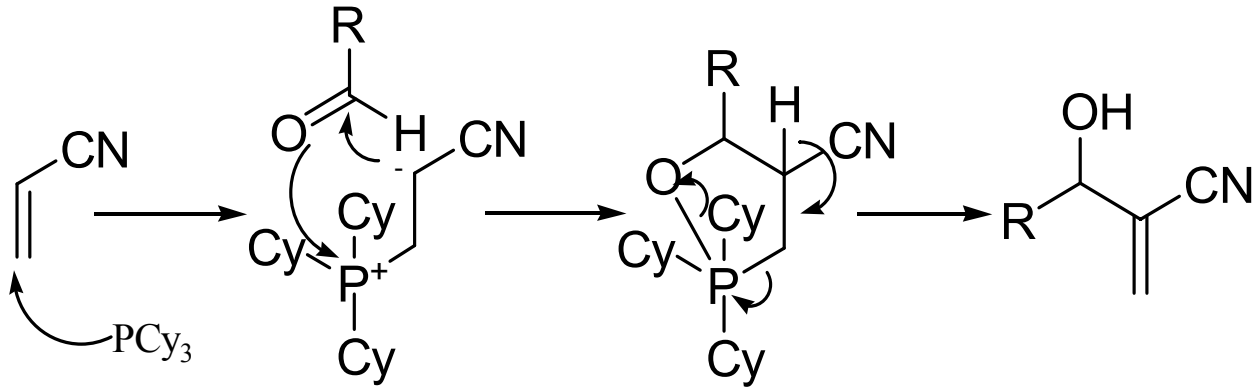
Contents

Introduction: Morita - First Nucleophilic Triggered Acrylic α-Substitution

- Morita, K., Suzuki, Z., and H. Hirose. **1968**. *Bull. Chem. Soc. Jpn.* 41, 2815.



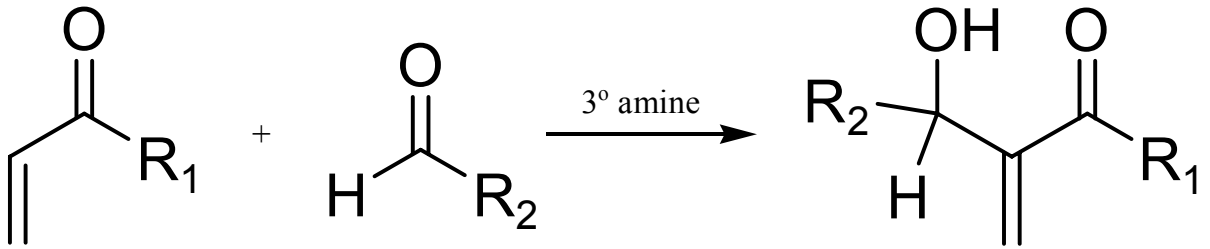
- Proposed Mechanism:



- Low Conversions (<23%); Negligible Utility.
- With PPh_3 (1 Eq), the Wittig product predominates.

Introduction: Baylis & Hillman Patents

German Patent DE-B 2,155,113 (1972) & US Patent 3,743,669 (1973) – To M. E. Hillman and A. B. Baylis (Celanese Corporation – North Plainfield, NJ)

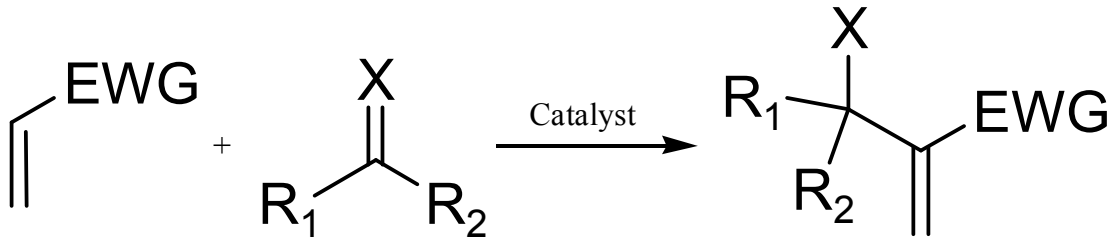


Claims: Method for the preparation of acrylic compounds from the reaction between α,β-unsaturated carboxylic acid derivatives and aldehydes in the presence of a sterically unhindered tertiary amine catalyst.

- High Conversions & Yields
- Versatile: Broad substrate/catalyst tolerance; Broad Temperature Range (0-200 C), but very slow at RT (days).
- No Journal Publications; First Prominent Journal Citation Appeared in 1982

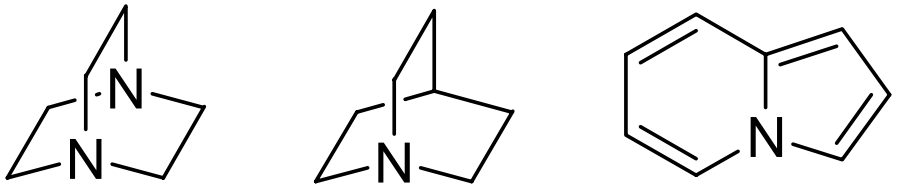
Introduction: Morita-Baylis-Hillman Reaction

General Form:



3 Essential components: An activated **alkene**, an **electrophile** and a **nucleophilic trigger (catalyst)**

Most effective catalysts are nucleophilic un-hindered tertiary amine such as DABCO, Pyrrocoline, and Quinuclidine



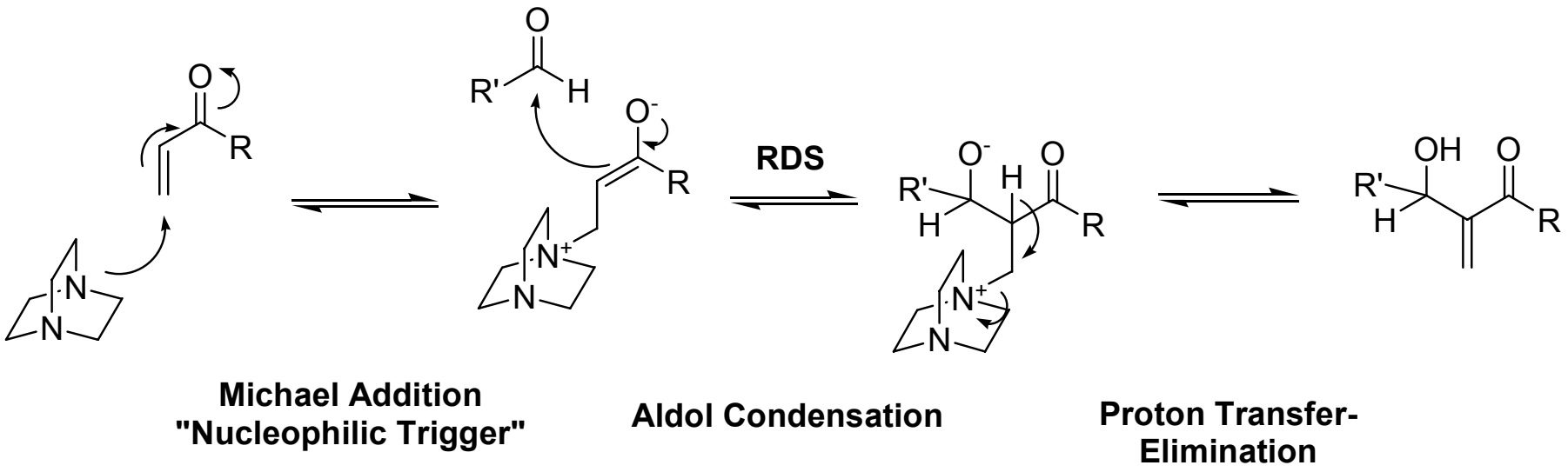
Some Advantages to the MBH:

- C-C Bond forming reaction w/ mild conditions.
- Wide range of substrates (electrophiles and alkenes).
- Atom economical.
- Synthetically useful products.

Introduction: Mechanism

Mechanism consists of 3 Steps:

1. Michael addition of the nucleophilic trigger catalyst to the activated alkene.
2. Quenching the Zwitterionic adduct with an electrophile.
3. Proton transfer and elimination of the catalyst.

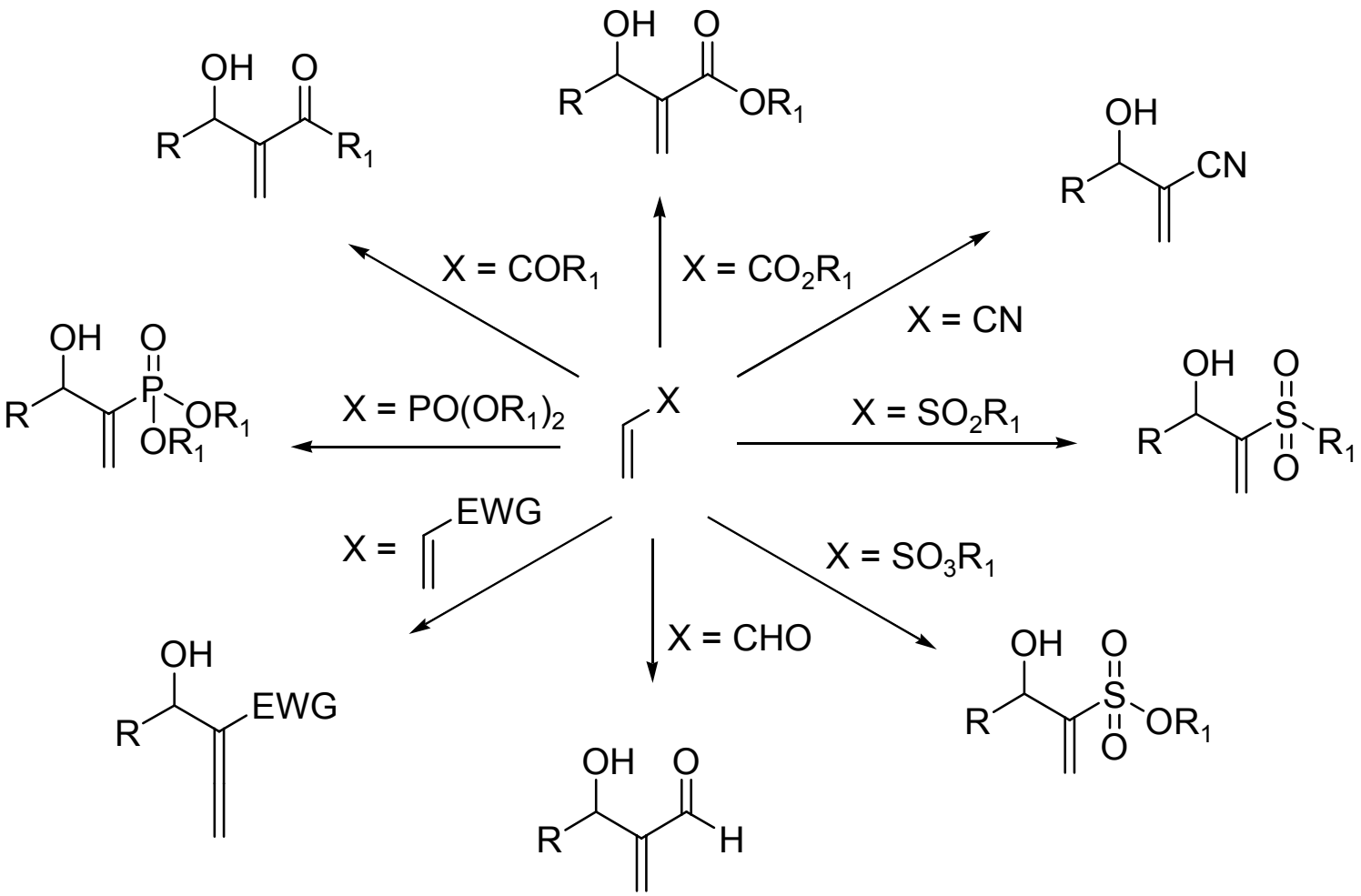


**Since the electrophilic quench is RDS, rate enhancement can be achieved by stabilizing the Zwitterion or by activating the aldehyde

