Asymmetric [3+2] Cycloaddition of Azomethine Ylides

-- From Chiral Starting Material to Asymmetric Catalysis --

Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174

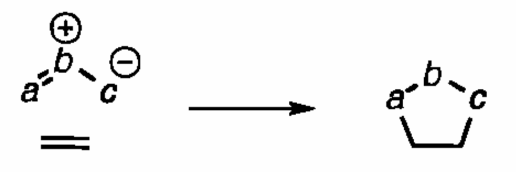
Gothelf, A. S.; Gothelf, K. V.; Hazell, Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4236

Longmire, J. M.; Wang,B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400

For an early review of asymmetric 1,3-dipolar cycloaddition reactions, see:
Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863

Introduction to 1,3-Dipolar Cycloaddition

- 1,3-Dipolar cycloaddition reactions:



- History of 1,3-dipoles and 1,3 -dipolar cycloaddition reactions:

-- Curtius discovered diazoacetic ester (1883)

-- Buchner studied the reaction of diazoacetic ester with α,β-unsaturated esters and described the first 1,3-DC reactrion. (1888)

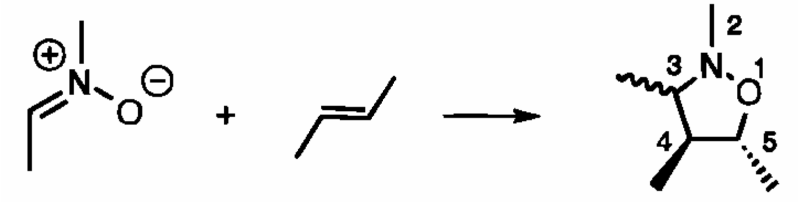
-- Huisgen established general application of 1,3-dipoles in organic synthesis (1960s)
-- Woodward and Hoffmann developed conservation of orbital symmetry

-- Newest challenge: Control of Stereochemistry

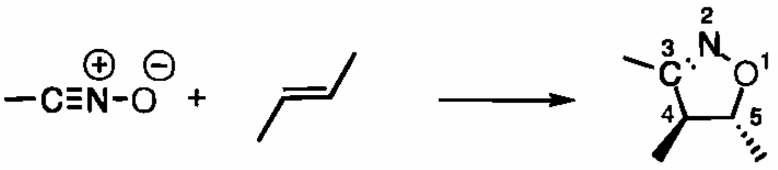
Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863

Examples of Typical 1,3-Dipolar Cycloadditions

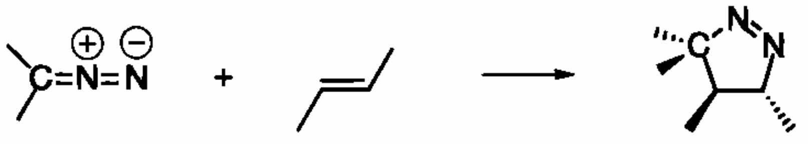
- 1,3-Dipolar Cycloaddition of Nitrones – Preparation. of isoxazolidines



- 1,3-Dipolar Cycloaddition of Nitrile Oxides – Preparation of 2-isoxazolines



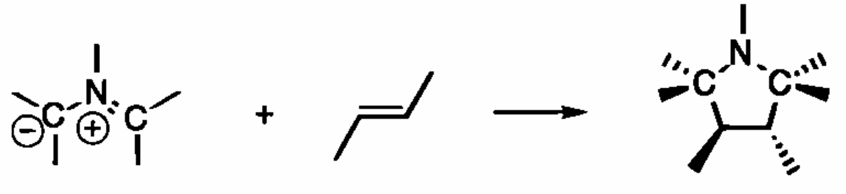
- 1,3-Dipolar Cycloaddition of Diazoalkanes – Preparation of 1-pyrazoline



Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863

1,3-Dipolar Cycloadditions of Azomethine Ylides

♦ 1,3-Dipolar Cycloaddition of Azomethine Ylides



-- Reaction forms highly substituted heterocycle.

-- Product can be used as new catalyst, or serve as important motifs in biologically active molecules.

-- Azomethine ylides are unstalbe. Generation of azomethine ylides include proton abstraction from imine derivatives, thermolysis or photolysis of aziridines, dehydrohalogenation of imonium salts.

How to perform the reaction in **asymmetric** fashion ?

Chiral Azomethine Ylides

Chiral Alkenes

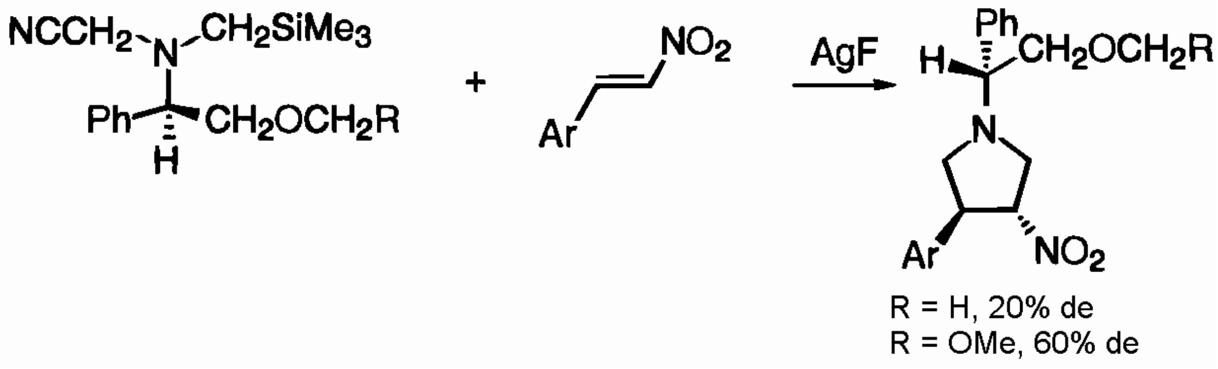
Intramolecular Reactions

Metal-Catalyzed Reactions

Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863

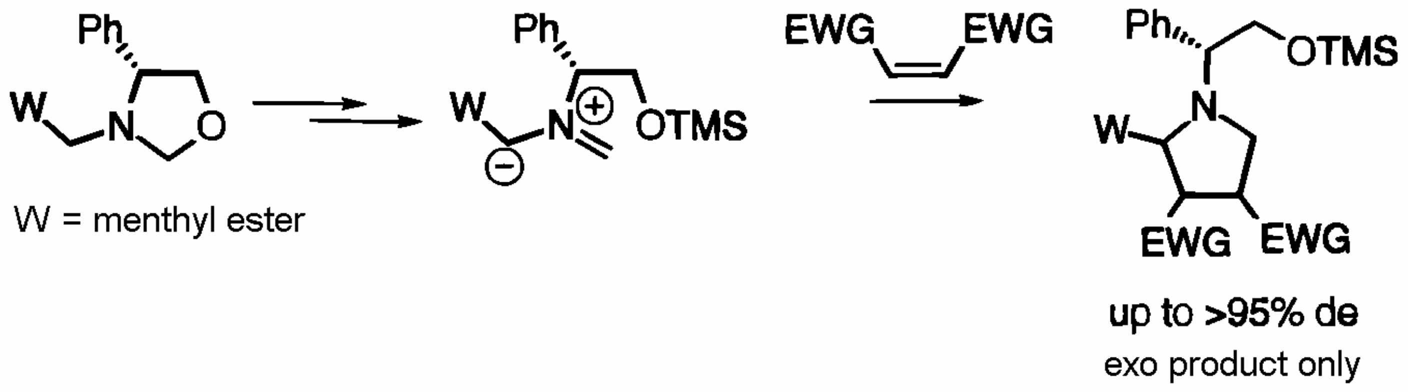
1,3-DC of Azomethine Ylides: Chiral Azomethine Ylides

- First example of diastero-facial selective 1,3-DC reaction of chiral azomethine ylides.



Padwa, A.; Chen, Y.-Y.; Chiacchio, U.; Dent, W. *Tetrahedron.* **1985**, *41*, 3529.

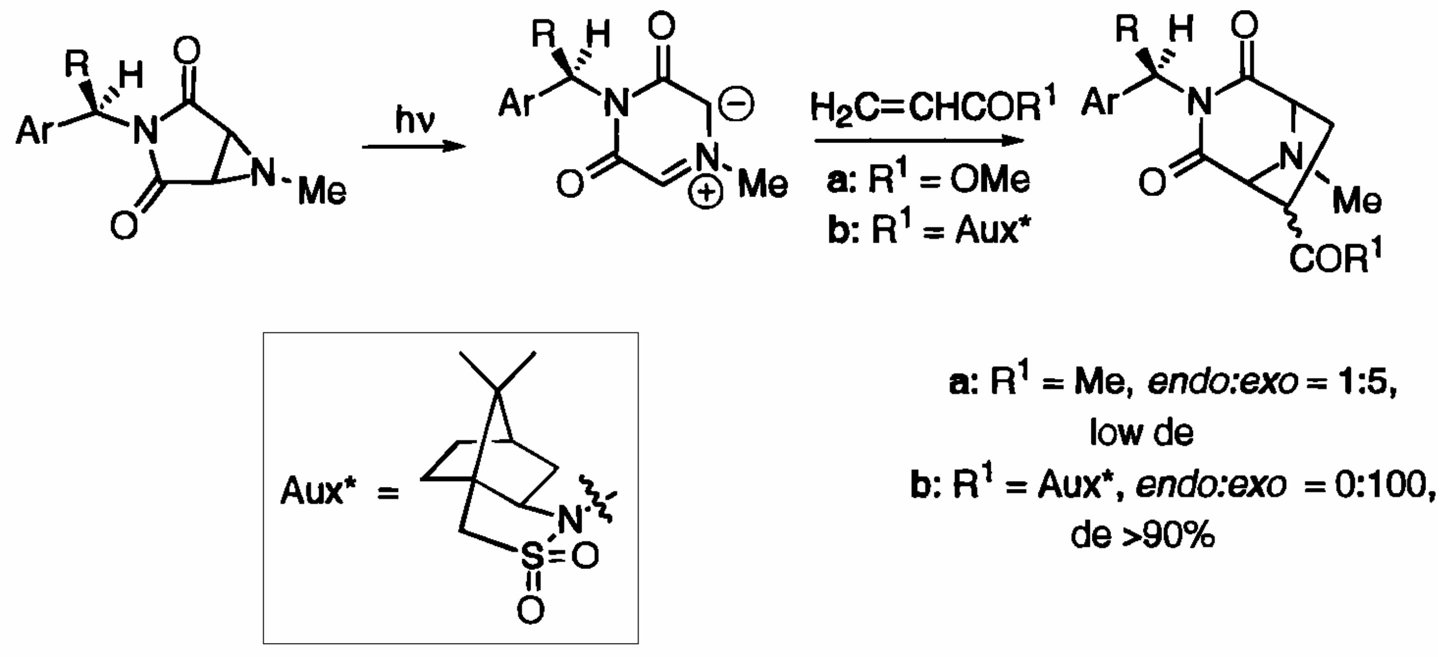
- Royer’s chiral azomehine ylide system:



Deprez, P.; Rouden, J.; Chiaroni, A.; Riche, C.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1991**, *32*, 7531.

