Transfer Hydrogenation of Imines, Olefins and Quinolines with Isopropanol as Hydride Donor

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Content

1. Introduction
2. Transfer Hydrogenation of Imines
3. Transfer Hydrogenation of Olefins
4. Transfer Hydrogenation of Quinolines
5. Conclusion

1. Introduction

The stereoselective reduction of prochiral compounds has been achieved by several methods, such as hydrogenation, **transfer hydrogenation**, hydroboration, reaction with aluminum or boron hydrides, hydrosilylation and enzymatic reduction.

1) It is operationally simple;

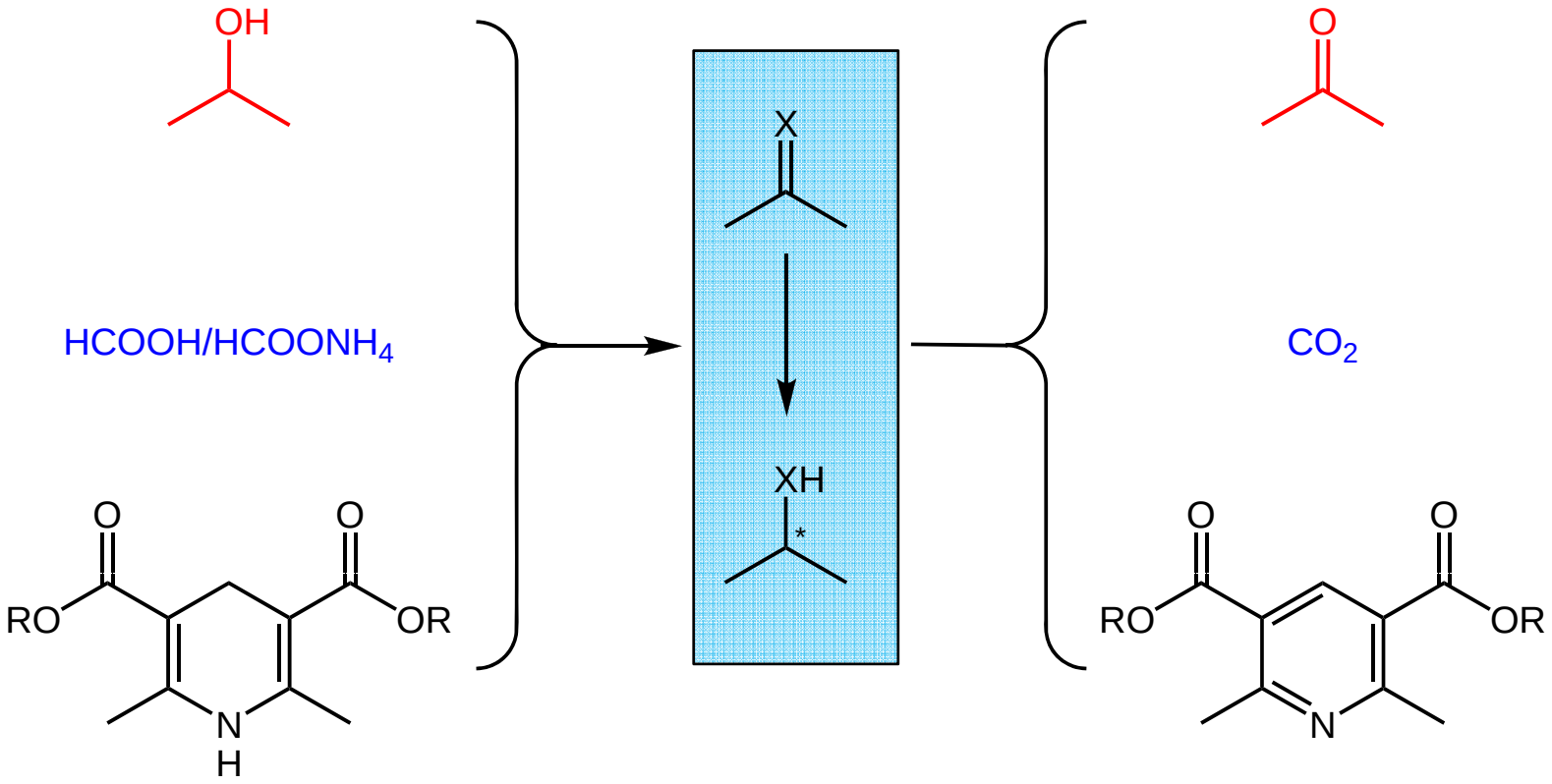
2) Low loadings of the metal catalysts are normally used;

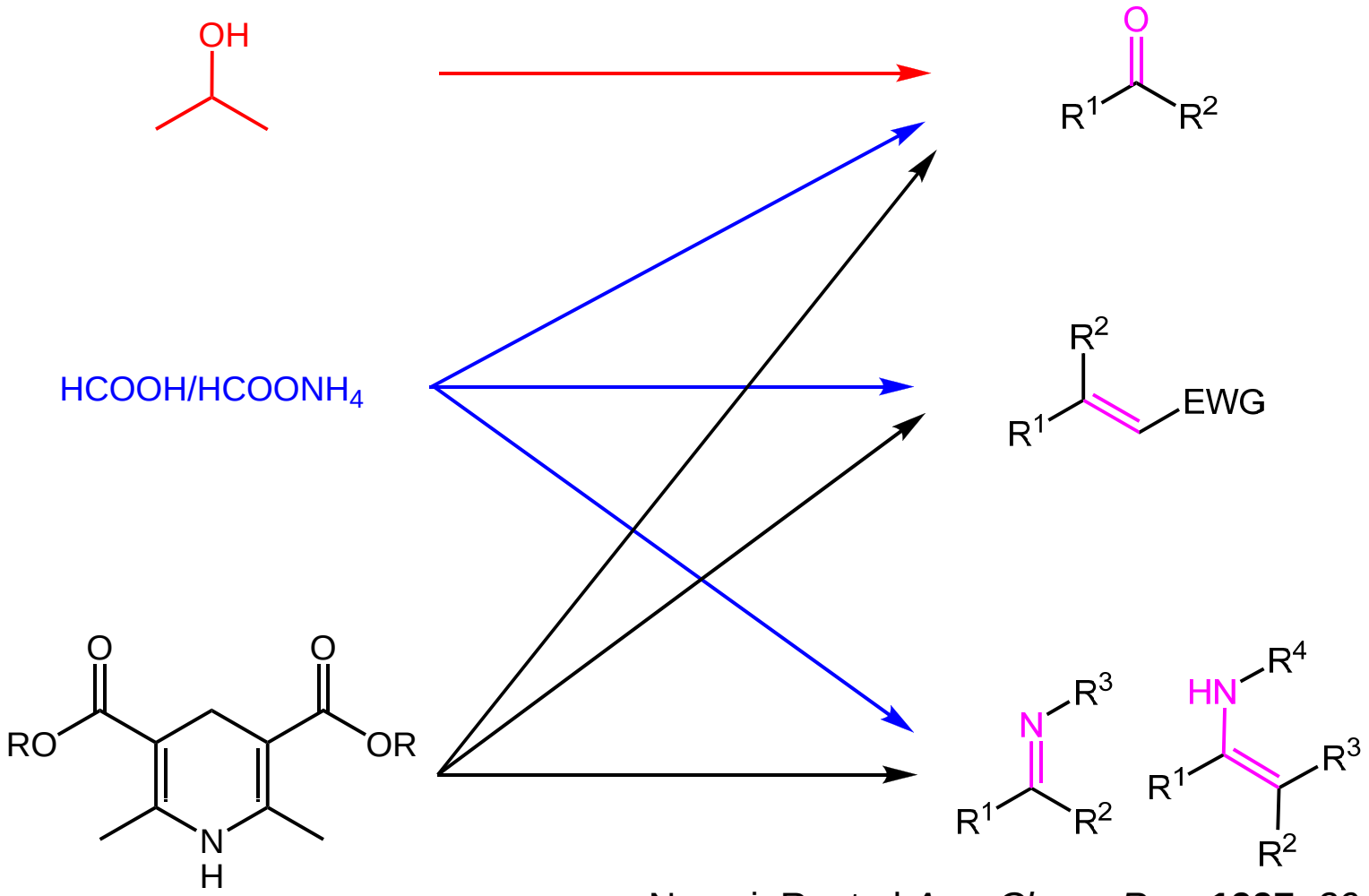
3) It avoids the handling of hazardous chemicals, such as molecular hydrogen or metallic hydrides;

4) The isolation of the reduction products is facilitated by the fact that volatile reaction byproducts are formed, such as acetone or carbon dioxide;

5) The reactions can be performed in environmentally benign solvents, like water;

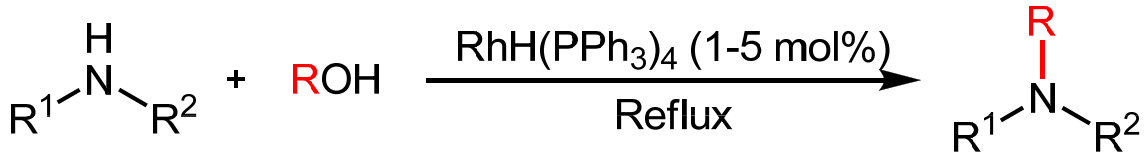
6) The methodology has been demonstrated to be applicable to industrial processes.


