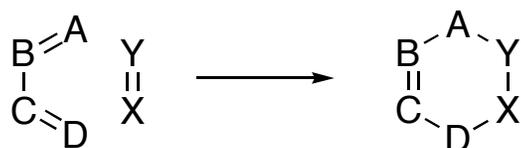


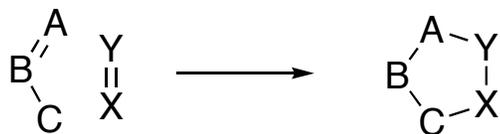
# A Survey of Recent Advances In Non-Lewis Acid Catalyzed Catalytic, Enantioselective Cycloadditions

## Scope:

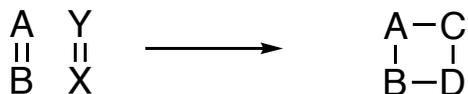
[4+2]



[3+2]



[2+2]



## The Limitations Imposed:

1. No Lewis Acid
2. No Transition metals
3. Published within last 10-15 years (not included in "Comprehensive Asymmetric Catalysis")
4. Trivial derivitization of known work is excluded (eg. Take a cross-section of the literature)

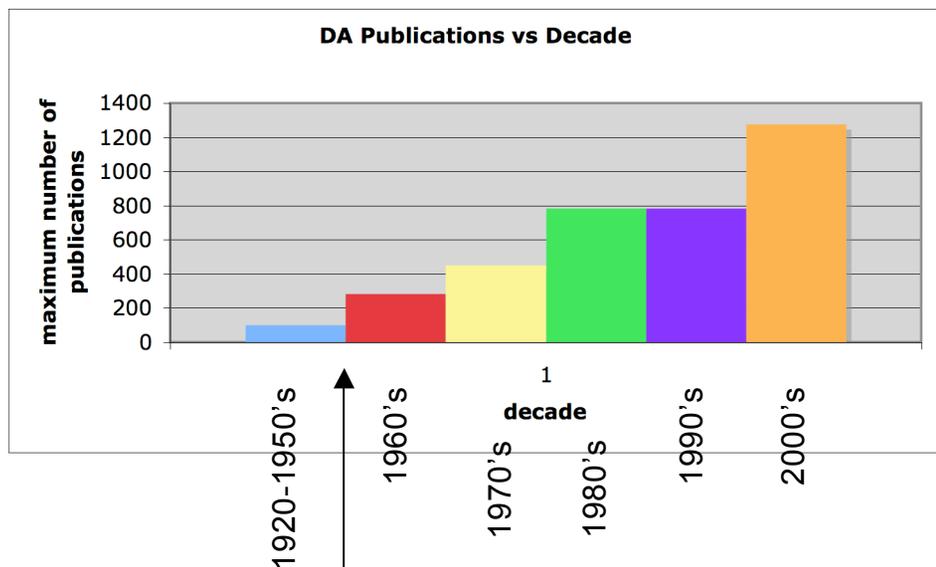
## Motivation:

1. Identify current directions of the field
2. Identify potential advantages (if any) to a non-Lewis Acid promoted pericyclic process
3. Identify modes of activation DIFFERENT than the LUMO-lowering function of LA's
4. Pay special attention to methods that DO NOT activate the 2π component

## Purposefully Excluded:

1. Chiral Bronsted Acids: see motivation 3 and we just had a group meeting on it
2. Antibodies (entire group meeting)

# Non-LA Catalyzed Pericyclic Reaction: Where to Start?



LA increases  
Rate  
Regioselectivity  
Stereoselectivity

Many Catalytic,  
Enantioselective  
LA's developed (ing)

“..., successful application of chiral Lewis acids to the Diels-Alder reaction is frequently a reliable indicator of the potential utility to other classes of reactions. Notably, facile extension to aldol, ene, Michael, dipolar cycloaddition, and hetero-Diels-Alder reactions are a common outgrowth of studies in the enantioselective catalysis of the carbocyclic Diels-Alder reaction.” (Evans and Johnson)

## Motivating Questions

- What do you do when your Substrate ( $4\pi$  or  $2\pi$ ) is not Stable to LA's?
- In the situation where LA's simply Fail, what methods are available?

## Corollaries:

- Are any of these other methods general?
- In what areas is there a dire need for New Methodology?

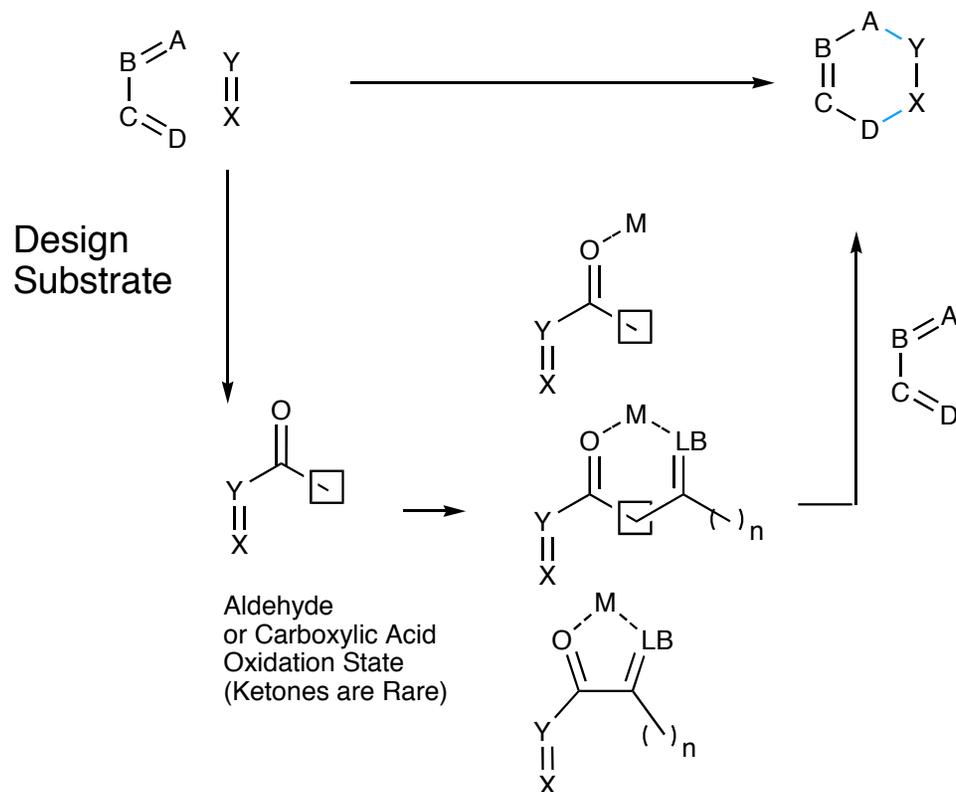
Yates, P., and Eaton, P., JACS, 1960, **82**, 4436;

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235

# 4+2 reviews ect.

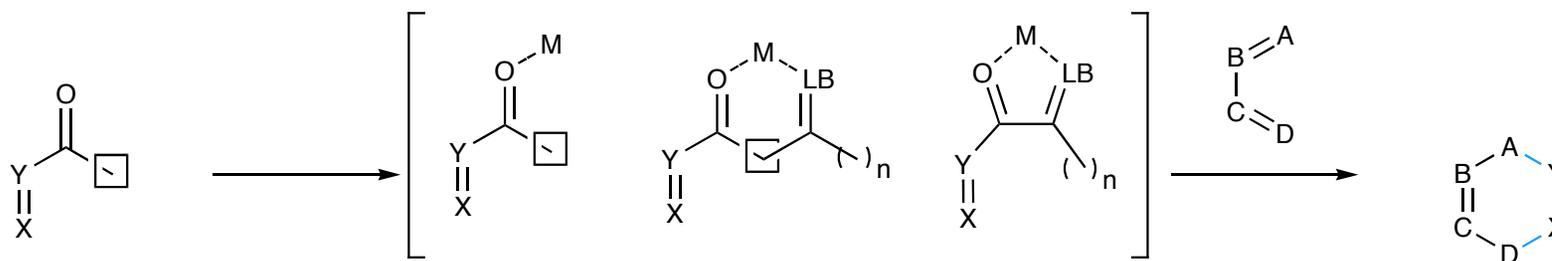
## A superabbreviated summary of the "Standard Method" (1992 review)

chiral catalyst (mol equiv)	reactants	ee max (%)
methylaluminum binaphtholate A (eq 2)	hetero Diels–Alder reaction	97
dichlorotitanium diolate + MS 4 Å (eq 8)	3-Acyl-1,3-oxazolidin-2-ones + Cp or isoprene	94
diborate from binaphthol (eq 16)	Cp + acrylate or methacrolein	90
acyloxy–borane (eq 18)	dienes + acrylic acid or $\alpha,\beta$ -unsaturated aldehydes	96
alkyldichloroborane (Figure 11)	dienes + $\alpha,\beta$ -unsaturated esters	97
oxazaborolidinone (Figure 12)	dienes + 2-bromoacrolein	95
$\text{BBr}_3$ + <i>N</i> -methylprolinol (eq 23)	Cp + $\alpha,\beta$ -unsaturated aldehydes	97
Co complex with chiral diphosphines	homo Diels–Alder reaction	98



Kagan and Riant, *Chem. Rev.* **1992**, 92, 1007-1019.; Evans, D. A.; Johnson J. S. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, 1999; Vol III, 1178-1235.; Dalko, *ACIEE* **2001** 40, 3726.; Houk, et al. *Acc. Chem. Res.*, **2004**, 37, 558.; Dalko, P., **2001**, *ACIEE* 40, 3726.; Nicolaou, *Angew Chem Int. Ed.* 2002, 41, 1668-1698.; Corey, *Angew Chem Int. Ed.* **2002**, 41, 1650-1667.; List, B. *Acc. Chem. Res.*, **2004**, 37, 548, *Acc. Chem. Res.* **2004**, 37, 580.; List, *Tetrahedron*, **2002**, 58, 5573.; List, *Synlett*, **2001**, 11, 1675.; Miller, S., *Tetrahedron*, **2002**, 58, 2481.; Stocking and Williams, *ACIEE.*, **2003**, 42, 3078-3115.; Narasaka, *Synthesis*, **1991**, 1-11.; Schreiber, *ACIEE.*, **1990**, 29, 256-272.

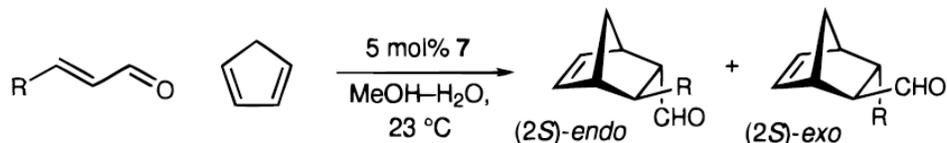
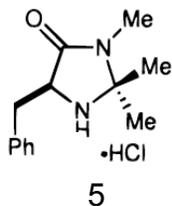
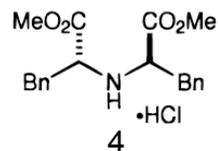
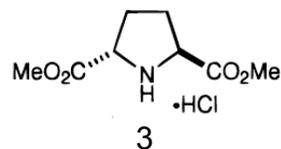
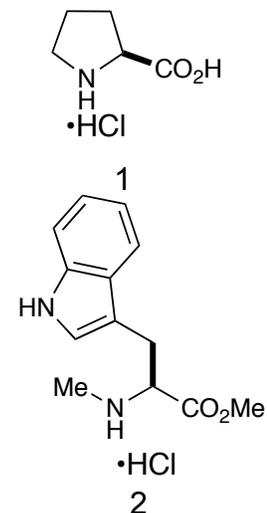
# Material Will be Covered in the order of “FG Complexity”



	$2\pi$	Aldehyde	Ketone	Carboxylic Acid Derivative	1,2 inclusive FG's (eg. Dimethylethylenedicarboxylate)	1,1-exclusive FG's (eg. Ketoester)	etc...
$4\pi$							
Carbocyclic only		□					
Acyclic							
O-substituted (danishefsky's diene)							
Heterocyclic (imine, special aldehydes)							
More complex Inverse electron demand (polycyclic, Heterocyclic, etc)							

Increasing FG complexity (more difficult to implement in a long synthesis)

# MacMillan: Extension from Imminium ion catalysis



## Catalyst survey

entry	catalyst	time (h)	yield (%)	<i>exo:endo</i>	<i>exo</i> ee (%)
1	1	27	81	2.7:1	48 (2 <i>R</i> )
2	2	10	80	2.3:1	59 (2 <i>S</i> )
4	4	23	92	2.6:1	57 (2 <i>R</i> )
3	3	84	82	3.6:1	74 (2 <i>R</i> )
5	5	8	99	1.3:1	93 (2 <i>S</i> ) <sup>c</sup>

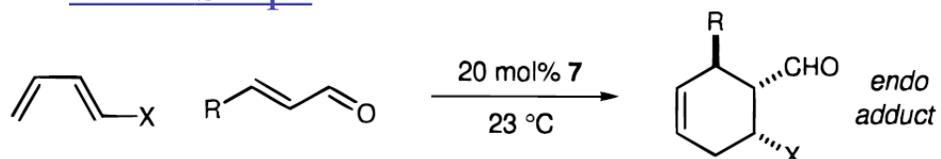
## Aldehyde scope

entry	R	time (h)	yield (%)	<i>exo:endo</i> <sup>a,b</sup>	<i>exo</i> ee (%)	<i>endo</i> ee (%)
1	Me	16	75	1:1	86 (2 <i>S</i> )	90 (2 <i>S</i> )
2	Pr	14	92	1:1	86 (2 <i>S</i> )	90 (2 <i>S</i> )
3	<i>i</i> -Pr	14	81	1:1	84 (2 <i>S</i> )	93 (2 <i>S</i> )
4	Ph	21	99	1.3:1	93 (2 <i>S</i> )	93 (2 <i>S</i> )
5	Furyl	24	89	1:1	91 (2 <i>S</i> )	93 (2 <i>S</i> )

Imine Lumo-lowering capability of imines extended to pericyclic process

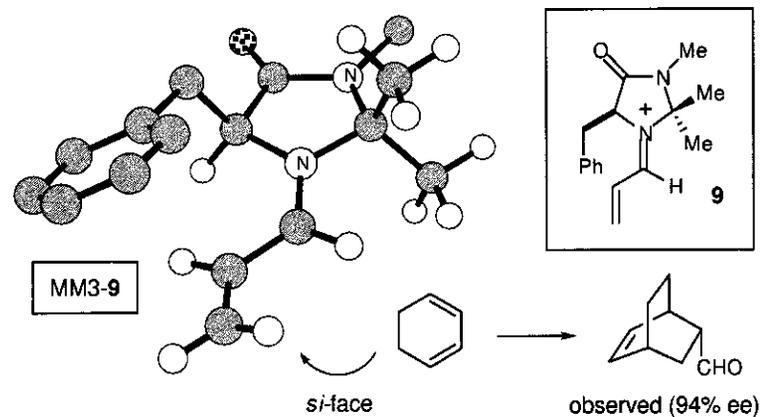
# MacMillan: [4+2] diene scope

## Diene Scope



entry	diene	R	product	yield	exo:endo	% ee <sup>a,b</sup>
1		Me		75	35:1	96 <sup>c</sup>
2		H		82	1:14	94 <sup>d</sup>
3		H		84	--	89
4		H		90	--	83
5		Me		75	--	90
6		H		75	1:5	90
7		H		72	1:11	85

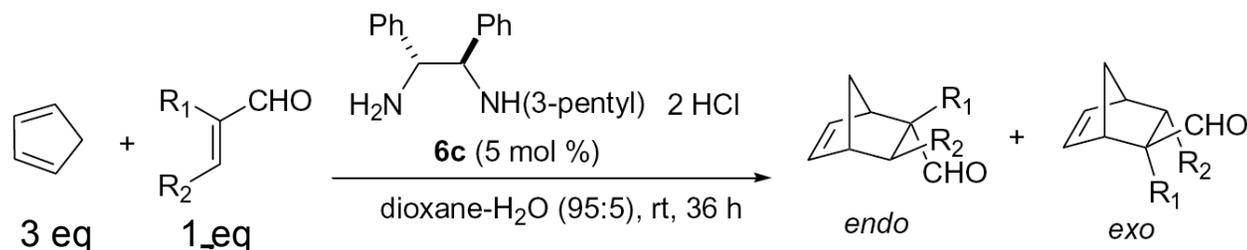
Gem-dimethyl group enforces E-enamine



Typically difficult substrates

# Enal dienophile: Broaden Scope and Increase Utility

- 1,2 Diamine Ha, D-H., *TL*, **2005**, 46, 5991-4.



