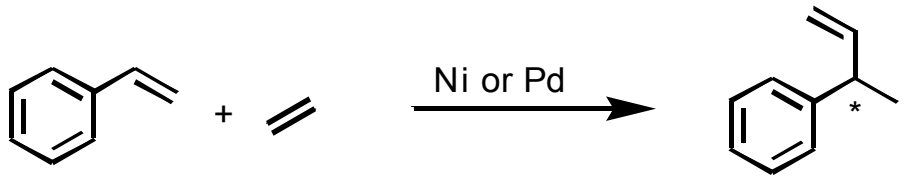
Asymmetric Hydrovinylation

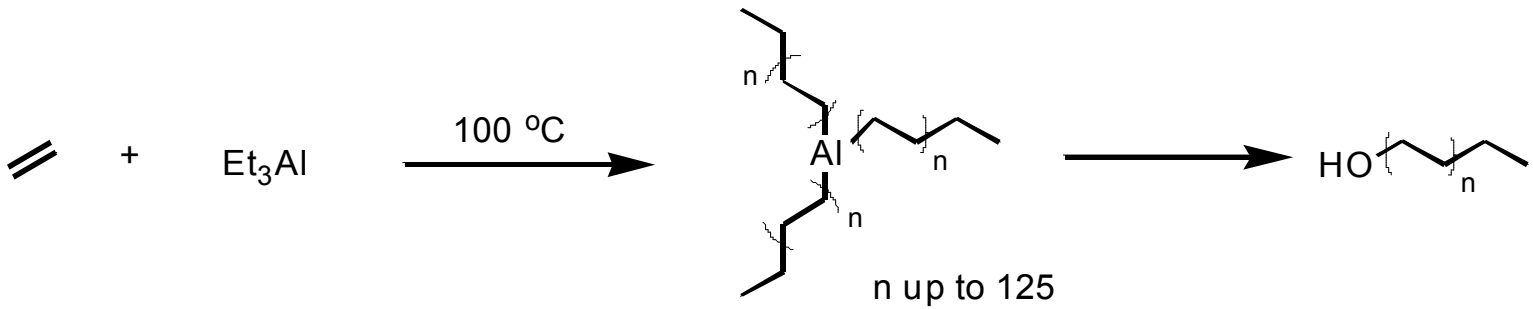


Jeff Kallemeyn

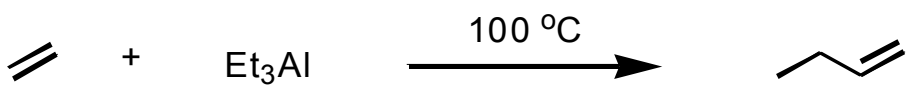
July 15, 2003

Olefin Polymerization

Ziegler (1953)



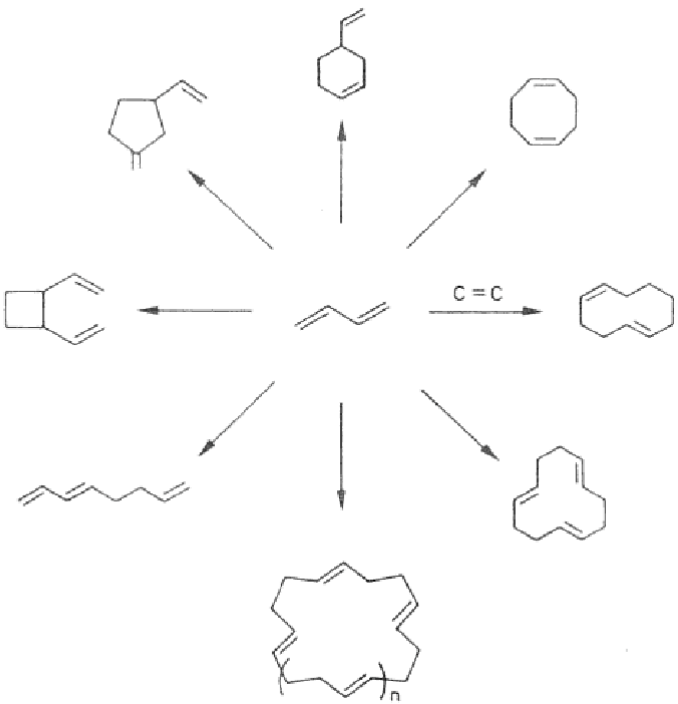
…then one day...



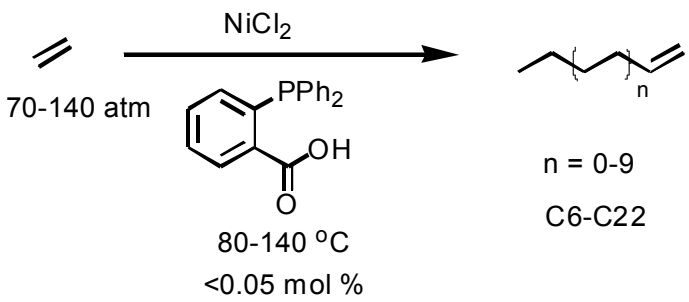
Attributed to cleaning centrifuge with H_2SO_4… leaving Ni salts behind

Applications of Ni Catalysts

Nickel catalyzed dimerization of butadiene



Shell Higher Olefin Process (SHOP):

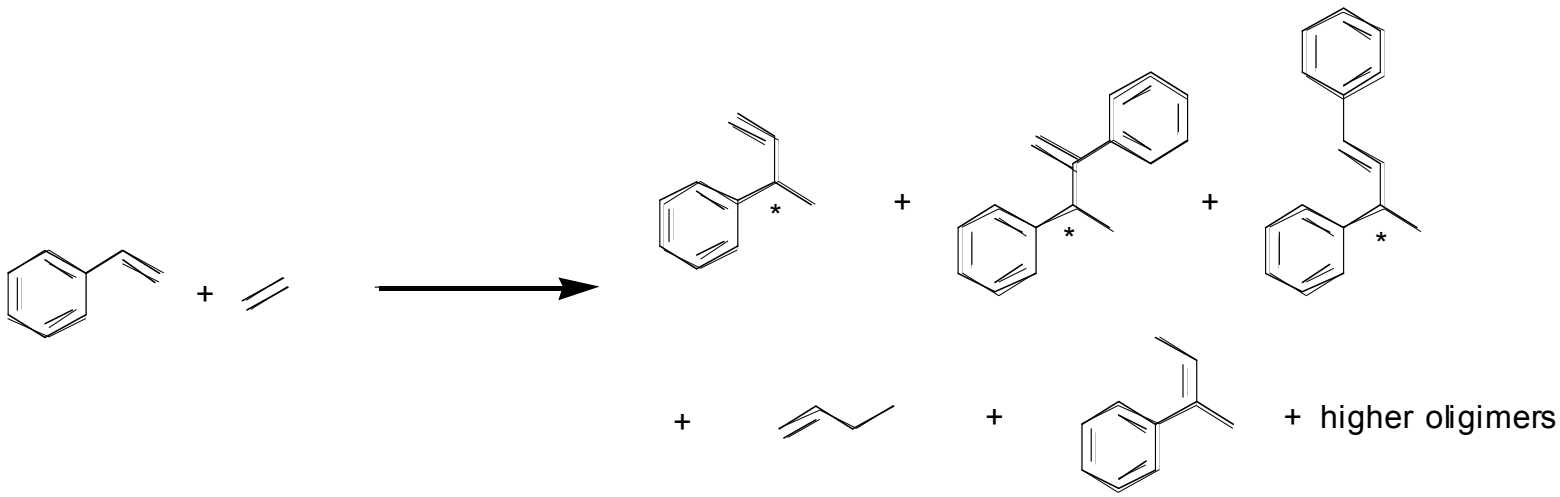


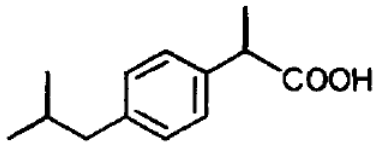
"NEODENE (SHOP) alpha and internal olefins are available directly from Shell in marine ships and barges, rail and road tank cars" www.shell.com

Nickel Catalysts are Used Widely

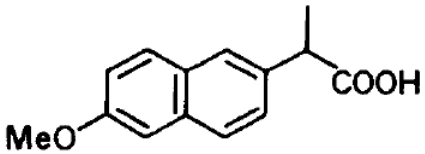
Keim, Angew. Chem. Int. Ed. 1990, 235.

