Catalytic Asymmetric Synthesis: The Formation of All Carbon Quaternary Centers

"Molecular complexity can be used as an indicator of the frontiers of synthesis, since it often causes failures which exposes gaps in existing methodology. The realization of such limitations can stimulate the discovery of new chemistry and new ways of thinking about synthesis" E.J. Corey, 1989

Christopher Rosenker
Wipf Group - Frontiers of Chemistry
May 26, 2012

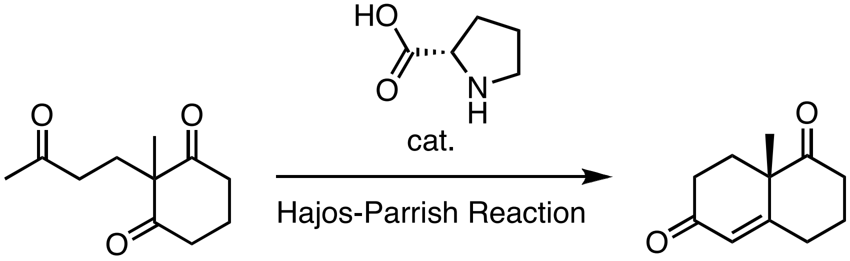
What is a frontier in chemistry?

- Frontier (n): the extreme limit of understanding or achievement in a particular area
- A topic that is currently being investigated in the field of chemistry that has the potential to be incredibly useful; however, lacks key findings or breakthroughs to allow it to gain widespread use.

Apple Dictionary, Version 2.1.3 (80.4)
Image from http://fineartamerica.com/featured/american-frontier-mick-burkey.html

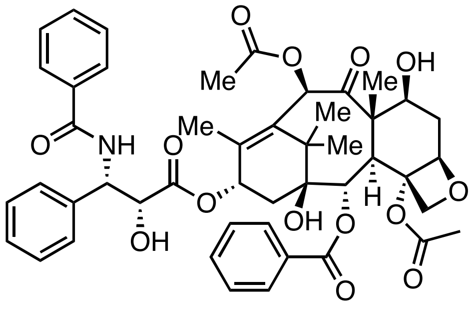
All Carbon Quaternary Stereocenters

- What reactions do we know that can install all carbon quaternary stereocenters?
  - Aldol, Enolate Alkylation, Diels-Alder, Allylic Alkylation, Conjugate Addition, S_N2', Cyclopropanation, Desymmetrization, Radical
  - Desymmetrizations can be done by any reaction not forming quaternary centers
    - The most famous of all is the Wieland-Miescher Ketone synthesis:

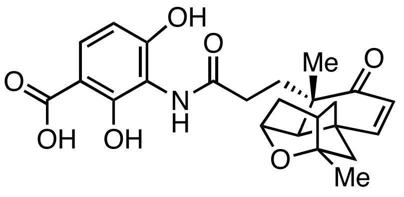


- All carbon quaternary stereocenters can be installed using:
  - Inherent substrate control (if the molecule has other stereocenters present)
  - Stoichiometric chiral auxiliary
  - **Catalytic asymmetric methodology**

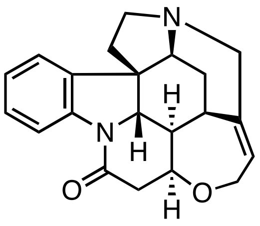
All Carbon Quaternary Stereocenters



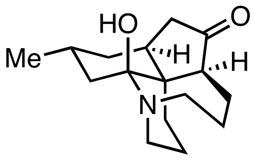
Paclitaxel



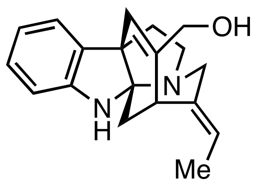
Platensimycin



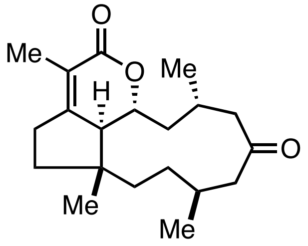
Strychnine



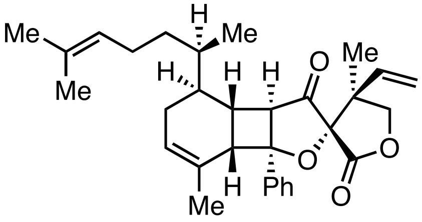
Fawcettimine



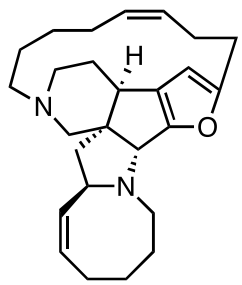
Minfiensine



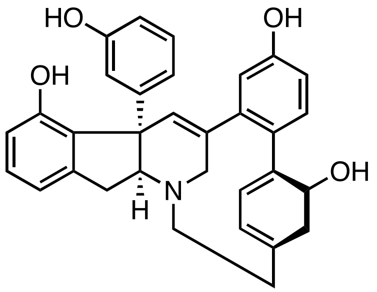
Clavirolide C



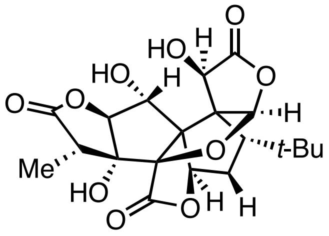
Biyouyanagin A



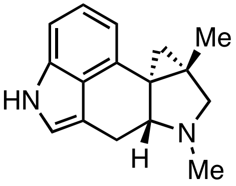
Nakadomarin A



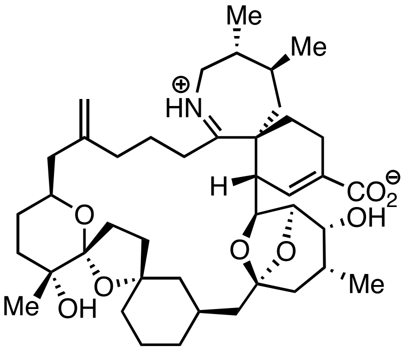
Haouamine A



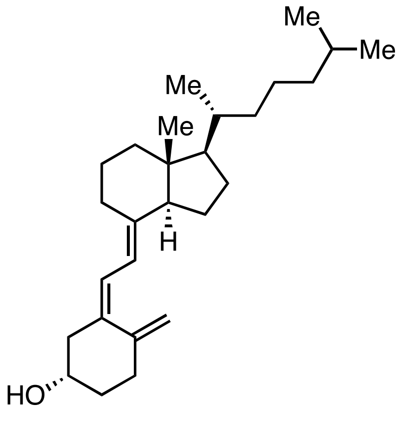
Ginkgolide B



Cycloclavine



Pinnatoxin A

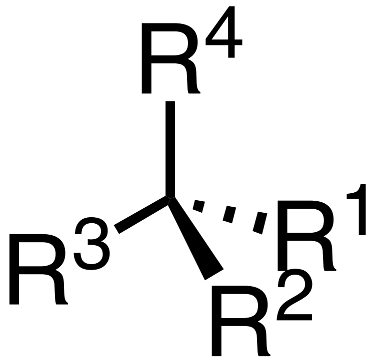


Vitamin D_3

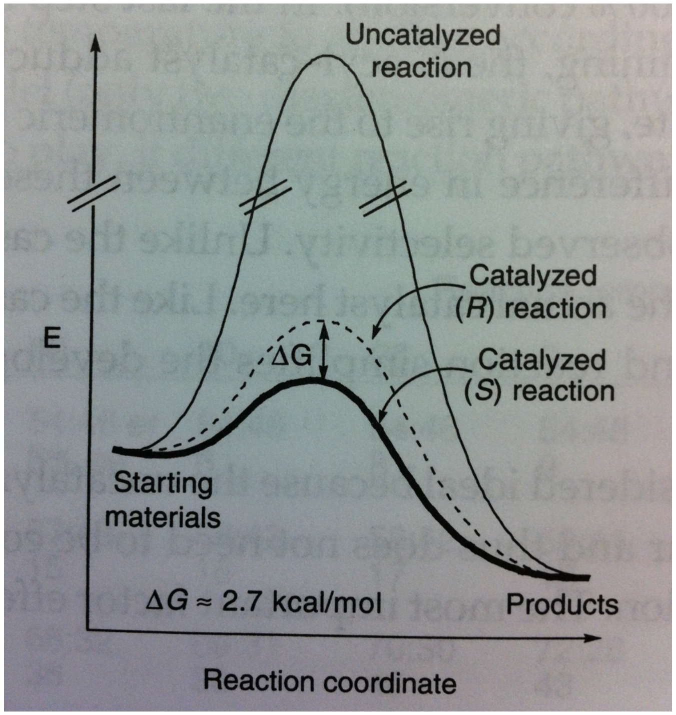
- The Top 200 drug chart contains **zero** non-steroid compounds containing all carbon quaternary stereocenters.

All Carbon Quaternary Stereocenters

"Within the area of asymmetric synthesis, the enantioselective construction of all-carbon quaternary stereocenters (C$R^1R^2R^3R^4$) is a particularly difficult challenge. One obstacle is low reactivity, due to steric congestion, which discourages the targeted carbon-carbon bond formation from occurring. Of course, even if this reactivity problem can be overcome, there is yet another formidable barrier to success: high enantioselectivity requires that, in the transition state for the formation of a new C-R^4 bond, the three groups (R^1, R^2, and R^3) already attached to the central carbon must be very effectively distinguished." Gregory C. Fu & Ara Mermerian (MIT, JACS 2005, 127, 5604.)*



Asymmetric Catalysis



- What is asymmetric catalysis?
  - Simplest reaction is combining two molecules; one prochiral and one achiral.
- Important properties of a catalyst:
  - Catalyst availability, preparation, stability, cost, high activity (ie low loading), recoverable, reusable
  - Broad substrate scope, predictable reactivity
  - Ideally, one catalyst would be able to give 100% yield, *er*, recovery, and be completely recyclable for a variety of chemical transformations.
  - Unfortunately we are not far from one catalyst, one reaction, for one substrate…

Image from Walsh, P. J. and Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis 2009, p3.*

Metal-Catalyzed Asymmetric Catalysis

- Catalyst activity is generally determined by a metal.
- Catalyst reactivity and enantioselectivity can be tuned by chiral organic ligands.
    - Catalyst efficiency is controlled by the balance between electronic and steric factors of the ligand.
    - Almost limitless combinations of metals and chiral organic molecules make catalyst choice challenging.
- Rational design and optimization of catalysts is unsuitable for unprecedented asymmetric reactions.
    - A good mechanistic understanding of the reaction can provide insight for rational catalyst design.

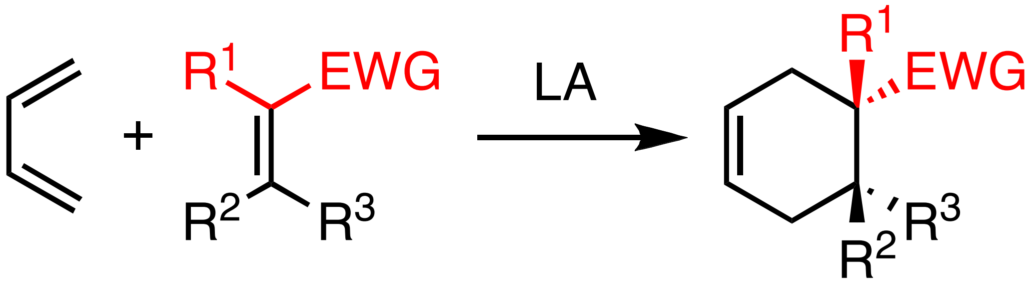
Shibasaki, M. and Matsunaga, S. In *Asymmetric Synthesis - The Essentials* **2008** Ed. Christmann, M. and Brase, S. p. 51-55.

Outline

- All Carbon Quaternary Stereocenters
    - Cycloaddition Reactions
    - Metal Catalyzed Cyclizations
    - Cyclopropanations
    - The Heck Reaction
    - Chiral Allyl-Metal Electrophiles
    - Alpha Carbonyl Alkylation
    - Aldol & Mannich Reactions
    - Addition to Chiral Carbon Electrophiles
    - S_N2’ Addition
    - Conjugate Addition

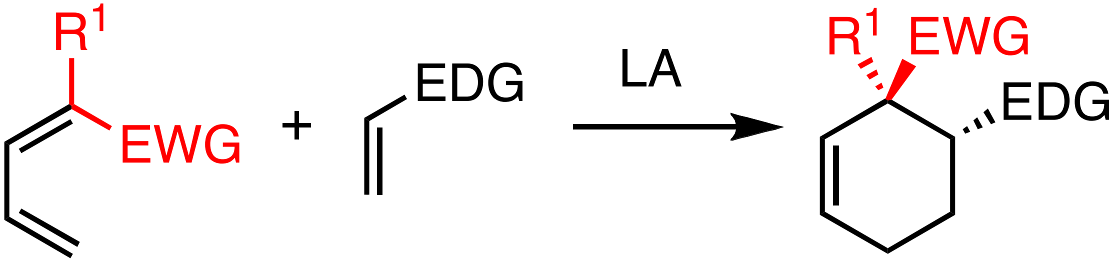
Cycloadditions: Diels-Alder

Type I



LA = B, Mg, Al, Ti, Cr, Fe, Cu, Ru, Sm, Gd

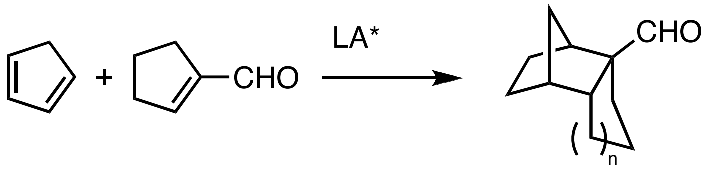
Type II



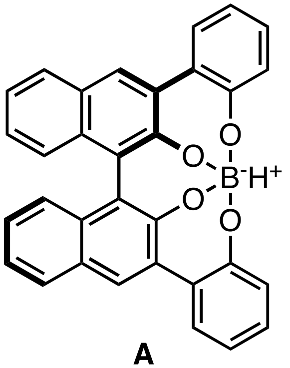
LA = Ti, Eu, Yb

Douglas, C. J.; Overman, L. E. *Proc Natl Acad Sci USA* **2004**, *101*, 5363.

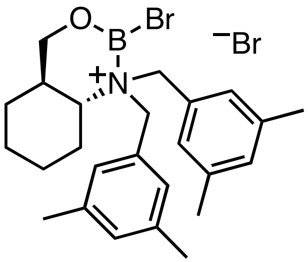
Cycloadditions: Diels-Alder



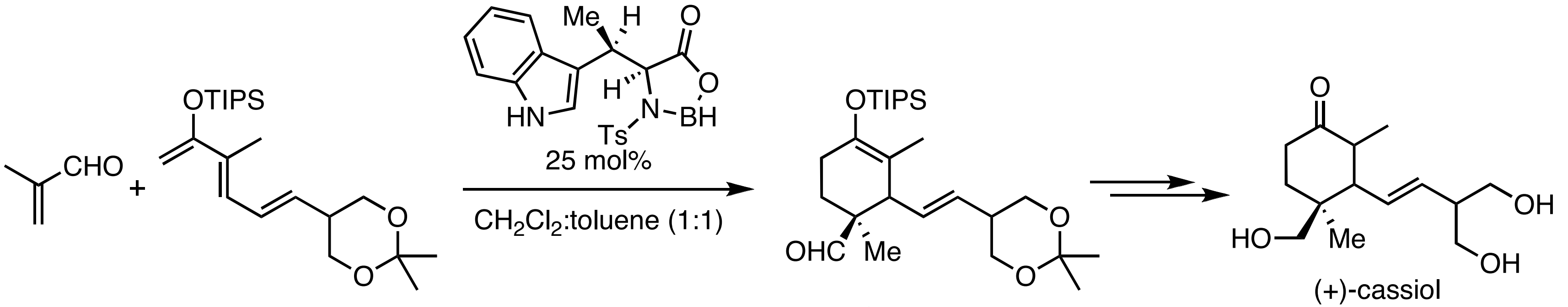
n=1; >99%, 93% *ee* (**A**)
n=2; 99%, 96% *ee* (**B**)



A



B



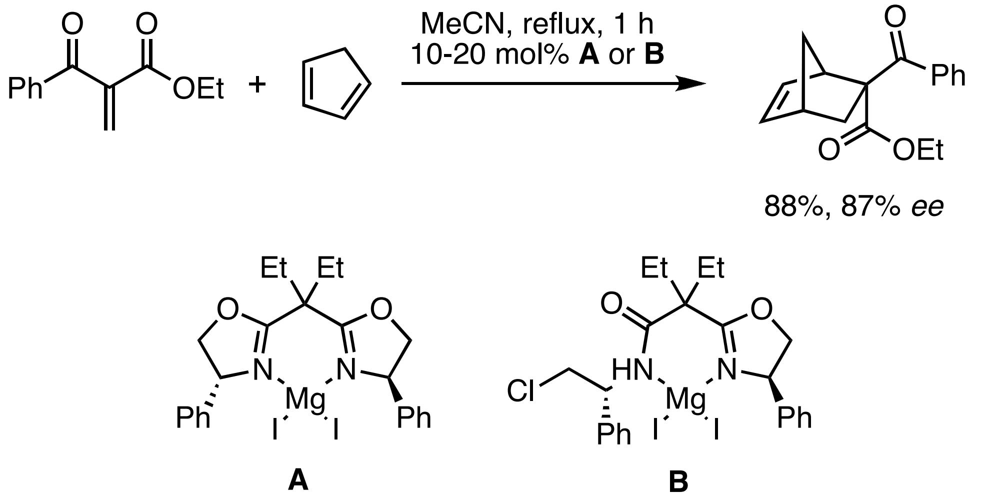
25 mol%

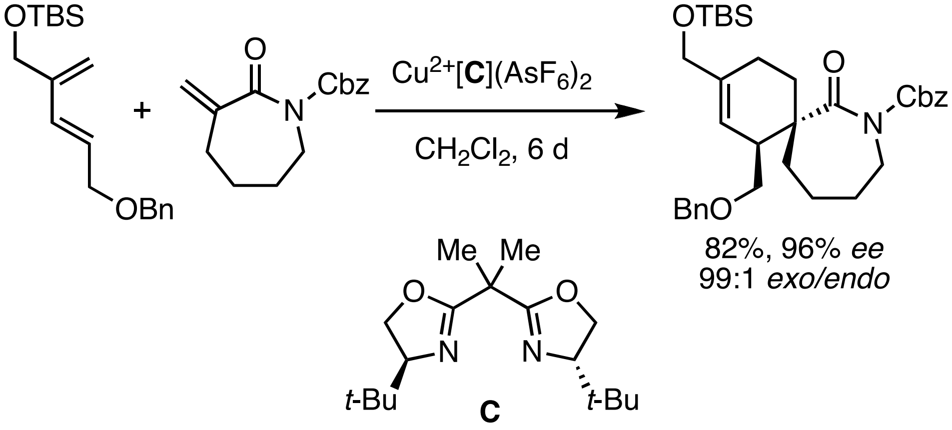
CH_2Cl_2:toluene (1:1)

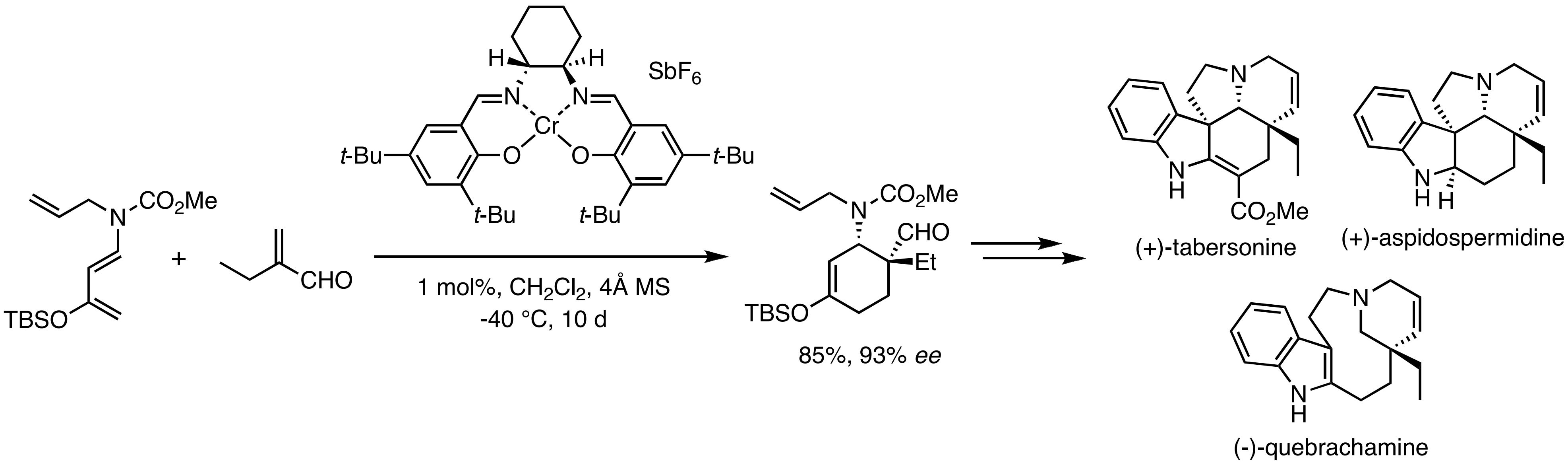
83%, 97% *ee*
single diasteroemer/
regioisomer

Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561.
Hayashi, Y.; Rohde, J. J.; Corey, E. *J. Am. Chem. Soc.* **1996**, *118*, 5502.
Corey, E.; Guzman Perez, A.; Loh, T. P. *J. Am. Chem. Soc.* **1994**, *116*, 3611.

Cycloadditions: Diels-Alder

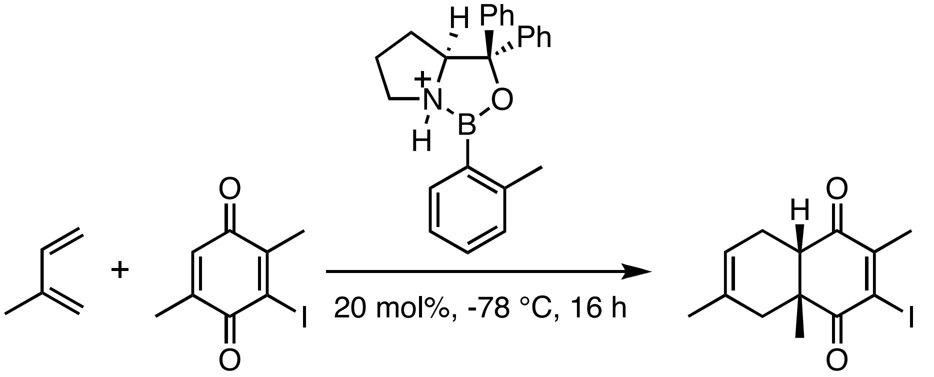




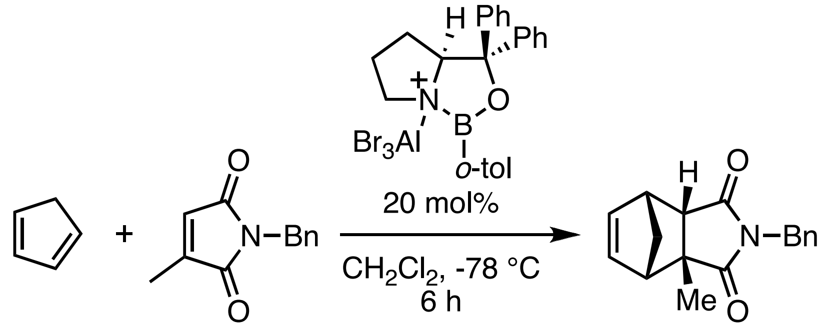


Honda, Y.; Date, T.; Hiramatsu, H.; Yamauchi, M. *Chem. Commun.* **1997**, 1411.
Ishihara, J.; Horie, M.; Shimada, Y.; Tojo, S.; Murai, A. *Synlett* **2002**, 259.
Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.

