university of groningen

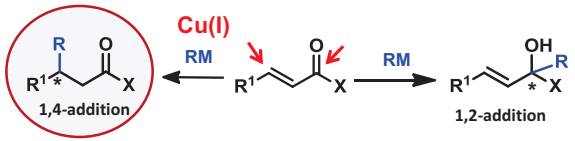
Enantioselective Synthesis of Chiral Tertiary Alcohols

Enabled by Copper(I) Catalysis

IASOC 2014

State of the Art

Addition to conjugated α,β-unsaturated systems



Cu(I)-based reagents have been used since 1941 to outcompete 1,2-selectivity in the addition of organometallics

RM = RLi, RMgX, R_3Al, R_2Zn

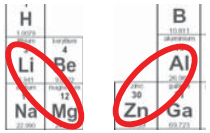
Copper (I) catalyzed asymmetric 1,4-addition of organometallics

1936 H. Gilman: preparation of MeCu

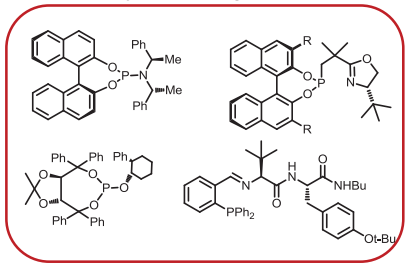
1941 Kharash: discovery of 1,4-selectivity over 1,2 when Grignard reagent in presence of Cu(I)

1952-1988 House , Corey, van Koten, Lipshutz: structural understanding and synthetic potential of organocuprates

RM



Some examples of chiral ligands



➢ **400 chiral ligands/catalyst s**

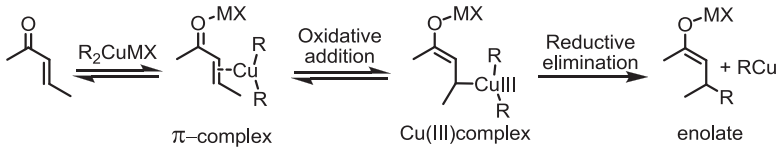
-excellent chemoselectivity, enantioselectivity

Alexakis, Feringa, Pfaltz , Woodward, Krause, Hoveyda, Zhang …….

Copper catalyzed asymmetric conjugate addition " in "Copper catalyzed asymmetric synthesis" eds: A. Alexakis, N. Krause, S. Woodward, Wiley-VCH, **2014**

Chem. Rev. **2008**, *108*, 2824.

Mechanism of Cu-catalyzed addition of organometallic reagents



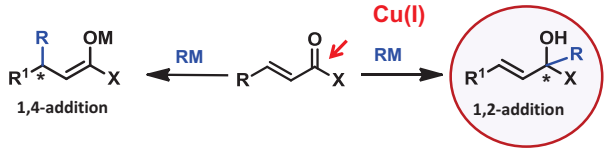
The proposed mechanism was supported by:

1. NMR observation of the π-complex and Cu(III)-species
2. Theoretical calculations
3. Kinetic isotope effect

a) Woodward S. *Chem. Soc. Rev.* **2000**, *29*, 393. b) Snyder J. P. *et. al. J. Am. Chem. Soc.* **1997**, *116*, 3383. c) Nakamura and Mori, *Angew. Chem. Intern. Ed.* **2000,** *39*, 3750 ; J. Canisiua, A. Gerold, N. Krause, *Angew. Chem. Intern. Ed.* **1999,** *3*, 1644; e) S. H. Bertz; S. Cope; M. Murphy; C. A. Ogle; B. Taylor *J. Am. Chem. Soc.* **2007,** *129*, 7208

Impossible or a new paradigm?

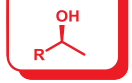
Addition to conjugated α,β-unsaturated systems



Paradigm change
(After > 70 years)

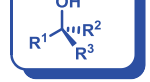
State of Art

2° alcohols



- Kinetic resolution
- Asymmetric hydrogenations
- Enantioselective addition to aldehydes

3° alcohols



- Hydrogenation reactions are not applicable
- Low reactivity

Tertiary alcohols using organometallic reagents

RM = R_2Zn

- ❑ Excellent enantioselectivities
- ❑ Superstoichiometric use of $Ti(OiPr)_4$ and R_2Zn
- ❑ Low atom efficiency, low reactivity
- ❑ 48-72h reaction times

Yus, Walsh, Fu, Kozlowski, Hoveyda, Ishihara...

