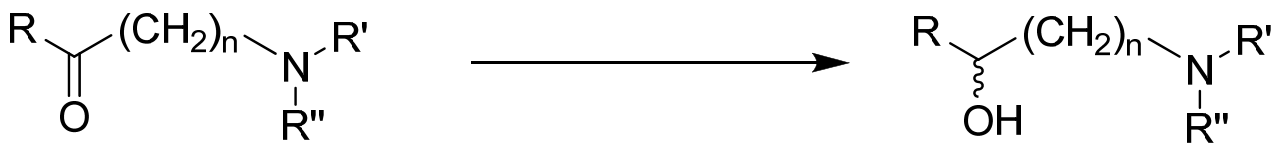
Asymmetric Hydrogenation of Prochiral Amino Ketones to Amino Alcohols for Pharmaceutical Use



Hui Guo
2010.11.27

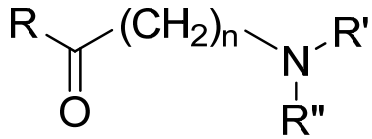
Content

Part 1:
Important Application of Chiral Amino Alcohol

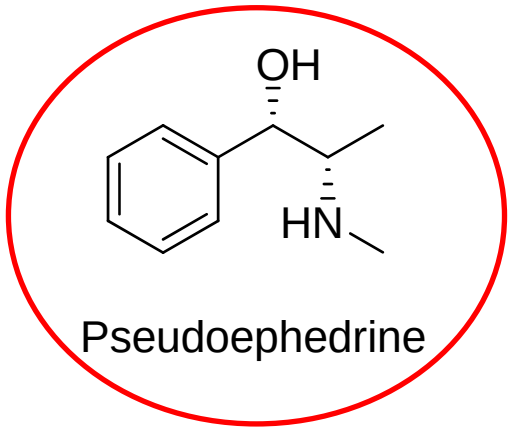
1 Pharmaceutical use

2 Used as auxiliaries and ligands

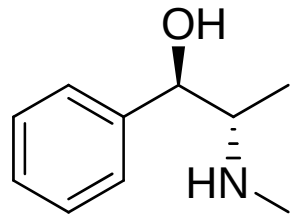
3 Components of oxazaborolidines and oxazoline



Pharmaceutical Use of Chiral Amino Alcohols

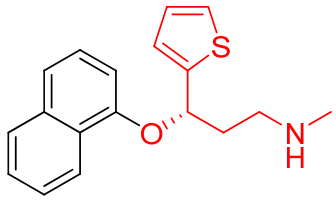


Pseudoephedrine



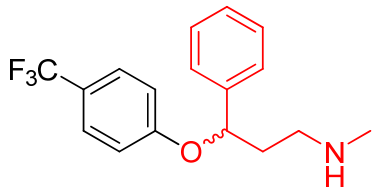
Ephedrine

Pharmaceutical Use of Chiral Amino Alcohols

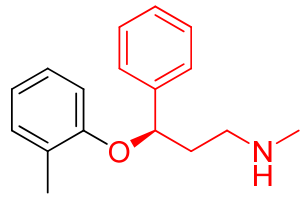


Duloxetine

Rank: 14 (2008)

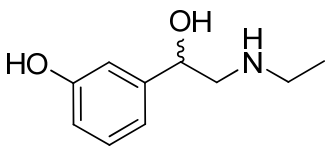


Fluoxetine

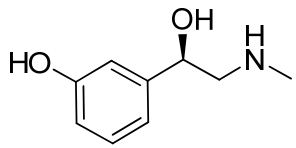


Atomoxetine

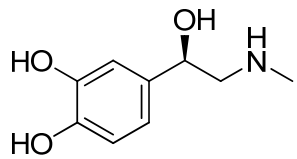
Rank: 78 (2008)



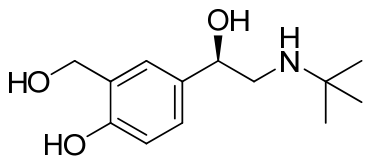
Etilefrine



Phenylephrine

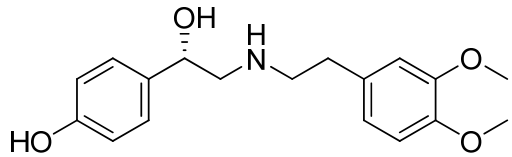


Adrenaline



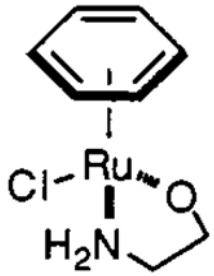
Salbutamol

Rank: 98 (2008)

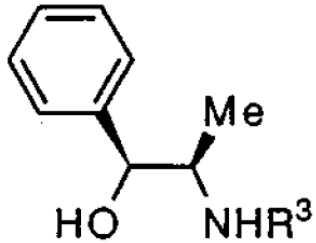


Denopamine

Application of Chiral Amino Alcohols as Auxiliaries and Ligands in Asymmetric Transfer Hydrogenation



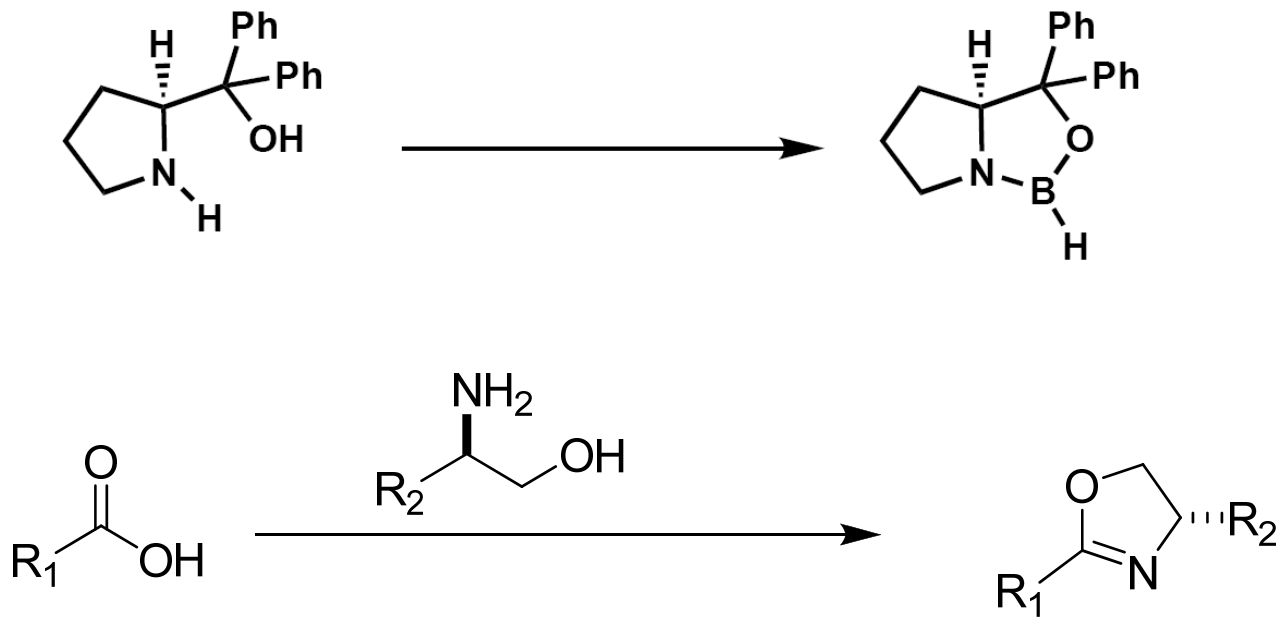
General (Amino alcohol)(arene) ruthenium(II) Complex



One kind of ligands adopted in asymmetric transfer hydrogenation

K. Everaere, A. Mortreux, M. Bulliard, J. Brussee, A. van der Gen, G. Nowogrocki, J.-F. Carpentier, *European Journal of Organic Chemistry* **2001**, *2001*, 275.

Components of Oxazaborolidines and Oxazoline



Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1988**, *37*, 1986–2012.

