Catalytic Asymmetric Pericyclic Reactions

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Shenvi Lab
11/7/2011

Catalytic Asymmetric Pericyclic Reactions - 11/7/2011

- Cycloadditions
    - Diels-Alder Reactions
        - Lewis Base
        - Brønsted Base
        - Organic Bifunctional Acids
        - Organic Brønsted Acids
    - 1,3 Dipolar Cycloadditions
    - [2+2] Cycloadditions
- Electrocyclic Reactions
    - Nazarov Cyclizations
- Sigmatropic Rearrangements
    - Claisen Rearrangements
    - Aza-Cope Rearrangements
- Group transfer reactions
    - Ene Reactions

Pericyclic Reactions

Reactions with a cyclic transition state that involves all σ and π-bonds to simultaneously break & form concertedly

Four classes of pericyclic reactions:

Cycloadditions

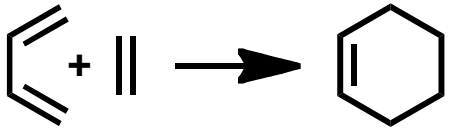
Electrocyclic reactions

Sigmatropic rearrangements

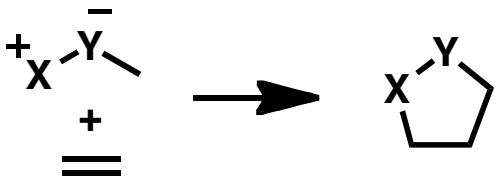
Group transfer reactions

Cycloaddition

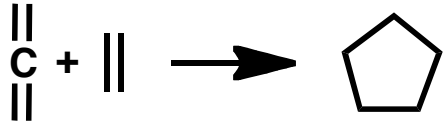
Two components coming together to form 2 new sigma-bonds, at the end of both components, joining them together to form a ring



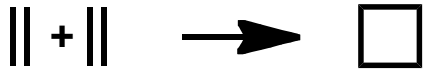
[4+2]



[3+2]

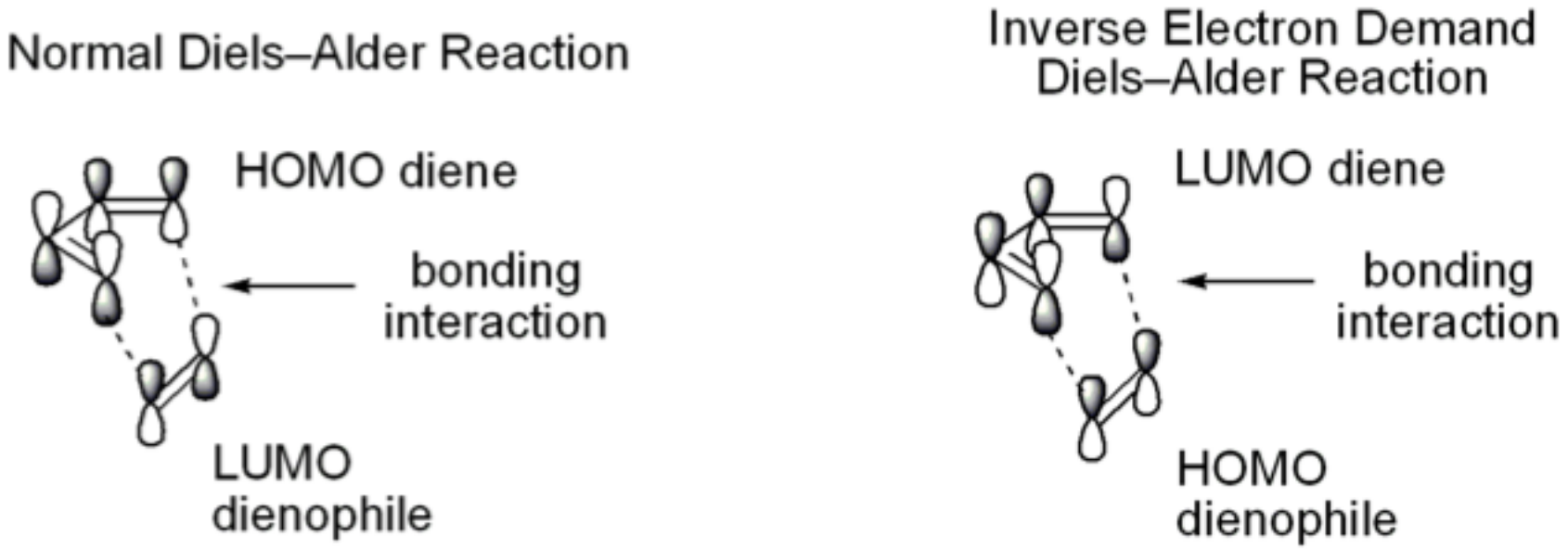


[3+2]



[2+2]

Diels-Alder Reaction

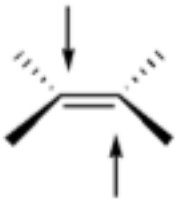


Boger, D. Modern Organic Synthesis Lecture Notes

Cycloaddition

Suprafacial

Antarafacial



- Generalization:

Total π electrons	Allowed in Ground State	Allowed in Excited State
4n	$m_s + n_a$	$m_s + n_s$
	$m_a + n_s$	$m_a + n_a$
4n + 2	$m_s + n_s$	$m_s + n_a$
	$m_a + n_a$	$m_a + n_s$

- Notations

orbital type ⇨ $\pi 2_s$ ⇦ suprafacial (s) or antarafacial (a)

π, σ, ω

⇧

number of e^-

Boger, D. Modern Organic Synthesis Lecture Notes

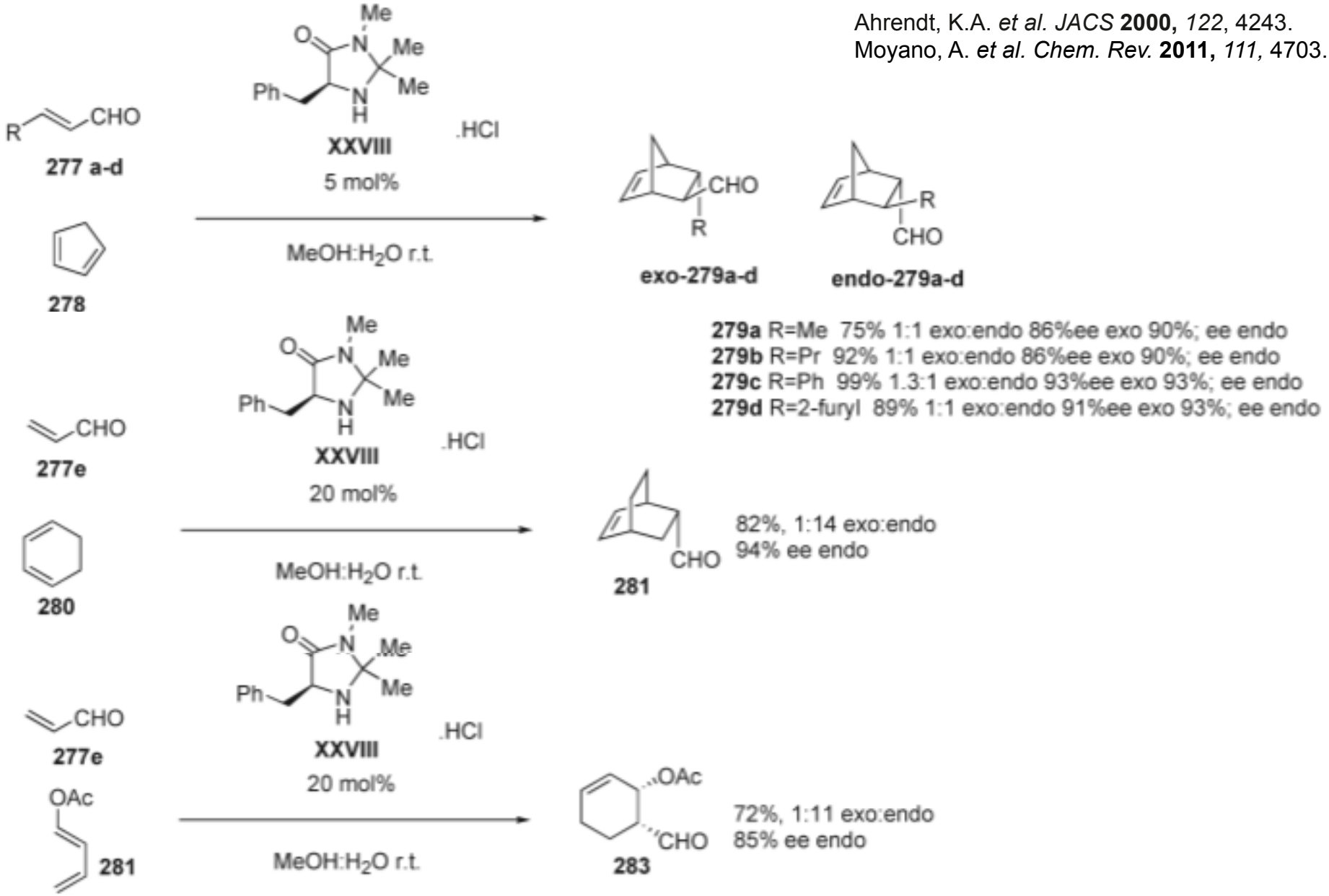
Diels-Alder Reaction: Different types

Catalysis by:

1. Lewis Bases
    1. Iminium Activation
    2. Enamine Activation
2. Brønsted Bases
3. Organic Bifunctional Catalysts
4. Organic Brønsted Acids

Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #1

Ahrendt, K.A. *et al. JACS* **2000,** *122*, 4243.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703..

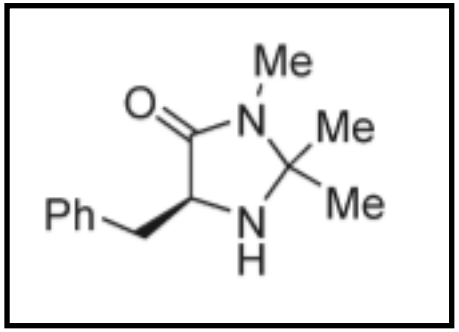


279a R=Me 75% 1:1 exo:endo 86%ee exo 90%; ee endo
279b R=Pr 92% 1:1 exo:endo 86%ee exo 90%; ee endo
279c R=Ph 99% 1.3:1 exo:endo 93%ee exo 93%; ee endo
279d R=2-furyl 89% 1:1 exo:endo 91%ee exo 93%; ee endo

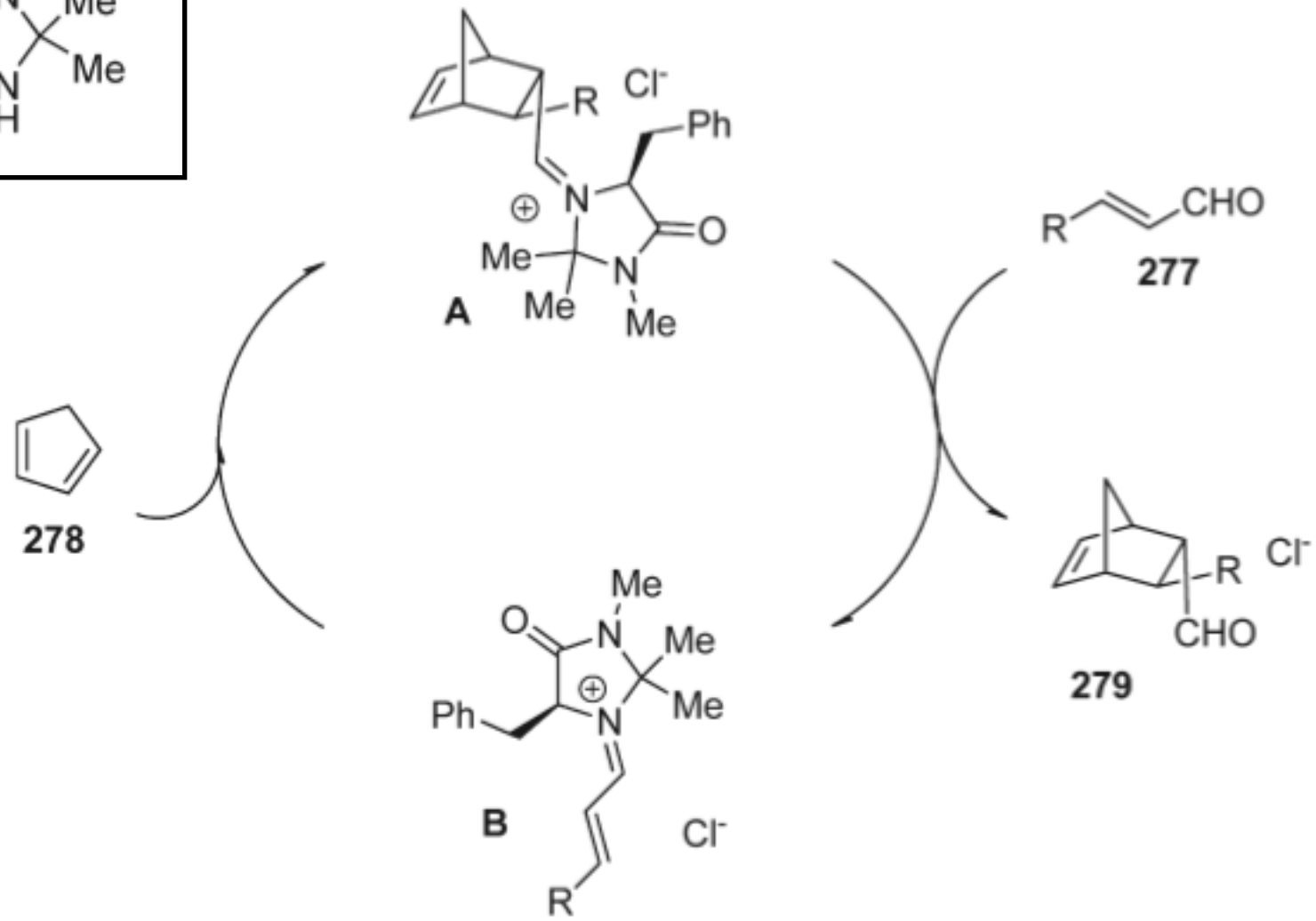
82%, 1:14 exo:endo
94% ee endo

72%, 1:11 exo:endo
85% ee endo

Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #1

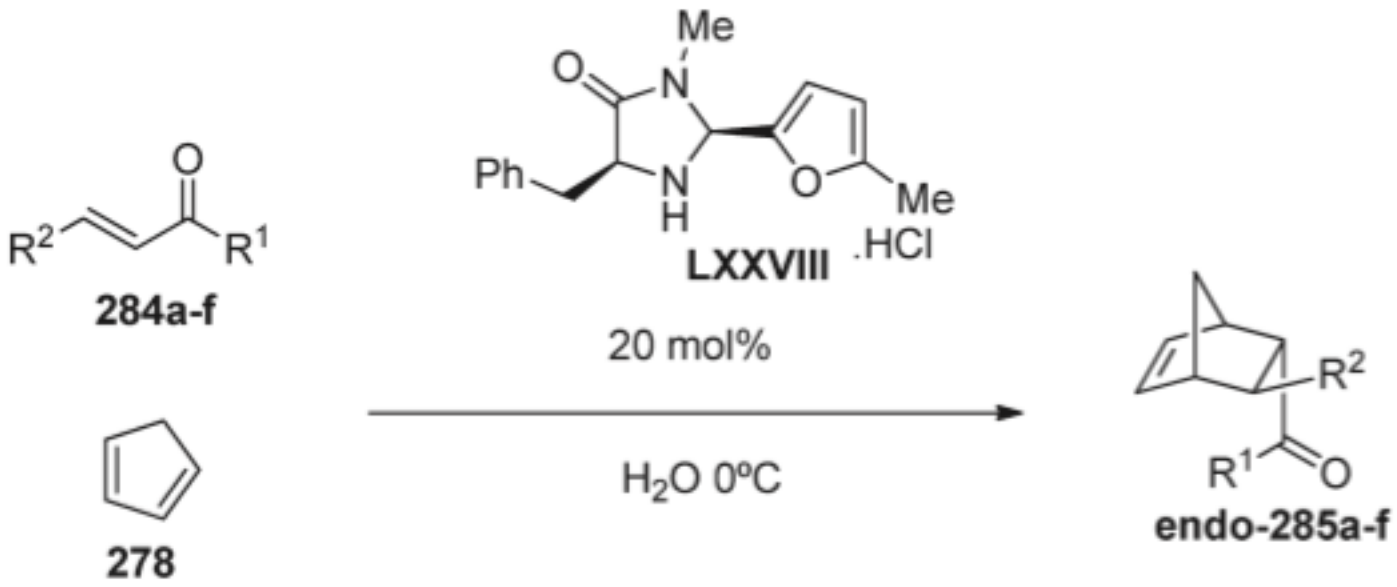


Ahrendt, K.A. *et al. JACS* **2000,** *122*, 4243.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #1

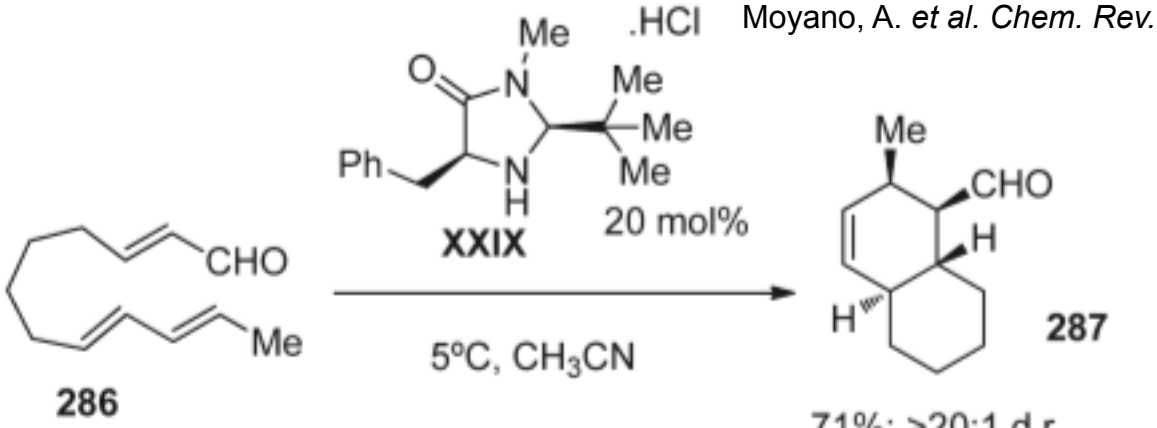
Northrup, A. B. *et al. JACS* **2002,** *124*, 2458.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



285a R^1=Me R^2= Me 85%; 1:14 exo:endo; 61% ee endo
285b R^1=Et R^2= Me 89%; 1:25 exo:endo; 90% ee endo
285c R^1=n-Bu R^2= Me 83%; 1:22 exo:endo; 92%; ee endo
285d R^1=Et R^2= *n*-Pr 84%; 1:15 exo:endo; 92%; ee endo
285e R^1=Et R^2= *i*-Pr 78%; 1:6 exo:endo 90% ee endo
285f R^1=*i*-Pr R^2= Me 24%; 1:8 exo:endo 0%; ee endo

Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #2

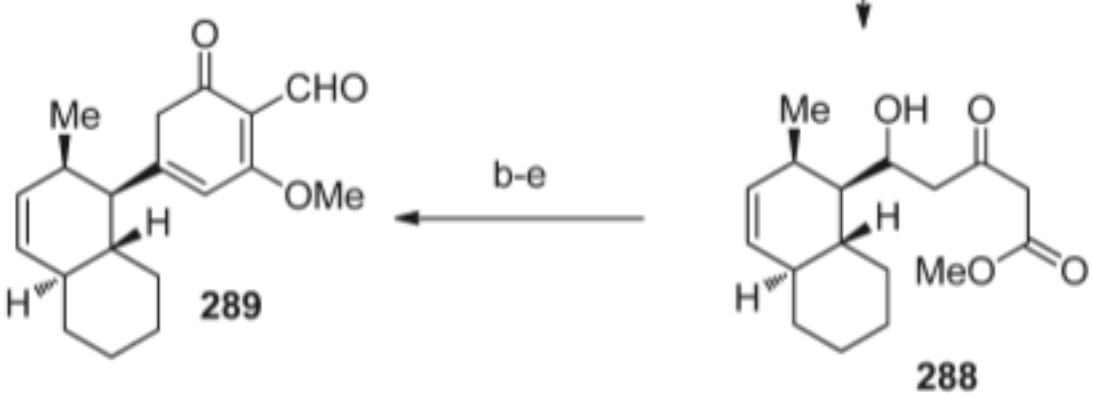
Wilson, R. *et al. JACS* **2005,** *127*, 11616.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



286

71%; >20:1 d.r.
90% ee

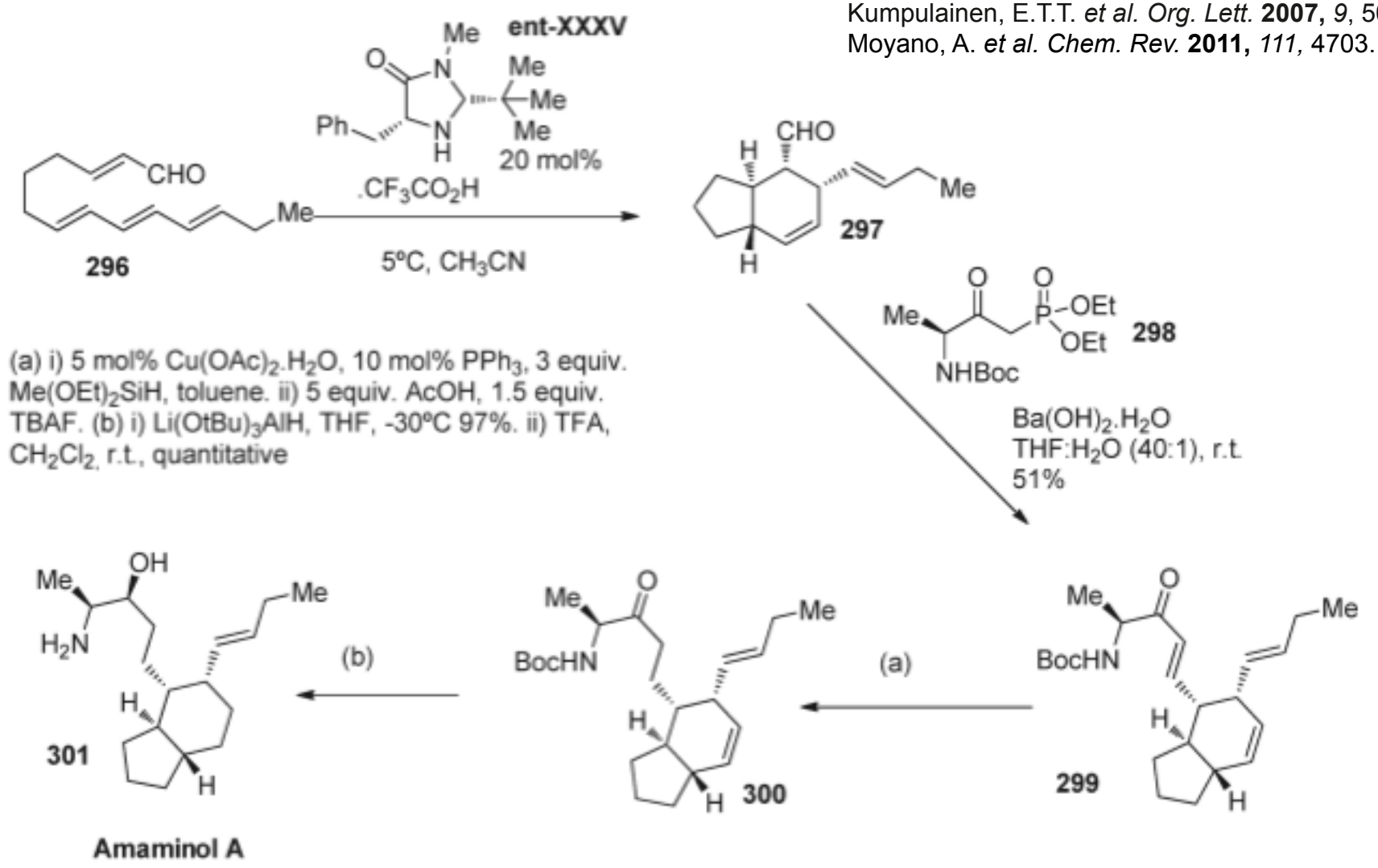
(a) Methyl acetoacetate bis (trimethylsilyl) enol ether, $TiCl_4$, CH_2Cl_2, -78ºC. (b) Dess-Martin periodinane, CH_2Cl_2, 71%. (c) DBU, benzene, 60ºC, 87%. (d) Methyl *p*-toluenesulfonate, K_2CO_3, DMF, r.t., 81%. (e) LDA, THF, -78ºC to 0ºC; methyl formate, -78ºC, 57%.



