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Asymmetric Hydrovinylation Reaction

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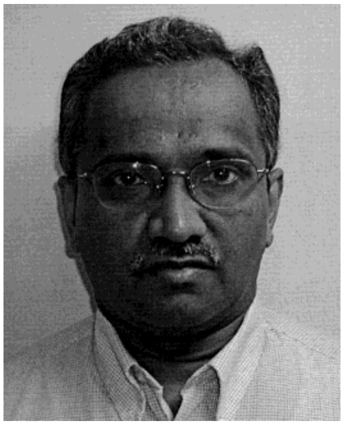
Contents

1. Introduction

Carbon−carbon bond-forming reactions are among the most important types of bond constructions in organic chemistry. Yet, the paucity of methods for the stereoselective incorporation of abundantly available carbon feedstocks such as CO, CO_2, HCN, or simple olefins to prochiral substrates is one of the major limitations in this area.[1] Ideally, from a manufacturing perspective, these reactions should proceed near ambient conditions under the influence of a catalyst capable of delivering very high turnover frequencies (number of moles of product/mole of catalyst/unit time) and high regio- and stereoselectivities. In addition to the obvious economic benefits, such reactions would also enrich our repertoire of environmentally benign chemical processes. One potentially important class of such reactions is the $[Ni^{+}-H]$-catalyzed oligomerization of olefins, which forms the basis of the dimersol technology (olefin dimerization, eq 1)[2] and the shell higher olefin process (SHOP, eq 2).[3] These two immensely successful commercial processes showcase the rewards of modern organometallic research, especially of the role of catalyst tuning to achieve highly selective carbon−carbon bond-forming reactions. The catalytic dimerization of propene proceeds with an astonishingly high rate of over 625 000 $[\text{propene}][\text{Ni}]^{-1}\,[\text{h}]^{-1})$ for the precatalyst, $[\eta^3\text{-(allyl)Ni(PR}_3)]^+\,[\text{RAlX}_3]^-$, making this one of the best homogeneously catalyzed reactions known.[4] Applications of this chemistry for the synthesis of fine chemicals have been the subject of much research ever since its initial discovery.



Dr. RajanBabu had his early education in India at Kerala University and the Indian Institute of Technology, Madras. He obtained a Ph.D. degree from the Ohio State University in 1978 working with Professor Harold Shechter, and was a postdoctoral fellow at Harvard University with the late Professor R. B. Woodward. He then joined the research staff of DuPont Central Research and Development, becoming a Research Fellow in 1993. He returned to Ohio State as a Professor of Chemistry in 1995. His primary research interests are in applications of organometallic reagents for stereoselective synthesis, asymmetric catalysis, free radical chemistry, and organic chemistry in aqueous medium.

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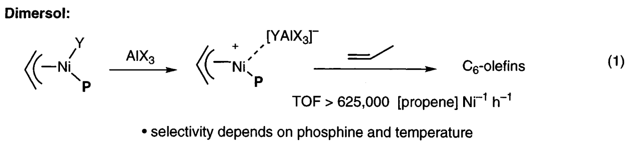
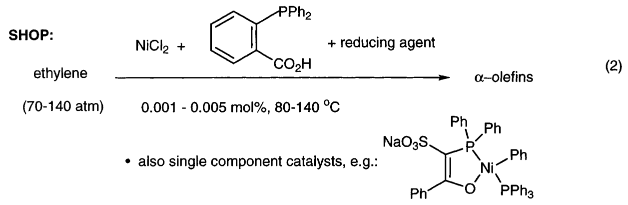
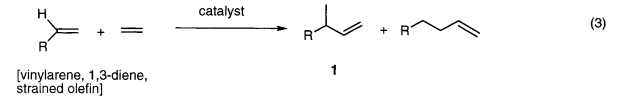
Among these, hydrovinylation, the addition of a vinyl group and a hydrogen across a double bond (eq 3), which is a prototypical example of a heterodimerization reaction, has attracted the most attention.[4,5] Since the branched product (**1** in eq 3) is chiral, a regio- and enantioselective version of the reaction would provide easy access to a variety of olefin-derived products including carboxylic acids.

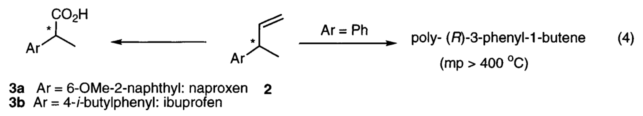


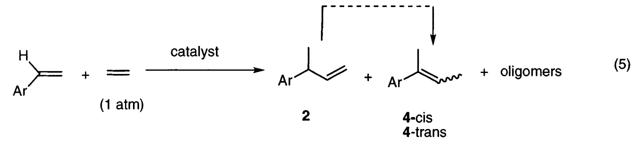


We begin this review with a brief history of the development of the hydrovinylation reaction and follow that by a more comprehensive coverage of the various asymmetric variants. Unfortunately, much of the details of the pioneering studies on asymmetric catalysis of hydrovinylation from the Mulheim group have appeared only in doctoral dissertations,[6] review articles,[4a,5a] and patents, making a meaningful comparisons with the more recent work difficult.[6j] Of special concern are the enantiomeric ratios of chiral products, many of which appear to have been determined only by measurements of optical activity. In many instances, precise data on selectivity (the proportion of the chiral product among *all* dimeric/oligomeric products) are also not available. The data presented in this review are restricted to what is available in the open literature, the values being extracted principally from a review article[5a] and a US patent.[7] Only hydrovinylation reactions that give a chiral product (for example, reactions between ethylene and vinylarenes, cyclic 1,3-dienes and strained olefins) are discussed in this review. Among these, the hydrovinylation of vinylarenes (eq 3, R = aryl) is the most investigated reaction, since the branched product can be easily transformed into widely used antiinflammatory 2-arylpropionic acids (eq 4).[8] Except for naproxen, (*S*)-2-(6-methoxynaphthyl)-2-propionic acid, these drugs are sold as racemates, even though the major bioactive component is the (*S*)-enantiomer. Asymmetric hydrovinylation of styrene is also of interest because one of the products, (−)-(*R*)-3-phenyl-1-butene, has been reported to give a very high-melting (>400 °C) isotactic polymer under Ziegler conditions.[4a]

Publications that appeared until the end of 2002 have been reviewed for this article.







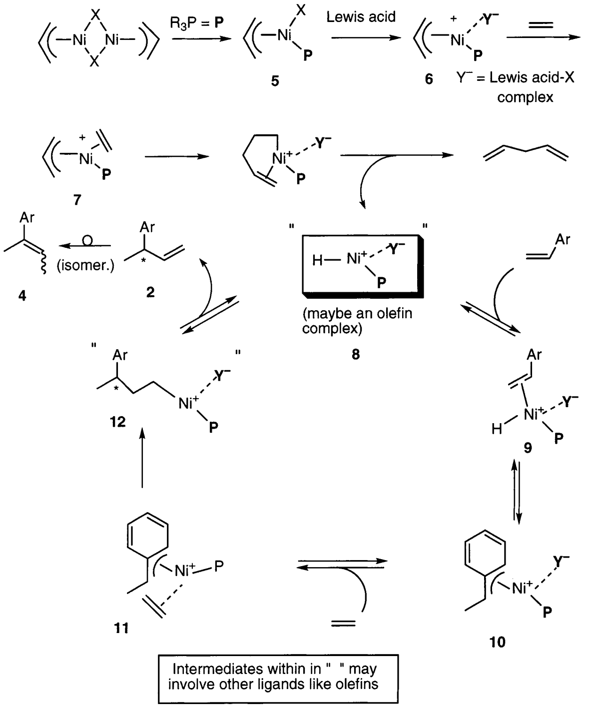
2. Early History

The hydrovinylation reaction has a long history. The first reference in the open literature to transition-metal catalyzed heterodimerization reactions[9] involving ethylene can be traced to Alderson, Jenner, and Lindsey[10a] who used hydrated Rh and Ru chlorides to effect codimerization of ethylene at high pressures (1000 psi) with a variety of olefins including styrene and butadiene. Styrene served as a prototypical test case for most of the investigations reported to date. In many instances, especially those involving metals other than nickel, the reactions are complicated by isomerization of the initially formed 3-aryl-1-butene (**2**) to a mixture of the *Z*- and *E*-2-aryl-2-butenes (**4**) and oligomerization of the starting olefins (eq 5). Among the catalysts that have been used in these early studies are $RhCl_3{\cdot}3H_2O$,[10] $NiCl_2(PBu_3)_2/Et_2AlCl$,[10c] $Ni(acac)_2/Et_3Al/BF_3.OEt_2/P(OPh)_3$,[11] $Ni(Ar)(Br)(PR_3)_2{-}BF_3{\cdot}OEt_2$,[12] $NiX_2/AlEt_3/BF_3{\cdot}OEt_2/P(OPh)_3$,[13] $Ni(acac)_2/DPPE/Et_yAl_2Cl_{6-y}$,[14a] $PdCl_2(PhCN)_2$,[15] $Pd(OAc)_2/Et_2P(CH_2)_3PEt_2$/*p*-toluenesulfonic acid,[16] $PhPd(PPh_3)_2X{-}H_2O$,[17] $Co(acac)_x/DPPE/Et_yAl_2Cl_{6-y}$,[14a] and $RuCl_3/RuCl_4{\cdot}nH_2O$.[10a,10b] Notable among these early studies are also the first examples of asymmetric hydrovinylations of 1,3-cyclooctadiene,[18a] norbornene, norbornadiene, and a codimerization of propene and 2-butene using a combination of $[(\eta^3\text{-}C_3H_5)NiCl]_2/Et_3Al_2Cl_3$ and monoterpene-derived chiral phosphines.[18b] Even though the selectivities are poor, these historically important results will be discussed in greater detail later under asymmetric catalyzed reactions.

