Developing New Chiral Ferrocenyl Ligands for Asymmetric Catalysis: A Personal Account

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Abstract. The wide scope of application of chiral ferrocenyl ligands in asymmetric catalysis is illustrated. This class of compounds has constituted the main scientific interest of the author during the last nine years, first at the Central Research Laboratories of *Ciba*, and more recently at the ETH. Their easy synthetic accessibility offers, *e.g.*, the opportunity to study electronic and steric effects on enantioselectivity for different transition-metal-catalyzed reactions. These studies have led to the most selective catalysts known for model reactions, such as the hydroboration of styrenes with catecholborane and the allylic amination.

1. Introduction

This brief review should fulfill multiple purposes. First of all, it is intended to be a timely account about progresses achieved in our laboratories in the field of asymmetric catalysis utilizing ferrocenyl ligands [1]. Secondly, it should provide some background information about the reasons that led me to enter this particular research field, and a quite special class of chiral auxiliaries. Furthermore, I hope to be able to convey some of the leading ideas that guide current work, and are anticipated to open new opportunities for future studies.

In 1986 *Hayashi*, *Ito*, and *Sawamura* [2], at Kyoto University, reported a remarkable and unique asymmetric reaction catalyzed by Au(I) (*Scheme 1*). The aldol- (or *Knövenagel*) type reaction of an aldehyde with isocyanoacetates affording mainly *trans*-configurated 4,5-disubstituted 4,5-dihydro-oxazoles was effectively achieved with a high degree of enantioselection (*ca.* 90% ee). The particular and very unique ligand they used was the chiral 1,1'-bis(diphenylphosphino)ferrocenyl derivative **1**.

At that time, I was at the Central Research Laboratories of *Ciba-Geigy Ltd.* in Basel trying to develop new homogene-

ous catalysts, in particular for stereoselective C–C-bond forming reactions. Colleagues in the pharmaceutical division were interested in stereoselective methods for the preparation of amino-phosphonic acids such as **2**, important because of their

anticonvulsive properties. One possible synthetic pathway dealt with the oxazoline **3** as an intermediate [3] (*Scheme 2*).

This was a sufficiently meaningful reason for me to *1*) reproduce *Hayashi*'s work, in terms of a feasibility study, and *2*) try to optimize and scale-up the procedure, in order to produce kg quantities of the desired compound. In retrospect, however, I must say that I was quite reluctant to carry out the work, since I was much more inclined to do my own (albeit less useful) chemistry, and because I had the impression that a 'me-too-project' was nothing for me. In the end, however, my supervisor succeded in convincing me, in particular by putting forward the argument that the ligands needed for this reaction were *organometallic* compounds, thus touching a subjectively very important point. Soon thereafter, we were able to produce the required amounts of the chiral ligand, as well as of **3**. We were even able to show that the Au catalyst could be easily recovered by simple precipitation and filtration, and that it could be reused several times without loss of activity or selectivity [4]. Based on this initial success and on a very spontaneous fascination, it did not take much time to realize that homogeneous catalysis using ferrocenylphosphines would constitute 'my' main research in-
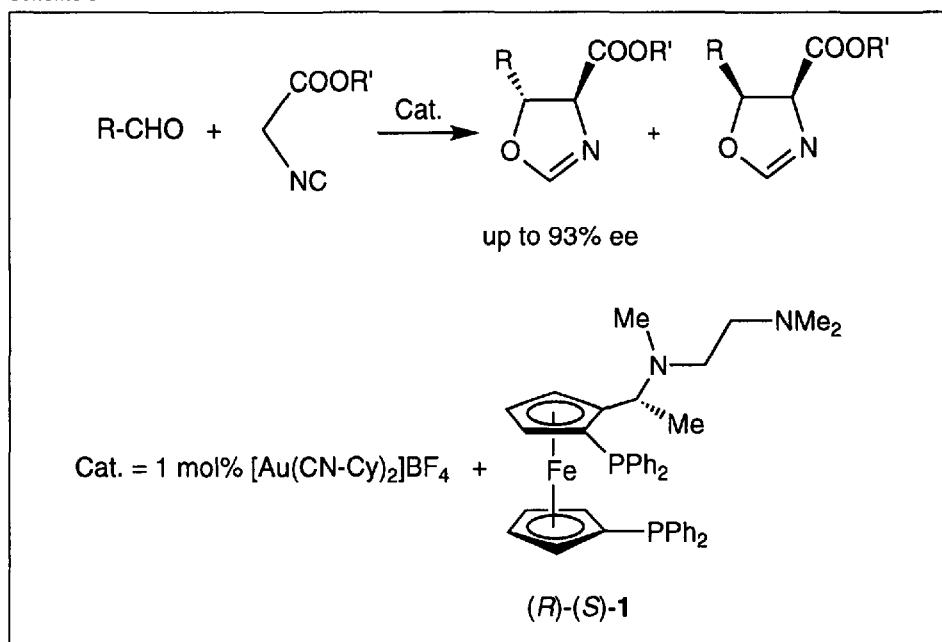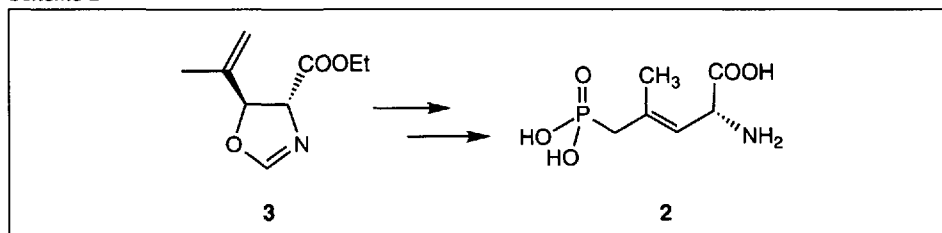
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Scheme 1

up to 93% ee

Cat. = 1 mol% [Au(CN-Cy)₂]BF₄ +

(R)-(S)-**1**

Scheme 2

terest for years to come. Being an industrial chemist, I was now no longer hesitant to interfere with the Kyoto group, who was clearly the initiator and leader of this particular area. This was probably because in industry the obligations to scientific originality are less stringent than in academia. This thought, whether or not it reflects the truth, helped me at least overcome the ethical reluctance I had, before taking up a research area that 'belonged' to someone else. As a first step, hopefully toward own new contributions to the field, I decided to study the Au-catalyzed aldol reaction from a mechanistic point of view. The work, done in collaboration with my colleague *Pastor*, is documented in a series of publications, appeared between 1989 and 1992 [5].

