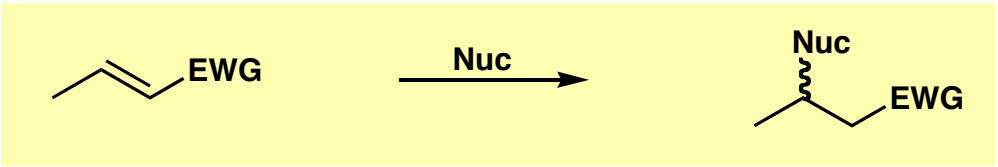
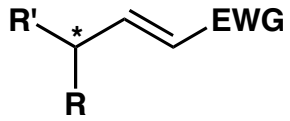
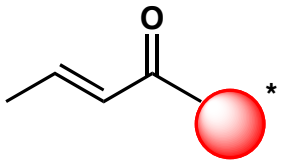
Conjugate Additions: Introduction



Chiral Acceptor

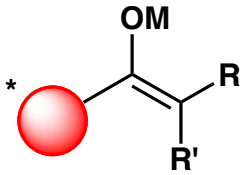


Inherent Chirality



Chiral Auxiliary

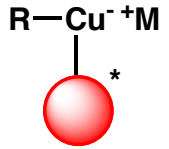
Chiral Donnor



Inherent Chirality

Chiral Auxiliary

Chiral Additives/Ligands



Chiral Reagent

Chiral Catalysts

Review: Merino *Eur. J. Org. Chem.* **1998**, 2051. Leonard *Comtemporary Org. Synthesis*, **1994**, 387. Rossiter *Chem. Rev.* **1992**, 771.

Conjugate Additions: Soft Nucleophiles

Organocopper Reagent

•Copper-Catalyzed Grignard Reagents RMgX + ≤ 25 mol% CuX

Review: Erdik, *Tetrahedron* **1984**, *40*, 641.

•Monoalkylcopper reagents RLi + CuX $\xrightarrow[-LiX]{Et_2O/THF}$ RCu ↓

RCu: -Unreactive, explosive, polymer and insoluble

RCu•LA : -More reactive, displays unique reactivity and selectivity patterns

Review: Nakamura *Tetrahedron* **1989**, *45*, 349. Also: *JACS* **2000**, 1826.

•Homocuprate reagents (Gilman-Cuprates)

RLi + CuX $\xrightarrow[-LiX]{Et_2O/THF}$ RCu ↓ $\xrightarrow{RLi}$ R_2CuLi

CuX = CuI, CuBr, CuBr•SMe_2

-reactive againts a wide variety of electrophiles: the most widely used.
-Stable <0°C (generally -78°C), low basicity
-Higher order homocuprates: R_3Cu_2Li, R_3CuLi_2, R_5Cu_3Li

•Mixed Homocuprate reagents R_TM + CuR $\xrightarrow{Et_2O/THF}$ $R_TCu(R)M$

-R_T = transferable ligand

-R = Dummy ligand: C≡CR, $CH_2S(O)Me$, 2-Thienyl, $CH_2S(O)_2Me$, Mesityl

Review on dummy ligands: Hamon and Levisalles, *Tetrahedron* **1989**, *45*, 489.

Heteronucleophile

•Nitrogen

R_2NH

$N_3^{\ominus}$

•Sulfur

RSH

•Alcohol

ROH (oxymercuration)

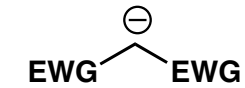
PhOH

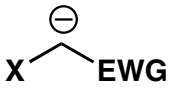
Carbon Nucleophile

•Cyanide

$^{\ominus}CN$

•Enolate (Michael)





Conjugate Additions: Heterocuprates

$R_TM + CuZ \xrightarrow{Et_2O/THF} R_TCu(Z)M$

- R_T = transferable ligand
- CuZ (usually commercially available) =

CuCN, CuSPh, CuO*t*-Bu, $CuPPh_2$, $CuN(C_6H_{11})_2$, $CuP(t\text{-}Bu)_2$

$RM + R_TM + CuZ \longrightarrow R_T(R)Cu(Z)M_2$

- R_T = transferable ligand
- CuZ (usually commercially available) =

CuCN, CuSPh, CuO*t*-Bu, $CuPPh_2$, $CuN(C_6H_{11})_2$, $CuP(t\text{-}Bu)_2$

- R = Dummy ligand
  - 2-Thienyl
  - *N*-Pyrrolyl
  - *N*-Imidazolyl

Combined Stability of Heterocuprates with the reactivity of Homocuprates.

From Functionnalized Organocopper Reagents (Knochel Reagents)

Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117; Lipshutz, B. H. *Acc. Chem. Res.* **1997**, *30*, 277.

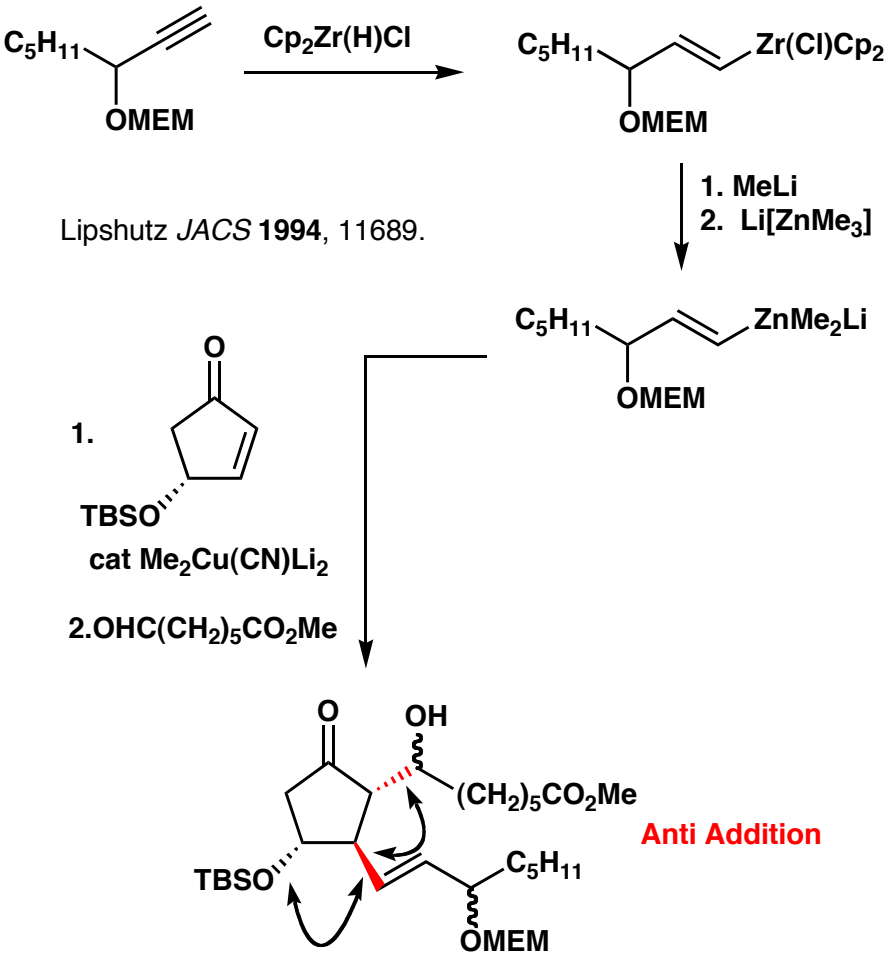
$FG\text{-}RI \xrightarrow{Zn} FG\text{-}RZnI \xrightarrow{CuCN\cdot 2LiCl} FG\text{-}RCu(CN)ZnI$

Conjugate Additions: Relative Stereocontrol

Cyclic Systems

Facial Selectivity dictated by steric effects

•Classic Case: Prostanglandin's Synthesis

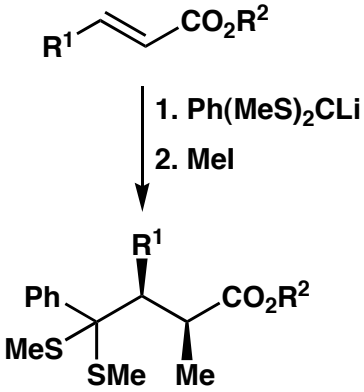


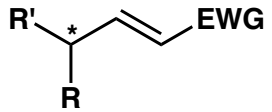
Lipshutz *JACS* **1994**, 11689.

Anti Addition

Acyclic Systems

Tomioka *TL* **1985**, 3031.



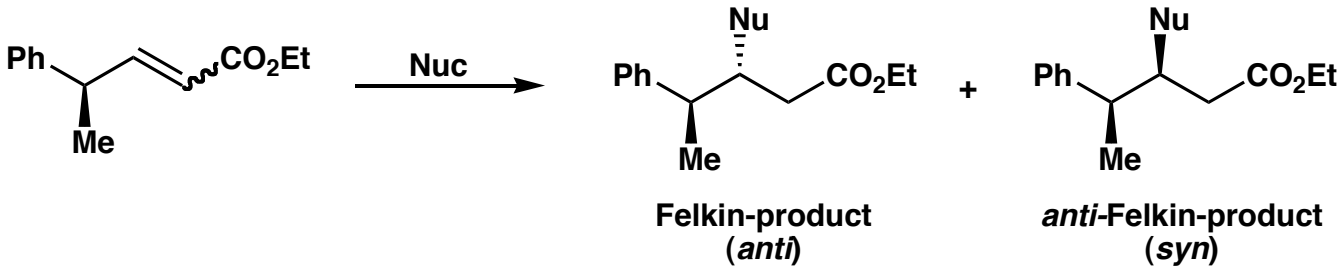


Felkin-Anh Rule

Review:
Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, 1191.

Conjugate Additions to Chiral Electrophiles

Yamamoto *Chem. Commun.* **1987**, 1572. *JACS* **1988**, 617.

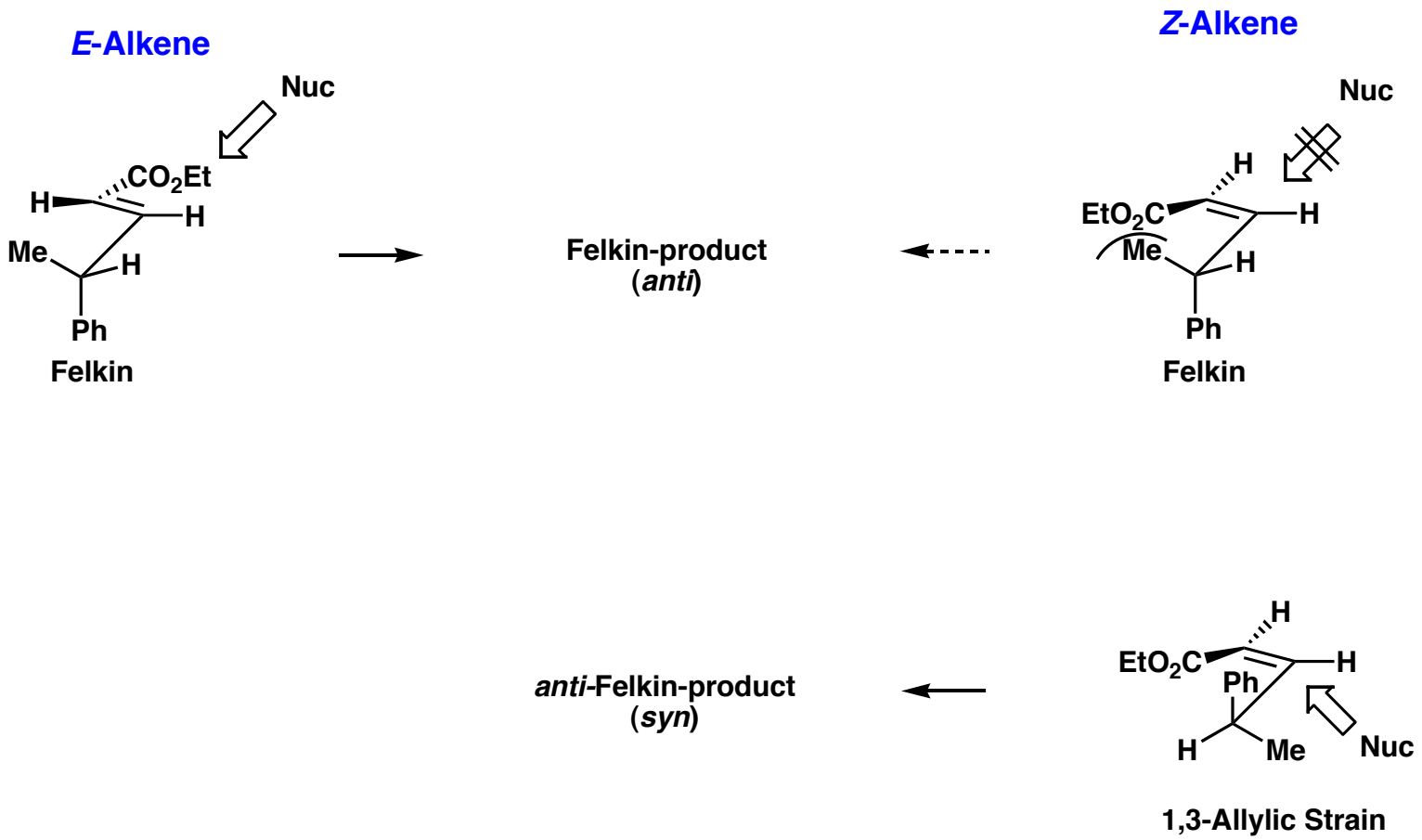


Felkin-product (*anti*) | ***anti*-Felkin-product (*syn*)**

Entry	*E/Z*-alkene	Nucleophile	Yield	Ratio *anti:syn*
1	*E*	$BuCu{\cdot}BF_3$	82%	7:1
2	*E*	$Bu_2CuLi{\cdot}BF_3$	90%	2.3:1
3	*E*	$Bu_2Cu(CN)Li_2{\cdot}BF_3$	29%	4:1
4	*E*	$Me_3CuLi_2{\cdot}BF_3$	46%	7:1
5	*Z*	$Bu_2CuLi{\cdot}BF_3$	89%	1:2.3
6	*Z*	$Bu_2Cu(CN)Li_2{\cdot}BF_3$	26%	1:2
7	*Z*	$Me_3CuLi_2{\cdot}BF_3$	67%	1:3.8

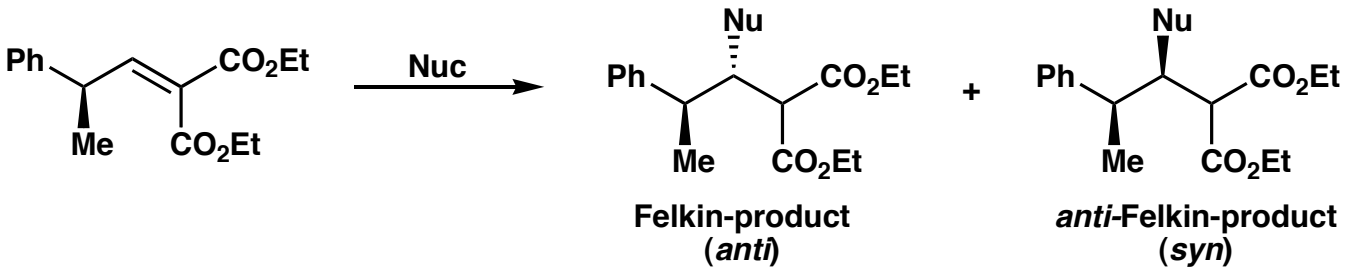
•Felkin with *E*-alkene and *anti*-Felkin with *Z*-alkenes

Proposed Transition Structures



Conjugate Additions to Chiral Electrophiles

Yamamoto *Chem. Commun.* **1987**, 1572.



Entry	Nucleophile	Yield	Ratio *anti:syn*
1	$Bu_2CuLi{\cdot}BF_3$	67%	1:2.1
2	$BuCu{\cdot}BF_3$	90%	2.8:1
3	$Me_3CuLi_2{\cdot}BF_3$	90%	1:1.6
4	Bu_2CuLi	87%	1:18
5	$MeCu{\cdot}BF_3$	95%	3.8:1
6	MeMgBr	89%	1.5:1
7	Me_4AlLi	88%	1.6:1
8	$AllylSnBu_3$	93%	24:1

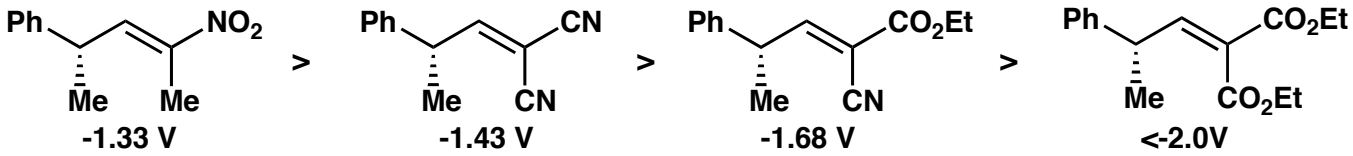
·Trisubstituted alkenes show the same tendency than *Z*-alkenes

Important Factors to Consider

•Important Factors:

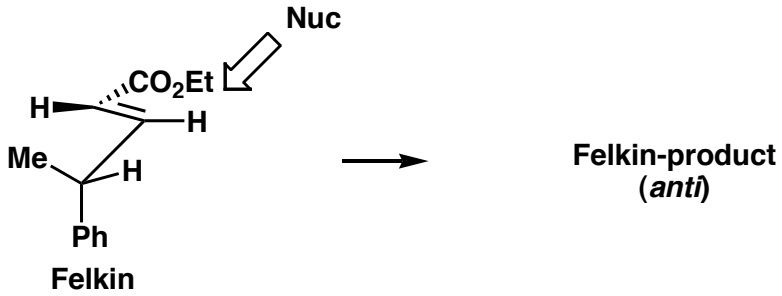
-Cuprate's electron-donating ability (oxidation potential) : $Me_2CuLi >> Me_2Cu(CN)Li_2 > MeCu > MeCu(CN)Li$

-Michael acceptor's electron-accepting ability (reduction potential):



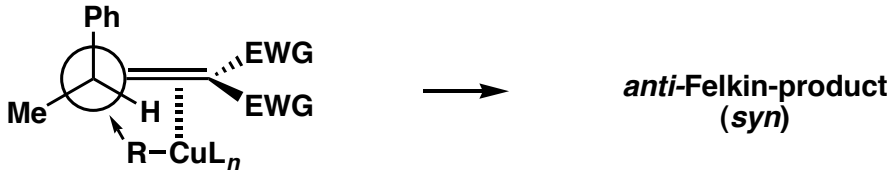
Michael acceptor with low reduction potentials + RCu or RCuCNLi (lower electron-donating ability):

Normal Felkin-Ahn TS : *anti*-product is the major isomer



Michael acceptor with high reduction potentials + R_2CuL or $R_2CuCNLi_2$ (higher electron-donating ability):

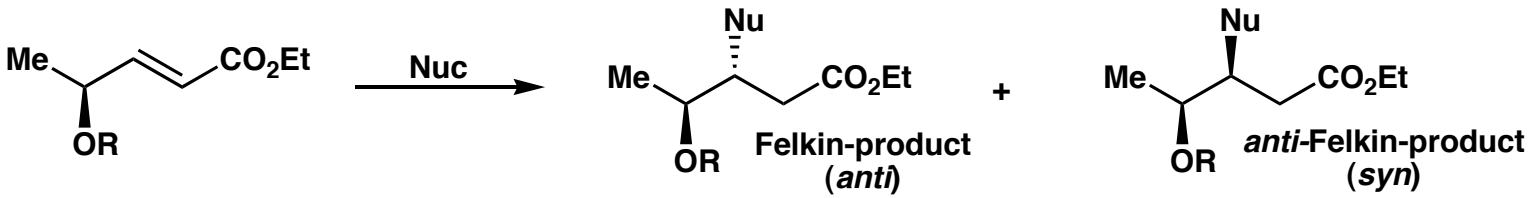
π-complex TS : *syn*-product is the major isomer



"acute" angle of attack (suggested by ab initio calculations)

Conjugate Addition to Chiral Electrophiles

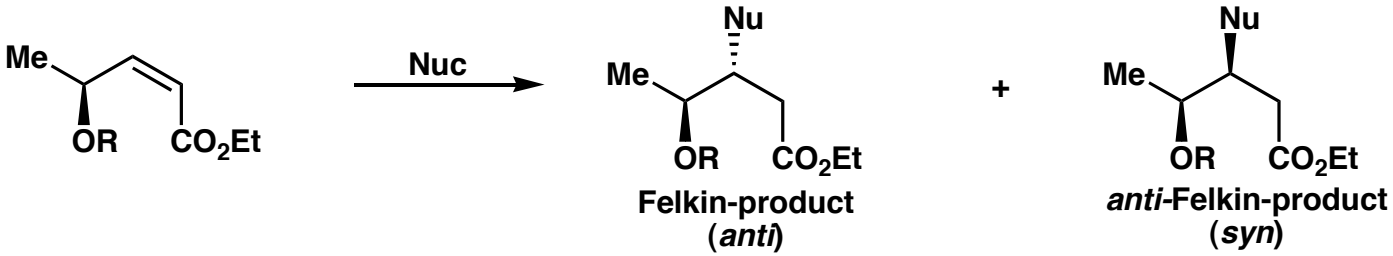
Yamamoto *J. Am. Chem. Soc.* **1992**, 7652.