OH
HCOOH/HCOONH4
O
O
RO
OR
N
H
X
XH
*
O
CO2
O
O
RO
OR
N



Noyori, R. et al *Acc. Chem. Res.* **1997***, 30,* 97;
Xiao, J. et al *Chem. Asian J.* **2008**, *3*, 1750;
You, S.-L. et al *Chem. Soc. Rev.* **2012**, *41*, 2498

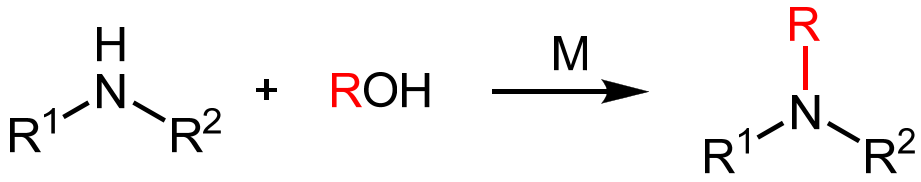
2. Transfer Hydrogenation of Imines



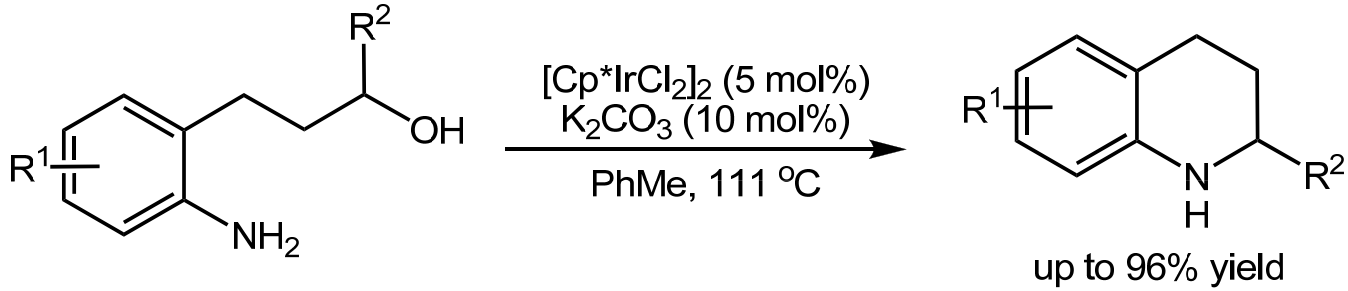
up to 99% yield

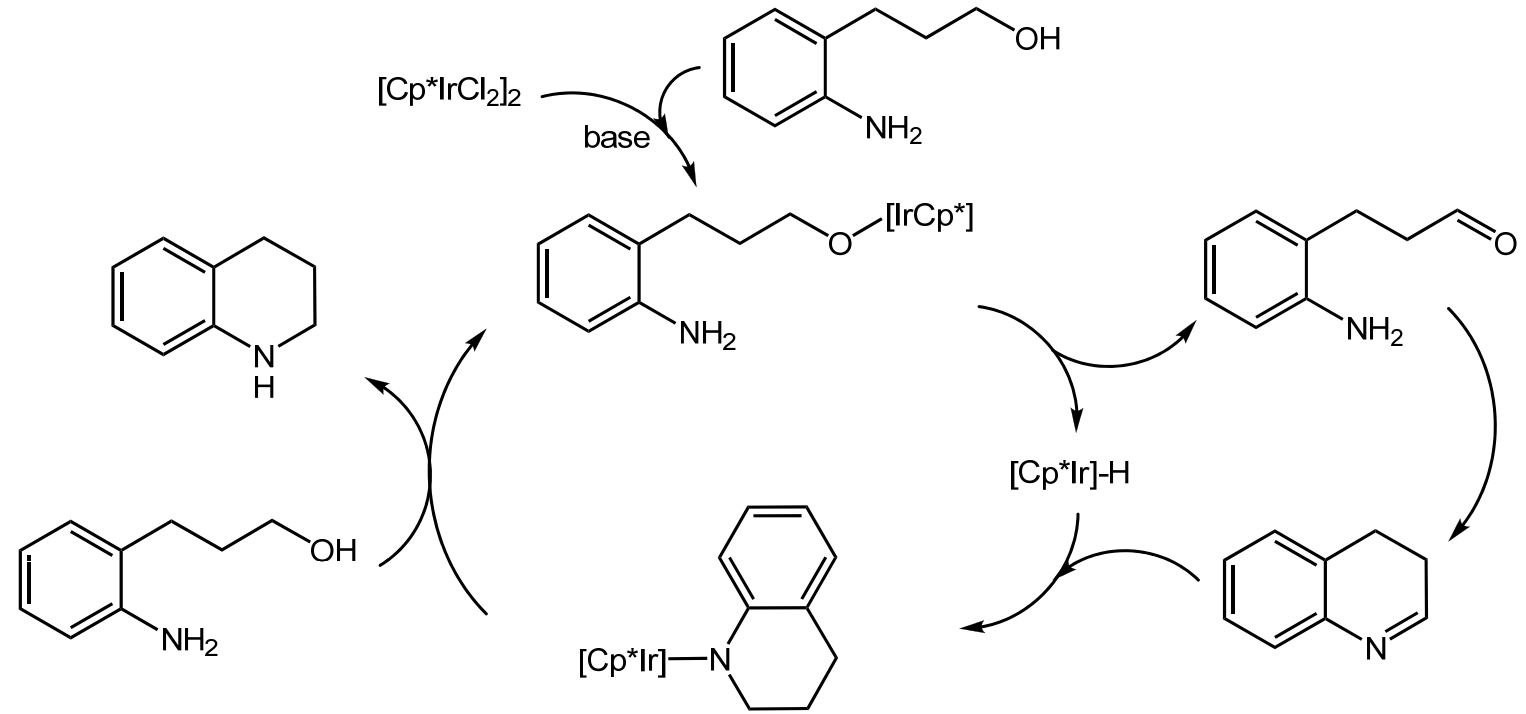
Grigg, R. et al *J. Chem. Soc., Chem. Commun.* **1981**, 611

hydrogen-transfer process

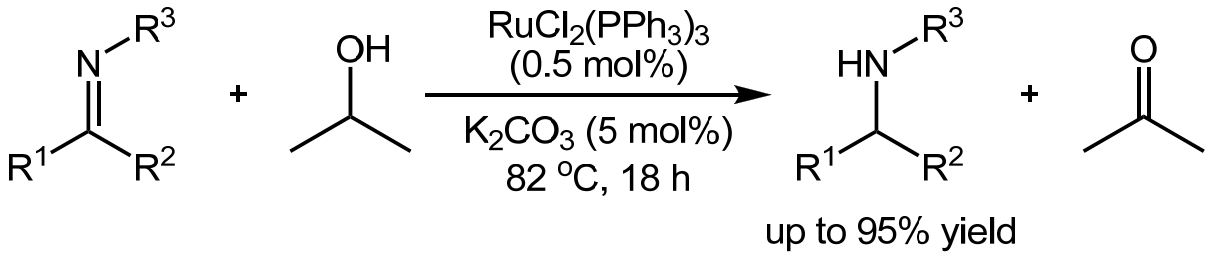


Beller, M. et al *ChemCatChem* **2011**, *3*, 1853;
Yus, M. et al *Chem. Rev.* **2010**, *110*, 1611;
Williams, J. M. J. et al *Adv. Synth. Catal.* **2007**, *349*, 1555