1,3-DC of Azomethine Ylides: Chiral Azomethine Ylides

- Azomethine ylides derived from chiral aziridines.



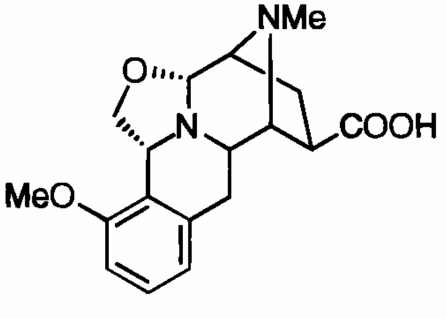
a: R^1 = Me, *endo:exo* = 1:5,
low de

b: R^1 = Aux*, *endo:exo* = 0:100,
de >90%

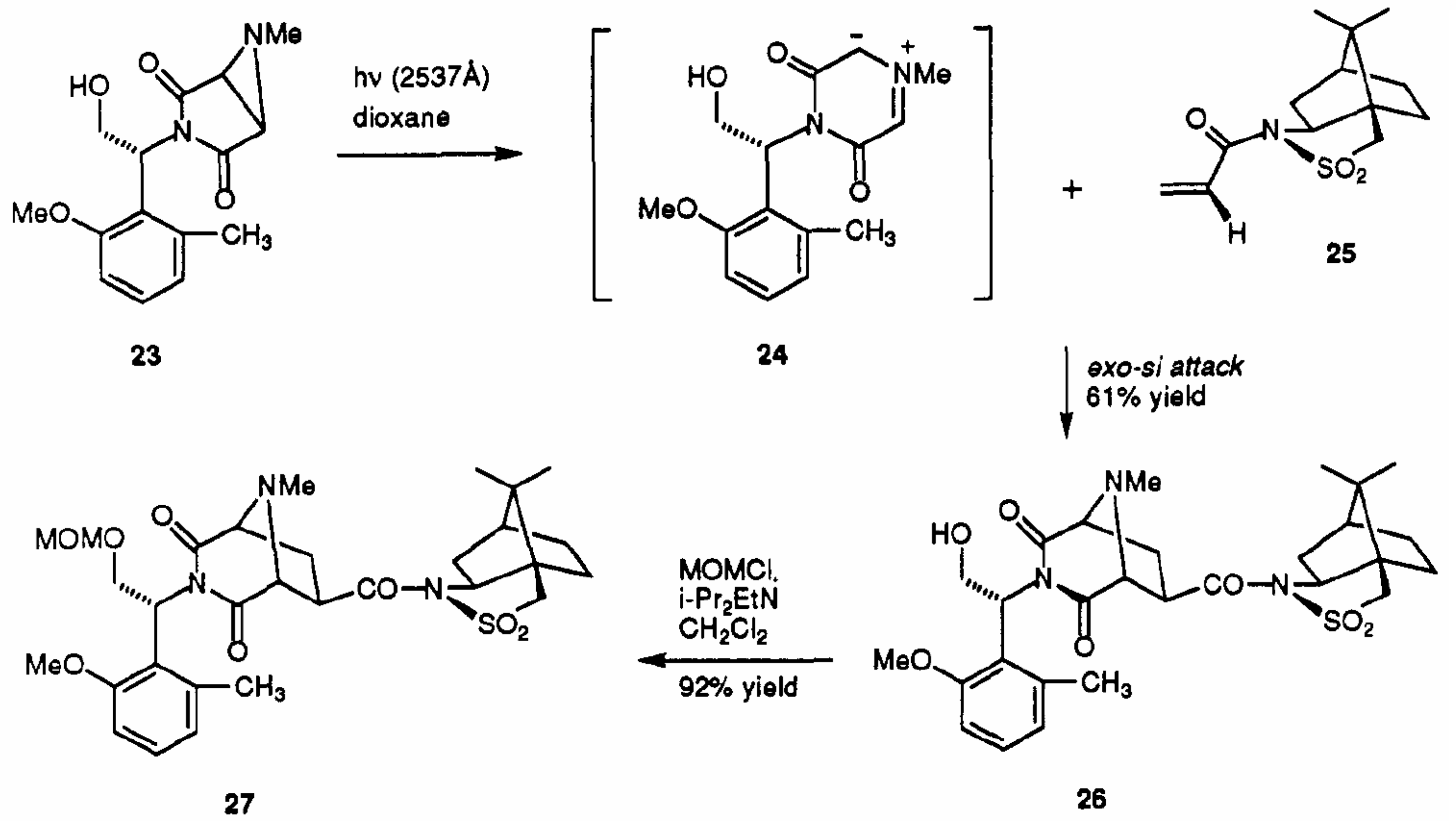
Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy,V. O. *J. Org. Chem.* **1991**, *56*, 5893.

1,3-DC of Azomethine Ylides: Chiral Azomethine Ylides

- Azomethine ylides derived from chiral aziridines.
  - -- Application in the total synthesis of (-)-quinocarcin



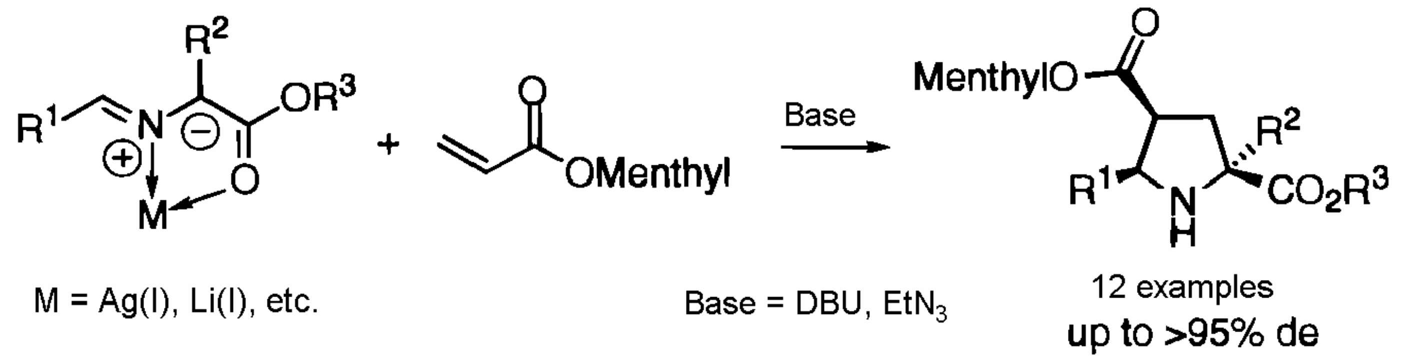
(-)-quinocarcin



Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1993**, *115*, 10742.

1,3-DC of Azomethine Ylides: Chiral Alkenes

- Cycloaddition using chiral alkenes: Grigg's system.



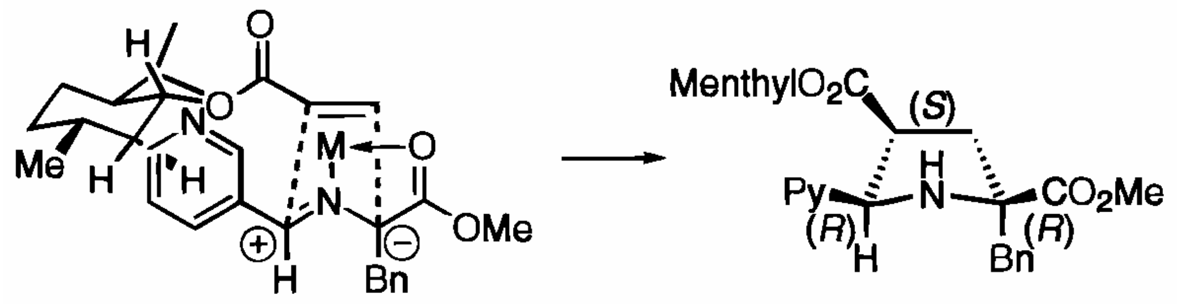
M = Ag(I), Li(I), etc.

Base = DBU, EtN_3

12 examples

up to >95% de

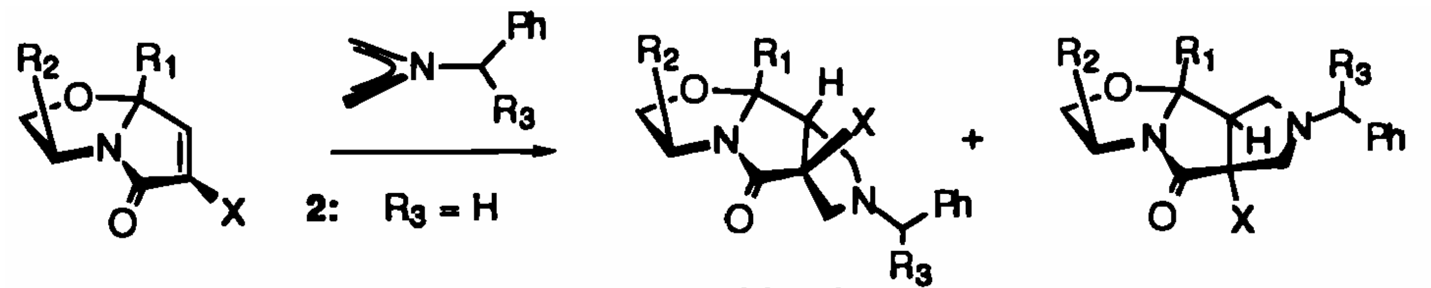
- Proposed transition state model based on regioselectivities, endo and diasterofacial- selectivities



Barr, D. A.; Dorrity, M. J.; GriggR.; Hargreaves, S.; Malone, J. F.; Montgomery, J.; Redpath, J.; Stevenson, P.; Thornton-Pett, M. *Tetrahedron* **1995**, *51*, 273.

