Catalytic Enantioselective Additions to C=N Bonds

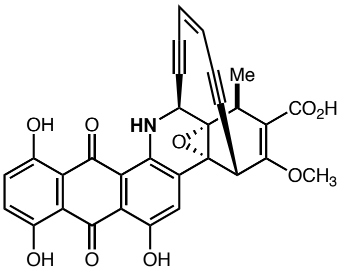
MacMillan Group Meeting
January 16, 2002

Tehshik Yoon

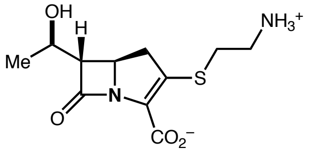
I. Reduction of imines
II. Alkylation of imines
III. Strecker reactions
IV. Mannich-type reactions
V. Cycloadditions

Reviews: Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069
Yet, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 875 (Strecker catalysts)
Buonora, P.; Olsen, J.-C.; Oh, T. B. *Tetrahedron* **2001**, *57*, 6099 (aza-Diels-Alder)

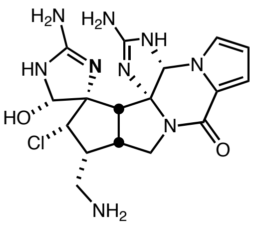
Biologically Active Compounds with Nitrogen-bearing Stereocenters



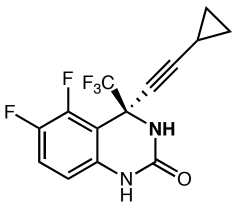
dynemycin A
anticancer



thienamycin
antibiotic



palau'amine
immunosuppressant

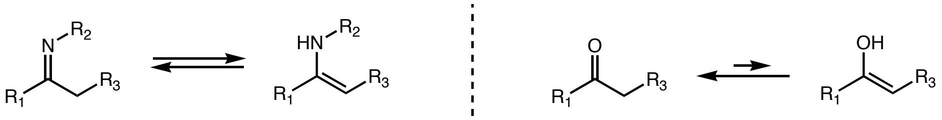


DPC 963
reverse transcriptase
inhibitor

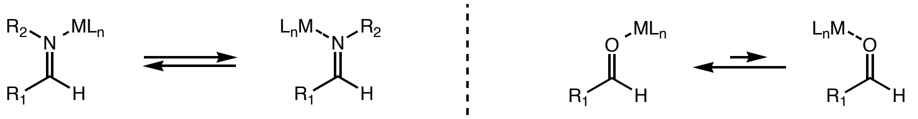
Properties of Imines vs Aldehydes

> *"While much progress has been made recently in catalytic enantioselective reactions of aldyhdes and ketones such as aldol, allylation, Diels–Alder, cyanation reactions, reduction, etc., progress in catalytic enantioselective reactions of imines is rather slow."* – Kobayashi

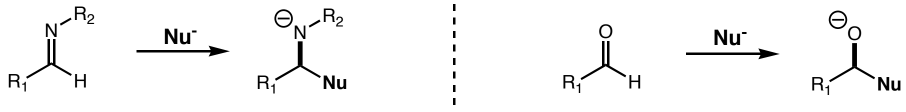
- Facile imine–enamine tautomerization



- Geometrical control of metal-imine complex



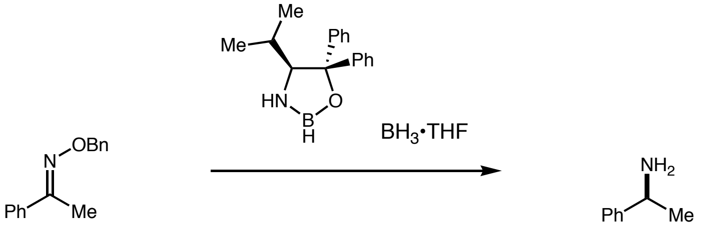
- Basicity of nitrogen



pKa ~ 7 pKa ~ 38 pKa ~ -6 pKa ~ 16

Enantioselective Borane Reductions of Imines

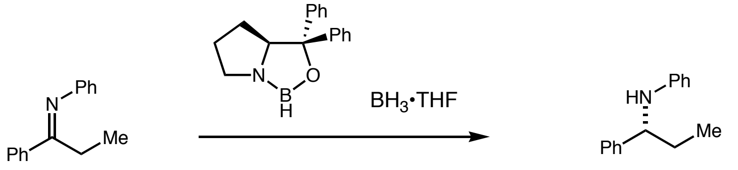
- Itsuno, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395



25 mol% 90% ee (100% yield)

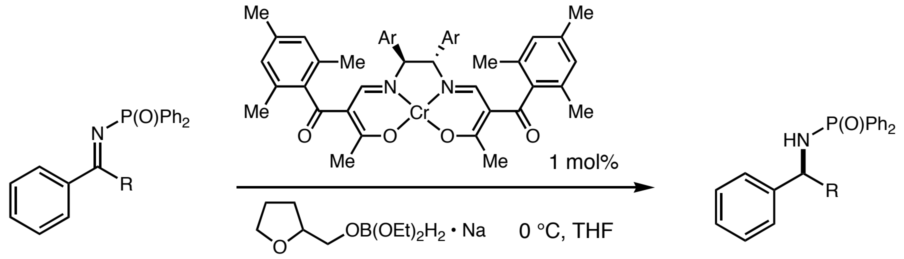
10 mol% 52% ee (100% yield)

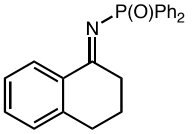
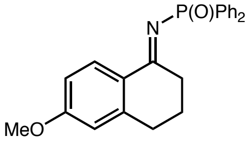
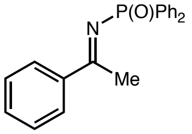
- Cho and Chun, *Tet. Asymmetry* **1992**, *3*, 1583



10 mol% 70% ee (90% yield)

Cobalt-mediated Catalytic Enantioselective Borohydride Reduction



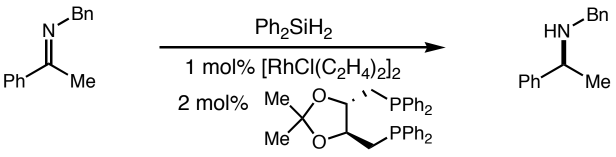
	Ar	ee	yield
	3,5-dimethylphenyl	98%	85%
	3,5-dimethylphenyl	99%	97%
	mesityl	90%	81%

- six examples, with one acyclic case. ee's range from 90–99%
- phosphoryl group cleavable under mildly acidic conditions without loss of ee