Optimized  
Substrate, crotonaldehyde,  
Yield 97%, endo:exo (7.8:1),  
er (96:4)

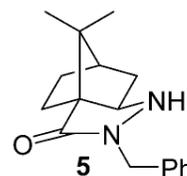
Yield, er and 2π facial selectivity  
Are low when R1 ≠ H, and R2 ≠ Ary or *i*-Pr

- Hydrazide Derived

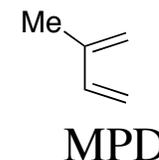
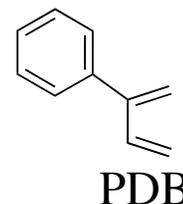
Use of HClO<sub>4</sub> and F<sub>3</sub>CSO<sub>3</sub>H  
as cocatalyst increases rates  
and selectivity

Goal: Increase rate via α-effect  
don't provide reaction times  
do show that imminium ion  
formation is faster than imidazolidinone

entry	diene	dienophile	yield (%) <sup>c</sup>	exo:endo	exo ee (%) <sup>11,14</sup>
1	CP <sup>b</sup>	( <i>E</i> )-PhCH=CHCHO	96	1.9:1	90
2	CP	( <i>E</i> )-4-NO <sub>2</sub> -PhCH=CHCHO	93	2.2:1	92
3	CP	( <i>E</i> )-4-Cl-PhCH=CHCHO	92	2:1	90 <sup>d</sup>
4	CP	( <i>E</i> )-4- <i>i</i> Pr-PhCH=CHCHO	84	1.7:1	90 <sup>d</sup>
5	PBD	( <i>E</i> )-4-NO <sub>2</sub> -PhCH=CHCHO	86	-	85
6	MPD	( <i>E</i> )-4-NO <sub>2</sub> -PhCH=CHCHO	71	1.9:1	69 <sup>d</sup>
7	CP	( <i>E</i> )-2-NO <sub>2</sub> -PhCH=CHCHO	90	1.2:1	87
8	CP	( <i>E</i> )-3-NO <sub>2</sub> -PhCH=CHCHO	88	2.1:1	94 <sup>d</sup>
9	CP	( <i>E</i> )-PrCH=CHCHO	83	1.6:1	81
10	CP	( <i>E</i> )- <i>i</i> Pr CH=CHCHO	84	2.6:1	85

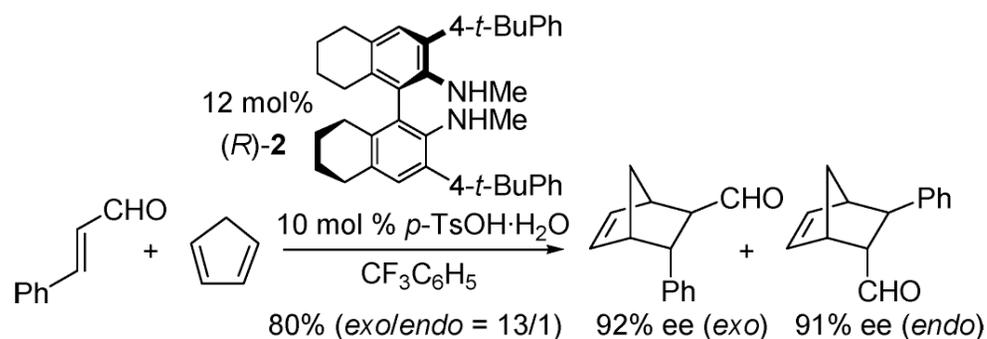


1 equiv aldehyde  
3 equiv diene  
0.2 equiv Catalyst  
0.2 equiv Acid (triflic)  
No time given



# A highly Exo Selective Catalyst

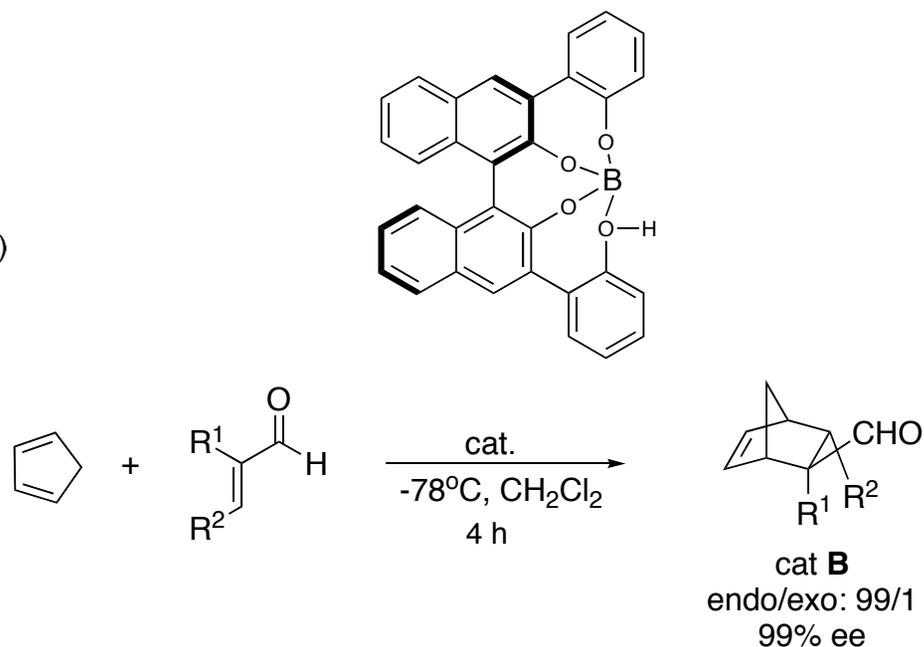
- Binam Derived



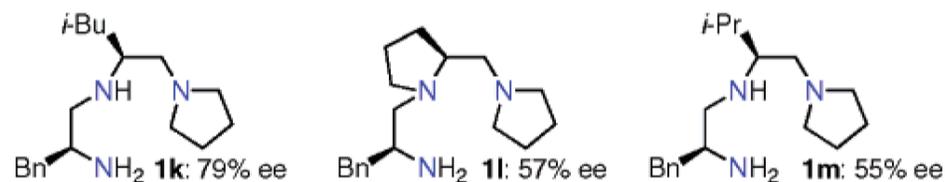
RT, 20h, 87%  
Exo:endo (6.5:1),  
er (86:14)

Need -20, 160h  
To get higher Er or Exo selectivity  
Rxn's are still slow

For Comparison

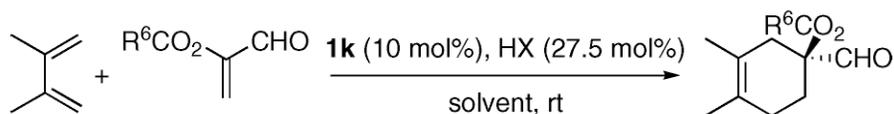


# Extension to $\alpha$ -Acetoxy Substituted Aldehydes



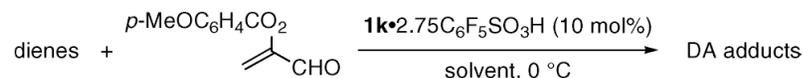
Standard Catalysts (a-j) gave low yields, and poor selectivity,

## Ester Scope

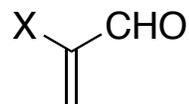


entry	R <sup>6</sup>	HX	solvent	time (h)	yield (%)	ee (%)
1	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> F <sub>5</sub> SO <sub>3</sub> H	EtNO <sub>2</sub>	8	>99	90
2	Ph	C <sub>6</sub> F <sub>5</sub> SO <sub>3</sub> H	EtNO <sub>2</sub>	16	97	87
3	Ph	C <sub>6</sub> F <sub>5</sub> SO <sub>3</sub> H	no solvent	12	95	85
4	Ph	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SO <sub>3</sub> H	EtNO <sub>2</sub>	12	85	85
5	Ph	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SO <sub>3</sub> H	H <sub>2</sub> O	20	81	82
6	Ph	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SO <sub>3</sub> H	H <sub>2</sub> O-C <sub>4</sub> H <sub>8</sub> O <sub>2</sub> <sup>b</sup>	20	67	80
7	Ph	TsOH	EtNO <sub>2</sub>	15	60	78
8	Me	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SO <sub>3</sub> H	EtNO <sub>2</sub>	24	56	83

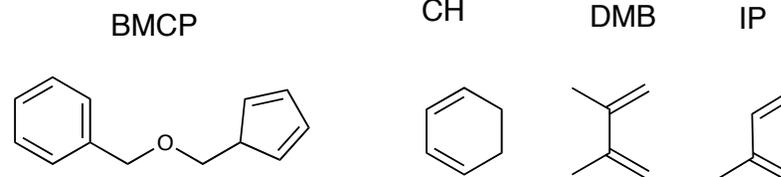
## Diene Scope



entry	diene	solvent	time (h)	yield (%)	<i>exo:endo</i>	ee (%) <sup>b</sup> [config]
1	CP <sup>c</sup>	THF	11	97	86:14	80 [2 <i>S</i> ]
2 <sup>d</sup>	CP <sup>c</sup>	THF	48	99	87:13	83 [2 <i>S</i> ]
3	BMCP <sup>c</sup>	THF	24	72	81:19	74 [2 <i>S</i> ]
4 <sup>d</sup>	BMCP <sup>c</sup>	THF	28	81	88:12	83 [2 <i>S</i> ]
5	CH <sup>c</sup>	EtNO <sub>2</sub>	48	84	7:93	91 [2 <i>R</i> ]
6	DMB	EtNO <sub>2</sub>	24	92		92 [-]
7 <sup>e</sup>	DMB	EtNO <sub>2</sub>	12	95		88 [-]
8	IP <sup>c</sup>	EtNO <sub>2</sub>	48	90	99:1 <sup>f</sup>	88 [-]



X = Halide (Br)  
Work well with LA's. Is the point moot?

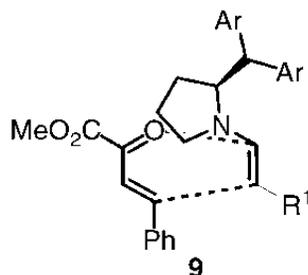


# Enamine intermediates: Hetero-Diels-Alder

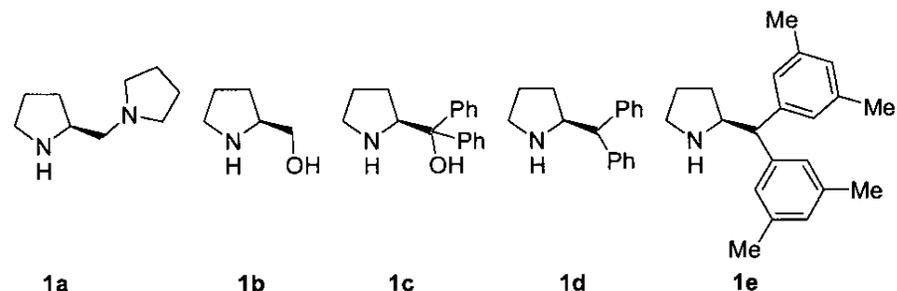
## Screening and Optimization

Entry	Catalyst (mol%)	Enone [equiv]	Solvent <sup>[a]</sup>	T <sup>[b]</sup>	Yield <sup>[c]</sup> [%]	ee <sup>[d]</sup> [%]
1	<b>1a</b> (20)	1.1	CH <sub>2</sub> Cl <sub>2</sub>	RT	69	51
2	<b>1b</b> (20)	1.1	CH <sub>2</sub> Cl <sub>2</sub>	RT	54	56
3	<b>1c</b> (20)	1.1	CH <sub>2</sub> Cl <sub>2</sub>	RT	6	97
4	<b>1d</b> (20)	1.1	CH <sub>2</sub> Cl <sub>2</sub>	RT	46	88
5	<b>1e</b> (10)	2	CH <sub>2</sub> Cl <sub>2</sub>	RT	71	87
6	<b>1e</b> (10)	1.5	CH <sub>2</sub> Cl <sub>2</sub>	-15 °C → RT	70	91
7	<b>1e</b> (10)	2	CH <sub>2</sub> Cl <sub>2</sub>	-15 °C → RT	93	89
8	<b>1e</b> (10)	2	toluene	-15 °C → RT	77	90
9	<b>1e</b> (10)	2	CDCl <sub>3</sub>	-15 °C → RT	69	92
10	<b>1e</b> (10)	2	ClCH <sub>2</sub> CH <sub>2</sub> Cl	-15 °C → RT	74	90
11	<b>1e</b> (10)	2	MeCN	-15 °C → RT	59	90

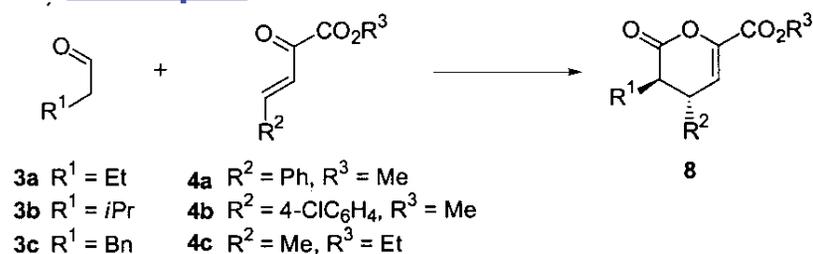
[a] Solvent (0.5 mL). [b] RT = room temperature. [c] Combined yield of **6ba** and **7ba**. [d] The ee values were determined by HPLC.