Hydrovinylation

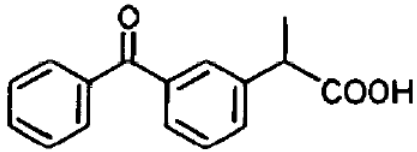




Ibuprofen

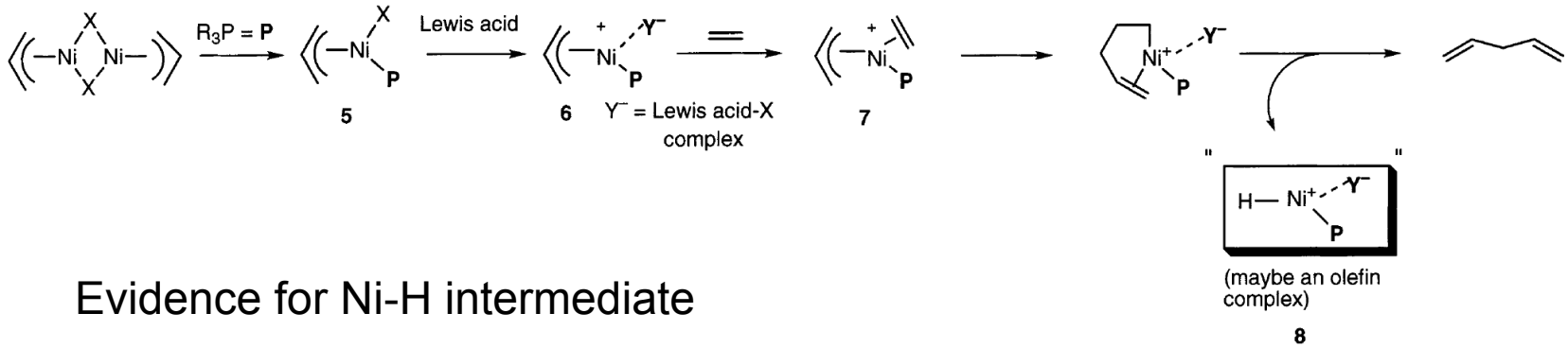


Naproxen

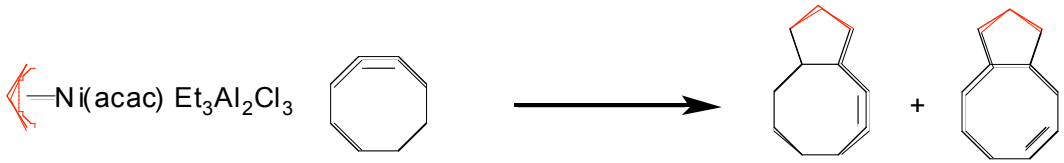


Ketoprofen

Mechanism: Initiation

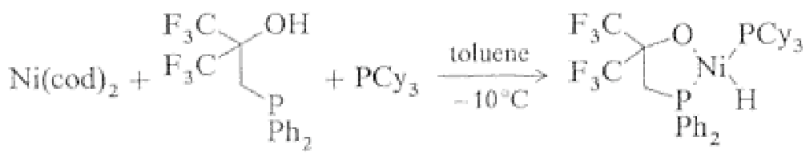


Evidence for Ni-H intermediate

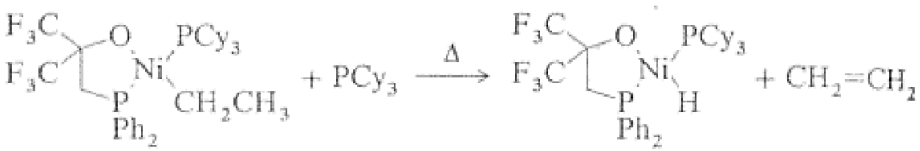
1) 

85% yield

No evolution of H_2 is observed

2) 

Ni-H detected by NMR analysis
which disappears upon addition of ethylene

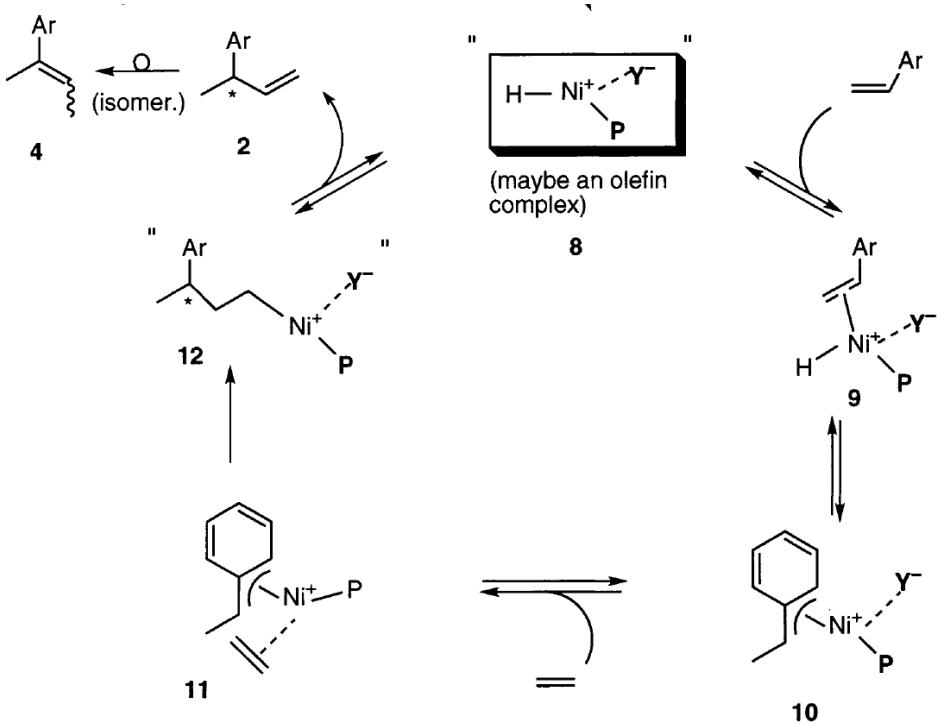


Isolated

3) Deuterium incorporation into products when D_4 ethylene is used

Bogdanovic, Adv. Organometallic Chem. 1979, 105.

Mechanism: Catalytic Cycle

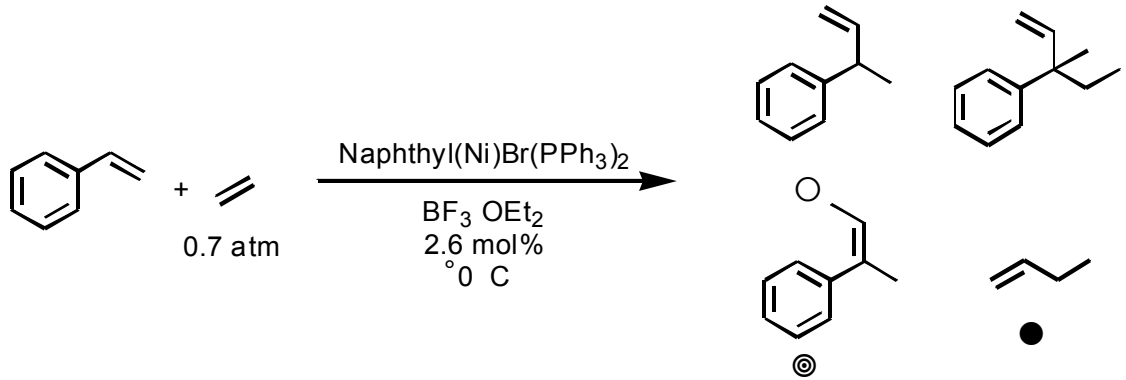


Evidence for **11** as catalytic resting state. (DiRenzo Ph.D. thesis (Brookhart))

Lewis acid (Y) creates coordinatively unsaturated Ni species.
Phosphine ligand (P) influences relative rates of dimerization (hetero- and homo-), oligimerization and isomerization.

RajanBabu, Chem. Rev. **2003**, ASAP

Reaction Course



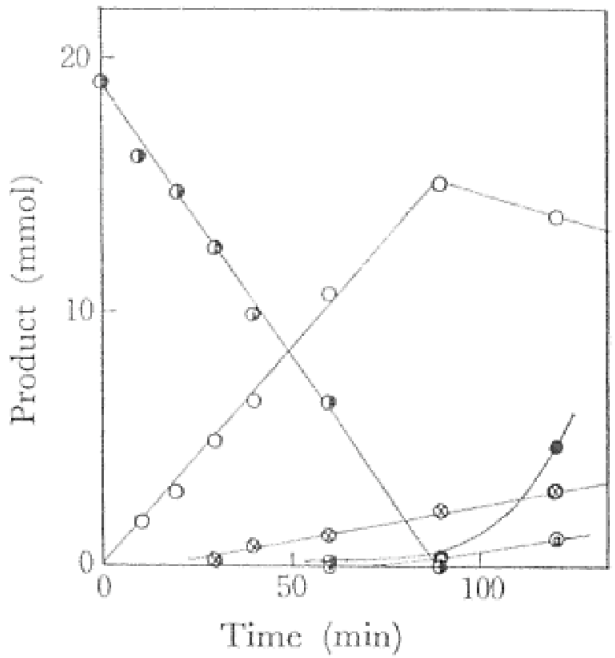
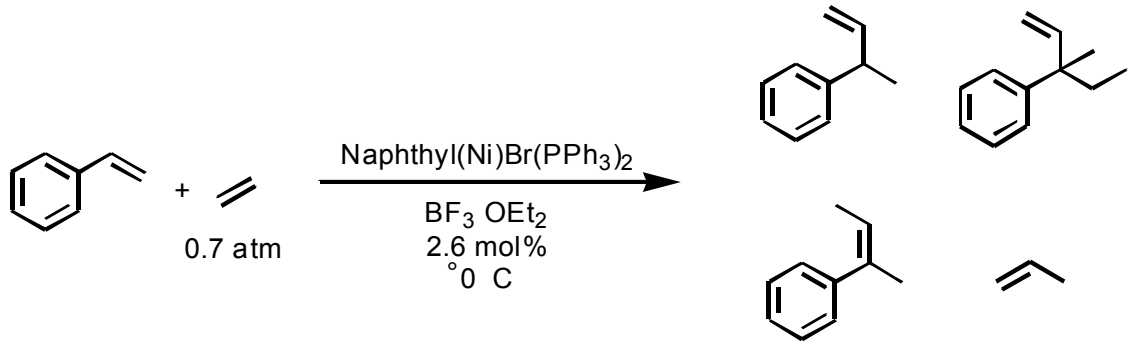


Fig. 1. Product distribution during the course of co-dimerization.
(1-naphthyl)NiBr($P\phi_3$)$_2$, 0.5 mmol; $BF_3 \cdot OEt_2$, 0.5 mmol; styrene 19.1 mmol; CH_2Cl_2, 30 ml; $P_{C_2H_5}$, 50 cmHg; temp. 0°C. ◑: styrene, ○: 3-phenyl-1-butene, ⊗: 3-methyl-3-phenyl-1-pentene, ◎: 2-phenyl-2-butene, ●: butenes.

