Catalytic, Enantioselective, Transfer Hydrogenation

Org. Reactions Vol. 100, Ch 6

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Travis Menard

June 20th, 2020

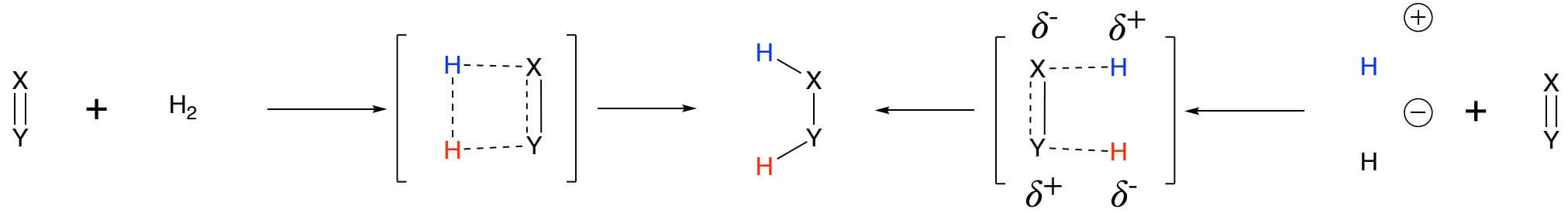
Outline

- General Mechanisms
- History and Early Examples
- Scope
  - Carbonyl Compounds
  - Imines and Derivatives
  - Activated Alkenes
  - Heteroarenes
  - Other Applications
  - Vs. Hydrogenation

What is Transfer Hydrogenation?

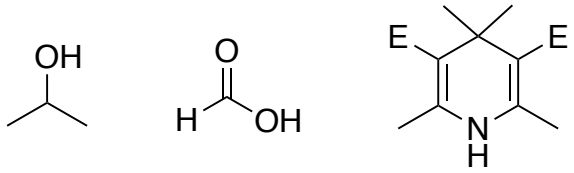
Hydrogenation

Transfer Hydrogenation



Required Elements:

Sacrificial reductant
(Source of H^+ and H^-)



Method of transfer

Chiral recognition element

Advantages Over Hydrogenation:

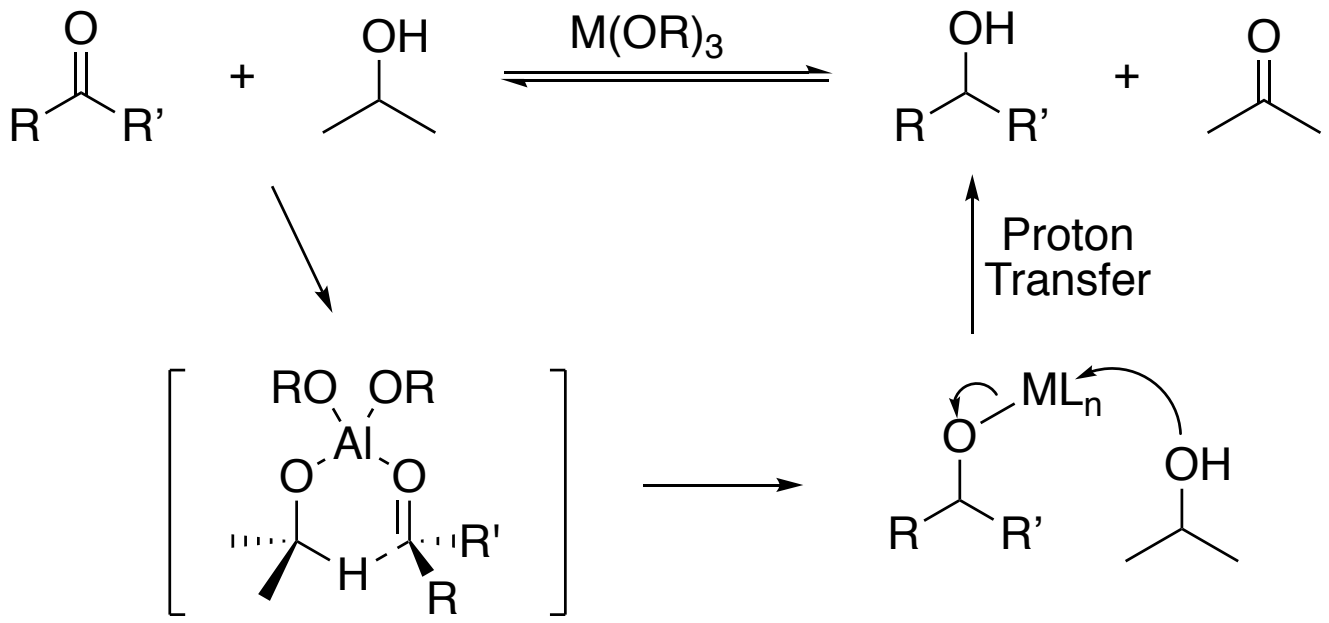
Avoids the use of hydrogen

Operationally simple

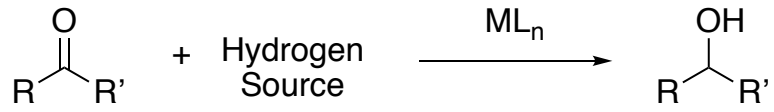
Mild conditions

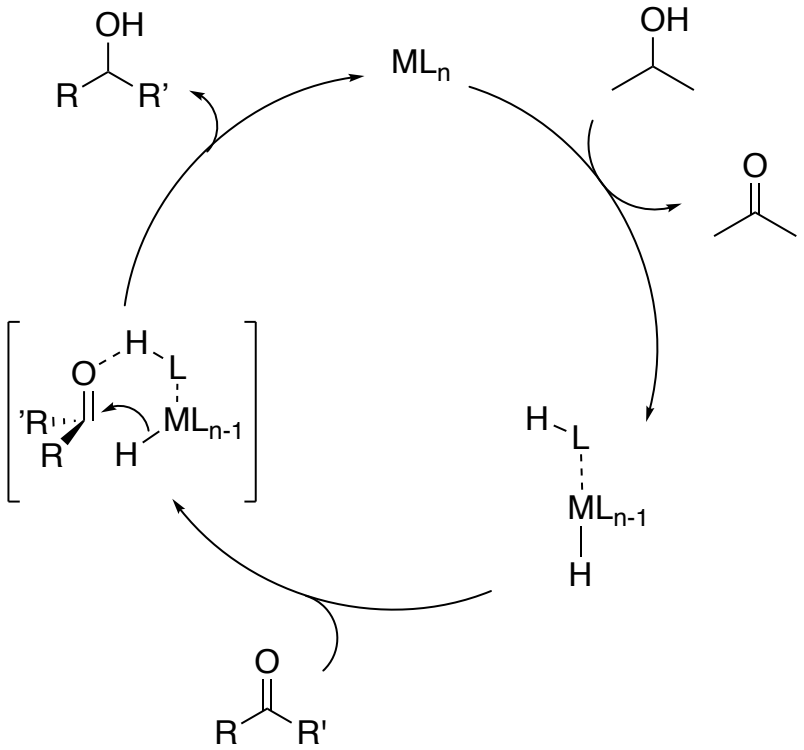
Highly efficient

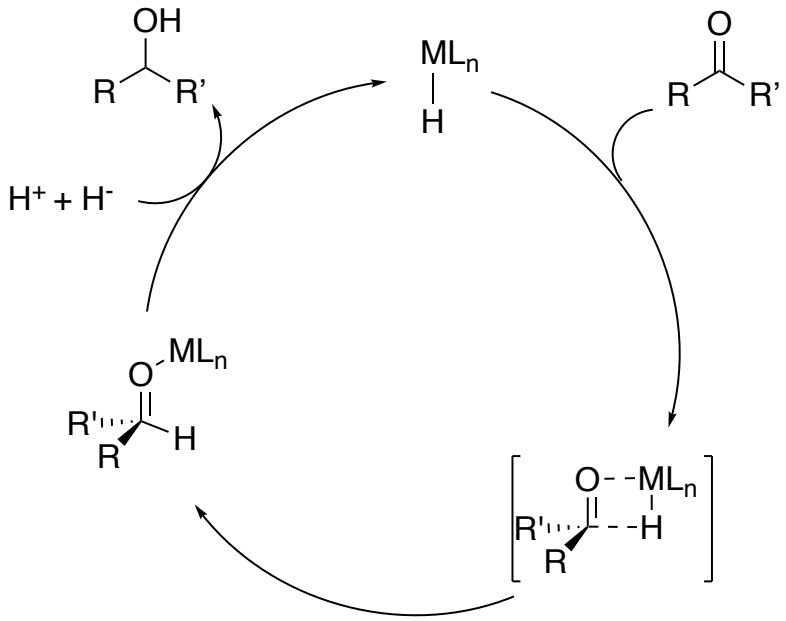
General Mechanism: Main Group Metals



General Mechanism: Transition Metals

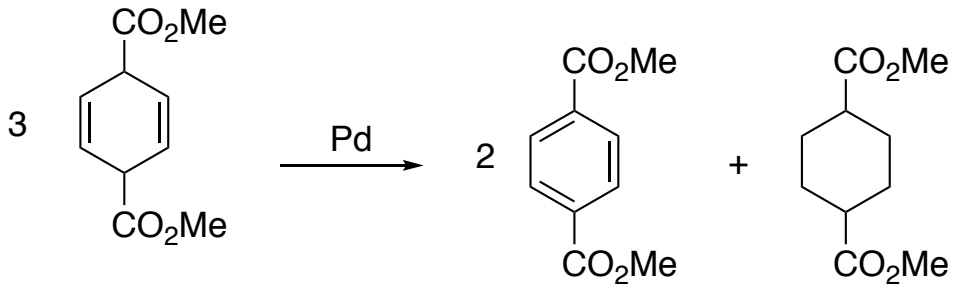




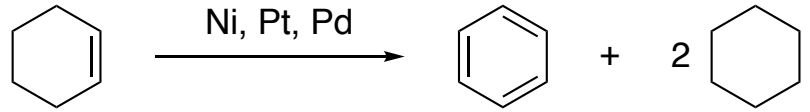


Discovery and Early History

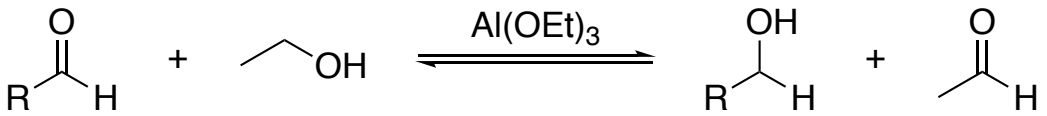
Knoevenagel (1903):



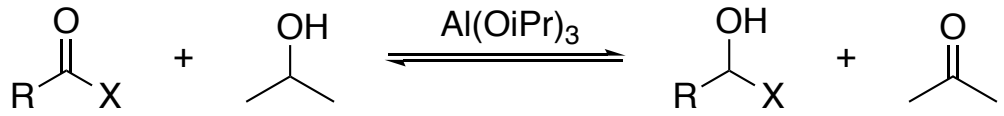
(1912-1939):



Meerwein and Verley (1925):



Ponndorf (1926):

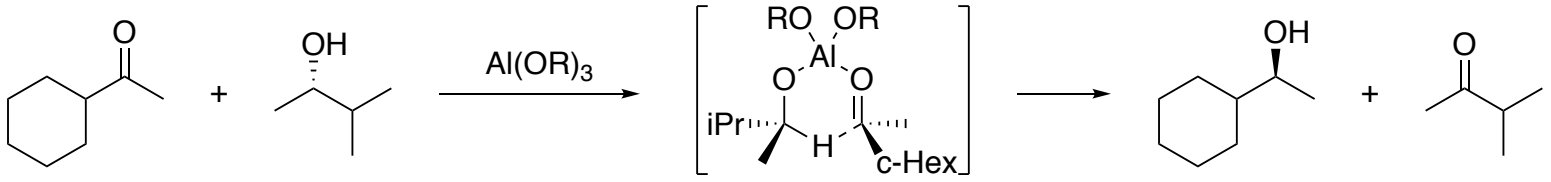


X = H or R'

Chem. Ber. 1903, 36, 2857–2860
Bull. Soc. Chim. Fr. 1925, 37, 537–542
Liebigs Ann. Chem. 1925, 444, 221–238
Angewandte Chemie. 39 (5): 138–143

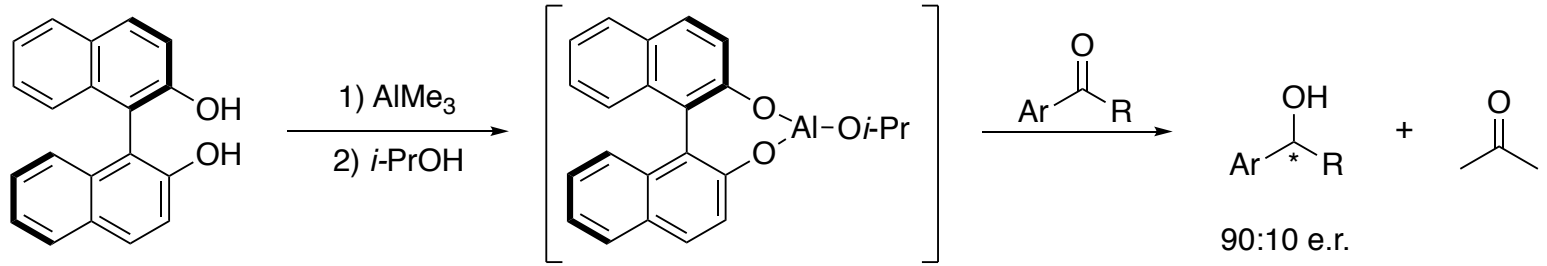
Enantioselective MPV Reduction

Doering (1950):

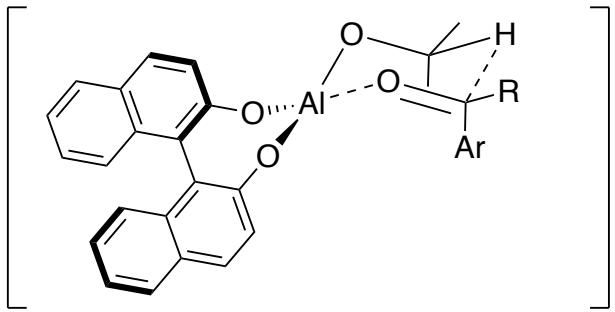


61:39 e.r.

