

# Phosphine-Initiated Enolate Transformations

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Evans Group Seminar

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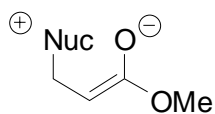
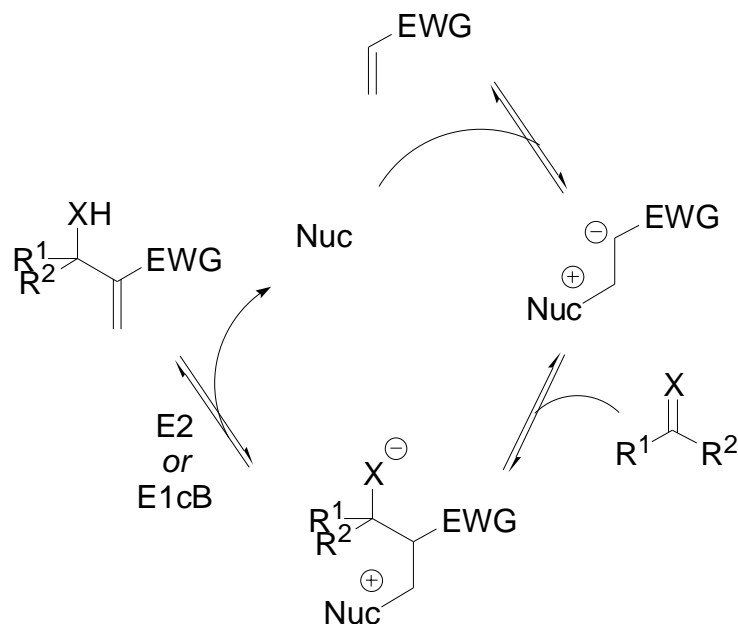
## Contents

- I. Mechanism of Baylis-Hillman Reaction
- II. Activated Alkenes as the Latent Enolates
  - II-I. Rauhut-Currier Reaction
  - II-II. Morita-Baylis-Hillman Reaction
  - II-III. Miscellaneous Reactions
- III. Activated Alkynes and Allenes
  - III-I. Internal Redox Reaction
  - III-II. Umpolung Addition
  - III-III. [3+2] Annulation
  - III-IV. Miscellaneous Reactions

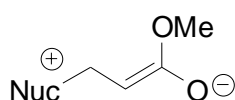
## Review Articles

- 1) Ciganek, E. *Organic Reactions*; Paquette, L.A., Ed.; Wiley: New York, 1997; Vol. 51, p 201.
- 2) Basavaiah, D. et. al. *Chem. Rev.* **2003**, *103*, 811.
- 3) Krische, M. J. et. al. *Synlett* **2003**, 12.
- 4) Lu, X. et. al. *Acc. Chem. Res.* **2001**, *34*, 534.
- 5) Janey, J. " Asymmetric Catalysis with Chiral Lewis Bases (Part IV) : The Asymmetric Baylis-Hillman Reaction", *Evans Group Seminar* **2001**.

# Mechanism of Morita-Baylis-Hillman Reaction



**E enolate**  
Thermodynamic  
less charge separation  
less reactive



**Z enolate**  
kinetic  
more charge separation  
less stable

- All mechanistic studies were done with tertiary amines as catalysts.

## - Pressure<sup>a</sup>

“the most highly pressure-dependent reactions ever observed”,  $\Delta V_a^\ddagger$ :  $-79 \text{ cm}^3 \text{ mol}^{-1}$  ( $-35$  for Diels-Alder)

## - Proton Sources

Alcoholic solvents accelerate reaction.

Rate acceleration with various proton donors.

(additives, solvents and catalysts).

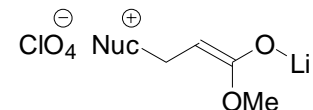
## - Temperature<sup>b</sup>

Increased reaction rate at  $0^\circ\text{C}$  as compared to  $25^\circ\text{C}$  suggests kinetic *E* enolate reacts faster than the thermodynamic *Z* enolate.

## - Salt Effect<sup>c</sup>

$\text{LiClO}_4$  increases the yield and rate in ethereal solvent.

Authors proposed that the formation of a salt may stabilize the kinetic *E* enolate.



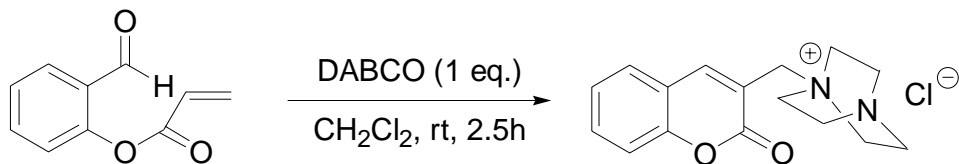
a) Hill *TL* **1986**, 27, 5007.

*JPOC* **1990**, 3, 285.

b) Leahy *JOC* **1997**, 62, 1521.

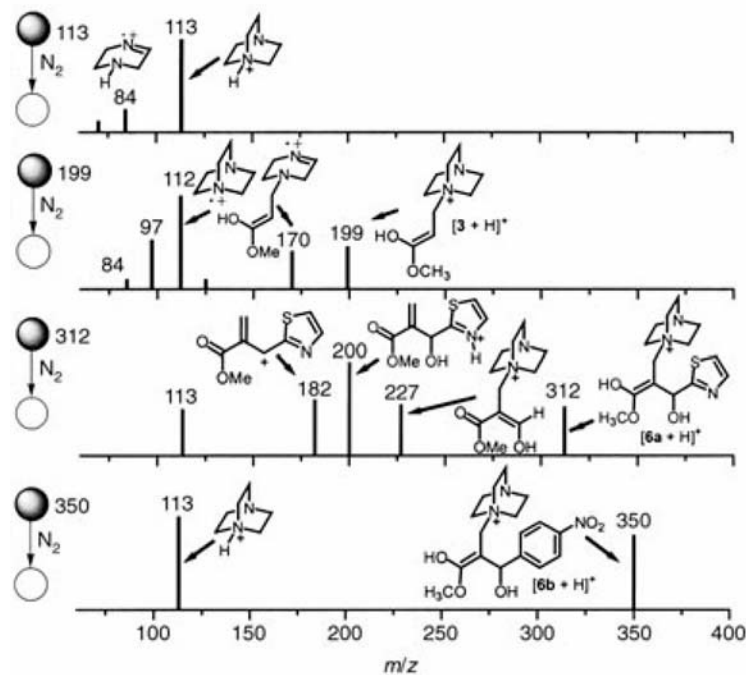
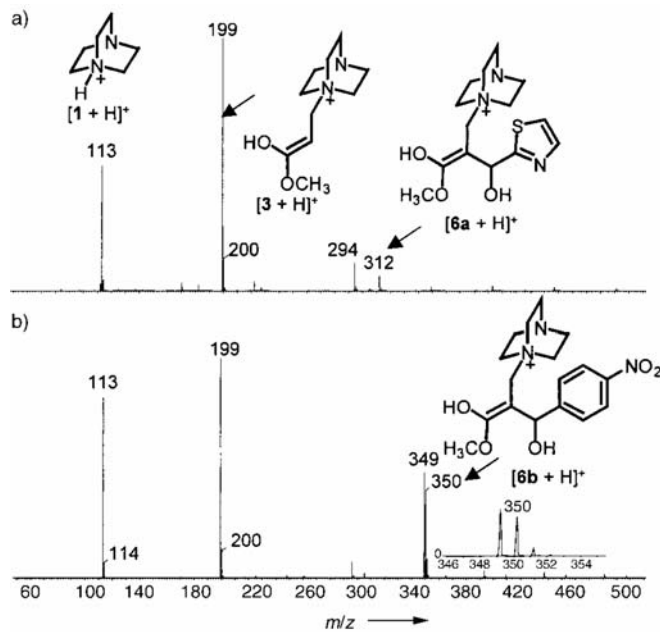
c) Kobayashi *TL* **1999**, 40, 1539.

## Evidence for the Intermediates



81% yield, X-ray

Drewes SC **1993**, 23, 2807.



ESI(+)-MS spectra for the Baylis-Hillman reaction

ESI(+)-MS/MS spectra for structural characterization

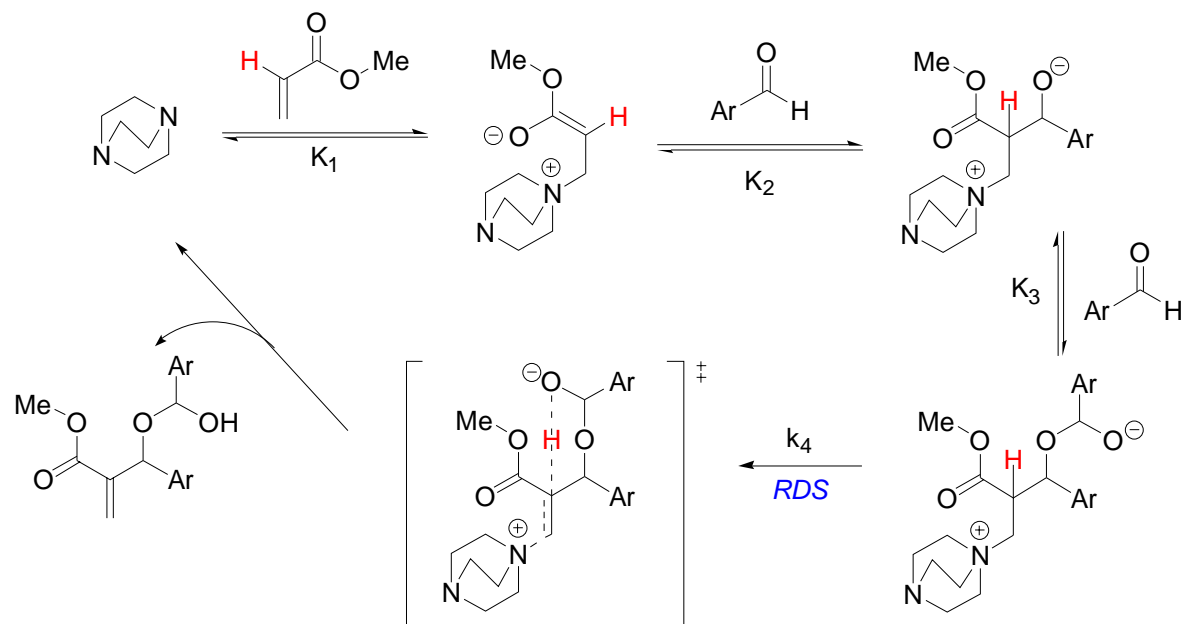
Coelho ACIE **2004**, 43, 4330.

# MBH Kinetics : Kinetic Study in Aprotic Solvents

"The reaction rate seems to be determined by the aldol addition step because the dipole moment is increased by further charge separation." Coelho ACIE 2004, 43, 4330.

"The rate-limiting step of the reaction has been determined as aldol addition step on the basis that no primary kinetic isotope effect (KIE) was observed." Aggarwal ACIE 2005, 44, 2.

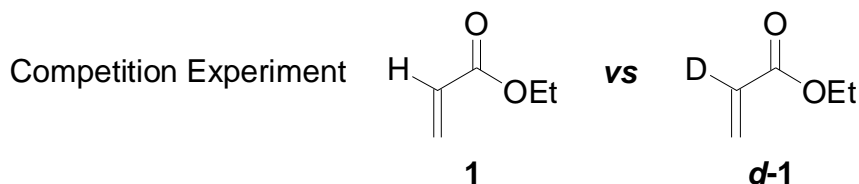
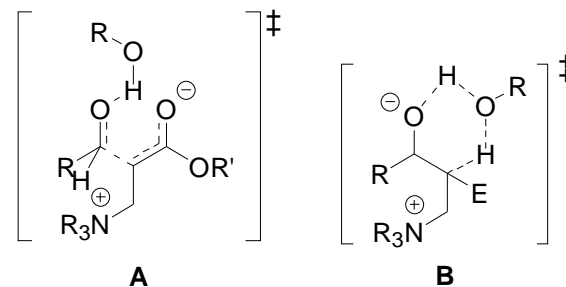
- From the kinetic order plots,  $\text{rate} = k_{\text{obs}} [\text{aldehyde}]^2 [\text{DABCO}] [\text{acrylate}]$
- Primary KIE for  $\alpha\text{-}^2\text{H}$  acrylate : C-H bond cleavage in the RDS
- Inverse EIE for deuterio-aldehyde :  $sp^2$  to  $sp^3$  geometry changes during the 1,2-addition pre-equilibrium



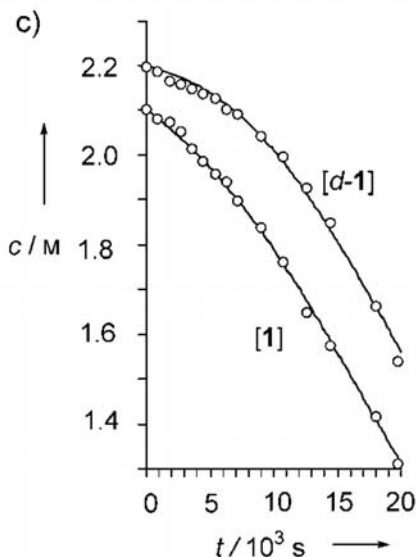
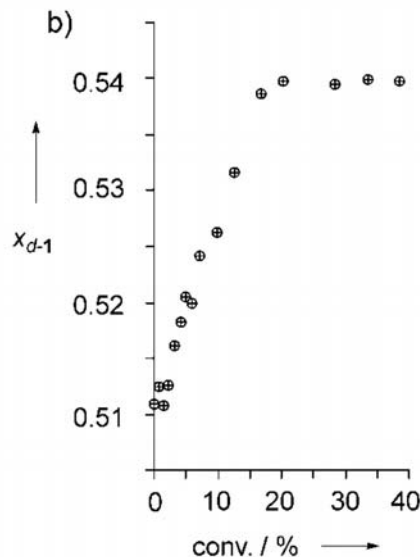
# MBH Kinetics : RDS Shift According to the Phase of the Reaction

“Protic solvents are known to accelerate the reaction through activation of the aldehyde by hydrogen-bonding to thereby promote aldol addition step.” (A)

Rate acceleration from both protic solvent and MBH product (autocatalysis) can be explained by proton-transfer mechanism. (B)



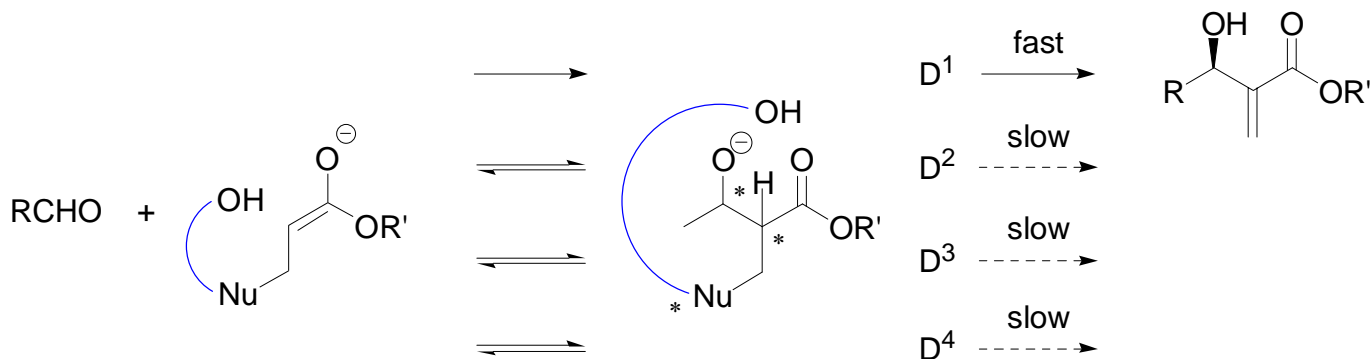
" In the absence of added protic species, the initial stage of the BHR involves rate-limiting proton transfer step. As the product concentration builds, proton transfer becomes increasingly efficient and the RDS is then aldol addition step."



- b) Relationship between conversion and mole fraction of **d-1**: primary KIE in the early phase
- c) Simulated variation of the concentrations of **1** and **d-1**: lines - predicted, circles - observed model for simulation :substantial primary KIE ( $k_H/k_D = 5 \pm 2$ ) for the noncatalyzed proton transfer step,  $k_H/k_D = 1$  for autocatalysis.