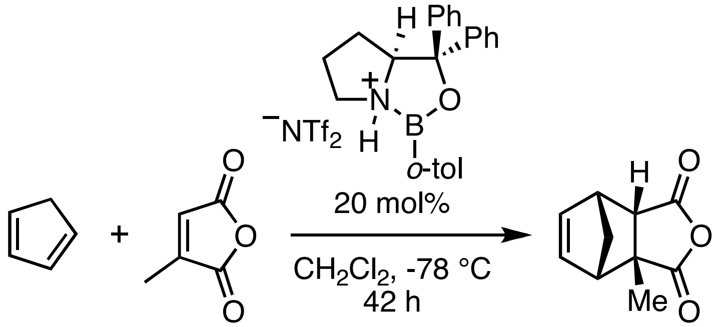
Cycloadditions: Diels-Alder



99%, >99% *ee*
93:7 regioselectivity



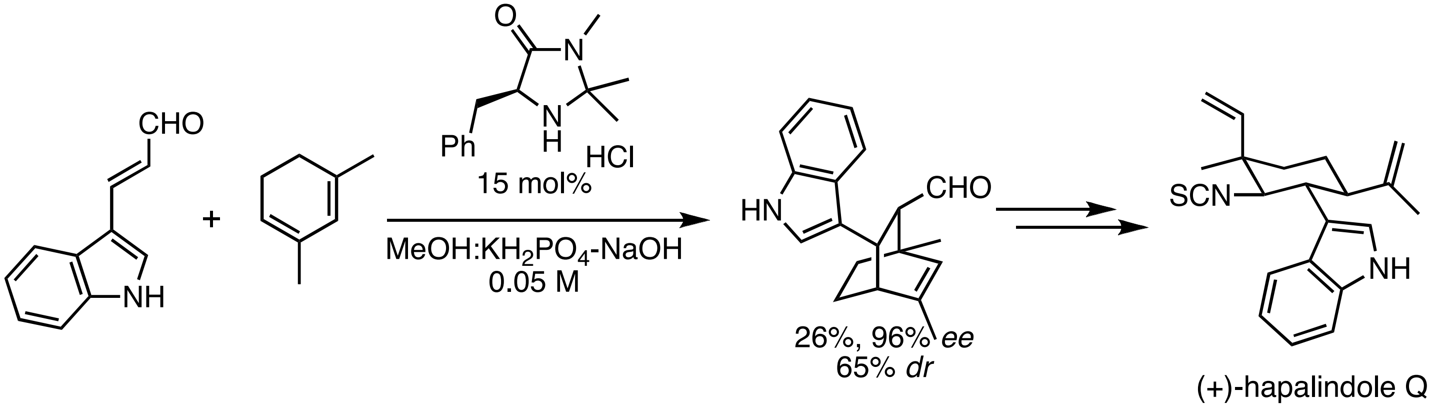
96%, 99% *ee*
>99:1 *endo/exo*

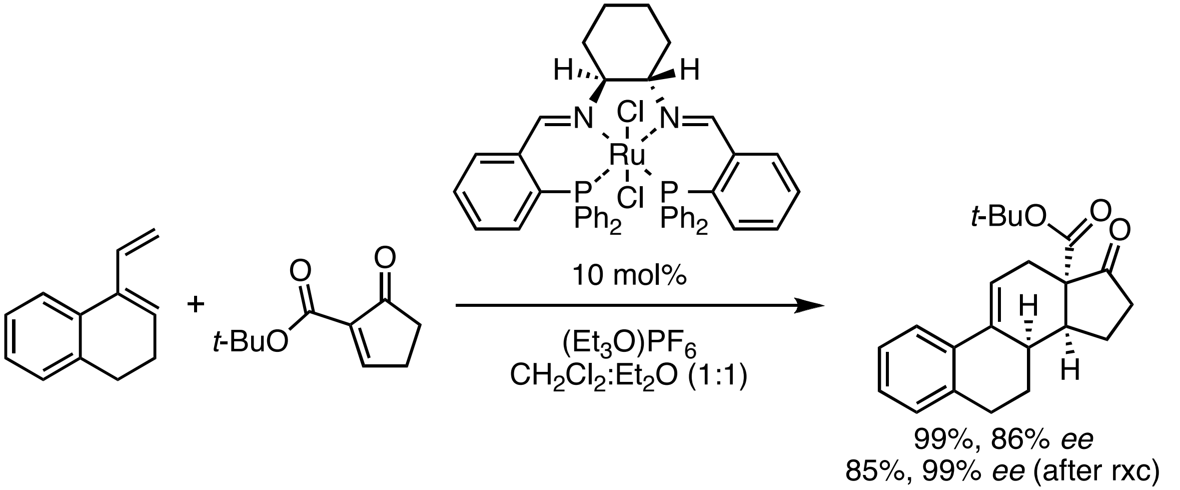


75%, 91% *ee*
>99:1 *endo/exo*

Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.
Mukherjee, S.; Corey, E. J. *Org. Lett.* **2010**, *12*, 632.

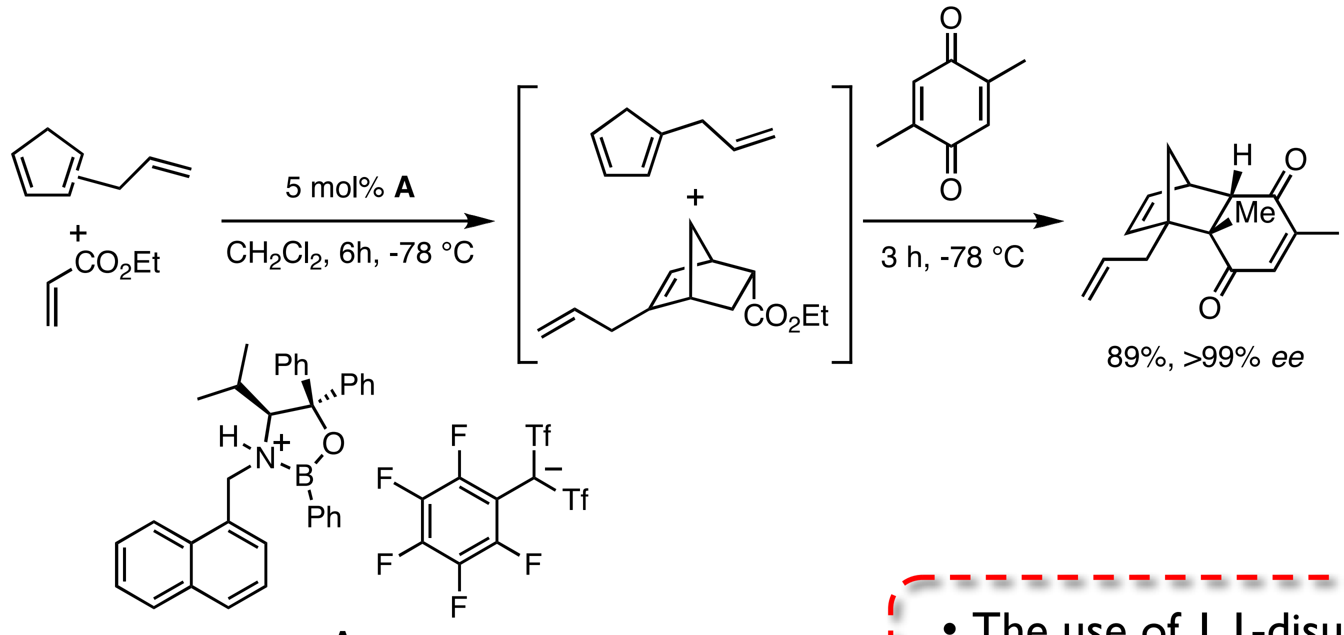
Cycloadditions: Diels-Alder





Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120.
Schotes, C.; Mezzetti, A. *J. Am. Chem. Soc.* **2010**, *132*, 3652.
Schotes, C.; Althaus, M.; Aardoom, R.; Mezzetti, A. *J. Am. Chem. Soc.* **2012**, *134*, 1331.

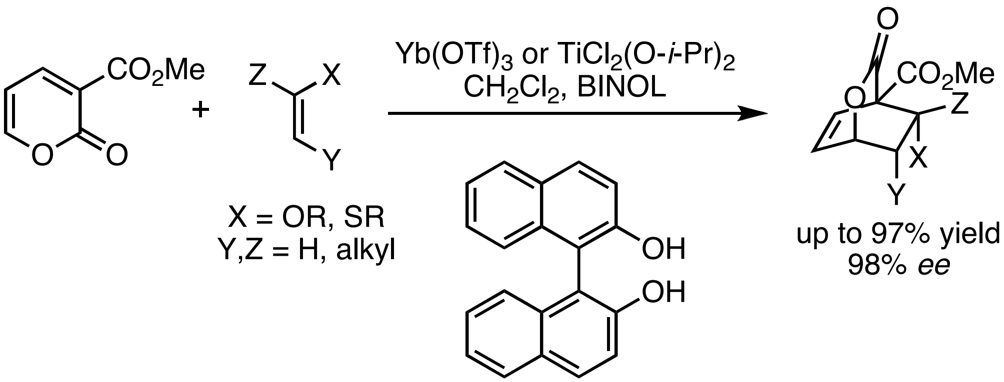
Cycloadditions: Diels-Alder



89%, >99% *ee*

A

- The use of 1,1-disubstituted dienes has been limited. This remains relatively uninvestigated.



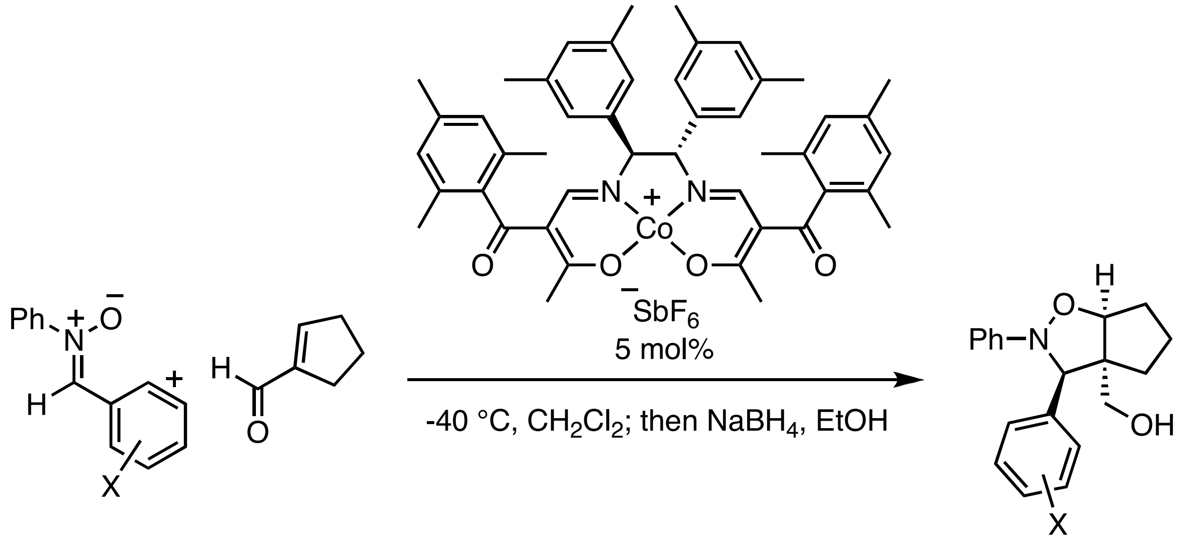
X = OR, SR
Y,Z = H, alkyl

up to 97% yield
98% *ee*

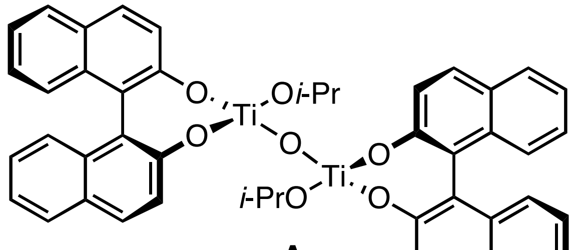
BINOL

Payette, J. N. and Yamamoto, H. J. Am. Chem. Soc., **2007**, 129, 9536.
Marko, I. E.; Evans, G. R. *Tetrahedron Lett* **1994**, *35*, 2771.
Posner, G. H.; Eydoux, F.; Lee, J.; Bull, D. S. *Tetrahedron Lett.* **1994**, *35*, 7541.

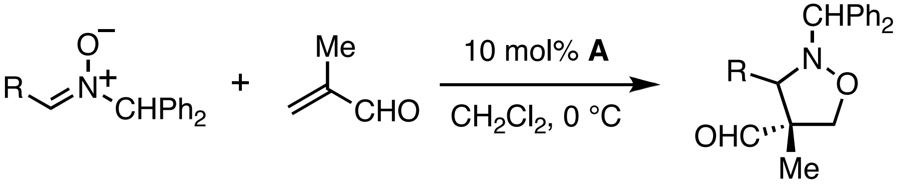
Other Cyclizations



85-100%, 83-91% *ee*



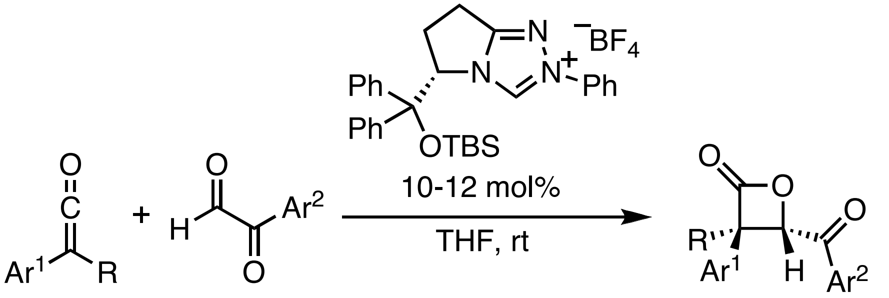
A



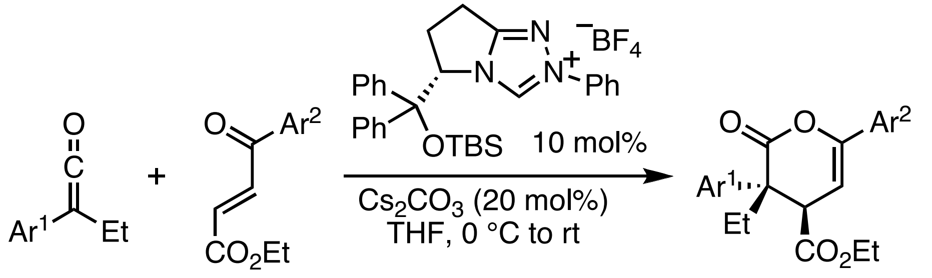
R = aryl, substituted vinyl
46- 80%; 70-99% *ee*

Mita, T.; Ohtsuki, N.; Ikeno, T. Yamada, T. *Org. Lett.* **2002,** *4,* 2457.
Hashimoto, T.; Omote, M.; Hato, Y.; Kano, T.; Maruoka, K. *Chem. Asian J.* **2008**, *3*, 407.

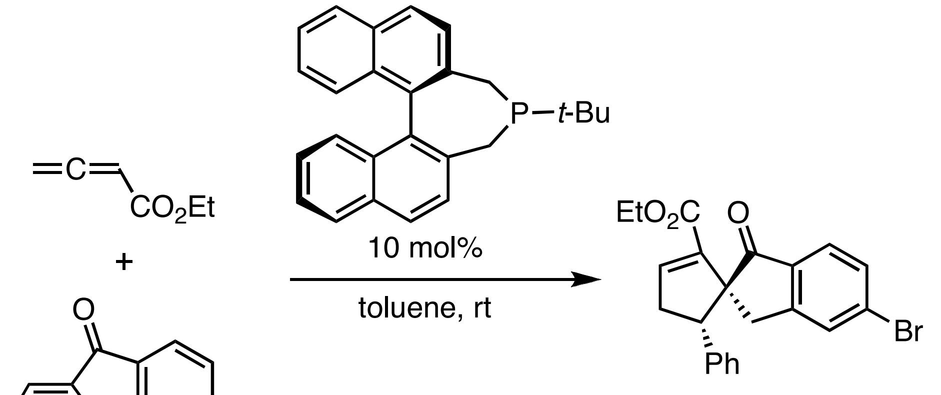
Other Cyclizations



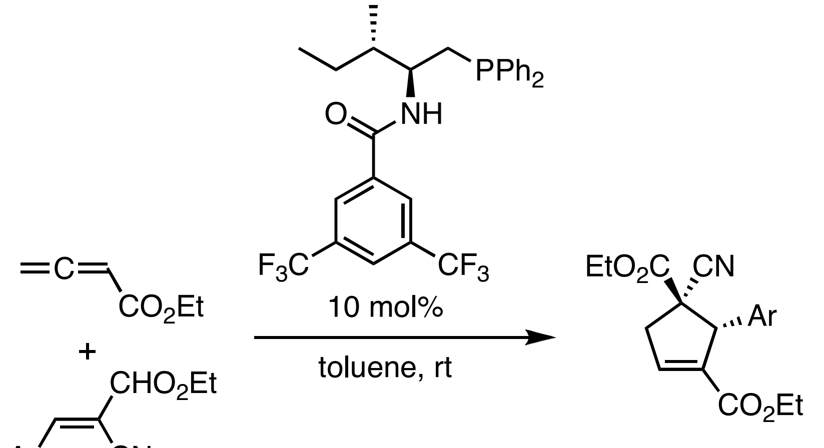
R = Et, *i*-Pr
63-99%, 78-99% *ee*
>4:1 *dr*



57-93%; 84-92% *ee*
>15:1 *dr*



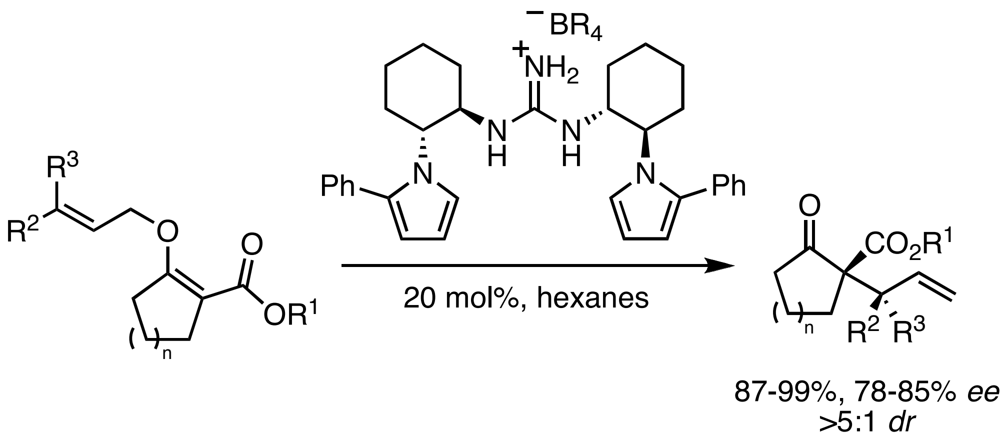
97%, 89% *ee*



80-93%, 80-99% *ee*
95:5 *dr*

He, L.; Lv, H.; Zhang, Y.-R.; Ye, S. *J. Org. Chem.* **2008**, *73*, 8101.
Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem.-Eur. J.* **2008**, *14*, 8473.
Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 1426.
Xiao, H.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4467.

Claisen Rearrangement

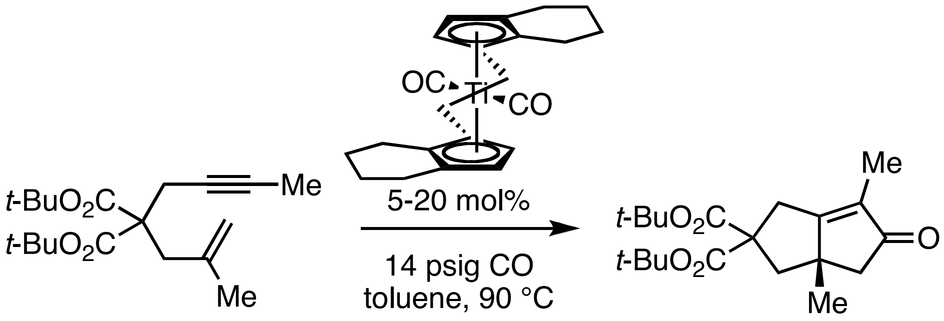


- The substrate scope for these type of cyclizations are relatively limited.

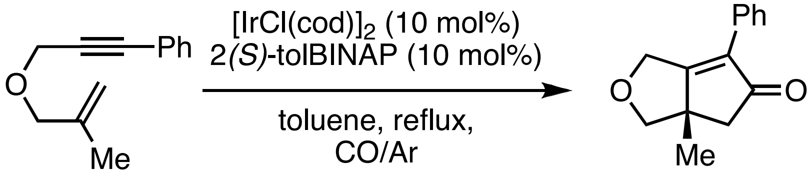
Uyeda, C.; Roheli, A. R.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 9753.

Metal Catalyzed Cyclizations

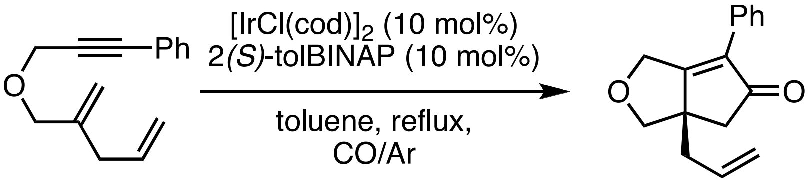
- **Pauson-Khand**



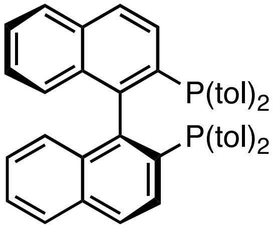
90%, 72% *ee*

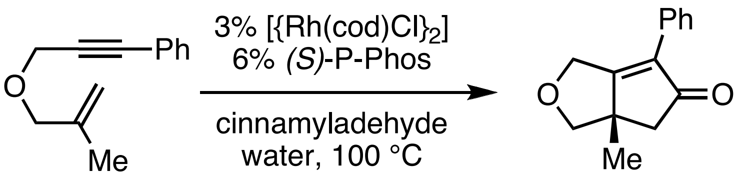


86%, 93% *ee*

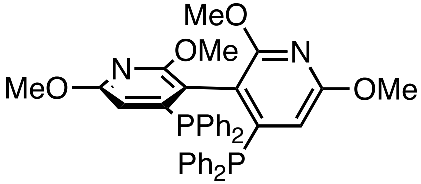


62%, 94% *ee*





71%, 90% *ee*

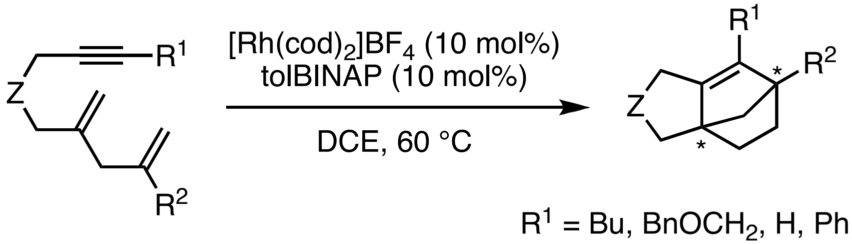


(S)-P-Phos

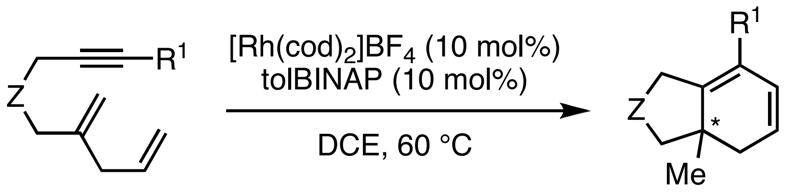
Hicks, F.; Buchwald, S. *J. Am. Chem. Soc.* **1996**, *118*, 11688.
Kwong, F. Y.; Li, Y.-M.; Lam, W. H.; Qiu, L.; Lee, H. W.; Yeung, C. H.; Chan, K.-S.; Chan, A. S. C. *Chem-Eur. J.* **2005**, *11*, 3872.
Shibata, T.; Toshida, N.; Yamasaki, M.; Maekawa, S.; Takagi, K. *Tetrahedron* **2005**, *61*, 9974.

Metal Catalyzed Cyclizations

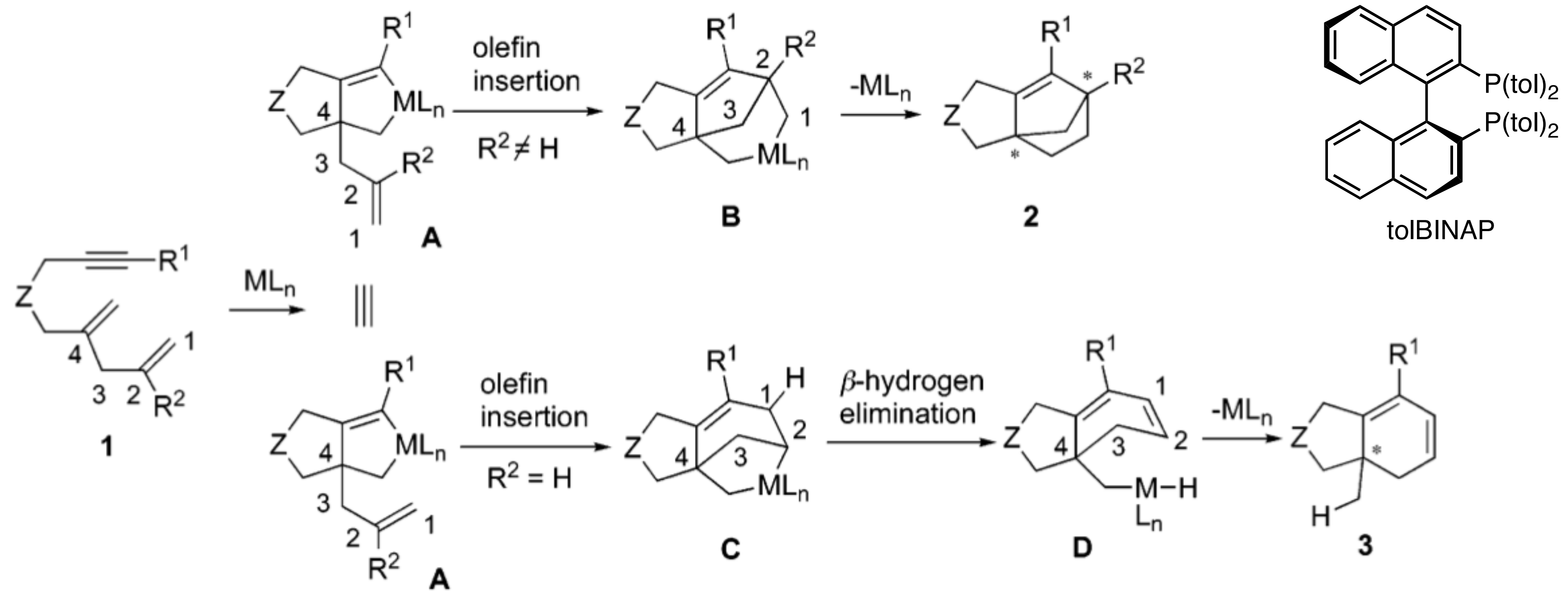
- **Ene-yne cyclizations**



R^1 = Bu, $BnOCH_2$, H, Ph
R^2 = Me, Ph
Z = NTs, $C(CO_2Bn)_2$, O
46-83%; 88-99% *ee*



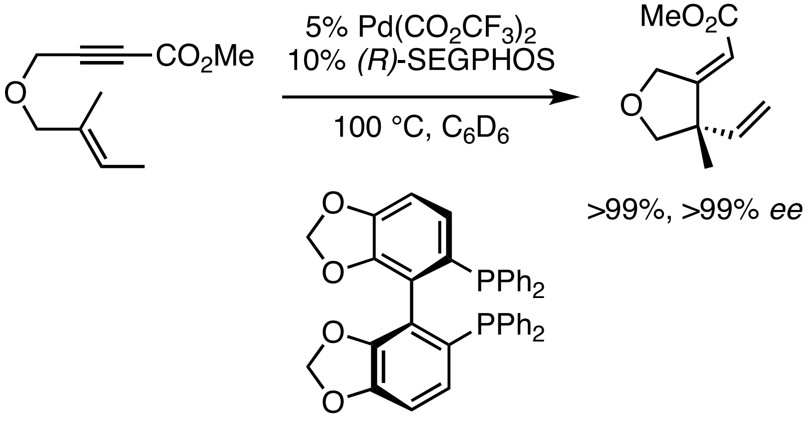
R^1 = Me, H, Ph, $Ph(CH_2)_3$
Z = NTs, $C(CO_2Bn)_2$, O
55-91%; 90-99% *ee*



Shibata, T.; Tahara, Y.-K.; Tamura, K.; Endo, K. *J. Am. Chem. Soc.* **2008**, *130*, 3451.
Shibata, T.; Tahara, Y.-K. *J. Am. Chem. Soc.* **2006**, *128*, 11766.

