Advancement of Direct Catalytic Mannich-type Reactions with Esters or Ester-equivalents as Donors

Yong Guan

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Michigan State University

Outline

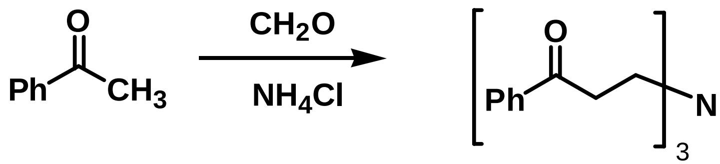
- Background Information

- Esters or Ester-equivalents
  - Glycine Schiff-bases
  - *β*-Keto Esters or Malonates
  - Trichloromethylketones
  - *N*-acylpyrroles
  - *N*-Boc-anilides
  - Diazoacetates

- Conclusions

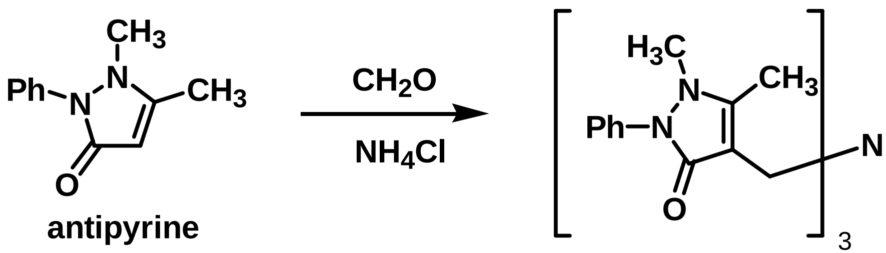
Background Information

Tollens and von Marle (1903)

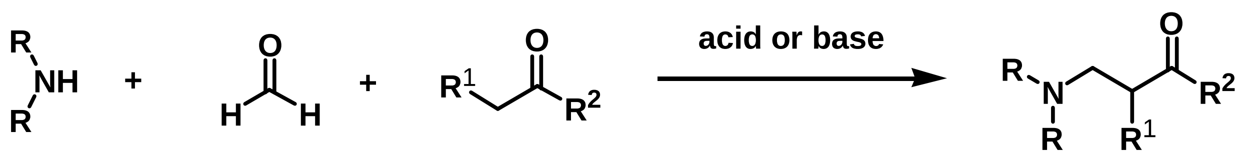


Carl Mannich

Mannich (1917)



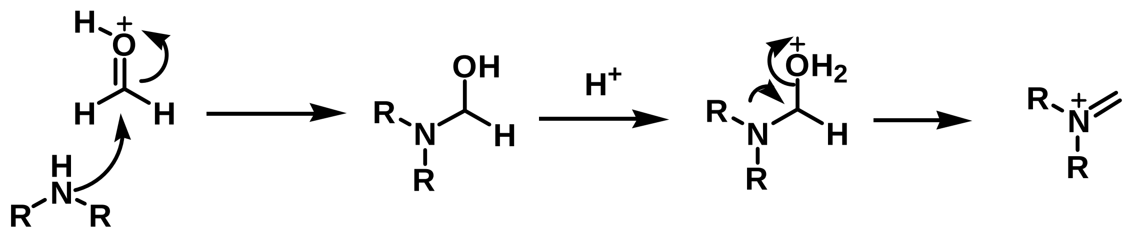
Mannich reaction



Tollens, B.; Marle, v. *Ber.* **1903**, *36*, 1351.
Mannich, C. *J. Chem. Soc., Abstracts* **1917**, *112*, 634.
Mannich, C. *Arch. Pharm.* **1917**, *255*, 261.
http://www.dphg.de/images/dphg_ap_mannich.gif

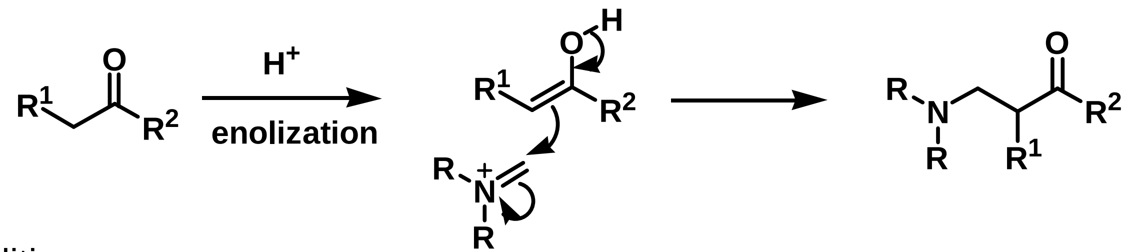
Reaction Mechanism

Step 1. Formation of the Schiff base

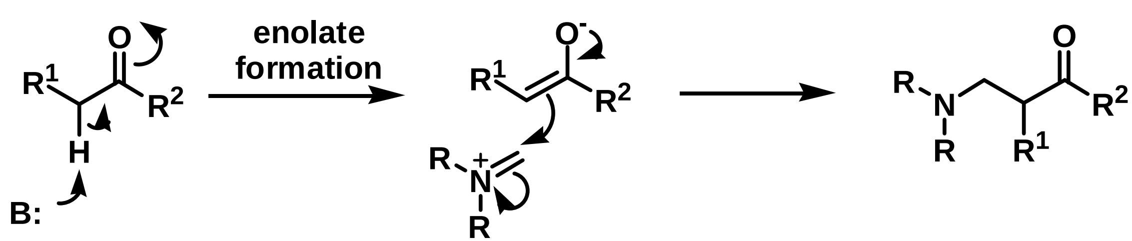


Step2. Amino alkylation of an acidic hydrogen containing compound

Acidic conditions



Basic conditions



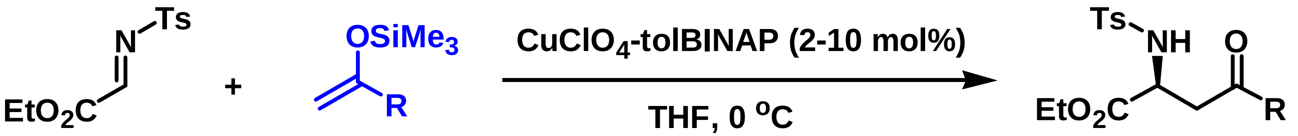
Name Reactions – A Collection of Detailed Reaction Mechanisms. Jie Jack Li. Springer-Verlag, Berlin. 2002.

Background Information

- Indirect-type Mannich Reaction

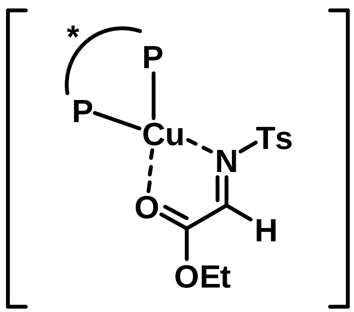
- Direct-type Mannich Reaction

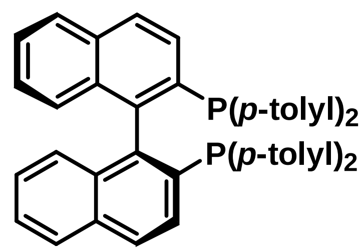
Indirect-type Mannich Reaction



8 examples
65-92% Yield
89-98% *ee*

Silyl enol ether

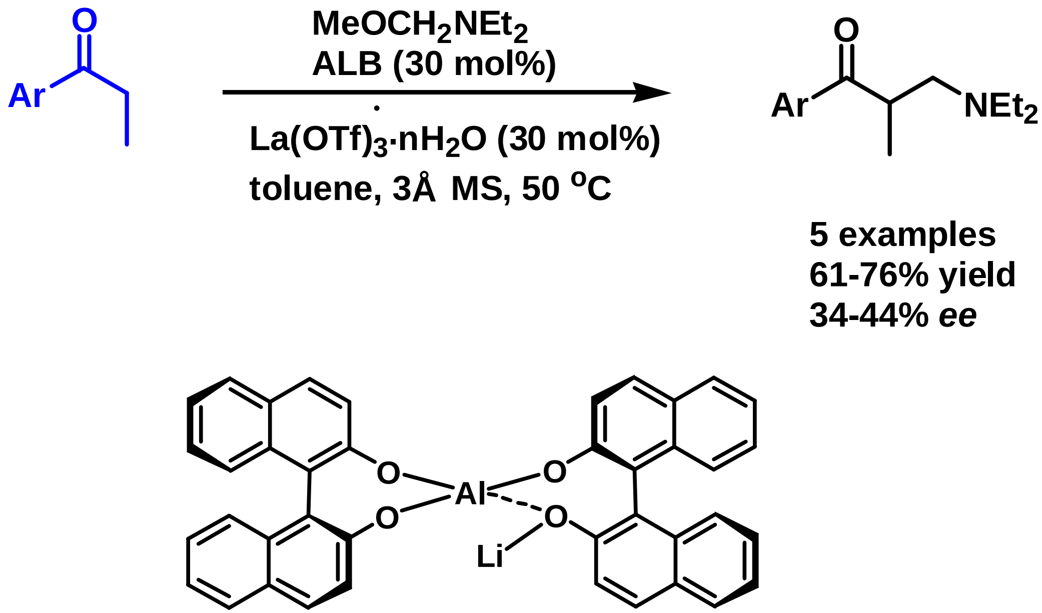




tolBINAP

Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548.

Direct-type Mannich Reaction



(*R*)-ALB = AlLibis(binaphthoxide)

The First Direct Catalytic Asymmetric Mannich Reaction

Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999,** *41*, 307.

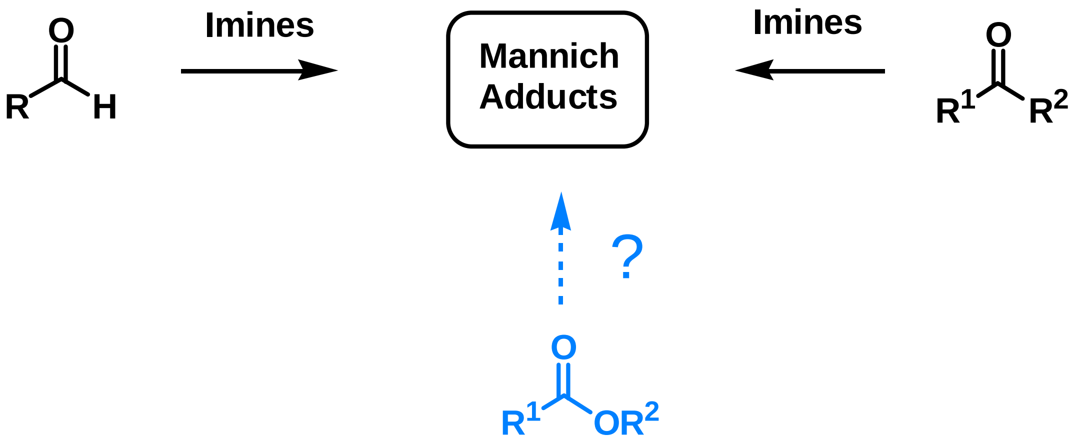
General Difficulties

- Many Lewis acids are deactivated or sometimes decomposed by the nitrogen atoms of starting materials or products (trapped by the nitrogen atoms)

- Imine-chiral Lewis acid complexes are rather flexible and often have several stable conformers (including *E/Z*-isomers of imines). Multiple transition states would exist.

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

Background Information



pK$_a$ 20 pK$_a$ 24.5

Marques, M. M. B. *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 348.
Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089
Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102

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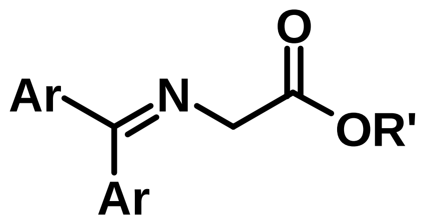
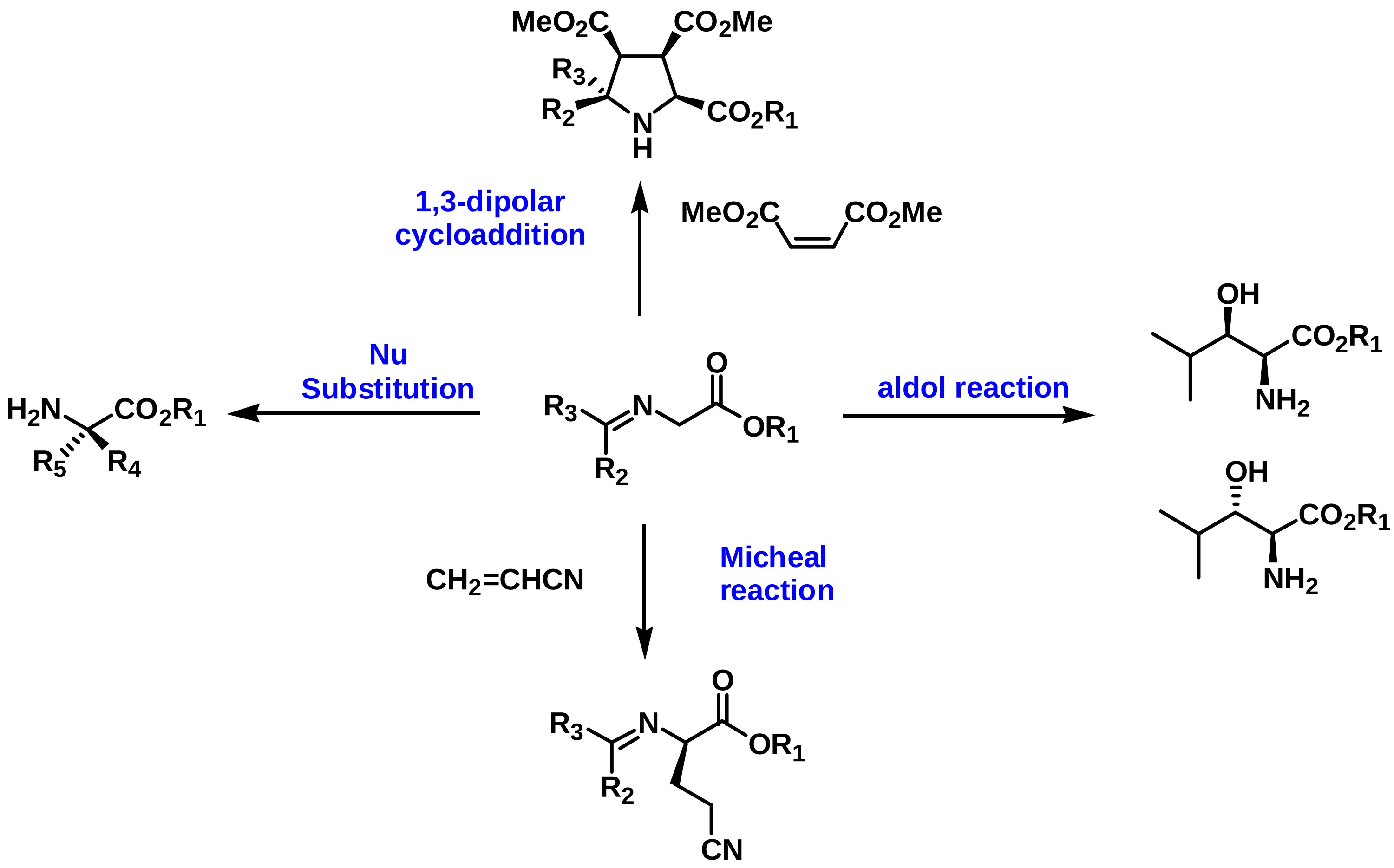


