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Some new aspects of asymmetric catalysis with chiral ferrocenyl ligands*

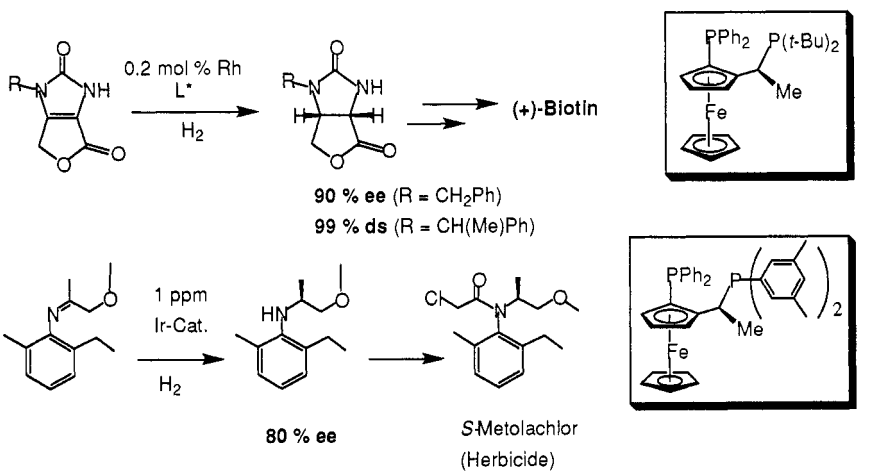
Antonio Togni*, Romano Dorta, Christoph Köllner, and Giorgio Pioda

Laboratory of Inorganic Chemistry, Swiss Federal Institute of Technology ETH-Zentrum, Universitätstrasse 6, CH-8092 Zürich, Switzerland

Abstract: Chiral bindentate ferrocenyl ligands have been used in a variety of asymmetric catalytic reactions. Three different recent developments are illustrated here. Firstly, using P, N systems containing a p-acidic phosphine and a bulky pyrazole very high enantioselectivities were obtained in the Pd-catalyzed hydrosilylation of norbornene with trichlorosilane (up to 99% ee). Secondly, selective functionalization of the "lower" Cp ring affords derivatives suited for dendrimer synthesis. Well characterized dendrimers containing up to eight peripheral Josiphos units were used in the Rh-catalyzed hydrogenation of dimethyl itaconate giving ee's up to 98.6%. Finally, the enantioselective Ir-catalyzed addition of aniline to norbornene (up to 95% ee), via N-H activation, was achieved using dinuclear Ir(I) complexes as catalyst precursors.

INTRODUCTION

It has been previously demonstrated that chiral ligands, derived from a 1,2-disubstituted ferrocene constitute one of the most successful class of auxiliaries used in asymmetric catalysis (ref.1). Thus, ligands of the *Josiphos*-type (ref.2) have recently reached the stage of industrial applications. As shown in Scheme 1, a new synthesis of biotin (vitamine H) was developed at LONZA Ltd., involving the use of such ligands in a Rh-catalyzed asymmetric hydrogenation reaction of a fully substituted C-C double bond (ref.3). Moreover, what appears to be the largest-scale industrial application of asymmetric catalysis so far, is an Ir-catalyzed imine reduction that makes use of a ferrocenyl diphosphine for the synthesis of the herbicide (*S*)-Metolachlor at Novartis Ltd. (ref.4).



Scheme 1. Examples of production-scale applications of ferrocenyl diphosphine

The modular synthetic approach to this kind of ligands represents one of their most important and unique features. Indeed, it is possible to readily vary the nature of the two ligating fragments L^1 and L^2 attached to the 1-ferrocenylethyl backbone by a two-step procedure, starting from a common precursor (see Scheme 2).

