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Highlights of 45 years of research: A personal account

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ABSTRACT

This part of my biosketch, which I prepared on invitation by the Editors, made me realize again how entangled my interest for doing research and teaching and management have been over the years. Working together with my students and colleagues has always been a strong motivation and pleasure for me and I hope that this sketch of our research reflects our common enthusiasm for what we achieved.

In hindsight, trying to overlook almost 45 years of research, various main themes can be discerned that marked my fundamental research in the subsequent periods at TNO Utrecht (1968–1977), University of Amsterdam (1977–1986) and University of Utrecht (1986–2007). Overarching has been my preference and fascination for working with nitrogen based ligands (culminating in the design and use of the NCN-pincer ligand platform, vide infra), the study of synthetic routes for organometallics (most importantly trans- and cyclo-metallation routes), the use of NMR for the study of the stereochemistry of organometallics (cf. the early use of ^{107,109}Ag NMR for detecting and following the formation of coordination compounds with helical structures), chemistry involving organometallic radicals (cf. organozinc and aluminum α-diimine chemistry, development of β-lactam synthesis routes), self-assembly of organometallics to discrete aggregated species (cf. organo-Cu, -Li and cuprate chemistry), the development of palladium complexes and homogeneous metal catalysts with simple amine ligands, the synthesis of, and catalysis with, dendrimers decorated with organometallic catalysts, mimicking the active center of metallo-enzymes as well as the synthesis of organometal-lipase hybrids for catalysis.

Being educated in an "eco"-system of contract research, in concert with fundamental research, the results of the above outlined items were not only published in journals with peer review (>850) but also in the patent literature (>40). Most important were the results reported in over 85 PhD theses that I had the privilege to supervise as PI. The references refer to key-papers describing this body of work. The respective reference numbers are given at the heading of each paragraph. The full list of publications in peer reviewed Journals can be found in http://www.gerardvankoten.nl and www.uu.nl/staff/GvanKoten.

1. General

As indicated above, nitrogen ligands fascinated me throughout my research career, right from the very beginning. Whereas in my early days ligands with phosphorous donor atoms were the dominating "privileged" ligands in inorganic and organometallic chemistry; they have remained so up until now. However, my interest for nitrogen-containing ligands was fortified for a number of reasons; *i,* Nitrogen is one of the smallest donor atoms. This results in short N-metal bond distances thus affecting/interfering with its (N)R-substituents (also because of the short N-C bonds, *viz.* N-cone angle considerations) and strongly with other ancillary groupings within the metal coordination sphere, *ii,* N-donor atoms facilitate the formation (and stabilization) of higher oxidation states of the metal center and so can direct redox processes generally in a different redox range than comparable P-donor ligands do, *iii*, N-donor sites in π-N=X systems (sp^2-N) promote one-electron metal-to-ligand (M→N=X) charge transfer processes resulting in ligand centered radical chemistry, iv, generally, N-centers are stronger Lewis basic sites (exclusive σ-donators) than *e.g.* corresponding P-, S-, or O-centers and thus are more effective proton binders assisting, for example, the effective activation of C-H bonds (as occurs, for example, in cyclometallation processes); for frequently used ligands, see Fig. 1.

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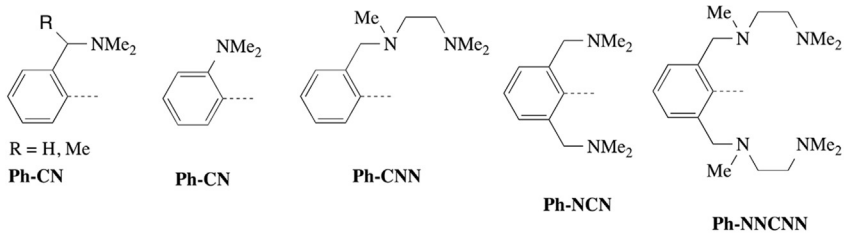


Fig. 1. Some of the frequently used monoanionic C,N_n-donor ligands.

2. Chemistry at TNO (1968–1977): fundamental and applied chemistry

2.1. Organo-copper and -lithium chemistry [1–5]

At the start of my organometallic research, during the late 60ies early 70ies, the use of nitrogen-based ligands was rare, or considered a rarity. However, in the framework of the designated INCRA contract, my task was to create novel organocopper(I) compounds that, in open waters, would slowly hydrolyze so producing certain concentrations of biocidal copper ions, *i.e.*, to reach this goal I deliberately chose to refrain from the expected stabilizing effect of phosphorus ligands on the Cu(I)-C bond. It is for this reason that right from the beginning of my organocopper research, I preferred to work with nitrogen donor atom based ligands, *cf.* Fig. 1. Ultimately, this turned out to be a fascinating choice and led to the discovery of the first examples of thermally very stable arylcopper(I) compounds with a σ-C_{ipso}-Cu(I) bond; these included one or two *ortho*-substituents with heteroatom atoms that could potentially also coordinate with copper(I), see **1**. The aggregated structure (*e.g.*, **1** is a tetramer) is a key structural feature of organocopper(I) compounds, see Fig. 2.

Mass spectroscopic studies of mixtures of pure RCu compounds revealed that these aggregates undergo inter-aggregate exchange in solution. NMR studies established that the aryl rings of *e.g.*, **1**, rotates along the C_{ipso}-C(4) axis of the electron deficient two electron-three center bond; the complex stereochemistry of arylcopper aggregates containing chiral *ortho*-substituents could likewise be studied in detail. Initially, the impurity of the synthesized organocopper(I) material created a major problem which hampered their testing as biocides. Careful study of this phenomenon showed, however, that not only RCu aggregates undergo interaggregate exchange but that also, and sometime with high selectivity, R'Cu and CuX (and MX in general) species can become involved to the effect that thermodynamically stable hetero aggregate species can be formed and isolated in almost quantitative yield; an example of this is $Cu_6Br_2(C_6H_4NMe_2\text{-}2)_4$ **2** [3]. In this case, the heteroaggregate is more stable than the homoaggregate $Cu_n(C_6H_4NMe_2\text{-}2)_n$ to the effect that isolation of the pure organocopper (from the reaction of $Li(C_6H_4NMe_2\text{-}2)$ with CuBr in Et_2O) is impossible. This finding pointed out that selection of the nature and purity of the reagents in the organometallic chemistry with coinage metals is of crucial importance. Key success factors in our organocopper (and related -silver and -gold) studies appeared the isolation and structural characterization of the corresponding organolithium reagents as pure starting materials. This insight led also to an understanding of the exciting structural features of organolithium compounds and provided easy access to the corresponding ate-complexes, *e.g.*, cuprate **3**. This latter species obviously results from reaction of equivalent amounts of the corresponding pure lithium and copper (**1**) compounds.

In the early 70ies, getting structural information of one's compounds in the solid state was not as easy as it is nowadays. Accordingly, it still amazes me that already at that time the distinct aggregated structure of **3** and its corresponding silver-lithium species in solution could be unambiguously established by the study of ^{1}H, ^{13}C, $^{6,7}Li$ and $^{107,109}Ag$ (for the corresponding argentate $Ag_2Li_2R_4$) NMR spectra. The structures in the solid state were solved much later during my years at the UvA.

It is obvious that in our organometallic chemistry of coinage metals (already during the early 70ies), we started to think in terms of handling RM and MX building blocks that form by self-assembly, inter- and/or intra-aggregate exchange as isolable, thermodynamically stable homo- and hetero-aggregates, *i.e.* using terms that nowadays represent common approaches in the chemistry based on the use of non-covalent interactions for the construction of new materials.

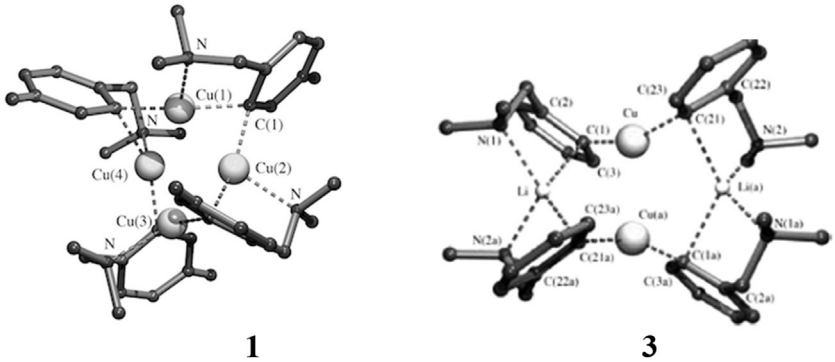


Fig. 2. Structures of **1** $Cu_4(C_6H_3CH_2NMe_2\text{-}2\text{-}Me\text{-}4)_4$ [6] and **3** $Cu_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ [7]. (Reproduced with permission from ref 3; copyright Wiley-VCH Verlag GmbH & Co. KGaA.).

2.2. Applications

As part of a contract research project, directed to make hydrogenation catalysts, we deposited pure organocopper and cuprate compounds on suitable supports and reacted these, subsequently, with either Rh, Pd or Pt salts to make what nowadays would be called, mixed Cu-transition metal nano-layers. However, in those days we had no means to analyze these nano-layers. Many years later, in collaboration with Prof. John Geus at the UU, I returned to this subject and could show that these materials are indeed very small nanosized species and are excellent semi-hydrogenation catalysts of acetylenes [8].

2.3. Stereochemistry of organometallics

Right from the beginning I became particularly interested in the study of the stereochemistry of organometallics by using the emerging power of novel NMR machines and techniques. A first subject of study (1976) addressed questions concerning the stereochemistry and intramolecular dynamics of potentially five-coordinate chiral R'R″R‴LSnBr compounds (L = neutral N donor ligand). Rather than using an external amine ligand, we used an intramolecularly positioned one, *i.e.*, a (*S*)- or (*R*)-Me_2NCHR-substituent, in one of the organo groupings at the tin center, *e.g.*, as in κ^2-*C,N*-[2-(Me_2NCHR)C_6H_4]MePhSnBr. This appeared to be an excellent choice allowing for the monitoring of the stereogenity of the tin center, *i.e.*, of the intramolecular coordination of the amine substituent leading to a five-coordinate tin center and the fluxionality of the penta-coordinated state of the molecule [9]. Information gathered in this initial study appeared to be of great interest for much of our later stereochemical studies. It was also during this time that we embarked on the NCN-pincer chemistry. In a quest for water-soluble triorganotin compounds, we synthesized a bis-*ortho*-amine substituted, *i.e.*, a NCN-pincer tin compound which appeared very soluble in water. It exists in water as a dissociated salt comprising of five-coordinate κ^3-*N,C,N*-[2,6-(Me_2NCHR)C_6H_3] MePhSn cations **4** and Br anions [10], see Fig. 3.

