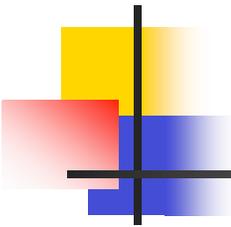


The aza-Baylis-Hillman Reaction: Mechanism, Asymmetric  
Catalysis, & Abnormal Adducts

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Larry Wolf  
SED Group Meeting  
04-10-07



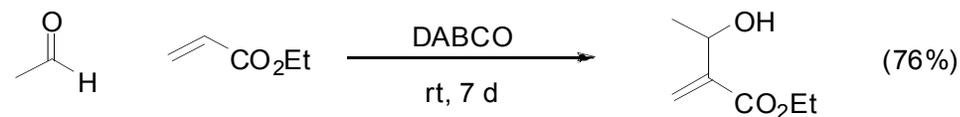
## Outline

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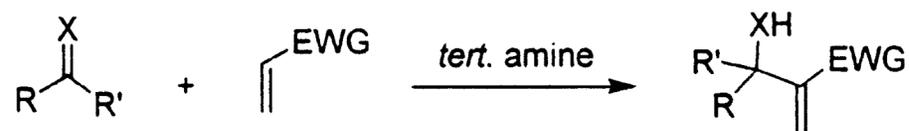
- Brief historical account and Utility
- Mechanism
- Different methods for asymmetric catalysis
- Abnormal aza-Baylis-Hillman adducts

## The Baylis-Hillman or the Morita-Baylis-Hillman Reaction?

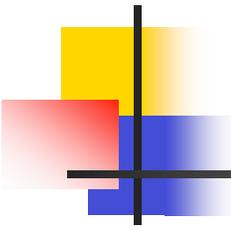
- Baylis and Hillman reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of DABCO to give  $\alpha$ -hydroxyethylated products in 1972.



- Although, Morita, 5 years earlier, reported the same reaction with the exception that tertiary phosphines were used as the catalysts, and he also proposed the accepted mechanism at this time



- The reactions will be termed the MBH and AMBH reaction throughout this talk. Both uses are found in the literature.



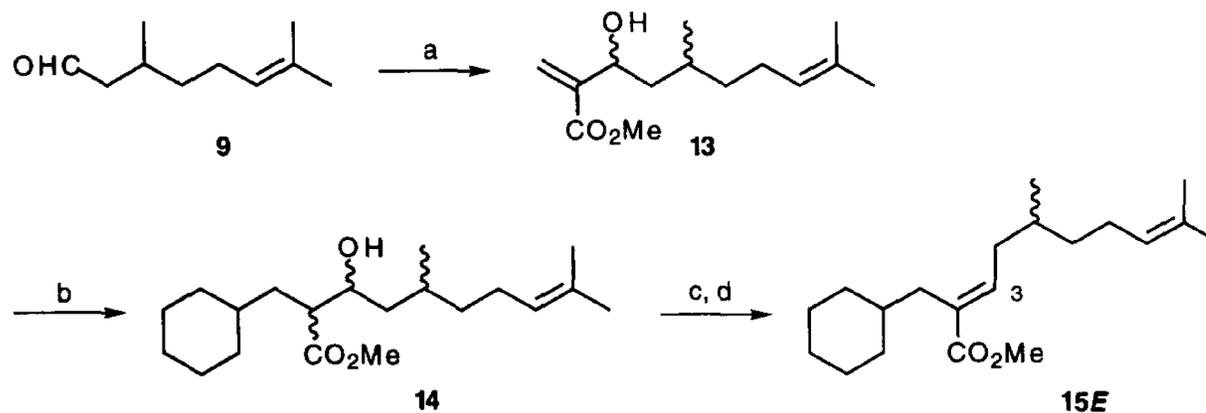
## Pros and Cons

### Pros

- unique C-C bond forming reaction
- can generate a high degree of functionality
- atom economical
- potential has not yet been fully realized

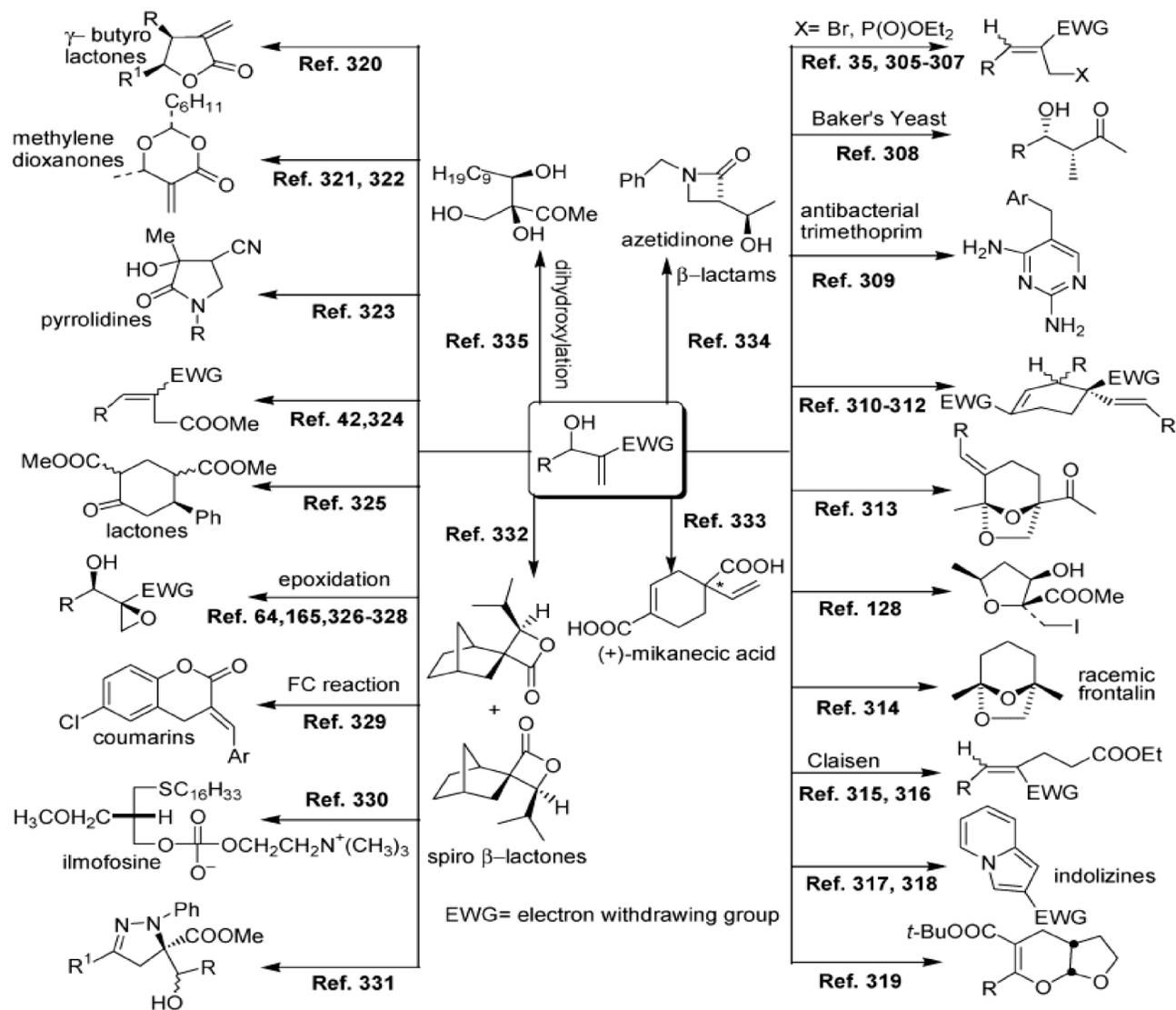
### Cons

- reaction times can at times be quite long (days-weeks-a month!), although improvements have been made
- somewhat underdeveloped
- Stereochemistry is difficult to control

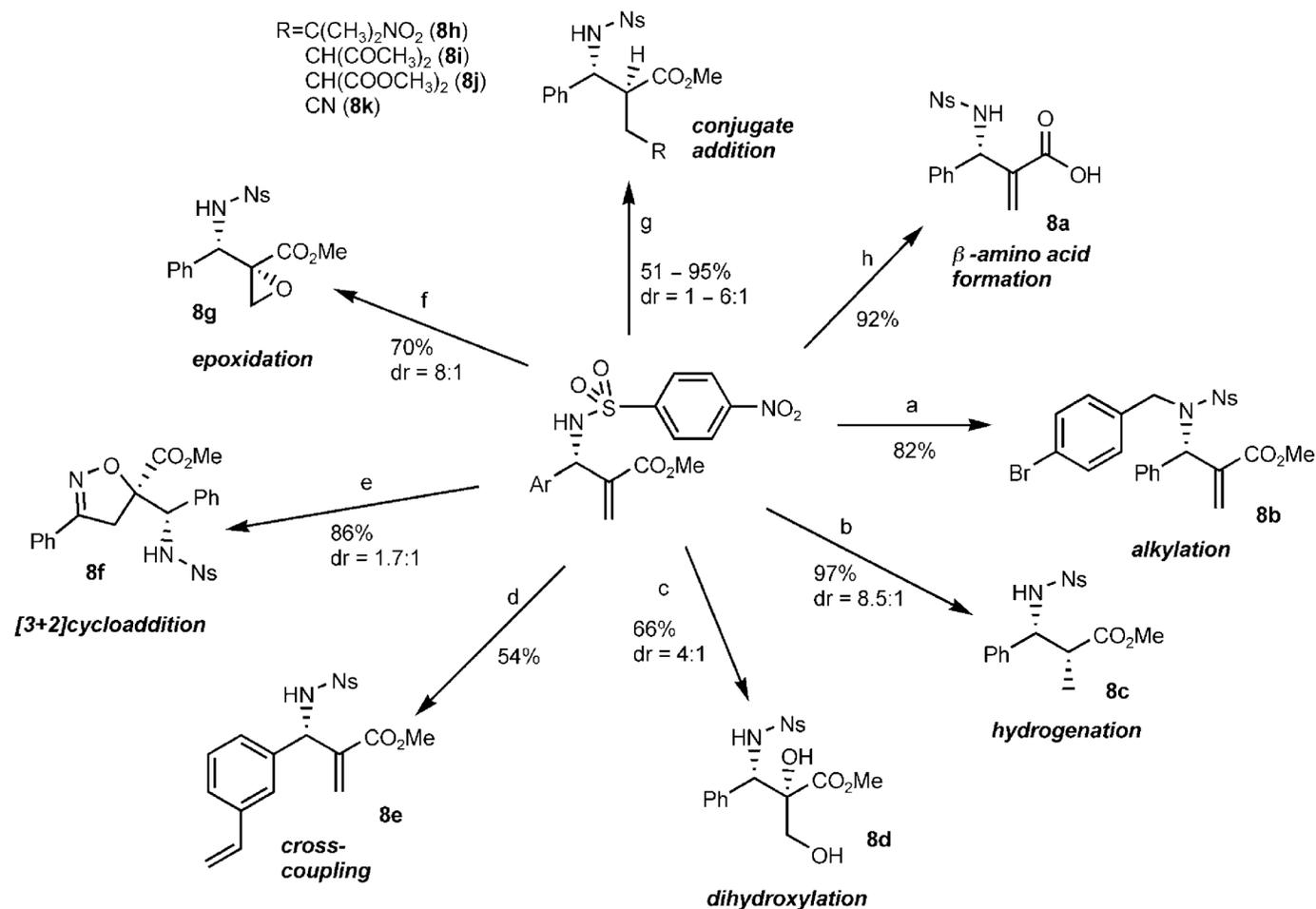


**Scheme 4.** a) methyl acrylate, quinuclidin-3-ol, 35 days (88%); b) cyclohexyl bromide, *n*-Bu<sub>3</sub>SnH, Et<sub>2</sub>O, hv (300 W tungsten lamp), 24 h (38%); c) MsCl, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 0.25 h; d) DBU, toluene, reflux, 9 h (94%, **15E/15Z** = 93/7)