Part 2:

Asymmetric Synthesis of Chiral Amino Alcohols

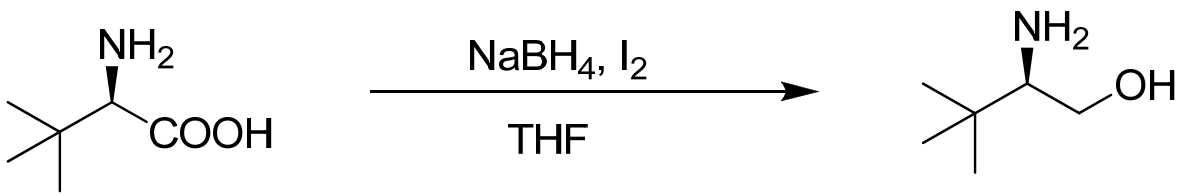
Traditional Methods：

1 Biotechnology (enzyme)

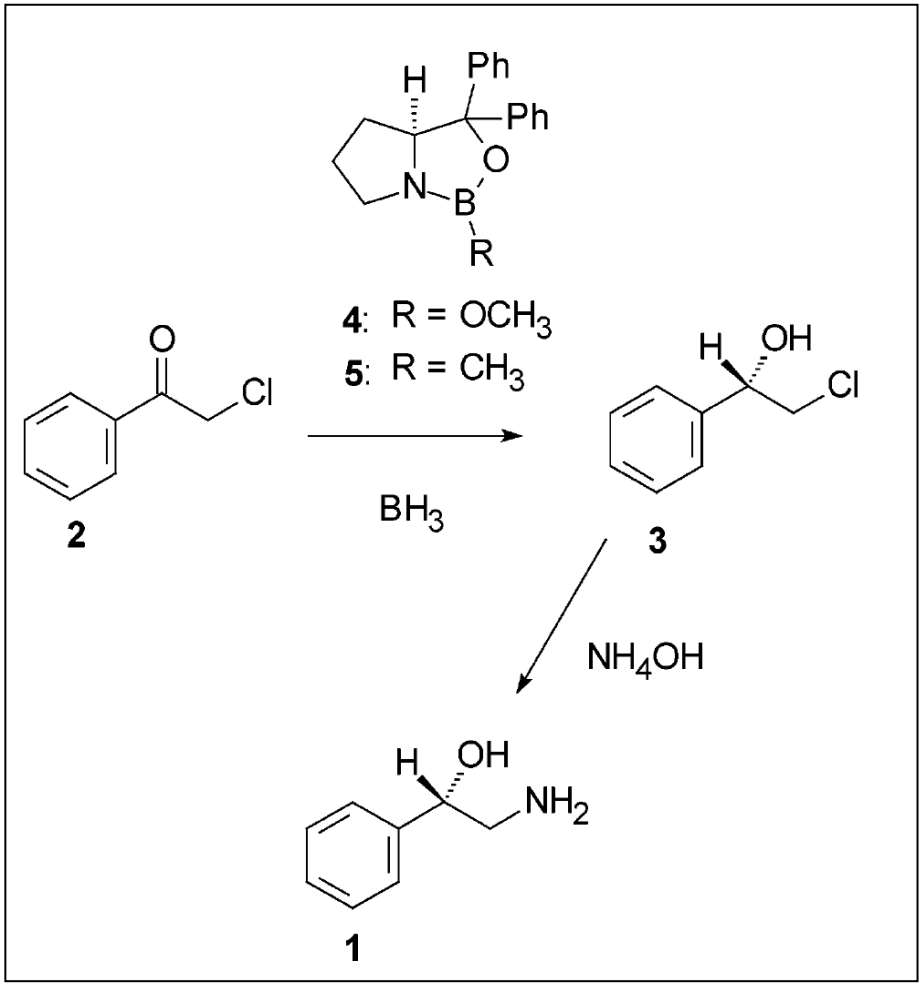
2 Resolution (dominant route)

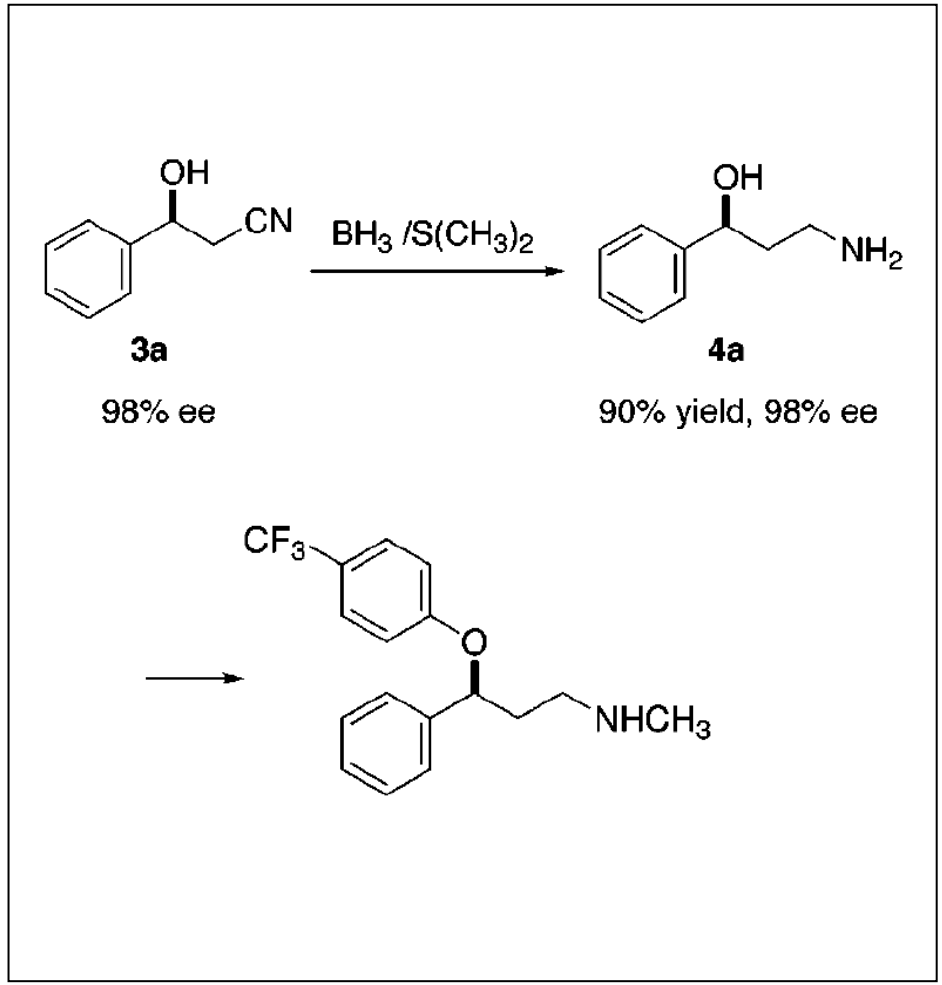
3 From natural hydroxyacids or sugars
(e.g. : Pseudoephedrine: Starting from benzaldehyde and dextrose)

4 Reduction of amino acids



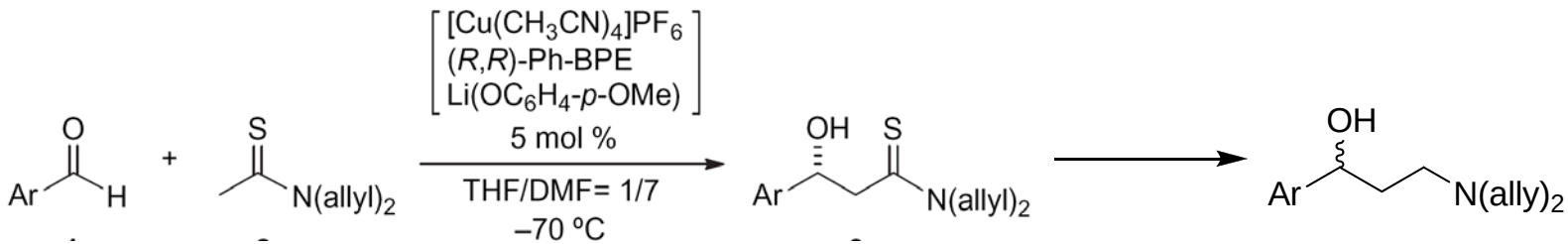
5 Asymmetric reduction of haloketones or other substituted ketones



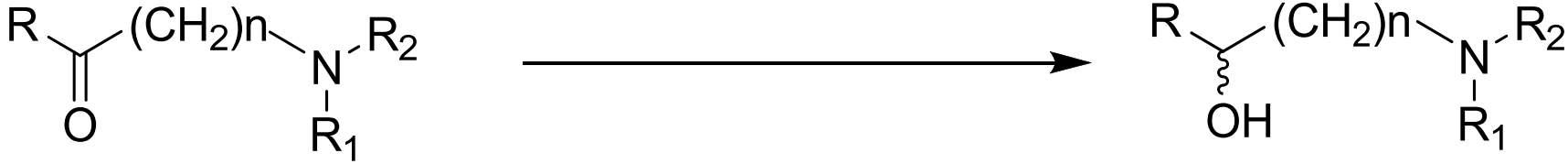


a)S. K. Tanielyan, N. Marin, G. Alvez, R. L. Augustine, *Organic Process Research & Development* **2006**, *10*, 893; b)M. Watanabe, K. Murata, T. Ikariya, *The Journal of Organic Chemistry* **2002**, *67*, 1712.

