Pincer Ligands as Powerful Tools for Catalysis in Organic Synthesis

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Dedicated to the memory of Prof. Dr. F. G. A. Stone

Abstract

Present trends in homogeneous catalysis are moving towards the development of multi-step, one-pot processes where salt waste is reduced to a minimum and in the lowest possible volumes of solvent. Energy efficiency is also maximized to produce the most cost-effective end product(s). However, these one pot cascade, tandem, or domino catalyzed reaction sequences rely on catalyst, substrate and solvent compatibility, on catalyst stability and on the possibility to protect these catalysts from mutual deactivation. This can be facilitated, for example, by binding these to suitable (in)soluble supports or by using compatible, stable catalysts that can be used to mediate a variety of different reactions.

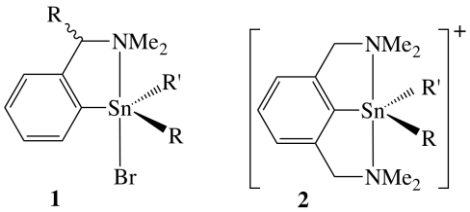
Pincer organometallics are powerful tools that can be used to achieve many of these objectives. The synthesis and properties of a variety of "molecularly enlarged" pincer organometallics displaying both surprising stability and versatile catalytic properties is discussed. A fascinating, recent development is the site-selective inhibition of a bead-immobilized lipase, *i.e.,* Cutinase, containing a single pincer-metal catalytic site. The resulting bio-organometallic hybrid catalyst (see X-ray), in combination with uninhibited lipase, can operate as a heterogeneous bifunctional catalytic material for the kinetic resolution of racemic alcohols to yield enantiopure product(s).

Keywords

Pincer metal building blocks, self-assembling, molecularly enlarged homogeneous catalyst, site inhibited organometallic-lipase hybrids, DKR racemic alcohol

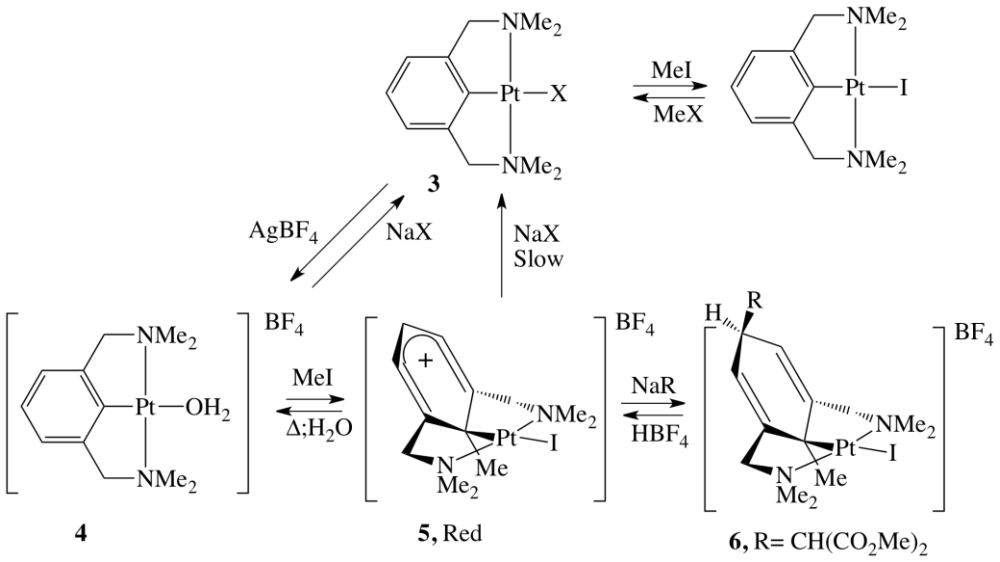
1. Introduction

My first project in the Organic Chemistry Institute (OCI-TNO) was directed towards the synthesis and isolation, obviously with high purity, of stable organocopper(I) derivatives with well-defined composition.[1] To this purpose we started to employ C, N-chelating ligands, as an application of the well-known chelate effect, to impart higher stability to these, then rare, organometallics. This marked our first successes in organocopper(I) chemistry as described in detail in a recent review article in *Organometallics*.[2] We used these same C, N-chelating ligands in a parallel project aimed at the synthesis of novel triorganotin halides. It was found that application of these formally monoanionic C, N-chelates resulted in the formation of five-coordinate triorganotin complexes featuring an *ax*,*eq* spanning motif of the chelate, see **1**.[3]-[5] The next question that arose was whether introduction of a second $-CH_2NMe_2$ substituent in the remaining *ortho*-position of the aryl group of **1** would give rise to the formation of a five-coordinate triorganotin cation following loss of Br^-: indeed, this was what was found, see **2**.[6]



This finding spurred our interest in the synthesis of NCN-pincer transition metal compounds and a study of the effect(s) that such a tridentate, monoanionic NCN-ligand would have on the reactivity and structural properties surrounding a transition metal center. It was assumed that the metal would be held in a fixed planar geometry by the σ-C-metal bonded aryl group and the two metal-N interactions arising from bis-*ortho*-chelation. Indeed this binding motif had already been encountered in cation **2**, that, moreover, was one reason for the enhanced water solubility and stability of this material.[6] As a "proof-of-principle" we synthesized the NCN-pincer platinum compound **3** (Scheme 1) and set out to study its reactivity towards electrophiles, *e.g.*, CH_3^+ *via* methyl iodide. It was anticipated that the preference for the planar (*i.e.*, meridional) *N,C,N*-coordination of the pincer would affect the course of oxidative addition (OA) and eventual reductive elimination (RE) processes occurring at the

metal center. However, the actual findings were even more surprising, see Scheme 1.[7]-[10] Obviously, OA had occurred but what was observed was the quantitative formation of a very stable arenonium-platinum compound (**5**) involving a surprising, novel C-C bond-forming process. Subsequently, **5** could be reacted with a nucleophile yielding a stable tetra-substituted 1,1,4,4-hexadienenyl compound (**6**); its formation, by the way, is completely in-line with similar, known conversions in organic chemistry.[10] In the presence of a base, this whole process, from the NCN-pincer platinum cation, **4**, to the hexadienyl-platinum compound, **6**, could be made reversible as testified by the isolation of the neutral NCN-pincer-Pt halide, **3**. During these reaction steps, the pincer ligand remains bonded to the Pt center. As such, this reversible C-C bond making and cleavage process was a first demonstration of the stunning effect that application of NCN-pincer ligands could have in transition metal chemistry.



