Asymmetric hydroformylation of alkenes

Cyril Godard

Trieste, May 2024

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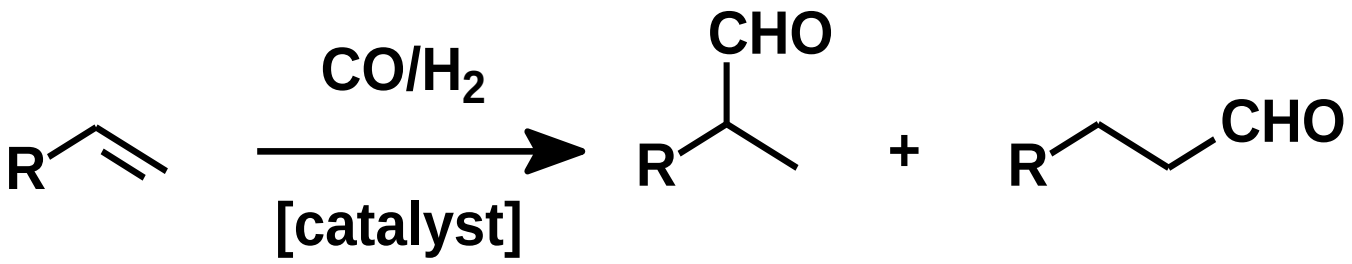
- Hydroformylation of alkenes: general concepts
- Rh-based Mechanism and catalysts
- Type of selectivities in hydroformylation
- Asymmetric hydroformylation: interest and history
- Results according to the type of substrate
- Perspectives

Hydroformylation

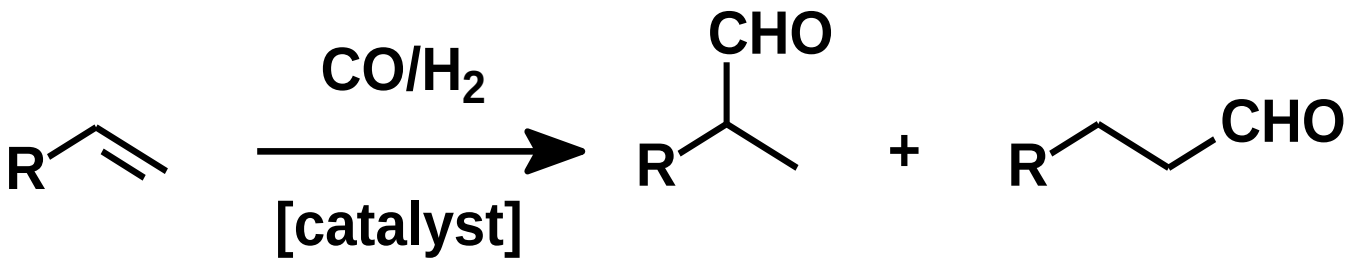


reaction discovered by O. Roelen in 1938 during his work on Fischer-Tropsch synthesis

= addition of CO and H_2 across the π-system of a C=C double bond

Reaction catalysed by various transition metals:
Pt, Pd, **Co**, **Rh**, Ir, Ru, etc…

Hydroformylation



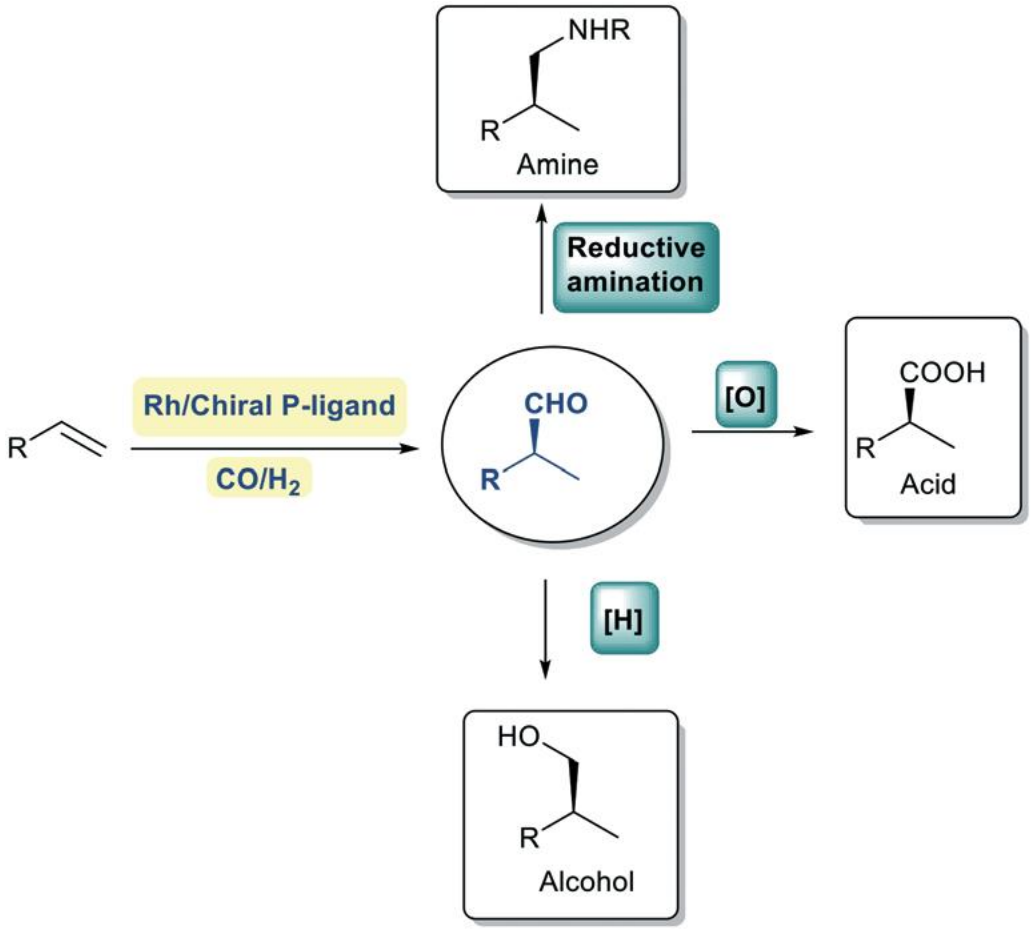
Atom economic process

several million tons of oxo-products are manufactured per year, mainly through the hydroformylation of propene

- Very important reaction for the production of softeners for plastics and detergent alcohols.

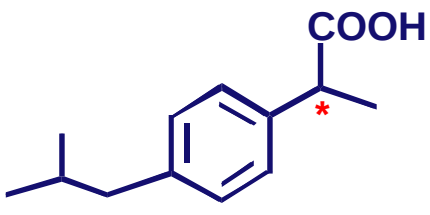
Asymmetric hydroformylation: interest and history

chiral aldehydes are products of interest due to their potential in terms of subsequent functionalization

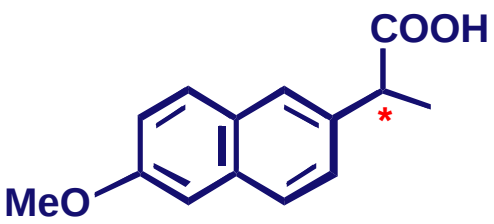


Asymmetric hydroformylation: interest and history

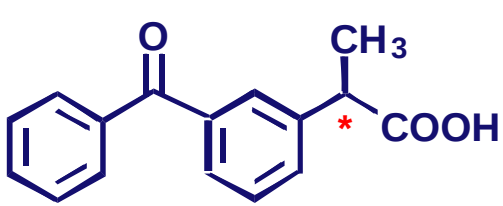
Anti-inflammatory drugs



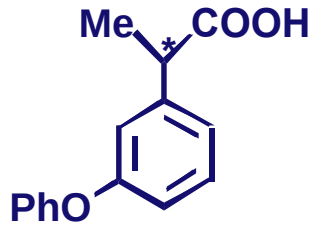
Ibuprofen



Naproxen

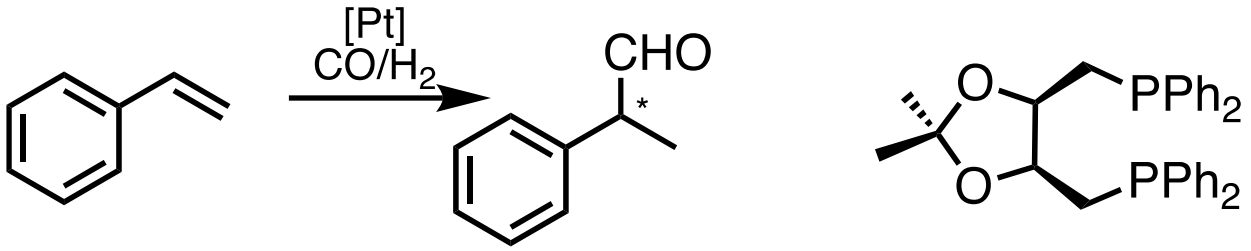


Ketoprofen



Fenoprofen

Asymmetric hydroformylation (AHF)

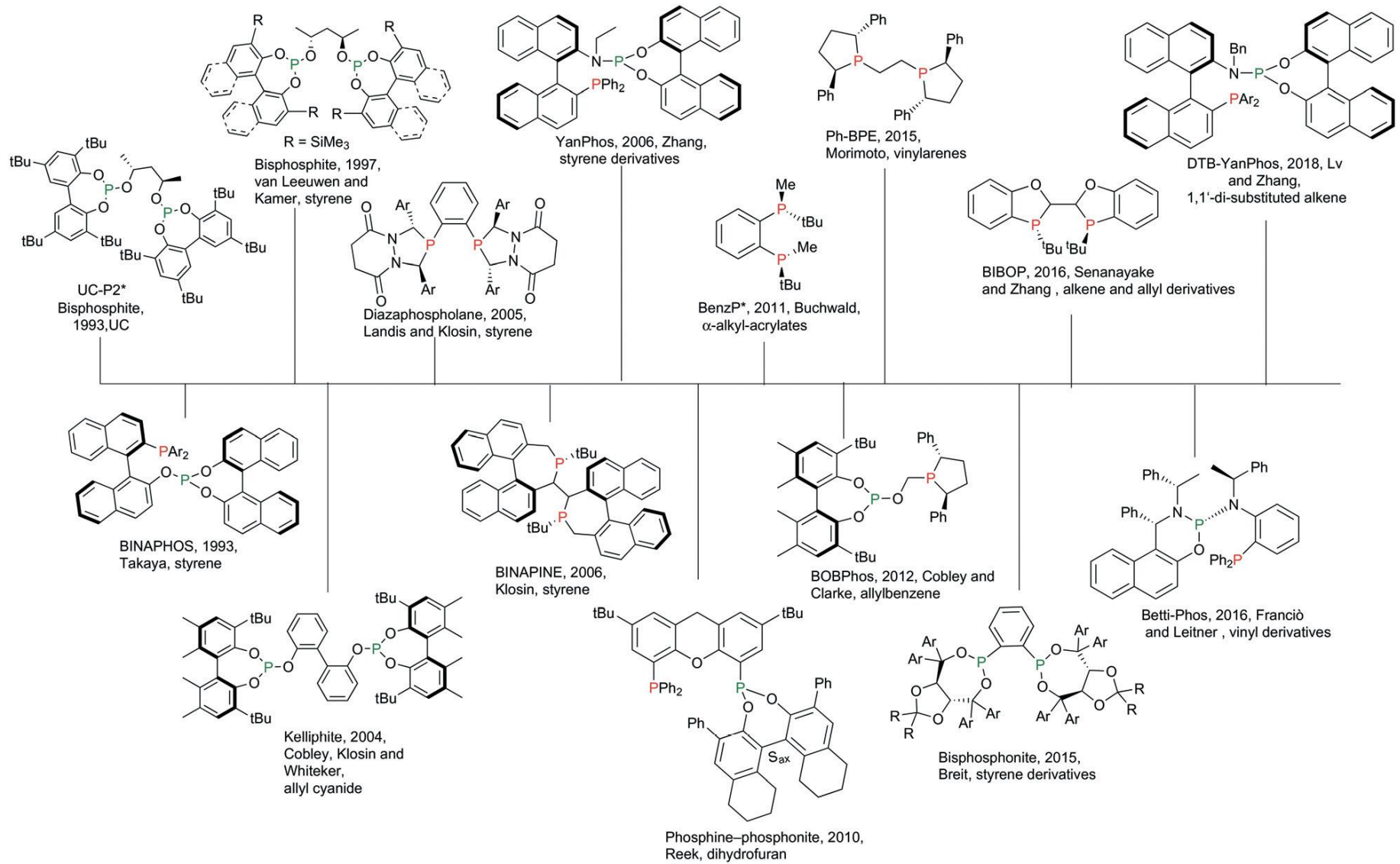


- First high ee's obtained with Pt based catalysts using DIOP type ligands (ee's up to ca. 90%)
  - Low reaction rates
  - Tendency to hydrogenate
  - Low regioselectivity

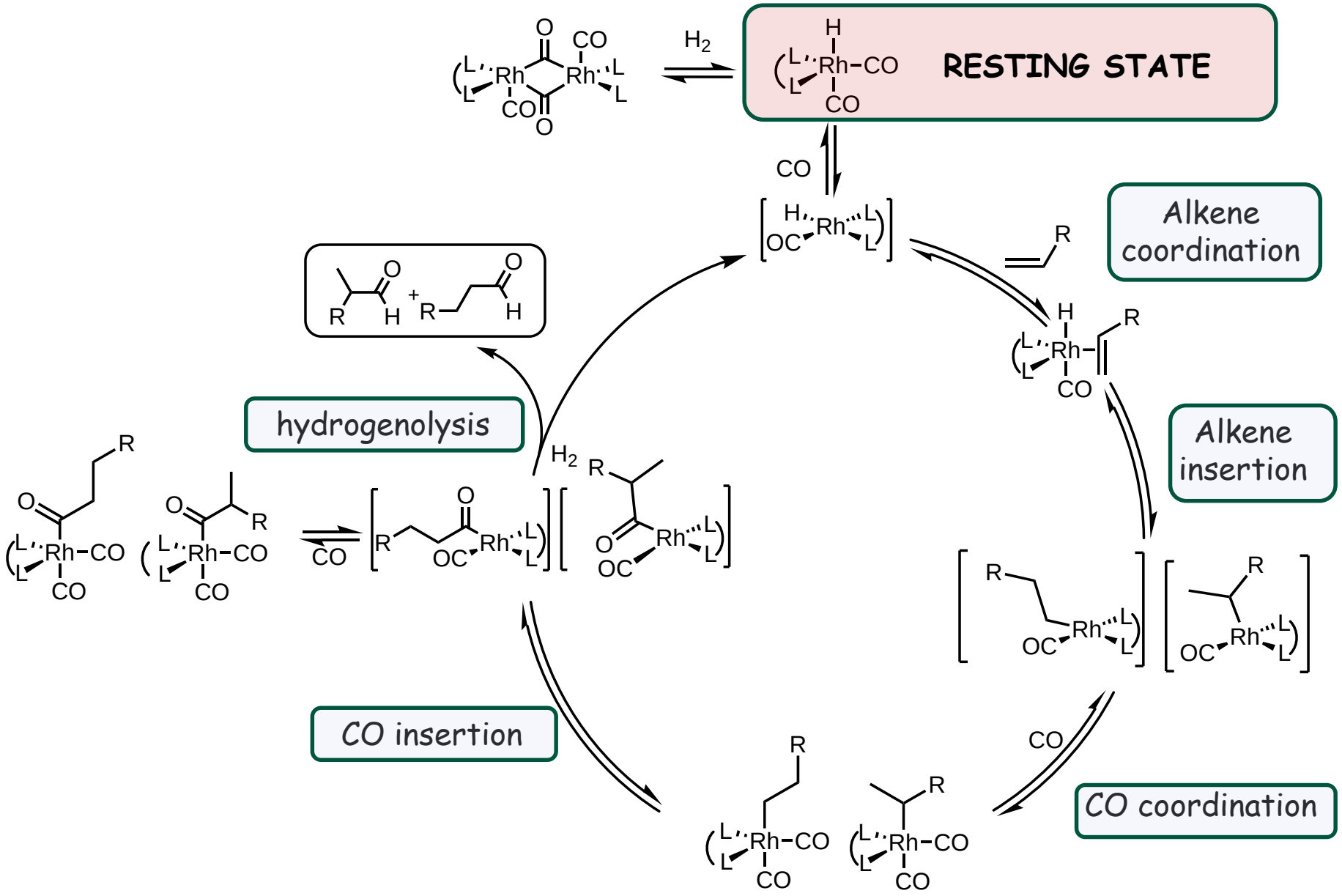
Rhodium

Consiglio, G.; Nefkens, S. C. A.; Borer, A. *Organometallics* **1991**, *10*, 2046-2051; Stille, J. K.; Su, H.; Brechot, P.; Parrinello, G.; Hegedus, L. S. *Organometallics* **1991**, *10*, 1183-1189.

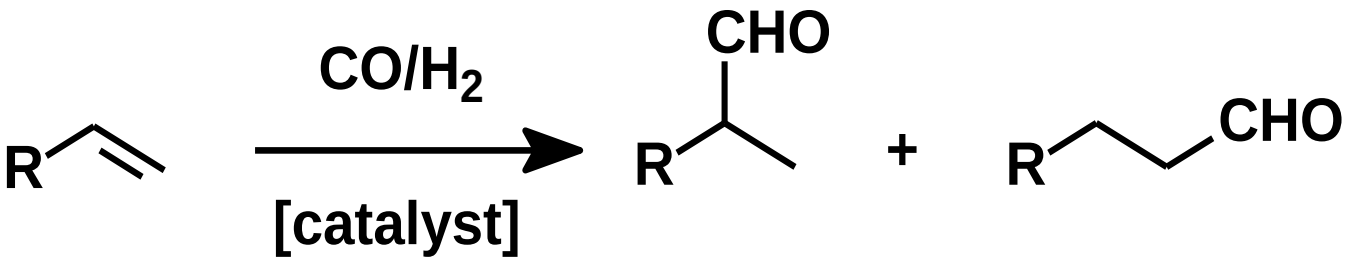
Asymmetric hydroformylation: ligand design



Hydroformylation mechanism



Selectivity in hydroformylation



- **Chemoselectivity**:

hydroformylation vs hydrogenation / isomerization

- Regioselectivity

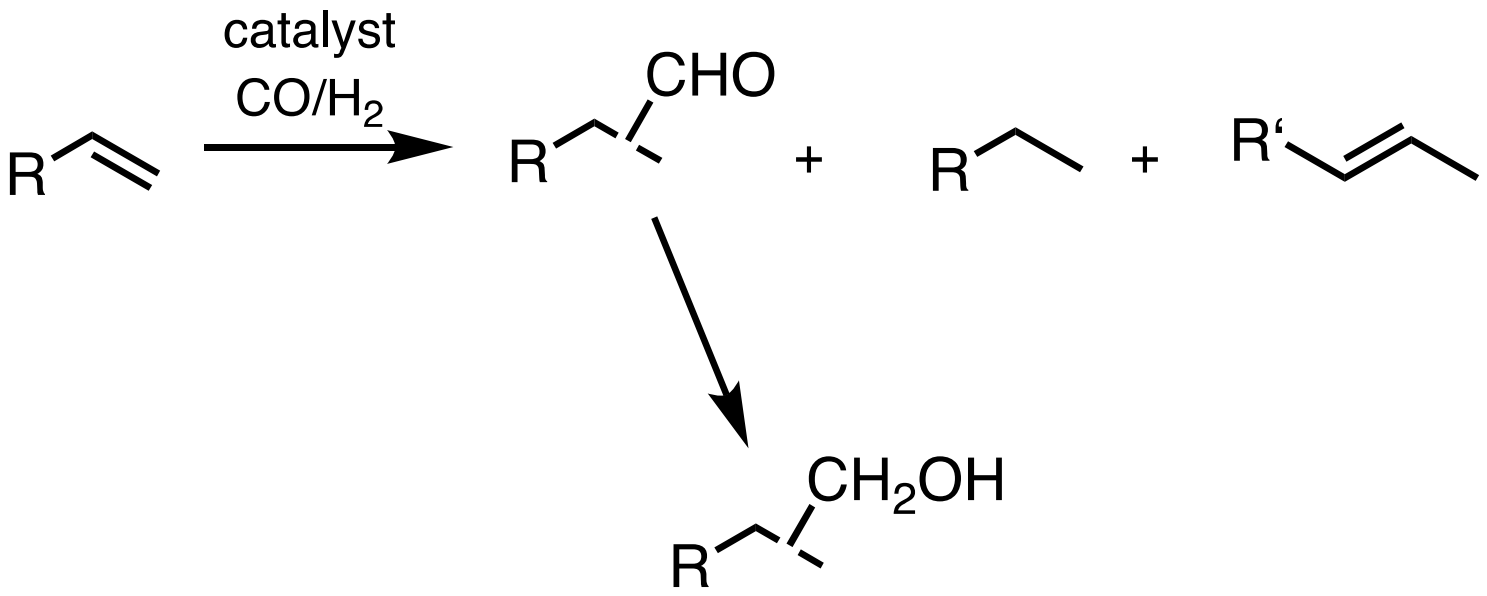
Linear vs branched aldehydes

- Enantioselectivity

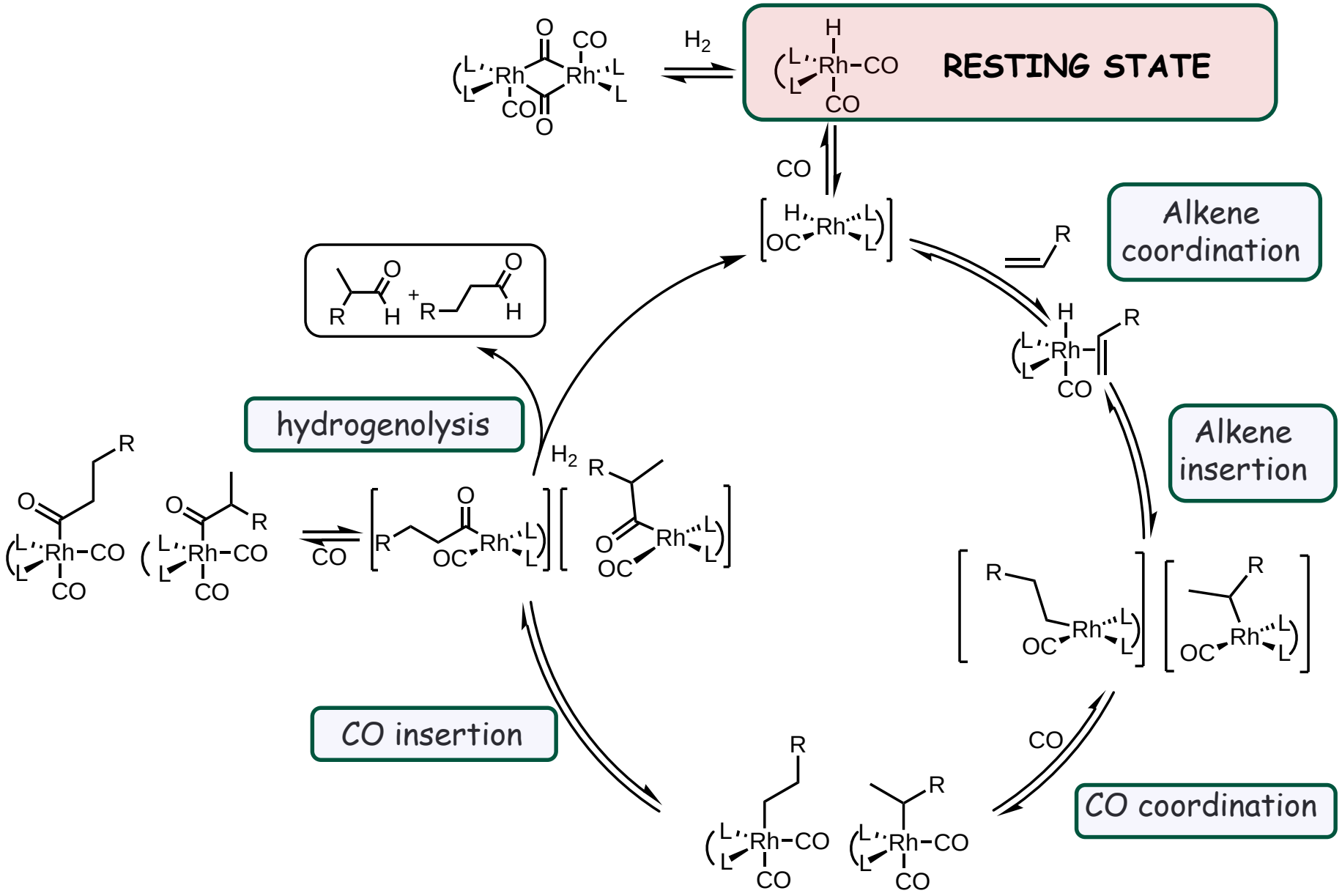
R vs S enantiomer

Chemoselectivity

hydroformylation vs hydrogenation / isomerization

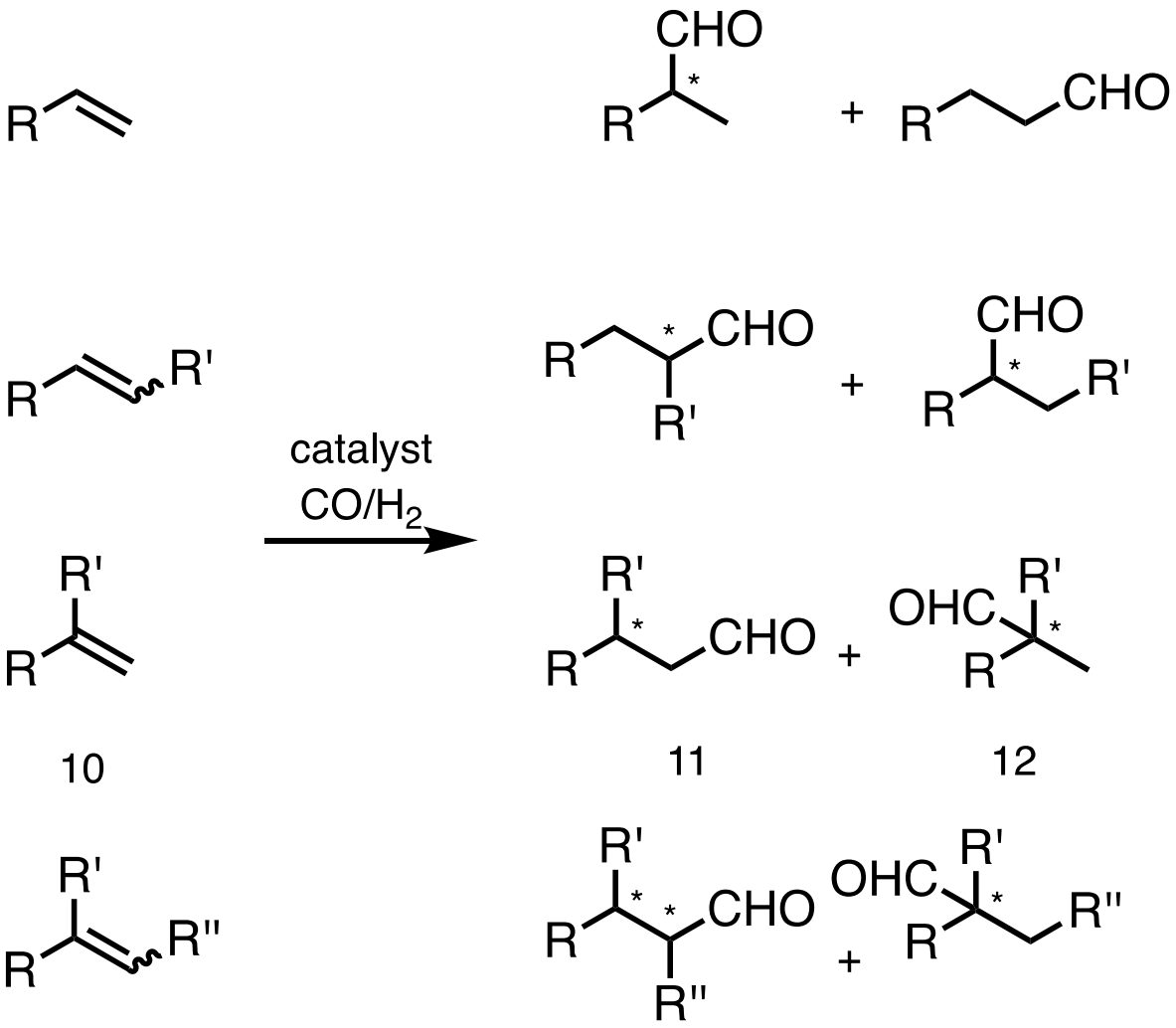


Hydroformylation mechanism

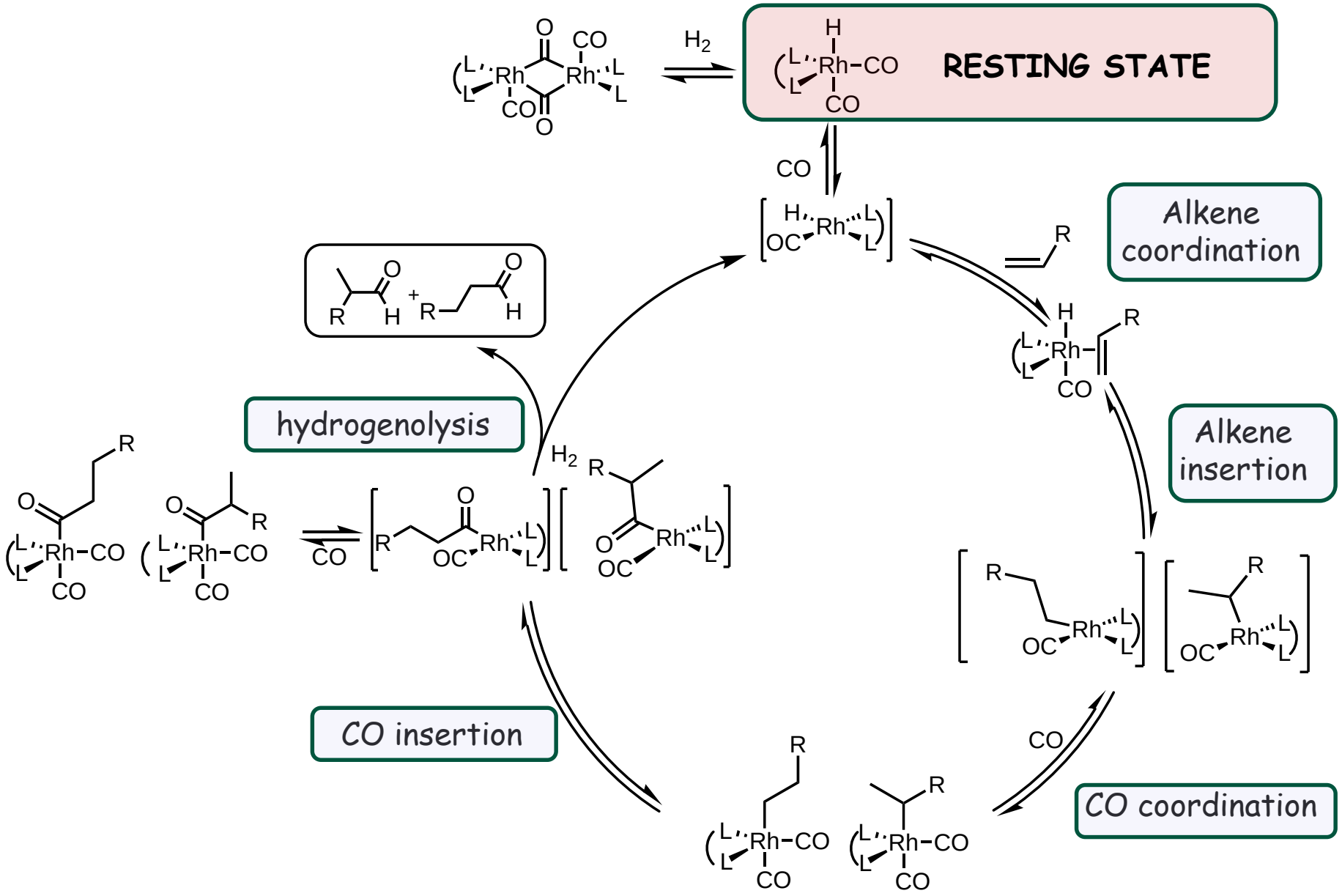


Regioselectivity

Linear vs branched aldehydes

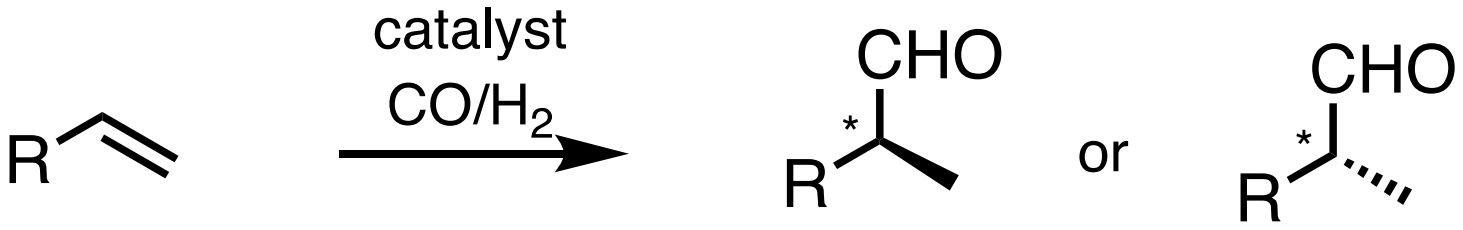


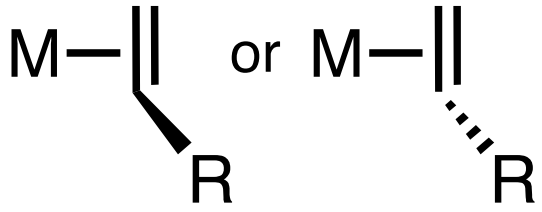
Hydroformylation mechanism



Enantioselectivity

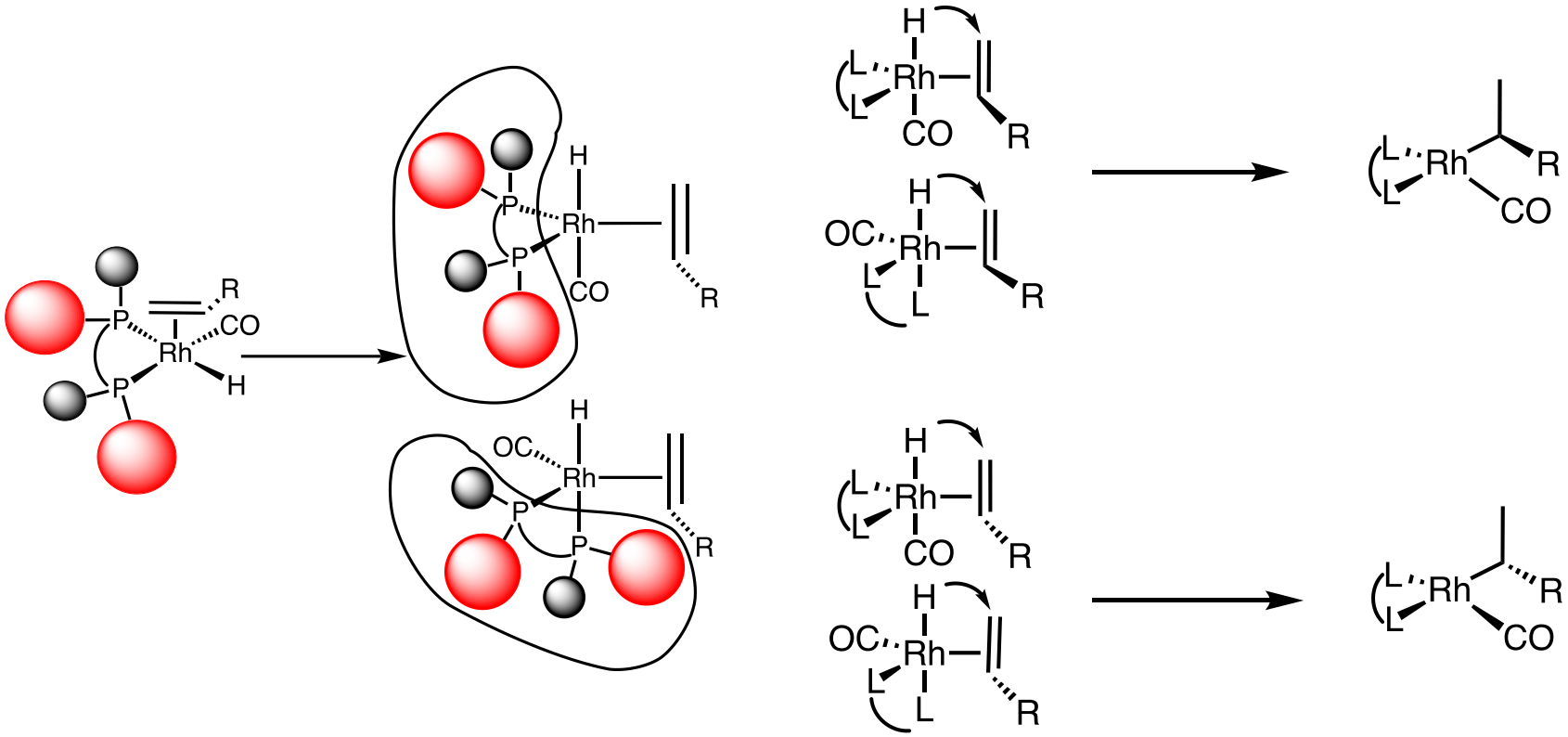
R vs S enantiomer





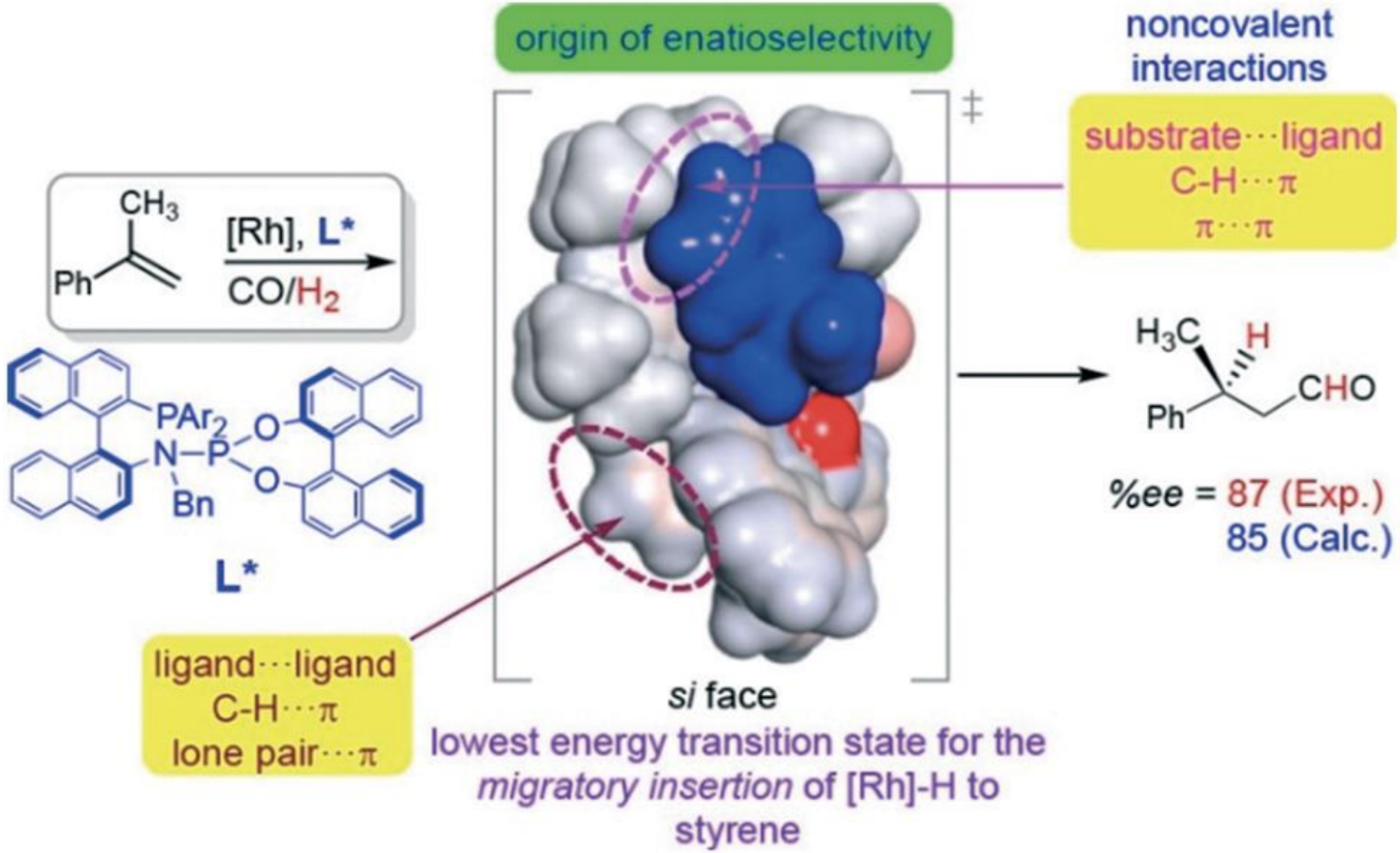
enantioface discrimination

Enantiodiscrimination in Hydroformylation



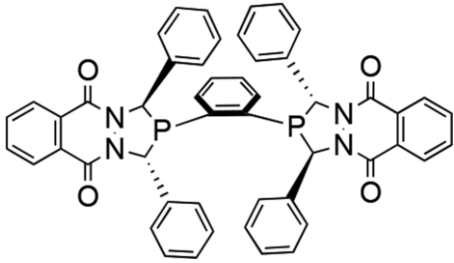
Shape of the chiral pocket influenced by the steric hindrance / interactions induced by the catalyst ligands

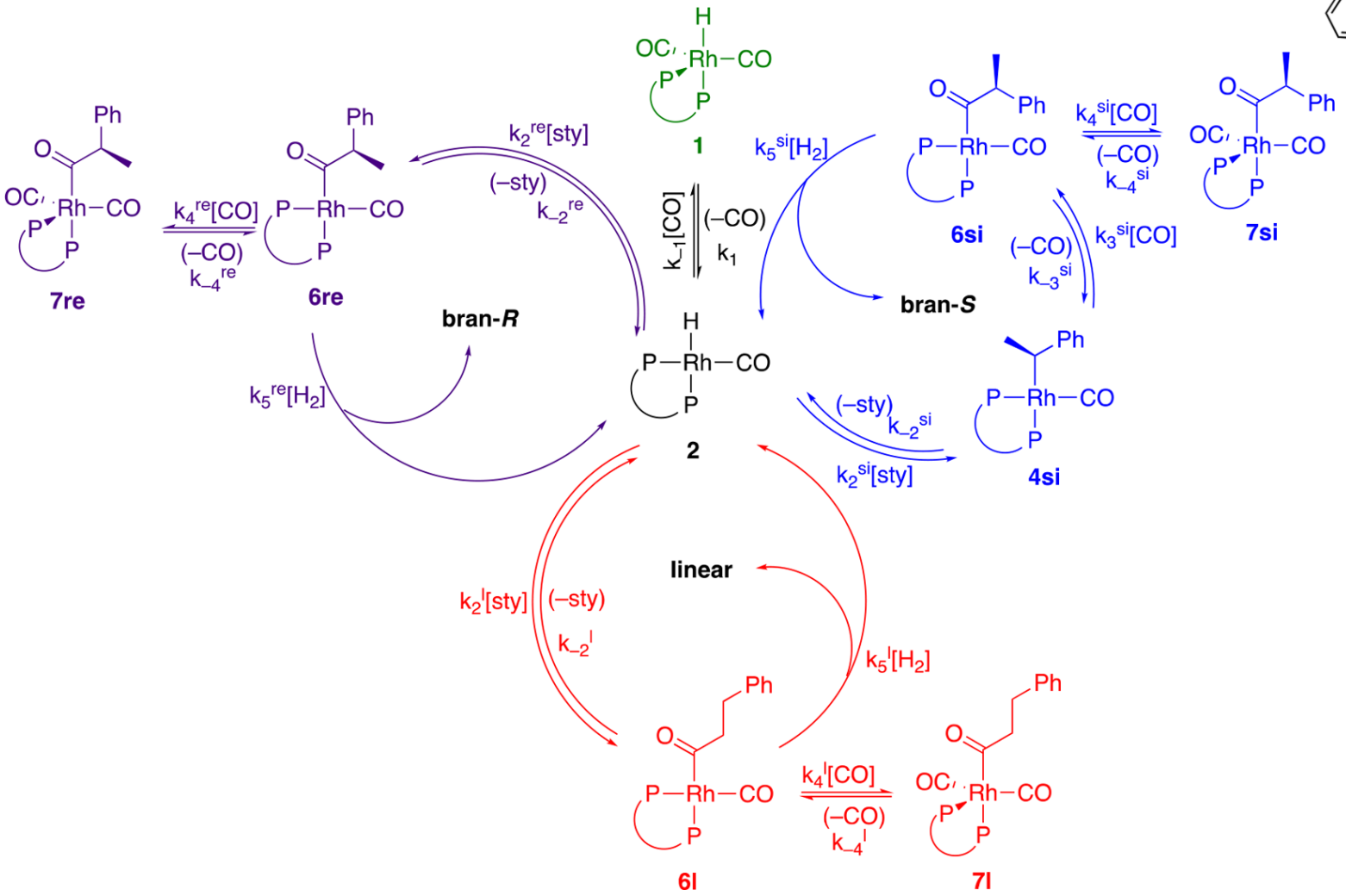
Enantiodiscrimination in Hydroformylation



Importance of non-covalent interactions between the substrate and the catalyst's ligand(s)

Microkinetics in AHF

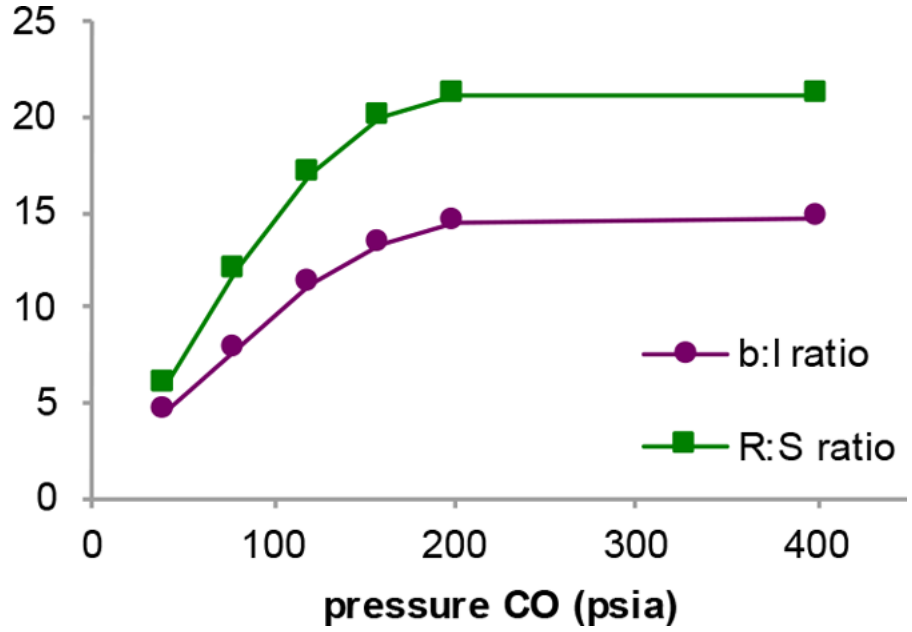




Brezny, A. C.; Landis, C. *ACS Catal*. **2019**, *9*, 2501−2513

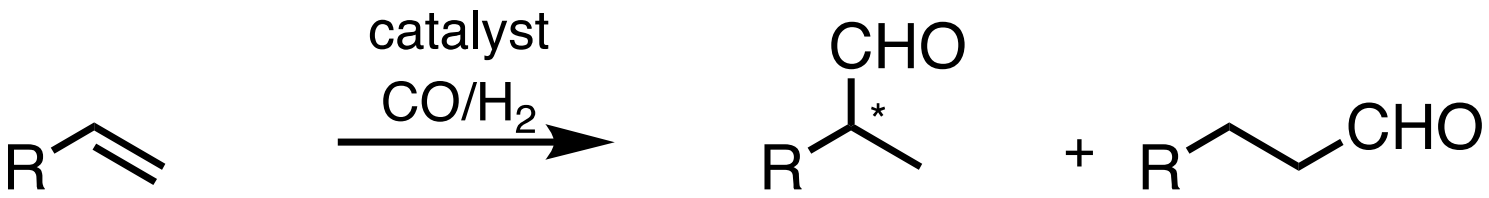
Microkinetics in AHF

Hydroformylation regio- and enantioselectivity depend on CO pressure



hypothesis: a kinetic preference for forming the branched alkyl, but a competing thermodynamic preference for a linear intermediate.