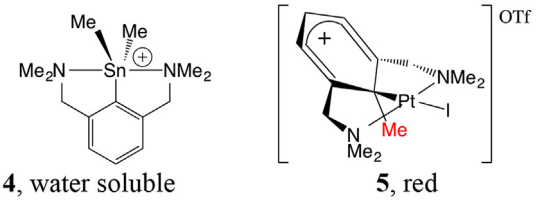


Fig. 3. The first examples of NCN-pincer metal compounds.

This discovery of the first example of this congener of a carbocation initiated my interest in the exploration of what is nowadays called the "Pincer"-platform as a privileged ligand with its potentially tridentate metal binding manifold. Concurrent with this tin-pincer chemistry, we began to explore the synthesis and reactivity of metal-d^8 pincer compounds, *e.g.* formation of seminal **5** [11], for which real support came during my time at the UvA, vide infra.

3. Chemistry at University of Amsterdam (1977–1986): inorganic chemistry

When I moved to the University of Amsterdam (UvA), it was time to start new projects. In the beginning these, on the one hand, were related to the interest of the Kees Vrieze-laboratory, in particular α-diimine chemistry [12], but, on the other hand, I moved into new directions in which emphasis of my research was more on (bio)inorganic chemistry and metal-mediated or catalyzed organic synthesis. Highlights (for me) were the excursions in reactions of α-diimine-ligands with organometallic reagents, R_nM (M = Li, Mg or Zn and Al), some studies with the corresponding, in situ prepared, 1,4-tetraaza-1,3-butadiene ligands, which central 1,3-diene system comprises four N-atoms, more organocopper chemistry because of the increasing power of X-ray diffraction methods which was indispensable to obtaining the structural features of these aggregated species, and some studies in the realm of bioinorganic chemistry including copper and silver complexes that may mimic copper containing active sites of the few metalloenzymes of which the structures at that time were known.

3.1. α-Diimines as ligands/reactants in organo-zinc and -aluminum chemistry [13–16]

One of these projects involved reactions of α-diimines, R'N=CHCH=NR' (R′-DAB) and 2-PyCH=NR″ (R″-Pyca), with organometallic reagents of which its metal center primarily addresses the two N-donor atom's lone pair of the diimine ligand but leaves the α-diimine π-system unaffected, see Fig. 4. We concentrated on the reactions of common organo-zinc and -aluminum reagents, R_2Zn and R_3Al, respectively, with R′-DAB and R″-Pyca, respectively. The expected 1:1 R_2Zn(R′-DAB) complexes were formed indeed but could only be isolated (X-ray) for R = Me; the homologous complexes (R = Et, iPr and t-Bu) appeared to be increasingly less stable and observable only at lower temperatures. At higher temperature, e-transfer from one of the σ-R-Zn bonds (*i.e.*, homolytic Zn-C

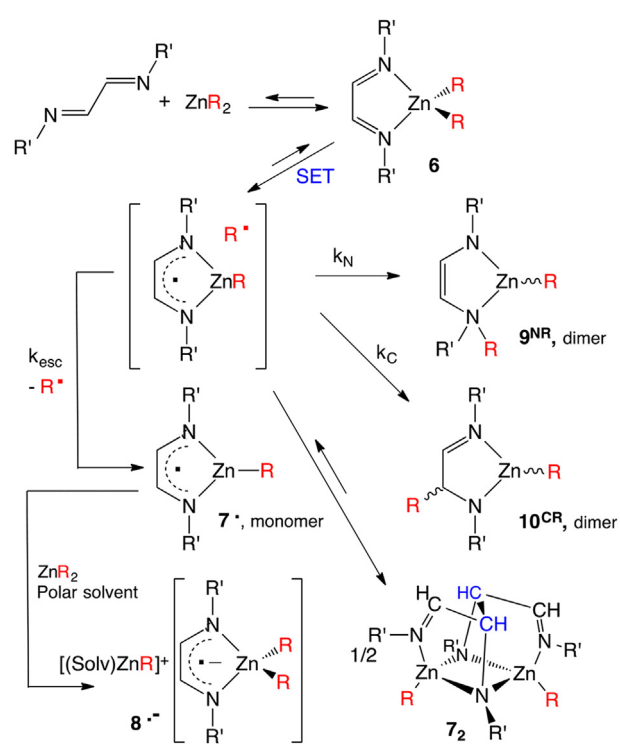


Fig. 4. Reactions between ZnR_2 with α-diimine ligands: postulated SET mechanism and characterized compounds, **6** (X-ray, R = Me), **7•** (EPR), $\mathbf{7_2}$ (NMR, Xray, for R″-Pyca), $\mathbf{8^{\bullet -}}$, $\mathbf{9^{NR}}$ and $\mathbf{10^{CR}}$ [15].

bond cleavage) into the π*-orbital of the *N,N*-bidentate bonded α-diimine ligand occurred thus forming a persistent organozinc radical [R-Zn(R′-DAB)]• (**7•**) and the corresponding, highly reactive R•-radical. In the reaction mixture, the presence of [R-ZnR′-DAB]•, which later has been prepared and isolated pure via an independent route, has been clearly shown by EPR spectroscopy; the electron is primarily located on the N=CC=Ns' π*-system indicating that in this chemistry the α-diimine behave as, what is now termed, "non-innocent" ligand. Moreover, in the case of [R-Zn(R″-Pyca)]•, the persistent organometallic radical is in equilibrium with its dimer (cf. $\mathbf{7_2}$, characterized by X-ray structure determination [16]) resulting from the formation of a central C-C bond between two central Cα atoms; this dimer formation is reversible and could be studied by NMR spectroscopy. Depending on the reactivity (lifetime) of the R•-radical initially formed, radical escape occurs from the solved cage (for R = Me) or back reacts (for R = Et) on the center with the highest spin density, which in fact are the N-atoms of the NCCN system (EPR studies) thus forming a N-alkylated product, RZn(NR-CH=CH-NR'R), cf. $\mathbf{9^{NR}}$. This N-alkylated product formation route was a big surprise as the formation of the C-alkylated product, RZn(NR-CR'H-CH=NR), $\mathbf{10^{CR}}$, following a classic polar 2e-mechanism was anticipated. Later studies with corresponding aluminum compounds revealed that the N-alkylated compounds are kinetic products whereas the C-alkylated product is the thermodynamic one: as thermal experiments with the pure N-alkylated products pointed out [17]. Extension of this study to α-imino ketones, which contain the 1-aza-4-oxa-1,3-butadiene system, afforded, in reaction with R_2Zn, the corresponding organozinc enolate, *i.e.* selective N-Et alkylation occurred, in concert with the intermediacy of the persisting organozinc(α-imino ketone) radical (electron on the π*-orbital) and subsequent back reaction of the Et• radical on the N-center of the N=CC=O manifold [18].

It is interesting to note that the discovery of the latter, facile route, to the formation of organozinc enolates initiated the discovery of a new route to β-lactams that we later extensively studied at the UU, vide infra.

3.2. An excursion into bioinorganic chemistry; discovery of double helix and polymeric structures [19–21]

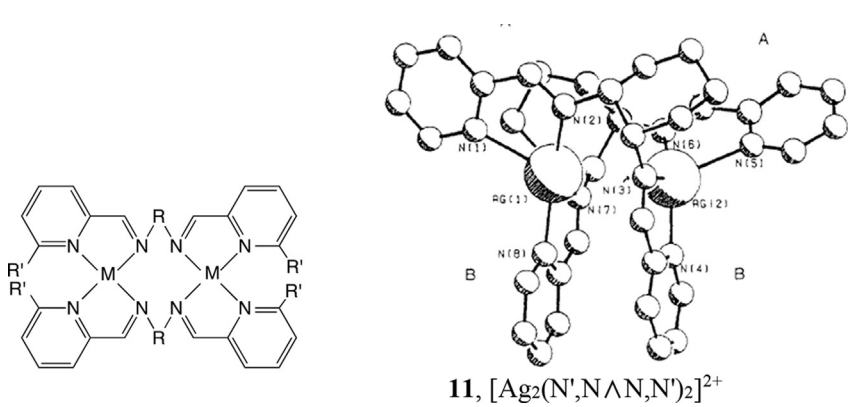
As an extension of our studies with the Pyca ligands, I started a program to study dicationic copper(I) complexes which are formed between copper or silver triflate and new tetradentate ligands consisting of either two Pyca (N′, N) or two 2-thienylcarbaldimine (S, N) ligands linked by a (*R*,*S*)-cyclohexanediyl bridge (*viz.* R in Fig. 5) via its imine-N atoms. The ligands in these dicationic complexes, which have $[M_2(N',N\wedge N,N')_2]^{2+}$ and $[M_2(S,N\wedge N,S)_2]^{2+}$ stoichiometry, act either as bis N,N'- or bis N,S-bidentate donors. The conformation of the chiral cyclohexanediyl linker forces a double-helix structure on the resulting Cu(I) and Ag(I) structures in which the (two) metal centers either have both Δ or Λ configuration, see Fig. 5 for the Ag(I) complex. In this study, our earlier developed experience with $^{107,\ 109}$Ag and ^{15}N NMR spectroscopy (which is now standard on NMR machines) appeared crucial and helped to provide extensive information about the conformational and configurational stability of these complexes in solution [19,20].

This experience was used in another project centered around a polydentate donor ligand system N-[N-((5-R-thienyl)methylidene)-L-methionyl]histamine (R = H, Th-Met-Histam, **12**) comprising two amino acids and having only a single stereogenic carbon center. Although "modeling" (with a simple molecule building kit) of this tetradentate ligand suggested, that by folding, it could coordinate with its N and S donor atoms to one, central, metal (this is the case for the Cu(II) complex), thus mimicking what is present in, for example, a copper-protein. In a reaction of AgOtf with one equivalent of Th-Met-Histam the actual silver-to-ligand self-assembly turned out to result in the formation of a polymer **13** in which the ligand bridges out to three different cationic silver centers, see Fig. 6.