1,3-DC of Azomethine Ylides: Chiral Alkenes

- Cycloaddition using chiral alkenes: Meyers' system.



1 (a-e)

4 (a-m)
major when R_1 = Me

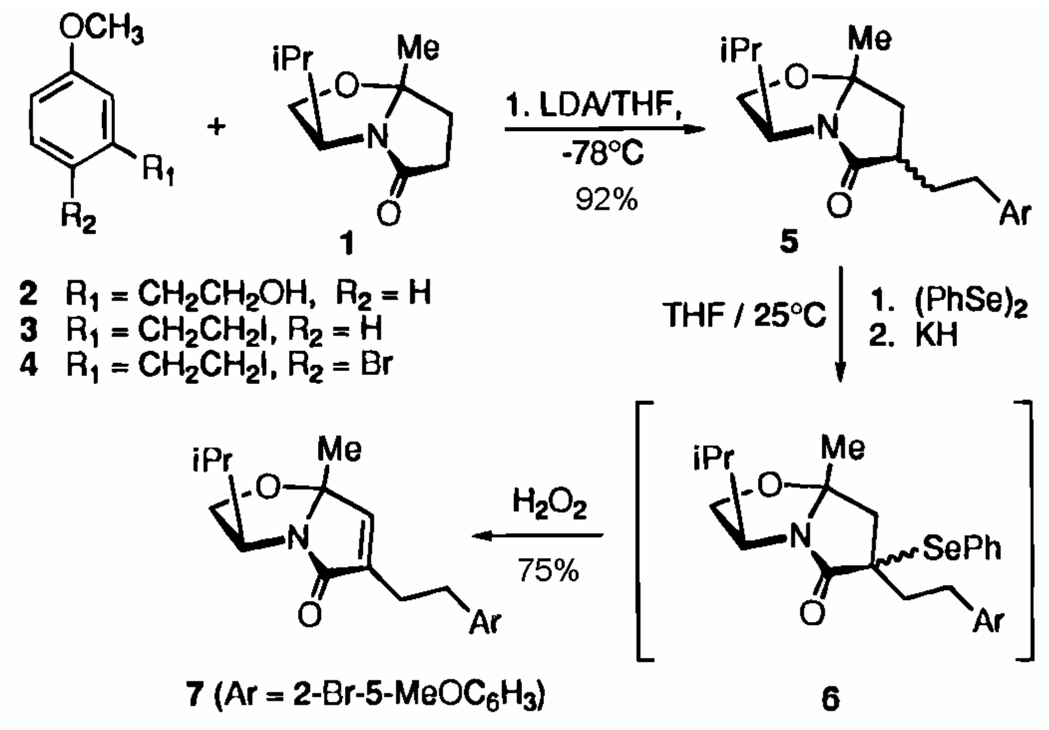
5 (a-m)
major when R_1 = H

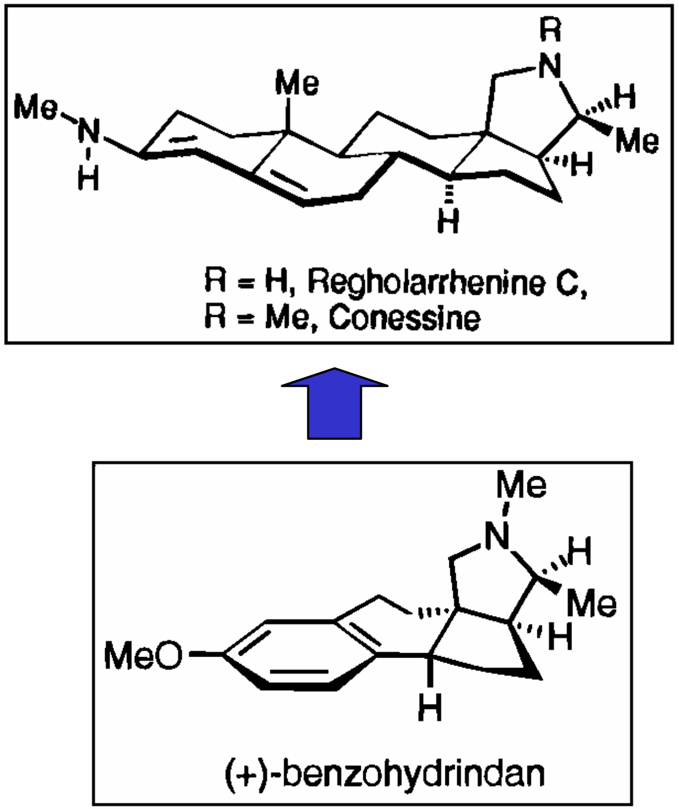
	lactam **1**				ylide **2**
entry	R_2	R_1	X	lactam	(A)-**4**:**5**[a]
1	*i*-Pr	Me	H	**1a**	91:9
2	Ph	Me	H	**1b**	94:6
3	Ph	H	H	**1c**	17:83
4	*i*-Pr	Me	CO_2Me	**1d**	71:29
5	*i*-Pr	Me	CO_2*t*-Bu	**1e**	72:28
6	*i*-Pr	Ph	CO_2Me	**1m**	74:26

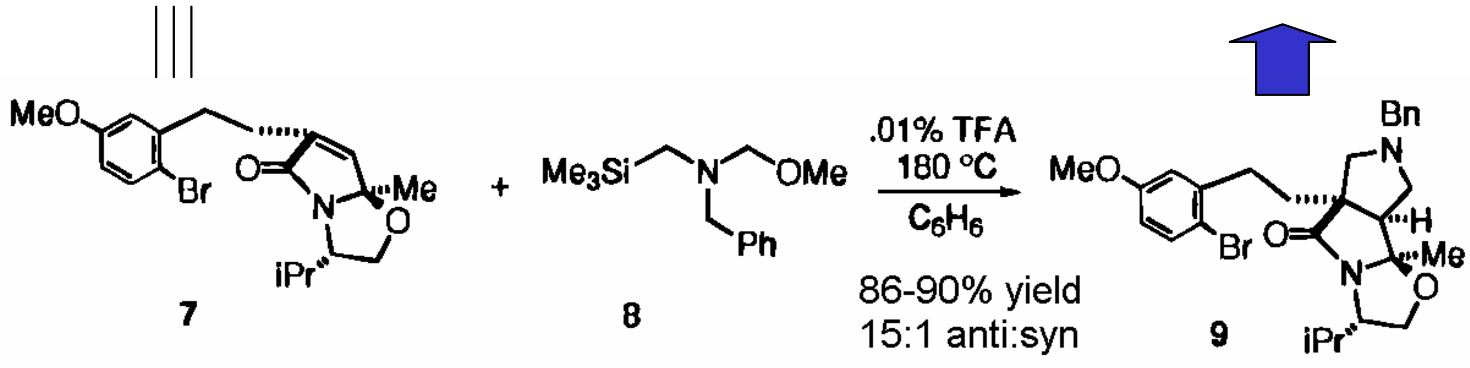
Fray, A. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3362.

1,3-DC of Azomethine Ylides: Chiral Alkenes

- Application in the total synthesis of benzohydrindan.



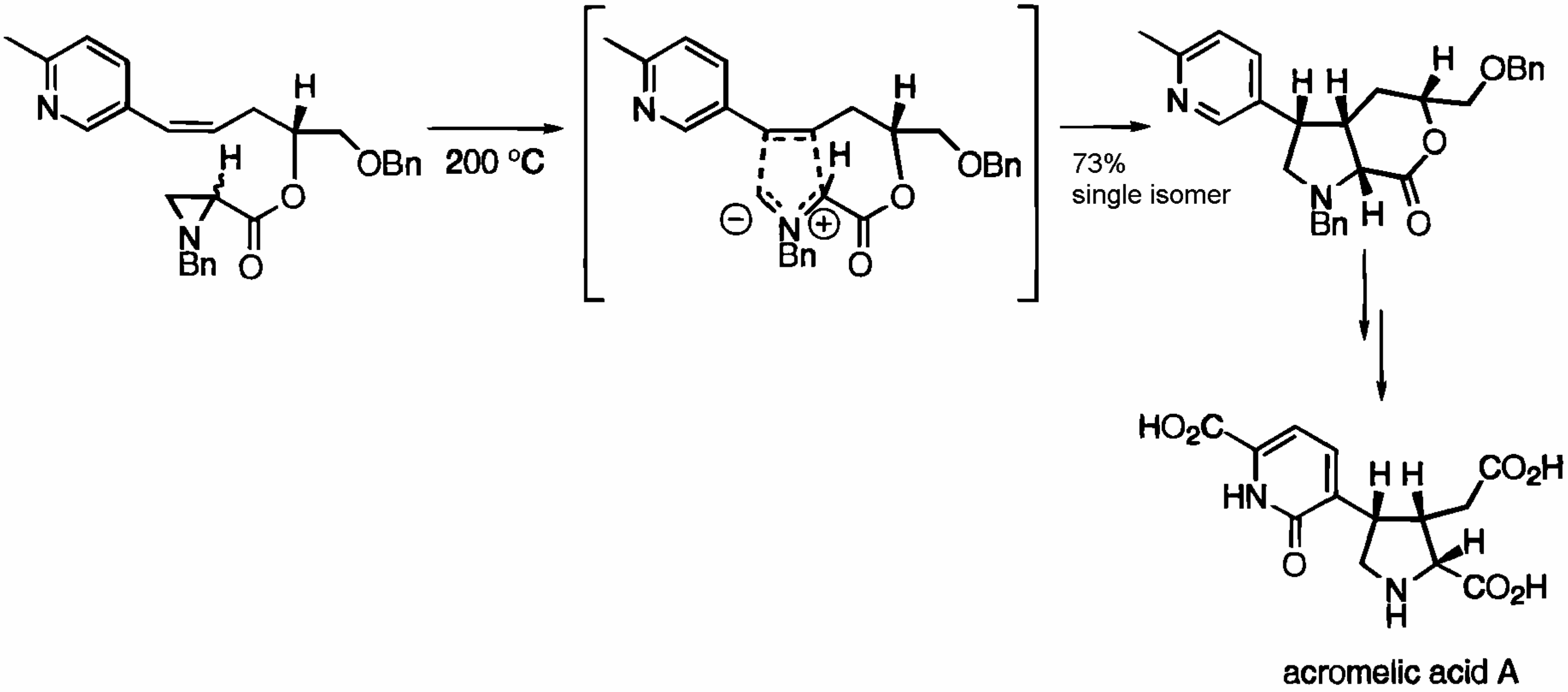




Kopach, M. E.; Fray, A. H.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 9876.

