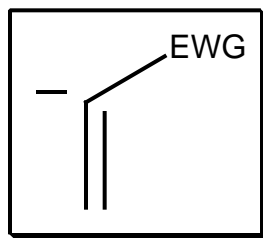
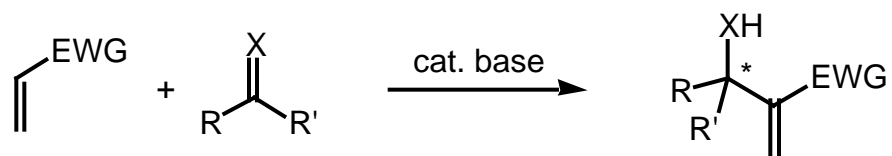


Asymmetric Catalysis with Chiral Lewis Bases (Part IV) The Asymmetric Baylis-Hillman Reaction

An Evans Group Afternoon Seminar
Jake Janey
March 29th, 2001



Leading References:

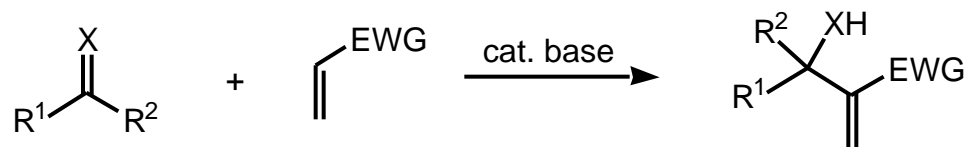
Langer, P. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 3049-3052.

Ciganek, E. *Org. React.* **1997**, 51, 201-350.

Basavaiah, D.; *et. al. Tetrahedron*, **1996**, 52, 8001-8062.

Drewes, S. E.; Roos, G. H. P. *Tetrahedron*, **1988**, 44, 4653-4670.

Baylis-Hillman Reaction Scope



X = O, NTs, NCO₂R, NPh₂, NSO₂Ph

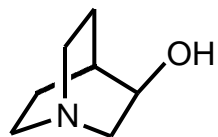
R¹ = alkyl, aryl

R² = H, alkyl, EWG

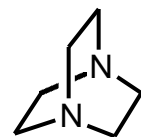
EWG = CO₂R, CN, POEt₂,

CHO, COR, SO₂Ph, SO₃Ph

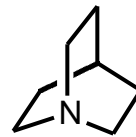
cat. bases:



3-hydroxyquinuclidine (3-QDL)



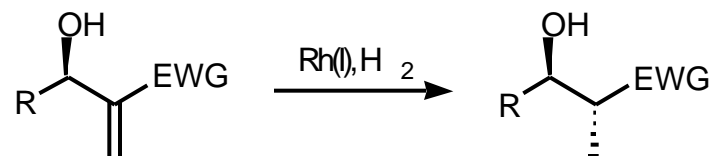
DABCO



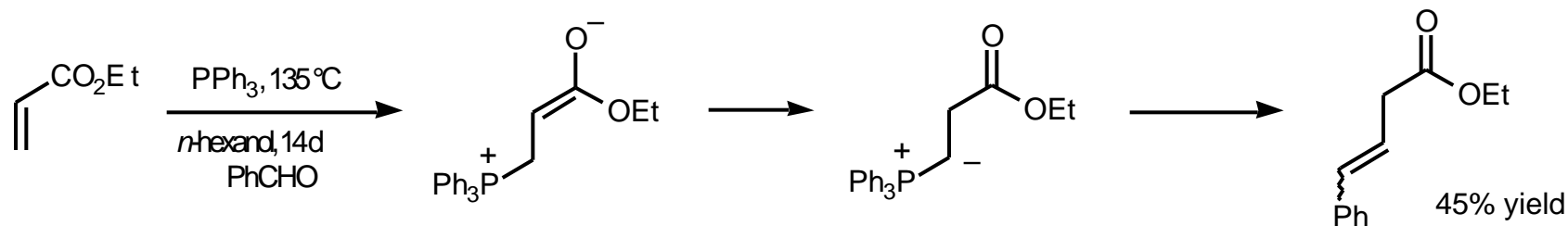
quinuclidine

n-Bu₃P:

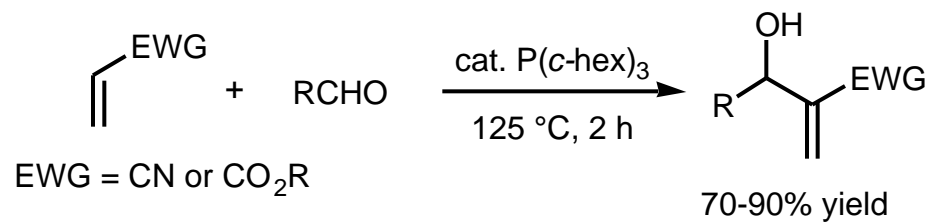
An anti propionate aldol equivalent...



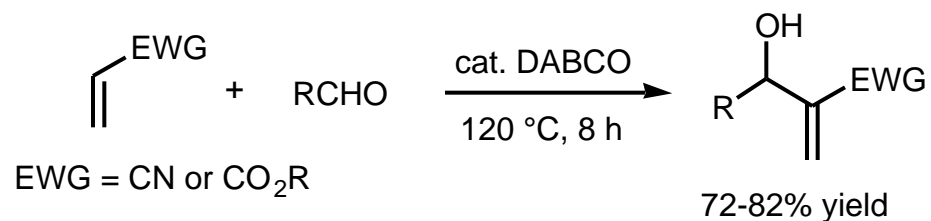
History...Morita-Baylis-Hillman Reaction?



Oda, R.; Tanimoto, S. *Tetrahedron Lett.* **1964**, 25, 1653-1657.



Morita, K.; *et. al.* *Bull. Chem. Soc. Jpn.* **1968**, 41, 2815.

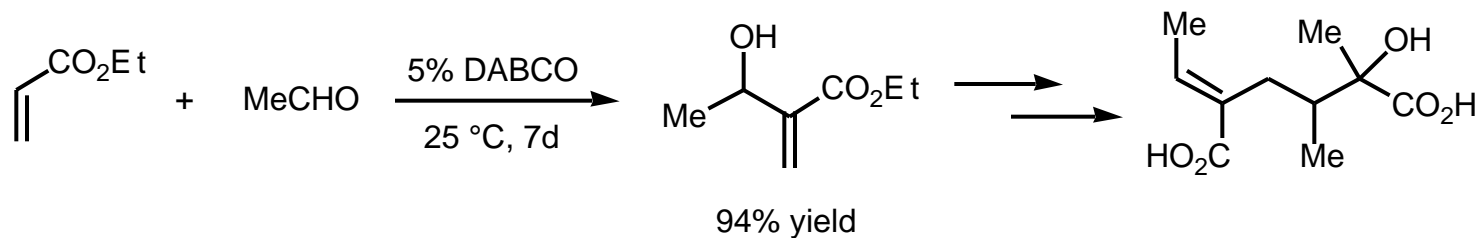


- quinuclidine may also be used

Baylis, A. B.; Hillman, M. E. D. Celanese Corp. *Ger. Offen.* 2,155,113 **1972**.
U.S. Patent Appl. 87,591 **1970** (*U.S. Patent* 3,743,669 **1973**).

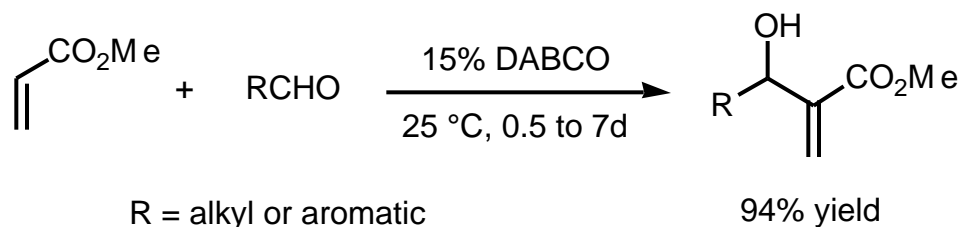
Early Synthetic Examples

10 years after the Baylis-Hillman German patent...used in a C_{10} integerrinecic acid synthesis:



Drewes, S. E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079-2083.

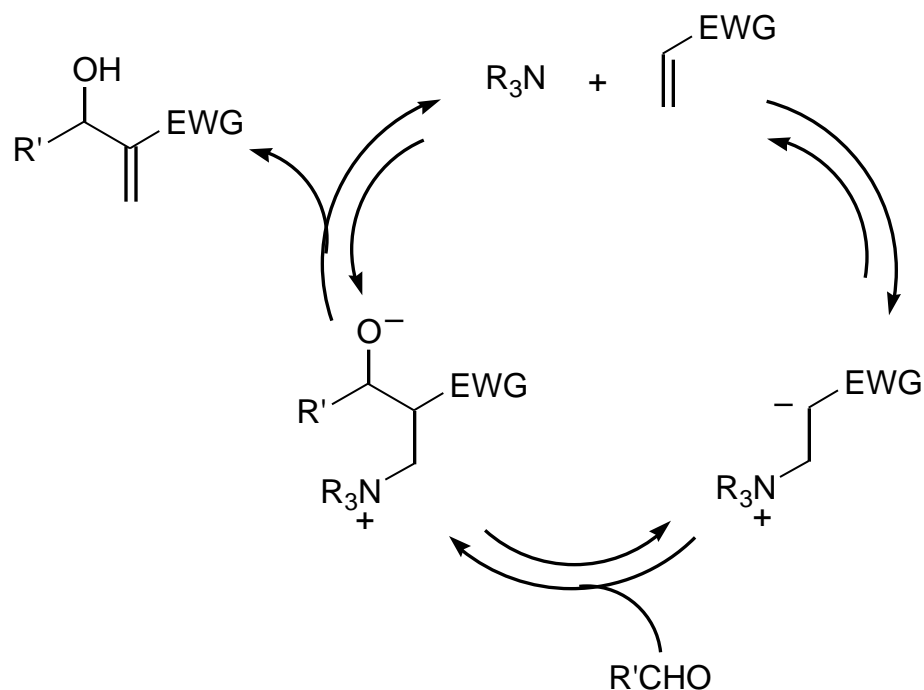
Shortly thereafter, a more extensive, published study:



- All reactions run neat in a sealed tube with 1.5-2 equivalents of acrylate.

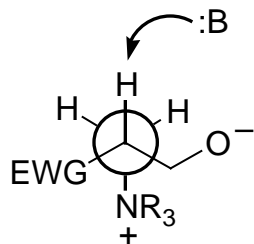
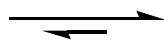
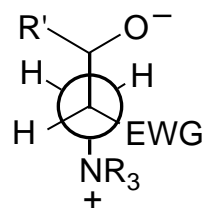
Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 795-797.