The polymeric structure of this 1:1 $[Ag(I)Th\text{-}Met\text{-}Histam]^+$ (and isostructural Cu(I)) complex possesses an intriguing helical polycationic structure, both in the solid state and in solution. The origin of the observed self-organization could be related to the specific structure of the Th-Met-Histam molecule, which, as a result of steric constrains and the number, nature, and partitioning of its donor and acceptor functions, apparently is pre-organized to each coordinate to three different Ag(I) cations [21]. A noteworthy aspect of the structure of **13** was its unique stereoregularity that is induced by the ligand's single stereogenic carbon center Cα. This chemistry I found fascinating, however, as was the case in a number of other "excursions" we proposed to science financiers, the peers of our proposals were not always that enthusiastic.

3.3. Pincer-Metal Chemistry [22]

Right from its beginning in the TNO-laboratories, this chemistry was full of big surprises. It started with the quest for water-soluble triorganotin halide compounds as potential biocides and, as a consequence of our studies of pentacoordinate-triorganotin halide compounds, vide supra, water soluble $[SnPhMe\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}]^+Br^-$ **4** was synthesized. The fact that in the latter pentacoordinate tin cation the three donor atoms of the pincer platform



11, $[Ag_2(N',N\wedge N,N')_2]^{2+}$

Fig. 5. Dicationic complex Ag(I) complex **11**. The chiral cyclohexanediyl linker (R) forces a double-helix structure providing the Ag(I) centers either to have both Δ or Λ configuration. (Figure of **11** reprinted with permission from ref 19; copyright {2017} American Chemical Society.)

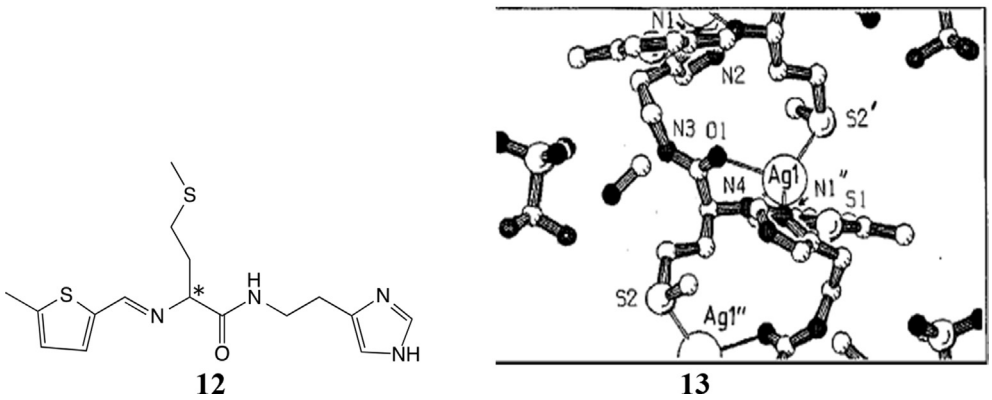


Fig. 6. Free, enantiopure ligand Th-Met-Histam **12**; *(C_α) is a stereogenic center; $[Ag(I)Th\text{-}Met\text{-}Histam]^+$ complex **13** (polycationic coordination polymer: Reproduced with permission from ref 21; copyright Wiley-VCH Verlag GmbH & Co. KGaA.).

are situated in one plane is an obvious structural feature of the NCN-pincer platform. To me, in relation to processes taking place at a transition metal center during oxidative addition/reductive elimination processes, this observation seemed highly important. So, one day we used NCN-pincer lithium as precursor for the synthesis of the corresponding NCN-pincer platinum compounds. Subsequent reaction of this platinum(II) compound with MeI, in order to study redox processes, led to the discovery of the first example of a stable arenium platinum(II) compound **5** [11] showing that a (pincer)C_{ipso}-C(Me) bond had been formed; in further studies, this C-C bond formation appeared to be a reversible process. This discovery represents a seminal finding for TM compounds with the monoanionic XCX-pincer platform in which X represents not only N donor atom groupings but likewise groupings with either P or S donors, vide infra. In my laboratories at both the UvA and the UU, XCX-pincer-metal research became an important subject.

During the UvA period, our main attention was directed to further studies of the reactivity of NCN-pincer metal-d^8 complexes towards various electrophiles, *e.g.* MeI, X_2, Lewis acidic and redox active metal halides ($Cu^{II}X_2$) [22,23]. This led, among others, to classic examples in which the filled metal's d_z^2 orbital plays a donating role in binding the electrophile as, for example in $[Pt^{II}I(\eta^1\text{-}I_2)\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}]$ **14** (see Fig. 7).

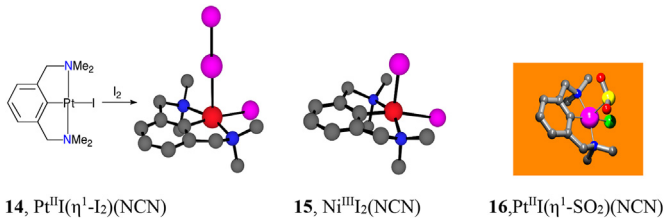


Fig. 7. Pt's formally filled d_z^2 orbital acting as donor to electrophiles (acceptors) I_2 **14**, and SO_2 (**16**). Reaction of $Ni^{II}I(NCN)$ with I_2 resulting in one e-transfer yielding paramagnetic d^7-**15**.

This species contains an end-on bonded η^1-I_2 involving a $Pt^{II}\rightarrow I_2$ interaction (X-ray and EXAFS) and later examples of formulae $[Pt(M)(ZZ')\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}]$ (ZZ' = monoanionic bridging ligand RNYNR′, M = HgX_2 or AgX) featuring direct $Pt^{II}\rightarrow Hg^{II}$ and $Pt^{II}\rightarrow Ag^{I}$ interactions, respectively (NMR and X-ray). Another highlight was the isolation and characterization (X-ray and ESR) of the first series of stable aryl-nickel(III) compounds $[Ni^{III}X_2\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}]$, **10** (X = I) from the reaction of $[Ni^{II}X\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}]$ with electrophiles such as $Cu^{II}X_2$ (X = Cl or Br) or X_2 (X = Cl, Br, I). These d^7 Ni(III) species are air and water stable paramagnetic species. Obviously, this reaction involved selective one-electron, ligand transfer (oxidation) of the NCN-pincer nickel compound to the electrophile. Finally, a fully reversible binding of SO_2 to $[Pt^{II}I\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}]$ affording $[Pt^{II}I(\eta^1\text{-}SO_2)\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}]$ was observed, again involving the Pt's formally filled d_z^2 orbital to bind the SO_2 molecule (via its σ^*-S antibonding orbital). Later studies revealed that this reaction is highly selective towards SO_2 and quantitative and, moreover, is resistant against atmospheric impurities such as acids and water. The observation that the presence of SO_2 results in a fast and significant color change opened possibilities to use $[Pt^{II}I\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}]$ for diagnostic purposes [24].

A big surprise was the discovery of the selective rearrangement of $[Ir^{I}COD\{C_6H_3(CH_2NMe_2)_2\text{-}2,6\}]$ **12,** having two *ortho*-CH_2NMe_2 substituents, one free and one N-bonded to Ir, to rearranged $[Ir^{I}\text{-}COD\{C_6H_3(CH_2NMe_2)_2\text{-}2,4\}]$ **12′** with one *ortho*, N-bonded to Ir, but now one *para* as a free, non-coordinated CH_2NMe_2 substituent. The mechanism of this rearrangement could be fully unraveled (*e.g.* by deuterium labeling, see Fig. 8). This appeared to be a common feature in XCX-pincer metal chemistry and becomes particularly dominant when the metal-ancillary ligand(s) substituent is either very bulky or when exclusively one of the *ortho*-CH_2NMe_2 substituents is coordinated to the metal center, see Fig. 8.

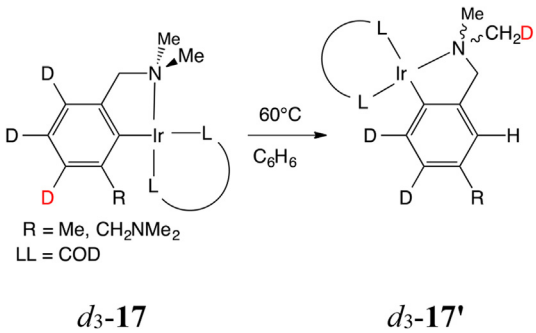


Fig. 8. Rearrangement (quantitative) of d_3-**17** to d_3-**17′** driven by constraints of *ortho*-R via a sequence of Ir-C^2_{sp}, Ir-C^3_{sp}, H(D)-C^2_{sp}, H(D)-C^3_{sp} bond cleavage and bond formation steps; likewise documented for Ru(II) and Ta(V)-pincer complexes [25].

4. Chemistry at Utrecht University (1986–2007): organic chemistry and catalysis

My move to Utrecht marked the start of an exciting time both regarding my teaching duties (now Organic Chemistry) and my research in a context of emerging homogeneous catalysis, upcoming ideas about sustainability, atom economy, selectivity, less waste producing reactions/processes, etc. Another important development was the ever-growing possibilities to analyze and monitor ones chemistry whether it be molecules, materials or processes. During late 80ies - early 90ies research in the Netherlands was financed by one PhD project at the time, continuation of projects appeared difficult irrespective the quality of preceding projects. Nevertheless, during the Utrecht period we managed to work on four lines, project by project, with PhD and postdoctoral researchers. During this period the EEC, later EU, installed programs promoting exchange of students in Europe and collaborations in science-networks to the effect that nowadays financial support on EU-level is an important factor for individual research groups, Consortia and Institutes. Personally I am very grateful for the support I got for my coworkers and the group as a whole and the international collaborations that this support enabled. Last but not least I like to mention the successful collaboration with Arkema Vlissingen. Within a "lab-in-lab" construction in Utrecht we did fundamental studies on a variety of subjects while development studies where carried out in the application's lab Arkema, Vlissingen. For students working in this setting it was an excellent chance to get a feel for the discovery-development time line, *i.e.* what it takes to bring an initial finding in fundamental chemistry to a real product produced on the industrial level. In this context, novel perfluorotriarylphosphine ligands were developed and used for the synthesis of sustainable and recyclable Wilkinson type catalysts for applications in *e.g.* selective hydrogenation of alkenes. These fluorous catalysts were applied in fluorous phase separation techniques in homogeneous catalysis [26]. Moreover, novel routes for alkyl tin(IV) compounds, free from (toxic) triorganotins, were developed; for example, the synthesis of alkyltin trihalides, in one step, from reaction of alkenes, $SnCl_2$ and HCl catalyzed by a suitable homogenous palladium catalyst.