Mukaiyama, *Chem. Let.* **1997**, 493

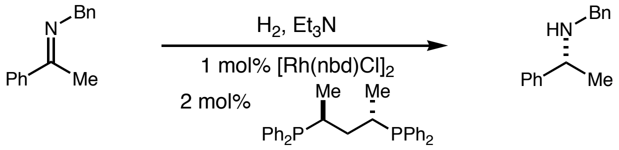
Rhodium-catalyzed Enantioselective Imine Reductions

- Kagan (*TL* **1973**, 4865). First example:



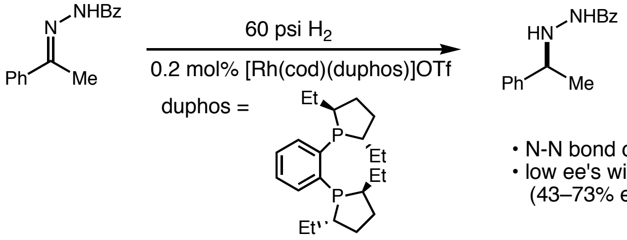
50% ee

- Bakos (*J. Organomet. Chem.* **1989**, *370*, 263).



83% ee
100% conv.

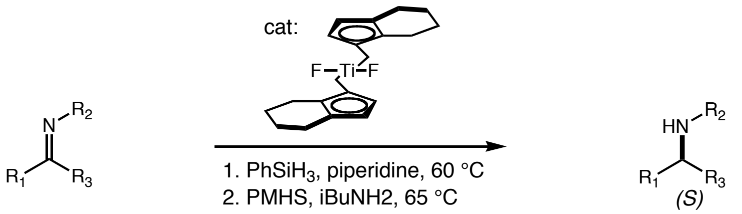
- Burk (*J. Organomet. Chem.* **1989**, *370*, 263.



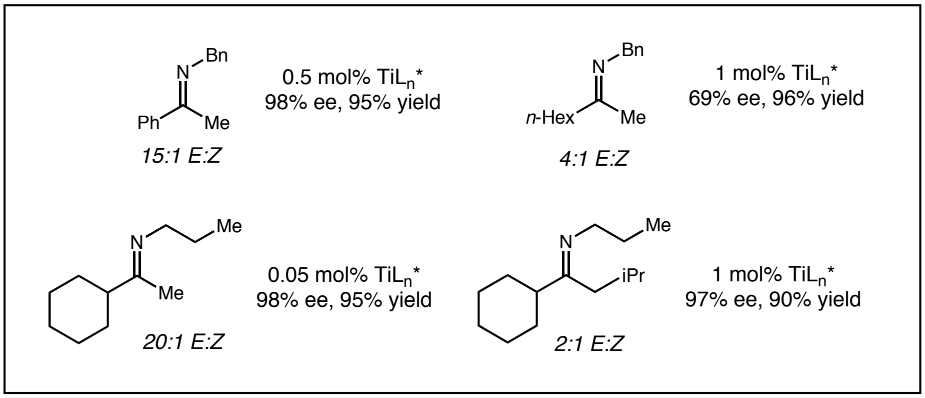
95% ee

- N-N bond cleaved with SmI_2
- low ee's with aliphatic substrates (43–73% ee)

Chiral Titanocene Catalysts for Imine Reduction



1. $PhSiH_3$, piperidine, 60 °C
2. PMHS, iBuNH2, 65 °C



15:1 E:Z — 0.5 mol% TiL_n*, 98% ee, 95% yield

4:1 E:Z — 1 mol% TiL_n*, 69% ee, 96% yield

20:1 E:Z — 0.05 mol% TiL_n*, 98% ee, 95% yield

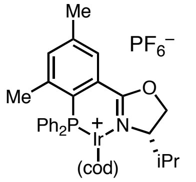
2:1 E:Z — 1 mol% TiL_n*, 97% ee, 90% yield

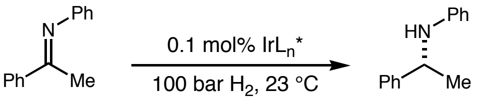
- Amine additive facilitates turnover of the product amido-titanium species
- Slow addition of 1.5-4 equiv. primary amine additive required

Buchwald, *ACIE*, **1998**, *37*, 1103

Other Metal-Catalyzed Asymmetric Imine Reductions

- Pfaltz (*Chem. Eur. J.* **1997**, *3*, 887)





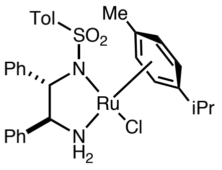
0.1 mol% IrL_n*

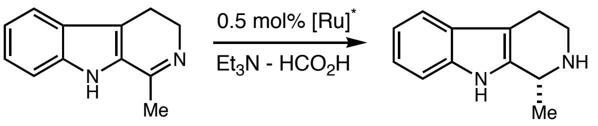
100 bar H_2, 23 °C
CH_2Cl_2

89% ee
99% yield

other substrates <80% ee

- Noyori (*JACS.* **1996**, *118*, 4926)



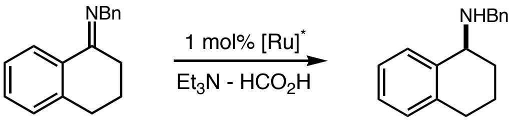


0.5 mol% [Ru]*

Et_3N - HCO_2H

97% ee, 86% yield

scope limited
to cyclic imines



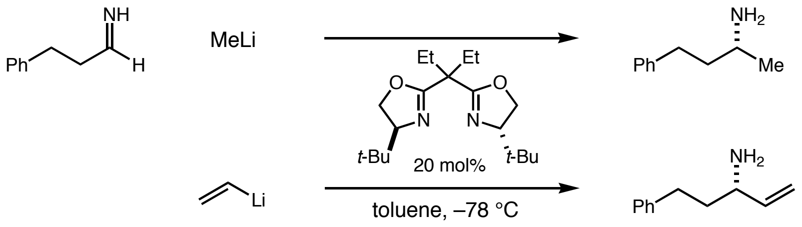
1 mol% [Ru]*

Et_3N - HCO_2H

89% ee, 90% yield

Enantioselective Alkylations of Imines

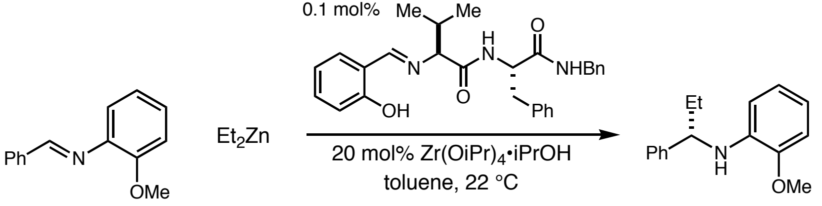
- Denmark, *JACS*, **1994**, *116*, 8797