Solanapyrone D

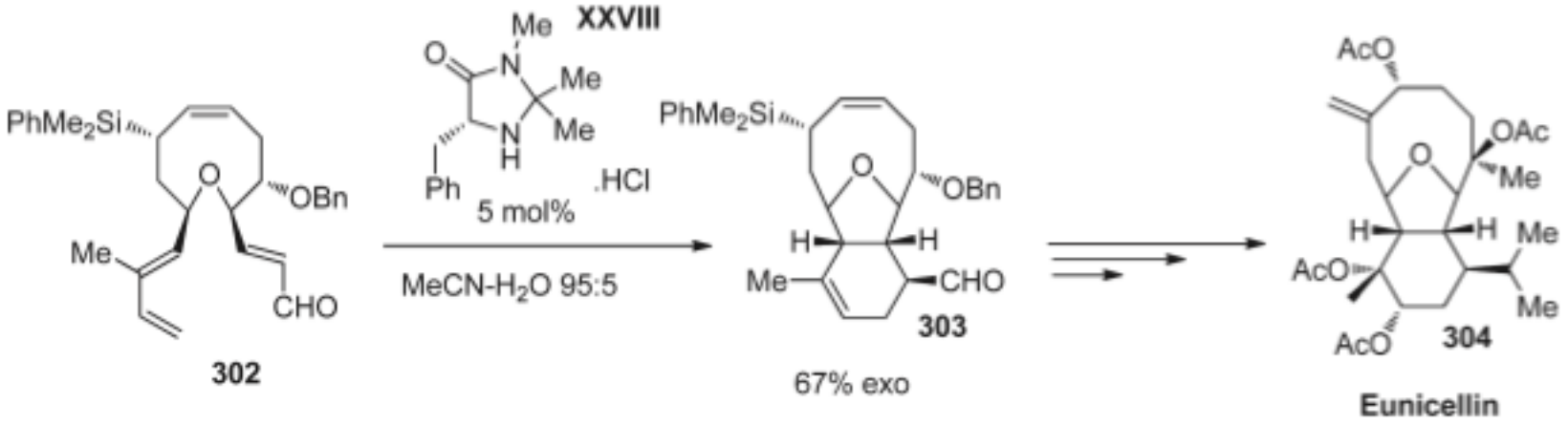
Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #3

Kumpulainen, E.T.T. *et al. Org. Lett.* **2007,** *9*, 5043.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



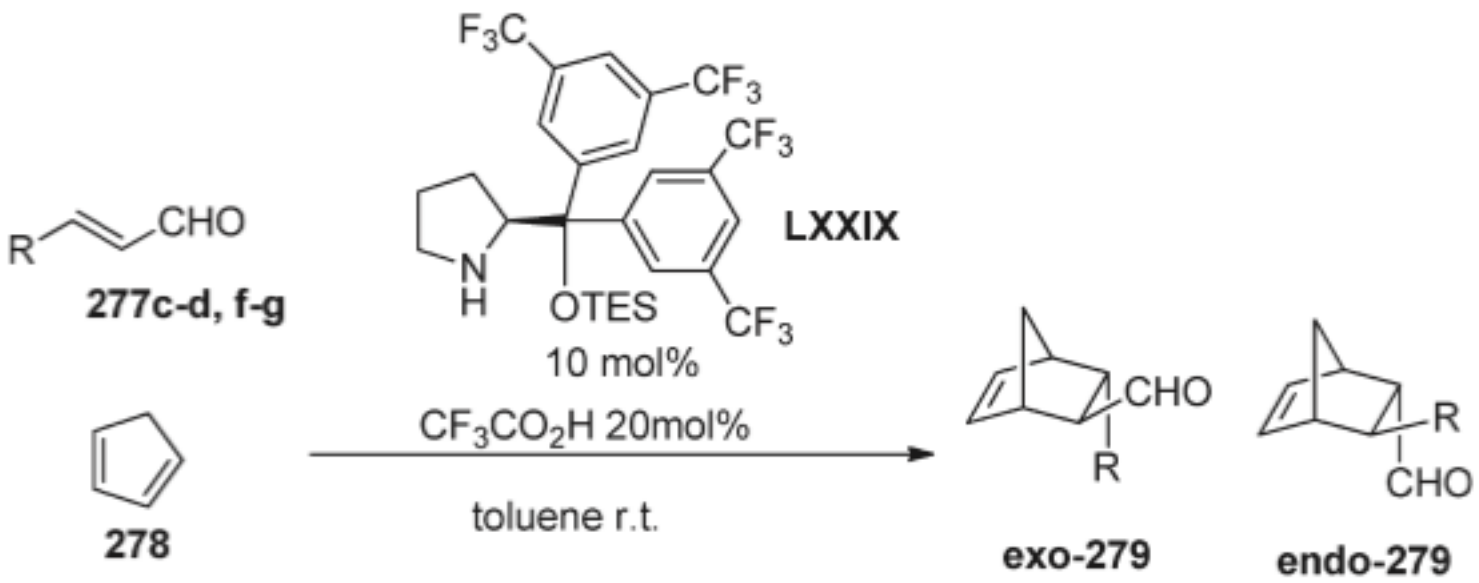
Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #4

Gilmour, R. *et al. Chem Commun.* **2007,** *3954*.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #5

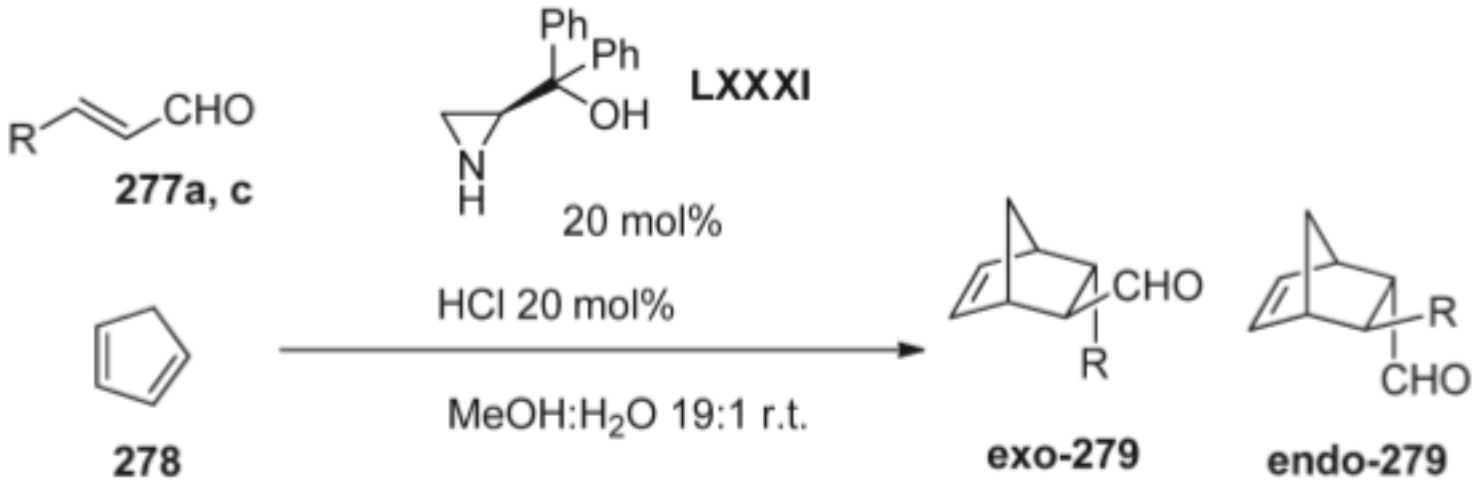
Gotoh, H. *et al. Org. Lett.* **2007,** *9,* 2859.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



279c R=Ph 99% 85:15 exo:endo; 97% ee exo; 88% ee endo
279d R=2-furyl 89% 80:20 exo:endo; 94% ee exo; 78% ee endo
279f R=n-Bu 75% 78:22 exo:endo; 94% ee exo; 91% ee endo
279g R=CO_2Et 92% 70:30 exo:endo; 84% ee exo; 64% ee endo

Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #6

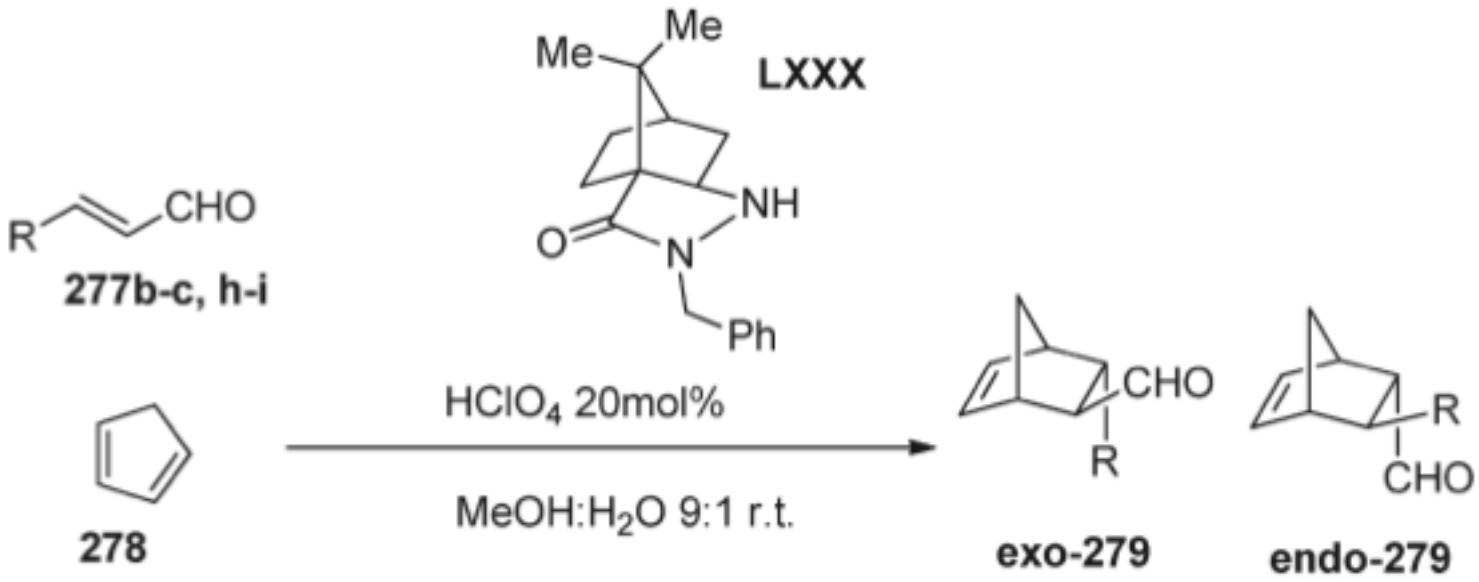
Bonini, B.F. *et al. Tet. Asym.* **2006,** *17,* 3135
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



279a R=Me 85% 1:1 exo:endo; 24% ee exo; 22% ee endo
279c R=Ph 33% 1:1.8 exo:endo; 36% ee exo; 37% ee endo

Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #7

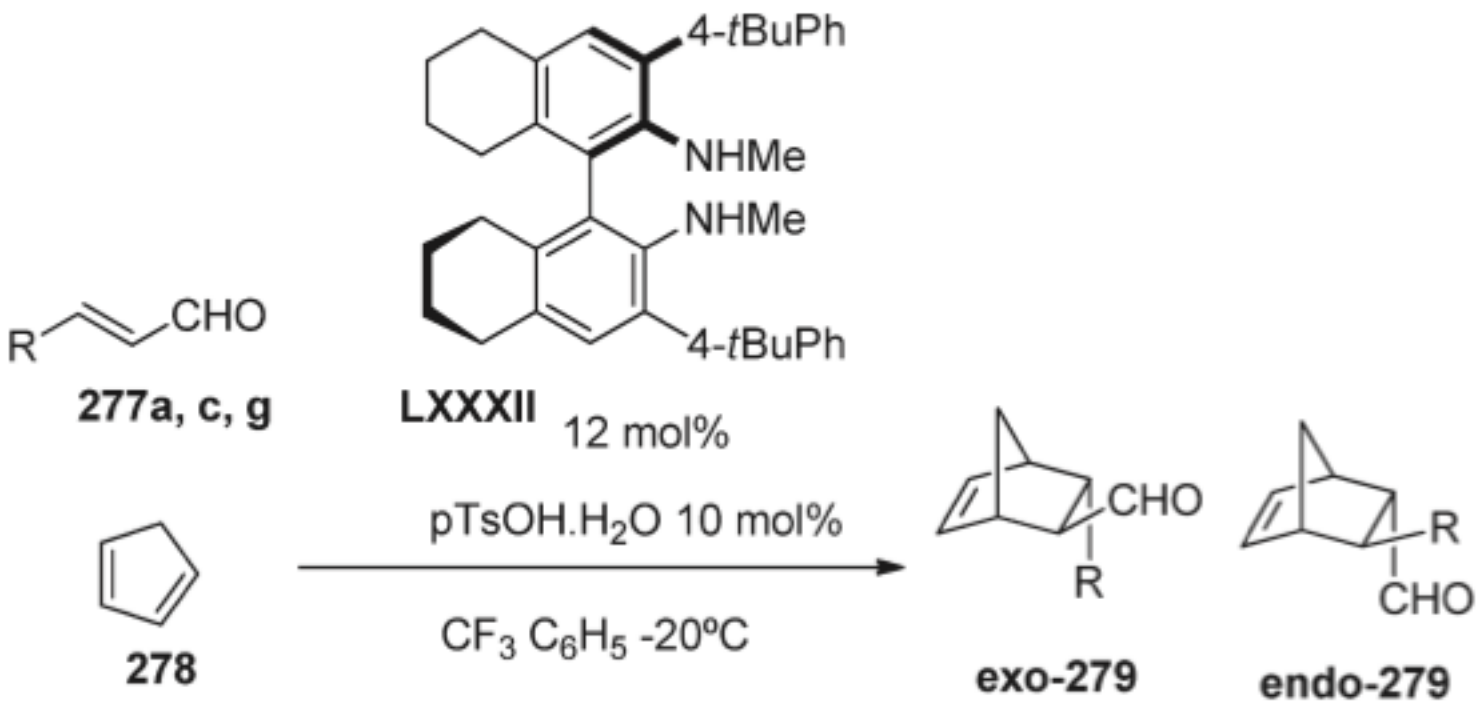
Lemay, M. *et al. Org. Lett.* **2005,** *7,* 4141.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



279b R=Pr 83% 1.6:1 exo:endo; 81% ee exo
279c R=Ph 96% 1.9:1 exo:endo; 90% ee exo
279h R=p$NO_2C_6H_4$ 93% 2.2:1 exo:endo; 92% ee exo
279i R=pClC_6H_4 92% 2:1 exo:endo; 90% ee exo

Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #8

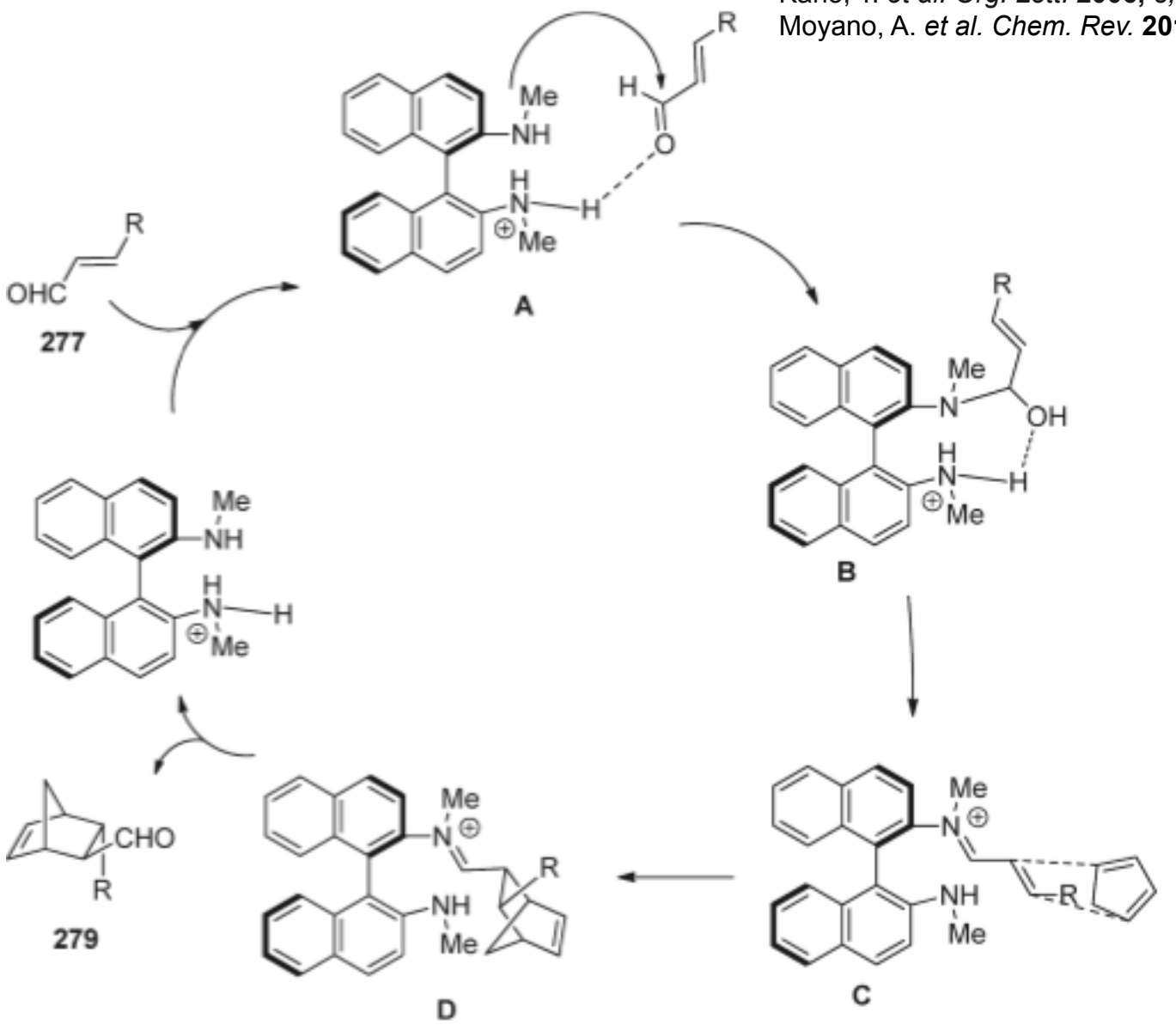
Kano, T. *et al. Org. Lett.* **2006,** *8,* 2687.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



279a R=Me 72% >20:1 exo:endo; 88% ee exo
279c R=Ph 80% 13:1 exo:endo; 92% ee exo; 91% ee endo
279g R=CO_2Et 90% 5:1 exo:endo; 83% ee exo; 56% ee endo

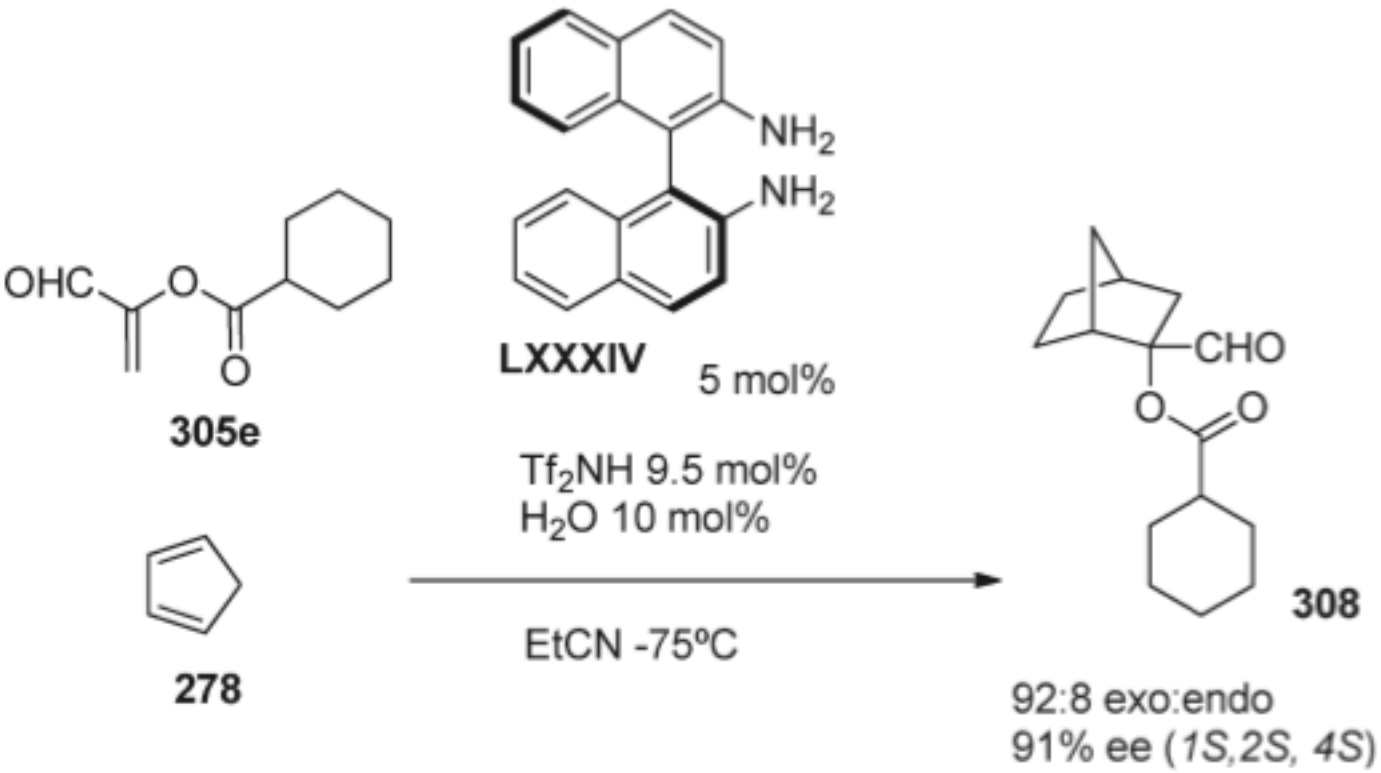
Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #8

Kano, T. *et al. Org. Lett.* **2006,** *8,* 2687.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.

