Asymmetric catalysis with chiral metal complexes: general strategies and ligand design

Marie Curie Catalysis Workshop

September 25, 2019

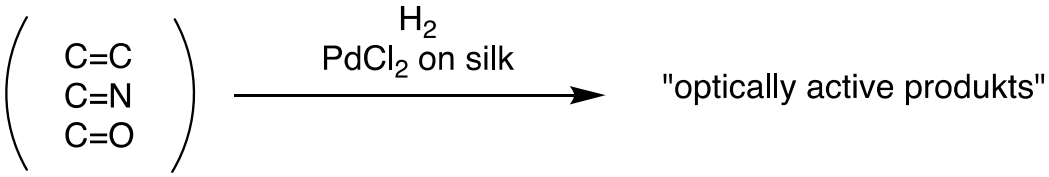
Andreas Pfaltz

Department of Chemistry, University of Basel

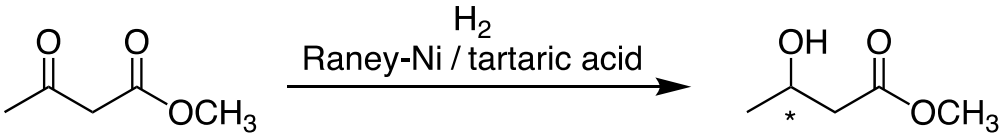
Asymmetric catalysis: early results

AKABORI et al. (1956)

Catalytic hydrogenation

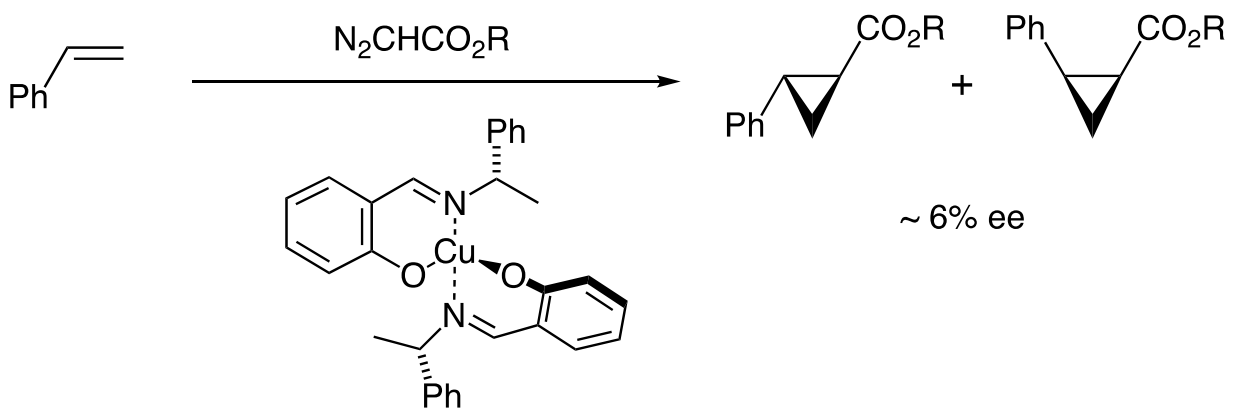


ITSUMI et al. (1963)



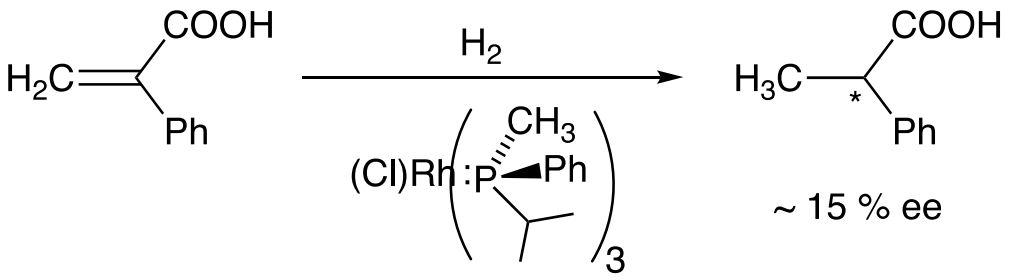
80 - 90 %ee

NOZAKI, TAKAYA, MORIUTI, NOYORI (1966)



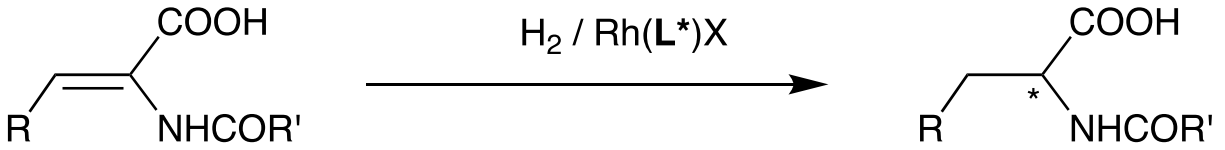
~ 6% ee

Enantioselective hydrogenation: early developments

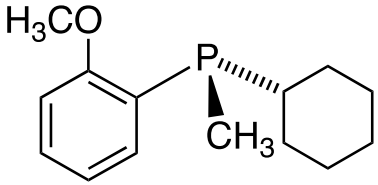


~ 15 % ee

HORNER et al. (1968)
KNOWLES & SABACKY (1968)



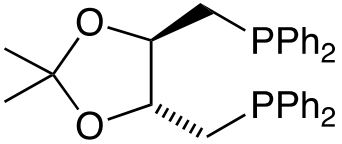
L* =



CAMP

88 % ee

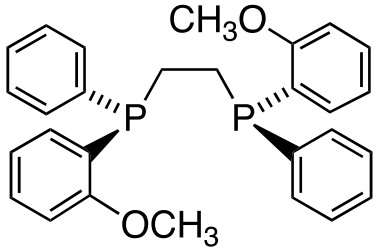
KNOWLES et al. (1970)



DIOP

~ 70 % ee

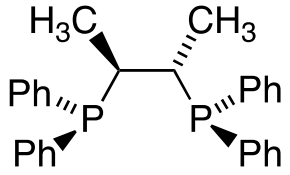
KAGAN & DANG (1971)



DIPAMP

96 % ee

KNOWLES et al. (1974)



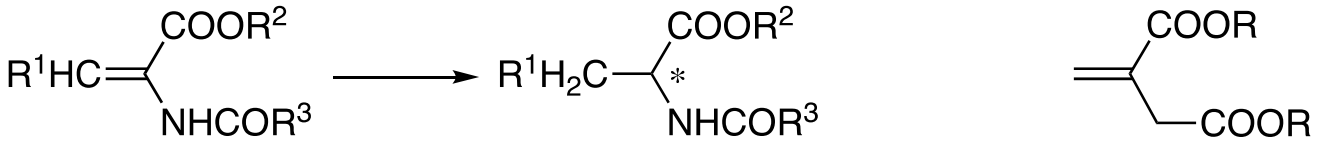
CHIRAPHOS

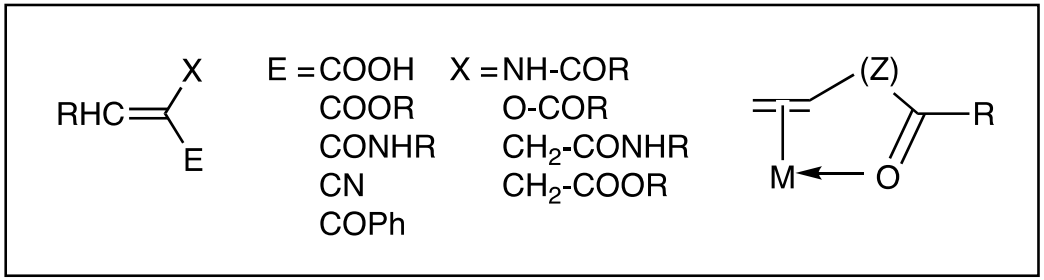
~100 % ee

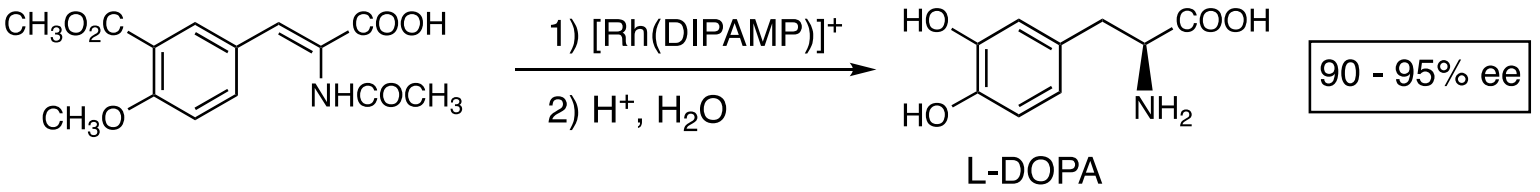
BOSNICH and FRYZUK (1977)

Rh-diphosphine catalysts: substrates

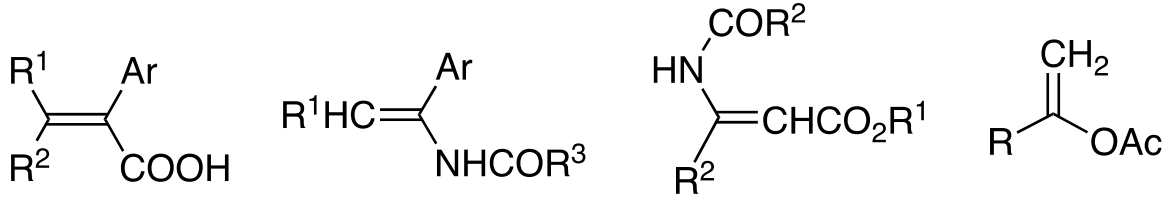
"Classical" substrates: dehydro-α-amino acid derivatives, itaconic acid or ester





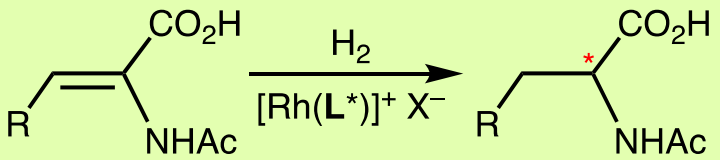


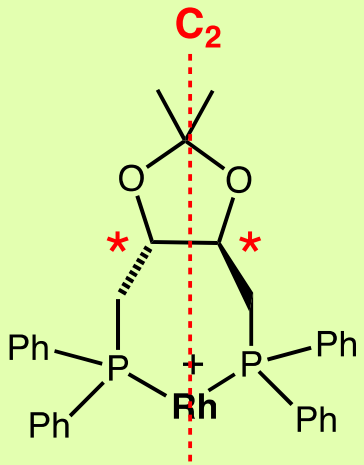
High enantioselectivity also with:



Chiral ligands: design concepts

Asymmetric hydrogenation



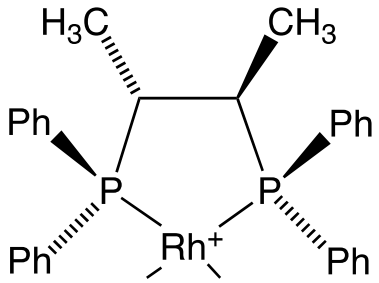


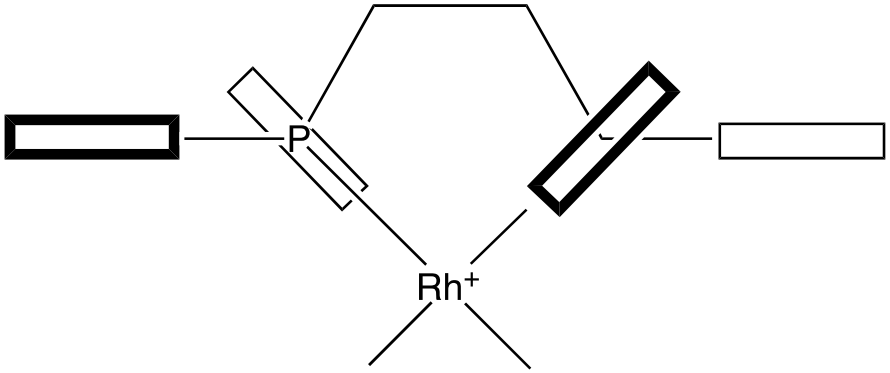
DIOP

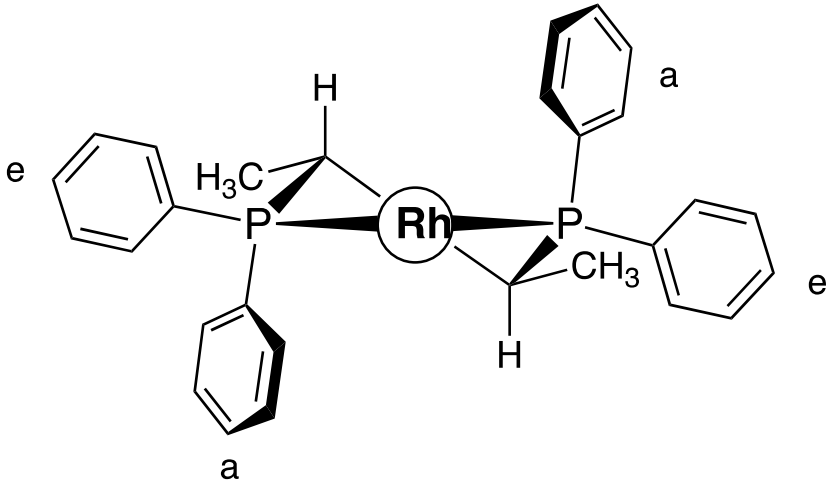
Henri Kagan

- Bidentate chelate ligand
- Stereogenic centers in the backbone (not at the P atom)
- C_2 symmetry
- Easy synthesis

