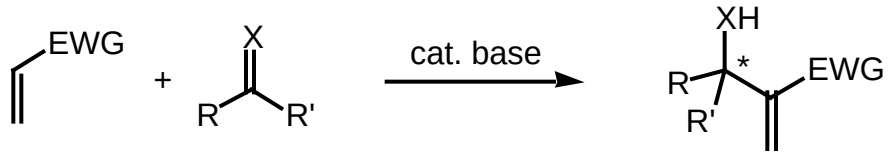
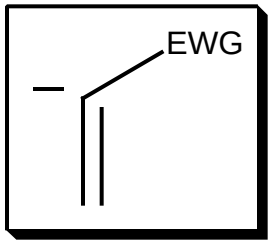
# Asymmetric Catalysis with Chiral Lewis Bases (Part IV)
# The Asymmetric Baylis-Hillman Reaction

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




Leading References:

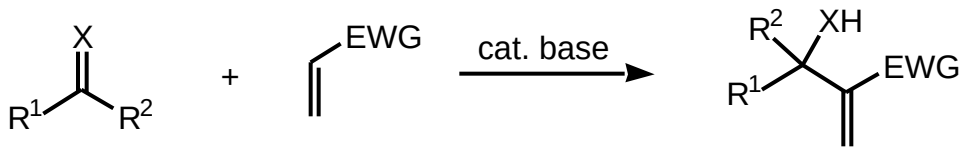
Langer, P. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3049-3052.

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



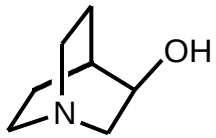

X = O, NTs, $NCO_2R$, $NPPh_2$, $NSO_2Ph$

$R^1$ = alkyl, aryl

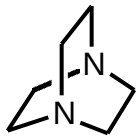
$R^2$ = H, alkyl, EWG

EWG = $CO_2R$, CN, $POEt_2$, CHO, COR, $SO_2Ph$, $SO_3Ph$

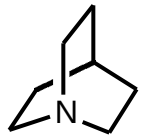
cat. bases:




3-hydroxyquinuclidine (3-QDL)



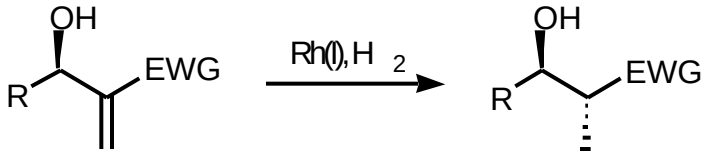

DABCO



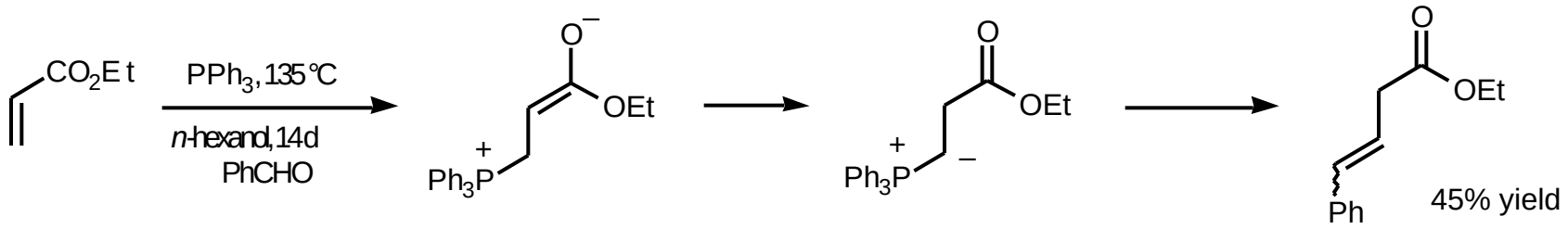

quinuclidine

*n*-$Bu_3P$:

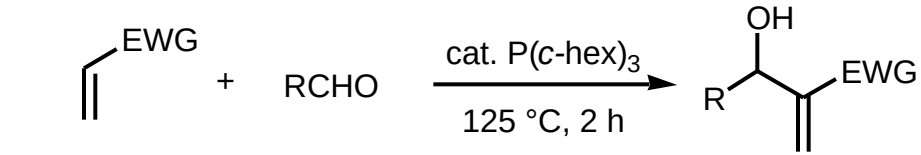
*An anti propionate aldol equivalent...*



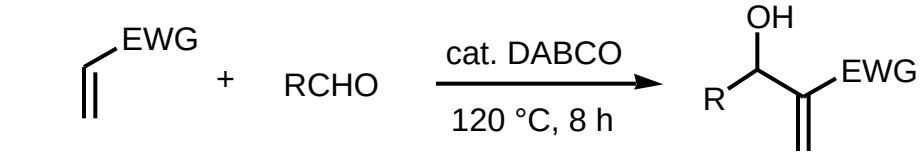
# History...Morita-Baylis-Hillman Reaction?




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




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

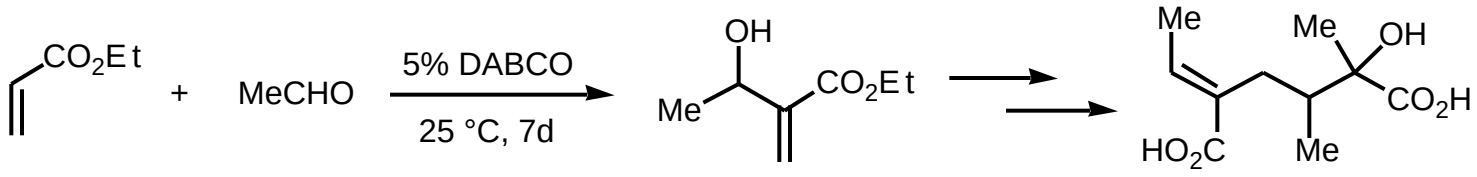



• quinuclidine may also be used

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

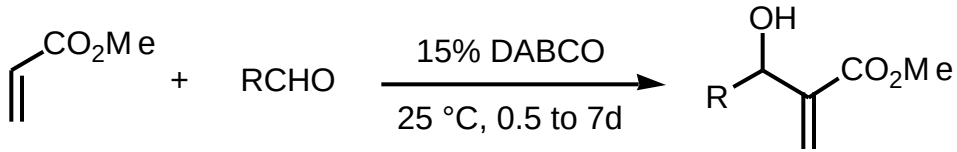
*10 years after the Baylis-Hillman German patent...used in a $C_{10}$ integerrinecic acid synthesis:*




94% yield

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

*Shortly thereafter, a more extensive, published study:*



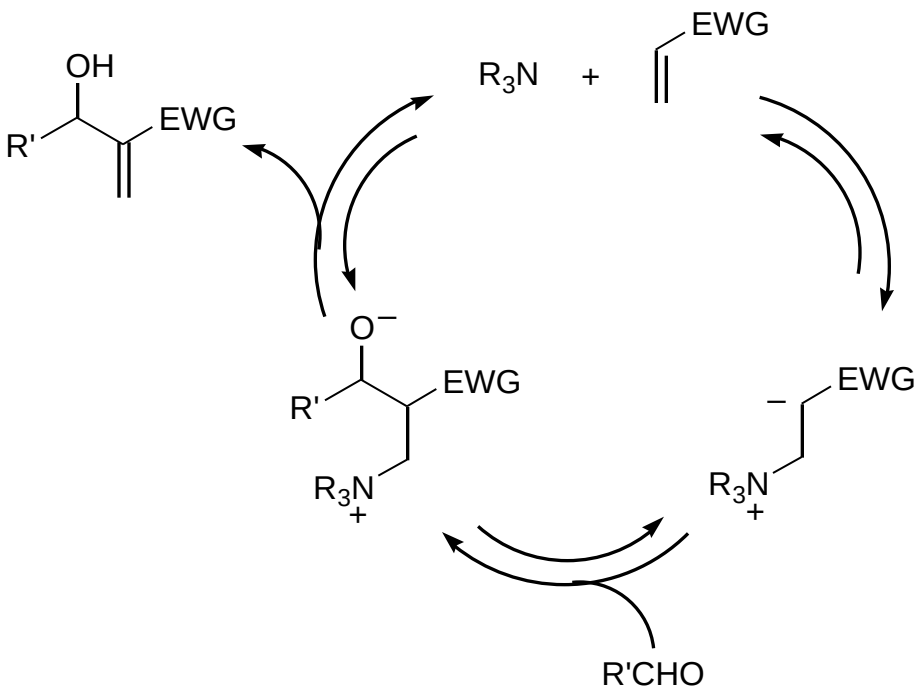

R = alkyl or aromatic

94% yield

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

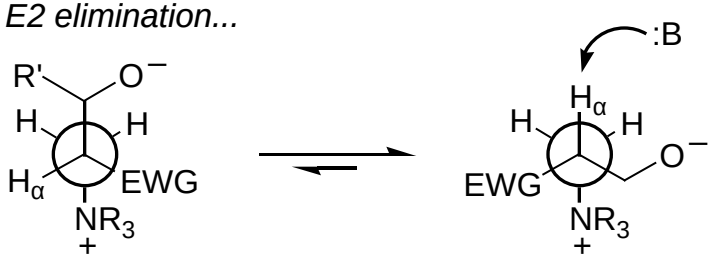
Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795-797.