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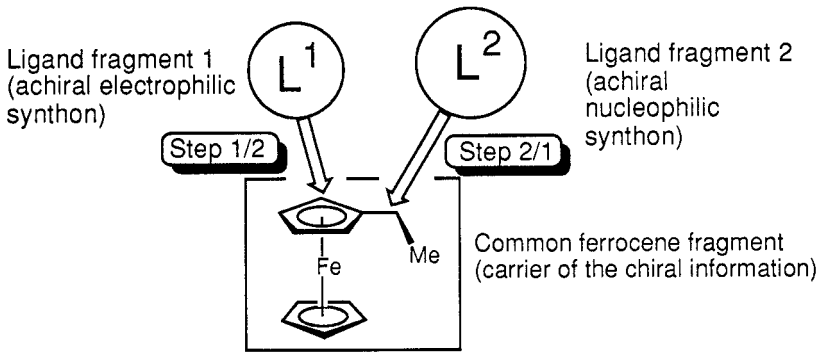
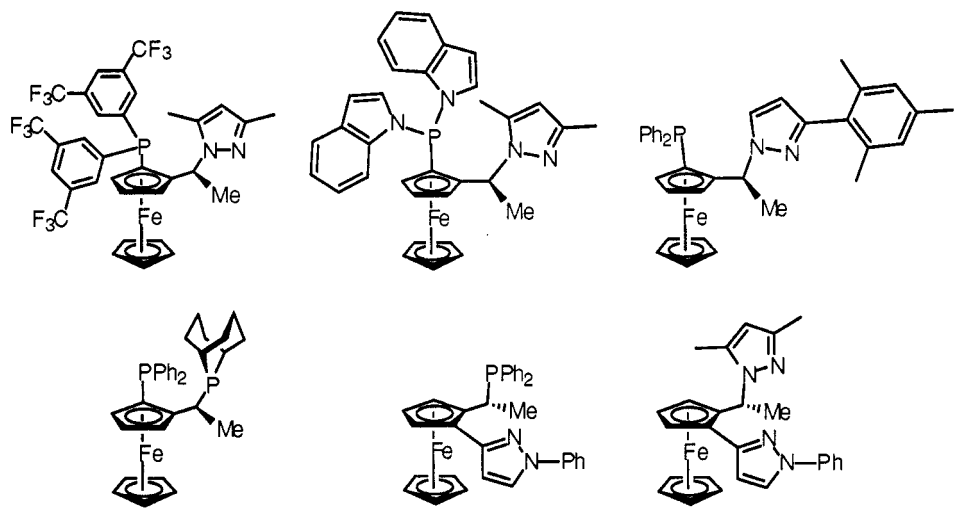
L^1 and L^2 are typically phosphino and/or pyrazolyl fragments. Thus, the opportunity is given to expeditiously fine-tune both the steric and electronic properties of the ligands, according to the needs of a particular reaction, with a particular substrate.



Scheme 2. General strategy for the synthesis of new ferrocenyl ligands bearing two different ligand fragments L^1 and L^2.

Examples of ligands that have been recently prepared following this strategy and that were successfully applied in asymmetric reactions, such as Rh-catalyzed hydroboration of olefins (ref.5), Pd-catalyzed allylic amination (ref.6), hydrosilylation (ref.7), Heck-reactions (ref.8), Ir-catalyzed olefin hydroamination (ref.9), etc., are shown in Scheme 3.



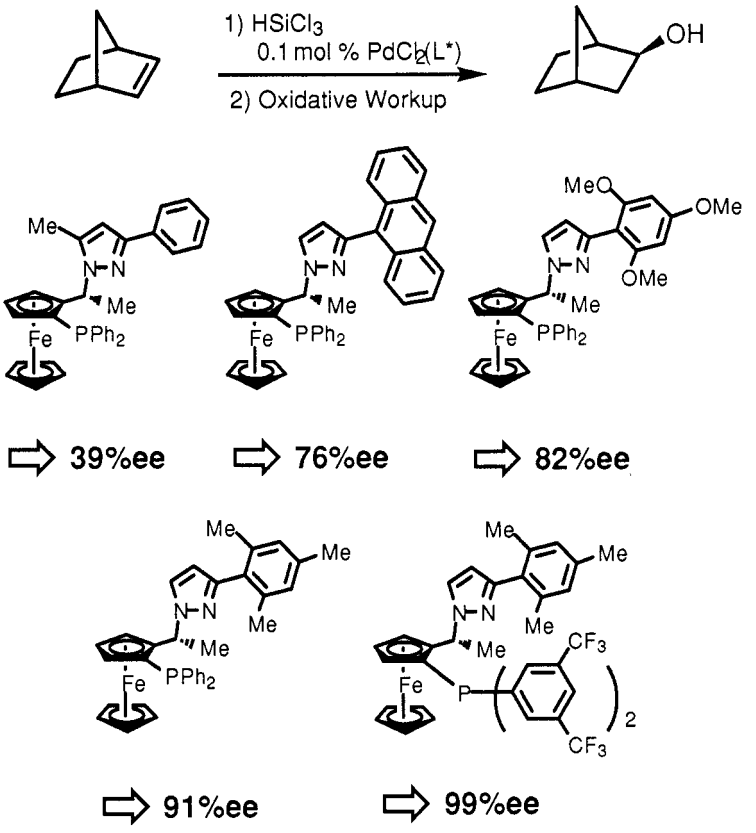
Scheme 3. Examples of ferrocenyl ligands bearing a variety of phosphino- and pyrazolyl fragments.

