Transition Metal-catalysed Enantioselective Conjugate Additions

MacMillan Group Literature Meeting 11/19/08

Allan J. B. Watson

Review Literature

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Transition Metal-mediated Catalytic Enantioselective Conjugate Additions

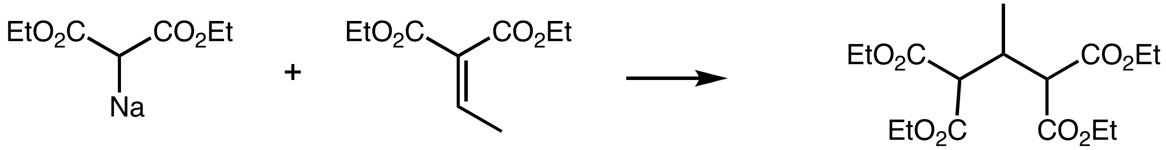
Overview

- Historical perspective and challenges
- Cobalt-catalysed processes
- Ni-catalysed processes
- Cu-catalysed processes
- Zn-catalysed processes
- Rh-catalysed processes
- Pd-catalysed processes
- Summary

Introduction

Historical Perspective

- The first example of a conjugate addition was reported in 1883 by Komnenos



Komemnos, T. *Liebigs Ann. Chem.* **1883**, *218*, 145.

Introduction

Historical Perspective

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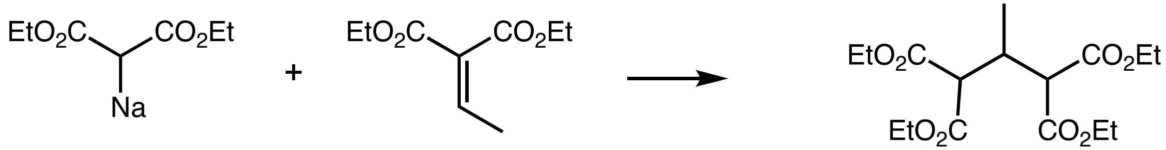
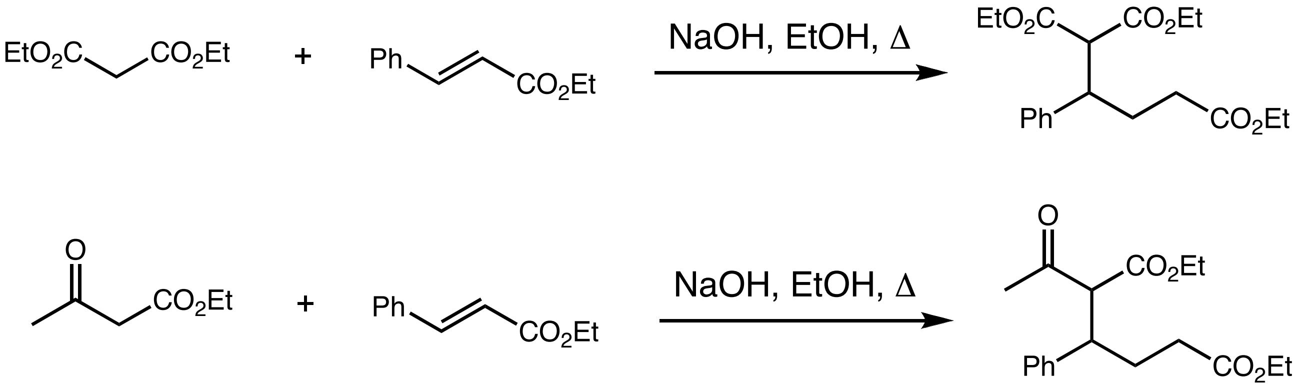


Komemnos, T. *Liebigs Ann. Chem.* **1883**, *218*, 145.

- Conjugate additions as a research field really only began following the work of Michael in 1887



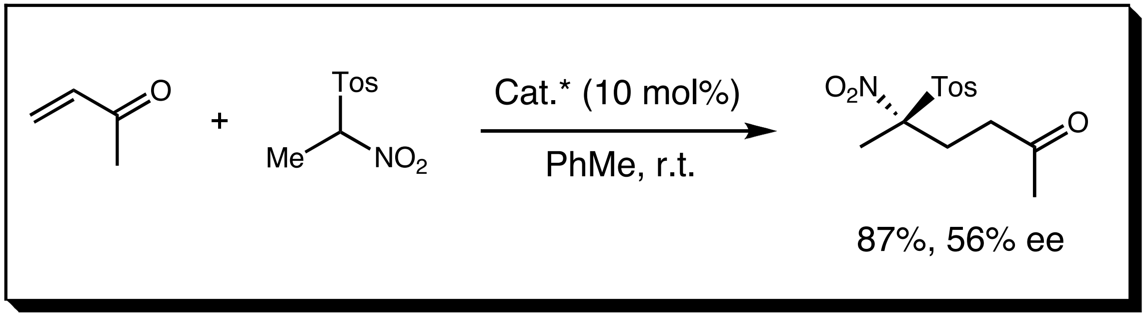
(a) Michael, A. *J. Prakt. Chem.* **1887**, *3*, 349. (b) Michael, A. *Am. Chem. J.* **1887**, *9*, 112.

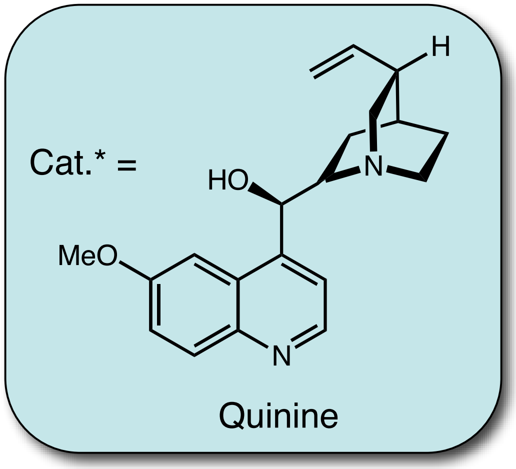
- Following this initial work, the conjugate addition has become a staple of organic synthesis

Introduction

Historical Perspective

- The first example of an enantioselective conjugate addition was reported in 1975





Quinine

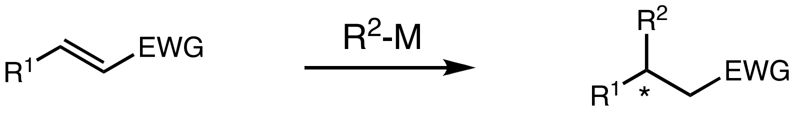
Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057.

- Transition metal catalysis of such processes soon followed

Introduction

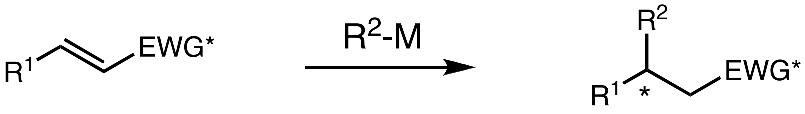
Strategies for Stereoselective Conjugate Addition Reactions

- Conjugate additions often lead to the generation of one (or more) stereocentres



- Several approaches exist for controlling the stereoselectivity of this process

Diastereoselective Conjugate Addition



Introduction

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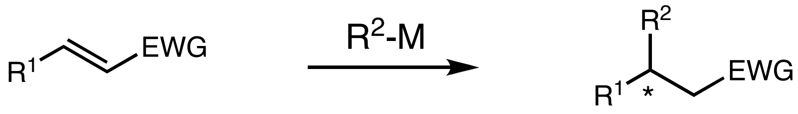

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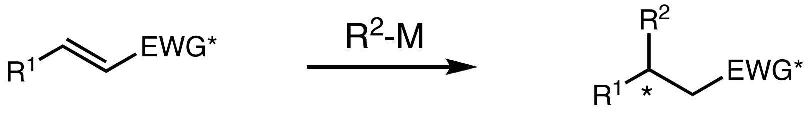
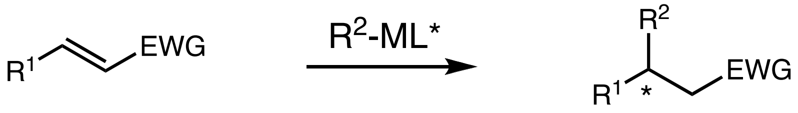


Enantioselective Conjugate Addition



Introduction

Strategies for Stereoselective Conjugate Addition Reactions

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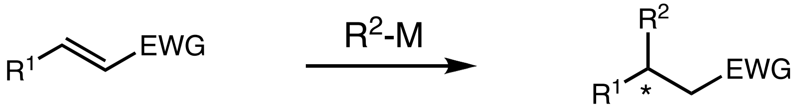

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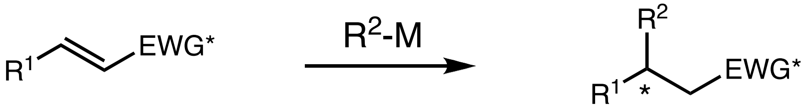
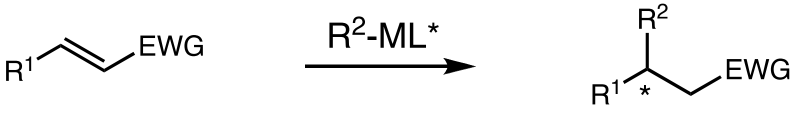
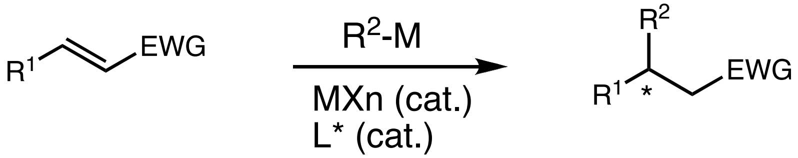


Enantioselective Conjugate Addition



Catalytic Enantioselective Conjugate Addition



Conjugate Addition Reactions

Promotion by a Large Range of Elements

- A wide range of elements have found use as promoters within conjugate addition reactions

^{1}H																	^{2}He
^{3}Li	^{4}Be											^{5}B	^{6}C	^{7}N	^{8}O	^{9}F	^{10}Ne
^{11}Na	^{12}Mg											^{13}Al	^{14}Si	^{15}P	^{16}S	^{17}Cl	^{18}Ar
^{19}K	^{20}Ca	^{21}Sc	^{22}Ti	^{23}V	^{24}Cr	^{25}Mn	^{26}Fe	^{27}Co	^{28}Ni	^{29}Cu	^{30}Zn	^{31}Ga	^{32}Ge	^{33}As	^{34}Se	^{35}Br	^{36}Kr
^{37}Rb	^{38}Sr	^{39}Y	^{40}Zr	^{41}Nb	^{42}Mo	^{43}Tc	^{44}Ru	^{45}Rh	^{46}Pd	^{47}Ag	^{48}Cd	^{49}In	^{50}Sn	^{51}Sb	^{52}Te	^{53}I	^{54}Xe
^{55}Cs	^{56}Ba	^{57}La	^{72}Hf	^{73}Ta	^{74}W	^{75}Re	^{76}Os	^{77}Ir	^{78}Pt	^{79}Au	^{80}Hg	^{81}Tl	^{82}Pb	^{83}Bi	^{84}Po	^{85}At	^{86}Rn
^{87}Fr	^{88}Ra	^{89}Ac	^{104}Rf	^{105}Db	^{106}Sg	^{107}Bh	^{108}Hs	^{109}Mt									

^{58}Ce	^{59}Pr	^{60}Nd	^{61}Pm	^{62}Sm	^{63}Eu	^{64}Gd	^{65}Tb	^{66}Dy	^{67}Ho	^{68}Er	^{69}Tm	^{70}Yb	^{71}Lu
^{90}Th	^{91}Pa	^{92}U	^{93}Np	^{94}Pu	^{95}Am	^{96}Cm	^{97}Bk	^{98}Cf	^{99}Es	^{100}Fm	^{101}Md	^{102}No	^{103}Lr

Conjugate Addition Reactions

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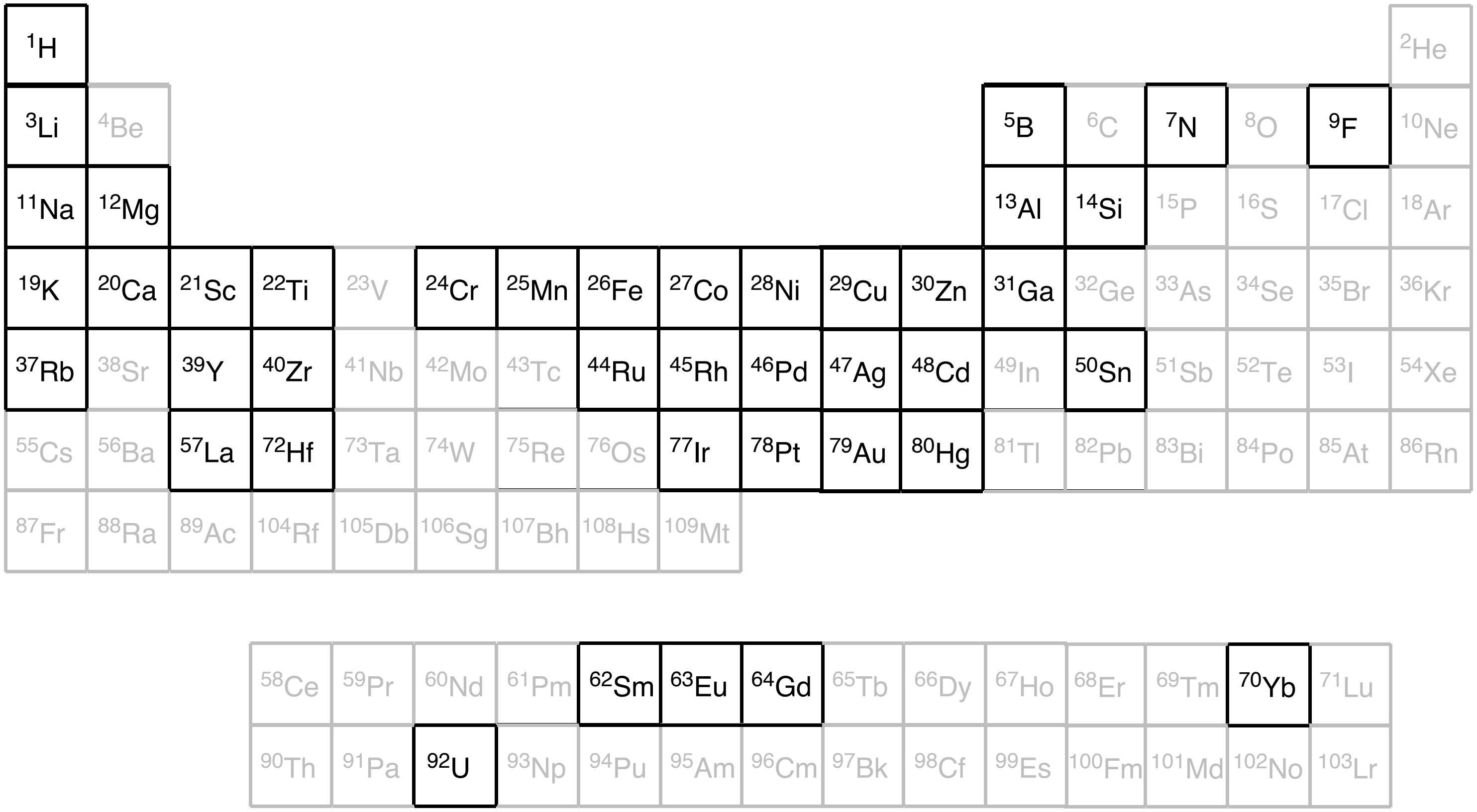

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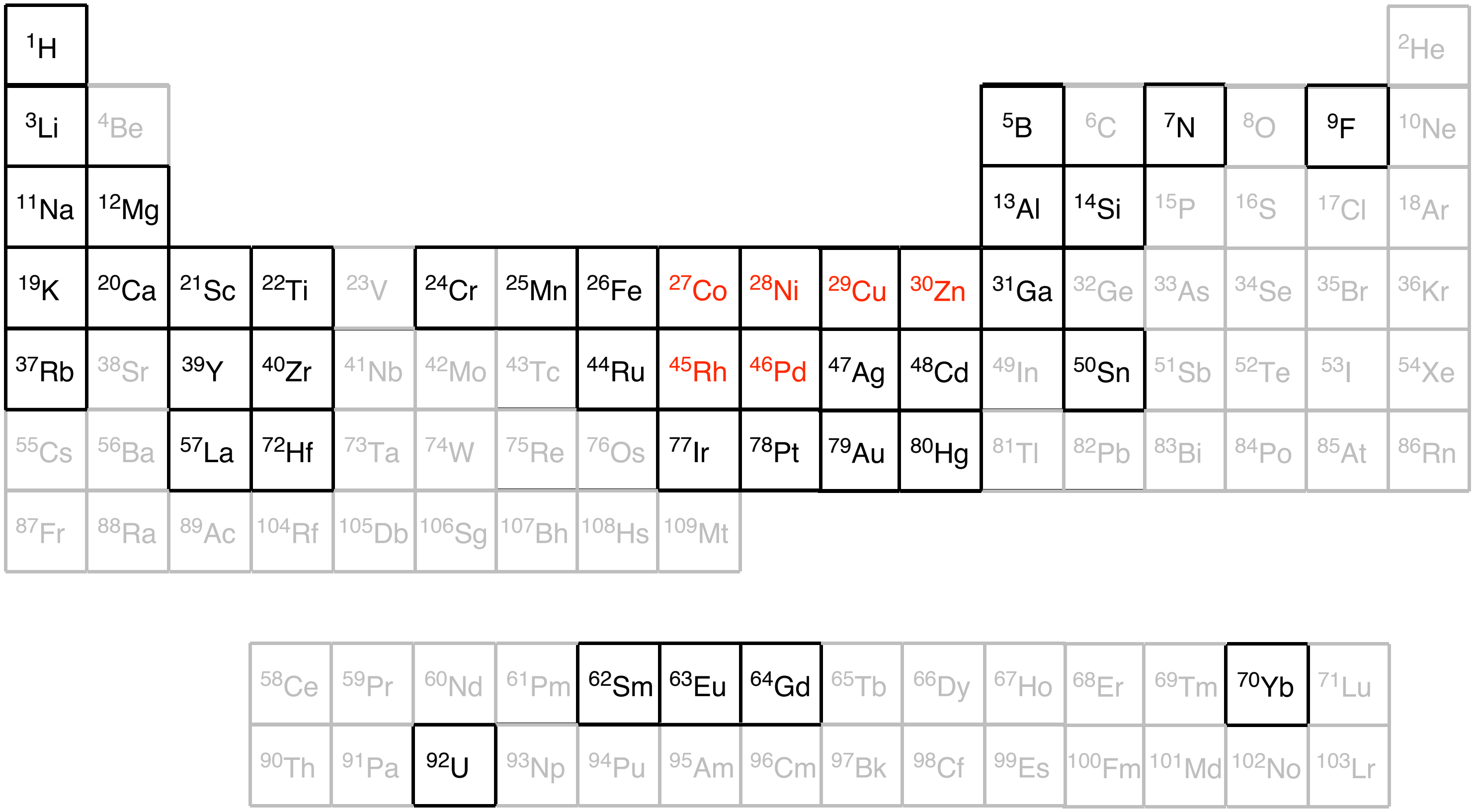
Conjugate Addition Reactions

Promotion by a Large Range of Elements

- Transition metals have been extensively studied



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- Several of these will be discussed

Transition Metal-catalysed Enantioselective Conjugate Addition Reactions

Selected Metals for Discussion

- Selected transition metals

^{27}Co (1984)

^{28}Ni (1988)

^{29}Cu (1988)

^{30}Zn (1988)

^{45}Rh (1992)

^{46}Pd (2002)

- Represent some of the most extensively studied metals

Enantioselective Conjugate Additions using Transition Metal Catalysis

Challenges

> *"The Holy Grail in this area of research has been a chiral Lewis acid that exhibits broad generality for asymmetric catalysis in more than one reaction family."*

D. A. Evans, 2000

Enantioselective Conjugate Additions using Transition Metal Catalysis

Challenges

"The Holy Grail in this area of research has been a chiral Lewis acid that exhibits broad generality for asymmetric catalysis in more than one reaction family."

"Since the demands of each reaction are quite varied, the realization of this goal may not even be attainable."

D. A. Evans, 2000

Catalytic Enantioselective Conjugate Addition Reactions

Transition Metal Catalysts - Cobalt

^{27}Co

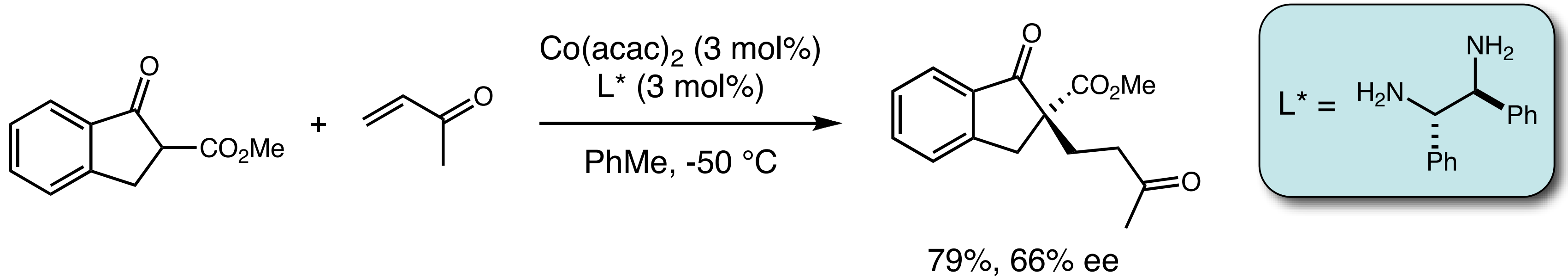
Seminal work:

Brunner, H.; Hammer. B. *Angew. Chem., Int. Ed.* **1984**, *23*, 312.