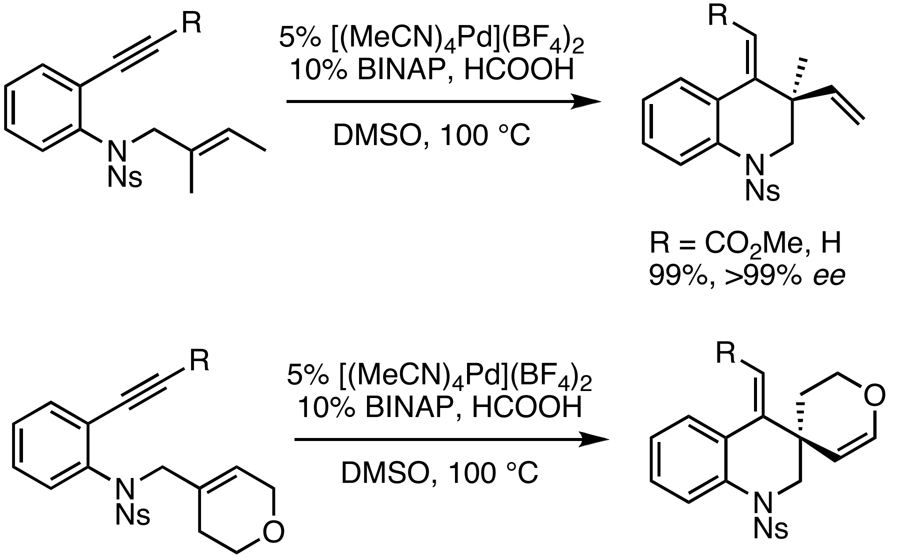
Metal Catalyzed Cyclizations

- **Ene-yne cyclizations**


5% $Pd(CO_2CF_3)_2$
10% *(R)*-SEGPHOS
100 °C, C_6D_6

>99%, >99% *ee*

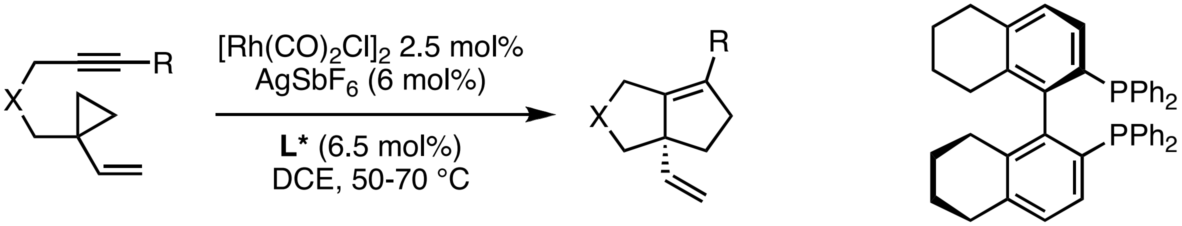
(R)-SEGPHOS


5% $[(MeCN)_4Pd](BF_4)_2$
10% BINAP, HCOOH
DMSO, 100 °C

R = CO_2Me, H
99%, >99% *ee*

5% $[(MeCN)_4Pd](BF_4)_2$
10% BINAP, HCOOH
DMSO, 100 °C

R = CO_2Me, H
>99%, 98-99% *ee*


$[Rh(CO)_2Cl]_2$ 2.5 mol%
$AgSbF_6$ (6 mol%)
L* (6.5 mol%)
DCE, 50-70 °C

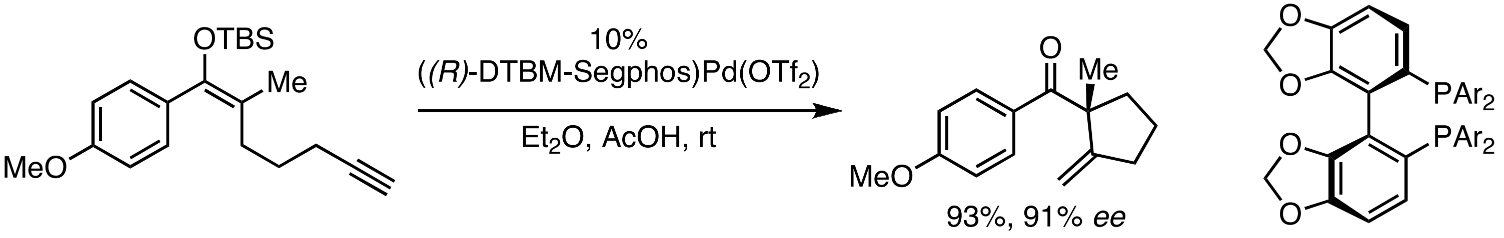
R = Alkyl, COMe, CO_2Me, Ph
X = NTs, O, $C(CO_2Bn)_2$
41-90%, 48-99% *ee*

L*

Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 249.
Tsuchikama, K.; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc.* **2006**, *128*, 13686.
Lin, M.; Kang, G.-Y.; Guo, Y.-A.; Yu, Z.-X. *J. Am. Chem. Soc.* **2012**, *134*, 398.

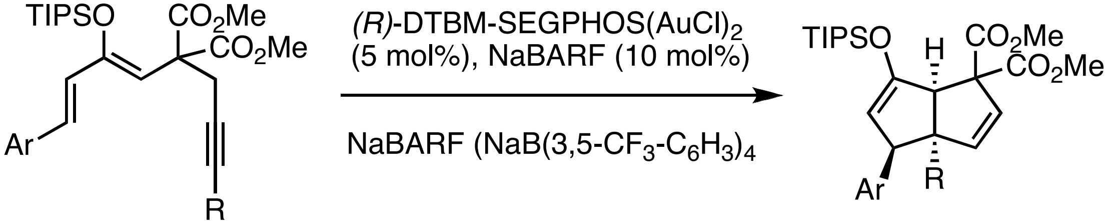
Metal Catalyzed Cyclizations

- **Silyloxyenyne cyclization**

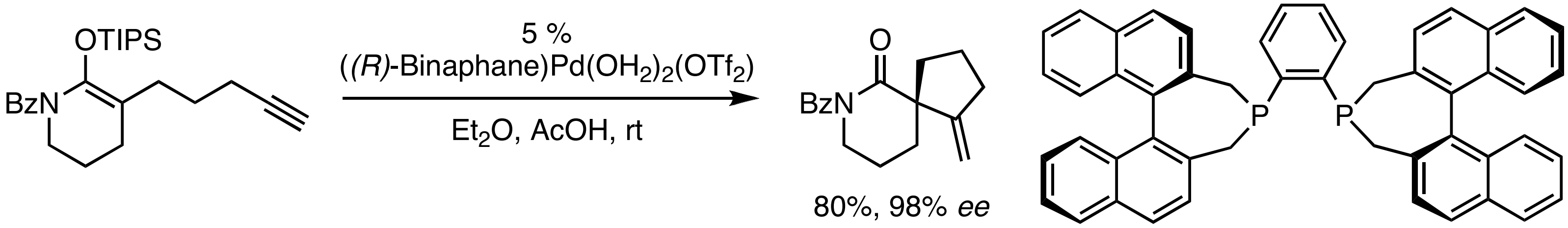


93%, 91% *ee*

(R)-DTBM-SEGPHOS
Ar = 3,5-(*t*-Bu)-4-MeO-C_6H_2



R = Me, Et
61-82%; 81-98% *ee*



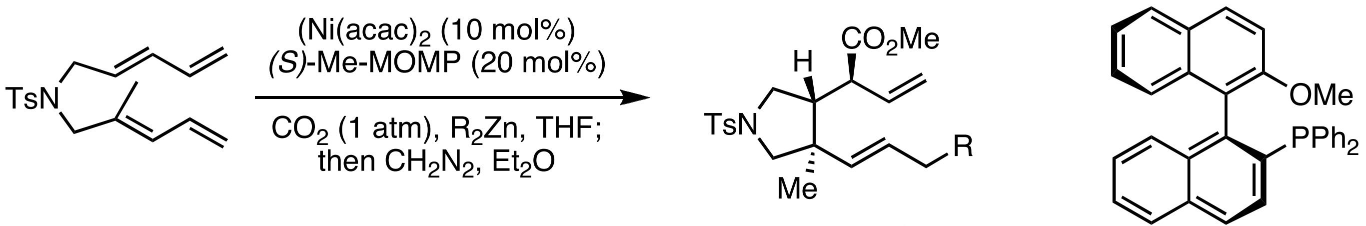
80%, 98% *ee*

(R)-Binaphane

Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764.
Brazeau, J.-F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 2742.

Metal Catalyzed Cyclizations

- **Diene cyclization**



R = Me, Ph
87-88%, 91-96% *ee*

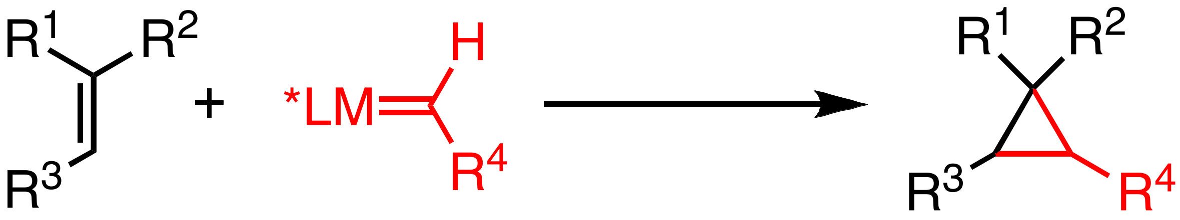
(S)-MeO-MOP

- Gives complex chiral structures from linear SM
- Can achieve high enantioselectivity; yield if often lower than other transformations
- Requires significant optimization: Metal, L*, solvent, T, additive, O_2
- Reactions sensitive to minor changes in substrate

Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* **2004**, *126*, 5956.

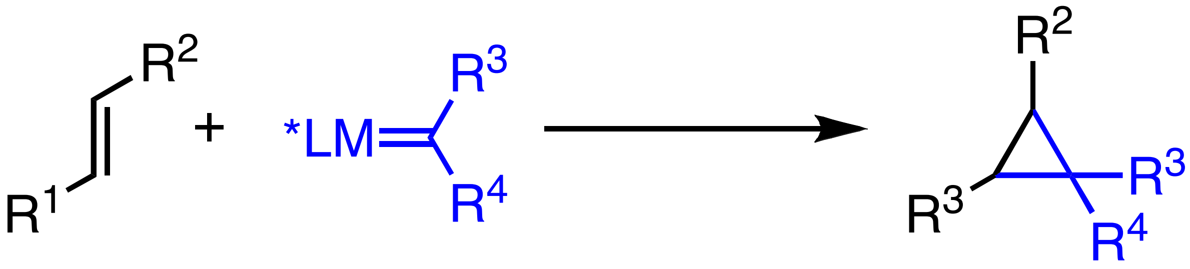
Cyclopropanations

Type I



M = Cu, Rh, Co, Zn, Ti

Type II

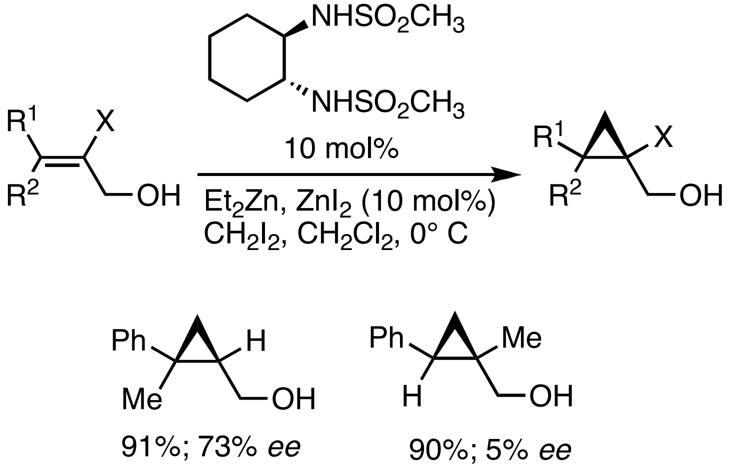


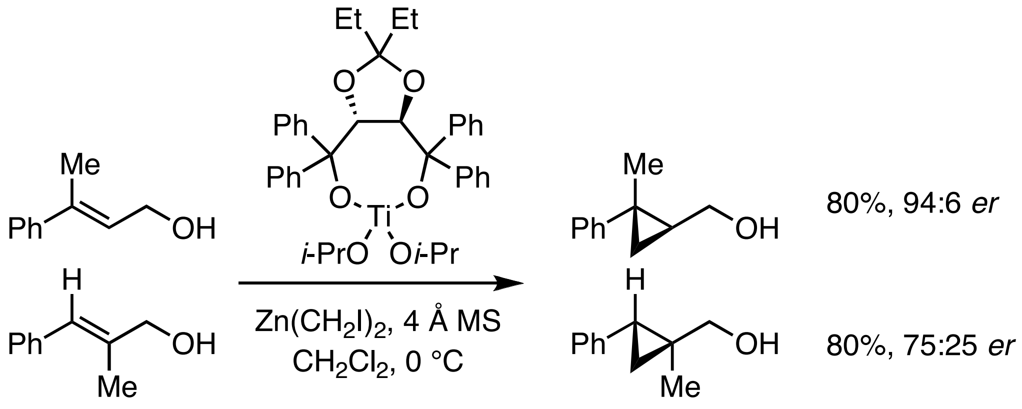
M = Cu, Rh

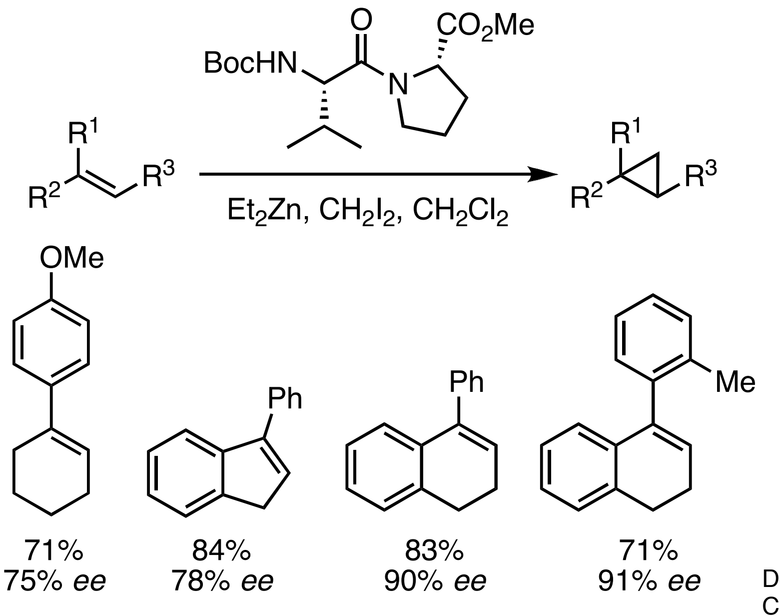
Douglas, C. J.; Overman, L. E. *Proc Natl Acad Sci USA* **2004**, *101*, 5363.

Cyclopropanations

- **Cyclopropanations using diiodomethane**





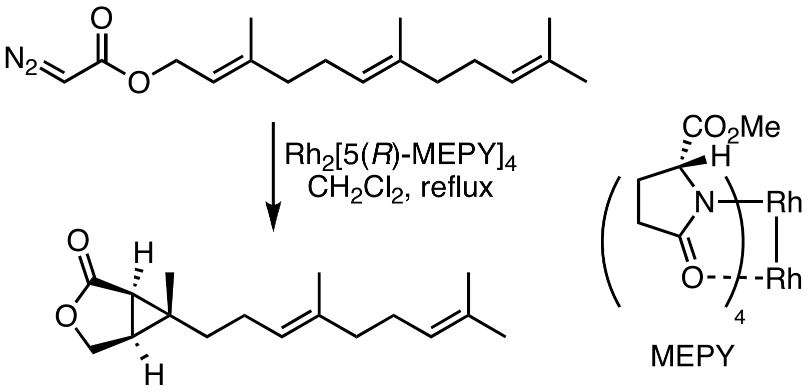


- Limited substrate scope:
  - allylic alcohols
  - unfunctionalized olefins

Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584.
Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168.
Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13632.

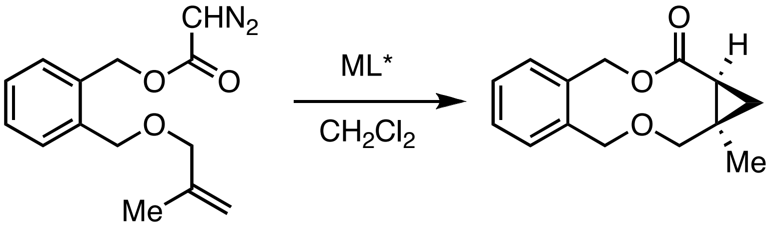
Cyclopropanations

- **Intramolecular cyclopropanation**

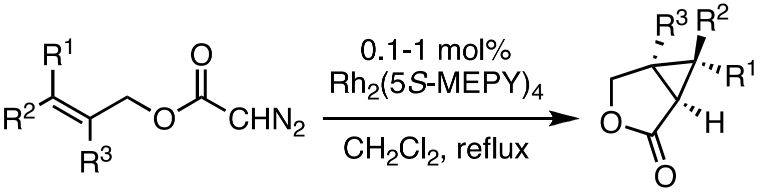


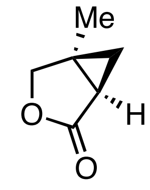
96%, ≥94% *ee*

MEPY

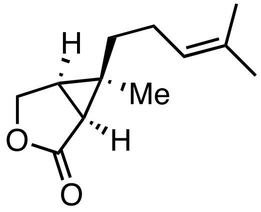


ML*	**Result**
$[Cu(MeCN)_4]PF_6$	82%, 90% *ee*
$Rh_2(5S\text{-MEPY})_4$	77%, 47% *ee*

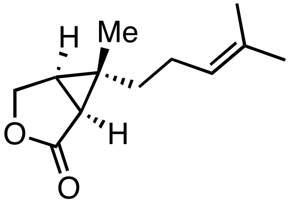




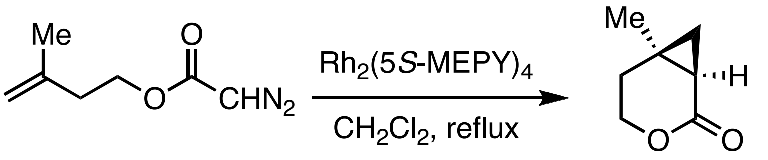
72%, 7% *ee*



79%, 93% *ee*



88%, 95% *ee*

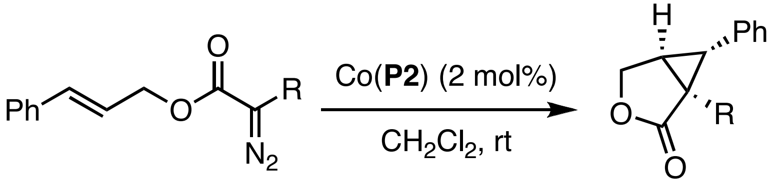


76%, 83% *ee*

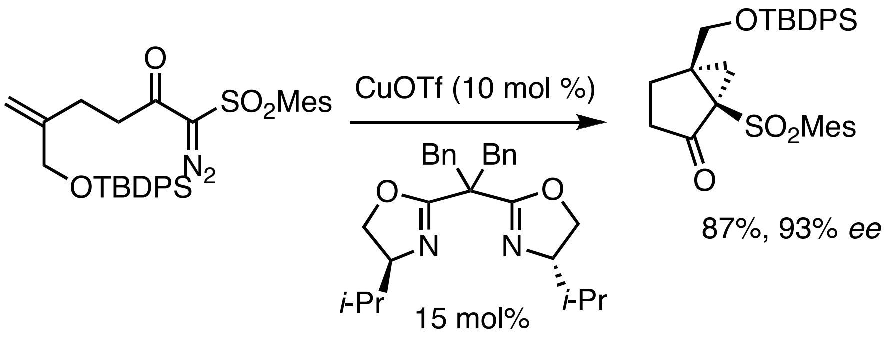
Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* **2004**, *126*, 5956.
Doyle, M.; Peterson, C.; Parker, D. *Angew. Chem. Int. Ed.* **1996**, *35*, 1334.
Doyle, M.; Austin, R.; Bailey, A.; Dwyer, M.; Dyatkin, A.B.; Kalinin, A.; Kwan, M.; Liras, S.; Oalmann, C.; Pieters, R.; Protopopova, M.; Raab, C.; Roos, G.; Zhou, Q.; Martin, S. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

Cyclopropanations

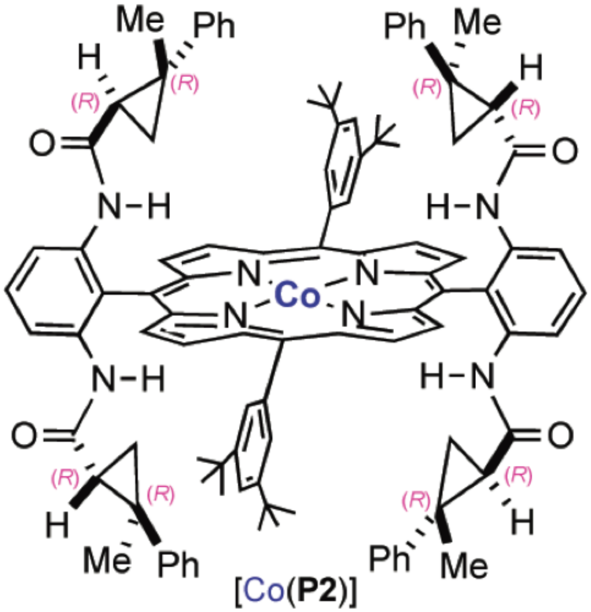
- **Intramolecular cyclopropanation**



R = Me, CN, CO_2Et, CO_2Me
62-99%, 73-99% *ee*
(*cis* olefin gives low *ee*)



87%, 93% *ee*



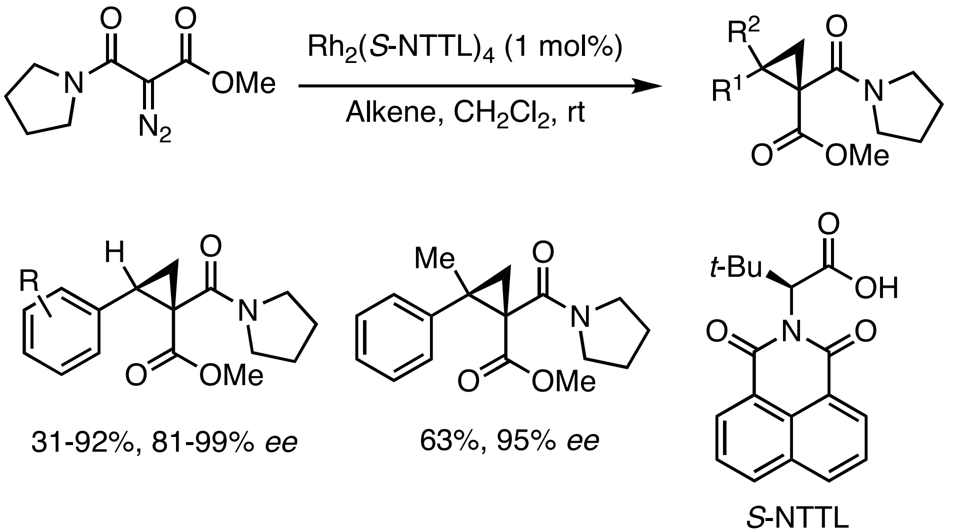
[Co(**P2**)]
(**P2** = 3,5-Di^{t}Bu-QingPhyrin)

- small changes in catalyst and/or substrate can have profound effects on *er*
- highlights the general inability to predict the proper substrate catalyst combinations

Watanabe, H.; Nakada, M. *Tetrahedron Lett.* **2008**, *49*, 1518.
Xu, X.; Lu, H.; Ruppel, J. V.; Cui, X.; Lopez de Mesa, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 15292.