2. Making and Applying New Ferrocenyldiphosphines

The ferrocenyl ligands known from the Kyoto school can be subdivided into two classes. Most representatives are 1,2,1'-trisubstituted ferrocenes, whereby derivative 1 is one of the most prominent examples [6]. The 1,1'-positions are occupied by two equivalent P-atoms, in most cases bearing two Ph substituents. This limitation stems from synthetic reasons, the introduction of two different ligating moieties being much more difficult, and the application of such derivatives being so far unsignificant. One further common feature is the presence of a branched, at the α-position heteroatom-substituted stereogenic side chain. The invariably N- or O-containing side chain can be modeled, in order to fulfill the purpose of a secondary interaction with the substrate coordinated to the metal center in the catalytically active complex. One of the major merits of the Japanese colleagues is to have shown the advantages of this principle, and to have demonstrated its potency in an impressive manner [7]. The second, less important class of ligands is constituted by 1,2-disubstituted ferrocenes, bearing only one phosphino group and the usual stereogenic side chain. An example is 7, which finds applications in enantioselective Ni- and Pd-catalyzed *Grignard* cross-coupling reactions [8]. Key compounds in both classes are the acetates 6 and 9. They serve as starting materials for the introduction of the desired side-chain *via* a retentive nucleophilic substitution reaction [9]. A 'family tree' of the most important Kyoto ligands is illustrated in *Scheme 3*.

My first contribution toward the development of new ferrocenyl ligands was led

Scheme 3

Scheme 4

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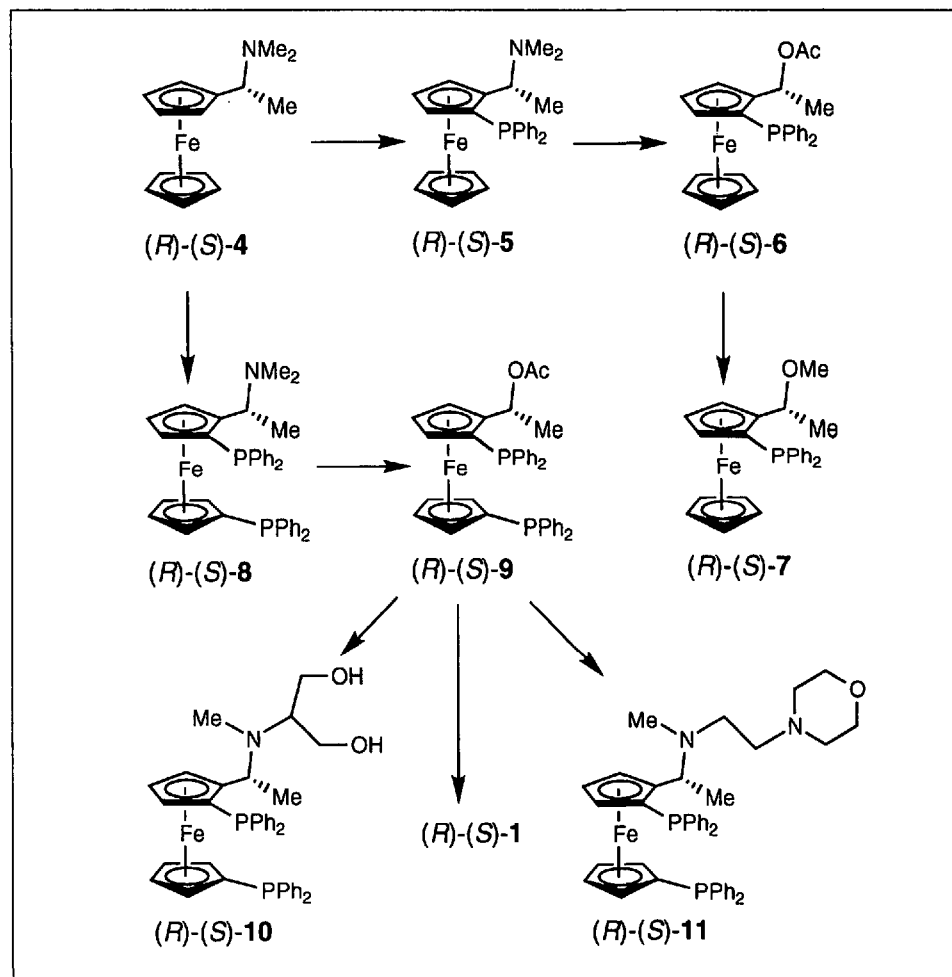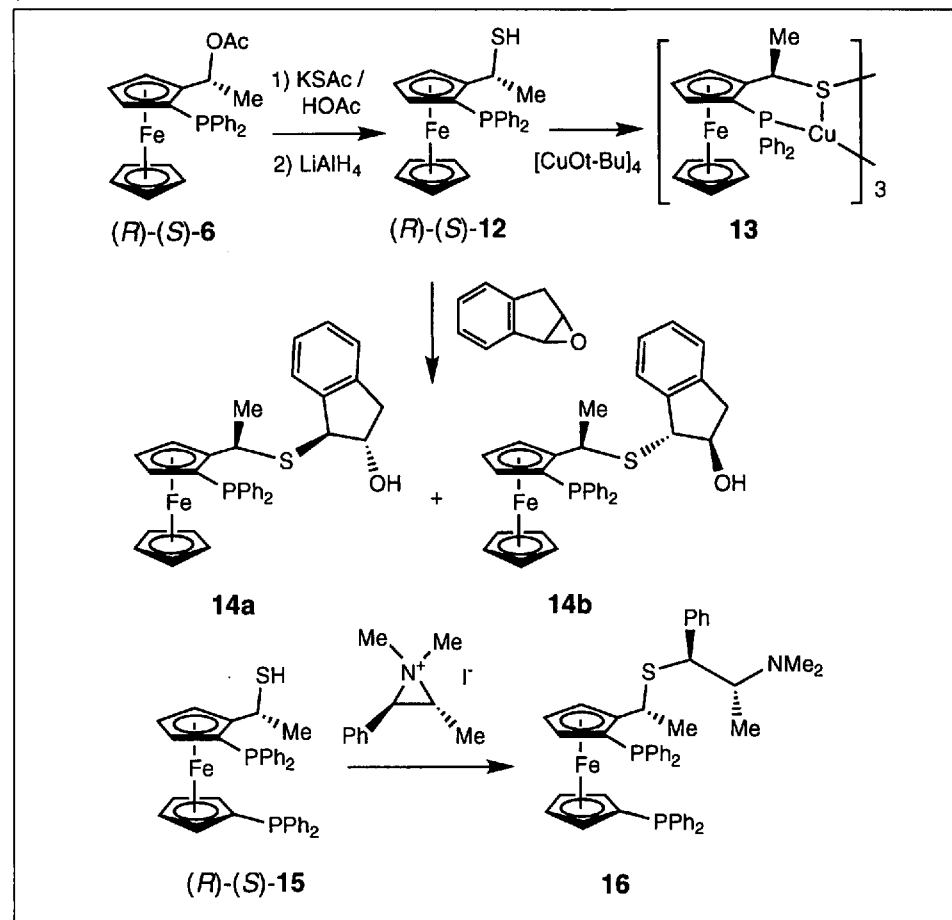
by the idea óf introducing heteroatom substituents at the stereogenic center other than nitrogen and oxygen, in an efficient manner. In this context, a very simple but significant experimental finding was that 6 and 9 would smoothly react with KSAc in acetic acid to afford the corresponding