Yamaguchi, R. et al *Org. Lett.* **2002**, *4*, 2691

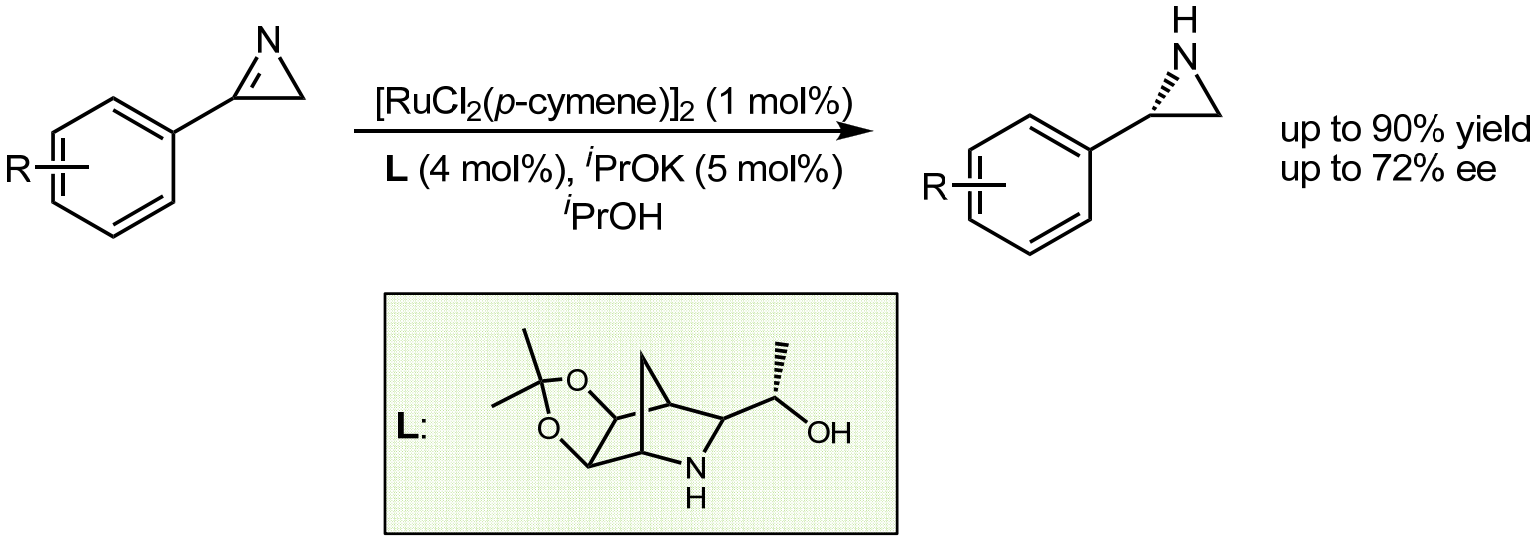


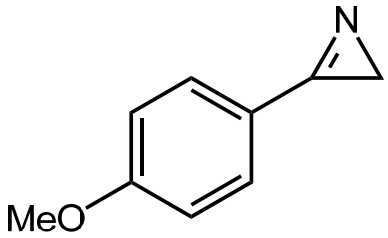
1. Aldimines generally react faster than ketimines,
   Aliphatic imines are more reactive than aromatic imines.

2. When compared with the ruthenium-catalysed transfer hydrogenation of ketones, the reaction rate of imines is much lower.

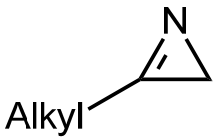
Backvall, J.-E. et al *J. Chem. Soc., Chem. Commun.* **1992**, 980

Asymmetric Version

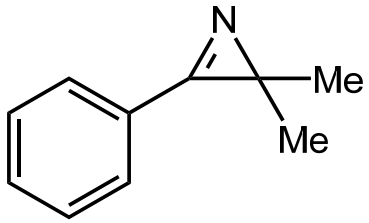




72% yield, 0% ee

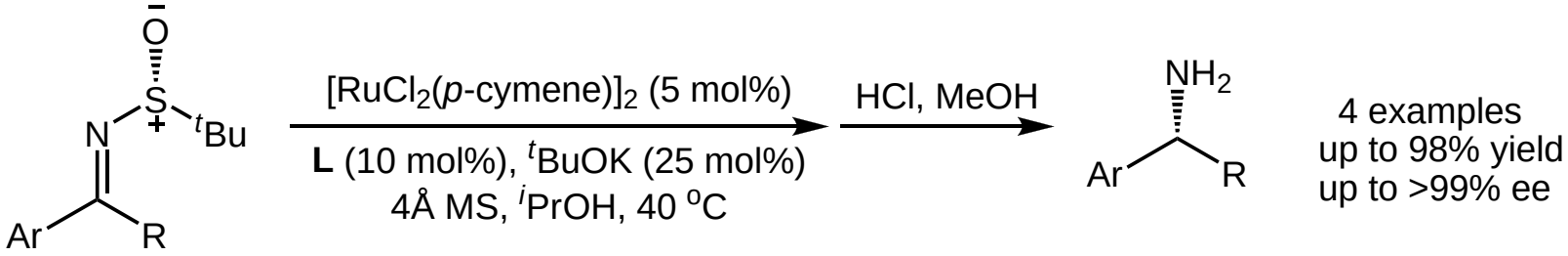


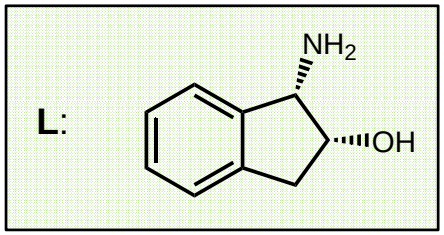
less stable
difficult to isolate



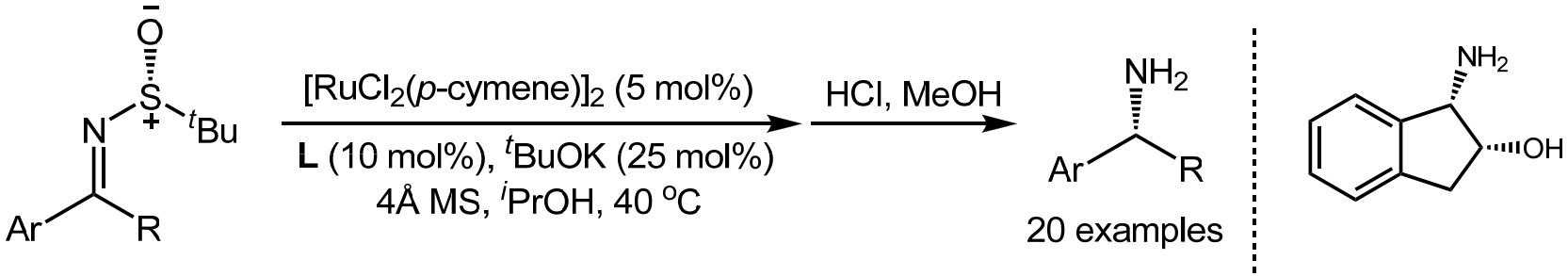
<5% conv.