4.1. Chemistry of organozinc (1,4-diaza- and 1-oxa-4-aza-1,3-butadiene) radicals: novel routes to, e.g., cis- and trans-β-lactams and indolizines [27,28]

The discovery of the organozinc and aluminum α-diimine radical chemistry and the promise for novel routes in the field of β-lactam synthesis initiated a long lasting collaboration with Gist-Brocades, Delft, The Netherlands. Direct synthesis of the zinkenolates from suitable substrates with a 1,4-diaza- and 1-oxa-4-aza-1,3-butadiene grouping was developed. Subsequent reaction with a suitable electrophile provided stereoselective routes to a variety of *cis*- and *trans*-β-lactams, see Fig. 9.

In separate projects, we continued to study the formation of organozinc α-diimine and α-iminoester radicals and their conversion into respective *N*- or *C*-alkylated products. This study resulted likewise in the discovery of novel routes towards the syntheses of 3-pyrrolidinones and indolizines. Particularly rewarding were the supporting synthetic and theoretical studies on the radical chemistry of the organozinc intermediates and the role of persistent organozinc (1,4-diaza- and 1-oxa-4-aza-1,3-butadiene) radicals in driving their subsequent reactions with electrophiles, cf. Fig. 4 [15,16].

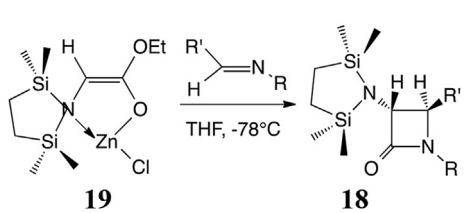


Fig. 9. Conversion of Zn-enolates **19** with (chiral) imines to *trans*-β-lactams **18**.

4.2. Organocopper chemistry: self-assemblage, stereochemistry and catalysis [3,4]

Previous work taught us that organocopper compounds R_nCu_n exist as aggregated species both in solution and in the solid state, and that this situation is quite comparable with that encountered in organolithium chemistry. This notion has helped us enormously in the synthesis of novel aggregated organocopper species that contain next to alkyl, aryl, alkenyl or alkynyl anions also alkoxy, thiolate, halide or cyanide anions. Our simple approach was to combine pure (!) reactants, RCu, RLi, $R_{2-n}MgX_n$ (n = 0,1) or pure (!) CuX, in a suitable (either polar or apolar) solvent. Consequently this allowed, for example, CuR and CuX units to self-assemble during the reaction resulting in formation of the thermodynamically most stable, aggregated species $Cu_{n+m}R_nX_m$. A notable and early illustration from our TNO-studies is $Cu_6R_4X_2$ (R = $C_6H_4NMe_2$-2, X = halide). It appeared that its $[Cu_6R_4]^{2+}$-core is intrinsically very stable to the effect that, *e.g.* X = halide can be substituted for X = acetylide with retention of the initial $[Cu_6R_4]^{2+}$-core structure. Without going into detail, the N-donor substituent and 2e-3c bonded C_{ipso} are playing a crucial role during the assemblage process and provides the spatial arrangement by each bridging one Cu_3-face of the Cu_6-bipyramide that leads to the observed stability of $Cu_6R_4X_2$ aggregates [4].

The use of various *ortho*-amine donor substituents (see Fig. 1) in arylcopper and cuprate chemistry was also key for other successes. One example, cyanocuprate $[Ar_2Cu(CN)Li_2(THF)_4]_n$, **20**, Ar = $C_6H_4CH_2NMe_2$-2 (resting state of an important reagent in copper catalyzed organic synthesis) is a polymer comprising $[Ar_2Cu]$-anions and [LiCNLi]-cations [29]. In this structure, the amine donor takes the position of a solvent molecule (*i.e.* THF). Examples of discrete, neutral aggregates (both with inclusive N-Li coordination) are $Cu_2Li_2Ar_4$ (**3**) and $CuLi_2R'_2Br$, **21**, R' = $C_6H_4CH_2N(Me)CH_2CH_2NMe_2$-2. In $CuLi_2R'_2Br$ bidentate LiNN′ coordination keeps the cuprate-anion, $[R'_2Cu]^-$, in close proximity to the [LiBrLi]-cation [30] (see Fig. 10).

In conjunction with our organocopper research, we also studied the formation and structural features of pure organolithiums that were our commonly used starting materials. In particular, we studied how the polarity of the reaction solvent

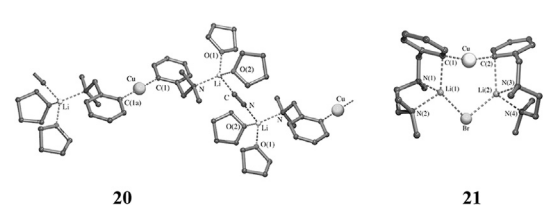


Fig. 10. Two cuprate species; coordination polymer $[Ar_2Cu(CN)Li_2(THF)_4]_n$, **20** and neutral aggregate $CuLi_2R'_2Br$, **21.** The Br-anion can be replaced by a CN anion with retention of the structural features present in **21.** (Figures of **20** and **22** reproduced with permission from ref 3; copyright Wiley-VCH Verlag GmbH & Co. KGaA.)

affected aggregation state, composition and (stereo)selectivity of the organolithiums. For example: it turned out that R'_2Li_2 (R′ see above) is kinetically and thermodynamically stable because of intramolecular bidentate LiNN′ coordination of the *ortho*-diamine substituent. The latter LiNN′ binding results in induced chirality at both Li and the ("inner")N centers. In corresponding $Li_2(C_6H_4CH\mathit{Me}N(Me)CH_2CH_2NMe_2\text{-}2)_2$ material, chirality has been rigorously defined by introduction of a secondary chiral center, *i.e.* the benzylic-C center. NMR studies showed that it is this single chiral center that makes the aggregation process of the two monomeric aryllithium units to one dimer highly diastereoselective [31].

Likewise, we synthesized a number of thermodynamically stable mixed aryl/alkyl $Ar^*_nR_mLi_{n+m}$ aggregates, for example: $Li_4(C_6H_4CH\mathit{Me}NMe_2\text{-}2)_2(Bu)_2(OEt)_n$ (Bu = n-butyl; n = 0, 1 is or 2). The resulting Li_4-aggregate is assembled from a $Li_2Ar^*_2$-dimer unit (with chelate *C, N*-bonding) and two LiBu units; because of the presence of a defined chiral center in Ar*, self-assemblage to the mixed aggregate likewise is a diastereoselective process. Note that, for example for n = 0, *i.e.* $Li_4Ar^*_2Bu_2$ **22**, two of the Li-atoms in the Li_4-core are each deprived from their fourth ligand (*i.e.* Et_2O), see Fig. 11 [32].

An important development in copper(I) catalyzed organic synthetic chemistry was the introduction of so-called "dummy", or non-transferable, ligands. To this end, we studied Cu^I aminoarenethiolate compounds, as novel "dummy" groupings, but now bearing an *ortho*-substituent with a defined chiral center, *e.g.* the tri-nuclear aggregate $Cu_3(SC_6H_4CH\mathit{Me}NMe_2\text{-}2)_3$ (abbr. as $Cu_3(SAr^*)_3$) [33,34]. The idea was that the stereoselectivity of copper catalyzed cross-coupling reactions of, *e.g.* Grignard reagents with electrophiles could be steered by the presence (through self-assemblage) of chiral SAr* ligands, as non-transferable groupings, in kinetic intermediates of these reactions. The Cu^I aminoarenethiolates appeared to have an extensive self-assembly repertoire with RCu, CuX and R_2Mg aggregates indeed: *e.g.* **23** was selectively formed by mixing mesitylcopper and copper aminoarenethiolate in 1:1 M ratio and then transferred to **23** by addition of one equivalent of PPh_3 (mimicking the addition of an electrophilic substrate to the cuprate intermediate), see Fig. 12 [33,35]. To summarize: the reaction of MgIMe with a diethyl ether solution of benzylideneacetone and 3 mol% of [CuSAr*] (providing the "dummy", non-transferable anion), at 0 °C gives rise to the formation of the 1,4-addition product in 57% ee

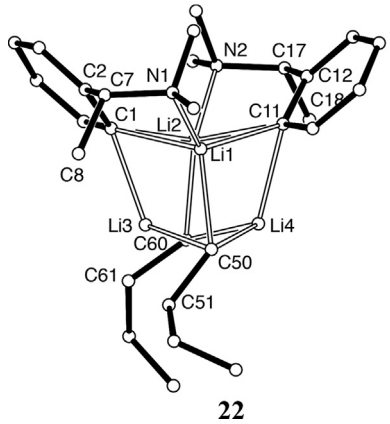


Fig. 11. Enantiopure, mixed aryl/alkyl lithium aggregate $Li_4(C_6H_4CH\mathit{Me}NMe_2\text{-}2)_2(Bu)_2$ **22**. (Figure of **22** reproduced with permission from ref 22; copyright Wiley-VCH Verlag GmbH & Co. KGaA.)

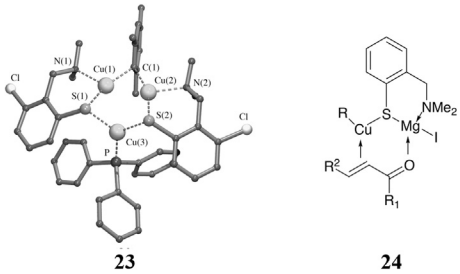


Fig. 12. $Cu_3(Mes)$ $(SC_6H_4CH_2NMe_2\text{-}2)_2(PPh_3)$ **23** resulting from addition of PPh_3 to $Cu_4(Mes)_2(SC_6H_4CH_2NMe_2\text{-}2)_2$; **24** proposed structure of the kinetic intermediate, see text. (Figure of **23** reproduced with permission from ref 3; copyright Wiley-VCH Verlag GmbH & Co. KGaA).