Scheme 1. Reversible C-C bond making and bond breaking in NCN-pincer platinum chemistry. [7]-[10]

It is this chemistry, shown in Scheme 1, that I presented at one of the Leeds-Sheffield meetings that I attended during the late 1970s and it was also then that I met, for the first time, with Prof. F. G. A. Stone.

It must be noted that our attempts to enter the process, shown in Scheme 1, by making **5** by direct C(arene)-C(methyl) bond cleavage of 2,6-bis[(dimethylamino)-methyl]toluene, **7**, with a suitable Pt complex or salt, were not successful. Later elegant studies by Milstein *et al.* demonstrated that this reaction is in fact feasible in

transition metal chemistry by applying, instead of NCN-pincer ligands, the corresponding, more strongly coordinating PCP-pincer analogues of **7**.[11][12]

Our more recent research in pincer-metal chemistry concentrated primarily on the development of novel synthetic routes to selectively functionalized pincer-metal complexes and their subsequent use as building blocks in a variety of diverse applications,[13] *e.g.,* in homogeneous catalysis,[14]-[17] in the recycling of molecularly enlarged catalysts (nanosized species such as dendrimers [17] or polymers [18] carrying multiple pincer-metal units as catalysts), applying nanofiltration, for sensoring,[19] in bio-organometallic chemistry,[20] and more recently as luminescent materials[21a] and for the synthesis of organometallic pincer-Ru complexes for applications in dye sensitized solar cells.[21b] Some of these examples were discussed in my lecture (J.2.5; 25th ICOMC, Lisbon, 3 September 2012) but in the present discussion I would like, after having presented some comments about the synthesis of *para*-substituted pincer-metal building blocks (see 2.1), to concentrate on a short discussion of our results in three distinct areas:

i, The use of *para*-substituted pincer-metal building blocks for the synthesis of shape-persistent molecularly enlarged metallodendrimers, see 2.2,

ii, The synthesis of *para*-substituted pincer-metal building blocks for the construction of self-assembled molecular-enlarged homogeneous catalysts, see 2.3,

iii, The synthesis of bioconjugates consisting of a single organometallic pincer-metal unit covalently immobilized in a lipase enzyme, see 2.4.

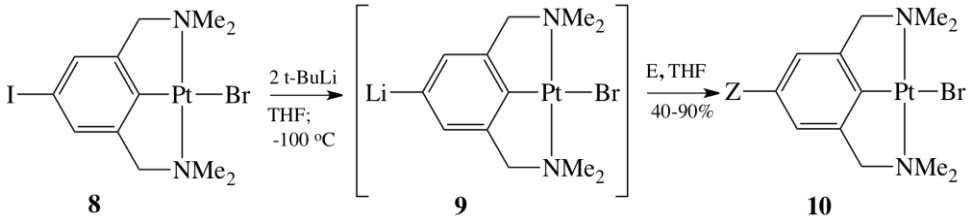
Moreover, for each of the three types of molecularly enlarged organometallics, one example of its use in homogeneous catalysis will also be discussed.

2. Discussion

2.1. Para-substituted pincer-metal building blocks

The syntheses of "molecularly-enlarged" organometallic catalysts requires a number of reaction steps of which the final one is commonly the most vulnerable as it involves the introduction of the σ-metal-carbon bond. The alternate (and more attractive) route would be to initially synthesize the complete organometallic catalytic site that is subsequently connected, in the final step, onto the nanosized carrier molecule. It is this latter more convergent approach that we used in our most recent studies.

In the case of a pincer-metal unit, the *para*-position of the arene ring seems to be the most obvious place for the introduction of a substituent Z that, at a later stage, becomes the "connector" to the carrier molecule, *cf.* the examples in refs 17c and 17d. Key to this approach is the fact that in many pincer-metal complexes the σ-C-metal bond displays an unprecedented stability towards both strong electrophiles and nucleophiles. This opened the unique possibility to realize the synthetic sequence shown in Scheme 2 leading to, for example, the synthesis of a range of [PtBr(NCN-Z-*p*] complexes **10**.[22]



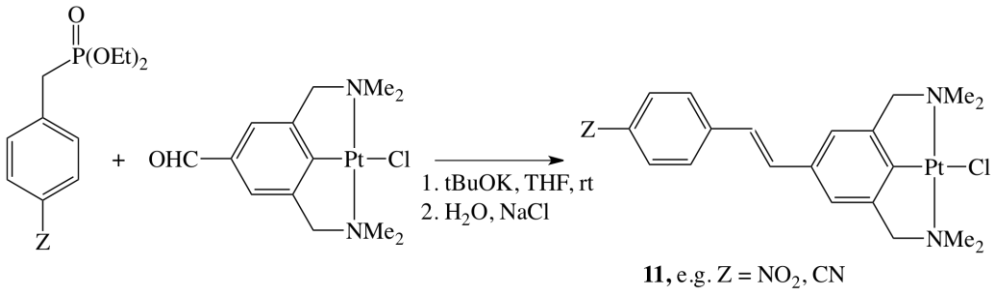
8 **9** **10**

Scheme 2. An example of the post-derivatization of NCN-pincer platinum bromide. E is an electrophile: *e.g.*, CO_2, $ClSiR_3$, $ClPO(OR)_2$, RSSR, DMF.[22]

The regio-selective conversion of 2-bromo-4-iodo-2, 6-bis[(dimethylamino)methyl]-benzene with $[Pt(p\text{-tolyl})_2(SEt_2)]_2$ afforded, in 95% yield, the *para*-iodo pincer platinum compound **8**. This material could be converted at low temperature to 4-lithio-phenyl-1-platinum, **9**. This is a rare example of a heteroleptic 1, 4-bismetallo-benzene compound of which one of the metals is a highly reactive Li centre. *In situ* reaction of **9** with desired electrophiles E gives the *p*-Z-NCN-pincer platinum compounds in reasonable to good yields.[22][23]