Pd-CATALYZED HYDROSILYLATION OF OLEFINS

We have previously shown that P,N-ferrocenyl ligands may be easily tuned in both a steric and electronic manner, in order to achieve optimum stereoselectivities. We recently found that such ligands are suitable auxiliaries in the Pd-catalyzed hydrosilylation of olefins with trichlorosilane (ref.10). As shown in Scheme 4, a relatively brief, empirical screening of ligand structures allowed us to achieve an enantioselectivity of 99% ee for the model olefin norbornene.

The representative ligand series of Scheme 4, clearly shows that this particular reaction requires a relatively large substituent at position 3 of the pyrazolyl fragment. In the present case, the best substituent appears to be 2,4,6-trimethylphenyl. Furthermore, the replacement of the unsubstituted phenyls at the phosphorus atom by 3,5-bis(trifluoromethyl)phenyl groups, i.e., by increasing the π-acidity of the phosphine, led to the ligand affording the highest known enantioselectivity for this hydrosilylation. This is an illustration that the steric optimization of the ligand should be followed by a corresponding electronic fine-tuning, best achieved

by the introduction and/or a variation of peripheral substituents, in terms of their electron-withdrawing or donating properties.



Scheme 4. Steric and electronic tuning of P,N-ferrocenyl ligands for the Pd-catalyzed hydrosilylation of norbornene with trichlorosilane.

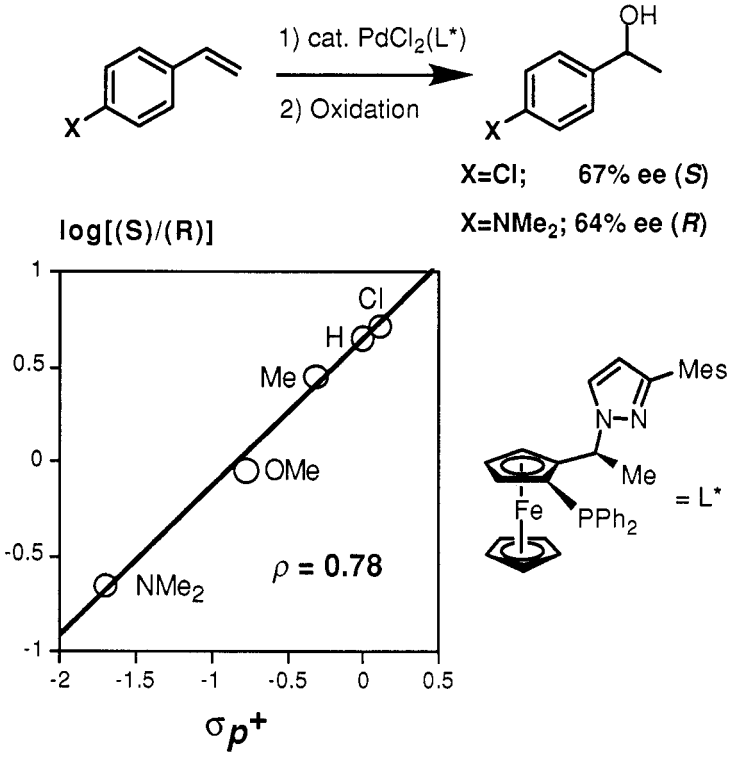
For this Pd-catalyzed hydrosilylation important electronic effects exerted by the substrate olefin have also been observed. As shown in Scheme 5, the *para*-substituents in styrenes were found to affect the enantioselectivity of the reaction in a very important manner. Thus, electron-withdrawing and electron-donating groups, respectively, lead to the formation of opposite product enantiomers. Furthermore, the correlation of log[(*S*)/(*R*)] with σ_p^+ indicates the development of a positive charge in the transition state of the enantio-selectivity-determining step, thus suggesting that after hydride insertion and before the formation of the carbon-silicon bond, the benzyl ligand is coordinated in an η^3 mode (allylic). This is an important piece of information for a reaction for which a detailed mechanistic understanding is still lacking.

THE DEVELOPMENT OF DENDRITIC CATALYST SYSTEMS.