Cyclopropanations

- **Intermolecular cyclopropanation**



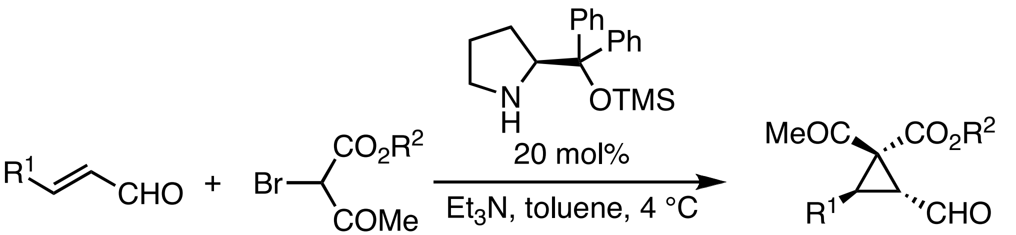
Rh_2(*S*-NTTL)$_4$ (1 mol%)

Alkene, CH_2Cl_2, rt

31-92%, 81-99% *ee*

63%, 95% *ee*

S-NTTL



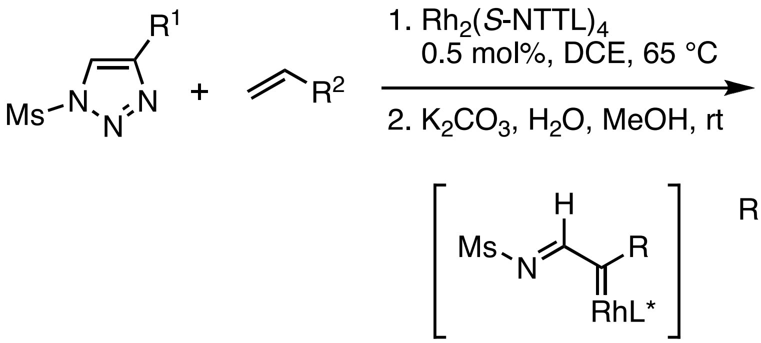
20 mol%

Et_3N, toluene, 4 °C

R^1 = Ar; R^2 = Et, Me

88-92%; *dr* = >7.5:1;

94-98% *ee*

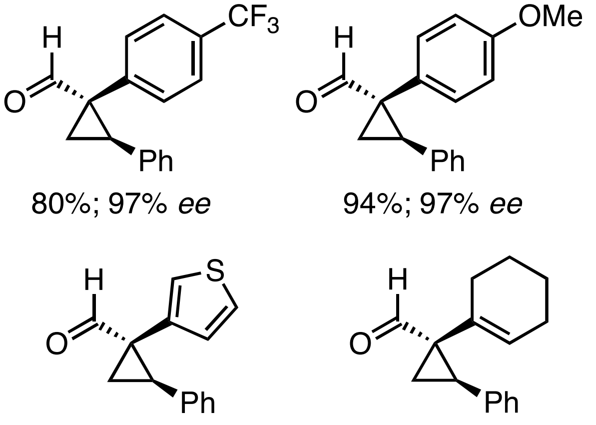


1. Rh_2(*S*-NTTL)$_4$ 0.5 mol%, DCE, 65 °C

2. K_2CO_3, H_2O, MeOH, rt

R^1 = Ph; R^2 = Aryl, Bu

69%, 96-98% *ee*



80%; 97% *ee*

94%; 97% *ee*

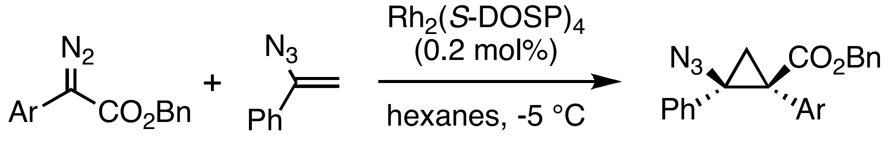
57%; 93% *ee*

57%; 98% *ee*

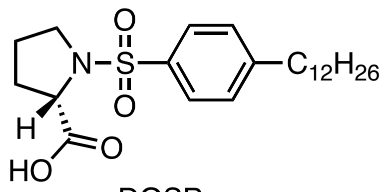
Marcoux, D.; Goudreau, S. R.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 8939.
Companyo, X.; Alba, A.-N.; Cardenas, F.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2009**, *2009*, 3075.
Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034.

Cyclopropanations

- **Intermolecular cyclopropanation**

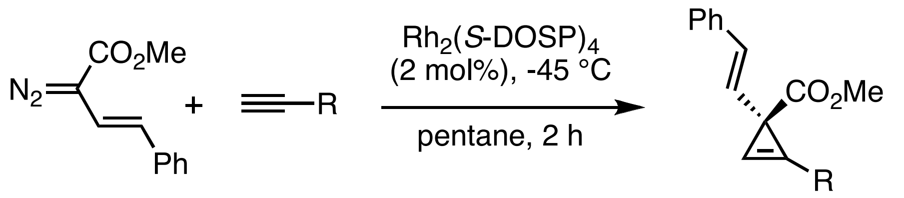


70-97%; 75-95% *ee*

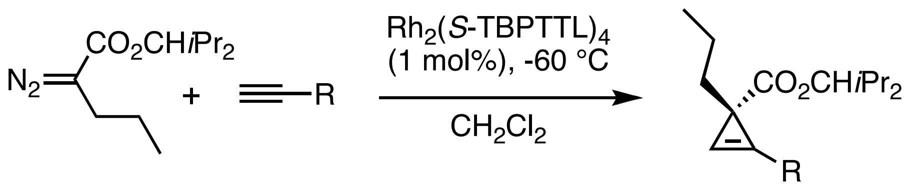


DOSP

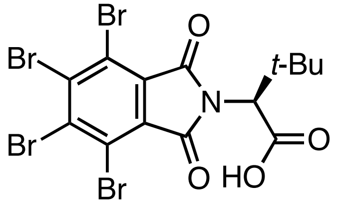
- **Intermolecular cyclopropenylation**



R = alkyl, *t*-Bu, TMS
46-89%; 95-99% *ee*



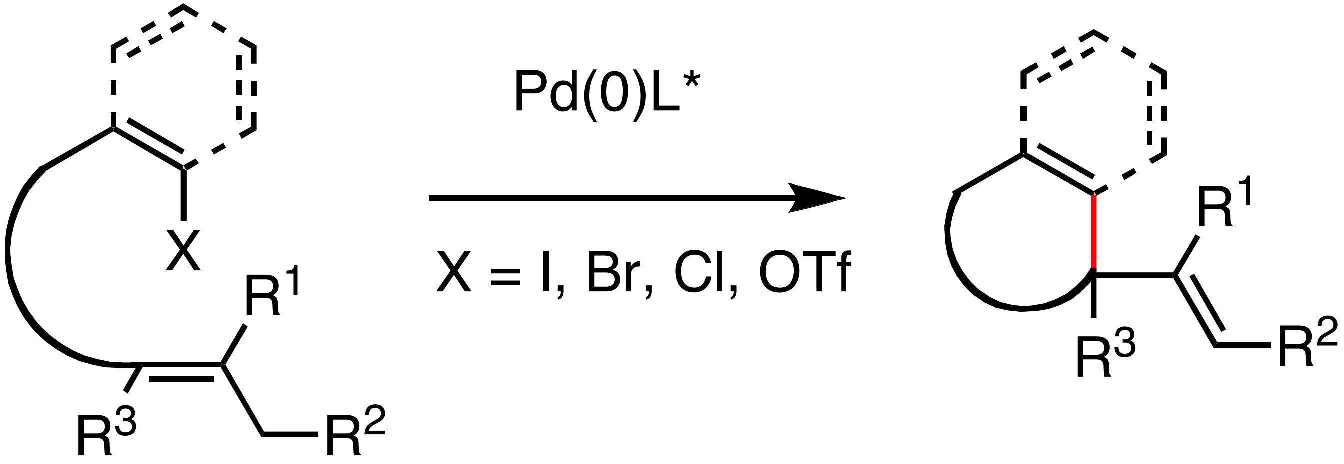
R = Aryl
61-90%; 96-99% *ee*



S-TBPTTL

Gu, P.; Su, Y.; Wu, X.-P.; Sun, J.; Liu, W.; Xue, P.; Li, R. *Org. Lett.* **2012**, *14*, 2246.
Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211.
Goto, T.; Takeda, K.; Shimada, N.; Nambu, H.; Anada, M.; Shiro, M.; Ando, K.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 6803.

The Heck Reaction

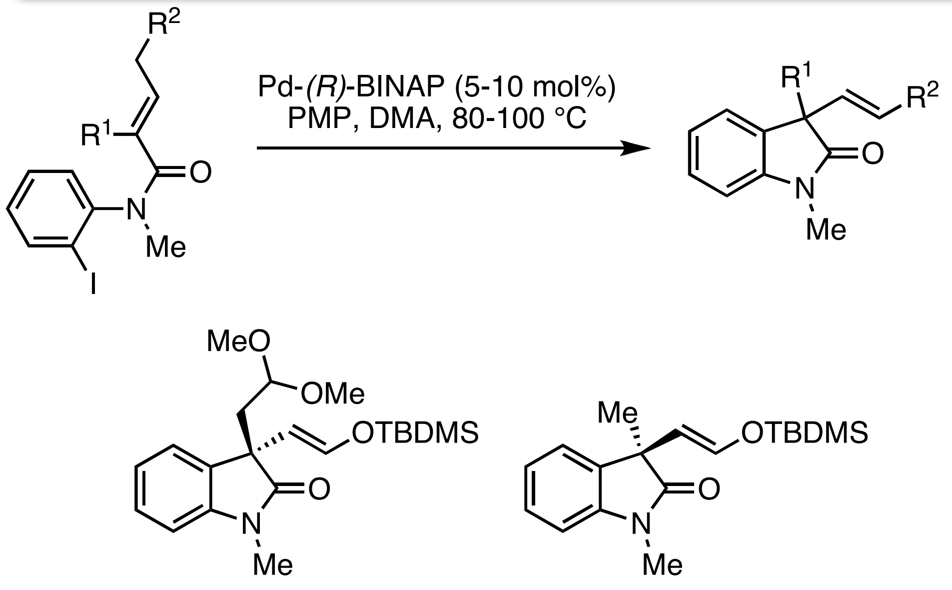


Pd(0)L*

X = I, Br, Cl, OTf

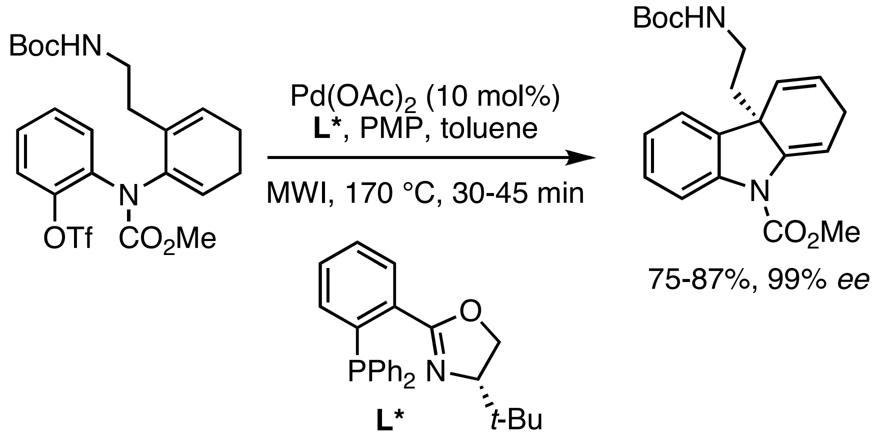
Douglas, C. J.; Overman, L. E. *Proc Natl Acad Sci USA* **2004**, *101*, 5363.

The Heck Reaction

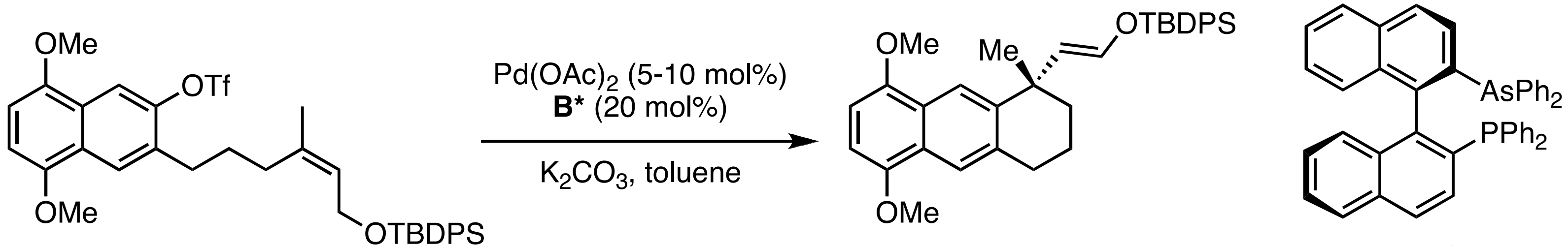


93%, 91% *ee*

80%, 92% *ee*



75-87%, 99% *ee*

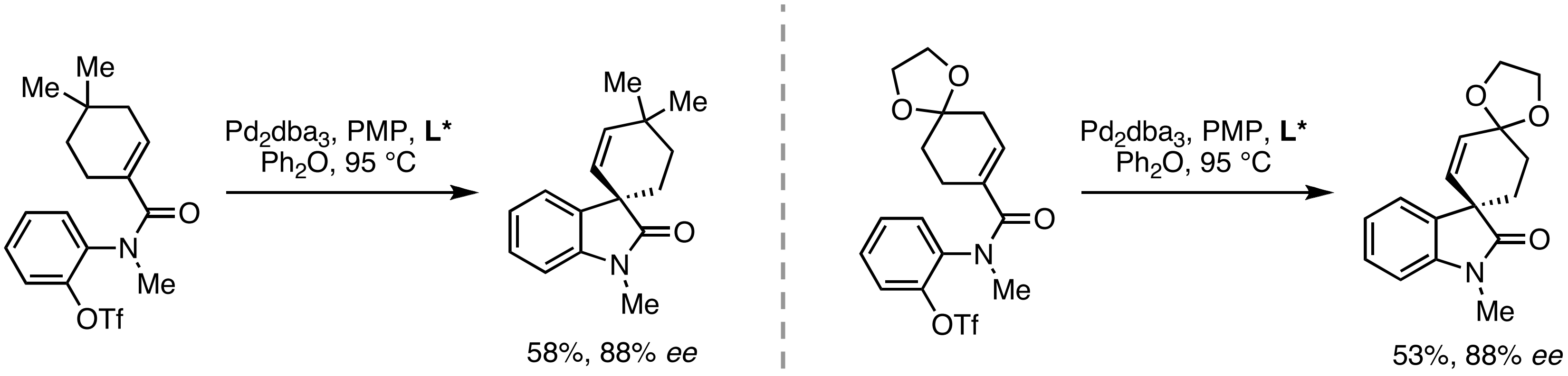


91%, 88% *ee*

B*
(R)-BINAPAs

Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477.
Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368.
Cho, S. Y.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 1773.

The Heck Reaction

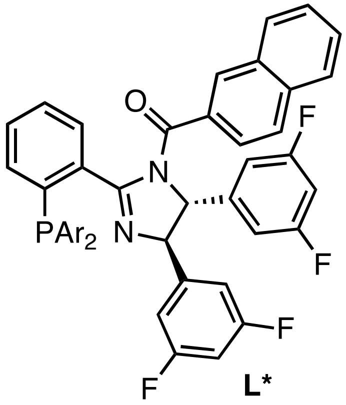


Pd_2dba_3, PMP, **L***
Ph_2O, 95 °C

58%, 88% *ee*

Pd_2dba_3, PMP, **L***
Ph_2O, 95 °C

53%, 88% *ee*

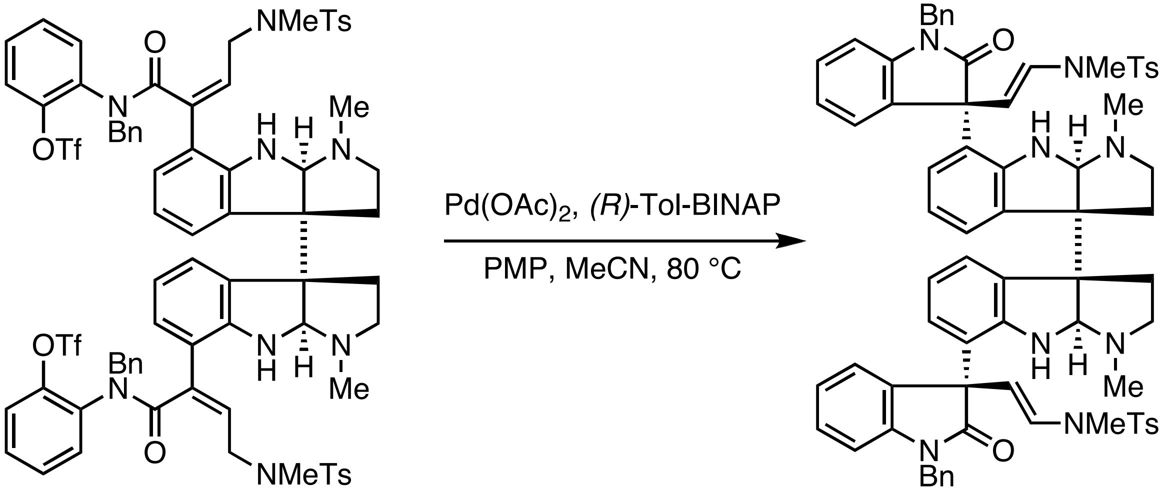


L*

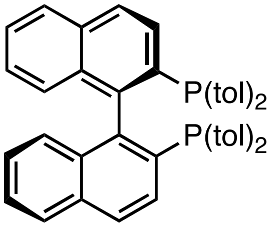
Ar = 3,5-F_2Ph

Busacca, C. A.; Grossbach, D.; Campbell, S. J.; Dong, Y.; Eriksson, M. C.; Harris, R. E.; Jones, P.-J.; Kim, J.-Y.; Lorenz, J. C.; McKellop, K. B.; O'Brien, E. M.; Qiu, F.; Simpson, R. D.; Smith, L.; So, R. C.; Spinelli, E. M.; Vitous, J.; Zavattaro, C. *J. Org. Chem.* **2004**, *69*, 5187.

The Heck Reaction



62%, 90% *ee*



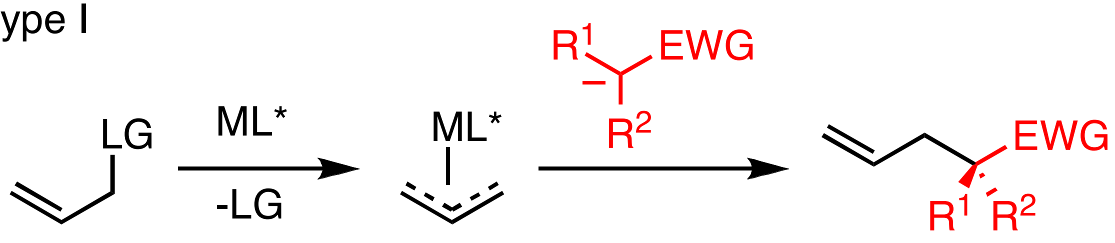
(*R*)-Tol-BINAP

- Limited to ***intramolecular*** reaction for the preparation of all-carbon quaternary centers
- Reaction limited by relatively high catalyst loading
- Substrates limited by olefin isomerization side products and pre-organized configuration

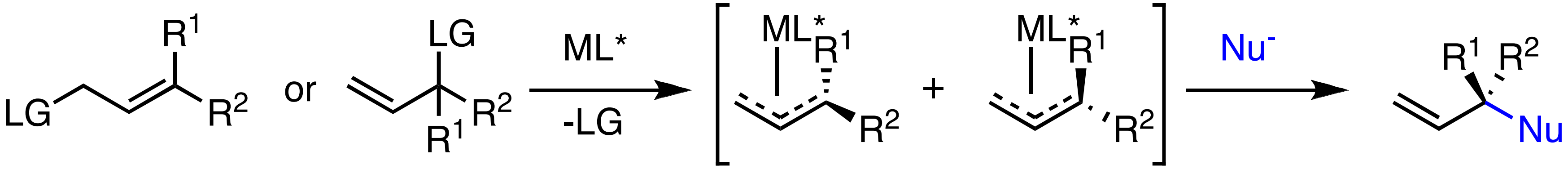
Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008.

Chiral allyl-metal electrophiles

Type I

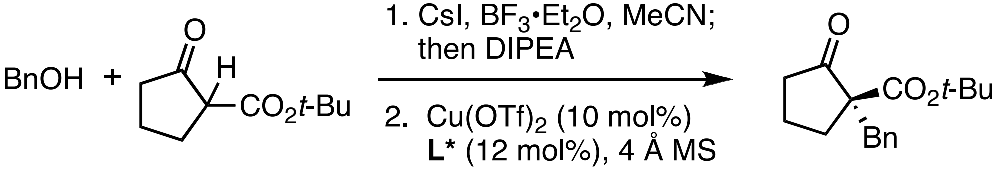


Type II



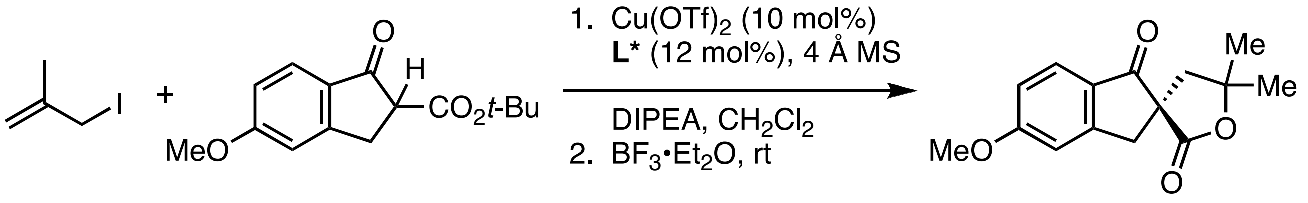
Douglas, C. J.; Overman, L. E. *Proc Natl Acad Sci USA* **2004**, *101*, 5363.

Chiral allyl-metal electrophiles

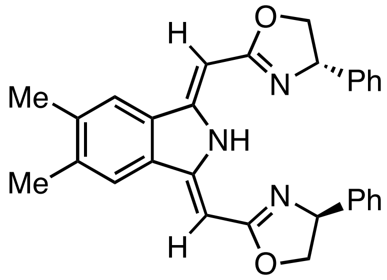

BnOH +

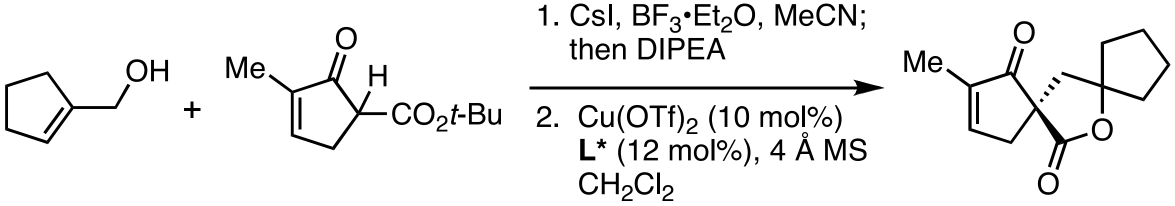
1. CsI, BF_3•Et_2O, MeCN; then DIPEA
2. $Cu(OTf)_2$ (10 mol%) **L*** (12 mol%), 4 Å MS CH_2Cl_2

91%, 97% *ee*

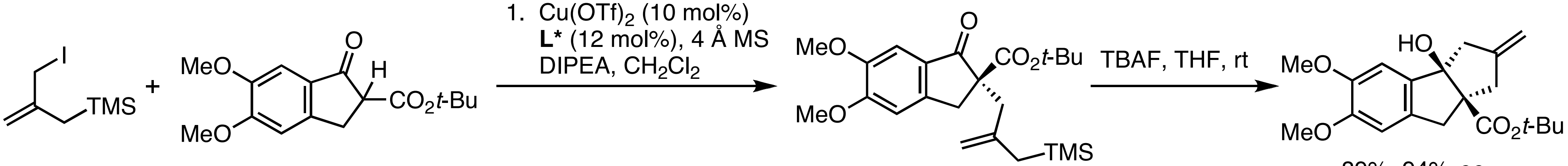

1. $Cu(OTf)_2$ (10 mol%) **L*** (12 mol%), 4 Å MS DIPEA, CH_2Cl_2
2. BF_3•Et_2O, rt

88%, 95% *ee*


L*


1. CsI, BF_3•Et_2O, MeCN; then DIPEA
2. $Cu(OTf)_2$ (10 mol%) **L*** (12 mol%), 4 Å MS CH_2Cl_2
3. BF_3•Et_2O, rt

85%, 96% *ee*


1. $Cu(OTf)_2$ (10 mol%) **L*** (12 mol%), 4 Å MS DIPEA, CH_2Cl_2

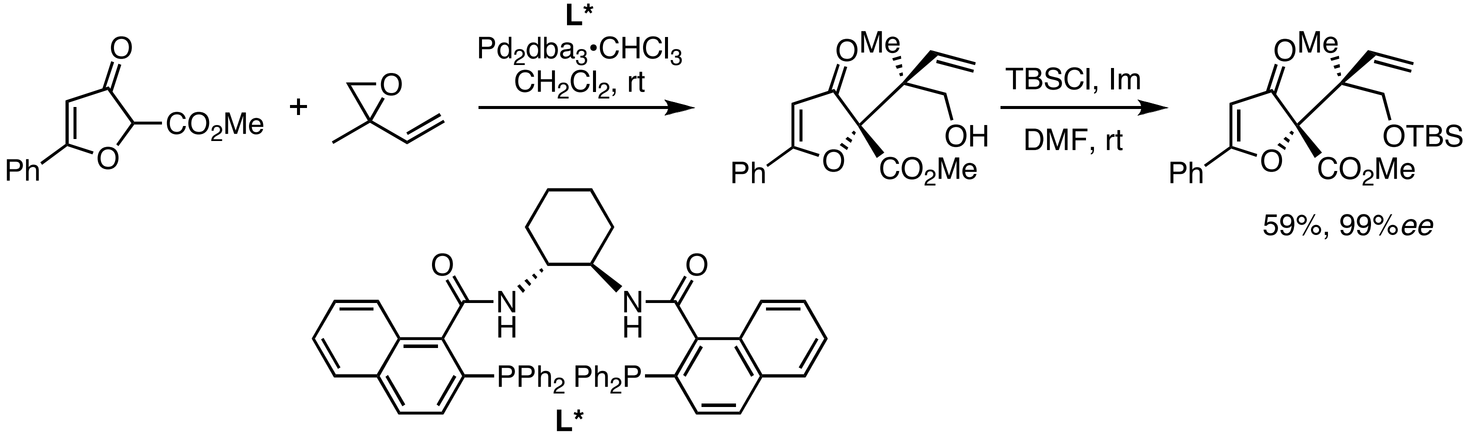
78%, 95% *ee*

TBAF, THF, rt

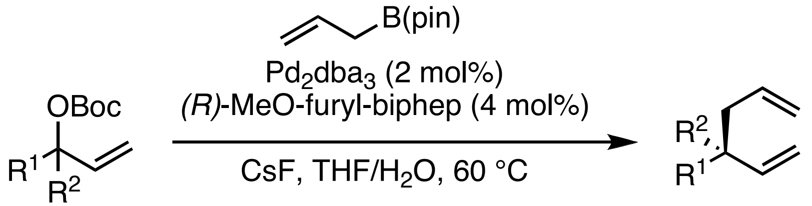
89%, 94% *ee*

Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 2946.

