

# In Pursuit of an Ideal Carbon–Carbon Bond-Forming Reaction: Development and Applications of the Hydrovinylation of Olefins

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**Abstract:** Attempts to introduce the highly versatile vinyl group into other organic molecules in a chemo-, regio-, and stereoselective fashion via catalytic activation of ethylene provided challenging opportunities to explore new ligand and salt effects in homogeneous catalysis. This review provides a personal account of the development of enantioselective reactions involving ethylene.

- 1 Introduction
- 1.1 The Origins
- 1.2 Olefin Dimerization Reactions
- 2 Hydrovinylation Reactions
- 2.1 A Brief History of Hydrovinylation Reactions
- 2.2 Ruthenium- and Cobalt-Catalyzed Hydrovinylation Reactions
- 2.3 Best Practices prior to 1997: Nickel-Catalyzed Hydrovinylation Reactions
- 2.4 Mechanism of the Nickel-Catalyzed Hydrovinylation of Vinylarenes
- 2.5 A New Protocol for Hydrovinylation Amenable to Asymmetric Catalysis
- 2.6 Heterodimerization of Vinylarenes with Other Olefins
- 2.7 Other Heterodimerization Reactions
- 2.8 Hydrovinylation of Norbornene
- 3 Enantioselective Hydrovinylation Reactions
- 3.1 Azaphospholene Ligands
- 3.2 Aminophosphine/Phosphinite Ligands
- 3.3 Use of Chelating Phosphines
- 4 Synergistic Relation between Hemilabile Ligands and Counterions
- 4.1 New Ligands for Asymmetric Hydrovinylation Reactions: 2-Alkoxy-2'-diphenylphosphino-1,1'-binaphthyl Derivatives
- 4.2 Effect of Hemilabile Groups
- 4.3 Solvent and Salt Effects
- 4.4 Electronic Effects
- 4.5 Other Protocols for Nickel-Catalyzed Hydrovinylation Reactions
- 4.6 A Model for Asymmetric Induction in Hydrovinylation Reactions
- 4.7 De Novo Design of an Asymmetric Ligand: Hemilabile Phospholanes
- 4.8 Diarylphosphinite Ligands
- 4.9 Phosphite Ligands
- 4.10 Phosphoramidite Ligands
- 5 Generation of All-Carbon Quaternary Centers
- 6 Asymmetric Hydrovinylation of 1,3-Dienes
- 7 Asymmetric Hydrovinylation of Norbornene
- 8 Applications of Asymmetric Hydrovinylation Reactions
- 8.1 (*S*)-2-Arylpropionic Acids
- 8.2 (*R*)- $\alpha$ -Curcumene and (*R*)-*ar*-Turmerone

- 8.3 Control of the Configuration of the Steroidal D-Ring Side Chain
- 8.4 Intramolecular Reactions: Synthesis of Carbocyclic and Heterocyclic Compounds
- 9 Large-Scale Synthesis
- 10 Summary and Future Prospects

**Key words:** carbon–carbon bond formation, hydrovinylation, asymmetric catalysis, ligand effects, transition metals

## 1 Introduction

### 1.1 The Origins

Unlike most of my peers, I started my academic career late after more than a decade in industry. Having benefited from my experience at the highly nurturing and scientifically exciting environment of DuPont Central Research, where I spent my formative years as an independent scientist, I moved to my current position at The Ohio State University in 1995. Just prior to the move, in a highly productive collaboration with two talented colleagues, Dr. Al Casalnuovo and Dr. Tim Ayers, I published several papers on the use of readily available carbohydrate-derived ligands in asymmetric catalysis. These studies provided some of the first pieces of unequivocal evidence for the electronic tuning of an asymmetric catalyst for the enhancement of enantioselectivity. The first practical asymmetric hydrocyanations of olefins and a general synthesis of 2-arylpropionic acids, including (*S*)-naproxen, followed. Cheap hydrogenation catalysts based on readily available D-sugars (D-glucose and *N*-acetyl-D-glucosamine) for the synthesis of D- and L-amino acids were also disclosed. With the intellectual property aspects of these discoveries adequately covered, there was little further interest at DuPont to follow up this research for reasons that had to do more with business than science. So, after moving back to The Ohio State University, I decided to base my first research proposal on what I thought were some exciting initial leads in asymmetric hydrocyanation, a carbon–carbon bond-forming reaction of immense potential. In trying to solve the remaining problems of substrate scope and selectivity, we were going to take a rather empirical approach based on ligand tuning, an approach that had served us well. In the event, the proposal received mixed reviews and I decided to look elsewhere for a new project, still keeping the focus on the underlying theme of selectivity and efficiency in broadly applicable organic reactions.

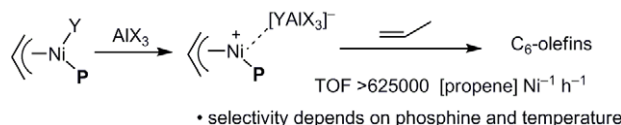
In initiating a new project, I was convinced that the asymmetric catalysis of carbon–carbon bond-forming reactions that involve neutral feedstocks would be a fertile area for research, providing ample opportunities for training graduate and postdoctoral students. After all, nature makes exquisite use of the most basic of feedstocks, carbon dioxide and water, to make many of the molecules that sustain life on earth. Such a project would bring challenges in two prominent areas of modern organic synthesis: *activation* and *stereoselective incorporation* of readily available carbon sources for the synthesis of valuable intermediates. If successful, this research would add to our repertoire of very powerful synthetic methods with implications for how we make such intermediates in the laboratory and for manufacture on a larger scale in industry. Under the best of circumstances, such processes could even be ‘green’ if we operated under ambient (energy efficient) conditions, used only catalytic amounts of metal, and made only the desired products (i.e., high selectivity), thereby avoiding costly separation processes.

In this review, I shall attempt to summarize our contributions to the area of the heterodimerization of olefins in a more or less chronological order. A review<sup>1a</sup> that we published in 2003 should be consulted for the detailed history of early developments, which have been summarized here for the sake of completion. In any comprehensive account of this nature, repetition of some of the already reported results is inevitable, but they are discussed here from a perspective that is often lost in the more traditional narrative of a journal article. One seldom hears about the blind alleys traveled, or about the ill-conceived conjectures that eventually pay off for the wrong reasons. This account also includes significant results on the hydrovinylation reactions of dienes, the generation of all-carbon quaternary centers, and applications to natural product synthesis that involve the reactions of highly functionalized substrates.

## 1.2 Olefin Dimerization Reactions

The search for an efficient carbon–carbon bond-forming reaction that uses feedstock carbon sources led us to a remarkable review by Wilke.<sup>2</sup> In this paper, the author summarized several years of work on allylmetal and metal

hydride intermediates carried out at the Max-Planck-Institut für Kohlenforschung in Mülheim, Germany. Among the many carbon–carbon bond-forming reactions catalyzed by a cationic nickel hydride described in this paper is the homodimerization of propene, which forms the basis of the Dimersol technology (Scheme 1).<sup>3</sup> This reaction is one of the most-efficient homogeneous catalyzed carbon–carbon bond-forming reactions known outside the realm of single-site olefin polymerization catalysis. The active catalyst, generated from  $[\eta^3\text{-allyl}]\text{NiX}_2$ , a trivalent phosphorus ligand, and a Lewis acid, produces a mixture of C<sub>6</sub>-olefins from propene with turnover frequencies in excess of 625000 [propene][Ni]<sup>-1</sup>h<sup>-1</sup>.<sup>3,4</sup> Conspicuously absent in these early studies were the applications of such dimerization reactions for the synthesis of fine chemicals, especially functionalized small molecules.<sup>1</sup>



Scheme 1

## 2 Hydrovinylation Reactions

Among the olefin dimerization reactions, the hydrovinylation reaction, i.e. the addition of a vinyl group and a hydrogen across a double bond, looked especially promising for fine chemical synthesis if the pesky issues of scope and selectivity could be adequately resolved. Since the branched product **1** (Scheme 2) is chiral, a regio- and stereoselective version of this reaction, in principle, could provide a variety of olefin-derived products in enantiomerically pure form. For example, the enantioselective hydrovinylation of vinylarene derivatives will lead to 3-arylbut-1-enes **3** that can be used for the synthesis of widely used anti-inflammatory 2-arylpropionic acids.<sup>5</sup> In addition, one of the hydrovinylation products of styrene, (*R*)-3-phenylbut-1-ene, has been reported to give a very high melting (>400 °C) isotactic polymer under Ziegler conditions (Scheme 2).<sup>2</sup> Yet another application might be in finding a solution to the long-standing problem of the control of exocyclic stereochemistry, an example of

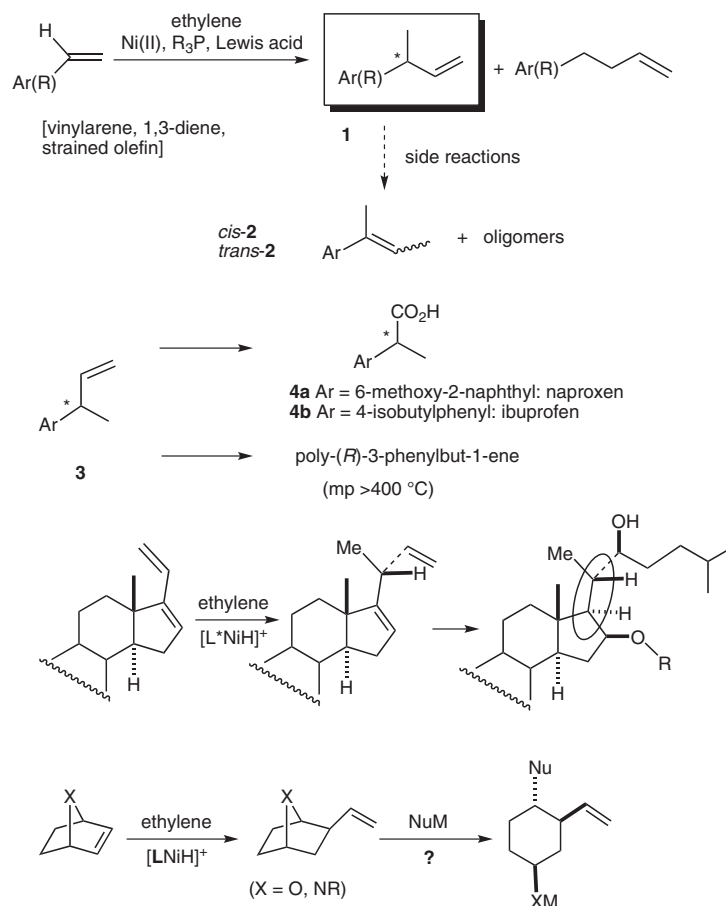
## Biographical Sketch



**T. V. (Babu) RajanBabu** received his undergraduate education in India (Kerala University and IIT, Madras). He obtained his Ph.D. from The Ohio State University, USA, under the direction of Professor Harold Shechter, and was a post-

doctoral fellow at Harvard University with the late Professor R. B. Woodward. He then joined the research staff of DuPont Central Research. He returned to The Ohio State University as Professor of Chemistry in 1995. His research interests

are in new practical methods for stereoselective synthesis focusing on enantioselective catalysis, free radical chemistry, applications in natural product synthesis, and organic reactions in water.



Scheme 2

which is shown in the context of steroid D-ring functionalization via the hydrovinylation of a diene (Scheme 2). As seen in steroids, a chiral side chain carrying a methyl group is a very common structural motif in many important natural products, and often this side chain is attached to a stereogenic center in a ring. Classical procedures for the installation of these stereocenters often involve circuitous routes. Further, can the reaction be used for the carba-functionalization of strained double bonds as shown at the end of Scheme 2?

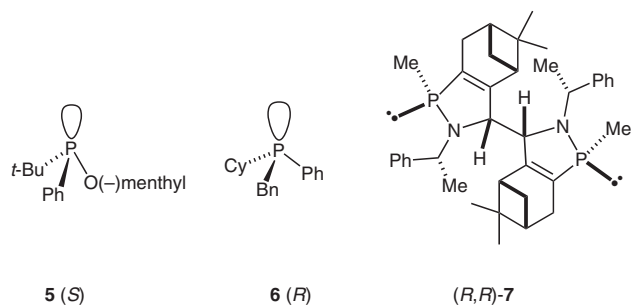
## 2.1 A Brief History of Hydrovinylation Reactions

The hydrovinylation reaction has a long history<sup>1a</sup> dating back to 1965 when Alderson et al.<sup>6a</sup> first reported the use of hydrated rhodium and ruthenium chlorides to effect codimerization of ethylene at high pressures (1000 psi) with a variety of olefins, including styrene and butadiene. Styrene has served as a prototypical test case for most investigations reported to date. In early studies, in addition to rhodium,<sup>6,7</sup> other metals such as ruthenium,<sup>6</sup> cobalt,<sup>8</sup> palladium,<sup>9</sup> and nickel<sup>10</sup> were also used, and in most instances the reactions were complicated by isomerization of the initially formed 3-arylbut-1-enes and oligomerization of the starting olefins (as shown at the top of Scheme 2). Notable among the early studies are also the first examples of the asymmetric hydrovinylation of cycloocta-1,3-diene,

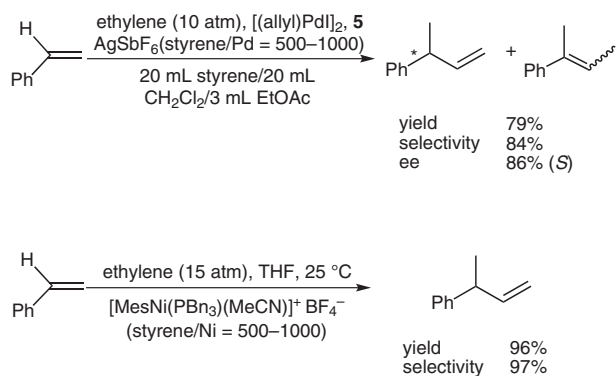
norbornene, and norbornadiene (using a combination of  $[\eta^3\text{-(allyl)NiCl}]_2/\text{Et}_3\text{Al}_2\text{Cl}_3$  and a monoterpene-derived chiral phosphine), even though the selectivities were unacceptably poor.<sup>11</sup>

Even though some initial reports<sup>9,12</sup> seemed to indicate that the palladium-catalyzed reactions gave mostly linear products and/or extensive isomerization, subsequent studies have shown that use of ligands such as **5**<sup>13</sup> and **6**<sup>14</sup> (Figure 1) under carefully chosen reaction conditions permit the isolation of the branched product. Acceptable yields and the best selectivities are achieved under low conversions since isomerization of the primary product is a persistent problem with many of these reactions. Among these ligands, phosphinite **5** is particularly noteworthy (Scheme 3).<sup>13</sup> With the appropriate counterion ( $\text{SbF}_6^-$ ), 3-phenylbut-1-ene can be synthesized in a reasonable yield and in enantiomeric excess (ee) of up to 86% (*S*).

Recent improvements in the nickel-catalyzed heterodimerization reaction includes the use of  $[\text{ArNi}(\text{PR}_3)(\text{MeCN})]^+ \text{BF}_4^-$  (Ar = Mes, R = Bn), which served as an efficient catalyst for the hydrovinylation of styrene (Scheme 3).<sup>15</sup> High turnover numbers ( $<1915 \text{ h}^{-1}$ ) and selectivities in the synthesis of 3-arylbut-1-enes can be achieved with a variety of styrenes and ethylene at 15 atmospheres. Heteroatom substituents are tolerated, but ring-alkylated styrenes give poor yields. The reaction rates fall unaccept-



**Figure 1** Assorted ligands useful for asymmetric hydrovinylation

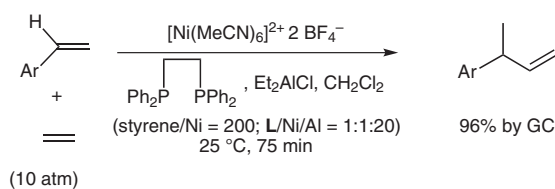


**Scheme 3**

ably low below 20 °C, and as the temperature is increased isomerization of the initially formed product is seen. The substitution of the tribenzylphosphine ligand with *cis*-myrtyranyldiphenylphosphine gives high selectivity towards 3-phenylbut-1-ene, albeit with a disappointing enantioselectivity (~7% ee). Since there is an exothermic polymerization of ethylene at the end of the relatively more facile heterodimerization, control of the temperature is crucial to get good selectivities under these reaction conditions. Monteiro and co-workers<sup>16</sup> reported the use of dicationic nickel complexes ( $[\text{Ni}(\text{MeCN})_6]^{2+} 2\text{BF}_4^-$ ,  $\text{Ph}_3\text{P}$ ,  $\text{Et}_2\text{AlCl}$ ) at room temperature and 10 atmospheres of ethylene to get 68–87% yields of various hydrovinylation products. Isomerization of the primary product can be prevented by maintaining a high pressure of ethylene (>10 atm). A unique feature of this catalyst system that is not seen in any other nickel-catalyzed reactions is that chelating phosphines {e.g., 1,2-bis(diphenylphosphino)ethane (dppe) or *N,N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine (dppfa)} do not inhibit the reaction (Scheme 4). Preparatively useful nickel-catalyzed asymmetric hydrovinylation reactions will be dealt with in greater detail in Section 2.3.

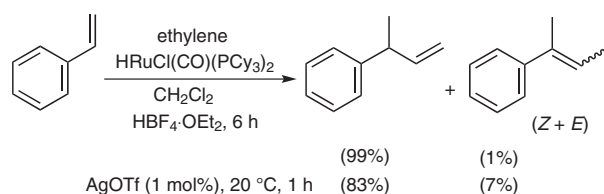
## 2.2 Ruthenium- and Cobalt-Catalyzed Hydrovinylation Reactions

While this review is not intended to be exhaustive, two notable results that show considerable promise are worthy of mention before discussing our own contributions in the area of nickel-catalyzed hydrovinylation reactions. Re-



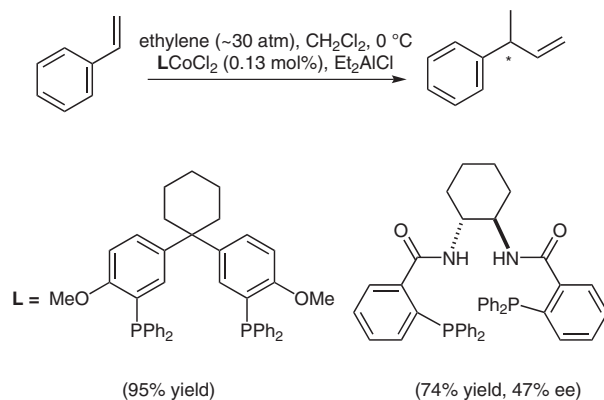
**Scheme 4**

cently, Yi et al. introduced a ruthenium system [a combination of  $\text{HRuCl}(\text{CO})(\text{PCy}_3)_2$  and  $\text{HBF}_4 \cdot \text{OEt}_2$ ] for the hydrovinylation of styrene.<sup>17a</sup> With only scanty details reported, the scope and generality of this procedure still remain to be established (Scheme 5). We found that this reaction can be carried out under 1 atmosphere of ethylene using silver(I) triflate as an additive.<sup>17b</sup>



**Scheme 5**

Vogt and co-workers reported<sup>18</sup> that the hydrovinylation of styrene can be accomplished using a cobalt chelate under ca. 30 atm of ethylene, even though the conversion and selectivity in an enantioselective version remain poor (Scheme 6).