Structure of Rh-CHIRAPHOS

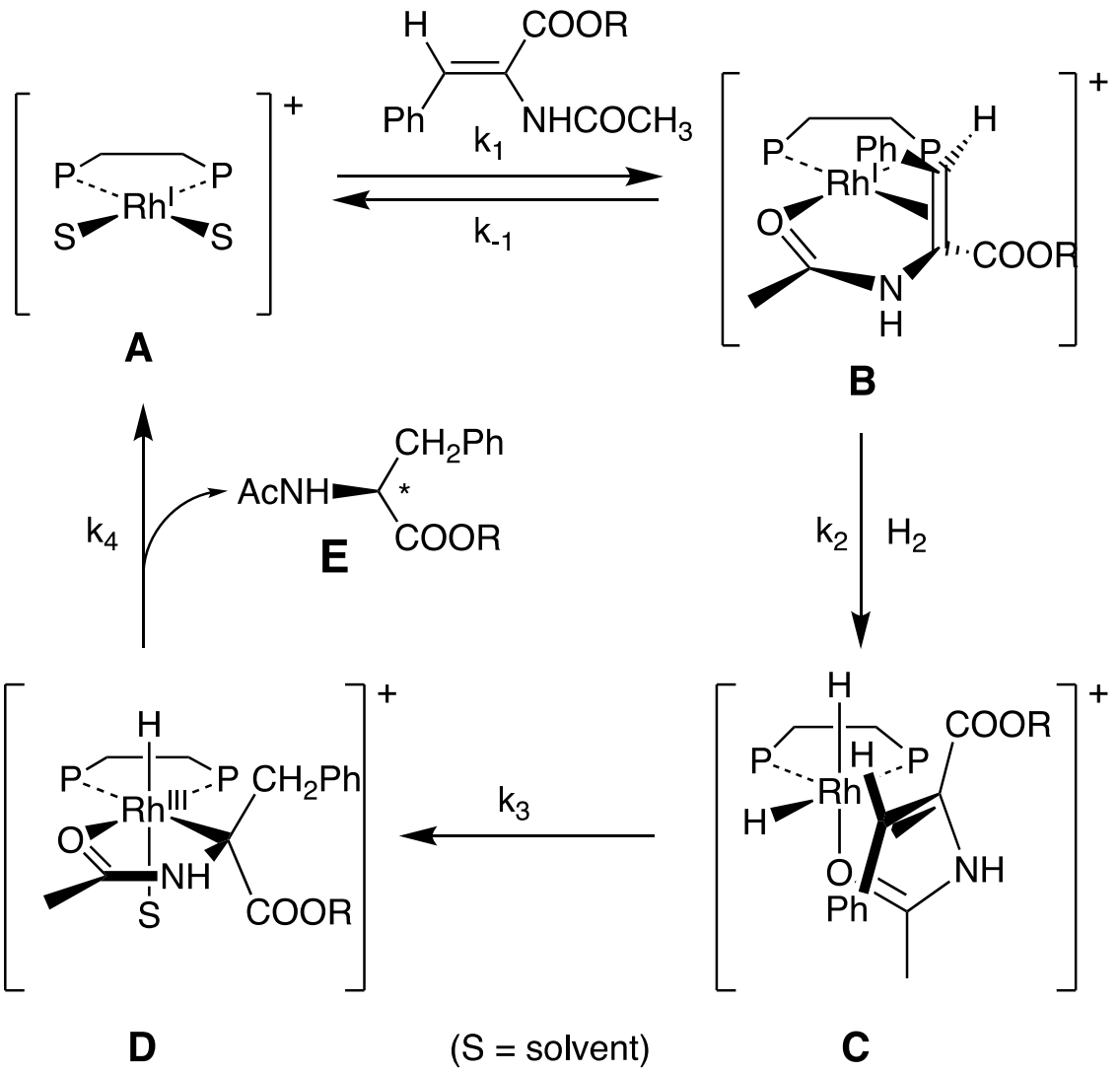




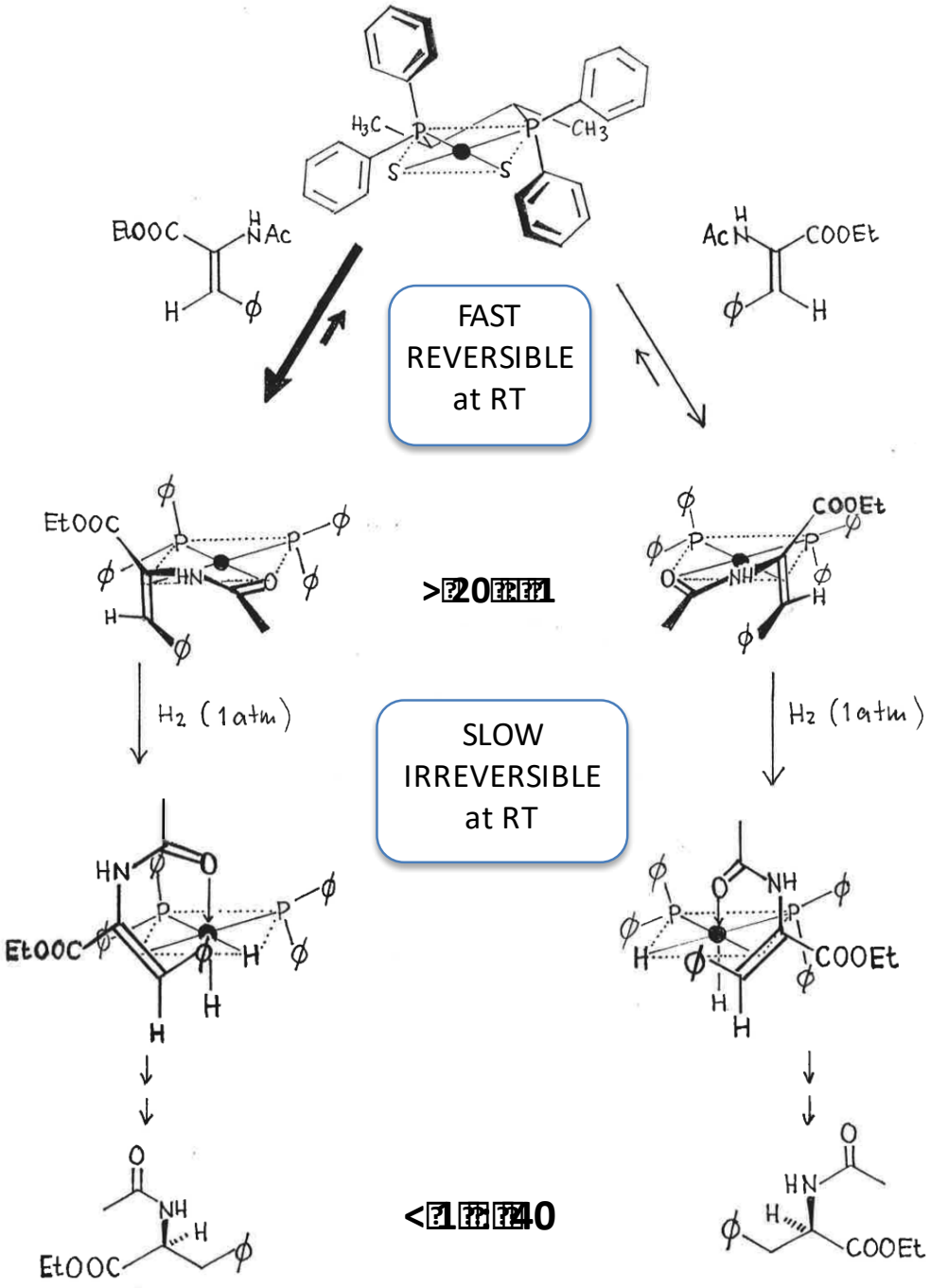


HALPERN
BROWN

Mechanism of enantioselective hydrogenation with Rh-diphosphine catalysts

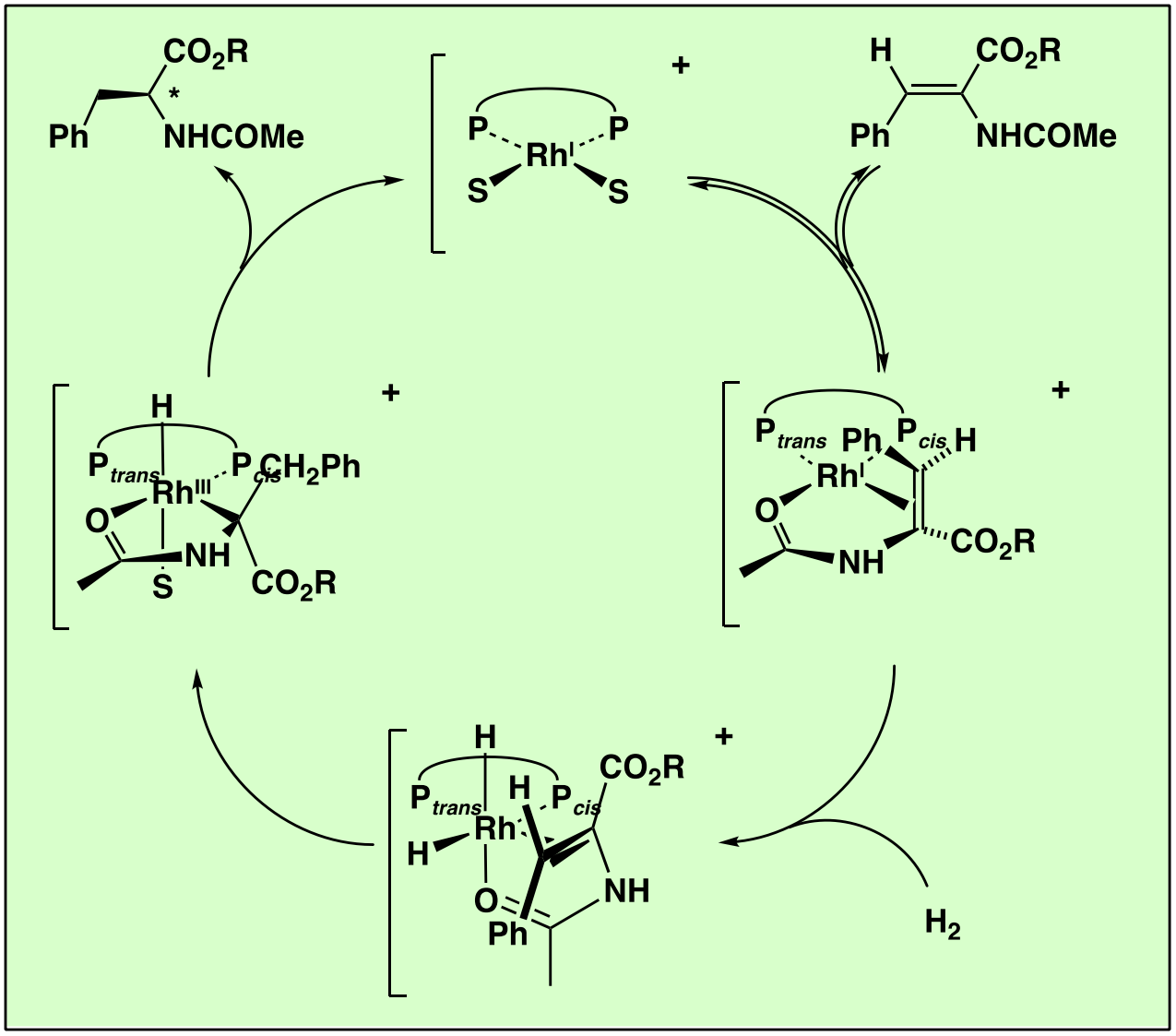


C. R. Landis, S. Feldgus, *Angew. Chem. Int. Ed.* **2000**, *39*, 2863; *J. Am. Chem. Soc.* **2000**, *122*, 12727. R. Giernoth, H. Heinrich, N. J. Adams, R.J . Deeth, J. Bargon, J. M. Brown, *J. Am. Chem. Soc.* **2000**, *122*, 12381. I. D. Gridnev, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2001**, *123*, 4631.


FAST
REVERSIBLE
at RT
SLOW
IRREVERSIBLE
at RT
>20:1
<1:40

Achiwa's "Respective Control Concept"

Synlett **1992**, 169



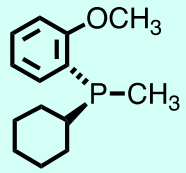
P_{trans} and P_{cis} have different steric and electronic interactions with the substrate

⇩

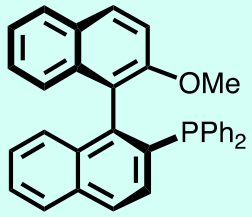
P_{trans} and P_{cis} have different effects on the **enantioselectivity** and **rate**

⇩

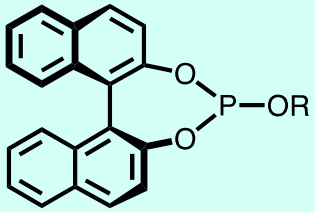
P_{trans} and P_{cis} groups must perform different functions and, therefore, **should be optimized individually**.

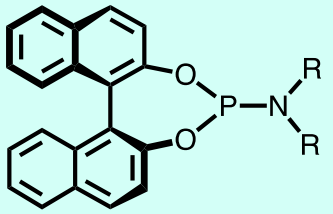


CAMP

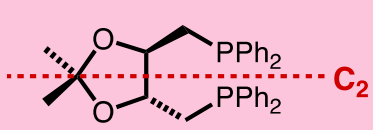


MOP

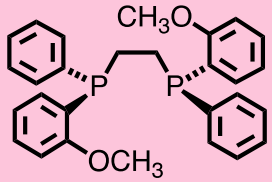




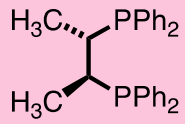
MonoPhos



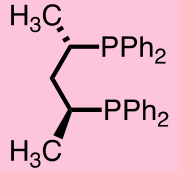
DIOP



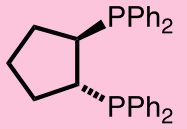
DIPAMP



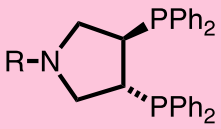
Chiraphos



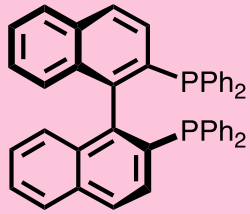
Skewphos



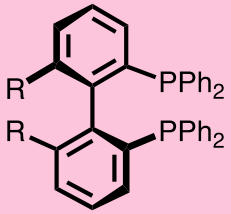
DPCP



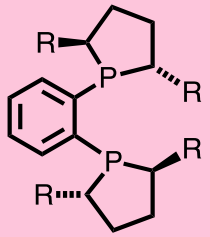
Pyrphos
Deguphos



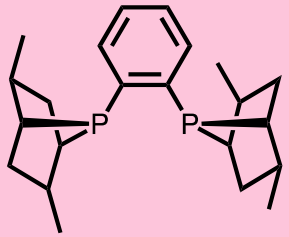
BINAP



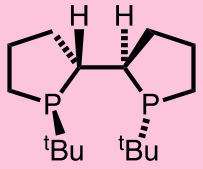
BIPHEP



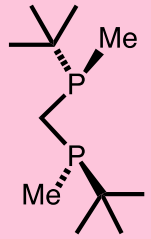
Duphos



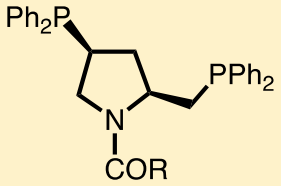
PennPhos



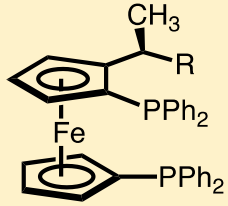
TangPhos



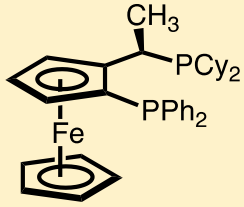
MiniPHOS



BPPM (R=O*t*-Bu)



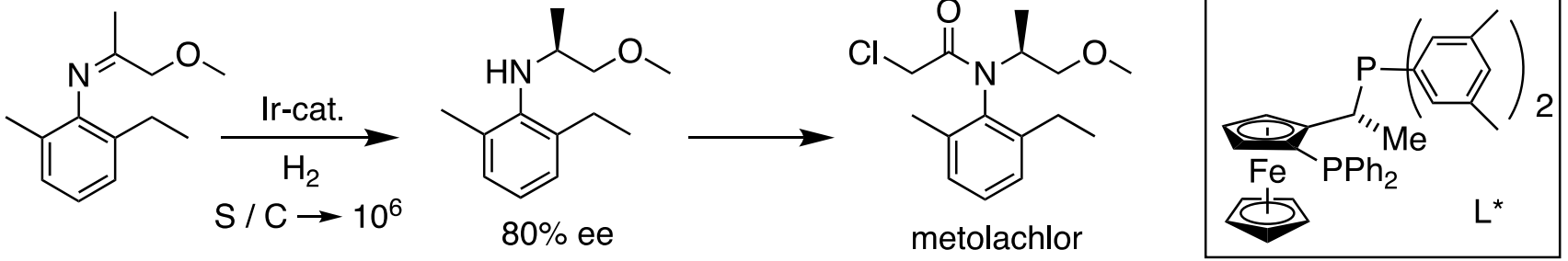
BPPFA (R=NMe_2)



Josiphos

Josiphos ligands (Ciba-Geigy central research, SOLVIAS)

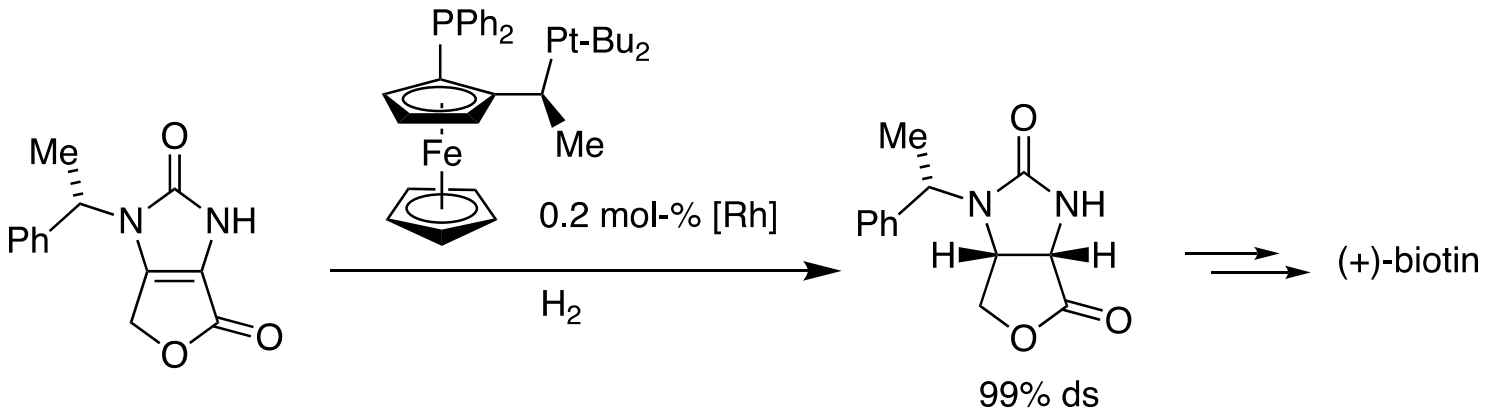
Technical synthesis of the herbicide metolachlor



catalyst system:
Ir(I) / L* / I^- / H_2SO_4

H.-U. Blaser, *Adv. Synth. Catal.* **2002**, *344*,17-31

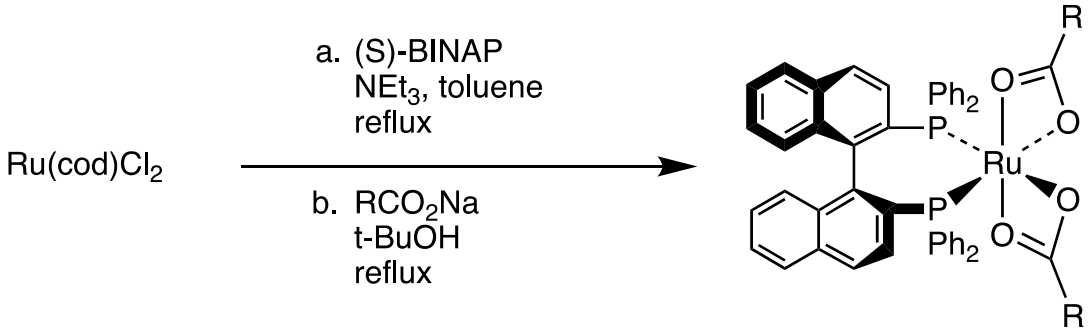
Synthesis of biotin on an industrial scale