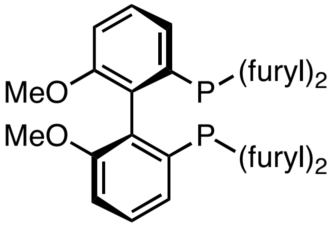
Chiral allyl-metal electrophiles



59%, 99%*ee*



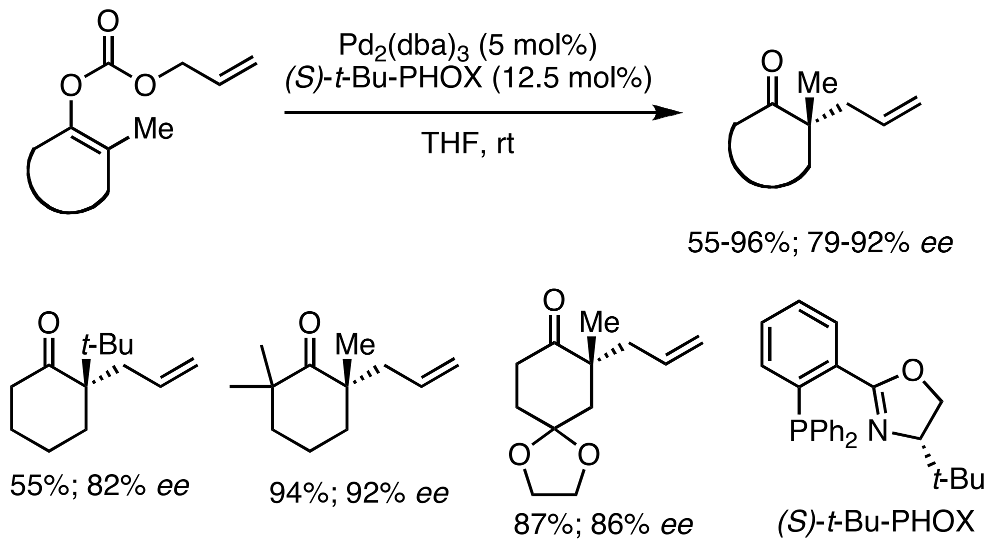
R^1 = Ph, *c*-hex, alkyl
R^2 = Me, Et, CH_2OMOM, butyl
58-97%, 76:24 to 96:4 *er*



(R)-MeO-furyl-biphep

Du, C.; Li, L.; Li, Y.; Xie, Z. *Angew. Chem. Int. Ed.* **2009**, *48*, 7853.
Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716.

Chiral allyl-metal electrophiles



$Pd_2(dba)_3$ (5 mol%)
(S)-*t*-Bu-PHOX (12.5 mol%)
THF, rt

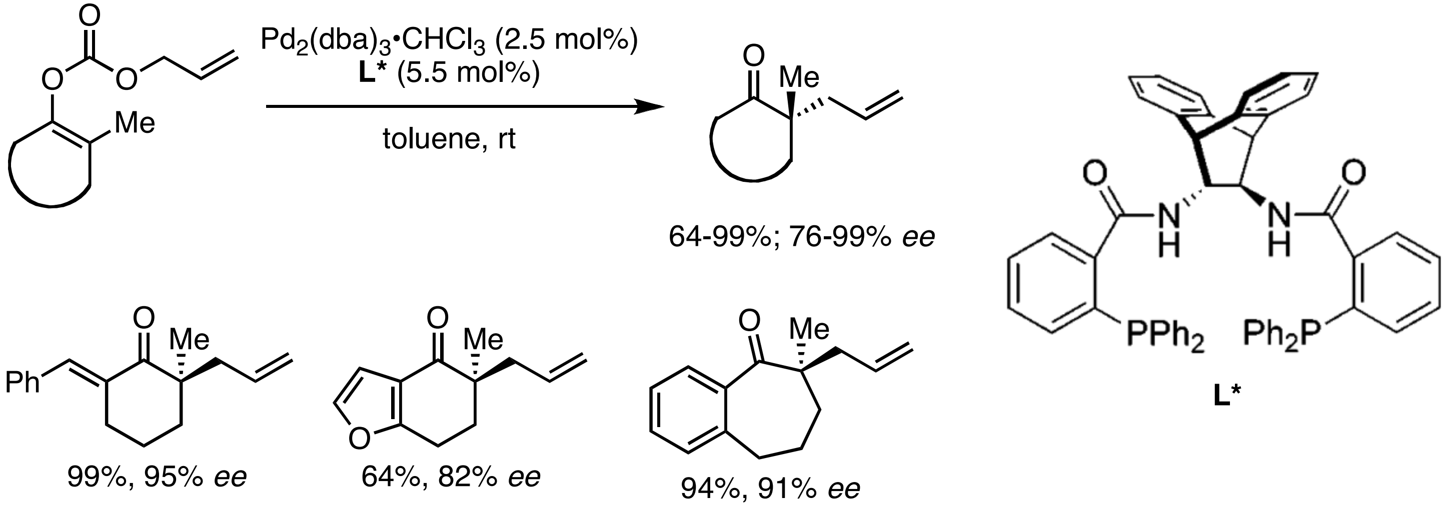
55-96%; 79-92% *ee*

55%; 82% *ee*

94%; 92% *ee*

87%; 86% *ee*

(S)-*t*-Bu-PHOX



$Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%)
L* (5.5 mol%)
toluene, rt

64-99%; 76-99% *ee*

99%, 95% *ee*

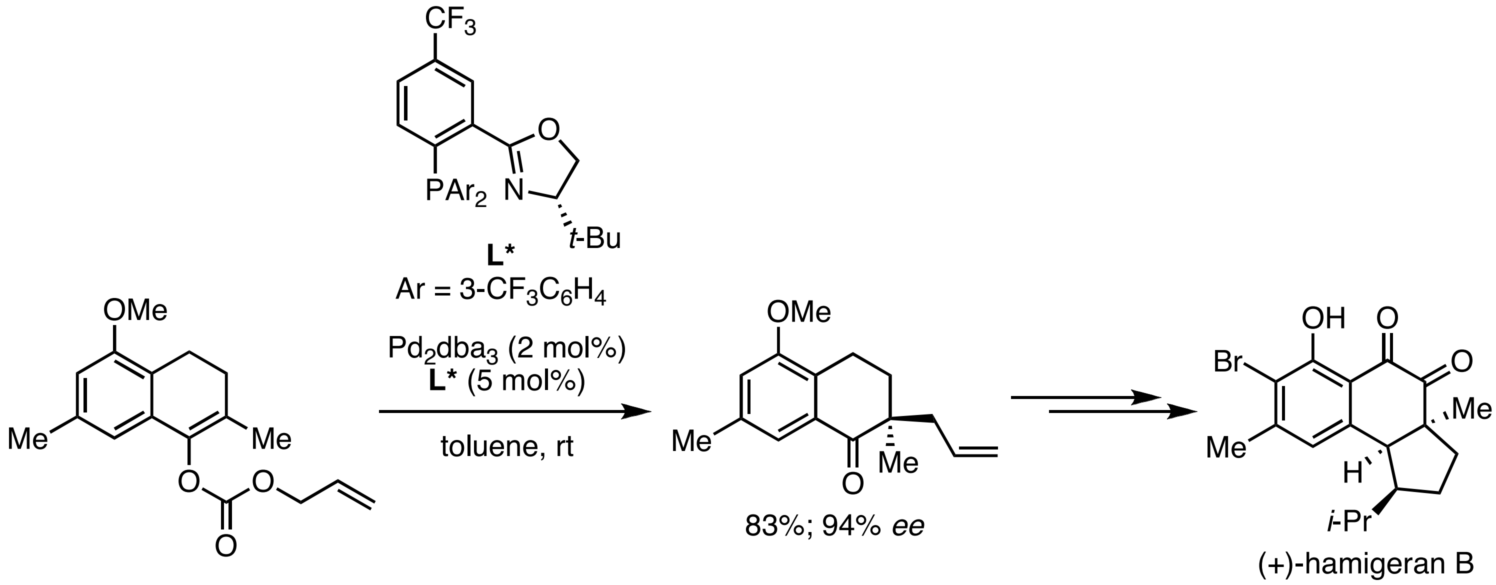
64%, 82% *ee*

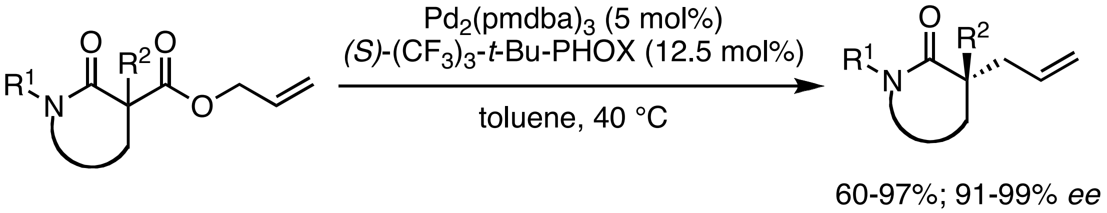
94%, 91% *ee*

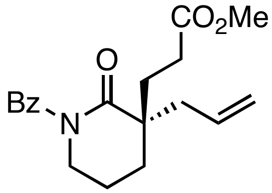
L*

Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044.
Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846.

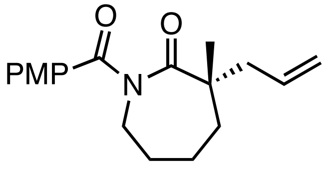
Chiral allyl-metal electrophiles



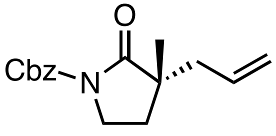




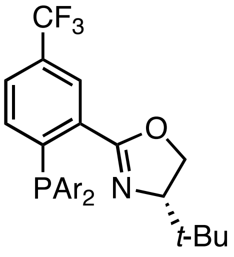
92%; 99% *ee*



83%; 93% *ee*



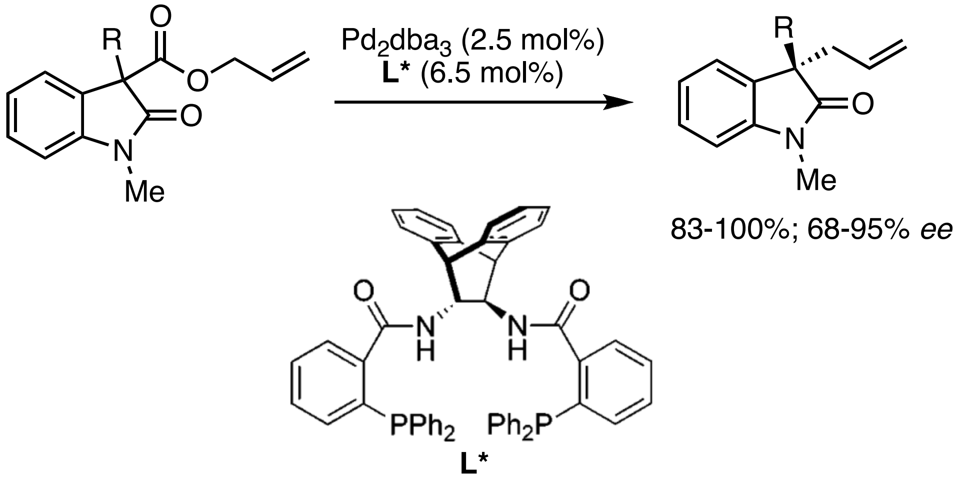
86%; 91% *ee*



(S)-$(CF_3)_3$-*t*-Bu-PHOX
Ar = 3-$CF_3C_6H_4$

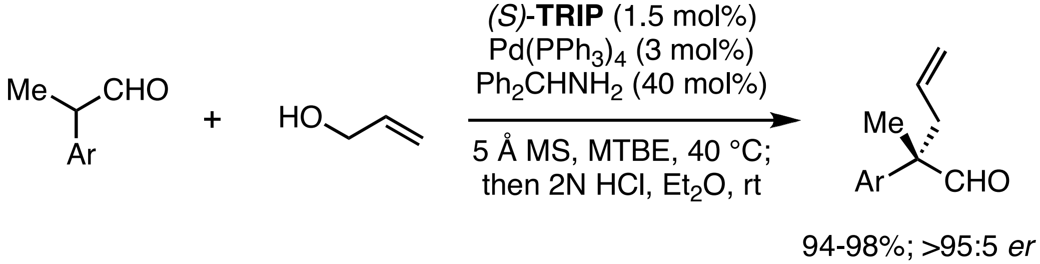
Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 2946.
Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2011**, *4*, 130.

Chiral allyl-metal electrophiles



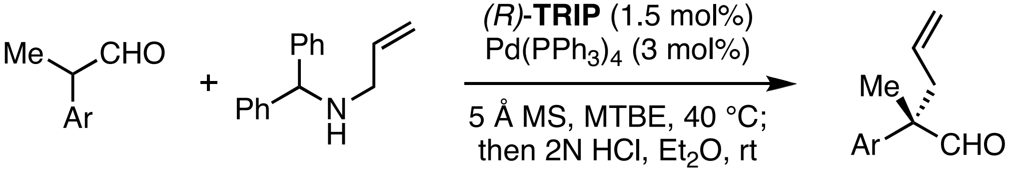
Pd_2dba_3 (2.5 mol%)
L* (6.5 mol%)

83-100%; 68-95% *ee*



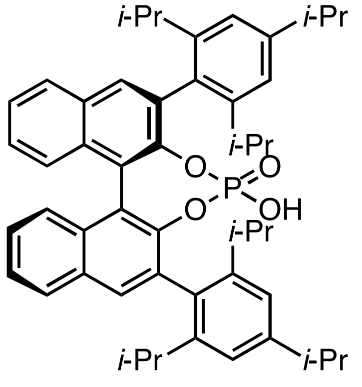
(S)-**TRIP** (1.5 mol%)
$Pd(PPh_3)_4$ (3 mol%)
Ph_2CHNH_2 (40 mol%)
5 Å MS, MTBE, 40 °C;
then 2N HCl, Et_2O, rt

94-98%; >95:5 *er*

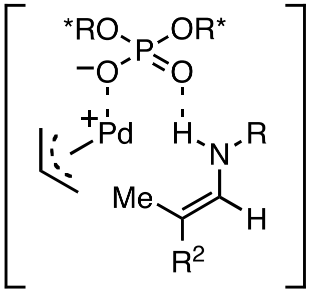


(R)-**TRIP** (1.5 mol%)
$Pd(PPh_3)_4$ (3 mol%)
5 Å MS, MTBE, 40 °C;
then 2N HCl, Et_2O, rt

71-89%; >93:7 *er*

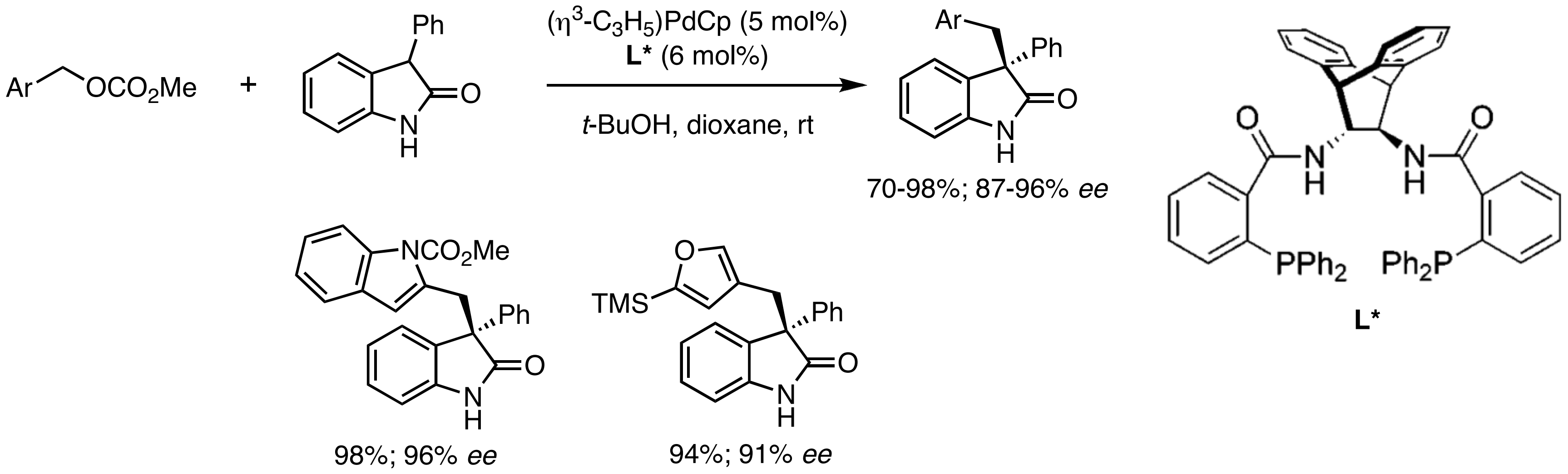


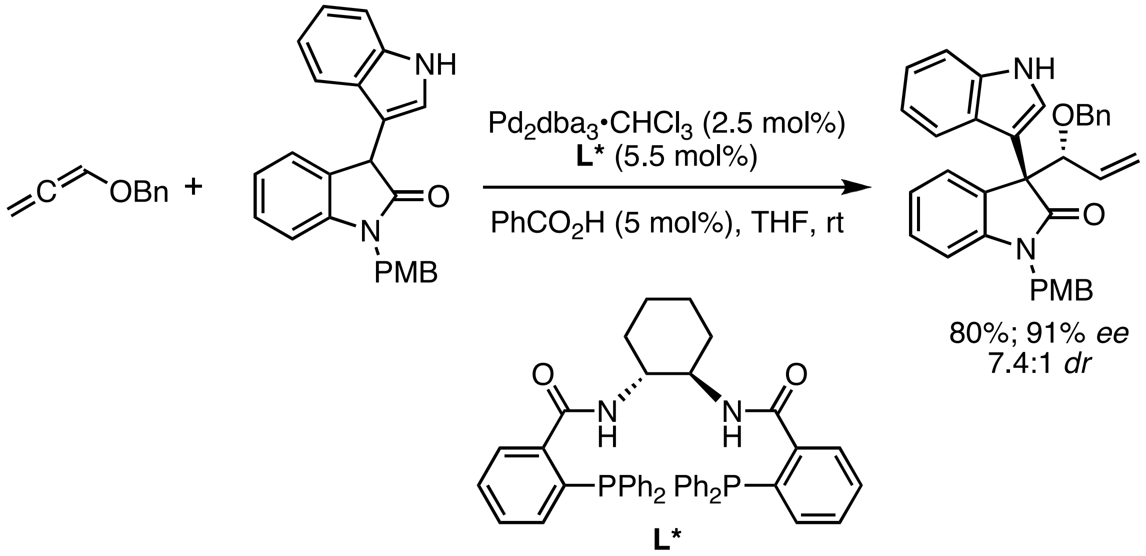
(R)-**TRIP**



Franckevičius, V.; Cuthbertson, J. D.; Pickworth, M.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2011**, *13*, 4264.
Jiang, G.; List, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 9471.
Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336.

Chiral allyl-metal electrophiles

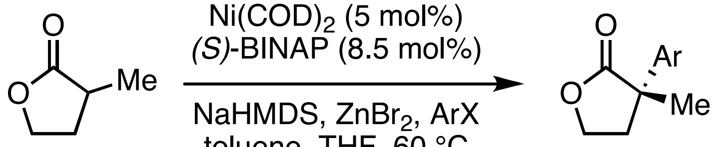




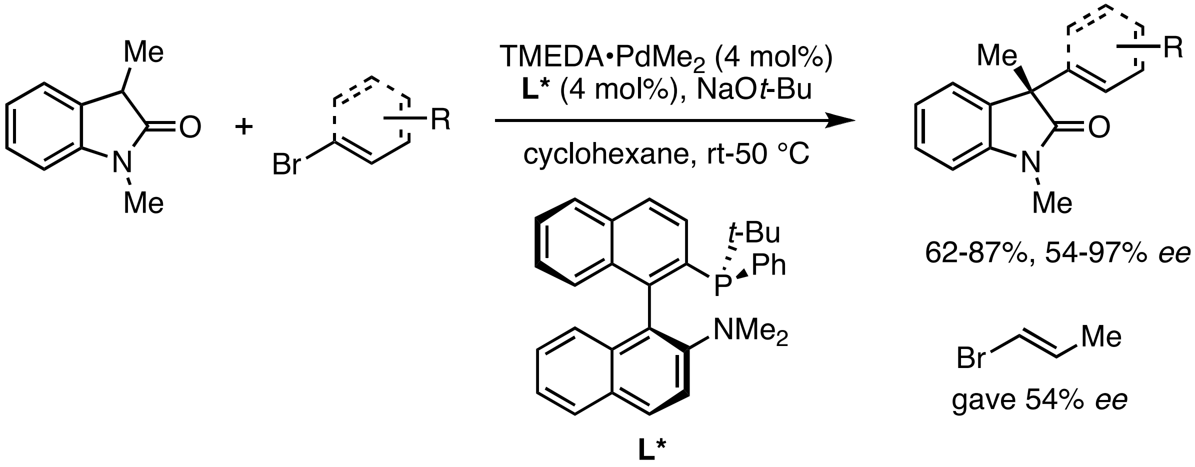
- chiral π-allyl complex gives high enantioselectivity
- nucleophiles are limited to stabilized anions (ie dicarbonyls & α-Ar carbonyls)

Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2010**, *132*, 15534.
Trost, B. M.; Xie, J.; Sieber, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 20611.

Alpha Carbonyl alkylation

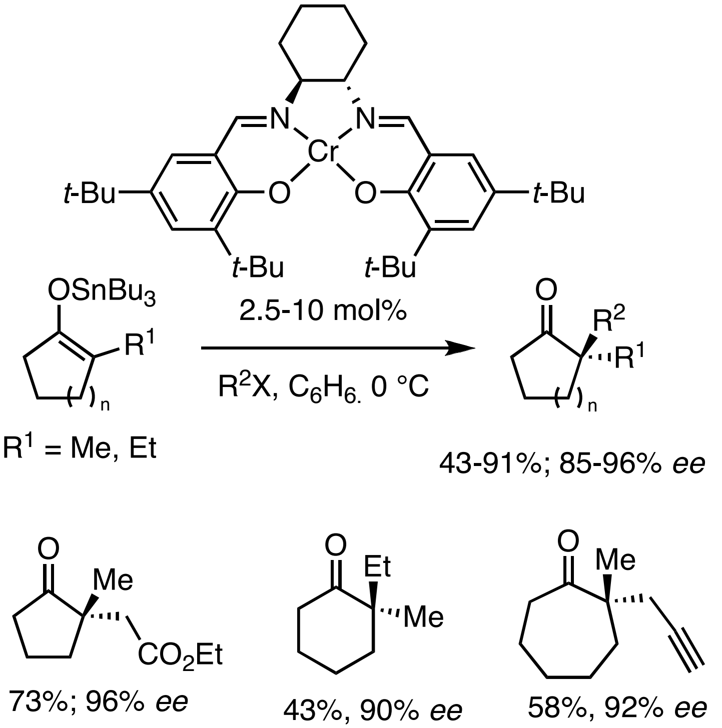


57-95%; 90-99% *ee*



62-87%, 54-97% *ee*

gave 54% *ee*

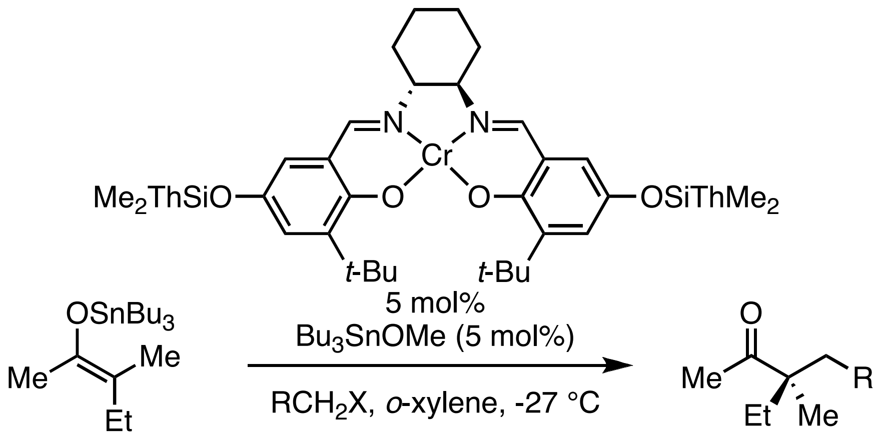


43-91%; 85-96% *ee*

73%; 96% *ee*

43%, 90% *ee*

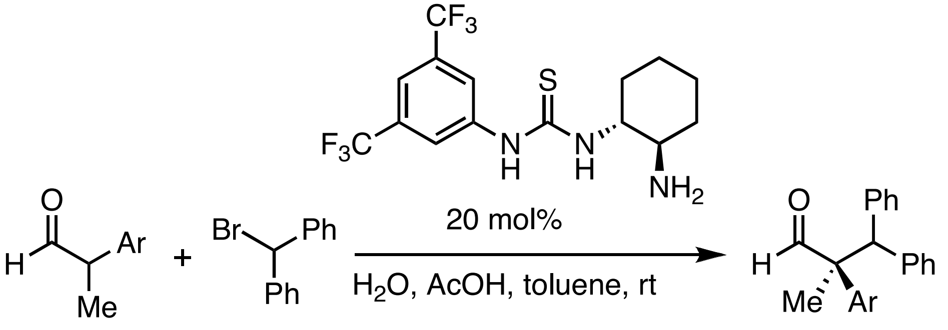
58%, 92% *ee*



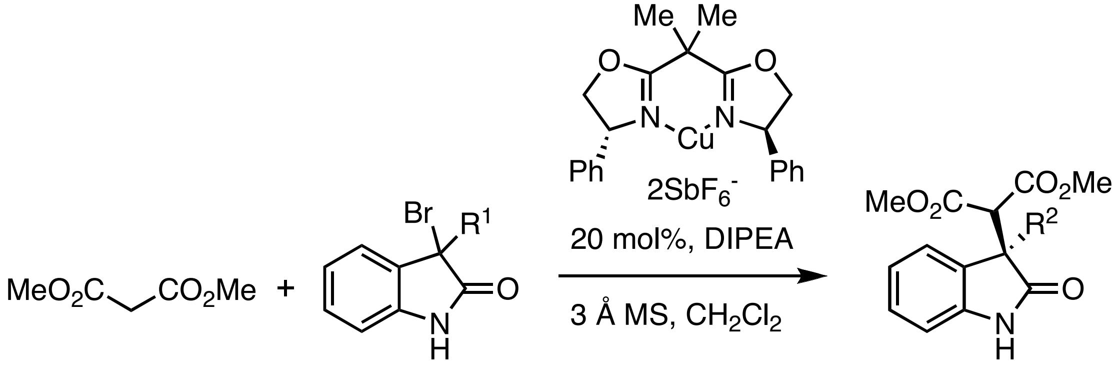
73-97%; 76-87% *ee*
R = Ph, CO$_2$Et

Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500.
Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900.
Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62.
Doyle, A. G.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2007**, *46*, 3701.

