Asymmetric Hydrovinylation: New Perspectives through Use of Modular Ligand Systems**

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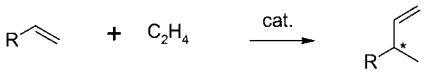
Asymmetric Hydrovinylation of Olefins

Reaction steps in which readily accessible synthetic building blocks are regio- and enantioselectively incorporated into complex molecular frameworks without producing side products are essential for the development of modern atom-economical syntheses.[1] Prominent examples that fulfil these requirements are asymmetric hydrogenation, hydroformylation, and Diels–Alder reactions. In contrast, the hydrovinylation of olefins has received much less attention over the last few years, although the synthetic potential of this reaction is comparable.[2]

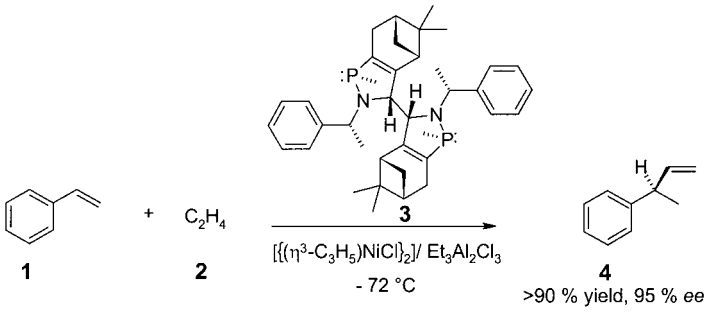
In 1953 Ziegler et al. observed that the buildup of polyethylene on alkylaluminum compounds is suppressed when traces of nickel are present in the reaction mixture, which results in the formation of 1-butene ("nickel effect").[3] Wilke et al. reported in 1963 the selective dimerization of propylene using nickel–phosphane catalysts and found that the product distribution is strongly dependent on the phosphane ligand employed.[4] When analogous reactions of mixtures of two different olefins (e.g. ethylene and norbornene) were carried out in the presence of certain nickel–phosphane catalysts, highly selective heterocodimerization was achieved, in this case to give 2-*exo*-vinylnorbornane.[5] This represented the birth of a new reaction, which has come to be known as hydrovinylation: formally, a hydrogen atom and a vinyl group are added to an olefin (Scheme 1).



Scheme 1. Hydrovinylation of olefins.

The use of chiral phosphanes to achieve asymmetric hydrovinylation was first mentioned in 1967,[2d] and a few years later Bogdanović and Wilke observed asymmetric inductions of up to 70% *ee* for the coupling of 1,3-octadiene and ethylene in the presence of (−)-dimenthylisopropylphosphane.[6]

The highpoint of these initial developments came in 1988 when Wilke et al. isolated the dimeric azaphosphole **3** from a rather complex reaction of a pinene derivative and a chiral amine. The azaphosphole **3** turned out to be an excellent ligand for asymmetric hydrovinylation.[7] For the codimerization of styrene **1** and ethylene **2** to give (*R*)-3-phenyl-1-butene (**4**) an enantiomeric excess above 95% was observed—a record that has not been surpassed yet (Scheme 2).



Scheme 2. Asymmetric hydrovinylation of styrene.

A systematic tuning of the properties of ligand **3** was limited because of its complex structure. Therefore, in the following years a lot of effort was put into the development of alternative ligand systems that could be obtained more easily. Different approaches were investigated, for example palladium complexes with P-chiral ligands that gave good *ee* values but low yields, and nickel complexes bearing 2-diphenylphosphanyl-2′-alkoxy-1,1′-binaphthyl ("MOP") ligands that gave high yields but low asymmetric induction.[8, 9] Significant breakthroughs in this area were not forthcoming and thus interest in hydrovinylation dwindled.

Recently, Leitner et al. and RajanBabu et al. independently published new catalysts that are comparable in terms of activity and enantioselectivity to the system developed by Wilke.[10, 11] The major advance made lies in the modular strategy that allows the development of new ligands with a diverse range of variable building blocks. Thus the necessary prerequisites were in place to permit the design of catalysts for hydrovinylation on a rational basis, which has led to a reawakening of this area of research.

