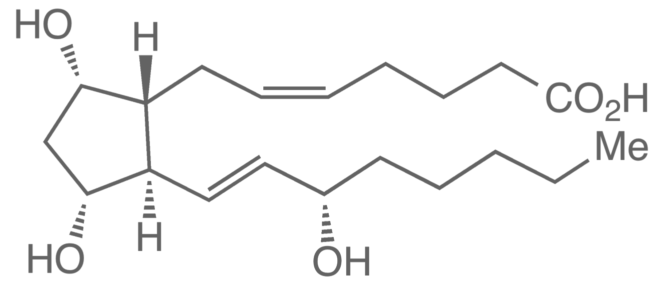
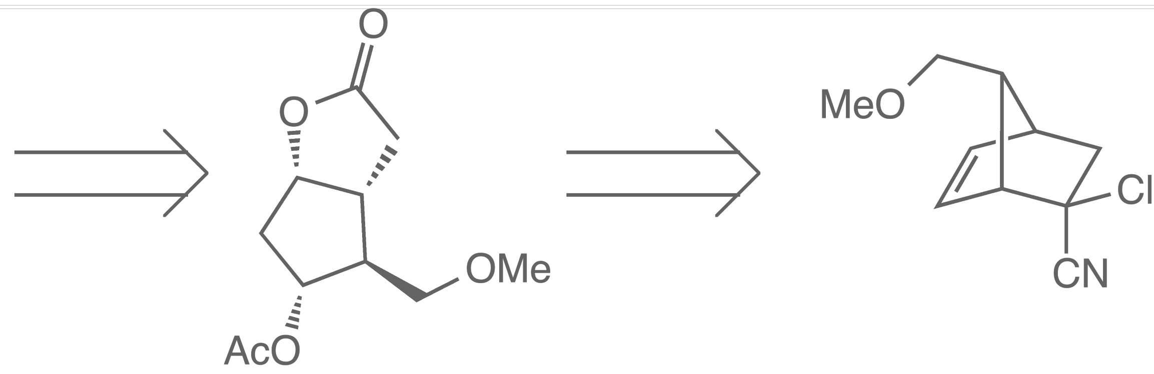


PGF$_{2\alpha}$



The Prostaglandins:

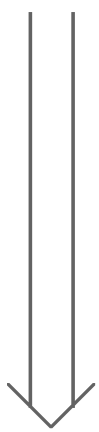
Synthesis & Significance

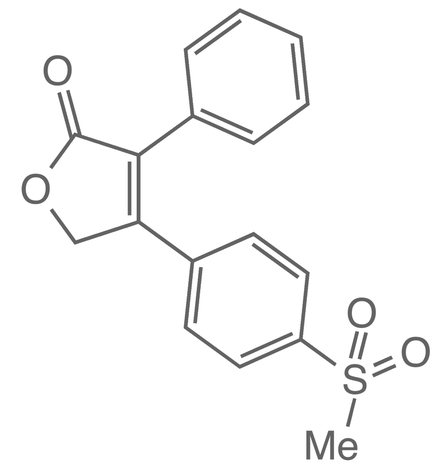
Alexander Goldberg

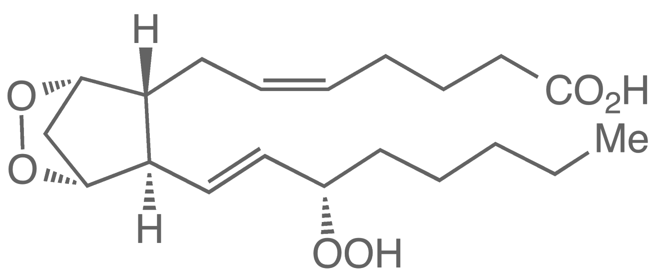
Stoltz Group Literature Presentation

February 7, 2011

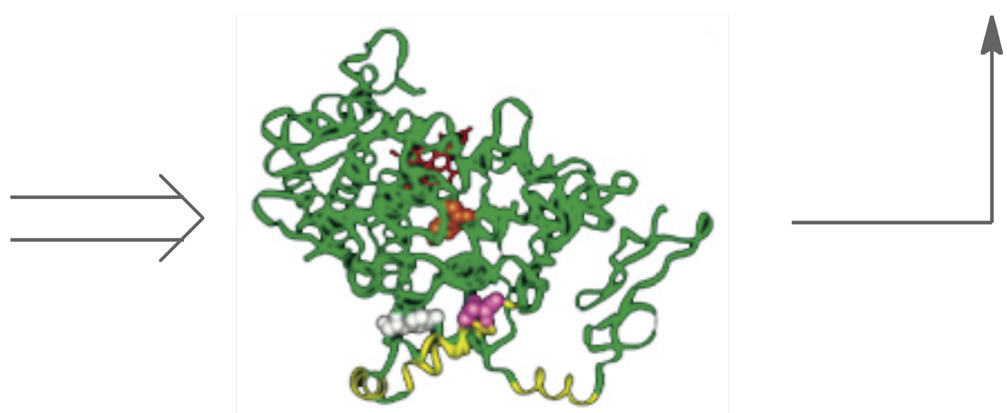
8 PM, 147 Noyes



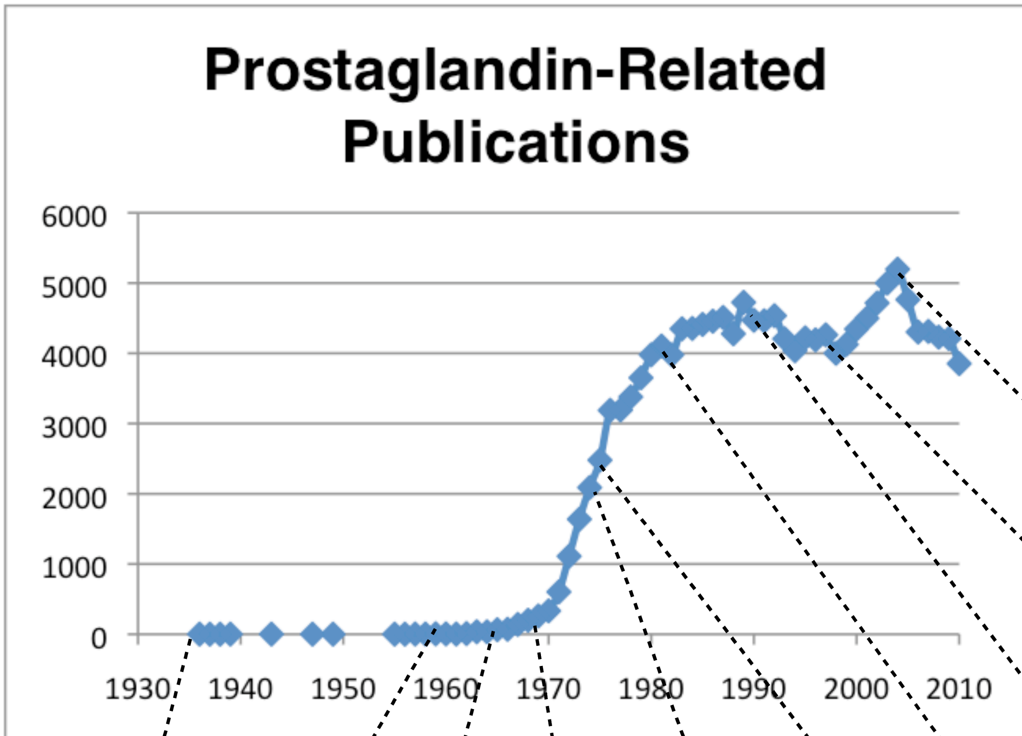


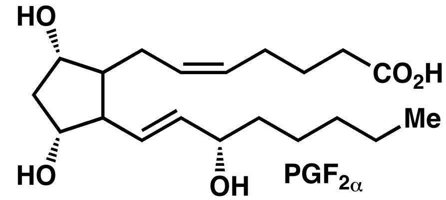


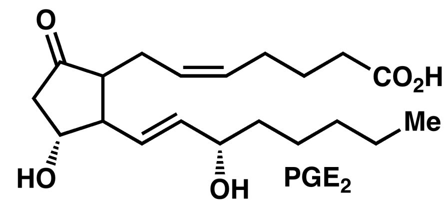
PGG$_2$



Historical Background







158,000 Total publications with word "prostaglandin"

890 are related to "total synthesis"

1934
Prostaglandins Discovered (Von Euler)

1957
$PGF_{1\alpha}$ & PGE_1 Isolated/ Structure Elucidated (Bergström)

1966
Entire PG Family Characterized

1969
Corey's Landmark Bicycloheptane Route to $PGF_{2\alpha}$ & PGE_2

1975
Stork's 1st PG synthesis

1976
Cyclooxygenase Purified (Hemler/Miyamoto)

1975
Noyori 1st 3 Component PG synthesis

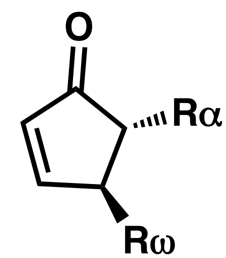
1991
COX-2 isolated (Simmons)

1999
Vioxx (rofecoxib), Selective COX-2 inhibitor, approved by FDA

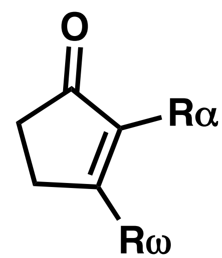
2004
Vioxx withdrawn from market

Prostaglandin Nomenclature

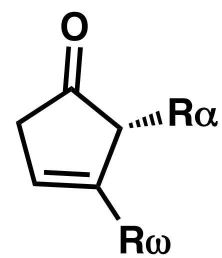
Letter refers to cyclopentane structure



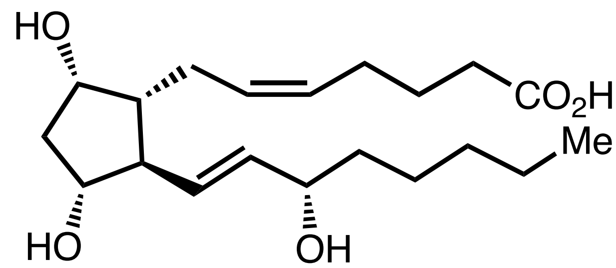
A



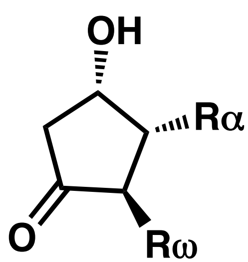
B



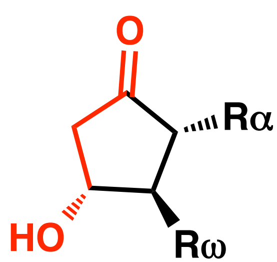
C



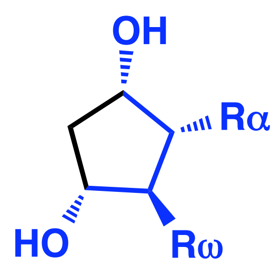
e.g. ***PGF***$_{2\alpha}$



D



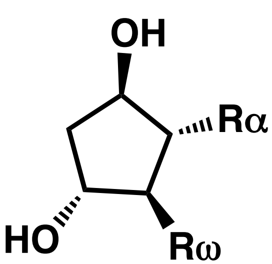
E



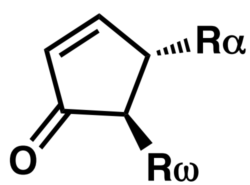
F$_{\alpha}$

PGF: Four contiguous stereocenters

PGE: Labile β-hydroxyketone



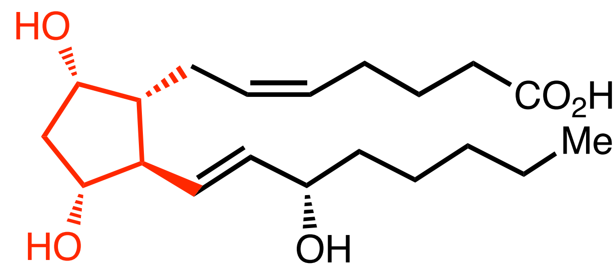
F$_{\beta}$



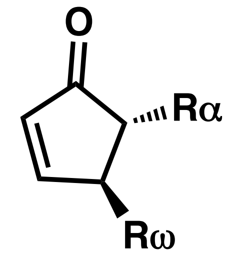
J

Prostaglandin Nomenclature

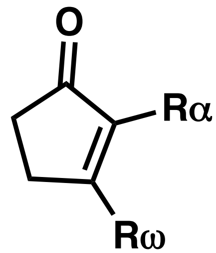
Letter refers to cyclopentane structure



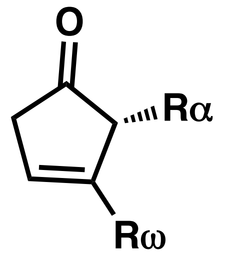
e.g. ***PGF$_{2\alpha}$***



A

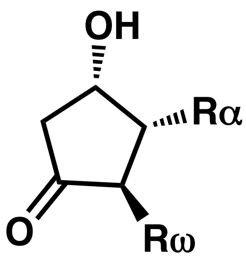


B

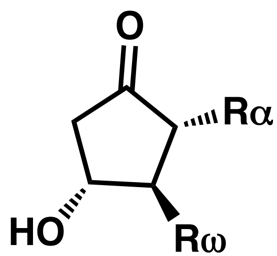


C

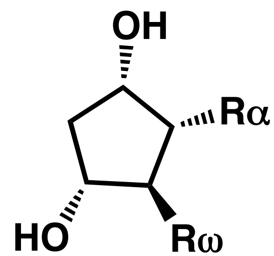
G, H, I?



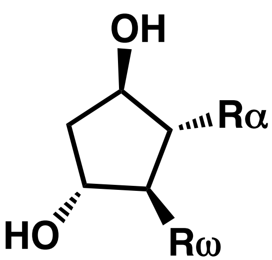
D



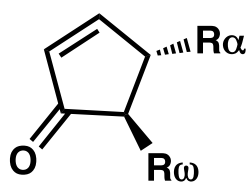
E



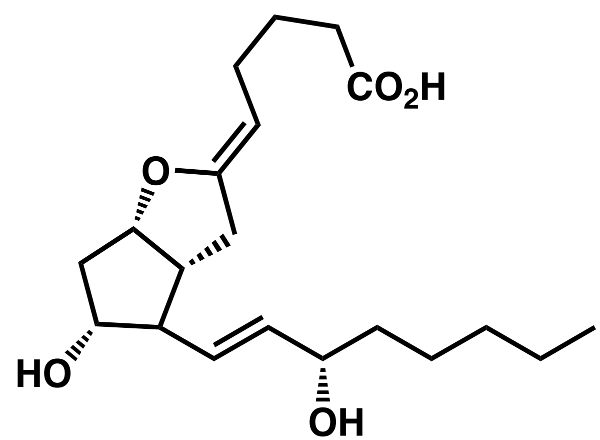
F$_{\alpha}$



F$_{\beta}$



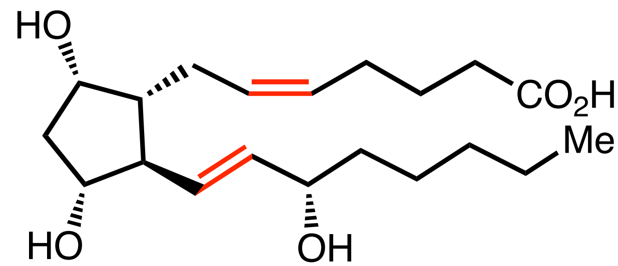
J



PGI$_2$: Prostacyclin

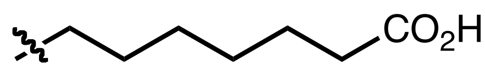
Prostaglandin Nomenclature

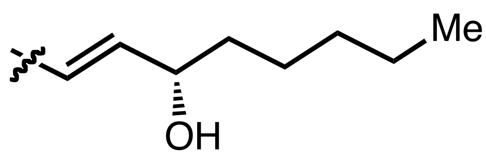
Number refers to degree of unsaturation on side-chains.