Glycine Schiff-bases

- Cu(I) Catalyst

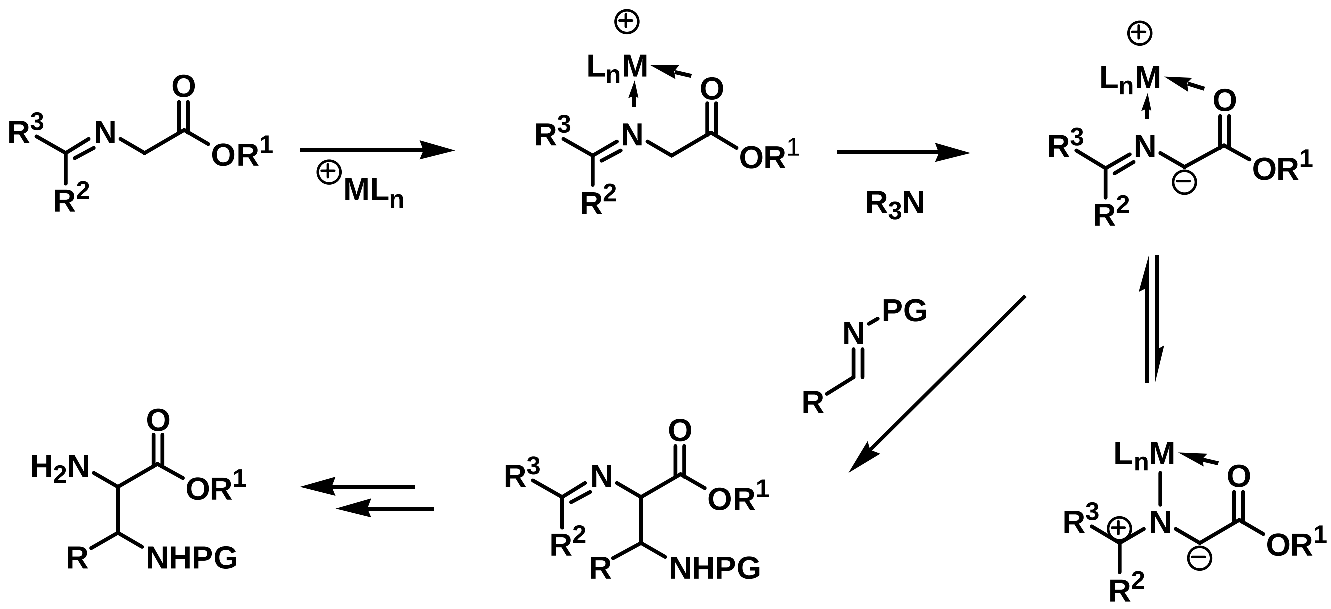
- Phase-Transfer Catalyst

Glycine Schiff-bases



Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.
Ooi, T.; Takeuchi, M.; Kamede, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.
Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.
Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.

Glycine Schiff-bases



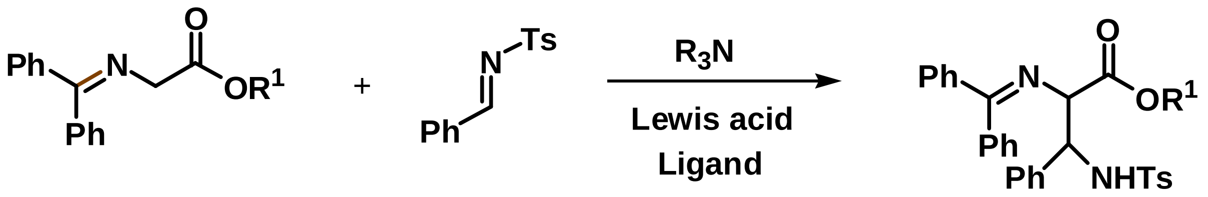
- **Challenges**

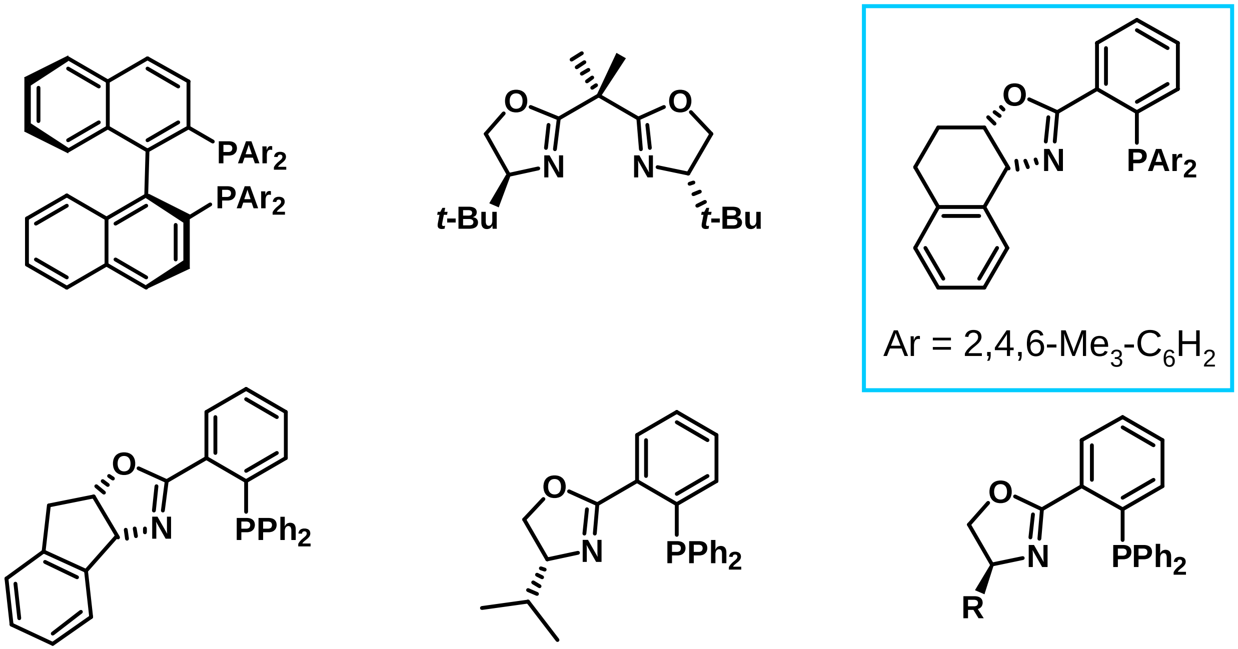
(1) "Force" the Lewis acid stabilized imino glycine alkyl ester to act as a nucleophile rather than a 1,3-dipolar species

(2) Develop a chiral catalyst that can catalyze both a diastereo- and enantioselective addition of imino glycine alkyl ester to imines.

Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003,** *68*, 2583.

Cu(I) Catalyst



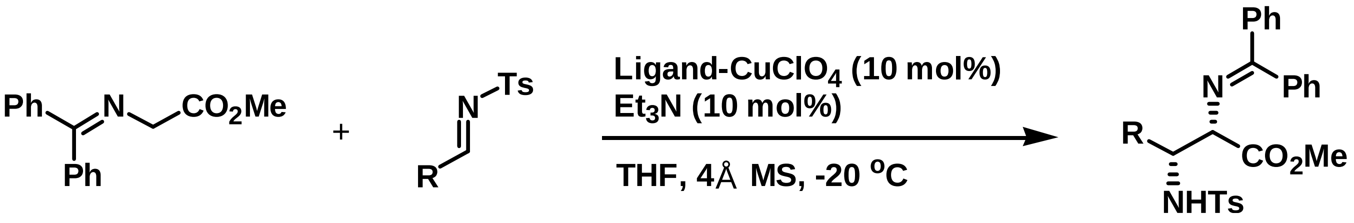


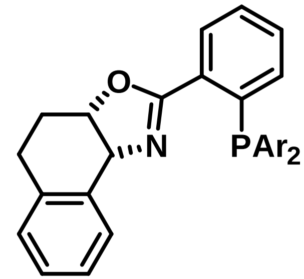
Optimal condition

Ligand -$CuClO_4$ (10 mol%), Et_3N (10 mol%), -20 °C, THF, 4 Å MS

Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003,** *68*, 2583.

Substrate Scope



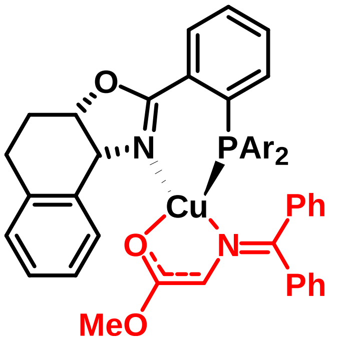


Ar = 2,4,6-Me_3-C_6H_4

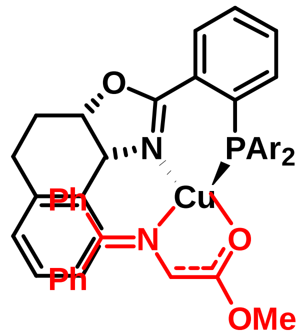
R	yield (%)	*syn/anti*	*ee* (%)
Ph	94	79:21	97
4-MeO-C_6H_4	90	82:18	97
2-Br-C_6H_4	99	61:39	96
2-furyl	88	54:46	90
*i*Pr	73	>95:5	96
Cy	85	>95:5	92
*n*Bu	61	>95:5	88

Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003,** *68*, 2583.

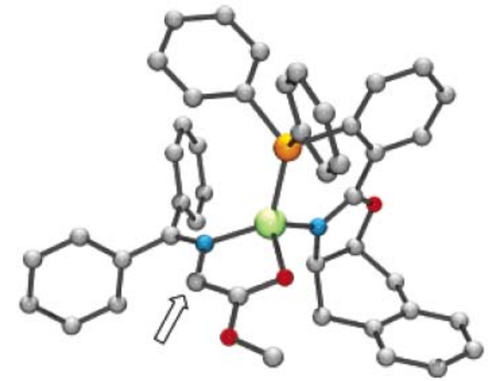
Coordination Modes

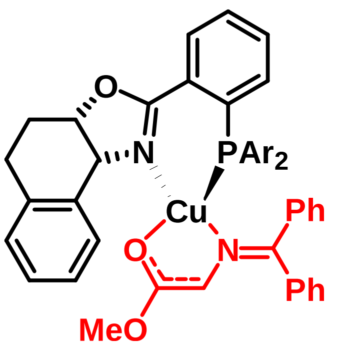


Ar = Ph
Δ H_f^{Θ} = -11.1 kcal/mol

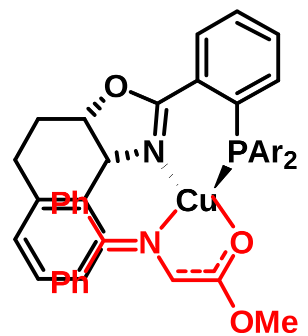


Ar = Ph
Δ H_f^{Θ} = -10.9 kcal/mol
14% *ee*

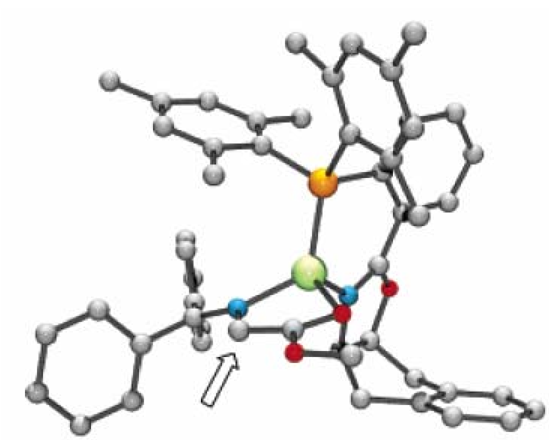




Ar = 2,4,6-Me_3-C_6H_2
Δ H_f^{Θ} = -39.2 kcal/mol
97% *ee*



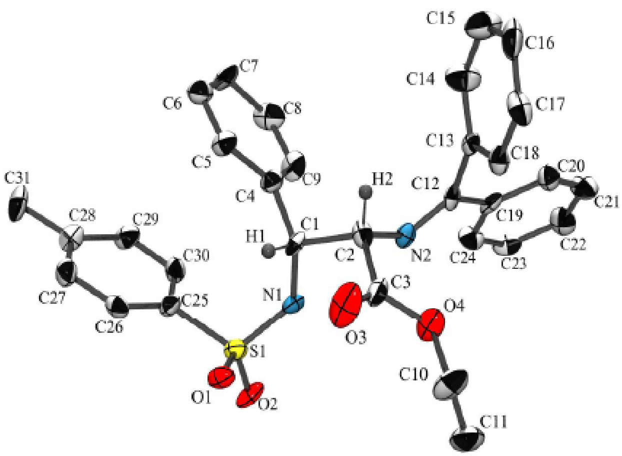
Ar = 2,4,6-Me_3-C_6H_2
Δ H_f^{Θ} = -26.8 kcal/mol



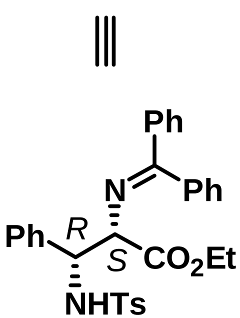
Semiempirical PM3 calculation

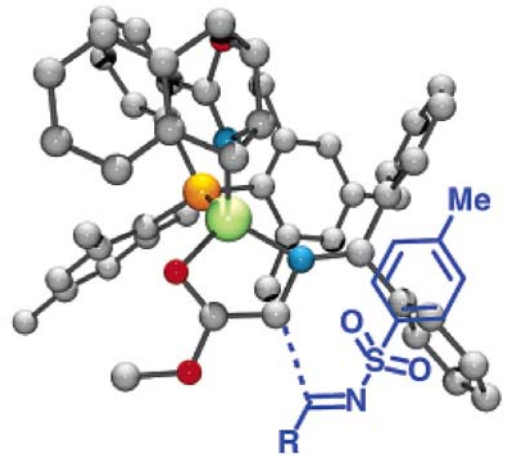
Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003,** *68*, 2583.

