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Phosphinoferrocene carboxamides

Komise pro obhajoby doktorských disertací v oboru Anorganická chemie

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Acknowledgements

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Contents

Résumé

Amidation reactions of 1'-(diphenylphosphino)ferrocene-1-carboxylic acids with functional amines open access to a range of specific class of hybrid donors combining soft phosphine moiety with changeable amide substituents. Analogous donors of this type are accessible in a formally inverted manner, via reactions of [1'-(diphenylphosphino)ferrocenyl]methylamine with acids or isocyanates. Phosphinoferrocene amides can be utilised as synthetic building blocks and versatile ligands for coordination chemistry and catalysis. The latter applications particularly benefit from modular structures of these donors that allow the design and synthesis of extensive ligand libraries and, hence, fine tuning of the ligands' properties with respect to their use. Importantly, phosphinoferrocene donors can easily be made chiral either from chiral ferrocene precursors or *via* a covalently attached chiral pendant. The structurally defined amide linking group endows phosphinoferrocene amides with an ability to form hydrogen bonding and, consequently, defined supramolecular assemblies in the solid state. It can also be used to attach a phosphinoferrocene moiety onto a larger molecular scaffold and create multi-donor arrays.

Shrnutí

Amidační reakce 1’-(difenylfosfino)ferrocen-1-karboxylové kyseliny s různými funkčními aminy otevírají cestu k celé řadě specifických hybridních donorů, jež ve svých molekulách kombinují měkké fosfinové donorové skupiny s široce proměnnými amidovými substituenty. Typově obdobné donory lze získat přístupné také formálně inverzním přístupem, tj. reakcemi [1’-(difenylfosfino)ferrocenyl]methylaminu s kyselinami nebo izokyanáty. Fosfinoferrocenové amidy mohou být použity jako výchozí látky pro další syntézu a také jako všestranné ligandy pro využití v koordinační chemii a katalýze. Zvláště dvě posledně jmenované aplikace mohou těžit z modulárních struktur těchto donorů, které umožňují prakticky neomezenou variaci jejich struktur a přípravu rozsáhlých knihoven sloučenin a potažmo i optimalizaci jejich struktur vzhledem k danému využití. Fosfinoferrocenové donory lze poměrně snadno připravit v chirální podobě – ať reakcemi chirálních ferrocenových prekurzorů či připojením chirálního motivu. Strukturně dobře definovaná amidová skupina umožňuje tvorbu vodíkových vazeb a tím i definovaných supramolekulárních uspořádání fosfinoferrocenových amidů v pevném stavu. Může být rovněž využita k připojení fosfinoferrocenových jednotek k jiným fragmentům a tvorbě polydentatních donorů.

1. Introduction

The research into the chemistry of ferrocene-based donors started shortly after the discovery of ferrocene itself[1] and the determination of its real structure.[2] The iconic diphosphine, 1,1′-bis(diphenylphosphino)ferrocene (dppf), was firstly reported in 1965.[3] Since then it has found use as a versatile ligand in coordination compounds and essential component of catalysts for various transition metal-mediated organic transformations.[4]

Developments in the area of phosphinoferrocene donors naturally reflected the practical success of "organic" phosphine ligands that are nowadays indispensable donors for coordination chemistry and catalysis owing to their widely tuneable steric and electronic properties as well as an easy modification via introduced functional moieties. Although an enormous number of phosphinoferrocene derivatives have been reported to date, there can be recognised two distinct major lines along which the design of such donors is pursued, namely the preparation of chiral phosphines for applications in enantioselective catalysis and the synthesis of achiral donors related to dppf.[5]

During attempts to expand the family of non-chiral phosphinoferrocene donors, the molecule of the parent dppf has been often modified at the phosphine phosphorus. The replacement of phenyl substituents with other groups led, *inter alia*, to electron rich dialkylphosphine dppf congeners, the analogous phosphites and P-chiral derivatives.[6] Another approach towards the modification of the dppf structure was based on the replacement of one of the phosphine substituents with another functional moiety.[7] The latter approach allows for the preparation of donor-unsymmetric ligands combining two donor moieties with different coordination ability

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[1]) T. J. Kealy, P. L. Pauson, *Nature*, 1951, **168**, 1039; b) S. A. Miller, J. A. Tebboth, J. F. Tremaine, *J. Chem. Soc.*, 1952, 632.

[2] a) G. Wilkinson, M. Rosenblum, M. C. Whiting, R. B. Woodward, *J. Am. Chem. Soc.*, 1952, **74**, 2125; b) E. O. Fischer, W. Pfab, *Z. Naturforsch. B*, 1952, **7**, 377.

[3] G.P. Sollot, J. L. Snead, S. Portnoy, W. R. Peterson, H. E. Mertwoy, *U. S. Dept. Com., Office Tech. Serv., PB Rep.* **1965**, vol. II, pp. 441–452 (*Chem. Abstr.* **1965**, *63*, 18174).

[4] S. W. Chien, T. S. A. Hor in *Ferrocenes: Ligands, Materials and Biomolecules*, P. Štěpnička, P., Ed.; Wiley, Chichester, 2008; Part I – Ligands, Chapter 2, pp. 33–116. (b) K.-S. Gan, T. S. A. Hor in *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science*, A. Togni, T., Hayashi, Eds.; Wiley-VCH, Weinheim, 1995; Part 1 – Homogeneous Catalysis, Chapter 1, pp. 3-104. (c) G. Bandoli, A. Dolmella, *Coord. Chem. Rev.* **2000**, *209*, 161.

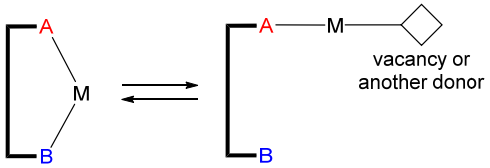
[5] a) *Ferrocenes: Ligands, Materials and Biomolecules*, P. Štěpnička, Ed.; Wiley, Chichester, 2008; b) *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science*, A. Togni, T. Hayashi, Eds.; Wiley-VCH, Weinheim, 1995; c) R. C. J. Atkinson, V. Gibson, N. J. Long, *Chem. Soc. Rev.*, 2004, **33**, 313; d) R. Goméz Arrayás, J. Adrio and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2006, **45**, 7674.

[6] T. J. Colacot, S. Parisel in *Ferrocenes: Ligands, Materials and Biomolecules*; P. Štěpnička, Ed.; Wiley, Chichester, 2008; Part I – Ligands, Chapter 3, pp. 117–140.

[7] P. Štěpnička in *Ferrocenes: Ligands, Materials and Biomolecules*, P. Štěpnička, Ed.; Wiley, Chichester, 2008, chapter 5, p. 177-204.

and preferences, synthesis of tailored molecules, whose "new" functional substituent affects their physicochemical properties (e.g., solubility) or can be used to append the phosphinoferrocene unit to another fragment or a molecular scaffold. This is why we have led our research along such a line, focusing firstly on phosphinoferrocene carboxylic acids[8] and then also on the corresponding amides.

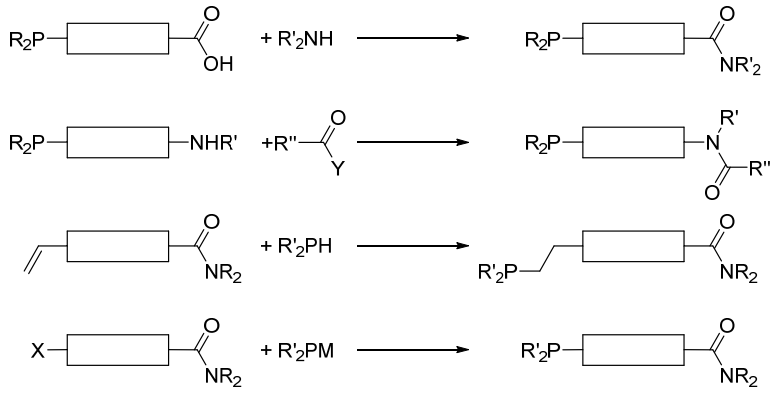
Phosphine donors modified by carboxamide[9] substituents represent archetypal examples of the so-called hybrid ligands.[10] The particular combination of the unlike donor moieties according to the Hard and Soft Acids and Bases concept,[11] *viz*. the soft phosphine group and the hard-donor amide moiety, allows phosphinocarboxamide ligands to ligate the whole range of transition metals in diverse coordination modes. Of particular interest is a possible hemilabile coordination of phosphinoamides towards soft transition metals, mainly because its relevance to catalysis. In this case, the phosphine donors, which forms strong dative bonds to the soft metal ion and act as firmly bound pivots, while the relatively weaker coordination bonds to the amide unit (*via* its oxygen atom in the native, non-deprotonated state) can be under certain circumstances cleaved and formed again. The cleavage can be induced, for instance, by the addition of further donors showing a higher affinity to the metal centre than the amide unit. During a catalytic cycle involving transition metal ligated in hemilabile fashion, the additional substituting donor may well be the substrate of the catalytic process. Once the metal-mediated transformation is completed and the product released from the coordination sphere, the bond to the amide moiety can formed again (in fast intramolecular fashion, see Scheme 1-1), preventing interactions of the metal centre with other donors present in the reaction system. In this manner, ligand coordinated in hemilabile fashion can protect the catalytically active metal centres from deactivation and thus increase their life-time and efficacy per the metal centre.



Scheme 1-1. Schematic representation of hemilabile coordination of a hybid ligand (A, B = donor moieties, M = metal).

[8] For a review, see: P. Štěpnička, *Eur. J. Inorg. Chem.* **2005**, 3787
[9] For a review, see: P. Štěpnička, *Chem. Soc. Rev.* **2012**, *41*, 4273.
[10] a) A. Bader, E. Lindner, *Coord. Chem. Rev.*, 1991, **108**, 27; b) C. S. Slone, D. A. Weinberger, C. A. Mirkin, *Progr. Inorg. Chem.*, 1999, **48**, 233.
[11] R. G. Pearson, *J. Am. Chem. Soc.* **1963**, *85*, 3533.

Another notable feature of phosphinoamide donors can be seen in their modular structures and relatively easy synthesis. These compounds are advantageously prepared by the reactions of phosphinocarboxylic acids with amines or, in an inverted manner, from carboxylic acids and phosphinoamines (Scheme 1-2). All these starting materials are either well established or can be synthesised by applying general routes previously reported in the literature. The assembly of the new molecules can be achieved by using the conventional synthetic protocols for amide bond formation as well as by coupling methods developed for use in peptide chemistry,[12] making use of the use of various condensation agents, active ester methodology, *etc*.



Scheme 1-2. Common synthetic methods for the preparation of phosphinocarboxylic amides.

Besides, a number of alternative synthetic approaches towards phosphinocarboxamides can be of course derived from the synthetic routes developed with non-functional substrates. Yet, in this case, attention must be paid to compatibility of the functional groups with the reaction conditions. Nevertheless, possible limitations can be eliminated by a proper choice of the synthetic approach, use of temporary protecting groups and also by a carefully chosen sequence of the individual reaction steps.

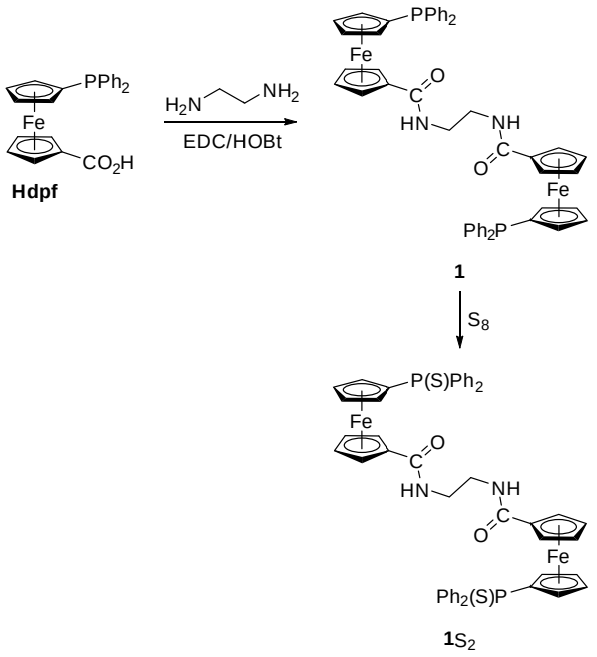
The virtually unlimited choice of the building blocks and the whole palette of complementary and functional group tolerant methods available for their combination and modification allow for a highly modular and practically unrestricted molecular design (molecular LEGO) and thus provide access to extensive libraries of chemically related compounds tailored for applications in various fields. All this makes phosphinocarboxamides attractive research targets and widens the scope of their possible practical use.

[12] See, for instance: A. El-Faham, F. Albericio, *Chem. Rev.* **2011**, *111*, 6557.

2. Phosphinocarboxylic amides – A personal account

2.1 Multi-donor phosphinoamide ligands

As it is often the case, the research into the chemistry of phosphinoferrocene carboxamides started rather unintentionally in my research group. In 2007, we reported about the synthesis and catalytic use of a ferrocene diamide-diphosphine **1** (Scheme 2-1; Appendix I in the Thesis).[T1] The preparation of such a ligand reflected our interest in multidonor assemblies derived from 1′-(diphenylphosphino)ferrocene-1-carboxylic acid (Hdpf),[13] which has been studied as a new hybrid donor.[8] Compound **1** was obtained *via* amide coupling reaction between Hdpf and 1,2-diaminoethane mediated by 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide (EDC) and 1-hydroxybenzotriazole as the common peptide coupling agents. Rather unexpectedly, compound **1** was isolated also from the reactions with sub-stoichiometric amounts of the acid, even at the Hdpf/diamine ratio of 1:1. Amide **1** was subsequently converted to a better crystallizing bis(phosphane sulfide) $\mathbf{1}S_2$, which was structurally characterised in the form of its stoichiometric solvate $\mathbf{1}S_2 \cdot 2AcOH$ (Figure 2-1).