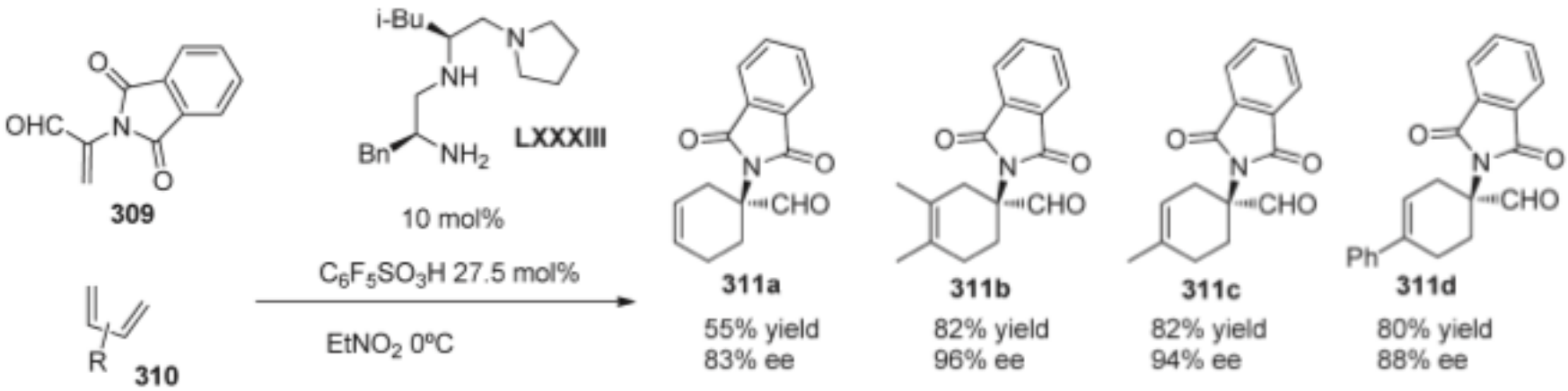


Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #9

Sakakura, A. *et al. Org. Lett.* **2006,** *8,* 2229.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



Diels-Alder Reaction: Lewis Bases - Iminium Activation Ex. #10

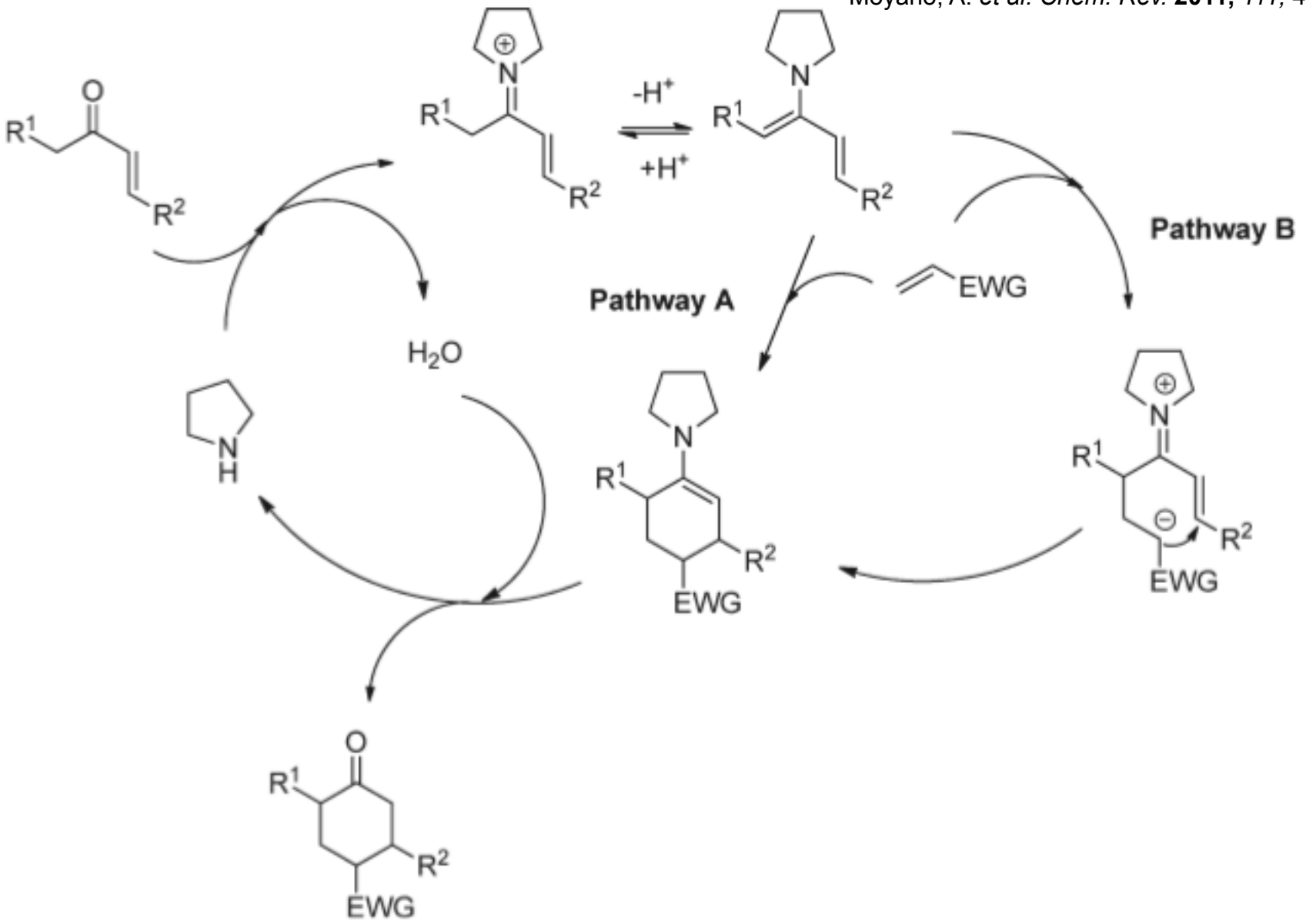


307a R=Ph 97%; 87% ee
307b R=Me 56%: 83% ee
307c R=pMeOC$_6$H$_4$ 99%; 90% ee
307d R=phtalimide 97%; 92% ee

Ishihara, K. *et al. JACS* **2005,** *127,* 10504.
Ishihara, K. *et al. Org. Lett.* **2008,** *10,* 2893.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.

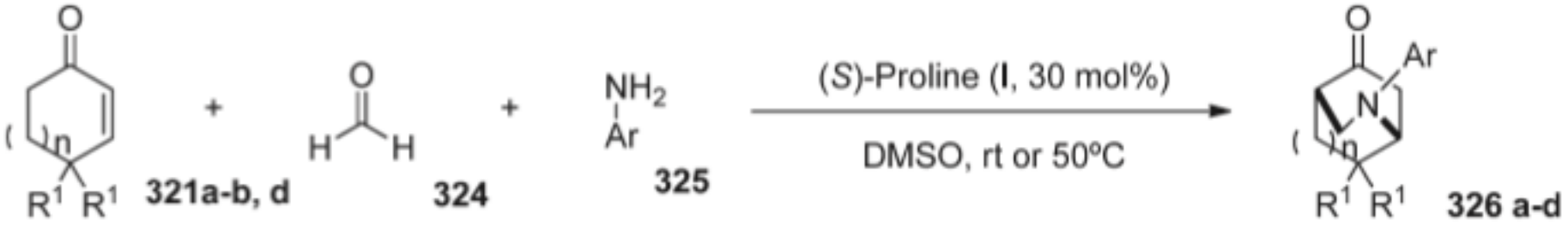
Diels-Alder Reaction: Lewis Bases - Enamine Activation

Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



Diels-Alder Reaction: Lewis Bases - Enamine Activation Ex #1

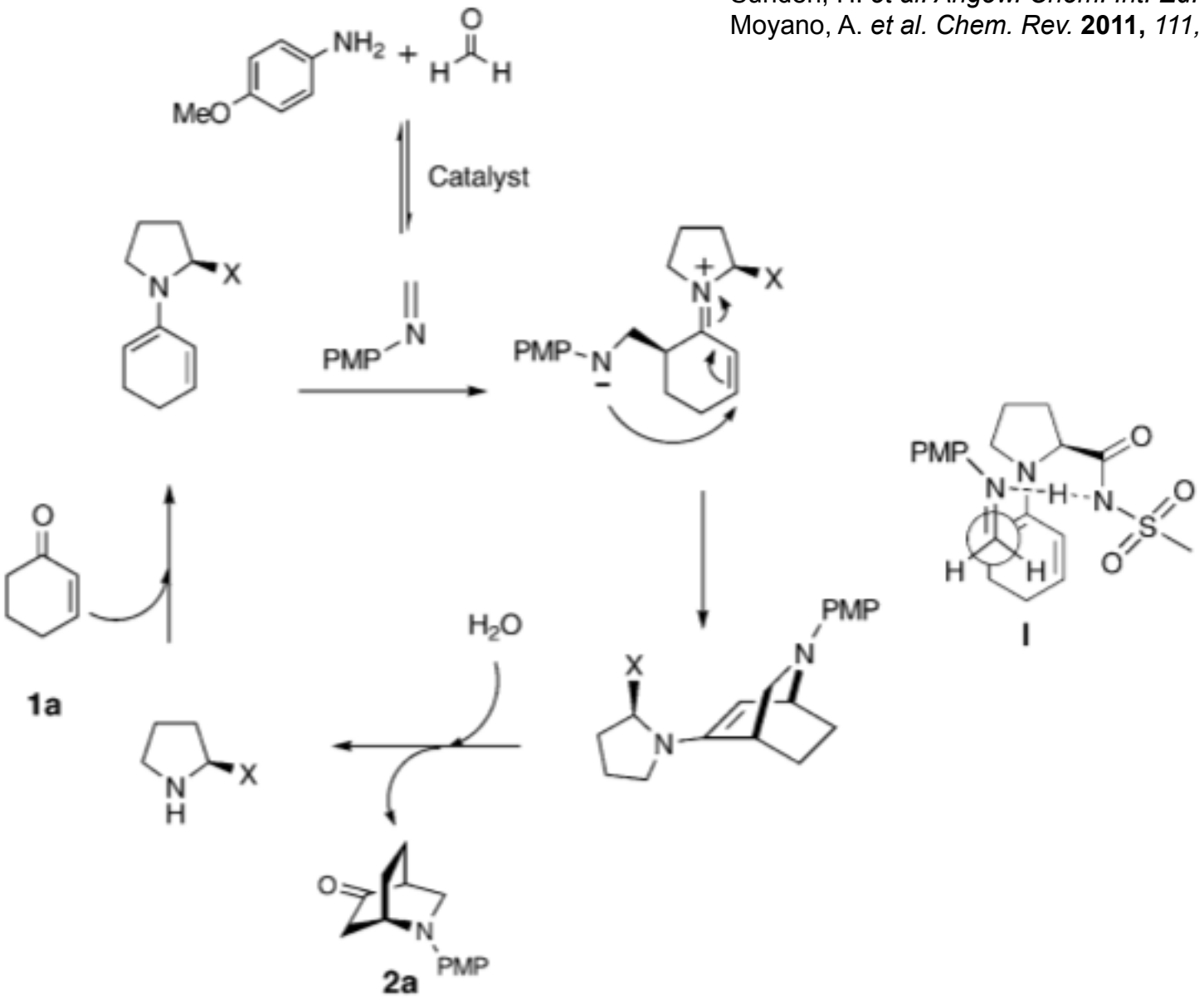
Sunden, H. *et al. Angew. Chem. Int. Ed.* **2005,** *44,* 4877.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703..



326a n=1 R^1=H Ar=PMP 82%; 99% ee
326b n=1 R^1=Me Ar=PMP 72%; >99% ee
326c n=2 R^1=H Ar=PMP 90%; 98% ee
326d n=1 R^1=Me Ar=Ph 54%; 96% ee

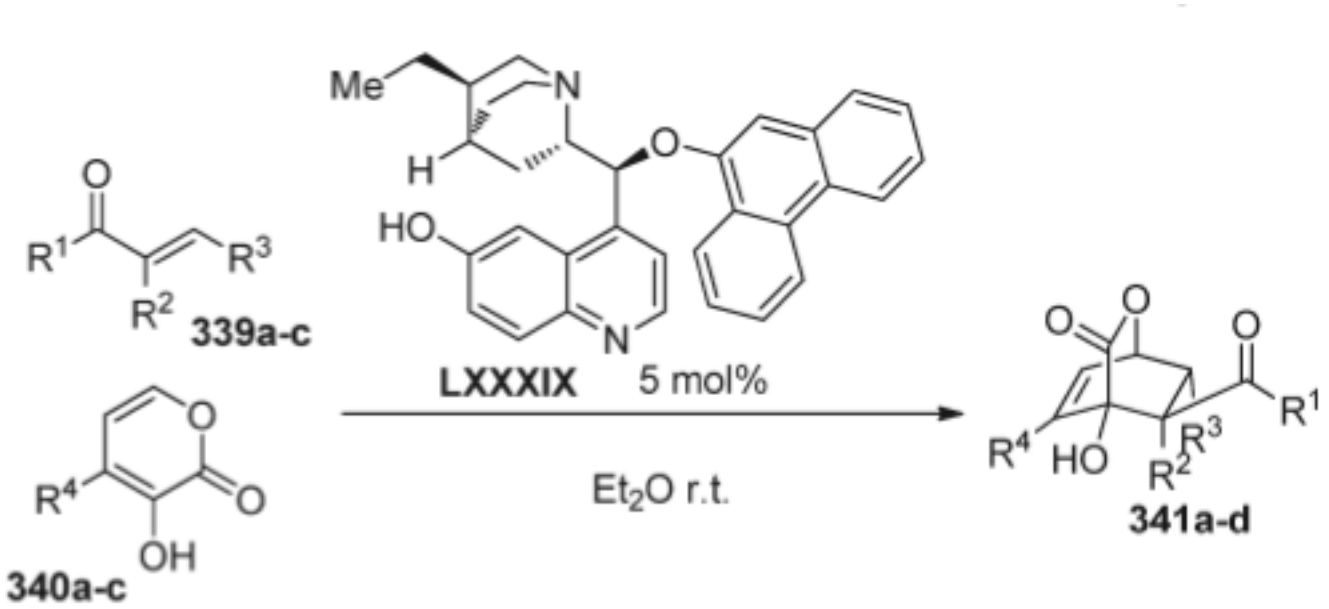
Diels-Alder Reaction: Lewis Bases - Enamine Activation Ex #1

Sunden, H. *et al. Angew. Chem. Int. Ed.* **2005,** *44,* 4877.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



Diels-Alder Reaction: Brønsted Bases Ex. #1

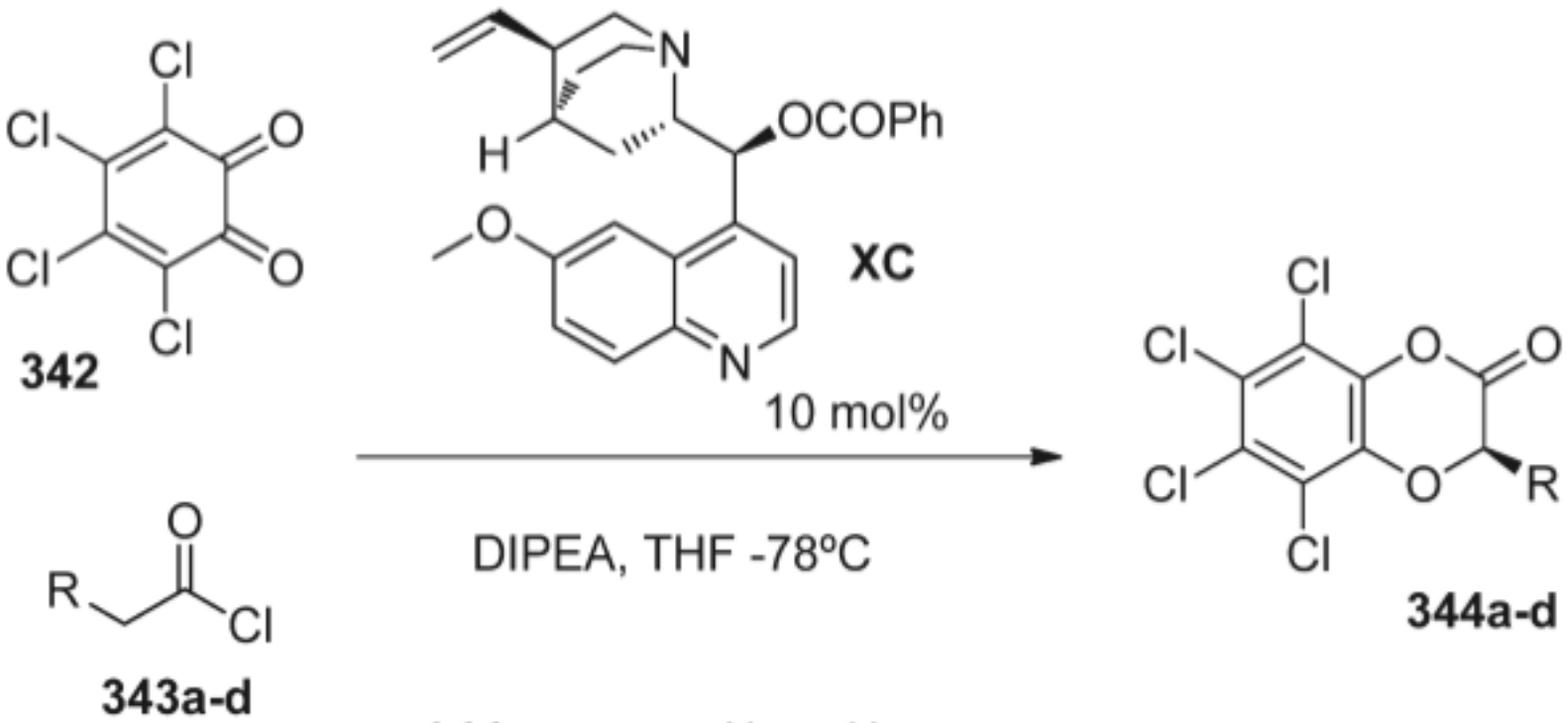
Singh, R, P. *et al. JACS.* **2008,** *130,* 2422.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



341a R^1=Ph R^2=H R^3=CO_2Et R^4=H 87%; 93:7 exo:endo; 94% ee exo
341b R^1=Me R^2=Me R^3=H R^4=H 65%; 24:76 exo:endo; 91% ee endo
341c R^1=Ph R^2=H R^3=CO_2Et R^4=Me 77%; 88:12 exo:endo; 82% ee exo
341d R^1=Ph R^2=H R^3=CO_2Et R^4=Cl 75%; 86:14 exo:endo; 84% ee exo

Diels-Alder Reaction: Brønsted Bases Ex. #2

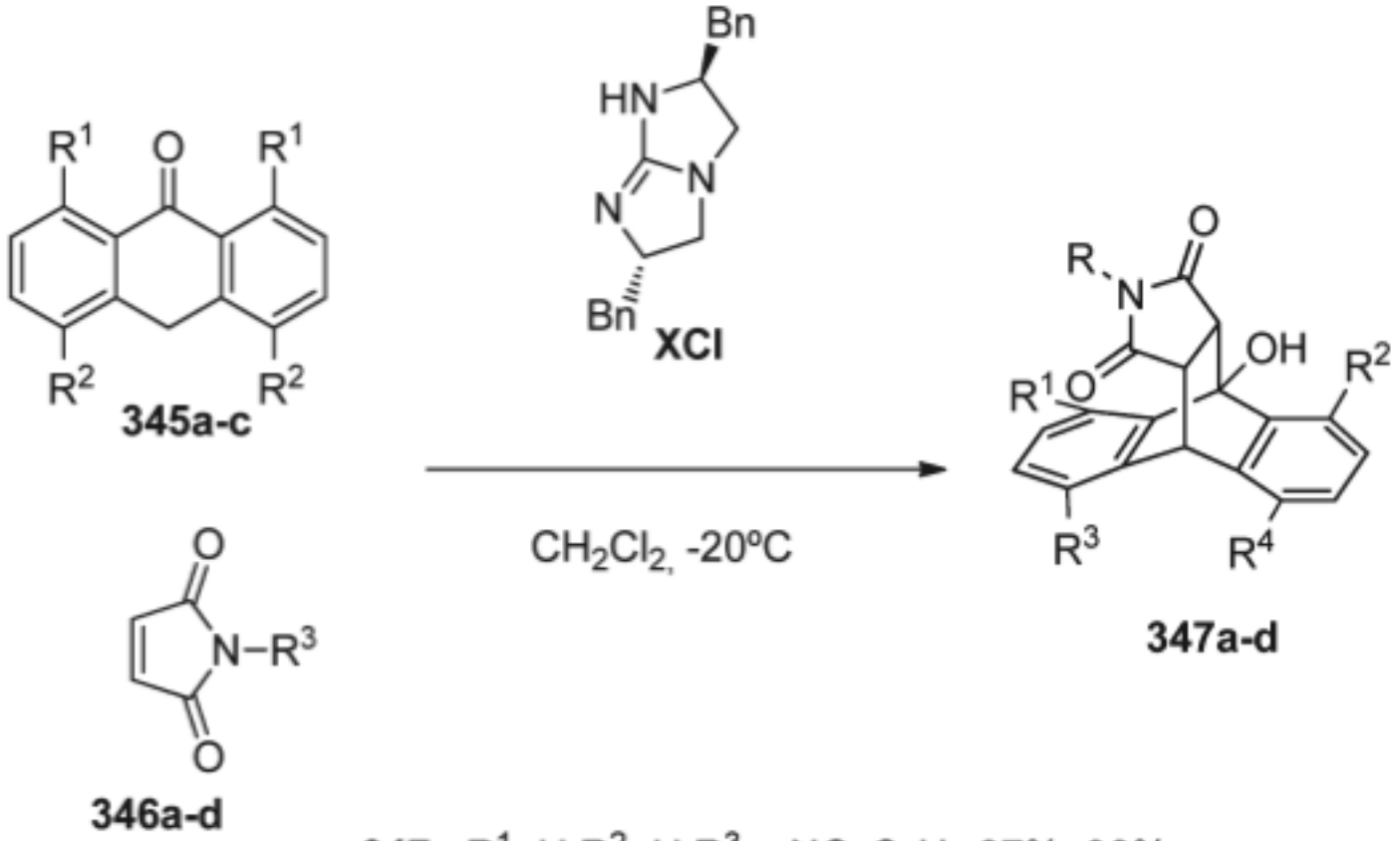
Bekele, T. *et al. JACS.* **2006,** *128,* 1810.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



344a R=Et 91%, 99% ee
344b R=Ph 90%; 90% ee
344c R=Bn 72%; 99% ee
344d R=*p*MeOC$_6$H$_4$ 58%; 99% ee

Diels-Alder Reaction: Brønsted Bases Ex. #3

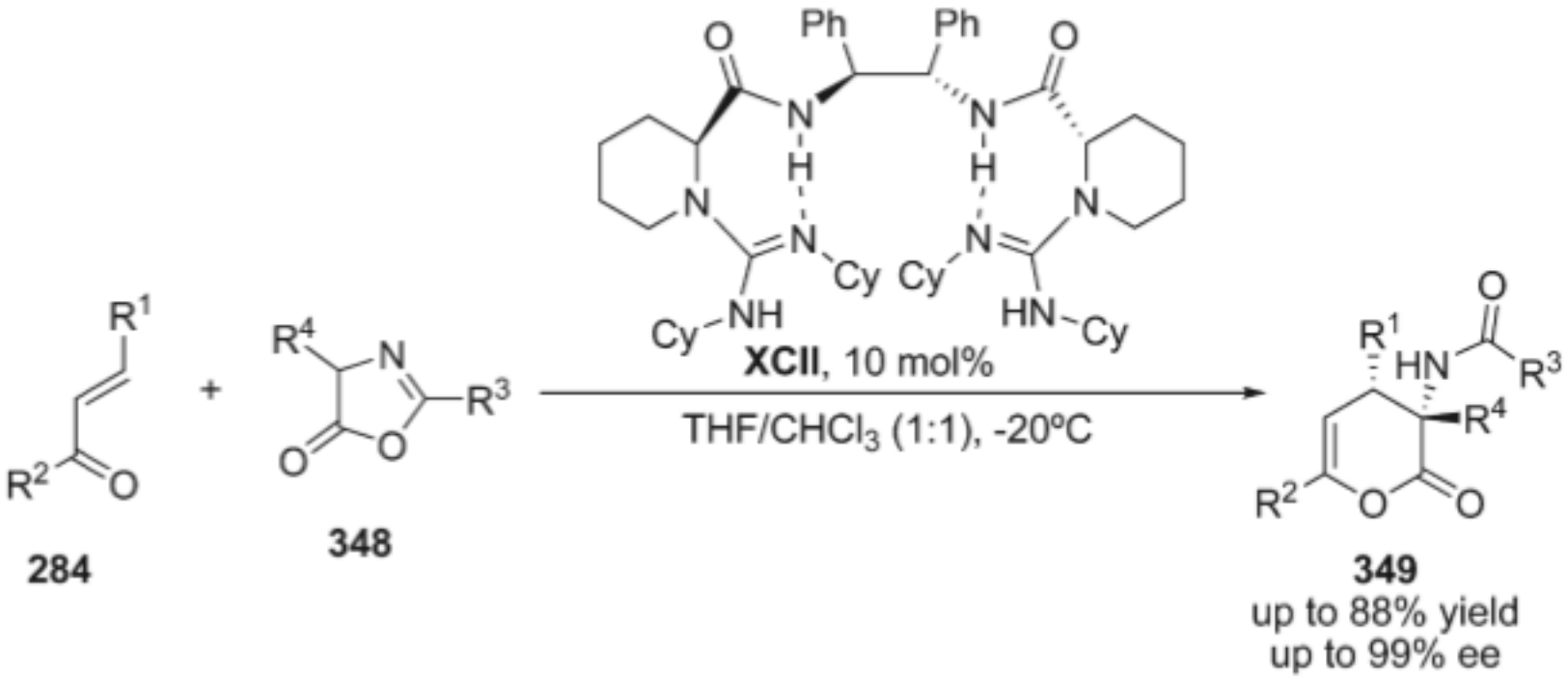
Leow, D. *et al. Chem. Asian J.* **2009,** *4,* 488.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