1,3-DC of Azomethine Ylides: Intramolecular Reactions

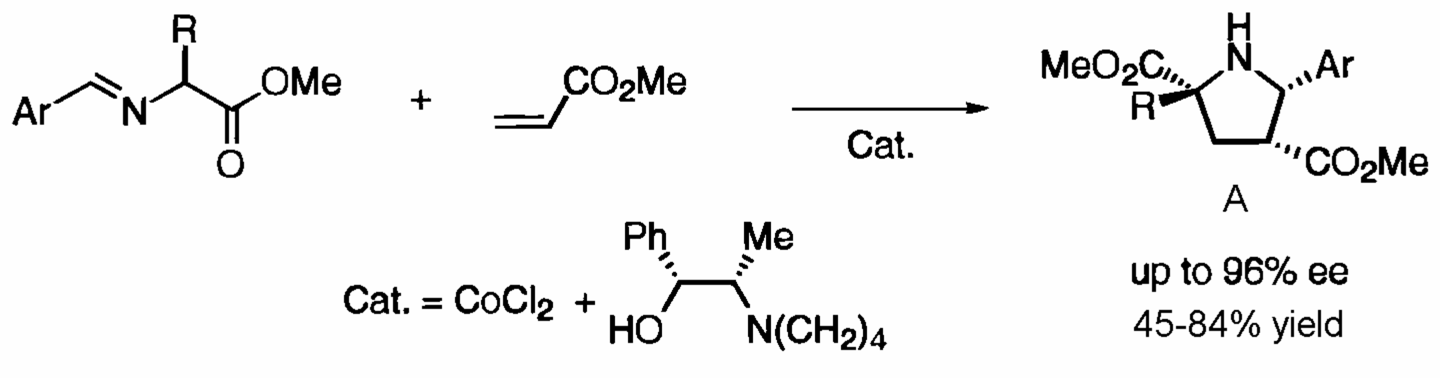
♦ Intromolecular cycloaddition in the application of synthesis of Acromelic acid A.



Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*, 5523.

1,3-DC of Azomethine Ylides: Metal-Catalyzed Reactions

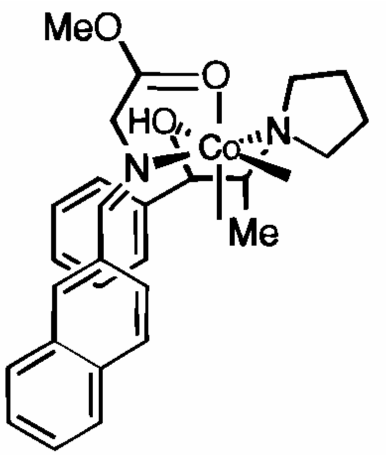
- ♦ Early studies (and the only case) on metal-catalyzed reactions.



up to 96% ee
45-84% yield

-- Higher ee when Ar = 2-naphthyl, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, and use methyl acrylate as solvent.
-- Stiochiometric amount of Co(II) (1 mol) and ligand(2 mol) were used.
-- Up to 70% ee was reported using AgOTf and bisphosphine ligand, details not revealed.

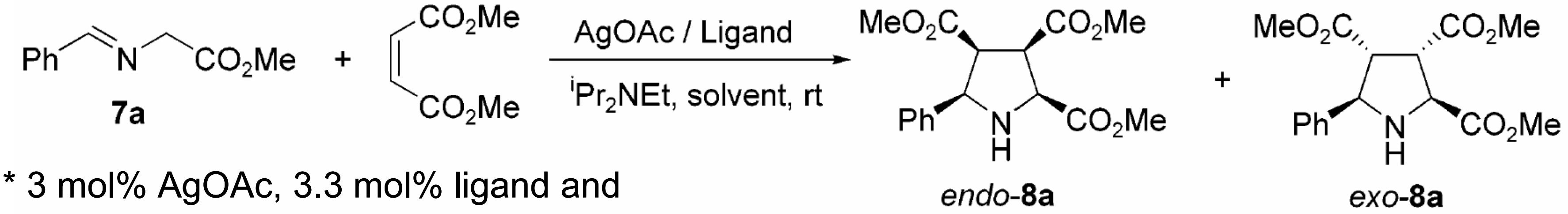
Proposed working model:



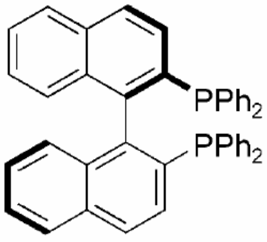
Allway, P.; GriggR. *Tetrahedron Lett.* **1991**, *32*, 5817.
GriggR. *Tetrahedron: Asymmetry.* **1995**, *6*, 2475

Catalytic Asymmetric 1,3-DC of Azomethine Ylides

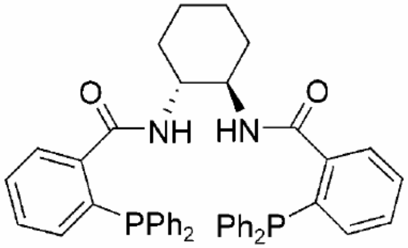
- First successful substiochiometric catalyst system – Ligand Screening.



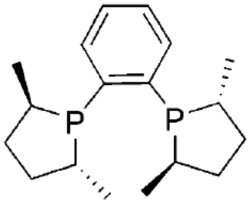
* 3 mol% AgOAc, 3.3 mol% ligand and
10 mol% amine used


(*R*)-BINAP (**1**)

13% ee

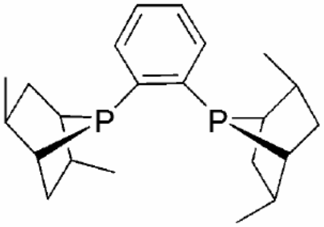

(*R*, *R*)-Trost Ligand (**2**)

59% ee

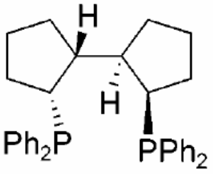

(*R*, *R*)-Me-DuPhos (**3**)

23% ee

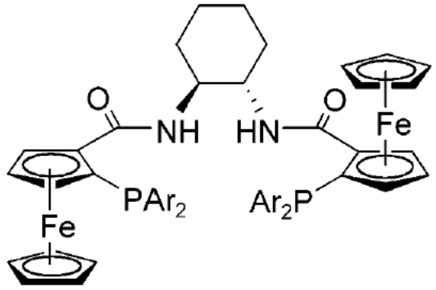
* All ligands (except BINAP) give endo pdt only.


(*R*, *S*, *R*, *S*)-PennPhos (**4**)

27% ee


(*R*, *R*, *R*, *R*)-BICP (**5**)

13% ee

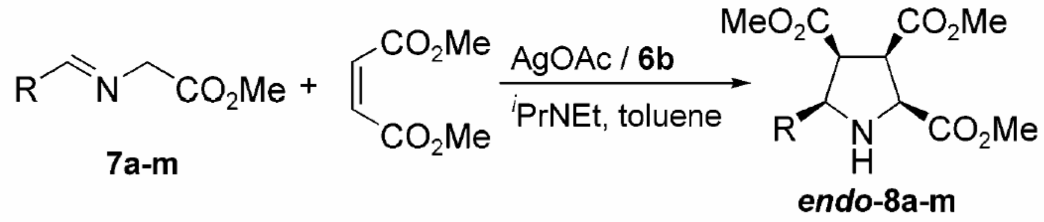

(*S*, *S*, S_p)-FAP: Ar = phenyl (**6a**)
(*S*, *S*, S_p)-xylyl-FAP: Ar = 3,5-dimethylphenyl (**6b**)

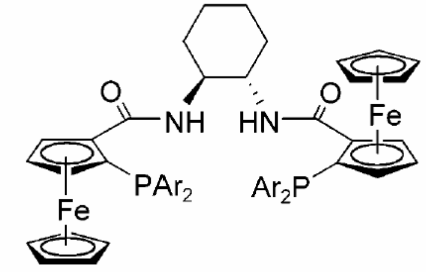
- 76% ee with **6a**;
- 86% ee with **6b.**

Longmire, J. M.; Wang, B., Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400

