IASOC

ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY

Ischia (Naples), September 27 - October 2, 2008

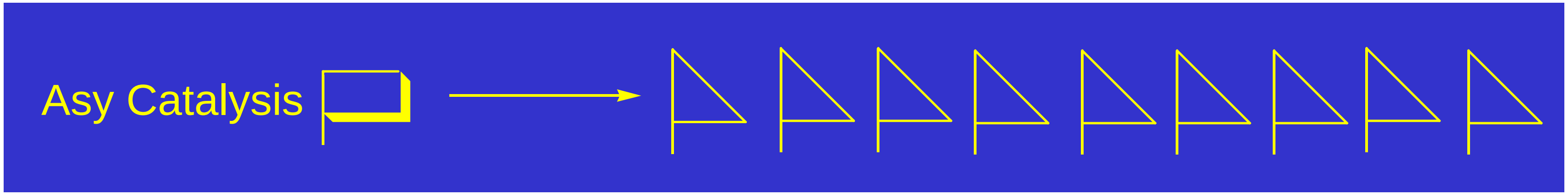
(50+10 min)

A Self-Supporting Strategy for Chiral Catalyst Immobilization

Kuiling Ding

Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, China

Some Challenges in Asymmetric Catalysis



- **Selectivity: There is no given catalyst that is universal for all substrates. ⇨ Catalyst diversity**
- **Reactivity and Efficiency : 1-10 mol% catalyst loading is not practical. ⇨ 0.1-0.01% or less.**
- **Process chemistry: speed up the rate for catalyst discovery in customer synthesis.**
- **Catalyst recovery and reuse.**
- **Cost, energy, solvent, safety, and others…….**

Combinatorial Approach to Asymmetric Catalysis

Chiral Ligand Library A with *m* Members + M^{n+} + **Ligand Library B with *n* Members (chiral, achiral or racemic)**

Kagan
Oguni, Noyori
Brown (1986)
Yamamoto(1989)
Faller (1993)
Mikami (1997)

Related Concepts
asymmetric amplification
chiral poisoning
asymmetric activation

Related Concepts
molecular recognition and assembly
dynamic combinatorial chemistry

Lehn (1999)

Modular Chiral Catalyst Library with *m* x *n* Members!

Chemspeed Synthesizer

High Throughput Screening (HTS) on Target Reactions

HPLC-CD

Highly Efficient and Enantioselective Catalysts

***ACIE* 2001*, 40,* 544.**
***ACIE* 2003*, 42,* 5478.**
***JACS* 2002*, 124,* 10.**
***JACS* 2002*, 124,* 14866.**
***JACS* 2005, *127*, 10488.**
***JACS* 2006, *128*, 14212.**
JACS* 2008,*130, in press.
***CEJ* 2002*, 8,* 5033.**
***CEJ* 2003, *9*, 5989.**
***CEJ* 2008, *14*, in press**
***ASC* 2005*, 347,* 1193.**
***ASC* 2006, *348*, 1049.**
***OL* 2002, *4*, 4349.**
***OL* 2003, *5*, 1091.**
***JOC* 2004, 69, 146.**
***EJOC* 2006, 3606.**
***EJOC* 2008, 2248.**

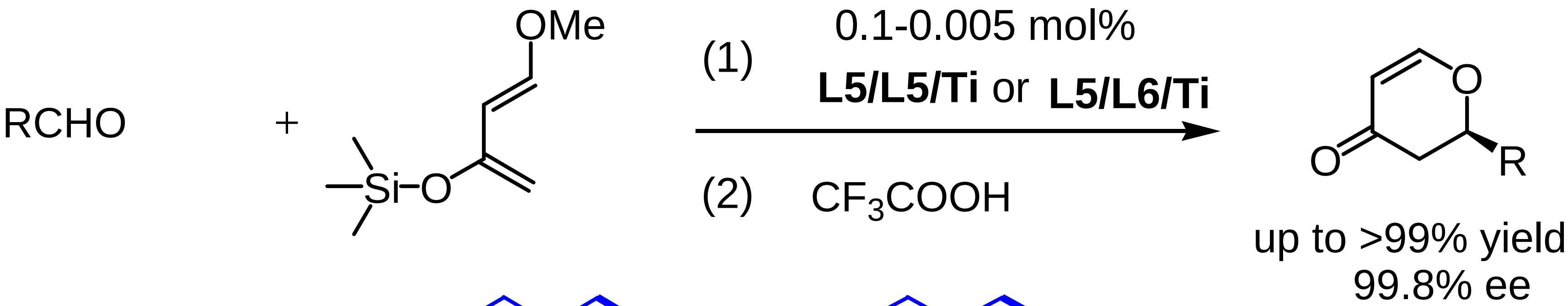
Concept Article

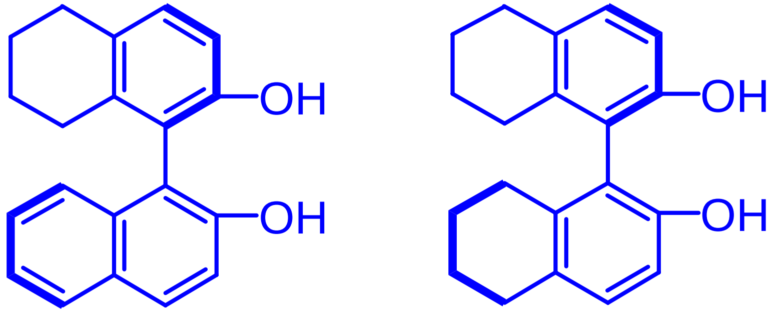
***Chem. Eur. J.* 2004, *10*, 2872-2884.**

Feature Article

***Chem. Commun.* 2008, 909- 921.**

Exceptionally Efficient Catalysts for Enantioselective Hetero-Diels-Alder Reaction



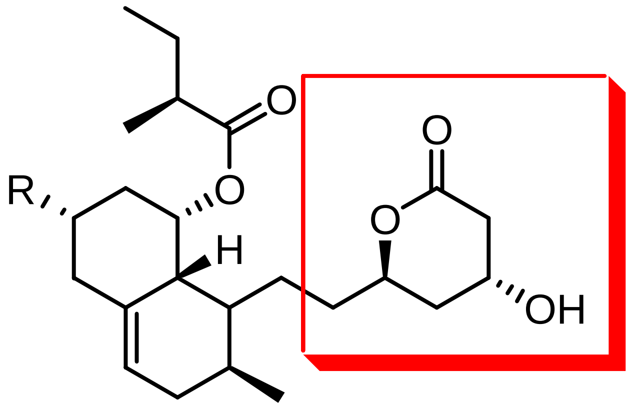


L5 **L6**

Highly efficient: 0.1% - 0.005% of cat. loading!
Very high yield and enantioselectivity
Room temperature and solvent free

J. Long, K. Ding, et al., *J. Am. Chem. Soc*. **2002**, *124*, 10-11.

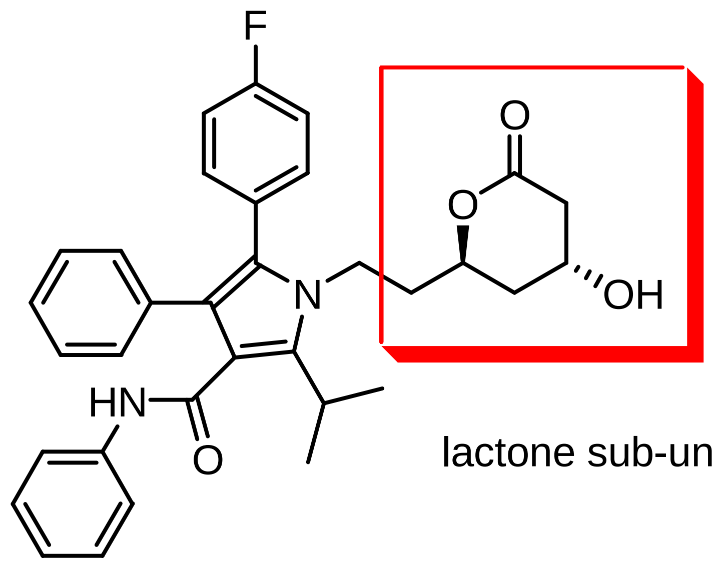
Asymmetric HDA Reaction: A Facile Approach to Lactone Sub-unit of Chiral Drugs



lactone sub-unit

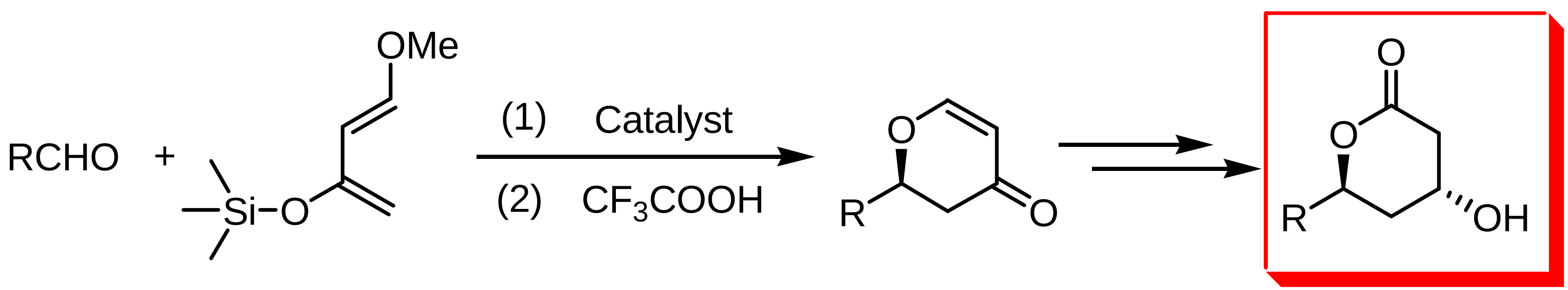
R = H, compactin

R = Me, Mevacor

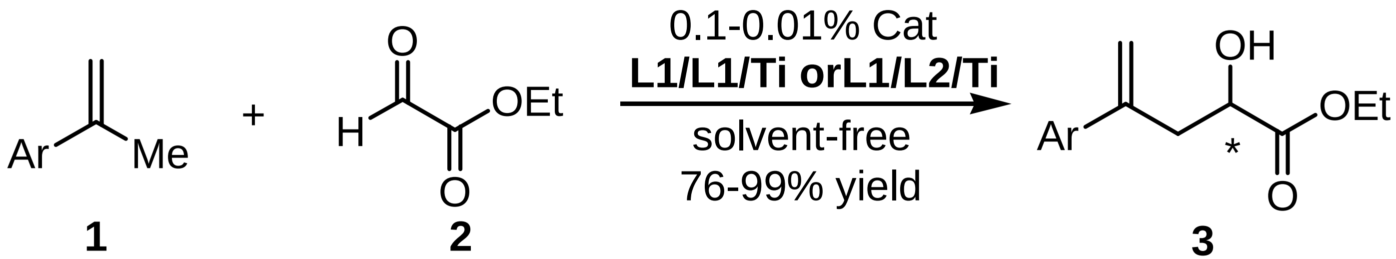


lactone sub-unit

Lipitor, $13.6 billion (2006)

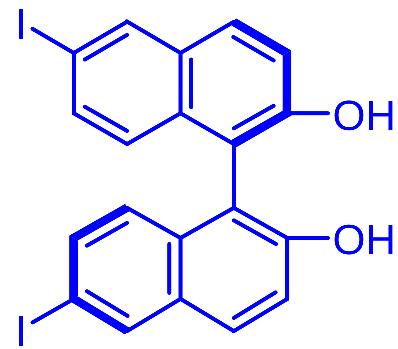


Exceptionally Efficient Catalysts for Quasi Solvent-Free Enantioselective Carbonyl-Ene Reaction

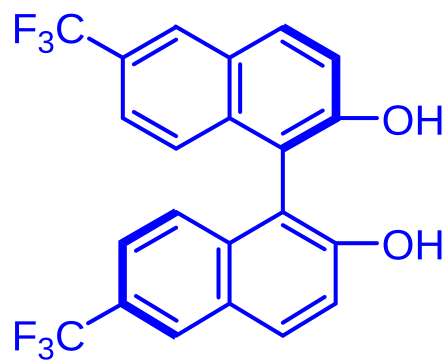


1a: Ar = C_6H_5
1b: Ar = 4-ClC_6H_4
1c: Ar = 4-FC_6H_4
1d: Ar = 4-$CH_3C_6H_4$

3a: Ar = C_6H_5 (98.2% ee)
3b: Ar = 4-ClC_6H_4 (99.4% ee)
3c: Ar = 4-FC_6H_4 (98.4% ee)
3d: Ar = 4-$CH_3C_6H_4$ (97.1% ee)