thioacetates. These compounds can easily be converted to the thiols 12 and 15 upon reductive treatment, and these may be used as nucleophiles for chain-extension processes, and for the construction of, *e.g.*, P,S,O-tridentate ligands, such as 14 [10] [11]. Furthermore, the coordination chem-

istry of the monophosphine-thiol 12 has been studied [12]. The chemistry of the S-containing derivatives is shown in *Scheme 4*.

In view of the chemistry to be discussed below, however, the most important aspect deriving from these first studies is indeed the use of acetic acid as the solvent for the crucial nucleophilic substitution reactions. It was for the first time possible to obtain high yields of the substitution products by using stoichiometric amounts of the nucleophilic agents, as opposed to large excesses when operating in (typically) MeOH solvent. Not only, the amines 5 and 8 were found to be the even better substrates than the acetates for this kind of reaction, thus shortening the corresponding syntheses by one step [13].

With an improved methodology in hand for the retentive substitution reaction at the stereogenic center of the classical ferrocenyl ligands, my colleague *Spindler* and I decided to look at bidentate ligands, in which one of the coordinating fragments is directly attached at that center. The general idea was to easily access new ligands by using a simple construction kit constituted by *1*) the carrier of the chiral information (amine 4), *2*) a set of electrophiles for the introduction of ligand groups on the Cp ring(s), and *3*) a virtually infinite array of nucleophiles for complexing fragments at the side chain. The assembly of the chelating ligands occurs in two consecutive steps, and allows for a variation of the electronic and steric properties of both coordinating fragments, independently from one another (*Scheme 5*). We first started by looking at the combination of a diphenyl- with a dicyclohexylphosphino group. The resulting chelating ligand, which we named *Josiphos* (17), from the name of the technician who first prepared it, turned out to be a very effective auxiliary for Rh-catalyzed asymmetric hydrogenation reactions of the classical dehydroamino-acid substrates, for itaconi-acid derivatives, and for some β-keto-esters [14].