Transition State

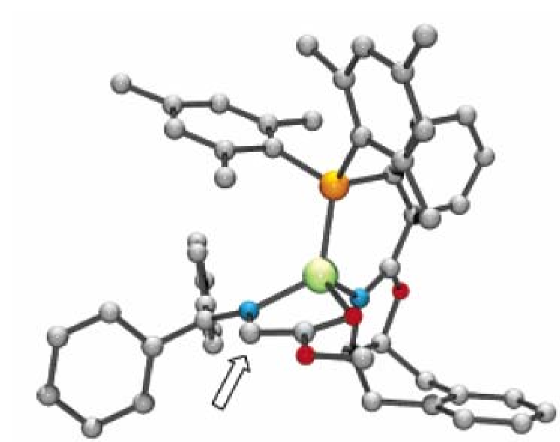


X-ray structure



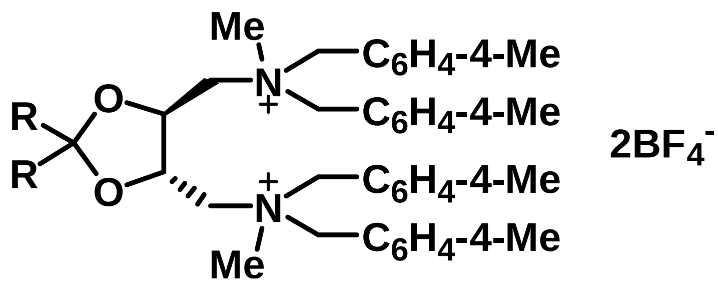


Approach of the imine (blue) to the *Si* face of the benzophenone imine glycine methyl ester anion

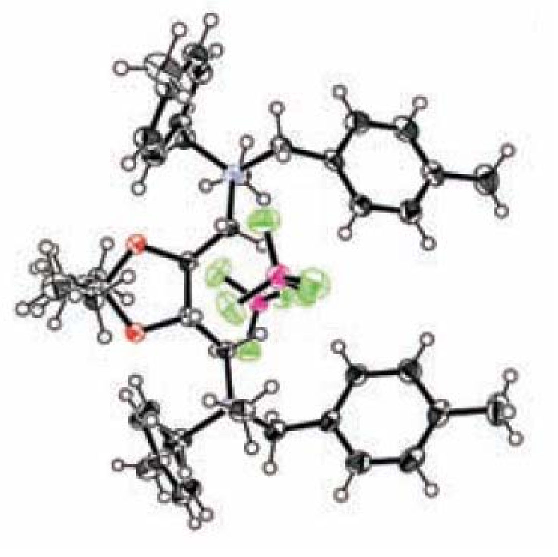


Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003,** *68*, 2583.

Phase-Transfer Catalyst



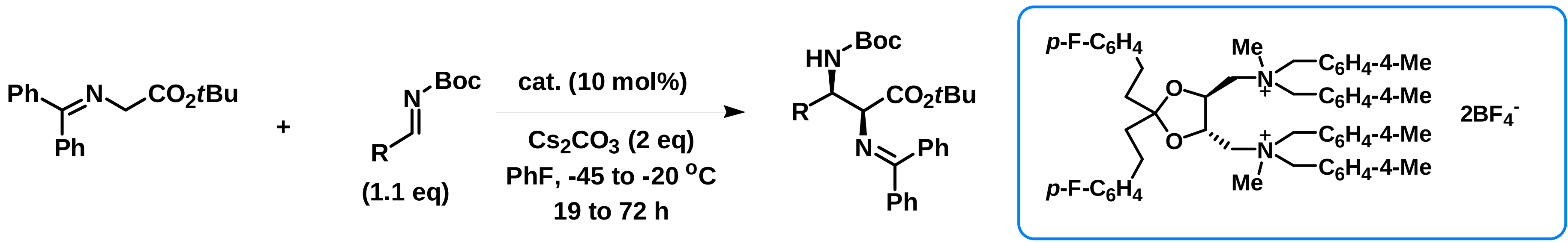
tartrate-derived diammonium salt
(TaDiAS)



Crystal Structure (R = *n*Pr)

Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 4564.

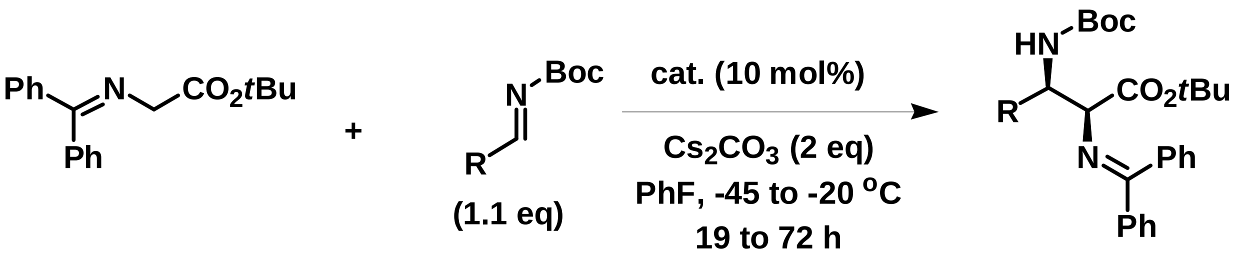
Substrate Scope



R	yield (%)	dr (*syn*/*anti*)	*ee* (%)
Ph	98	99:1	70
4-MeO-C_6H_4	95	95:5	82
4-Me-C_6H_4	98	98:2	80
2-Me-C_6H_4	99	97:3	68
4-Cl-C_6H_4	87	98:2	58
2-thiophenyl	98	98:2	80
(*E*)-PhCH=CH_2	86	98:2	66

Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 4564.

Kinetic Study



- **Initial rate kinetic studies:**

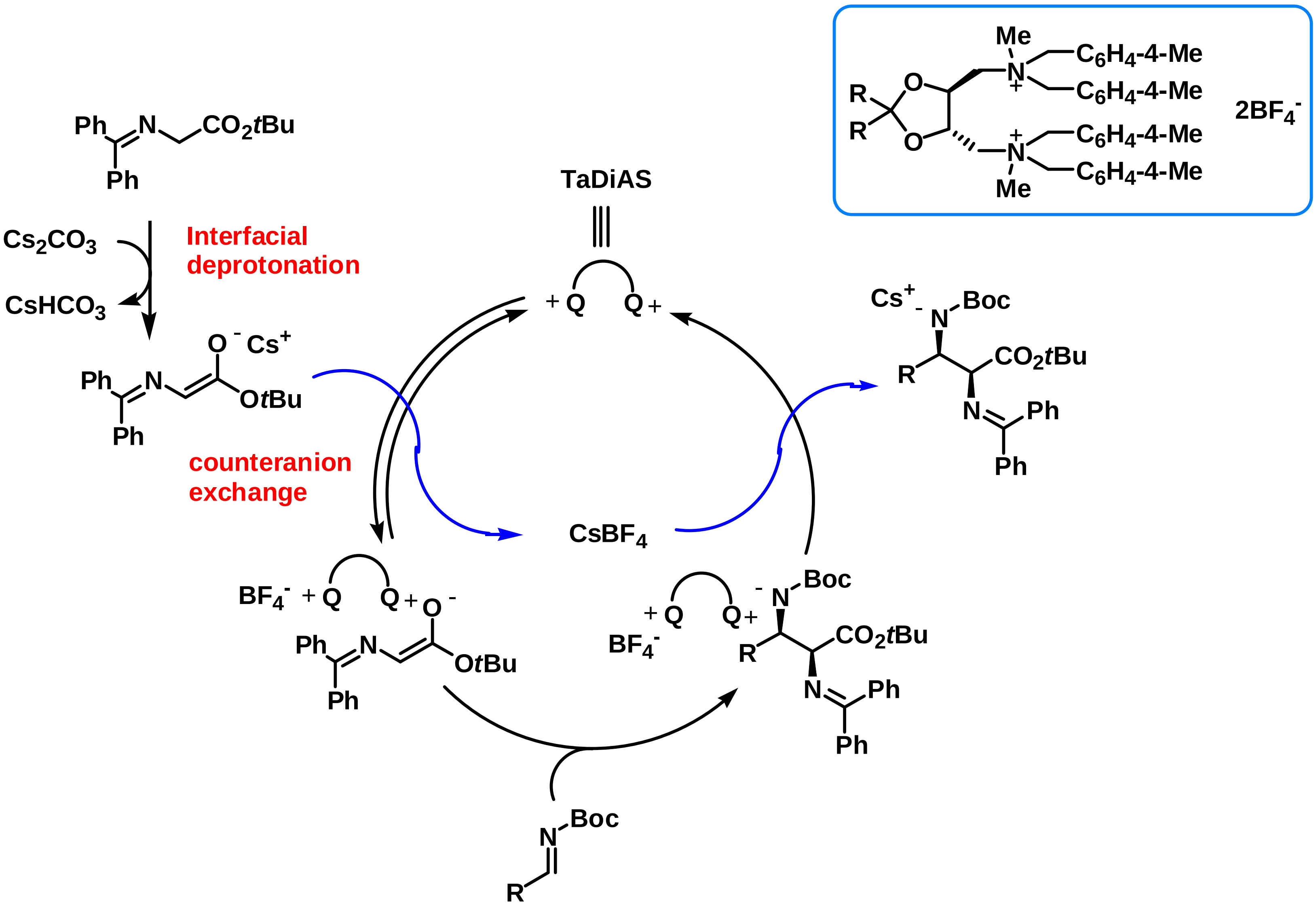
1) First-order dependency for the glycine Schiff base and Cs_2CO_3
2) Zero-order dependency for the imine and the catalyst

- **Conclusions:**

1) The rate-determining step is deprotonation of the glycine Schiff base by Cs_2CO_3
2) The catalyst is not involved in this step

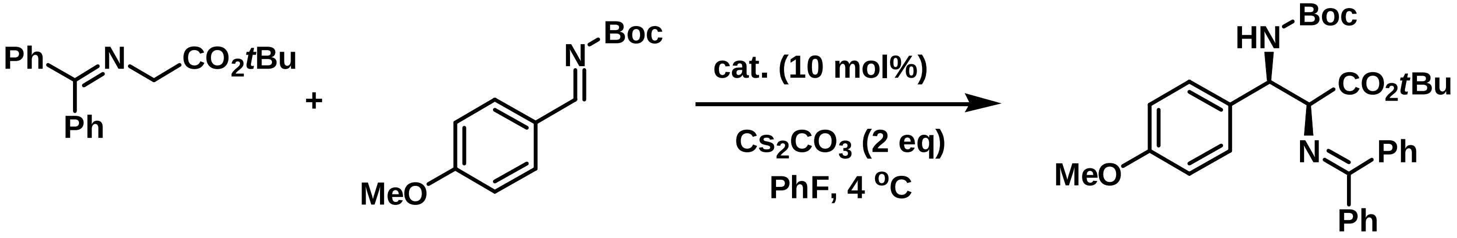
Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 4564.

Catalytic Cycle



Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4564.

