

Catalytic, Enantioselective Addition of Carbon Nucleophiles to C=N Double Bonds

Evans Group Friday Seminar

June 28, 2002

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1. Background
2. Activation of the electrophile
 - 2.1. Activation via bidentate complexation
 - Basic sites present on imine (ex. Acylhydrazones)
 - Basic sites present on substrate (ex. Imino esters)
 - 2.2. Activation via single point binding
3. Activation of the nucleophile
4. Bifunctional catalysis

Keywords: Amines, Allylation, Asymmetric, Bifunctional Catalysis, Catalytic, Chiral, Enantioselective, Imine, Imine Aldol, Mannich, Nucleophilic Addition, Staudinger

Leading References

"Stereoselective Imine Aldol Reactions"

Tedrow, J. S. *Evans Group Evening Seminar* **1997**

"Catalytic Enantioselective Addition to Imines"

Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, 99, 1069-1094

"Modern Variants of the Mannich Reaction"

Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, 37, 1045-1070

"Asymmetric Synthesis of Amines by Nucleophilic 1,2-Addition of Organometallic Reagents to the CN-Double Bond"

Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, 8, 1895-1946

"Addition of Organometallic Reagents to C=N Bonds: Reactivity and Selectivity"

Bloch, R. *Chem. Rev.* **1998**, 98, 1407-1438

"*syn-anti* Isomerizations and Rearrangements"

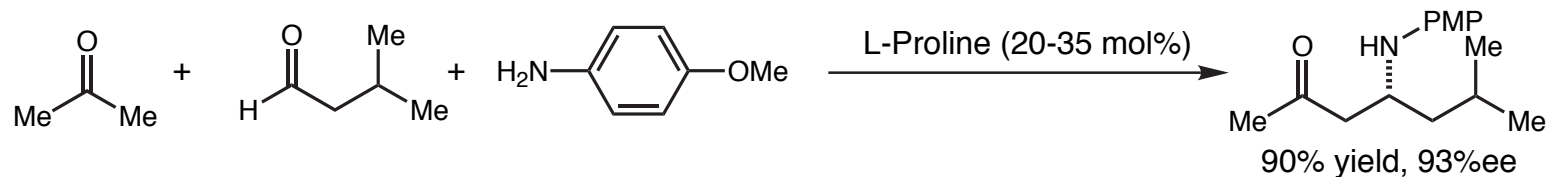
McCarty, C. G. in *The Chemistry of the Carbon-Nitrogen Double Bond*, Patai, S., Ed., John Wiley & Sons (London), 1970, chapter 9.

"Rearrangements and tautomerizations of enamines"

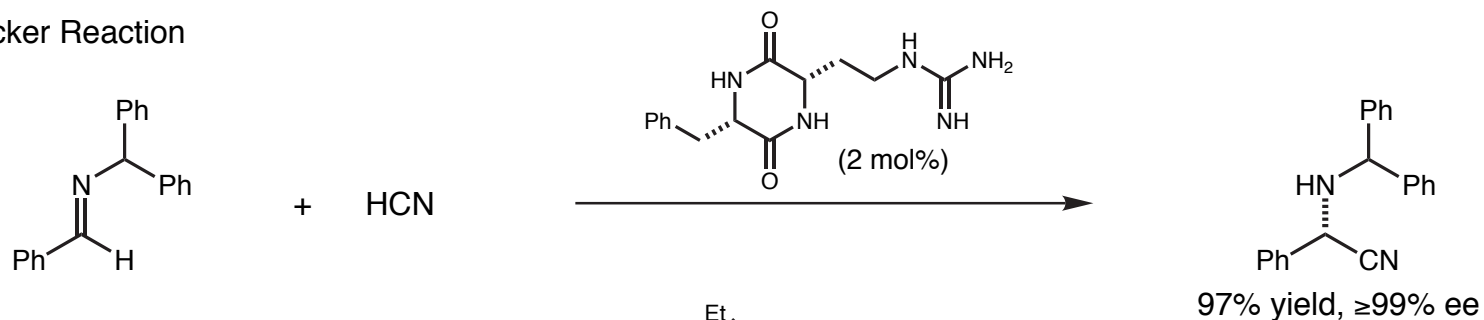
Huang, Z.-T.; Wang, M.-X. in *The Chemistry of Enamines*, Rappoport, Z., Ed., John Wiley & Sons (London), 1994, chapter 16.

Other Catalytic Enantioselective Synthesis of Chiral Amines

Direct 3-Component Mannich Reaction

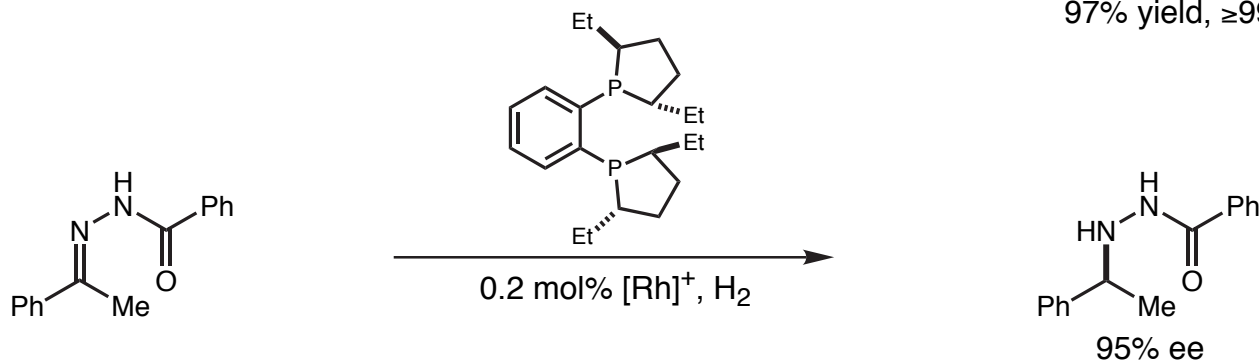


Strecker Reaction

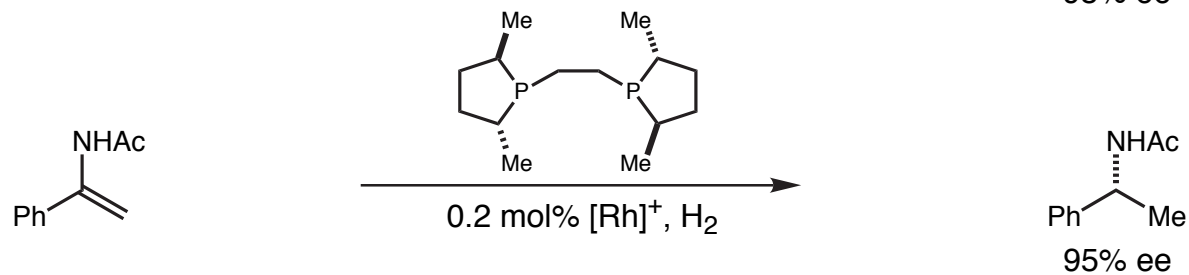


Reduction

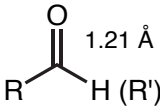
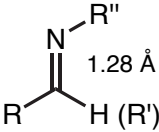
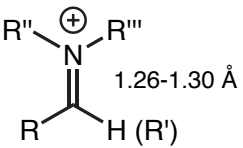
• imines



• enamines



Comparison between C=O and C=N

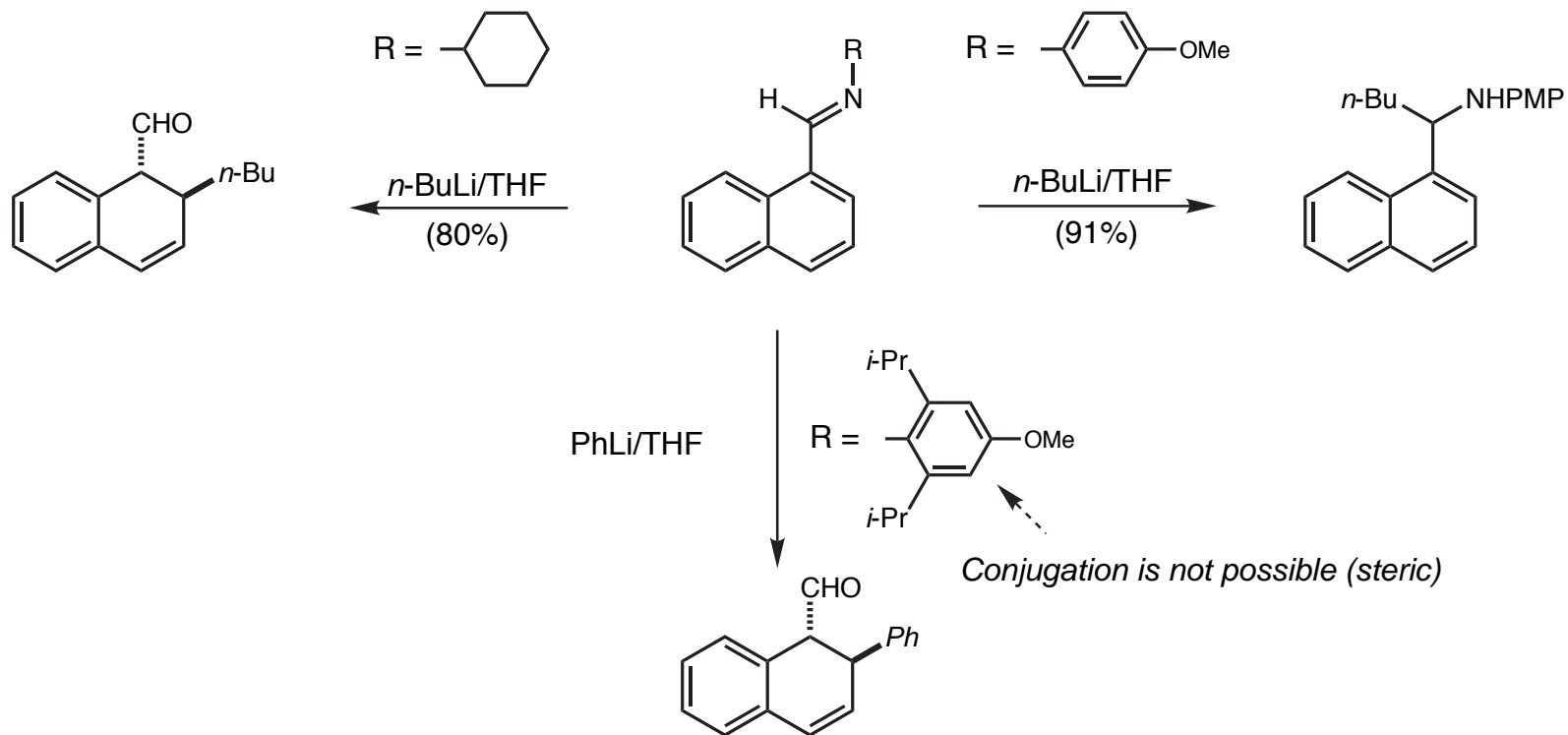
				
C=X bond E:	173-181	143	XXX	kcal.mol ⁻¹
Polarization (δ):	+ 0.51	+ 0.33	+ 0.54	

Reduced electrophilicity of the C=N double bond

Side reactions observed with organometallics

E-Z geometry problem associated with C=N double bonds

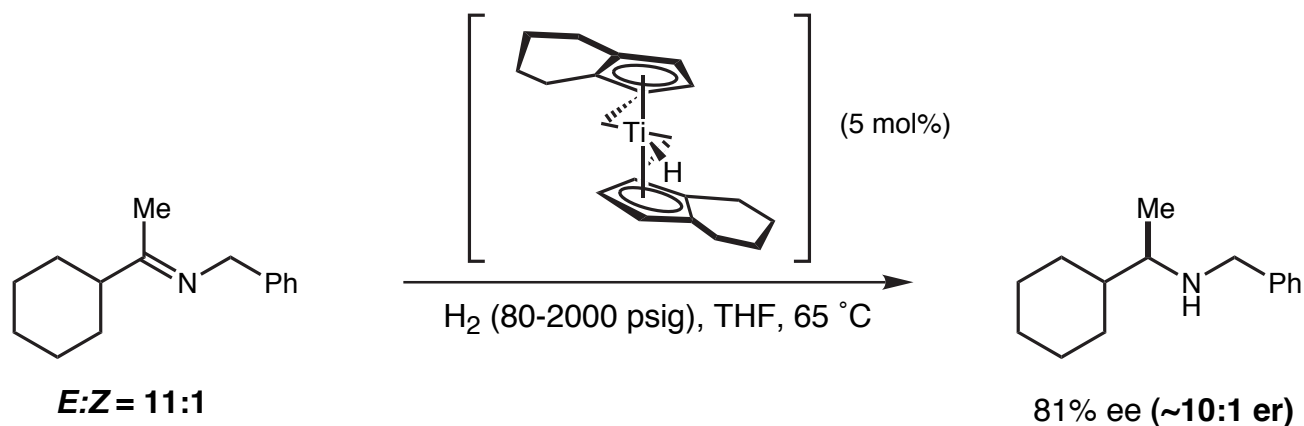
Tomioka: Imine Substituent Influences the Reaction Pathway



Relative magnitude of the LUMO coefficients account for the regioselectivity

Tomioka et al. *Tetrahedron* **1994**, 50, 4429
For calculations (MOPAC PM3): *J. Org. Chem.* **2001**, 66, 7051

Buchwald: Different Behavior of *E* and *Z* Isomers under Reaction Conditions



- Reaction is stereodivergent: *E* imine gives *R* amine; *Z* imine gives *S* amine
- Reaction shows ee dependence on H₂ pressure
- *Z* imine reacts faster than *E* imine; interconversion of imines is slow
- Best ee obtained at high temperature and pressure

Buchwald et al. *J. Am. Chem. Soc.* **1994**, 116, 8952; 11703

Related hydrosilylation (*Optimized*) system: Buchwald et al. *J. Am. Chem. Soc.* **1996**, 118, 6784

Similar stereodivergent results were observed in the reduction of ketoximes ethers:

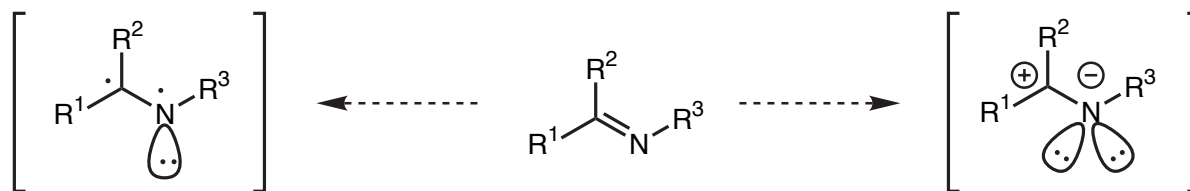
Stoichiometric reduction: Sakito et al. *Tetrahedron Lett.* **1988**, 29, 223

