Pure Appl. Chem., Vol. 71, No. 8, pp. 1531–1537, 1999.
Printed in Great Britain.

Recent studies in asymmetric catalysis using ferrocenyl ligands*

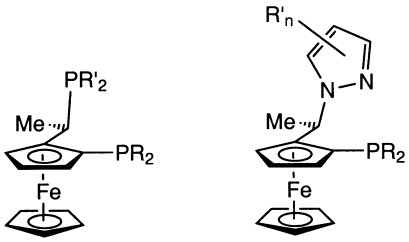
Antonio Togni,† Nikolaus Bieler, Urs Burckhardt, Christoph Köllner, Giorgio Pioda, Raoul Schneider and Anita Schnyder

Laboratory of Inorganic Chemistry, Swiss Federal Institute of Technology, ETH Zentrum, CH-80092, Zürich, Switzerland

Abstract: Chiral bidentate ferrocenyl ligands have been fined-tuned in terms of their steric and electronic properties, and thus adapted to a variety of reactions catalyzed by transition metals. The position of the two ligating units (two different PR_2 groups, two pyrazolyl, or a combination thereof) attached to the ferrocenylethyl fragment may be interchanged. A comparison of P,N-ligands with their corresponding inversed (N,P) counterpart is presented for the Pd-catalyzed allylic amination. Dendrimers containing Josiphos-type ligands up to the third generation have been prepared and used in e.g. Rh-catalyzed hydrogenation reactions. The intramolecular Ir-catalyzed hydroamination reaction has been found to require an acidic N–H functionality and the presence of co-catalytic amounts of base. Olefin isomerization was found to be an important competing side-reaction. Kinetic/mechanistic studies of the Pd-catalyzed hydrosilylation of styrenes have been carried out.

INTRODUCTION

We have previously shown that chiral ferrocenyl ligands of the types **1** and **2** may be successfully applied to a variety of asymmetric catalytic reactions [1]. By virtue of the modular synthetic access to these ligands, it is possible to prepare a variety of derivatives having in common the basic ferrocenyl-diphosphine or phosphine/pyrazole structural unit. Although these ligands have not been prepared utilizing the techniques of combinatorial chemistry, it is nevertheless appropriate to refer to the total number of compounds that are available in our laboratories as to a ligand library (Scheme 1).



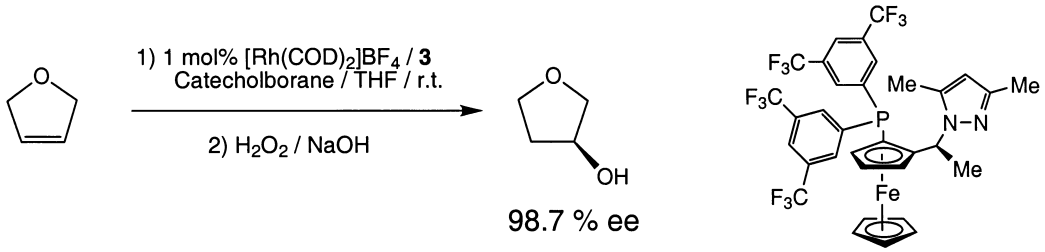
1 **2**

Scheme 1

* Lecture presented at the 10th IUPAC Symposium on Organo-Metallic Chemistry Directed Towards Organic Synthesis (OMCOS 10), Versailles, France, 18–22 July 1999, pp. 1381–1547.

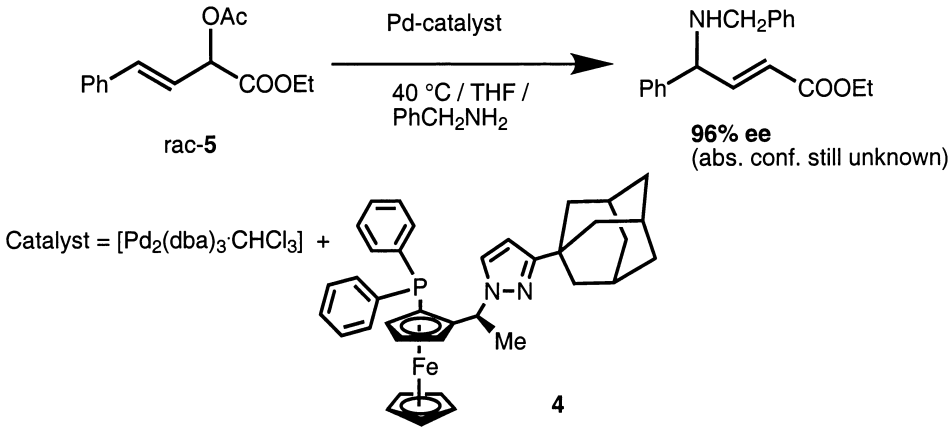
† *Corresponding author:* E-mail: togni@inorg.chem.ethz.ch

