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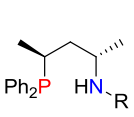
Advanced fine tuning of catalysts: stereoselective coordination and catalysis towards biologically active compounds

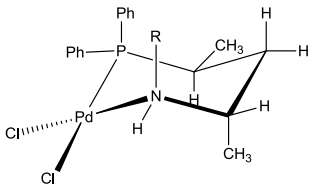
In asymmetric synthesis, the application of transition metal catalysts containing chiral donor atoms is a fruitful approach for achieving high enantioselectivities. The potential of these systems is due to the ability of an efficient transfer of chirality from the catalyst to the substrate. A challenging direction of research in asymmetric synthesis is the design of new catalysts that are composed of metal-ligand assemblies with meta-stable stereochemistries, i.e. the ligand structure is held in a specific spatial arrangement solely due to metal coordination. In this respect, ligands with chiral backbone and with stereogenic N-donors are of great interest.

Six-membered chelate complexes [Pd(**1a–e**)Cl_2], (**2a–e**), [Pd(**1a–e**)(η^3-PhCHCHCHPh)]BF_4, (**3a–e**) of P,N-type ligands **1a-e** with stereogenic nitrogen atom (Figure 1., a) have been prepared [1,2,4]. Unexpectedly, the coordination of the all-carbon-backbone aminophosphines **1a**, **c** and **e** resulted in not only a stereospecific locking of the donor nitrogen atom into one of the two possible configurations (Figure 1., b) but also the conformation of the six-membered chelate rings containing three alkyl substituents was forced into the same single chair structure showing the axially placed substituent on the coordinated N-atom [10,12,13]. The stereodiscriminative complexation of these ligands led to the formation of a palladium catalyst with a conformationally rigid chelate having configurationally fixed nitrogen and electronically different coordination sites due to the presence of P and N donors [1,2].



1a R = *i*Pr
1b R = Me
1c R = Bn
1d R = Et
1e R = (*S*)-CH(CH$_3$)Ph
1f R = (*R*)-CH(CH$_3$)Ph
1g R = (*R*)-CH(CH$_3$)(1-Npth)
1h R = Cy
1i R = Ph
1j R = o-tolyl
1k R = 1-Ad
1l R = CH$_2$CH$_2$OH
1m R = CH$_2$CH$_2$OMe
1n R = (*S*)-CH$_2$CH(CH$_3$)OMe
1o R = CH$_2$CH$_2$NMe$_2$
1p R = CH$_2$CH$_2$CH$_2$NMe$_2$
1q R = CH$_2$-2-Py
1r R = CH$_2$CH$_2$-2-Py

a



b

Figure 1. (**a**) Pentane-2,4-diyl based aminoalkyl-phosphines **1a-g**, (**b**) the stereoselective coordination of **1a**, **1c** and **1e**

A very good correlation has been observed between the steric demand of the N-substituent and the distortion of the chelate in complexes **2a–e** and **3a–e** [2]. Furthermore, it has been proved by spectroscopic and computational methods and X-ray crystallography that sterically more demanding N-substituents are capable of distorting the chelate to a larger extent along one single, well defined conformational pathway (Figure 2., a). The careful variation of the N-substituent thus allows a precise stereochemical fine tuning of the metal's coordination sphere. As a substantiation of this concept, the investigation of complexes **3a-e** revealed that the *exo*/*endo* ratio as well as the rotation of the allyl moiety around the Pd-allyl axis (Figure 2., b) can easily be modified by the proper choice of the nitrogen substituent that has a profound effect on the catalytic properties of these metal species [2].

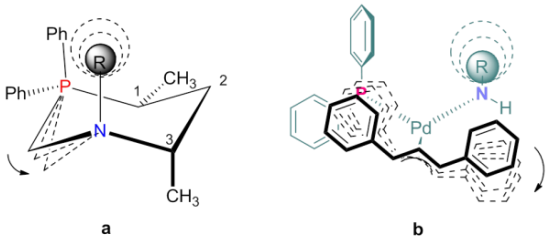
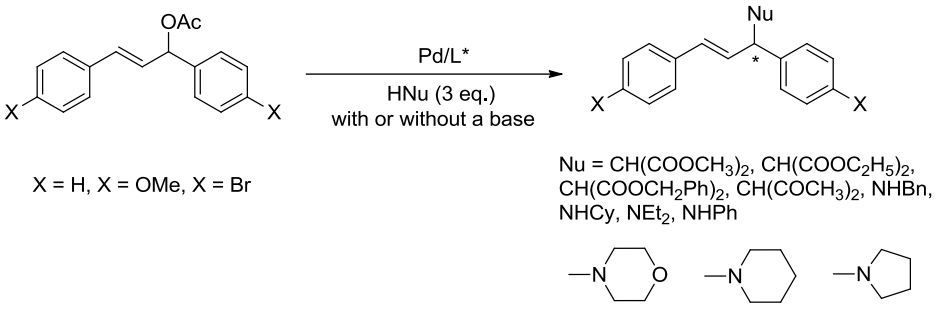