91% selectivity for desired product

Kawata et al. Bull. Chem. Soc. Jpn. 1974 413.

Pressure and Lewis Acid Effects



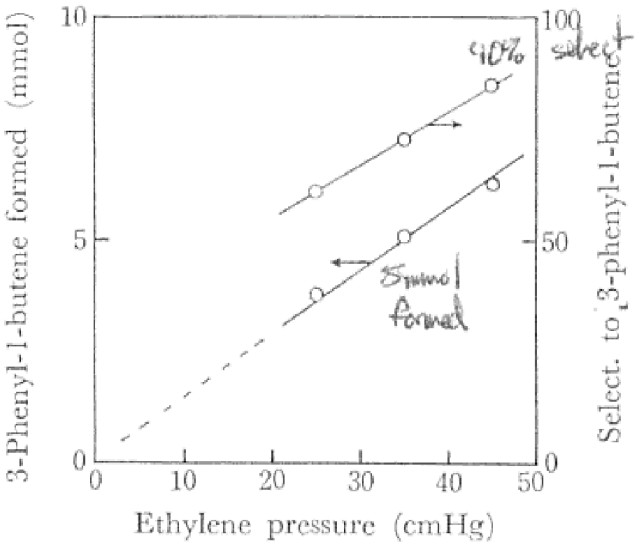


Fig. 2. Effect of ethylene pressure on the rate of co-dimerization; (1-naphthyl)NiBr($P\phi_3$)$_2$, 0.5 mmol; $BF_3 \cdot OEt_2$, 0.5 mmol; styrene, 19.1 mmol; CH_2Cl_2, 30 ml; temp. 0°C; time. 30 min.

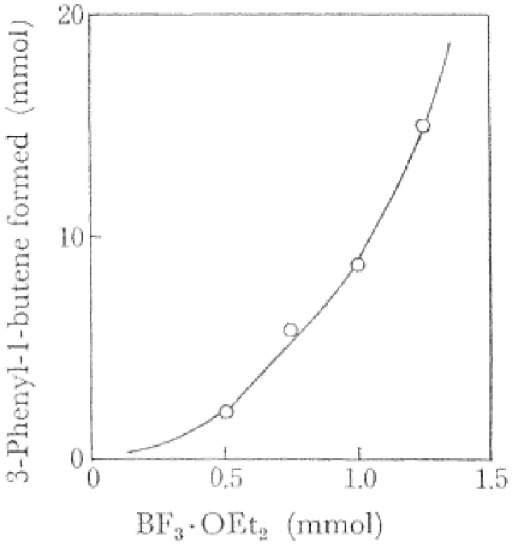


Fig. 3. Effect of the amount of $BF_3 \cdot OEt_2$. (1-naphthyl)NiBr($P\phi_3$)$_2$, 0.5 mmol; styrene, 19.1 mmol; CH_2Cl_2, 30 ml; $P_{C_2H_4}$, 35 cmHg; temp. 0°C; time 15 min.

Kawata et al. Bull. Chem. Soc. Jpn. 1974 413.

Temperature Effects

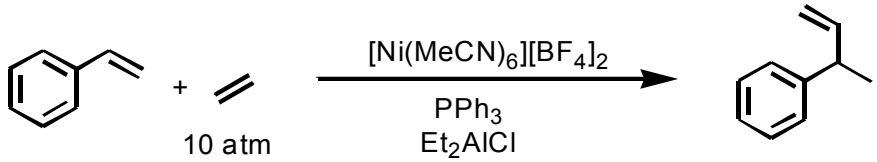


Table 1. Optimization of the reaction conditions towards **2a** (0.1 mmol $[Ni(MeCN)_6][BF_4]_2$; P=10 bar; 20 mL CH_2Cl_2, [Al]/[Ni]=5). Unless otherwise noted, total conversion of styrene was observed

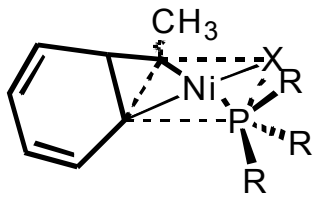
Entry	Time (min)	Sty/Ni	T (°C)	L	[L]/[Ni]	Yield (%)[a]
1	240	400	50	PPh_3	2	2
2	60	400	50	PPh_3	2	4
3	60	400	25	PPh_3	2	20
4	30	400	25	PPh_3	2	61
5	60	400	25	PPh_3	4	96
6	50	400	25	PPh_3	4	98
7[b]	360	1500	25	PPh_3	4	93
8[c]	360	6600	25	PPh_3	4	92
9[d]	75	200	25	dppe[e]	1	96

Styrene polymerization

[b] P=30 bar.
[c] P=35 bar, [Al]/[Ni]=8.
[d] [Al]/[Ni]=20.

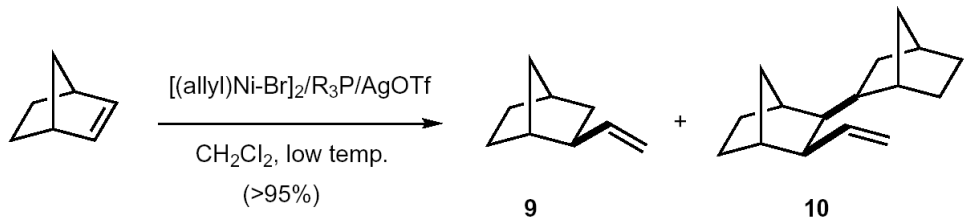
Monteiro, Tetrahedron, 2000, 7403

Influence of Ligand



Larger R on phosphine disfavors coordination of second styrene over ethylene.

R = *i*-Bu gives more dimerization than R = Bn

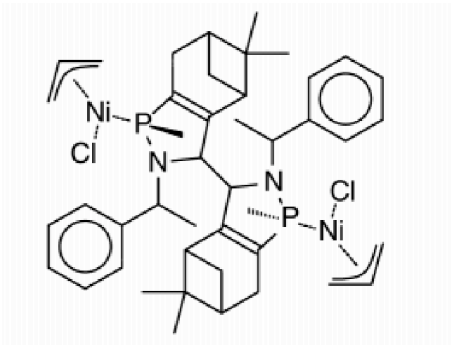


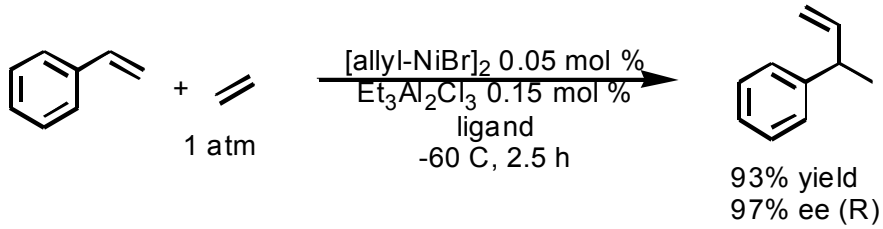
Phosphine	Cone angle	Temp.	**9**	**10**
$[cyhex]_3P$	180^0	-70 °C	100	0
Ph_3P	145^0	-55 °C	1	97

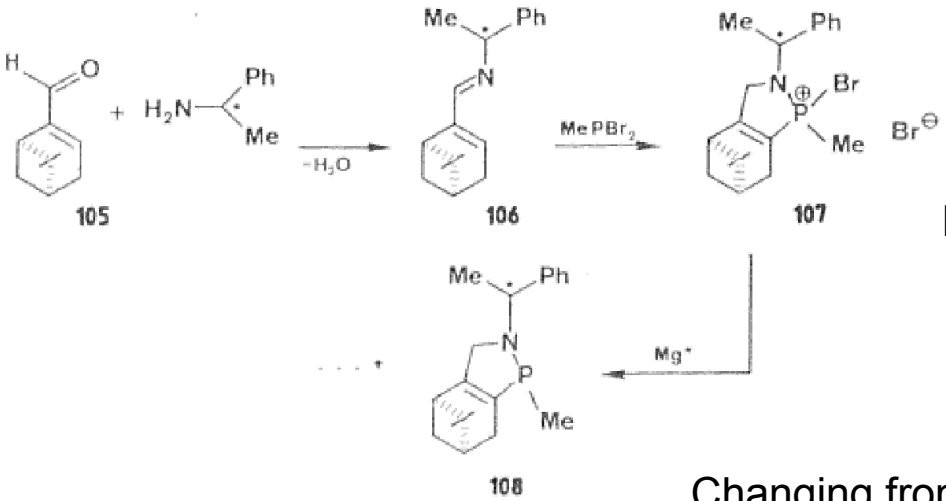
Ligand effect is largely steric in nature

RajanBabu, Chem. Eur. J. 1999, 1963.

Asymmetric Hydrovinylation







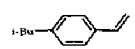
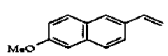
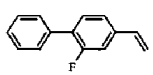
Isolated active component from mixture

Changing from (R)-phenylethylamine (RR ligand)
to (S)-phenylethylamine (RS ligand) gives poor ee's (6%)

Wilke Angew. Chem. Int. Ed. 1988, 186

Counterion Effects

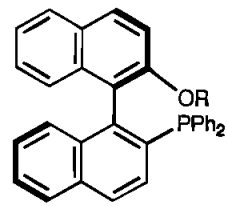
Al Lewis acids can cause problems with Lewis basic substrates

Entry	Substrate	% Yield[a]	Conditions[b]
1	styrene	>95 (99+)	(i)
2	3-methylstyrene	>95 (98)	(i)
3	4-methoxystyrene	>95 (98)	(i)
4	4-chlorostyrene	81 (89)	(i)
5	4-bromostyrene	>95 (98)	(i)
6	2-vinylnaphthalene	(99+)	(i)
7		(90) (97)	(i) with 0.5 mole% cat. (ii)
8		> 90 (99+) >97 (99+)	(i) with 1.4 mole% cat. (iii)
9		(88)	(i)

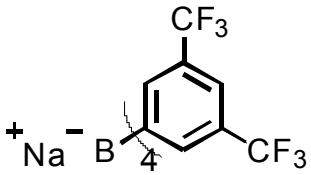
i) $[(allyl)NiBr]_2$ (0.35 mol %) PPh_3 AgOTf -55 °C 2h

ii) $[(allyl)NiBr]_2$ (0.7 mol %) (R)-MOP **8a** NaBARF -56 °C 2h

iii) $[(allyl)NiBr]_2$ (0.7 mol %) (R)-MOP **8b** NaBARF -56 °C 2h

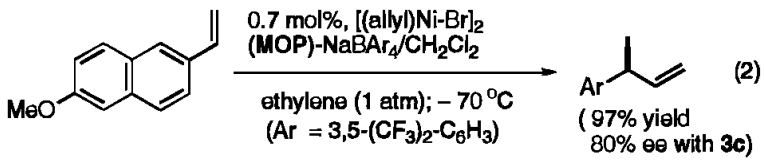


8a R = CH_3
8b R = CH_2Ph



RajanBabu, JACS 1998, 459.