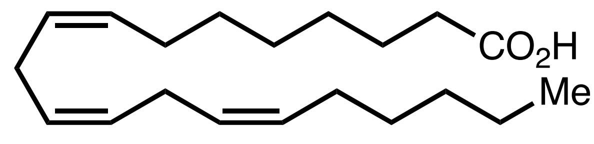


e.g. ***PGF***$_{2\alpha}$

1:

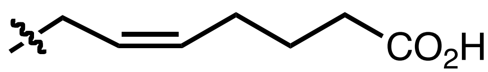
R$_\alpha$ **=** 

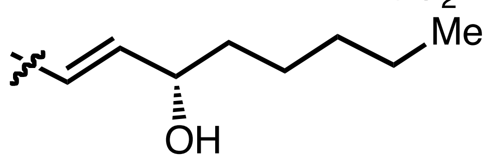
R$_\omega$ **=** 

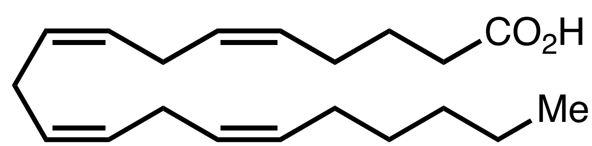


dihomo-γ-linolenic acid

2:

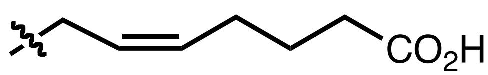
R$_\alpha$ **=** 

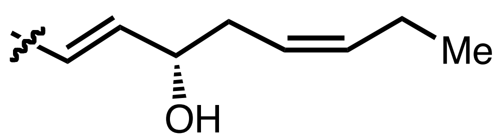
R$_\omega$ **=** 

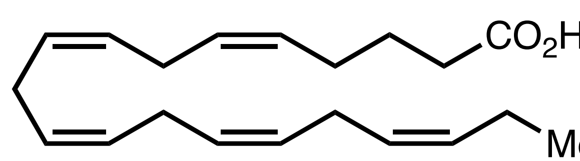


arachidonic acid

3:

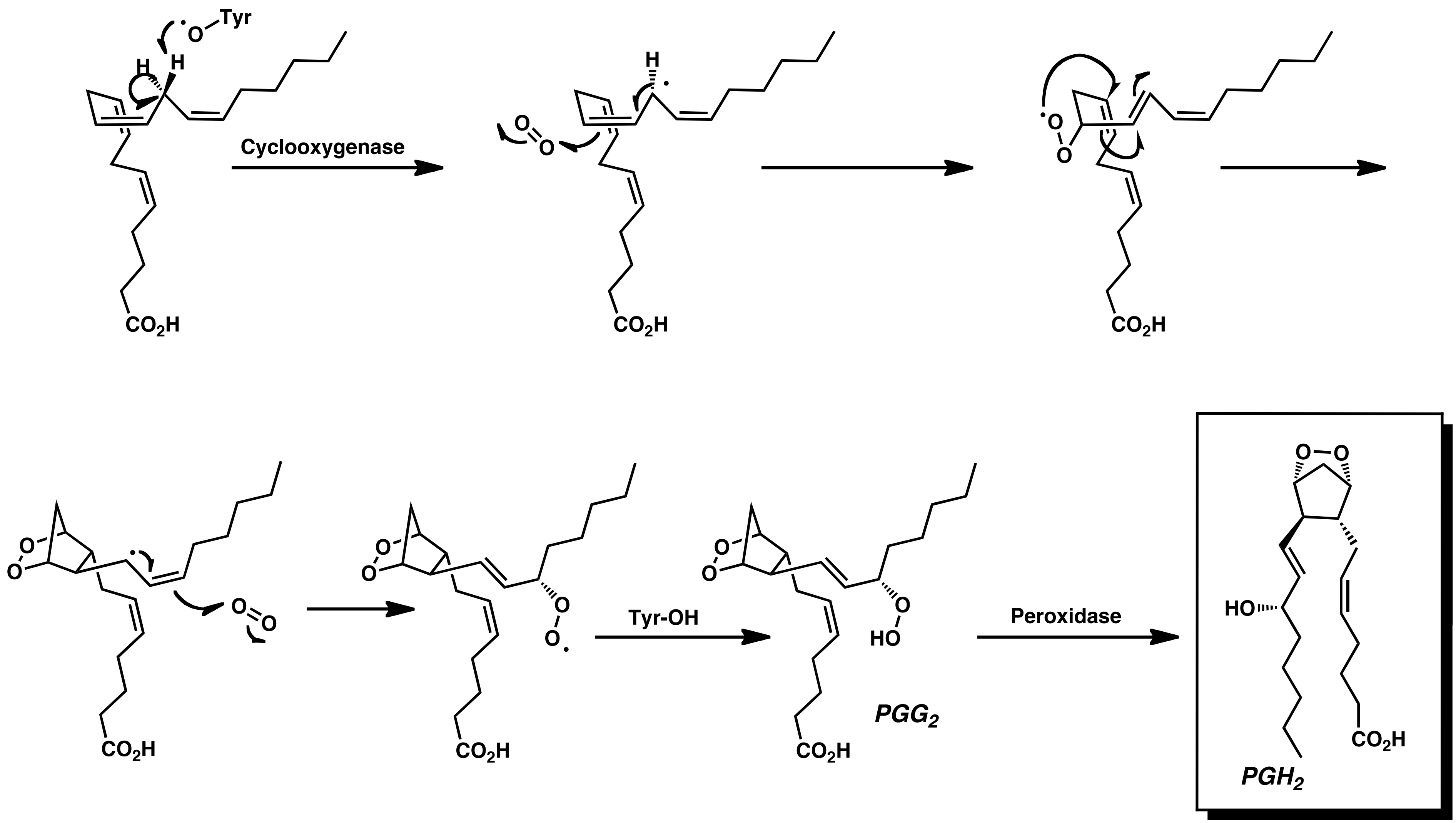
R$_\alpha$ **=** 

R$_\omega$ **=** 



eicosapentaenoic acid

Prostaglandin Biosynthesis

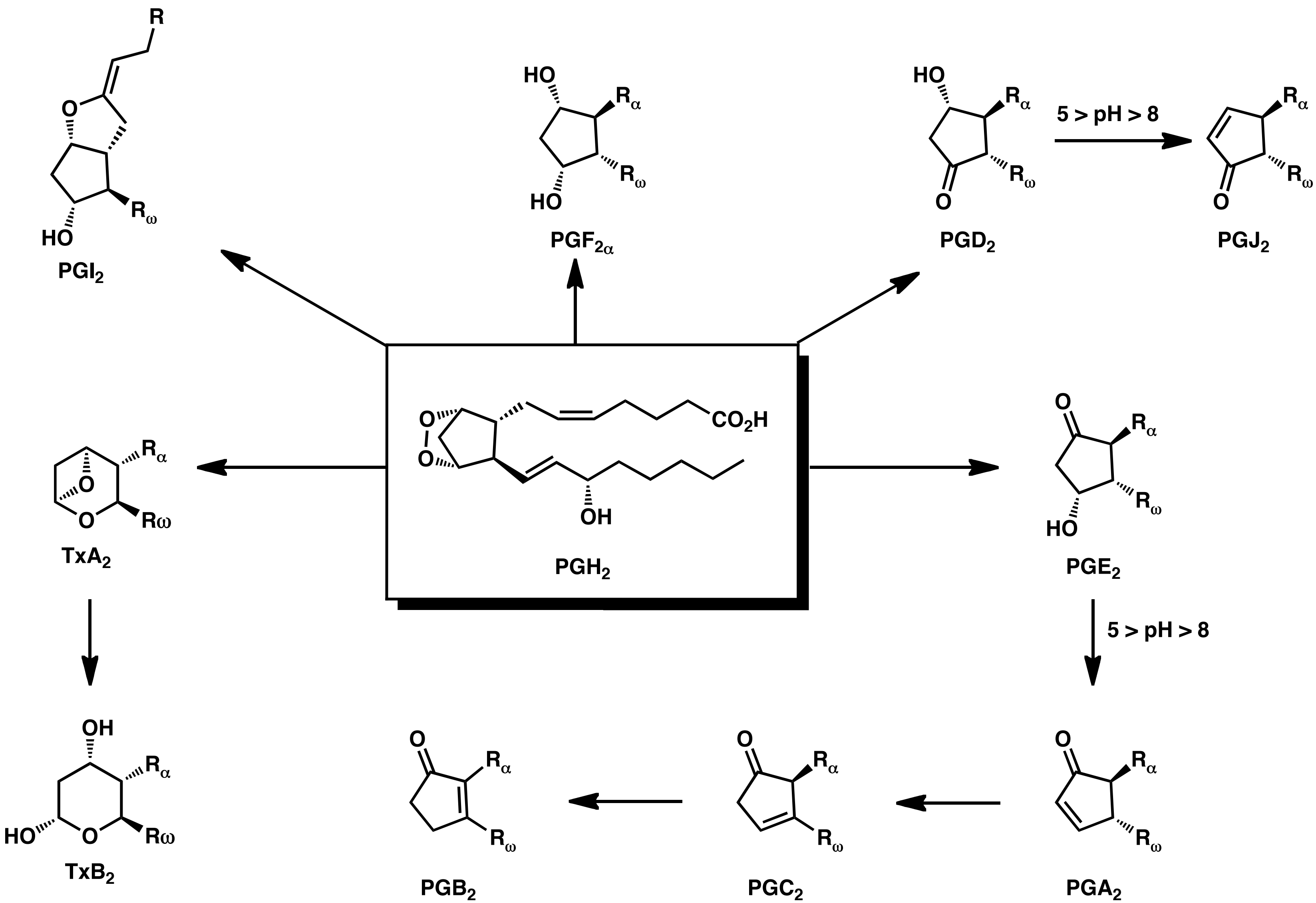


Cyclooxygenase and Peroxidase functionality exist in the same enzyme

PGH_2: Key biosynthetic intermediate to Prostaglandins, related compounds

Rouzer, C. A.; Marnett, L. J. *Chem. Rev.* **2003,** *103*, 2239–2304.

Prostaglandin Biosynthesis



Das, S. et al. *Chem. Rev.* **2007**, *107*, 3286–3337.
Rouzer, C. A.; Marnett, L. J. *Chem. Rev.* **2003,** *103*, 2239–2304.
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996; p 66.

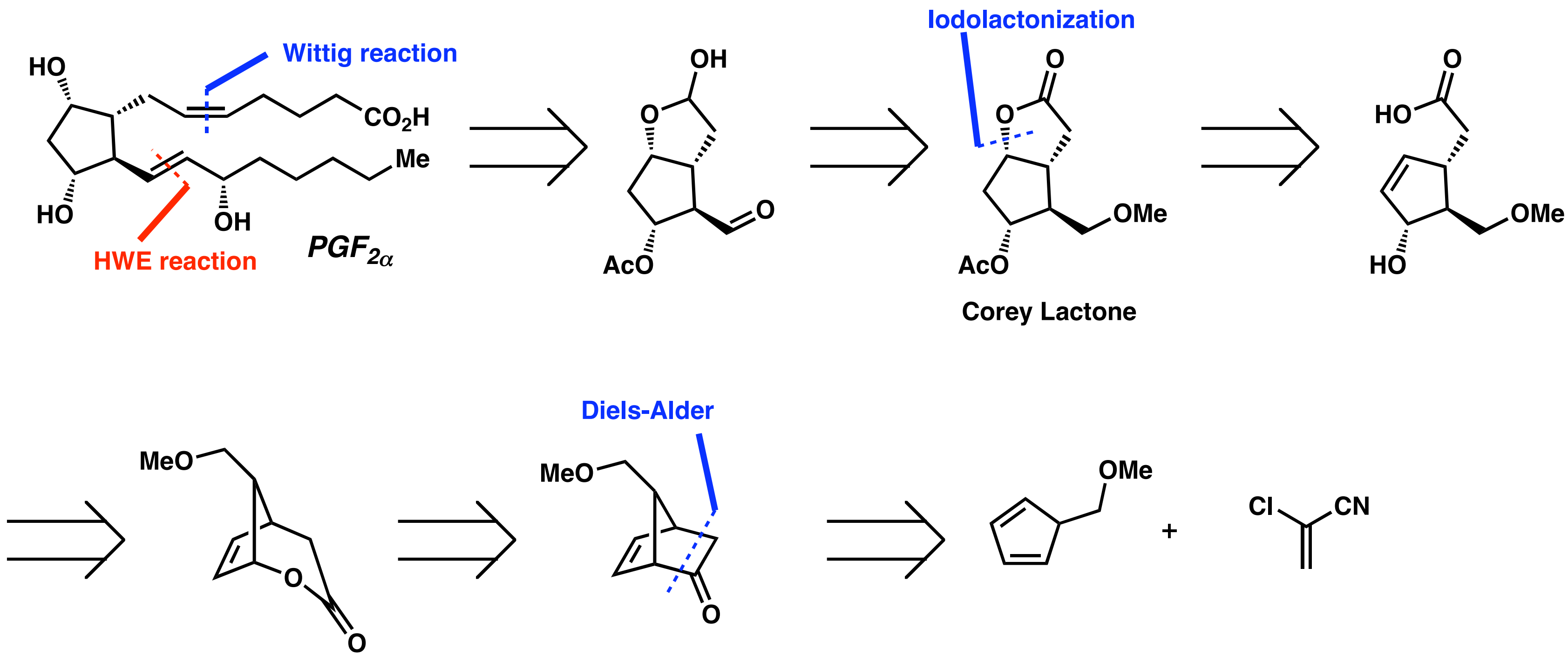
Corey's Prostaglandin Syntheses

"It was in 1969 when Corey disclosed his elegant and versatile bicycloheptane prostaglandin synthetic strategy. Over the course of the ensuing two and half decades, Corey's original strategy has evolved in a manner that closely parallels the development of the science of organic synthesis..."

- K.C. Nicolaou & E. J. Sorensen

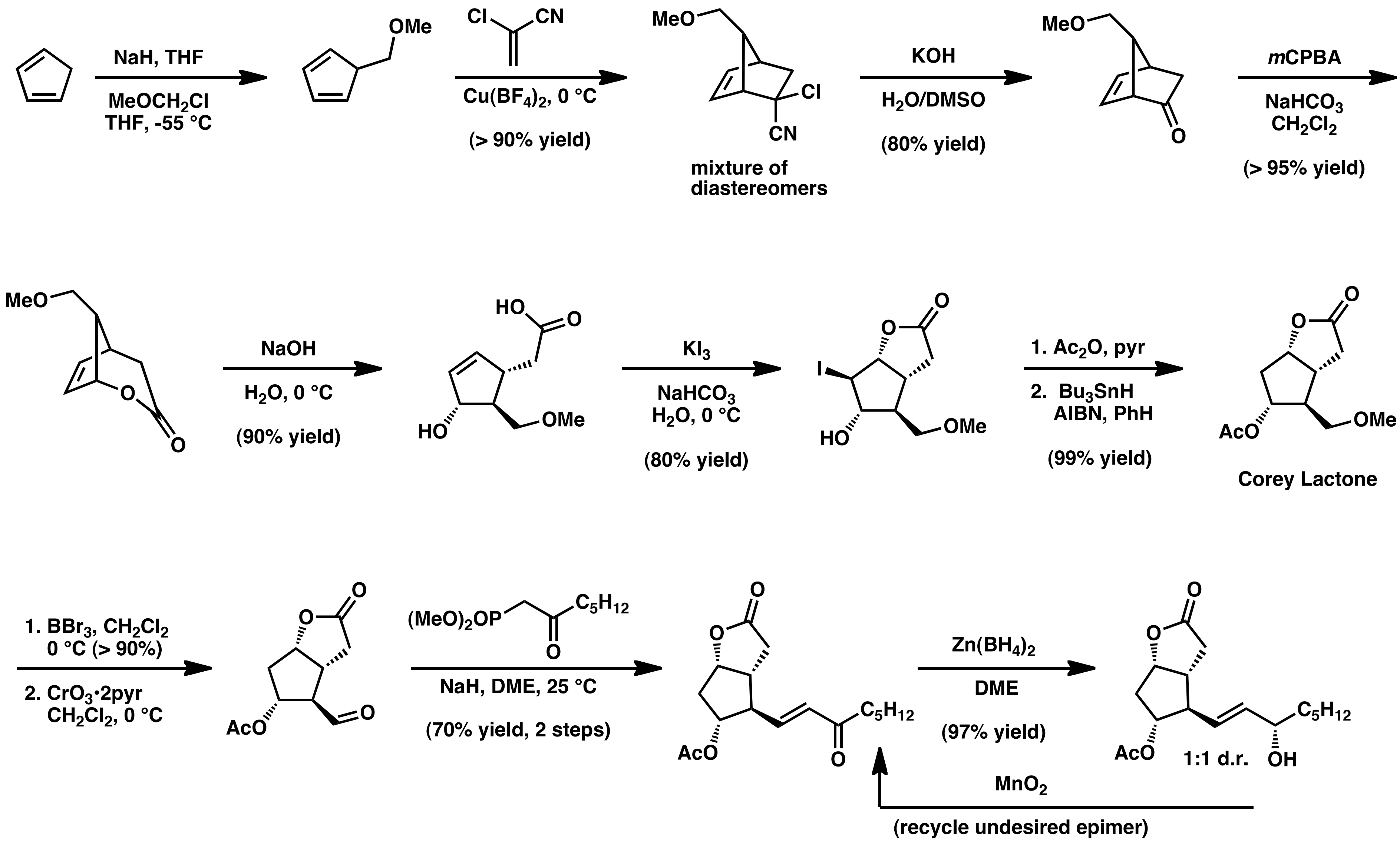
More generally:
Prostaglandin research embodies the intertwined nature of target oriented synthesis & methodology development

<u>Original Bicycloheptane Retrosynthesis:</u>



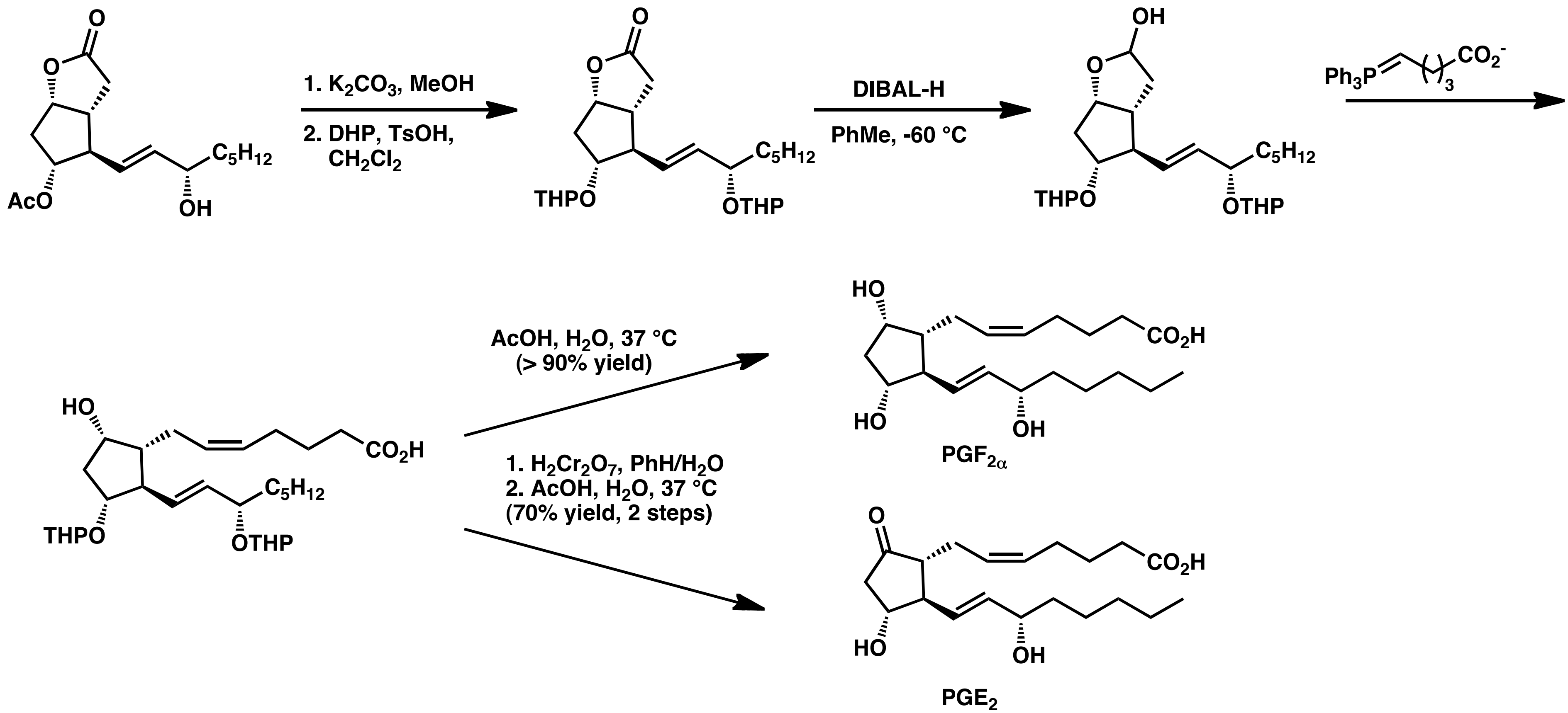
Corey, E. J. et al. *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677.
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996; pp 65–81.