[33,35,36]. This preliminary result (later improved to 76%) represented, to the best of our knowledge, one of the first reported examples of the catalytic use of a copper salt with a chiral auxiliary in an enantioselective 1,4-addition reaction of self-assembled cuprate reagents. The self-assembly properties of a number of [CuSAr]-aggregates with CuR, LiR, (R_2Zn) [37] and $RMgX/R_2Mg$ were likewise studied. The results led to the formulation of a model for the kinetic intermediate **24** in CuSAr catalyzed reactions of Grignard reagents in conjugate addition reactions; note the preference of the amine-ligand to bind to magnesium, see ref 34, p. 44 (see Fig. 12).

4.3. Palladium(II) and (IV) chemistry: ortho-metallation, and oxidation chemistry

A common view, during the early 90ies, was that dialkylPd(II)L_2 complexes with good stability required the use of good σ-donor ligands, *e.g.* tertiary phosphines; complexes with ancillary amines ligands L were expected to be too unstable to be handled. Nevertheless, we quickly found that, for example, Me_2Pd(tmeda) is stable and can be stored for weeks. We, and others, used it as an excellent, and very versatile starting material in our further palladium research [38]. For example, reaction of Me_2Pd(tmeda) with MeCl resulted in formation of an early example of a rather stable organoPd^{IV}diamine complex *fac*-$Pd^{IV}Me_3Cl$(tmeda). Moreover, it allowed study of organo group exchange between Pd(IV) and Pd(II) species.

Study of reactions of *ortho*-chelated-aryl- or bis(*ortho*-chelated)-arylpalladium(II) compounds (oxygenation or protonation) appeared difficult. Although we did develop V-, Mo- and Rh-catalyzed oxygenation reactions of bis-*C,N*-chelated arylpalladium compounds (obtained by *ortho*-metallation) with peroxides to yield aryloxypalladium compounds [39], protonation reactions gave inconclusive results. In contrast, surprising mechanistic insights in protonation processes of *ortho*-chelated aryl groupings in palladium and platinum chemistry (role of the amine ligand and conformational rigidity of the amine *ortho*-substituent) were obtained when the protonation of corresponding *cis*-Ar_2Pt^{II} compounds (*e.g.* Ar = *C,N*-1-$C_{10}H_6NMe_2$-8) was studied instead. Reaction with HCl afforded quantitatively novel Zwitterionic complexes, *e.g.* *C,N*-$ArPt^{II}Cl$(*C*-1-$C_{10}H_6$-8-$NHMe_2$) **25**. The proton in the latter compound bridges (or is caught) between the formally filled Pt^{II}'s d_z^2 and the amine's sp^3 lone electron pairs forming a $Pt(II)^-$ … $H\text{-}N^+$ unit [40, 41]. Reaction with an organic acid, CF_3COOH, afforded its tautomer: a six-coordinate Pt(IV)-H complex (see Fig. 13).

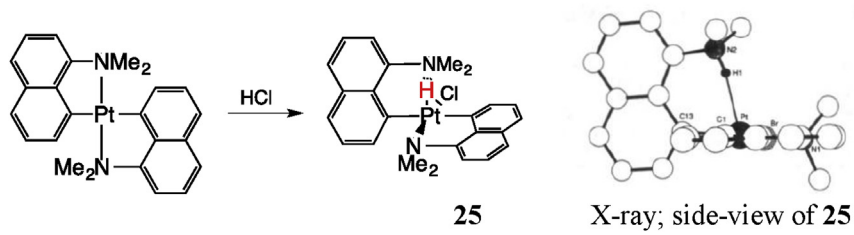
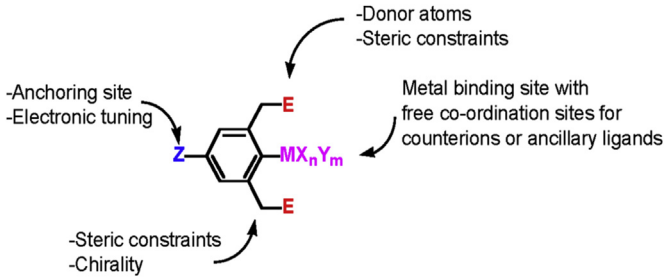


Fig. 13. Reaction of *cis*-$Ar_2Pt^{II}(C_{10}H_6NMe_2\text{-}8)_2$ with HCl yielding **25**. ((Figure of **25** reprinted with permission from ref 40; copyright {2017} American Chemical Society.).

4.4. NCN- (and some XCX-) pincer chemistry: fundamentals, catalysis and materials

The versatility of the pincer platform has fascinated me right from the time that we isolated the water-soluble NCN-pincer tin halide **4** and the pincer-type arenium platinum compounds **5**, in the 70ies, as discussed above. The exciting results that we obtained later, during my time in Amsterdam, then prepared the ground for enhanced efforts in Utrecht. During this period I got a real chance to focus some of our attention to the chemistry of the NCN-pincer platform and to make excursions to the synthesis and applications of novel NCN-, SCS-, and PCP-type pincer metal complexes in a variety of different areas. Most of our results were subject of reviews while some appeared in very recent articles and book chapters. For this reason, the biosketch on this subject can be kept relatively short in spite of the fact that it has been subject of almost half of our output in peer-reviewed journals. It will be based on the graphical representation of the *aryl* pincer manifold in the figure below. Of course, nowadays, it can be considered as a rudimentary representation of the privileged pincer-platform but aryl and an alkyl versions were the first pincer ligands with E is P-ligand used by the pioneer Bernard Shaw, Bill Kaska and for E is N-ligand in the same period by van Koten's group [42–44].



4.5. Organometallic chemistry

4.5.1. Synthesis aspects [43]

As our chemistry initially was concentrated on the $MC_6H_3(CH_2NMe_2)_2$-2,6 aryl pincer platform a variety of approaches to install the M–C bond had to be developed. These routes included transmetallation via the corresponding aryl pincer lithiums, electrophilic substitution of the $SiMe_3$ grouping in corresponding (pincer)C_{ipso}-$SiMe_3$ compounds, regio- and chemoselective oxidative addition of (pincer)C_{ipso}-Halide bonds and transcyclometallation by reaction of the NCN-pincer metal compound with (XCX-pincer)C_{ipso}-H arene precursors to yield respective SCS- and PCP-pincer metal compounds and the free NCN-pincer arene.

Initially the potentially terdentate, monoanionic NCN-pincer platform was selected because it was expected to bind preferably to metal centers in the (planar) *mer*-terdentate configuration as was the case indeed in κ^3-*N,C,N*-[2,6-$(Me_2NCHR)C_6H_4$] MePhSn cations. In later studies we found, however, that the NCN-pincer platform has diverse coordination possibilities to bind the metal center ranging from monodentate *C*-coordination, to bidentate *C*, *N*- and tridentate mer- and fac-*N*, *C*, *N* coordination depending on the metal fragment MX_nL_m (metal and ancillary ligands). Moreover, compounds featuring 2e-3c bonding of C_{ipso}-anion were encountered in NCN-pincer lithium and cuprate chemistry but also in NCN-pincer tantalum-zinc bimetallic compounds [43]. Finally, the binding of $[MX_nL_m]$-cations in the η^5-mode to the arene system of arylpincer metal species was realized which likewise lead to bimetallic pincer complexes [44] (see Fig. 14).

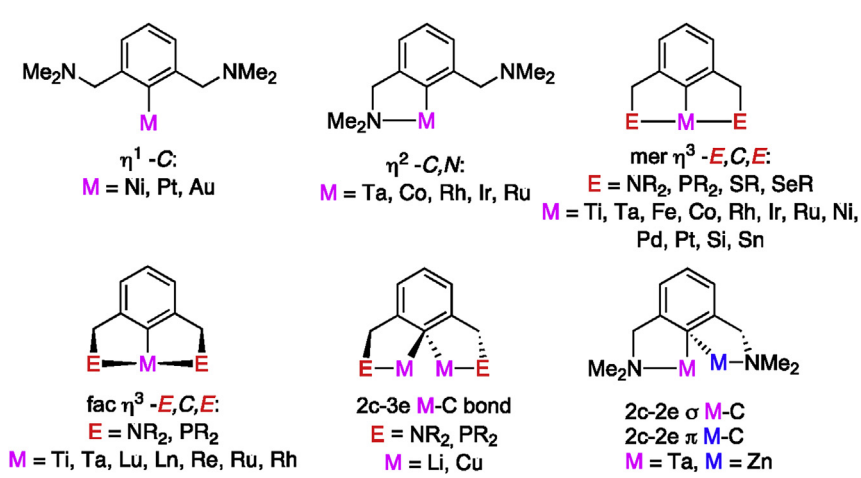


Fig. 14. Examples of the versatile bonding of the NCN-pincer platform [45,46].

4.5.2. Physico-chemical aspects

The co-planarity of the arene's C_6-ring and NCN-M coordination plane is a special structural feature of the pincer-metal platform. In principal, it allows for Donor-Acceptor communication between *para*-substituent Z and the MX_nL_m fragment in $MX_nL_m\{C_6H_2(CH_2NMe_2)_2$-2,6-Z-4} complexes.

An early example and use of D-A communication in substituted NCN-pincer metal compounds was encountered in the catalysis studies of the Kharasch addition reaction (Atom Transfer Radical Addition, ATRA) of polyhalogeno alkanes on alkenes, *e.g.* the addition of CCl_4 to alkenes catalyzed by NiBr $\{C_6H_2(CH_2NMe_2)_2$-2,6-Z-4} (Z = H, NO_2, NH_2, N(H)C(O)Me, Cl, N=CHPh, C(O)Me). This ATRA reaction involves one-electron redox steps in which square pyramidal, paramagnetic Ni^{III} species $Ni^{III}Br_2\{C_6H_2(CH_2NMe_2)_2$-2,6-4-Z} (*cf.* **15**, Z = H, see Fig. 7) play a crucial role as a persistent radical driving the selectivity of the catalytic reaction; its single electron is located in the SOMO comprising of the Ni atom and apical halido ligand. A nice correlation between Hammett σ_p of the *para*-substituent Z of the $[C_6H_2(CH_2NMe_2)_2$-2,6-4-Z]$^-$ ligand and the oxidation potentials ($E_{p,a}$) of the corresponding organonickel(II) complexes was found [47].