3. Mechanism of the Hydrovinylation Reaction

All the available evidence[1d,3a,4a,11−13,19,20] points to a mechanism involving a cationic nickel hydride intermediate associated with a weakly coordinated counterion (**8,** Scheme 1). This species is formed by the Lewis-acid-assisted dissociation of the Ni−X bond from the 16-electron phosphine complex **5**, coordination of ethylene (or styrene), insertion into the allyl-Ni bond, and subsequent β-hydride elimination. If the resulting metal hydride (**8**) is the true catalyst, its addition to the prochiral faces of styrene will determine the enantioselectivity of the process when the attached phosphine is chiral. The hydride addition would give a benzylic complex **10**, which can be stabilized through η^3-coordination. Ligand substitution by ethylene leads to the cationic intermediate **11**. At higher concentrations of ethylene and styrene, in related $(allyl)Pd^+/[BARF]^-/Cy_3P$-mediated hydrovinylation of styrene, Brookhart and DiRenzo have provided strong support for the structure of a catalyst

Scheme 1. Proposed Mechanism for the Heterodimerization of Ethylene and of Styrene



resting state depicted as **11**.[20] Insertion of ethylene followed by β-hydride elimination from **12** regenerates the metal-hydride catalyst **8** and the product **2**. If this mechanism has any validity, some of the limitations encountered in early experiments could be explained as follows:

(a) Poor reactivity of substrates carrying heteroatoms could result from interaction of the Lewis acid (e.g., Et_2AlCl) with these centers.

(b) Isomerization of the initially formed 3-aryl-1-butene to 2-aryl-2-butenes (**2** → **4**) could be mediated by the metal hydride via sequential addition–elimination reactions.

(c) Inhibition of the reaction by chelating phosphines (vide infra) might arise from the lack of a coordination site for a second olefin in the putative (allyl)Ni^+[**P**∼**P**] intermediate similar to **6** (or the benzyl-Ni intermediate **10**).

(d) Diminished reactivity of electron-deficient vinylarenes might arise from low rate of metal hydride addition (**8** → **10**).

Even though most of the early studies are characterized by lack of any selectivity, they provided significant mechanistic information such as kinetic evidence for the addition of a cationic nickel hydride [Ni^+–H] to styrene as a key step in the reaction.[11,13] Studies of D-distribution in the products when the hydrovinylation is carried out with $D_2C{=}CD_2$ provide further evidence for the involvement of the $[Ni{-}H]^+$ intermediate.[12c] Reactivities of various substituted styrenes and solvent effects were also probed in these studies. It has been found that the reactivity pattern of 4-substituted styrenes in the Ni-catalyzed reactions is best explained by a mechanism in which coordination of the vinyl arene to a cationic Ni species is a key step (**8** → **9**, Scheme 1). Deactivating effect of a solvent was found to increase in the order, CH_2Cl_2, PhF, PhCl, PhMe, $PhNO_2$, Et_2O, consistent with an inhibitory effect of a Lewis basic species.[13b]

4. Improved Procedures for the Reaction

In more recent work, yield and selectivity of the Ni- and Pd-catalyzed hydrovinylation reactions have been improved considerably by varying the ligands and reaction conditions. A lone example of a better Ru-catalyzed reaction has also been reported.[21a,b] Careful examination of the published procedures reveals that only a few of these are preparatively useful. These results are summarized in Table 1. Even though some asymmetric variations are included in this list (entries 7, 14–17) to illustrate the viability of the various ligand types, these reactions will be discussed separately in greater detail under sections 6 and 7.

4.1 Nickel-Catalyzed Reactions

By modifying the conditions originally reported by by Kawata et al.[12] (entry 1, Table 1), Muller discovered[22a] that $[ArNi(PR_3)_2(MeCN)]^+\ BF_4^-$ (Ar = mesityl, R = benzyl) served as an efficient catalyst for the hydrovinylation of styrene (entry 2). Very high turnover rates (1915 h^{-1}) at substrate/catalyst ratios of 1000 are observed in THF at room temperature under 15 atm of ethylene. Excellent selectivity for 3-arylbutenes (>97% among coupling products) at shorter reaction times can be achieved under these conditions. Methoxy and chloro substituents on the aromatic ring are tolerated well, but not a nitro group, where very low conversion is observed. Activity decreases with substituents in the sequence $Cl{\sim}OMe{\sim}CH{=}CH_2{\sim}H{\sim}Et > Me \gg NO_2$. Poor yields of the 3-arylbutenes from ring-alkylated styrenes is indeed surprising. The rate of reaction falls unacceptably low below 20 °C, whereas at higher temperatures, isomerization to the conjugated products is seen. Since there is an exothermic ethylene polymerization at the end of the relatively more facile heterodimerization, control of temperature is crucial to get good selectivities. Substitution on the olefinic carbons leads to very low conversions even at higher temperatures. Solvents such as THF, CH_2Cl_2, and dioxane are acceptable, where as MeOH and water are not. 2-Vinylnaphthalene gives lower yield of the product. Studies of ligand effects show that a smaller phosphine, P(*i*-Bu)$_3$ [cone angle = 143°, vs 165° for (benzyl)$_3$P] gives more styrene dimerization and lower reactivity and selectivity. Neutral complexes such as *trans*-$[NiBr(mesityl)(PBn_3)_2]$ or cationic ones with chelating ligands (e.g., $[Ni(mesityl)(CH_3CN)(Bn_2PCH_2CH_2PBn_2]^+$) are not catalytically competent. Finally, detection of 2,4,6-trimethylstyrene under the reaction conditions indicates aryl-ethylene coupling followed by the formation of the $[Ni{-}H]^+$ intermediate, which is the true catalyst in the reaction (see Scheme 1). The reaction has been applied to norbornene, which gives acceptable yields (∼94%) of 2-exo-vinylnorbornane (entry 3).[22b] Very low yields of heterodimerization are observed with other typical olefins such as allylbenzene, cyclopentene, indene, methyl acrylate, vinyl acetate, acrylonitrile, vinylcy-

Table 1. Prototypical Hydrovinylation Reactions Using Ni, Pd, and Ru Complexes

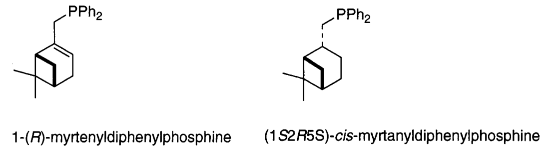
entry	catalyst precursor	reaction conditions	yield %	selectivity for major product (%)[a]	remarks	ref
1	$(Ph_3P)_2Ni$ (mesityl)Br	styrene/Ni = 17 BF_3. OEt_2, 0 °C, 15 min, <1 atm C_2H_4, CH_2Cl_2	67	91	9% isomers and styrene dimer	12
2	$[(PhCH_2)_3P]_2Ni^+$ (mesityl) (CH_3CN) BF_4^-	styrene/Ni = 500−1000 25 °C, 1 h, 15 atm C_2H_4, THF, TOF 1915 h^{-1}	96	97	poor yield with α-Me-styrene, 2-vinylnaphthalene; tolerant to Cl, OMe groups; exotherm at the end of reaction	22a
3	$[(PhCH_2)_3P]_2Ni^+$ (mesityl) (CH_3CN) BF_4^-	norbornene/Ni = 1000 25 °C, 15 atm C_2H_4, THF, TOF >4300 h^{-1}	94	94	6% ($C_9 + C_{11} + C_{16}$) hydrocarbons; poor reaction with functional olefins	22b
4	$[Ni(CH_3CN)_6]^{2+}$ $2[BF_4]^-$/ Ph_3P/Et_2AlCl	styrene/Ni = 400, Al/Ni = 5 25 °C, 50 min, 10 atm C_2H_4, CH_2Cl_2	98	87	tolerance to Lewis basic groups (Cl, OMe) depends on the order of addition of reagents and Ni/Al ratios	23a,b
5	$[Ni(CH_3CN)_6]^{2+}$ $2[BF_4]^-$/ Ph_3P/Et_2AlCl	6-OMe-2-vinylnaphthalene/ Ni = 100, Al/Ni = 20; ligand/Ni = 4; 25 °C, 40 min, 10 atm C_2H_4, CH_2Cl_2	96	76	optimized conditions based on entry 4	23b
6	$[Ni(CH_3CN)_6]^{2+}$ $2[BF_4]$-/ dppe[b]/Et_2AlCl	styrene/Ni = 200, Al/Ni = 20, 1ligand/Ni = 1, 25 °C, 75 min, 10 atm C_2H_4, CH_2Cl_2	96	96	similar result with another chelating ligand, ppfa[c] Al/Ni = 15, 89% yield	23b
7	$[\eta^3\text{-(allyl)NiCl}]_2$/(*RR*)-**15**/ $Et_3Al_2Cl_3$	styrene/Ni = 1948 -72 °C, 2.5 h, 1 atm C_2H_4, CH_2Cl_2; Al/Ni = 3	97	[d]	93% ee (*R*) for styrene; 85−95% ee for various vinylarenes; limited to **15** as ligand; best ee's with coordinating anions (See Table 4)	7
8	$Pd(OAc)_2$/ $Et_2P(CH_2)_3PEt_2$/ *p*-toluenesulfonic acid	styrene/Pd = 692 (?) MeOH, 80 °C, 20 atm ethylene, 5 h, 50% conversion	45	90	5% styrene dimer, rest linear dimers	16
9	$(\eta^3\text{-}(C_4H_7)Pd^+$-**13**) BF_4^-	(a) styrene/Pd = 400 25 °C, 30 atm C_2H_4, CH_2Cl_2, 1 h	41	92	8% isom.	24
		(b) same, 3 h	100	9	91% isom.	
10	$(\eta^3\text{-}(C_4H_7)Pd^+$- **14-racemic**) BF_4^-	styrene/Pd = 1000 15 °C, 60 min, 15 atm C_2H_4, CH_2Cl_2 TOF = 947 h^{-1}, >99% conv.	83	83	5% styrene dimer; CH_3CN complex is less reactive, 21% conv. in 30 min; but 100% selectivity	25
11	$(PCy_3)_2(CO)Ru(Cl)H$, $HBF_4{\cdot}OEt_2$	styrene/Ru = 200, 1−2 equiv $HBF_4{\cdot}OEt_2$, rt, 6, 20 °C	93	98	PCy_3-dissociation by H^+?	21a
			90	83	improved reactivity with AgOTf in place of HBF_4; see eq 6a	21b
12	[(allyl)Ni−Br]$_2$/Ph_3P/ AgOTf	styrene/Ni = 286; CH_2Cl_2, −56 °C, 2 h	>99	>99	excellent yields (>95% in many cases, eq 7, Table 2); tolerant to halogen, alkoxy, $N(Ts)_2$, OC(O)R, CO_2R works with propene (Table 3, eq 8); amenable to asymmetric catalysis	27
13	[(allyl)Ni−Br]$_2$/Cy_3P/ AgOTf	norbornene/Ni = 100; 1 atm ethylene, CH_2Cl_2, −70 °C, 2 h	>99	>99	with Ph_3P 2:1 (norbornene: ethylene) adduct, 97% yield, see eq 9)	29