6 Reductions of thioamide

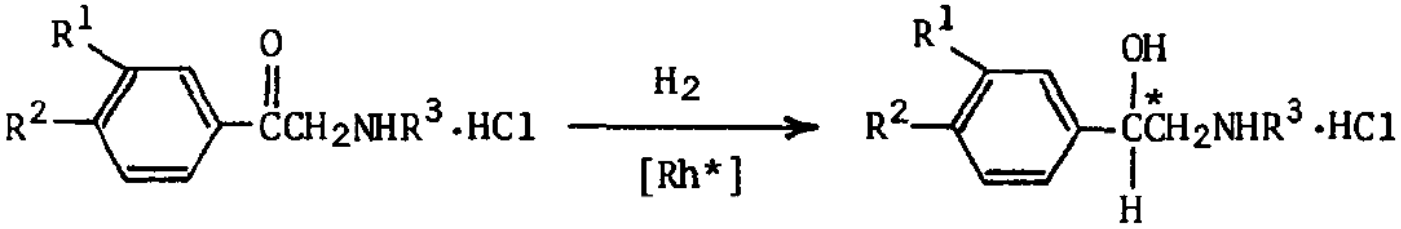


7 Asymmetric reduction of prochiral amino ketones



Iwata, M.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1688.

Rh-BPPFOH Catalyzed Asymmetric Hydrogenation



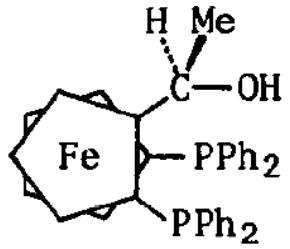
1a, $R^1=R^2=OMe$; $R^3=H$

1b, $R^1=R^2=R^3=H$

1c, $R^1=H$; $R^2=OH$; $R^3=H$

1d, $R^1=R^2=OH$; $R^3=Me$

2a ∿ 2d

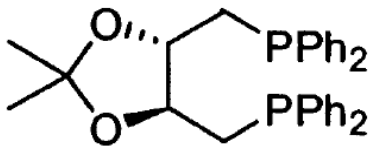


(*R*) - (*S*) - BPPFOH

TON: 100 ; Time: 2-4 days; Conversion: 80-100 % ; Ee: 12-95 %

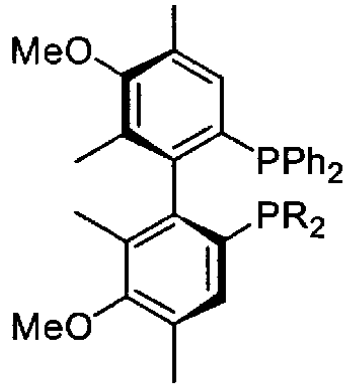
Hayashi, T.; Katsumura, A.; Konishi, M.; Kumada, M. *Tetrahedron Letters* **1979**, *20*, 425.

Rh-DIOP and Rh-BIMOP Catalyzed Asymmetric Hydrogenation



(*S*,*S*)-DIOP

Substrate: α-NEt_2-acetophenones
Ee: 88-95%
S/C: 200:1



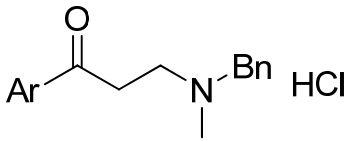
(*S*)-BIMOP: R = Ph
(*S*)-MOC-BIMOP: R = Cy

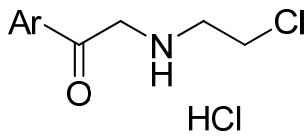
Substrate: α-amino-acetophenone
Ee: 93 % (with MOC-BIMOP)
Asymmetric ligands shows better enantioselectivity

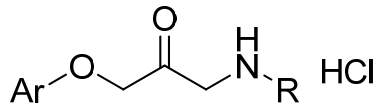
Not effctive to β **or** γ **amino ketones**

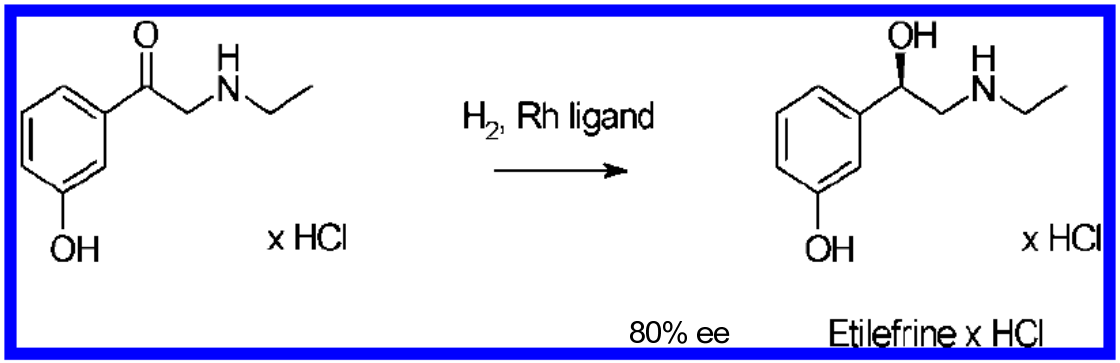
Brown JM, Chaloner PA (1980) J Chem Soc Chem Commun 344
Törös S, Kollár L, Heil B, Markó L (1982) J Organomet Chem 232:C17

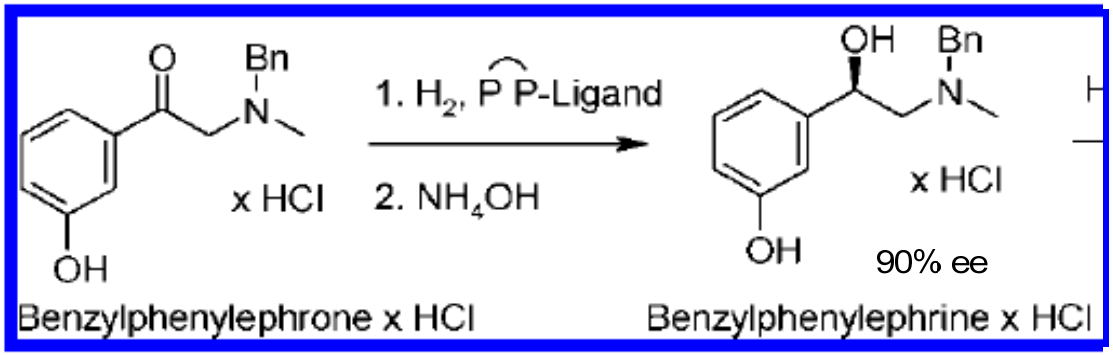
Rh-MCCPM Catalyzed Asymmetric Hydrogenation

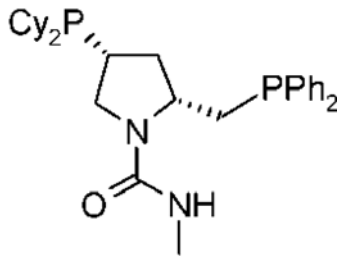






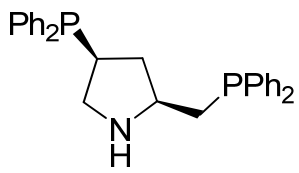






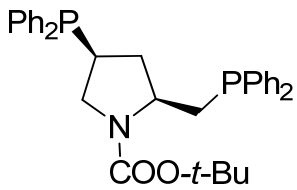
MCCPM

Achiwa, K. et al. *Synlett* **1992**. 169.