Enantioselective Conjugate Addition using Cobalt Catalysis

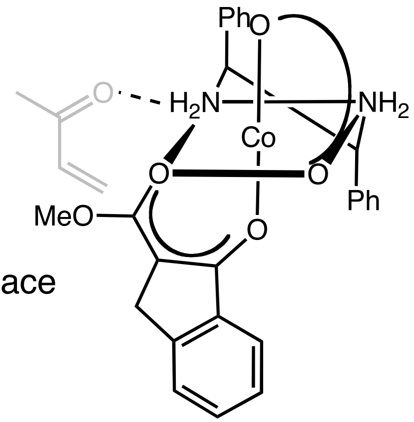
Discovery

- Brunner published the first Co-catalysed conjugate addition in 1984
- Using a chiral 1,2-diamine ligand, moderate levels of enantioselectivity were obtained



79%, 66% ee

- Proposed structure of keto-ester enolate bound catalyst:



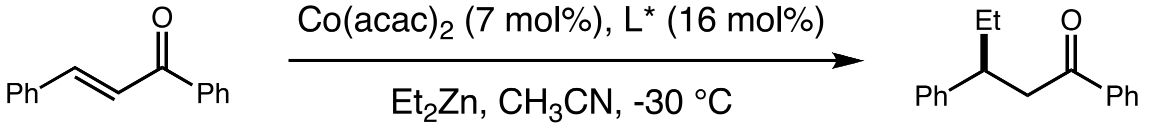
Attack from *si*-face

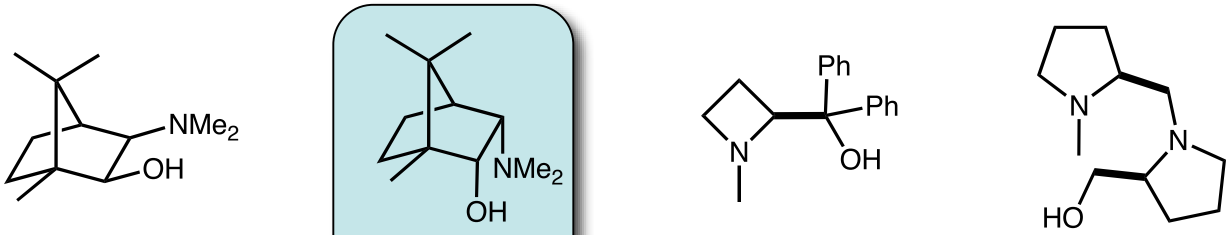
Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed.* **1984**, *23*, 312.

Enantioselective Conjugate Addition using Cobalt Catalysis

Historical Perspective

- Feringa pursued a Co-catalysed system in the late 1990's
- Results from this study encouraged further research





67% ee

83% ee

33% ee

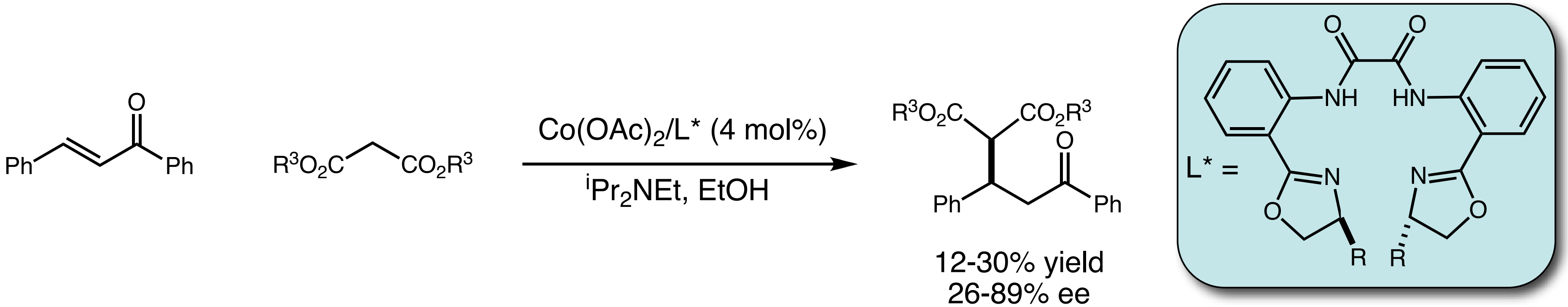
28% ee

de Vries, A. H. M.; Feringa, B. L. *Tetrahedron Asymm.* **1997**, *8*, 1377.

Enantioselective Conjugate Addition using Cobalt Catalysis

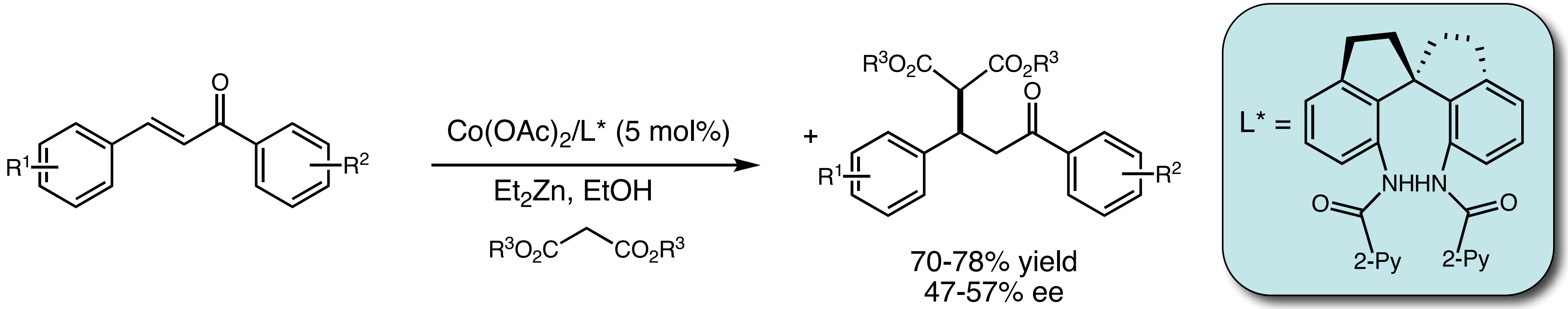
Developments

- In the late 1990's/2000 several groups continued to investigate cobalt catalysis



12-30% yield
26-89% ee

End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem. Eur. J.* **1998**, *4*, 818.



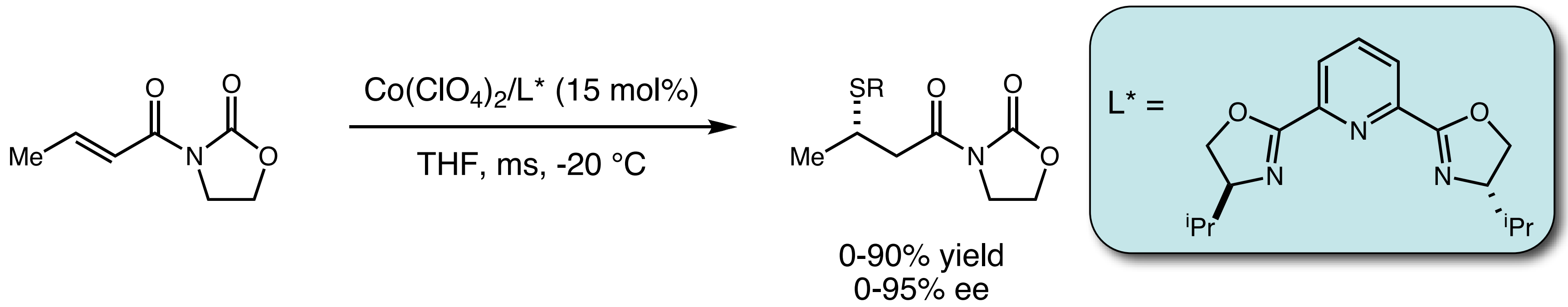
70-78% yield
47-57% ee

Chen. C.; Zhu, S.-F.; Wu, X.-Y.; Zhou, Q.-L. *Tetrahedron Asymm.* **2006**, *17*, 2761.

Enantioselective Conjugate Addition using Cobalt Catalysis

Developments

- However, research gradually waned due to: (i) generally poor performance of Co catalysts
  (ii) the arrival of other more promising metal systems
- Research into cobalt catalysis of this reaction does continue

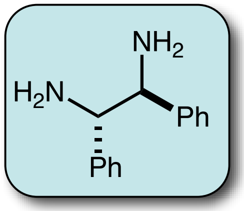


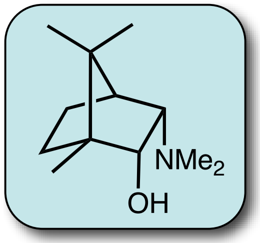
Kawatsura, M.; Komatsu, Y.; Yamamoto, M.; Hayase, S.; Itoh, T. *Tetrahedron* **2008**, *64*, 3488.

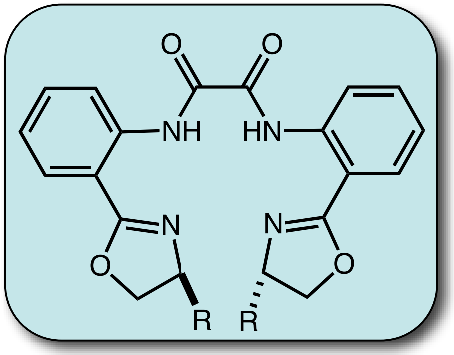
Enantioselective Conjugate Addition using Cobalt Catalysis

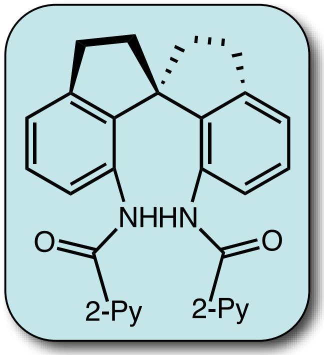
Overview

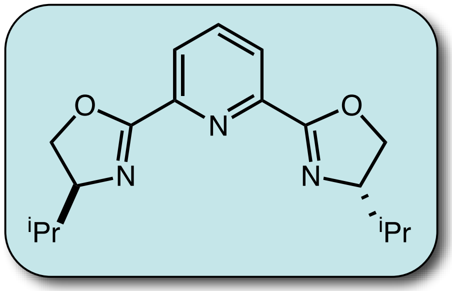
- Cobalt was the first TM employed for enantioselective conjugate additions
- Ultimately, the effectivity of Co-mediated processes was low
- The arrival of Ni, Cu, Zn, Rh, Pd etc. resulted in declined interest in Co
- As a general method, Co catalysis is not viable - open for research











Catalytic Enantioselective Conjugate Addition Reactions

Transition Metal Catalysts - Nickel

^{28}Ni

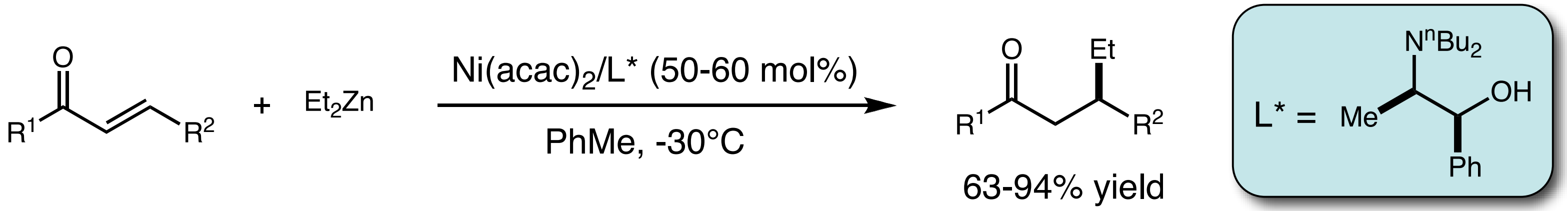
Seminal work:

(a) Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4149.
(b) Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S. *Chem. Lett.* **1988**, 1571.
(c) Soai, K.' Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516.

Enantioselective Conjugate Additions using Nickel Catalysis

Historical Perspective

- Conjugate additions under Ni catalysis began in the late 1980's



63-94% yield
12-45% ee

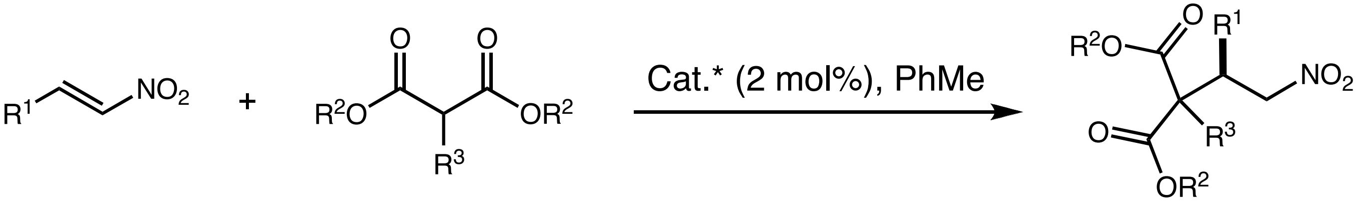
Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4149.

- A general catalytic platform using Ni has proved elusive
- Only recently have several highly selective procedures been developed

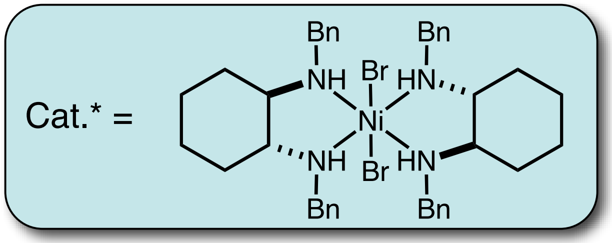
Enantioselective Conjugate Additions using Nickel Catalysis

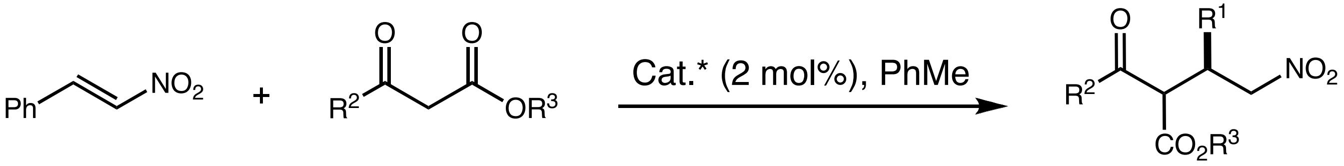
Successful Applications

- One of the most successful systems was developed by Evans
- A nickel(II) salt with *trans*-1,2-cyclohexanediamine ligands provided high enantioselectivities



82-99% yield
88-95% ee





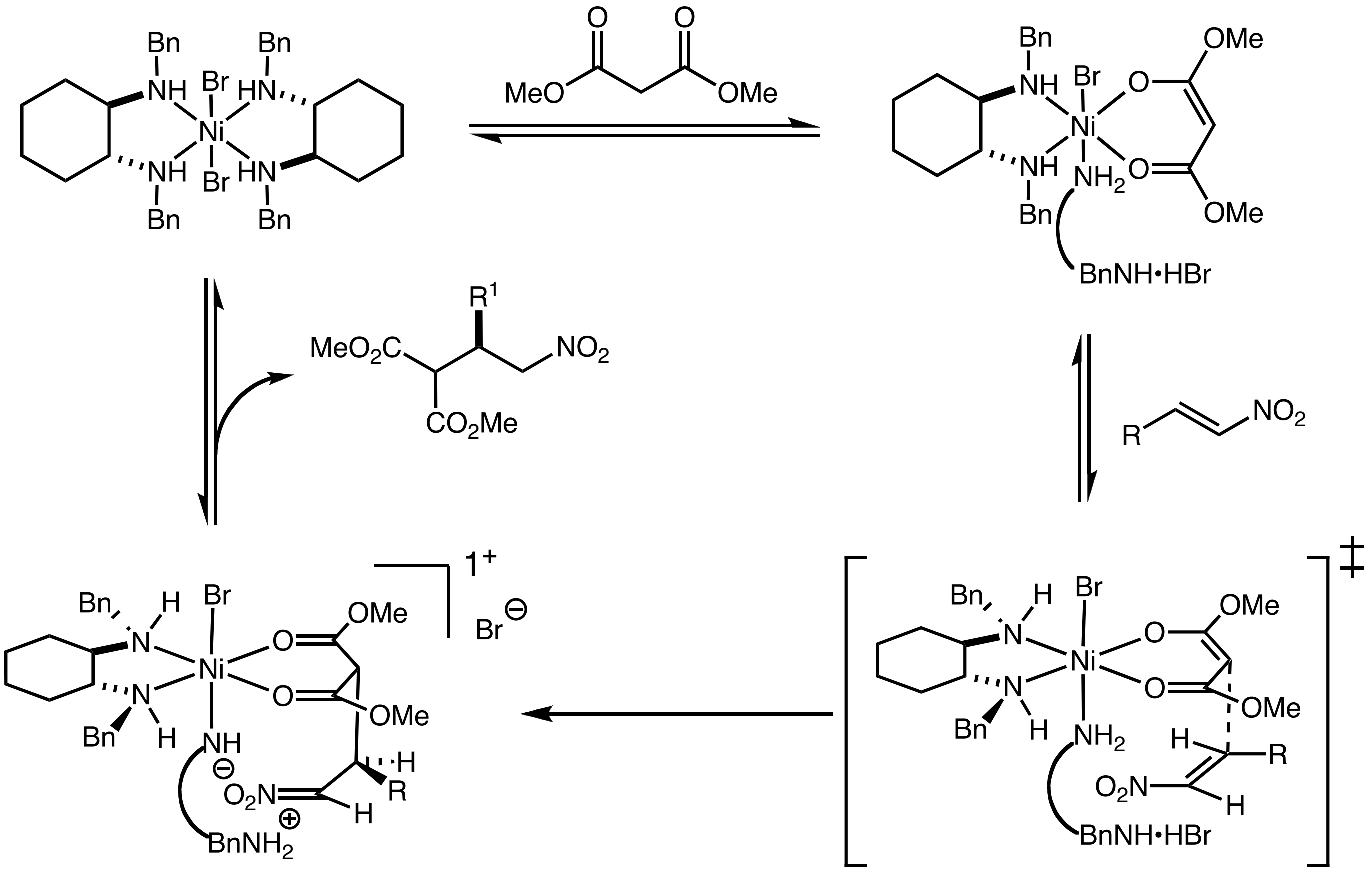
94-97% yield
1:1-2.5:1 dr
90-94% ee

Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958.

Enantioselective Conjugate Additions using Nickel Catalysis

Successful Applications

- Use of two diamine ligands was thought to be crucial to the success of the process

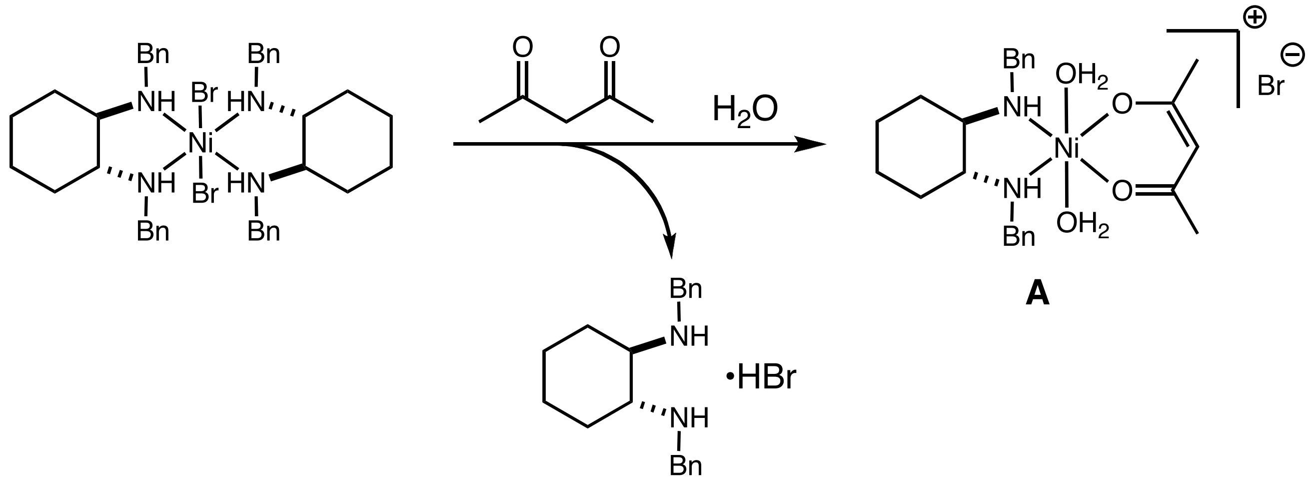


(a) *J. Am. Chem. Soc.* **2005**, *127*, 9958. (b) *J. Am. Chem. Soc.* **2007**, *129*, 11583.