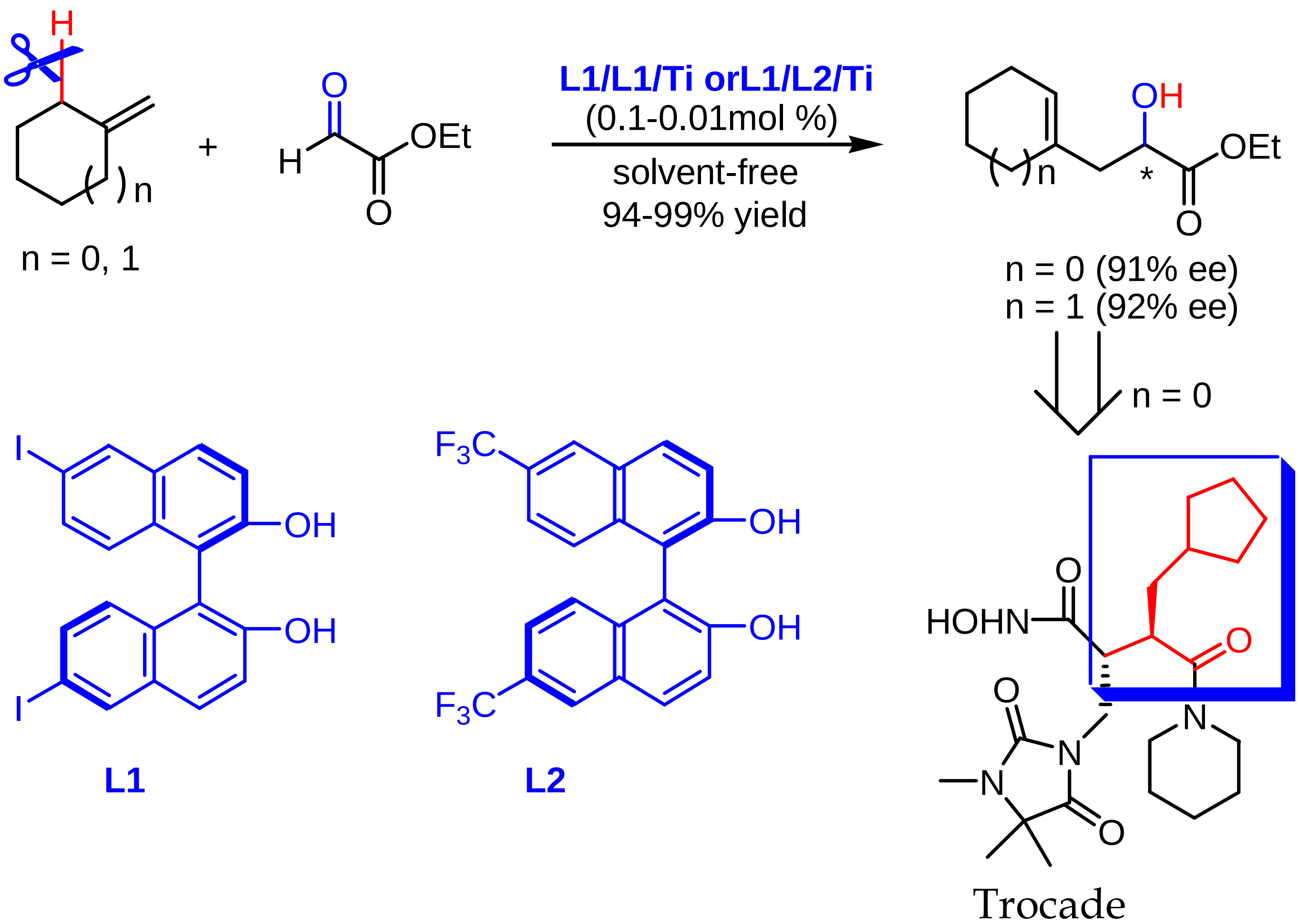
L1



L2

Y. Yuan & K. Ding, *Angew. Chem. Int. Ed.* **2003**, *42*, 5478.

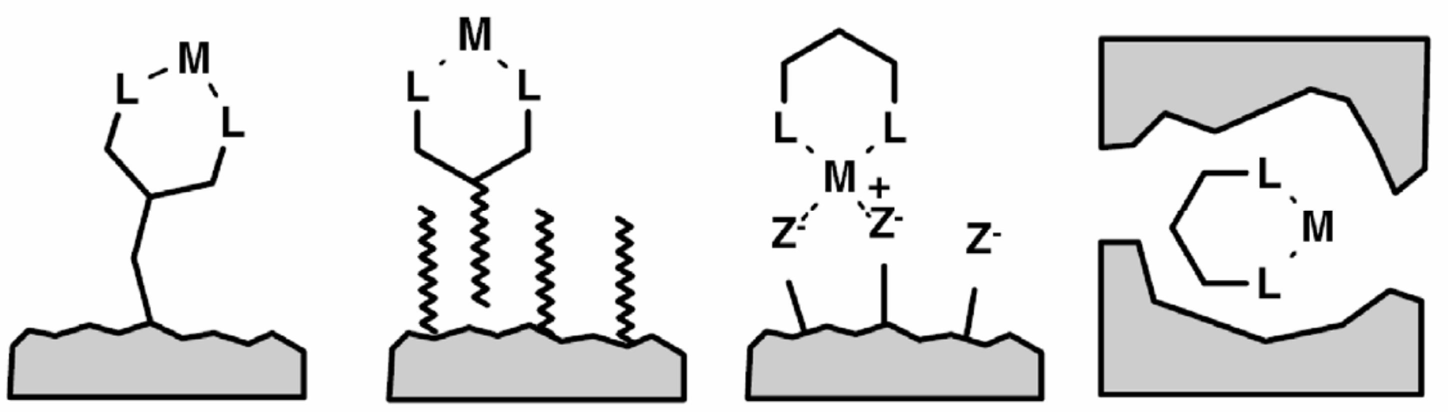
Exceptionally Efficient Catalysts for Quasi Solvent-Free Enantioselective Carbonyl-Ene Reaction



Y. Yuan & K. Ding, *Angew. Chem. Int. Ed.* **2003**, *42*, 5478.

General Strategy for Chiral Catalyst Immobilization

Bonding Patterns



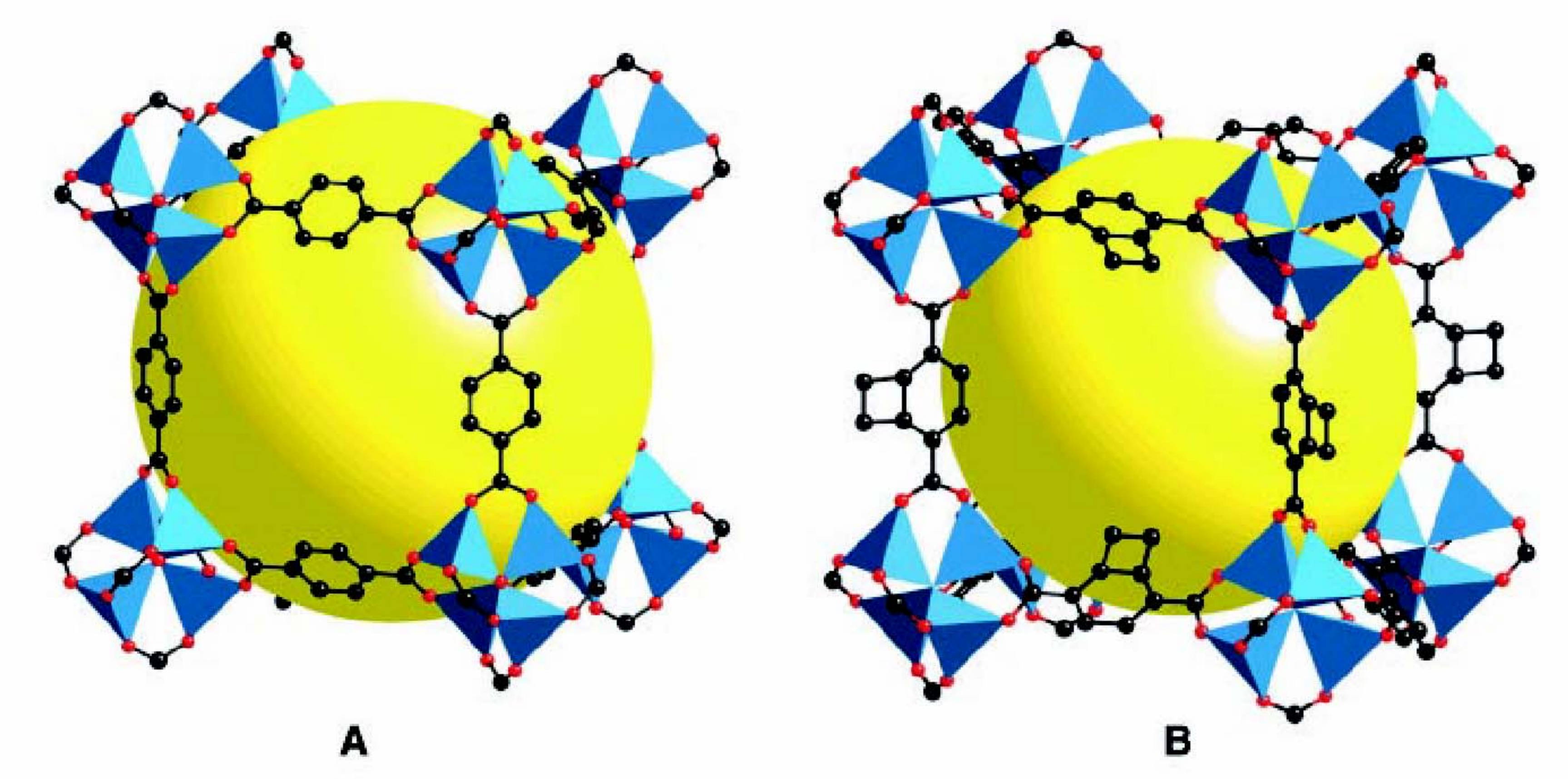
Covalent bonding | Physisorption | Electrostatic interactions | Entrapment

Supports or Media

★ Organic Polymers and Dendrimers;
★ Inorganic Supports;
★ Non-Conventional Media (such as water, fluorous inated liquids, ionic liquids, and Sc CO_2…)

Fan, Q.; Li, Y.-M.; Chan, A. S. C. *Chem. Rev.* 2002, *102*, 3385.
D. E. De Vos, I. F. J. Van Kelecom, P. A. Jacobs, Eds. *Chiral Catalyst Immobilization and Recycling*, Wiley-VCH, Weinheim, 2000.

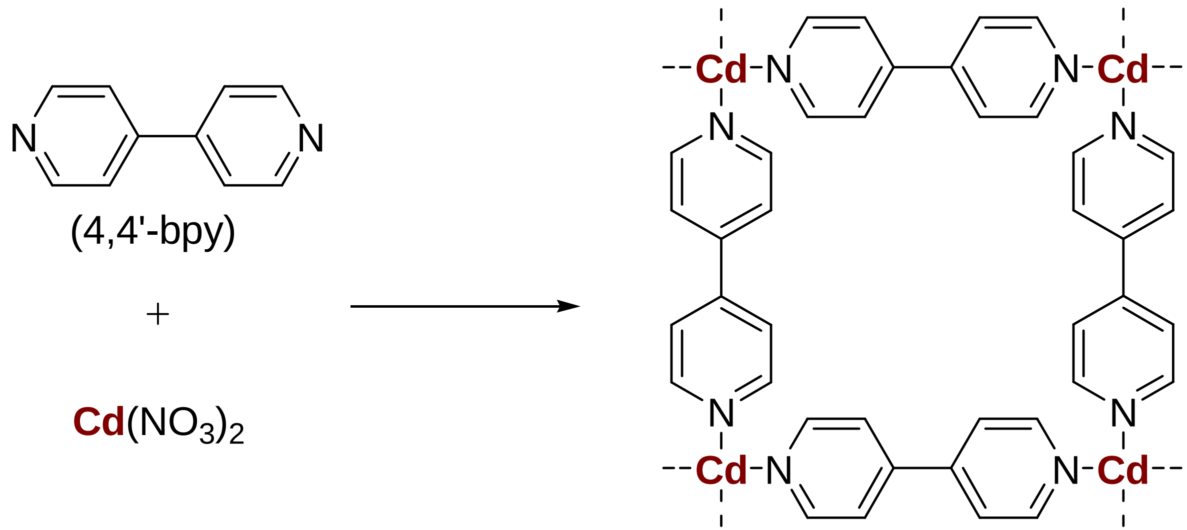
Microporous Metal-Organic Frameworks



O. M. Yahgi, et al. *Nature*, **2003**, *423*, 705;

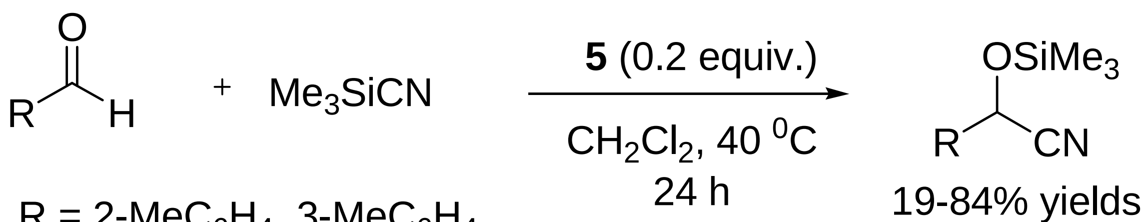
Science, **2003**, *300*, 1127.

Coordination Network Material as A Zeolite-Like Heterogeneous Catalyst



5

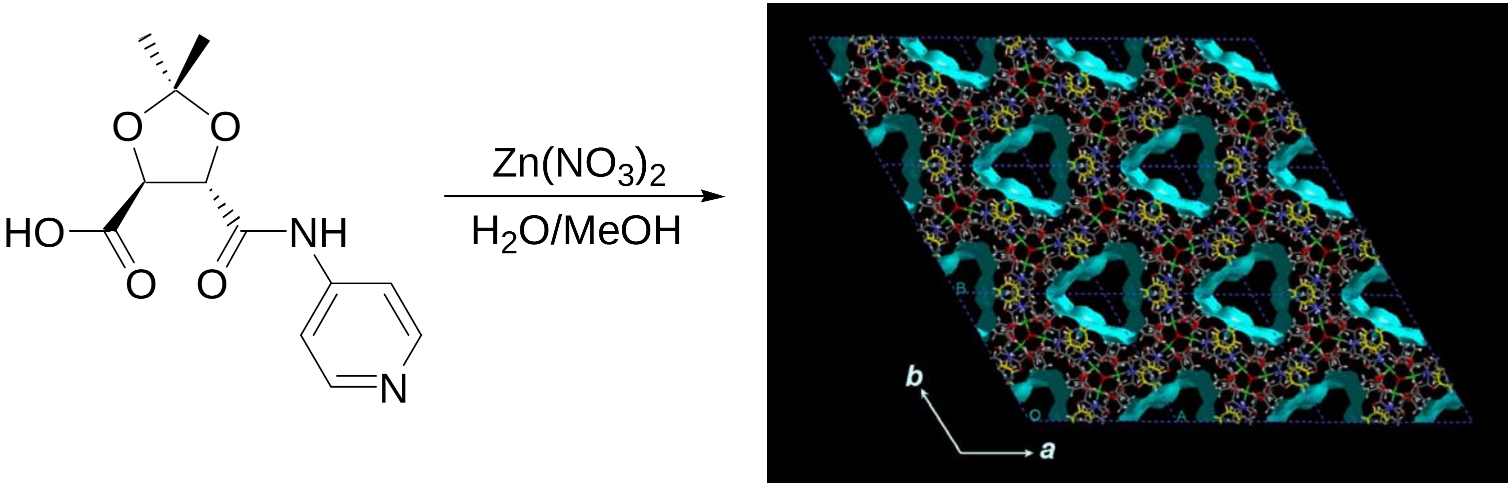
(Counter ions are omitted for clarity)



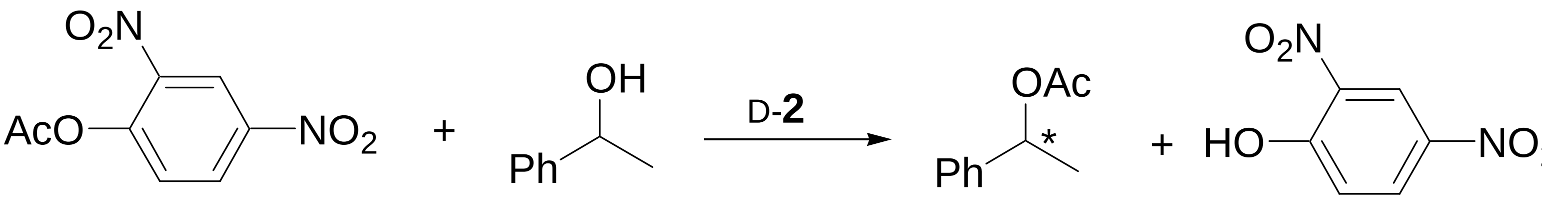
R = 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$,
1-naphthyl, 2-naphthyl.