Scope & Limitations: The Alkene

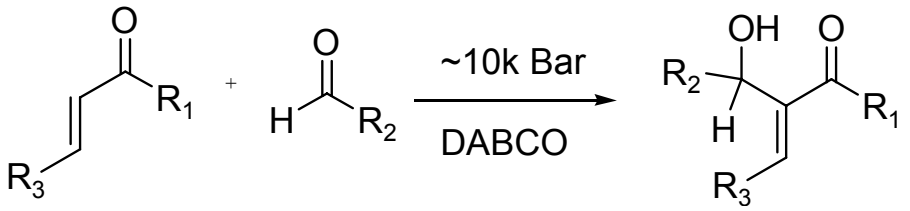
- MBH reaction tolerates a wide range of activated alkenes:

Reaction with aldehydes at atmospheric pressure with DABCO catalyst:

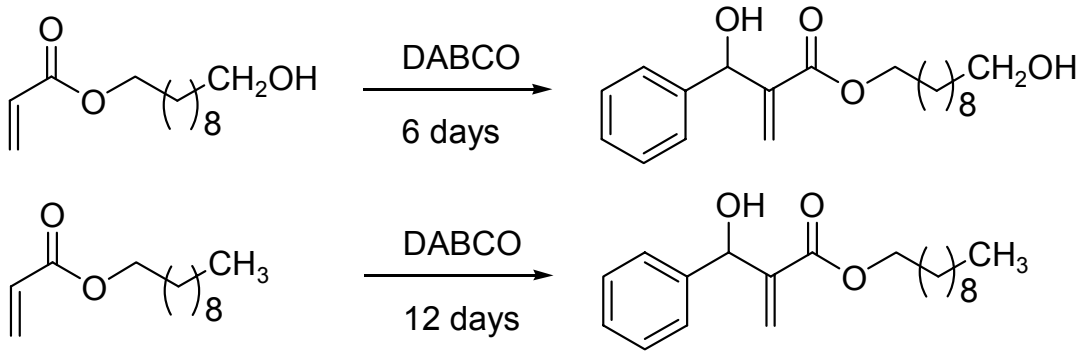


Scope & Limitations: The Alkene

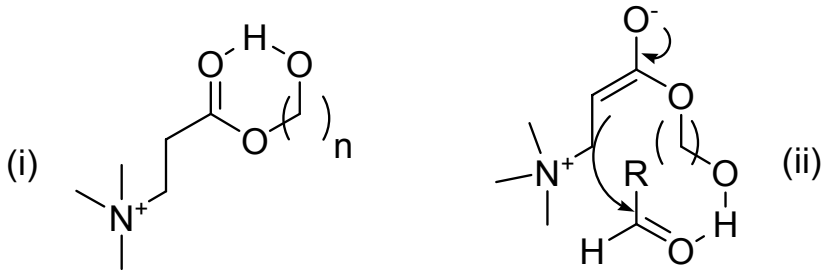
- Sterics: Hindered β-substituted derivatives require higher pressures: (Hill, J. S. and N. S. Isaacs. **1988**. *J. Chem. Res.* 330):



- Hydrogen bonding groups increase reaction rates (Ameer, F. *et. al*. **1988**. *Synth. Comm*. 18, 495; Drewes, S. E. *et. al.* **1988**. *Synth. Comm.* 18, 1565):
  - Example:

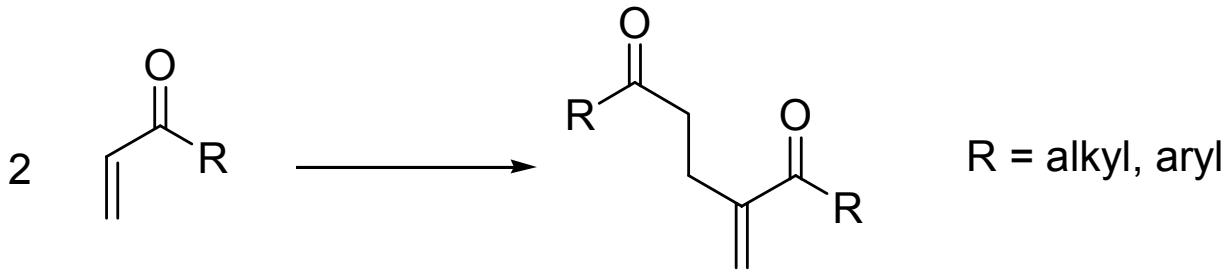


  - Explanation: Stabilization of the adduct (i) and/or activation of the aldehyde.

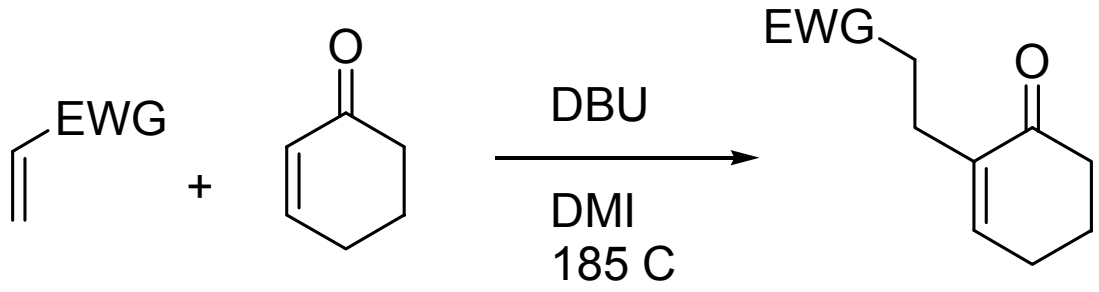


Scope & Limitations: The Electrophile

- Most common electrophiles for atmospheric pressure reactions:
  - Aldehydes, α-keto-esters, fluorinated ketones, aldimines.
- Ketones are inert at atmospheric pressure. High pressures are required (Hill, J. S. and N. S. Isaacs. **1986**. *Tetrahedron Lett.* 27 (41) 5007-5010).
- In the absence of a good electrophile the alkene can dimerize (Basavaiah, D. et. al. **1987**. *Tetrahedron Lett.* 28, 4591):

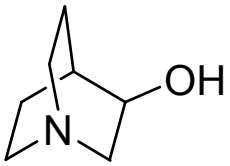


- 1,4-Addition electrophiles (Hwu, J. R. *et. al.* **1992**. *Tetrahedron Lett.* 33, 6469):

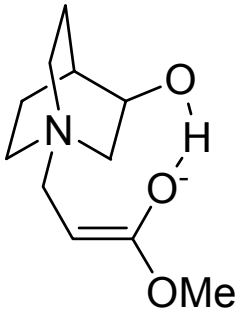


Scope & Limitations: The Catalyst

- Un-hindered – nucleophilic catalysts are preferred.
- Basicity of the Catalyst: Reaction rates generally increase with increased basicity (Hine, J. and Y. J. Chen. **1987**. *J. Org. Chem.* 52. 2091-2094)
- Hydrogen bonding catalysts increase reaction rates:



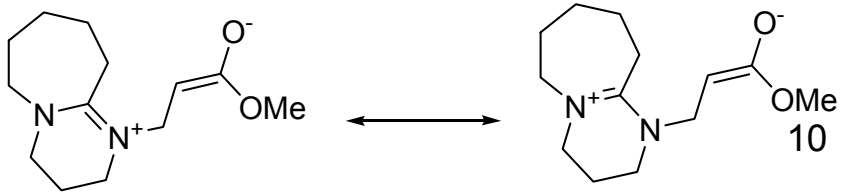
3-Quinuclidine



3-quinuclidinole stabilizes the Zwitterionic intermediate by H-bonding (Drewes, S. E. et. al. **1988**. *Synth Comm.* 18, 1565-1568)

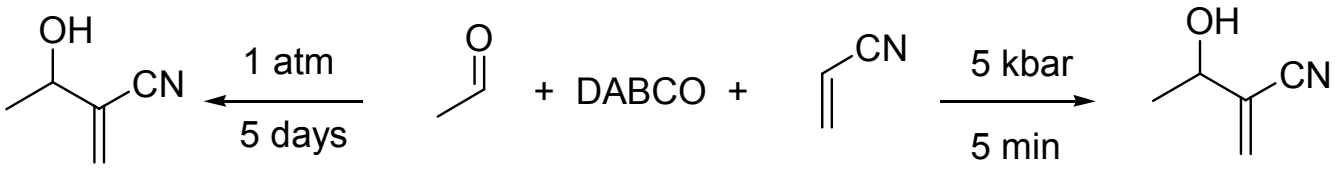
- Lanthanide lewis acid triflates (i.e. $La(OTf)_3$) accelerate the reaction up to 5-fold (Aggarwal, V. K. et. al. **1998**. *J. Org. Chem.* 63, 7183-7189) – also stabilizes zwitterion and/or activates aldehyde.
- DBU was recently found to be a superior catalyst (10-fold rate enhancement observed vs. 3-QDL) (Aggarwal, V. K. et. al. **1999**. *Chem. Comm.* 2311-2312). – <u>hindered</u> and <u>non-nucleophilic</u>.