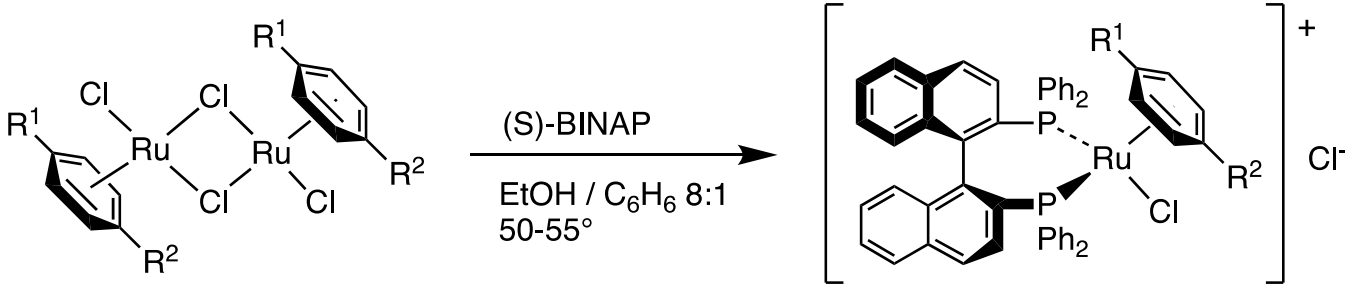
99% ds

J. McGarrity, F. Spindler, R. Fuchs, M. Eyer (Lonza AG), EP-A 624 587 A2, **1995**

Synthesis of Ru-diphosphine complexes



1a (R = CH_3)
1b (R = $C(CH_3)_3$)

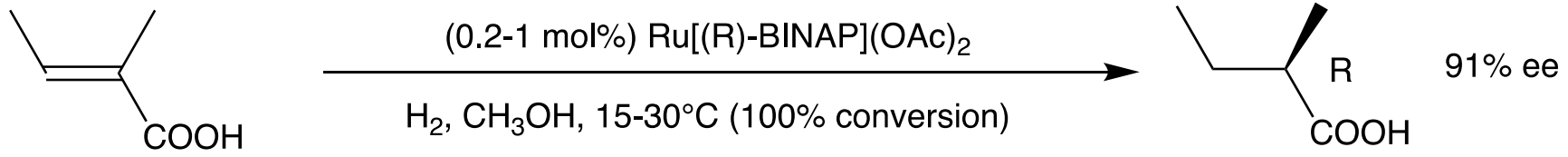


2a (R^1 = H, R^2 = H)
2b (R^1 = CH_3, R^2 = $CH(CH_3)_2$)

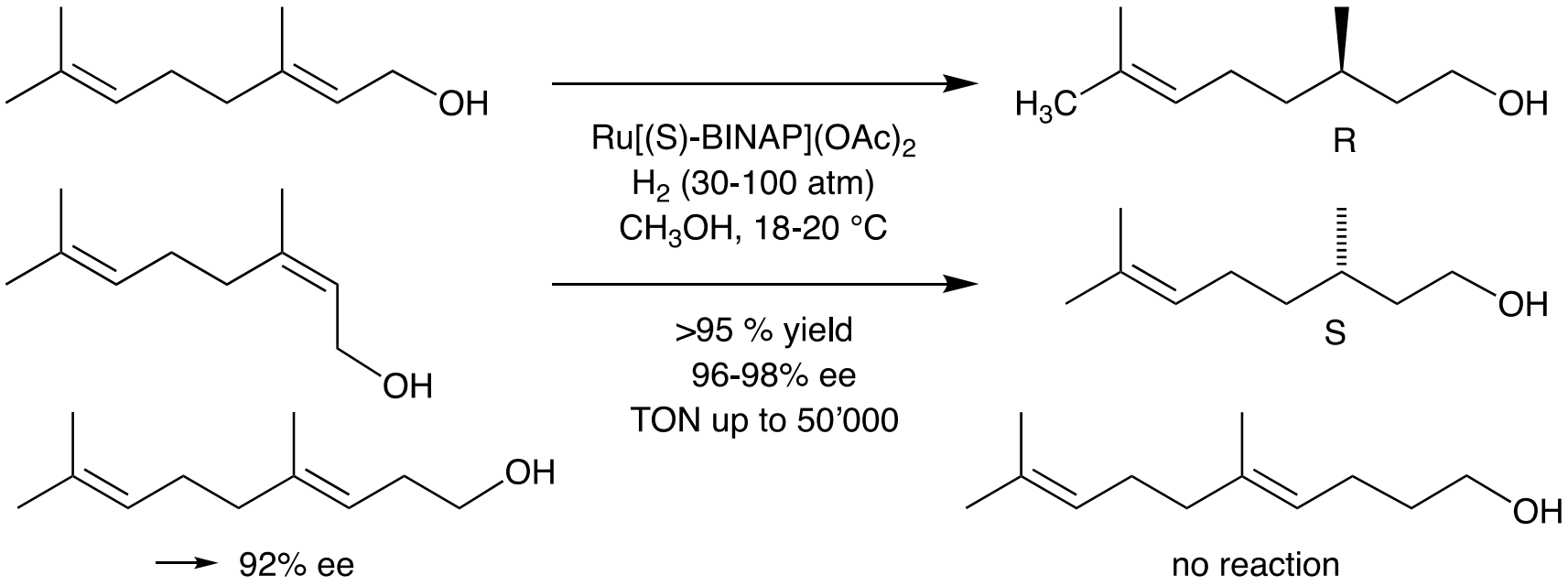
3a (R^1 = H, R^2 = H)
3b (R^1 = CH_3, R^2 = $CH(CH_3)_2$)

R. Noyori, H. Takaya, Acc. Chem. Res. **1990**, *23*, 345

Ru(BINAP)-catalyzed asymmetric hydrogenation of C=C bonds

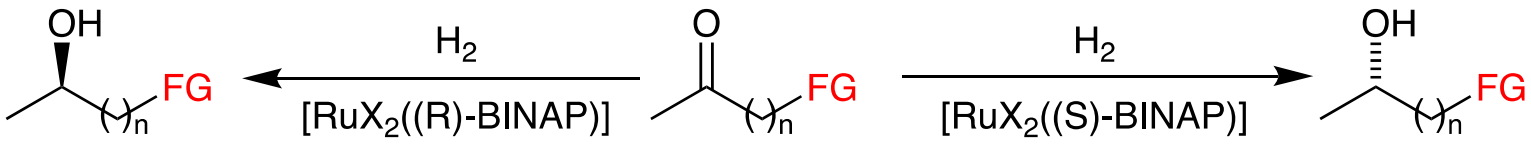


R. Noyori, H. Takaya, *Acc. Chem. Res.* ***1990****, 23*, 345



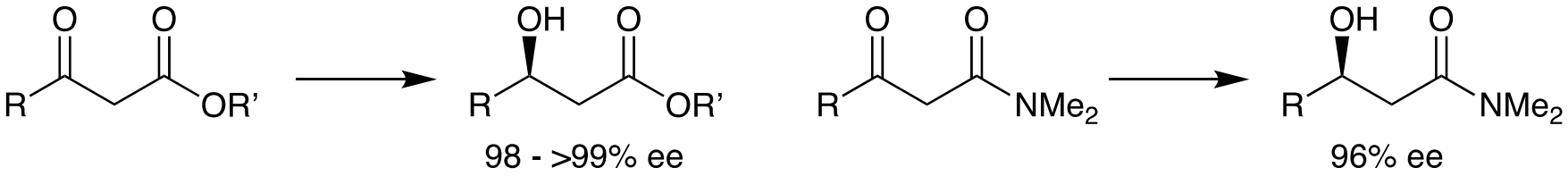
R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345. R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008 (Nobel lecture)

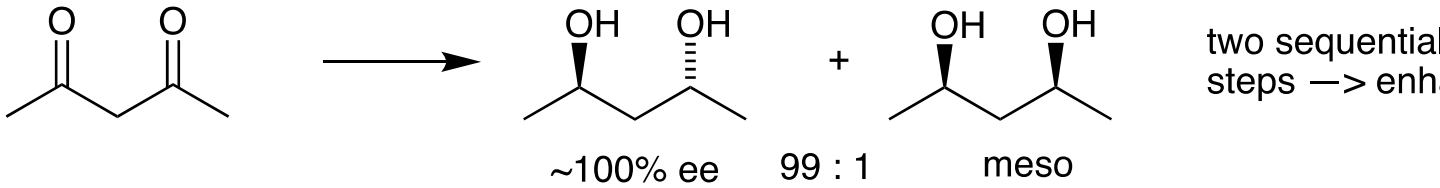
Enantioselective reduction of ketones with Ru(BINAP) catalyts



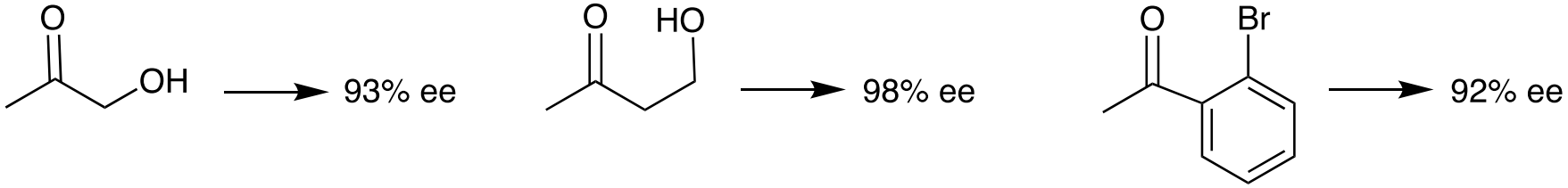
n = 1-3

FG = coordinating functional group



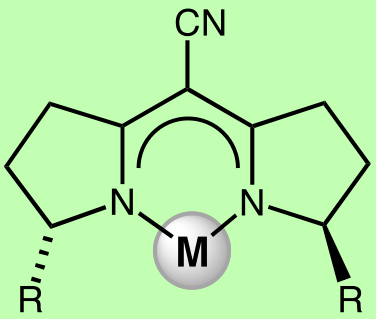


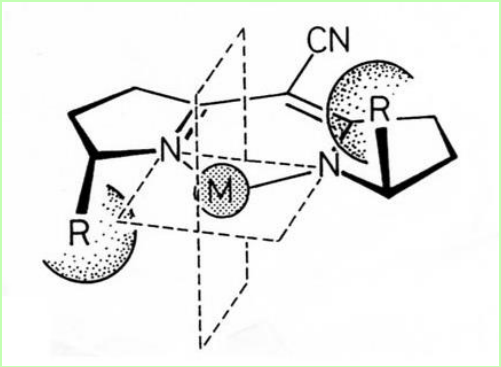
two sequential stereoselective steps —> enhancement of ee

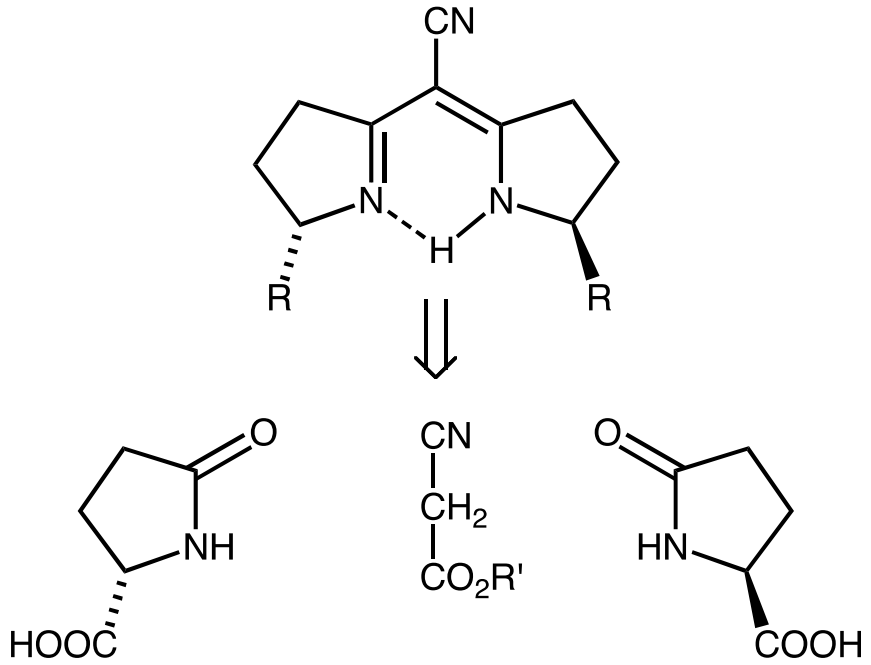


R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345. R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008 (Nobel lecture)

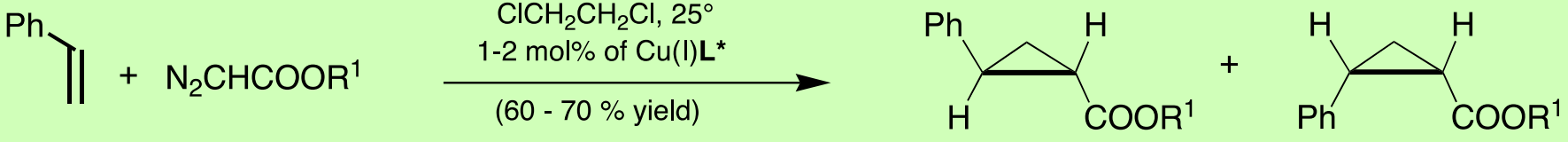
C_2-Symmetric Semicorrin Ligands

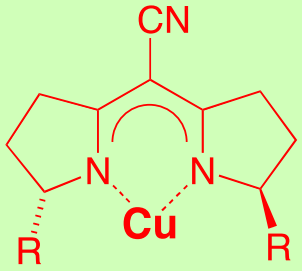






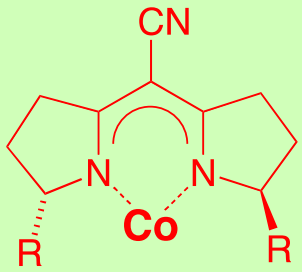
Applications of semicorrin ligands

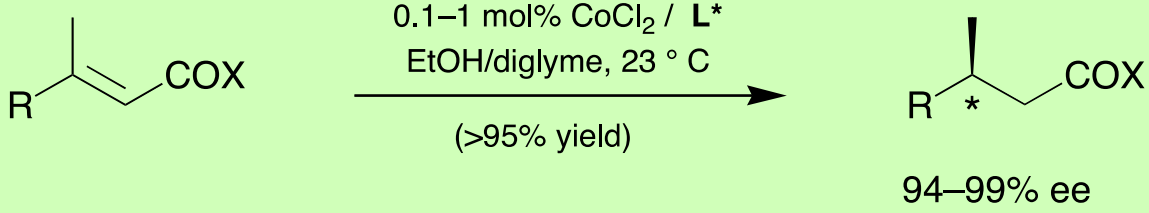




R^1 = ethyl	92 % ee	(3 : 1)	80 % ee
R^1 = *tert*-butyl	93 % ee	(4 : 1)	92 % ee
R^1 = *d*-menthyl	97 % ee	(4 : 1)	95 % ee