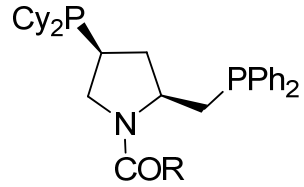
PPM

Achiwa, K. 1976



BPPM

Achiwa, K. 1976



R=OC(CH$_3$)$_3$ BCPM
R=OCH$_3$ MCPM
R=NHCH$_3$ MCCPM

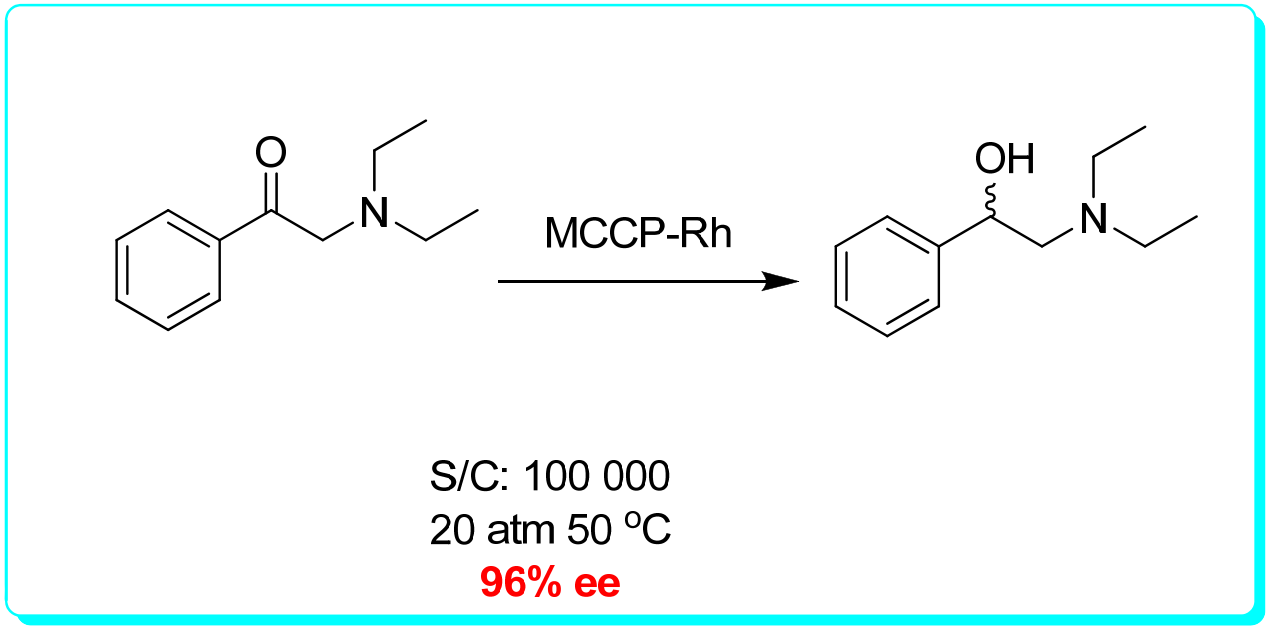
Achiwa, K. 1992

L*: chiral bisphosphine

entry	catalyst: chiral bisphosphine	P/M-chirality	confign.	convn.	%ee	condition: [subst.]/[Rh]	condition: atm/°C/h.
1	(*R*,*R*)-MOD-DIOP	M	*R*	100	19.0	10^2	50/50/72
2	(*S*)-BIMOP	M	*R*	78	11.3	10^3	50/50/48
3	(*R*,*R*)-PPCP	P	*S*	100	15.1	10^2	50/50/72
4	(2*S*,4*S*)-BCPM	M	*S*	100	81	10^3	20/50/20
5	(*R*)(*S*)-BPPFOH	P	*R*	100	43.4	10^3	50/50/48
6	(*S*)(*S*)-BPPFOH	P	*R*	100	46.7	10^3	50/50/48
7	(*S*)-BPPEF	P	*S*	100	26.7	10^2	50/50/72

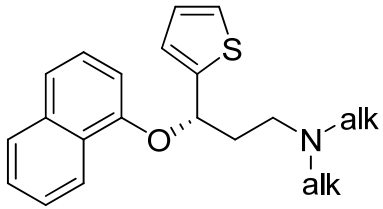
K. Achiwa, *Journal of the American Chemical Society* **1976**, *98*, 8265.
Achiwa, K. et al. *Synlett* **1992**. 169.

Further Development:

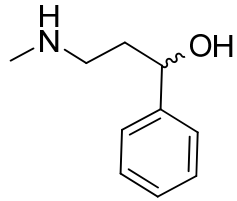


Takeda, H.; Tachinami, T.; Aburatani, M.; Takahashi, H.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett*. **1989**, *30*, 363-366.

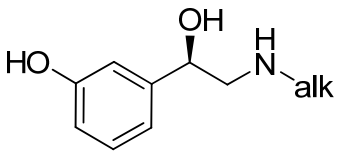
Pharmaceutical Use



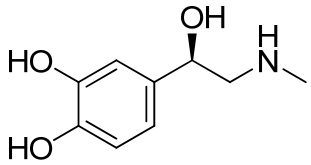
Duloxetine
WO/2005/085192



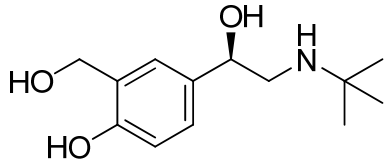
Key Intermediate of Fluoxetine and Amotoxetin
(US) 7294744



Etilefrine
(US) 6187956

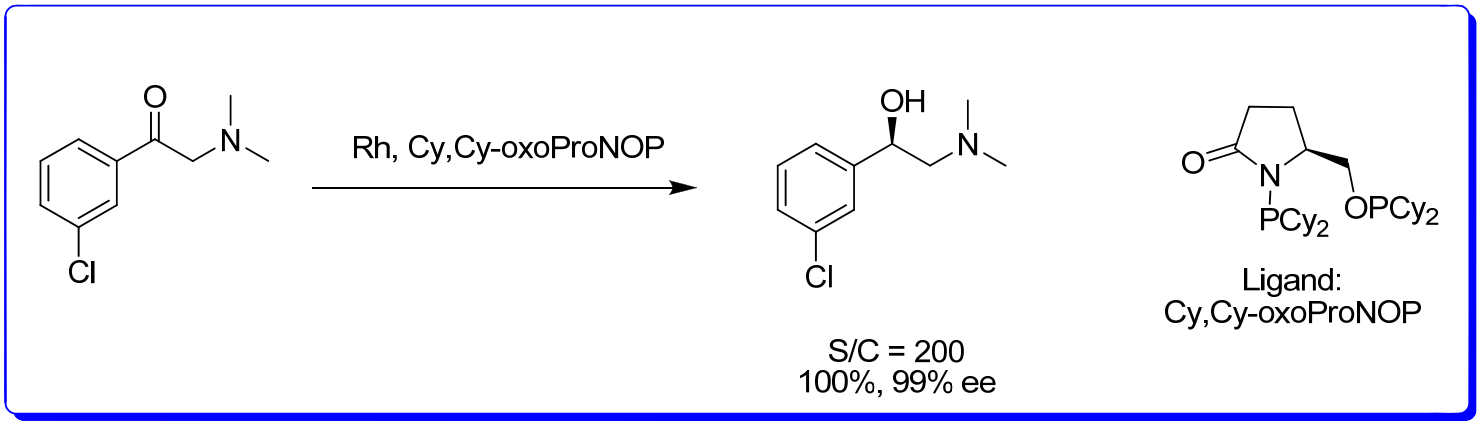


Adrenaline
WO/2001/012583

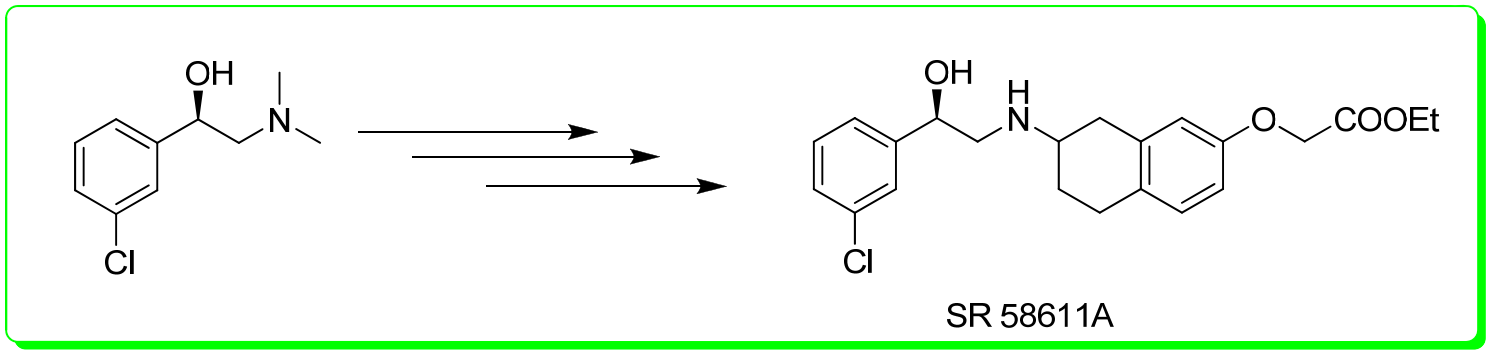


Salbutamol
WO/2004/037767

Rh-Cy,Cy-oxoProNOP Catalyzed Asymmetric Hydrogenation

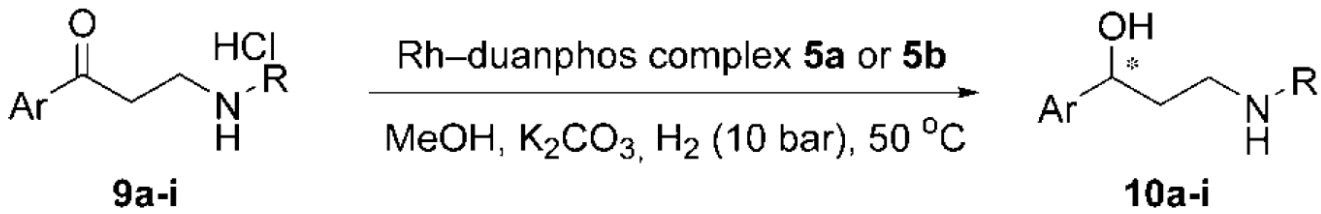


Pharmaceutical use



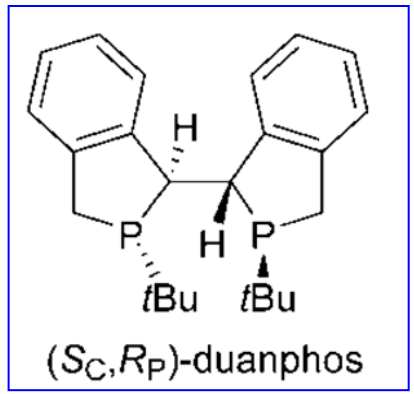
M. Devocelle, A. Mortreux, F. Agbossou, J.-R. Dormoy, *Tetrahedron Letters* **1999**, *40*, 4551.