Hemilabile Ligands

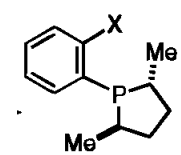


entry	ligand	group X in **3**	yield (%)	%ee	remarks
1	(*R*)-BINAP	Ph_2Ph	0		
2	**3b** (MOP)	OCH_3	>98	62	
3	**3c**	OCH_2Ph	97	73	−55 °C
			87	73	$AgNTF_2$
4	**3c**	OCH_2Ph	93	80	at −70 °C
5	**3d**	O-*i*-Pr	69	70	
6	**3e**	CH_2CH_3	12	<3	
7	**3f**	$OC(O)CH_3$	0		
8	**3g**	$P(O)Ph_2$	0		
9	**4a**	$OC(H)(Ph)(CH_3)$	96	71	(*R*,*R*)
10	**4b**	$OC(H)(Ph)(CH_3)$	79	65	(*R*,*S*)

[a] See eq 2 for typical procedure.[6] Isolated yield; ee determined by HPLC.

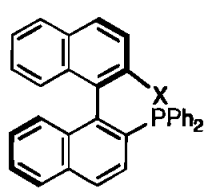
Hydrovinylation of Styrene

entry	additive	yield of product (%) **5a**	yield of product (%) **5c**	remarks
1	AgOTf	94	<4	37%ee *(S)* with **5a**
2	$AgClO_4$	95	<2	29% isom. with **5a**
3	$AgNTf_2$	<2	48	47%ee *(S)*, 9% isom. with **5c**
4	$AgSbF_6$	<2	94	48%ee *(S)* with **5c**
5	$NaBAr_4$[b]	<2	97	50%ee *(S)* with **5c**



5 a-d

	X
5a	H
5b	OCH_2Ph
5c	CH_2OCH_2Ph
5d	CH_2OCH_3

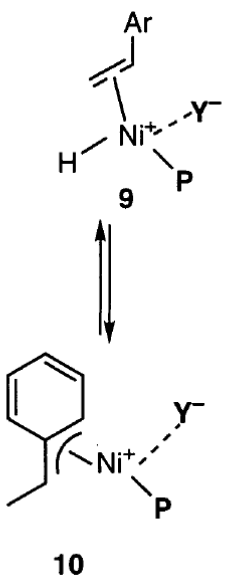


BINAP X = PPh_2
3a X = OH
3b X = OMe (MOP)
3c X = OCH_2Ph
3d X = O-*i*-Pr
3e X = CH_2CH_3
3f X = $OC(O)CH_3$
3g X = $P(O)Ph_2$

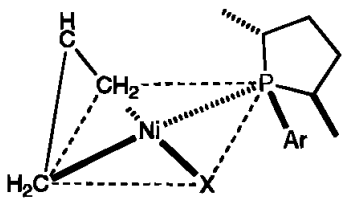
^1H NMR studies show instability of (allyl)Ni**5a** complexes with Br, OTf, SbF_6 and BARF counterions.
(allyl)Ni**5c**BARF complexes are highly stable (rt for 2 days)

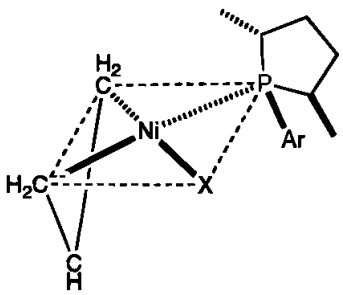
RajanBabu, JACS 1999, 9899.

Stereochemical Determining Step

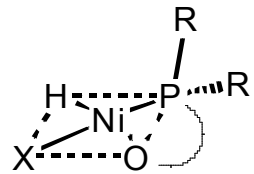


Enantiotopic face of styrene chosen at this step. Resulting allyl complex assumed to be stable through remainder of steps.

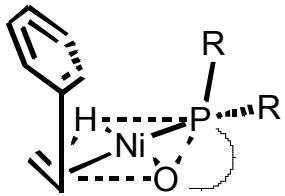




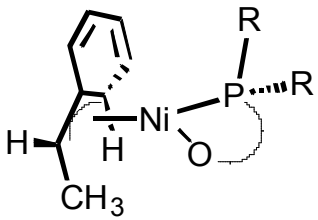
Diastereomers of ((allyl)[Ni][5a](Br)



H should be cis to P
due to sterics and ligand directing

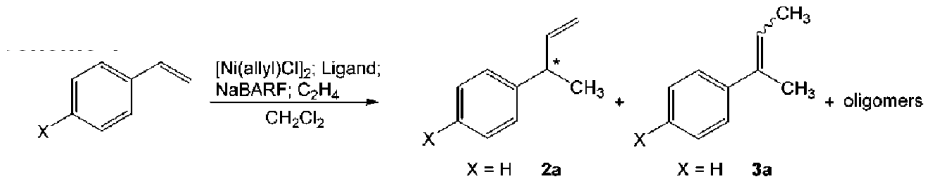


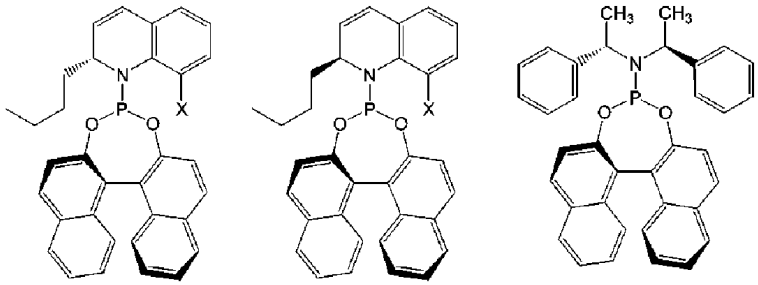
Coordination of styrene



Transfer of H, face is selected from steric influences of P(R)

Phosphoramidite Ligands





(R_a,R_C)-**5**; X = OMe
(R_a,R_C)-**6**; X = Cl

(R_a,S_C)-**5**; X = OMe
(R_a,S_C)-**6**; X = Cl

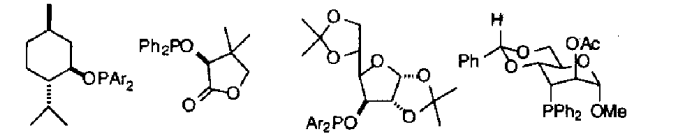
(R_a,S_C,S_C)-**7**

entry	ligand	substrate	T [°C]	p (C_2H_4) [bar]	t [h]	**1**/Ni	conv. [%]	selectivity [%] **2**	**3**	oligomers[a]	ee (**2**) [%]
1	(R_a,R_C)-**5**	**1a**	0	44	1	280	99.7	85.4	13.3	<1.5	7.6 (*R*)
2	(R_a,S_C)-**5**	**1a**	−30	49	2	280	13.5	93.3	3.1	3.7	56.4 (*R*)
3	(R_a,S_C)-**6**	**1a**	−32	12	2	300	100	<1	<1	100	–
4	(R_a,R_C)-**6**	**1a**	−32	12	2	300	33.1	96.2	0.4	3.7	87.2 (*S*)
5	(R_a,S_C,S_C)-**7**	**1a**	−70	~1	4	620	100	84.9	4.3	8.1	94.8 (*S*)
6a	(R_a,S_C,S_C)-**7**	**1a**	−65	~1	4	4600	89.2	100	<1	<1	91.1 (*S*)
6b			−65→rt	~1	16	5490	82.7	96.4	<1	3.0	91.4 (*S*)
7	(R_a,S_C,S_C)-**7**	**1a**	0	~1	2	13270	100	78.1	9.1	12.7	76.2 (*S*)
8[b]	(R_a,S_C,S_C)-**7**	**1a**	−50	~1	0.3	1330	99.5	99.1	0.9	<1	89.7 (*S*)

Modular Ligands Show Promise

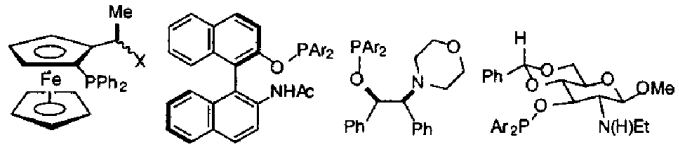
Leitner, JACS 2002, 736.