Baylis-Hillman Mechanism



- rate = $K_{obs}[\text{aldehyde}][\text{alkene}][\text{amine}]$
- pseudo-second order if [amine] constant
- addition to aldehyde is r.d.s. because the dipole is increased by further charge separation
- acrylonitrile and methyl acrylate studied
- enolate geometry not considered
- ethereal solvent inhibits reaction whereas alcohols (especially diols) accelerate reaction
- huge volume of activation: V^\ddagger of $-79 \text{ cm}^3 \text{ mol}^{-1}$ (the Diels-Alder is $-35 \text{ cm}^3 \text{ mol}^{-1}$) found by plotting $\ln k_{obs}$ vs. P. 5000 bar increases rate by 1.1×10^6
- Reaction is reversible (i.e. a Grob type fragmentation), thus mechanism could be ternary, with no discrete enolate intermediate (supported by V^\ddagger and temperature effects).

E2 elimination...



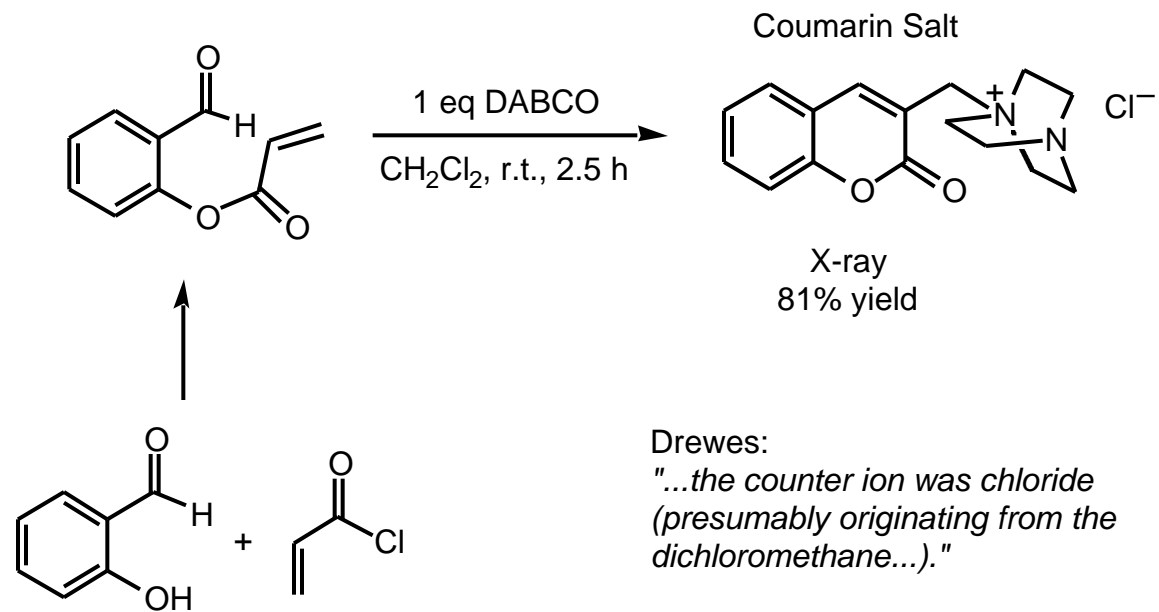
initially formed

eliminates

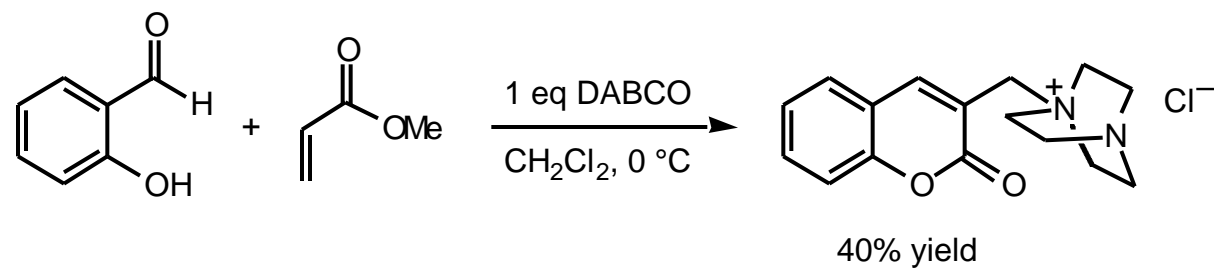
E1cB is also possible

Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.* **1990**, 3, 285-288.
 Kaye, P. T.; Bode, M. L. *Tetrahedron Lett.* **1991**, 32, 5611-5614.

Evidence for an Intermediate

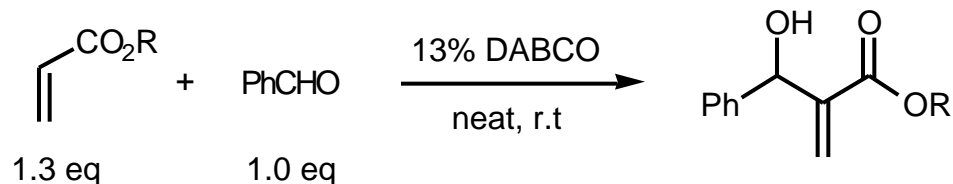


Or...



Drewes, S. E.; *et. al. Syn. Comm.* **1993**, 23, 2807-2815.

Effects of Acrylate Ester Substituent



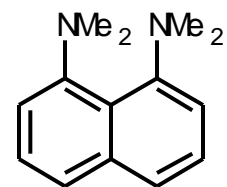
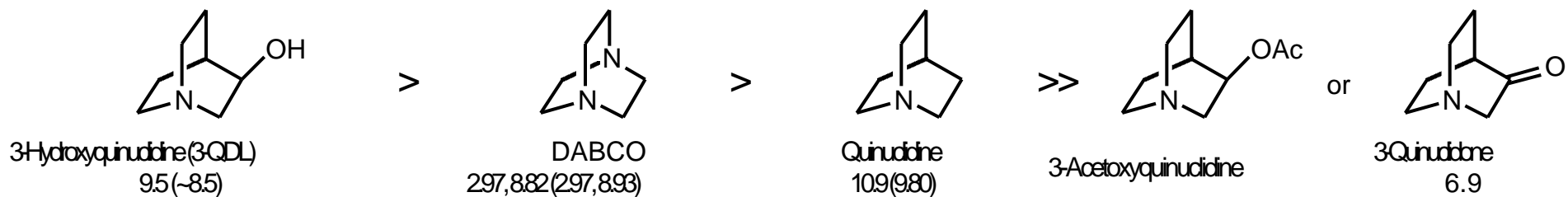
R	time (days)	yield (%)
Me	6	89
Et	7	79
Bn	2	88
<i>n</i> -C ₁₀ H ₂₁	14	75
<i>t</i> -Bu	65	65
2-adamantyl	62	40
CH ₂ CH ₂ F	3	81
CH ₂ CH ₂ Br	2	NR
CH₂CF₃	15 h	58
CH ₂ CH ₂ OMe	4	89
CH ₂ CH ₂ NMe ₂	8	82
(CH ₂) ₆ Cl	15	NR

- For aryl substituted benzyl ethers, no clear relation between values and reactivity was observed.
- Trends hold for furfural.
- The products undergo retro Baylis-Hillman, i.e. the reaction is reversible.

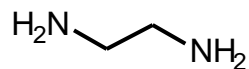
Caubere, P.; *et. al. Tetrahedron* **1992**, *48*, 6371-6384.

Bases for Catalysis

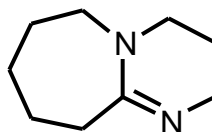
pK_a H_2O (DMSO)



Proton sponge
12.0 (7.50)



6.90, 9.95



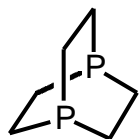
DBU
(~12)

Sterics also important:

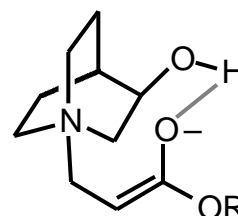
$Me_2NH > Me_2NEt > MeNEt_2 > NEt_3$ 10.75 (9.00)

Many, many phosphines screened...the winner: $n-Bu_3P$ ~9

- $n-Bu_3P$ is only a slightly better catalyst than DABCO.

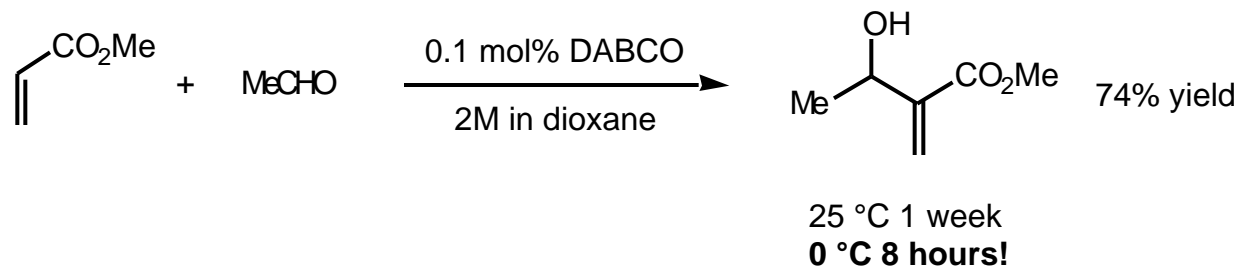


unreactive

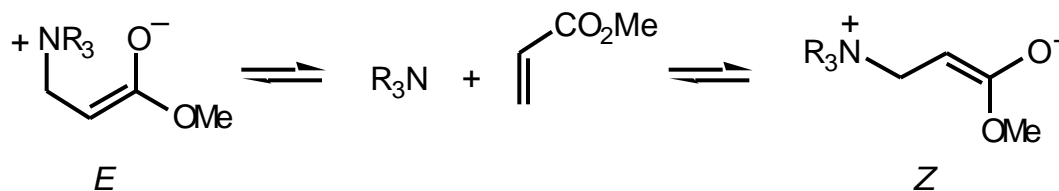


...or could accelerate protonation of intermediate, as any alcohol additive will accelerate reaction

Temperature Effects



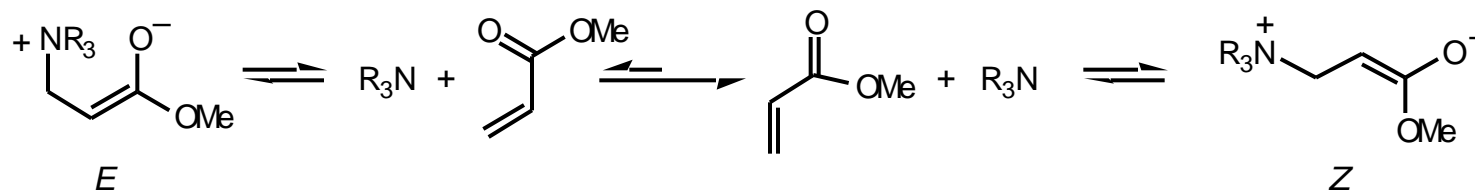
- Reaction is accelerated for a wide variety of aldehydes when conducted at 0 °C
- Temperature effect not seen with acrylonitrile (cannot form enolate)
- Author concludes that one enolate must react faster than another (i.e. a kinetic versus a thermodynamic enolate).



Which enolate is more stable and which is more reactive?

Leahy, J. W.; Rafel, S. *J. Org. Chem.* **1997**, *62*, 1521-1522.