## Utility of Morita-Baylis-Hillman Adducts



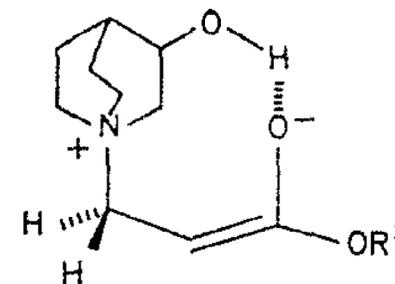
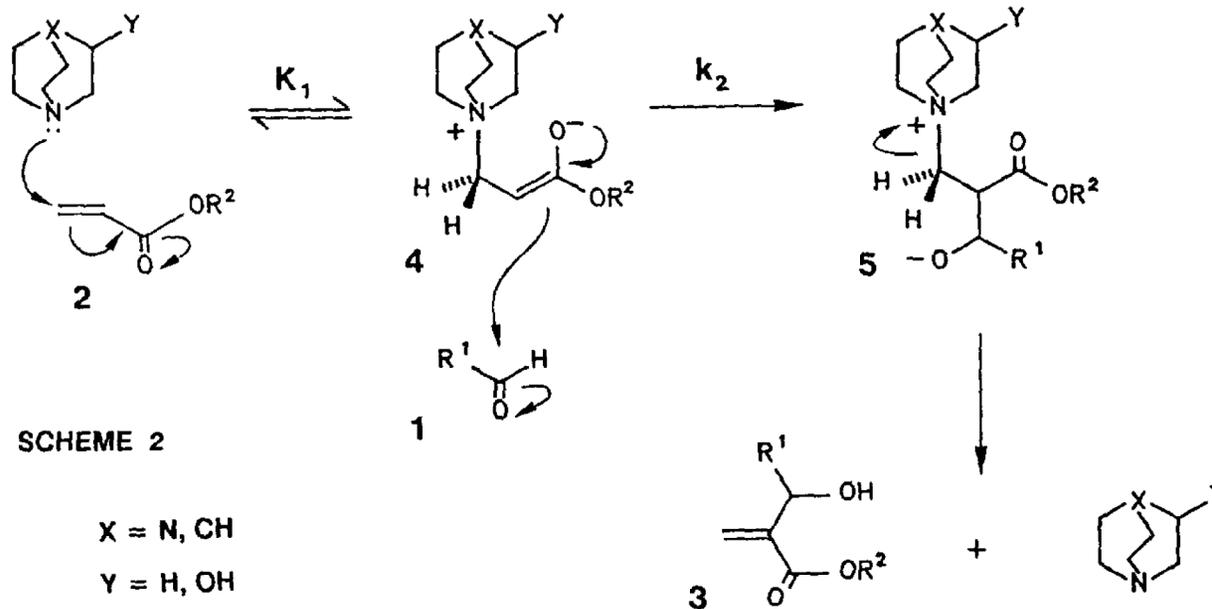
## Utility of the aza-Morita-Baylis-Hillman Reaction



**Scheme 2.** Some representative synthetic transformations of aza-Baylis-Hillman adducts. *Conditions:* (a)  $\text{Cs}_2\text{CO}_3$ ,  $\text{ArCH}_2\text{Br}$ , DMF; (b) Pfaltz catalyst,<sup>[10]</sup>  $\text{H}_2$ ,  $\text{CH}_2\text{Cl}_2$ , 1 atm; (c)  $\text{OsO}_4$  (5 mol %), NMO,  $\text{H}_2\text{O}/\text{acetone}$ ; (d) tributylvinyltin,  $\text{Pd}(\text{OAc})_2$ , S-Phos,<sup>[11]</sup> DMF; (e) chlorobenzaldoxime,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; (f) *t*-BuOOH, Triton B, THF; (g) See Supporting Information; (h) 20% aqueous HCl, reflux. See Supporting Information for full details.

## Mechanism of Old

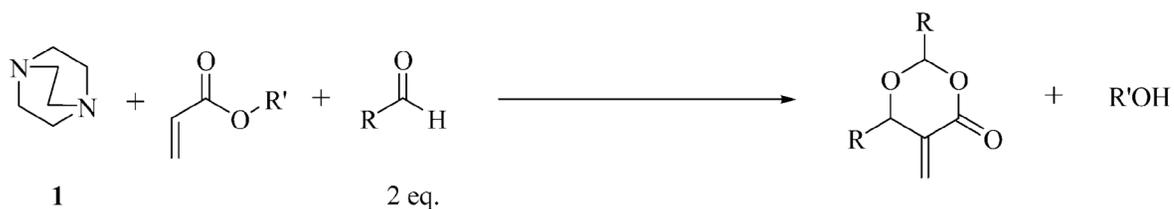
- Rate determining step is believed to be step 2
- Experimental rate data appear to afford a 3<sup>rd</sup> order process: (1<sup>st</sup> order in catalyst, acrylate, and aldehyde)
- Determined Rate =  $k_2 K_1 [1][2][\text{amine}]$
- The hydrogen-bonding model shown is supported by an observed KIE=1.3



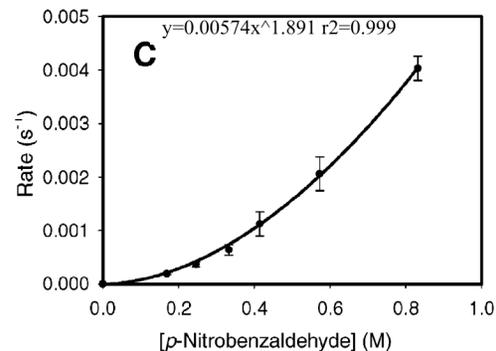
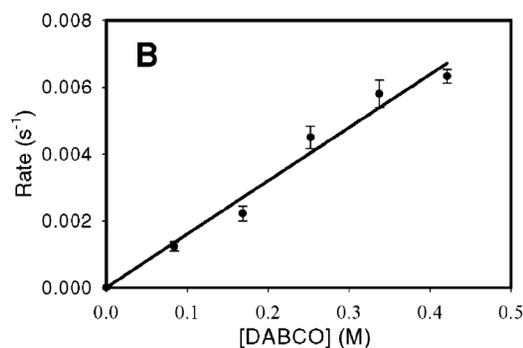
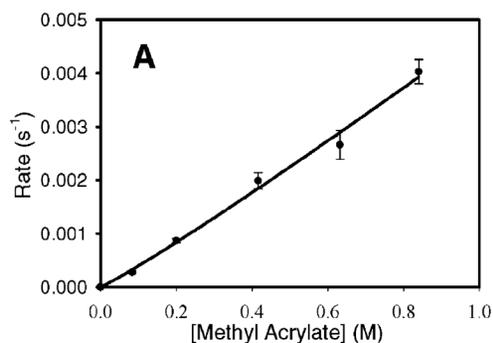
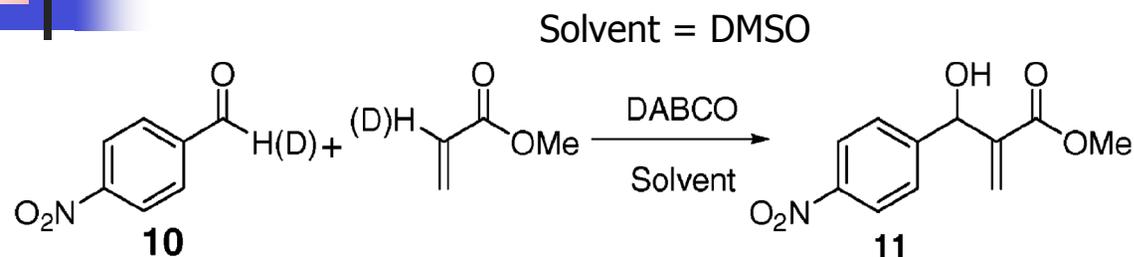
## In Need of A New Mechanism

The old mechanism can't explain the following observations for this reaction

- reaction rates are typically very slow
- stereochemistry is often difficult to control
- rate acceleration with protic solvents
- dioxanone formation



## Kinetic Data Leading to Mechanism of New



Experimental rate data yields the following conclusions:

Acrylate = 1<sup>st</sup> order

DABCO = 1<sup>st</sup> order

Aldehyde = 2<sup>nd</sup> order?

The result that the reaction is second order in aldehyde is contrary to the previous mechanism.

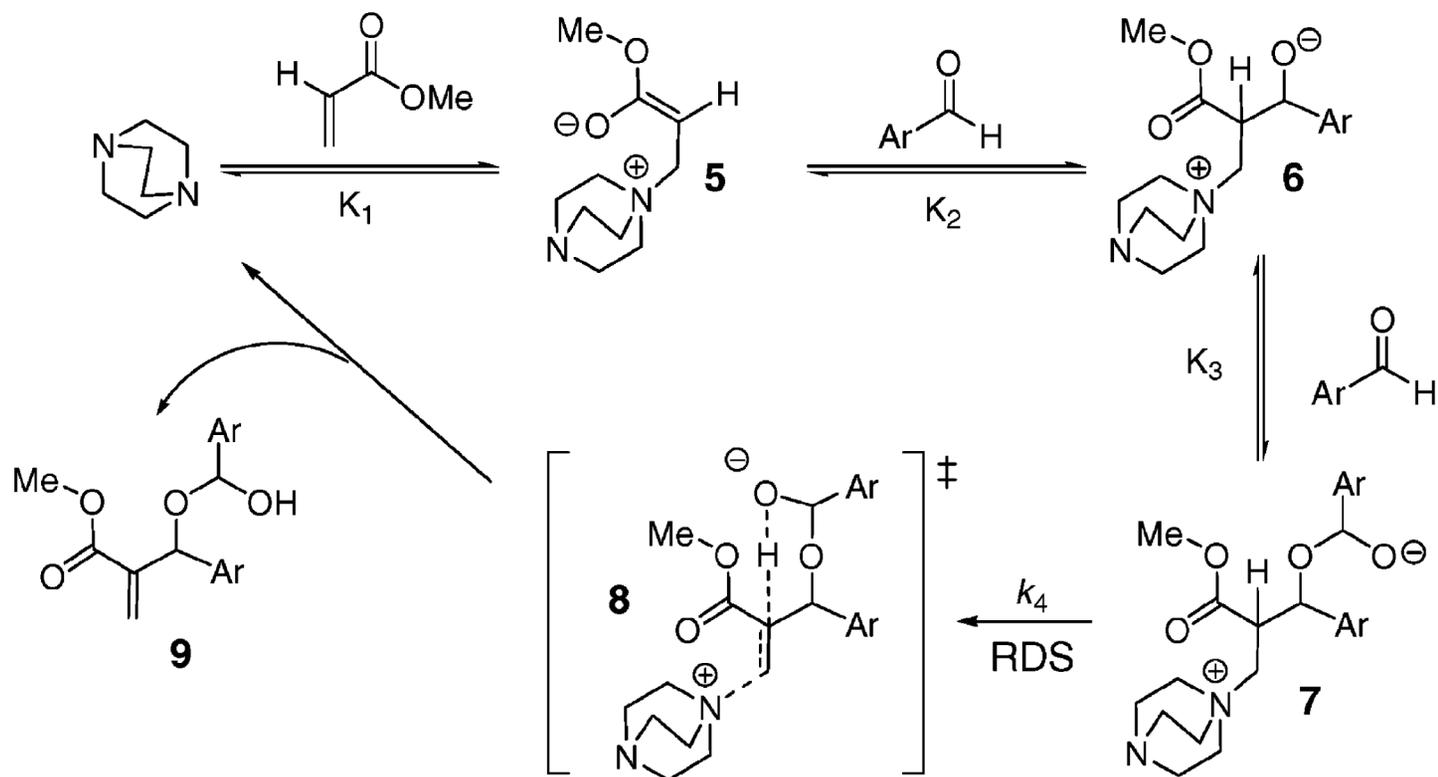
KIE (acrylate) = 2-6

KIE (aldehyde) = 0.7-0.8

Indicating change from an sp<sup>2</sup> to an sp<sup>3</sup> center

How does this change in order effect the mechanism?