The opportunity to easily tune the steric and/or electronic properties of these ligands constitute one of the advantages inherent with this class of chiral compounds. Thus, variations of the nature of peripheral substituents, not significantly influencing the overall ligand and complex conformation, have been demonstrated to be a tool for the optimization of a particular ligand with respect to a selected reaction. We have reported previously the implementation of this principle in the case of Rh-catalyzed hydroboration of styrenes (electronic tuning) [2], Pd-catalyzed allylic amination (steric tuning) [3], and Pd-catalyzed hydrosilylation (both steric and electronic tuning) [4]. In the former case the best ligand for the model reaction of styrene with catecholborane was found to be derivative **3**, affording very high enantioselectivities. The same ligand could then be used in catayltic reactions with further, synthetically more interesting substrates, such as, e.g. 2,5-dihydrofuran. The corresponding hydroboration followed by oxidative workup gave 3-hydroxy-THF in 98.7% enantiomer excess, as shown in Scheme 2 [5]. Similarly, ligand optimization for the allylic amination of the very common substrate 1,3-diphenylallyl-ethyl carbonate with benzylamine led to the identification of **4** as one of the best possible ligands for the unsymmetrical functionalized allylic substrate **5** shown in Scheme 3, and leading to an insaturated γ-amino acid derivative [6].



3

Scheme 2 Highly enantioselective hydroboration of 2,5-dihydrofuran with catecholborane using ligand **3**.



rac-**5**

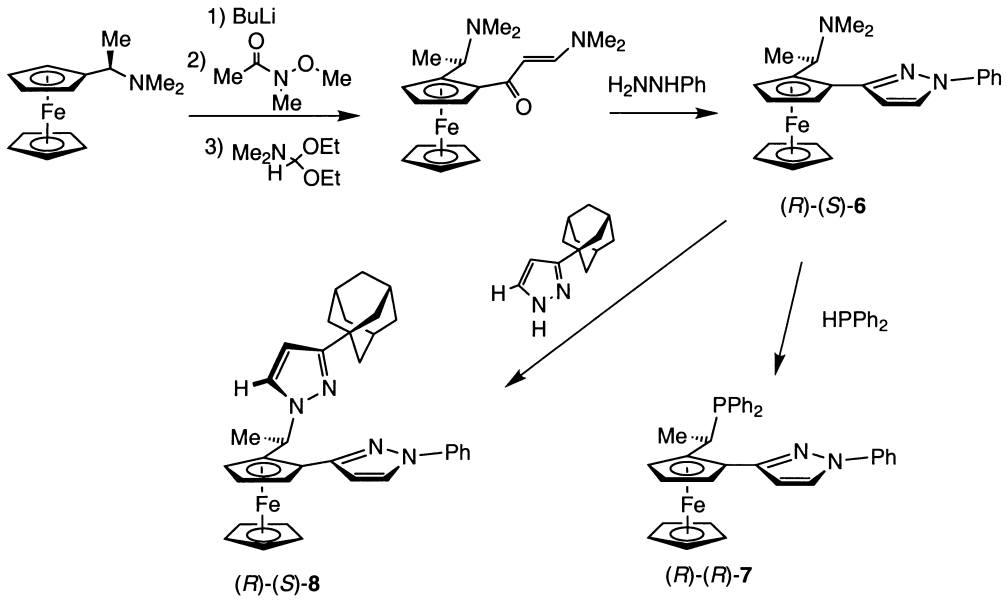
4

Scheme 3 Synthesis of an insaturated γ-amino acid derivative by Pd-catalyzed allylic amination.