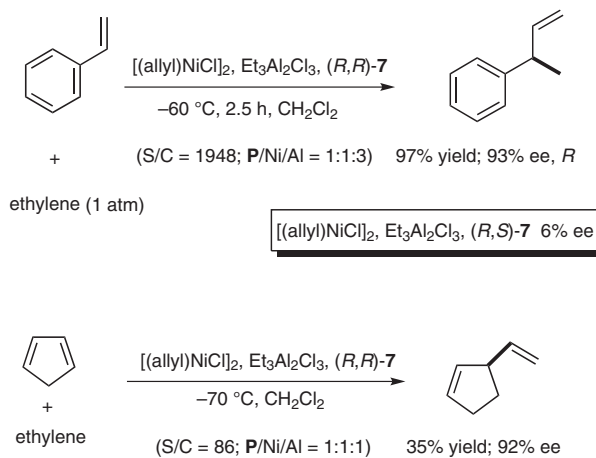


**Scheme 6**

## 2.3 Best Practices prior to 1997: Nickel-Catalyzed Hydrovinylation Reactions

A careful examination of the published research before 1997, when we initiated the new project, showed that the best catalyst reported for the hydrovinylation reaction was also the one that gave the best enantioselectivity; this was the Wilke system  $\{[\eta^3\text{-}(\text{allyl})\text{NiCl}]_2/(\text{R,R})\text{-7}/\text{Et}_3\text{Al}_2\text{Cl}_3\}$ .<sup>1c,19,20</sup> With this catalyst, varying ee values are obtained depending on the reaction conditions. Azaphospholene (R,R)-7 (Figure 1) is a very special ligand for the

hydrovinylation of vinylarenes and 1,3-dienes, and the nickel complexes derived from this ligand were claimed in a patent<sup>19</sup> to give unprecedented enantioselectivities in the reactions of many of these substrates (Scheme 7). A variety of vinylarenes, including 4-chlorostyrene, 4-isobutylstyrene, 2-methylstyrene, and 2-methoxy-6-vinylnaphthalene (MVN), gave very high ee values in the hydrovinylation reaction. Ligand (*R,R*)-**7** is prepared from (*R*)-(-)-myrtenal and (*R*)-(+)-1-phenylethylamine in a multistep process.<sup>1c</sup> One other congener of this compound, diastereomer (*R,S*)-**7** [prepared from (*R*)-(-)-myrtenal and (*S*)-(-)-1-phenylethylamine] is much less active and selective in the hydrovinylation of styrene (Scheme 7). Monomeric and structurally related versions of this ligand have been prepared<sup>1c,21</sup> in an attempt to simplify the synthesis, but it has been found that the catalytic activity and enantioselectivity invariably fall below useful levels.

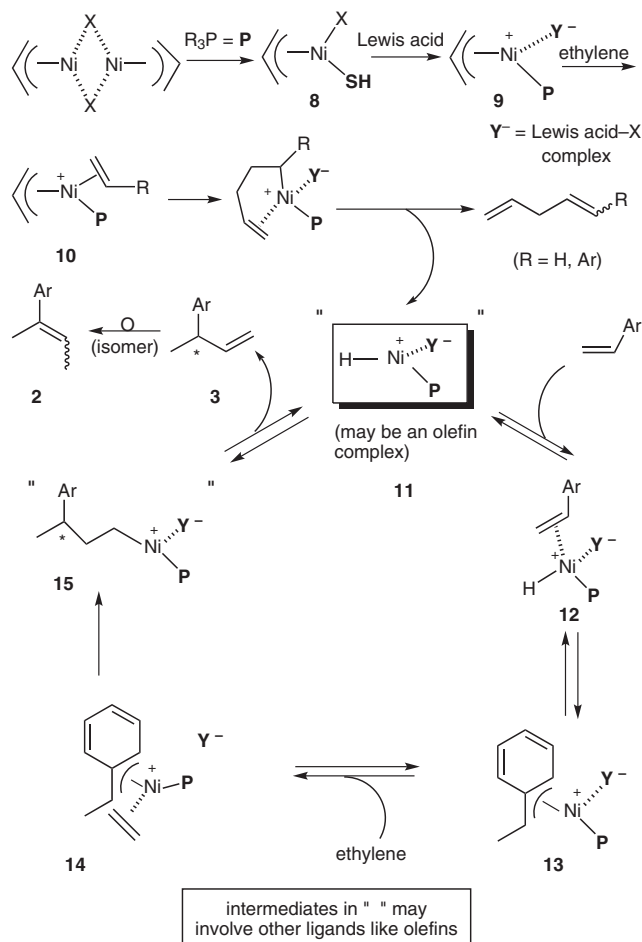


Scheme 7

## 2.4 Mechanism of the Nickel-Catalyzed Hydrovinylation of Vinylarenes

In the absence of meaningful mechanistic work, we started our research with a working hypothesis for the mechanism of the nickel-catalyzed hydrovinylation reaction.<sup>22</sup> Even though many of the early studies on the hydrovinylation of styrene are characterized by a lack of any selectivity, they provide significant mechanistic insights into the reaction. For example, kinetic and solvent effect studies of hydrovinylation [with  $NiX_2$ ,  $Et_3Al$ ,  $BF_3 \cdot OEt_2$  and  $(PhO)_3P$ ]<sup>10e-g</sup> provided some early indications of the coordination of  $[Ni-H]^+$  to a styrene and subsequent addition. The deactivating effect of a solvent was found to increase in the order dichloromethane, fluorobenzene, chlorobenzene, toluene, nitrobenzene, and diethyl ether, consistent with the inhibitory effect of a coordinating Lewis base. Studies of deuterium distribution in the product when the hydrovinylation was carried out with ethylene-*d*<sub>4</sub> provided further evidence for the involvement of a cationic nickel hydride intermediate.<sup>10f</sup> Even though a catalytically active  $[LNi-H]^+$  system has not been isolated, its genera-

tion and inter-<sup>2</sup> and intramolecular<sup>23</sup> additions have been documented. Since these early studies, Brookhart and DiRenzo have provided more details of their mechanistic study of the closely related palladium-catalyzed co-dimerization of styrene and ethylene.<sup>24</sup> Based on all the available evidence and our own initial observations (*vide infra*), a hypothetical mechanism can be proposed for this reaction (Scheme 8).



Scheme 8 Proposed mechanism for the hydrovinylation of styrene

The functional equivalent of the catalyst can be represented by complex **11**, a cationic metal hydride intermediate associated with a weakly coordinated counterion and a phosphine. This species is formed by Lewis acid assisted dissociation of the Ni-X bond in 16-electron phosphine complex **8**, coordination of ethylene (or styrene) to form **10**, insertion into the allyl-nickel bond, and subsequent  $\beta$ -hydride elimination. Several crystal structures of complexes related to allylnickel compounds **8** and **9** are known containing tricyclohexylphosphine ( $X = MeAlCl_3$ ),<sup>11b</sup> *tert*-butyl(menthyl)methylphosphine ( $X = Cl$ ),<sup>25</sup> and dimethyl(methyl)phosphine ( $X = Me$ ).<sup>26</sup> The addition of metal hydride **11** to the vinylarene would lead to benzyl complex **13**, which is shown as a 16-electron  $\eta^3$ -structure. Ligand substitution with ethylene leads to intermediate **14**. At higher concentrations of ethylene and styrene, this species could serve as a catalyst resting state. Strong evidence for

such a situation has been provided by Brookhart and DiRenzo<sup>24</sup> in a mechanistically related, palladium-mediated {with [(allyl)Pd(PCy<sub>3</sub>)]<sup>+</sup>[BARF]<sup>-</sup>} dimerization of styrene. Insertion of ethylene followed by  $\beta$ -hydride elimination from **15** regenerates metal hydride catalyst **11** and product **3**. A number of anecdotal observations reported in the literature and some made during our studies can be accommodated by this mechanism:

(a) The diminished reactivity of electron-deficient vinylarenes that might arise from a low rate of metal hydride addition (**11**  $\rightarrow$  **13**).

(b) The apparent poor reactivity of substrates carrying heteroatoms when R<sub>2</sub>AlX-type Lewis acids are employed that could be the result of the coordination of these atoms to aluminum.

(c) The deactivating effects of the coordinating solvents.

(d) The isomerization of the initially formed 3-arylbut-1-enes to 2-arylbut-2-enes (**3**  $\rightarrow$  **2**) that could be mediated by the metal hydride via sequential addition–elimination reactions.

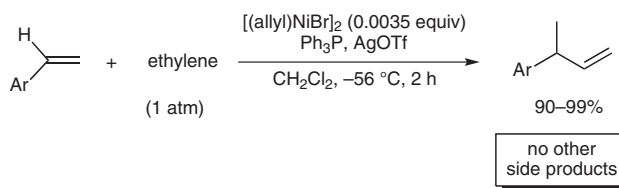
(e) The total inhibition of the reaction by chelating phosphines (*vide infra*).

## 2.5 A New Protocol for Hydrovinylation Amenable to Asymmetric Catalysis

We have already alluded to the fact that among earlier developments, only Wilke's azaphospholene ligand (*R,R*)-**7**<sup>2,19</sup> gave satisfactory yields and selectivities for this potentially important reaction (see Scheme 7). Subsequent work has shown that the protocols using this ligand are possibly of limited value for the development of a broadly applicable hydrovinylation reaction. At the outset of our work, we speculated that the scope and selectivity of hydrovinylation could be increased significantly by eliminating the troublesome Lewis acids from the Wilke system. In their place, we would use a silver salt whose weakly coordinating anion can be easily replaced in the coordination sphere of nickel by an olefin prior to the insertion step (**8**  $\rightarrow$  **9**  $\rightarrow$  **10** in Scheme 8). 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 Wilke and co-workers.<sup>1b,2</sup> As for the effect of the counterion (Y<sup>-</sup> in Scheme 8), the situation appeared uncertain as it was known that the selectivity varied considerably with the nature of the phosphorus ligand. For example, coordinating anions (e.g., Et<sub>2</sub>AlCl<sub>2</sub><sup>-</sup>, OTf<sup>-</sup>, and BF<sub>4</sub><sup>-</sup>) give higher ee values with ligand (*R,R*)-**7**,<sup>1c</sup> but an opposite effect is observed with highly basic ligands, like isopropyl(dimethyl)phosphine, where the best anions are the highly dissociating ones (e.g., SbF<sub>6</sub><sup>-</sup> and PF<sub>6</sub><sup>-</sup>).<sup>1b</sup>

I still recall the day this project was assigned to Dr. Nobu Nomura, an exceptionally bright and hard-working post-doctoral fellow who came from Nagoya University (to which he has since returned as a faculty member), with a warning of many of the risks that might lie ahead. Nobu

proceeded to methodically investigate the effects of variations of ligands, counterions, and other parameters on the course of the hydrovinylation of styrene. After extensive effort, he discovered a new protocol for this highly demanding reaction (Scheme 9).<sup>22</sup>



Scheme 9

During these investigations, Nobu encountered every conceivable problem in trying to react two alkenes to get a third alkene as the major product in a coupling reaction. These difficulties included oligomerization of styrene, polymerization of ethylene, isomerization of the initially formed 3-phenylbut-1-ene, precipitation of the metal (Ni or Pd), or a complete lack of reactivity, depending on the phosphine, the silver salt, the solvent, and the temperature. However, several reactions gave just enough encouraging results<sup>17b</sup> to feed his persistence. In the end, a reliable protocol was determined that gave *unprecedented* chemical yield and selectivity in the hydrovinylation of a series of substituted vinylarenes. This method involved the use of a combination of [(allyl)NiBr]<sub>2</sub>, triphenylphosphine, and a weakly coordinating counterion (OTf<sup>-</sup>) as the precatalyst (Scheme 9 and Table 1). Typically, the reaction is carried out under 1 atmosphere of ethylene at –56 °C in dichloromethane as the solvent and using 0.007 equivalents of the catalyst. Under these conditions, no oligomerization of ethylene or styrene or rearrangement of the initially formed product was 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 (Table 1, entries 2, 5, and 9). Derivatives such as 4-isobutylstyrene, 3-fluoro-4-phenylstyrene, MVN, and 3-benzoylstyrene, all potential precursors of important anti-inflammatory agents, give excellent yields of the hydrovinylation products (entries 6, 7, 5, and 9, respectively). The hydrovinylation products of 4- and 3-bromostyrene (entries 3 and 8, respectively) are also 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 bis-diarylphosphinites gave no products under otherwise identical conditions. These ligands included 1,3-bis(diphenylphosphino)propane (dppp), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), [2,2-dimethyl-1,3-dioxolane-4,5-diylbismethylene]bis(diphenylphosphino) (DIOP), and 1-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BPPM).

**Table 1** Hydrovinylation of Vinylarenes

Entry	Vinylarene	Conditions <sup>a</sup>	Yield (%) <sup>b</sup>
1	styrene	(i)	>95 (99)
2	4-methoxystyrene	(i)	>95 (98)
3	4-bromostyrene	(i)	>95 (98)
4	2-vinylnaphthalene	(i)	(99)
5	MVN	(i) (ii)	(90) (97)
6	4-isobutylstyrene	(i) (ii)	>90 (99) >97 (99)
7	3-fluoro-4-phenylstyrene	(i)	(88)
8	3-bromostyrene	(i)	(99)
9	3-benzoylstyrene	(i)	(99)
10	3-methylstyrene	(i)	(>99)
11	4-methylstyrene	(i)	(>99)
12	2-chlorostyrene	(i)	30
13	4-chlorostyrene	(i)	(>99)

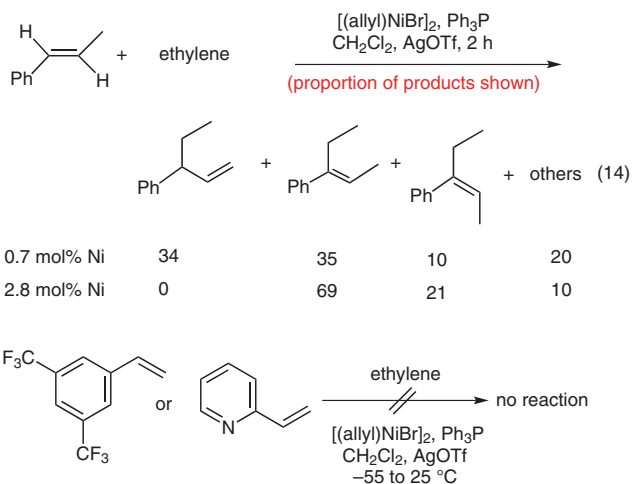
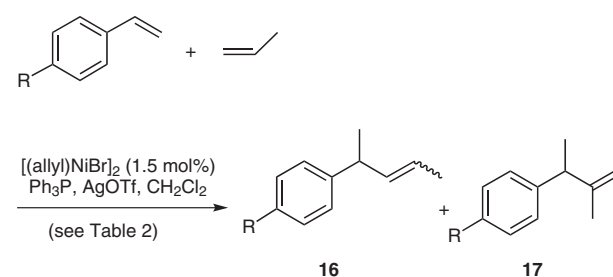
<sup>a</sup> See also Scheme 9; (i) catalyst (0.007 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -55 °C, 2 h; (ii) (*R*)-MOP, NaBARF, CH<sub>2</sub>Cl<sub>2</sub>, -56 °C, 2 h (see Section 4.1).

<sup>b</sup> Isolated yield; selectivity >98% in all cases. The values in brackets are yields based on GC.

Methyl substitution at  $\alpha$ - or  $\beta$ -carbons of styrene also leads to poor yields. At higher temperature (-0 °C), up to 34% yield of the primary product is formed from (*E*)- $\beta$ -methylstyrene. The rest of the material consists of isomerized products (Scheme 10). (*Z*)-Stilbene gives a mixture of olefinic products in low yields. Not unexpectedly, the recovered stilbene is a mixture of *Z*- and *E*-isomers, providing further support for a [LNi-H]<sup>+</sup> intermediate in these reactions. Other related substrates that fail to undergo the hydrovinylation reaction under a variety of conditions include 3,5-bis(trifluoromethyl)styrene, 2-vinylpyridine, and 9-vinyl-9*H*-carbazole. While the electron-deficient nature of the styrene may retard nickel coordination, the lack of reactivity of the vinylpyridine may have its origin in the formation of stable intermediates assisted by the pyridine nitrogen (Scheme 10).

## 2.6 Heterodimerization of Vinylarenes with Other Olefins

Unlike the heterodimerization reactions of ethylene, synthetically useful heterodimerizations using propene were not known before our work. We found that propene reacts with styrene and substituted styrenes under conditions slightly modified from those previously described for the reactions with ethylene giving excellent yields of the expected products (Scheme 11 and Table 2). The reaction with propene proceeds at a higher temperature (-15 to 10 °C

**Scheme 10****Scheme 11**

in most cases vs -56 °C for the ethylene reaction), especially in the cases of the more-electron-deficient styrene derivatives.<sup>27</sup> As expected, a mixture of regioisomeric products is obtained; the major product **16** results from the addition of propene at C-1 to the benzylic position of the vinylarene.

**Table 2** Heterodimerization of Propene and Vinylarenes<sup>a</sup>

Entry	R	Temp (°C)	Time (min)	Yield (%) <sup>b</sup>	Ratio ( <b>16/17</b> )
1	<i>i</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 <sup>c</sup>	-40	30	98	5:1
6	Bz <sup>d</sup>	10	15	94	4:1
7	NTS <sub>2</sub> <sup>d</sup>	10	25	92	2:1
8	MVN <sup>d,e</sup>	-5	60	88	10:1

<sup>a</sup> See also Scheme 11.

<sup>b</sup> Isolated yield.