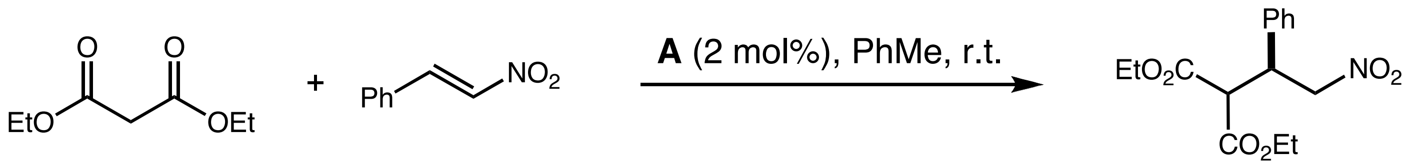
Enantioselective Conjugate Additions using Nickel Catalysis

Successful Applications

- Subsequent studies sugested this was not the case



- Second amine acts solely as a base
- Bisaqua complex **A** also performs as catalyst



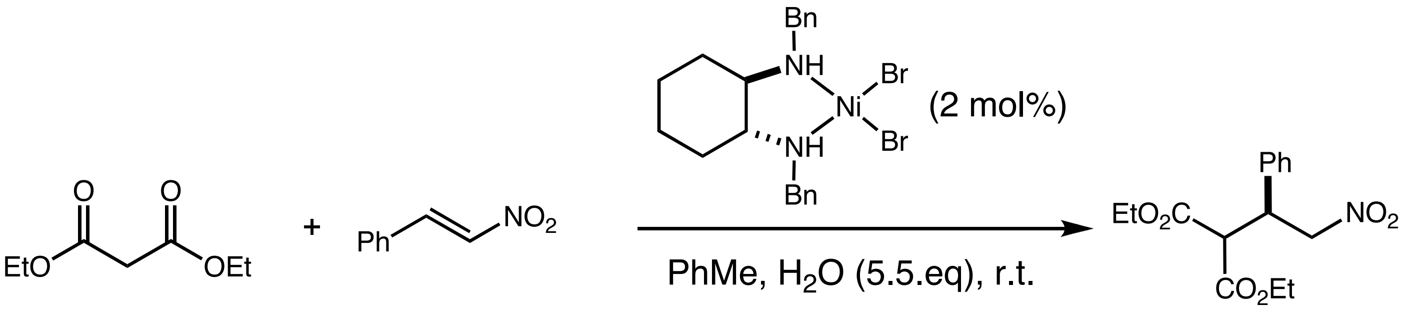
86%, 96% ee

J. Am. Chem. Soc. **2007**, *129*, 11583.

Enantioselective Conjugate Additions using Nickel Catalysis

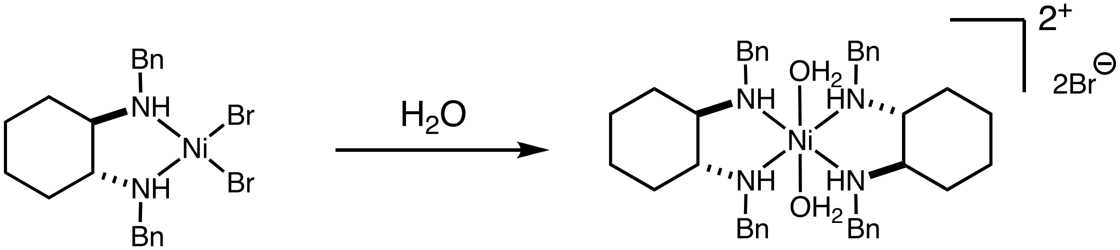
Successful Applications

- This led to the development of a new catalyst system using less chiral amine



99%, 94% ee

- Water was found to be crucial for reaction efficiency
- Speculated that a *bis*-diamine catalyst is formed *in situ*



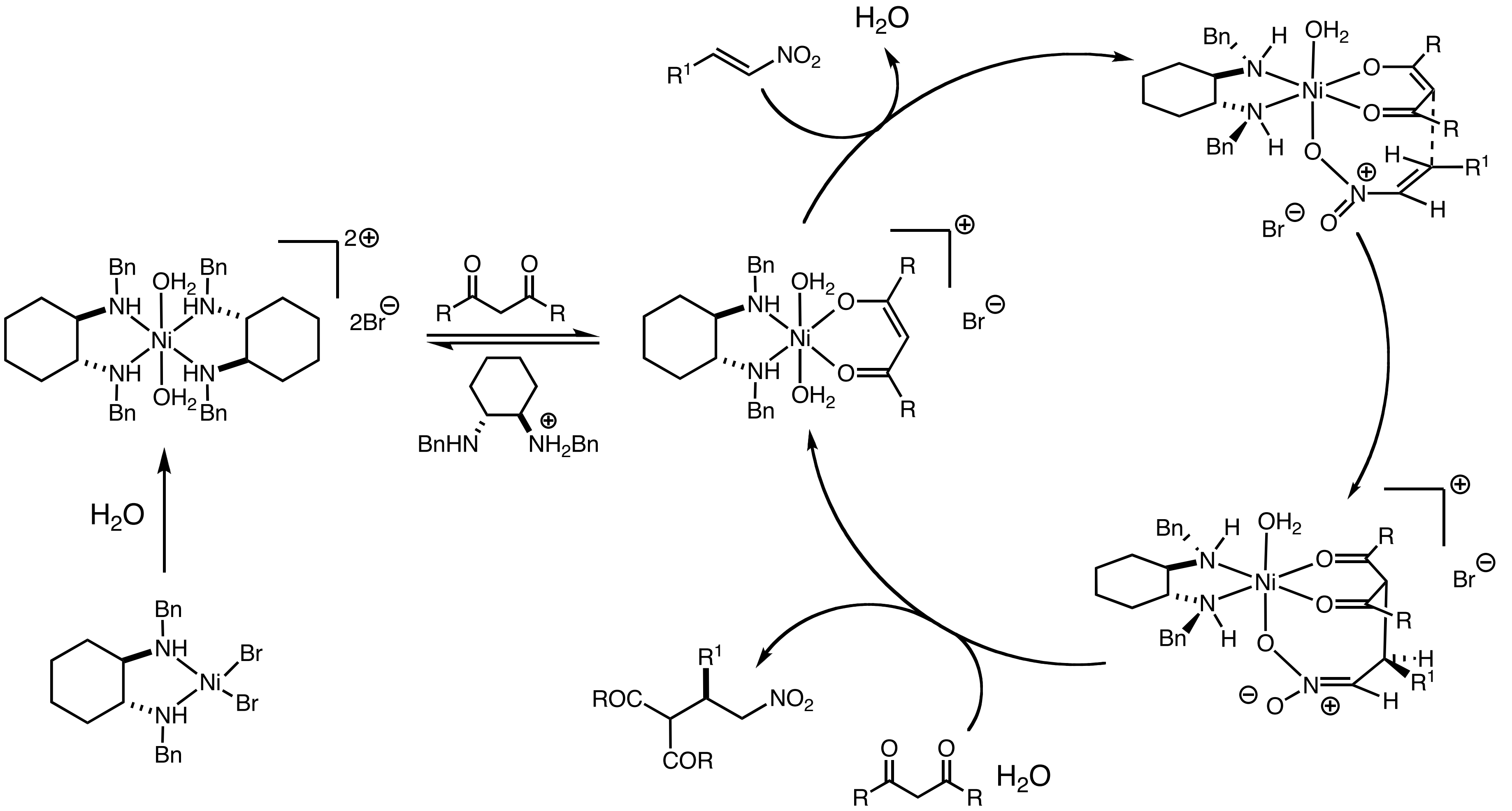
- The catalytic cycle was also reconsidered

J. Am. Chem. Soc. **2007**, *129*, 11583.

Enantioselective Conjugate Additions using Nickel Catalysis

Successful Applications

- Proposed catalytic cycle

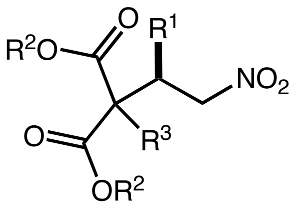


J. Am. Chem. Soc. **2007**, *129*, 11583.

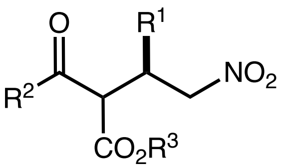
Enantioselective Conjugate Additions using Nickel Catalysis

Successful Applications

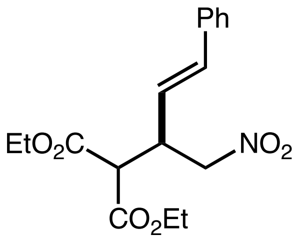
- The developed catalytic systems operate well for several nucleophiles and electrophiles



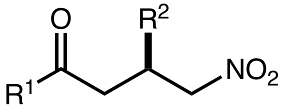
82-99% yield
88-95% ee
R^1 = alkyl, aryl



94-97% yield
1:1-2.5:1 dr
90-94% ee



95%, 95% ee



50-99% yield
77-94% ee

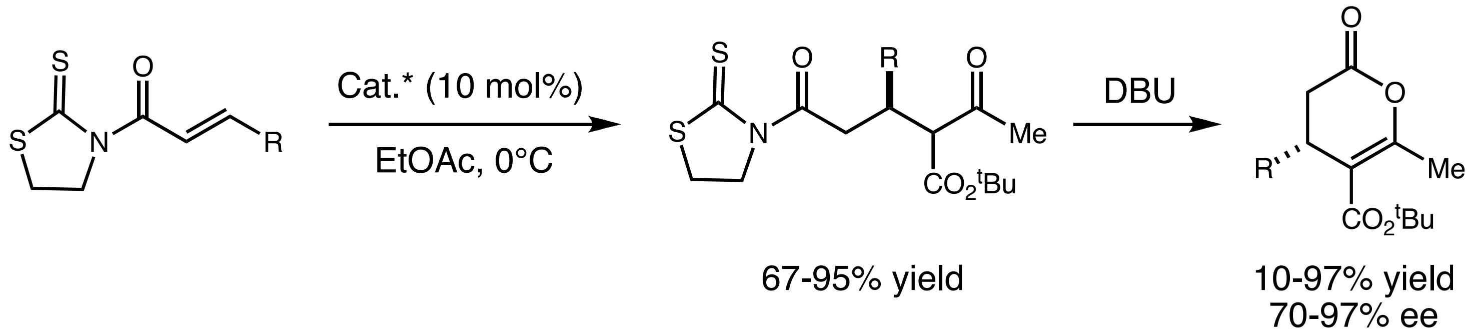
- Whether this system is more broadly applicable remains to be seen

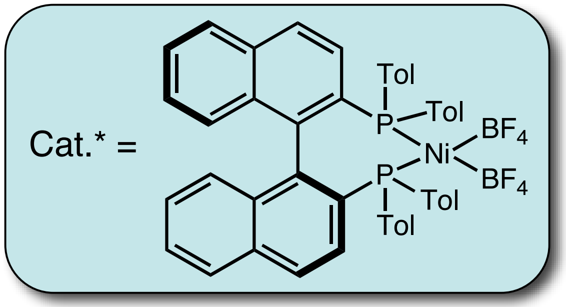
(a) *J. Am. Chem. Soc.* **2005**, *127*, 9958. (b) *J. Am. Chem. Soc.* **2007**, *129*, 11583.

Enantioselective Conjugate Additions using Nickel Catalysis

Successful Applications

- Evans subsequently developed a second Ni-catalysed system using BINAP





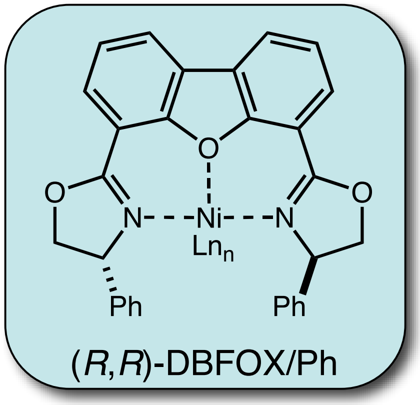
- Activation proposed via formation of square planar complex of enone with Ni-Tol-BINAP
- Notably, this catalyst did not catalyse the previously described addition to nitro-alkenes

Evans, D. A.; Thompson, R. J.; Franco, F. *J. Am. Chem. Soc.* **2005**, *127*, 10816.

Enantioselective Conjugate Additions using Nickel Catalysis

Successful Applications

- A greater breadth of scope has been demonstrated using a Ni-DBFOX catalyst system



- All examples have an auxiliary capable of chelating to Ni as a fundamental feature

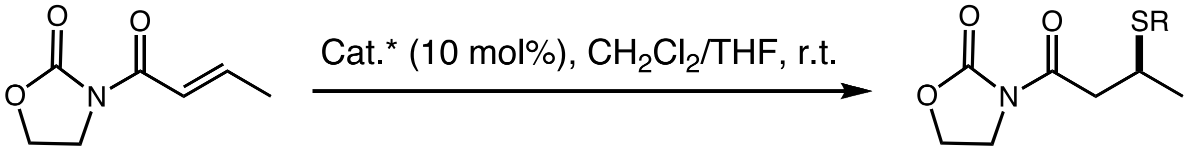
DBFOX developed by Kanemasa, see: *J. Org. Chem.* **1997**, *62*, 6454 (Diels-Alder)
First use in conjugate additions, see: *J. Am. Chem. Soc.* **1999**, *121*, 8675.

Enantioselective Conjugate Additions using Nickel Catalysis

Successful Applications

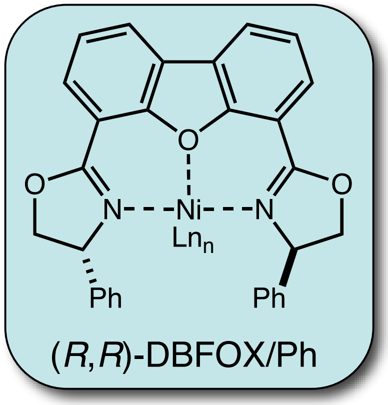
- Several highly enantioselective procedures have been developed

Conjugate addition of thiols



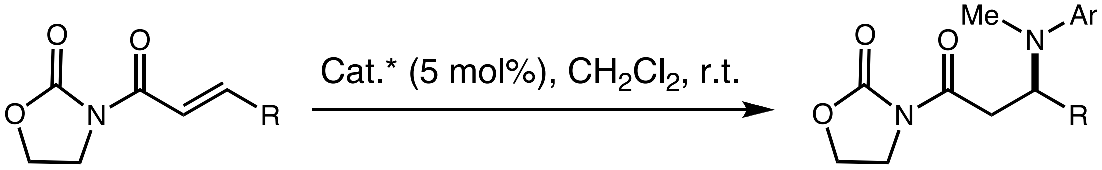
26-100% yield
78-97% ee

Kanemasa, S.; Oderatohi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675.



(*R*,*R*)-DBFOX/Ph

Conjugate addition of amines



6-93% yield
0-96% ee

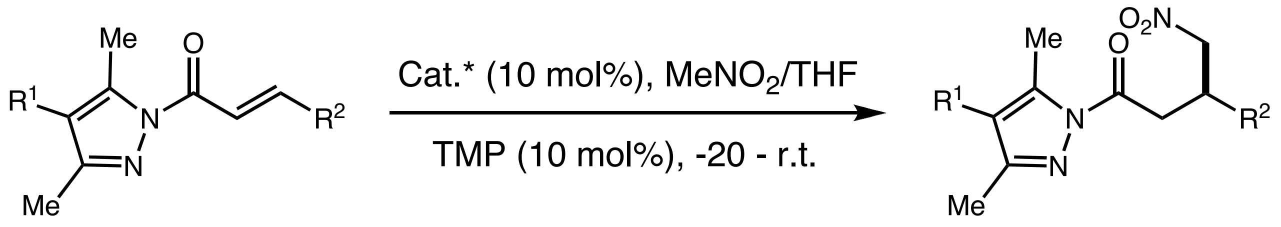
Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240.

Enantioselective Conjugate Additions using Nickel Catalysis

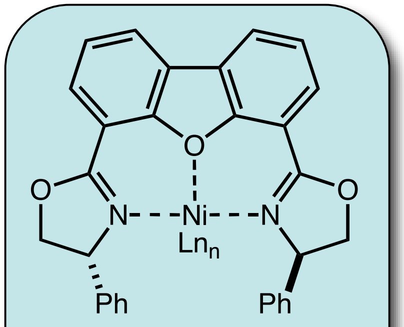
Successful Applications

- Several highly enantioselective procedures have been developed

Conjugate addition of nitromethane



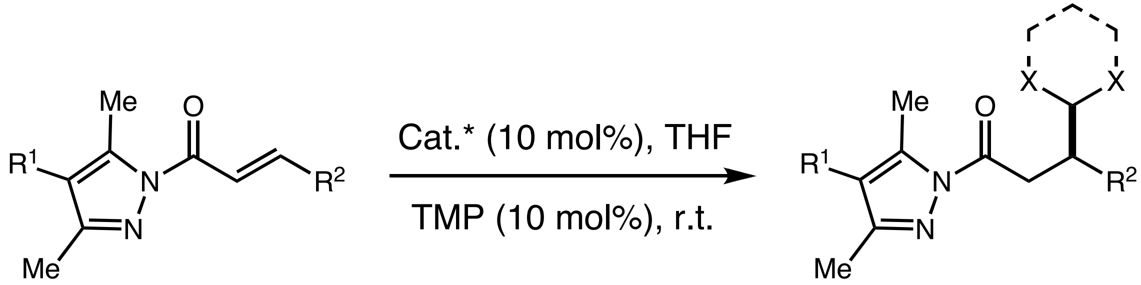
39-97% yield
77-98% ee



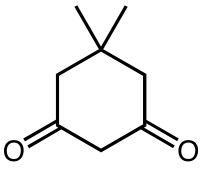
(*R*,*R*)-DBFOX/Ph

Itoh, K.; Kanemasa, S.; Oderatohi, Y *J. Am. Chem. Soc.* **2002**, *124*, 13394.

Conjugate addition of 1,3-dicarbonyls/1,3-dicarbonyl equivalents

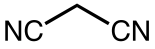


(a)



53-99% yield
89-99% ee

(b)



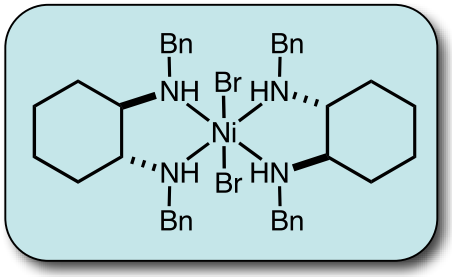
78-94% yield
55-93% ee

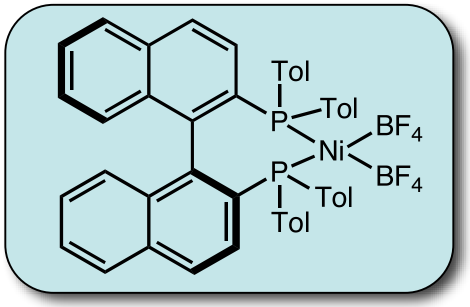
(a) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005**, *7*, 979.
(b) Itoh, K.; Kanemasa, S.; Oderatohi, Y *Tetrahedron Asymm.* **2003**, *14*, 635.

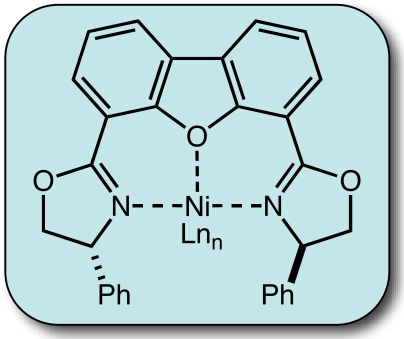
Enantioselective Conjugate Additions using Nickel Catalysis

Overview

- Ni-catalysis of enantioselective conjugate additions has been known for 20 years
- To date, no broadly utilisable procedure has been developed
- Many other ligands have been assessed in the benchmark reactions but have limited scope
- Evans' protocols are robust but tend to be substrate specific
- Kanemasa-type procedures offer better scope but efficiency and selectivity varies
- Ni-catalysis field is very much open for research







Catalytic Enantioselective Conjugate Addition Reactions

Transition Metal Catalysts - Copper

^{29}Cu

Seminal work:

(a) Villacorta, G. M.; Rao, Ch. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175.
(b) Ahn, K. H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178.
(c) Desimoni, G.; Quadrelli, P.; Righetti, P. P. *Tetrahedron* **1990**, *46*, 2927.

Reviews:

(a) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407.
(b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, **33**, 325.
(c) Alexakis, A.; Benhaim, C. Eur. *J. Org. Chem.* **2002**, 3221.

Enantioselective Conjugate Addition using Copper Catalysis

Historical Perspective

- 1923: Reich prepares the first organocopper reagent (PhCu)

Reich, *J. Compt. Rend.* **1923**, *177*, 322.

- 1936: Gilman realises the utility of organocopper species for organic synthesis

Gilman, H.; Straley, J. M. *Rec. Trav. Chem.* **1936**, *55*, 821.

- 1941: Kharasch provides evidence for Cu halides promotion of conjugate additions

Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.

- 1972: Saegusa describes conjugate additions under Cu-catalysis

Saegusa, T.; Ito, Y.; Tomita, S.; Kinoshita, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 496.

- 1988: Lippard describes the first Cu-catalysed enantioselective conjugate addition of RMgX

Villacorta, G. M.; Rao, Ch. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175.

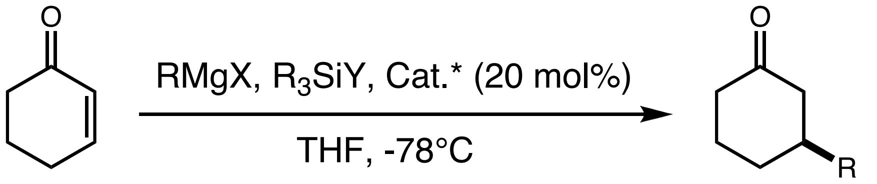
- 1990: Desimoni describes the first Cu Lewis acid catalysed enantioselective conjugate addition

Desimoni, G.; Quadrelli, P.; Righetti, P. P. *Tetrahedron* **1990**, *46*, 2927.

Enantioselective Conjugate Addition using Copper Catalysis

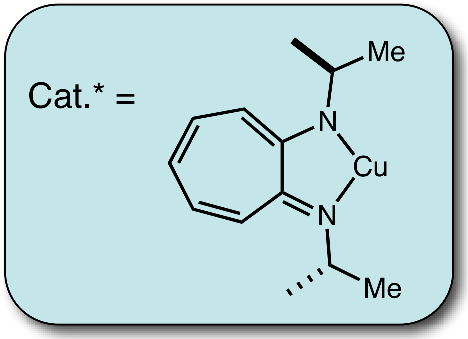
Historical Perspective

Lippard's system


RMgX, R_3SiY, Cat.* (20 mol%)

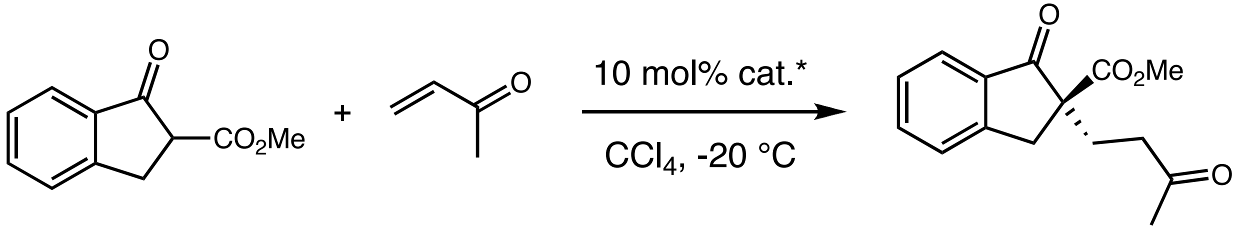
THF, -78°C

26->98% yield
-72-78% ee



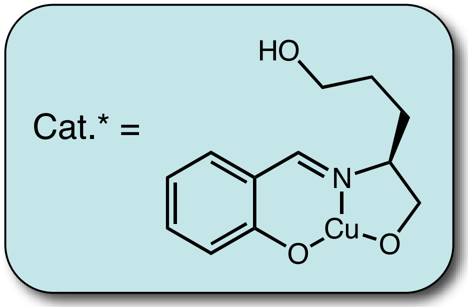
Ahn, K. H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178.

Desimoni's system


10 mol% cat.*

CCl_4, -20 °C

100%, 69% ee



Desimoni, G.; Quadrelli, P.; Righetti, P. P. *Tetrahedron* **1990**, *46*, 2927.