Nguyen (2002):



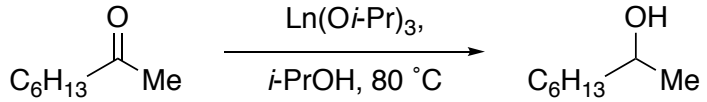
10 mol%



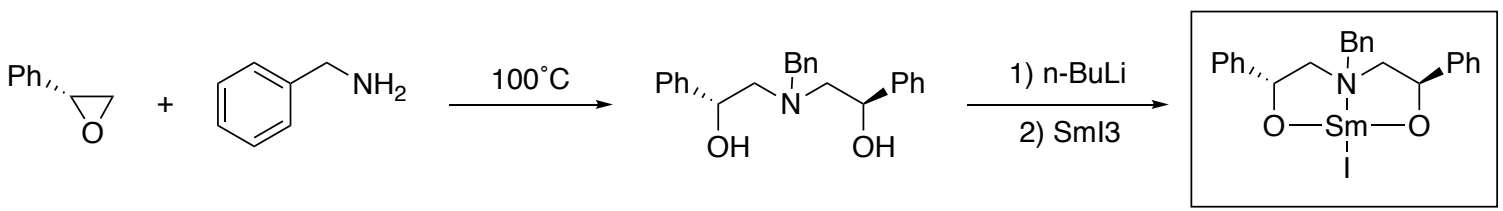
J. Am. Chem. Soc. 1950, 72, 631.
Angew. Chem. Int. Ed., 41: 1020-1022

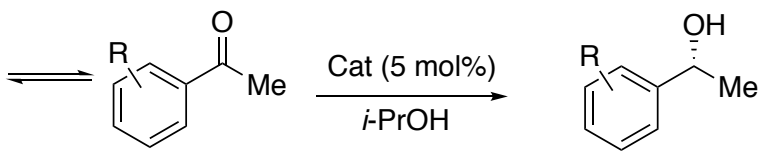
Use of Lanthanide Alkoxides

Kagan (1991):

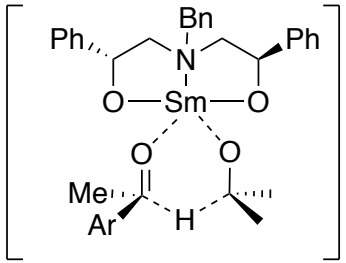


Evans (1993):





8 examples
>96:4 e.r.



MPV-Type Reduction:

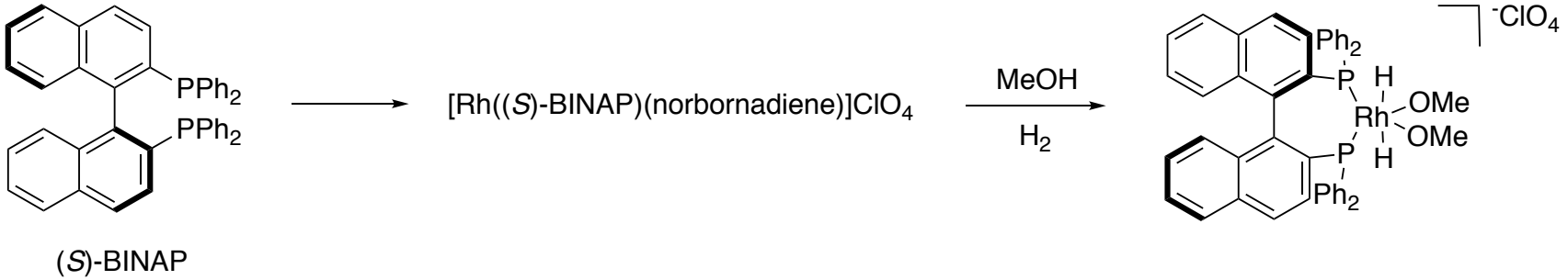
Ln	Cat (mol%)	Time (h)	Yield (%)
La	5	18	>98
La	1	48	15
Ce	10	24	95
Ce	5	48	55
Sm	10	18	>98
Sm	5	24	80
Yb	5	24	40

Tehahedron Letters. Vo1.32, No.21, pp 2355-2358.1991
J. Am. Chem. Soc. 1993, 115, 9800-9801

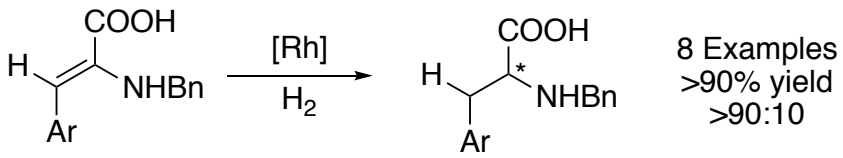
Ryoji Noyori

2001 Nobel Prize

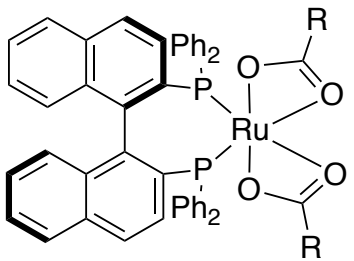
(1980):

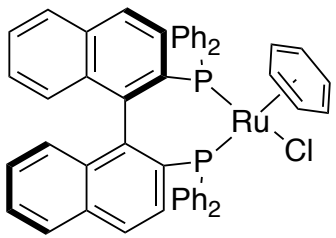


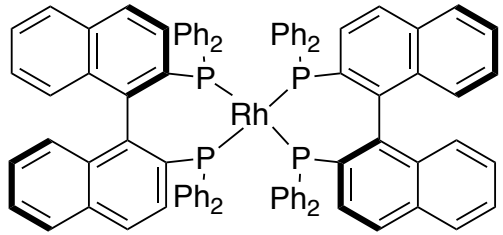
(*S*)-BINAP



8 Examples
>90% yield
>90:10

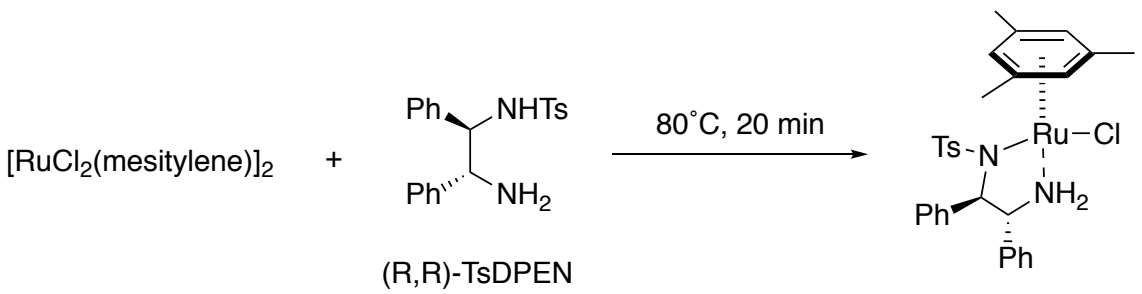


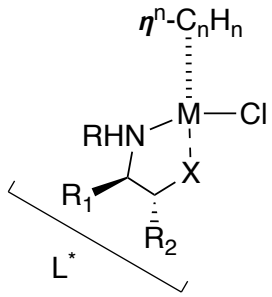




J. Am. Chem. Soc., Vol. 102, No. 27, 1980
Acc. Chem. Res., Vol. 23, No. 10, 1990

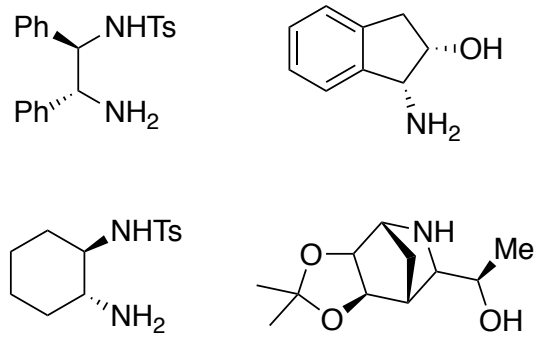
Noyori Transfer Hydrogenation (1995)

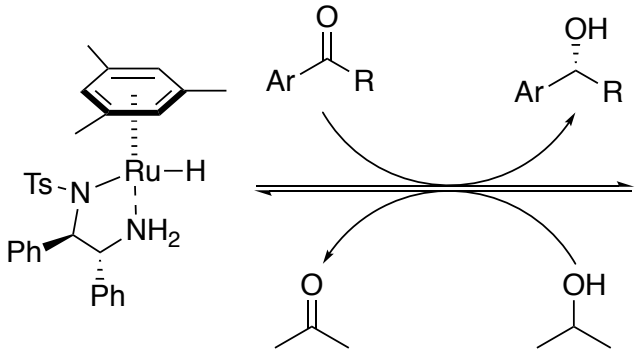


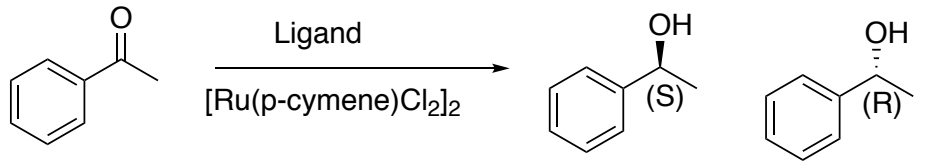


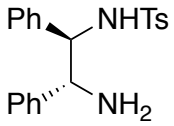
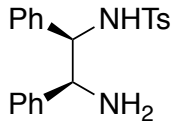
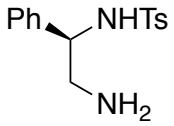
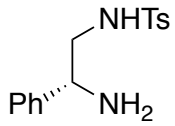
M = Ru N = 6
Rh 5
Ir 5

L*



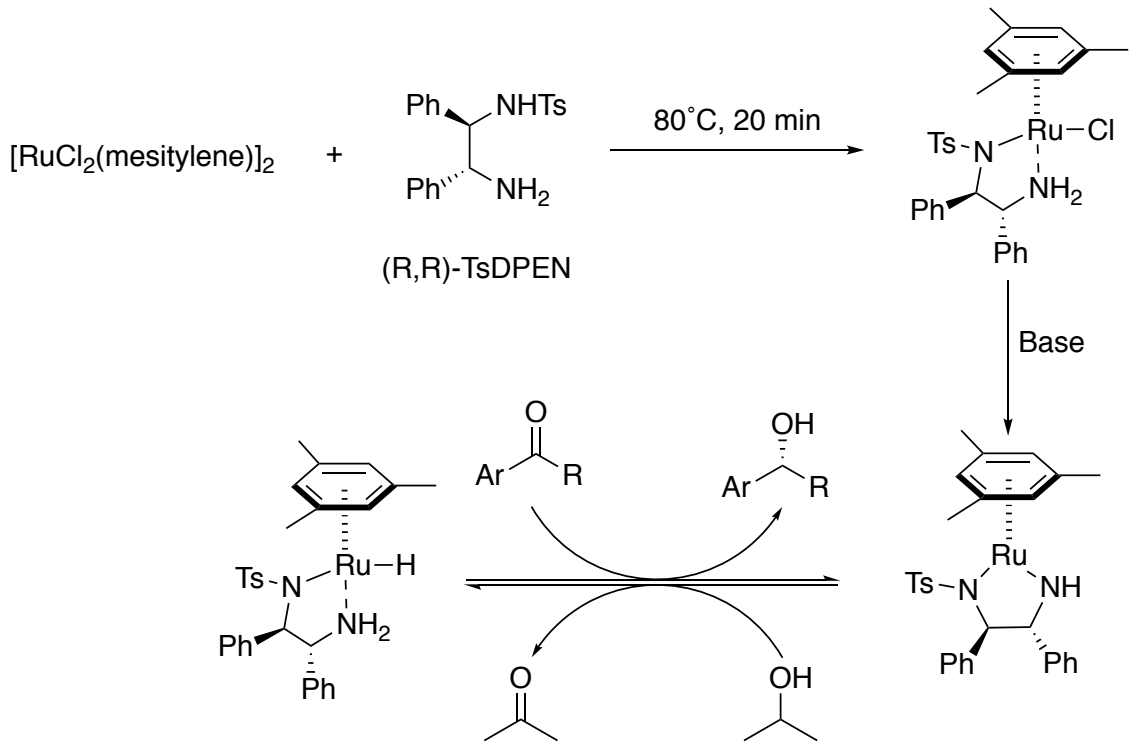


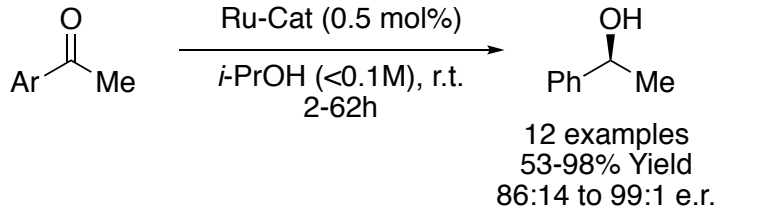


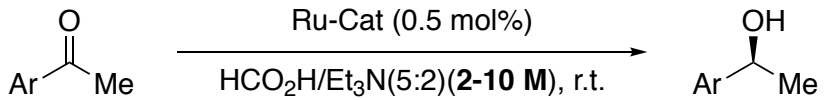
				
Time	22h	220h	48h	13 days
Conv	100	32	95	46
e.r.	99:1 (R)	85:15 (S)	84:16 (S)	67:33 (R)

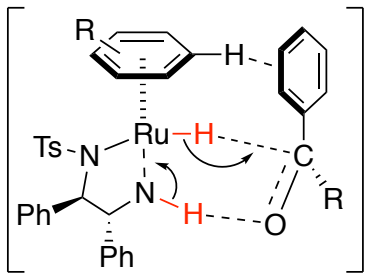
J. Am. Chem. Soc. 1995,117, 7562-7563
Chem. Soc. Rev., 2006, 35, 226–236

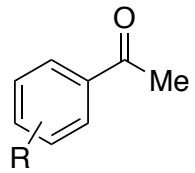
Noyori Transfer Hydrogenation (1995)