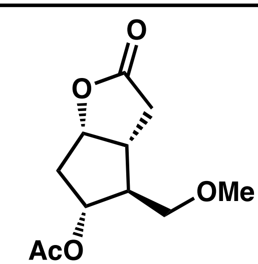
Corey's Original Bicycloheptane Route



Corey, E. J. et al. *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677.
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996; pp 65–81.

Corey's Original Bicycloheptane Route - 1969





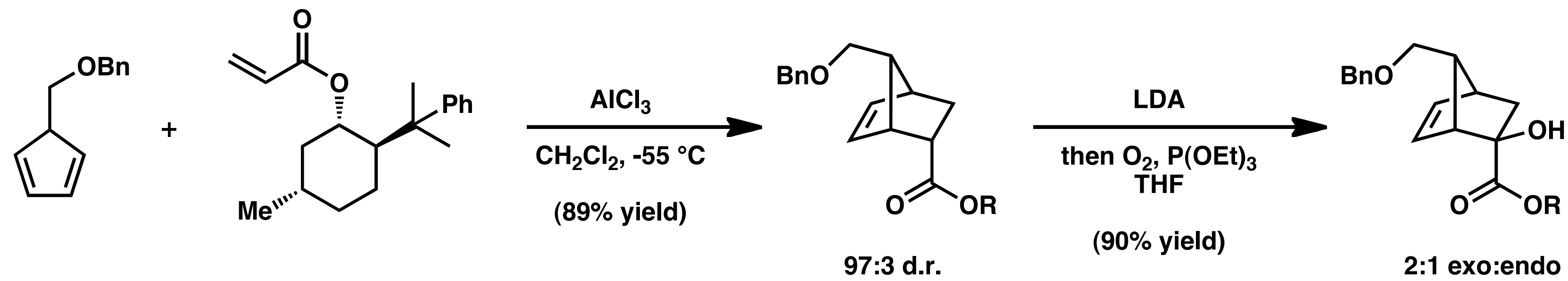
Corey Lactone

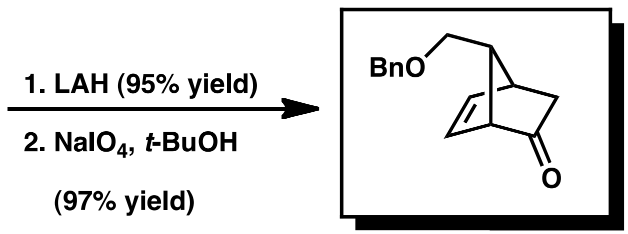
- **Limitations:**
  Diels-Alder gives racemic product, non selective enone reduction

- **Corey Lactone applied in the synthesis of a variety of PG derivatives in a search for pharmaceuticals**

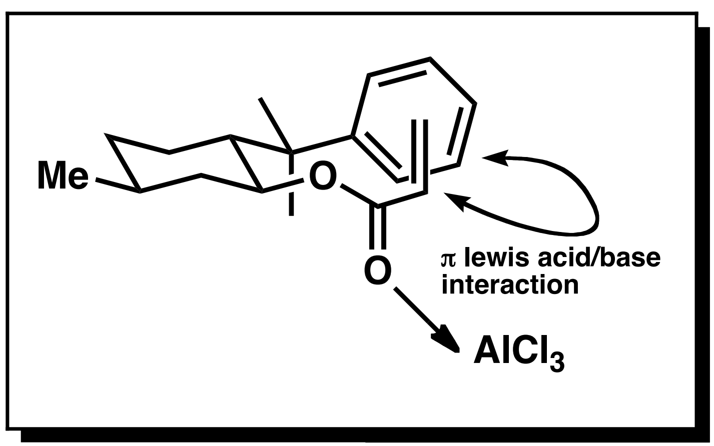
Corey, E. J. et al. *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677.
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996; pp 65–81.

Chiral Auxilliary Modification - 1975





- **Menthol derivative could be recycled after LAH reduction**
- **Phenyl substitution gives remarkably higher e.e. than ordinary menthol**



Phenyl group blocks Diels Alder @ Si face of olefin

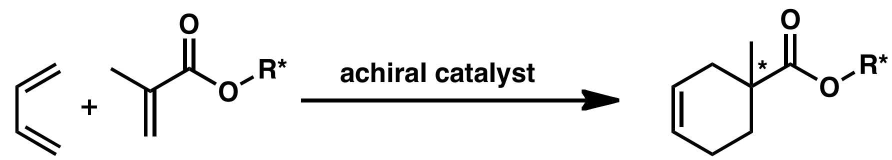
"The first highly enantioselective version of the Diels–Alder reaction"

Oh, and a novel enolate oxidation method as well.

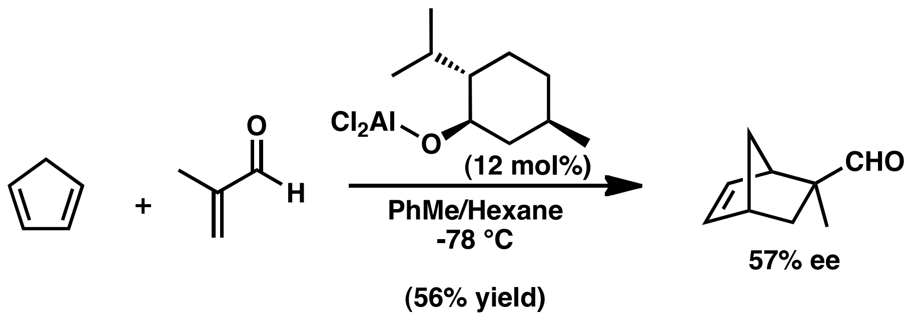
Farmer, R. F.; Hamer, J. *J. Org. Chem.* **1966**, *31*, 2418–2419.
Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908–6909.
Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667.

Development of Catalytic Enantioselective Diels Alder Reactions: 1979–1989

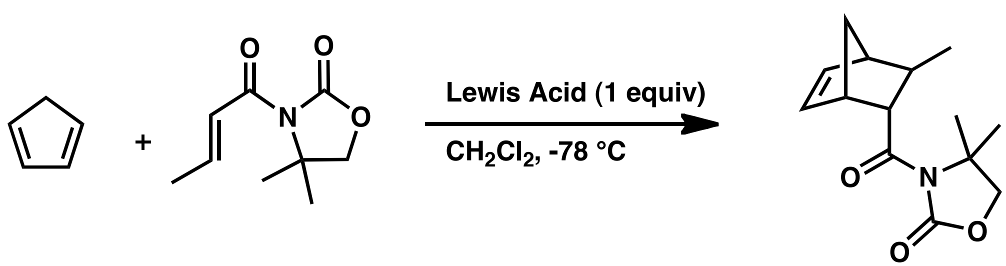
Prevailing strategy:

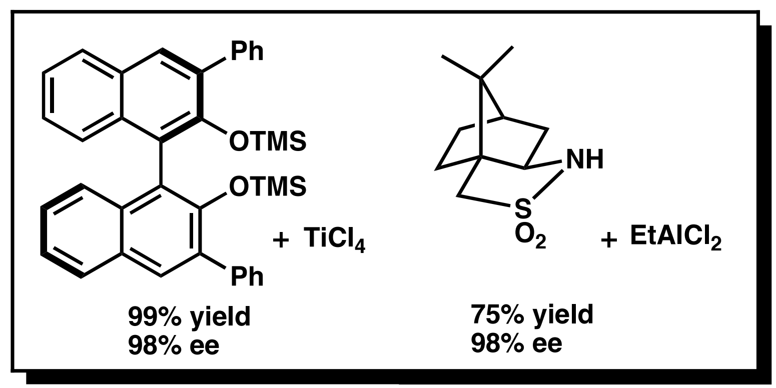


First catalytic enantioselective Diels-Alder Reaction: Koga, 1979



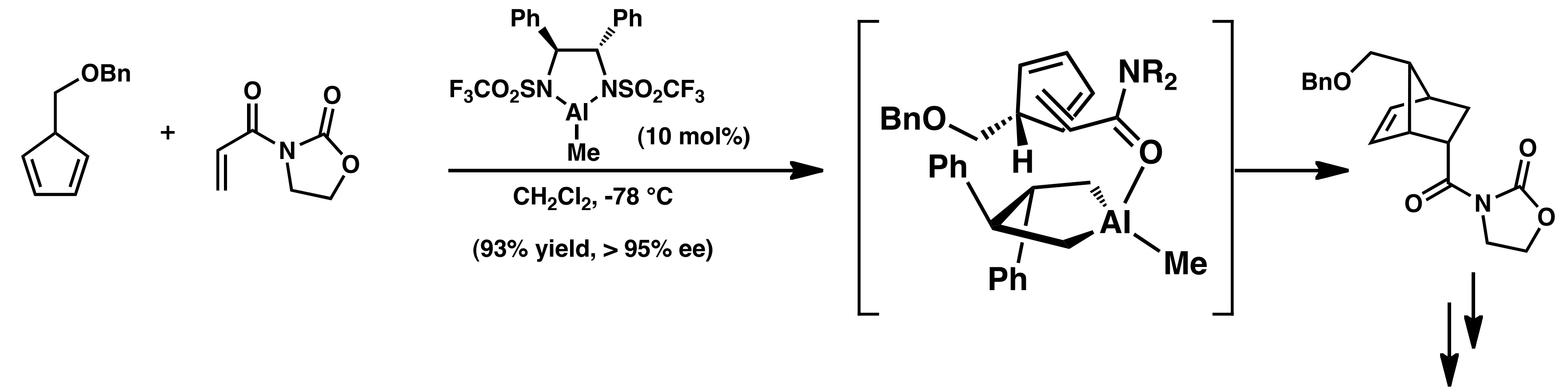
Two point substrate binding: Chapuis, 1987

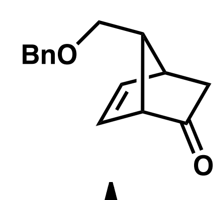




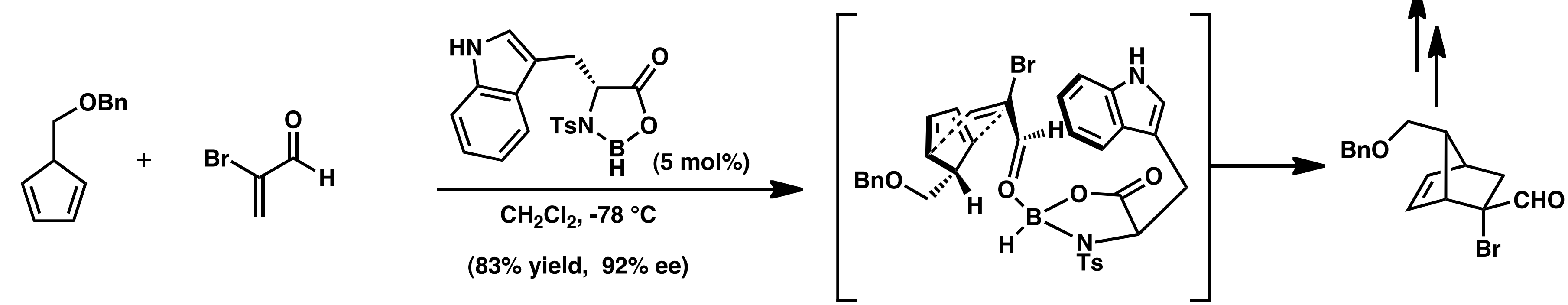
Reviews: (a) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876–889. (b) Kagan, H.B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019.
Hashimodo, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.
Chapuis, C.; Jurczak, J. *Helv. Chim. Acta.* **1987**, *70*, 436–440.

Catalytic Enantioselective Diels–Alder - 1989–1991





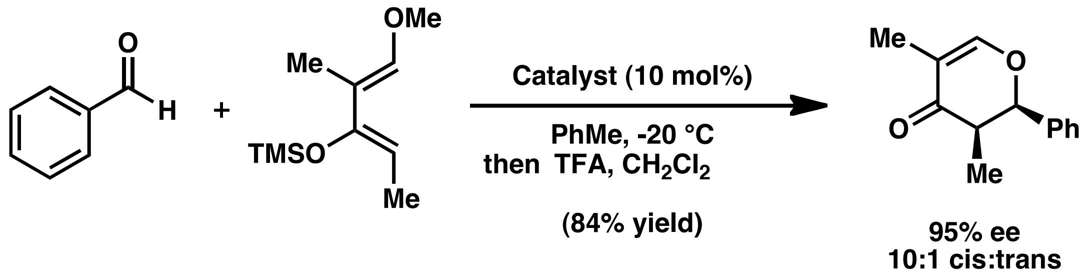
Catalytic variant of Chapuis system applied to bicycloheptane synthesis



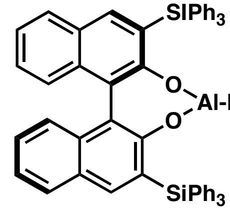
Attractive interaction between acrylate & tryptophan proposed:
With non aromatic side-chains, opposite enantiomeric series observed

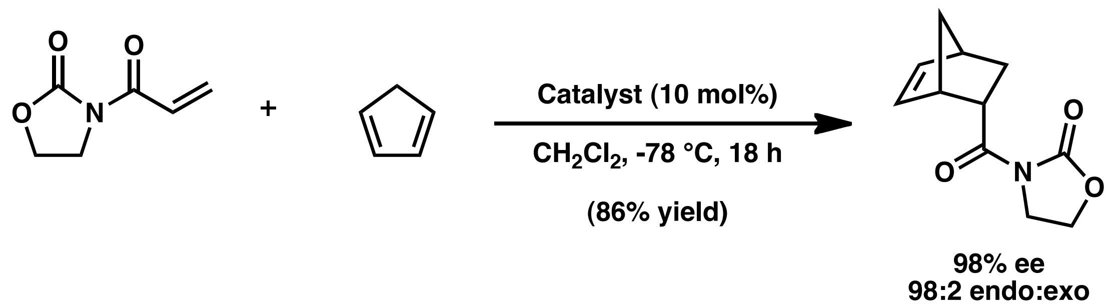
For a review on Enantioselective D-A developed by Corey, see: Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650-1667.
Corey, E. J. et al. *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495.
Corey, E. J.; Imai, N.; Pikul, S. *Tetrahedron Lett.* **1991,** *32,* 7517–7520.
Corey, E. J.; Loh, T. P. *J. Am. Chem. Soc.* **1991**, *113*, 8966-8967