- Note two step procedure
- Reaction time ~15-40h



## Scope



Entry	3	4	8	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	<b>a</b>	<b>a</b>	<b>aa</b>	69	84
2	<b>b</b>	<b>a</b>	<b>ba</b>	93	89
3 <sup>[d]</sup>	<b>b</b>	<b>a</b>	<b>ba</b>	69	92
4 <sup>[e]</sup>	<b>c</b>	<b>a</b>	<b>ca</b>	65	86
5 <sup>[f]</sup>	<b>a</b>	<b>b</b>	<b>ab</b>	79	85
6 <sup>[f]</sup>	<b>b</b>	<b>b</b>	<b>bb</b>	70	90
7 <sup>[e,f]</sup>	<b>c</b>	<b>b</b>	<b>cb</b>	62	80
8	<b>a</b>	<b>c</b>	<b>ac</b>	81	86
9	<b>b</b>	<b>c</b>	<b>bc</b>	75	94
10 <sup>[e]</sup>	<b>c</b>	<b>c</b>	<b>cc</b>	72	89

[a] Reaction conditions (0.5 mmol scale): 1) **1e** (10 mol%), silica (50 mg), -15 → RT, CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL), 17 h; 2) PCC, CH<sub>2</sub>Cl<sub>2</sub>. [b] Combined yield of **6** and **7**. [c] The ee values were determined by HPLC or GC (entries 8 and 9) of **8**. [d] CDCl<sub>3</sub> used as solvent. [e] Reaction time = 40 h. [f] Solvent (2 mL).

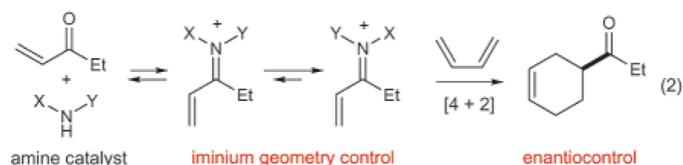
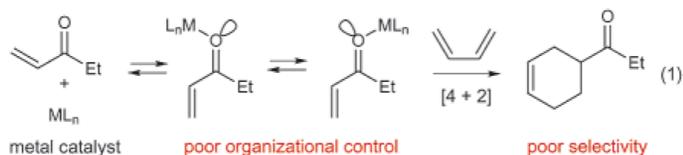
# Outline

	Aldehyde	Ketone	Carboxylic Acid Derivative	1,2 inclusive FG's (eg. Dimethylethylenedicarboxylate)	1,1-exclusive FG's (eg. Ketoester)	etc...
$4\pi$ / $2\pi$						
Carbocyclic only						
Acyclic						
O-substituted (danishefsky's diene)						
Heterocyclic (imine, special aldehydes)						
More complex Inverse electron demand (polycyclic, Heterocyclic, etc)						

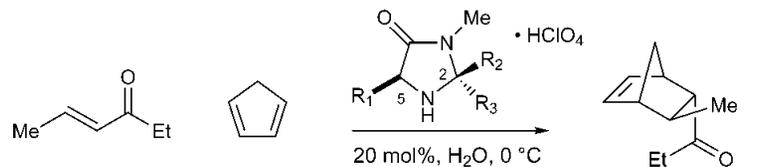
Increasing FG complexity (more difficult to implement in a long synthesis)

# MacMillan: Ketone Substrates

## Obstacles to overcome

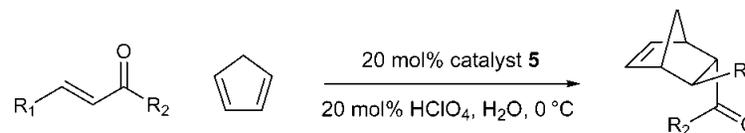


**Table 1.** Effect of Amine Architecture on the Diels–Alder Reaction between 4-Hexen-3-one and Cyclopentadiene

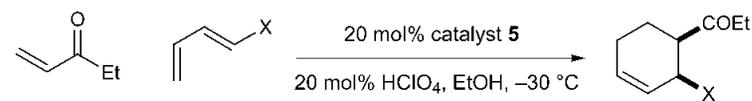


entry	cat.	R <sub>1</sub>	R <sub>2</sub> (R <sub>3</sub> )	time (h)	% yield	endo:exo	% ee <sup>a,b</sup>
1	<b>1</b>	Bn	Me (Me)	48	20 <sup>c</sup>	7:1	0
2	<b>2</b>	Bn	<i>t</i> -Bu (H)	48	27 <sup>c</sup>	9:1	0
3	<b>3</b>	Ph	Ph (H)	22	88	21:1	47
4	<b>4</b>	Bn	Ph (H)	42	83	23:1	82
5	<b>5</b>	Bn	5-Me-furyl (H)	22	89	25:1	90

## Scope



entry	R <sub>1</sub>	R <sub>2</sub>	% yield	endo:exo	% ee <sup>a,b</sup>
1	Me	Me	85	14:1	61
2	Me	Et	89	25:1	90
3	Me	<i>n</i> -Bu	83	22:1	92 <sup>c</sup>
4	Me	<i>i</i> -Am	86	20:1	92
5	Me	<i>i</i> -Pr	24	8:1	0
6	<i>n</i> -Pr	Et	84	15:1	92
7	<i>i</i> -Pr	Et	78	6:1	90



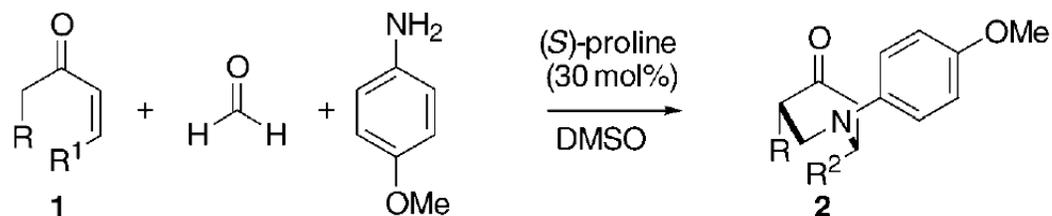
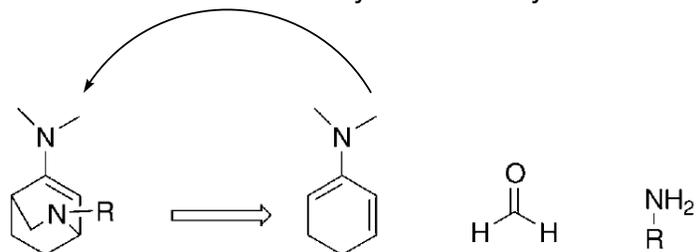
entry	diene	product	endo:exo	% yield	% ee <sup>a,b</sup>
1			>200:1	88	96
2			>100:1	91	98
3 <sup>c</sup>			>200:1 <sup>d</sup>	92	90
4			>200:1	90	90
5 <sup>e</sup>			>200:1 <sup>d</sup>	79	85 <sup>f</sup>

## Note perchlorate counterion

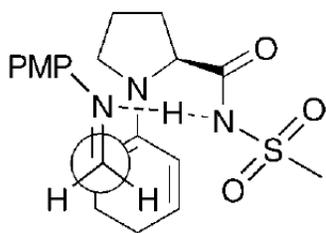
For rate acceleration  
with perchlorate (5.0 M) see  
Grieco, *JACS*, **1990**, *112*, 4595.

# Extension to Inverse Electron Demand: Imine Dienophile: Enaminediene

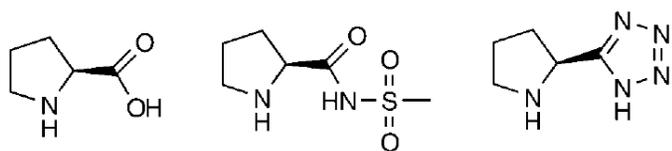
1. Generate Imine
2. Generate enamine
3. Undergo reaction
4. Release secondary amine catalyst



## TS Model, Implying stepwise mechanism



## Catalysts Surveyed



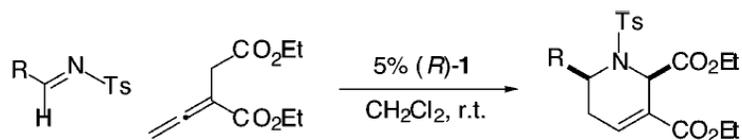
Slower reaction  
~ 1/2 rate

## Scope

Entry	Ketone	Product	<i>t</i> [h]	<i>T</i> [°C]	Yield [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
1		<b>1a</b>	<b>2a</b> 24	50	82 <sup>[d]</sup>	99
2		<b>1b</b>	48	50	72	>99
3		<b>1b</b>	17	RT	70	>99
4		<b>1c</b>	24	50	90 <sup>[e]</sup>	98
5		<b>1c</b>	24	RT	75	98
6		<b>1c</b>	24	RT	20 <sup>[f]</sup>	96 <sup>[f]</sup>
7		<b>1d</b>	<b>2d</b> 24	RT	40	94
8		<b>1e</b>	<b>2e</b> 24	RT	10	n.d. <sup>[g]</sup>

# Imine Dienophile 1,1-disubstituted allene = Diene equivalent

## The reaction



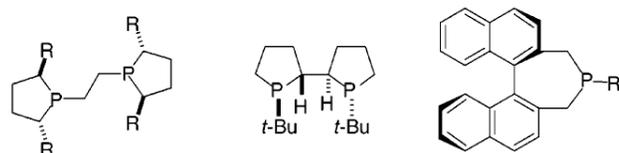
## Mechanism?

## Scope

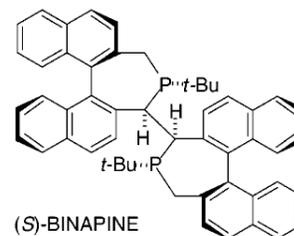
entry	R	ee (%) <sup>b</sup>	cis:trans	isolated yield (%)
1	Ph	98	91:9	93
2	3-MeC <sub>6</sub> H <sub>4</sub>	98	93:7	98
3	3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	96	96:4	86
4	4-(MeO)C <sub>6</sub> H <sub>4</sub>	98	93:7	42
5	4-ClC <sub>6</sub> H <sub>4</sub>	96	91:9	99
6	3-BrC <sub>6</sub> H <sub>4</sub>	99	89:11	98
7	2-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	68	96:4	98
8	2-ClC <sub>6</sub> H <sub>4</sub>	60	79:21	75
9	2-naphthyl	99	93:7	96
10	2-furyl	97	87:13	98
11	3-pyridyl	97	91:9	76

er moderate with electron poor substrates

## Catalysts: Bis-phosphines and phosphepines



R = Me: (*R,R*)-Me-BPE  
 R = Et: (*R,R*)-Et-BPE  
 (*S,S,R,R*)-TANGPHOS  
 R = Ph ((*R*)-**2**)  
 R = 4-MeO-C<sub>6</sub>H<sub>4</sub> ((*R*)-**3**)  
 R = NEt<sub>2</sub> ((*R*)-**4**)  
 R = Et ((*R*)-**5**)  
 R = *i*-Pr ((*R*)-**6**)  
 R = *t*-Bu ((*R*)-**1**)



entry	phosphine	ee (%) <sup>b</sup>	cis:trans	isolated yield (%)
1	Me-BPE	-72	72:28	94
2	Et-BPE	-87	66:34	99
3	TANGPHOS	-44	34:66	99
4	<b>2</b>	-21	74:26	80
5	<b>3</b>	-7	75:25	99
6	<b>4</b>	-62	72:28	53
7	<b>5</b>	0	70:30	46
8	<b>6</b>	51	69:31	99
9	<b>1</b>	98	91:9	93
10	BINAPINE	-	-	0

dr with bisphosphines variable in  
Benzaldehyde imine test substrate

For the initial racemic report see:

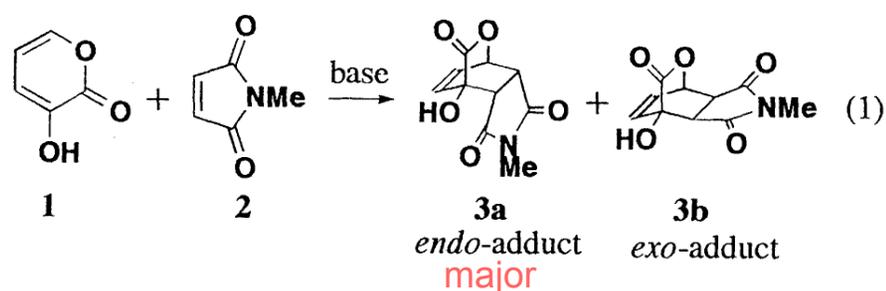
Zhu, X-F.; Lan, J.; Kwon, O. *JACS*, **2003**, *125*, 4716-4717.