Scheme 2-1. Preparation of amides **1** and $\mathbf{1}S_2$.

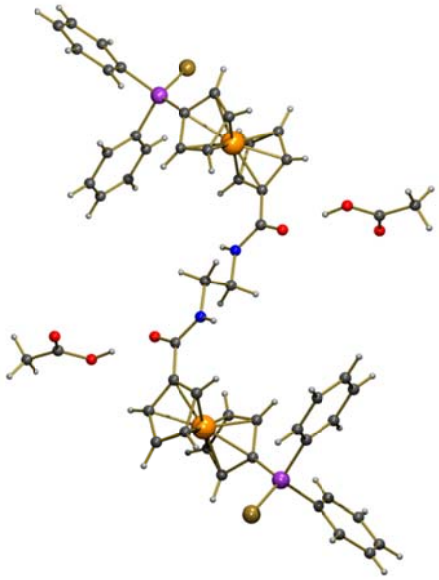
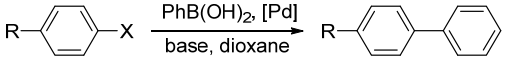


Figure 2-1. View of the crystal structure of $\mathbf{1}S_2 \cdot 2AcOH$ (colour code: N – blue, O – red, Fe – orange, P – violet, S – brown).

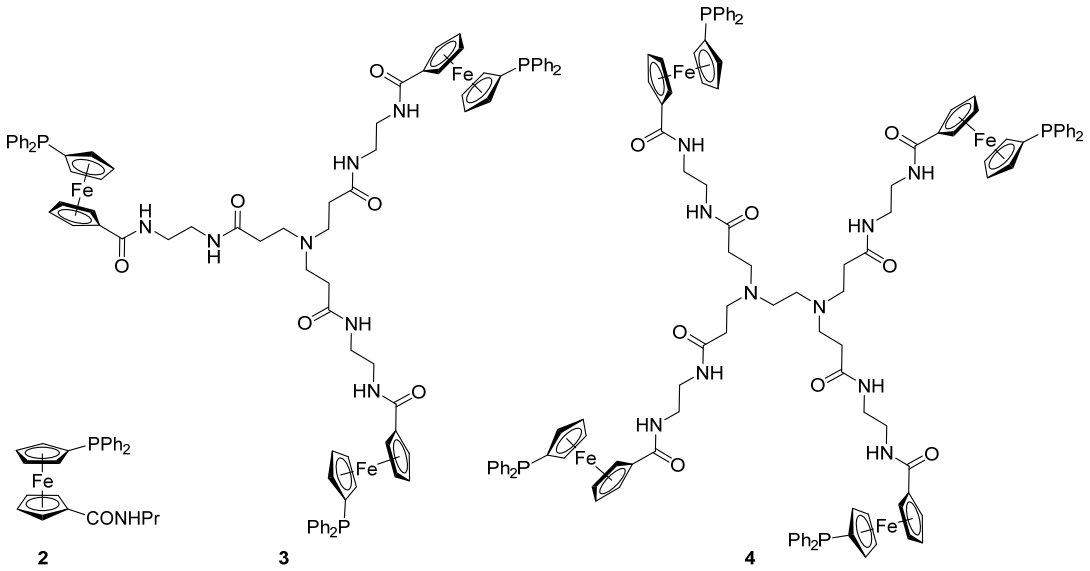
[13] J. Podlaha, P. Štěpnička, J. Ludvík, I. Císařová, *Organometallics* **1996**, *15*, 543.

In view of encouraging results obtained during previous catalytic evaluation of palladium catalysts with Hdpf and its methyl ester,[14] amides **1** and **1**S_2 were examined as ligands for palladium-catalysed Suzuki-Miyaura cross-coupling[15] of chloro- and bromobenzenes with phenylboronic acid to afford 4-substituted biphenyls (Scheme 2-2). While the reactions of the more reactive bromobenzenes performed in the presence of a catalyst generated *in situ* from **1** and palladium(II) acetate (1 mol.% Pd, Pd:ligand = 1:1.2) provided the respective biphenyls in yields exceeding 90%, reactions with the corresponding chlorobenzenes proceeded either with poor yields (with substrates activated by an electron-withdrawing substituent such as 4-$O_2NC_6H_4Cl$) or in practically negligible extent. The yields of the coupling products decreased upon replacing ligand **1** by its phosphine sulfide **1**S_2, most likely because of its less favourable ligating properties.



Scheme 2-2. Model Suzuki-Miyaura reactions (X = Cl and Br, R = Me, MeO, Ac and NO_2).

Catalytic results achieved with **1** led us to prepare a series of multidonor amidoamine donors bearing up to four terminal phosphinoferrocenyl units (Scheme 2-3; Appendix II).[T2] These compounds were prepared similarly to **1** from first generation poly(amido-amine) dendrimers (PAMAM). A model monophosphine **2** was included in the series for a comparison.

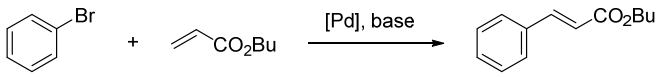


Scheme 2-3. Structures of monophosphine **2** and the multidonor ligands **3** and **4**.

[14] P. Štěpnička, M. Lamač, I. Císařová, *Polyhedron* **2004**, *23*, 921.
[15] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

Preliminary screening tests were performed for the cross-coupling of 4-bromotoluene with phenylboronic acid using catalysts generated *in situ* from palladium(II) acetate and ligands **2** and **4** that represent the extremes in the series. The Pd-to-phosphorus ratio was maintained at 1:1.2 in all cases and the reactions were performed in dioxane at 100 ºC with K_2CO_3 as the base. Kinetic profiles for such reactions (see Appendix II) revealed that the conversion of the starting aryl bromide to the biphenyl is complete within approximately 8 h with both catalysts. However, the catalyst based on the multidonor ligand **4** reacted faster than its analogue resulting from **2**. The different activity was clearly observed during approximately the first three hours of the reaction and was quantified by the initial reaction rates calculated from the kinetic profiles being 1.50(6) mmol h^{-1} and 1.00(2) mmol h^{-1} for the catalysts based on **4** and **2**, respectively. Subsequent tests performed with various *para*-substituted aryl bromides further demonstrated the superiority of the multidonor ligands over monophosphine **2**.

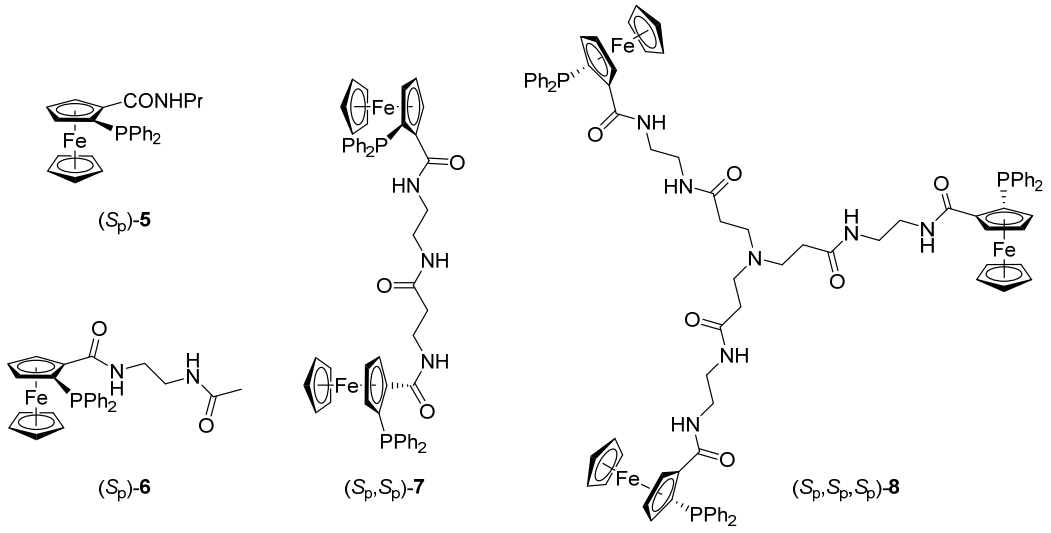
Ligands **1**-**4** were further evaluated in the Heck reaction of *n*-butyl acrylate with bromobenzene to give *n*-butyl cinnamate (Scheme 2-4). Even in this case, the catalysts based on multidonor ligands performed better than their counterpart resulting from phosphino-amide **2**. This can be exemplified by the yields determined by gas-chromatography, which increased with the number of the phosphinoferrocenyl termini (at constant palladium loading and Pd:P ratio): 21% for **2**, 31% for **1**, 39% for **3**, and 48% for **4** after 8 h of reaction (reaction at 155 ºC in dry *N*,*N*-dimethylformamide and with 0.5 mol.% of Pd).



Scheme 2-4. Heck coupling of *n*-butyl acrylate with bromobenzene to give *n*-butyl cinnamate.

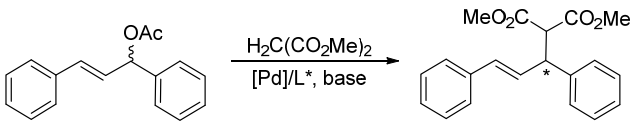
These promising results obtained with the rather simple albeit multidonor ligands led us to further investigate analogous chiral donors possessing (S_p)-2-(diphenylphosphino)-1-ferrocenecarbonyl terminal substituents (Scheme 2-5; see Appendix III in the Thesis; see also Section 2.3).[T3] These compounds bearing up to three phosphinoferrocenyl pendants were prepared analogously to their non-chiral counterparts starting from (S_p)-2-(diphenylphosphino)ferrocene-1-carboxylic acid (Hpfc).[16] Two monophosphine donors, *viz*. (S_p)-**5** and (S_p)-**6**, were included in the series of ligands to evaluate a possible influence of the coordinating amido-amine moieties on the catalytic properties of these donors.

[16] P. Štěpnička, *New J. Chem.* **2002**, *26*, 567.



Scheme 2-5. Planar-chiral phosphinoamides evaluated in Pd-catalysed asymmetric allylic alkylation.

Compounds **5-8** were studied as chiral ligands in palladium-catalysed asymmetric allylic alkylation[17] of 1,3-diphenylallyl acetate with "instant" nucleophile[18] generated from dimethyl malonate and *N,O*-bis(trimethylsilyl)acetamide (BSA; Scheme 2-6).



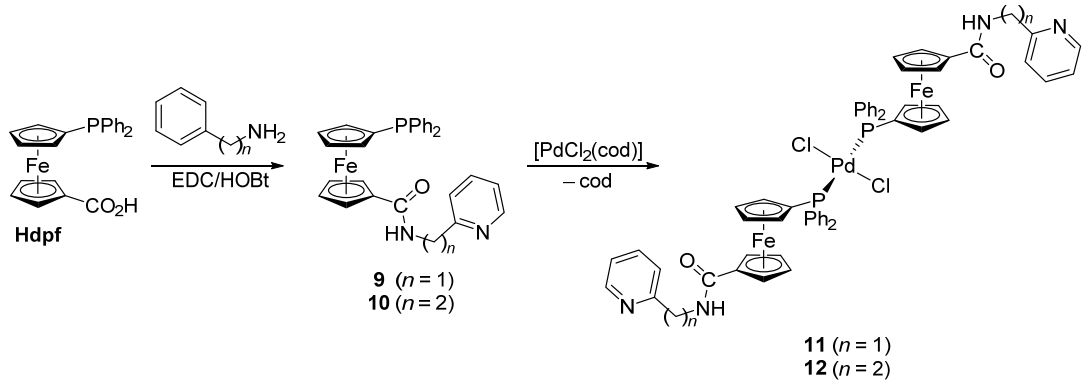
Scheme 2-6. Enantioselective alkylation of 1,3-diphenylallyl acetate with dimethyl malonate.

Reactions performed with catalyst formed *in situ* from $[PdCl(\eta\text{-}C_3H_5)]_2$ and the chiral amido-phosphines afforded the alkylation product with varying enantioselectivity [enantiomeric excess (*ee*): 82-91%] and in markedly different yields [(S_p)-**5**: 65%, (S_p)-**6**: 70%; (S_p, S_p)-**7**: 7%, and (S_p, S_p, S_p)-**8**: 22%]. Further experiments performed with the most efficient ligand (S_p)-**6** revealed that reaction rate (conversion) can be increased by the addition of alkali metal acetates without affecting the enantioselectivity. Upon addition of a catalytic amount of caesium acetate into the reaction mixture, the alkylation product was obtained in a 96% NMR yield and with 91% *ee*.

[17] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; b) B. M Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.
[18] B. M. Trost, D. J. Murphy, *Organometallics* **1985**, *4*, 1143.