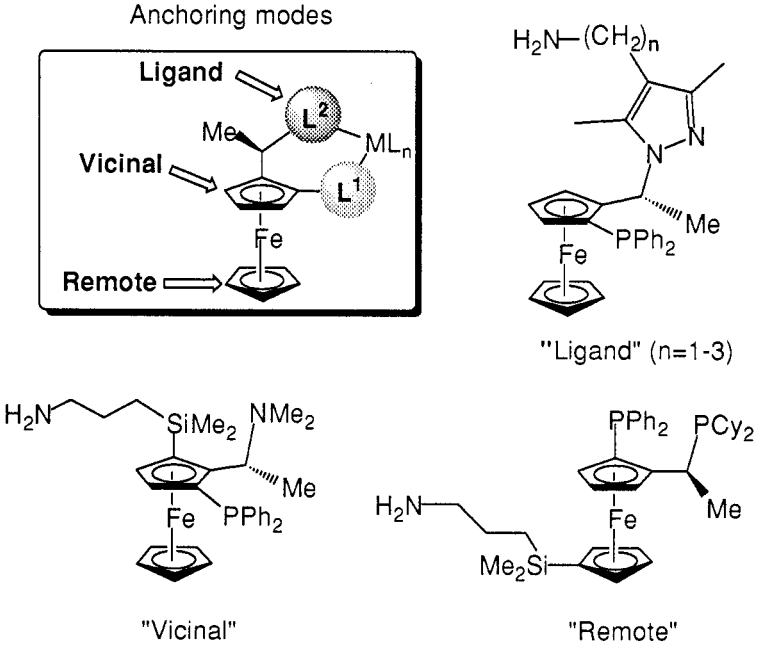
Because of the proven efficacy of chiral ferrocenyl ligands in a number of asymmetric reactions, we set up a study aimed at creating dendrimers which carry catalytically active units at their periphery (ref.11). Thus, combining several, otherwise independent catalysts into one single nanoscopic particle, several advantages related to the properties of such macromolecules could be envisaged. Catalytically active dendrimers, in particular if they contain cationic transition metal complexes should be less soluble than their monomeric counterpart. Recovery by selective precipitation may thus be an opportunity. Furthermore, due to their size, these materials are amenable to ultrafiltration methods (membrane reactor).

For the incorporation of ferrocenyl ligands into dendritic structures a functionalization is required. The choice of the point of attachment of the spacer on the ferrocenyl ligand molecule is of great potential importance. From a synthetic point of view, different anchoring points may entail different, more or less complex synthetic routes. From a structural point of view, location and length of the spacer may influence

catalyst performance, by virtue of intramolecular interactions. Scheme 6 illustrates this general idea and gives the structure of the currently used intermediates according to their anchoring strategy.