We were then able at the ETH to extend the scope of this very first ligand and to show that high enantioselectivities could be obtained also in, *e.g.*, the Rh-catalyzed hydroboration of styrenes with catecholborane (up to 92% ee), and the Pd-catalyzed allylic alkylation (up to 93% ee). Furthermore, in a nice example of industrial collaboration, *Spindler* and colleagues at *Lonza Ltd.* found later that the related derivative 18 containing the bulky di(*tert*-butyl)phosphino group was the best ligand for the hydrogenation of the fully substituted C=C bond in compound 19, an
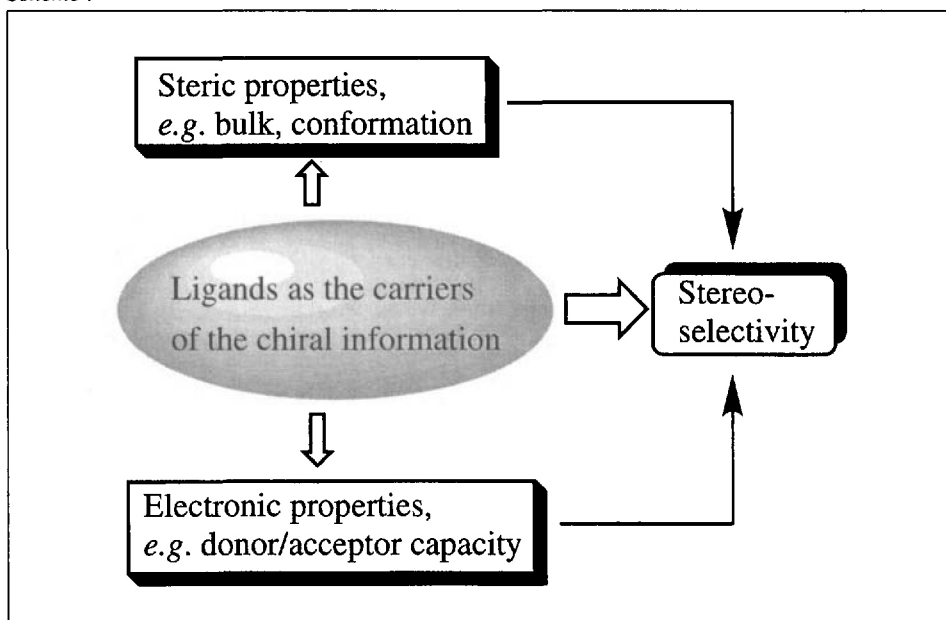
Scheme 5
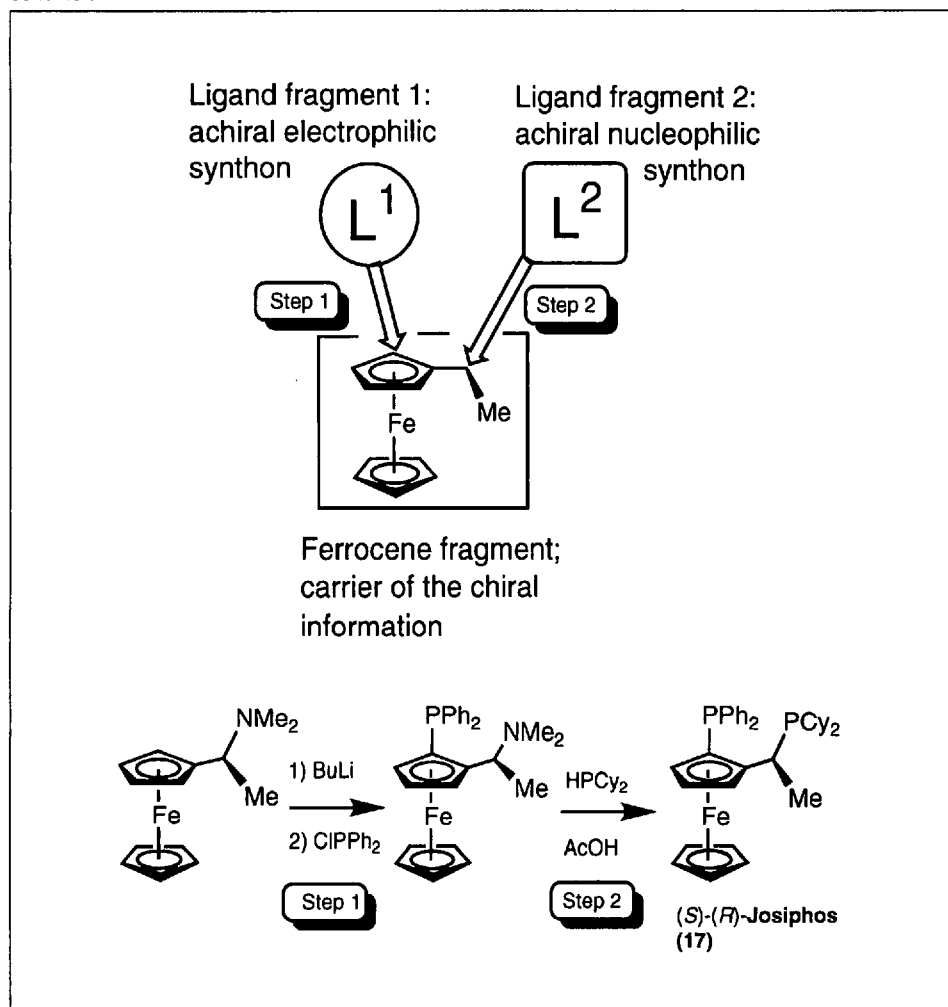
Scheme 6
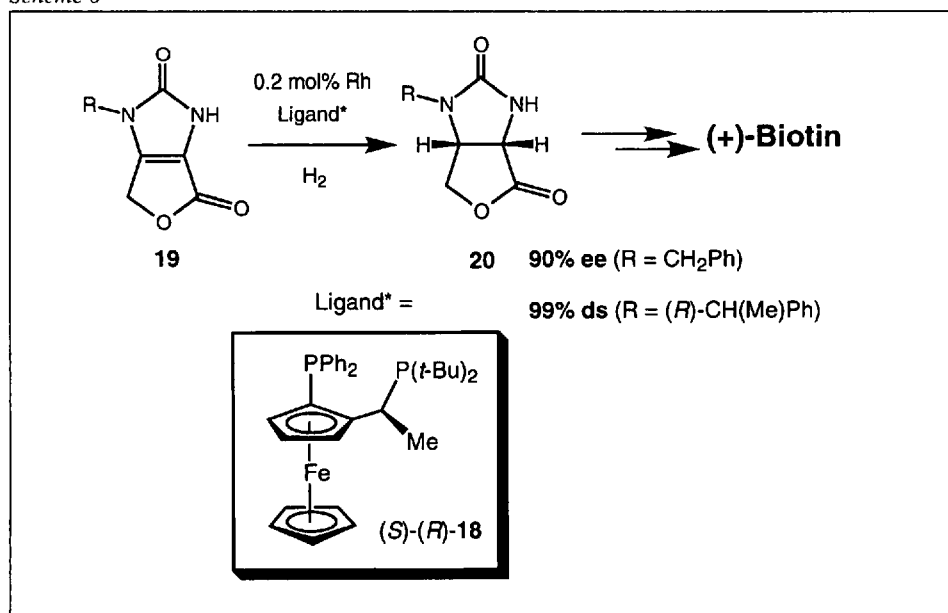
intermediate in a new synthesis of biotin [15]. This catalytic procedure is currently being applied on a commercial scale (*Scheme 6*).

Considering the wide scope of application and the high selectivities obtained in several different reaction types utilizing these new diphosphines, it was tempting to try to understand their secret, if there is any. Being able to control the steric and electronic nature of the two ligand fragments, part of our studies focussed on the question whether the electronic difference between the two donor atoms would create a bias as to the stereochemical course of the catalytic reactions occuring at the metal center. Essentially, that meant chasing electronic effects on stereoselectivity. At this point, it is important to realize what is meant by electronic effect on stereoselectivity, since electronic and steric properties cannot be completely separated from one another. However, when comparing two ligands differing in an only insignificant manner from a steric point of view (bulk, conformation), but possessing, *e.g.*, different donor capabilities, it is appropriate to speak of electronic effects on stereoselectivity, when the two ligands lead to significantly different stereochemical outcomes in a catalytic reaction (*Scheme 7*).

Of course, different electronic properties of ligating groups may be responsible for different steric behaviors of the corresponding complexes, such that the effects being observed are ultimately steric in nature, because of *e.g.*, different trajectories of approach of the substrate or reagent to the catalyst, their possibly different coordination modes, and altered complex geometry. Nevertheless, the primary and most evident difference between the ligands being of electronic nature, a pertinent description of the different selectivities obtained with the two ligands will be in terms of electronic effects [16]. It is clear that understanding such effects may be a very difficult task, since it means unraveling the mechanistic features that translate differences in *e.g.*, ligand donor capacities into different enantiomer ratios for the catalytic reaction. We designed ligands with which predominantly electronic or steric effects, respectively, should be observable. *Fig. 1* shows two couples of diphosphines that have been prepared for this purpose. In the Pd-catalyzed allylic substitution reaction of 1,3-diphenyl-propenyl acetate with dimethyl malonate, a significantly different enantioselectivity is observed when the two ligands **21** (57% ee) and **22** (70% ee) are used. However, to make a long story short, our studies show that for this kind of ligands the steric