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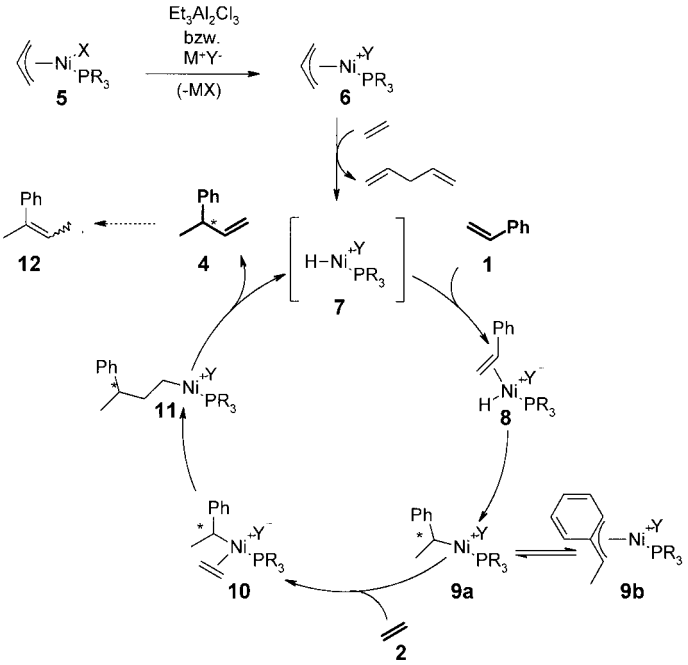
Problems Asscoiated with Developing New Catalyst Systems

A look at the catalytic cycle explains why it is inherently difficult to design new catalysts for the hydrovinylation of olefins (Scheme 3).[2b] First, the active catalyst, which is most



Scheme 3. Catalytic cycle for Ni-catalyzed hydrovinylation.[2b]

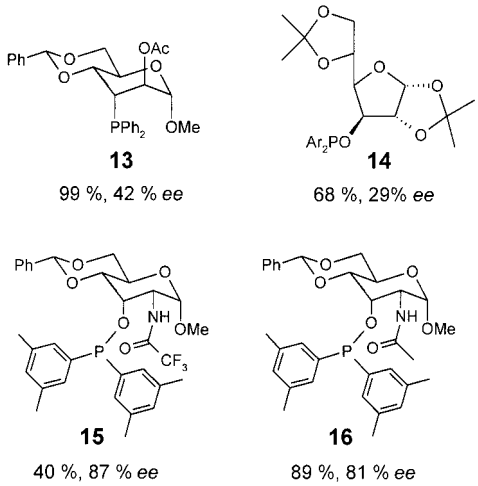
likely a phosphane-stabilized nickel-hydride species, has to be generated in situ from a readily available nickel precursor. Usually [{Ni(allyl)Cl}$_2$] is treated with a phosphane to give the monomeric complex **5**. In the next step the strongly coordinating chloride ion is replaced by a weakly coordinating anion. In the original process this exchange was achieved by using highly flammable alkylaluminum halides that are difficult to handle. In addition, the high Lewis acidity of these compounds limited the application of the process. New techniques for the activation of the given precatalyst involve a much more facile anion exchange with metal salts such as $Na^+BPh_4^-$. By using different metal salts, a number of counter anions can be incorporated into the catalytic system thus providing additional possibilities to tune the catalytical properties.

Cleavage of the allyl substituent leads to the actual catalyst, the highly active and coordinationally unsaturated nickel–hydride species **7**, which is most likely stabilized during the whole catalytic process by additional ligands. This nickel–hydride species **7** should selectively coordinate to only one of the two olefins present, so that only this olefin inserts into the Ni–H bond. Vinylarenes are electronically favored, especially since the resulting benzylic complex **9** can be further stabilized through η^3-coordination of the olefin. The asymmetric induction through the chiral phosphane ligands occurs at this stage.[2d] In the subsequent step, a molecule of the second olefin (usually ethylene (**2**)) coordinates to the metal center, whereas the competing reaction with another molecule of the vinylarene should be suppressed. The second insertion must happen only once, otherwise oligomers will be formed rather than the desired dimers. Therefore the last step in the catalytic cycle, the cleavage of the target molecule **4** and the regeneration of the catalytically active nickel–hydride species **7** by β-hydride elinimation, must be significantly favored. This is usually achieved by the use of sterically demanding ligands.