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

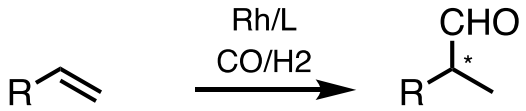


Only the branched aldehyde is chiral

- Vinyl arenes R= Ar
- Allyl cyanide R= CH_2CN
- Vinyl acetate R= OAc

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Diphosphite ligands



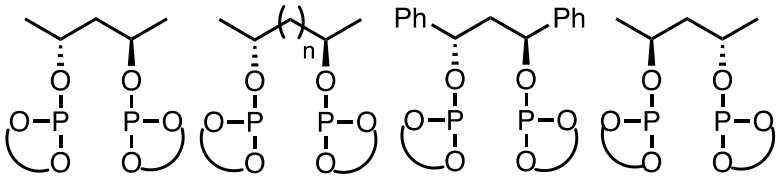
L	Product	Regio (%)	ee (%)
L1a,d	R= Ph	99	90
L1a	R= CH_2CN	87	13
L1a	R= OAc	99	58

(***ee up to 90%*** at 20 bar of syngas and 25 °C)

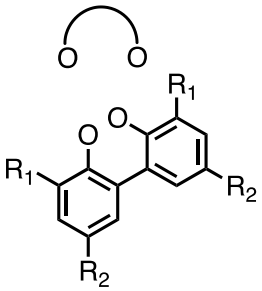
Eq-eq coordination of L1 in resting state

Low to moderate ee for allylcyanide and vinyl acetate

(2*R*, 4*R*)-pentane-2,4-diol diphosphite



(2R, 4R)-**L1** (2R, 3R)- n =0 **L2** (2R, 5R)- n =2 **L3** (2R, 4R)- **L4** (2S, 4S)- **L5**



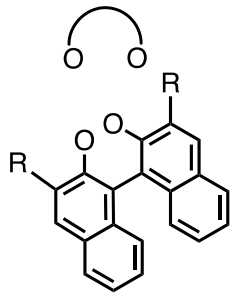
biphenyl

a R_1= tBu; R_2= OMe

b R_1= R_2 = tBu

c R_1= R_2 = H

d R_1= Si(alkyl)$_3$; R_2= H

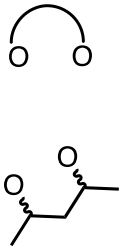


binaphthyl

e (R/S)ax; R = Si(alkyl)$_3$

f (R)ax ; R = Si(alkyl)$_3$

g (S)ax ; R = Si(alkyl)$_3$



pentane-2,4-diol

h (2R, 4R)

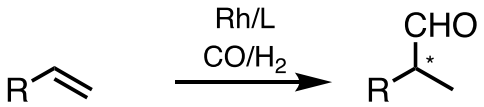
i (2S, 4S)

initial success in the rhodium-catalyzed asymmetric hydroformylation of vinylarenes by Union Carbide

van Leeuwen, P.W.N.M. and coworkers 203rd Meet. of the American Chemical Society, New York, 1992 Abstract I&EC 104; *J. Chem. Soc. Dalton Trans*. **1995**, 409-417; *Organometallics* **1997**, *16*, 2929-2939

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Diphosphite ligands



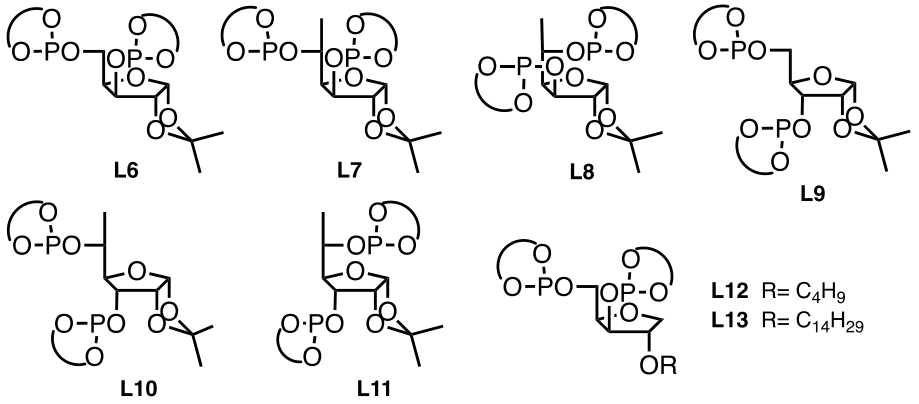
L	Product	Regio (%)	ee (%)
L7a,d	R= Ph	99	93
L7a	R= OAc	99	73

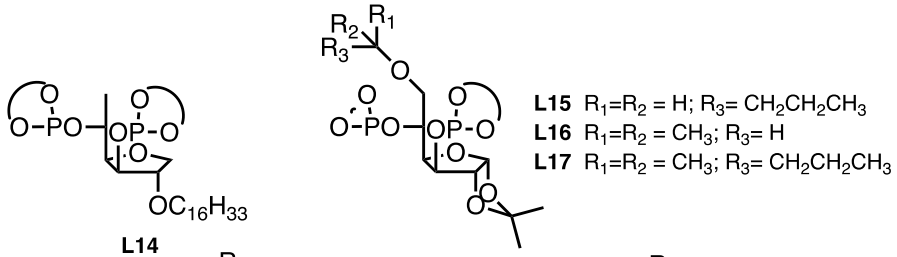
Diphosphites with sugar-based backbone

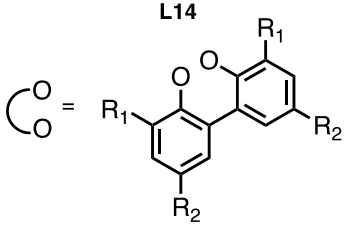
(*ee up to 93%* at 20 bar of syngas and 25 °C)

Eq-eq coordination of L7 in resting state

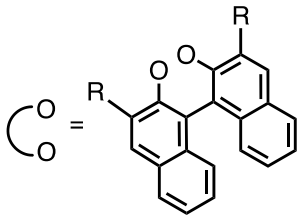
Lower ee for vinyl acetate







biphenyl
a R_1= tBu; R_2= OMe
b R_1= R_2 = tBu
c R_1= R_2 = H
d R_1= Si(alkyl)$_3$; R_2= H

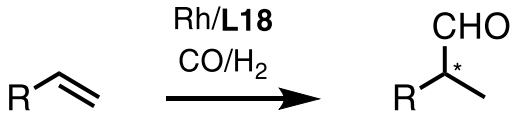


binaphthyl
e (R/S)ax; R = Si(alkyl)$_3$
f (R)ax ; R = Si(alkyl)$_3$
g (S)ax ; R = Si(alkyl)$_3$

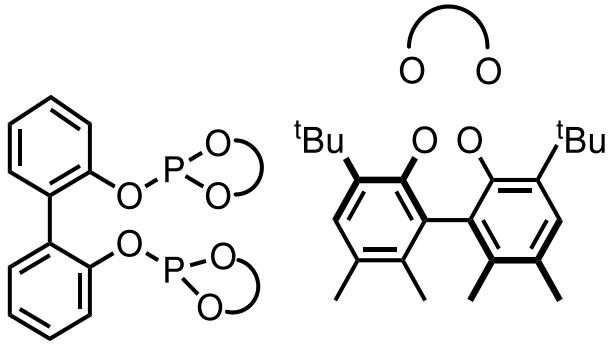
van Leeuwen, P.W.N.M. et al. *Tetrahedron: Asymmetry* **1995**, *6*, 719-738; Claver, C. et al. *Tetrahedron: Asymmetry* **2000**, *11*, 1097-1108; *Chem. Eur. J.* **2001**, *7*, 3086-3094; *New. J. Chem.* **2002**, *26*, 827-833; *Eur. J. Org. Chem.* **2009**, 1191-1201.

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Diphosphite ligands



Product	Regio (%)	ee (%)
R= Ph	98	16
R= CH_2CN	94	78
R= OAc	99	88



KELLIPHITE (**L18**)

developed by Dow Chemical Company

Achiral backbone + chiral bisphenol unit

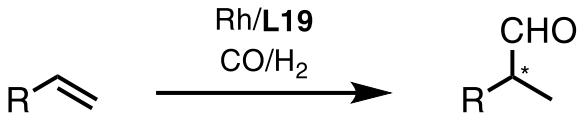
High ee's for vinyl acetate and allyl cyanide but low for styrene

Cobley, C.J.; Klosin, J.; Qin, C.; Whiteker, G.T. *Org. Lett*. **2004**, *6*, 3277-3280; Cobley, C.J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G.T.; Zanotti-Gerosa, A. *J. Org. Chem.* **2004**, *69*, 4031-4040.

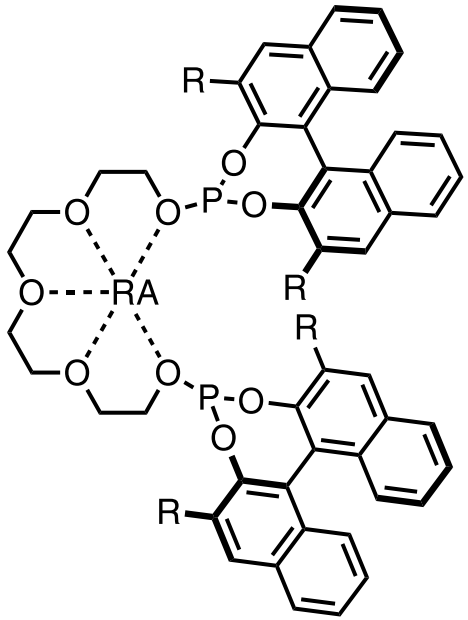
Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Diphosphite ligands

a,w-bisphosphite-polyether ligands



Product	Regio %	ee %
R = OAc	>99	99
R = $EtCO_2$	>99	99
R = $PhCO_2$	>99	96
R = Ph	80	5
R = CH_2OSiMe_3	18	25



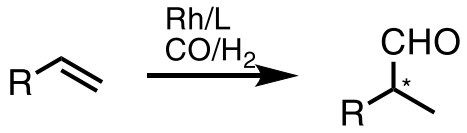
L19 RA = RbBArF

Supramolecularly regulated bisphosphite ligands with a distal regulation site

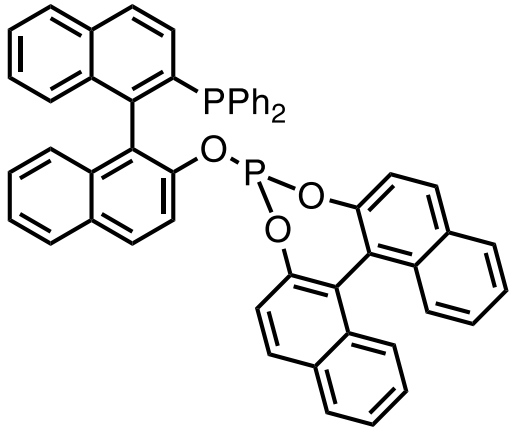
Vidal-Ferran, A.; Mon, I.; Bauzá, A.; Frontera, A.; Rovira, L. *Chem. Eur. J.* **2015**, *21*, 11417-11426; Rovira, L.; Vaquero, M.; Vidal-Ferran, *J. Org. Chem.* **2015**, *80*, 10397−10403

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Phosphine-phosphite ligands



R	Ph	CH_2CN	OAc	C_6F_5	CF_3	Et	Phth	S(4-tolyl)
Regio (%)	90	72	86	96	95	21	89	96
ee (%)	94	66	92	98	93	83	85	74



(R,S)-BINAPHOS (**L20**)
(S,R)-BINAPHOS (**L21**)

significant advance was made in the Rh-catalyzed asymmetric hydroformylation reaction

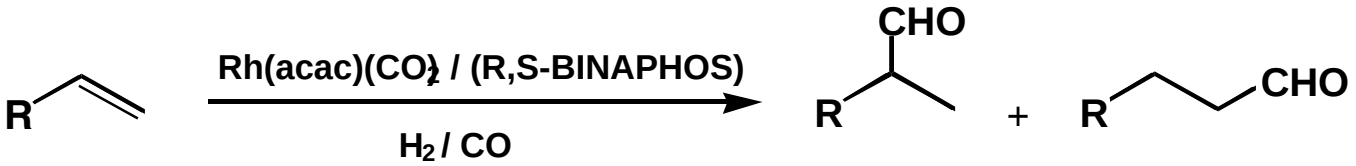
high enantioselectivity for several classes of monosubstituted alkenes

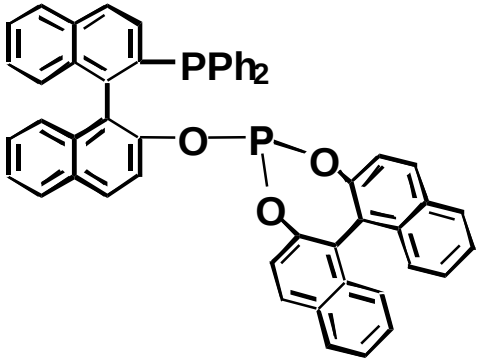
Nozaki, K. *Chem. Record* **2005**, *5*, 376-384 and ref. therein

Phosphine-Phosphite Ligands

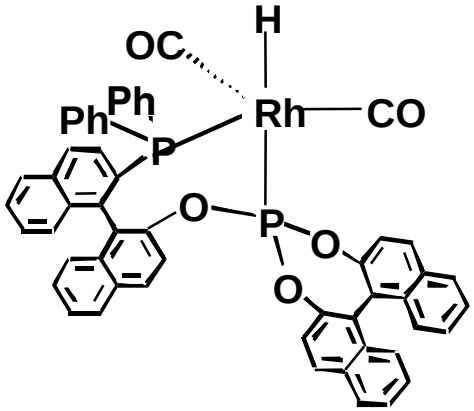
Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

BINAPHOS ligand





T	60 °C
P	100 atm
br(%)	88
ee(%)	94

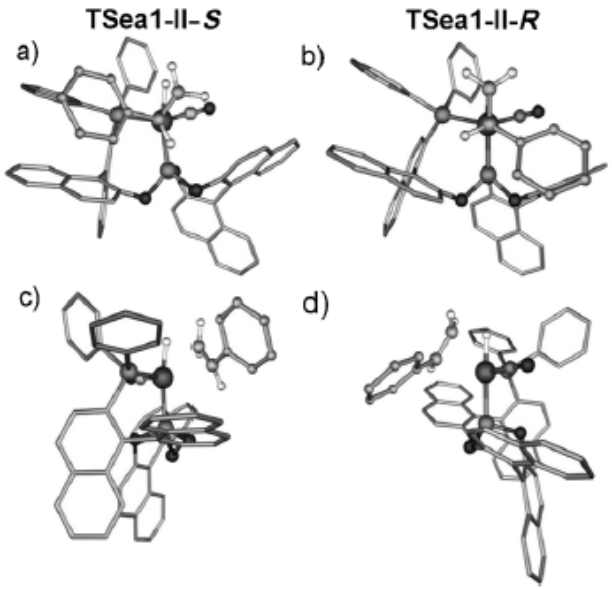


Eq-ax coordination

H. Takaya et al., *J. Am. Chem. Soc* 1993, 115, 7033.

BINAPHOS ligand: DFT calculations

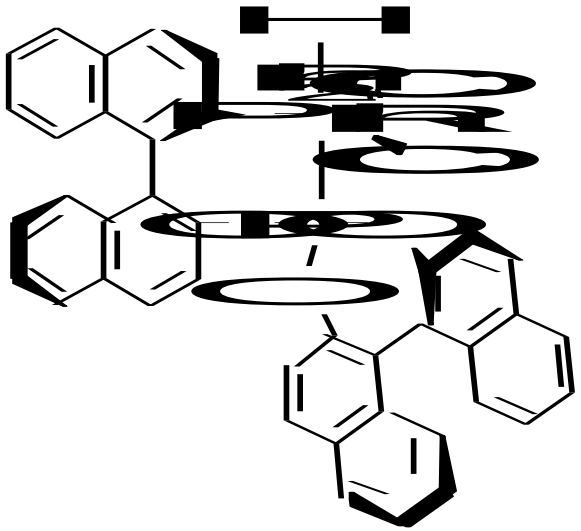
- coordination of this ligand with the phosphite moiety in apical position is key for the stereoselectivity
- the presence of a second chiral center plays a role in determining the *R* or *S* configuration of the aldehyde product



main substrate-ligand interactions occur between the styrene and the phosphite moiety and that these interactions are repulsive in nature

Aguado-Ullate, S.; Saureu, S.; Guasch, L; Carbó, J. *Chem. Eur. J.* **2012**, *18*, 995-1005.

BINAPHOS ligand: match / mismatch



$RhH(CO)_2$(R,S-BINAPHOS)

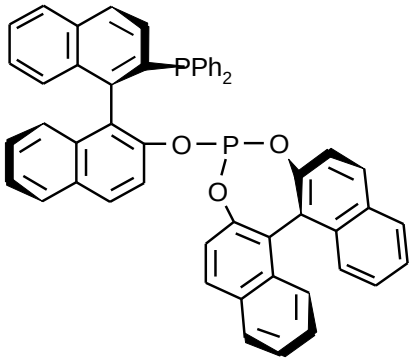
(R,R)	25%ee
(R,S)	85%ee

Importance of the combination of chiral units

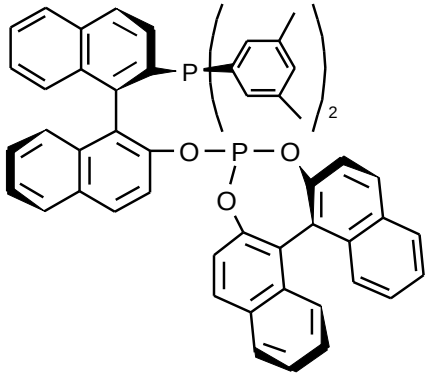
Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413-4423

Asymmetric Hydroformylation match-mismatch effects BINAS

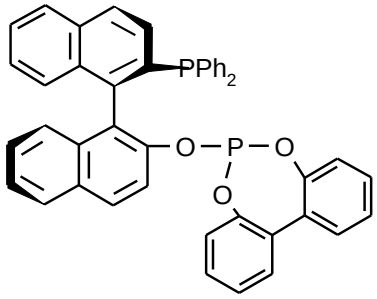
Ligand	% e.e.
46 (S,R)	94 (S)
46 (R,R)	25 (R)
47 (R,S)	85 (R)
48 (R,--)	83 (R)
49 (S,R)	94 (S)
49 (R,R)	16 (R)
50 (--,R)	69 (S)



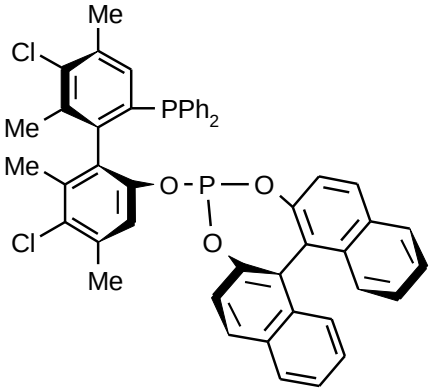
46 (R,S)-BINAPHOS



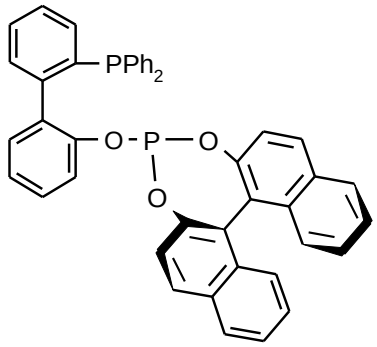
47 (R,S)



48(R)



49a (S,R)
49b (R,R)



50 (R)

J. Am. Chem. Soc. **1998**, *120*, 4051−4052

Asymmetric Hydroformylation of Olefins in a Highly Cross-Linked Polymer Matrix

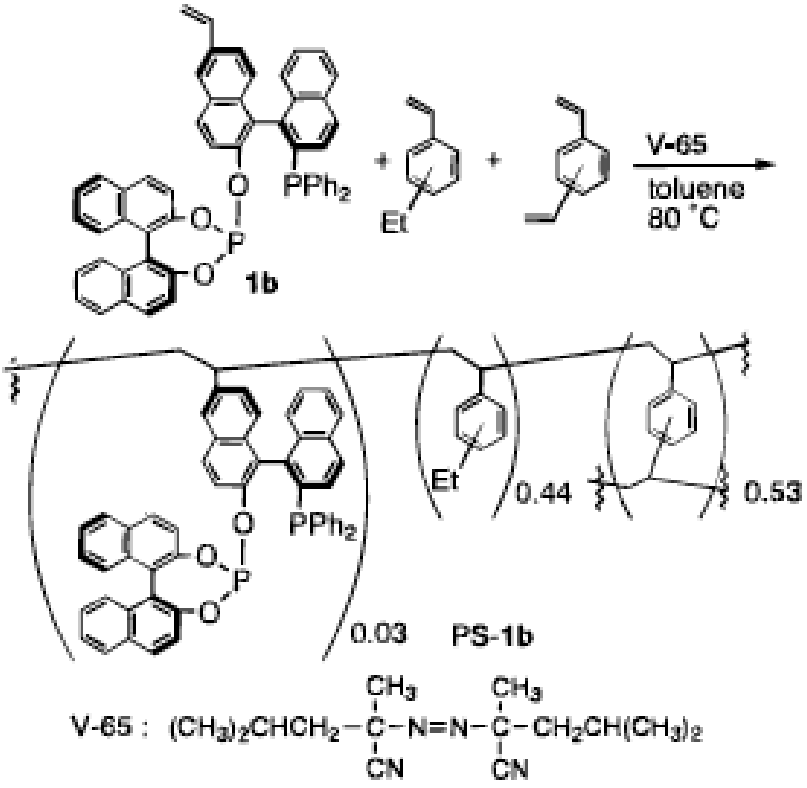


Table 1. Asymmetric Hydroformylation of Styrene Catalyzed by Polymer-Supported (*R*,*S*)-BINAPHOSs[a]