# Baylis-Hillman Mechanism




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

*E2 elimination...*

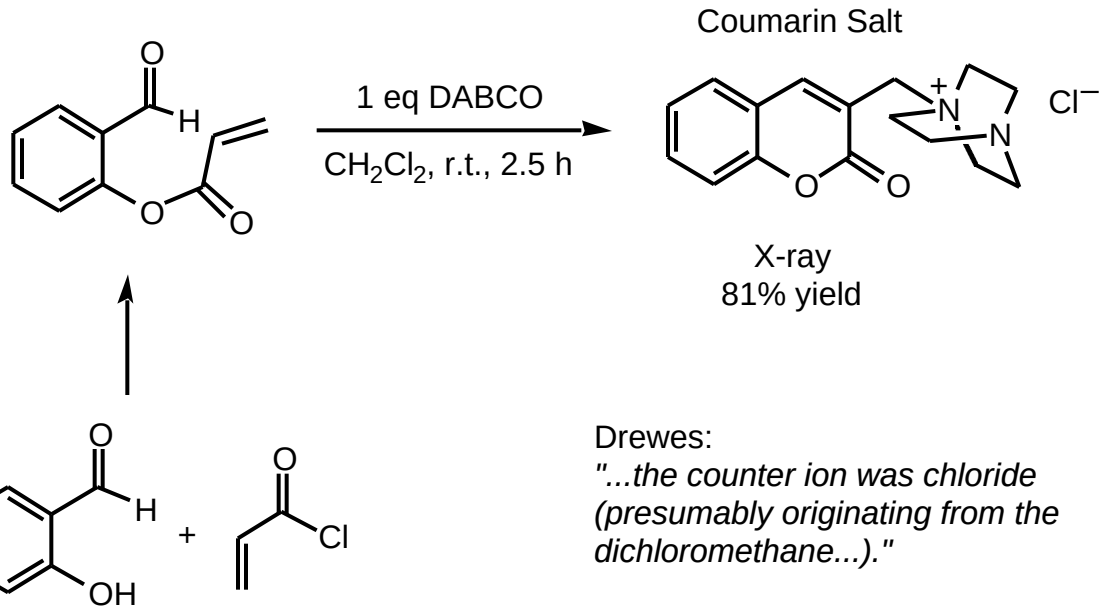



initially formed eliminates

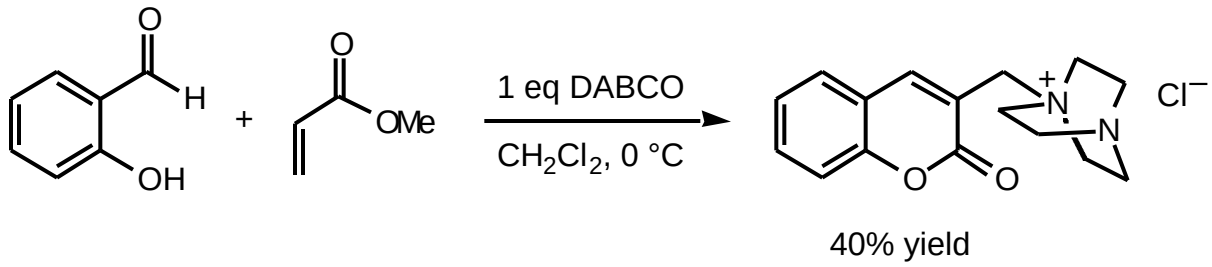
E1cB is also possible

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

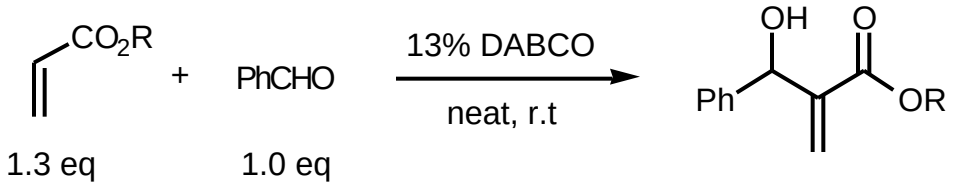



*Or...*




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

# Effects of Acrylate Ester Substituent




1.3 eq 1.0 eq

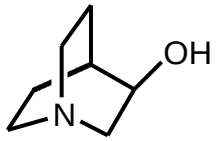
| R | time (days) | yield (%) |
|---|---|---|
| Me | 6 | 89 |
| Et | 7 | 79 |
| Bn | 2 | 88 |
| *n*-$C_{10}H_{21}$ | 14 | 75 |
| *t*-Bu | 65 | 65 |
| 2-adamantyl | 62 | 40 |
| $CH_2CH_2F$ | 3 | 81 |
| $CH_2CH_2Br$ | 2 | NR |
| **$CH_2CF_3$** | **15 h** | **58** |
| $CH_2CH_2OMe$ | 4 | 89 |
| $CH_2CH_2NMe_2$ | 8 | 82 |
| $(CH_2)_6Cl$ | 15 | NR |

- For aryl substituted benzyl ethers, no clear relation between σ 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.

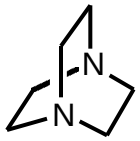
# Bases for Catalysis

*p$K_a$ $H_2O$ (DMSO)*



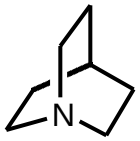

3-Hydroxyquinuclidine (3-QDL)
9.5 (~8.5)

>



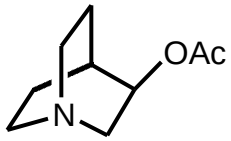

DABCO
2.97, 8.82 (2.97, 8.93)

>



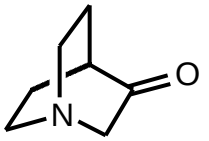

Quinuclidine
10.9 (9.80)

>>

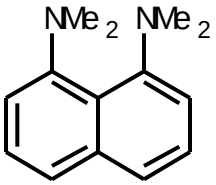



3-Acetoxyquinuclidine

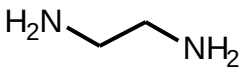
or



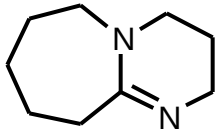

3-Quinuclidone
6.9




Proton sponge
12.0 (7.50)




6.90, 9.95



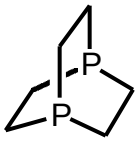

DBU
(~12)

*Sterics also important:*

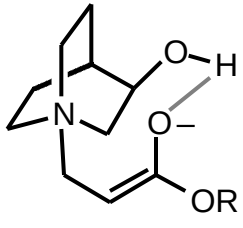
$Me_2NH$ > $Me_2NEt$ > $MeNEt_2$ > $NEt_3$ 10.75 (9.00)

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

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

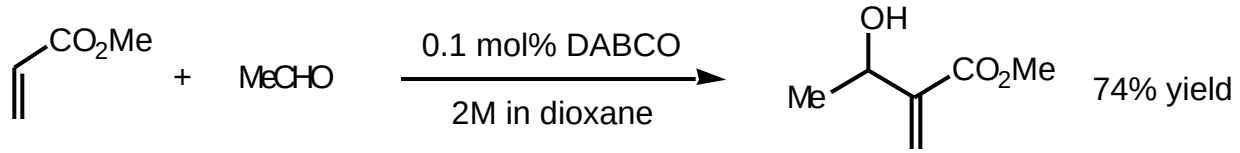



unreactive



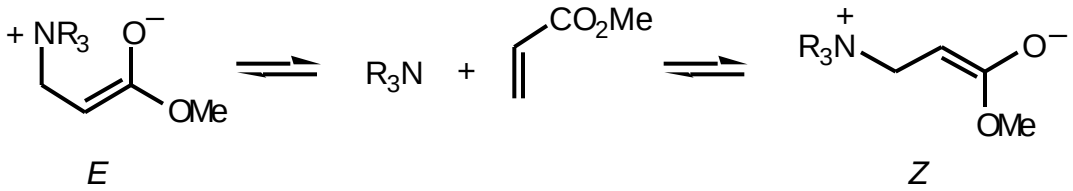

...or could accelerate protonation of intermediate, as any alcohol additive will accelerate reaction

# Temperature Effects




25 °C 1 week
**0 °C 8 hours!**

- 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).

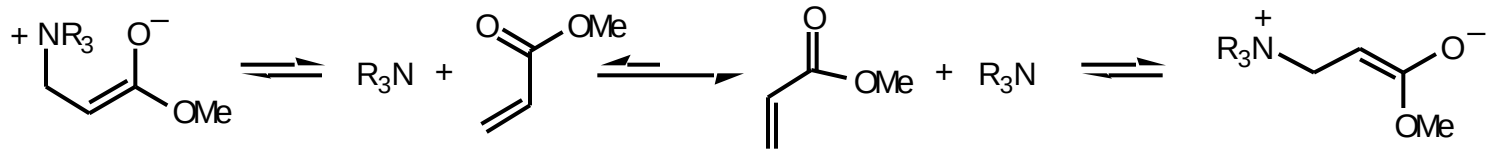



*E* *Z*

*Which enolate is more stable and which is more reactive?*

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

# Enolate Geometry




*E*

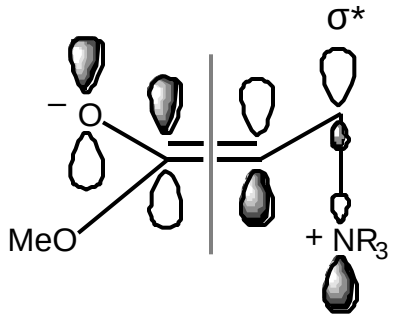
**Thermodynamic**

- less charge seperation
- less reactive

*Z*

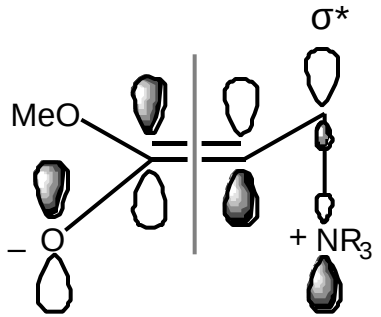
**Kinetic**

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



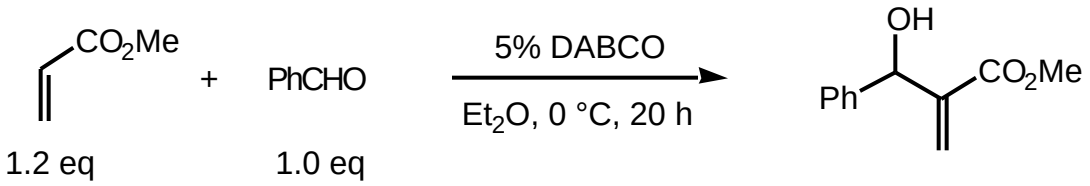

$4\pi\ e^-$

HOMO



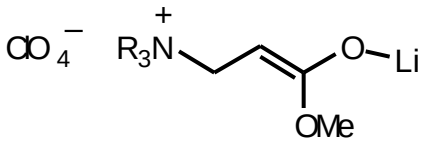

better conjugation into σ*

# 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.

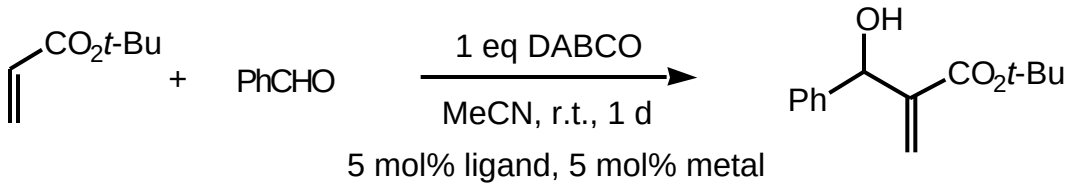



Stablize enolate?