M. Fujita & K. Ogura, et al., *J. Am. Chem. Soc*. **1994**, *116*, 1151-1152.

Microporous Homochiral Metal-Organic Frameworks



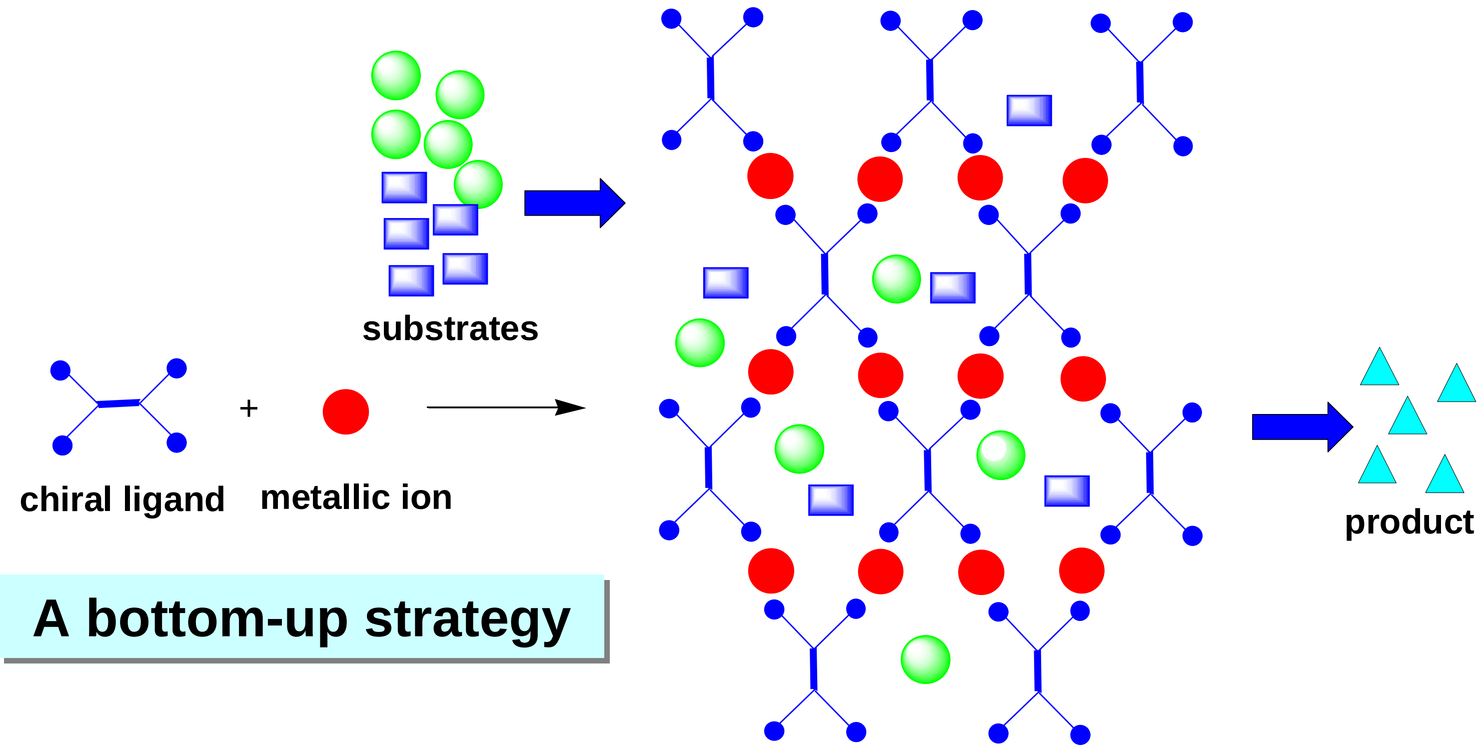
1 **2**



3 **4** **5**, 8% *ee* **6**

K. Kim et al., *Nature,* **2000**, *404*, 982.

Self-Supported Chiral Catalysts for Heterogeneous Enantioselective Catalysis

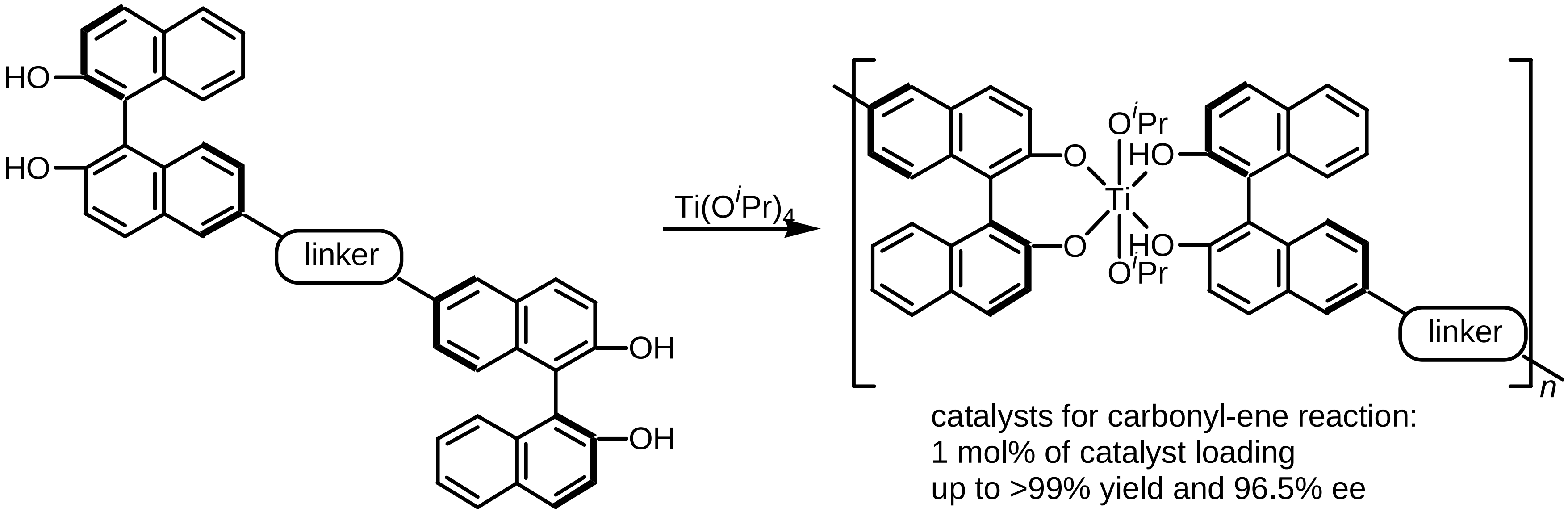


A bottom-up strategy

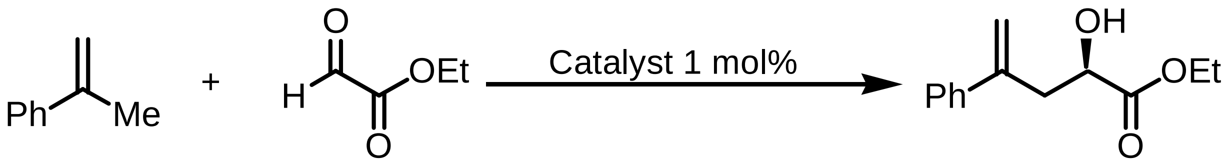
chiral metal-organic framworks
or chiral metal-organic coordination polymer

K. Ding et al. *Chem. Eur. J.* **2006**, *12,* 5188-5197.

Self-Supported BINOL-Ti Catalysts for Carbonyl-Ene Reaction



catalysts for carbonyl-ene reaction:
1 mol% of catalyst loading
up to >99% yield and 96.5% ee



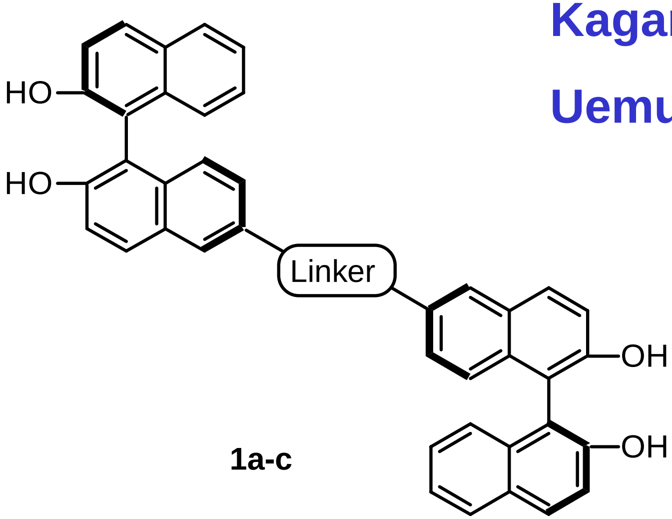
up to 99% yield
96.5% ee

H. Sasai et al., *Angew. Chem. Int. Ed*. **2003**, *42*, 5711-5714.
H. Guo, X. Wang et al, *Tetrahedron Lett*. **2004**, *45*, 2009-2012.
X. Wang, H. Guo et al. *Chem. Eur. J*. **2005**, *11*, 4078-4088.

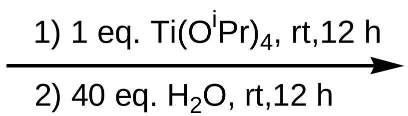
Highly Stable and Enantioselective Heterogeneous Titanium Catalysts for Asymmetric Oxidation of Sulfides

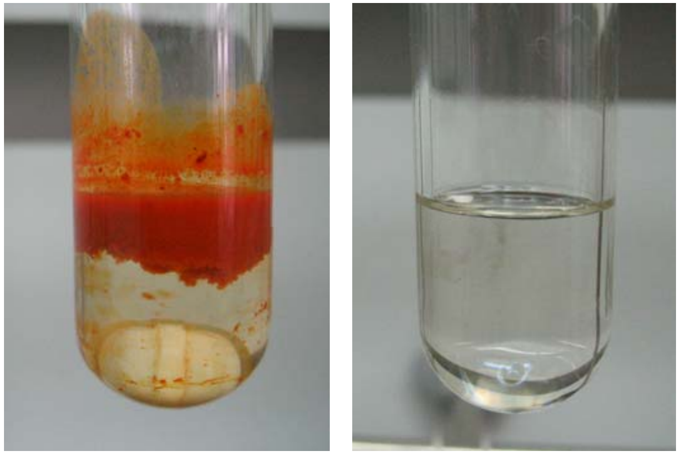
Kagan, Modena,

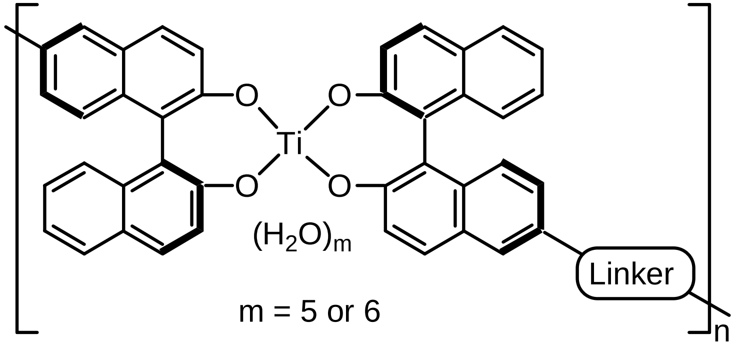
Uemura, Bolm



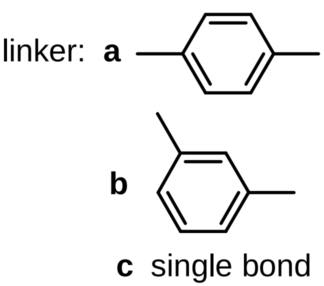
1a-c

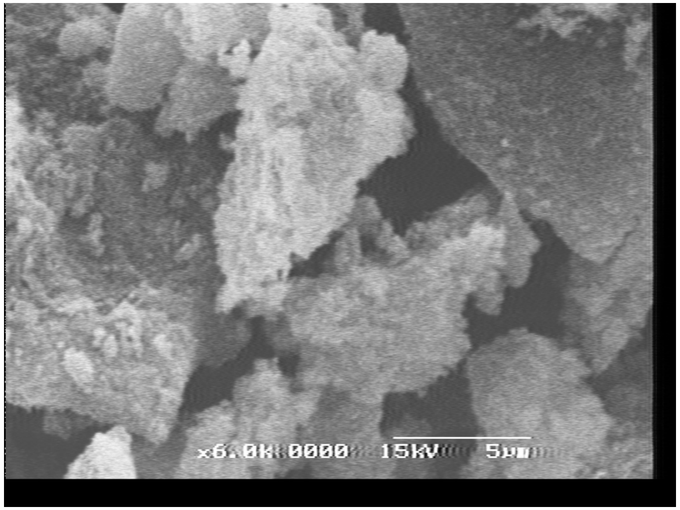






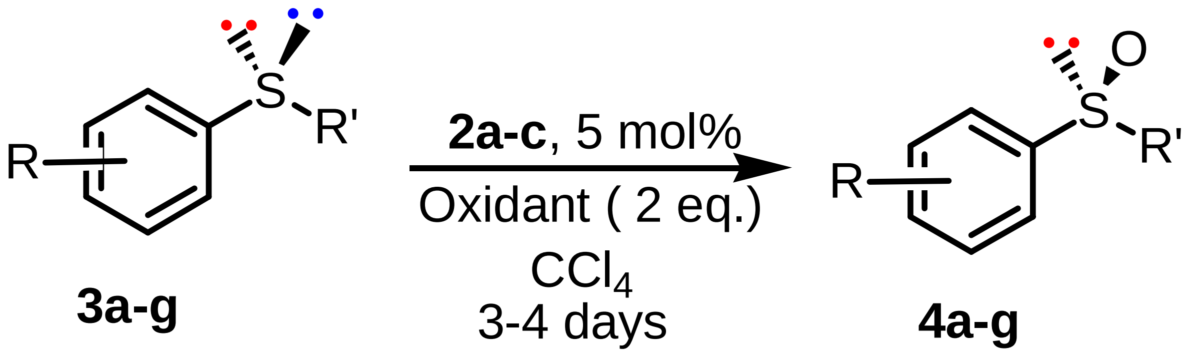
2a-c





X. Wang, H. Guo, et al., *Chem. Eur. J.* **2005**, *11*, 4078-4088.

Highly Stable and Enantioselective Heterogeneous Titanium Catalysts for Asymmetric Oxidation of Sulfides



3a: R = H, R' = Me
3b: R = 4-Me, R' = Me
3c: R = 4-Br, R' = Me
3d: R = 4-F, R' = Me
3e: R = 3-Br, R' = Me
3f: R = NO_2, R' = Me
3g: R = H, R' = Et

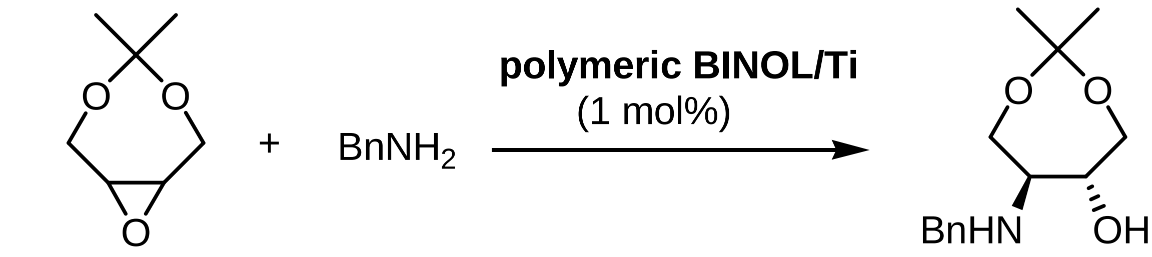
Reused for 8 times,
Life time > 1 month
98.2->99.9% ee

up to >99.9% ee
35-45% yield

Run	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Y (%)	**39**	**34**	**42**	**39**	**30**	**38**	**32**	**34**
Ee (%)	**98.2**	**99.1**	**99.2**	**99.2**	**99.0**	**99.1**	**>99.9**	**99.1**

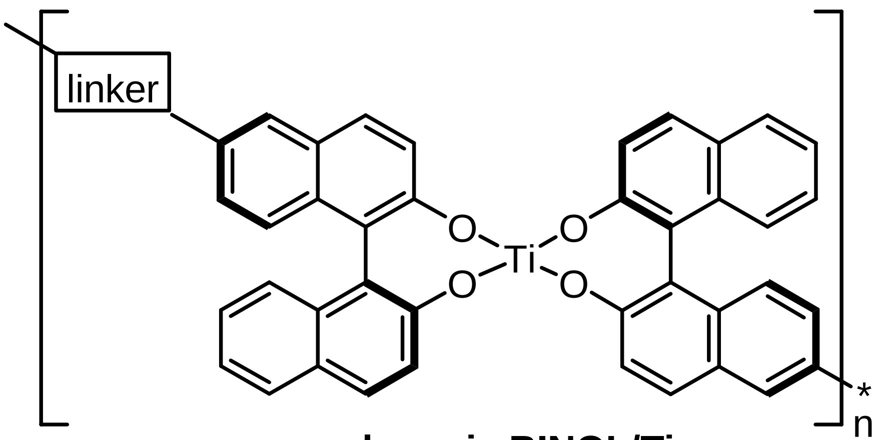
X. Wang, H. Guo et al., *Chem. Eur. J.* **2005**, *11*, 4078-4088.