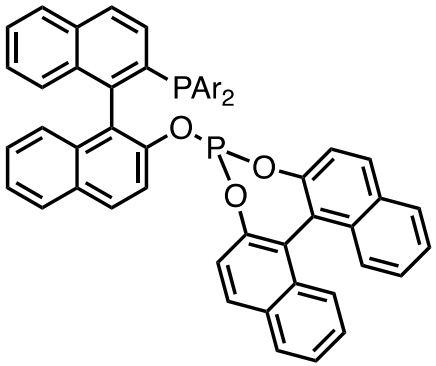
run	catalyst	*i*-/*n*-	ee (%)	run	catalyst	*i*-/*n*-	ee (%)
1	Rh(acac)(**1a**)	89:11	92	7	(PS-**1c**)−Rh(acac)	89:11	89
2	(PS-**1b**)−Rh(acac)	84:16	89	8	(PS-**1d**)−Rh(acac)	88:12	68
3[b]	(PS-**1b**)−Rh(acac)	83:17	89	9	PS-[Rh(acac)(**1b**)]	85:15	90
4[c]	(PS-**1b**)−Rh(acac)	80:20	81	10	PS-[Rh(acac)(**1c**)]	90:10	87
5[d]	(PS-**1b**)−Rh(acac)	84:16	89	11	PS-[Rh(acac)(**1d**)]	87:13	85
6[d]	(PS-**1b**)−Rh(acac)[e]	79:21	86				

Table 2. Asymmetric Hydroformylatyion of Vinyl Acetate Catalyzed by Polymer-Supported (*R*,*S*)-BINAPHOS[a,b]

run	catalyst	convn (%)	*i*-/*n*-	ee (%)
1	Rh(acac)(**1a**)	98	84:16	92
2	(PS-**1b**)−Rh(acac)	75	85:15	91
3	(PS-**1c**)−Rh(acac)	54	90:10	92
4	(PS-**1d**)−Rh(acac)	61	87:13	78
5	PS-[Rh(acac)(**1b**)]	67	87:13	92
6	PS-[Rh(acac)(**1c**)]	83	90:10	93
7	PS-[Rh(acac)(**1d**)]	78	90:10	89

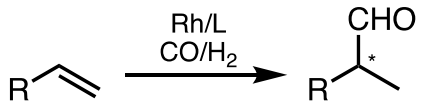
Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Phosphine-phosph(oramid)ite ligands

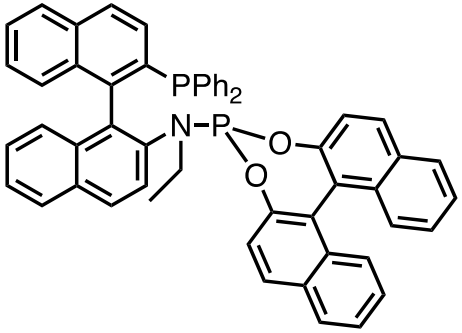


L22 Ar = 3-$MeOC_6H_4$

L22	Regio(%)	ee(%)
R= Ph	95	97
R= 2-vinylfuran		79
R= 3-vinylfuran		99
R= 2-vinylthiophene		93
R= 3-vinylthiophene		91



second generation of Binaphos type ligands



(*R,S*)-Yanphos (**L23**)

L23	Regio(%)	ee(%)
R= Ph	89	99
R= CH_2CN	80	96
R= OAc	93	98
R= CH_2NHBOC	66	94
R= CH_2NBz	78	95
R= $CH_2NHPhthaloyl$	84	96
R= CH_2NHSO_2(p-MeOPh)	71	96

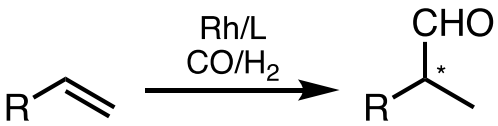
increased regio- and enantioselectivity in the AHF of styrene, vinylfuranes, and thiophenes

Zhang, X. and coworkers *J. Am. Chem. Soc.* **2006**, *128*, 7198-7202; *Org. Chem. Front.* **2017**, *4* (2), 288–291.

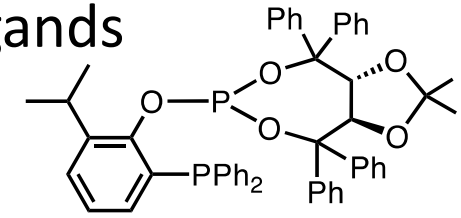
Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Phosphine-phosphite ligands

Taddol-based ligands

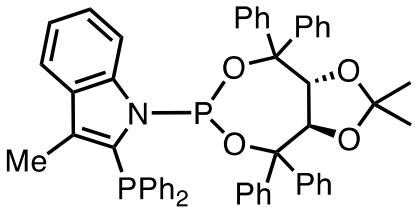


L24	Regio(%)	ee(%)
R= Ph	98	85



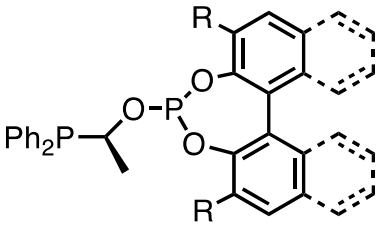
L24

L25	Regio(%)	ee(%)
R= Ph	97	71
R= CH_2CN	82	59
R= OAc	94	74

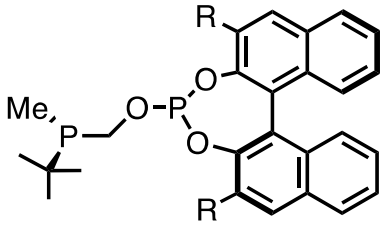


INDOLPHOS (**L25**)

		Regio(%)	ee(%)
L26a	R= Ph	99	57
	R= OAc	99	74
L26b	R= Ph	95	64
	R= OAc	95	61

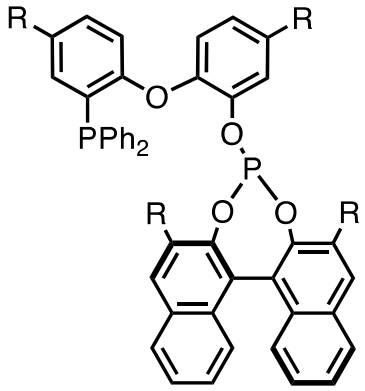


L26a



L26b

L27	Regio(%)	ee(%)
R= Ph	91	35

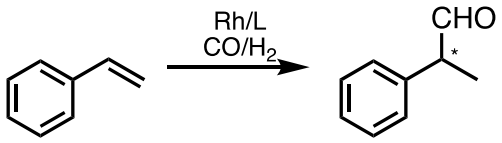


L27

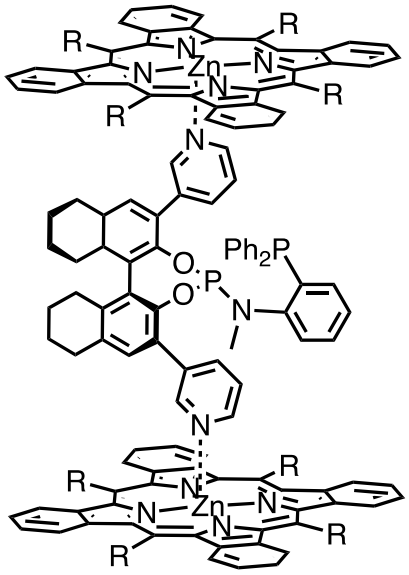
Reek, J. N. H. and coworkers *Organometallics* **2010**, *29*, 478-483; *Organometallics* **2010**, *29*, 2767-2776.

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

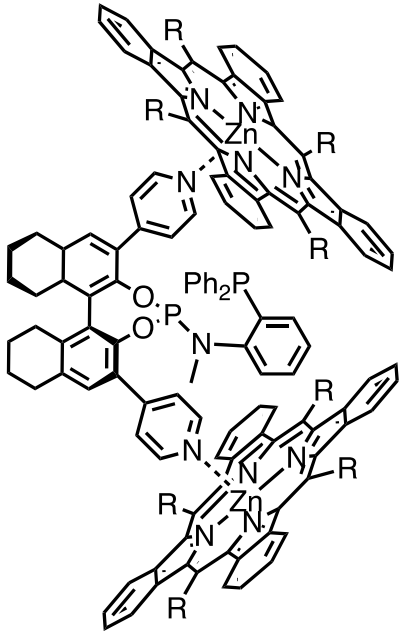
Supramolecular Phosphine-phosphoramidite ligands



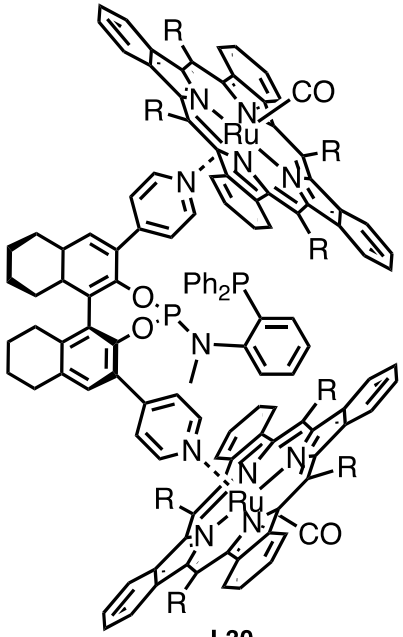
L	Regio (%)	ee(%)
L28	94	52
L29	99	51
L30	92	59



L28



L29



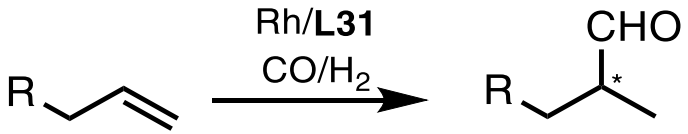
L30

electronic and steric properties of the M(II) (M=Zn, Ru) templates had a significant effect on the outcome of the reaction

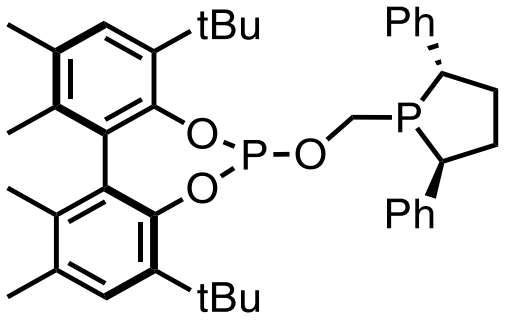
Bellini, R.; Reek, J. N. H. *Chem. - A Eur. J.* **2012**, *18* (42), 13510–13519.

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Phosphine-phosphite ligands



L31	regio (%)	ee (%)
R= Ph	80	90
R= C_6F_5	86	91
R= 4-*t*-BuC_6H_4	75	92
R= Bn	70	75
R= Pr	75	93
R= CN	89	71
R= CONPh(Me)	82	92



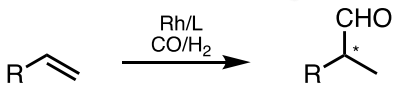
($S_{ax}S,S$)-Bobphos (**L31**)

High regio- and ee's for this type of substrate for the first time

Noonan, G.M.; Fuentes, J.A.; Cobley, C.J.; Clarke, M.L *Angew. Chem. Int. Ed*. **2012**, *51*, 2477-2480.

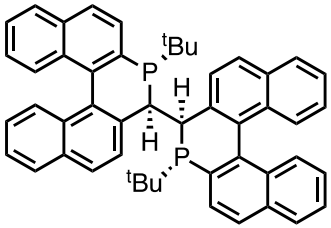
Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Bisphosphacyclic ligands

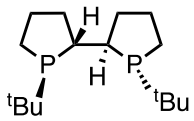


L	R= Ph		R= CH_2CN		R= OAc	
	Regio (%)	ee(%)				
L32	90	94	87	94	97	87
L33	93	90	88	93	97	83
L34	91	67			96	82
L35a	98	94	88	90	99	82
L36					94	89
L37a	97	82	83	87	98	96

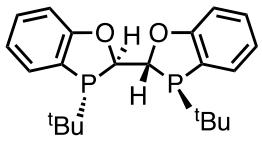
highest ever reported for the allyl cyanide



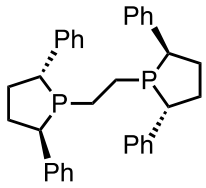
(*R,S*)-Binapine (**L32**)



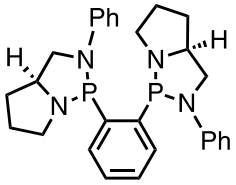
(*S,S,R,R*)-Tangphos (**L33**)



(*R*)-BIBOP (**L34**)

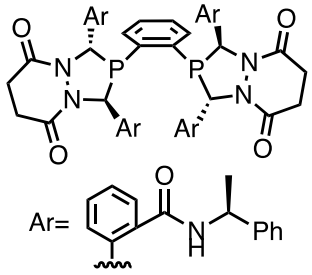


(*R,R*)-Ph-BPE (**L35a**)



Esphos (**L36**)

Tetrahedron: Asymmetry, **2004**, *15*, 1787-1792.

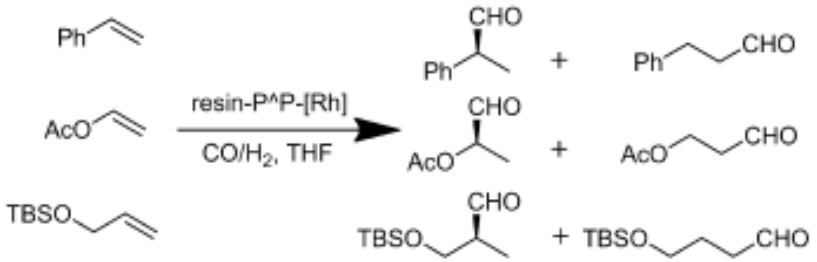


Bis-3,4-diazaphospholane (**L37a**)

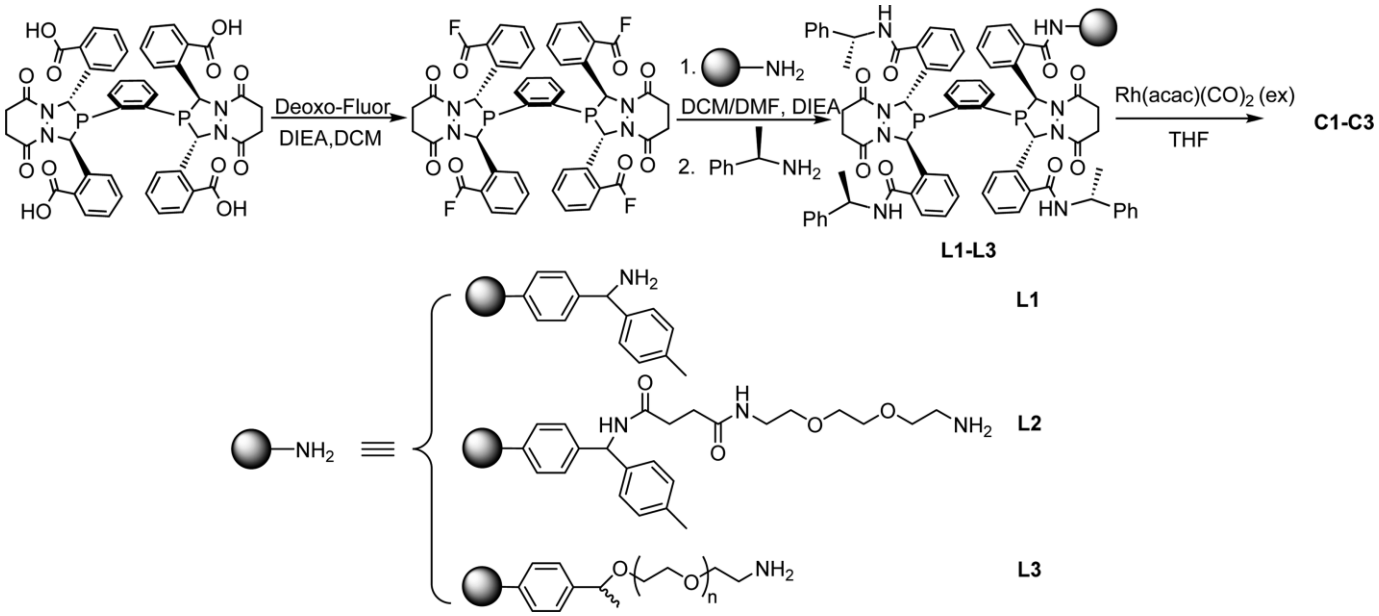
bis-2,5-diazaphospholanes

Landis, C.R.; and co-workers *J. Am. Chem. Soc.* **2005**, *127*, 5040-5042; *J. Am Chem. Soc.* **2015**, *137*, 14208-14219; *Organometallics* **2017**, *36* (16), 3142–3151.

Immobilized Bisdiazaphospholane Catalysts



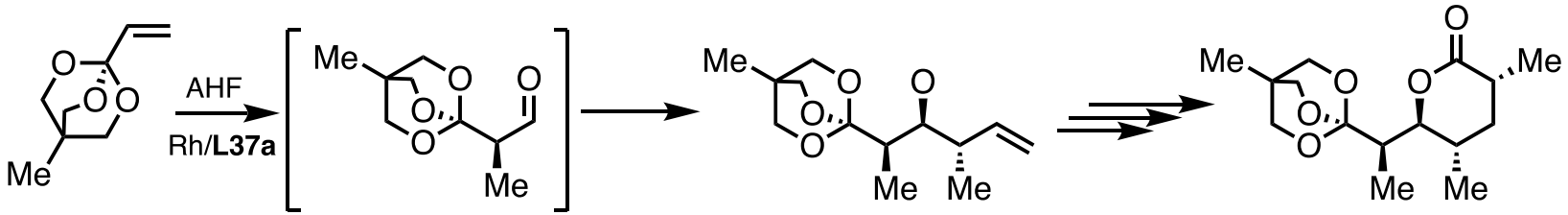
Ee's up to 92%



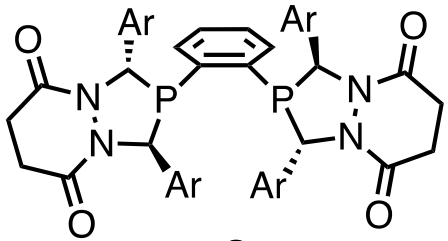
Adint, T. T.; Landis, C. R. *J. Am. Chem. Soc.* **2014**, *136* (22), 7943–7953.

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Synthesis of the Prelog-Djerassi Lactone via asymmetric hydroformylation/crotylation tandem sequence



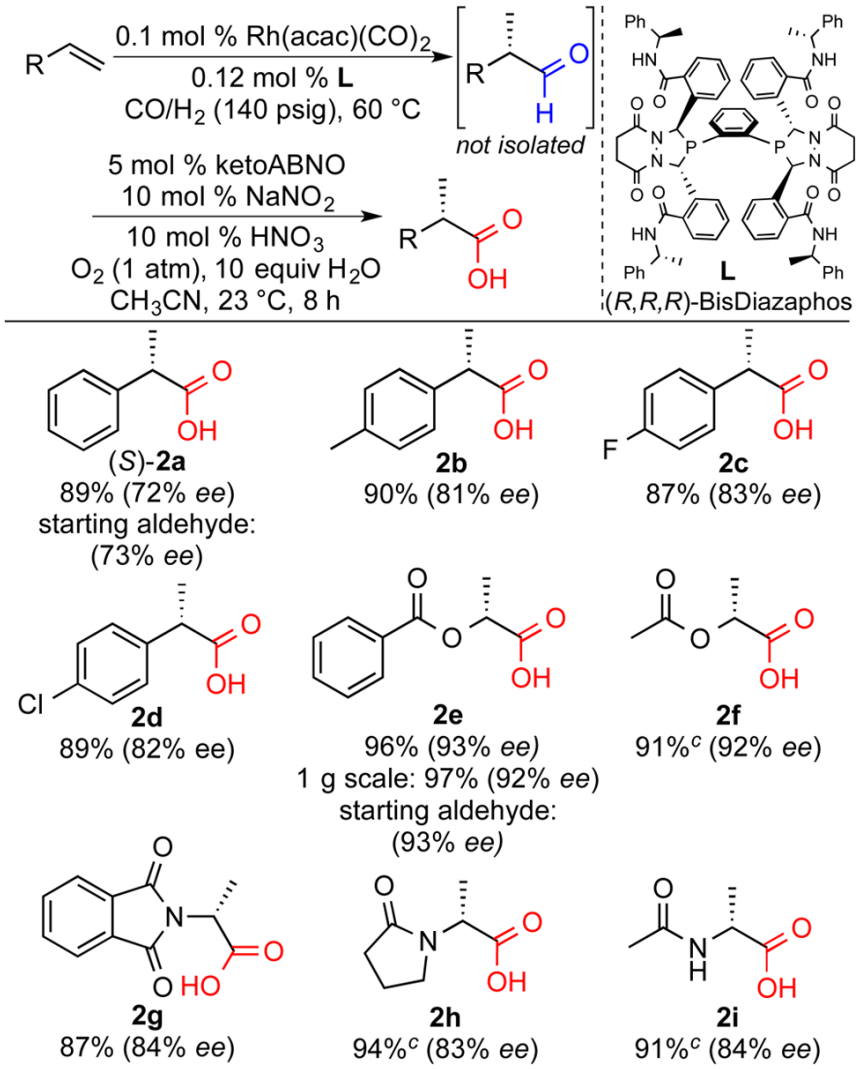
100 conv.
93% ee



Bis-3,4-diazaphospholane (**L37a**)

Risi, R. M.; Burke, S. D. *Org. Lett*. **2012**, *12*, 2572-2575.

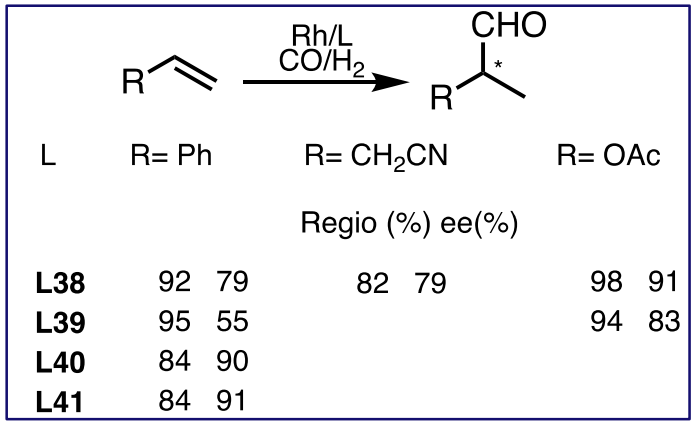
Sequential Asymmetric Hydroformylation/Oxidation



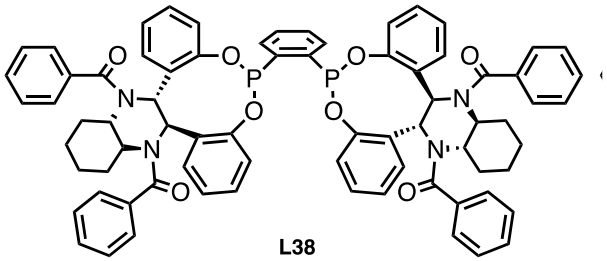
Miles, K. C.; Abrams, M. L.; Landis, C. R.; Stahl, S. S. *Org. Lett*. **2016**, *18*, 3590-3593.