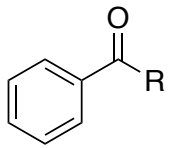




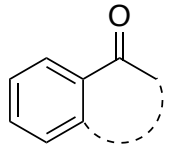




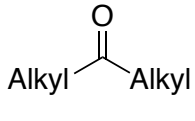
2,3, or 4-substitution



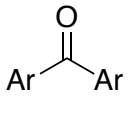
Straight chain alkyl



Cyclic ketones



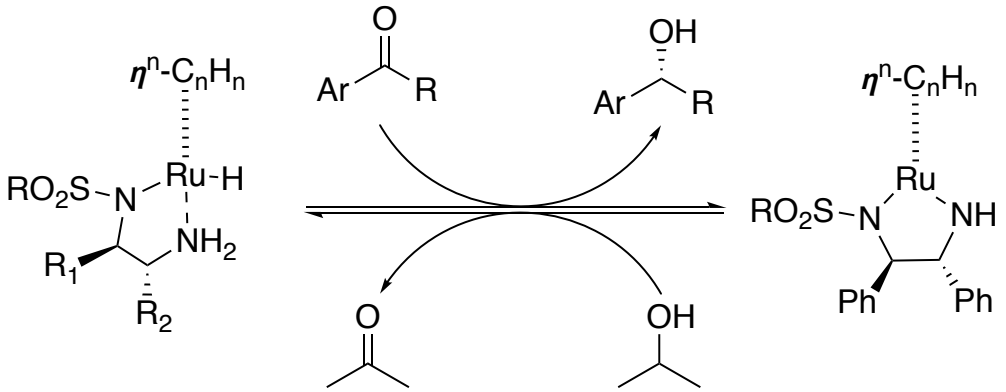
Alkyl-Alkyl



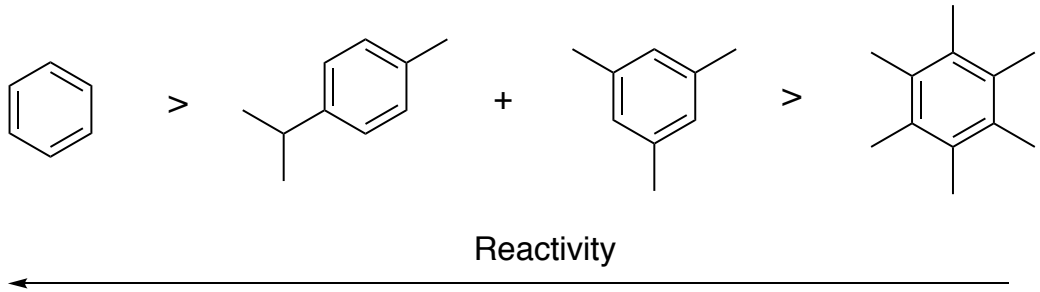
Ar-Ar

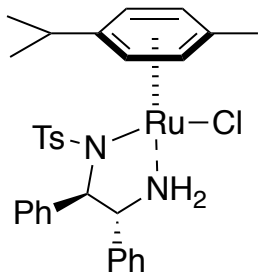
J. Am. Chem. Soc. 1995,117, 7562-7563
J. Am. Chem. Soc. 1996, 118, 10, 2521–2522

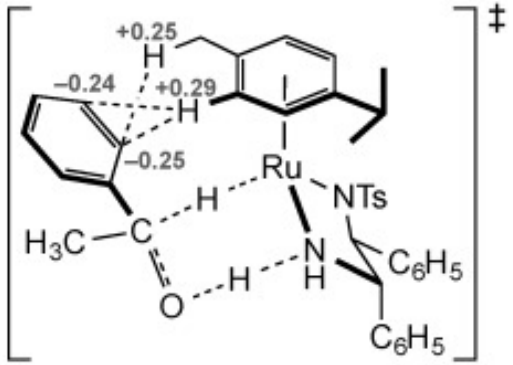
Noyori Catalyst Modifications



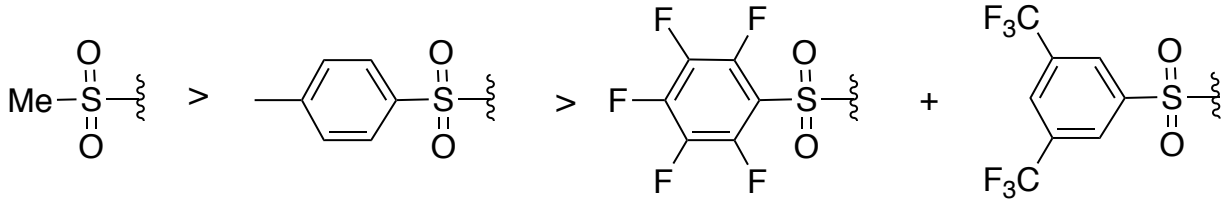
Arene:







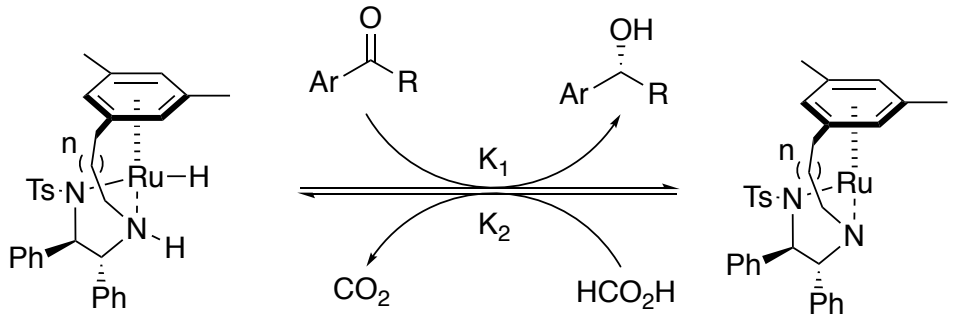
Re-**6**$_1$ (0.0 kJ mol^{-1})

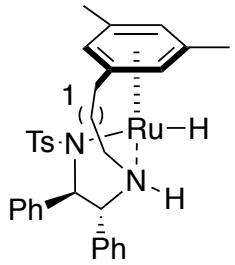


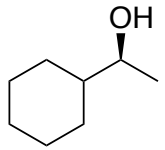
J. Am. Chem. Soc. 2016, 138, 10084–10087
Org. Lett. 2007, 9, 22, 4659–4662
Chem. Asian J., 10: 112-115

Tethered Catalysts

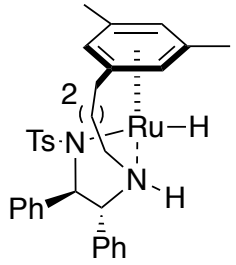
Wills (2007):

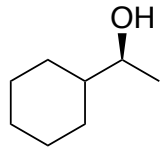




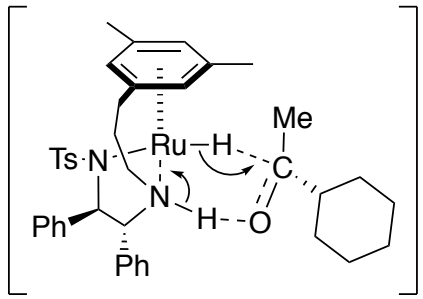


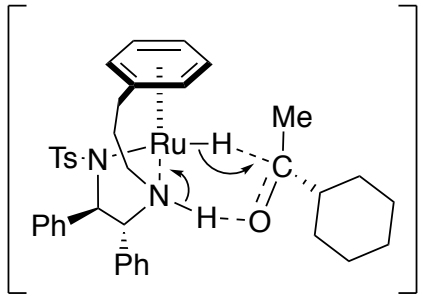
95:5 e.r.

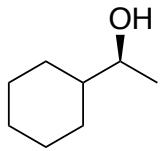




80:20 e.r.

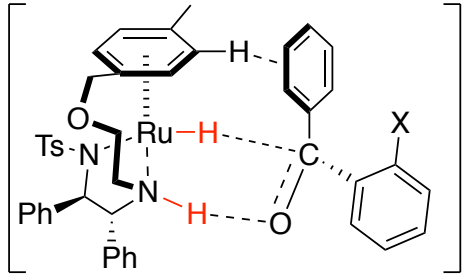


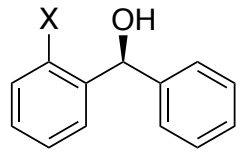




85:15 e.r.

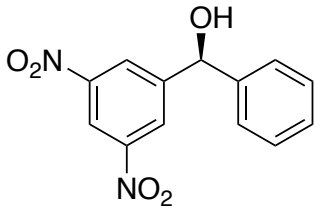
Touge and Kayaki (2016):





X = F, 95:5
X = Cl, 99:1
X = Br, >99:1
X = CF_3, >99:1

or



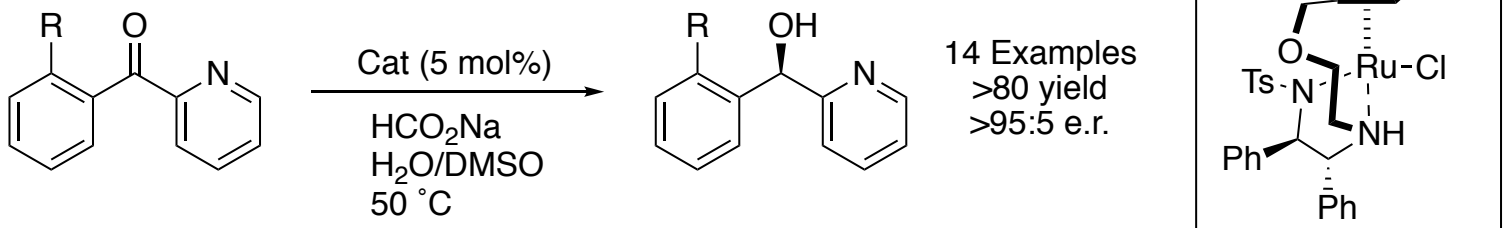
>99:1

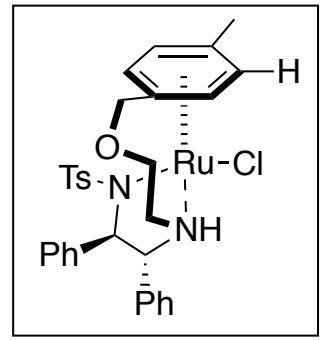
Org. Lett., Vol. 9, No. 22, **2007**

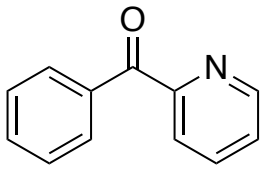
J. Am. Chem. Soc. 2016, 138, 10084−10087

Aryl N-Hetero Aryl Ketones

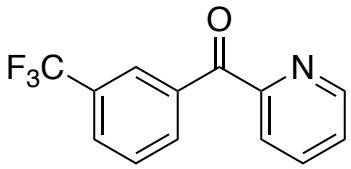
Zhou (2017):



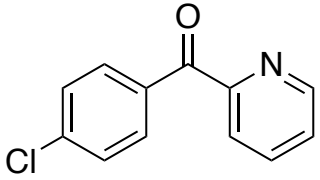




57:43 e.r.

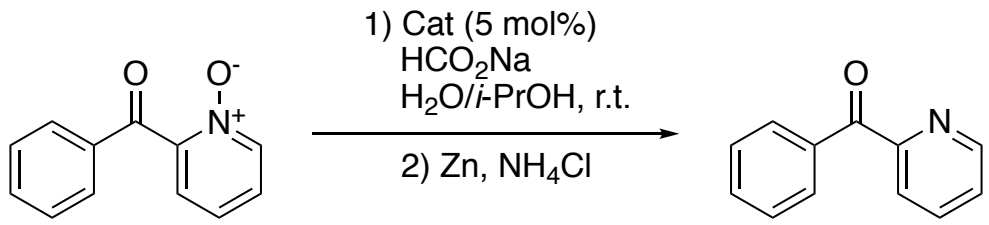


77:23 e.r.

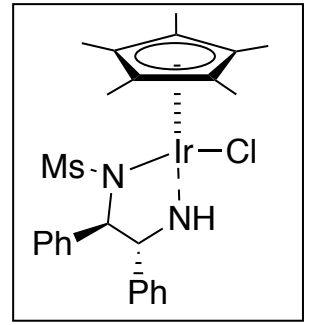


70:30 e.r.

Zhou and Fu (2018):

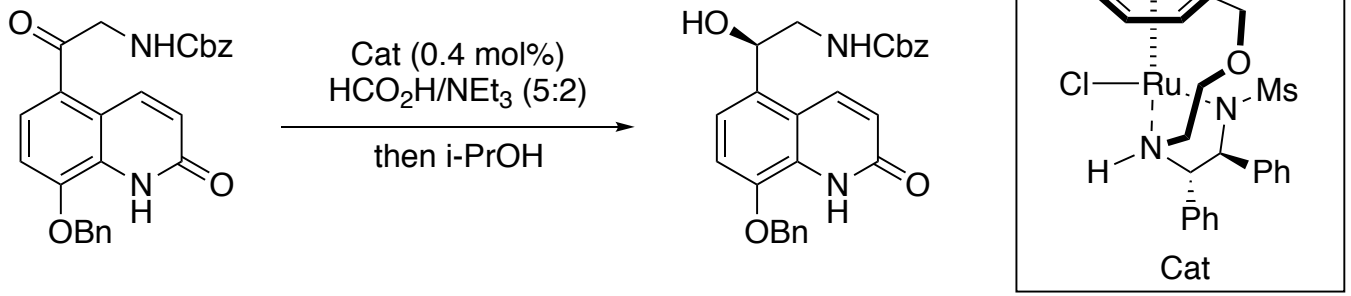


78% Yield
96:4 e.r.