Heterogeneous Titanium Catalysts for Asymmetric Ring Opening of Expoide

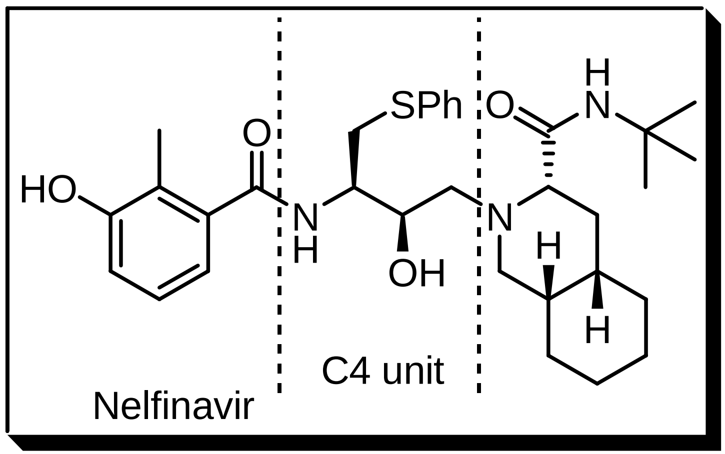


recycled 12 times

>90% yield
94-97% ee

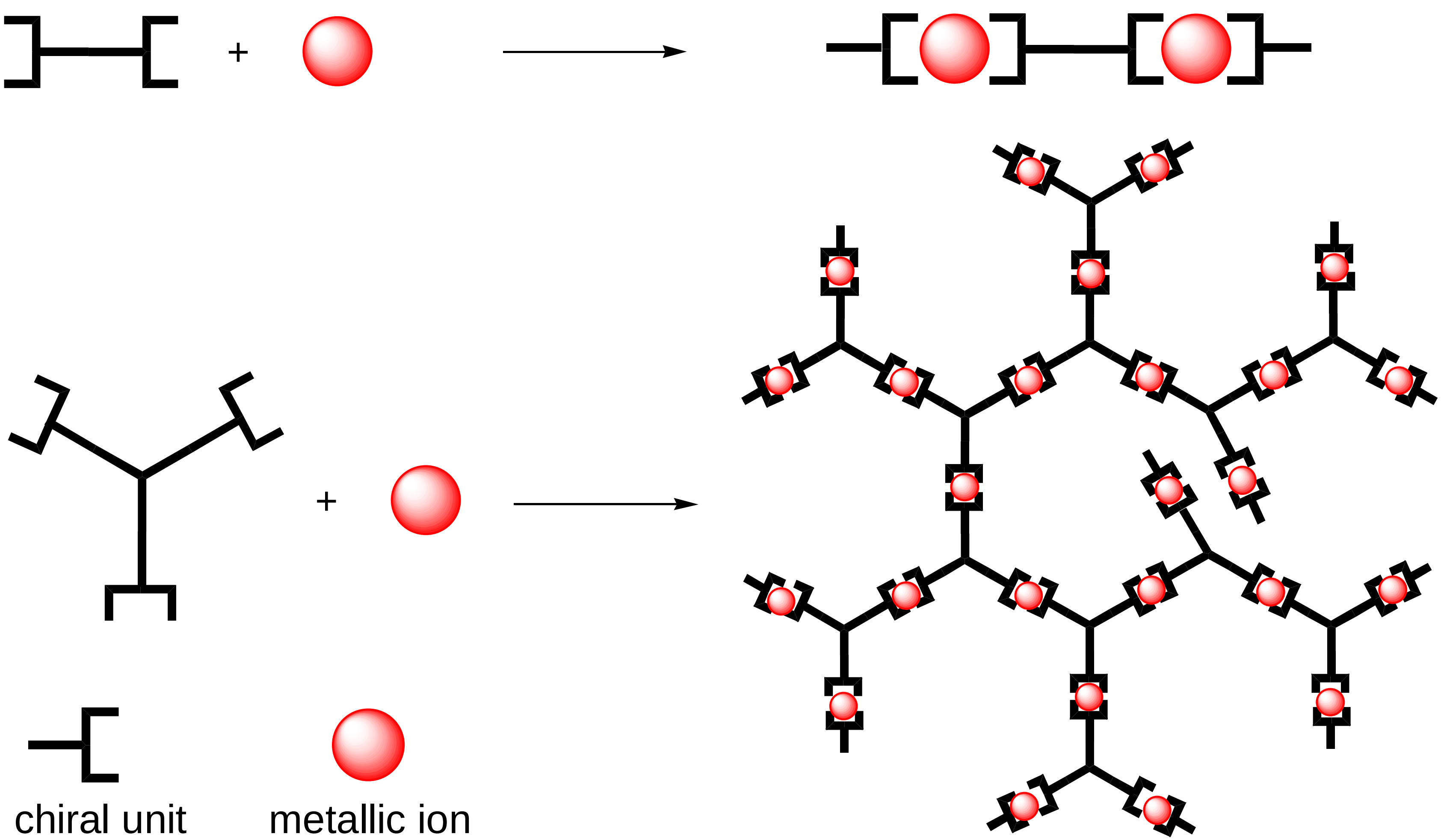


polymeric BINOL/Ti
linker = 1,4-phenylene
linker = $-CH_2CH_2CH_2CH_2-$

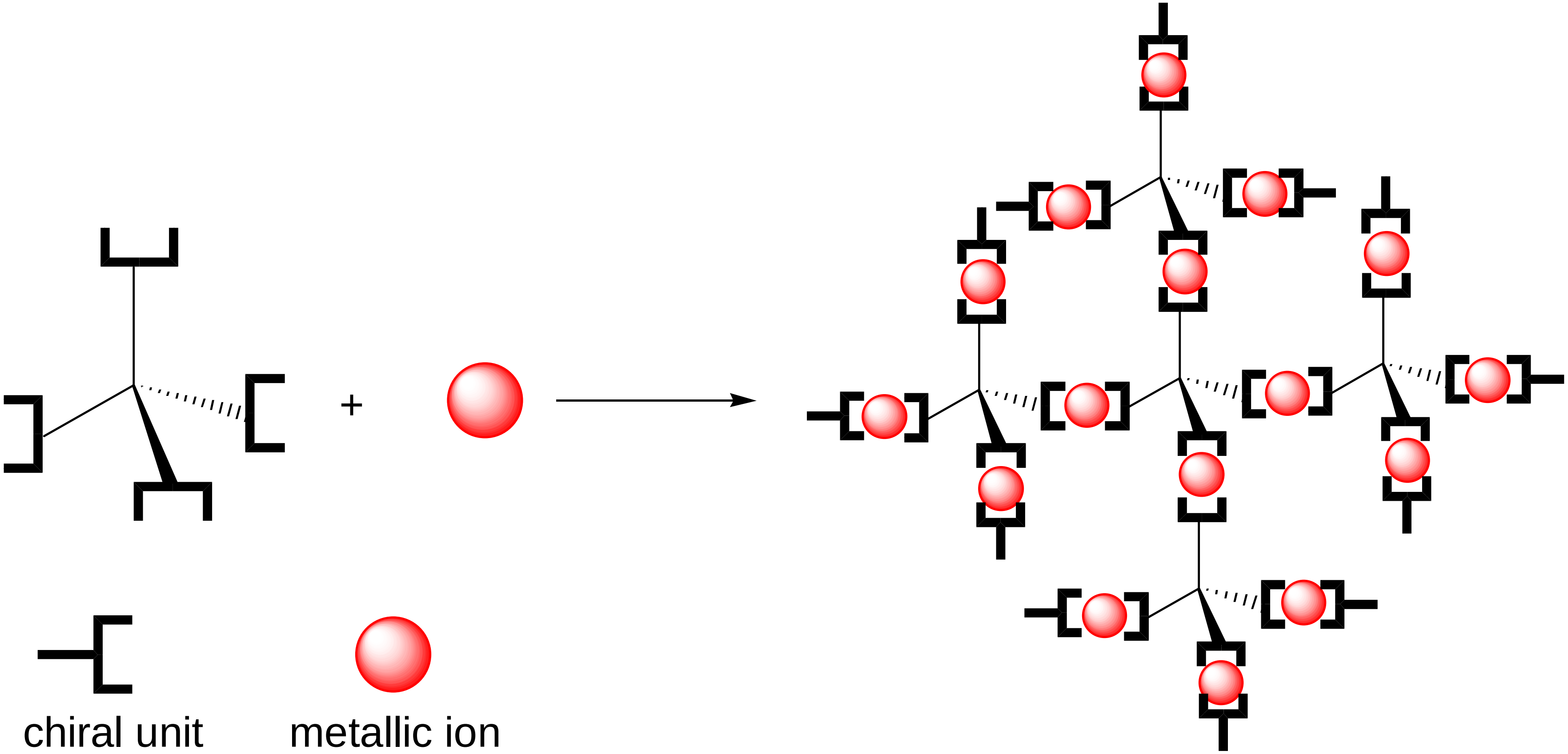


Cf.
Sagawa, S.; Inaba, T. *J. Org. Chem.* **1999**, *64*, 4962.
H. Bao, Z. Wang & K. Ding et al., *J. Am. Chem. Soc.* **2008**, in the press.

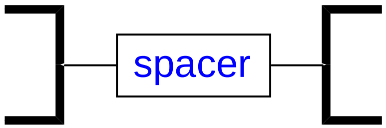
The Impact of Bridging Spacers on the Self-Supported Catalysts



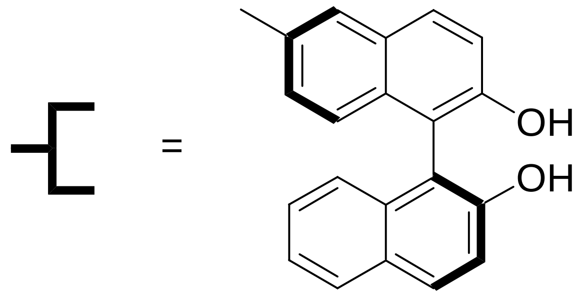
The Impact of Bridging Spacers on the Self-Supported Catalysts