Stabilization of Zwitterion



Scope & Limitations: Reaction Conditions

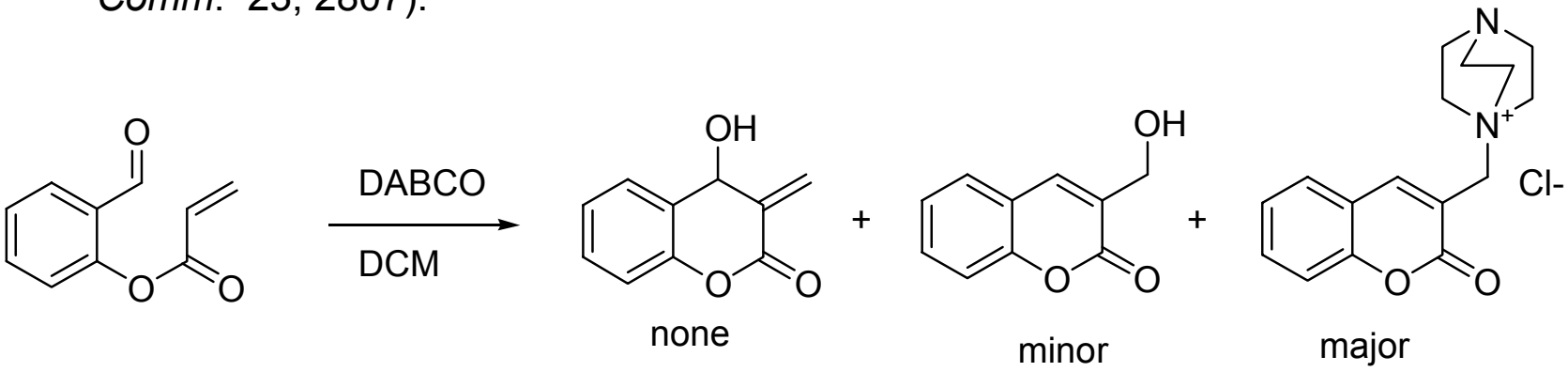
- Reaction Pressure: (Hill, J. S. and N. S. Isaacs. **1986**. *Tetrahedron Lett.* 27 (41) 5007-5010)
  - High pressures Increase rates of reaction (volume of activation = -70 cm^3/mol).



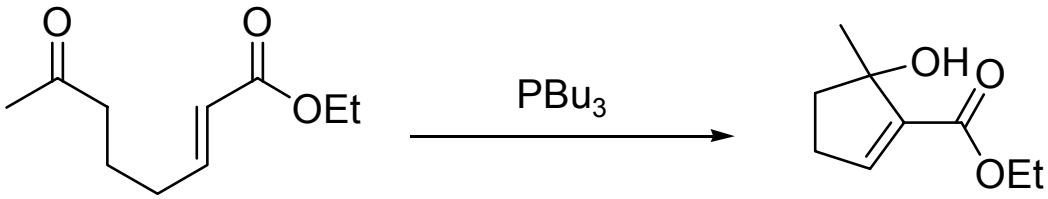
  - Making a wider variety of substrates available (β-substituted and electron poor alkenes; ketones as electrophiles).
  - The reaction gives better yields with less reactive catalysts (triethylamine over DABCO) at high pressures.
- Solvent effects:
  - Hydrogen bonding increases the rate of the reaction (Ameer, F. et. al. **1988**. *Synth. Comm*. 18, 495).
    - Significant rate enhancements seen with methanol and water as additives or solvents (Auge, J. et. al. **1994**. *Tetrahedron Lett*. 35(43) 7947-7948).
- Temperature – highly substrate dependent. Microwave utilization can shorten times from days to minutes (Kundu, M.K. et. al. **1994**. *Synlett.* 444)

Intramolecular Morita-Baylis-Hillman

- Activated alkene and electrophile in the same molecule:
  - Few amine catalyzed examples (Drewes, S. E. et. al. **1993**. *Synth. Comm*. 23, 2807):

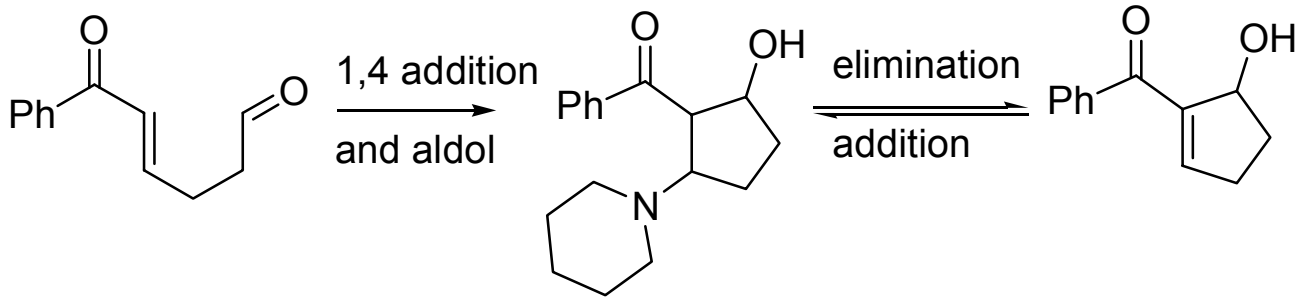


  - Phosphine catalysis gives the desired MBH product (Roth, F. et. al. **1992**. *Tetrahedron Lett.* 33, 1045):



Intramolecular Morita-Baylis-Hillman

- Secondary Amines Catalyze Intramolecular MBH (Black, G. P. et. al. **1997**. Tetrahedron Lett. 38(49) 8561-8564):

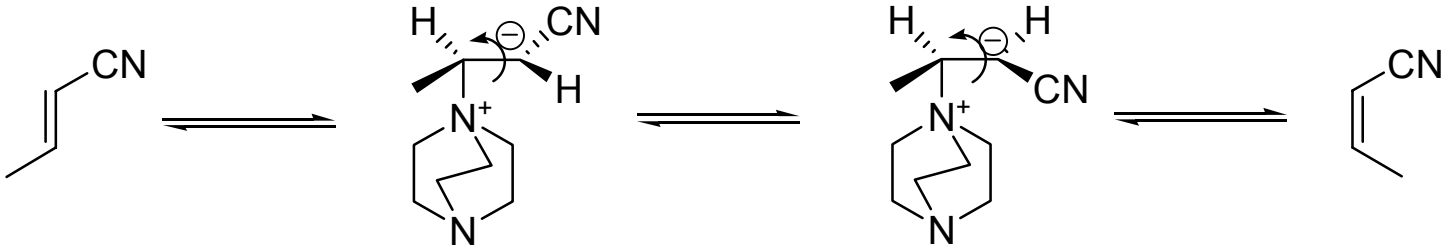


- Conditions: catalyst (30%), $CDCl_3$, 7 days
- Catalysts: Various cyclic secondary amines including piperidine, piperazine, pyrrolydine.
- Best conversion and yields with piperidine (93% (55%))

E/Z Selectivity in the Baylis-Hillman

Rozendaal, E. Van *et. al.* **1993**. *Tetrahedron.* 49(31) 6931-6936.

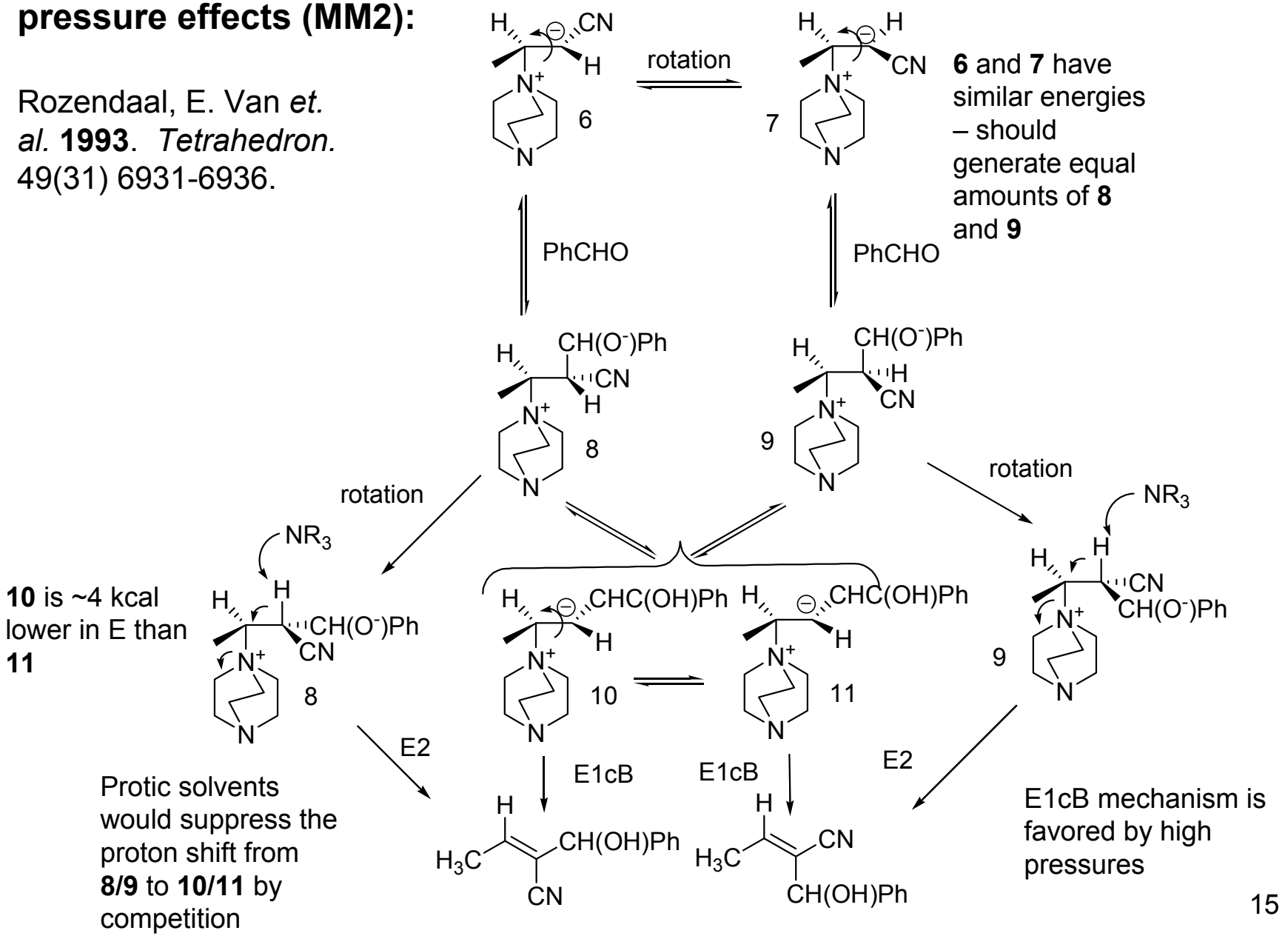
- When the alkene is β-substituted the product is a mixture of E/Z isomers:
  - Because the first step is reversible, the SM will be equilibrated prior to the reaction:



  - Solvent Effects vs. Pressure:
    - E/Z ratio (RT/1 atm)(crotonaldehyde/benzaldehyde/DABCO):
      neat = 1; THF = 1.3; $CHCl_3$ = 1.5; MeCN = 3; MeOH = 4
    - Higher pressures enhance this ratio dramatically for less polar solvents, and neat reactions (p = 15 kbar)
      neat = 13; THF = 12; $CHCl_3$ = 25; MeCN = 7; MeOH = 4
  - Catalyst Effects:
    - Decreased basicity of the base leads to increased E/Z ratios:
      triethylamine = 4; quinuclidine = 2; DABCO = 1

Proposed Explanation of pressure effects (MM2):

Rozendaal, E. Van *et. al.* **1993**. *Tetrahedron.* 49(31) 6931-6936.