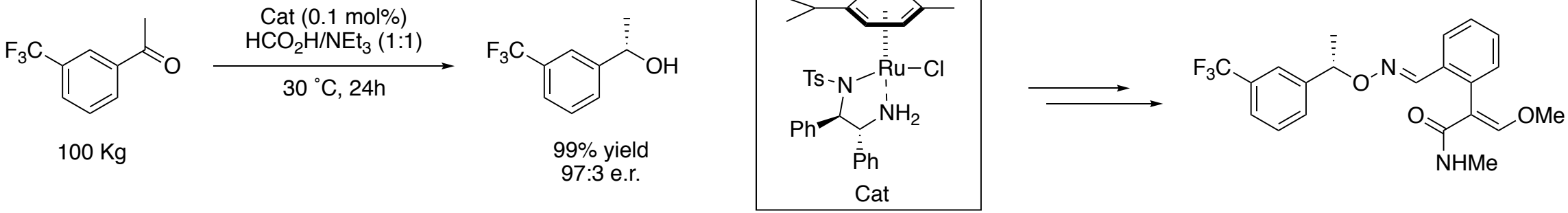


Org. Lett. 2017, 19, 2094–2097
Org. Lett. 2018, 20, 971–974

Industrial Applications



Multi-Kg

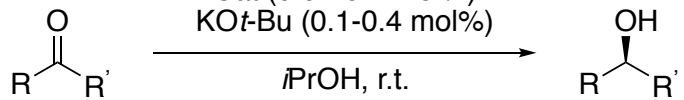


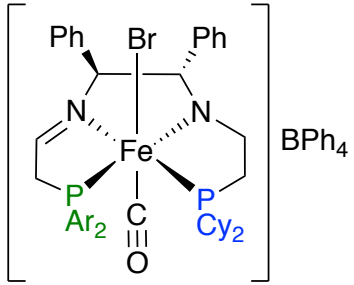
100 Kg

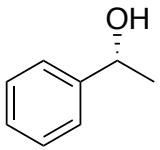
99% yield
97:3 e.r.

Org. Process Res. Dev. 2015, 19, 315–319
Org. Proc. Res. Dev. 2000, 4, 5, 346–348

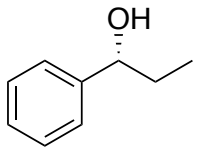
Iron P-N-N-P Complexes



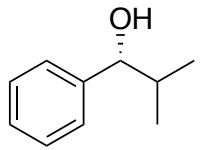




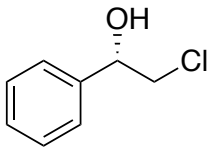
83% conv.
90:10 e.r.
20 min



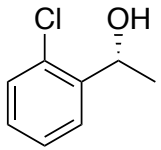
80% conv.
97:3 e.r.
60 min



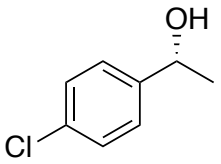
0% conv.



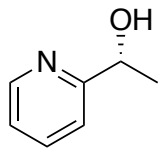
98% conv.
>99:1 e.r.
2 min



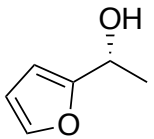
>99% conv.
97:3 e.r.
10 min



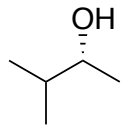
99% conv.
76:24 e.r.
10 min



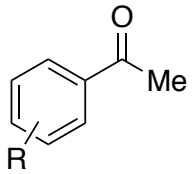
>99% conv.
77:23 e.r.
20 min



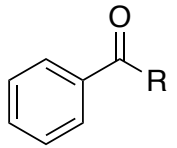
0% conv.



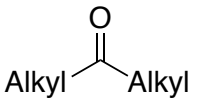
44% conv.
71:29 e.r.
50 min



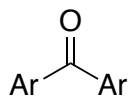
2,3, or 4-substitution



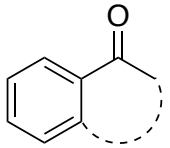
Straight chain alkyl



Alkyl-Alkyl



Ar-Ar

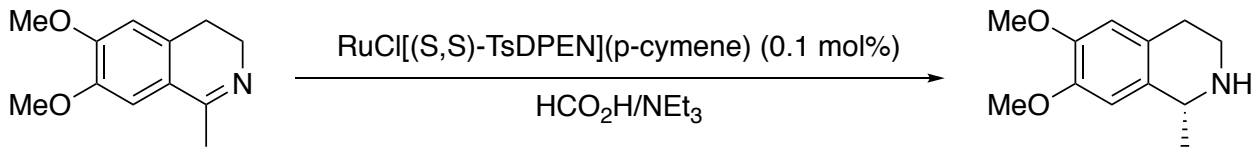


Cyclic ketones

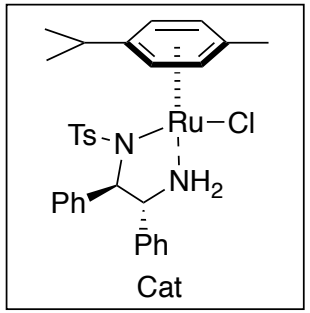
Synthesis 2015; 47(12): 1775-1779

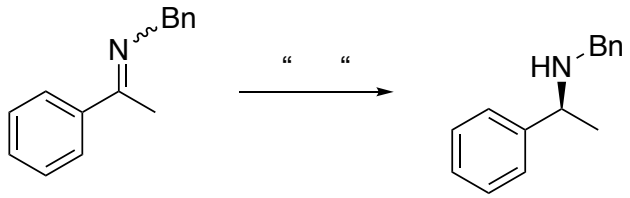
TH of Imines

Noyori (1996):

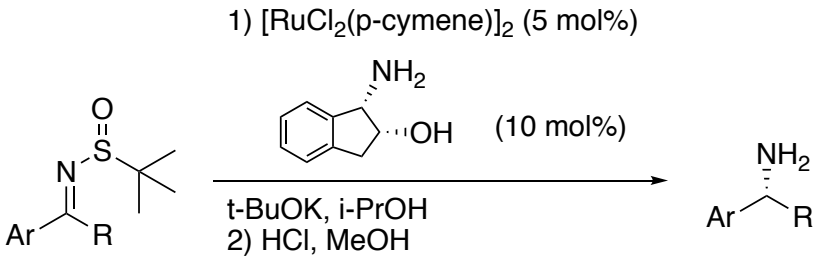


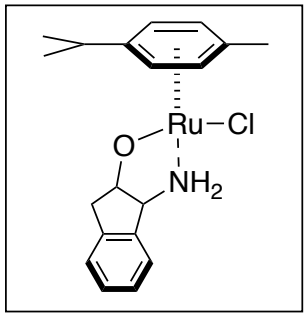
97% yield
97:3 e.r.

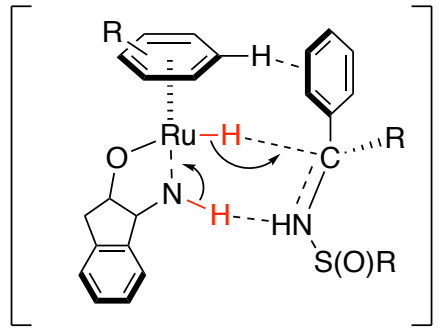


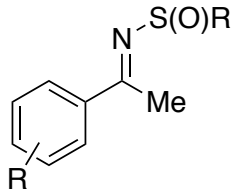


88:12 e.r.

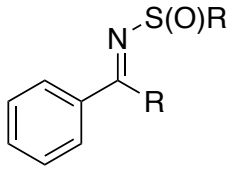




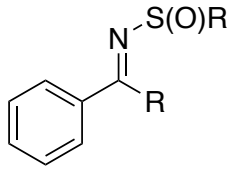




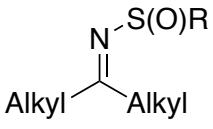
3 or 4-substitution



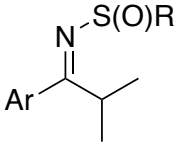
Straight chain alkyl



Cyclic imines



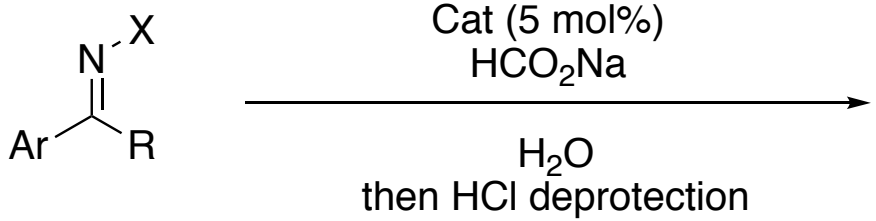
Alkyl-Alkyl

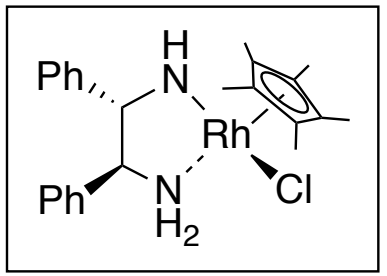


Branching

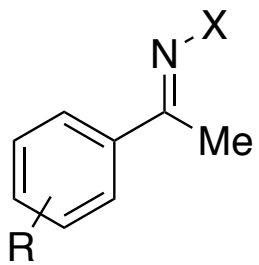
J. Am. Chem. Soc., Vol. 118, No. 20, 1996
J. Org. Chem. 2010, 75, 5265–5270

Rh-Cp Complexes for Hydrogenation on Water

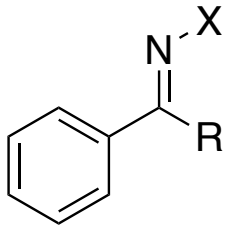




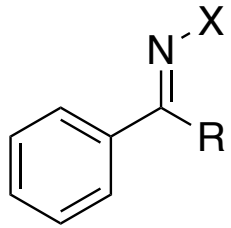
X = S(O)R or $P(O)Ph_2$



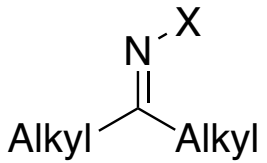
3 or 4-substitution



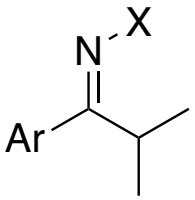
Straight chain alkyl



Cyclic imines



Alkyl-Alkyl

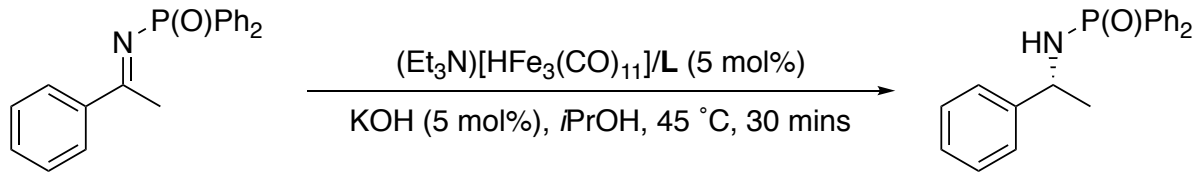


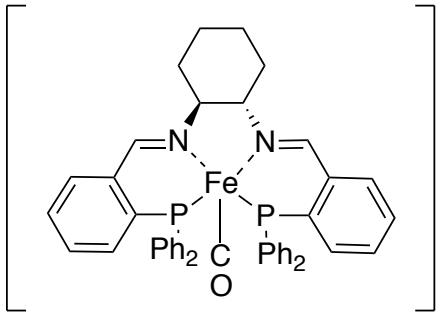
Branching

Tetrahedron, Volume 69, Issue 31, 5 August 2013, Pages 6500-6506
Campbell, L. A.; Martin, J. European Patent 1210305 B1, July 20, 2005.

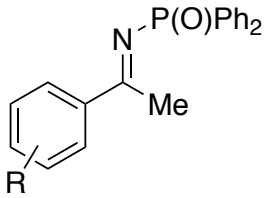
Iron P-N-N-P Complexes

Beller (2010):

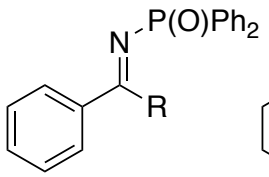




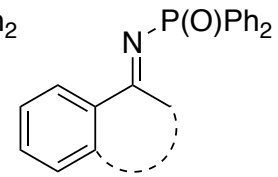
19 Examples
up to 99% yield
up to 99:1 e.r.



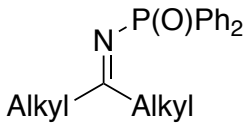
2,3, or 4-substitution



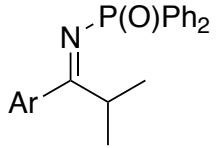
Straight chain alkyl



Cyclic imines

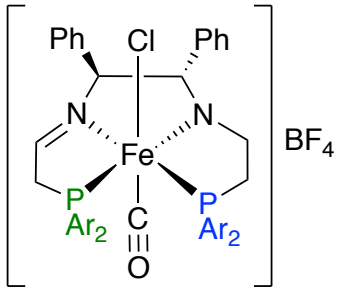


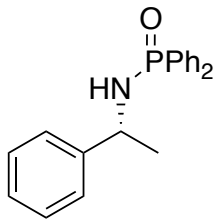
Alkyl-Alkyl



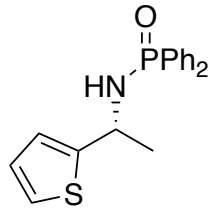
Branching

Morris (2014):





20 s
>99:1 e.r.

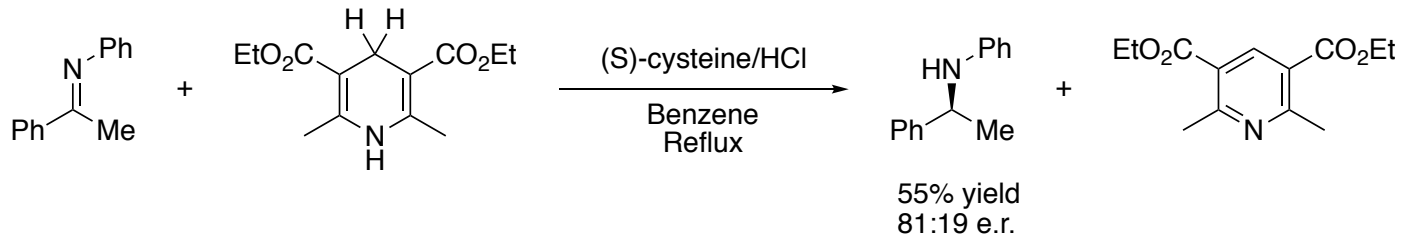


180 s
>99:1 e.r.