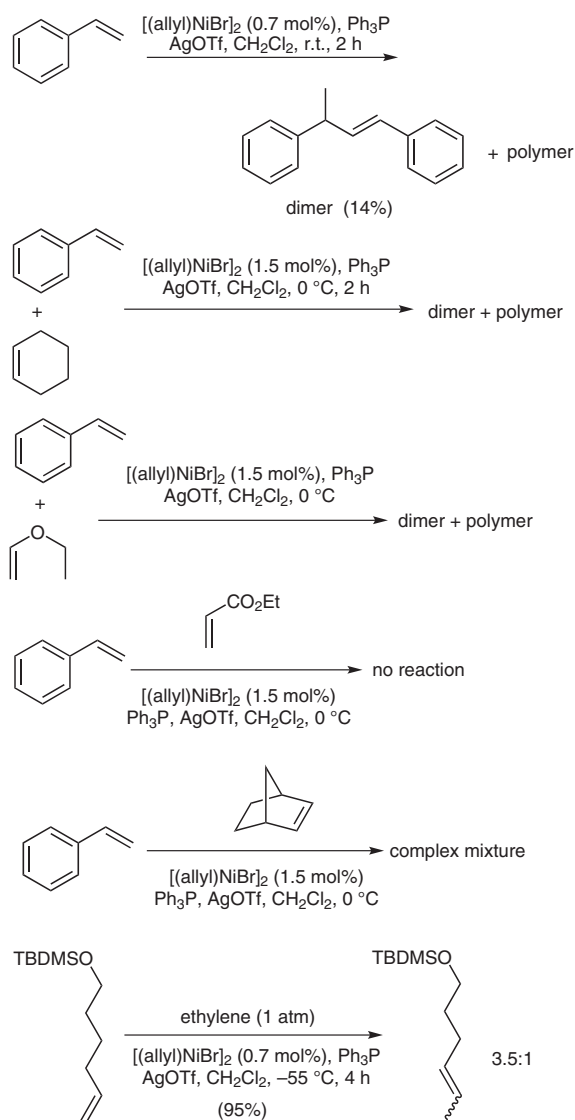
<sup>c</sup> 1.4 mol% Ni used.

<sup>d</sup> 3 mol% Ni used.

<sup>e</sup> The substrate was MVN.

## 2.7 Other Heterodimerization Reactions

The reaction of styrene alone with  $[(\text{allyl})\text{NiBr}]_2$  and triphenylphosphine at room temperature in the presence of silver(I) triflate leads to the formation of a styrene dimer in 14% yield, along with extensive polymerization (Scheme 12). Attempts to effect the heterodimerization of styrene and cyclohexene or ethyl vinyl ether also lead to polymer formation; varying amounts of a styrene dimer can be detected in gas chromatography under these conditions. Co-dimerization of styrene and ethyl acrylate does not proceed under the standard hydrovinylation conditions using triphenylphosphine and silver(I) triflate; whereas with norbornene, a complex mixture of hydrocarbons is obtained (Scheme 12). Finally, the treatment of a typical terminal olefin, 1-(*tert*-butyldimethylsiloxy)hex-5-ene, with ethylene under hydrovinylation conditions leads to clean isomerization of the double bond to give a mixture of (*Z*)- and (*E*)-1-(*tert*-butyldimethylsiloxy)hex-4-enes (Scheme 12). The Wilke azaphospholene (*RR*)-7 has been used for Ni-catalyzed asymmetric hydrovinylation in supercritical carbon dioxide.<sup>20</sup>

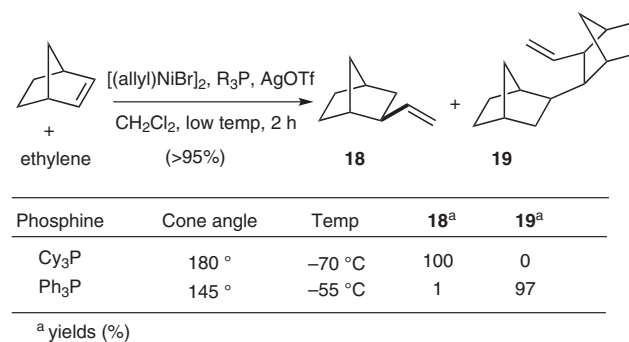


**Scheme 12**

Synlett 2009, No. 6, 853–885 © Thieme Stuttgart · New York

## 2.8 Hydrovinylation of Norbornene

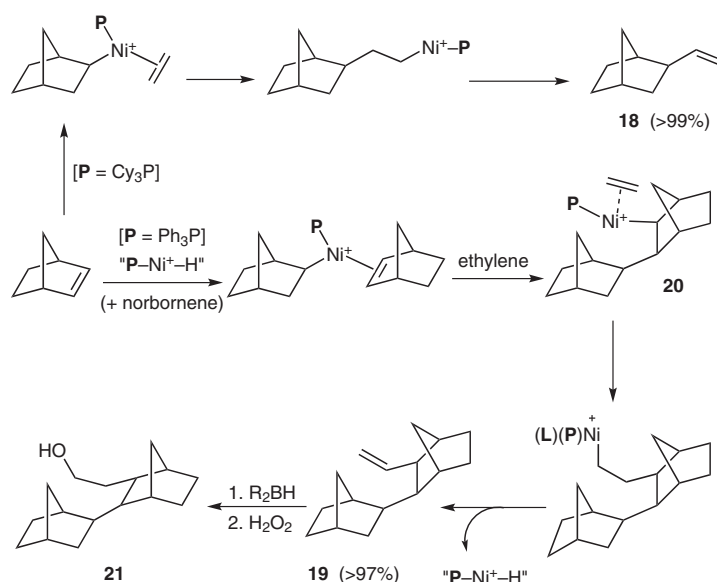
Similar to using the differences in electronic properties and size between two olefins, ring strain is another differentiating factor that could be exploited to effect a selective heterodimerization. We found that the protocol using  $[(\text{allyl})\text{NiBr}]_2$ /phosphine/AgOTf works equally well for the heterodimerization of norbornene and ethylene (Scheme 13), with the course of the reaction being dependent on the phosphine that is employed.<sup>28</sup> The use of tricyclohexylphosphine gives the expected 1:1 adduct **18** in nearly quantitative yield, whereas the reaction with triphenylphosphine gives a 2:1 adduct of norbornene and ethylene, i.e. compound **19**. For further identification, trimer **19** was converted into alcohol **21** (Scheme 14). This remarkable selectivity is presumably related to the cone angles of the two phosphines (Scheme 13) 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 ( $\text{Ph}_3\text{P}$ ) is used (Scheme 14). The initially formed  $\sigma$ -nickel complex **20**, for stereoelectronic reasons, cannot undergo  $\beta$ -hydride elimination and, hence, reacts with another olefin, i.e. ethylene, to give finally the 2:1 adduct **19**. With a bulky phosphine, only addition to ethylene is feasible, giving the 1:1 adduct.



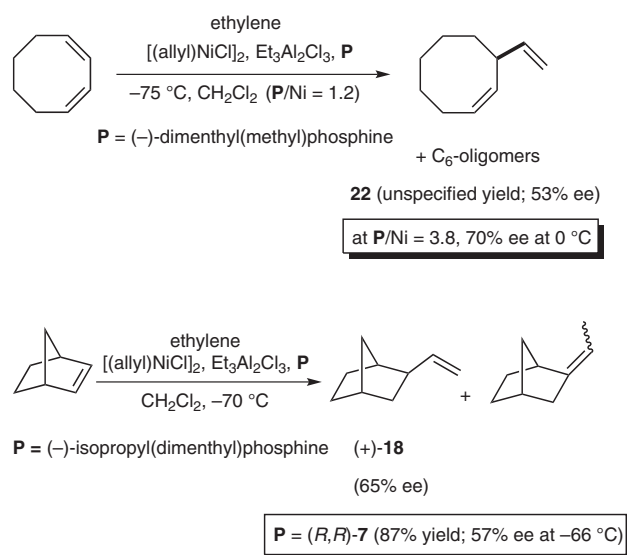
**Scheme 13**

## 3 Enantioselective Hydrovinylation Reactions

The asymmetric hydrovinylation of cycloocta-1,3-diene using dimethylmethylphosphine as a ligand is one of the first examples<sup>11a,c</sup> of an asymmetric carbon–carbon bond-forming reaction ever reported, even though the selectivity was unacceptably low (up to 70% ee, unspecified yield) by today's standards (Scheme 15). Under somewhat similar conditions, norbornene (Scheme 15) and norbornadiene give the corresponding 2-*exo*-vinyl products in 65 (at –70 °C) and 78% ee (at –65 °C), respectively.<sup>11b</sup> Depending on the temperature, varying degrees of isomerization to the ethylidene derivatives (*E* and *Z*) are observed in both cases. The full details of the reaction conditions and the characterization of the products in these and many other early hydrovinylations are difficult to locate.



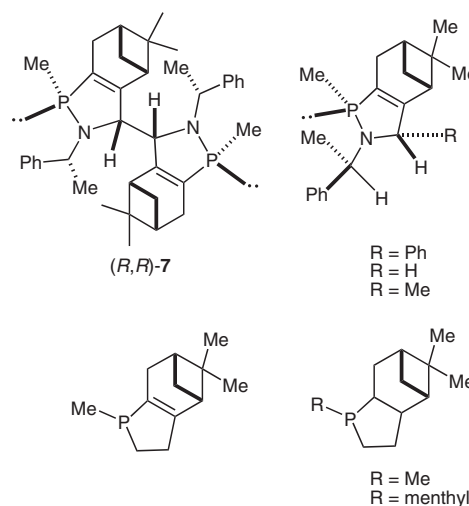
**Scheme 14** Ligand dependence in the hydrovinylation of norbornene



**Scheme 15**

### 3.1 Azaphospholene Ligands

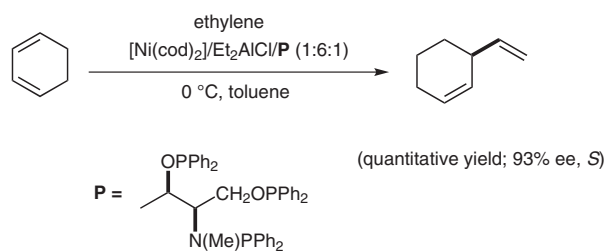
Before the recent resurgence of activity in this area, the best ligand for the hydrovinylation of vinylarenes (Scheme 7), cyclopentadiene (Scheme 7), and norbornene (Scheme 15) was azaphospholene (*R,R*)-**7** (Figure 2), used in conjunction with an allylnickel halide dimer and a Lewis acid (e.g.,  $\text{Et}_3\text{Al}_2\text{Cl}_3$ ).<sup>1c,19</sup> Attempts to modify the azaphospholene ligand (Figure 2) suggest that this class of compounds is of narrow scope and possibly limited value for the development of a broadly applicable hydrovinylation reaction, especially for a *practical* enantioselective version. The use of pyrophoric alkylaluminum Lewis acids is another major limitation of this protocol, especially if the scope of the reaction is to be expanded to heteroatom-containing substrates.



**Figure 2** Phospholene ligands for asymmetric hydrovinylation

### 3.2 Aminophosphine/Phosphinite Ligands

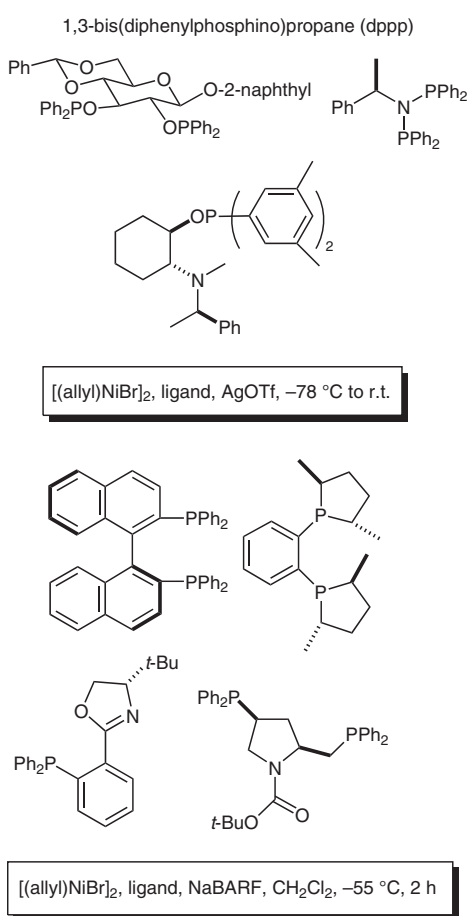
A nickel complex prepared in situ from an aminophosphine/phosphinite (AMPP) ligand derived from (*2S,3R*)-threonine is an efficient catalyst for the hydrovinylation of cyclohexa-1,3-diene (Scheme 16).<sup>29</sup> Other amino alcohol derived AMPP ligands give lower selectivities.



**Scheme 16**

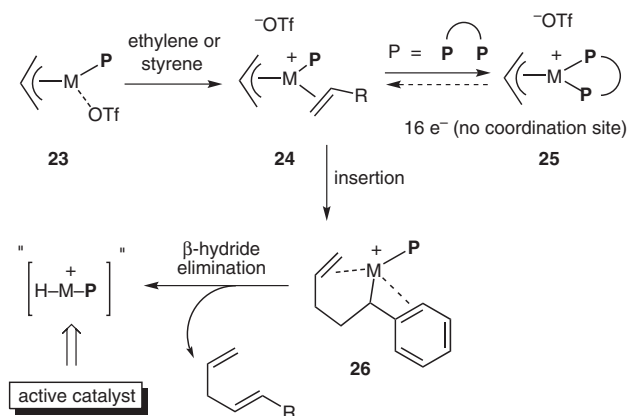
### 3.3 Use of Chelating Phosphines

If the proposed mechanism (Scheme 8) has any validity, there is only one ligand per metal in the catalytically active species. A number of studies have indicated that the nickel-catalyzed hydrovinylation reaction might be inhibited by chelating phosphines, even when the reactions are carried out under widely different conditions.<sup>1b,15a</sup> Nonetheless, we investigated the viability of using different classes of chelating phosphines under the newly discovered protocol (see Scheme 9). A list of ligands and some of the typical reaction conditions tested are given in Figure 3. Careful examination of the crude reaction products by gas chromatography and NMR spectroscopy revealed that no carbon-carbon coupling products (oligomers and hetero- or homodimers) were formed under these reaction conditions, even when the reaction was run at higher temperatures.



**Figure 3** Chelating ligands examined for the nickel-catalyzed hydrovinylation reactions

In retrospect, the conspicuous lack of activity in the hydrovinylations involving the chelating phosphines is not surprising. As shown in Scheme 17, the generation of the active catalyst is possible only if OTf<sup>-</sup> in the initially formed complex **23** is efficiently displaced by one of the olefins (ethylene or styrene), and this event is followed by an insertion (e.g., to form **26**) and a β-hydride elimination.



**Scheme 17** Why a chelating ligand may be unsuitable for the hydrovinylation of an olefin

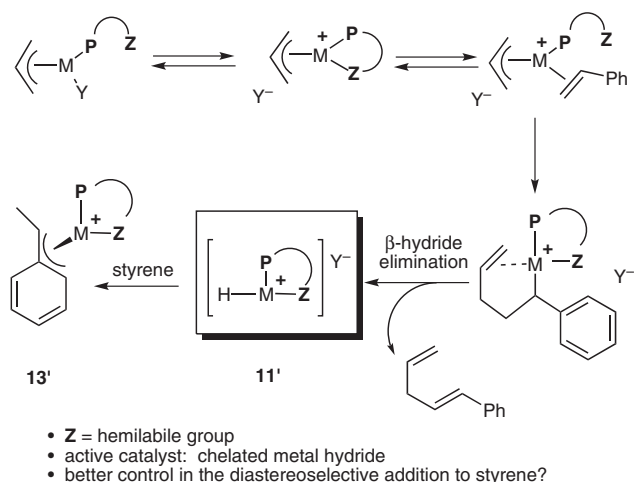
A strongly chelating bis-phosphine would either prevent the formation of **24** or effectively reduce its concentration such that the insertion pathway is no longer available.

## 4 Synergistic Relation between Hemilabile Ligands and Counterions

### 4.1 New Ligands for Asymmetric Hydrovinylation Reactions: 2-Alkoxy-2'-diphenylphosphino-1,1'-binaphthyl Derivatives

Considering the requirement of an open coordination site for ethylene in the critical steps of the hydrovinylation reaction (Scheme 8), we wondered whether the use of a monophosphine that also carried a hemilabile group<sup>30,31</sup> might have an advantage, since such a group could stabilize the putative cationic intermediates by internal coordination. The argument was that the weakly coordinated group could be displaced by the olefin at the appropriate stage. In addition, such coordination might lead to chelated metal hydride **11'** with better diastereoselective discrimination in the key addition to the prochiral faces of the olefin, e.g. in the formation of the η<sup>3</sup>-benzylnickel intermediate **13'** (Scheme 18) (**11'** and **13'** correspond to **11** and **13**, respectively, in the general mechanism shown in Scheme 8). Making the reasonable assumption that all the subsequent steps proceed with retention of configuration, it can be argued that the enantioselectivity is determined at the stage of the metal hydride addition.

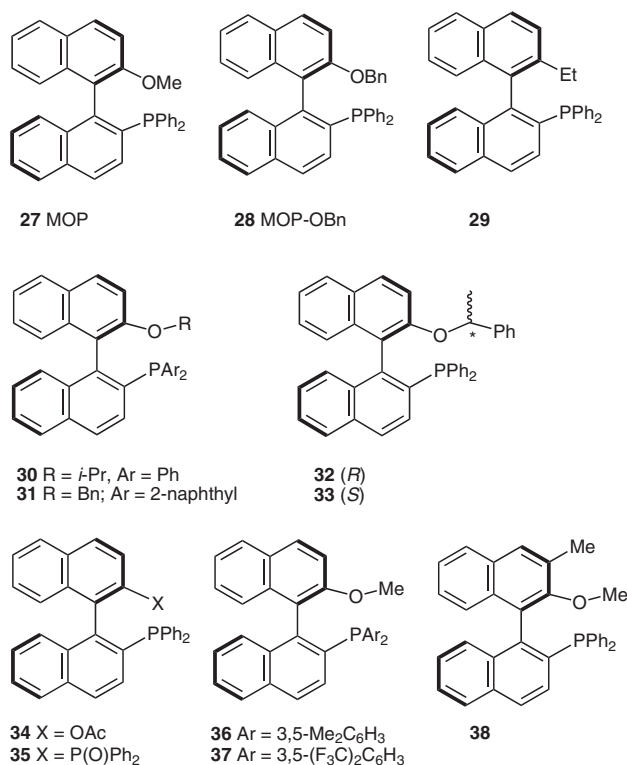
A number of 'hemilabile' groups, including carboxylate (anionic), ester carbonyl, triarylphosphoryl, and sulfur (from a thiophene) moieties, have been investigated in a variety of reactions, such as the co-dimerization of ethylene and styrene,<sup>32a</sup> oligomerization of ethylene,<sup>32a-d</sup> and ethylene and carbon monoxide oligomerization.<sup>12a,b</sup> Since our eventual goal was to develop an asymmetric version of the hydrovinylation reaction, we decided to explore the use of a hemilabile ligand in the context of a chiral ligand. In the absence of any clear lead, an ether oxygen was chosen as the hemilabile moiety in the first ligands we investigated (Figure 4). This choice was not entirely arbitrary



**Scheme 18** Use of a chelated metal hydride: better diastereoselectivity?

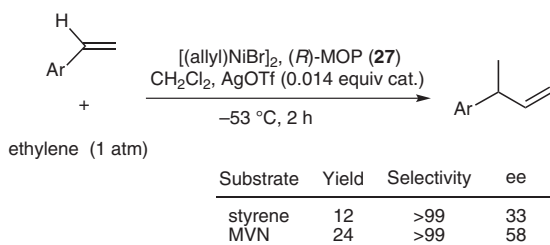
since phosphine/ether systems have been extensively investigated,<sup>31</sup> starting with 2-(diphenylphosphino)anisole, which was the first hemilabile ligand to be so named.<sup>31a</sup>

In the event, (*R*)-2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl (**27**, MOP),<sup>33</sup> in which the methoxy moiety would play the role of the hemilabile ligand, was chosen for our initial study. The BINAP structural motif was considered especially attractive since it allowed considerable flexibility in ligand tuning, including variations of the 2'-substituents, which would permit further explorations of the hemilabile ligand concept.