- 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



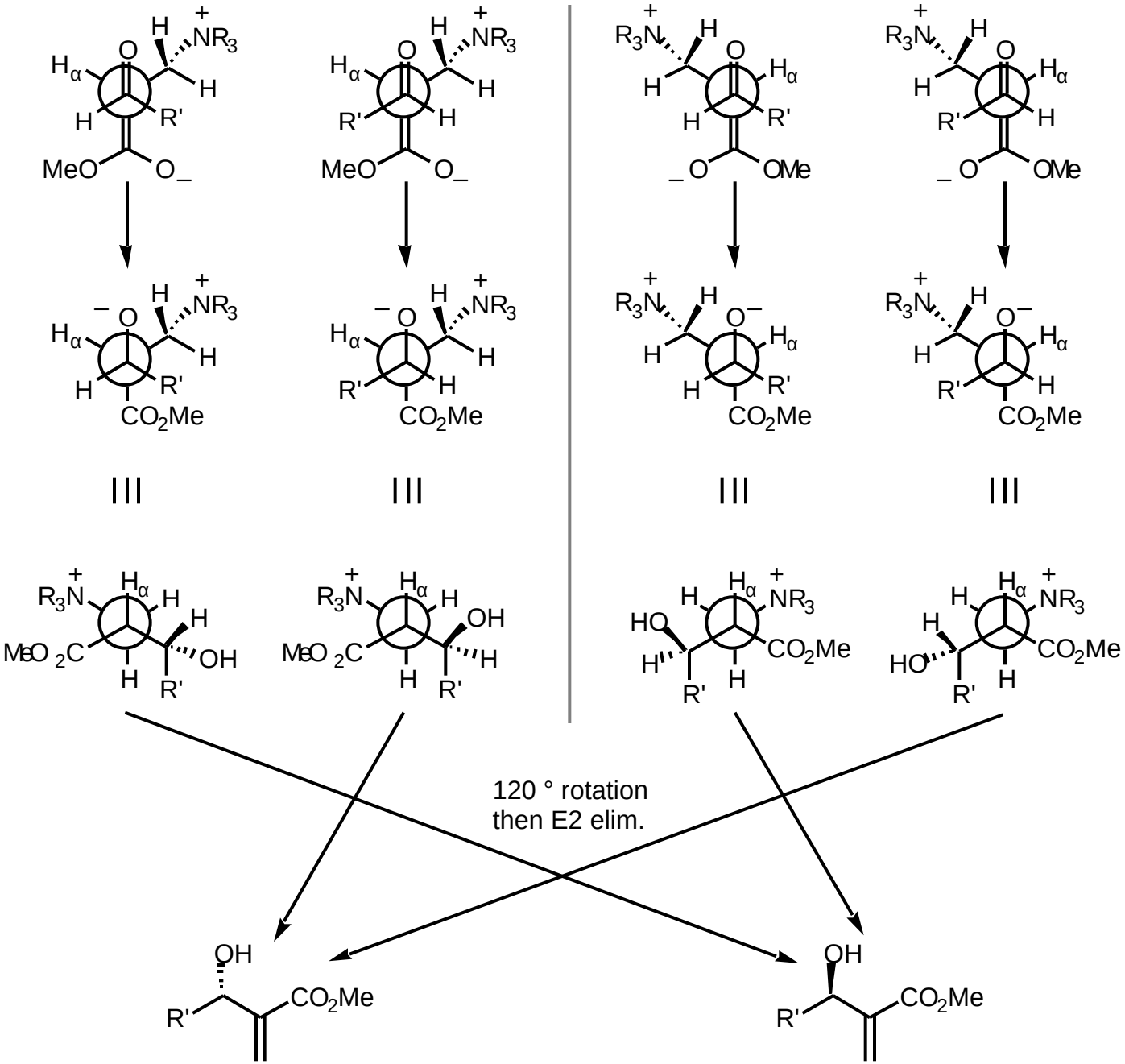

**Relative Reaction Rates**

| 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 | | | |
| *N*-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.

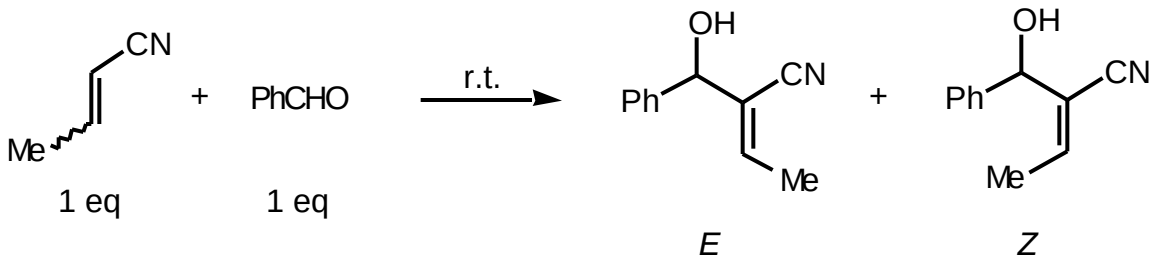
# Possible Stereoisomers




Assumptions:

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

# *E/Z* Selectivity with Crotononitrile



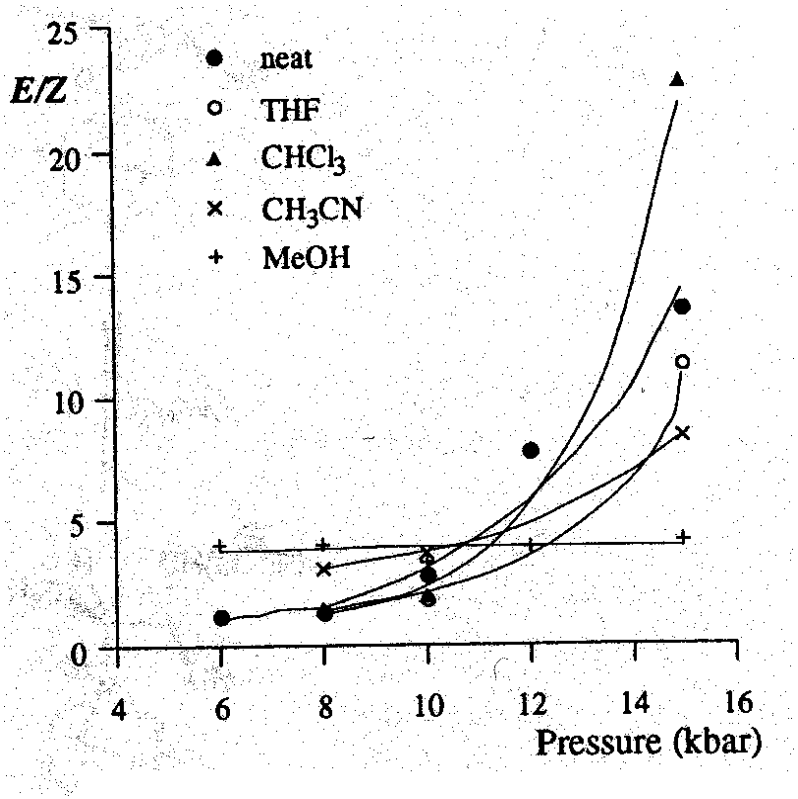

1 eq 1 eq *E* *Z*

| Solvent | *E/Z* ratio |
|---|---|
| neat | 1.2 : 1 |
| THF | 1.4 : 1 |
| $CHCl_3$ | 1.5 : 1 |
| $CH_3CN$ | 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, $CHCl_3$ 50 vol%

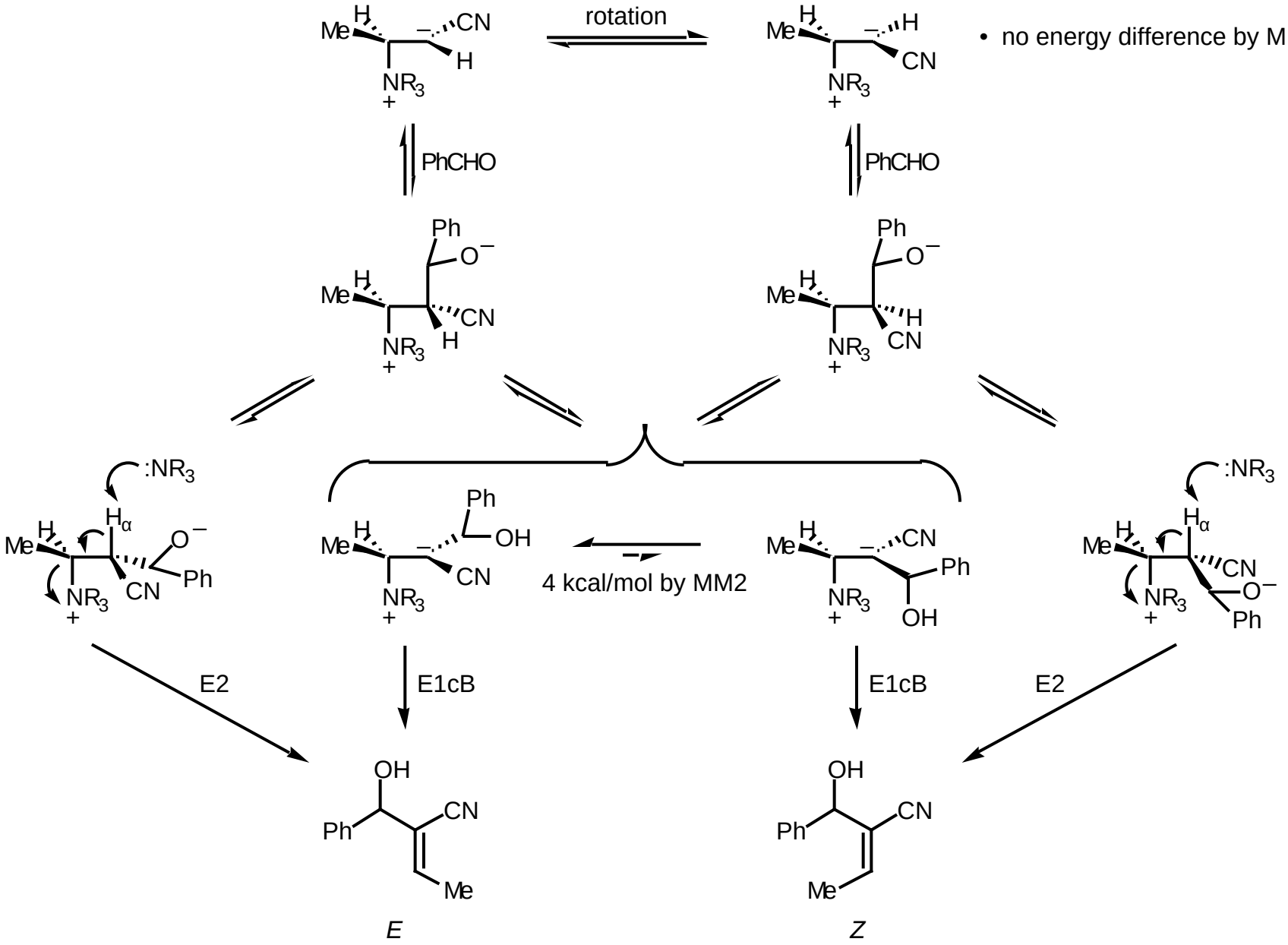



5 mol% DABCO,17 h, solvent 50 vol%

- *E* and *Z* crotononitrile is easily isomerized under the reaction conditions.
- Products did not undergo retro-Baylis-Hillman.

Rozendaal, E. L. M.; Voss, B. M. W.; Scheeren, H. W. *Tetrahedron* **1993**, *49*, 6931-6936.