Multitopic Ligands Containing BINOL Units with Various Bridging Spacers

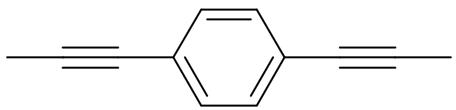


1a-g



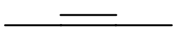
spacer

a

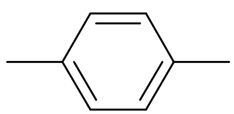


b single bond

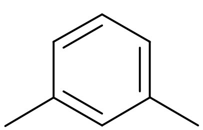
c

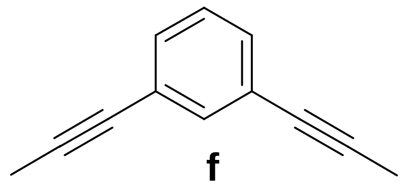


d

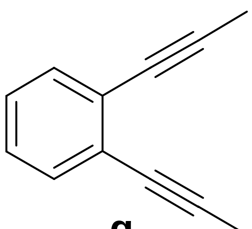


e

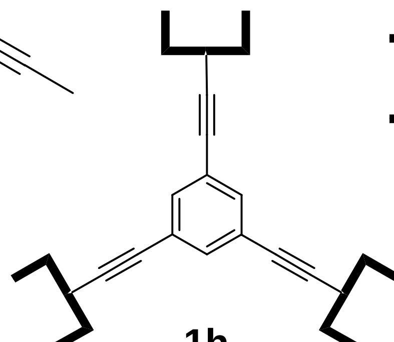




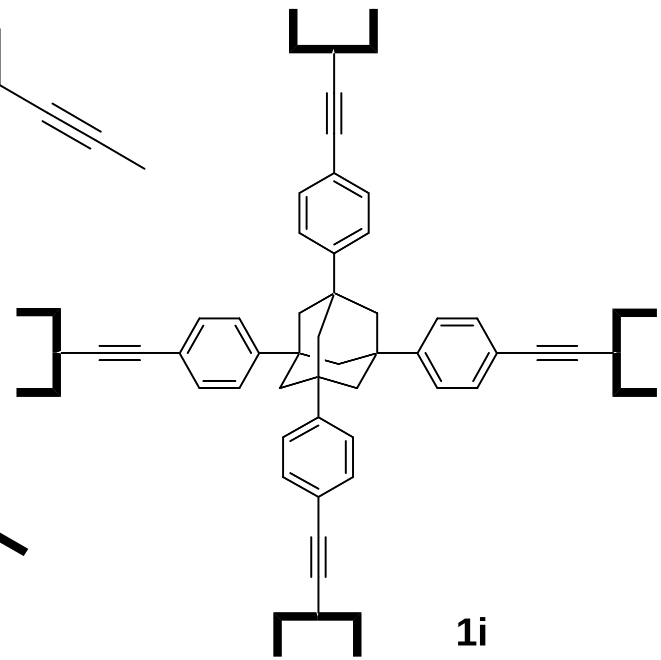
f



g

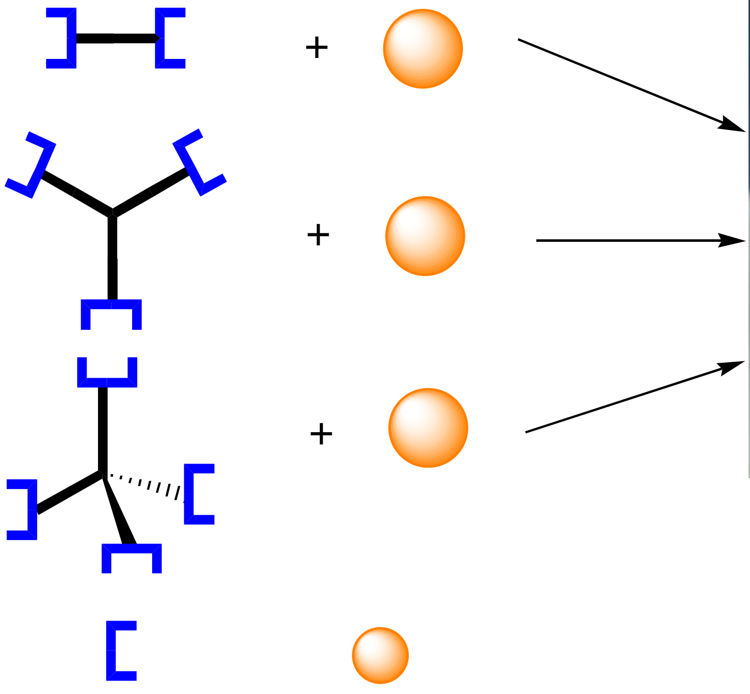


1h

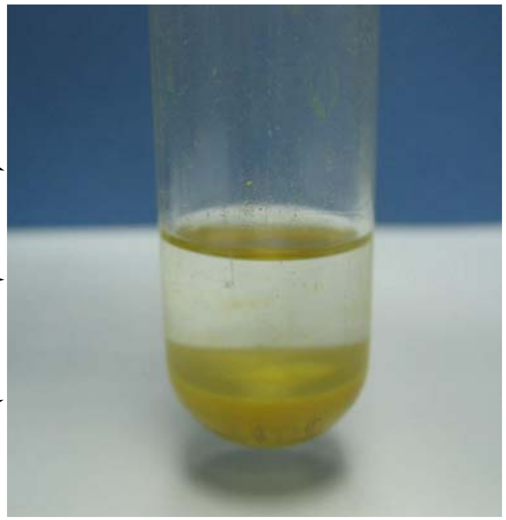


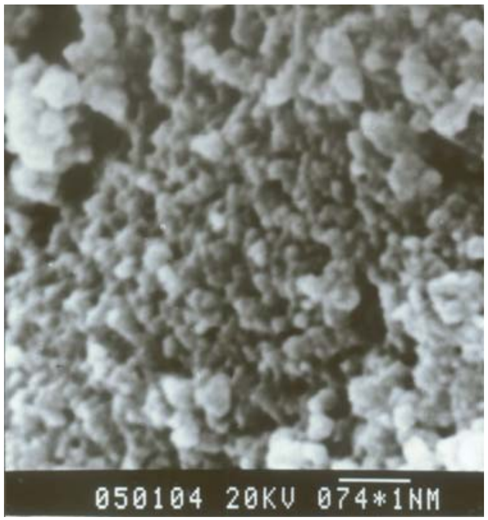
1i

Self-Supported BINOL-La Catalysts with Various Bridging Spacers



(*S*)-BINOL **La(III)**





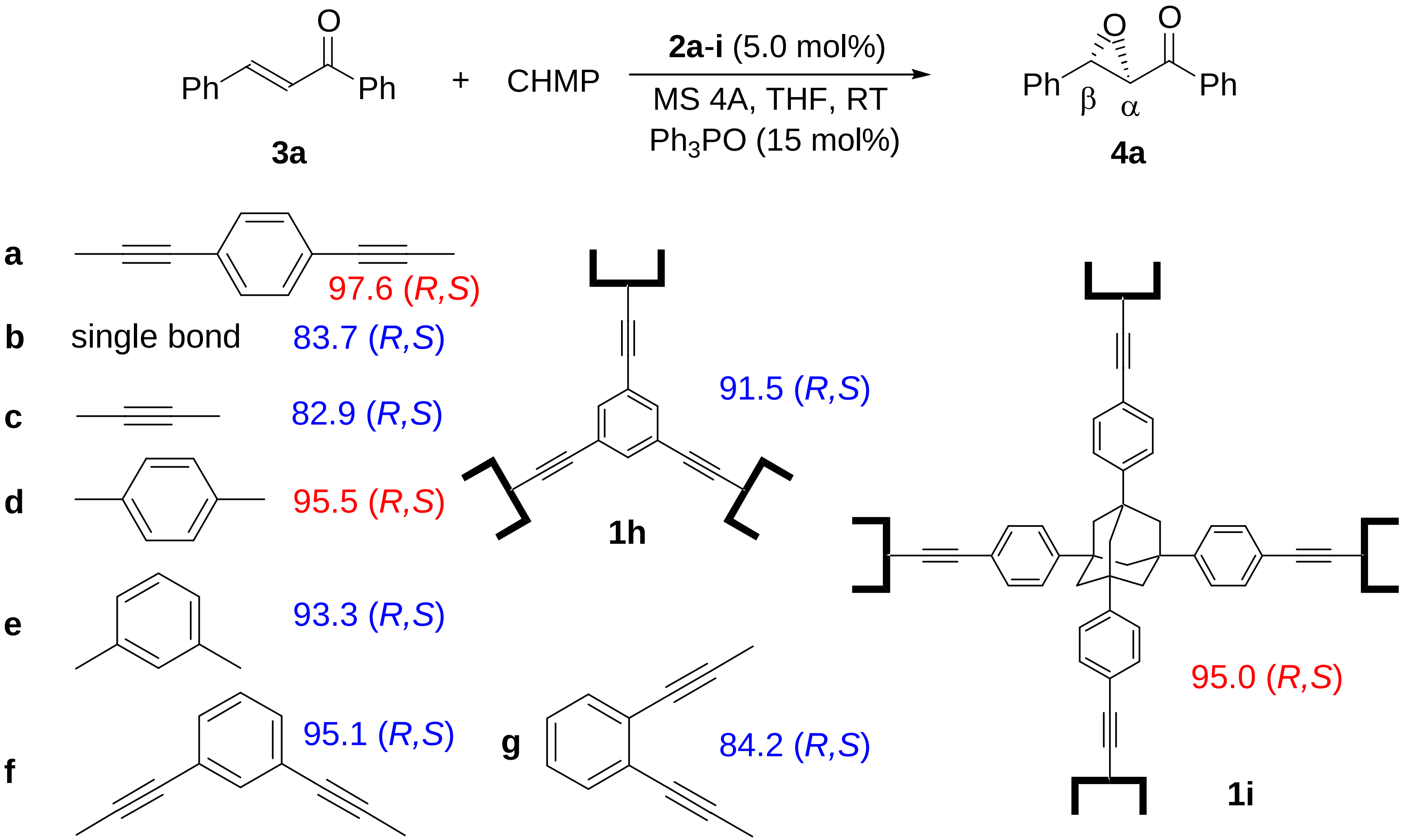
Self-supported BINOL/La catalyst

Cf.

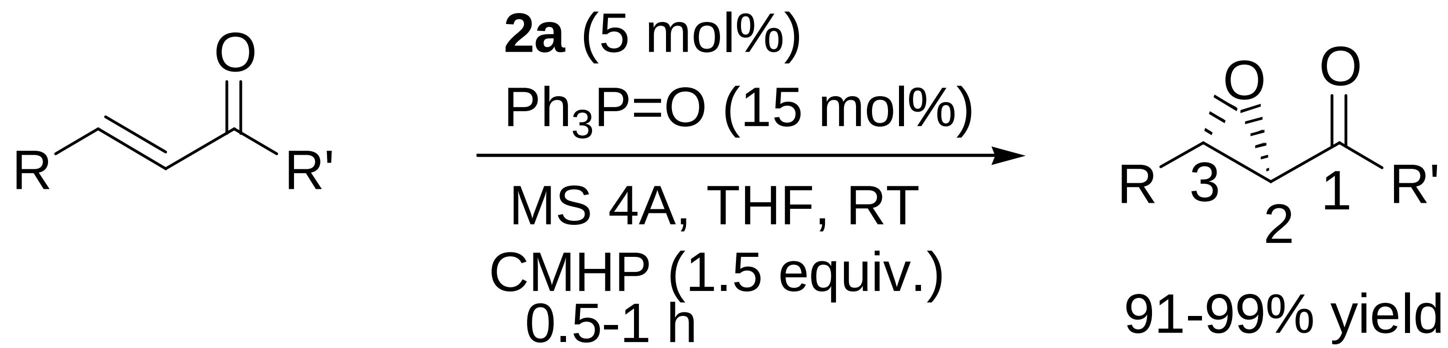
M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc*. **1997,** *119*, 2329.

K. Daikai, M. Kamaura, J. Inanaga, *Tetrahedron Lett*. **1998,** 39, 7321-7322

Self-Supported BINOL-La Catalysts for Epoxidation of Enones



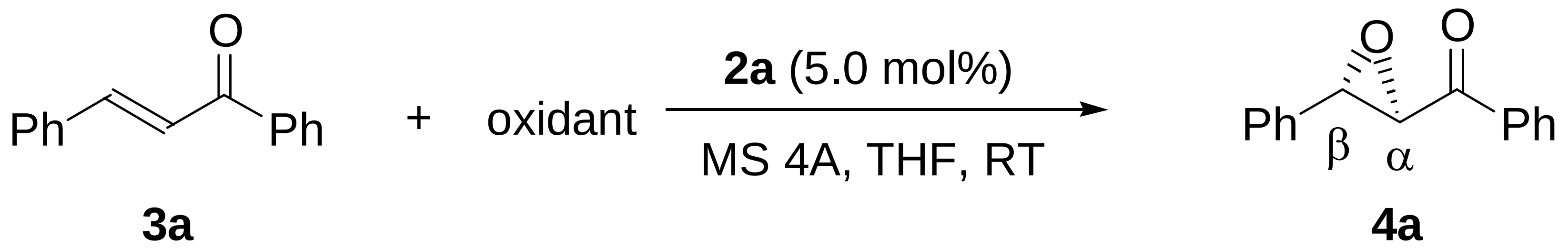
Self-Supported BINOL-La Catalysts for Epoxidation of Enones



4a: R = Ph, R' = Ph	97.6% ee (*R*,*S*)
4b: R = 4-F-Ph, R' = Ph	96.2% ee (*R*,*S*)
4c: R = 4-Cl-Ph, R' = Ph	96.0% ee (*R*,*S*)
4d: R = 4-Br-Ph, R' = Ph	95.6% ee (*R*,*S*)
4e: R = 4-NO_2-Ph, R' = Ph	95.7% ee (*R*,*S*)
4f: R = 4-NC-Ph, R' = Ph	94.3% ee (*R*,*S*)
4g: R = Ph, R' = 4-MeO-Ph	95.0% ee (*R*,*S*)
4h: R = *i*-Pr, R' = Ph	84.9% ee (*R*,*S*)

X. Wang, L. Shi, et al. *Angew. Chem. Int. Ed*. **2005**, *44*, 6362-6366.

Recovery and Reuse of Self-Supported BINOL-La Catalysts

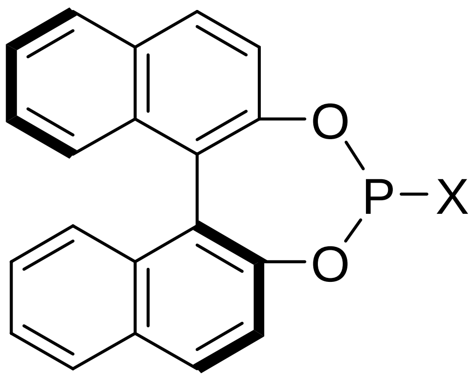


Run	Ph_3PO [mol%]	Time [h]	Yield [%][b]	*Ee*[c] [%] (Config.)[d]
1	15	0.5	>99	96.5 (*R*,*S*)
2	10	0.5	>99	96.3 (*R*,*S*)
3	10	0.5	>99	95.8 (*R*,*S*)
4	10	0.5	>99	94.9 (*R*,*S*)
5	10	0.5	95	94.5 (*R*,*S*)
6	10	1	83	93.2 (*R*,*S*)

La leaching: <0.4 ppm

X. Wang, L. Shi, et al. *Angew. Chem. Int. Ed*. **2005**, *44*, 6362-6366.

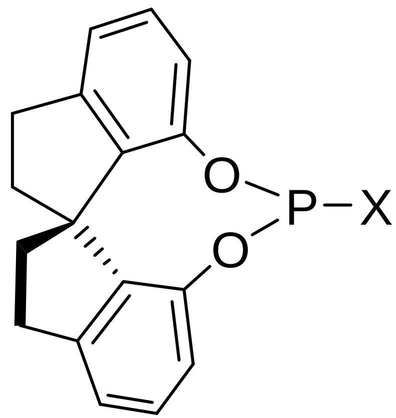
Modular Monodentate Phosphorous Ligands for Rh(I)-Catalyzed Asymmetric Hydrogenation



1a X = OR

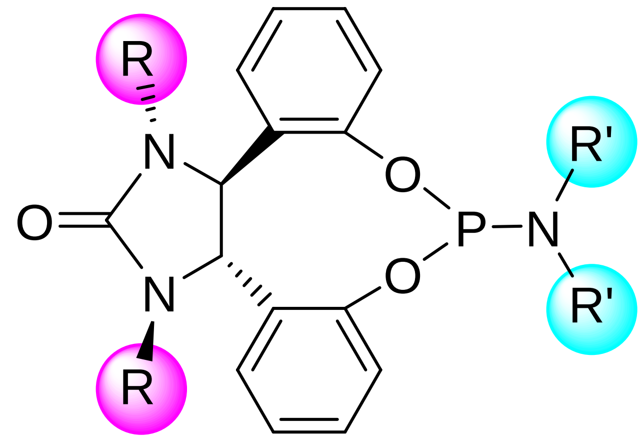
1b X = alkyl or aryl

1c X = NR_2, MonoPhos



2a X = OR

2b X = NR_2, SpiroPhos



3, DpenPhos

M. Reetz (2000)

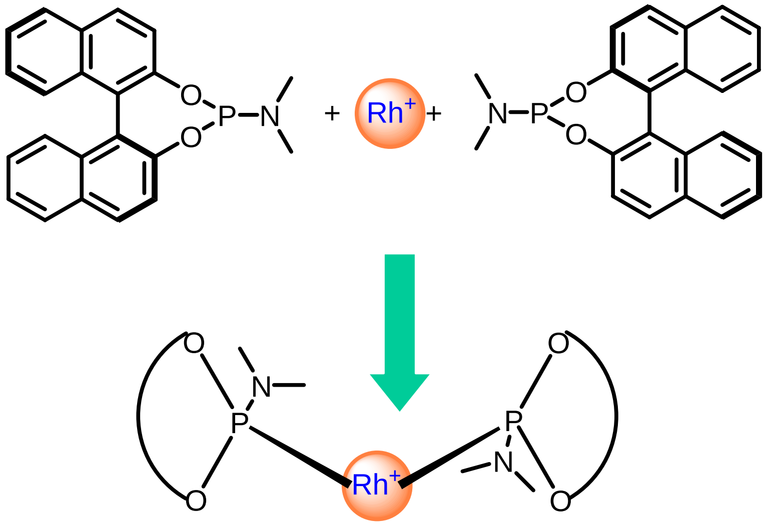
B. L. Feringa (2000)

P. Pringle (2000)

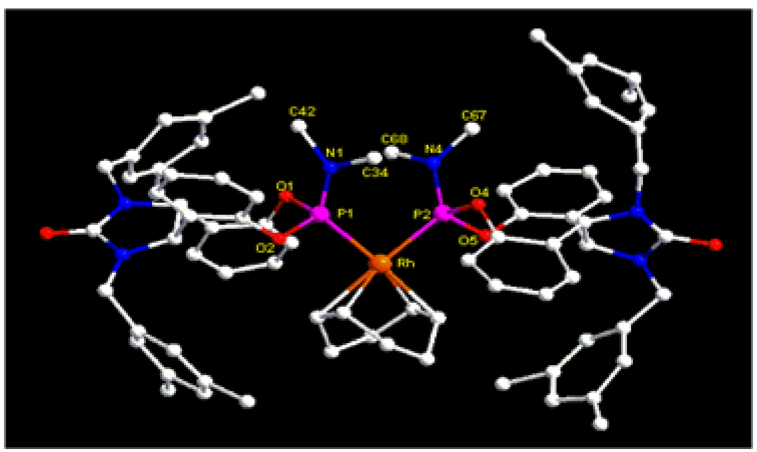
Q. Zhou (2002)

