Enantioselective iron-catalysed O-H bond insertions

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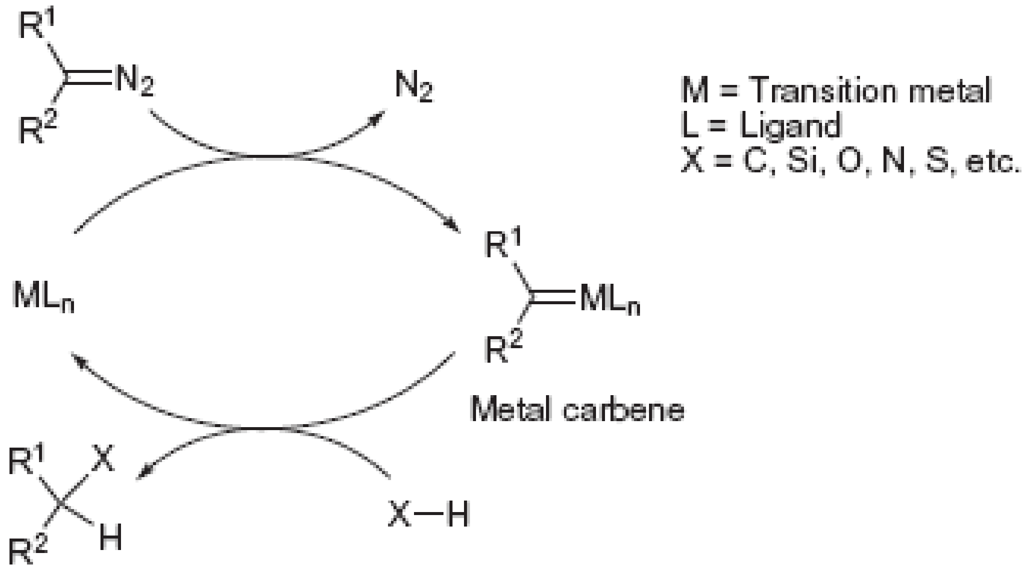
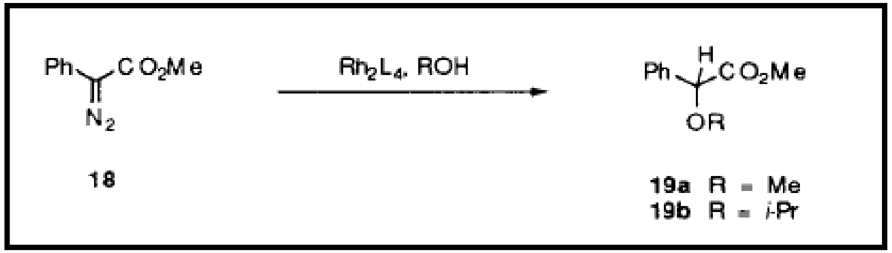
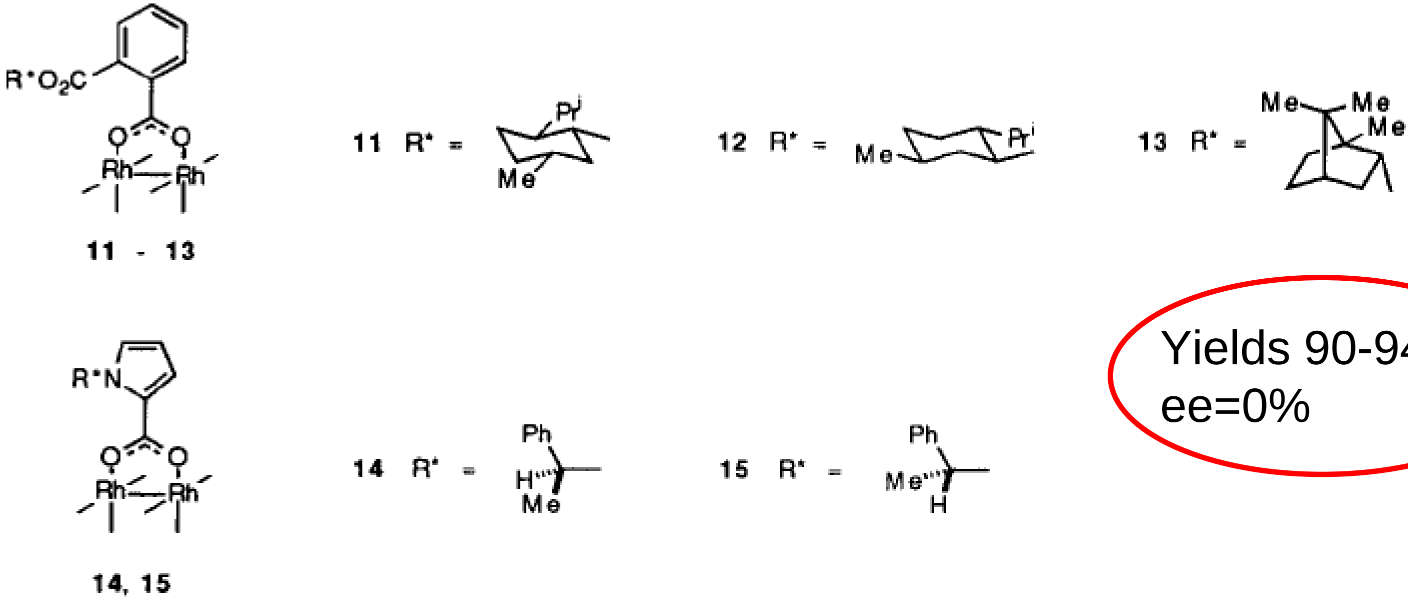
Transition-metal-catalysed insertion reaction starting with diazo compounds