Entry	OR	Nucleophile	Ratio *anti:syn*	Yield
1	OBn	$(Methallyl)_2CuLi$	1:1.4	87%
2	OBn	MethallylCu	1:1.5	99%
3	OBn	$(Vinyl)_2CuLi$	2.6:1	99%
4	OBn	$(Vinyl)_2CuLi{\cdot}BF_3$	15:1	58%
5	OBn	$(Vinyl)_2Cu(CN)Li_2$	2.6:1	83%
6	OBn	$(Vinyl)_2Cu(CN)Li_2{\cdot}BF_3$	19:1	66%
7	OBn	$MeCu{\cdot}BF_3$	2.2:1	60%
8	OBn	$MeCu(CN)Li{\cdot}BF_3$	19:1	62%
9	OBn	$BuCu{\cdot}BF_3$	12:1	64%
10	OTBS	$MeCu{\cdot}BF_3$	2:1	6%
11	OTBS	$Me_2CuLi{\cdot}BF_3$	2.7:1	26%
12	OTBS	$Me_2Cu(CN)Li_2{\cdot}BF_3$	12:1	55%

- Nature of the cuprate reagent is important (entry 1 and 3)
- Nature of OR does not interfere (entry 9 and 12): no chelation vs non-chelation control

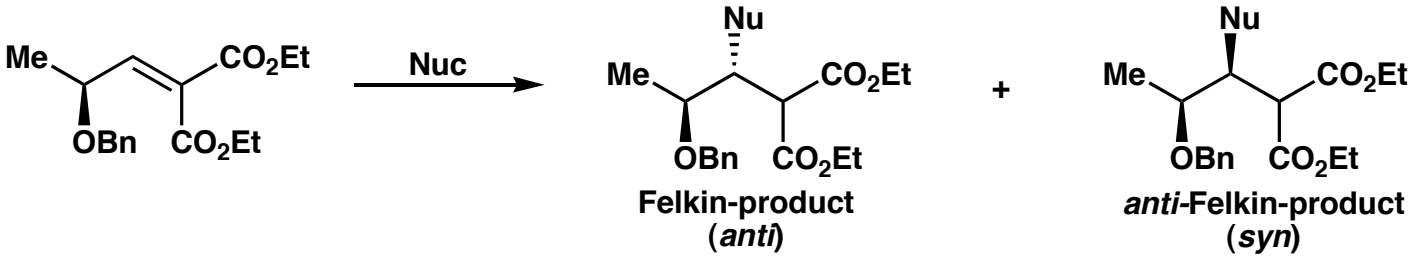
Conjugate Addition to Chiral Electrophiles



Entry	OR	Nucleophile	Ratio *anti:syn*	Yield
1	OBn	$(Methallyl)_2CuLi$	1:4	99%
2	OBn	MethallylCu	1:4.5	45%
3	OBn	$(Vinyl)_2CuLi$	>99:1	82%
4	OBn	$(Vinyl)_2CuLi{\cdot}BF_3$	1.1:1	63%
5	OBn	$(Vinyl)_2Cu(CN)Li_2$	24:1	58%
6	OBn	$(Vinyl)_2Cu(CN)Li_2{\cdot}BF_3$	1:3.4	64%
7	OBn	$MeCu{\cdot}BF_3$	1:3.5	30%
8	OBn	$MeCu(CN)Li{\cdot}BF_3$	1:2.8	45%
9	OBn	$BuCu{\cdot}BF_3$	1:3.5	56%
10	OTBS	$MeCu{\cdot}BF_3$	1:6	2%
11	OTBS	$Me_2CuLi{\cdot}BF_3$	1:7	12%
12	OTBS	$MeCu(CN)Li{\cdot}BF_3$	1:5	17%
13	OTBS	$Me_2Cu(CN)Li_2{\cdot}BF_3$	1:5	36%

- *Z*-Alkenes are *syn*-selective, excepted for the addition of vinylcuprate
- The influence of of BF_3 is very important but not well understood.
- Low yields are observec with γ-silyloxy α,β-unsaturated esters.

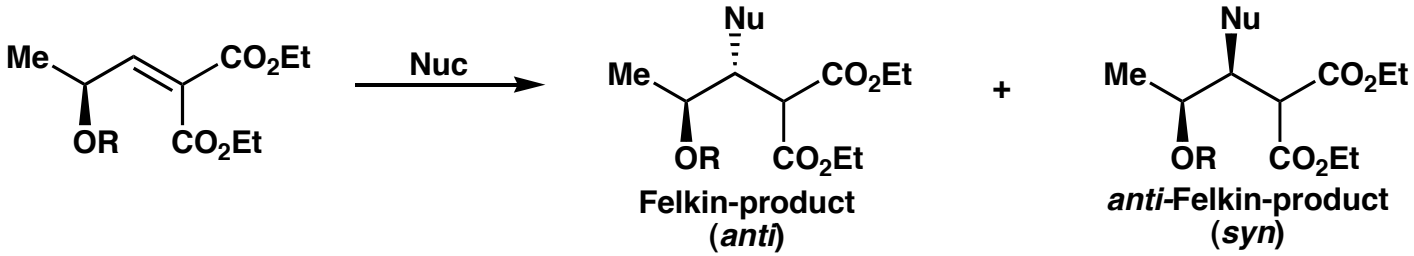
Conjugate Addititon to Chiral Electrophiles



Entry	Nucleophile	Ratio *anti:syn*	Yield	Entry	Nucleophile	Ratio *anti:syn*	Yield
1	MethallylCu	1:13	99%	9	(Vinyl)Cu	1:2.2	45%
2	MethallylCu·BF_3	1:32	86%	10	(Vinyl)Cu·BF_3	1:3.5	72%
3	(Methallyl)$_2$CuLi	1:9	79%	11	(Vinyl)$_2$CuLi	1:1.6	91%
4	(Methallyl)$_2$CuLi·BF_3	1:12	99%	12	(Vinyl)$_2$CuLi·BF_3	1:1.6	91%
5	(Methallyl)Cu(CN)Li	1:5	88%	13	(Vinyl)Cu(CN)Li	1:2.3	88%
6	(Methallyl)Cu(CN)Li·BF_3	1:24	95%	14	(Vinyl)Cu(CN)Li·BF_3	1:1.9	83%
7	(Methallyl)$_2$Cu(CN)Li$_2$	1:13	99%	15	(Vinyl)$_2$Cu(CN)Li$_2$	1:2.4	94%
8	(Methallyl)$_2$Cu(CN)Li$_2$·BF_3	1:3	87%	16	(Vinyl)$_2$Cu(CN)Li$_2$·BF_3	1:2.2	96%

- The *syn* isomer is major with trisubstituted alkenes using vinyl and methallyl cuprates.
- The best results were observed with low order cuprates and BF_3

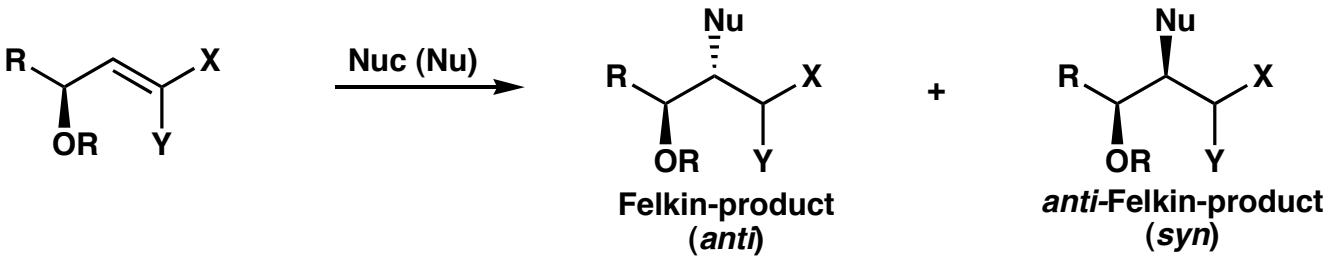
Conjugate Addition to Chiral Electrophiles



Entry	OR	Nucleophile	Ratio *anti:syn*	Yield
1	OBn	MeCu	1:8	58%
2	OBn	$MeCu{\cdot}BF_3$	1:16	54%
3	OBn	Me_2CuLi	1:1.7	75%
4	OBn	BuCu	1:2.3	75%
5	OBn	$BuCu{\cdot}BF_3$	1:19	52%
6	OBn	Bu_2CuLi	1:2.1	63%
7	OBn	$Bu_2CuLi{\cdot}BF_3$	1:4.3	51%
8	OTBS	MeCu	1:6	92%
9	OTBS	$MeCu{\cdot}BF_3$	1:5	98%
10	OTBS	Me_2CuLi	1:1.6	89%
11	OTBS	MeCu(CN)Li	1:12	92%
12	OTBS	$MeCu(CN)Li{\cdot}BF_3$	1:10	94%

- Good Selectivities with low order cuprates
- More reactive substrates: good yield with γ-silyloxy α,β-unsaturated esters.
- Nature of OR does not interfere (entry 2 and 9): no chelation vs non-chelation control

Conjugate Addition to Chiral Electrophiles



	Reagent		
Substrate	(vinyl)CuL_n	(alkyl)CuL_n	(methallyl)CuL_n
E-Alkene	*anti*	*anti*	*syn*
Z-Alkene	*anti* (*syn*)*	*syn*	*syn*
Trisubstituted	*syn*	*syn*	*syn*

**syn*-selectivity was observed in a certain case.

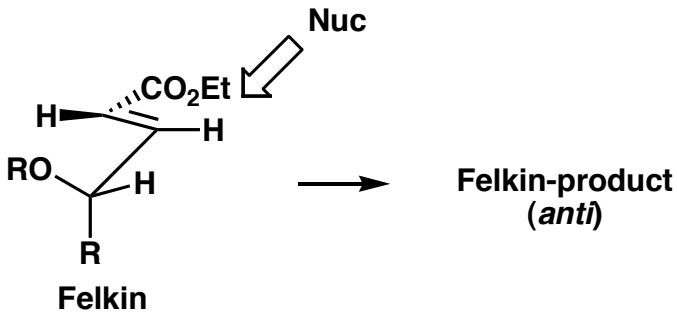
-Cuprate's electron-donating ability (oxidation potential): Methallyl >> *n*-butyl > vinyl

Proposed Transition Structures

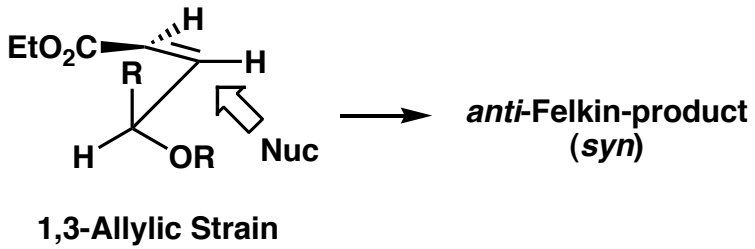
Disubstituted Alkenes + RCu or RCuCNLi (lower electron-donating ability):

Felkin-Anh TS : ratio is dependant of the geometry of the alkenes

***E*-Alkenes**

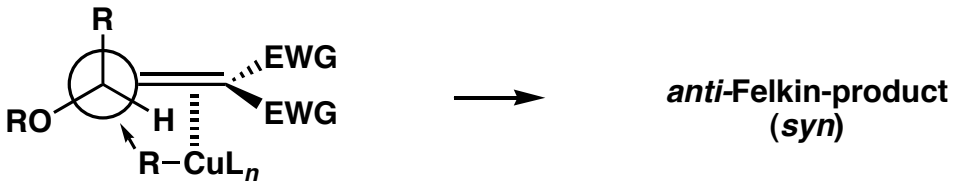


***Z*-Alkenes**



Disubstituted alkenes + methallyl cuprates and trisubstituted alkenes

π-complex TS : *syn*-product is the major isomer

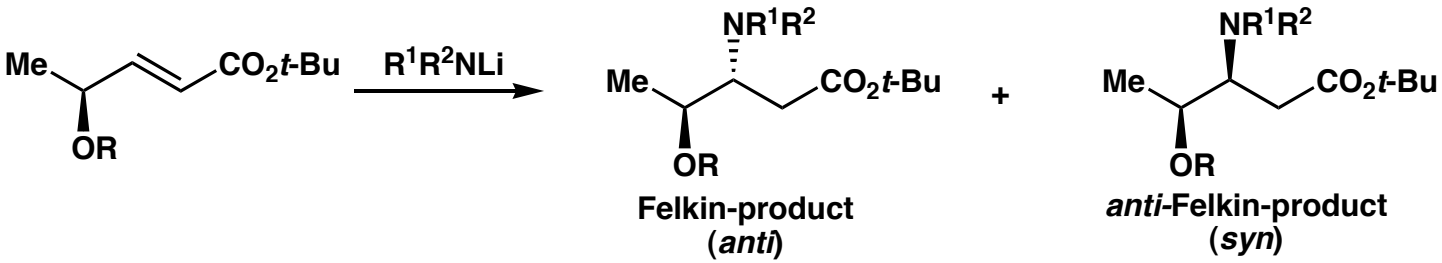


"acute" angle of attack (suggested by ab initio calculations)

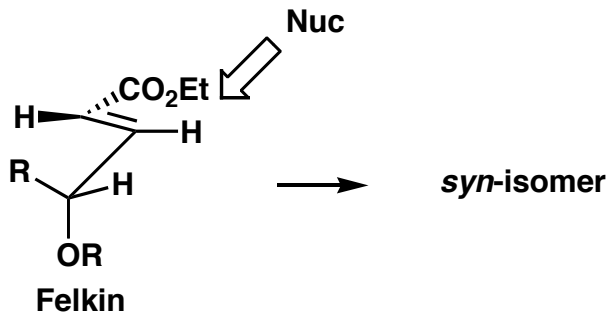
⇨ **OR is the "medium size" group : steric effects are more important than stereoelectronic effects.**

Conjugate Addition of Lithium Amides

Yamamoto *J. Org. Chem.* **1997**, 6274.

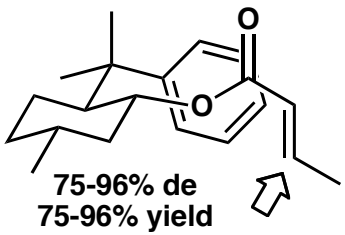


Entry	OR	Lithium Amides	Ratio *anti:syn*	Yield
1	OTBS	LiNBnTMS	1:1.2	91%
2	OTBDPS	LiNBnTMS	1:8	99%
3	OTIPS	LiNBnTMS	1:9	95%
4	$OCPh_3$	LiNBnTMS	<1:99	79%
5	OTIPS	$LiNBn_2$	2.3:1	77%
6	OMe	$LiNBn_2$	1:1.7	83%



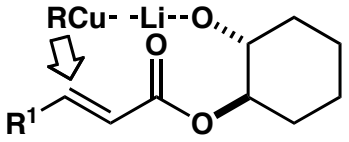
•Chelation control interfer when $LiNBn_2$ is used

Chiral Auxiliaries for Conjugate Addition Reactions



75-96% de
75-96% yield

Oppolzer *Helv. Chim. Acta* **1980**, *63*, 2015.
Oppolzer *TL* **1983**, 4971.

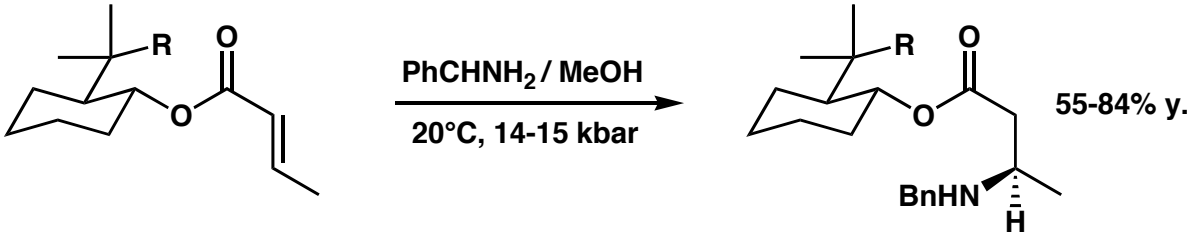


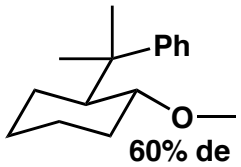
R^1, R^2 = Alkyl, aryl

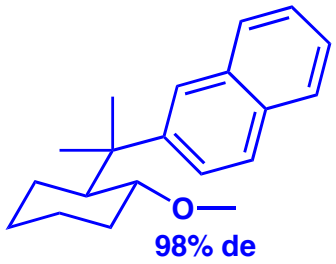
72-88% de
66-91% yield

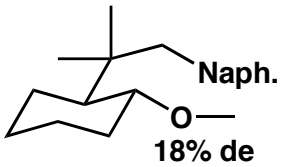
Suemune *TL* **1990**, 4751
Tet. Asym. **1991**, 389

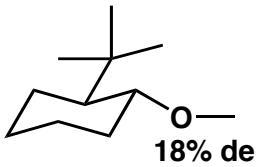
Dumas and d'Angelo
JOC **1994**, 500; *JOC* **1996**, 2293.

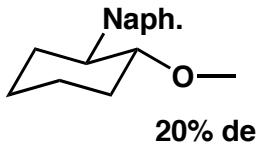


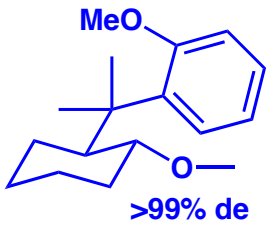


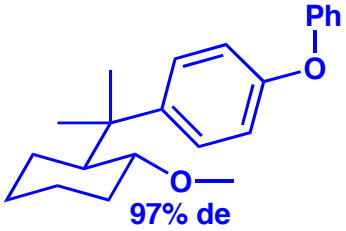


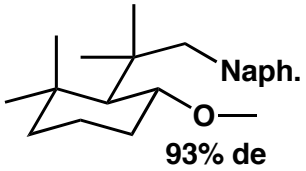


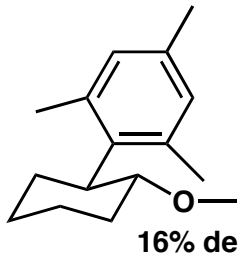


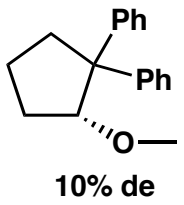






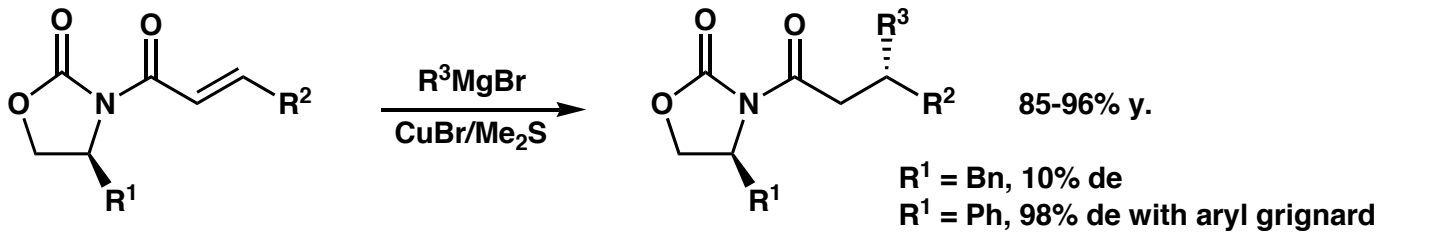




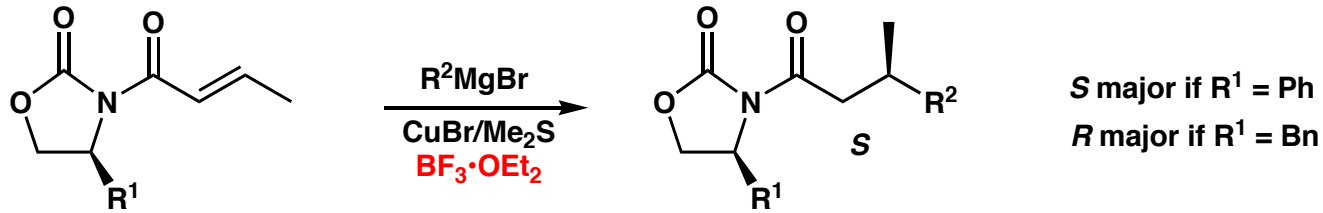


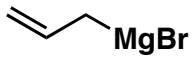
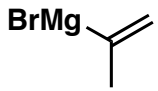
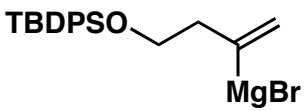
Chiral Auxiliaries for Conjugate Addition Reactions

Hruby *JOC* **1993**, 7565.

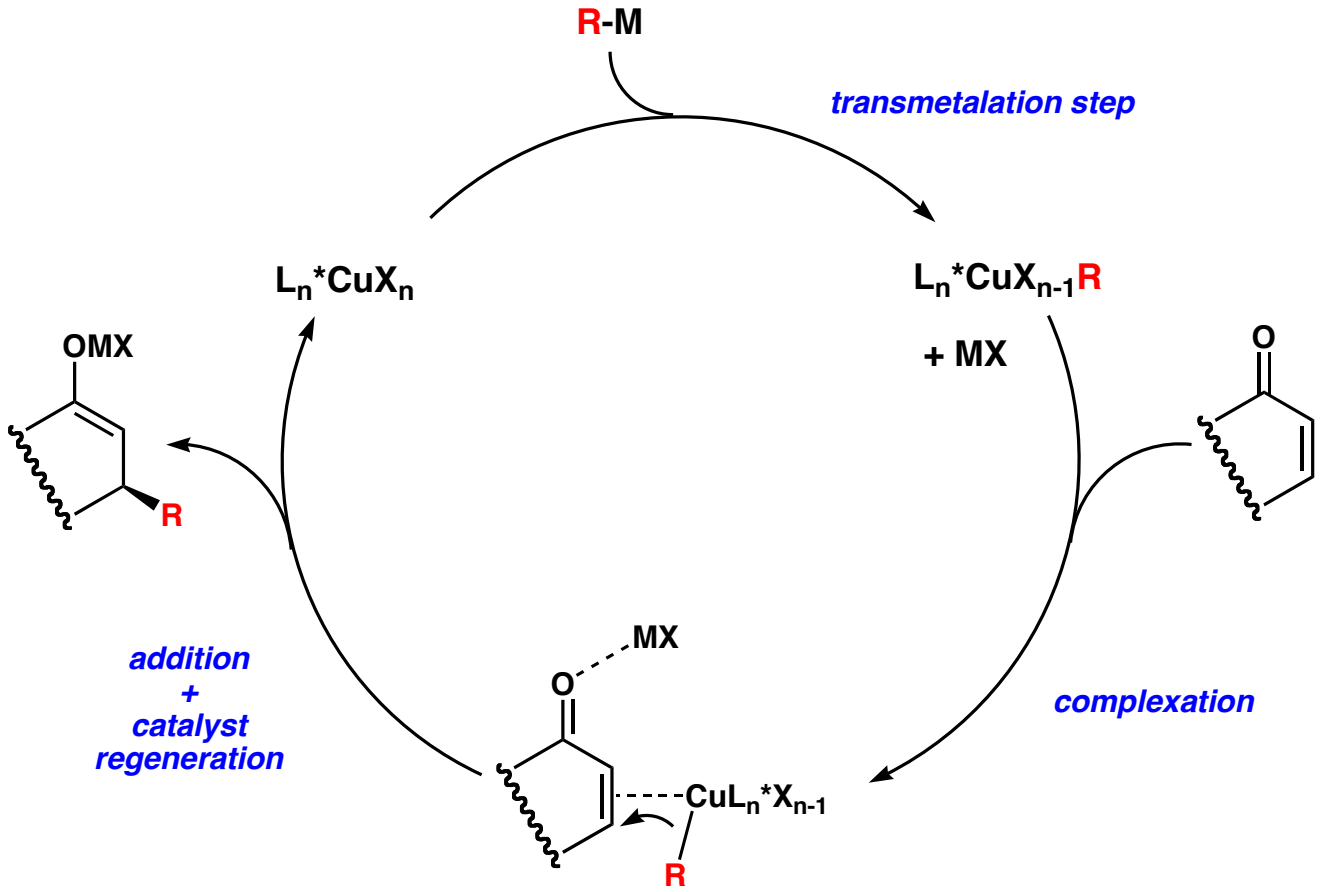


Williams *Tet. Lett.* **1998**, 8593



	R¹ = Bn		R¹ = Ph	
R²MgBr	Yield	de	Yield	de
EtMgBr	78%	53% (*R*)	89%	67% (*S*)
i-PrMgBr	99%	62% (*R*)	99%	81% (*S*)
PhMgBr	66%	54% (*R*)	65%	98% (*S*)
	74%	97% (*S*)	85%	≥97% (*S*)
	90%	15%	95%	≥97% (*S*)
	---	---	95%	≥99% (*S*)

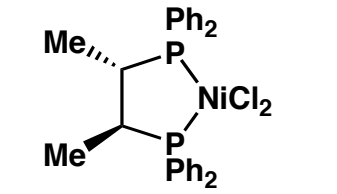
Catalytic Asymmetric Conjugate Addition Reactions



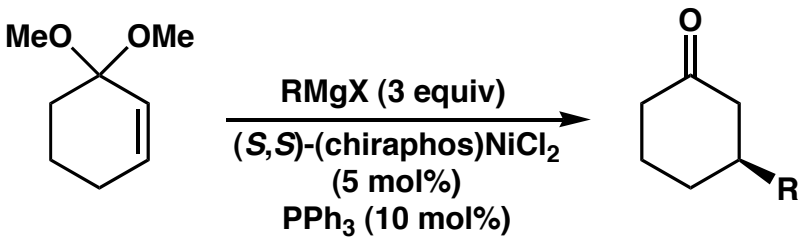
•Dynamic ligand-exchange processes : formation of a highly reactive and selective catalyst by self-assembly

Nickel-Catalyzed Grignard Addition

Hoveyda *J. Am. Chem. Soc.* **1998**, 7649.