Didler et al. *Tetrahedron* **1991**, 47, 4941

Catalytic reduction: Bolm et al. *Synlett* **1994**, 655

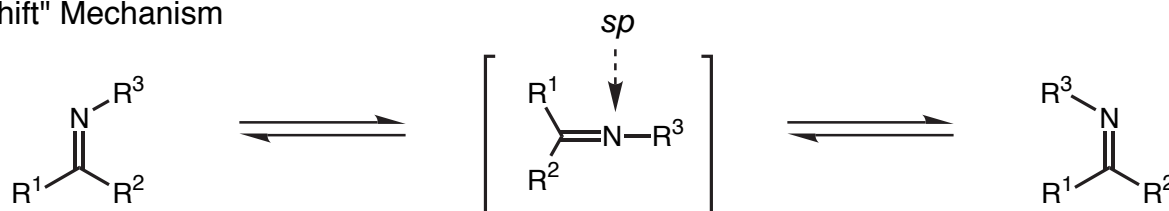
Mechanisms of Interconversion between *E* and *Z* Imines

Homolytic or Heterolytic π -Bond Cleavage



- E_{act} estimated to be 50 kcal/mol or higher; lower energy pathways available
- Equilibrium can be **induced using $h\nu$**

"Lateral Shift" Mechanism



- Rates studies are consistent with this mechanism
 - Hammett ρ of 1.5 found for substituents on $R^3 = \text{Ar}$ (EWG at 4-position accelerate isomerization)
 - Rate enhancement increases with increasing size of *ortho* substituents ($R^3 = \text{Ar}$)

Equilibration via formation of N,O-acetal

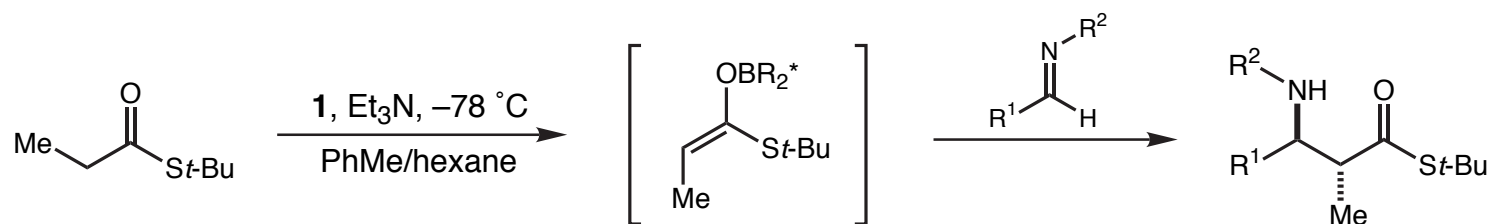
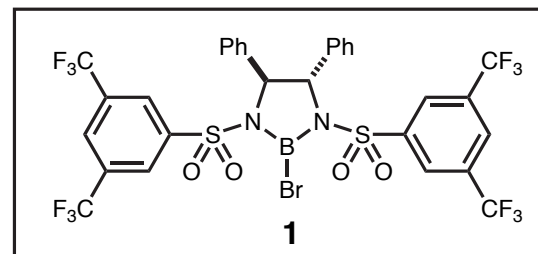
- Pathway only available when H_2O or ROH present

Tautomerization

- C-H bond must be present α to the imine group

"*syn-anti* Isomerizations and Rearrangements" McCarty, C. G. in *The Chemistry of the Carbon-Nitrogen Double Bond*, Patai, S., Ed., John Wiley & Sons (London), 1970, chapter 9.

Corey: First Example Using
an "External" Source of Chirality

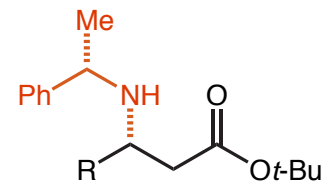
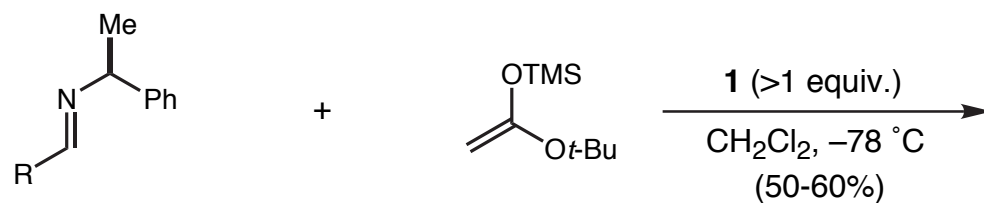
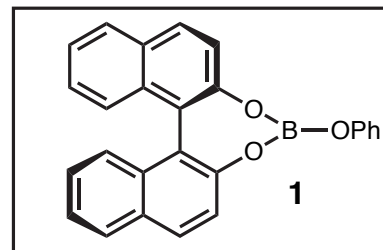


R ¹	R ²	yield (%)	<i>anti:syn</i>	ee (%)
Ph	allyl	92	>99:1	90
Ph	Bn	96	>99:1	92
1-naphthyl	allyl	91	>99:1	>99
(<i>E</i>)-PhCH=CH	allyl	86	>99:1	>99
Ph(CH ₂) ₂	allyl	90	97:3	90
Ph(CH ₂) ₂	Bn	86	92:8	90

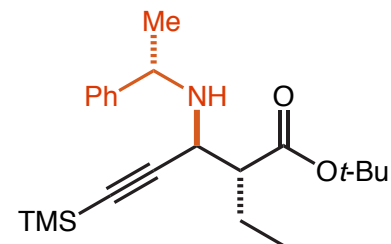
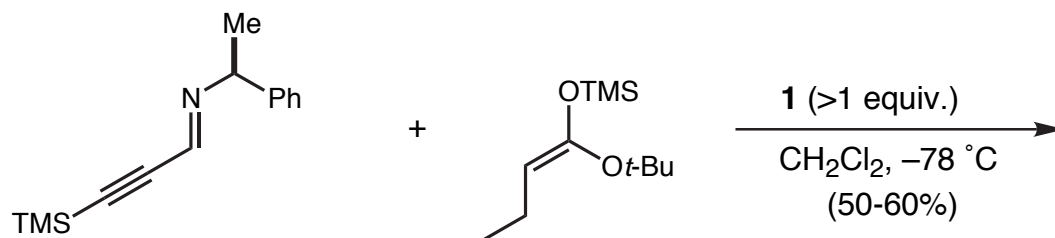
- Chair transition state with *Z* imine accounts for the results

Corey et al. *Tetrahedron Lett.* **1991**, 32, 5287

Yamamoto: Synthesis of β -Amino Esters via Double Stereodifferentiation



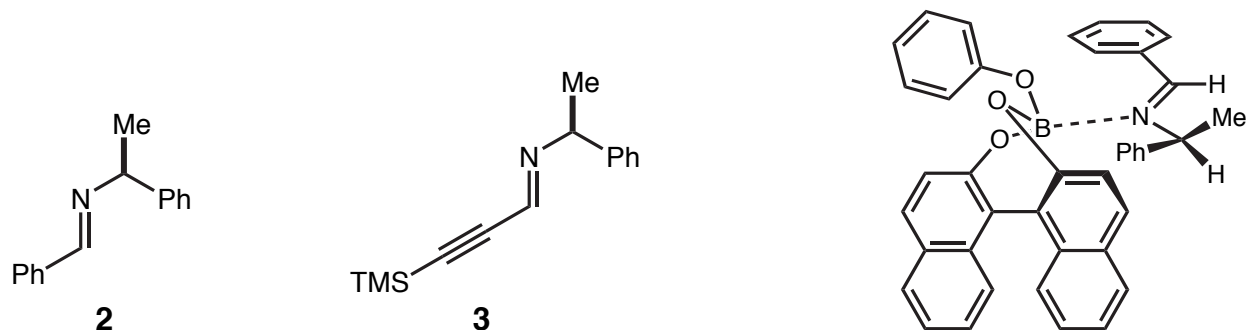
R = Ph, <i>R</i> -1	92% de
R = Ph, <i>S</i> -1	74% de
R = <i>n</i> -Pr, <i>R</i> -1	94% de
R = <i>n</i> -Pr, <i>S</i> -1	86% de



<i>R</i> -1: anti/syn = 40:1, dr (anti) = 99:1
<i>S</i> -1: anti/syn = 2:1, dr (anti) = 94:6

Yamamoto et al. *J. Am. Chem. Soc.* **1993**, *115*, 1151

Yamamoto: Effect of Lewis Acid on Imine Geometry

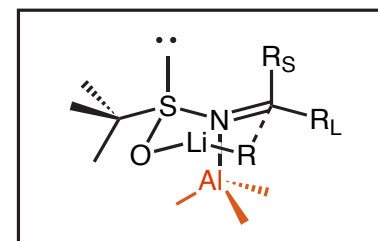
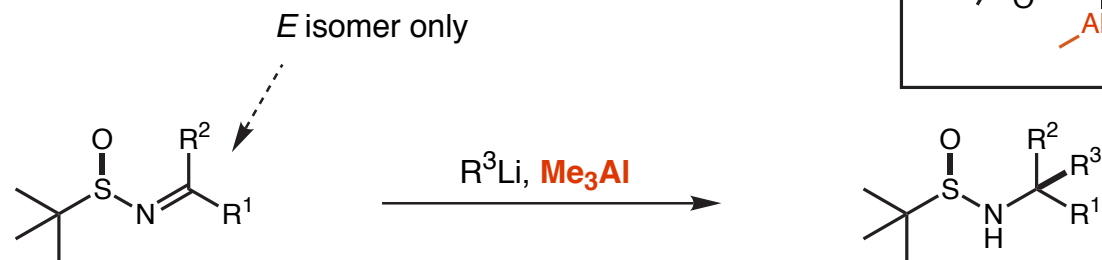


equiv. of (<i>R</i>)-1	<i>E:Z</i> ratio (−60 °C, CD ₂ Cl ₂)	
	Imine 2	Imine 3
0	≥95:5	67:33
0.3	≥95:5	60:40
0.7	≥95:5	41:59
1.0	≥95:5	29:71
2.0	≥95:5	≤5:95

Observed imine geometry explains the stereochemical outcome of the reaction

Yamamoto et al. *J. Am. Chem. Soc.* **1993**, *115*, 1151

Ellman: Synthesis of Chiral Tertiary Amines



R ¹	R ²	R ³	Me ₃ Al (equiv.)	yield (%)	dr
<i>i</i> -Pr	Me	Ph	0	65	94:6
		Ph	1.1	93	97:3
		<i>n</i> -Bu	1.1	61	99:1
Ph	Me	<i>n</i> -Bu	0	26	99:1
		<i>n</i> -Bu	1.1	86	98:2
Ph	<i>n</i> -Bu	Me	1.1	>99	99:1
<i>n</i>-Bu	Me	Ph	1.1	93	89:11*

* *E*:*Z* ratio of imine in CDCl₃ = 83:17

Me₃Al required for both high yield and diastereoselectivity

Ellman et al. *J. Am. Chem. Soc.* **1999**, 121, 268

For a review on synthesis of chiral 2° amines using this auxiliary: Davis et al. *Chem. Soc. Rev.* **1998**, 27, 13

1. Background

- E-Z geometry problem
- C=N reduced electrophilicity

2. Activation of the electrophile

2.1. Activation via **bidentate complexation**

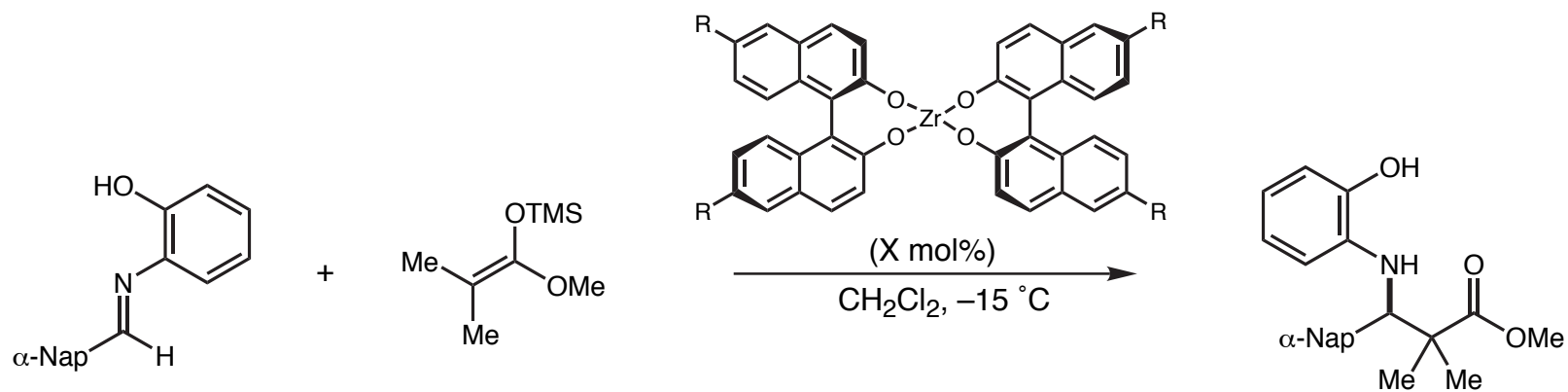
- **Basic sites present on azomethine group**
- Basic sites present on substrate (ex. Imino esters)

2.2. Activation via single point binding

3. Activation of the nucleophile

4. Bifunctional catalysis

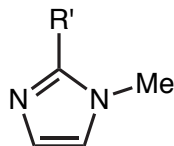
Kobayashi: Optimization of the Reaction Procedure



R	X (mol %)	Additive (X mol%)	yield (%)	ee (%)
H	20	—	>99	34
H	20	NMI	80	70
Br	20	NMI	73	90
Br	10	NMI	>99	92*
Br	5	DMI	>99	91
Br	2	NMI	75	86*