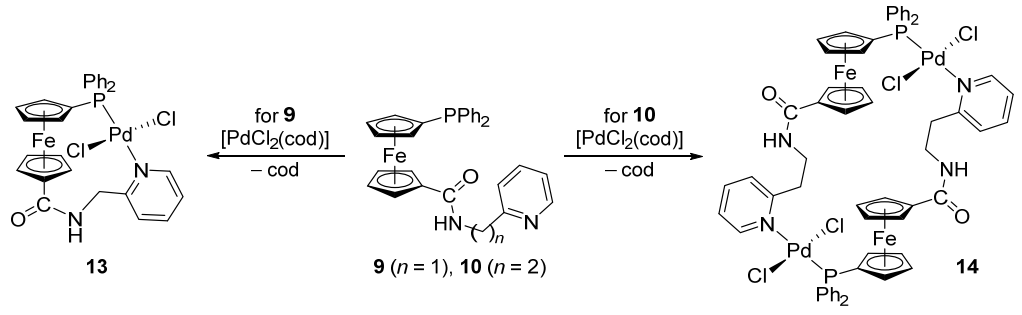
2.2 Phosphinoferrocene amides with donor substituents at the amide nitrogen

In addition to the multi-donor ligands described in the previous chapter, we have also focused on compounds bearing donor substituents at the amide nitrogen with an aim of studying the influence of the introduced terminal donor group on the coordination properties of the phosphinoferrocene carboxamides. Initially, we chose homologous phosphino-amide ligands equipped with 2-pyridyl groups, amides **9** and **10** (Scheme 2-7; see Appendix IV).[T4] These compounds, accessible by amidation of Hdpf with 2-(aminoalkyl)pyridines, reacted with $[PdCl_2(cod)]$ (cod = cycloocta-1,5-diene) at the Pd:P ratio of 1:2 to afford bis(phosphine) complexes **11** and **12**, employing only their soft phosphine donor moieties in coordination.



Scheme 2-7. Synthesis of ligand **9** and **10** and bis(phosphine) Pd(II) complexes thereof.

Upon lowering the amount of the ligand in the reaction mixture to one equiv. (*i.e.*, at Pd:P ratio 1:1), the complexation reactions produced crystalline complexes of the type $[PdCl_2(L)]$ with strikingly different structures (Scheme 2-8). Whereas the reaction with amide **9** possessing the shorter methylene linker gave *trans*-P,N monopalladium(II) complex **13**, that with the more flexible, homologous donor **10** furnished (after crystallisation) compound **14**, in which two phosphino-amide ligands symmetrically bridge two Pd(II) centres.



Scheme 2-8. The formation of "$PdCl_2(L)$" complexes from ligands (L) **9** and **10**.

The crystal structures determined for **12**·4$CHCl_3$, **13**·CH_3CO_2H and **14**·8$CHCl_3$ revealed the coordination environments of the Pd(II) ions in these compounds to be largely undistorted square planar, irrespective of the mode of coordination of the phosphinoferrocene amides (chelating or bridging donor). For instance, the ligand bite angle[19] (P-Pd-N) in **13** of 173.67(6)º does not depart much from the value expected for an ideal square planar coordination sphere (see Figure 2-2). It is also noteworthy that the polar pendants are involved in hydrogen bonding interactions that either stabilise molecular structure or give rise to defined supramolecular assemblies.

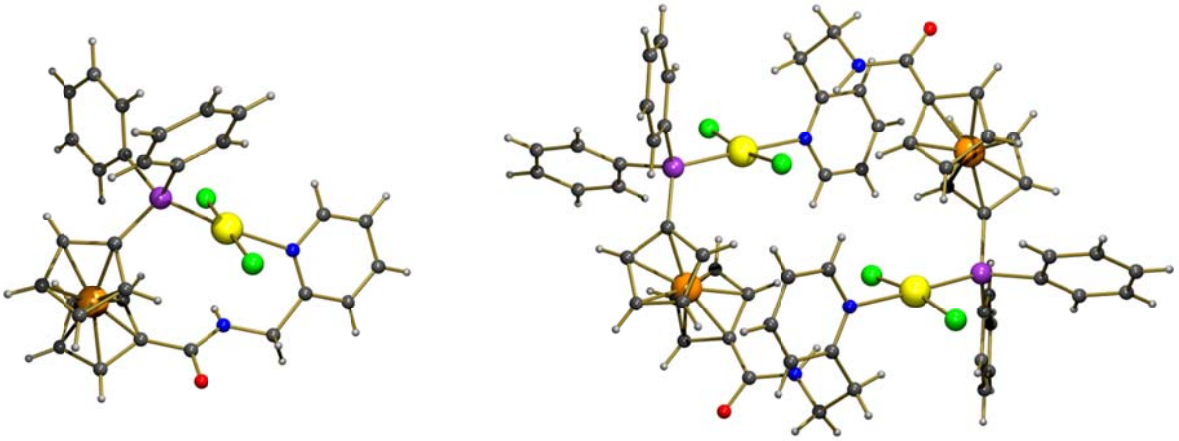
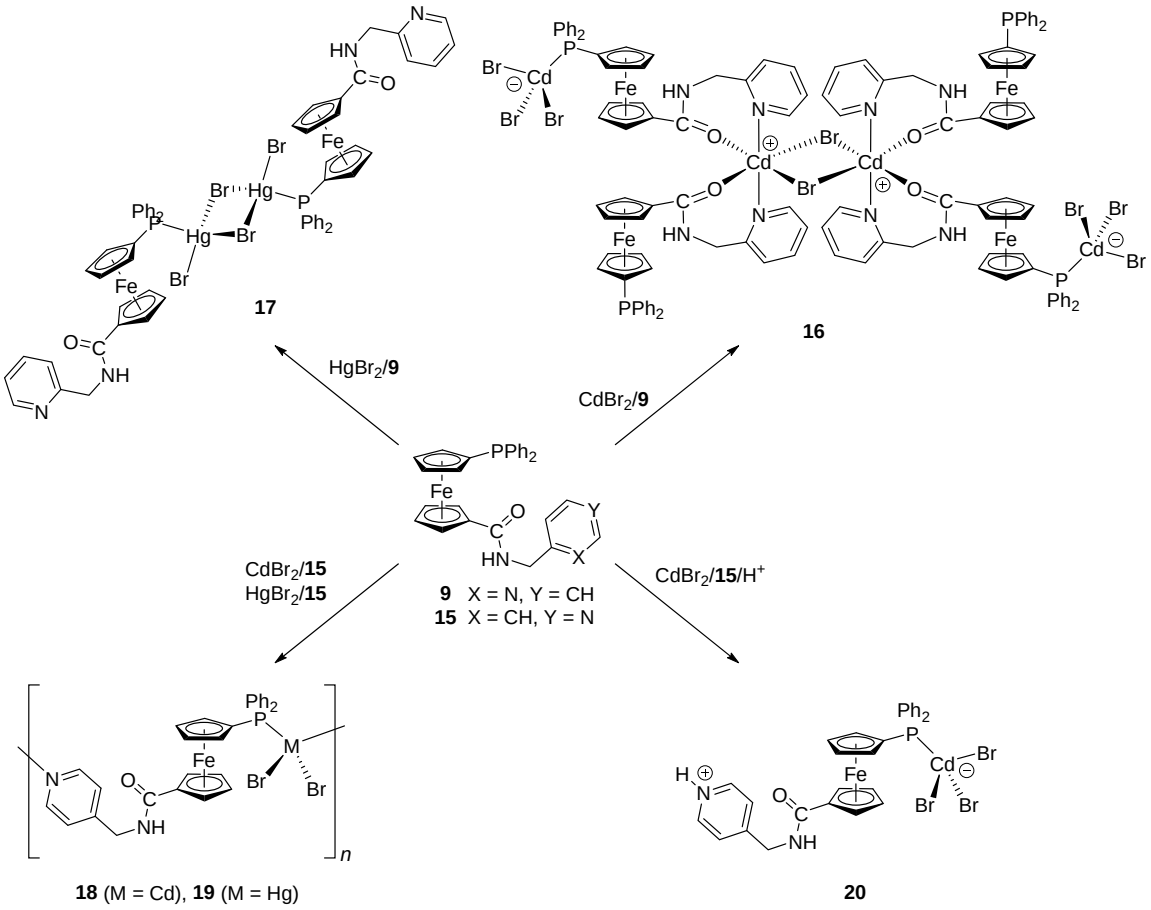


Figure 2-2. The complex molecules in the structures of **13**·CH_3CO_2H (left) and **14**·8$CHCl_3$ (right; colour code: N – blue, O –red, Fe – orange, P – violet, Cl – green, and Pd – yellow).

In a following study (Appendix V),[T5] the coordination properties of ligand **9** and its 4-pyridyl analogue **15** were examined towards Group 12 metal ions. These metal ions, introduced in the form of the dibromides MBr_2, were chosen mainly because their coordination preferences change greatly with their hardness and, because of the lack of ligand-field stabilisation resulting from closed shell (d^{10}) configuration, also with steric factors. In view of the previous work, the complexation reactions were performed at the metal-to-ligand ratio of 1:1 to avoid formation of simple phosphine complexes. Unfortunately, repeated experiments with $ZnBr_2$ did not afford any defined solid (crystalline) products, presumably due to their high solubility. On the other hand ,the reactions of $CdBr_2·4H_2O$ and $HgBr_2$ with **9** produced discrete, doubly zwitterionic tetracadmium complex [$Cd_2(\mu\text{-}Br)_2$(**9**-κ^2O,N^2)$_2$\{μ-1κ^2O,N^2:2κP-($C_5H_4N^2$)CH_2-N^1HCOfcPPh_2–$CdBr_3$\}$_2$] (**16**) and bromide-bridged dimeric complex [$HgBr(\mu\text{-}Br)$(**9**-κP)]$_2$

[19] M.-N. Birkholz, Z. Freixa, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.* **2009**, *855*, 1099.

(**17**), respectively (see Scheme 2-9 and Figure 2-3) while the analogous reactions with the isomeric ligand **15** bearing the 4-pyridyl substituent led to isostructural coordination polymers $[MBr_2\{\mu(P,N)\text{-}\mathbf{10}\}]_n$ (**18**: M = Cd; **19**: M = Hg) with tetrahedral coordination environments around both Cd(II) and Hg(II) (Scheme 2-9). Formation of such one-dimensional coordination assemblies with **15** apparently reflects steric properties of this donor, namely a favourable positioning of the terminal donor moieties. In the presence of acetic acid, the reaction of $CdBr_2{\cdot}4H_2O$ with **15** took a different course, leading to a monocadmium complex **20** featuring protonated ligand $(\mathbf{15}H)^+$ as a P-monodentate donor. This compound, crystallising as a monohydrate, is a zwitterion, combining the positively charged pyridinium group with an anionic terminal $CdBr_3^-$ moiety (Scheme 2-9 and Figure 2-3).



Scheme 2-9. Synthesis of Group 12 metal complexes **16**-**20**.

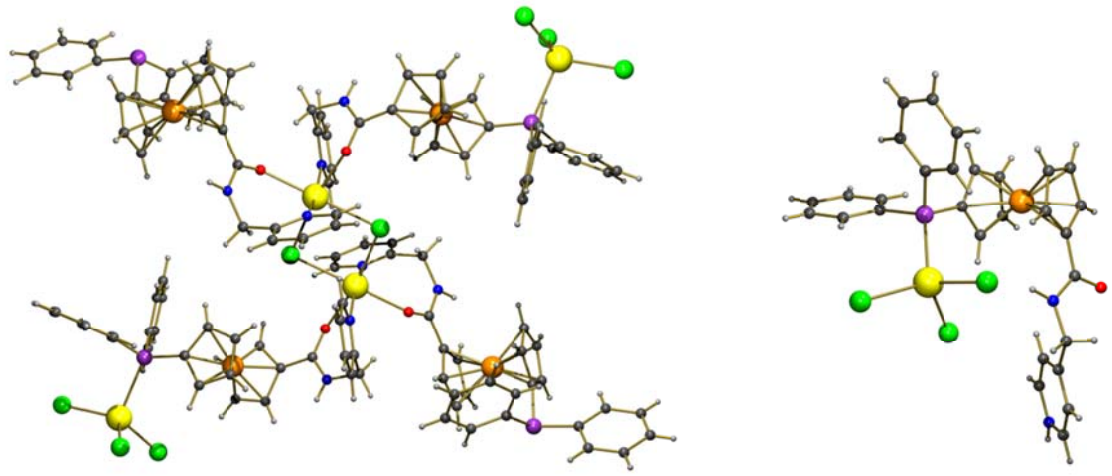
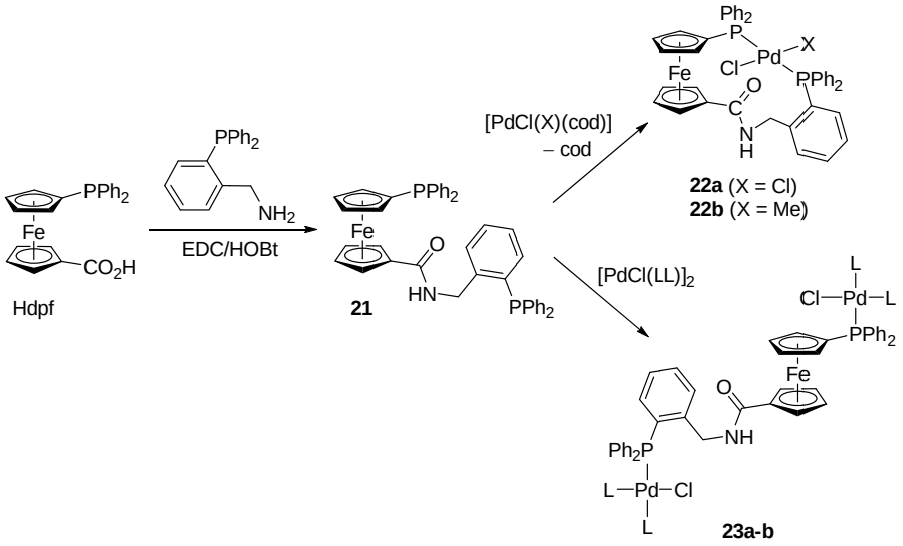


Figure 2-3. Views of the complex molecules in the structures of **16** (left) and **20**·H_2O (right; colour code: Cd – yellow, Fe – orange, P – violet, Br – green, O – red, N – blue).