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

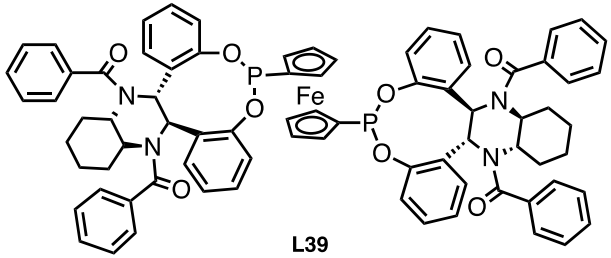
Bisphosphinite ligands



L	R= Ph		R= CH_2CN		R= OAc	
			Regio (%)	ee(%)		
L38	92	79	82	79	98	91
L39	95	55			94	83
L40	84	90				
L41	84	91				

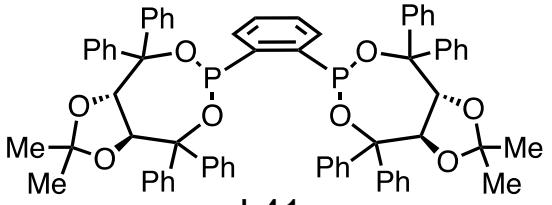


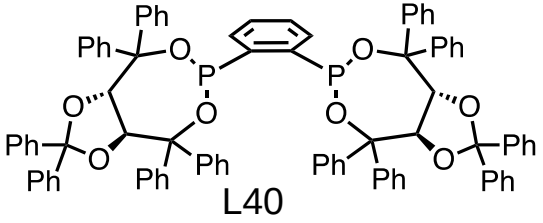
Ding, K. *et al. Chem. Eur. J.* **2008**, *14*, 7847-7857.



Ding, K. et al. *Tetrahedron Letters* **2008**, *49*, 4862-4864.

TADDOL-derived

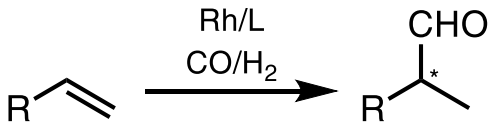


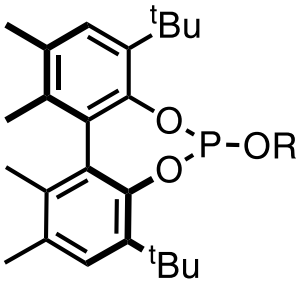


Breit, B. et al. Adv. Synth. Catal. **2015**, *357*, 41-45.

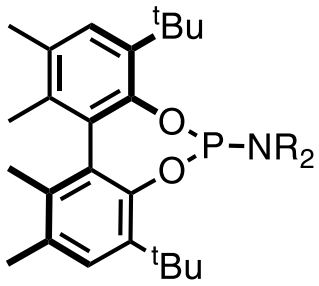
Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Monodentate P-based ligands





L43



L44

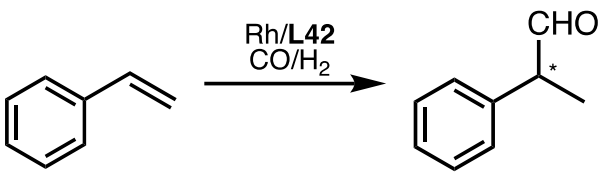
highest enantiomeric excess (80%) ever reported with a monodentate ligand

L	R= Ph		R= CH_2CN		R= OAc	
	Regio (%)	ee(%)				
L43	94	38	84	43	93	8
L44			96	80		

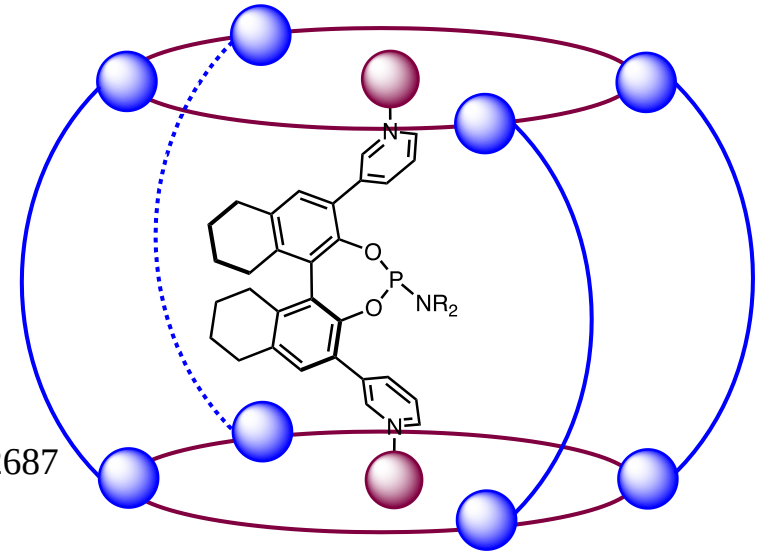
Ojima, I. et al. *P.N.A.S.*, **2004**, *101*, 5411-5416

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Monodentate P-based ligands

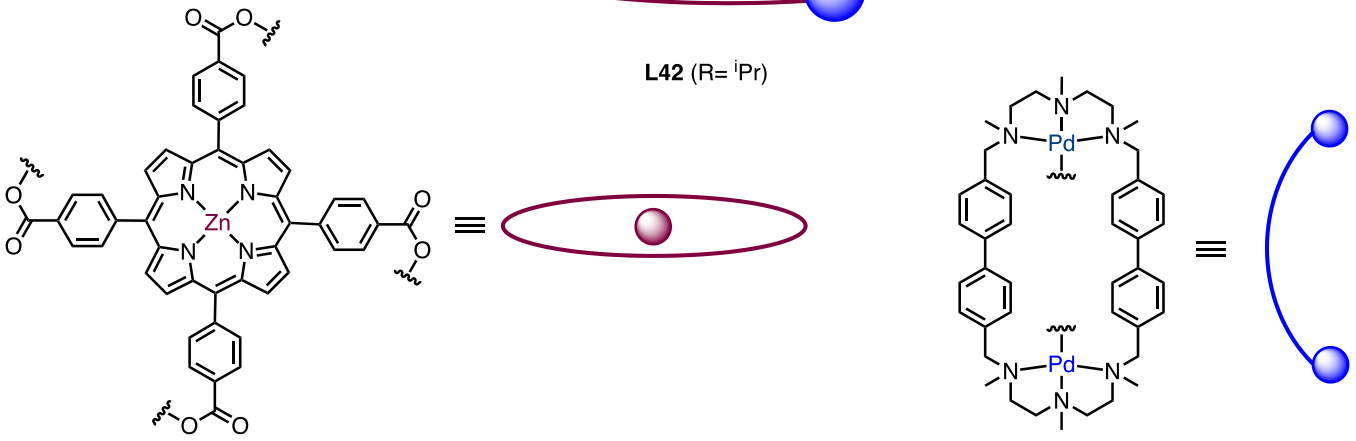


ee up to 77%



L42 (R= ^{i}Pr)

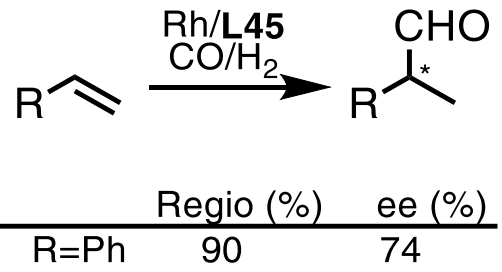
Reek, J. N. H. *J. Am. Chem. Soc.* **2015**, *137*, 2680-2687

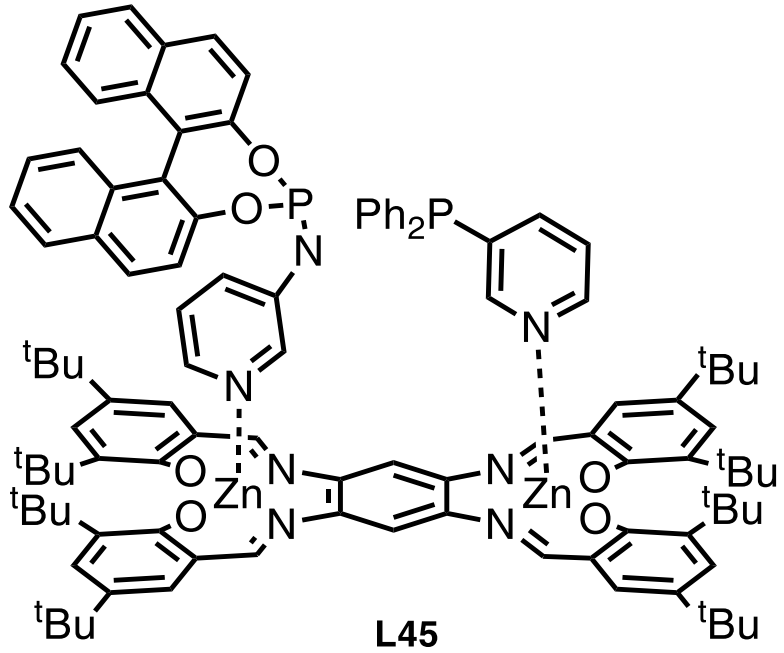


monodentate phosphoramidite ligand encapsulated in a self-assembled molecular cage

Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes

Templated monodentate P-based ligands





rigid bis-zinc(II)-salphen template

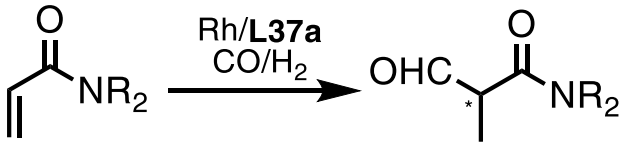
template-induced formation of chelating heterobidentate ligands

much higher ee's than any of the corresponding homobidentate ligands or non-templated mixed ligand combinations (*ee* up to 13%)

van Leeuwen, P.W.N.M.; Reek, J.N.H. et al. *Chem. Commun.* **2006**, 4679-4681

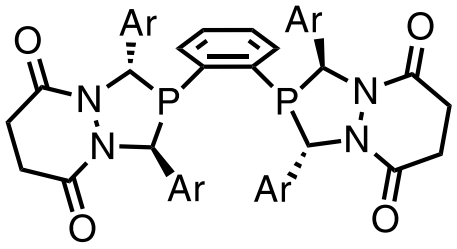
Rh-catalyzed asymmetric hydroformylation of other monosubstituted alkenes

N,N-dialkylacrylamides.

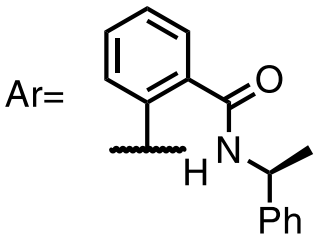


Initially, low ee's (20-50%) were reported for these susbtrates

J. Organomet. Chem. **1990**, *396*, 375-383
Chem. Commun. **2006**, 191-193



Bis-3,4-diazaphospholane (**L37a**)

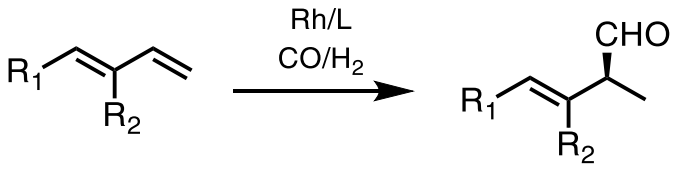


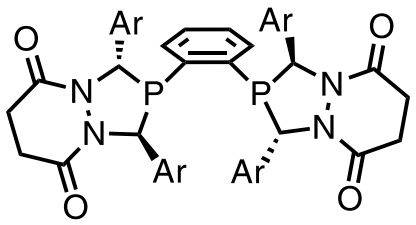
L37a	Regio (%)	ee(%)
R= Me	98	68
R= Et	97	82
R= i-Pr	98	74
NR_2=NMe(OMe)	98	71

Noonan, G. M.; Newton, D.; Cobley, C. J.; Suárez, A.; Pizzano, A.; Clarke, M. L. *Adv. Synth. Catal.* **2010**, *352*, 1047

Rh-catalyzed asymmetric hydroformylation of other monosubstituted alkenes

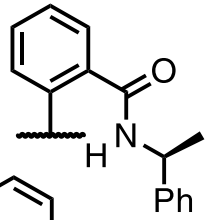
1,3-dienes, N-vinyl carboxamides, allyl carbamates and allyl ethers



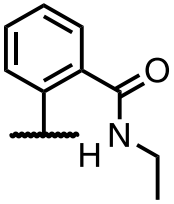


Bis-3,4-diazaphospholane

L37a (*S,S,S*) Ar=



L46 (*S,S*) Ar=



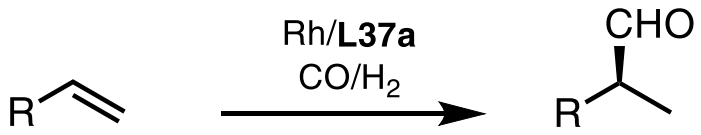
bis-3,4-diazaphospholane type ligands

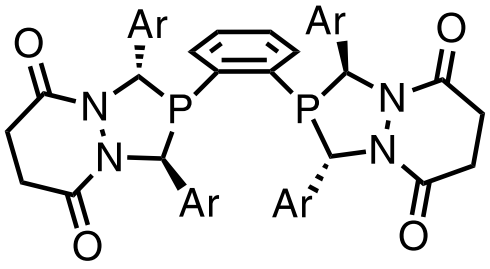
L37a	Regio (%)	ee(%)
R1= Ph, R2= H	99	91
R1= 2-furan, R2= H	99	97
R1= MeO, R2= H	99	94

L46	Regio (%)	ee(%)
R1= Ph, R2= Me	88	93
R1= 2-furan, R2= Me	98	93

Landis, C. R. et al. *Org. Lett.* **2011**, *13*, 164-167; *J. Am. Chem. Soc.* **2010**, *132*, 14027-14029

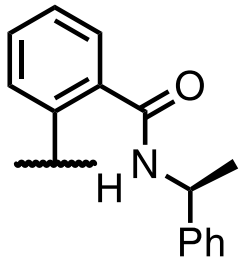
Rh-catalyzed asymmetric hydroformylation of other monosubstituted alkenes
monosubstituted enamides and other allylic substrates





Bis-3,4-diazaphospholane

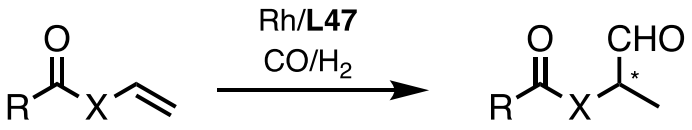
L37a Ar=

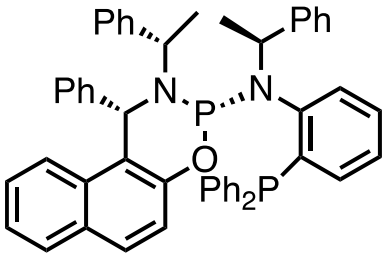


L37a	Regio (%)	ee(%)
R= NHCOOBn	99	94
R= NHCOOtBu	97	99
R= $NHCOCF_3$	98	99
R= CH_2OTMS	67	97
R= CH_2OPh	72	96
R= $CH(OAc)_2$	82	93

Landis, C. R. et al. *Org. Lett.* **2011**, *13*, 164-167; *J. Am. Chem. Soc.* **2010**, *132*, 14027-14029

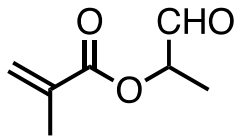
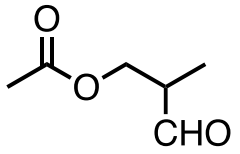
Rh-catalyzed asymmetric hydroformylation of other monosubstituted alkenes
vinyl esters



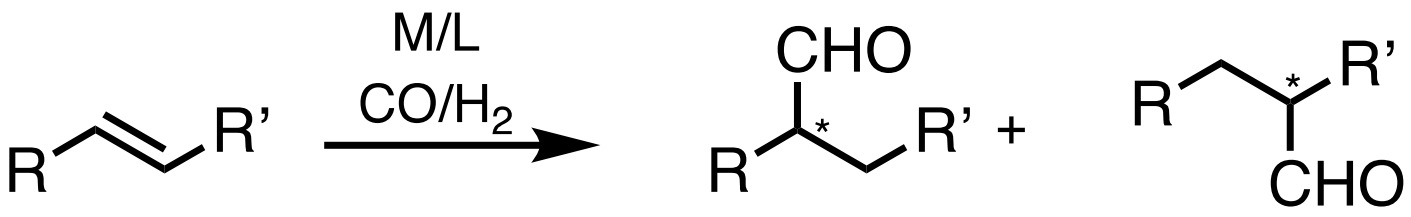


BettiPhos (**L47**)

Schmitz, C.; Holthusen, K.; Leitner, W.; Franciò, G. *ACS Catal*. **2016**, *6*, 584-1589

Product	Regio %	ee %
R = Et; X = O	>99	94
R = tBu; X = O	>99	95
R = Ph; X = O	>99	94
R = 4-MeOC$_6$H$_4$; X = O	>99	91
R = 4-FC$_6$H$_4$; X = O	>99	92
R = naphthyl; X = O	98	88
R = CH$_3$(CH$_2$)$_{10}$; X = O	>99	95
	>99	96
	-	5
R = CH$_3$; X = NH	96	82
R = CH$_3$; X = NCH$_3$	86	83

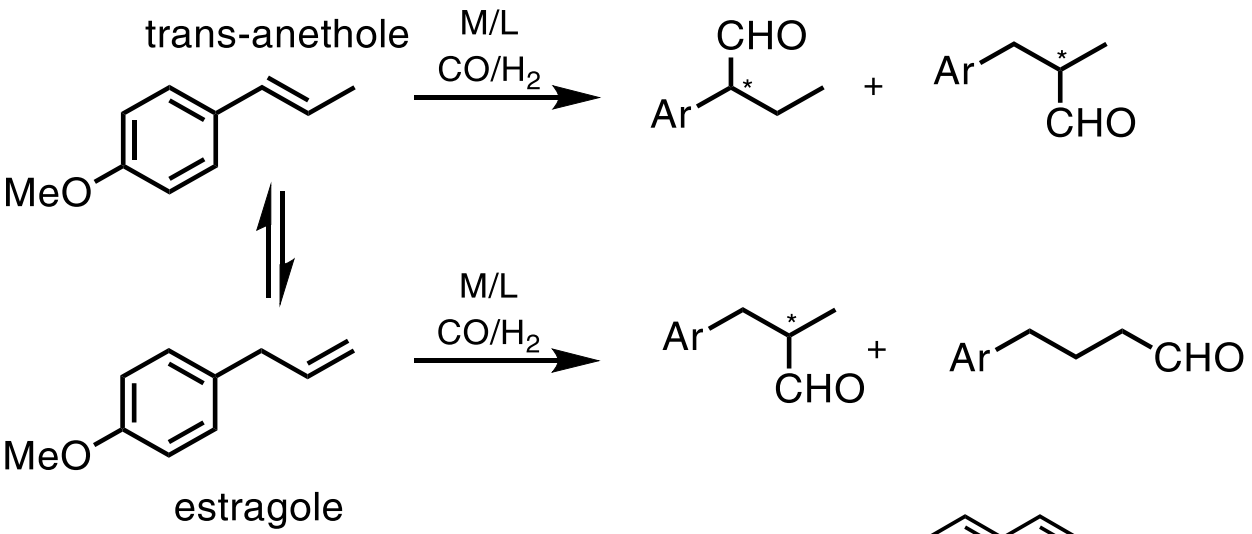
Rh-catalyzed asymmetric hydroformylation of 1,2-disubstituted alkenes

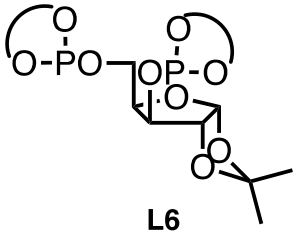


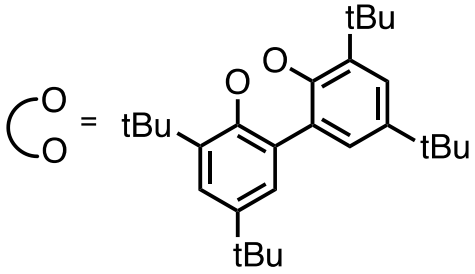
Two posible chiral aldehyde products

Possibility of isomerization

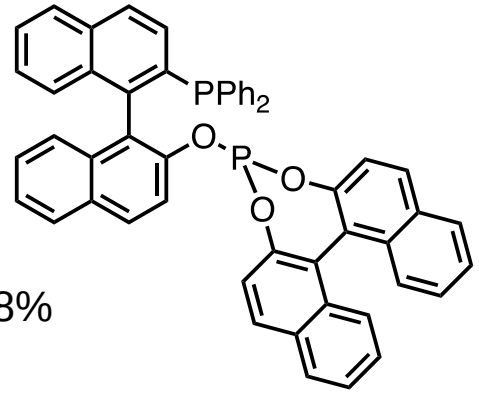
Rh-catalyzed asymmetric hydroformylation of 1,2-disubstituted alkenes







ee up to 15%



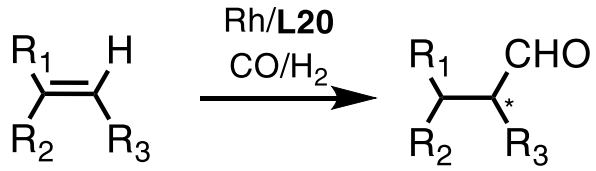
Regio: 98%
Ee: 80%

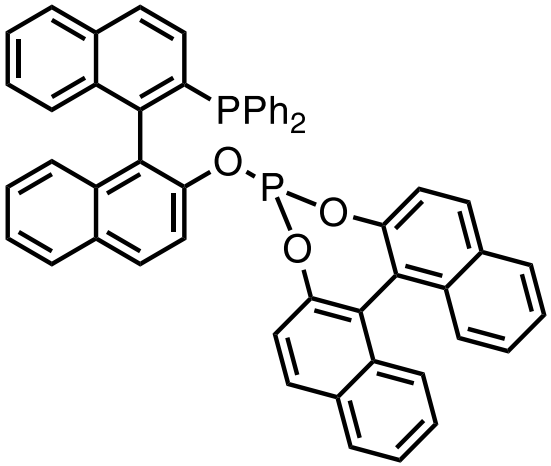
(R,S)-BINAPHOS (**L20**)

Axet, M.R.; Castillón, S.; Claver, C. *Inorg. Chim. Acta* **2006**, *359*, 2973-2979.

Nozaki, K.; Takaya, H.; Hiyama; T. Top. Catal. 1997, 4, 175-185; Sakai, N.; Nozaki, K.; Takaya, H. Chem. Commun. 1994, 395-396.