* Reaction was carried out at -45°C

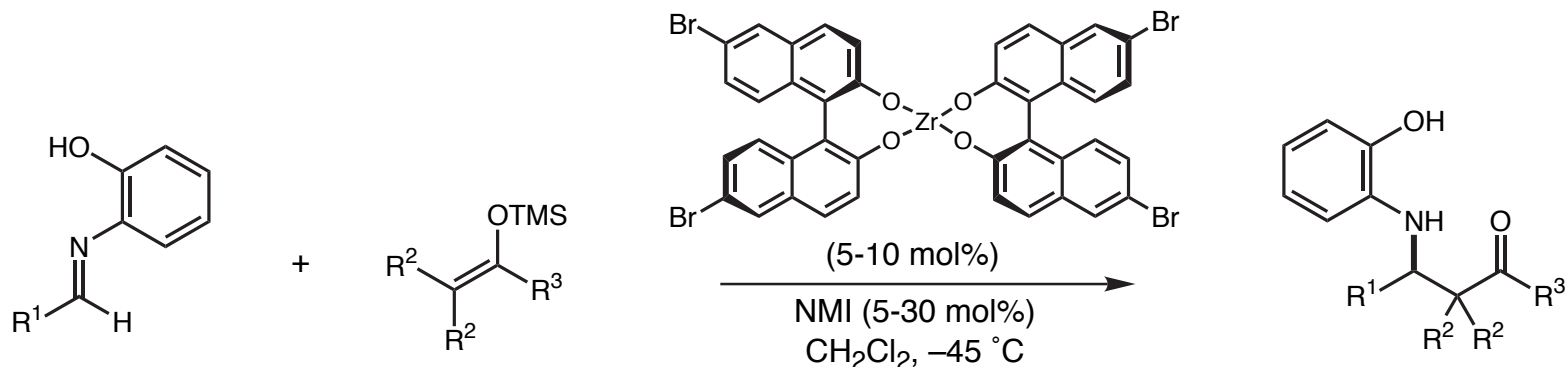
- Imine prepared from aniline or 2-methoxyaniline showed almost no chiral induction



R' = H : **NMI**
R' = Me : **DMI**

Kobayashi et al. *J. Am. Chem. Soc.* **1997**, 119, 7153

Kobayashi: Scope of the Zr-Catalyzed Addition



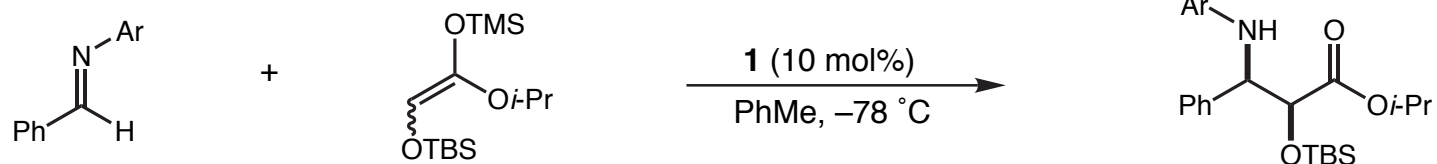
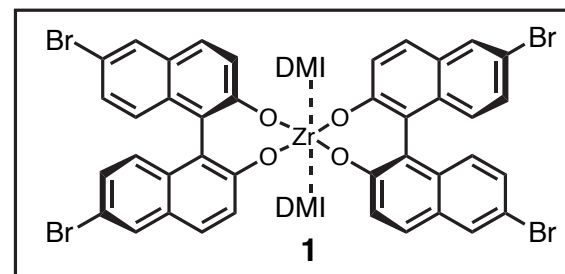
R ¹	R ²	R ³	yield (%)	ee (%)
Ph	Me	OMe	70	87
4-(Cl)C ₆ H ₄	Me	OMe	86	83
Ph	H	SEt	78	88
1-naphthyl	H	SEt	>99	>98
2-furyl	H	SEt	89	89
c-C ₆ H ₁₁	H	SEt	56	80*

* Imine prepared using 2-amino-3-methylphenol

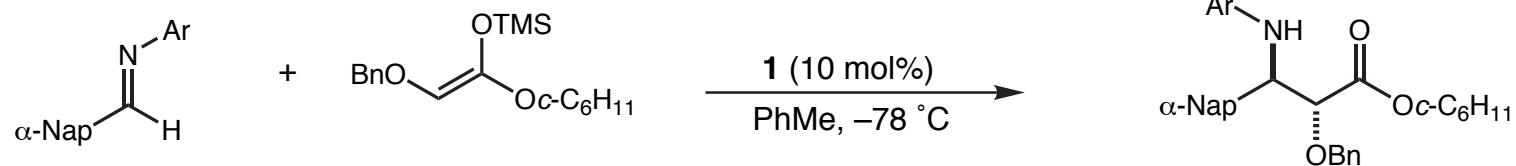
Substitution of -Br for -CF₃ at the 6,6' positions of BINOL increase catalyst efficiency (2 mol%)

Kobayashi et al. *J. Am. Chem. Soc.* **1997**, 119, 7153
J. Am. Chem. Soc. **2000**, 122, 8180

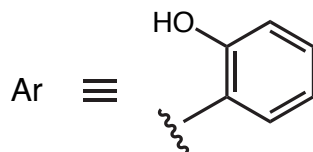
Kobayashi: Scope of the Zr-Catalyzed Addition-2



E-OTBS: >99% yield, syn/anti = 96/4, 99% ee (syn)
Z-OTBS: 65% yield, syn/anti = >99/1, 96% ee (syn)

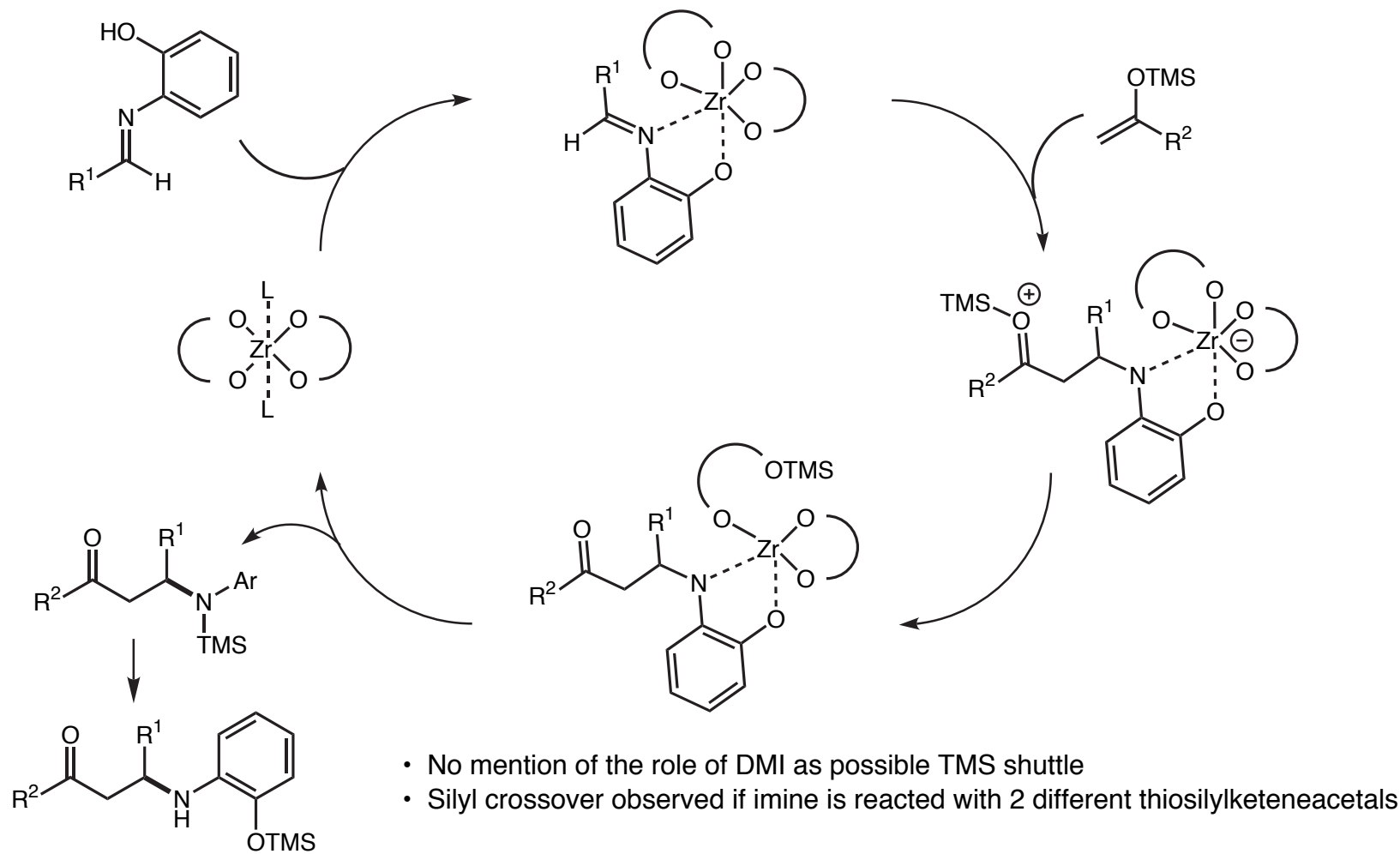


91% yield, syn/anti = 6:94
 80% ee (anti)



Kobayashi et al. *J. Am. Chem. Soc.* **1998**, 120, 431

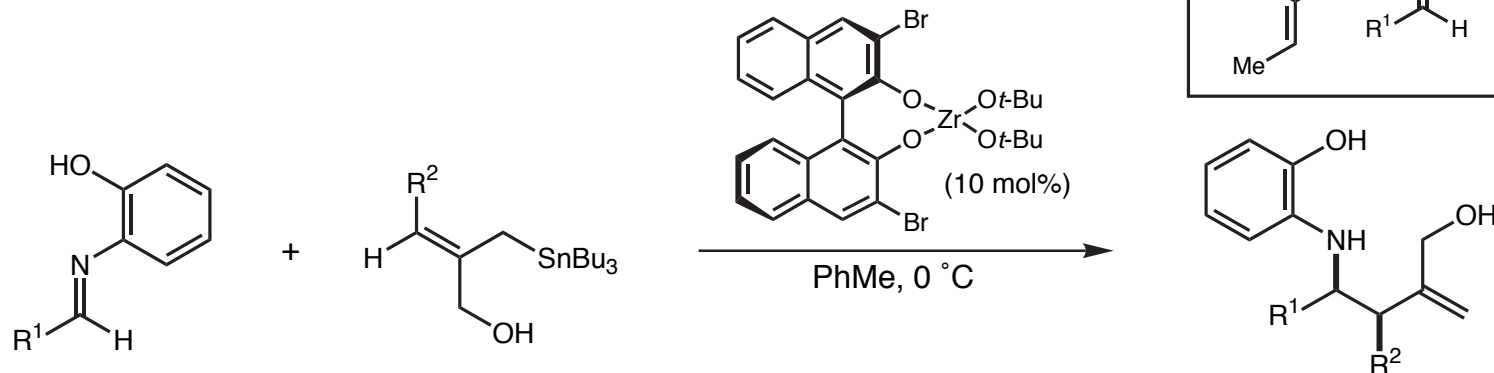
Kobayashi: Mechanism of the Zr-Catalyzed Addition



- No mention of the role of DMI as possible TMS shuttle
- Silyl crossover observed if imine is reacted with 2 different thiosilylketeneacetals

Kobayashi et al. *J. Am. Chem. Soc.* **1997**, *119*, 7153
J. Am. Chem. Soc. **2000**, *122*, 8180
Tetrahedron **2001**, *57*, 861

Kobayashi: Scope of the Zr-Catalyzed Addition



R ¹	R ²	yield (%)	ee (%)
Ph	Me	84	93
2,3-(MeO) ₂ C ₆ H ₃	Me	72	91
2-furyl	Me	76	92*
Ph	H	77	96**
2,3-(MeO) ₂ C ₆ H ₃	H	80	87**
2-furyl	H	68	96**

} *syn:anti*
> 95:5

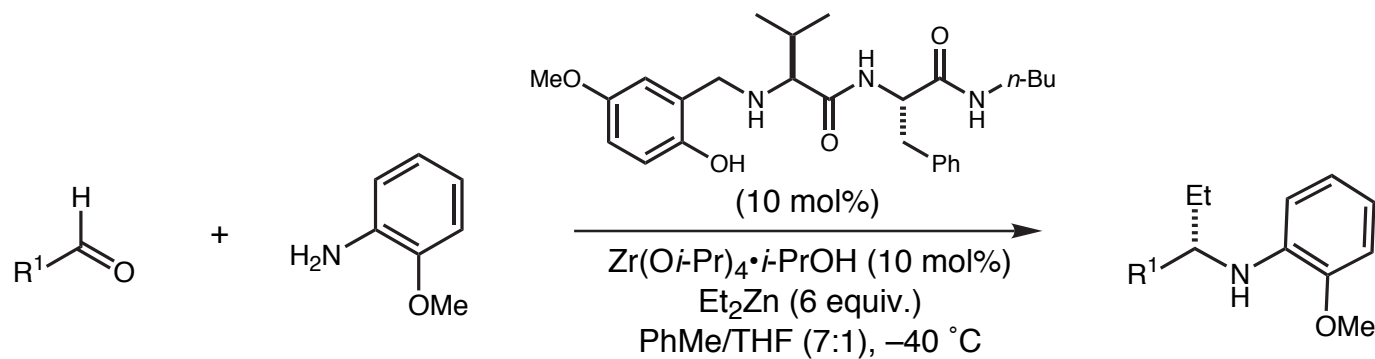
* 3,3'-Cl₂BINOL-derived catalyst was used

** Catalyst prepared with 2 equivalent of MeOH in THF; then 0.1 mmHg

- Replacement of CH₂OH for Me or CH₂OTBS results in enantioselection (~55% ee)

Kobayashi et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 1896

Hoveyda & Snapper: Three-Component Catalytic Asymmetric Synthesis of Aromatic and Aliphatic Amines

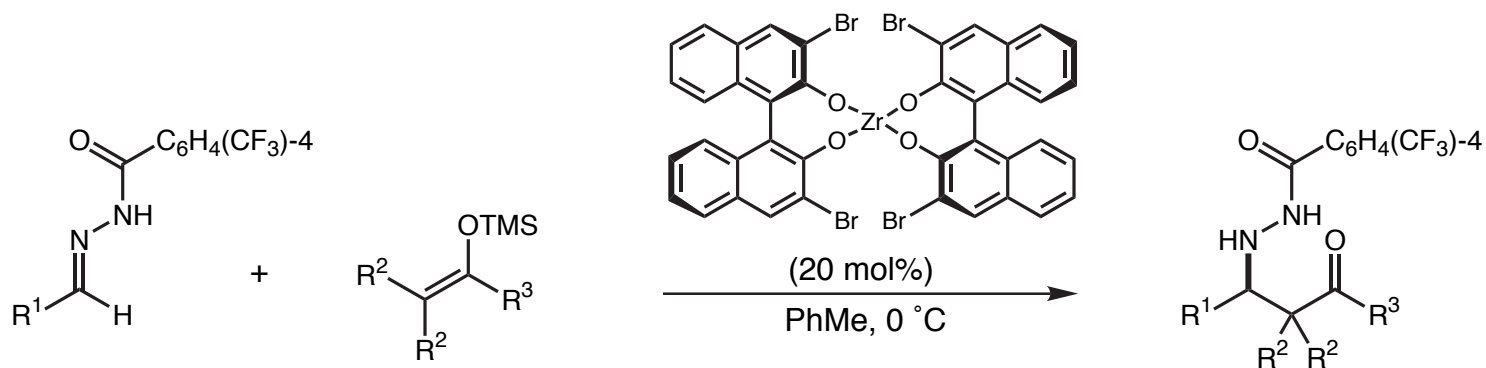


R ¹	yield (%)	ee (%)
Ph	92	91
2-furyl	98	83
3-pyridyl	>98	85
<i>n</i> -Bu	69	97
<i>i</i> -Bu	58	95
<i>c</i> -C ₃ H ₅	83	98
TBDPSOCH ₂	48	>98