In contrast to the spectator role taken by the NCN-pincer ligand in the above example, we found that the pincer platform can also behave as non-innocent ligand. For example, in the C_4-$C_{4'}$ coupling reaction of $[Ru^{II}\{C_6H_3(CH_2NMe_2)_2$-2,6}(terpy)]X with $Cu^{II}X_2$ the oxidized Ru^{III} (paramagnetic) intermediate $[Ru^{III}\{C_6H_3(CH_2NMe_2)_2$-2,6}(terpy)]$^{2+}$ is the key species in the subsequent C_4-$C_{4'}$ coupling reaction; *i.e.* the single electron activation occurs at the *para* position of the pincer platform (see Fig. 15).

Conversely, the question arose whether it would be possible to measure the inductive and mesomeric effects of a MX_nL_m fragment at the *para*-position of the aryl ring of a NCN-pincer metal compound. To this end, we selected $PtCl\{C_6H_2(CH_2NMe_2)_2$-2,6-Z-4} (Z = CH=$NC_6H_4Y$ in which Y = NMe_2, Me, H, Cl, CN) to monitor this by ^{13}C NMR data in the CH=N bridge and compared these data with those reported in the literature for analogous organic azomethine compounds [48]. Using the results of the single substituent parameter (Hammett σ_p) and the Swain-Lupton dual substituent parameter (σ_F, σ_R) method of the azomethine ^{13}C NMR shifts, it can be concluded that: "the Pt-Cl grouping is very strong EW (comparable with NO_2) whereas mesomerically it behaves as very strong ED; *i.e.* its overall effect equals that of a NMe_2 group".

Independently, this conclusion was supported by a study of the Hammett σ_p value of *para*-$PtIN_2$ group in $PtI\{C_6H_2(CH_2NMe_2)_2$-2,6-COO*H*-4}. This Hammett σ_p data could be derived from pH measurements in water/methanol (1/1) and was calculated to amount to −0.72 which data is likewise close to that of the NMe_2 group [49].

Using this knowledge luminescent Donor-Acceptor materials similar to DANS (D = NMe_2 and A = NO_2) were synthesized, *e.g.* PtCl $\{C_6H_2(CH_2NMe_2)_2$-2,6-Z-4} (Z equals CH=CHC_6H_4Y in which Y = CN).

4.5.3. Organic synthesis on pincer metal compounds; post-functionalization [50]

The above developed ideas, concerning the inductive and mesomeric effects of MX_mL_n substituent on aromatic substitution reactions, initiated the synthesis of *para*-substituted NCN-pincer platinum and palladium compounds via post-modification of MX $\{C_6H_2(CH_2NMe_2)_2$-2,6-I-4}. A great variety of $MI\{C_6H_2(CH_2NMe_2)_2$-2,6-Z-4} (M = Pd, Pt; Z = CH(O), OH, CH_2OH, $SiMe_3$, $CCSiMe_3$, P(O)$(OR)_2$, CH_2NHR, etc), derivatives could be obtained in excellent yields. Instrumental was the possibility to convert MI $\{C_6H_2(CH_2NMe_2)_2$-2,6-I-4} into $MI\{C_6H_2(CH_2NMe_2)_2$-2,6-*Li*-4}. In fact, this [M-C_6-Li] derivative could undergo the usual reaction palette that is known for parent phenyllithium. Most exciting was to find that $MI\{C_6H_2(CH_2NMe_2)_2$-2,6} undergoes direct sulphonation with $ClSO_3H$ on the arene ring to $MI\{C_6H_2(CH_2NMe_2)_2$-2,6-SO_3H-4} (M = Pd, Pt) although in moderate yields (20%) and together with some *meta*-SO_3H product. It is notable to observe that even with sulphonic acid hardly any decomposition of the pincer metal starting material is noted. These results paved the way for the clean and directed anchoring of pincer metal catalysts, a single or in great numbers, to nanosized supports such as carbosilane and Frechet-dendrimers, C_{60}, rigid cart wheels, hyperbranched polymers from polyglycerines and polystyrenes carrying dendritic wedges; *i.e.* by first performing the multistep synthesis of the support material followed by installing the ready pincer metal catalytic sites to the molecular support.

4.5.4. Reversible binding of SO_2 in crystalline $PtCl(\eta^1$-$SO_2)$ $\{C_6H_2(CH_2NMe_2)_2$-2,6-Z-4} (Z = H or OH)

4.5.4.1. Non-covalent bonding. Interesting cases of non-covalent hydrogen bonding were discovered to occur between hydrogen donor atoms present in the *para*-substituent Z of MX $\{C_6H_2(CH_2NMe_2)_2$-2,6-Z-4} on the one end and the hydrogen accepting site X of the metal-X grouping. For example, both in the solid state and in solution $MCl\{C_6H_2(CH_2NMe_2)_2$-2,6-Z-4}, M = Pt, Z = OH [51], forms polymers via intermolecular OH···Cl H-bonding. However, when more conformational flexibility is present in Z, as is the case for M = Pd, Z = CH_2OH, a dimeric structure is formed through mutual head-to-tail OH···Cl H-bonding.

A combination of H-bonding and (reversible) SO_2-to-Pt binding is present in the single crystals of $PtCl(\eta^1$-$SO_2)\{C_6H_2(CH_2NMe_2)_2$-2,6-OH-4} **27** (**26-$SO_2$**). Interestingly we discovered a rare (in year 2000) case of the controlled release and binding of SO_2 without loss of crystallinity (*i.e.*, the cell volume can shrink and expand by about 15% of its volume). This was obvious from monitoring this process at single crystals by X-ray diffraction techniques. It must be noted that the supramolecular arrangement by H-bonding is not essential for the observed crystalline transformations resulting from reversible uptake and binding of a small molecule [52] (see Fig. 16).

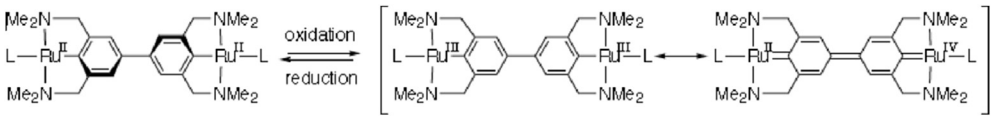


Fig. 15. 4, 4′-Bisruthenium biphenyl system: a molecular redox switch [46].

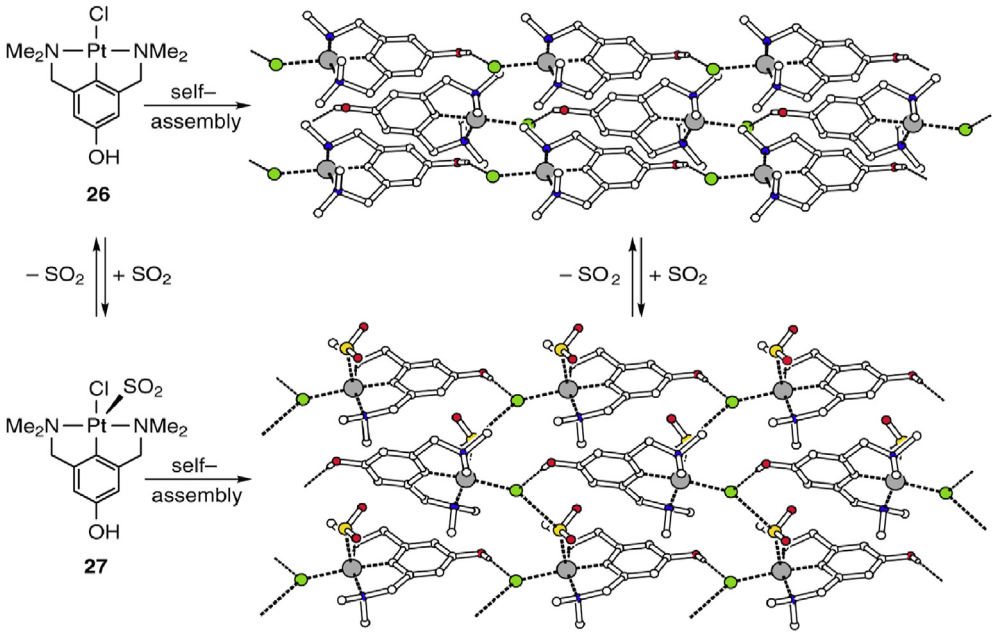


Fig. 16. Reversible uptake and release of SO_2 by crystalline $PtCl\{C_6H_2(CH_2NMe_2)_2$-2,6-OH-4} **26.**

4.5.5. Templated organic synthesis (large ring macrocyclic compounds) [53,54]

The tricationic cart-wheel type molecule, $[C_6H_3$-1,3,5-(1-$C_6H_2(CH_2NMe_2)_2$-3,4-PtL-4)$_3]^{3+}$ (L = neutral ligand) appeared an excellent template for the synthesis of large ring macrocycles. The system uses bis-*ortho*-olefin functionalized pyridine ligands that selectively bind to the three cationic platinum centers of the template resulting in pre-organization of the olefinic tails. By subjecting these pre-organized complexes to olefin metathesis reaction conditions, the olefinic tails were interconnected affording several macroheterocycles of different compositions and sizes. The resulting macrocyclic ligands could easily be detached from the template by blocking the platinum cation sites with Cl-ions.

The product was hydrogenated in order to prevent isolation of a mixture of isomers (cis/trans olefinic isomers). As an example, in this way (polyether)pyridine macrocycles could be isolated in pure form comprising of an 81-membered ring containing as much as 24 oxygen and 3 (pyridine) nitrogen atoms. Re-coordination of one of these macrocycles afforded the complex of the template with the macrocyclic ring wrapped around the template and anchored by the three pyridine-Pt interactions, see Fig. 17.