Enolate Geometry

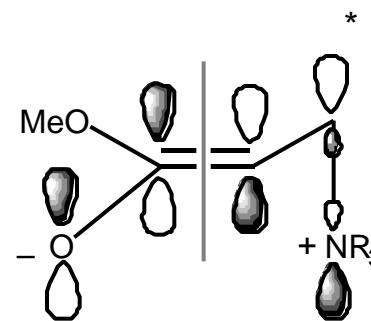
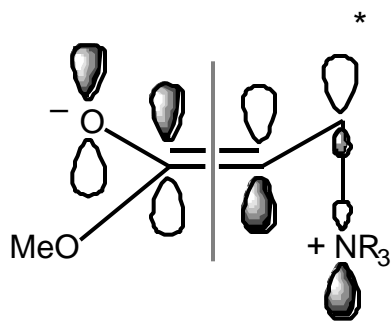


Thermodynamic

- less charge separation
- less reactive

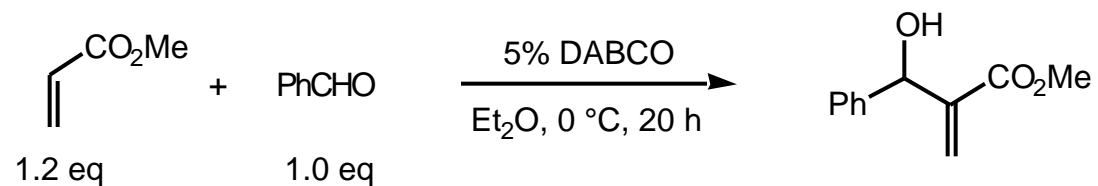
Kinetic

- more charge separation
- less stable
- enolate twists out of plane by PM3



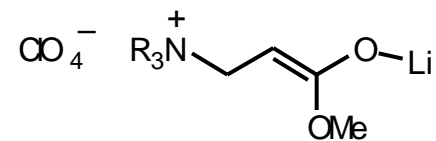
better conjugation into *

Salt Additive



LiClO ₄ (mol%)	yield (%)
0	trace
5	12
10	40
50	63
70	72 (81) ^a
100	25
200	12
500	trace

^a 15 mol% DABCO was used.

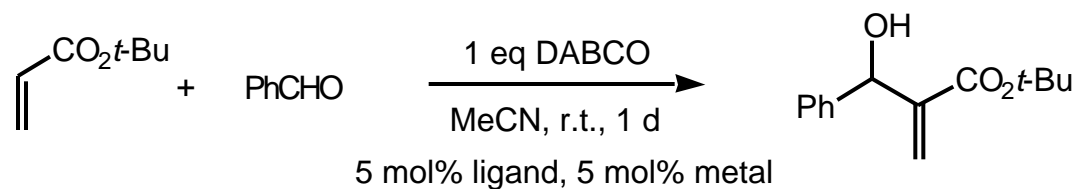


Stablize enolate?

- Ether was found to be optimal from solvent screening.
- General for a variety of alkenes and aldehydes.

Kobayashi, S.; Kawamura, M. *Tetrahedron Lett.* **1999**, *40*, 1539-1542.

Lewis Acid Catalysis



Relative Reaction Rates

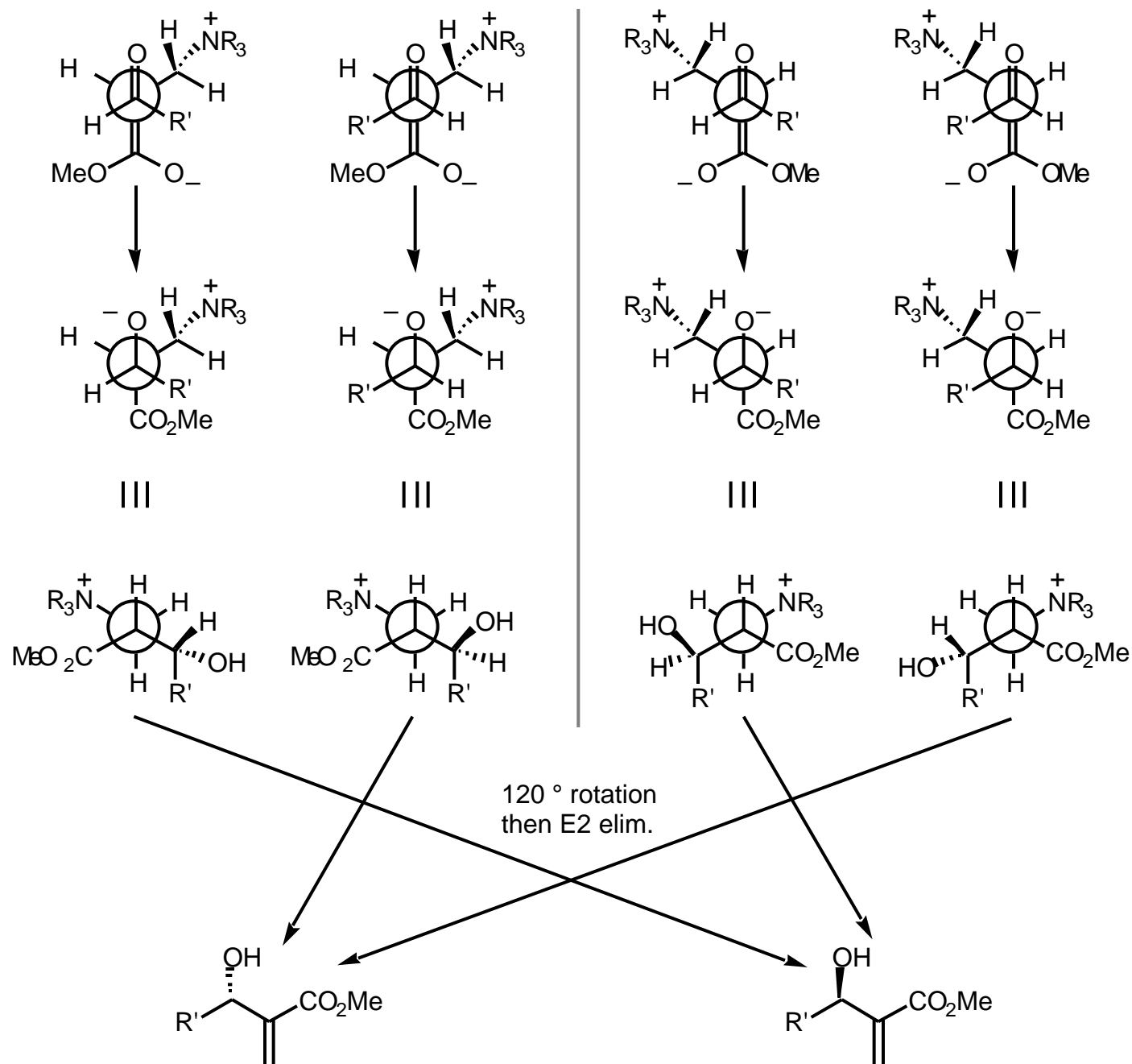
ligand	Sc(OTf) ₃	Yb(OTf) ₃	Eu(OTf) ₃	La(OTf) ₃
none	3.3	3.6	3.5	4.7
(+)-BINOL	9.4	14.4	12.8	14.6
(+)-diethyl tartrate	5.2	9.7	5.5	7.3
(+)-diisopropyl tartrate	3.5	9.5	4.6	8.1
(+)-TMTDA	4.1	8.0	3.6	4.0
(+)-hydrobenzoin	3.5	16.2	5.8	5.3
(+)-triphenylethanediol	3.2	5.2	2.2	5.9
(+)-TADDOL	2.9	4.5	3.8	4.7
ethylene glycol	3.3			
triethanolamine	4.65			10.8
salen	2.31	6.3	5.2	4.0
box	3.6			
<i>N</i> -methylephedrine	2.87	5.8	3.2	4.4

- no enantioselectivity observed
- DABCO loading dropped to <10 mol% with (+)-BINOL
- *rac*-BINOL showed no rate acceleration

Aggarwal, V. K.; *et. al. Chem. Commun.* **1996**, 2713-2714.

Aggarwal, V. K.; *et. al. J. Org. Chem.* **1998**, 63, 7183-7189.

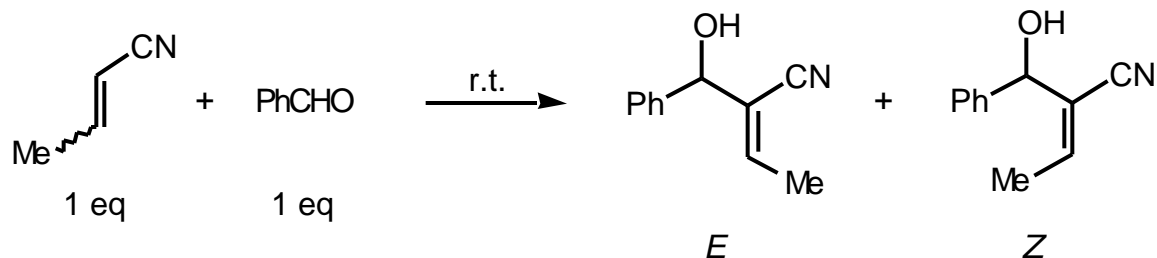
Possible Stereoisomers



Assumptions:

- *E* enolate formed
- E2 favored over E1 pathway
- -NR_3^+ is orthogonal to face (stereoelectronics)

E/Z Selectivity with Crotononitrile



Solvent	E/Z ratio
neat	1.2 : 1
THF	1.4 : 1
CHCl ₃	1.5 : 1
CH ₃ CN	3.1 : 1
MeOH	4 : 1

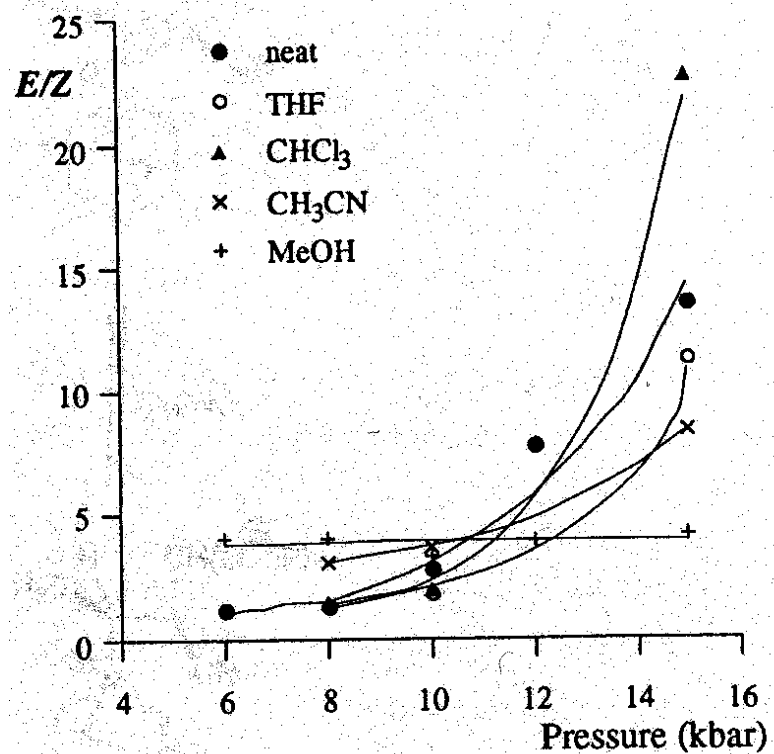
5 mol% DABCO, 8 kbar, 17 h, solvent 50 vol%