H. Fritschi, U. Leutenegger, A. P., *Angew. Chem. Int. Ed.* **1986**, *25*, 1005

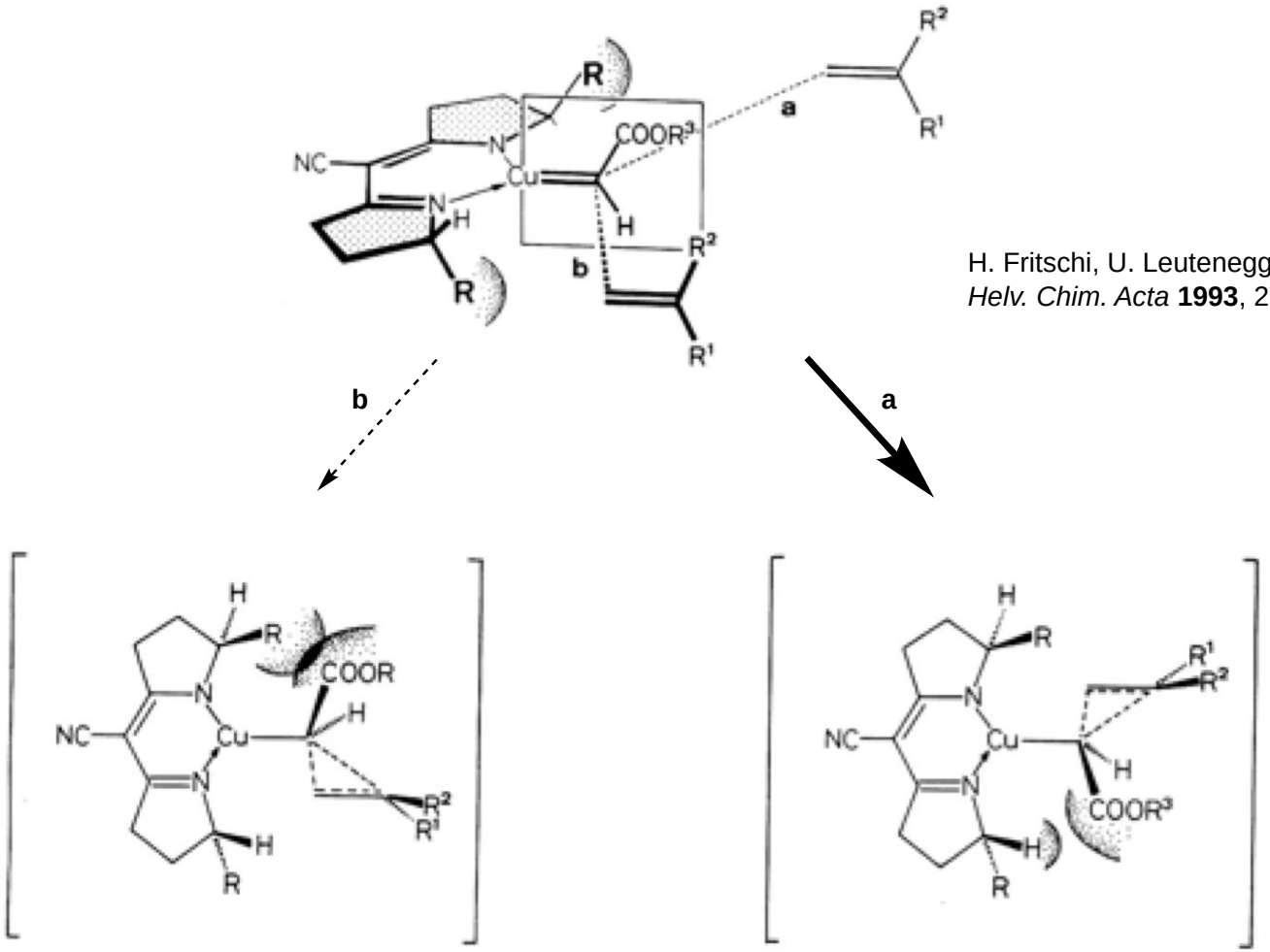




94–99% ee

U. Leutenegger, A. Madin, A. P, *Angew. Chem. Int. Ed.* **1989**, *28*, 60

Enantioselective cyclopropanation: transition-state model

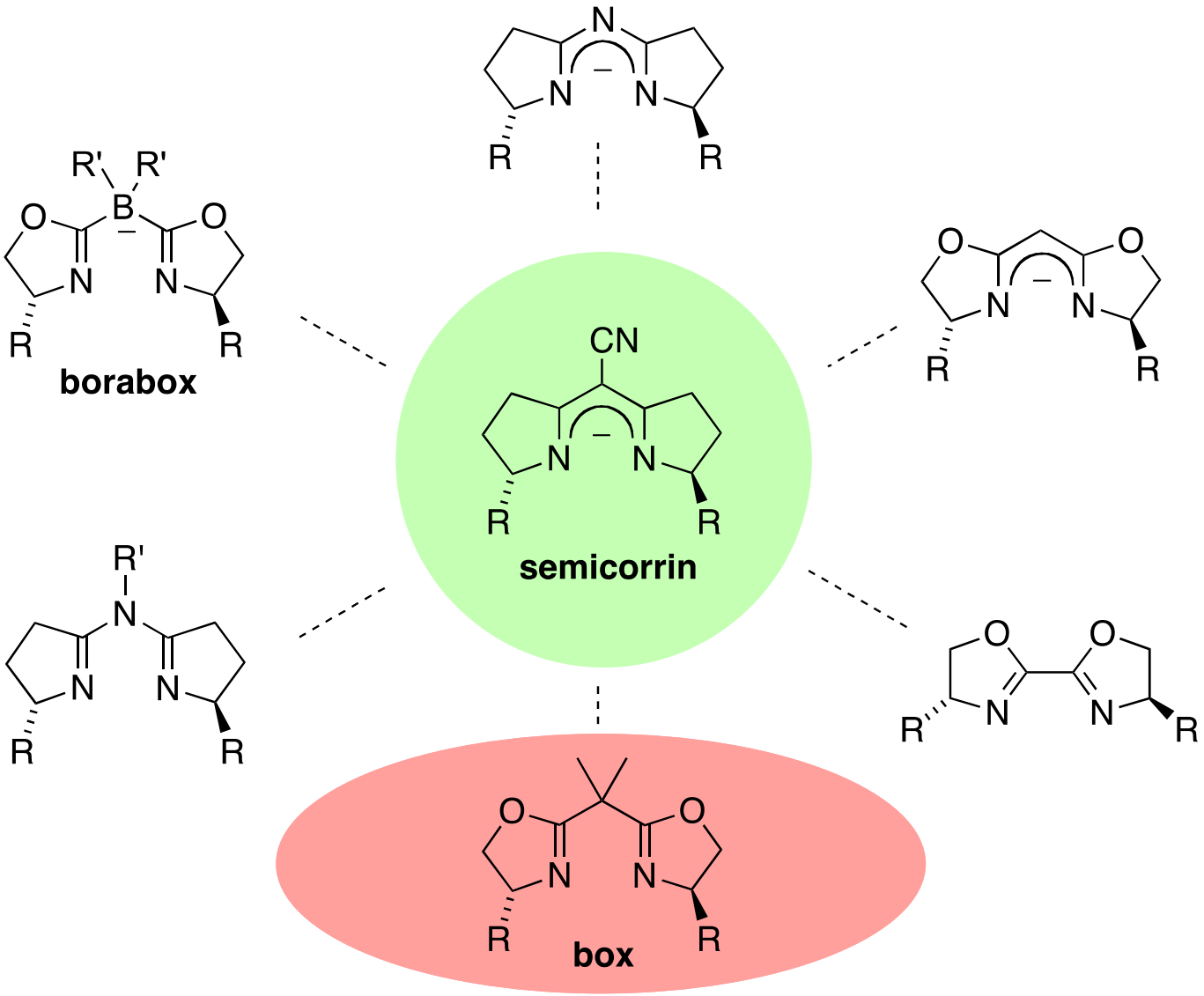


H. Fritschi, U. Leutenegger, A. Pfaltz, *Helv. Chim. Acta* **1993**, 26, 339.

Isolation of a Cu-carbene intermediate: F. Straub, P. Hofmann, *Angew. Chem. Int. Ed.* **2001**, *40*, 1288.

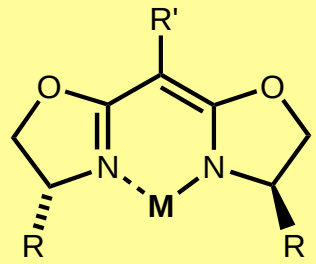
DFT calculations: J. M. Fraile, J. L. García, V. Martínez-Merino, J. A. Mayoral, L. Salvatella, *J. Am. Chem. Soc.* **2001**, *123*, 7616

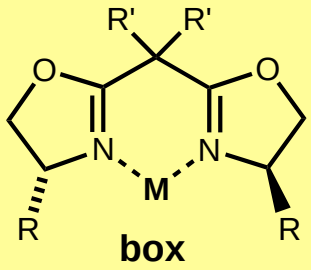
C_2-Symmetric aza-semicorrins and bisoxazoline ligands



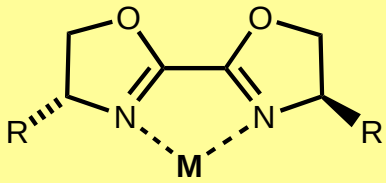
A. P., *Acc. Chem. Res.* **1993**, *26*, 339.

Applications of C_2-Symmetric Bisoxazolines





box



M = Li, Mg, Fe, Cu, Zn, Pd, Rh, Os, Ir

Cyclopropanation

Masamune et al. (Tetrahedron Lett. 1990, 31, 6005)
Evans et al. (J. Am. Chem. Soc. 1991, 113, 726)
Pfaltz et al. (Helv. Chim. Acta 1991, 74, 232)

Diels-Alder reaction

Corey et al. (J. Am. Chem. Soc. 1991, 113, 728)
Evans et al. (J. Am. Chem. Soc. 1993, 115, 6460)

Hydrosilylation

Helmchen et al. (*Synlett* **1991**, 257)

Transfer hydrogenation

Pfaltz et al. (*Helv. Chim. Acta* **1991**, *74*, 232)

Dihydroxylation of olefins

Lixin Dai et al. (Acta Chim. Sinica **1991**, *49*, 1038)

Pd-catalyzed allylic substitution

Pfaltz et al. (*Tetrahedron* **1992**, *48*, 2143)
Larock and Zenner (*J. Org. Chem.* **1995**, *60*, 482)

Aziridination

Evans et al. (*J. Am. Chem. Soc.* **1993**, *115*, 5328)

Cyanohydrin formation

Corey and Wang (*Tetrahedron Lett.* **1993**, *34*, 4001)

Addition of RLi to imines

Denmark et al. (*J. Am. Chem. Soc.* **1994**, *116*, 8797)

Co-polymerization

Brookhart et al. (*J. Am. Chem. Soc.* **1994**, *116*, 3642)
Musco et al. (*Macromol. Rapid Commun.* **1995**, *16*, 9)

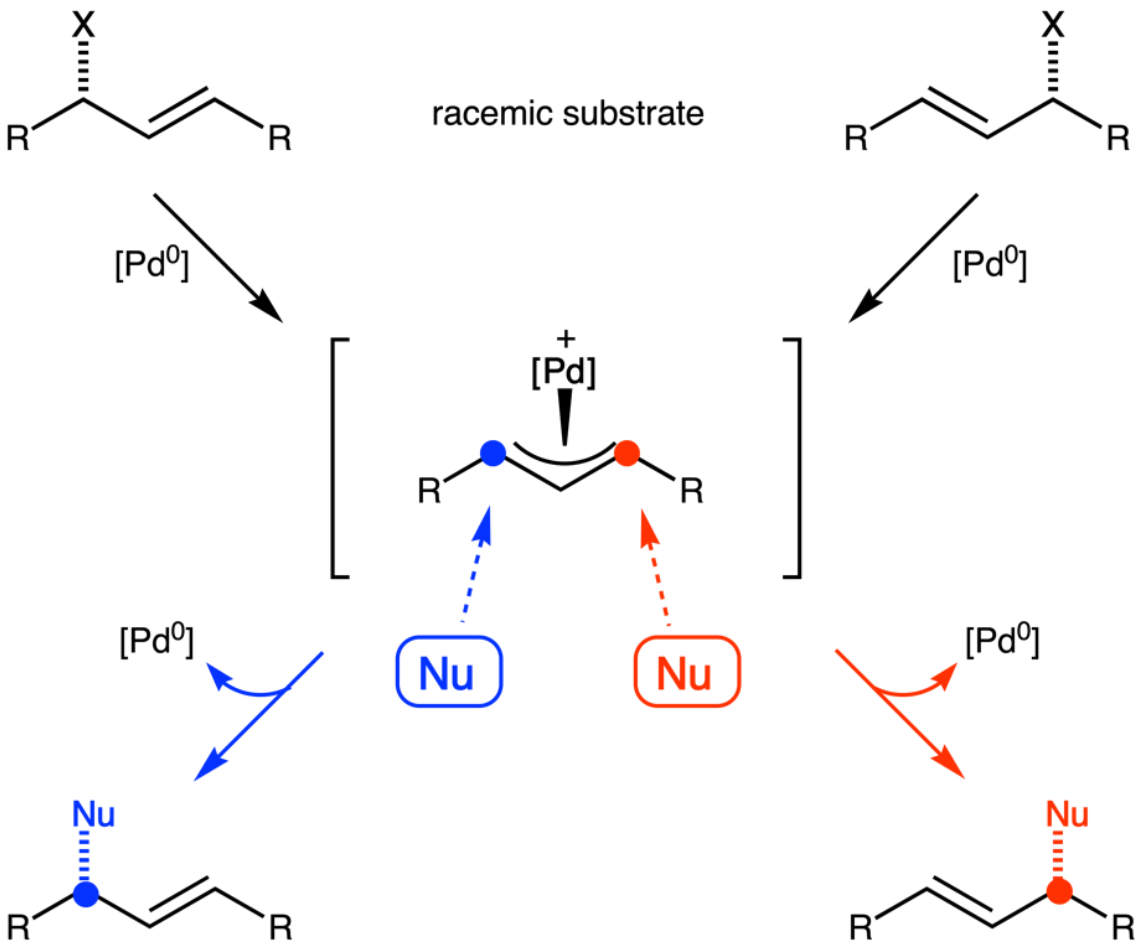
Carbometalation

Nakamura et al. (*J. Am. Chem. Soc.* **1995**, *117*, 1179)

Allylic oxidation of olefins

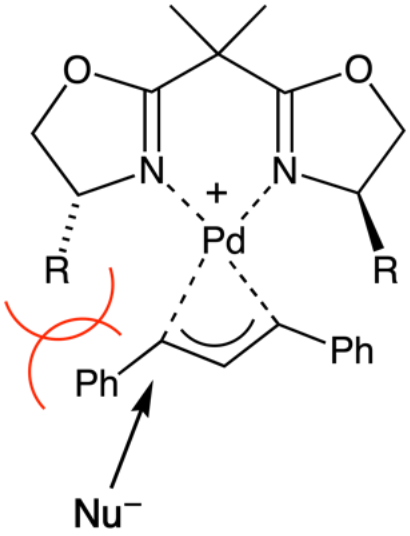
Pfaltz et al. (*Tetrahedron Lett.* **1995**, *36*, 1831)
Andrus et al. (*Tetrahedron Lett.* **1995**, *36*, 2945)

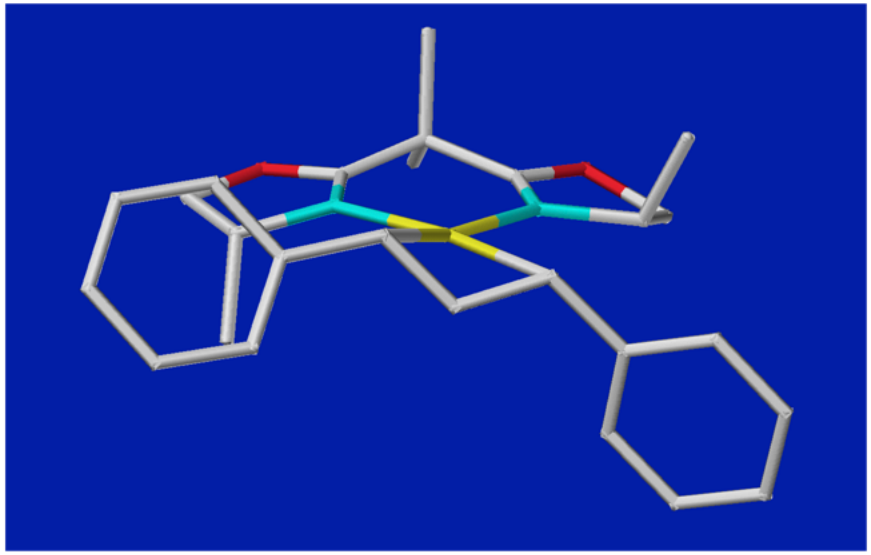
Pd-catalyzed allylic substitution

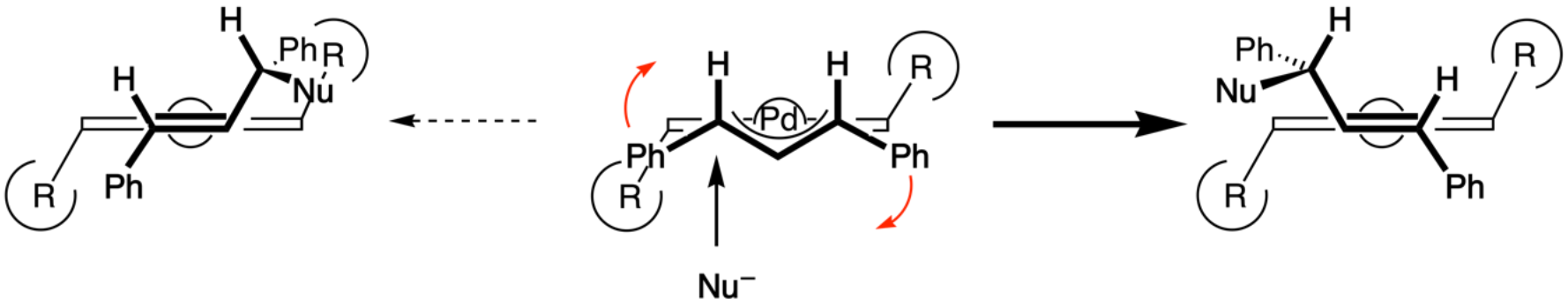


Enantioselectivity ≡ Regioselectivity

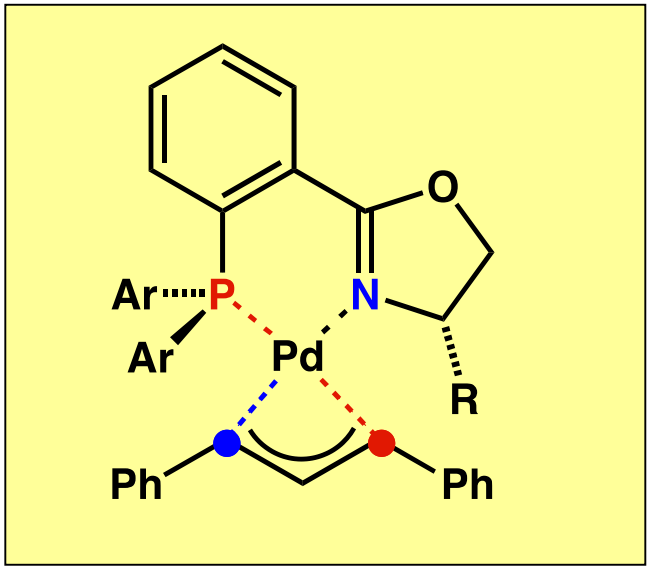
Pd-catalyzed allylic substitution: mechanism of enantioselection