82% ee
81% yield

82% ee
82% yield

- Hoveyda, *JACS*, **2001**, *123*, 985

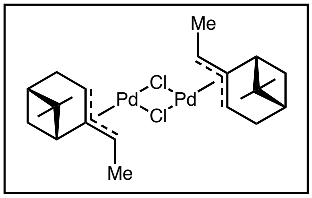


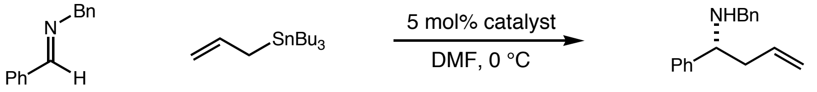
93% ee
82% yield

- Me_2Zn and $Zn(C_8H_{17})_2$ also react, but require modified ligands for optimal ee.
- 7 examples of imines derived from naphthlyl, furyl, and substituted phenyl aldehydes (>88% ee)

Asymmetric Allylation of Imines

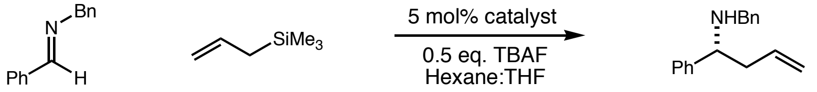
Y Yamamoto, *JACS,* **1998**, *120*, 4242; *JOC*, **1999**, *64*, 2614





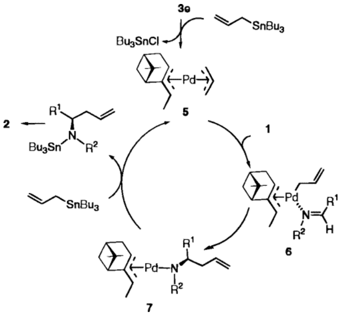
81% ee
62% yield

- 7 examples, 40–82% ee. Aromatic aldimines more successful than alkyl aldimines.



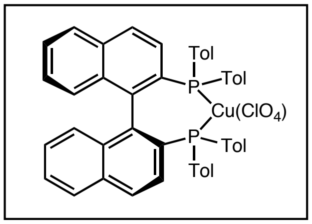
80% ee
79% yield

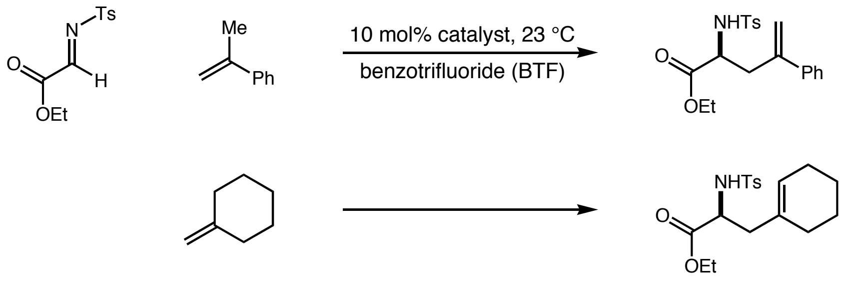
- 6 examples. Selectivities generally a bit lower than in stannyl cases (64–84% ee)



Catalytic Asymmetric Imino-Ene Reactions

Lectka, *JACS*, **1998**, *120*, 11006
Jørgensen, *Chem Comm*, **1998**, 2547

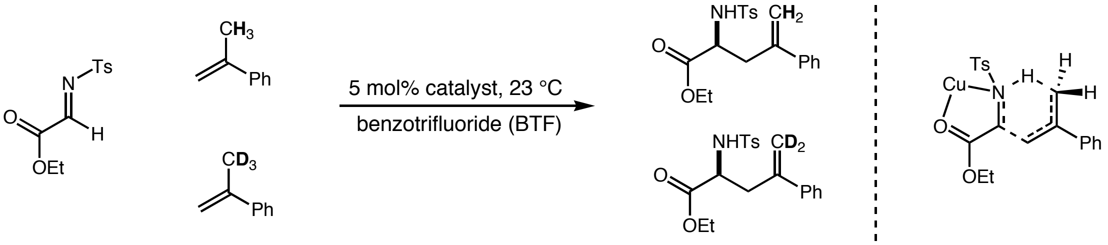




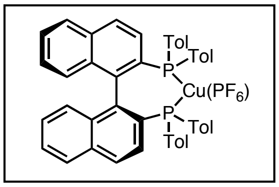
99% ee
92% yield

95% ee
85% yield

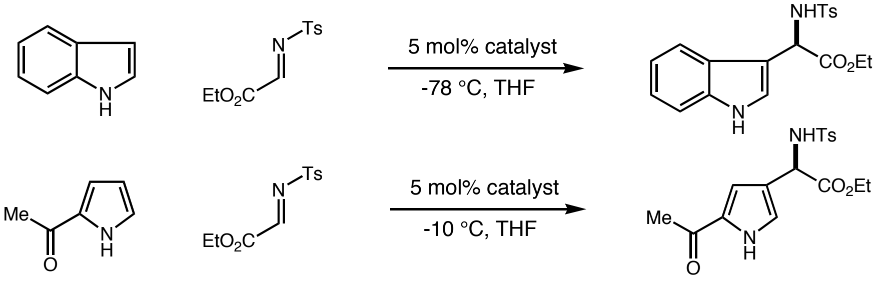
- ■ 5 examples, 85–99% ee.
- ■ Concerted transition state indicated by large primary kinetic isotope effect ($k_H/k_D = 4.4$):



Copper-catalyzed Arylation of Imines



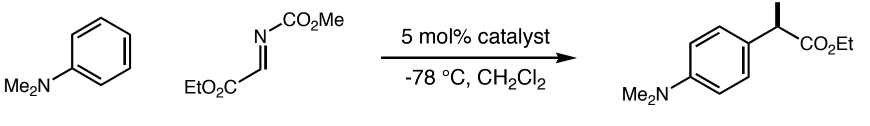
- ■ Heteroaromatic nucleophiles – Johannsen (*Chem. Comm.* **1999**, 2233)



96% ee
89% yield

94% ee
76% yield

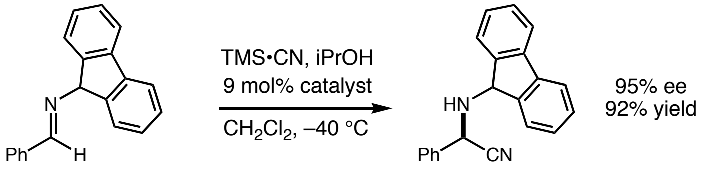
- ■ Aniline nucleophiles – Jørgensen (*ACIE.* **2000**, *39,* 4114)



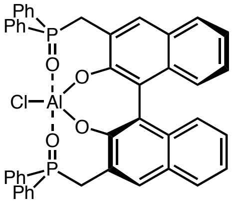
93% ee
75% yield

- Modest generality – 3-methoxyaniline gives only 72% ee.
- Other examples range from 52–98% ee.
- 1,3-Dimethoxybenzene gives 79% ee, 83% yield (10 mol% catalyst).