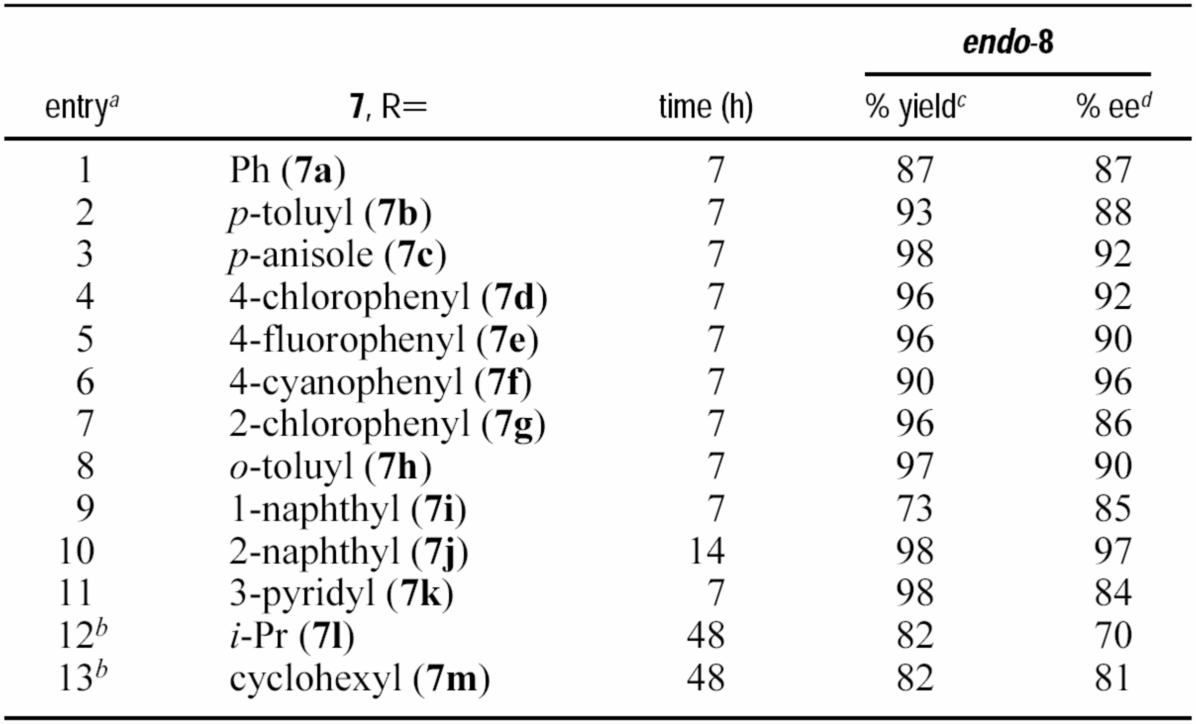
Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Variation of α-iminoester substrates.





(S, S, S_p)-FAP: Ar = phenyl (**6a**)
(S, S, S_p)-xylyl-FAP: Ar = 3,5-dimethylphenyl (**6b**)



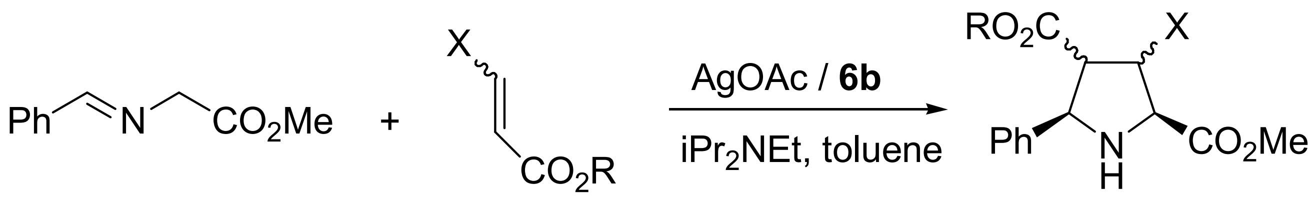
entry[a]	**7**, R=	time (h)	*endo*-**8** % yield[c]	*endo*-**8** % ee[d]
1	Ph (**7a**)	7	87	87
2	*p*-toluyl (**7b**)	7	93	88
3	*p*-anisole (**7c**)	7	98	92
4	4-chlorophenyl (**7d**)	7	96	92
5	4-fluorophenyl (**7e**)	7	96	90
6	4-cyanophenyl (**7f**)	7	90	96
7	2-chlorophenyl (**7g**)	7	96	86
8	*o*-toluyl (**7h**)	7	97	90
9	1-naphthyl (**7i**)	7	73	85
10	2-naphthyl (**7j**)	14	98	97
11	3-pyridyl (**7k**)	7	98	84
12[b]	*i*-Pr (**7l**)	48	82	70
13[b]	cyclohexyl (**7m**)	48	82	81

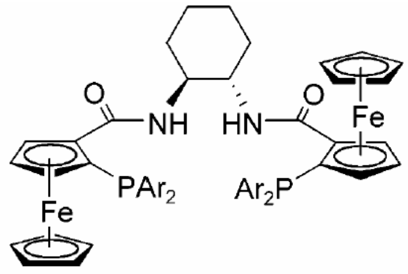
[a] Conditions: imine (1.0 equiv), dimethyl maleate (1.2 equiv), AgOAc (3 mol %), ligand **6b**(3.3 mol %), *i*Pr_2NEt (10.0 mol %), toluene (3 mL) at 0^{o}C, unless indicated otherwise.
[b] Reactions were run at room temperature.

Longmire, J. M.; Wang, B., Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400

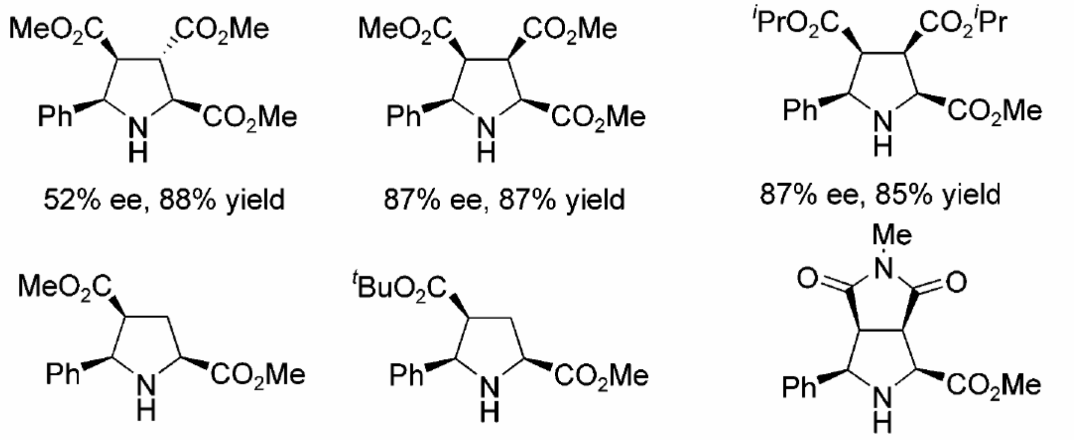
Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Cycloaddition of **7a** with Various Dipolarophile Substrates Catalyzed by Ag(I)-**6b**





(*S*, *S*, S_p)-FAP: Ar = phenyl (**6a**)
(*S*, *S*, S_p)-xylyl-FAP: Ar = 3,5-dimethylphenyl (**6b**)



52% ee, 88% yield

87% ee, 87% yield

87% ee, 85% yield

60% ee, 90% yield

93% ee, 85% yield

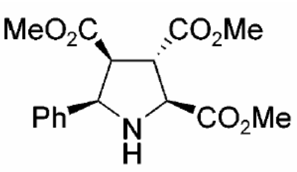
79% ee, 87% yield

Longmire, J. M.; Wang, B., Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400

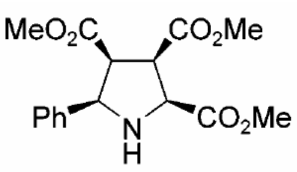
Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Working model of Zhang's system:

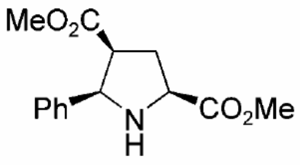
  1) Coordination of α-iminoester to chiral Ag(I) catalyst;
  2) Deprotonation with iPr_2NEt;
  3) Ligand blocks one enantiotopic face of azomethine ylide.



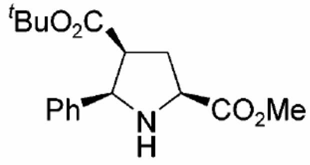
52% ee, 88% yield



87% ee, 87% yield

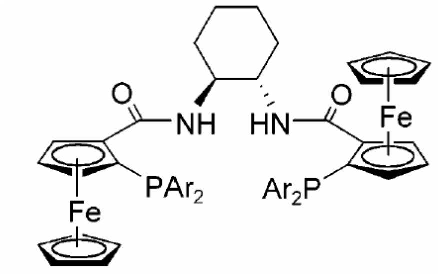


60% ee, 90% yield



93% ee, 85% yield

- Difference in ee can be explained by endo transition state model.



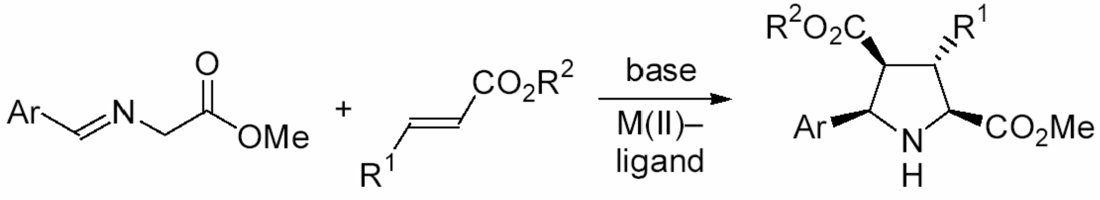
(*S*, *S*, S_p)-FAP: Ar = phenyl (**6a**)
(*S*, *S*, S_p)-xylyl-FAP: Ar = 3,5-dimethylphenyl (**6b**)

- The 3,5-dimethyl substitution extends the steric environment of ligand **6b**.