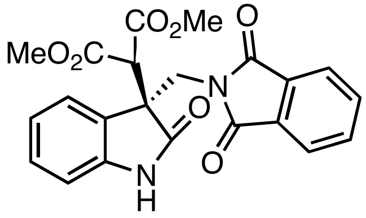
Alpha Carbonyl alkylation



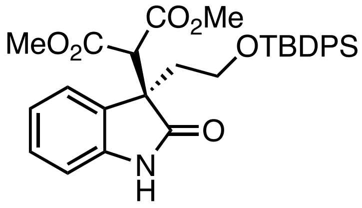
52-70%; 85-94% *ee*



42-78%; 83-94% *ee*



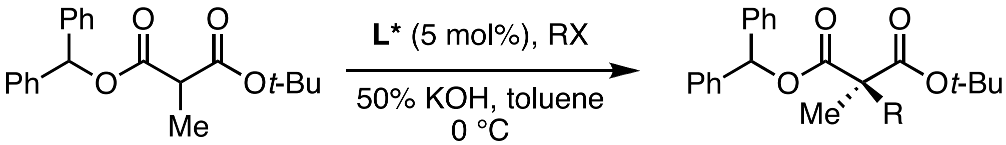
42%, 81% *ee*



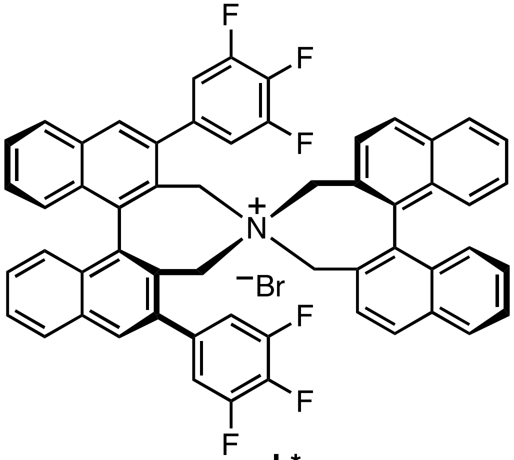
78%, 88% *ee*

Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286.
Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8037.

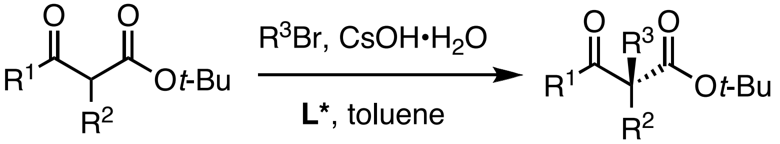
Alpha Carbonyl alkylation

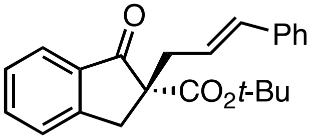


R = Alkyl, Allyl, Bn
80-95%; 92-97% *ee*

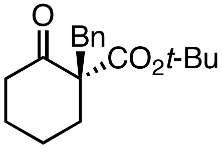


L*

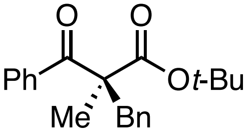




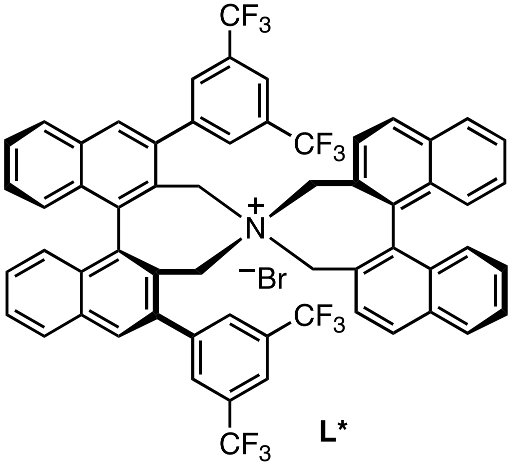
93%; 96% *ee*



88%; 92% *ee*



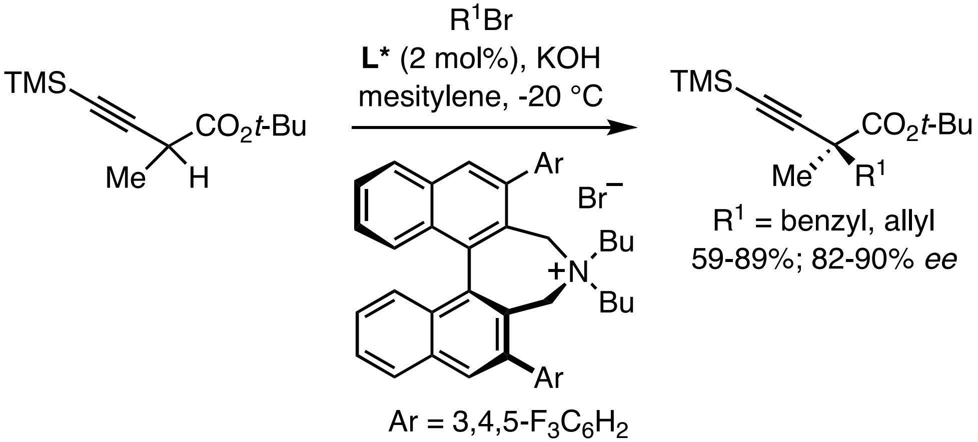
96%, 85% *ee*



L*

Hong, S.; Lee, J.; Kim, M.; Park, Y.; Park, C.; Kim, M.-H.; Jew, S.-S.; Park, H.-G. *J. Am. Chem. Soc.* **2011**, *133*, 4924.
Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 3796.

Alpha Carbonyl alkylation

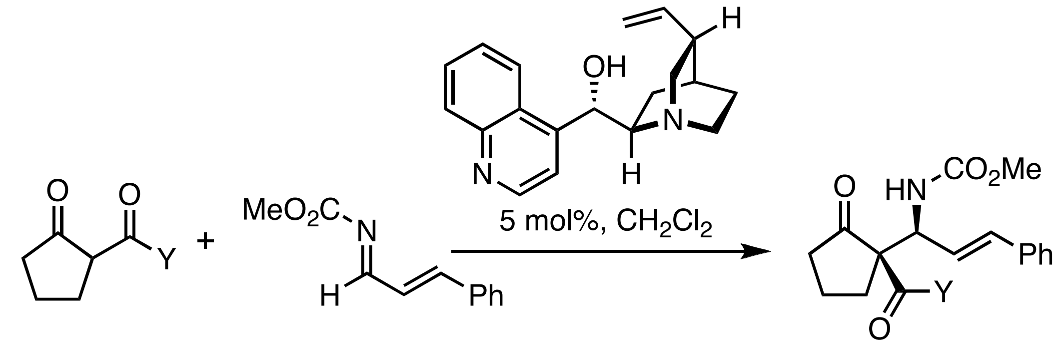


R^1 = benzyl, allyl
59-89%; 82-90% *ee*

- demonstrated scope of electrophiles is typically limited
- cyclic alpha-carbonyl compounds provide higher ee

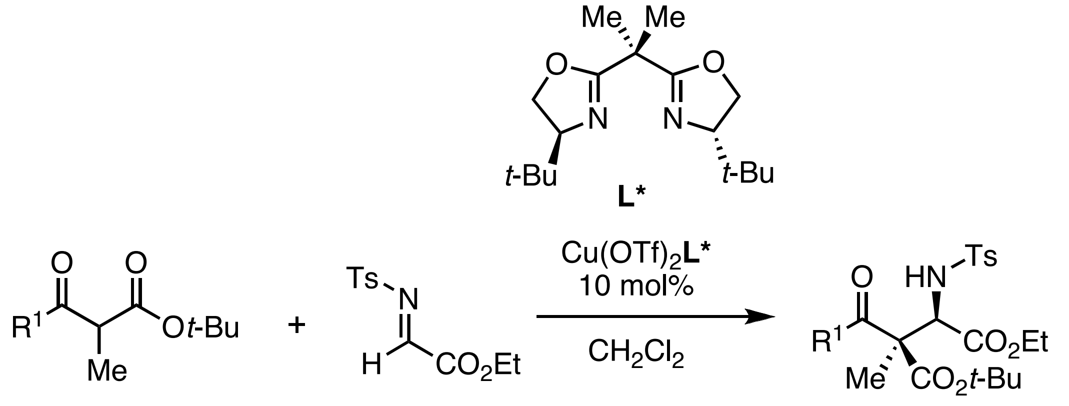
Hashimoto, T.; Sakata, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 5014.

Aldol & Mannich Reactions



Y = OMe, OEt, Me

98%; 98-99% *ee*
90-95 *de*

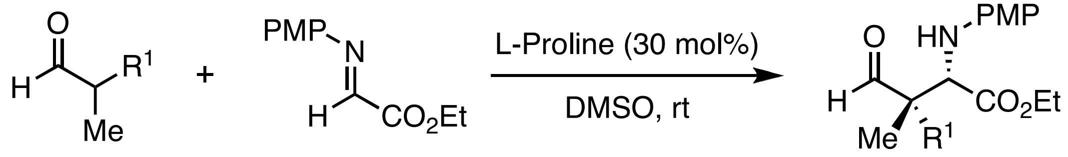


R^1 = Me, Et, *i*-Pr

15-80%; 88-95% *ee*
>84:16 *dr*

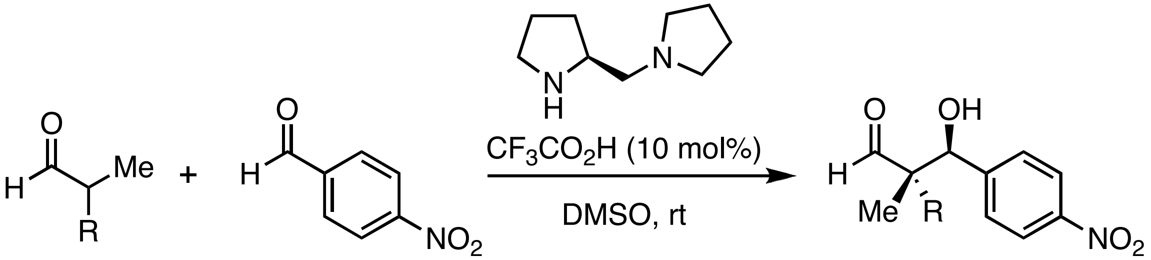
Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003.
Marigo, M.; Kjaersgaard, A.; Juhl, K.; Gathergood, N.; Jorgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359.

Aldol & Mannich Reactions



R^1 = Ar, Bn

66-91%; 86-99% *ee*
dr ~6:4 to 95:5

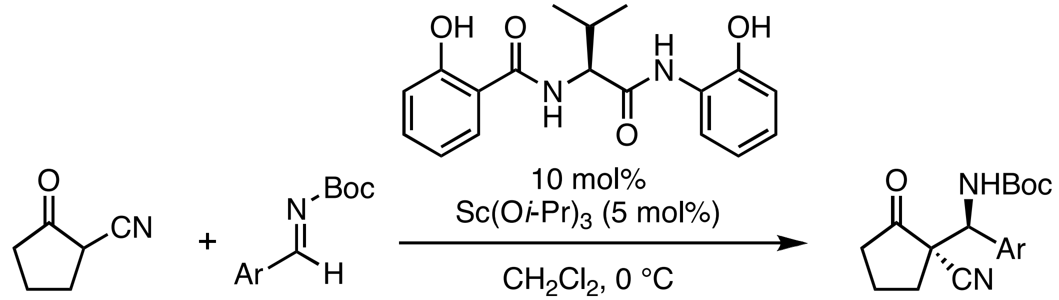


R = Et, Pr, nonyl, Bn
$(CH_2)_2C{=}C(CH_3)_2$

91-97%; 89-96% *ee*
~6:4 to 8.5:1.5 *dr*

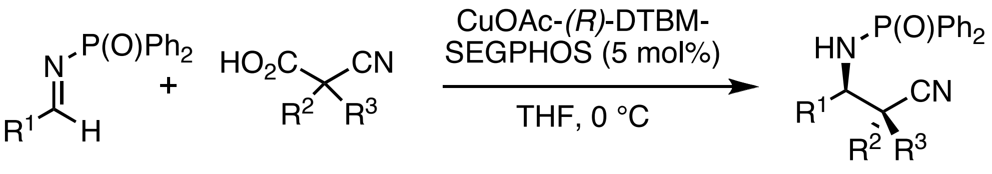
Chowdari, N. S.; Suri, J. T.;Barbas, C. F. *Org. Lett.* **2004**, *6*, 2507
Mase, N.; Tanaka, F.; Barbas, C. F. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 2420.

Aldol & Mannich Reactions



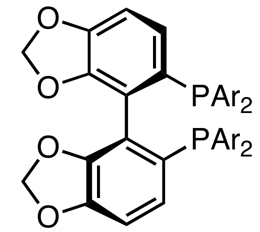
10 mol%
$Sc(Oi\text{-}Pr)_3$ (5 mol%)
CH_2Cl_2, 0 °C

80-99%; 77-96% *ee*
~6:4 to 95:5 *dr*

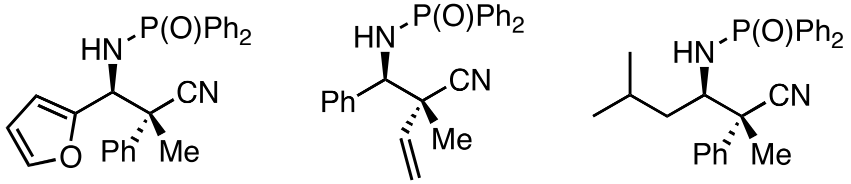


CuOAc-*(R)*-DTBM-SEGPHOS (5 mol%)
THF, 0 °C

51-96%; 70-97%*ee*



(R)-DTBM-SEGPHOS
Ar = 3,5-(*t*-Bu)-4-MeO-C_6H_2



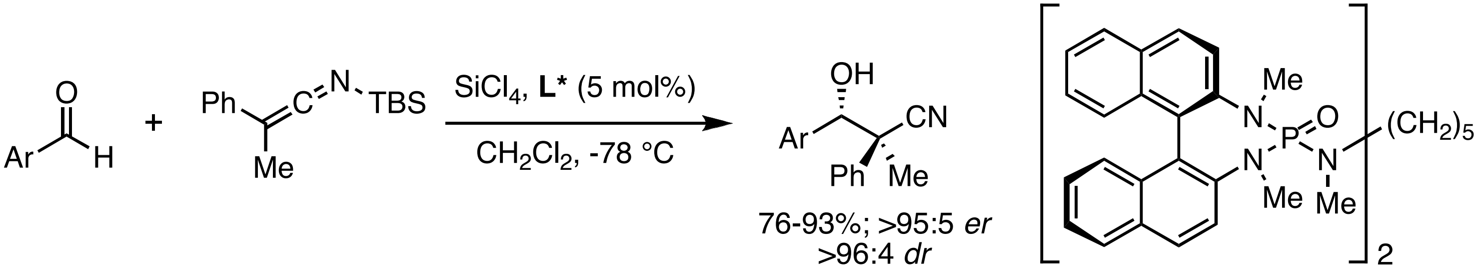
94%; 85% *ee*
8.9:1 *dr*

70%; 70% *ee*
4.5:1 *dr*

75%; 84% *ee*
2.4:1 *dr*

Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 5630.
Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610.

Aldol & Mannich Reactions



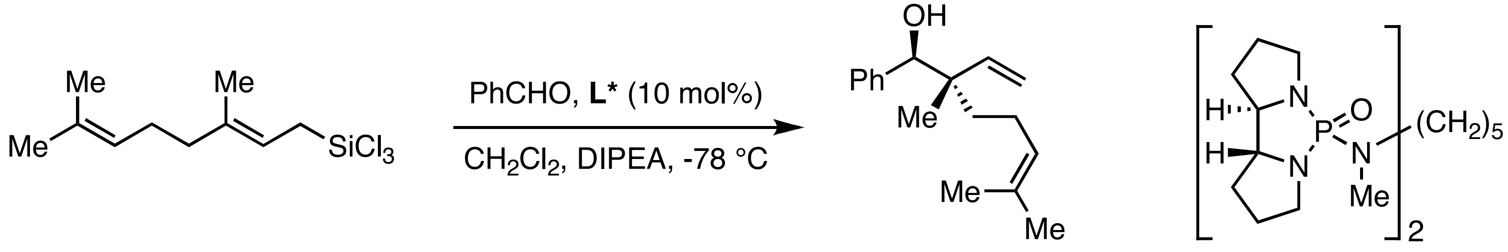
L*

- Acyclic enolates tend to provide less diastereoselectivity
- Similar substituent size on nucleophile leads to diminished enantioselectivity (mixture of enol/enolate/anion geometry)

Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, J. R. *J. Am. Chem. Soc.* **2007**, *129*, 14864.

Allyl addition to Aldhydes

Allyl addition to aldehydes

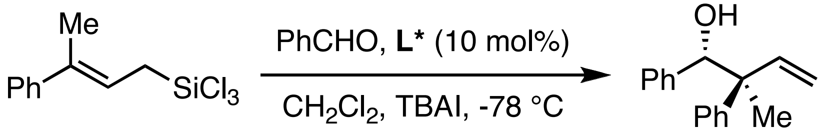


PhCHO, **L*** (10 mol%)

CH_2Cl_2, DIPEA, -78 °C

83%, 94% *ee*

L*



PhCHO, **L*** (10 mol%)

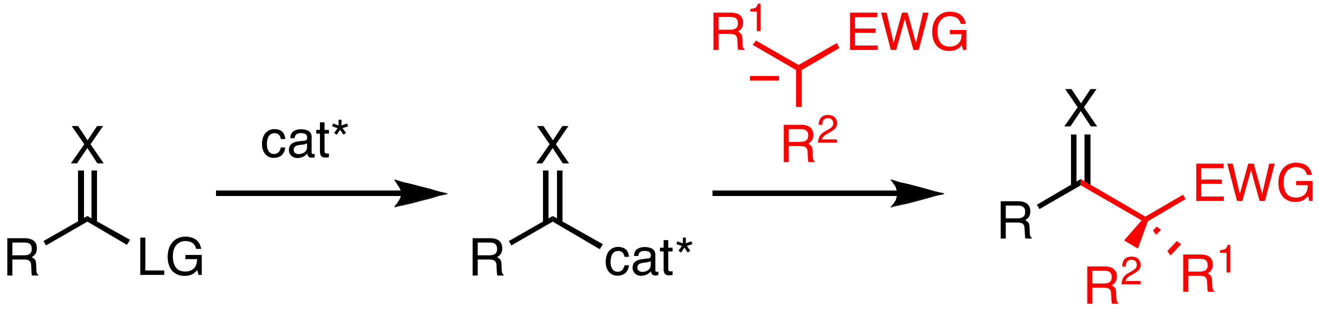
CH_2Cl_2, TBAI, -78 °C

64%; 97:3 *er*
99:1 *dr*

- Limited investigation into substrate scope for the formation of all carbon quaternary centers
- Addition to other electrophiles has not been reported

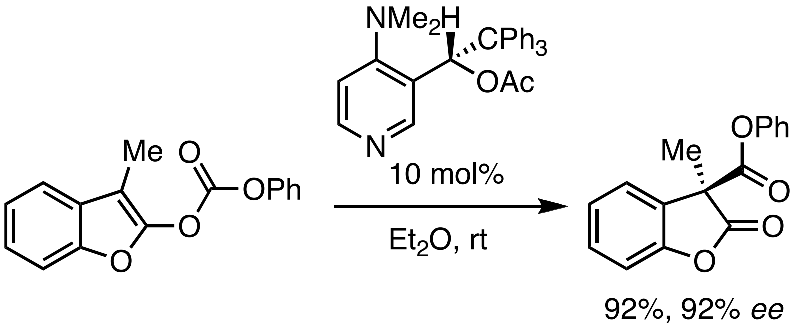
Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488.
Denmark, S. E.; Fu, J. *Org. Lett.* **2002**, *4*, 1951.
Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523.

Addition to Chiral Carbon Electrophiles

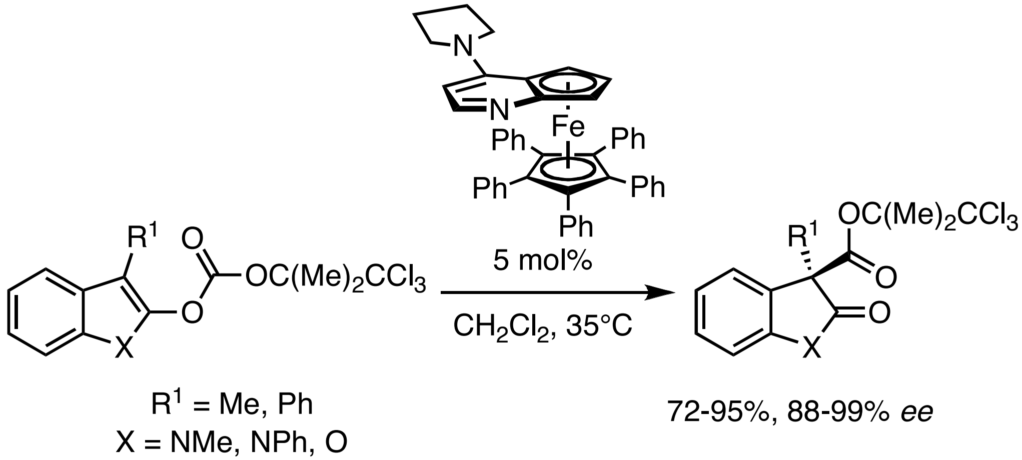


Douglas, C. J.; Overman, L. E. *Proc Natl Acad Sci USA* **2004**, *101*, 5363.