4.6. Pincer metal compounds as homogeneous catalysts, soluble catalytic materials with pincer metal catalysts, recycling [55]

4.6.1. General

An important disadvantage of homogeneous metal catalysts is their sensitivity to degradation during catalysis and the fact that, finally, all reagents, product(s) and catalyst are together in the same phase and thus require separation. A common approach, at least to solve the separation problem, is to heterogenize the homogeneous catalyst by binding it to an insoluble support. In fact, we choose to molecularly enlarge the catalyst by anchoring it to a soluble support to the effect that the resulting, soluble, catalytic material could be

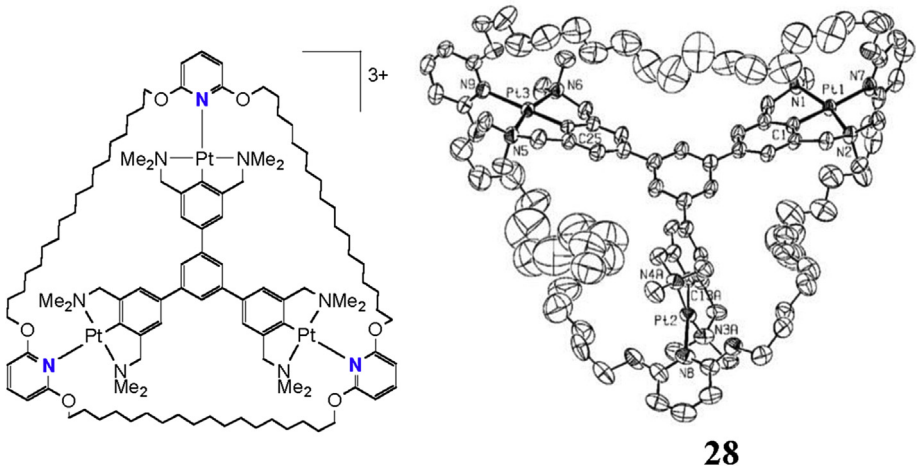


Fig. 17. The macrocylic compound can be removed from **28** by addition of Cl-anions; the template can be reused [53,54]. (Figure of **28** reproduced with permission from ref 53; copyright Wiley-VCH Verlag GmbH & Co. KGaA.).

separated by nano-filtration. This approach, which fills the gap between heterogenous and homogeneous catalysis, does not only solve the catalyst/product separation problem but also allows for use of the catalytic material in continuous processes under homogeneous reaction conditions. As long-lasting catalyst stability is of crucial importance to make immobilization useful, it is exactly this property for which many of the XCX-pincer catalysts stands out as compared with commonly used homogeneous catalysts, *e.g.* in organic synthesis. Furthermore, it appeared that a single pincer metal compound can act as pre-catalyst for different conversions, see the example of tandem catalysis in which PdCl{$C_6H_3(CH_2SPh)_2$-2,6} acts as pre-catalyst in two different conversions, mentioned below. It is for these reasons that we set out to develop ways for their "immobilization"/integration inside or at the periphery of filterable, nanosized species. This approach could count for solutions of both the separation problem and the wish to perform catalytic processes in the continuous mode rather than batch wise.

4.6.2. Pincer Metal Catalysts [46]

Nowadays, the pincer platform is a privileged ligand in homogeneous catalysis. This was not the case at the time when we started much of this research. The first catalytically active NCN-pincer metal compound came from my Amsterdam laboratories, *i.e.* NiBr{$C_6H_2(CH_2NMe_2)_2$-2,6-Z-4} that is an excellent catalyst for both ATRA and Atom Transfer Radical Polymerization reactions, vide supra. The excellent catalytic activity of Ru(OTf) (PPh_3) {$C_6H_2(CH_2NMe_2)_2$-2,6} in transfer hydrogenation of ketones was a surprise too [56]. The activity PdCl{$C_6H_2(CH_2SPh)_2$-2,6} as a Lewis acidic catalyst in C-C cross coupling reactions was known but that this palladium pincer compound also can act as a bifunctional catalyst, for example, in the tandem stannylation/electrophilic allylic substitution of allyl chlorides with hexamethylditin and benzaldehydes, provided new opportunities for the development of continuous catalytic processes [57] (see Fig. 18).

(4-Z) to the dendrimer's $SiMe_2$ groupings. This G_1-Ni_{12} pincer catalyst had a somewhat lower catalytic activity as compared with its parent Ni-pincer compound. This lower catalytic activity, however, was ascribed to imperfectness of the divergent multistep synthesis procedure for the dendritic catalyst. Deactivation of the soluble G_1-Ni_{12} pincer catalyst during the Kharasch addition reaction was not observed most likely because of sufficient separation between the Ni centers. In later designs, the NCN-pincer Ni catalysts were: *i.* directly attached to the CS-dendrimer surface by covalent C-Si bonding to exclude unintentional loss of catalytic sites, *ii*, the coverage of the dendrimer surface with catalytic sites was varied to study catalyst deactivation by "talking to and between neighboring sites" (important reason of catalyst deactivating side-reaction in one-electron catalysis) [59,60]. Furthermore, the use of these dendrimer-catalytic materials under continuous reaction conditions using membrane reactors was thereafter evaluated [61]. This study revealed that loss of catalytic material likely occurred by creeping of the rather flexible dendritic polymer (*cf.* above mentioned G_1-Ni_{12}) through (imperfections of) the applied membrane. To improve retention of the nanosized catalyst, we then made supports that allowed better control over the size and shape-persistency of the molecularly enlarged catalytic material. Our best results were obtained with (soluble) so-called "cart-wheel" material involving a core shell structure with a hexa-substituted benzene ring as core and rather stiff wedges that overall provided a catalyst that carried twelve catalytic cationic sites, [Pd(solvent or H_2O){C_6H_2-2,6-$(CH_2NMe_2)_2$-4-O-}]$^+$ at its periphery (see Fig. 19).

We developed synthetic methods that allowed for the synthesis of almost pure catalytic material in a relatively small number of steps. This material showed, in combination with MPF50 membrane, excellent retention even under continuous reaction conditions. Interestingly, the retention of these cart-wheel catalysts could be measured quantitatively by using the corresponding NCN-

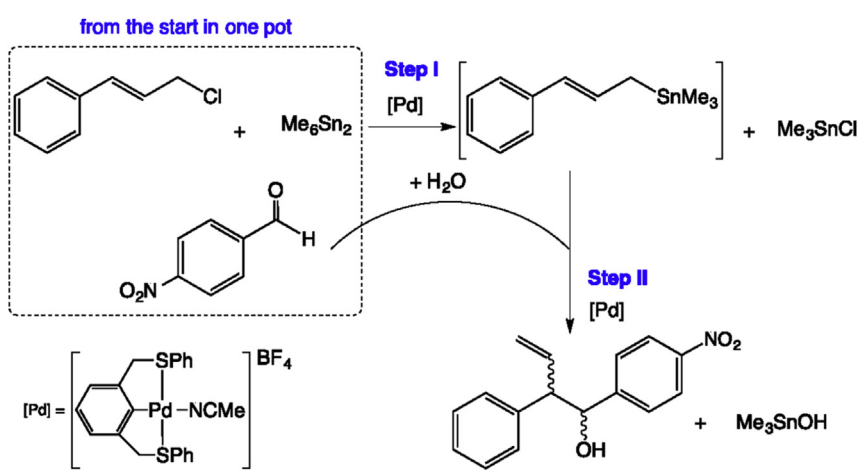


Fig. 18. Example of bifunctional catalysis by [Pd(NCMe){$C_6H_2(CH_2SPh)_2$-2,6}]BF_4; auto-tandem catalytic formation of C-C′ coupling product.

4.6.3. Proof-of-Principle

The first proof-of-principle of the viability of nanofiltration as a technique for the recycling of molecularly enlarged homogeneous catalysts was demonstrated by nanosized carbosilanes dendrimers, *e.g.* $Si((CH_2)_3Si((CH_2)_3SiMe_2X)_3)_4$ of which its surface was decorated with twelve NCN-pincer nickel catalytic units X, X = NiBr{$C_6H_2(CH_2NMe_2)_2$-2,6-Z-4} [58]. The nickel catalyst is tethered with a -$O(CH_2)_4OC(=O)NH$- linker, via its *para*-position

pincer material but with platinum(II) instead of the catalytic metal. With SO_2, the number of pincer platinum sites (*i.e.* presence of Pt^{II} η^1-SO_2 coordination monitored with UV spectroscopy) in the effluent of the membrane reactor could be measured. This approach provided a rather precise estimate/indication of the retention of the actual cartwheel catalyst material by the membrane in the membrane reactor [62].

In conclusion, in the case of the cartwheel-pincer metal catalytic

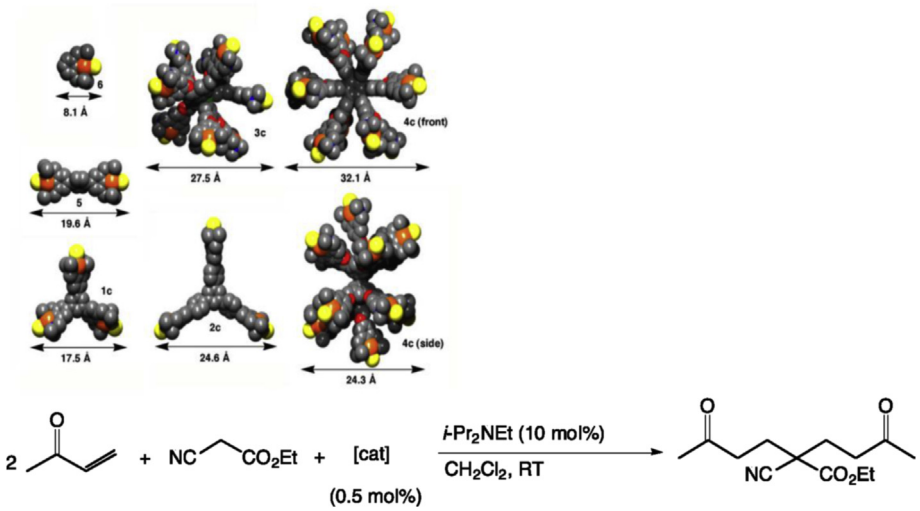


Fig. 19. Application of the [Cartwheel-Pd_{12}]$^{12+}$-cat (size 32/24 nm) in a membrane reactor (MPF50 membrane; >99.9% retention, continuous conditions) produces double Michael addition product with >3000 TTN/Pd, 4.2 mM [Pd], 30 mL h^{-1} [62]. (Scheme containing various cartwheel variants has been reprinted with permission from ref 62; copyright {2017} American Chemical Society.).

materials, we succeeded in recycling, with high efficiency, the homogeneous catalyst. Thanks to the good stability of both catalyst and support, even for processes with relatively low turn-over numbers, impressive product formation levels could be realized under continuous process conditions.