Longmire, J. M.; Wang, B., Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400

Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Jorgensen's Zn-*t*-Bu-BOX catalyst system:



1

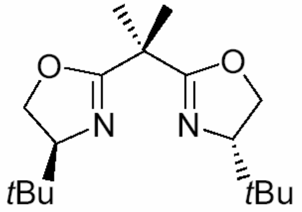
a: Ar = Ph
b: Ar = 2-Np
c: Ar = *p*-BrC_6H_4

3

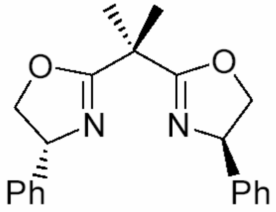
a: R^1 = H, R^2 = Me
b: R^1 = H, R^2 = Et
c: R^1 = H, R^2 = *t*Bu
d: R^1 = CO_2Me, R^2 = Me

4

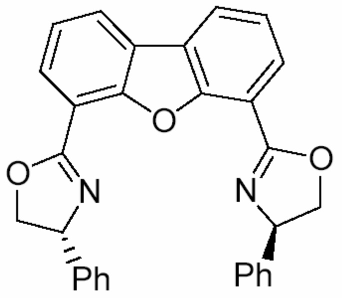
a: Ar = Ph, R^1 = H, R^2 = Me
b: Ar = 2-Np, R^1 = H, R^2 = Me
c: Ar = 2-Np, R^1 = H, R^2 = Et
d: Ar = 2-Np, R^1 = H, R^2 = *t*Bu
e: Ar = *p*-BrC_6H_4, R^1 = H, R^2 = Me
f: Ar = Ph, R^1 = CO_2Me, R^2 = Me
g: Ar = 2-Np, R^1 = CO_2Me, R^2 = Me
h: Ar = *p*-BrC_6H_4, R^1 = CO_2Me, R^2 = Me



5a: (*S*)-*t*-Bu-BOX



5b: (*R*)-Ph-BOX

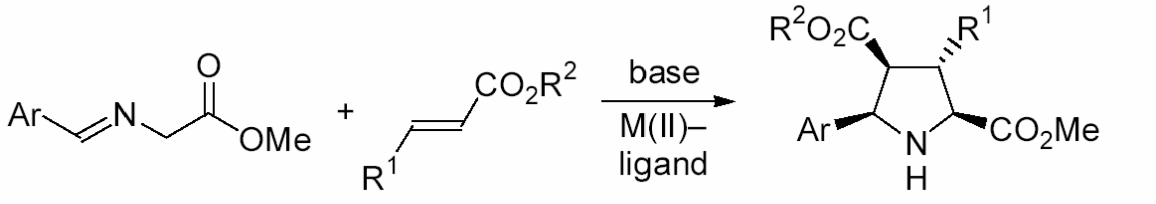


5c: (*R,R*)-Ph-DBFOX

Gothelf, A. S.; Gothelf, K. V.; Hazell, Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4236

Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Jorgensen's Zn-*t*-Bu-BOX catalyst system – Condition optimization.



1

a: Ar = Ph
b: Ar = 2-Np

3

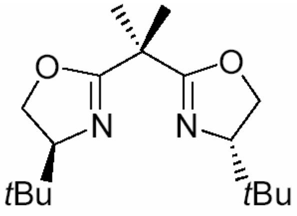
a: R^1 = H, R^2 = Me
b: R^1 = H, R^2 = Et

4

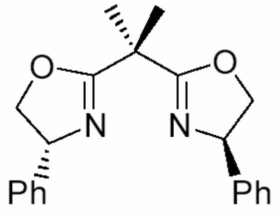
a: Ar = Ph, R^1 = H, R^2 = Me
b: Ar = 2-Np, R^1 = H, R^2 = Me

	Entry	Lewis acid	Ligand	Solvent	1	Conversion[b] (%)	*ee*[c] [%]
	1	$\mathrm{Cu(OTf)_2}$	**5a**	THF	**a**	**4a** (>95)	rac
	2	$\mathrm{Cu(OTf)_2}$	**5b**	THF	**a**	**4a** (<10)	n.d.[d]
→	3	$\mathrm{Zn(OTf)_2}$	**5a**	THF	**a**	**4a** (>95)	78
	4	$\mathrm{Zn(OTf)_2}$	**5a**	neat	**a**	**4a** (>95)	79
	5	$\mathrm{Zn(OTf)_2}$	**5b**	THF	**a**	**4a** (<50)	n.d.[d]
→	6	$\mathrm{Zn(OTf)_2}$	**5a**	THF	**b**	**4b** (>95)	78
	7	$\mathrm{Zn(OTf)_2}$	**5a**	neat	**b**	**4b** (>95)	76
	8	$\mathrm{Zn(OTf)_2}$	**5b**	neat	**b**	**4b** (>95)	17
	9	$\mathrm{Zn(OTf)_2}$	**5c**	neat	**b**	**4b** (>95)	7

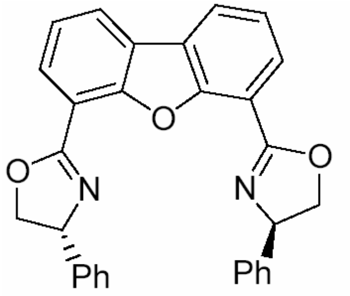
[a] Lewis acid, ligand, and Et_3N (10 mol% each) were used.



5a: (*S*)-*t*-Bu-BOX



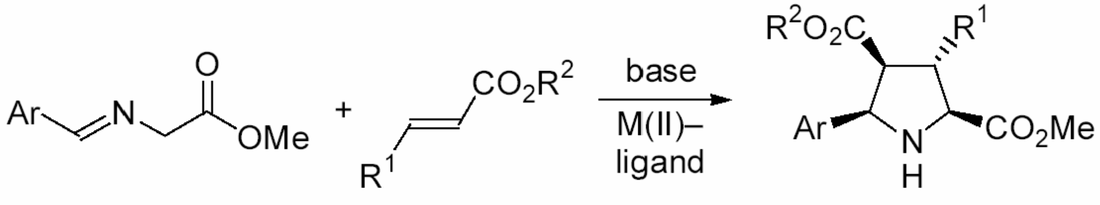
5b: (*R*)-Ph-BOX



5c: (*R,R*)-Ph-DBFOX

Gothelf, A. S.; Gothelf, K. V.; Hazell, Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4236

Catalytic Asymmetric 1,3-DC of Azomethine Ylides



1

a: Ar = Ph
b: Ar = 2-Np
c: Ar = *p*-BrC_6H_4

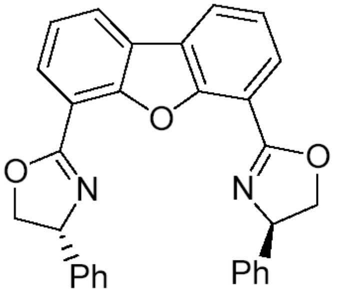
3

a: R^1 = H, R^2 = Me
b: R^1 = H, R^2 = Et
c: R^1 = H, R^2 = *t*Bu
d: R^1 = CO_2Me, R^2 = Me

4

a: Ar = Ph, R^1 = H, R^2 = Me
b: Ar = 2-Np, R^1 = H, R^2 = Me
c: Ar = 2-Np, R^1 = H, R^2 = Et
d: Ar = 2-Np, R^1 = H, R^2 = *t*Bu
e: Ar = *p*-BrC_6H_4, R^1 = H, R^2 = Me
f: Ar = Ph, R^1 = CO_2Me, R^2 = Me
g: Ar = 2-Np, R^1 = CO_2Me, R^2 = Me
h: Ar = *p*-BrC_6H_4, R^1 = CO_2Me, R^2 = Me

Entry	Azomethine ylide	Dienophile	Yield[b] (%)	*ee*[c] [%]
1	**1a**	**3a**	**4a** (> 95[d])	78
2[e]	**1a**	**3a**	**4a** (80)	88
3	**1b**	**3a**	**4b** (93)	78
4[e]	**1b**	**3a**	**4b** (84)	91
5[e,f]	**1b**	**3a**	**4b** (86)	87
6	**1b**	**3b**	**4c** (76)	68
7	**1b**	**3c**	**4d** (12)	< 5
8	**1c**	**3a**	**4e** (89)	61
9[e]	**1c**	**3a**	**4e** (89)	94
10[e]	**1a**	**3d**	**4f** (78)	76
11	**1b**	**3d**	**4g** (84)	90
12	**1c**	**3d**	**4h** (87)	68



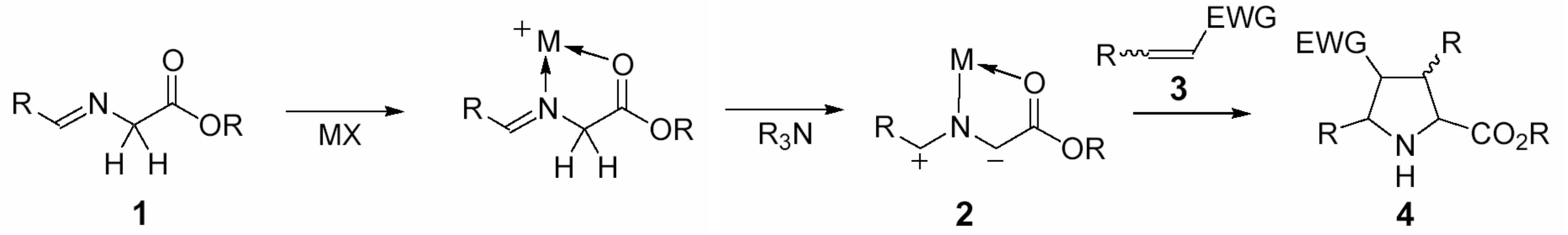
5c: (*R*,*R*)-Ph-DBFOX

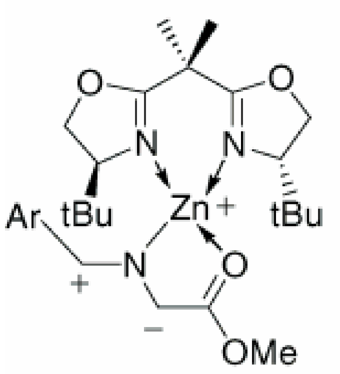
[a] Lewis acid, ligand, and Et_3N (10 mol% each) were used.
[e] Temperature -20°C. [f] No solvent.