**Figure 4** 2,2'-Disubstituted 1,1'-binaphthyl ligands for asymmetric hydrovinylation

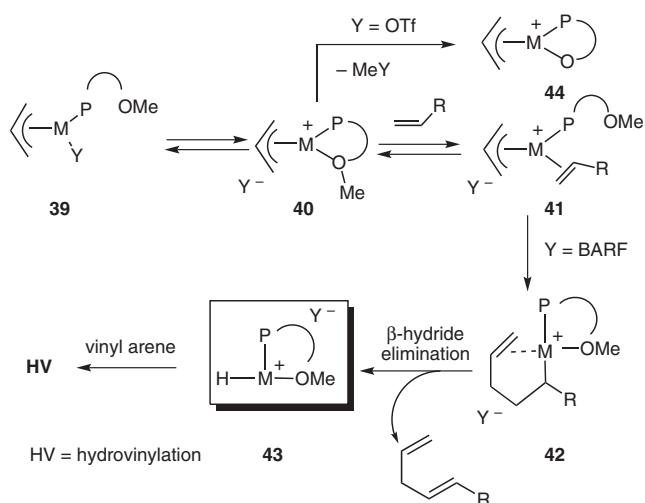
The hydrovinylation of styrene and MVN were carried out with MOP ligand **27** under the standard protocol using silver(I) triflate described earlier (see Scheme 9), and the results are shown in Scheme 19. A highly selective reaction ensues yielding the expected product, albeit with disappointingly low conversion (12 and 24% yield, respectively) and enantioselectivity (33 and 58% ee, respectively). The conversions were of special concern since nearly *quantitative* results were routinely observed in the reactions reported earlier (Table 1).



**Scheme 19**

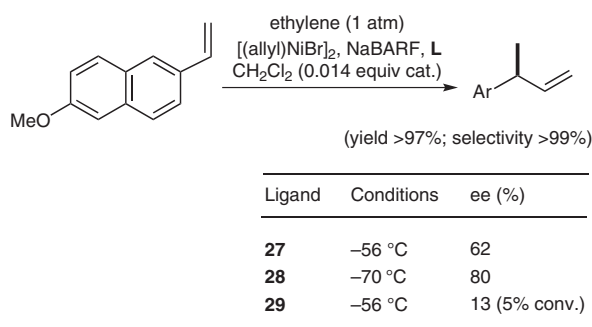
Even though the exact origin of the diminished activity of the nickel catalyst with a hemilabile ligand under these conditions remained unknown, for the further development of the reaction we relied on the following rationale (Scheme 20): The initially formed complex **39** could be in equilibrium with a chelated complex **40**. The generation of the catalyst is possible only if the hemilabile ligand is successfully displaced by an olefin to form **41**. The relative concentrations of **39–41**, thus, become an important factor in the catalyst turnover. Low concentrations of the catalytically competent species **41** and/or side reactions, which remove the catalyst (e.g., by methylation of the triflate to give catalytically inactive<sup>34</sup> **44**), may account for the poor reactivity under these reaction conditions.

Support for this conjecture comes from the fact that upon replacement of OTf<sup>-</sup> by a totally dissociated, nonnucleophilic counterion, tetrakis[3,5-bis(trifluoromethyl)phenyl]-



**Scheme 20** Effect of counterions on [(*R*)-2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl]nickel-mediated hydrovinylation

borate (BARF),<sup>35</sup> the activity of the catalyst system is completely restored. The primary products from the hydrovinylation of 4-isobutylstyrene and MVN (Scheme 21) are formed in greater than 95% yields and with enantioselectivities of 40% and 62% ee, respectively.



Scheme 21

Further studies revealed that a minor modification in the ligand structure (change of OMe to OBn to give **28**) improved the enantioselectivity of the reaction of MVN to 80% ee when the reaction is carried out at -70 °C. The corresponding hydrovinylation of 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 the yield and enantioselectivity resulting from the use of ligand **29**, with an ethyl in place of the methoxy group, are only 13% and 3% ee, respectively, in the hydrovinylation of MVN with BARF<sup>-</sup> as the counterion (Scheme 21).

## 4.2 Effect of Hemilabile Groups

To the best of our knowledge, the above work was the first reported explicitly planned use of hemilabile coordination to amplify the enantioselectivity of a chemical reaction. Therefore, we decided to take a closer look at the effect of various groups at the 2'-position of the binaphthyl scaffold on the hydrovinylation reaction. Table 3 lists the results of the reactions of MVN done under the standard protocol (see Scheme 21) using different MOP-type ligands with various 2'-substituents.

Increasing the steric bulk of the 2'-*O*-alkyl substituent has little effect on the enantioselectivity of the MVN hydrovinylation reaction, but the yield of the product is reduced. Thus, the use of isopropoxy derivative **30** instead of MOP **27** under identical conditions gave the product in 69% yield and 70% ee (Table 3, entry 3). However, as previously mentioned, the use of the benzyloxy analogue of MOP **28** resulted in 80% ee when the reaction was carried out at -70 °C (entry 5). Evidence of the involvement of hemilabile oxygen may also be inferred from the different activities of catalysts prepared from BINAP derivatives with (*R*)- and (*S*)-1-phenylethoxy side chains, compounds **32** and **33**, respectively. While the former gave the product in excellent yield (>98%, 71% ee), the reaction involving the latter resulted in only 79% yield (65% ee) (entries

Table 3 Effect of BINAP 2'-Substituents on the Hydrovinylation of 2-Methoxy-6-vinylnaphthalene<sup>a</sup>

Entry	Ligand <sup>b</sup>	2'-Substituent	Yield (%)	ee (%)
1	( <i>R</i> )-BINAP	PPh <sub>2</sub>	0	–
2	<b>27</b>	OMe	>98	62
3	<b>30</b>	<i>i</i> -Pr	69	70
4	<b>28</b>	OBn	97	73 <sup>c</sup>
5	<b>28</b>	OBn	93	80 <sup>d</sup>
6	<b>32</b> ( <i>R<sub>a</sub>,R</i> )	OCH(Ph)Me	>98	71
7	<b>33</b> ( <i>R<sub>a</sub>,S</i> )	OCH(Ph)Me	79	65
8	<b>29</b>	Et	13	3
9	<b>34</b>	OAc	0	–
10	<b>35</b>	P(O)Ph <sub>2</sub>	0	–
11	<b>36</b>	OMe	94	63
12	<b>37</b>	OMe	93	63
13	<b>38</b>	OMe	99	81

<sup>a</sup> See Scheme 21 for the general procedure; reactions conducted at -56 °C.

<sup>b</sup> See Figure 4 for the structures of the ligands.

<sup>c</sup> At -55 °C.

<sup>d</sup> At -70 °C.

6 and 7, respectively). In an attempt to probe the effect of the hemilabile ligand, we prepared 2'-ethyl analogue **29** and tested this ligand under both sets of conditions using silver(I) triflate and NaBARF as additives. For the hydrovinylation of MVN involving the BARF counterion, 13% yield and 3% ee of the product were obtained (entry 8), whereas the corresponding reaction involving silver(I) triflate gave less than 2% conversion. If the hemilabile ligation is important, one should expect different reactivities from ligands with varying donor properties.<sup>31,32</sup> Allylnickel complexes of 2'-acetoxy **34** and 2'-diphenylphosphoryl analogues **35** failed to produce any hydrovinylation products under the standard reaction conditions (entries 9 and 10, respectively). Phosphine oxide is known to be strongly coordinating,<sup>32a</sup> and it is not surprising if the catalyst generation is prevented because of the inability of an olefin to displace this phosphoryl group. As for the acetoxy derivative **34**, a carbonyl oxygen is known to be a strongly coordinating atom as compared with an ether oxygen in a variety of metal complexes.<sup>36</sup> A limited effort made to modify the diaryl substituents of MOP led to no significant improvements in the hydrovinylation of styrene.<sup>17b,37</sup>

## 4.3 Solvent and Salt Effects

As expected from the proposed mechanism, the reaction shows pronounced solvent effects.<sup>17b</sup> For hydrovinylation of MVN, under conditions described in Scheme 21 {0.7

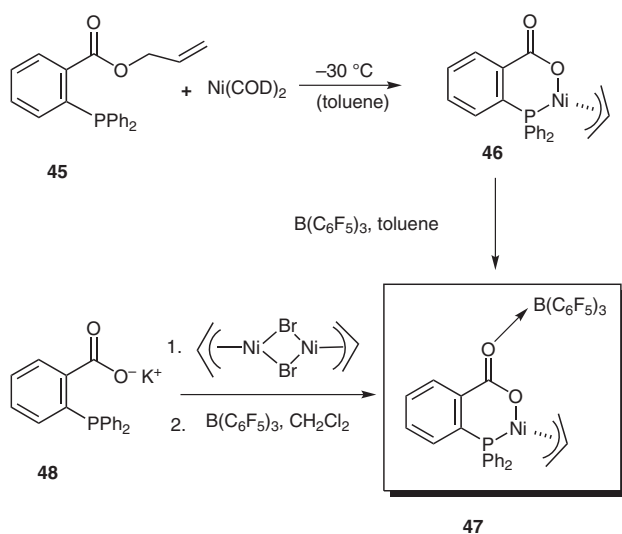
mol% [(allyl)NiBr]<sub>2</sub>, NaBARF, -55 °C, 2 h}, the following yields and enantioselectivities were observed for the solvents indicated: dichloromethane (97%, 73% ee), diethyl ether (87%, 77% ee), toluene (88%, 74% ee), and tetrahydrofuran (0%, 0% ee). Tetrahydrofuran is a strongly coordinating solvent, and it is no surprise that under these conditions hydrovinylation is not observed. The experiments using styrene also showed for the first time that other dissociated silver salts (AgSbF<sub>6</sub> and AgNTf<sub>2</sub>) could effectively replace NaBARF in these reactions.<sup>17b</sup>

#### 4.4 Electronic Effects

Finally, the electronic effects of ligands on the hydrovinylation selectivity were examined by comparison of the ee values obtained using ligands **36** and **37** with that from using **27** (Table 3, entries 11, 12, and 2, respectively). In sharp contrast to nickel(0)-catalyzed hydrocyanation, rhodium(I)-catalyzed hydrogenation, or palladium(0)-catalyzed allylation,<sup>38</sup> ligand electronic properties appear to have little effect on hydrovinylation; using the above ligands for the latter, in each case the chemical yield and ee were almost identical. It is noteworthy that mechanistically the most significant difference between these other metal-catalyzed reactions and hydrovinylation is that there is *no change in the oxidation state of the metal* in the catalytic cycle of the hydrovinylation reaction. Nickel(II) with its ligands plays the role of a complex Lewis acid!

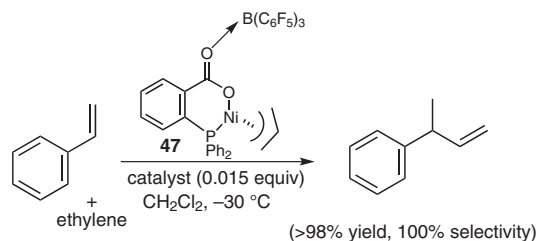
#### 4.5 Other Protocols for Nickel-Catalyzed Hydrovinylation Reactions

During the course of these investigations, we have uncovered a number of other viable procedures for this exacting reaction. Thus, catalyst **47** prepared from allyl 2-(diphenylphosphino)benzoate (**45**) and bis(cycloocta-1,5-diene)nickel(0) [Ni(cod)<sub>2</sub>] or from the corresponding potassium salt of the acid **48** and [(allyl)NiBr]<sub>2</sub>



**Scheme 22** A single component catalyst for the hydrovinylation of styrene

(Scheme 22) shows very good activity and excellent selectivity in the hydrovinylation reaction of styrene when activated with tris(pentafluorophenyl)borane<sup>39</sup> (Scheme 23). Structurally related catalysts have been used for the oligomerization of ethylene.<sup>32a-c,39</sup> These novel methods for the preparation of neutral carboxylate complexes (e.g., **46**, Scheme 22) from the corresponding allyl ester or acid might find other applications.

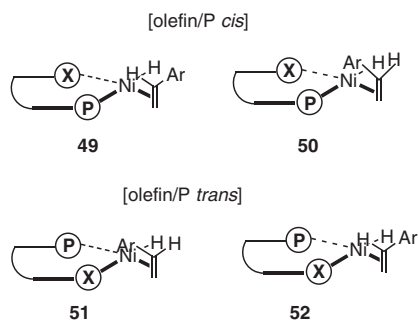


**Scheme 23**

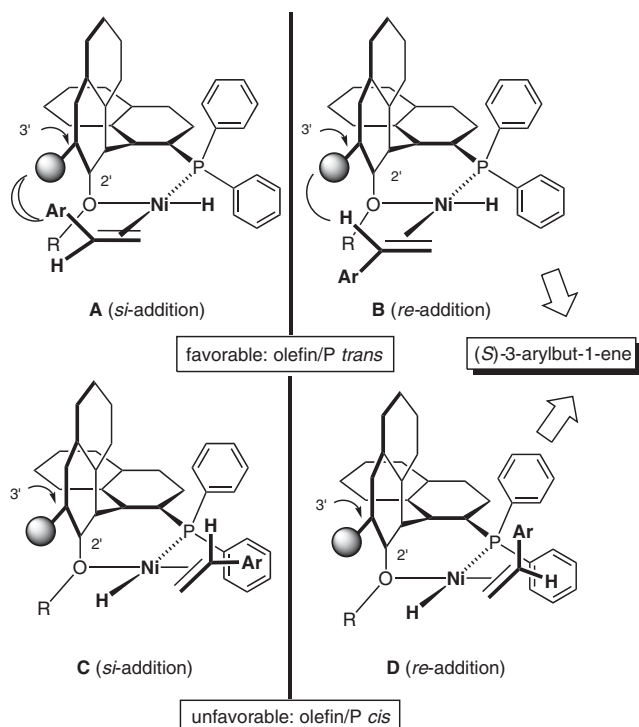
#### 4.6 A Model for Asymmetric Induction in Hydrovinylation Reactions

Even though the details of the mechanism of asymmetric hydrovinylation, including the nature of the turnover limiting and enantioselectivity determining steps, remain unknown, a useful working model for the transition state may be constructed based on reasonable assumptions derived from experimental observations. In connection with this, we regarded the absence of electronic effects, which could complicate simple steric arguments, as a consolation. Maybe we did not have to worry about inscrutable reactivity differences between diastereomeric intermediates. If that was the case, the first stereo-differentiating step could be used to build a model. This would be the addition of a chelated metal hydride through one of the four possible square planar nickel(II) complexes **49–52** shown in Figure 5. In the preferred intermediate/transition state, the olefin will be coordinated *trans* to the diarylphosphino group (sterically less encumbered compared with the corresponding *cis*-olefin/P structures) and the metal hydride addition will take place from the *re*-face of the olefin (i.e., through transition state **B** in Figure 6), eventually leading to the observed major product. In this orientation, the interaction between the hydrogen *ortho* to the alkoxy group of the ligand and the aromatic moiety of the vinylarene is minimized as the distance between the nickel atom and the benzylic carbon is reduced during the bond formation. Such interaction would retard addition to the *si*-face.

In partial support of this argument, the observed ee for a bulky vinylarene (e.g., MVN) is significantly higher than that for simple styrene derivatives (e.g., 80 vs <30% ee) under identical conditions. Further, in the hydrovinylation of styrene and 4-methylstyrene, the use of 3'-methyl-substituted MOP derivative **38** (see Figure 4) gave significantly higher enantioselectivity compared with that obtained using the 3'-unsubstituted ligand (e.g., 60 vs <25% ee).<sup>37</sup> It is expected that a 3'-substituent in MOP



**Figure 5** Possible modes of olefin complexation to a cationic nickel(II) hydride intermediate; X represents the hemilabile coordination site



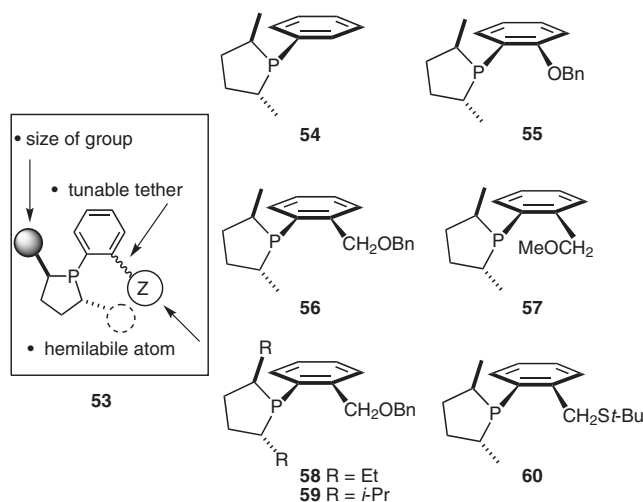
**Figure 6** A model for asymmetric induction in the hydrovinylation of a vinylarene using an (*R*)-2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl-containing nickel complex

would destabilize transition state A leading to *si*-face addition.