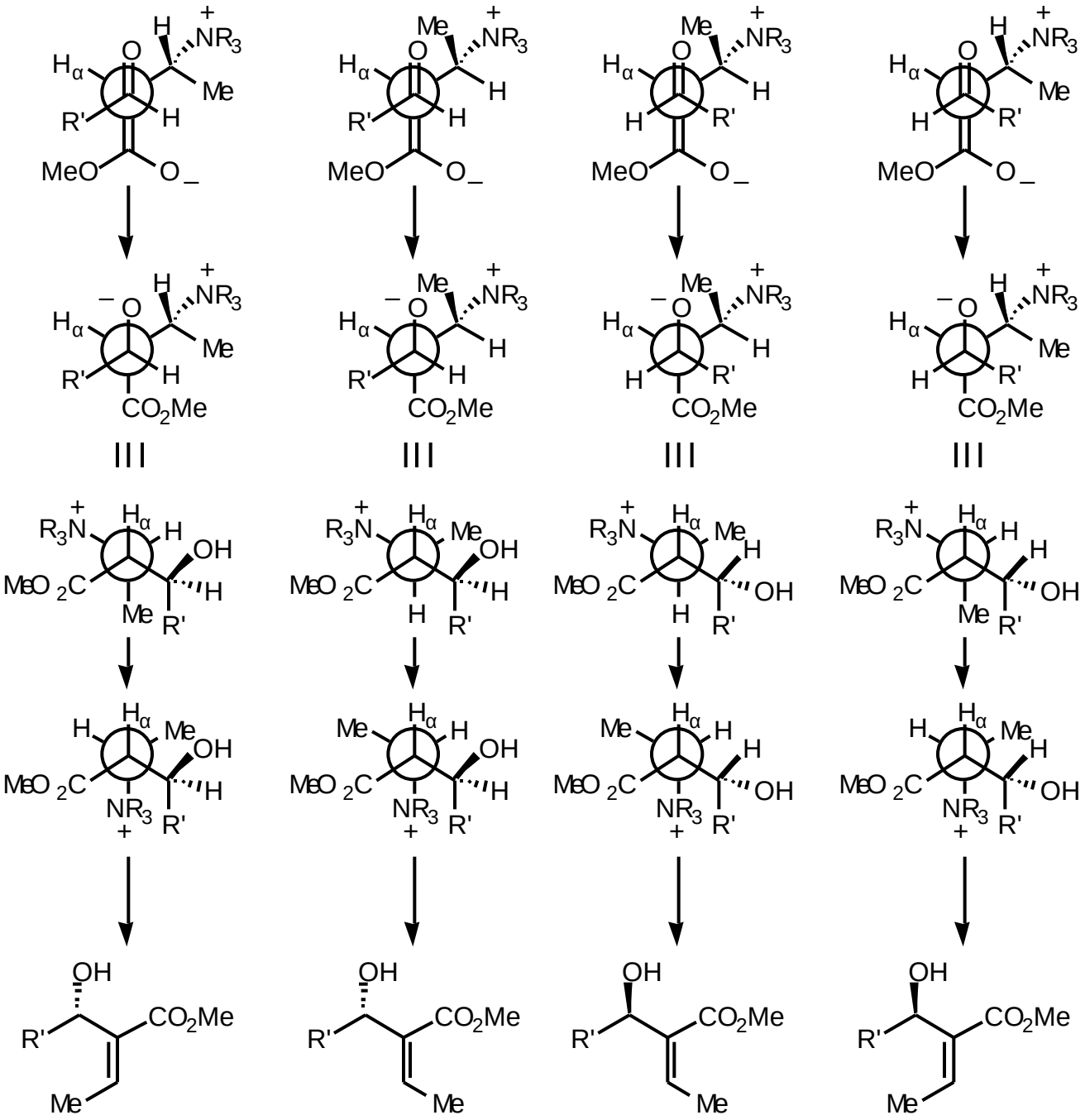
# *E/Z* Selectivity Rationalization






Rozendaal, E. L. M.; Voss, B. M. W.; Scheeren, H. W. *Tetrahedron* **1993**, *49*, 6931-6936.

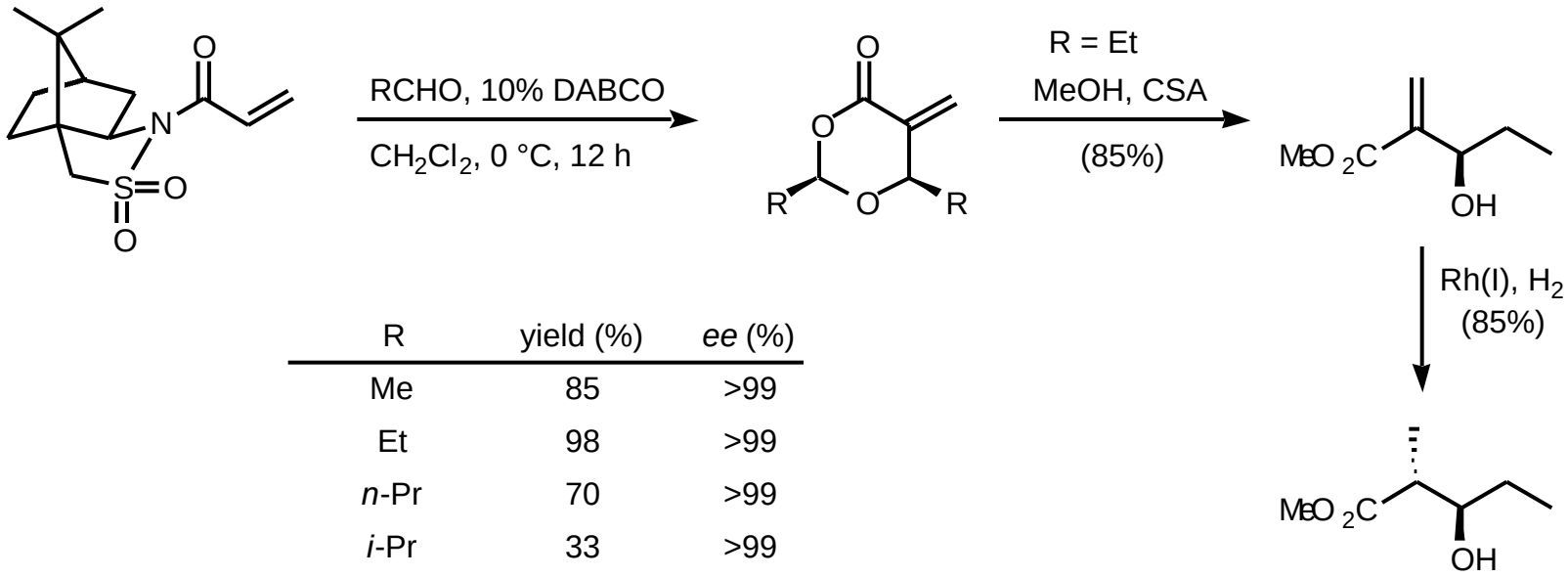
# Possible Stereoisomers for Methylcrotonate



Assumptions:

- *E* enolate formed
- E2 favored over E1 pathway, only after rotation of ammonium to *anti* conformation
- $-NR_3^+$ is orthogonal to π face (stereoelectronics)
- only **one** π 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

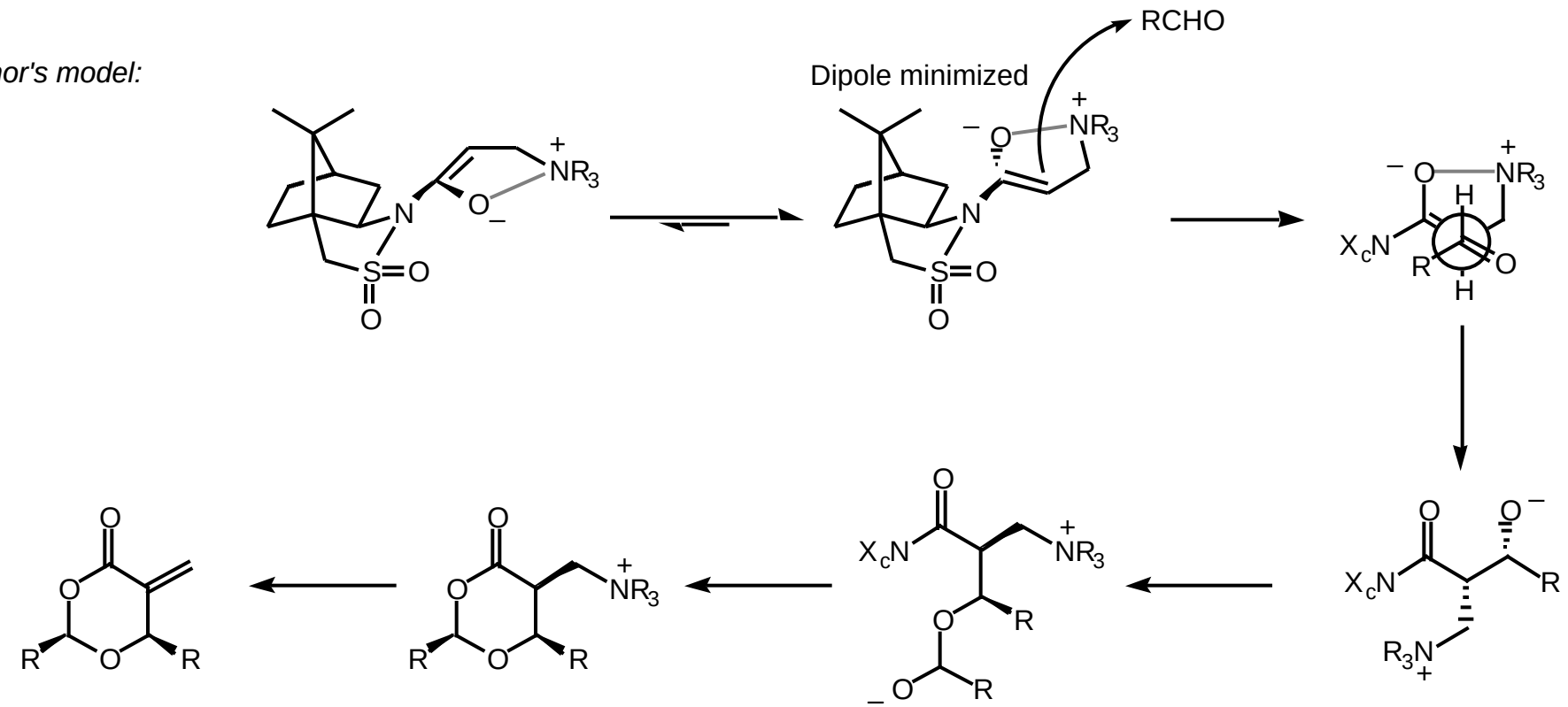



| R | yield (%) | *ee* (%) |
|---|---|---|
| Me | 85 | >99 |
| Et | 98 | >99 |
| *n*-Pr | 70 | >99 |
| *i*-Pr | 33 | >99 |
| $PhCH_2CH_2$ | 68 | >99 |
| $AcOCH_2$ | 68 | >99 |
| $(CH_3)_2CHCH_2$ | 67 | >99 |
| Ph | 0 | |

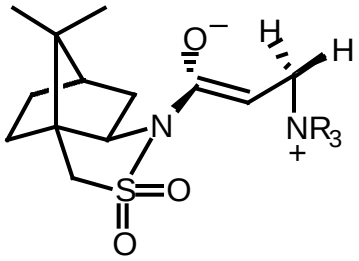
Leahy, J. W.; *et. al. J. Am. Chem Soc.* **1997**, *119*, 4317-4318.