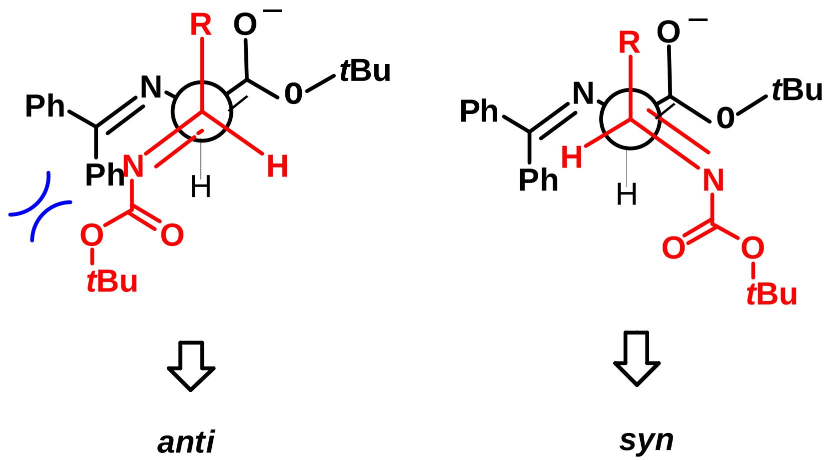
Control of Diastereoselectivity



1h, 77% *ee*, d.r. = 95:5

without cat. , 24h, d.r. = 94:6

The reaction may proceed via the nonchelate, acyclic transition-state model

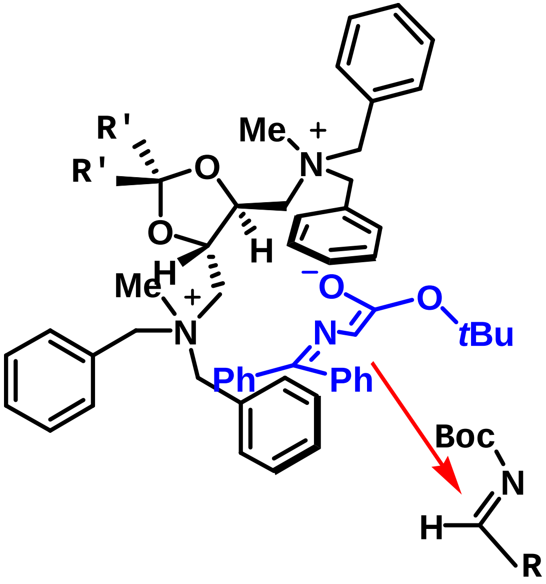


Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007,** *2*, 794

Control of Enantioselectivity

- The benzyl moieties around one ammonium cation covers the *Si* face of the *Z* enolate of the glycine Schiff base

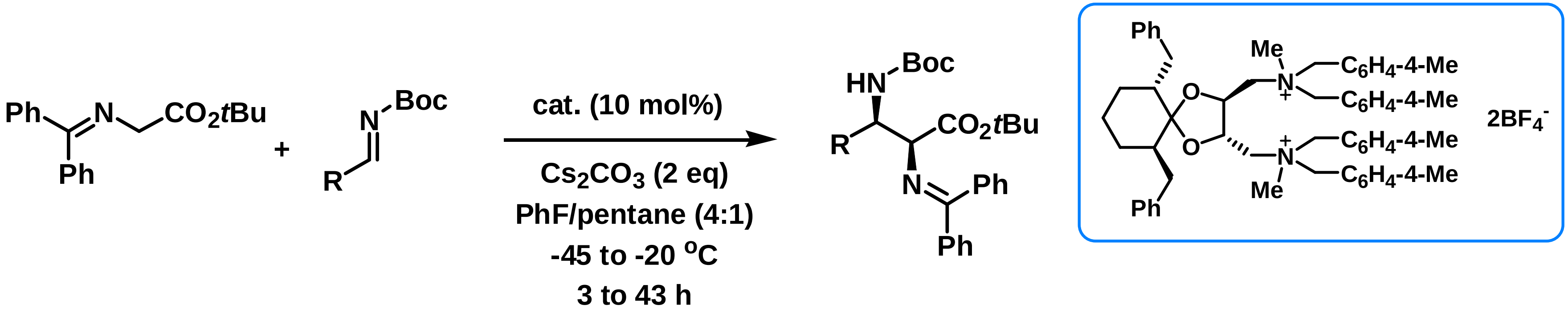
- The electrophiles approach from the less-hindered face (*Re* face) to afford the products with *S* configuration



Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4564.

Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007,** *2*, 794

Improvement



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4-MeO-C_6H_4	96	99:1	90
4-Me-C_6H_4	92	99:1	88
4-Cl-C_6H_4	88	98:2	70
2-thiophenyl	89	98:2	83
*n*Pr	95	>20:1	71
(E)-PhCH=CH	89	>20:1	75

Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007,** *2*, 794

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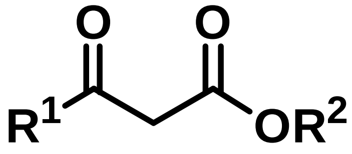
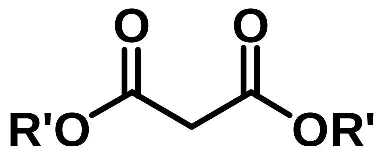
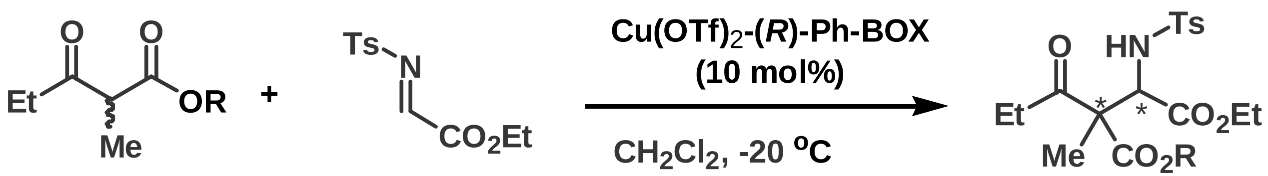


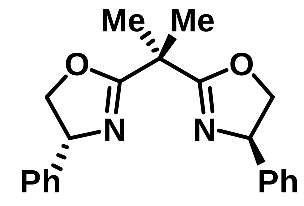


β-Keto Esters or Malonates

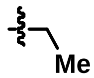
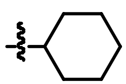
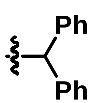
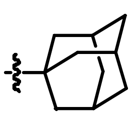
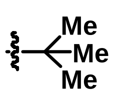
- Cu(II) Catalysts
- Pd Catalysts
- Cinchona Alkaloid Catalysts

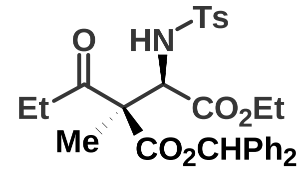
Cu(II) Catalysts





(*R*)-Ph-BOX

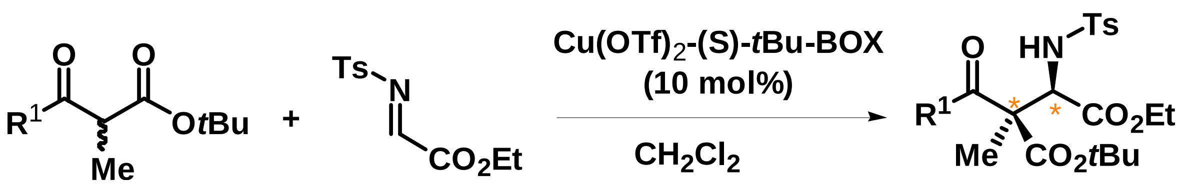
R	yield (%)	dr	*ee* (%)
	76	84:16	23
	75	93:7	51
	81	>95:5	53
	43	>95:5	-66
	33	>95:5	-88

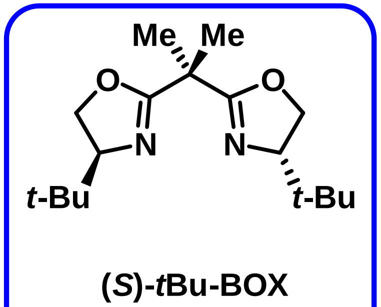


(*R,R*)
from X-ray structure

Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359.

Cu(II) Catalysts

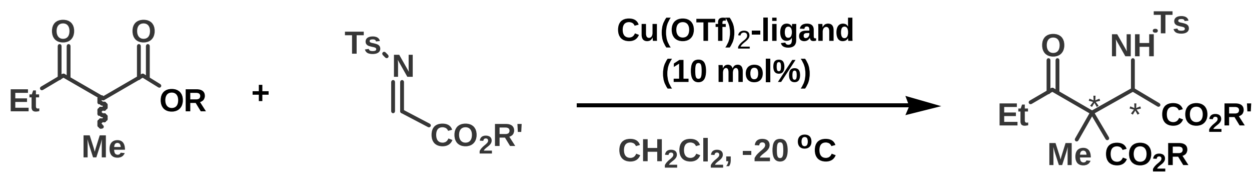


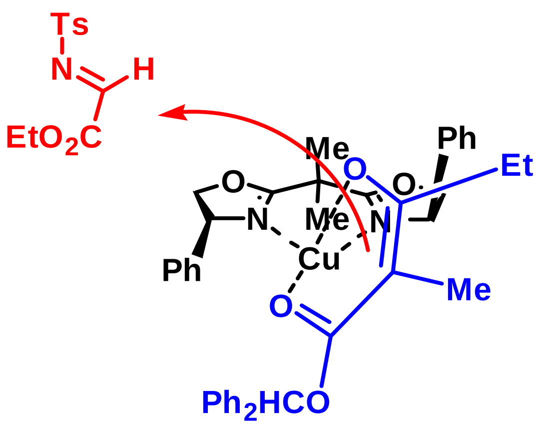


R^1	T (^oC)	t (h)	yield (%)	dr	*ee* (%)
Me	-20	40	55	97:3	95
*i*Pr	-20	40	15	84:16	92
Me	RT	16	87	93:7	88
*i*Pr	RT	16	55	84:16	91

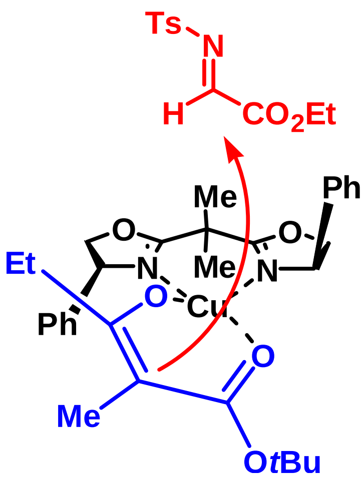
Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359.

Transition States

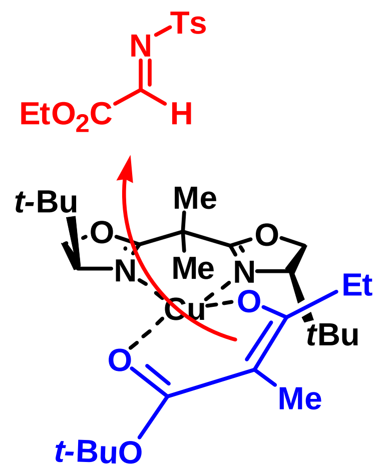




81% yield, 53% ee
dr = >95:5



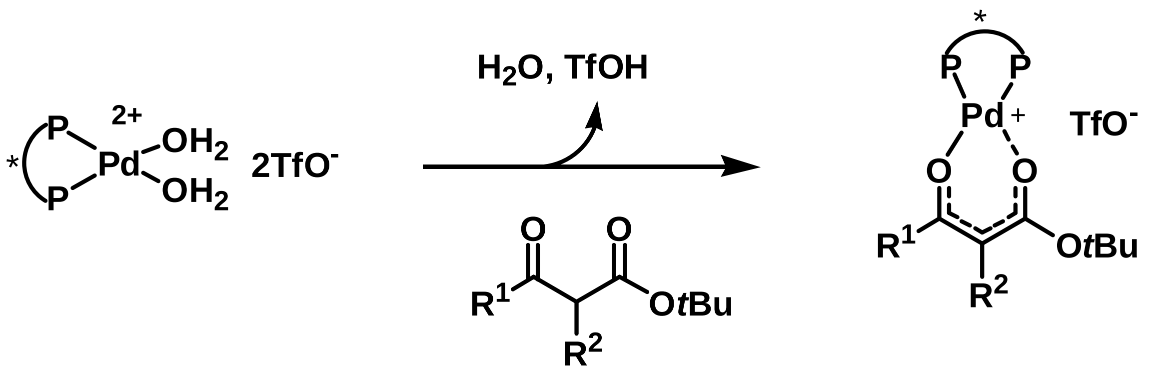
33% yield, -68% ee
dr = >95:5

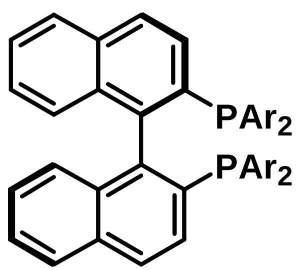


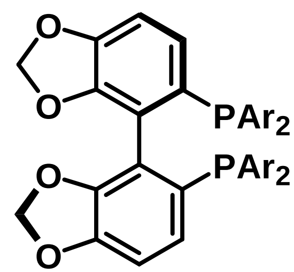
80% yield, 92% ee
dr = 98:2

Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359.

Pd Catalysts





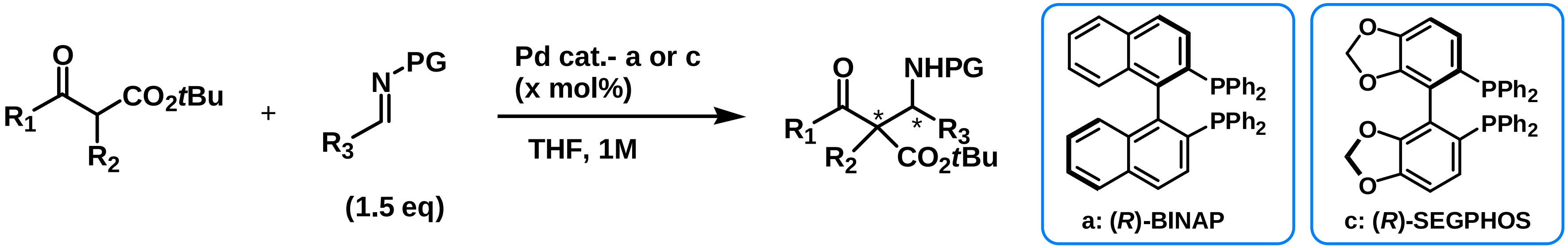


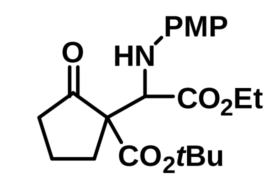
a: Ar = C_6H_5: (*R*)-BINAP
b: Ar = 4-Me-C_6H_4: (*R*)-TOL-BINAP

c: Ar = C_6H_5: (*R*)-SEGPHOS
d: Ar = 3,5-Me_2-C_6H_3: (*R*)-DM-SEGPHOS

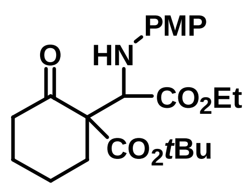
Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1525.