As an intermission, it is of interest to note that variations of the *para*-substituent Z drew our attention not only as a possible connector but also as a substituent that can influence the electronic properties of the metal site, *i.e.* we have shown that through variation in the nature of Z that the catalytic, spectroscopic and diagnostic properties of pincer complexes can be fine-tuned in a predictable manner.[23][24][25] A striking example of the electronic tuning is the modification of the catalytic activity of the Ni^{II} center of [NiX(NCN-Z-*p*] in the *Kharasch* addition reaction, *i.e.*, the addition of halocarbons to activated alkenes. The Hammett parameters of the *p*-Z substituent show a clear linear relationship with the Ni^{II}/Ni^{III} redox potentials and consequently with its observed catalytic activity in ATRA reactions.[14][26] Similar linear

correlations were found between both the ^{195}Pt NMR chemical shift values and the calculated natural population charge on Pt and the σ_p Hammett substituent constants in a series of [PtX(NCN-Z-*p*] complexes (Z-*p* = -NO_2, -COOH, -SO_3, -$PO(OEt)_2$, -PO(OH)(OEt), -$PO(OH)_2$, -CH_2OH, -SMe and -NH_2). Conversely, the Hammett σ_p value of the *p*-PtI moiety in [PtI(NCN–COOH-*p*)] was determined to have an empirical value of -1.18 (in pure MeOH) and -0.72 in water/methanol (1:1). The value and sign (negative) of this Hammett substituent constant implied that the *para* platinum iodide group can be considered as an electron-donating substituent comparable in strength to that of a -NMe_2 group (σ_p = –0.83 (polar solvent); *n.b.*, the tabulated σ_m value of the $CH_2N(Me)_2$ group is 0.00).[23] These observations were used to synthesize a series of analogues of the well-known donor-acceptor molecule DANS in which the N,N-(dimethylamino)benzene moiety was replaced by a NCN–PtCl fragment. These various *stilbene*-pincer compounds were obtained in one step applying the Horner–Wadsworth–Emmons reaction of [PtCl(NCN–CHO-*p*)] with an appropriate phosphonate ester derivative (*vide supra* for Z). The compounds with Z = -CN and -NO_2 show luminescent properties;[21a] for a review of this chemistry, see [27].

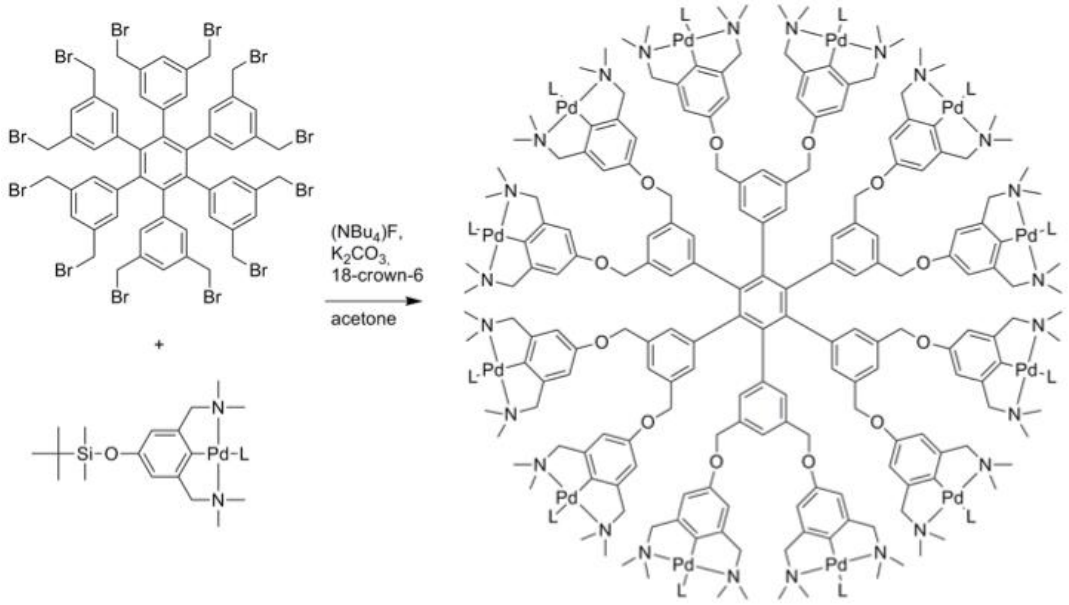


Scheme 3. Direct synthesis of 4, 4'-disubstituted organometallic stilbenes with luminescent properties using a *para*-aldehyde substituted NCNPtCl building block.[21a]

2.2. Anchoring para-substituted pincer-metal building blocks to dendritic molecules with a rigid core structure; Cartwheel metallodendrimers

An example of this approach is the synthesis of the cartwheel metallodendrimer **11** that features twelve pincer-metal units.[17a] It can be constructed in one step from the dodeca-bromide **12** and the appropriate number of NCN-pincer palladium units **14**. Scheme 4 shows this strategy involving *in situ* deprotection of the para-OH grouping and subsequent coupling of the pincer palladium units. The resulting enlarged

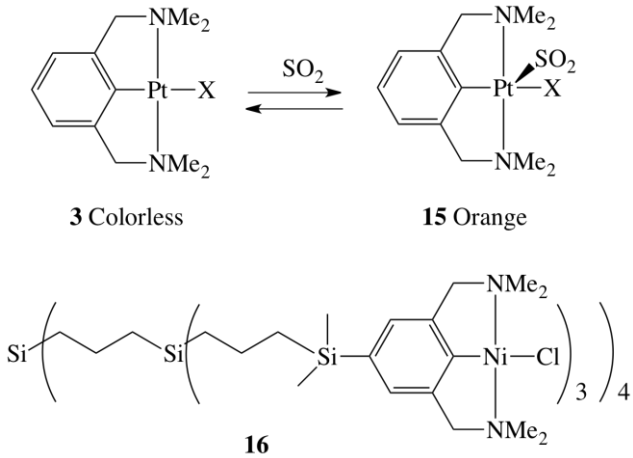
molecule, which was obtained in high yield, has a diameter of 3.21 by 2.43 nm. It has a rigid shape because of its hexaphenylbenzene core while the ether connection to the NCN-pincer palladium catalytic units still allows for some flexibility of the catalytic sites at the cartwheel periphery.



Scheme 4. One step synthesis of a cartwheel metallodendrimer (**11**) with twelve NCNPdL (L = Cl or solvent) units starting from the dodecabromide **12** using *t*-BuMe$_2$Si-NCNPdL (**14**, L = Cl or (H$_2$O)[BF$_4$]) building blocks.[17a]

Similarly, a series of shape-persistent multi(NCN-palladium and/or -platinum) complexes having one-dimensional (one or two NCNM-units), two-dimensional (three NCNM-units) or two- or three-dimensional, depending on the core-stereochemistry (eight or twelve NCNM-units), geometries were prepared in moderate to good yields (see Figure 3 in ref [17a] which also provides the space filling models of the calculated structures as well as their dimensions). These complexes were subjected to nanofiltration (NF) experiments in order to investigate the influence of rigidity and geometry on the retention of these molecules by NF membranes. For this purpose, the corresponding (NCN-Pt-X)$_{12}$ complexes (i.e. the compound in which the twelve Pd atoms in **11** have been replaced by Pt, see scheme 4), were used since exposing the Pt-derivatives to sulfur dioxide in solution resulted in the formation of bright orange complexes, *cf.* **15** in Scheme 5.[19] This allows the use of UV/Vis. spectroscopy to accurately determine the concentrations of the respective cartwheel complexes in both the filtrate and the retentate.