6 and **7** have similar energies – should generate equal amounts of **8** and **9**

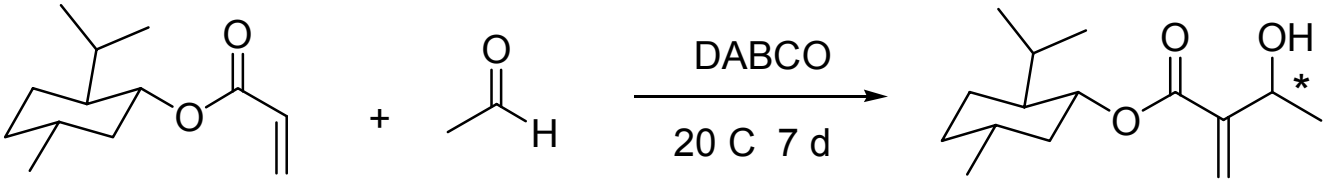
10 is ~4 kcal lower in E than **11**

Protic solvents would suppress the proton shift from **8/9** to **10/11** by competition

E1cB mechanism is favored by high pressures

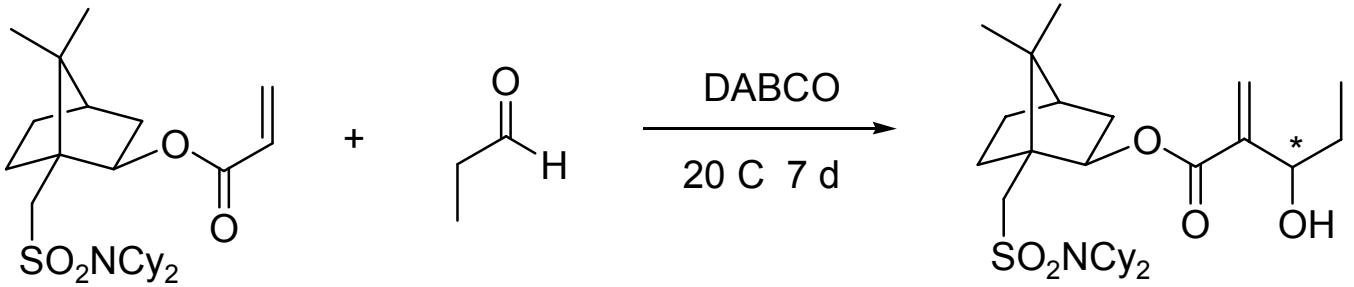
Asymmetric Morita-Baylis-Hillman Reactions

- Chiral Auxiliaries on the acrylate at atmospheric pressure:
  - Menthyl acrylates: poor d.e. at 1 atm (Brown, J. M. et. al. **1986**. *Tetrahedron Lett*. 27(28) 3307-3310):



58:42 diasteromer mix

  - Oppolzer's Auxiliary: up to 70% d.e. at 1 atm (Basavaiah, D. et. al. **1990**. *Tetrahedron Lett*. 31(11) 1621-1624):



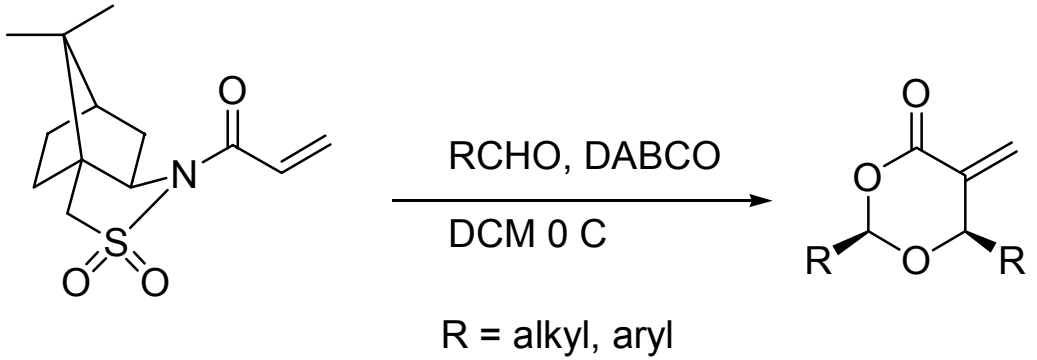
Asymmetric Morita-Baylis-Hillman Reactions

- Chiral Auxiliaries on the acrylate at elevated and lowered pressures

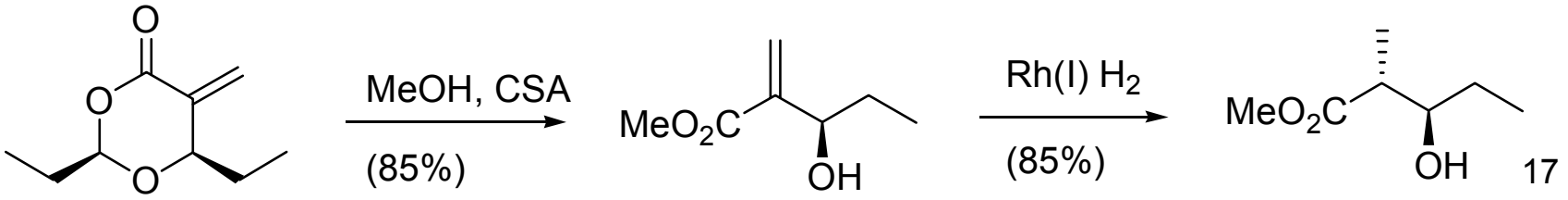
(Gilbert, A. et. al. **1991**. *Tetrahedron: Asymmetry*. 2(10) 969-972)

  - Using (-) menthyl and (-) bornyl chiral auxiliaries were employed to give elevated d.e. in most cases.
  - Highly substrate dependent

- Leahy's Sultame improvement (Brzezinski, L. J. et. al. **1997**. *J. Am. Chem. Soc*. 119, 4317-4318):

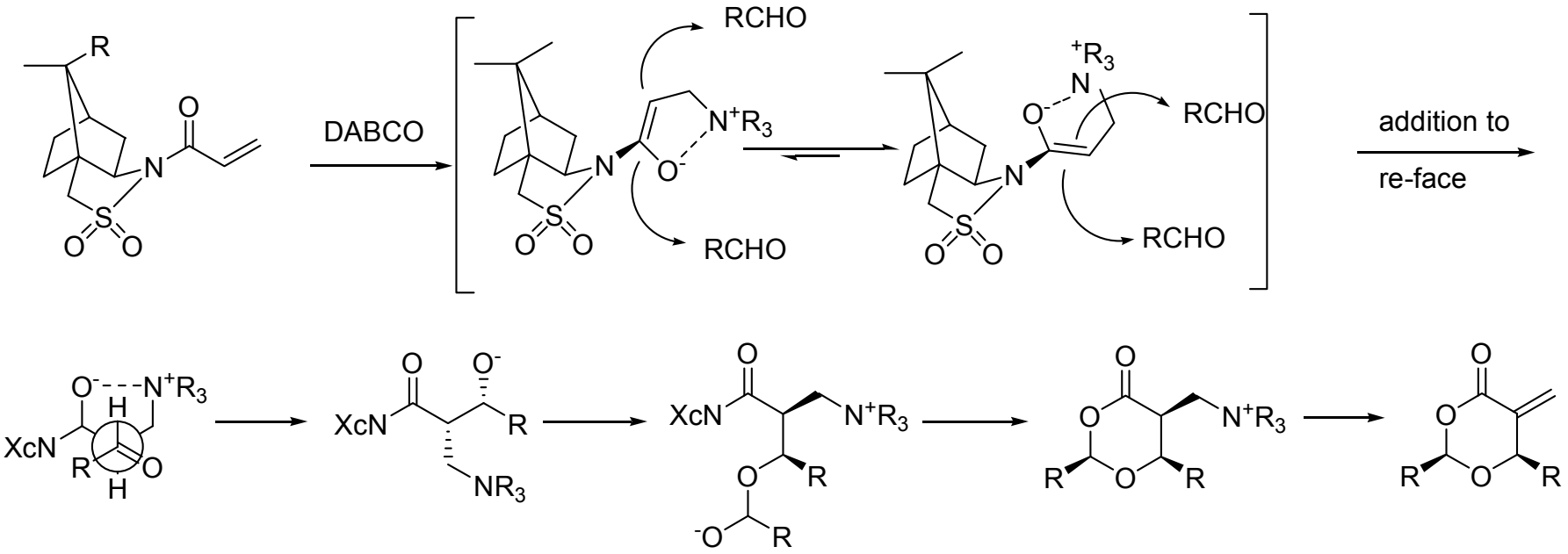


- ~15 equivalents of aldehyde
- α-branched aldehydes give poor yields



Asymmetric Morita-Baylis-Hillman Reactions

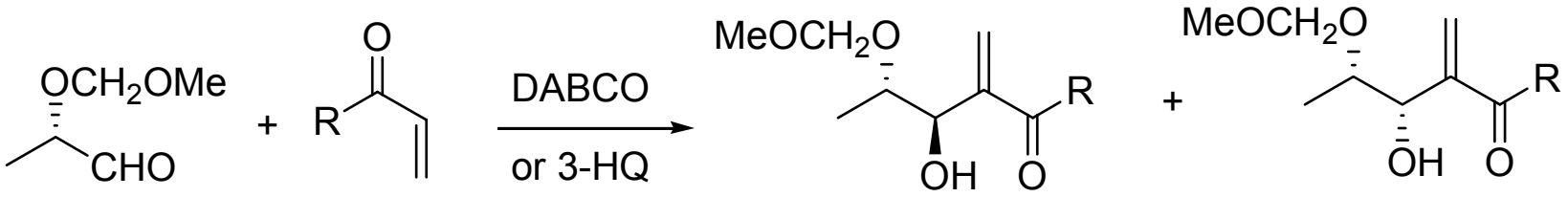
Explanation of diastereoselectivity:



Preferential *re* (α) face addition to the favored rotamer (**9**) accounts for the selectivity – *si* (β) face is blocked by the sulfonyl oxygens.