Pd Catalysts

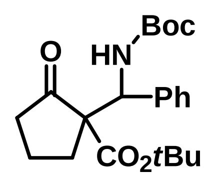




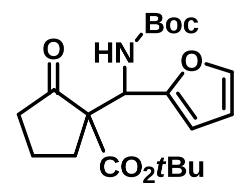
c (5 mol%), 35 h
63%, dr = 77:23, 99% *ee*



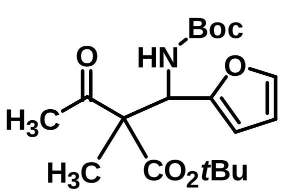
a (5 mol%), 42 h
70%, dr = 74:26, 86% *ee*



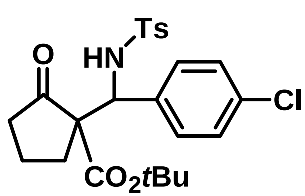
c (2.5 mol%), 5 h
93%, dr = 88:12, 99% *ee*



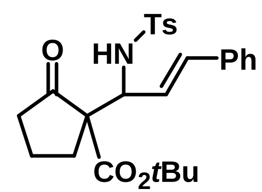
a (2.5 mol%), 2 h
75%, dr >95:5, 86% *ee*



a (2.5 mol%), 3 h
71%, dr = 82:18, 96% *ee*



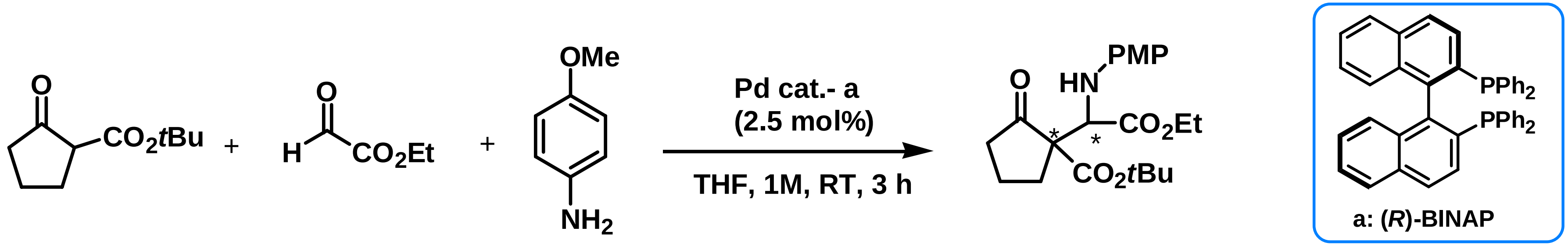
c (5 mol%), 9 h
99%, dr = 85:15, 97% *ee*



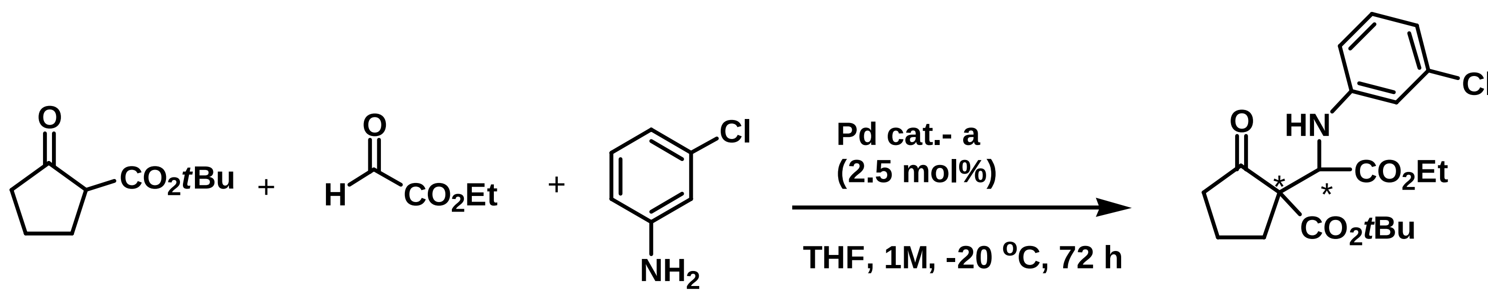
c (1 mol%), 24 h
88%, dr = 90:10, 99% *ee*

Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1525.

One-Pot Reactions



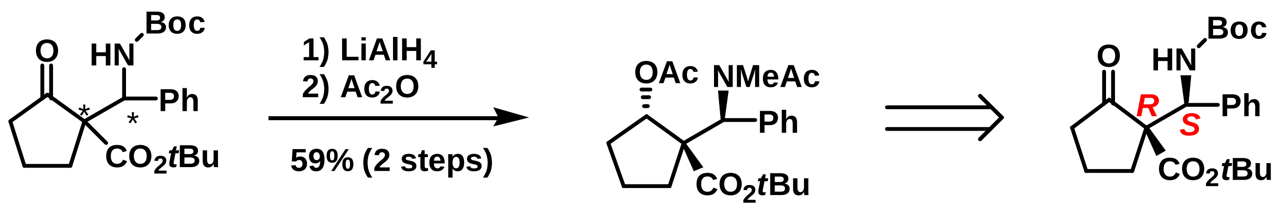
61% yield, dr = 70:30
96% ee (major), 96% ee (minor)

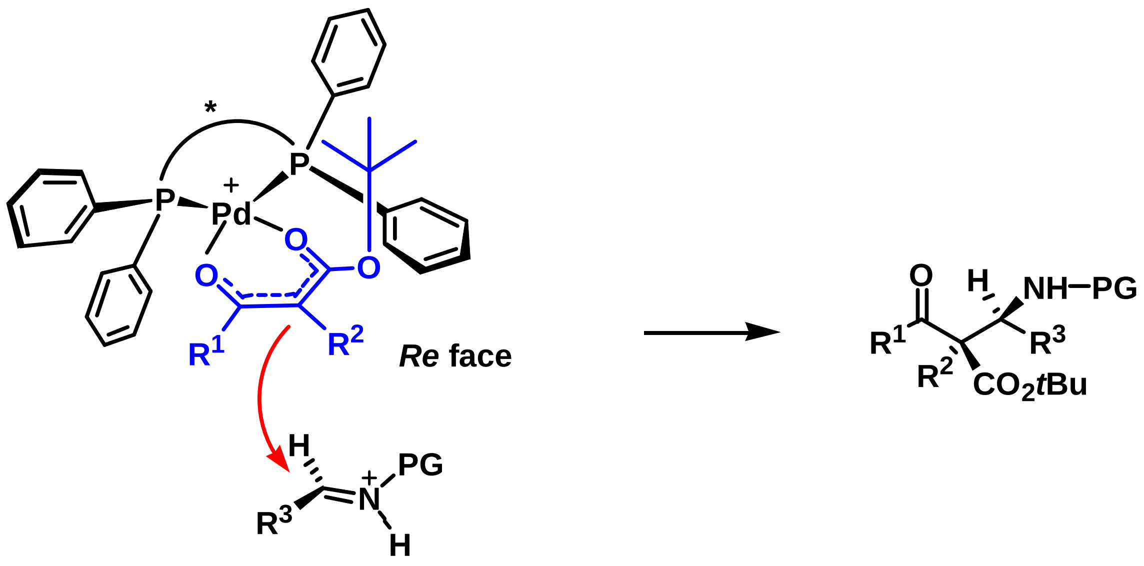


85% yield, dr = 95:5
98% ee (major), 88% ee (minor)

Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1525.

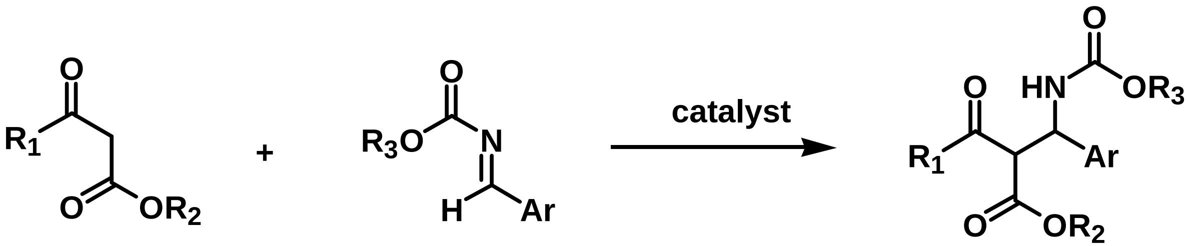
Transition-State Model

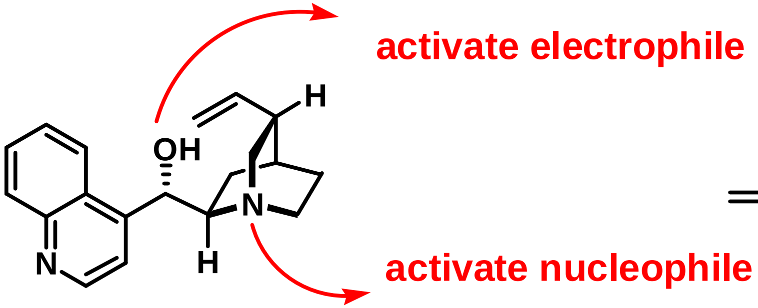




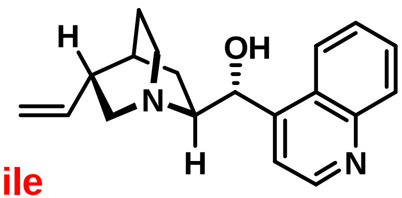
Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1525.

Cinchona Alkaloid Catalysts

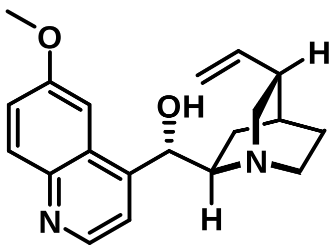




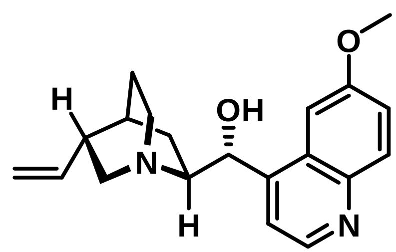
cinchonine



cinchonidine



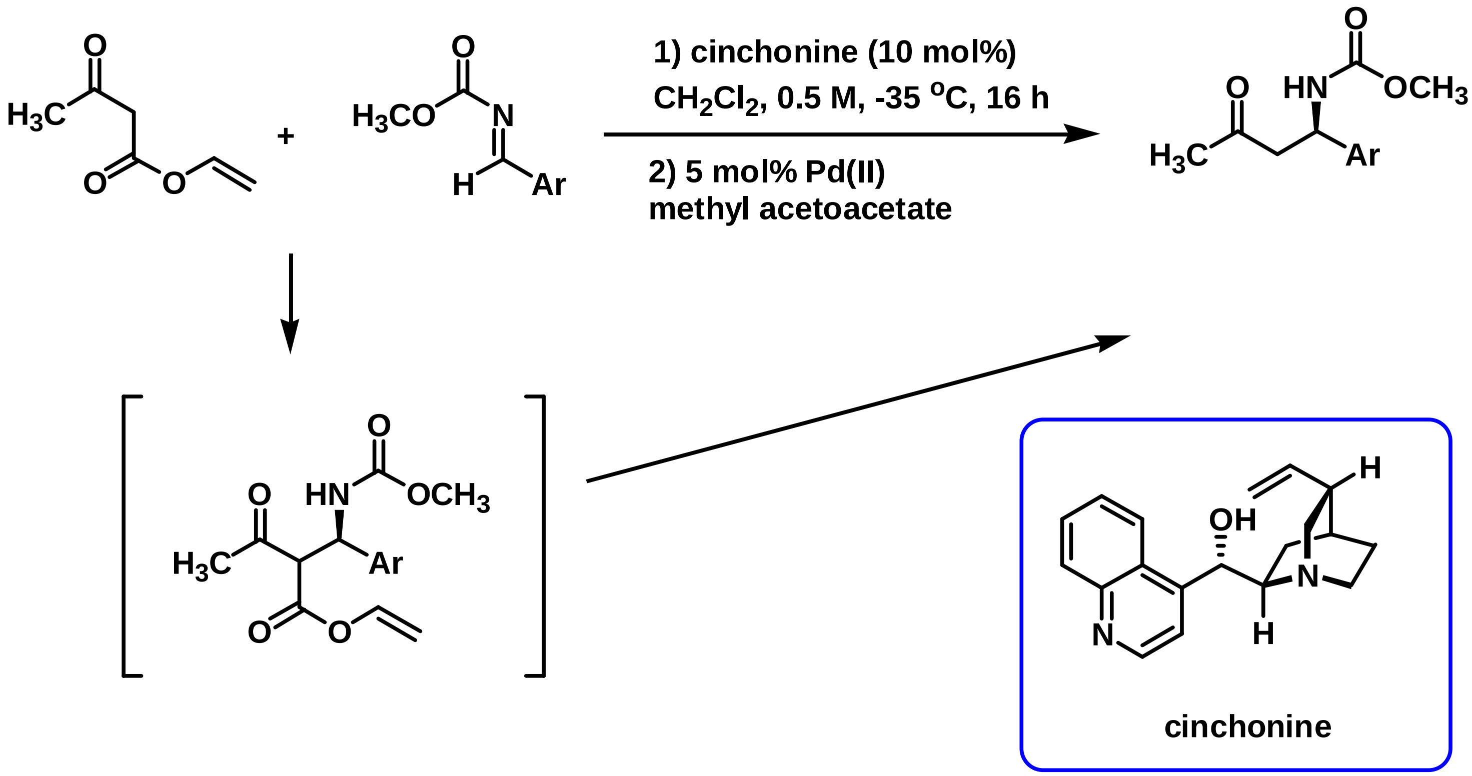
quinidine



quinine

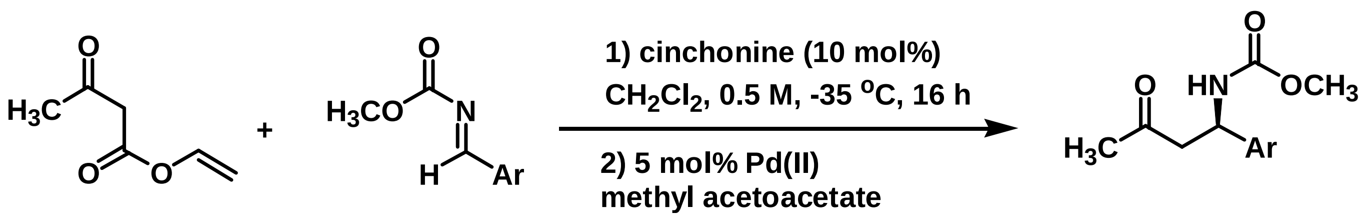
Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256.