NEW N,P- AND N,N-LIGANDS

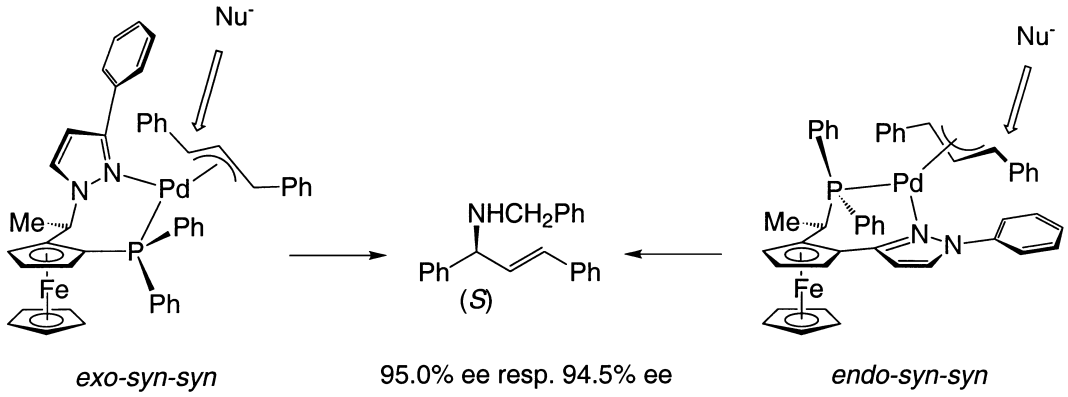
Because of the inherent electronic bias of chelating P,N-ligands, strongly influencing, e.g, the site of nucleophilic attack onto corresponding Pd(II)-π-allyl complexes [7], it was of interest to prepare and investigate new auxiliaries related to those of type **2** in which the relative phosphine/pyrazole position is inversed. Thus, precursor **6** was prepared from Ugi's amine in three steps and used for the synthesis of the inversed P,N-ligand **7** and the N,N-system **8**, as illustrated in Scheme 4 [8].

When used in the Pd-catalyzed amination of 1,3-diphenylallyl ethyl carbonate with benzylamine, ligand (*R*)-(*R*)-**7** afforded the product in 94.5% enantiomer excess, practically the same value given by its isomer of type (*R*)-(*S*)-**2** (95% enantiomer excess). Moreover, the sense of induction (*S*-product) was in the two cases the same. A 2D-NMR study of the corresponding intermediate π-(1,3-diphenylallyl)



Scheme 4 Synthesis of new 'inversed' P,N- and N,N-ligands.

complexes revealed that the major diastereomeric forms display opposite allyl configuration, as shown in Scheme 5. Since nucleophilic attack occurs preferentially *trans* to phosphorus, it is obvious that the same enantiomer is formed.



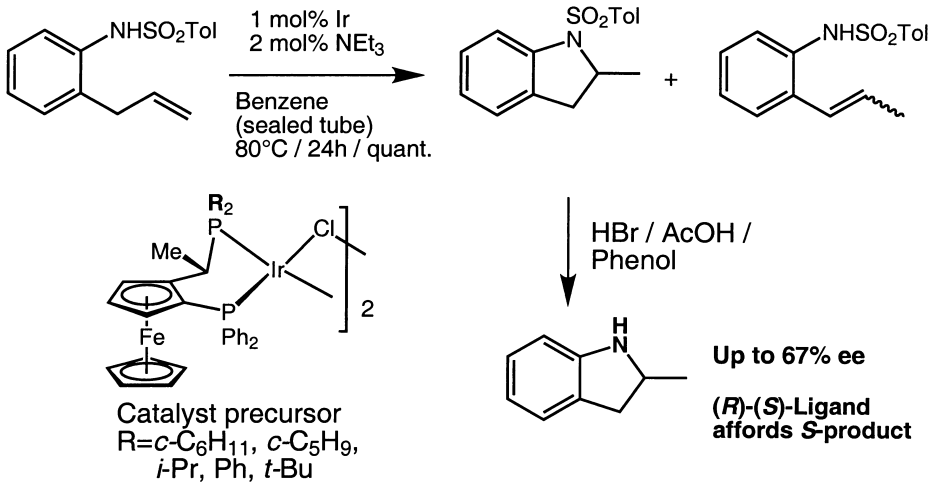
Scheme 5 Different allyl configuration of major diastereoisomeric intermediate lead to product of same configuration.