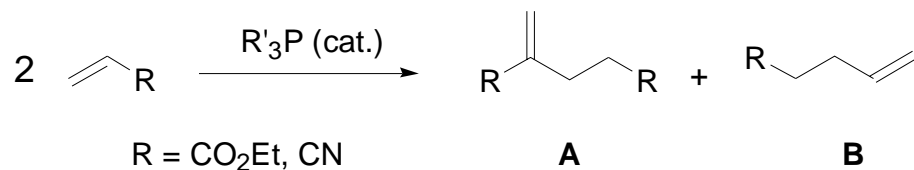
# MBH Kinetics : Implications for Asymmetric Catalysis

- Little success in the design of chiral catalysts for MBH : Focus has been on the stereocontrol of aldol addition step.
- Successful catalysts to date with >80% ee have appended hydrogen-bond donors.
- Positioning of suitable hydrogen-bond donors for selective proton transfer is likely to be more successful.
- Use of aprotic solvent may be crucial for high stereoselectivity.
- Stereoselectivity may be decreased by the competitive nonselective autocatalysis.

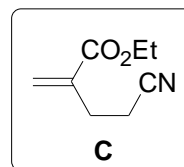


Aggarwal *ACIE* **2005**, Early View.

# Rauhut-Currier Reaction – Dimerization of Activated Alkenes



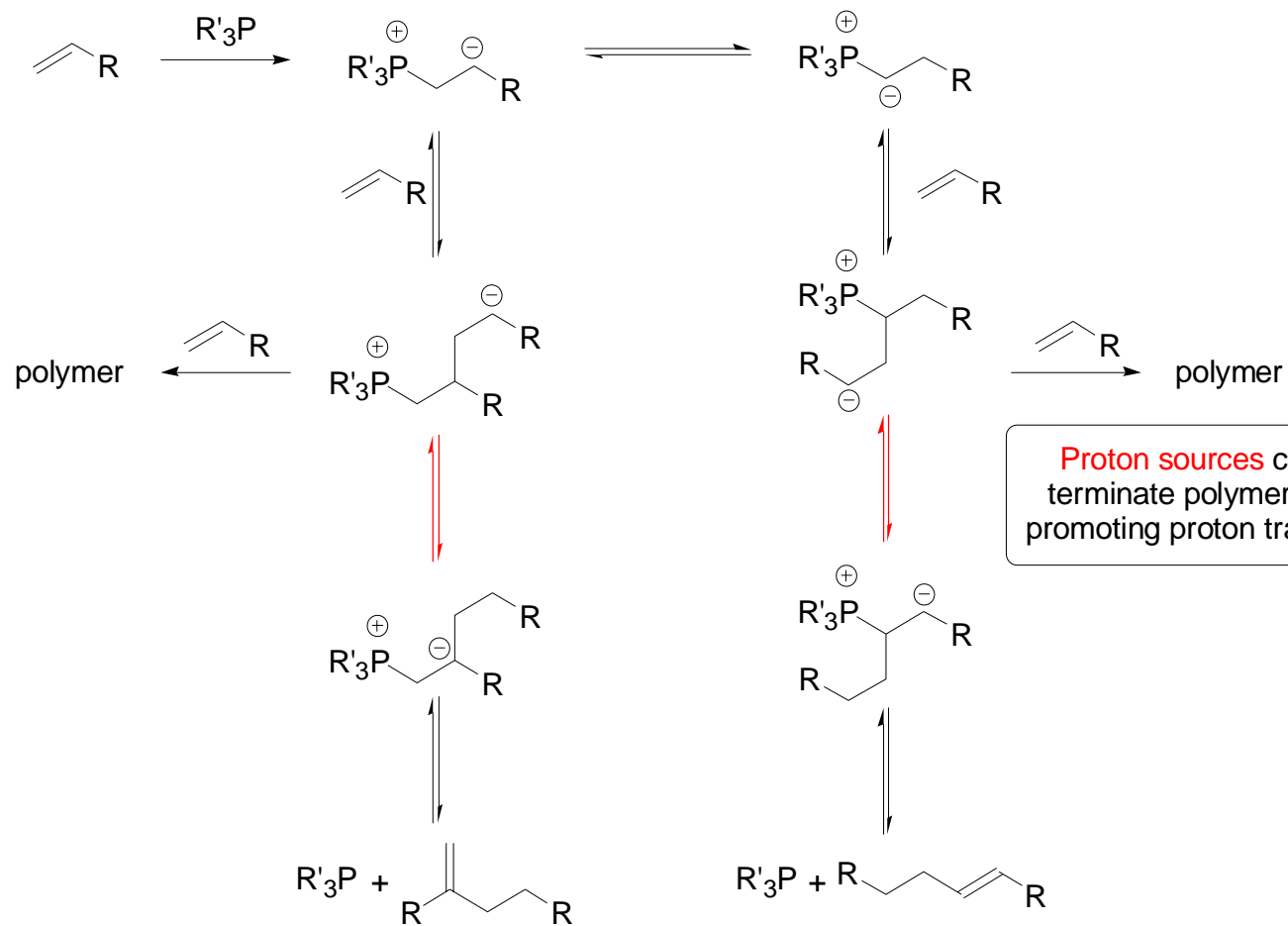
Researchers	Substrates (R)	Conditions	Results
Rauhut/Currier	CO <sub>2</sub> Et	Bu <sub>3</sub> P in CH <sub>3</sub> CN	only A observed
Baizer/Anderson	CN	Ph <sub>3</sub> P (1.6 mol%) in <i>t</i> -BuOH <sup>a</sup> /CH <sub>3</sub> CN, rt, 3h	5.3% yield A:B = 60:40
McClure	CN	( <i>p</i> -Tol) <sub>3</sub> P (0.4 mol%) in Et <sub>3</sub> SiOH <sup>a</sup> 160 °C, 11h	36% conv. 85% yield A:B = 68:32
	1:1 mixture of CN and CO <sub>2</sub> Et	Bu <sub>3</sub> P (1.3 mol%) in <i>t</i> -BuOH <sup>a</sup> 100 °C, 7h	21% conv. 48% of C <sup>b</sup>
	COMe	Ph <sub>3</sub> P (2.5 mol%) in Et <sub>3</sub> SiOH <sup>a</sup> 118 °C, 8h	60% conv. 78% yield only A
Amri	CO <sub>2</sub> <i>t</i> -Bu	(Me <sub>2</sub> N) <sub>3</sub> P (10 mol%) 20 °C, 16h	72% (GLC)



- a) *t*-BuOH and Et<sub>3</sub>SiOH are proton sources which were required to suppress vigorous polymerization of acrylonitrile.  
b) By products were observed. 25% of A (R=CN) and 22% of A (R=CO<sub>2</sub>Et).

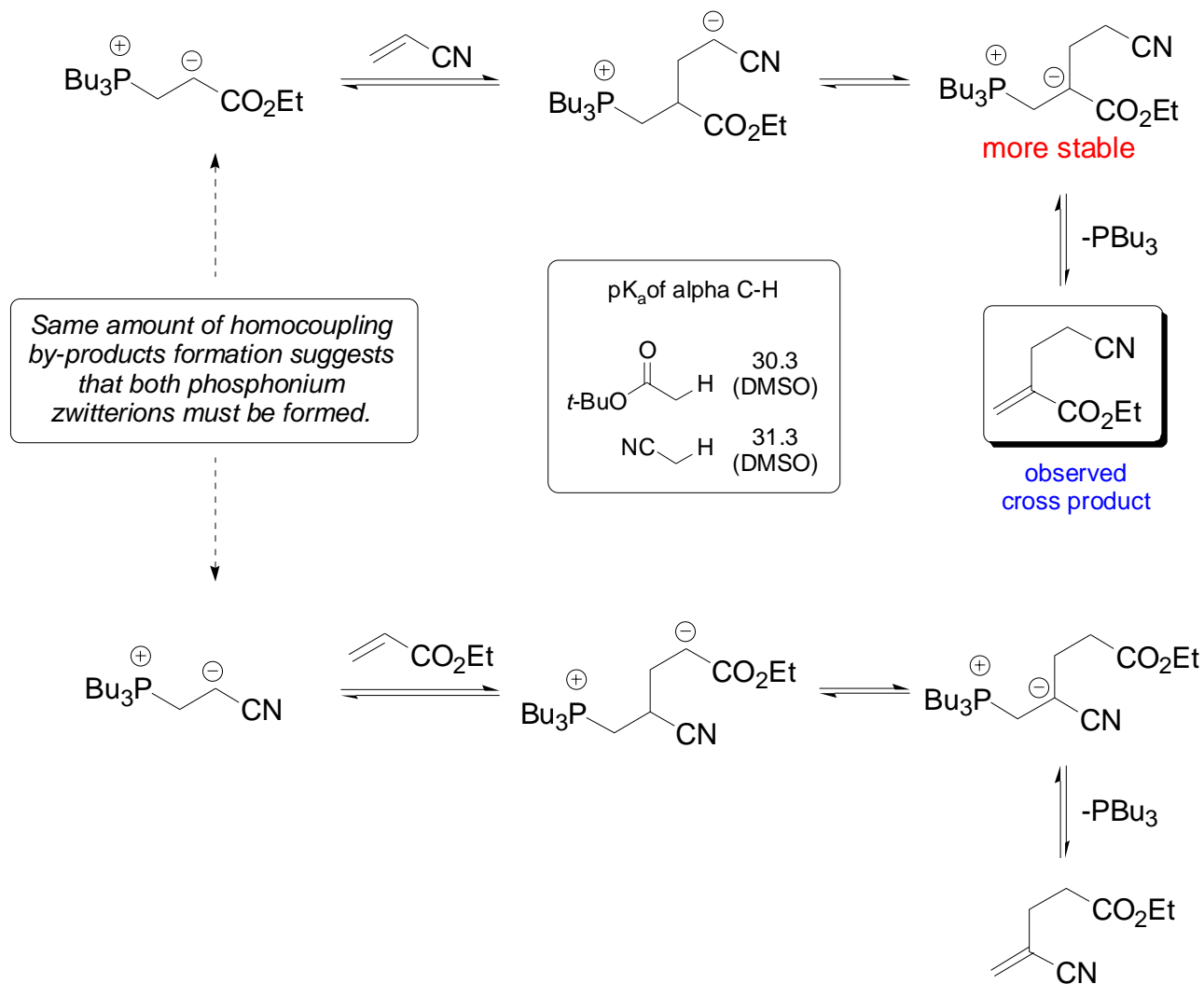
Rauhut and Currier *U. S. Patent* **1963**, 3074999.  
Baizer and Anderson *JOC* **1965**, 30, 1357.  
McClure *U. S. Patent* **1965**, 3225083.  
McClure *JOC* **1970**, 35, 3045.  
Amri *TL*, **1989**, 30, 7381.

# Rauhut-Currier Reaction – Mechanism

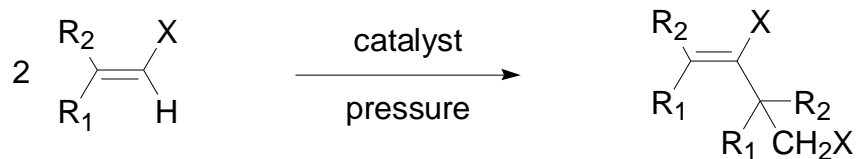




# Mechanism for the Selective Cross-Condensation



# Rauhut-Currier Reaction – Pressure Dependence



dimerization of crotononitrile ( $\text{R}_1=\text{Me}$ ,  $\text{R}_2=\text{H}$ ,  $\text{X}=\text{CN}$ ) (bulk,  $50^\circ\text{C}$ , 24 h, catalyst 5 mol%)

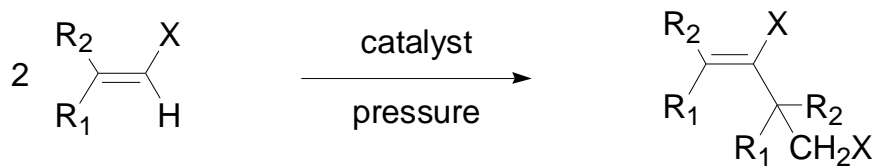
Catalyst	Pressure (MPa)	Yield (%)	<i>trans</i> : <i>cis</i> <sup>a</sup>	Catalyst	Pressure (MPa)	Yield (%)	<i>trans</i> : <i>cis</i> <sup>a</sup>
DABCO or 3-quinuclidinol	0.1	0	-	$\text{Bu}_3\text{P}$	0.1	7	75 : 25
	300	0	-	$\text{Bu}_3\text{P}$	300	100	77 : 23
DBU	0.1	3	-	$\text{Hx}_3\text{P}^{\text{b}}$	300	0	-
DBU	300	19	65 : 35	$\text{Ph}_3\text{P}^{\text{b}}$	300	0	-
DBN	0.1	6	-	$(\text{NMe}_2)_3\text{P}$	0.1	87	71 : 29
DBU	300	54	68 : 32	Phosphazene <sup>c</sup>	0.1	72	68 : 32

a) Initial ratio in crotononitrile (*trans* : *cis* = 65 : 35)

b) A small amount of dry THF was added to dissolve phosphines before reaction

c) Phosphazene Base  $\text{P}_4\text{-}t\text{-Bu}$  solution. Polymeric material was also present

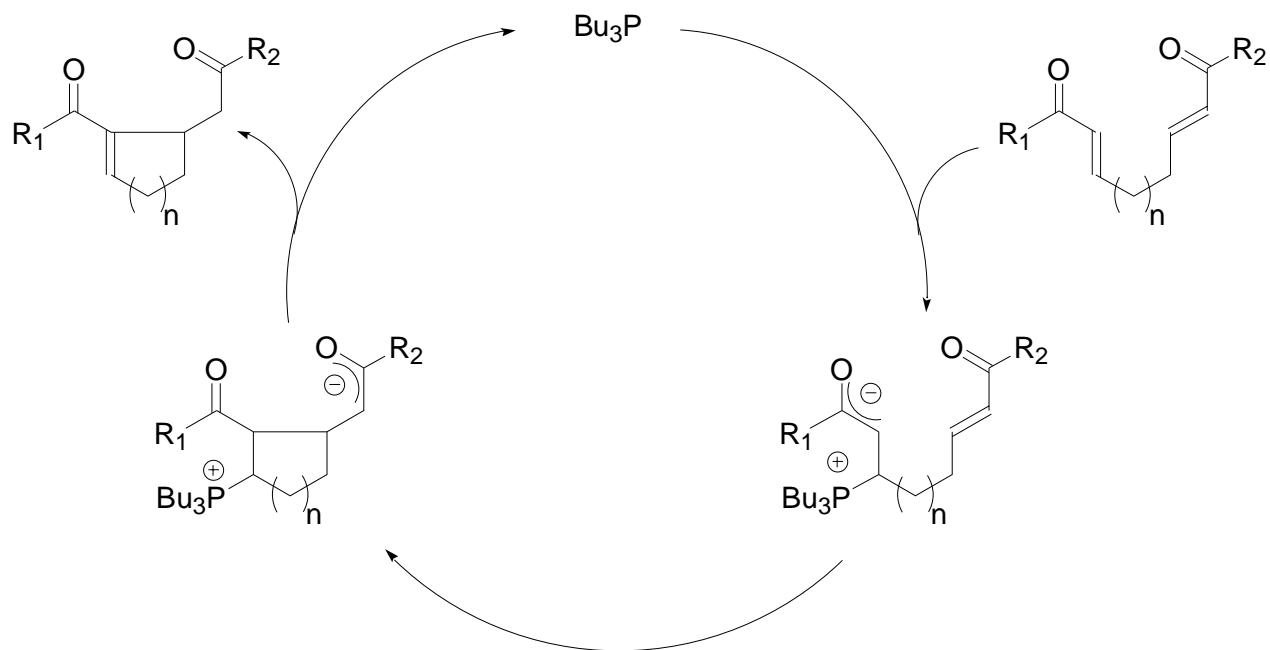
## Rauhut-Currier Reaction – Phospine Catalysts



R <sub>1</sub>	R <sub>2</sub>	X	catalyst	% Yields	
				0.1 MPa	300 MPa
H	H	CN	Bu <sub>3</sub> P (5%)	98 <sup>a</sup>	NA
Me	H	CN	[NMe <sub>2</sub> ] <sub>3</sub> P (5%)	87	NA
Et	H	CN	Bu <sub>3</sub> P (5%)	0	86
Et	H	CN	[NMe <sub>2</sub> ] <sub>3</sub> P (5%)	8	96
H	H	CO <sub>2</sub> Me	Bu <sub>3</sub> P (5%)	59	NA
Me	H	CO <sub>2</sub> Me	Bu <sub>3</sub> P (10%)	0	0
			[NMe <sub>2</sub> ] <sub>3</sub> P (30%)	0	88

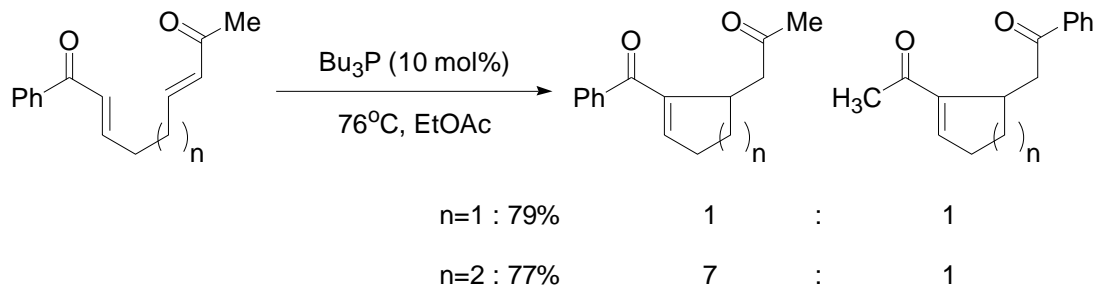
a) Solvent was necessary to prevent the rapid polymerization  
DABCO catalyzed the dimerization only under 300 MPa.