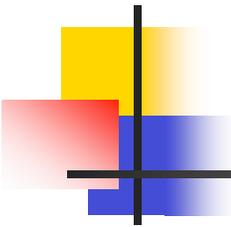
## Mechanism of New



The rate determining step is now proposed to be the deprotonation-elimination step

It is proposed that without an external base, the alkoxide **6** is unable to undergo an intramolecular deprotonation due to geometrical constraints

Hemiacetal **7** can deprotonate the  $\alpha$ -position via the 6 membered transition state **8** without severe geometrical constraints



## Rate Law

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From the mechanism, the following rate law can be derived by using the SSA:

$$\text{Rate} = \frac{k_1 k_2 k_3 k_4 [\mathbf{1}] [\mathbf{2}] [\mathbf{4}]^2}{k_2 k_3 k_4 [\mathbf{4}]^2 + k_{-1} k_3 k_4 [\mathbf{4}] + k_{-1} k_{-2} k_{-3} + k_{-1} k_{-2} k_4}$$

Using the equilibrium approximation, and if  $k_4$  is assumed to be small, then the rate law can be further reduced to:

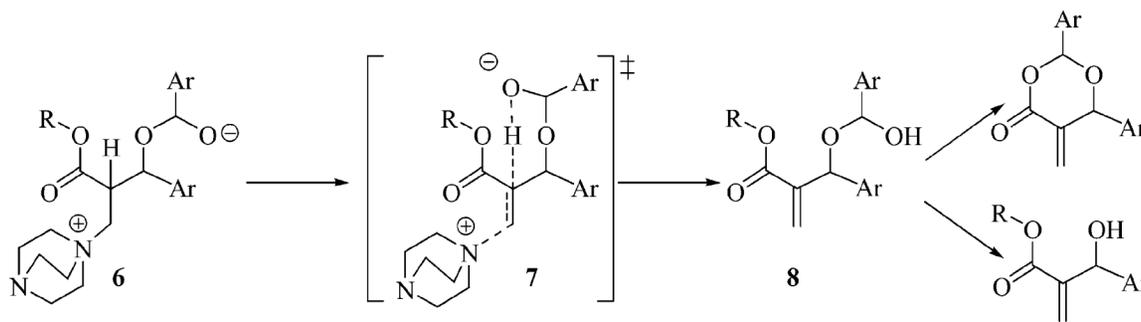
$$\text{Rate} = \frac{k_1 k_2 k_3 k_4 [\mathbf{1}] [\mathbf{2}] [\mathbf{4}]^2}{k_{-1} k_{-2} k_{-3}} = K_1 K_2 K_3 k_4 [\mathbf{1}] [\mathbf{2}] [\mathbf{4}]^2$$

The order is consistent with the kinetic data

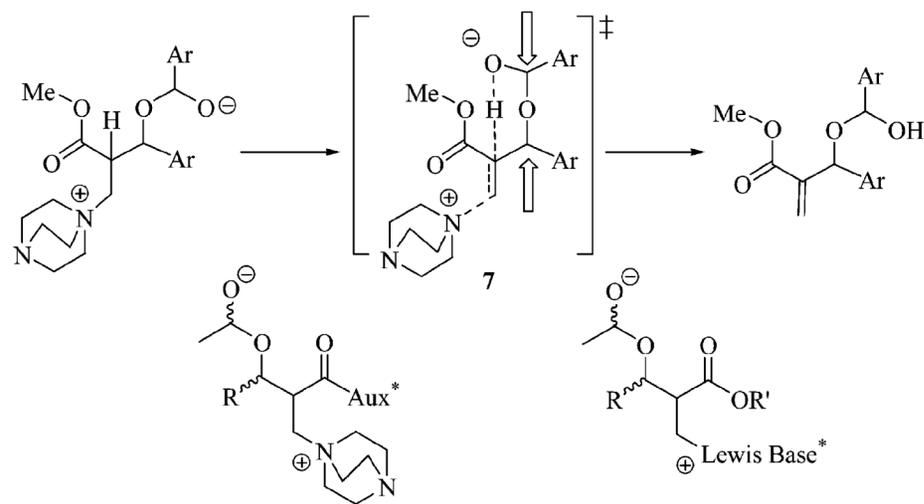
The reaction slows dramatically as a function of aldehyde consumption for difficult substrates

## Dioxanone Formation and Stereochemical Control

The following hypothesis accounts for the observation of dioxanone formation



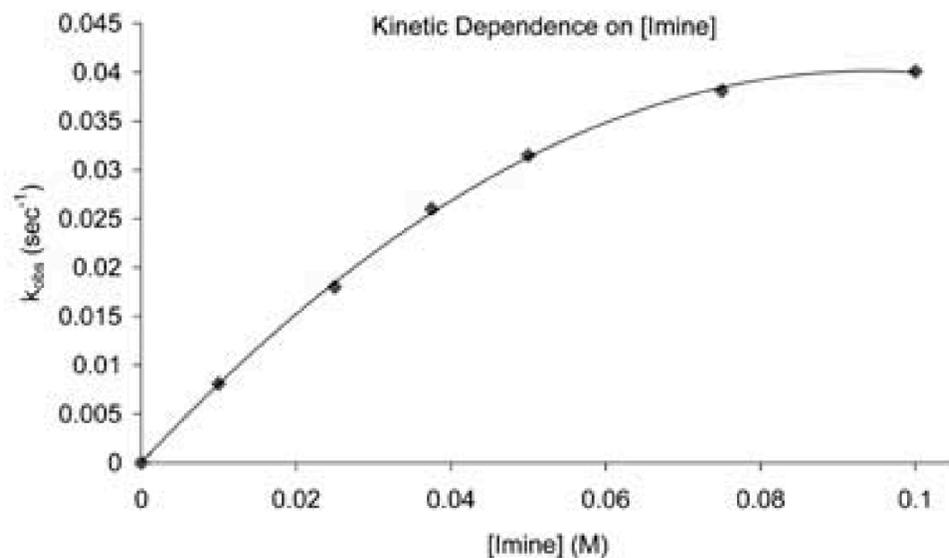
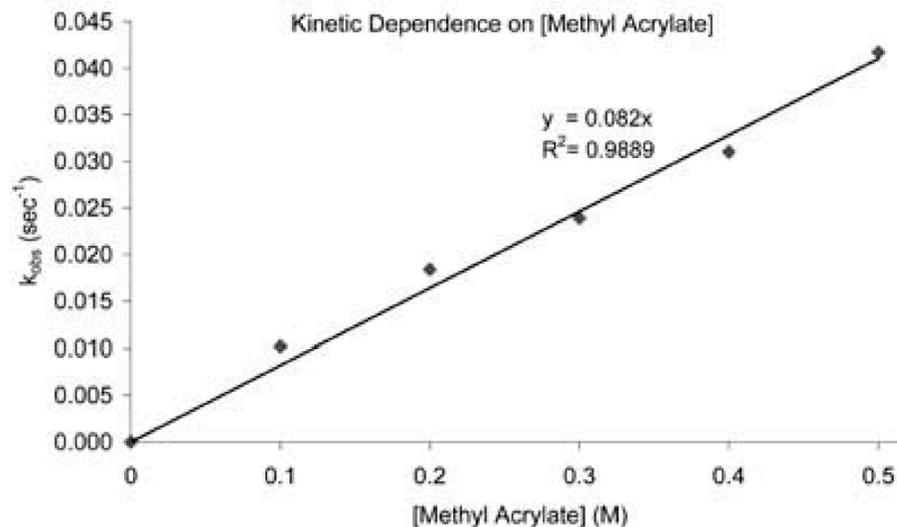
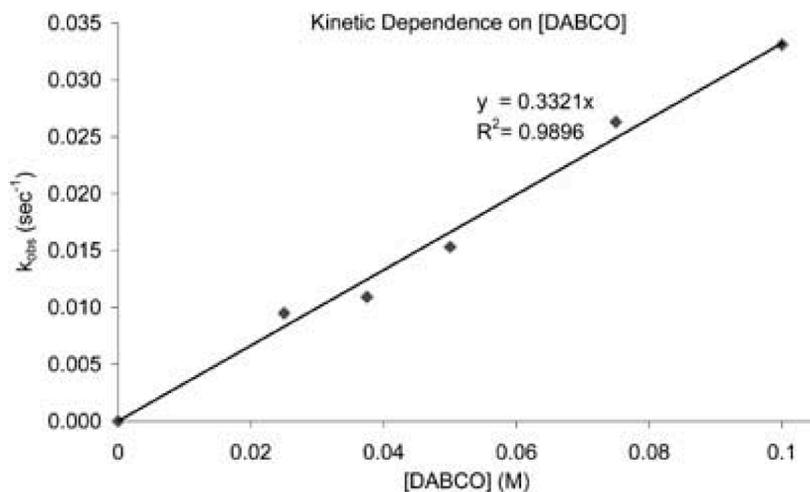
The elimination proceeds through a diastereomeric transition state 7. As a result, the number of stereocenters in the transition state increases from 2 to 3 leading to 4 stereoisomers. 4 pathways are thus provided toward products which will render the auxiliary approach in controlling the stereochemical outcome difficult.



The Chiral Auxiliary Approach

The Optically Active Lewis Base Approach

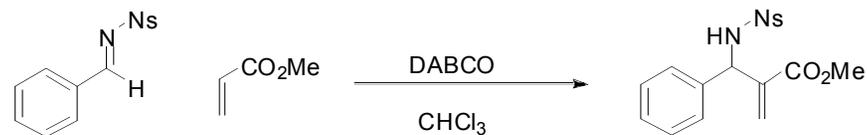
# Mechanism of the aza-Morita-Baylis-Hillman Reaction



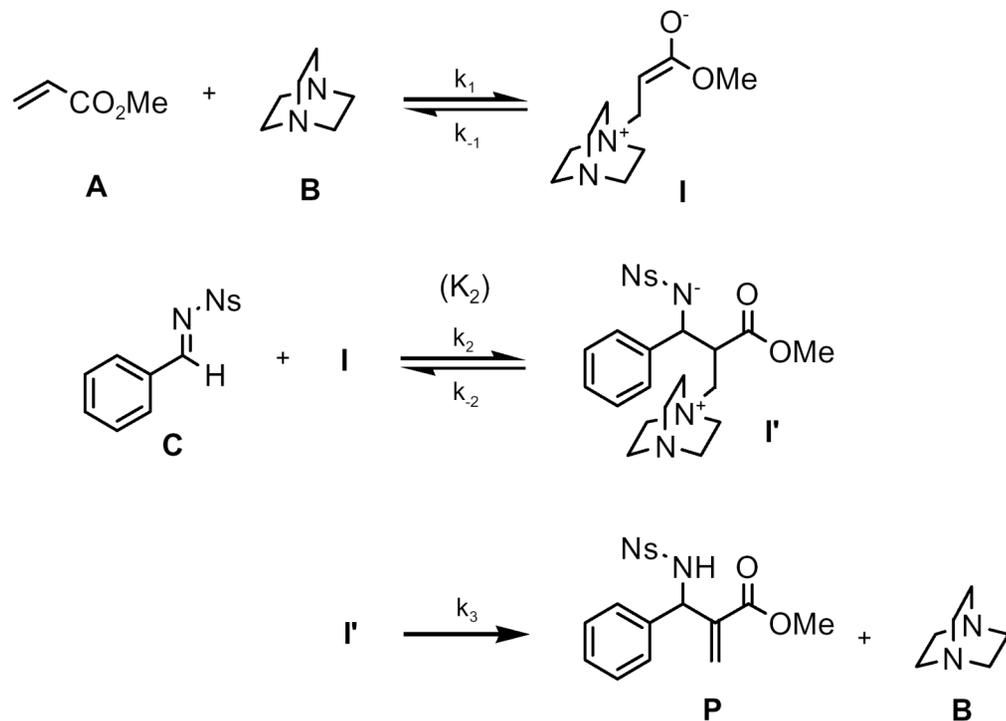
As with the MBH reaction, the AMBH reaction displays 1<sup>st</sup> order in DABCO and acrylate.