Fu, G., et al., *JACS*, **2005**, *127*, 12234-12235

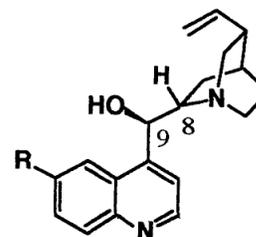
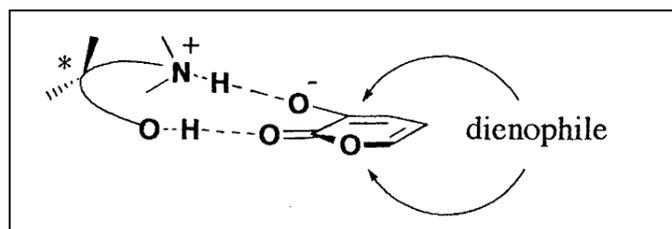
# Outline

$4\pi$	$2\pi$	Aldehyde	Ketone	Carboxylic Acid Derivative	1,2 inclusive FG's (eg. Dimethylethylen- dicarboxylate)	1,1- exclusive FG's (eg. Ketoester)	etc...
Carbocyclic only							
Acyclic							Increasing FG complexity (more difficult to implement in a long synthesis)
O-substituted (danishefsky's diene)							
Heterocyclic (imine, special aldehydes)							
<p>More complex Inverse electron demand (polycyclic, Heterocyclic, etc)</p>							

# Chiral Base Activation of Diene (1,2-inclusive)

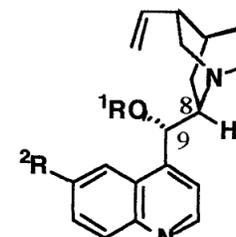


via



4: R = H, cinchonidine

5: R = OMe, quinine

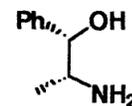


6a: R<sup>1</sup>, R<sup>2</sup> = H, cinchonine

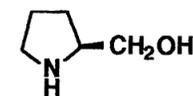
6b: R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = H

6c: R<sup>1</sup> = PhCO, R<sup>2</sup> = H

7: R<sup>1</sup> = H, R<sup>2</sup> = OMe, quinidine



8: (+)-norephedrine



9: (+)-prolinol

## Catalyst survey

entry	catalysts (eq)	time/h	yield/% <sup>b</sup>	3a:3b <sup>c</sup>	%ee <sup>d</sup>
1	4 (1.0)	0.5	91	7.8:1	74 (-)
2	5 (1.0)	0.5	100	8.2:1	53 (-)
3	6a (0.1) <sup>e</sup>	0.5	95	7.1:1	71 (+)
4	7 (1.0)	0.5	100	7.2:1	42 (+)
5	8 (1.0)	0.5	84	9.6:1	14 (+)
6	9 (1.0)	0.5	98	8.5:1	9 (-)
7	6b (1.0)	1.0	93	5.9:1	17 (+)
8	6c (1.0)	1.5	93	6.6:1	0

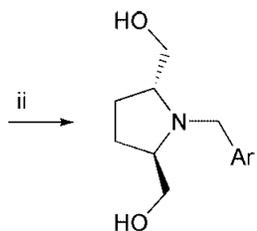
18h →

## Solvent and Temperature

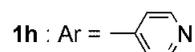
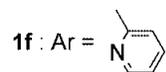
entry	catalysts	solvent	temp/°C	yield/% <sup>b</sup>	3a:3b	%ee <sup>c</sup>
1	4 (1.0)	CH <sub>2</sub> Cl <sub>2</sub>	-78--20	98	11:1	77
2	4 (1.0)	CH <sub>2</sub> Cl <sub>2</sub>	0	91	7.8:1	74
3	4 (0.1)	CH <sub>2</sub> Cl <sub>2</sub>	0	100	6.9:1	66
4	4 (<0.1) <sup>d</sup>	toluene	0	89	2.6:1	63
5	4 (1.0)	THF	0	96	2.1:1	33
6	4 (1.0)	MeOH	0	98	7.7:1	0
7	6a (<0.1) <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	-78--20	95	12:1	51
8	6a (0.1) <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	0	95	7.1:1	71
9	6a (<0.1) <sup>d</sup>	toluene	0	93	3.7:1	44
10	6a (0.5) <sup>d</sup>	THF	0	95	4.6:1	35
11	6a (1.0)	MeOH	0	100	10:1	0

# Chiral Base: Recent Application to Anthrone

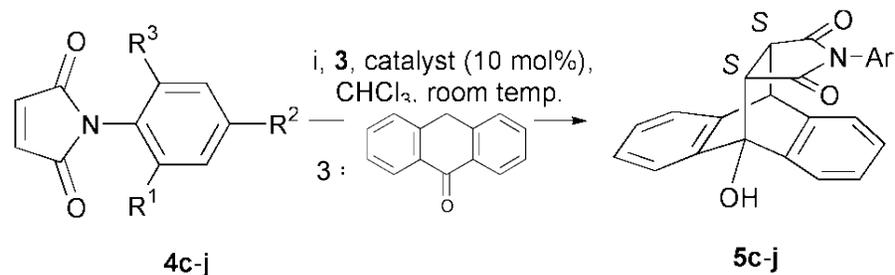
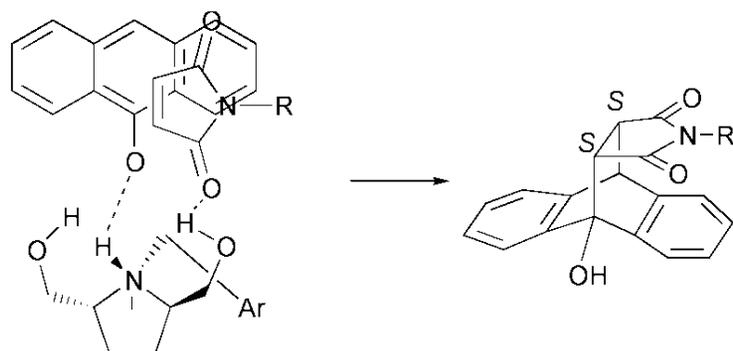
## Catalysts



1d : Ar = Ph



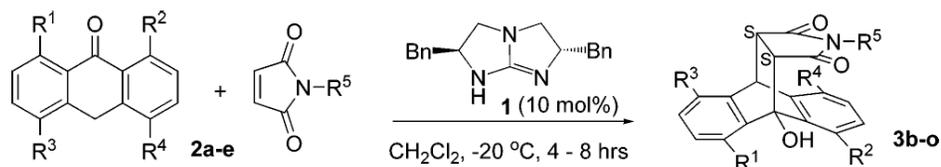
## Proposed Model



Product	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Catalyst	t/h	Yield (%)	Ee (%)
<b>5c</b>	H	H	H	<b>2</b>	1	93	20
				<b>1b</b>	2	95	51
				<b>1h</b>	24	91	61
<b>5d</b>	H	CF <sub>3</sub>	H	<b>2</b>	0.75	86	33
				<b>1b</b>	0.25	80	46
				<b>1h</b>	18	85	50
<b>5e</b>	H	F	H	<b>2</b>	0.25	89	30
				<b>1b</b>	1	93	55
				<b>1h</b>	18	88	57
<b>5f</b>	H	OMe	H	<b>2</b>	0.2	68	27
				<b>1b</b>	1	95	74
				<b>1h</b>	18	96	62
<b>5g</b>	Cl	H	Cl	<b>2</b>	4	80	38
				<b>1b</b>	2	72	59
				<b>1h</b>	24	55	63
<b>5h</b>	Br	Br	H	<b>2</b>	1.5	80	25
				<b>1b</b>	2	73	63
				<b>1h</b>	96	56	52
<b>5i</b>	Me	Me	H	<b>2</b>	10	75	11
				<b>1b</b>	5	53	50
				<b>1h</b>	72	50	47
<b>5j</b>	Bu'	H	H	<b>2</b>	0.25	95	40
				<b>1b</b>	0.25	99	81
				<b>1h</b>	3	97	87

# C2 Symmetric Guanidine as Chiral Base

## Solvent effect



entry	solvent	temp/ $^\circ\text{C}$	time/h	yield/% <sup>a</sup>	ee/% <sup>b</sup>
1	THF	rt	1	92	7
2	toluene	rt	1	88	12
3	$\text{CH}_2\text{Cl}_2$	rt	1	91	52
4	$\text{CHCl}_3$	rt	1	95	52
5	$\text{ClCH}_2\text{CH}_2\text{Cl}$	rt	1	90	44
6	$\text{CH}_2\text{Cl}_2$	0	1.5	90	68
7	$\text{CH}_2\text{Cl}_2$	$-20$	3	90	81 <sup>c</sup>
8	$\text{CH}_2\text{Cl}_2$	$-40$	6	91	75

Only halogenated  
Gives good er

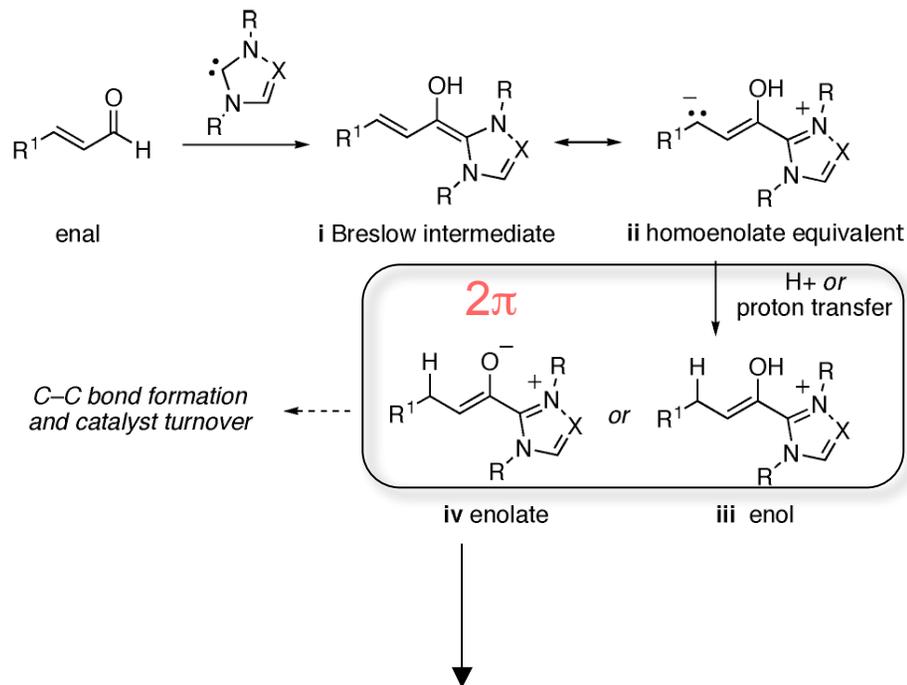
entry	<b>2</b> [ $\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4$ ]	$\text{R}^5$	<b>3</b>	yield/% <sup>a</sup>	ee/% <sup>b</sup>
1	<b>2a</b> [H, H, H, H]	2- $\text{NO}_2\text{C}_6\text{H}_4$	<b>3b</b>	87	98
2	<b>2a</b>	2,5- $\text{Cl}_2\text{C}_6\text{H}_3$	<b>3c</b>	88	95
3	<b>2b</b> [Cl, Cl, H, H]	Bn	<b>3d</b>	92	95
4	<b>2b</b>	<i>c</i> -hexyl	<b>3e</b>	88	98
5	<b>2b</b>	<i>t</i> -butyl	<b>3f</b>	87	93
6	<b>2b</b>	<i>i</i> -butyl	<b>3g</b>	92	91
7	<b>2b</b>	4- $\text{ClC}_6\text{H}_5\text{CH}_2$	<b>3h</b>	85	98 <sup>c</sup>
8	<b>2c</b> [H, H, Cl, Cl]	Ph	<b>3i</b>	92	99
9	<b>2c</b>	2,6- $\text{F}_2\text{C}_6\text{H}_3$	<b>3j</b>	92	99
10	<b>2c</b>	2- $\text{MeOC}_6\text{H}_4$	<b>3k</b>	90	98
11	<b>2d</b> [H, Cl, Cl, H]	Ph	<b>3l-1</b>	87	99
12	<b>2d</b>	2,4,6- $\text{Me}_3\text{C}_6\text{H}_2$	<b>3m-1</b>	85	99
13	<b>2e</b> [H, H, NHMe, H]	Et	<b>3n-1</b>	95	98
14	<b>2e</b>	<i>c</i> -hexyl	<b>3o-1</b>	96	85

Mechanism papers:  
Rickborn, B. *Org. Lett.* 2002, 4, 1711-1713.  
Koemer, M., Rickborn, B. *J. Org. Chem.* 1990, 55, 2662-2672.  
Koemer, M.; Rickborn, B. *J. Org. Chem.* 1989, 54, 6-9.  
For a review (er max 80:20) see:  
Kagan, *TL*, **1989**, 30, 7403-7406.  
Okamura, H., et al., *Tetrahedron*, **2001**, 57, 1903.

# Outline

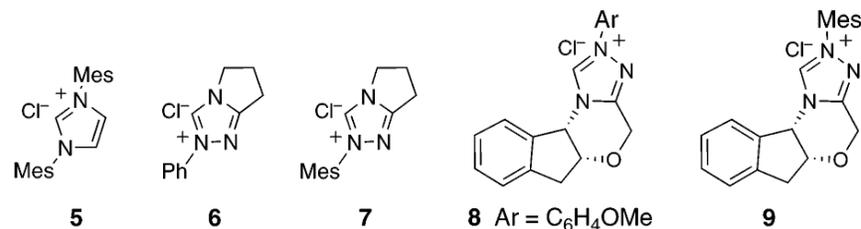
$4\pi$ / $2\pi$	Aldehyde	Ketone	Carboxylic Acid Derivative	1,2 inclusive FG's (eg. Dimethylethylenedicarboxylate)	1,1-exclusive FG's (eg. Ketoester)	etc...
Carbocyclic only						Increasing FG complexity (more difficult to implement in a long synthesis)
Acyclic						
O-substituted (danishefsky's diene)						
Heterocyclic (imine, special aldehydes)						
More complex Inverse electron demand (polycyclic, Heterocyclic, etc)						

# Ketenes dienophiles!? (from Enals!)

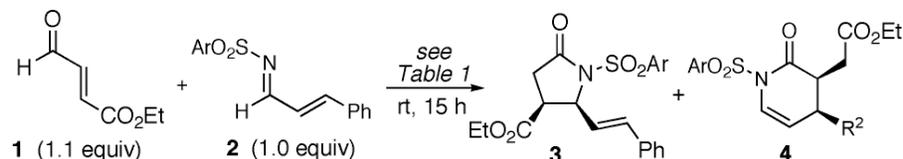


[4+2] ?