(*S*,*S*)-(chiraphos)$NiCl_2$

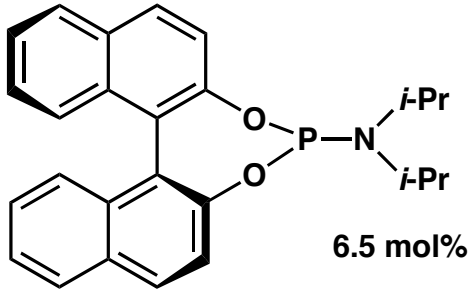


Grignard Reagent	Yield	ee
EtMgBr	90%	85%
n-BuMgBr	85%	85%
i-BuMgBr	63%	70%
PhMgBr	67%	83%
$PhCH_2CH_2MgBr$	81%	84%

- Without the phosphine, less than 10% ee was observed
- 15-53% ee were obtained with cyclopentenylacetal.

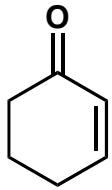
Phosphoramidite Ligands for Conjugate Addition

Feringa *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2374-2376.

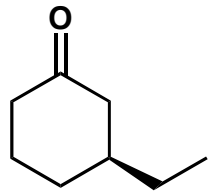


6.5 mol%

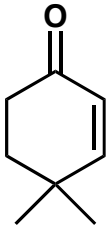
$Cu(OTf)_2$, 3 mol% / Toluène, -15 °C



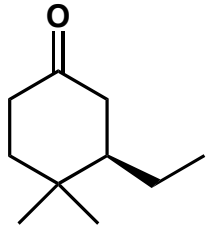
+ Et_2Zn (1.5 equiv) →



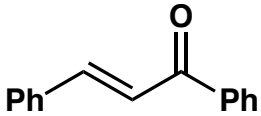
78% y.; 63% ee



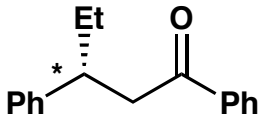
+ Et_2Zn (1.5 equiv) →



76% y.; 81% ee



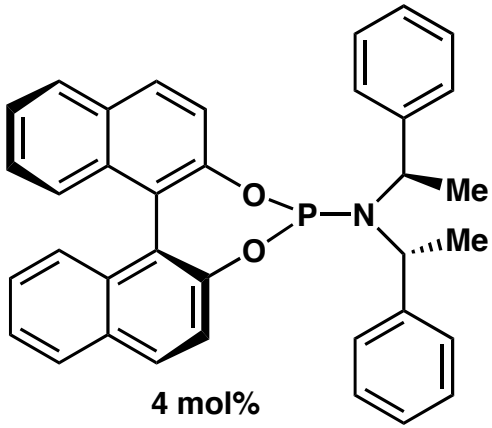
+ Et_2Zn (1.5 equiv) —(-50 °C)→



88% y.; 90% ee

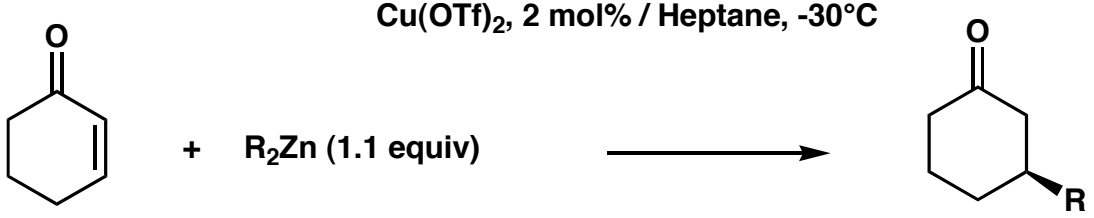
Catalytic Asymmetric Conjugate Addition

Feringa *Angew. Chem., Int. Edit.* **1997**, 2620.



4 mol%

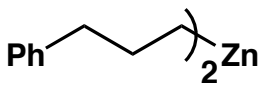
$Cu(OTf)_2$, 2 mol% / Heptane, -30°C



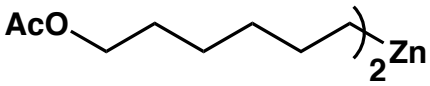
Me_2Zn
68% y. >98% ee

Hep_2Zn
95% y. 95% ee

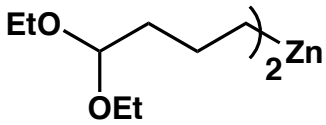
i-Pr_2Zn
95% y. 94% ee



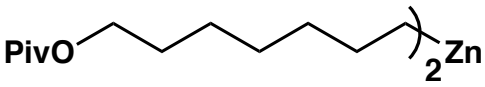
53% y. 95% ee



77% y. 95% ee



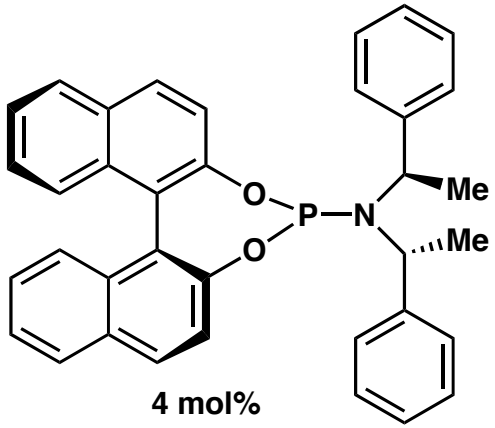
91% y. 97% ee



87% y. 93% ee

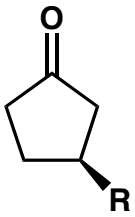
Catalytic Asymmetric Conjugate Addition

Feringa *Angew. Chem., Int. Edit.* **1997**, 2620.

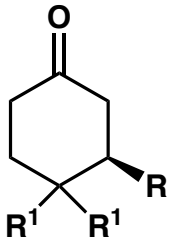


4 mol%

$Cu(OTf)_2$, 2 mol% / Heptane, -30°C

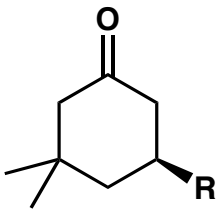


10% ee

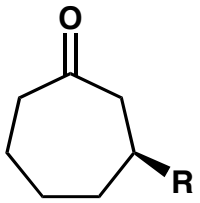


R^1 = H, Me, Ph

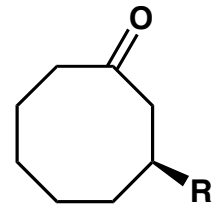
>98% ee



84-88% ee



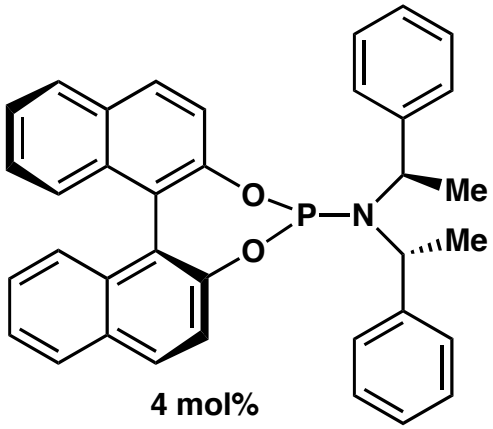
>98% ee



97% ee

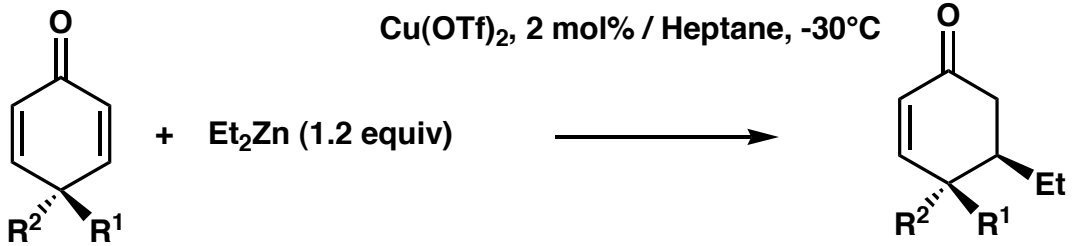
Catalytic Asymmetric Conjugate Addition

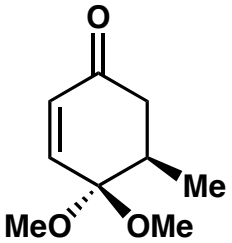
Feringa *et al. Org. Let.* **1999**, *1*, 623.



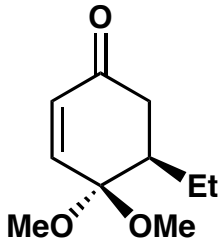
4 mol%

$Cu(OTf)_2$, 2 mol% / Heptane, -30°C

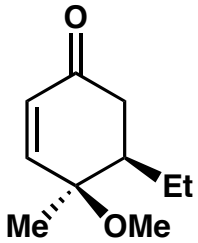




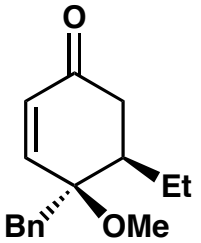
99% ee



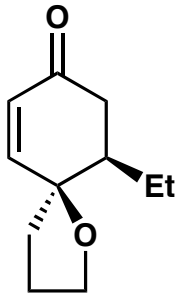
97% ee



9 : 1(*cis*:*trans*)
97% ee (*cis*)

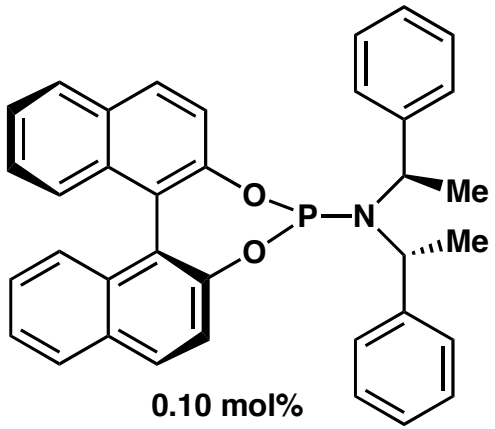


32 : 1 (*cis*:*trans*)
93% ee (*cis*)

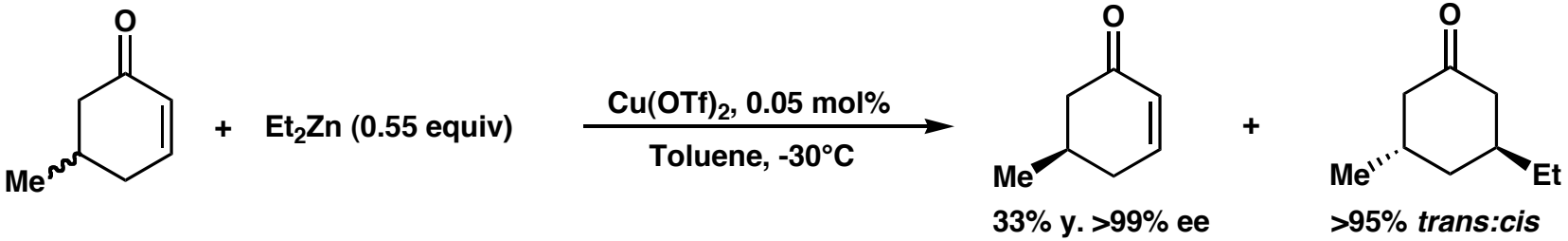


99 : 1 (*cis*:*trans*)
65% ee (*cis*)

Catalytic Asymmetric Conjugate Addition: Kinetic Resolution



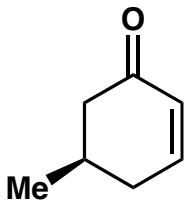
0.10 mol%



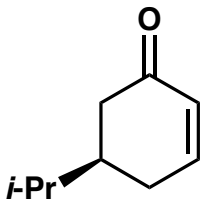
33% y. >99% ee

>95% *trans:cis*

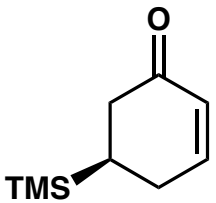
Using *n*-Bu_2Zn:



54% conv. >99% ee
s >200

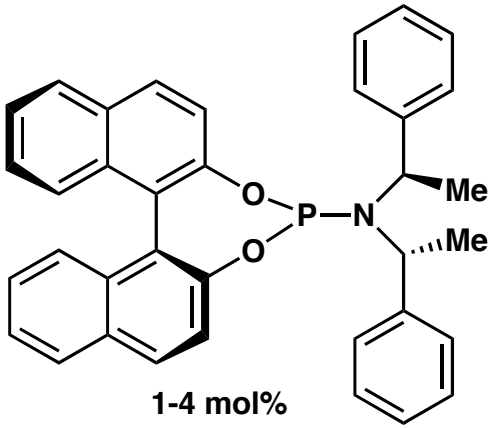


53% conv. 99% ee
s >200

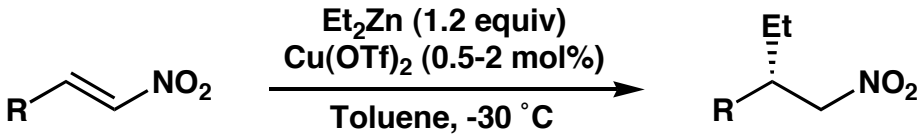


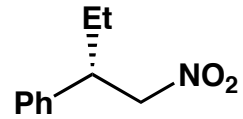
52% conv. >99% ee
s >200

Catalytic Asymmetric Conjugate Addition

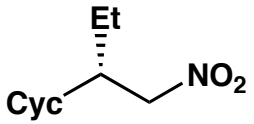


1-4 mol%

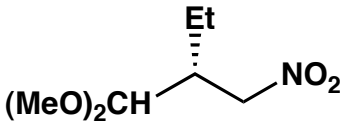




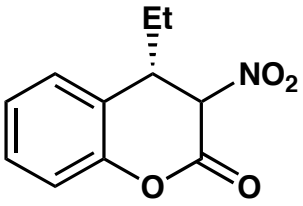
90% conv. 48% ee



100% y. 94% ee



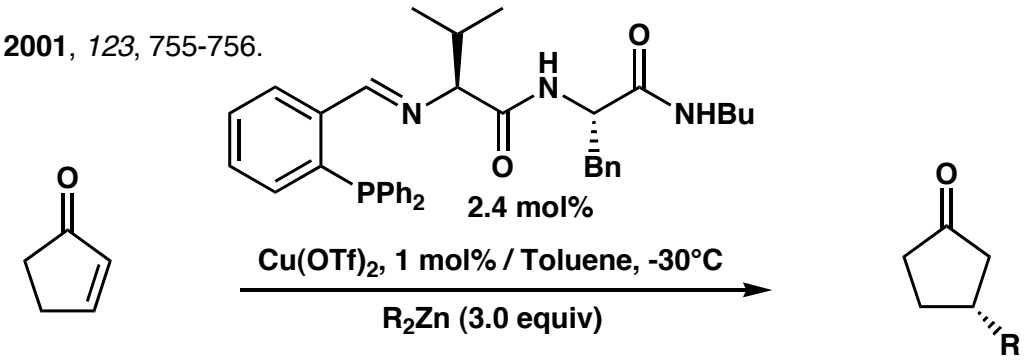
100% conv. 86% ee

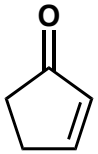
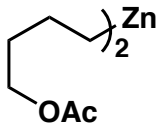
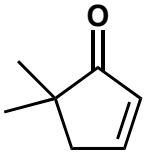
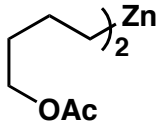
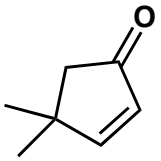


79%y. 10 : 1 dr, 92% ee

Catalytic Asymmetric Conjugate Addition

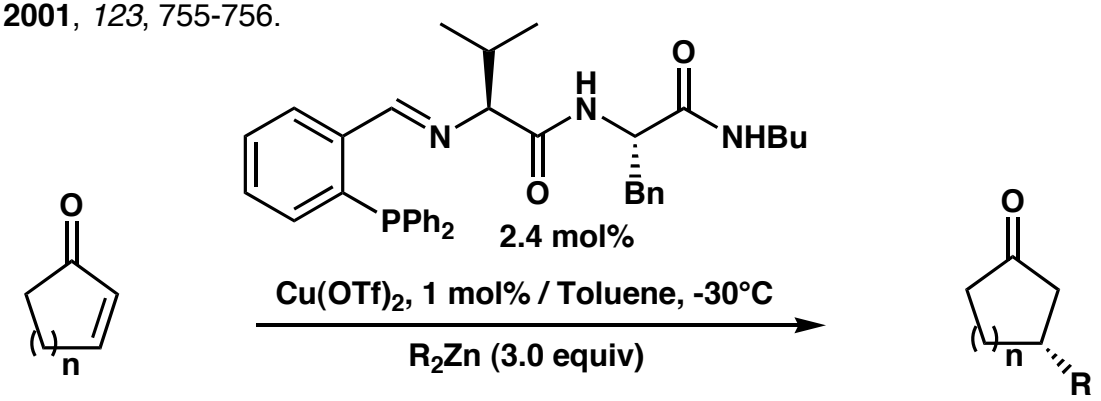
Hoveyda *J. Am. Chem. Soc.* **2001**, *123*, 755-756.

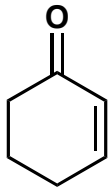
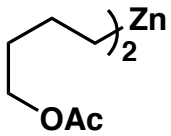
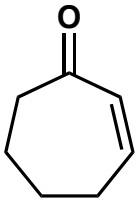


Substrate	Dialkylzinc (3.0 equiv.)	Yield	ee
	Et_2Zn	78%	97%
	Bu_2Zn	92%	98%
	i-Pr_2Zn	90%	79%
		56%	>98%
	Et_2Zn	72%	>98%
	Bu_2Zn	64%	>98%
		55%	>98%
	Et_2Zn	56%	97%

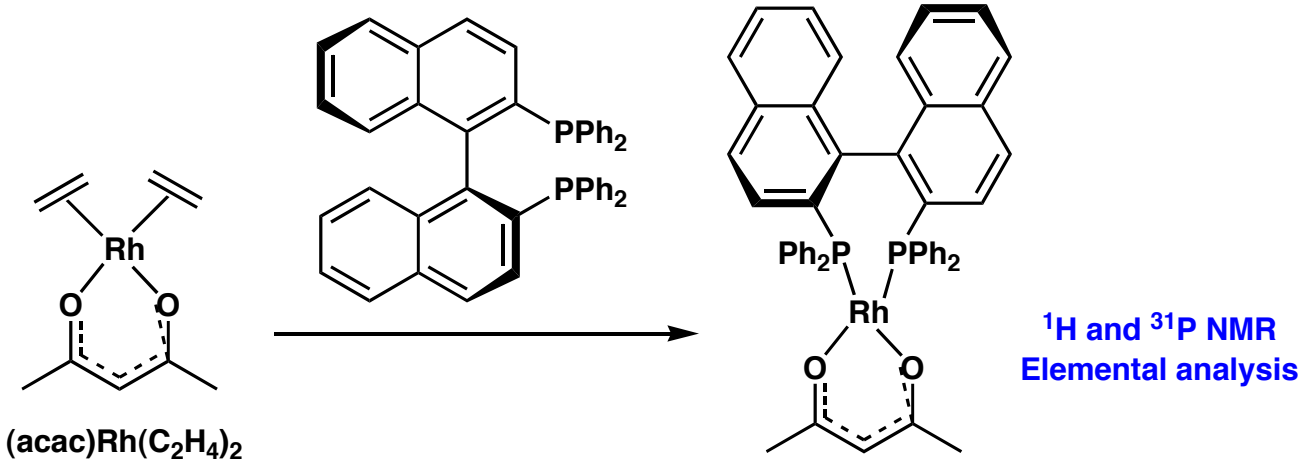
Catalytic Asymmetric Conjugate Addition

Hoveyda *J. Am. Chem. Soc.* **2001**, *123*, 755-756.