Tunable Ligands



6 (86%; <5%) 7 (87%; 6%) 8 (68%, 29%) 9 (>99%, 42%)

No activity:



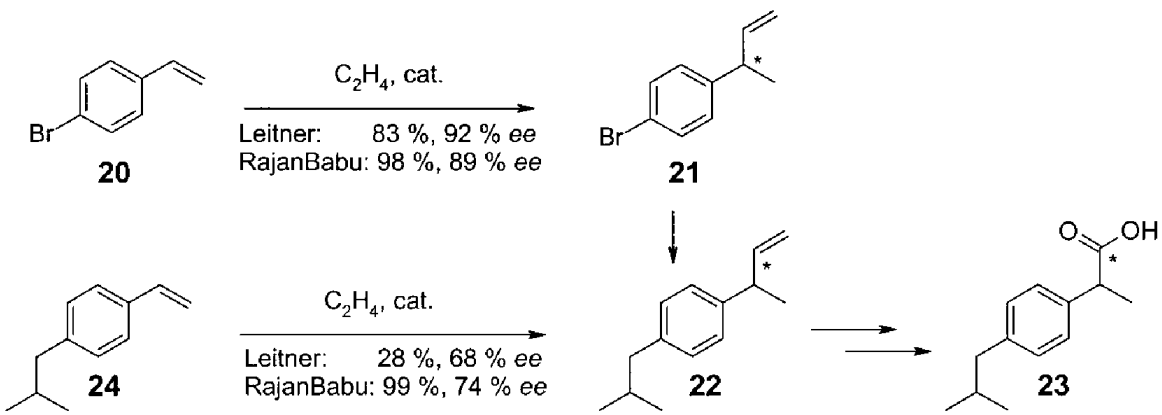
10, X = NMe_2, OMe 11 12 13

[Ar = 3,5-*bis*-CH_3-C_6H_3] [Ar = 3,5-*bis*-CF_3-C_6H_3]

No.	ligand	Ar	yield[2]	selectivity[3]	%ee[4]
1.	14	A	62	>99	32 (S)
		B	35	>99	28 (*S*)
2.	15	A	93	96	9 (S)
		B	93	>99	45 (*S*)
3.	16	A	89	89	81 (*S*)
		B	42	>99	62 (*S*)
4.	17	Z = CF_3CO	40[5]	40	87 (*S*)
	18	Z = PhCO	23[5]	23	82 (*S*)

Ar = A

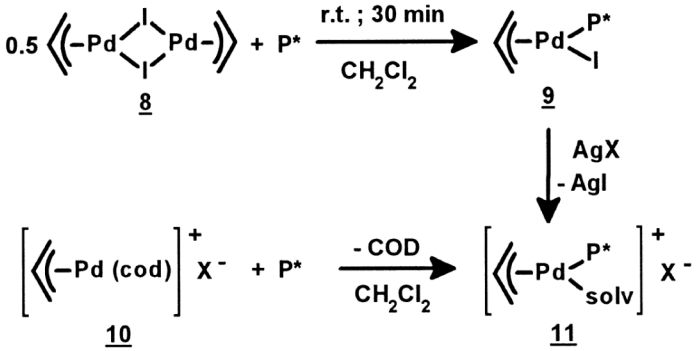
[1] See eq 1. **A** Ar = 3,5-$(CH_3)_2$−C_6H_3; **B** Ar = 3,5-$(CF_3)_2$-C_6H_3. [2] Isolated yield of 3-phenyl-1-butene. [3] Percentage of 3-phenyl-1-butene among all products. [4] Determined by HPLC. [5] Conversion >99%.



Scheme 6. Asymmetric synthesis of Ibuprofen.

RajanBabu, JACS 2002, 734.

Palladium Catalyzed Hydrovinylation



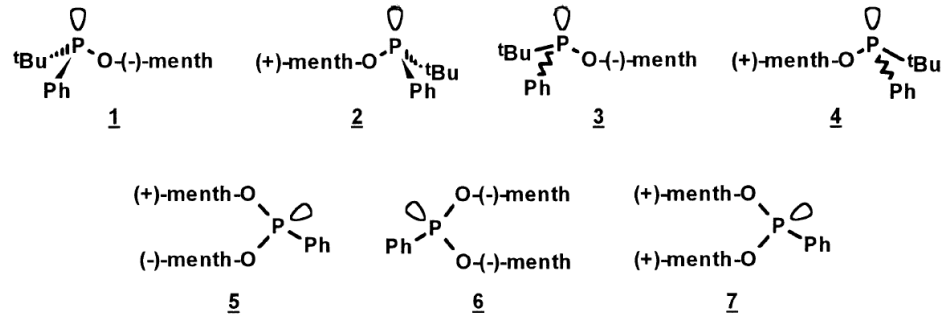


Table 3
Effect of cosolvents

Run	Cosolv.	Conv.[a] /%	Yield[b] /%	$S^c_{codimers}$ /%	S^d_{3PB1} /%	% ee	Isomer Yield
1	–	76	48	64	98	85	27
2	EtOAc	91	70	80	96	82	18
3	*t*-BuOAc	77	52	70	96	85	23
4	menthOAc	76	53	72	97	86	21

$T = 0°C$; reaction time = 2 h; 10 bar initial pressure; P/Pd = 1; styrene/Pd = 500–1000; 20 ml CH_2Cl_2; 2 ml styrene (17.4 mmol); 3 ml cosolvent added; complex **8** as precursor.
[a]Conversion of styrene.
[b]Yield of 3PB1.
[c]Σ(codimers)/conv.
[d](3PB1)/Σ(codimers).

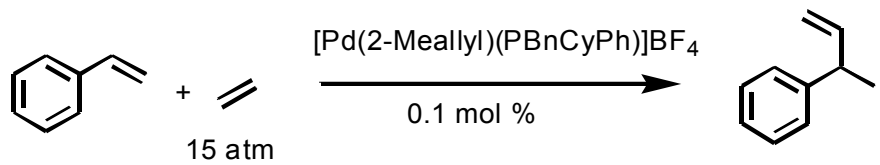
Table 4
Cooperativity of chiral auxiliary and chiral phosphorus

Ligand	Conv.[b] /%	Yield[c] /%	$S^d_{codimers}$ /%	S^e_{3PB1} /%	% ee	Config.	Isomer Yield
1	95	79	89	94	86	*S*	10
2	100	74	91	82	83	*R*	9
3	89	70	86	92	37	*S*	13
4	84	65	83	93	29	*R*	14
5[a]	74	39	77	68	–	–	18
6[a]	75	44	94	62	42	*R*	5
7[a]	49	34	85	81	38	*S*	7

$T = 10°C$; reaction time = 1 h; 10 bar initial pressure, P/Pd = 1; styrene/Pd = 500–1000; 20 ml CH_2Cl_2; 2 ml styrene (17.4 mmol); complex **10** as precursor.
[a]Complex **8** as precursor; reaction time = 4 h.
[b]Conversion of styrene.
[c]Yield of 3PB1.
[d]Σ(codimers)/conv.
[e](3PB1)/Σ(codimers).

Vogt, J. Organometallic Chem. 1998, 187.

Palladium Catalyzed Hydrovinylation



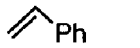
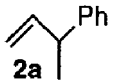
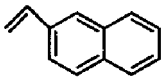
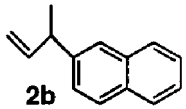
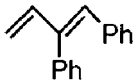
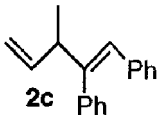
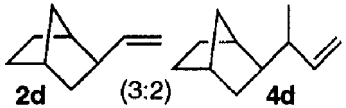
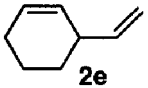
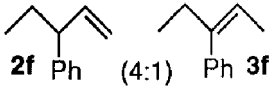
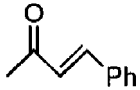
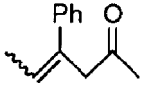
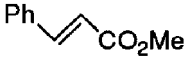
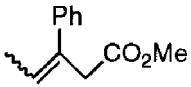
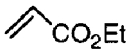
run	catalyst[b]	olefin	solvent	T (°C)	t (min)	conversion (%)[c]	selectivity (%)[d]	C16-fraction (%)[e]	TOF/h[f]	ee (%)
1	rac	styrene	THF	10	60	16.2	100	0.6	56	
2	*R*	styrene	THF	25	60	33.2	99	3.0	300	45-*S*
3	rac	styrene	CH_2Cl_2	0	120	13.2	100	0.8	62	
4	*R*	styrene	CH_2Cl_2	5	90	64.8	99	4.3	405	61-*S*
5	rac	styrene	CH_2Cl_2	10	60	61.5	97	3.2	585	
6	*R*	styrene	CH_2Cl_2	15	30	61.5	98	5.5	1290	60-*S*
7	*S*	styrene	CH_2Cl_2	15	30	32.5	99	2.9	590	59-*R*
8	rac	styrene	CH_2Cl_2	15	60	99.9	83	5.2	947	
9	*S*	2-vinylnaphthalene	CH_2Cl_2	15	20	83.0	98.5		250	84-*R*
10	*R*	2-vinylnaphthalene	CH_2Cl_2	15	60	100	58		100	85-*S*
11	**6**	styrene	CH_2Cl_2	15	30	21.3	100	1.2	400	

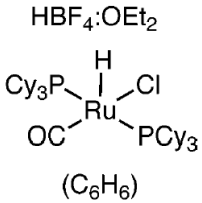
[a] Initial ethylene pressure 15 bar; ratio olefin/catalyst 1000:1 for styrene and 100:1 for 2-vinylnaphthalene. [b] Catalyst: filtered solutions of (R_P)-**5** or (S_P)-**5** + olefin + $AgBF_4$, except for run 11, where compound **6** was used. [c] Conversion of starting olefin. [d] Selectivity: % of 3-aryl-1-butene with respect to the hydrovinylation fraction (3-aryl-1-butene and 2-aryl-2-butenes). [e] C16-fraction: styrene dimers. [f] TOF/h calculated as the total amount of arylbutenes formed.

Isomerization major drawback to Pd catalysts

Granell, Organometallics, 1999, 3511.