No examples of *functionalized* dialkylzincs

Hoveyda, Snapper et al. *J. Am. Chem. Soc.* **2001**, 123, 984
J. Am. Chem. Soc. **2001**, 123, 10409

Kobayashi: Zr-Catalyzed Addition to Acylhydrazones

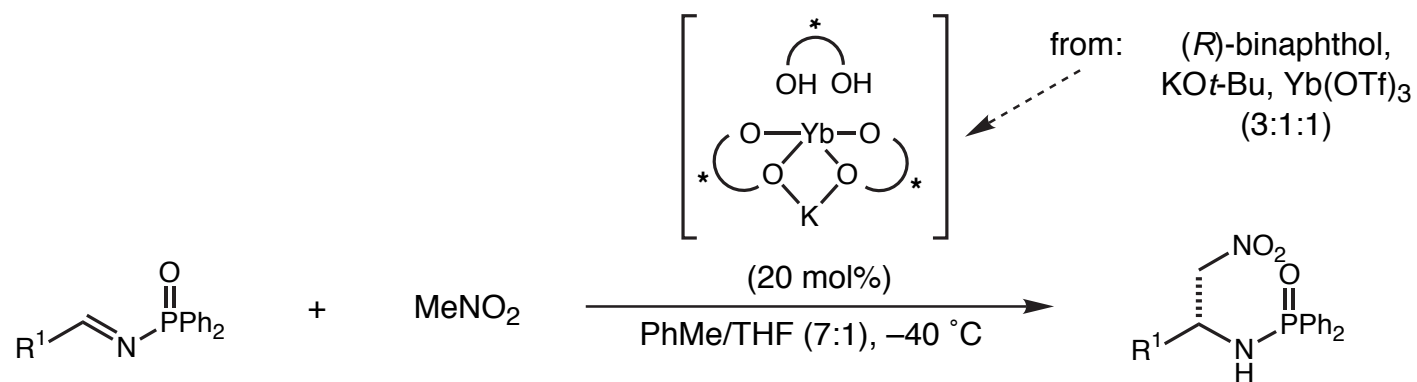


R ¹	R ²	R ³	yield (%)	ee (%)
Ph(CH ₂) ₂	Me	OMe	66	86
	H	SEt	42	88
C ₆ H ₁₃	Me	OMe	60	96
	H	SEt	39	87
Ph	Me	OMe	59	81*
ClCH ₂	Me	OMe	59	93

* 50 mol% catalyst was used

Kobayashi et al. *Chem. Lett.* **1998**, 1131

Shibasaki: Catalytic Asymmetric Nitro-Mannich-Type Reaction

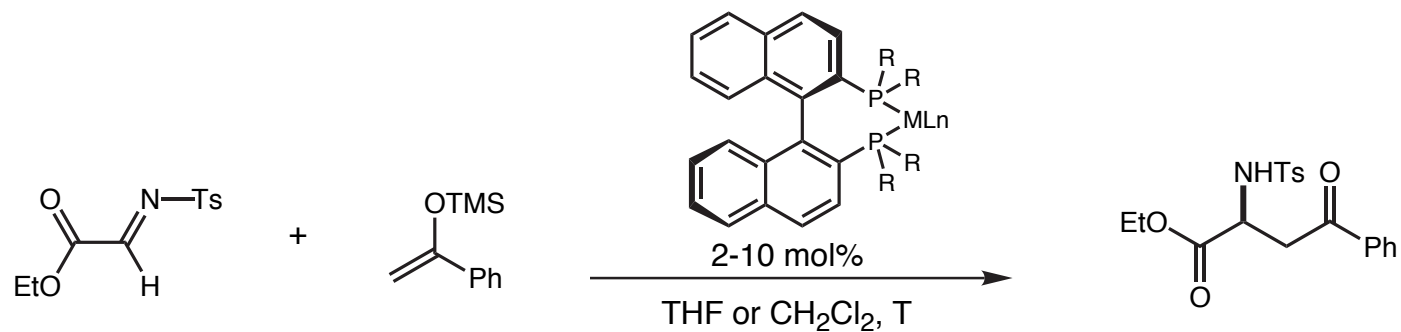


R^1	yield (%)	ee (%)
Ph	79	91
4-(Cl) C_6H_4	93	87
4-(Me) C_6H_4	85	89
2-furyl	57	83
2-(HS) C_6H_4	41	69

Shibasaki et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504

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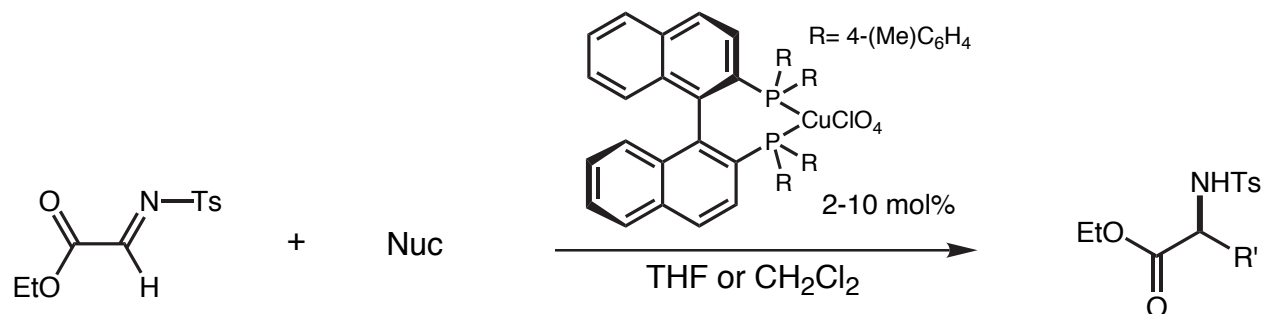
Lectka: Catalytic Enantioselective Alkylation of Imino Esters



MLn	R	T (°C)	ee (%)
AgSbF ₆	Ph	-80	90
		-40	67
Pd(ClO ₄) ₂	Ph	-	80
CuClO ₄	Ph	-78	89
CuClO₄	4-(Me)C₆H₄	0	98
Ni(SbF ₆) ₂	Ph	-	30

Lectka et al. *J. Am. Chem. Soc.* **1998**, *120*, 4548
J. Am. Chem. Soc. **2002**, *124*, 67

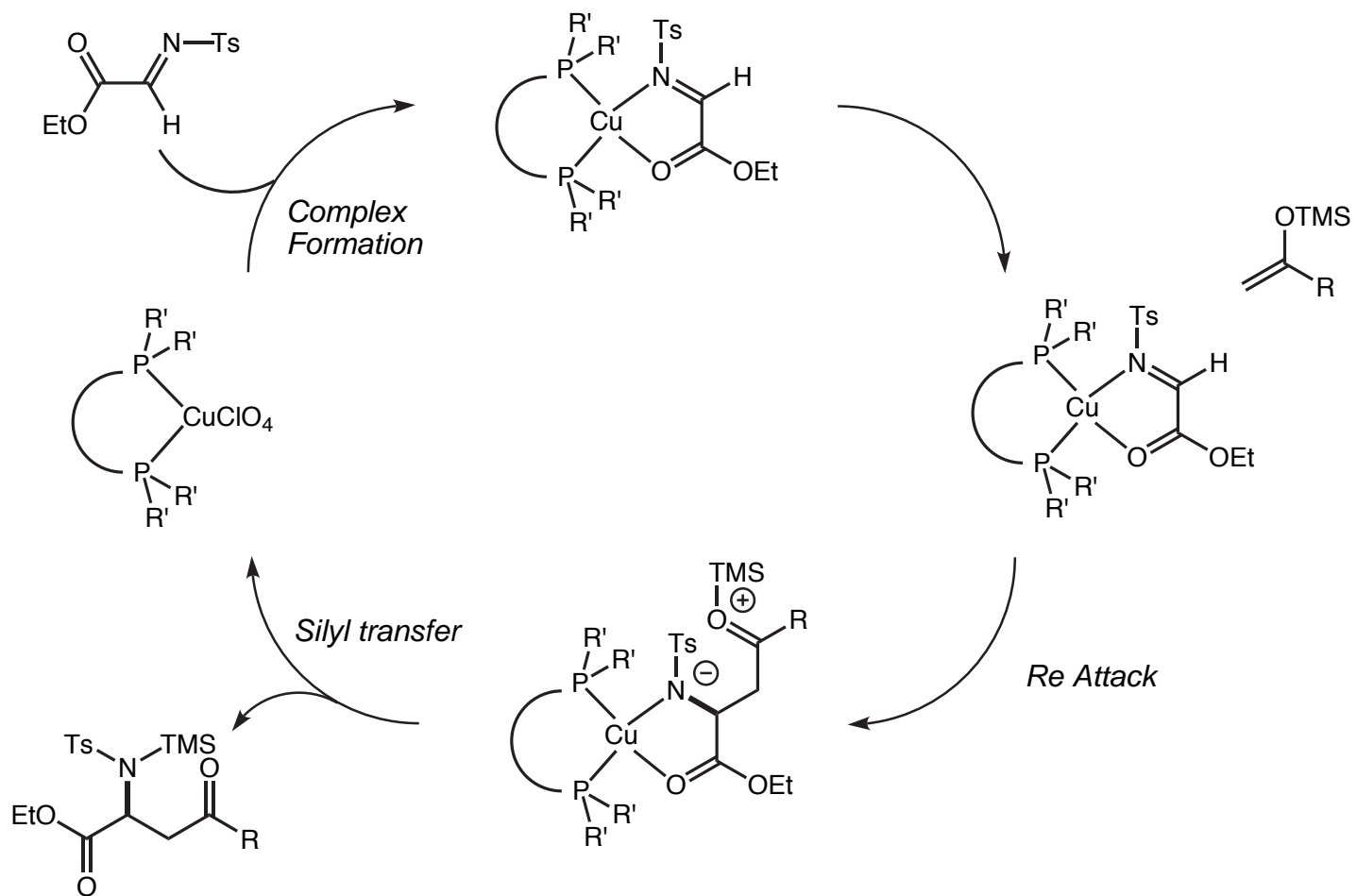
Lectka: Scope of the Alkylation Reaction



Nuc	yield (%)	<i>anti/syn</i>	ee (%)
	83	—	72
	95	—	98
	87	—	94
	94	—	86
	65	—	90
	86	25:1	98
	82	20:1	>99

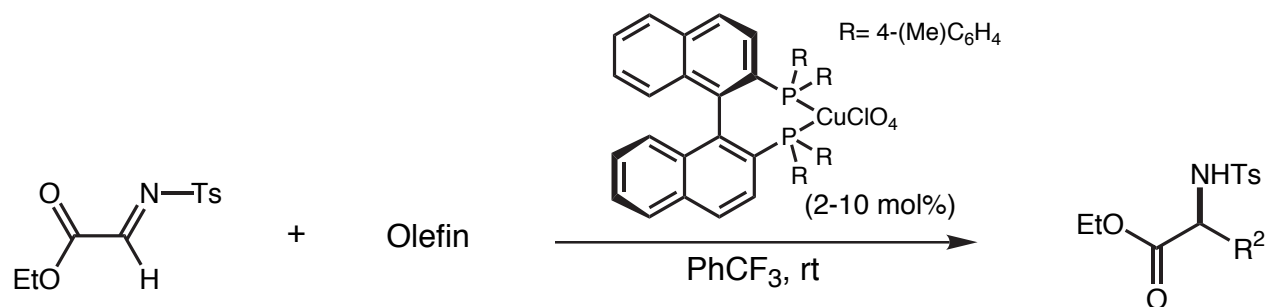
Lectka et al. *J. Am. Chem. Soc.* **1998**, 120, 4548
J. Org. Chem. **1998**, 63, 6090
J. Am. Chem. Soc. **2002**, 124, 67

Lectka: Proposed Mechanism



Lectka et al. *J. Am. Chem. Soc.* **2002**, 124, 67

Lectka: Scope of the Ene Reaction



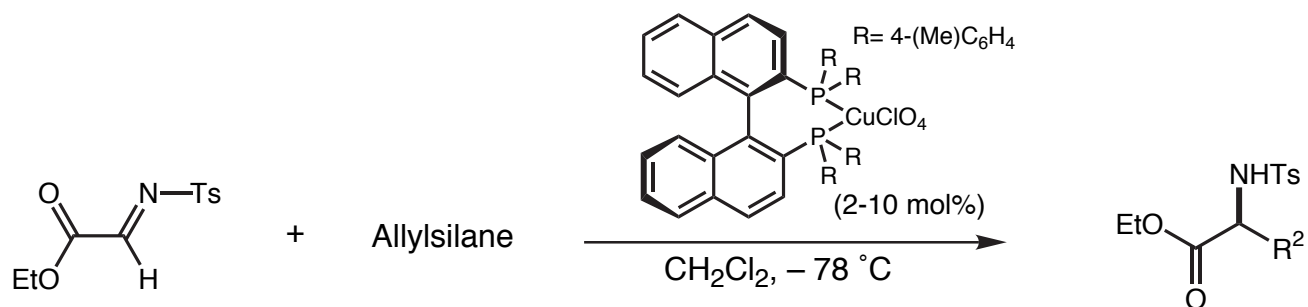
Olefin	Product	yield (%)	ee (%)
		92	99
		85	98
		85	95
		94	99
		85	89
		90	85

Lectka et al. *J. Am. Chem. Soc.* **1998**, *120*, 11006

J. Am. Chem. Soc. **2002**, *124*, 67

See also: Jørgensen et al. *J. Chem. Soc., Chem. Commun.* **1998**, 2547 (CuPF₆ catalyst)