Enantioselective Conjugate Addition using Copper Catalysis

Development

- Following these initial studies, chiral copper complexes became an attractive area of research
- The development of improved chiral ligands was an major focus for several research groups


Feringa


Pfaltz


Chan


Reetz


Evans


Waldmann


Alexakis

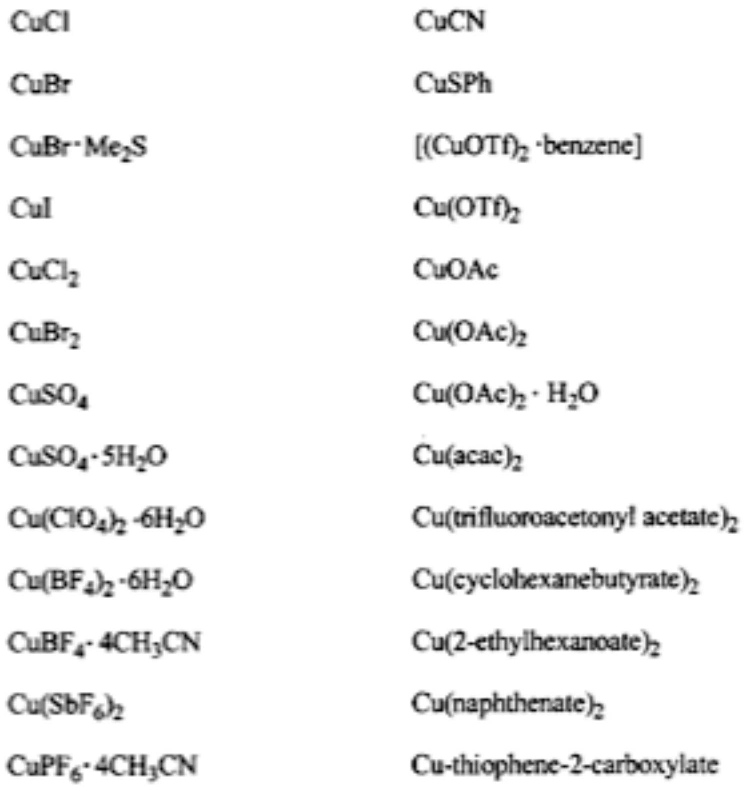

Woodward


Zhang

Enantioselective Conjugate Addition using Copper Catalysis

Development

- A variety of copper sources have been used



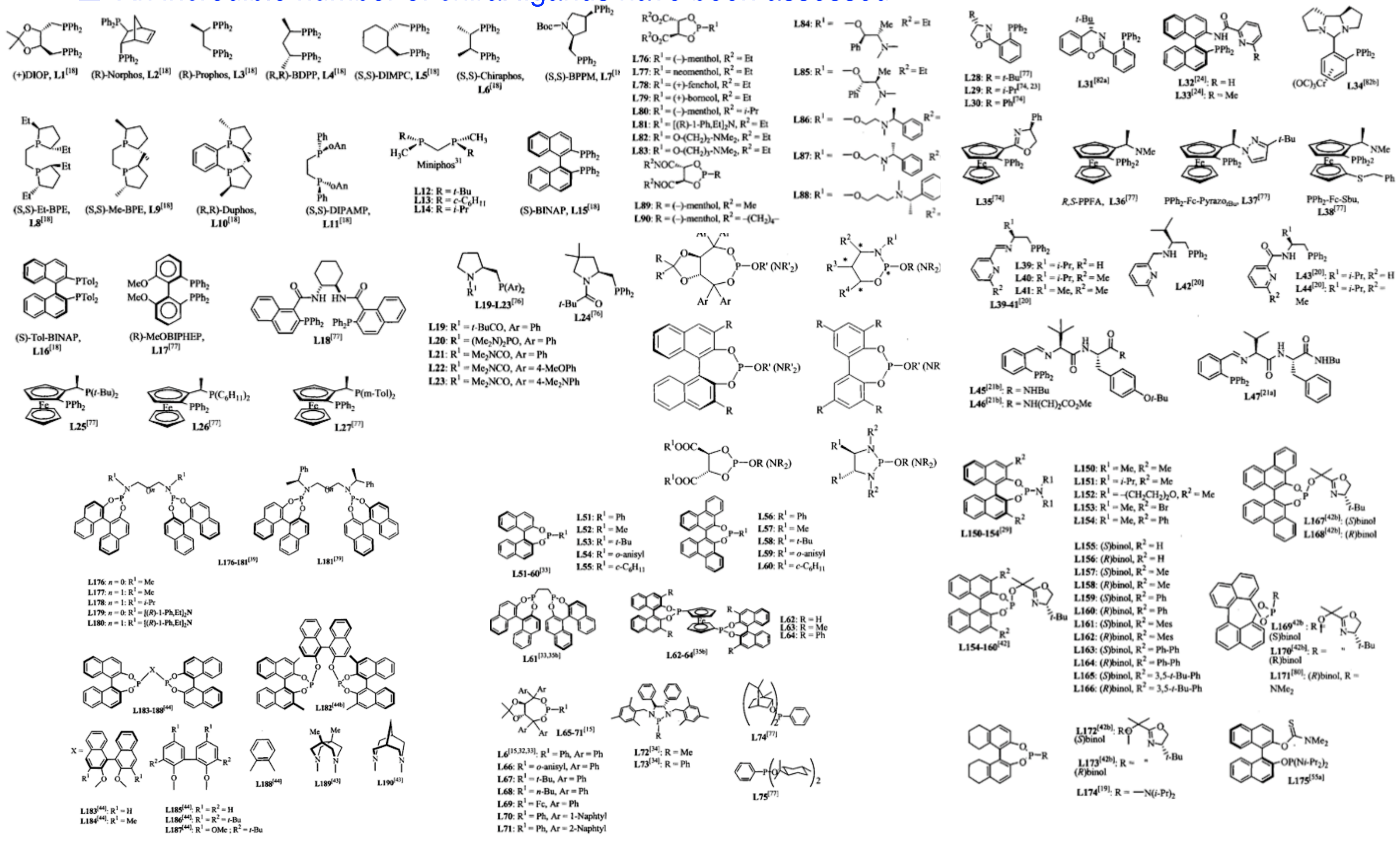
$CuCl$
$CuBr$
$CuBr \cdot Me_2S$
CuI
$CuCl_2$
$CuBr_2$
$CuSO_4$
$CuSO_4 \cdot 5H_2O$
$Cu(ClO_4)_2 \cdot 6H_2O$
$Cu(BF_4)_2 \cdot 6H_2O$
$CuBF_4 \cdot 4CH_3CN$
$Cu(SbF_6)_2$
$CuPF_6 \cdot 4CH_3CN$
$CuCN$
$CuSPh$
$[(CuOTf)_2 \cdot \text{benzene}]$
$Cu(OTf)_2$
$CuOAc$
$Cu(OAc)_2$
$Cu(OAc)_2 \cdot H_2O$
$Cu(acac)_2$
$Cu(\text{trifluoroacetonyl acetate})_2$
$Cu(\text{cyclohexanebutyrate})_2$
$Cu(\text{2-ethylhexanoate})_2$
$Cu(\text{naphthenate})_2$
Cu-thiophene-2-carboxylate

Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.

Enantioselective Conjugate Addition using Copper Catalysis

Development

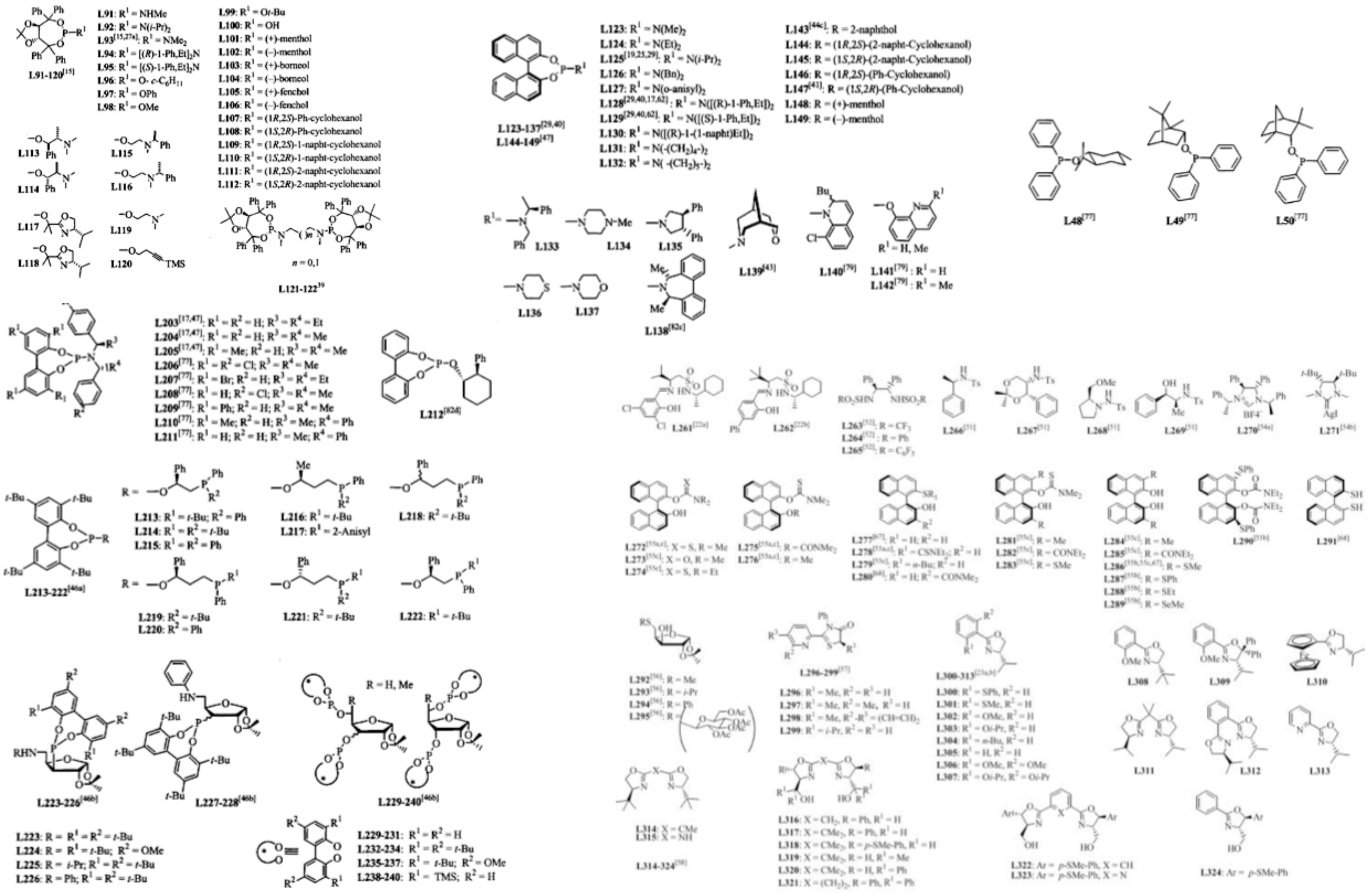
- An incredible number of chiral ligands have been assessed



Enantioselective Conjugate Addition using Copper Catalysis

Development

- An incredible number of chiral ligands have been assessed



Enantioselective Conjugate Addition using Copper Catalysis

Development

- The most successful/widely utilised copper salts and ligands

Copper Salts

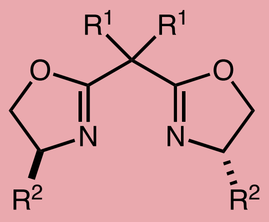
$Cu(OTf)_2$

$Cu(OAc)_2.H_2O$

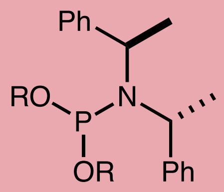
CuTc

$Cu(naphenate)_2$

Chiral Ligands



Bis(oxazoline) ligands



Phosphoramidite ligands

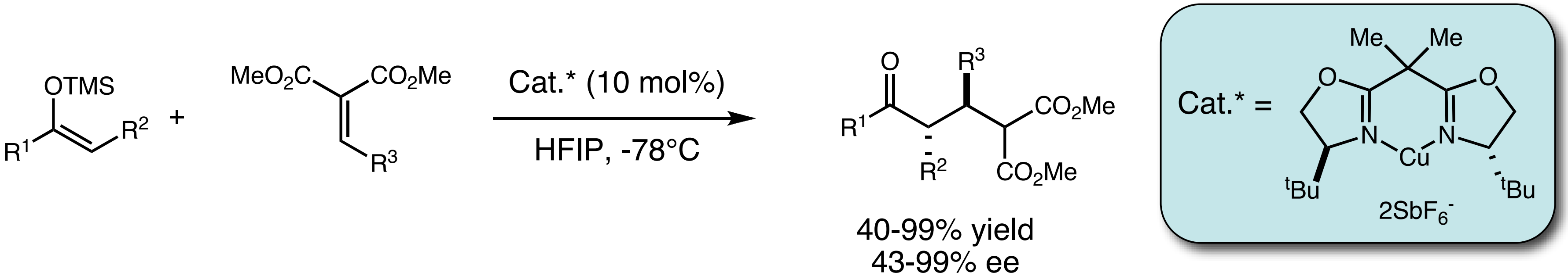
Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.

Enantioselective Conjugate Additions using Copper Catalysis

Cu Bis(oxazoline) Complexes

- Bis(oxazoline) ligands have shown broad scope in asymmetric synthesis
- Cu-box complexes have provided several highly enantioselective conjugate addition procedures

Mukaiyama-Michael Processes



40-99% yield
43-99% ee

(a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994.
(b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134.
(c) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.
See also: Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865.

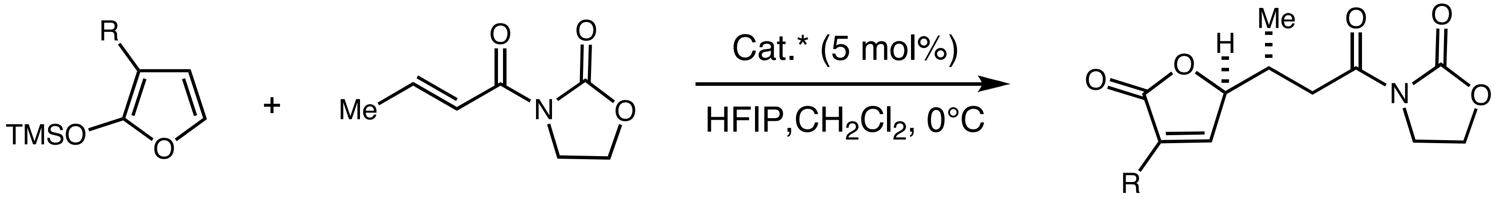
For a review on the semicorrinato and related ligands, see: Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

Enantioselective Conjugate Additions using Copper Catalysis

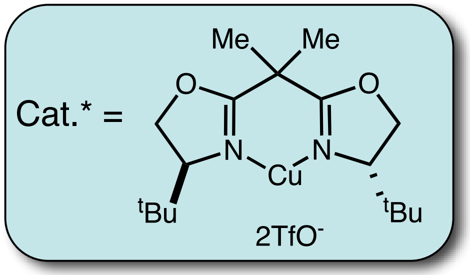
Cu Bis(oxazoline) Complexes

- Katsuki used a similar approach to prepare butenolide derivatives

Butenolide Synthesis



89-95% yield
8.5:1-24:1 *anti*:*syn*
91-95% ee

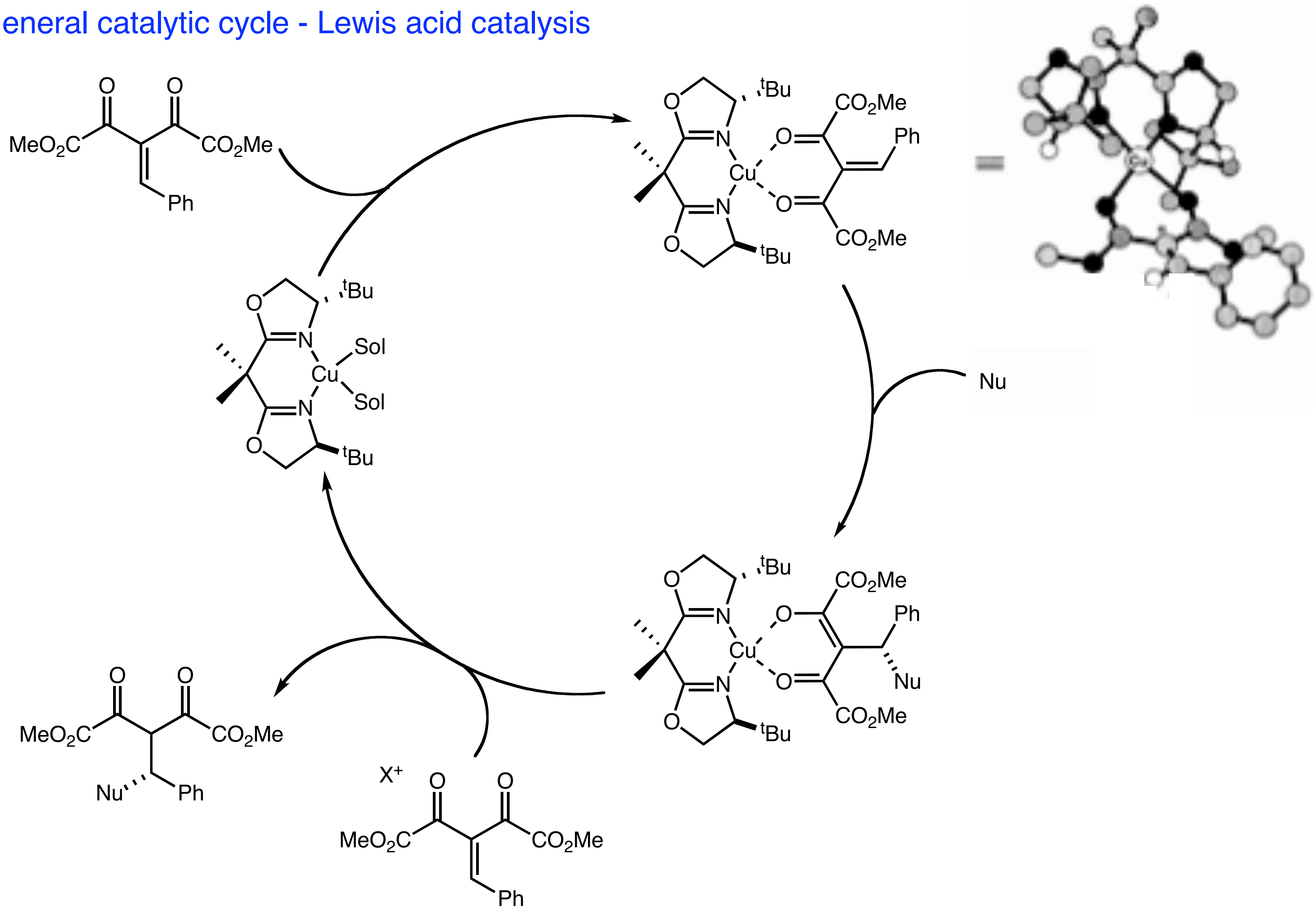


Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568.
See also: (a) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015.
(b) Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921.

Enantioselective Conjugate Additions using Copper Catalysis

Catalytic Cycle

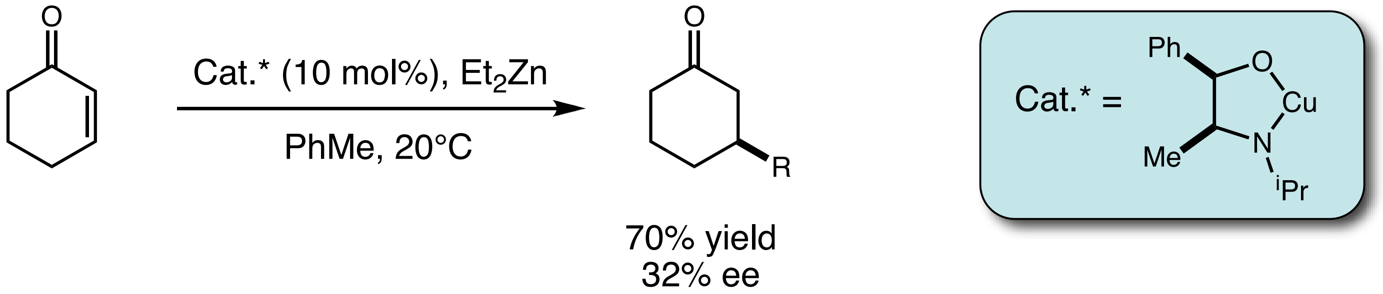
- General catalytic cycle - Lewis acid catalysis



Enantioselective Conjugate Additions using Copper Catalysis

Historical Perspective

- A major breakthrough was realised by Alexakis in 1993
- Previously Grignard reagents were utilised - reactivity problems
- Alexakis introduced R_2Zn - less reactive, more selective conjugate addition processes



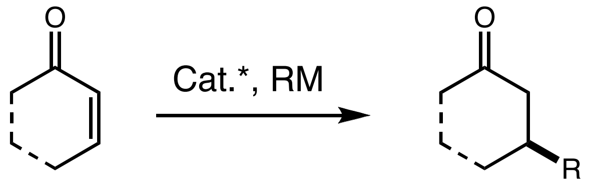
Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron Asymm.* **1993**, *4*, 2427.