# Intramolecular Rauhut-Currier Reaction - Mechanism

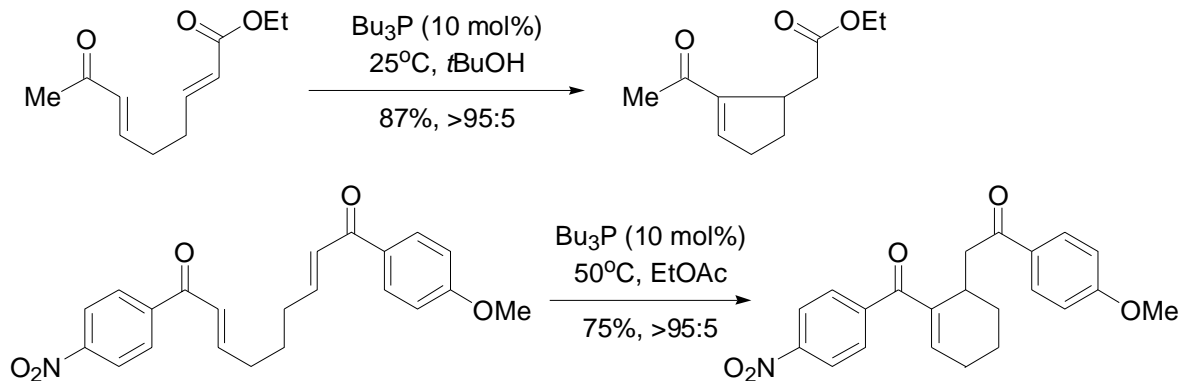


Krische *JACS* **2002**, 124, 2402.

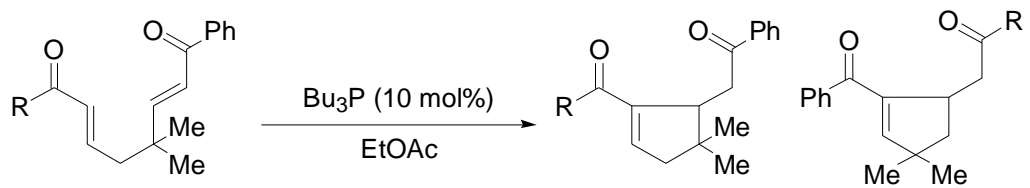
## Electronic Differentiation of Bis-Enones



“ These data suggest the initial formation of tributylphosphine adducts is indiscriminate. For five-membered ring formation, the kinetic phosphine adducts are trapped via cyclization. For six-membered ring formation, the attenuated cyclization rate enables a preequilibrium, whereby cyclization becomes the product- and rate-determining step. “

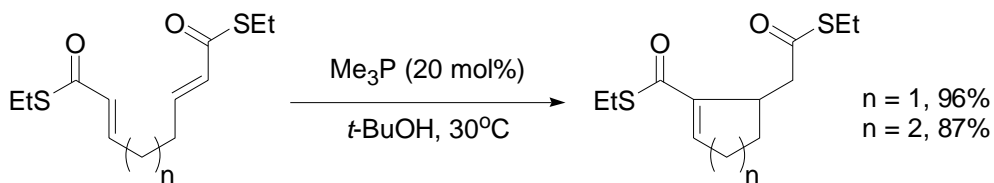
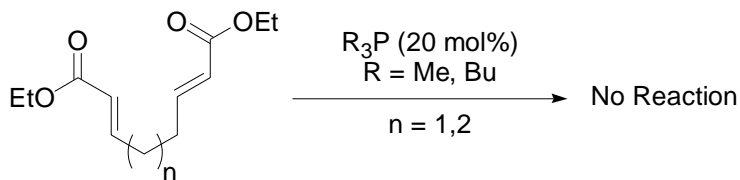


# Steric Differentiation and Alkoxyester vs Thioester

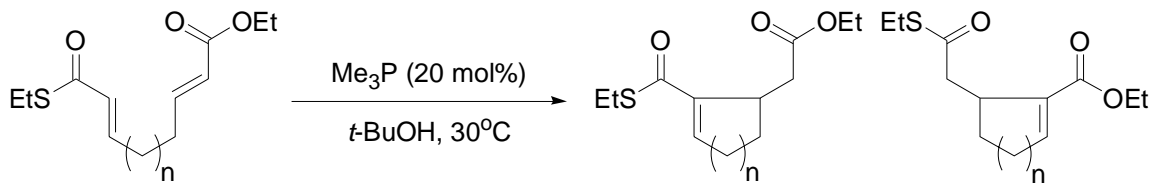


R = Ph	50°C	85%	not observed
R = Me	76°C	81%	not observed

Krische *JACS* **2002**, 124, 2402.



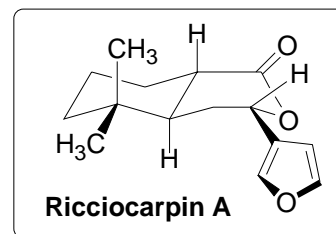
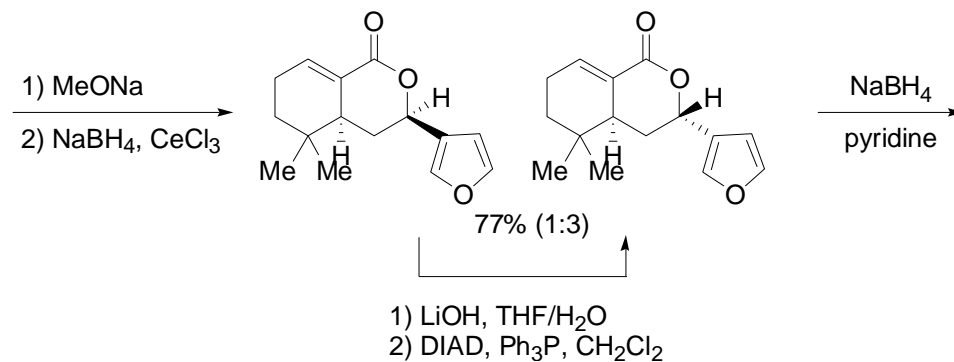
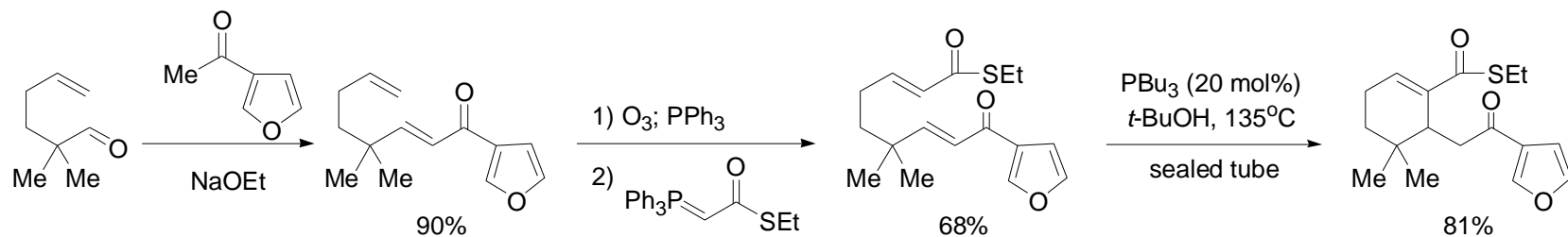
$n = 1$ , 96%  
 $n = 2$ , 87%



$n = 1$ : 89%	98	:	1
$n = 2$ : 82%	99	:	1

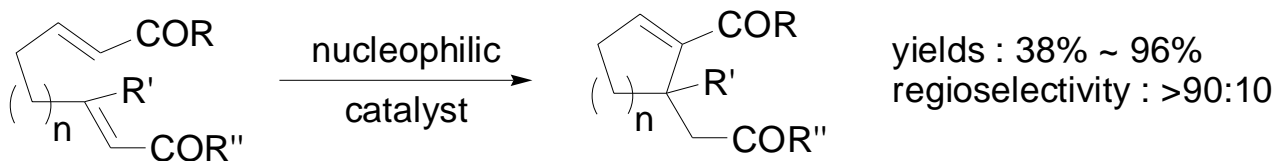
Krische *OL* **2003**, 5, 1737.

# Concise Total Synthesis of Ricciocarpin A



- Isolated from the liverwort (*Ricciocarpos natans*)
- exhibit potent molluscicidal activity against water snail *Biomphalaria glabrata*, a vector of schistosomiasis

## Intramolecular Rauhut-Currier Reaction - Roush



-Roush reported this intramolecular Rauhut-Currier reaction on the next page to Krische and refer to as a '*vinyllogous Intramolecular Morita-Baylis-Hillman reaction*'.

-n = 1 or 2, R / R' = Me or H, R'' = OMe, OEt, Me, or H

- Amine nucleophiles (DABCO, DBU, Et<sub>2</sub>NH, and DMAP) are ineffective.

-Stoichiometric Ph<sub>3</sub>P (CH<sub>2</sub>Cl<sub>2</sub>, rt) gave no reaction.

-Reactivity of phosphine catalysts :

Ph<sub>3</sub>P (NR) < (c-Hex)<sub>3</sub>P (low conv.) < Bu<sub>3</sub>P < Me<sub>3</sub>P

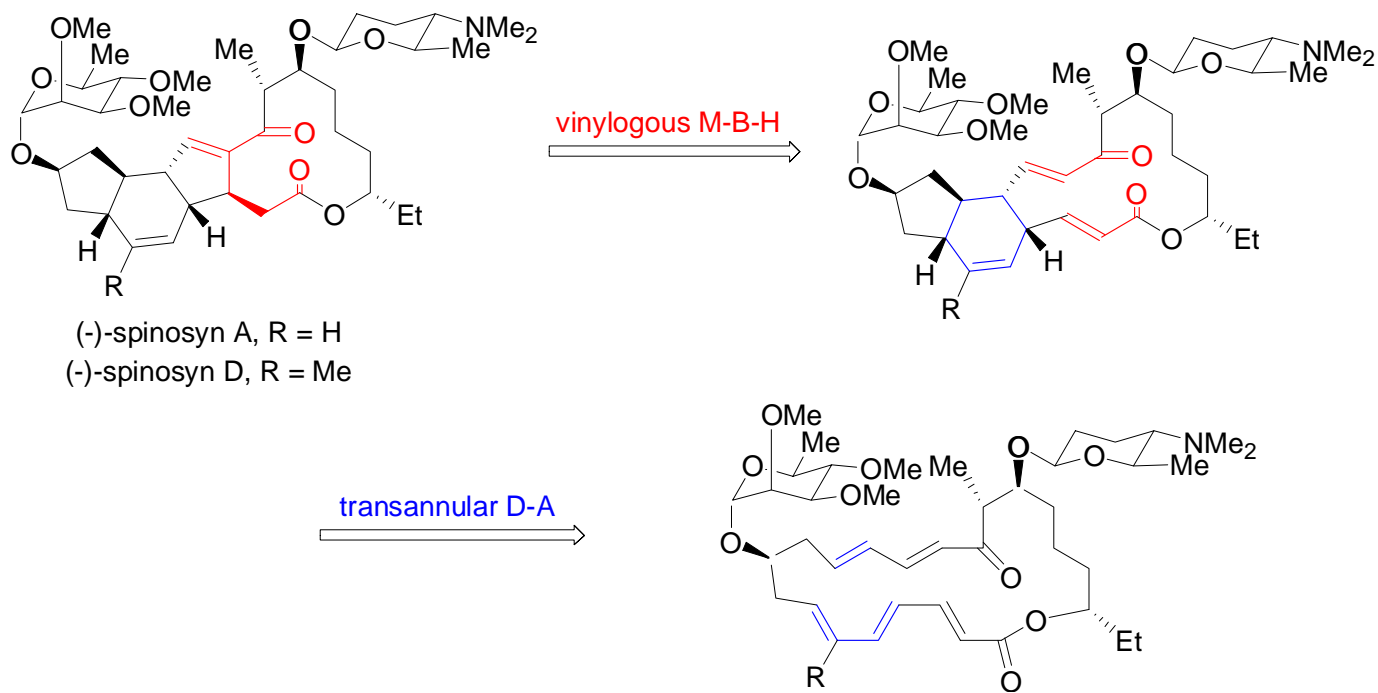
- major competitive pathways : bimolecular reaction, aldol condensation

Roush *JACS* **2002**, 124, 2404.



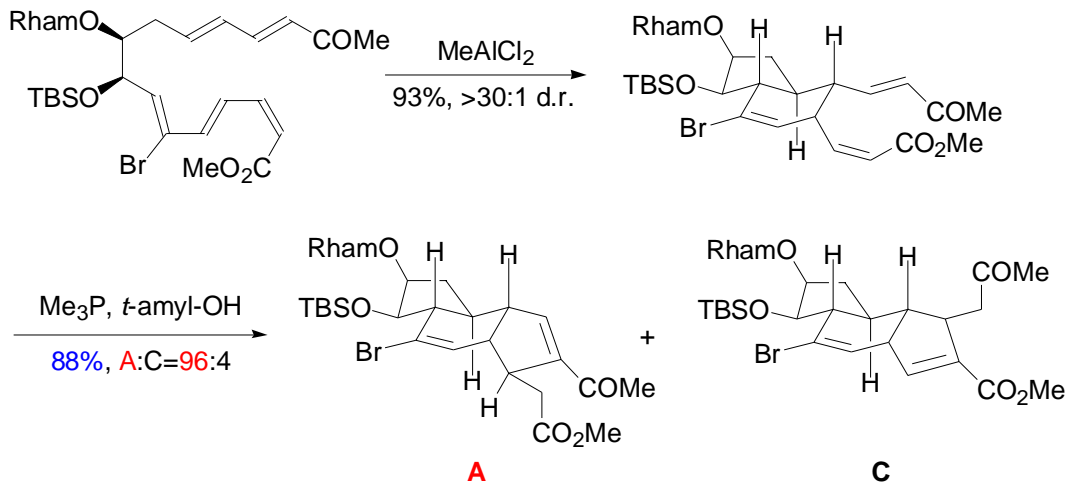
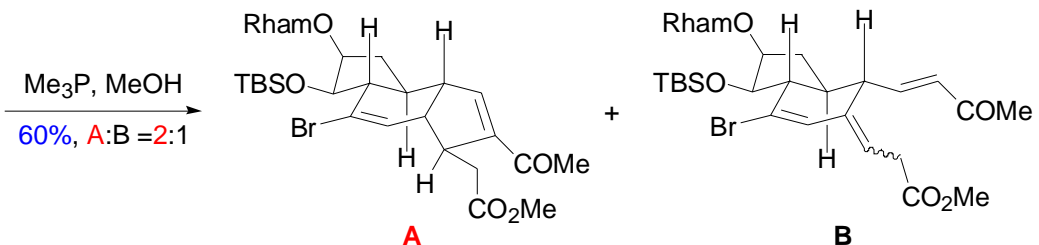
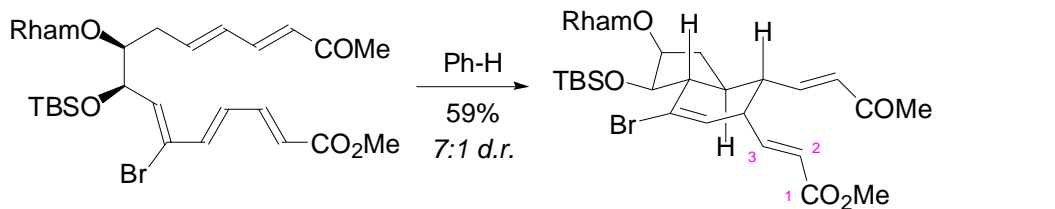
# Toward the Synthesis of the Spinosyn A Tricyclic Nucleus