Ruthenium Catalyzed Hydrovinylation

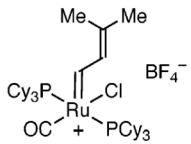
entry	alkene	product (s)	1 (mol%)	time (h)	temp (°C)	% yield[b]
1		 **2a**	0.5	6	20	98 (93)
2		 **2b**	0.5	8	20	94 (89)
3		 **2c**	1.0	6	75	92 (90)
4		 **2d** (3:2) **4d**	0.25	1	20	95[c]
5		 **2e**	2.0	6	50	94[c]
6		 **2f** (4:1) **3f**	2.0	15	50	55-60
7		 **3g** (*E*/*Z* = 3:1)	3.0	15	75	65
8		 **3h** (*E*/*Z* = 2.5:1)	2.0	24	50	65-70
9		 **3i** (E/Z = 2.5:1)	1.0	6	75	70[d]



No asymmetric examples

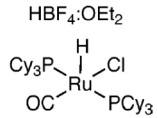
Yi, Organometallics, 2001, 802.

Ruthenium Catalyzed Hydrovinylation



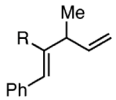
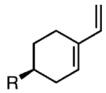
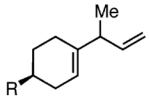
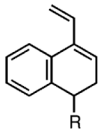
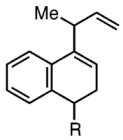
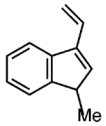
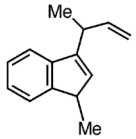
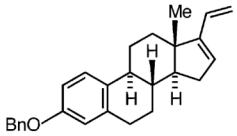
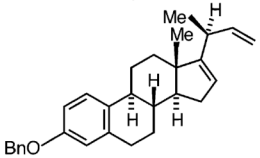
(CH_2Cl_2)

1

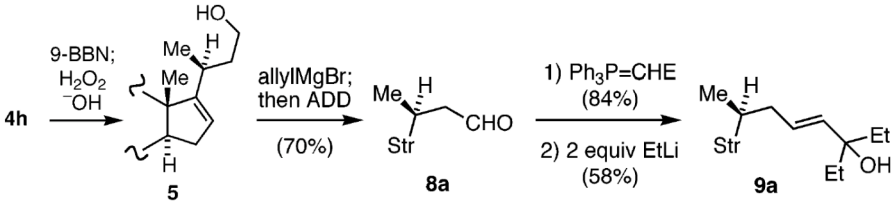


(C_6H_6)

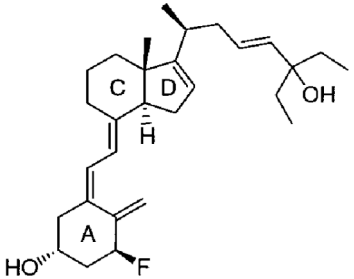
2

1-vinylcycloalkene	catalyst/rxn time	product (isolated yield)
 **3a**, R = Ph **3b**, R = Me	1% **2**, 6 h 1% **1**, 16 h	 **4a**, R = Ph (90%)[a] **4b**, R = Me (75%)
 **3c**, R = H **3d**, R = C(Me)=CH_2	1% **1**, 22 h 1% **2**, 20 h	 **4c**, R = H (62%) **4d**, R = C(Me)=CH_2 (57%)[b]
 **3e**, R = H **3f**, R = Me	1% **2**, 20 h 1.5% **1**, 15 h	 **4e**, R = H (67%) **4f**, R = Me (75%)[b]
 **3g**	1.5% **1**, 15 h	 **4g**, (56%)[b]
 **3h**	2% **2**, 7 h	 **4h**, (88%)[c]

[a] From ref 5b. [b] Mixture of diastereomers (1:1). [c] Single diastereomer.



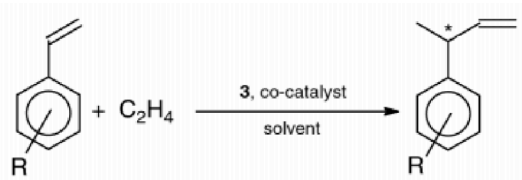
Lack of methods for preparation of (S) side chain in vitamin D analogs

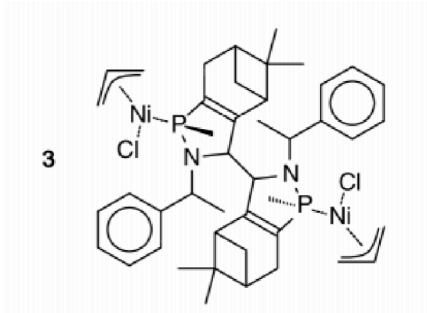


3: Ro 26-9228

Yi, Org. Lett. 2003, 1567.

Applications of Hydrovinylation





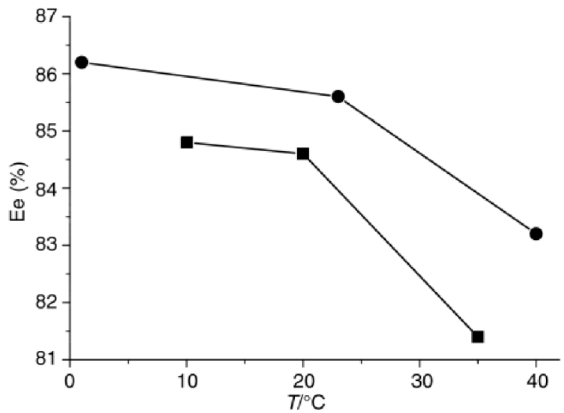


Fig. 1 Enantiomeric excess of **2a** obtained from hydrovinylation using the **3**–NaBARF catalyst in (●) CO_2 and (■) CH_2Cl_2 at different temperatures.

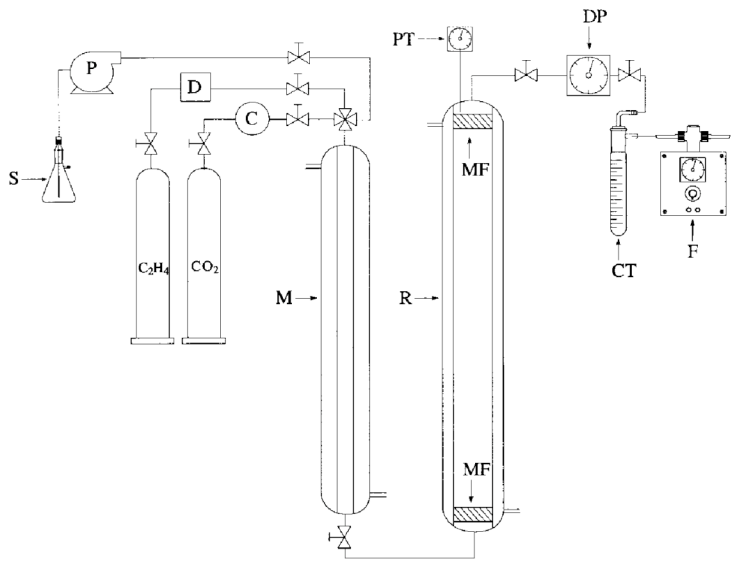


Figure 1. Schematic view of the continuous-flow reaction apparatus. The parts are labeled as follows: C: compressor, CT: cold trap, D: dosimeter, DP: depressurizer, F: flowmeter, M: mixer, MF: metal filter, P: HPLC pump, PT: pressure transducer and thermocouple, R: reactor, S: styrene.

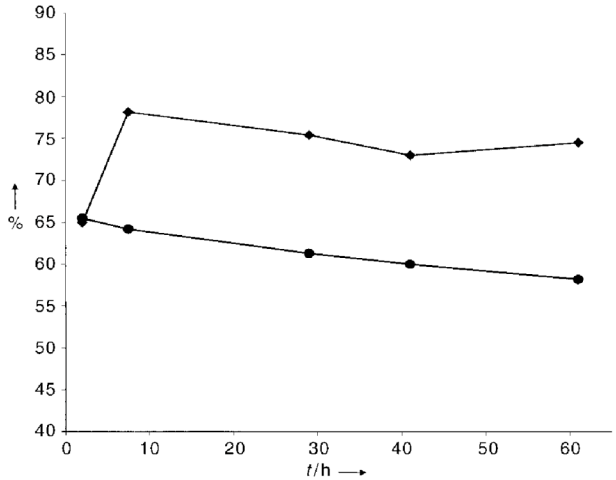
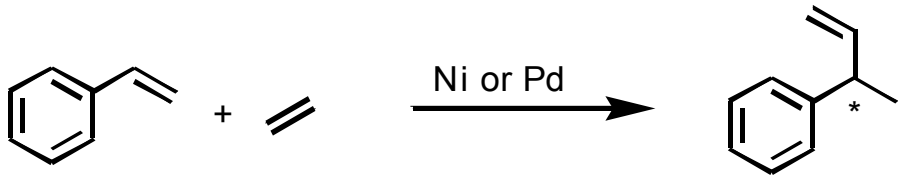


Figure 2. Lifetime study for catalyst **1** activated and immobilized in the system [EMIM][$(CF_3SO_2)_2N$]/compressed CO_2 during the hydrovinylation of styrene,(●: *ee* value; ◆: conversion).

Leitner, Chem. Comm. 1999, 1583; Angew. Chem. Int. Ed. 2001, 2697.

Conclusion



Nickel catalysis are the most developed.

Low catalyst loadings are amenable to industrial procedures.

Atom economical.

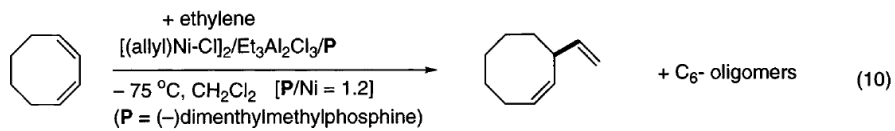
Terminal alkene is a good handle for additional chemistry.