- Most chemists subsequently adopted this method
- An enormous number of publications ensued - ligand optimisation

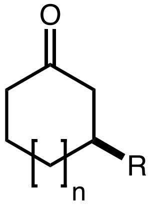
Enantioselective Conjugate Additions using Copper Catalysis

Cu-catalysed RM Addition

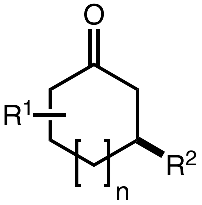
General scheme



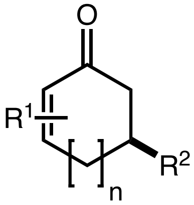
Conjugate acceptor scope



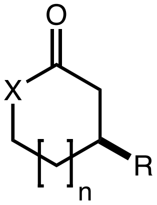
n = 0,1,2,3,10
7->98% ee



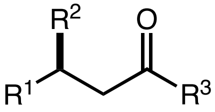
n = 0,1,2
65->99% ee



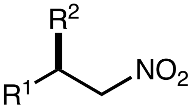
n = 0,1,2
65->99% ee



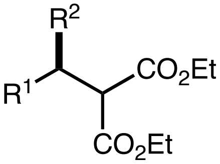
n = 0,1,2
56-92% ee



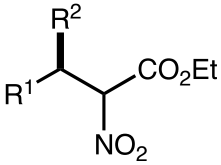
R^1 = alkyl, aryl, heteroaryl
R^3 = alkyl, aryl, heteroaryl
18-97% ee



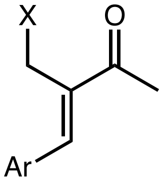
R^1 = alkyl, aryl, heteroaryl
23-95% ee



R^1 = alkyl, aryl
64-73% ee



R^1 = alkyl, aryl, heteroaryl
2-26% ee



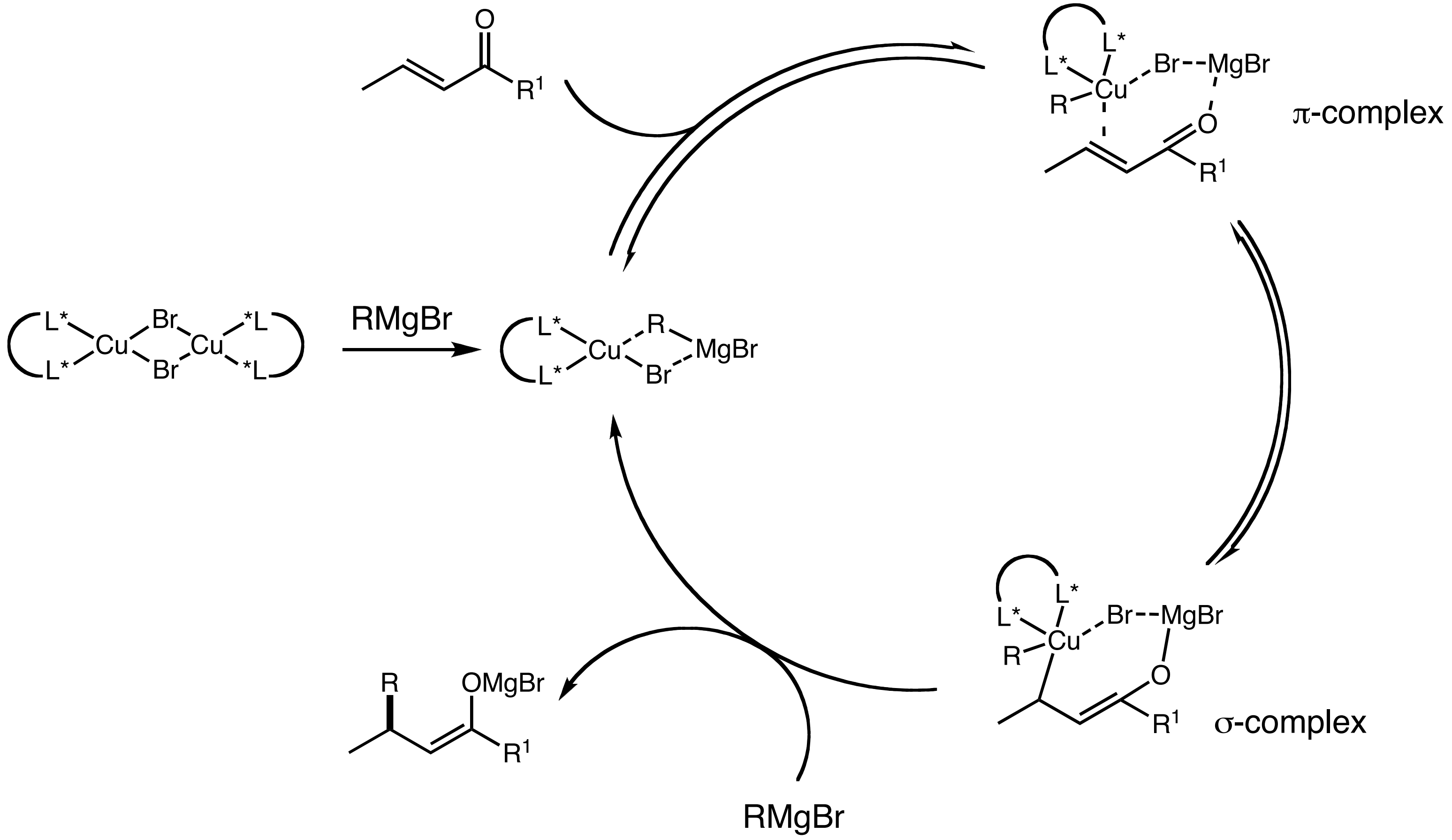
X = Cl, Br, OCHO, OSO_2Me
2-64% ee

Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221

Enantioselective Conjugate Additions using Copper Catalysis

Catalytic Cycle

■ General catalytic cycle - use of RMgX

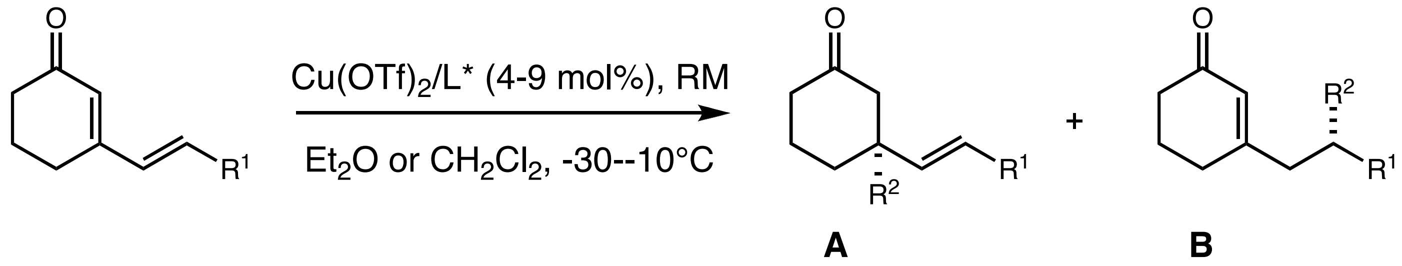


Feringa *et al. J. Am. Chem. Soc.* **2006**, *128*, 9103.

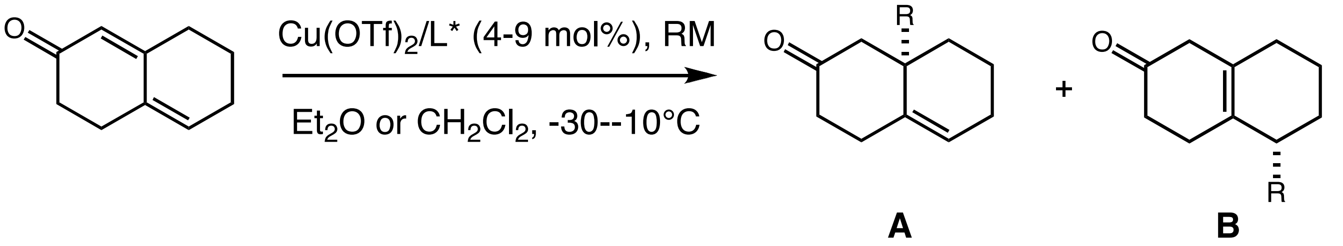
Enantioselective Conjugate Additions using Copper Catalysis

Recent Developments

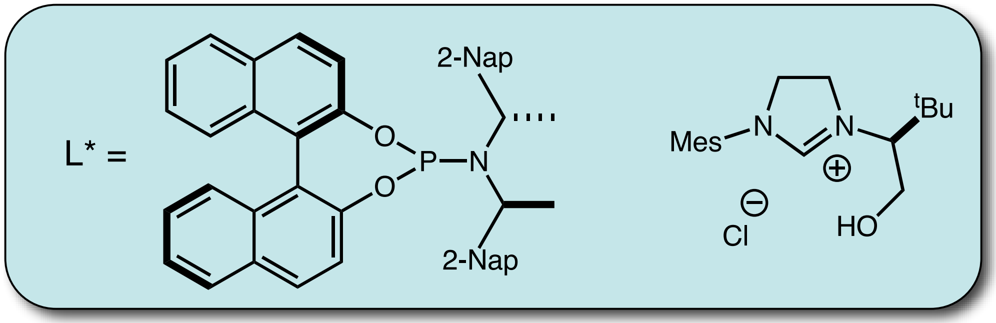
- 1,6-Additions have recently received renewed attention



25-67% yield
100:0-<1:99 **A**:**B**
68->99% ee



45-73% yield
100:0-2:98 **A**:**B**
11-96% ee

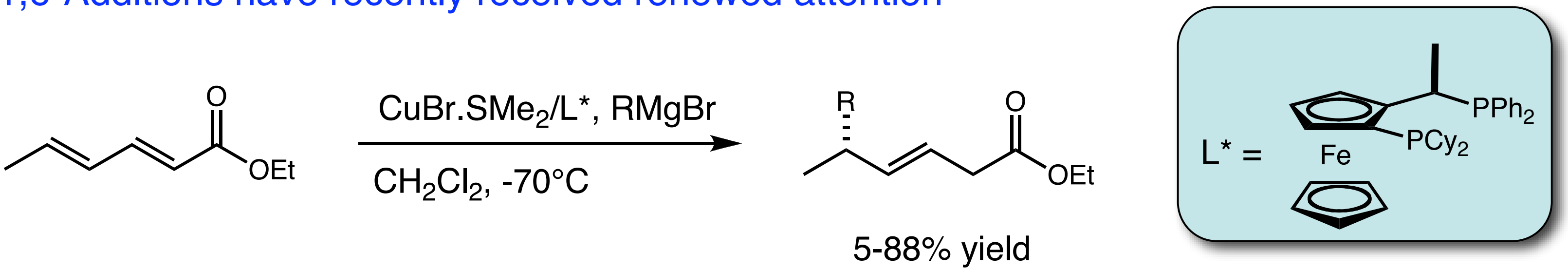


Henon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem. Int. Ed.* **2008**, *47*, Early View.

Enantioselective Conjugate Additions using Copper Catalysis

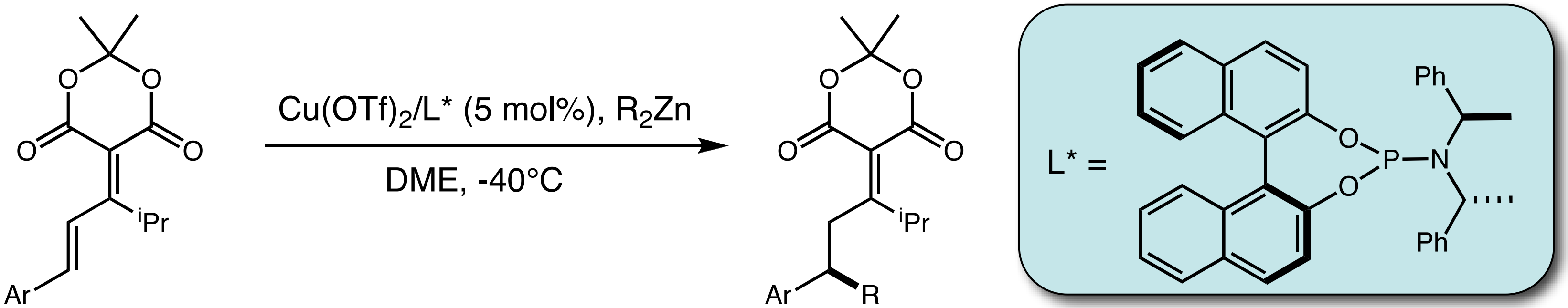
Recent Developments

- 1,6-Additions have recently received renewed attention



5-88% yield
>95:5 regioselectivity
73-97% ee

de Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 398.



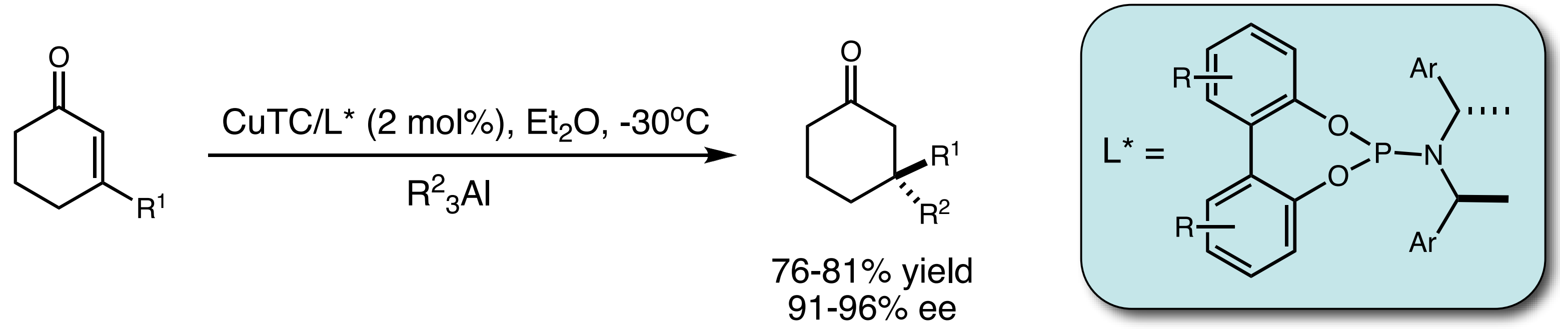
19-65% yield
60-84% ee

Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron Asymm.* **2006**, *17*, 2957.
See also: Henon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, Early View.

Enantioselective Conjugate Additions using Copper Catalysis

Recent Developments

- Quaternary centres can be easily accessed



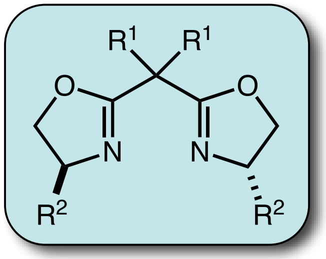
76-81% yield
91-96% ee

d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 398.
See also: d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647.
For a recent review, see: Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688.

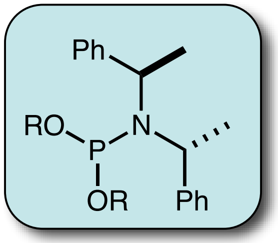
Enantioselective Conjugate Additions using Copper Catalysis

Overview

- Enantioselective conjugate addition using Cu catalysis has received unprecedented attention
- Broad scope of conjugate acceptor is offered
- Problems can be encountered using more reactive organometallics (RMgX)
- Using R_2Zn, side reactions are generally avoided
- However, only several R_2Zn reagents are available - nucleophile scope is limited
- R_3Al reagents can also be employed
- Evans/Katsuki-type Lewis acid catalysis offers an extension of substrate scope
- Cu catalysis continues to be developed - a more general solution may yet be found



Cu(II)



Catalytic Enantioselective Conjugate Addition Reactions

Transition Metal Catalysts - Zinc

^{30}Zn

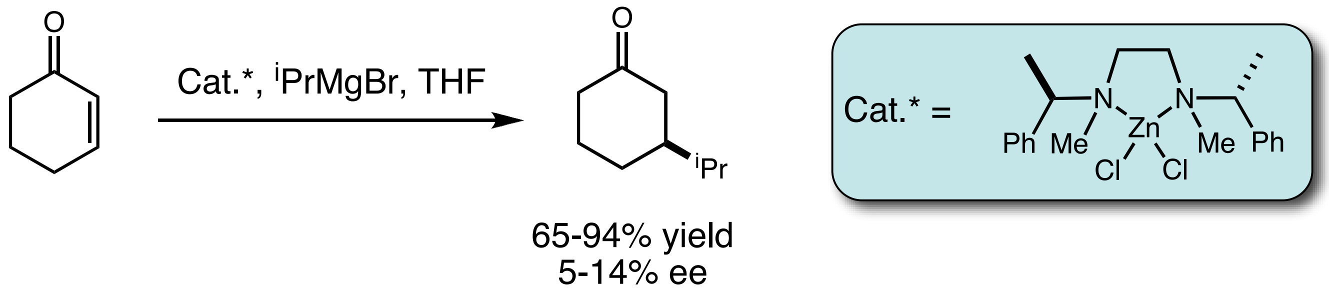
Seminal work:

(a) Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 3593.
(b) Jansen, J. F. G. A.; Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1989**, 741.
(c) Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1990**, *55*, 4168.
(d) Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95.

Enantioselective Conjugate Additions using Zinc Catalysis

Historical Perspective

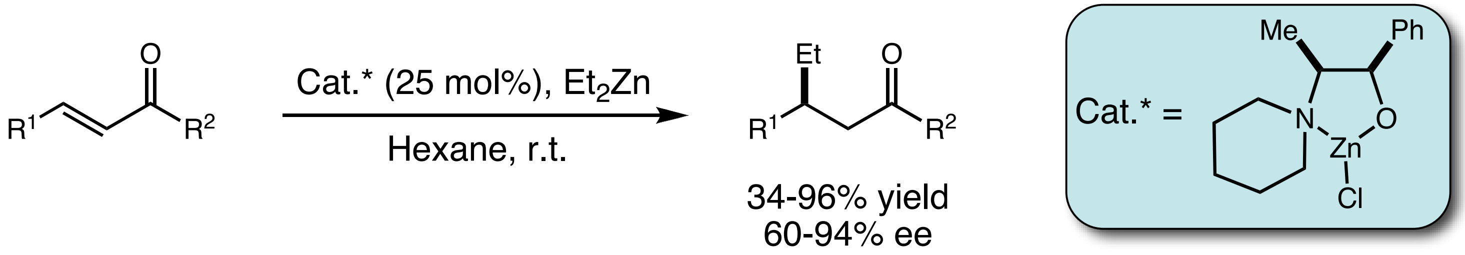
- Feringa described enantioselective zinc-catalysed conjugate additions in the late 1980's



65-94% yield
5-14% ee

Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 3593.

- Soai's method delivered much improved enantioselectivity



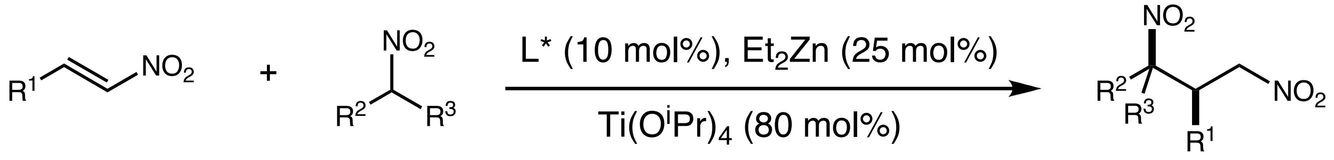
34-96% yield
60-94% ee

Soai, K.; Makoto, O.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95.

Enantioselective Conjugate Additions using Zinc Catalysis

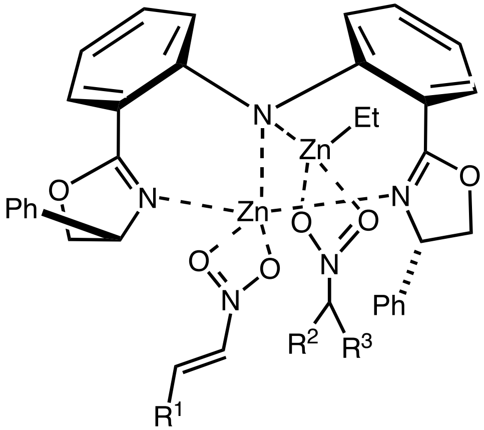
Development of Catalytic Systems

- Zhang developed bis(oxazoline) ligands to effect the addition of nitroalkanes

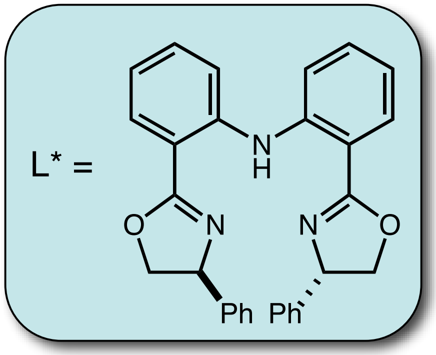


0-90% yield
3.4:1-11.7:1 dr
72-95% ee

- Proposed TS



re-face attack

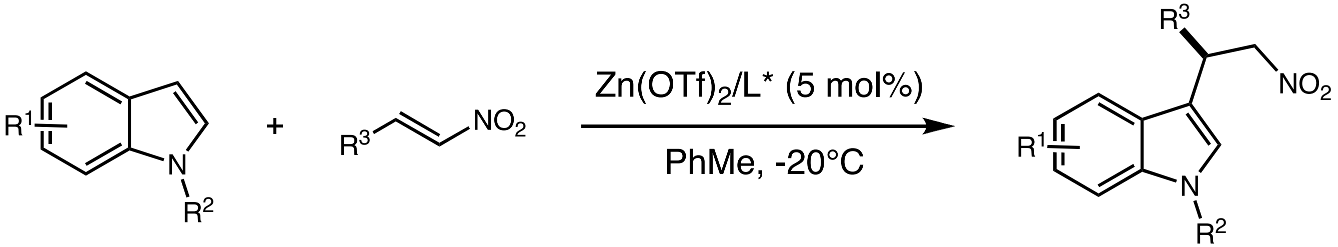


Lu, S.-F.; Du, D.-M.; Xu, J.; Zhang, S.-W. *J. Am. Chem. Soc.* **2006**, *128*, 7418.
For TS, see: *J. Org. Chem.* **2005**, *70*, 3712.