Addition to Chiral Carbon Electrophiles

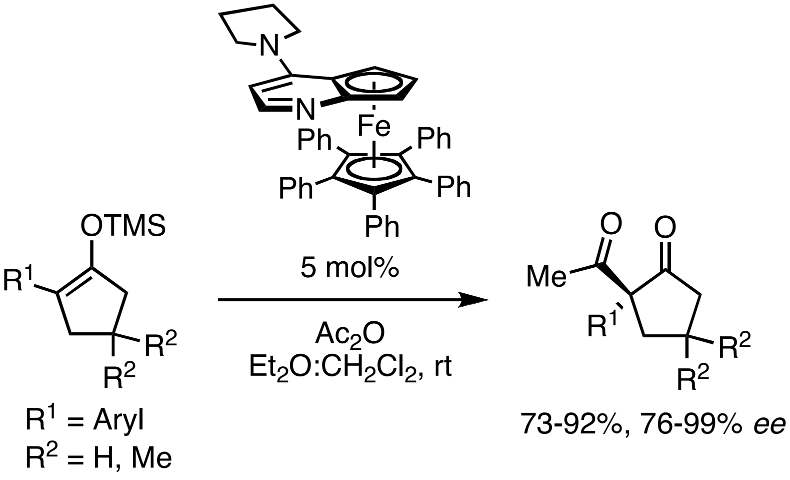


92%, 92% *ee*



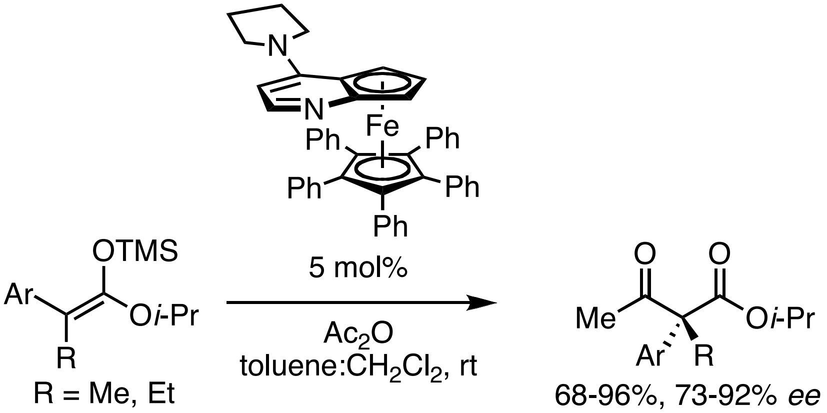
R^1 = Me, Ph
X = NMe, NPh, O

72-95%, 88-99% *ee*



R^1 = Aryl
R^2 = H, Me

73-92%, 76-99% *ee*

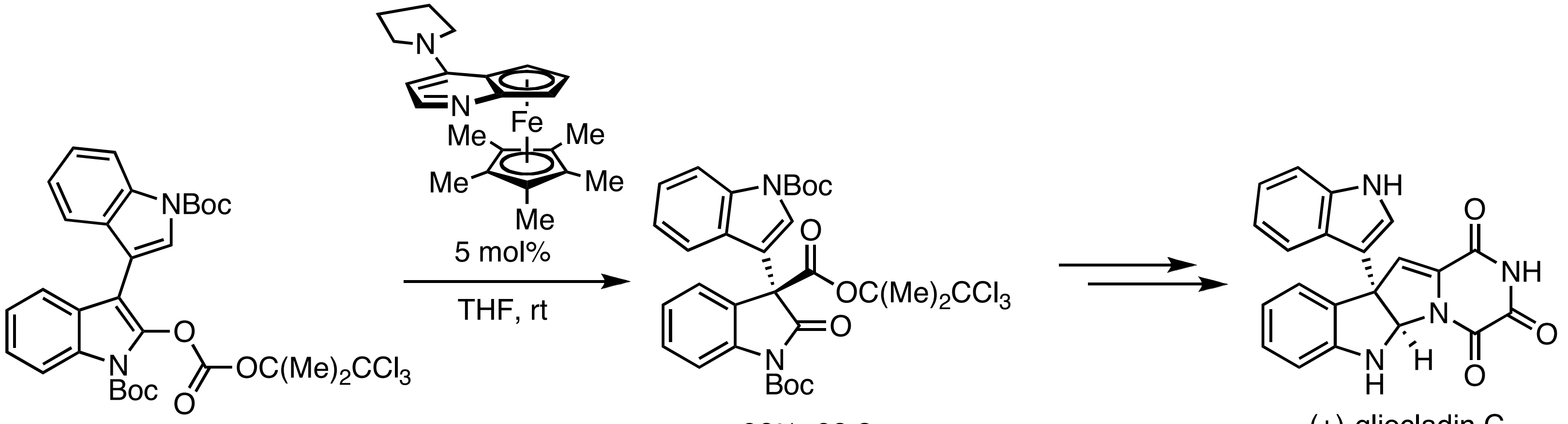


R = Me, Et

68-96%, 73-92% *ee*

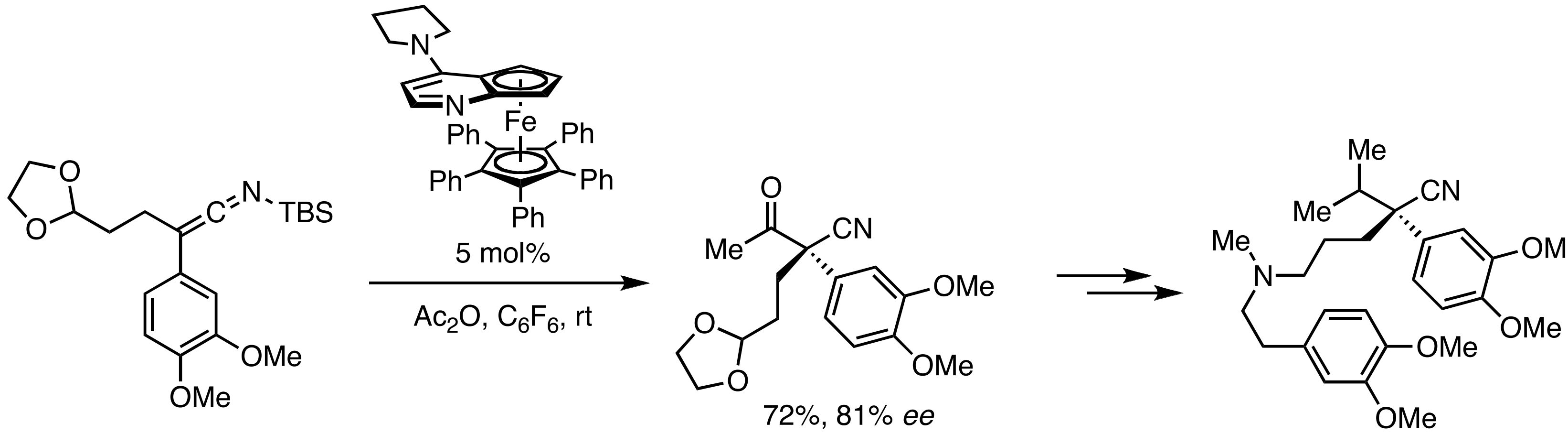
Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368.
Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 3921.
Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050.
Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604.

Addition to Chiral Carbon Electrophiles



96%, 98:2 *er*

(+)-gliocladin C

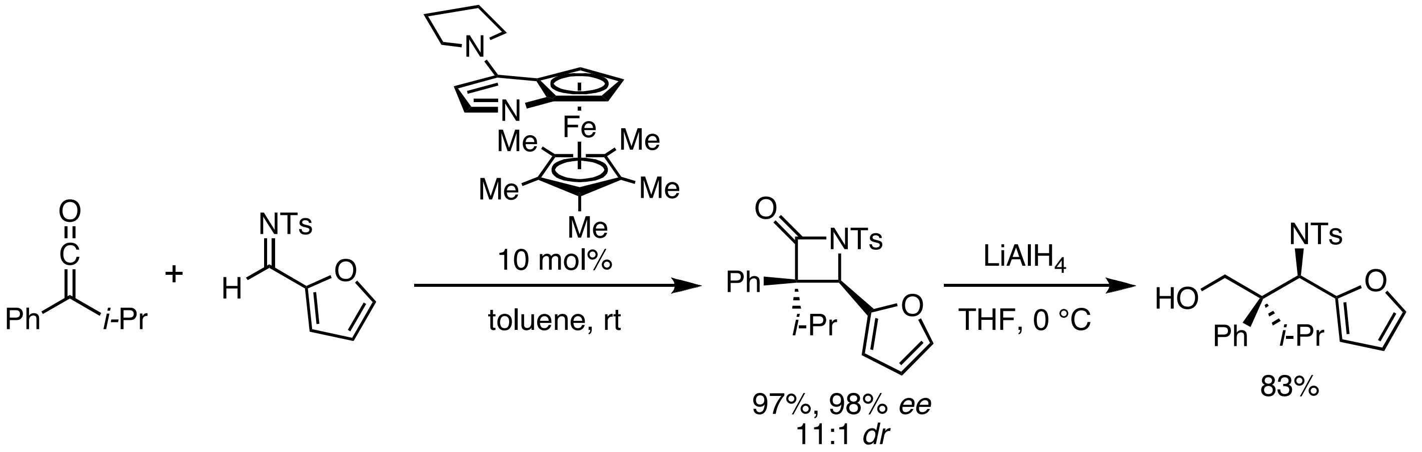


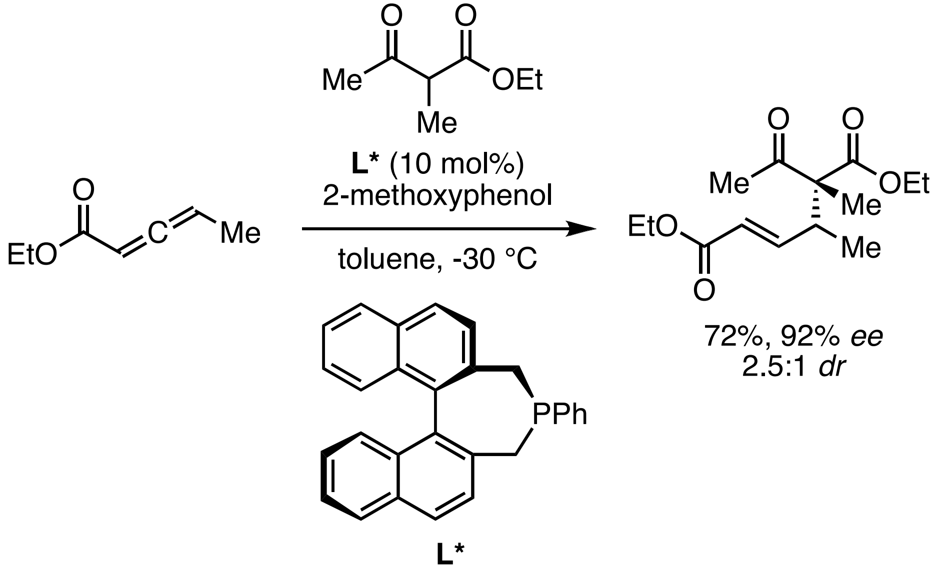
72%, 81% *ee*
(90% recovered cat.)

(S)-verapamil

DeLorbe, J. E.; Jabri, S. Y.; Mennen, S. M.; Overman, L. E.; Zhang, F.-L. *J. Am. Chem. Soc.* **2011**, *133*, 6549.
Mermerian, A. H.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 949.

Addition to Chiral Carbon Electrophiles

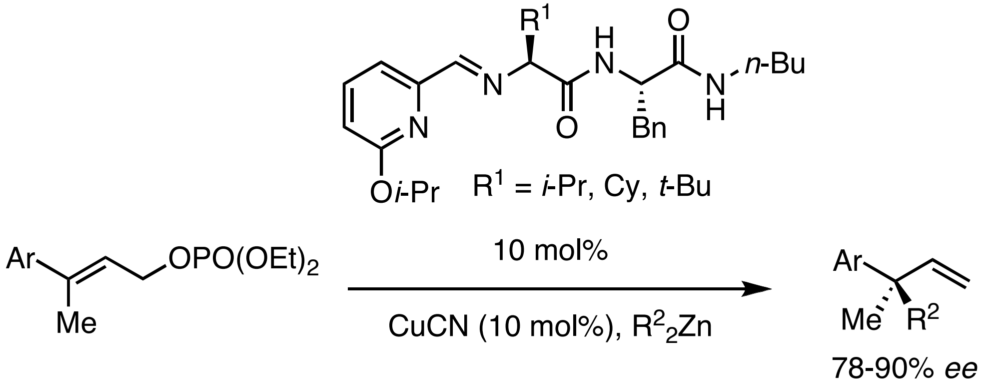




- Limited electrophile scope
- Somewhat high catalyst loading

Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578
Sinisi, R.; Sun, J; Fu, G. C. *Proc. Nat. Am. Soc.* **2010**, *107*, 20652.

S_N2' Addition Chemistry

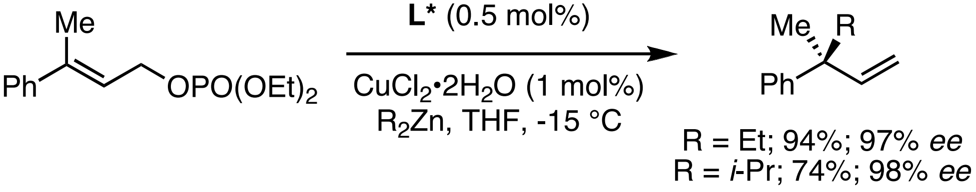


R^1 = *i*-Pr, Cy, *t*-Bu

10 mol%

CuCN (10 mol%), R^2_2Zn

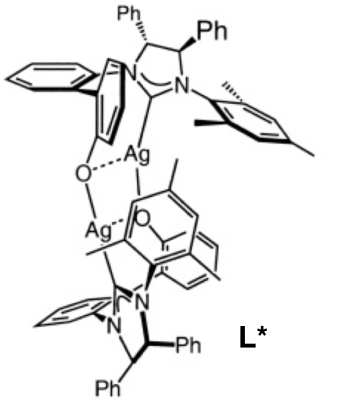
78-90% *ee*



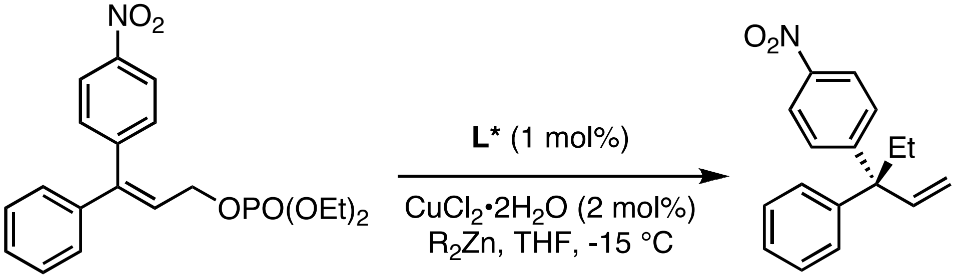
L* (0.5 mol%)

$CuCl_2•2H_2O$ (1 mol%)
R_2Zn, THF, -15 °C

R = Et; 94%; 97% *ee*
R = *i*-Pr; 74%; 98% *ee*



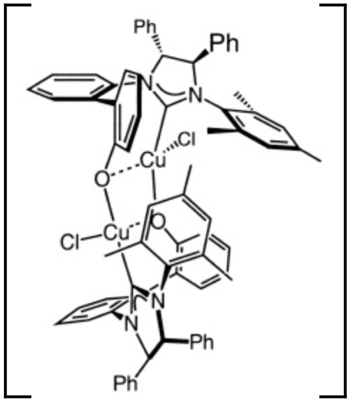
L*



L* (1 mol%)

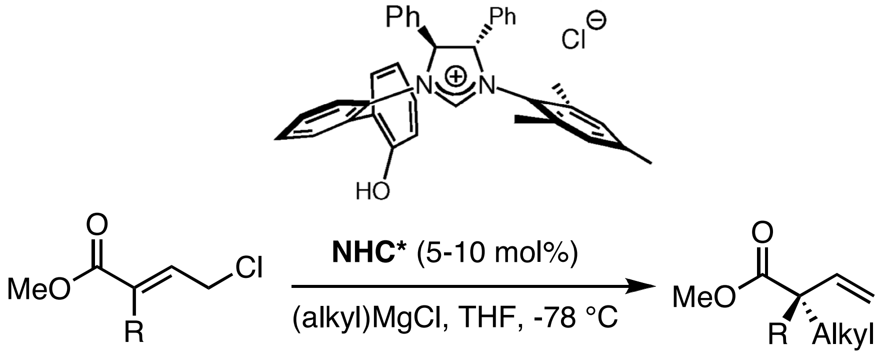
$CuCl_2•2H_2O$ (2 mol%)
R_2Zn, THF, -15 °C

79%; 85% *ee*



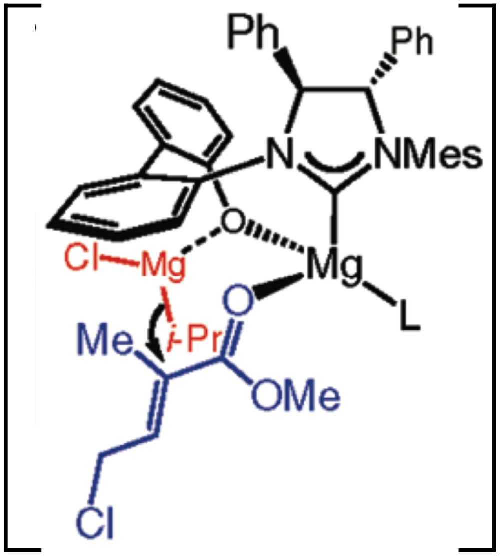
Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676.
van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877.

S_N2' Addition Chemistry



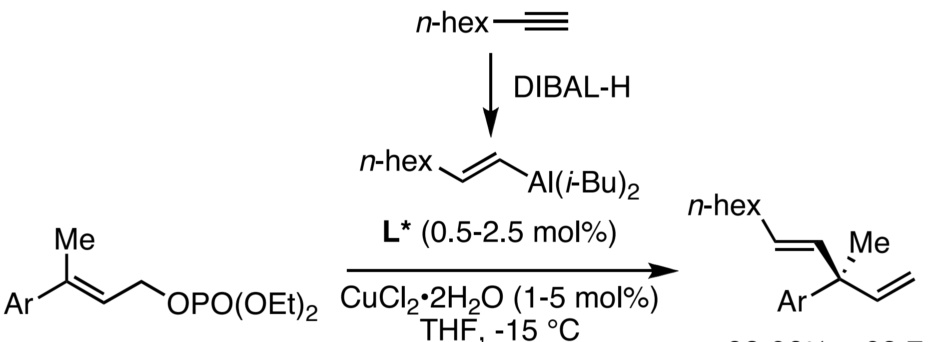
R = Me, Et, *n*-Bu
alkyl = *i*-Pr, *c*-pent, *c*-hex, *n*-Bu

34-80%;
63-98% *ee*



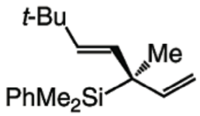
Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 15604.

S$_N$2’ Addition Chemistry



82-96%; >93:7

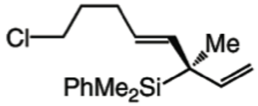
Sterically hindered alkyne:



3

(0.5 mol % **1b**; –15 °C, 12 h)
>98% yield (<2% alkynyl addn)
91:9 er, >98% *E*

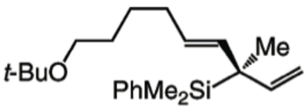
Halogen-containing alkyne:



4

(0.5 mol % **1b**; –15 °C, 3 h)
91% yield (<2% alkynyl addn)
96:4 er, >98% *E*

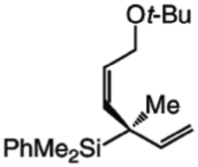
Heteroatom-containing alkyne:



5

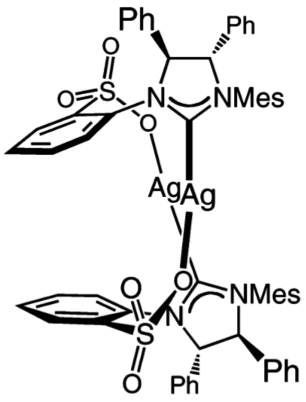
(0.5 mol % **1b**; –15 °C, 3 h)
91% yield (<2% alkynyl addn)
96:4 er, >98% *E*

Propargyl ether:

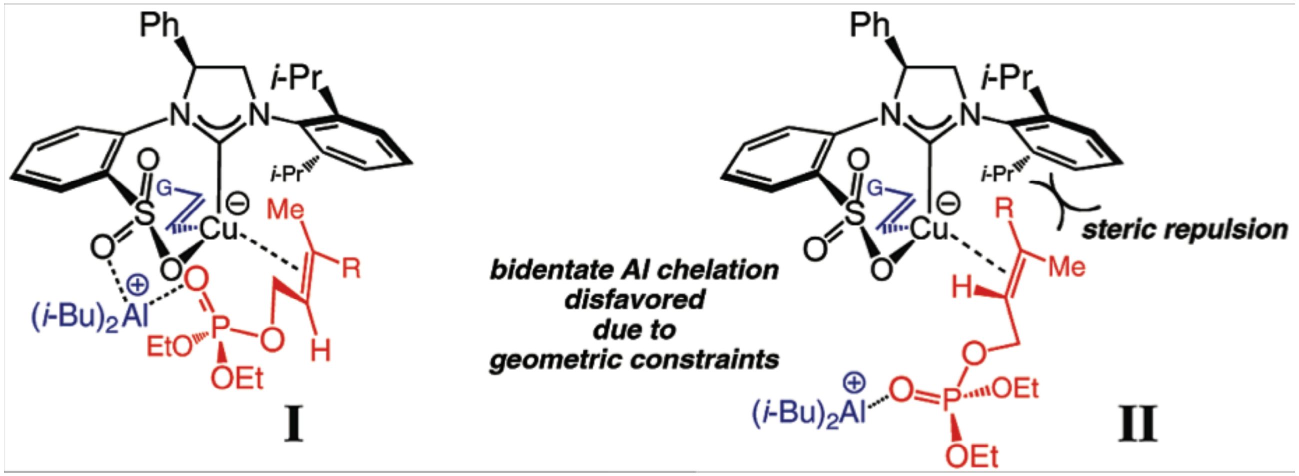


6

(0.5 mol % **1c**; –50 °C, 24 h)
82% yield (<2% alkynyl addn)
94.5:5.5 er, >98% *Z*

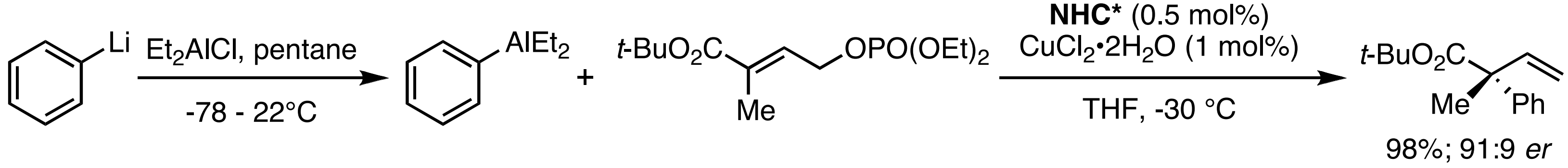


L*



Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315.

S_N2' Addition Chemistry



Et_2AlCl, pentane

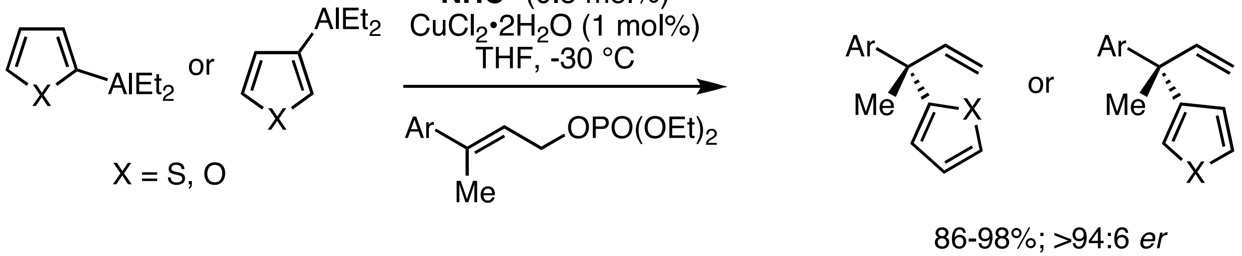
-78 - 22°C

NHC* (0.5 mol%)

$CuCl_2 \cdot 2H_2O$ (1 mol%)

THF, -30 °C

98%; 91:9 *er*



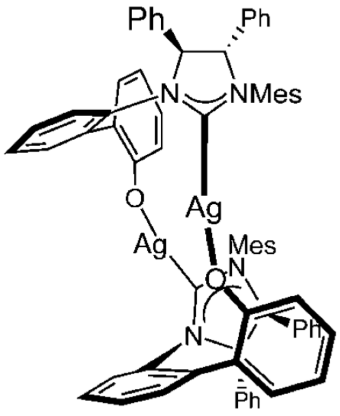
X = S, O

NHC* (0.5 mol%)

$CuCl_2 \cdot 2H_2O$ (1 mol%)

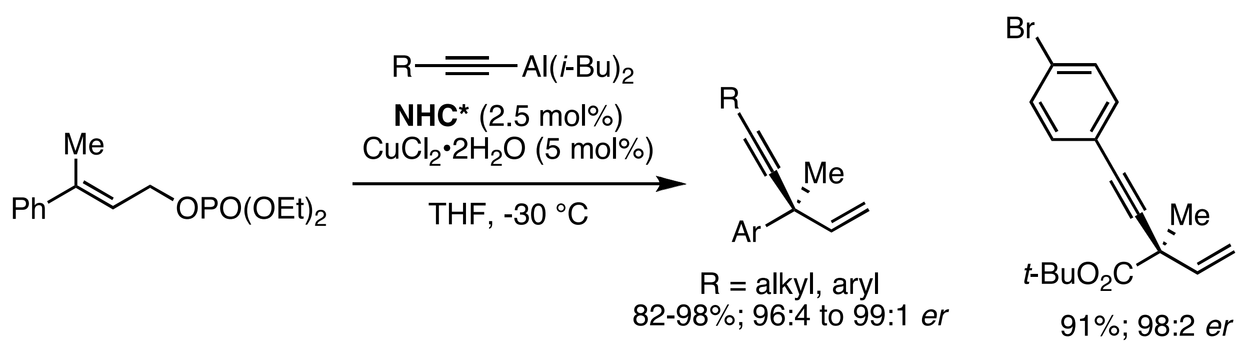
THF, -30 °C

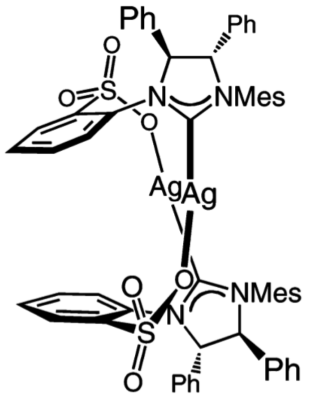
86-98%; >94:6 *er*



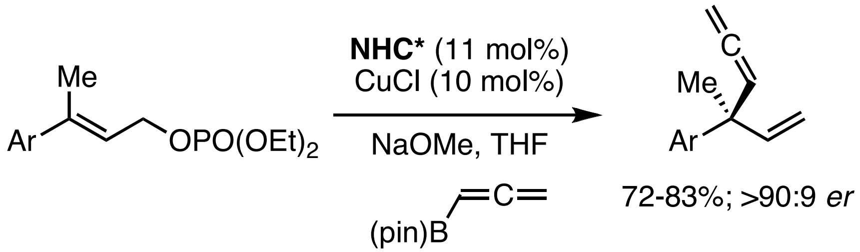
Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 8370.