Lectka: Scope of the Allylation Reaction

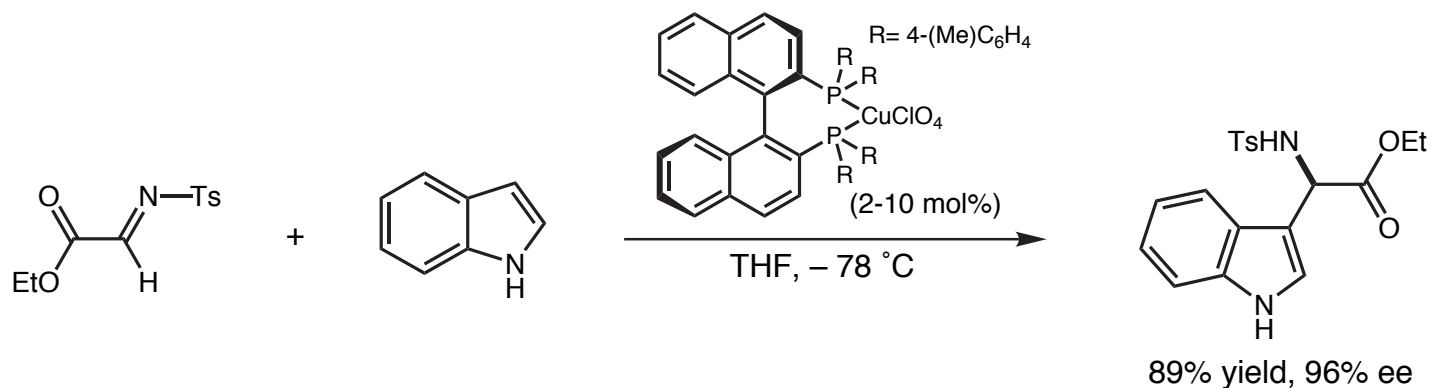


Allylsilane	Product	yield (%)	anti:syn	ee (%)
		88	—	72*
		91	—	94
		85	—	75
		88	20:1	92
		88	10:1	87

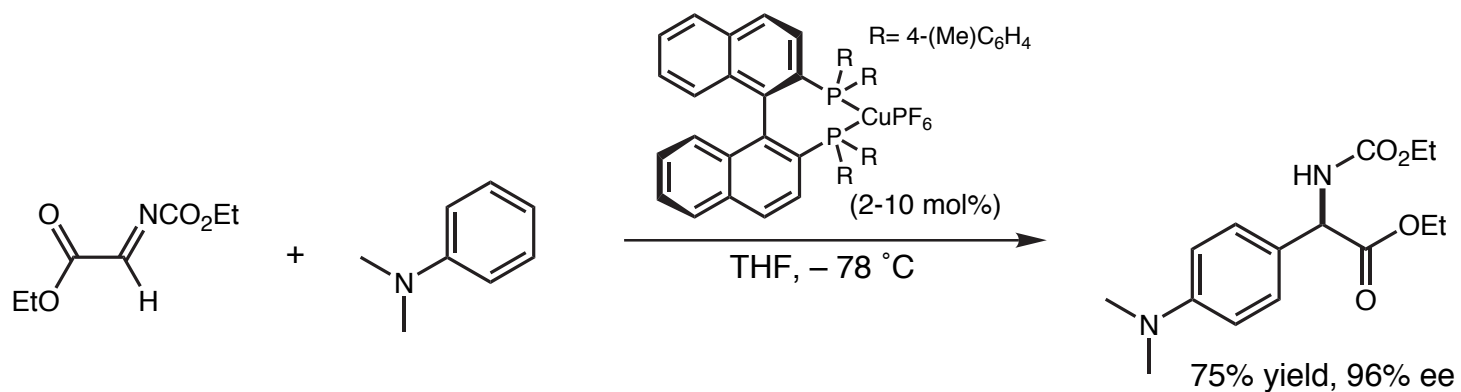
* Can be improved to 80% ee by using CuPF₆ catalyst and tri(*n*-butyl)allylstannane (Jørgensen)

Lectka et al. *J. Am. Chem. Soc.* **2002**, 124, 67
See also: Jørgensen et al. *J. Org. Chem.* **1999**, 64, 4844

*Johannsen, Jørgensen: Catalytic Enantioselective Friedel-Crafts
Reactions of α -Imino Esters*

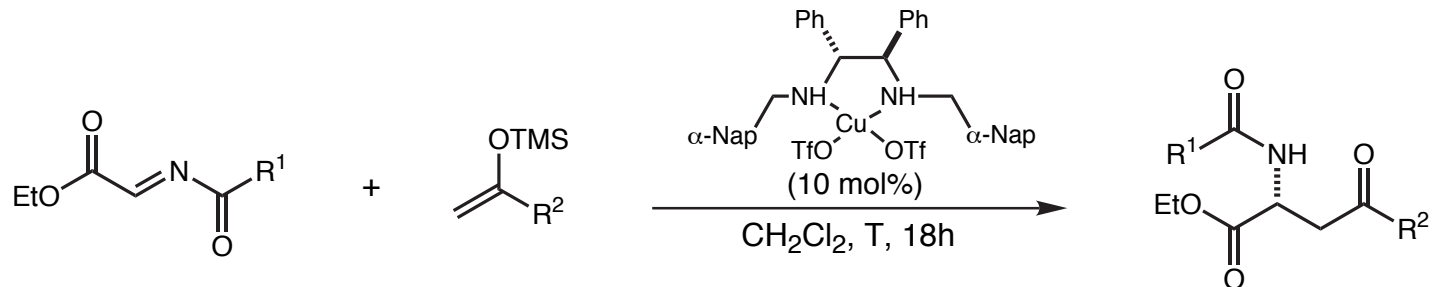


Johannsen, M. *J. Chem. Soc., Chem. Commun.* **1999**, 2233



Jørgensen et al. *Angew. Chem., Int. Ed.* **2000**, 39, 4114

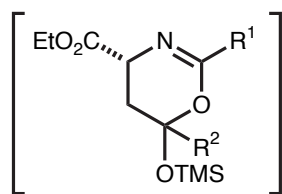
Kobayashi: Reaction of *N*-Acylimino Esters using Cu(II)-Catalyst



R ¹	R ²	T (°C)	yield (%)	ee (%)
C ₁₁ H ₂₃	Ph	0	92	94
	4-(MeO)C ₆ H ₄	0	97	92
	4-(Cl)C ₆ H ₄	0	88	93
Me	Ph	0	85	94
Ph	Ph	-78	79	97
	OMe	-78	81	96
	SEt	-78	76	90

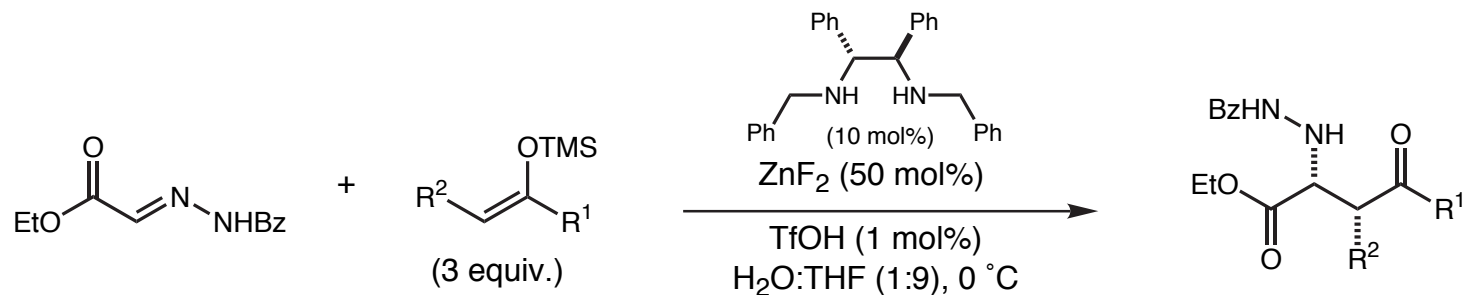
• Reaction is also efficient with methyl enol ethers, to afford the parent "internal" methyl enol ether in similar yields and ee

• Proposed: [4+2]-cycloaddition



Kobayashi et al. *Org. Lett.* **2002**, 4, 143

Kobayashi: Reaction using Zn(II)-Catalyst in Aqueous Media



R ¹	R ²	yield (%)	<i>syn:anti</i>	ee (%)
Ph	H	19	—	90*
Ph	H	89	—	92
4-(Cl)C ₆ H ₄	H	88	—	89
4-(Me)C ₆ H ₄	H	82	—	91
4-(MeO)C ₆ H ₄	H	63	—	91
Ph	Me	91	96:4	91
<i>i</i> -Pr	Me	30	90:10	30

* Reaction run without TfOH

Kobayashi et al. *J. Am. Chem. Soc.* **2002**, 124, 5640

1. Background

- E-Z geometry problem
- C=N reduced electrophilicity

2. Activation of the electrophile

2.1. Activation via bidentate complexation

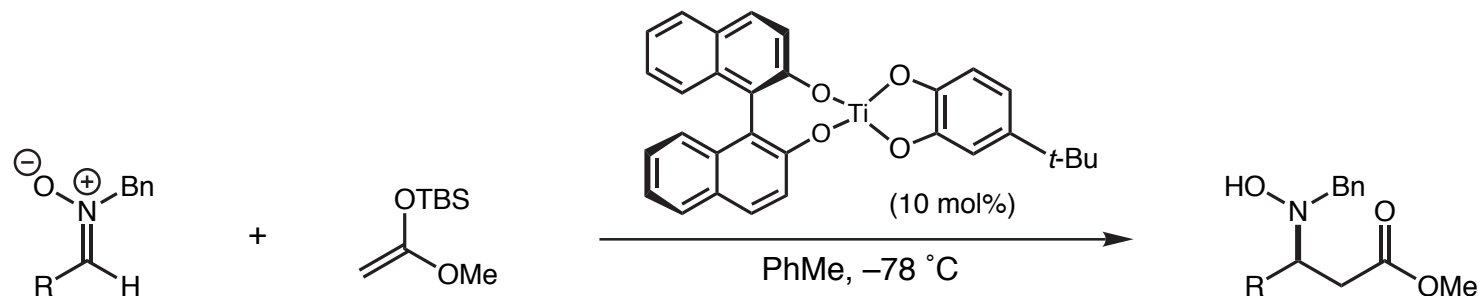
- Basic sites present on imine
- Basic sites present on substrate (ex. Imino esters)

2.2. Activation via **single point binding**

3. Activation of the nucleophile

4. Bifunctional catalysis

Murahashi: Titanium-Catalyzed Enantioselective Addition to Nitrones



R	yield (%)	ee (%)
Ph	99	92
2-naphthyl	94	88
4-(Me)C ₆ H ₄	66	88
3-pyridyl	90	80
3,4-(OCH ₂ O)C ₆ H ₃	74	80

- Reaction exhibit a **positive nonlinear relationship**
- Biphenoxide catalyst affords the *opposite enantiomer* (55% ee, R = Ph)

Murahashi et al. *J. Am. Chem. Soc.* **2002**, *124*, 2888

1. Background

- E-Z geometry problem
- C=N reduced electrophilicity

2. Activation of the electrophile

2.1. Activation via bidentate complexation

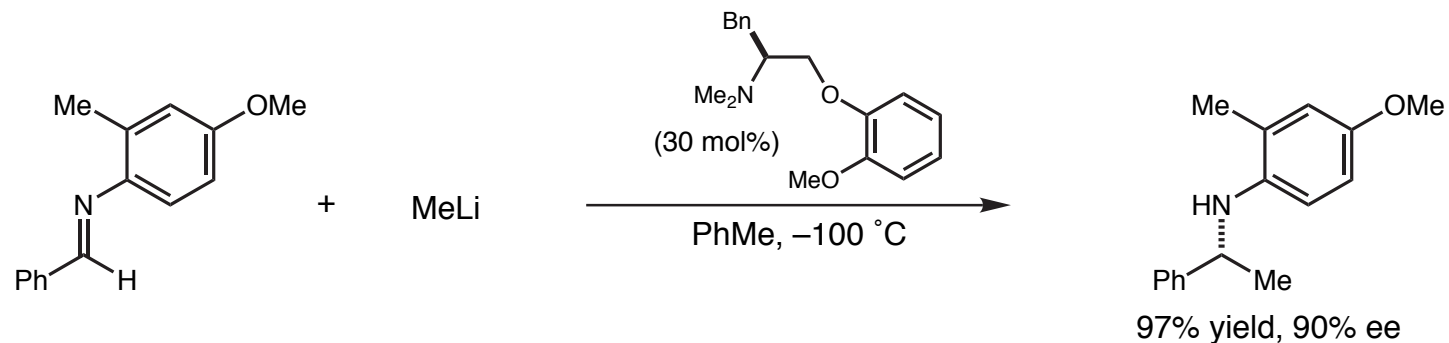
- Basic sites present on imine
- Basic sites present on substrate (ex. Imino esters)

2.2. Activation via single point binding

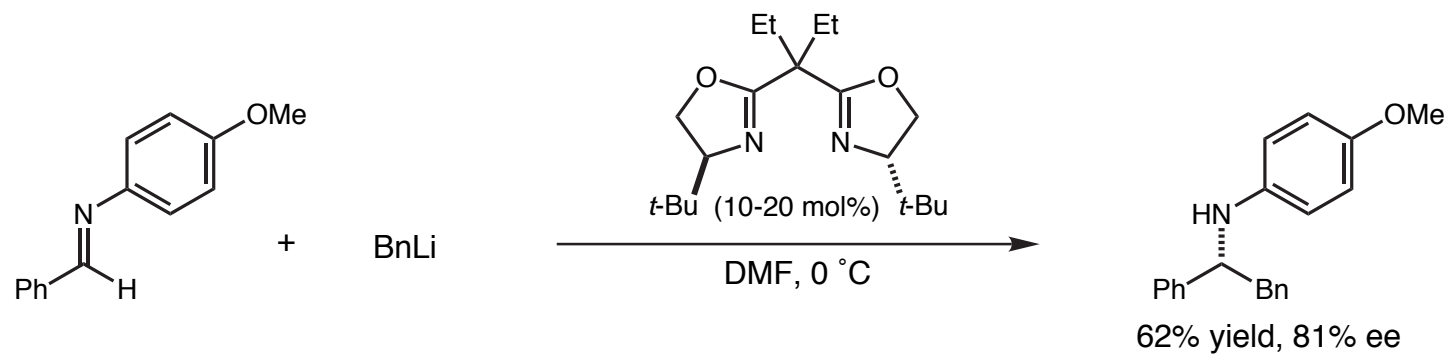
3. Activation of the nucleophile

4. Bifunctional catalysis

Tomioka, Denmark: Catalytic Asymmetric Addition of Organolithium Reagents



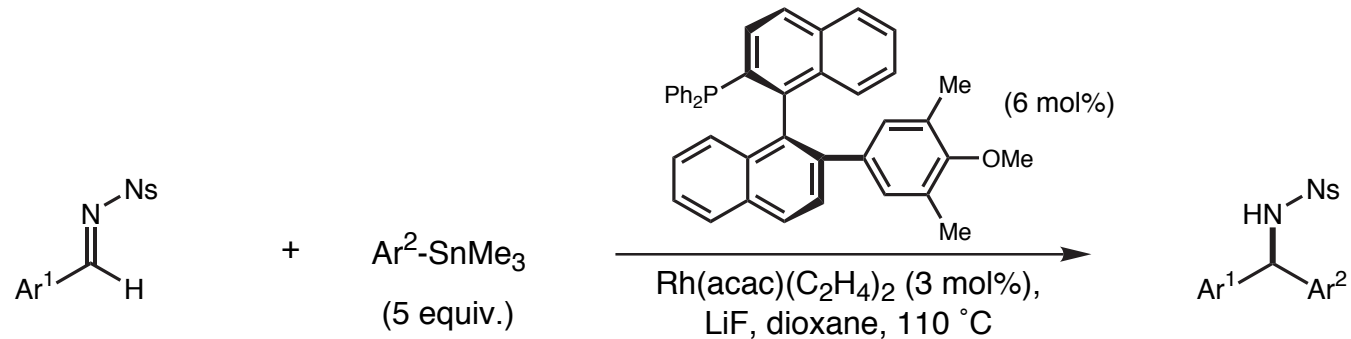
Tomioka et al. *Tetrahedron Lett.* **1991**, 32, 3095
Tetrahedron **1994**, 50, 4429