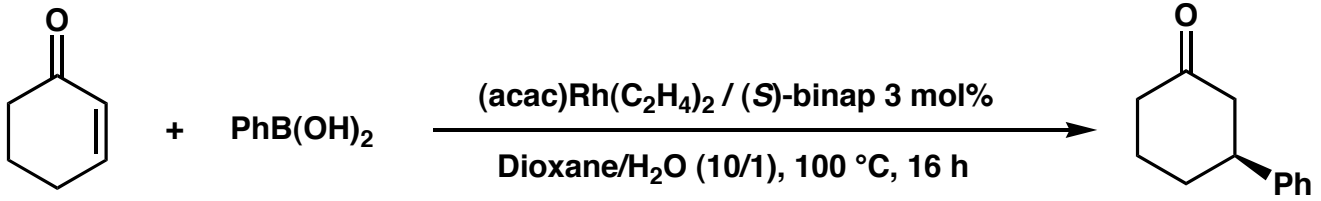
Substrate	Dialkylzinc (3.0 equiv.)	Yield	ee
	Me_2Zn	71%	>98%
	Et_2Zn	98%	98%
	Bu_2Zn	93%	95%
	i-Pr_2Zn	98%	72%
		76%	95%
	Me_2Zn	80%	>98%
	Et_2Zn	98%	98%
	Bu_2Zn	81%	95%
	i-Pr_2Zn	78%	62%

Catalytic Asymmetric Conjugate Addition



(acac)Rh(C_2H_4)$_2$

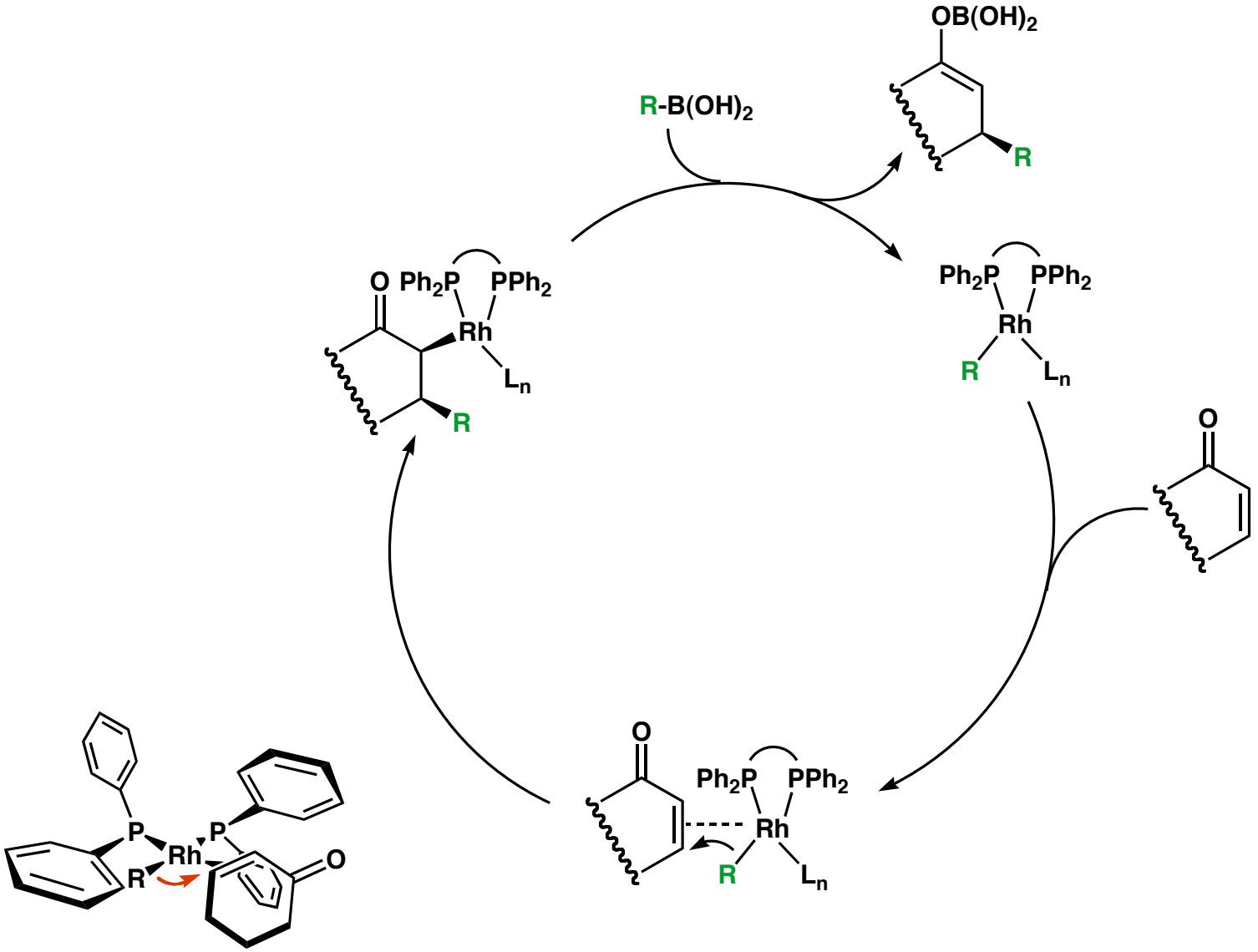
^{1}H and ^{31}P NMR
Elemental analysis



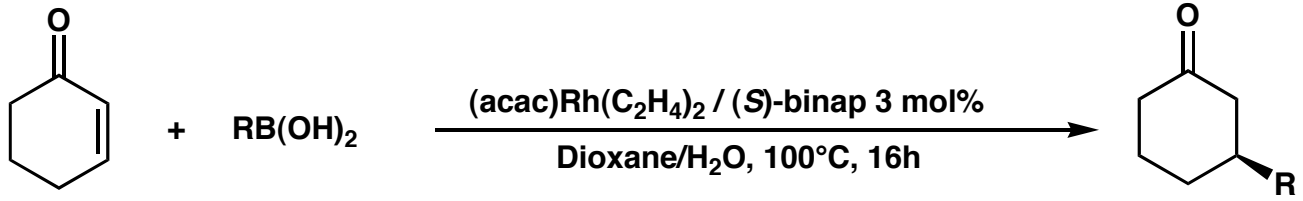
1.4 equiv	64% y. 97% ee
2.5 equiv	93% y. 97% ee
5.0 equiv	>99% y. 97%ee

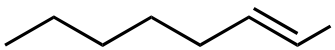
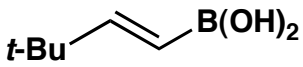
Hayashi and Miyaura, *JACS*, **1998**, *120*, 5579-5580.

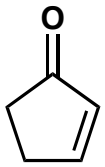
Catalytic Asymmetric Conjugate Addition



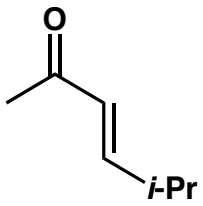
Catalytic Asymmetric Conjugate Addition



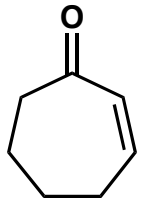
4-MePhB(OH)$_2$ (5.0 equiv)	>99% y. 97% ee
4-CF$_3$PhB(OH)$_2$ (2.5 equiv)	70%y. 99% ee
3-MeOPhB(OH)$_2$ (5.0 equiv)	97% y. 96% ee
3-ClPhB(OH)$_2$ (5.0 equiv)	94% y. 96% ee
 B(OH)$_2$ (2.5 equiv)	88% y. 94% ee
	76% y. 91% ee



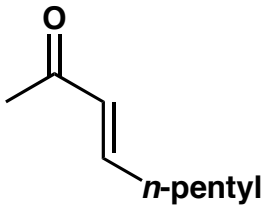
PhB(OH)$_2$ (1.4 equiv)
93% y. 97% ee



PhB(OH)$_2$ (5.0 equiv)
82% y. 97% ee

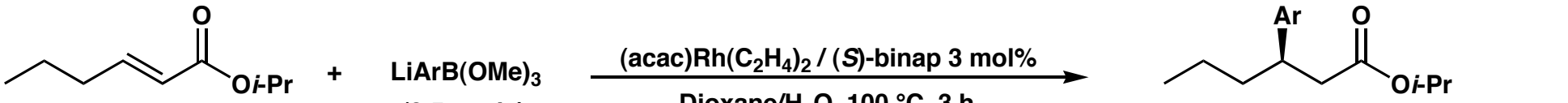


PhB(OH)$_2$ (1.4 equiv)
51% y. 93% ee

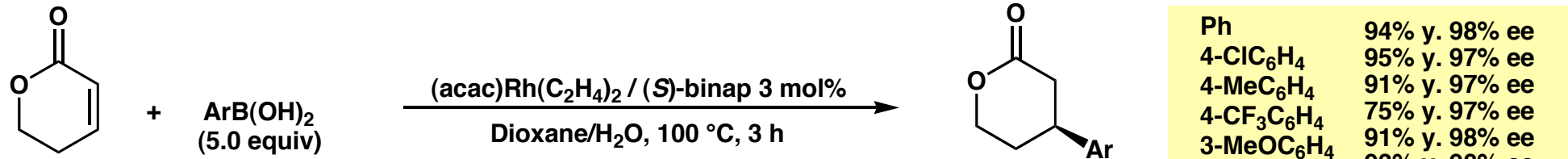


PhB(OH)$_2$ (2.5 equiv)
88% y. 92% ee

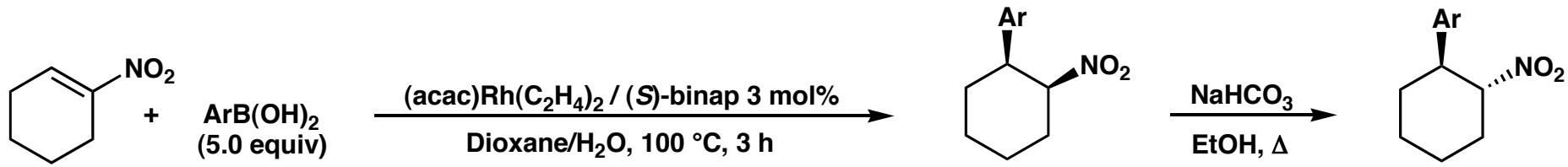
Catalytic Asymmetric Conjugate Addition



4-ClC_6H_4	95% y. 97% ee
4-MeC_6H_4	88% y. 97% ee
4-$CF_3C_6H_4$	98% y. 96% ee
3-$MeOC_6H_4$	83% y. 94% ee
2-naphtyl	96% y. 93% ee



Ph	94% y. 98% ee
4-ClC_6H_4	95% y. 97% ee
4-MeC_6H_4	91% y. 97% ee
4-$CF_3C_6H_4$	75% y. 97% ee
3-$MeOC_6H_4$	91% y. 98% ee
2-naphtyl	93% y. 98% ee

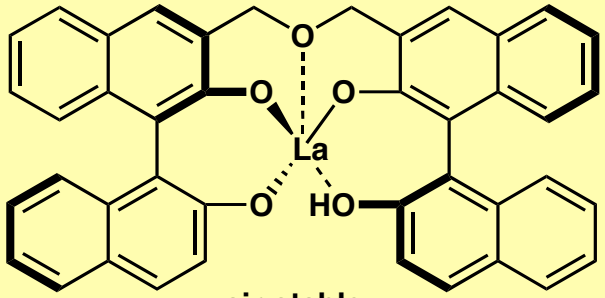


71-90% y.
98-99%ee
3:1 à 8:1
cis:trans

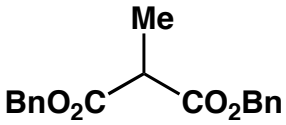
9:1 à 49:1
trans:cis

Catalytic Asymmetric Conjugate Addition

94% yield
>99% ee (R = Me)

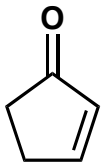


air-stable

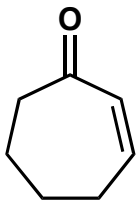


84% yield
98% ee

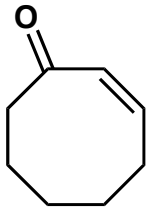
96% yield
>99% ee
(85 h)
R = Me



97% yield
>99% ee
(85 h)
R = Me



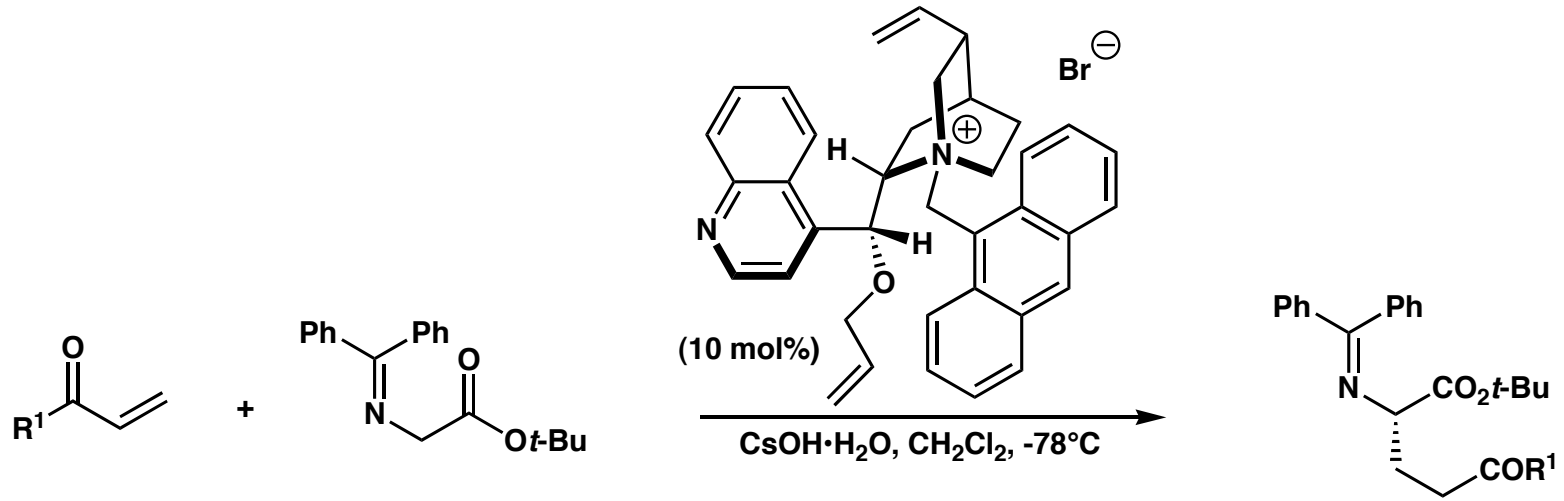
82% yield
99% ee
(96 h)
R = Me



ee's are lower with acyclic ketones

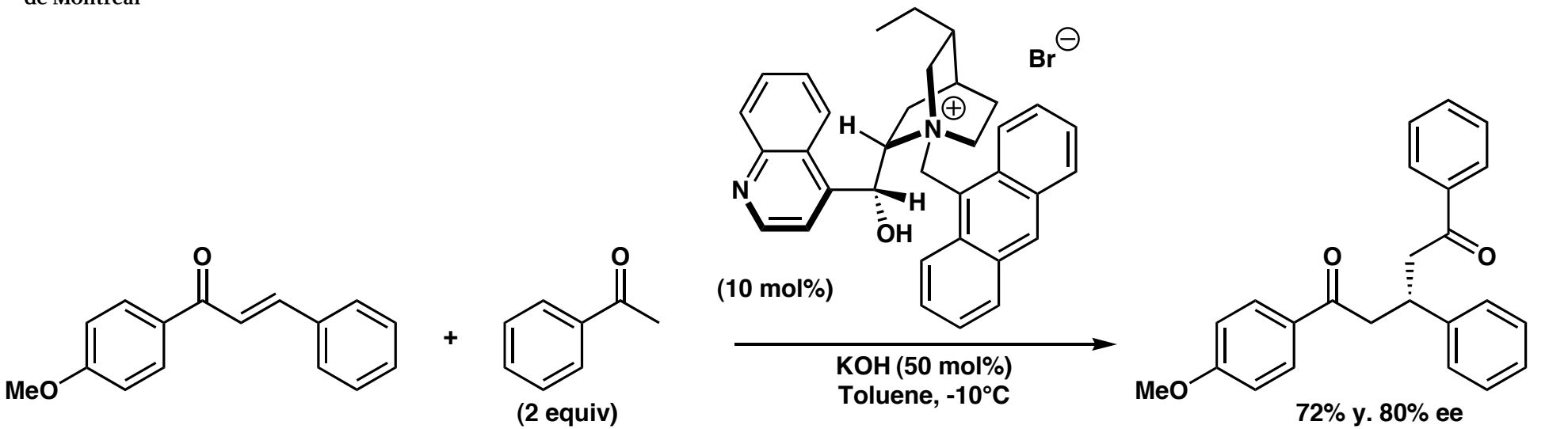
Catalytic Asymmetric Conjugate Addition

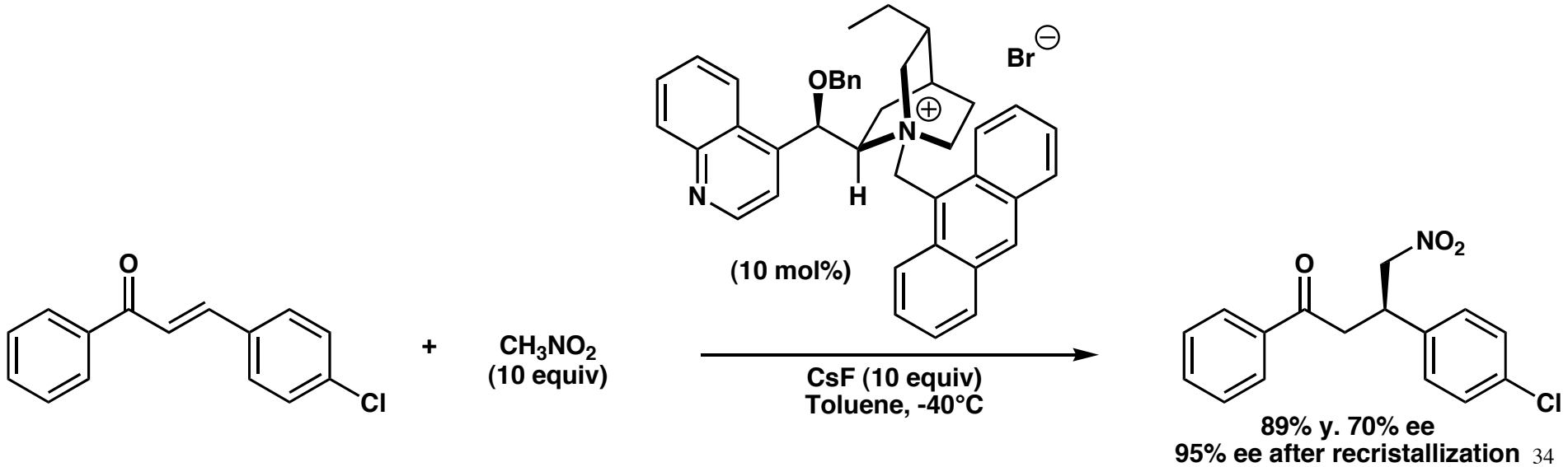
Corey, *Tetrahedron Lett.* **1998**, 5347.



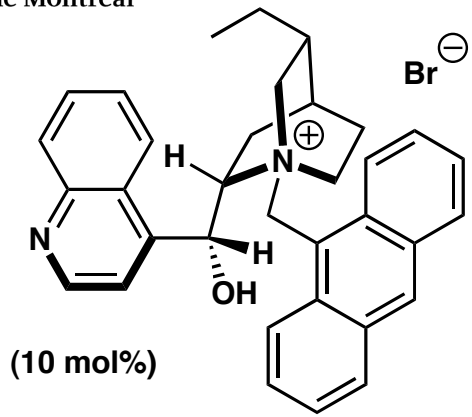
Acceptor	yield	ee
EtCO	85%	91%
MeO_2C	85%	95%
NC (Base : KOH)	85%	91%
O	88%	99%

Catalytic Asymmetric Conjugate Addition

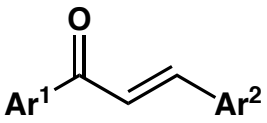


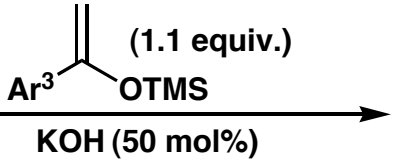


Catalytic Asymmetric Conjugate Addition

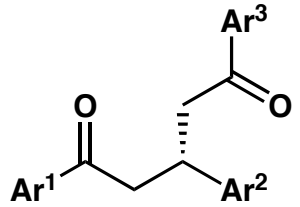


(10 mol%)

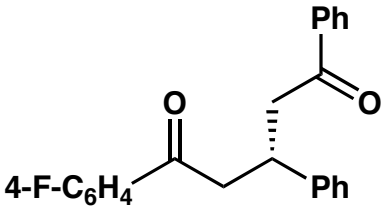




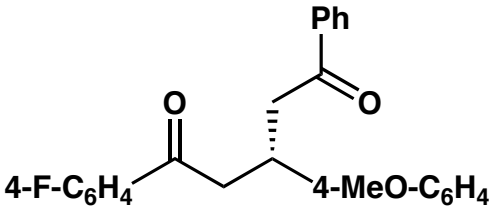
KOH (50 mol%)
Toluene, -20°C



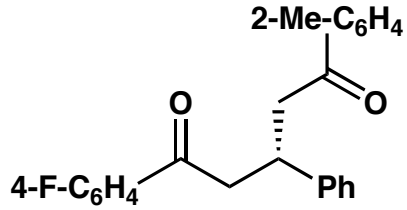
79%-94% y.
91-95% ee



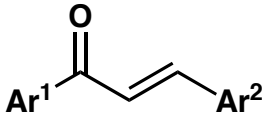
85% y., 95% ee

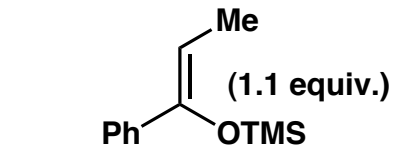


92% y. 94% ee



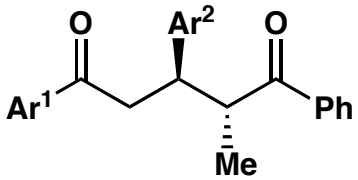
79% y., 92% ee





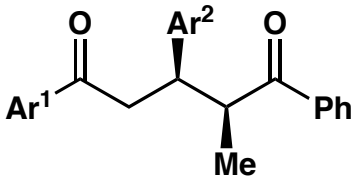
KOH (50 mol%)
Toluene, -20°C

3 : 1 to 20 : 1 (*anti:syn)*



65-86% y. 92-99% ee

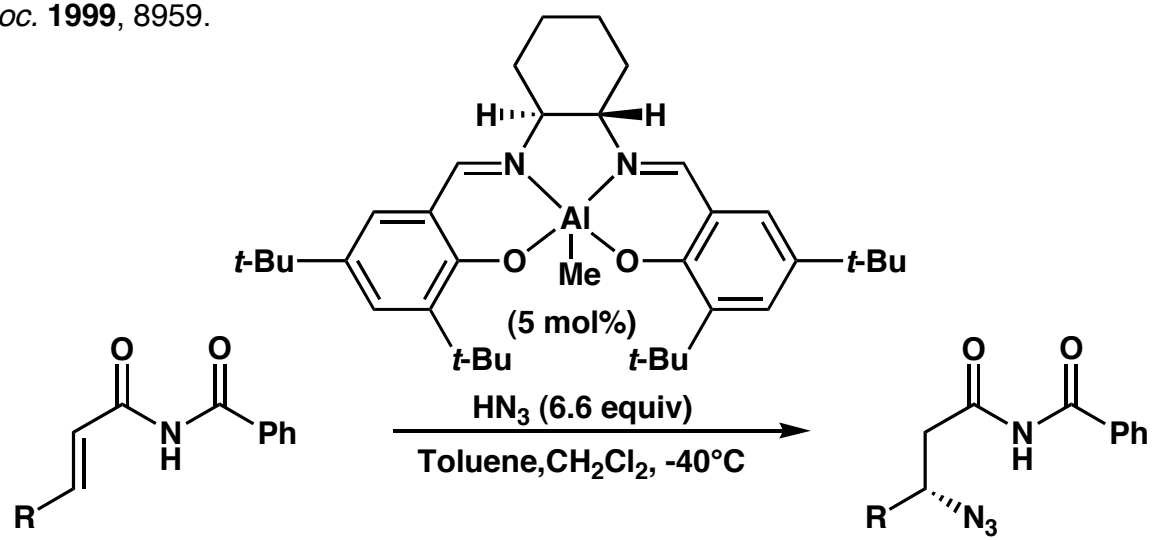
+



9-22% y. 81-95% ee

Catalytic Asymmetric Conjugate Addition: Azide

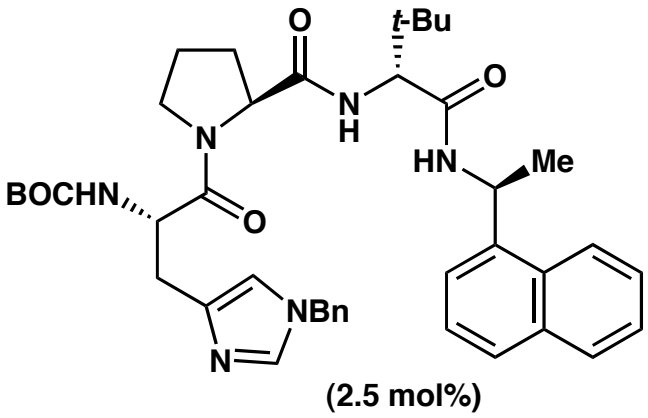
Jacobsen *J. Am. Chem. Soc.* **1999**, 8959.