# Camphorsultam Acrylate Mechanism

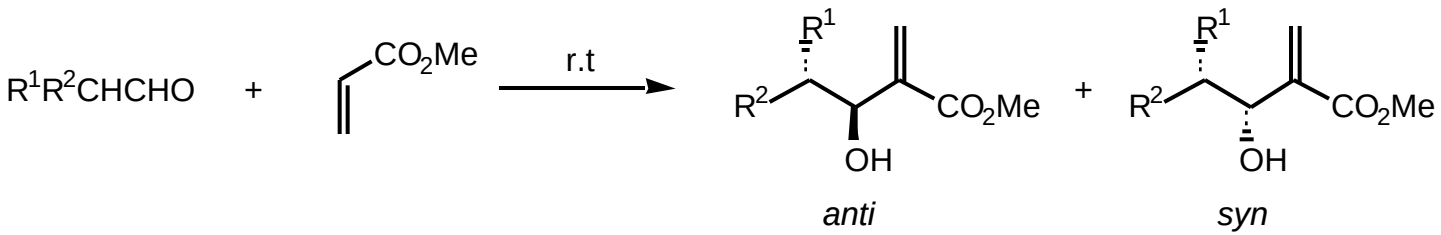
*Author's model:*



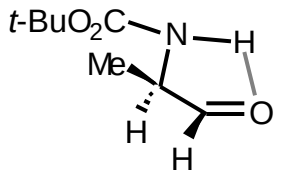

*Alternative (stereoelectronics):*



# α-Branched Aldehydes: Modest Felkin-Anh Selection




| $R^1$ | $R^2$ | Conditions | yield (%) | *anti:syn* |
|---|---|---|---|---|
| $MeOCH_2O$ | Me | DABCO, 4 d | 55 | 70:30 |
| $MeOCH_2O$ | Me | 3-QDL, 1.5 d | 60 | 72:28 |
| $BnOCH_2O$ | Me | DABCO, 6 d | 42 | 70:30 |
| $MeOCH_2O$ | Ph | DABCO, 10 d | 42 | 37:63 |
| Me | *n*-Pr | 3-QDL, 60 d | 30 | 35:65 |
| -OC(Me)$_2$OCH$_2$- | | DABCO, 55 d | 62 | 69:31 |
| $NHCO_2t$-Bu | Me | DABCO, 7 d | 80 | 26:74 |
| *N*-Phthalimidyl | Me | DABCO, 3.5 d | 28 | 46:54 |
| -N($CO_2t$-Bu)C$(Me)_2OCH_2$- | | DABCO, 11 d | 43 | 89:11 |

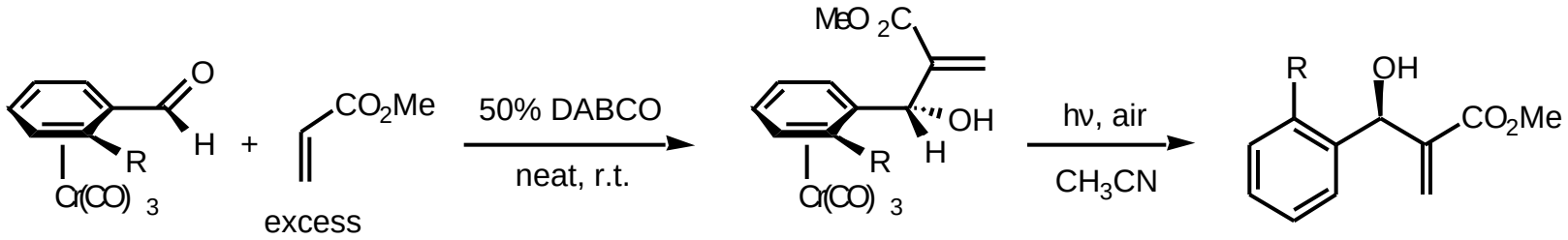



*syn* selective

- Varying the amount of catalyst only affects the rate, not selectivity.
- *Anti* and *syn* drawn incorrectly in review, should be reversed.

Ciganek, E. *Org. React.* **1997**, *51*, 217-218.

# Chiral Aldehydes: Chromium Auxiliary

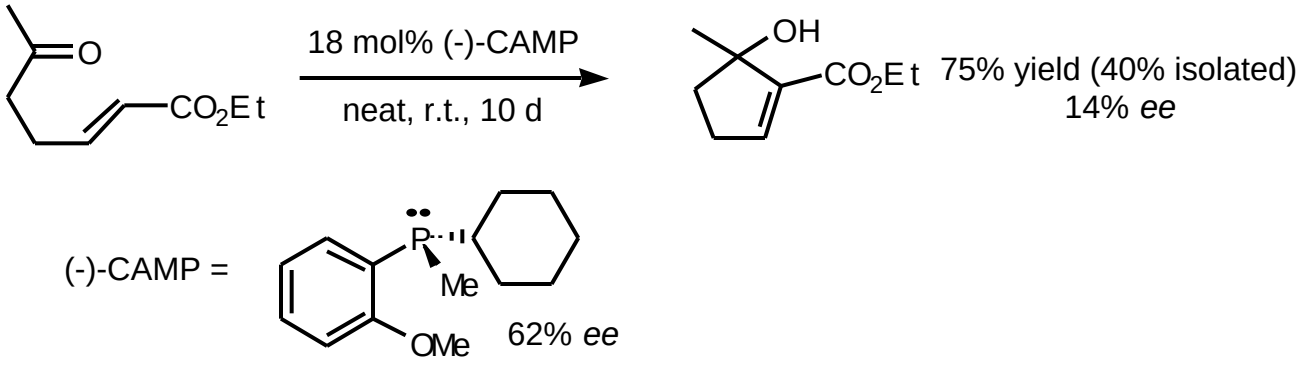



| aldehyde | R | time (h) | yield (%) | dr |
|---|---|---|---|---|
| *rac* | OMe | 93 | 87 | >98:2 |
| *rac* | Cl | 6 | 89 | >98:2 |
| *rac* | F | 7 | 92 | 92:8 |
| *rac* | Me | 58 | 90 | 84:16 |
| *S*-(+) | OMe | 93 | 85 | >98:2 |
| *S*-(+) | Cl | 8 | 97 | >98:2 |

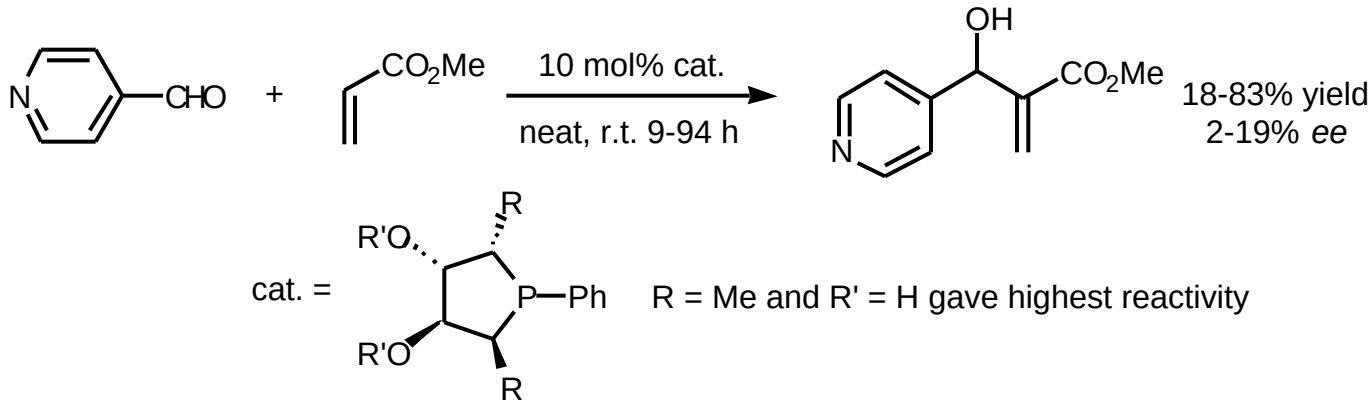
- dr determined by 200 MHz $^{1}$H NMR
- *N*-Tosyl arylimine chromium complex also reacts

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

# Chiral Phosphine Catalysts

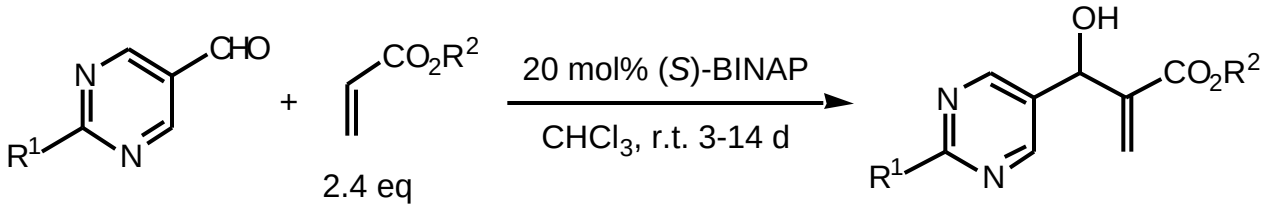



Frater, G.; *et al. Tetrahedron Lett.* **1992**, *33*, 1045-1048.




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

# The High Point of Chiral Phosphine Catalysts



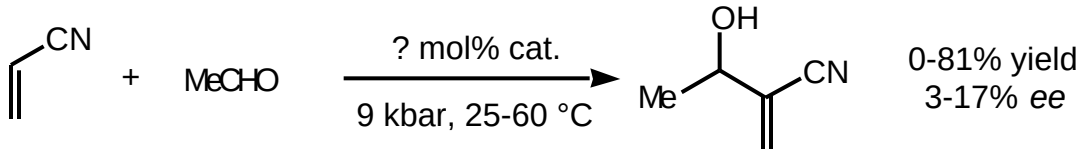

| $R^1$ | $R^2$ | time (d) | yield (%) | *ee* (%) |
|---|---|---|---|---|
| H | *i*-Pr | 4 | 8 | 9 |
| H | Et | 3 | 12 | 25 |
| H | Me | 4 | 24 | 44 |
| Me | Me | 14 | 18 | 37 |
| Me | Me | 3 | 26 | 30[a] |

[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.

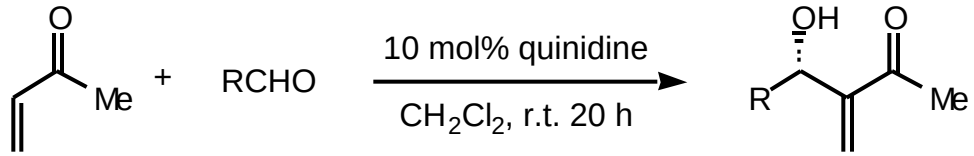
# Naturally Occurring Alkaloids as Chiral Catalysts




0-81% yield
3-17% *ee*

- (-)-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.