Next, the structure of amido-phosphine **9** was (formally) modified through replacement of the nitrogen atom in the pyridyl ring with the C–PPh_2 moiety to give amido-diphosphine **21** (Scheme 2-10, Appendix VI).[T6] Even this compound reacted with [PdCl(X)(cod)] (X = Cl, Me) to afford the corresponding *trans*-chelate complexes **22a** and **22b** whereas the cleavage reactions with chloride-bridged dimers $[Pd(\mu\text{-}Cl)(LL)]_2$ (L/L = Cl/PBu_3 or chelating 2-[(dimethylamino-κ*N*)methyl]phenyl-κC^1) produced usymmetric dipalladium(II) complexes **23a** and **23b** (Scheme 2-10). The ligand bite angle (P^1-Pd-P^2) determined for **22**·5/4$CHCl_3$ by single-crystal X-ray diffraction analysis was 171.91(3)º.

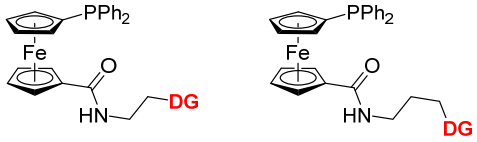


Scheme 2-10. Synthesis of amido-diphosphine **21** and its Pd(II) complexes. Legend: L/L = Cl(PBu_3) (**23a**), and 2-(dimethylamino-κ*N*)phenyl-κC^1 (**23b**).

Similarly to the simple and multi-donor ligands mentioned in Section 2-1, catalysts generated *in situ* from palladium(II) acetate and amides **9** and **10** (0.5 or 1 mol.% Pd, Pd:P = 1:1.2)[T4] or from $Pd(OAc)_2$ and diphosphine **21** (0.5 mol.% Pd, Pd:P = 1:1) as well as the defined complex **22a**[T6] were demonstrated to efficiently mediate Suzuki-Miyaura cross-coupling of 4-substituted aryl bromides with phenylboronic acid to give the corresponding biphenyls. Similar reactions with aryl chlorides furnished the coupling products in only poor to moderate yields.

The selective formation of *trans*-chelate palladium(II) complexes with ligands **9** and **21** attracted our attention because donors capable of traversing *trans* positions in transition metal complexes are rare. Typically, they are represented by symmetrical diphosphines[20] whose donor moieties are brought into positions suitable for *trans*-chelation by means of a rigid organic backbone, whereas those possessing flexible molecular parts as well as donors combining two different donor groups remain scarce.[21] With this in mind, we have expanded our studies into this area.

First, we have focused on P,N- and P,P-donors possessing the flexible 1,2-ethanediyl and 1,3-propanediyl groups as the spacers (Scheme 2-11; Appendix VII).[T7] These compounds were readily prepared by amidation of Hdpf with the respective Me_2N- or Ph_2P-substituted amines.



24 (DG = NMe_2)
26 (DG = PPh_2)
28 (DG = SMe)

25 (DG = NMe_2)
27 (DG = PPh_2)

Scheme 2-11. Donor-unsymmetric functional amides **24-28** (DG = donor group).

Coordination tests with donors **24** and **26** revealed that these compounds indeed give rise to *trans*-chelate complexes, *trans*-[$PdCl_2$(**24**-κ^2*N*,*P*)] and *trans*-[$PdCl_2$(**26**-κ^2*P*,*P*)] (Figure 2-4). Similar reactions with the homologous donors **25** and **27** proved to be less selective, leading to complicated mixtures (at the Pd:ligand ratio of 1:1). As indicated by *in situ* ^{31}P NMR measurements, the reaction of [$PdCl_2$(cod)] with **25** is relatively fast and affords one dominant

[20] C. A. Bessel, P. Aggarwal, A. C. Marschilok, K. J. Takeuchi, *Chem. Rev.* **2001**, *101*, 1031.
[21] For examples of donor-unsymmetric *trans*-spanning ligands, see: a) I. R. Butler, M. Kalaji, L. Nehrlich, M. Hursthouse, A. I. Karaulov, K. M. A. Malik, *J. Chem. Soc., Chem. Commun.* **1995**, 459; b) K. Tani, M. Yabuta, S. Nakamura, Y. Yamagata, *J. Chem. Soc., Dalton Trans,* **1993**, 2781.

product which, however, could not be isolated by crystallization. Analogous reaction with **27** was less selective but (1) the equilibrium gradually shifted towards one species and, (2) crystallisation of the reaction mixture furnished one of the possible products, which was in turn structurally characterised as the symmetric dimer $[PdCl_2(\mu(P:P)\text{-}\mathbf{27})]_2$. The fact that this compound was isolated in a 78% yield, which is much more than determined by NMR analysis, points to dynamic (hemilabile) nature of the Pd-**27** complexes in which the least soluble or most easily crystallising component separates and is supplemented by reaction equilibria.

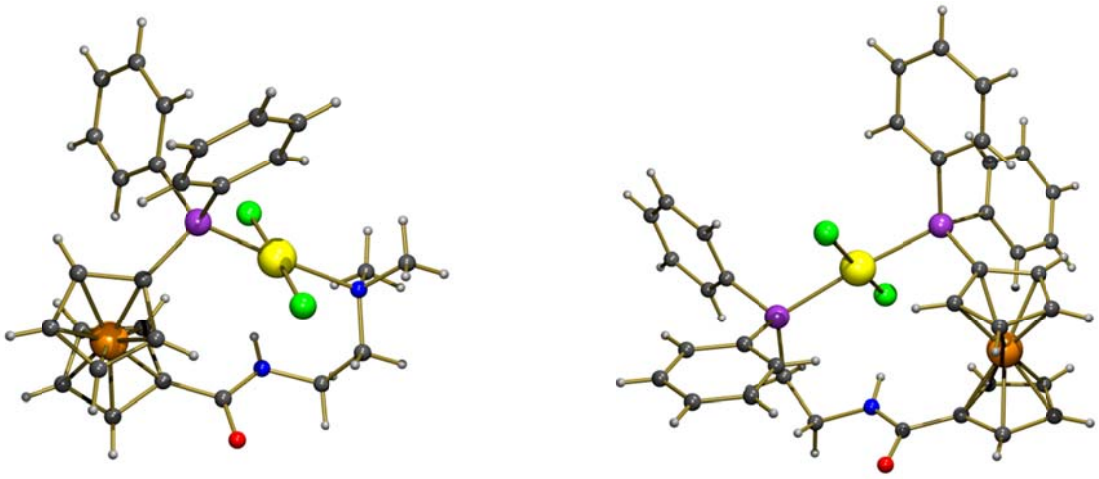


Figure 2-4. Views of the molecular structures of *trans*-[$PdCl_2$(**24**-κ^2*N*,*P*)] (left) and *trans*-[$PdCl_2$(**26**-κ^2*P*,*P*)] (right) (colour code as in Figure 2-2).

As a part of studies focused on compounds **24**-**27**, we have also prepared the *N*-methylammonium phosphine $[Ph_2PfcCONHCH_2CH_2NMe_3]X$ (**29**, X = Cl/I), an analogue of the original AMPHOS ligand, $[Ph_2PCH_2CH_2NMe_3]I$.[22] Because of competitive alkylation at the phosphine group, the synthesis of **29** required the phosphine moiety to be protected as the corresponding phosphine sulfide. After alkylation of the terminal amine group, the phosphine moiety was regenerated by desulfuration with Raney nickel. Compounds **24**, **26** and **29** were evaluated as ligands for Pd-catalysed cross-coupling of 4-bromoacetophenone with phenylboronic acid in dioxane and water. In the former solvent, the NMR yields of 4-acetybiphenyl after 6 h increased in the sequence: **29** < **24** < **26** (0.1 mol.% $Pd(OAc)_2$ + 0.12 mol.% of the ligand were used and the reaction was carried out at 90 ºC). In reactions performed in water, the isolated yields of the coupling products were 94% or higher with *all* catalysts after 2 h but considerably inferior yields were achieved in toluene-water biphase

[22] a) R. T. Smith, M. C. Baird, *Trans. Met. Chem.* **1981**, *6*, 197; b) R. T. Smith, R. K. Ungar, M. C. Baird, *Trans. Met. Chem.* **1982**, *7*, 288.

system under otherwise similar conditions (*cf*. 67% yield after 6 h for Pd/**26**; the remaining catalysts performed even worse: **26** > **29** > **24**). After increasing the amount of $Pd(OAc)_2$ and the ligand **29** to 1 mol.% and to 1.2 or 2.4 mol.%, respectively, good product yields were obtained also in this solvent mixture (> 90%). However, the catalyst could not efficiently recycled, losing their activity during consecutive runs.

In the subsequent research, we have turned also to a potential P,S-donor **28** (see Scheme 2-11 above, Appendix VIII)[T8] and have included also Ni(II) and Pt(II) in the coordination tests. Compound **28** was obtained similarly to its P,N- and P,P-donor counterparts from Hdpf and 2-(methylthio)ethylamine. Whereas repeated attempts to prepare some Ni(II)-**28** complexes were unsuccessful because of an extensive decomposition of the reaction mixtures, the reaction of amido-phosphine **28** with $[PdCl_2(cod)]$ at the Pd:P molar ratio of 1:1 afforded stable *trans*-chelate complex *trans*-[$PdCl_2$(**28**-κ^2*P*,*S*)] as the sole product. Similar reaction with $[PtCl_2(cod)]$ produced a mixture of *cis*-[$PtCl_2$(**28**-κ^2*P*,*S*)] and *trans*-[$PtCl_2$(**28**-κ^2*P*,*S*)], which could be separated by fractional crystallisation and were structurally characterised (Figure 2-5). The formation of both possible isomers of these square-planar complexes reflects kinetic inertness of Pt(II) whilst the ligand bite angles determined in complexes *cis*-[$PtCl_2$(**28**-κ^2*P*,*S*)] and *trans*-[$PtCl_2$(**28**-κ^2*P*,*S*)] of 92.86(2)º and 173.05(2)º, respectively, suggest that ligand **28** is accommodated in the coordination sphere of platinum(II) equally well as both the *cis*- and *trans*-chelating donor.

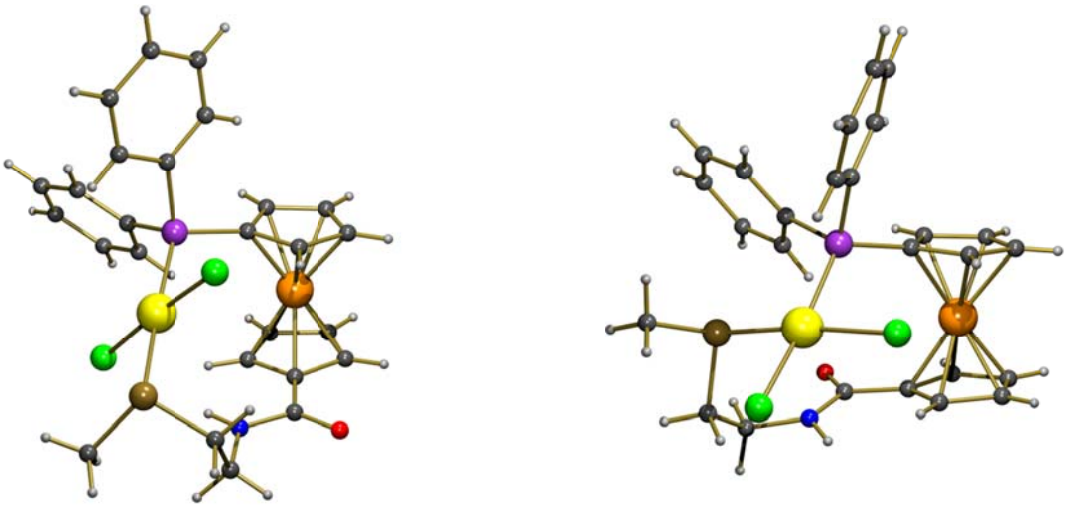
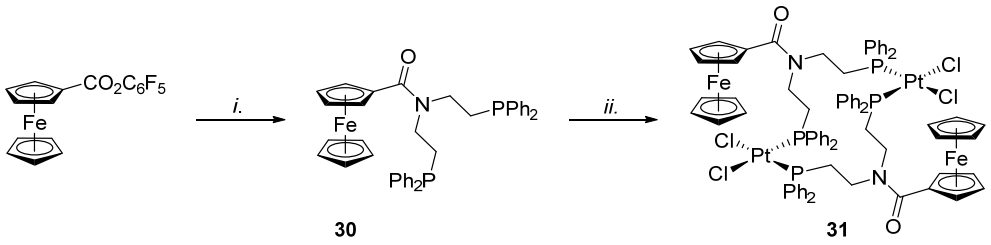


Figure 2-5. Views of the molecular structures of *trans*-[$PtCl_2$(**28**-κ^2*P*,*S*)] (left) and *cis*-[$PtCl_2$(**28**-κ^2*P*,*S*)] (right; colour code: N – blue, O –red, Fe – orange, P – violet, Cl – green, S – brown, and Pt – yellow).