BINOL-Aluminum Catalyst for Enantioselective Strecker Reaction

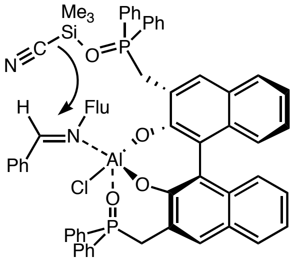


■ 6 aromatic examples, >89% ee. All aliphatic aldimines <80% ee.



"bifunctional" catalyst

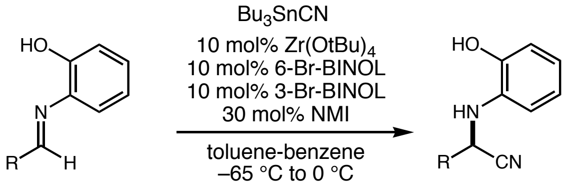
Proposed transition state



- Use of HCN instead of TMS•CN results in 2-fold decrease in rate and 54% ee.
- Reactivity and enantioselectivity can be restored with 20 mol% TMS•CN and slow addition of HCN (regenerating TMS•CN).
- Replacement of P(O)Ph_2 group with $CHPh_2$ results in formation of the opposite enantiomer in 15% ee.

Shibasaki *ACIE* **2000**, *39*, 1650

BINOL-Zirconium Catalyst for Asymmetric Strecker Reactions

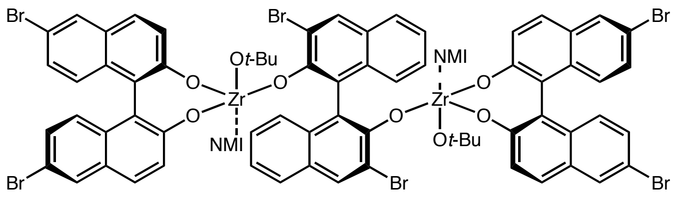


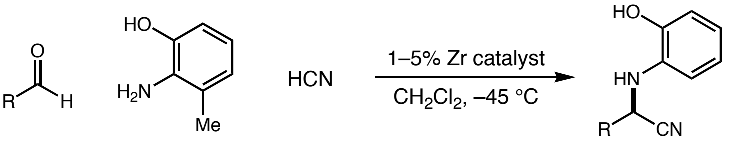
R = Ph	91% ee, 92% yield
R = CH_2CH_2Ph	83% ee, 55% yield
R = isobutyl	83% ee, 79% yield

(NMI = *N*-methylimidazole)

stable catalyst

structure deduced from NMR

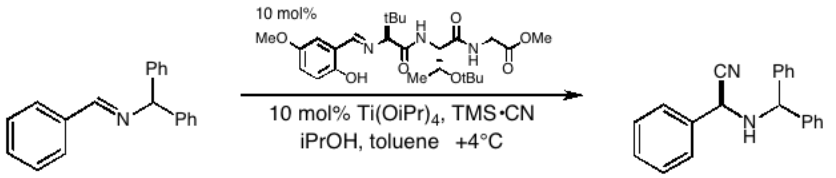




	ee	yield
R = Ph	86%	80%
R = octyl	91%	93%
R = cHex	94%	94%

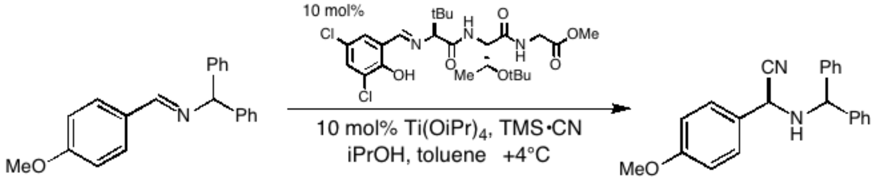
Kobayashi, *ACIE*, **1998**, *37*, 3186
JACS, **2000**, *122*, 762

Combinatorial Approach to Catalyst Discovery



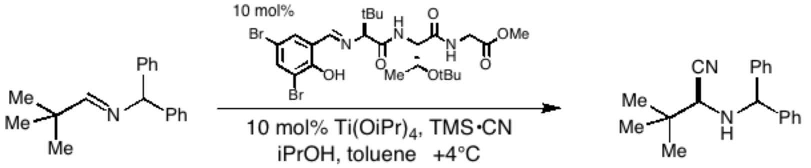
97% ee
99% yield

(>99% ee
after rx)



94% ee
100% yield

(>99% ee
after rx)



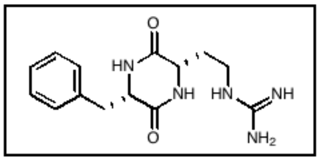
85% ee
100% yield

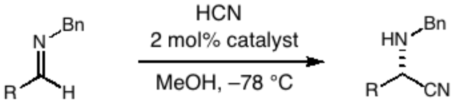
- Aromatic substrates uniformly display excellent selectivity (>90% ee)
- One aliphatic example gives poorer enantioselectivity (tBu, 85% ee)
- Optimal selectivity requires optimization of ligand for even small structural changes on substrate

Snapper, Hoveyda *JACS*, **1999**, *121*, 4284

Organocatalytic Approaches to Strecker Reactions

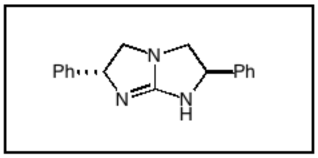
- Lipton, *JACS*, **1996**, *118*, 4910

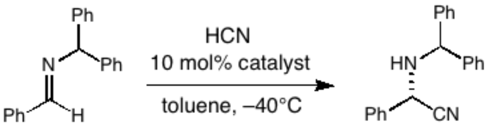




R = Ph, >99% ee, 97% yield
R = PMP, 96% ee, 90% yield
R = 3-pyridyl, <10% ee, 86% yield
R = iPr, <10% ee, 81% yield
R = tBu, 17% ee, 80% yield