Andersson, P. G. et al *Chem. Commun.* **2002**, 1752



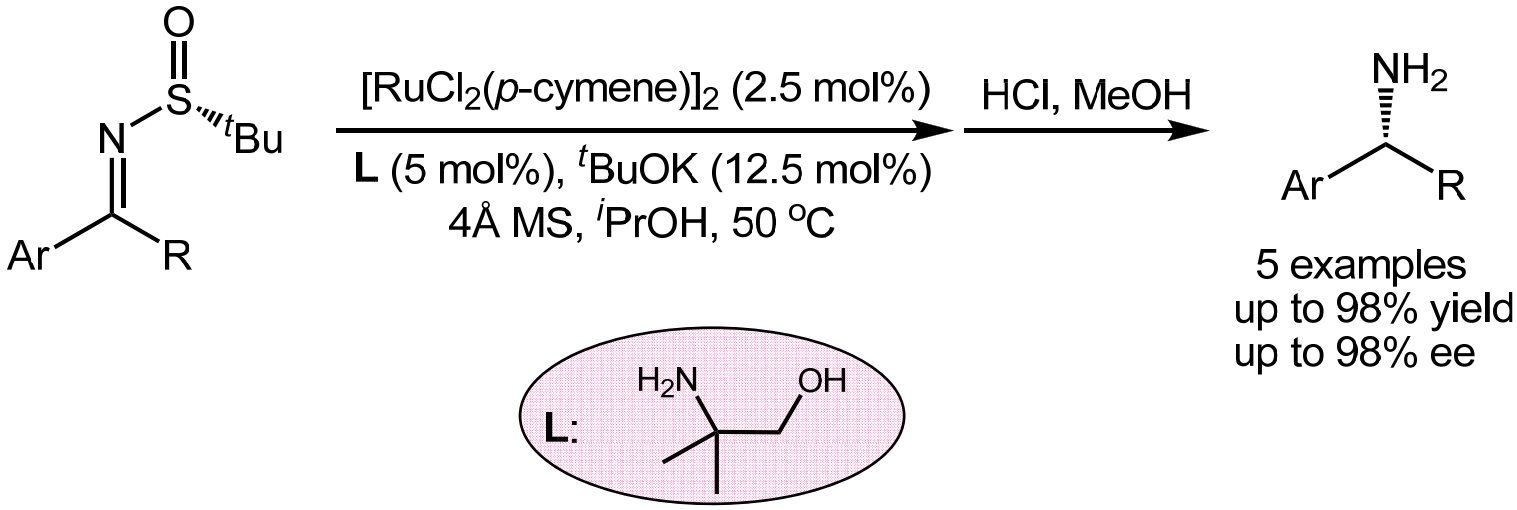


Yus, M. et al *Tetrahedron Lett.* **2009**, *50*, 5386

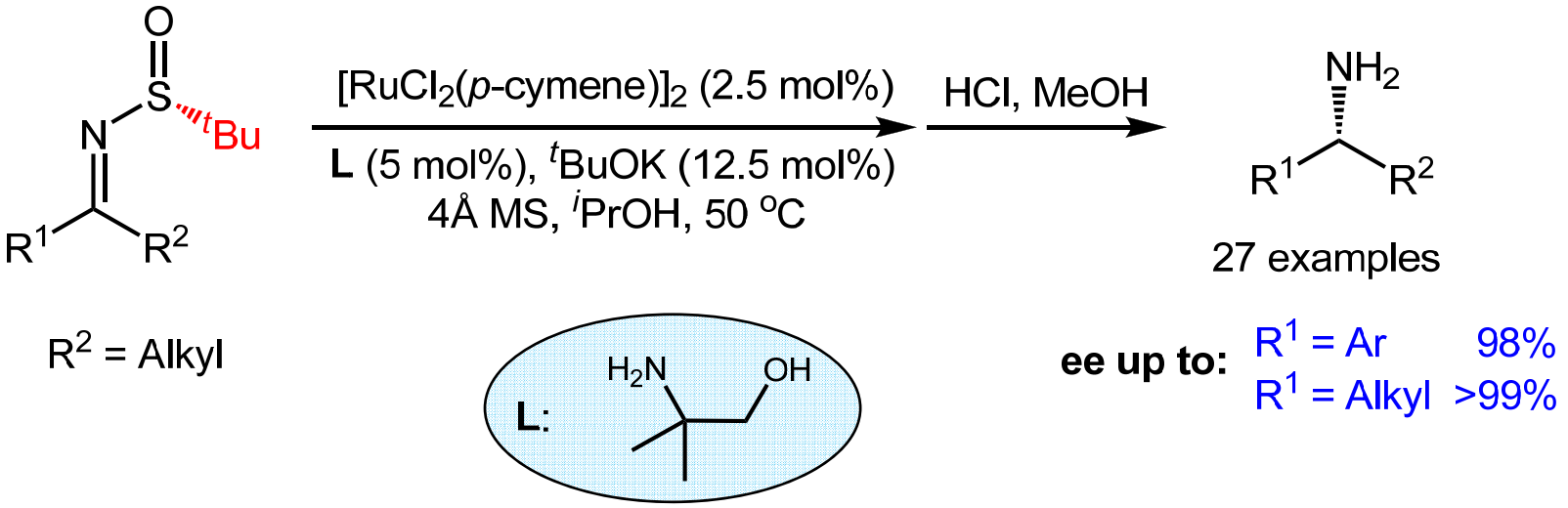


The configuration of the imine plays a leading role in determining the stereochemical outcome of the reaction, but the structure of the ligand also has an influence on the stereoselectivity.

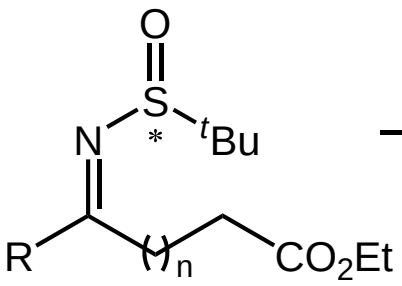
Yus, M. et al *J. Org. Chem.* **2010**, *75*, 5265



Yus, M. et al *Tetrahedron Lett.* **2011**, *52*, 789



Yus, M. et al *Chem. Eur. J.* **2012**, *18*, 1969



(n = 1-3)

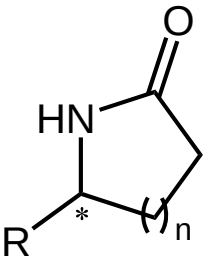
$[RuCl_2(p\text{-cymene})]_2$ (x mol%)

L (y mol%), ^{t}BuOK (z mol%)

4Å MS, ^{i}PrOH, 50 ^{o}C

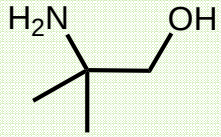
HCl, MeOH;

Basic extraction



ee up to >99%

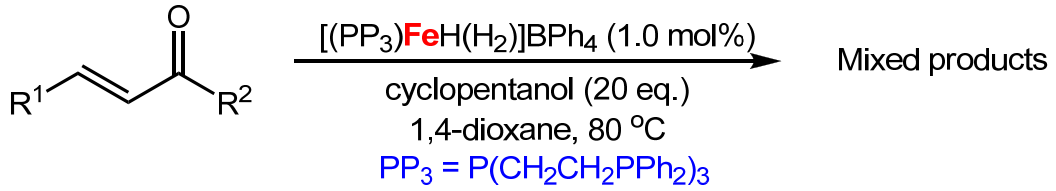
L:

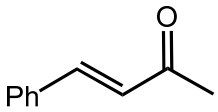
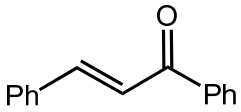
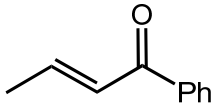
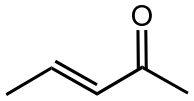
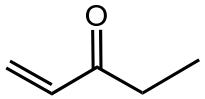


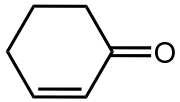
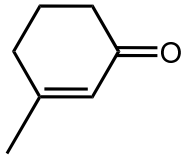
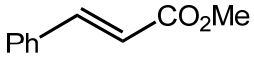
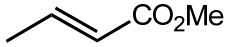
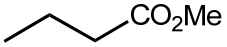
R = Ar:	x = 2.5,	y = 5,	z = 12.5
R = Alkyl:	x = 5,	y = 10,	z = 25

Yus, M. et al *J. Org. Chem.* **2013**, *78*, 3647

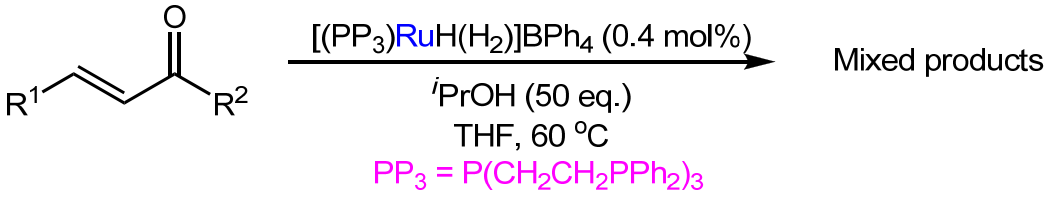
3. Transfer Hydrogenation of Olefins

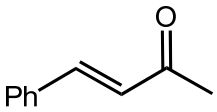
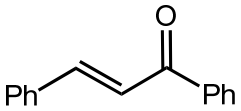
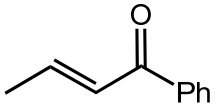
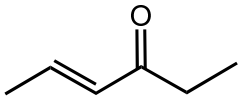
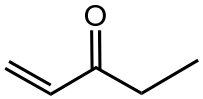


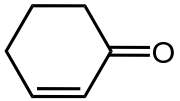
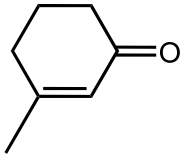
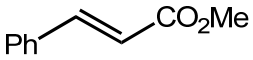
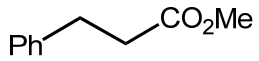
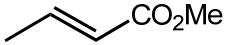
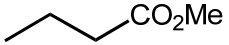
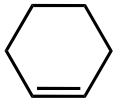
substrate	% conv. (time, h)	% sat. ketone	% sat. alcohol	% unsat. alcohol
	95 (7)	0	0	95
	30 (7)	30	0	0
	7 (5)	7	0	0
	19 (5)	19	0	0
	100 (1)	100	0	0

substrate	% conv. (time, h)	% sat. ketone	% sat. alcohol	% unsat. alcohol
	72 (5)	0	44	28
	31 (7)	0	0	31
	0 (7)			
	25 (7)			
	0 (7)			

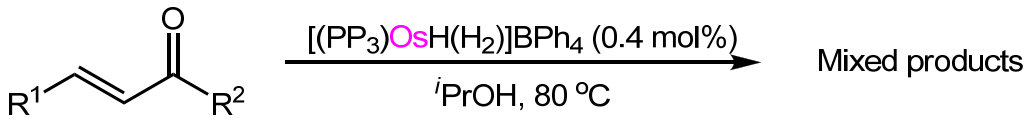
Bianchini, C. et al *Organometallics* **1993**, *12*, 3753



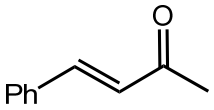
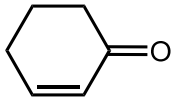
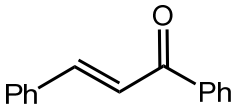
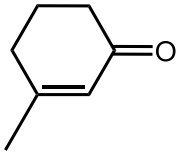
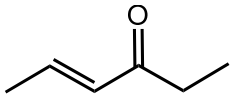
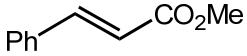
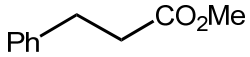
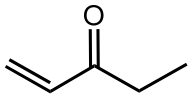
substrate	% conv. (time, h)	% sat. ketone	% sat. alcohol	% unsat. alcohol
	85 (2)	5	6	74
	97 (2)	18	79	0
	20 (1)	20	0	0
	58 (3)	56	2	0
	75 (4)	3	72	0

substrate	% conv. (time, h)	% sat. ketone	% sat. alcohol	% unsat. alcohol
	95 (1)	8	83	4
	55 (5)	0	24	31
	75 (7)			
	48 (7)			
	0 (7)			

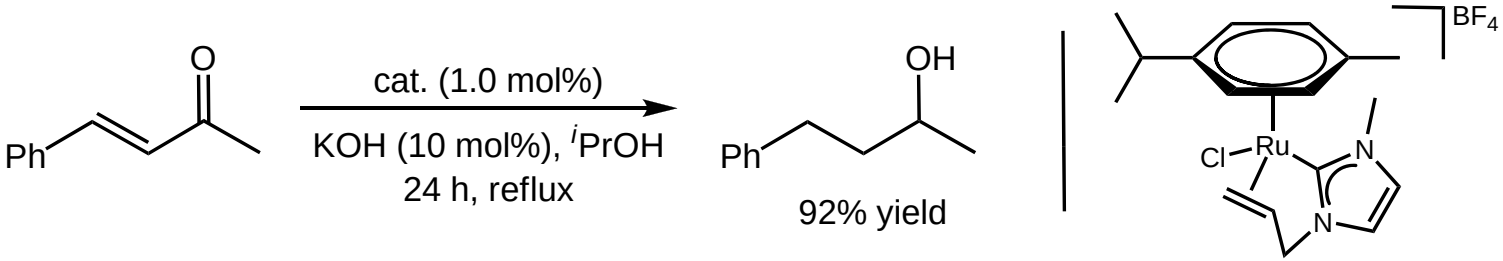
Bianchini, C. et al *Organometallics* **1993**, *12*, 3753