Denmark et al. *J. Am. Chem. Soc.* **1994**, 116, 8797
J. Org. Chem. **2000**, 65, 5875

N.B. The *best* results obtained by the authors are shown on this slide

Hayashi: Rhodium Catalyzed Arylation of Imines

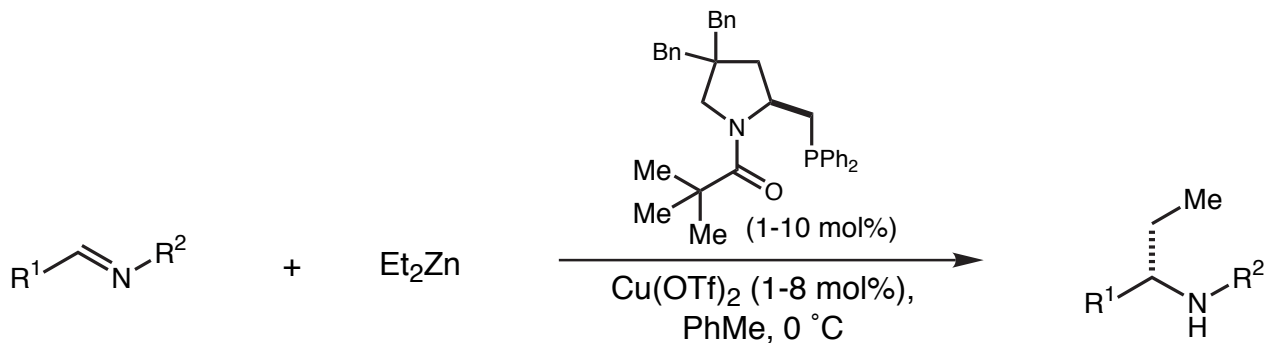


Ar ¹	Ar ²	yield (%)	ee (%)
4-(CF ₃)C ₆ H ₄	Ph	90	96
	4-(MeO)C ₆ H ₄	89	96
4-(MeO ₂ C)C ₆ H ₄	Ph	90	92
	4-(F)C ₆ H ₄	69	92
Ph	4-(MeO)C ₆ H ₄	86	92
	4-(CF ₃)C ₆ H ₄	31	82

Reactions with bidentate phosphines were very slow

Hayashi et al. *J. Am. Chem. Soc.* **2000**, 122, 976

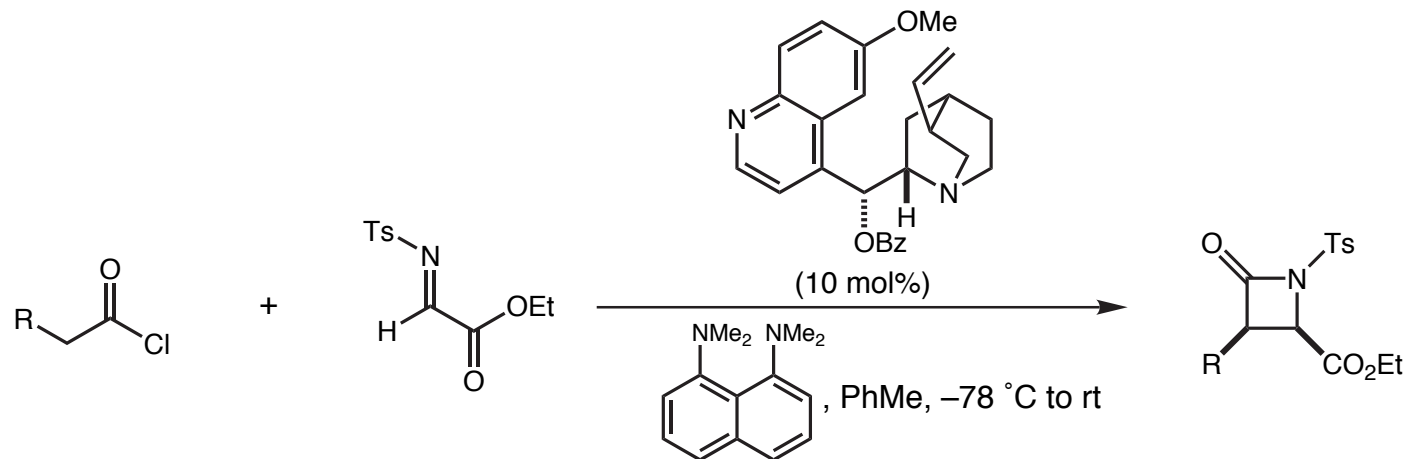
Tomioka: Copper-Amidophosphine Catalyst for Asymmetric Addition of Diethylzinc to Imines



R ¹	R ²	yield (%)	ee (%)
Ph	Ts	98	93
	Ms	97	94
	SES	98	90
4-(MeO)C ₆ H ₄	Ms	83	92
4-(Cl)C ₆ H ₄	Ms	95	94
2-(Cl)C ₆ H ₄	Ms	95	92
2-furyl	SES	98	93

Tomioka et al. *J. Am. Chem. Soc.* **2000**, 122, 12055

Lectka: Catalytic Asymmetric Staudinger Reaction

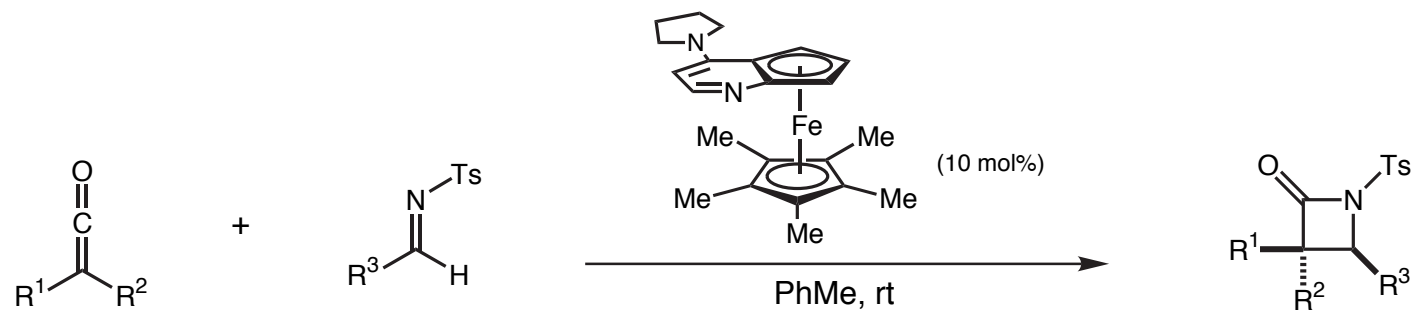


R	yield(%)	<i>cis:trans</i>	ee (%)
Ph	65	99:1	96
Et	57	99:1	99
OPh	45	99:1	99
OAc	61	>99:1	98
OBn	56	99:1	95

Catalyst plays two distinct roles: base (ketene generation) and nucleophilic catalyst

Lectka et al. *J. Am. Chem. Soc.* **2000**, 122, 7831

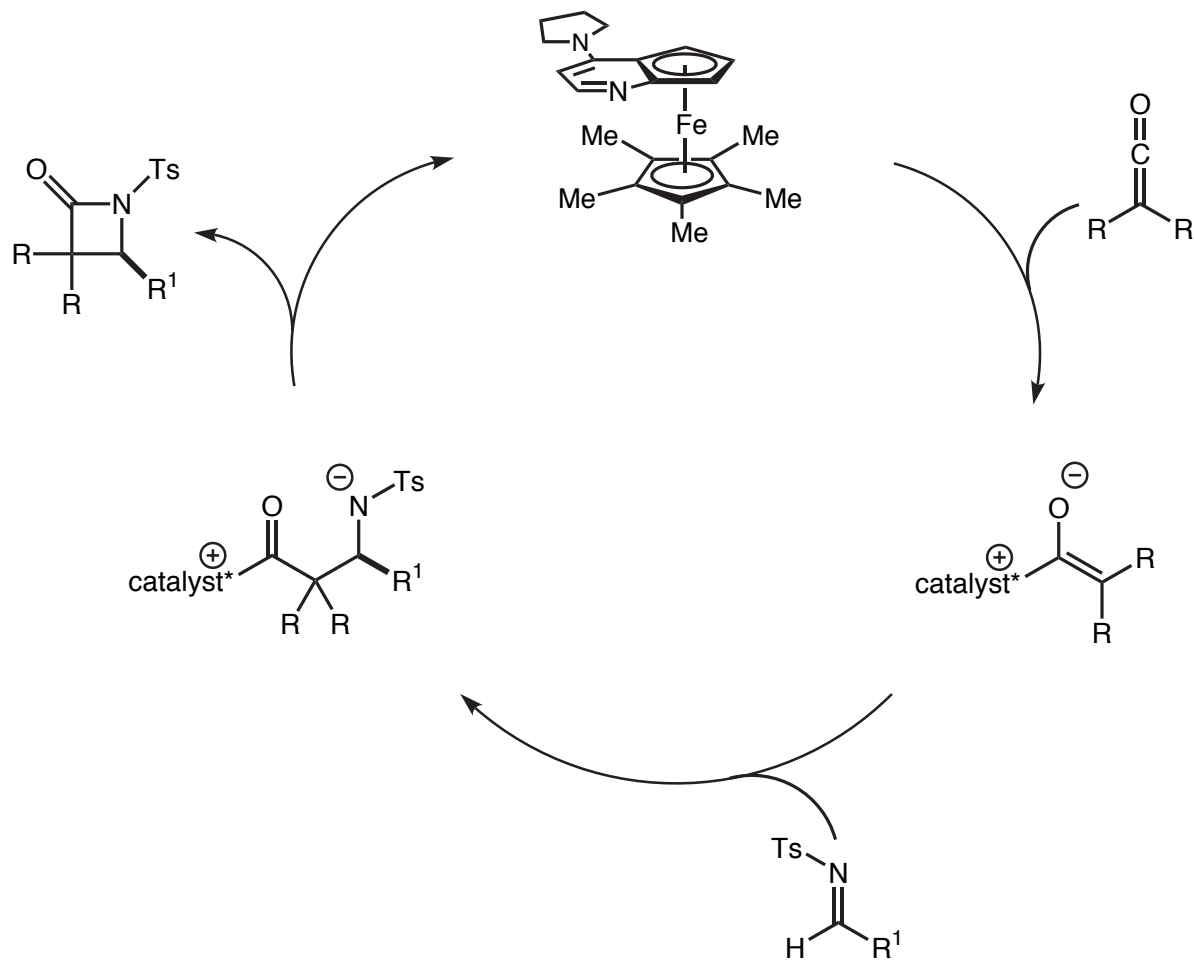
Fu: Catalytic Asymmetric Staudinger Reaction



R ¹	R ²	R ³	yield (%)	cis/trans	ee (%)
-(CH ₂) ₆ -		Ph	84	—	81
-(CH ₂) ₆ -		(<i>E</i>)-PhCH=CH ₂	91	—	91
-(CH ₂) ₆ -		<i>c</i> -C ₆ H ₁₁	76	—	94
Ph	<i>i</i> -Bu	Ph	88	8:1	98
Ph	<i>i</i> -Bu	(<i>E</i>)-PhCH=CH ₂	95	10:1	95
Ph	Et	2-furyl	97	9:1	95
Ph	Et	<i>c</i> -C ₃ H ₅	98	10:1	98

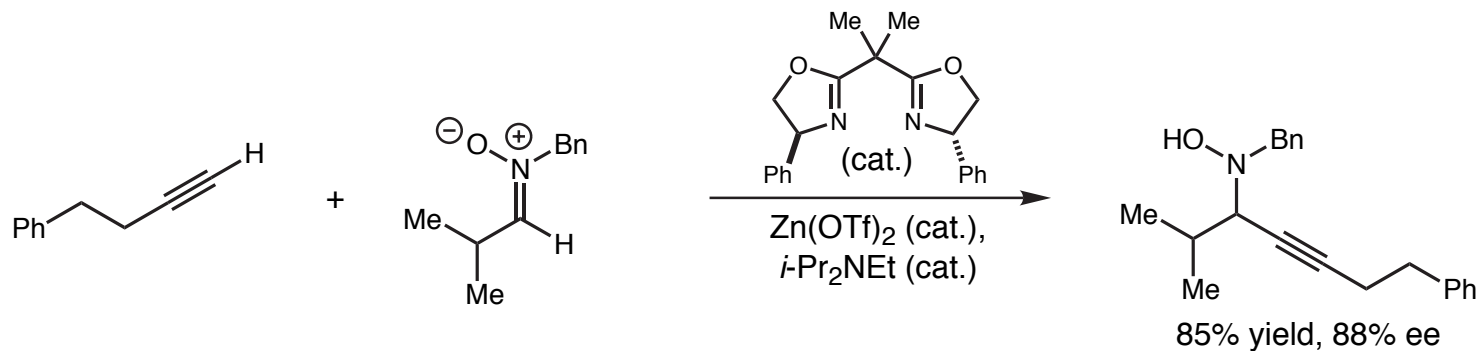
Fu et al. *J. Am. Chem. Soc.* **2002**, 124, 1578