Figure 2. Bending (**a**) of the chelate and rotation (**b**) of the diphenylallyl moiety controlled by the effective steric bulk of the nitrogen side chain (Pd atom in **a** and the chelate ring in **b** are omitted for clarity).

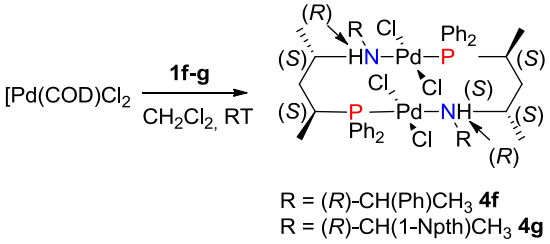
Additionally, Pd-catalysts with ligands **1a-k** (Figure 1., a) provided high enantioselectivities in asymmetric allylic alkylation (up to 96% *ee*) and amination (up to 90% *ee*) reactions (Scheme 1.) [1,2,4]. One of the key principles of green chemistry is the elimination of solvents in chemical processes. When the amount of nucleophile/solvent ratio in amination processes was increased the activity of the catalyst also increased. Under solventfree conditions using preformed [Pd(η^3-Ph_2-C_3H_3)(**1a**)]BF_4 complex (**3a**) as catalyst moderate *ee*s (up to 40%) and complete conversions in 0.5 min was obtained resulting in a remarkably high turnover frequency of >12000 1/h [4]. It was also proved that the L/Pd molar ratio has a profound effect on the selectivity of the catalytic process [1,4].



Scheme 1. Asymmetric allylic substitution reactions

Furthermore, new classes of potentially tridentate alkane diyl based P,N,N and P,N,O type ligands (**1l-r**, Figure 1) have been synthesized and applied in palladium-catalyzed asymmetric allylic alkylation and in iridium catalyzed enantioselective hydrogenation of ketones. The coordination chemistry of the ligands was thoroughly studied by spectroscopic and computational methods and X-ray crystallography. It has been established that the stereoselectivity of the ligand's coordination in a square planar metal platform is affected by the same factors as was found for simple bidentate P,N-systems. It was also found that the activity and enantioselectivity of the transition metal catalyst can strongly be influenced by the structure of the third coordination site with a nitrogen or an oxygen donor atom. Especially, the hemilabile character of this sidearm affects the catalytic process. The new iridium catalysts proved to be extremely active, chemo- and enantioselective (up to 96% ee) in the asymmetric hydrogenation of chalcones.

It was surprisingly found that in the reaction of ligands **1f-g** with $Pd(COD)Cl_2$ dimeric complexes of the type $[Pd(\mathbf{1f\text{-}g})Cl_2]_2$ (**4f-g**) are formed (Scheme 2.) instead of the mononuclear systems [8]. The novel palladium(II)-complexes **4f-g** have been studied by various 1D and 2D NMR techniques in solution and by single-crystal X-ray diffraction. As an unprecedented case, ligands **1f-g** were found to yield exclusively 12-membered cyclic dinuclear Pd(II)-complexes with stereospecific coordination of both of the donor nitrogen atoms.



Scheme 2. Formation of binuclear complexes **4f-g** with stereospecific coordination of N-functionalities

Phosphite and phosphoramidite type ligands constitute a particurlaly interesting class of compounds due to their unique catalytic properties [11,15]. The asymmetric hydrogenation of benchmark substrates dimethyl itaconate and (*Z*)-α-acetamido cinnamic acid methyl ester with chiral pentane-2,4-diyl based phosphine-phosphite (**1s**-t) Rh-complexes immobilized on the support with heteropolyacid (phosphotungstic acid, PTA) as anchoring agent has been studied (Figure 3.) [5].