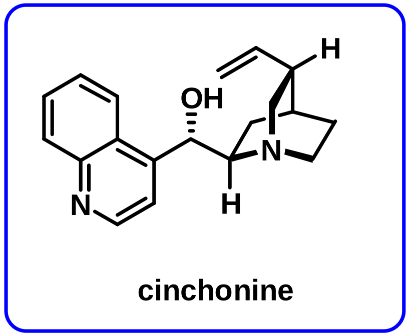
Cinchona Alkaloid Catalysts



Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256.

Substrate Scope

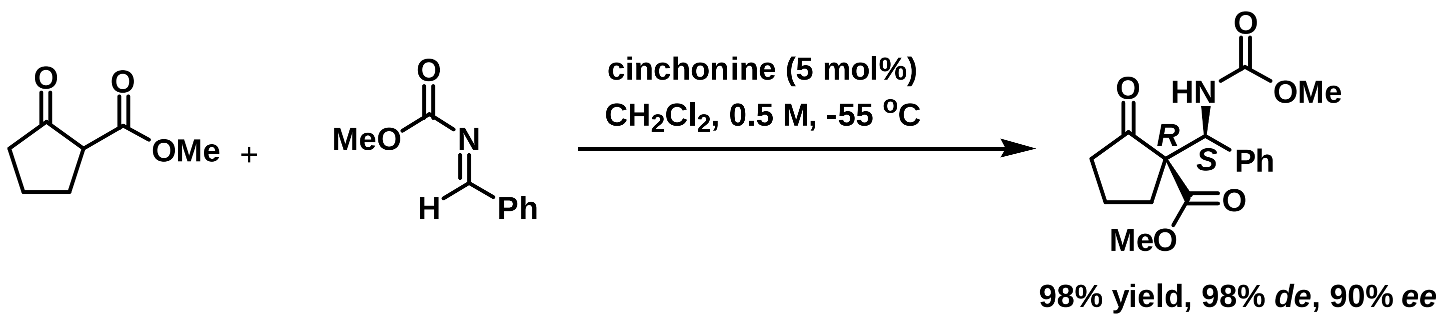


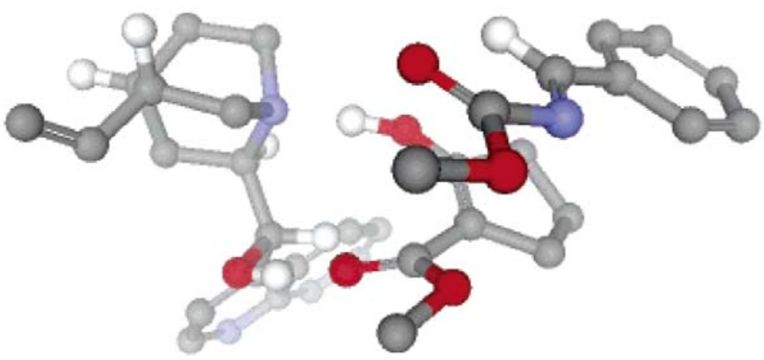


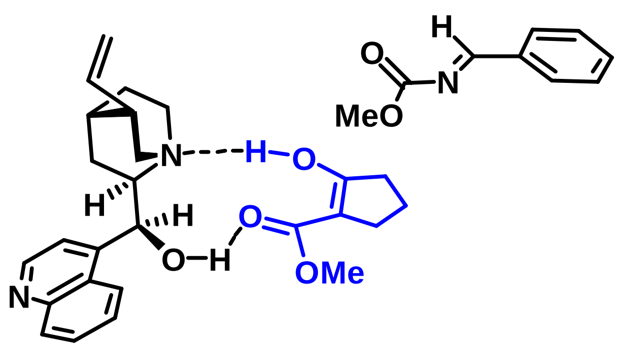
Ar	yield (%)	*ee* (%)
Ph	79	92
4-F-C_6H_4	95	93
3-CH_3-C_6H_4	78	96
3,4-(OCH_2O)C_6H_3	77	80
2-furyl	78	93
2-thienyl	69	92
2-naphthyl	80	95

Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256.

Transition-State Model



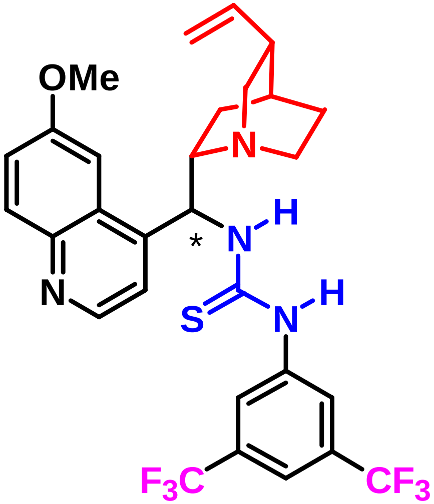




Cinchonine/methyl 2-oxocyclopentanecarboxylate enol tautomer complex (MMFF) approaching the *Re* face of methyl benzylidenecarbamate

Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003.

Cinchona Alkaloid Derivatives



Thiourea moiety

-activate electrophiles

-two coplanar protons for H-bond donation

-rigid

Thiourea *N*-aryl group

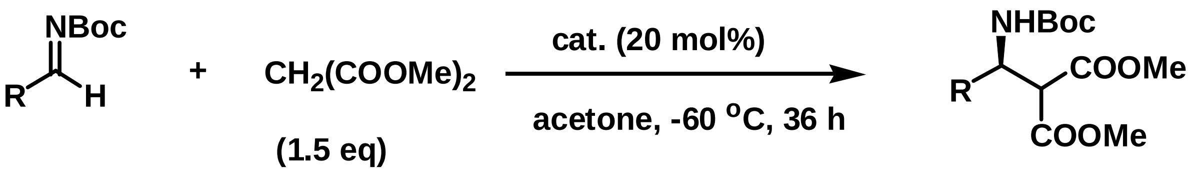
-relatively unhindered

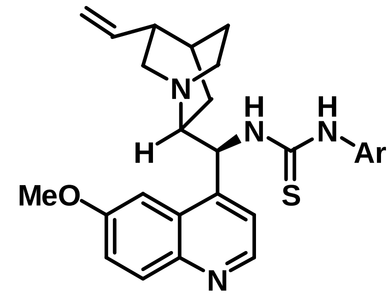
-substitution variable

-CF_3 gruops serve as non Lewis basic EWG

McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367.

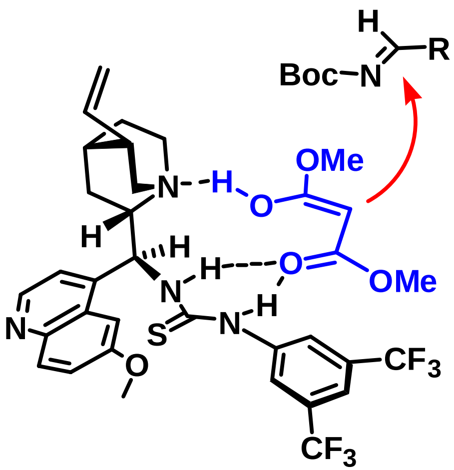
Cinchona Alkaloid Derivatives





Ar = 3,5-*bis*CF_3-C_6H_3

R	yield (%)	*ee* (%)
2-Me-C_6H_4	98	99
4-Me-C_6H_4	92	97
4-Cl-C_6H_4	98	99
4-MeO-C_6H_4	98	97
2-furyl	99	97
2-thienyl	95	97
Et	63	89
*n*Bu	64	92

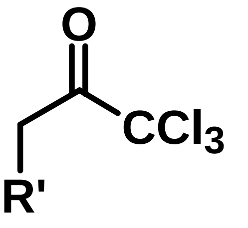


Song, J.; Wang, Y.; Deng, L. *J. Am.Chem. Soc.* **2006**, *128*, 6048.

Outline

- Background Information

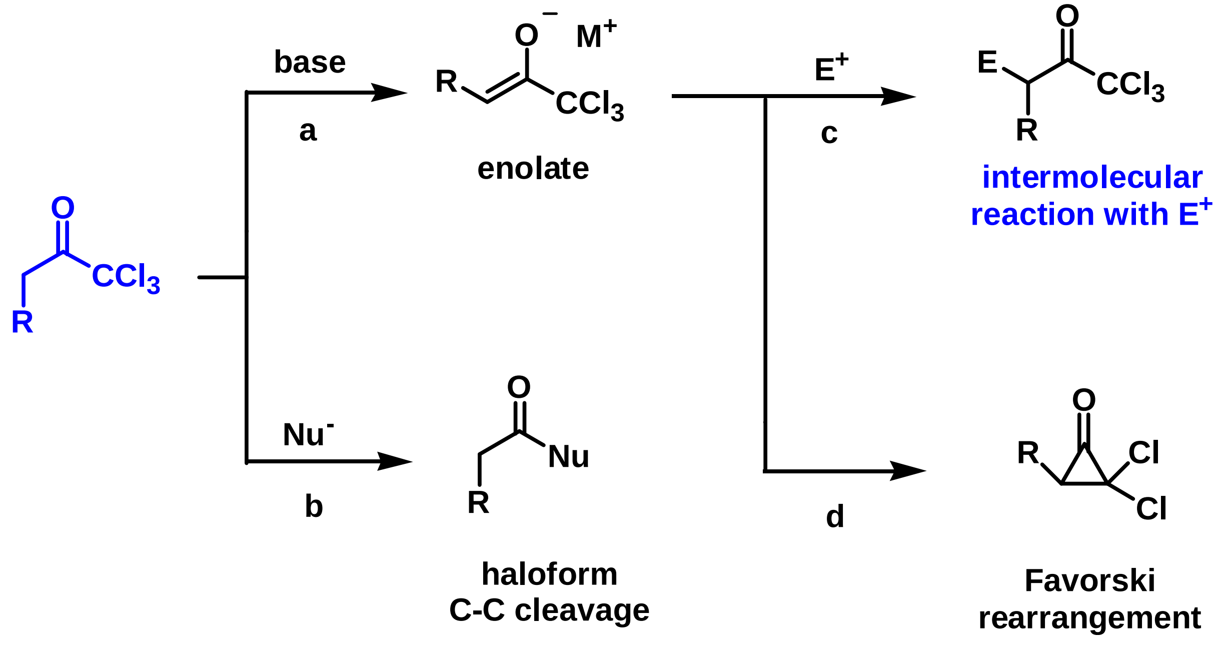
- Esters or Ester-equivalents
  - Glycine Schiff-bases
  - *β*-Keto Esters or Malonates
  - Trichloromethylketones
  - *N*-acylpyrroles
  - *N*-Boc-anilides
  - Diazoacetates