Biomimetic Strategy : transannular Diels-Alder reaction and a Michael ring closure



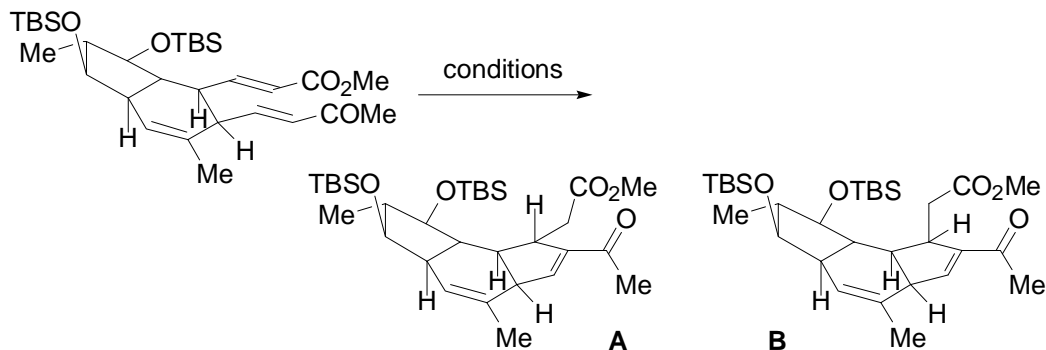
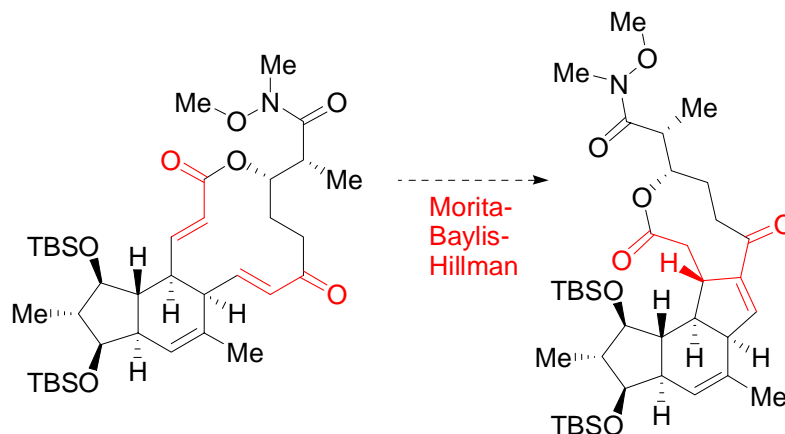
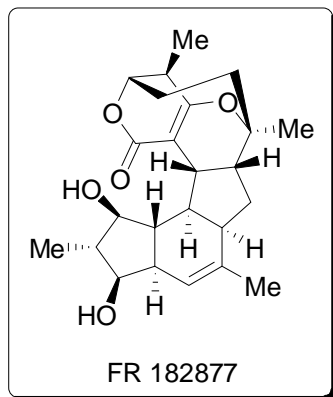
Roush *OL* **2002**, 4, 3157.

# Stereocontrol by the Olefin Geometry



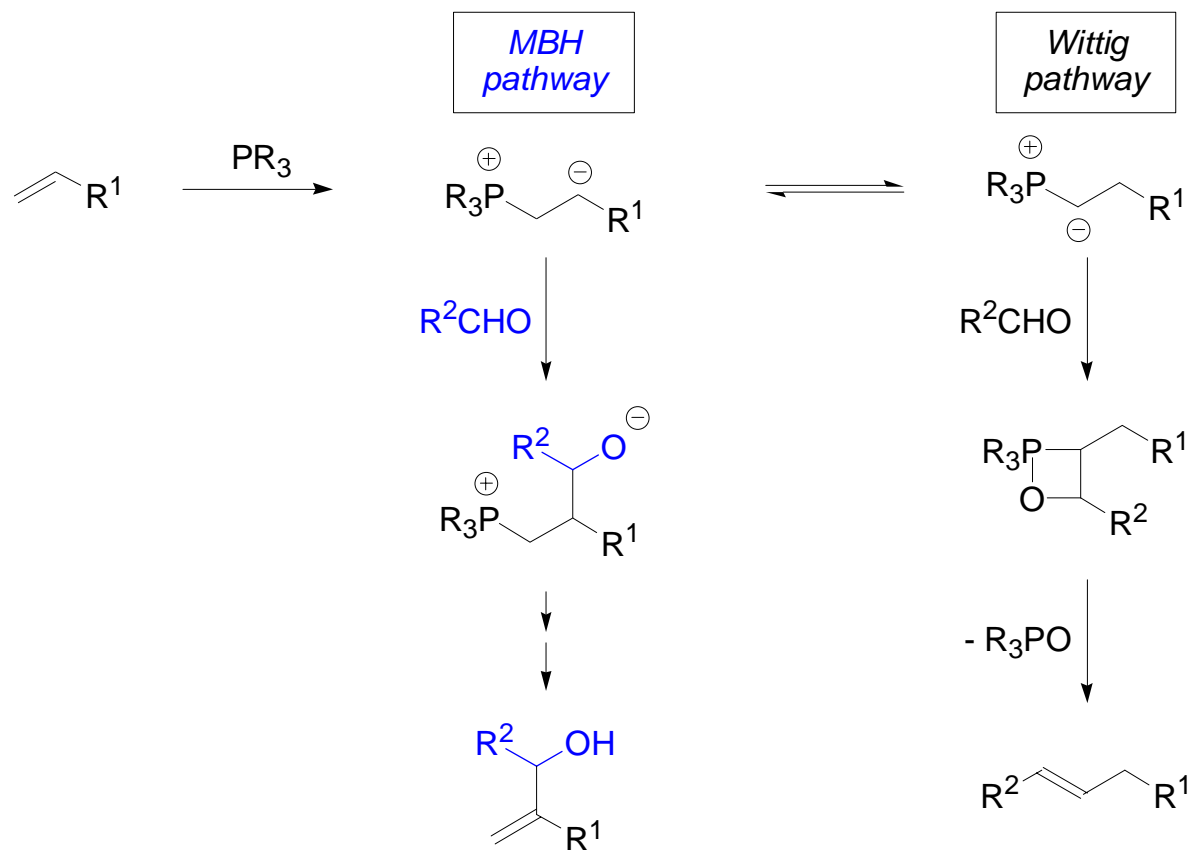
*Conformational analysis suggested that changing the C(2)-C(3) olefin geometry from (E) to (Z) would change the orientation of C(4)-H relative to the C(2,3)- $\pi$ -system owing to the need to minimize allylic strain interactions, thereby disfavoring deprotonation of C(4)-H and suppressing the problematic olefin migration to give product B.*

# Synthetic Studies toward FR182877



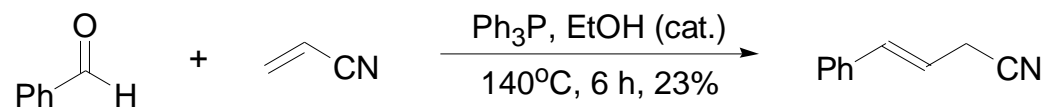
conditions	yields	selectivity (A:B)
10 equiv Me <sub>3</sub> P, 0.03 M <i>t</i> -amyl-OH	56%	6:1
4 equiv Me <sub>3</sub> P, 0.03 M THF/H <sub>2</sub> O (3/1)	84%	6:1
10 equiv Me <sub>3</sub> P, 0.03 M CF <sub>3</sub> CH <sub>2</sub> OH	62%	4:1

# Phosphine-Catalyzed Morita-Baylis-Hillman Reaction



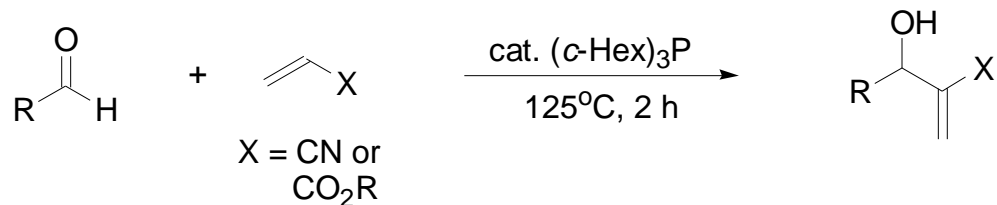
# Wittig Pathways Are Not Problematic

- Wittig pathway requires elevated temperatures.



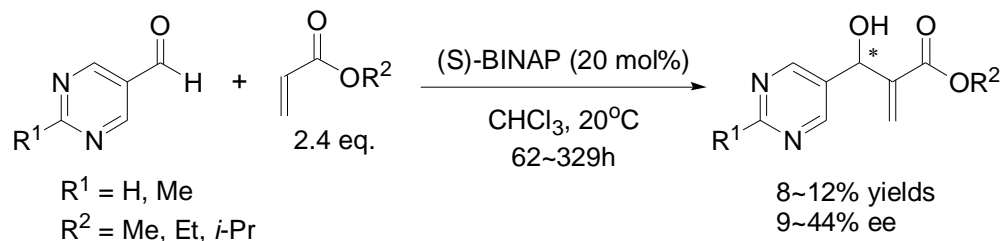
Oda *TL* **1964**, 5, 1653.

- Wittig products were not observed under mild conditions and with tertiary alkyl or mixed arylalkylphosphines.

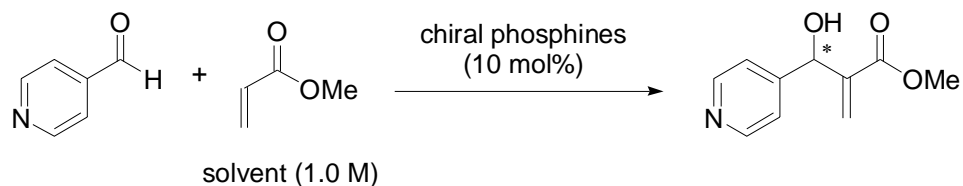


Morita, *Bull. Chem. Soc. Jpn.* **1968**, 41, 2815.

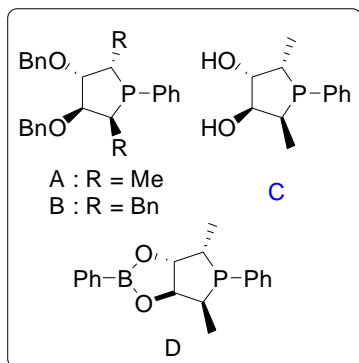
# Enantioselective MBH – BINAP and Chiral Phosphines



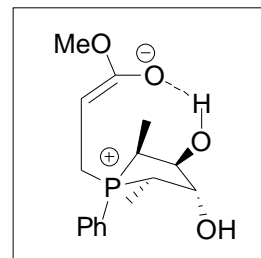
Soai CC 1998, 1271.



catalyst



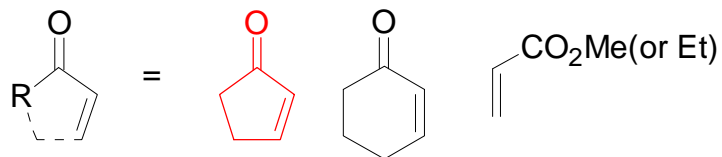
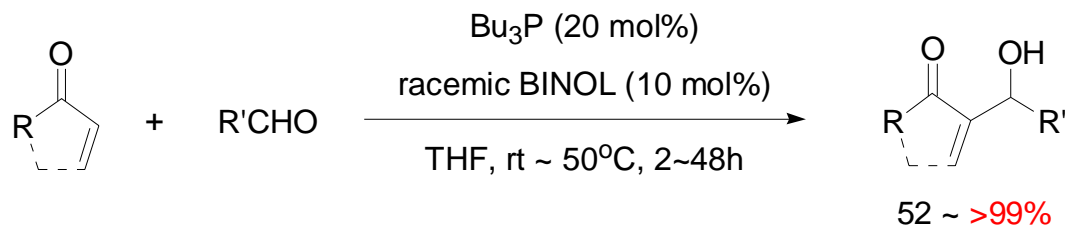
catalyst	time	yield	ee
A	70h	29%	19%
B	94h	18%	-2%
<b>C</b>	<b>9h</b>	<b>83%</b>	<b>17%</b>
D	31h	56%	18%



rate acceleration  
with catalyst **C**

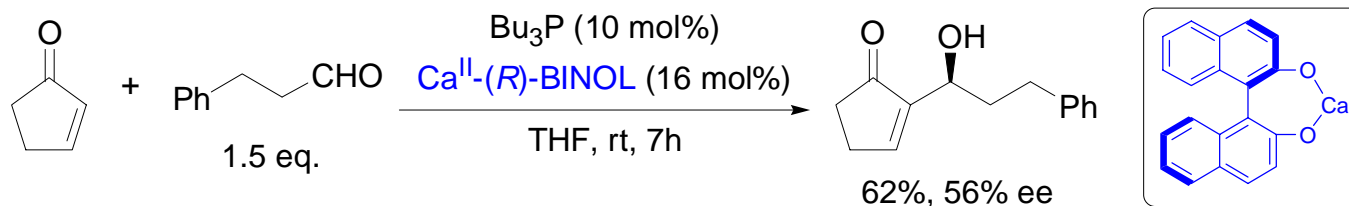
Zhang *JOC* 2000, 65, 3489.

# Enantioselective MBH – Chiral Brønsted Acid

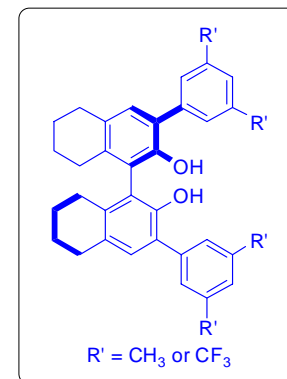
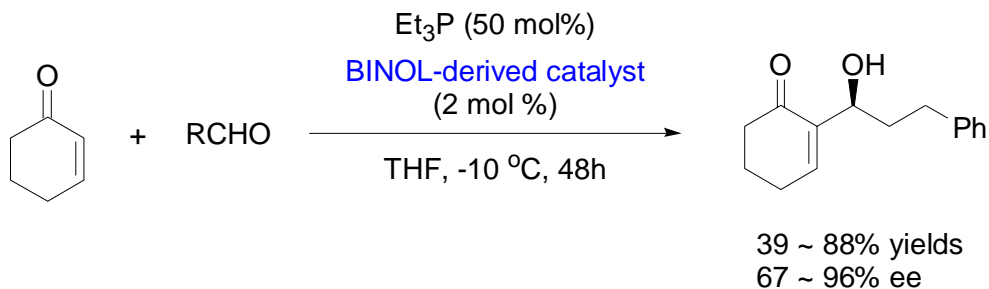


R' = Et, MEMO(CH<sub>2</sub>)<sub>3</sub>, Hex, Hept, Ph, PhCH<sub>2</sub>CH<sub>2</sub>

- 1) No reaction with DABCO, Ph<sub>3</sub>P, Bu<sub>2</sub>S and Bu<sub>3</sub>P without BINOL.
- 2) Lower yields with mono-methoxy (80%) and di-methoxy (24%) BINOL.
- 3) Other Brønsted acids (phenol (>99%), *p*-toluenesulfonamide(70%)) are also effective.
- 4) Optically pure (R)-BINOL gave only low ee (<10% ee).