Efficient tool for the construction of C-X bonds under mild reaction conditions

First attempts of metal-catalysed O-H insertion reactions

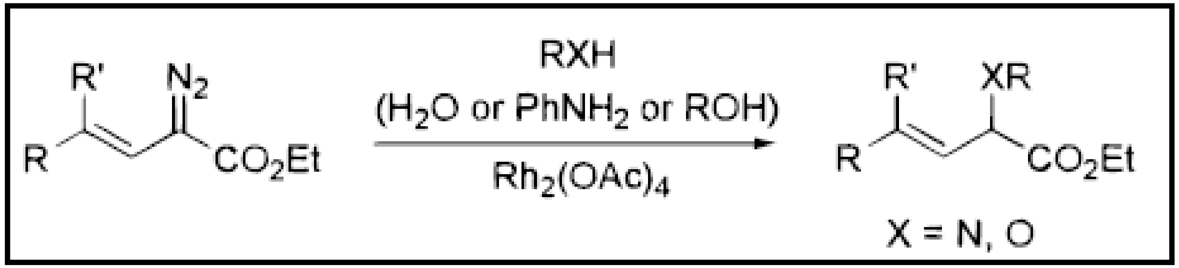


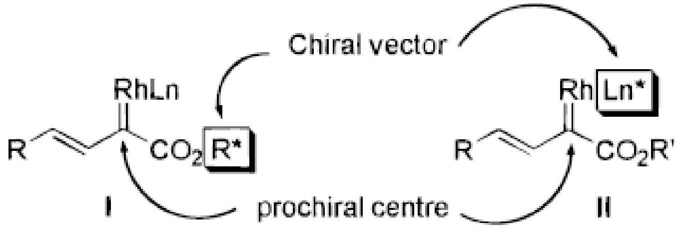


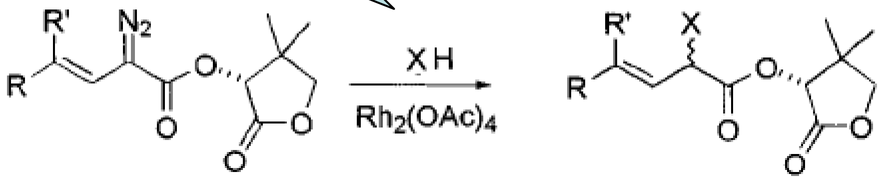
Yields 90-94%, ee=0%

Ferris, L. Haigh, D. Moody, C. J. *Tetrahedron Letters*, **1996,** *37*, p.107-11.