Enantioselective Conjugate Additions using Zinc Catalysis

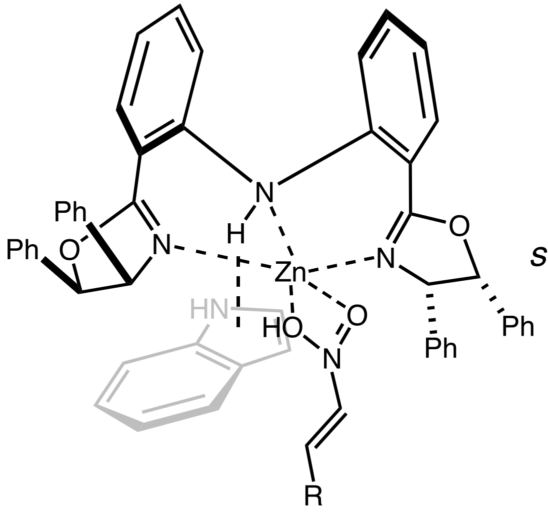
Development of Catalytic Systems

- Du utilised a similar approach to effect asymmetric Friedel-Crafts alkylations

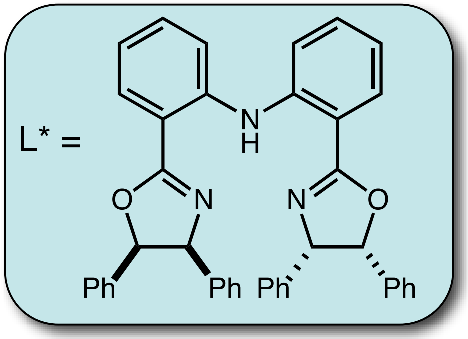


85-99% yield
73-98% ee

- Proposed TS



si-face attack

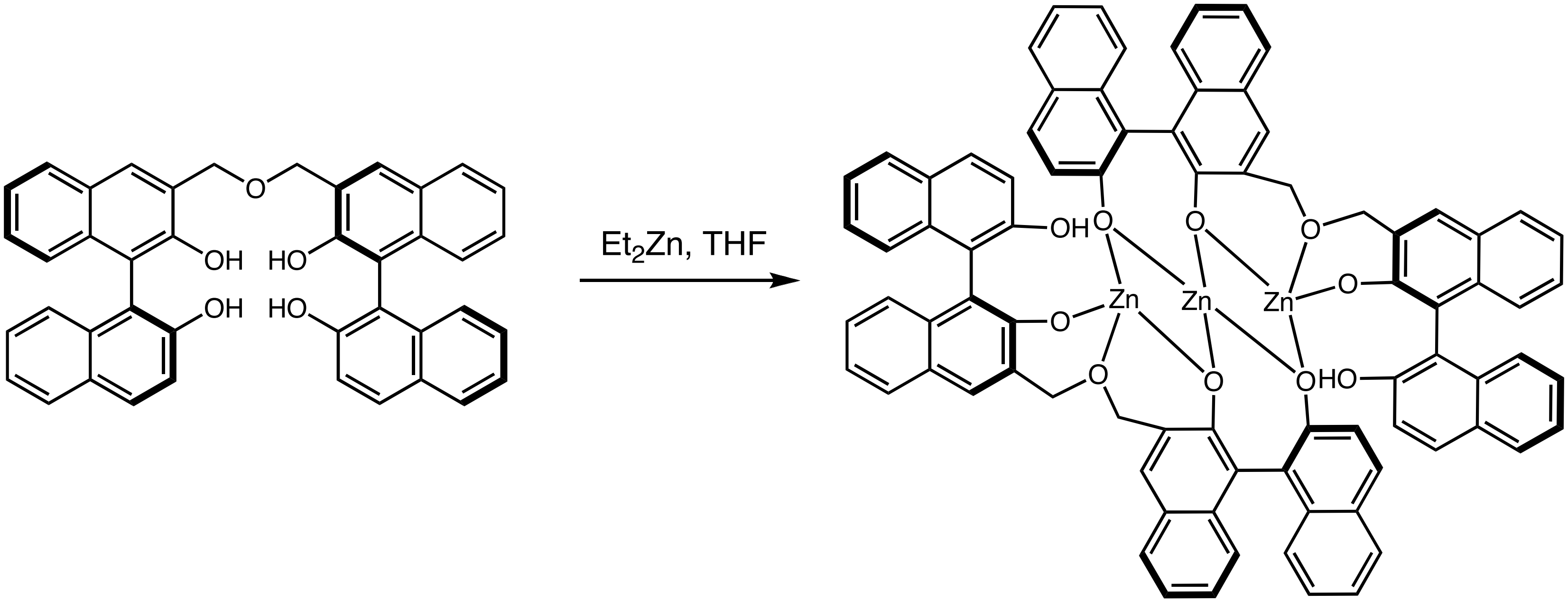


Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115.

Enantioselective Conjugate Additions using Zinc Catalysis

Development of Catalytic Systems

- Shibasaki developed Zn-analogues of the La-linked BINOL catalyst



- This catalyst has been successful in a series of conjugate addition processes

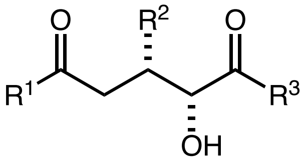
For reviews, see: (a) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269.
(b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3.

Enantioselective Conjugate Additions using Zinc Catalysis

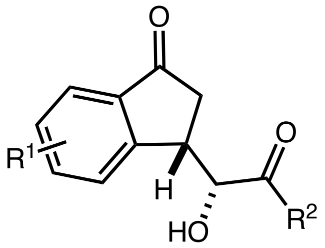
Development of Catalytic Systems

General scheme

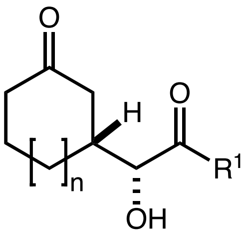
Substrate scope



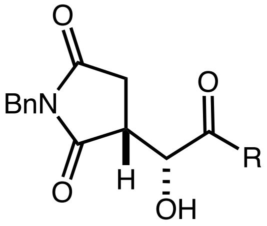
82-90% yield
73:27-84:16 dr
91-95% ee



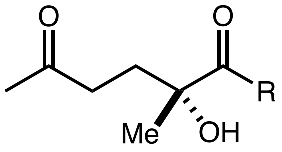
65-80% yield
97-99% ee



45-81% yield
>98:2 dr
85-98% ee



84% yield
94:6 dr
>99% ee



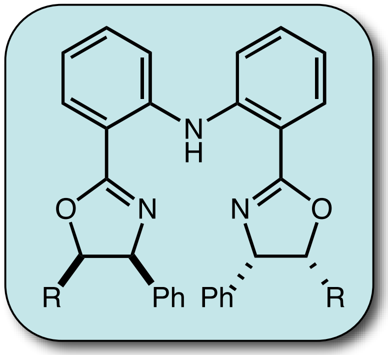
78-95% yield
90-96% ee

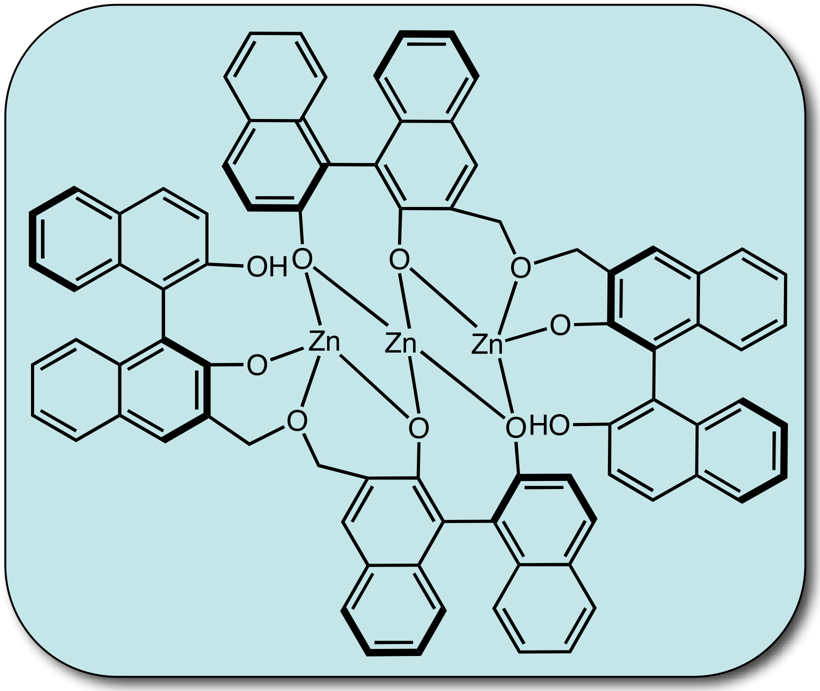
(a) *Org. Lett.* **2001**, *3*, 4251. (b) *J. Am. Chem. Soc.* **2003**, *125*, 2582. (c) *J. Am. Chem. Soc.* **2004**, *126*, 7559.

Enantioselective Conjugate Additions using Zinc Catalysis

Overview

- Enantioselective conjugate additions using Zn-catalysis began in the late 1980's
- Early attempts showed poor selectivity
- Most progress has been made since ~2000
- Of the progress made, Shibasaki's linked BINOL method has been most successful
- However, substrate specificity may impair further application





Catalytic Enantioselective Conjugate Addition Reactions

Transition Metal Catalysts - Rhodium

^{45}Rh

Seminal work:

(a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295.
(b) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439.
(c) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1995**, *36*, 6479.
(d) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.
(e) Takaya, Y.; Ogasawara, M.; Hayashi, H. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

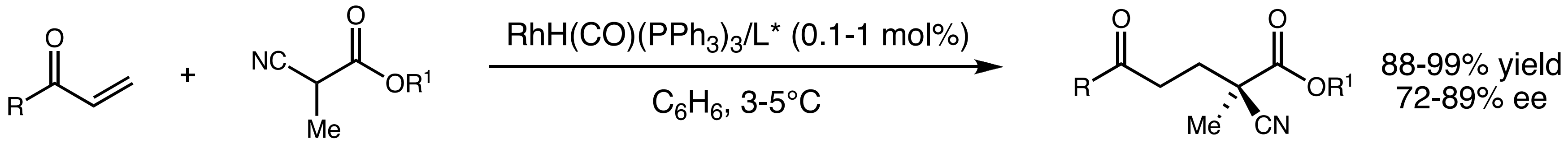
Reviews:

(a) Hayashi, T. *Synlett* **2001**, 879.
(b) Hayashi, T. Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.
(c) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Bull. Synth. Org. Chem. Jpn.* **2006**, *64*, 1112.

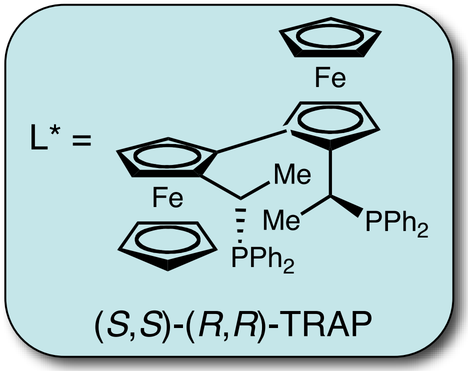
Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

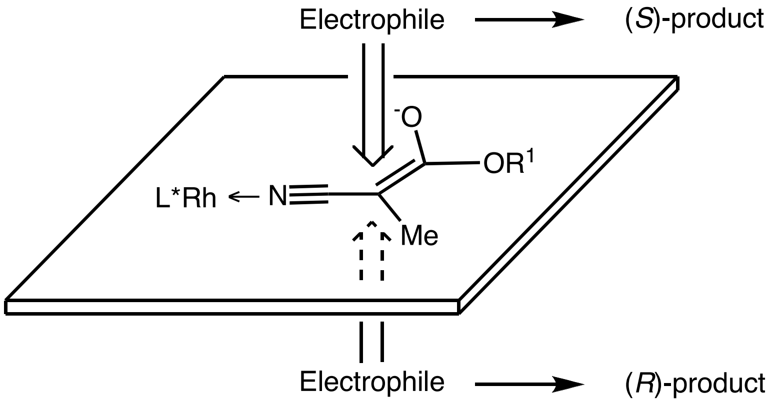
- The first highly enantioselective catalytic conjugate addition using Rh was described by Ito in 1992



Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295.



(*S*,*S*)-(*R*,*R*)-TRAP



- Cyano group essential (crystal structure obtained of achiral *N*-bound Rh complex)
- Remote enantiofacial differentiation due to concave chiral surround of *trans* ligand

See also: (a) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439.
(b) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1995**, *36*, 6479 (application to Weinreb amides).

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

- This area of research began from studies from Ito, Hayashi and Miyaura
- Most contributions in this area have come from the Hayashi group

Ito

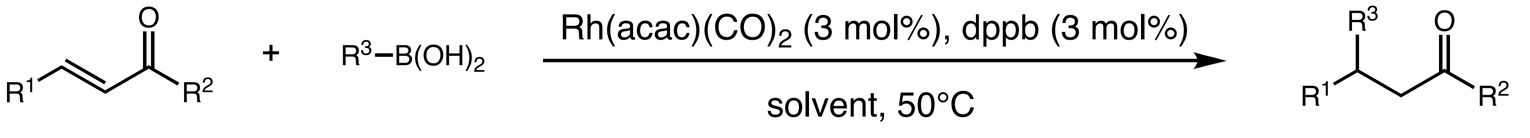
Hayashi

Miyaura

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

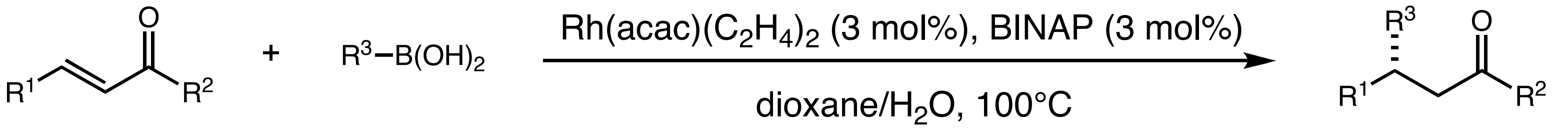
- Hayashi and Miyaura subsequently developed Rh-catalysed addition of organoboronic acids



up to 99% yield

Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

- Replacing dppb with a chiral phosphine (BINAP) results in an asymmetric protocol



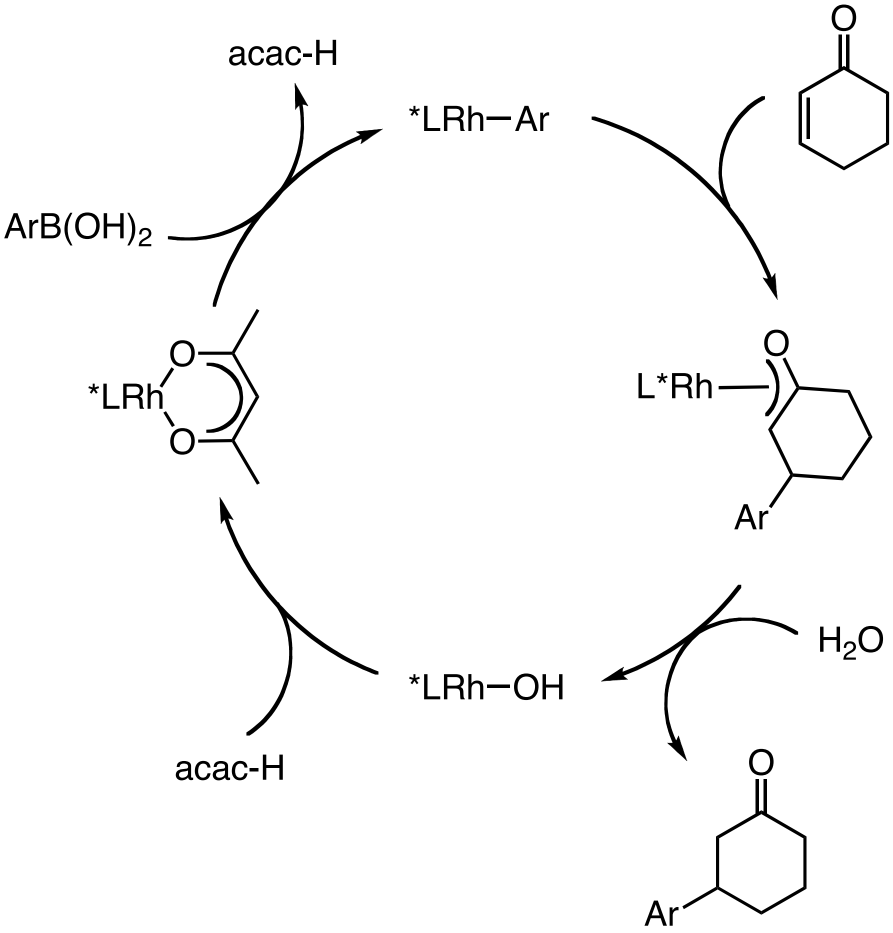
up to 99% yield
up to 99% ee

Takaya, Y.; Ogasawara, M.; Hayashi, H. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

- Studies towards elucidation of the catalytic cycle revealed a potentially faster catalyst system



J. Am. Chem. Soc. **2002**, *124*, 5052.

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

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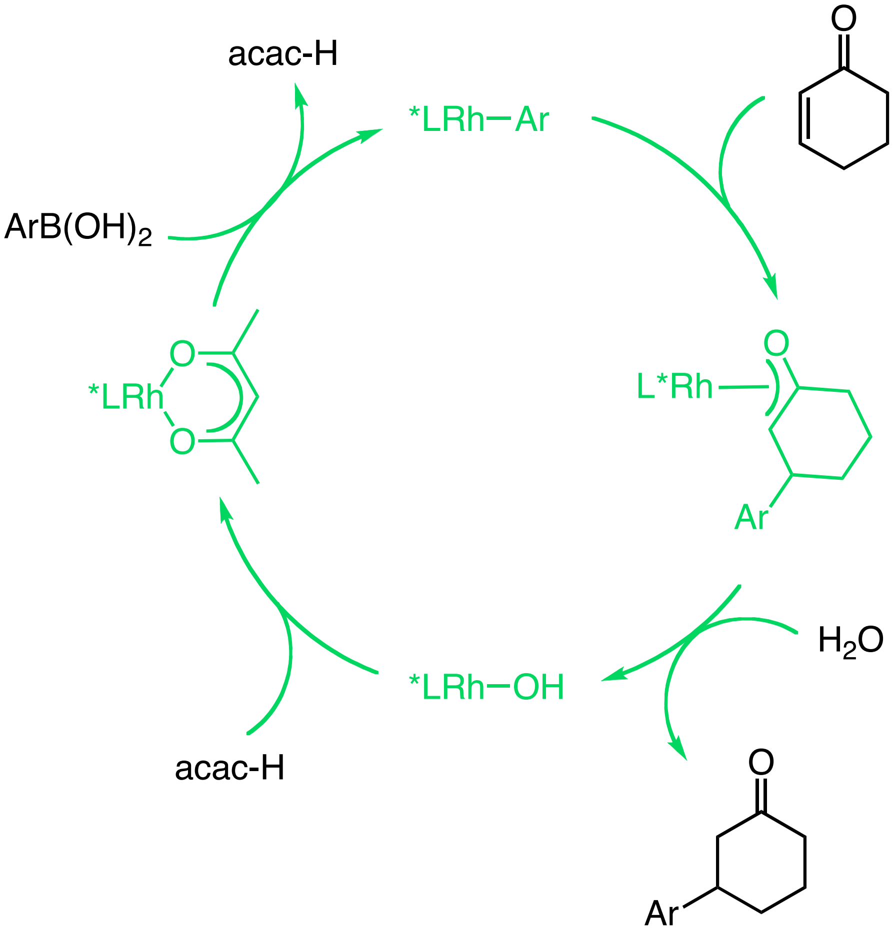

● = observed at 25°C

J. Am. Chem. Soc. **2002**, *124*, 5052.

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

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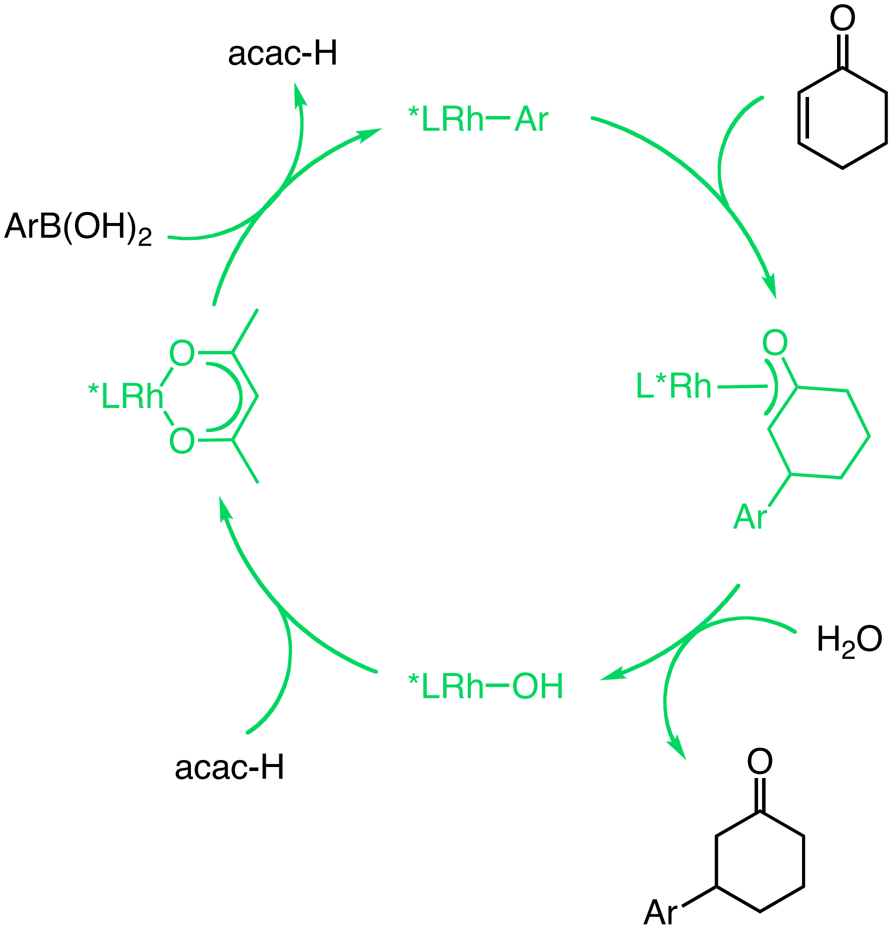

● = observed at 25°C

Why does the system require 100°C?

J. Am. Chem. Soc. **2002**, *124*, 5052.

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

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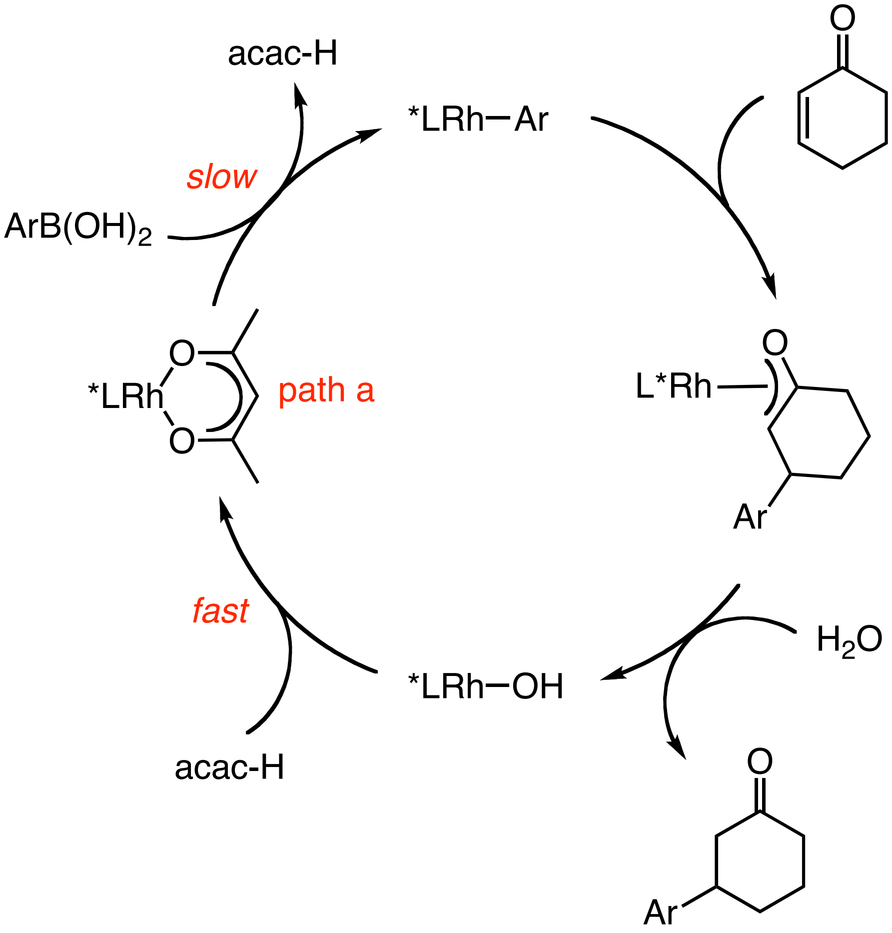

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J. Am. Chem. Soc. **2002**, *124*, 5052.