However, saturation kinetics is observed for the imine electrophile.

How does this experimental data affect the mechanism and the rate law



## Mechanism cont.



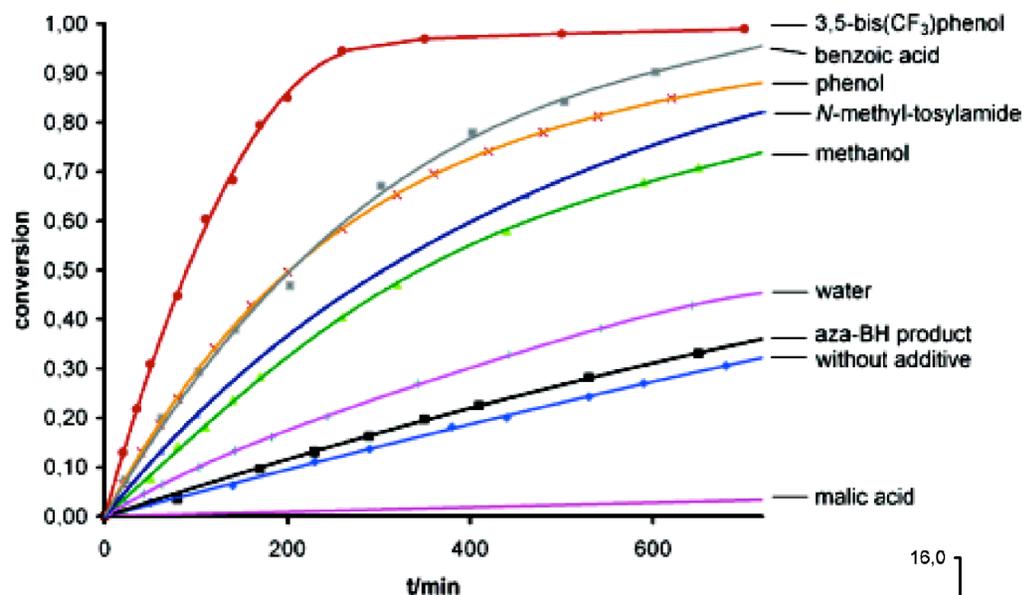
A primary KIE was observed to be  $K_H/K_D = 3.81$  suggesting that deprotonation is rate-limiting.

$$\text{rate} = \frac{a[\text{DABCO}][\text{Acrylate}][\text{Imine}]}{1 + b[\text{Imine}]}$$

Question: Derive the rate law given above for this mechanism and solve for constants a and b in terms of rate constants and equilibrium constants.

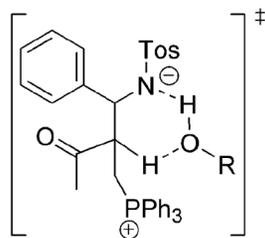
Assumption: step 2 is a fast equilibrium

## Rate Dependence on Acid Media

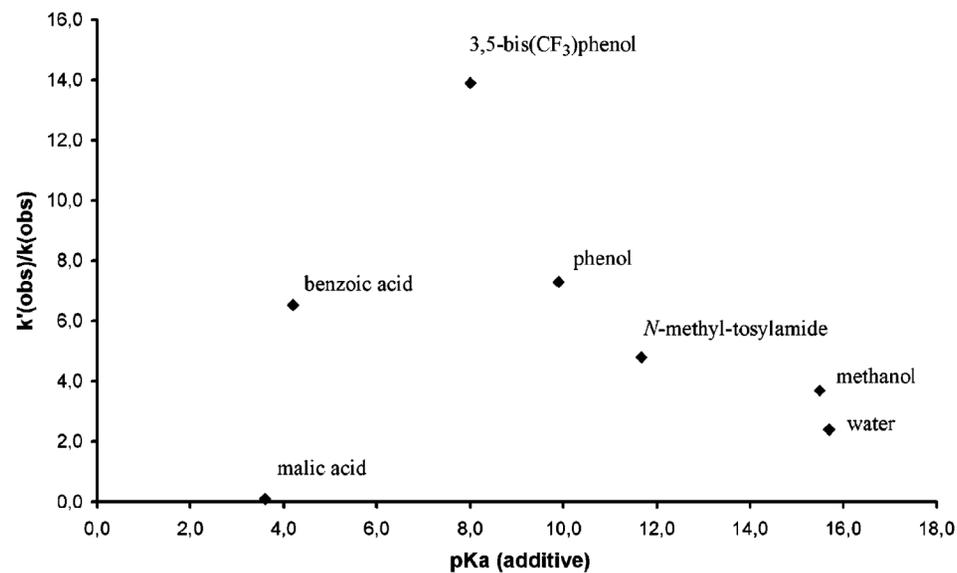


It's observed that the order in imine changes from 0.5 to 1 in the presence of phenol.

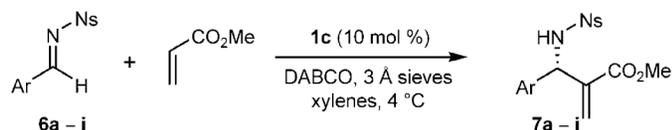
This demonstrates that the elimination step is not involved in the RDS anymore. The proton transfer-elimination step must be accelerated.



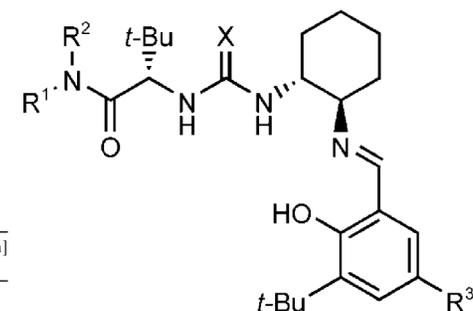
Why does malic acid decrease the rate?



## Catalytic Asymmetric Induction with Chiral Thioureas



Entry	Ar	Time [h]	Product	Yield [%]	ee [%] <sup>[a]</sup>
1	C <sub>6</sub> H <sub>5</sub> ( <b>6a</b> )	36	<b>7a</b>	49	95
2	3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>6b</b> )	24	<b>7b</b>	40	93
3	3-(OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> ( <b>6c</b> )	24	<b>7c</b>	42	96
4	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>6d</b> )	16	<b>7d</b>	36	87
5	3-ClC <sub>6</sub> H <sub>4</sub> ( <b>6e</b> )	16	<b>7e</b>	33	94
6	3-BrC <sub>6</sub> H <sub>4</sub> ( <b>6f</b> )	16	<b>7f</b>	39	92
7	1-Naphthyl ( <b>6g</b> )	24	<b>7g</b>	27	91
8	2-Thiophenyl ( <b>6h</b> )	36	<b>7h</b>	30	99
9	3-Furyl ( <b>6i</b> )	36	<b>7i</b>	25	98



- 1 a:** R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = OCOBu-*t*, X = S  
(optimal Strecker and phosphite addition catalyst<sup>[4c-d]</sup>)
- b:** R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = OCOBu-*t*, X = O
- c:** R<sup>1</sup> = Bn, R<sup>2</sup> = Me, R<sup>3</sup> = *t*-Bu, X = S  
(optimal Mannich catalyst<sup>[4e]</sup>)

-Nosyl protecting group was found to be optimal affording the highest ee's

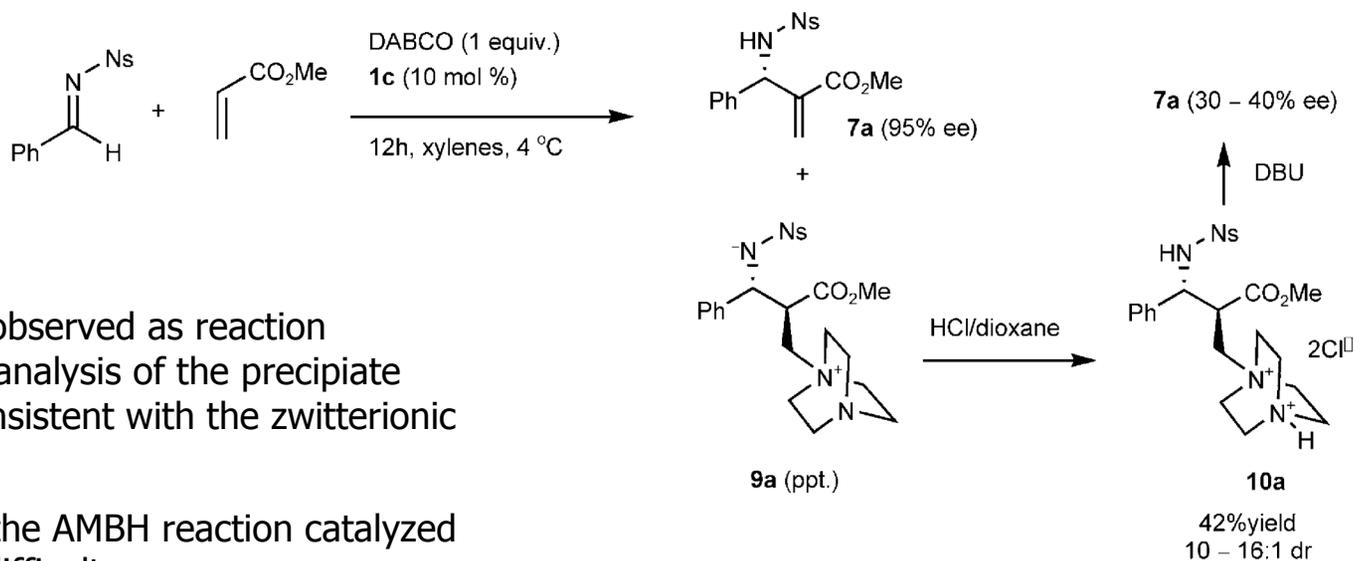
-Phosphine catalysts gave poor selectivities relative to DABCO

-Thioureas **1a** and **1c** gave optimal results. **1c** was chosen due to synthetic accessibility

-Non-polar solvents were discovered to give the highest ee's, but producing highly heterogeneous mixtures leading to low yields of product. More polar solvents afforded a higher degree of solubility and increased yields, but also diminished ee's.