Complexation reactions performed at the metal-to-ligand ratio of 1:2 were more complicated. Thus, the reaction with [$PdCl_2$(cod)] afforded a mixture of bis(phosphine) complex *trans*-[$PdCl_2$(**28**-κ*P*)$_2$] (major component), *trans*-[$PdCl_2$(**28**-κ^2*P*,*S*)] and phosphine oxide of ligand **28** (**28O**). In a similar reaction with [$PtCl_2$(cod)], the crude reaction mixture resulting at room temperature contained the isomeric bis(phosphine) complexes, *cis*- and *trans*-[$PtCl_2$(**28**-κ*P*)$_2$], in a *ca*. 2:1 ratio according to ^{31}P NMR spectra (*N.B.* the compounds are easily distinguished by the $^1J_{PtP}$ coupling constants) and, in minor amounts, also *both* isomeric monophosphine complexes and phosphine oxide **28O**. The ratio of the bis(phosphine) complexes changed in favour of the thermodynamically preferred *trans*-isomer upon refluxing in chloroform for 18 h (*cis*:*trans* ≈ 1:2). When anhydrous Zeisse salt (K[$PtCl_3$(η^2-C_2H_4)]) was employed as the Pt(II) source, the isomers *cis*- and *trans*-[$PtCl_2$(**28**-κ*P*)$_2$] were formed in an inverted 1:2 molar ratio in a "kinetic" reaction mixture (at room temperature after 90 min) and this ratio did not change after refluxing for 18 h. Even in this case, however, minor amounts of *cis*- and *trans*-[$PtCl_2$(**28**-κ^2*P*,*S*)] and **28O** could be detected. The inverted isomer ratio for [$PtCl_2$(**28**-κ*P*)$_2$] apparently reflects the nature of the leaving groups and a large *trans*-influence of the η^2-ethene ligand in the Zeise salt.

In an independent report, we have described the synthesis of a ferrocenecarbonyl diphosphine **30** (Scheme 2-12, Appendix IX).[T9] This compound, bearing two 2-(diphenylphosphino)ethyl arms as the amide nitrogen, was prepared from pentafluorophenyl ferrocenecarboxylate and bis[2-(diphenylphosphino)ethyl]amine and was further converted to bis(phosphine sulfide) **30S$_2$**. Diphosphine **30**, which exerts limited molecular mobility in solution, reacts with [$PtCl_2$(cod)] to afford the P,P-bridged, sterically encumbered diplatinum(II) complex **31**.



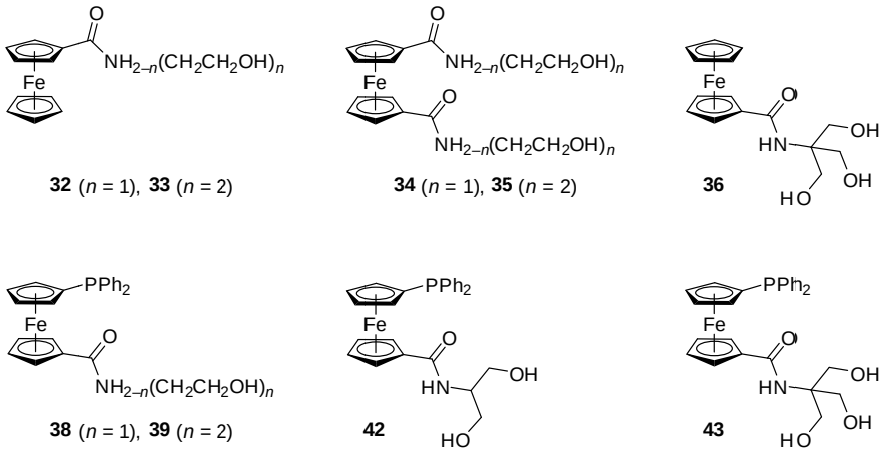
Scheme 2-12. Synthesis of ligand **30** and its Pt(II) complex **31** (Legend: *i*. (Ph_2PCH_2-CH_2)$_2$NH·HCl/trimethylamine, 4-(dimethylamino)pyridine, pyridine, *ii*. [$PtCl_2$(cod)])

2.3 Phosphinoferrocene amides bearing polar substituents at the amide nitrogen

In view of prospective applications of phosphinoferrocene donors in aqueous and biphase reaction media, we have next turned to phosphinoferrocene amides possessing hydrophilic

substituents at the amide nitrogen. In addition to compound **29** mentioned above, the following four compounds classes were studied to date: phosphinoferrocene amides with hydroxyalkyl substituents, amino acid-based amides, phosphinoferrocene amidosulfonates and phosphinoferrocene donors with urea pendants.

The interest in the former compounds arose from our previous study focused on the crystal structures of ferrocene *N*-(2-hydroxyethyl) amides **32-35** (Scheme 2-13; Appendix X) resulting by the reactions of the corresponding acyl chlorides and amines.[T10] This work demonstrated that the complexity of crystal assembly constituted by these compounds increases with the number of available hydrogen bond donors and acceptors. In a separate work, a related amide **36** was prepared and converted to a cationic hexavanadate decorated by two ferrocenyl pendants at the periphery, $(Bu_4N)_2[\{FcCONHC(CH_2O)_3\}_2V_6O_{13}]\cdot 2HCONMe_2$ (**37**; see Figure 2-6). This compound was characterised by spectroscopic methods, X-ray diffraction analysis, cyclic voltammetry and further studied by DFT computations (Appendix XI).[T11]



Scheme 2-13. Ferrocene amides **32-35** and their phosphinylated analogues **38**, **39**, **42** and **43**.

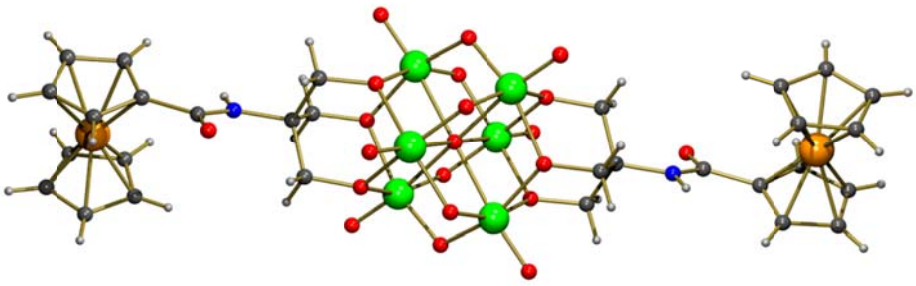
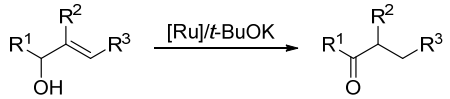


Figure 2-6. View of the hexavanadate anion in the crystal structure of **37** (colour code: Fe – orange, V – green, N – blue, and O – red).

Phosphinoferrocene amide **38**, the most simple representative among hydroxyalkyl-substituted Hdpf amides, was obtained by direct amidation of Hdpf with 2-hydroethylamine in the presence peptide coupling agents whereas its congener **39** had to be synthesised *via* active ester $Ph_2PfcCO_2C_6F_5$, because a similar direct coupling afforded only Hdpf-benzotrialozyl ester (Appendix XII).[T12] These amides were subsequently utilised in the synthesis of Pd(II) bis(phosphine) complexes *trans*-[$PdCl_2$(**38**-κ*P*)$_2$] (**40**) and *trans*-[$PdCl_2$(**39**-κ*P*)$_2$] (**41**) and both the starting phosphinoamides and their Pd(II) complexes were structurally characterised by single-crystal X-ray diffraction analysis (the latter in the form of different solvates). The complexes were examined as defined precatalysts for Suzuki-Miyaura reaction (*cf*. Scheme 2-2) in polar organic solvents, water and in toluene-water mixture. Although both complexes gave rise to active catalysts for the coupling of aryl bromides with phenylboronic acid, the catalyst resulting from **40** proved to be more stable and could be reused for five consecutive runs in toluene-water mixture without loss of activity.

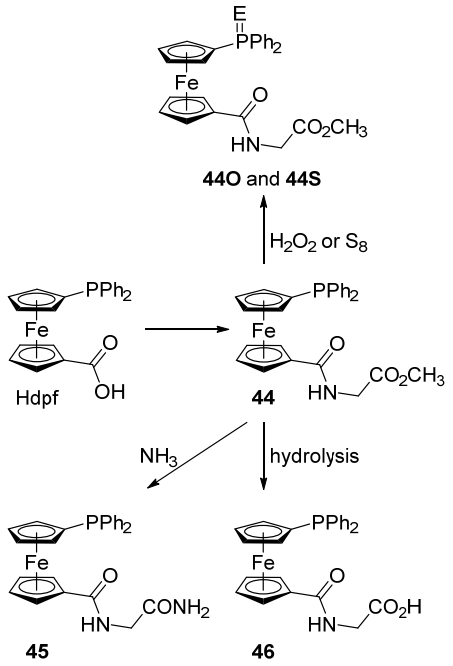
Later on, we have completed yet another series of Hdpf amides equipped with the $–CH_{3–n}(CH_2OH)_n$ pendants by synthesizing the missing representatives **42** and **43** (Scheme 2-13). Together with the parent amide **38**, these compounds were used to prepare a series of (η^6-arene)ruthenium(II) complexes of the type [(η^6-arene)$RuCl_2$(L-κ*P*)], where arene = benzene, *p*-cymene and hexamethylbenzene (all nine combinations with L = **38**, **42** and **43**). The complexes were fully characterised and examined as catalysts (with potassium *tert*-butoxide co-catalyst) for redox isomerization of various allylic alcohols to ketones in 1,2-dichloroethane (Scheme 2-14). Complex [(η^6-*p*-cymene)$RuCl_2$(**36**-κ*P*)] comprising the most simple phosphinoferrocene ligand was found particularly attractive due to its high catalytic activity (especially in reactions of less sterically hindered substrates with R^2 and R^3 = H) and an easy synthesis (Appendix XIII).[T13]



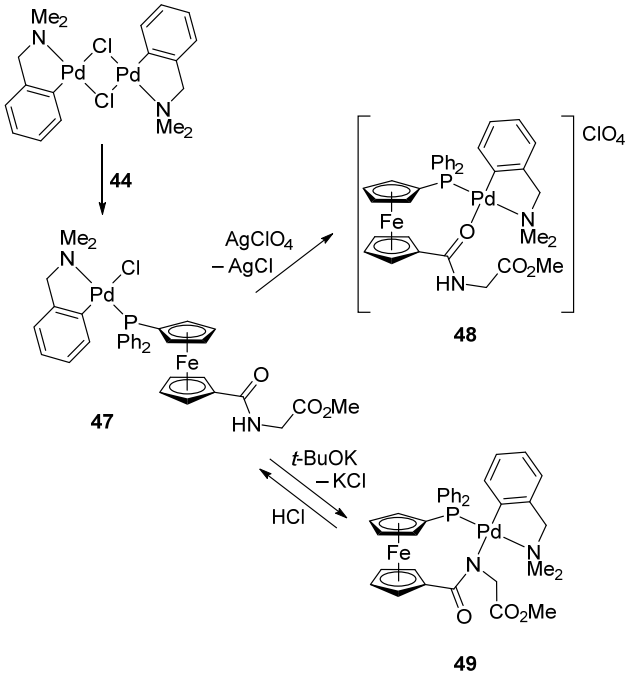
Scheme 2-14. Ru-catalysed isomerization of allylic alcohols to carbonyl compounds

In a subsequent work, glycine was employed as a polar "amine" in the design of functional phosphinoferrocene carboxamides (Appendix XIV),[T14] though not its native form due to possible competitive coupling at the glycine carboxyl group but as the corresponding methyl ester hydrochloride, $H_2NCH_2CO_2Me{\cdot}HCl$, which was *in situ* converted to the free base by

treatment with triethylamine. Amidation reaction with Hdpf provided the desired amidophosphine **44** (Scheme 2-15), which was further converted to the corresponding phosphine oxide **44O** and sulfide **44S**, bis-amide **45** and acid **46**.



Scheme 2-15. Synthesis of glycine amides.



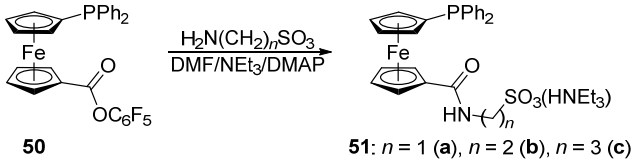
Scheme 2-16. Synthesis of L^{NC}Pd(II) complexes with ligand **44**.

Compounds **44**-**46** were reacted with $[PdCl_2(cod)]$ to give bis(phosphine) complexes *trans*-$[PdCl_2(L\text{-}\kappa P)_2]$. In addition, amide **44** was evaluated as a ligand in complexes with auxiliary [2-(dimethylamino)methyl-κ*N*]phenyl-κC^1 (L^{NC}) ligand (Scheme 2-16). The reaction of the starting dimer $[(L^{NC})Pd(\mu\text{-}Cl)]_2$ with **44** afforded the expected bridge-cleavage product **47**, which was treated with silver(I) perchlorate to give a cationic bis(chelate) complex **48**. Deprotonation of **47** by potassium *tert*-butoxide produced another bis(chelate) **49**, in which the phosphinoferrocene ligand coordinates *via* phosphorus and the deprotonated amide nitrogen. Amides **44**-**46** were evaluated as supporting ligands in the model Suzuki-Miyaura coupling of 4-bromobiphenyl with phenylboronic acid. All catalysts generated *in situ* from palladium(II) acetate and the appropriate donor showed good catalytic performance in dioxane, ethanol and their aqueous mixtures, and even in pure water (0.5 mol.% Pd at 80 °C).