40-50% yield

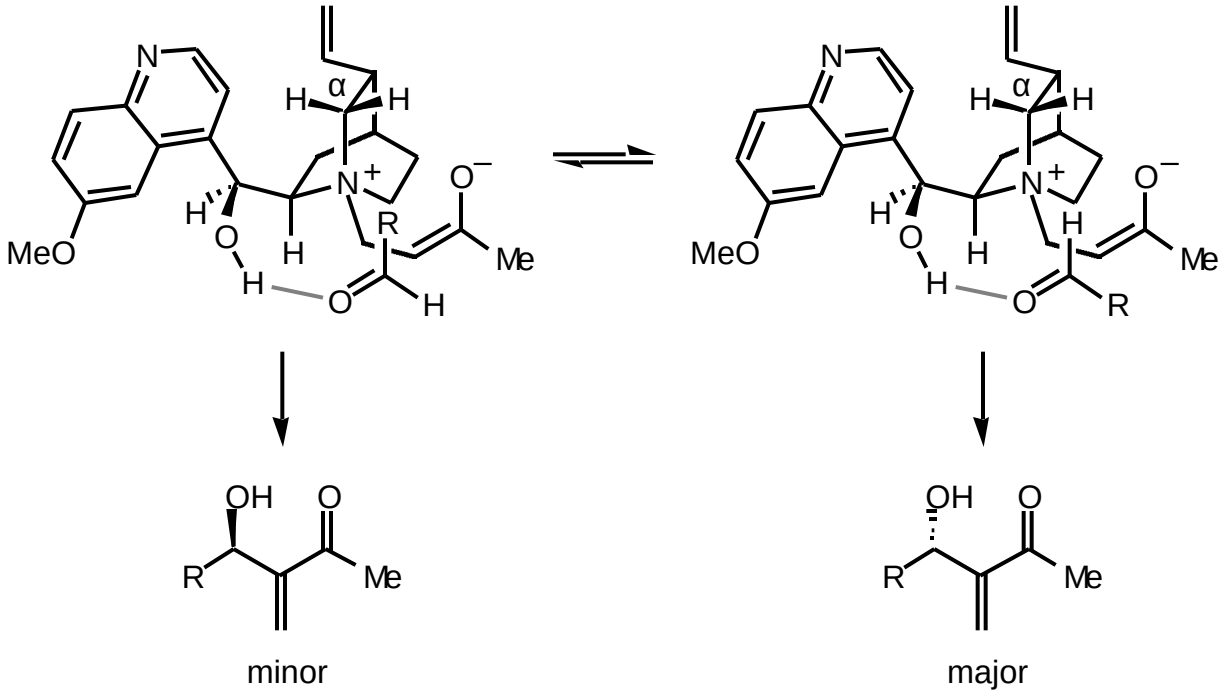
| R | Pressure | *ee* (%) |
|---|---|---|
| *n*-Pr | 3 kbar | 18 |
| *n*-$C_9H_{19}$ | 10 kbar | 31 |
| *i*-Pr | 3 kbar | 37 |
| *c*-hex | 3 kbar | 45 |

- 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

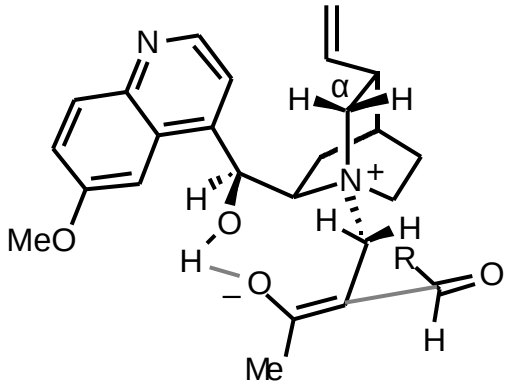
*Author's model:*




- $C_\alpha$ hydrogens control π 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:*

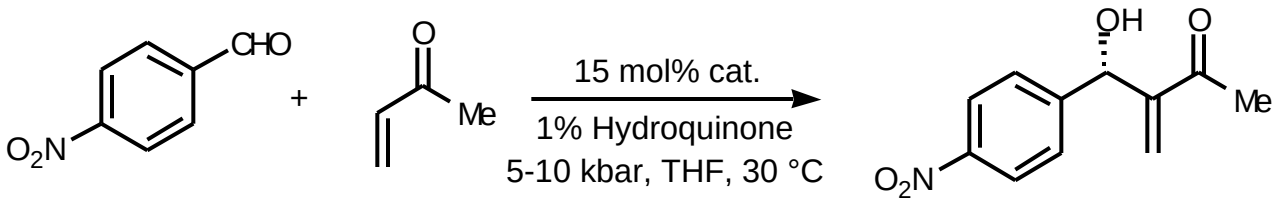
major



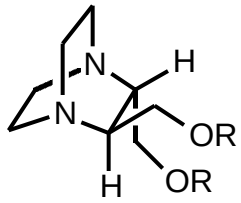



Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015-1024.

# $C_2$ Symmetric DABCO Catalyst



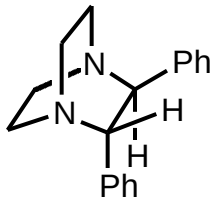

cat. =

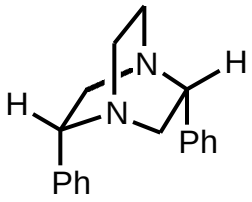


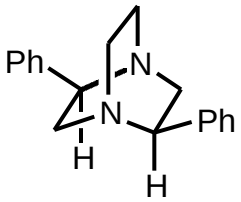

| R | time (h) | yield (%) | *ee* (%) |
|---|---|---|---|
| Bn | 12 | 45 | 47 |
| TBDPS | 12 | 23 | 34 |
| TIPS | 28 | 33 | 19 |
| Ph | 16 | 60 | 35 |
| Mesityl | 28 | 67 | 16 |
| 1-naphthyl | 16 | 66 | 42 |
| 1-anthranyl | 24 | 9 | 11 |
| 1-napththoyl | 17 | 68 | 15 |
| *N*-Cbz-Gly | 24 | 63 | 21 |

- racemic alcohol product can be easily resolved by kinetic resolution with Sharpless asymmetric epoxidation

- other chiral DABCO's made, but not tested...



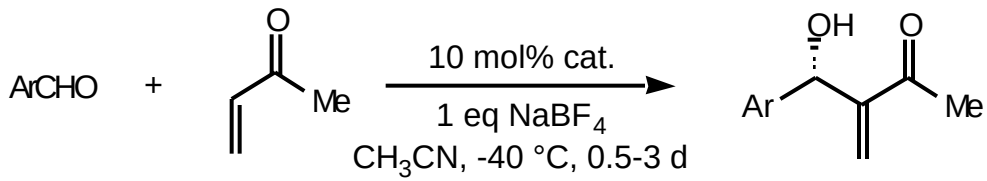





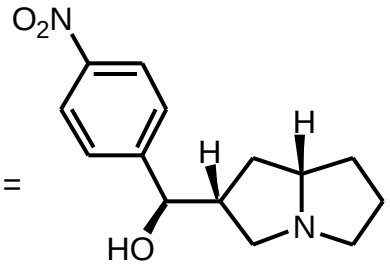

Hirama, M.; *et. al. Tetrahedron: Asymm.* **1995**, *6*, 1241-1244.

# Chiral Pyrrolizidine Catalyst

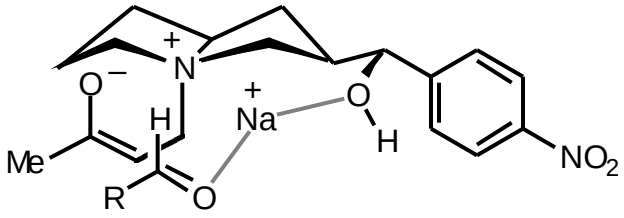



| Ar | yield (%) | *ee* (%) |
|---|---|---|
| 2-$NO_2$ | 71 | 67 |
| 2-F | 31 | 63 |
| 2-Cl | 58 | 72 |
| 2-Br | 63 | 71 |
| 3-$NO_2$ | 51 | 37 |
| 2-pyridyl | 83 | 21 |
| 3-pyridyl | 93 | 49 |
| 4-quinolinyl | 63 | 70 |
| 4-$NO_2$ | 17 | 39 |

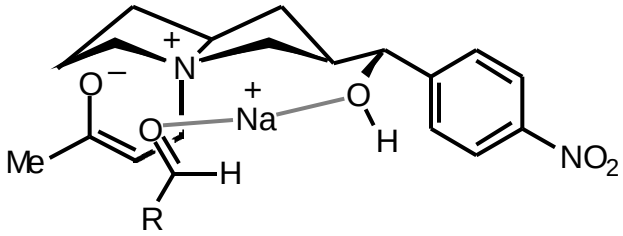
cat. =




*Author's model:*



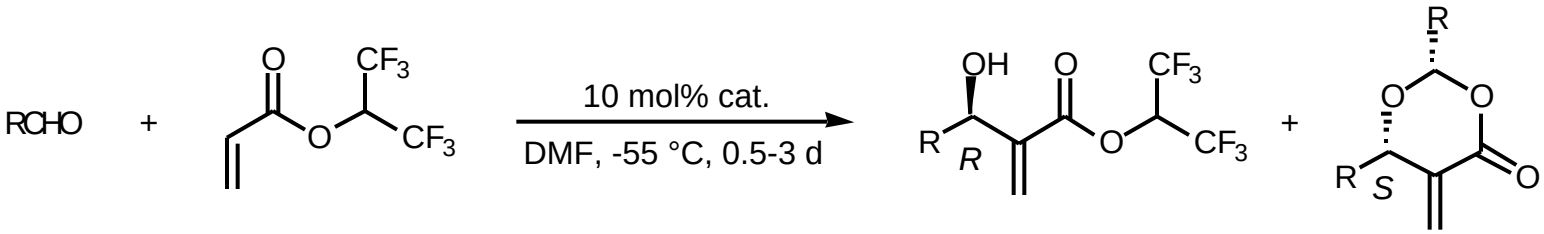

favored



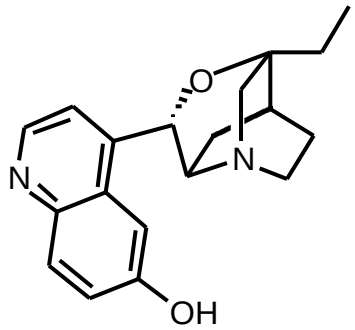

disfavored

Barrett, A. G. M.; *et. al. Chem. Commun.* **1998**, 2533-2534.