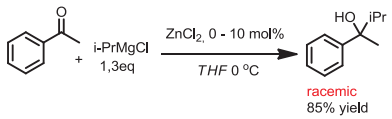
a) *Chem. Rev.* **2008,** *108,* 2853. b) *Tetrahedron Asymmetry* **2009**, *20*, 981. c) *Org. Prep. Proc. Int*. **2011**, 43.
d) *Synthesis* **2008**, *11*, 1647. e) *Chem. Rev*. **2001**, *101*, 757

Goal / State of Art

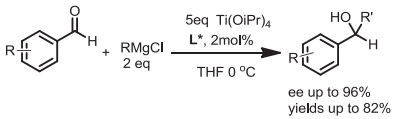
RMgX ?

Problems

- ❑ Fast non-catalysed reactions
- ❑ High basicity causes enolisations/side products
- ❑ Competitive reduction via β-H transfer

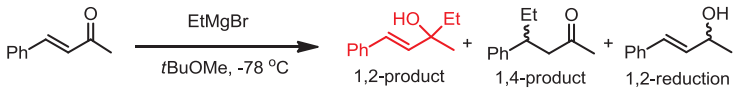


K. Ishihara et al.
a) *J. Am. Chem. Soc.*, **2006**, *128*, 9998
b) *Chem. Commun.*, **2010**, *46*, 2674
c) *J. Org. Chem.*, **2010**, *75*, 5008



T. Harada et. al.
a) *Angew. Chem. Int. Ed.* **2008**, *47*, 1088
b) *Bull. Chem. Soc. Jpn.* **2010**, *83*, 19

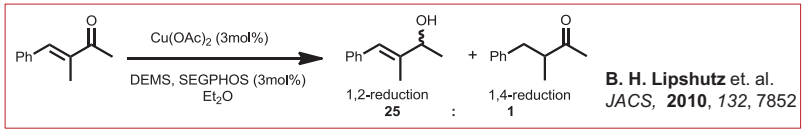
Asymmetric 1,2-addition of Grignard reagents to ketones



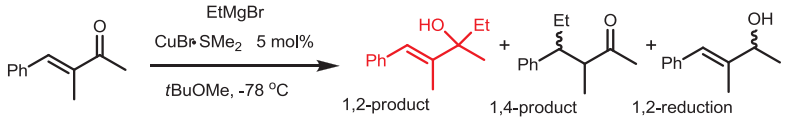
CuBr (5 mol%):	**21%**	:	**79%**	:	**0%**
CuBr (5mol%), **L*** (6 mol%):	**~20%** racemic	:	**~ 80%** various ee	:	**0%**
CuBr (5 mol%), **L***  (6 mol%):	**16%**	:	**84%**	:	**0%**

e.r. 65:35

Cu(I) catalysed 1,2-reduction of ketones C-H versus C-C bond formation



B. H. Lipshutz et. al. *JACS*, **2010**, *132*, 7852

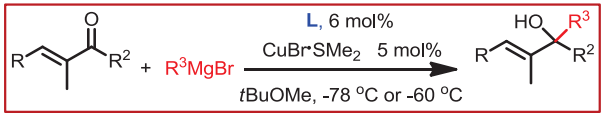


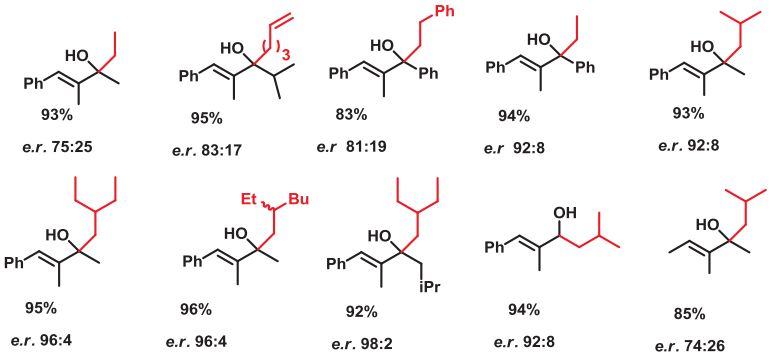
CuBr (5 mol%) **25% : 21% : 9% : 45% SM**