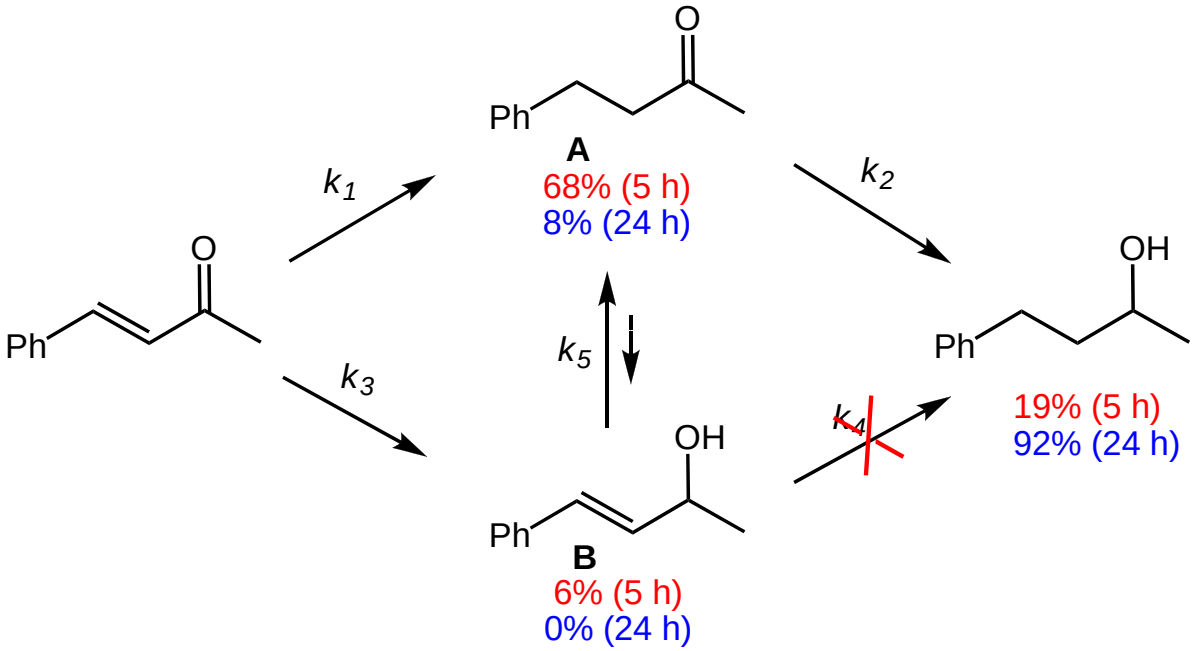


$PP_3 = P(CH_2CH_2PPh_2)_3$

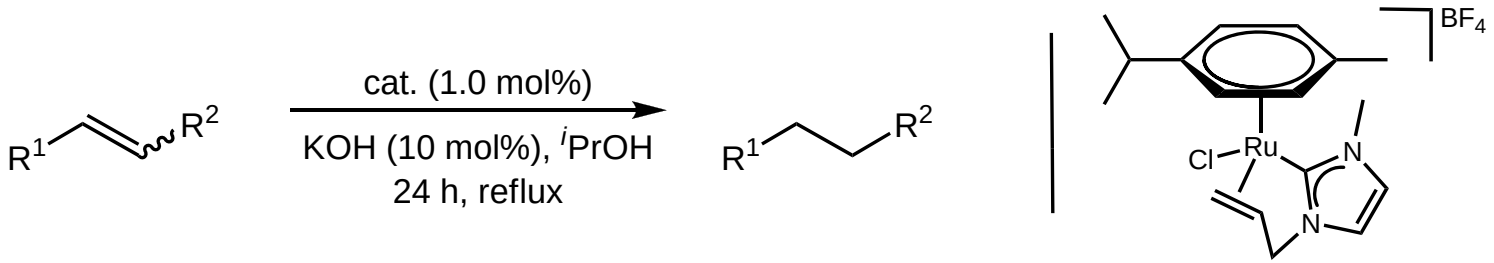
substrate	% conv. (time, h)	% sat. ketone	% sat. alcohol	% unsat. alcohol	substrate	% conv. (time, h)	% sat. ketone	% sat. alcohol	% unsat. alcohol
	91 (3)	72	10	9		91 (3)	9	77	5
	93 (7)	64	29	0		43 (7)	0	6	37
	11 (7)	11	0	0		3 (7)			
	100 (8)	95	5	0		0 (7)			

Bianchini, C. et al *Organometallics* **1993**, *12*, 3753





Albrecht, M. et al *Eur. J. Inorg. Chem.* **2011**, 2863

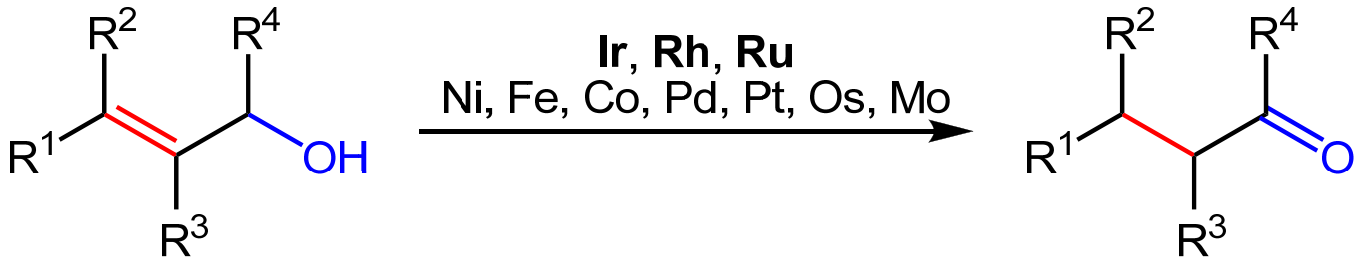


Substrate	Product	Conv.
$C_{10}H_{21}$	$C_{10}H_{21}$	100%
Ph	Ph	30%
Ph, Ph	Ph, Ph	7%
Ph	Ph	48%
Ph	Ph	92%

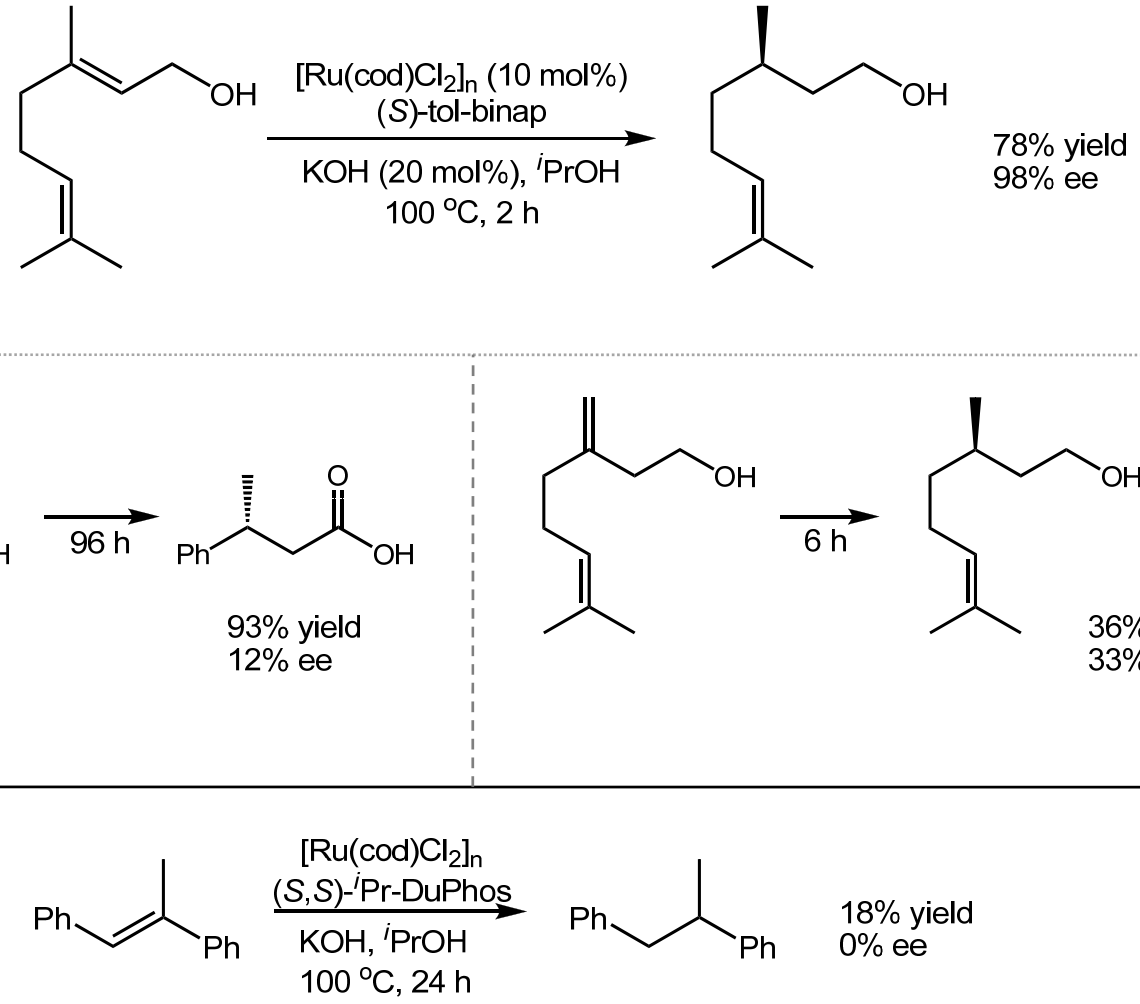
Substrate	Product	Conv.
		100%
C_3H_7, C_3H_7	C_3H_7, C_3H_7	84%
Ph	Ph	17%
C_6H_{13}	C_6H_{13}	9%
C_3H_7, C_3H_7	C_3H_7, C_3H_7	21%