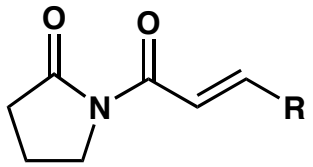
R	yield	ee
Me	96%	96%
Et	97%	97%
n-Pr	97%	95%
i-Pr	98%	97%
t-Bu	99%	97%
CH_2Ph	97%	95%
CH_2OBn	93%	96%
Ph	60%	58%

Catalytic Asymmetric Conjugate Addition: Azide

Miller *Angew. Chem., Int. Edit.* **2000**, 3635.

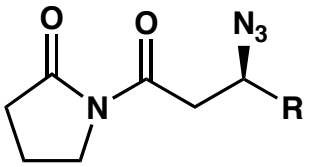


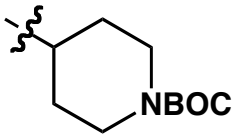
(2.5 mol%)

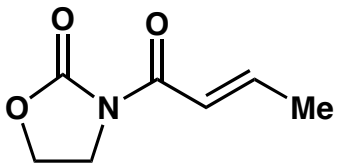


$TMSN_3$ (3.8 equiv)

RCO_2H (1.0 equiv.)
Toluene, 25°C

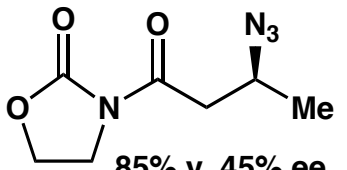


R	yield	ee
Me	97%	63%
Et	91%	71%
C_6H_{11}	79%	85%
i-Pr	84%	82%
	84%	71%



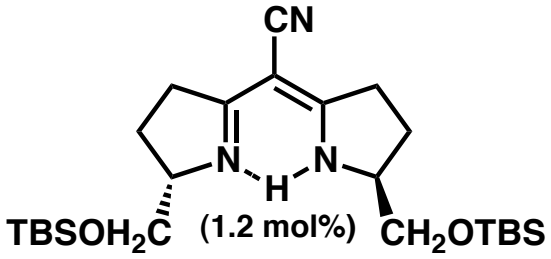
$TMSN_3$ (3.8 equiv)

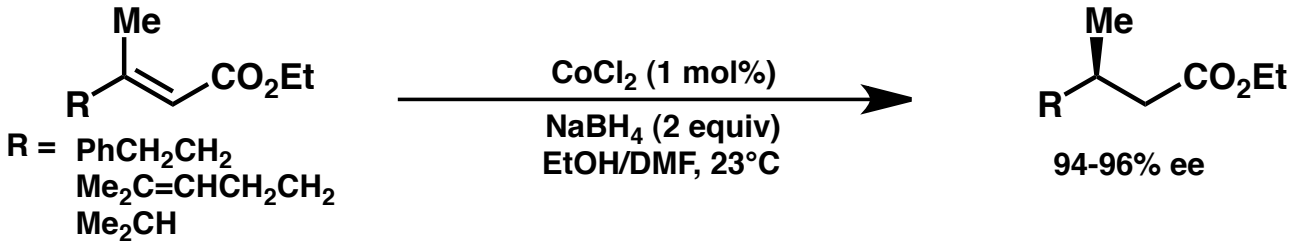
RCO_2H (1.0 equiv.)
Toluene, 25°C

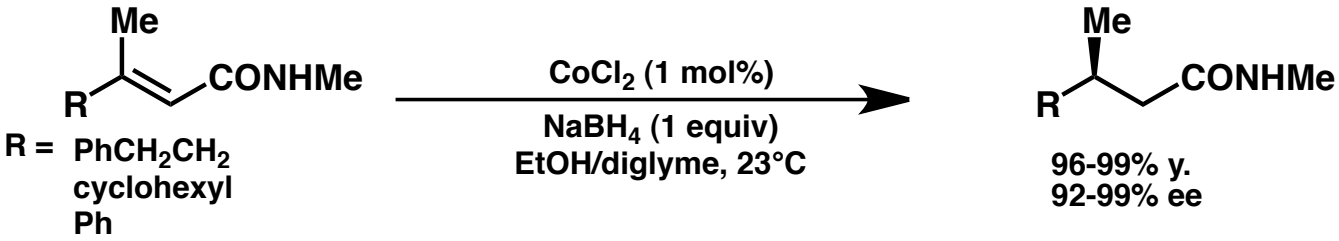


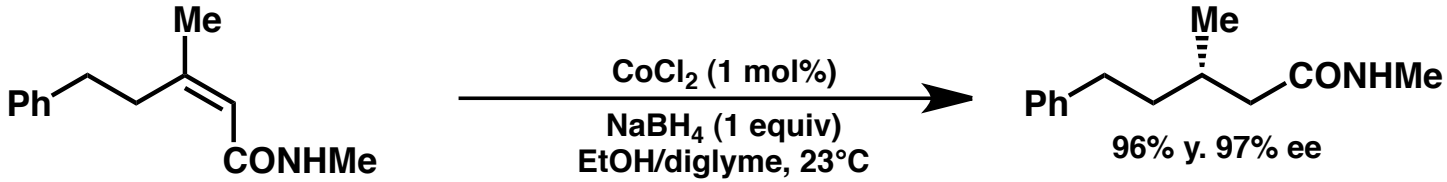
85% y. 45% ee

Catalytic Asymmetric Conjugate Reduction

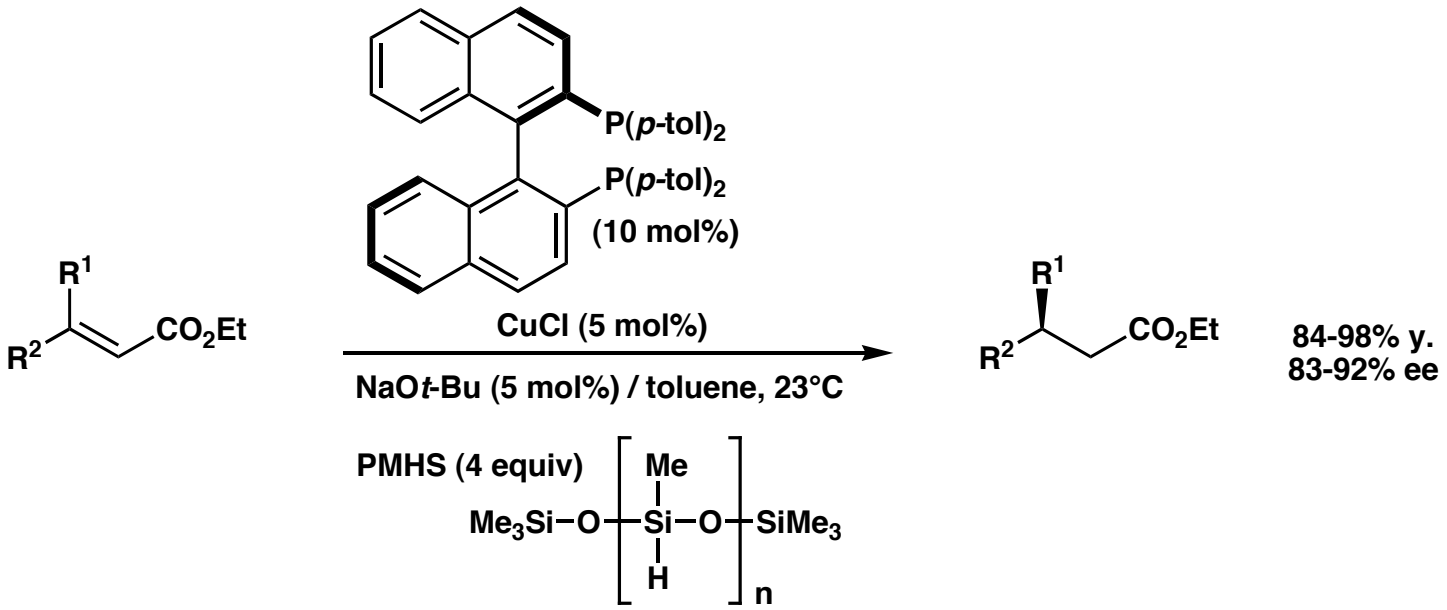


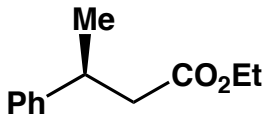


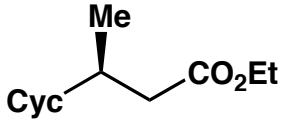


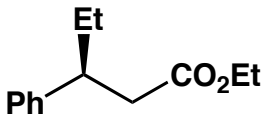


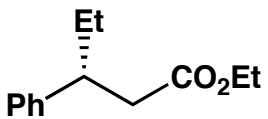
Catalytic Asymmetric Conjugate Reduction



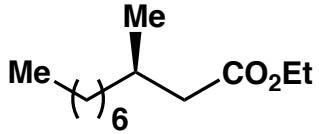


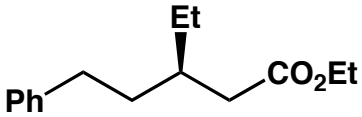


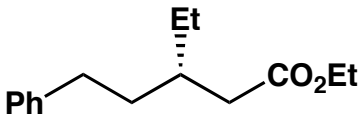




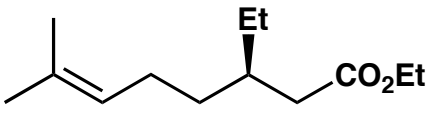
(From *Z*-alkene)

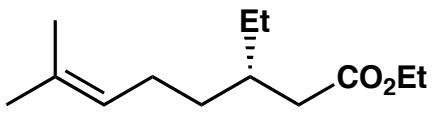






(From *Z*-alkene)



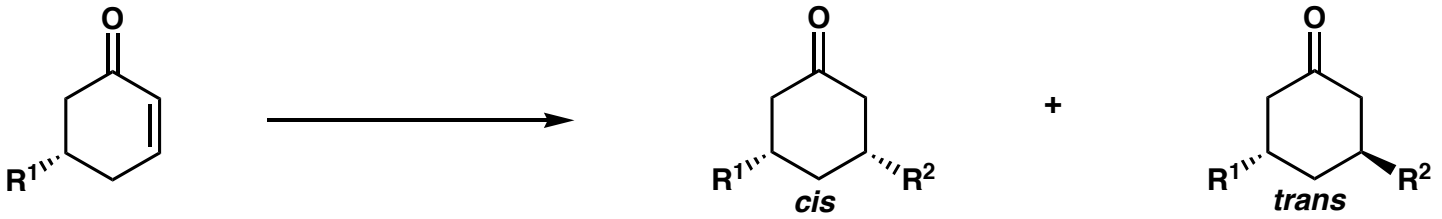


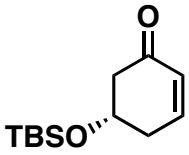
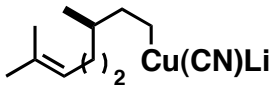
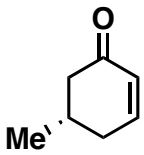
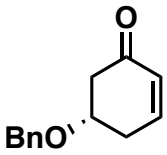
(From *Z*-alkene)

Extra Slides

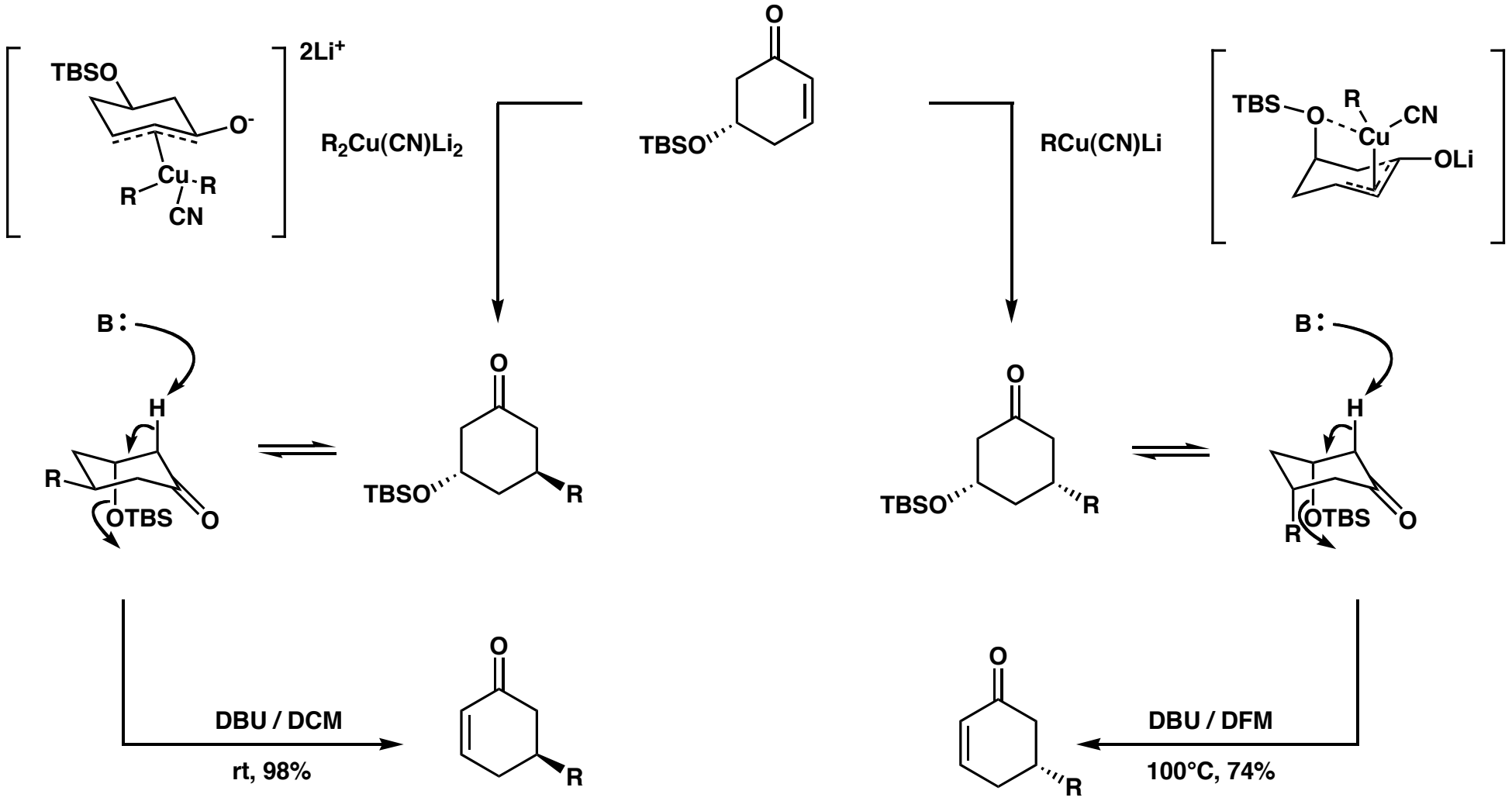
Importance of the Reagents and Reaction Conditions

Sato *J. Am. Chem. Soc.* **1999**, 3640; *Angew. Chem., Int. Edit.* **1998**, 2099.



Enone	Cyanocuprate[a]	Yield	*cis:trans*	Cyanocuprate[b]	Yield	*cis:trans*
	[MeCu(CN)Li]	77%	>99:1	[$Me_2Cu(CN)Li_2$]	83%	1:32
	[*n*-BuCu(CN)Li]	91%	>99:1	[*n*-$Bu_2Cu(CN)Li_2$]	92%	1:50
	[*n*-BuCu(CN)MgBr]	73%	9:1			
	[*s*-BuCu(CN)Li]	84%	50:1	[*s*-$Bu_2Cu(CN)Li_2$]	---	<1:50
	[*t*-BuCu(CN)Li]	78%	3:1	[*t*-$Bu_2Cu(CN)Li_2$]	92%	<1:50
		87%	50:1			
	[PhCu(CN)Li]	25%	4:1	[$Ph_2Cu(CN)Li_2$]	80%	1:32
	[CH_2=CHCu(CN)Li]	45%	1:3	[$(CH_2=CH)_2Cu(CN)Li_2$]	75%	1:19
	[*n*-BuCu(CN)Li]	95%	<1:99			
	[*n*-BuCu(CN)Li]	80%	>50:1	[*n*-$Bu_2Cu(CN)Li_2$]	87%	1:9

Effect of the Reagent Structure



Modes of Asymmetric Induction Using Organocatalysis

- Covalent Catalysis

✓ Increased nucleophilicity of nuclephiles (HOMO activation)
  - Enamine catalysis
  - Lewis bases activation
  - Stetter Reaction (NHC ligands)

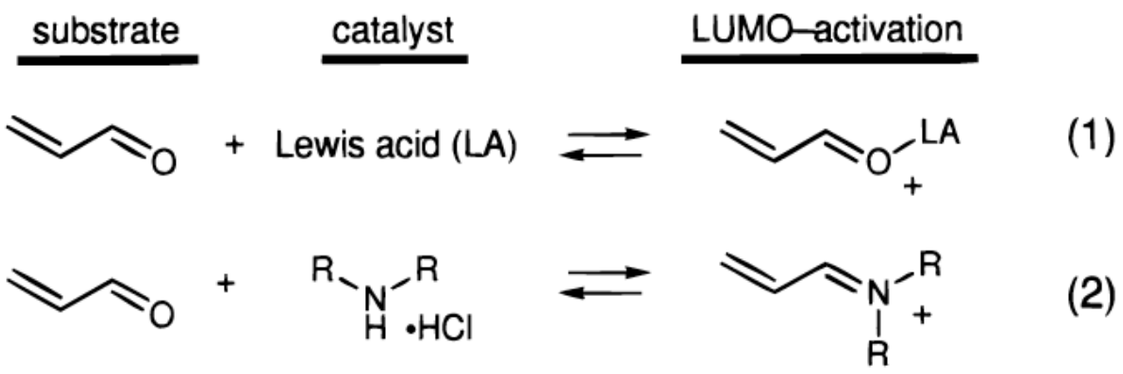
✓ Increases electrophilicity of electrophiles (LUMO activation)
  - **Iminium catalysis**

✓SUMO activation
  - Enamine catalysis

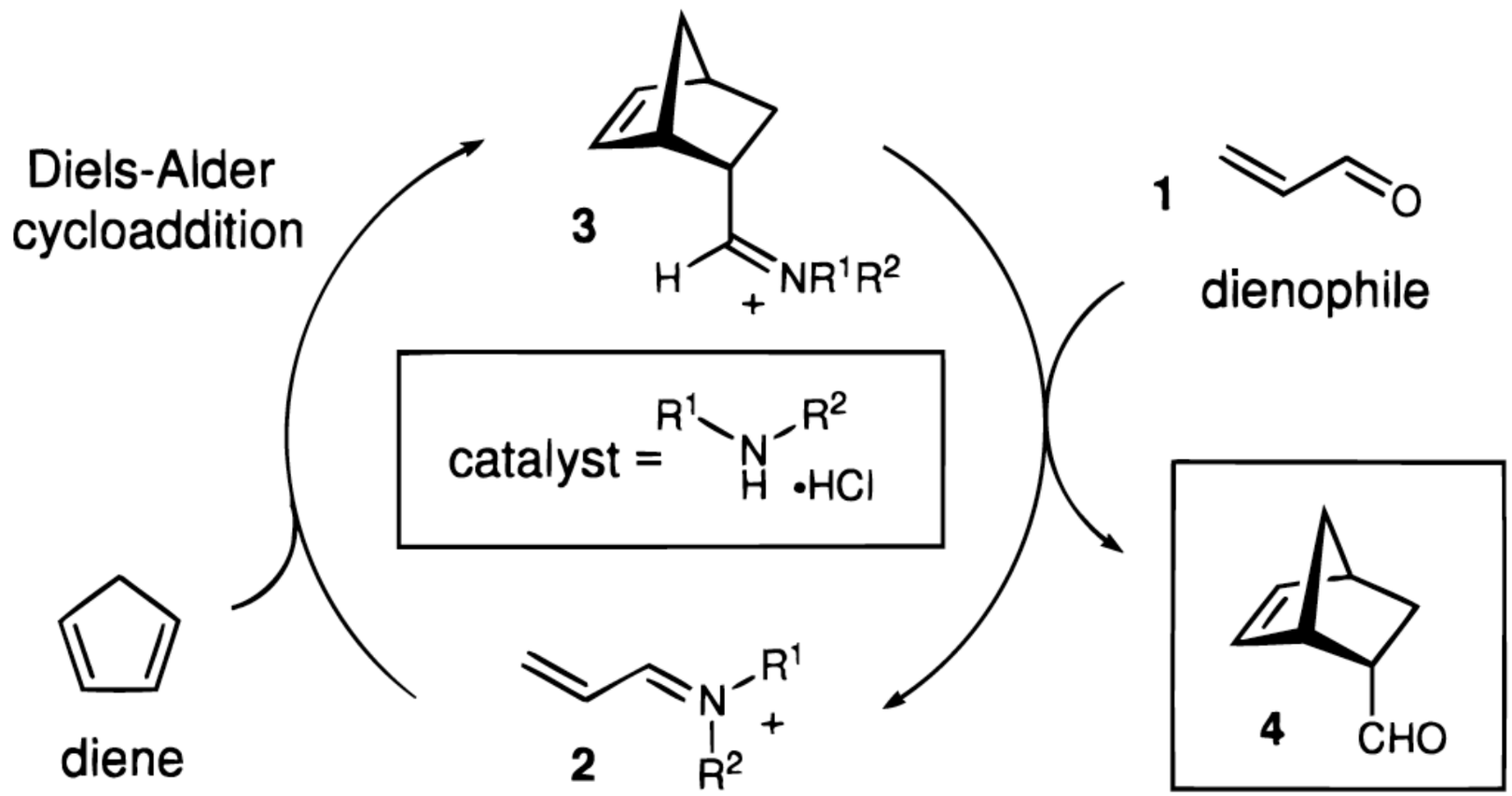
- Non-covalent Catalysis

✓ Hydrogen bonding catalysis
✓ Chiral ion pairs (chiral cations, chiral anions)

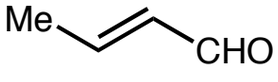
LUMO Activation: Asymmetric Diels-Alder Reaction

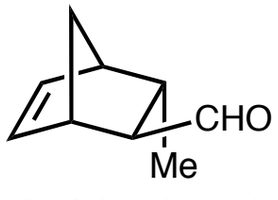


Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C.
J. Am. Chem. Soc. **2000**, *122*, 4243-4244.