CuBr (5 mol%), **L*** (6 mol%) **97% : 2 % : 1 %**

e.r. 75:25

1,2-addition products from α-methyl substituted enones and enals

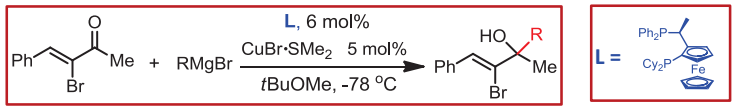


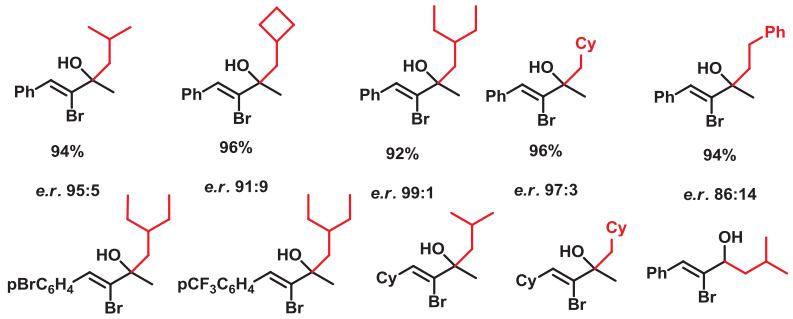


Reaction times: 5-10h

Chem. Comm. **2012**, *48*, 1478

1,2-addition products from α-bromo substituted enones and enals

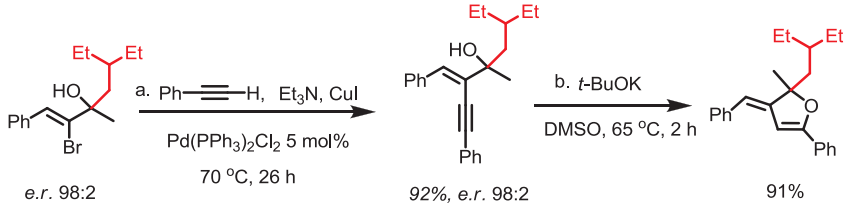




Reaction times:5-10h

Org. Biomol. Chem., **2012**, 10, 2878

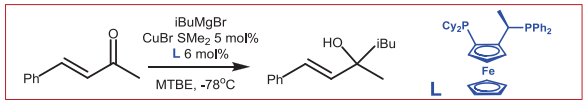
Application of the methodology in the synthesis of chiral dihydrofurane



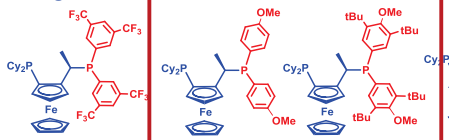
e.r. 98:2 — *92%, e.r.* 98:2 — 91%

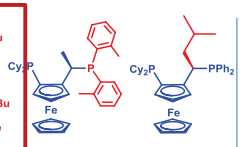
Eur.J.Org. Chem., *2014, 3, 575*

Addition nonsubstituted conjugated ketones

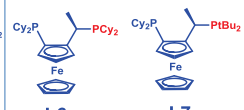


New ligands



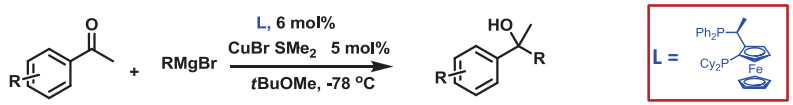


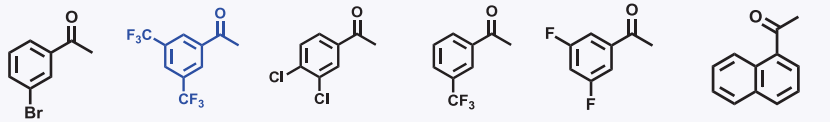
Commercial ligands

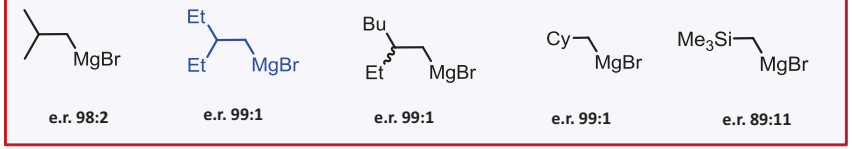


Ligand	1,2 : 1,4	*e. r.* 1,2
L	16:84	65:35%
L1	5:95	racemic
L2	43:57	75:25%
L3	62:38	85:15%
L5	20:80	racemic
L6 and L7	41:59	60:40%