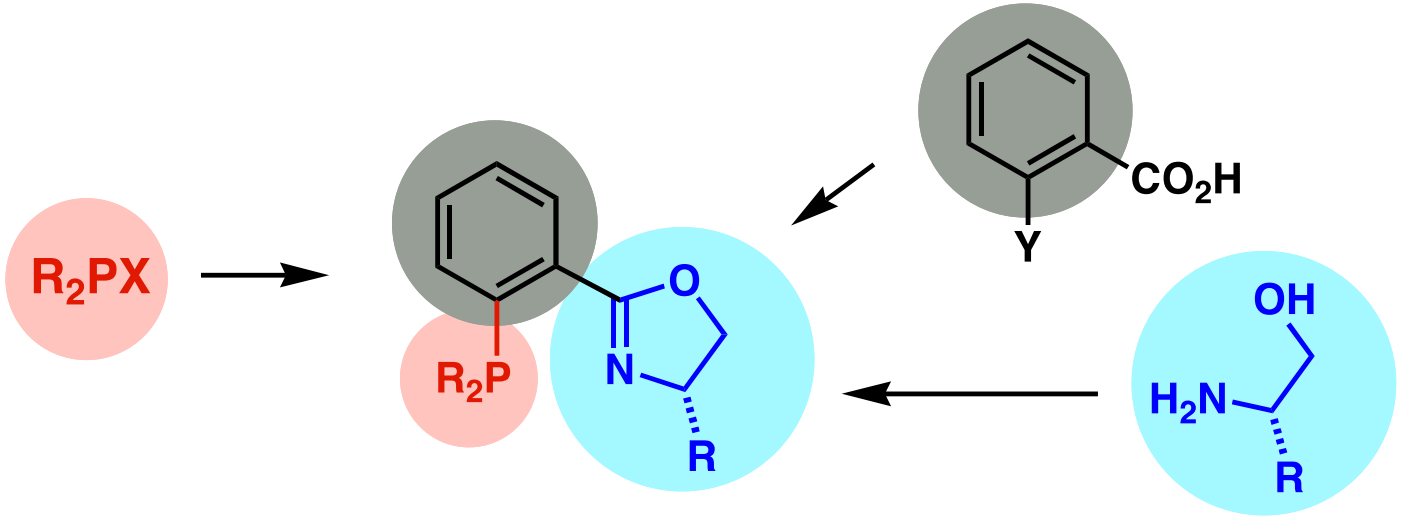
Phosphinooxazolines (PHOX ligands)

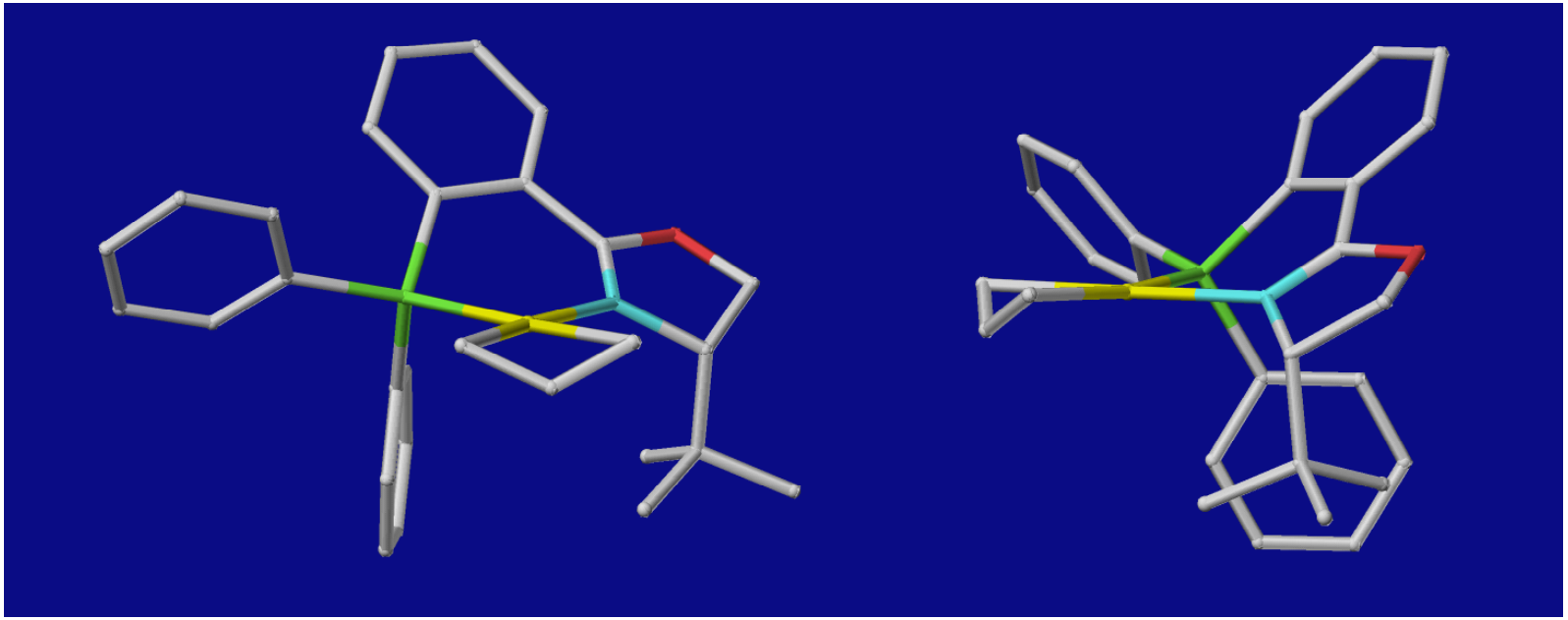


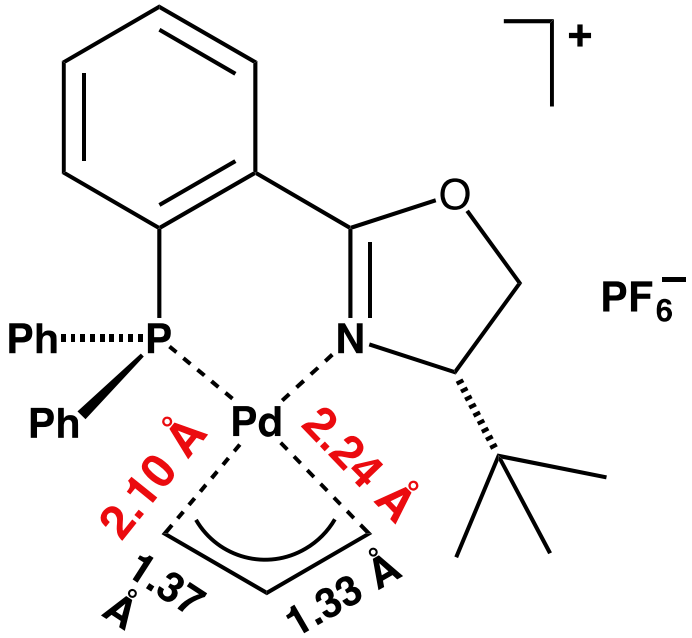
P. von Matt, A. Pfaltz
Angew. Chem. Int. Ed. **1993**, *32*, 566

J. Sprinz, G. Helmchen
Tetrahedron. Lett. **1993**, *34*, 1769

G. J. Dawson, C. G. Frost, J. M. J. Williams,
S. J. Coote, T*etrahedron. Lett.* **1993**, *34*, 3149



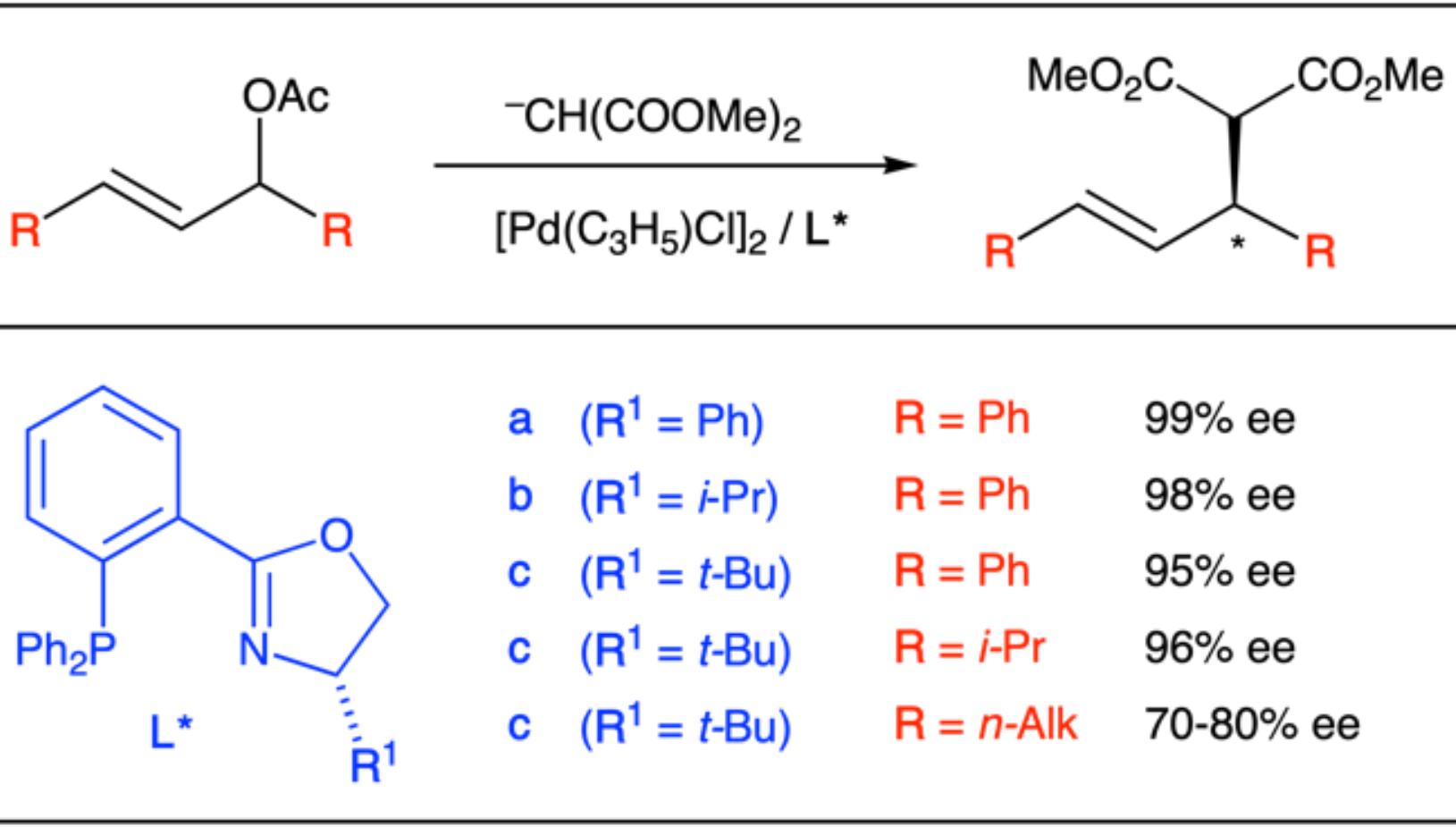




X-ray analysis:

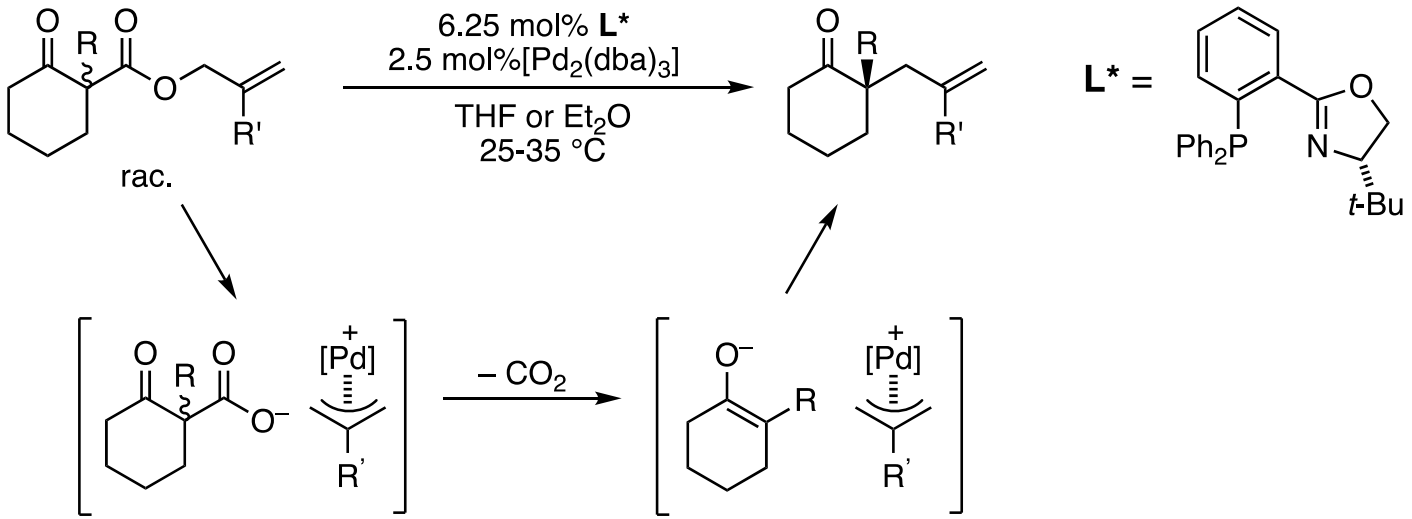
M. Zehnder, M. Neuburger,
L. Macko

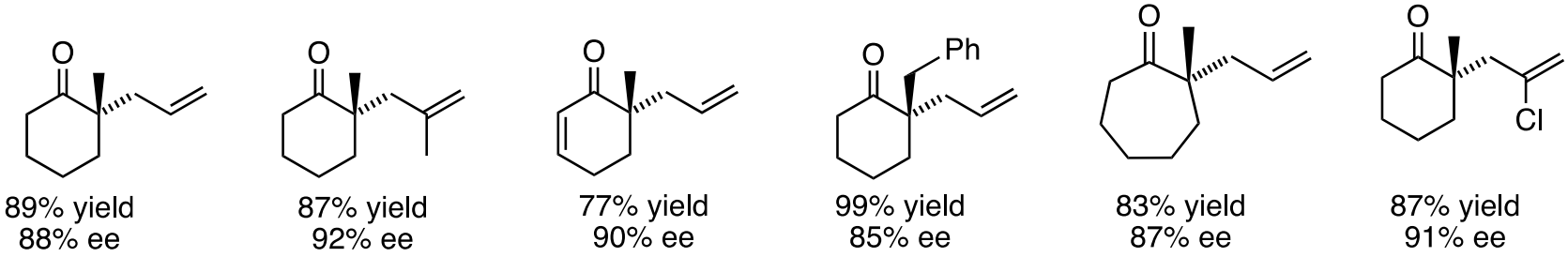
University of Basel



Peter von Matt

Enantioselective Tsuji allylation with β-keto allyl esters

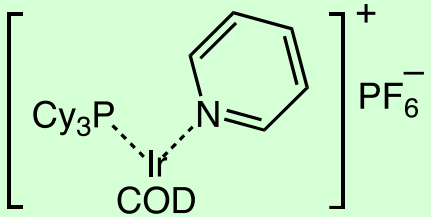


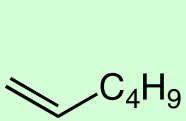
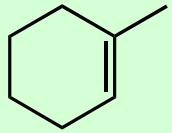
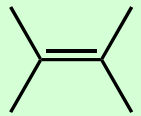