Scheme 7

Scheme 8

Yield and regioselectivity up to 80%
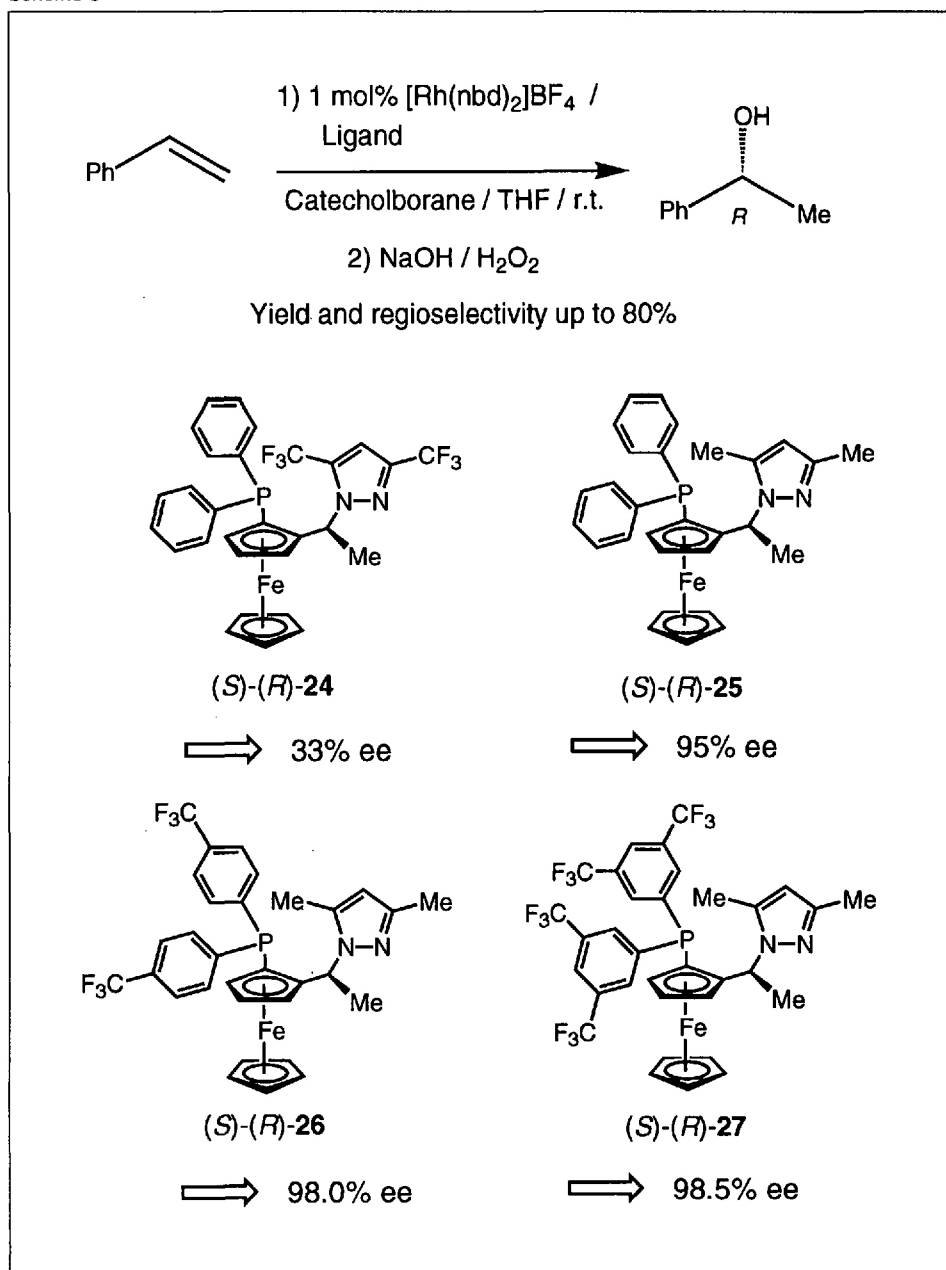
effects are always predominant. Structural studies on complexes containing the prototype ligand 17 demonstrate, e.g. that this ligand is able to retain a specific conformation in different complexes with different metals and different co-ligands [17]. Fig. 2 shows a schematic superposition of several solid-state structures illustrating this aspect. We interpret this as an expression of the conformational rigidity of 17, thus being able to create a well-defined chiral environment around the coordinated metal center. Conformational rigidity is thus recognized, among others, as one very important features of a 'good' ligand for asymmetric catalysis. In our diphosphine system the fitting of the sizes of the phosphorus substituents seems to be quite crucial for the obtention of an optimum conformation. In fact, when the dicyclohexylphosphino group is replaced by the so-called 'phobyl' fragment [18], a smaller but electronically very similar phosphorus donor, the conformational

flexibility is increased, as reflected by the superposition of the solid-state structures of 23 and two of its Pd-complexes, as shown in Fig. 3. Compared to 17, ligand 23 leads in general to lower enantioselectivities. For example in the above mentioned allylic alkylation 23 affords 72% ee, while, under the same reaction conditions (room temperature, 1 mol% catalyst) 17 gave 93% ee. This difference is larger than the one observed in the case of the electronically different ligands 21 and 22.

3. The Extension to P,N-Ligands: Pyrazolyl Ferrocenes

In recent years there have been several contributions to asymmetric catalysis dealing with the use of chelating P,N-ligands [19]. The successes obtained with such auxiliaries contributed to the erosion of the in part only dogmatic principle asking for C_2-symmetric ligands [20] (recall that

all ferrocenyl ligands presented here are of C_1 symmetry). We envisaged the development of a ferrocene-based P,N-ligand system, having comparable features as the diphosphines described above, i.e., easy accessibility and optimal tuning qualities. We chose pyrazoles as N-carrying moieties because this heterocycle provides several positive properties. One of the two sp^2 hybridized N-atoms functions as anchoring point to the ferrocenyl side chain, the second one as donor for the coordinated metal. Hundreds (or maybe thousands) of pyrazole derivatives are known in the literature, thus providing a priori the opportunity to modifying steric and electronic properties. The coordination ability of, e.g., hydrotris(pyrazolyl)borates(1–) has been previously demonstrated [21], but the combination of a phosphine and the five-membered heterocycle in a chelating ligand was unknown before our work. Our pyrazolyl ligands would also form seven-membered chelate rings, a less common ring size for homogeneous asymmetric catalyst complexes.

The synthetic approach to this new class of ligands reflects the way how their diphosphine congeners are prepared [22]. Simple reaction of the pyrazole derivative with the ferrocenylamine 5 in acetic acid affords in moderate to good yields the desired P,N-system. These new compounds were soon found to afford the highest known enantioselectivities in the Rh-catalyzed hydroboration of styrenes (up to 99% ee) [23] and in the Pd-catalyzed allylic amination of 1,3-diphenylallyl derivatives with benzylamine (up to more than 99% ee)[24]. These two reactions are illustrated in Schemes 8 and 9, respectively.