Table 1 (Continued)

entry	catalyst precursor	reaction conditions	yield %	selectivity for major product (%)[a]	remarks	ref
14	[(allyl)Ni−Br]$_2$/MOP[e] **28b**/ NaBARF	2-methoxy-6-vinylnaphthalene/ Ni =70, 1 atm ethylene, CH_2Cl_2, −55 °C, 25	97	>99	~10% yield with OTf as counterion; (see eq 17, Table 5)	27, 37
15	[(allyl)Ni−Br]$_2$/ phospholane **32c**/ NaBARF	styrene/Ni =71, 1 atm ethylene, CH_2Cl_2, −45 °C	97	>99	50% ee (see eq 18, Table 6)	37
16	[(allyl)Ni−Br]$_2$/ *β*-acetamido-diarylphosphinite **41A**/$AgSbF_6$	4-Br-styrene/Ni = 71, −52°C, CH_2Cl_2	98	>99	89% ee (see eq 22, Table 7)	40
17	[(allyl)Ni−Cl]$_2$/ phosphoramidite **49**/BARF	4-Br-styrene/Ni = 2650, −70 °C, CH_2Cl_2	83	99	92% ee (see eq 23)	44

[a] 3-Phenyl-1-butene or exo-2-vinylnorbornene. [b] 1,2-Diphenylphosphinoethane. [c] *N,N*-Me$_2$-1-[2-(diphenylphosphino)ferrocenyl]-ethylamine. [d] Not available in the open literature. See footnote 6. [e] 2-Diphenylphosphino-2′-alkoxy-1,1′-binaphthyl (R = Bn) **28b** (Figure 4).

clohexane, α-pinene, and 2-carene.[22b] Cyclic and acyclic 1,3-dienes give poor yields of a mixture of hyrovinylation products. Substitution of the tribenzylphosphine with *cis*-myrtanyl- or myrtenyl-diphenylphosphines gives Ni complexes that imparts very high selectivity (~97%) toward 3-phenyl-1-butene, albeit with disappointing ee's (~7%).[22b]

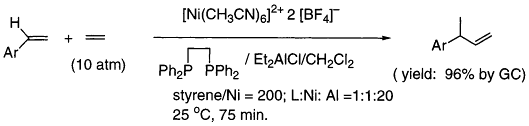


1-(*R*)-myrtenyldiphenylphosphine (1*S*2*R*5S)-*cis*-myrtanyldiphenylphosphine

Figure 1. *cis*-Myrtanyl- or myrtenyl-diphenylphosphines

Monteiro et al.[23] reported the use of dicationic nickel complexes ([Ni(CH$_3$CN)$_6$]$^{2+}$ 2[BF$_4$]$^-$/Ph$_3$P/Et$_2$-AlCl) for hydrovinylation of a variety of vinylarenes (Table 1, entries 4 and 5). The originally reported[23a] limitations caused by the Lewis basic sites on the substrate have since been overcome[23b] by the judicious choice of order of addition of reagents and optimized Ni-to-Al ratios. Under the modified conditions, the following yields (estimated by GC, with isolated yields shown in brackets) have been obtained for the indicated vinylarenes at room temperature and 10 atm of ethylene: styrene 98% (87%); 4-isobutylstyrene 94% (68%); 3-benzoylstyrene 99% (84%); 2-methoxy-6-vinylnaphthalene 96 (76%). This paper also reports that the isomerization of the primary product can be prevented by maintaining higher pressures of ethylene (>10 bar) in the reactor. If the disparity between gas chromatographic and isolated yields of products can be resolved, this will become a potentially important route for the synthesis of 3-aryl-1-butenes and the 2-arylpropionic acids that could be derived from them.

A unique feature of the dicationic nickel system[23b] that is not seen in any of the other hydrovinylation catalysts is that under these reaction conditions a chelating phosphine *does not inhibit* the reaction (eq 6, entry 6). Thus, 1,2-diphenylphosphinoethane (dppe) or *N,N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]-ethylamine (ppfa) in the presence of ([Ni(CH$_3$CN)$_6$]$^{2+}$ 2[BF$_4$]$^-$ (ligand/Ni = 1) gives a ~90% yield of 3-phenyl-1-butene from styrene and ethylene. The question of whether chiral diphosphines can be used for enantioselective hydrovinylation has not yet been addressed.



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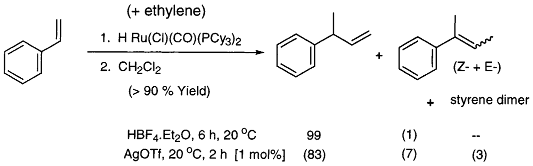


(6a)

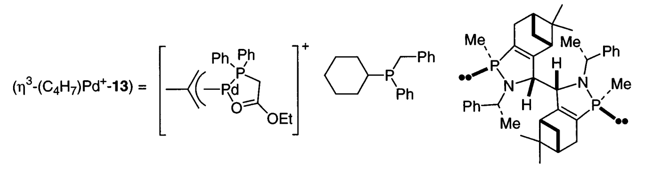
A critical analysis of the work published before 1994 shows that the best Ni-catalyst was also the one that gave high enantioselectivity (entry 7, Table 1 and eq 13).[5a,7] This is the Wilke system that uses [(η^3-C$_3$H$_5$)Ni(Cl)]$_2$/[(*RR*)-**15**]]/Et$_3$Al$_2$Cl$_3$]. Incidentally, the description (*RR*) in the ligand refers to the origin of the components (*R*-myrtenal and *R*-1-phenylethylamine) used for its synthesis, rather than a formal definition of the absolute configuration of this molecule which contains a total of 12 chiral centers. The use of [(*RR*)-**15** will be discussed in greater detail under section 6 (Nickel-Catalyzed Enantioselective Asymmetric Hydrovinylation Reactions).

Several modular, highly tunable ligands that enable the Ni-catalyzed asymmetric hydrovinylation of vinylarenes have recently appeared in the literature. Typical examples are 1-(2-alkoxymethylphenyl-2,5-dialkylphospholanes (entry 15, Table 1), *β*-acetamido-diarylphosphinites (entry 16, Table 1), and phosphoramidites derived from 1,1′-binaphthols (Feringa's ligands, entry 17, Table 1). These will be discussed in greater detail under section 6.

4.2 Palladium-Catalyzed Reactions

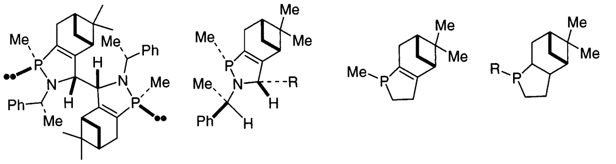
The Pd-catalyzed reactions in general give linear adducts (eq 3) and extensive isomerization of the primary products.[15-17] Under special conditions[16] (entry 8, Table 1) or using a hemilabile ligand **13** (entry 9),[24] some selectivity for 3-phenyl-1-butene can be achieved, especially at low conversions.

Use of basic phosphine ligands such as **14**[25] (entry 10, Table 1), **55** (entry 1, Table 10), and **56** (entry 3, Table 10) also retards the isomerization of 3-aryl-1-butenes to the more stable conjugated olefins. Further improvements could come from fine-tuning of the ligands such as **14**, **55**, and **56** (Figures 2 and 7, Table 10 and eq 24).



13 **14** (racemic) (*RR*)-**15**

Figure 2. Ligands **13**, **14**, and (*RR*)-**15**



(*RR*)-**15**

25a R = Ph
25b R = H
25c R = Me

26

27a R = Me
27b R = menthyl

Figure 3. Azaphospholene derivatives

4.3 Ruthenium-Catalyzed Reactions

A mixture of hydrated ruthenium chloride [Ru(III) and Ru(IV)] was among the first reagents studied for hydrovinylation of styrenes.[10a,10b] Recently, Yi introduced[21a] a combination of $(PCy_3)_2(CO)Ru(Cl)H$ and $HBF_4{\cdot}OEt_2$ for the hydrovinylation of styrene (entry 11, Table 1). The scope and generality of this procedure still remain to be established. Preliminary results indicate that the replacement of $HBF_4{\cdot}OEt_2$ by silver salts significantly improves the yield in selected cases (eq 6a).[21b]

5. A New Hydrovinylation Protocol Amenable to Asymmetric Catalysis: The Crucial Role of Counteranions

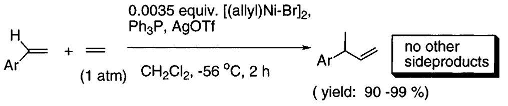
5.1 Vinylarenes

We have already alluded to the fact that among the earlier developments only the Wilke's system (entry 7, Table 1 and eq 13)[5a,7] gave satisfactory yield and selectivity suitable for large scale synthesis for this potentially important reaction. Subsequent work[26] directed at simplifying the uncommon structure of the azaphospholene, [(*RR*)-**15**], used in this study, has shown that this ligand class has a narrow scope (see Asymmetric Hydrovinylation, Section 6.2, see also entries 1 and 7, Table 4). It is possibly of limited value for the development of a broadly applicable hydrovinylation reaction, especially for a *practical* enantioselective version. At the outset of our work in this area, we speculated that the scope and selectivity of hydrovinylation could be increased significantly by eliminating the troublesome Lewis acid from the Wilke system. In its place, we would use a silver salt whose weakly coordinating anion can be easily replaced from the coordination sphere of Ni by an olefin prior to the insertion step (**10** → **11** → **12** in Scheme 1). Further, we expected the phosphine ligand to play a crucial role in dictating the selectivity of the reaction, as was apparent from some of the seminal ligand tuning studies that had been carried out by the Wilke group.[1d,4a] As for the effect of the counteranion (Y in Scheme 1), the situation appeared uncertain, as it was known that the selectivity varied considerably with the nature of the ligand. For example, coordinating anions ($Et_2AlCl_2^-$, OTf^-, BF_4^-) give higher ee's with ligand (*RR*)-**15**,[5a] but an opposite effect is observed with highly basic ligands such as $(menthyl)_2PPr^i$, where the best anions are the highly dissociating ones such as SbF_6^- and PF_6^-.[1d]

Table 2. Heterodimerization of Ethylene and Vinylarenes (eq 7)

entry	vinylarene	% yield[a]	conditions[b]
1	styrene	>95 (99)	(i)
2	4-methoxystyrene	>95 (98)	(i)
3	4-bromostyrene	>95 (98)	(i)
4	2-vinylnaphthalene	(99)	(i)
5	6-MeO-2-vinyl-naphthalene (MVN)	(90); (97)	(i), 0.5 mol % cat.; (ii)
6	4-*i*-Bu-styrene	>90 (99); >97 (99)	(i), 1.4 mol % cat.; (ii)
7	3-F-4-C_6H_5-styrene	(88)	(i)
8	3-bromostyrene	(99)	(i)
9	3-Ph-C(O)-styrene	(99)	(i)

[a] Isolated yield; selectivity >98% in all cases. In brackets are yields based on gas chromatography. [b] (i) 0.7 mol %. cat., CH_2Cl_2/-55 °C/2 h. (ii) (*R*)-MOP/Ar_4B^- Na^+/ CH_2Cl_2/-56 °C/2 h.