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

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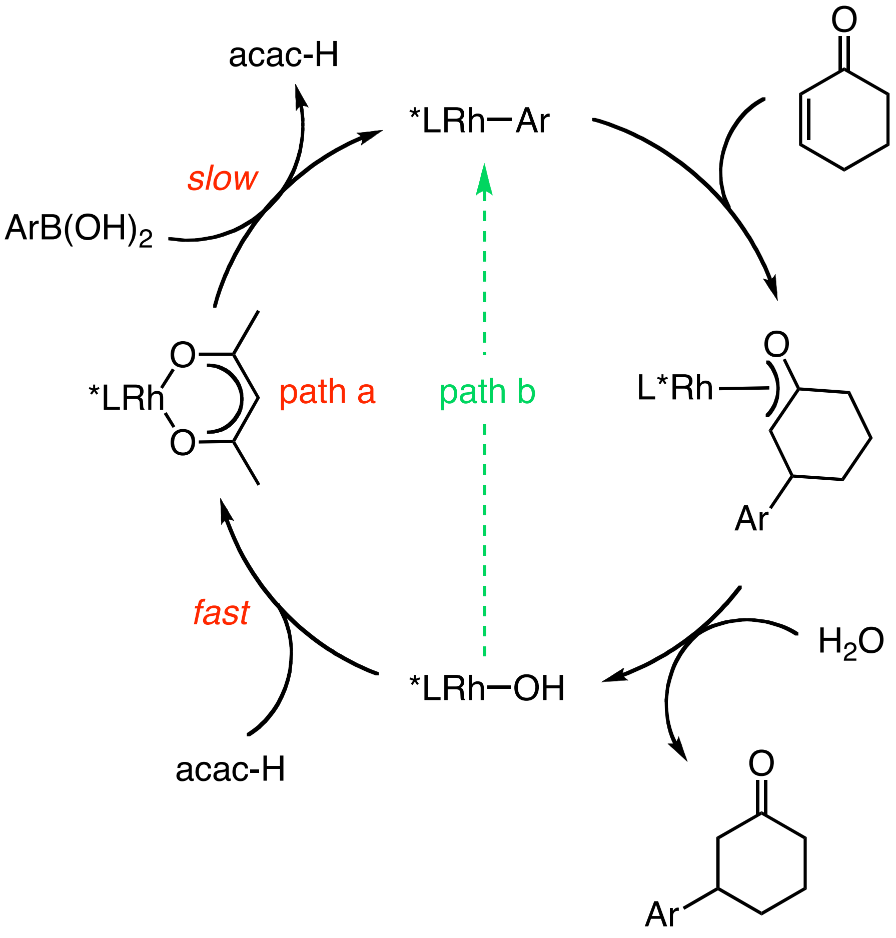


More efficient catalytic system?

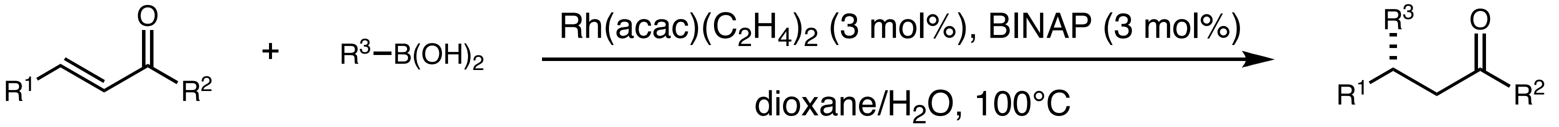
J. Am. Chem. Soc. **2002**, *124*, 5052.

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

- Using a hydroxo-rhodium complex, a more efficient system was developed

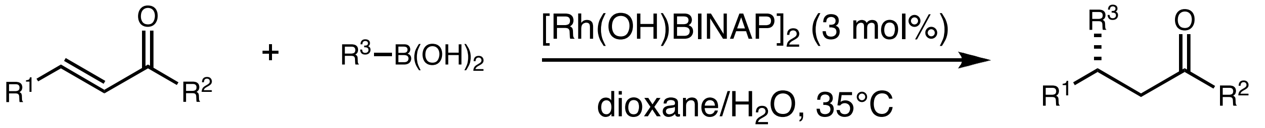
Original Rh(acac)-based system



up to 99% yield
up to 99% ee

Takaya, Y.; Ogasawara, M.; Hayashi, H. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

Improved Rh(OH)-based system



up to 98% yield
up to >99% ee

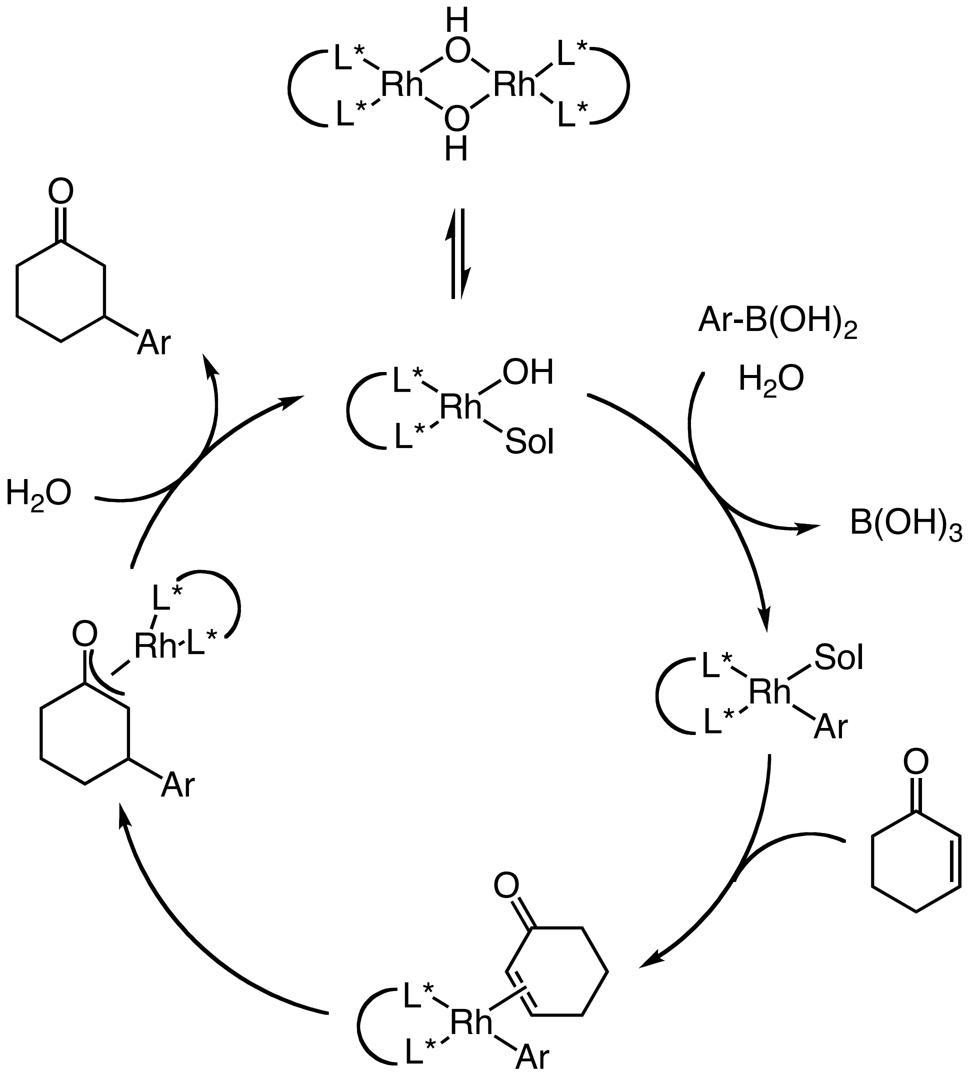
Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

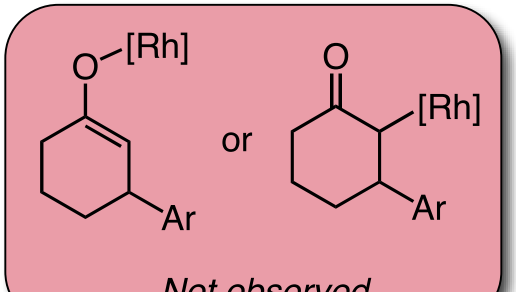
- Lower reaction temp. → less proto-deborylation → lowered quantities of boronic acid

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

- Hayashi's catalytic cycle





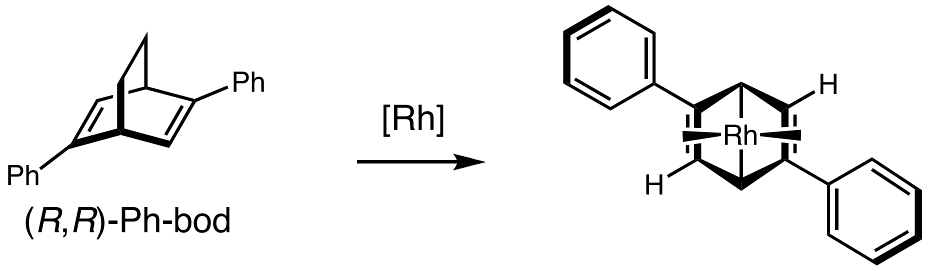
Not observed

(a) *J. Am. Chem. Soc.* **2002**, *124*, 5052. (b) *J. Am. Chem. Soc.* **2006**, *128*, 3904.

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

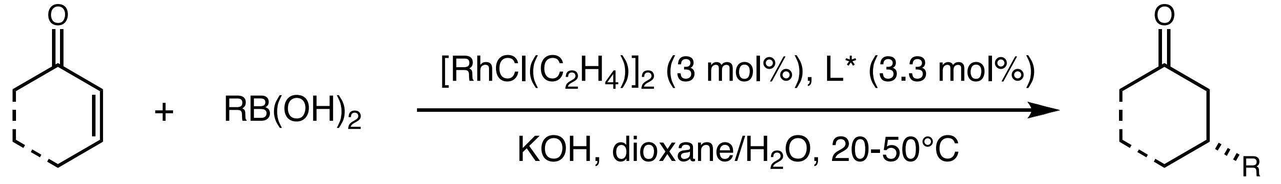
- Hayashi introduced a chiral diene as a ligand for Rh-catalysed conjugate addition processes



(*R*,*R*)-Ph-bod

J. Am. Chem. Soc. **2007**, *129*, 2130 and references therein.

- This ligand (and analogues) proved very successful, for example:

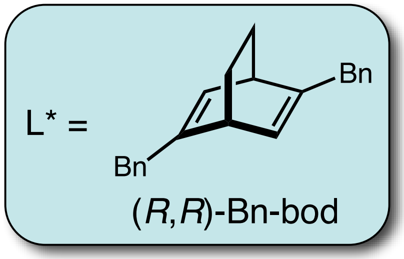


$RB(OH)_2$

$[RhCl(C_2H_4)]_2$ (3 mol%), L* (3.3 mol%)

KOH, dioxane/H_2O, 20-50°C

73-96% yield
88-99% ee



(*R*,*R*)-Bn-bod

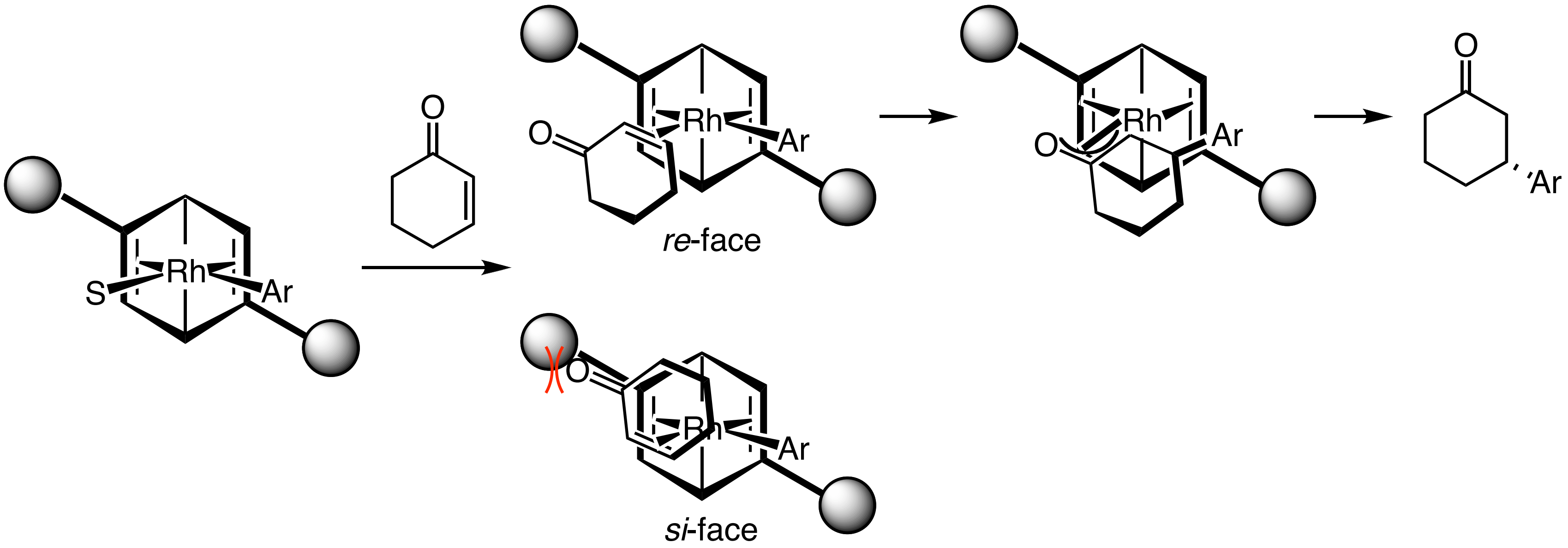
J. Am. Chem. Soc. **2003**, *125*, 11508.

- This provides an alternative approach to the use of chiral phosphines
- Often, when phosphine-based processes fail, diene catalysts can be effective (and vice versa)

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

- Hayashi's mechanism for the origin of enantioselectivity

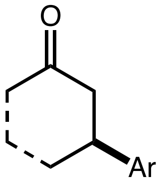


J. Am. Chem. Soc. **2003**, *125*, 11508.

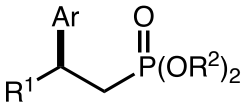
Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

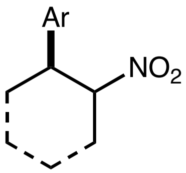
- Developments and extensions have led to a very useful catalytic system
- A range of conjugate acceptors are tolerated



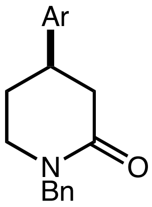
51->99% yield
91-99% ee
JACS **1998**, *120*, 5579.



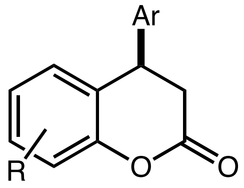
5-99% yield
84-99% ee
JACS **1999**, *121*, 11591.



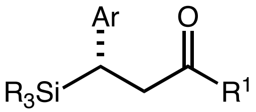
5-93% yield
17:83-89:11 *cis*:*trans*
38-99% ee
JACS **2000**, *122*, 10716.



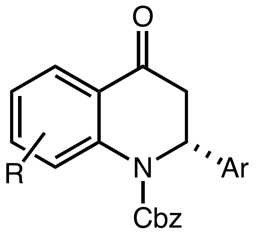
73-88% yield
97-99% ee
JOC **2001**, *66*, 6852.



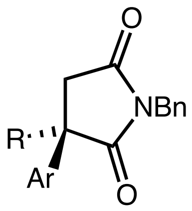
28-94% yield
>99% ee
OL **2005**, *7*, 2285.



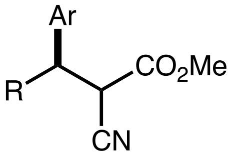
86-95% yield
93->99% ee
OL **2005**, *7*, 4757.



72-100% yield
86-99% ee
OL **2005**, *7*, 5317.



82-98% yield
90-98% ee
(81:19 - >98:2 regio)
JACS **2006**, *128*, 5628.



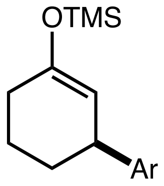
90-99% yield
96-99% ee
OL **2008**, *10*, 589.

Tandem conjugate addition/aldol sequence, see: *J. Am. Chem. Soc.* **2002**, *124*, 10984.

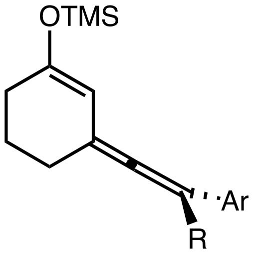
Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

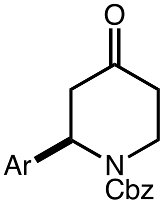
- Developments and extensions have led to a very useful catalytic system
- A range of nucleophiles can be employed



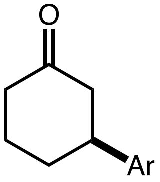
Using ArTi(O^{i}Pr)$_4$Li
62-84% yield
94->99% ee
JACS **2002**, *124*, 12102.



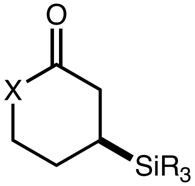
Using ArTi(O^{i}Pr)$_4$Li
60->99% yield
26-93% ee
OL **2004**, *6*, 305.
Angew. **2005**, *44*, 4224



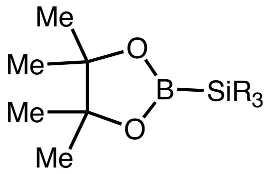
Using ArZnCl
87-100% yield
99->99% ee
JACS **2004**, *126*, 6240.
See also: *OL* **2005**, *7*, 2071.



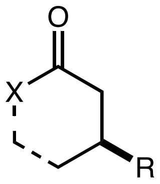
Using (ArBO)$_3$
79-100% yield
94-97% ee
OL **2006**, *8*, 341.



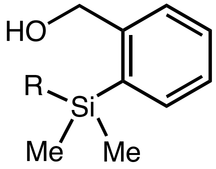
Using



22-70% yield
92-97% ee
Angew. **2006**, *45*, 5675.



Using



R = Ar/olefin

70-94% yield
86-99% ee
JACS **2007**, *129*, 9137.

Enantioselective Conjugate Addition using Rhodium Catalysis

Conjugate Addition of Organoboronic Acids

- Benefits of the Hayashi-Miyaura system

Rh(I) L*

- Readily available catalyst/chiral phosphine
- Readily available/bench stable nucleophiles
- Relatively mild/insensitive reaction conditions
- Approaching a "universal catalyst system"
- Tolerant of a wide variety of functional groups on nucleophile and conjugate acceptor
- Operates effectively with both linear and cyclic conjugate acceptors
- Effective with notoriously difficult cyclopentenone
- Nucleophile no longer restricted to organoboron species

Catalytic Enantioselective Conjugate Addition Reactions

Transition Metal Catalysts - Palladium

^{46}Pd

Seminal work:

(a) Cacchi, S.; La Torre, F.; Misiti, D. *Tetrahedron Lett.* **1979**, *20*, 4591.
(b) Cacchi, S.; Misiti, D.; Palmieri, G. *Tetrahedron* **1981**, *37*, 2941.
(c) Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2341.
(d) Ohe, T.; Wakita, T.; Motofusa, S.; Cho, C. S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2149.
(e) Ohe, T.; Uemura, S. *Tetrahedron Lett.* **2002**, *43*, 1269.
(f) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 111240.

Reviews:

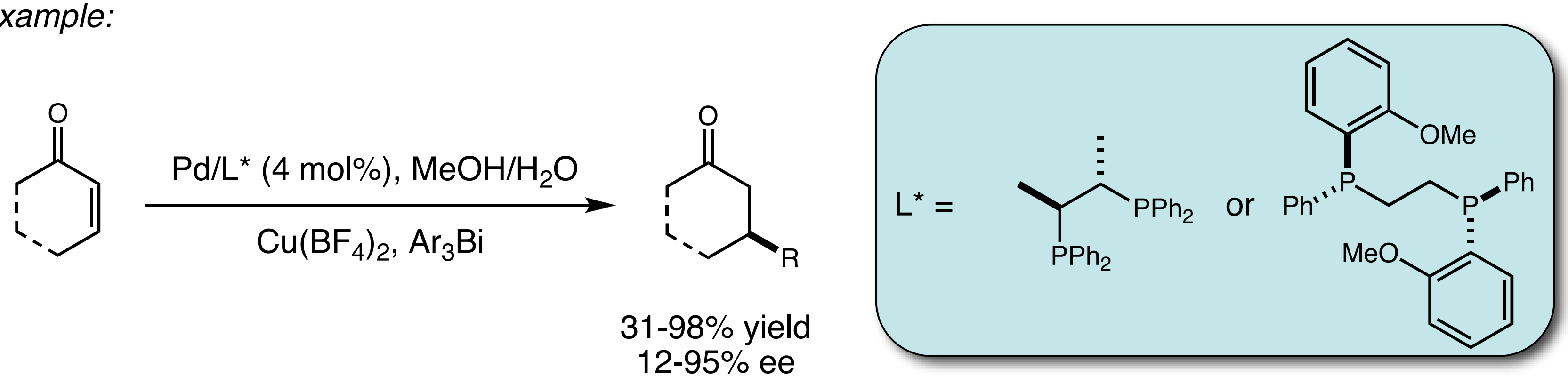
(a) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547.
(b) Hamashima, Y. *Chem. Pharm. Bull.* **2006**, *54*, 1351.
(c) Sodeoka, M. Hamashima, Y. *Pure Appl. Chem.* **2006**, *78*, 477.
(d) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Bull. Synth. Org. Chem. Jpn.* **2006**, *64*, 1112.