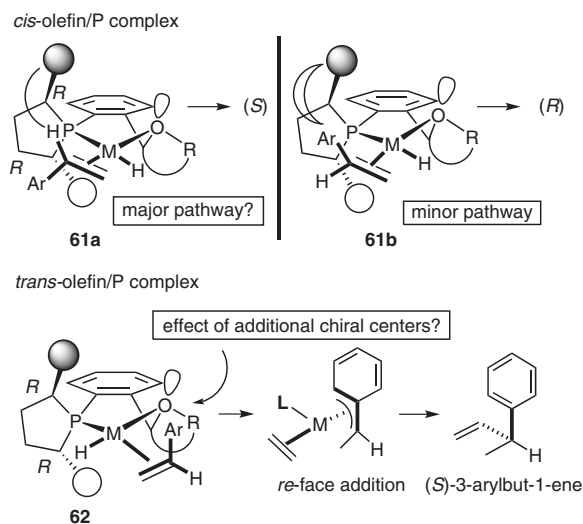
#### 4.7 De Novo Design of an Asymmetric Ligand: Hemilabile Phospholanes

Our search for an in-house catalyst for nickel-catalyzed asymmetric hydrovinylation followed a minimalist approach that was based on the following requirements for the ligand: (i) a source of chirality, in the form a chiral phosphorus atom or chiral scaffolding; and (ii) an appropriately placed group, capable of forming a kinetically labile chelate. With regard to the second item, one could try heteroatoms of various donor abilities or operate on the size of the chelate ring to modulate the critical hemilabile properties of the group.

One example that fits the design criteria outlined above is phospholane **53** shown in Figure 7, and the proposed model for asymmetric induction is depicted in Figure 8. Note that the *cis*-olefin/P complex might appear to prefer *re*-face addition (**61a**). There is no such discernable preference for the *trans*-olefin/P complex **62**. Our conjecture, admittedly without much rationale, was that additional elements of chirality near the hemilabile atom might increase selectivity, even though the exact nature of such control may have to be learned by further experimentation.



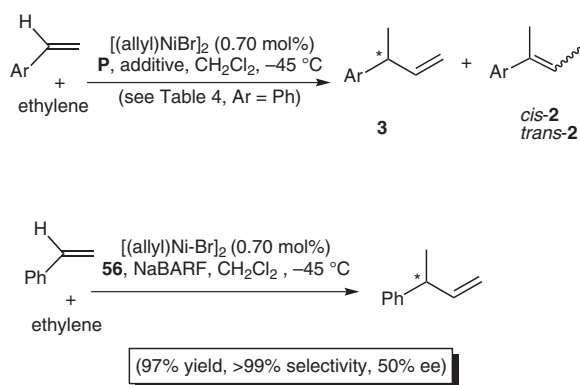
**Figure 7** Elements of a minimalist ligand for asymmetric hydrovinylation and some examples



**Figure 8** A working model for asymmetric induction in (phospholane)nickel(II) catalysis

A series of simple phospholane derivatives **54–60** (Figure 7) were prepared and tested for their use in asymmetric hydrovinylation.<sup>30</sup> We started with 1-arylphospholane ligand **54** and a close analogue **55** containing a potential hemilabile group at the *ortho*-position. While we found **54** to be an excellent ligand for the nickel-catalyzed

hydrovinylation of vinylarenes, especially with OTf<sup>-</sup> as the counterion (Scheme 24 and Table 4, entry 1), **55** led to significant isomerization of the initially formed product **3** to give **2** (Scheme 24) under the standard reaction conditions, even at -55 °C. One of the principal differences between **55** and the versatile MOP derivative **28**, we conjecture, is the placement of the hemilabile alkoxy group with respect to the phosphorus. In ligand **55**, it is on the β-carbon and in **28** it is on the δ-carbon, resulting in a five- versus seven-membered nickel chelate intermediate in the respective cases. This difference might have consequences with respect to the reversibility of the nickel hydride addition once product **3** is formed. To probe the effect of the relative positioning of the hemilabile group, *o*-(benzyloxy)methyl analogue **56** was prepared and, most gratifyingly, this ligand proved to be one of the best for highly selective hydrovinylation reactions (Scheme 24). No traces of isomerization products **2** were detected under optimum conditions!



Scheme 24

Table 4 Effect of Counterions on the Hydrovinylation of Styrene Using Hemilabile Phospholane Ligands

Entry	Additive	Yield (%) [ee (%)]		Remarks
		Using <b>54</b>	Using <b>56</b>	
1	AgOTf	94 (37)	<4 (-)	37% ee ( <i>S</i> ) with <b>54</b>
2	AgClO <sub>4</sub>	95 (low)	<2 (-)	29% isomerization with <b>54</b>
3	AgNTf <sub>2</sub>	<2	48	47% ee ( <i>S</i> ); 9% isomerization with <b>56</b>
4	AgSbF <sub>6</sub>	<2	94	48% ee ( <i>S</i> ) with <b>56</b>
5	NaBARF	<2	97	50% ee ( <i>S</i> ) with <b>56</b>
6	NaBARF	<2	97	42% ee using ligand <b>57</b> instead of <b>56</b>

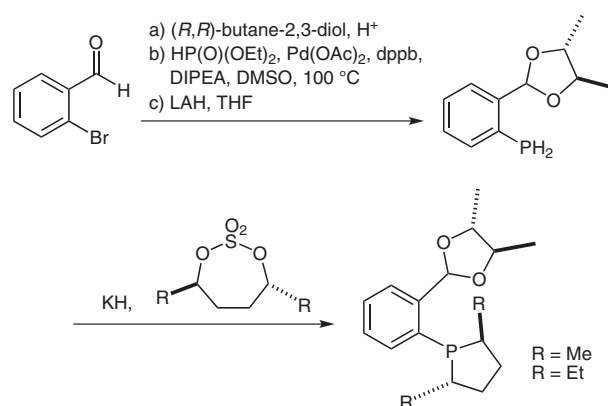
The results of the hydrovinylation of styrene<sup>30</sup> using ligands **54** and **56** shown in Table 4 deserve some comment. For the simplest phospholane ligand **54**, with *no possibility of hemilabile coordination*, the reaction does not proceed unless a weakly coordinating anion (e.g., OTf<sup>-</sup>) is used (entries 1 and 2). Incidentally, with perchlo-

rate (ClO<sub>4</sub><sup>-</sup>), significant isomerization of the primary product is observed when ligand **54** is used. Other additives (i.e., AgBF<sub>4</sub>, NaBPh<sub>4</sub>, AgNTf<sub>2</sub>, AgSbF<sub>6</sub>, and NaBARF) used in conjunction with **54** gave practically *no reaction* under the standard conditions (e.g., entries 3–6), mostly because of immediate precipitation of nickel(0) from the solution. In sharp contrast, for the reactions involving ligand **56** (or **57**) containing an *o*-alkoxymethyl substituent, the best results were obtained with non-coordinating counterions (i.e., SbF<sub>6</sub><sup>-</sup> and BARF<sup>-</sup>, entries 4 and 5, respectively). The catalyst solution containing these combinations also appeared to be remarkably stable for at least two days at room temperature, as judged by <sup>31</sup>P NMR spectroscopy. Not surprisingly, silver(I) triflate, silver(I) perchlorate, and silver(I) tetrafluoroborate were found to be ineffective with ligands **56** and **57**. Some support for the hemilabile coordination has been obtained by NMR spectroscopy.<sup>30</sup>

Increasing the size of the 2- and 5-substituents on the phospholane improves the enantioselectivity. Thus, the use of diethyl derivative **58** (Figure 7) gave ee values of 63 and 67% in the hydrovinylation of styrene and 4-isobutylstyrene, respectively, in highly selective reactions. For 4-isobutylstyrene, a precursor of ibuprofen, this represented one of the highest overall selectivities recorded at the time that we reported these ligands. 2,5-Diisopropylphospholane **59** appears to be too bulky to effect the hydrovinylation reaction; even at 25 °C, most of the starting material was recovered.

Finally, ligand **60** (Figure 7), containing an *o*-(*tert*-butylsulfanyl)methyl group in place of the alkoxymethyl substituent, did not give any reaction. The sulfur atom in this ligand is likely to be a strong donor.

Based on the working model for asymmetric induction in this reaction (Figure 8), we decided to examine the effect of introducing additional elements of chirality at the hemilabile position (see structure **62**, Figure 8). We prepared a series of 2,5-dialkyl-1-(2-*X*-phenyl)phospholanes (*X* = 1,3-dioxan-2-yl or dioxolan-2-yl, Table 5) via the modification of a procedure we had published earlier (Scheme 25).<sup>30,40</sup>



Scheme 25 Synthesis of a prototypical phospholane/acetal ligand

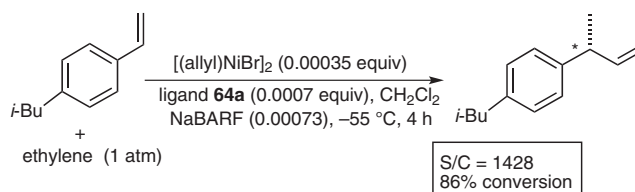
**Table 5** Asymmetric Hydrovinylation of 4-Isobutylstyrene with Phospholane Ligands

Entry	Ligand	Conversion (%)	Selectivity (%) <sup>a</sup>	ee (%)
1		>99.5	>99.5	85 ( <i>R</i> )
2		>99.5	>99.5	91 ( <i>R</i> )
3		83	>99.5	88 ( <i>R</i> )
4		>99.0	90 <sup>b</sup>	71 ( <i>R</i> )
5		>99.5	>99.5	85 ( <i>R</i> )
6		>99.5	>99.5	90 ( <i>S</i> )

<sup>a</sup> Selectivity for the 3-arylbut-1-ene.<sup>b</sup> The other products were the *cis*- and *trans*-2-arylbut-2-enes.

In scouting experiments, the hydrovinylation reaction of 4-isobutylstyrene was carried out using 0.007 equivalents of nickel and the phosphine ligand in an atmosphere of ethylene at  $-55\text{ }^{\circ}\text{C}$ , and the results are shown in Table 5. The acetal-containing phospholanes **63**–**67**, in general, are excellent ligands for asymmetric hydrovinylation, giving near quantitative yields and selectivities for the expected 3-arylbut-1-ene products.

Ligand **63**, with an achiral acetal appendage, gives the desired product in 85% ee in the asymmetric hydrovinylation

**Scheme 26**

ation of 4-isobutylstyrene (Table 5, entry 1). The combination of (*S,S*)-2,5-dimethylphospholane and an acetal derived from (*R,R*)-butane-2,3-diol, ligand **64a**, gives the best selectivity (91% ee, entry 2). Increasing the size of the phospholane 2- and 5-substituents from methyl to ethyl groups, e.g. using **64b** instead of **64a**, appears to have little effect on ee, but significantly, the rate of the reaction is slower (entries 2 and 3). A change in the configuration at C-4 and C-5 of the 1,3-dioxolane substituent with the use of **65** leads to the onset of the isomerization of the primary product (up to 10%, entry 4); significant deterioration of the enantioselectivity (71% ee) is also observed. Structurally analogous ligands **66** and **67** with a 1,3-dioxane side chain behave in a similar fashion. In these cases, as expected, the (*R,R*)-phospholane/(*S,S*)-dioxane combination **67** gives the best results (entry 6). An examination of the results from Table 5 shows that the stereoselectivity of the reaction is dictated by the chirality of the phospholane ring, with the (*R,R*)-phospholane favoring (*S*)-3-arylbut-1-ene formation, in accordance with the proposed model (Figure 8).

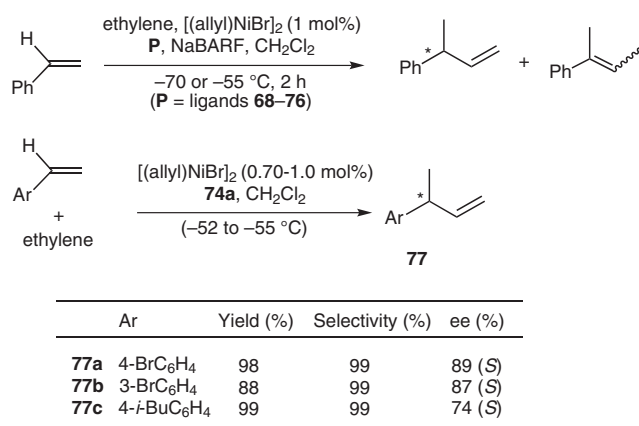
Use of ligand **64a** in the hydrovinylation of other vinylarenes gave the corresponding products with the following ee values under the typical reaction conditions (0.70 mol% Ni,  $-55\text{ }^{\circ}\text{C}$ , >99.5% yield unless specified otherwise): styrene (88% ee), 4-methylstyrene (86% ee), 4-bromostyrene (71% ee), 4-methoxystyrene (73% ee), MVN (86% ee, 73% yield). With the exception of the ee for the product from 4-bromostyrene, at the time of writing this account, these values were among the highest enantioselectivities reported for the asymmetric hydrovinylation of these substrates.

Finally, the efficiency of the catalyst for the reaction was examined using ligand **64a**. In a reaction carried out with a 4-isobutylstyrene/[Ni(II)/**64a**] ratio of 1428 (0.07 mol% catalyst), a yield of 86% (with the rest being starting material) was realized (Scheme 26).

#### 4.8 Diarylphosphinite Ligands

Even though the initial studies with the MOP (Scheme 21) and 2,5-dialkyl-1-arylphospholane ligands (Scheme 26) provided a number of useful parameters, such as the effect of hemilabile coordination and counterions, 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 screened a large number of ligands and found that readily accessible diarylphosphinites serve as excellent ligands for this exacting reac-

tion.<sup>41,28b</sup> Sugar phosphinites are a class of easily synthesized ligands that we had used before with remarkable success in other asymmetric reactions, such as hydrocyanation,<sup>38c,f,g</sup> hydrogenation,<sup>38d,h,i</sup> and allylation reactions.<sup>38j</sup> They are readily amenable to steric and electronic tuning, a highly desirable attribute for ligands for asymmetric catalysis. The results of the hydrovinylation of styrene using these ligands (Scheme 27) are shown in Table 6.



**Scheme 27**

Principally, bis(3,5-dimethylphenyl)- and bis[3,5-bis(trifluoromethyl)phenyl]phosphinites were chosen for this study. In general, outstanding selectivity for the formation of the 3-phenylbut-1-ene product is observed with a variety of phosphinites. Whether a 3,5-dimethylphenyl or a 3,5-bis(trifluoromethyl)phenyl substituent on phosphorus is better depends on the configuration at the carbon to which the diarylphosphinite moiety is attached. In the *gluco*-series (Table 6, entries 7 and 8), the trifluoromethyl-containing aromatic substituent is better, whereas in the *allo*-series (entries 9 and 10) the methyl-substituted derivative is better. The *allo*-configuration for the ligand (entries 9 and 10) is clearly superior compared with the *gluco*-derivative (entries 7 and 8) with respect to higher enantioselectivity. Finally, altering the acyl group on the nitrogen in the ligand showed a pronounced effect on the selectivity of the reaction. Whereas the acetyl substituent on nitrogen gives consistently high selectivity (most of the time >99%) for the desired product, *N*-alkyl groups inhibit the reaction (entry 6). The *N*-trifluoroacetyl and *N*-benzoyl derivatives promote concomitant isomerization of the initially formed 3-phenylbut-1-ene to give a mixture of 2-phenylbut-2-enes under the reaction conditions, reducing the selectivity for the former to 40 and 23%, respectively (entries 11 and 12). Remarkably, the highest ee resulting from the hydrovinylation of styrene in this series is observed using the *N*-trifluoroacetyl derivative (87% ee, entry 11).

Based on overall yield and selectivity, diarylphosphinite **74a** is one of the best ligands for the nickel-catalyzed asymmetric hydrovinylation of styrene (Table 6, entry 9). Most gratifyingly, ligand **74a** is also one of the best

ligands for the hydrovinylation of other derivatives, such as 4-bromostyrene, 3-bromostyrene, and 4-isobutylstyrene (Scheme 27). In the case of 4-bromostyrene, the corresponding hydrovinylation product is obtained in up to 98% isolated yield (>99% selectivity for the desired product) with 89% ee. Selectivities for **74a** and other related ligands in the hydrovinylation of 4-bromostyrene are shown in Table 7.

A study of the effect of the counterion on this reaction shows that hexafluoroantimonate (SbF<sub>6</sub><sup>-</sup>) is marginally better than BARF<sup>-</sup> (Table 7, entries 1 and 2, respectively), whereas BF<sub>4</sub><sup>-</sup> and OTf<sup>-</sup> appear to be inferior (entries 3 and 4, respectively).

The best results gave 3-(4-bromophenyl)but-1-ene (**77a**) in 89% ee; 2-arylpropionic acids could be prepared from this product using cross-coupling chemistry. For example, the Kumada coupling of **77a** and isobutylmagnesium bromide in the presence of 1 mol% of [(dppe)NiCl<sub>2</sub>] gave **77c**. Subsequent ozonolysis and oxidation of the resulting aldehyde gave ibuprofen, whose configuration and ee were established through its conversion into the known (-)-menthyl esters. Gas chromatographic analysis of these esters using a 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 (i.e., *S*) of the hydrovinylation of 4-bromostyrene.

The hydrovinylation of 3-bromostyrene using **74a** as a ligand gives the corresponding 3-arylbut-1-ene in 88% yield and 87% ee (Scheme 27).

Finally, studies with 4-isobutylstyrene (Scheme 27) serve as a reminder that a single ligand is unlikely to have broad applicability, and further fine-tuning may be needed before practical levels of asymmetric induction can be achieved for individual substrates.

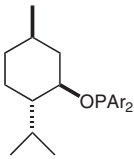
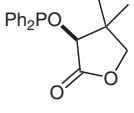
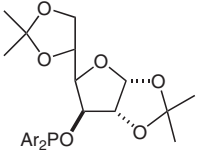
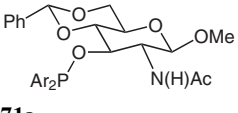

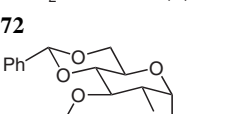
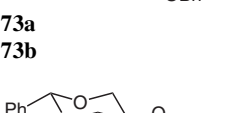
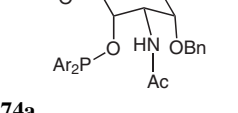
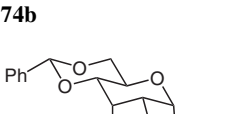
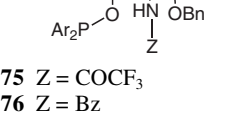
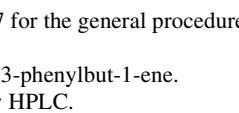

## 4.9 Phosphite Ligands

Binaphthol-derived phosphites prepared from carbohydrate diols are also competent ligands<sup>28b,41,42</sup> for the hydrovinylation of styrene under the conditions described in the bottom reaction of Scheme 27, using BARF<sup>-</sup> as a counterion. The yield and enantioselectivity for the styrene hydrovinylation are modest and appear to be dictated by the configuration of the BINAP unit rather than that of the carbohydrate backbone.