Fu: Mechanism of the Staudinger Reaction

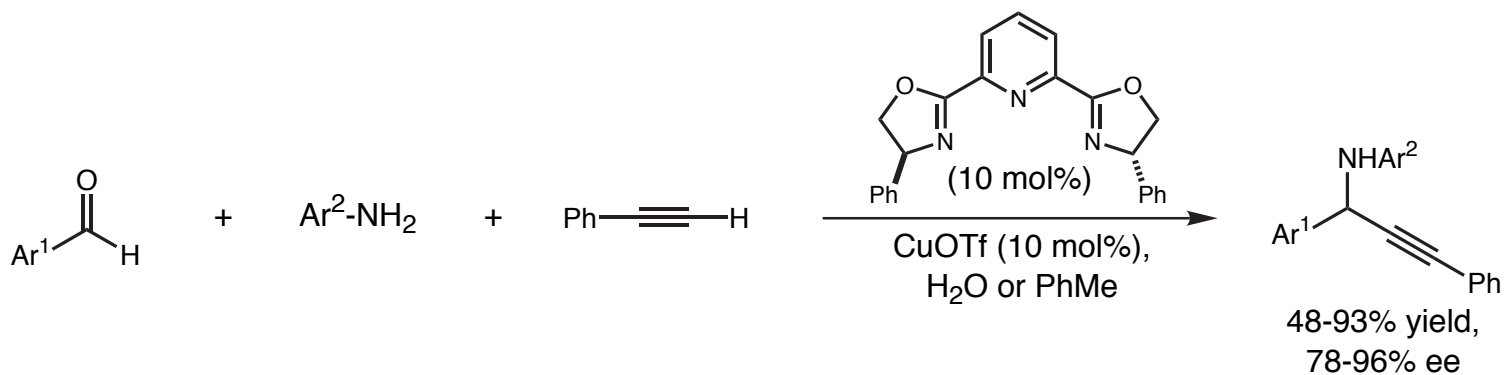


Fu et al. *J. Am. Chem. Soc.* **2002**, 124, 1578

Carreira, Li: Catalytic Asymmetric Addition of Metal Acetylides



Carreira et al. *Acc. Chem. Res.* **2000**, 33, 373



Li et al. *J. Am. Chem. Soc.* **2002**, 124, 5638

For more on Catalytic Additions of M-acetylides: Janey, J. *Evans Group Friday Seminar 2002*

1. Background

- E-Z geometry problem
- C=N reduced electrophilicity

2. Activation of the electrophile

2.1. Activation via bidentate complexation

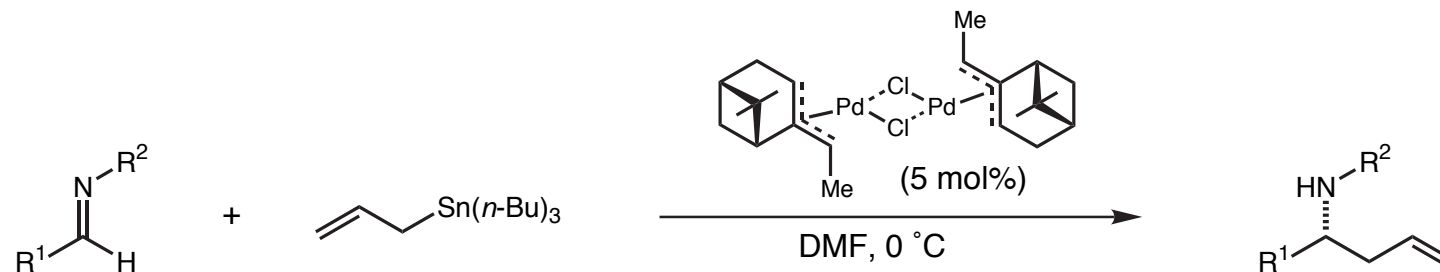
- Basic sites present on imine
- Basic sites present on substrate (ex. Imino esters)

2.2. Activation via single point binding

3. Activation of the nucleophile

4. Bifunctional catalysis

Yamamoto: Catalytic Asymmetric Allylation of Imines

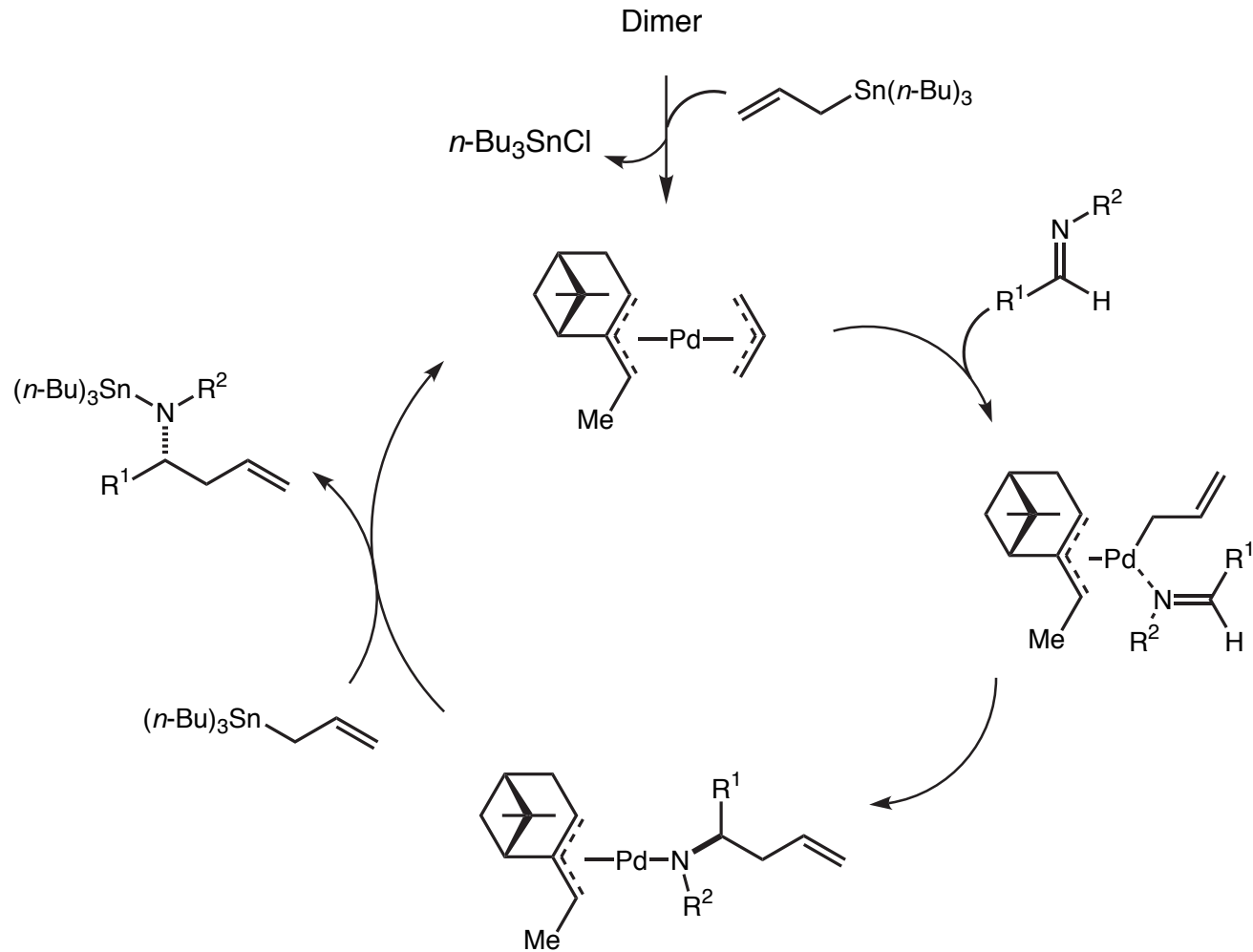


R ¹	R ²	yield (%)	ee (%)
Ph	Bn	62	81
	PMB	50	80
	Ph	74	0
	<i>n</i> -Pr	30	70
4-(MeO)C ₆ H ₄	Bn	48	78
(<i>E</i>)-PhCH=CH	Bn	68	61

Running the reaction with *allylsilane* also possible under the following conditions:
 5 mol% cat., allyltrimethylsilane (2 equiv.), TBAF (0.5 equiv.), *n*-hexane/THF, 0 °C
 (similar yields and ee)

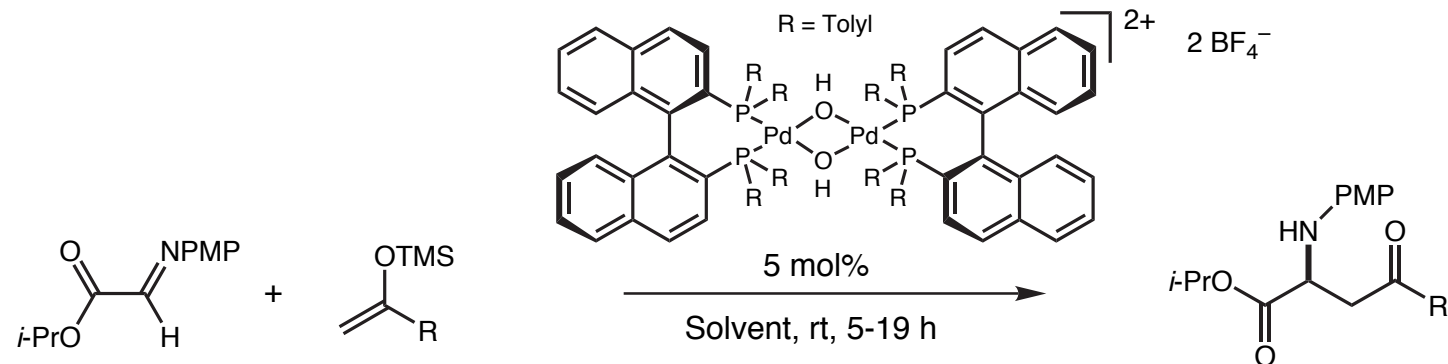
Yamamoto et al. *J. Am. Chem. Soc.* **1998**, *120*, 4242
J. Org. Chem. **1999**, *64*, 2614

Yamamoto: Catalytic Asymmetric Allylation of Imines



Yamamoto et al. *J. Am. Chem. Soc.* **1998**, 120, 4242

Sodeoka: Catalytic Enantioselective Alkylation of Imino Esters

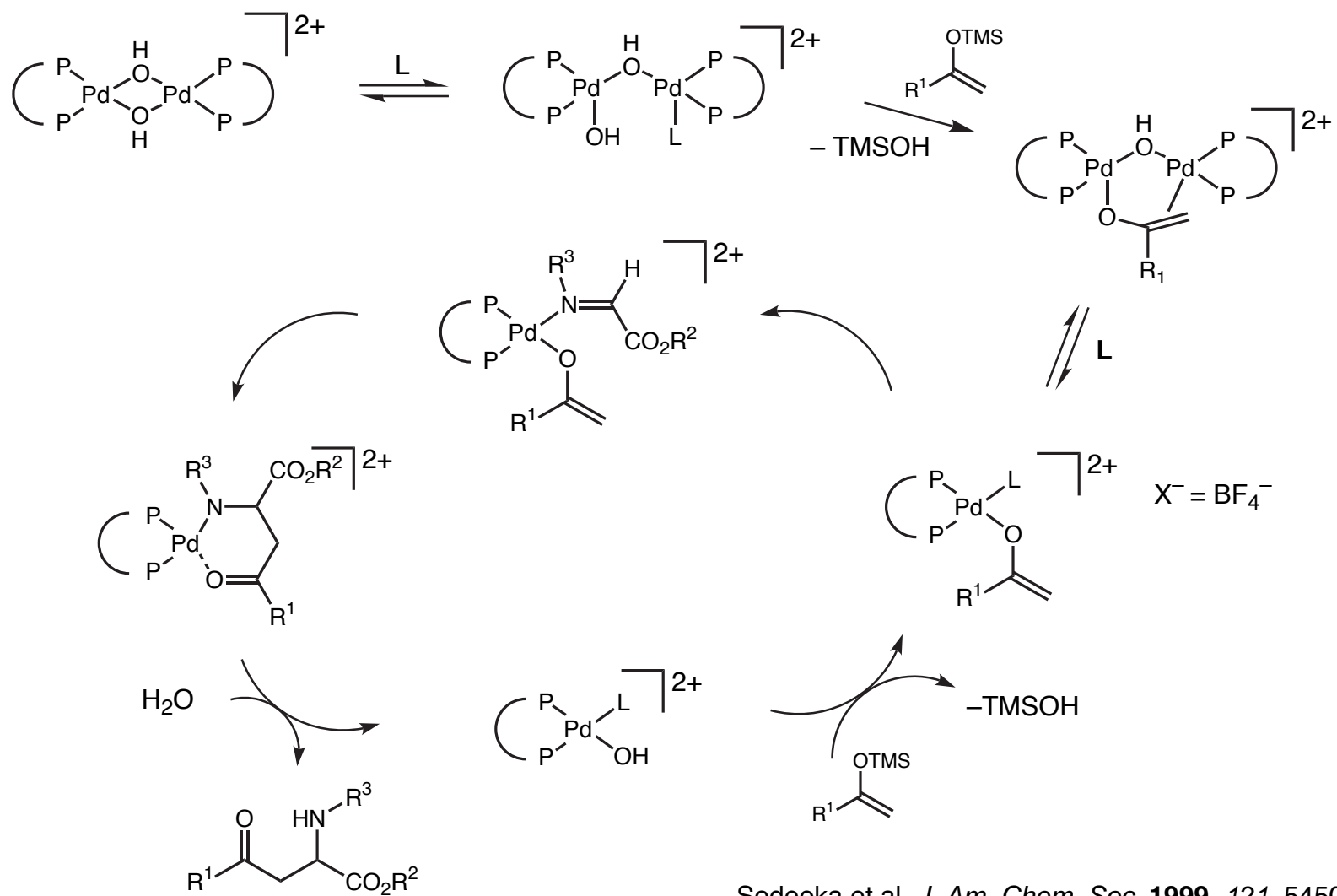


R	Solvent	yield (%)	ee (%)
Ph	DMF	95	90
	THF	60	67*
	CH_2Cl_2	45	53*
2-naphthyl	DMF	82	83
3,4-(Cl) $_2$ C $_6$ H $_4$	DMF	80	84
2-(MeO)C $_6$ H $_4$	DMF	87	71
3-(NO $_2$)C $_6$ H $_4$	DMF	62	60
Me	DMF	79	53