First attempts of metal-catalysed O-H insertion reactions







R = Ph; R' = H; X = OH

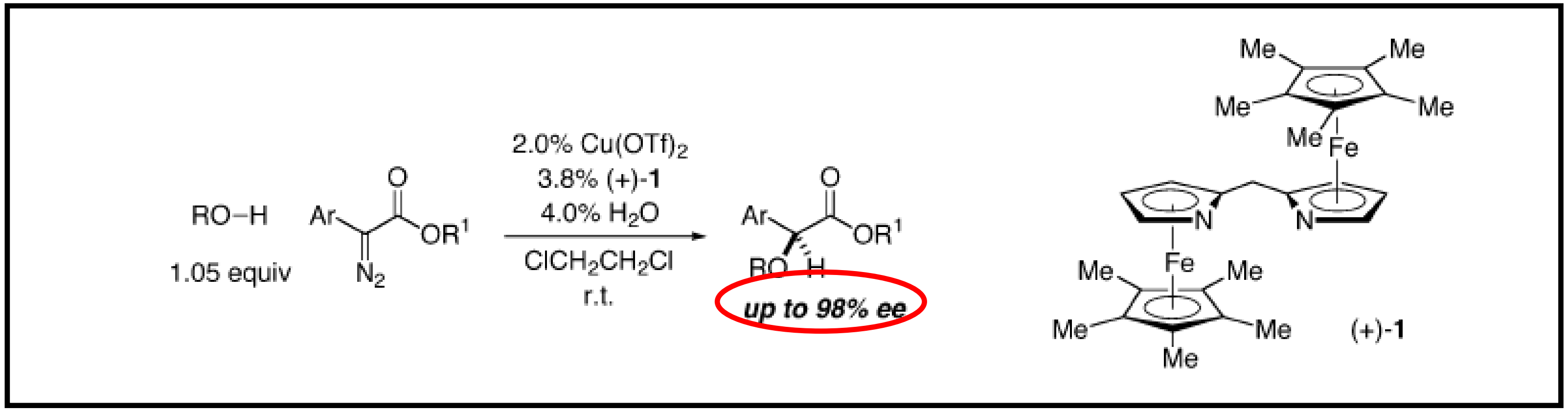
R = Me; R' =H; X = OMe

Yields 75%,
de=5% (MeOH), 50% ($H_2$0)

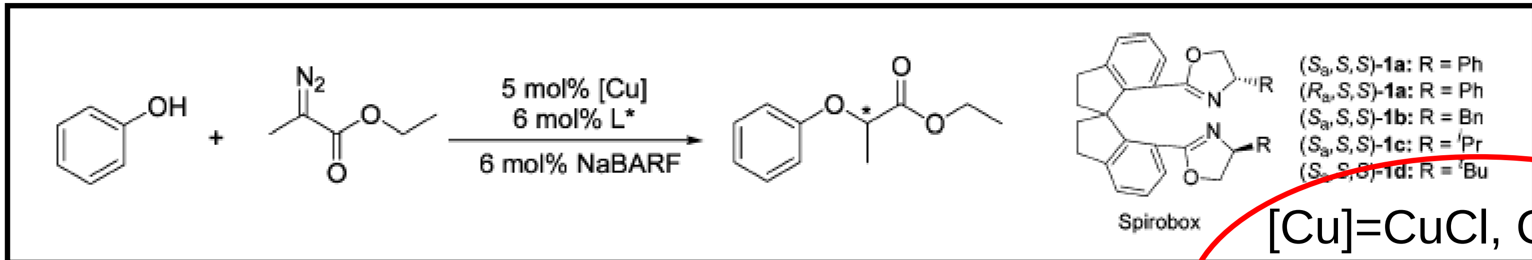
[Rh]=Rh_2(5 S-MEPY)$_4$
Yields 59%,
ee=8%

Bulugahapitiya, P. Landais, Y. Parra-Rapado, L. Planchenault, D. Weber, V. *J. Org. Chem*. **1997**, *62*, p. 1630-41.