Using the MPF-50 (MWCO) 700) NF-membrane, excellent retention rates (> 99.9%) were found. A clear relationship is observed between the dimensions calculated by molecular modeling and the degree of retention of the various shape-persistent molecules that were investigated. Comparison of **11** with, for example, the flexible carbosilane nickelated G1-dendrimer **16** with similar dimensions, see Scheme 5,[17b, c] proved that a high degree of rigidity in the backbone of macromolecular complexes indeed leads to more efficient retention characteristics of these multimetallic materials by NF-membranes.



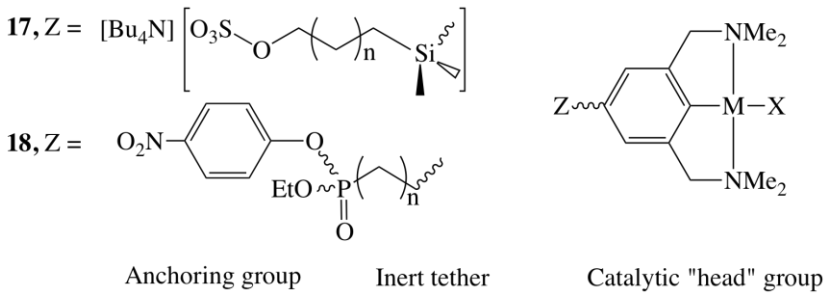
Scheme 5. NCN-pincer platinum chloride **3** as a sensor for SO_2.[19] Carbosilane nickelated G1-dendrimer **16** carrying twelve NCN-pincer nickel chloride units has been used as a catalyst for the Kharasch addition reaction of e.g. haloalkanes to activated alkenes.[17b,c]

Cartwheel compound **11**, as the aquo complex (L = H_2O), was also applied as a homogeneous catalyst for the double Michael reaction between methyl vinyl ketone and ethyl α-cyanoacetate under continuous reaction conditions in a NF- membrane reactor (with MPF-50 (MWCO**)** 700) NF-membrane).[28] The dodeca-cationic palladium catalyst was found to be stable under these continuous reaction conditions as a constant activity was obtained at prolonged reaction times (26 h, 65 exchanged reactor volumes). The turnover number of the catalyst was thus increased by a factor greater than 40 from 80 (batch) up to > 3000 mol/mol Pd.[28]

2.3. para-Substituted pincer-metal building blocks for the construction of self-assembled molecular-enlarged homogeneous catalysts using either dendritic containers with a polycationic core or lipase enzymes

In general, the synthesis of metallodendrimers comprises extensive synthetic protocols involving a large number of reaction steps. Each step has to be as synthetically quantitative as possible, not only because of the yield of the final product, but in particular because of its purity. It should be noted that purification of dendritic intermediates is cumbersome because of the high molecular weights involved. This almost invariably leads to retention of unreacted chains or "mistakes" that are present in one or more of the dendritic side chains. Moreover, multi-step synthetic procedures are obviously detrimental for large-scale applications. To overcome the above discussed problems, we explored two different designs comprising both the construction of the so-called "cartwheel" metallodendrimers (as already discussed in section 2.2) [17a][28][29] and the metallodendrimers made by non-covalent binding of a number of catalytic organometallic groupings to a dendritic carrier molecule.[30][31] Moreover, we studied the single site-selective inhibition of a lipase with a tailor made Z-NCN-pincer reagent that ultimately yields to a pincer metal-lipase hybrid catalyst, *vide infra*.[32] An obvious difference between the latter two approaches are the nature of the molecular enlargement; whereas the non-covalent anchoring affords metallodendrimers with a larger number of pincer-metal head groups (as are the cartwheel molecules discussed above), the single site inhibition approach leads to the lipase enzyme having its active site inhibited with a *single* pincer metal head group. Both approaches will be discussed below, see 2.3.1 and 2.3.2, in some detail.

Two different types (with either an anionic sulfato group (**17**) or a reactive phosphonato grouping (**18**)) of Z-NCN-pincer building blocks were prepared, Scheme 6. Each was used in either the non-covalent anchoring to dendritic containers with a cationic core or in the site-inhibition project involving a lipase enzyme as the carrier molecule.



Scheme 6. Z-NCN-pincer building blocks: **17** can be used for non-covalent anchoring to a core shell dendrimer with an octa-cationic core; **18** has been applied in site-selective inhibition of lipases.

Their syntheses (M = Pd or Pt and for various tether lengths) can be found in references 31 and 32, respectively. The tether with the anionic sulfato group in **17** is firmly connected *via* a robust Si-C bond to the arene ring of the pincer building block, [31] while the tether in **18** with the reactive phosphonato group is connected to the pincer metal "head" group through a covalent C-C linkage.[32] In both cases, the distance between the "head" group and the anionic or the reactive phosphonato site, respectively, can be varied by adjustment of the length of the alkanediyl linker (*i.e.* varying the value of *n* between 0 and 4).

The palladium head group in **17** (n = 4) is neutral. Application of **17** (n = 4) in Lewis acid catalysis (*vide infra*) requires the cationic form of **17** (n = 4); *i.e.* the Cl ion has to be removed, a situation which implies the creation of a zwitterionic organometallic species. It appeared that treatment of **17** (n = 4) with a silver BF_4 salt (removal of AgCl), careful purification of the resulting species followed by re-dissolution in methylene dichloride (removal of $[Bu_4N][BF_4]$) resulted in the formation of the pure organometallic zwitterion comprised of the anionic sulfato group and the cationic NCN-pincer palladium(aqua) head group. Interestingly, the hygroscopic zwitterionic species **19** (n = 4) is soluble in various organic solvents (*e.g.*, acetone and dichloromethane) but is insoluble in water. Hydrogen bonding between the coordinated water molecule and the sulfato group is proposed to play a major role in the interaction between the zwitterions, see Figure 1.[31]