Angew. Chem. Int. Ed. 2010, 49, 8121 –8125
Science 29 Nov 2013: Vol. 342, Issue 6162, pp. 1080-1083

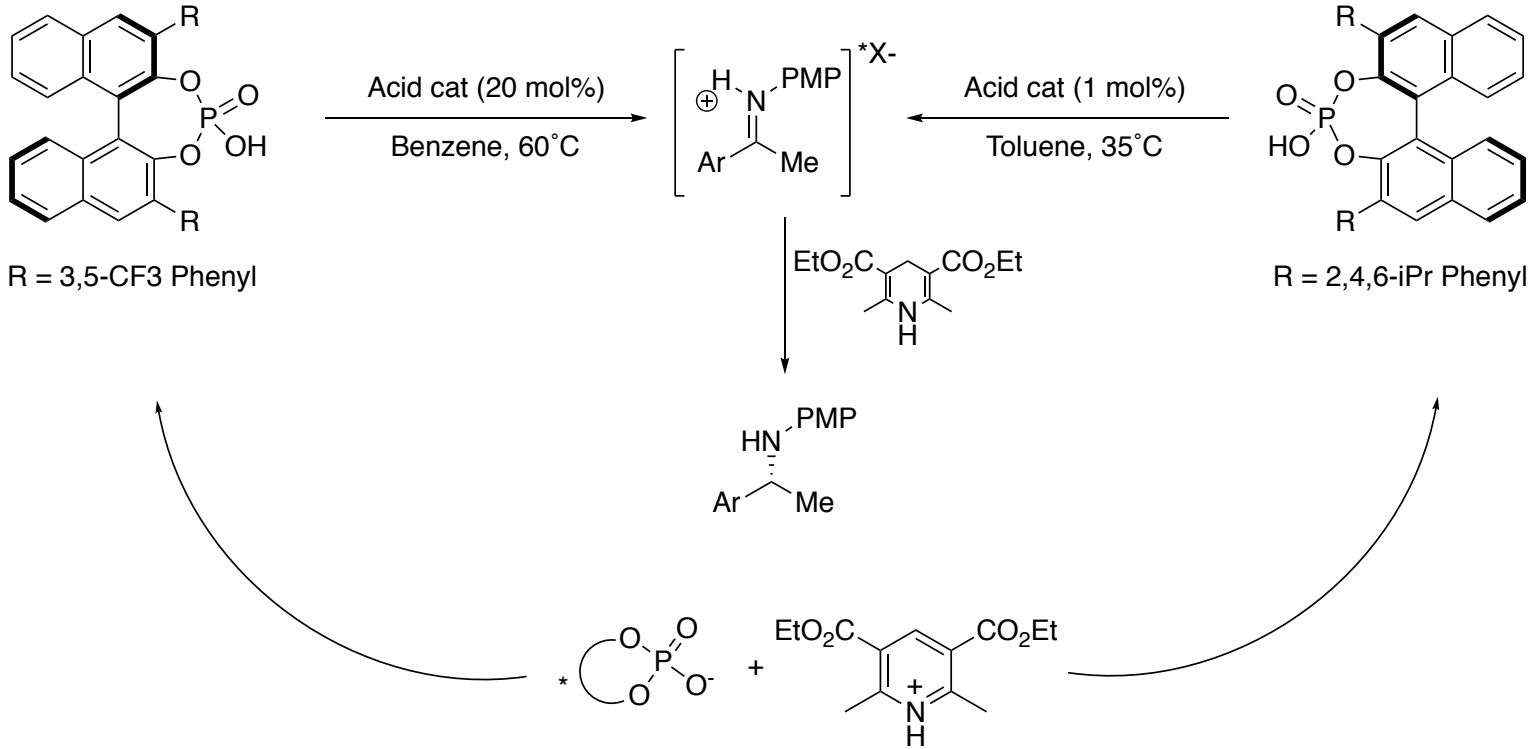
Biomimetic Hydrogenation of non-Activated Imines

Batra and Singh (1989)



Reuping (2005)

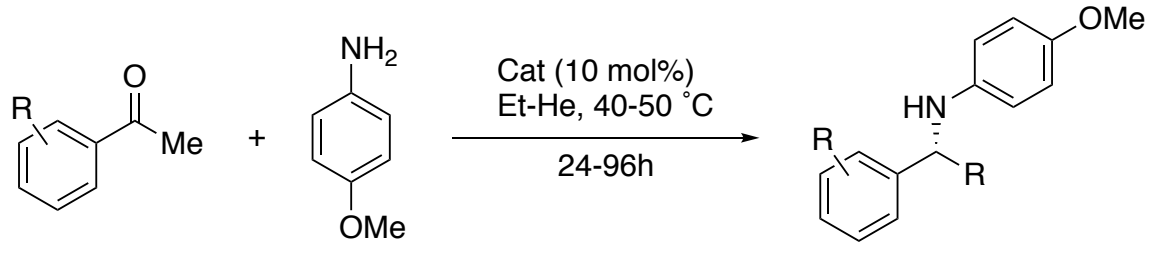
List (2005)



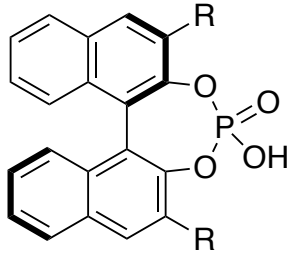
Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem. 1989, 28, 1.
Org. Lett., Vol. 7, No. 17, 2005
Angew. Chem. Int. Ed. 2005, 44, 7424 –7427

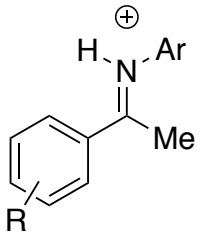
Asymmetric Reductive Amination

MacMillan (2006):

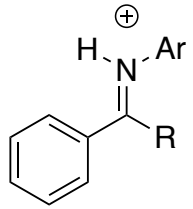


12 Examples
60-87% yield
>90:10 e.r.

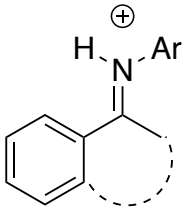




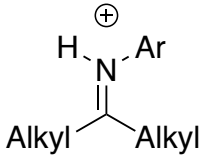
2,3, or 4-substitution



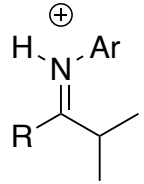
Straight chain alkyl



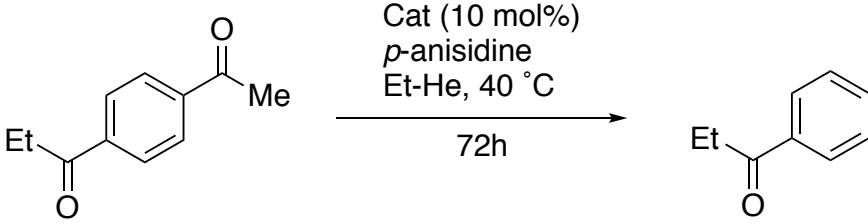
Cyclic imines



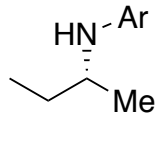
Alkyl-Alkyl



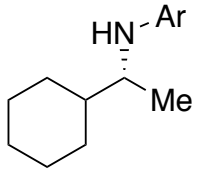
Branching



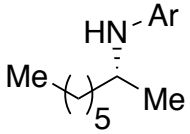
18:1 Me:Et
85% yield
98:2 e.r.



71% yield
92:8 e.r.



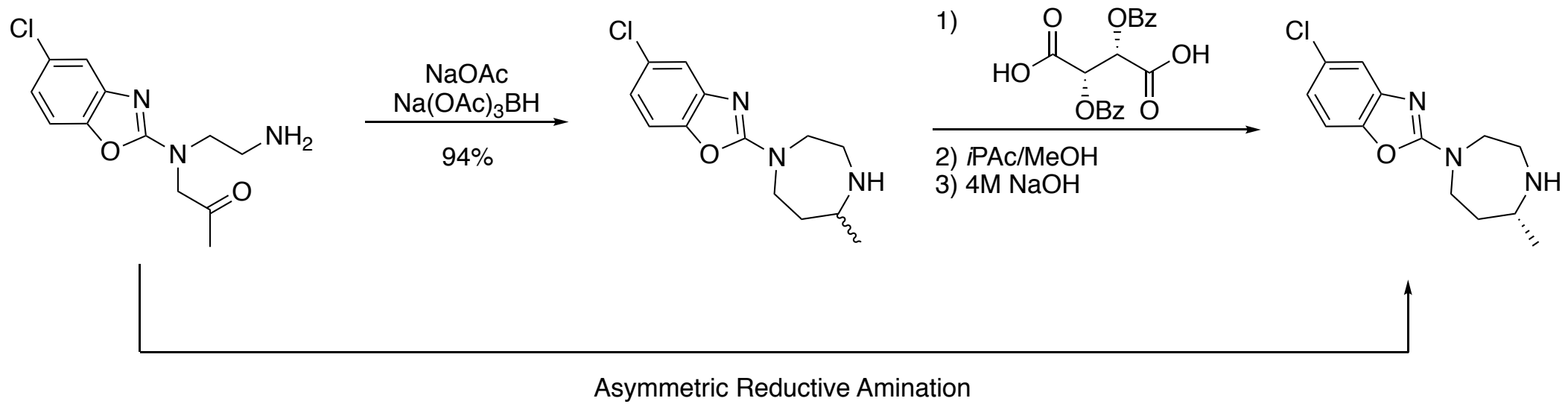
49% yield
93:7 e.r.

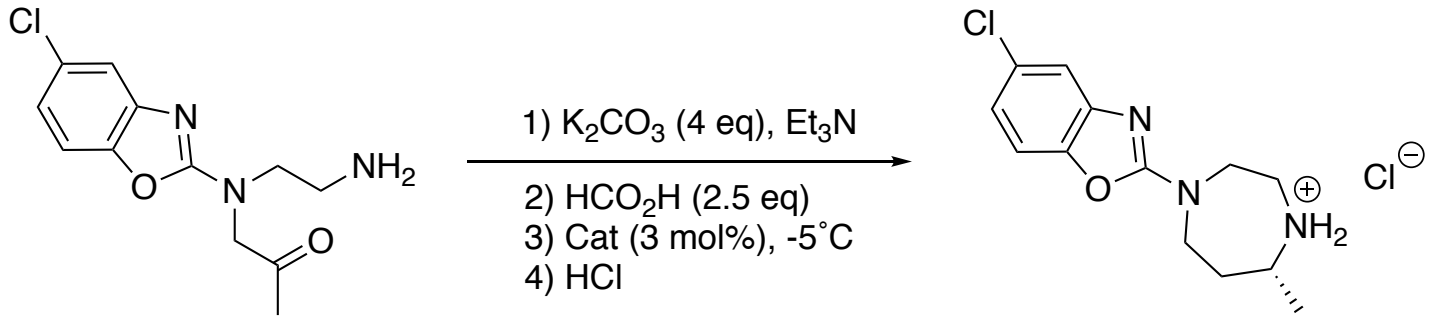


71% yield
92:8 e.r.

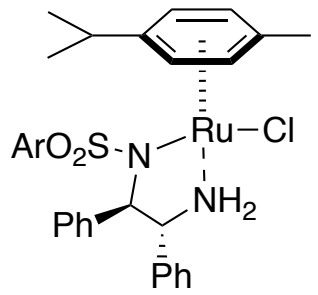
J. Am. Chem. Soc. 2006, 128, 1, 84–86

Asymmetric Reductive Amination Merck Process





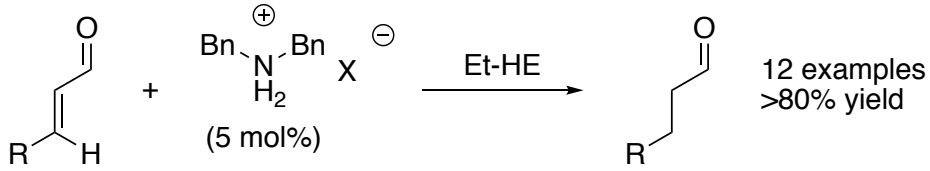
>100 Kg

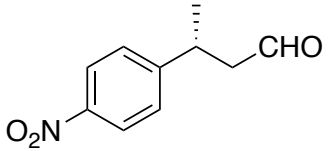


J. Am. Chem. Soc. 2011, 133, 8362–8371

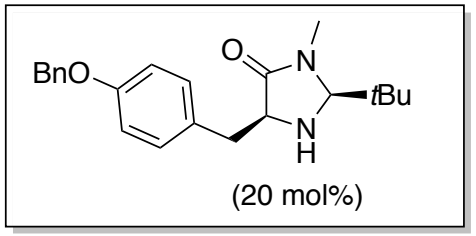
Hydrogenation of Enones

List (2005):

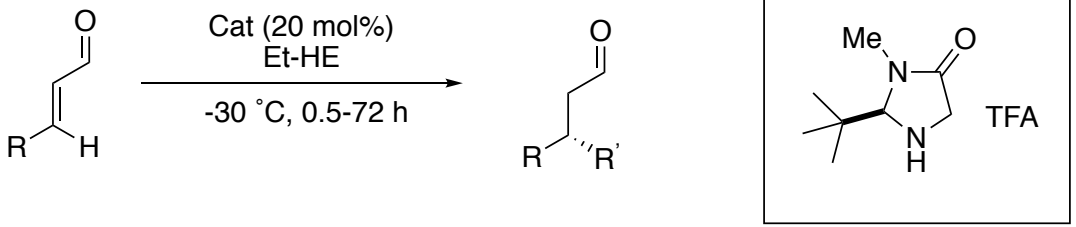


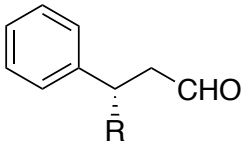


81% yield
91:9 e.r.

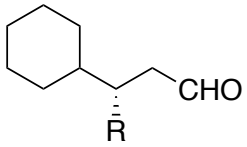


MacMillan (2005):

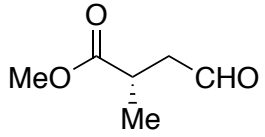




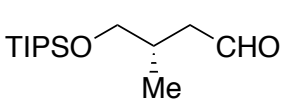
R = Me 91%, 97:3 e.r.
R = Et 74%, 97:3



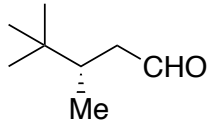
R = Me 91%, 98:2 e.r., 5:1 e/z
R = Et 95%, 95:5, 3:1 e/z



83% yield
95:5 e.r.

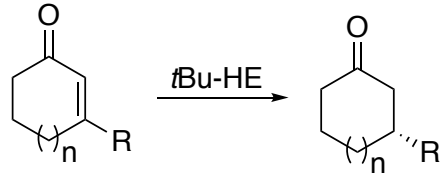


74% yield
95:5 e.r.



