Application of a Homogeneous Dodecakis(NCN-Pd^{II}) Catalyst in a Nanofiltration Membrane Reactor under Continuous Reaction Conditions

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Abstract: A shape-persistent nanosize dodecakis(NCN-Pd^{II}-aqua) complex (**4b**) was applied as a homogeneous catalyst in the double Michael reaction between methyl vinyl ketone and ethyl α-cyanoacetate under continuous reaction conditions in a nanofiltration membrane reactor. Due to its macromolecular dimensions, the catalyst is retained in the reactor ($R = 99.5\%$ determined by ICP-AAS) during catalysis. In addition, the catalyst was found to be stable under the 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. Further development of this technology will allow an increase of the number of (industrial) catalytic processes in which homogeneous catalysts are applied.

Keywords: continuous homogeneous catalysis; Lewis acids; N ligands; membrane reactor; organometallic compounds

Introduction

Homogeneous catalysts are frequently used in highly selective organic transformations. Especially in asymmetric syntheses, the contribution of homogeneous catalysts is significant.[1] Nevertheless, in industry most catalytic processes are still catalyzed by heterogeneous catalysts because of their facile separation from the product stream. In the field of homogeneous catalysis, separation of the catalyst from the product mixture is often complicated, making these catalysts inefficient and too expensive, preventing industrial applications.[2] In addition, the often toxic metal is still present in the product mixture, making an extra purification step necessary. In recent years, a number of methods have been developed to separate homogeneous catalysts from the product-containing solution for reuse. Often biphasic systems are used in which the catalyst dissolves in one phase and the substrates and products in the other phase, e.g., aqueous biphasic systems,[3] fluorous biphasic systems[4] or non-conventional solvents such as ionic liquids,[5] allowing separation of the catalyst from the product mixture. Another method is anchoring the homogeneous catalyst to a solid support,[6] creating a hybrid catalytic system possessing the catalytic properties of a homogeneous catalyst and the recycling properties of a heterogeneous catalyst.

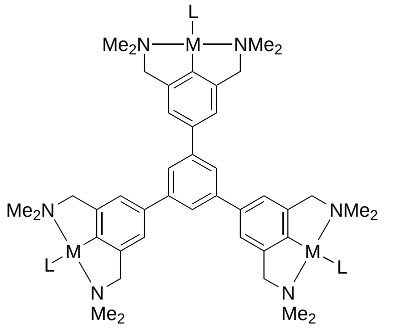
A promising development in the field of homogeneous catalyst recycling is the development of molecularly enlarged homogeneous catalysts which can be recycled by means of nano- or ultrafiltration.[7,8] Since the catalysts are homogeneously dissolved and catalysis takes place in a single phase, such a setup can be operated under continuous reaction conditions. For this purpose often dendrimer- and polymer-enlarged homogeneous catalysts are used. These materials possess many ligand sites suitable for coordinating transition metal ions, creating the catalytically active species. Especially, the so-called *metallodendrimers* have attracted wide-spread attention in recent years, because of their well-defined structures which can be altered in a controlled way, making fine-tuning of the multimetallic catalyst possible.[9] Also, a direct comparison with the mononuclear analogues is feasible.

Recently, we started to explore the application of shape-persistent multi(pincer-metal) complexes **1–4**

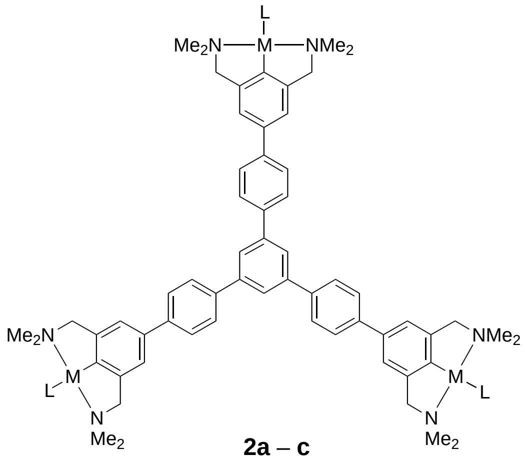
(Figure 1) in a nanofiltration membrane reactor.[10] These complexes were selected because they cannot undergo shape-changes in solution which was found to be important for obtaining optimal retentions of these complexes by nanofiltration membranes.[10c] Retentions greater than 99.9% were found using the commercially available MPF-60 and MPF-50 nanofiltration membranes.[10c,11] Here, we report the application of the dodecakis(NCN-Pd^{II}-aqua) complex **4b** as a homogeneous catalyst in a double Michael reaction in a nanofiltration membrane reactor under continuous operating conditions. This catalyst was selected because of the excellent retentions obtained with the isostructural platinum analogue **4c** in combination with the commercial MPF-60 ($R > 99.9\%$) and MPF-50 ($R = 99.9\%$) NF-membranes, creating the opportunity for running catalytic reactions for prolonged reaction times.