Base	E/Z ratio
DABCO	1 : 1
3-QDL	2 : 1
NEt ₃	4 : 1

10 mol% base, 8 kbar, 17 h, CHCl₃ 50 vol%

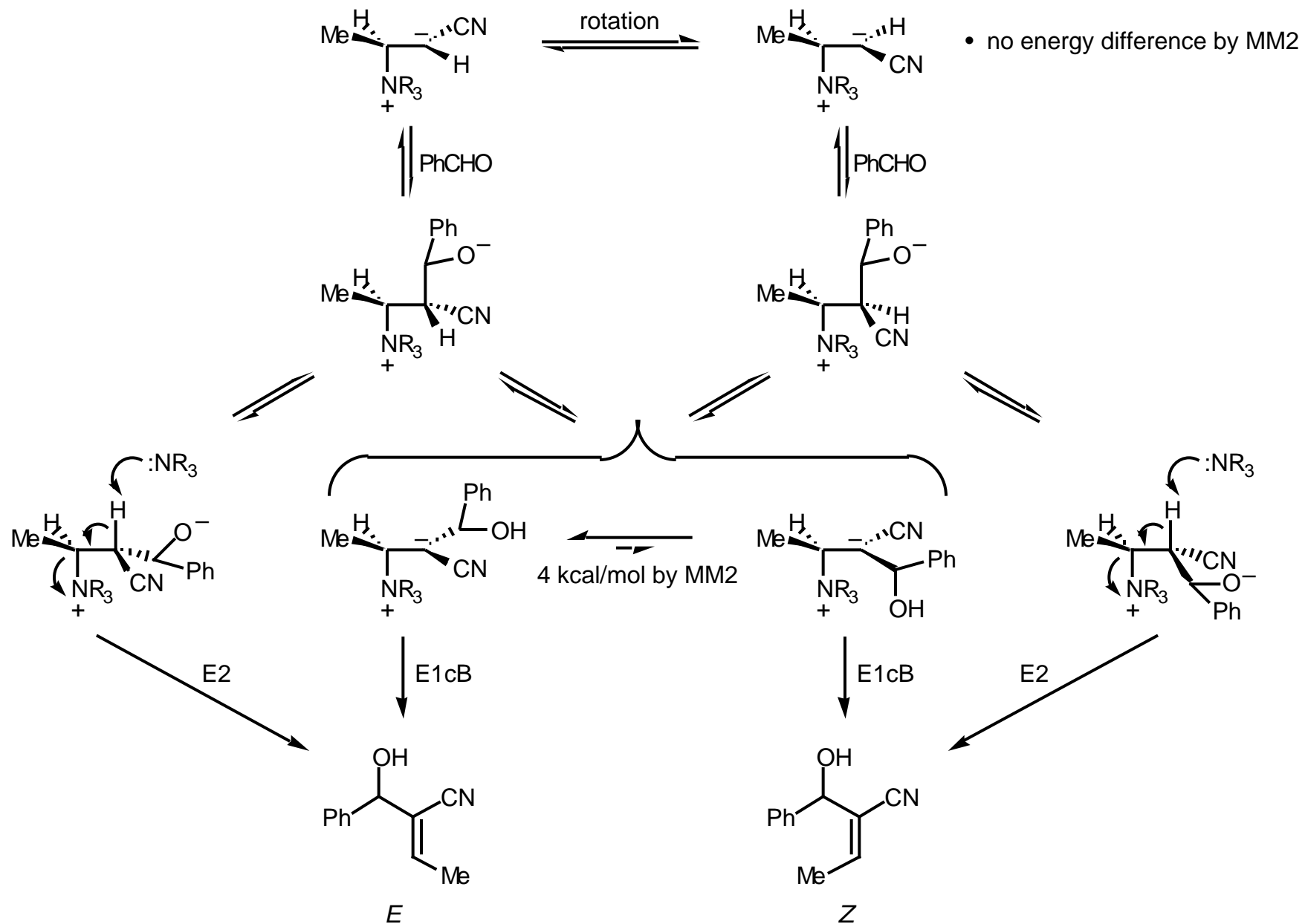
- E and Z crotononitrile is easily isomerized under the reaction conditions.

- Products did not undergo retro-Baylis-Hillman.

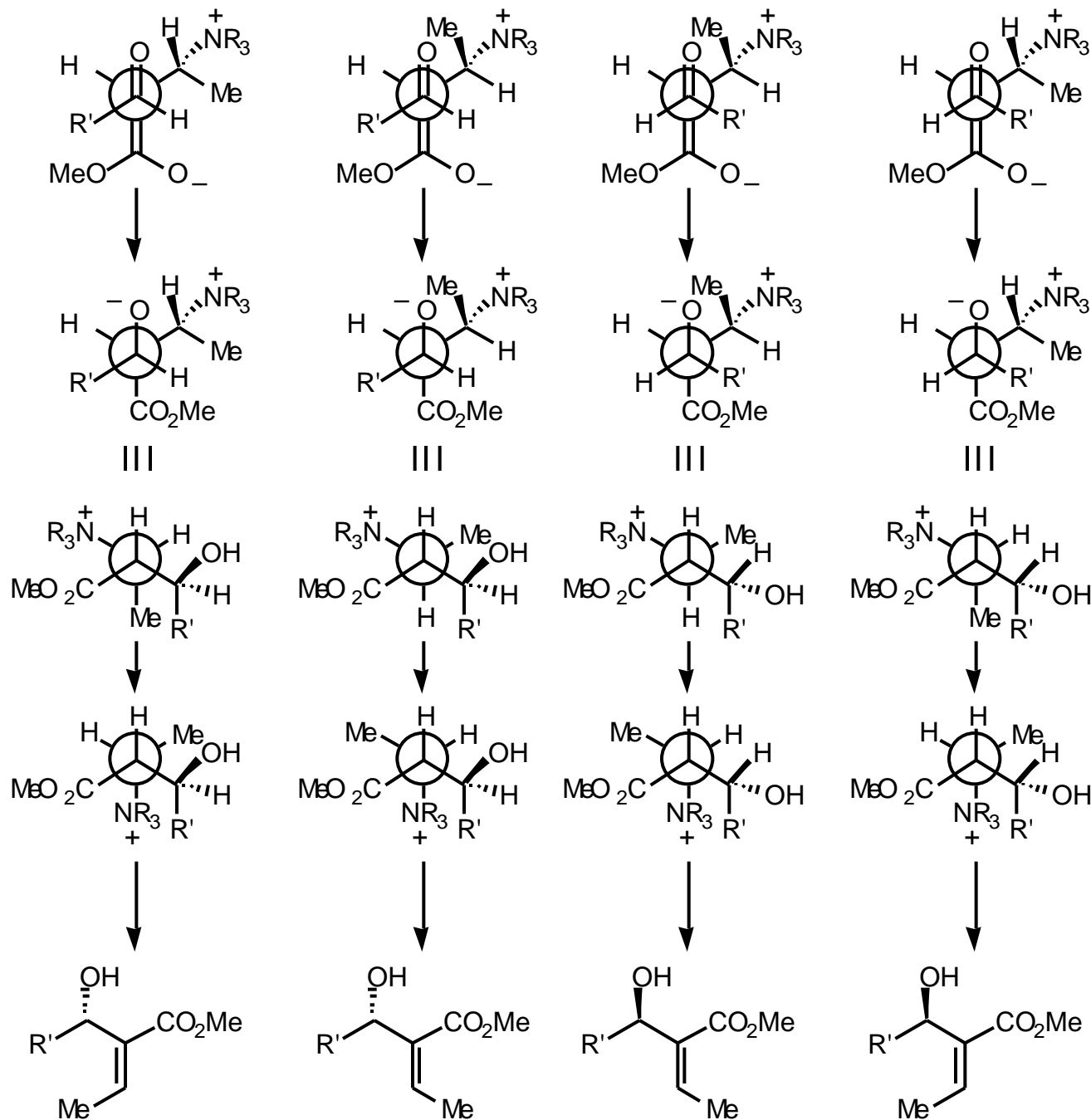


5 mol% DABCO, 17 h, solvent 50 vol%

E/Z Selectivity Rationalization



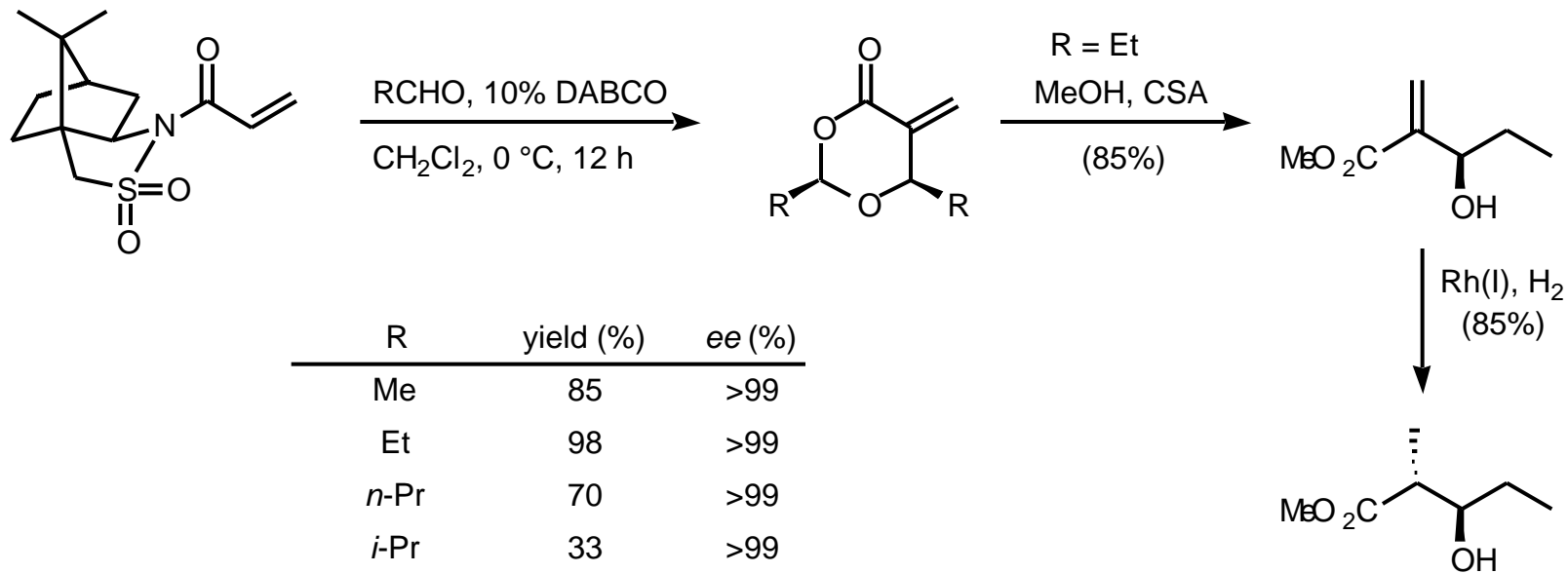
Possible Stereoisomers for Methylcrotonate