## 4.10 Phosphoramidite Ligands

Phosphoramidites, originally introduced by Feringa and co-workers<sup>43,44</sup> for the asymmetric copper-catalyzed conjugate addition of dialkylzinc reagents to enones, are among the most versatile and tunable ligands for carbon-carbon and carbon-hydrogen bond-forming reactions.<sup>45</sup> Phosphoramidites were introduced for the hydrovinylation of vinylarenes by Leitner and co-workers<sup>46</sup> and, later, for norbornene by our group<sup>28</sup> under the conditions we

**Table 6** Hydrovinylation of Styrene Using Diarylphosphinite Ligands<sup>a</sup>

Entry	Ligand	Ar	Conversion (%) / yield (%) <sup>b</sup>	Selectivity (%) <sup>c</sup>	ee (%) <sup>d</sup>
1		3,5-(F <sub>3</sub> C) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	99/86	86	>5
2		–	–/87	99	6
3		3,5-(F <sub>3</sub> C) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	68/68	99	29 ( <i>R</i> )
4		3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	62/62	99	32 ( <i>S</i> )
5		3,5-(F <sub>3</sub> C) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	35/35	99	28 ( <i>S</i> )
6		3,5-(F <sub>3</sub> C) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	0/0	–	–
7		3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	97/93	96	9 ( <i>S</i> )
8		3,5-(F <sub>3</sub> C) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	93/93	99	45 ( <i>S</i> )
9		3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	99/89	89 (–70 °C)	81 ( <i>S</i> )
10		3,5-(F <sub>3</sub> C) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	42/42	99	62 ( <i>S</i> )
11		3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	99/40	40 <sup>e</sup>	87 ( <i>S</i> )
12		3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	99/23	23 <sup>e</sup>	82 ( <i>S</i> )
	<b>75</b> Z = COCF <sub>3</sub>				
	<b>76</b> Z = Bz				

<sup>a</sup> See Scheme 27 for the general procedure.<sup>b</sup> Isolated yield.<sup>c</sup> Selectivity for 3-phenylbut-1-ene.<sup>d</sup> Determined by HPLC.<sup>e</sup> Conversion >99%.

**Table 7** Asymmetric Hydrovinylation of 4-Bromostyrene Using Phosphinite Ligands<sup>a</sup>

Entry	Ligand (counterion X)	Yield (%)	Selectivity (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>74a</b> (SbF <sub>6</sub> )	98	>99	89 (S)
2	<b>74a</b> (BARF)	94	94	89 (S)
3	<b>74a</b> (BF <sub>4</sub> )	24	>99	86 (S)
4	<b>74a</b> (OTf)	70	>99	74 (S)
5	<b>74b</b> (BARF)	19	>99	43 (S)
6	<b>70</b> , Ar = 3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> (BARF)	88	>99	13 (S)
7	<b>70</b> , Ar = 3,5-(F <sub>3</sub> C) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> (BARF)	41	>99	47 (S)

<sup>a</sup> Reaction conditions: ethylene (1 atm), 1 mol% [(allyl)NiP]<sup>+</sup> X<sup>-</sup>, CH<sub>2</sub>Cl<sub>2</sub>, -55 °C, 2 h.

<sup>b</sup> Selectivity for 3-arylbut-1-ene; >99% means no other hydrocarbon products were observed.

<sup>c</sup> Determined by HPLC.

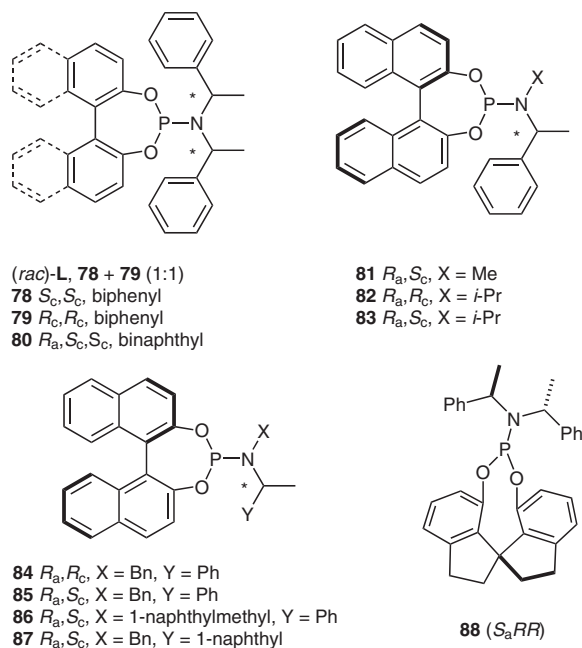
originally prescribed for these reactions.<sup>22</sup> For the reactions of several vinylarenes, including 4-bromostyrene,<sup>46</sup> and norbornene,<sup>28</sup> the highest efficiencies and selectivities were recorded. However, the hydrovinylation of 4-isobutylstyrene (a precursor of ibuprofen) gave only 28% conversion and 68% ee. To expand the scope of the reaction, we undertook a systematic study of ligand tuning using phosphoramidites derived from 1,1'-bi(2-naphthol), 2,2'-biphenol, and a variety of  $\alpha$ -methyl-substituted arylmethanamines. These studies resulted in the highest enantioselectivities reported to date for the hydrovinylation of a broad spectrum of vinylarenes.<sup>47</sup> A selection of the ligands examined in this study are shown in Figure 9.<sup>47b</sup>

The feasibility of ligand control in hydrovinylation was initially investigated using the reaction of 4-methoxystyrene, an electron-rich model substrate that consistently

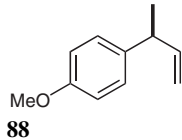
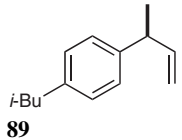
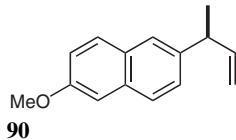
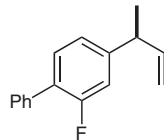
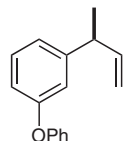
had given some of the poorest results among the vinylarenes tested previously. We started these investigations using a modified protocol that had originally been developed for MOP and phospholane ligands (see the bottom reaction in Scheme 24).

Among the ligands examined,<sup>47</sup> in addition to the original Feringa ligand **80** (Table 8, entry 2), two stand out: Ligand **78** (or its enantiomer **79**), which has only a lowly biphenyl backbone instead of a chiral binaphthyl unit and is significantly cheaper, still yields similar selectivities and conversions (entry 1). Ligand **87**, in which the (*S*)-*N*- $\alpha$ -methylbenzyl groups are replaced with an achiral benzyl and a chiral (*S*)- $\alpha$ -methyl-1-naphthyl group, is by far the best ligand for this exacting reaction<sup>48</sup> resulting in high enantioselectivity and also nearly quantitative conversion and selectivity (entry 3). Surprisingly, ligands prepared from achiral dibenzylamine and enantiopure 1,1'-bi(2-naphthol) (not shown) gave no conversion.

Once the best ligands were identified, the studies were extended to several vinylarenes and the results are tabulated in Table 8. The enantioselectivities observed for the 3-arylbut-1-enes **89–92**, which are precursors for the arylpropionic acids ibuprofen, naproxen, flurbiprofen, and fenoprofen (entries 4–15), represent the highest overall selectivities reported to date for any viable intermediates for these important compounds.<sup>49</sup> In one case, Craig Smith, who has been involved with the development of the phosphoramidite ligands, has shown that the hydrovinylation of 4-isobutylstyrene can be accomplished with 0.00014 equivalents of catalyst [(substrate/catalyst) ratio of 7142] in 4.67 hours at 0 °C. For the biphenyl-derived ligands **78** and **79**, the configuration of the amine determines the sense of asymmetric induction; with the *S*-chiral moiety in the amine portion of ligand **78**, the product configuration in all cases is also *S*. As seen in Table 8, the lack of axial chirality in the ligand leads to little erosion of the ee, suggesting that for simple substrates, a more-elaborate (and expensive) binaphthol-based phosphoramidite is not necessary to achieve high stereoselectivity. In all the cases examined, **87** yielded the best results in terms of overall

**Figure 9** Selected phosphoramidite ligands used for hydrovinylation

**Table 8** Asymmetric Hydrovinylation of Vinylarenes Using Finely Tuned Phosphoramidites<sup>a</sup>

Entry	Ligand	Product	Conversion (%) / yield (%)	Selectivity (%)	ee (%) <sup>b</sup>
1	<b>78</b>		>99/82	>99	95 (S)
2	<b>80</b>		>99/79	>99	95 (S)
3	<b>87</b>		>99/77	>99	97 (S)
4	<b>78</b>		>99/97	98	90 (S)
5	<b>80</b>		>99/98	99	90 (S)
6	<b>87</b>		97/97	>99	96 (S)
7	<b>78</b>		>99/93	>99	90 (S)
8	<b>80</b>		>99/94	>99	95 (S)
9	<b>87</b>		>99/89	>99	99 (S)
10	<b>78</b>		>99/90	>99	80 (S)
11	<b>80</b>		>99/93	>99	86 (S)
12	<b>87</b>		>99/92	>99	97 (S)
13	<b>78</b>		>99/91	>99	95 (S)
14	<b>80</b>		>99/96	>99	97 (S)
15	<b>87</b>		>99/92	>99	97 (S)

<sup>a</sup> See ref. 47 for details and a complete set of ligands.

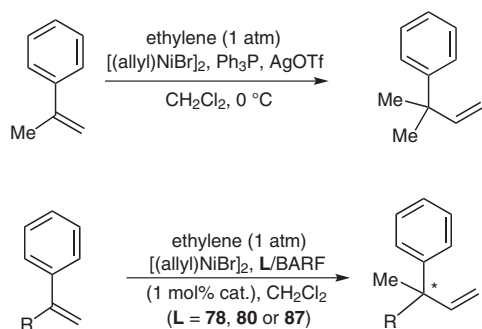
<sup>b</sup> Determined by GC except for **90**, which was determined by HPLC.

yield and selectivity. To the best of our knowledge, this is a novel ligand.

## 5 Generation of All-Carbon Quaternary Centers

The search for new methods for the stereoselective generation of all-carbon quaternary centers is a subject of considerable topical interest.<sup>50</sup> Several important pharmaceutically relevant compounds, among them anal-

gesic (–)-eptazocine,<sup>51</sup> protein kinase C activator lyngbyatoxin,<sup>52</sup> cognitive enhancing agent (–)-phenserine,<sup>53</sup> and serotonin antagonist LY426965,<sup>54</sup> contain all-carbon quaternary centers at the benzylic position. The hydrovinylation of 2-arylalk-1-enes<sup>17b</sup> generates a quaternary center at the benzylic position and introduces a highly versatile latent functionality in the form of a vinyl group (Scheme 28). The resulting substances could be quite valuable for further synthetic elaboration. An asymmetric variant of this reaction is also shown (Scheme 28).<sup>55</sup>



Scheme 28

In scouting studies using 2-phenylbut-1-ene (**93**) (see Table 9) as the substrate, catalysts derived from MOP ligand **28** (Figure 4) showed no reactivity, while those derived from phospholane ligand **56** (Figure 7), which gave high ee values and turnover numbers in the hydrovinylation of a number of styrene derivatives<sup>40</sup> and 1,3-dienes (*vide infra*),<sup>56</sup> showed only moderate reactivity under similar conditions.<sup>55</sup> Among the chiral ligands examined, phosphoramidites **78**,<sup>47</sup> **80**,<sup>55a,57</sup> **87**,<sup>47</sup> and **88**<sup>55b</sup> were found to provide the best results. These ligands, when treated with [(allyl)NiBr]<sub>2</sub> followed by NaBARF, gave a very active precatalyst that effects the hydrovinylation at low temperature with as little as 1 mol% of catalyst to give a nearly quantitative reaction.<sup>57</sup> Under these conditions, no oligomerization product is detected, as judged by careful GC analysis and <sup>1</sup>H NMR spectroscopy. The yields and selectivities are highly reproducible and, as expected, the best selectivity is observed at low temperatures. These results are independent of the catalyst loading or extent of the reaction, clearly indicating the total absence of nonselective reactions.

The results of the asymmetric hydrovinylation of several 2-arylalk-1-enes under the optimal conditions are given in Table 9. While substrates **93** and **94** gave excellent selectivity for the formation of the expected product (entries 1 and 2, respectively), 4-chloro derivative **95** gave up to 5% isomerization of the starting olefin (entry 3). A similar minor side reaction was also observed for substrates **97** and **99** (entries 5 and 7, respectively). An isopropyl group at the benzylic position of styrene, as in **96**, retards the reaction (entry 4), and it is best accomplished at 24 °C with 10 mol% of catalyst. Even though the yield of the reaction is only moderate, very high ee (>95%) was observed for the isolated product. 2-Naphthyl derivative **98** gave the expected product in excellent yield (>98%) and selectivity (>99%) (entry 6). Tetralin derivative **99** represents a different class of substrates and underwent the hydrovinylation reaction giving the product in >95% ee (entry 7); significant isomerization (~30%) of the starting material to give an endocyclic olefin is a major detraction of this otherwise useful reaction.

Compounds structurally related to hydrovinylation product **100a** from the reaction of **99**, e.g. **100b** (Figure 10), have been synthesized previously via intramolecular

asymmetric Heck reactions (~93% ee),<sup>51</sup> stoichiometric oxazoline-directed alkylation (~99% ee),<sup>58a</sup> and enzyme-catalyzed desymmetrization of a chiral malonate (97% ee).<sup>58b</sup> By comparison, the asymmetric hydrovinylation route is significantly shorter and operationally simpler.

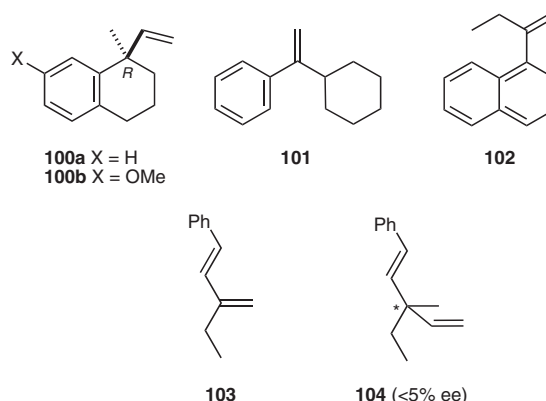


Figure 10

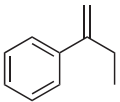
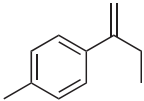
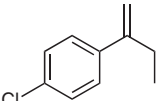
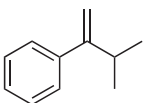
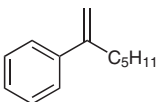
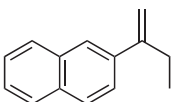
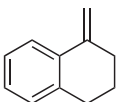
Among olefins **101**–**103**, only acyclic diene **103** undergoes hydrovinylation, and the corresponding product **104** is formed in nearly racemic form (Figure 10), contaminated with a product of ethylene addition at the benzylic position.

## 6 Asymmetric Hydrovinylation of 1,3-Dienes

Although the asymmetric hydrovinylation of cycloocta-1,3-diene (Scheme 15) is one of the earliest reported metal-catalyzed asymmetric carbon–carbon bond-forming reactions,<sup>11a,59</sup> no satisfactory solution to the problem of the hydrovinylation of 1,3-dienes emerged until 2006.<sup>1</sup> Both the Wilke conditions,<sup>19</sup> using azaphospholene ligand (*R,R*)-**7** (Figure 2 and Scheme 7), and the use of a catalyst derived from an AMPP ligand (with [Ni(cod)<sub>2</sub>] and Et<sub>2</sub>AlCl),<sup>29</sup> reported for cyclohexa-1,3-diene (Scheme 16), are limited either by the esoteric nature of the azaphospholene ligand, which permits no structural simplifications,<sup>21</sup> and/or by the constraints imposed by the need for a strong Lewis acid. The isomerization of the 1,4-diene product at higher conversion could be one of the limitations of a more-recently reported non-asymmetric ruthenium-catalyzed reaction (Scheme 29).<sup>60,61</sup> An asymmetric version of this reaction remained largely unexplored until our work.

We wondered whether the beneficial synergistic effects between ligands and counterions could be applied to develop a viable nickel-catalyzed hydrovinylation reaction of 1,3-dienes. An asymmetric version of this reaction would be especially attractive for 1-vinylcycloalkenes, since the 1,4-diene products would allow the control of the absolute and relative configurations of the side chains and of other stereogenic centers on the ring, a common feature in many important natural products, including ste-

**Table 9** Asymmetric Hydrovinylation of 2-Arylalk-1-enes: Generation of All-Carbon Quaternary Centers<sup>a</sup>

Entry	Vinylarene	Temp (°C)/time (h)	Conversion (%) / yield (%)	Selectivity (%)	ee (%)
1		-70/4	>99/>95	>99	>95
	<b>93</b>				
2		-69/12	>99/>90	>99	90
	<b>94</b>				
3		-70/11	>94/>90	>95	90
	<b>95</b>				
4		24/20	61/60	>97	>95
	<b>96</b>				
5		-70/8	>98/>93	>96	>50
	<b>97</b>				
6		-70/14	>99/>98	>99	93
	<b>98</b>				
7		-70/4	>98/>70	71	>95
	<b>99</b>				

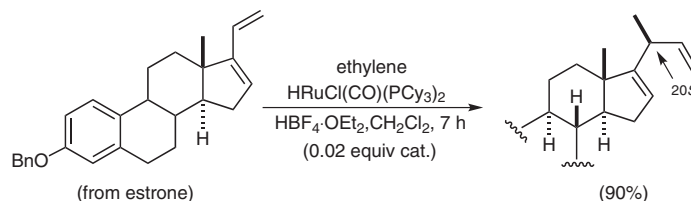
<sup>a</sup> Using ligand **80**; see refs. 55 and 57 for details.