(7)

After an extensive scouting program in which we systematically investigated the effects of variations of ligands and counterions on the course of the hydrovinylation of styrene, we discovered[27] a new protocol (eq 7, entries 12, 13, Table 1) for this reaction. Thus, hydrovinylations of a series of substituted vinylarenes proceed with *highest* chemical yield and selectivity when a combination of [(allyl)-$NiBr]_2$, triphenylphosphine, and a weakly coordinating counteranion such as triflate (OTf^-) is employed as the precatalyst (eq 7 and Table 2). Typically, the reaction is carried out under 1 atm of ethylene at −56 °C in methylene chloride as the solvent, using 0.007 equiv of the catalyst (0.0035 equiv of $[(allyl)NiBr]_2$). Under these conditions, no oligomerization of ethylene or styrene is detected. In sharp contrast to the previously observed diminished reactivity for vinylarenes with Lewis basic centers, no such limitations are apparent under the new conditions (entries 2, 5, 9, Table 2). Derivatives such as 4-isobutylstyrene, 3-fluoro-4-phenylstyrene, 2-methoxy-6-vinylnaphthalene, and 3-benzoylstyrene—all potential precursors of important antiinflammatory agents—give excellent yields of the hydrovinylation products. Hydrovinylation product of 3- and 4-bromostyrenes (entries 3 and

Table 3. Heterodimerization of Propene and Vinylarenes (eq 8)

no.	R	temp °C	time (min)	yield[a]	16:17
1	*i*-Bu	−15	15	96	3:1
2	OMe	−15	60	86	4:1
3	Cl	0	15	94	4:1
4	Br	0	10	95	4:1
5	OAc	−10	30	93	4:1
6	PhC(O)−[b]	10	15	94	4:1
7	NTs_2[b]	10	25	92	2:1
8	MVN[b,c]	−5	60	88	10:1

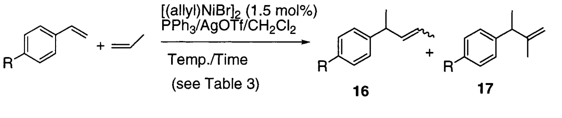
[a] Isolated yield. [b] 3 mol % Ni used. [c] 2-Metoxy-6-vinylnaphthalene.

8) are other potentially important intermediates that can be transformed into useful products through organometallic cross-coupling reactions. As expected, the use of a number of chelating bis-phosphines, aminophosphines, and 1,2-bis-diarylphosphinitites give no products under otherwise identical conditions. These include 1,3-bis-diphenylphosphinopropane (DPPP), 2,2′-bis-diphenylphosphino-1,1′-binaphthyl (BINAP), [2,2,-dimethyl-1,3-dioxolane-4,5-diylbismethylene]bisdiphenylphosphine (DIOP), *N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BPPM). Olefins with strongly electron-withdrawing aromatic substituents (for example, 3,5-bis-(trifluoromethyl)styrene, 2-vinylpyridine) are poor substrates for the reaction. Methyl substitution at α- or *β*-carbons of styrene also leads to poor yields (21 and 49%, respectively).

In our attempts to find an asymmetric version of the reaction, we found that several phosphine ligands with a weakly coordinating ("hemilabile") auxiliary groups are superb ligands for the hydrovinylation reaction, especially in the presence of noncoordinating counterions such as $BARF^-$ ($B[3,5-(CF_3)_2-C_6H_3]_4^-$). One example is the binaphthyl ligand, 2-diphenylphosphino-2′-alkoxy-1,1′-binaphthyl (MOP, Figure 4) shown in Table 1, entry 14.[27] This and other similar ligands will be discussed in greater detail under Asymmetric Catalyzed Reactions (Section 6.4).

5.2 Other Related Heterodimerization Reactions

The heterodimerization protocol is broadly applicable if the two olefins have sufficiently different reactivities. Two synthetically useful examples that use our procedure[27] are listed below.



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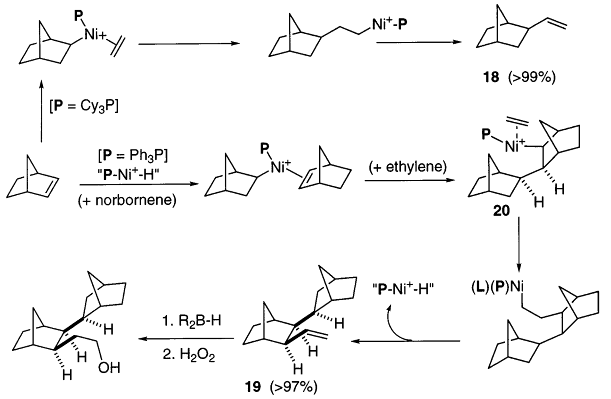
5.2.1 Dimerization of Propene and Vinylarenes

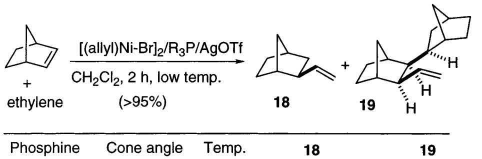
Unlike heterodimerization reactions of ethylene, no synthetically useful heterodimerization reaction using propene was known before our work.[28] We find[29] that propene reacts with styrene and substituted styrenes under conditions slightly modified from what was previously described for ethylene (eq 8, Table 3) giving excellent yields of the expected products. The reaction with propene proceeds at a higher temperature (−15° to 10 °C vs. −56 °C for ethylene), especially in the case of the more electron-deficient styrene derivatives. As expected, a mixture of regioisomeric products (with propene-C_1 addition to the benzylic position, **16**, as the major one) is obtained.

Scheme 2. Ligand Dependence in Norborene Hydrovinylation



5.2.2 Dimerization of Ethylene and Norbornene

Ring strain is one of the differentiating factors between the olefins that could be exploited to effect a successful heterodimerization. We find[30] that the protocol using $[(allyl)NiBr]_2$/phosphine/AgOTf works equally well for the heterodimerization of norbornene and ethylene (eq 9, entry 13, Table 1), the course of the reaction being dependent on the phosphine that is employed. Tricyclohexylphosphine gives the expected 1:1 adduct (**18**) in nearly quantitative yield, whereas triphenylphosphine gives a 2:1 adduct (**19**) between norbornene and ethylene. This remarkable selectivity is presumably related to the cone angles of the two phosphines and the relative reactivities of the two olefins. It is conceivable that norbornene is more reactive than ethylene and thus undergoes a fast initial dimerization, when a smaller phosphine (Ph_3P) is used (Scheme 2). The initially formed *σ*-nickel complex **20,** for stereoelectronic reasons, cannot undergo *β*-hydride elimination, and hence react with another olefin, ethylene, giving finally the 2:1 adduct **19**. The structure of **19** is tentative and is based on the calculated relative stability (∼5 kcal mol^{-1} more stable) of the diastereomeric structure depicted with respect to the alternate exo−exo isomer (**19′**). With a bulky phosphine, only addition to ethylene is feasible giving the 1:1 adduct, **18**.



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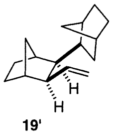
Phosphine	Cone angle	Temp.	18	19
$[cyhex]_3P$	180^0	-70 °C	100	0
Ph_3P	145^0	-55 °C	1	97



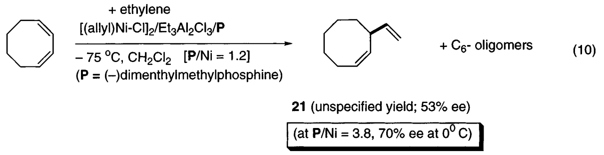
19'

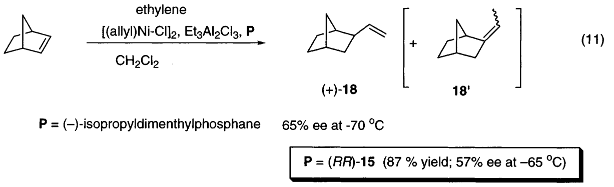
(less stable *exo-exo* diastereomer)

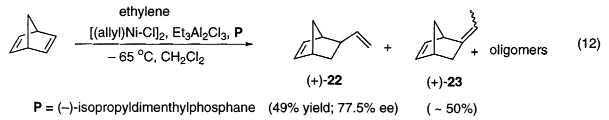
6. Nickel-Catalyzed Enantioselective Hydrovinylation Reactions

6.1 Nickel-Catalyzed Reactions Using Horner Phosphines

Asymmetric hydrovinylation of 1,3-cyclooctadiene (eq 10) using (−)-isopropyldimenthylphosphine as a ligand is one of the first examples[18a] of a metal-catalyzed asymmetric carbon−carbon bond-forming reaction ever reported,[31] even though the selectivity was unacceptably low (up to 70% ee, unspecified yield) by today's standards. Under somewhat similar conditions, norbornene (eq 11) and norbornadiene (eq 12) give the corresponding 2-*exo*-vinyl products in 65% ee (at −70 °C) and 78% ee (−65 °C), respectively.[18b] Depending on the temperature, varying degrees of isomerization to the ethylidene derivatives (for example, **18′**, *E* and *Z*) are observed in both cases. The full details of reaction conditions and characterization of products in these and many other early hydrovinylations are difficult to locate.