Addition to ketones: substrate and Grignard reagents scope



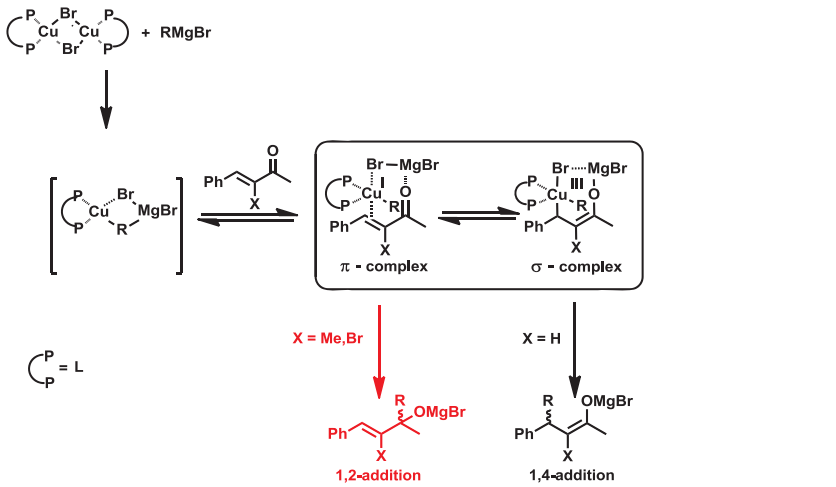




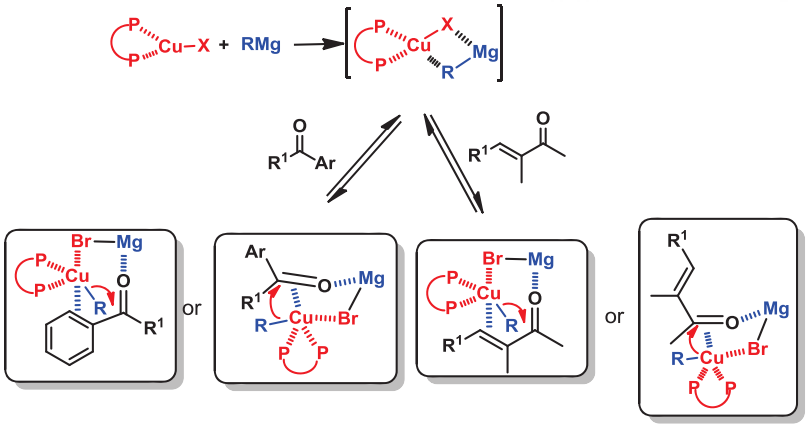
Reaction times: 5-10h, yields > 95%

Angew. Chem. Int. Ed. 2012, 51, 3164

Working hypothesis



Mechanistic rationale for Cu(I)-catalysed 1,2-addition

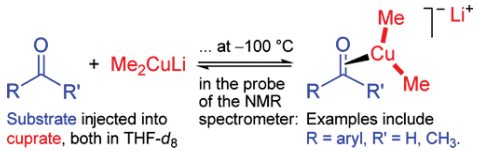


- Activation of an organometallic
- Double activation of an electrophilic substrate

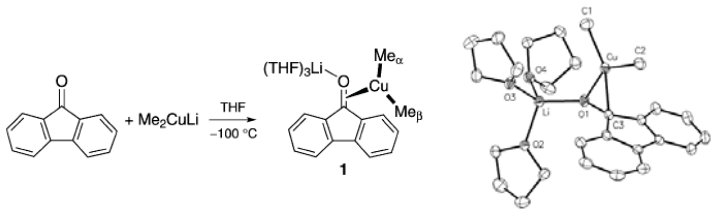
with S. Bertz, C. Ogle

Angew. Chem. Int. Ed. 2012, 51, 3164

π-Complex formation between Gilman reagents and ketones observed by RI-NMR and X-ray