Ligand **44** was further used to prepare complexes $[(\eta^6\text{-arene})RuCl_2(\mathbf{44}\text{-}\kappa P)]$ (arene = C_6H_6, *p*-cymene and C_6Me_6) and their cationic counterparts $[(\eta^6\text{-arene})RuCl(MeCN\text{-}\kappa N)(\mathbf{44}\text{-}\kappa P)][PF_6]$ and $[(\eta^6\text{-arene})Ru(MeCN\text{-}\kappa N)_2(\mathbf{44}\text{-}\kappa P)][PF_6]_2$. Together with $[(\eta^6\text{-}p\text{-cymene})RuCl_2(\mathbf{45}\text{-}\kappa P)]$,

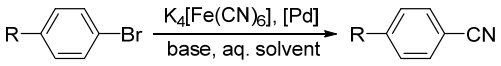
these compounds were evaluated as catalysts for aqueous oxidation of secondary alcohols to ketones with *tert*-butyl hydroperoxide as the oxidizing agent. All compounds showed very high catalytic activities at room temperature, the most active being complex [(η^6-*p*-cymene)$RuCl_2$(**44**-κ*P*)], which showed a catalytic turnover frequency of 13 200 h^{-1} in the oxidation of 1-phenylethanol at the substrate/catalyst ratio of 10^5 (Appendix XV).[T15]

Reactions of Hdpf-pentafluorophenyl ester **50** with ω-aminosulfonic acids in the presence of triethylamine and 4-(dimethylamino)pyridine afforded a series of anionic *N*-sulfonatoalkyl amides which were isolated in the form of air-stable, crystalline triethylammonium salts **51a-c** (Scheme 2-17, Appendix XVI).[T16] These compounds were found to be highly water soluble, a property not commonly encountered among phosphinoferrocene ligands, and were therefore studied as ligands in Pd(II) complexes and for Pd-catalysed cyanation[23] of aryl bromides with $K_4[Fe(CN)_6]$ as a non-toxic cyanide source in aqueous dioxane (Scheme 2-18). An extensive screening of the reaction conditions revealed that reaction outcome depends on the structure of the pre-catalysts (2 mol.% of defined complex [$PdCl_2$(**51**-κ*P*)$_2$] were used), the dioxane-water ratio and also on the substituents in the aryl bromide substrate.



50 **51**: *n* = 1 (**a**), *n* = 2 (**b**), *n* = 3 (**c**)

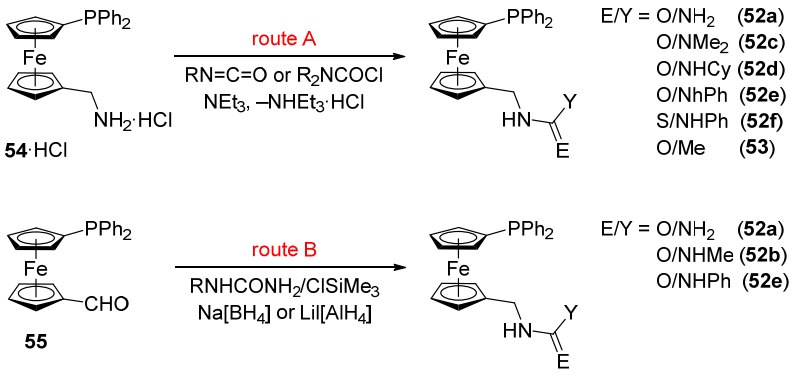
Scheme 2-17. Synthesis of phosphinoferrocene amidosulfonates **51a-c**.



Scheme 2-18. Pd-Catalysed cyanation of aryl bromides with $K_4[Fe(CN)_6]$.

The same testing reaction was utilised for an evaluation of catalytic properties of phosphinoferrocene ureas **52** and the related acylamino derivative **53**. These compounds were prepared either by using a formally inverted approach, *i.e.*, by functionalisation of [1'-(diphenylphosphino)ferrocenyl]methylamine **54** (route A; the amine was liberated from its hydrochloride *in situ*) or *via* reductive amination of 1'-(diphenylphosphino)ferrocene-1-carbaldehyde **55** (route B; see Scheme 2-19 and Appendix XVII).[T17]

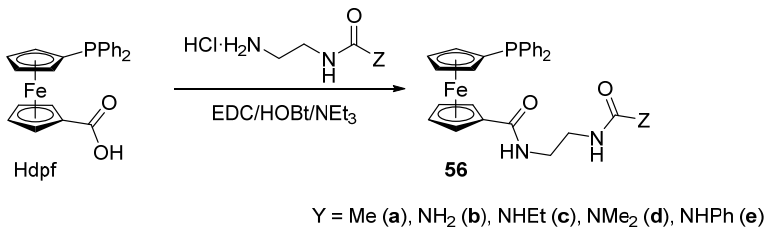
[23] For a recent review, see: P. Anbarasan, T. Schareina, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 5049.



Scheme 2-19. Synthesis of phosphinoferrocene ureas **52** and acetamido derivative **53**.

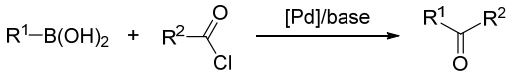
Compound **52e** as the representative was used to prepare Pd(II) complexes [$PdCl_2$(**52e**-κ*P*)$_2$], [PdCl(μ-Cl)(**52e**-κ*P*)]$_2$ and monophosphine complexes with other supporting ligands, [(LL)PdCl(**52e**-κ*P*)], where LL stands for 2-[(dimethylamino-κ*N*)methyl]phenyl-κ*C*^{1} and η^3-allyl. Attempts to involve the urea pendant in coordination (either by halogen removal or deprotonation) were unsuccessful. The mentioned cyanation reaction of aryl bromides bearing electron-donating substituents proceeded very well with catalysts based on these donors, affording high yields of the nitriles within reasonable time (optimised conditions: 1 mol.% of palladium acetate and 2 mol.% of **52e**, 1 equiv. of Na_2CO_3, and 0.5 equiv. of $K_4[Fe(CN)_6]\cdot 3H_2O$; reaction in dioxane-water (1:1) at 100 ºC). On the other hand, cyanations of substrates possessing electron-withdrawing substituents were complicated by hydrolysis of the primary nitrile products to the respective amides.

Analogous donors **56** in which the polar pendants are separated from the amidoferrocenyl unit by ethane-1,2-diyl spacer were obtained by conventional amidation of Hdpf with pre-formed amino-urea and amino-amide building blocks (Scheme 2-20, Appendix XVIII).[T18]



Scheme 2-20. Synthesis of phosphinoferrocene amido-ureas **56** by amide coupling (Legend: EDC = 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide, HOBt = 1-hydroxybenzotriazole).

Ligands **56** were converted to a series of Pd(II) complexes, [(LL)PdCl(**56**-κ*P*)] (LL = 2-[(dimethylamino-κ*N*)methyl]phenyl-κC^1 and η^3-allyl), which were in turn evaluated in Pd-catalysed cross-coupling of acyl chlorides with boronic acids to give ketones (Scheme 2-21). This reaction[24] offers an alternative access to ketones with defined substitution, being particularly useful when conventional routes (*e.g.*, Friedel-Crafts reactions and oxidation of secondary alcohols) fail due to their low selectivity and poor functional group tolerance.



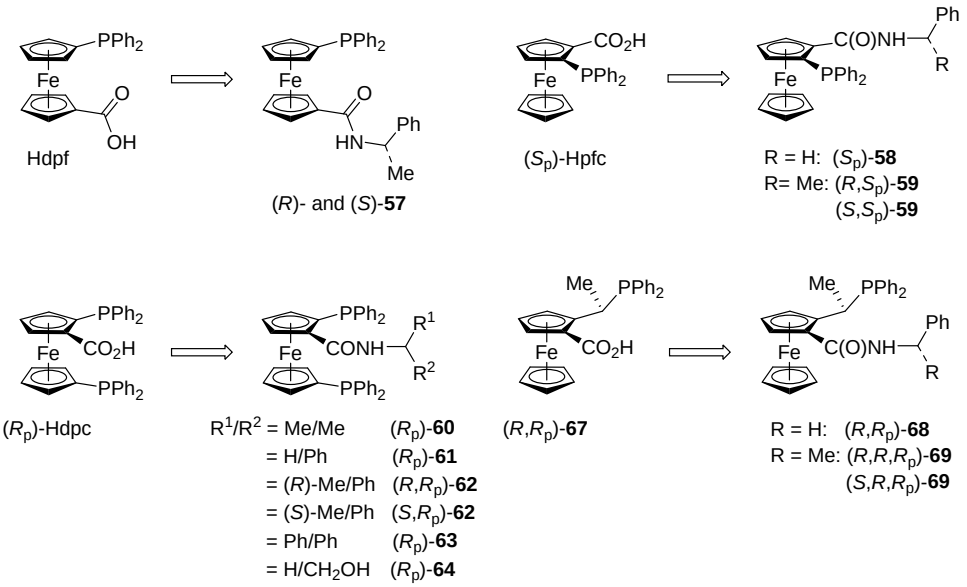
Scheme 2-21. Pd-catalysed reaction of boronic acids and acyl chlorides.

After optimisation, these C-C bond forming reactions were carried out in the presence of [(η^3-C_3H_5)PdCl(**56e**-κ*P*)] (0.2 mol.%), which showed good catalytic performance and was readily accessible in a defined crystalline state, in toluene-water biphase mixture using Na_2CO_3 as the base at 50 ºC. The coupling reactions proceeded well with aromatic substrates except for the cases, when the reaction was hampered by poor solubility of the starting materials in the reaction medium. However, these complications could be eliminated by a proper selection of the reaction partners, *e.g.*, through transposition of the substituents between the two reaction partners ($R^1B(OH)_2$ + R^2COCl *vs.* $R^2B(OH)_2$ + R^1COCl).

2.4 Chiral phosphinoferrocene carboxamide donors

Alongside with the development of variously functionalised, non-chiral phosphinoferrocene carboxamides, we have also focused on the design of donors, aiming at their utilisation in enantioselective, metal-mediated reactions. Already in 2007, we reported the synthesis of a small series of *N*-benzyl amides from Hdpf and (S_p)-Hpfc with different combination of chirality elements (Scheme 2-22 and Appendix XIX).**[T19]**

[24] T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, N. Miyaura, *J. Org. Chem.* **1998**, *63*, 4726.

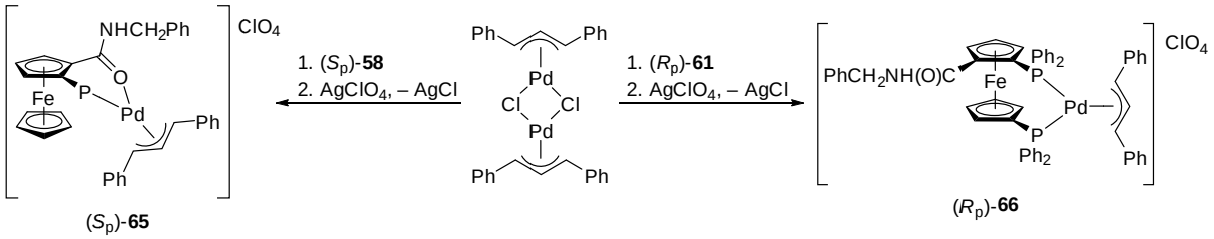


Scheme 2-22. Chiral phosphinoferrocene amides evaluated in asymmetric allylic alkylation..

Catalytic properties of these donor were probed in model Pd-catalysed alkylation of 1,3-diphenylallyl acetate with dimethyl malonate anion (see Scheme 2-6 above). Thus, reactions with catalyst generated *in situ* from $[(\eta^3\text{-}C_3H_5)Pd(\mu\text{-}Cl)]_2$ and ligands derived from Hdpf, (S_p)- and (R_p)-**57**, furnished the coupling product with full conversion but in racemic form (at room temperature with BSA/potassium acetate as the base). Under similar conditions, the reactions with Hpfc-based catalysts **58** and **59** proceeded with full conversions and modest enantioselectivity (*ee*'s in the range 21-58%). An improvement in terms of stereoselectivity was accomplished through removing potassium acetate from the reaction system, which led to 90% *ee* for the least sterically congested and best performing *N*-benzyl amide (S_p)-**58**.

Analogous donors containing an additional phosphine moiety, which can be regarded planar-chiral and amide-functionalised dppf derivatives, compounds **60-64** in Scheme 2-22 (Appendix XX),[T20] also afforded relatively fast reacting catalysts but the achieved enantioselectivity was relatively lower and less dependent on the ligand structure (*ee* 55-67% with BSA/AcONa). The lower degree of asymmetric induction can be ascribed to a lack of electronic discrimination of the enantiotopic allylic termini because the donors obtained from (R_p)-1',2-bis(diphenylphosphino)ferrocene-1-carboxylic acid, (R_p)-Hdpc, coordinate Pd(II) as symmetrical P,P-bidentate ligands and thus do not significantly differentiate allylic termini in the reaction intermediate. Besides, the P,P-coordination reduces a possible influence of the amide substituents that are varied. In contrast, the monophosphine donors **58** and **59** coordinate palladium(II) to form O,P-chelate species with considerable electronic asymmetry

and with the amide substituent in the vicinity of the metal centre. This was corroborated by model coordination studies and, mainly, structural characterization of the plausible reaction intermediates **65** and **66** (Scheme 2-23 and Figure 2-7), which revealed the variation in the Pd-C(Ph) bonds lengths to be more pronounced in the O,P-chelate than in the P,P-chelate.



Scheme 2-23. Synthesis of presumed reaction intermediates in allylic alkylation.