Method limited in the short term to conjugated dienes.

Use in fine chemical synthesis will require additional ligand development.

Poor understanding of the factors that influence side reactions
--(Isomerization, Dimerization and Oligimerization)

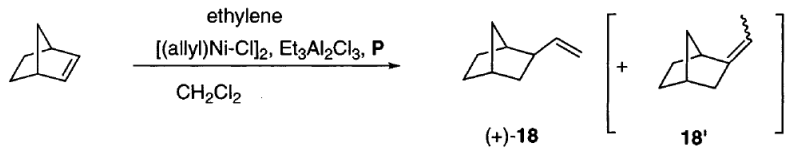
Other Substrates



(10)

21 (unspecified yield; 53% ee)

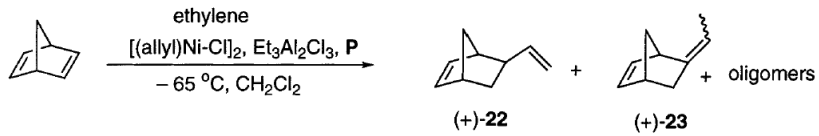
(at **P**/Ni = 3.8, 70% ee at 0^0 C)



(11)

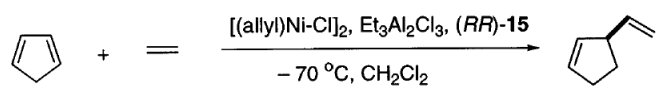
P = (–)-isopropyldimenthylphosphane 65% ee at -70 °C

P = (*RR*)-**15** (87 % yield; 57% ee at –65 °C)



(12)

P = (–)-isopropyldimenthylphosphane (49% yield; 77.5% ee) (~ 50%)

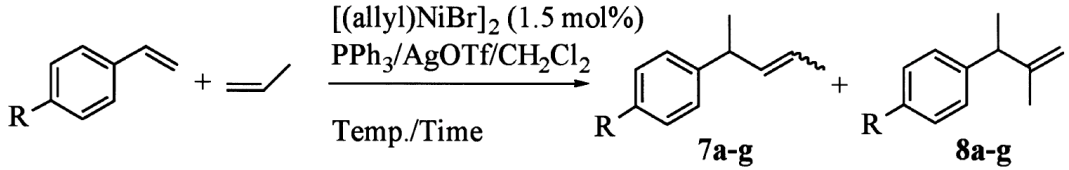


(S/C = 86; **P**:Ni:Al =1:1:1)

(35 % yield; 92% ee)

24

Propene



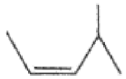
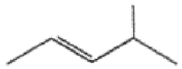
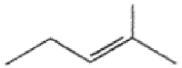
Entry	R	Temperature (°C)	Time (min)	Isolated yield (%)	Ratio of products (**7**:**8**)
a	*i*-Bu	−15	15	96	3:1
b	OMe	−15	60	86	4:1
c	Cl	0	15	94	4:1
d	Br	0	10	95	4:1
e	OAc	−10	30	93	4:1
f	C(O)Ph[a]	10	15	94	4:1
g	$N(Ts)_2$[a]	10	25	92	2:1

[a] 3 mol% of $[(allyl)NiBr]_2$ was used.

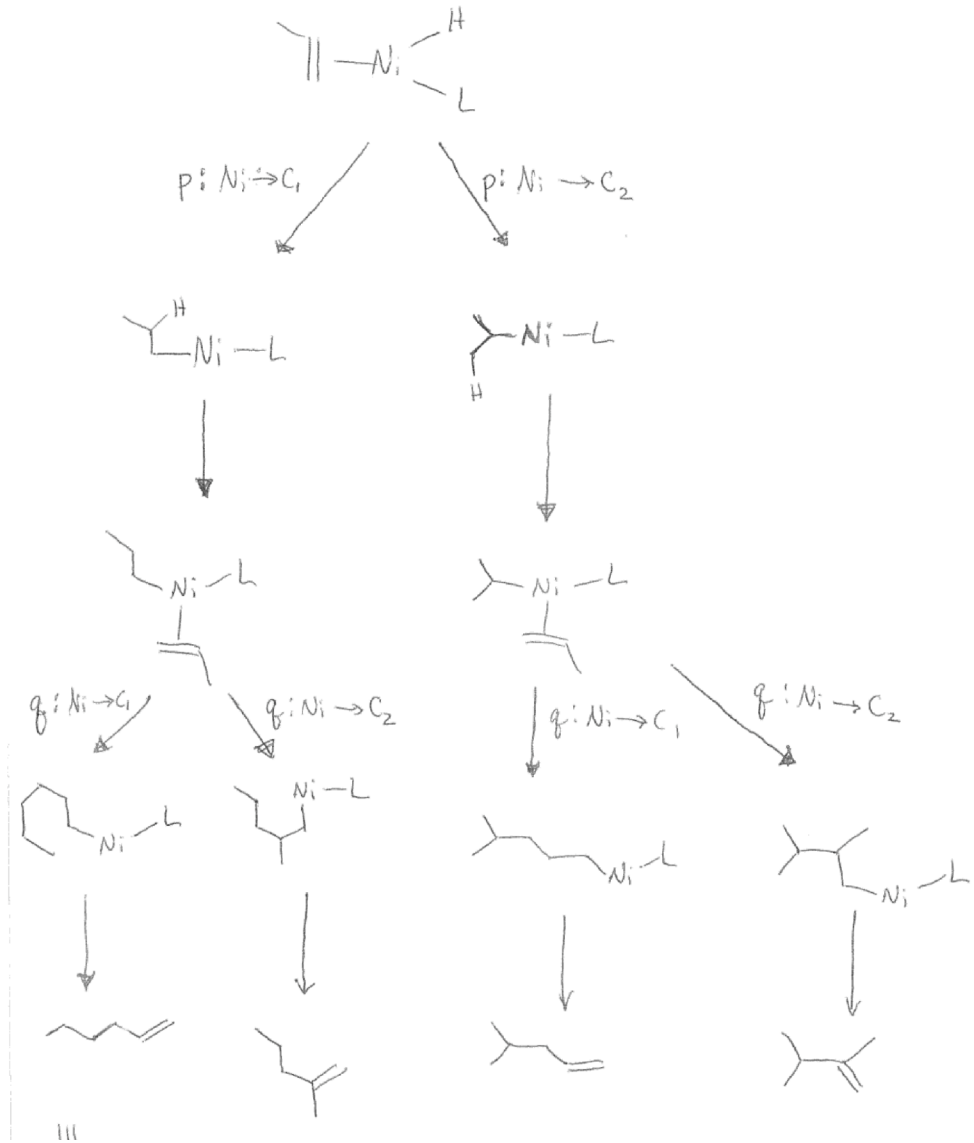
RajanBabu, Tetrahedron 2000, 2145

Influence of Ligand on Propene Dimerization

TABLE II
ISOMERIZATION OF 4-METHYL-1-PENTENE AT 0°C[a,b]

Olefin	Concentration (%)
	0.2
	0.9
	7.1–7.3
	83.6–84.0
	7.8–8.6

[a] Catalyst: π-$C_3H_5NiCl[P(CH_3)_3]$–$C_2H_5AlCl_2$.
[b] From Karmann (*51*).



Ref

Influence of Ligand on Propene Dimerization

Phosphine	Σ*n*-Hexene	ΣMethylpentene	Σ2,3-Dimethylbutene
—	19.8	76.0	4.2
$P(C_6H_5)_3$	21.6	73.9	4.5
$(C_6H_5)_2PCH_2P(C_6H_5)_2$	12.2	83.0	4.7
$(C_6H_5)_2PCH_2C_6H_5$	19.2	75.4	5.1
$(C_6H_5)_2P(CH_2)_3P(C_6H_5)_2$	20.1	73.3	6.6
$P(CH_3)_3$	9.9	80.3	9.8
$(C_6H_5)_2P\text{-}i\text{-}C_3H_7$	14.4	73.0	12.6
$P(C_2H_5)_3$	9.2	69.7	21.1
$P(C_4H_9)_3$	7.1	69.6	23.3
$P(CH_2C_6H_5)_3$	6.7	63.6	29.2
$(\text{cyclo-}C_6H_{11})_2P—P\text{-}(\text{cyclo-}C_6H_{11})_2$	4.4	46.5	49.2
$P(\text{cyclo-}C_6H_{11})_3$	3.3	37.9	58.8
$P(i\text{-}C_3H_7)_3$	1.8	30.3	67.9
$(t\text{-}C_4H_9)_2PCH_3$	1.2	24.5	74.0
$(t\text{-}C_4H_9)_2PCH_2CH_3$	0.6	22.3	77.0
$(i\text{-}C_3H_7)_2P\text{-}t\text{-}C_4H_9$	0.1	19.0	80.9
$(t\text{-}C_4H_9)_2P\text{-}i\text{-}C_3H_7$	0.6	70.1	29.1

PROPENE[a,b]

[a] Catalyst: $(\pi\text{-}C_3H_5NiX)_2$–$(C_2H_5)_3Al_2Cl_3$–Ligand; −20°C; 1 atm.
[b] From Bogdanović *et al.* (*4*) and Karmann (*51*).