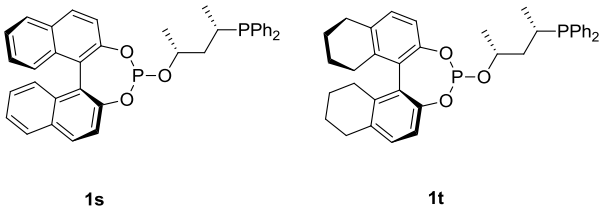
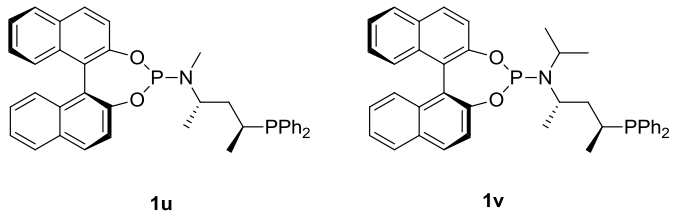


Figure 3. Phosphine-phosphite type ligands used for asymmetric hydrogenation in flow reactor

The complexes have been supported on commercially available Al_2O_3 by the Augustine method. The novel heterogeneous catalysts were applied in a high throughput flow reactor. The effect of the pressure, temperature, substrate concentration and flow rate was thoroughly screened to optimize reaction conditions. The immobilized catalysts proved to be remarkably stable and could be used six hours in the microfluidic based reactor without a significant loss of activity and selectivity. Furthermore, under optimized conditions the hydrogenation product could be obtained with high activity (TOF > 2000 h^{-1}) and enantioselectivity (up to 99% *ee*). As the first precedent, the potential of supported Rh(P-OP)-complexes under flow conditions has been presented [5].

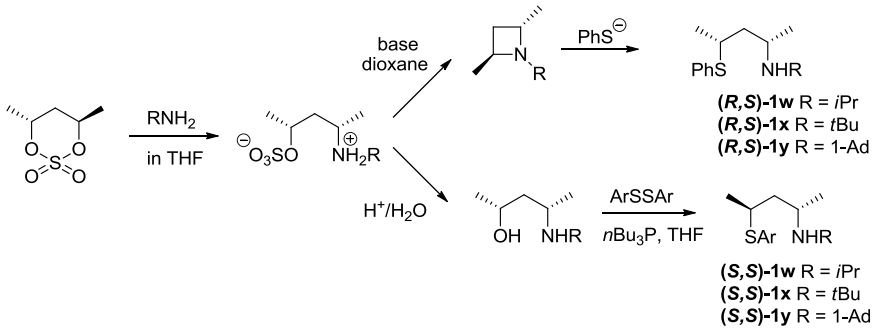
Single crystal of the phosphine-phosphoramidite (PPA) (11b*S*)-*N*-((2*S*,4*S*)-4-(diphenylphosphino)pentan-2-yl)-*N*-methyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine **1u** was prepared and structurally characterized by single-crystal X-ray diffraction and DFT calculation (Figure 4.) [3]. Structure elucidation revealed unique features which are providing excellent chemical stability. The ligand conformation provides optimal chelating structure. Further evidence was found for through-space ^{31}P-^{31}P NMR coupling. Iridium complex of UPPhos (**1v**, Figure 4.) was tested in the iridium-catalysed asymmetric hydrogenation of imines and prochiral quinoline derivatives, where excellent *ee*s (up to 92%) could be obtained [3].



1u 1v

Figure 4. Phosphine-phosphoramidites used for the asymmetric hydrogenation of imines

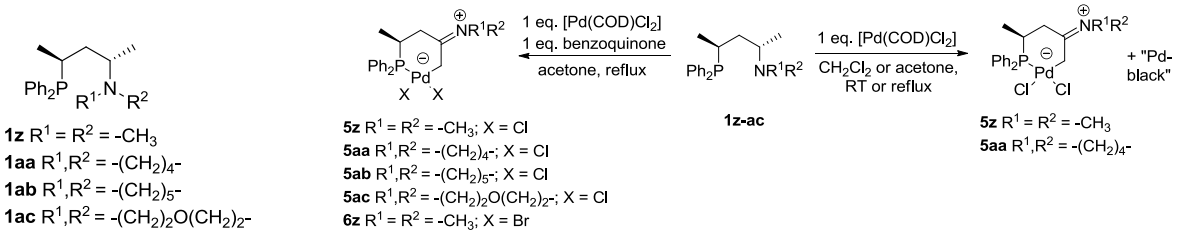
Novel (*S*,*S*)- and (*S*,*R*)-PhSCH(CH_3)CH_2CH(CH_3)NHR types ligands (R = *iso*propyl, *tert*butyl, 1-adamantyl) were prepared according to Scheme 3 ((*R*,*S*)-**1w-y** and (*S*,*S*)-**1w-y**) [9,16,17]. The synthesis of a valuable intermediate chiral N-substituted azetidine and its reaction with NaSPh, gives the heterochiral ligand in an optically pure form (Scheme 3.). The homochiral analogues could be prepared by the hydrolysis of the corresponding aminoalkyl sulfate and by the substitution of the OH-group of the alcohol with complete inversion of the stereogenic center. The palladium complexes of the ligands were thoroughly investigated by 1D and 2D NMR spectroscopy as well as X-ray crystallography. It was demonstrated that both the sulfur and nitrogen donoratom of the homochiral ligands coordinate stereoselectively to the metal. This exceptional coordination ability was utilized in asymmetric allylation reactions, where high enantioselectivities (up to 92%) were obtained.