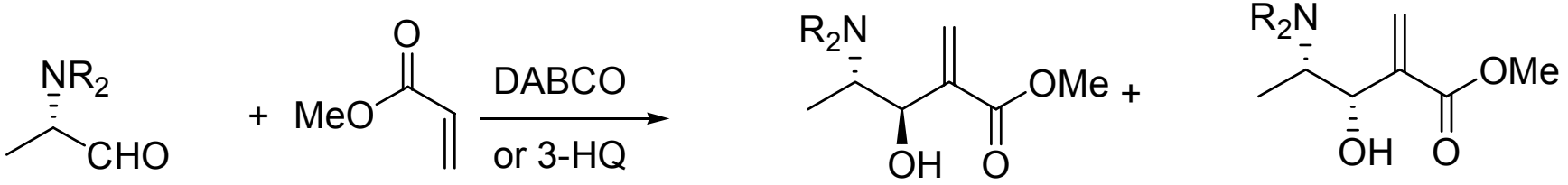
Asymmetric Morita-Baylis-Hillman Reactions

- Chiral Electrophiles:
  - Initial Attempts (Drewes, S. E. et. al. **1988**. *Synth Comm.* 18, 1565-1568):



70 : 30

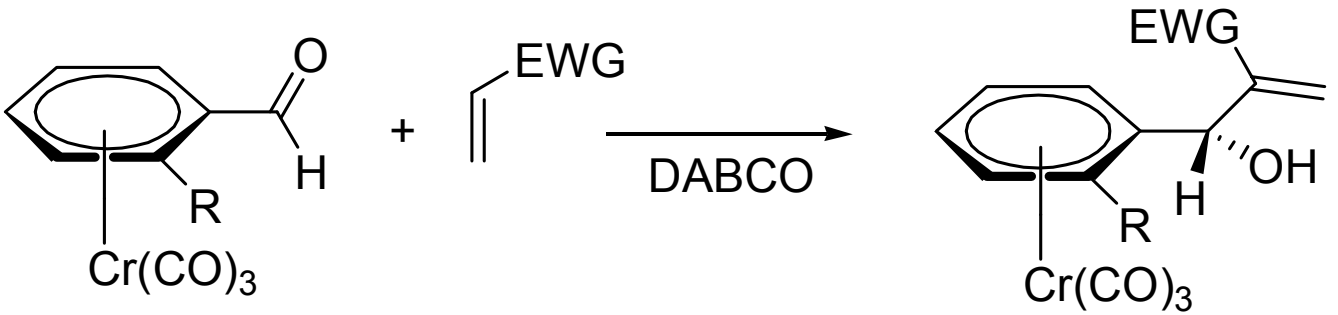
  - Increased pressures has shown no improvement in d.e. (Gilbert, A. et. al. **1991**. *Tetrahedron: Asymmetry*. 2(10) 969-972)
  - Better results have been seen with chiral amino aldehydes (Manickum, T. et. al. **1993**. *Synth. Comm*. 23, 183):



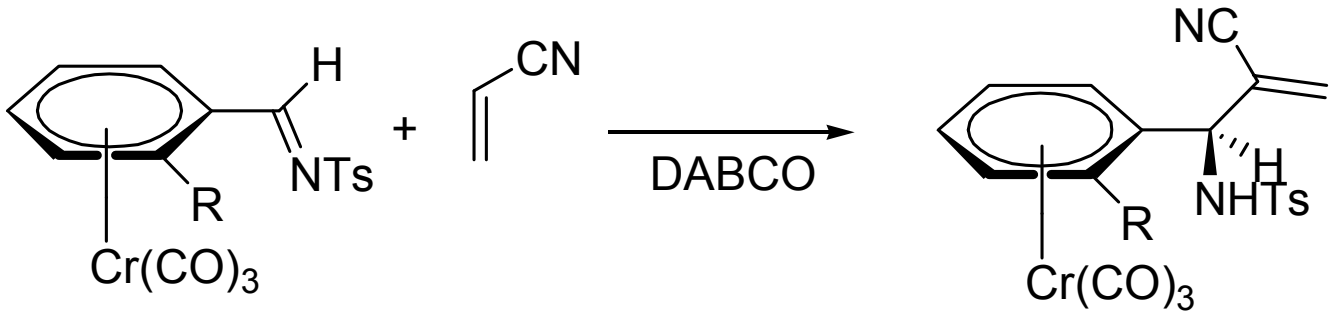
Up to 76% d.e. observed

Asymmetric Morita-Baylis-Hillman Reactions

- Chiral Electrophiles (con't):
  - Chromium tricarbonyl complexes (Kundig, E. P. et. al. **1993**. *Tetrahedron Lett.* 34, 7049):



>95% d.e.

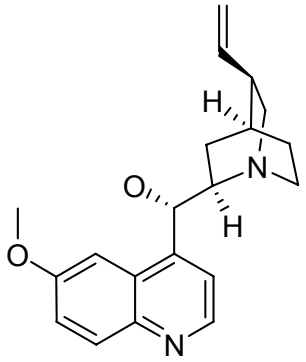


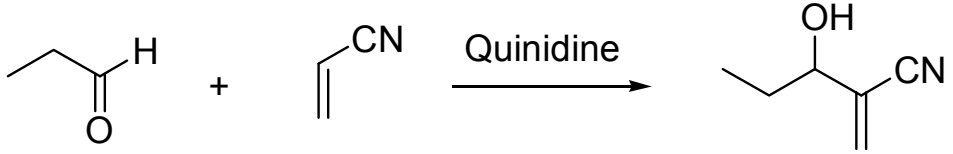
>95% d.e.

>99% e.e. after decomplexation

Asymmetric Morita-Baylis-Hillman Reactions

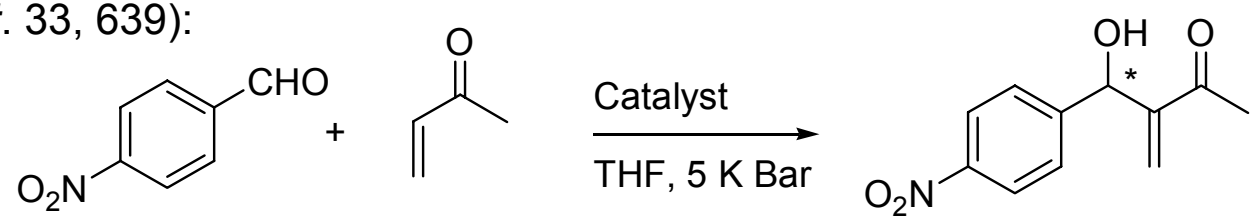
- Chiral Catalysts:
  - Early Attempts (Basavaiah, D. *et. al.* **1996**. *Tetrahedron*. 8001-8062):

Quinidine = 

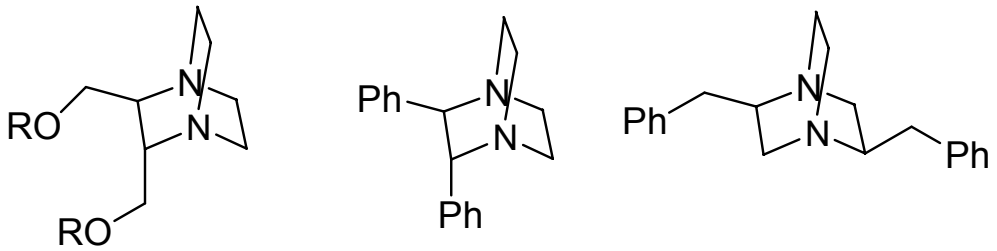


20% ee

  - C-2 symmetric DABCO derivatives (Oishi, T. et. al. **1992**. *Tetrahedron Lett*. 33, 639):

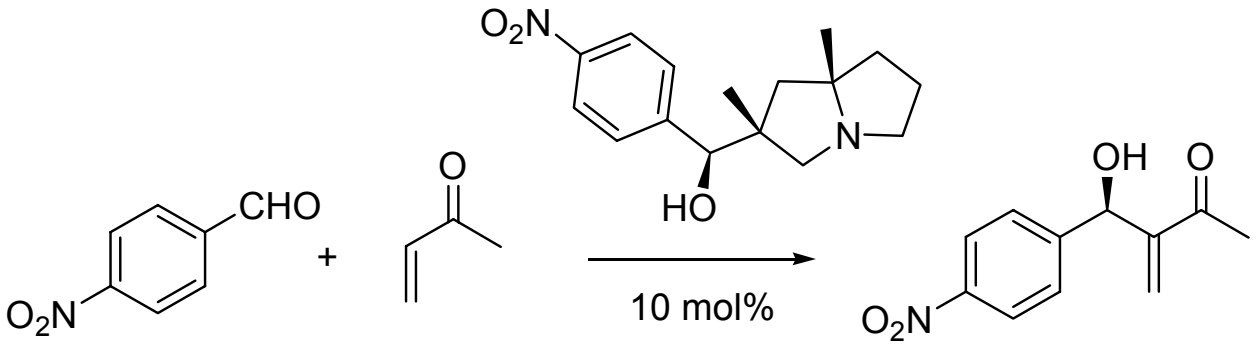


up to 47% ee

Catalysts: 

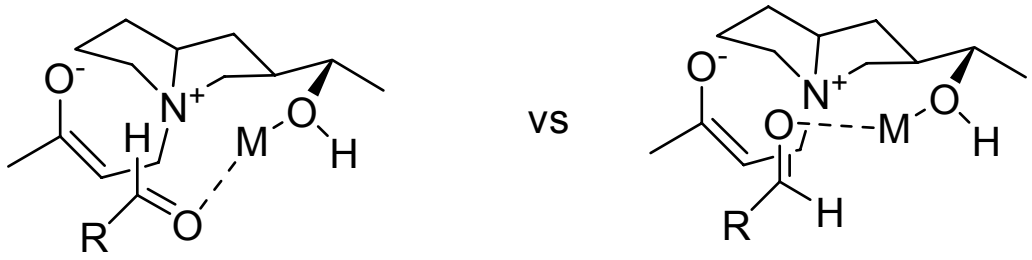
Asymmetric Morita-Baylis-Hillman Reactions

- Improved Chiral Catalysts (Barrett, A. G. M. et. al. **1998**. *Chem. Commun.* 2533-2534):