Gothelf, A. S.; Gothelf, K. V.; Hazell, Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4236

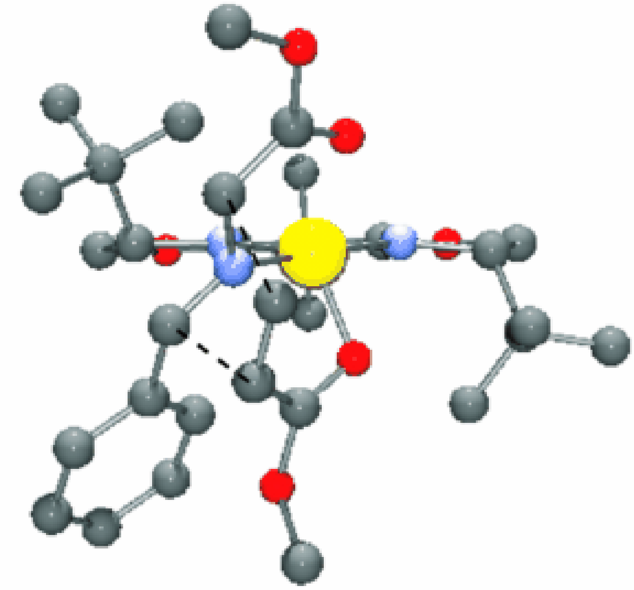
Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Working model for Jorgensen's Zn-*t*-Bu-BOX catalyst system.





Proposed intermediate:
18-electron complex
-- tetrahedral conformation would give
opposite enantiomer!

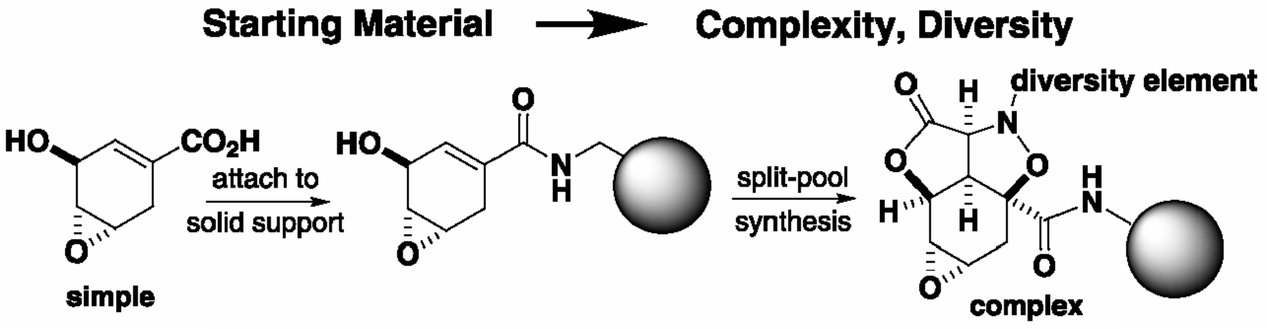


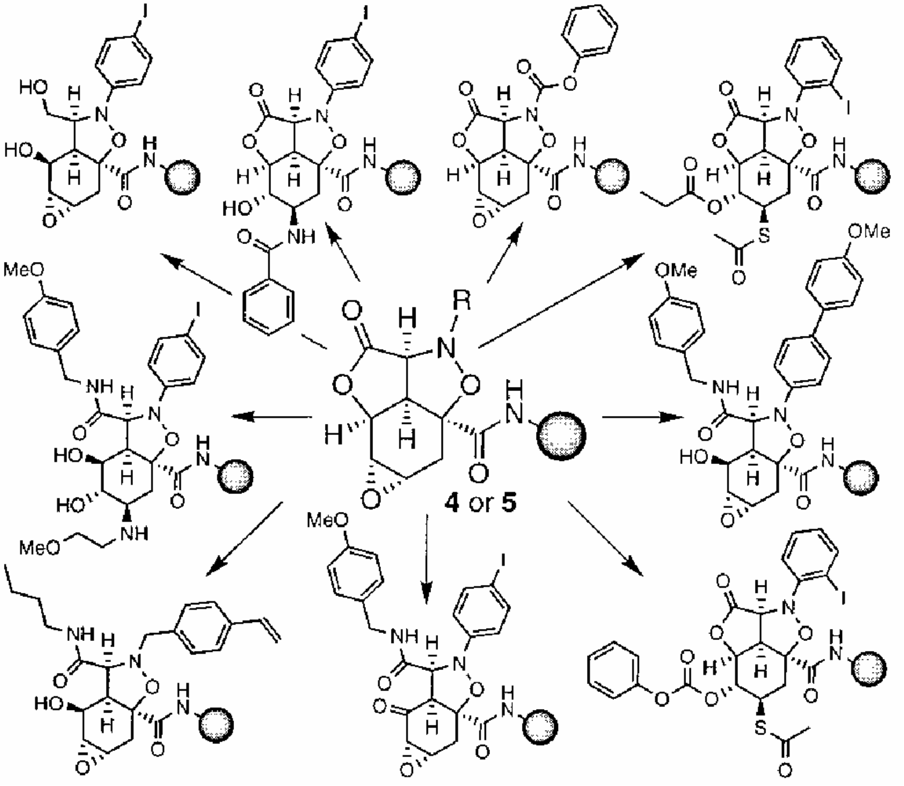
Proposed bipyramidal intermediate:
Involves coordination of α,β-unsaturated
ester carbonyl to metal center.
(Acrylnitrile does not react!)

Gothelf, A. S.; Gothelf, K. V.; Hazell, Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4236

Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Diversity-Oriented Synthesis (DOS)



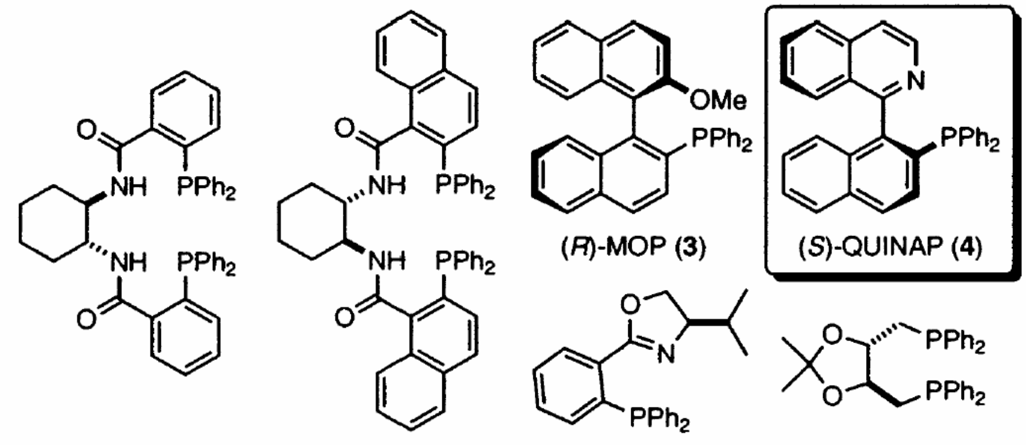


Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998***, 120*, 8565.
Schreiber, S. L. *Science*, **2000**, *287*, 1964

Catalytic Asymmetric 1,3-DC of Azomethine Ylides

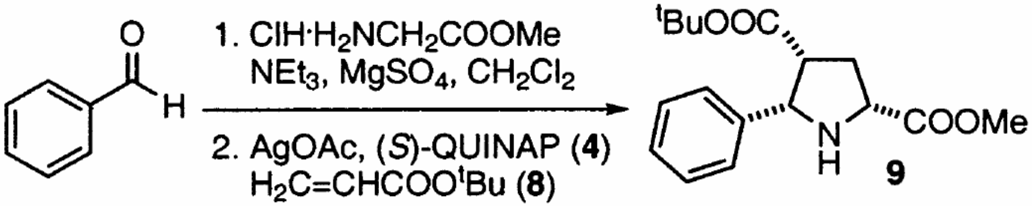
- Schreiber's silver(I)-QUINAP catalyst system.

-- Chiral phosphine ligands screened for the azomethine ylide cycloadditions.



(*R*)-MOP (**3**) (*S*)-QUINAP (**4**)

(*R*,*R*)-Trost ligand (**1**) (*S*,*S*)-NAPHTHYL (**2**) (*R*)-PHOX (**5**) (*S*,*S*)-DIOP (**6**)



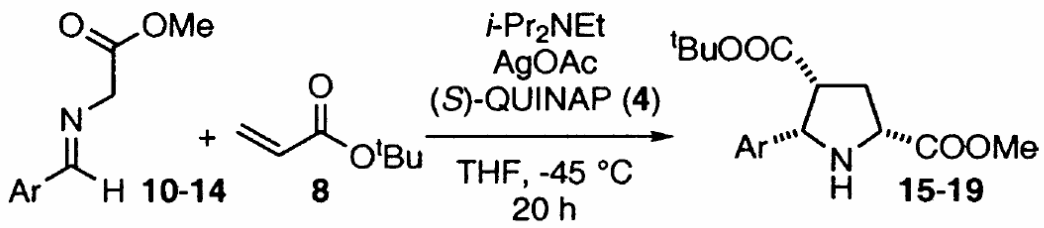
84% yield, 91% ee

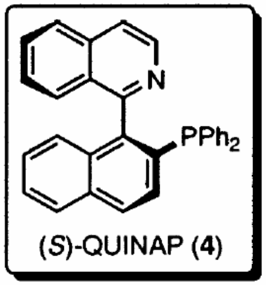
* 3 mol% catalyst used.