-The obvious inverse relationship between enantioselectivity and conversion required deeper mechanistic insight

## Chiral Thioureas cont.



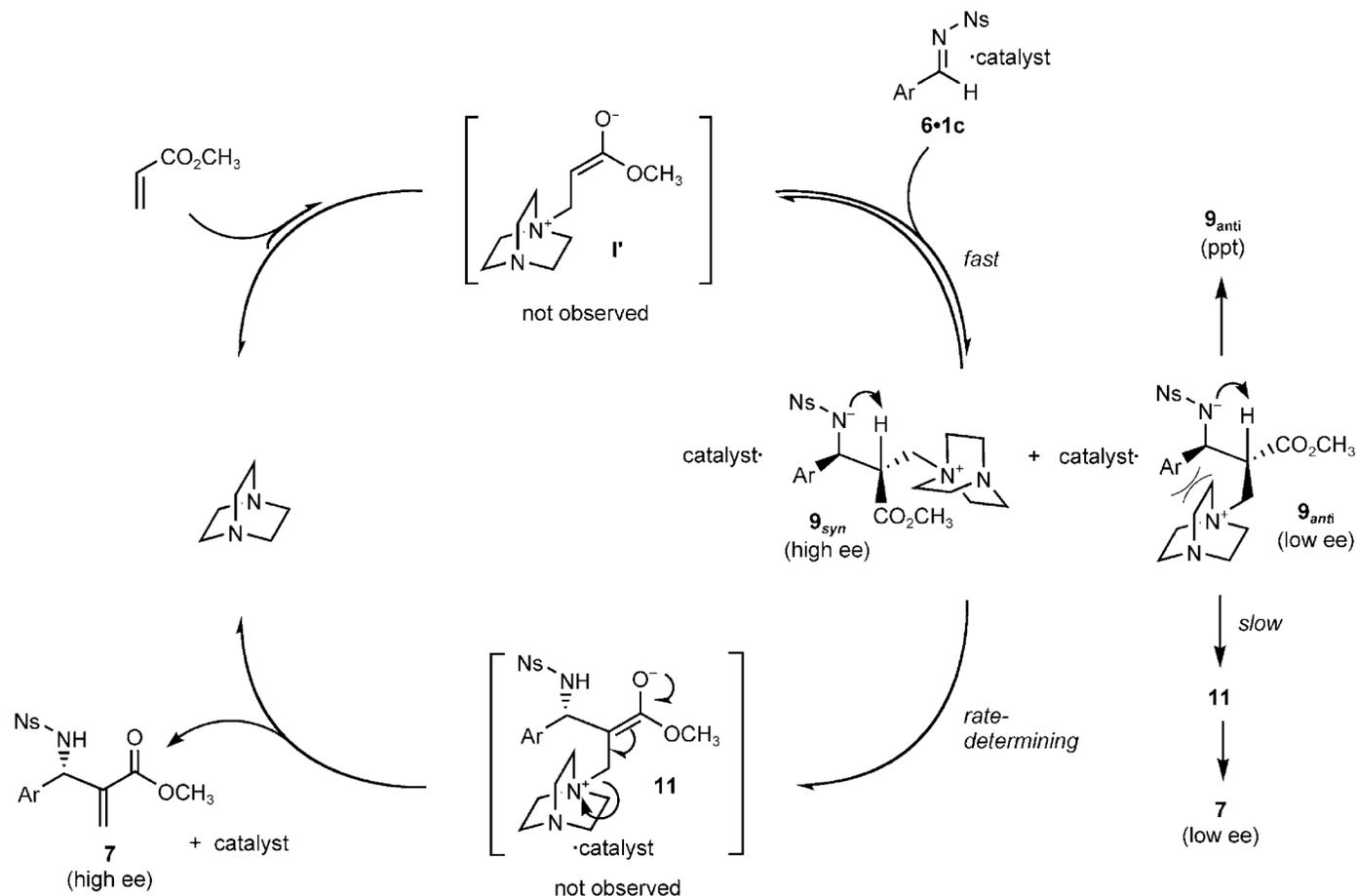
Yellow precipitate formation is observed as reaction progresses. ESI mass spectral analysis of the precipitate isolated from the reaction is consistent with the zwitterionic intermediate **9a**.

The heterogeneous mixture of the AMBH reaction catalyzed by **1c** rendered kinetic studies difficult

**7a** obtained from **9a** afforded lower ee's than the material produced via the direct AMBH reaction

Added imine had no effect on the rate of elimination, which is in contrast to the MBH reaction where a rate dependence on the concentration of the electrophile during elimination is observed

## Mechanism of Thiourea catalyzed aza-MBH reaction



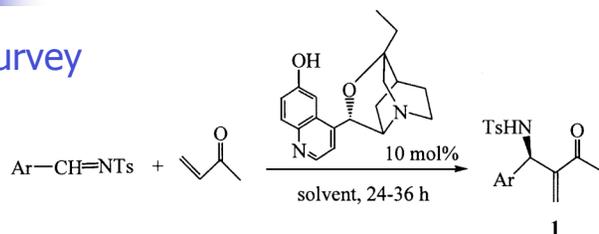
9<sub>anti</sub> may undergo precipitation selectively due to slow elimination relative to 9<sub>syn</sub>

9<sub>syn</sub> may undergo decomposition rapidly by intramolecular proton transfer relative to 9<sub>anti</sub> to generate 7 in high yield

Solvents that solubilize both diastereomers of 9 afford 7 in low ee

## Quinuclidine catalysts

### -Solvent Survey



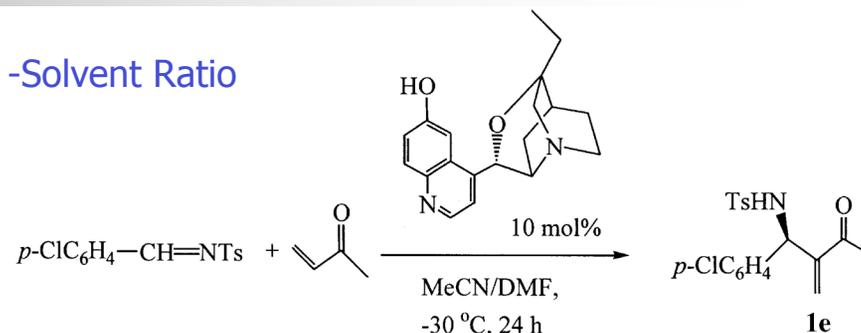
Entry	Ar	<b>1</b>	Solvent	<i>t</i> [h]	<i>T</i> [°C]	Yield of <b>1</b> [%] <sup>[a]</sup>	<i>ee</i> value [%]
1	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	<b>c</b>	THF	36	20	30	62
2	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	<b>c</b>	THF	24	-25	33	76
3	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	<b>c</b>	MeCN	24	0	50	78
4	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	<b>c</b>	MeCN	24	-20	64	86
5	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	<b>c</b>	DMF	24	-20	55	93
6	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	<b>c</b>	DMF	24	-40	50	96
7	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>e</b>	THF	24	0	71	42
8	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>e</b>	THF	24	-20	65	63
9	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>e</b>	MeCN	24	-30	80	81
10	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>e</b>	DMF	24	-30	51	95

Highest yields were attained at -30°C with MeCN, and the highest *ee* values were attained with DMF.

The best solvent ratio was determined to be 1:1 DMF/MeCN to afford 68% yield and 93% *ee* for the *p*-chloro aryl aldimine

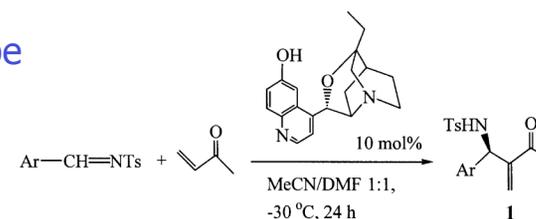
Attempt to synthesize aliphatic adducts resulted in the generation of “many unidentified products” without any observation of desired product.

### -Solvent Ratio



Entry	MeCN/DMF	Yield of <b>1e</b> [%] <sup>[a]</sup>	<i>ee</i> value [%]	Absolute configuration
1	5:1	76	78	<i>R</i>
2	4:1	78	90	<i>R</i>
3	1:1	68	93	<i>R</i>
4	1:2	66	93	<i>R</i>

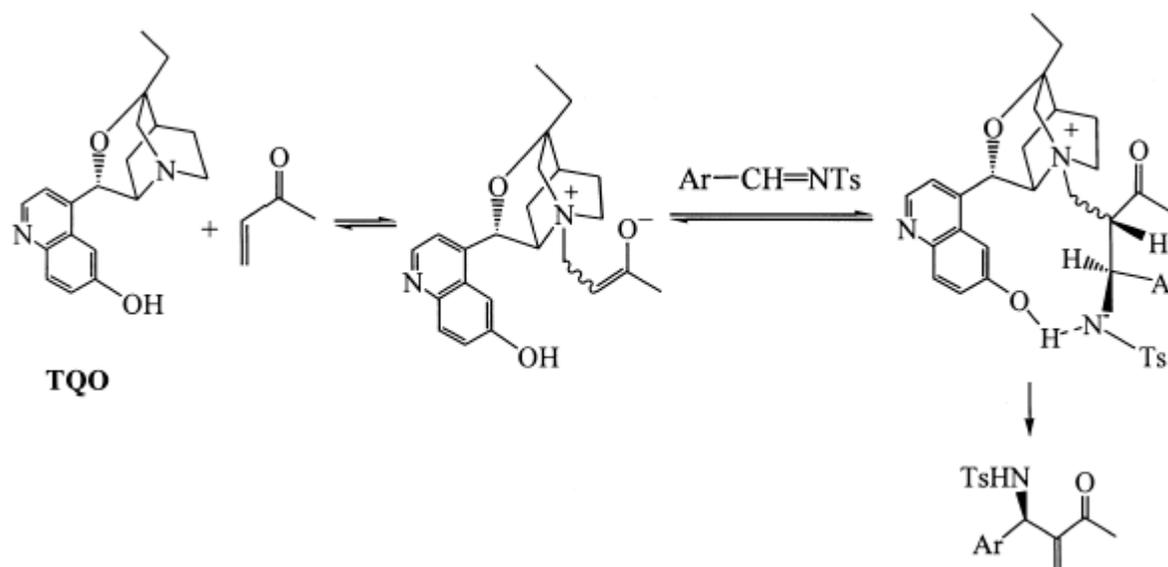
### -Scope



Entry	Ar	<b>1</b>	Yield of <b>1</b> [%] <sup>[a]</sup>	<i>ee</i> value [%]	Absolute configuration
1	C <sub>6</sub> H <sub>5</sub>	<b>a</b>	80	97 <sup>[b]</sup>	<i>R</i>
2	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>b</b>	76	96	<i>R</i>
3	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	<b>c</b>	74	96	<i>R</i>
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>d</b>	64	99 <sup>[c,d]</sup>	<i>R</i>
5	<i>m</i> -FC <sub>6</sub> H <sub>4</sub>	<b>f</b>	55	90	<i>R</i>
6	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>g</b>	60	74 <sup>[e]</sup>	<i>R</i>
7	2-furyl	<b>h</b>	58	73 <sup>[d]</sup>	<i>R</i>
8	C <sub>6</sub> H <sub>5</sub> -CH=CH	<b>i</b>	54	46 <sup>[d]</sup>	<i>R</i>

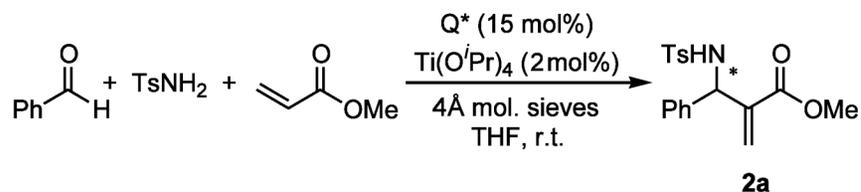
[a] Yields of isolated products. [b] In DMF, 57% yield, 96% *ee*. [c] In DMF, 59% yield, 99% *ee*. [d] The reaction mixture was stirred for 36 h. [e] In DMF, no imine Baylis-Hillman adduct was formed because the imine decomposed rapidly.