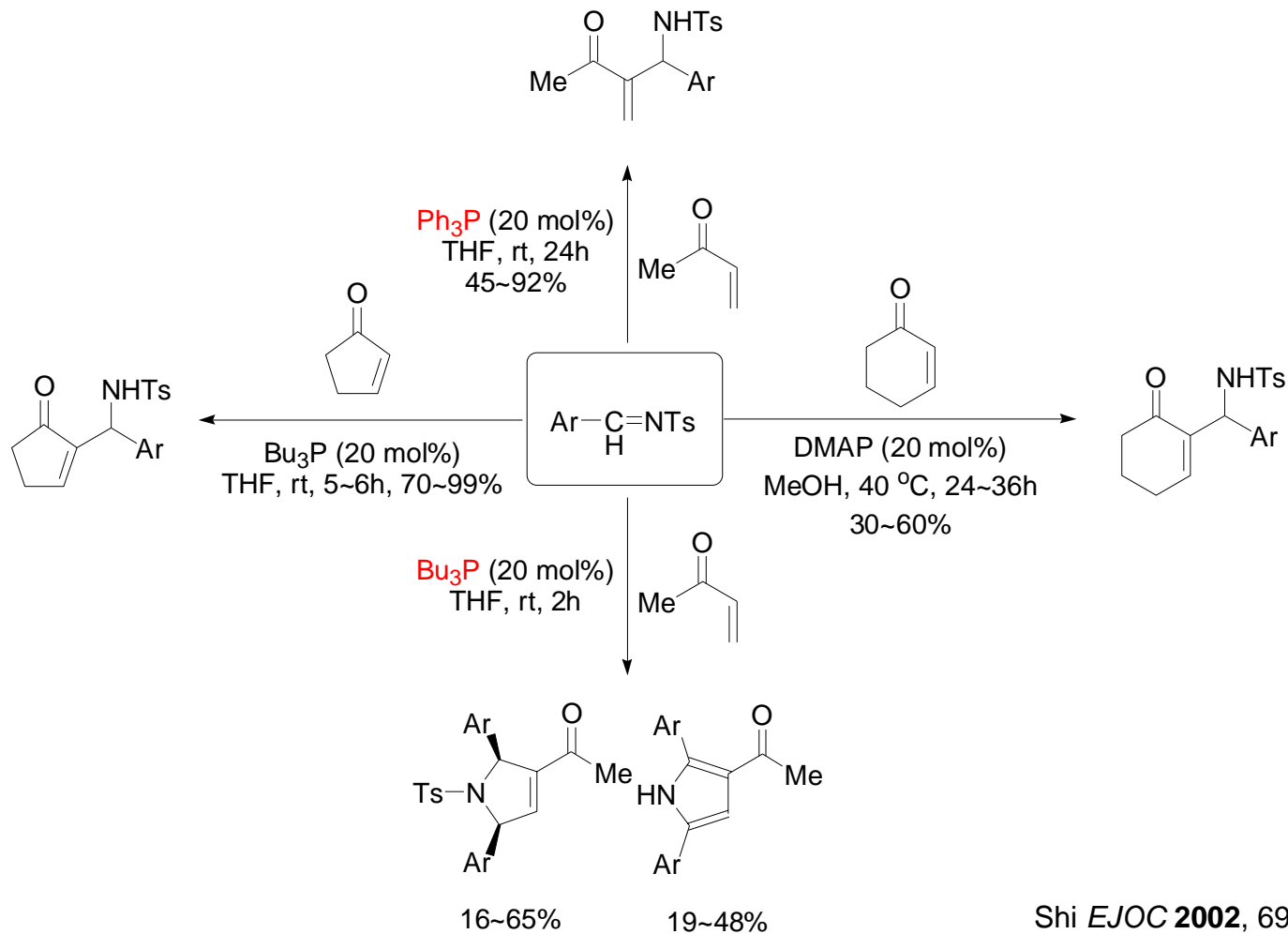
# Enantioselective MBH – Chiral Brønsted Acid



- R = PhCH<sub>2</sub>CH<sub>2</sub>, BnOCH<sub>2</sub>CH<sub>2</sub>, Ph, c-Hex, i-Pr, 3-Hexenyl, etc.
- Optimal catalyst : R' = CF<sub>3</sub> (aliphatic aldehyde), R' = CH<sub>3</sub> (more hindered aldehyde)
- Removal of one Brønsted acid equivalent from the BINOL-derived catalyst : diminished catalytic activity and no stereoselectivity.
- Me<sub>3</sub>P and Bu<sub>3</sub>P gave similar yields but lower stereoselectivity.  
(Me<sub>3</sub>P : 50% ee, Bu<sub>3</sub>P : 64% ee, Et<sub>3</sub>P : 88% ee)
- The Brønsted acid may serve to promote the conjugate addition step of the reaction, and then remain hydrogen-bonded to the resulting enolate in the stereoselectivity-determining aldol addition step
- Quinidine-derived chiral amine catalyst can be regarded as the combination of tertiary amine and Brønsted acid.  
 references; 1) Marko *T* **1997**, 53, 1015. 2) Hatakeyama *JACS* **1999**, 121, 10219.  
 3) Shi *T:A* **2002**, 13, 1941. 4) Hatakeyama *OL* **2003**, 5, 3103.



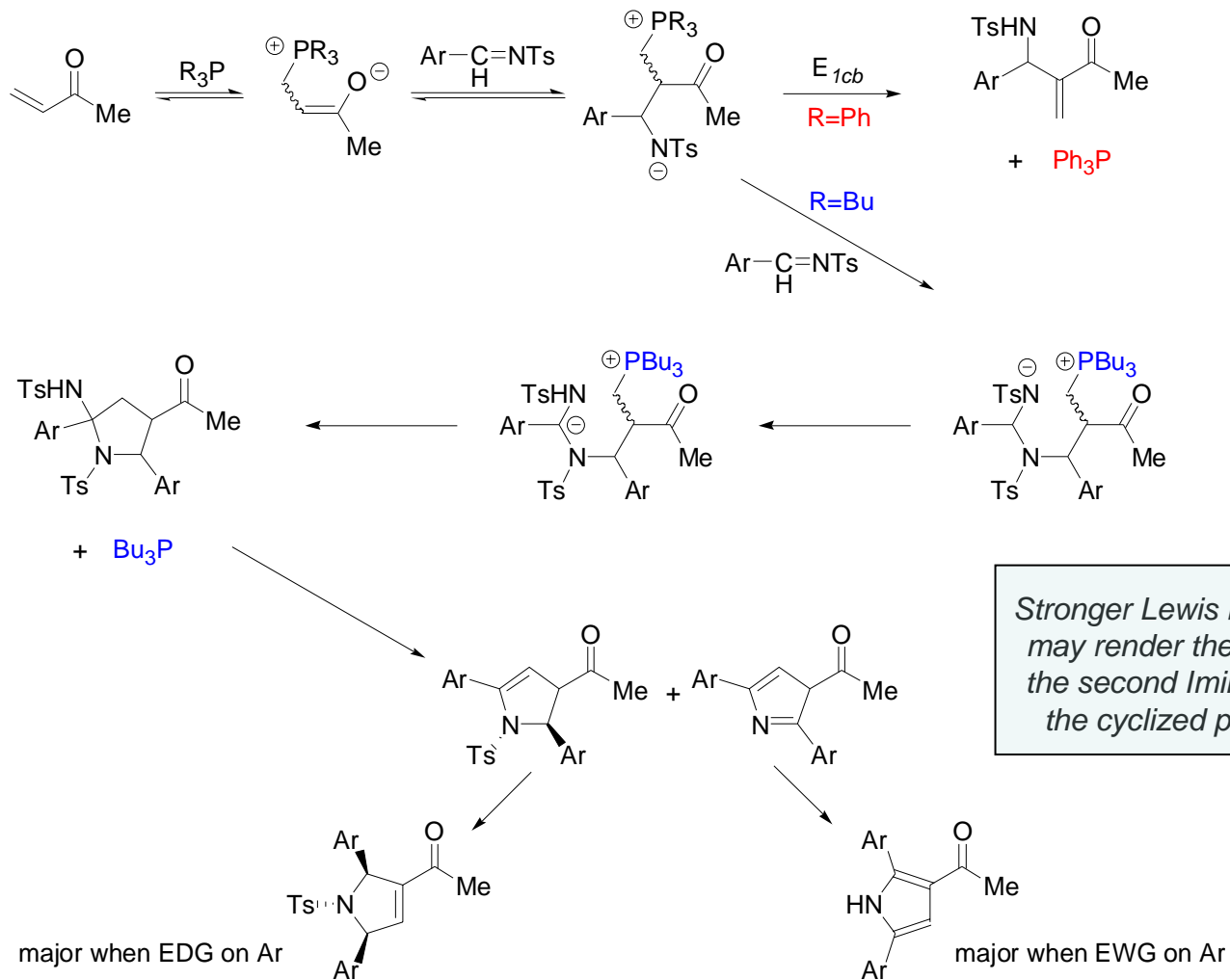
# *N*-Benzylidene-4-methylbenzenesulfonamides as the Electrophilic Partners



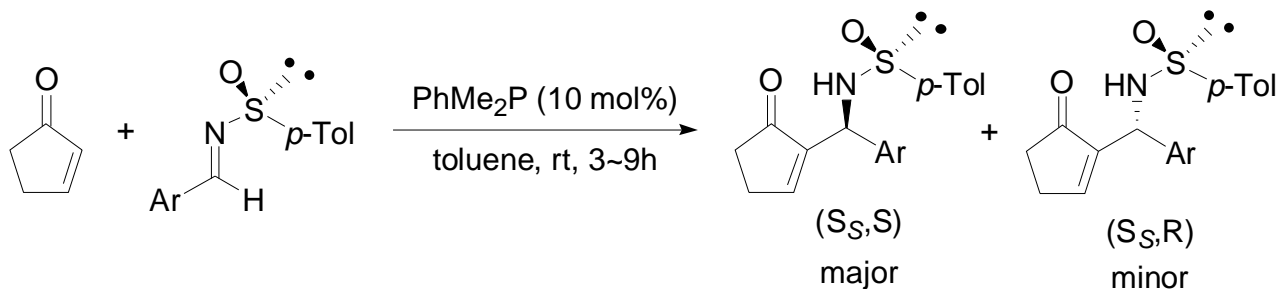
Shi *EJOC* **2002**, 696.

Shi *EJOC* **2002**, 3666.

# Mechanism for the Abnormal MBH Adducts

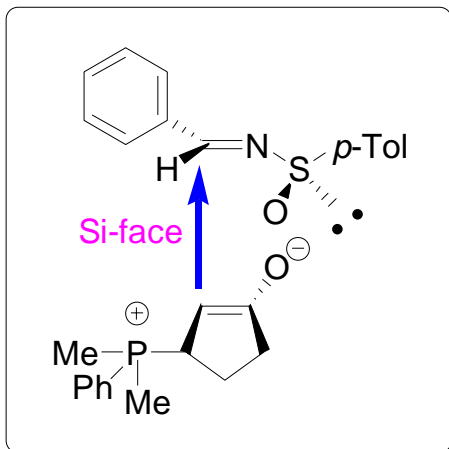


# Non-Racemic *N*-Sulfinimines as the Electrophilic Partners



- $\text{Ph}_3\text{P}$ ,  $\text{Ph}_2\text{MeP}$ , DABCO were ineffective.
- Cyclohex-2-en-1-one gave no reaction.

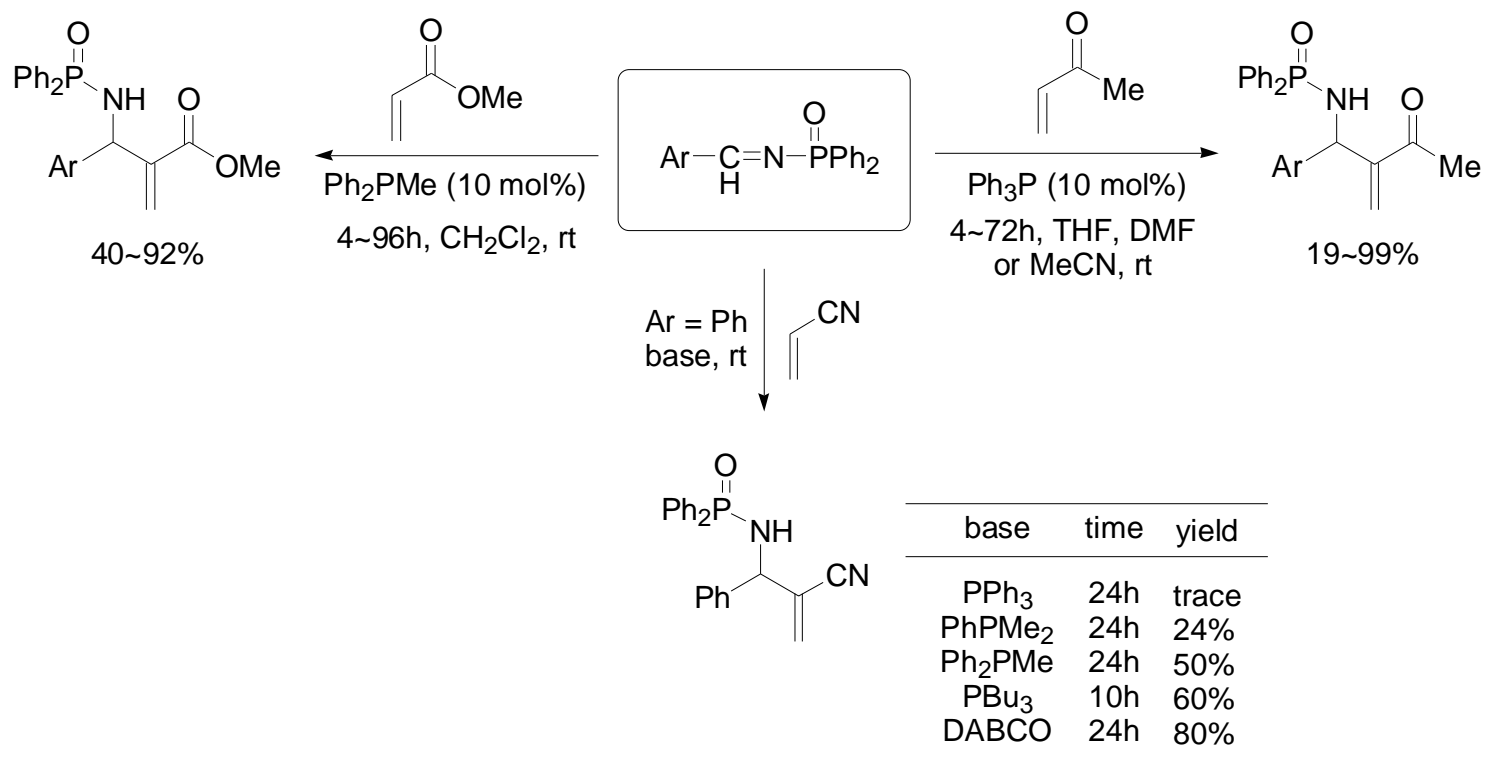
52~83% yields  
76~86% de



*"Bu<sub>3</sub>P has greater nucleophilicity than PhMe<sub>2</sub>P, but PhMe<sub>2</sub>P is the more stable of the two, which is important when long reaction times are used. Additionally, PhMe<sub>2</sub>P is more sterically encumbered than Bu<sub>3</sub>P. These factors may explain why the use of PhMe<sub>2</sub>P gives higher diastereoselectivities than Bu<sub>3</sub>P."*

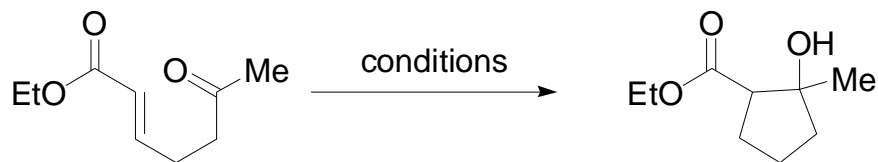
Shi T:A **2002**, 13, 696.

# *N*-Arylidenediphenylphosphinamides As the Electrophilic Partners



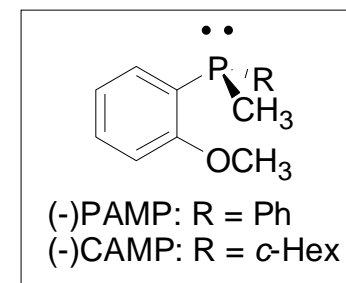
Shi *TL* **2002**, 43, 4499.