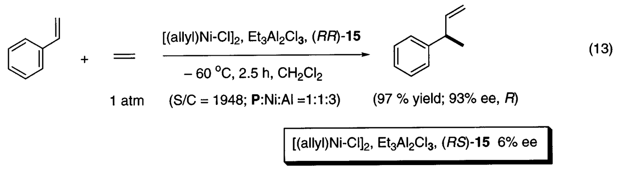


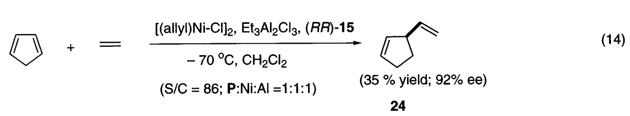


6.2 Nickel-Catalyzed Reactions with 1,2-Azaphospholene Ligands [(*RR*)-15 and Related Compounds]

Before the recent resurgence of activity in this area,[20−27] the best ligand for the hydrovinylation of norborne (eq 11), vinylarenes (eq 13 and Table 4), and cyclopentadiene (eq 14) has been the azaphospholene [(*RR*)-**15**, Figure 3], used in conjunction with an (allyl)nickel halide dimer and a Lewis acid such as $Et_3Al_2Cl_3$.[5a,7]

With a catalyst derived from [(allyl)NiCl]$_2$, [(*RR*)-**15**] and [$Et_3Al_2Cl_3$], (S/C = 16241, phosphine/Ni/Al = 3:1:10), hydrovinylation of norbornene proceeds at −65 °C giving an yield of 87% and an ee of 57% (eq 11).[7]





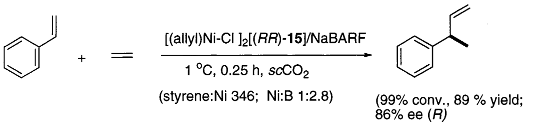
The 1,2-azaphospholene ligand (*RR*)-**15** is a very special ligand for the hydrovinylation of vinylarenes, and the Ni-complexes derived from this ligand have been claimed in a patent[7] to give the highest ee recorded to date for many of these substrates (Table 4). It is prepared from (−)(*R*)-myrtenal and (+)(*R*)-1-phenylethylamine, and hence the somewhat misleading description (*RR*).[4a] One other congener of this compound [the diastereomer [(*RS*)-**15**, prepared from (*R*)-myrtenal and (*S*)-1-phenylethylamine] is a much less active and less selective ligand (for (*RR*)-**15**: ee 95% at −70 °C, TOF 1800 h^{-1}; for (*RS*)-**15**: ee 8%, TOF 50 h^{-1}). Monomeric versions of these ligands have been prepared in an attempt to simplify the synthesis, and it has been found that catalytic activity and enantioselectivity are highly dependent on the structure of the ligand. Thus, the phenyl derivative **25a** (Figure 3) is a good ligand for hydrovinylation of styrene (99% conversion of styrene, 60%

Table 4. Asymmetric Hydrovinylation of Vinylarenes Using Ni Complexes of (*RR*)-15 and Related Ligands

entry	catalyst	reaction conditions	yield %	remarks	ref
1	[η^3−(allyl)NiCl]$_2$ + (*RR*)-**15** + $Et_3Al_2Cl_3$	styrene/Ni = 1948 −60 °C, 2.5 h, 1 atm C_2H_4, CH_2Cl_2, Al/Ni = 3	97	93% ee (*R*) for styrene (at −70 °C, 95% ee); limited to (*RR*)-**15** as ligand; (*RS*)-**15** gives only 6% ee)	7; 5a
2	[η^3−(allyl)NiCl]$_2$ + (*RR*)-**15** + $Et_3Al_2Cl_3$	4-isobutylstyrene/Ni = 103; −72 °C, 1 atm C_2H_4, CH_2Cl_2; Al/Ni = 3	85	85% ee (*R*) for product; $[\alpha]^{20}_D = 6.18$, see ref 40 for possible correction of ee value	7
3	[η^3−(allyl)NiCl]$_2$ + (*RR*)-**15** + $Et_3Al_2Cl_3$	4-Cl-styrene/Ni = 118; −72 °C, 1 atm C_2H_4, CH_2Cl_2; Al/Ni = 2	98	95% ee (*R*) for product	7
4	[η^3−(allyl)NiCl]$_2$ + (*RR*)-**15** + $Et_3Al_2Cl_3$	2-Me-styrene/Ni = 43; -72 °C, 2.5 h, 1 atm C_2H_4, CH_2Cl_2; Al/Ni = 3	72	92% ee (*R*) for product	7
5	[η^3−(allyl)NiCl]$_2$ + (*RR*)-**15** + $Et_3Al_2Cl_3$	2-methoxy-6-vinylnphthalene/Ni = 66, −70 °C, 1 atm C_2H_4, CH_2Cl_2; Al/Ni = 2	72	83% ee (*R*)	7
6	Ni(OAc)$_2$ + (*RR*)-**15** +AgBF$_4$	styrene/Ni = 685, −30 °C, 80 min, 1 atm C_2H_4, CH_2Cl_2, Ag/Ni = 4	46	75% ee (*R*) for styrene;	7
7	[η^3 −(allyl)NiCl]$_2$ + **25a** +MAO	styrene, −60 °C, 2.5 h, 1 atm C_2H_4, CH_2Cl_2, Ni/P = 1	>99	60% ee; no reaction with ligands **25b** and **25c**	5a

ee), but there is no reaction with either the unsubstituted phospholene **25b** or the methyl-substituted derivative **25c** as the ligand. Structurally related phospholene and phospholane derivatives **26** and **27** have also been reported to be ineffective.[5a]

Leitner et al. have since shown[32a] that the hydrovinylation of styrene, 4-chlorostyrene, and 4-*t*-butylstyrene can be accomplished in supercritical CO_2 using a combination of (*RR*)-**15**, [(allyl)NiCl]$_2$ and sodium tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (Na BARF) (eq 15). With substrate/Ni ratios approaching 10 000, and no halogenated solvent involved, this has the potential to be a very environmentally friendly process. Use of $Et_3Al_2Cl_3$, which was the Lewis acid of choice in the original Wilke studies in place of NaBARF lead to low ee's (70 vs 86% for the hydrovinylation of styrene at 1 °C). This study also showed[32b] that even in CH_2Cl_2 the counteranion BARF serves as a better alternative (vis-á-vis the chloroaluminates) in reactions using (*RR*)-**15**/[(allyl)NiCl]$_2$. In 1998, we had pioneered[27] the use of BARF in hydrovinylation reactions and made similar observations in connection with the use of MOP ligands (vide infra, eq 17). Use of *sc*CO_2 allows for recycling of the catalyst. A continuous flow system that uses *sc*CO_2 and an ionic liquid (for example, 1-ethyl-3-methyl imidazolium bis-trifluromethyl triflamide, EMIM Tf_2N), which also serves as a catalyst activator, has been developed for the Ni/azaphospholene-catalyzed asymmetric hydrovinylation reaction.[32b] Even though the overall selectivity drops considerably under these conditions (best: 64% yield of 3-phenylbutene, 89% ee), this study represents an outstanding example of novel reaction engineering and process design.

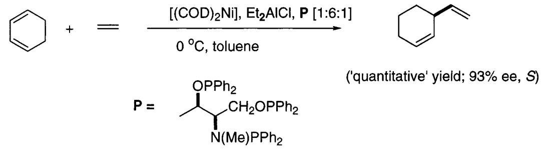


(15)

- at 40 °C (styrene/Ni: 10000): TOF 1300 cycles h^{-1}

6.3 Ni-Catalyzed Reactions Using Aminophosphine/Phosphinite (AMPP) Ligands

A nickel complex prepared in situ from an aminophosphine/phosphinite ligand derived from (2*S*3*R*)-threonine is an efficient catalyst for the hydrovinylation of 1,3-cyclohexadiene (eq 16).[33] Other amino alcohol-derived AMPP ligands gave lower selectivities. Surprisingly, no further studies on this promising ligand system have since appeared in the literature.



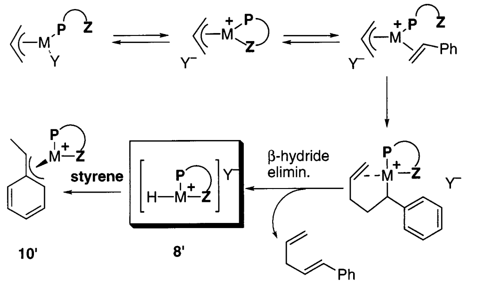
(16)

6.4 Synergistic Relation Between Hemilabile Ligands and Counteranions. New Ligands for the Asymmetric Hydrovinylation Reaction

6.4.1 Use of 2-Diphenylphosphino-2′-alkoxy-1,1′-binaphthyl (MOP) Ligands (Figure 4)

Earlier we noted that our newly discovered protocol for the hydrovinylation reaction (section 5.1, eq 7) fails *completely* when chelating phosphines are employed.[27] Considering the requirement of an open coordination site for ethylene in the critical steps of the reaction (Scheme 1), we wondered whether a monophosphine that also carried a hemilabile group[34] might have an advantage, since such a group can stabilize the putative cationic intermediates by internal coordination. The argument goes that the weakly coordinated group could be displaced by the olefin at the appropriate stage. In addition, such coordination might lead to a chelated metal hydride (**8′** = [**P**∼**Z**−Ni−H]$^+$) with better diastereoselective discrimination (Scheme 3) in the key addition to the prochiral faces of the olefin (for example, in the formation of the η^3-benzyl-Ni- intermediate **10′**). Making the reasonable assumption that all the subsequent steps proceed with retention of configuration, it can be argued that the enantioselectivity is determined at this stage (see Scheme 1). To validate these ideas, we initially chose Hayashi's 2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl (MOP) ligand (**28a**),[35] which carries a methoxy group in addition to the tertiary phosphine. The ether oxygen could now serve as a hemilabile ligand. After a disappointing start with AgOTf as the promoter, which gave very poor yields, we recognized that this phosphine (**28a**) served as an efficient ligand in the presence of the BARF counteranion.[36] 2-Methoxy-6-vinylnaphthalene (MVN) and 4-isobutylstyrene gave nearly quantitative yields (>97% yield and >99% selectivity for the 3-aryl-1-butene) of the hydrovinylation products in 62 and 40% ee (*S*-isomers), respectively (eq 17).[27] Further studies revealed that a minor modification in the ligand structure (change of OMe to OCH_2Ph, **28b**) improves the ee for MVN to 80% when the reaction is carried out at −70 °C (Table 5). Styrene gave a disappointing 20% ee. The weakly coordinating *O*-alkyl groups in these ligands appear to be crucial for the success of the reaction since yield and enantioselectivity for the ligand with ethyl group (**28c**) in the place of the methoxy group are only 13

Scheme 3. Use of a Chelated Metal Hydride for Better Diastereoselectivitity



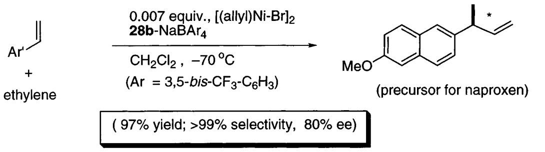
- **Z** = hemilabile group
- active catalyst: chelated metal hydride
- better control in the diastereoselective addition to styrene?