One additional requirement for a good hydrovinylation catalyst is its low activity for isomerization, since moving the double bond in the product **4** would result in the formation of less valuable and optically inactive olefins **12**. Owing to the large number of possible side reactions small changes to the catalyst often have an unpredictable influence on the outcome of the reaction, a fact that makes improvements of the catalysts even more difficult.

Approaches to New Ligand Systems

In their search for a suitable lead structure for a new generation of ligand systems RajanBabu et al. decided after numerous preliminary investigations to focus on chiral diarylmonophosphinites (Scheme 4).[10] These compounds can be synthesized readily from diarylchlorophosphane and one of the numerous enantiopure alcohols that are commercially available.[13]



Scheme 4. Phosphane and phosphinite ligands for the hydrovinylation of styrene with ethylene.

Good chemoselectivities in favor of the heterocodimerization were observed with these ligands in the reaction of styrene with ethylene according to Scheme 2. The best results were obtained by using monophosphinites derived from sugars especially 2-acetamido-2-deoxyglycopyranoside derivatives.

The modular construction of the ligands **13**–**16** allows a multitude of variations through the use of different sugars, through derivatization by introducing different functional groups at the sugar moiety, and through the use of different aryl substituents at the phosphorous atom. The enormous impact of these fine tunings is clearly apparent from a comparison of the results obtained by using **15** and **16**: The

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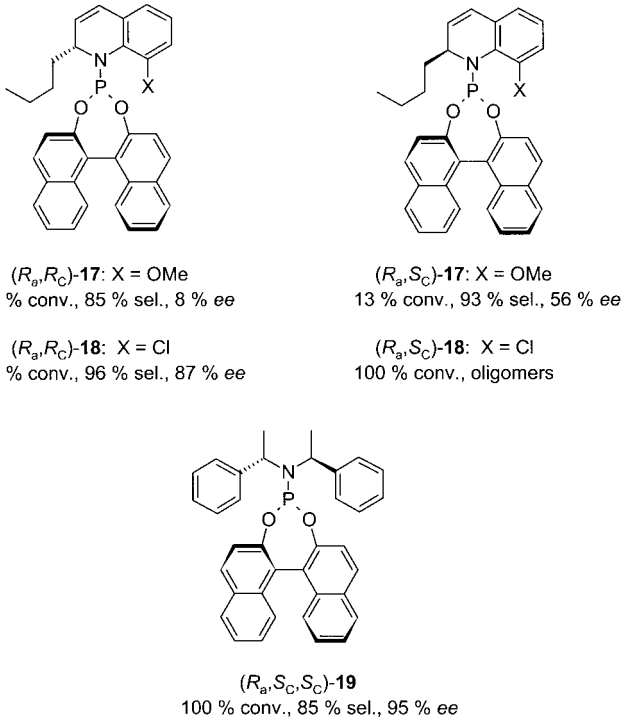
replacement of only one group on the ligand resulted in a doubling of the yield.

Interestingly, the counterion used has a big influence on the activity and selectivity of the catalyst. The best results were obtained with tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate ("BARF") or SbF_6^-, whereas BF_4^- and $CF_3SO_3^-$ (OTf^-, triflate)-derived complexes were significantly less reactive. This is surprising since Wilke et al. had observed in their correlation of data from catalysis experiments with those from conductivity measurements[12] that higher activities of the catalyst were obtained for weakly coordinating rather than noncoordinating counterions.

A comparable degree of modularity to that shown by the systems developed by RajanBabu et al. is displayed by the phosphoramidites introduced by Leitner et al. (Scheme 5).[11] A large number of these compounds is readily accessible from chiral alcohols and amines on reaction with PCl_3.[13] Owing to the excellent asymmetric induction together with lower costs for the syntheses, phosphoramidites[14] and phosphites,[15] for example for asymmetric hydrogenation, have recently become viable alternatives to well-established ligands such as BINAP.



Scheme 5. Phosphoramidites for the hydrovinylation of styrene with ethylene.

For the Ni-catalyzed hydrovinylation of styrene with ethylene the phosphoramidites again turned out to be excellent ligands. Particularly good results were obtained with (R_a,S_c,S_c)-**19** (Scheme 5): almost 95 % *ee* and 85 % selectivity for the desired heterocodimer. As side products only 4 % isomerized product and 8 % oligomers were detected.