Phosphine	*p*	*q*
$P(C_6H_5)_3$	25:75	18:82
$(C_6H_5)_2PCH_2P(C_6H_5)_2$	21:79	13:87
$(C_6H_5)_2PCH_2C_6H_5$	27:73	13:87
$(C_6H_5)_2P(CH_2)_3P(C_6H_5)_2$	24:76	10:90
$P(CH_3)_3$	15:85	15:85
$(C_6H_5)_2P\text{-}i\text{-}C_3H_7$	29:71	27:73
$P(C_2H_5)_3$	17:83	29:71
$P(C_4H_9)_3$	18:82	34:66
$P(CH_2C_6H_5)_3$	22:78	45:55
$(\text{cyclo-}C_6H_{11})_2PP(\text{cyclo-}C_6H_{11})_2$	18:82	62:38
$P(\text{cyclo-}C_6H_{11})_3$	26:74	83:17
$P(i\text{-}C_3H_7)_3$	20:80	86:14
$(t\text{-}C_4H_9)_2PCH_3$	12:88	85:15
$(t\text{-}C_4H_9)_2PC_2H_5$	20:80	97: 3
$(i\text{-}C_3H_7)_2P\text{-}t\text{-}C_4H_9$	15:85	97: 3
$(t\text{-}C_4H_9)_2P\text{-}i\text{-}C_3H_7$	69:31	98: 2

[a] Taken from Karmann (*51*).

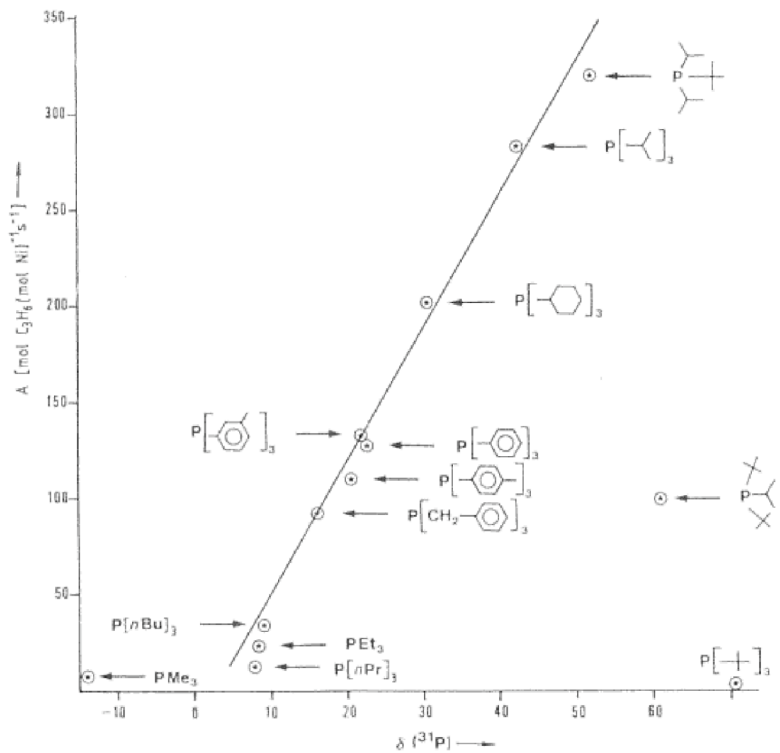
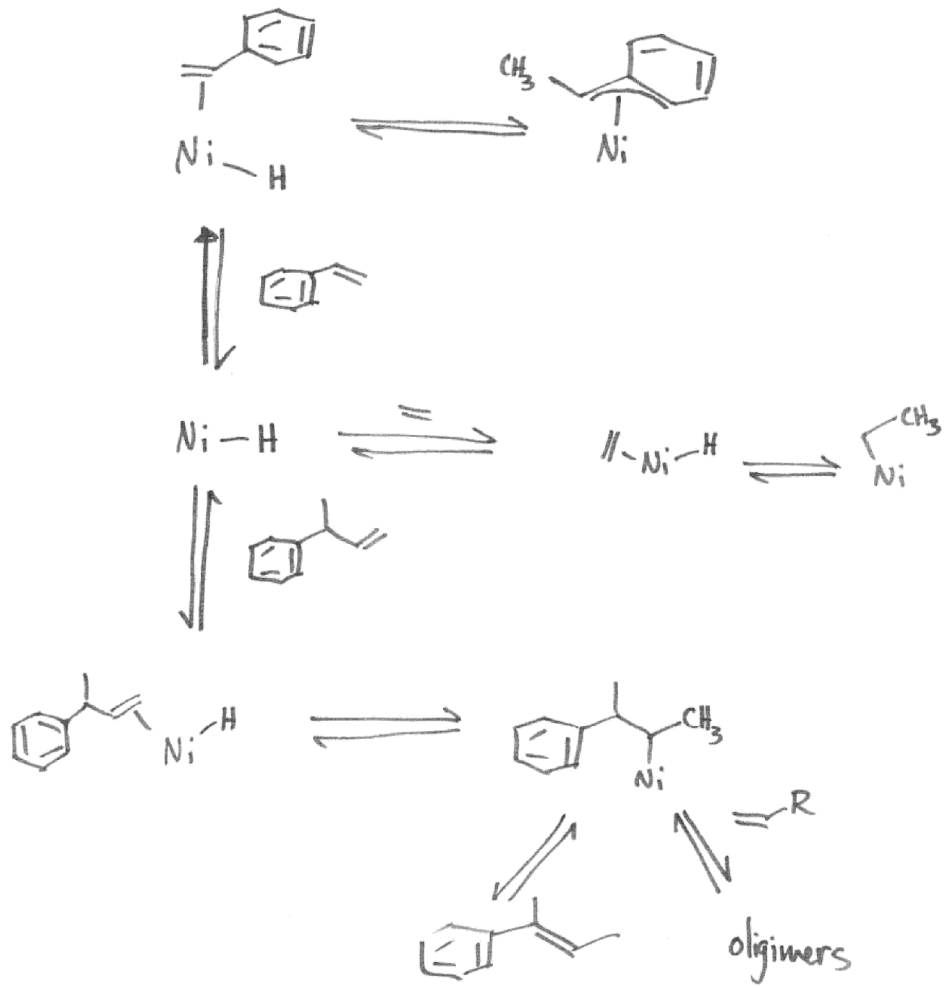


Fig. 11. The dependence of catalyst activity A on the phosphane ligand and the correlation of the activity with the $\delta(^{31}P)$-NMR values of the complexes **89**, X = $BrAlEtCl_2$, at −45°C.

Ref

Oligimerization and Isomerization



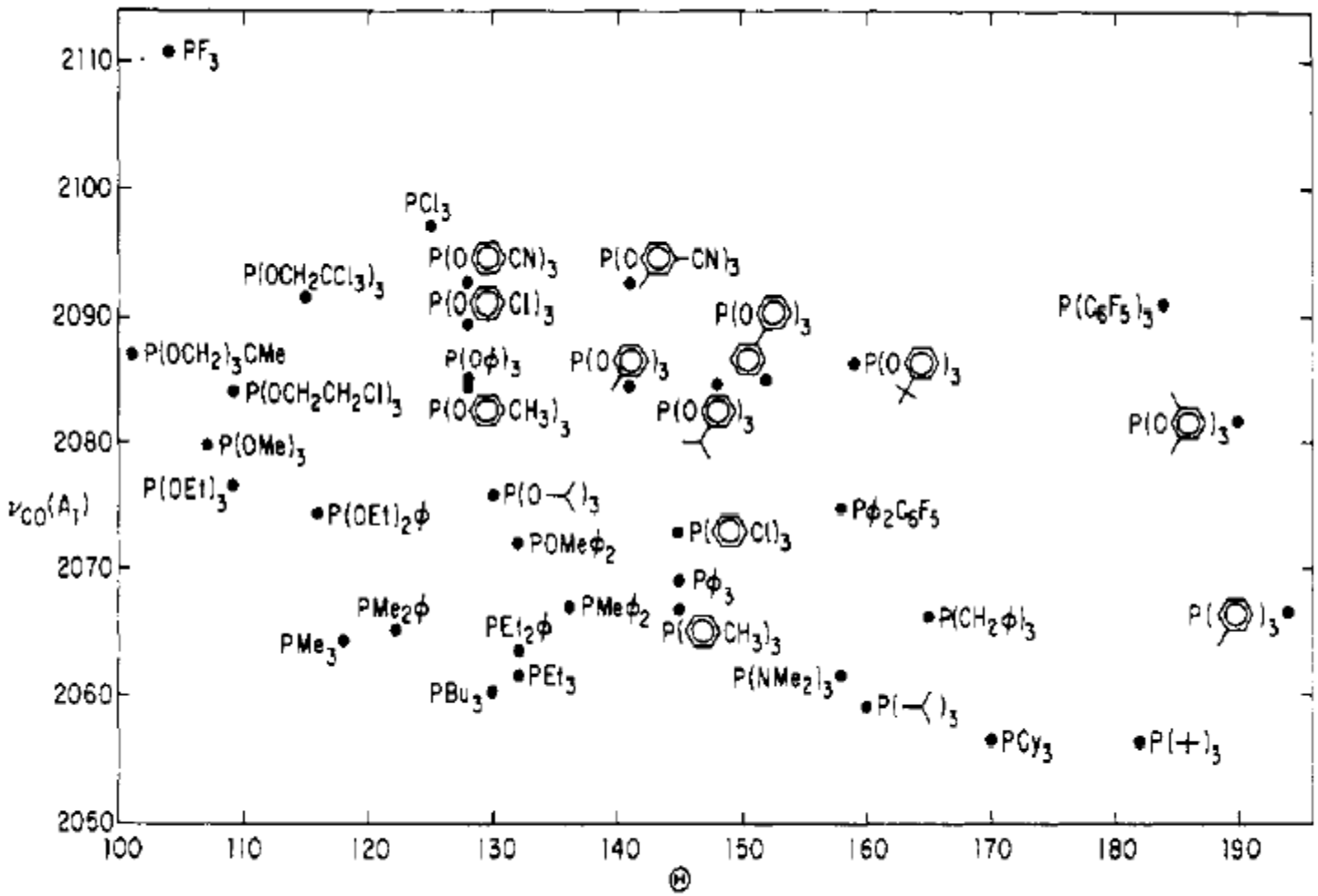


Figure 25. Steric and electronic map.

Tolman Chem. Rev. 1977 313