- Conclusions

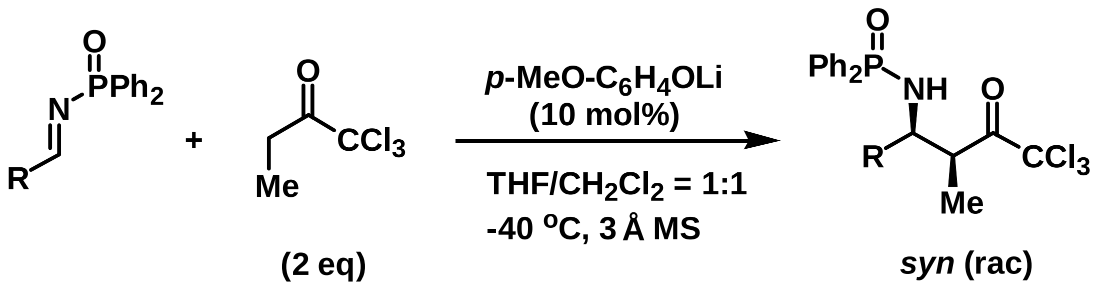
Trichloromethylketones

- $-CCl_3$ is a good leaving group
- Strong inductive effect of $-CCl_3$



Morimoto, H.; Wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 3146

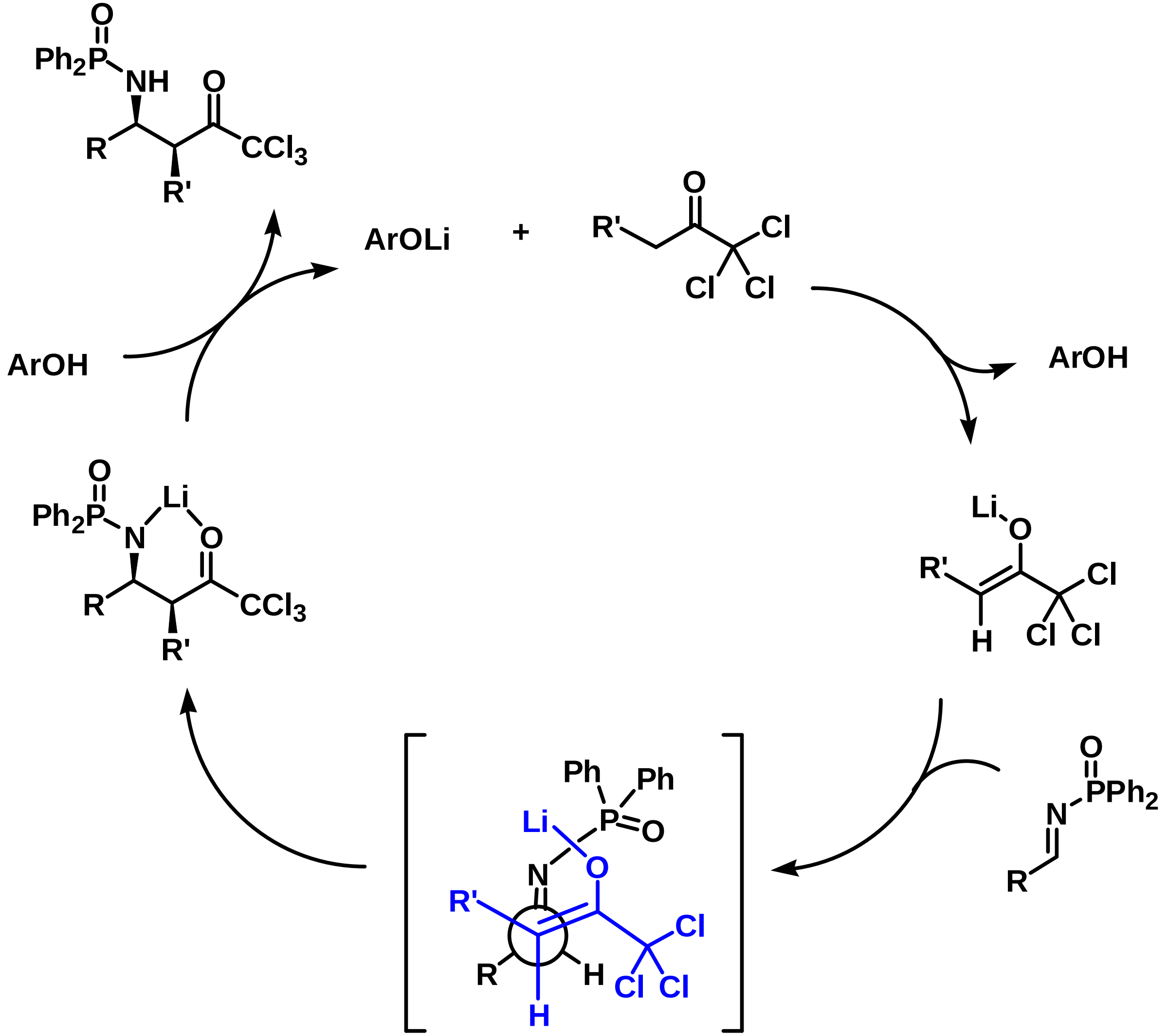
Substrate Scope



R	t (h)	yield (%)	*syn*/*anti*
Ph	3	96	>20:1
4-Cl-C_6H_4	4	93	>20:1
4-MeO-C_6H_4	5	68	>20:1
2-furyl	1	88	6:1
2-thienyl	2	89	8:1
(*E*)-PhCH=CH	1	81	7:1
Cy	2	78	>20:1
*i*Pr	3	71	>20:1
*n*Bu	3	73	>20:1

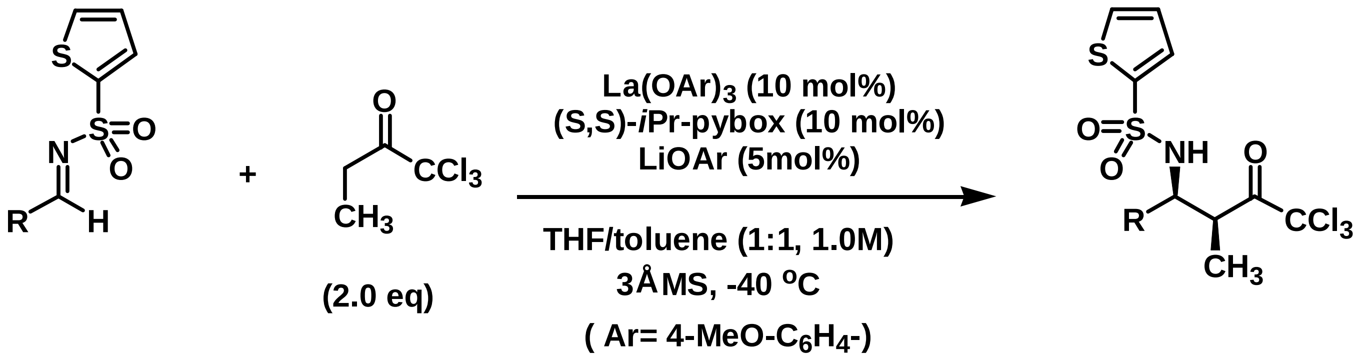
Morimoto, H.; Wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M.
Angew. Chem., *Int. Ed.* **2006**, *45*, 3146

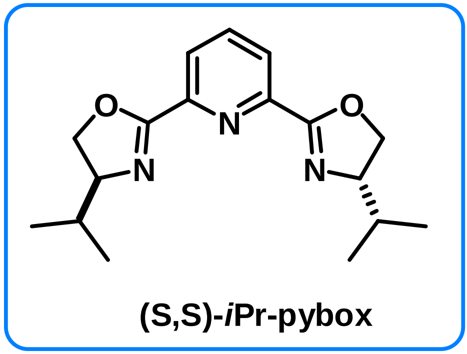
Catalytic Cycle



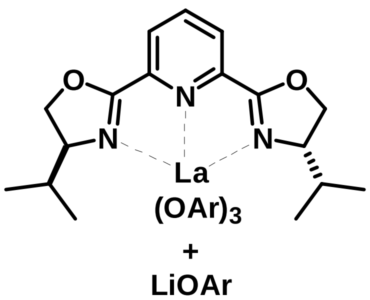
Morimoto, H.; Wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 3146

Asymmetric Variant





R	t (h)	yield (%)	dr (*syn*/*anti*)	*ee* (%)
Ph	9	96	21:1	96
4-Cl-C_6H_4	20	97	20:1	96
4-MeO-C_6H_4	21	96	22:1	95
2-furyl	4	98	8:1	96
2-thienyl	19	98	20:1	95
(*E*)-PhCH=CH	19	75	21:1	96
Cy	22	85	>30:1	96
*i*Bu	25	72	30:1	98



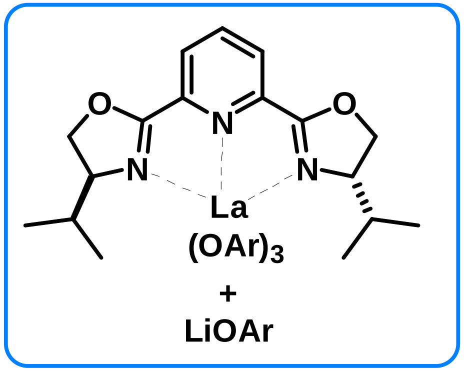
Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.*, **2007**, *129*, 9588

Mechanism Study

- La-OAr moiety functions as a Brønsted base to form La-enolate
- Preliminary kinetic studies on the concentration of trichloromethyl ketone suggested that the enolate formation is the RDS in the absence of LiOAr.
- Two possibilities for the role of LiOAr:

(a) Complexation with $La(OAr)_3$/pybox to form more basic ate complex

(b) LiOAr deprotonates trichloromethyl ketone to form Li-enolate, followed by rapid transmetallation to generate La-enolate.



Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.*, **2007**, *129*, 9588

Outline

- Background Information

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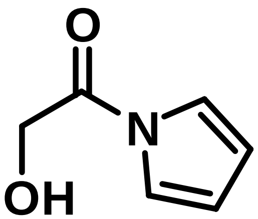
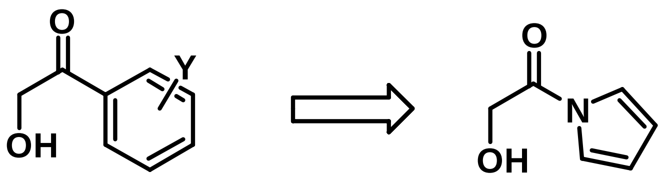
    - Glycine Schiff-bases
    - *β*-Keto Esters or Malonates
    - Trichloromethylketones
    - *N*-acylpyrroles
    - *N*-Boc-anilides
    - Diazoacetates



- Conclusions

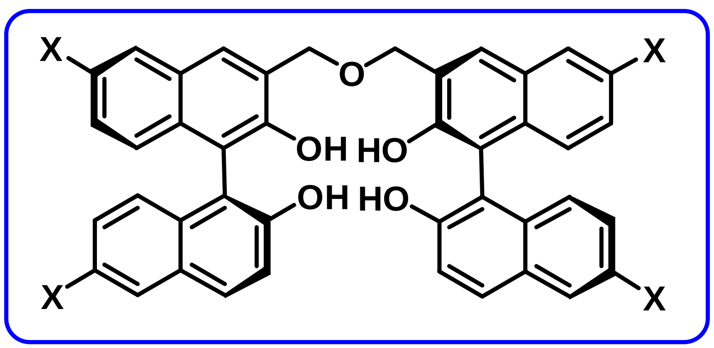
N-acylpyrroles



aromatic ketone

***N*-acylpyrrole**

aromaticity of pyrrole
same coordination mode as ketone
activated carboxylic acid derivative

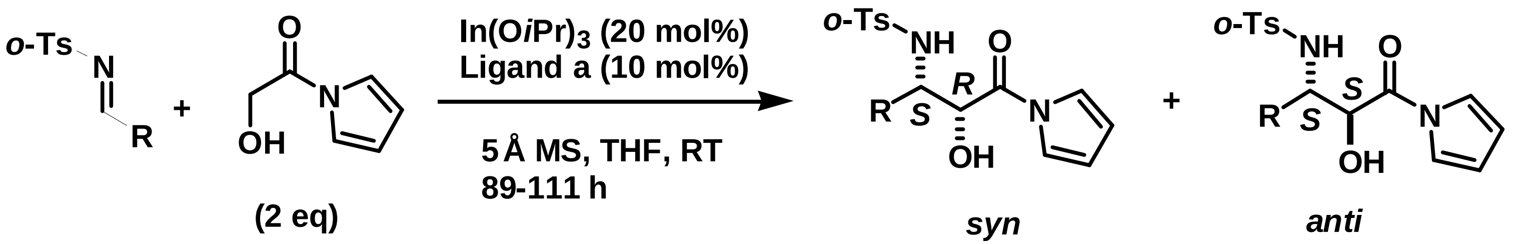


+ In(O*i*Pr)$_3$

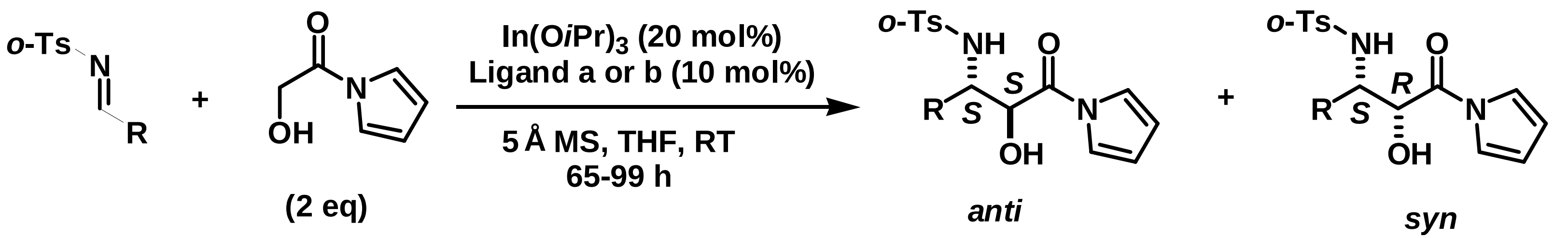
a: X= H: (*S*, *S*)-linked-binol
b: X= TMS: (*S*, *S*)-6,6',6'',6'''-TMS-linked-binol

Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem.*,*Int. Ed.* **2005**, *44*, 4365