347a R^1=H R^2=H R^3=*p*$NO_2C_6H_4$ 87%; 98% ee
347b R^1=Cl R^2=H R^3=Bn 92%; 95% ee
347c R^1=H R^2=Cl R^3=Ph 92%; 99% ee
347d R^1=Cl R^2=H R^3=$MeCO_2$ 83%; 64% ee

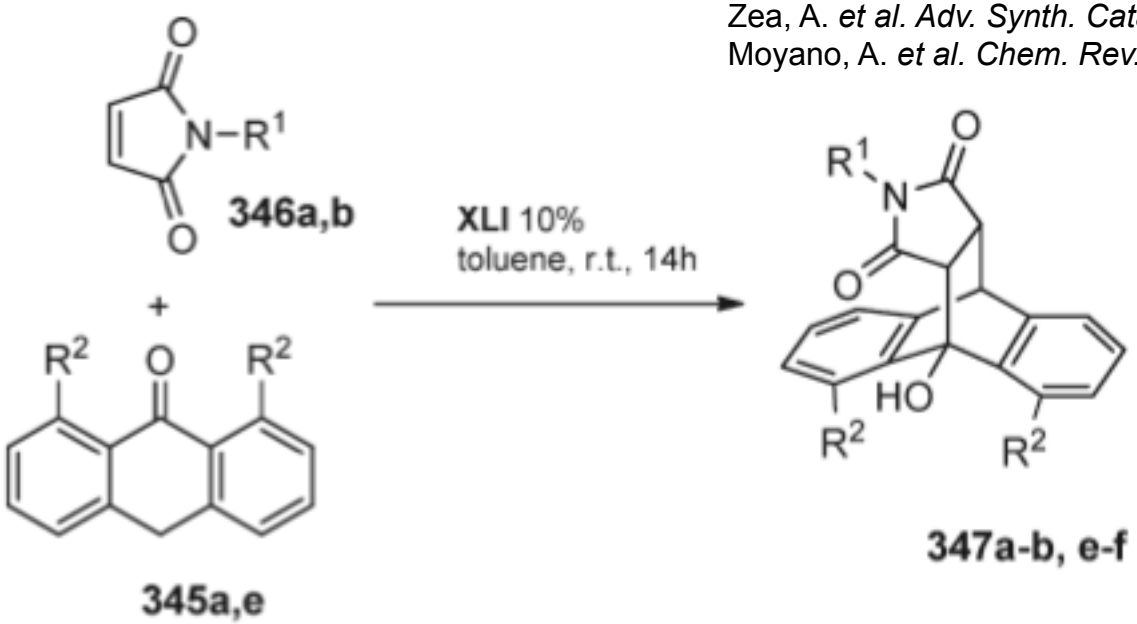
Diel.s-Alder Reaction: Brønsted Bases Ex. #4

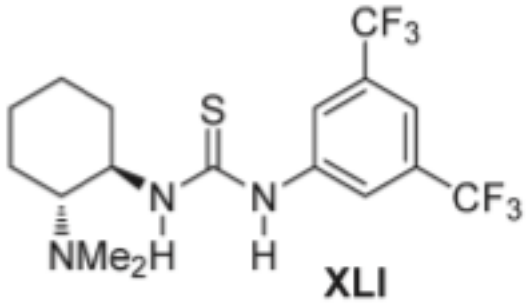
Dong, S. *et al. JACS.* **2010,** *132,* 10650.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



Diels-Alder Reaction: Organic Bifunctional Catalysts Ex. #1

Zea, A. *et al. Adv. Synth. Catal.* **2010,** *352,* 1102.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.

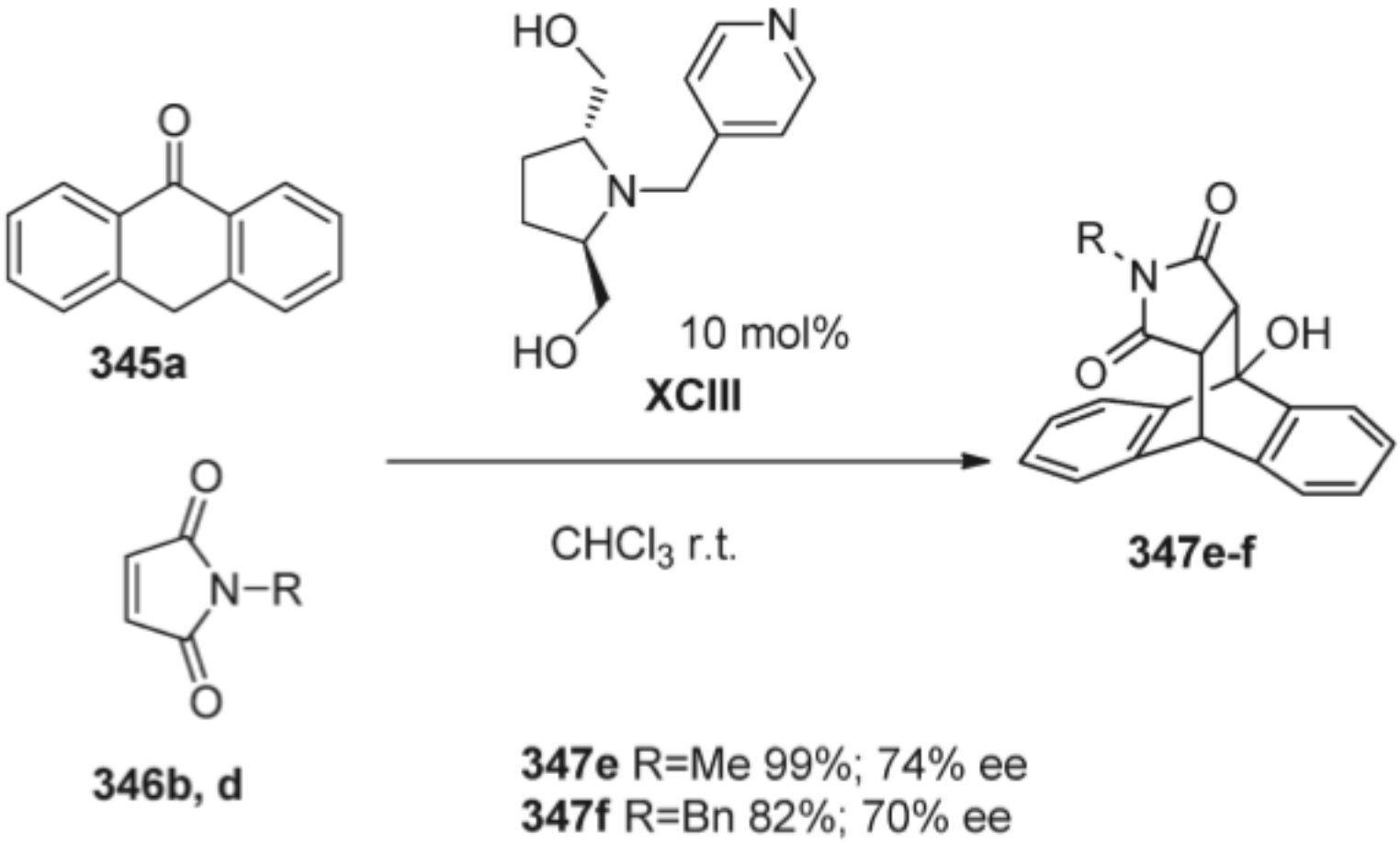




347a R^1=Ph R^2=H 91%; 90% ee
347b R^1=Bn R^2=H 92%; 83% ee
347e R1=Ph R^2=OH 93%; 99% ee
347f R^1=Bn R^2=OH 92%; 86% ee

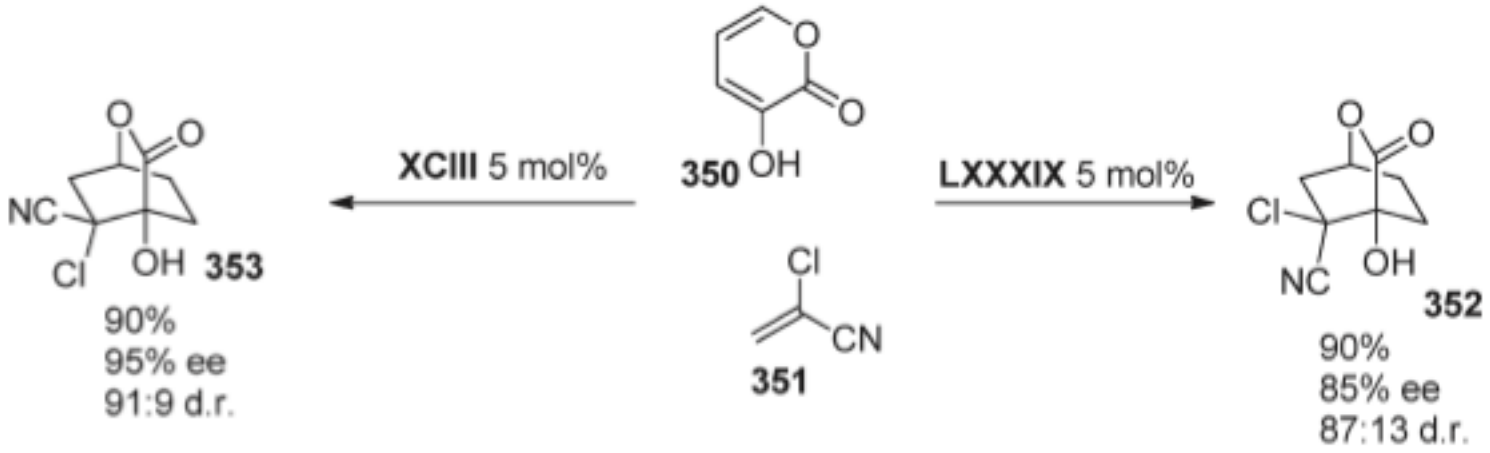
Diels-Alder Reaction: Organic Bifunctional Catalysts Ex. #1

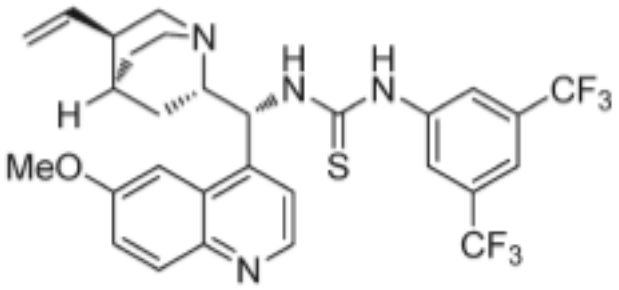
Uemae, K. *et al. J. Chem. Soc, Perkin Trans.* **2001,** 1002.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



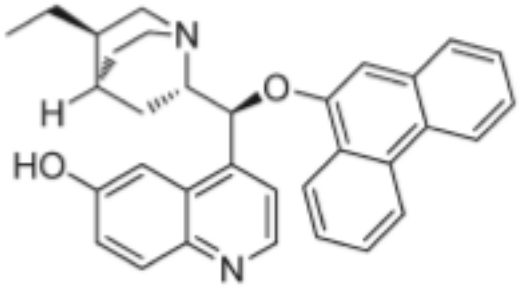
Diels-Alder Reaction: Organic Bifunctional Catalysts Ex. #2

Wang, Y. *et al. JACS.* **2007,** *129,* 6364.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.





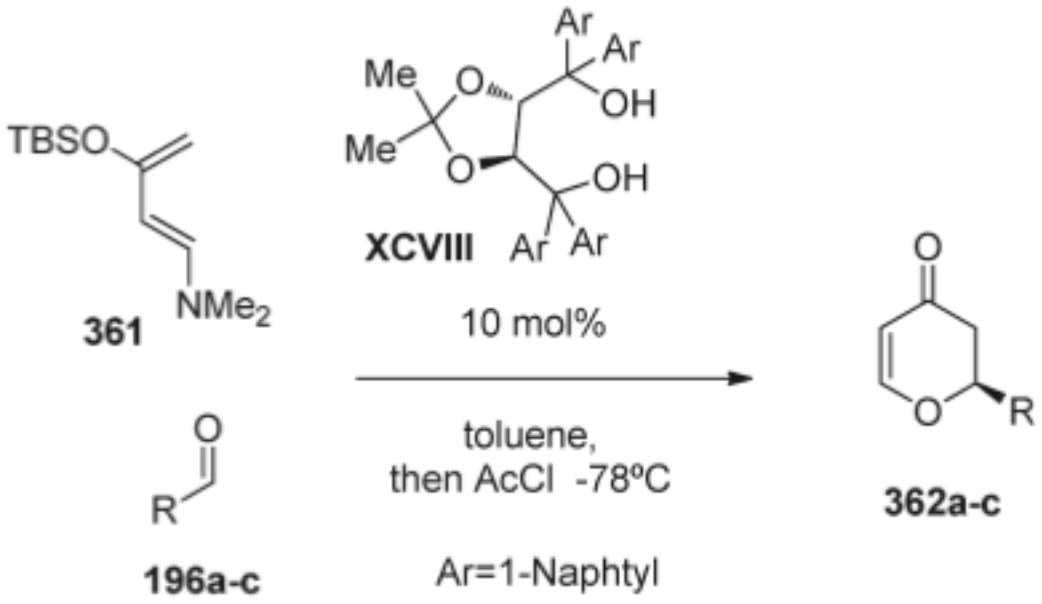
XCIII



LXXXIX

Diels-Alder Reaction: Organic Brønsted Acid Ex. #1

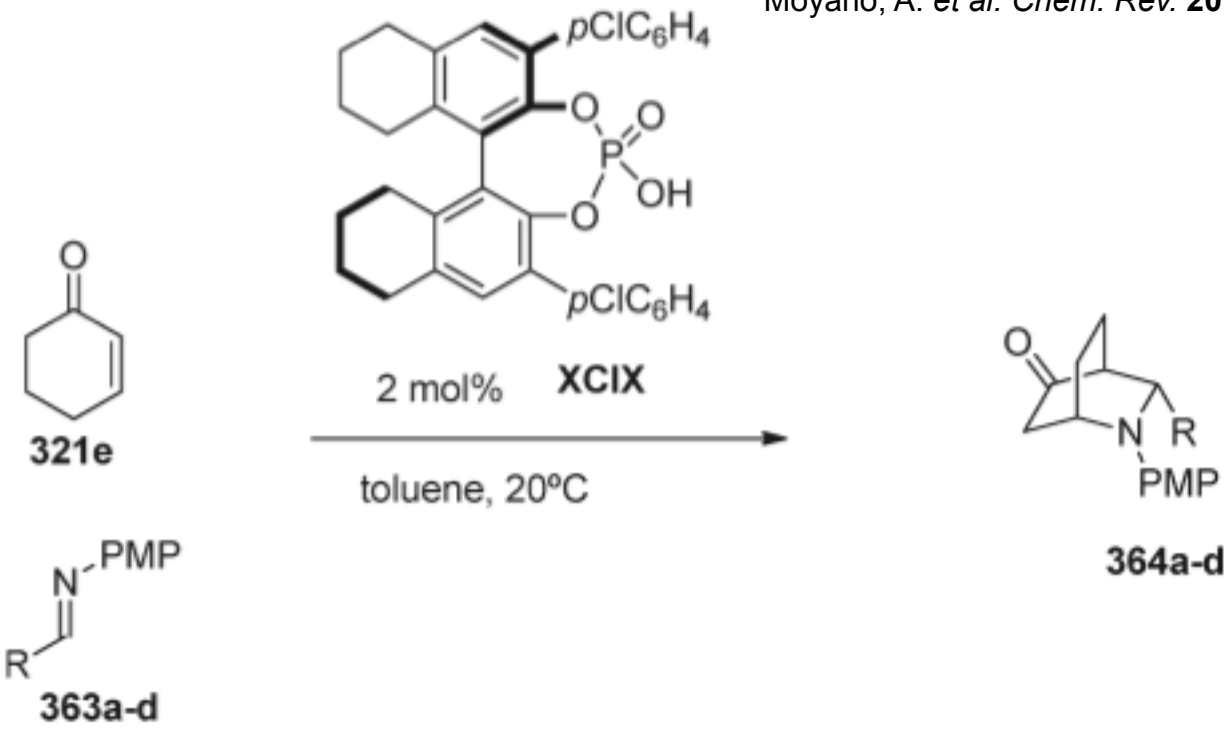
Huang, Y. *et al. Org. Lett.* **2003,** *42,* 146.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



362a R= Ph, 70%; 99% ee
362b R=2-furyl 67%; 92% ee
362c R=cyclohexyl 64%; 86% ee

Diels-Alder Reaction: Organic Brønsted Acid Ex. #2

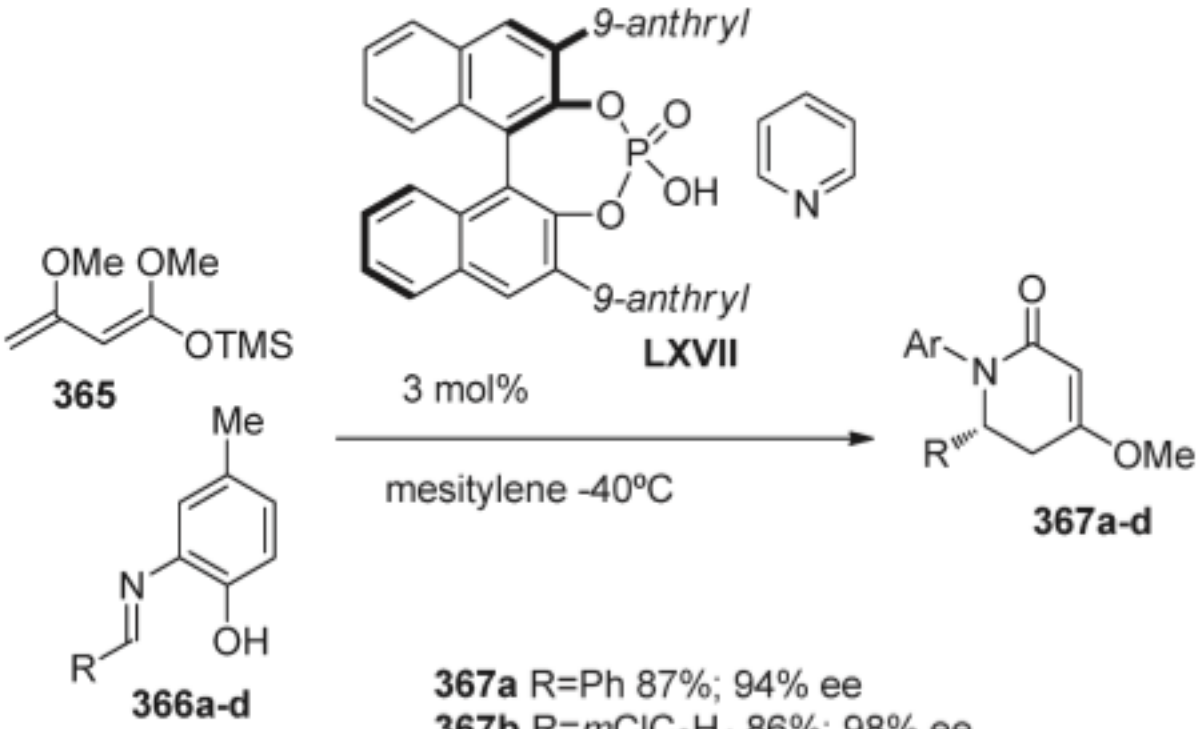
Liu, H. *et al. Org. Lett.* **2006,** *8,* 6023.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



364a R=Ph 76%; 84:16 endo:exo; 87% ee
364b R=*m*ClC_6H_4 73%; 81:19 endo:exo; 77% ee
364c R=*p*FC_6H_4 72%; 80:20 endo:exo; 85% ee
364d R=Tol 81%; 83:17 endo:exo; 83% ee

Diels-Alder Reaction: Organic Brønsted Acid Ex. #3

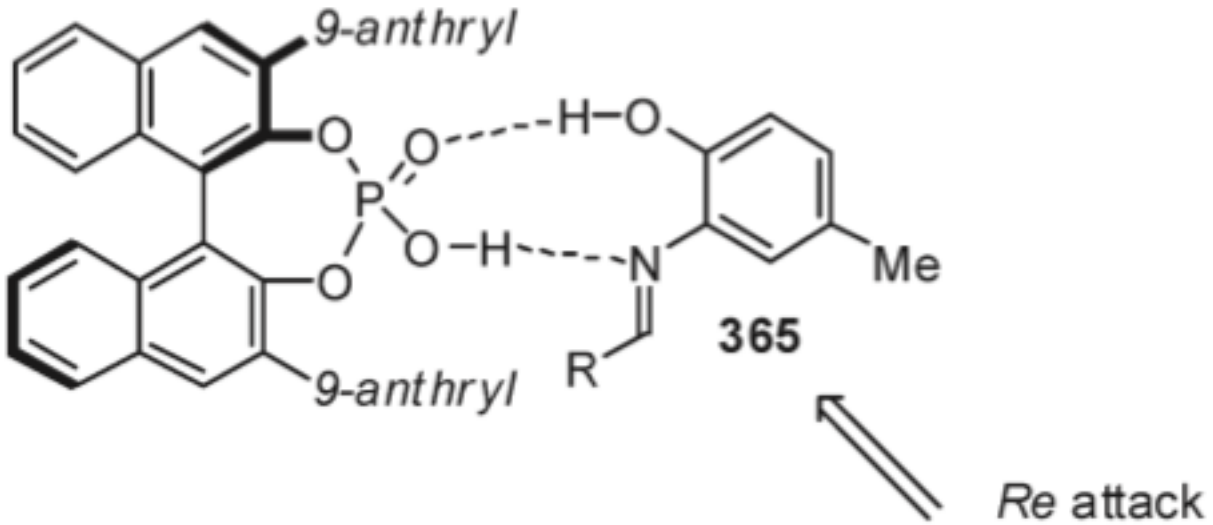
Itoh, J., *et al. Angew. Chem., Int. Ed.* **2006,** *45,* 4796.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



367a R=Ph 87%; 94% ee
367b R=*m*ClC$_6$H$_4$ 86%; 98% ee
367c R=*p*FC$_6$H$_4$ 76%; 98% ee
367d R=cyclohexyl 69%; 99% ee

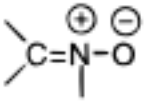
Diels-Alder Reaction: Organic Brønsted Acid Ex. #3

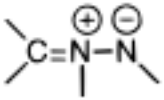
Itoh, J., *et al. Angew. Chem., Int. Ed.* **2006,** *45,* 4796.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.