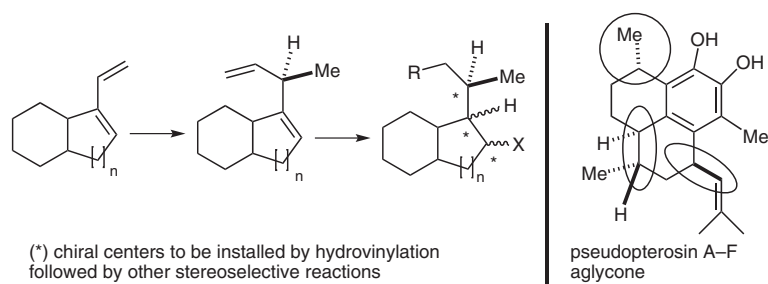
roid D-rings, serrulatanes, and pseudopterosins (Scheme 30).<sup>56</sup>

Our studies<sup>56</sup> started with an examination of the hydrovinylation of cyclohexa-1,3-diene (**106**) and 4-*tert*-butyl-1-vinylcyclohexene (**107**) (see Table 10) using the procedure we successfully employed for the hydrovinylation of vinylarenes {ethylene (1 atm), Ph<sub>3</sub>P, [(allyl)NiBr]<sub>2</sub>, AgOTf (0.07 equiv Ni), low temp, CH<sub>2</sub>Cl<sub>2</sub>; Scheme 9}. It soon became apparent that under these conditions, 1,3-dienes were much less reactive compared with vinylar-

enes, and higher temperatures (~25 °C) were needed for the reaction.

We decided to explore new protocols for this potentially useful reaction by systematically examining the use of hemilabile ligand effects<sup>30</sup> using 1,3-diene **107** as a substrate and ligands **105a–c** (Scheme 31). These studies revealed that the best ligand for this reaction was [2-(benzyloxy)phenyl]diphenylphosphine (**105a**). Thus, 0.14 mol% of a catalyst generated from **105a**, [(allyl)NiBr]<sub>2</sub>, and NaBARF effects the reaction of **107** with ethylene (1 atm) to give near quantitative yield of product **116**, as a mixture

**Scheme 29**



**Scheme 30** Hydrovinylation of 1,3-dienes and control of the exocyclic stereochemistry

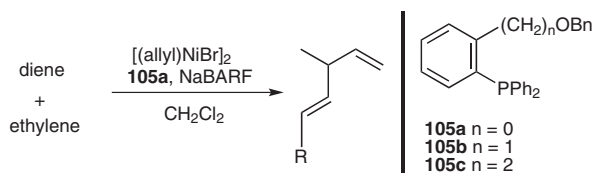
**Table 10** Hydrovinylation of 1,3-Dienes<sup>a</sup>

Entry	Diene	Product(s)	Conversion (%)	Regioselectivity (%)
1			94	>99
2			>99	98
3			>99	68
4			>99	72
5			>99	>99
6			>99	98
7			~97	>99
8			>99	95
9			99	98

<sup>a</sup> See ref. 56 for details.

<sup>b</sup> Mixture of two diastereomers (~2:1).

of two diastereomers (Scheme 31 and Table 10, entry 2). This product is formed with exquisite regioselectivity (1,2-addition at the less-hindered olefin). The racemic, axially chiral olefin **107** gave a nearly ~2:1 mixture of diastereomers. The results of the hydrovinylation of other typical dienes are shown in Table 10. In general, excellent yields (>97%) and selectivities (>95%) are observed for the hydrovinylation of both cyclic and acyclic dienes (entries 1, 2, and 5–9) under 1 atmosphere of ethylene. Lack of selectivity is seen only in the reactions of 1-vinylcyclohexene (**108**) (entry 3) and 1-vinylcyclopentene **109** (entry 4), which gave a mixture of 1,2- and 1,4-addition products.



Scheme 31

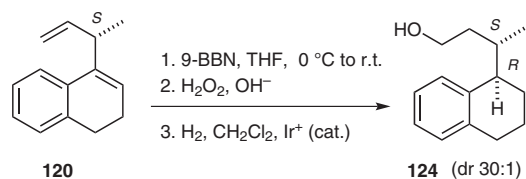
Table 11 shows the results of the asymmetric hydrovinylation of 1,3-dienes. Thus, the hydrovinylation of cyclic 1,3-dienes **110**, **111**, and **112** under our standard conditions (Scheme 31) using phospholane **64a**<sup>40</sup> or phosphoramidite ligand **80** generally gave exceptionally high yields and regio- and enantioselectivities (Table 11, entries 1–3, respectively). Acyclic diene **113** under these conditions gave low selectivity, even with phosphoramidite **80** (entry 4). However, the structurally related ligand **78** (Figure 9), derived from biphenol, gave the product in up to 84% ee.<sup>47</sup> The high selectivity achieved for the reaction of this acyclic diene is noteworthy since this is a challenging class of substrates for asymmetric transformations.<sup>61,62</sup>

A number of different strategies can be envisaged for controlling the configuration at the ring carbon to which the side chain is attached.<sup>63</sup> One example is shown in

Table 11 Asymmetric Hydrovinylation of 1,3-Dienes

Entry	Diene	Ligand	Conversion (%) [selectivity (%)] ee (%)	Conversion (%) [selectivity (%)] ee (%)
1	<b>110</b>		>99 (>99) 85 ( <i>R</i> )	>99 (>99) 96 ( <i>S</i> )
2	<b>111</b>		>99 (97) 93 ( <i>R</i> )	>99 (>99) >99 ( <i>S</i> )
3	<b>112</b>		>99 (99) 38 ( <i>R</i> )	>99 (>99) 95 ( <i>S</i> )
4	<b>113</b>		88 (>99) <5%	>99 (~96) 77

Scheme 32. The hydroboration (9-BBN, H<sub>2</sub>O<sub>2</sub>) of (*S*)-**120** followed by directed hydrogenation using Crabtree's catalyst {[(cod)Ir(PCy<sub>3</sub>)(py)]<sup>+</sup>PF<sub>6</sub><sup>-</sup>} gives the reduced product **124** (dr 30:1) with very high stereoselectivity.

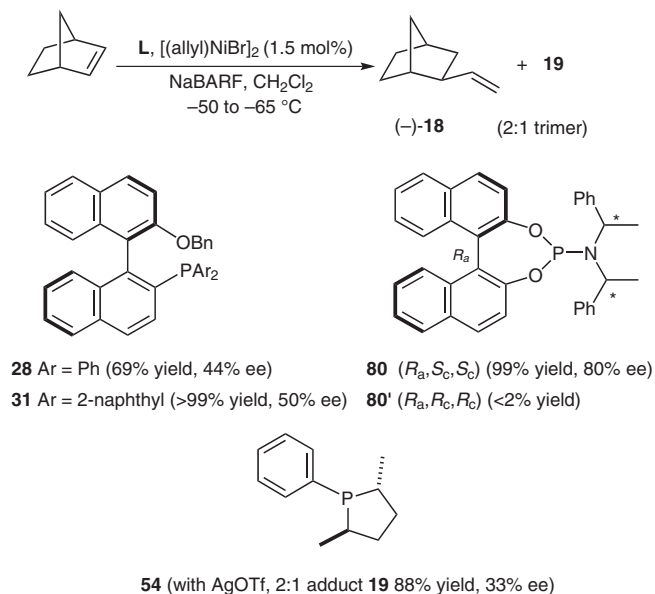


Scheme 32

## 7 Asymmetric Hydrovinylation of Norbornene

We have already alluded to the initial results on the hydrovinylation of norbornene as one of the first metal-catalyzed asymmetric carbon–carbon bond-forming reactions (Scheme 15) and the remarkable dependence of the reaction on the cone angle of the phosphine employed (Scheme 13).<sup>11b,19</sup> The results of this reaction obtained using the new ligands are shown in Scheme 33 and Table 12.<sup>28</sup>

Ozonolysis of **18** followed by oxidation of the resulting aldehyde gave norbornane-2-carboxylic acid, the enantiomers of which were converted into esters of (*S*)-methyl mandelate by the standard procedure using *N,N'*-dicyclohexylcarbodiimide. The absolute configuration of these diastereomers has been fully established before.<sup>64</sup> As expected for the hydrovinylation, phosphines with large cone angles (e.g., **28**, **31**, and **80**) give exclusively the 1:1 adduct **18**, generally in nearly quantitative yield and with modest enantioselectivity (Table 12, entries 1–5). Note the use of highly dissociated counterions in these reactions. No trace of the 2:1 adduct **19** is observed under these conditions. The selectivity with the phosphoramidite ligands (entries 5–8) depends on both the counterion and the nature of the amine appendage. Whereas *R<sub>a</sub>*,*S<sub>c</sub>*,*S<sub>c</sub>*-



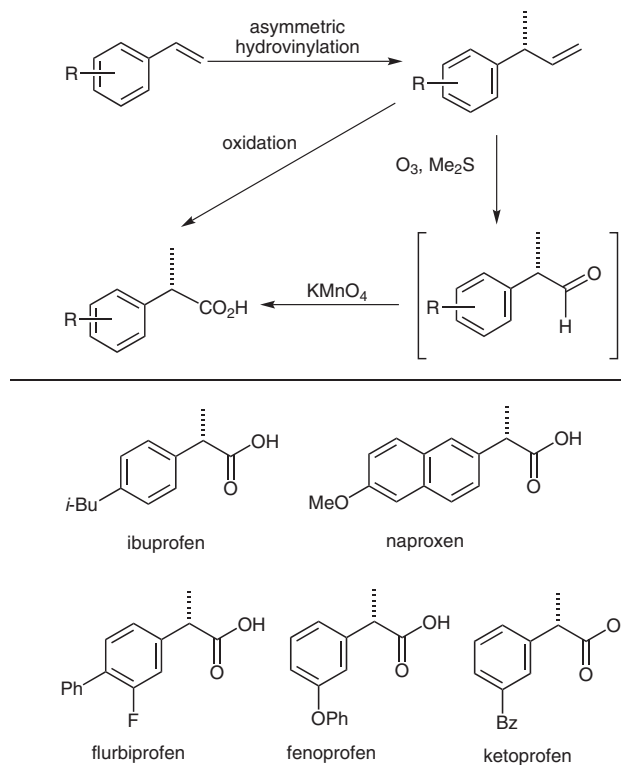
Scheme 33

Table 12 Asymmetric Hydrovinylation of Norbornene<sup>a</sup>

Entry	Ligand	Additive	Yield (%)		ee (%)
			<b>18</b>	<b>19</b>	
1	<b>28</b>	NaBARF	69	0	44
2	<b>28</b>	AgSbF <sub>6</sub>	>99	0	50
3	<b>28</b>	AgNTf <sub>2</sub>	>99	0	50
4	<b>31</b>	AgSbF <sub>6</sub>	>99	0	44
5	<b>80</b> ( $R_a, S_c, S_c$ )	NaBARF	>99	0	80
6	<b>80</b> ( $R_a, S_c, S_c$ )	AgOTf	20	0	–
7	<b>80</b> ( $R_a, S_c, S_c$ )	AgSbF <sub>6</sub>	0	99	34 ( <b>19</b> )
8	<b>80'</b> ( $R_a, R_c, R_c$ )	NaBARF	<2	0	–
9	<b>54</b>	AgOTf	11	88	33 ( <b>19</b> )

<sup>a</sup> See Scheme 33 for the general procedure and ref. 28 for details.

isomer **80** is a good ligand (entry 5), the corresponding  $R_a, R_c, R_c$ -diastereomer **80'** gives less than 2% yield of the product (entry 8). Surprisingly, for ligand **80**, the counterion determines whether the 1:1 or 1:2 adduct is produced: with NaBARF, only 1:1 adduct **18** is produced (entry 5), whereas AgSbF<sub>6</sub> (which we successfully used in place of NaBARF in some early hydrovinylation experiments<sup>41</sup>) now gives exclusively 2:1 adduct **19** in *nearly quantitative* yield (entry 7)! Phospholane **54** gives mostly the 2:1 adduct (entry 9). A modest enantioselectivity of 33% ee has been observed for this product as determined by the Mosher ester method.<sup>28</sup> As we have documented before, the use of silver(I) triflate as an additive is important for ligands like **54** with no hemilabile side chain. Chelating ligands inhibit the reaction under the typical conditions reported here.



Scheme 34 General synthesis of 2-arylpropionic acids

## 8 Applications of Asymmetric Hydrovinylation Reactions

### 8.1 (*S*)- or (*R*)-2-Arylpropionic Acids

2-Arylpropionic acids are the most widely used nonsteroidal anti-inflammatory agents (NSAID).<sup>65</sup> Naproxen, 2-(6-methoxy-2-naphthyl)propionic acid, is the only NSAID currently sold in enantiomerically pure form (i.e., as the *S*-isomer) and is resolved by a classical resolution.<sup>66</sup> Most members of this important class of compounds can, in principle, be synthesized by oxidative cleavage of the double bond of the hydrovinylation products of vinylarenes (Scheme 34). With our recent syntheses of various 3-arylbut-1-enes of very high enantiomeric purity (>96% ee),<sup>47</sup> this becomes a viable route. Table 8 shows the highly enantioselective syntheses of compounds **89–92**, precursors of ibuprofen, naproxen, flurbiprofen, and fenoprofen, respectively, via the hydrovinylation of the appropriate vinylarenes using ligand **87**.<sup>66</sup> We have since carried out the hydrovinylation of 3-bromostyrene in very high ee, and the product from this reaction has been converted into ketoprofen via 2-arylpropionic acid **125** (see Table 13).<sup>67</sup>

Oxidative cleavage by ozone of the double bond in the hydrovinylation products, followed by further oxidation of the resulting aldehydes by potassium permanganate or sodium chlorite gave ibuprofen (from **89**) and flurbiprofen (from **91**) in acceptable yield *without any racemization* at

**Table 13** Synthesis of 2-Arylpropionic Acids via Oxidation<sup>a</sup>

Entry	Product	Oxidant	Yield (%)	ee (%)
1	ibuprofen	O <sub>3</sub>	98	98 (S)
2	naproxen	KMnO <sub>4</sub> , NaIO <sub>4</sub>	67	>97 (S)
3	flurbiprofen	O <sub>3</sub>	95	98 (S)
4	fenoprofen	RuCl <sub>3</sub> , NaIO <sub>4</sub>	91	>99 (S)
5		KMnO <sub>4</sub> , NaIO <sub>4</sub>	93	91 (S)

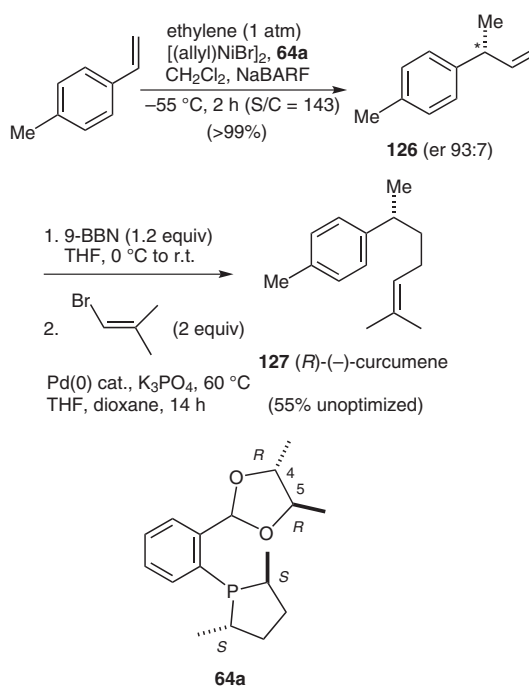
<sup>a</sup> Enantiomers of compounds **89–92** (Table 8) and 3-(3-bromophenyl)but-1-ene were used for the syntheses.

the intermediate aldehyde stage (Table 13, entries 1 and 3, respectively). The more-electron-rich substrate **90** for naproxen was best oxidized with potassium permanganate and sodium periodate (entry 2). These conditions also gave the best yields for the oxidation of the ketoprofen precursor 3-(3-bromophenyl)but-1-ene (entry 5). Likewise, fenoprofen was obtained from the corresponding 3-arylbut-1-ene using ruthenium(III) chloride and sodium periodate (entry 4). In each case, the ee of the final product was confirmed by chiral stationary phase gas chromatography of the L-menthyl esters.<sup>28b,41</sup>

## 8.2 (R)- $\alpha$ -Curcumene and (R)-*ar*-Turmerone

Several important classes of natural products, among them bisabolanes, heliannanes, serrulatanes, and pseudopterosins, are characterized by a benzylic chiral center, often carrying a methyl group at this position.<sup>68</sup> Diverse biological activities exhibited by these compounds include anti-inflammatory, antiviral, and antimycobacterial properties, and the substances have attracted considerable attention from synthetic chemists. No less than 12 nonracemic syntheses of the simplest member of this class of compounds, (R)-(-)- $\alpha$ -curcumene, are known. (R)-(-)- $\alpha$ -Curcumene and the related compound (R)-(-)-*ar*-turmerone are the constituents of a large number of essential oils, and it has been amply demonstrated that the intermediates for their synthesis could in principle be used for a number of other bisabolane and related terpenes.<sup>68a</sup>

In spite of their rather simple structures, the stereocenter at the benzylic position poses a significant challenge in their asymmetric synthesis, even for curcumene.<sup>69</sup> Arguably, the ‘shortest (incidentally, also the most recent) route’ starts with citronellal and involves six steps and multiple chromatographic separations to produce curcumene in 28% overall yield.<sup>70</sup> An exceptionally short synthesis based on the asymmetric hydrovinylation of 4-methylstyrene is shown in Scheme 35. This synthesis starts with the hydrovinylation of 4-methylstyrene. In the racemic series, the hydrovinylation of 4-methylstyrene

**Scheme 35** Synthesis of  $\alpha$ -curcumene from 4-methylstyrene

can be achieved in nearly quantitative yield and >99% selectivity for the desired 3-arylbut-1-ene using ethylene at 1 atmosphere and catalytic amounts of [(allyl)NiBr]<sub>2</sub>, triphenylphosphine, and silver(I) triflate (see Scheme 9). Chiral ligands, like MOP derivative **28**, sugar-derived diarylphosphinite **74a**, and binaphthol-derived phosphoramidite **80**, which gave high ee values for the hydrovinylation of other styrene derivatives, gave unacceptably low ee values in those reactions of 4-alkylstyrenes. However, the use of the nickel(II) complex from 1-aryl-2,5-dialkylphospholane ligand **64a** gave greater than >99% yield of 3-arylbut-1-ene **126** with a ratio (R/S) of 93:7 (Scheme 35).<sup>71</sup> Treatment of compound **126** with 9-borabicyclo[3.3.1]nonane in tetrahydrofuran, followed by the addition of 2 equivalents of 1-bromo-2-methylpropene [with Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%), K<sub>3</sub>PO<sub>4</sub> (1.5 equiv), and THF–dioxane] and stirring at 60 °C afforded (-)- $\alpha$ -curcumene (**127**) as a colorless oil in 55% overall yield in three steps from 4-methylstyrene (Scheme 35).