# Quinidine Ether Catalyst




cat. =




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

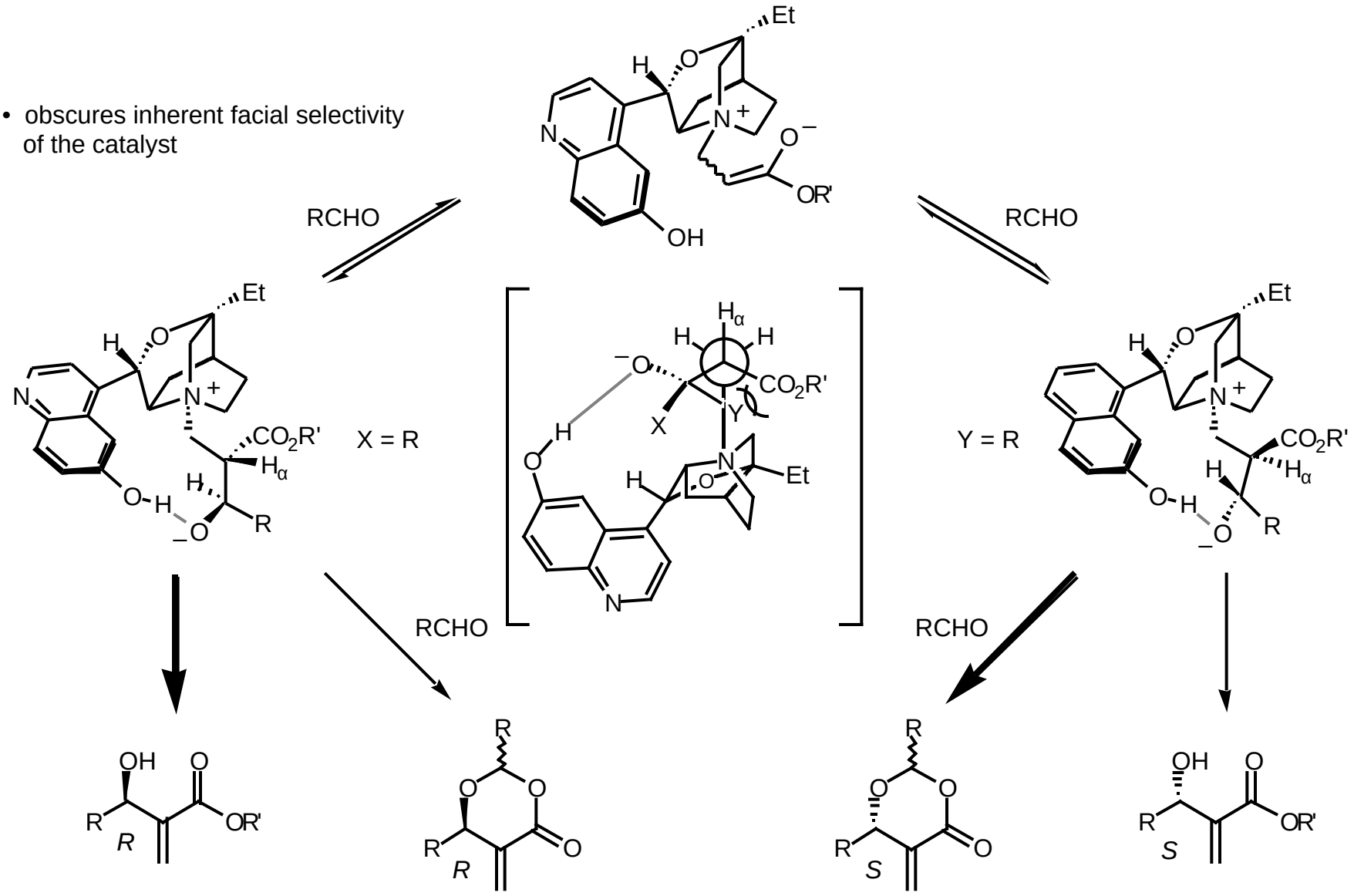
| | ester | | dioxanone | |
|---|---|---|---|---|
| R | yield (%) | *ee* (%), (config) | yield (%) | *ee* (%), (config) |
| *p*-$NO_2$ | 58 | 91 (*R*) | 11 | 4 (*R*) |
| Ph | 57 | 95 (*R*) | -- | -- |
| (*E*)-PhCH=CH | 50 | 92 (*R*) | -- | -- |
| Et | 40 | 97 (*R*) | 22 | 27 (*S*) |
| *i*-Bu | 51 | 99 (*R*) | 18 | 18 (*S*) |
| *i*-Pr | 36 | 99 (*R*) | 25 | 25 (*S*) |
| *c*-Hex | 31 | 99 (*R*) | 23 | 23 (*S*) |
| *t*-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.

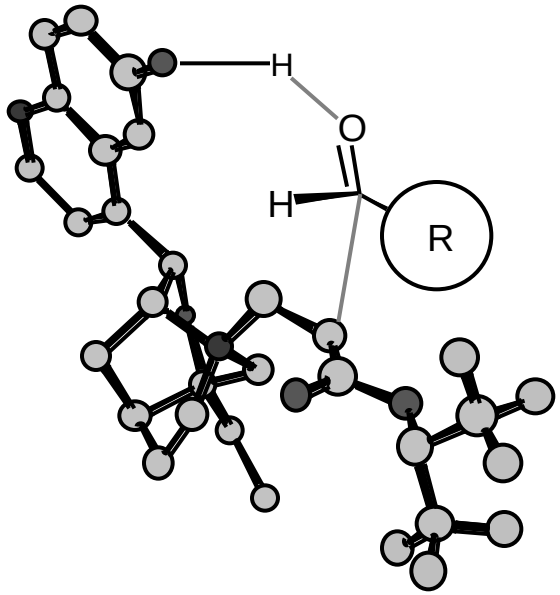
Hatakeyama, S.; *et. al J. Am. Chem. Soc.* **1999**, *121*, 10219-10220.

# Proposed Mechanism: Partial Kinetic Resolution

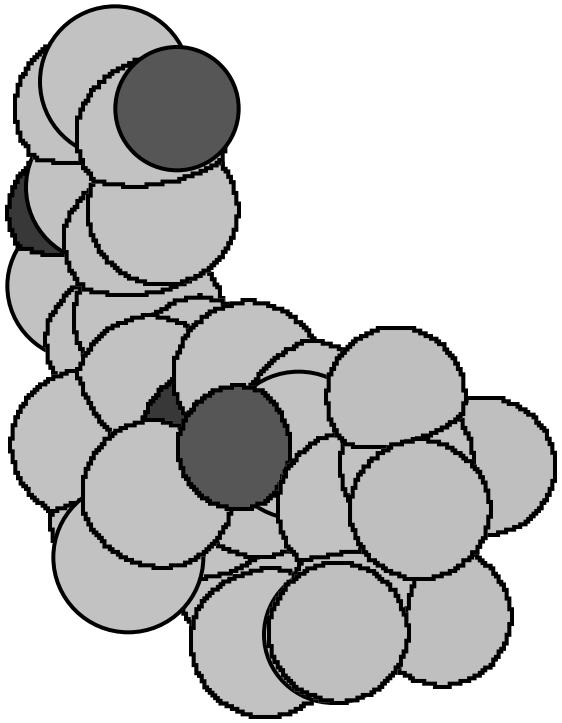
- obscures inherent facial selectivity of the catalyst

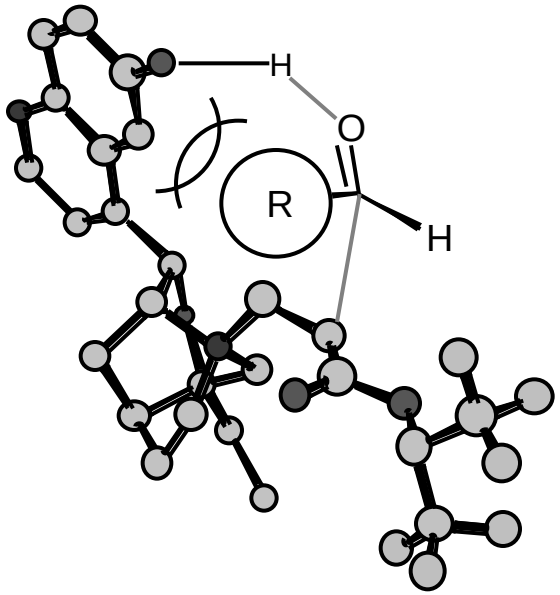


# A Model for Facial Selectivity




Favored



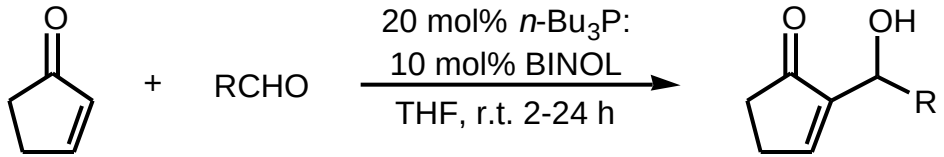



Disfavored

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

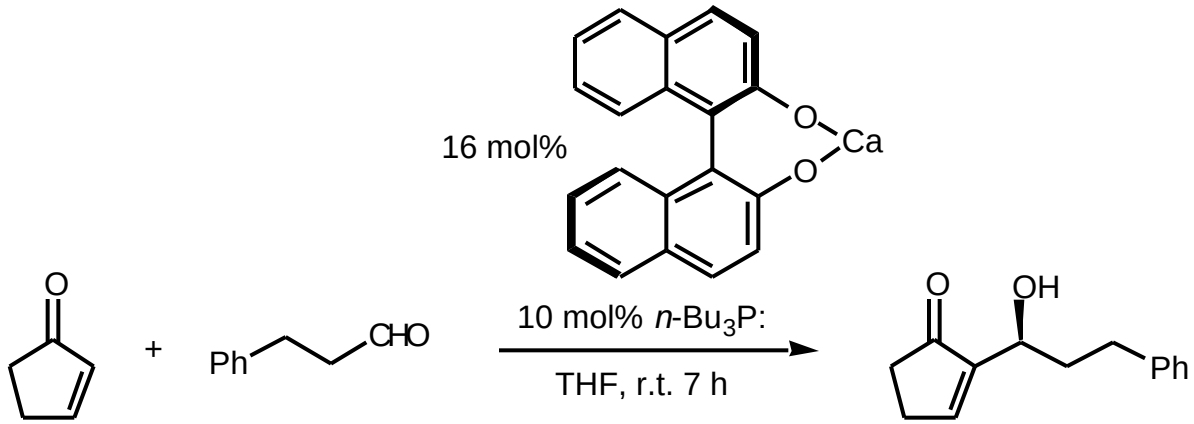
- Catalyst orthogonal to opposite π face of the enolate leads to same major enantiomer after elimination.