## Catalysts



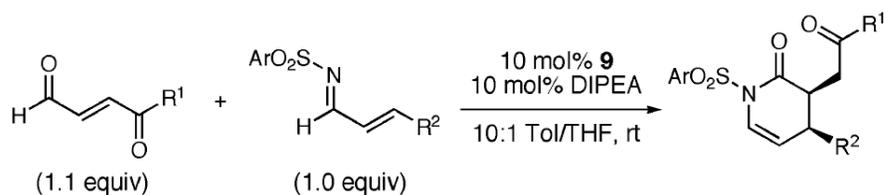
## Optimized for 4: base, solvent, catalyst



entry	cat. (%)	conditions	3:4 <sup>a</sup>	% conv. <sup>b</sup>
1	5 (15)	10 mol % of DBU, 0.1 M THF	>10:1	36 (7:1 dr)
2	5 (15)	10 mol % of DIPEA, 0.1 M THF	>10:1	13 (2:1 dr)
3	6 (15)	10 mol % of DBU, 0.1 M THF		nr
4	7 (15)	10 mol % of DBU, 0.1 M THF	1:8	47
5	7 (15)	10 mol % of DBU, 0.1 M EtOAc	1:5	38
6	7 (15)	10 mol % of DBU, 0.1 M toluene	1:10	44
7	7 (15)	10 mol % of DIPEA, 0.1 M toluene	>1:20 <sup>c</sup>	44
8	7 (10)	10 mol % of DIPEA, 23 h 0.05 M 10:1 toluene:THF	>1:20 <sup>c</sup>	63
9	8 (10)	10 mol % of DIPEA, 23 h 0.05 M 10:1 toluene:THF		nr
10	9 (10)	10 mol % of DIPEA, 23 h 0.05 M 10:1 toluene:THF	>1:20 <sup>c</sup>	90% yield <sup>d</sup> 99.5% ee

# Ketenes dienophiles!? (from Enals!)

## Scope



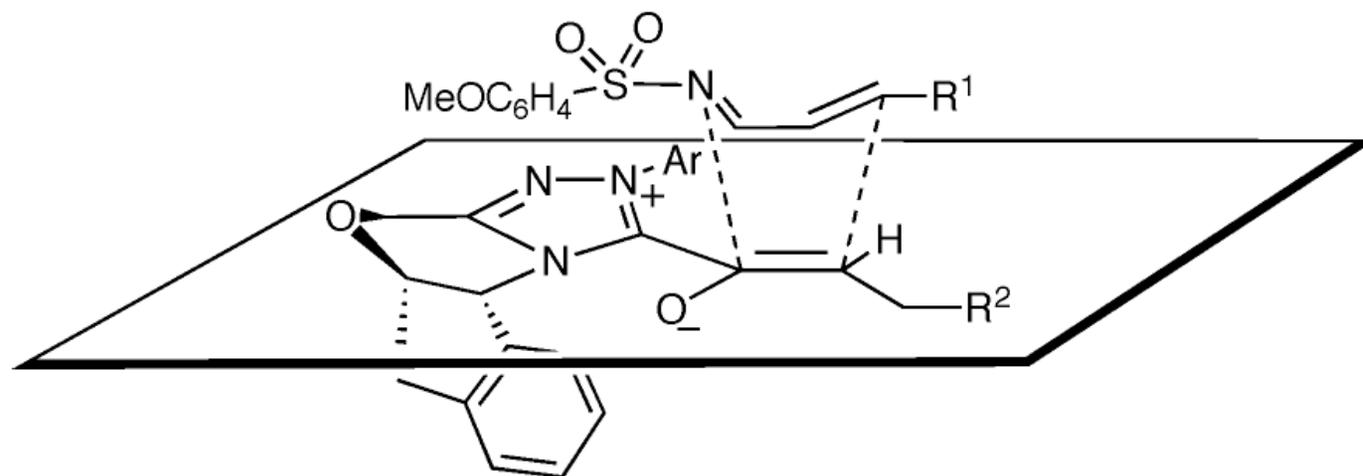
entry	R <sup>1</sup>	R <sup>2</sup>	product	% yield <sup>b</sup>	% ee <sup>d</sup>
1	OEt	Ph		90	99 ( <i>S,S</i> )
3	OEt			81	99 ( <i>S,S</i> )
4	OEt			55	99 ( <i>S,S</i> )
5	OEt			71	99 ( <i>S,S</i> )
6	OEt	<i>n</i> -Pr		58	99 ( <i>S,S</i> )

## Ketones too

entry	R <sup>1</sup>	R <sup>2</sup>	product	% yield <sup>b</sup>	% ee <sup>c</sup>
1	O <sup>t</sup> Bu	Ph		70	97 ( <i>S,S</i> )
2 <sup>b</sup>	Me	Ph		51	99 ( <i>S,S</i> )
3	Me	<i>n</i> -Pr		71	98 ( <i>S,S</i> )
4	Ph			52	99 ( <i>S,S</i> )

Ketones show slightly depressed Yields (still excellent er's!)

# Bode ketene [4+2] model



- Intermediate geometry from stoichiometric experiments and by analogy to other reactions with same intermediate (maybe)

Similar transformations

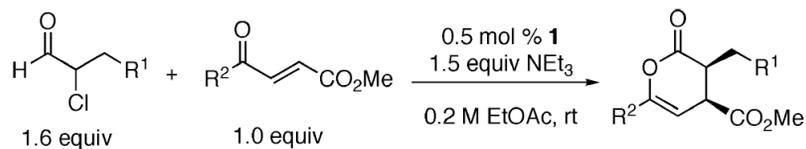
Boger, *JACS*, **1989**, *111*, 1517-1519. And  
*JACS*, **1991**, *113*, 1713-1729.

Fower, *TL*, **1989**, *30*, 2481-2484. And  
*JOC*, **1996**, *61*, 3715-3728.

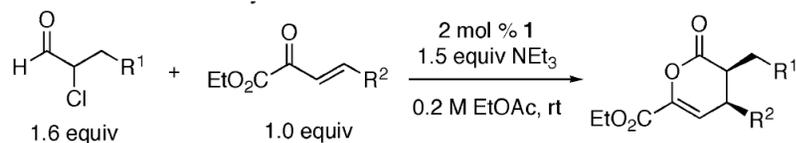
Hsung, R. P. *Tetrahedron*, **2004**, *60*, 7629-7636.

# Extension to synthesis of $\delta$ -lactones

## Reaction



## Scope



entry	R <sup>1</sup> =	R <sup>2</sup> =	product	% yield <sup>b</sup>	% ee <sup>c</sup>
1	Ph	<i>p</i> -Tol		74	97 ( <i>S,S</i> )
2	Ph	<i>n</i> -Pr		84	98 ( <i>S,S</i> )
3	Ph	<i>c</i> -Hex		85	95 ( <i>S,S</i> )
4	<i>n</i> -C <sub>9</sub> H <sub>19</sub>	<i>p</i> -Tol		70	99 ( <i>S,S</i> )
5	OTBS	<i>p</i> -Tol		83	95 ( <i>R,S</i> )

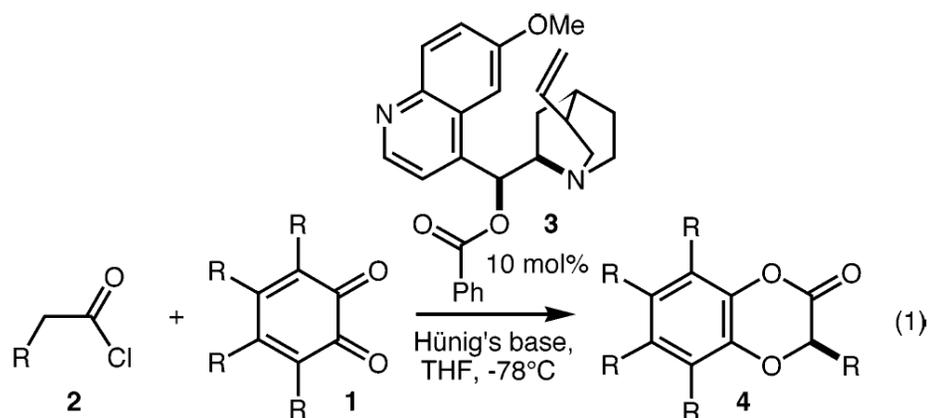
Dr's typically >10:1  
OTBs substrate 3:1

# Outline

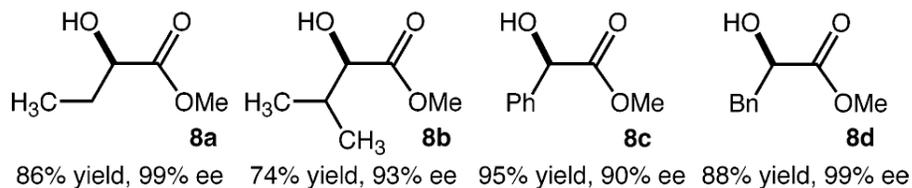
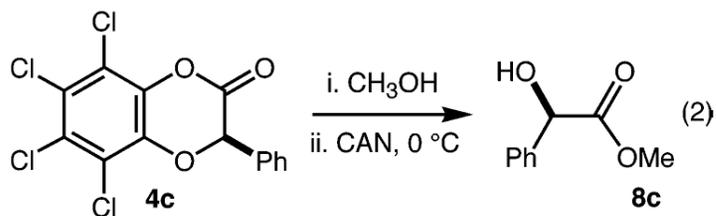
$4\pi$ / $2\pi$	Aldehyde	Ketone	Carboxylic Acid Derivative	1,2 inclusive FG's (eg. Dimethylethylenedicarboxylate)	1,1-exclusive FG's (eg. Ketoester)	etc...
Carbocyclic only						
Acyclic						
O-substituted (danishefsky's diene)						
Heterocyclic (imine, special aldehydes)						
More complex Inverse electron demand (polycyclic, Heterocyclic, etc)						

Increasing FG complexity (more difficult to implement in a long synthesis)

# Carboxylic Acid to Ketene + o-quinone: Extension of [2+2]



## Ultimate applicability



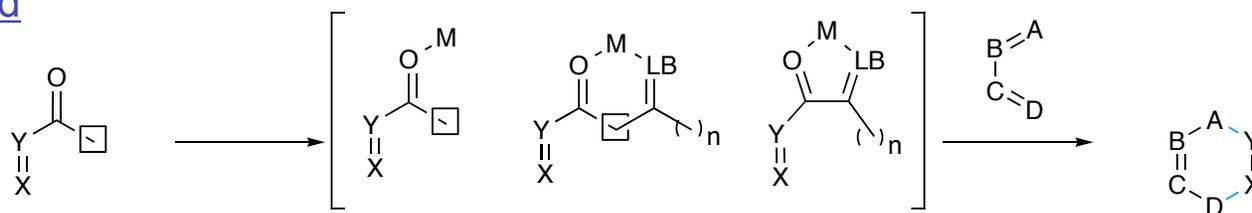
**Table 1.** Synthesis of o-Chloranil-Derived Cycloadducts

entry	acid chloride	product	% ee	% yield <sup>a</sup>
1			99	91
2			93	75
3			90	90
4			99	72
5			99	58
6			93	75

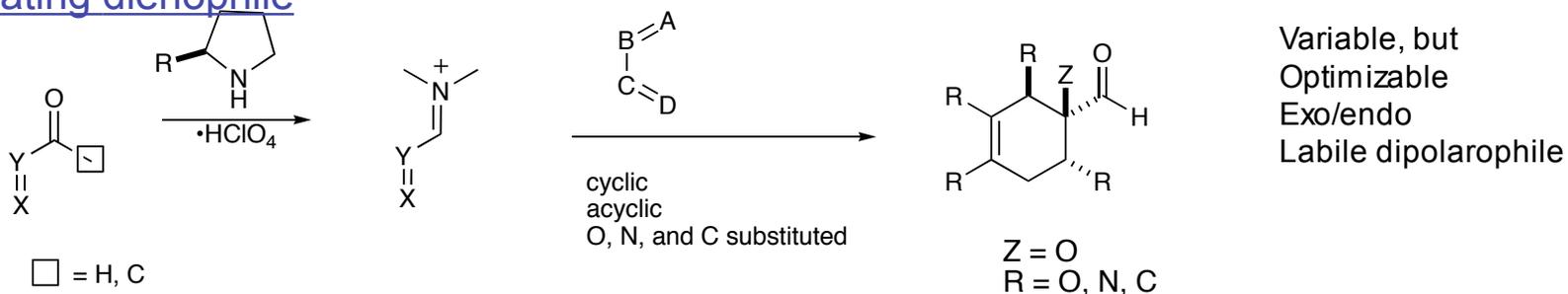
<sup>a</sup> Reactions run with 10 mol % catalyst, 0.55 mmol Hunig's base, 0.55 mmol acid halide, and 0.55 mmol **1a** at -78 °C with slow addition of the acid halide over 5 h employed for α-aryl acid halides (**2c**, **e**, **f**). Yields given are for isolated products.