Again, as it was the case for the diphosphines above, our strategy focussed more on an optimization of the ligand than on a wide substrate-screening. The choice of well-known, although synthetically probably less useful standard reactions, should facilitate the work directed toward the understanding of the origin of enantioselectivity. A detailed mechanistic knowledge of the crucial reaction step where the absolute configuration of the product is defined, is necessary for a classification of the ligands in terms of substrate/catalyst specificity. In other words, knowing in details why a particular ligand affords the best enantioselectivity for a particular substrate will be of great importance for the choice of the best ligand for a new substrate. However, the mechanistic features of catalytic reactions may sometime reach such a degree of complexity that the work required in order to obtain the desired
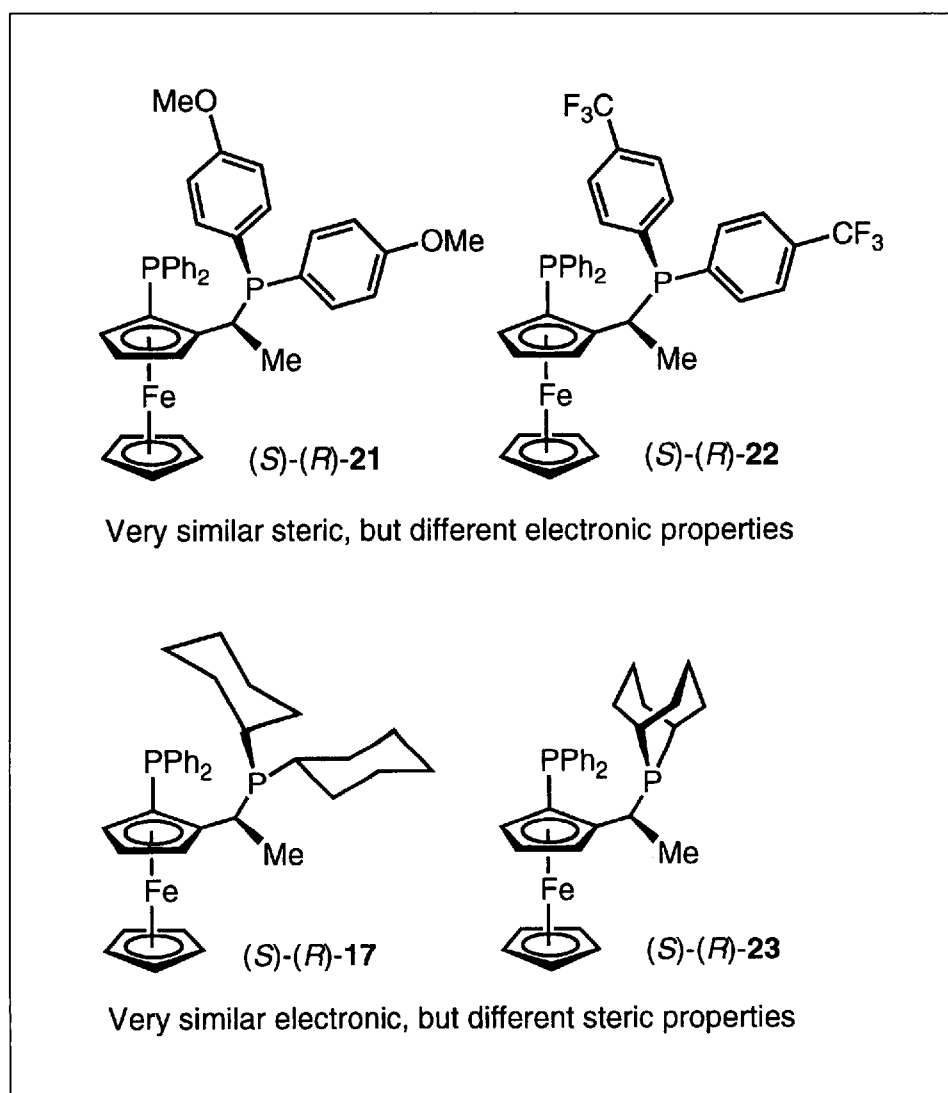

Fig. 1. Two couples of ferrocenyl ligands illustrating the opportunities of varying mainly the electronic, or mainly the steric properties

detailed knowledge at the molecular level becomes almost prohibitive. It is, therefore, important to judge whether or not it is appropriate to imbark in such studies and to what extent they should constitute the main focus of a particular project. An example where the results were worth the 'investment' is the allylic amination reaction mentioned above. Relatively simple structural studies, both in solution and in the solid state, of selected π-allyl complexes forming as intermediates in the catalytic cycle, afforded a sufficiently large amount of information to allow us to draw important conclusions about the origin of enantioselectivity and the possible nature of the transition state [24]. Key observations in this context were that *1*) ligand **29**, bearing a 3-(9-anthryl)pyrazole, gave a much lower ee (40%) and, more importantly, as compared to all other ligands of the series having the same absolute configuration, it afforded the opposite enantiomer of the product, preferentially, and *2*) ligand **30** afforded a catalytically inactive complex. From these studies, we know now that both the site-specific nucleophilic attack of the amine onto the allyl ligand (*trans* to phosphorus), and the configuration of the π-allyl complex determine the enantioselectivity. These two aspects are the result of a complex interplay of subtle electronic and steric features controlled by the ligand (a detailed account about this system just appeared [24]). The situation is completely different in the hydroboration reaction, where large electronic effects on stereoselectivity are observed (*Scheme 8*). This reaction is much more complex from a mechanistic point of view than the allylic amination. The very simple consequence of this is that the degree of understanding is much lower.

As it was the case for the diphosphine system **17**, we observe in the P,N-ligands of this new generation a pronounced conformational rigidity, as illustrated in *Fig. 4*. I believe that the structural characterization of chiral ligands and their catalytically active complexes (or precursors thereof) is a very important aspect in modern asymmetric catalysis. However, one should always be careful when drawing conclusions about catalyst properties, or making interpretations of enantioselectivities, solely from structural data. It has been in fact our experience that structures determined by X-ray crystallography mostly correlate with those determined in solution by 2D-NMR methods [25], but exceptions to this general rule may well be responsible for mistakes and misinterpretations, when only the crystal structure is available. The π-allyl complex **31** shown
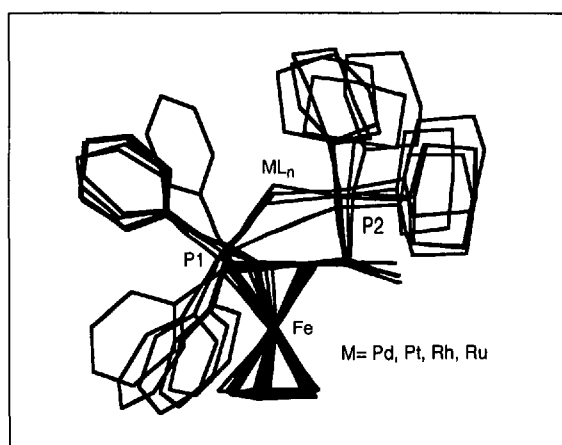