Assumptions:

- *E* enolate formed
- E2 favored over E1 pathway, only after rotation of ammonium to *anti* conformation
- $-\text{NR}_3^+$ is orthogonal to face (stereoelectronics)
- only **one** face of enolate considered, thus there are an **additional 4 stereoisomers** possible
- starting geometry of methylcrotonate and *in situ* isomerization not considered
- retro-Baylis-Hillman not considered

Camphorsultam Acrylate Baylis-Hillman

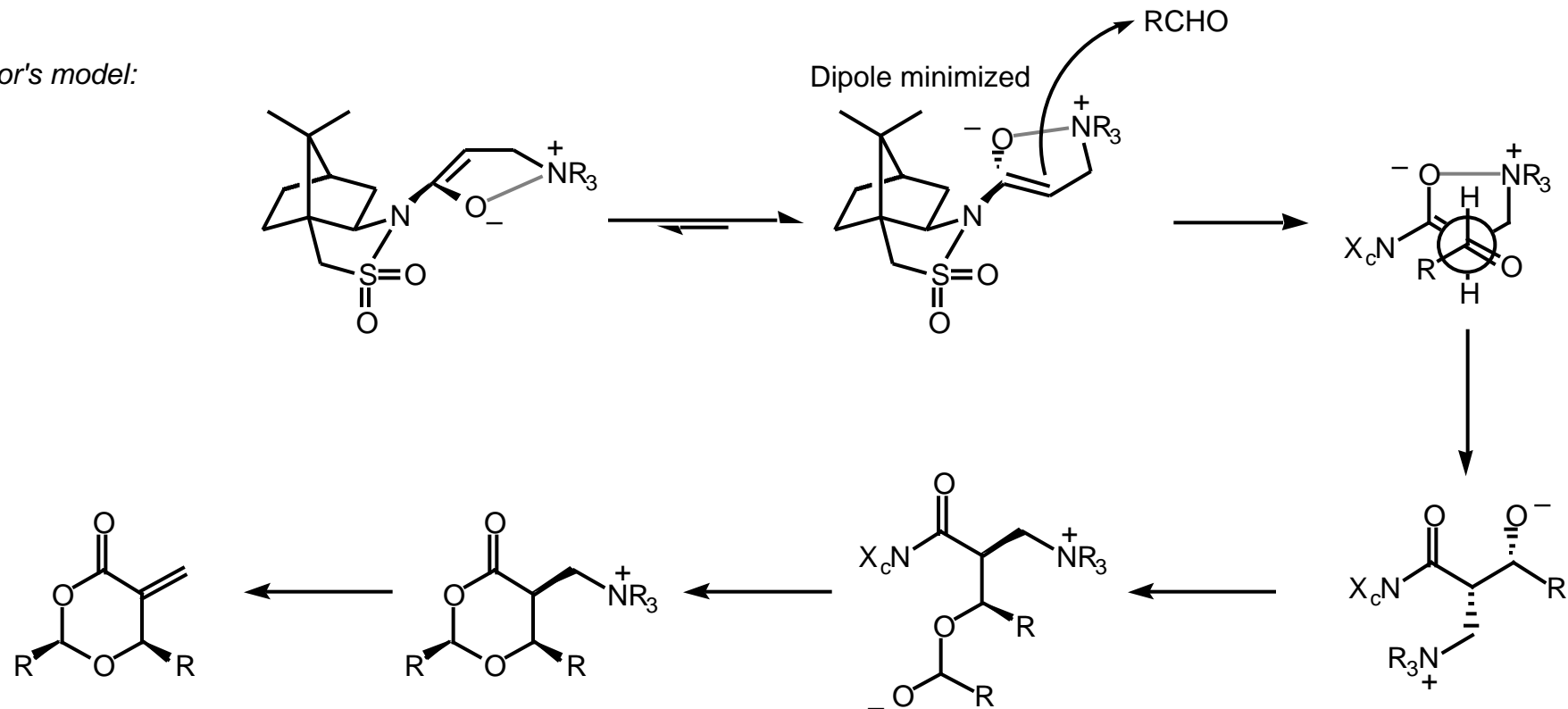


R	yield (%)	ee (%)
Me	85	>99
Et	98	>99
<i>n</i> -Pr	70	>99
<i>i</i> -Pr	33	>99
PhCH ₂ CH ₂	68	>99
AcOCH ₂	68	>99
(CH ₃) ₂ CHCH ₂	67	>99
Ph	0	

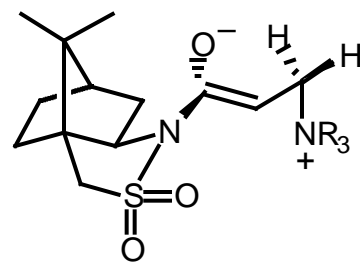
Leahy, J. W.; *et. al.* *J. Am. Chem Soc.* **1997**, *119*, 4317-4318.

Camphorsultam Acrylate Mechanism

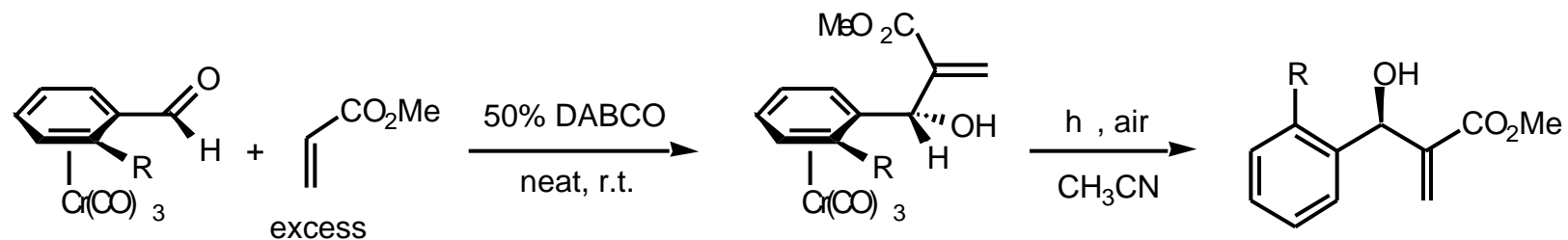
Author's model:



Alternative (stereoelectronics):



Chiral Aldehydes: Chromium Auxiliary

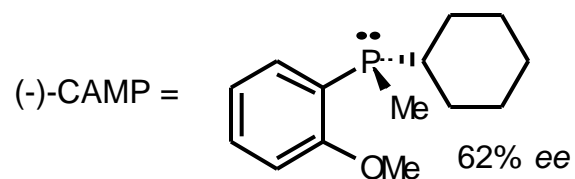
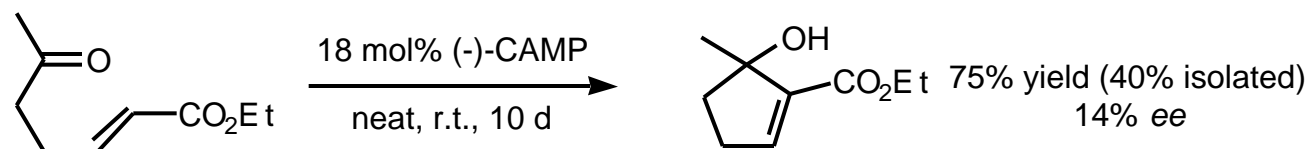


aldehyde	R	time (h)	yield (%)	dr
<i>rac</i>	OMe	93	87	>98:2
<i>rac</i>	Cl	6	89	>98:2
<i>rac</i>	F	7	92	92:8
<i>rac</i>	Me	58	90	84:16
<i>S</i> -(+)	OMe	93	85	>98:2
<i>S</i> -(+)	Cl	8	97	>98:2

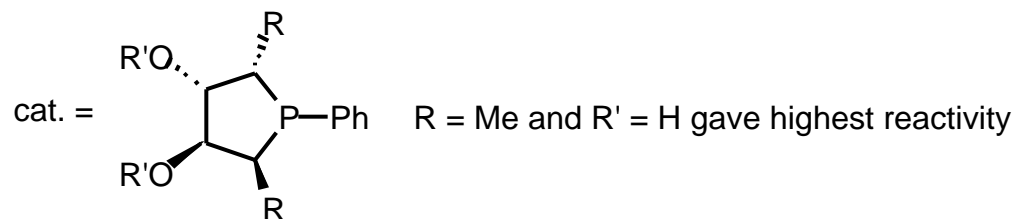
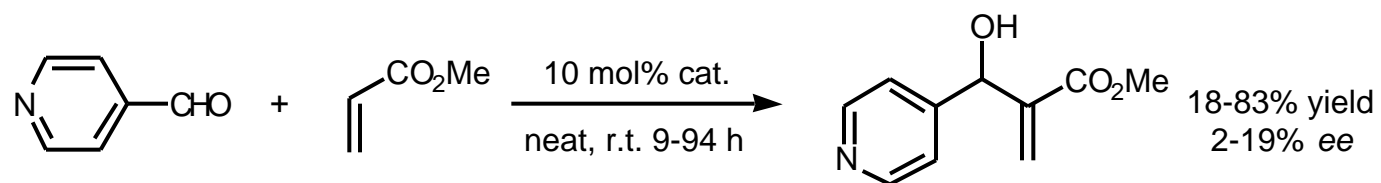
- dr determined by 200 MHz ¹H NMR
- *N*-Tosyl arylimine chromium complex also reacts

Kundig, P. E.; *et. al. Tetrahedron Lett.* **1993**, 34, 7049-7052.

Chiral Phosphine Catalysts

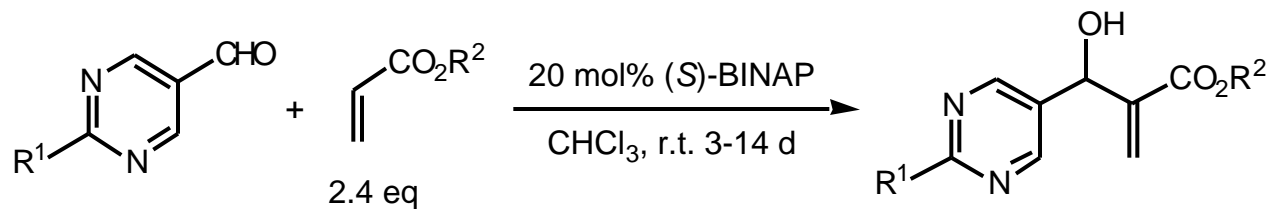


Frater, G.; *et al. Tetrahedron Lett.* **1992**, 33, 1045-1048.



Zhang, X.; *et al. J. Org. Chem.* **2000**, 65, 3489-3496.