Ligand **8** was found to form very unstable complexes and could not be used in catalytic reactions. A possible reason for the instability of, e.g. Pd-allyl complexes could be the larger chelate ring size (eight-membered), as compared to complexes containing ligands of type **1**, **2** or **7**. On the other hand, precursor **6**, an sp^3-N/sp^2-N-system, gave an active and quite enantioselective catalyst for the allylic alkylation with dimethylmalonate (93.8% enantiomer excess in the case of the diphenylallyl substrate).

IRIDIUM-CATALYZED HYDROAMINATION

In contrast to the previously reported Ir-catalyzed addition of aniline to norbornene that requires the presence of a co-catalytic amount of fluoride to ensure high enantioselectivity and higher activity [9], the intramolecular hydroamination of 2-(propen-3-yl)aniline turned out to be surprisingly difficult. Conversion to the cyclic product occurs only when the amine is activated by a sulfonyl group and a base (typically triethylamine) is added as a co-catalyst. Competitive olefin isomerization to the corresponding 2-(propen-1-yl)

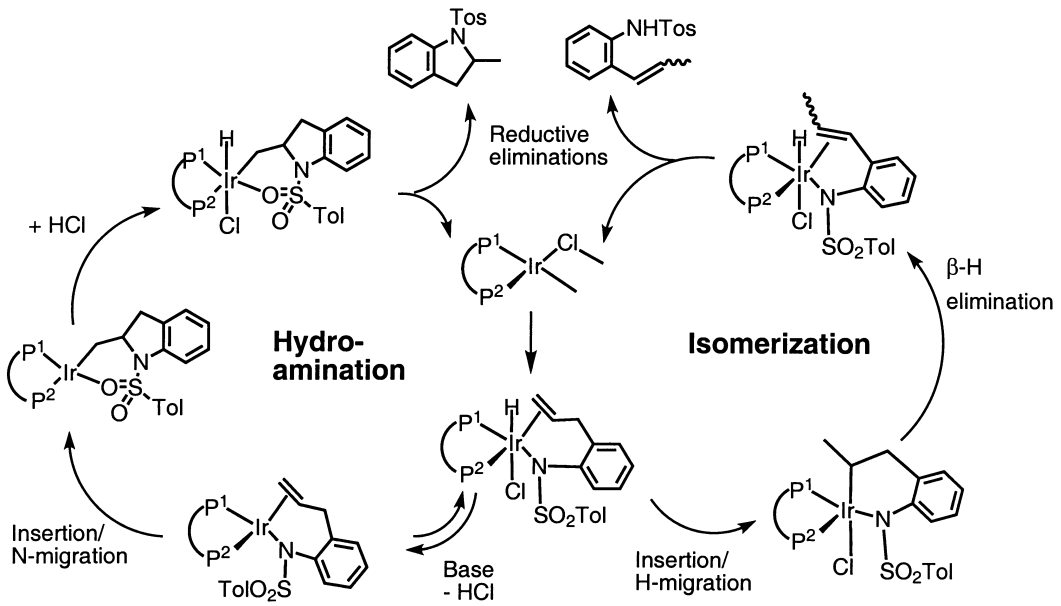
derivative, unreactive toward hydroamination, constitutes however, still the major reaction path. Thus, the hydroamination product is obtained in only up to 40% yield and 67% enantiomer excess, depending on the reaction conditions and the ligand used. The highest selectivity is obtained with Josiphos (see Scheme 6) [10].



Scheme 6 Ir-catalyzed asymmetric intramolecular hydroamination of an activated aniline derivative.

After cleavage of the sulfonyl activating group, 2-methyl indoline is obtained. An enantiomerically pure sample of the major enantiomer of absolute configuration *S* was obtained upon formation of a salt using *S*-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate, as previously reported [9]. An X-ray crystallographic study of this salt allowed to establish the absolute configuration of the product.