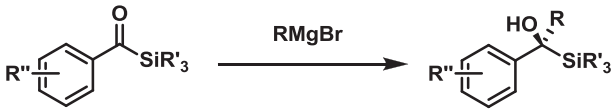


S. H. Bertz, R. A. Hardin, C. A. Ogle *JACS.*, **2013**, *135,* 9656

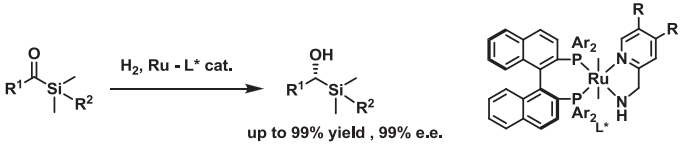


S. H. Bertz, R. A. Hardin, T. J. Heavey, C. A. Ogle
Angew. Chem. Int. Ed. **2013**, *52*, 10250

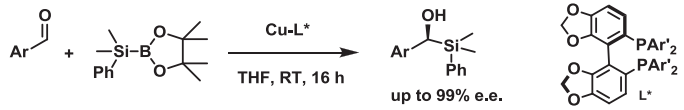
Synthesis of tertiary chiral hydroxysilanes



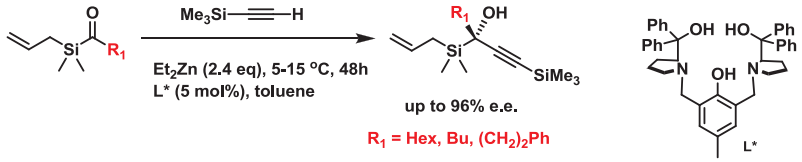
Previous work



N. Arai , K, Suzuki, S, Sugizaki, H, Sorimachi, T, Ohkuma *Angew. Chem. Int. Ed.,* **2008**, 47, 1770

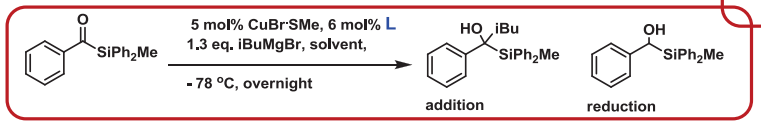


V. Cirriez, C. Rasson, T. Hermant, J. Petrignet, J. Díaz Álvarez, K. Robeyns, O. Riant, *Angew. Chem. Int. Ed.* **2013**, 52, 1785



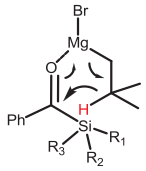
P.-O. Delaye, D. Didier, I. Marek, *Angew. Chem. Int. Ed.* **2013**, 52, 1

Synthesis of chiral tertiary α-hydroxysilane

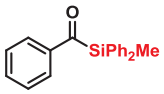
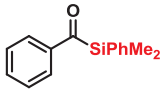
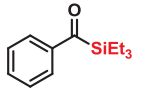
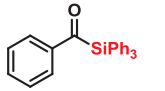