The High Point of Chiral Phosphine Catalysts



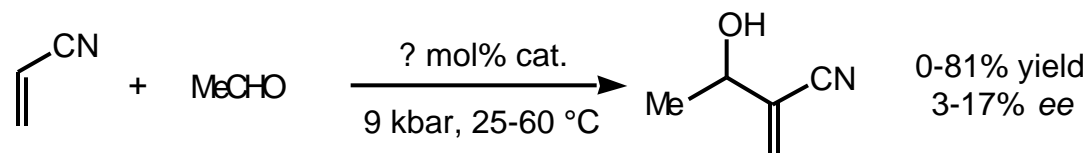
R^1	R^2	time (d)	yield (%)	ee (%)
H	<i>i</i> -Pr	4	8	9
H	Et	3	12	25
H	Me	4	24	44
Me	Me	14	18	37
Me	Me	3	26	30 ^a

^a Tol-BINAP was used

- other phosphines screened gave ~racemic products: DIOP, NORPHOS, BPPFOH, and MOP

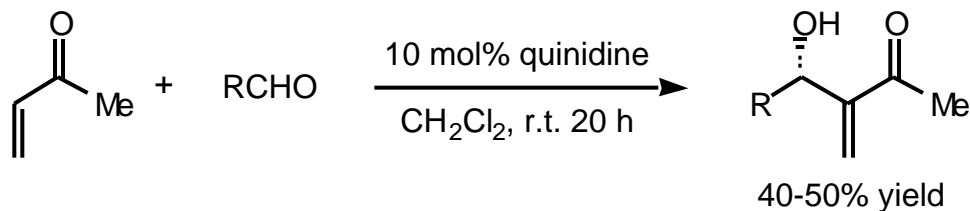
Soai, K.; *et. al. Chem. Commun.* **1998**, 1271-1272.

Naturally Occurring Alkaloids as Chiral Catalysts



- (-)-quinine, (1*R*,2*S*) *N*-methylephedrine, *S*-(-)-nicotine, *S*-(-)-*N*-methylprolinol screened
- (-)-menthyl acrylate ester gave 100% *de* with aromatic aldehydes and DABCO under high P

Isaacs, N. S.; *et. al. Tetrahedron: Asymm.* **1991**, 2, 969-972.



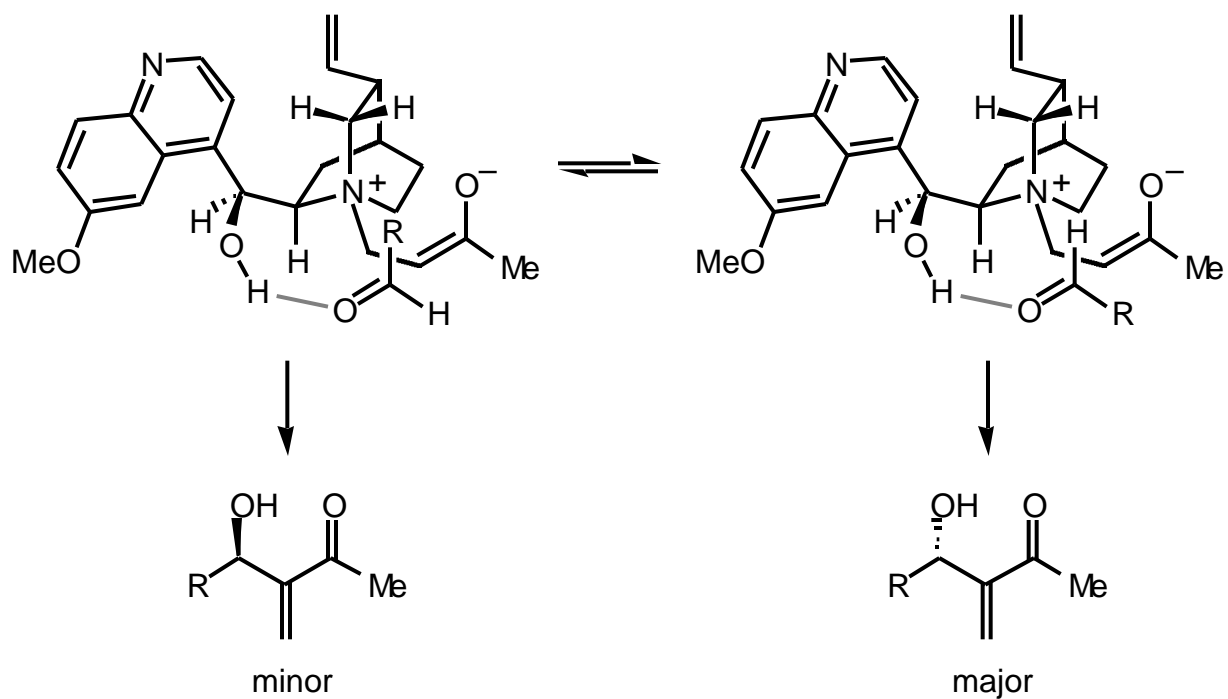
R	Pressure	ee (%)
<i>n</i> -Pr	3 kbar	18
<i>n</i> -C ₉ H ₁₉	10 kbar	31
<i>i</i> -Pr	3 kbar	37
<i>c</i> -hex	3 kbar	45

- 3-QDL, quinine, cinchonine, cinchonidine, *O*-acetyl quinidine, *N*-methylprolinol, *N*-methylephedrine also screened
- ee is highly pressure dependent, optimized pressure is shown in table

Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, 53, 1015-1024.

Model For Quinidine Catalyst

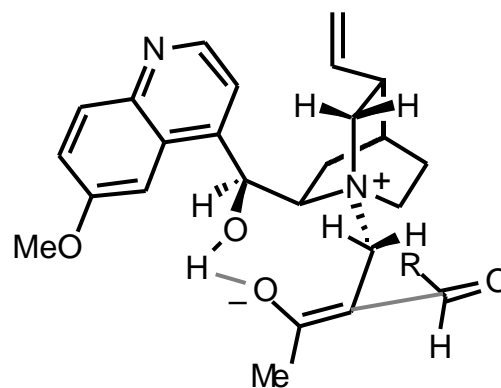
Author's model:



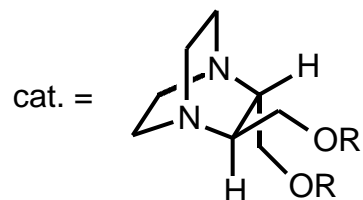
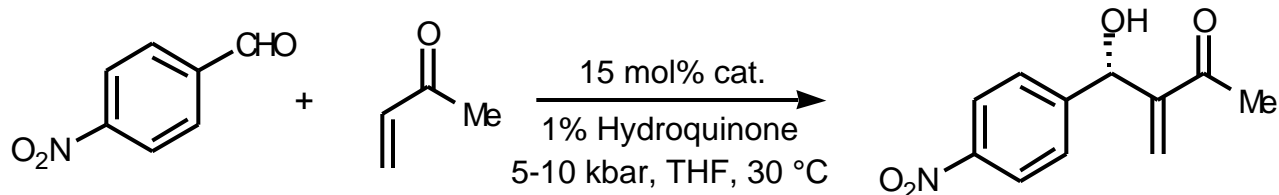
- C hydrogens control face of the aldehyde
- bulky R should enhance selectivity, a trend that they say is "...clearly visible."
- H-bonding plays a "clear role" as O-acyl quinidine gives no enantioselectivity

Alternative:

major ←

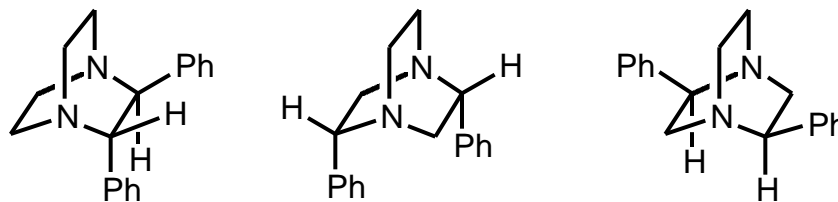


C₂ Symmetric DABCO Catalyst

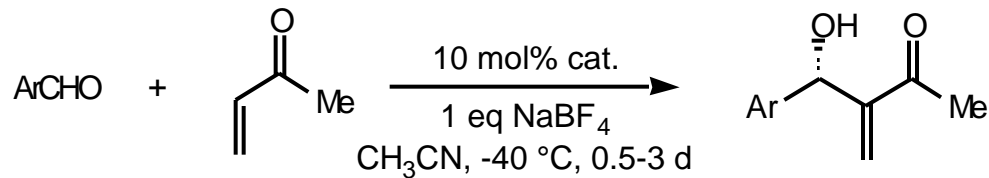


R	time (h)	yield (%)	ee (%)
Bn	12	45	47
TBDPS	12	23	34
TIPS	28	33	19
Ph	16	60	35
Mesityl	28	67	16
1-naphthyl	16	66	42
1-anthranlyl	24	9	11
1-naphthoyl	17	68	15
<i>N</i> -Cbz-Gly	24	63	21

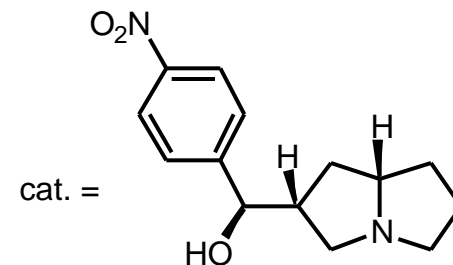
- racemic alcohol product can be easily resolved by kinetic resolution with Sharpless asymmetric epoxidation
- other chiral DABCO's made, but not tested...



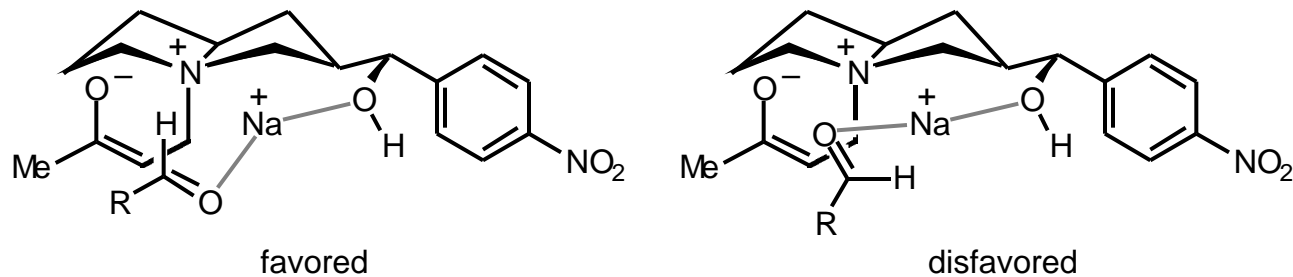
Chiral Pyrrolizidine Catalyst



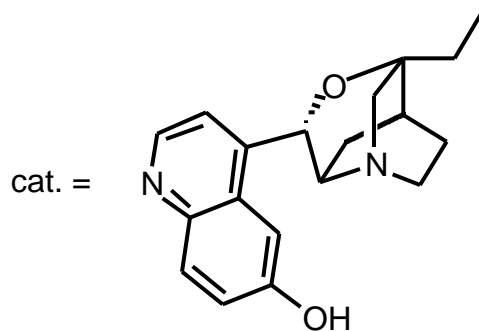
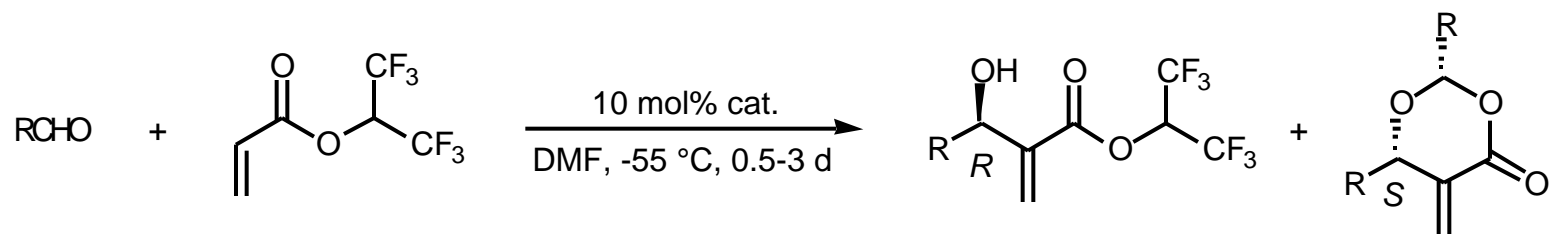
Ar	yield (%)	ee (%)
2-NO ₂	71	67
2-F	31	63
2-Cl	58	72
2-Br	63	71
3-NO ₂	51	37
2-pyridyl	83	21
3-pyridyl	93	49
4-quinolinyl	63	70
4-NO ₂	17	39