First attempts of metal-catalysed O-H insertion reactions



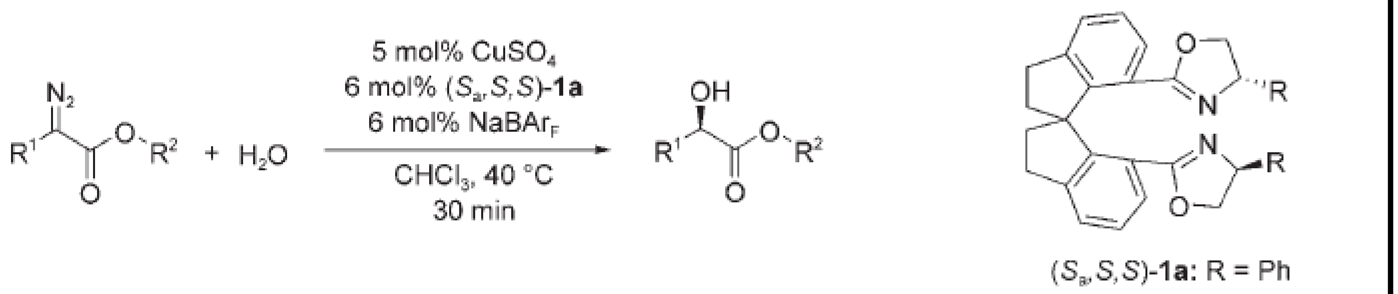
Maier, T. C. Fu, G. C. *J. Am. Chem. Soc*. **2006**, *128*, p. 4594-5.



Chen, C. Zhu S-F. Liu, B. Wang, L-X. Zhou Q-L. *J. Am. Chem. Soc.* **2007**, *129*, p. 12616-7.

[Cu]=CuCl, Cu(OTf)2
Or CuPF6
Yields 63-79%,
ee=98%

First attempts of metal-catalysed O-H insertion reactions



Entry	R^1	R^2	Product	Yield [%]	*ee* [%]
1	Ph	Me	**3a**	91	90 (*R*)
2	Ph	Et	**3b**	91	88 (*R*)
3	Ph	*i*Pr	**3c**	81	86 (*R*)
4	4-MeC_6H_4	Me	**3d**	83	92 (*R*)
5	4-PhC_6H_4	Me	**3e**	87	92
6	4-FC_6H_4	Me	**3f**	90	92 (*R*)
7	4-ClC_6H_4	Me	**3g**	83	92 (*R*)
8	4-BrC_6H_4	Me	**3h**	86	91 (*R*)
9	3-MeC_6H_4	Me	**3i**	87	92
10	3-$MeOC_6H_4$	Me	**3j**	89	91 (*R*)
11	3-FC_6H_4	Me	**3k**	85	89
12	3-ClC_6H_4	Me	**3l**	88	88 (*R*)
13	3-BrC_6H_4	Me	**3m**	92	88
14	3,4-$Cl_2C_6H_3$	Me	**3n**	91	94 (*R*)
15	2-MeC_6H_4	Me	**3o**	81	89
16	2-$MeOC_6H_4$	Me	**3p**	71	50 (*R*)
17	2-ClC_6H_4	Me	**3q**	90	36 (*R*)
18	2-naphthyl	Me	**3r**	76	90 (*R*)
19	3-thienyl	Me	**3s**	70	90
20	Me	Bn	**3t**	78	78 (*R*)

Yields 70-91%, ee=50-94%

Zhu S-F. Chen C. Cai Y. and Zhou Q-L. *Angew. Chem*. **2008**, *47*, p. 932-4.