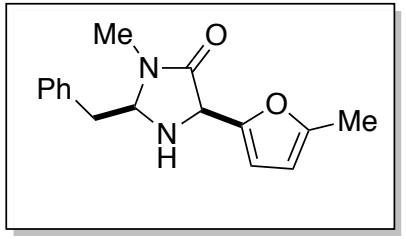
95% yield
99:1 e.r.

MacMillan (2006):



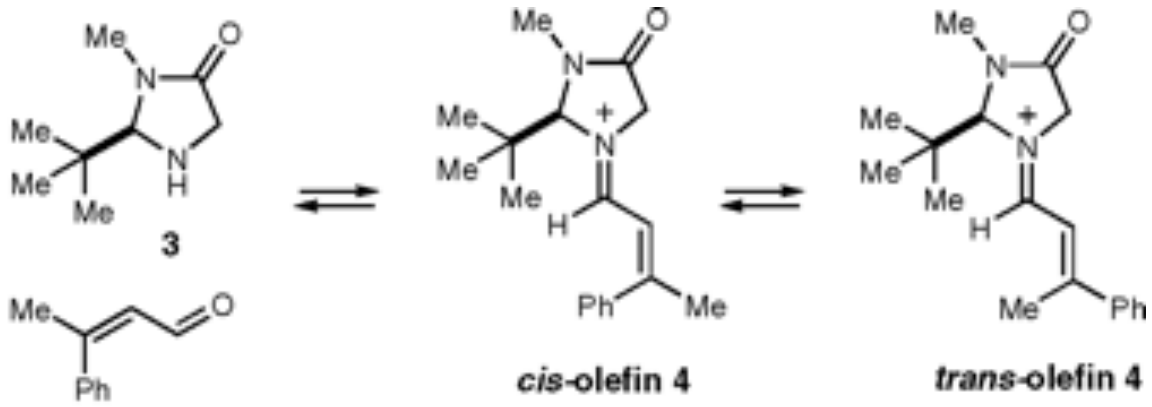
n = 0,1,2

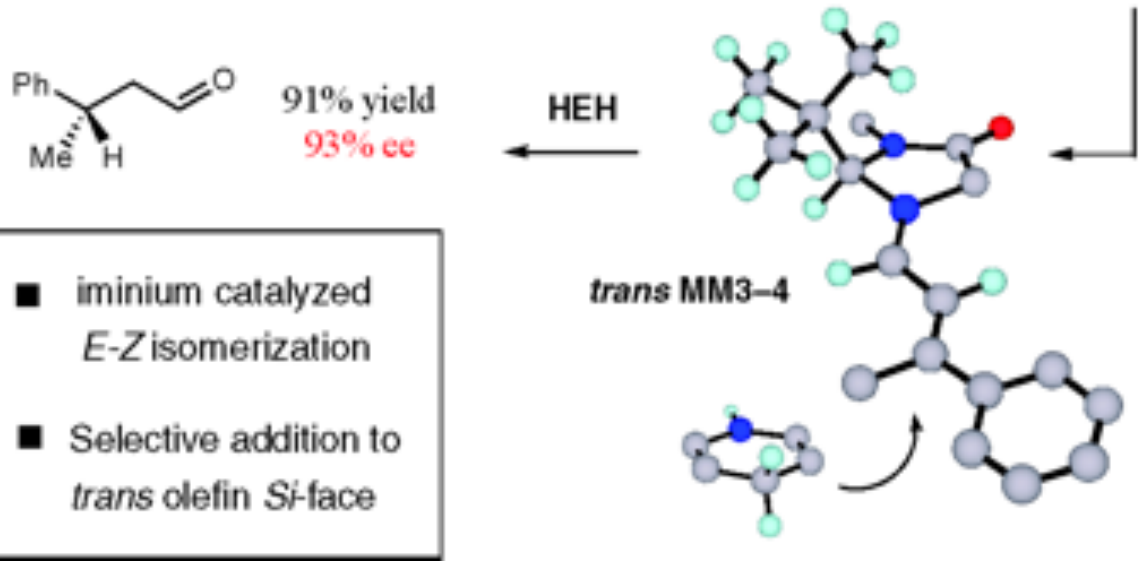
12 examples
>70% yield
>94:6 e.r.



Angew. Chem. Int. Ed. 2004, 43, 6660 –6662; J. Am. Chem. Soc. 2005, 127, 1, 32–33; J. Am. Chem. Soc. 2006, 128, 39, 12662–12663

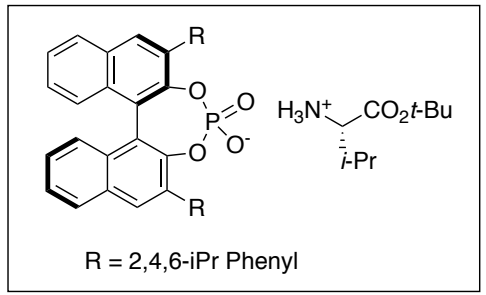
Hydrogenation of Enones

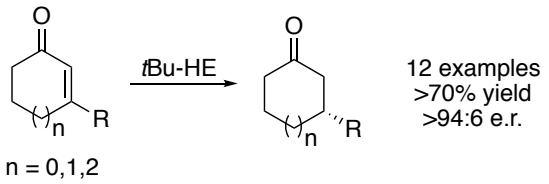


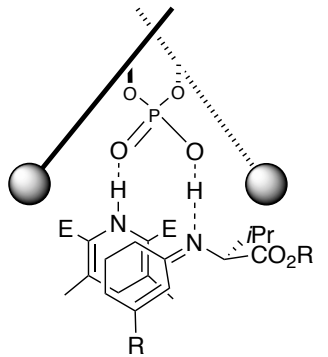


- iminium catalyzed *E-Z* isomerization
- Selective addition to *trans* olefin *Si*-face

List (2006):



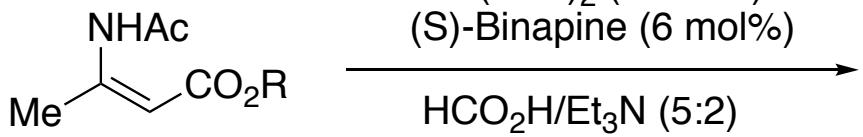




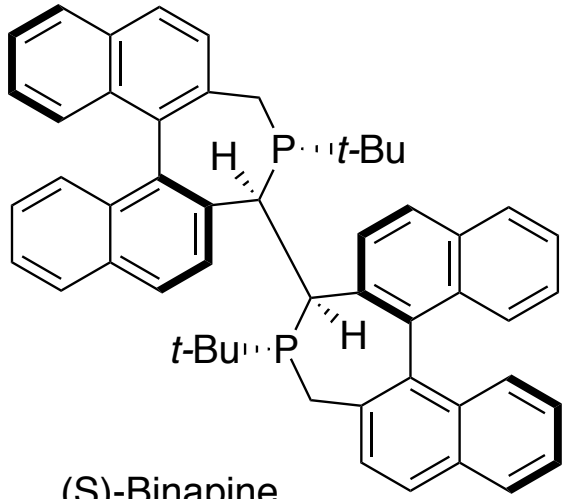
Acc. Chem. Res. 2007, 40, 12, 1327–1339
J. Am. Chem. Soc. 2006, 128, 41, 13368–13369

Synthesis of Enriched β-Amino-Acids

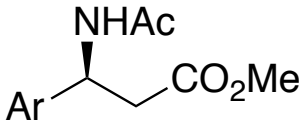
Zhou (2014):



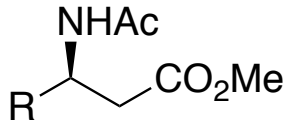
R = Me, 94%, 99:1 e.r.
Et, 97%, 98:2 e.r.
i-Pr 97%, 97:3 e.r.



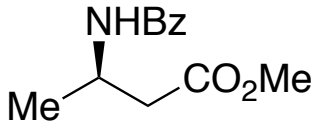
(S)-Binapine



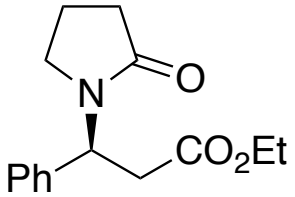
11 examples
>95% yield
>99:1 e.r.



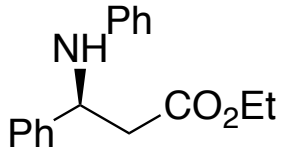
R = Me, 94%, 99:1 e.r.
Et, 96%, 98:2 e.r.
i-Pr 99%, 99:1 e.r.



98% yield
99:1 e.r.



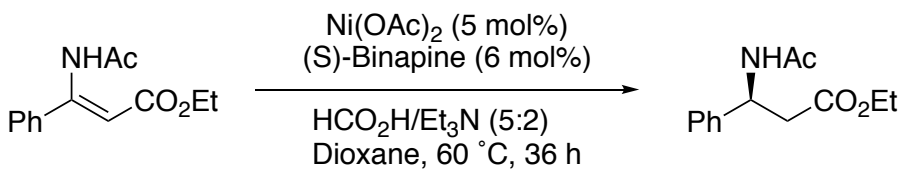
78% yield
98:2 e.r.

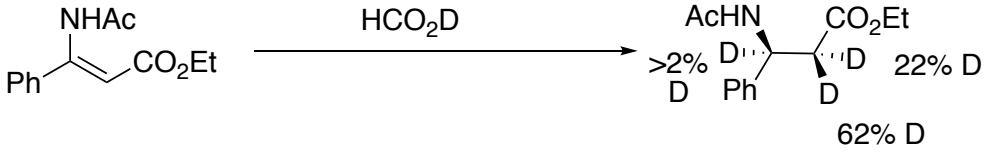


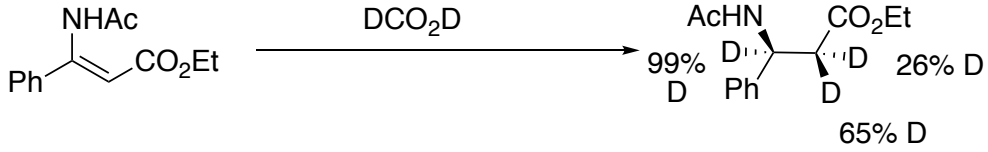
65:35 e.r.

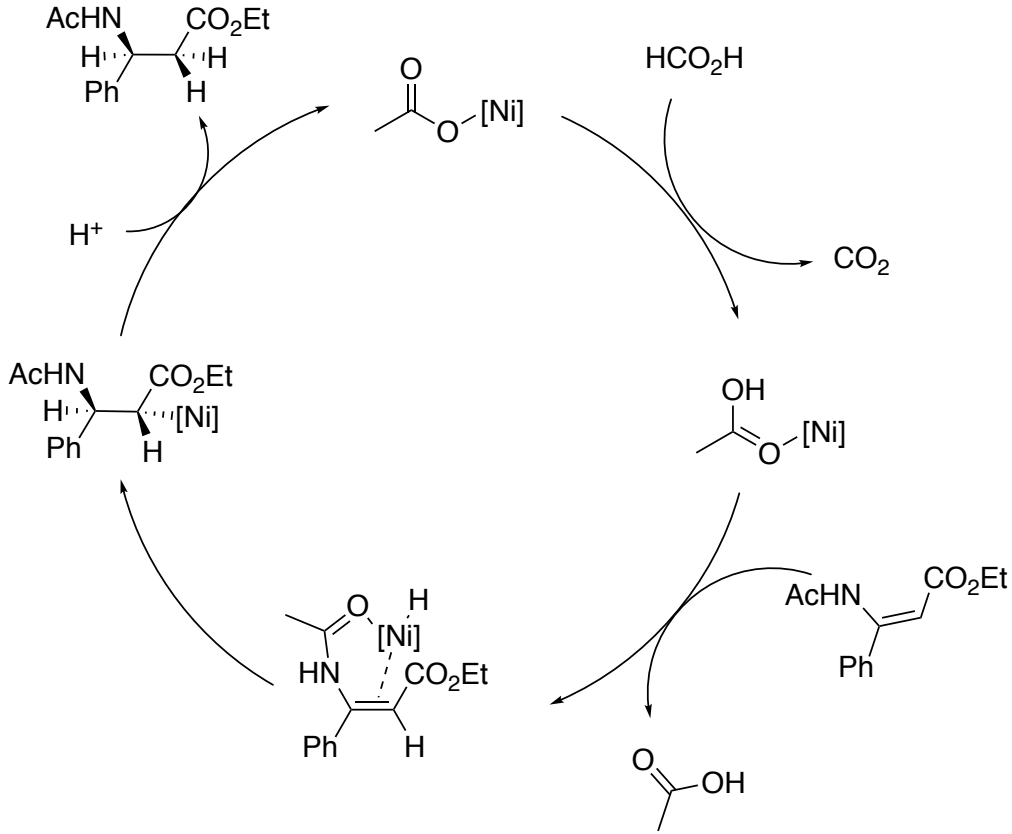
Angew. Chem. Int. Ed. 2014, 53, 12210 –12213

Mechanism?