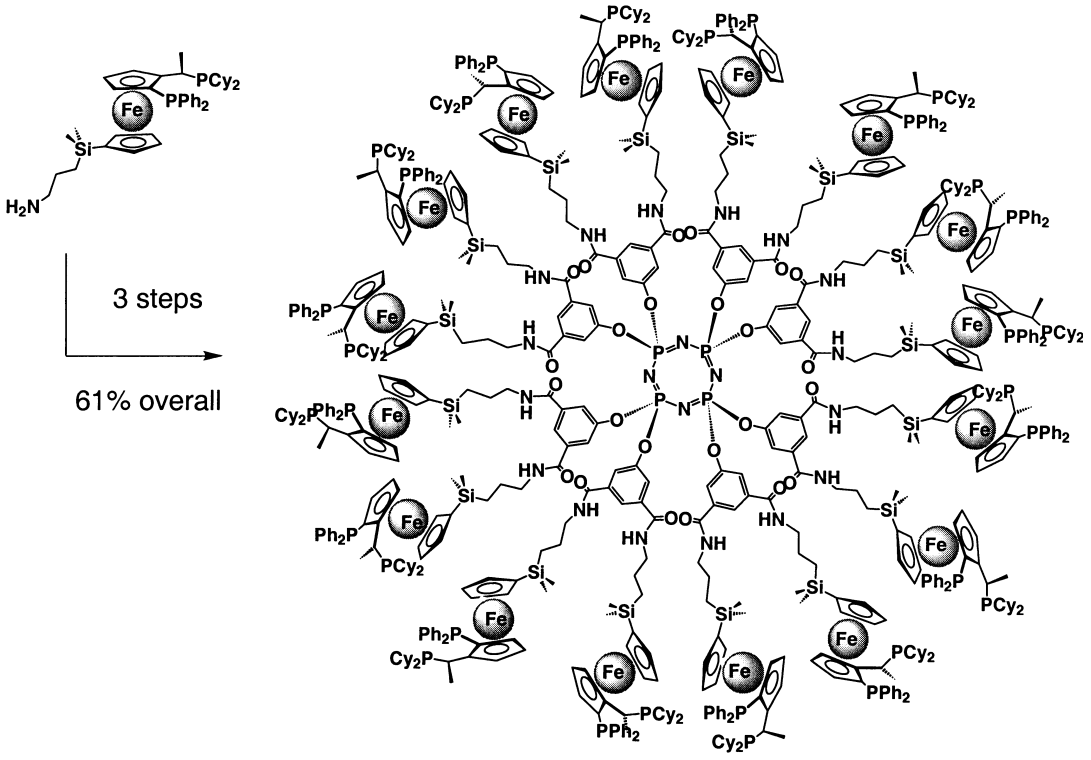
A tentative mechanistic picture of this particular hydroamination reaction, taking into account the possible role of the added base, is shown in Scheme 7. After addition of the substrate, the Ir(III) amido-hydrido complex thus formed may undergo olefin hydride insertion equilibria leading to isomerization. Base-induced reductive elimination of HCl, on the other hand, triggers the hydroamination pathway.



Scheme 7 Postulated mechanism for the intramolecular hydroamination and competing olefin isomerization.

DENDRIMERS CONTAINING PERIPHERAL FERROCENYL LIGANDS

As recently reported from our laboratory [11] ferrocenyl ligands of the Josiphos type could be successfully attached to the periphery of dendrimers following a convergent approach. It has been found that such macromolecules, when used in catalytic reactions, do not show relevant differences in terms of stereoselectivity and catalytic activity, as compared to their monomeric congeners. More recent work has been directed toward the synthesis of larger macromolecules (up to the third generation) containing up to 24 Josiphos units and the use of cyclophosphazene-type dendrimer cores. An example of such dendrimers is shown in Scheme 8 [12]. The N_4P_4-cyclophosphazene core (accessible from $N_4P_4Cl_8$, [13] offers more branching points, as compared to more commonly used internal fragments, such as trisubstituted benzene-, or tetrasubstituted adamantane fragments. This means that for an equal number of synthetic steps, dendrimers containing a higher number of ligand units may be obtained. Furthermore, because of the higher internal branching, dendritic particles approaching a spherical shape may be obtained with a lower number of generations. Although the N_3P_3-cyclophosphazene core has been used previously in dendrimer chemistry [14], to the best of our knowledge it does not appear that the next larger oligomeric phosphazene N_4P_4 has been exploited before.