## Proposed H-Bonding Model



The steric interaction of the COMe group with the aromatic group in this transition state causes the formation of the adduct with the (R) configuration

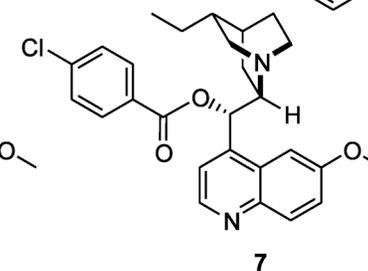
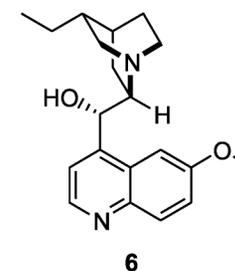
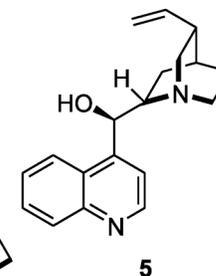
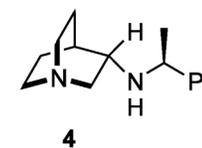
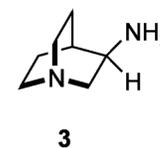
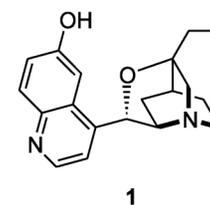
## A 1-Pot, 3-Component Synthesis



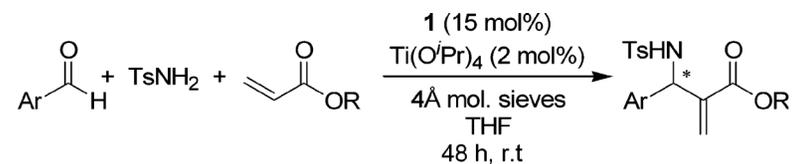
Entry	Amine (Q*)	Time (h)	Yield (%) <sup>b</sup>	Ee (%) <sup>c,d</sup>
1	<b>3</b>	24	50	5 ( <i>S</i> )
2	<b>4</b>	24	80	5 ( <i>R</i> )
3	<b>5</b>	144	35	40 ( <i>R</i> )
4	<b>6</b>	144	60	43 ( <i>S</i> )
5	<b>7</b>	96	—	—
6	<b>1</b>	48	78	68 ( <i>R</i> )

One pot 3-component synthesis of the aza-MBH adducts

A Lewis acid,  $\text{Ti(O}^i\text{Pr)}_4$ , was required for the rapid in situ formation of the N-sulfonylimine



## Scope of the 3-Component System

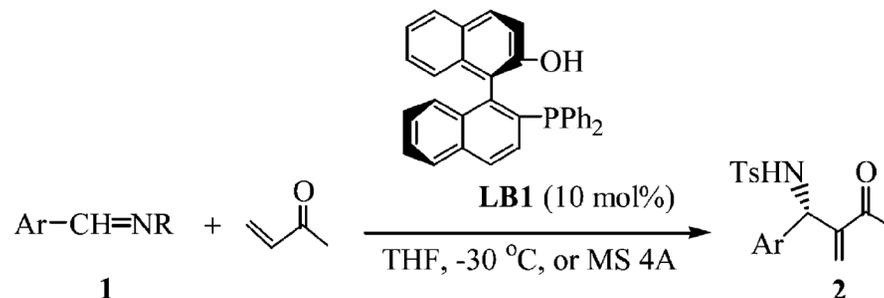


Entry	Ar	R	Product	Yield <sup>b</sup> (%)	Ee <sup>c</sup> (%)
1		-CH <sub>3</sub>	<b>2a</b>	78 (75) <sup>d</sup>	68
2		"	<b>2b</b>	79	49
3		"	<b>2c</b>	94	63
4		"	<b>2d</b>	95	61
5		"	<b>2e</b>	95	67
6		"	<b>2f</b>	95	50
7		"	<b>2g</b>	95	74
8		-Bu <sup>t</sup>	<b>2h</b>	12	52

In general, 3-component system yields only modest ee's relative to using preformed imine.

<sup>a</sup> Reaction conditions: aldehyde, *p*-toluenesulfonamide and alkyl acrylate (1:1:1.1), **1** (15 mol%), Ti(O<sup>i</sup>Pr)<sub>4</sub> (2 mol%) and molecular sieves (4 Å, 200 mg/mmol substrate) in THF (substrate concentration: 2 M) at ambient temperature. <sup>b</sup> Yields determined by <sup>1</sup>H NMR using benzyl alcohol as internal standard. <sup>c</sup> Enantiomeric excess determined by <sup>1</sup>H NMR using Eu(hfc)<sub>3</sub> as chiral shift reagent. <sup>d</sup> Isolated yield.

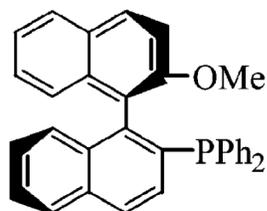
## Bifunctional Chiral Phosphine Lewis Bases



entry	Ar	R	No.	time/h	yield/% <sup>a</sup> /2	ee/% <sup>b</sup>	absolute configuration
1	C <sub>6</sub> H <sub>5</sub>	Ts	<b>1a</b>	24 (36) <sup>c</sup>	<b>2a</b> , 49 (83) <sup>c</sup>	83 (83) <sup>c</sup>	<i>S</i>
2	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Ts	<b>1b</b>	24 (36)	<b>2b</b> , 53 (82)	80 (81)	<i>S</i>
3	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	Ts	<b>1c</b>	36 (36)	<b>2c</b> , 62 (84)	76 (79)	<i>S</i>
4	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	Ts	<b>1d</b>	18	<b>2d</b> , 84	81	<i>S</i>
5	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Ts	<b>1e</b>	24 (24)	<b>2e</b> , 72 (90)	94 (87)	<i>S</i>
6	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	Ts	<b>1f</b>	18	<b>2f</b> , 85	83	<i>S</i>
7	<i>m</i> -FC <sub>6</sub> H <sub>4</sub>	Ts	<b>1g</b>	36 (24)	<b>2g</b> , 26 (96)	91 (85)	<i>S</i>
8	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	Ts	<b>1h</b>	18 (24)	<b>2h</b> , 62 (88)	88 (88)	<i>S</i>
9	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ts	<b>1i</b>	12 (24)	<b>2i</b> , 60 (86)	94 (92)	<i>S</i>
10	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ts	<b>1j</b>	12 (24)	<b>2j</b> , 54 (91)	90 (88)	<i>S</i>
11 <sup>d</sup>	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	Ts	<b>1k</b>	24	<b>2k</b> , 85	61	<i>S</i>
12 <sup>d</sup>	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ts	<b>1l</b>	24	<b>2l</b> , 88	84	<i>S</i>
13 <sup>d</sup>	<i>trans</i> -C <sub>6</sub> H <sub>5</sub> -CH=CH	Ts	<b>1m</b>	24	<b>2m</b> , 94	95	<i>S</i>
14 <sup>d</sup>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Ms	<b>1n</b>	24	<b>2n</b> , 94	82	<i>S</i>
15 <sup>d</sup>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	<b>1o</b>	24	<b>2o</b> , 94	89	<i>S</i>
16 <sup>d</sup>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Ns	<b>1p</b>	24	<b>2p</b> , — <sup>e</sup>	— <sup>e</sup>	<i>S</i>
17 <sup>d</sup>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	SES	<b>1q</b>	72	<b>2q</b> , 53	89	<i>S</i>

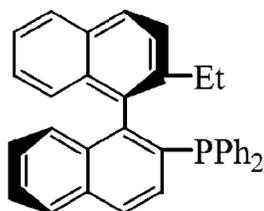
<sup>a</sup> Isolated yields. <sup>b</sup> Determined by chiral HPLC. <sup>c</sup> Values in parentheses are the results in the presence of MS 4A (100 mg). <sup>d</sup> The reaction was carried out at  $-20\text{ }^\circ\text{C}$  in the presence of MS 4A (100 mg). <sup>e</sup> The corresponding aza-Baylis–Hillman adduct was not formed because this N-sulfonated imine decomposed quickly under reaction conditions.