# BINOL as an Additive or Ligand




| R | yield (%) |
|---|---|
| $n$-$C_7H_{15}$ | quant. |
| Ph | 92 |
| $MEMO(CH_2)_3$ | 98 |
| Et | 91 |
| $PhCH_2CH_2$ | quant. |

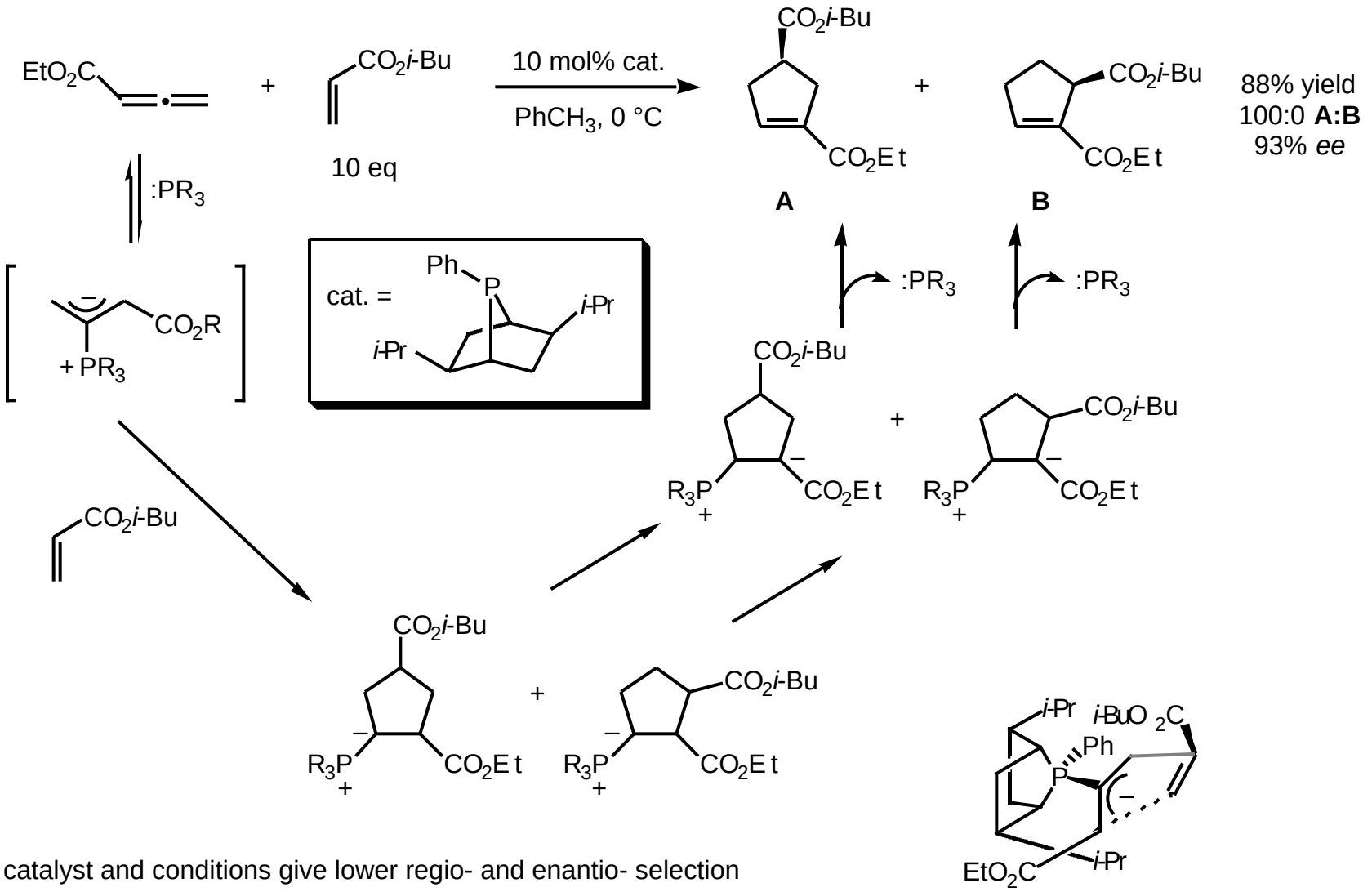
- *ee* were all <10%
- phenol also accelerates reaction
- other acrylates also tolerated




62% yield, 56% *ee*

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

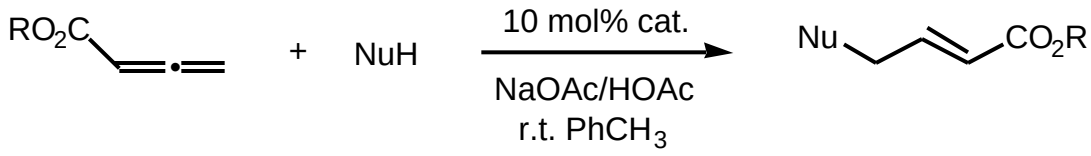
# A Related Phosphine Catalyzed Reaction

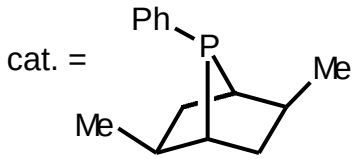


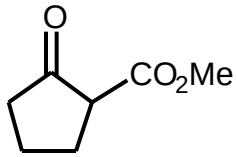
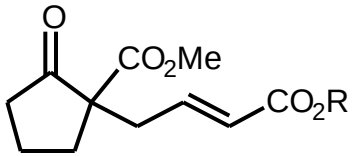
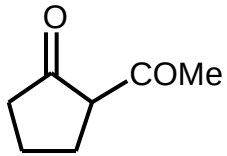
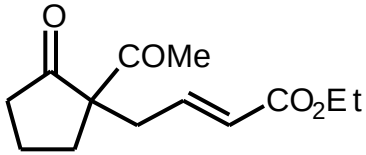
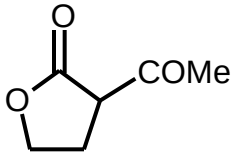
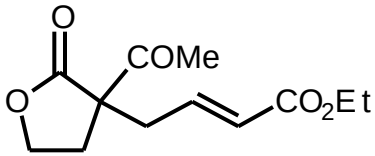
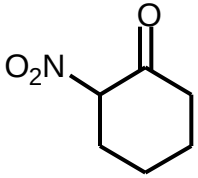
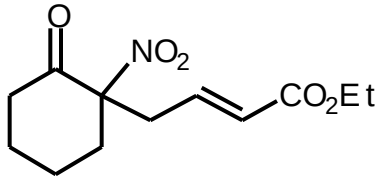
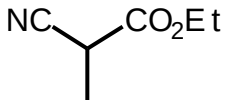
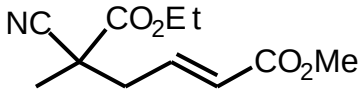

- other catalyst and conditions give lower regio- and enantio- selection


Zhang, X.; *et. al. J. Am. Chem. Soc.* **1997**, *119*, 3836-3837.
Lu, X.; *et. al. J. Org. Chem.* **1995**, *60*, 2906-2908.

# Phosphine Catalyzed Addition



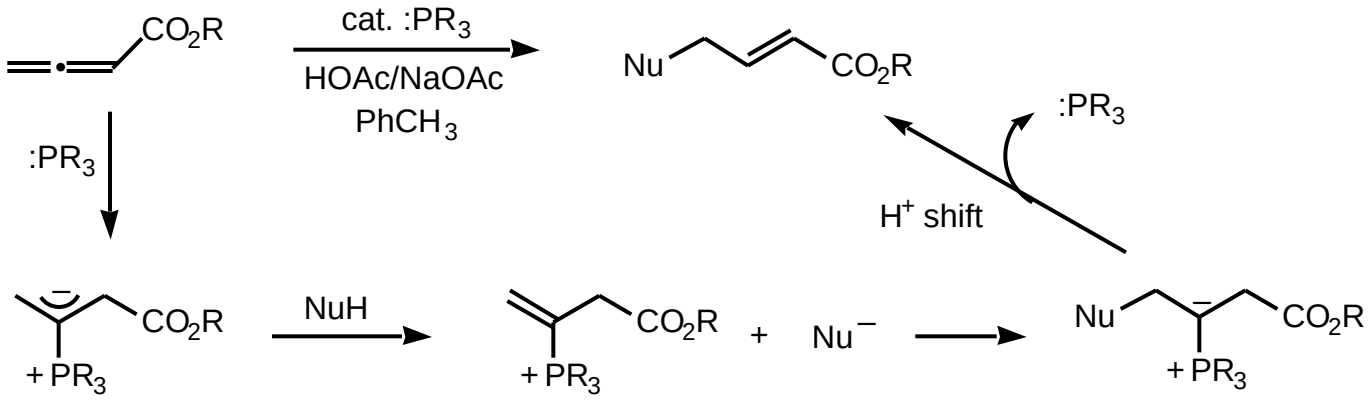

| NuH | R | yield (%) | *ee* (%) | product |
|---|---|---|---|---|
|  | Me | 80 | 73 |  |
| | Et | 76 | 74 | |
| | *t*-Bu | 74 | 75 | |
|  | Et | 67 | 56 |  |
|  | Et | 83 | 48 |  |
|  | Et | 31 | 41 |  |
|  | Me | 47 | 45 |  |



Zhang, X.; *et. al. J. Org. Chem.* **1998**, *63*, 5631-5635.

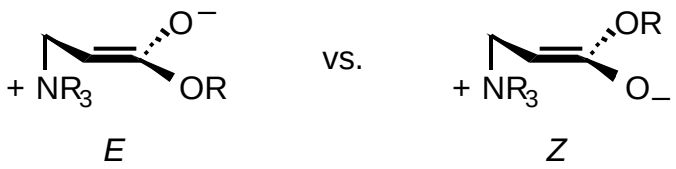
# Addition Mechanism

*Author's proposal:*

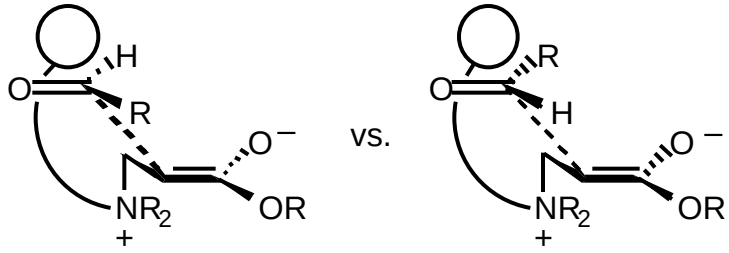


# Recipe for a Good Catalyst?

*Control enolate geometry...*

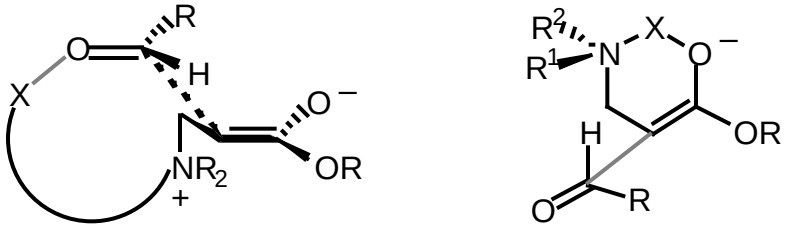



*Control aldehyde π face...*




- for substituted acrylates, must control enolate π facial selectivity
- chirality on catalyst may also gear ester substituent to influence aldehyde approach

*or*



# 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.