4.6.4. Non-covalent anchoring of catalysts to molecular supports; "tulips in a vase" approach [46,55,63]

Next to the covalent attachment of catalytic groupings to nanosized supports, we also studied an approach in which the catalytic unit(s) and support could be realized by self-assembling rather than by divergent synthesis. To this end, we synthesize core-shell material with a distinct rigid, octa-cationic core and a neutral shell comprising dendritic wedges. Catalytic units MX {$C_6H_2(CH_2NMe_2)_2$-2,6-Z-4}, in which Z is an appropriate tether with an anionic sulphato end group, were synthesized by post-modification (see Fig. 20).

Like putting "tulips in a vase", these tethered catalysts are placed and bound, primarily by Coulombic forces, with their anionic end groups near the cationic charges at the core of the core-shell support. These "vases", loaded with catalysts, can also be unloaded again by anion exchange with, *e.g.* [NBu_4]Br, which provides possibilities to reuse the support and exchange the catalytic material. By changing either thickness of the shell or the length of the tether (or both), the local surrounding of the catalytic site could be modulated. Due to their size, which in our study has estimated volumes in the range of 64–120 nm^3, these assemblies can be separated and purified by nano-filtration techniques.

4.6.5. Catalytic hybrids: combining pincer metal catalysts, polypeptides, carbohydrates and lipases [64]

These studies were likewise enabled by the versatile post-modification techniques that we had developed. For example, amino acids could be coupled, via its Cα position, to C_{para} of a pincer metal unit. Subsequently, the amino acid-functionalized pincer metal sites could be placed at specific sites in polypeptide sequences (*i.e.,* the place of a pincer-Pt unit could be located with SO_2 marking) [65]. Labeling of low-molecular mass carbohydrates with a pincer platinum unit via PtCl(NCN-R) (R = *para*-activated ester grouping) increased the sensitivity of SPR (surface plasma resonance) response tremendously. This allowed for the detection of binding events between mono-saccharides and lectins at very low analyte concentrations [66].

To our delight, *covalent*, stereoselective anchoring of a pincer metal catalyst in the active site of serine hydrolases, by its inhibition, appeared possible [67]. To this end, a tether ending in a *para*-

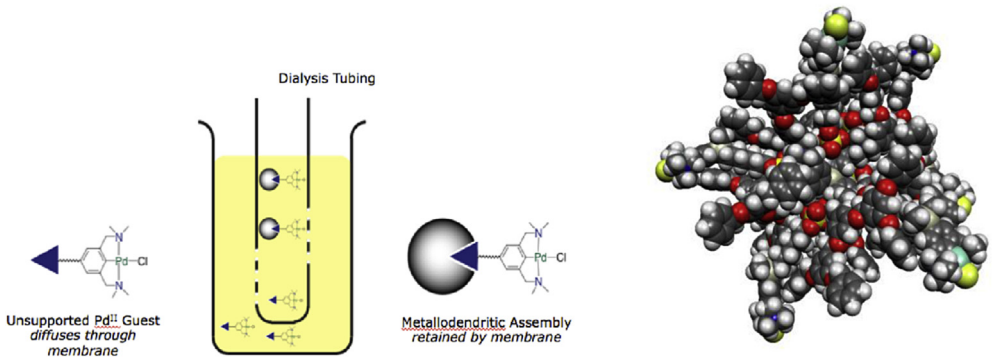


Fig. 20. Left; schematic representation of the loading of the container with the catalyst; right; a model of a loaded catalyst assembly (5.0 × 4.2 × 4,5 nm,; volume 95 nm^3), yellowish and green spheres are the exposed pincer palladium chloride sites [63]. (Spacefilling model has been reprinted with permission from ref 63; copyright {2017} American Chemical Society.).

nitrophenyl phosphonate ester group was installed at the *para*-position of the parent pincer metal compound. A series of ECE-pincer-metal groupings were used with different bis-*ortho*-chelating ECE-pincer ligands and metal-anion combinations. Reaction of the resulting (racemic) MX(ECE-$(CH_2)_n$P(=O) (OEt) ($OC_6H_4NO_2$-4)) with the serine ester-C center in the active center of the lipase (*i.e.*, Cutinase) afforded the enantioselective and covalent coupling of the pincer metal grouping by inhibition of the formerly active site of the lipase (see Fig. 21).

A series of pure MX(ECE)-lipase hybrids were synthesized and characterized. Obviously, the inhibition rate depends on the nature of the metal-halide, the ECE-pincer (E = NMe_2 or SMe) "head grouping" and the length of the alkanediyl tether. The purpose of this endeavor was *i*, to molecularly enlarge the pincer metal catalyst to the effect that easy separation of the resulting hybrid by filtration became possible, *ii*, the chiral information of the lipase surface could be transmitted to the metal site by selecting the right tether length, and *iii*, the hybrid as a whole would become water soluble thus enabling catalysis in water. The overlay of X-rays of two MX(ECE)-Cutinase hybrids, *i.e.* P^*_n-ECE-MX = (S_p)-NCNPtCl and (R_p)-SCSPdBr), respectively reveals opposite chirality of the respective phosphorous centers at their inhibition point in the lipase [68] (see Fig. 22).

Unexpected results were obtained when inhibition of Cutinase with PtCl(NCN-$(CH_2)_3$P(=O) (OEt) ($OC_6H_4NO_2$-4) was carried out in chloride poor *aqueous* reaction medium: formation of a chloride bridged diplatinum species of the type [Cutinase-(NCN) PtClPt(NCN)-Cutinase]$^+$ could be isolated and crystallized. This type of coordination chemistry, in which a single Cl-bridge binds together two bis-pincer-platinum cations, had been observed earlier in reactions of parent PtCl(NCN) with half an equivalent of $AgBF_4$. This result indicates that the covalent anchoring of the platinum pincer moiety did not affect its coordination chemistry. However, a^{31}P NMR and ESI-MS study of [Pt(H_2O) (NCN)-Cutinase]$^+$ showed that the coordination of various triarylphosphines to the enzyme-embedded cationic platinum center is affected by the surrounding protein backbone; thus discriminating between phosphines on the basis of their size and charge [69].

In a related study (collaboration with the group of Jan-Ehring Bäckvall), a novel ruthenium phosphonate inhibitor was synthesized and subsequently covalently anchored to a lipase immobilized on a solid support (CALB, Novozym®435) (inhibiting the lipase activity only partly). The *heterogeneous* bifunctional catalytic system showed activity in both racemization of (*S*)-1-phenylethanol and stereoselective acylation of 1-phenylethanol [70].

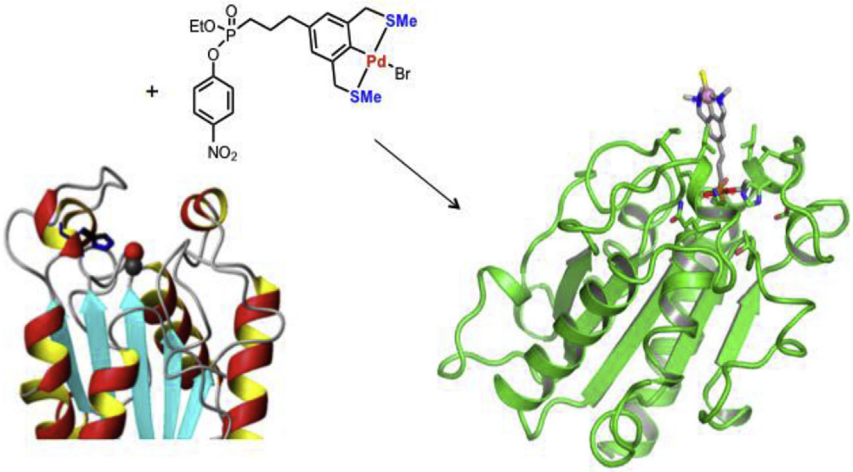


Fig. 21. Formation of the SCS-pincer palladium chloride-cutinase hybrid catalyst. (Structure on the right reproduced with permission from ref 67; copyright Wiley-VCH Verlag GmbH & Co. KGaA.)

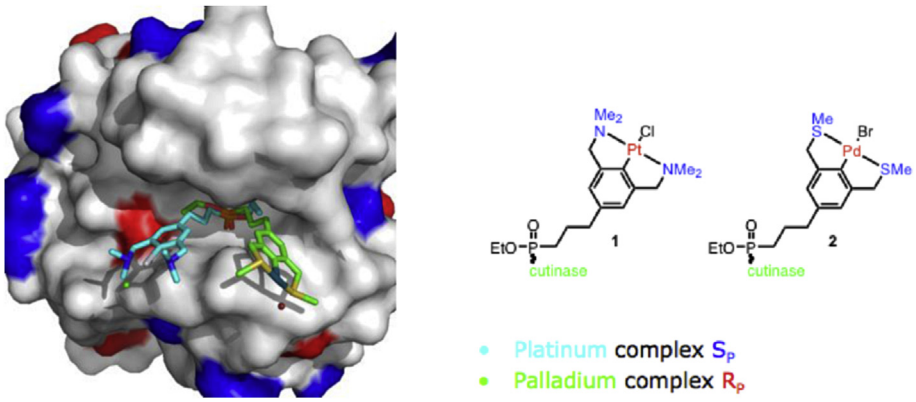


Fig. 22. Overlay of two MX(ECE)-Cutinase hybrids, *i.e.* P^*_n-ECE-MX = (S_p)-NCNPtCl and (R_p)-SCSPdBr) showing the different positioning of the anchored pincer-metal halide groupings in lipase's inhibited active site [67,68]. (Overlay Reproduced with permission from ref 68; copyright Wiley-VCH Verlag GmbH & Co. KGaA.).

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