## How Important is the Phenolic Hydroxy Group?



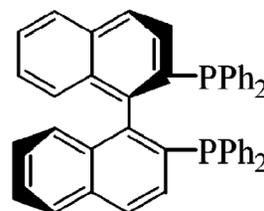
**LB2**

Yield: 13%,  
ee: 20%, *R*



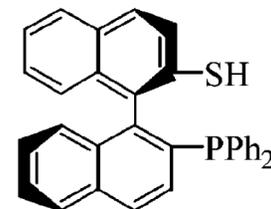
**LB3**

Yield: 17%,  
ee: 22%, *R*



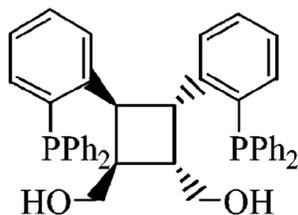
**LB4**

no reaction



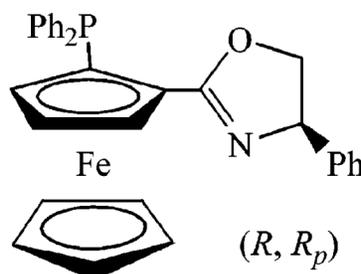
**LB5**

Yield: 35%,  
ee: 39%, *R*



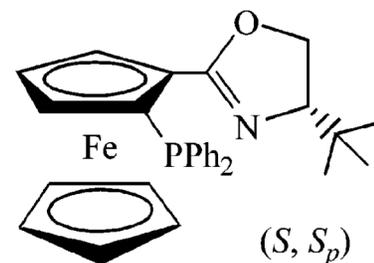
**LB6**

Yield: 78%,  
ee: 18%, *S*



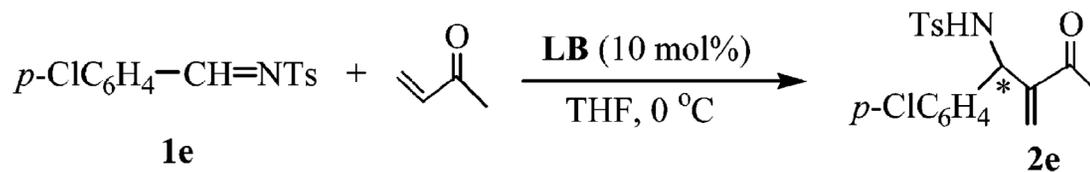
**LB7**

Yield: 45%,  
ee: 65%, *S*



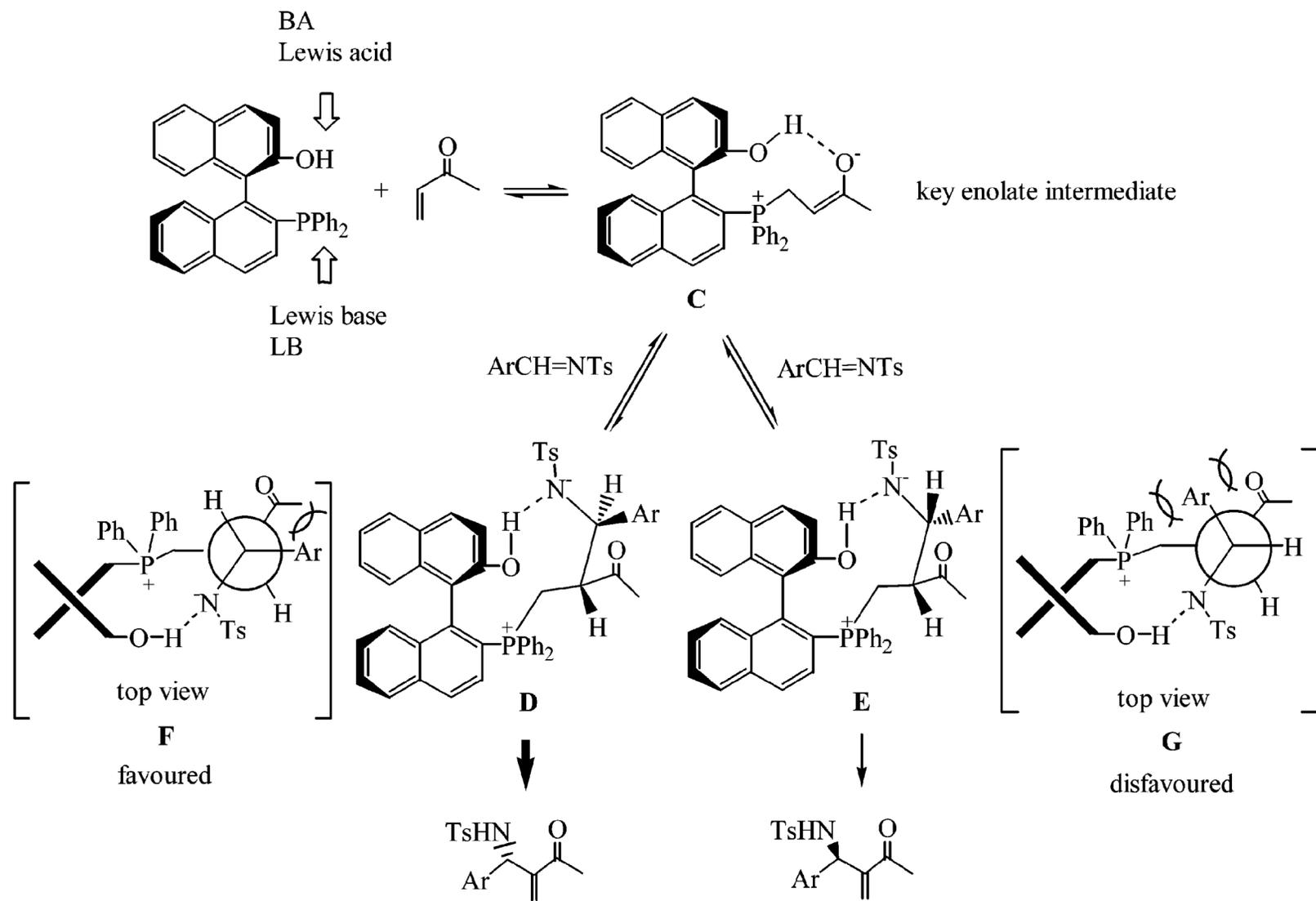
**LB8**

Yield: 44%,  
ee: 38%, *R*

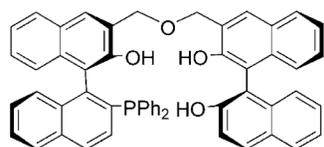
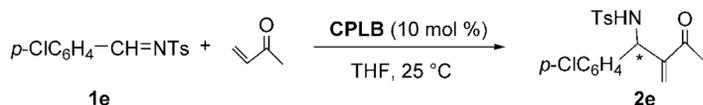


Very

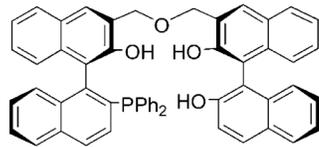
## Mechanistic Explanation



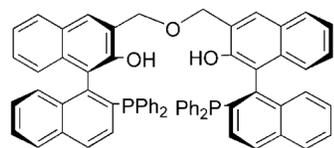
## Phosphines with Multiple Phenol Groups

**(R,R)-CPLB1**

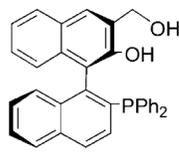
12 h, yield: 98%, ee: 92%

**(R,S)-CPLB2**

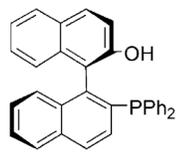
12 h, yield: 90%, ee: 90%

**(R,R)-CPLB3**

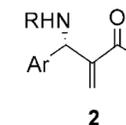
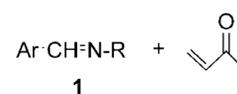
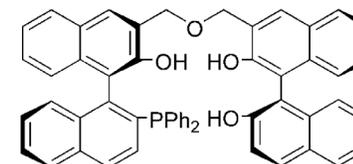
12 h, yield: 94%, ee: 92%

**(R)-CPLB4**

12 h, yield: 96%, ee: 91%

**(R)-CPLB5**

12 h, yield: 86%, ee: 84%



Entry	Ar	R	Time [h]	Yield [%] <sup>[a]</sup> <b>2</b>	ee [%] <sup>[b]</sup>	Absolute configuration <sup>[c]</sup>
1	C <sub>6</sub> H <sub>5</sub>	<b>1a</b> , Ts	36	<b>2a</b> , 97	92	S
2	<i>p</i> -C <sub>2</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	<b>1b</b> , Ts	48	<b>2b</b> , 94	96	S
3	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>1c</b> , Ts	48	<b>2c</b> , 70	95	S
4	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	<b>1d</b> , Ts	24	<b>2d</b> , 83	96	S
5	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>1e</b> , Ts	24	<b>2e</b> , 94	96	S
6	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>1f</b> , Ts	24	<b>2f</b> , 85	95	S
7	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>1g</b> , Ts	24	<b>2g</b> , 97	92	R
8	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>1h</b> , Ts	24	<b>2h</b> , 87	94	S
9	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>1i</b> , Ts	24	<b>2i</b> , 93	93	S
10	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>1j</b> , Ts	36	<b>2j</b> , 85	90	R
11	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>1k</b> , Ts	24	<b>2k</b> , 89	96	S
12	<i>trans</i> -C <sub>6</sub> H <sub>5</sub> CH=CH	<b>1l</b> , Ts	36	<b>2l</b> , 97	90	S
13	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>1m</b> , Ms	36	<b>2m</b> , 90	91	S

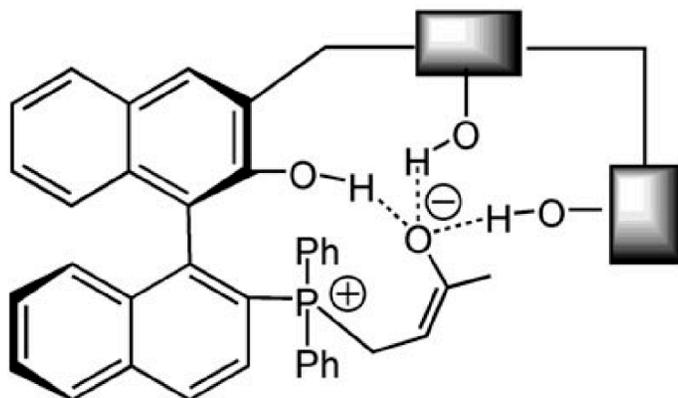
Better yields and ee's are achieved with multiple phenol groups compared to one phenol group

<sup>[a]</sup> Yield of isolated product

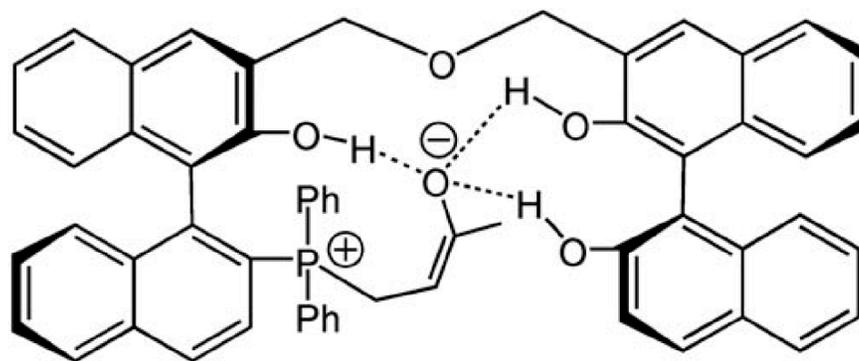
<sup>[b]</sup> Determined by chiral HPLC.

<sup>[c]</sup> Determined by the sign of specific rotation.<sup>[2f]</sup>

## H-Bonding Structures

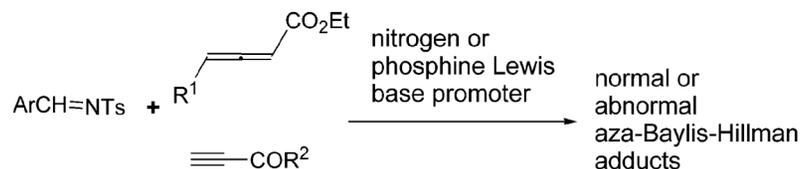


 = aromatic moiety



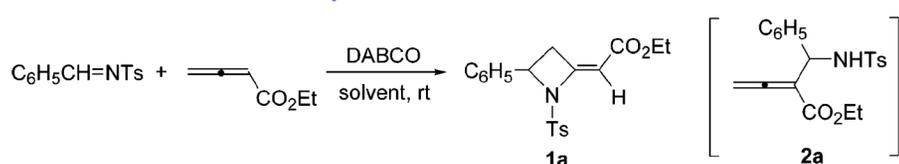
CPLBs bearing multiple phenol groups

# Abnormal AMBH Adducts



Ar = various aromatic groups or aliphatic group, R<sup>1</sup>  
= H, Me, R<sup>2</sup> = Me, OEt

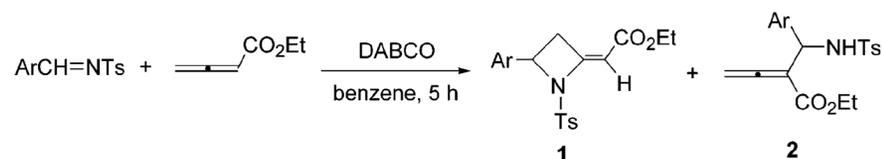
## -Solvent Survey



entry	solvent	yield <sup>a</sup> of <b>1a</b> (%)
1	THF	56
2	DMF	27
3	MeCN	25
4	Et <sub>2</sub> O	42
5	CH <sub>2</sub> Cl <sub>2</sub>	28
6	C <sub>6</sub> H <sub>6</sub>	57 <sup>b</sup> (82) <sup>c</sup>
7	Me <sub>2</sub> C=O	54

<sup>a</sup> Isolated yield. <sup>b</sup> In the absence of MS 4A, **2a** was formed in 41% yield. <sup>c</sup> In the presence of MS 4A.

## -Scope

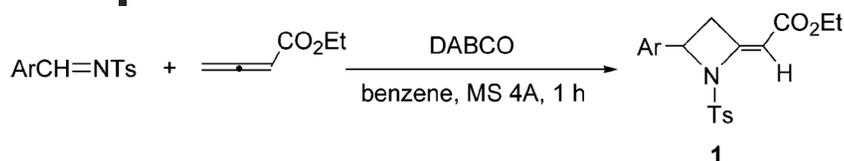


entry	Ar	yield <sup>a</sup> (%)	
		<b>1</b>	<b>2</b>
1	C <sub>6</sub> H <sub>5</sub>	<b>1a</b> , 57	<b>2a</b> , 41
2	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>1b</b> , 64	<b>2b</b> , 11
3	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>1c</b> , 45	<b>2c</b> , 14
4	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	<b>1d</b> , 58	<b>2d</b> , 13
5	<i>m</i> -FC <sub>6</sub> H <sub>4</sub>	<b>1e</b> , 49	<b>2e</b> , 13
6	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>1f</b> , 61	<b>2f</b> , 10
7	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>1g</b> , 69	<b>2g</b> , 8

<sup>a</sup> Isolated yields.