# Intramolecular MBH



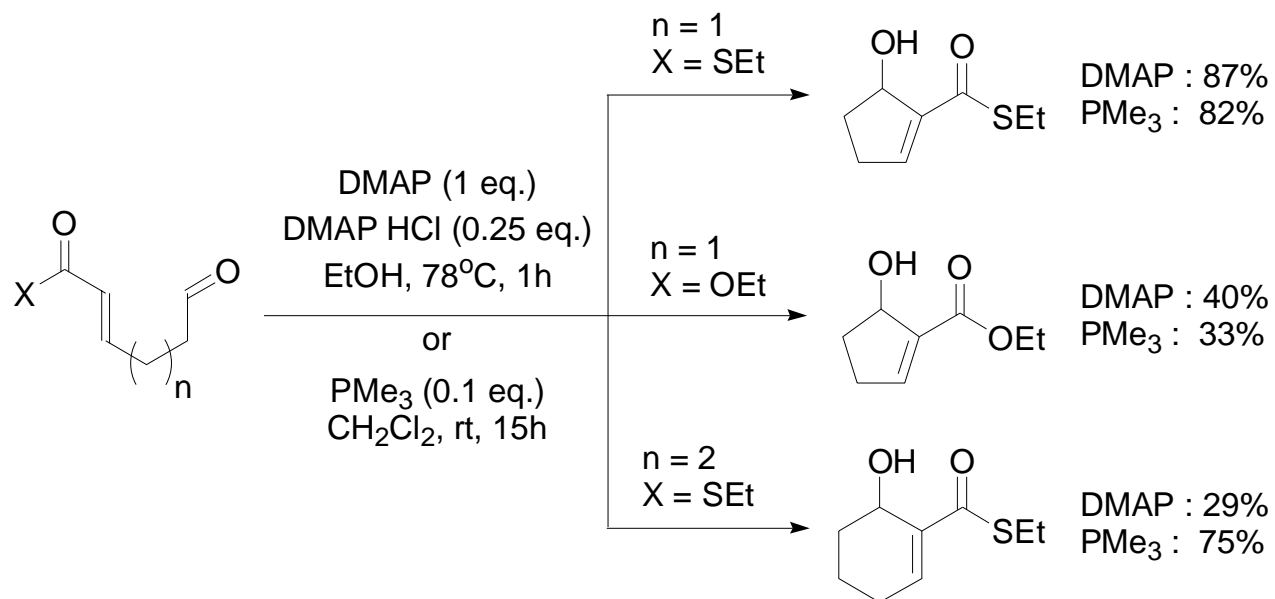
Catalyst	Solvent	Time	GLC ratio (SM) (PD)		Isolated Yield
DABCO (15 mol%)	neat	32d	81		19% cis
DABCO (37 mol%)	THF	30d	80		20% cis
Quinidine (10 mol%)	EtOH, THF	10d	100		
<b>PBu<sub>3</sub> (25 mol%)</b>	neat	1d	25	75	<b>39%</b>
PMe <sub>2</sub> Ph (25 mol%)	neat	1d	35	65	
	CH <sub>3</sub> CN	5d	70	30	
PMePh <sub>2</sub> (25 mol%)	neat	40d	100		
(-)-PAMP (20 mol%)	neat	20d	100		
(-)-CAMP (18 mol%)	neat	10d	25	75	40% (14% ee)

All reactions were carried out at room temperature.



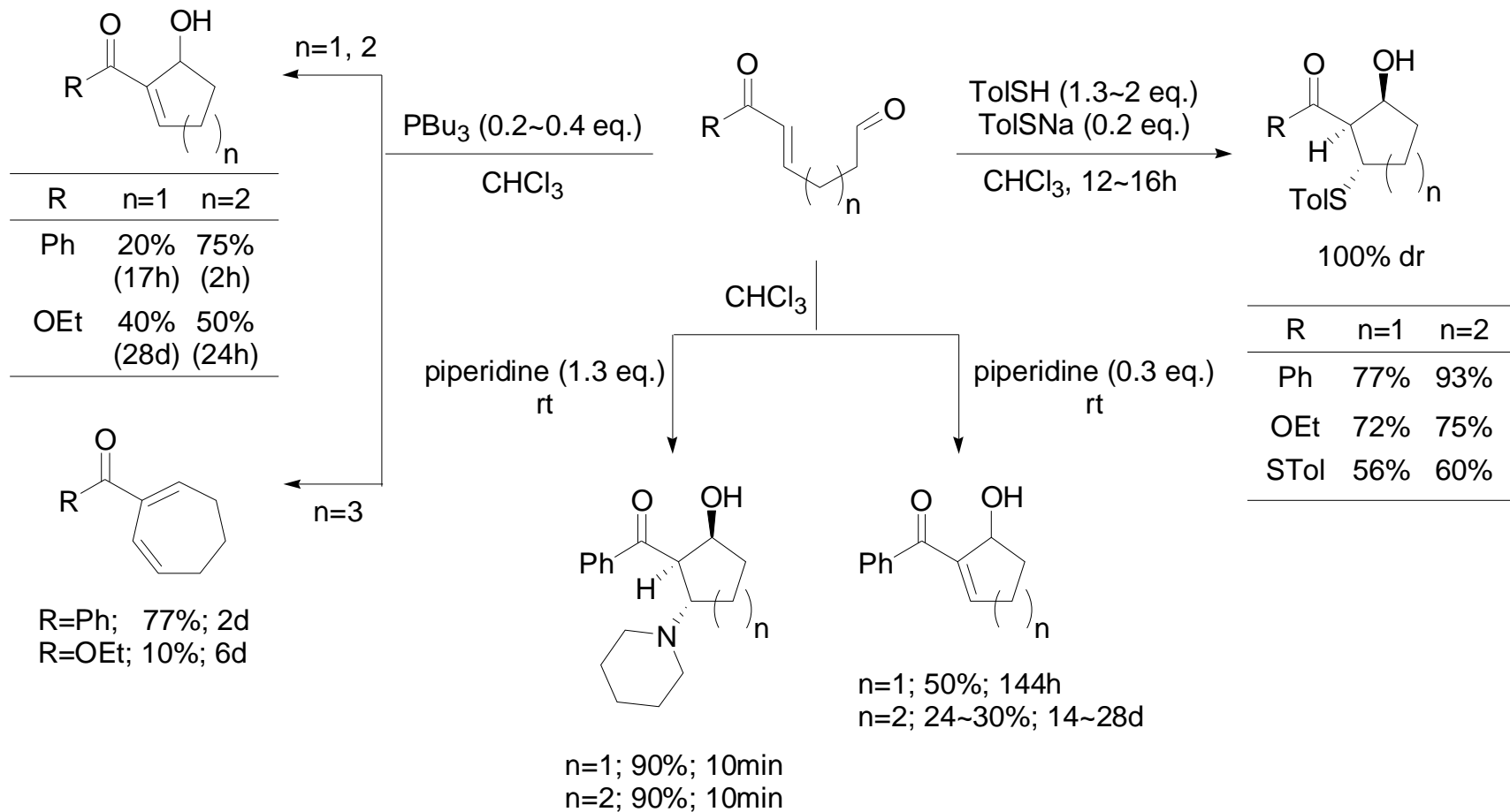
Frater *TL* **1992**, 33, 1045.

# Intramolecular MBH – Unsaturated Thioesters



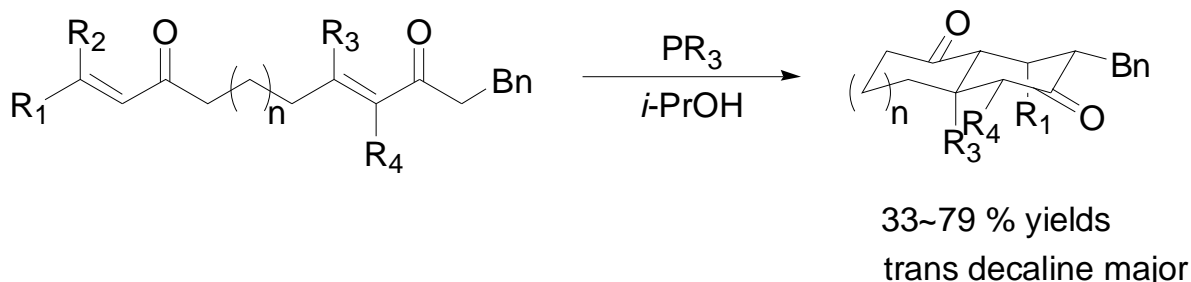
Keck *OL* **2002**, 4, 3687.

# Intramolecular MBH – Murphy



Murphy *TL* **1997**, 38, 8561.  
 Murphy *TL* **1999**, 40, 3279.  
 Murphy *T* **2001**, 57, 7771.

## **[4+2] Annulation of Bis-Enones “Mock Diels-Alder” Reaction**



n = 0                    decomposition under the reaction condition

n = 2                    slower but comparable yield and selectivity with n = 1

R<sub>1</sub> or R<sub>2</sub> = Me    need of less hindered Me<sub>3</sub>P rather than Cy<sub>3</sub>P for R<sub>1</sub> and R<sub>2</sub> = H

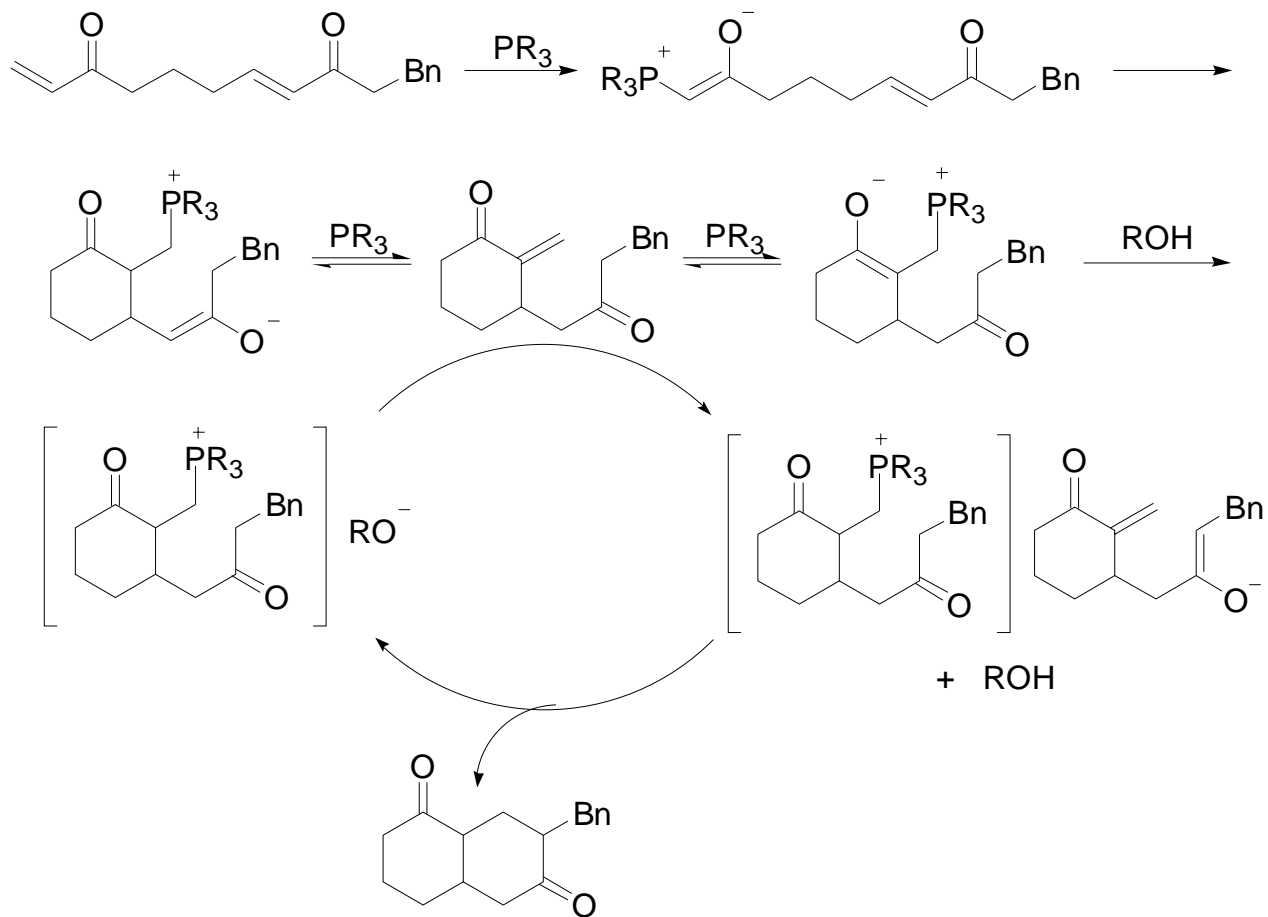
Screening of the common amine nucleophiles used in Baylis-Hillman reactions (e.g., DABCO, DBU) showed no conversion.

When aprotic solvents (e.g., benzene, MeCN) were used, bases were employed to promote the third Michael addition. In the presence of water or protic solvent, the overall cycloisomerization to the decalin occurred without additive base

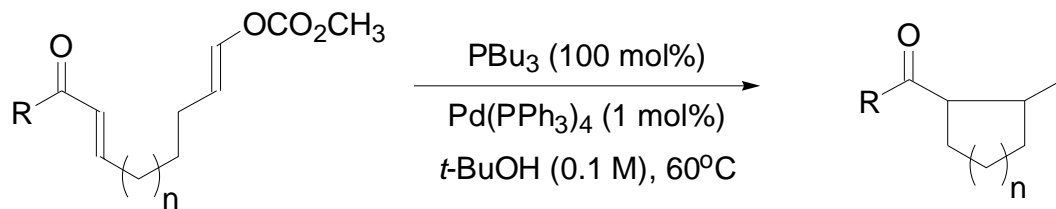
single-pot , two C-C bonds generation, up to five contiguous stereocenters in one step starting from achiral, aliphatic substrates



## [4+2] Annulation of Bis-Enones : Mechanism

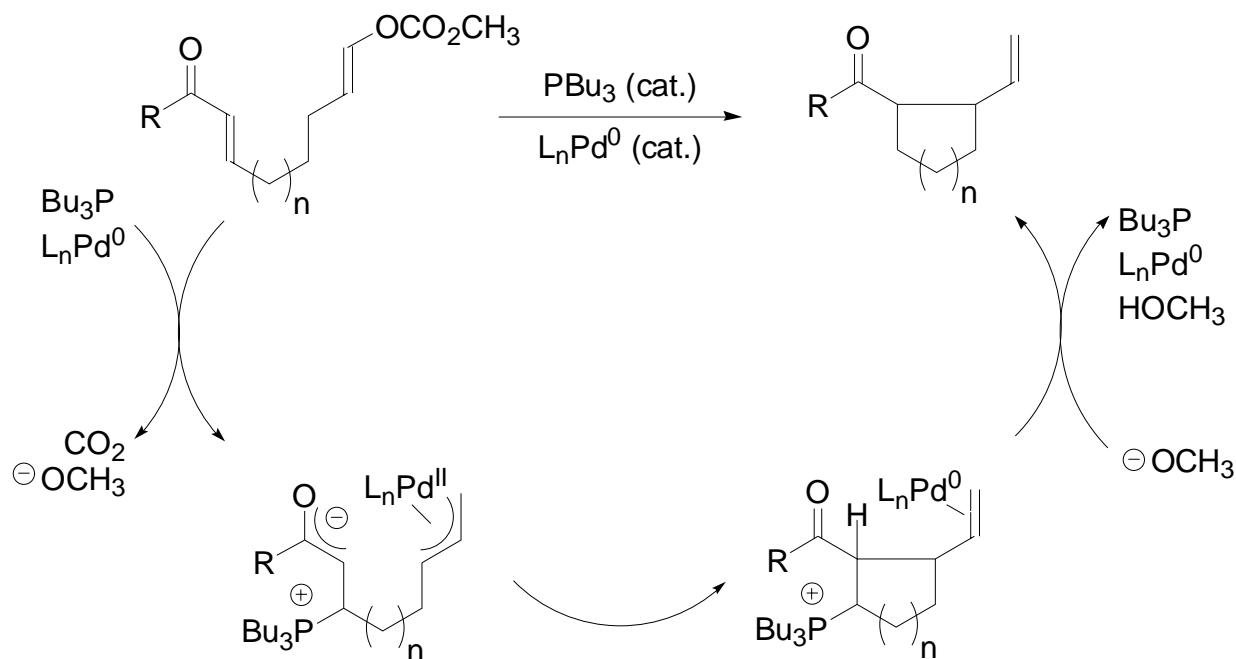


# Catalytic Enone Cycloallylation (Morita-Baylis-Hillman) + (Trost-Tsuji)



$n = 1$  (71~92%),  $2$  (64~66%)

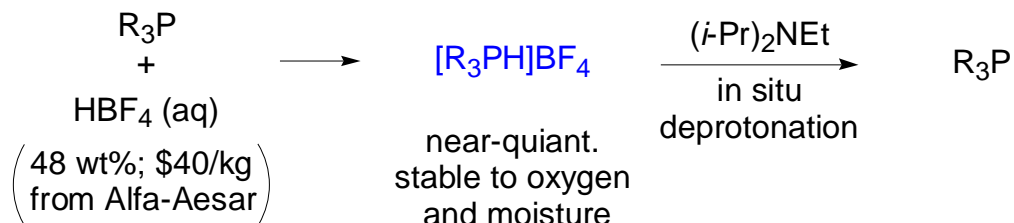
$\text{R} = \text{Ph, Naphtyl, 2-Furyl, Me, BzOCH}_2, \text{ cyclopropyl, SEt(73\% vs OEt (trace))}$