The synthesis of (R)-(-)-*ar*-turmerone is accomplished starting with 3-arylbut-1-ene **126**. Olefin **126** was subjected to hydroboration with disiamylborane in tetrahydrofuran, followed by oxidation with hydrogen peroxide to give alcohol **128** in 84% isolated yield in two steps (Scheme 36). The Swern oxidation of alcohol **128** gave aldehyde **129** in 90% yield. Then, treatment of aldehyde **129** with 2-methylprop-1-enylmagnesium bromide in tetrahydrofuran at -78 °C followed by warming to room temperature and workup gave a diastereomeric mixture (at C-8, 6:5) of alcohol(s) **130** in 78% isolated yield. Finally, the Swern oxidation of alcohol **130** gave (R)-(-)-*ar*-turmerone **131** in 44% yield.

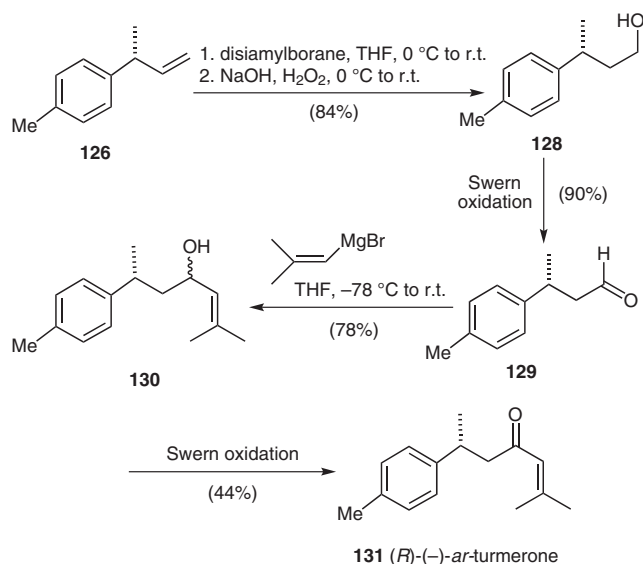
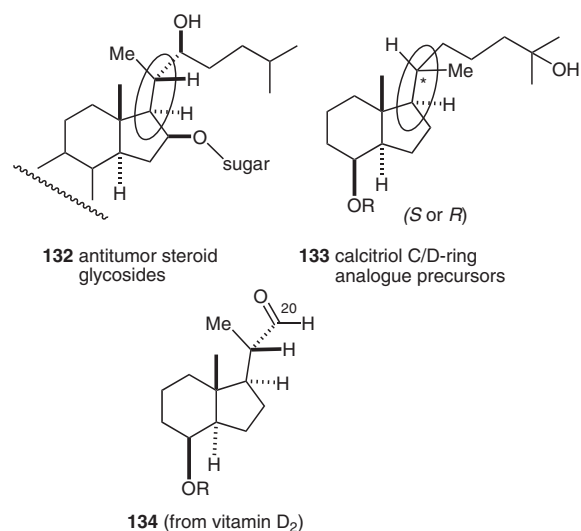
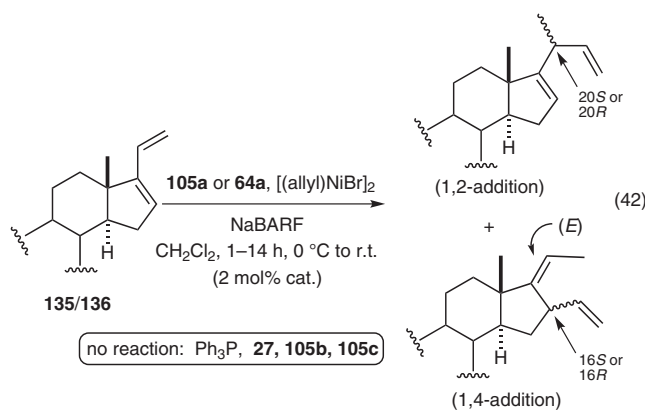
Scheme 36 Synthesis of (*R*)-(-)-*ar*-turmerone

Figure 11 Steroids with functionalized D-rings

### 8.3 Control of the Configuration of the Steroidal D-Ring Side Chain

Several creative solutions to the problem of the installation of stereogenic centers in the steroid D-ring and its side chains (e.g., as in **132–134**, Figure 11) have been developed over the years, even though no broadly applicable methods that use readily available precursors have emerged.<sup>72</sup> The problem is especially acute for the synthesis of the nonnatural 20*S*-epimers. For example, compound **133** is a precursor of calcitriol analogues with exocyclic 20*S*-configuration which have been shown to have significant biological activity.<sup>73</sup> These molecules are currently prepared by circuitous routes that involve the equilibration of aldehyde **134**, obtained from vitamin D<sub>2</sub>, and the subsequent reactions of the minor isomer isolated from the mixture.<sup>74</sup>



Scheme 38

The hydrovinylation of steroid-derived diene **135** (Figure 12) has already been performed in a ruthenium-catalyzed reaction to prepare 20*S*-compound **137** in a highly stereoselective fashion (Scheme 37).<sup>60</sup> We wondered whether *both* the 20*S*- and 20*R*-compounds could be prepared by overcoming the inherent selectivity of the steroid nucleus through the use of enantiomerically pure ligands in a nickel-catalyzed reaction.

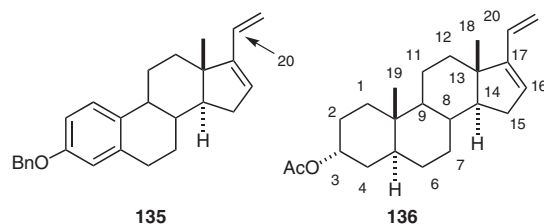
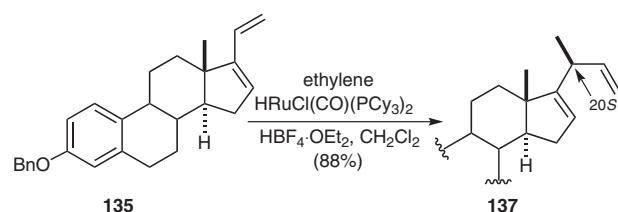


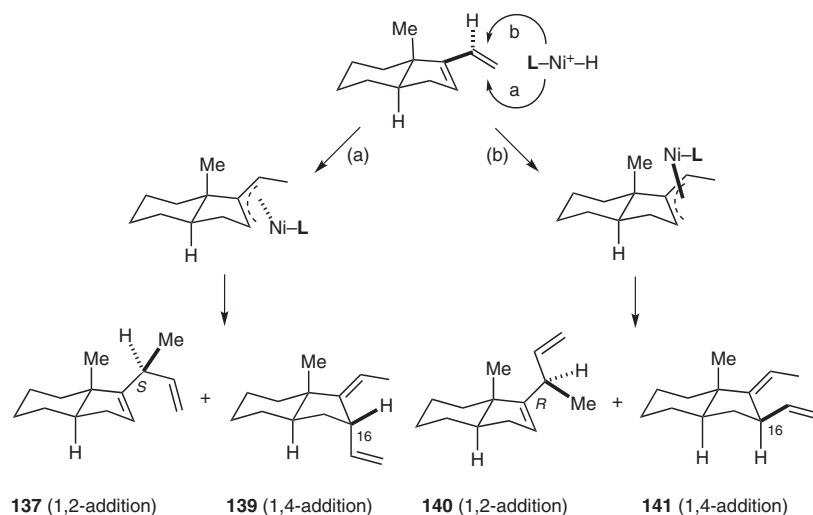
Figure 12 Prototypical steroidal dienes for hydrovinylation



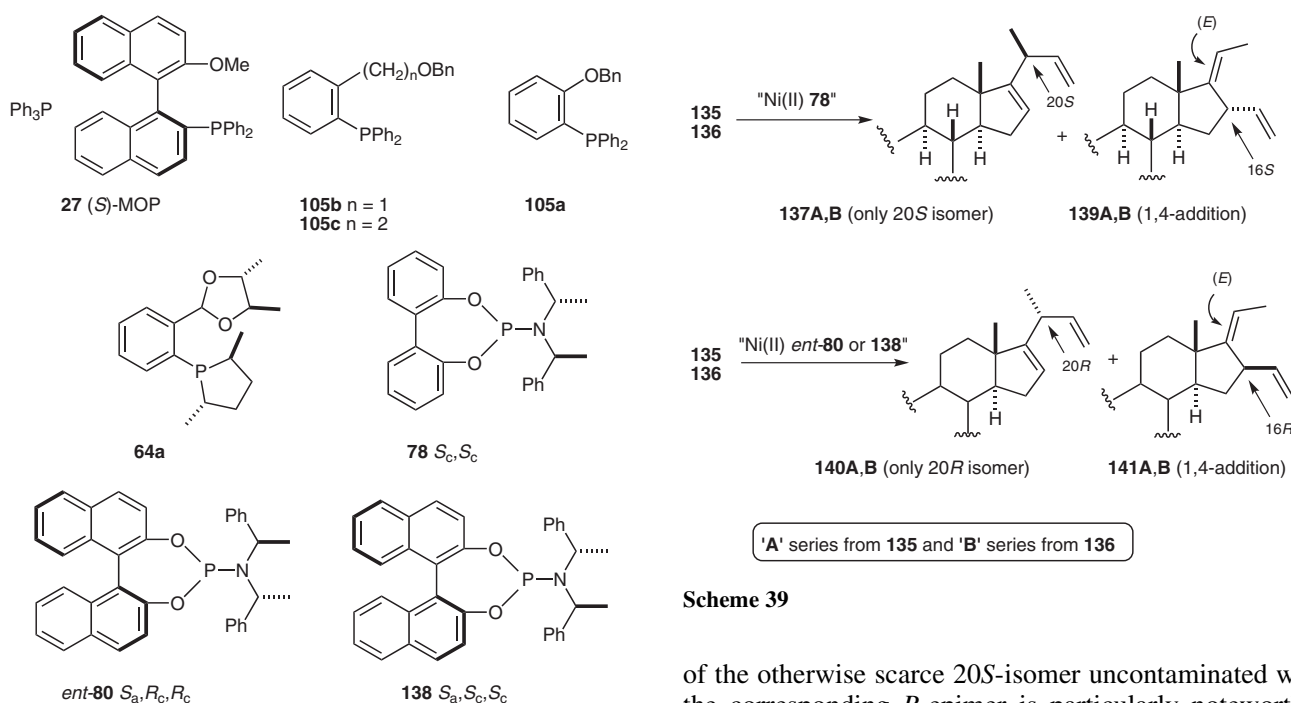
Scheme 37

We explored the nickel-catalyzed hydrovinylation of two prototypical steroidal dienes **135** and **136** (Figure 12) using the ligands shown in Figure 13. Several ligands that we had successfully employed for the hydrovinylation of vinylarenes and other dienes either did not react [i.e., Ph<sub>3</sub>P, MOP (**27**), **105b**, and **105c**] or gave mixtures (i.e., use of **105a** or **64a**) of stereo- and regioisomers (Scheme 38).

We anticipate this lack of selectivity to be a recurring problem in the context of this and other future synthetic objectives in which the hydrovinylation of key *chiral* intermediates will be involved. It is entirely conceivable that the inherent diastereoselectivity in such substrates



**Scheme 40** Origin of the 1,2- and 1,4-adducts in the hydrovinylation reactions of steroidal dienes



**Scheme 39**

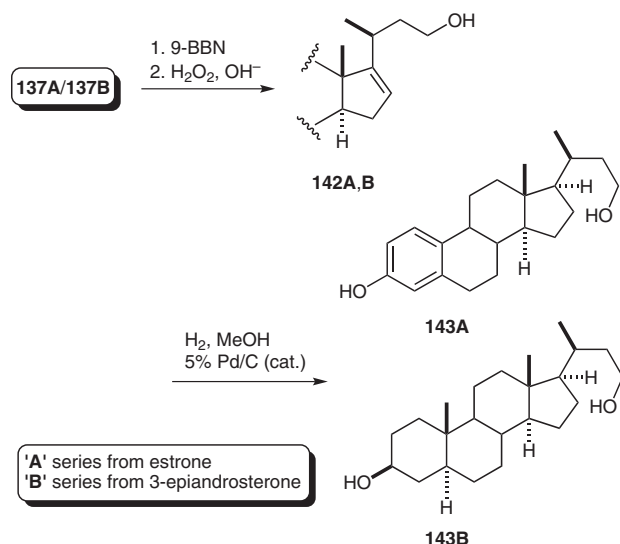
**Figure 13** Ligands for the hydrovinylation of steroidal dienes

could be low, or even opposite to what would be desired. Thus, from a synthetic perspective, either the enhancement of the inherent selectivity or overriding such an outcome with the use of a tunable asymmetric catalyst became a highly desirable goal. Looking for a general solution to this problem, we decided to examine the selectivity of the hydrovinylation reactions using fine-tuned phosphoramidites that served us well in other situations. The results are shown in Scheme 39.<sup>75</sup>

Preparatively, the most useful reactions involve the use of ligands **78** and *ent*-**80**, which give the 20*S*- or 20*R*-compound, respectively, along with minor amounts of a 1,4-adduct (Scheme 39). The highly stereoselective formation

of the otherwise scarce 20*S*-isomer uncontaminated with the corresponding *R*-epimer is particularly noteworthy. The stereochemistry of the  $\alpha$ -vinyl appendage at C-16 in the 1,4-adduct **139A** is deduced from the fact that this is *the only other product formed* concomitant with 20*S*-compound **137A**. It is reasonable to assume that these two products originate from the same allylnickel intermediate arising from the  $\alpha$ -face addition of [LNi-H]<sup>+</sup> to the starting diene (Scheme 40). The same arguments hold for the formation of **140A** and **141A**, except the reaction starts with the  $\beta$ -face addition of the metal hydride.

The steroid D-ring can be elaborated in a myriad of ways using the diene functionality in the adducts. For example, the selective hydroboration of the mono-substituted olefin in **137A**, derived from estrone, followed by oxidation gives alcohol **142A** (Scheme 41), which could serve as a precursor for more advanced intermediates. The catalytic hydrogenation of this alcohol gives a single product, com-

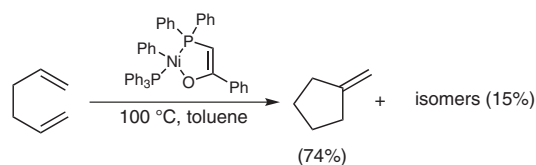


Scheme 41 Steroid D-ring functionalization

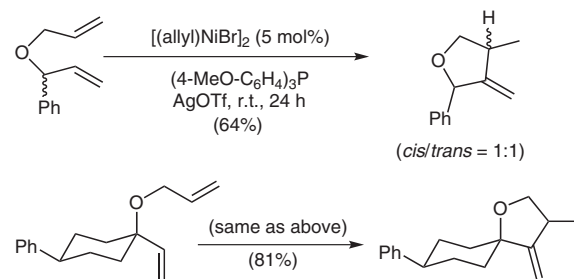
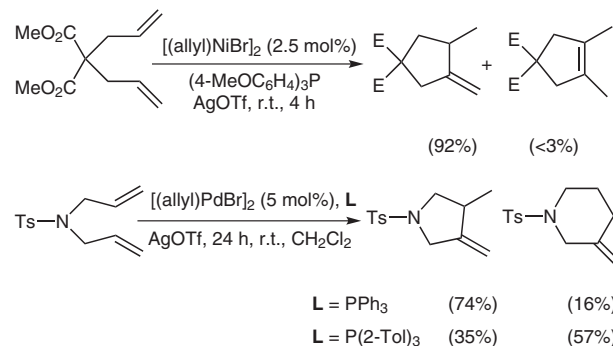
compound **143A**. The endocyclic  $\pi$ -bond (i.e., the C-16–C-17 double bond) in **142A** will also be a useful handle for the oxygenation of the D-ring, a key feature in many important steroidal glycosides, including the potent anticancer agent OSW-1.<sup>72k</sup> Compounds in series **B**, derived from 3-epiandrosterone, can also be prepared by similar routes.

#### 8.4 Intramolecular Reactions: Synthesis of Carbocyclic and Heterocyclic Compounds

The dimerization reaction can be applied for the synthesis of cyclic compounds if the reaction is carried out in an intramolecular fashion. In this context, the palladium-catalyzed cyclization of enynes, which in principle could involve a  $[L_nPd-H]^+$  intermediate, is a well-known reaction.<sup>76</sup> However, relatively little attention has been paid to the corresponding cyclization of  $\alpha,\omega$ -dienes using late-metal catalysts.<sup>77</sup> Apart from a few isolated reports,<sup>78</sup> such palladium- and nickel-catalyzed reactions had not been explored for the synthesis of carbocyclic compounds until our initial report.<sup>79,80</sup> One of the earlier examples is shown in Scheme 42.<sup>78d</sup> We found that the conditions developed for the hydrovinylation of vinylarenes<sup>22</sup> can be applied for the efficient cyclization of  $\alpha,\omega$ -dienes (Scheme 43).<sup>79</sup> The ease of synthesis of the starting materials and the diminished Lewis acidity of these metals (cf. early transition metals<sup>77</sup>) should make this process especially attractive for substrates that contain heteroatoms. As illustrated in Scheme 43, with unsymmetrical dienes, there is also the possibility of very good regiochemical control. An enantioselective version of this reaction has also been reported.<sup>80a</sup>



Scheme 42



Scheme 43

## 9 Large-Scale Synthesis

A patent claims nickel-catalyzed asymmetric hydrovinylation of styrene at  $-60$  °C on an 8.26 kg (79.6 mol) scale using azaphospholene ligand (*R,R*)-**7**.<sup>19</sup> The low yield (41%) and moderate enantioselectivity (87% ee) achieved suggest that further developmental efforts are needed before the reaction can be practiced on a manufacturing scale for the synthesis of pharmaceutical intermediates, such as 3-arylbut-1-enes. Several recent discoveries, including new protocols, and the use of highly tunable ligands brighten the prospect of developing a practical process. For example, the hydrovinylation of several 2-arylpropionic acid precursors have been carried out on a laboratory scale using ligand **87** (Figure 9) to give products in 89–97% yield and with ee values >96%.<sup>47,48,67</sup> In the case of the ibuprofen precursor, a (substrate/catalyst) ratio of 7142 (0.014 mol% catalyst) has been realized. A detailed procedure for a 50 mmol-scale hydrovinylation has been published recently.<sup>57</sup>

## 10 Summary 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 size and electronic factors (e.g., use of vinylarenes, dienes) or in the higher reactivity of a partner because of inherent strain in the molecule (e.g., use of norbornene, norbornadiene). Demonstrated examples validate the claim that very high turnover frequency and exquisite selectivity for the desired product can be realized in many reactions. The reaction conditions are tolerant to a wide spectrum of common organic functional groups. The reaction has been shown to proceed under the catalysis of nickel, palladium, cobalt and ruthenium, and a number of tunable ligand systems for these metals have been identified. With further improvements in ligand design and reaction engineering, expansion of the scope and selectivity of asymmetric hydrovinylation can be expected in the near future. Applications in complex molecule synthesis can also be anticipated.

### Acknowledgment

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