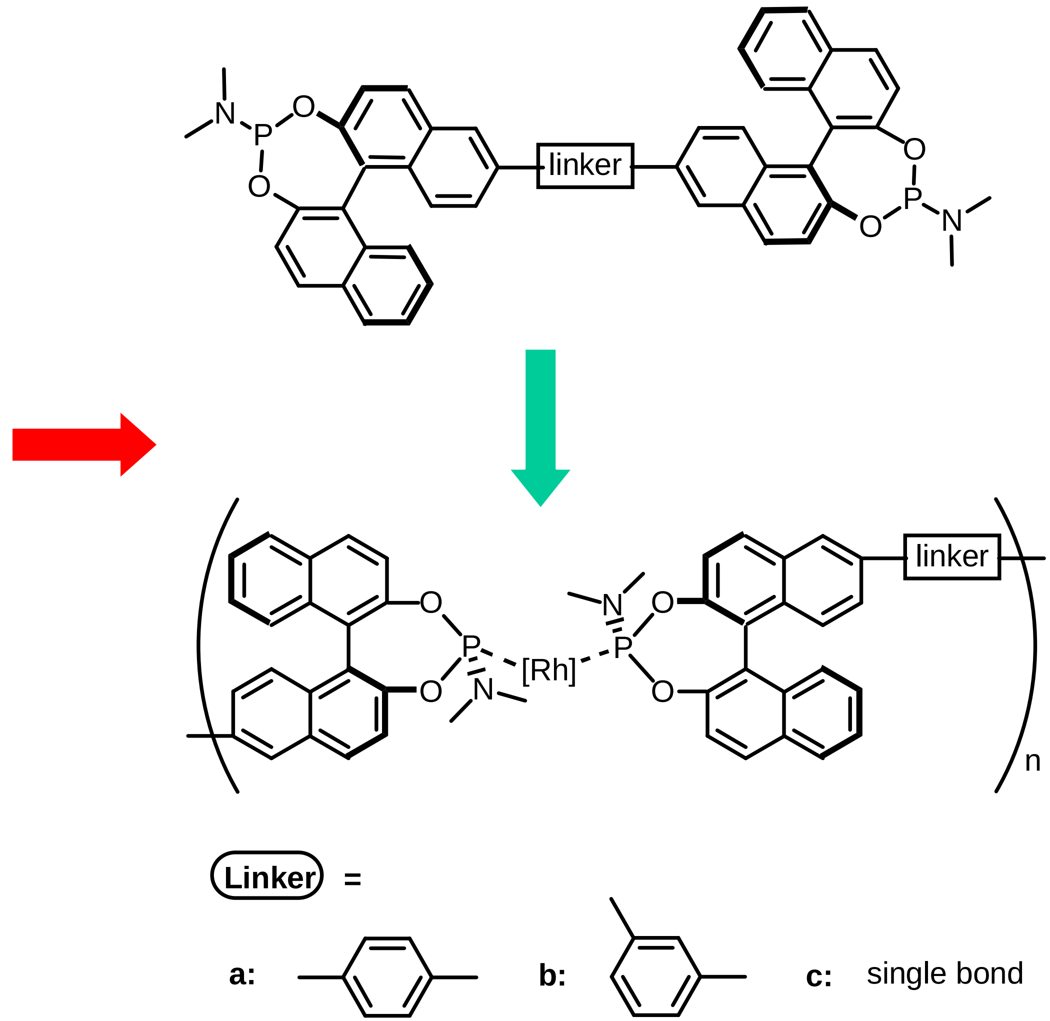
K. Ding (2005)

MonoPhos/Rh Catalyst:
from Homogeneous to Heterogeneous



Excellent catalyst for asymmetric hydrogenation

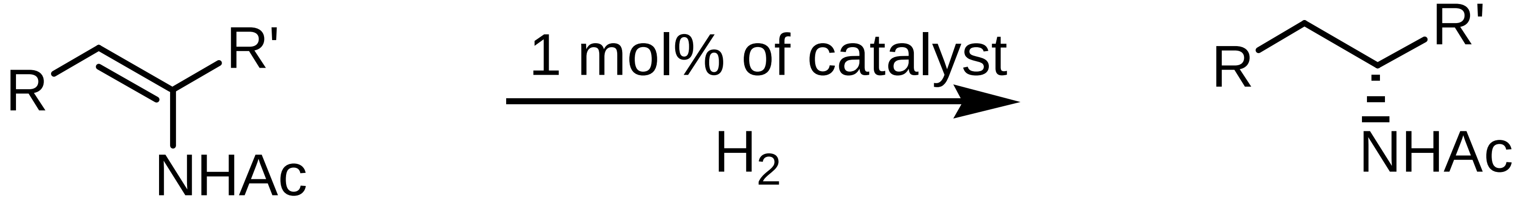




B. L. Feringa, et al, *J. Am. Chem. Soc.* 2000, *122*, 11539

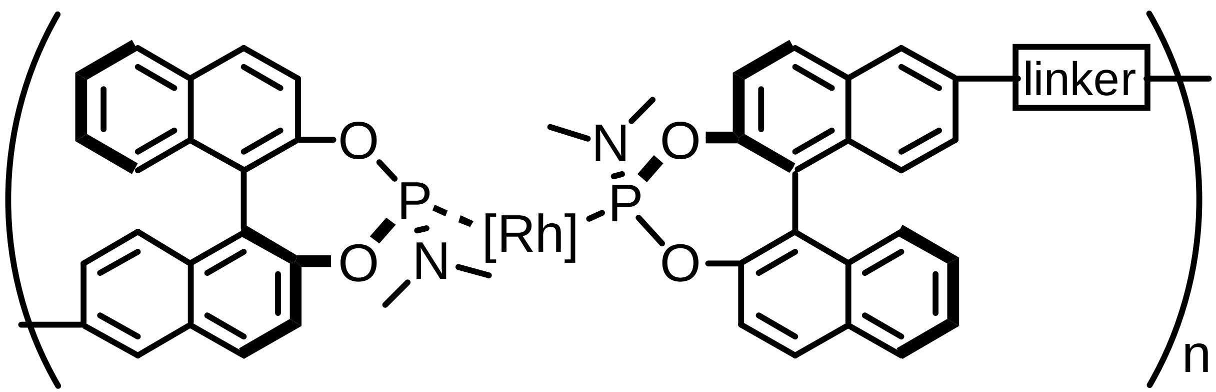
Y. Liu & K. Ding, *J. Am. Chem. Soc.* 2005, *127*, 10488-10499

Self-Supported Catalysts for Heterogeneous Enantioselective Hydrogenation

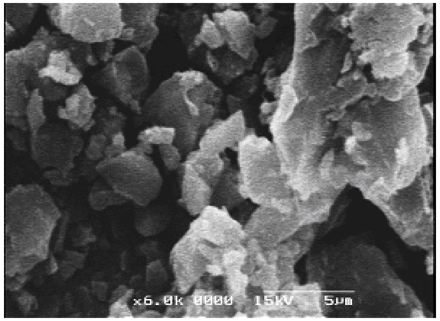


R = H, Ph, Me; R' = COOMe, H

94-97% ee

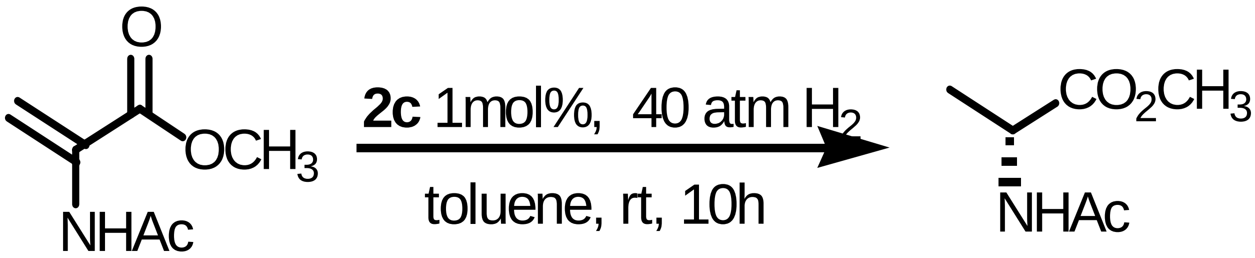


self-supported catalyst



X. Wang *et al*. *J. Am. Chem. Soc.* **2004**, *126*, 10524.

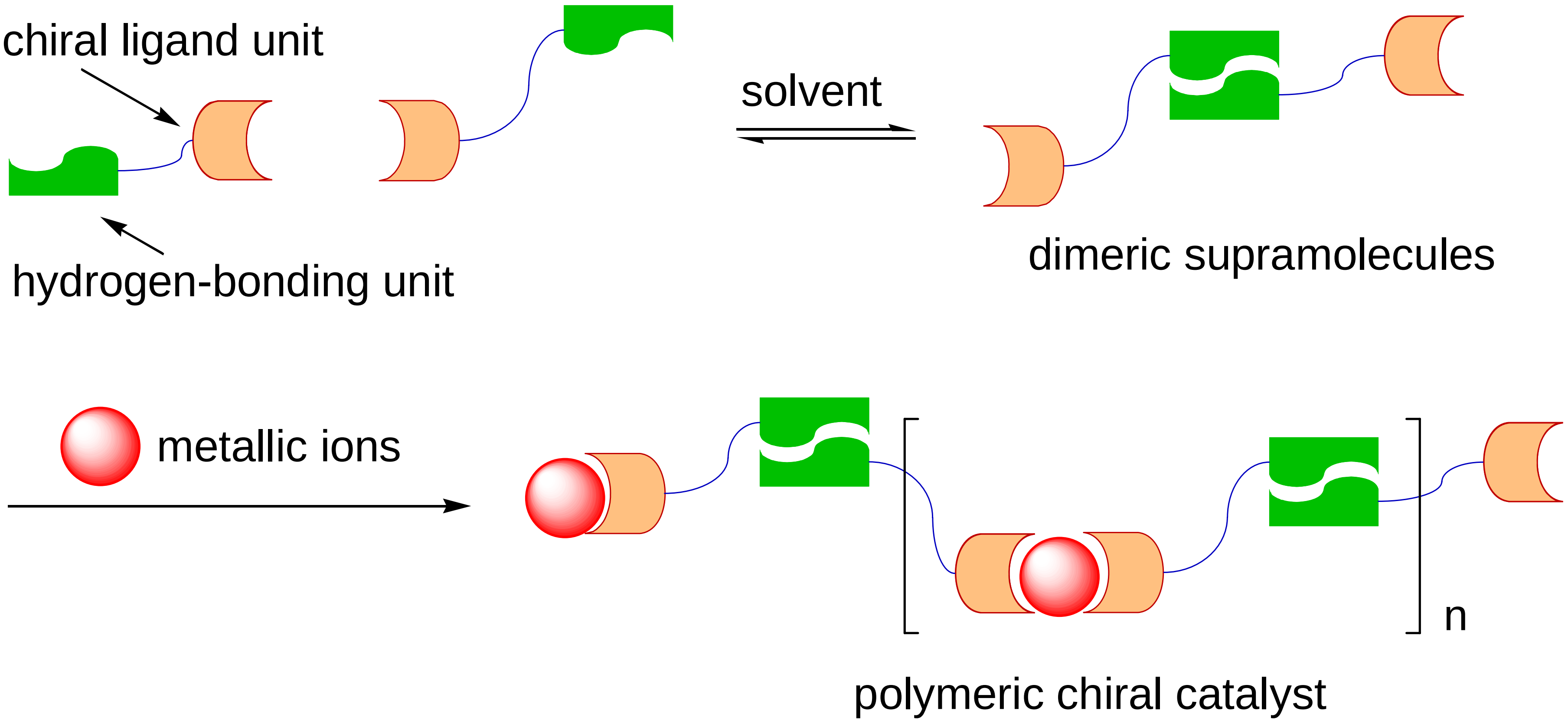
Catalyst Recycling



3a **4a**

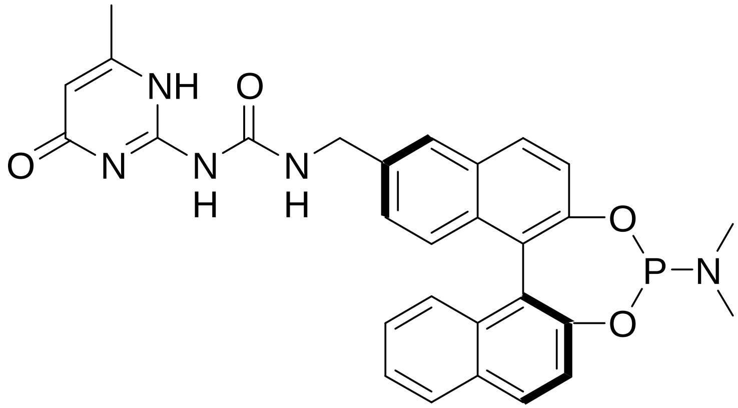
Run	1	2	3	4	5	6	7	8	9	10
Conv.(%)[b]	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
E.e. (%)[c]	95.0	93.5	90.2	90.9	90.5	90.0	89.5	87.7	87.3	87.3

Use of Hydrogen Bonds as the Bridging Linker: From Dimeric Supramolecules to Polymeric Chiral Catalyst

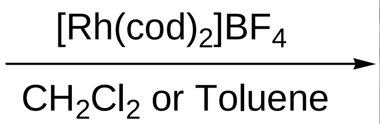


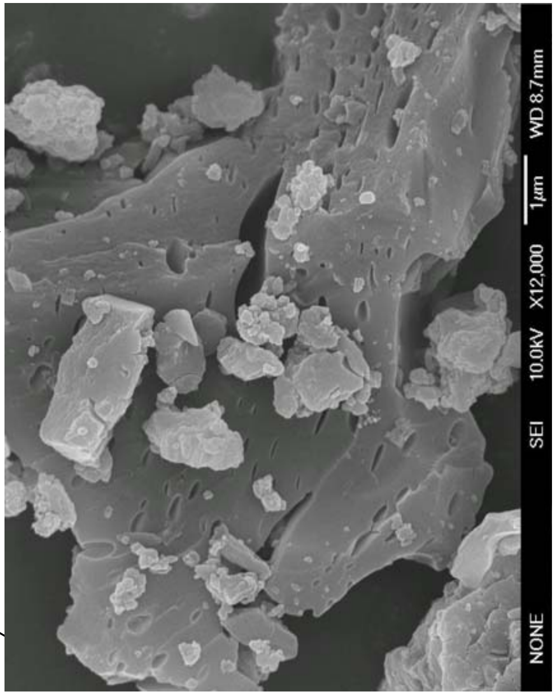
L. Shi & K. Ding, *Angew. Chem. Int. Ed*. 2006, ***45***, 4108-4112

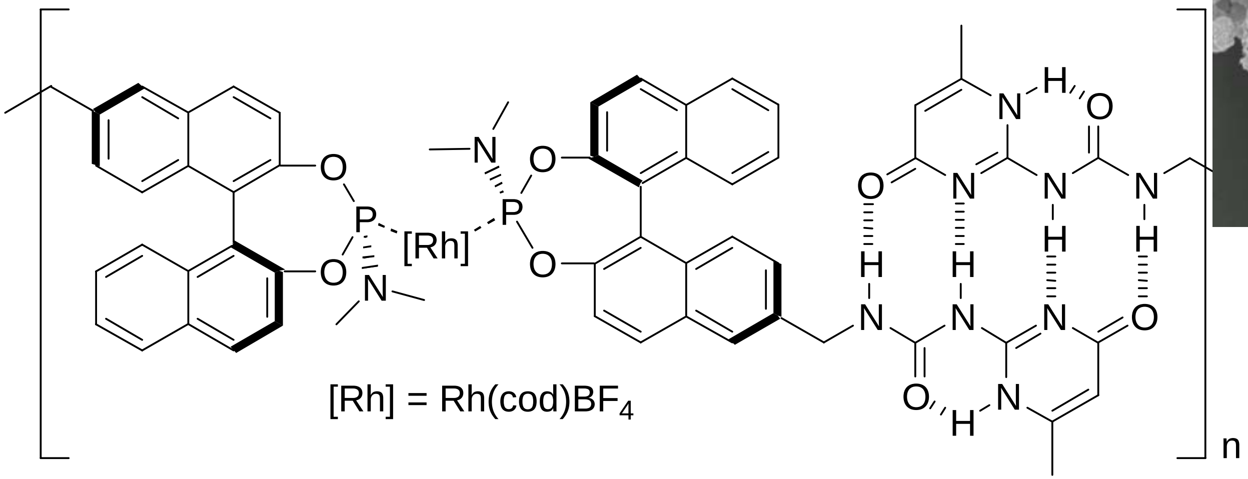
Self-Supported MonoPhos/Rh(I) Catalyst



SupraMonoPhos (1a)