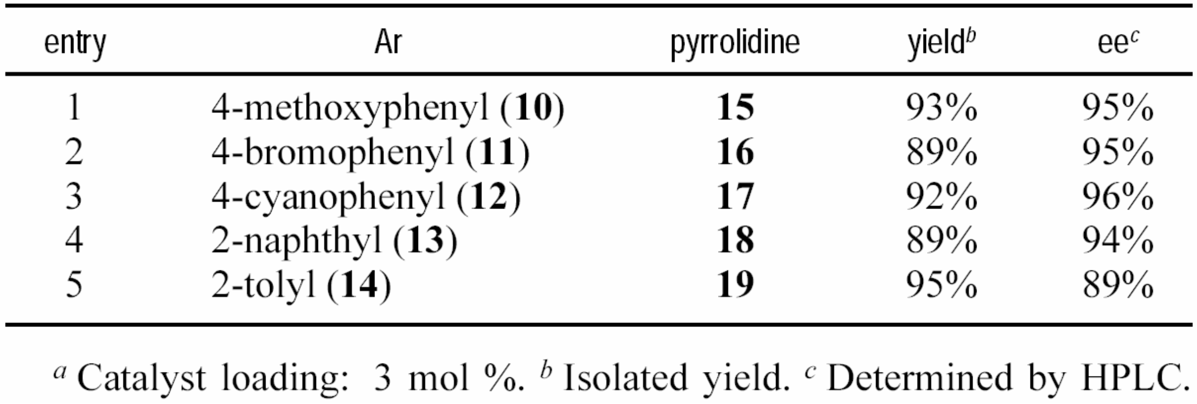
Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174

Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Exploration of the reactivity of the aromatic moiety




(S)-QUINAP (4)



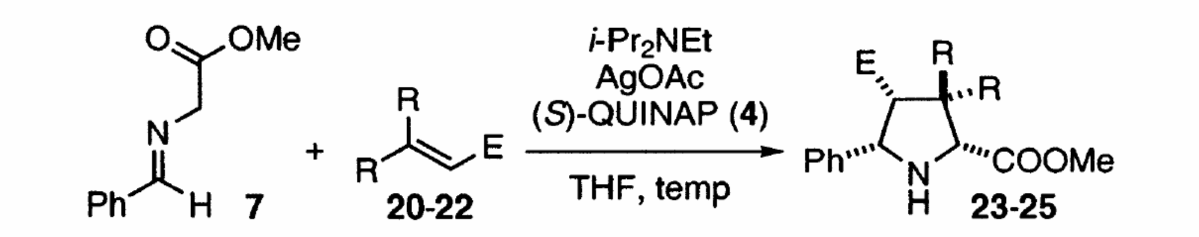
entry	Ar	pyrrolidine	yield[b]	ee[c]
1	4-methoxyphenyl (**10**)	**15**	93%	95%
2	4-bromophenyl (**11**)	**16**	89%	95%
3	4-cyanophenyl (**12**)	**17**	92%	96%
4	2-naphthyl (**13**)	**18**	89%	94%
5	2-tolyl (**14**)	**19**	95%	89%

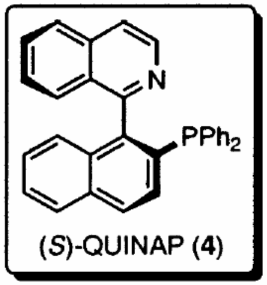
[a] Catalyst loading: 3 mol %. [b] Isolated yield. [c] Determined by HPLC.

Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174

Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Exploration of the reactivity of dipolarophiles.





(*S*)-QUINAP (**4**)

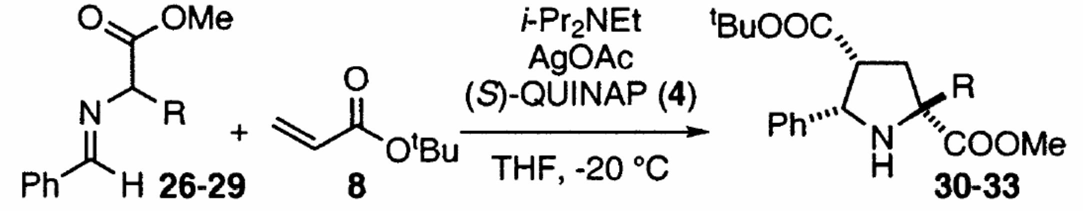
entry	dipolarophile	temp	time	yield[c]	endo:exo[d]	ee[e]
1[a]	dimethyl maleate (**20**)	−60 °C	48 h	88%	(**23**) >20:1	60%
2[b]	*tert*-butyl crotonate (**21**)	−20 °C	85 h	97%[f]	(**24**) >20:1	84%
3[b]	*tert*-butyl cinnamate (**22**)	−20 °C	85 h	62%[g]	(**25a**, **25b**) 2:1	81%, 50%[h]

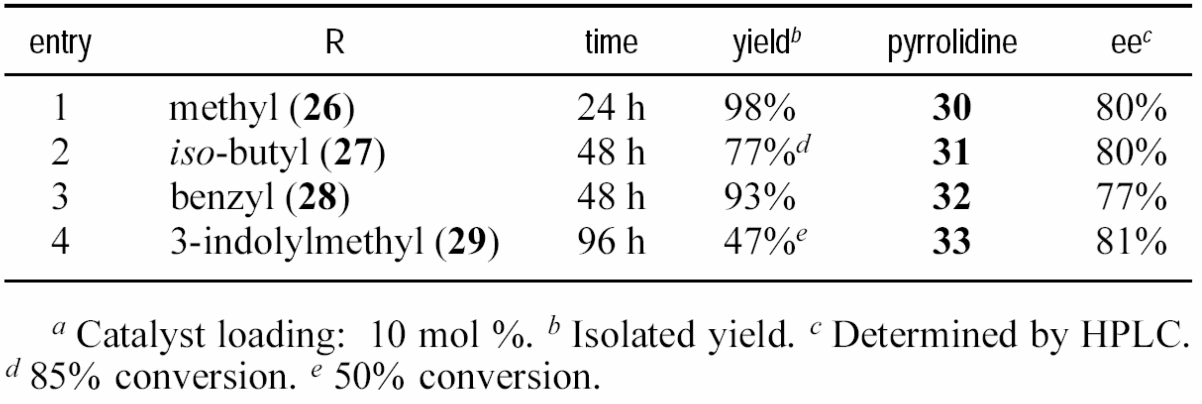
[a] Catalyst loading: 3 mol %, solvent: toluene. [b] Catalyst loading: 10 mol %. [c] Isolated yield. [d] Determined by crude ^{1}H NMR spectra. [e] Determined by HPLC. [f] ca. 95% purity. [g] Combined yield of endo and exo products. [h] Enantioselectivity of the exo product **25b**.

Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174

Catalytic Asymmetric 1,3-DC of Azomethine Ylides

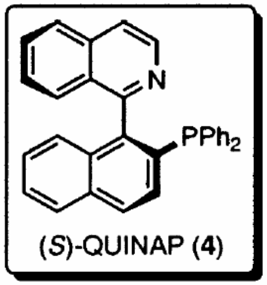
- Extending of the scope of the silver(I)-QUINAP-catalyzed [3+2] azomethine ylide cycloadditions.



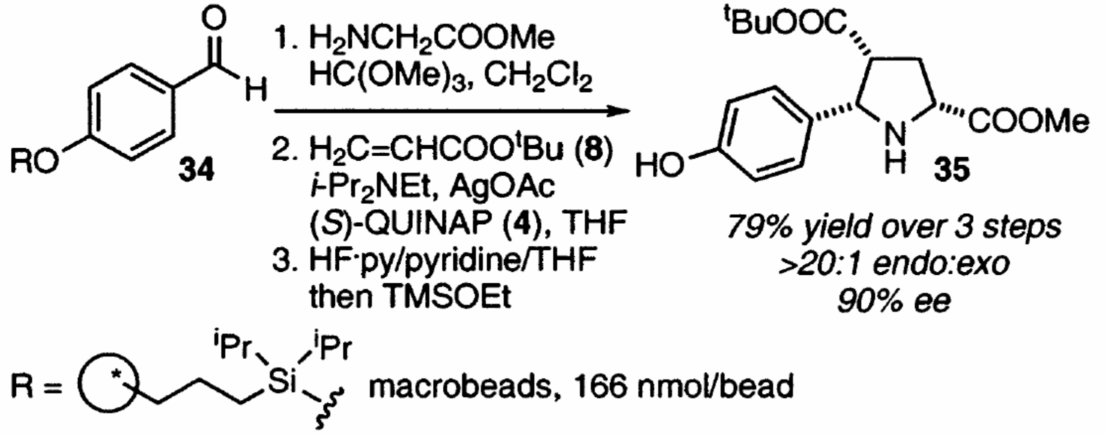


entry	R	time	yield[b]	pyrrolidine	ee[c]
1	methyl (**26**)	24 h	98%	**30**	80%
2	*iso*-butyl (**27**)	48 h	77%[d]	**31**	80%
3	benzyl (**28**)	48 h	93%	**32**	77%
4	3-indolylmethyl (**29**)	96 h	47%[e]	**33**	81%

[a] Catalyst loading: 10 mol %. [b] Isolated yield. [c] Determined by HPLC. [d] 85% conversion. [e] 50% conversion.



(S)-QUINAP (4)



Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174

Catalytic Asymmetric 1,3-DC of Azomethine Ylides

- Brief comparison of three catalytic systems:

	Zhang	**Jorgensen**	**Schreiber**
Salt	AgOAc	Zn(OTf)$_2$	AgOAc
Ligand	Xylyl-FAP	*t*-Bu-BOX	QUINAP
Loading	3 mol%	10 mol%	3-10 mol%
ee	70-97%	Up to 91%	60-96%
Substrate Scope	Aromatic, aliphatic ylide; Limted dipolarphile.	Aromatic ylide; Limited dipolarphile.	Aromatic ylide*; Limited dipolarphile.

- Limitation and possible future works of current systems:
  -- None of the system can catalyze the aliphatic ylide highly enantioselectively.
  -- Each system is only efficient for certain substrates.
  -- Understanding of the mechanism/transition state limited.
  -- …

Summary of Asymmetric [3+2] Cycloaddition of Azomethine Ylides

- The [3+2] cycloaddition of azomethine ylide with alkene is an extremely versatile and atom economical process.

- Many highly efficient and stereoselective methods have been developed for the synthesis of various highly-substituted pyrrolidines.

- While chiral auxiliary approach has been studied extensively, asymmetric catalysis is still a brand-new area and deserves more attention.

"Compared to the development of the asymmetric metal-catalyzed carbo- and hetero-Diels-Alder reactions, the development of the analogous approach to asymmetric 1,3-DC reactions is several years behind."
-- Jorgensen, *Chem. Rev*. **1998**, *98*, 863