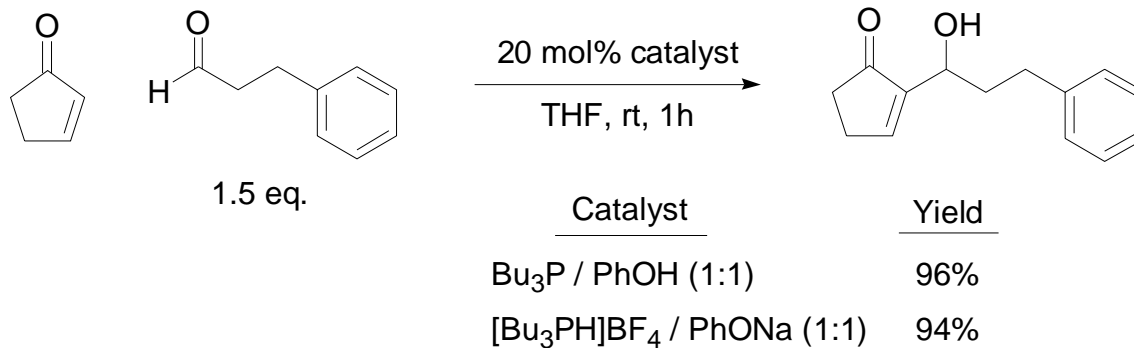
# Air-Stable Trialkylphosphonium Salt

"Improperly stored bottles of  $Bu_3P$  are invariably contaminated with tributylphosphine oxide and butyl dibutylphosphinate... Oxygen should be rigorously excluded to avoid free radical chain oxidation. Tributylphosphine is pyrophoric..." Encyclopedia of Reagents for Organic Synthesis

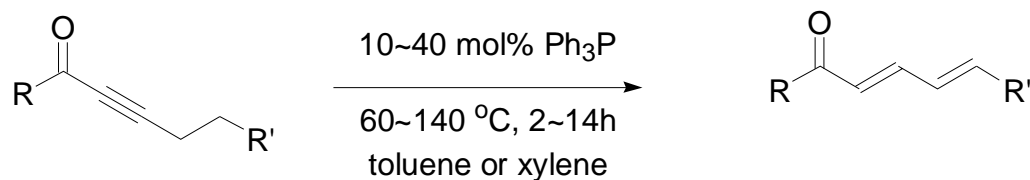
## Preparation and Liberation



## Application to MBH



# Internal Redox Reaction



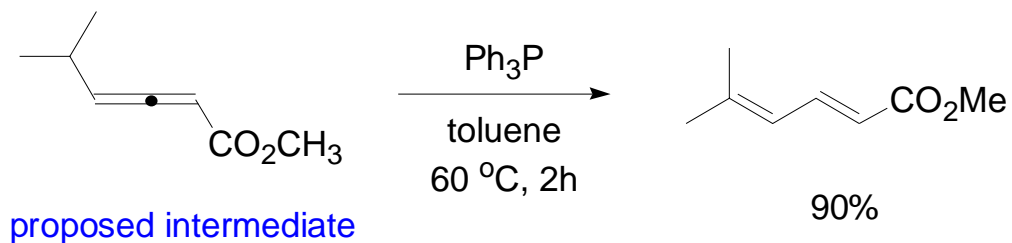
reactivity for R : ketone > ester > amide

<u>R</u>	<u>Yield</u>
Ph, Alkyl	83~88%
OBn, OAlly, NHPH	75~84% (50 mol% acetic acid added at higher temperature)

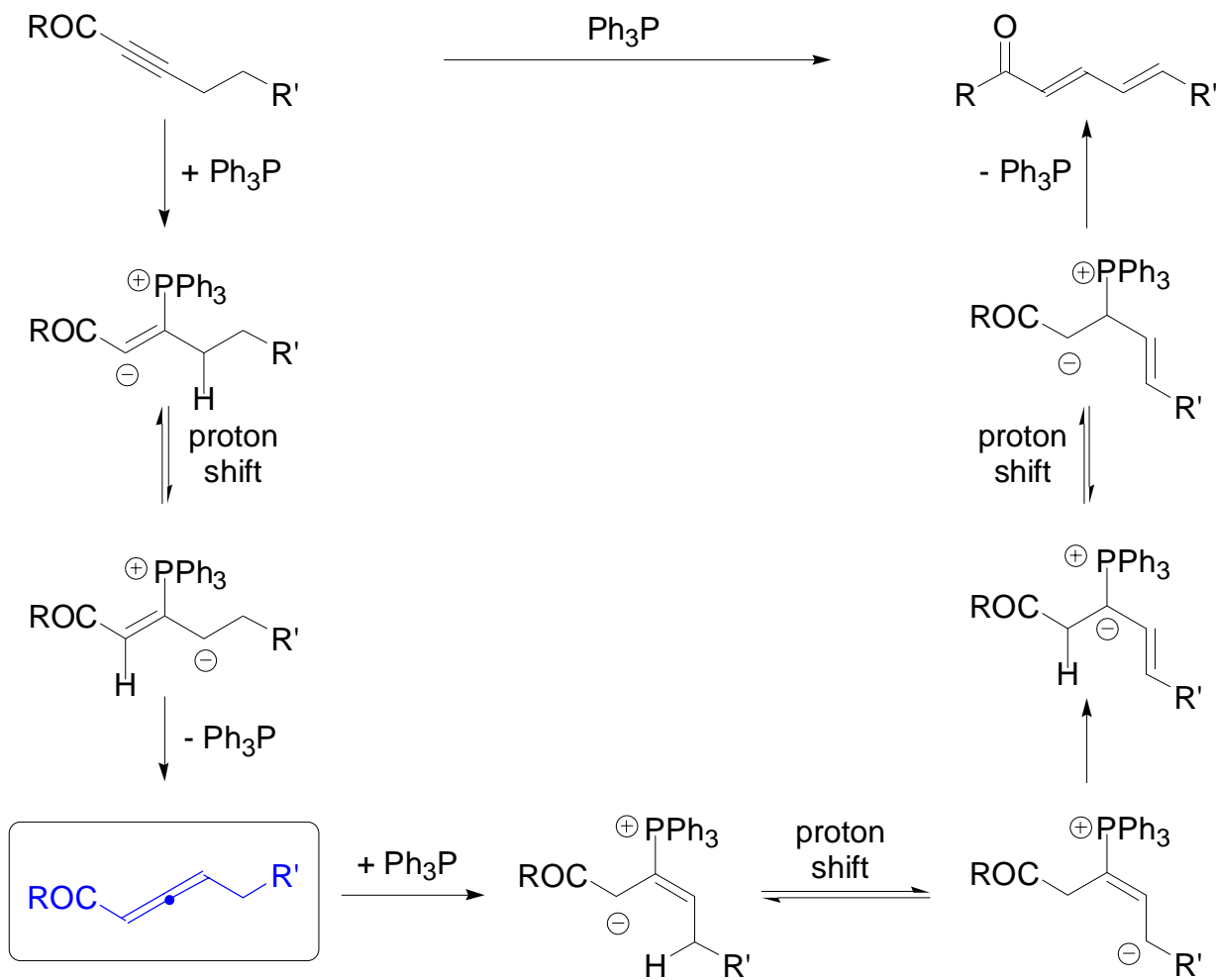
## Proposed Mechanism

: "a series of proton shifts triggered by nucleophilic addition of the phosphine"

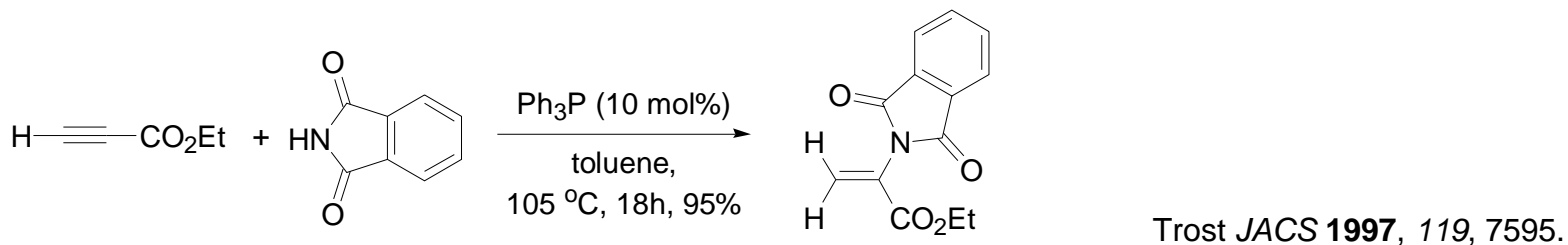
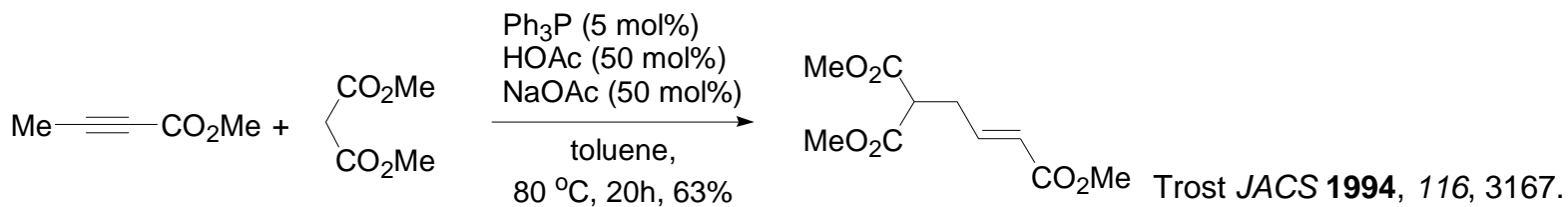
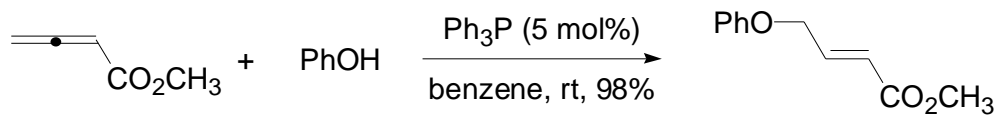
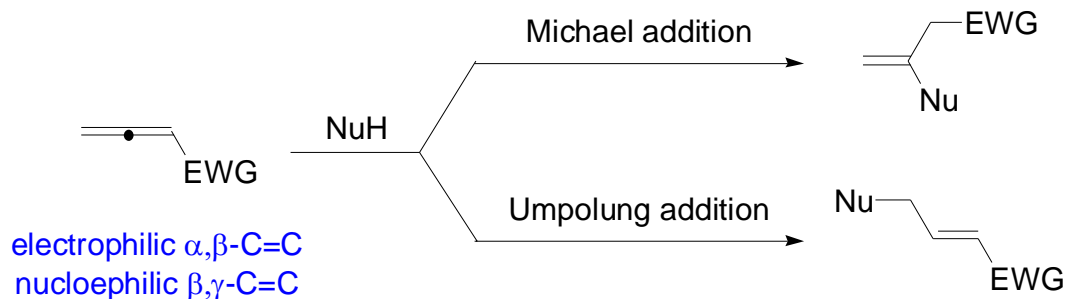
: No reaction with tertiary amine



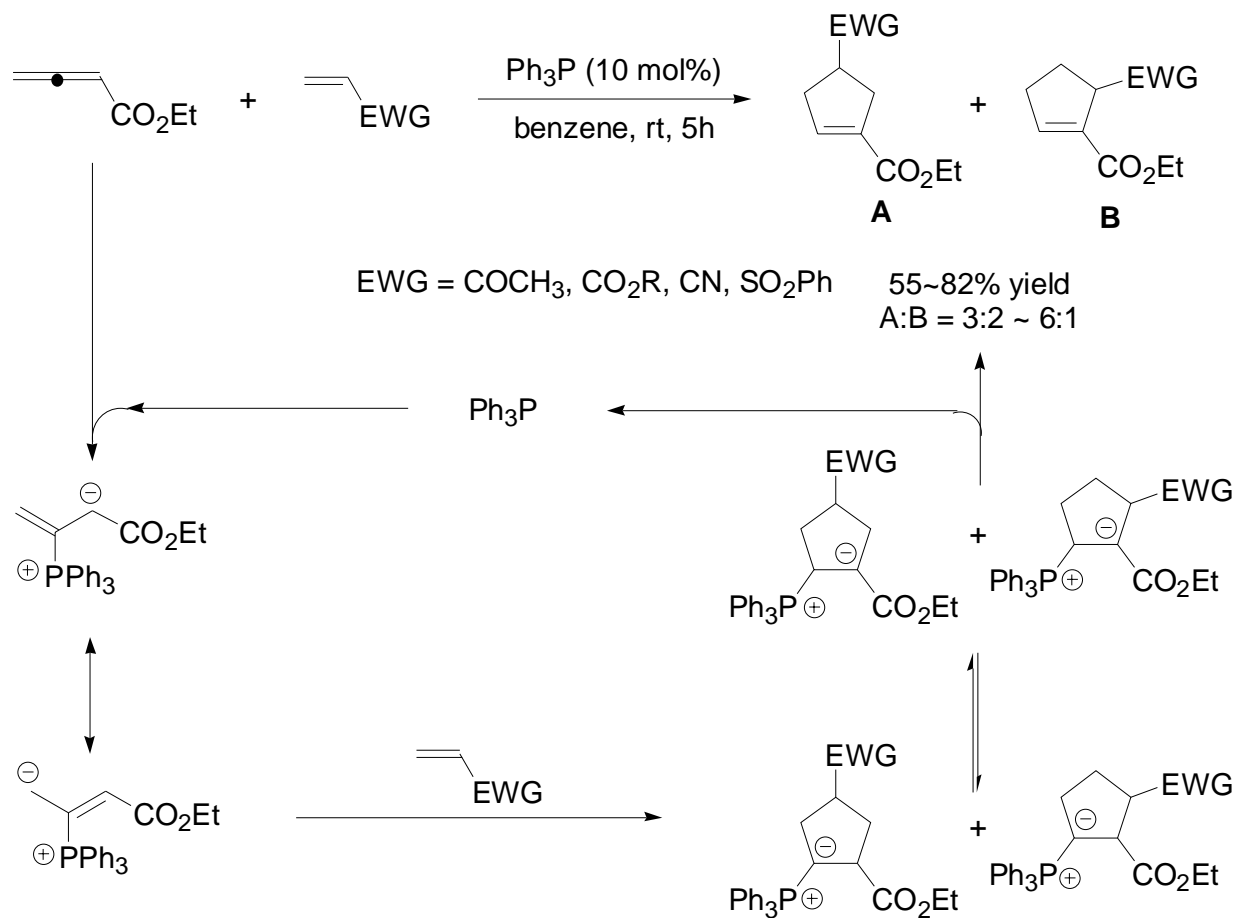
# Internal Redox Reaction - Mechanism



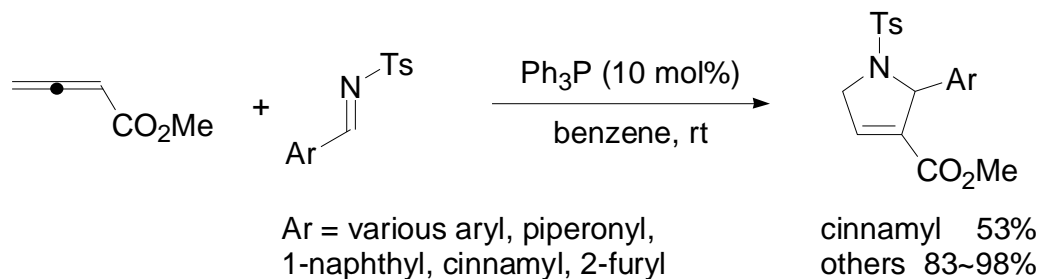
# Umpolung Addition



# [3+2] Annulation of 2,3-Butadienoates

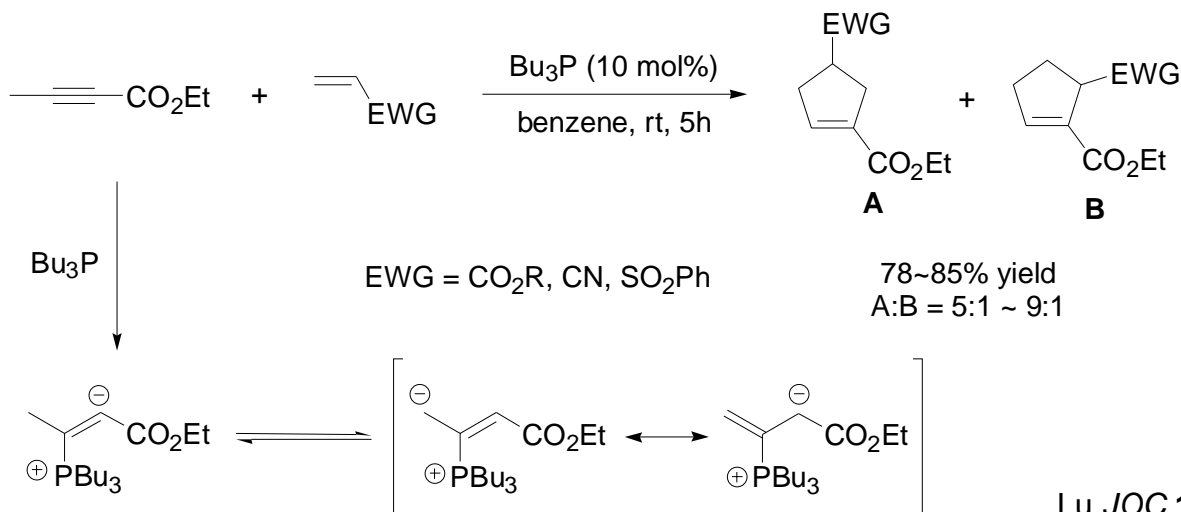


## [3+2] Annulation with *N*-Tosylimines



Lu *JOC* **1998**, 63, 5031.  
Lu *TL* **1997**, 38, 3461.