Fig. 2. *Schematic superposition of the structures of Josiphos* (**17**) *and of four of its complexes, showing the similar conformations of the ligand in different compounds.* The major deviation from the common orientation of the phenyl groups at P1 is found in **17** itself (ancillary ligands omitted for clarity).
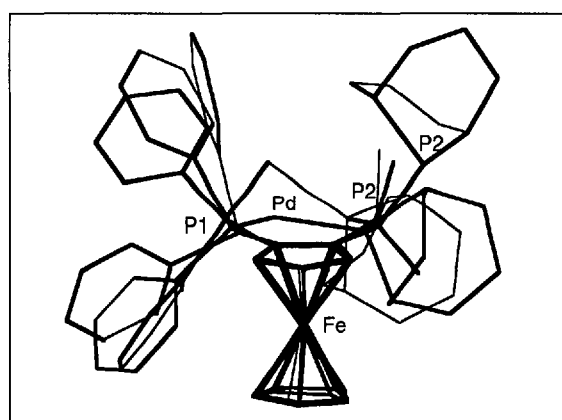

Fig. 3. *Schematic superposition of the structures of Phobyphos* (**23**) *and of two of its Pd complexes, showing the bad fit of conformation* (ancillary ligands omitted for clarity)
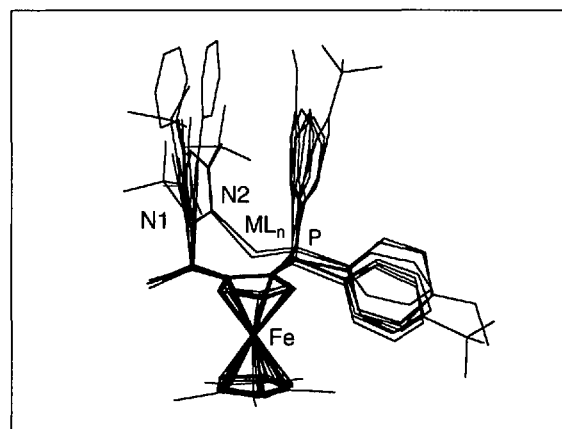

Fig. 4. *Schematic superposition of the structures of eight different pyrazole-containing ferrocenyl ligands and their complexes, showing the constant conformation of the common fragment of the ligands*
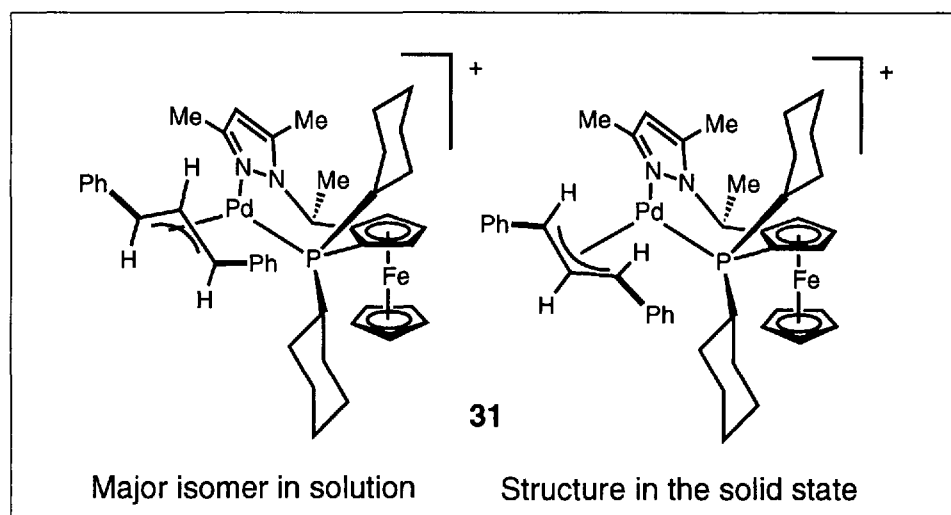