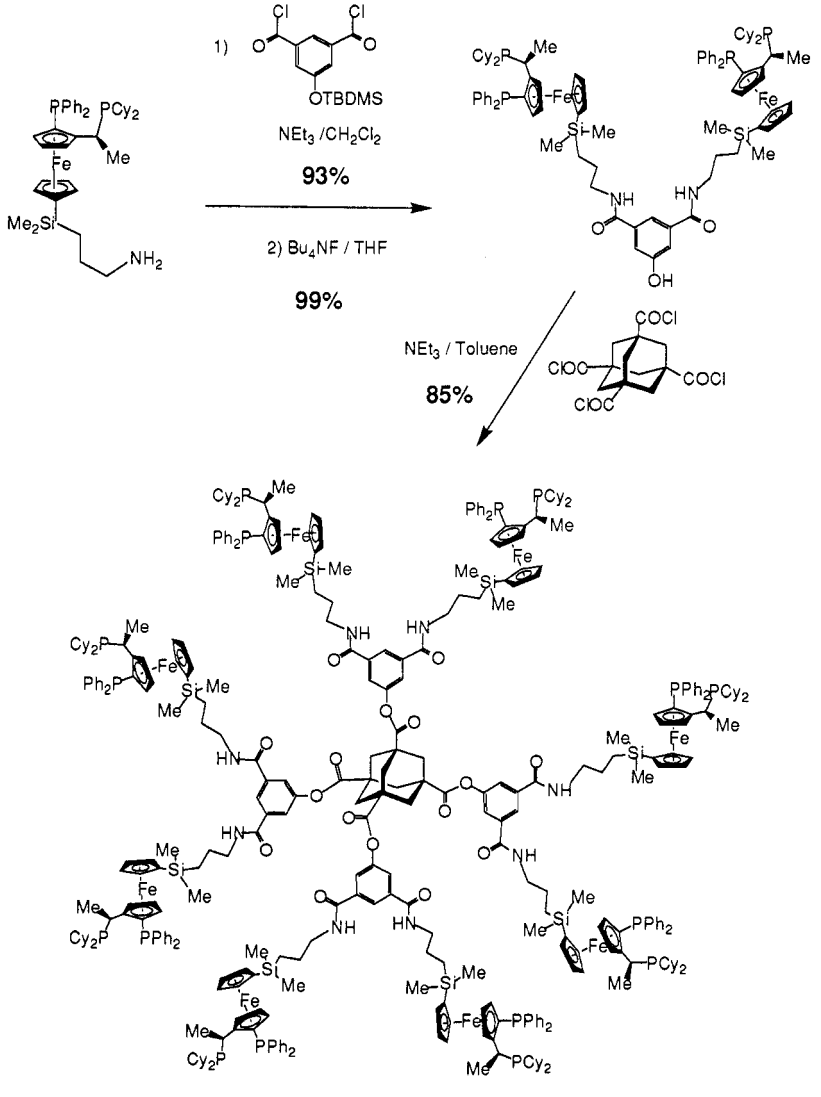


Scheme 5. Linear free-energy relationship for the hydrosilylation of *p*-substituted styrenes



Scheme 6. Illustration of the different anchoring modes for ferrocenyl ligands to dendrimers. The three specific compounds shown are currently being used for the synthesis of G0, G1, and G2 dendrimers.

The derivatives depicted in Scheme 6 are accessible in three, four, and six steps, respectively, from the common, enantiomerically pure starting material (*R* or *S*)-N,N-dimethyl-1-ferrocenyl ethylamine in moderate to good overall yields. The remote anchoring mode intuitively appears to be the best suited because of the minimized intramolecular steric interactions between ligand fragments and linker. Thus, using the corresponding intermediate the so far largest dendrimers of this type containing six or eight Josiphos units has been prepared, as illustrated in Scheme 7, in good yields and in gram quantities. The core of the dendrimers is constituted in these two cases by a 1,3,5-trisubstituted benzene ring and by a 1,3,5,7-tetrasubstituted adamantane, respectively. By way of example, the discussion shall be focussed on these two derivatives only. As one would expect, in the ^{31}P NMR spectra only one pair of doublets is observed, with the typical long range $^{4}J_{PP}$ coupling constant of ca. 34 to 37 Hz. This indicates the equivalence of the ferrocenyl units. However, broad signals in the ^{1}H NMR 300 MHz spectra are observed at room temperature, possibly indicating slow conformational equilibria in the sterically rather crowded inner core of the dendrimers.



Scheme 7. Typical convergent synthesis of Josiphos-containing dendrimer.

Nonetheless, well resolved spectra for these two compounds are obtained when corresponding DMSO-d_6 solutions are measured at 80°C and 120°C, respectively. The new high-molecular-weight compounds were also characterized by MALDI-TOF mass spectrometry. Molecular peaks at m/z values in very good agreement with the calculated ones, as well as in-source fragmentation (ref.12) patterns very similar to those

of the „monomeric" counterpart Josiphos under EI conditions were observed. Sections of such MALDI-TOF spectra are illustrated in Figure 1.

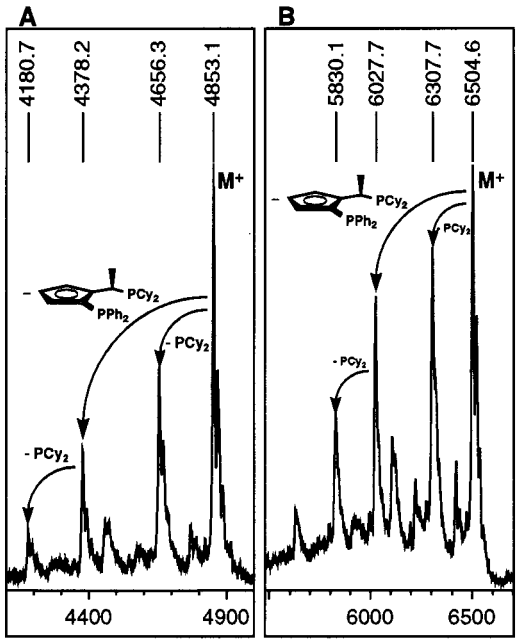


Fig. 1 Sections of the MALDI-TOF mass spectra of dendrimers containing six (A) and eight (B) Josiphios units, showing typical in-source fragmentation patterns (calculated molecular mass = 4853.15 and 6502.95, respectively).