Rh-duanphos Catalyzed Asymmetric Hydrogenation



9a-i **10a-i**

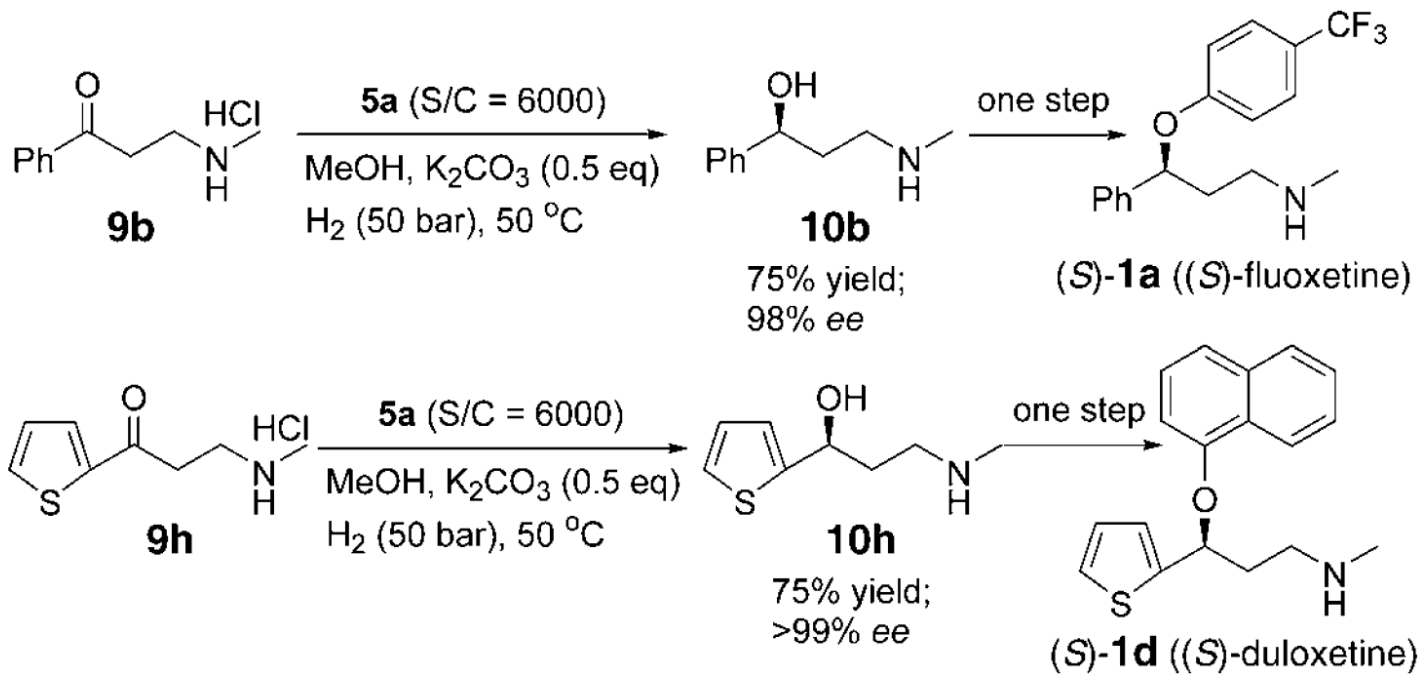
Entry	9	Ar	R	Yield [%][b]	*ee* [%]	Configuration[c]
1	**a**	2-Me-phenyl	Me	92	99[d]	*S*
2	**b**	phenyl	Me	90	98[d]	*S*
3	**c**	3-Br-phenyl	Me	90	96[d]	*S*
4	**d**	4-Br-phenyl	Me	93	> 99[d]	*S*
5	**e**	2-OMe-phenyl	Me	93	93[d]	*S*
6	**f**	4-OMe-phenyl	Me	93	> 99[d]	*S*
7	**g**	2-naphthyl	Me	92	99[e]	*S*
8	**h**	2-thienyl	Me	93	> 99[e]	*S*
9	**h**	2-thienyl	Me	93	> 99[e]	*R*[f]
10	**i**	phenyl	Bn[g]	90	96[d]	*S*



(S_C,R_P)-duanphos

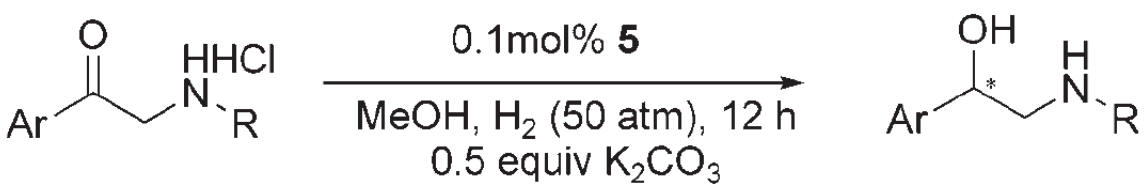
D. Liu, W. Gao, C. Wang, X. Zhang, *Angewandte Chemie International Edition* **2005**, *44*, 1687.