Albrecht, M. et al *Chem. Commun.* **2011**, *47*, 8802

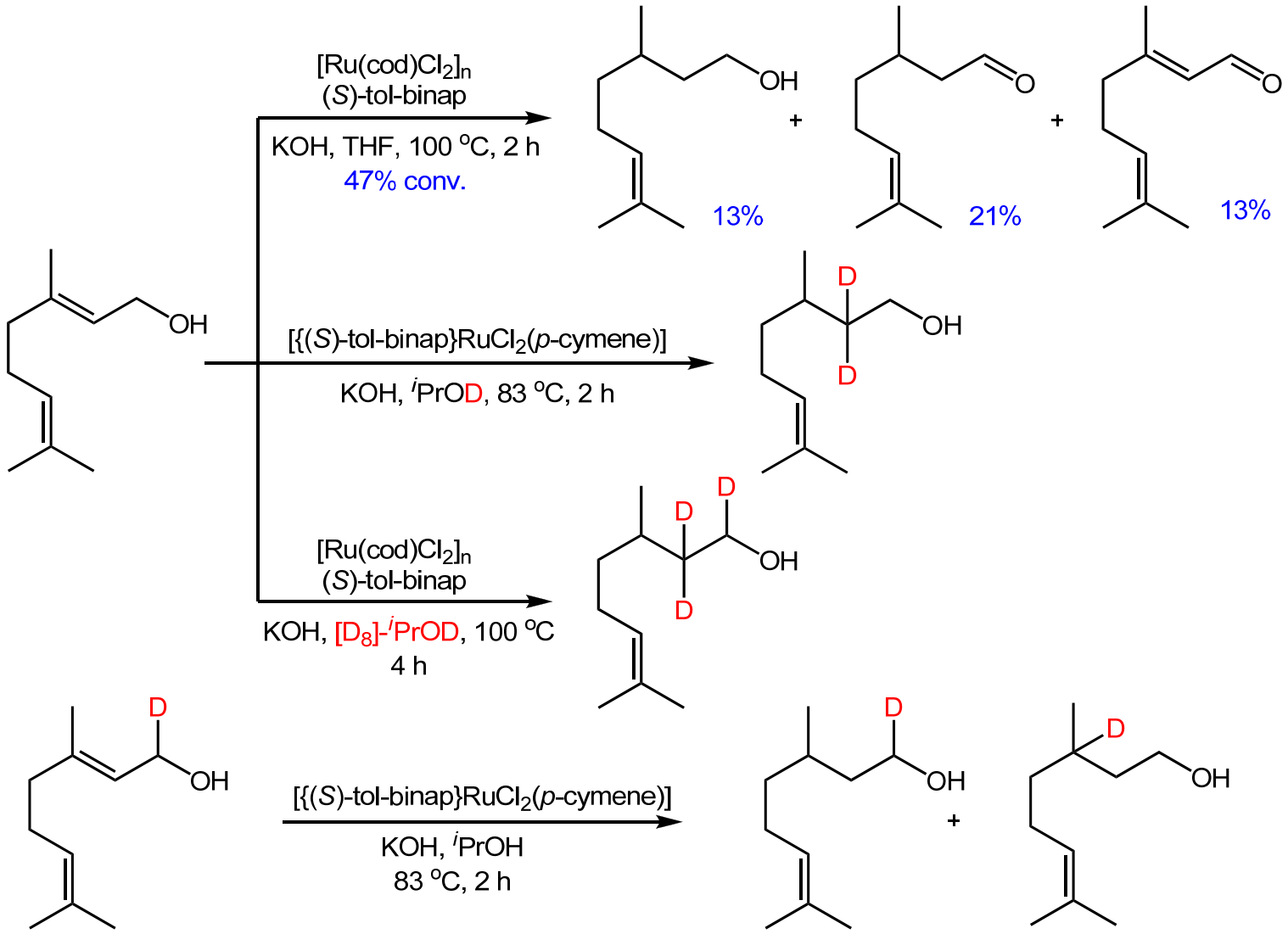
Asymmetric Version

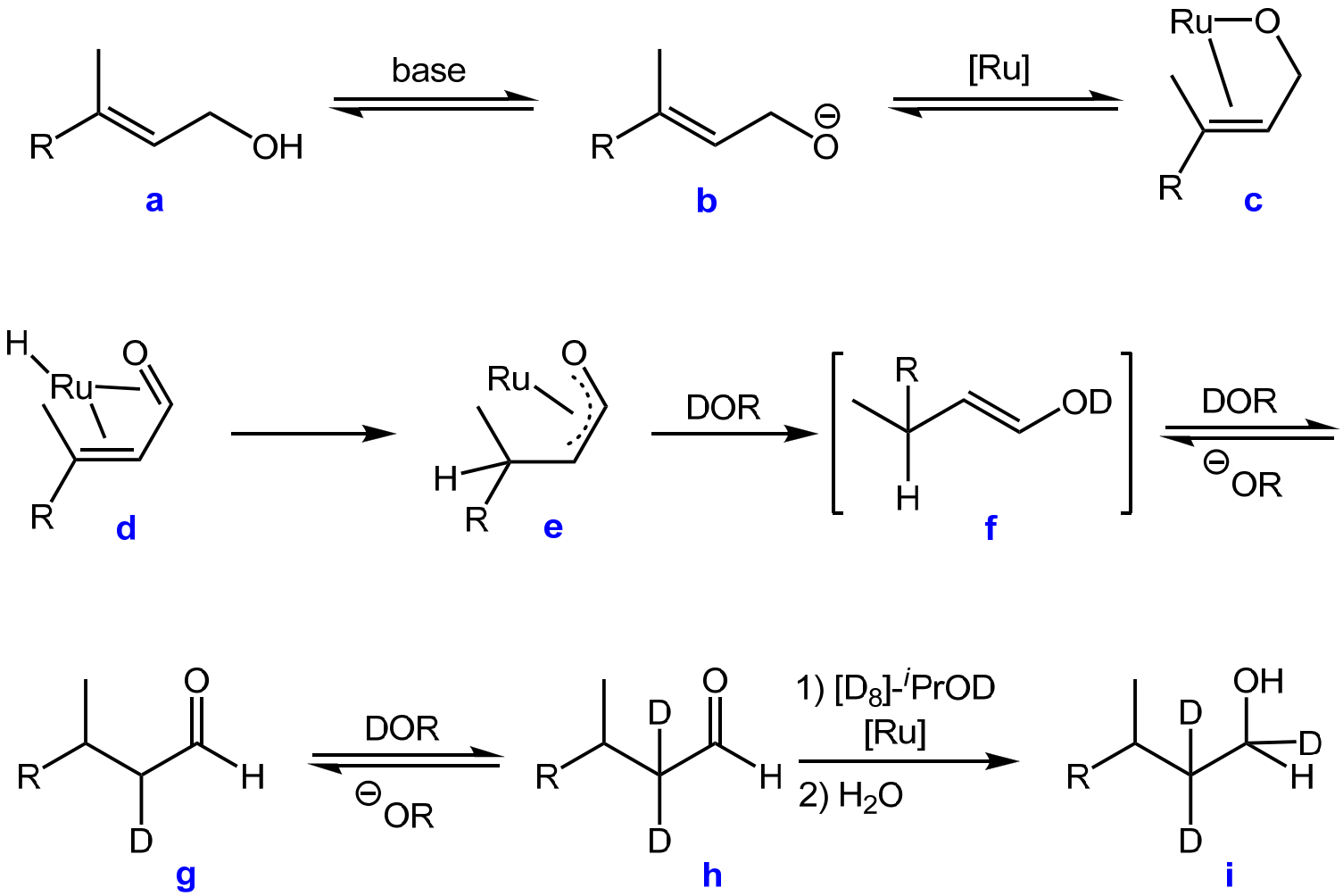


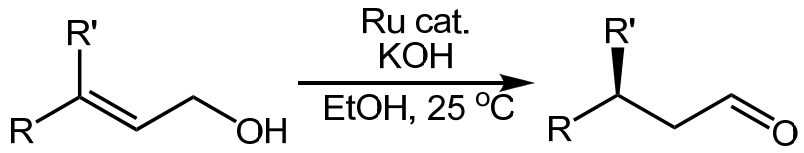
Bouwman, E. et al *J. Organomet. Chem.* **2002**, *650*, 1;
Grée, R. et al *Chem. Rev.* **2003**, *103*, 27;
Mazet, C. et al *Chem. Lett.* **2011**, *40*, 34