add:red	e.e. %
1:2	90%

reduction via β–hydride transfer



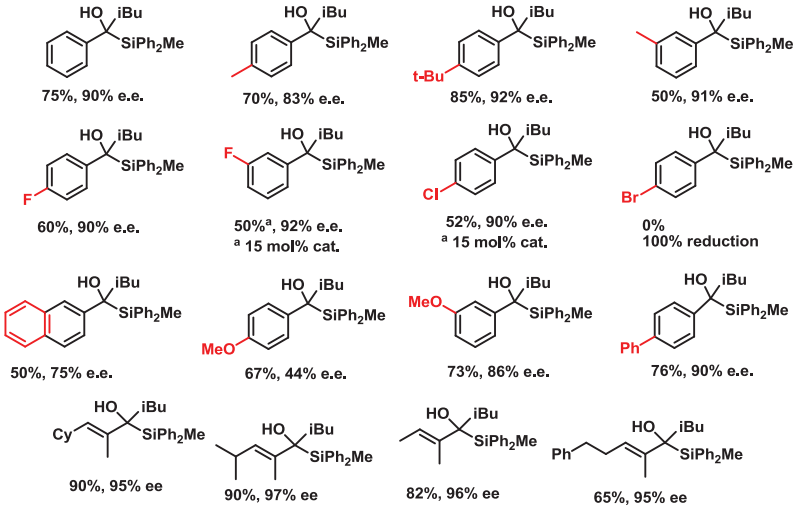
Effect of sila substituent

	add:red	e.e. %
	1:2	90%
	1:1.3	80%
	0:1	-
	0:1	-

Synthesis of chiral α-hydroxysilane/addition of Lewis acid

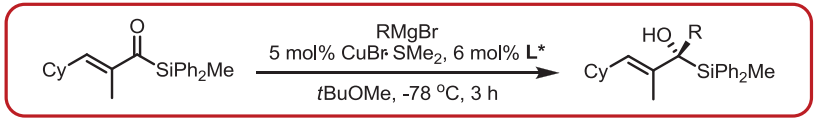
Entry	Lewis acid	Conversion	Add:red	e.e. %
1	None	Full	1:2	90
2	$BF_3{\cdot}Et_2O$ 2eq	Full	3:1	86
3	TMSCl 2eq	Full	1:1.6	91
4	$CeCl_3$ 1.3 eq	Full	1:1.3	93
5	$MgCl_2$ 2 eq	Full	1:2	91

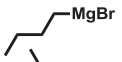
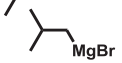
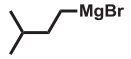
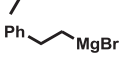
Substrate scope



Submited

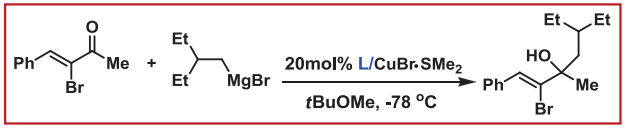
Grignard reagent scope



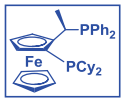
Entry	RMgBr	Yield (%)	e.r.
1		95	92:8
2		93	92:8
3		90	98:2
4		89	93:7
5		95	91:9
6		97	93:7
7		96	95:5

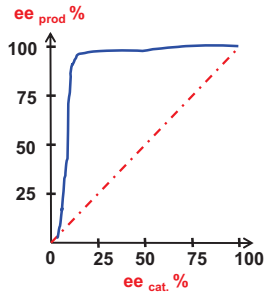
Submited

Asymmetric amplification



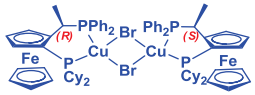
L =



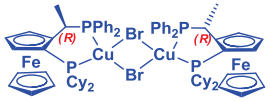


ee L	ee 1,2-product
0	0
10	94
20	94
40	96
60	94
80	96
100	98

Kagan's ML_2 model?



heterochiral dimer



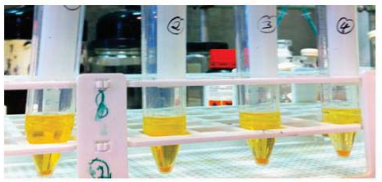
homochiral dimer

T. Satyanarayana, S. Abraham, H. B. Kagan *Angew. Chem. Int. Ed.* **2009,** *48,* 456 *Nonlinear Effects in Asymmetric Catalysis*

The origin of asymmetric amplification

(*R,S*)-L + (*S,R*)-L $\xrightarrow{\text{CuBr SMe}_2}$ L/CuBr complex ee : 0, 20, 40, 60, 80, 100

L/CuBr in tBuOMe



ee 80 60 40 20

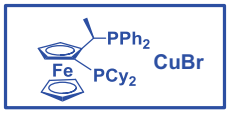
Supernatant: ee > 90%

Precipitates: ee <15

(determined by CD and polarimetry)

Chem. Comm. 2013, *49*, 5450, 2013

Analysis of the solution and the precipitate

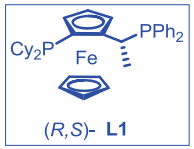


Mass-spectroscopy: ESI (solution) and DART (solid)
Both dimer and monomer are present in racemic and enantiopure complexes

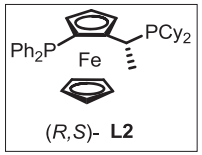
Solubility in tBuOMe
enantiopure: 70mg/ml (0.12M)
racemic: less than 1mg/15ml

Melting points
enantiopure complex: 180 - 186 °C
racemic complex: 210 - 216 °C

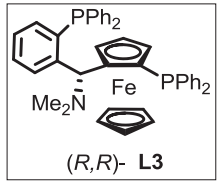
What about metals other than Cu ?