Applications in Drug Synthesis

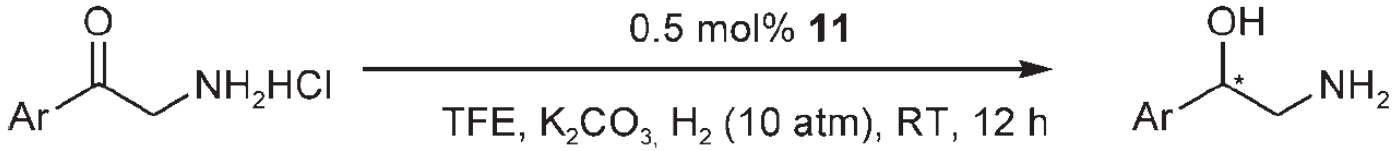


D. Liu, W. Gao, C. Wang, X. Zhang, *Angewandte Chemie International Edition* **2005**, *44*, 1687.

Rh-Binapine Catalyzed Asymmetric Hydrogenation

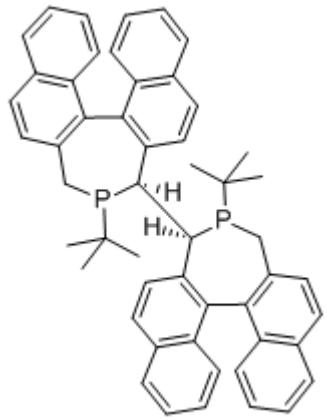


Up to 95 % ee



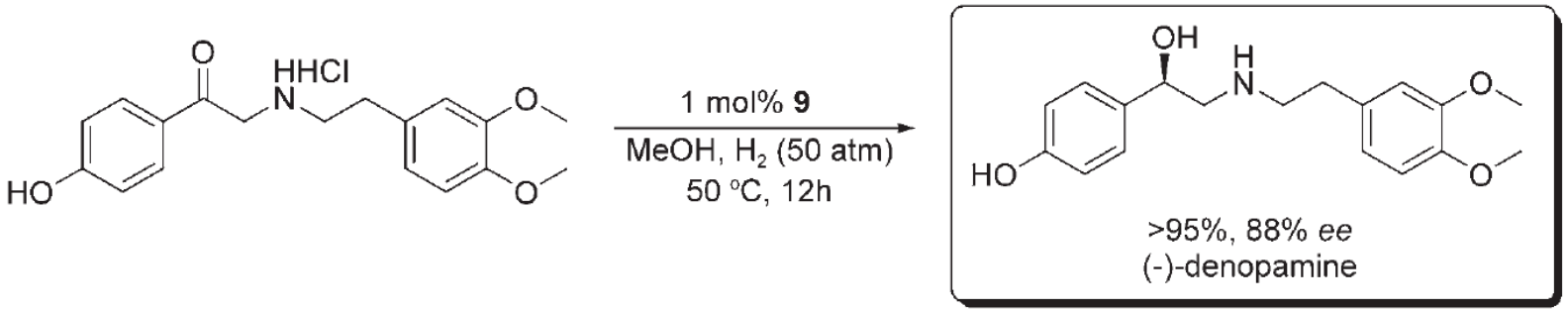
Up to 90 % ee

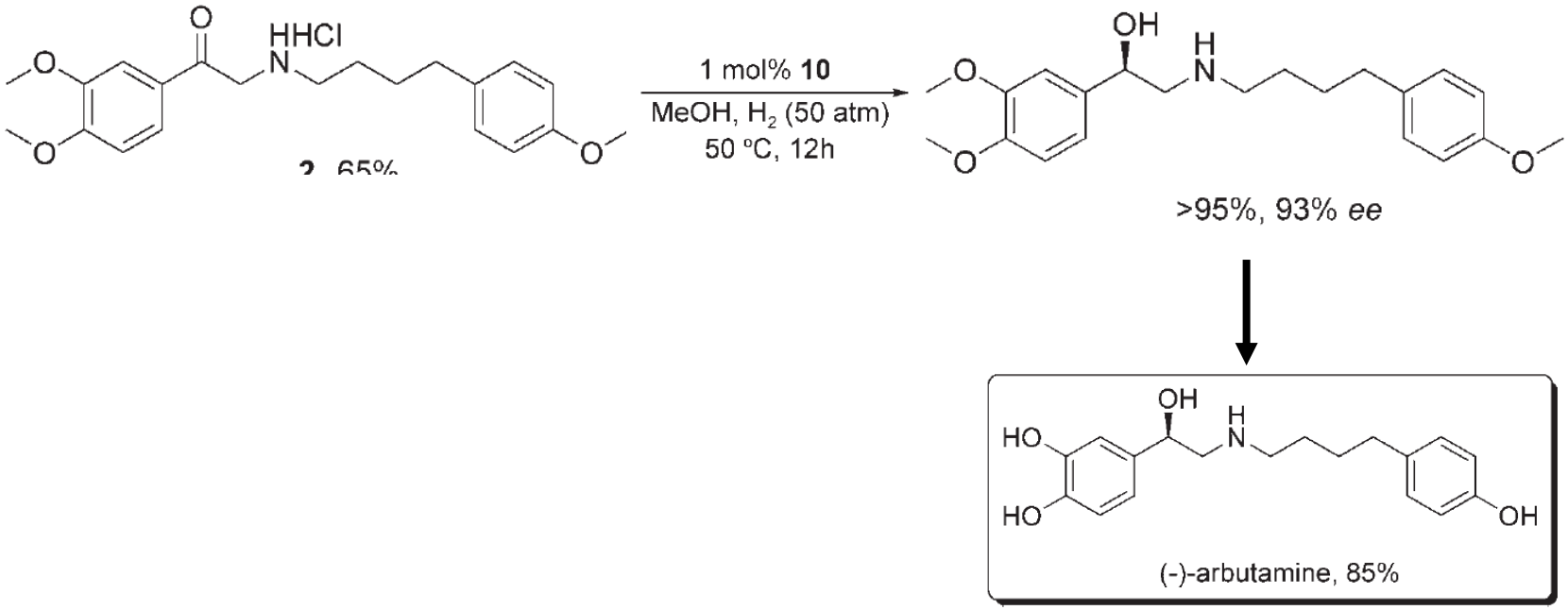
Ligand:
Binapine



Shang, G.; Liu, D.; Allen, S. E.; Yang, Q.; Zhang, X. *Chemistry – A European Journal* **2007**, *13*, 7780

Application in Drug Synthesis

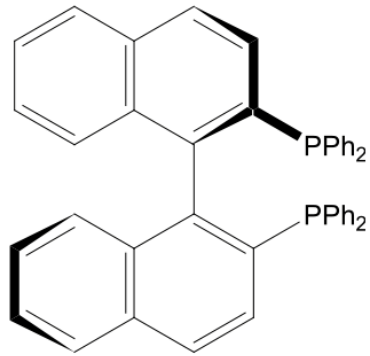




Shang, G.; Liu, D.; Allen, S. E.; Yang, Q.; Zhang, X. *Chemistry – A European Journal* **2007**, *13*, 7780.

Ru-BINAP Catalyzed Asymmetric Hydrogenation

substrate	S/C	conditions		product		
		H_2, atm	time, h	% yield[b]	% ee[c]	confign[c]
$CH_3COCH_2N(CH_3)_2$	780	50[d,e]	12	72	96	*S*
$(CH_3)_2CHCOCH_2N(CH_3)_2$	390	100[d,e]	24	83	95	*S*
$C_6H_5COCH_2N(CH_3)_2$	490	100[d,e]	24	85	95	*S*
$C_6H_5COCH_2N(CH_3)_2$	530	100[d,e]	8	92	93	*S*

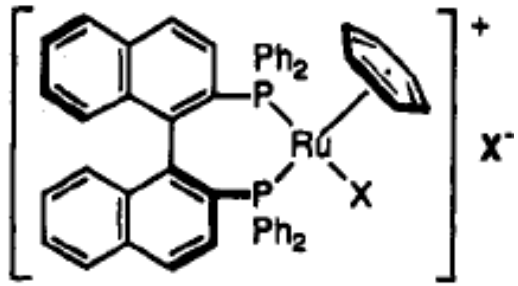


(R)-BINAP

M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *Journal of the American Chemical Society* **1988**, *110*, 629.

Further Development of Ru-BINAP Catalyzed Asymmetric Hydrogenation

Up to 99% ee value



(*S*)-5

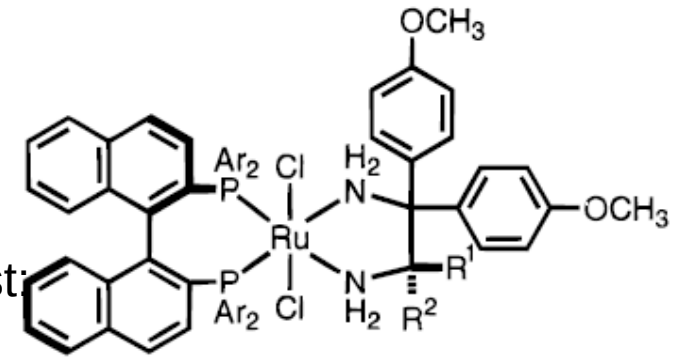
a: X = Cl
b: X = Br
c: X = I

[2] K. Mashima, K.-h. Kusano, N. Sato, Y.-i. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, *The Journal of Organic Chemistry* **1994**, *59*, 3064.

Further Development of Ru-BINAP Catalyzed Asymmetric Hydrogenation

S/C: 2 000-10 000:1
ee: up to 99.8%

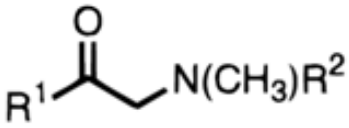
Catalyst:



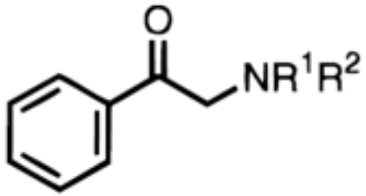
(*R*,*R*)-**1a**: Ar = 3,5-$(CH_3)_2C_6H_3$; R^1 = $(CH_3)_2CH$; R^2 = H
(*R*,*S*)-**1b**: Ar = 3,5-$(CH_3)_2C_6H_3$; R^1 = H; R^2 = $(CH_3)_2CH$

T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, *Journal of the American Chemical Society* **2000**, *122*, 6510.

Further Development of Ru-BINAP Catalyzed Asymmetric Hydrogenation with α-amino Ketone

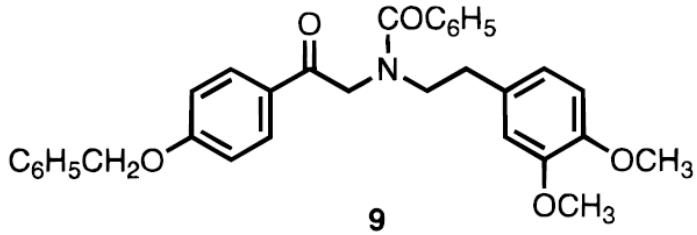


a: $R^1 = R^2 = CH_3$, **92% ee**
b: $R^1 = CH_3$; $R_2 = C_6H_5$, **81% ee**
c: $R^1 = C_6H_5$; $R_2 = CH_3$, **93% ee**



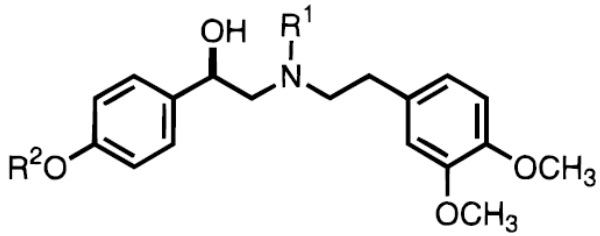
a: $R^1 = CH_3CO$; $R^2 = CH_3$, **99% ee**
b: $R^1 = C_6H_5CO$; $R^2 = H$, **95% ee**
c: $R^1 = C_6H_5CO$; $R^2 = CH_3$, **99.8% ee**
d: $R^1 = CH_3OCO$; $R^2 = CH_3$, **99% ee**
e: $R^1 = (CH_3)_3COCO$; $R^2 = CH_3$, **99% ee**

Application:

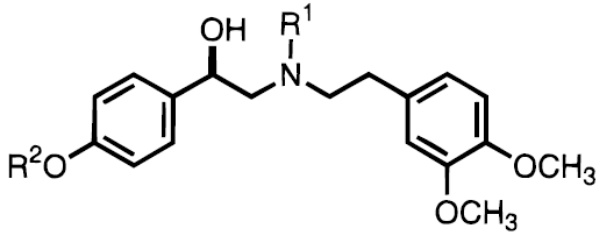


9

97 %



(*R*)-**10**: $R^1 = C_6H_5CO$; $R^2 = C_6H_5CH_2$

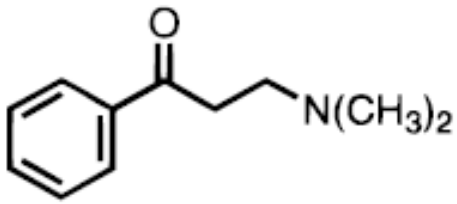


(*R*)-**11**: $R^1 = R^2 = H$ (HCl salt)

Denopamine

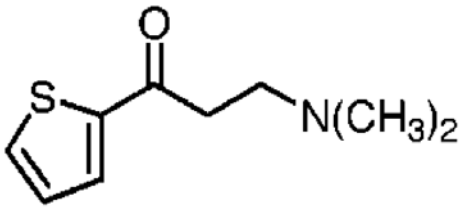
T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, *Journal of the American Chemical Society* **2000**, *122*, 6510.