Table 5. BINAP 2′-Substituent Effects on Hydrovinylation of 2-Methoxy-6-vinylnaphthalene[a]

entry	ligand	(2′ group, Figure 4)	yield (%)	% ee[b]	remarks
1	(*R*)-BINAP	Ph_2Ph	0		
2	**28a**	OCH_3	>98	62	
3	**28b**	OCH_2Ph	97	73	−55 °C; $AgNTf_2$ 87%
4	**28b**	OCH_2Ph	93	80	at −70 °C
5	**28c**	CH_2CH_3	12	<3	styrene 13%
6	**28d**	$OC(O)CH_3$	0		
7	**28e**	N(H)Ac	0		
8	**28f**	$P(O)Ph_2$	0		
9	**29a** (*R*,*R*)	$OC(H)(Ph)(CH_3)$	96	71	(R,R)
10	**29b** (*R*,*S*)	$OC(H)(Ph)(CH_3)$	79	65	(R,S)
11	**30a**	OMe	94	63	
12	**31a**	OMe	93	63	

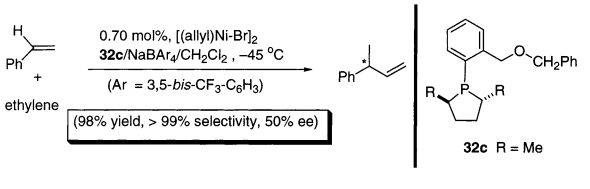
[a] See eq 17 for typical procedure. [b] ee determined by HPLC.

and 3% ee, respectively, with BARF as the counteranion. Table 5 lists the results of other hydrovinylation reactions of 6-methoxy-2-vinylnaphthalene done under this protocol (eq 17) using different MOP ligands.



(17)

Further support for the hemilabile coordination comes from the different reactivities of the two diastereomers of ligands **29a** and **29b**. The former gave a nearly quantitative yield (>99%) of the product in 71% ee, whereas the latter gave 79% yield and 65% ee under otherwise identical conditions. Substitution at the 2′-position of the binaphthyl moiety with better coordinating groups such as acetoxy (**28d**), acetamido (**28e**), and diphenylphosphinoxy (**28f**) totally inhibits the reaction at low temperature.[37] Finally, the electronic effect of the ligand on the hydrovinylation selectivity was examined with the ligands **28a**, **30a**, and **31a**. In sharp contrast to the Ni-catalyzed hydrocyanation, Rh-catalyzed hydrogenation, or Pd-catalyzed allylation,[38] ligand electronic properties appear to have little effect on the hydrovinylation; in each case the chemical yield and ee were almost identical.



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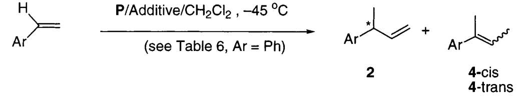

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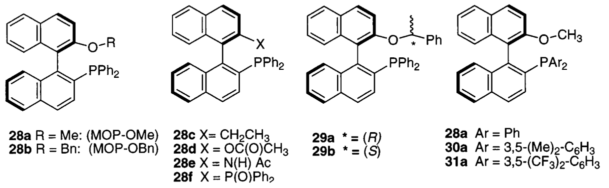


Figure 4. MOP Ligands **28**∼**31**

Scheme 4. Synthesis of 1-Aryl-2,5-dialkylphospholanes

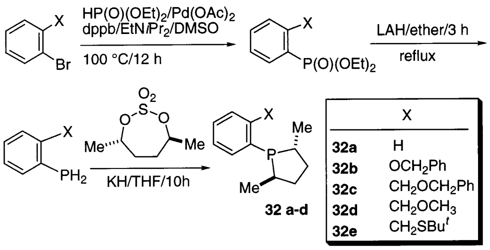
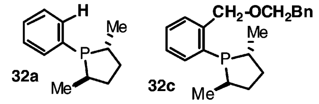


Table 6. Effect of Counterions on the Hydrovinylation of Styrene Using "Hemilabile" Ligands[a]



entry	additive	yield of product (%) 32a	32c	remarks
1	AgOTf	94	<4	37%ee (*S*) with **32a**
2	$AgClO_4$	95	<2	29% isom. with **32a**
3	$AgNTf_2$	<2	48	47%ee (*S*), 9% isom. with **32c**
4	$AgSbF_6$	<2	94	48%ee(*S*) with **32c**
5	$NaBAr_4$[b]	<2	97	50%ee (*S*) with **32c**

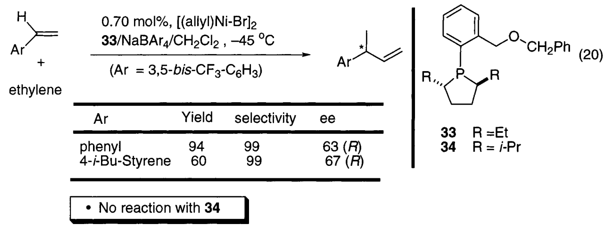
[a] For reaction conditions see eq 19. [b] Ar = $3,5-(CF_3)_2-C_6H_3$.

6.4.2 Use of 1-Aryl-2,5-dialkylphospholane Ligands

Since the recognition of the importance of the hemilabile group in a ligand for hydrovinylation (e.g., the OR group in MOP, **28**∼**31**, Figure 4), we have designed other ligands with this structural principle in mind. One such example is the phospholane **32c** shown in eq 18.[37] A series of simple phospholane derivatives **32a**−**e** were prepared according to Scheme 4. Our initial investigations started with ligands **32a**, and a close analogue, **32b,** with a potential hemilabile group at the *ortho*-position. While we find **32a** to be an excellent ligand (yields of products >94%, selectivity >98%) for the Ni-catalyzed hydrovinylation of vinylarenes, especially with OTf as the counterion (vide infra Table 6), **32b** leads to significant isomerization of the initially formed product **2** (to **4**, eq 19) under the standard reaction conditions even at −55 °C. One of the principal differences between **32b** and the versatile MOP ligand (**28a**), we conjecture, is the placement of the hemilabile alkoxy group with respect to the phosphorus. In **32b**, it is on the β-carbon and in **28a** it is on the δ-carbon, resulting in a 5- vs 7-membered Ni-chelate intermediate in the respective cases. To probe the effect of the relative positioning of the hemilabile group, the *o*-benzyloxymethyl analogue **32c** was prepared, and most gratifyingly, this ligand proved to be one of the best for highly selective hydrovinylation reactions.

The results of hydrovinylation of styrene using **32a** and **32c** are shown in Table 6.[37] For the simple phospholane ligand **32a**, with *no possibility of hemilabile coordination*, the reaction does not proceed unless a weakly coordinating anion such a OTf is used (entries 1 and 2). Incidentally, with ClO_4^- significant isomerization of the primary product is observed when this ligand is used. Additives such as $AgBF_4$, $NaBPh_4$, $AgNTf_2$, $AgSbF_6$, and $Na(B[Ar = 3,5\text{-}(CF_3)_2\text{-}C_6H_3)]_4)$ gave practically *no reaction* under the standard conditions (entries 3–5), mostly because of immediate precipitation of Ni(0) from the solution. In sharp contrast, for ligand **32c** (or **32d**) with the *o*-alkoxymethylphenyl substituent, the best results were obtained with noncoordinating counteranions $BARF^-$ and SbF_6^- (entries 4 and 5). This catalyst solution also appeared to be remarkably stable for at least 2 days at room temperature, as judged by ^{31}P NMR. Not surprisingly, AgOTf, $AgClO_4$, $AgBF_4$, $NaBPh_4$ were found to be ineffective in these cases.

Increasing the size of the 2,5-substituents on the phospholane improves the enantioselectivity. Thus, the diethyl derivative **33** gave 63 and 67% ee's for styrene and 4-isobutylstyrene in highly selective reactions (eq 20).[39a] For 4-*i*-butylstyrene, a precursor for ibuprofen, this represents one of the highest overall selectivities recorded (vide infra). The 2,5-diisopropylphospholane (**34**) appears to be too bulky to effect the hydrovinylation reaction. Even at 25 °C, most of the starting material was recovered.



(20)

Ar	Yield	selectivity	ee
phenyl	94	99	63 (*R*)
4-*i*-Bu-Styrene	60	99	67 (*R*)

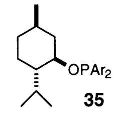
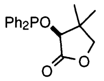
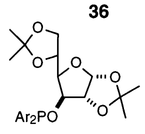
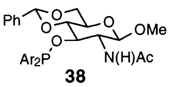
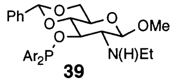
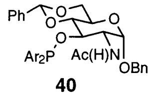
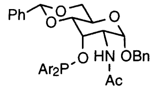
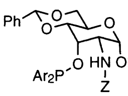
- No reaction with **34**

Finally, the ligand **32e** (Scheme 4) with an *o*-CH_2-Bu^tS group in place of the CH_2OR substituents does not give any reaction.[39a] The sulfur atom in this ligand is likely to be a strong donor.