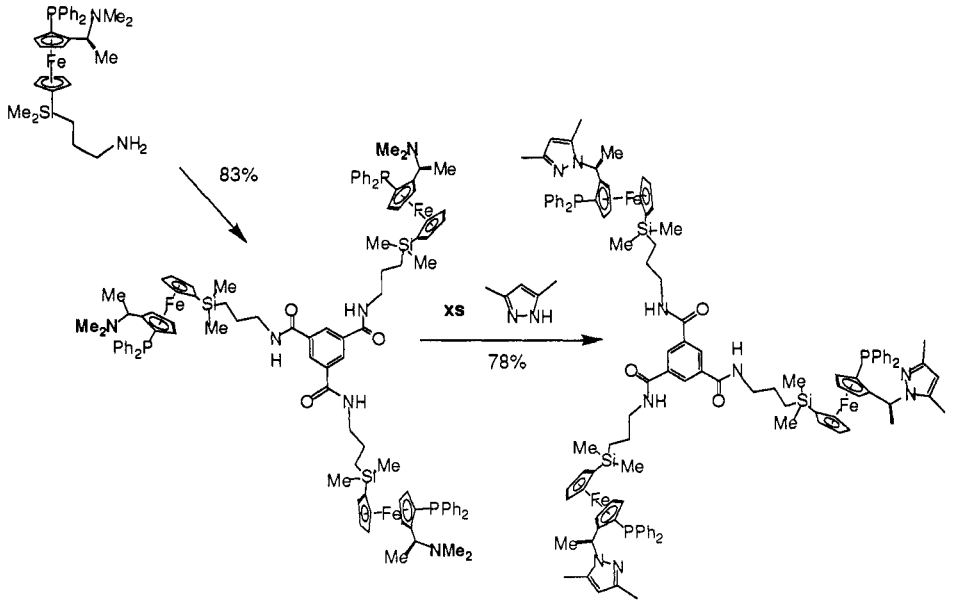
In order to gain insight as to the behavior of the new dendritic ligands in catalytic reactions, the simple Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate in MeOH was chosen as a standard reaction for comparing their performances. In situ catalyst preparation was attained by mixing the ligand (1 eq / number of ferrocenyl units) with 1 eq of $[Rh(COD)_2]BF_4$ in CH_2Cl_2 and stirring for 15 min under Ar. The orange solid obtained after evaporation of the solvent was used as a catalyst precursor. ^{31}P NMR spectra of these materials showed a single AMX spin-system, as expected when all ferrocenyl sites are bonded to Rh. Hydrogenation experiments performed using 1 mol% Rh under 1 bar of hydrogen pressure, as previously reported(ref.2a), gave very similar results. In all cases hydrogen take-up ceased after ca. 20 min, and substrate was no longer detectable. The enantioselectivities afforded by the dendritic catalysts (between 98.0% ee and 98.6% ee) are only slightly lower than that obtained using the corresponding mononuclear Josiphos catalyst (99.0% ee). However, a weak trend to lower enantioselectivities seems to parallel the increasing size of the dendritic ligands.

The synthetic strategy illustrated in Scheme 7 implies an intrinsic limitation, since it starts from the complete functionalized ligand Josiphos. For a wider scope of application, one would like to modify the ligand fragments according to the needs of a specific reaction. From this point of view it is desirable to complete the ligand synthesis *after* assembling the dendrimer. Thus, a PPFA derivative, still containing a dimethylamino group amenable to nucleophilic substitution reactions (Scheme 6) , has been prepared and incorporated into a G0 dendrimer. In order to test the possibility of a multiple functionalization, the preparation of a P,N-ligand system has been achieved in the last syntetic step, as (Scheme 8). We are currently exploiting compounds of the type shown in Scheme 8, however of higher dendrimer generation for the preparation of ligands having different combinations of donor fragments (both P,P and P,N).