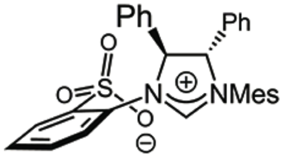
S_N2' Addition Chemistry





NHC*

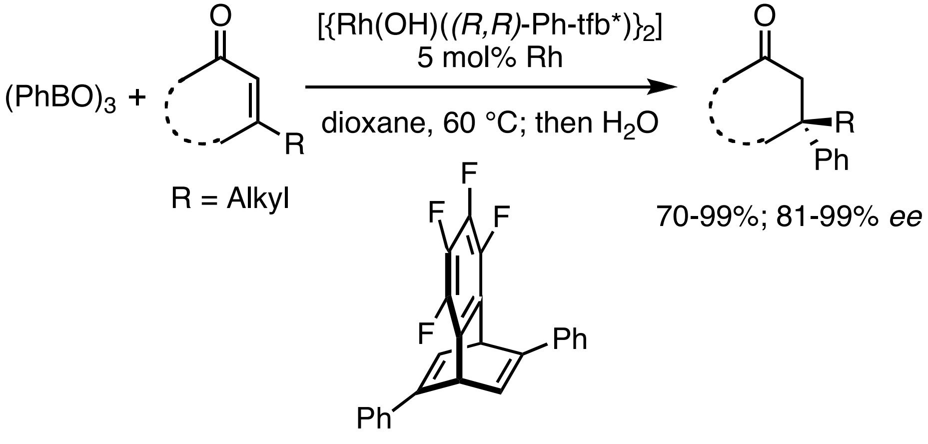




NHC*

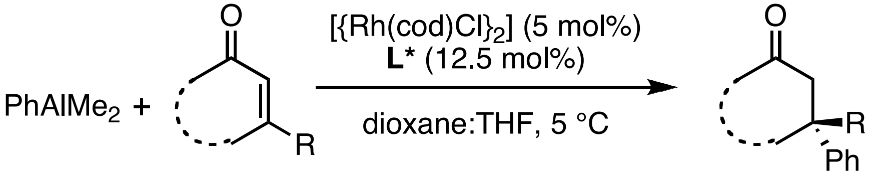
Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778.
Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490.

Conjugate Additions

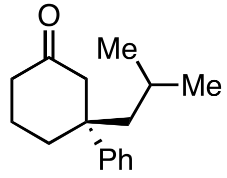


(*R,R*)-Ph-tfb*

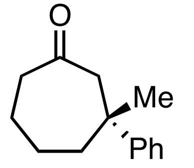
70-99%; 81-99% *ee*



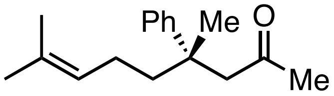
35-66%; 93-99% *ee*



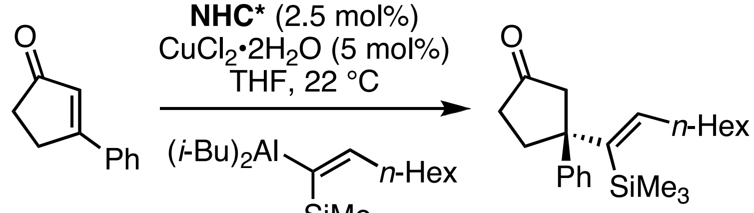
35%; 99% *ee*



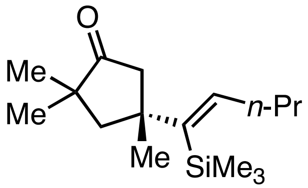
56%; 95% *ee*



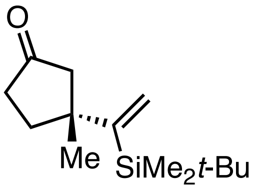
52%; >95% *ee*



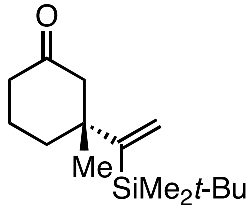
84:16 vinyl:*i*-Bu
48%; 89:11 *er*



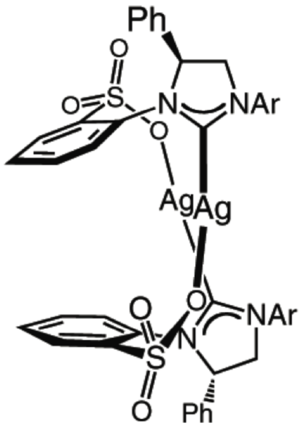
95:5 vinyl:*i*-Bu
70%; >98:2 *er*



95:5 vinyl:*i*-Bu
60%; 92.5:7.5 *er*



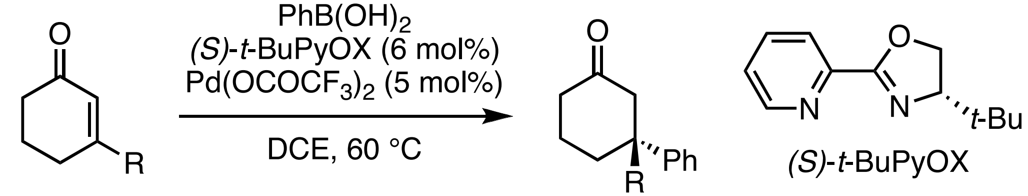
80:20 vinyl:*i*-Bu
71%; 95:5 *er*



NHC*
Ar = 2,6-(Et)$_2$C$_6$H$_3$

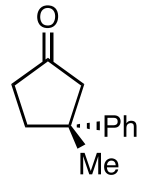
Shintani, R.; Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 3969.
Hawner, C.; Muller, D.; Gremaud, L.; Felouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 7769.
May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736.

Conjugate Additions

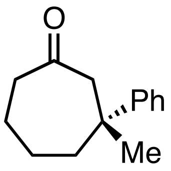


R = alkyl, c-alkyl

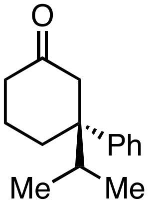
68-96%; 79-93% *ee*



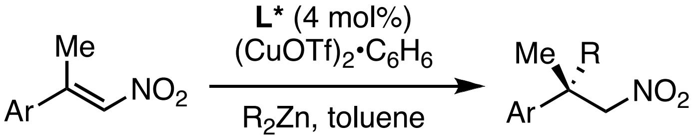
84%; 91% *ee*



85%; 93% *ee*

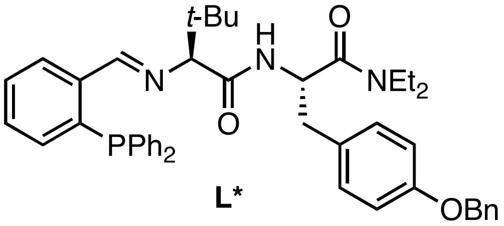


86%; 79% *ee*

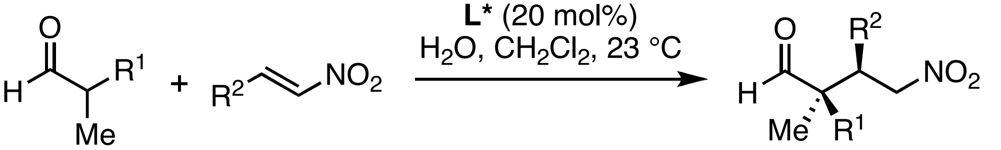


R = alkyl

55-81%; 85-98% *ee*

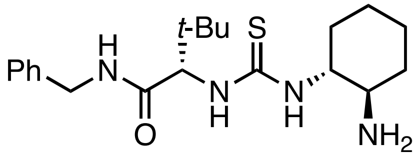


L*



R^1 = aryl, alkyl, Bn
R^2 = aryl, alkyl

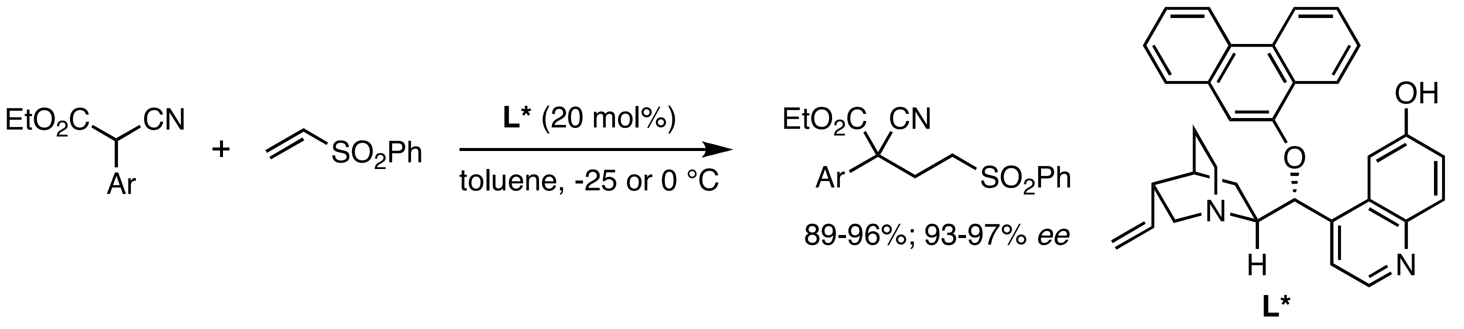
34-98%; 92-99% *ee*
2.1:1 to >50:1 *dr*

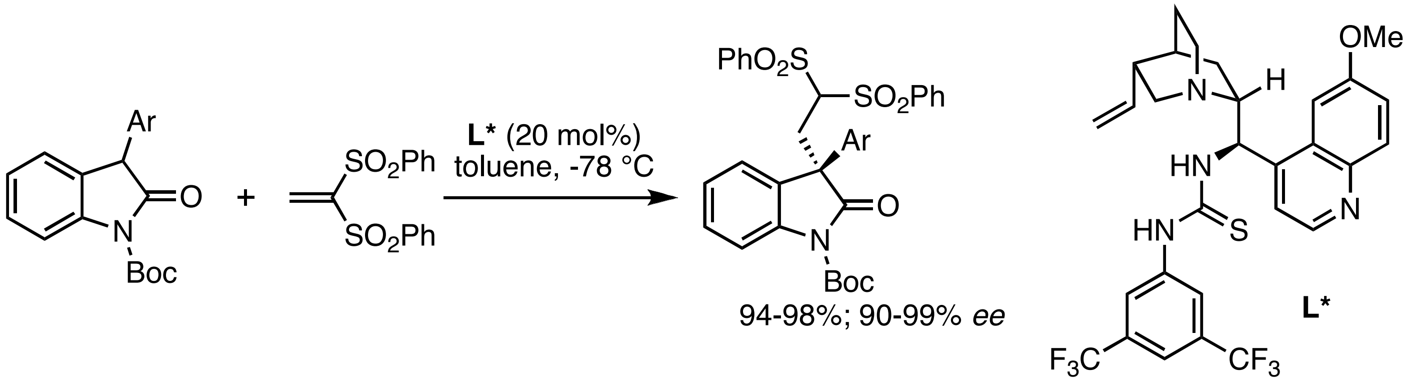


L*

Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902.
Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584.
Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 6366.

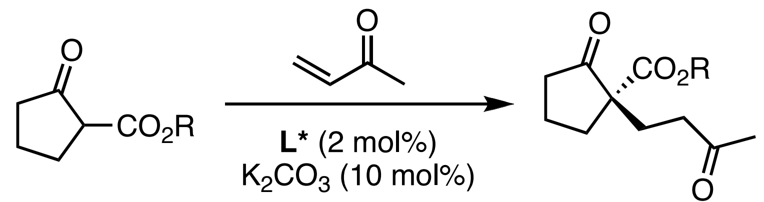
Conjugate Additions



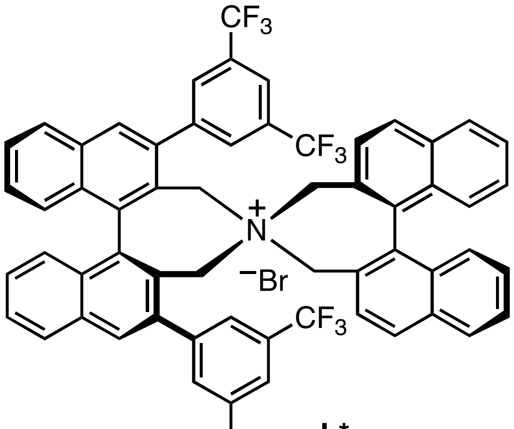


Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948.
Zhu, Q.; Lu, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 7753.

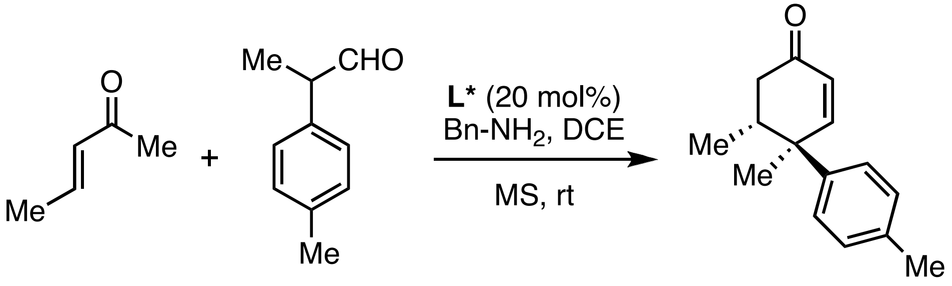
Conjugate Additions



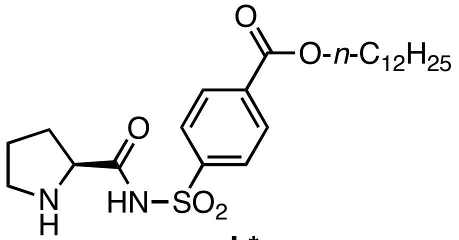
R = 9-fluorenyl
quant.; 97% *ee*



L*



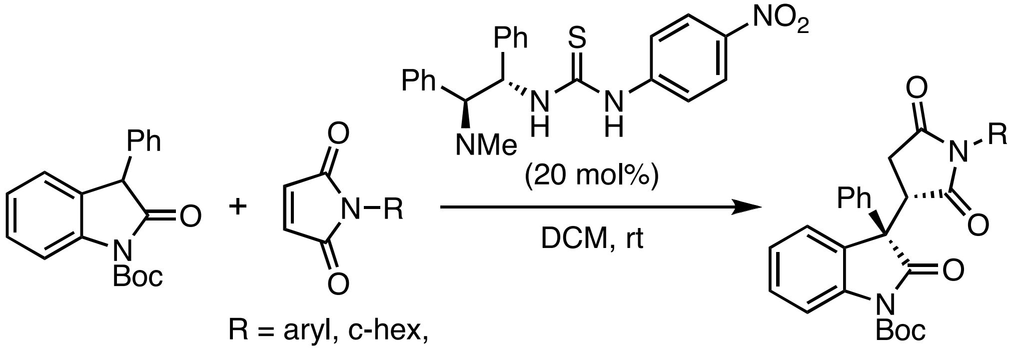
56%; 94:6 *er*
>20:1 *dr*



L*

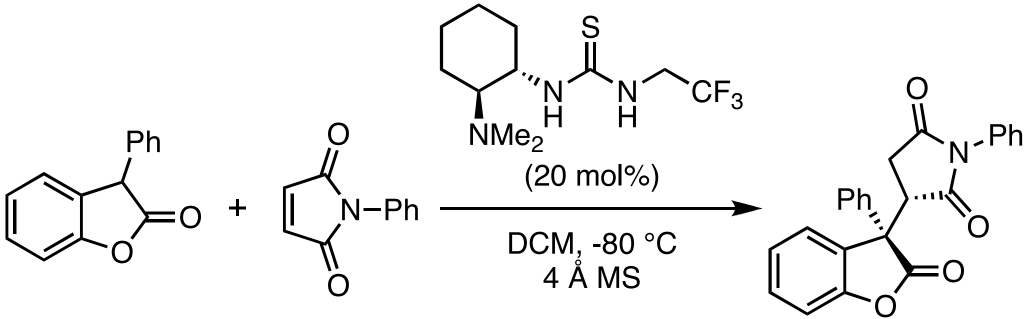
Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 3796.
Yang, H.; Carter, R. G. *Org. Lett.* **2010**, *12*, 3108.

Conjugate Additions



R = aryl, c-hex,
i-Pr, allyl

64-92%; 85-98% *ee*
87:13 to 96:4 *dr*

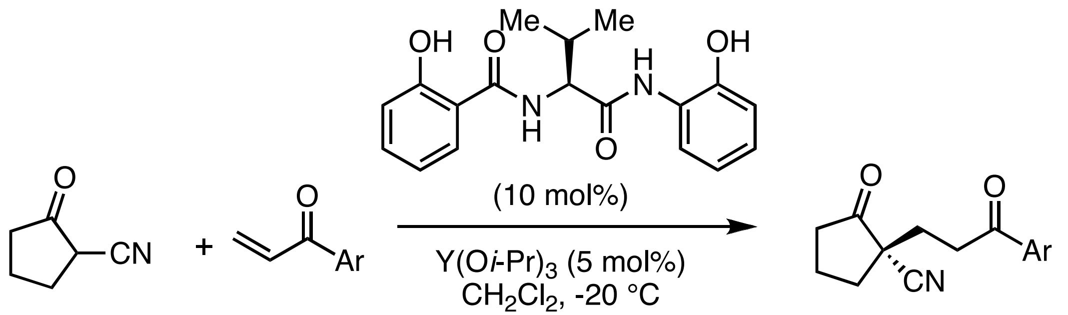


R = aryl, c-hex,
i-Pr, allyl

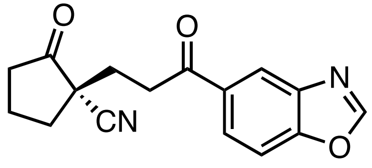
99%; 96% *ee*
>20:1 *dr*

Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 2896.
Li, X.; Hu, S.; Xi, Z.; Zhang, L.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 8697.

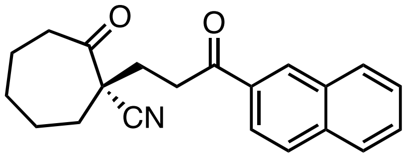
Conjugate Additions



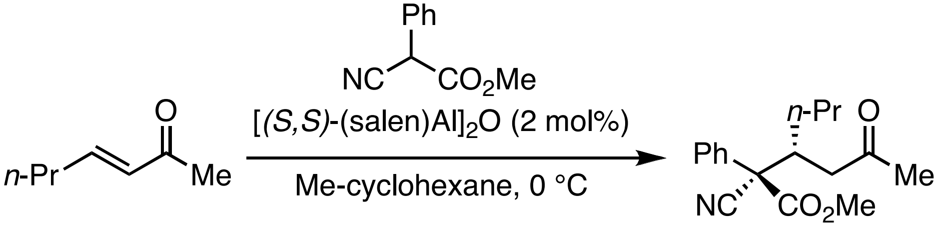
48-98%; 70-98% *ee*



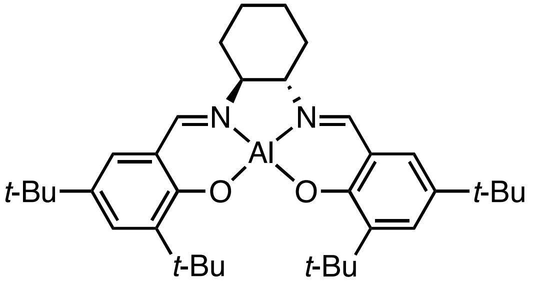
88%, 86% *ee*



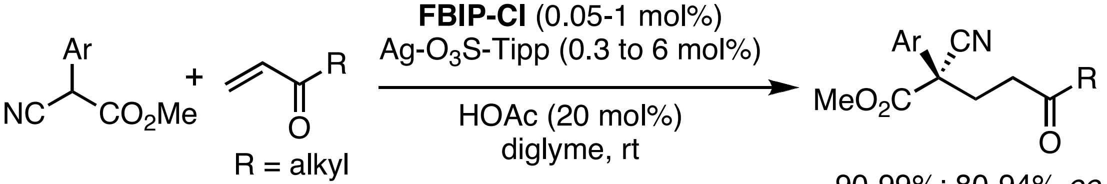
73%, 95% *ee*



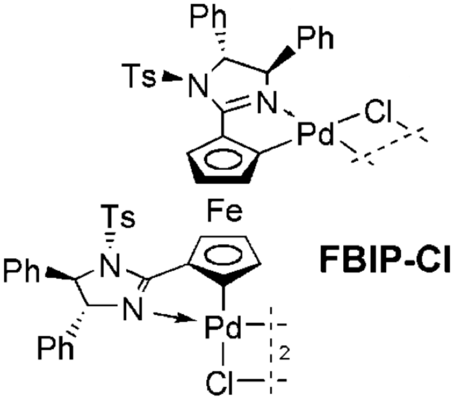
88%; 89% *ee*
>30:1 *dr*



[*(S,S)*-(salen)Al]



90-99%; 80-94% *ee*



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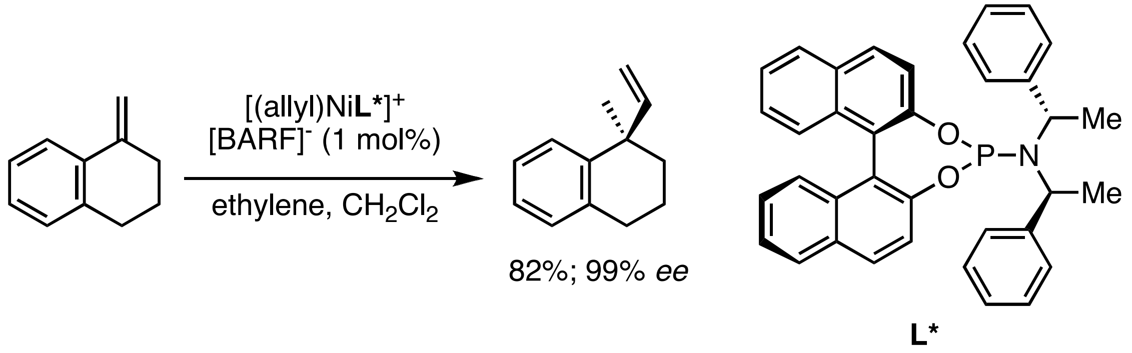
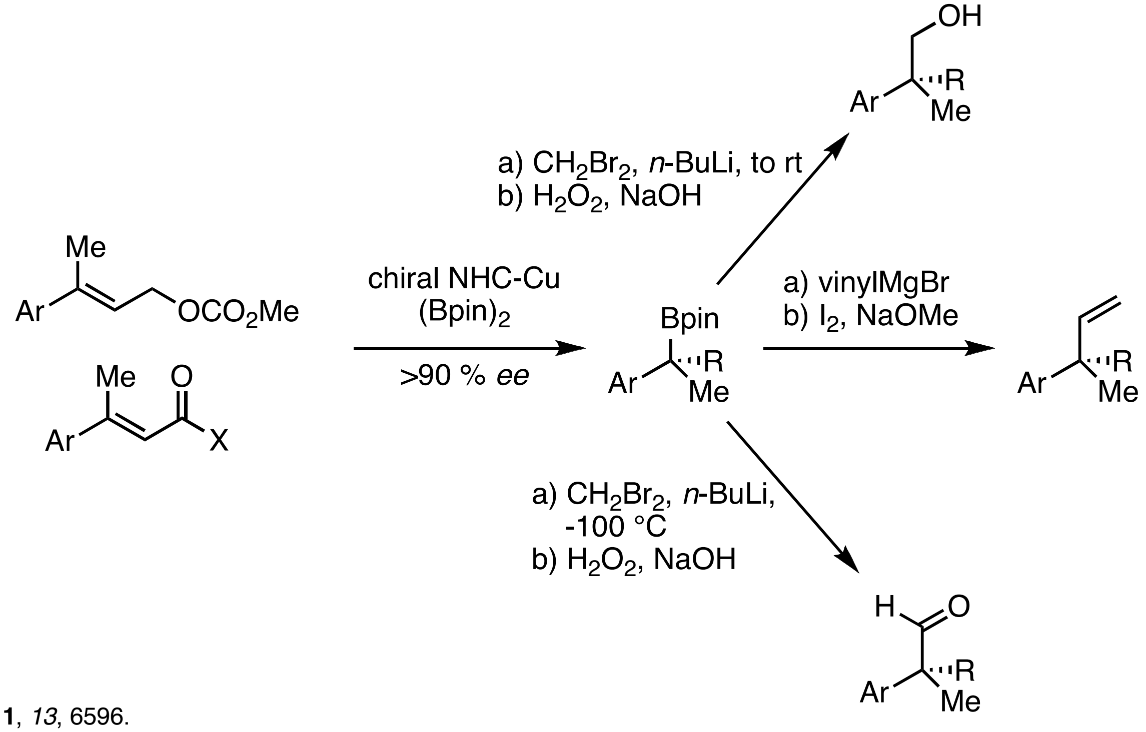
Micellaneous Quaternary Center Formations





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Conclusion

- Discussed the frontier of the catalytic asymmetric synthesis of all carbon quaternary stereocenters
- Where do we go from here?
  - Application of these methodologies to complex molecules
  - Better understand the mechanistic aspects of the methodologies to pursue rationally designed catalysts.
  - Be creative in preparing all carbon quaternary stereocenters
    - New reaction discovery

> "It is safe to predict that this field of chemistry will continue to grow exponentially in the coming decades and the ready availability of a wide range of these chiral entities will provide an excellent opportunity to further enrich mainstream synthetic methodologies"
>
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