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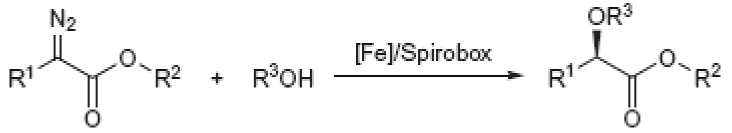
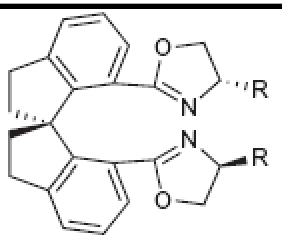
Metal and ligand evaluation:

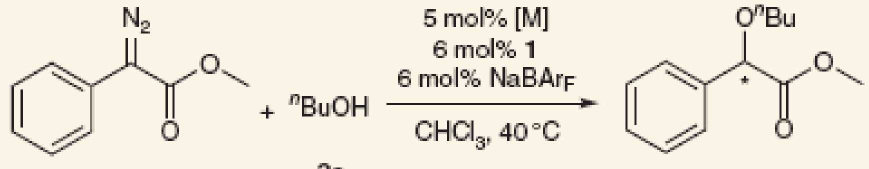


Up to 99% e.e.



Spirobox

(S_a,S,S)-**1a**: R = Ph
(S_a,S,S)-**1b**: R = Bn
(S_a,S,S)-**1c**: R = *i*-Pr
(S_a,S,S)-**1d**: R = *t*-Bu



2a **3a** **4a**

Entry	[M]	Ligand	Time (h)	Yield (%)	e.e. (%)*
1	$FeCl_2 \cdot 4H_2O$	(S_a,S,S)-1a	15	87	86
2	$FeCl_2 \cdot 4H_2O$	(R_a,S,S)-1a	8	86	38
3	$FeCl_2 \cdot 4H_2O$	(S_a,S,S)-1b	24	86	88
4	$FeCl_2 \cdot 4H_2O$	(S_a,S,S)-1c	15	93	98
5	$FeCl_2 \cdot 4H_2O$	(S_a,S,S)-1d	30	63	50
6	$FeCl_2$	(S_a,S,S)-1c	15	90	98
7	$Fe(ClO_4)_2 \cdot xH_2O$	(S_a,S,S)-1c	40	68	95
8	$FeSO_4 \cdot 7H_2O$	(S_a,S,S)-1c	40	85	92
9	$FeCl_3$	(S_a,S,S)-1c	15	93	76
10	CuCl	(S_a,S,S)-1c	1	90	80
11	$CoCl_2$	(S_a,S,S)-1c	48	23	82
12	$NiCl_2$	(S_a,S,S)-1c	48	3	81
13	AuCl	(S_a,S,S)-1c	48	NR†	—
14	AgOTf	(S_a,S,S)-1c	4	63	42
15	$[RhCl(CO)_2]_2$	(S_a,S,S)-1c	2	27	15
16	$[RuCl_2C_6H_6]_2$	(S_a,S,S)-1c	2	45	67

Reaction conditions: [M]/1/$NaBAr_F$/2a/3a = 0.015/0.018/0.018/0.3/0.45 mmol, in 4 ml $CHCl_3$ at 40 °C. $NaBAr_F$, sodium tetrakis[3,5-*bis*(trifluoromethyl)phenyl]borate.
*Determined by HPLC (high-performance liquid chromatography) using a Chiralcel OD-H column.
†NR, no reaction.