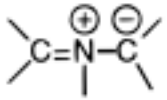


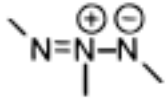
Allyl anion type

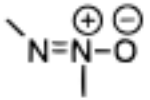
Nitrogen in the middle

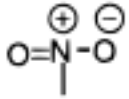

Nitrones


Azomethine Imines

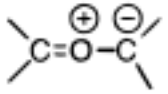

Azomethine Ylides

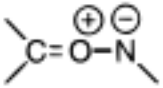

Azimines

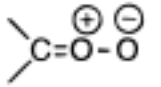

Azoxy Componds

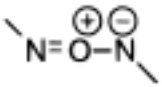

Nitro Compounds

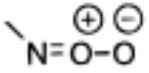
Oxygen in the middle

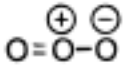

Carbonyl Ylides


Carbonyl Imines


Carbonyl Oxides

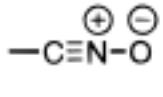

Nitrosimines

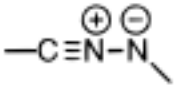

Nitrosoxides

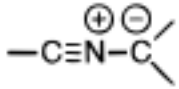

Ozone

Propargyl/allenyl anion type

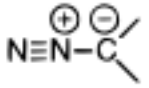
Nitrillium Betaines

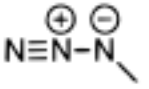

Nitrile Oxides

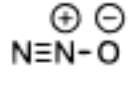

Nitrile Imines


Nitrile Yildes

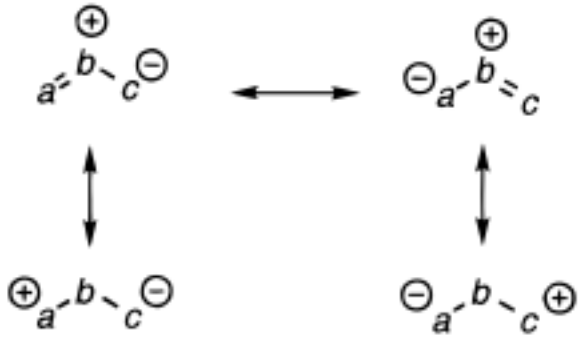
Diazonium Betaines


Diazoalkanes

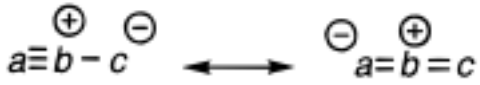

Azides


Nitrous Oxide

(A) Allyl anion type

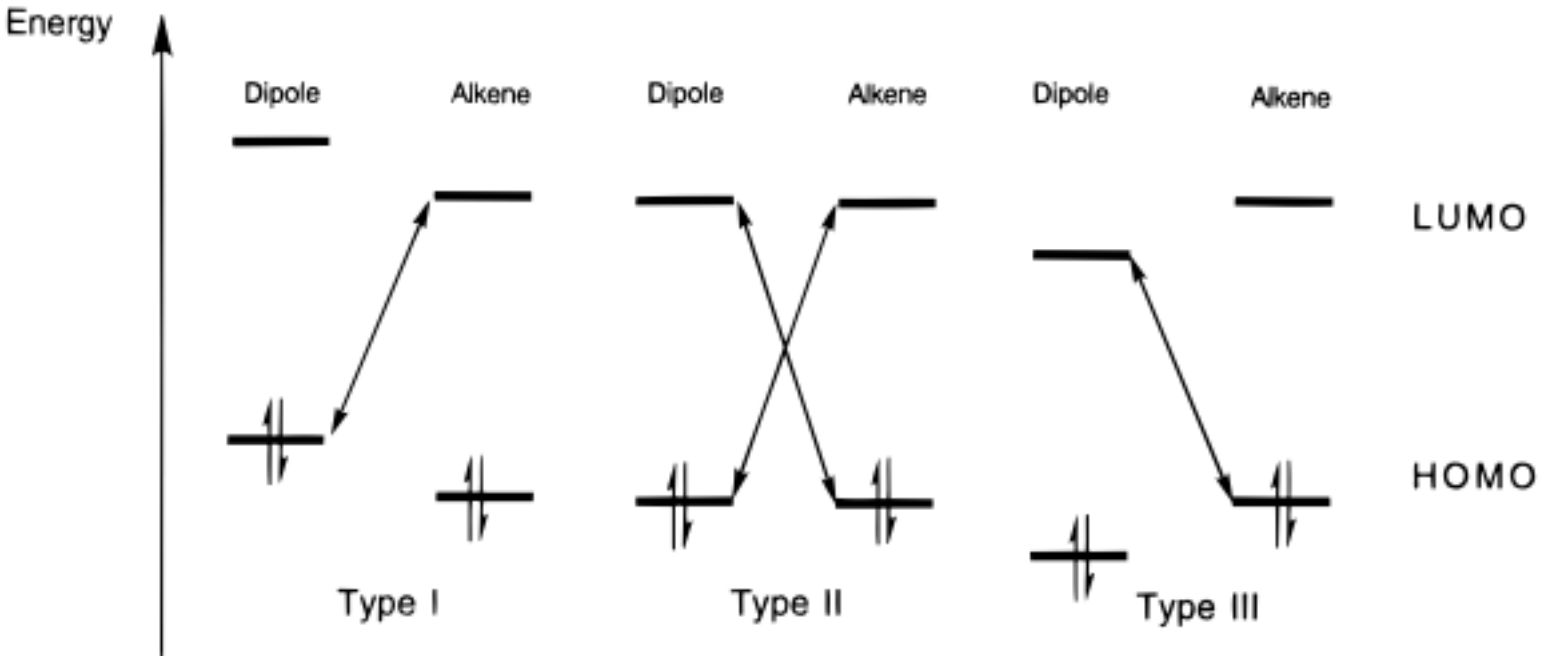


(B) Propargyl/allenyl anion type



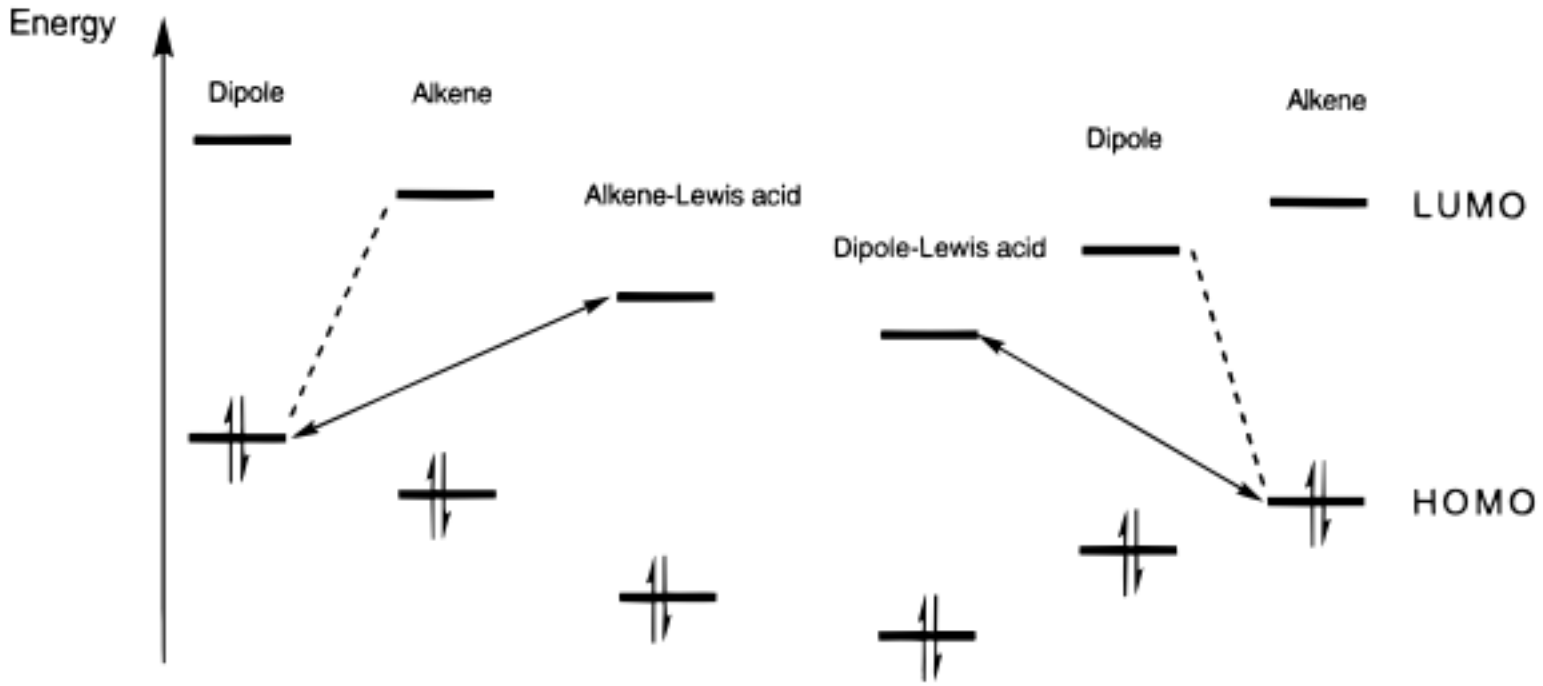
Gothelf, K. *et al. Chem. Rev.* **1998,** *98,* 863.

1,3 Dipolar Cycloaddition



Gothelf, K. *et al. Chem. Rev.* **1998,** *98,* 863.

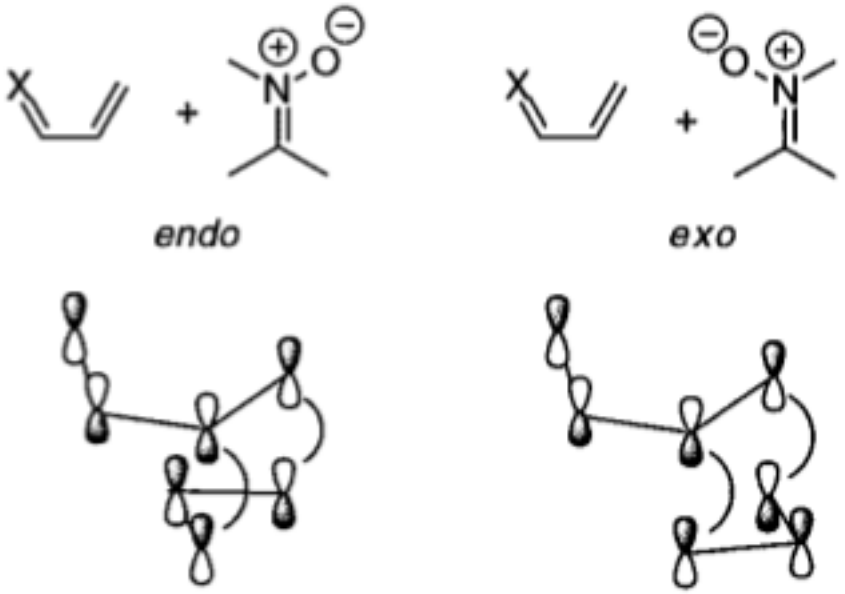
1,3 Dipolar Cycloaddition

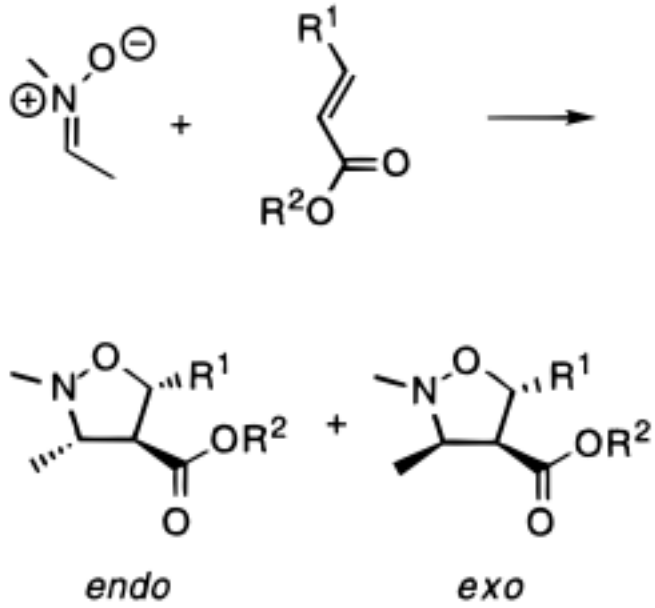


Gothelf, K. *et al. Chem. Rev.* **1998,** *98,* 863.

1,3 Dipolar Cycloaddition

Transition state for 1,3-dipolar cycloaddition





Gothelf, K. *et al. Chem. Rev.* **1998,** *98,* 863.

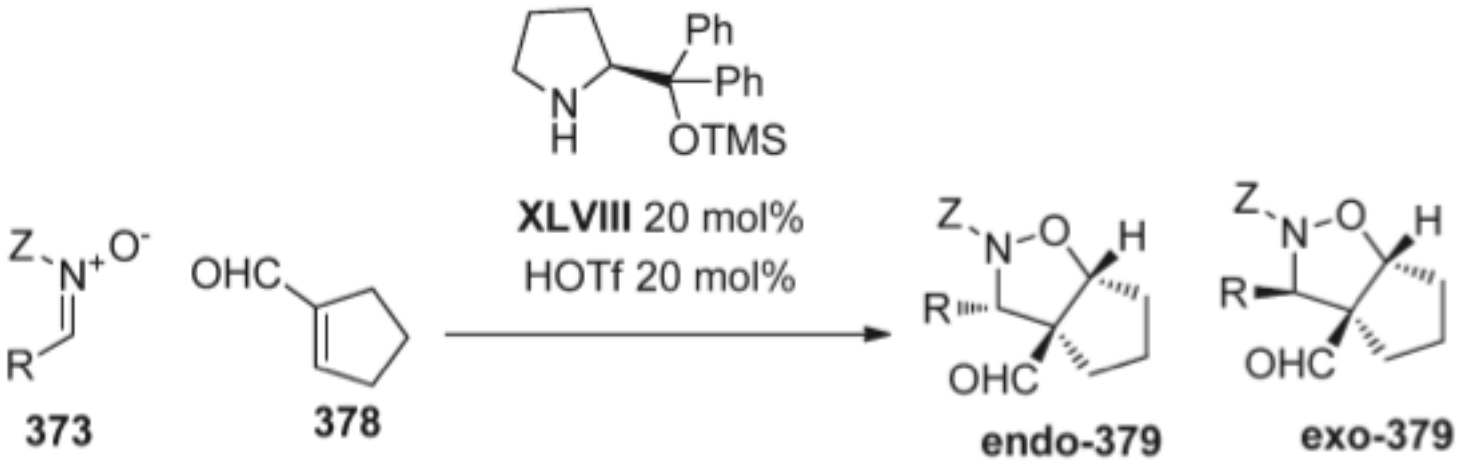
1,3 Dipolar Cycloaddition: Ex. #1

Jen, W.S. *et al. JACS.* **2000,** *122,* 9874.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.

374a Z=Bn R^1=Me R^2=Ph 98%; 94:6 endo:exo; 94% ee endo
374b Z=Allyl R^1=Me R^2=Ph 73%; 93:7 endo:exo; 98% ee endo
374c Z=Me R^1=Me R^2=Ph 66%; 95:5 endo:exo; 99% ee endo
374d Z=Bn R^1=Me R^2=cyclohexyl 70%; 99:1 endo:exo; 99% ee endo
374e Z=Bn R^1=H R^2=Ph 72%; 81:19 endo:exo; 90% ee endo

1,3 Dipolar Cycloaddition: Ex. #2

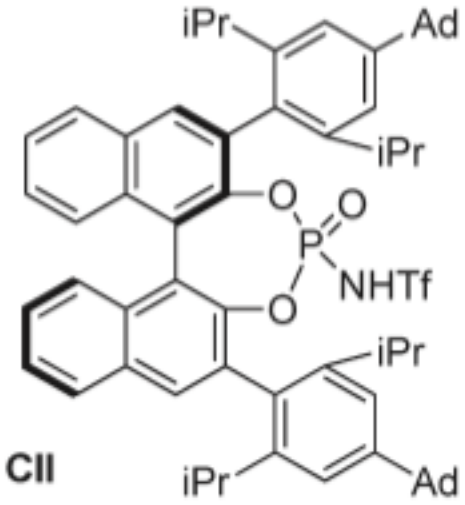
Chow, S.S. *et al. Tet. Lett.* **2006,** *48,* 277.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



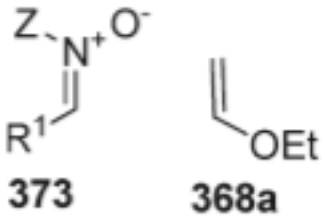
379a Z=Bn R=Ph 66%; 80:20 endo:exo 46% ee
379b Z=Me R=Ph 75%; 79:21 endo:exo 83% ee
379c Z=Bn R=Naph 75%; 90:10 endo:exo 37% ee

1,3 Dipolar Cycloaddition: Ex. #3

Diao, P. *et al. Angew. Chem., Int. Ed.* **2008,** *47,* 5168.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



CII

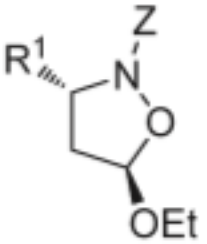


373

368a

5 mol%

$CHCl_3$, -40°C

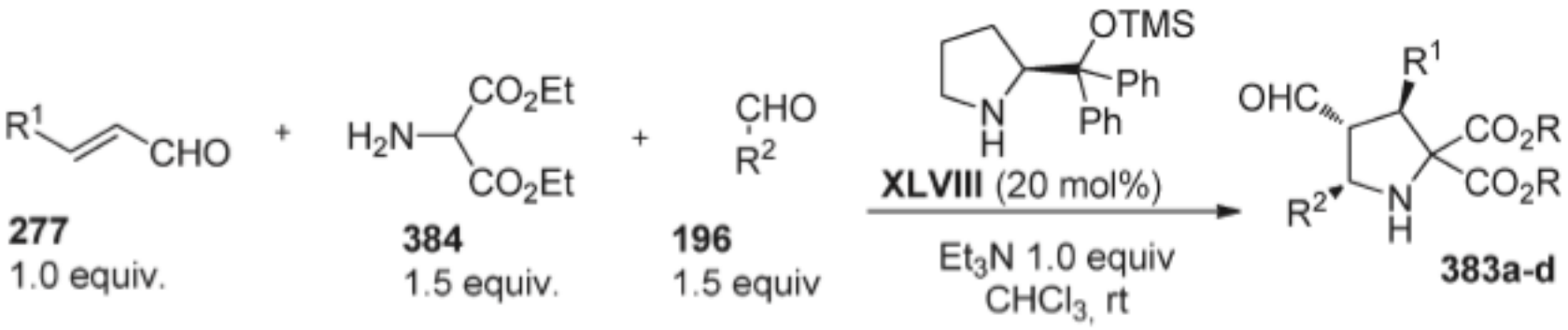


381a-d

381a Z=Ph R^1=Ph 85%; 96:4 endo:exo; 70% ee
381b Z=*p*FPh R^1=*p*FPh 76%; 87:13 endo:exo 85% ee
381c Z=*p*FPh R^1=2-furyl 90%; 88:12 endo:exo 87% ee
381d Z=*p*FC_6H_4 R^1=2-thienyl 97%; 93:7 endo:exo 87% ee

1,3 Dipolar Cycloaddition: Ex. #4

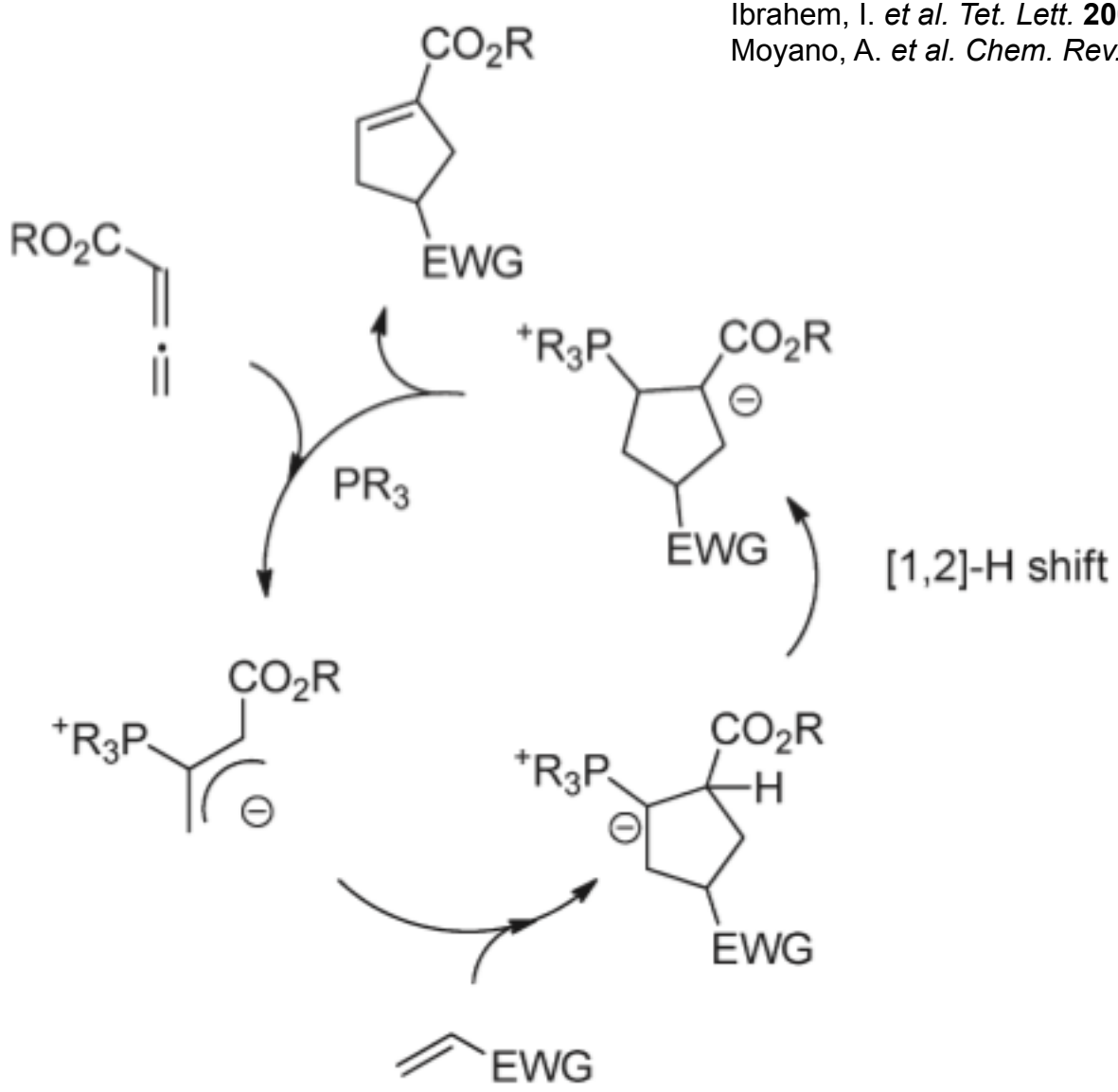
Ibrahem, I. *et al. Tet. Lett.* **2007,** *48,* 6252.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



383a R^1=Ph R^2=Ph 63% 10: d.r.; 95% ee
383b R^1=*n*-Bu R^2=Ph 51% 10: d.r.; 95% ee
383c R^1=n-Pr R^2=*p*BrC_6H_4 57% 5: d.r.; 98% ee
383d R^1=Et R^2=*p*ClC_6H_4 55% 5: d.r.; 92% ee

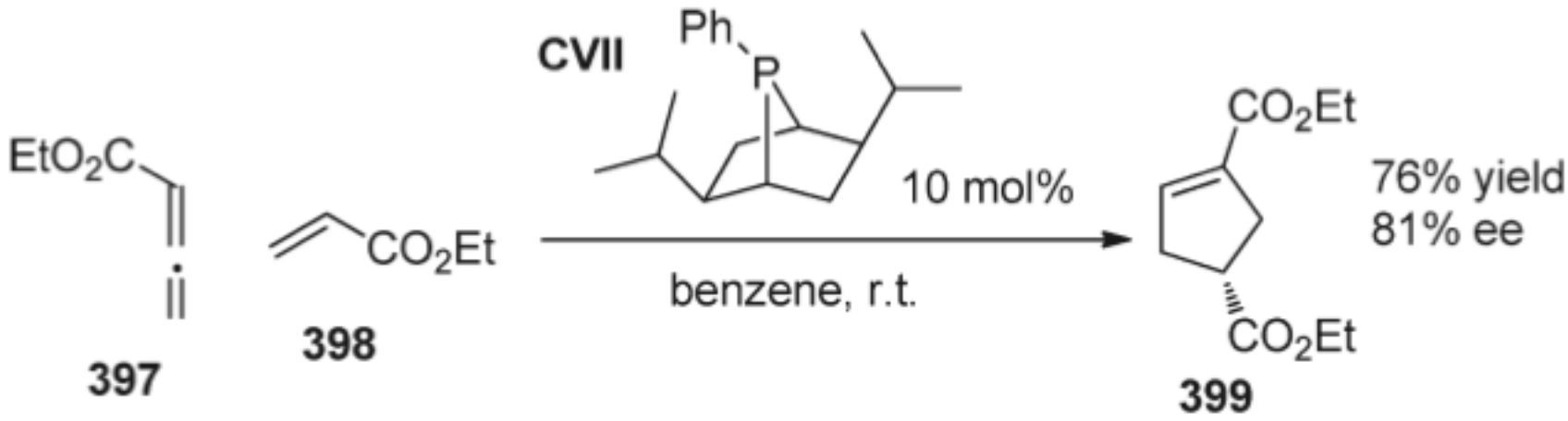
1,3 Dipolar Cycloaddition: Ex. #5

Ibrahem, I. *et al. Tet. Lett.* **2007,** *48,* 6252.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



1,3 Dipolar Cycloaddition: Ex. #5

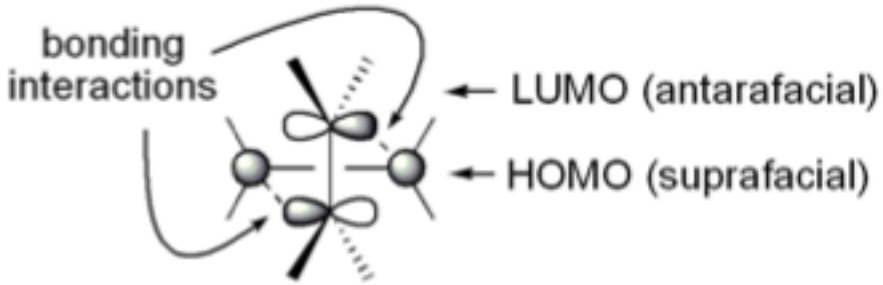
Zhu, G. *et al. JACS.* **1997,** *119,* 3836.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



[2+2] Cycloaddition

[2 + 2] Cycloaddition (4π e^-)

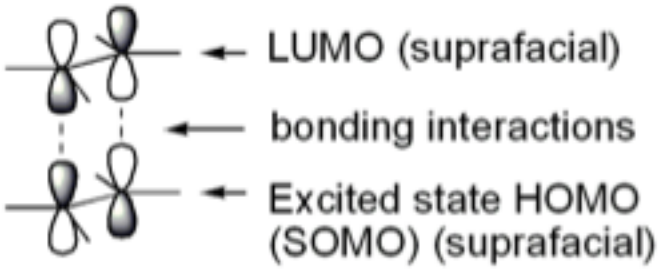
Ground State (thermal)



$[\pi 2_a + \pi 2_s]$ cycloaddition

- Antarafacial with respect to one olefin and suprafacial with respect to the second: dicates perpendicular approach to permit bonding.