# [4+2] Summary: By Catalyst and Reaction Type

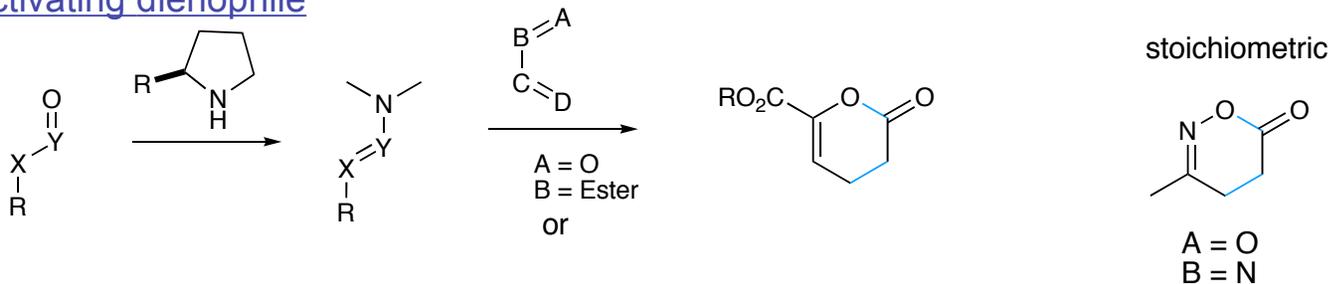
## Lewis Acid



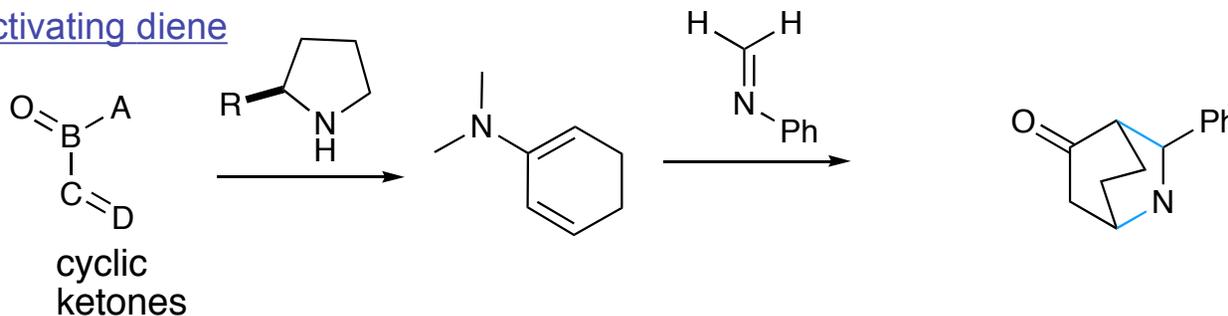
## Imine Activating dienophile



## Enamine Activating dienophile

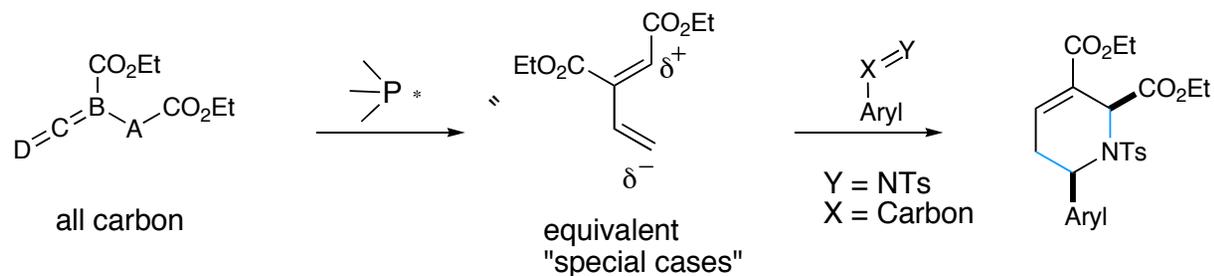


## Enamine Activating diene

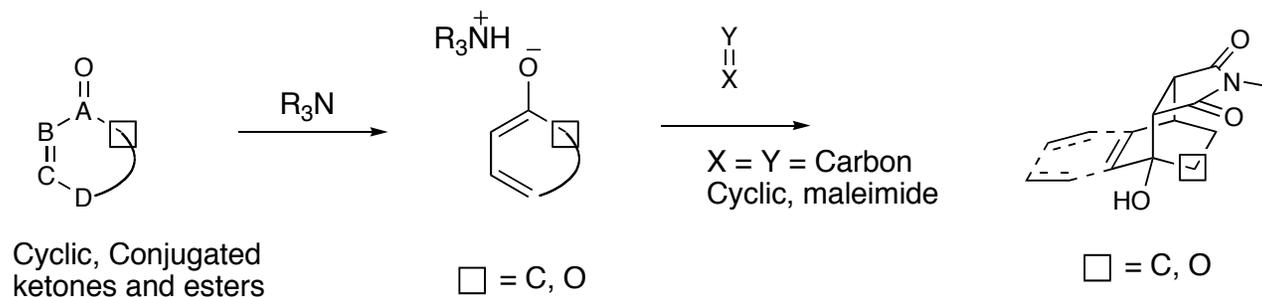


# [4+2] Summary

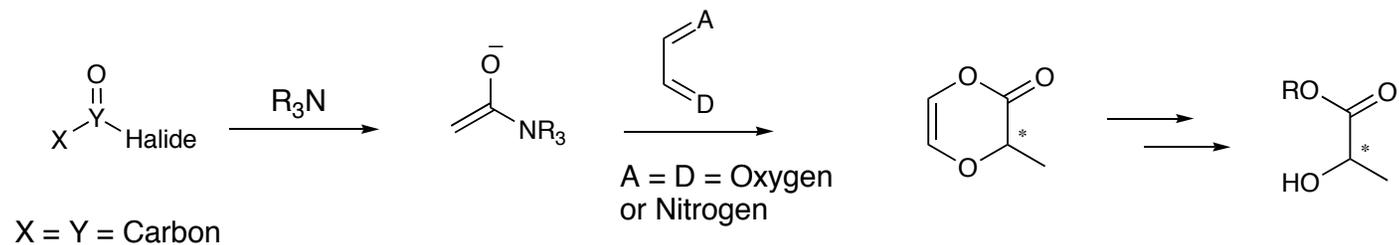
## Tertiary Phosphines Activating "diene"



## Tertiary Amines Activating "diene"

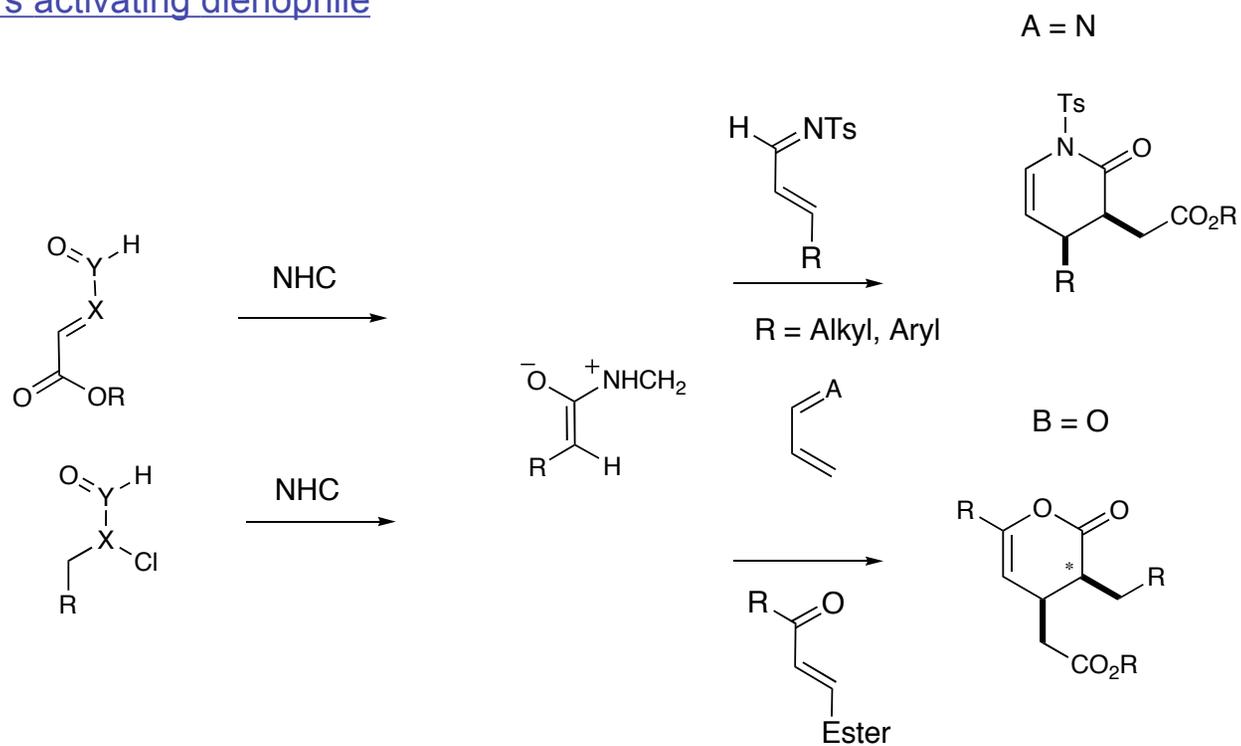


## Tertiary Amines Activating dienophile



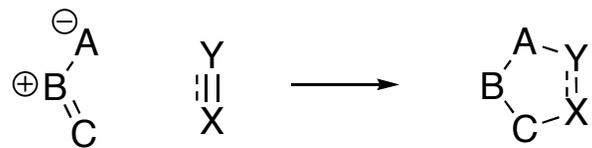
# [4+2] Summary

## NHC's activating dienophile



## [3+2]: Outline:

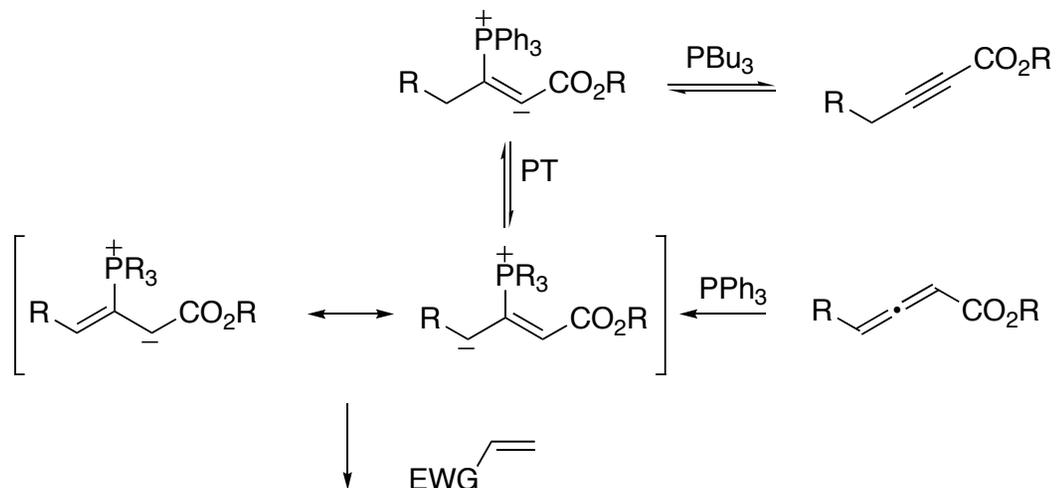
---



- A=B=C=X=Y=Carbon
- A, B, or C are heteroatoms

# All Carbon [3+2]: Activate the 4π (3 atom) Method is predominant

- Background literature, Proof of principle and Preliminary reports



## Limitations / Trends

Crotonates and methyl methacrylate  
 Dimerize too fast ---> Need  
 Activated alkene  
 Alkynes need more nucleophilic  
 Phosphine,



major in  
 all cases >4:1

yield 60-80's (methyl ketone 55)

1995: X = OMe  
 EWG = Ester, Ketone, Nitrile  
 0.1 equiv PR<sub>3</sub>, Benzene, rt  
 TEA does not work

## Other reactions too

For reviews see:

Roush, W., and Methot. J., *Adv. Synth. Catal.*,  
**2004**, **346**, 1035-1050

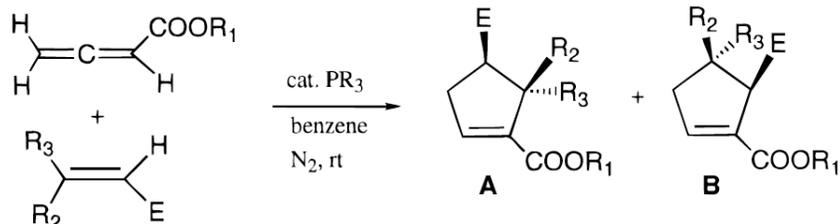
and

Denmark, S. E., Beutner, G. E., *Lewis Base Catalysis:  
 An Emerging Paradigm in Organic Synthesis...*

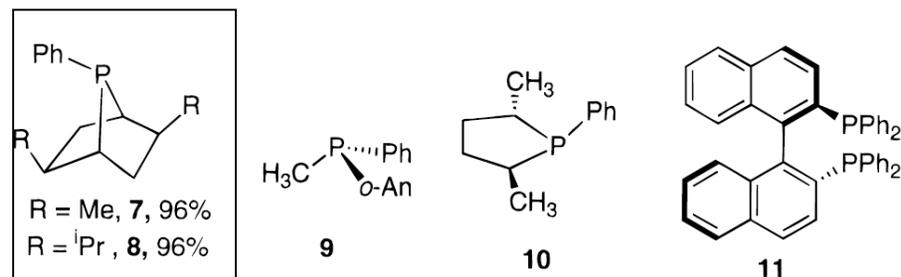
Zhang, C.; Lu, X. *J. Org. Chem.* 1995, 60, 2906. Xu, Z.; Lu, X. *Tetrahedron Lett.* 1997, 38, 3461. (b) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* 2005, 70, 6369. Lu, X.; Lu, Z.; Zhang, X. *Tetrahedron* 2006, 61, 457. Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* 1997, 119, 3836. Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* 2006, 45, 1426. Jean, L.; Marinetti, A. *Tetrahedron Lett.* 2006, 47, 2141. Scherer, A.; Gladysz, J. A. *Tetrahedron Lett.* 2006, 47, 6335. Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* 2003, 125, 4716. Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* 2005, 127, 12234. Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* 2005, 7, 1387. Dudding, T.; Kwon, O.; Mercier, E. *Org. Lett.* 2006, 8, 3643. Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* 2002, 67, 8901.

# Enantioselective All Carbon [3+2]!

## The Reaction



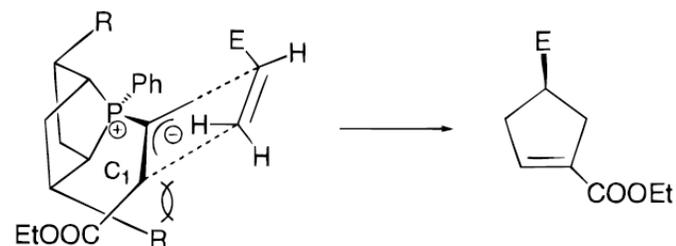
## Catalysts



## Results

entry	phosphine	E	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	solvent	T (°C) <sup>e</sup>	yield (%)	A:B <sup>b</sup>	% ee of A <sup>b</sup>	config <sup>c</sup>
1	<b>7</b>	COOEt	Et	H	H	benzene	rt	66	95:5	81	(-) R
2	<b>8</b>	COOEt	Et	H	H	benzene	rt	76	97:3	81	(-) R
3	<b>9</b>	COOEt	Et	H	H	benzene	rt	80	80:20	56	(+) S
4	<b>10</b>	COOEt	Et	H	H	benzene	rt	83	72:29	6	(+) S
5	<b>11</b>	COOEt	Et	H	H	benzene	rt	33	73:27	12	(-) R
11	<b>8</b>	COO <sup>t</sup> Bu	Et	H	H	toluene	0	<b>88</b>	<b>100:0</b>	<b>93</b>	(-) R

## Proposed TS: concerted [3+2]

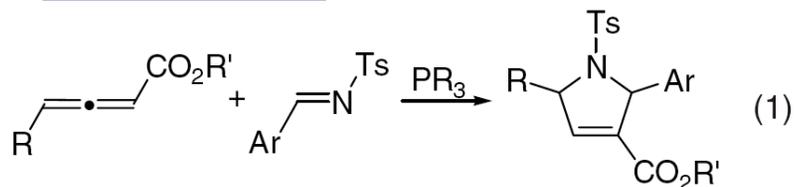


Geometry of Acceptor Olefin unchanged  
Acrylonitrile, fumarate and maleate give  
depressed yields and er's.

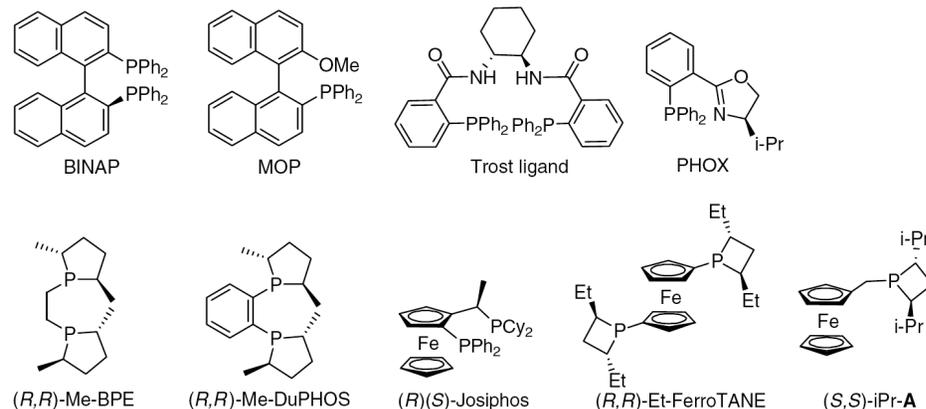
Zhang, X., *JACS*, **1997**, *119*, 3836-3837.