Rh-catalyzed asymmetric hydroformylation of 1,2-alkyl disubstituted alkenes





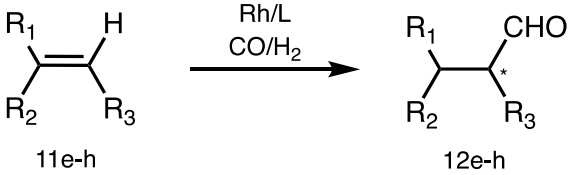
(R,S)-Binaphos (**L20**)

Product	ee (%)
(*Z*) R_1= H, R_2=R_3= Me	85
(*E*) R_1= Me, R_2= H, R_3= Me	48
(*Z*) R_1= H, R_2=R_3= Et	79
(*E*) R_1= Et, R_2= H, R_3= Et	69

E-isomers yielded lower enantioselectivity than their *Z*-counterparts

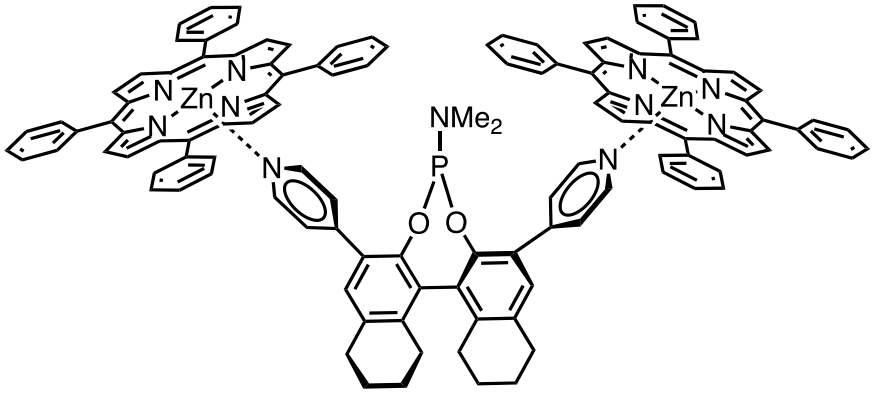
Nozaki, K.; Takaya, H.; Hiyama; T. Top. Catal. 1997, 4, 175-185; Sakai, N.; Nozaki, K.; Takaya, H. Chem. Commun. 1994, 395-396.

Rh-catalyzed asymmetric hydroformylation of 1,2-alkyl disubstituted alkenes

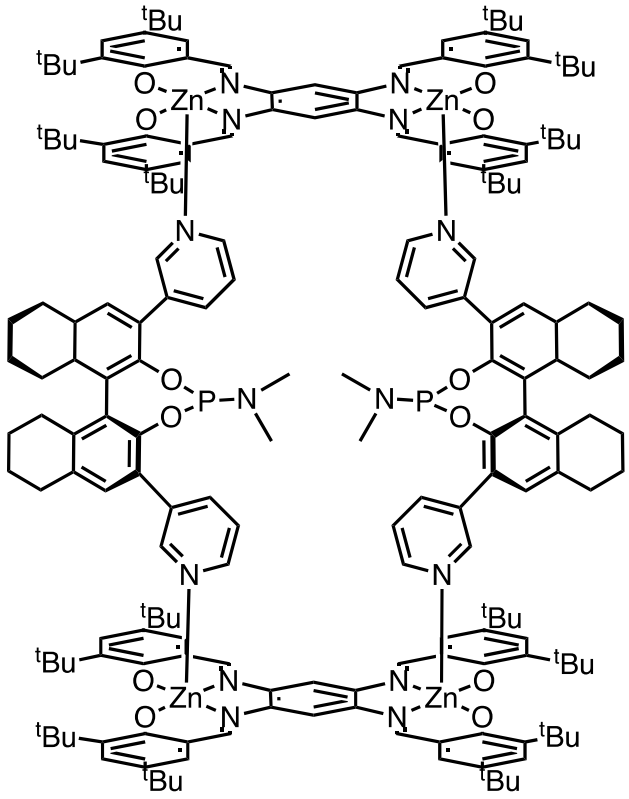


11e-h 12e-h

Product	L	ee (%)
R_1= Me, R_2=H, R_3= Pent	**L48**	45
	L49	72
R_1= Me, R_2=H, R_3= hex	**L49**	62
R_1= H, R_2=Me, R_3= Pent	**L49**	80
R_1= H, R_2=Me, R_3= Bu	**L49**	82



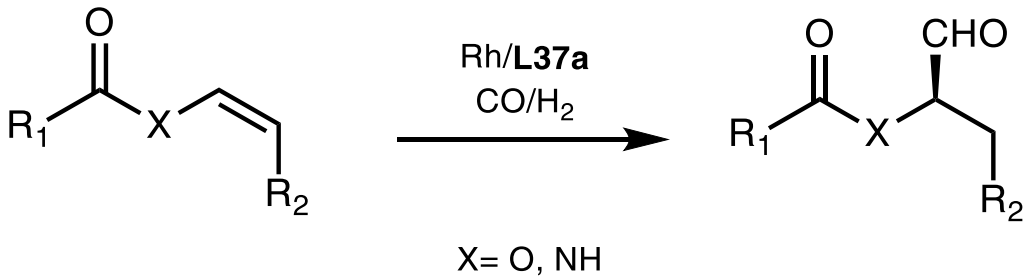
L48

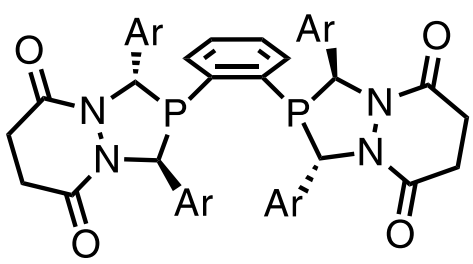


L49

Bellini, R.; Chikkali S. H.; Berthon-Gelloz, G.; Reek, J. N. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7342-7345; Gadzikwa, T.; Bellini, R.; Dekker, H.L.; Reek, J. N. H. *J. Am. Chem. Soc.* **2012**, *134*, 2860-2863.

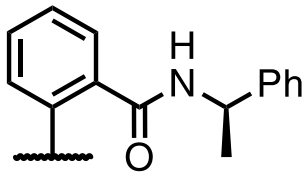
Rh-catalyzed asymmetric hydroformylation of Z-enamides and enol esters





(*S,S,S*)-**L37a**

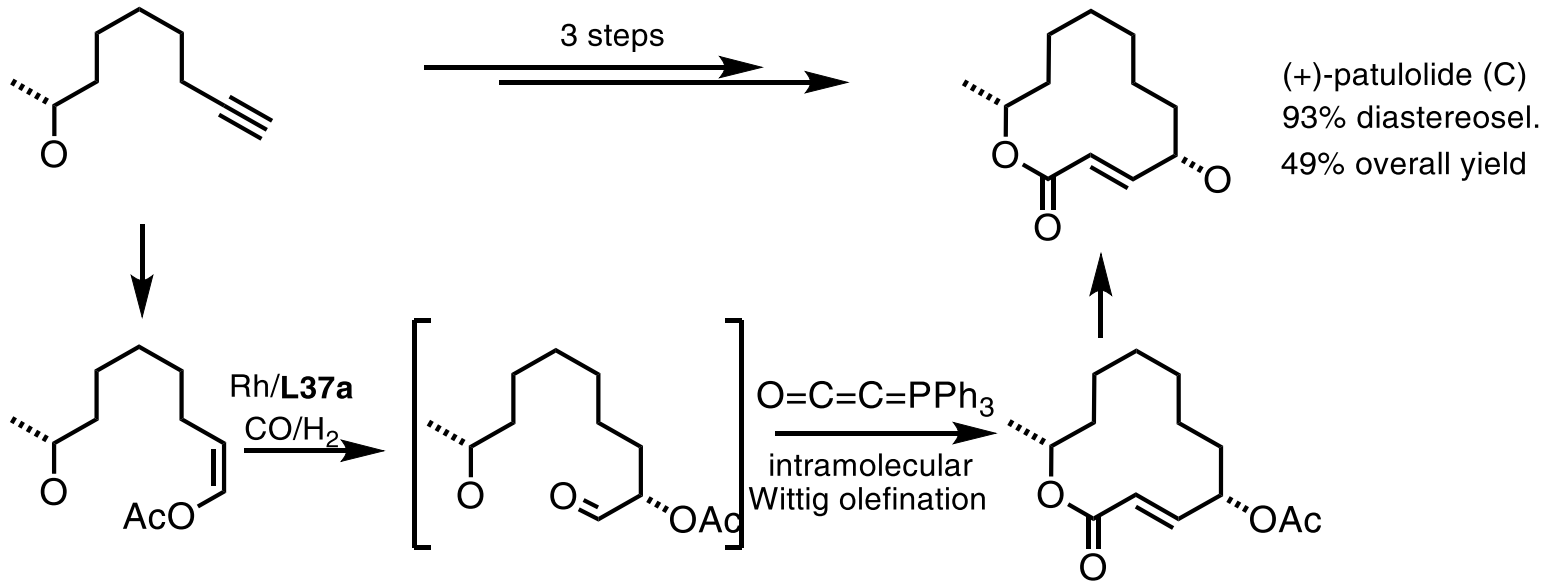
Ar=



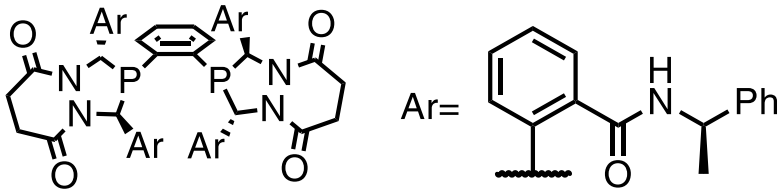
Product	Regio(%)	ee(%)
X=O, R_1= Ph, R_2= Bu	>99	97
X=O, R_1= p-C_6H_4-OH, R_2= Bu	>99	99
X=O, R_1= Me, R_2= CH_2-CH_2-Ph	>99	93
X=NH, R_1= Ph, R_2= Bu	>99	85
X=NH, R_1= Ph, R_2= CH_2-CH_2Ph	>99	90
X=NH, R_1= Ph, R_2= CH_2-CH_2Cl	93	92
X=NH, R_1= Ph, R_2= CH_2-CH_2CN	>99	94
X=NH, R_1= Ph, R_2= CH_2-C_6H_{11}	>99	84
X=NH, R_1= Ph, R_2= Ph	86	98
X=NH, R_1= CF_3, R_2= Ph	92	90

Leigh Abrams, M.; Foarta, F.; Landis, C.R.. *J. Am. Chem. Soc*. **2014**, *136*, 14583-14588.

Rh-catalyzed asymmetric hydroformylation for the synthesis of (+)-patulolide *C*.



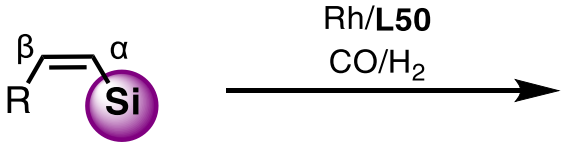
only one product detected by NMR



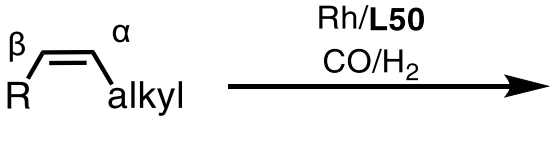
Bis-3,4-diazaphospholane
(*S,S,S*)-**L37a**

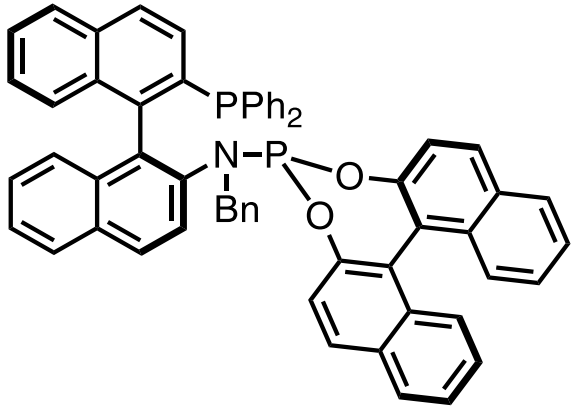
Risi, R.M., Burke, S.D., *Org. Lett.*, **2012**, *14*, 1180-1182

Rh-catalyzed asymmetric hydroformylation of 1,2-disubstituted alkenylsilanes

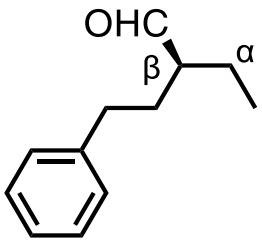


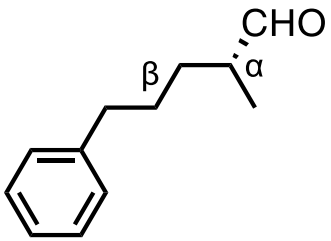
up to 98% yield and 97% ee



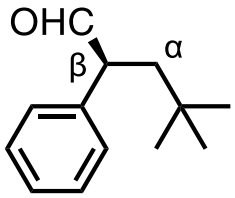


(*S,R*)-(*N* -Bn)-YanPhos (**L50**)





30% yield, β/α = 40:60
β = 92% ee, α = 93% ee



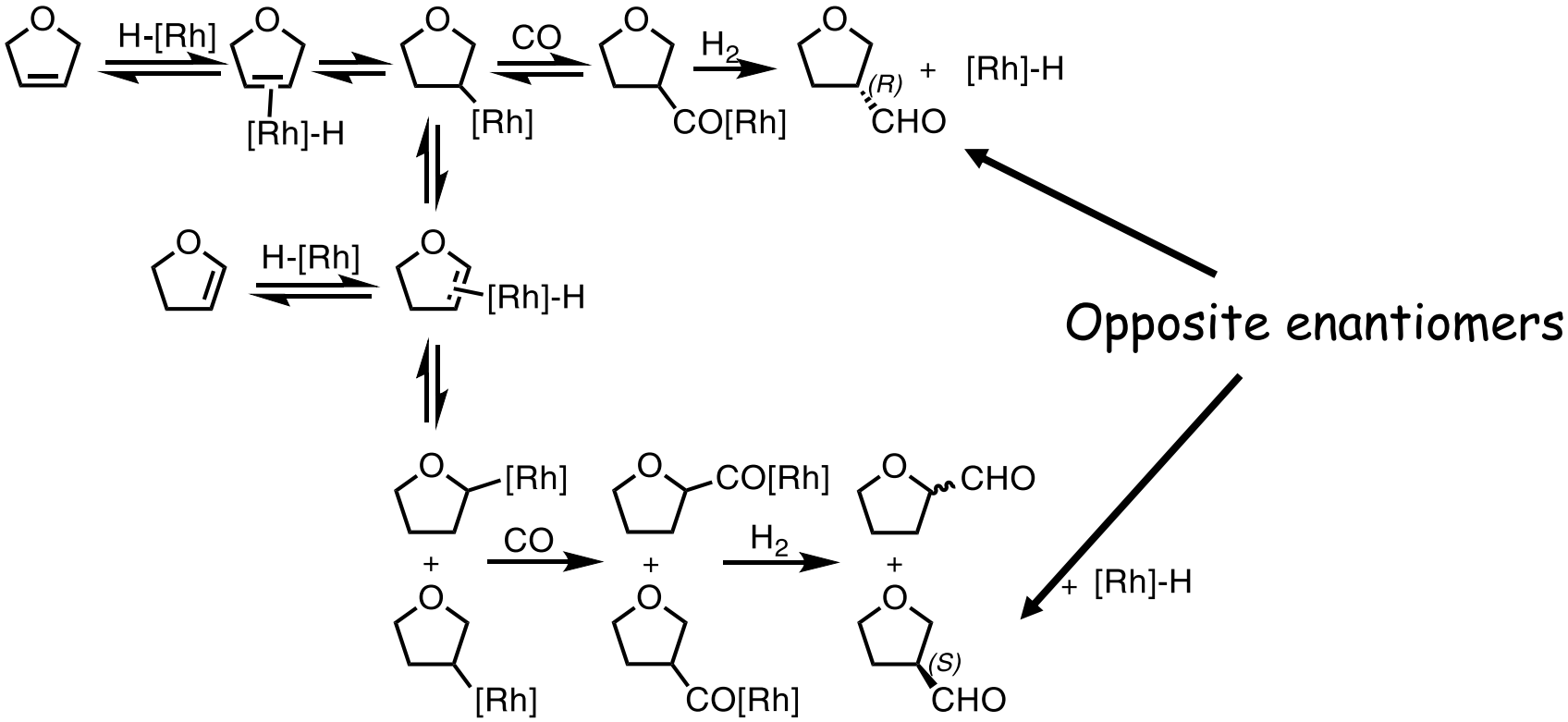
Trace conversion

Critical role of silicon group for regiocontrol and activation of the substrate

Zhang, X. and co-workers *Nat. Commun.* **2018**, *9* (1).

Rh-catalyzed asymmetric hydroformylation of monocyclic 1,2-Disubstituted alkenes

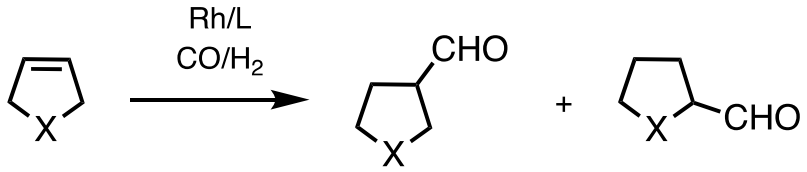
dihydrofurans and dihydropyrroles are the most studied



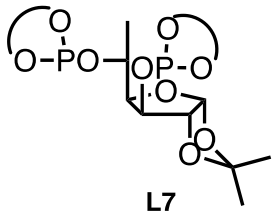
isomerization has a direct influence on both the regioselectivity and the enantioselectivity

del Río, I.; van Leeuwen, P.W.N.M.; Claver, C. *Can. J. Chem.* **2001**, *79*, 560-565

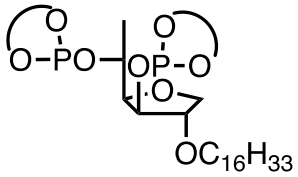
Rh-catalyzed asymmetric hydroformylation of five-membered heterocyclic alkenes



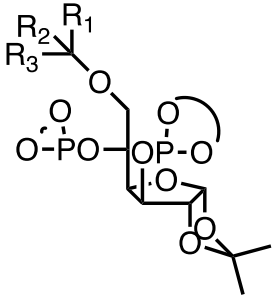
L	X = O Regio (%)	ee(%)	X = *N*-Boc Regio (%)	ee(%)	X = *N*-Ac Regio (%)	ee(%)
L7b	99	75 (S)			99	71 (-)
L14b	99	88 (S)				
L20	99	68 (R)	99	73 (R)	99	66 (+)
L51	99	91 (S)				
L26a	99	72 (R)				
L52	99	84 (S)	99	92 (S)		



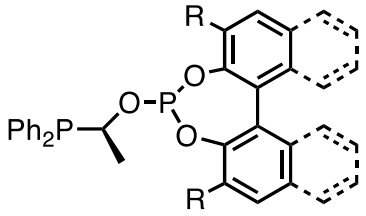
L7



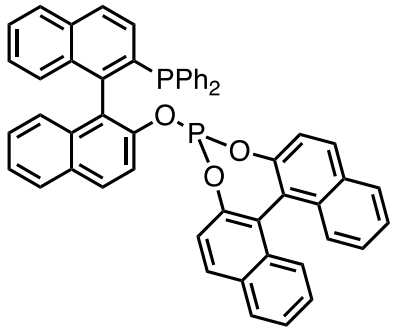
L14



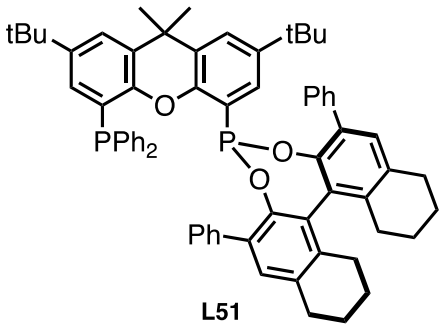
L15 $R_1=R_2$ = H; R_3= $CH_2CH_2CH_3$
L16 $R_1=R_2$ = CH_3; R_3= H



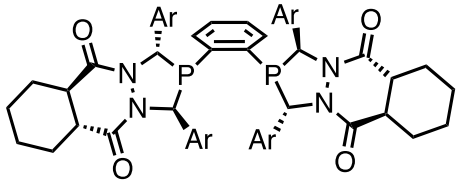
L26a



(R,S)-BINAPHOS (**L20**)



L51

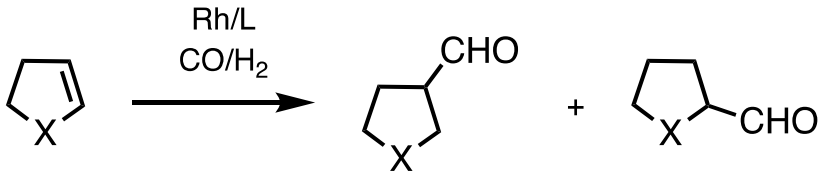


Ar= 2-Cl-C_6C_4

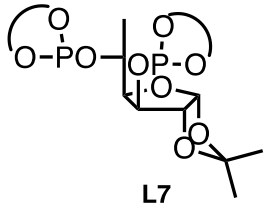
L52

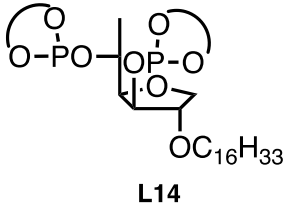
Nozaki, K.; et al. *J. Org. Chem*. **1997**, *62*, 4285-4292; Claver, C. et al. *Chem. Commun*. **2005**, 1221-1223; Reek, J.N.H. et al. *Chem. Commun*. **2010**, *46*, 1244-1246; *J. Am. Chem. Soc*. **2012**, *134*, 6607-6616; Zhang, X. *Tetrahedron Lett*. **2015**, *56*, 1149-1152.