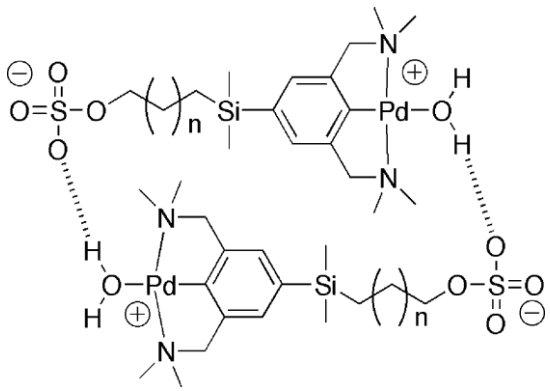
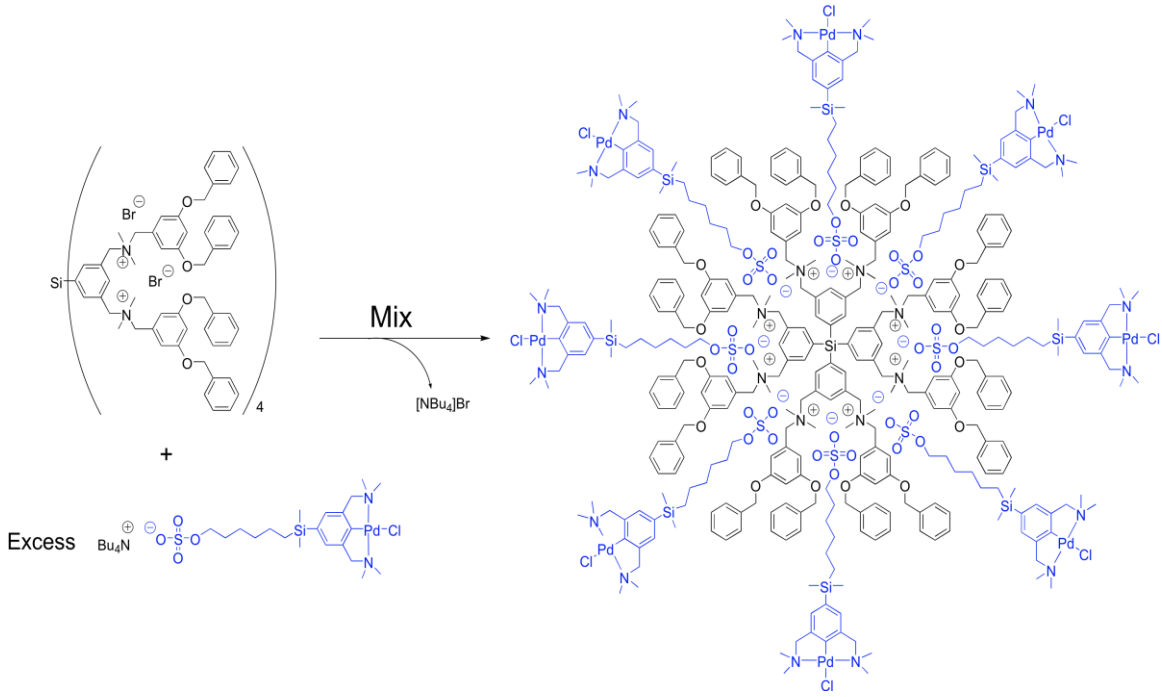


Figure 1. Proposed structure of the organometallic zwitterion **19** (n = 1 or 4) based on the IR spectra and negligible observed molecular conductivity.

2.3.1. Self-assembling of the octa-cationic dendrimer **20** with eight *para-sulfato* substituted pincer-metal building blocks **17** to give molecularly enlarged assembly **21**.

This study clearly represents a "proof-of-principle" study on the non-covalent immobilization of homogeneous catalysts. These species are designed to be soluble and molecularly-enlarged catalytic materials that can be applied in membrane reactors.[33] For a detailed discussion the reader is directed to reference [30]. In a separate study, we already had developed a novel class of ionic core-shell dendrimers, which are comprised of eight quaternary ammonium sites in the core and a shell of Fréchet-type polybenzyl aryl ether dendrons. These dendrimers can be assembled in one step under mild conditions by a simple quaternerization reaction of (again Fréchet type) benzyl bromides with the core aryl amine groupings. As an example, the formation of the dendritic assembly **20**, shown in Scheme 7, will be discussed in more detail.



Scheme 7. Non-covalent anchoring of eight catalysts by anion exchange between **17** (n = 4) and the bromide anions of the respective octacationic silicon dendritic species affording the assemblies **20** (having G_1-dendritic wedges), **21 (**with G_2) and **22 (**with G_3), respectively. Note that in the catalytic reactions discussed below, the Cl anions of the catalytic head groups in the assemblies are replaced by H_2O (by reaction of the assembly with aq. $AgBF_4$).

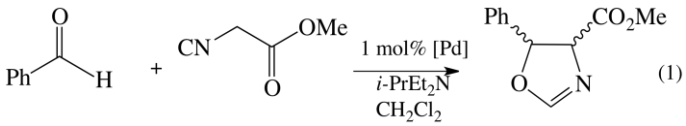
Assembly **20** comprises a tetrahedral tetraphenylsilicon core of which each phenyl grouping is bis-*meta*-substituted with ammonium groups. Each ammonium N-center carries a G_1-polybenzyl aryl ether dendron that, however, can be varied in size (*i.e.* G_2, G_3, etc). This adjustment can be used in order to create the desired distance between the cationic core of ammonium centers and the periphery of the dendrimer, *i.e.* to employ the thickness of the dendritic shell. Moreover, the properties, (*e.g.*, hydro-phobicity and –philicity and therefore solvent compatibility, accessibility of the core for molecules to bind to the core) of the octa-cationic dendritic species can be controlled by variation of the decoration of the dendritic periphery with specific substituents on the outer phenyl rings, see figure 4 in reference [30]. The Br-anions, *e.g.*, in the case of **20** (having the G_1-dendritic shell), reside near the cationic core and can each be exchanged by, for example the sulfato-anion of **17** (n = 4). Due to the nanoscopic size of these ionic core-shell dendrimers, their corresponding dendritic assemblies can be easily recovered and thus purified, by means of dialysis. We

established that a maximum of eight monoanionic NCN-pincer palladium molecules were bound, *i.e.* the number of permanent ammonium sites in the core of the carrier determines the maximum number of arylpalladium complexes that can be attached to this kind of dendritic support. Binding studies revealed that the anionic (anchoring) sulfato group of the NCN-pincer palladium grouping is located close to the cationic core of the carrier. The number of Pd(II) complexes appeared independent of the steric bulk or the nature of the dendritic shell as was demonstrated by experiments with carriers having higher generation dendritic wedges. These results suggest a relatively "open" structure for all of the dendrimer generations that were studied.[30]

PGSE NMR spectroscopy and conductivity measurements revealed that the octacationic dendritic carrier and the arylpalladium complex **17** (n = 4) are strongly associated in dichloromethane solution as well as in the solid state (TEM analysis) revealing the nanoscopic size dimensions of assembly **20** in solution.