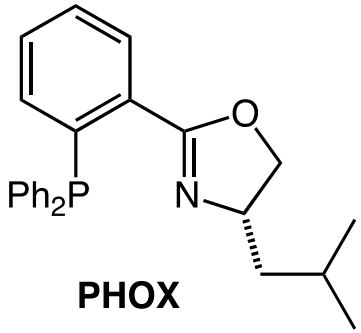
J. T. Mohr, B. M. Stoltz, *Chem. Asian J.* **2007**, *2*, 1476

Asymmetric hydrogenation of olefins lacking coordinating groups

Crabtree catalyst

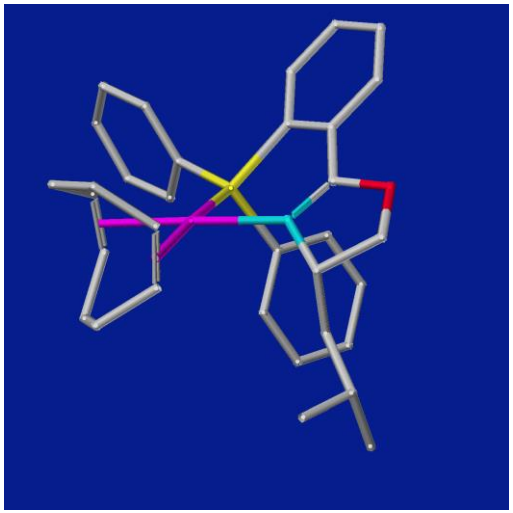


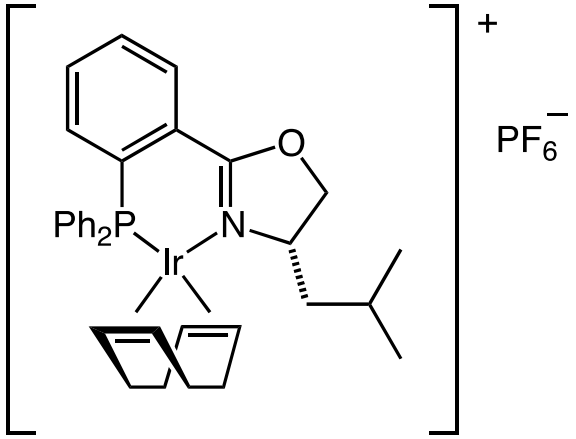
			
TOF (h^{-1})	6400	3800	4000



PHOX

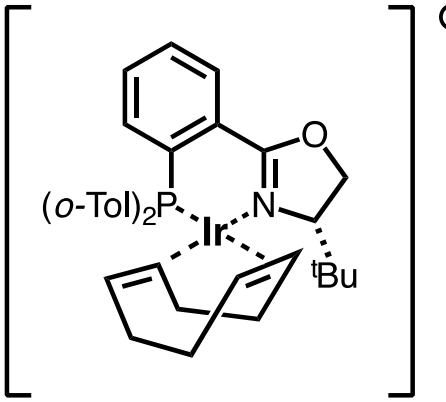
1) $[Ir(COD)Cl]_2$, CH_2Cl_2, reflux
2) NH_4PF_6, H_2O / CH_2Cl_2
3) crystallization (CH_2Cl_2 / Et_2O)



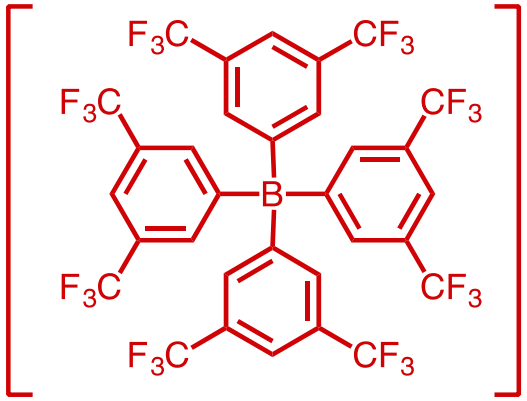


X-Ray analysis:
L. Macko & M. Zehnder
(University of Basel)

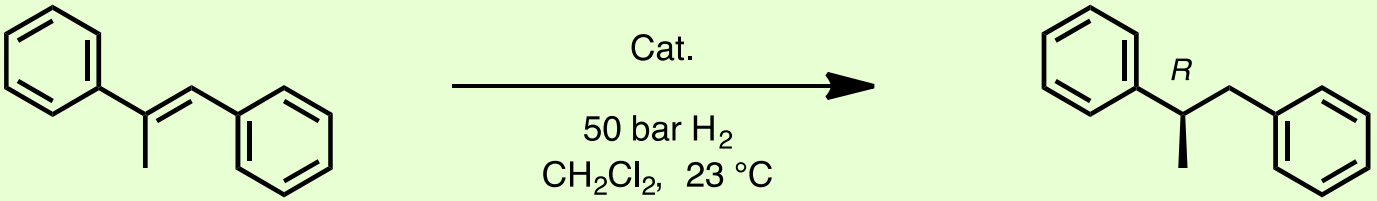
Initial Experiments - Influence of the Counterion



$X^{\ominus}$ $\quad X^{\ominus} = [PF_6]^{\ominus}$ or



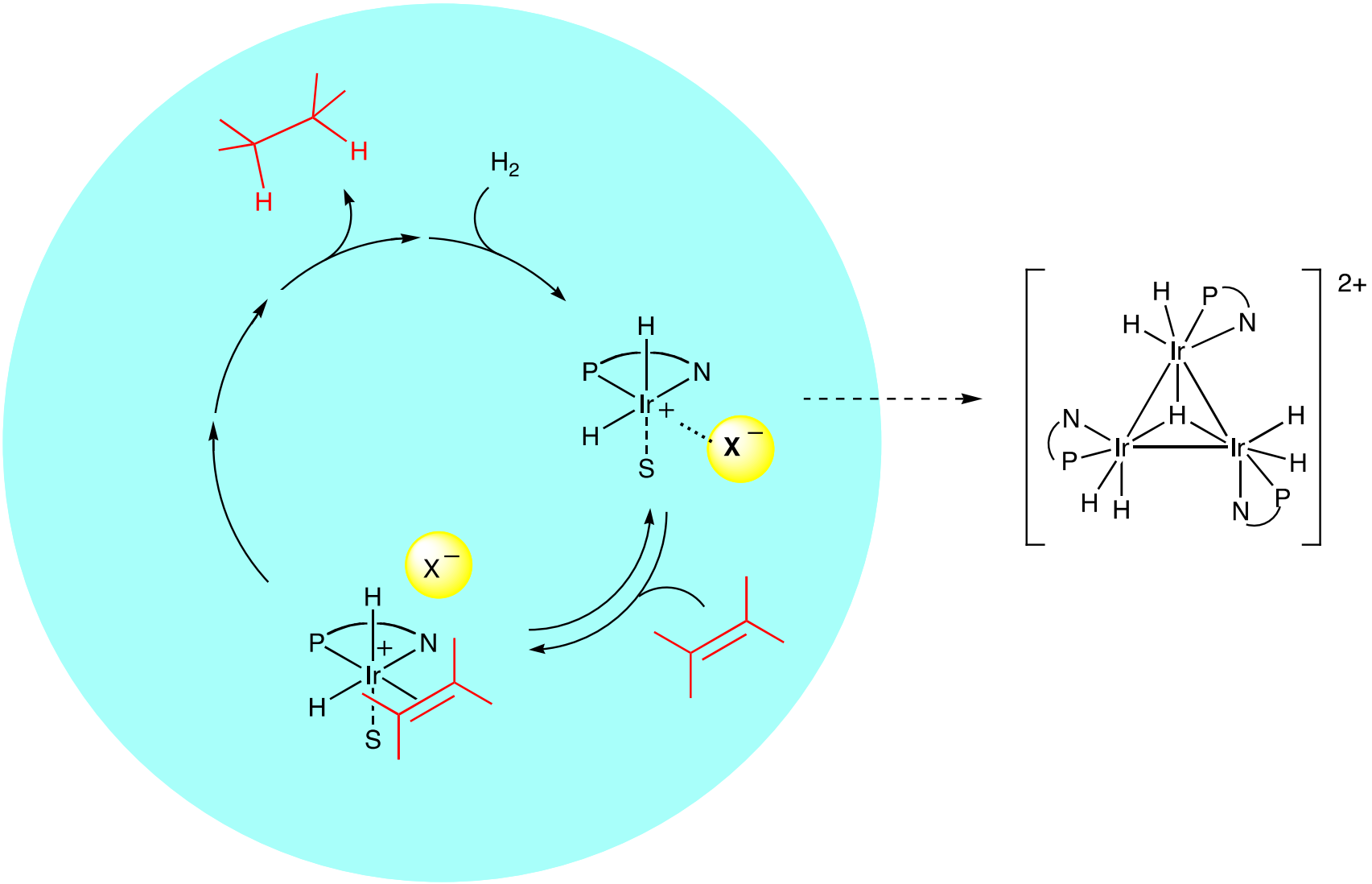
BAr_F



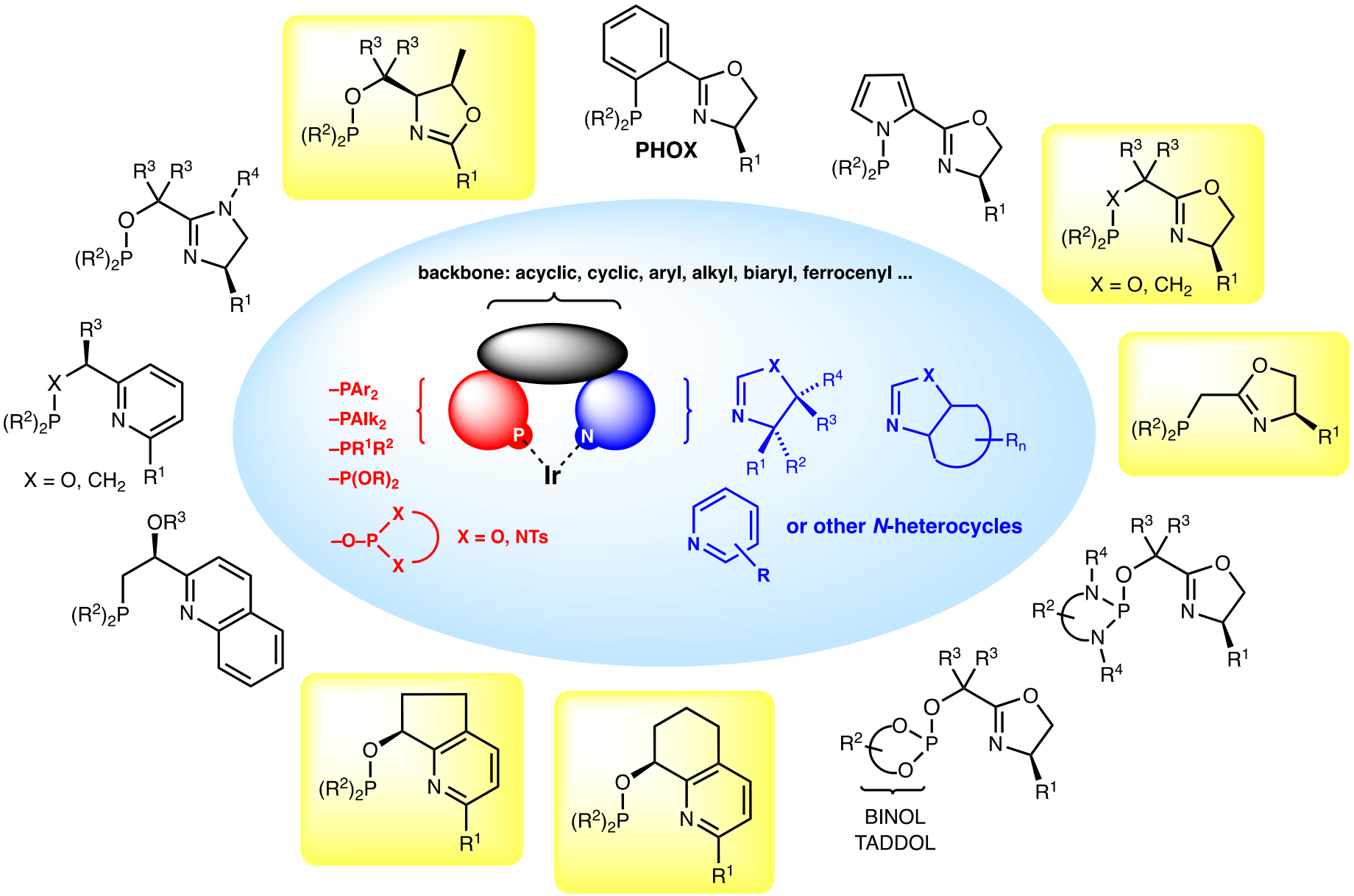
$X = PF_6$:	4 mol% catalyst	57% conversion	97% ee	TOF 2400 h^{-1}
$X = BAr_F$:	0.02 mol% catalyst	> 99% conversion	98% ee	TOF > 5000 h^{-1}