* Reaction required 4.5 days

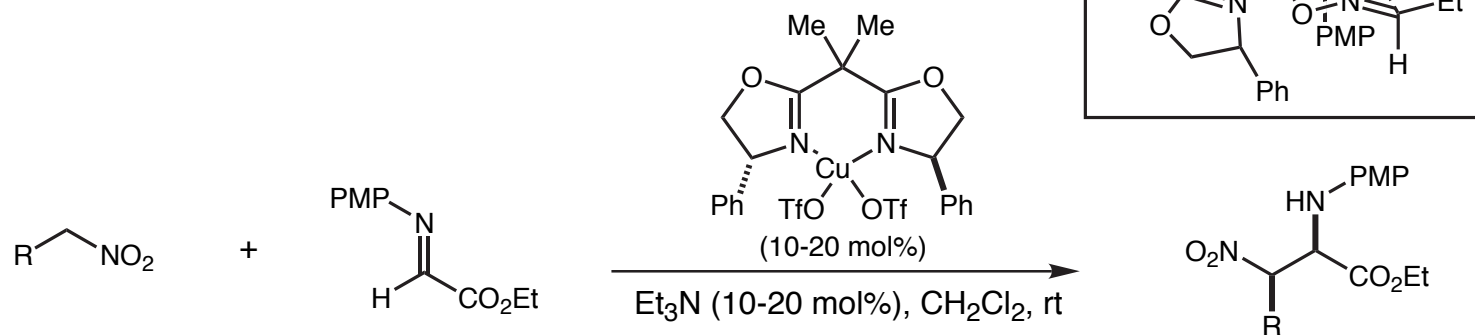
Sodeoka et al. *J. Am. Chem. Soc.* **1998**, 120, 2474
J. Am. Chem. Soc. **1999**, 121, 5450

Sodeoka: Proposed Mechanism



Sodeoka et al. *J. Am. Chem. Soc.* **1999**, 121, 5450

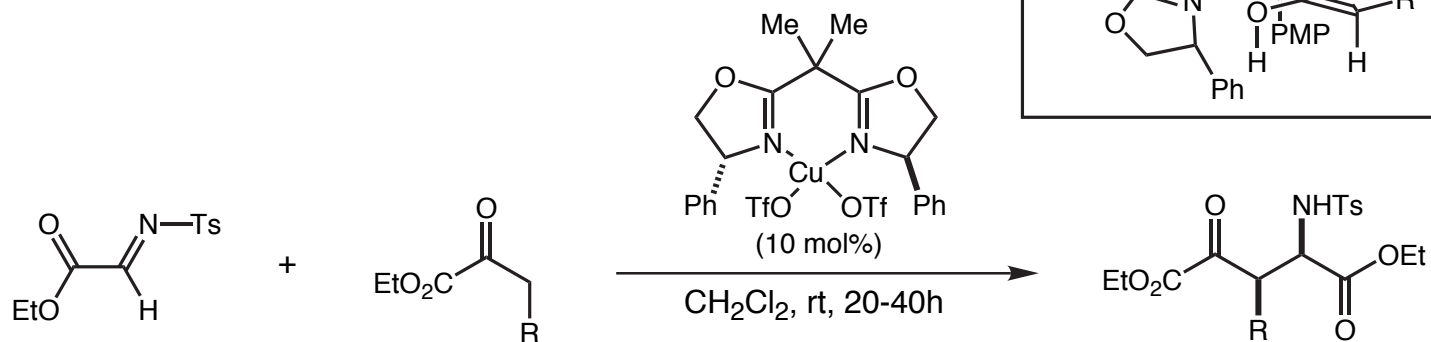
Jørgensen: Catalytic Asymmetric Aza-Henry Reaction



R	yield (%)	syn/anti	ee, syn (%)
H	38	—	87
Me	61	70:30	97
Et	81	95:5	97
<i>n</i> -C ₅ H ₁₁	52	93:7	97
Bn	80	95:5	95
Ph	59	55:45	74

Jørgensen et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992
 See also: *J. Am. Chem. Soc.* **2001**, *123*, 5843 (silyl nitronates: in Appendix)

Jørgensen: Catalytic Enantioselective Direct Mannich Reaction of α -Imino Esters

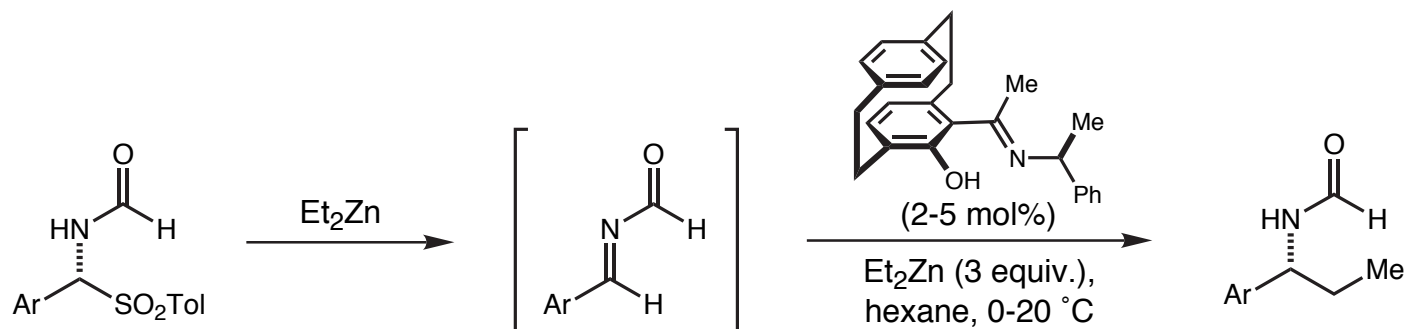


R	yield (%)	syn:anti	ee (%)
H	70	–	89
Me	89	>10:1	>98
Me	98	>10:1	94*
Bn	94	>10:1	97
Br	79	>10:1	78

* 5 mol% catalyst was used

Jørgensen et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995

Bräse: Catalytic Asymmetric Addition of Dialkylzincs



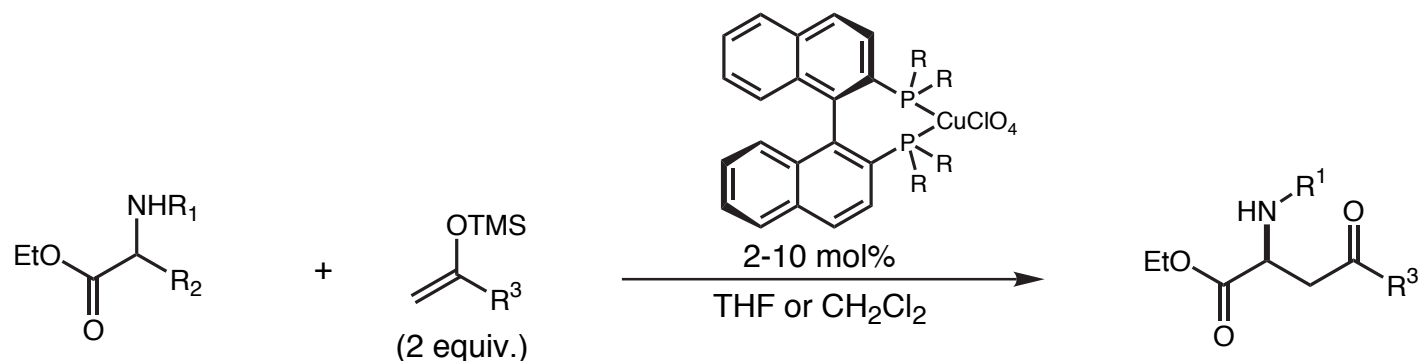
Ar	yield (%)	ee (%)
Ph	>99	95
3-(Cl) C_6H_4	99	93
4-(Cl) C_6H_4	>99	89
4-(MeO) C_6H_4	97	95
2,6-(Cl) $_2\text{C}_6\text{H}_3$	98	95
4-(<i>t</i> -Bu) C_6H_4	>99	75

Bräse et al. *J. Am. Chem. Soc.* **2002**, 124, 5940

Conclusion

- Great progress has been made over the past 5 years in the development of catalytic, enantioselective additions to C=N double bonds
- Catalysis via nucleophile activation was achieved
- Catalysis via electrophile activation was achieved
- Bifunctional catalysis was achieved
- However, most systems have poor generality with regards to
 - aromatic vs. aliphatic (C=N)
 - nucleophile
 - nitrogen protective group
- No catalytic, enantioselective approaches to tertiary amines reported to date...

Lectka: Reaction with *N,O*- and *N,N*-Acetals and Hemiacetals

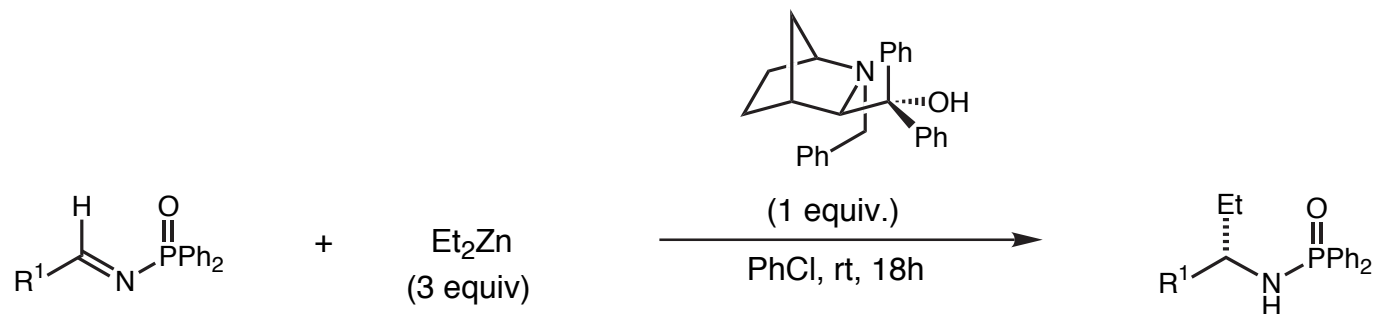


R ¹	R ²	R ³	yield (%)	ee (%)
Ts	OH	Ph	93	95
Ts	OH	TMSCH ₂	85	90
Ts	OH	OPh	81	76
Ts	NTs	Ph	90	95
Ns	OEt	Ph	89	87
SES	OH	Ph	78	96

- First equivalent of enol ether leads to formation of the iminoester (alternatively, 1 equiv. of TMSCl can be used, followed by 1 equiv. of enolsilane)
- Desilylated material is isolated after the reaction (no need for F⁻) in contrast with parent reaction with iminoester
- If R¹ = Bz, exclusive formation of the ethyl glyoxylate adduct!!!

Lectka et al. *J. Org. Chem.* **1999**, *64*, 2168
Tetrahedron **1999**, *55*, 8869

Andersson: Chiral Aminoalcohol-Promoted Addition of Diethylzinc

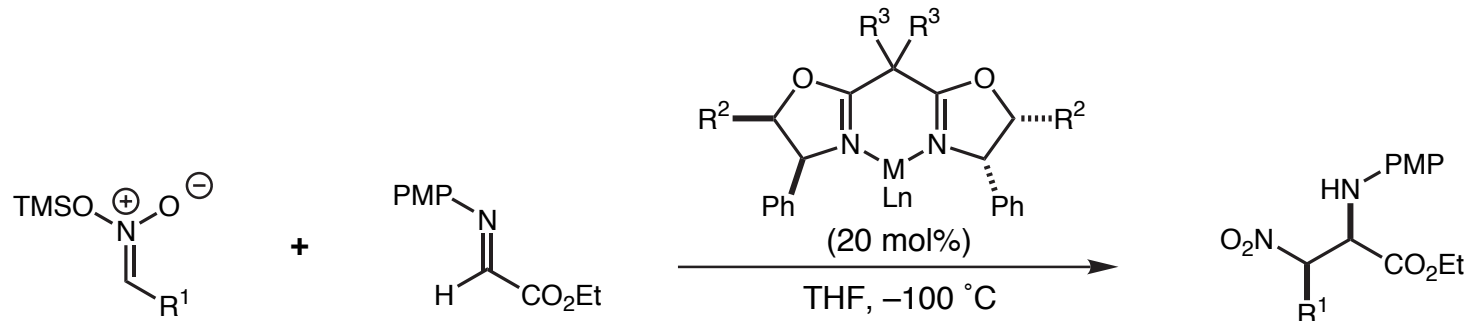


R^1	yield (%)	ee (%)
Ph	75	98
2-furyl	92	89
3-pyridyl	70	87
(4-MeO) C_6H_4	91	98
(4-Me) C_6H_4	70	97
(4-Cl) C_6H_4	67	95

Attempts to make this process catalytic failed

Andersson et al. *Tetrahedron* **2001**, 57, 1615
Many other reports of chiral *promoters* for the same transformation (aminoalcohols)

Jørgensen: Catalytic Asymmetric Aza-Henry Reaction

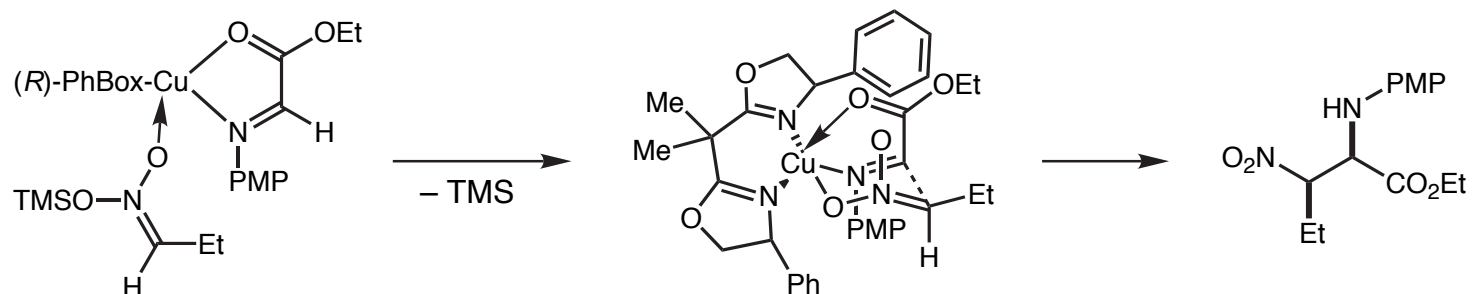


R ¹	R ²	R ³	MLn	yield (%)	<i>syn/anti</i>	ee (%)
Et	H	Me	Cu(I)ClO ₄	90	3:1	90
	H	Me	Cu(II)(OTf) ₂	67	18:1	89
	Ph	H	Cu(I)PF ₆	68	10:1	97
	Ph	H	Cu(II)(SbF ₆) ₂	94	25:1	95*
Me	H	Me	Cu(I)ClO ₄	67	5:1	>98
<i>n</i> -C ₅ H ₁₁	Ph	H	Cu(II)(SbF ₆) ₂	87	39:1	83*
Bn	Ph	H	Cu(I)ClO ₄	93	32:1	88

* CH₂Cl₂ was used as solvent

Jørgensen et al. *J. Am. Chem. Soc.* **2001**, *123*, 5843

Jørgensen: Proposed Mechanism and Transition State Model



Rapid equilibrium between the *E* and *Z* form of the copper nitronate is assumed
(TMS nitronate = ca. 10 kcal/mol: Dunitz, Seebach et al. *Helv. Chim. Acta* **1980**, 63, 697)

No clear statement about the dissociation of the TMS group...

Jørgensen et al. *J. Am. Chem. Soc.* **2001**, 123, 5843