Its calculated dimensions are 4.2 × 4.5 × 3.4 nm^3 and clearly increases on going from an assembly with a G_1-shell, as in **20**, to assembly **22** with a G_3-shell. Notably, these calculated dimensions are comparable to the dimensions derived from the PGSE NMR experiments and from TEM analysis. Obviously, the dimensions of assembly **20** are determined by the length of the palladium(II) guest molecules whereas the sizes of the assemblies with the thicker shells (G_2-and G_3-wedges) are gradually set by the dendritic backbone; with increasing shell thickness the shape of the assemblies are becoming more spherical while the catalytic head group becomes eventually immersed in the dendrimer periphery, see figure 10 in reference [30].

Catalytic applications of the metallodendritic assemblies such as **20** (note that the palladium centers are now cationic) were tested in an Aldol condensation reaction between benzaldehyde and methyl isocyanoacetate (dichloromethane), see equation 1 and were compared to those of the unsupported Pd(II) complexes [Bu_4N][**17**].



(1)

Only minor decreases in catalytic activity of the catalytic palladium sites of **20** were observed, while the product selectivity remained comparable to that of parent [Bu_4N][**17**] species. Moreover, the catalytic assembly and reactants/products could be easily separated by membrane filtration techniques.

This study proves that the approach for the immobilization of catalysts onto a core-

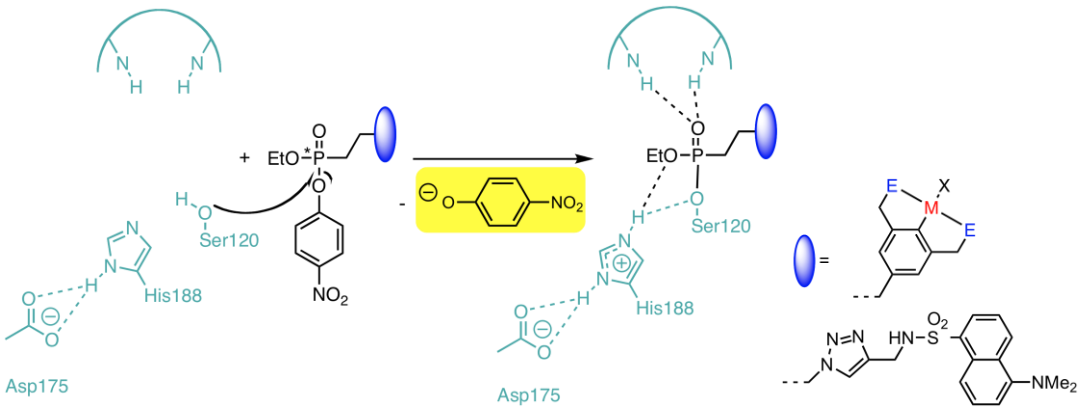
cationic dendritic support under mild conditions by means of reversible non-covalent binding interactions is possible. Obviously, these non-covalent interactions are sufficiently strong to prevent leaching of the catalyst. In this context, it is interesting to note that controlled removal of the catalytic moiety from the dendritic support, in the presence of excess Bu_4NBr, could also be demonstrated. This possibility to reverse the binding of the catalysts is of interest because it would allow for controlled removal of the (deactivated) catalyst, recovery of the (often expensive) dendritic support and, subsequently, its reuse after reloading it with a fresh batch of the same or a different catalyst. However, in the case of assembly **20**, all but one of the eight palladium catalysts could be removed.[34]

2.3.2. Site-selective inhibition of Cutinase and CALB beads with an organometallic (pincer or CpRu) building block; application in DKR of a racemic alcohol.

So far I have discussed various studies of molecularly enlarged (up to 4 nm) molecules comprising a dendritic carrier with a number of pincer metal groupings, either bonded covalently to the dendrimer periphery or attached to the octacationic of a dendritic carrier in a non-covalent manner. In this section enlarged catalytic materials of similar nano dimensions will be discussed, in which an enzyme, rather than a dendritic molecule, is the carrier of a *single* catalytic grouping. The enzyme selected for this purpose was a lipase (Cutinase). This particular lipase has a serine group in its active center that can be addressed in a site-selective manner. We found that by using a phosphonate of type **18** (n = 1) that a pincer metallic (or another organometallic) grouping could be site-selectively attached to the active site of the lipase, *i.e.*, in this case, a *single* organometallic grouping becomes enlarged indeed.[20][32] The resulting lipase-organometallic hybrid catalyst can be used in environmentally friendly aqueous media. In addition, the chiral protein environment, by creating a second coordination sphere around the metal center, can positively influence the stereo- and enantio-selectivity of the bound achiral transition-metal catalyst. This approach was inspired by the landmark report of Whitesides and Wilson who demonstrated the site-specific modification of avidine with an achiral bisphosphine rhodium catalyst that was bonded via a linker to a bovine anchoring group. Initially only a moderate enantioselectivity was observed when this avidine-Rh hybrid catalyst was used as catalyst in the hydrogenation of α-acetamidoacrylic acid;

however, it represents an exciting "proof-of-principle" concept that inspired many related studies.[35] In more recent years, this approach has been further explored by the group of Ward *et al*., see [36] and references cited therein.

As indicated, our endeavors in this field started with the synthesis of Z-NCN-pincer metal building blocks linked to a reactive phosphonato grouping (*cf*. **18** (n = 1)).[32] Note that in this reaction the respective phosphonates are formed as a racemic mixture. Whereas lipases catalyses the hydrolysis of fatty acids ester bonds, the application of phosphonates with a *para*-nitrophenolate leaving group leads to site-selective inhibition of the lipase active site due to the resulting covalent attachment of the phosphorus grouping; *i.e.* to the binding of the ECE-pincer metal halide (E = R_2N or RS; M = Pd or Pt) grouping to the lipase, see Scheme 8.[37] The lipase (Wild type) Cutinase that was used is stable up to 50 ^{0}C, has a molecular weight of about 21 kD and contains an active site that is directly accessible to soluble substrates. The inhibition requires a 2 : 1 molar ratio of the racemic phosphonate to the lipase because the inhibition proceeds enantio-selectively. The progress of the inhibition was followed by UV/Vis. spectroscopic monitoring of the formation of the *para*-nitrophenolate anion.[32] Purification of the hybrids occurred by dialysis also allows for the separation of the unreacted phosphonate enantiomer and the hybrid. Mass spectrometry of these hybrids confirmed the 1:1 molar ratio of Cutinase (M/Z calc'd: 20604; found: 20603.9 ± 0.2) and the bonded ECE-pincer metal group (e.g., **18** with M = PtCl and n = 4; calc'd: M/Z 21122.16; found: M/Z 21120.9 ± 0.4).