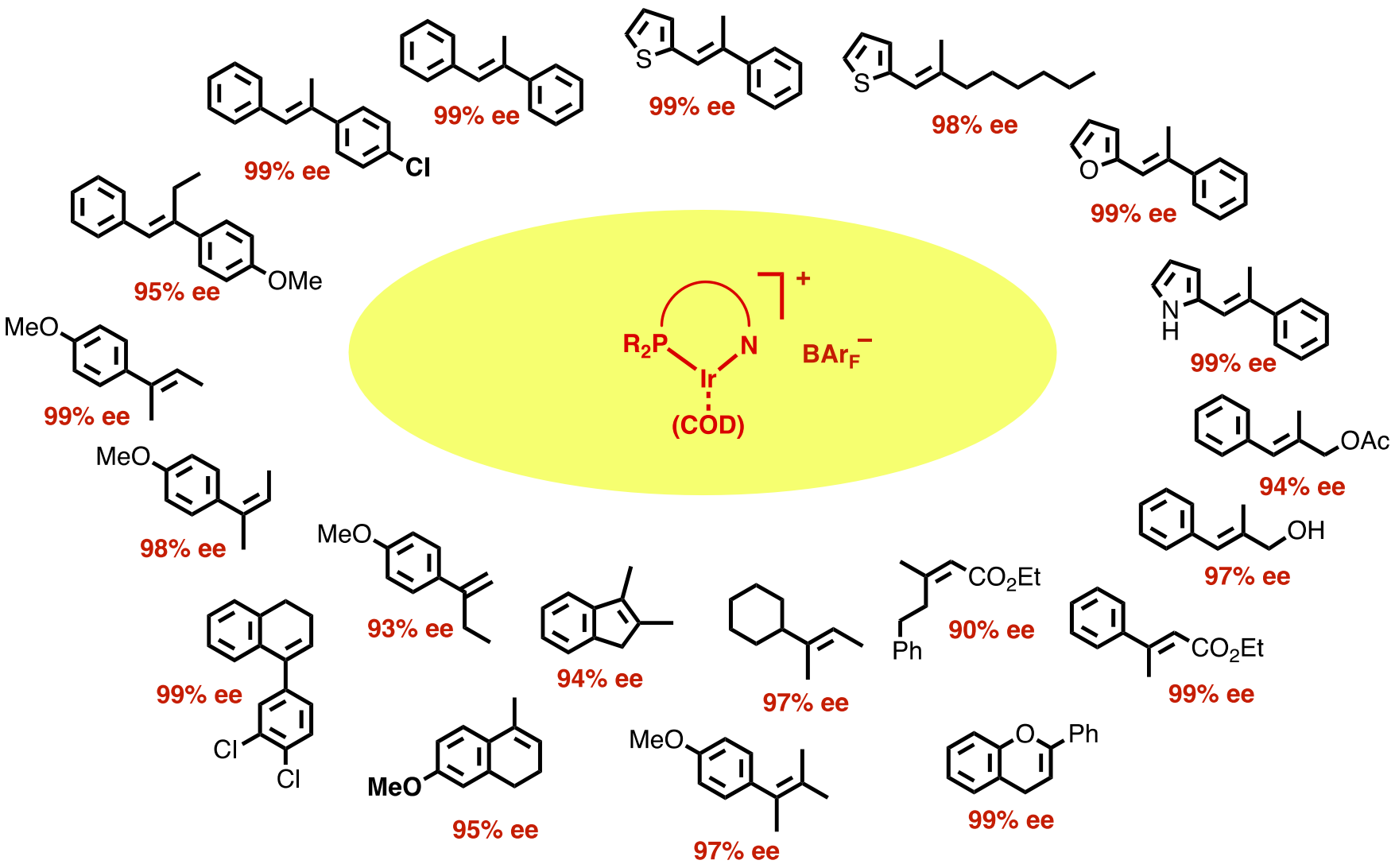
Andrew Lightfoot

Hydrogenation vs. catalyst deactivation: influence of the anion

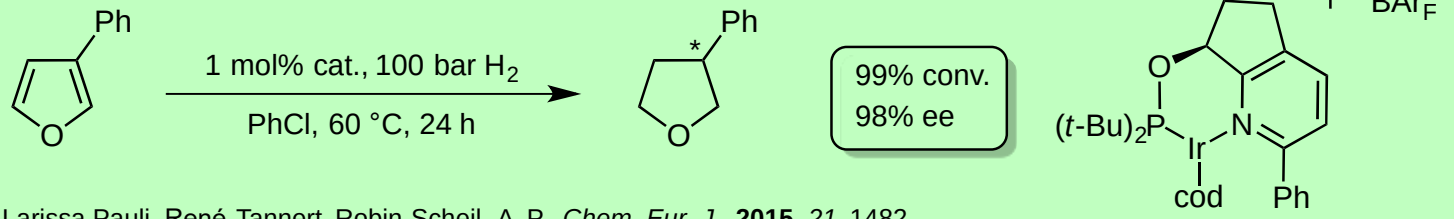


Variation of the Catalyst Structure

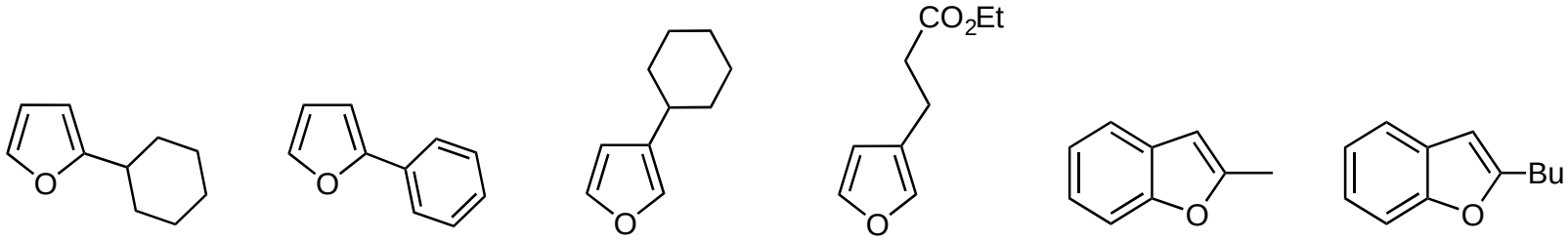



99% ee
99% ee
99% ee
98% ee
99% ee
95% ee
OMe
MeO
99% ee
MeO
98% ee
99% ee
OAc
94% ee
OH
97% ee
MeO
93% ee
94% ee
97% ee
CO2Et
Ph
90% ee
CO2Et
99% ee
99% ee
Cl
Cl
MeO
95% ee
MeO
97% ee
O
Ph
99% ee
R2P
N
Ir
(COD)
BArF−
+

Furans, Benzofurans, Indoles



Larissa Pauli, René Tannert, Robin Scheil, A. P., *Chem. Eur. J.* **2015**, *21*, 1482



96% conv.
82% ee

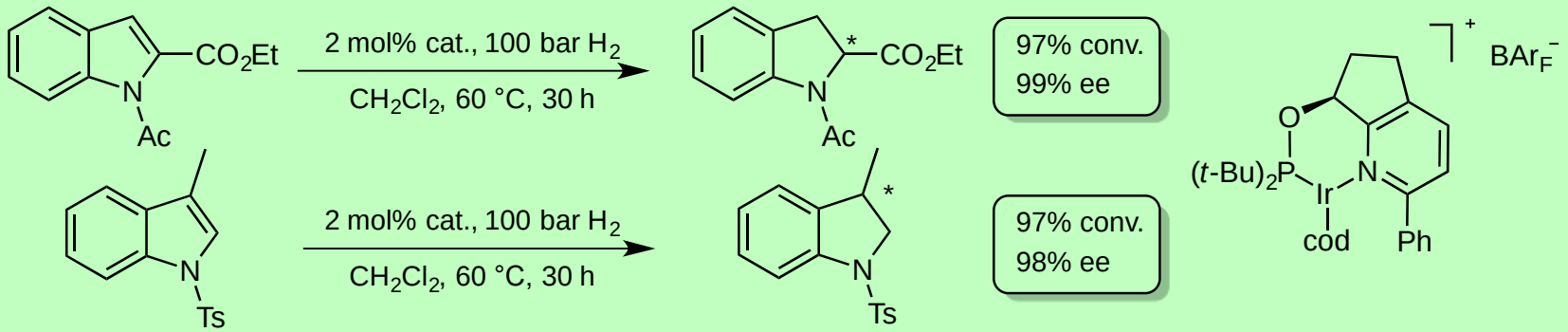
15% conv.
2% ee

>99% conv.
98% ee

>99% conv.
93% ee

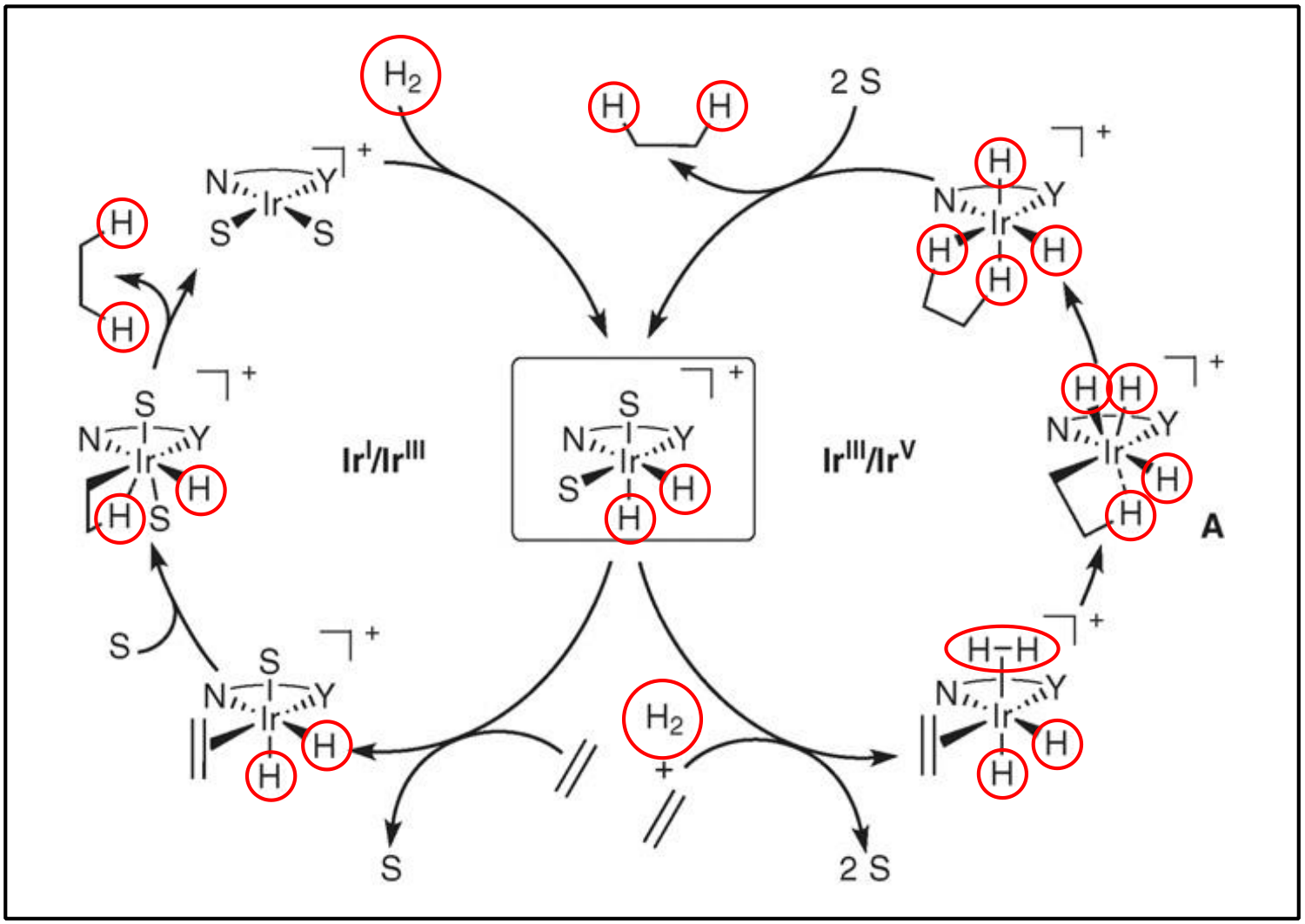
93% conv.
98% ee

99% conv.
99% ee



Alex Baeza, A. P., *Chem. Eur. J.* **2010**, *16*, 2036

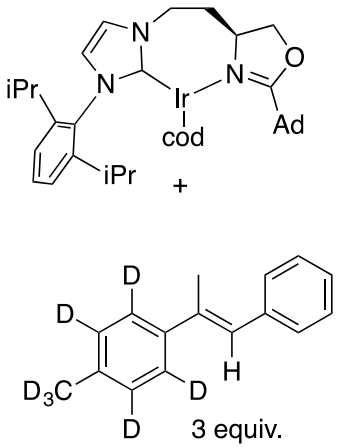
Proposed catalytic cycles

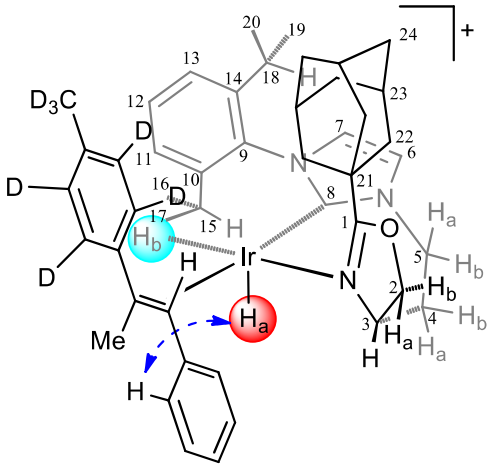


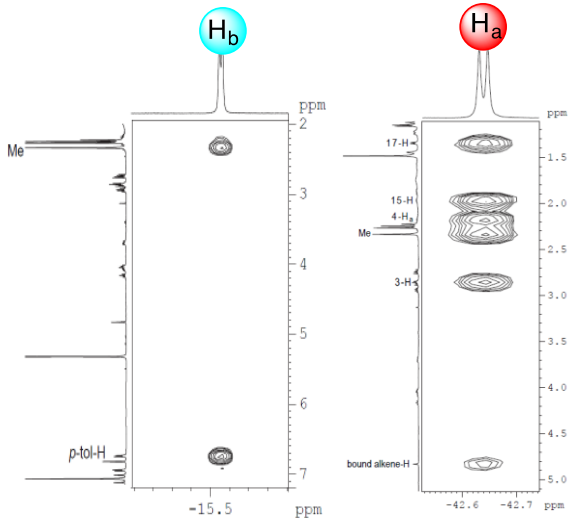
P. Brandt, P. G. Andersson *et al*, *Chem. Eur. J.* **2003**, *9,* 339.

K. Burgess, M. B. Hall *et al.*, *JACS* **2004,** *126,* 16688.

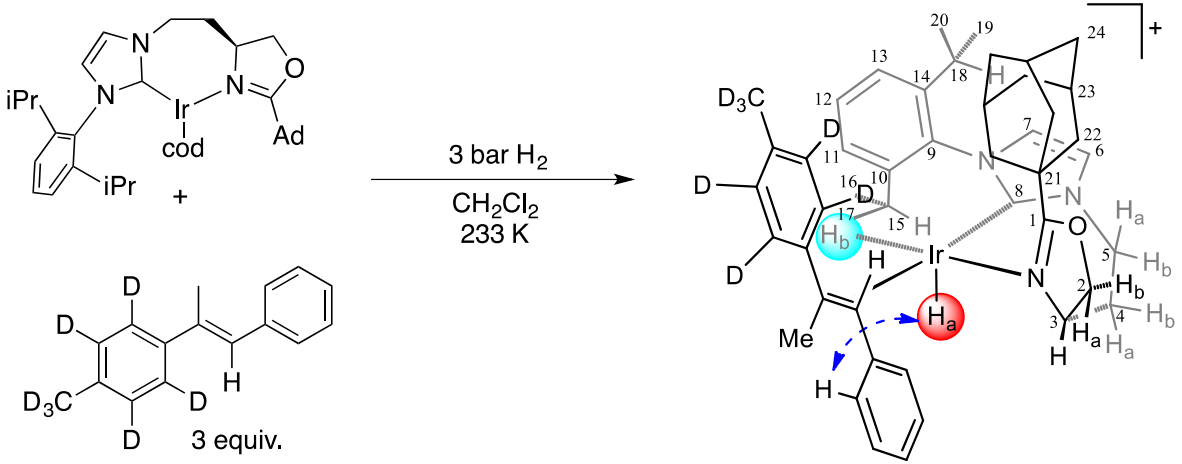
K. H. Hopmann, A. Bayer, *Organometallics* **2011**, *30*, 2483.