Sowa, J. R., Jr. et al *Angew. Chem. Int. Ed.* **2012**, *51*, 2106

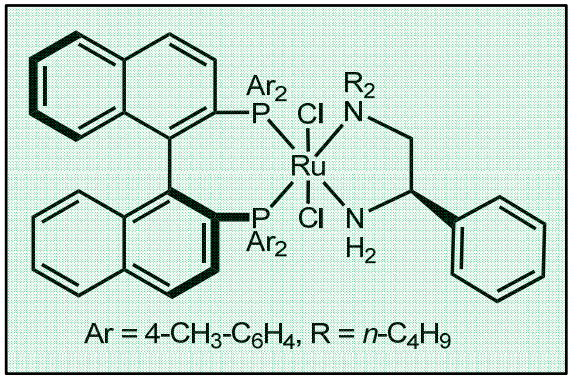

[Ru(cod)Cl2]n
(S)-tol-binap
KOH, THF, 100 °C, 2 h
47% conv.
OH
O
O
13%
21%
13%
[{(S)-tol-binap}RuCl2(p-cymene)]
KOH, iPrOD, 83 °C, 2 h
D
D
OH
[Ru(cod)Cl2]n
(S)-tol-binap
KOH, [D8]-iPrOD, 100 °C
4 h
D
D
D
OH
D
OH
[{(S)-tol-binap}RuCl2(p-cymene)]
KOH, iPrOH
83 °C, 2 h
D
OH
D
OH

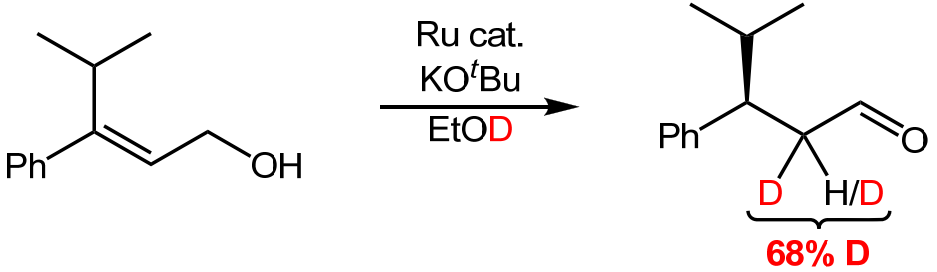

base
[Ru]
Ru
O
R
OH
a
b
c
H
d
e
DOR
OD
f
OR
D
g
h
1) [D8]-iPrOD
[Ru]
2) H2O
OH
i

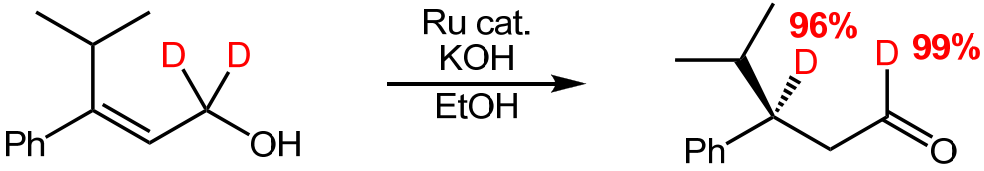


R,R' = *n*- and *sec*-alkyl, aryl, CF_3
substrate/Ru = 100-2000

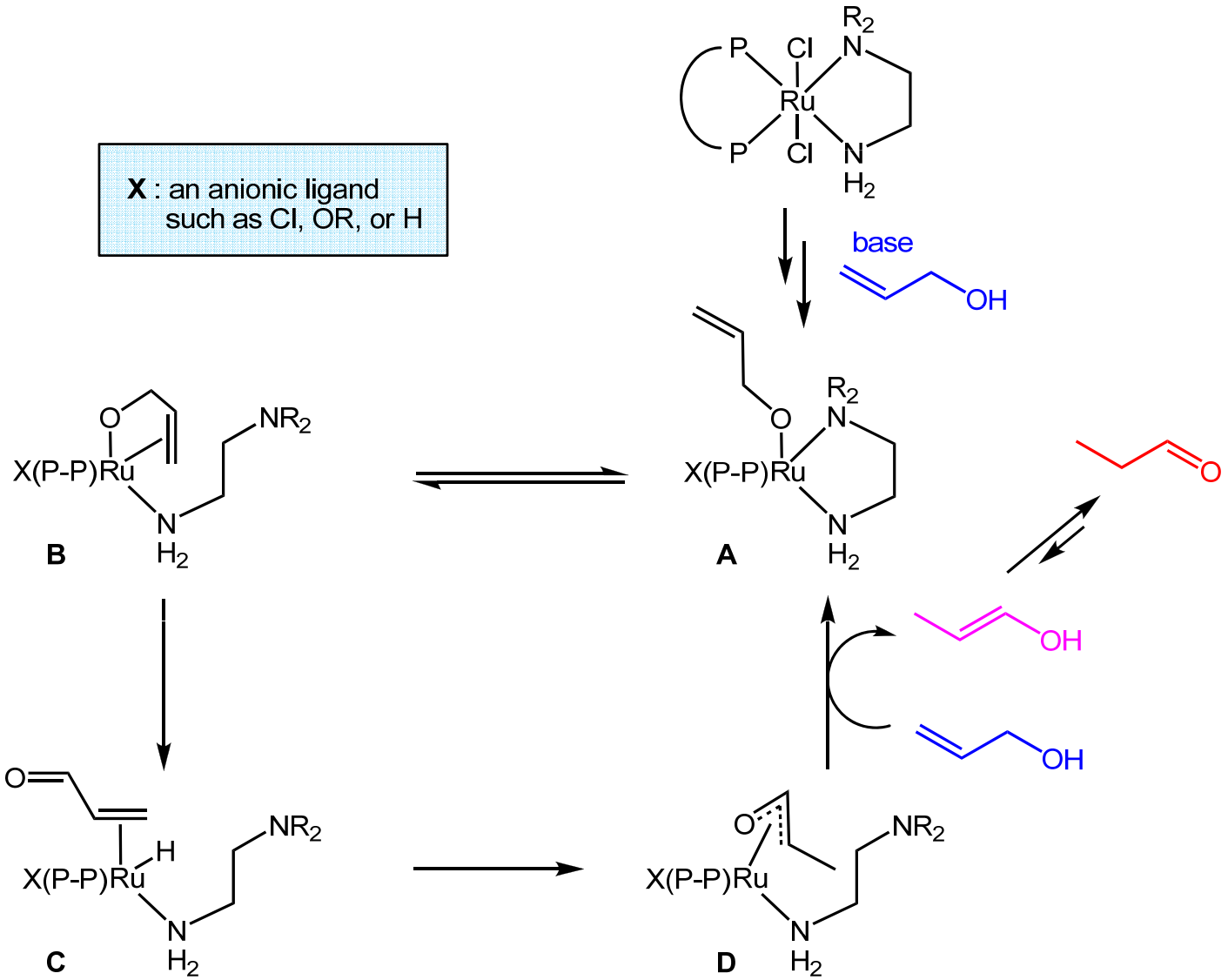
up to 92% yield
up to >99% ee



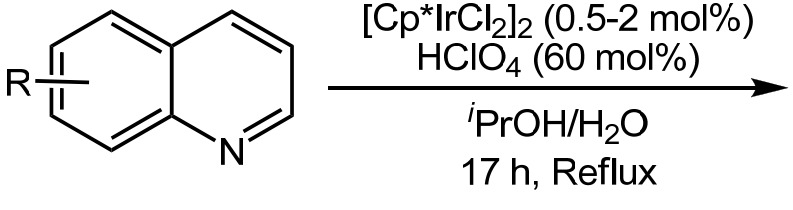




Ohkuma, T. et al *Angew. Chem. Int. Ed.* **2013**, *52*, 7500

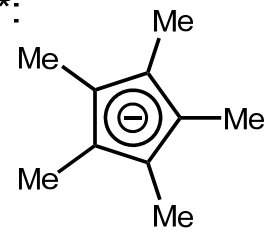

X : an anionic ligand
such as Cl, OR, or H
base
OH
OH
OH
B
A
C
D

4. Transfer Hydrogenation of Quinolines

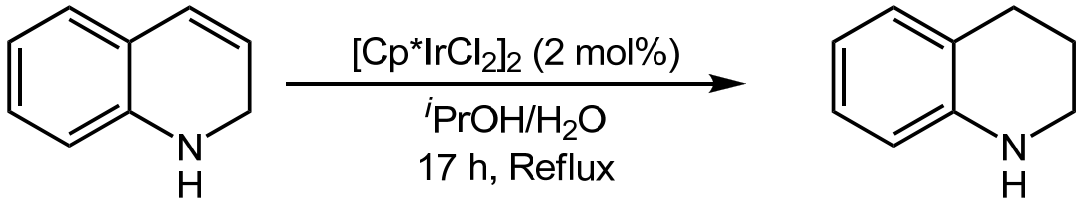


up to 94% yield

Cp*:

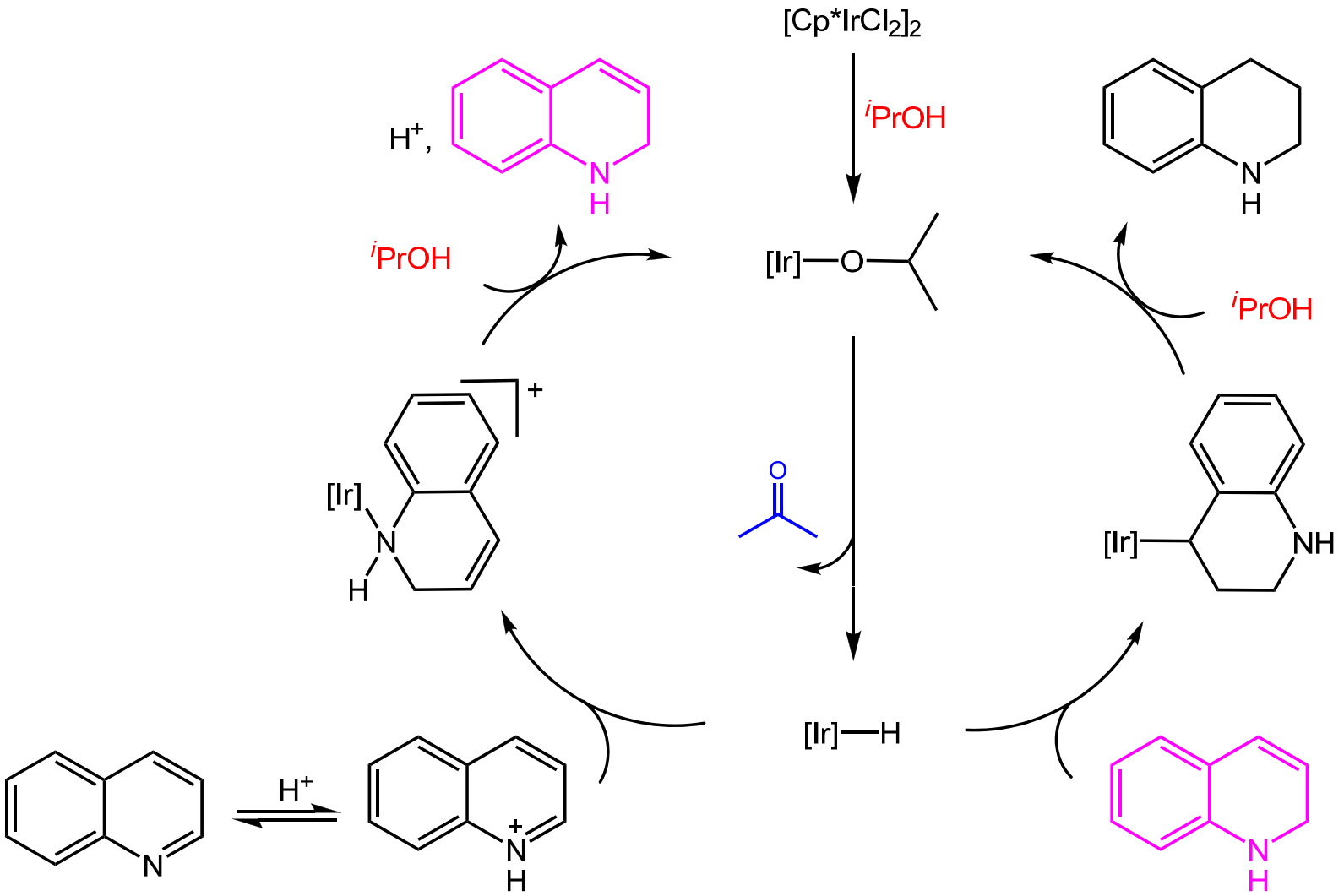


R = H, Me, NO_2, Cl, Br, CO_2H and OMe

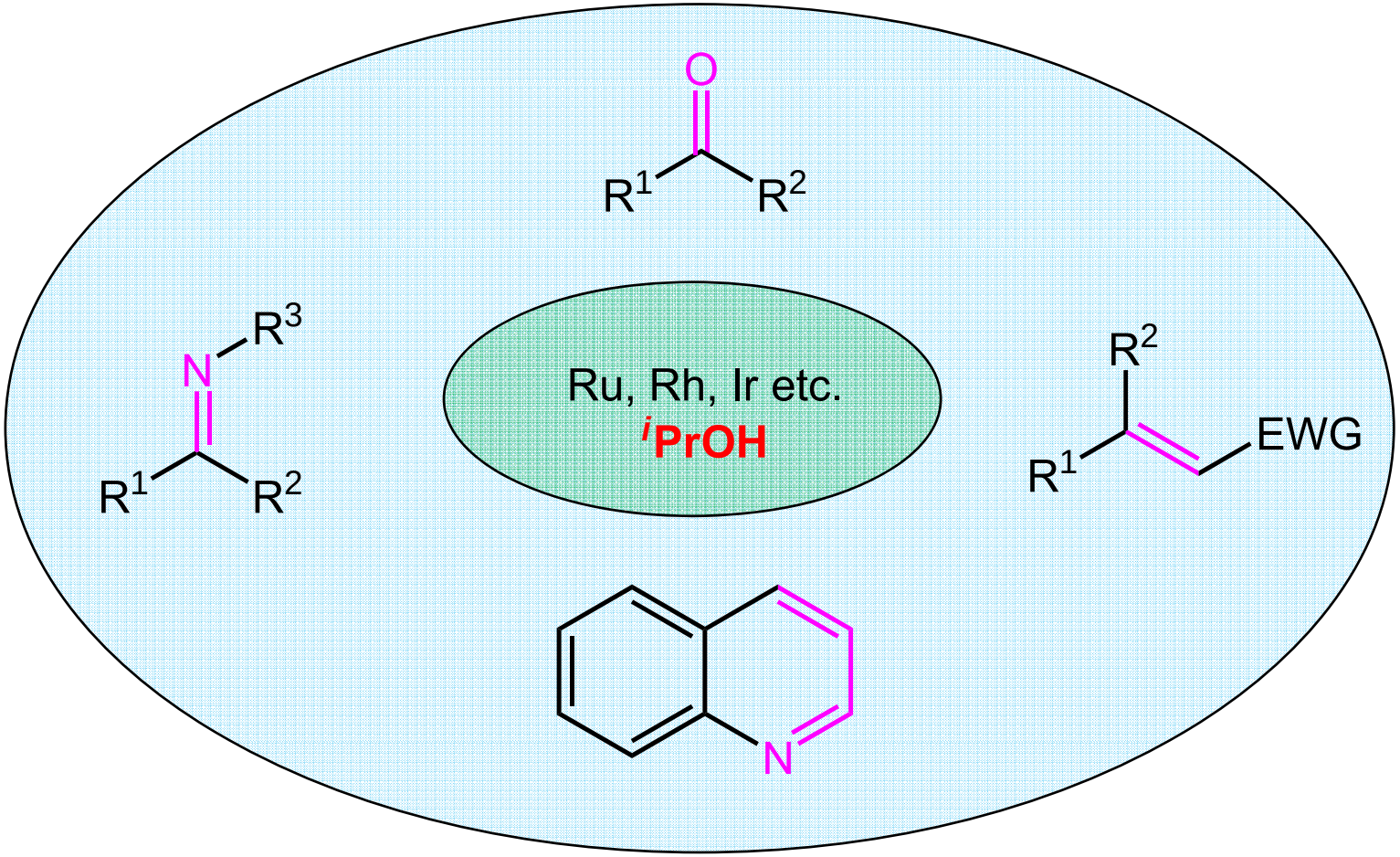


87% yield

Yamaguchi, R. et al *Tetrahedron Lett.* **2004**, *45*, 3215

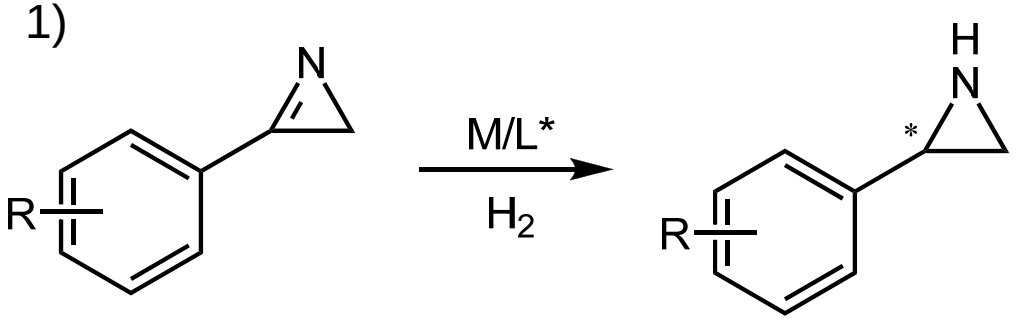

[Cp*IrCl2]2
iPrOH
[Ir]—O
H+,
iPrOH
iPrOH
[Ir]
N
H
+
O
[Ir]—H
[Ir]
NH
H+
N
H

5. Summary



6. Discussion

1)



It is feasible and unreported;

Substrate scope

Khlebnikov, A. F. et al *Tetrahedron* **2013**, *69*, 3363

2)