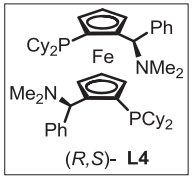
(*R,S*)- **L1**



(*R,S*)- **L2**



(*R,R*)- **L3**

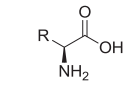


(*R,S*)- **L4**

Pd(II) as well as Rh(I) complexes of chiral biphosphine ligands behave similar Cu(I) analogues

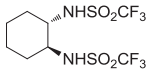
Chem. Comm. 2013, *49*, 5450, 2013

Asymmetric amplification based on the equilibrium solid-liquid phase behavior

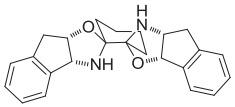


Morowitz, H. J. *J. Theor. Biol* , *25*, **1969**, 491

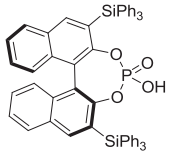
D. Blackmond et. al *Nature*, *44*, **2006,** 621



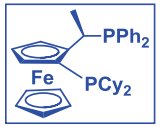
H. B. Kagan et al. Org. Lett., *9*, **2007,** 251



C. Wolf et. Al. *Org. Lett.*, *9*, **2007** 2965



L.-Z. Gong et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 6378



Monomer or dimer?

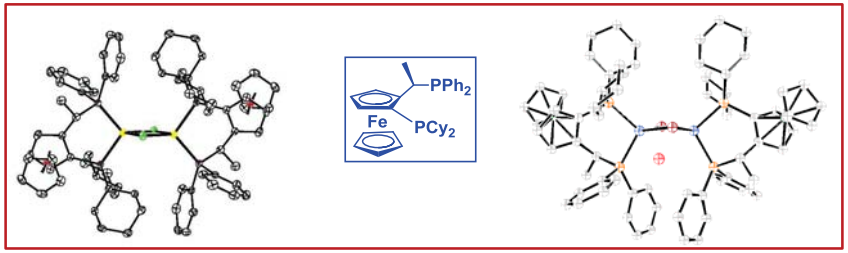
The origin of the phenomenon

monomer dimer

or

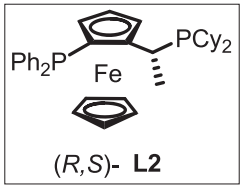
Homochiral dimer heterochiral dimer

*(R,S)-L/ (S,R)-L/2*CuBr *(R,S)-L/ (R,S)-L/2*CuBr

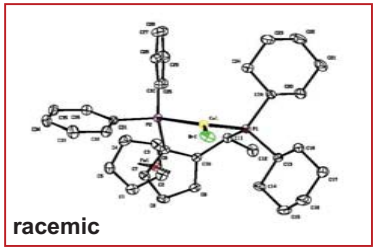


Chem. Comm. 2013, *49*, 5450, 2013

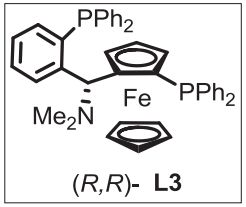
Structure of racemic CuBr complexes of chiral biphosphine ligands



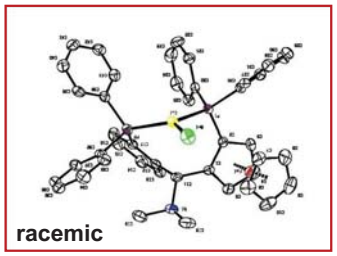
(*R,S*)- **L2**



racemic



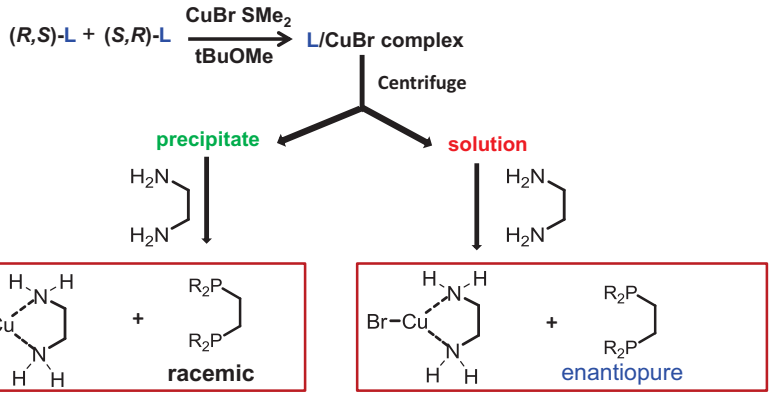
(*R,R*)- **L3**



racemic

Access to enantiopure ligand:

experiments with Cu- complexes with ee's of 20%



Determined by CD and polarimetry