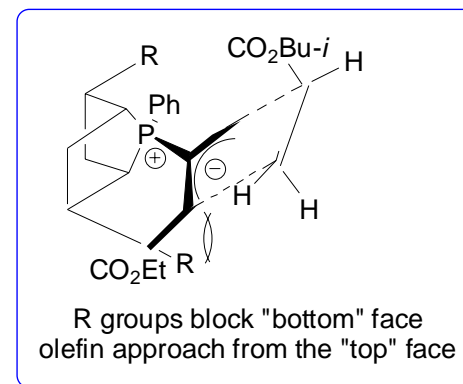
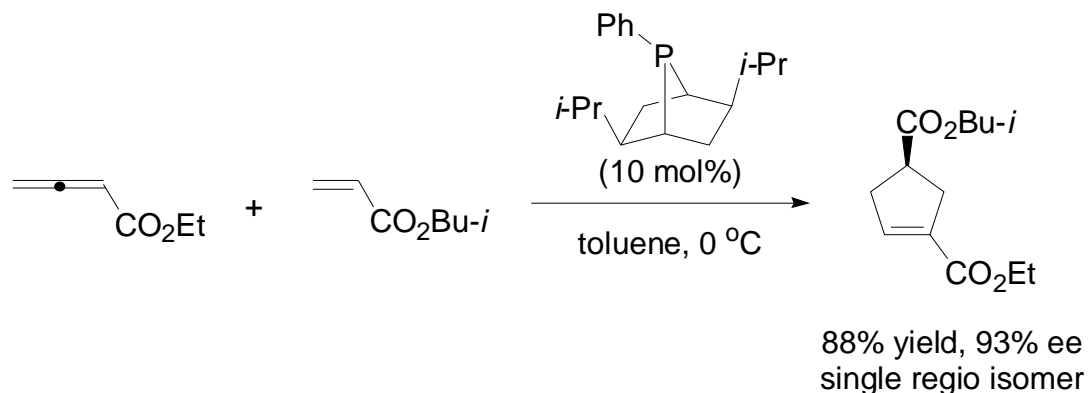
## [3+2] Annulation of 2-Butynoates



Lu *JOC* **1995**, 60, 2906.

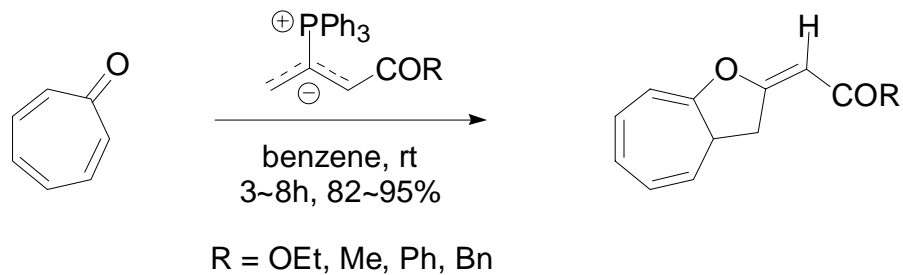


## Asymmetric [3+2] Catalyzed by Chiral Phosphines



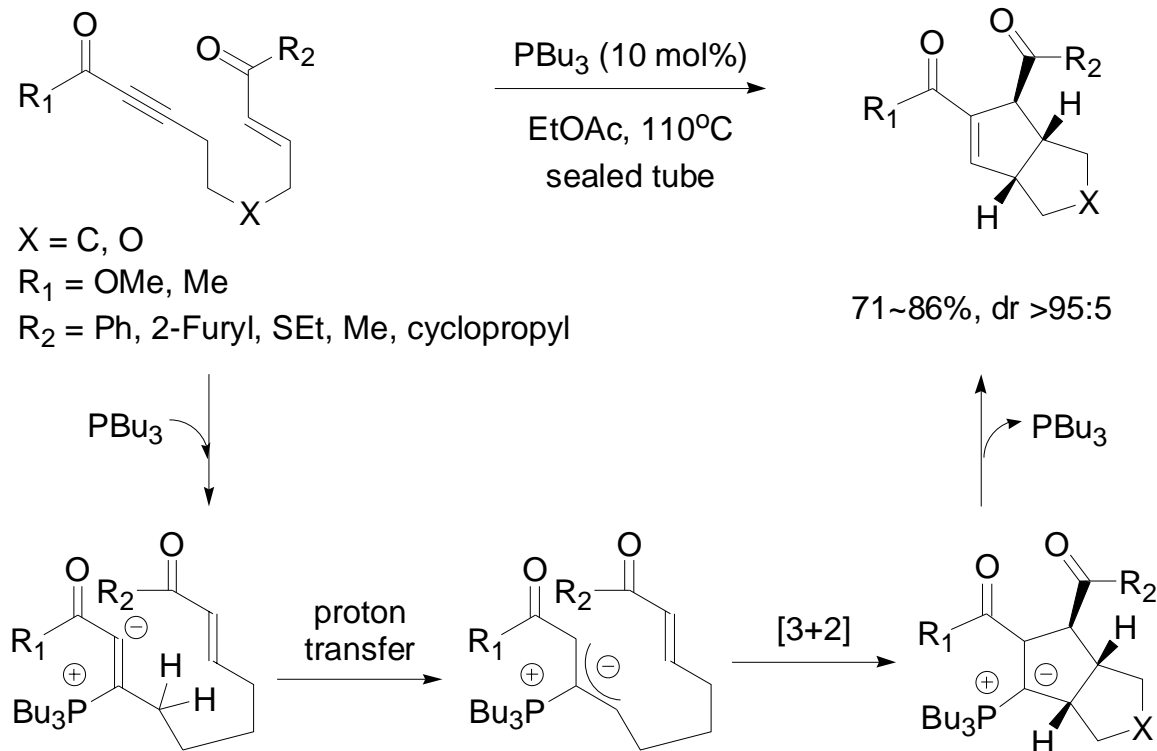
Zhang *JACS* **1997**, *119*, 3836.

## Unusual [8+2] Annulation with Tropone

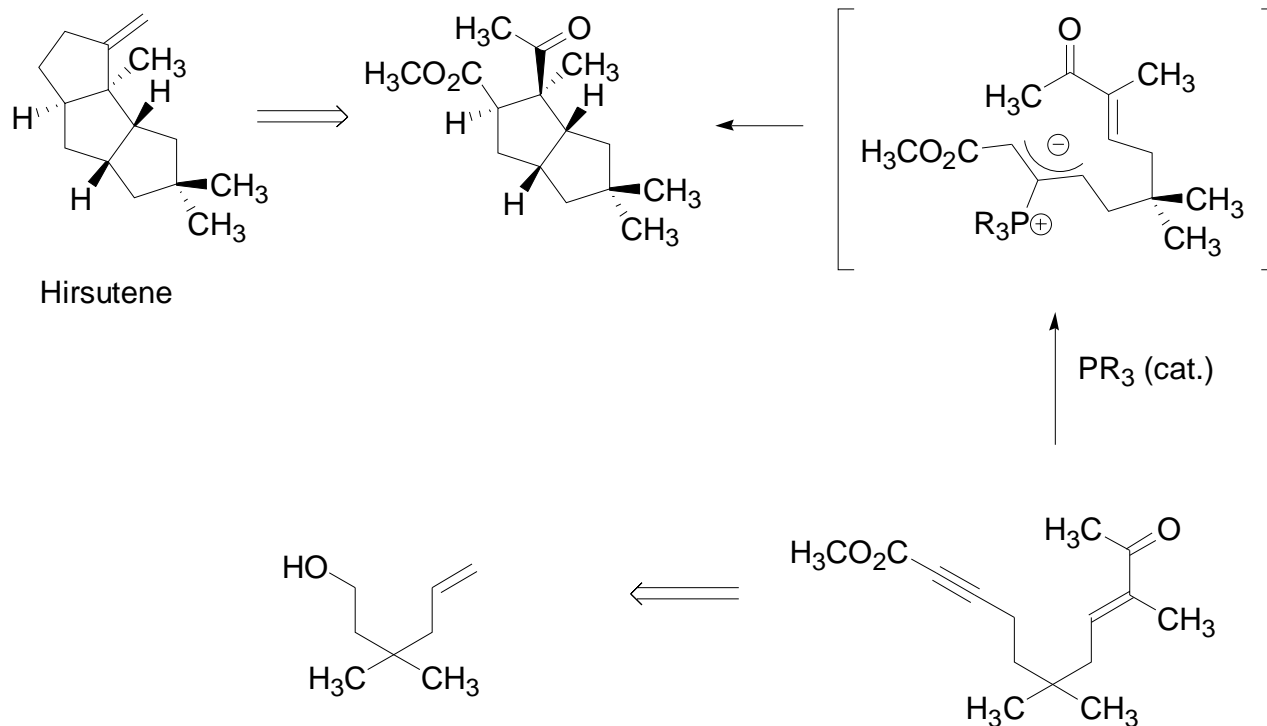


Ishar *OL* **2000**, *2*, 787.

# Intramolecular [3+2] Annulation Catalytic Diastereoselective Synthesis of Diquinanes

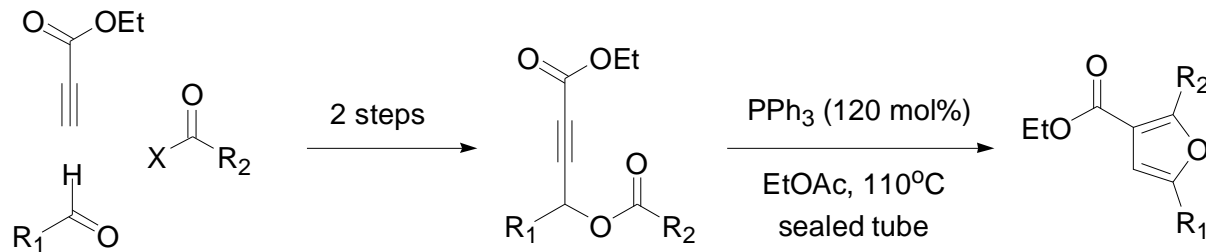


# Intramolecular [3+2] Annulation Total Synthesis of Hirsutene



Krische *ACIE* **2003**, *42*, 5855.

# Reductive Condensation of $\gamma$ -Acyloxy Butynoates

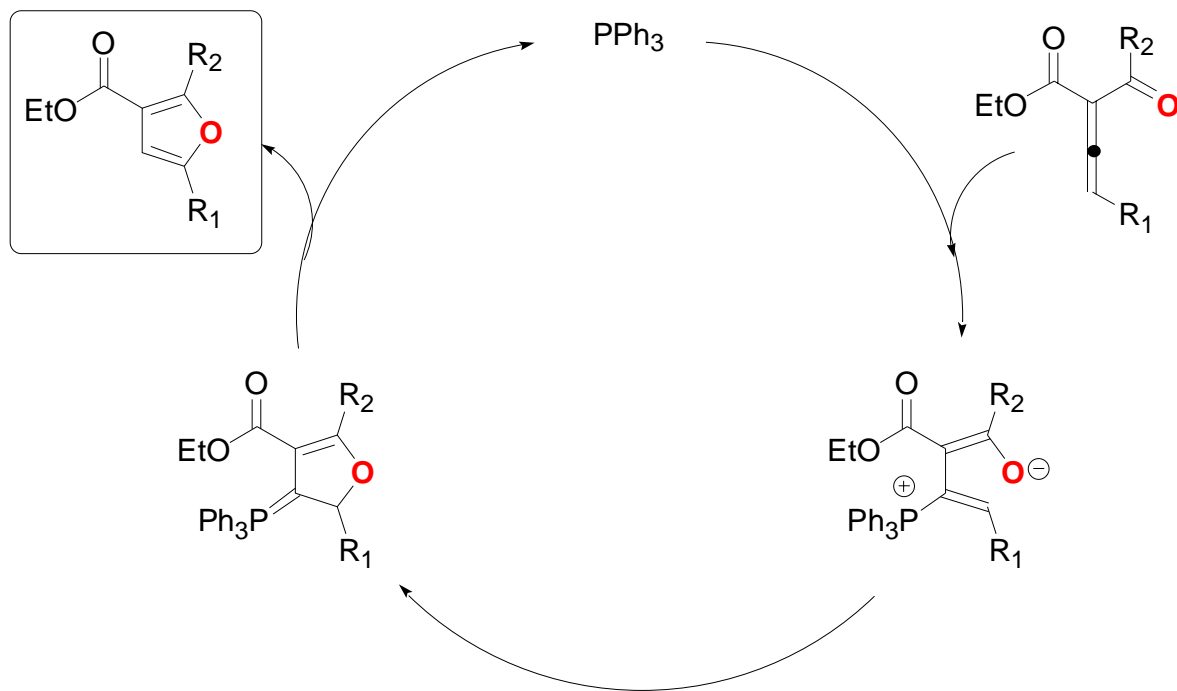
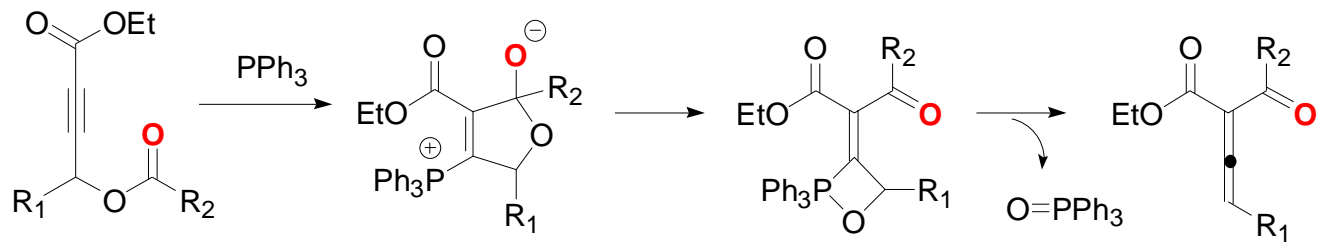


R <sup>1</sup> = H, R <sup>2</sup>	Yield	R <sup>1</sup> = H, R <sup>2</sup>	Yield	R <sup>1</sup>	R <sup>2</sup>	Yield
	72%		68%		H	79%
	77%		73%		H	71%
	71% <sup>b</sup>		83%			79%
	81%		83%			86%
	91%		84% <sup>b</sup>			60% <sup>a</sup>

a) The reaction was conducted at ambient temperature.

b) The reaction was conducted at ambient temperature using (*m*-Tol)<sub>3</sub>P.

## Reductive Condensation of $\gamma$ -Acyloxy Butynoates



## ***Conclusions***

- Phosphine-initiated enolate transformations has become one of the most powerful and useful carbon-carbon bond-forming reactions, providing a variety of densely functionalized molecules.
- Recent mechanistic studies of tertiary amine-catalyzed Morita-Baylis-Hillman reaction disclosed that the role of proton donors such as alcoholic additives and solvents is not only activating electrophilic partners but, more importantly, also facilitating proton transfer rate-determining steps, thus increasing rate of the reactions.
- Another mechanistic studies in aprotic medium, second molecule of aldehyde, used as a electrophilic partner, is associated with rate-determining step to form hemiacetal intermediate. In the absence of Brønsted acids, this hemiacetal intermediate is believed to deprotonate  $\alpha$ -H intramolecularly via six-membered transition state and extrude amine catalyst to form the product.
- Recently, Krische and Roush developed intramolecular Rauhut-Currier reaction and successfully applied their methodology for the total synthesis of complex natural products.
- Activated alkynes and allenes underwent internal redox reaction, umpolung addition and [3+2] annulation catalyzed by phosphines.