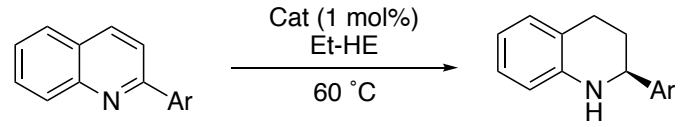




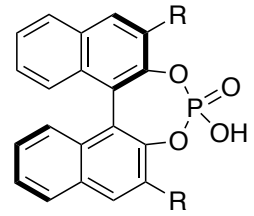
Angew. Chem. Int. Ed. 2014, 53, 12210 –12213

Hydrogenation of Quinolines

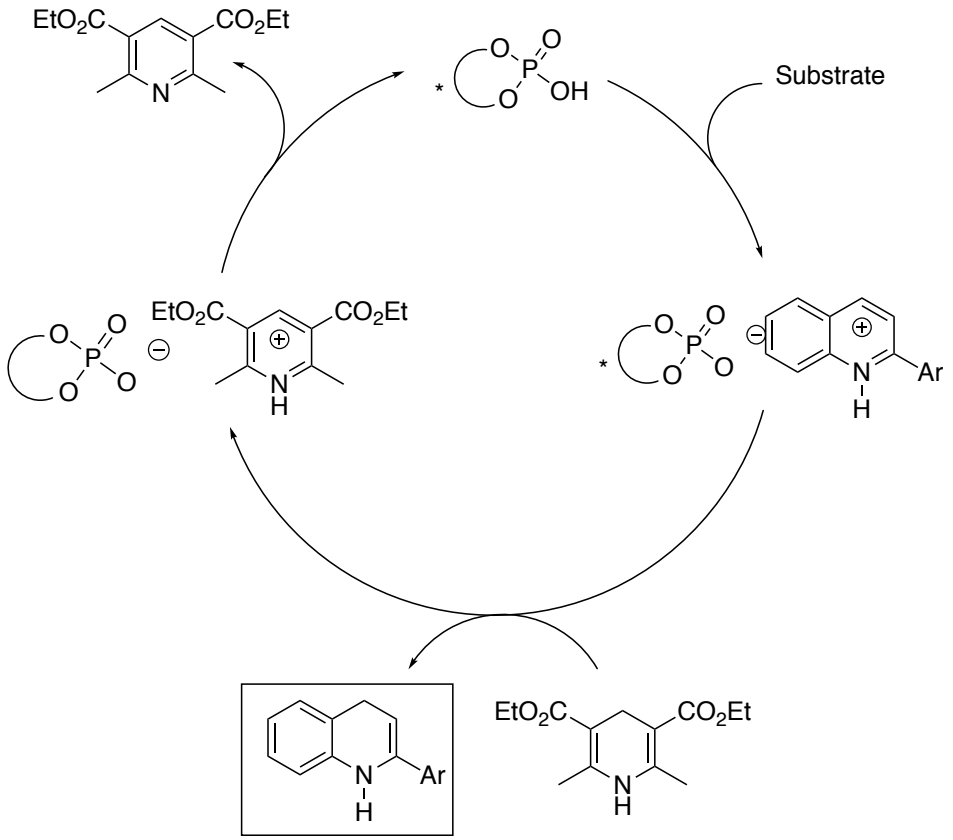
Reuping (2006):

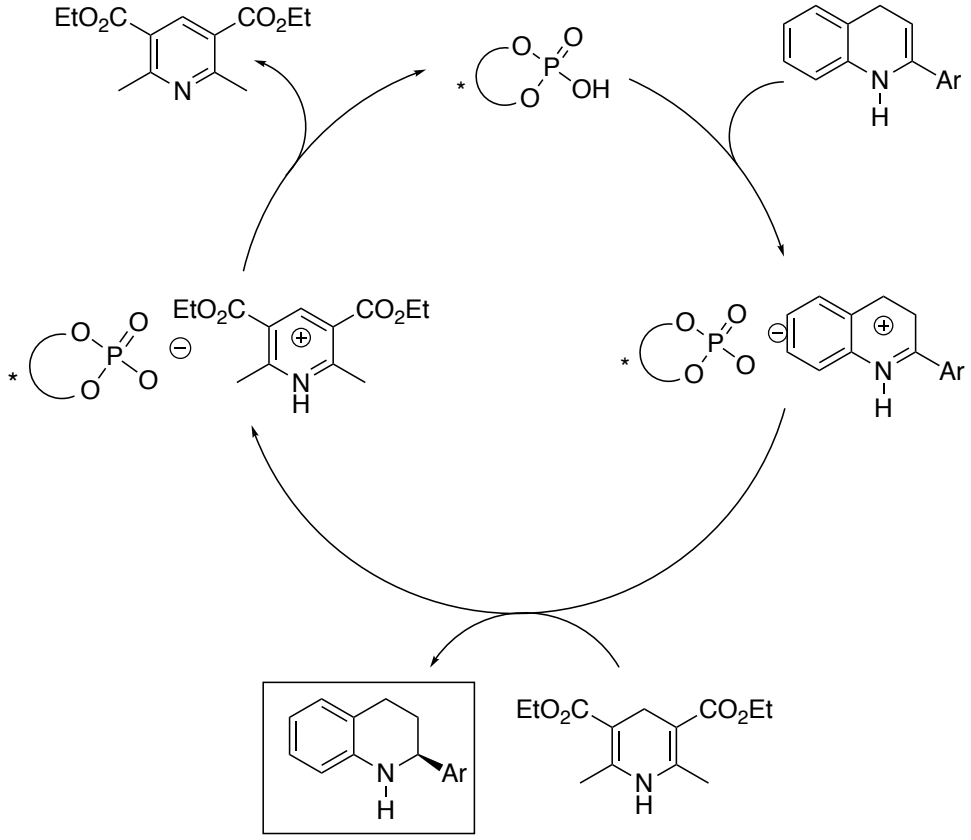


14 examples
>80% yield
>93:7 e.r.



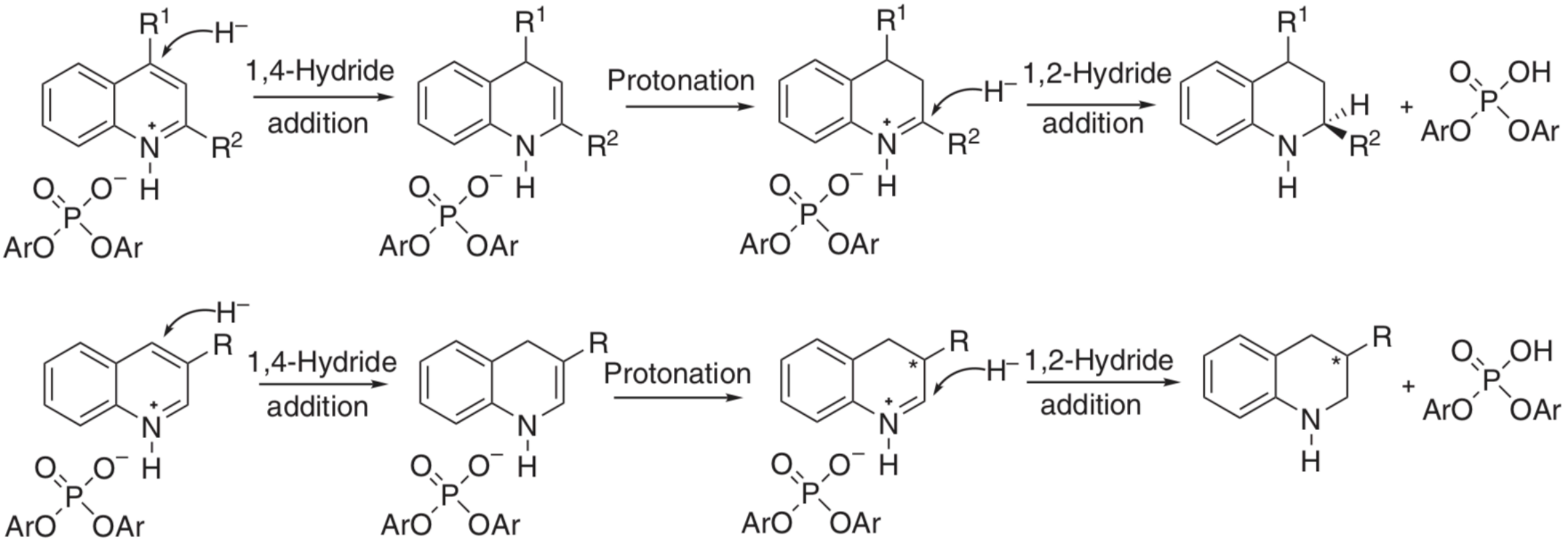
R = 9-phenanthryl





Angew. Chem. Int. Ed. 2006, 45, 3683 –3686

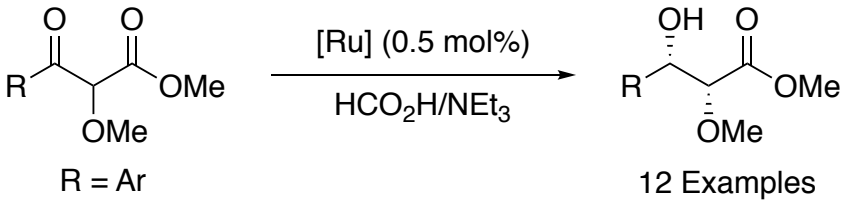
Hydrogenation of Quinolines



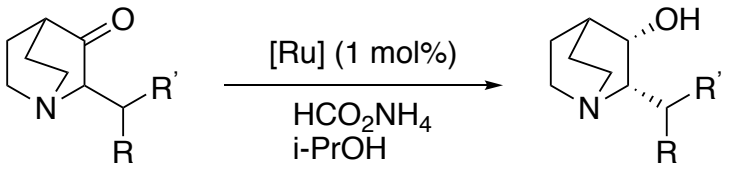
Angew. Chem. Int. Ed. 2006, 45, 3683 –3686

DKR Hydrogenations

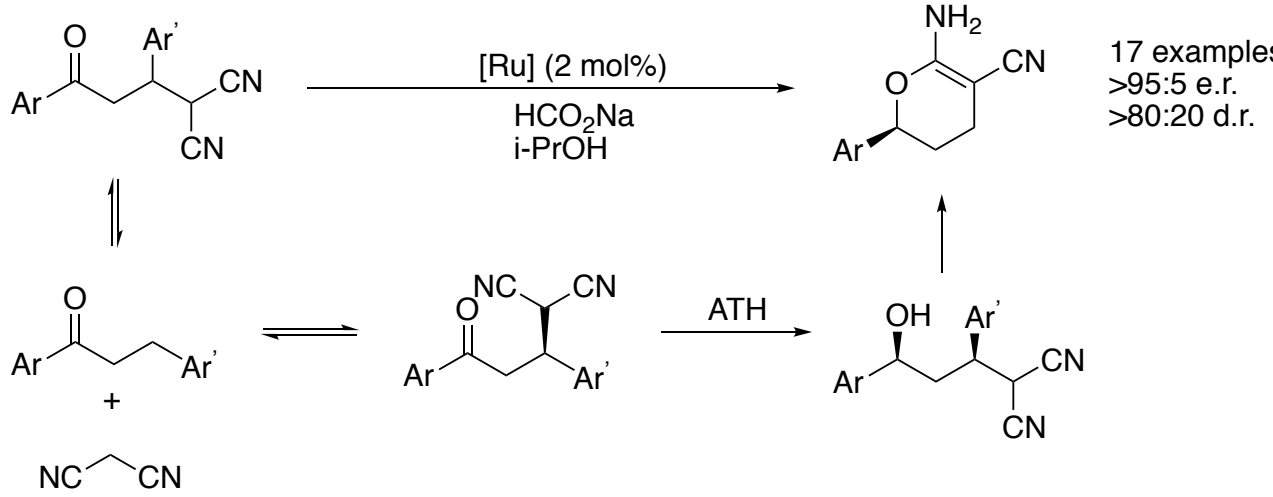
Phansavath and Ratovelomana (2019):

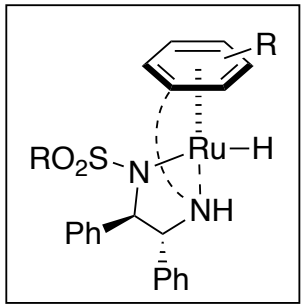


Wang and Zhang (2020):



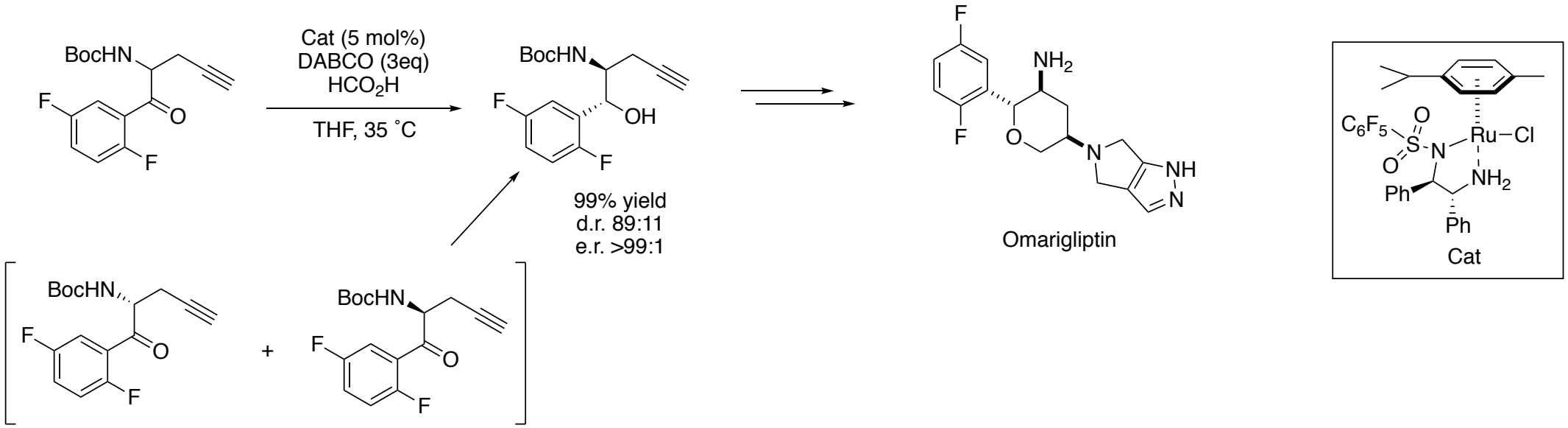
Liu and Wang (2017):

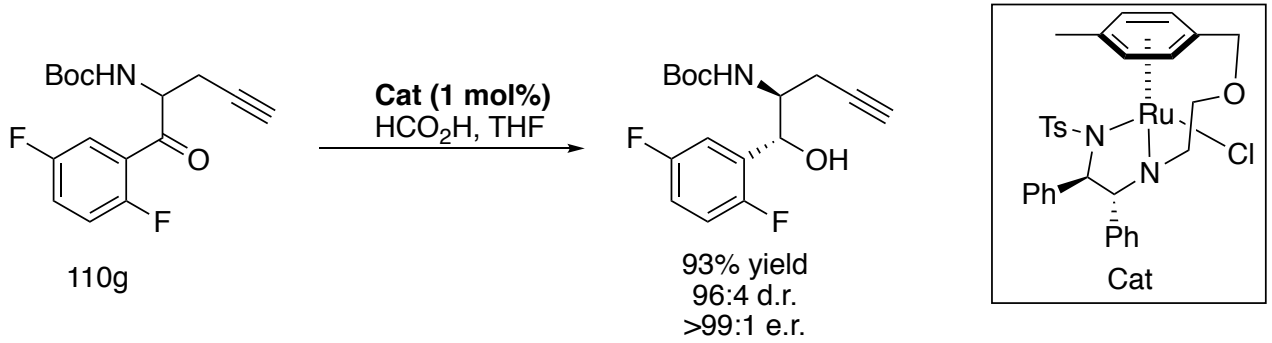




Chem.Commun.,2017,53,6113--6116
ChemSusChem 2019, 12,3032 –3036
Org. Lett. 2020, 22, 4322−4326