Excited State ($h\nu$)



$[\pi 2_s + \pi 2_s]$ cycloaddition

- Suprafacial with respect to both olefins: dictates parallel (stacked) approach to permit bonding.

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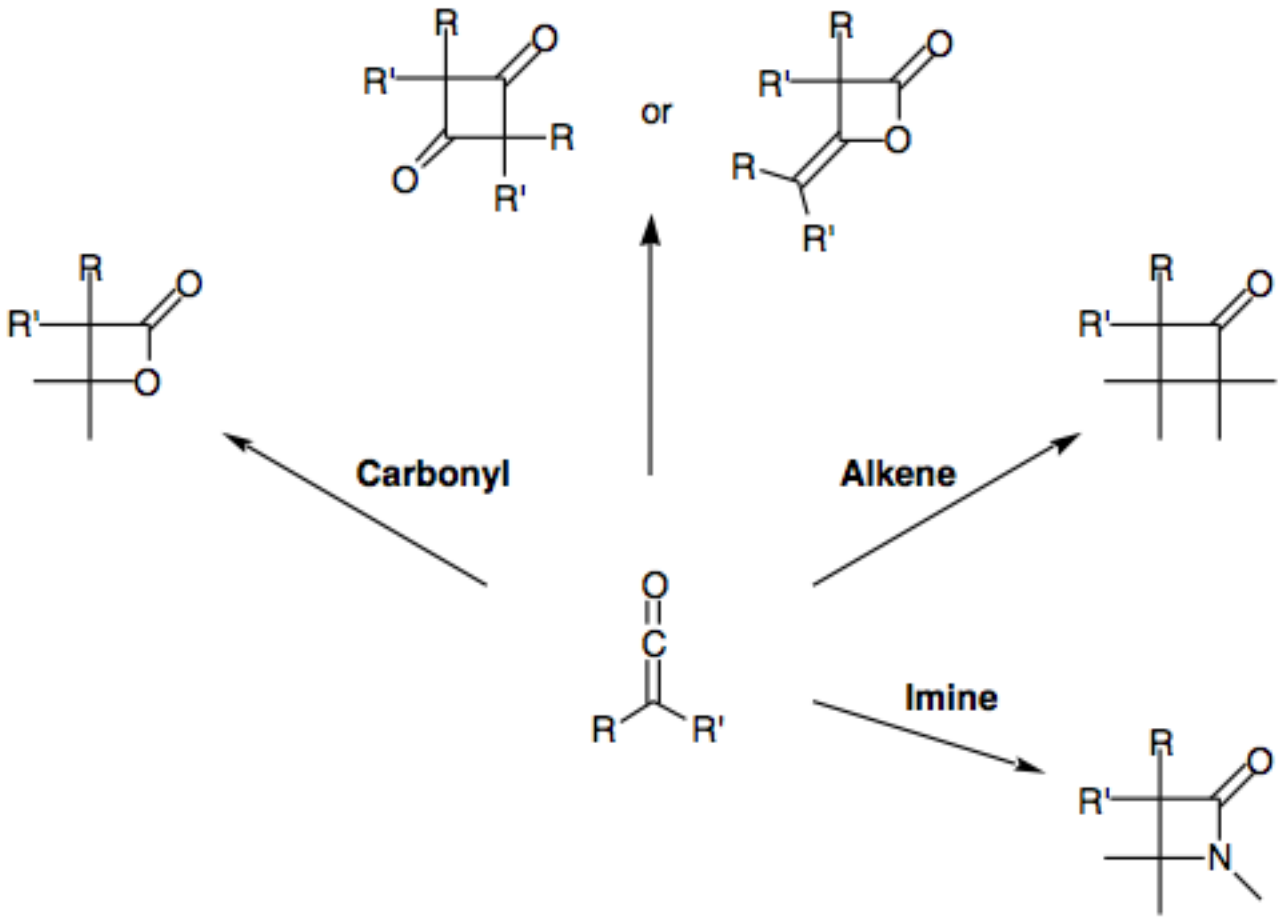
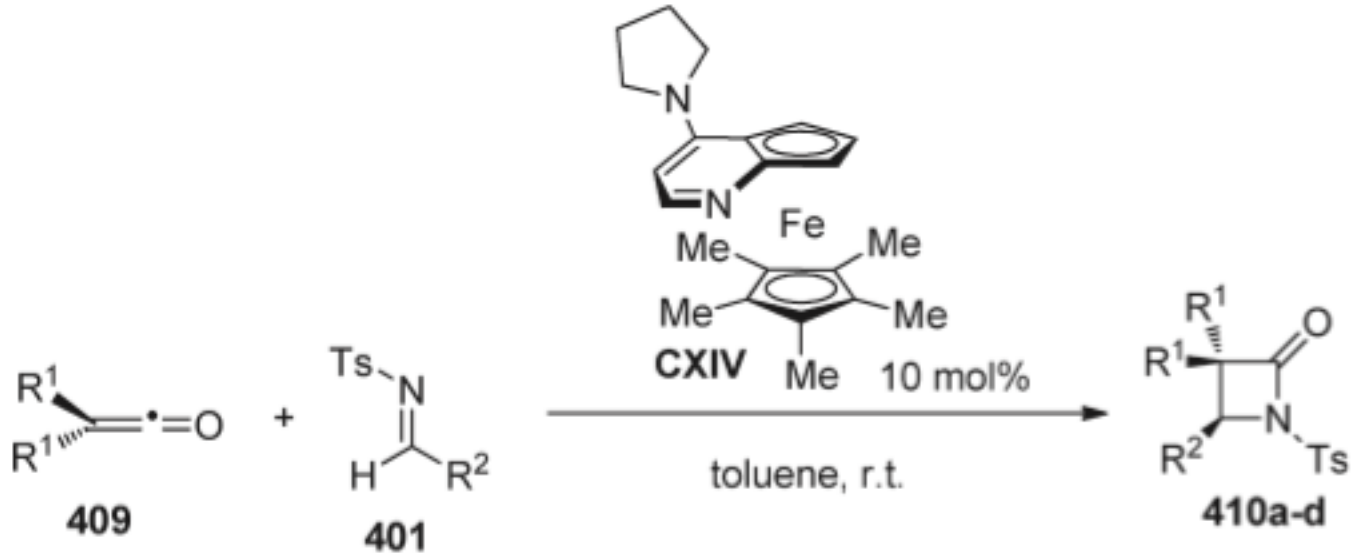
[2+2] Cycloaddition

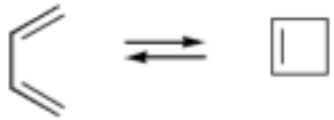
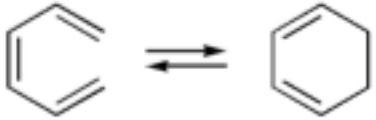
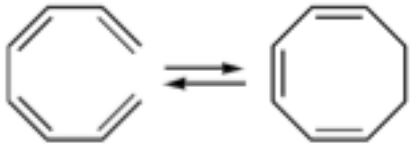
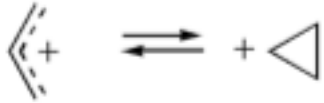
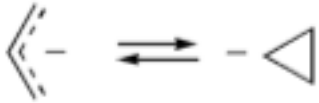
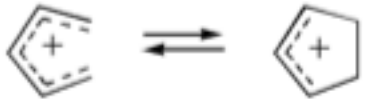
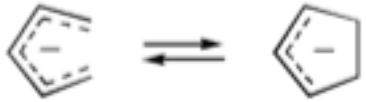


[2+2] Cycloaddition: Ex #1

Hodous, B. L. *et al. JACS.* **2002,** *124,* 1578.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703.



410a R^1=-$(CH_2)_5$- R^2=Ph 81%; 84% ee
410b R^1=-$(CH_2)_5$- R^2=furyl 92%; 90% ee
410c R^1=-$(CH_2)_5$- R^2=cyclopropyl 94%; 89% ee
410d R^1=Et R^2=furyl 92%; 93% ee

System	π electrons	Thermal Reaction Ground State (HOMO)	hν Reaction Excited State (LUMO)
	4 π e⁻	conrotatory	disrotatory
	6 π e⁻	disrotatory	conrotatory
	8 π e⁻	conrotatory	disrotatory
	2 π e⁻	disrotatory	conrotatory
	4 π e⁻	conrotatory	disrotatory
	4 π e⁻	conrotatory	disrotatory
	6 π e⁻	disrotatory	conrotatory

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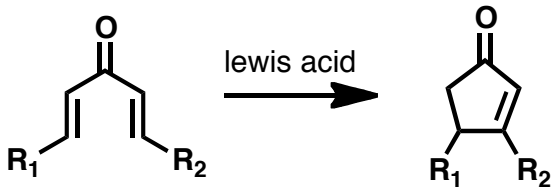
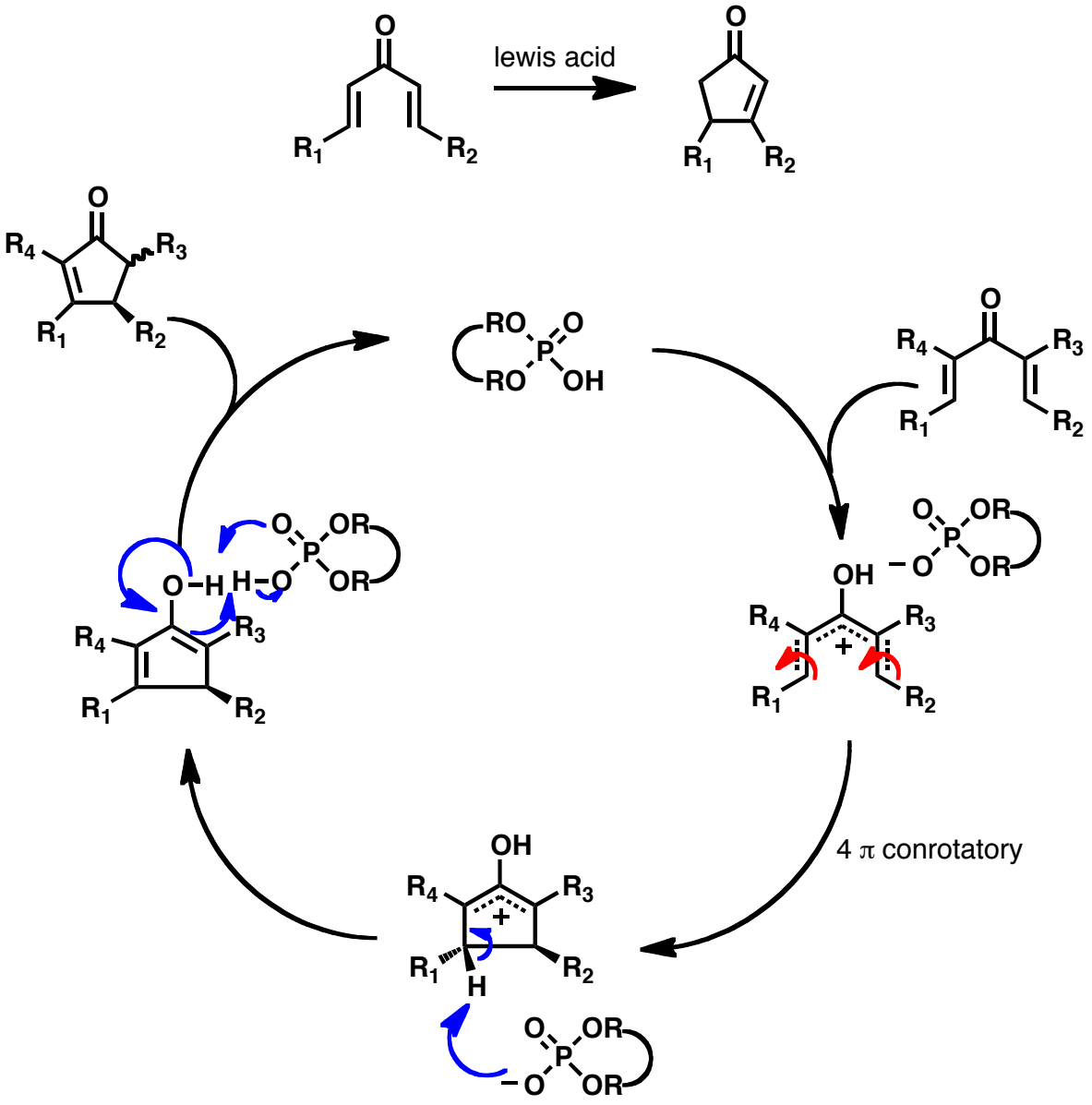
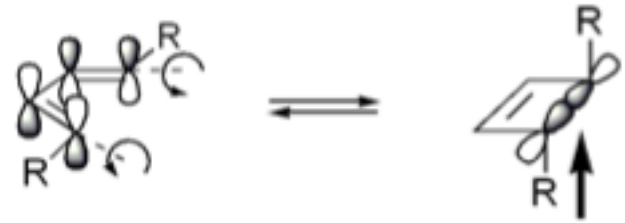
Nazarov Cyclization



Nazarov Cyclization

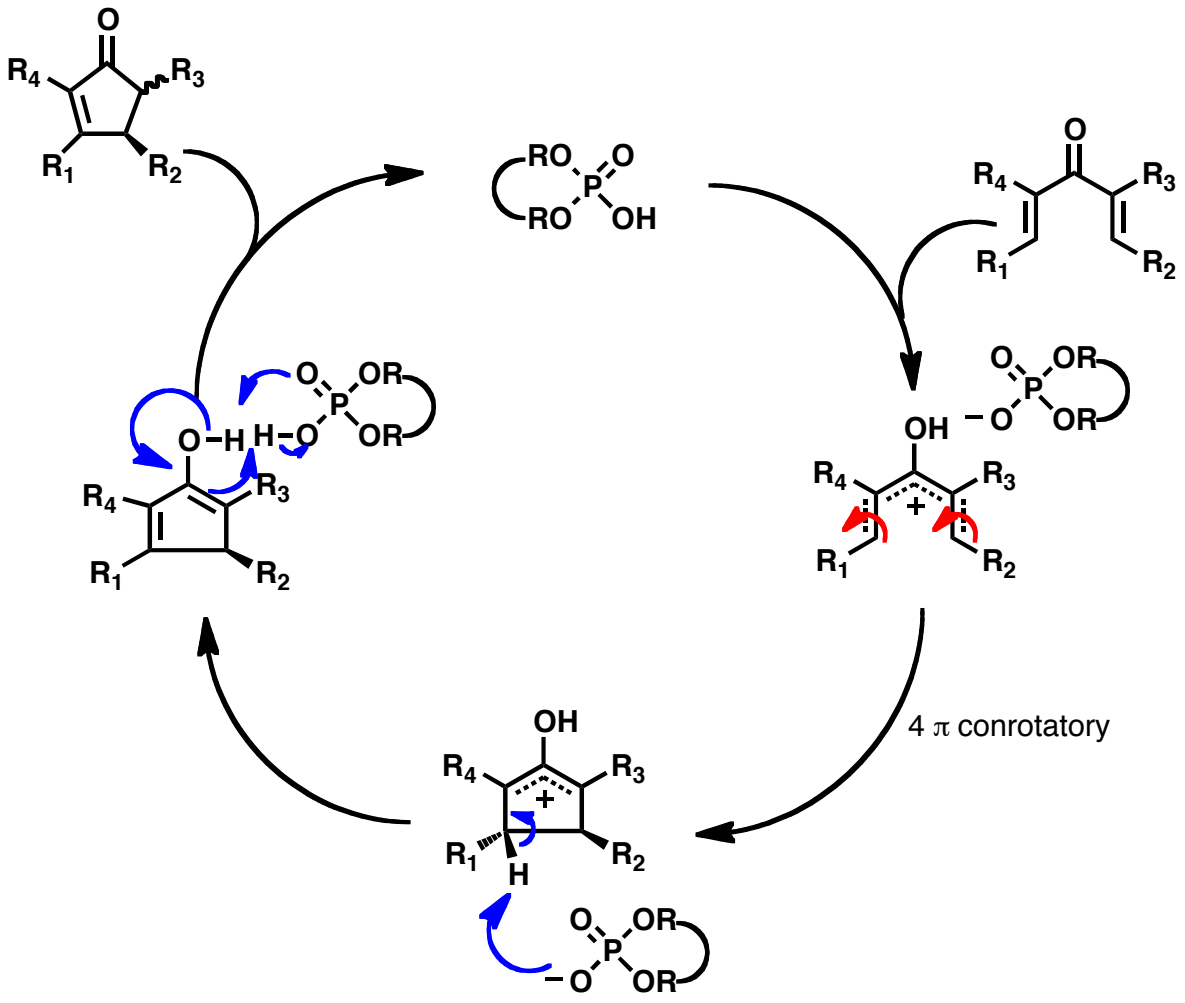


4 π e⁻ thermal reaction (ground state, HOMO)

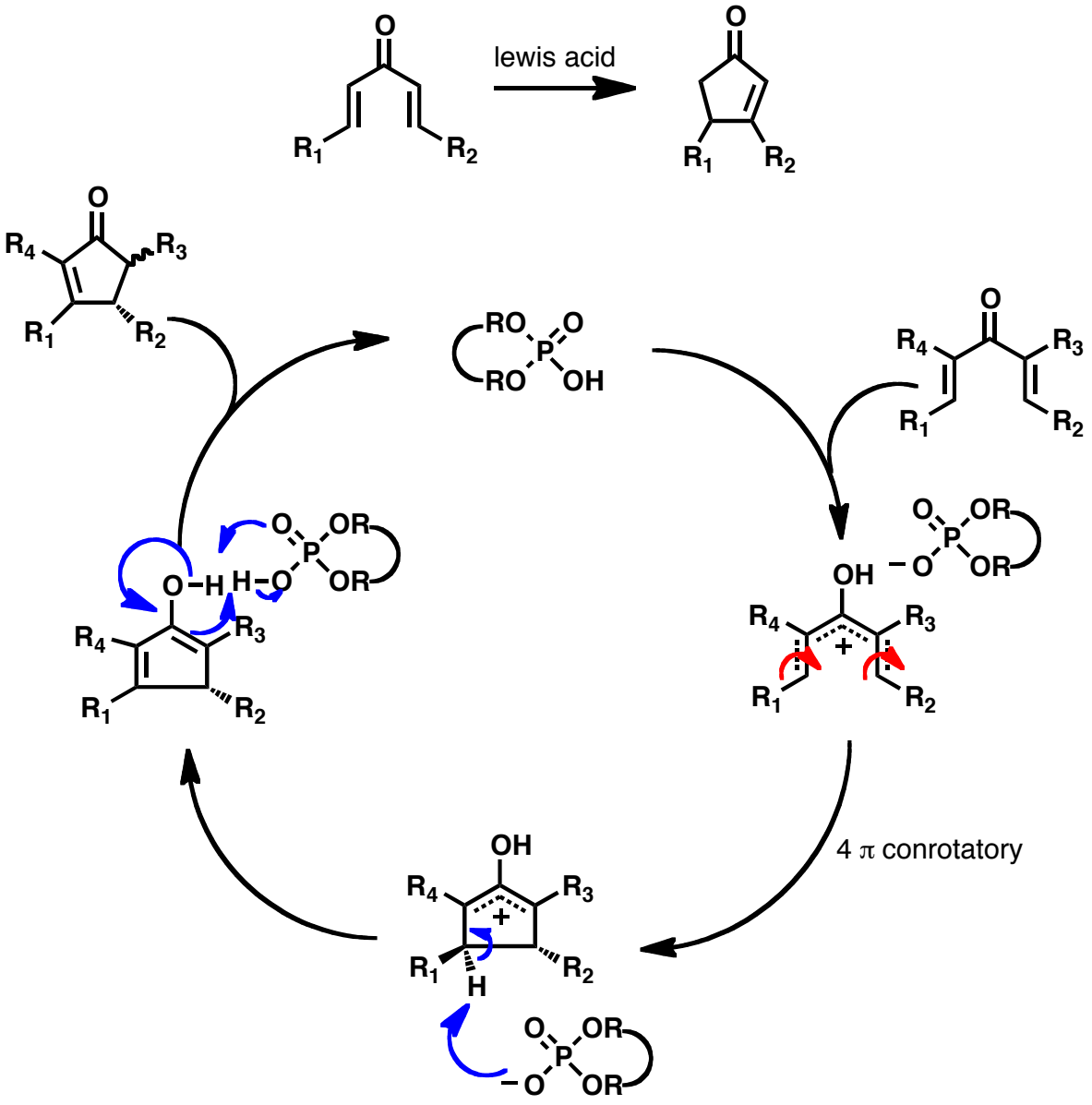


conrotatory movement ⟶ bonding interaction

- Stereochemistry dictated by the orbital symmetry allowed reaction course

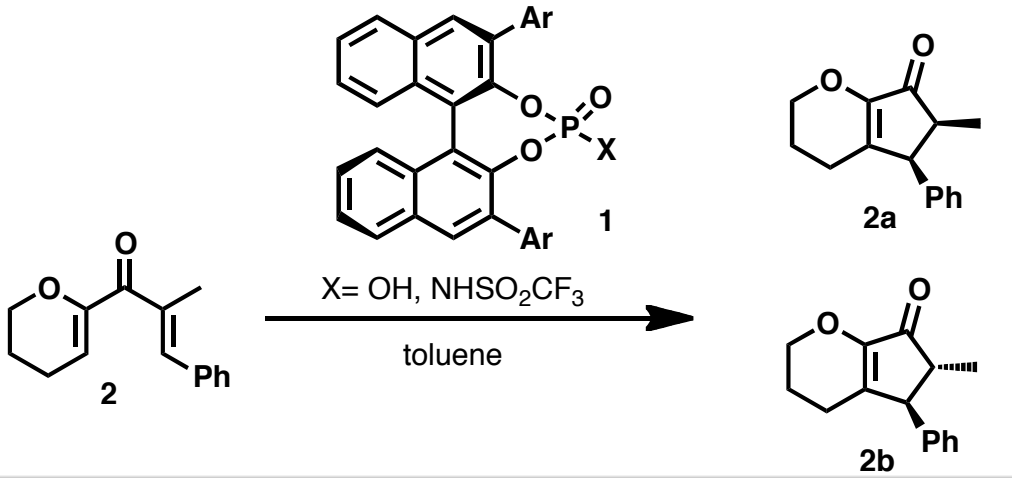


Nazarov Cyclization



Nazarov Cyclization: Ex. #1

Table 1: Evaluation of Brønsted acids **1a–1g** in the enantioselective Nazarov cyclization.[a]



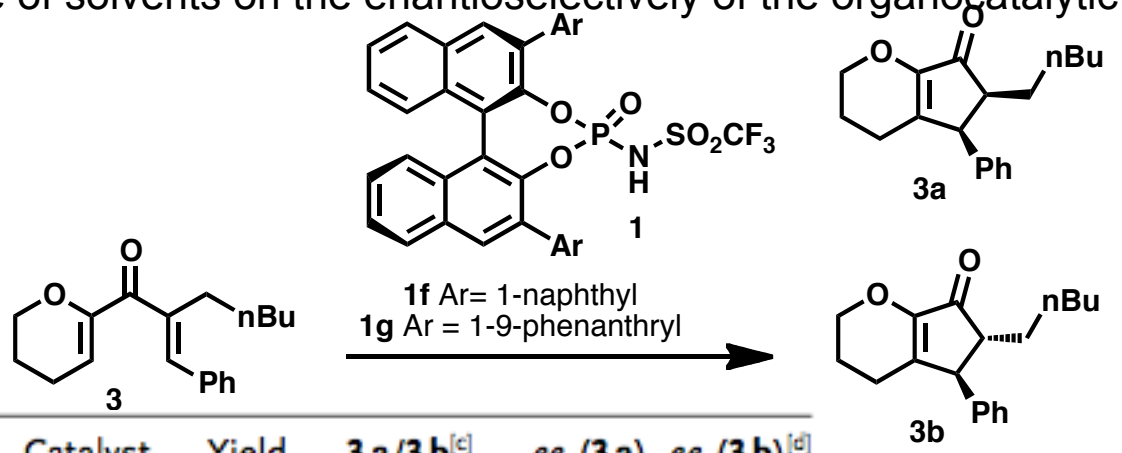
Entry	Ar	X	**2a/2b**[b]	*ee* (**2a**), *ee* (**2b**)[c]
1	phenyl (**1a**)	OH	1.5:1	64, 8
2	1-naphthyl (**1b**)	OH	2.3:1	81, 55
3	9-anthracenyl (**1c**)	OH	3.4:1	82, 60
4	4-biphenyl (**1d**)	OH	1:1.5	73, 22
5	2-naphthyl (**1e**)	OH	1:1	54, 9
6	1-naphthyl (**1f**)	$NHSO_2CF_3$[d]	5.2:1	83, 96
7	9-phenanthryl (**1g**)	$NHSO_2CF_3$[d]	7:1	86, 94

[a] Reaction conditions: **2**, 10 mol % 1, in toluene at 60 ˚C.
[b] Determined by 1H NMR spectroscopy and HPLC analysis.
[c] Enantiomeric excess (in %) determined by HPLC analysis (Chiralcel OD-H column).
[d] Reactions at 0 ˚C, 10 min.