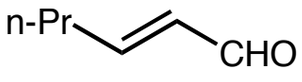


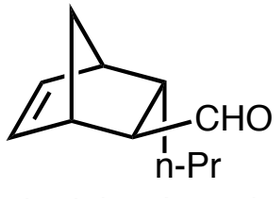
LUMO Activation: Asymmetric Diels-Alder Reaction



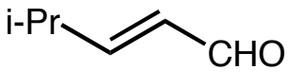


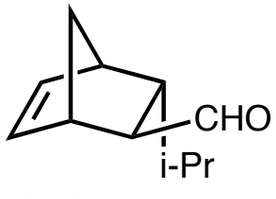
1 : 1 (*endo:exo*)
75% y. 86% ee



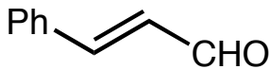


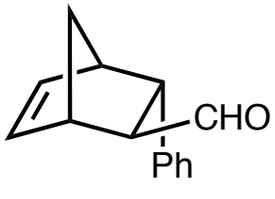
1 : 1 (*endo:exo*)
92% y. 86% ee



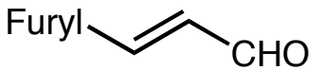


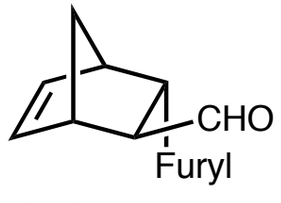
1 : 1 (*endo:exo*)
81% y. 84% ee



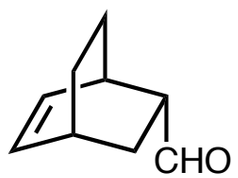


1 : 1.3 (*endo:exo*)
99% y. 93% ee

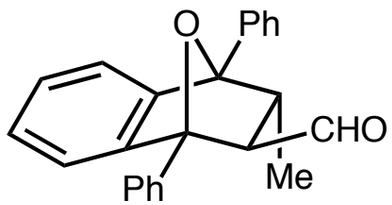




1 : 1 (*endo:exo*)
89% y. 91% ee

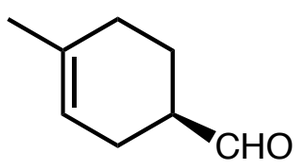


14 : 1 (*endo:exo*)
82% y. 94% ee

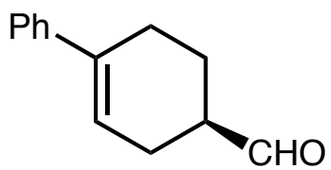


1 : 35 (*endo:exo*)
75% y. 96% ee

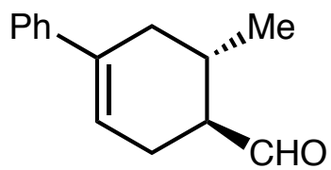
(5 mol%)
MeOH-H_2O, rt



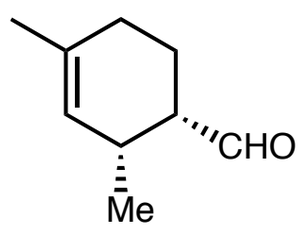
84% y. 89% ee



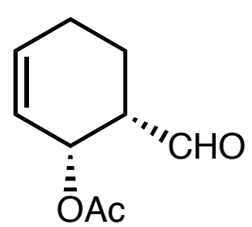
90% y. 83% ee



75% y. 90% ee

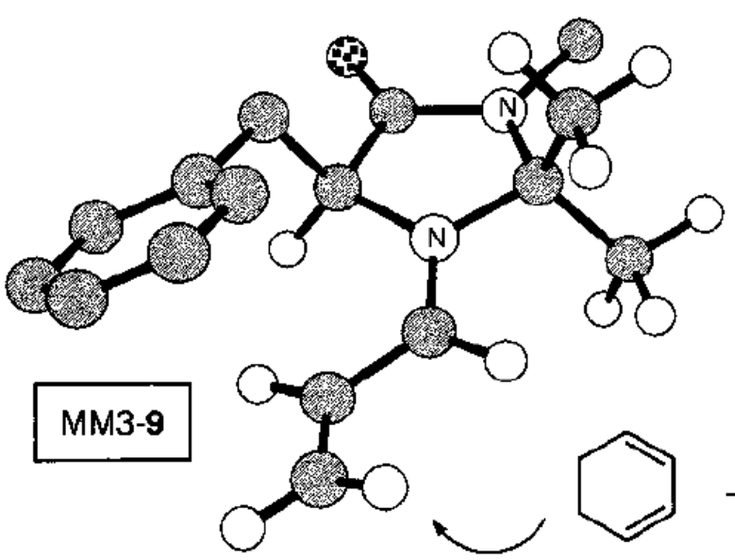


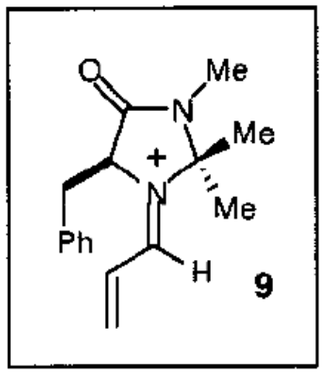
5 : 1 (*endo:exo*)
75% y. 90% ee

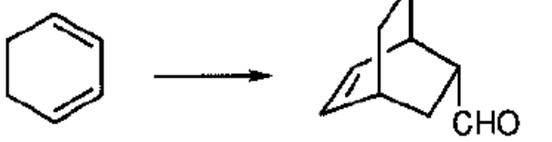


11 : 1 (*endo:exo*)
72% y. 85% ee

LUMO Activation: Asymmetric Diels-Alder Reaction



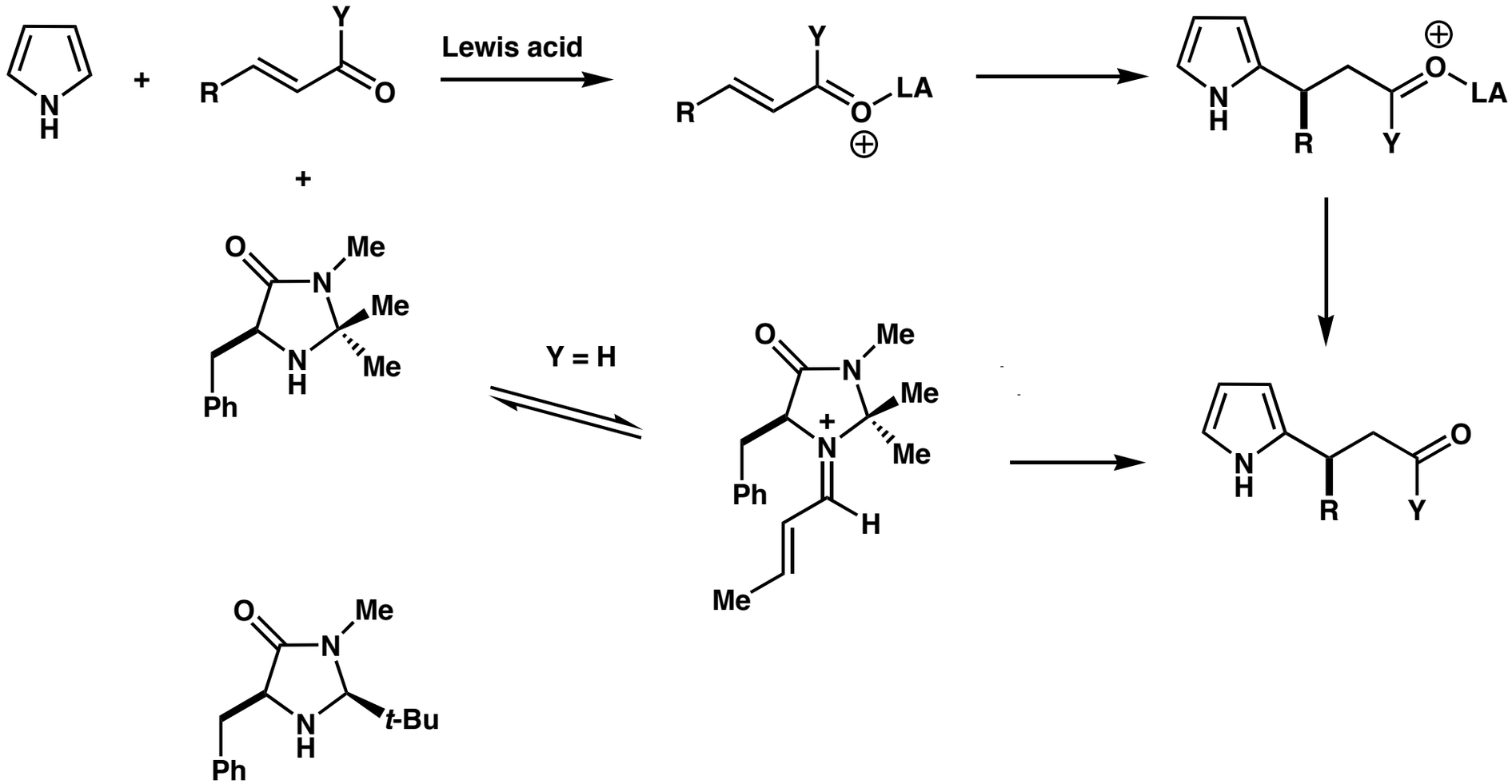




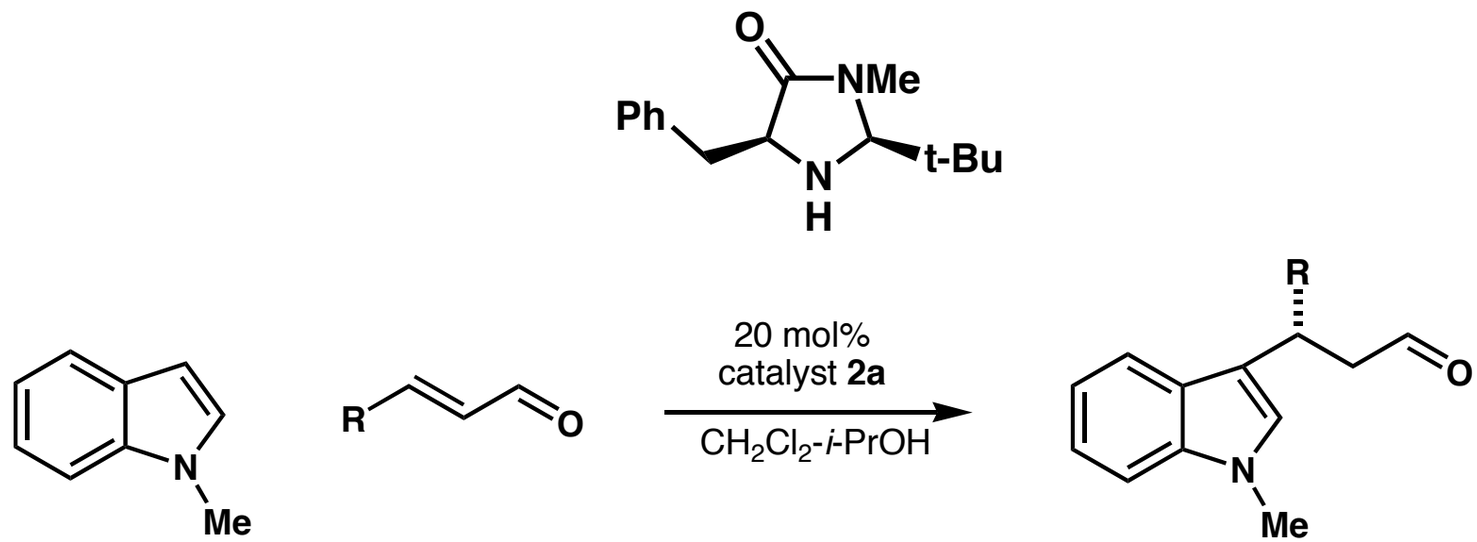
si-face

observed (94% ee)

LUMO Activation: Friedel-Craft Reaction



LUMO Activation: Friedel-Craft Reaction



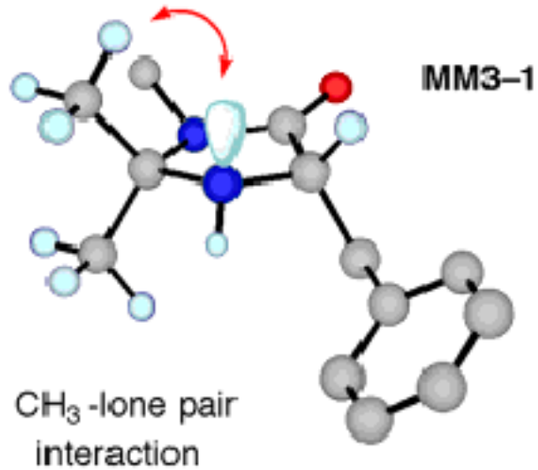
entry	R	temp °C	time (h)	% yield	% ee[a]
1	Me	-83	19	82	92[b]
2	Pr	-60	6	80	93
3	*i*-Pr	-50	32	74	93
4	CH_2OBz	-83	18	84	96[b]
5	Ph	-55	45	84	90
6	CO_2Me	-83	21	89	91

[a] product ratios determined by chiral HPLC.
[b] Absolute configuration determined by chemical correlation.

Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.

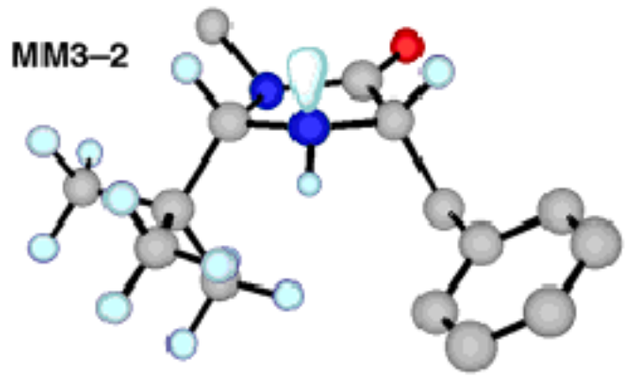
LUMO Activation: Friedel-Craft Reaction

Computational model of catalyst **1**



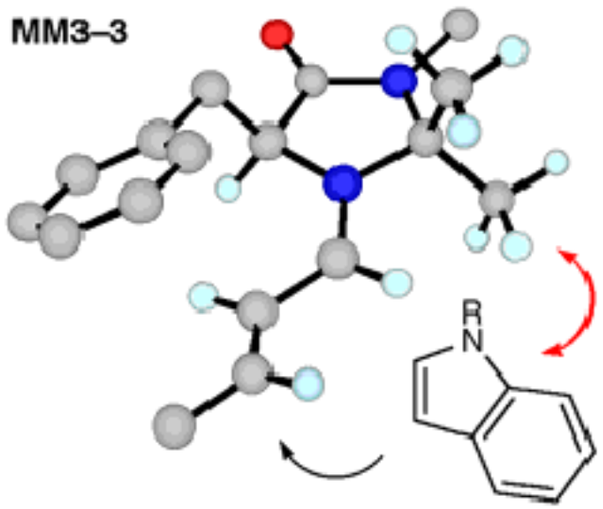
CH_3 -lone pair interaction

Computational model of catalyst **2**



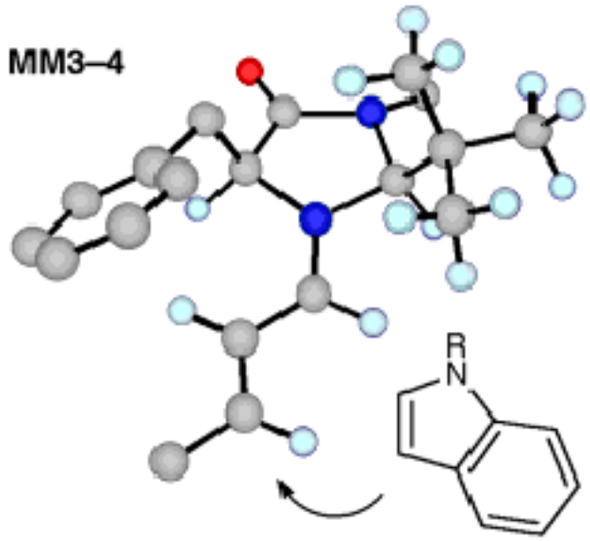
lone pair exposed

Computational model of iminium **3**



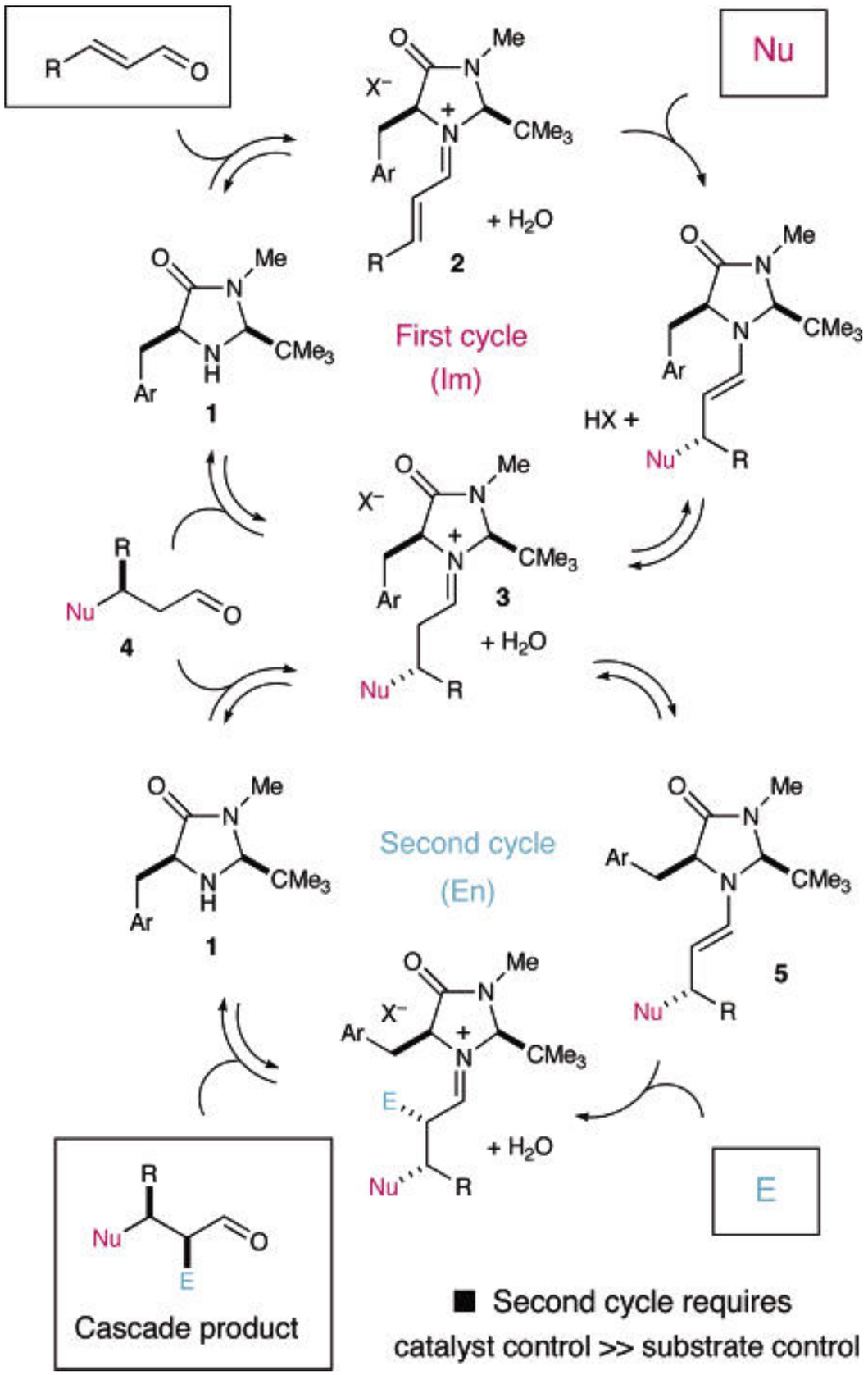
Effective *Si*-face coverage
Re-face CH_3 -substrate interaction
Diminished substrate addition rate

Computational model of iminium **4**

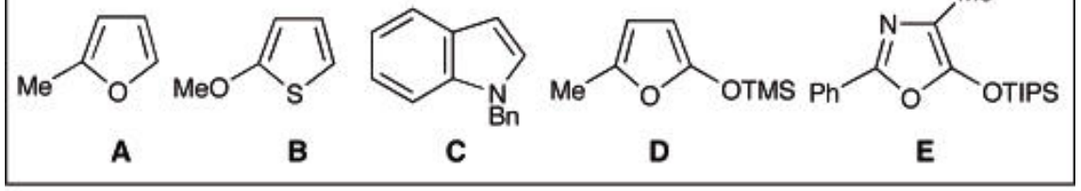


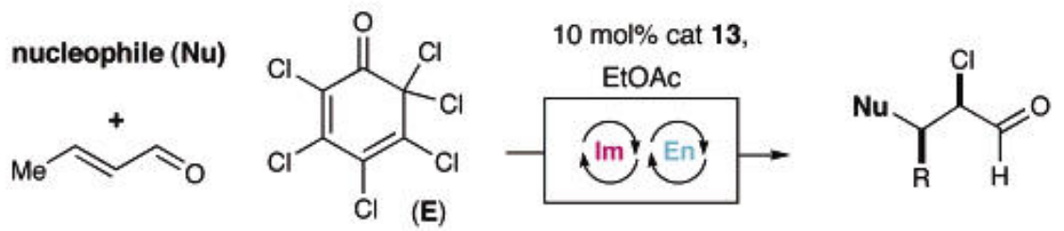
Increased *Si* -face coverage
Re-face addition unhindered
Increased substrate addition rate