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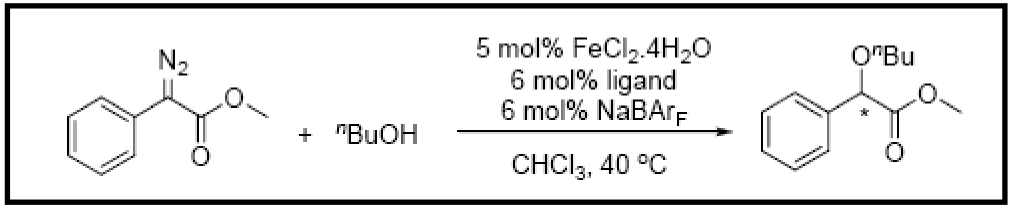
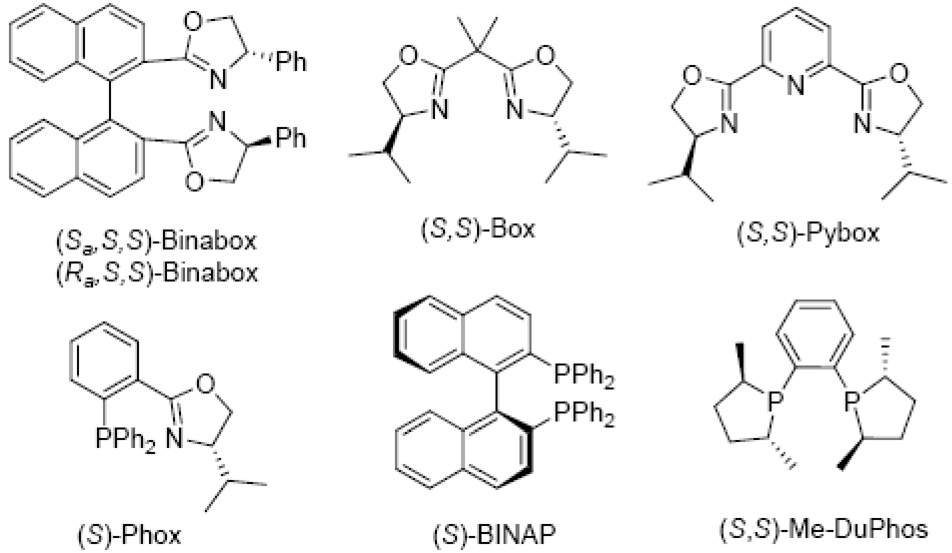
Ligand investigation for O-H insertion of Butanol :





entry	ligand	time (h)	yield (%)	ee (%)[b]
1	none	4	90	*Rac*
2	(*S,S*)-Box	40	56	-16
3	(*S$_a$,S,S*)-Binabox	10	90	13
4	(*R$_a$,S,S*)-Binabox	40	27	29
5	(*S,S*)-Pybox	40	60	-9
6	(*S*)-Phox	40	65	*Rac*
7	(*S*)-BINAP	40	NR[c]	--
8	(*S,S*)-Me-DuPhos	40	NR	--

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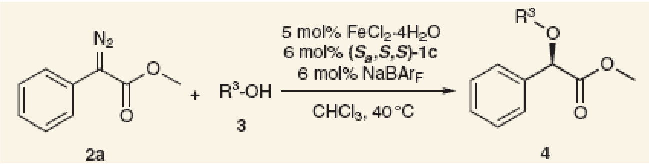
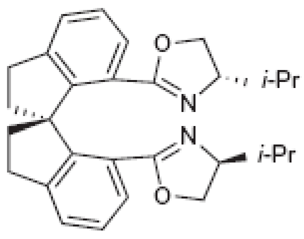
Screening of alcohols:





Spirobox

Entry	R^3OH	Product	Time (h)	Yield (%)	e.e. (%)*	Entry	R^3OH	Product	Time (h)	Yield (%)	e.e. (%)*
1	*n*BuOH, **3a**	4a	15	93	98	9	3i	4i	15	94	98 (77)
2	MeOH, **3b**	4b	10	85	96 (69)	10	3j	4j	15	91	93 (90)
3	EtOH, **3c**	4c	10	88	95 (87)	11	3k	4k	48	86	89 (27)
4	$CH_3(CH_2)_8CH_2OH$, **3d**	4d	15	92	95	12	3l	4l	3	92	93
5	3e	4e	20	90	94	13	3m	4m	12	90	95
6	3f	4f	20	92	98	14	3n	4n	24	88	95
7	3g	4g	15	95	98 (68)	15	3o	4o	24	91	95
8	3h	4h	10	95	99						