Further Development of Ru-BINAP Catalyzed Asymmetric Hydrogenation with β-amino Ketone



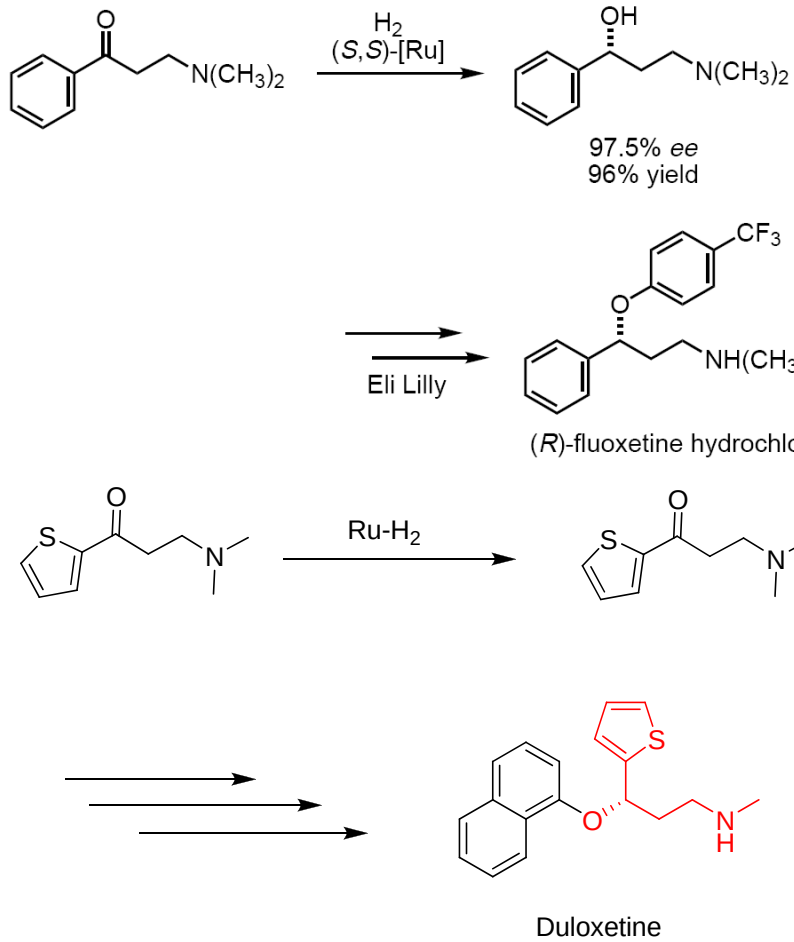
S/C=10 000, 96%, 97.5 % ee

100%, 97% ee under base free condition



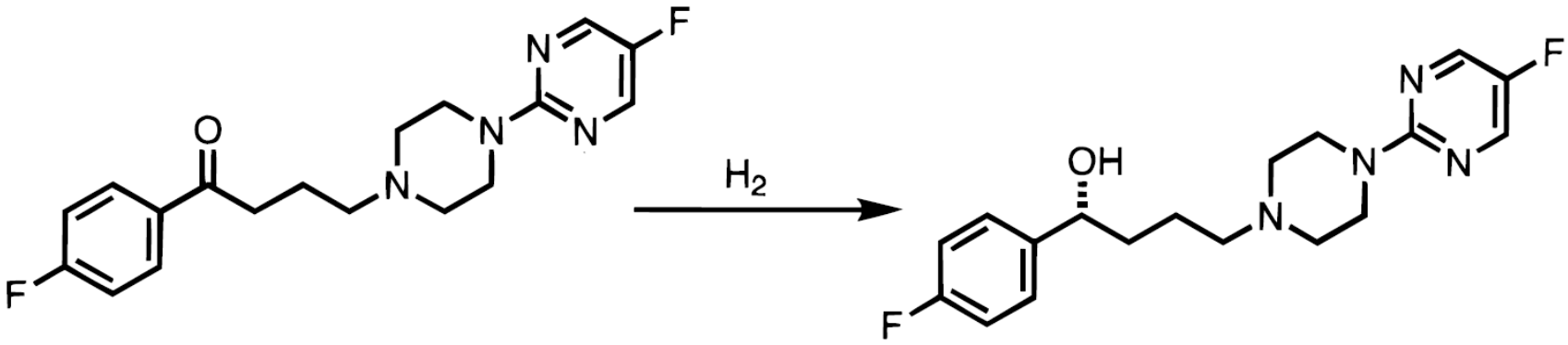
S/C=10 000, 92 % ee

Application:



T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, *Journal of the American Chemical Society* **2000**, *122*, 6510; T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto, R. Noyori, *Journal of the American Chemical Society* **2002**, *124*, 6508; T. Ohkuma, M. Koizumi, M. Yoshida, R. Noyori, *Organic Letters* **2000**, *2*, 1749.

Further Development of Ru-BINAP Catalyzed Asymmetric Hydrogenation with γ-amino Ketone



S/C=10 000, 97%, 99 % ee

BMS 181100

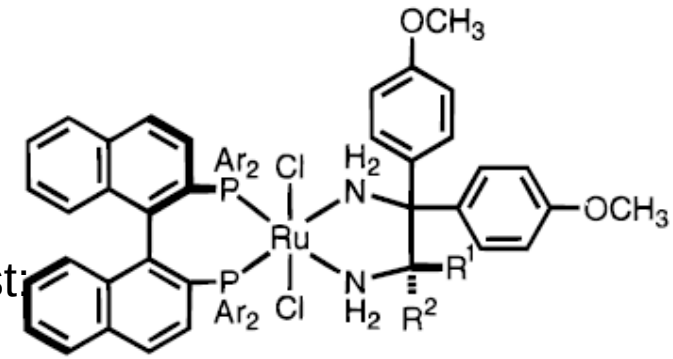
A potent antipsychotic agent,

T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, *Journal of the American Chemical Society* **2000**, *122*, 6510.

Advantages:
High ee value (up to 99.8 %)
High TON: (2 000- 10 000)
Mild conditions: (25 ^{o}C, 8 atm)

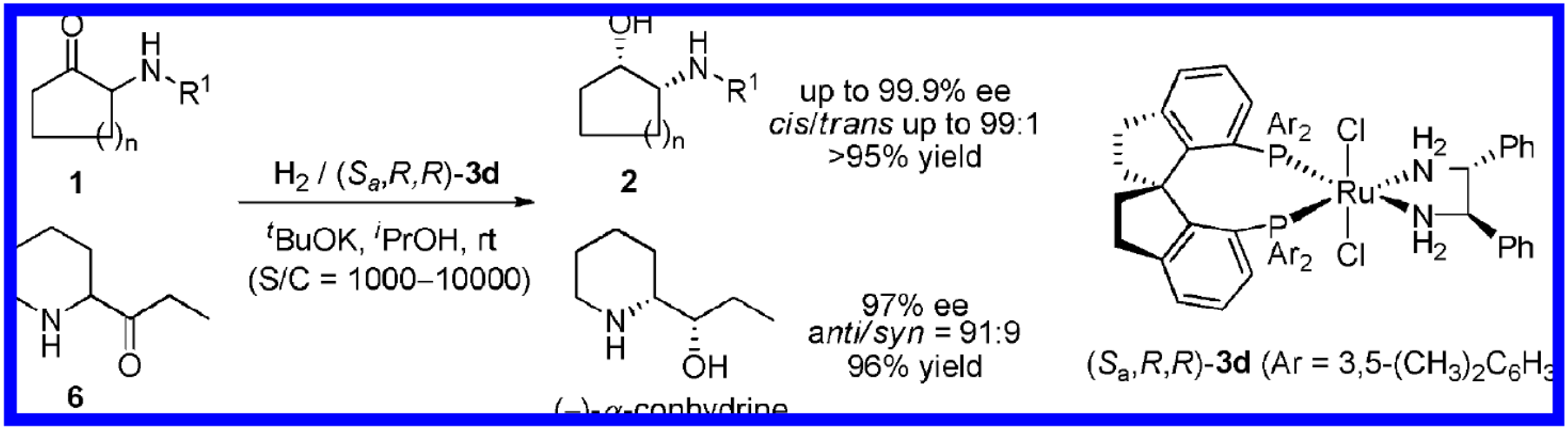
Disadvantages:
Subsequent selective removal of one *N*-methyl group is needed