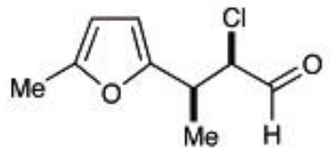
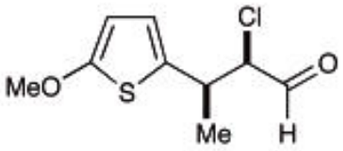
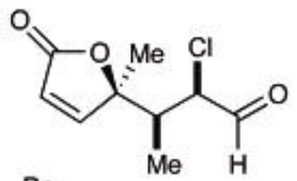
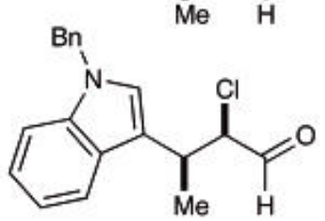
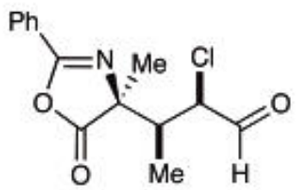
LUMO Activation: An Overview of the Asymmetric Transformations



nucleophiles (Nu)



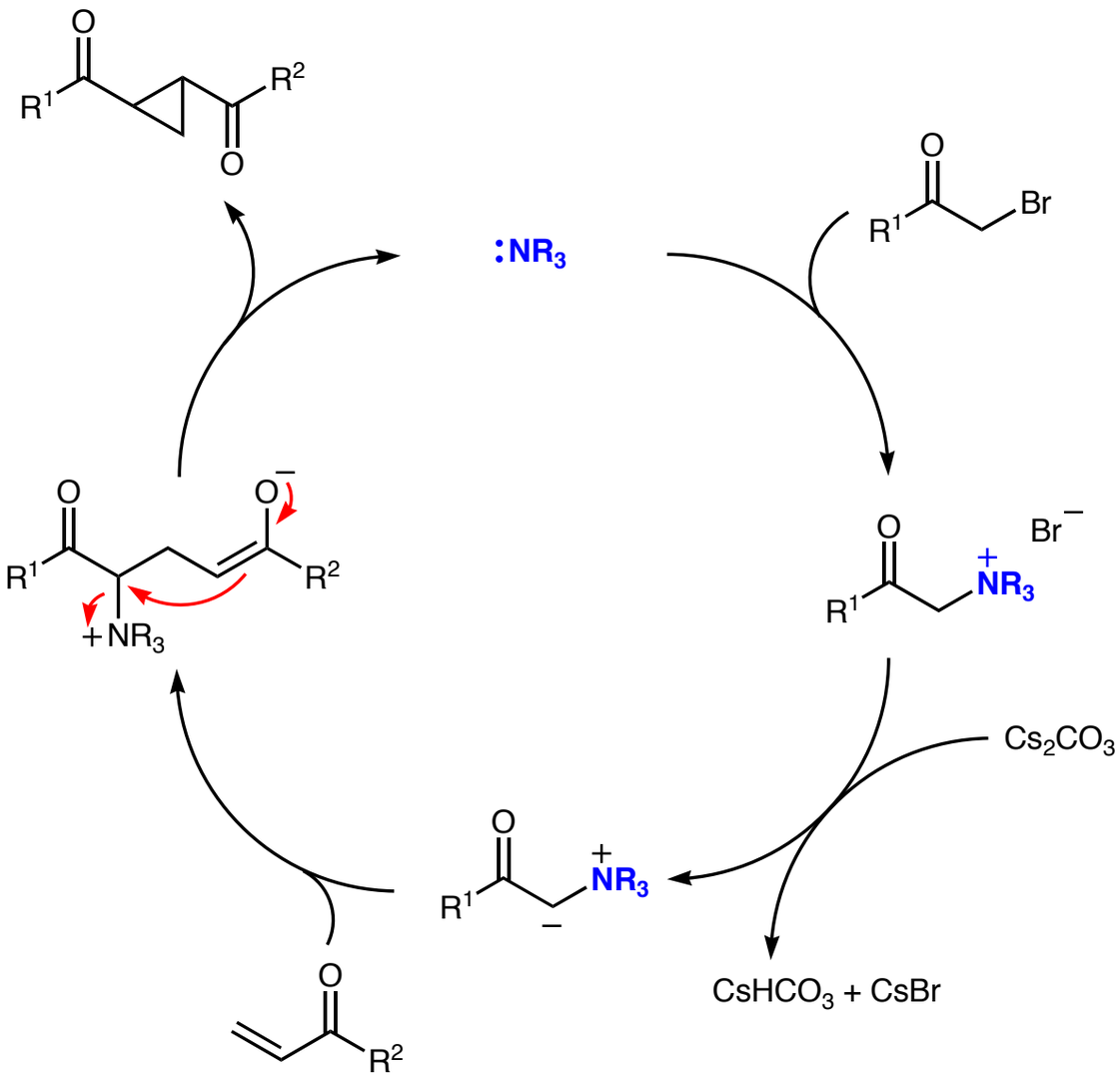


entry	nucleophile	product	temp (°C)	% yield	dr[a]	% ee
1	A		–50	86	14:1	99
2	B		–50	77	11:1	99
3[b]	D		–55	71	>25:1	>99
4	C		–60	75	12:1	>99
5	E		–40	97	9:1	>99

Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051.

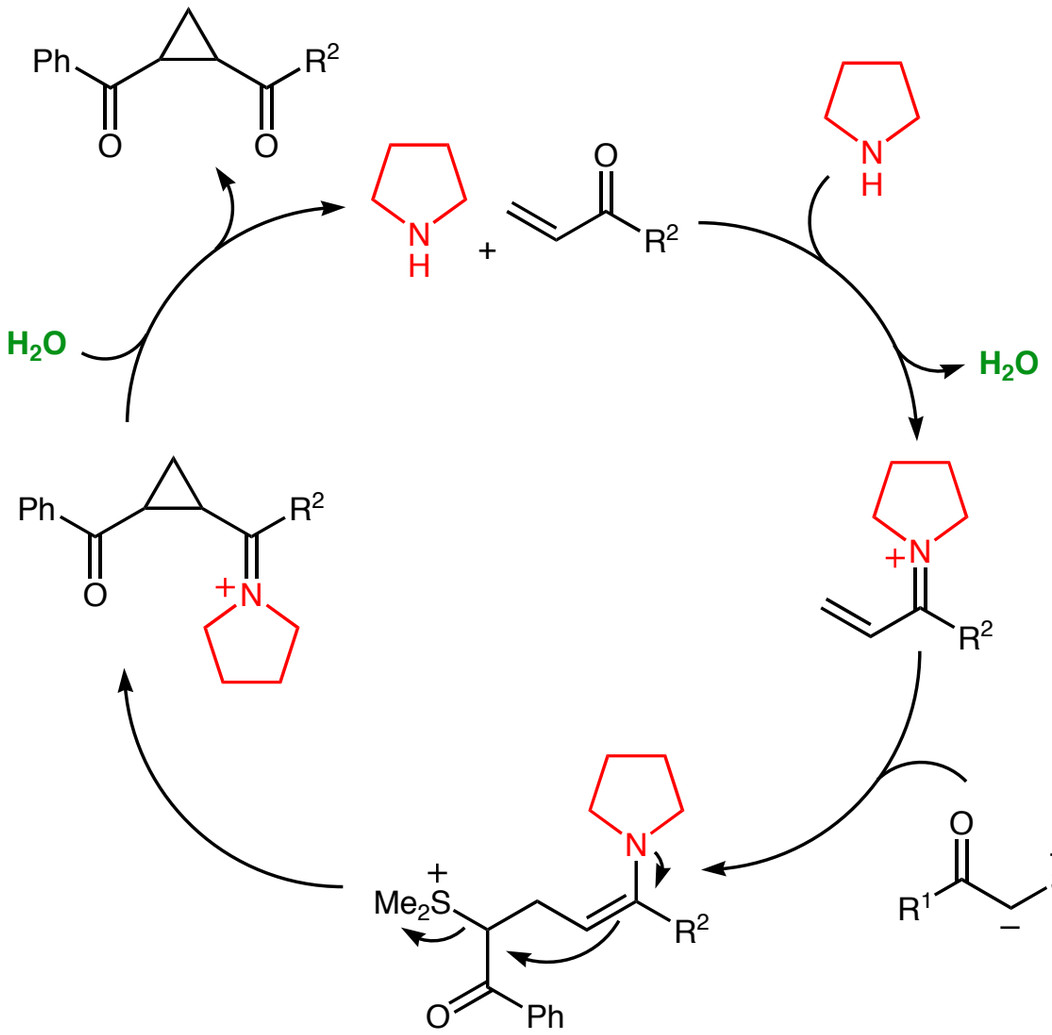
Catalytic Asymmetric MIRC Reaction

Gaunt, M. J. Angew. Chem. Int. Ed. **2004**, 43, 4641-4644.



Chiral nucleophile generated in catalytic amounts

MacMillan, D. W. C. J. Am. Chem. Soc. **2005**, 127, 3240-3241.



Chiral activated electrophile generated in catalytic amounts

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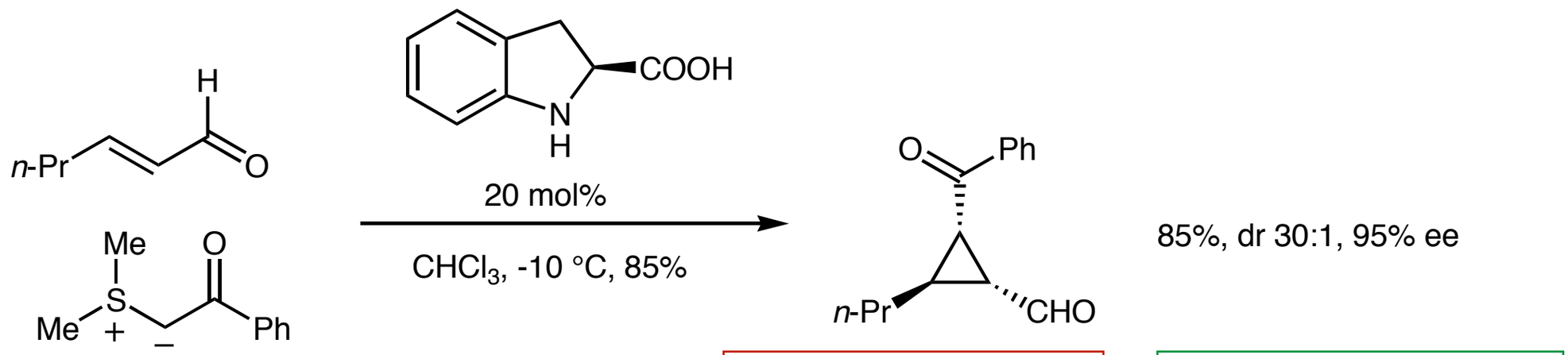
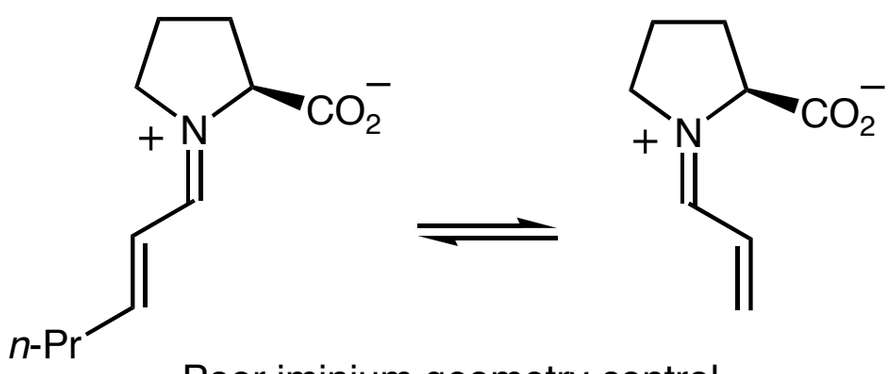
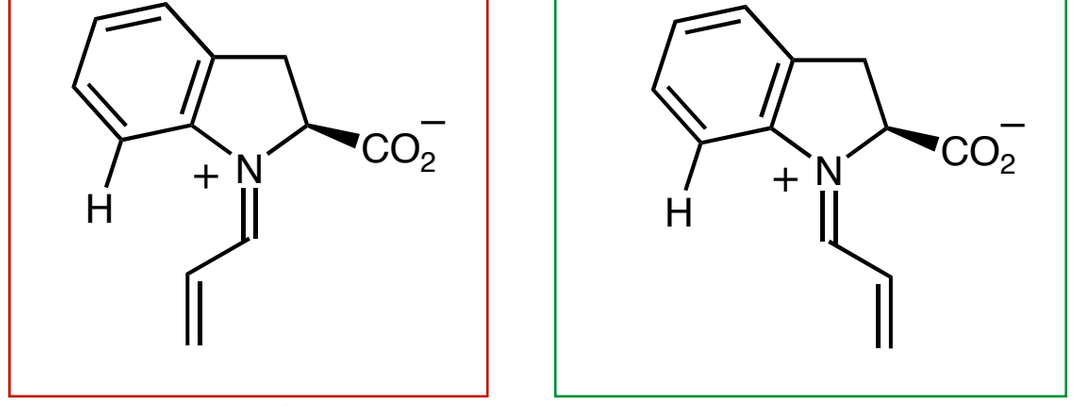
Catalytic Asymmetric MIRC Reaction

Kunz, R. K.; MacMillan, D. W. C. J. Am. Chem. Soc. **2005**, 127, 3240-3241.

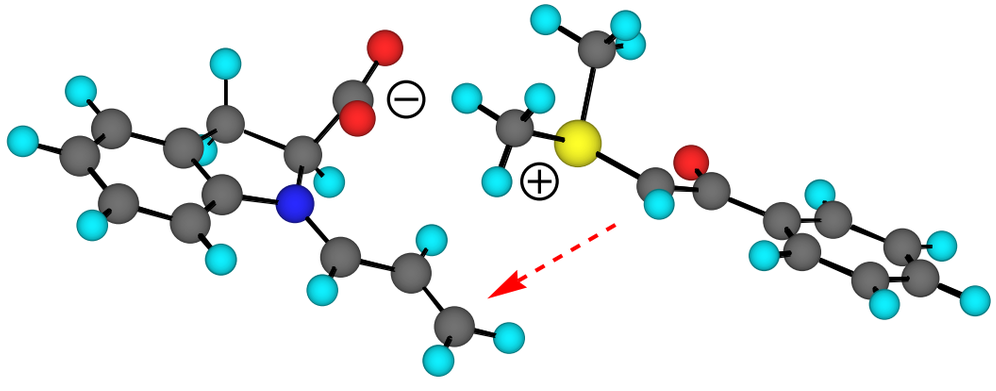




Poor iminium geometry control



Selective (*Z*)-iminium formation



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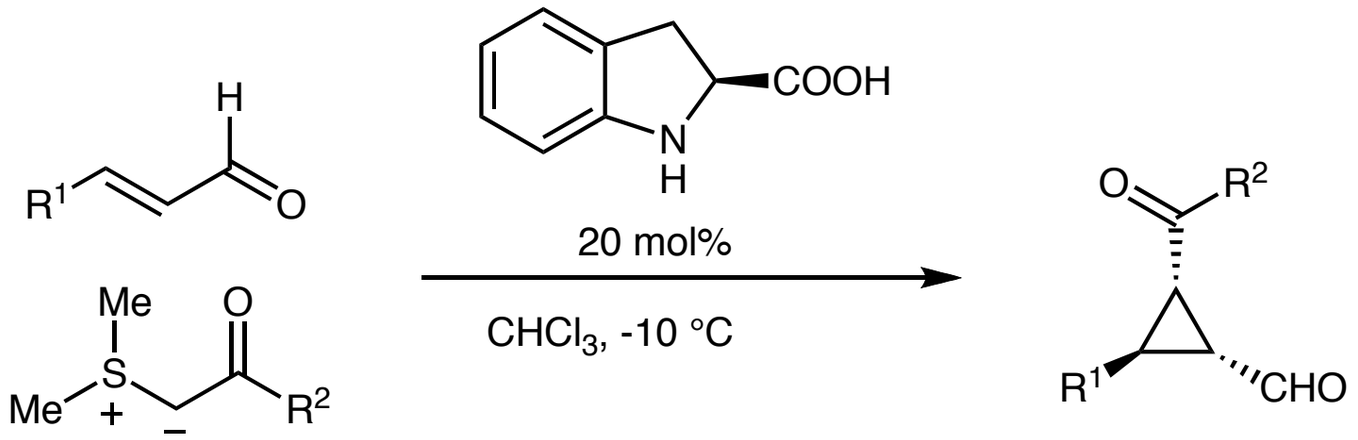
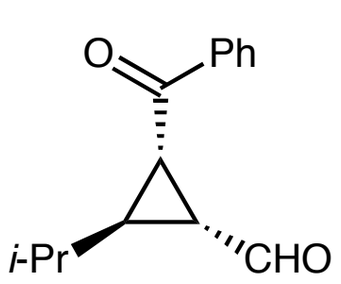
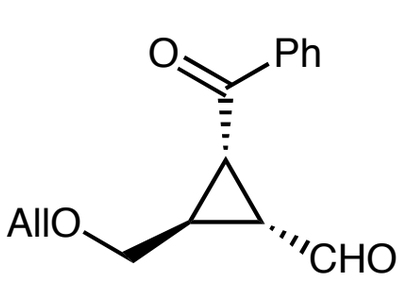
Catalytic Asymmetric MIRC Reaction

Kunz, R. K.; MacMillan, D. W. C. J. Am. Chem. Soc. **2005**, 127, 3240-3241.

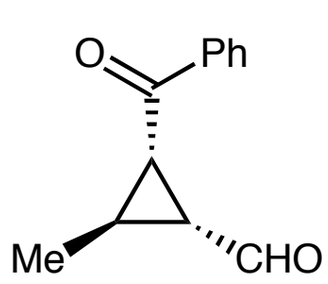




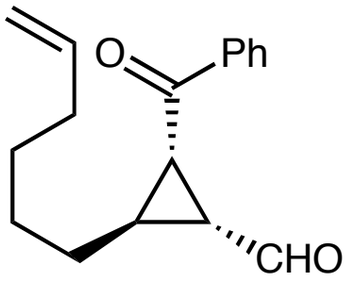
85%, dr 30:1
95% ee



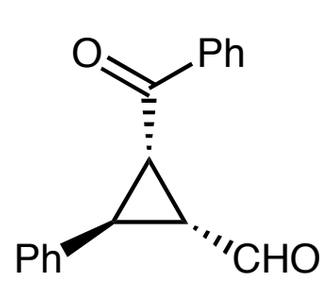
77%, dr 21:1
91% ee



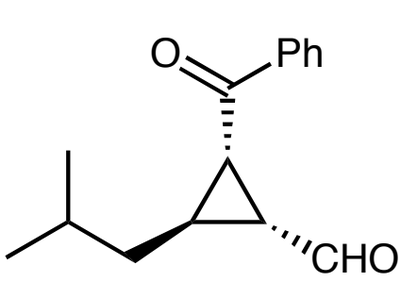
67%, dr >19:1
90% ee



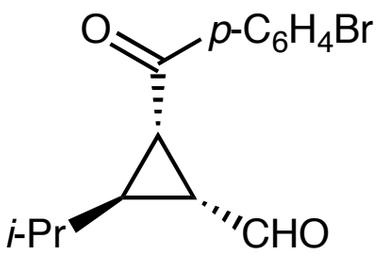
74%, dr 24:1
96% ee



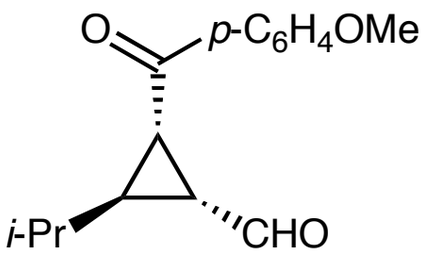
73%, dr 33:1
89% ee



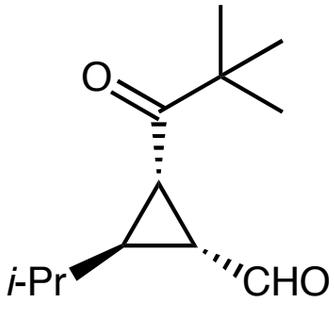
63%, dr 43:1
96% ee



67%, dr 72:1
92% ee



64%, dr >11:1
93% ee



82%, dr 6:1
95% ee

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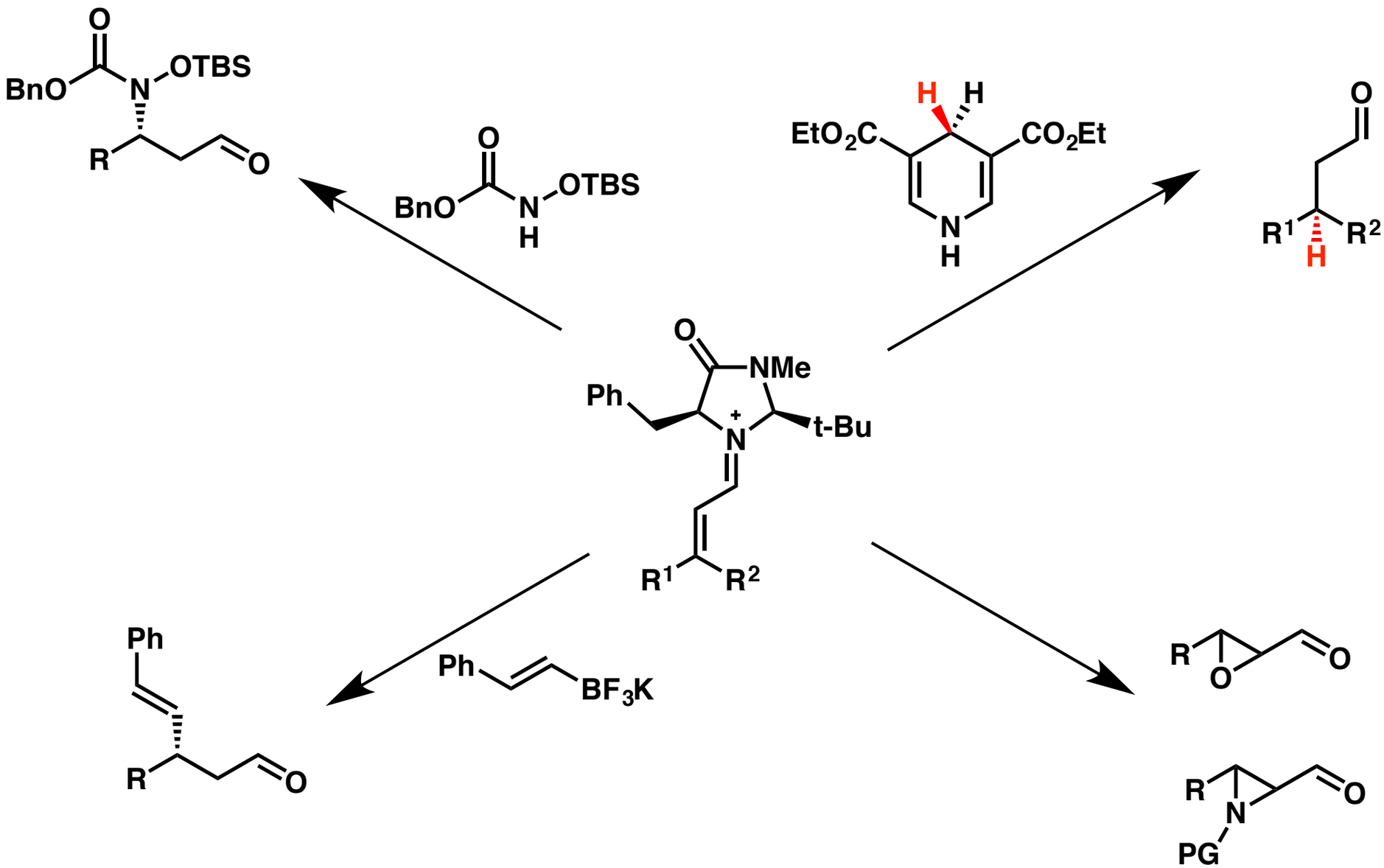
LUMO Activation: An Overview of the Asymmetric Transformations



Lee, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 15438.