Substrate Scope



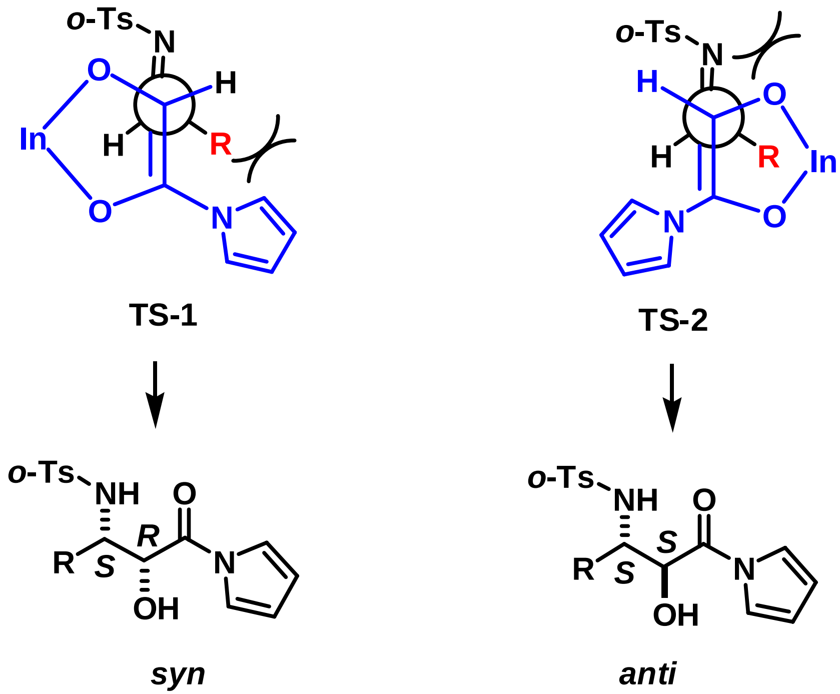
R	yield (%)	dr (*syn*/*anti*)	ee (%) (*syn, anti*)
(*E*)-PhCH=CH	94	91:9	96, 83
Ph	98	61:39	91, 81
4-Cl-C_6H_4	97	59:41	96, 94



R	yield (%)	dr (*anti*/*syn*)	ee (%) (*anti, syn*)
2-naphthyl	87	77:23	94, 89
2-MeO-C_6H_4	74	77:23	92, 86
Cyclopropyl	86	75:25	98, 90

Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem.,Int. Ed.* **2005**, *44*, 4365

Transition-State Model



R = alkenyl, **less hindered Ar**	**R = cyclopropyl,** ***o*-substituted Ar**

Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem.,Int. Ed.* **2005**, *44*, 4365

Outline

- Background Information

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    - Glycine Schiff-bases
    - *β*-Keto Esters or Malonates
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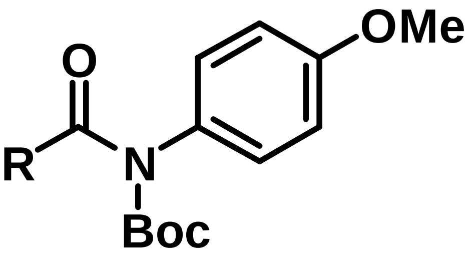
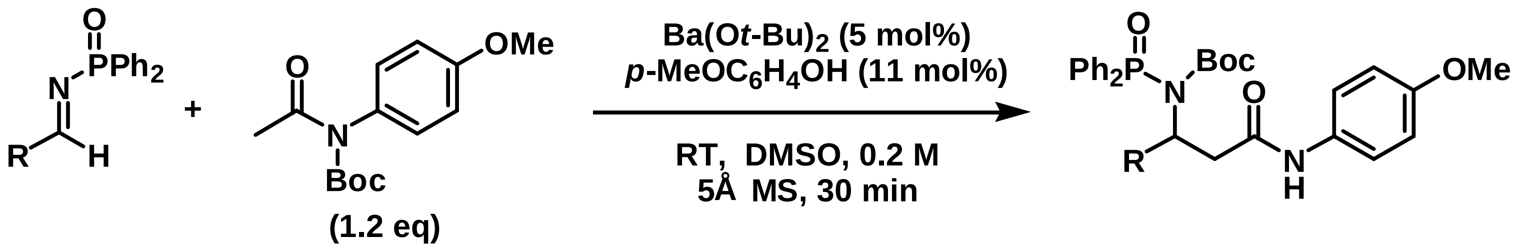
    - *N*-acylpyrroles
    - *N*-Boc-anilides
    - Diazoacetates



- Conclusions

N-Boc-anilides



R	yield (%)
Ph	91
4-MeO-C_6H_4	63
4-Cl-C_6H_4	81
1-naphthyl	95
2-furyl	78
2-thienyl	83
(*E*)-PhCH=CH	76

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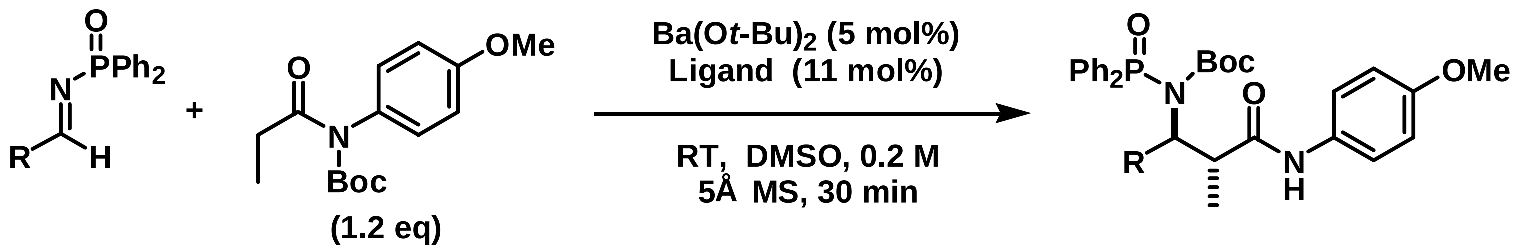
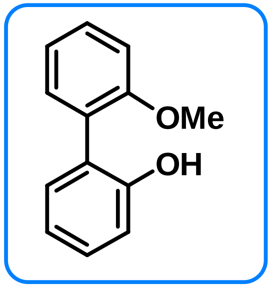
N-Boc-anilides



R	yield (%)	*syn*/*anti*
Ph	86	14:86
1-naphthyl	76	8:92
2-furyl	81	9:91
2-thienyl	81	15:85



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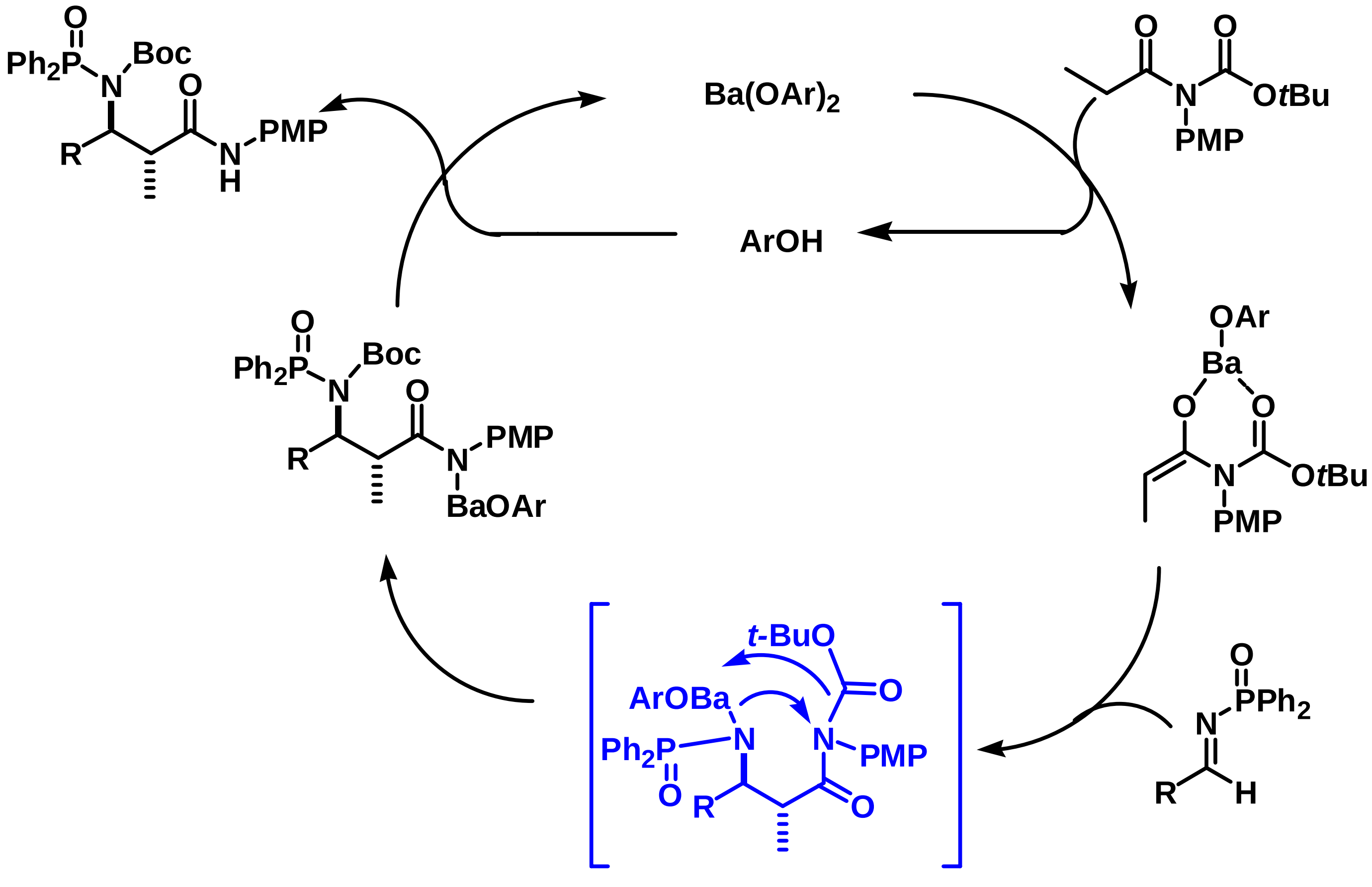
Catalytic Cycle

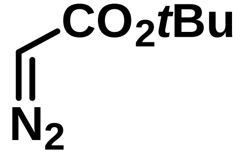


Saito, S.; Tsubogo, T.; Kobayashi, S. *Chem. Commun.* **2007**, 1236.

Outline

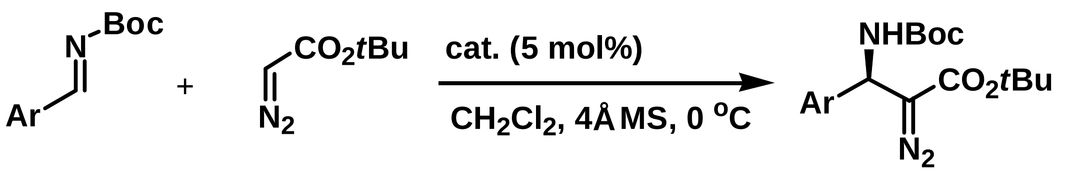
- Background Information

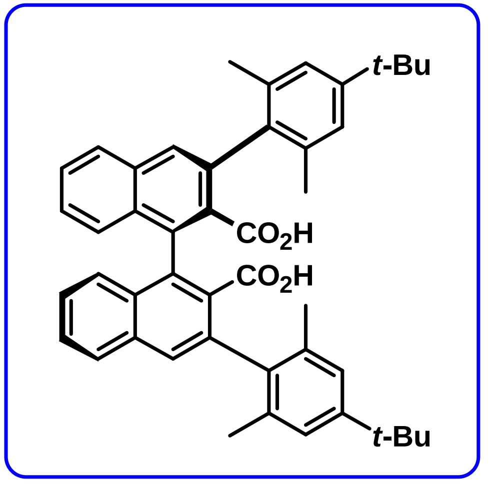
- Esters or Ester-equivalents
  - Glycine Schiff-bases
  - *β*-Keto Esters or Malonates
  - Trichloromethylketones
  - *N*-acylpyrroles
  - *N*-Boc-anilides
  - Diazoacetates



- Conclusions

Tert-Butyl Diazoacetate





Ar	t (h)	yield (%)	*ee* (%)
Ph	24	80	95
2-Me-C_6H_4	72	53	90
4-Me-C_6H_4	18	79	95
4-Cl-C_6H_4	26	89	96
4-MeO-C_6H_4	20	72	95
2-naphthyl	17	77	94
2-furyl	5	84	85

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Outline

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- Esters or Ester-equivalents
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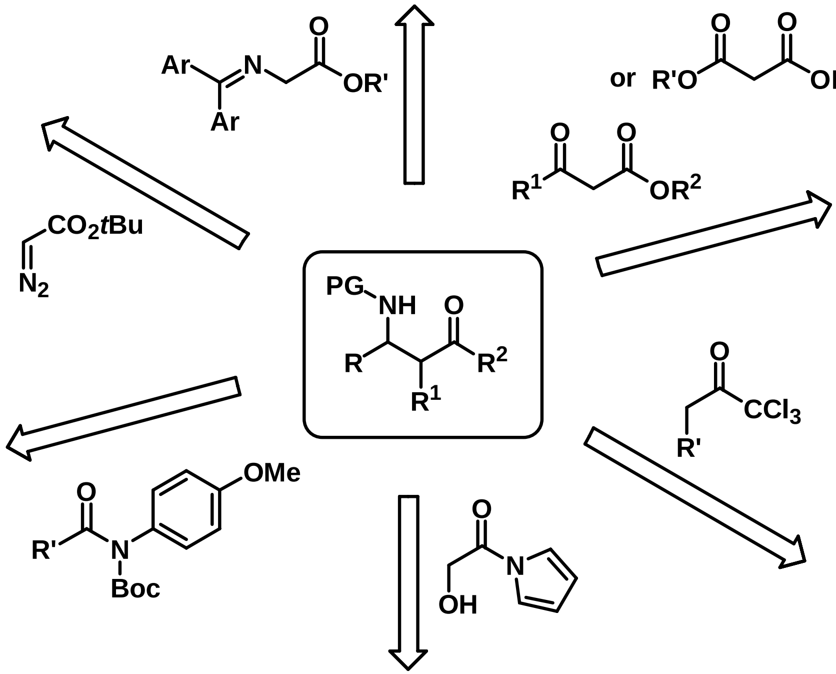
- Conclusions

Conclusions



- Future challenges

1) Expansion on esters or ester-equivalents
2) Development of catalytic versions of the racemic reactions
3) Improvement on the unsatisfactory reactions (new ligands, new metal sources, *etc.*)
4) One-pot cascades reactions

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