Major isomer in solution   Structure in the solid state

Fig. 5. *The two different allyl configurations for the complex* **31** *found in solution and in the solid state*
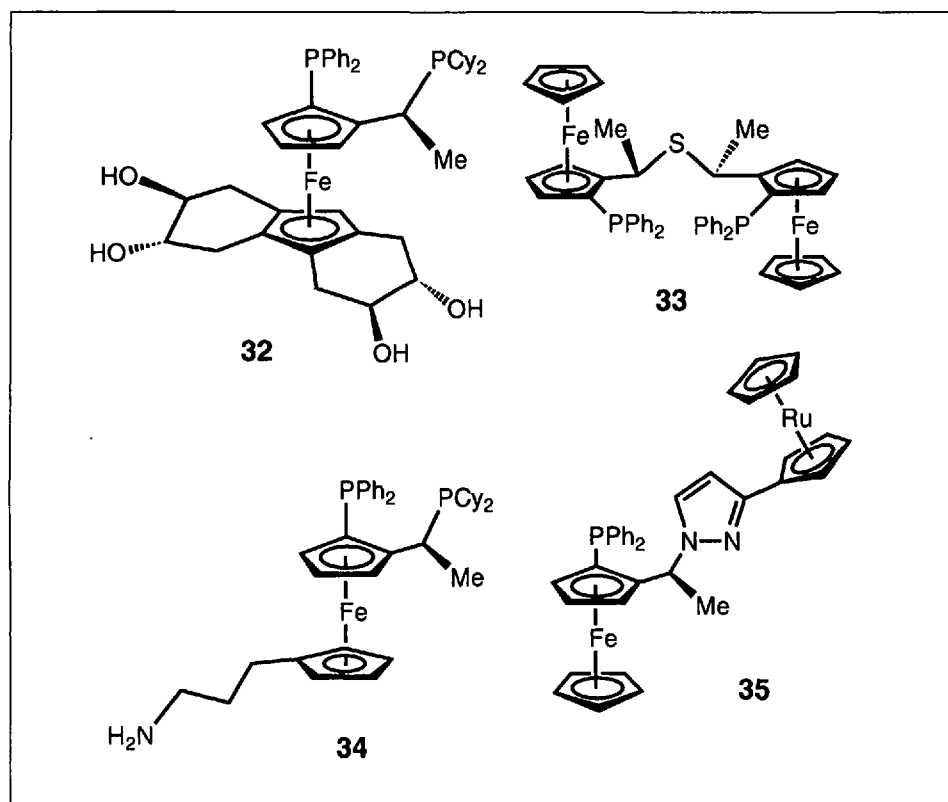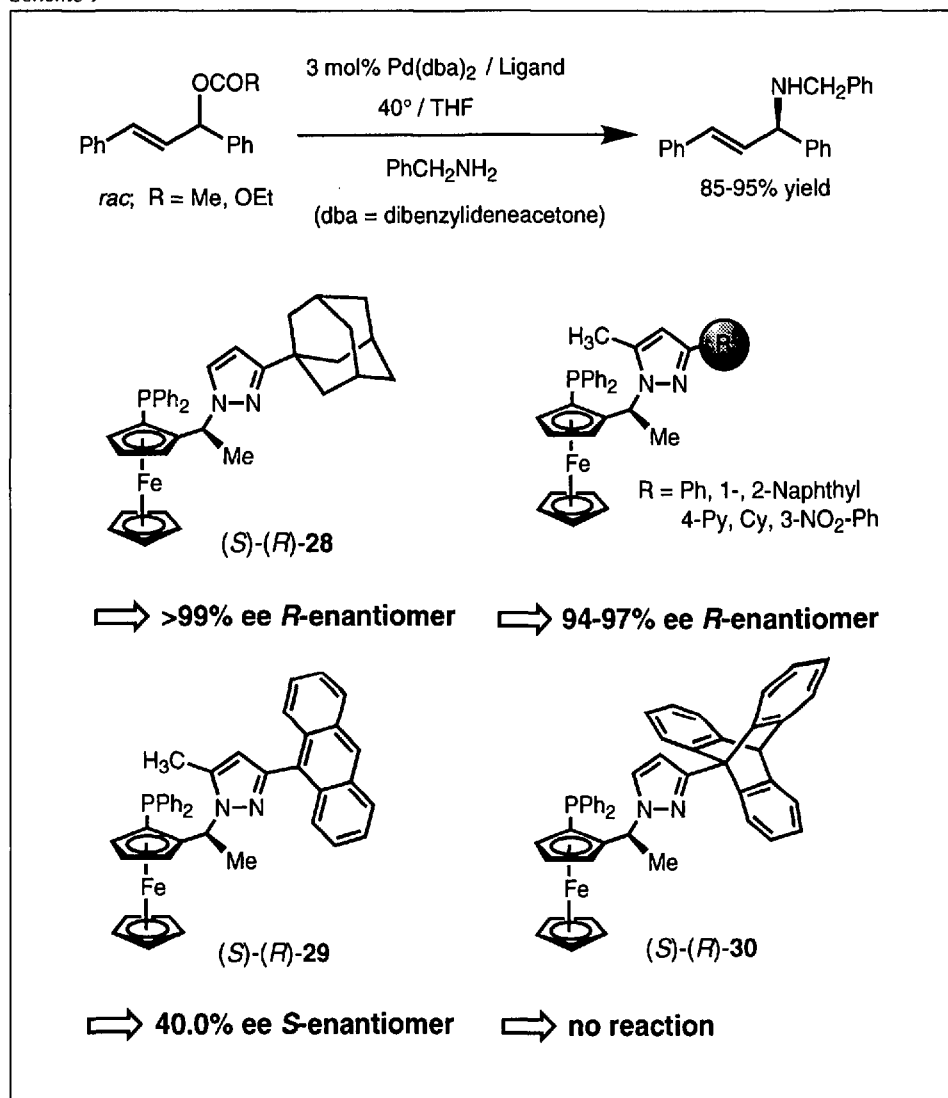
Scheme 9

in *Fig. 5* is an example, where solution and solid-state structures display different π-allyl configurations, a very important aspect when discussing enantioselectivities of reactions involving this intermediate [26].

4. Outlook

The chemistry briefly summarized above could be described by a skeptical and very critical observer as being indeed successful, but rather conventional. Where are the ideas that could turn out to be very important for 21st century chemistry?

No doubt, application of asymmetric catalysis will continue to gaining importance for years to come [27]. The need for new and more selective catalyst for a growing variety of synthetically useful reactions is going to guide research not only in academia but also in industry. This research is very much empirical in nature and will remain so for a while. There is almost no rational way to predict which catalyst should be used in order to obtain optimal stereoselectivity for a new reaction. This is why studying the problem of the origin of enantioselectivity is so important, and we will continue our activity in this area. Modern quantum-mechanical methods allow now to tackle catalytically active transition-metal complexes, thus opening up a possible synergism between theory and experiment [28]. From an experimental point of view, however, it is important to seek opportunities to branching out toward e.g., supramolecular chemistry and solid-state chemistry (relation to heterogeneous catalysis). Also the use of unconventional solvents, or the connection with electrochemical systems constitute areas of great interests for the future. Our ferrocenyl ligands are molecularly ideally suited for studies in these directions. We recently learned how to prepare derivatives containing extra functionalities attached to the second Cp ring [29], thus extending their synthetic potential. *Fig. 6* shows examples of target molecules currently being pursued. Compound **32** should be water-soluble, whereas ligand **34** should easily be incorporated into dendritic structures. Derivative **35** is a model for a possible asymmetric redox-switch catalyst system. Compound **33**, finally, is a representative of a new generation of chiral tridentate ligands to be used in *Lewis*-acid-catalyzed reactions [30].

In conclusion, one can really say that more interesting chemistry with ferrocenyl ligands is out there ready to be discovered.

Fig. 6. *Some of the new ligands currently under study*

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[25] Most structure elucidations in solution using 2D-NMR methods have been carried out in the group of my colleague Prof. *P.S. Pregosin*.

[26] U. Burckhardt, unpublished results (part of the planned Ph.D thesis at ETH).

[27] See, *e.g.*: S.C. Stinson, *Chem. Eng. News* **1994**, September 19 issue, 38.

[28] A collaboration with *P. Blöchl* (*IBM* Research Laboratories, Rüschlikon) has recently been started. Very promising results have been obtained from *ab-initio* molecular dynamics calculations (projector augmented wave method).

[29] a) H.C.L. Abbenhuis, A. Togni, B. Müller, A. Albinati, U. Burckhardt, V. Gramlich, *Organometallics* **1994**, *13*, 4481; b) H.C.L. Abbenhuis, U. Burckhardt, V. Gramlich, A. Martelletti, J. Spencer, I. Steiner, A. Togni, *ibid.* **1996**, *15*, in press.

[30] P. Barbaro, A. Togni, manuscript in preparation. For the preparation of similar triphosphines, see: P. Barbaro, A. Togni, *Organometallics* **1995**, *14*, 3570.