Enantioselective Conjugate Additions using Palladium Catalysis

Development of Efficient Catalyst Systems

- Conjugate additions using Pd-catalysis pioneered by Cacchi and Uemura
- Enantioselective processes are relatively new and are receiving much attention
- Following sucess with Rh, Miyaura employed Pd to effect enantioselective conjugate additions

For example:



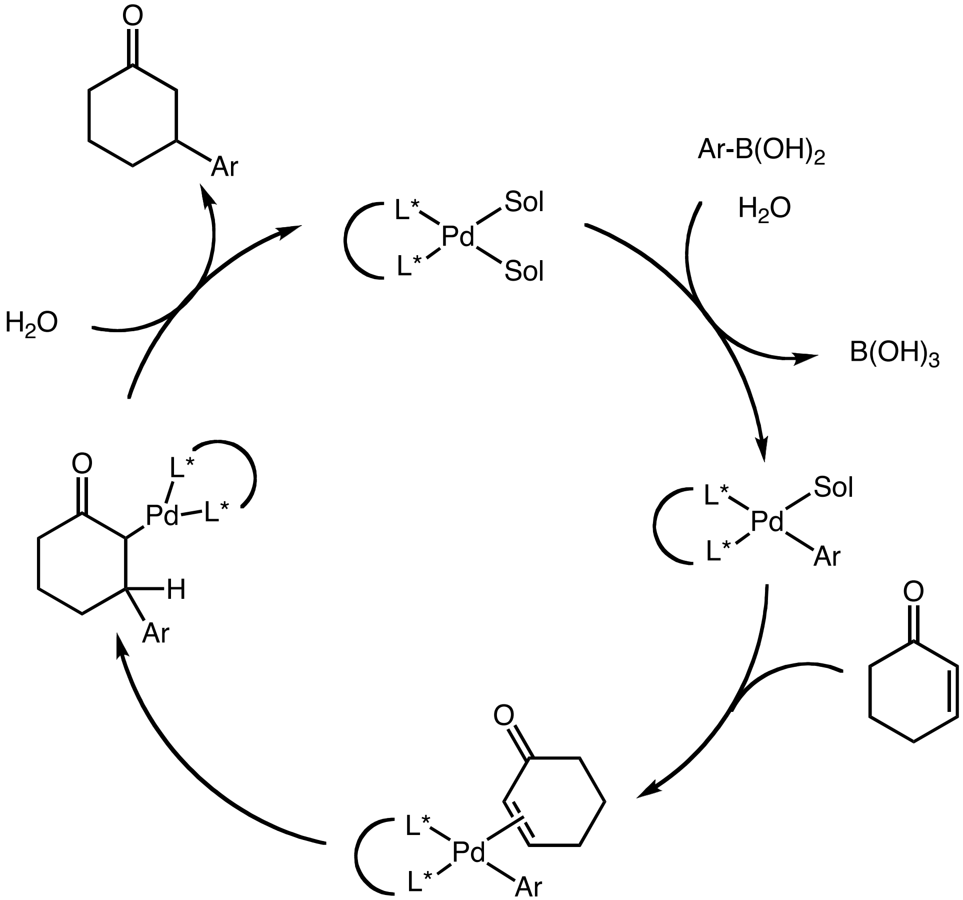
Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **2004**, 1822.
See also: Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2007**, 349, 1759.

- Research in this area has led to the development of a protocol complementary to Rh

Enantioselective Conjugate Additions using Palladium Catalysis

Development of Efficient Catalyst Systems

- General catalytic cycle

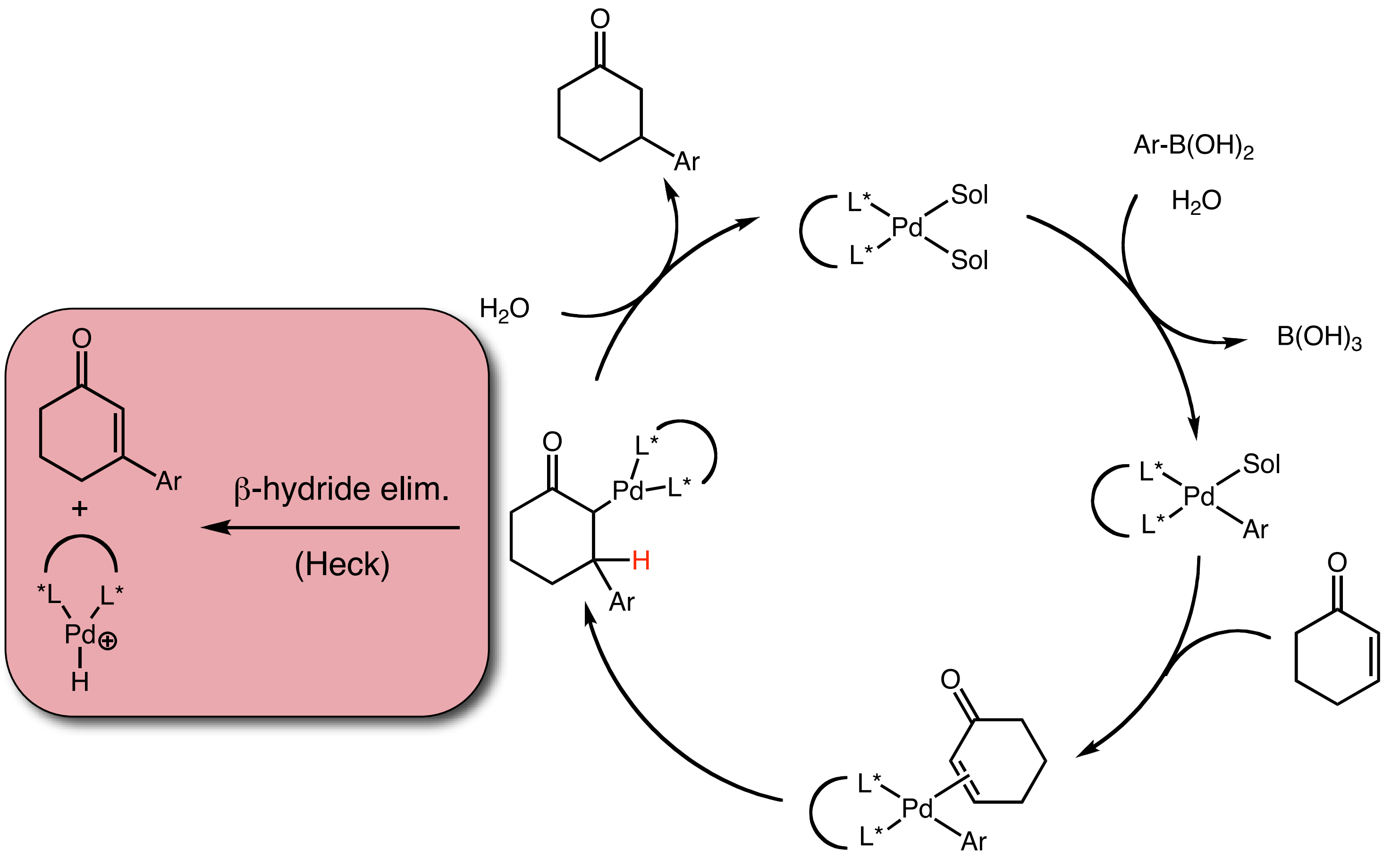


Gutnov, A. Eur. *J. Org. Chem.* **2008**, 4547.

Enantioselective Conjugate Additions using Palladium Catalysis

Development of Efficient Catalyst Systems

- General catalytic cycle

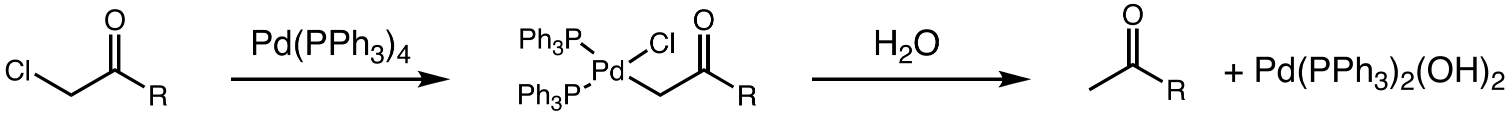


Gutnov, A. Eur. *J. Org. Chem.* **2008**, 4547.

Enantioselective Conjugate Additions using Palladium Catalysis

Development of Efficient Catalyst Systems

- In order for reaction to proceed as desired, Heck-type process must be avoided
- Espinet demonstrated the facile proto-depalladation of Pd-enolates



Albeniz, A. C.; Catalina, N. M.; Espinet, P.; Redon, R. *Organometallics* **1999**, *18*, 5571.

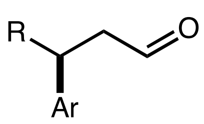
- In the presence of H_2O or acid this process is faster than β-hydride elimination

Enantioselective Conjugate Additions using Palladium Catalysis

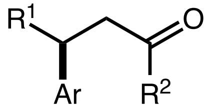
Application

- The use of Pd to mediate enantioselective conjugate additions has received massive attention
- These processes now offer broad scope and mild reaction conditions

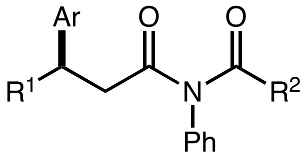
Electrophile scope



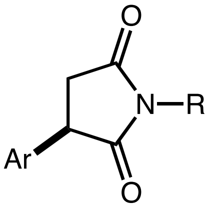
59-86% yield
86-97% ee
TL **2007**, *48*, 4007.



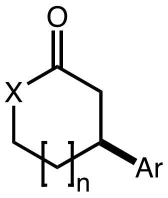
44-99% yield
>92% ee
Adv. Synth. Catal.
2007, *349*, 1759.



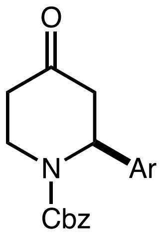
60-99% yield
90-98% ee
CL **2007**, *36*, 1442.



92-99% yield
40-90% ee
CL **2007**, *36*, 1442.



60-99% yield
82-99% ee
OL **2005**, *7*, 5309.
EJOC **2008**, 4547.



>99% yield
82-99% ee
OL **2005**, *7*, 5309.
EJOC **2008**, 4547.

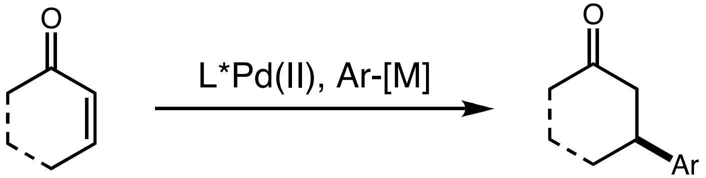
For a tandem conjugate addition/aldol sequence, see: *Synlett* **2007**, *19*, 3055.

Enantioselective Conjugate Additions using Palladium Catalysis

Application

- The use of Pd to mediate enantioselective conjugate additions has received much attention
- These processes now offer broad scope and mild reaction conditions

Nucleophile scope



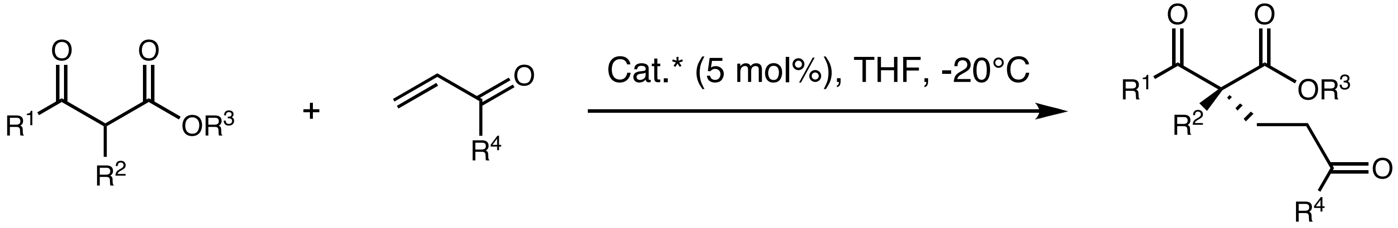
Using $ArB(OH)_2$: 60-99% yield, 40-98% ee	(*Chem Lett.* **2007**, *36*, 1442)
Using $ArBF_3K$: 22-99% yield, 82-97% ee	(*Chem. Lett.* **2005**, *34*, 720)
Using $ArSi(OR)_2$: 20-84% yield, 78-99% ee	(*Chem. Commun.* **2007**, 710)
Using $ArSiF_3$: 83-88% yield, 94-97% ee	(*Organometallics* **2005**, 5025)
Using Ar_3Bi: 31-98% yield, 12-95% ee	(*Chem. Commun.* **2004**, 1822)

See also: Gutnov, A. Eur. *J. Org. Chem.* **2008**, 4547 and references therein.

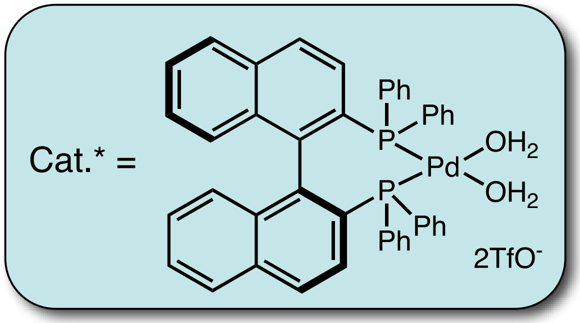
Enantioselective Conjugate Additions using Palladium Catalysis

Development of Efficient Catalyst Systems

- The relatively new field of Pd acid-base catalysis has been used for asymmetric conjugate additions
- Quaternary stereocentres are easily constructed in high levels of enantioselectivity



69-93% yield
86-93% ee

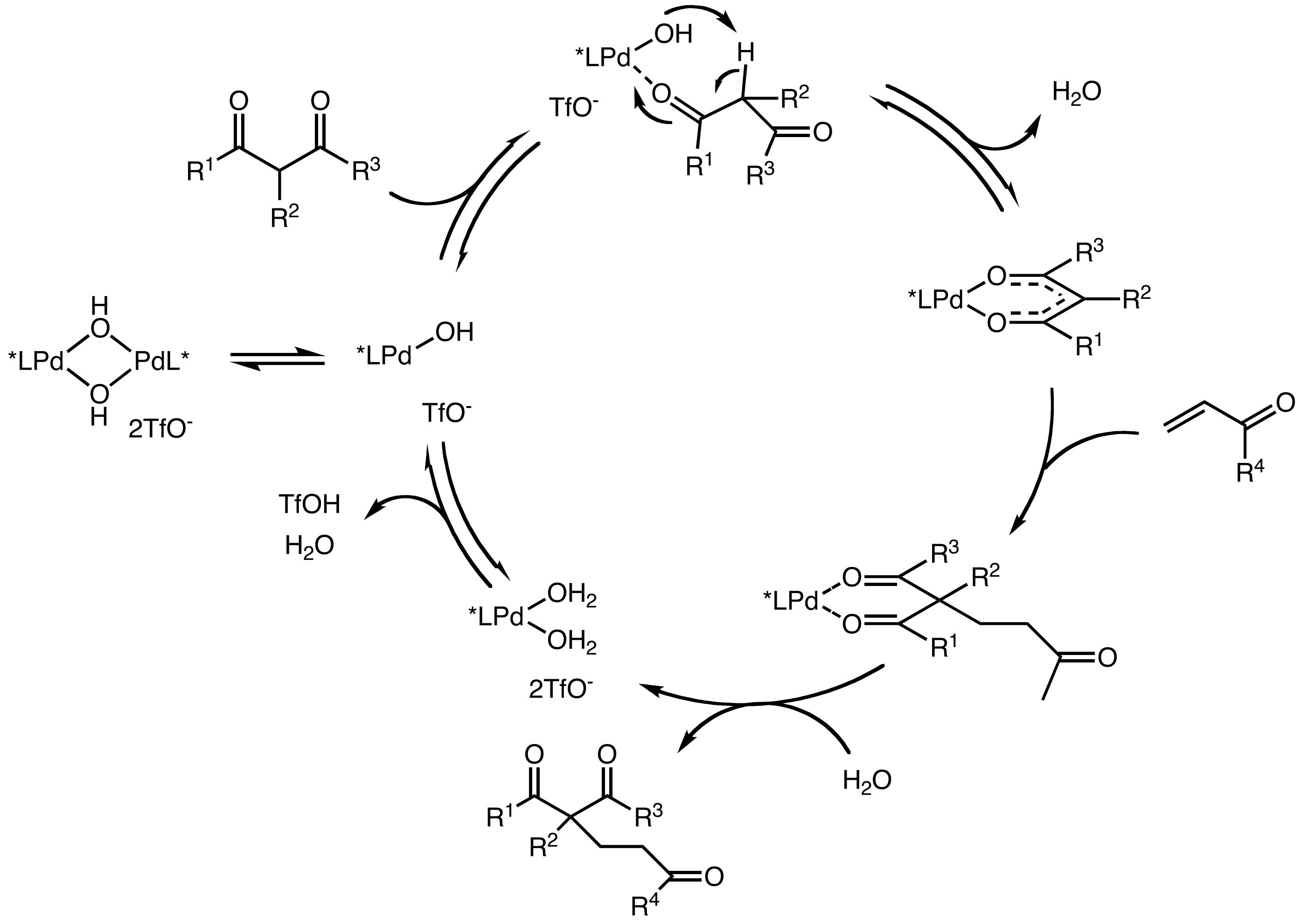


Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240.

Enantioselective Conjugate Additions using Palladium Catalysis

Development of Efficient Catalyst Systems

■ Sodeoka's/Hamashima's mechanistic rational

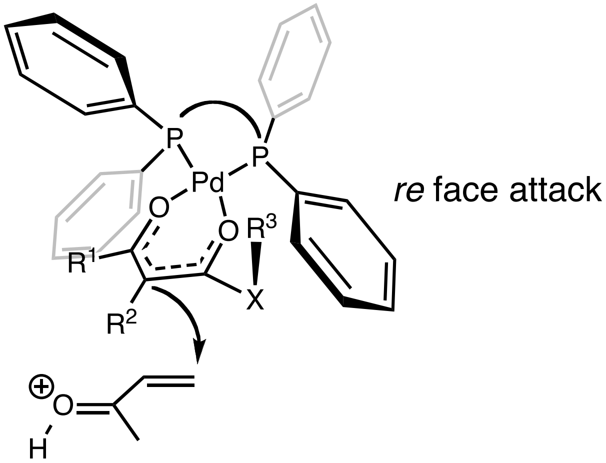


(a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240.
(b) Hamashima, Y. *Chem. Pharm. Bull.* **2006**, *54*, 1351.

Enantioselective Conjugate Additions using Palladium Catalysis

Development of Efficient Catalyst Systems

- Sodeoka's/Hamashima's mechanistic rational

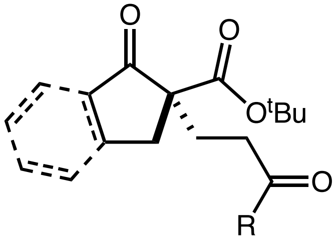


(a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240.
(b) Hamashima, Y. *Chem. Pharm. Bull.* **2006**, *54*, 1351.

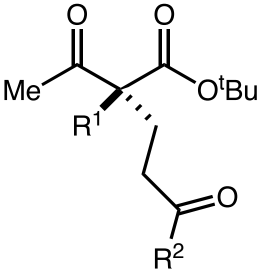
Enantioselective Conjugate Additions using Palladium Catalysis

Application

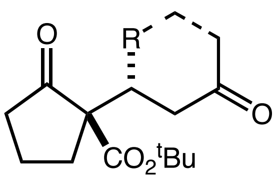
- Good scope has already been realised



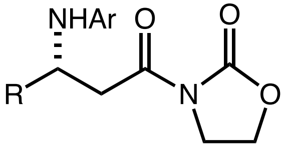
58-93% yield
71-93% ee



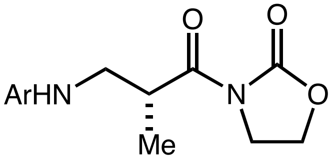
41-82% yield
65-94% ee



79-98% yield
1.2-8:1 dr
86-99% ee



49-98% yield
85-98% ee



80% yield
94% ee

(a) Hamashima, Y. *Chem. Pharm. Bull.* **2006**, *54*, 1351.
(b) Sodeoka, M.; Hamashima, Y. *Pure Appl. Chem.* **2006**, *78*, 477.

Enantioselective Conjugate Additions using Palladium Catalysis

Overview

Pd(II) L*

- Enantioselective conjugate additions using Pd catalysis is a recent development
- This approach has received a great deal of interest from several groups
- Benefits include:
- Most catalyst/ligands are commercially available
- Readily available/bench stable nucleophiles
- Relatively mild/insensitive reaction conditions
- Tolerant of a wide variety of functional groups on nucleophile and conjugate acceptor
- Operates effectively with both linear and cyclic conjugate acceptors
- Effective with notoriously difficult cyclopentenone
- Pd is much cheaper than Rh

Enantioselective Conjugate Additions using Transition Metal Catalysis

Summary and Conclusions

- Of the metals discussed, the newcomers are the most effective
- Co, Ni, Zn and Cu lack the broad generality of Pd and especially Rh

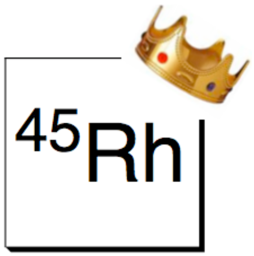
	Co	Ni	Cu	Zn	Rh	Pd
Efficiency	✗	✓	✓	✓✓	✓✓	✓✓
Selectivity	✗	✓	✓	✓✓	✓✓	✓
Nu Scope	✗	✓	✗	✗	✓✓	✓✓
E Scope	✗	✗	✓	✗	✓✓	✓✓
Catalyst/L availability	✗	✓	✓	✓	✓✓	✓✓
Generality	✗	✗	✗	✗	✓✓	✓✓

Enantioselective Conjugate Additions using Transition Metal Catalysis

Summary and Conclusions

- Of the metals discussed, the newcomers are the most effective
- Co, Ni, Zn and Cu lack the broad generality of Pd and especially Rh

	Co	Ni	Cu	Zn	Rh	Pd
Efficiency	✗	✓	✓	✓✓	✓✓	✓✓
Selectivity	✗	✓	✓	✓✓	✓✓	✓
Nu Scope	✗	✓	✗	✗	✓✓	✓✓
E Scope	✗	✗	✓	✗	✓✓	✓✓
Catalyst/L availability	✗	✓	✓	✓	✓✓	✓✓
Generality	✗	✗	✗	✗	✓✓	✓✓



- Rh is closest to achieving the Holy Grail of conjugate additions - a universal catalyst system