Catalytic Enantioselective Diels–Alder: Extensions

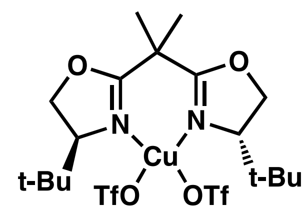


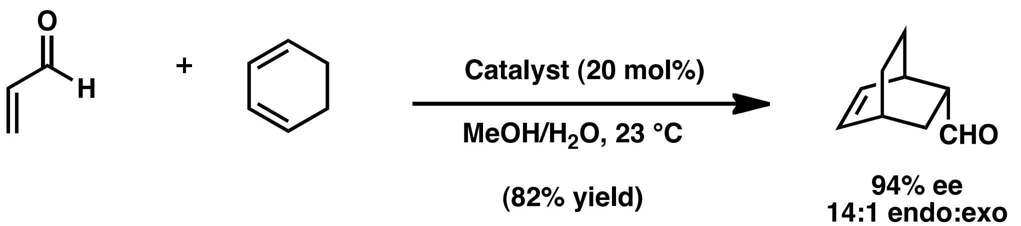
Yamamoto, 1988



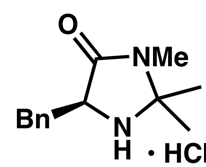


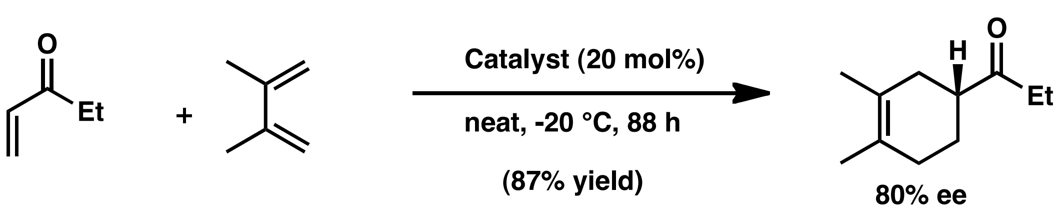
Evans, 1993



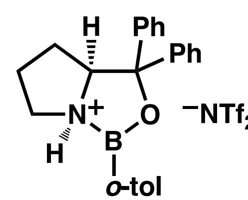


MacMillan, 2000



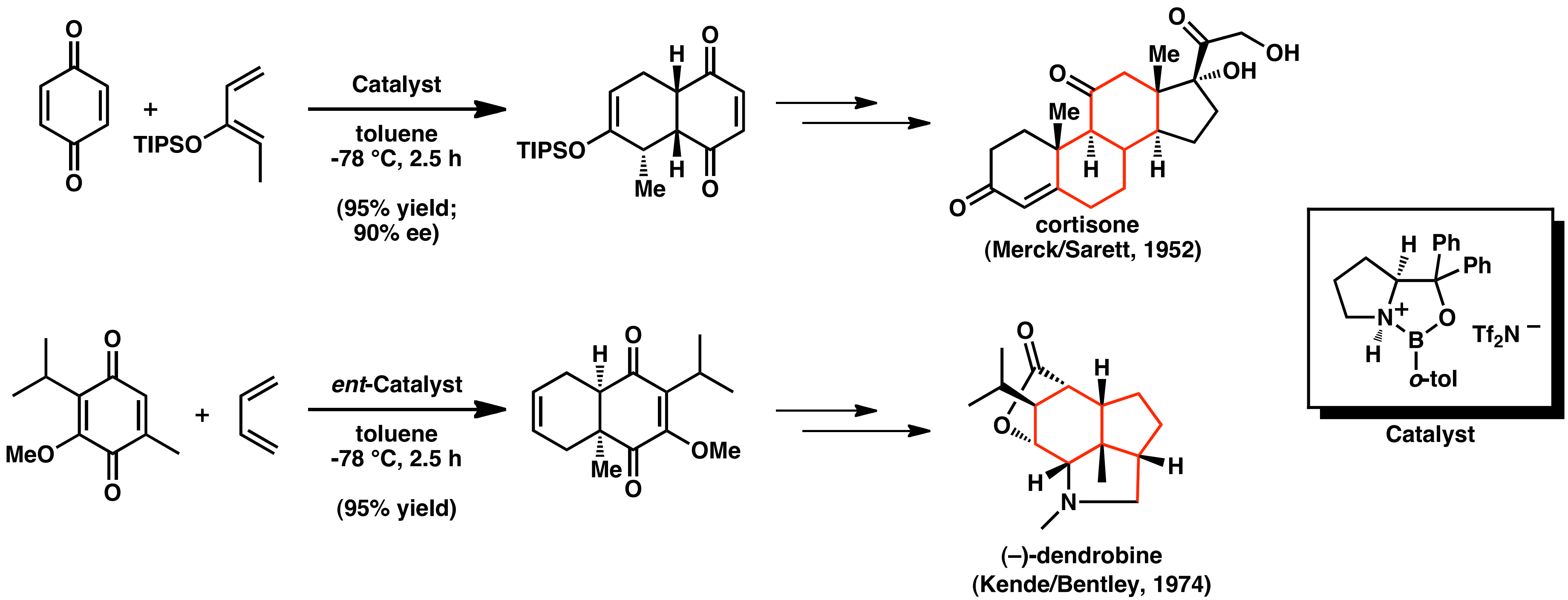


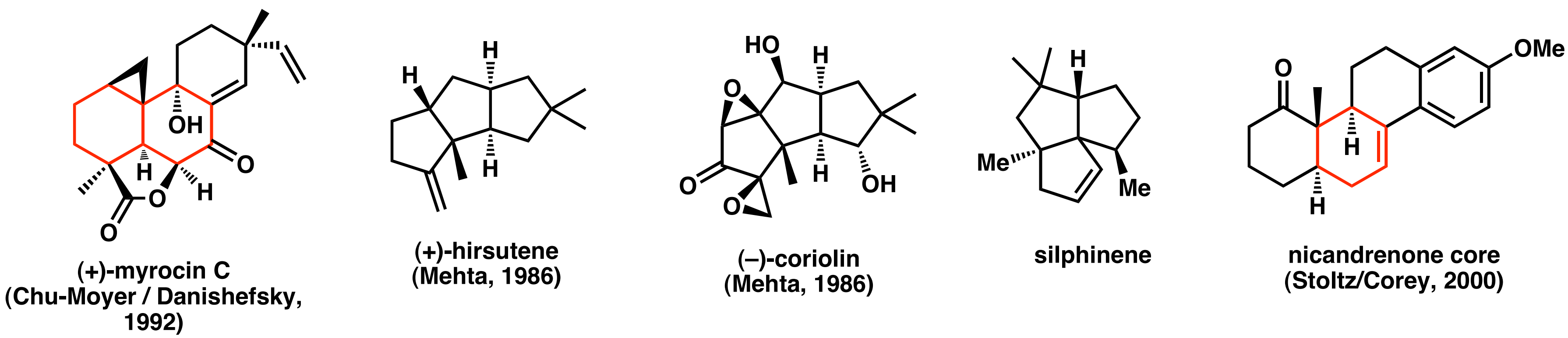
Corey, 2002–2003



Yamamoto, H. et al. *J. Am. Chem. Soc.* **1988**, *110*, 310–312.
Evans, D. A.; Miller, S. J.; Lectka, T. **1993**, *115*, 6460–6461.
Ahrendt, K. A.; Borths, C. J.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390.

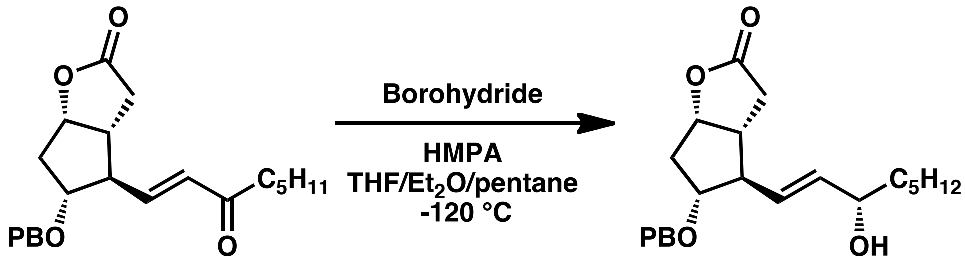
Catalytic Enantioselective Diels–Alder: Extensions



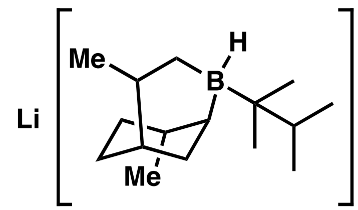


Review on cationic oxazaborolidines: Corey, E. J. *Angew. Chem. int. Ed.* **2009**, *48*, 2100–2117.
Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667.
Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002,** *124*, 3808–3809.
Hu, Q. Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708–13713.

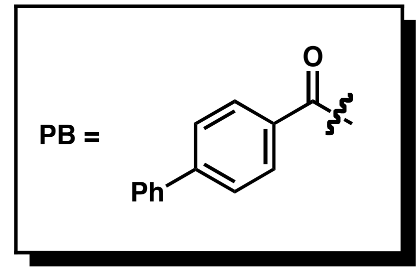
Strategies toward C(15) stereoselectivity - 1971–1987

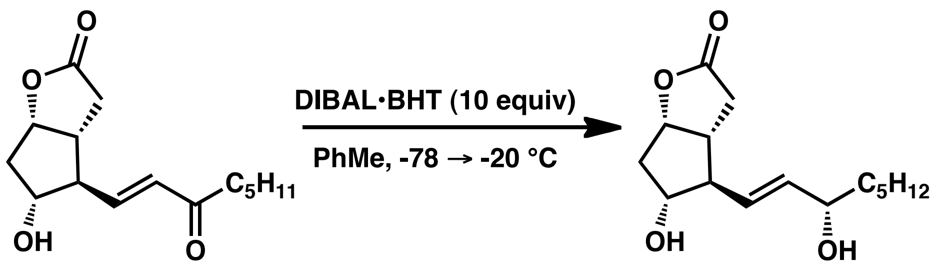


82:18 α : β
92:8 with carbamate analogue

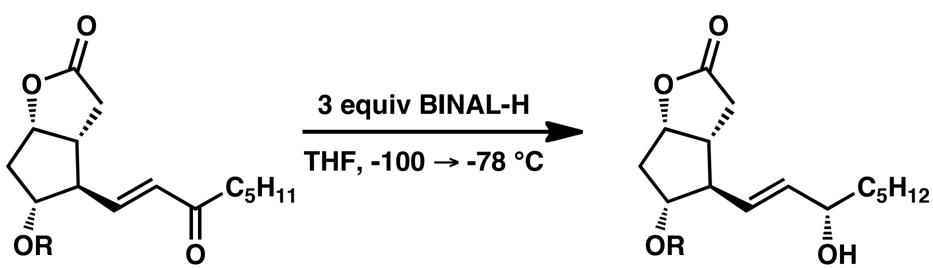


Borohydride
· Derived from (±)-limonene

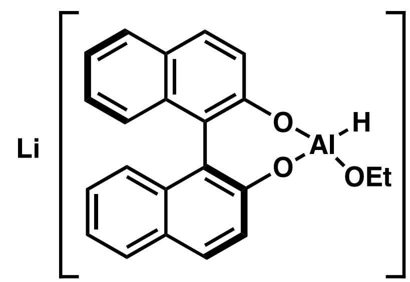




95% yield, 92:8 d.r.



R = THP, > 99:1
R = Ac, > 99:1

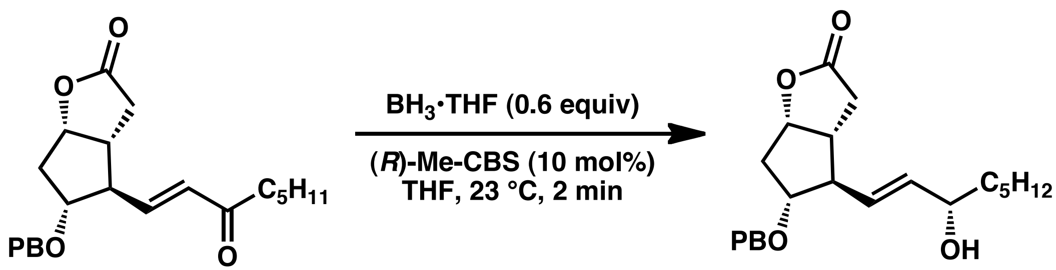


(S)-BINAL-H

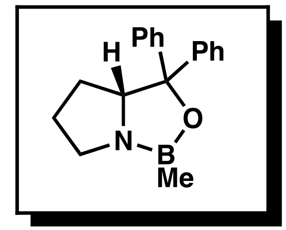
Match/Mismatch Effect Observed w/ (R) enantiomer

Corey, E. J. et al. *J. Am. Chem. Soc.* **1971**, *93*, 1491–1492.
Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616–8618.
Yamamoto, H. et al. *J. Org. Chem.* **1979**, *44*, 1363–1364.
Noyori, R.; Tomino, I.; Nishizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843–5844.

CBS Reduction & C(15) stereoselectivity - 1987

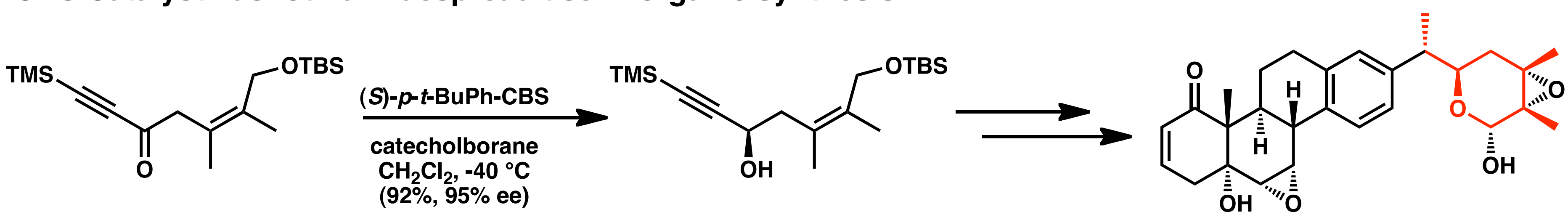


9:1 α : β

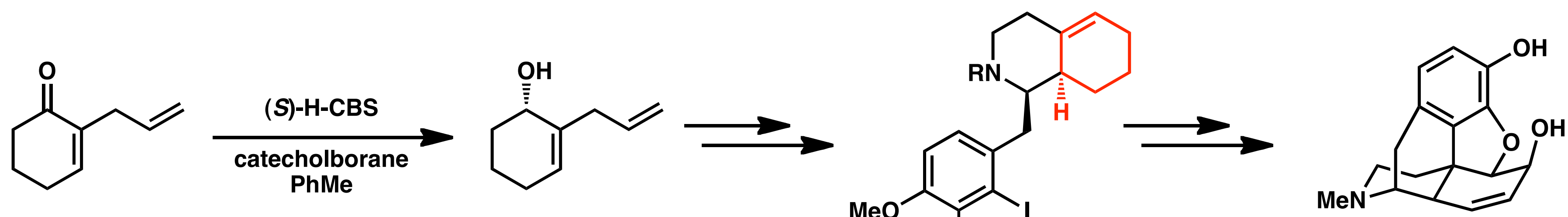


(*R*)-Me-CBS

CBS Catalyst has found widespread use in organic synthesis



NIC-1 & NIC-1 Lactone



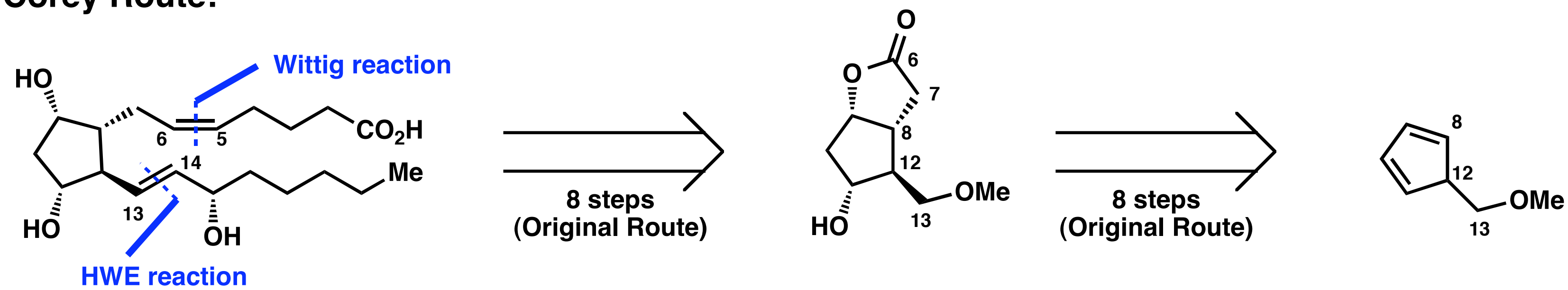
(93% yield, 96% ee)

(–)-morphine

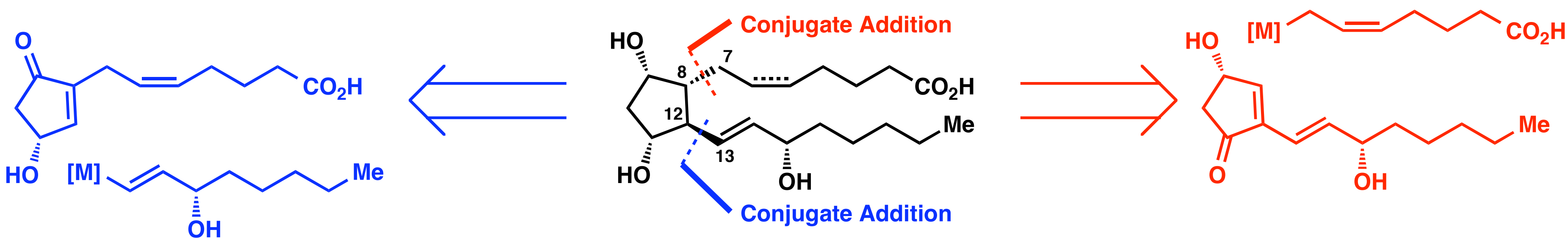
Review: Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1987–2012.
Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
Corey E. J. et al. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926
Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029
Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *122*, 9044–9045

Alternative Routes to Prostaglandins

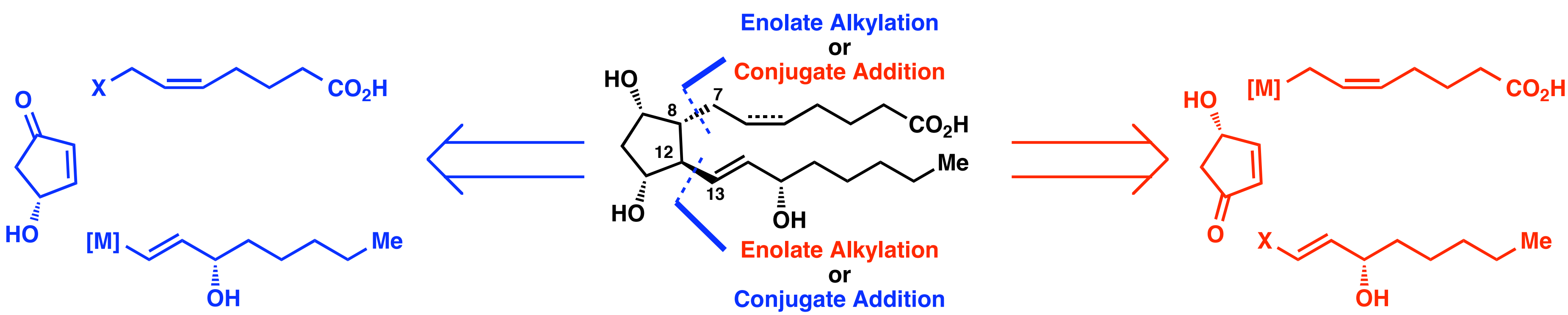
Corey Route:



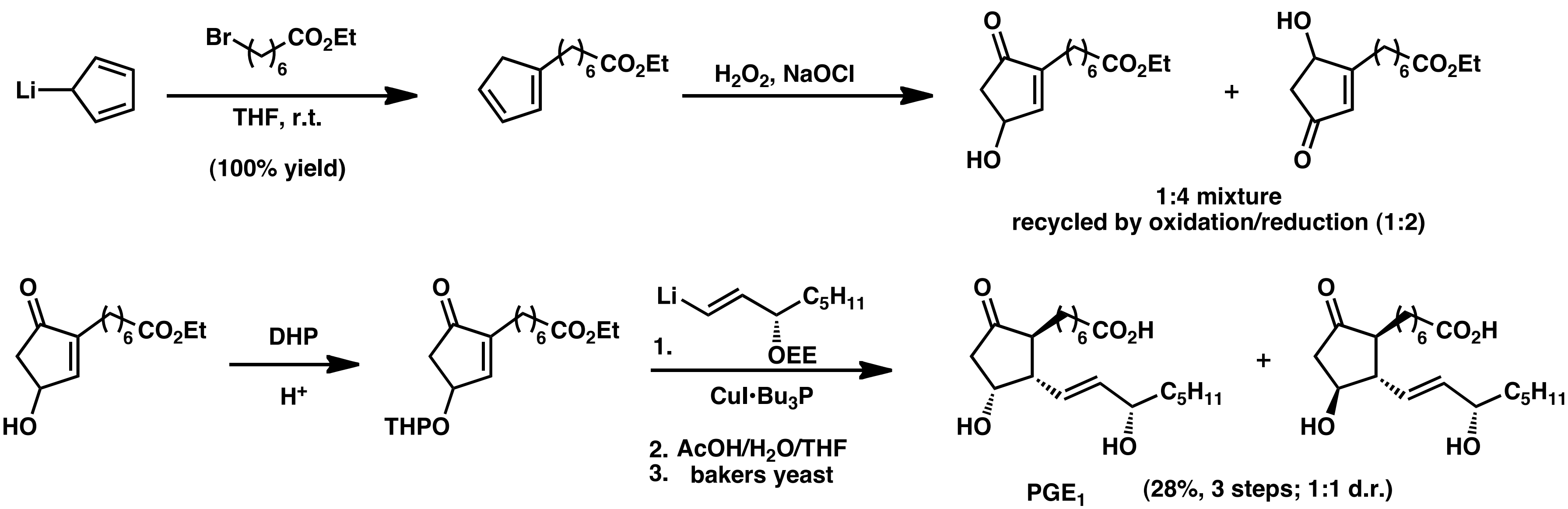
Conjugate Addition:

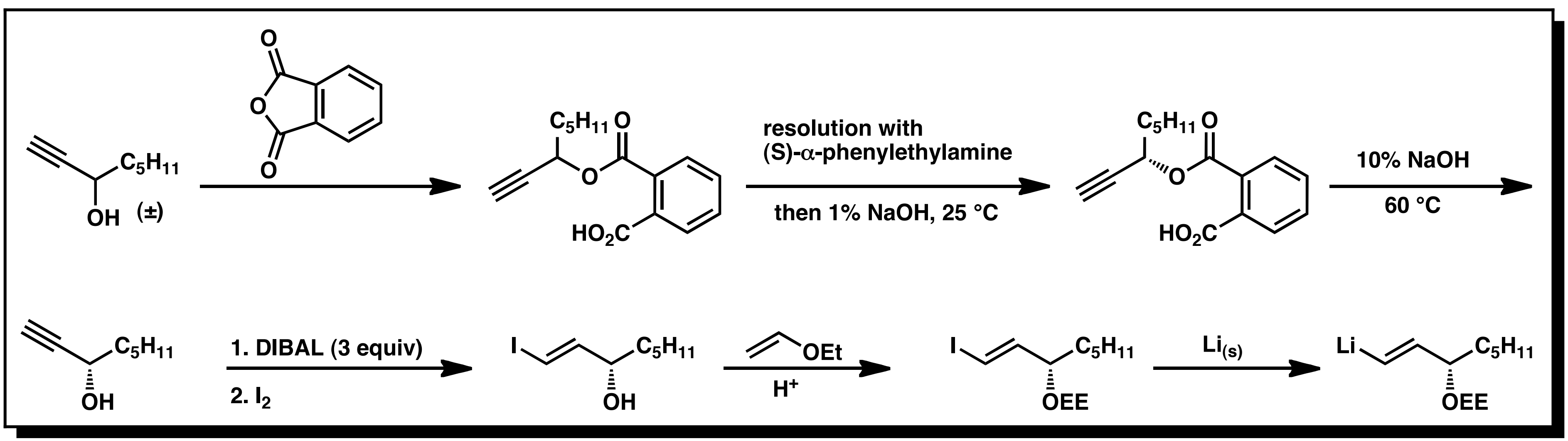


Three Component Coupling:



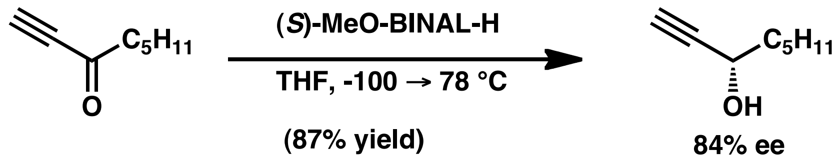
Approaches by Conjugate Addition - Sih, 1972



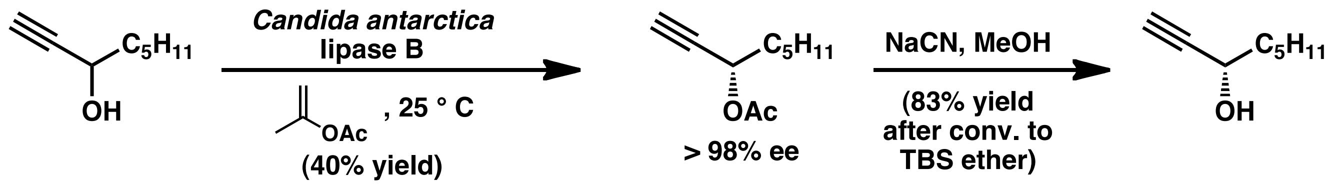


Sih, C. J. et al. *J. Chem. Soc., Chem. Commun.* **1972**, 240–241.
Sih, C. J. et al. *J. Am. Chem. Soc.* **1972**, *94*, 3643–3644.
Fried, J. et al. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 64.

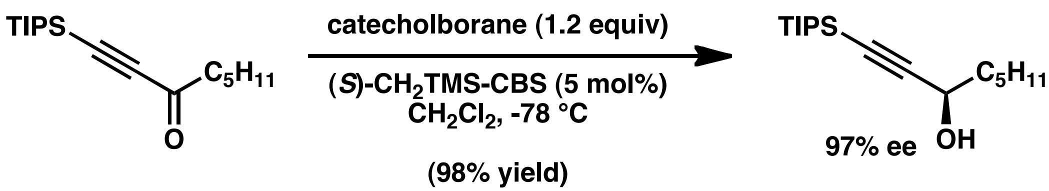
Synthetic Improvements - Propargyl Alcohol



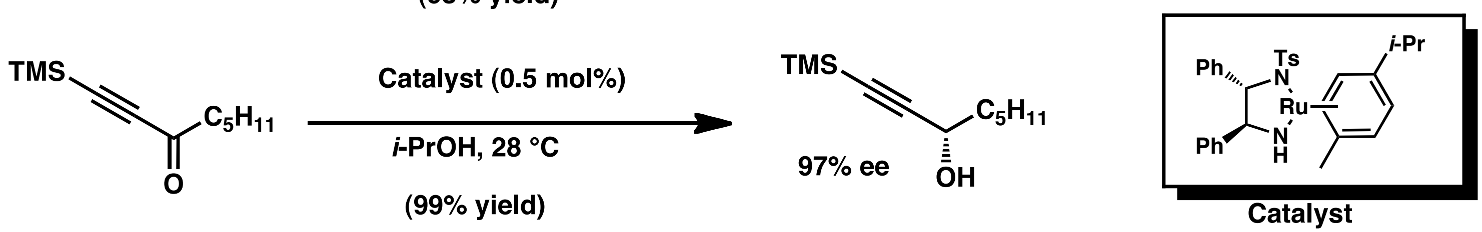
Noyori, 1984



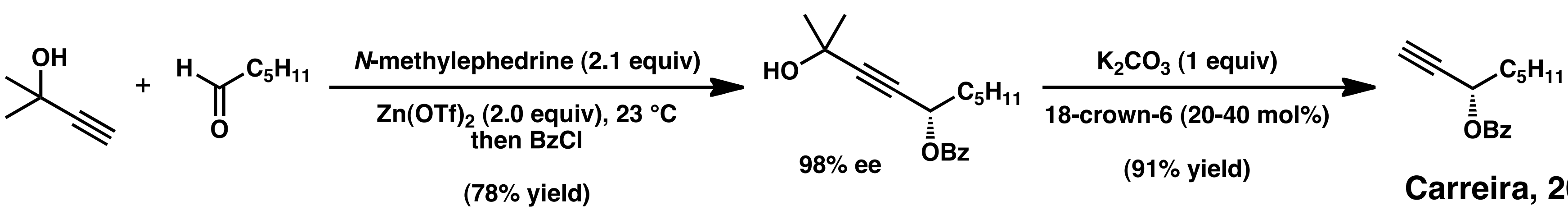
Johnson, 1993



Parker/Corey, 1996



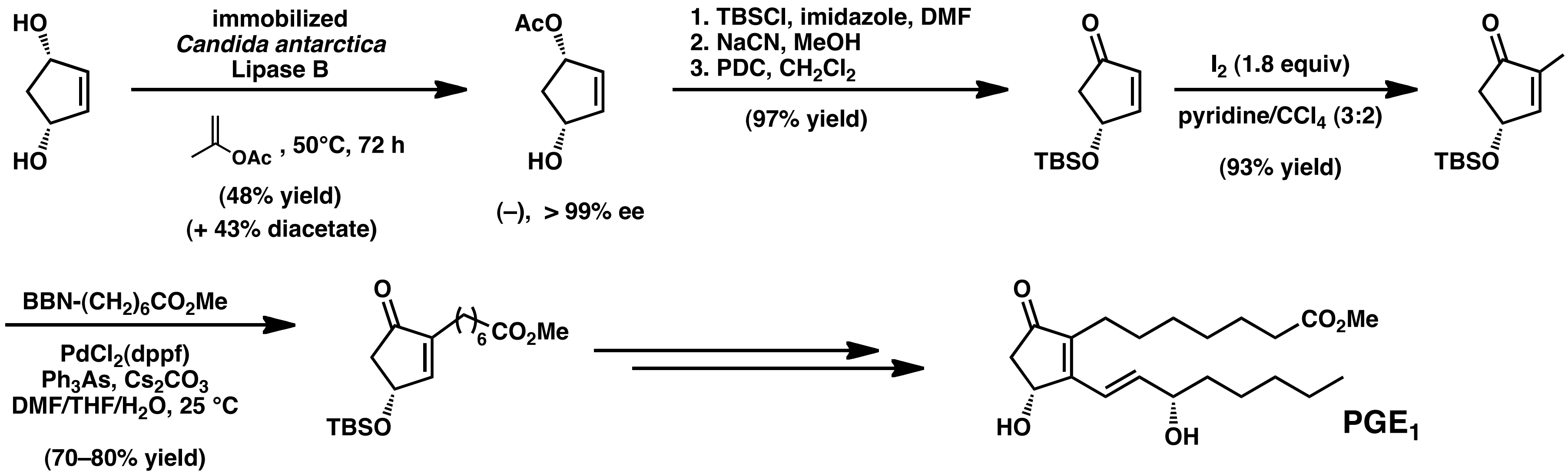
Noyori, 1996

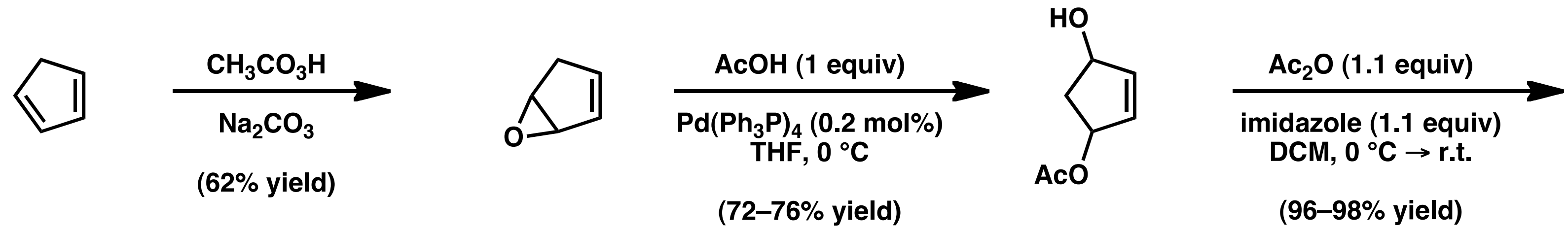


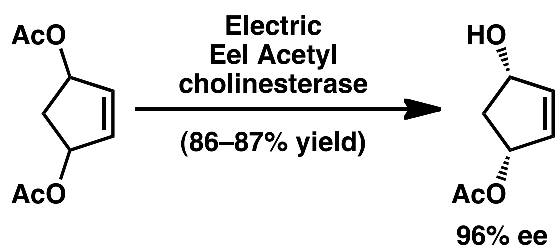
Carreira, 2000

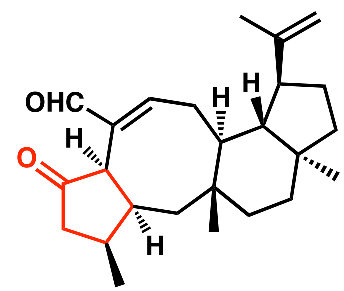
Noyori, R. et al. *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725.
Johnson, C. R. Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015.
CBS application: (a) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214–3217.
(b) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938–10939.
Noyori, R. et al. *J. Am. Chem Soc.* **1997**, *119*, 8738–8739.
Stoichiometric: Carreira, E. M. et al. *Org. Lett.* **2000**, *2*, 4233–4236.
Catalytic Enantioselective: Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.

Synthetic Improvements - Cyclopentenone







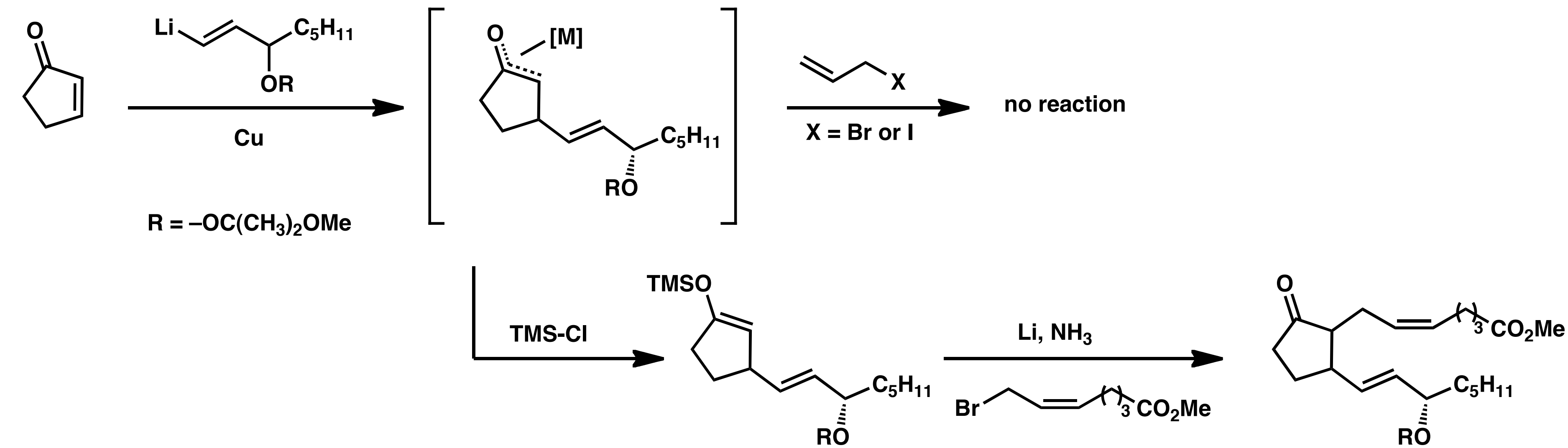


Variecolin

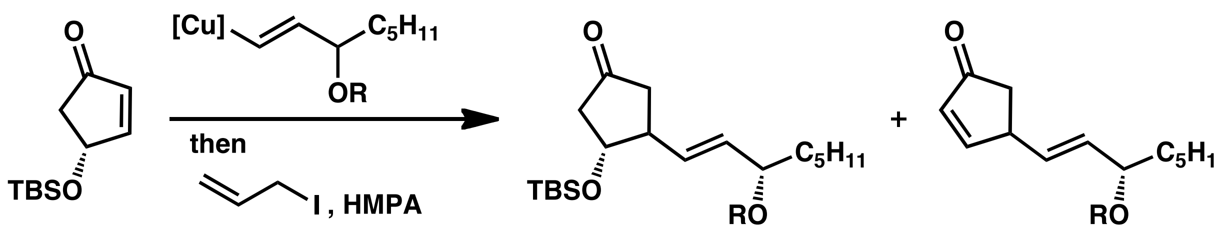
Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287–7290.
Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015.
Deardorff, D. R.; Myles, D. C. *Org. Synth., Coll. Vol. VIII* **1993**, 13–17.
Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Org. Synth., Coll Vol. IX* **1998**, 487–497
Krout, M. R. *Stoltz Group Research Seminar.* June 11, 2007.