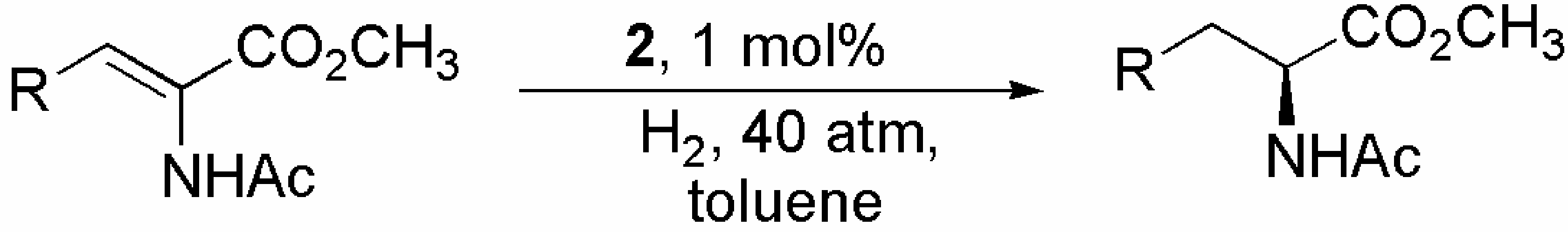




2

L. Shi & K. Ding, *Angew. Chem. Int. Ed*. 2006, ***45***, 4108-4112

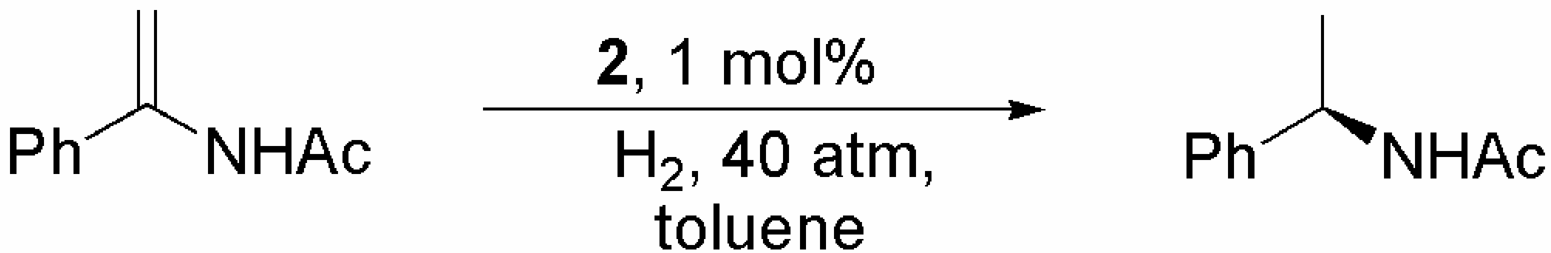
Self-Supported MonoPhos/Rh(I) Catalyst for Enantioselective Hydrogenation



3a-d **4a-d**

R = H (**a**), CH_3 (**b**), Et (**c**), *i*Pr (**d**)

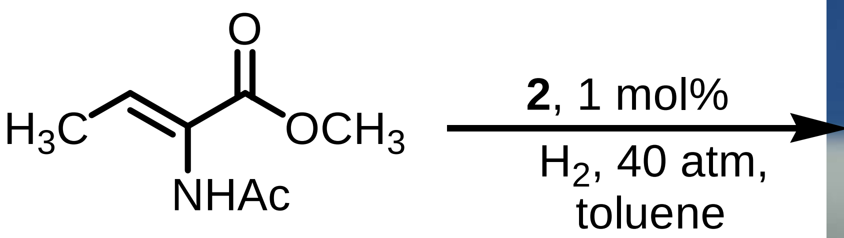
>99% conv.
93-96% ee

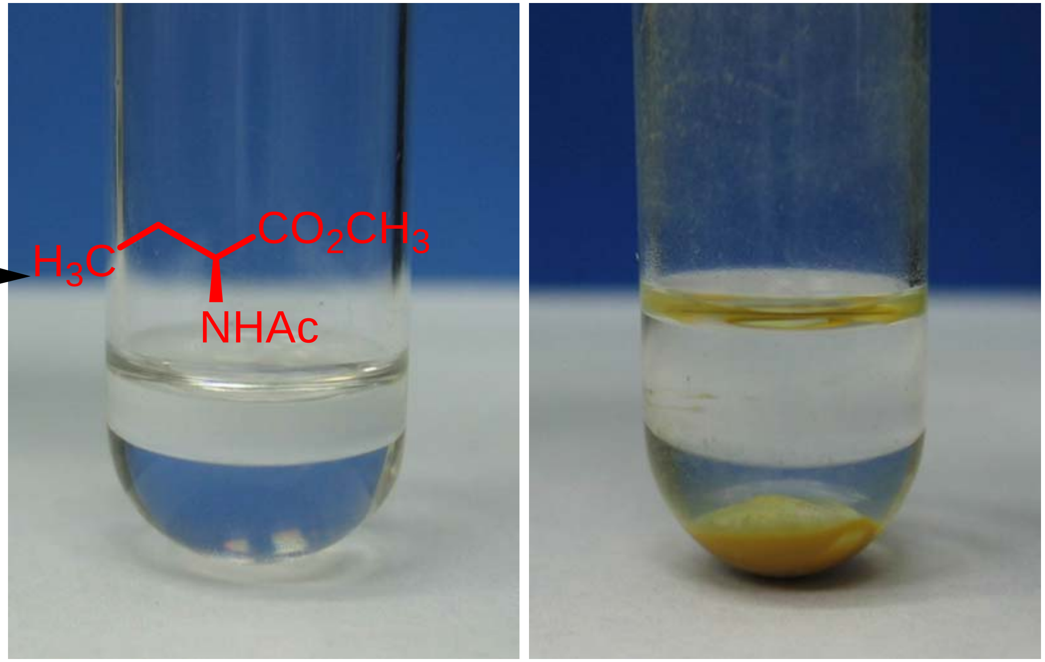


3e **4e**

>99% conv.
91% ee

High Enantioselectivity and Facile Recovery





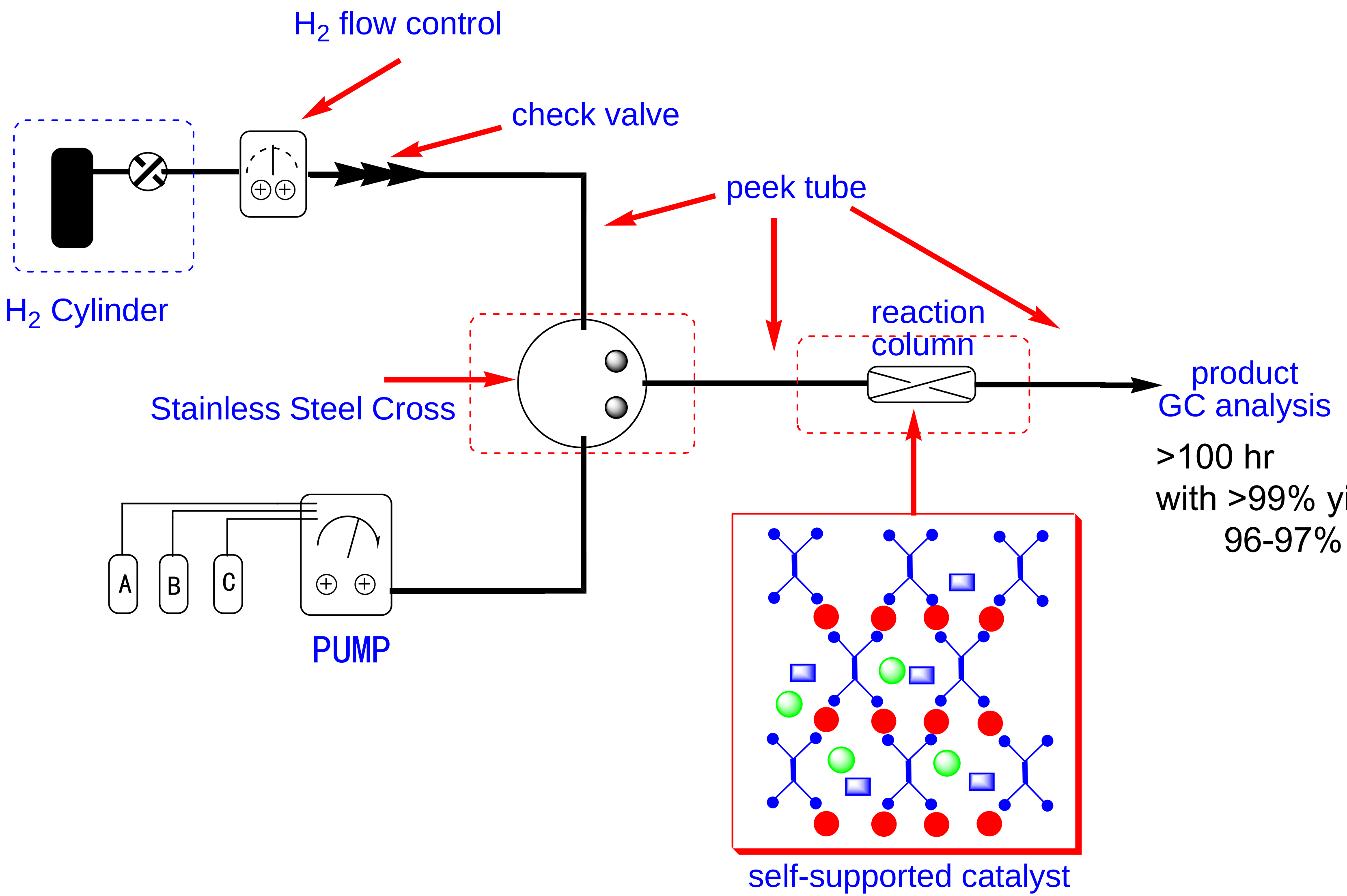
Rh leaching < 1 ppm

Table 2. Recycling and reuse of the self-supported catalysts 2b in enantioselective hydrogenation of 3b.[a]

Run	1	2	3	4	5	6	7	8	9	10	11
conv. [%][b]	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	96
Ee [%][c]	95.7	95.7	95.2	94.7	94.3	94.5	94.6	94.5	92.9	92.0	91.5

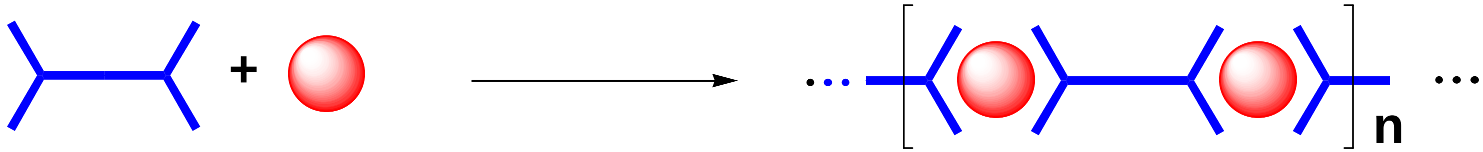
L. Shi & K. Ding, *Angew. Chem. Int. Ed*. 2006, ***45***, 4108-4112

Schematic Representation of Continuous Flow Reaction System for Chiral Catalysis

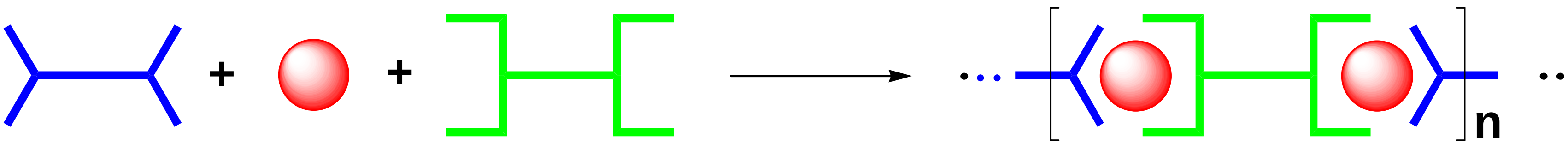


>100 hr
with >99% yield
96-97% ee

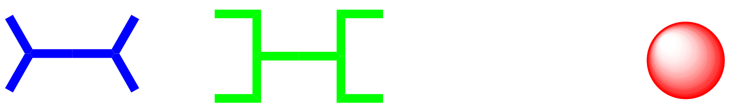
Schematic Representation of the Strategy



homo-ligand polymer

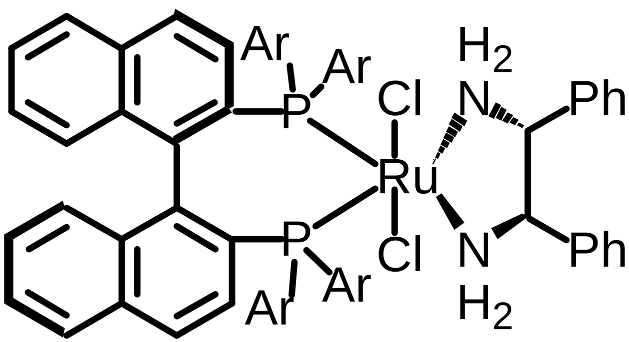


hetero-ligand polymer



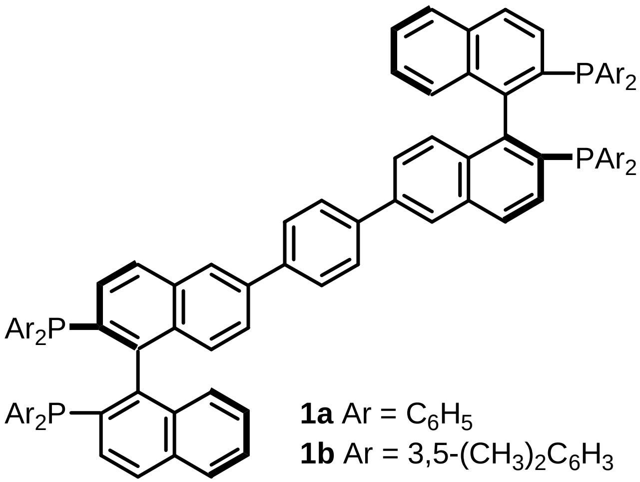
Multitopic Ligands **Metallic Ion**

Programmed Assembly

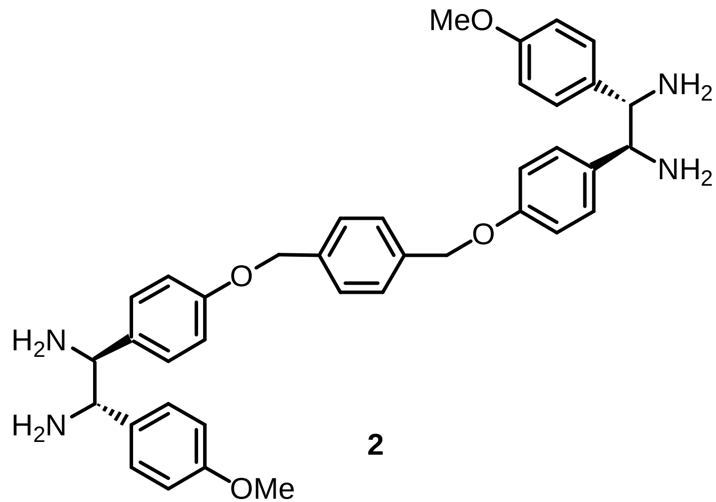


Cf. R. Noyori, et al.
J. Am. Chem. Soc. 1995, *117*, 2675.