Scheme 3. Synthesis of S,N type ligands

New type of zwitterionic palladium(II) complexes have been prepared starting from Pd(COD)X_2 (X = Cl or Br) and the corresponding aminoalkyl-phosphine ligands $Ph_2PCH(CH_3)CH_2CH(CH_3)NR^1R^2$ (**1z-ac**) (**1z** R^1 = R^2 = -CH_3; **1aa** R^1,R^2 = -$(CH_2)_4$-; **1ab** R^1,R^2 = -$(CH_2)_2O(CH_2)_2$-; **1ac** R^1,R^2 = -$(CH_2)_5$-) in the presence of one equivalent of

benzoquinone (Scheme 4.) [6]. The complexation reaction leads to the dehydrogenation of the ligand and the formation of air-stable palladium complexes **5z-ac** and **6z**. The analysis of the complexes in the solid phase by IR spectroscopy and X-ray crystallography revealed that the ligands coordinate to Pd via P,C-chelation forming six-membered palladacycles with a Pd-C(sp^3)-bond.



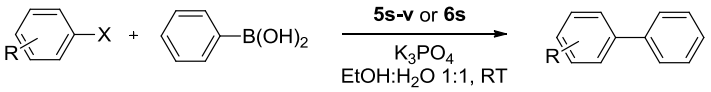
1z $R^1 = R^2 = -CH_3$
1aa $R^1,R^2 = -(CH_2)_4-$
1ab $R^1,R^2 = -(CH_2)_5-$
1ac $R^1,R^2 = -(CH_2)_2O(CH_2)_2-$

5z $R^1 = R^2 = -CH_3$; X = Cl
5aa $R^1,R^2 = -(CH_2)_4-$; X = Cl
5ab $R^1,R^2 = -(CH_2)_5-$; X = Cl
5ac $R^1,R^2 = -(CH_2)_2O(CH_2)_2-$; X = Cl
6z $R^1 = R^2 = -CH_3$; X = Br

5z $R^1 = R^2 = -CH_3$
5aa $R^1,R^2 = -(CH_2)_4-$

Scheme 4. Synthesis of six-membered P,C-type palladacycles

The observed structures were also confirmed by theoretical calculations and in solution by 1D and 2D NMR techniques. The novel zwitterionic complexes have been tested for their ability to catalyze room temperature Suzuki-Miyaura coupling reactions in ethanol/water 1:1 (Scheme 5.). The catalysts proved to be highly active in the reaction of aryl bromides/iodides and organoboron reagents exhibiting high functional group tolerance [7].



R = Me, OMe, tBu, CHO, CF_3, Cl, etc.

Scheme 5. Suzuki-Miyaura coupling catalyzed by complexes **5s-v** and **6s**.

Asymmetric transition metal catalysis represents one of the most important synthetic methodology to achieve the building blocks of biologically active compunds in an opically pure form. Higher atom economy, activity and selectivity can be achieved or more complicated reaction sequences can be substituted by simple catalytic steps. It is, therefore, not surprising that the design and synthesis of novel transition metal catalysts (ligands) providing high activity and (enantio)selectivity is a fundamental requirement for further progress in this field. The modular synthetic methodologies developed for the synthesis of several heterobidentate ligand families, their versatile coordination abilities and remarkable catalytic features reported herein underline the significance of such research.

Our studies clearly prove the fact that apparently “minor” but carefully chosen changes in the structure of the catalysts can dramatically improve their performances and also broaden the scope of the catalyst design, which can be taken as a rewarding justification of research efforts in this direction.

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