Three Component Coupling: Challenges to Overcome

Electrophile must be compatible with nascent enolate

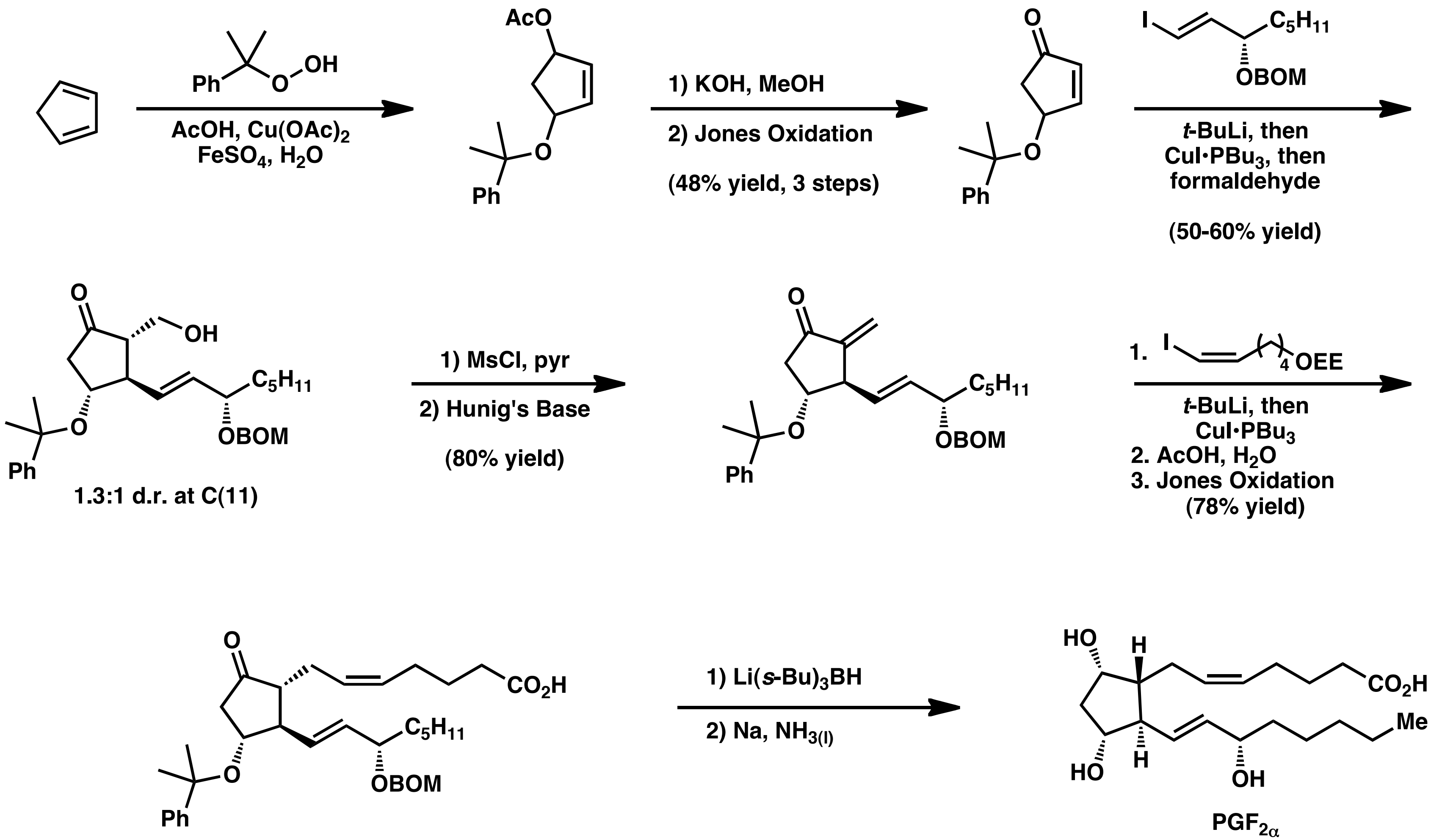


Enolate Isomerization & β-elimination must be avoided



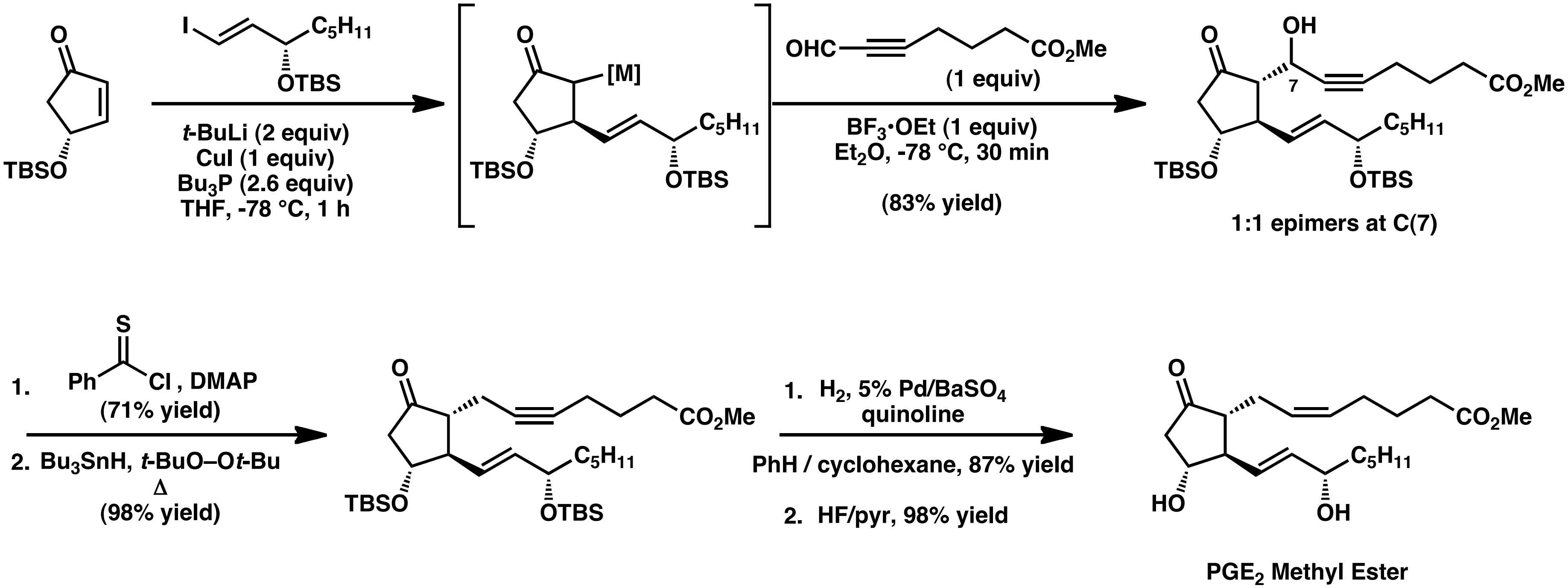
Patterson, J. W.; Fried, J. H. *J. Org. Chem*. **1979**, *39*, 2506–2509
Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755–3759
Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847–876.

Stork $PGF_{2\alpha}$ Synthesis via 3 component coupling - 1975



Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745–4746.
Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260–6261.
Stockdill, J. *Stoltz Group Literature Seminar*, January 29, 2007.

Noyori 3-Component Synthesis: 1982–1984



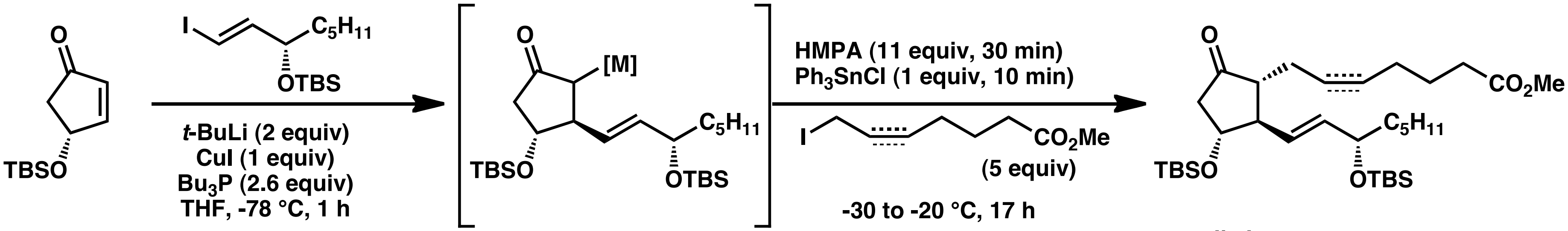
Requires a two-step deoxygenation:

A method for direct alkylation would be preferable for maximum efficiency

Limited Electrophile Choice - Alter enolate?

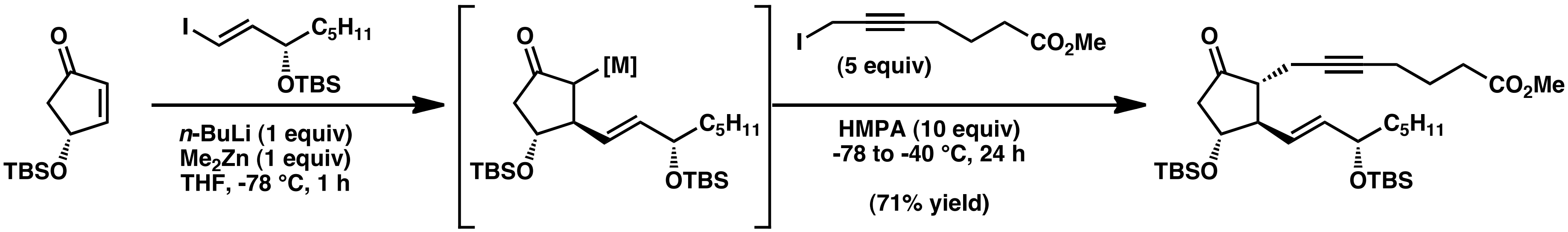
Review: Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847–876.
Suzuki, M.; Noyori, R. et al. *Tetrahedron Lett.* **1982**, *23*, 4057–4060.
Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 5563–5566.

Noyori 3-Component Synthesis: 1982–1989

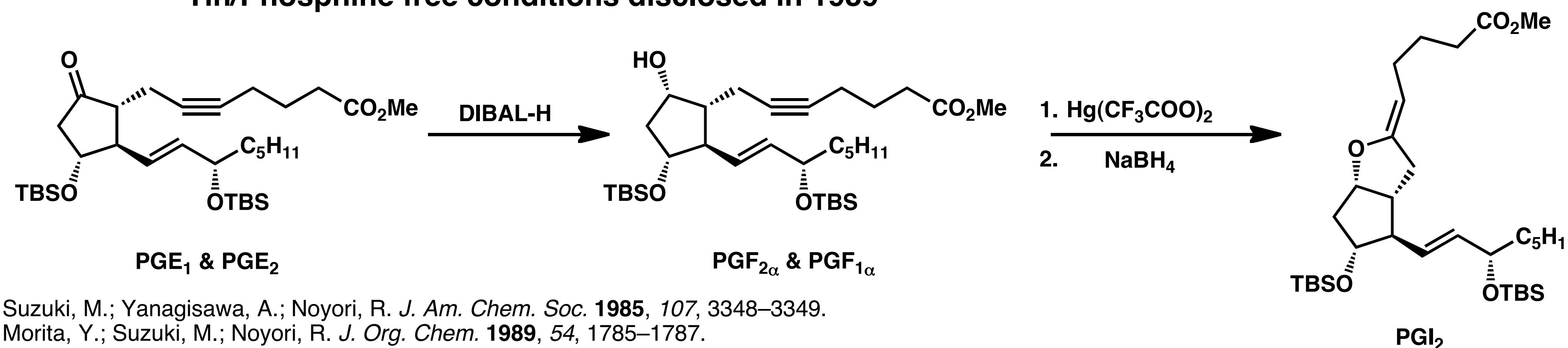


alkyl: 20% yield
allyl: 78% yield
propargyl: 82% yield

Transmetallation to tin enolate was the solution!
Limits enolate isomerization, allows warmer temperatures

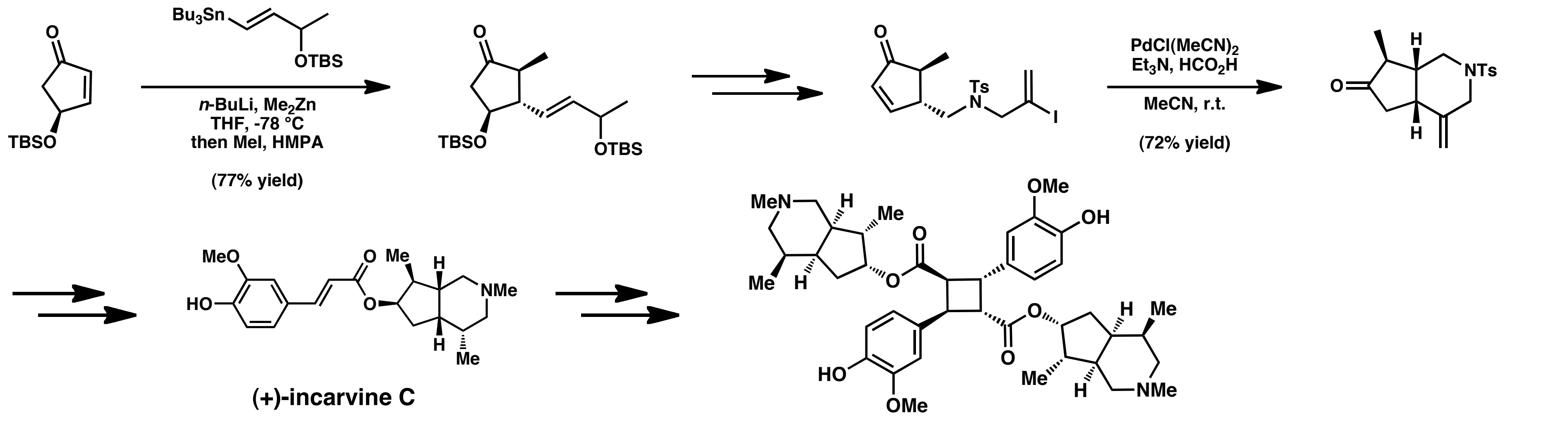


Tin/Phosphine free conditions disclosed in 1989

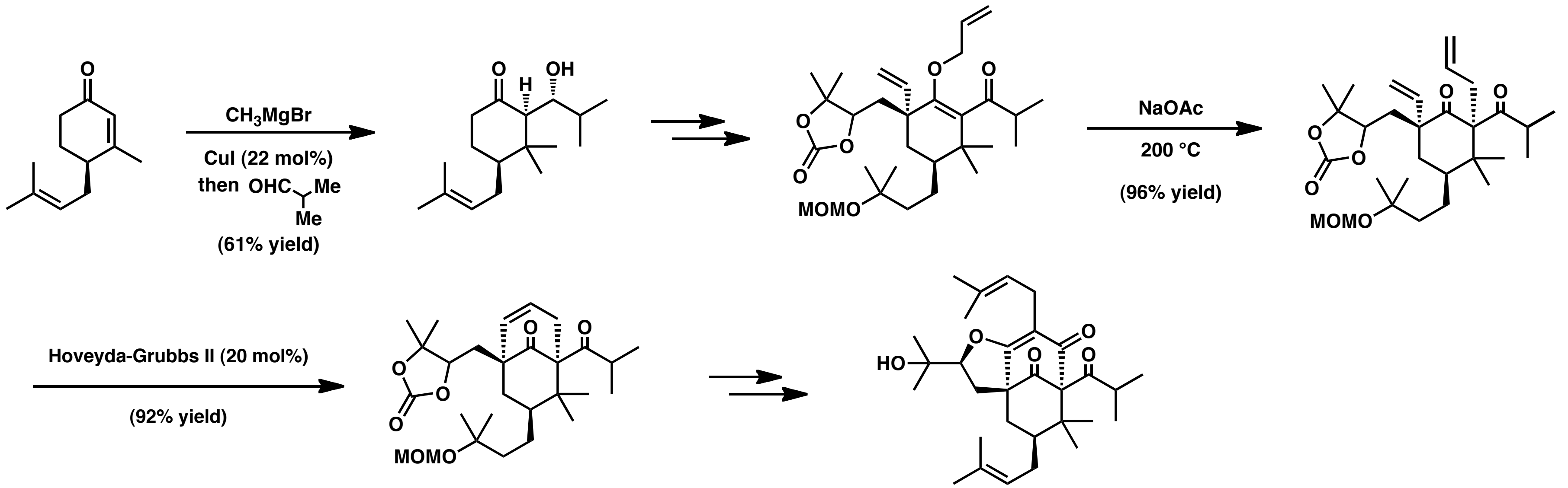


Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348–3349.
Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785–1787.
Tin enolates: a) Tardella, P. A. *Tetrahedron Lett.* **1969**, *14*, 1117–1120.
b) Nishiyama, H.; Sakuta, K.; Itoh, L. *Tetrahedron Lett.* **1984**, *25*, 223–226.
c) *ibid.* pp 2487–2488
Review on Multicomponent Couplings: Tourée, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486.
Catalytic Asymmetric α-alkylation of Sn-enolates to form 4° stereocenters: Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62–63.