6.4.3 Use of Diarylphosphinite Ligands

Even though the initial studies with the MOP (eq 17) and 1-aryl-2,5-dialkylphospholane (eqs 18 and 20) ligands provided a number of useful parameters such as the effect of hemilabile coordination and counteranions to improve the efficiency and selectivity of the catalyst system, the enantioselectivity in the hydrovinylation of styrene derivatives remained modest. In continued efforts to improve the enantioselectivity, we recently screened a large number of ligands and found that easily accessible diarylphosphinites serve as excellent ligands for this exacting reaction.[40,41] Sugar phosphinites are a class of easily synthesized ligands we used before with remarkable success in other asymmetric reactions such as hydrocyanation,[38a] hydrogenation,[38b] and allylation reactions.[38c] They are readily amenable to steric and electronic tuning, a highly desirable attribute for ligands for asymmetric catalysis. The results of hydrovinylation of styrene using these ligands are shown in Table 7. Principally, *bis*-(3,5-dimethylphenyl)- and *bis*-(3,5-di-trifluoromethylphenyl)- phosphinites were chosen for this study. In general, outstanding selectivity for 3-phenyl-1-butene is observed with variety of phosphinites. Among the limited set of ligands we have thus far examined, other things being equal, an α-glycoside appears to give better yield than a *β*-glycoside (entries 4,5 vs 7,8). Whether a 3,5-bis-CH_3-C_6H_3-substituent or a 3,5-bis-CF_3-C_6H_3-substituent on phosphorus is better depends on the configuration of the carbon to which is attached the diaryl phosphinite moiety. In the *gluco*-series (entry 7/8) the CF_3-aromatic substituent is better, where as in the *allo*-series (entry 9/10) the CH_3-aromatic substituent is better. The *allo*-config-

Table 7. Hydrovinylation of Styrene Using Sugar-Phosphinite Ligands[a]

No.	ligand	Ar	conv./yield[b]	selectivity [c]	%ee[d]
1.	 **35**	B	99/86	86	>5
2.	 **36**	-	--/87	99	6
3.	 **37**	B	68/68	99	29 (*R*)
4.	 **38**	A	62/62	99	32 (*S*)
5.	**38**	B	35/35	99	28 (*S*)
6.	 **39**	B	0	--	--
7.	 **40**	A	97/93	96	9 (*S*)
8.	**40**	B	93/93	99	45 (*S*)
9.	 **41**	A	99/89	89 (-70 °C)	81 (*S*)
10.	**41**	B	42/42	99	62 (*S*)
11.	 **42** Z = CF_3CO		99/40	40[e]	87 (*S*)
12.	**43** Z = PhCO Ar = **A**		99/23	23[e]	82 (*S*)

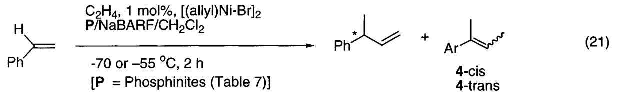
[a] see eq 21. **A** Ar= $3,5\text{-}(CH_3)_2\text{-}C_6H_3$; **B** Ar = $3,5\text{-}(CF_3)_2\text{-}C_6H_3$ [b] isolated yield of 3-phenyl-1-butene . [c] % of 3-phenyl-1-butene among all products. [d] determined by HPLC. [e] conversion >99%.

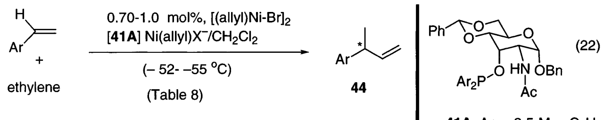
Table 8. Asymmetric Hydrovinylation of 4-Bromostyrene Using Phosphinite Ligands[a]

entry	ligand/counterion	yield (%)	selectivity[b]	% ee[c]
1	**41A** (SbF_6)	98	>99	89 (*S*)
2	**41A** (BARF)	94	94	89 (*S*)
3	**41A** (BF_4)	24	>99	86 (*S*)
4	**41A** (OTf)	70[d]	>99	74 (*S*)
5	**41B** (BARF)	19[d]	>99	43 (*S*)
6	**40A** (BARF)	88[d]	>99	13 (*S*)
7	**40B** (BARF)	41[d]	>99	47 (*S*)

[a] 1 atm ethylene, 1 mol % (allyl)Ni**P**]$^+$ X$^-$, CH_2Cl_2, -55 °C, 2 h. [b] For 3-aryl-1-butene; >99% means no other hydrocarbon products were observed. [c] Determined by HPLC. [d] Results of single experiments.

uration for the ligand (entries 9 and 10) is clearly superior compared to the *gluco*-derivative (entries 7 and 8) for higher enantioselectivity. Finally, the acyl group on nitrogen showed a pronounced effect on the selectivity of the reaction (entries 11 and 12). Whereas the acetyl substituent on nitrogen gives consistently high selectivity (most of the time >99%) for the desired product, alkyl groups inhibit the reaction (entry 6). The N−$COCF_3$ and N−COPh derivatives promote concomitant isomerization of the initially formed 3-phenyl-1-butene to a mixture of 2-phenyl-2-butenes under the reaction conditions, reducing the selectivity for the former to 40 and 23%, respectively (entries 11 and 12). Remarkably, the highest ee for styrene (87%) in this series is observed for the N−C(O)CF_3 derivative.





41A Ar = 3,5-Me_2-C_6H_3

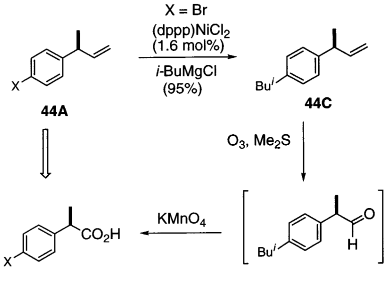
entry		Ar	yield	selectivity	ee
1.	**44A**	4-Br-phenyl	98	99	89 (*S*)
2.	**44B**	3-Br-phenyl	88	99	87 (*S*)
3.	**44C**	4-*i*-Bu-Styrene	99	99	74 (*S*)

In overall yield and selectivity, the diarylphosphinite **41A** is one of the best ligands for the Ni-catalyzed asymmetric hydrovinylation of styrene (Table 7, entry 9). Most gratifyingly, ligand **41A** is also one of the best ligands for the hydrovinylation of other derivatives such as 4-bromostyrene, 3-bromostyrene, and 4-isobutylstyrene (eq 22). In the case of 4-bromostyrene up to *98% isolated yield (>99% selectivity for the desired product) with 89% enantiomeric excess* is obtained. Selectivities for **41A** and other related ligands in the hydrovinylation of 4-bromostyrene are shown in Table 8.

A study of the effect of the counteranion on this reaction (Table 8) shows that SbF_6 is marginally better than BARF (entry 2), whereas BF_4 and OTf appear to be inferior (entries 3 and 4).

The enantiomeric excess of 3-(4-bromophenyl)-1-butene, **44A**, from which other 2-arylpropionic acids could be prepared by cross-coupling chemistry (Scheme 5), has been determined by three independent methods, and all agree within experimental error.[40] Kumada coupling of **44A** and *i*-BuMgBr in the presence of 1 mol % of (dppe)$NiCl_2$ gave **44C**. Subsequent ozonolysis and oxidation of the resulting aldehyde gave ibuprofen, whose configuration and enantiomeric excess were established by conversion to the known (−)-menthyl esters.[27] Gas chromatograpic analysis of these esters using chirasil-*L*-val column revealed baseline separation, with a diastereomeric excess of 89% for the (*R*)-ibuprofen ester. This establishes the overall selectivity and the absolute configuration of the primary product (*S*) of hydrovinylation of 4-bromostyrene.

Scheme 5. A General Synthesis of 2-Arylpropionic Acids



45 X= *i*-Bu: ibuprofen

The hydrovinylation of 3-bromostyrene using **41A** as a ligand gives the corresponding 3-aryl-1-butene in 88% yield (unoptimized) and 87% enantioselectivity (eq 22, entry 2).

Finally, studies with 4-isobutylstyrene serve as a reminder that a single ligand is unlikely to have broad applicability, and further fine-tuning maybe needed before practical levels of asymmetric induction can be achieved for individual substrates. The most promising ligand, **41A**, produced a very efficient catalyst (1 mol % loading, >99% yield and selectivity) for the hydrovinylation of this substrate, albeit with a modest 74% ee for the product (eq 22, entry 3). *Nonetheless, this represents the highest overall selectivity in the synthesis of this key intermediate.*[43]

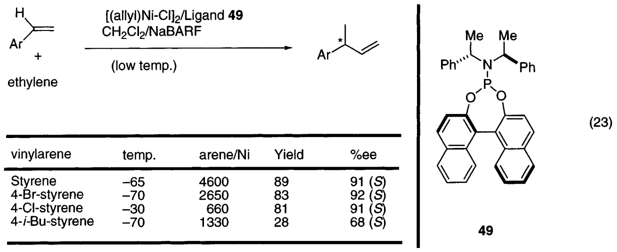
6.4.4 Phosphite Ligands

Binaphthol-derived phosphites **45**∼**48** are competent ligands[40] for the hydrovinylation of styrene under conditions described in eq 22, using BARF as a counterion. The yield and enantioselectivity for styrene hydrovinylation (shown under the respective structures) appear to be dictated by the configuration of the BINAP unit rather than of the carbohydrate backbone.

6.5 Ni-Catalyzed Reactions Using Phosphoramidite Ligands

Recently, Leitner et al. reported[44] that Feringa's phosphoramidite ligand **49**[45] gave very high enantioselectivities for a number of styrene derivatives (eq 23). Using either [BARF] or Al(OC$(CF_3)_2$Ph)$_4$ as a counteranion, spectacular catalyst efficiencies have been realized in this system. Thus, a combination of [(allyl)$NiCl$]$_2$, **49**, and NaBARF (styrene/Ni = 4600) effects the hydrovinylation of styrene at −65 °C to give the product in 89% yield and 91% ee. The 3-aryl-

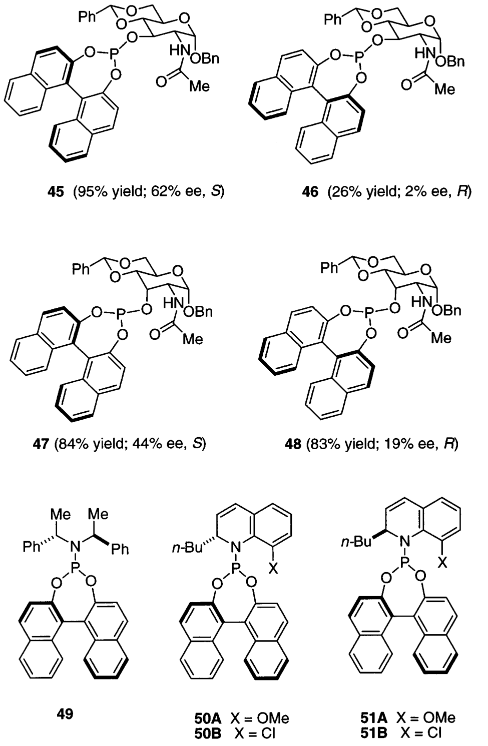
1-butene product from 4-bromostyrene is formed in 83% yield and 92% ee. This modular ligand system holds great promise for further improvements, even though the overall selectivities for 4-isobutylstyrene and 4-chlorostyrene are only moderate in this initial disclosure.



vinylarene	temp.	arene/Ni	Yield	%ee
Styrene	−65	4600	89	91 (*S*)
4-Br-styrene	−70	2650	83	92 (*S*)
4-Cl-styrene	−30	660	81	91 (*S*)
4-*i*-Bu-styrene	−70	1330	28	68 (*S*)

49

Other related ligands examined include **50A**, **50B**, **51A**, and **51B** (Figure 5).[44] The ligand **50A** is very efficient for hydrovinylation even though only low selectivity is observed. Ligands **50B** and **51A** show moderate activity, whereas **51B** is very effective for oligomerization of styrene, which is the *only* reaction seen with this ligand under the standard conditions except for slightly elevated pressures of ethylene (eq 23).