- Corey, *Org. Lett.* **1999**, *1*, 157

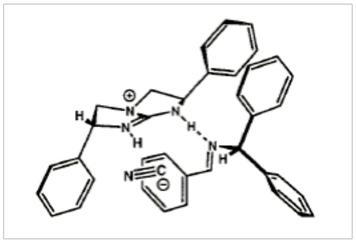


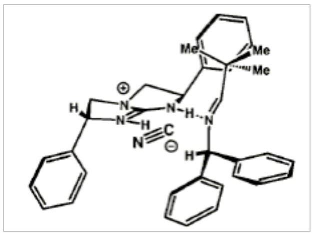


86% ee
96% yield

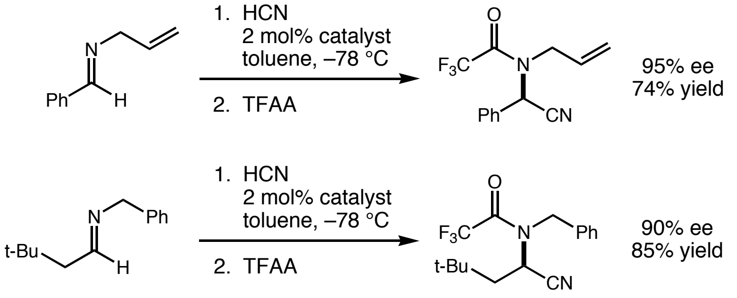
9 aromatic
examples,
50-88% ee

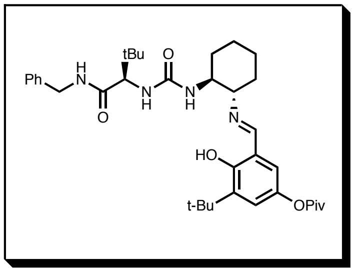
- aliphatic imines give the *opposite* enantiomer (tBu, 84% ee; cHex, 76% ee; nHept, 63% ee)

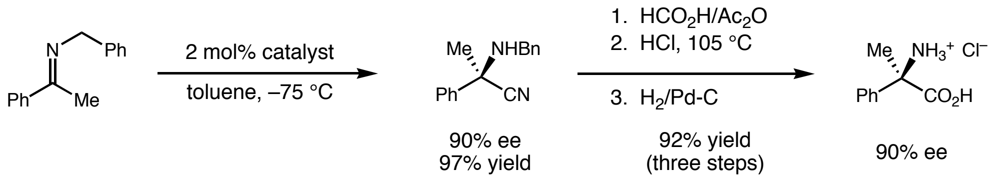




Jacobsen's Schiff Base Catalyst





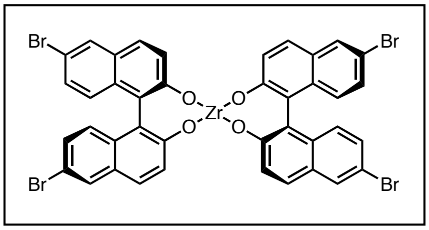


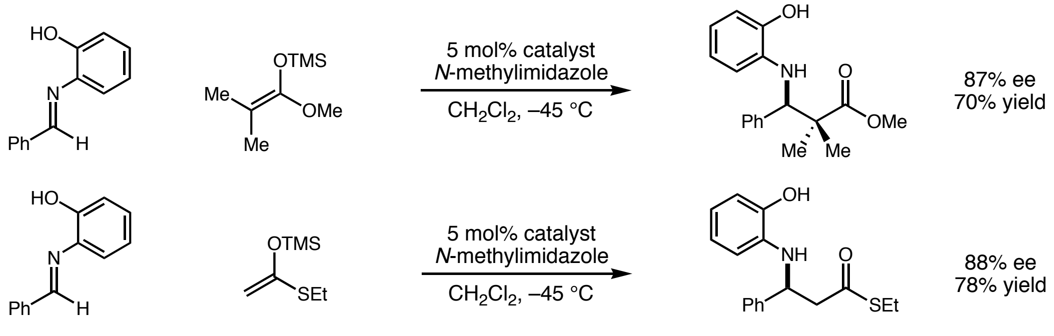
- Aldimine scope includes aromatic, branched alkyl, and even primary unbranched alkyl substituents with <77% ee. Methyl ketoimines highly selective (<88%) for aromatics with the exception of *o*-substituted phenyls. tBu-substituted ketoimine gives 70% ee.
- Catalyst recycled 10 times without loss of yield or enantioselectivity.
- Kinetic studies indicate Michaelis-Menton behavior involving pre-association of an imine-catalyst complex followed by rate-limiting addition of HCN
- NMR structural studies suggest a well-defined tertiary structure with an "active site" defined by the bulky t-butyl groups. Mechanism of imine activation presumed to be H-bonding to phenol and urea protons.

Jacobsen *ACIE* **2000**, *39*, 1279
Org. Lett. **2000**, *2*, 867

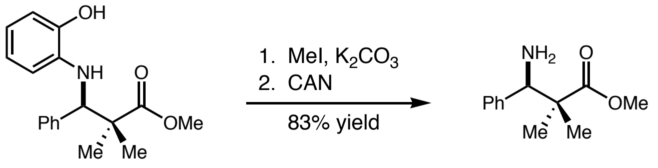
First Asymmetric Catalytic Mannich Reaction

Kobayashi, *JACS*, **1997**, *119*, 7153

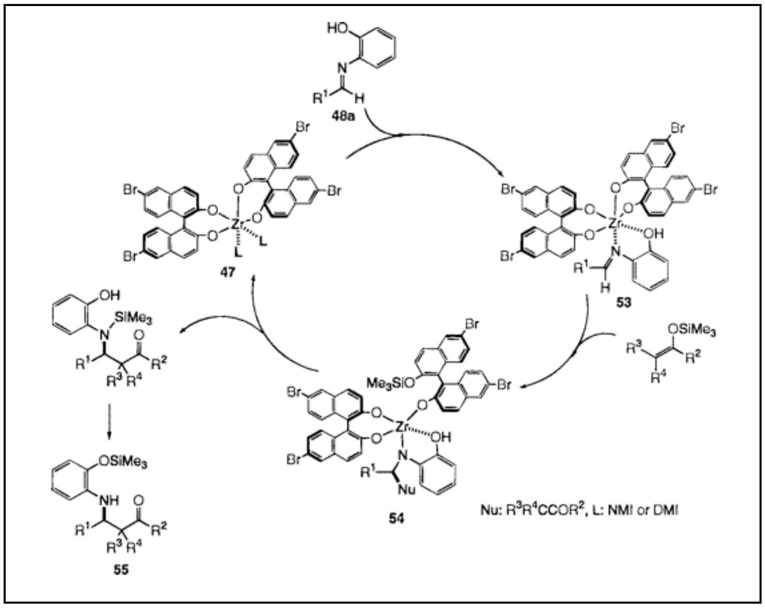




- 8 examples, all 80–90% ee except 1-naphthaldimine (up to 98% ee)
- 1 aliphatic example: cyclohexanecarboxaldimine (80% ee, 56% yield)
- *N*-substituent easily cleaved by CAN oxidation:



Kobayashi : Proposed Catalytic Cycle



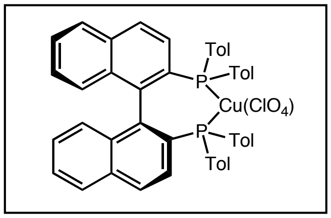
- ■ Role of NMI (*N*-methylimidazole) or DMI (1,2-dimethylimidazole) is presumably to break up and solublize Zr-BINOL oligomers.
- ■ Catalyst structure and absolute sense of stereoinduction not explicitly determined.

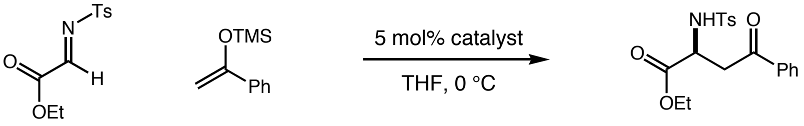
figure from Kobayashi, *Chem Rev*, **1999**, *99*, 1069

Catalytic Enantioselective Mannich Reactions:

Reaction of α-Imino Esters with Silyl Enol Ethers

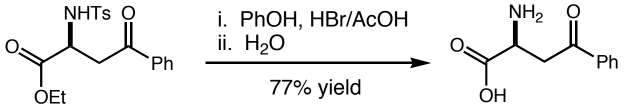
Lectka, *JACS*, **1998**, *120*, 4548





98% ee
91% yield

- ■ 8 examples, all aromatic or *t*-butyl (89–98% ee)
- ■ Hydrolysis of tosyl and ethyl groups possible without epimerization:

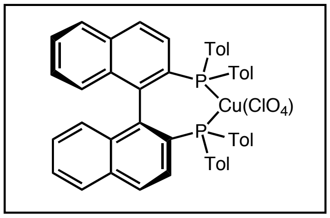


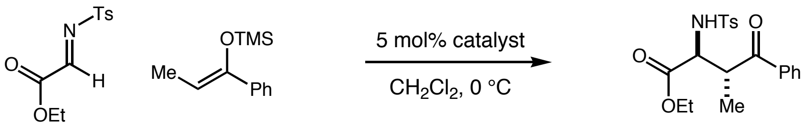
- ■ Silyl ketene acetals exhibit high levels of background reaction
- ■ IR spectroscopic evidence for chelation presented—carbonyl and imine stretching frequencies both shift (–38 and –18 cm^{-1}, respectively) upon addition of 1 eq catalyst
- ■ $AgSbF_6$, $Pd(ClO_4)_2$, and $Ni(SbF_6)_2$ complexes are less selective, but are also efficient catalysts. Possibility of a transmetallation–addition mechanism is not discussed. (cf. Carreira, *JACS*, **1998**, *120*, 837)

Catalytic Enantioselective Mannich Reactions:

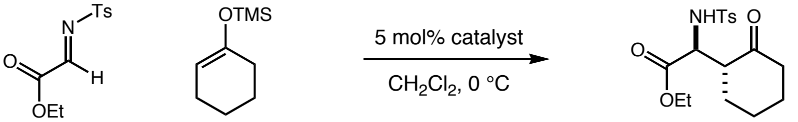
Diastereoselective Reaction of α-Imino Esters with Silyl Enol Ethers

Lectka, *JOC*, **998**, *63,* 6090





98% ee
25:1 *anti*:*syn*
85% yield

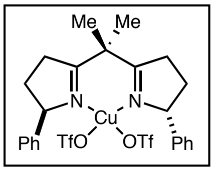


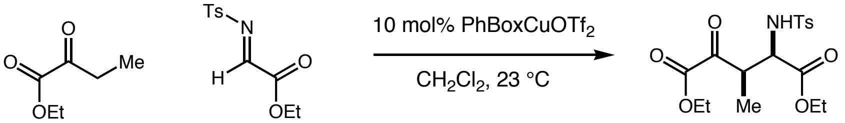
88% ee
11:1 *anti*:*syn*
71% yield

- Stereoconvergent reaction — (*E*) and (*Z*) isomers both give *anti* selectivity
- 7 examples. Aromatic silyl enol ethers give >95% ee, >11:1 *syn*:*anti*.
- Aliphatic examples are less successful: 46–88% ee, 2:1 to 11:1 *syn*:*anti*.

Direct Asymmetric Catalytic Mannich Reactions

- Jørgensen, *Angew. Chim. Int. Ed.* **2001**, *40*, 2995

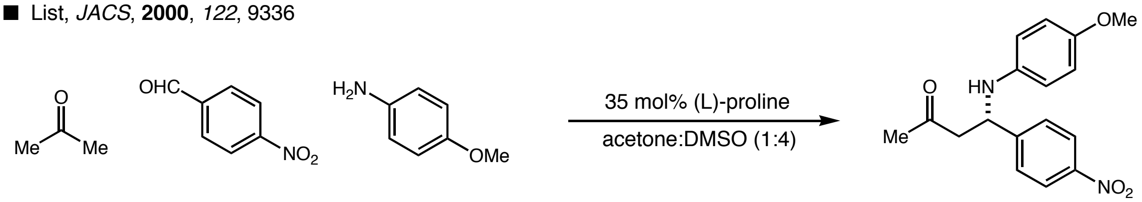




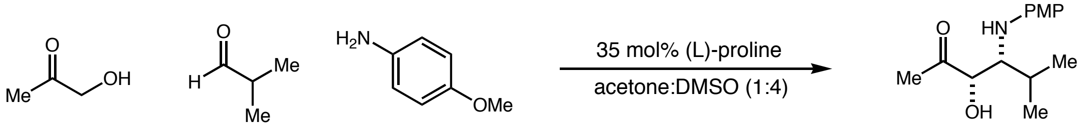
98% ee (90% minor)
>10:1 *syn*:*anti*
89% yield

- Reaction successful with H-, Me-, and Bn-substituted pyruvate esters (>10:1 *syn*:*anti*, 89–98% ee)