· Covalent Catalysis

✓ Increased nucleophilicity of nuclephiles (HOMO activation)
- Enamine catalysis
- Lewis bases activation
- **Stetter Reaction (NHC ligands)**

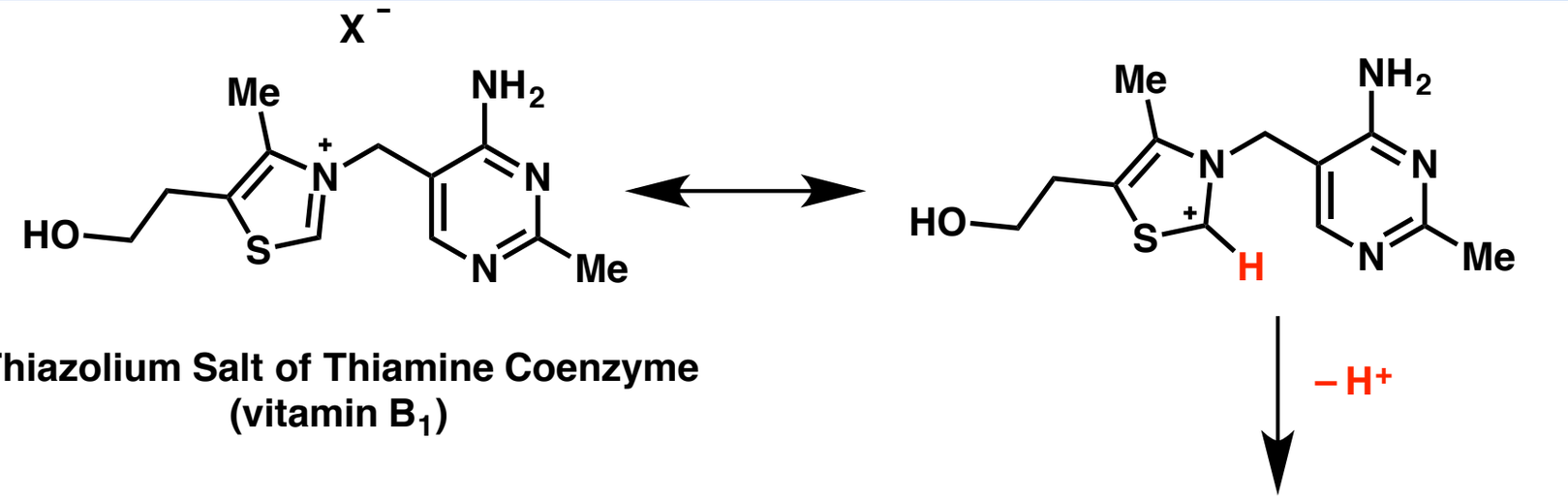
✓ Increases electrophilicity of electrophiles (LUMO activation)
- Iminium catalysis

✓SUMO activation
- Enamine catalysis

· Non-covalent Catalysis

✓ Hydrogen bonding catalysis
✓ Chiral ion pairs (chiral cations, chiral anions)

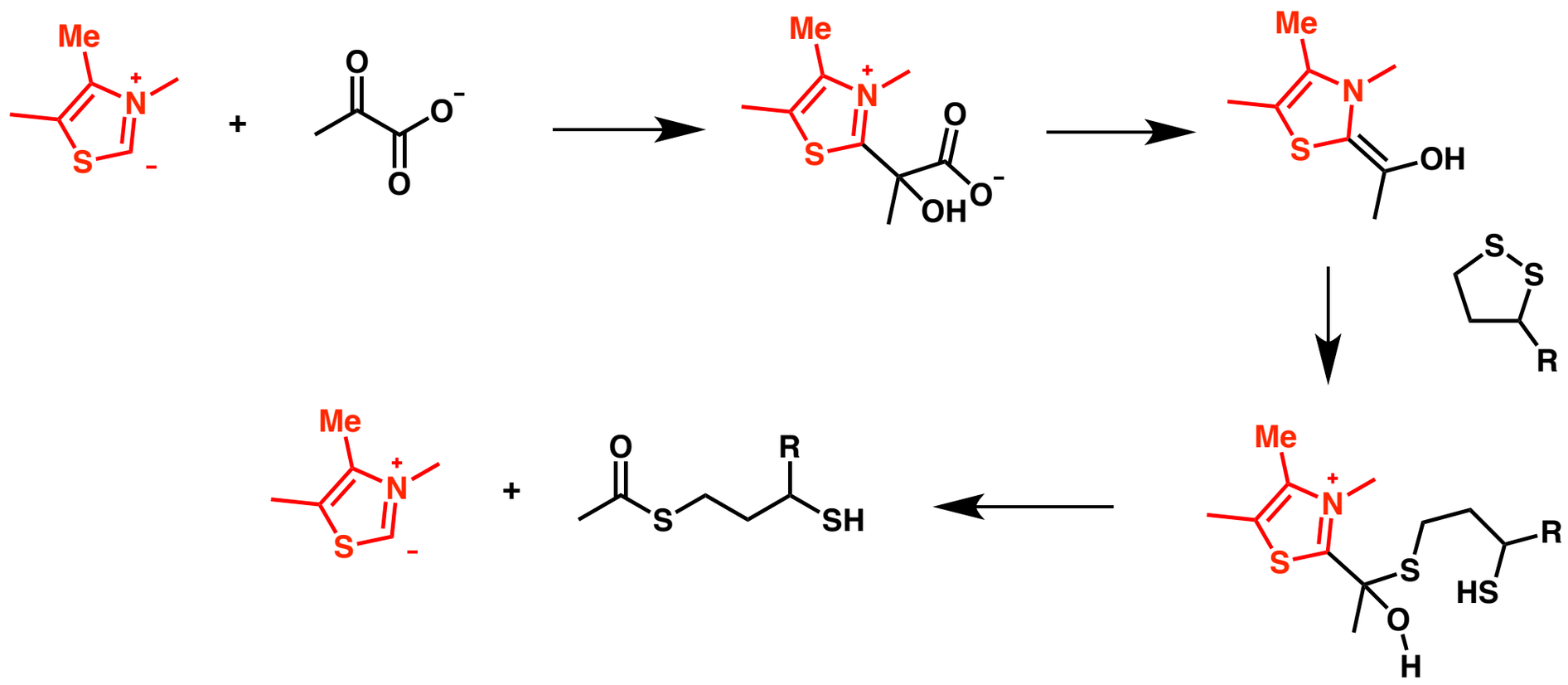
Thiamine Coenzyme: Pyruvate Dehydrogenase



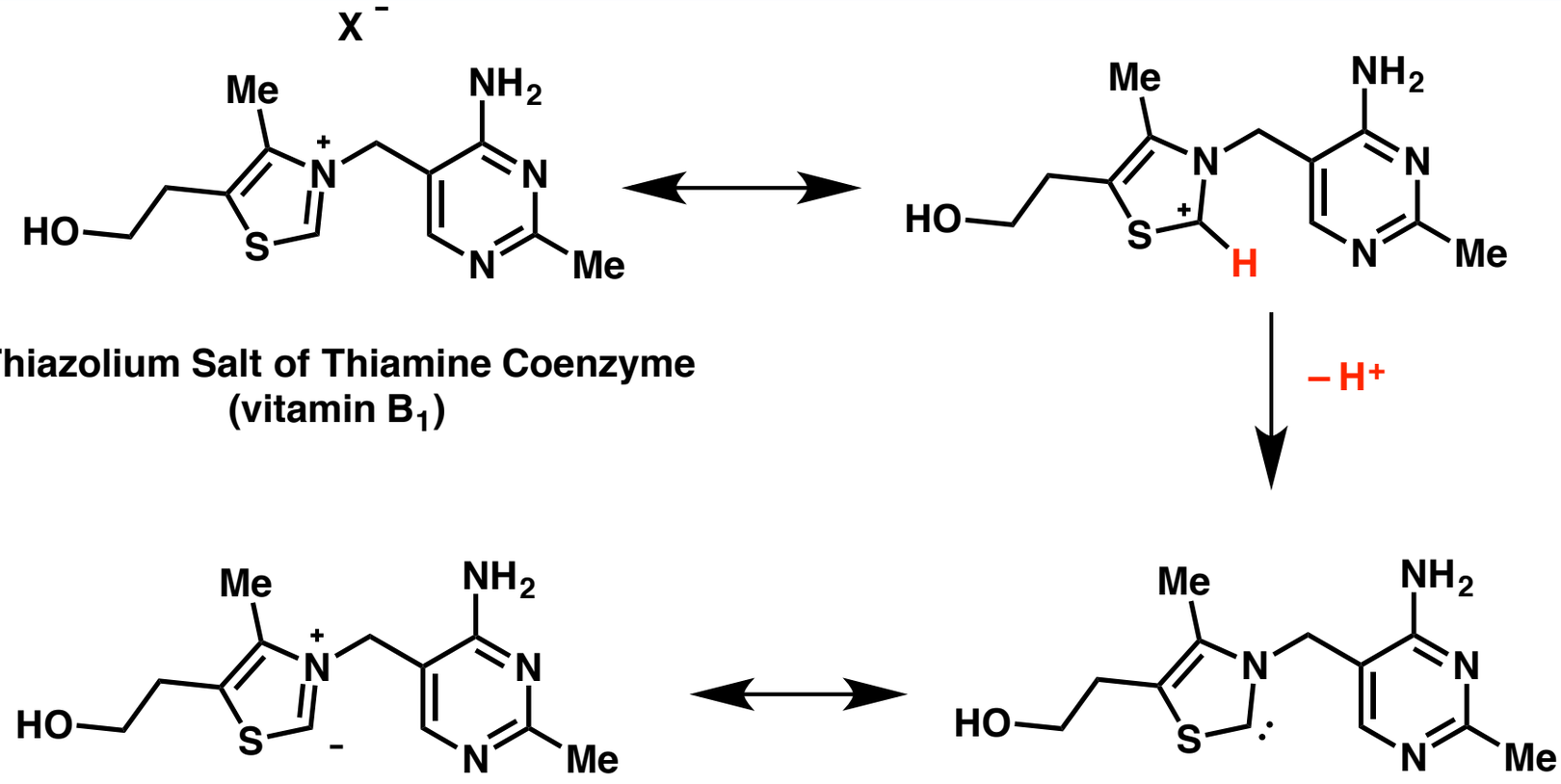
Thiazolium Salt of Thiamine Coenzyme (vitamin B_1)

Pyruvate Dehydrogenase

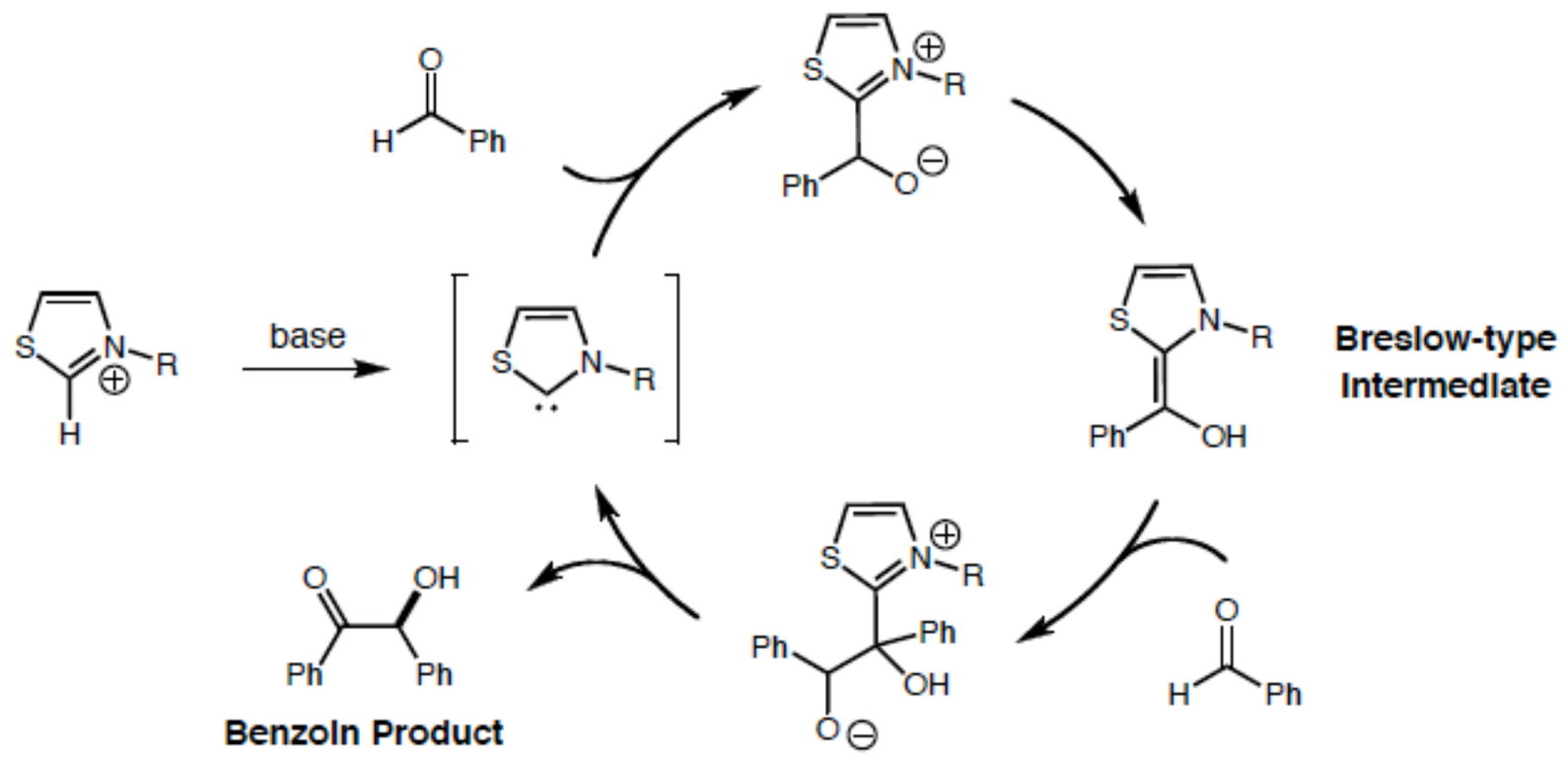
Nucleophlic Carbene



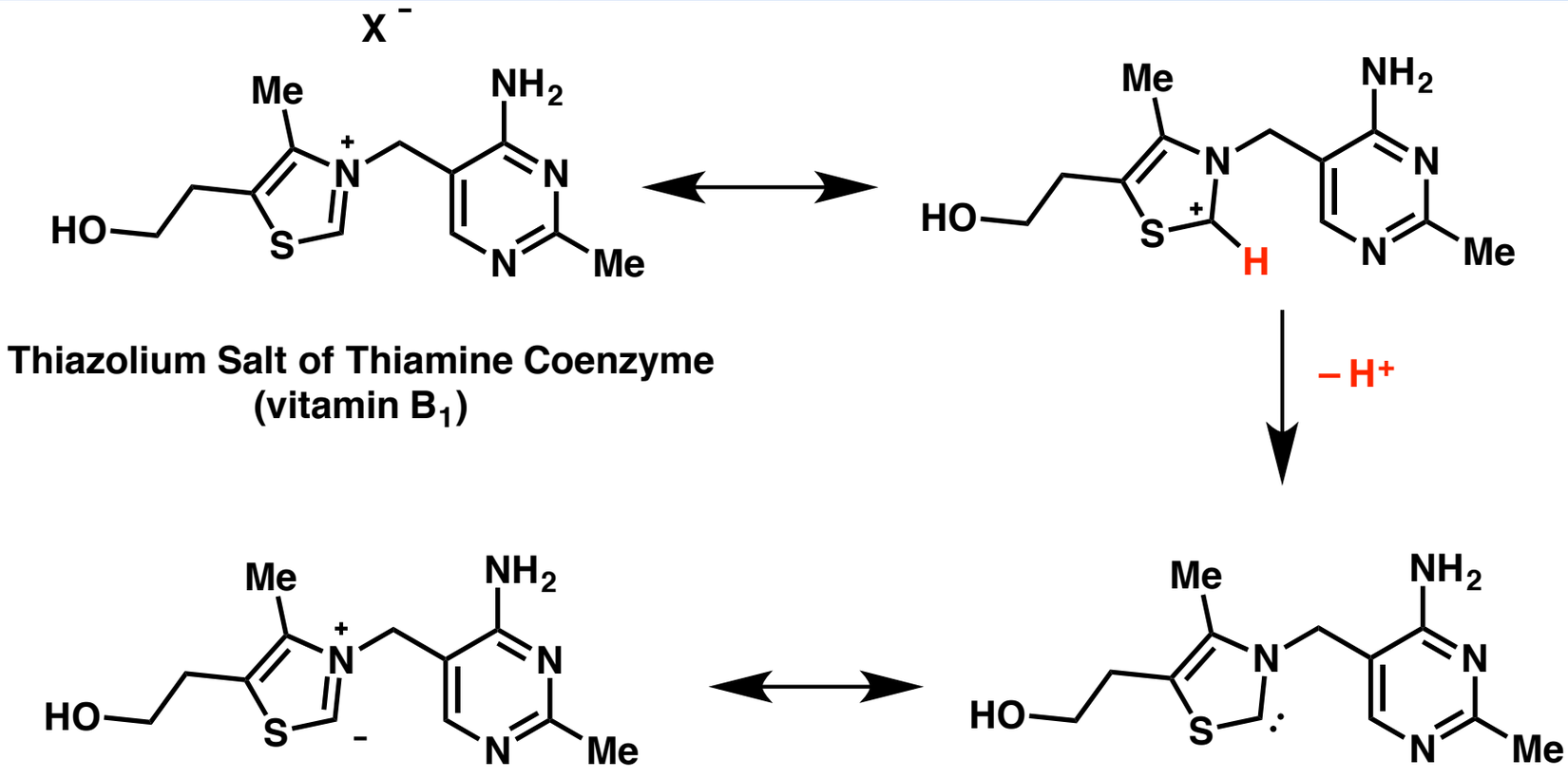
Thiamine Catalyzed Benzoin Condensation



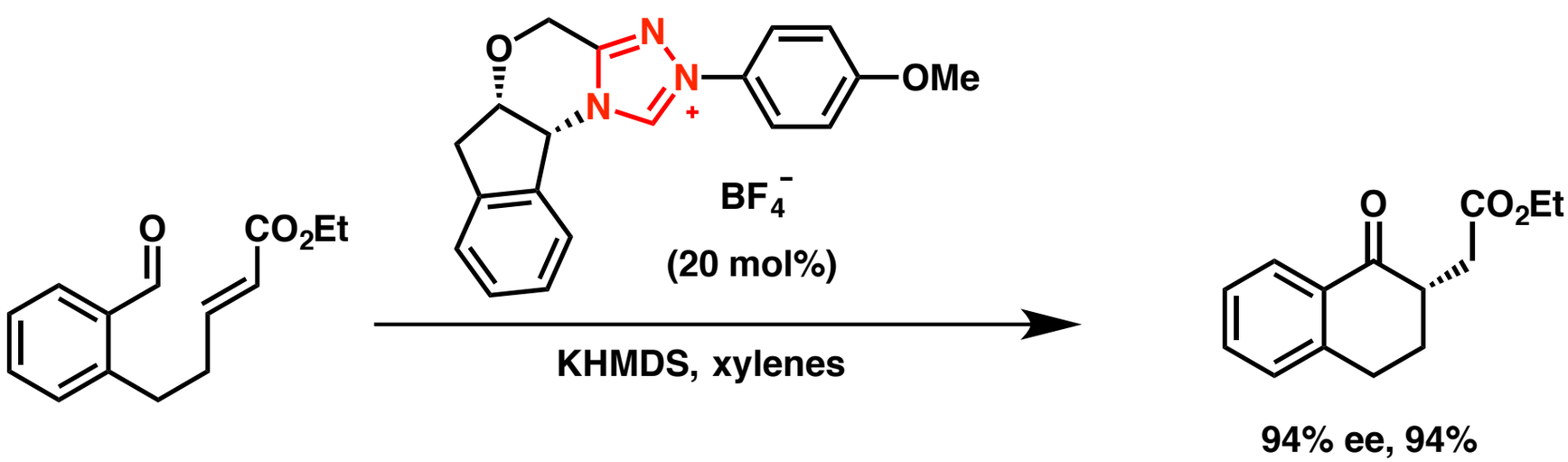
Nucleophlic Carbene



Thiamine Catalyzed Benzoin Condensation



Nucleophlic Carbene



Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

Review: Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem Rev* **2015**, *115*, 9307.