45 (95% yield; 62% ee, *S*)

46 (26% yield; 2% ee, *R*)

47 (84% yield; 44% ee, *S*)

48 (83% yield; 19% ee, *R*)

49

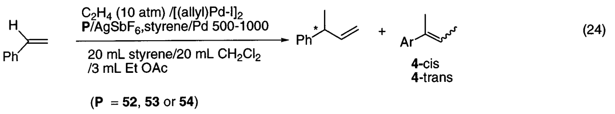
50A X = OMe
50B X = Cl

51A X = OMe
51B X = Cl

Figure 5. Phosphite and phosphoramidite ligands

7. Palladium-Catalyzed Asymmetric Hydrovinylation

The palladium-catalyzed asymmetric hydrovinylation has received much less attention mostly because of the concomitant isomerization of the primary product to 2-aryl-2-butenes (eq 24) even when the regiochemical problem is under control. Use of chiral menthyldiphenylphosphinite (58% ee, rt)[5a] and phosphino-carboxylic acids derived from lactic acid and mandelic acid (up to 33% ee, rt)[46] has been cited in the literature with no details.



The most promising result thus far comes from the use of menthol-derived phosphinite **52** and its enantiomer.[46] Preparation of the catalyst and its use for hydrovinylation of styrene are shown in Scheme 6 and eq 24, respectively. Enantioselectivities obtained with **52** and related ligands **53** and **54** are shown in Table 9. Several important observations have been reported in this study. With a 1:1 ratio of Pd/ligand precipitation of Pd occurs, and this can be avoided by using a weakly coordinating solvent such as ethyl acetate. Bidentate ligands and strongly coordinating solvents such as acetonitrile inhibit catalysis. As with the Ni-catalyzed reactions, counterions have a pronounced effect on the yield and selectivity of the reaction, with dissociating ions such as SbF$_6^-$ and PF$_6^-$ giving the best overall selectivities (entries 1−4, Table 9).

Scheme 6. Preparation of a Pd-Catalyst for Hydrovinylation (see eq 24)

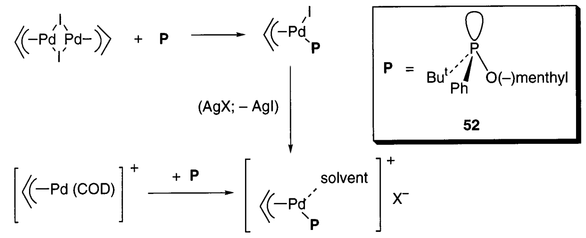


Table 9. Asymmetric Hydrovinylation of Styrene Using Pd Complexes[a]

entry	ligand/ counterion	convers/ yield (%)	selectivity codimers (%)	selectivity 3-Ph-1-butene (%)	% ee
1[b]	**52** (SbF$_6$)	95/79	89	94	86 (*S*)
2[c]	**52** (PF$_6$)	100/12	47	25	87 (*S*)
3[c]	**52** (BF$_4$)	93/49	55	95	77 (*S*)
4[c]	**52** (OTf)	23/6	25	97	0
5[b]	**53** (SbF$_6$)	89/70	86	92	37 (*S*)
6[b]	**54** (SbF$_6$)	75/44	94	62	42 (*R*)
7[d]	**40a** (BARF)[39b]	74/63		85	40 (*S*)
8[d]	**41a** (BARF)[39b]	70/57		81	60 (*S*)

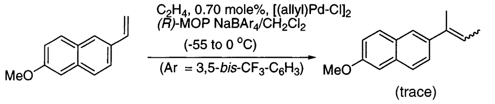
[a] Entries 1−6, see eq 24 (ref 46). [b] 10 °C, 10 atm. ethylene, 1 h, P/Pd = 1, styrene/Pd = 500−1000, CH$_2$Cl$_2$. [c] 0 °C, 2 h, CH$_2$Cl$_2$/EtOAc. [d] 0−10 °C, 2 h, P/[Pd(allyl)Cl]$_2$ = 0.5, styrene/Pd = 67, CH$_2$Cl$_2$.

Sugar phosphinites **40A** and **41A** with BARF counterion gave styrene hydrovinylation product in 74% (40% ee, *S*) and 70% (60% ee, *S*) yields, respectively.[39b] In each case, 10−12% isomerization of the primary product is also observed. Curiously, the MOP ligand that gave an excellent reaction under catalysis of Ni gave a poor yield of the isomerization

Table 10. Potentially Useful Asymmetric Hydrovinylation Reactions Using Pd Complexes of Chiral Phosphines

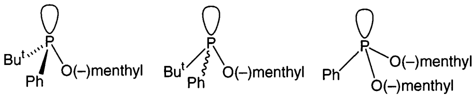
entry	catalyst precursor	reaction conditions	yield %	selectivity for 3-Ph-1-butene (1)	remarks	ref.
1	(η^3-$(C_4H_7)Pd^+$-**55**) BF_4^-	styrene/Pd = 1000; 15 °C, 30 min, 15 atm C_2H_4, CH_2Cl_2; TOF = 1290 h^{-1}	62	98	6% styrene dimer; 60% ee (*S*) with (*R*) ligand; isomerization of primary product upon 100% conversion	25
2	(η^3-$(C_4H_7)Pd^+$-**55**) BF_4^-	2-vinylnaphthalene/Pd = 100; 15 °C, 20 min, 15 atm C_2H_4, CH_2Cl_2; TOF = 250 h^{-1}	83	99	84% ee (*R*) with (*S*) catalyst	25
3	(η^3-$(C_4H_7)Pd^+$-**56**) BF_4^-	styrene/Pd = 1000; 25 °C, 60 min, 15 atm C_2H_4, CH_2Cl_2; TOF = 625 h^{-1}, 64% conversion		93	40% (*S*) with (*S*) ligand	47
4	(η^3-$(C_4H_7)Pd^+$-**57c**) BF_4^-	styrene/Pd = 696, 25 °C, 30 atm C_2H_4, CH_2Cl_2	59	95	79% ee	48
		15 min, 67% conversion	48	49	92% ee; kinetic resolution by isomerization of one of the enantiomers of the product	
		30 min, 99.9% conversion			low selectivity with **57a** and **57b**	

product (2-aryl-2-butene) in the Pd-catalyzed reaction (eq 25).[39c]



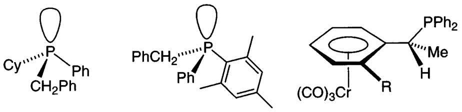
(25)

There has been a recent resurgence of activity in the use of highly basic phosphines for the Pd-catalyzed hydrovinylation reaction.[20,25,47,48] The structures of the more successful ligands are shown in Figure 7. The best results reported to date along with



52 **53** **54**

Figure 6. Ligands **52**, **53**, **54**



55 (*R*) **56** (*S*) **57a** R = H
57b R = Me
57C R = TMS

Figure 7.

the reaction conditions are compiled in Table 10. If the problem of isomerization of the primary product under higher conversions can be avoided, these protocols, often run at high arene/Pd ratios and under ambient conditions, might become quite attractive for large-scale synthesis. One solution to this problem might be to carry out the reaction with continuous feeding of styrene and ethylene to a catalyst system, which favors the heterodimerization vis-à-vis the isomerization of the primary product.

8. Large Scale Synthesis

The Ni-catalyzed hydrovinylation of styrene has been carried out at −60 °C on a 8.26 kg (79.6 mol) scale by the Wilke group using the azaphospholene ligand (*RR*)-**15**. The yield (41%) and enantioselectivity (87% ee) are lower than what is observed for small-scale reactions, and further developmental efforts are needed before the reaction can be practiced on a manufacturing scale. The low temperatures needed for the reaction and perhaps more importantly the restrictive nature of (*RR*)-**15** may also limit further applications of this chemistry. Discovery of new protocols that yield nearly quantitative yields[27,37,40,44] on a laboratory scale, the use of other metals (especially palladium),[46−48] and a new generation of ligands that are under investigation in several laboratories may ultimately overcome the current obstacles in devising a truly practical process.

9. Conclusion and Future Prospects

The heterodimerization of olefins has great potential as a selective carbon−carbon bond forming reaction when the two olefins involved have different reactivities. With ethylene as one of the reactants, this difference could have its origin in electronic (e.g., vinylarenes, dienes) factors or in the higher reactivity of the partner due to inherent strain in the molecule (e.g., norbornene, norbornadiene). Evidence thus far suggests that very high turnover frequencies can be realized for the reaction, and the reaction conditions are tolerant to a wide spectrum of common organic functional groups. The reaction has been shown to proceed under catalysis of Ni, Pd, and Ru, and a number of tunable ligand systems for these metals have been identified. Most promising among the successful ligands are the 3,5-dialkylphospholanes (eq 20), β-acetamido-diarylphosphinites (eq 22), and the phosphoramidites (eq 23). With further improvements in ligand design and reaction engineering, expansion of the scope and selectivity of asymmetric hydrovinylation can be expected soon.

10. Acknowledgment

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11. References

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