Self-Supported Noyori-Type Catalyst

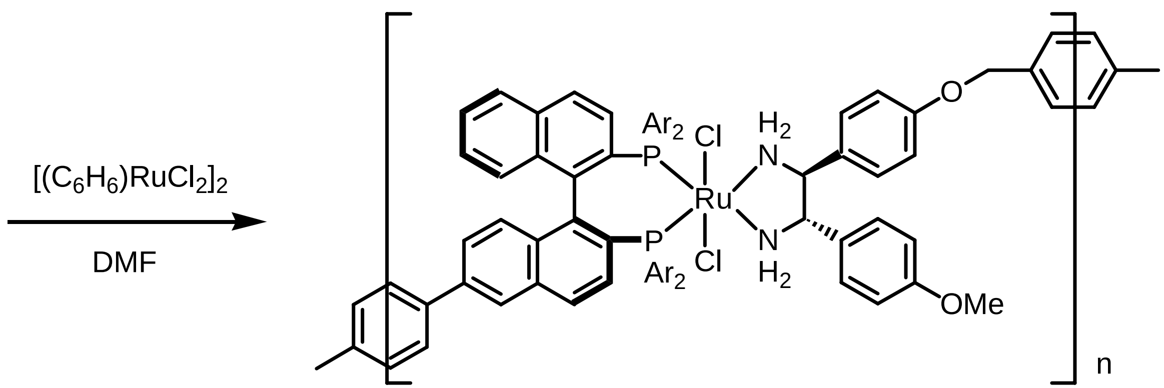


1a Ar = C_6H_5
1b Ar = 3,5-$(CH_3)_2C_6H_3$

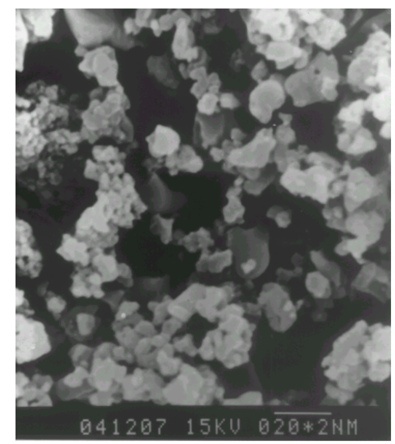


2

1 + **2**

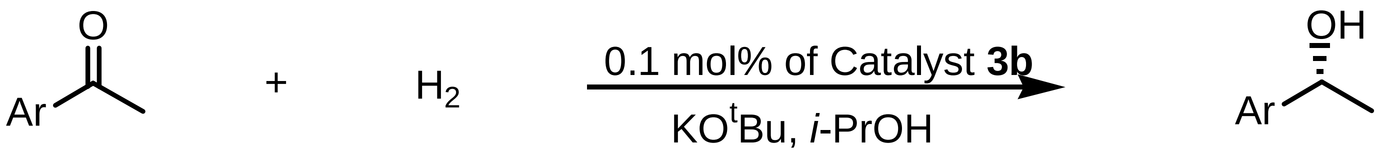


3a Ar = C_6H_5
3b Ar **=** 3,5-$(CH_3)_2C_6H_3$

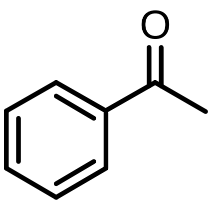


Liang, Y. et al. *J. Am. Chem. Soc*. **2005**, *127*, 7694-7695.

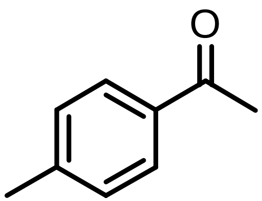
Self-Supported Noyori-Type Catalyst for Asymmetric Hydrogenation of Ketones



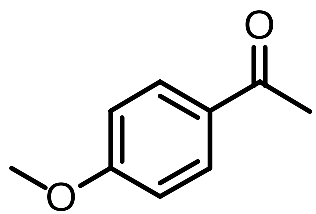
4a-h **5a-h**



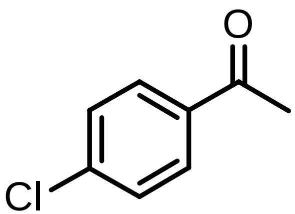
97.4% ee



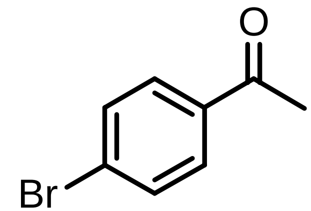
97.5% ee



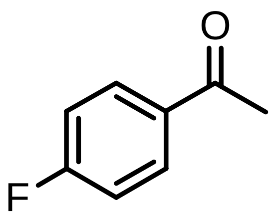
96.2% ee



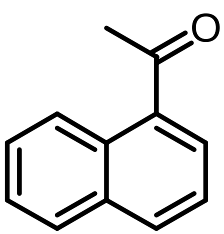
96.9% ee



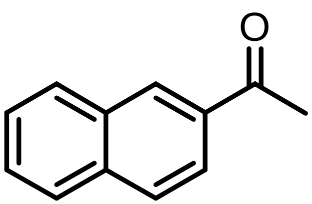
97.2% ee



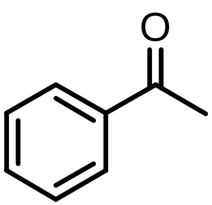
96.2% ee



98.1% ee

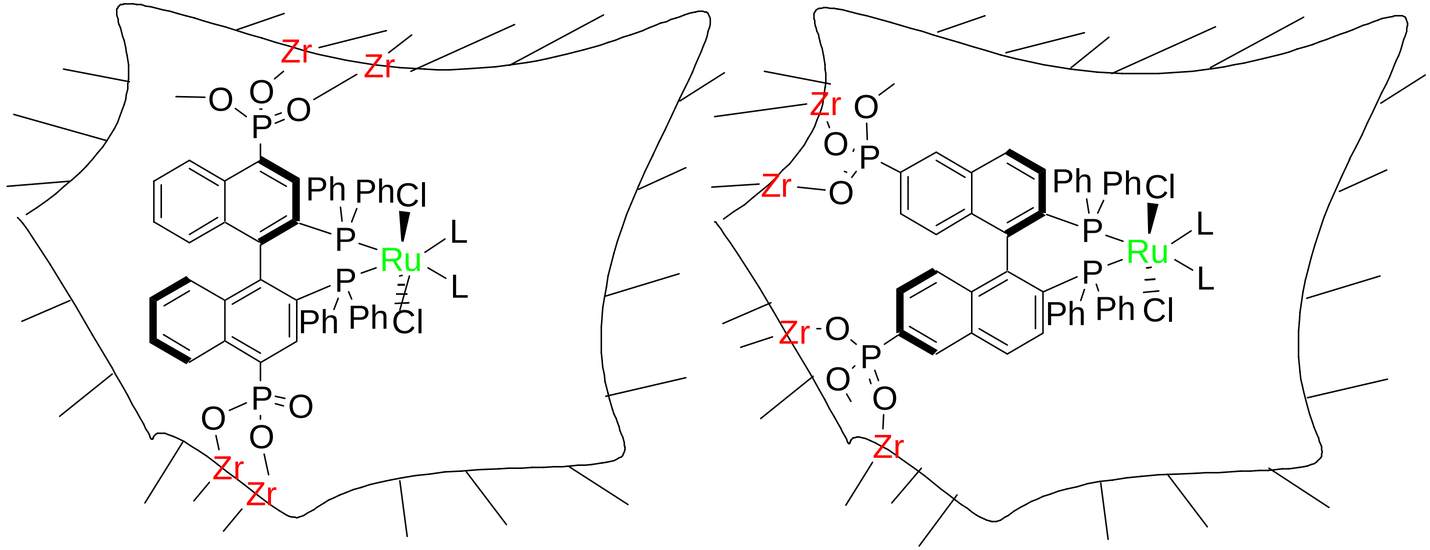


94.5% ee



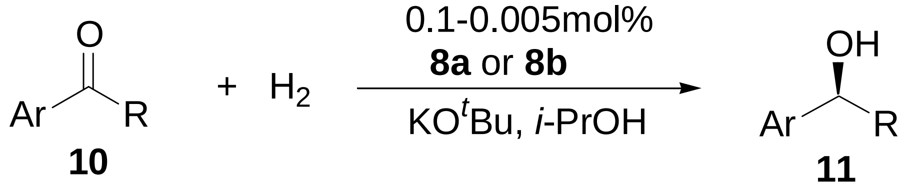
94.2% ee (0.01 mol % of cat)

Run	1	2	3	4	5	6	7
Y (%)	>99	>99	>99	>99	>99	>99	97
Ee (%)	97.4	97.6	97.3	96.5	95.6	96.1	95.4

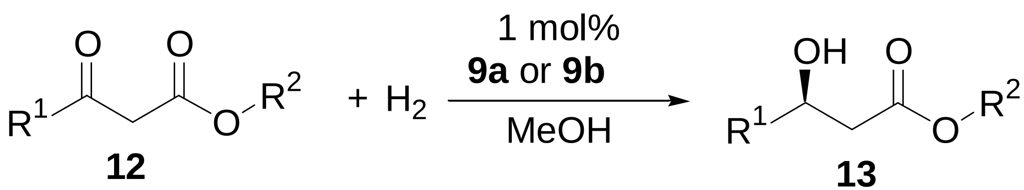


8a L-L = (*R*,*R*)-DPEN
9a L = DMF

8b L-L = (*R*,*R*)-DPEN
9b L = DMF



up to >99% yield; 99% ee, 8 recycles

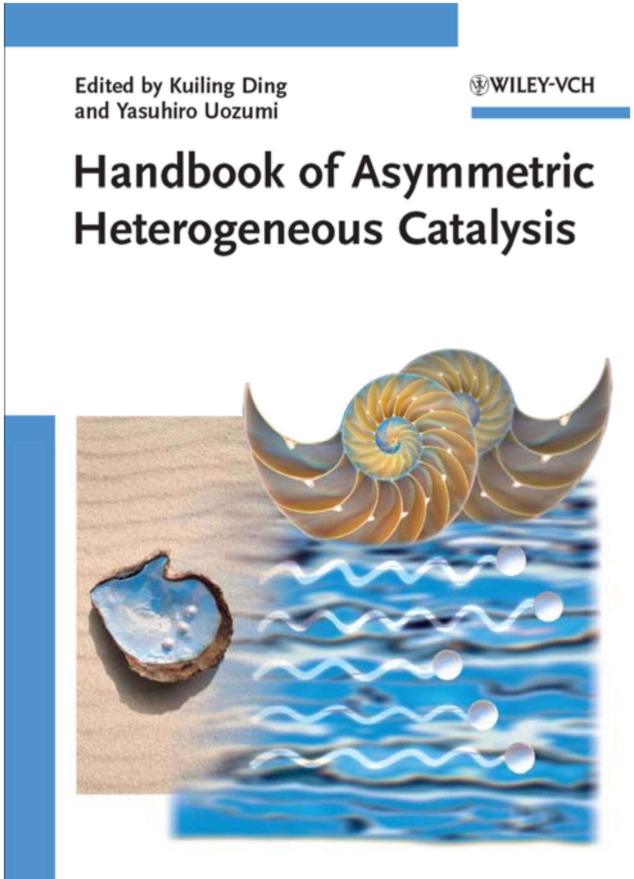


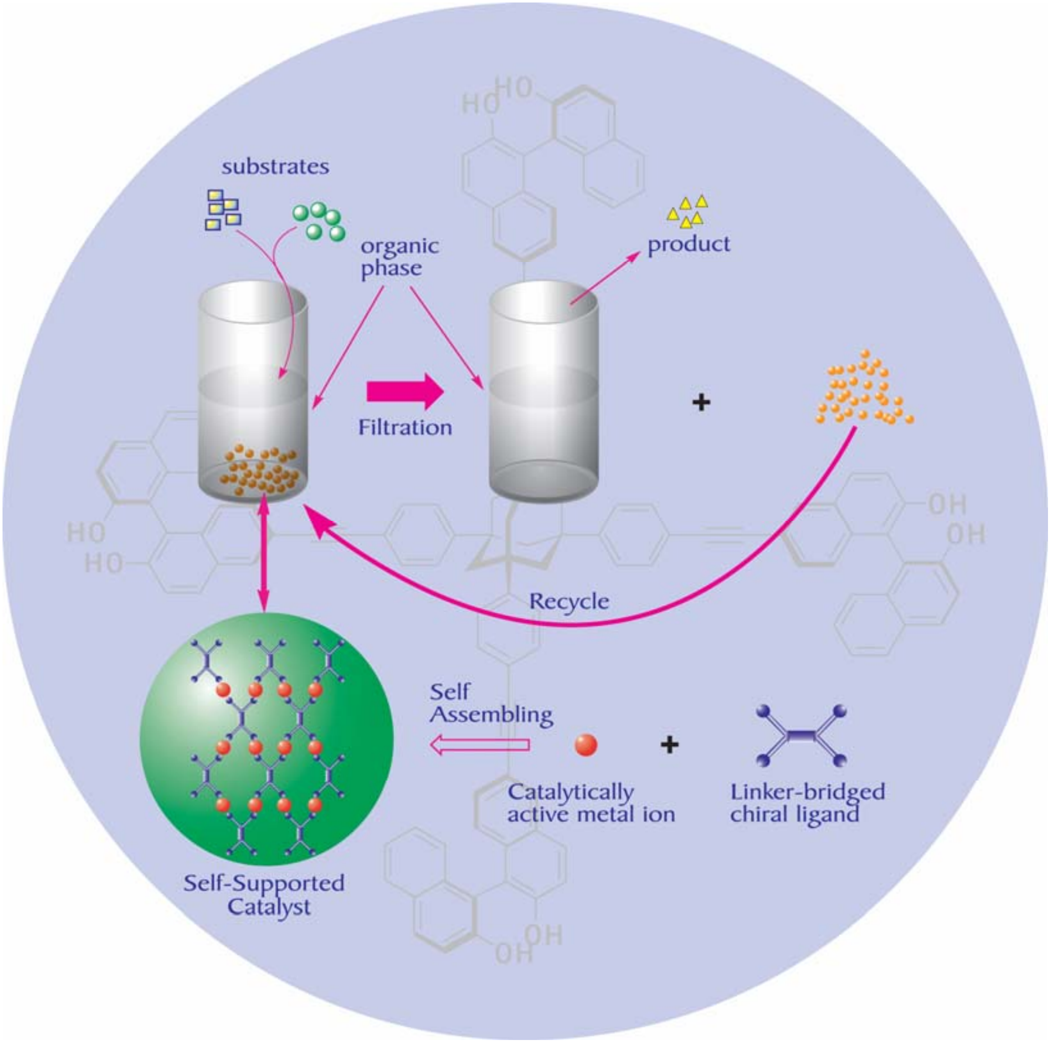
up to >99% yield, 95% ee, 5 recycles

Lin, W. et al. *J. Am. Chem. Soc.* 2003, *125*, 11490;
Lin, W. et al. *Anew. Chem. Int. Ed.* 2003, *42*, 6000.

Summary and Outlook

- Carbonyl-ene reaction
- Epoxidation
- Sulfoxidation
- Ring Opening of Epoxide
- Hydrogenation





A Concept Article, see:
K. Ding, et al. *Chem. Eur. J.* **2006**, *12*, 5188-5197.

Acknowledgements

- **Coworkers**
- **Dr. Wang Zheng** **Dr. Christian A. Sandoval**
- Dr. Long Jiang Dr. Yuan Yu Dr. Yuxue Liang
- Dr. Xisheng Wang Dr. Xingwang Wang Dr. Qing Jing
- Dr. Yan Liu Mr. Lei Shi Dr. Baoguo Zhao

- **Foundations**
- National Natural Science Foundation of China
- Major Basic Research Development Program of China (973 Project)
- Chinese Academy of Sciences
- Science & Technology Commission of Shanghai Municipality