Both, axial chirality within the diol fragment as well as the center of chirality in the amine are important for the asymmetric induction of the ligand. This is clearly apparent from the strong dependancy of the yields obtained on the diastereomer of the ligand used. For the "mismatched" isomers the optical as well as the chemical yield is significantly decreased. For (R_a,R_c)-**18** 93 % selectivity and 84 % *ee* were observed, whereas the diastereomeric ligand (R_a,S_c)-**18** led only to oligomerization due to the disfavored geometry of the ligands.

Likewise for these systems the counterions have a strong influence on the catalytic properties. The best results were obtained by using NaBARF as the activating agent. If $Na[Al\{OC(CF_3)_2Ph\}_4]$ is used instead of NaBARF a higher chemoselectivity can be achieved, whilst the enantiomeric excess drops to 89.7 %. Weakly coordinating counterions such as BF_4^- or NTf_2^- led to much poorer results.

The activities of these new catalysts are intriugingly high. Leitner et al. used (R_a,S_c,S_c)-**19** with a catalyst-to-substrate ratio of 1:13 000 and observed 69 % conversion at 0 °C within 30 min. This corresponds to a turnover frequency of approximately 18 000 h^{-1}. At lower temperatures this number drops to 8000 h^{-1} but higher chemo- and enantioselectivities can be achieved.

Applications of the Reaction

A potential application for hydrovinylation is the asymmetric synthesis of pharmacologically important phenylpropionic acids such as Ibuprofen or Naproxen.[16] In this context, other approaches using asymmetric hydroformylation, hydrocyanation, or hydrocarbonylation have already been tested; however, for a variety of reasons these proved to be no better than well established processes.[17] For hydroformylation the drawbacks are low turnover numbers as well as the tendency for racemization of the resulting aldehydes. Alternative approaches using the asymmetric hydrovinylation of styrene derivatives might have major advantages.[7, 12] Although the oxidative cleavage of the vinyl groups necessitates an additional synthetic step, the products obtained after the asymmetric steps are configurationally stable.

RajanBabu and Leitner and their respective co-workers demonstrated the potential of their new systems by way of synthesizing ibuprofen staring from *p*-bromo- or *p*-isobutylstyrene (Scheme 6).[10, 11] Hydrovinylation of *p*-bromostyrene was achieved with very good yields and enantioselectivities in both cases. For the phosphoramidite (R_a,S_c,S_c)-**19** a substrate-to-catalyst ratio larger than 2500 was used, and an enantiomeric excess of 92 % was achieved. For the monophosphonite **16** (with a higher catalyst loading) a yield of 98 % and an enantiomeric excess of 89 % was achieved.

To complete the synthesis of ibuprofen the vinyl group of the hydrovinylation product has to be oxidized to the corresponding carboxylic acid, and the bromo substituent replaced by an isobutyl group. The shorter route to ibuprofen starting from *p*-isobutylstyrene proved to be less favorable since poorer results were obtained in the hydrovinylation of this more electron-rich substrate: RajanBabu's system gave the desired product in 99 % yield but with only 74 % *ee*, whereas Leitner's system gave the product in only 28 % yield with 68 % *ee*.

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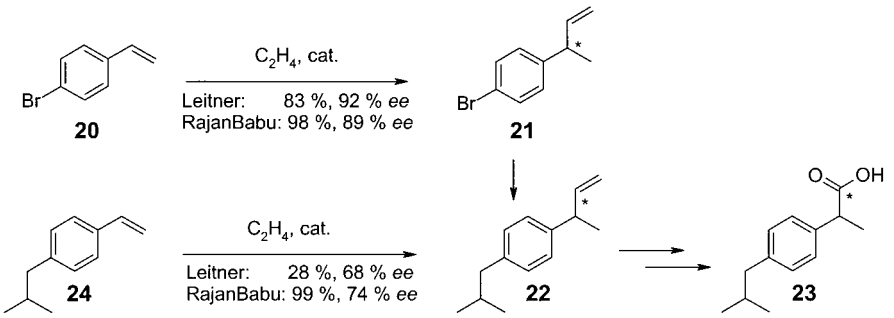

Scheme 6. Asymmetric synthesis of Ibuprofen.

Despite the significant advances, it is clear that there is still a lot of potential for further improvement. The optimization of the new systems is still in its infancy; however, given the modularity of the new ligands it is envisaged that even more efficient members of these new classes of ligands will be identified in the near future.

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