- List, *JACS*, **2000**, *122*, 9336



94% ee, 50% yield

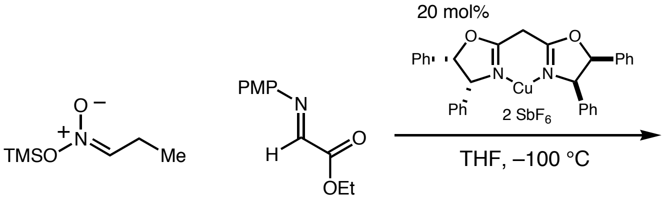


65% ee, 57% yield
17:1 dr

- 6 examples with acetone (70–96% ee), 4 examples of various α-substituted ketones (65–99% ee, 2:1 to 20:1 dr)

Copper-catalyzed Asymmetric Nitro-Mannich Reactions

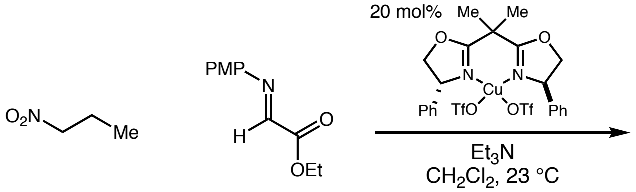
- From preformed nitronate ethers: Jørgensen, *JACS,* **2001**, *123,* 5843



95% ee
25:1 *anti*:*syn*
94% yield

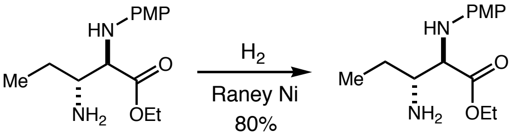
- 4 examples, 83–98% ee, 5:1 to 39:1 *anti*:*syn*.
- *N*-Tosylated products undergo retro-Henry or elimination of the nitro group.

- Direct nitro-Mannich (or aza-Henry) reaction: Jørgensen, *ACIE,* **2001**, 2992

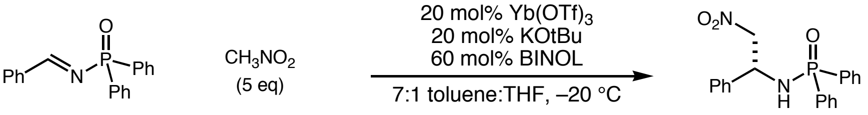


97% ee
95:5 *anti*:*syn*
81% yield

- 6 examples, 87–99% ee, >70:30 dr except for one case (α-nitrotoluene, 74% ee, 55:45 dr)
- Allows access to α,β-diaminoester chiral buidling blocks:



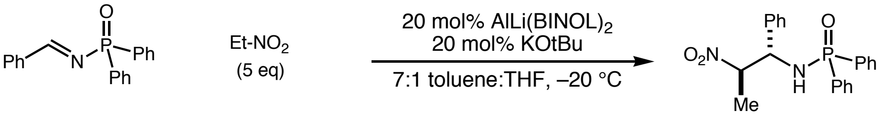
Enantioselective and Diastereoselective Catalytic Nitro-Mannich Reactions



91% ee
79% yield

- 5 examples, 69–91% ee, all nitromethane + aromatic aldimine

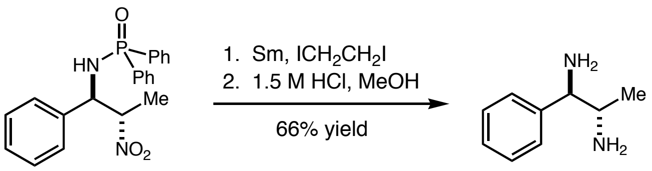
Shibasaki, *ACIE*, **1999**, *38*, 3504



83% ee
6:1 *anti*:*syn*
77% yield

- Nitroethane, 1-nitropropane, and 4-(benzyloxy)-1-nitrobutane are used as nucleophiles; p-OMe, p-Cl, and p-CH_3-substituted benzaldimines are used as electrophiles, 71–83% ee, 3:1 to 7:1 dr.

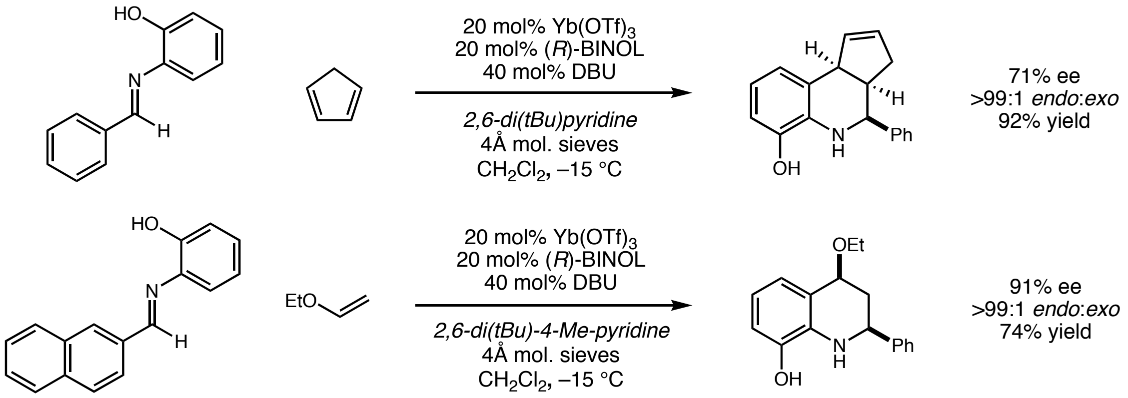
- Phosphinoyl group can be cleaved under mildly acidic conditions:



Shibasaki, *Synlett*, **2001**, 980

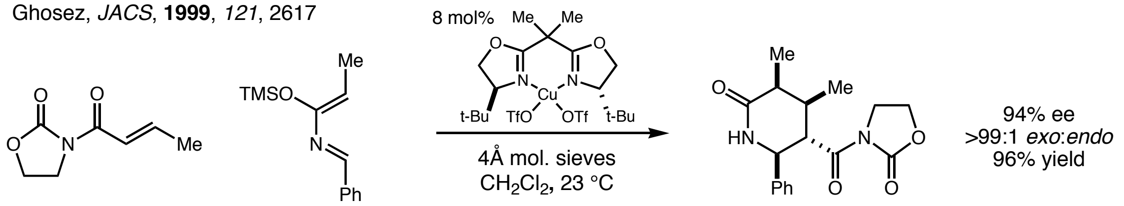
Hetero-Diels-Alder Reactions with Azadiene Substrates

■ Kobayashi, *TL* , **1996**, *37*, 7357



- 6 examples, 68–91% ee, typically >9:1 dr.
- Different substrates require optimization of amine additive for best results (2,6-dimethylpyridine, 2,6-diphenylpyridine, and *N*-methylimidazole also used).