- 30-75% e.e. with a variety of substrates

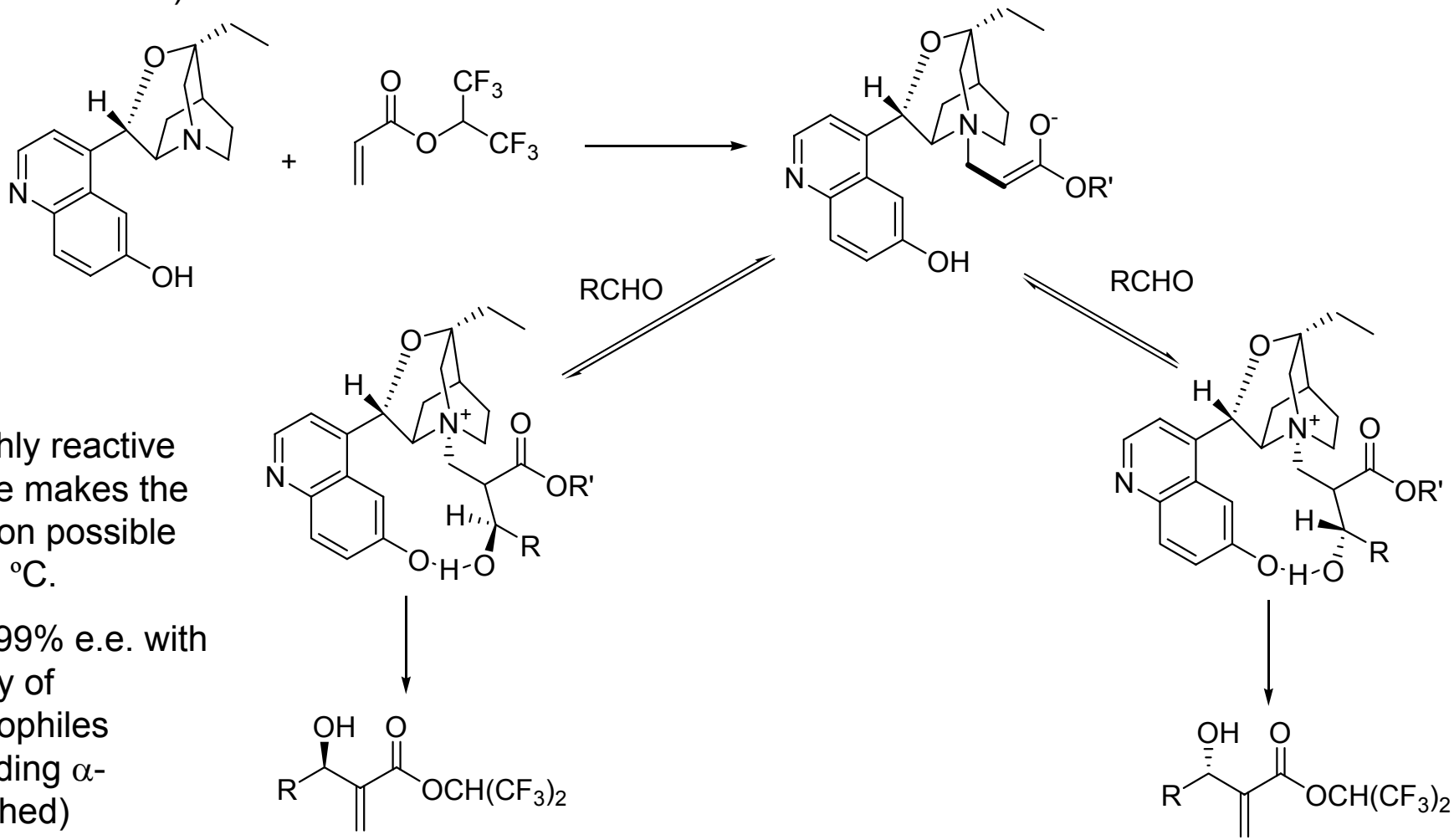
- Explanation:



Less sterically hindered!

Asymmetric Morita-Baylis-Hillman Reactions

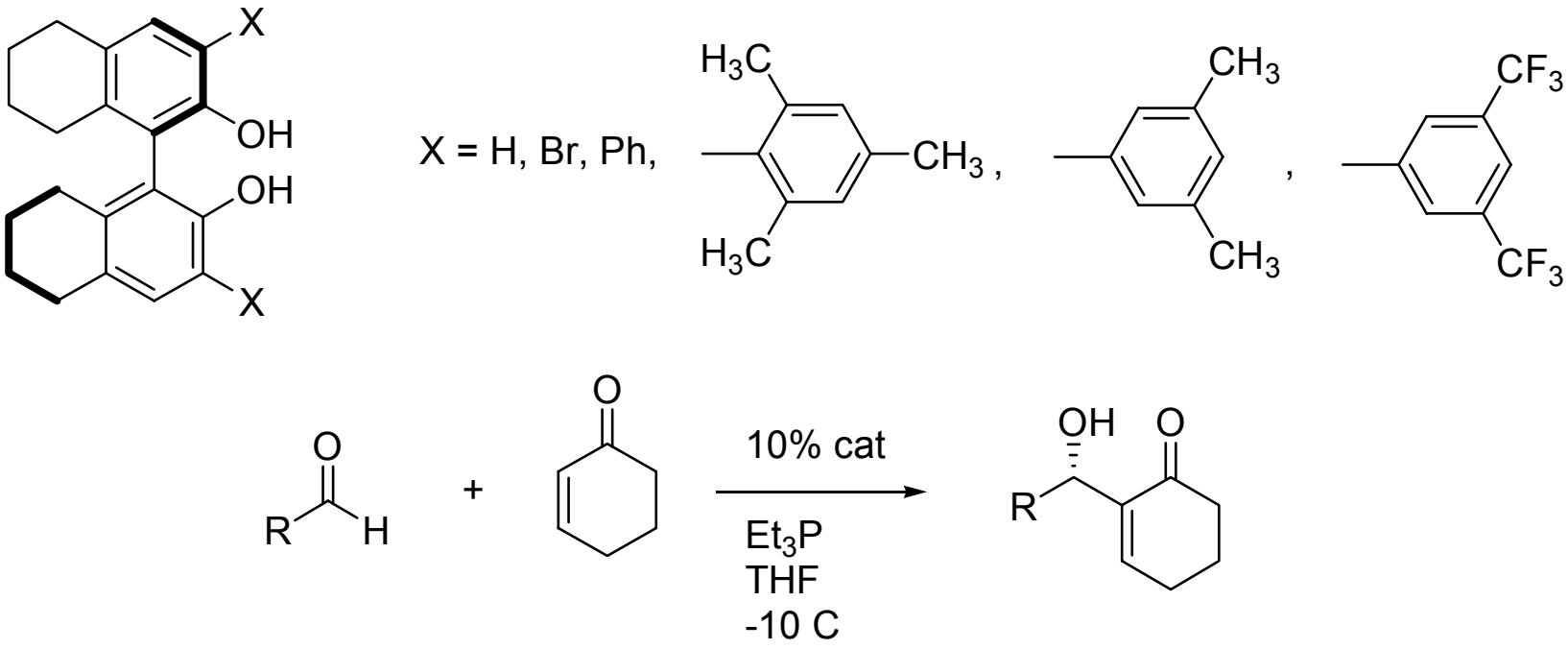
- Cinchona alkaloid catalysts (Iywabuchi, Y. **1999**. *J. Am. Chem. Soc*. 121, 10219-10220):



- Highly reactive alkene makes the reaction possible at -55 °C.
- 90-99% e.e. with variety of electrophiles (including α-branched)

Recent Applications of the Morita-Baylis-Hillman Reaction

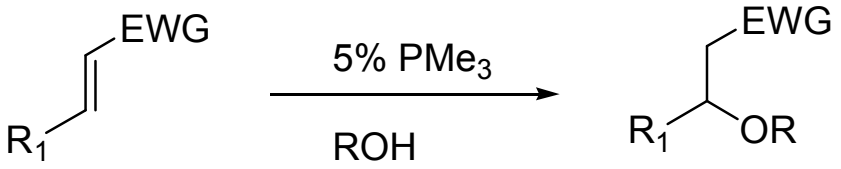
- **Asymmetric MBH Catalyzed by Chiral Brønsted Acids:** (McDougal, N. T. and S. E. Schaus. **2003**. *J. Am. Chem. Soc.* 125, 12094-12095)



80-96% ee on a variety of aldehydes

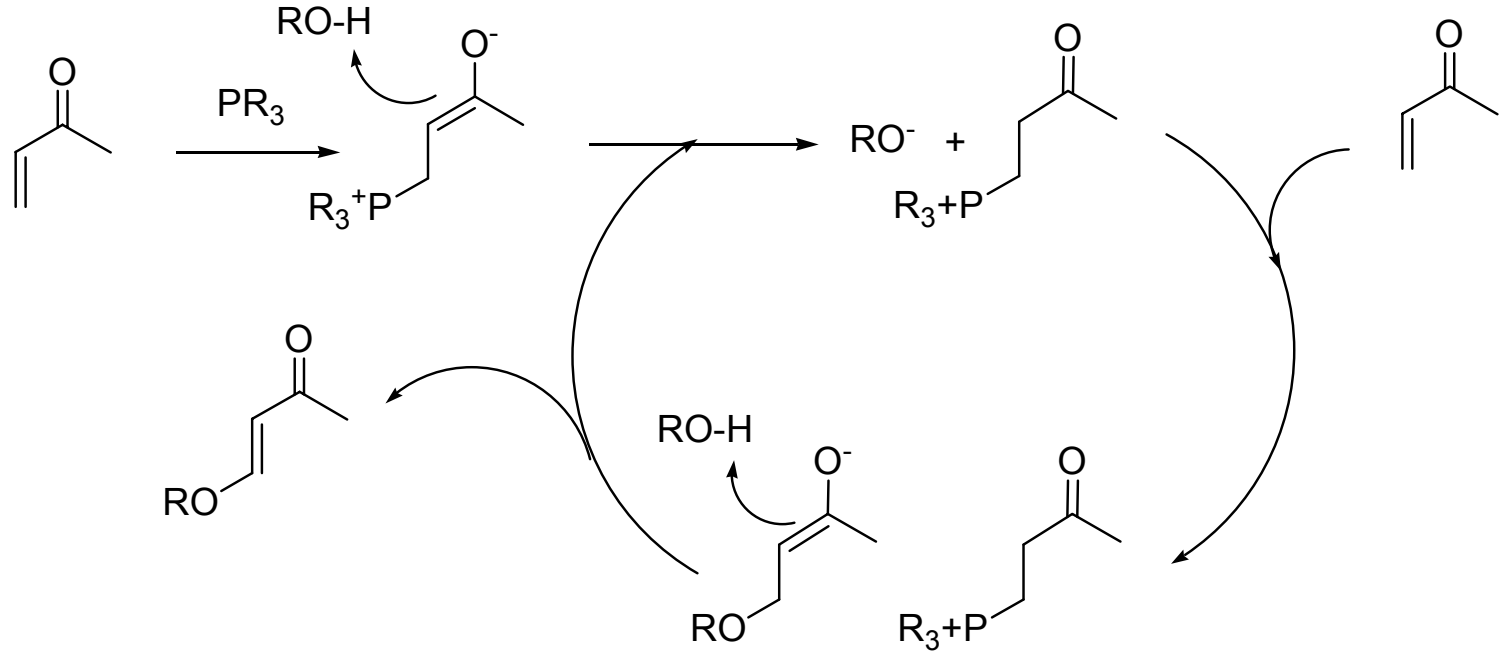
Recent Applications of the MBH Reaction

- **Phosphine Catalyzed β-Hydration Reactions** (Stewart, I. C., R. G. Bergman, and F. D. Toste. **2003**. *J. Am. Chem. Soc.* 125. 8696-8697)



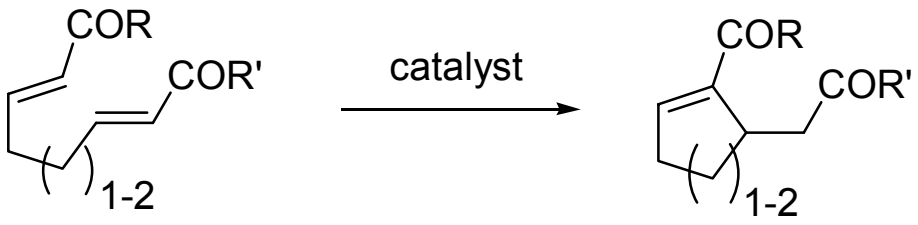
EWG = CO_2Et, COMe, CO_2Me, CN
R_1 = Me, H. Does not work with Ph
ROH = H_2O, MeOH, iPrOH, PhOH