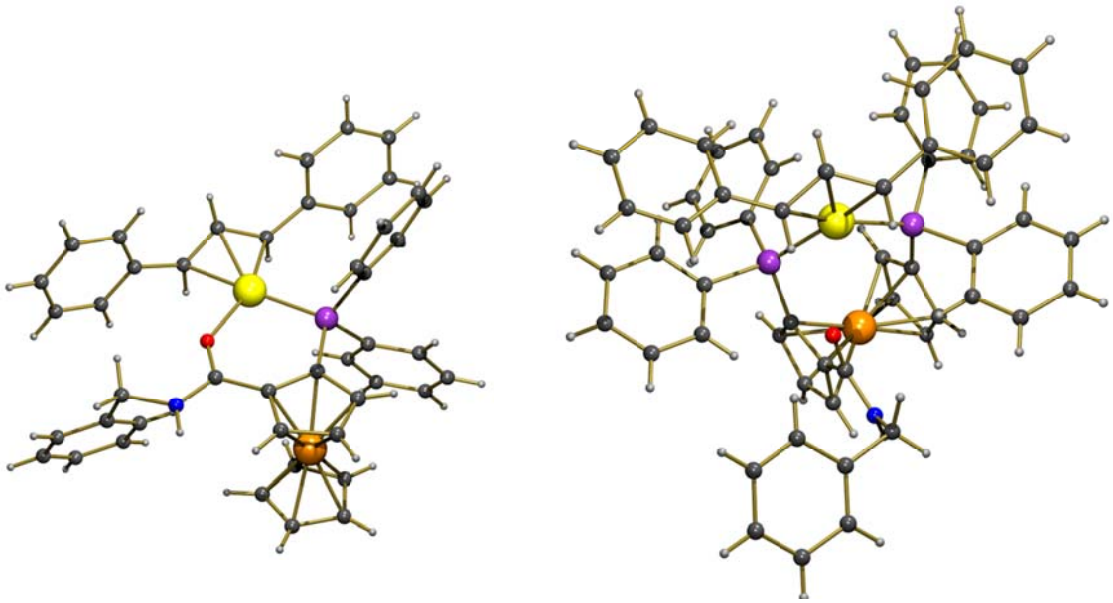
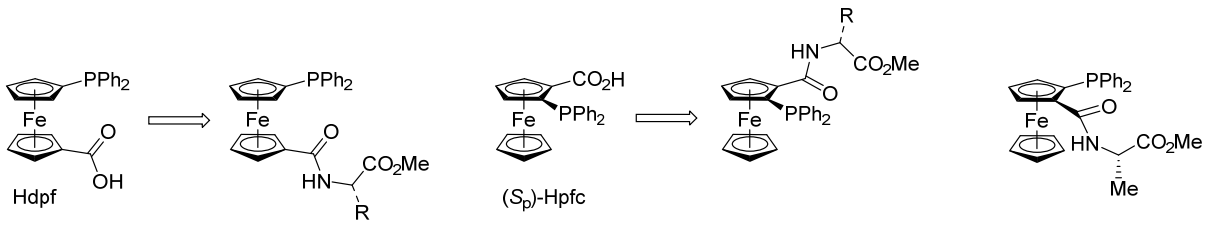


Figure 2-7. View of the complex cations in the structure of (S_p)-**65**·Me_2CO (left) and (R_p)-**66**·CH_3CO_2Et (right). Colour code as in Figure 2-4. Pd-C distances for allylic termini (in Å): (S_p)-**65**, Pd-C(*trans*-O) 2.133(3) Å, Pd-C(*trans*-P) 2.237(3) Å; (R_p)-**66**, Pd-C 2.256(6) Å and 2.226(6) Å (both *trans*-P).

Experiments with amides obtained from (R,R_p)-2-[1-(diphenylphosphino)ethyl]ferrocene-1-carboxylic acid ((R,R_p)-**67**), compounds **68** and **69** in Scheme 2-22, have shown that the amide substituents in this case have only rather minor influence on the enantioselectivity of the reaction (*ee*'s around 40% in this case) but affect the reaction rate (conversions ranged 22-45% under identical conditions; Appendix XXI).[T21]

Considering the easy preparation of amides from amino acid esters, which can serve as the source of chirality, we have prepared a library of chiral phosphinoferrocene carboxamides

with chiral amino acid esters differing by the substitution pattern at the ferrocene unit and in the amino acid side chain, and by chirality at the ferrocene unit (if applicable) and in the amino acid residue (Scheme 2-24).



44 [R = H]
(*S*)-**70** [R = (*S*)-Me]
(*R*)-**70** [R = (*R*)-Me]
(*S*)-**71** [R = (*S*)-*i*-Pr]
(*R*)-**71** [R = (*R*)-*i*-Pr]
(*S*)-**72** [R = (*S*)-CH_2Ph]
(*R*)-**72** [R = (*R*)-CH_2Ph]

(S_p)-**73** [R = H]
(S,S_p)-**74** [R = (*S*)-Me]
(R,S_p)-**74** [R = (*R*)-Me]
(S,S_p)-**75** [R = (*S*)-*i*-Pr]
(R,S_p)-**75** [R = (*R*)-*i*-Pr]
(S,S_p)-**76** [R = (*S*)-CH_2Ph]
(R,S_p)-**76** [R = (*R*)-CH_2Ph]

(S,R_p)-**74** [R = (*S*)-Me]

Scheme 2-24. Phosphinoferrocene carboxamides prepared from amino acid esters.

These donor were also evaluated as catalyst components for Pd-catalysed asymmetric allylic alkylation of 1,3-diphenylallyl acetate with dimethyl malonate (Appendix XXII).[T22] The results presented graphically in Figure 2-8 separately for Hdpf-derived ligands and their planar-chiral analogues clearly indicate that the reaction outcome in terms of both the reaction yield and enantioselectivity depends strongly on the ligand's structure (and also on the reaction conditions). Under the optimised conditions (5 mol.% of Pd catalysts generated from the ligand and $[(\eta^3\text{-}C_3H_5)Pd(\mu\text{-}Cl)]_2$, BSA as the base, reaction at room temperature in dichloromethane), the best results were surprisingly obtained with Hdpf-based ligands, among which the alanine amides **70** provided the best results. Larger substituents in the amino acid part decreased both the yield of the alkylation product and *ee*. In the case of Hfpc amides, the best results exerted planar-only chiral amide (S_p)-**73**, which is the least bulky ligand in the series. Coordination tests with non-chiral Hdpf amide **44** have shown that donors of this type coordinate palladium (at 1:1 Pd:ligand ratio) in O,P-chelating fashion. This not only brings the ligand's chirality to the proximity of the metal centre but also results in differentiation of allylic termini. However, upon increasing the Pd:ligand ratio to 1:2, the phosphinoamides preferentially coordinate as simple P-monodentate phosphines, which diverts the chirality source far from the active metal centre and the chirality transfer (in catalysts with Hdpf-based amides) is lost.

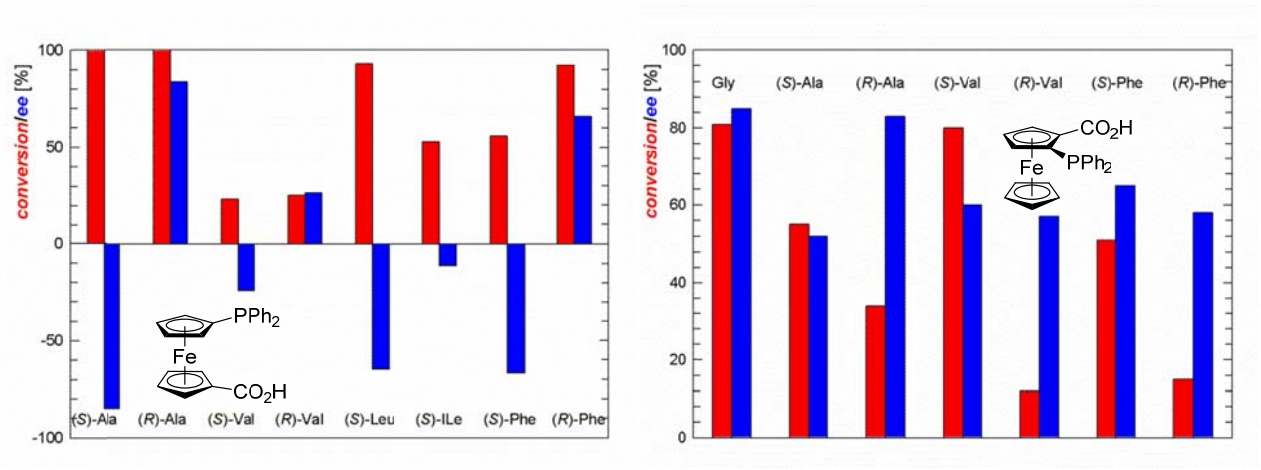
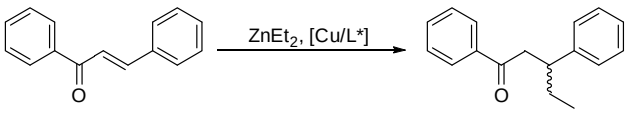


Figure 2-8. Graphical representation of the catalytic results achieved with ligands **70**-**76** in Pd-catalysed asymmetric allylic alkylation (red bars – conversion, blue bars – *ee*). For clarity, the amino acid residue and the parent phosphinocarboxylic acid are shown in the graphs.

Next, the amino acid phosphino-amides were evaluated in the Cu(I)-catalysed addition of diethyl zinc to chalcones. The reaction was found to proceed rapidly (at 0 ºC) and selectively to afford the product of 1,4-addition (Scheme 2-25) but required a careful optimisation of the conditions with respect to the copper-source and reaction solvent (copper(I) triflate/ligand in dichloromethane gave the best results; Appendix XXII).[T23]



Scheme 2-25. Asymmetric, Cu-catalysed conjugate addition of diethyl zinc to chalcone.

The results presented graphically in Figure 2-9 indicate the planar-chiral ligands to be rather poor ligands for this particular reaction. The Hdpf-based donors not only afforded higher yields of the alkylation products but also resulted in higher enantioselectivity. Among these, the best donors were the valine amides **71**, affording 1,3-diphenyl-1-pentanone with a full conversion (100% yield) and in 84% *ee*. As exemplified for a model compound [Cu(**44**-κ^2*O*,*P*)$_2$][CF_3SO_3], the ligands coordinate Cu(I) as P,O-chelating donors with the chiral centre inherent in the amino acid placed in the vicinity of the metal centre.

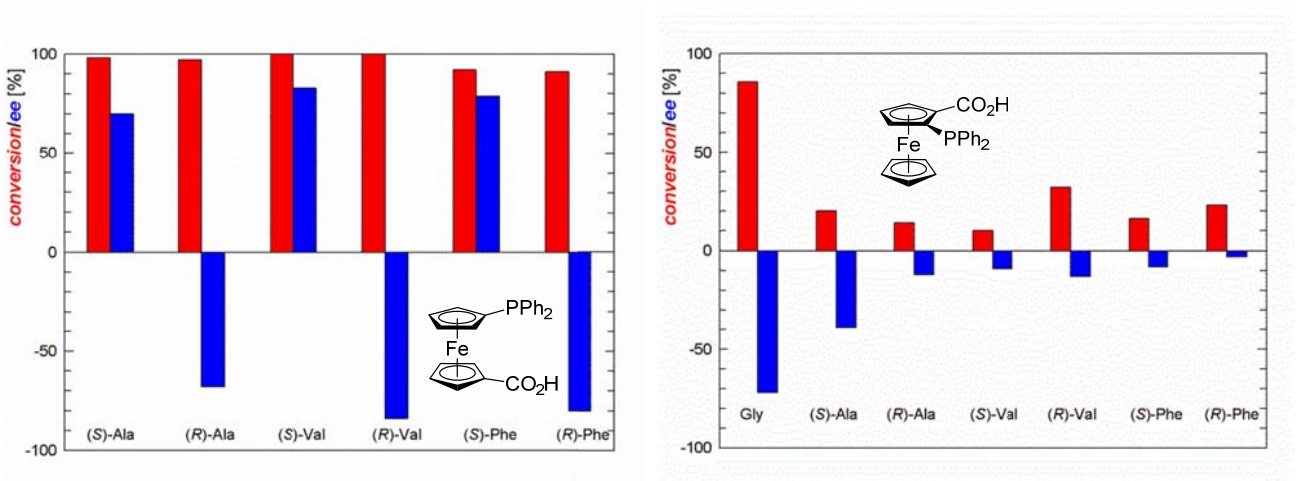
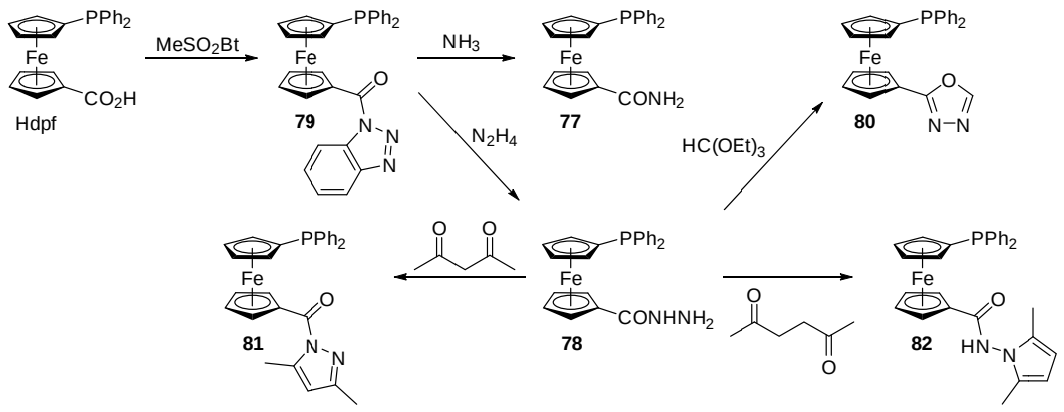


Figure 2-9. Graphical representation of catalytic results achieved with ligands **70**-**76** in Cu(I)-catalysed asymmetric conjugate addition of diethyl zinc to chalcone (red bars – conversion, blue bars – *ee*). For clarity, the amino acid residue and the parent phosphinocarboxylic acid are specified in the graphs.