Results and Discussion

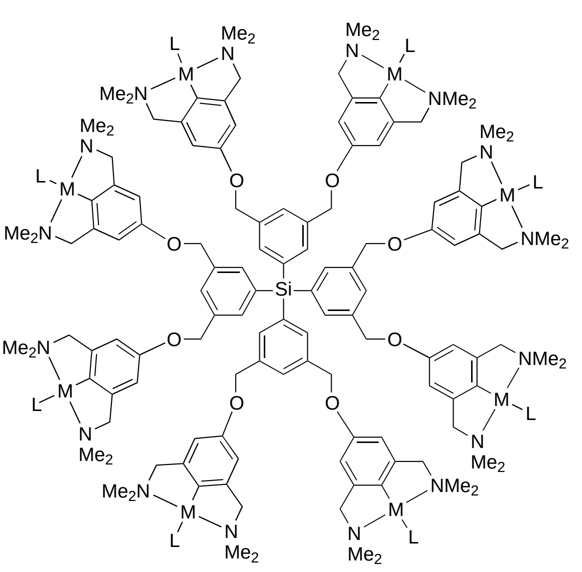
Recently, we reported the synthesis of dodecakis(NCN-metal) complexes applying a modular approach: the twelve-fold coupling of monometallic pincer building blocks **6a** and **6b**, respectively, to shape-persistent dodecabenzyl bromide **5** (Scheme 1).[10c] Important to note are the mild reaction conditions – acetone at room temperature – needed for these multi-fold couplings. Thus, the risk of destroying the individual organometallic sites is minimized, which is an absolute prerequisite in the synthesis of multimetallic materials. The alternative procedure would be to first prepare the complete multisite ligand, followed by permetalation, a procedure which often needs harsh reaction conditions and can lead to incomplete metalation, especially with increasing number of ligand sites to be metalated.[7h]



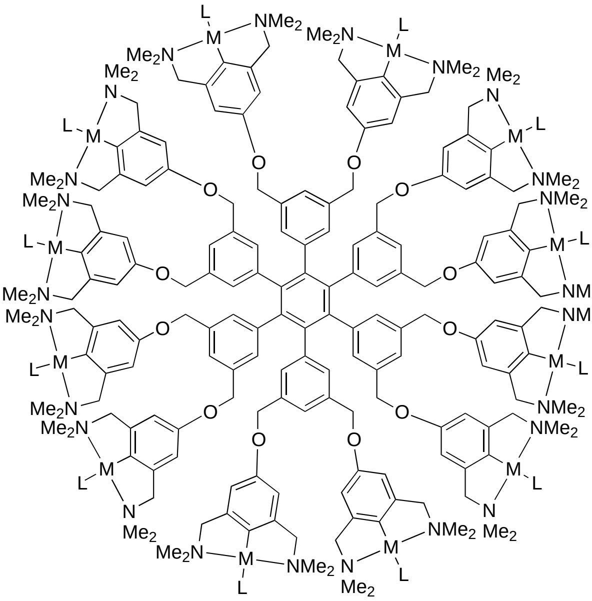
1a: M = Pd, L = halide
1b: M = Pd, L = OH$_2$(BF$_4$)
For retention measurements
1c: M = Pt, L = halide