Recent Applications: (–)-incarvillateine & (±)-Garsubellin A



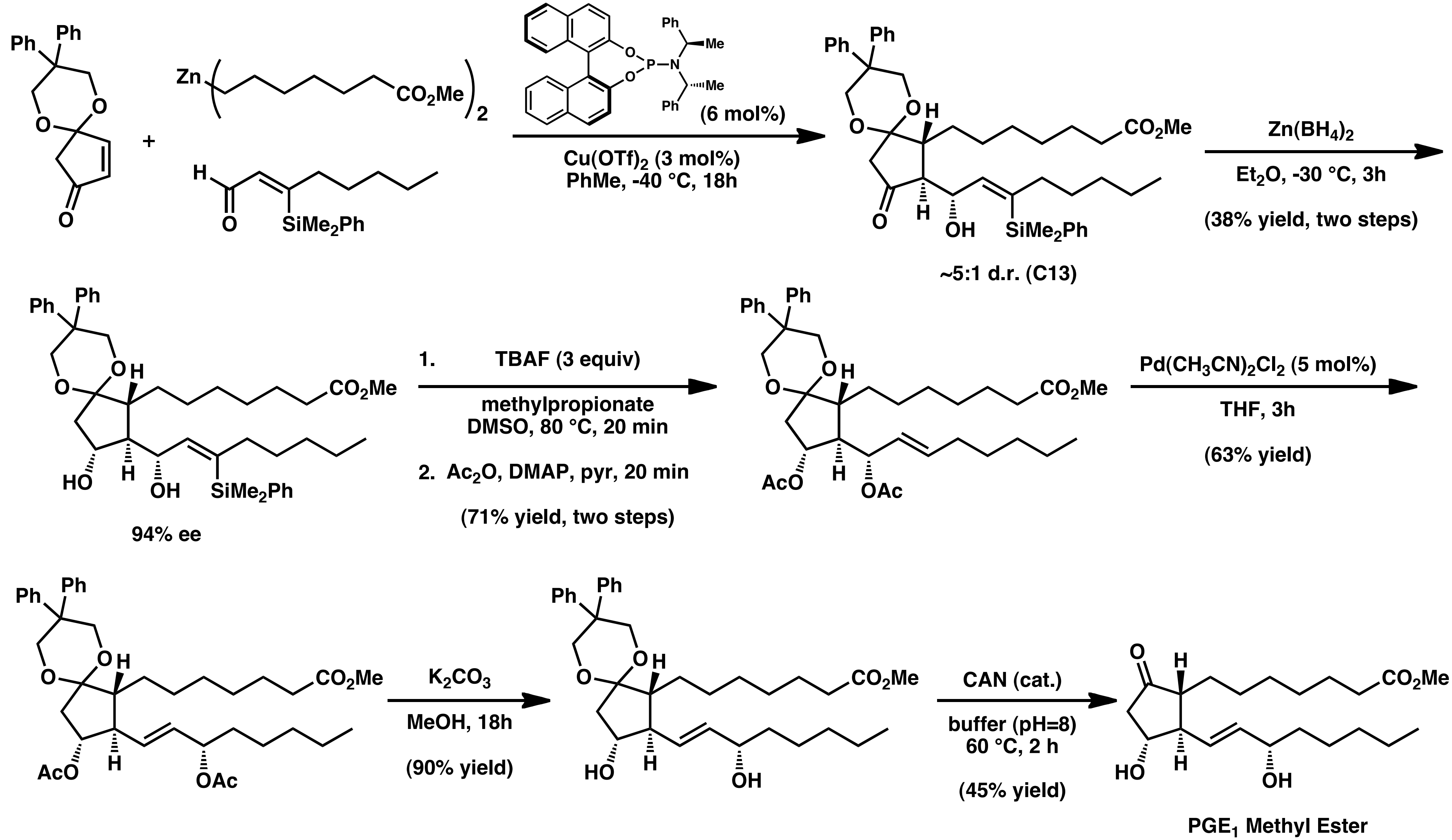
(+)-incarvillateine C



(±)-Garsubellin A

Review on Multicomponent Reactions in Synthesis: Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486.
Kibayashi, C. et al. *J. Am. Chem. Soc.* **2004**, *126*, 16553–16558.
Shibasaki, M. et al. *J. Am. Chem. Soc.* **2005**, *127*, 14200–14201.

Feringa Catalytic Enantioselective 3 Component Coupling - 2001

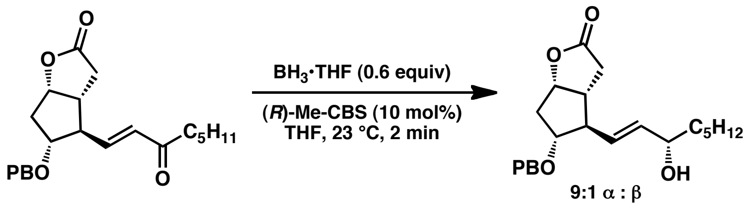


Vinylic Zn reagents were not compatible with 3CC

Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841–5842.
Full Paper: Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2002**, *67*, 7244–7254.
Allylic Transposition: Grieco, P. A. et al. *J. Am. Chem. Soc.* **1980**, *102*, 7587–7588.

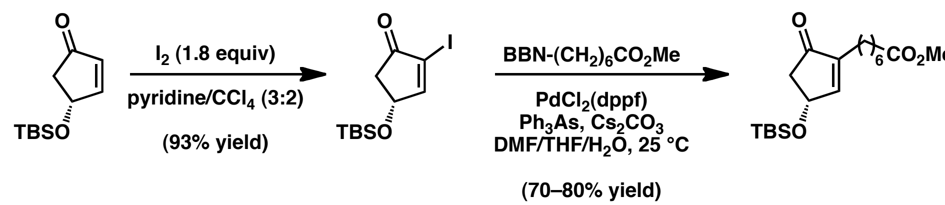
Summary

Synthetic testing ground for new methods:

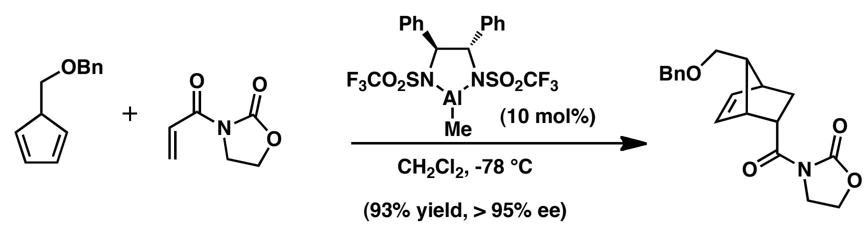


Corey–Bakshi-Shibata
Catalytic Enantioselective Reduction of Ketones

Direct α-iodination of enones

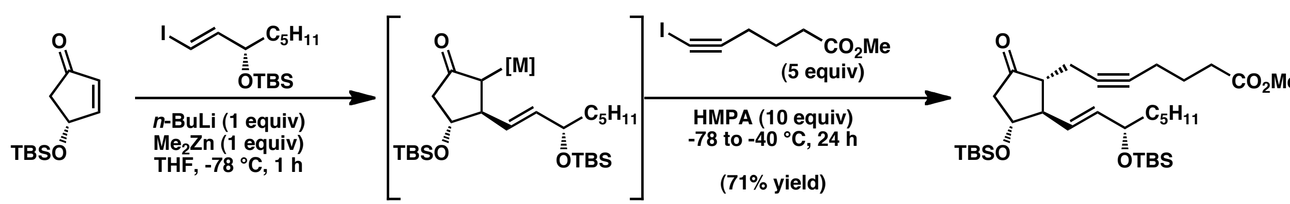


Inspiration for new synthetic methods:



Catalytic Enantioselective Diels–Alder Reaction

Tandem conjugate addition/aldol reaction



Useful References

Bindra, J. S. and Bindra, R., *Prostaglandin Synthesis*; Academic Press: New York, 1977.

Historical Background, Incl. Degradation Studies, Detailed breakdown of synthetic strategies through 1977

Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533–1564
Das, S.; Chandrasekhar, S.; Yadav, J. S.; Gree, R. *Chem. Rev.* **2007**, *107*, 3286–3337

Reviews of new synthetic approaches to prostaglandins & analogues.

Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis;* VCH: Weinheim, 1996

Detailed descriptions of Corey's bicycloheptane route & Stork's enantiospecific routes

Rouzer, C. A.; Marnett, L. J. *Chem. Rev.* **2003**, *103*, 2239–2304.

Overview of Mechanism of PG synthesis, including some isotopic studies, and later biochemical work.

Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876–889.
Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019.
Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667.
Corey, E. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2100–2117.

Various enantioselective Diels-Alder reviews

Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847–876.

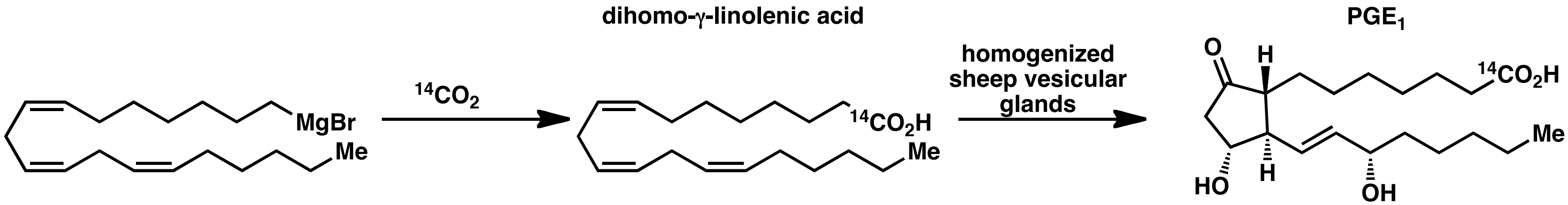
Account of 3 component coupling development (does not include most recent advances, i.e. tin and tin free alkylations)

Caton, M. P. L. *Tetrahedron* **1979**, *35*, 2705–2742.
Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847–876.

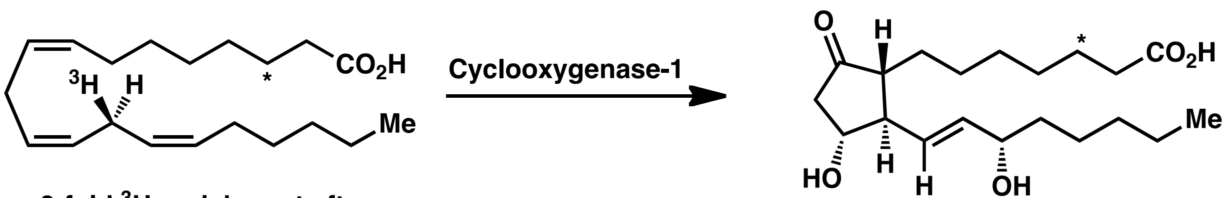
Describe new synthetic methodologies which arose as a result of prostaglandin research

Extra slides!

Prostaglandin Biosynthesis



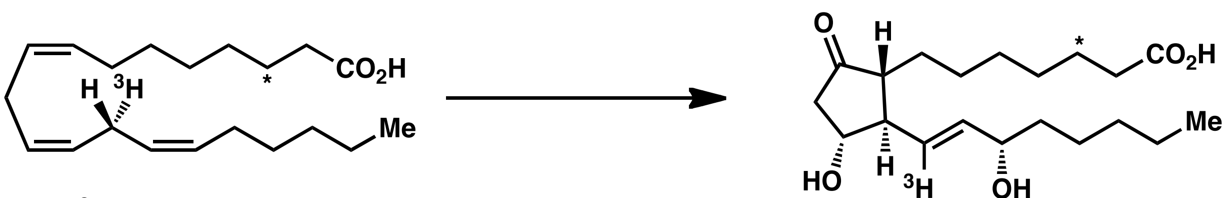
- Characterized by TLC, observation of radioactivity on product band
- First demonstration of biosynthesis of PGs from polyunsaturated fatty acids



3-fold ^{3}H enrichment after 75% conversion

0.05% retention of ^{3}H label

^{3}H labelled substrate mixed with ^{14}C labelled substrate, then incubated with enzyme



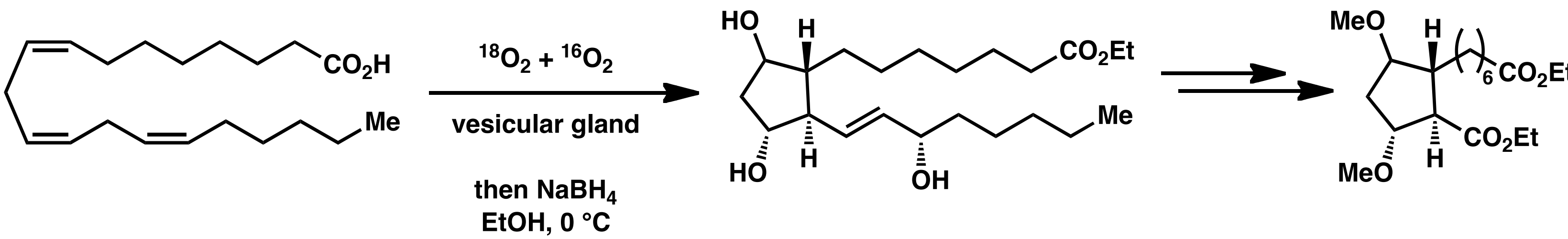
No ^{3}H enrichment in partially converted material

89% retention of ^{3}H label

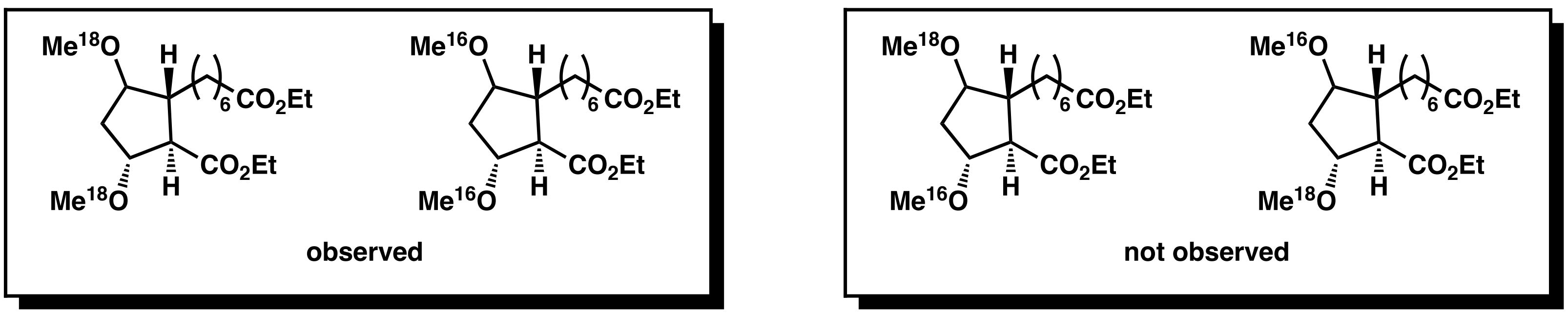
- *pro*-(*S*) hydrogen is selectively removed
- KIE consistent with H abstraction preceeding reaction with oxygen

Review on fatty acid oxygenation: Rouzer, C. A.; Marnett, L. J. *Chem. Rev.* **2003,** *103*, 2239–2304.
Labelling studies:
Van Dorp, D. A. et al. *Nature* **1964**, *203*, 839–841.
Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1967**, *242*, 5336–5343.

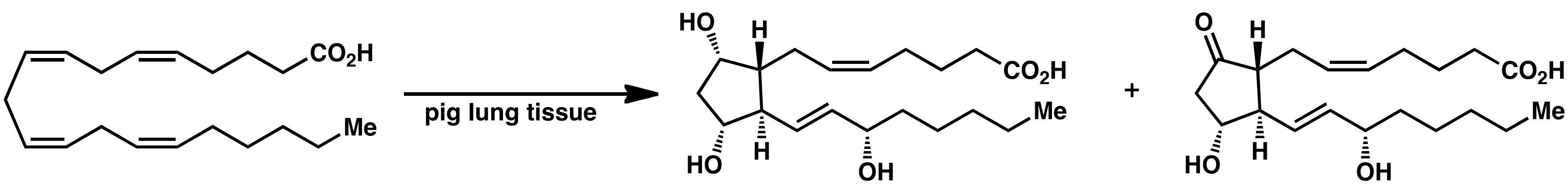
Prostaglandin Biosynthesis



- Reduction of ketone to prevent O label exchange
- Conversion to diethyl ester in order to distinguish losses in MS



- Both oxygen atoms on cyclopentane are derived from the same oxygen molecule

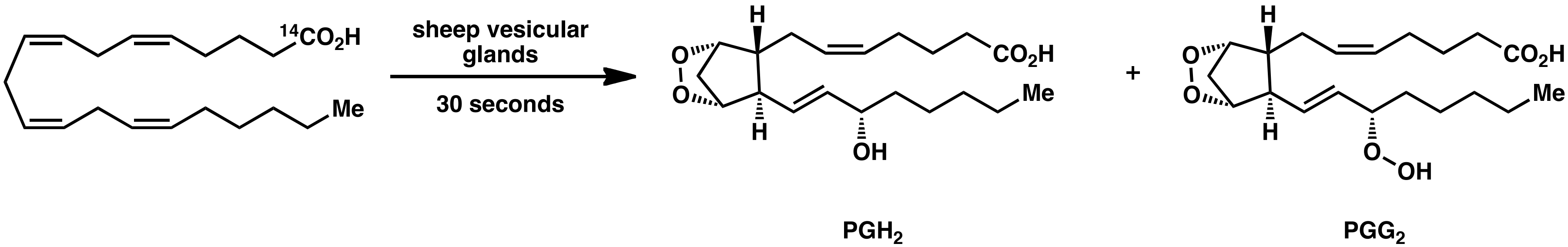


$PGF_{2\alpha}$ PGE_2

- Labelled PGE_2 is not converted to $PGF_{2\alpha}$ under reaction conditions: Derived from common intermediate

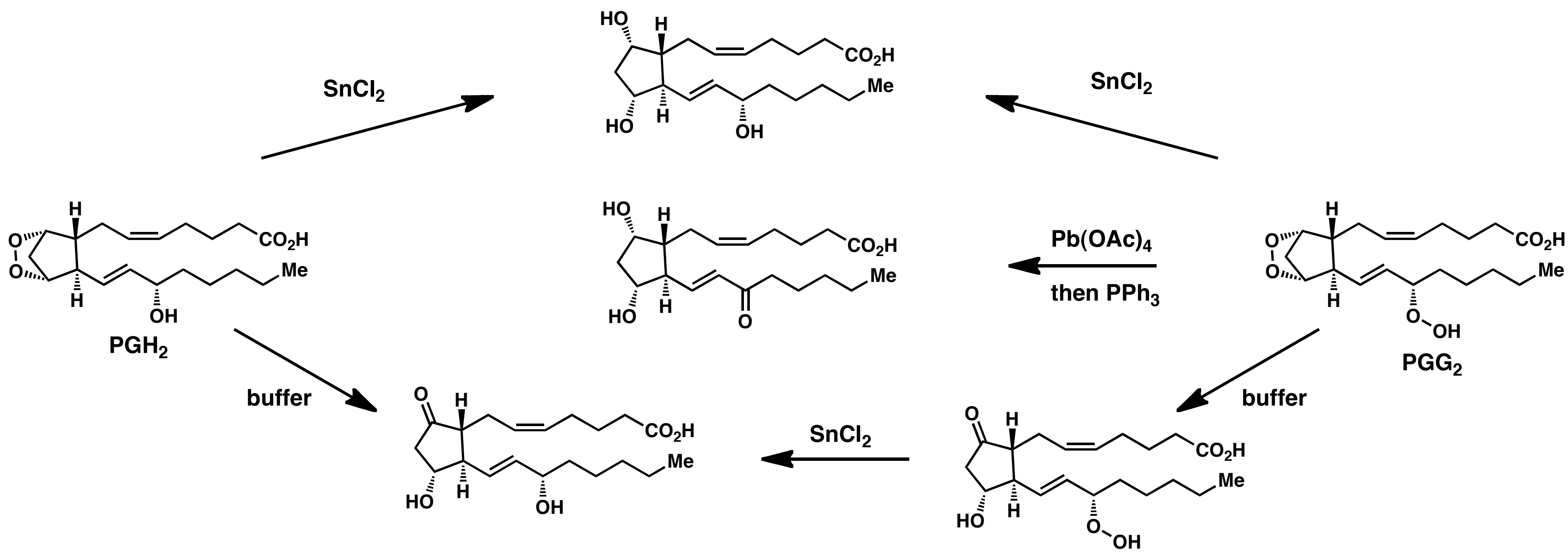
Rouzer, C. A.; Marnett, L. J. *Chem. Rev.* **2003,** *103*, 2239–2304.
Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1967**, *242*, 5329–5335.