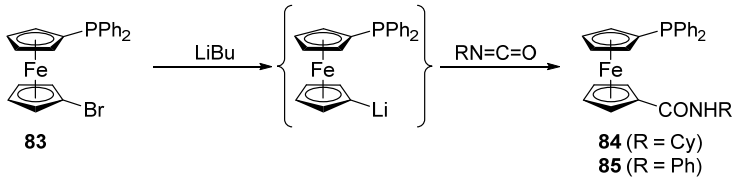
2.5 Elementary studies and new synthetic routes towards phosphinoferrocene amides

In addition to the design of new advanced ligands, attention has been paid also to archetypal phosphinoferrocene carboxamides and alternative synthetic routes towards these donors. For instance, we have synthesised of Hdpf amide **77** and hydrazide **78** (Appendix XXIV)[T24] from 1-(1*H*-benzotriazol-1-ylcarbonyl)-1'-(diphenylphosphino)ferrocene (**79** in Scheme 2-26) and prepared and structurally characterised representative Pd(II) complexes with these donors (*trans*-[$PdCl_2$(**77**-κ*P*)$_2$], [(L^{NC})Pd(**77**-κ*P*)], [(L^{NC})Pd(**77**-κ^2*O*,*P*)][SbF_6], and *trans*-[$PdCl_2$(**78**-κ*P*)$_2$]; L^{NC} = 2-[(dimethylamino-κ*N*)methyl]phenyl-κ*C*^{1}). Hydrazide **78** was next transformed *via* various condensation reactions into phosphinoferrocene heterocycles **80**-**82**, which were also studied as ligands in Pd(II) complexes



Scheme 2-26. Synthesis of amide **77**, hydrazide **78** and heterocycles **80**-**82**.

While searching for alternative methods for the synthesis of phosphinoferrocene carboxamides, we have investigated reactions of 1'-(diphenylphosphino)-1-lithioferrocene generated *in situ* from 1'-(diphenylphosphino)-1-bromoferrocene (**83**)[25] with isocyanates (Appendix XXV)[T25] and carbamoyl chlorides (Appendix XXVI).[T26] The first approach was exemplified by the synthesis of *N*-cyclohexyl amide **84** and *N*-phenyl amide **85** (Scheme 2-27), of which the latter was further converted to Group 10 metal complexes, *trans*-[$PdCl_2$(**85**-κ*P*)$_2$], *cis*- and *trans*-[$PtCl_2$(**85**-κ*P*)$_2$], [(L^{NC})Pd(**85**-κ*P*)], and [(L^{NC})Pd(**85**-κ^2*O*,*P*)][SbF_6].

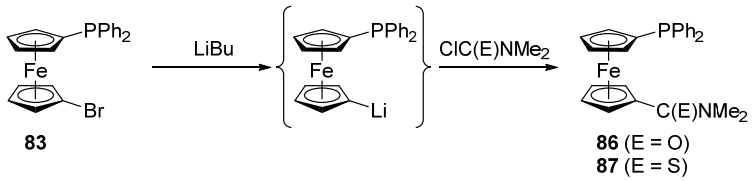


83

84 (R = Cy)
85 (R = Ph)

Scheme 2-27. Synthesis of phosphinoferrocene amides from isocyanates (Cy = cyclohexyl).

Although inherently limited to the synthesis of tertiary amides, the latter method making use of carbamoyl chlorides was found particularly attractive as it offers an access to both amides and their much less studied thio-analogues (Scheme 2-28).



83

86 (E = O)
87 (E = S)

Scheme 2-28. Synthesis of phosphinoferrocene amides from carbamoyl chlorides.

Coordination tests were performed with Group 11 metals and the newly prepared donors **86** and **87** as well as their model compounds **77** and Ph_2PfcCONHMe (**88**; fc = ferrocene-1,1'-diyl). When reacted with [AuCl(tht)] (tht = tetrahydrothiophene), these ligands provided the expected chloridogold(I) complexes of the type [AuCl(L-κ*P*)], while in reactions with [Cu($MeCN$)$_4$][BF_4], they uniformly afforded bis(chelate) complexes [Cu(L-κ^2*O*,*P*)$_2$][BF_4] (L = **77**, **86**-**88**). Complexation experiments with $AgClO_4$ led to analogous products [Ag(L-κ^2*O*,*P*)$_2$]ClO_4 with all (normal) amides (L = **77**, **86** and **88**). In contrast, a similar reaction with thioamide **87** afforded a unique ligand-bridged dimer [Ag(**88**)$_2$(ClO_4)]$_2$ featuring O-coordinated perchlorate anions (see Figure 2-10).

[25] a) I. R. Butler, R. L. Davies, *Synthesis* **1996**, 1350; b) P. Štěpnička, *1'-Functionalised Ferrocene Phosphines: Synthesis, Coordination Chemistry and Catalytic Applications* in *Ferrocenes: Ligands, Materials and Biomolecules*, P. Štěpnička, Ed.; ch. 5, pp. 177-204, Wiley, Chichester, 2008 and references cited therein.

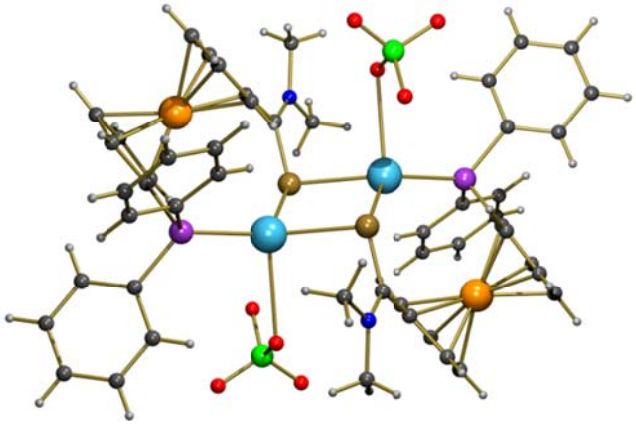


Figure 2-10. View of the molecular structure of complex $[Ag(\mathbf{88})_2(ClO_4)]_2$ (colour code: Ag – light blue, Fe – orange, N – blue, O – red, P – violet, and Cl – green).

A separate study was devoted to a detailed structural characterised and thermal behaviour of non-phosphinylated amide $FcCONH_2$ (Fc = ferrocenyl) and its corresponding hydrazide $FcCONHNH_2$ (Appendix XXVII).[T27] Pyrolysis in air was found to convert the amide into virtually pure hematite (α-Fe_2O_3) in the form of random aggregates of well crystalline nanoparticles.

2.6 Biological properties of transition metal complexes with phosphinoferrocene amides

As a part of our studies on phosphinoferrocene carboxamides bearing functional substituents at the amide nitrogen, we have also synthesised complexes with these donors and various biologically active metals, and examined their cytotoxicity against human ovarian cancer cells A2780 and the analogous cisplatin resistant cell line A2780R, hoping for a possible synergy between the metals (*e.g.*, resulting from a combination of cytotoxic properties of the ligated metal with Fenton chemistry of the iron centre).

The best results in the series of the Pd(II) and Pt(II) complexes with amide **38** equipped with the 2-hydroxyethyl substituent exerted *trans*-bis(phosphine) complexes, *trans*-$[PdCl_2(\mathbf{38}$-$\kappa P)_2]$, *trans*-$[PtCl_2(\mathbf{38}$-$\kappa P)_2]$, showing IC_{50} around 20 μM towards the A2780 cancer cells. The isomeric complex *cis*-$[PtCl_2(\mathbf{38}$-$\kappa P)_2]$ was surprisingly found to be less cytotoxic (IC_{50} = 155 μM; Appendix XXVIII).[T28] Gold(I) complexes studied next, [AuCl(L-κ*P*)], where L = **38**, **42**-**46** and **51**, showed considerably higher cytotoxicity (IC_{50} in the range 0.3-4 μM and 3-20 μM for A2780 and A2780R cell lines, respectively) with the complex possessing the

glycine amide ligand, [AuCl(**44**-κ*P*)], being the most active (Appendix XXIX).[T29] The most extensive series of compounds tested included the neutral (η^6-arene)Ru(II) complexes of the type [(η^6-arene)$RuCl_2$(L-κ*P*)] and two series of cationic complexes resulting *via* halogen removal, [(η^6-arene)RuCl(MeCN-κ*N*)(L-κ*P*)][PF_6] and [(η^6-arene)Ru(MeCN-κ*N*)$_2$(L-κ*P*)][PF_6]$_2$ (Appendix XXX[T30] and XXXI[T31]). The cytotoxicity of these compounds varied considerably with the type of complex, the π-coordinated ligand, the polar pendant in the amidophosphine donor. The lowest IC_{50} values showed the solvento complex [(η^6-C_6Me_6)Ru(MeCN-κ*N*)$_2$(**44**-κ*P*)][PF_6]$_2$ combining the most bulky arene ligand with Hdpf-glycine conjugate as the P-coordinated donor (IC_{50} ca. 4 and 7 μM for A2780 and A2780R cancer cell line, respectively).

3. Summary and outlook

The results discussed briefly in this text illustrate research work focused on the design of new polar phosphinoferrocene donors and studies into their structural chemistry, coordination properties and catalytic use that was carried out in my research group at the Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague during approximately the last decade. The type of this text inherently limits the coverage of the achieved results, which is thus far from exhaustive. No mention is made about, *e.g.*, further synthetic use of phosphinoferrocene amides, and electrochemical and computational studies that were used to complement result obtained by other methods and provide a deeper insight into the properties of the studied donors. Nevertheless, the results outlined above in my opinion demonstrate that phosphino-ferrocene carboxamides represent a versatile class of structurally modular hybrid donors with manifold potential applications. These compounds are accessible by several complementary methods and can be prepared with many structural variations, which in turn opens access to libraries of chemically similar compounds and consequently (after screening) to donors tailored for a particular application.

Personally, I am convinced that research on phosphinoferrocene amides is really worthwhile as it has already resulted, among other, in attractive donors for transition metal-catalysed organic transformations including enantioselective ones, unique donor-unsymmetric *trans*-chelating ligands and truly hydrophilic phosphinoferrocene donors. It also became a part of education of students at different levels of their study and helped in establishing fruitful scientific collaborations. The accumulated knowledge shows promise for the future, thus encouraging our further research in this area.

4. Articles included in this Thesis

[T1] P. Štěpnička, J. Schulz, I. Císařová, K. Fejfarová, *Collect. Czech. Chem. Commun.* **2007**, *72*, 453.

[T2] J. Kühnert, M. Lamač, J. Demel, A. Nicolai, H. Lang, P. Štěpnička, *J. Mol. Catal. A: Chem.* **2008**, *285*, 41.

[T3] M. Lamač, J. Tauchman, S. Dietrich, I. Císařová, H. Lang, P. Štěpnička, *Appl. Organomet. Chem.* **2010**, *24*, 326.

[T4] J. Kühnert, M. Dušek, J. Demel, H. Lang, P. Štěpnička, *Dalton Trans.* **2007**, 2802.

[T5] J. Kühnert, I. Císařová, M. Lamač, P. Štěpnička, *Dalton Trans.* **2008**, 2454.

[T6] P. Štěpnička, M. Krupa, M. Lamač, I. Císařová, *J. Organomet. Chem.* **2004**, *694*, 2987.

[T7] P. Štěpnička, B. Schneiderová, J. Schulz, I. Císařová, *Organometallics* **2013**, *32*, 5754.

[T8] J. Tauchman, I. Císařová, P. Štěpnička, *Dalton Trans.* **2014**, *43*, 1599.

[T9] P. Štěpnička, M. Verníček, J. Schulz, I. Císařová, *J. Organomet. Chem.* **2014**, *755*, 41.

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[T12] J. Schulz, I. Císařová, P. Štěpnička, *J. Organomet. Chem.* **2009**, *694*, 2519.

[T13] J. Schulz, I. Císařová, P. Štěpnička, *Eur. J. Inorg. Chem.* **2012**, 5000.

[T14] J. Tauchman, I. Císařová, P. Štěpnička, *Organometallics* **2009**, *28*, 3288.

[T15] J. Tauchman, B. Therrien, G. Süss-Fink, P. Štěpnička, *Organometallics* **2012**, *31*, 3985.

[T16] J. Schulz, I. Císařová, P. Štěpnička, *Organometallics* **2012**, *31*, 729.

[T17] K. Škoch, I. Císařová, P. Štěpnička, *Organometallics* **2015**, *34*, 1942.

[T18] H. Solařová, I. Císařová, P. Štěpnička, *Organometallics* **2014**, *33*, 4131.

[T19] M. Lamač, J. Tauchman, I. Císařová, P. Štěpnička, *Organometallics* **2007**, *26*, 5042.

[T20] M. Lamač, I. Císařová, P. Štěpnička, *New J. Chem.* **2009**, *33*, 1549.

[T21] M. Lamač, I. Císařová, P. Štěpnička, *Eur. J. Inorg. Chem.* **2007**, 2274.

[T22] J. Tauchman, I. Císařová, P. Štěpnička, *Dalton Trans.* **2011**, *40*, 11748.

[T23] J. Tauchman, I. Císařová, P. Štěpnička, *Eur. J. Org. Chem.* **2010**, 4276.

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[T26] T. A. Fernandes, H. Solařová, I. Císařová, F. Uhlík, M. Štícha, P. Štěpnička, *Dalton Trans.* **2015**, *44*, 3092.

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[T29] J. Tauchman, G. Süss-Fink, P. Štěpnička, O. Zava, P. J. Dyson, *J. Organomet. Chem.* **2013**, *723*, 233

[T30] J. Schulz, J. Tauchman, I. Císařová, T. Riedel, P. J. Dyson, P. Štěpnička, *J. Organomet. Chem.* **2014**, *751*, 604.

[T31] H. Charvátová, T. Riedel, I. Císařová, P. J. Dyson, P. Štěpnička, *J. Organomet. Chem.* **2016**, *802*, 21.