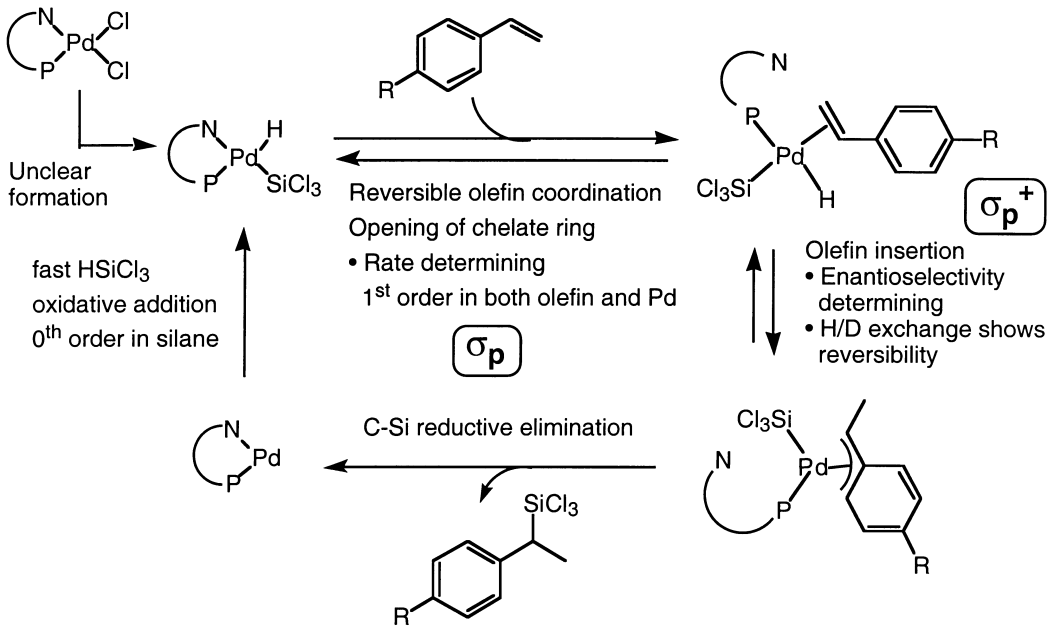


Scheme 8 Synthesis of a G2-dendrimer with 16 peripheral Josiphos units based on a cyclophosphazene core (MW = 12654.5).

PALLADIUM-CATALYZED HYDROSILYLATION OF OLEFINS

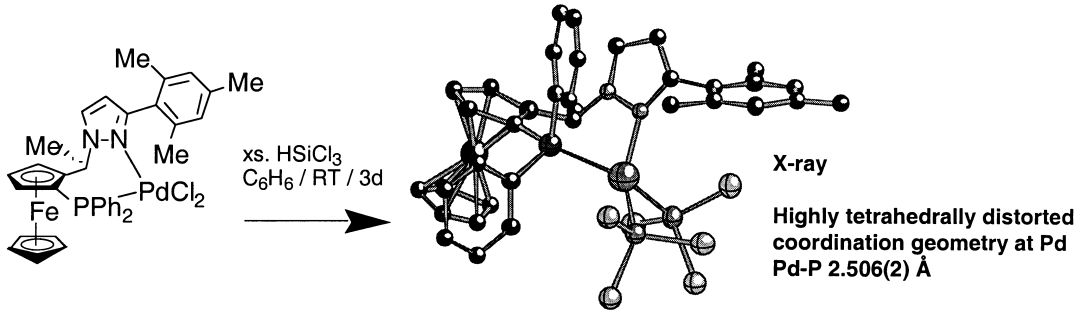
We have previously shown that P,N-ligands of type **2** afford very high enantioselectivity in the addition of trichlorosilane to norbornene [4]. In continuation of these studies, we performed kinetic/mechanistic investigations, coupled to DFT-calculations [15] for the corresponding reaction of *para*-substituted styrenes. A notable feature resulting from these studies is that dissociation of the nitrogen ligand is very much likely a decisive step in the catalytic cycle. A summary of the mechanistic results so far obtained is presented in Scheme 9 [16].