Rueping, M. *et al. Angew. Chem. Int. Ed.* **2007,** *46,* 2097-2100.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703-4832.

Nazarov Cyclization: Ex. #1

Table 2: Influence of solvents on the enantioselectively of the organocatalytic Nazarov Reaction



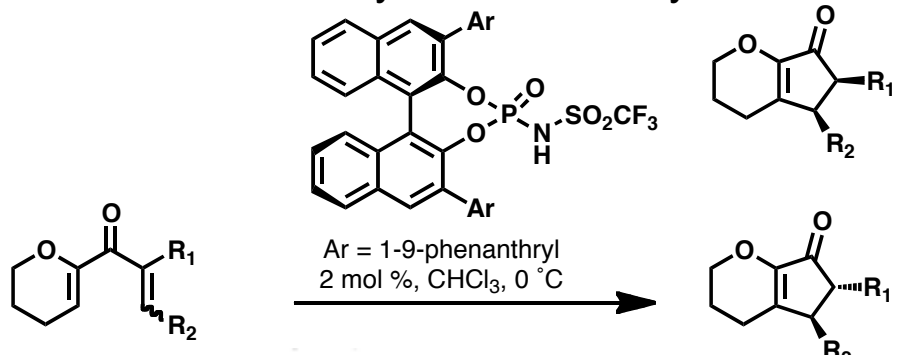
Entry[a]	Solvent	Catalyst	Yield [%][b]	3a/3b[c]	*ee* (3a), *ee* (3b)[d]
1	toluene[e]	**1f**	90	1.8:1	69, 80
2	toluene	**1f**	90	3.8:1	75, 81
3	benzene	**1f**	67	4.4:1	72, 75
4	$PhCF_3$	**1f**	65	2:1	67, 71
5	CH_3CN	**1f**	–	–	–
6	THF	**1f**	–	–	–
7	DCE	**1f**	53	1.9:1	51, 68
8	CH_2Cl_2	**1f**	77	2.1:1	68, 81
9	$CHCl_3$	**1f**	86	2:1	89, 95
10	$CHCl_3$	**1g**	95	3.5:1	90, 93
11	$CHCl_3$	**1g**[f]	85	2.9:1	89, 89
12	$CHCl_3$	**1g**[f,g]	78	3.2:1	91, 91

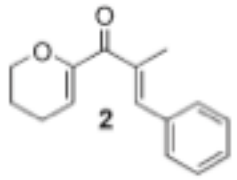
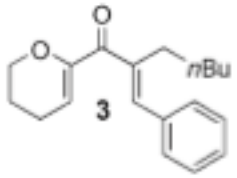
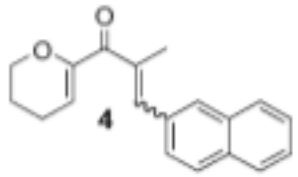
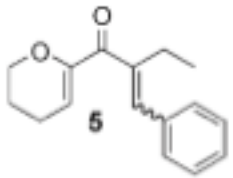
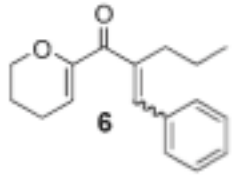
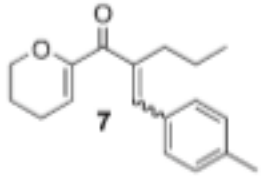
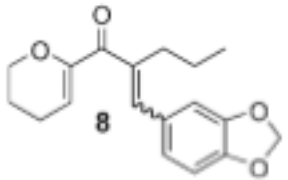
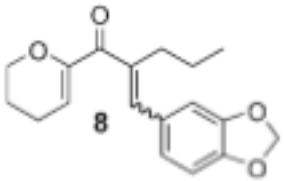
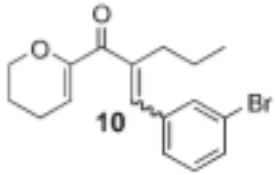
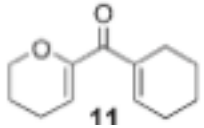
[a] Reaction conditions : 3, 10 mol % 1 in 2 mL solvent at 0 8C.
[b] Yields of isolated product after chromatography.
[c] Determined by 1H NMR spectroscopy.
[d] Determined by HPLC analysis (ee value in %).
[e] Reactions at room temperature.
[f] 2 mol % catalyst.
[g] In 1 mL CHCl3. DCE = 1,2-dichloroethane.

Rueping, M. *et al. Angew. Chem. Int. Ed.* **2007,** *46,* 2097-2100. Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703-4832.

Nazarov Cyclization: Ex, #1

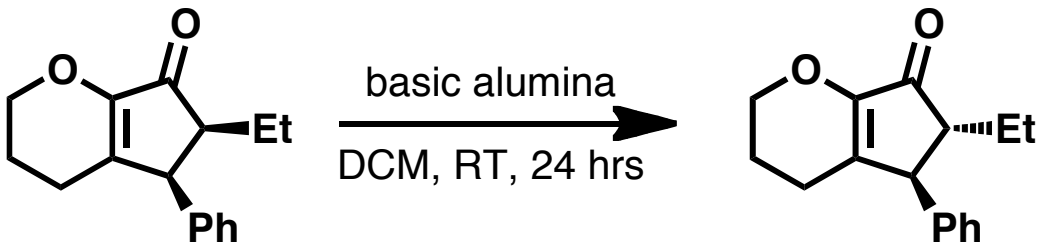
Table 3: Scope of the enantioselective Bronsted acid catalyzed Nazarov cyclization



Entry[a]	Substrate	t [h]	Yield [%][b]	*cis*/*trans*[c]	*ee* (*cis*), *ee* (*trans*)[d]
1		2	88	6:1	87, 95
2		1	78	3.2:1	91, 91
3		2	92	9.3:1	88, 98
4		2	61	4.3:1	92, 96
5		1	85	3.2:1	93, 91
6		1	77	2.6:1	91, 90
7		1	83	1.5:1	87, 92
8		1.5	87	4.6:1	92, 92
9		2	72	3.7:1	90, 91
10		4.5	68	*cis*	86, –

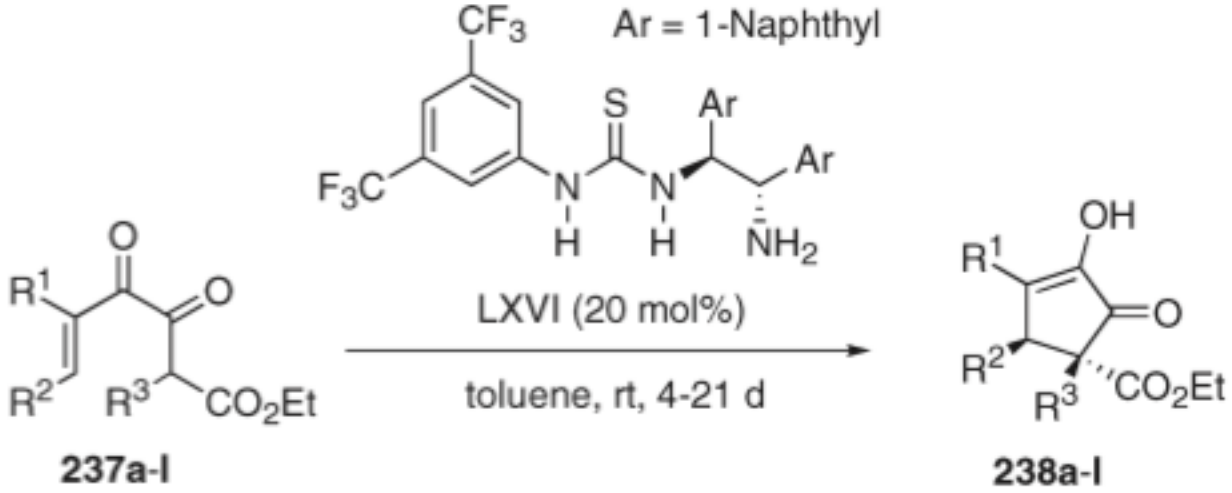
Rueping, M. *et al. Angew. Chem. Int. Ed.* **2007,** *46,* 2097-2100.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703-4832.

Nazarov Cyclization: Ex #1

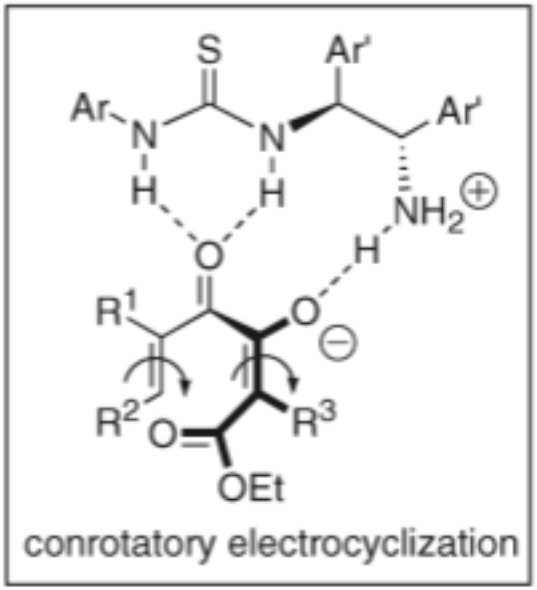


Rueping, M. *et al. Angew. Chem. Int. Ed.* **2007,** *46,* 2097-2100.
Moyano, A. *et al. Chem. Rev.* **2011,** *111,* 4703-4832.

Nazarov Cyclization: Ex #2



237a-l **238a-l**

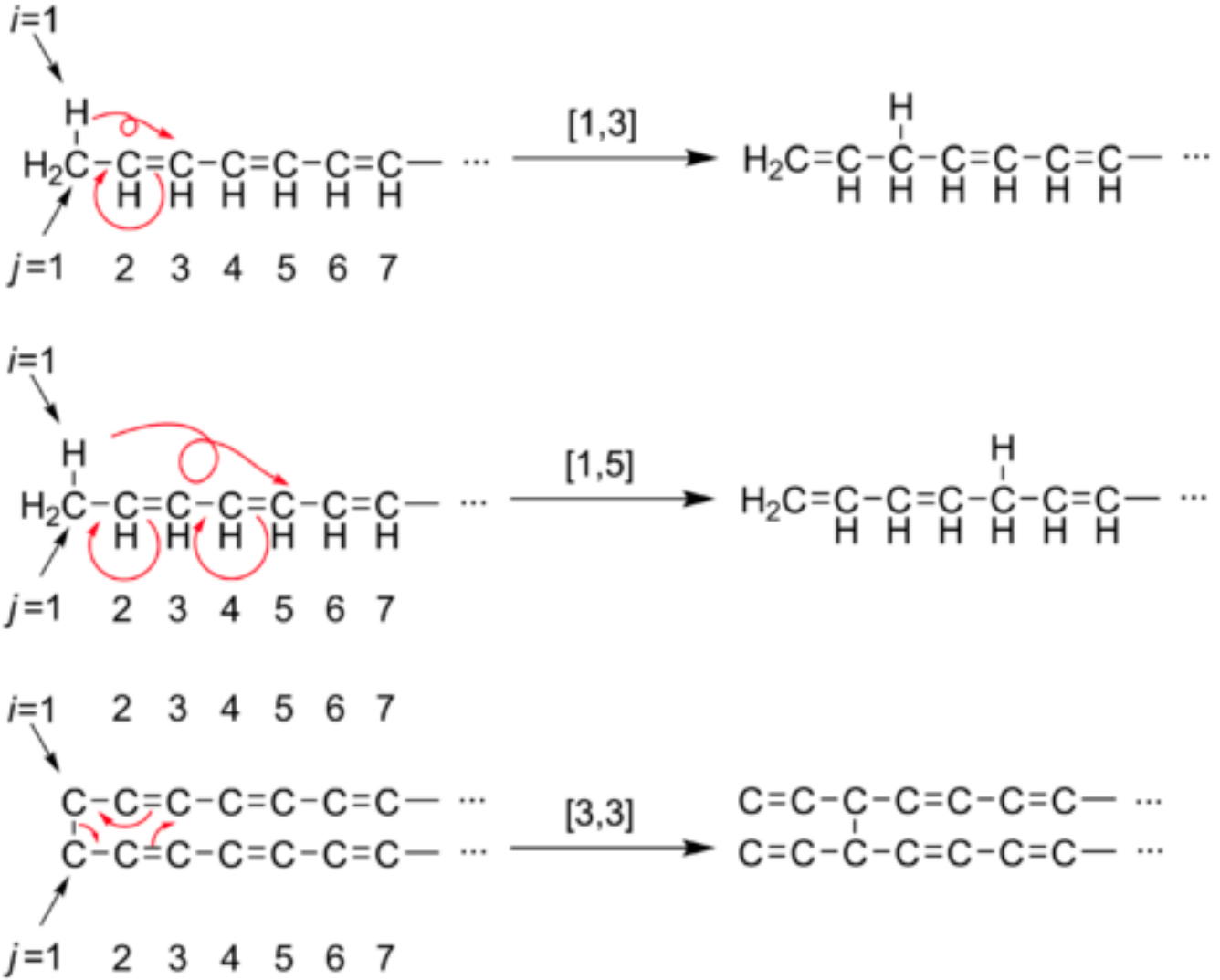


238a (R^1 = Me, R^2 = Ph, R^3 = Me): 67%, 81% ee
238b (R^1 = Me, R^2 = Ph, R^3 = Et): 65%, 90% ee
238c (R^1 = Me, R^2 = *p*-MeOPh, R^3 = Et): 60%, 91% ee
238d (R^1 = Me, R^2 = *p*-ClPh, R^3 = Et): 42%, 84% ee
238e (R^1 = Me, R^2 = 3,4-(OCH_2O)Ph, R^3 = Et): 58%, 89% ee
238f (R^1 = Ph, R^2 = Ph, R^3 = Et): 70%, 82% ee
238g (R^1 = Me, R^2 = Ph, R^3 = Ph): 70%, 87% ee
238h (R^1 = Me, R^2 = *p*-Tol, R^3 = Ph): 87%, 96% ee
238i (R^1 = Me, R^2 = *p*-ClPh, R^3 = Ph): 75%,85% ee
238j (R^1 = Me, R^2 = 3,4-(OCH_2O)Ph, R^3 = Ph): 95%, 85% ee
238k (R^1 = Me, R^2 = 2-Furyl, R^3 = Ph): 60%,91% ee
238l (R^1 = Et, R^2 = *p*-Tol, R^3 = Ph): 85%, 82% ee
238m (R^1 = OEt, R^2 = Ph, R^3 = Ph): 60%, 80% ee

Basak, A. K. *et al. JACS* **2010,** *132,* 8266.

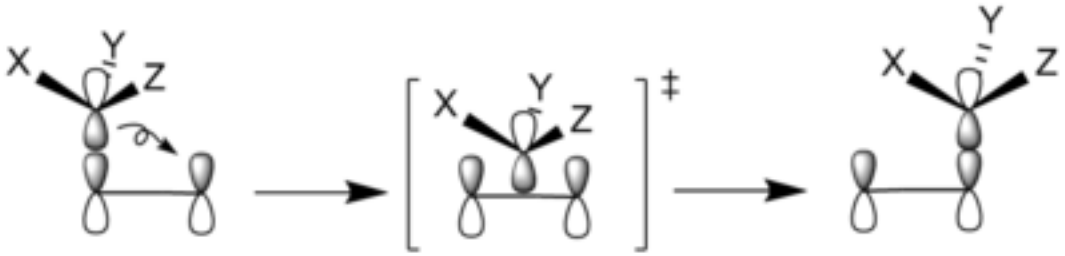
Sigmatropic Rearrangement

One σ-bond is changed to another in an intramolecular process, where a substituent moves from one part of a π-bonded system to another part

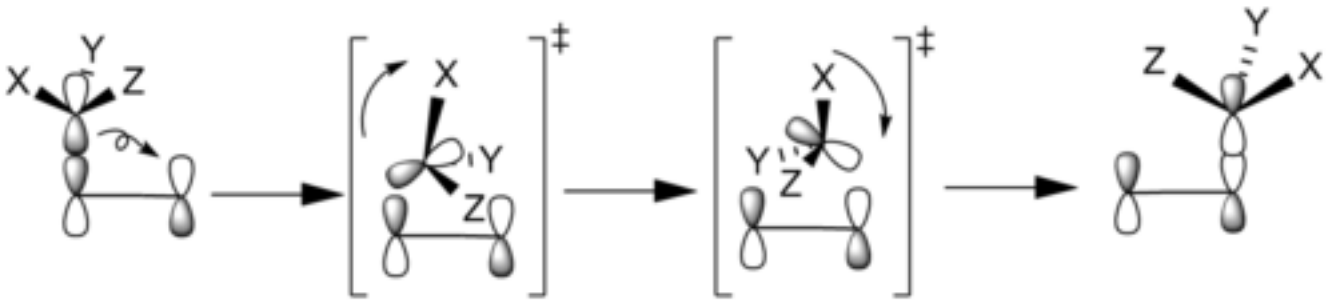


Sigmatropic Rearrangement

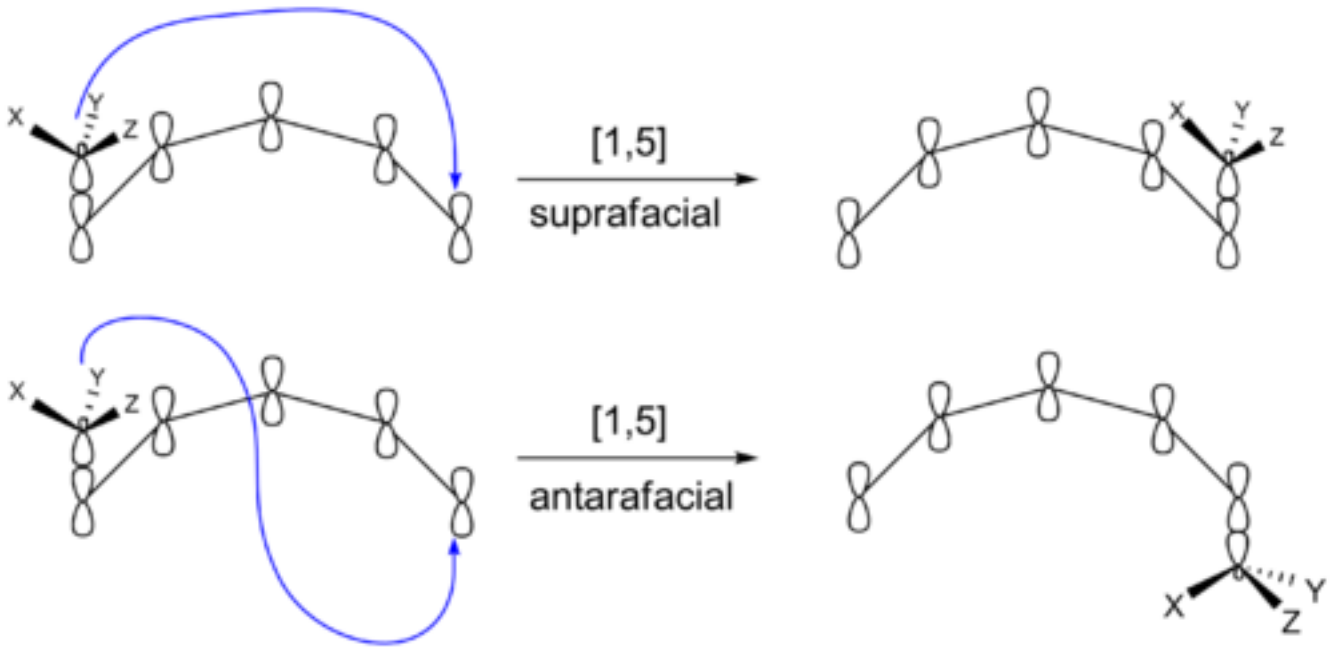
Sigmatropic Shift with Retention of Stereochemistry



Sigmatropic Shift with Inversion of Stereochemistry



Sigmatropic Rearrangement



Sigmatropic Rearrangement

Total π electrons	Ground State	Excited State
4n	antara - supra supra - antara	antara - antara supra - supra
4n + 2	supra - supra antara - antara	antara - supra supra - antara

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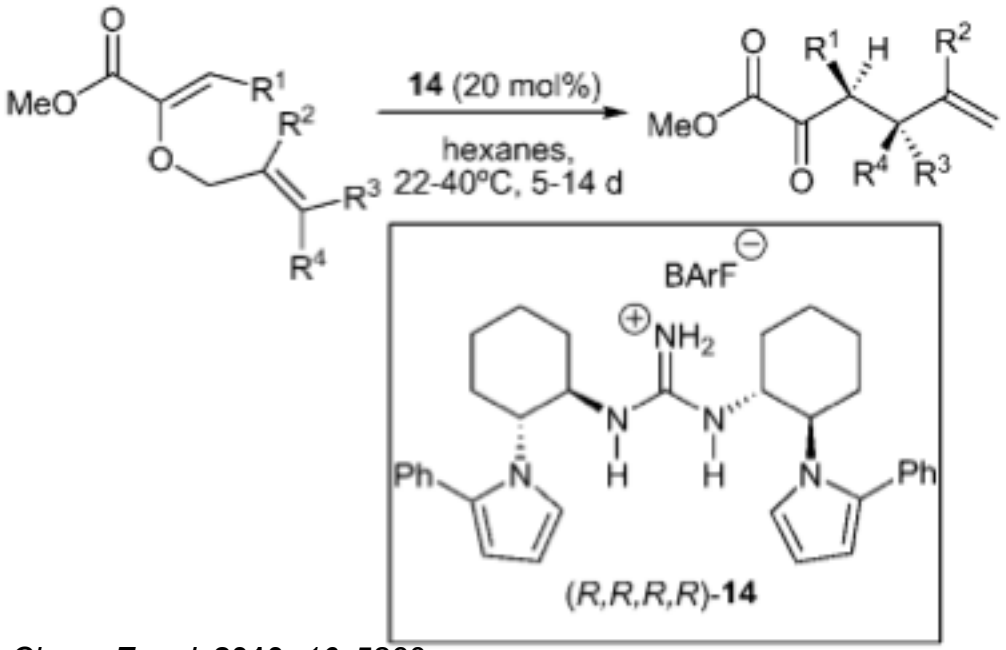
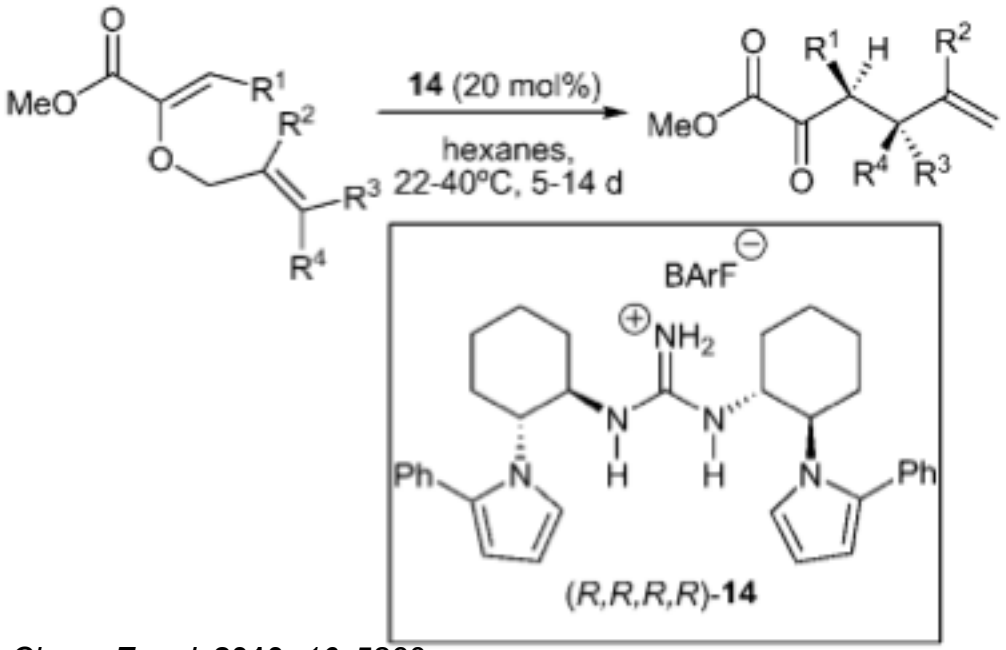
Catalyzed Claisen Rearrangement: Ex. #1

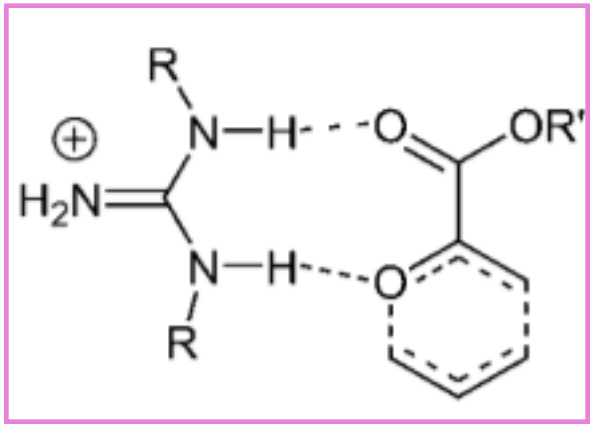


Moyano, A. *et al. Chem. Eur. J.* **2010,** *16,* 5260.