THE DEVELOPMENT OF CATALYTIC ASYMMETRIC HYDROAMINATION OF OLEFINS

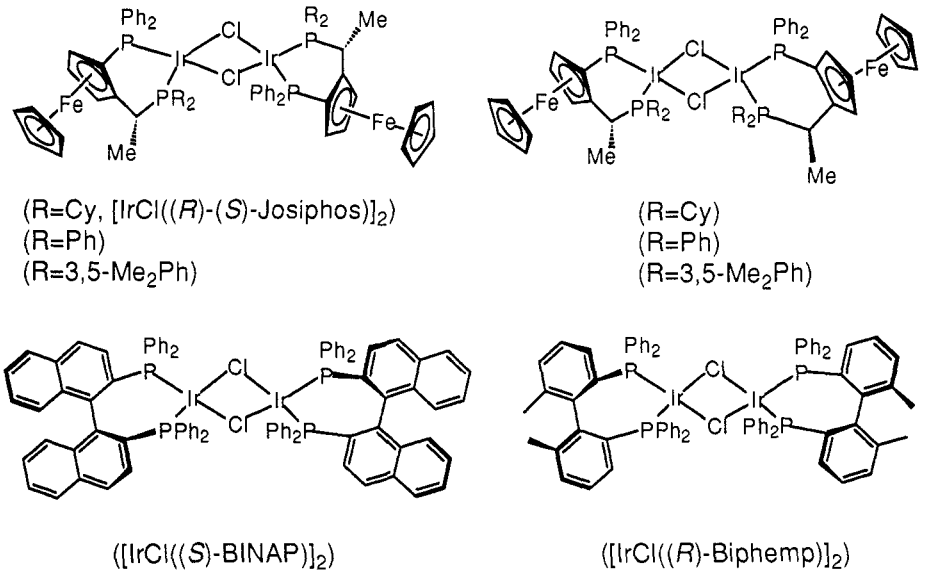
Despite its synthetic potential and practical relevance, the asymmetric catalytic olefin hydroamination is still an undeveloped reaction. Indeed, besides the lanthanide-catalyzed enantioselective olefin hydroamination / cyclization reported by Marks and co-workers (ref.13), to the best of our knowledge no intermolecular version of this reaction is known. So far, transition metal catalysts for the intermolecular hydroamination of unactivated olefins hardly afford turnover numbers of more than ca. 0.08 h^{-1} at 1 atm and medium

temperature (ref.14). Organo-f-element complexes are able to catalyze the same reaction of unactivated olefins, such as 1-pentene, at a rate of up to N_t 0.4 h^{-1} at 60°C (ref.13b).



Scheme 8. Multiple functionalization of a G0 dendrimer as the final step in the preparation of a P,N-ligand.

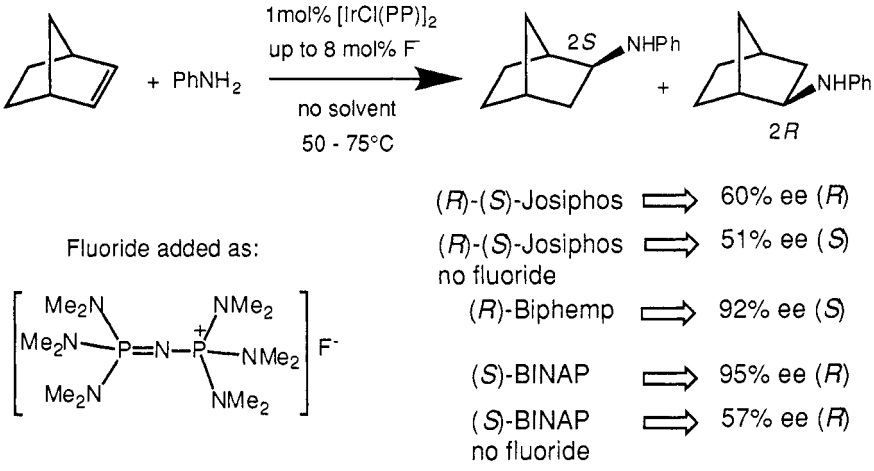
The feasibility of catalytic hydroamination via N-H activation has been demonstrated previously (ref.14a). In particular, it was shown that the electron-rich Ir complex $[Ir(PEt_3)_2(C_2H_4)Cl]$ cleanly oxidatively adds aniline. The Ir(III) hydrido amido species thus formed undergoes insertion of norbornene leading to a well characterized complex containing a chelating alkylamino ligand, from which the amination product is released upon reductive elimination. However, this system did not afford more than up to six turnovers in catalytic experiments, in the presence of apparently beneficial Lewis acids such as $ZnCl_2$.