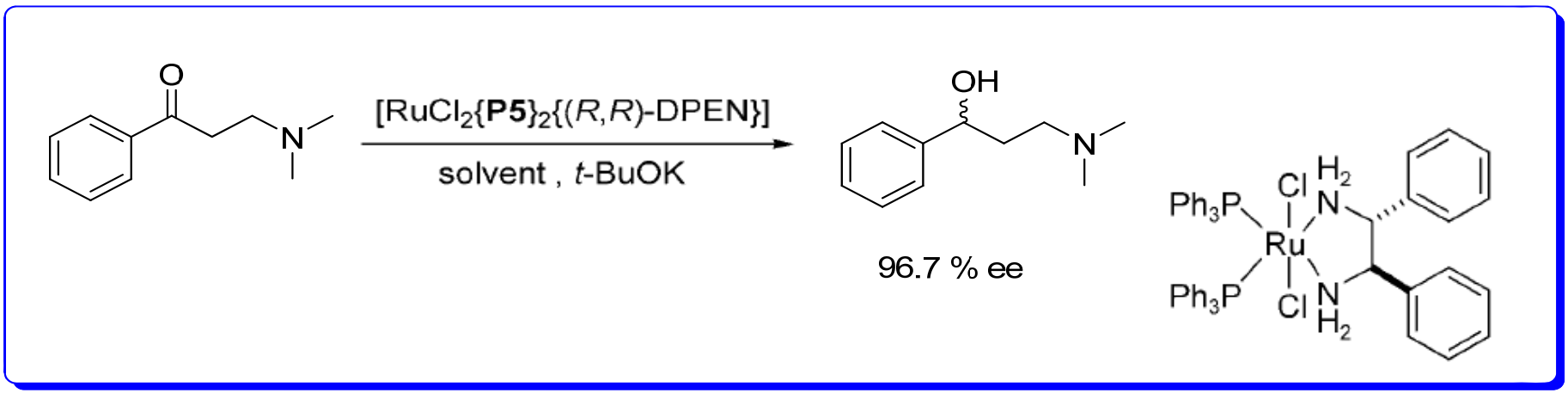
Catalyst:



(*R*,*R*)-**1a**: Ar = 3,5-$(CH_3)_2C_6H_3$; R^1 = $(CH_3)_2CH$; R^2 = H
(*R*,*S*)-**1b**: Ar = 3,5-$(CH_3)_2C_6H_3$; R^1 = H; R^2 = $(CH_3)_2CH$

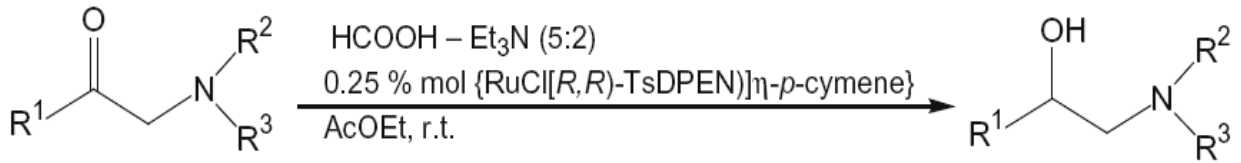
Other Examples of Ruthenium-Catalyzed Asymmetric Hydrogenation of Amino Ketone





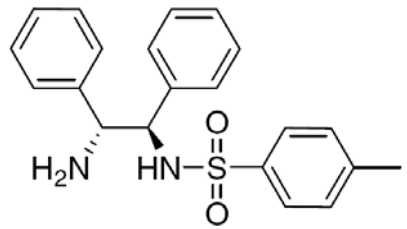
Liu, S.; Xie, J.-H.; Li, W.; Kong, W.-L.; Wang, L.-X.; Zhou, Q.-L. *Organic Letters* **2009**, *11*, 4994.
Jing, Q.; Zhang, X.; Sun, J.; Ding, K. *Advanced Synthesis & Catalysis* **2005**, *347*, 1193.

Ruthenium-Catalyzed Asymmetric Hydrogenation of Amino Ketone by Transfer Hydrogenation



1–9,11 **1a–9a, 11a**

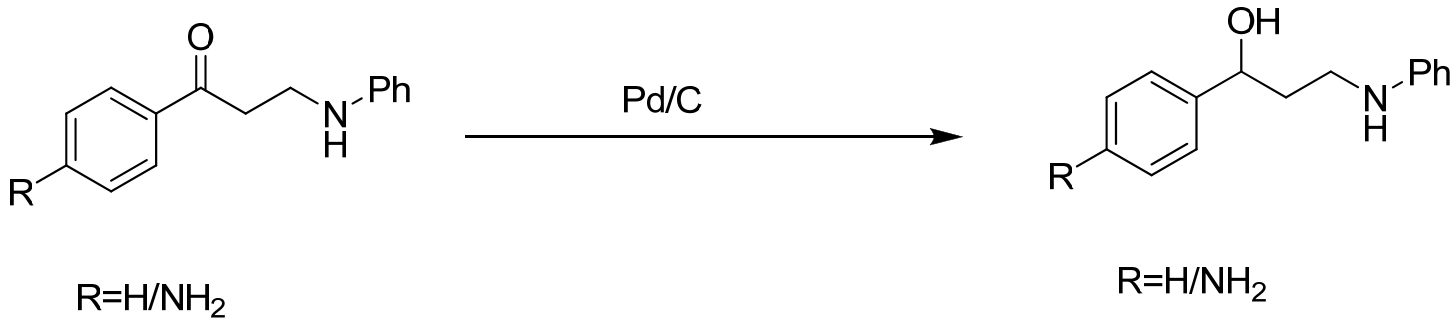
No.	Amino ketone			Time, days	Amino alcohol			
	R^1	R^2	R^3			Yield[a] (%)	ee (%)	Conf.
1	Ph	Me	Me	5	**1a**	58	97[b]	(*R*)[d]
2	Ph	Et	Et	6	**2a**	73	98[b]	(*R*)[d]
3	Ph	$(CH_2)_4$		3	**3a**	57	99[b]	(*R*)[d]
4	Ph	$(CH_2)_5$		3	**4a**	63	99[b]	(*R*)[d]
5	2-Naphthyl	Me	Me	6	**5a**	60	98[c]	(*R*)[e]
6	2-Benzofuryl	Me	Me	5	**6a**	69	98[c]	(*S*)[e]
7	2-Benzofuryl	$(CH_2)_2O(CH_2)_2$		7	**7a**	62	97[c]	(*S*)[e]
8	2-Furyl	Me	Me	5	**8a**	61	98[c]	(*S*)[f]
9	Me	Et	Et	7	**9a**	50	60[b]	(*R*)[d]
10	Ph	Bn	Bn	7	n.r.			
11	3,4-$(MeO)_2C_6H_3$	Me	Me	7	**11a**	55	98[c]	(*R*)[d]



Cat-**5**: Ts-DPEN

Kosmalski, T.; Wojtczak, A.; Zaidlewicz, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1138.

Hydrogenation of Amino Ketones Catalyzed by Pd



R=H/NH_2

R=H/NH_2

No asymmetric hydrogenation case is reported.

Too rigorous for substrates.

Du, R.; Zhu, C.; Zhang, P.; Fan, R. *Synth. Commun*. **2008**, *38*, 2889–2897.

Conclusions

1 Asymmetric hydrogenation of prochiral amino ketones tends to be a facile way and of great importance in synthesis of chiral amino alcohols.

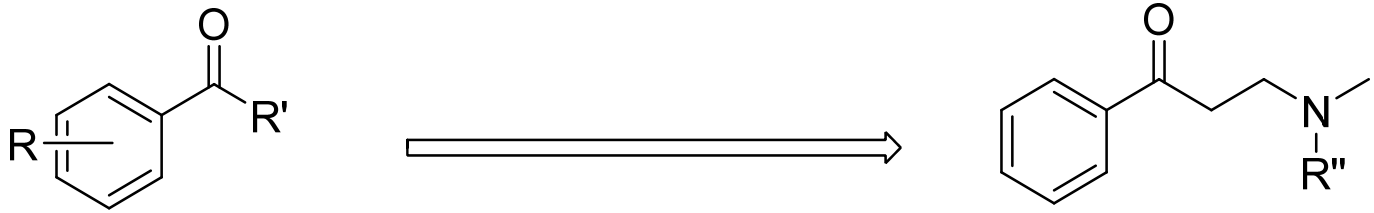
2 Few successful cases were reported and more attention should be paid to asymmetric hydrogenation of prochiral amino ketones.

Challenges

1 High efficiency (high TOF)

2 **Ru** or other metals catalyzed asymmetric hydrogenation of amino ketones with secondary or primary amino group

Inspiration



up to 99.7% ee

???

Thank you
for your attention