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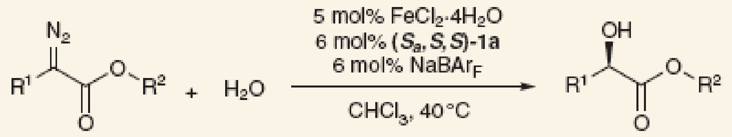
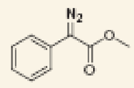
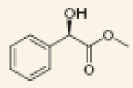
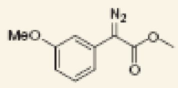
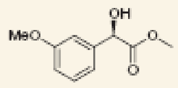
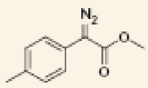
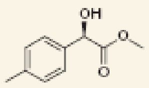
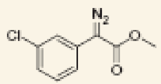
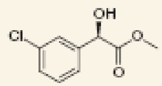
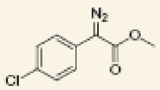
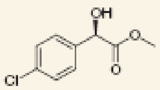
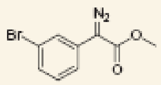
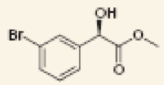
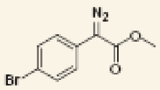
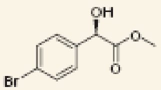
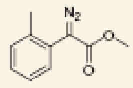
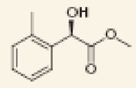
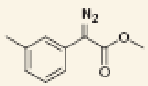
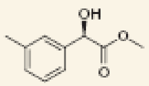
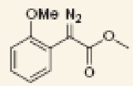
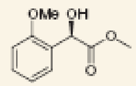
Insertion of water :



2 5

Entry	2	Product	Time (h)	Yield (%)	e.e. (%)*	Entry	2	Product	Time (h)	Yield (%)	e.e. (%)*
1	 2a	 5a	10	90	95	6	 2f	 5f	10	92	94
2	 2b	 5b	5	89	94	7	 2g	 5g	20	92	91
3	 2c	 5c	20	90	94	8	 2h	 5h	20	93	90
4	 2d	 5d	20	93	92	9	 2i	 5i	3	87	94
5	 2e	 5e	10	93	92	10	 2j	 5j	3	72	92

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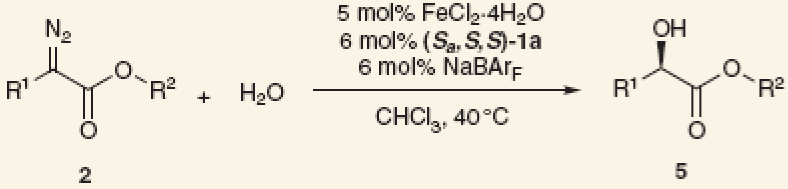
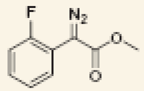
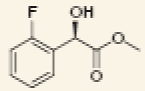
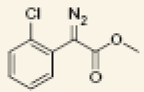
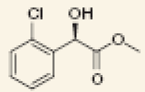
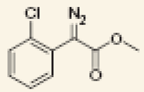
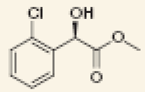
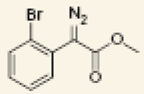
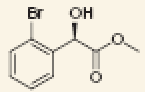
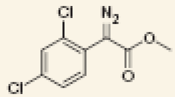
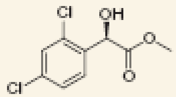
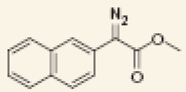
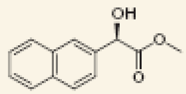
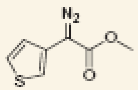
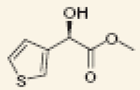
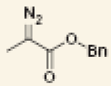
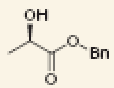
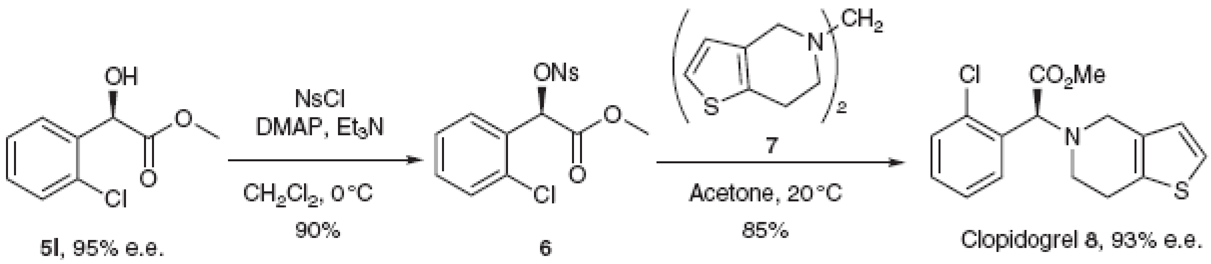
Insertion of water (continued):