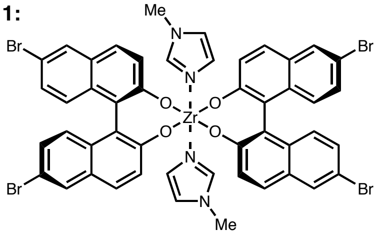
■ Ghosez, *JACS*, **1999**, *121*, 2617



- 5 examples, 90–98% ee. All highly *exo* selective, except acroloyl done + terminal enol silane (6:1 *exo*)
- Sense of stereoinduction is consistent with Evans' model.

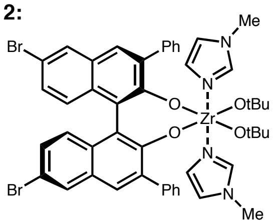
Aza-Diels-Alder Reactions with Imino Dienophiles

1:

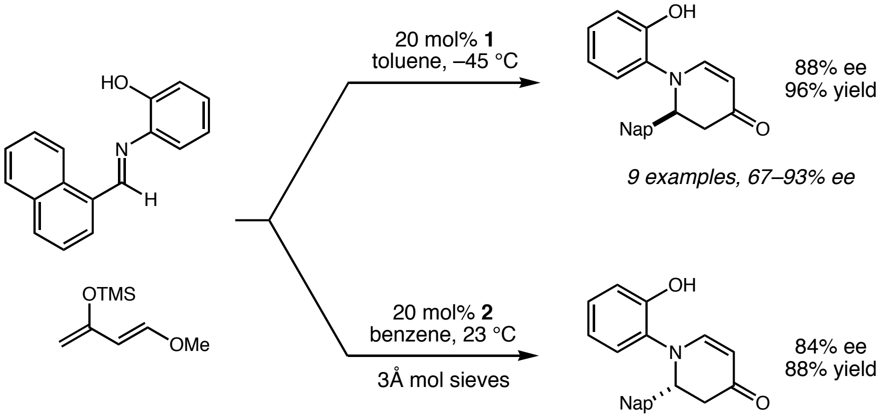


Kobayashi, *ACIE*, **1998**, *37*, 979

2:



Kobayashi, *JOC*, **1999**, *64* 4220

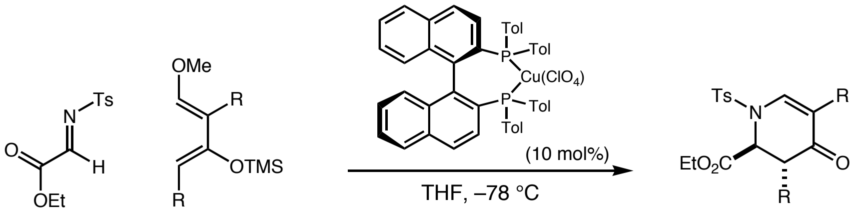


9 examples, 67–93% ee

14 examples, 80–91% ee

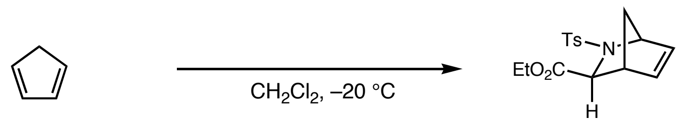
Aza-Diels-Alder Reactions with Iminoester Dienophiles

- ■ Jørgensen, *ACIE*, **1998**, *37*, 3121

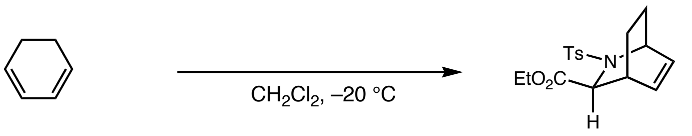


R = H 80% ee
78% yield
R = Me 84% ee
>10:1 dr
67% yield

- ■ Jørgensen, *Chem Eur J*, **2000**, *6*, 2435

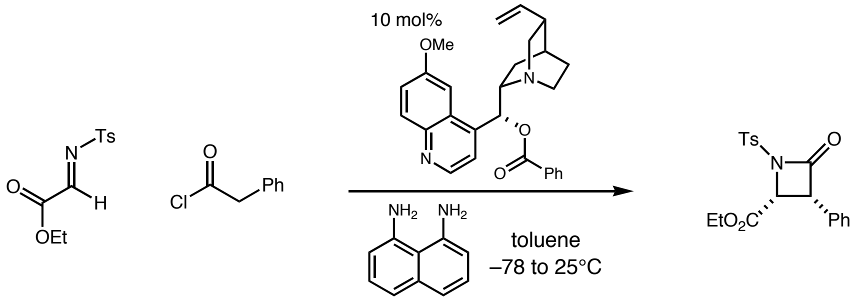


83% ee *exo*
(83% ee *endo*)
12:1 *exo*:*endo*
92% yield



95% ee *exo*
(37% ee *endo*)
7:1 *exo*:*endo*
59% yield

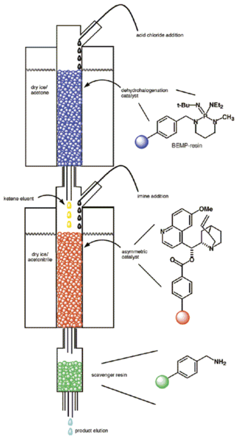
Asymmetric Synthesis of β-Lactams



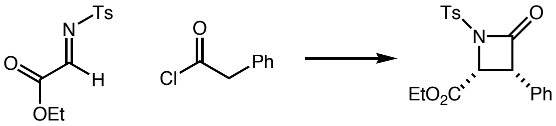
96% ee
99:1 cis:trans
65% yield

- Nucleophilic activation of ketene, formed in situ.
- 6 examples of ketenes (alkyl, aryl, alkoxy, and diaryl), 95–99% ee, 99:1 dr, 36–61% yield

Lectka, *JACS*, **2000**, *122*, 7831



- "column asymmetric catalysis" gives roughly the same results.



91% ee
99:1 cis:trans
65% yield

Lectka, *Org Lett*, **2000**, *2*, 3965

summary

- Good enantioselective methods for reduction of imines, Strecker reactions, and Mannich reactions exist.
- Imine alkylations and aza-Diels-Alders are relatively less-developed.
- In general, imine addition reactions are less well-developed than their carbonyl counterparts
- Difference in reactivity of carbonyls and imines has instigated the development of new modes of catalytic activation.