Proposed Mechanism:



Recent Applications of the MBH Reaction

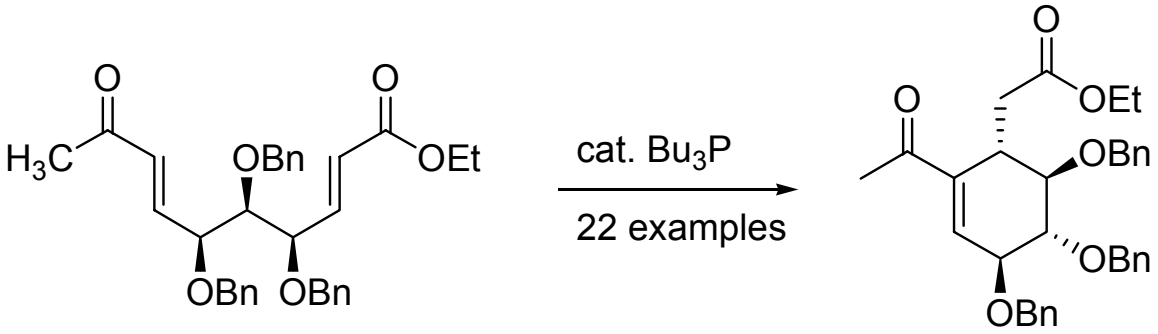
- **Intramolecular MBH with high Regioselectivity** (Frank, S., Megott, D. and W. Roush. **2002**. *J. Am. Chem. Soc*. 124(11) 2404-2405):



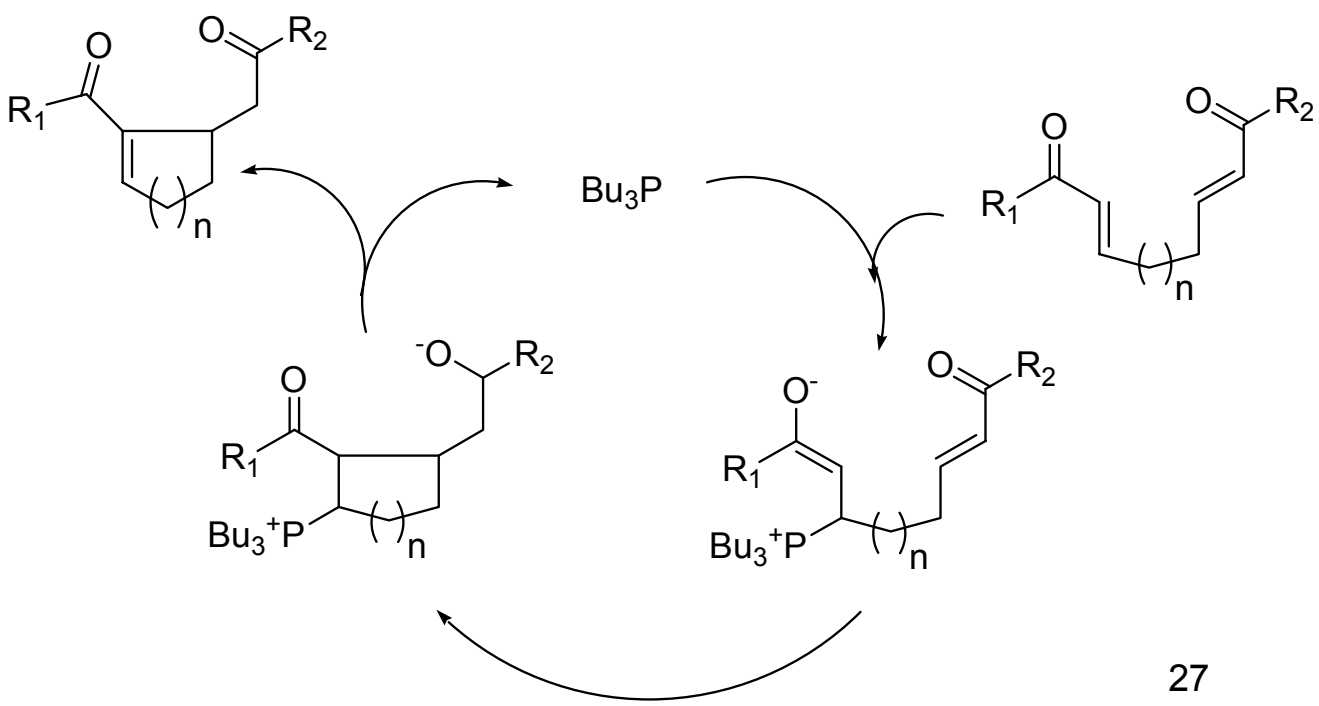
- **Catalysts: PMe_3, PBu_3**
- **Solvent: MeCN, tert-amyl alcohol**
- **Regioselectivity: Cyclization occurs almost exclusively from the ketone/aldehyde (R = alkyl, H) to the ester (R' = O-alkyl).**

Recent Applications of the MBH Reaction

- **Intramolecular Cycloisomerization of Bis-enones** (Wang, L.., Luis, A., Agapiou, K., Jang, H. and M. J. Krische. **2002**. *J. Am. Chem. Soc*. 124(11) 2402-2403):

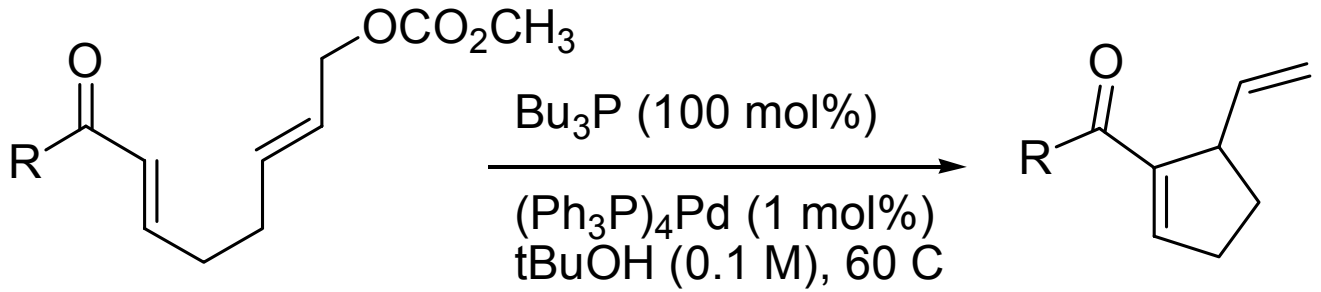


- **Wide range of 5 and 6 membered ring substrates with yields of 70-90%.**
- **Polar solvents accelerate rates but increase oligomerization.**
- **For mono-enone/mono-enoate compounds a single product is obtained.**
- **Electronic > Steric for selectivity.**



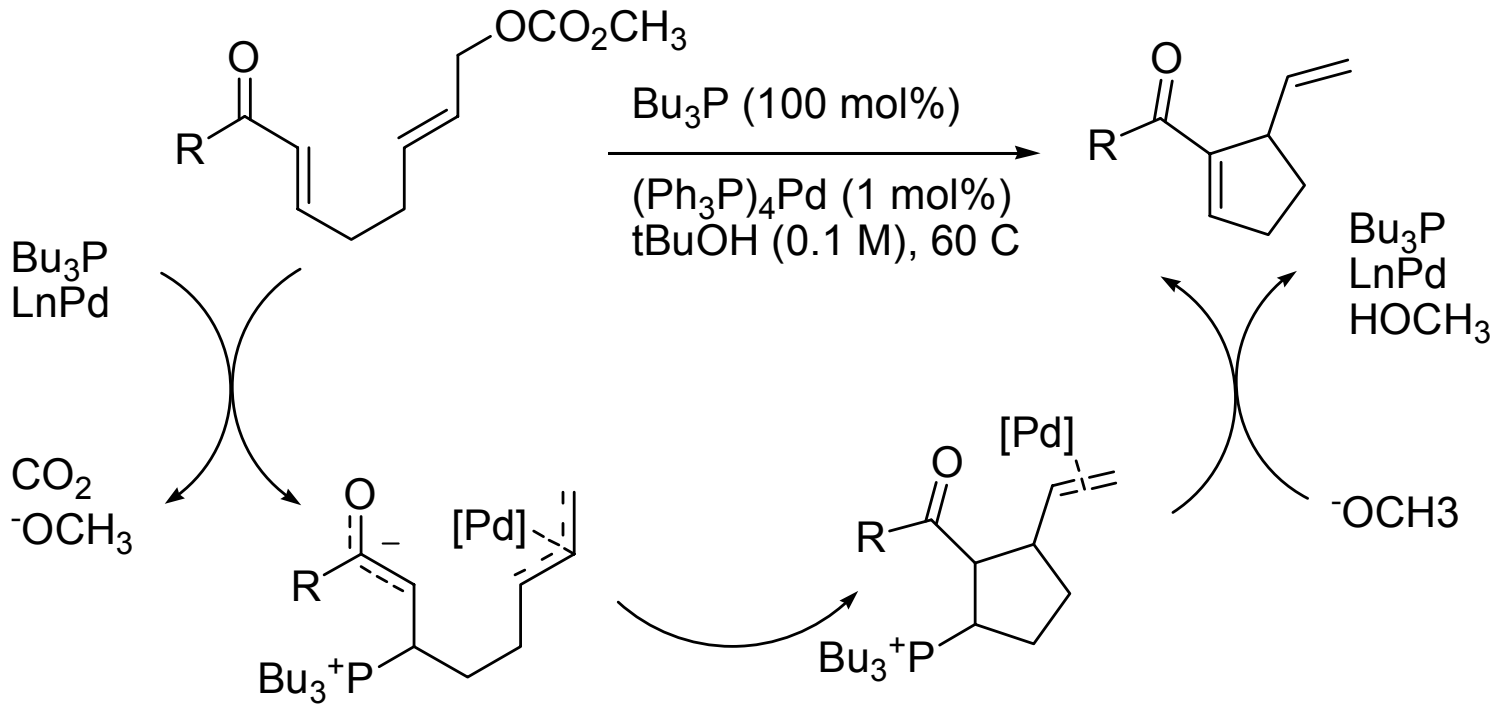
Problem Set

Problem 1: Michael Krische recently published a paper on the transformation below. A) Propose a mechanism for this reaction. B) Suggest a reason why the yields are lower when the carbonate (92%) is replaced with an acetate (67%).



Bradley G. Jellerichs, Jong-Rock Kong, and Michael J. Krische. *J. Am. Chem. Soc*. **2003.** 125. 7758-7759.