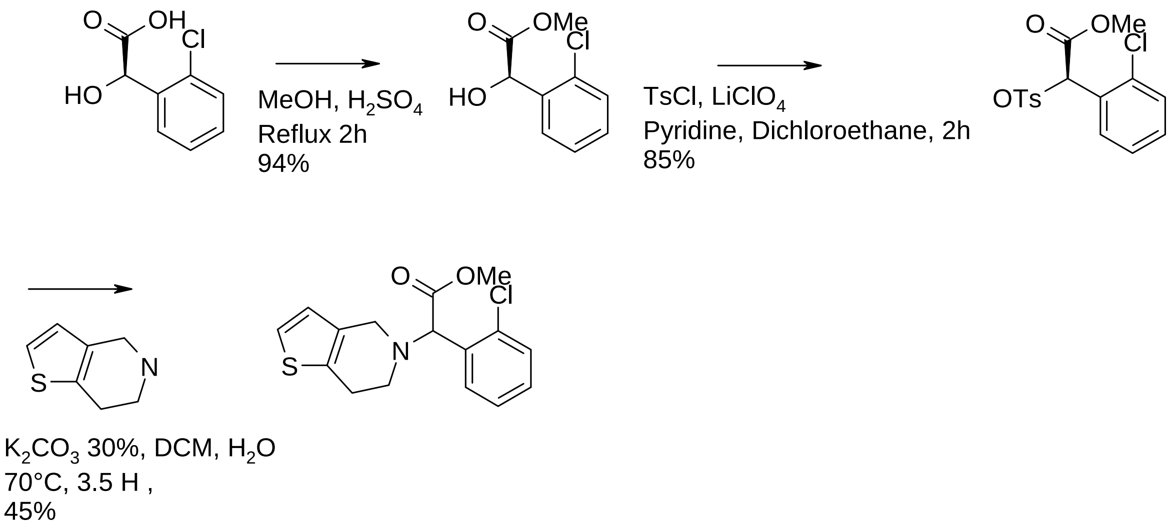
Entry	2	Product	Time (h)	Yield (%)	e.e. (%)*
11	 2k	 5k	3	91	90
12	 2l	 5l	2	92	95
13†	 2l	 5l	6	90	92
14	 2m	 5m	3	94	94
15	 2n	 5n	3	93	88
16	 2o	 5o	10	90	91
17	 2p	 5p	12	66	92
18	 2q	 5q	20	80	76

Enantioselective iron-catalysed O-H bond insertions

Application in total synthesis :



Contemporary Drug Synthesis, J. Li et al. Wiley Interscience, **2004** :



Conclusion

- For the first time enantioselectivities obtained with this O-H insertion reaction using iron catalyst surpass those obtained with other transition-metal catalyst.

- A catalyst stable enough to handle in air without loss of either reactivity or enantioselectivity

- Iron : low price, environmentally benign and ready available
  A ideal alternative to precious metal for catalytic asymmetric synthesis
  A new "Greener catalyst"