Scheme 8. Mechanism proposed for lipase inhibition by reactive phosphonates. Two examples of different "head groups" are shown; one an ECE-pincer metal halide and

the second a dansyl grouping connected via click chemistry to the phosphonate inhibiting grouping.[42]

For the two hybrids the molecular structure in the solid state could be established with X-ray structure determination.[37] An overlay of these structures is shown in Figure 2 which reveals that each ECE-pincer metal halide "head group" occupies a different pocket within the "mouth" of the lipase. Most interestingly, the phosphorus center in the respective hybrids has opposite configuration, see legend to Figure 2.[37] Whether this is connected to different kinetics and routes for the inhibition process is still subject to further study. Notably, we have observed that the inhibition process for the phosphonates with either a direct P-C_{para} bond, *i.e.* a phosphonate lacking the alkanediyl tether that is, for example, present in **18** (n = 1), or having a larger ECE-pincer "head group" (E = SPh rather than SMe) is much slower, *i.e.*, >500 times for the phosphonate lacking the tether as compared with the inhibition rate observed for **18** (n = 1, M = Pt).[38] Obviously, whereas in the latter hybrid the pincer metal head group resides at the periphery of the lipase in the tether-less hybrid, the organometallic head group is effectively positioned in the chiral surroundings of the active site of the cutinase.

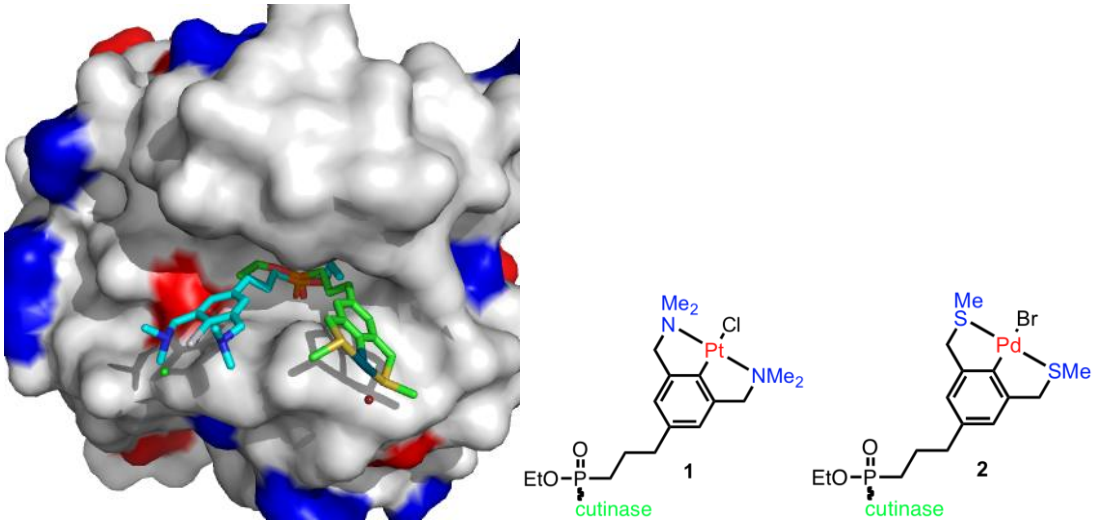


Figure 2. Overlay of the molecular structures of Cut-NCNPtCl (S_P) (blue) and Cut-SCSPdBr (R_P) (green).[37]

The above discussed inhibition reactions have been carried out in buffered solutions of the Cutinase (1 mmol) with rather high chloride ion concentrations. Performing the

same inhibition under chloride poor reaction conditions, however, resulted in the isolation of [Cut-NCNPt-Cl-PtNCN-Cut]$^{+}$-cationic hybrids of which the relevant part of the molecular structure is shown in Figure 3.

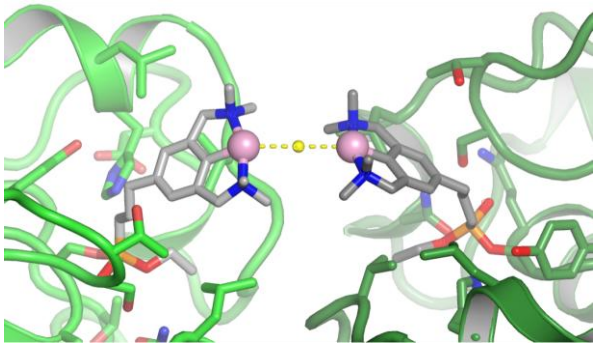
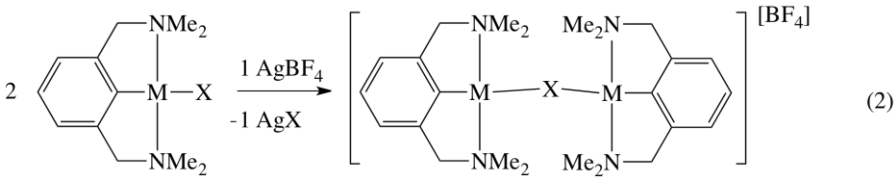


Figure 3. Part of the structure in the solid state showing the [Cut-NCNPt-Cl-PtNCN-Cut]$^{+}$-cationic structural feature.[37]

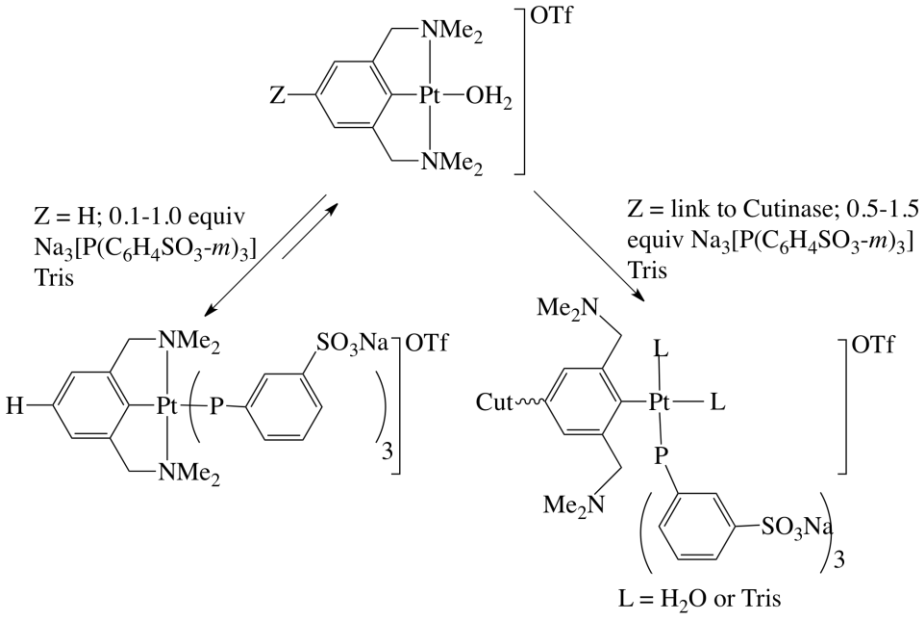
In this dimeric hybrid, it is a single chloride ion and two [Cut-NCNPt]$^{+}$-cations that self-assemble to yield a surprising structure with a μ-Cl bridge observed in the solid state. It is noteworthy that removal of half of the Cl anions of the parent NCNPtCl complex with $AgBF_4$ resulted in the formation of a similar dimeric structure with a μ-bridging halide; the structure in the solid state for the corresponding dimeric Pd-complex shows many similarities with those of the dimeric hybrid, see equation 2.[39] These reactions are reversible in the presence of excess NaCl, *i.e.*, the parent NCNMCl (M = Pd or Pt) complex is reformed quantitatively.