Large Scale DKR (Merck)



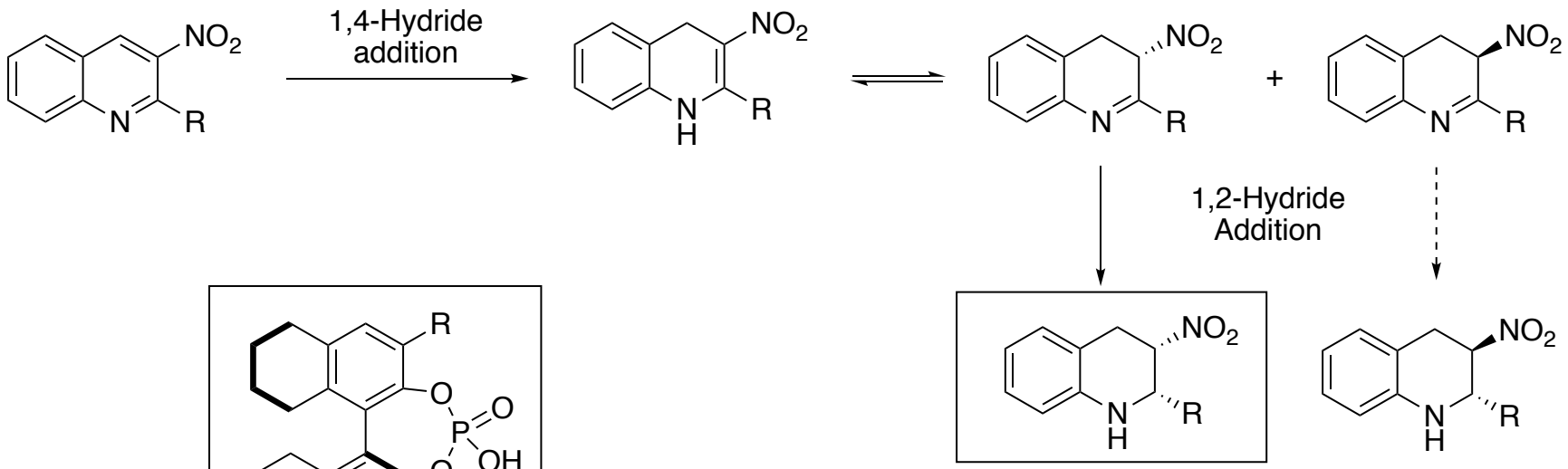


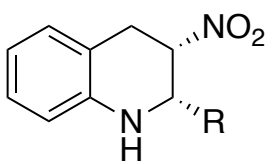
Org. Lett. 2014, 16, 20, 5422–5425

Org. Process Res. Dev. 2015, 19, 1760−1768

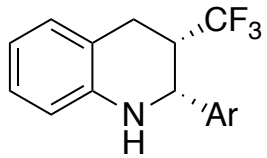
DKR of 2,3-Substituted Quinolines

Zhou (2013):





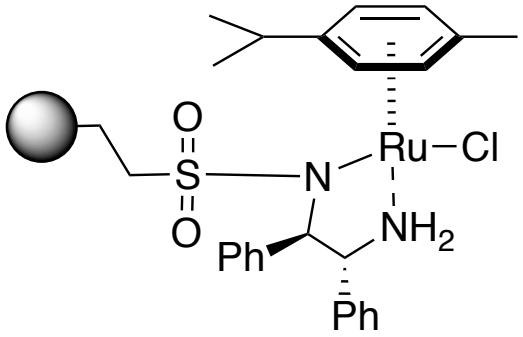
15 Examples
> 20:1 d.r.
>95:5 e.r.



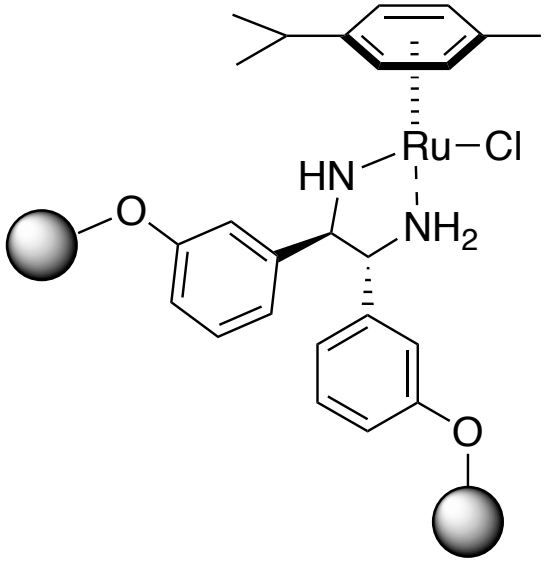
10 Examples
> 20:1 d.r.
>95:5 e.r.

Chem. Asian J. 2013, 8, 1381 – 1385
Synthesis 2014, 46, 2751–2756

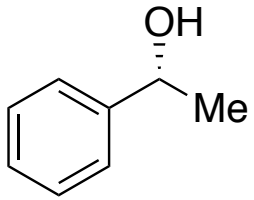
Supported “Green” Catalysts



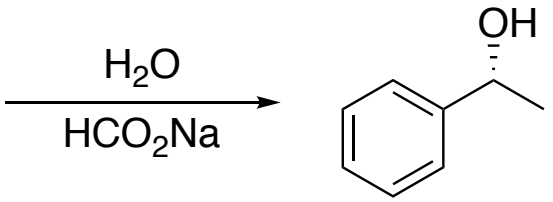
= Silica, Celite, PEG



= PEG



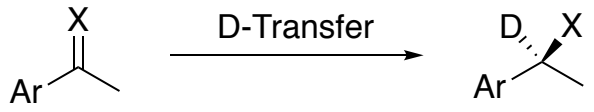
1st run: 99% yield, >99:1 e.r.
10th run: 95% yield, >99:1 e.r.



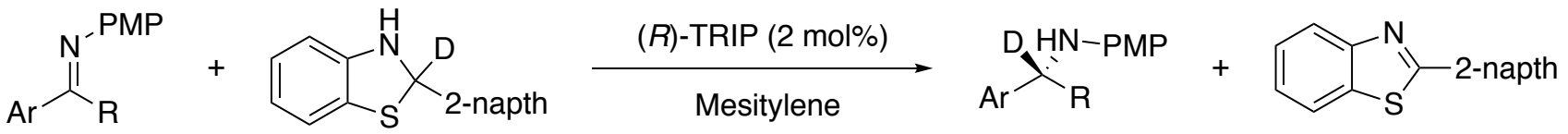
>10 runs
95:5 e.r.

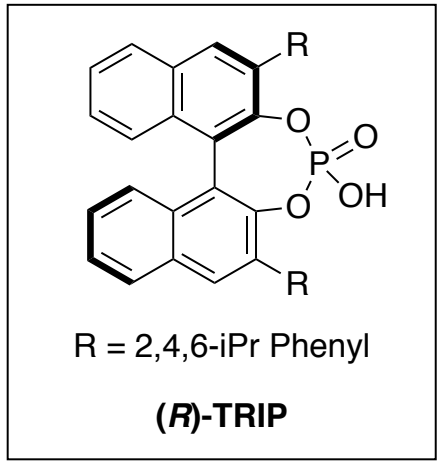
Org. Lett. 2004, 6, 19, 3321–3324
Org. Lett. 2004, 6, 2, 169–172

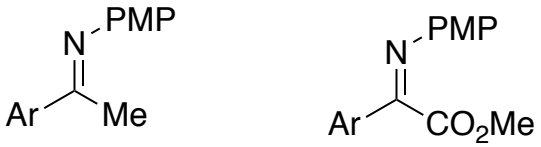
Transfer Deuteration

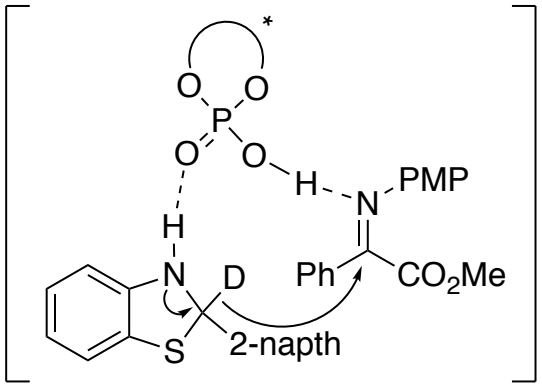


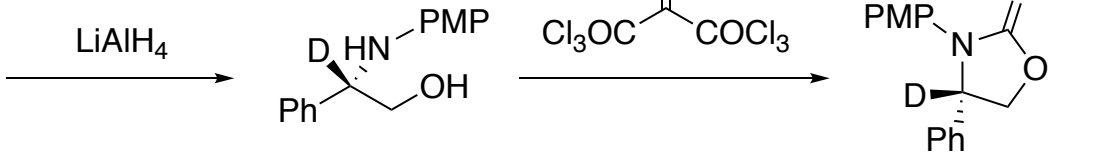
Akiyama (2012):





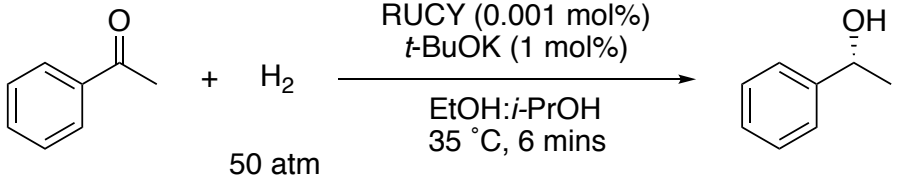






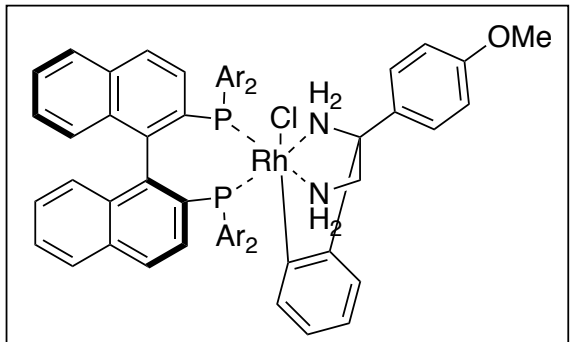
Org. Lett. 2012, 14, 13, 3312–3315

ETH vs EH

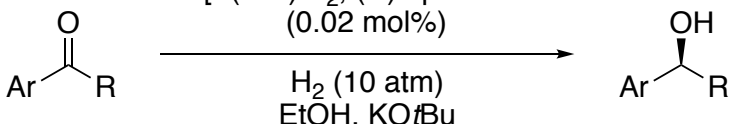


>99% yield
>99:1 e.r.

TOF: >500 s^{-1}

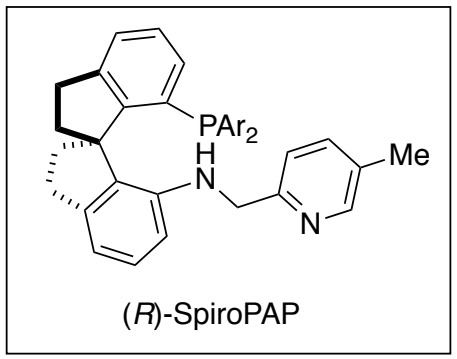


RUCY

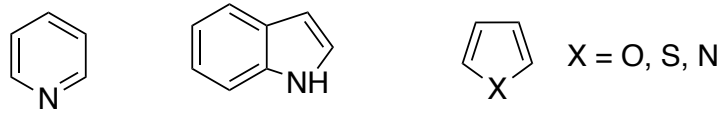


96-99% yield
>96:4 e.r.

TON: > 4,000,000



(*R*)-SpiroPAP

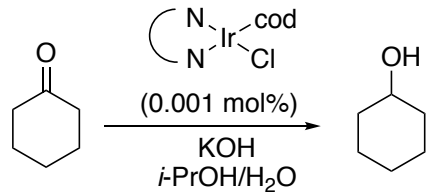


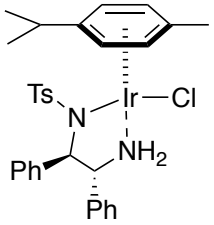
[Pd] [Ru] [Ir]

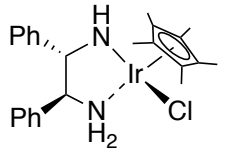
J. Am. Chem. Soc. 2011, 133, 10696–10699
Angew. Chem. Int. Ed. 2011, 50, 7329 –7332

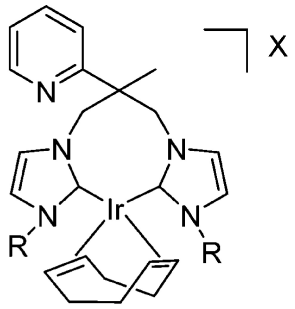
Honorable Mention Ir-TH

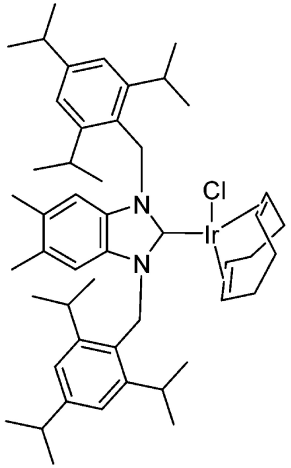
Mestroni (1976):



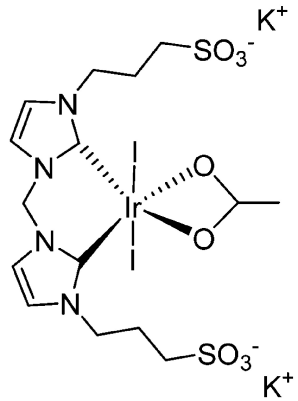








TOF: 800 s^{-1}



J. Organomet. Chem. 1977, 140, 63–72
Chem. Rev. 2015, 115, 13, 6621–6686

Questions?