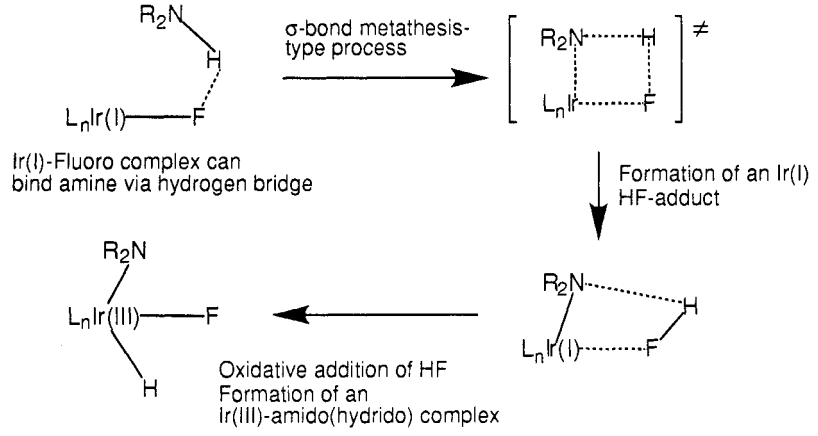
Scheme 9. The new dinuclear Ir(I) complexes used as catalyst precursors in the asymmetric addition of aniline to norbornene.

We found that $[IrCl(C_2H_4)_4]$, or $[IrCl(COE)_2]_2$ smoothly reacts with Josiphos-type ligands and with the axial chiral auxiliaries BINAP and Biphemp, respectively, in toluene solution, affording in good yields the new dinuclear derivatives shown in Scheme 9. The ferrocenyl derivatives were isolated as an inseparable mixture of cis/trans isomers (ref.9).

The complexes shown in Scheme 9 were used as catalyst precursors in the model hydroamination of norbornene with aniline. The reactions were performed without solvent and with a catalyst concentration of 1 or 2 mol% Ir. First experiments, performed with the (*R*)-(*S*)-Josiphos complexes at 50°C, have shown the clean but slow formation of exo-(2-phenylamino)norbornane in 51% ee (2*S*), accompanied by traces of the corresponding endo-isomer (ca. 15% conversion in 3d). We reasoned that the good π-donating properties of fluoride as a ligand, together with its tendency to form hydrogen bridges, could enhance the propensity towards N-H oxidative addition. However, we were not able so far to prepare the fluoro analogues of any of the complexes used as catalysts precursors. Nevertheless, both activity and enantioselectivity benefited from the addition of co-catalytic amounts of „naked" fluoride, added as a benzene solution of phosphazenium-fluoride-P2. For all catalysts used the addition of fluoride (0.5 to 4 eq per Ir) led to both an increase of activity and significantly higher enantioselectivity. Under the cocatalytic activity of fluoride it was possible to obtain the so far highest enantioselectivities for this kind of transformation, using BINAP as chiral ligand. A selection of results is shown in Scheme 10.



Scheme 10. Some examples of asymmetric Ir-catalyzed addition of aniline to norbornene using different chiral ligands, and with and without cocatalytic fluoride.



Scheme 11. A speculative role of fluoride in the Ir-catalyzed hydroamination of olefins, postulating the formation of reactive Ir fluoride complexes.

Due to the high basicity of the „naked" fluoride anion, anilide could be produced by deprotonation of aniline. It has been shown that addition of LiNHPh is necessary to promote the condensation of aniline with

norbornene when a rhodium catalyst is used (ref.14b,c). However, when one eq of LiNHPh per Ir was added to the catalyst, instead of fluoride, all the activity was lost. Furthermore, anilido-bridged Ir(I) complexes were prepared and characterized and shown not to posses any catalytic activity (ref.15). From these experiments we conclude that fluoride is likely to behave as a ligand, replacing chloride in the coordination sphere of Ir. The precise role of fluoride in enhancing both activity and selectivity is so far still a matter of speculation. Given that this anion is acting as a ligand, the formation of a hydrogen bridge to aniline would contribute in activating the N-H bond and at the same time in predetermining the relative orientation of the aniline molecule in the coordination sphere of Iridium. A schematic representation of the possible elementary processes leading to the formation of Ir(III) complexes containing fluoro, hydrido, and amido ligands is shown in Scheme 11. At the Ir(III) stage and after olefin insertion into the Ir-N bond, the lability of the fluoro ligand and hence the rapid dissociation of F^- could accelerate the final step in the catalytic cycle, i.e., the reductive elimination of the product.

CONCLUSION

We have shown that chiral ferrocenyl ligands derived from 1,2-disubstituted ferrocenens, by virtue of their modular synthetic approach, may be adapted successfully to several types of transition-metal catalyzed asymmetric reactions, thus affording very high stereoselectivities. Moreover, the possibility to further functionalize such ligands offers the opportunity to incorporate them into dendritic structures. The development of the asymmetric hydroamination of olefins, still very much in its infancy, has shown how important the effect of additives may be. In particular, fluoride is an anion whose possible role in catalytic processes has rather been neglected so far.

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