Entry	R^1	R^2	R^3	R^4	Yield [%]	*ee* [%]
1	Me	H	H	H	80	92
2	Et	H	H	H	86	92
3	Et	H	*n*Pr	H	92 (>20:1 d.r.)	85
4	Et	H	Ph	H	91 (19:1 d.r.)	81
5	Me	Me	H	H	73	96
6	Et	H	Me	Me	89	81
7	Et	H	Ph	Me	89 (>20:1 d.r.)	82
8	Et	H	$(CH_2)_2CH=CMe_2$	Me	73 (>20:1 d.r.)	84

Catalyzed Claisen Rearrangement: Ex. #1



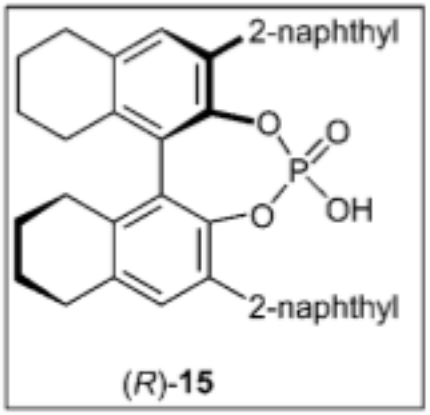


Moyano, A. *et al. Chem. Eur. J.* **2010,** *16,* 5260.

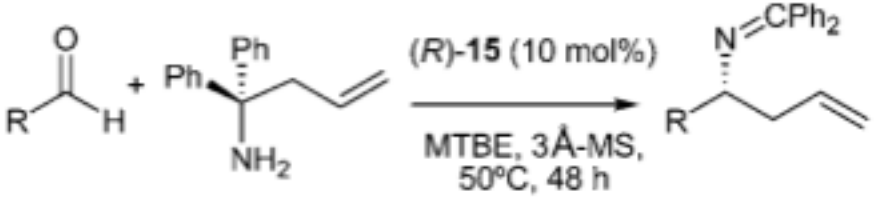
Entry	R^1	R^2	R^3	R^4	Yield [%]	*ee* [%]
1	Me	H	H	H	80	92
2	Et	H	H	H	86	92
3	Et	H	*n*Pr	H	92 (>20:1 d.r.)	85
4	Et	H	Ph	H	91 (19:1 d.r.)	81
5	Me	Me	H	H	73	96
6	Et	H	Me	Me	89	81
7	Et	H	Ph	Me	89 (>20:1 d.r.)	82
8	Et	H	$(CH_2)_2CH=CMe_2$	Me	73 (>20:1 d.r.)	84

Catalyzed Aza-Cope Rearrangement: Ex. #3

Moyano, A. *et al. Chem. Eur. J.* **2010,** *16,* 5260.

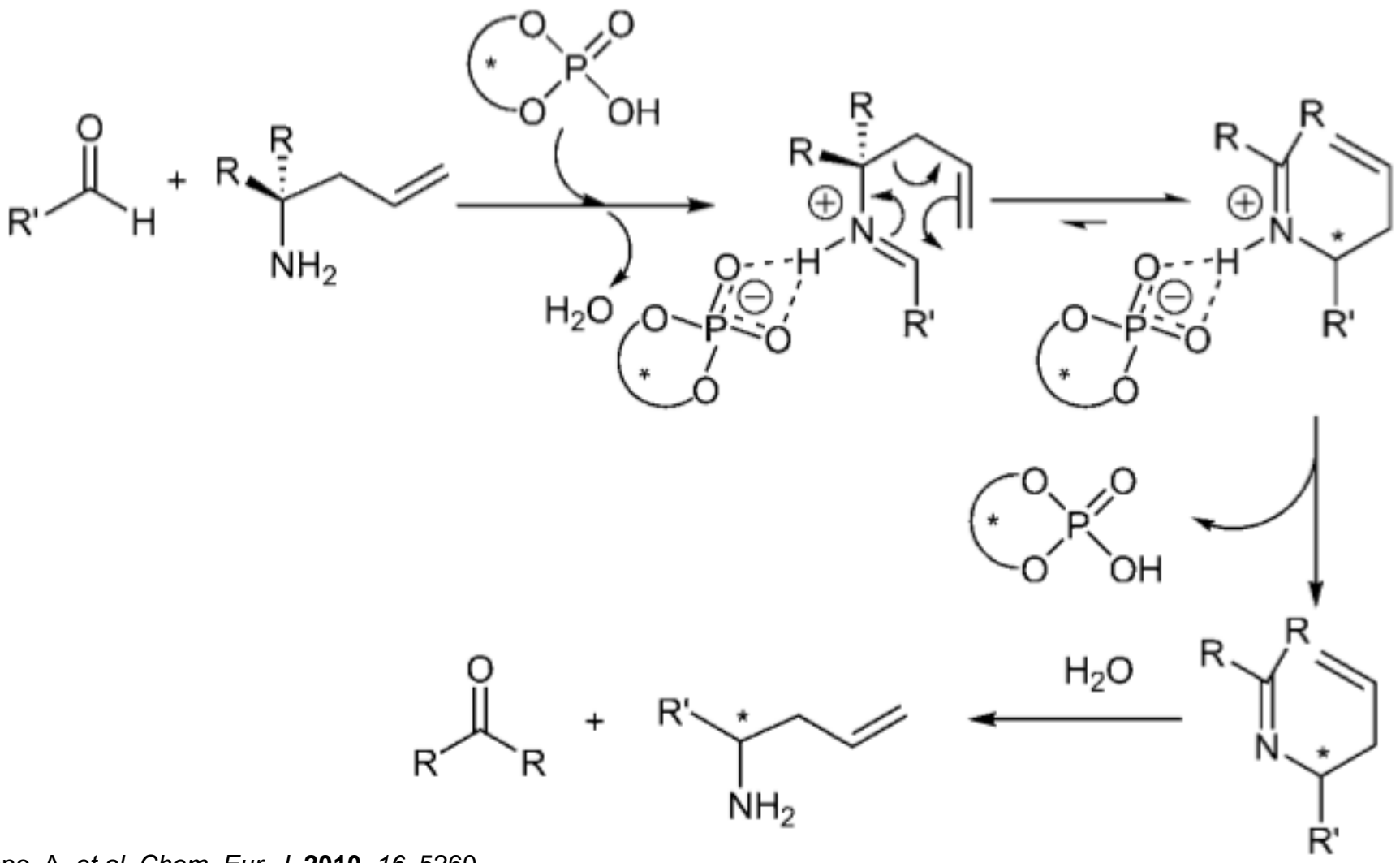


(*R*)-**15**



Entry	R	Yield [%]	*ee* [%]
1	2-naphthyl	77	82
2	*p*-*t*BuPh	67	85
3	*p*-CF_3Ph	87	81
4	3,4-$Cl_2C_6H_3$	61	87
5	3,3-$F_2C_6H_3$	74	88
6	3,3-Br_2-4-(OH)C_6H_2	52	85
7	*m*-CF_3Ph	69	82
8	*m*-BrPh	71	81
9	3-Br-2-FC_6H_3	76	80
10	3,3-$Br_2C_6H_3$	75	94
11	(*E*)-PhCH=CH	80	81

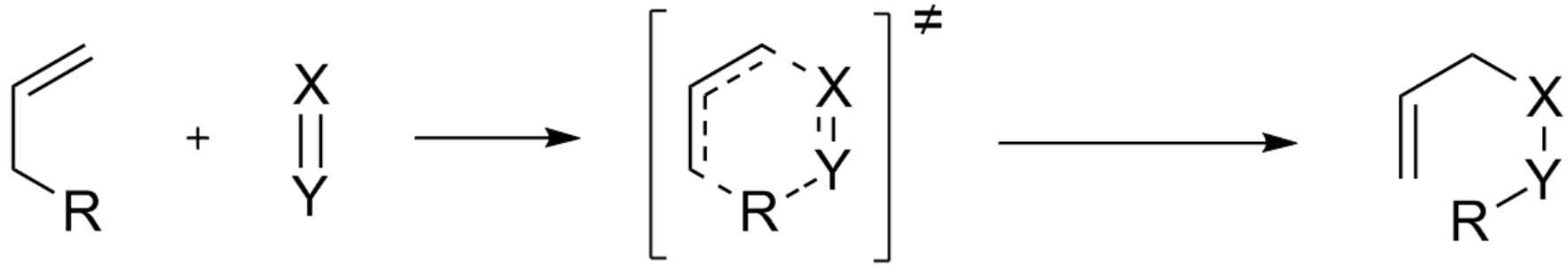
Catalyzed Aza-Cope Rearrangement: Ex. #3



Moyano, A. *et al. Chem. Eur. J.* **2010,** *16,* 5260.

Group Transfer Reactions

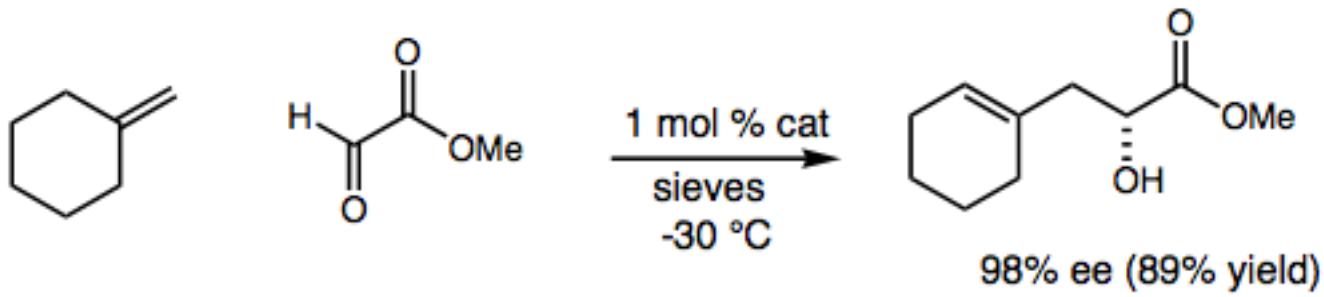
One π-bond is converted to a σ-bond at the same time that a σ-bond migrates



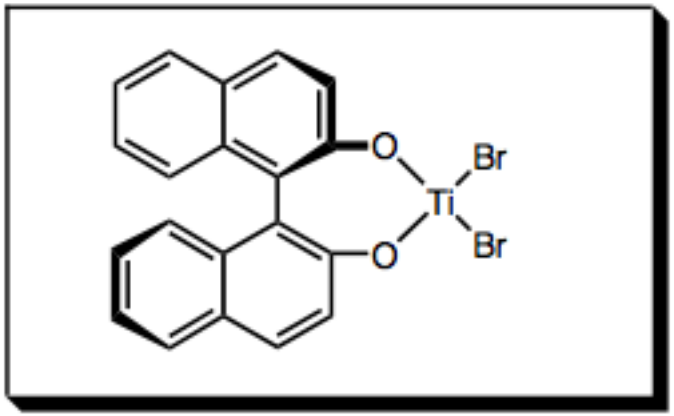
R: H, metal

X=Y: C=C, C≡C, C=O, C=S, C=N, N=N, N=O, etc.

Ene Reaction: Ex. #1



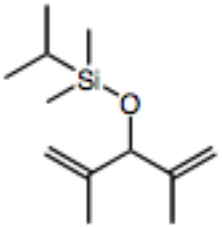
98% ee (89% yield)

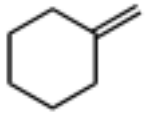


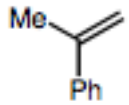
K. Mikami, *JACS*, **1989**, 1941.

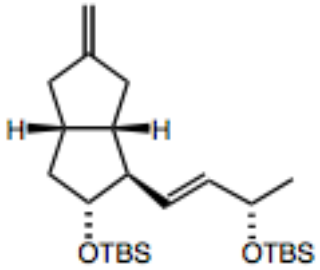
Ene Reaction: Ex. #1

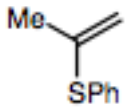
Enes

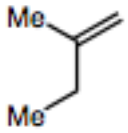




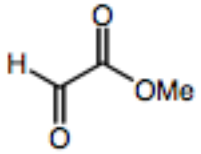


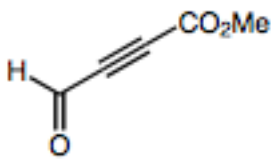


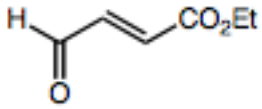


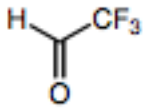


Electrophiles







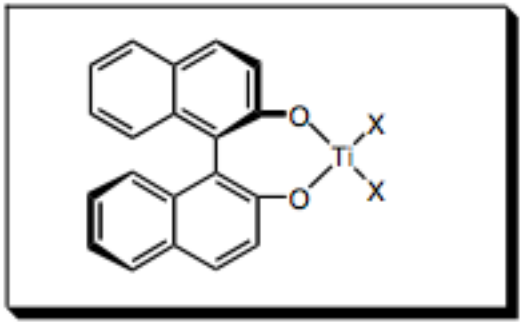


JACS, **1990**, 3949.
Tet. Lett., **1996**, 8515.
Tetrahedron, **1996**, 85.

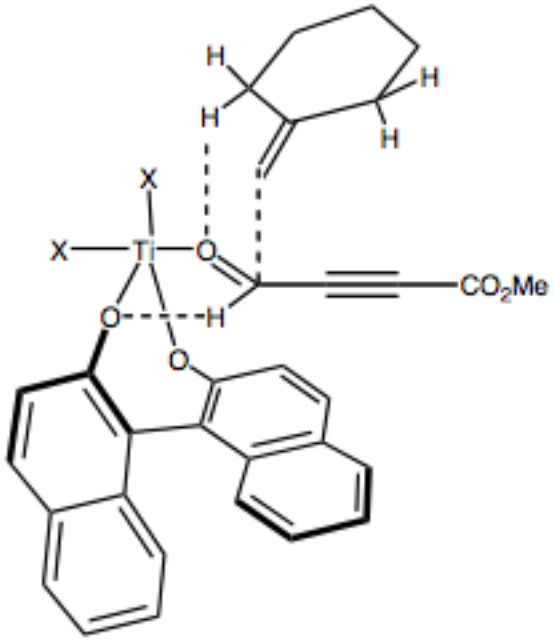
Ene Reaction: Ex. #1

Understanding the BINOL-Ti Complex:

Corey Hydrogen Bond Model



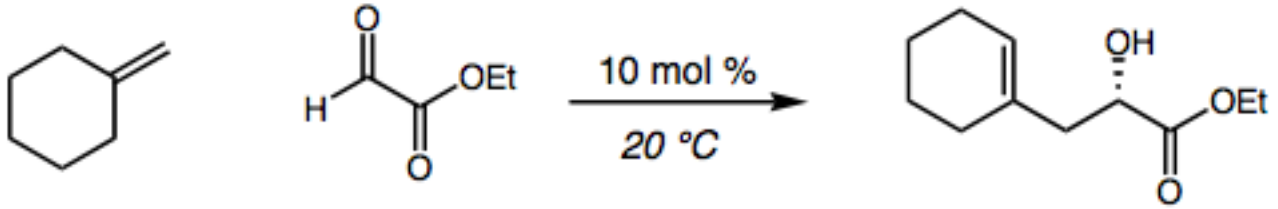
Tet. Lett, **1997**, 6513.



- Consistent with selectivity in monodentate electrophiles.
- TS organization based on association between BINOL oxygen and formyl hydrogen.
- Distorted trigonal bipyramidal Ti center with apical substituents being the coordinated aldehyde and the most lectronegative of the remaining ligands.

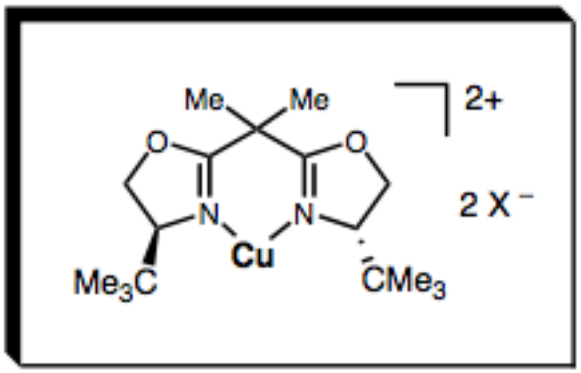
JACS, **1990**, 3949.
Tet. Lett., **1996**, 8515.
Tetrahedron, **1996**, 85.

Ene Reaction: Ex. #2



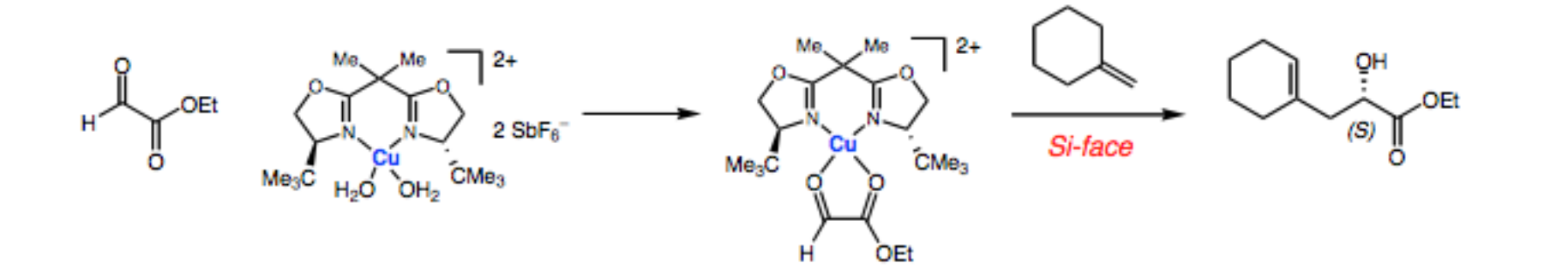
X = OTf: 20 h, 86% ee, 94% yield

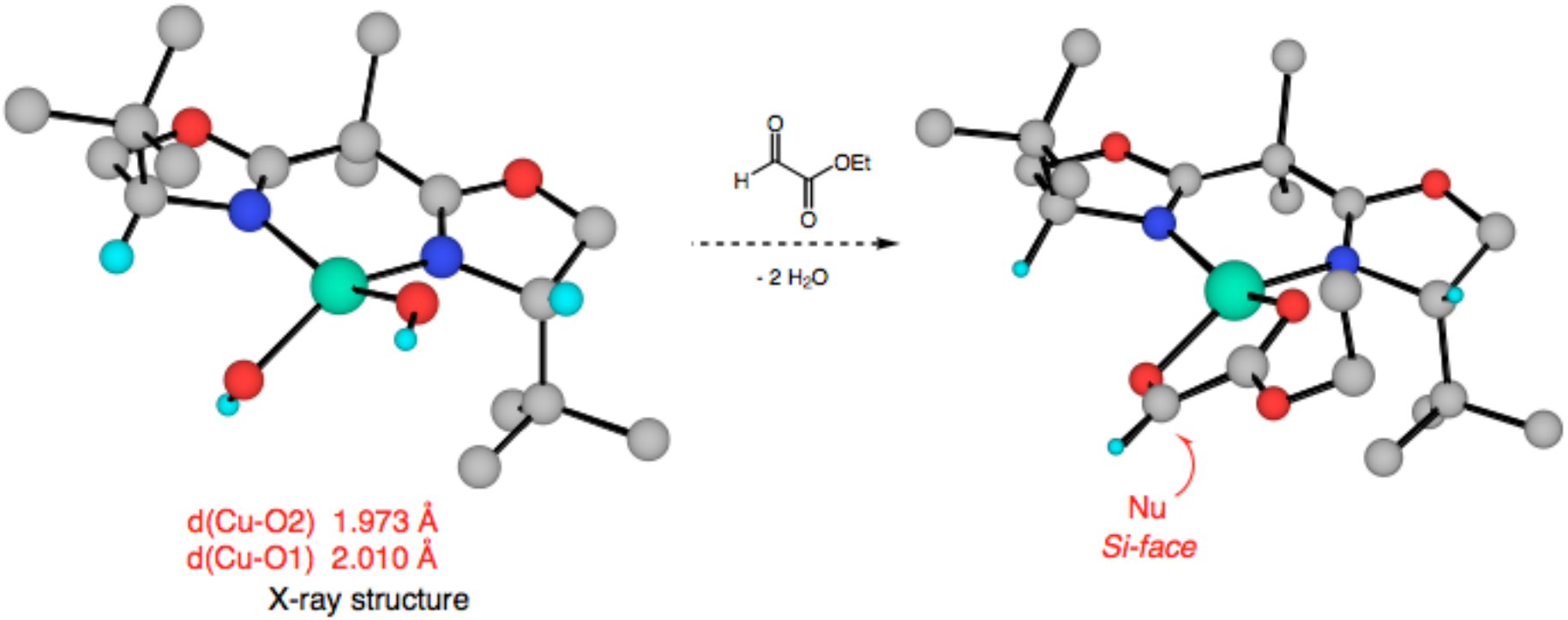
X = SbF_6 : <3 h, 96% ee, 99% yield



Evans, A. *JACS* **2000,** *122,* 7936.

Ene Reaction: Ex. #2





Evans, A. *JACS* **2000,** *122,* 7936.