Prostaglandin Biosynthesis



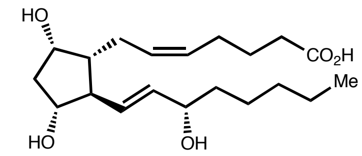
- Short reaction time allows for isolation of endoperoxide intermediates
- Stable for weeks in anhydrous Et_2O or Acetone at -20 °C. Decomposes rapidly in presence of H_2O or EtOH

Structural confirmation:

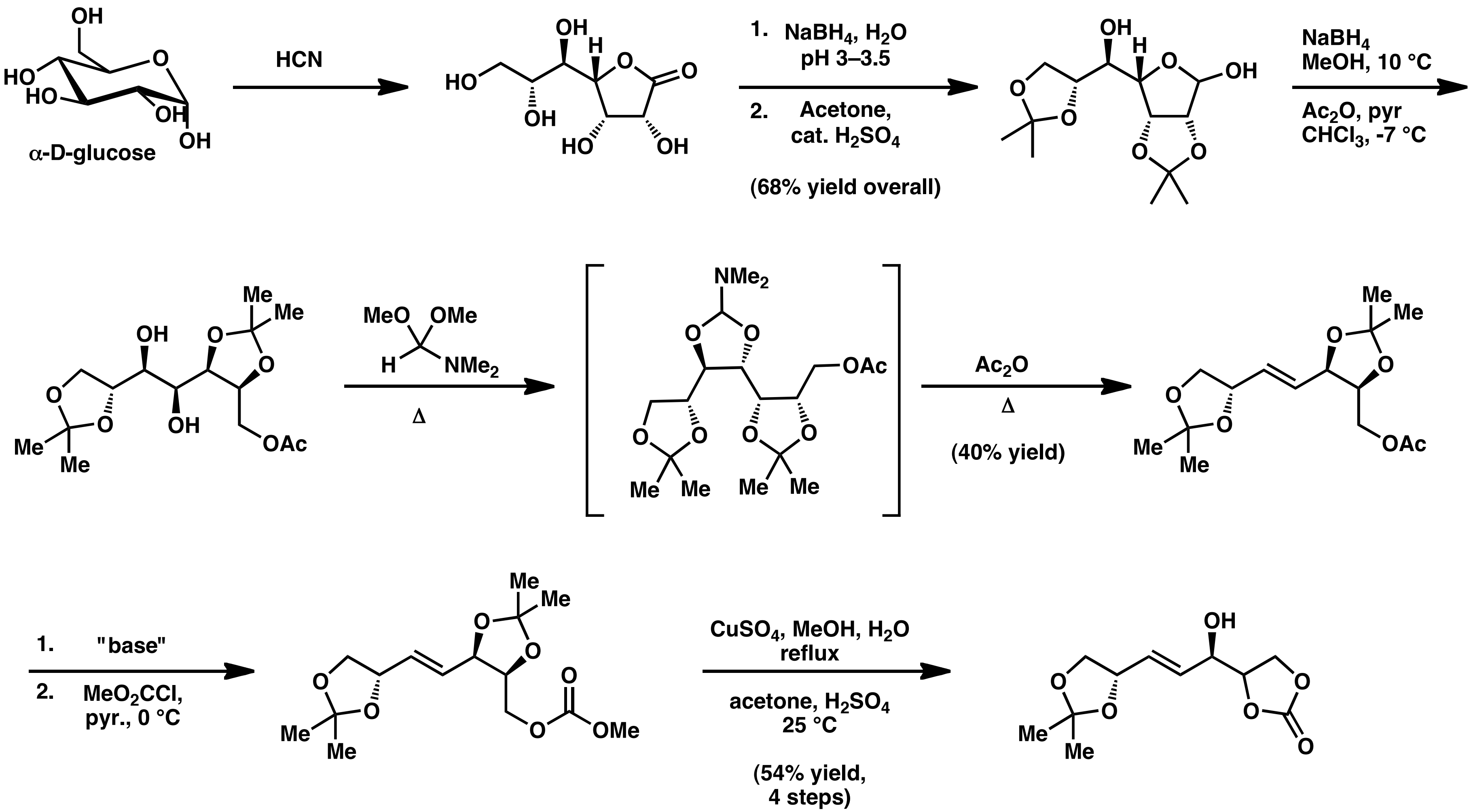


Rouzer, C. A.; Marnett, L. J. *Chem. Rev.* **2003,** *103*, 2239–2304.
Hamberg, M.; Svensson, J.; Wakabaya, T.; Samuelsson, B. *P. Natl. Acad. Sci. USA* **1974**, *71*, 345-349.

Stork Enantiospecific Route From Glucose – 1978

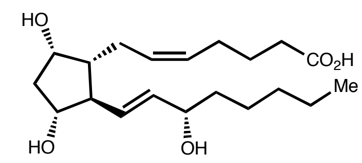


PGF$_{2\alpha}$

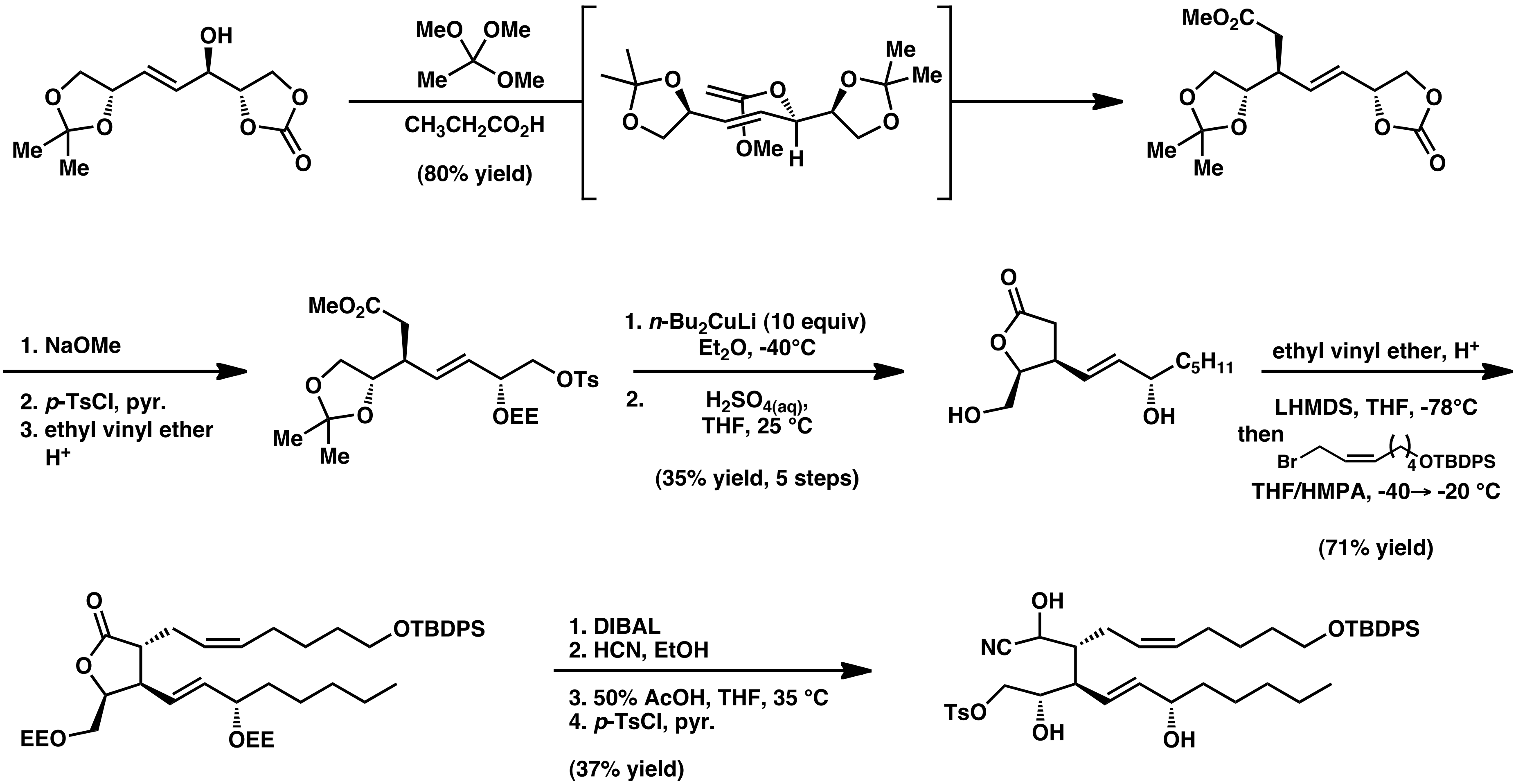


Stork, G. et al. *J. Am. Chem. Soc.* **1978**, *100*, 8272–8273.
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1966: pp 144–151.

Stork Enantiospecific Route From Glucose – 1978

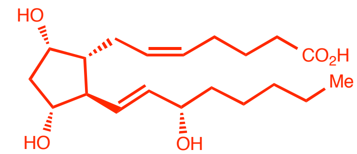


$PGF_{2\alpha}$

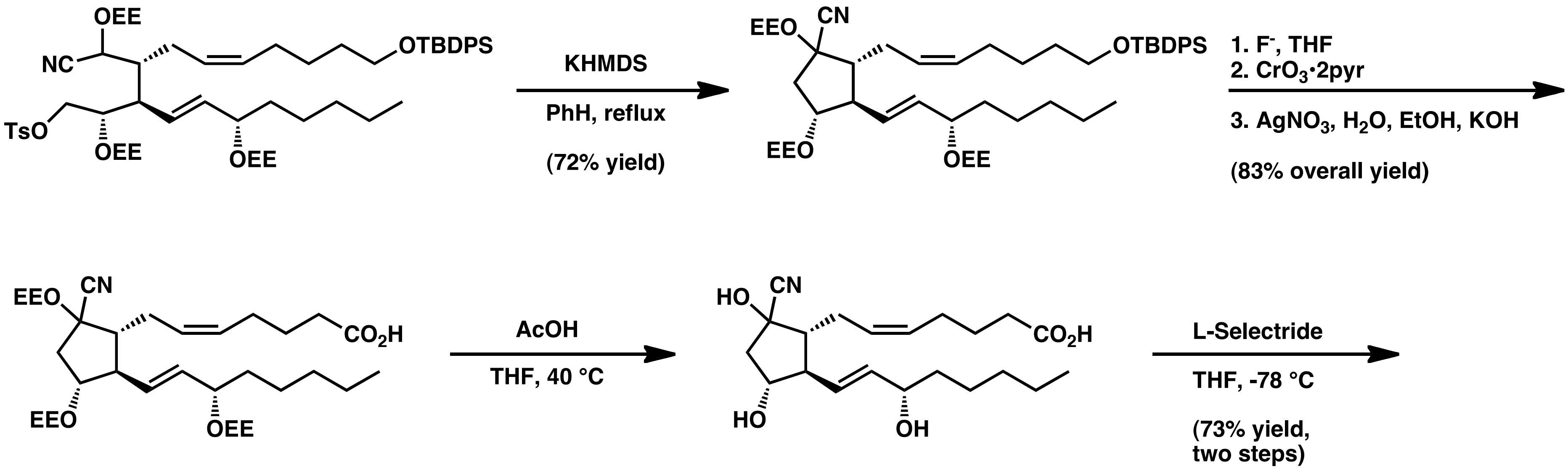


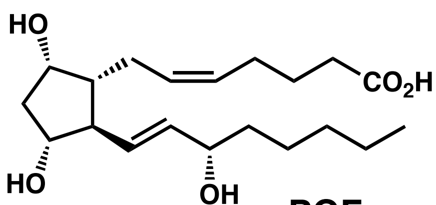
Stork, G. et al. *J. Am. Chem. Soc.* **1978**, *100*, 8272–8273.
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1966: pp 144–151.

Stork Enantiospecific Route From Glucose – 1978



$PGF_{2\alpha}$



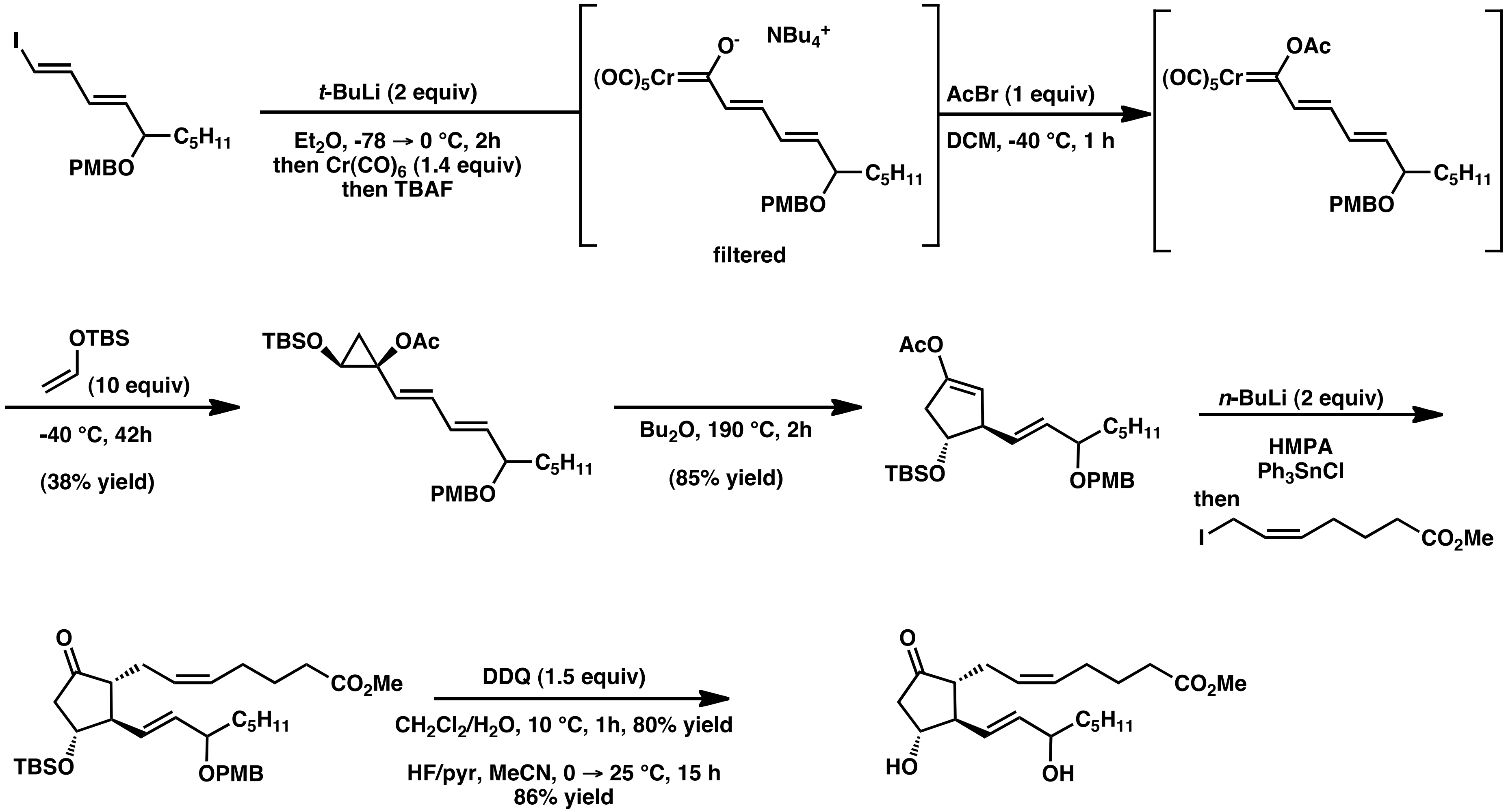


$PGF_{2\alpha}$

Stork's synthesis demonstrates synthetic utility of new technologies:
- **Umpolung acyl anion chemistry**
- **Johnson–Claisen rearrangement**

Stork, G. et al. *J. Am. Chem. Soc.* **1978**, *100*, 8272–8273.
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1966: pp 144–151.
Acyl Anion alkylation via cyanohydrin: Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286–5287
Overview of acyl anion equivalents: http://www.chem.wisc.edu/areas/reich/chem547/5-orgmet%7B06%7D.htm

Vinyl Cyclopropane Rearrangement Route - Wulff, 1990



PGE_2 Methyl ester & C15 epimer

First natural product synthesis employing a Fischer Carbene as a key intermediate

Murray, C. K.; Yang, D. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 5660–5662.