Rh-catalyzed asymmetric hydroformylation of five-membered heterocyclic alkenes

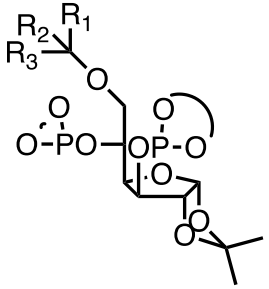


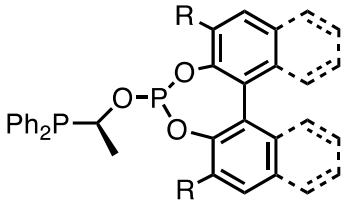
	X = O		X = *N*-Boc	
L	Regio (%)	ee(%)	Regio (%)	ee(%)
L7b	76	75 (R)		
L15b	78	83 (R)		
L16b	78	84 (R)		
L20	50	38 (S)	33	71 (S)
L51	80	91 (R)		
L26a	45	76 (S)		
L52	50	92 (R)	85	86 (R)


L7

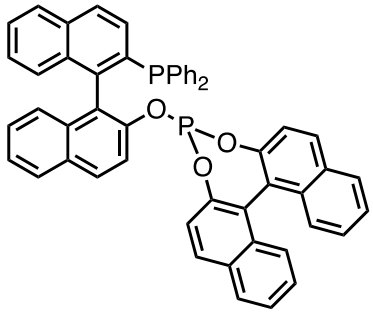


L14

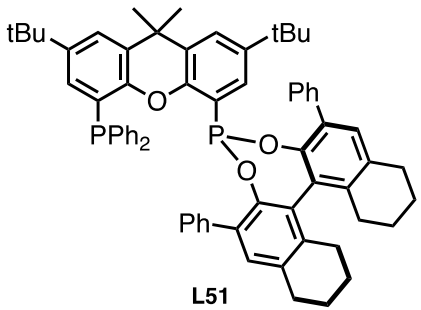

L15 $R_1=R_2=H$; $R_3=CH_2CH_2CH_3$
L16 $R_1=R_2=CH_3$; $R_3=H$



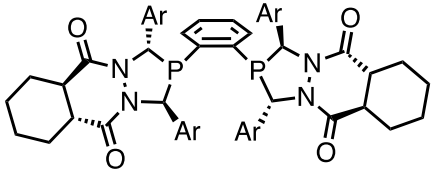
L26a



(R,S)-BINAPHOS (**L20**)



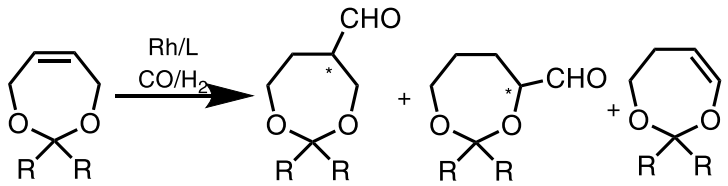
L51



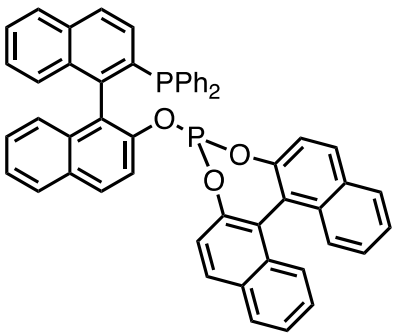
L52

Nozaki, K.; et al. *J. Org. Chem*. **1997**, *62*, 4285-4292; Claver, C. et al. *Chem. Commun*. **2005**, 1221-1223; Reek, J.N.H. et al. *Chem. Commun*. **2010**, *46*, 1244-1246; *J. Am. Chem. Soc*. **2012**, *134*, 6607-6616; Zhang, X. *Tetrahedron Lett*. **2015**, *56*, 1149-1152.

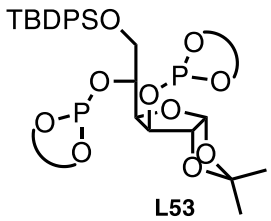
Rh-catalyzed asymmetric hydroformylation of 4,7-dihydro-1,3-dioxepine



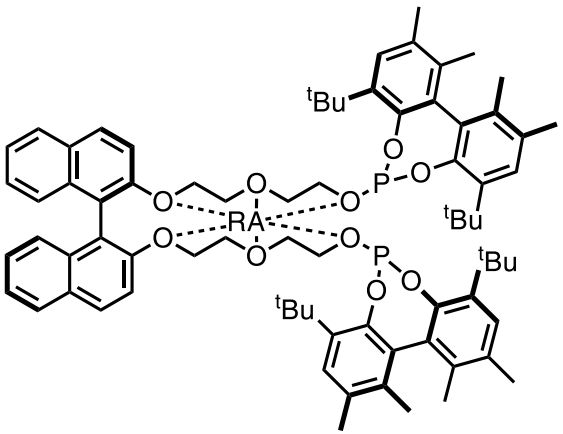
L	R=H		R= Me	
	Regio (%)	ee(%)		
L20	99	76 (-)	99	70 (R)
L53	99	68 (+)	99	55 (S)
L54	99	93 (+)		



(R,S)-BINAPHOS (**L20**)



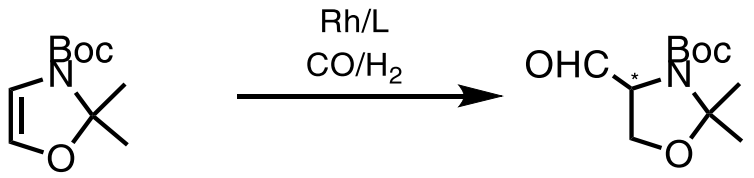
L53



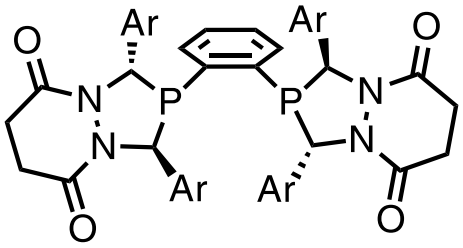
L54 RA= KBArF

Nozaki, K.; Takaya, H. *Chem. Commun*. **1994**, 395-396; Mazuela, J.; Coll, M.; Pàmies, O.; Diéguez, M. *J. Org. Chem.* **2009**, *74*, 5440-5445. Rovira, L.; Vaquero, M.; Vidal-Ferran, *J. Org. Chem*. **2015**, *80*, 10397−10403

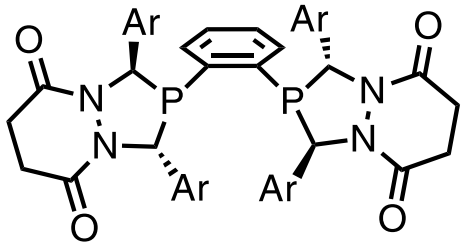
Synthesis of Garner's aldehyde through AHF of N-Boc-2,2-dimethyl-2,3-dihydrooxazole



S-product in 97% ee using **L37a**
R-product in 94% ee using **L37b**

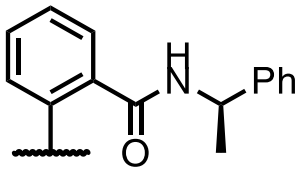


(S,S,S)-**L37a**



(R,R,S)-**L37b**

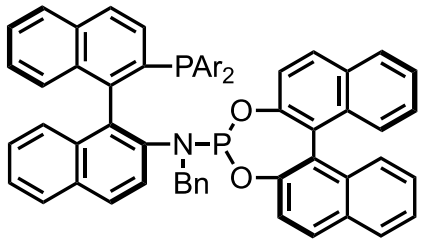
Ar=



Both enantiomers of this molecule were prepared using the diastereoisomeric bis-diazaphospholane ligands **L37a** and **L37b**

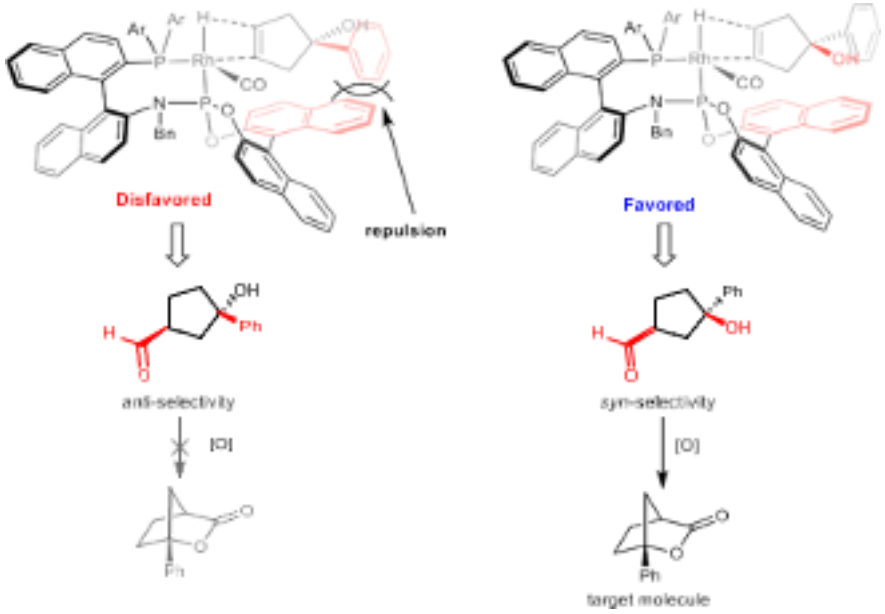
Clemens, A. J. L.; Burke, S. D., *J. Org. Chem.*, **2012**, *77*, 2983-2985.

Rh-catalyzed asymmetric hydroformylation of cyclopent-3-en-1-ols



(S,R)-DM-YanPhos (**L55**)
Ar = 3,5-Me-C_6H_3

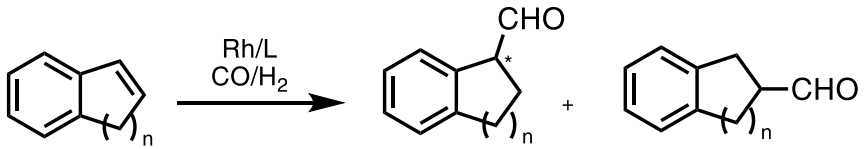
after oxidation, the bridged [2,2,1] bicyclic lactones were formed



Li, S.; Li, Z.; Li, M.; He, L.; Zhang, X.; Lv, H. *Nat. Commun.* **2021**, *12* (1), 1–9.

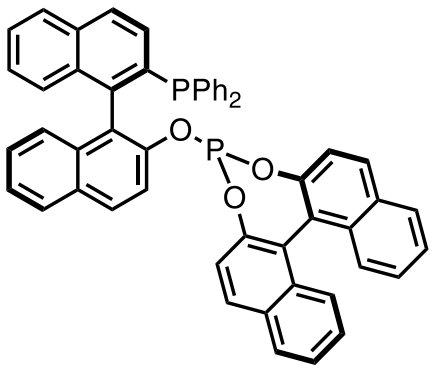
Rh-catalyzed asymmetric hydroformylation of bicyclic 1,2-disubstituted alkenes

indene and 1,2-dihydronaphthalene

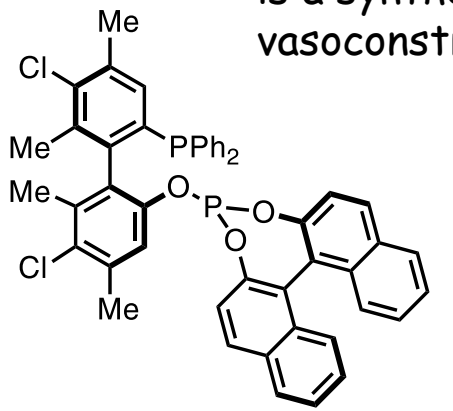


Product	L	Regio (%)	ee(%)
n=1	**L56**	92	88
	L20	92	83
n=2	**L56**	96	97
	L20	96	96

- 2,3-dihydro-1H-indene-1-carbaldehyde can be converted in a single step into the corresponding amine (hypotensive activity)
- 1,2,3,4-tetrahydronaphthalene-1-carbaldehyde is a synthetic intermediate to produce a vasoconstrictor tetrahydrozoline



(R,S)-Binaphos (**L20**)

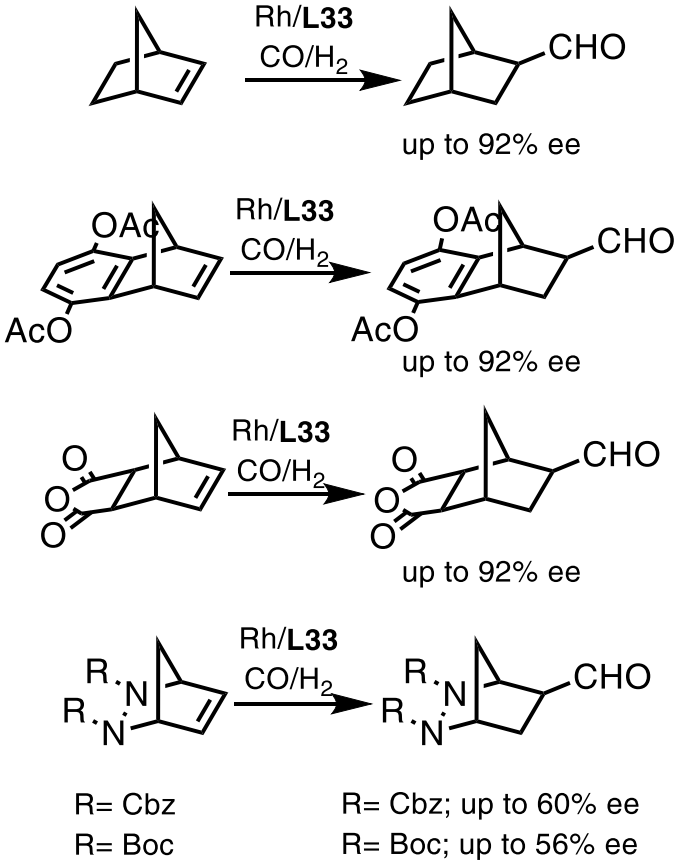


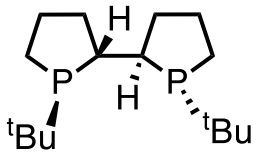
(S,R)-Biphemphos (**L56**)

Nozaki, K.; Takaya, H. *Chem. Commun.* **1994**, 395-396

Rh-catalyzed asymmetric hydroformylation of bicyclic 1,2-disubstituted alkenes

Norbornene derivatives



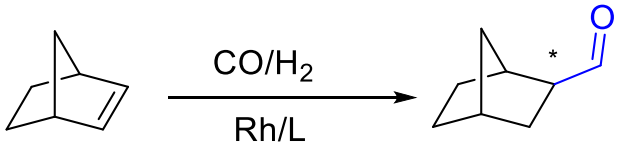


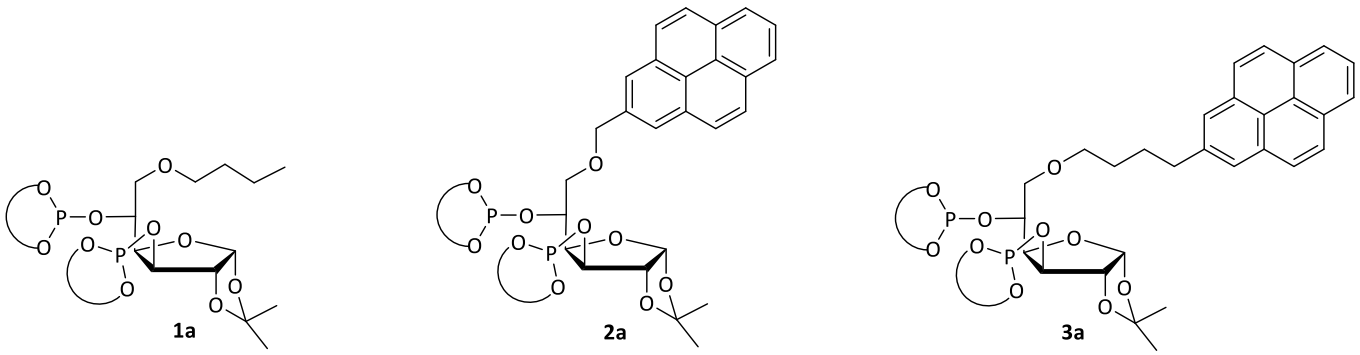
(S,S,R,R)-TANGPHOS (**L33**)

Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correl, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P.J. *Tetrahedron Letters* **2005**, *46*, 7831-7834

Rh-catalyzed asymmetric hydroformylation of bicyclic 1,2-disubstituted alkenes

Norbornene derivatives





Entry [a]	Ligand	Conversion % [b]	Stereoselectivity % [b]	ee %[c]
1	**1a**	14	>99 % (exo)	**62**
2	**2a**	15	>99 % (exo)	**62**
3	**3a**	16	>99 % (exo)	**65**

Batch experiments

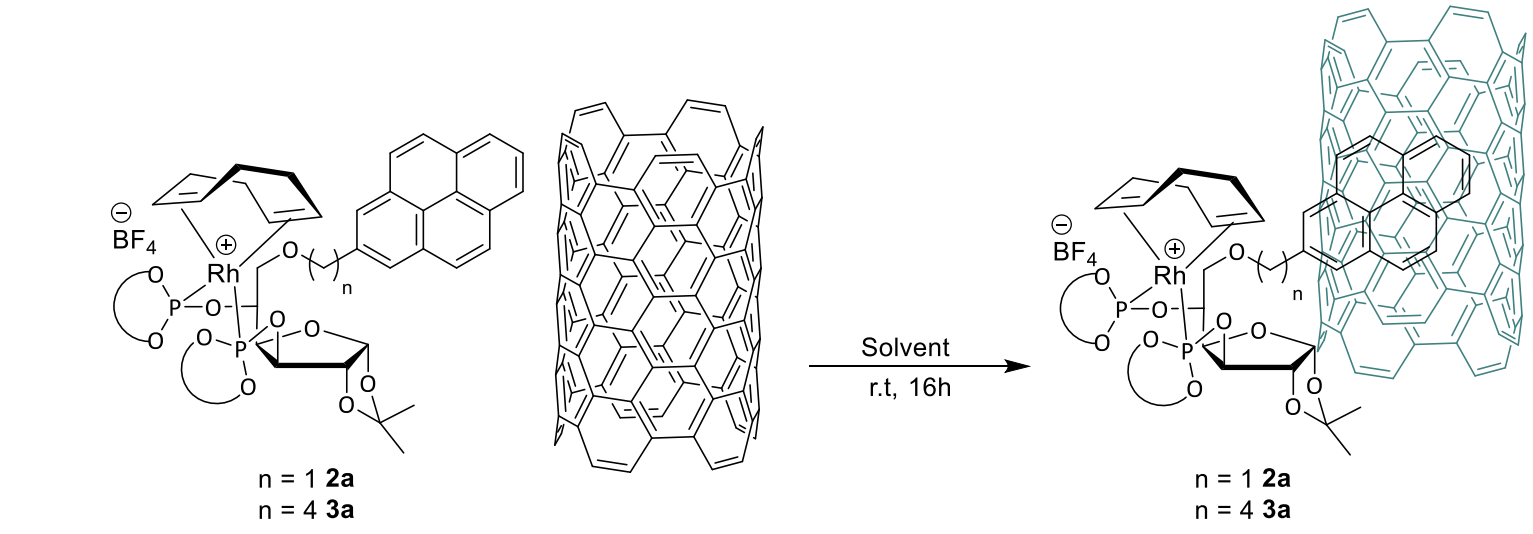
The pyrene moiety has no significant effects in the activity and selectivity

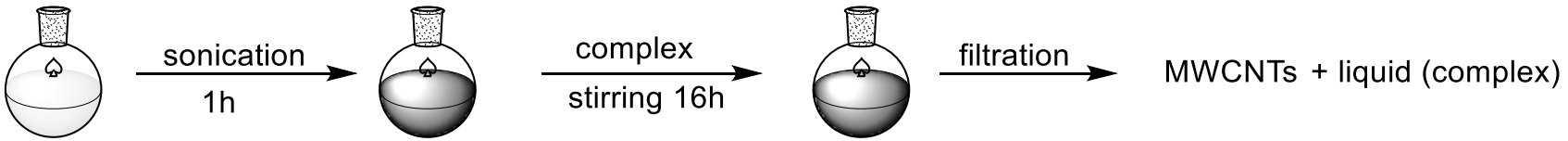
A. Cunillera, C. Godard et al. *ChemCatChem* **2019**, 11, 2195-2205

Diphosphite rhodium catalysts immobilisation onto MWCNTs

Rh-catalyzed asymmetric hydroformylation of bicyclic 1,2-disubstituted alkenes

Norbornene derivatives



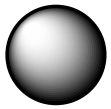


A. Cunillera, C. Godard et al. *ChemCatChem* **2019**, 11, 2195-2205

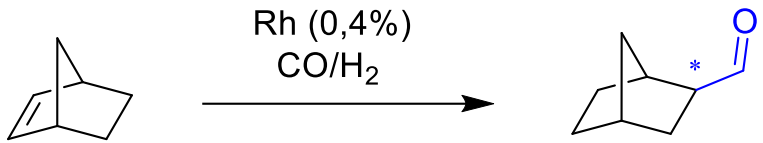
Flow experiments

Carbon beads

3 time more catalyst

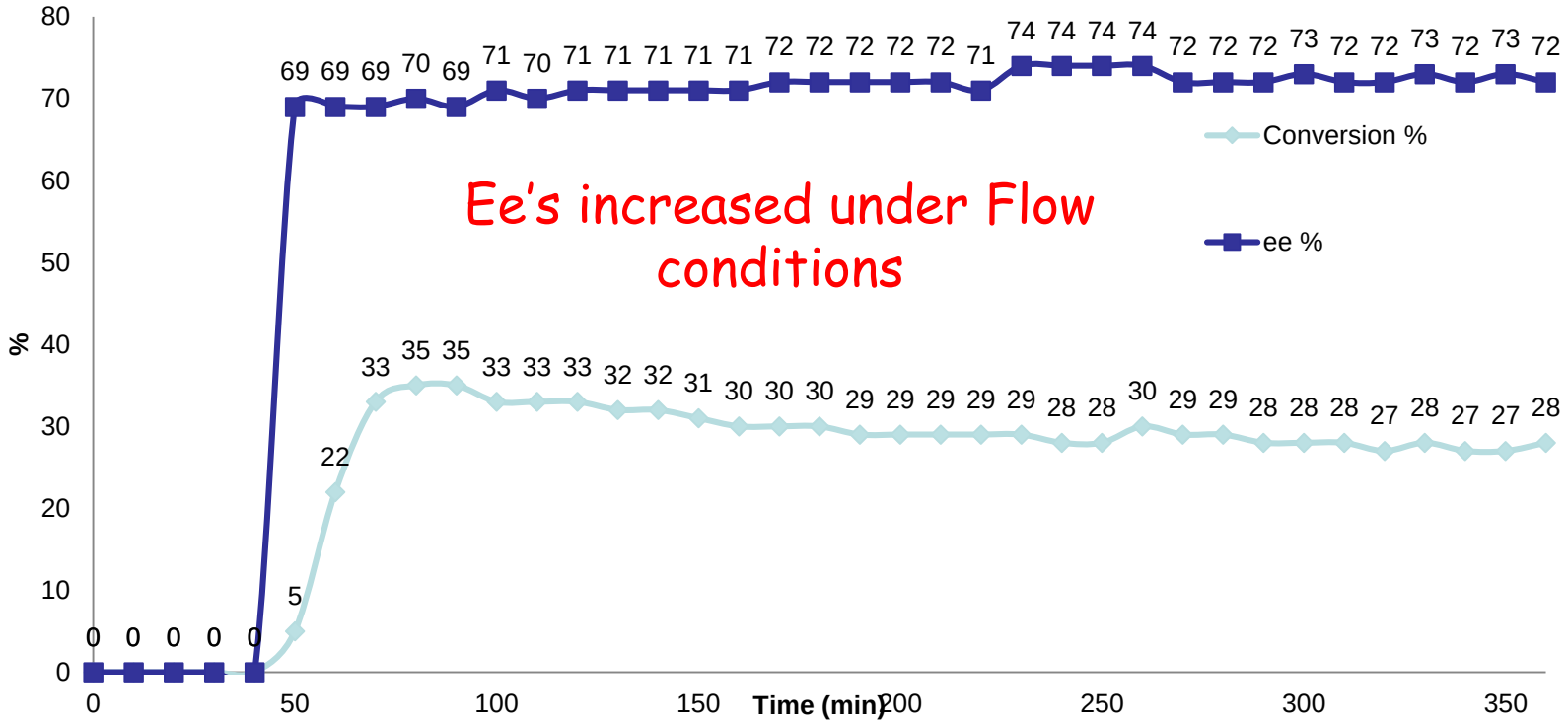


- 0,5 µm
- High carbon content
- Higher surface area
- Easy separation

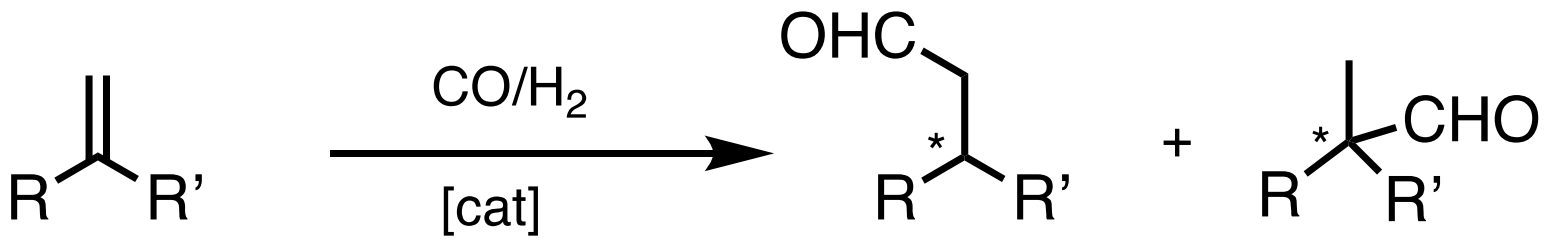


Conditions:

P	T	CO:H2	[Norbonene]	NBN flow	CO flow	H2 flow	Solvent
10 bar	20 °C	1	0,75	0.33 mL/min	22 mL/min	22 mL/min	EtOAc



Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes



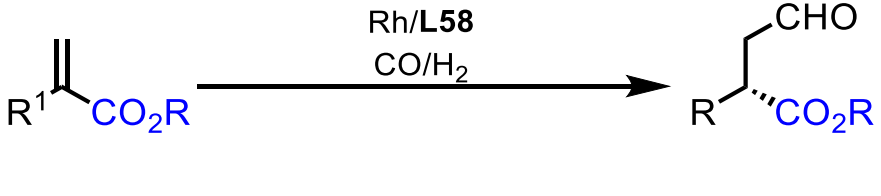
Both products can be chiral (if R and R' are not CH_3)

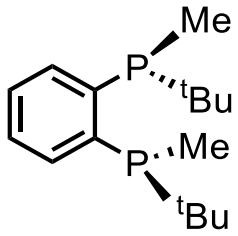
Keuleman's rule and steric hindrance favor the linear product

Selectivity affected by the coordinating properties of the substituents

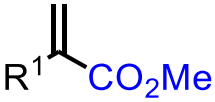
Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

with coordinative groups: acrylate derivatives

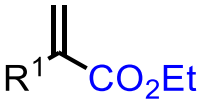




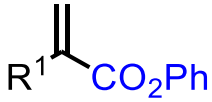
(R,R)-BenzP* (**L58**)



R^1 = Me, 83% ee, 54% yield
R^1 = nPr, 89% ee, 63% yield
R^1 = $(CH_2)_3$OTBS, 81% ee, 62% yield
R^1 = iPr, 92% ee, 91% yield
R^1 = cHex, 94% ee, 84% yield
R^1 = cPn, 93% ee, 85% yield



R^1 = Et, 87% ee, 68% yield



R^1 = Bn, 84% ee, 60% yield

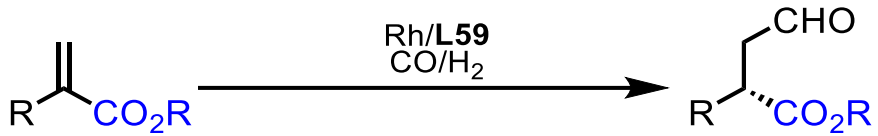
Short reaction times
10 bar of pressure were necessary
100 °C

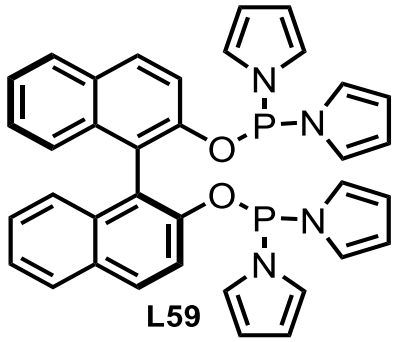
Alkenes bearing isopropyl, cyclohexyl, and cyclopentyl groups gave the highest yields and enantioselectivities

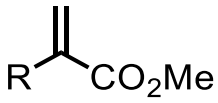
Wang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 19080−19083

Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

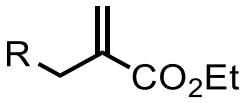
with coordinative groups: acrylate derivatives



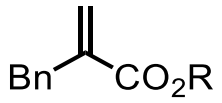




R= Me; 73% ee, 73% yield
R= Bn; 84% ee, 81% yield
R= CH_2CO_2Me; 78% ee, 64% yield



R= nPr; 80%ee, 75% yield
R= iPr; 85% ee, 85% yield
R= Bn; 82% ee, 72% yield
R= $(CH_2)_2CN$; 86% ee, 87% yield
R= $(CH_2)_2OTBS$; 75% ee, 80% yield



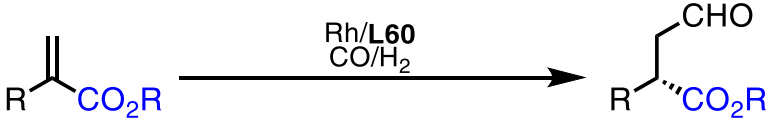
R= Bn; 85% ee, 81% yield
R= $(CH_2)_2$-2-Py; 84% ee, 86% yield
R= CH_2-2-furyl; R= 86% ee, 85% yield
R= CH_2-2-thienyl; 86% ee, 87% yield

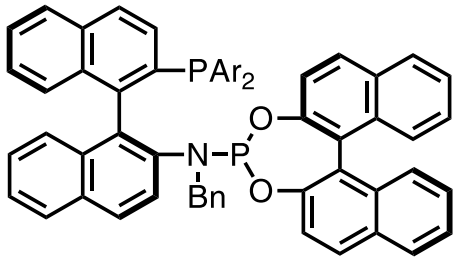
good-to-high enantioselectivities (73%-86% ee)

Xiaofei, J.; Xinyi, R.; Zheng, W.; Chungu, X.; Kuiling, D. *J. Chinese Chem. Soc.* **2019**, *39*, 207–214.

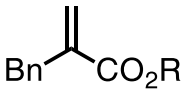
Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

with coordinative groups: acrylate derivatives

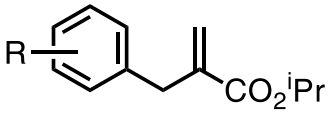




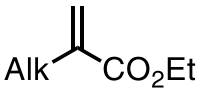
(S,S)-DTBM-YanPhos (**L60**)
Ar = 3,5-tBu-4-MeO-C_6H_3



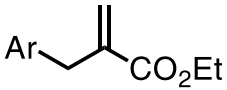
R= Et; 90% ee, 94% yield
R= Me; 89% ee, 83% yield
R= iPr; 91% ee, 88% yield
R= $CHPh_2$; 90% ee, 75% yield
R= Ph; 88% ee, 79% yield
R= Bn; 88% ee, 85% yield



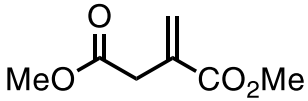
R= 4-F; 90% ee, 74% yield
R= 4-Cl; 90% ee, 78% yield
R= 4-Br; 90% ee, 77% yield
R= 2-MeO; 96% ee, 85% yield
R= 3-MeO; 91% ee, 80% yield
R= 4-MeO; 90% ee, 82% yield



Alk= $(CH_2)_2OBn$; 89% ee, 84% yield
Alk= C_5H_{11}; 88% ee, 83% yield
Alk= iPr; 73% ee, 86% yield



R= 4-tBuPh; 88% ee, 85% yield
R= 2-furyl; 88% ee, 81% yield
R= 4-CNPh; 88% ee, 60% yield

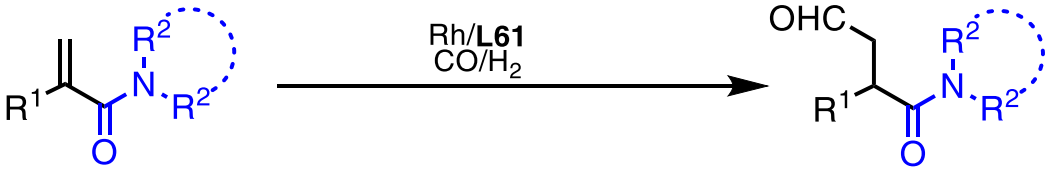


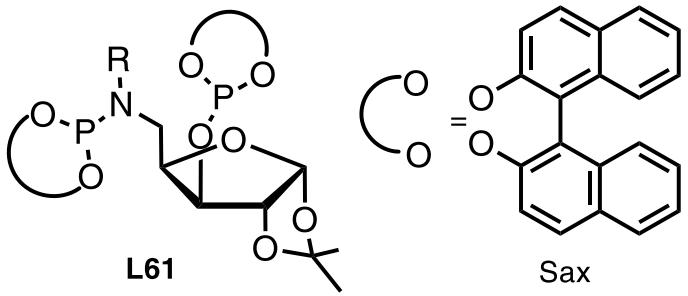
86% ee
91% yield

Li, S.; Li, Z.; You, C.; Li, X.; Yang, J.; Lv, H.; Zhang, X. *Org. Lett.* **2020**, *22*, 1108−1112.

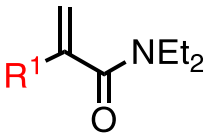
Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

with coordinative groups: acrylamides

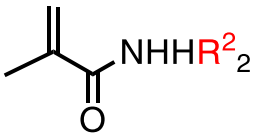




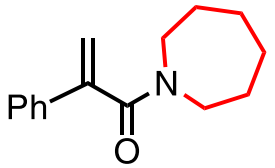
R= Cy, Me, Bn, iPr, (S)-CHMePh, tBu



R^1= Et; 90% ee, 74% yield[a]
R^1= Bn; 86% ee, 65% yield[a]
R^1= iPr; 66% ee, 74% yield[b]
R^1= cC_5H_9; 82% ee, 70% yield[b,c]
R^1= Ph; 78% ee, 55% yield[b]



R^2= Et; 90% ee, 87% yield[a]
R^2= Ph; 80% ee, 50% yield[a]
R^2= iPr; 99% ee, 80% yield[a]



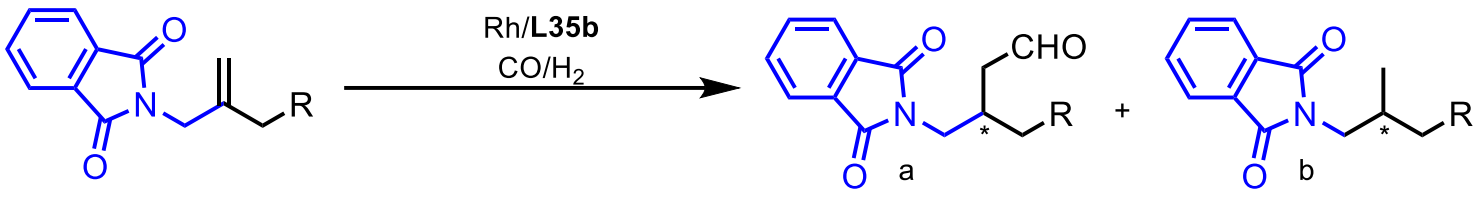
74% ee, 52% yield[a,c]

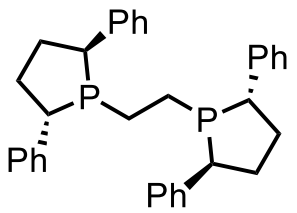
Catalysts previously reported for acrylates were not efficient for these substrates

Miró, R.; Cunillera, A.; Margalef, J.; Lutz, D.; Börner, A.; Pamiès, O.; Diéguez, M.; Godard, C. *Org. Lett.* **2020**, *22*, 9036−9040.

Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

with coordinative groups: allyl phthalimides





(S,S)-Ph-BPE (**L35b**)

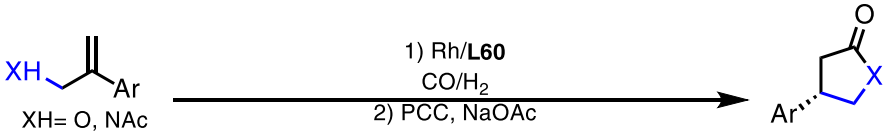
	%ee	% conv.	a/b
R = H	90	88	>99/1
R = Et	90	100	>99/1
R = nPr	75	36	>99/1
R = iPr	95	45	>99/1
R = nBu	77	54	97/3
R = iBu	55	22	86/14
R = cPn	57	36	>99/1
R = cHex	90	13	72/28
R = Bn	57	83	92/8

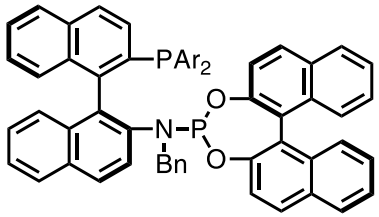
reaction to obtain chiral β^3-amino acids and alcohols through oxidation or reduction of the N-phthalimide-protected aldehydes

Zheng, X.; Cao, B.; Liu, T.-l.; Zhang, X. *Adv. Synth. Catal.* **2013**, *355*, 679–684.

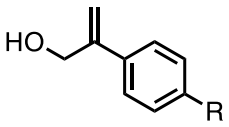
Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

with coordinative groups: allylic alcohols

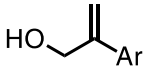




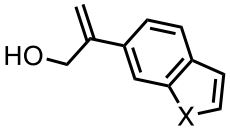
(S,S)-DTBM-YanPhos (**L60**)
Ar = 3,5-tBu-4-MeO-C_6H_3



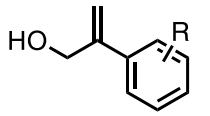
R	ee (%)	yield (%)
H	90	87
Me	90	95
iPr	89	71
tBu	88	87
Ph	85	71
MeO	90	88
CF_3	93	72
CO_2Et	86	80
F	92	78
Cl	90	73



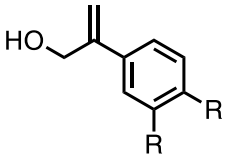
R	ee (%)	yield (%)
2-Naph	90	77
2-furyl	85	75



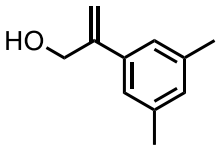
X	ee (%)	yield (%)
O	90	90
Sl	86	72



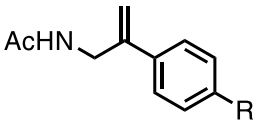
R	ee (%)	yield (%)
3-F	87	79
2-Me	90	90



R	ee (%)	yield (%)
Me	90	90
MeO	90	74
$-O(CH_2)_2O-$	88	80



92% ee; 83% yield



R	ee (%)	yield (%)
H	84	64
Me	83	60
MeO	84	64
CF3	80	69
F	86	63
Cl	82	60

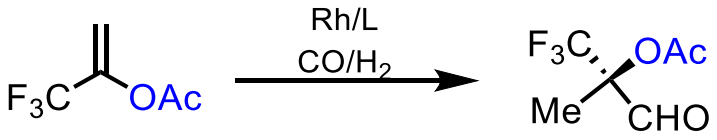
chiral linear aldehydes were oxidized to the corresponding lactones.

ee from 85 to 93%

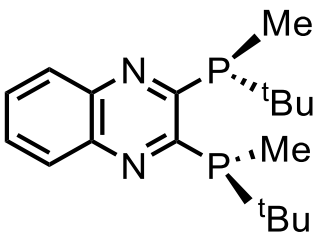
You, C.; Li, S.; Li, X.; Lv, H.; Zhang, X. *ACS Catal.* **2019**, *9*, 8529−8533.

Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

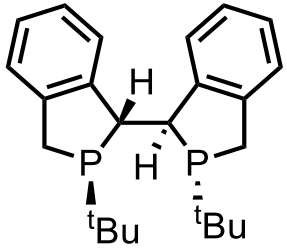
with coordinative groups



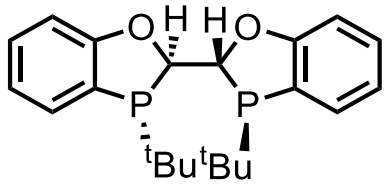
L	ee%
L62	91
L63	92
L34	80



(R,R)-QuinoxP* (**62**)



(R,R,S,S)-Duanphos (**L63**)



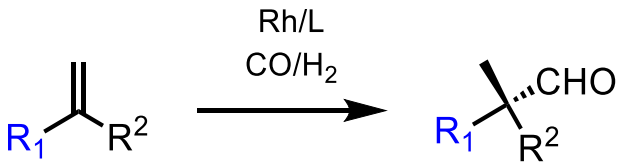
(R)-BIBOP (**L34**)

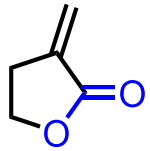
first efficient catalyst providing the branched aldehyde as the major product

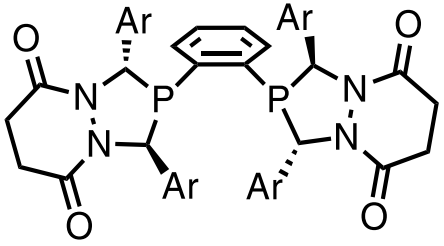
Wang, X.; Buchwald, S. L. *J. Org. Chem.* **2013**, *78*, 3429−3433.

Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

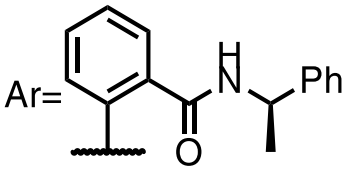
with coordinative groups

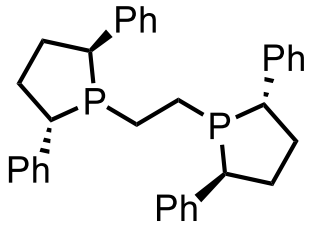


R1	R2	L	ee%
CO_2Me	OMe	37a	90
CO_2Me	F	37a	85
CO_2Me	CF_3	37a	15
CO_2Me	OAc	37a	85
CO_2Me	Me	35b	/
OAc	CF_3	35b	92
OAc	Me	37a	/
OAc	CN	37a	61
		35b	95



(S,S,S)-**L37a**





(S,S)-Ph-BPE (**L35b**)

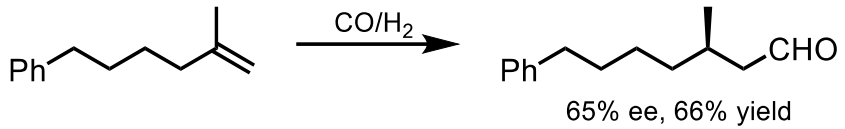
Electron-withdrawing substituents at the substrate favor branched selectivity

Eshon, J.; Foarta, F.; Landis, C. R.; Schomaker, J. M. *J. Org. Chem.* **2018**, *83*, 10207−10220.

Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

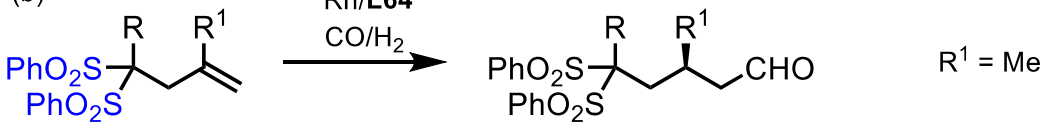
without coordinative groups: 1,1'-dialkyl alkenes

(a)



65% ee, 66% yield

(b)



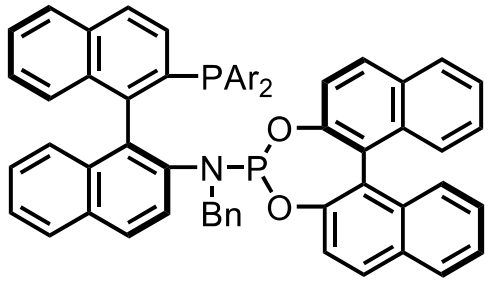
R^1 = Me

$R = (CH_2)_2Ph$, R^1 = Me

$R = (CH_2)_2Ph$, R^1 = Me

97% ee, 91% yield

Enhance reaction rate and ee



(S,S)-DTB-YanPhos (**L64**)

R	%ee	% yield
Me	90	88
Et	90	100
nPr	75	36
nBu	95	45
iBu	77	54
n-amyl	55	22
F	57	36
iPr	90	13
Bn	57	83
$(CH_2)_2Ph$	97	91
$(CH_2)_3Ph$	95	92
$(CH_2)_3SiMe_3$	94	94
$(CH_2)_3CF_3$	94	85
$(CH_2)_3CO_2Et$	97	91
$(CH_2)_3NBn_2$	86	84
$(CH_2)_2OPh$	96	88
$(CH_2)_2SPh$	95	92
R^1 = Et, $R = (CH_2)_2Ph$	95	82
R^1 = n-Hex, $R = (CH_2)_2Ph$	94	76

up to 97% yield and >99% ee

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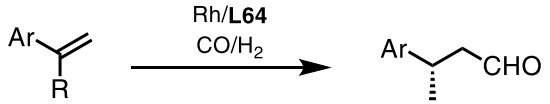
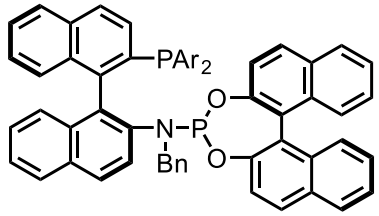
Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

without coordinative groups: 1-aryl-1-alkyl alkenes



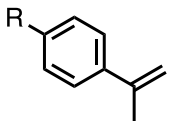


(S,S)-DTB-YanPhos (**L64**)
Ar = 3,5-tBu-C_6H_3

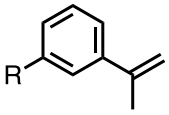
(*S,S*)-configured-binol group on the phosphite moiety and a hindered aryl group on the phosphine.

↓

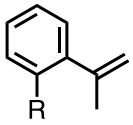
high conv. and ee



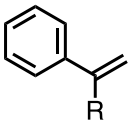
R	ee (%)	yield (%)
H	87	92
Me	87	92
OMe	89	90
Ph	90	95
CF_3	91	87
CO_2Me	90	91
F	90	88
Cl	90	93
Br	90	92



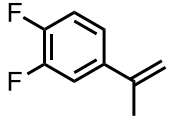
R	ee (%)	yield (%)
Me	86	88
CF_3	91	90



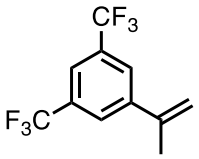
R	ee (%)	yield (%)
Me	90	87
CF_3	92	84



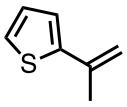
R	ee (%)	yield (%)
Et	91	90
nPr	90	93
nBu	90	93



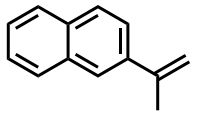
89% ee, 90% yield



91% ee, 93% yield



90% ee, 86% yield



85% ee, 94% yield

(*S,R*)-ligands

↓

conv. and ee drastically reduced.

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Asymmetric hydroformylation of alkenes
MAIN CONCLUSIONS

- Rh is currently the metal of choice in the AHF of a relatively large variety of alkene substrates.
- Characterization of resting states and mechanistic studies provided key data to develop efficient catalysts
- The discovery of several families of chiral ligands providing high ee's have made AHF a synthetically useful tool

QUESTIONS ????