Author's model:



Quinidine Ether Catalyst



prepared in 65% yield from quinidine in 85% phosphoric acid and KBr (100 °C, 5 d).

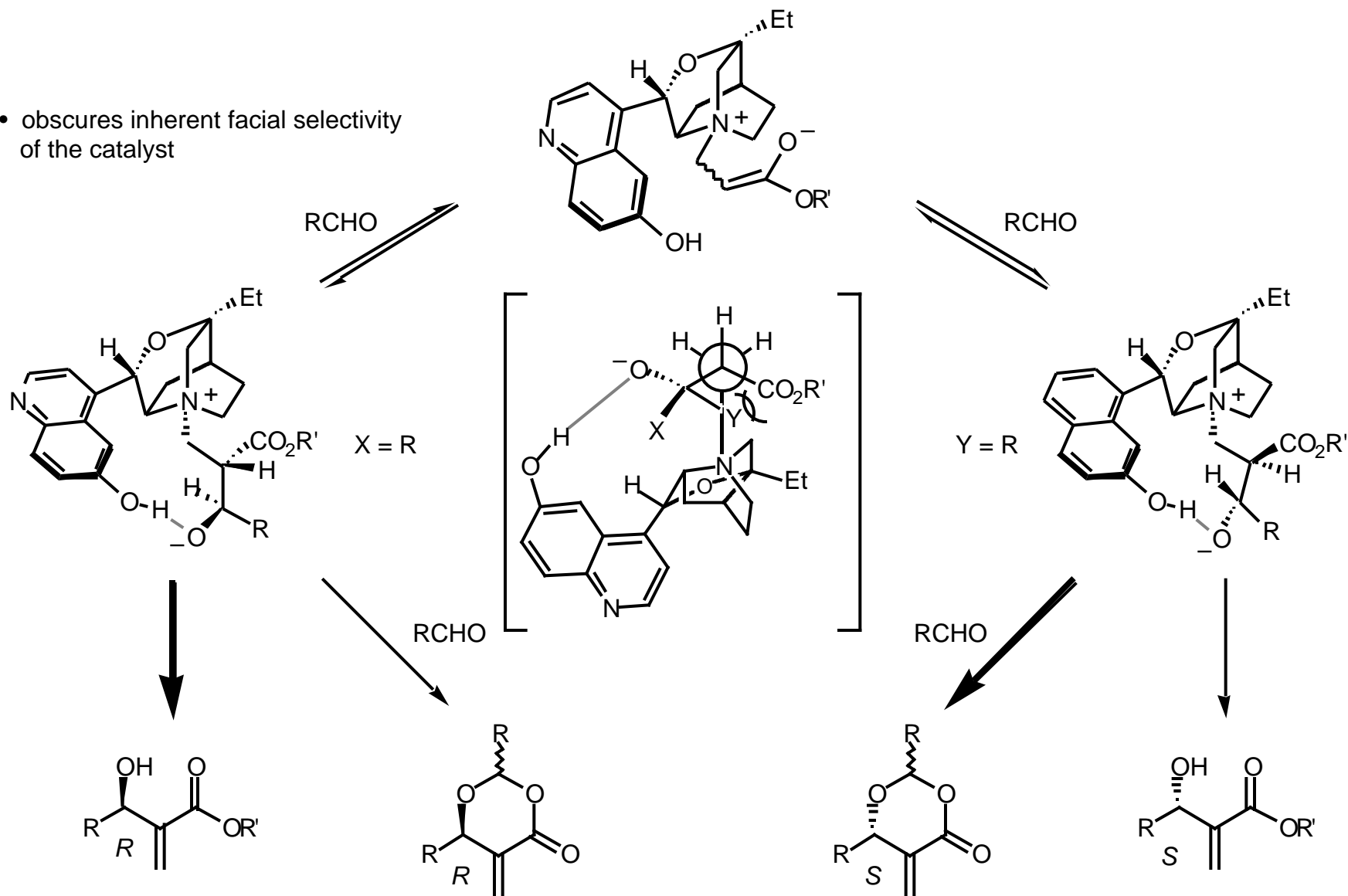
R	ester		dioxanone	
	yield (%)	ee (%), (config)	yield (%)	ee (%), (config)
<i>p</i> -NO ₂	58	91 (<i>R</i>)	11	4 (<i>R</i>)
Ph	57	95 (<i>R</i>)	--	--
(<i>E</i>)-PhCH=CH	50	92 (<i>R</i>)	--	--
Et	40	97 (<i>R</i>)	22	27 (<i>S</i>)
<i>i</i> -Bu	51	99 (<i>R</i>)	18	18 (<i>S</i>)
<i>i</i> -Pr	36	99 (<i>R</i>)	25	25 (<i>S</i>)
<i>c</i> -Hex	31	99 (<i>R</i>)	23	23 (<i>S</i>)
<i>t</i> -Bu	--	--	--	--

- Quinidine and other acyclic derivatives showed no enantioselection and very low reactivity.
- Free hydroxyl on quinoline is essential for enantioselectivity.
- Reactions conducted at room temperature showed lower enantioselection.
- Racemic ester does not react to give dioxanone under the reaction conditions.

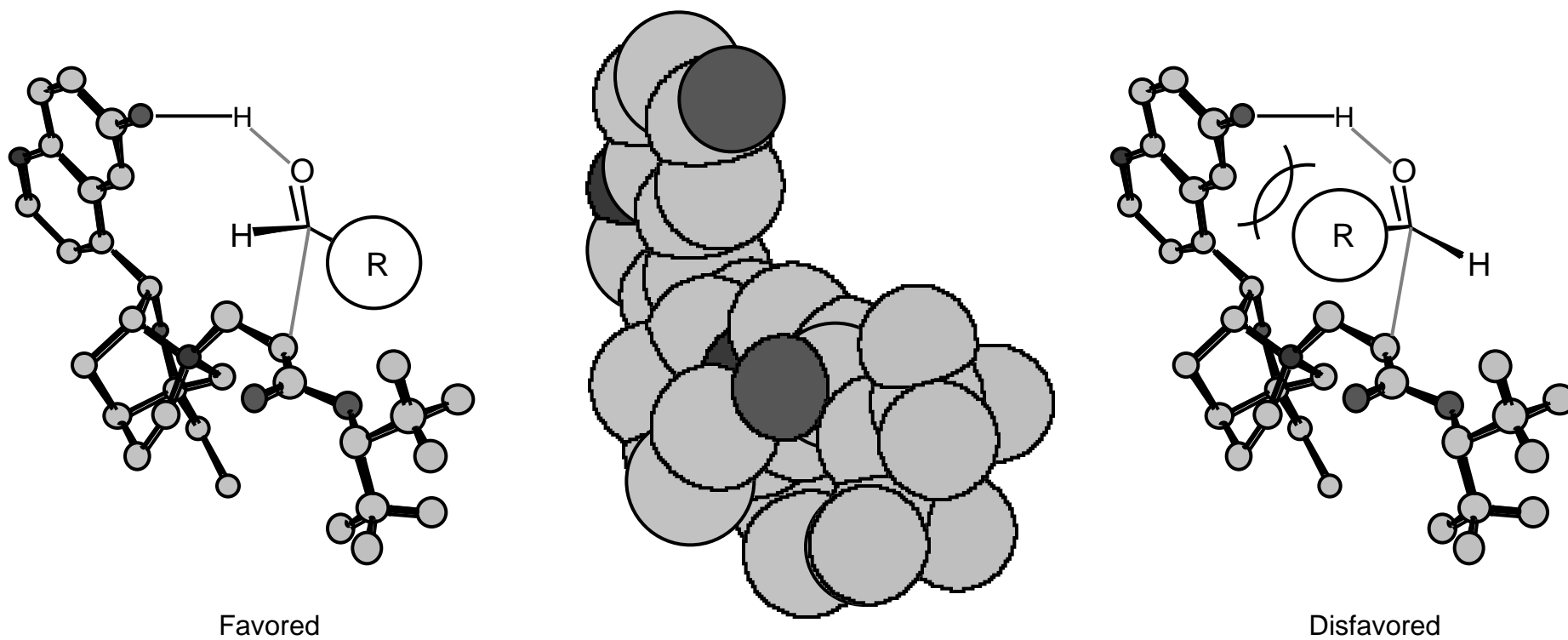
Hatakeyama, S.; *et. al J. Am. Chem. Soc.* **1999**, *121*, 10219-10220.