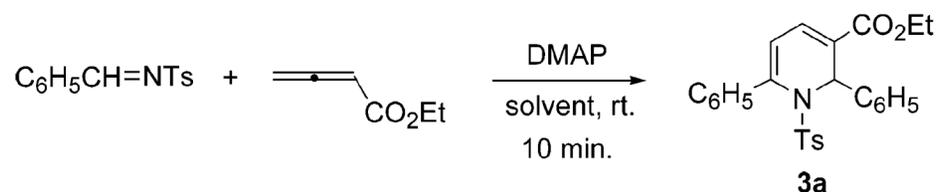
The role of molecular sieves is not clear, however the results indicate that **2** is not formed or to a small degree in the presence of molecular sieves

## Abnormal ABH adducts continued



entry	Ar	yield <sup>a</sup> of <b>1</b> (%)
1	C <sub>6</sub> H <sub>5</sub>	<b>1a</b> , 82
2	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>1b</b> , 92
3	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	<b>1c</b> , 90
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> <sup>b</sup>	<b>1d</b> , 75
5	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	<b>1e</b> , 93
6	<i>m</i> -FC <sub>6</sub> H <sub>4</sub>	<b>1f</b> , 76
7	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>1g</b> , 92
8	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>1h</b> , 99
9	<i>o,m</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>1i</b> , 99
10	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>1j</b> , 85
11	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>1k</b> , 87
12	1-naphthyl	<b>1l</b> , 99
13	3-pyridyl	<b>1m</b> , 42

<sup>a</sup> Isolated yield. <sup>b</sup> The reaction was carried out at room temperature for 3 h.

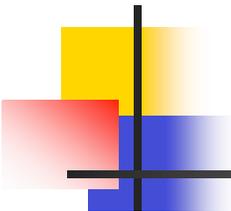


entry	solvent	yield <sup>a</sup> of <b>3a</b> (%)
1	THF	40
2	C <sub>6</sub> H <sub>6</sub>	40
3	CH <sub>2</sub> Cl <sub>2</sub>	60
4	DMF	20
5	MeCN	38
6	Et <sub>2</sub> O	23

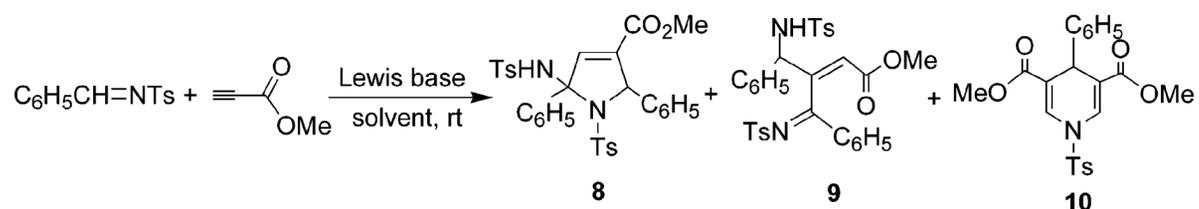
<sup>a</sup> Isolated yield.

Under identical conditions, aldimine is allowed to react with ethyl-2,3-butadienoate to yield either azetidine or dihydropyridine products depending on whether DABCO or DMAP is used as the catalyst.

Question: Can you provide a mechanism for the formation of each product that accounts for the dependence upon the catalyst?



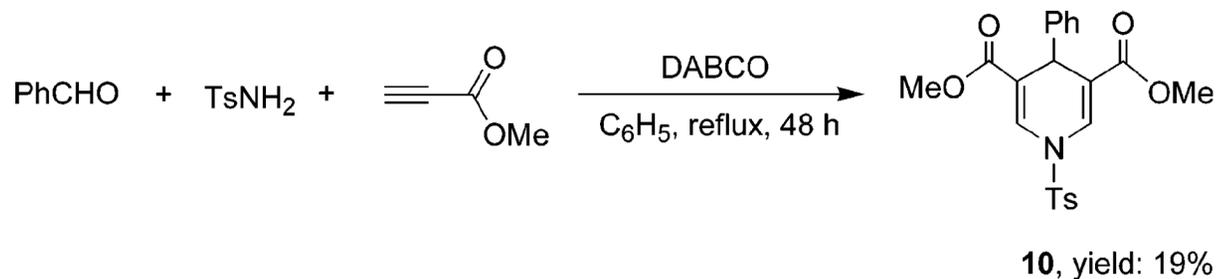
## AMBH with Methyl Propiolate



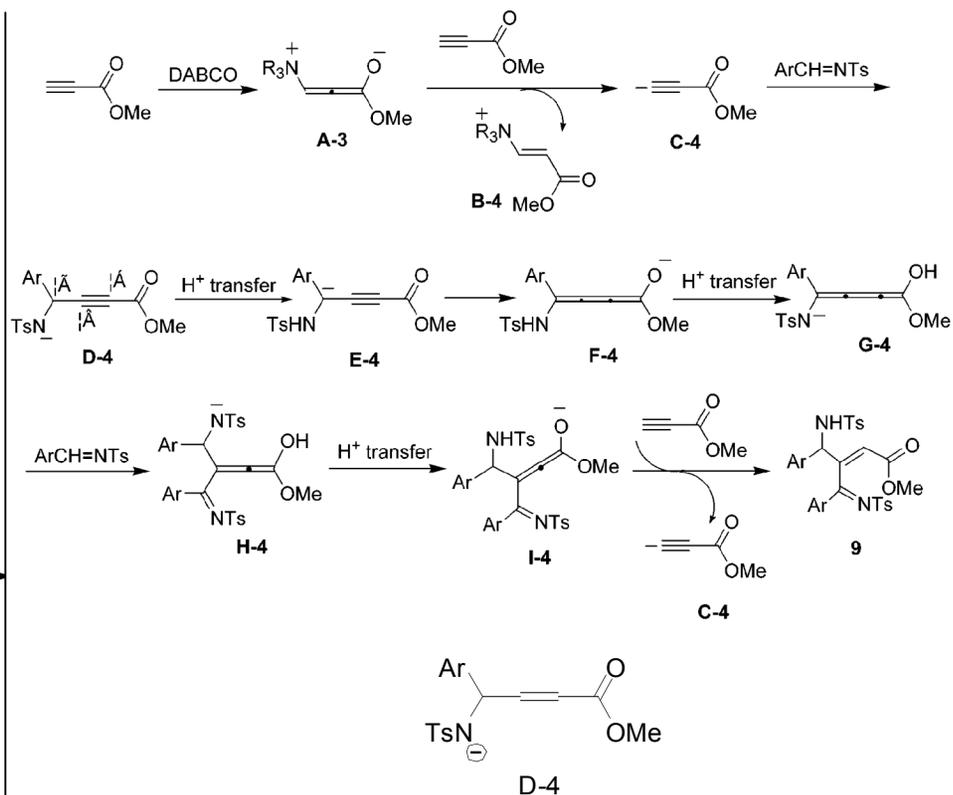
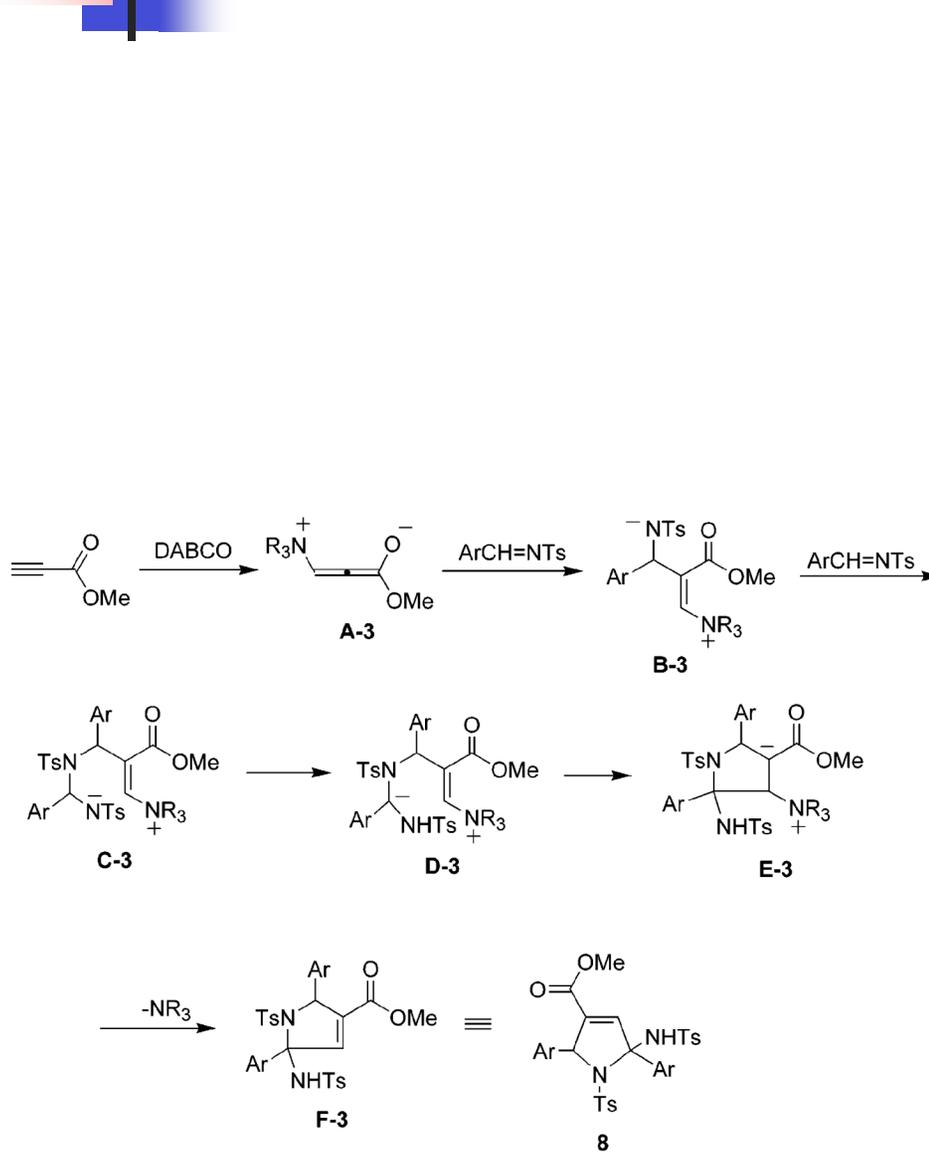
entry	Lewis base	solvent	time (h)	yield <sup>a</sup> (%)		
				<b>8</b>	<b>9</b>	<b>10</b>
1	PPh <sub>3</sub>	CH <sub>3</sub> CN	12	0	0	0
2	DABCO	C <sub>6</sub> H <sub>6</sub> <sup>b</sup>	48	0	0	<10
3	DABCO	DMF	10	21	20	0
4	DABCO	THF	10	23	37	0
5	DABCO	CH <sub>2</sub> Cl <sub>2</sub>	10	29	34	0

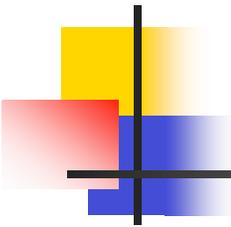
<sup>a</sup> Isolated yields. <sup>b</sup> The reaction was carried out in benzene under reflux.

Adduct **10** is believed to be a product of decomposed N-tosylated aldimine in the form of benzaldehyde in the presence of ambient water. To confirm this, a control experiment was run as indicated below



# Proposed Mechanisms for Adducts 8 and 9





## Conclusion

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- Rates of the AMBH reaction display a dependence upon the pH of the system, while the dependence in the MBH isn't as clear
- Currently the catalytic asymmetric methods for the AMBH reaction are restricted to aromatic imines albeit high ee's are attainable with these substrates. Therefore, the scope can still be broadened.
- Catalytic asymmetric methods for the MBH reaction are lacking, except for very specialized cases, due to the reduced electrophilicity of the aldehyde relative to the N-tosylated imines in the AMBH reaction. There is much room for improvement in this area.
- Some interesting new reactivity for the formation of so called "abnormal" AMBH adducts has surfaced recently