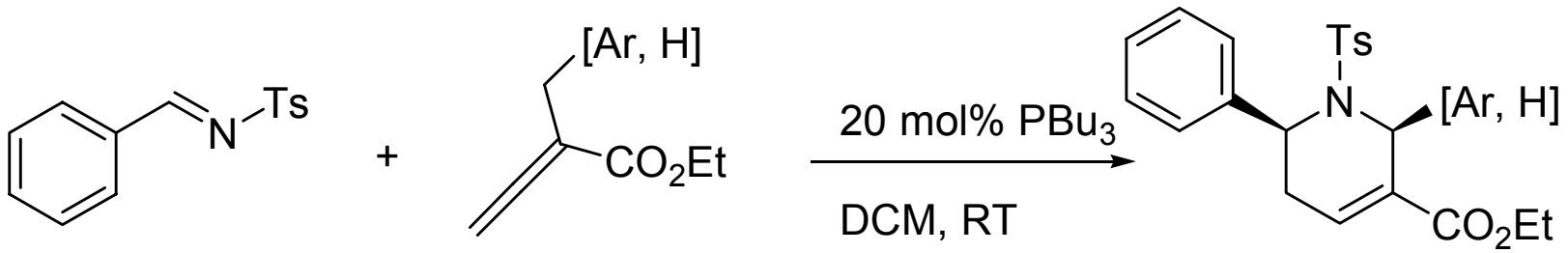
Krische's Proposal: Concomitant activation of latent nucleophilic and electrophilic partners.



Bradley G. Jellerichs, Jong-Rock Kong, and Michael J. Krische. *J. Am. Chem. Soc*. **2003.** 125. 7758-7759.

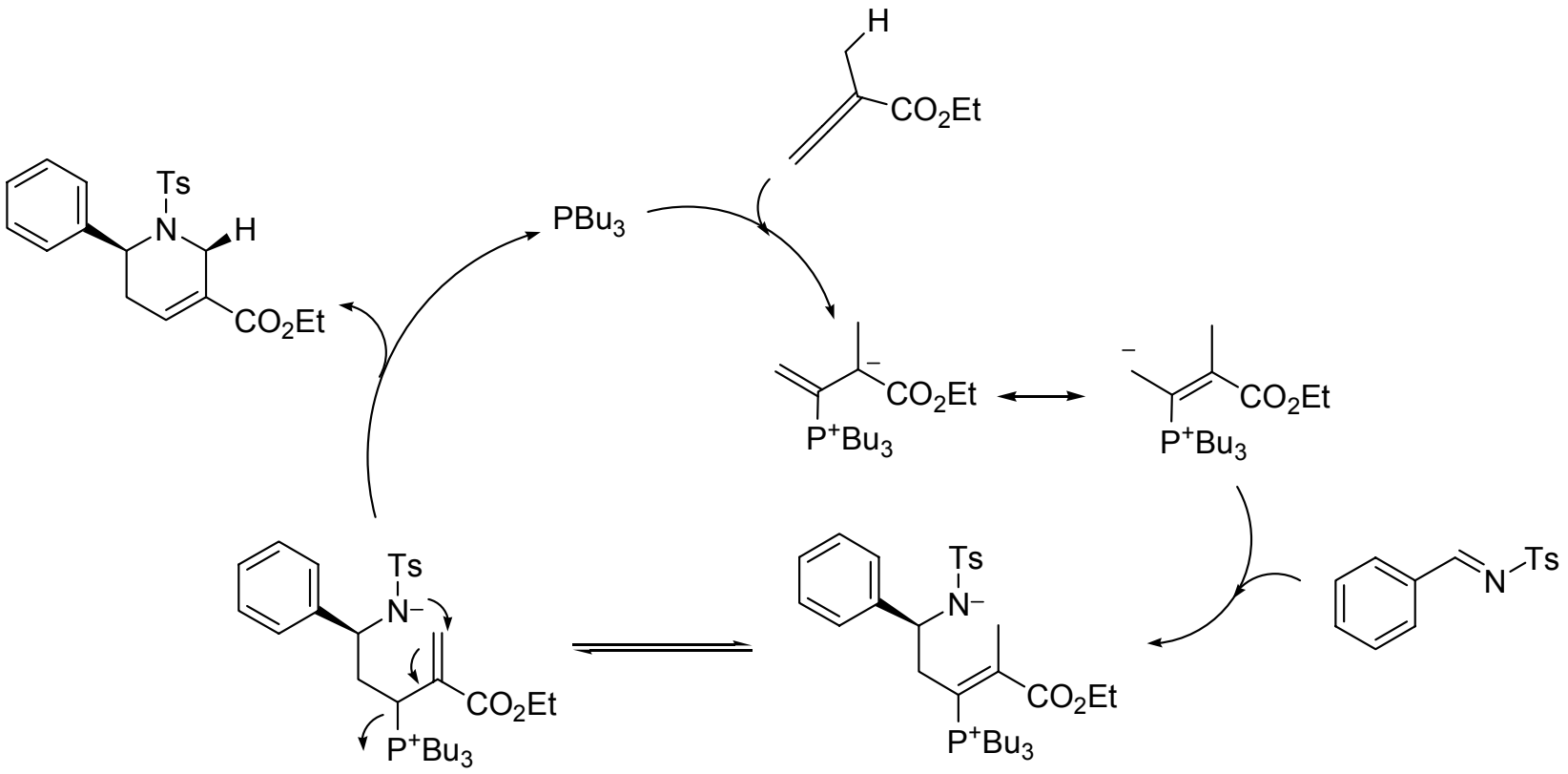
Problem Set

Problem 2: Kwon recently published a novel and efficient method for the synthesis of functionalized tetrahydropyridines. Provide a rational mechanism for this transformation.



Xue-Feng Zhu, Jie Lan, and Ohyun Kwon. *J. Am. Chem. Soc*. **2003.** 125. 4716-4717.

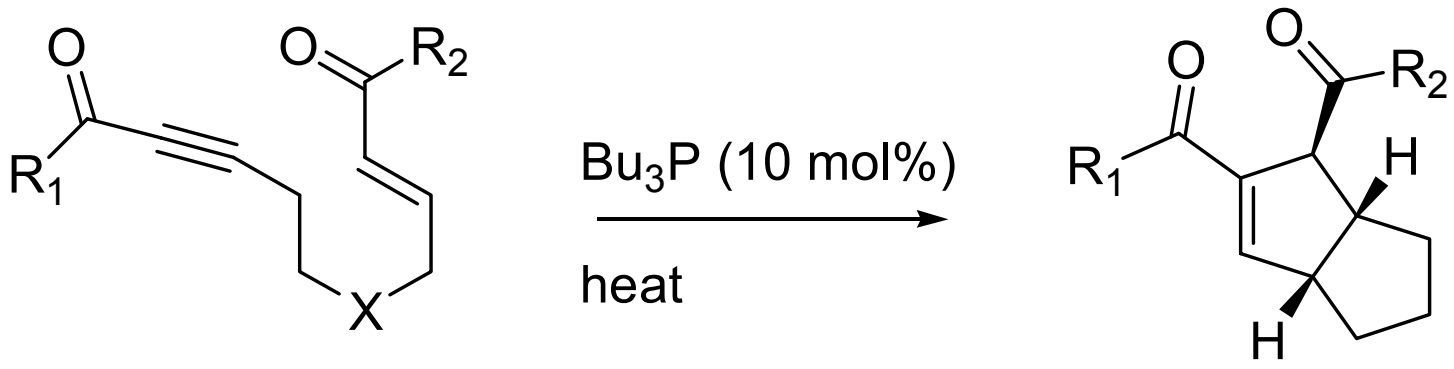
Kwon suggests the following…



Xue-Feng Zhu, Jie Lan, and Ohyun Kwon. *J. Am. Chem. Soc*. **2003.** 125. 4716-4717.

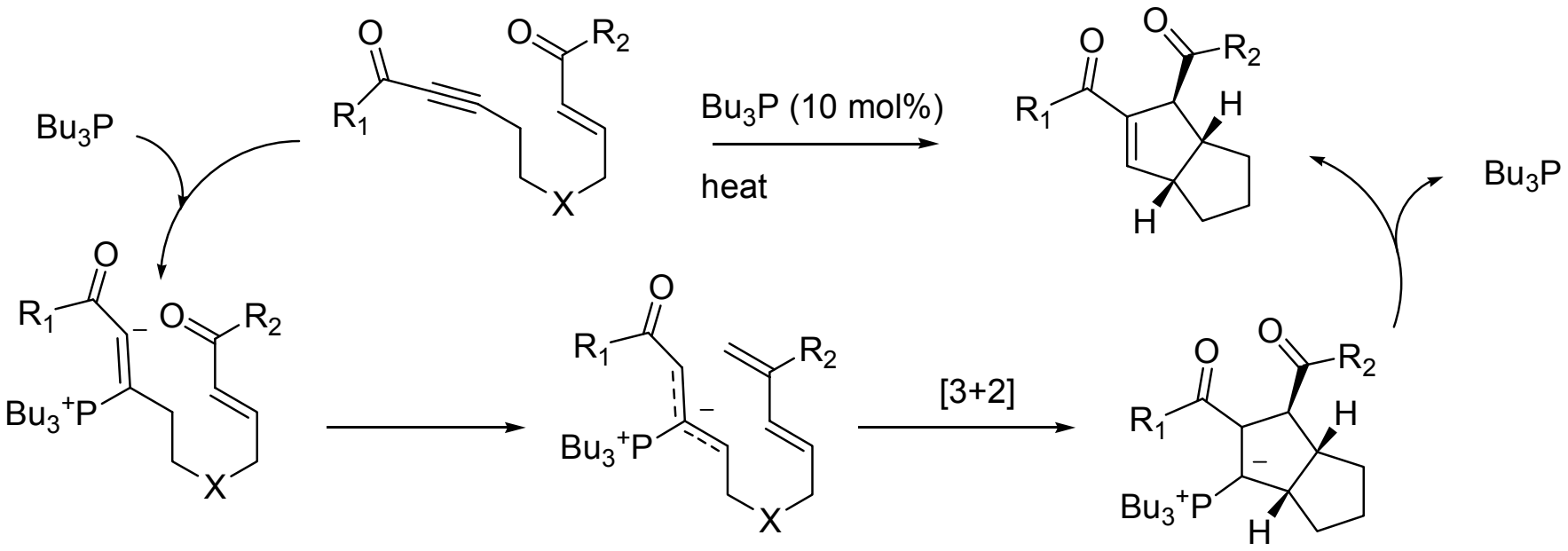
Problem Set

Problem 3: Earlier this year, Krische published a diastereoselective synthesis of diquinanes from acyclic precursors that is catalyzed by tributylphosphine. Once again, propose a catalytic cycle.



Jian-Cheng Wang, Sze-Sze Ng, and Michael J. Krische. *J. Am. Chem. Soc*. **2003.** 125. 3682-3683.

Proposed Catalytic Cycle:



Jian-Cheng Wang, Sze-Sze Ng, and Michael J. Krische. *J. Am. Chem. Soc*. **2003.** 125. 3682-3683.