Finally, it is worth mentioning that the catalyst precursor [Pd(P,N-ligand)Cl_2], when exposed to an excess of trichlorosilane in benzene forms quantitatively the corresponding bis(trichlorosilyl) derivative



Scheme 9 Proposed mechanism of the asymmetric Pd-catalyzed hydrosilylation of styrenes based on kinetic investigations.

[17]. The crystal structure of such a rare complex reveals a dramatic distortion of the expected square-planar geometry at Palladium, as well as an extremely long Pd–P bond (Scheme 10).



Scheme 10 Preparation and structure of a Pd bis(trichlorosilyl) complex.

CONCLUSION

We have shown that ferrocenyl ligands are remarkably versatile from a synthetic point of view and that they find a variety of applications. In the Pd-catalyzed allylic amination phosphine/pyrazole ligands of type **2** and their isomeric 'inversed' congeners such as **7** afford a very similar high enantioselectivity and the same sense of asymmetric induction, by virtue of the same topicity of the intermediate π-allyl complexes. The asymmetric Ir-catalyzed hydroamination of olefins remains a major challenge and the effect of co-catalysts is extremely important. For the preparation of recoverable dendritic catalyst the choice of the central fragment may significantly reduce the number of both synthetic steps and generations for a given number of peripheral units.

REFERENCES

1 (a) A. Togni. In *Metallocenes. Synthesis, Reactivity, Applications* (A. Togni, R.L. Halterman, eds), pp. 685–721. Wiley-VCH Weinheim, New York (1998), and references cited therein. (b) A. Togni, R. Dorta, C. Köllner, G. Pioda. *Pure Appl. Chem.* **70**, 1477 (1998).

2 (a) A. Schnyder, L. Hintermann, A. Togni. *Angew. Chem.* **107**, 996 (1995); *Angew. Chem. Int. Ed. Engl.* **34**, 931 (1995). (b) A. Schnyder, A. Togni, U. Wiesli. *Organometallics* **15**, 255 (1996).

3 (a) A. Togni, U. Burckhardt, V. Gramlich, P. S. Pregosin, R. Salzmann. *J. Am. Chem. Soc.* **118**, 1031 (1996). (b) U. Burckhardt, V. Gramlich, P. Hofmann, R. Nesper, P. S. Pregosin, R. Salzmann, A. Togni. *Organometallics* **15**, 3496 (1996).

4 G. Pioda, A. Togni. *Tetrahedron: Asymmetry* **9**, 3903 (1998).

5 A. Schnyder, S. Chaloupka, O. Werbitzky, A. Togni. Unpublished results.

6 U. Burckhardt. PhD Thesis no. 12267. ETH-Zürich (1997).

7 P. E. Blöchl, A. Togni. *Organometallics* **15**, 4125 (1996).

8 U. Burckhardt, D. Drommi, A. Togni. *Inorg. Chim. Acta* **296**, 183 (1999).

9 R. Dorta, P. Egli, F. Zürcher, A. Togni. *J. Am. Chem. Soc.* **119**, 10857 (1997).

10 N. Bieler, A. Togni. To be published.

11 C. Köllner, B. Pugin, A. Togni. *J. Am. Chem. Soc.* **120**, 10274 (1998).

12 R. Schneider, C. Köllner, I. Weber, A. Togni. *J. Chem. Soc. Chem. Commun.* 2415 (1999).

13 L. G. Lund, N. L. Paddock, J. E. Proctor, H. T. Searle. *J. Chem. Soc.* 2542 (1960).

14 See J.-P- Majoral, A.-M. Caminade. *Chem. Rev.* **99**, 845 (1999).

15 T. Woo, U. Röthlisberger, G. Pioda, A. Togni. To be published.

16 G. Pioda, A. Togni. To be published.

17 For a review on silyl complexes, see: J. Y. Corey, J. Braddock-Wilking. *Chem. Rev.* **99**, 175 (1999).