Proposed Mechanism: Partial Kinetic Resolution

- obscures inherent facial selectivity of the catalyst



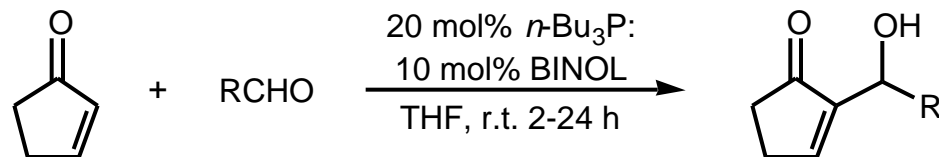
A Model for Facial Selectivity



PM3 minimized: C-N bond to enolate constrained to 1.6 Å

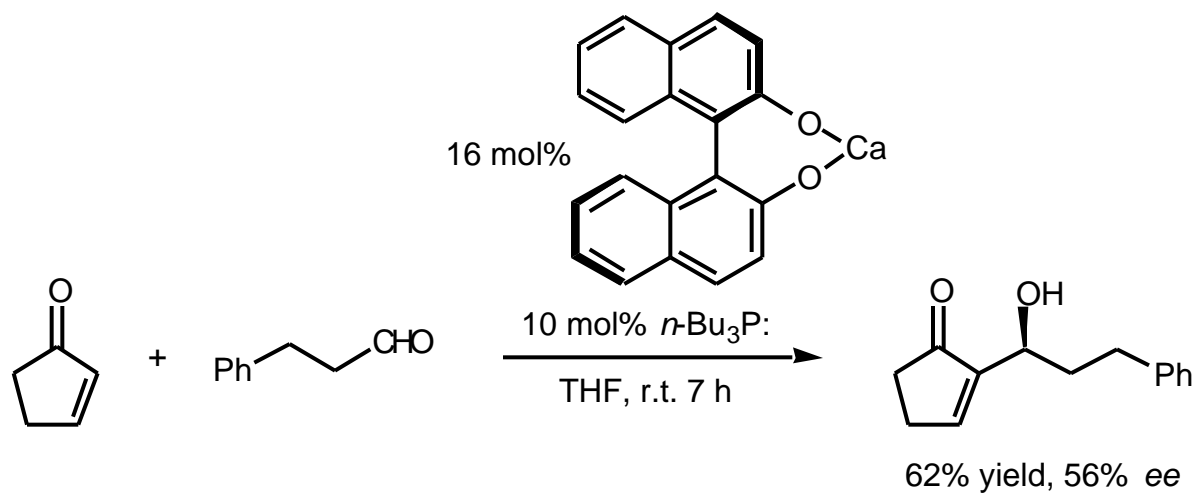
- Catalyst orthogonal to opposite face of the enolate leads to same major enantiomer after elimination.

BINOL as an Additive or Ligand



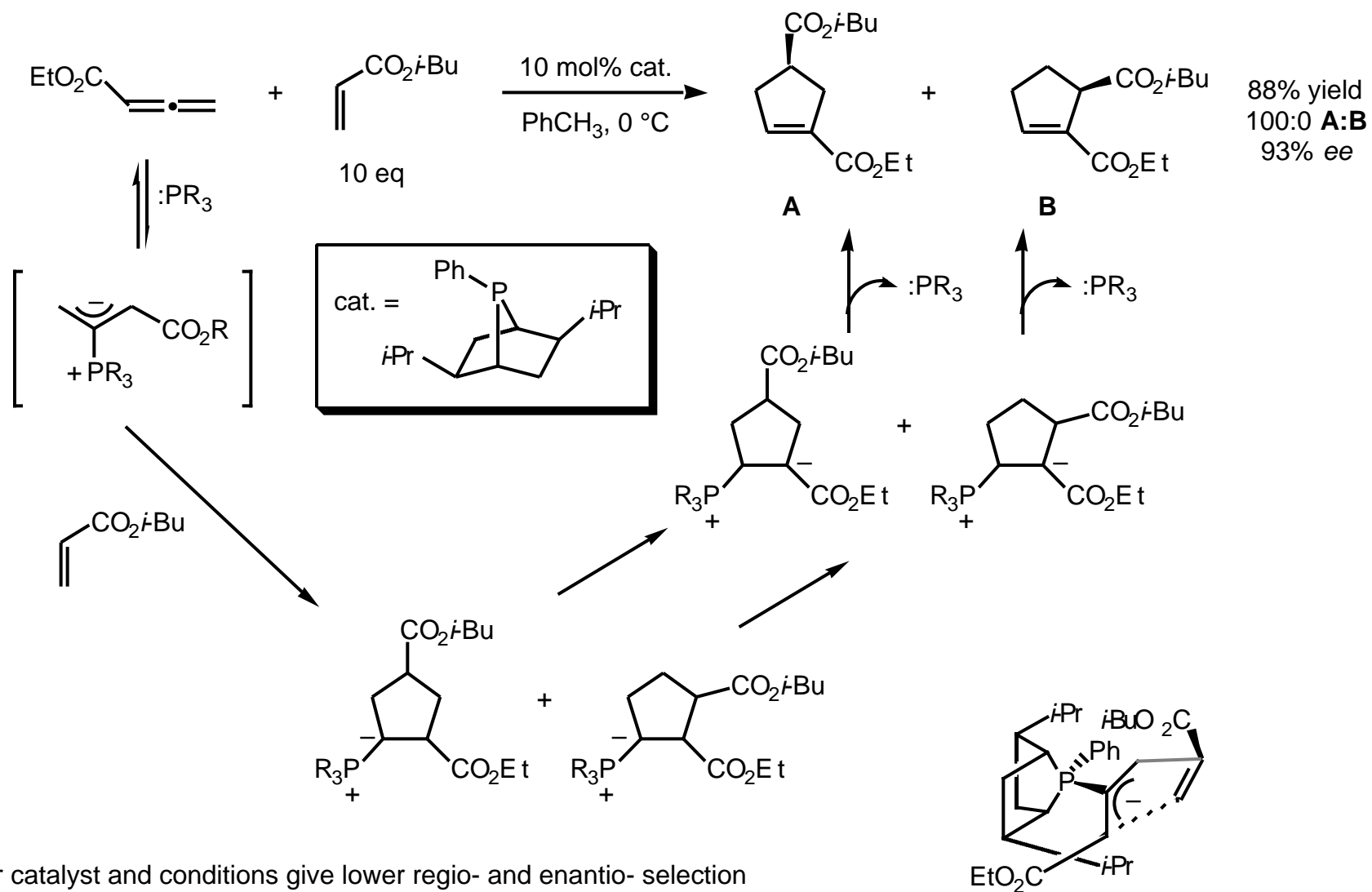
R	yield (%)
$n\text{-C}_7\text{H}_{15}$	quant.
Ph	92
MEMO(CH ₂) ₃	98
Et	91
PhCH ₂ CH ₂	quant.

- ee were all <10%
- phenol also accelerates reaction
- other acrylates also tolerated



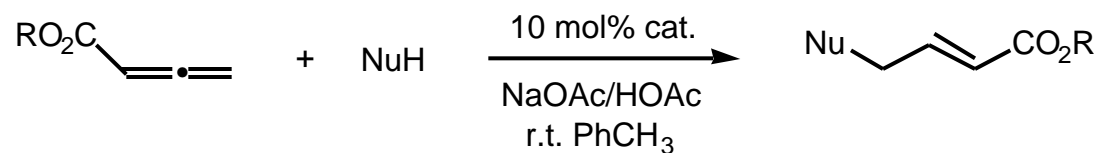
Ikegami, S.; Yamada, Y. M. A. *Tetrahedron Lett.* **2000**, 41, 2165-2169.

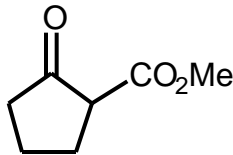
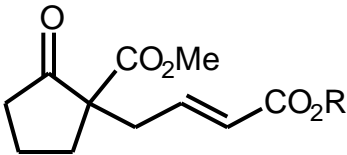
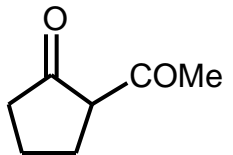
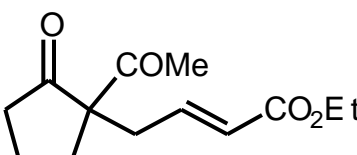
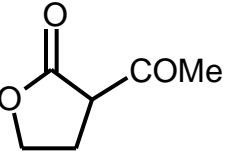
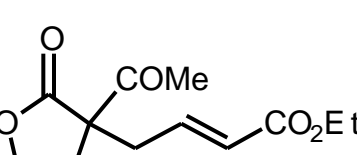
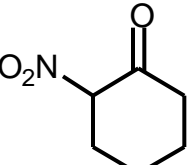
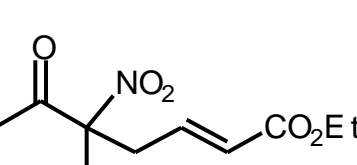
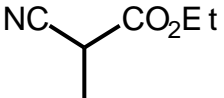
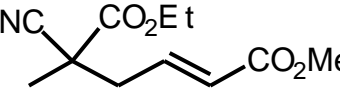
A Related Phosphine Catalyzed Reaction

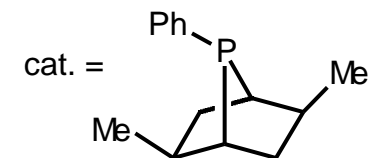


- other catalyst and conditions give lower regio- and enantio- selection

Phosphine Catalyzed Addition

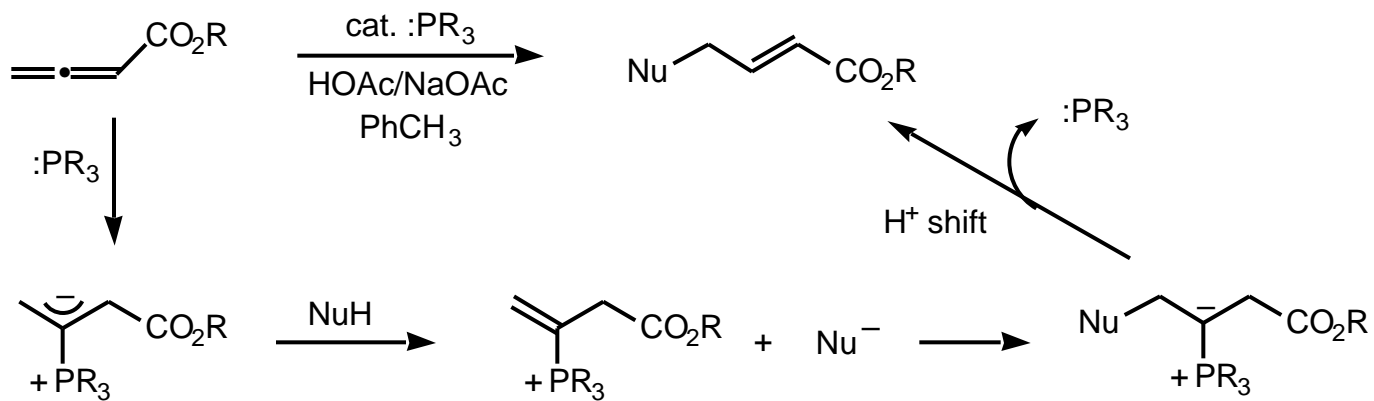


NuH	R	yield (%)	ee (%)	product
	Me	80	73	
	Et	76	74	
	<i>t</i> -Bu	74	75	
	Et	67	56	
	Et	83	48	
	Et	31	41	
	Me	47	45	



Addition Mechanism

Author's proposal:



Conclusions

- The Baylis-Hillman reaction provides convenient access to valuable allylic alcohol building blocks which may serve as synthetic equivalents to *anti*-propionate aldol addition products.
- The basics of the reaction mechanism are understood, but the mechanistic details still remain elusive at best.
- Few examples of a general, diastereoselective Baylis-Hillman have been reported and the successful ones are rather limited in scope.
- Only one synthetically useful enantioselective, base catalyzed Baylis-Hillman reaction exists. There is no rational design, nor models for asymmetric catalysis.
- The asymmetric, catalytic Baylis-Hillman reaction is very promising and attractive methodology, but remains an elusive goal of chiral Lewis base catalysis.