# Extension to Imine dipolarophiles

## The Reaction



## Catalysts



## Results

Unsubstituted (Ar = Ph, Naph)

Entry	Catalyst	ee <sup>b</sup>	Yield <sup>a</sup> (%)	ee	Yield (%)
1	(S)-BINAP	45% (+)	13	18% (+)	12
2	(R)(+)-MOP	11% (+)	45		
3	(R,R)-Trost ligand	19% (-)	60		
4	(R)-PHOX	0%	18		
5	(R,R)-Me-BPE	0%	70		
6	(R,R)-Me-DuPHOS			7% (-)	21
7	(R,S)-Josiphos			15% (+)	27
8	(R,R)-Et-FerroTANE	22% (+)	47	28% (+)	32
9	(S,S)-iPr-A	44% (+)	34	29% (+)	23

## Effect of Ester Substituent

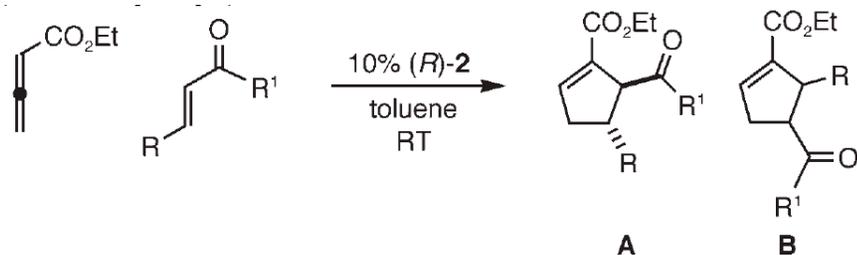
### 1-Naphyl imine

### Phenyl imine

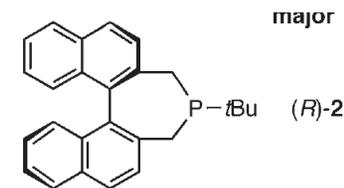
Substrate	(R,R)-Et-FerroTANE		(S,S)-iPr-FerroTANE		R-A		
	ee	Conv. <sup>b</sup> (%)	ee <sup>c</sup>	Conv. (%)	(S,S)-iPr	(S,S)-Cy	(R,R)-tBu
1a, R' = Et	22 (+)	60	37 (+)	82	44% (+)	48% (+)	28% (-)
1b, R' = i-Pr	52 (+)	44	44 (+)	27			
1c, R' = Cy	31 (+)	72 (98 <sup>a</sup> )	46 (+)	77 (96 <sup>a</sup> )		n.d. <sup>d</sup>	
1d, R' = t-Bu	60 (+)	36	48 (+)	10			
1e, R' = Ph	2 (+)	63	44 (+)	48			

# Phosphepines save the day!

## The Reaction

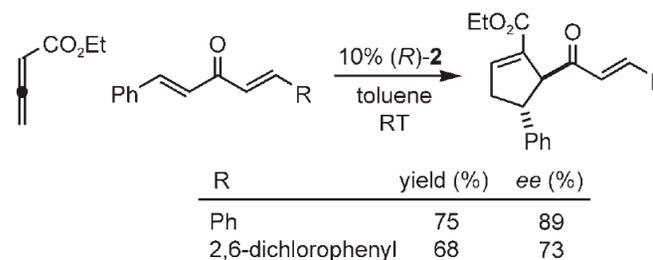
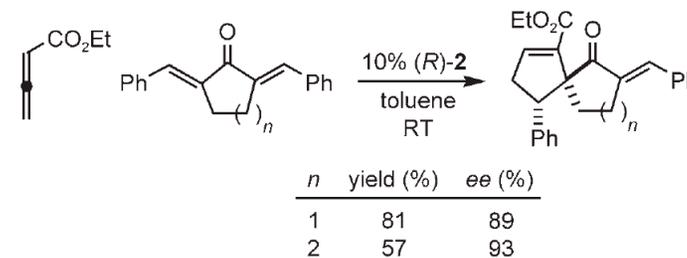


## Catalysts



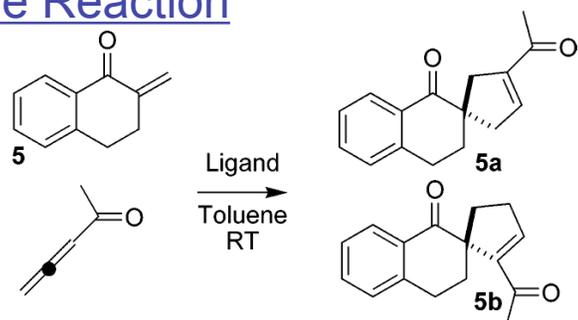
Entry	Phosphine <sup>[b]</sup>	Yield [%] <sup>[c]</sup>	ee [%] <sup>[d]</sup>	A:B
1	( <i>R</i> )-2	64	88	13:1
2	( <i>S</i> )-binapine	0	–	–
3	( <i>R</i> )-binap	2	50	> 20:1
4	( <i>R</i> )-nmdpp	4	–4	11:1
5	( <i>R,R</i> )-Me-bpe	61	–4	6:1
6	( <i>R,R</i> )-ferrotane	64	11	7:1
7	( <i>R,R</i> )-Et-DuPhos	61	58	7:1

Entry	R	R <sup>1</sup>	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>	A:B
1	Ph	Ph	64	88	13:1
2	Ph	4-chlorophenyl	76	82	7:1
3	Ph	4-methylphenyl	61	87	20:1
4	Ph	4-methoxyphenyl	54	88	> 20:1
5	4-chlorophenyl	Ph	74	87	9:1
6	4-methoxyphenyl	Ph	67	87	10:1
7	2-furyl	Ph	69	88	3:1
8 <sup>[d]</sup>	2-quinolyl	Ph	52	88	20:1
9 <sup>[d]</sup>	4-chlorophenyl	2-(5-methylfuryl)	54	89	> 20:1
10	Ph	2-thienyl	74	90	6:1
11	C≡CC <sub>5</sub> H <sub>11</sub>	Ph	65	85	6:1
12	C≡CTES	Ph	70	87	> 20:1
13	C <sub>5</sub> H <sub>11</sub>	Ph	39 <sup>[e]</sup>	75	> 20:1



# Exocyclic Enones as 2π components: Extension to spirocycles

## The Reaction



## Catalysts

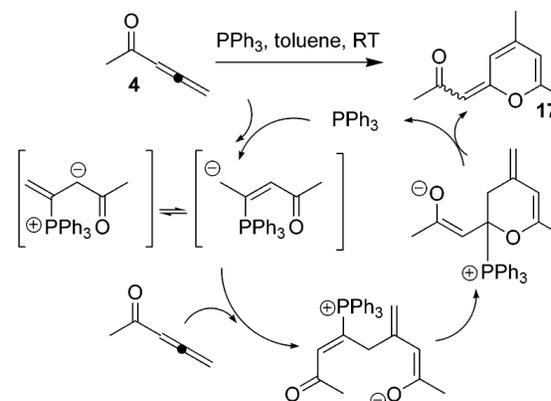
entry <sup>a</sup>	ligand	conversion <sup>b</sup>	5a:5b <sup>b</sup>	ee (5a) <sup>b</sup>
1	PPh <sub>3</sub>	75	62:38	
2	Xantphos	31	82:18	
3	P(o-Tol) <sub>3</sub>	0	-	
4	rac-BINAP	0	-	
5	PCy <sub>3</sub>	18	95:5	
6	dppf	67	93:7	
7	PBu <sub>3</sub>	81	97:3	
8	DIOP	90	90:10	61
9	DIOP <sup>c</sup>	90	97:3	62
10	Prophos	87	90:10	6
11	DIPAMP	85	87:13	34
12	Trost ligand	20	60:40	-
13	Pfaltz ligand	0	-	-
14	DIOP <sup>d6</sup>	100	97:3	68

## Results

Entry <sup>a</sup>	Starting Enone	Products	Yield <sup>b</sup>	PPh <sub>3</sub> a : b <sup>b</sup>	Yield <sup>c</sup>	DIOP a : b <sup>c</sup>	ee (a)
1			58	70 : 30	73	95 : 5	61
2			64	62 : 38	75	91 : 9	77
3			73	56 : 44	63	80 : 20	53
4			82	54 : 46	80	90 : 10	46
5			84	55 : 45	71	95 : 5	71
6			72 <sup>d</sup>	2 : 98	-	-	-
7			61 <sup>d</sup>	2 : 98	46 <sup>d</sup>	85 : 15	30 <sup>e</sup>

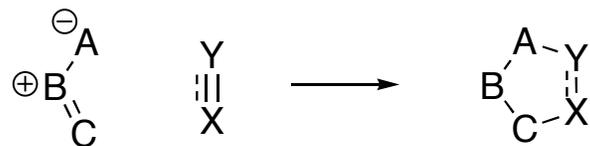
<sup>a</sup> Reaction conditions: 0.5 M in toluene, 15 mol % ligand, 1.3 equiv of allene, room temperature, 12 h. <sup>b</sup> Based on HPLC. <sup>c</sup> At 0 °C. <sup>d</sup> Using 30 mol % phosphine, or slow addition of allene at 0 °C.

## Major Side Rxn is Dimerization Of allenic ketone



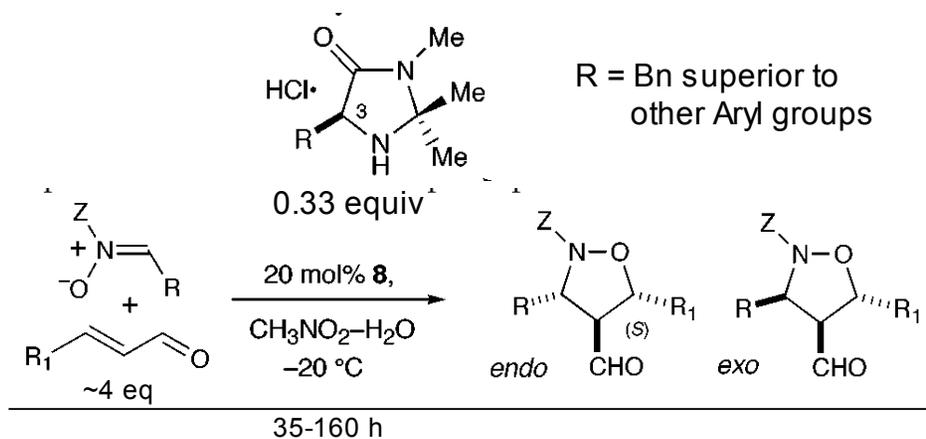
## [3+2]: Outline:

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- ✓ A=B=C=X=Y=Carbon
- A, B, or C are heteroatoms
- X or Y = heteroatoms not covered

# Back to “Normal” Dipolar Cycloaddition: Nitron + Enal



## Counterion Effect

entry	HX co-catalyst	Time (h)	% yield	<i>endo:exo</i>	% ee ( <i>endo</i> ) <sup>a</sup>
1	HCl ( <b>1a</b> )	108	70	88:12	95
2	TfOH ( <b>5</b> )	101	88	89:11	90
3	TFA ( <b>6</b> )	80	65	72:28	86
4	HBr ( <b>7</b> )	80	77	94:6	93
5	HClO <sub>4</sub> ( <b>8</b> )	80	86	94:6	90
6	HClO <sub>4</sub> ( <b>8</b> )	100	98	94:6	94 <sup>b</sup>

## Scope

entry	Z	R	R <sub>1</sub>	<i>endo:exo</i>	yield	% ee ( <i>endo</i> ) <sup>a,b</sup>
1	Bn	Ph	Me	94:6	98	94
2	Allyl	Ph	Me	93:7	73	98
3	Me	Ph	Me	95:5	66	99
4	Bn	C <sub>6</sub> H <sub>4</sub> Cl-4	Me	92:8	78	95
5	Me	C <sub>6</sub> H <sub>4</sub> Cl-4	Me	93:7	76	94
6	Bn	C <sub>6</sub> H <sub>4</sub> OMe-4	Me	98:2	93	91
7	Me	C <sub>6</sub> H <sub>4</sub> Me-4	Me	93:7	82	97
8	Bn	2-naph	Me	95:5	98	93
9	Bn	<i>c</i> -hex	Me	99:1	70	99
10	Bn	Ph	H	81:19	72	90
11	Bn	Ph	H	86:14	80	92 <sup>c</sup>
12	Bn	C <sub>6</sub> H <sub>4</sub> Me-4	H	85:15	80	90 <sup>c</sup>
13	Bn	C <sub>6</sub> H <sub>4</sub> Cl-4	H	80:20	80	91 <sup>c</sup>
14	Bn	2-naph	H	81:19	82	90 <sup>c</sup>
15	Bn	C <sub>6</sub> H <sub>4</sub> OMe-4	H	91:9	83	90 <sup>c</sup>