(2)

These observations indicated that the Pt center in the Cut-NCNMX hybrids would have enough conformational freedom to participate in a novel type of bio-coordination chemistry. This was substantiated by a recent study in which the cationic [Cut-NCNPt(H_2O)]$^{+}$ hybrid was reacted with water soluble triarylphosphines in aqueous media. A ^{31}P NMR and ESI-MS study showed that coordination of various triarylphosphines to the enzyme-embedded platinum center is affected by the surrounding protein backbone and depends on the size and charged of the aryl

phosphines. Some results of this chemistry are summarized in Scheme 9. [40]



Scheme 9. Comparison of the reaction cationic H-NCN-pincer platinum aqua complex and Cut-NCN-pincer platinum aqua hybrid with $P(C_6H_4(SO_3Na)\text{-}m)_3$; for ^{31}P NMR data see reference [40].

The results presented here have been used for the preparation of a heterogeneous, bi-functional catalytic system, combining the catalytic properties of an organometallic catalyst (racemization) with those of an enzyme (enantio-selective acylation). In collaboration with the group of Bäckvall, the novel ruthenium phosphonate inhibitor, see Figure 4, was synthesized and covalently anchored to a lipase immobilized on a solid support (CALB, Novozym®435).[41] The $Ph_5CpRuCl(CO)_2$-entity of this inhibitor is a known racemization catalyst of chiral 1-phenylethanol.[42] Its preparation involved the coupling of the *para*-acetylene substituent of one of the Ph substituents of the Ru entity with the azide functionalized phosphonate using "click" chemistry.[43]

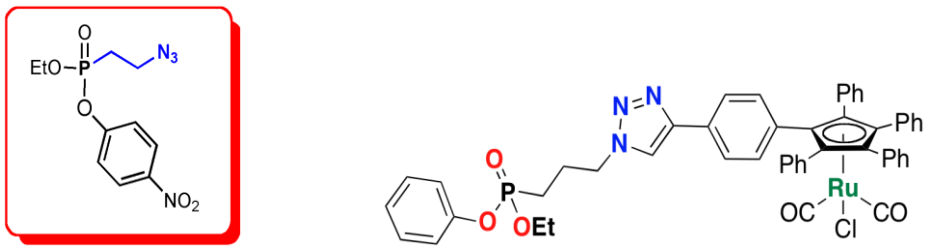


Figure 4. The azide functionalized phosphonate used for the synthesis of the organoruthenium racemization catalyst **23**.[43]

The resulting inhibitor **23** was loaded onto the surface thereby taking into account that only one enantiomer of the racemic phosphonate complex **23** would bind to the active site of the enantioselective lipase CALB immobilized on the beads. The amount of available (non-inhibited) catalytic sites of the CALB beads can be controlled relative to the amount of Ru sites, enabling one to vary and fine-tune the composition of the catalytic material, for experimental details see reference [41]. An explorative DKR experiment showed that the resulting immobilized *bifunctional* catalytic system can be used as both a racemization (of (**S**)-1-phenylethanol) and enantio-selective acylation (of (*rac*)-1-phenylethanol) catalyst. However, these proof-of-principle experiments also revealed that to achieve a successful DKR the partial inhibition of the lipase with the ruthenium catalyst **23** has to be further fine-tuned.

3. Conclusions

The Pincer platform is gaining increasing interest and use as one of the privileged ligands in the fields of organometallic chemistry, homogeneous catalysis and materials science.[44] Important factors that are promoting for this interest are its simple design and the possibilities to build and vary, in a modular manner, its molecular features to the effect that the desired properties of the bound metal site can be engendered.[44] The often surprising stability (thermal, and low reactivity to electrophiles or nucleophiles) of the pincer type organometallics arises from the tridentate ligand-metal interaction, of which the central one often is a covalent metal-carbon bond. This stability contributes to the versatility and applicability of pincer-metal units as building blocks. In the research presented herein, some approaches for the synthesis of molecularly-enlarged catalysts that can be applied in homogeneous catalysis were discussed. It has to be emphasized that these approaches have been

developed in an attempt to develop technologies for the sustainable use of catalytic materials. The examples presented have to be considered as "proof of principles" and certainly require further study to become, in the end, applicable from an economic point of view. However, for me personally it has been a privilege to work on the fundamental aspects and applications of chemistry using pincer-organometallics and I hope that this research has been an inspiration for many of the young students that were involved and hence led them to develop careers in which Science plays a crucial role.

4. Acknowledgments

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Abstract

Present trends in homogeneous catalysis are moving towards the development of multi-step, one-pot processes where salt waste is reduced to a minimum and in the lowest possible volumes of solvent. Energy efficiency is also maximized to produce the most cost-effective end product(s). However, these one pot cascade, tandem, or domino catalyzed reaction sequences rely on catalyst, substrate and solvent compatibility, on catalyst stability and on the possibility to protect these catalysts from mutual deactivation. This can be facilitated, for example, by binding these to suitable (in)soluble supports or by using compatible, stable catalysts that can be used to mediate a variety of different reactions.

Pincer organometallics are powerful tools that can be used to achieve many of these objectives. The synthesis and properties of a variety of "molecularly enlarged" pincer organometallics displaying both surprising stability and versatile catalytic properties is discussed. A fascinating, recent development is the site-selective inhibition of a bead-immobilized lipase, *i.e.,* Cutinase, containing a single pincer-metal catalytic site. The resulting bio-organometallic hybrid catalyst (see X-ray), in combination with uninhibited lipase, can operate as a heterogeneous bifunctional catalytic material for the kinetic resolution of racemic alcohols to yield enantiopure product(s).