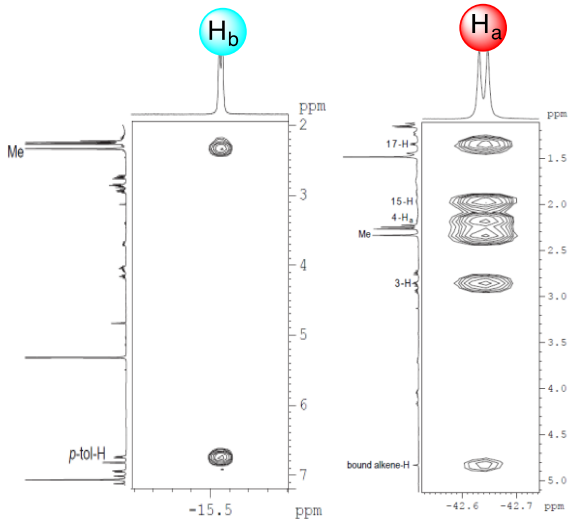


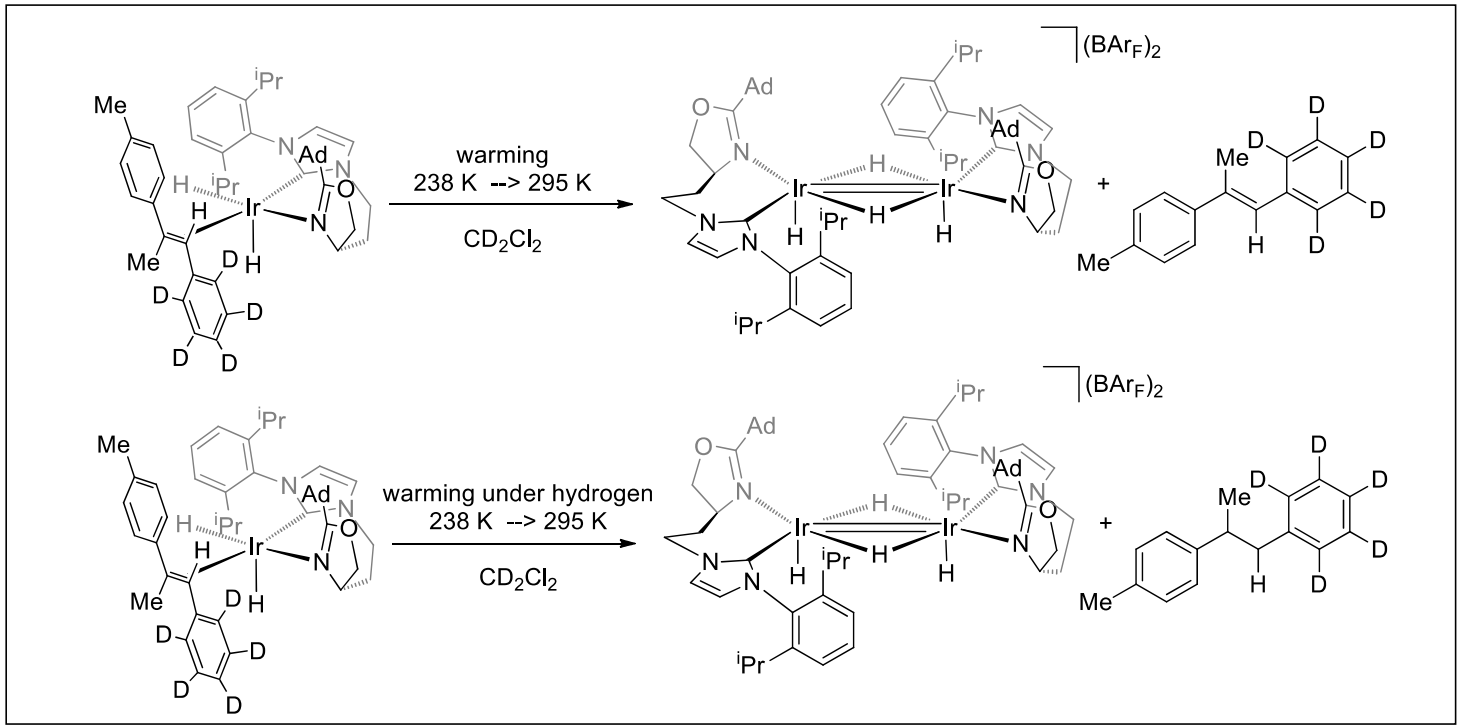




Stefan Gruber

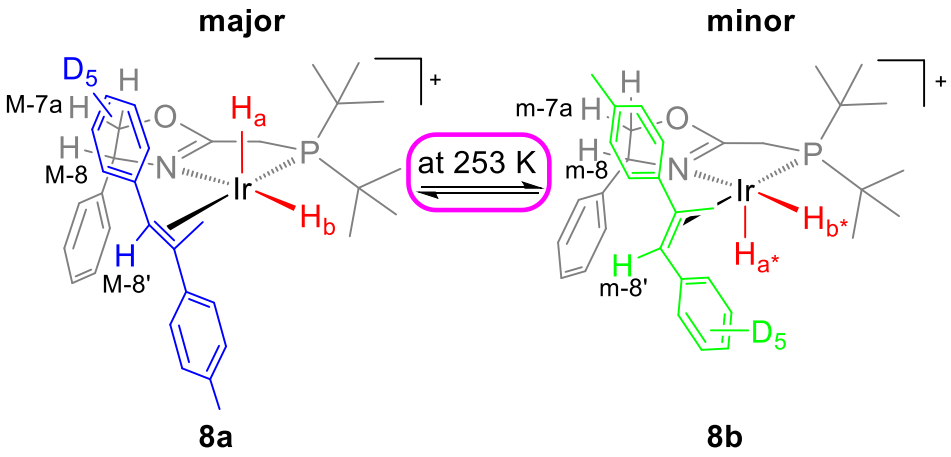




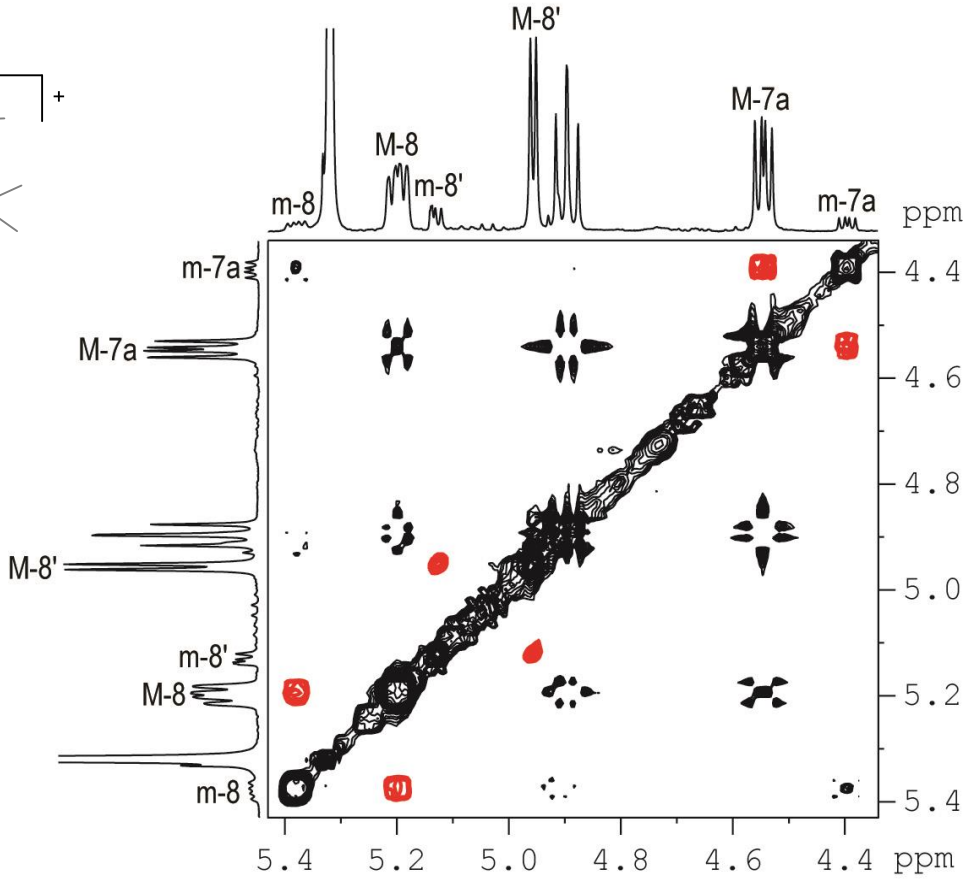


Stefan Gruber

Rapid enantioface exchange of Ir dihydride alkene complexes

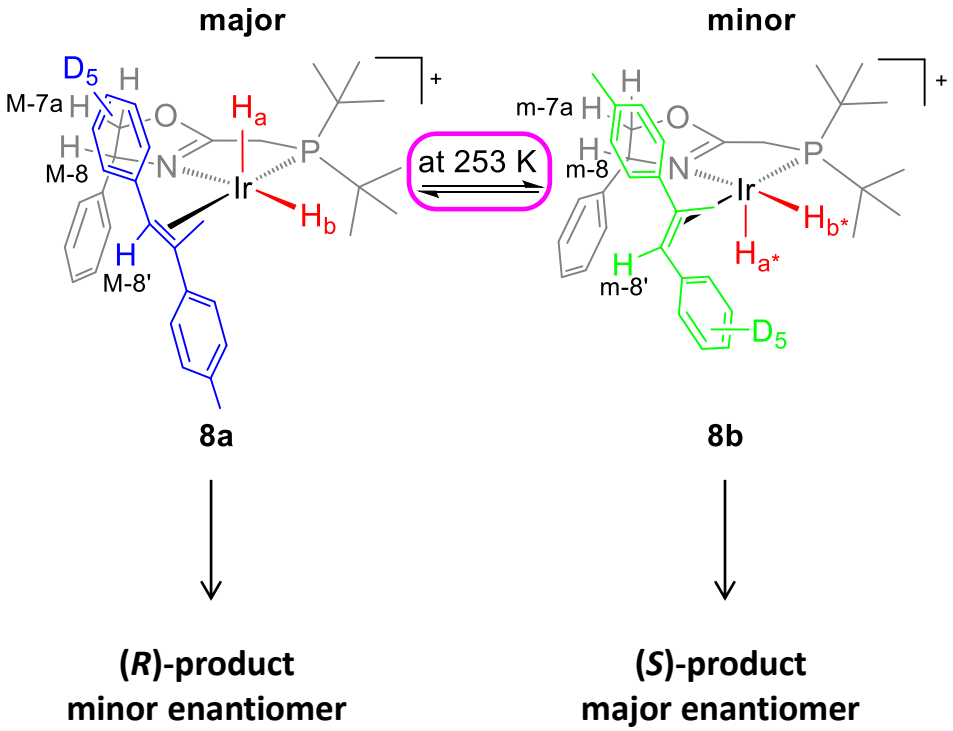


Stefan Gruber, A. P., *Angew. Chem. Int. Ed.* **2014**, *53*, 1896.



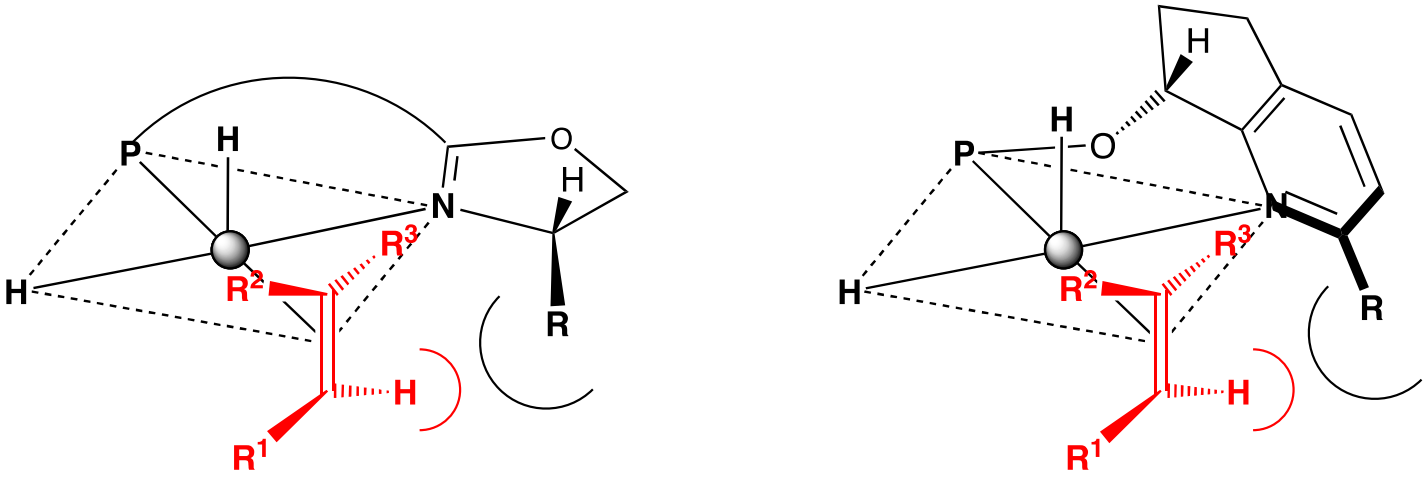
Section of the 2D NOESY spectrum showing the exchange cross-peaks (253 K, 500 MHz, CD_2Cl_2).

Rapid enantioface exchange of Ir dihydride alkene complexes



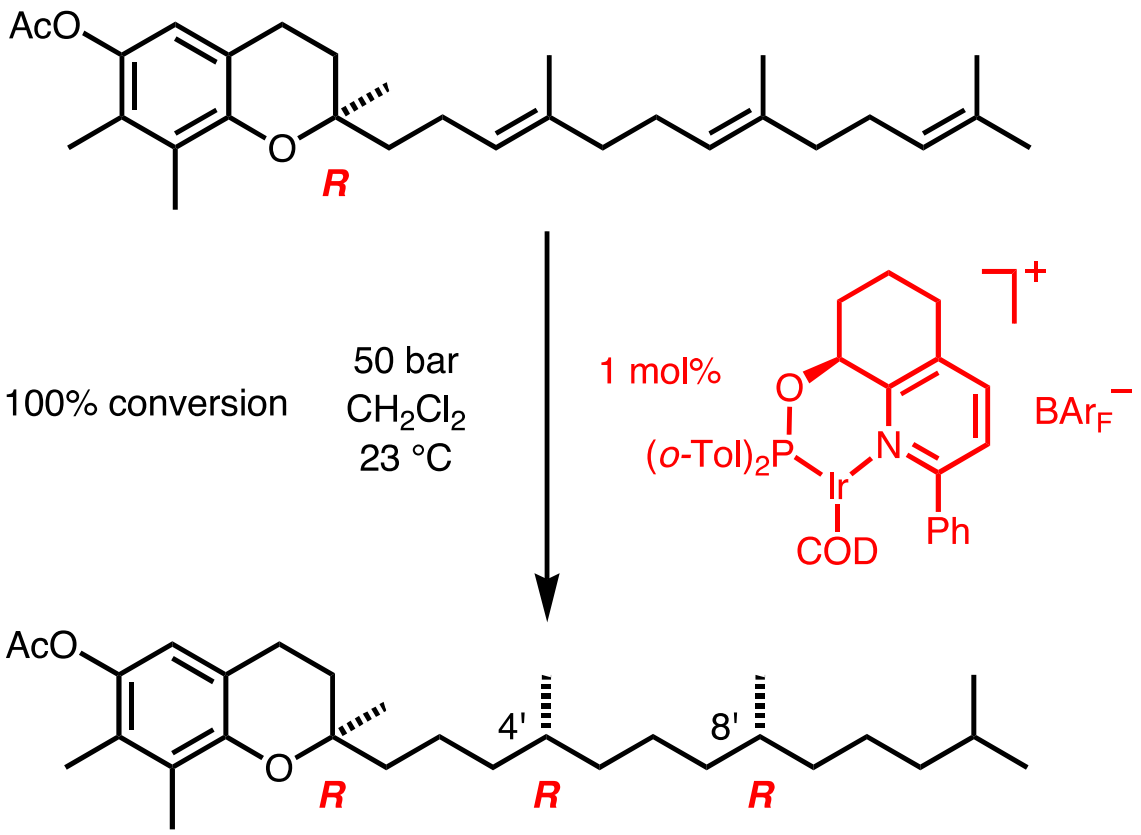
Stefan Gruber

Mechanistic Model



Computational studies: Pher Andersson (Uppsala University)
Kevin Burgess (Texas A&M)
Kathrin Hopmann (University of Tromsø)
Markus Meuwly (University of Basel))

(*R,R,R*)-Tocopherol (Vitamin E)

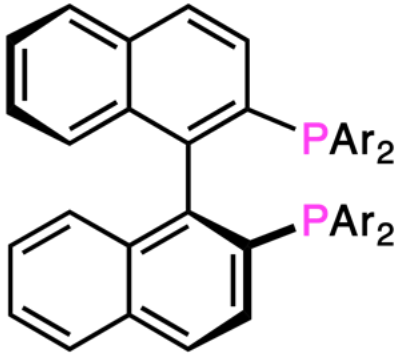


99% *RRR*; < 0.3% *RRS*; < 0.3% *RSR*; < 0.4% *RSS*

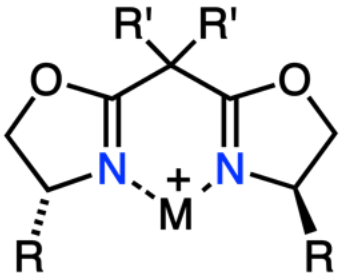
GC analysis: Vecchi et al. *Helv. Chim. Acta* **1990**,*73*, 782.

S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. P. *Science* **2006**, *311*, 642.

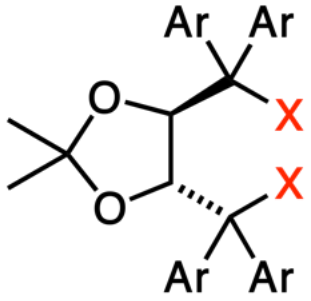
SOME PRIVILEGED LIGAND STRUCTURES



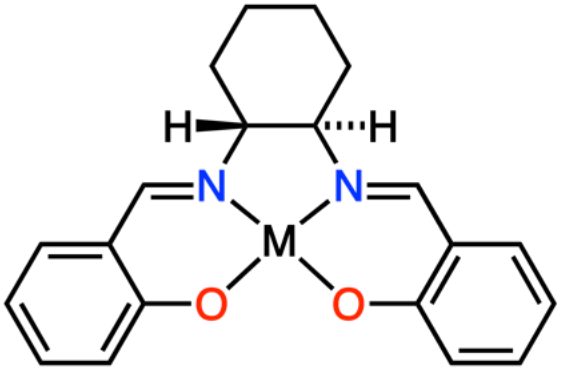
BINAP



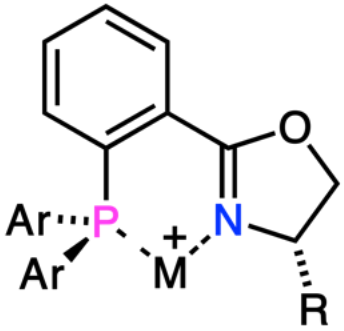
BOX



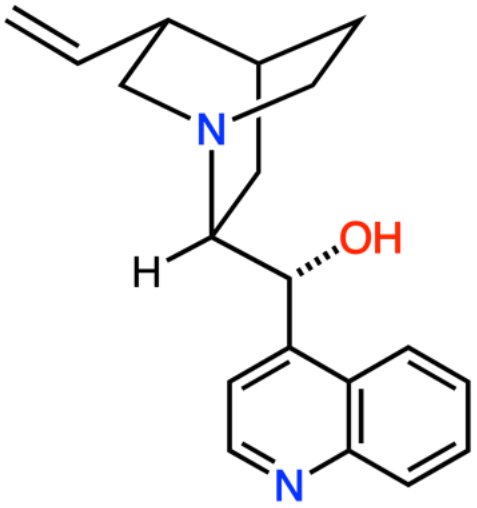
TADDOL



Salen



PHOX



Cinchona Alkaloids