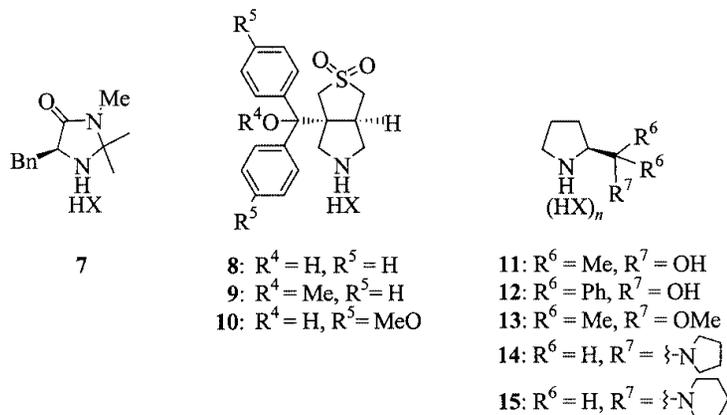
R = Aryl, Z = Me / Bn

# Nitrones + Cycloalkene carboxaldehydes

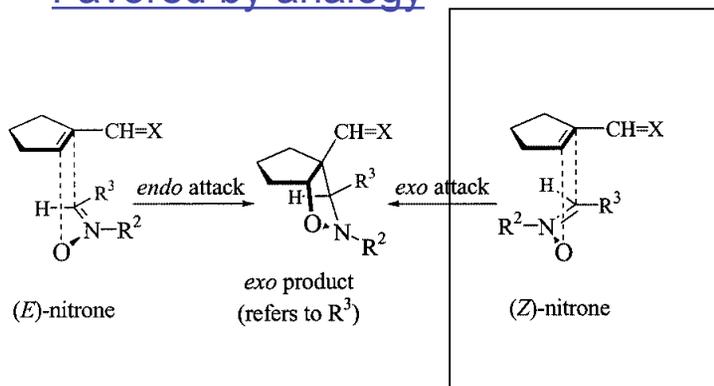
## Scope in nitronone

Entry <sup>[a]</sup>	Aldehyde	Nitronone	Temp.	Time	exo product	Yield <sup>[b]</sup>	dr exo/endo <sup>[c]</sup>	ee exo <sup>[d]</sup>
1 <sup>[e]</sup>		<b>1A</b>	<b>2a</b> +10 °C	72 h		<b>3a</b> 49 %	97:3	92 %
2 <sup>[e,f]</sup>	<b>1A</b>	<b>2a</b>	+10 °C	120 h	<b>3a</b>	63 %	89:11	83 %
3 <sup>[e,f]</sup>	<b>1A</b>	<b>2a</b>	-25 °C	120 h	<b>3a</b>	17 %	28:72	91 %
4	<b>1A</b>		<b>2b</b> +10 °C	120 h		<b>3b</b> 68 %	98:2	76 % (> 99 %) <sup>[g]</sup>
5 <sup>[h]</sup>	<b>1A</b>	<b>2b</b>	+10 °C	120 h	<b>3b</b>	63 %	99:1	84 % (> 99 %) <sup>[g]</sup>
6	<b>1A</b>	<b>2b</b>	-10 °C	120 h	<b>3b</b>	50 %	97:3	90 % (> 99 %) <sup>[g]</sup>
7	<b>1A</b>		<b>2c</b> -25 °C	144 h		<b>3c</b> 76 %	> 99:1	57 %
8	<b>1A</b>		<b>2d</b> +20 °C	24 h		<b>3d</b> 58 %	> 99:1	41 %
9	<b>1A</b>	<b>2d</b>	-20 °C	24 h	<b>3d</b>	48 %	> 99:1	41 %
10	<b>1A</b>		<b>2e</b> +20 °C	144 h		<b>3e</b> 51 %	98:2	53 %
11	<b>1A</b>		<b>2f</b> -20 °C	96 h		<b>3f</b> 56 %	> 99:1	70 % <sup>[i]</sup>
12	<b>1A</b>		<b>2g</b> +5 °C	72 h		<b>3g</b> -	56:44	-
13		<b>2d</b>	+20 °C	24 h		<b>5d</b> 19 %	> 99:1	48 %
14	<b>1B</b>	<b>2d</b>	+20 °C	120 h	<b>5d</b>	38 %	> 99:1	37 %

## Catalysts



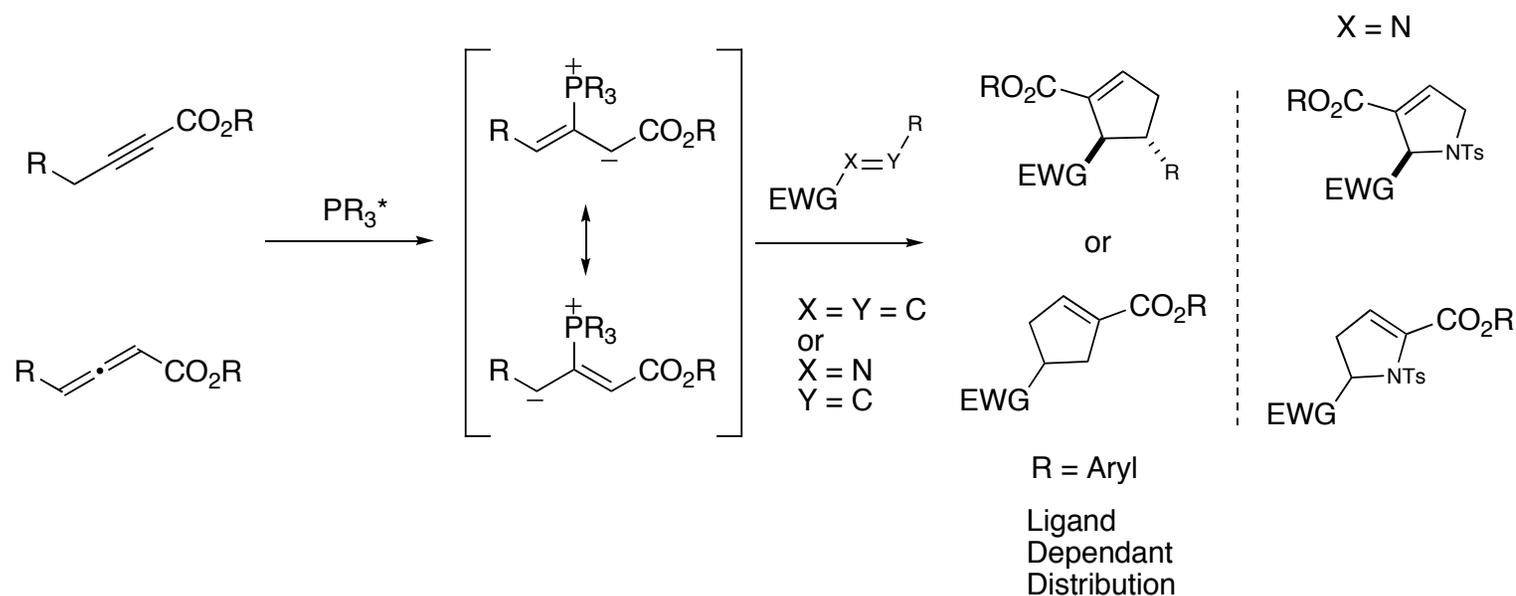
## Favored by analogy



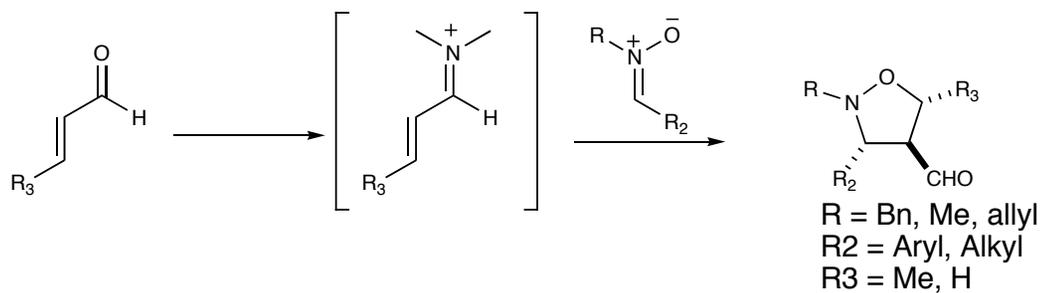
## Increased Scope in Nitronone

# [3+2] Summary

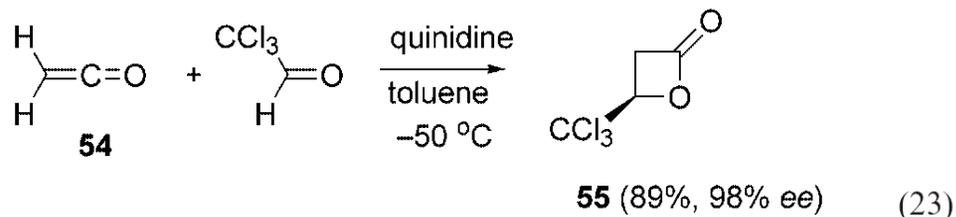
## Tertiary Phosphines activating all carbon dipoles



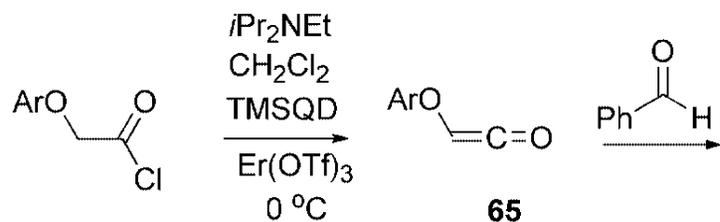
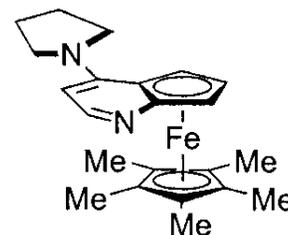
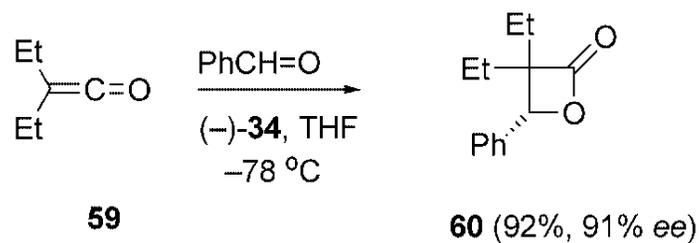
## Secondary Amines activating dipolarophiles



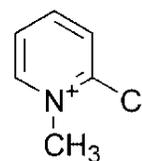
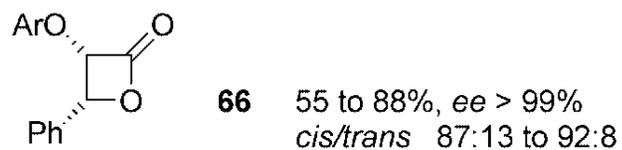
# [2+2] Harness the Ketene: Beta-lactones



H. Wynberg, E. G. J. Staring, *JACS*. **1982**, *104*, 166–168; H. Wynberg, E. G. J. Staring, *JOC*. **1985**, *50*, 1977–1979.



Can generate acyl chloride  
In-situ from with

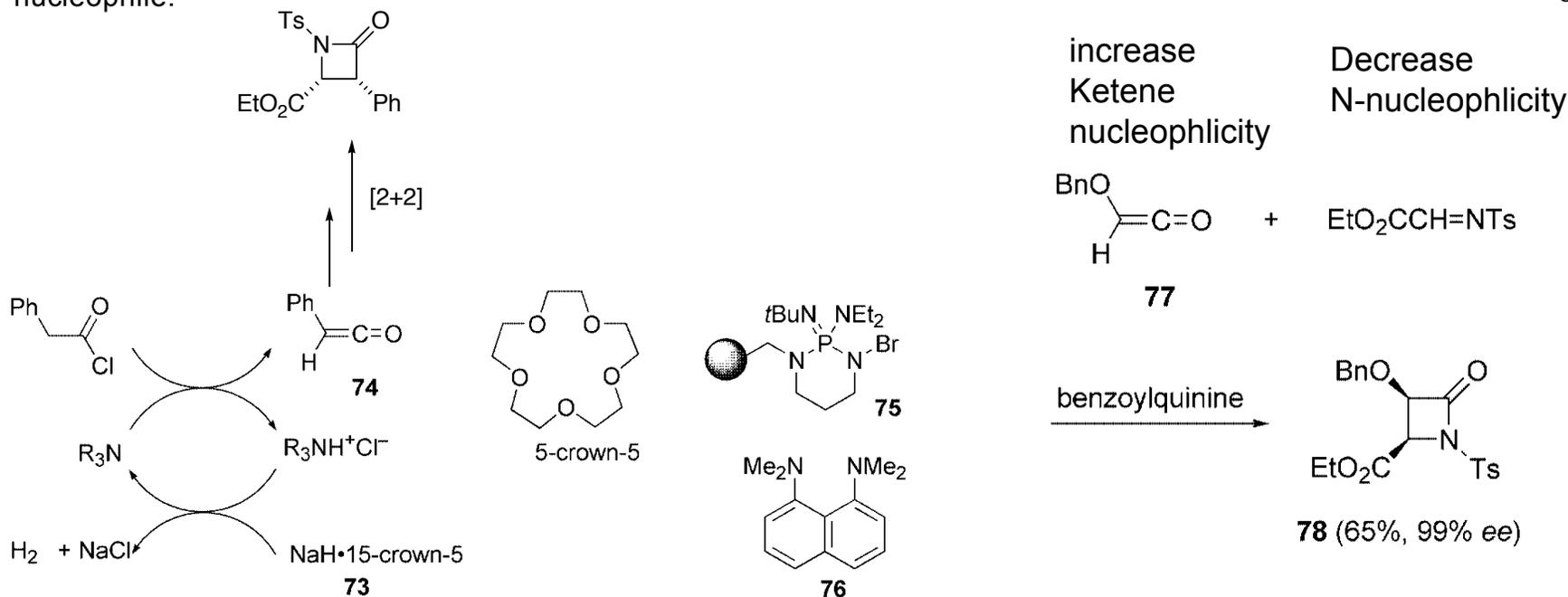
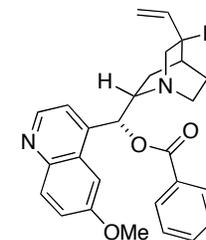


(27)

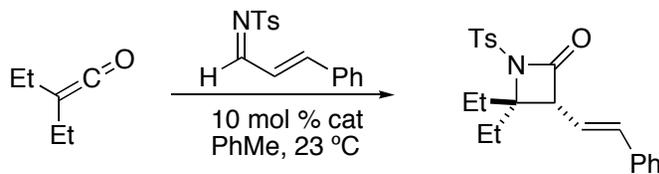
# Beta-Lactams:

“Background rates are often so high using this process that it was necessary for us to first break the reaction before we could fix it to render it catalytic, not to mention asymmetric.”

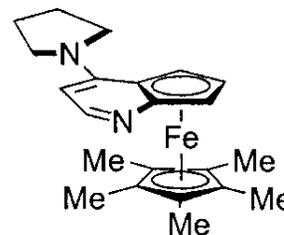
How so... By breaking the classical Staudinger pathway (in which the imine nitrogen acts as a nucleophile toward the ketene) and restart it with a reaction of reversed polarity (umpolung) in which the ketene and imine switch roles; namely, the imine becomes an electrophile and the ketene a nucleophile.



Preformed, disubstituted ketenes



83%, er 96:4



Electron donating  
And aryl ketenes  
EWG or alkene  
On imine

# Summary and Conclusions

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- Inadvertant tribute to LB catalysis
  - Many interesting opportunities
    - Activate diene
      - Phosphene + Allene
      - Chiral Base + diene (O or H acid)
      - Cross-conjugated enamine
    - Ketenes as dienophiles
      - NHC + “special aldehydes”
      - 3° amines + ketenes (limited dienes possible)
    - “Activate Dipole”
      - Phosphine + electron poor allene
    - Activate Diene/polarophile
      - 2° amine

- Pros/Cons

Most are rt-50 °C

Reaction times often long

Some still require acid

Often highly optimizable (at least it appears)

Interesting (new?) reactivity in many cases