2a – c

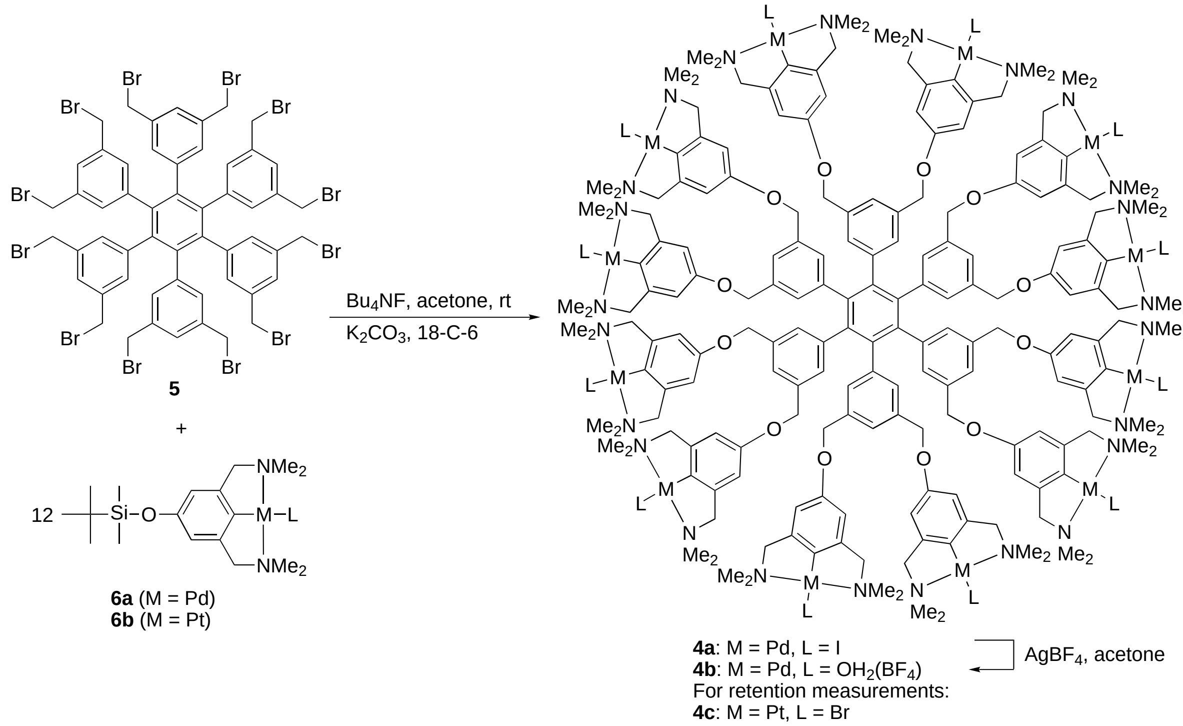


3a – c



4a – c

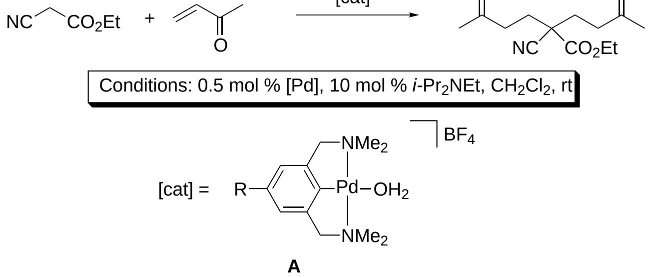
Figure 1. Shape-persistent multimetallic pincer complexes.



Scheme 1. Modular approach for the synthesis of multi(pincer-metal) complexes.

For an accurate retention determination, we made use of the ability of the [PtX(NCN)] unit (X = halide) to quantitatively absorb SO_2 in solution, a process which is accompanied by a characteristic color change from colorless to bright orange.[12] Submillimolar amounts of the SO_2-complexes in solution can already be detected by this technique. This allows the use of UV/Vis spectroscopy to accurately determine the concentration of the dodecakis(NCN-Pt^{II}) species in the retentate and in the permeate.

Previously in batch processes, it was found that palladated cationic NCN-pincer complexes **A** are very active as Lewis acid catalysts in the double Michael reaction between methyl vinyl ketone (MVK) and ethyl α-cyanoacetate (Scheme 2).[10b,13,14] Especially, dodecakis(NCN-Pd-aqua) catalyst **4b** showed a surprisingly high activity in this reaction; an almost three-fold increase in the catalytic activity per palladium center was found as compared to the mononuclear analogue.[14] Since this enhancement in activity was only observed for the dodecakis(pincer) complex, this behavior must be a result of the three-dimensional structure of this material, e.g., cooperativity between adjacent catalytic sites. The double Michael reaction can be performed under rather mild reaction conditions, i.e., CH_2Cl_2, Hünig's base, room temperature, making this reaction ideal for the commercially available MPF NF-membranes, and thus for application under continuous operating conditions in a nanofiltration membrane reactor. Important to note is that the solvent used for the retention rate determinations,[10c] i.e., CH_2Cl_2, is the same as the solvent in which catalysis is performed, making direct comparison feasible. In comparison with the retention measurements, the platinum centers of the dodecakis(NCN-metal) complex were replaced by catalytically active palladium centers. Molecular modeling studies revealed, that this metal exchange does not influence the size and geometry of the molecule.[10c] Therefore, the only marked difference with the retention measurements is that cationic (NCN-Pd^{II}) moieties are needed for catalysis, while the retention measurements were performed with neutral (NCN-Pt^{II}) groups.



Scheme 2. Double Michael reaction using cationic NCN-Pd^{II} catalysts.

For the continuous catalysis experiment in a membrane reactor (volume = 12 mL), the MPF-50 NF membrane was used. The concentration of the substrates in solution was kept the same as in the previously

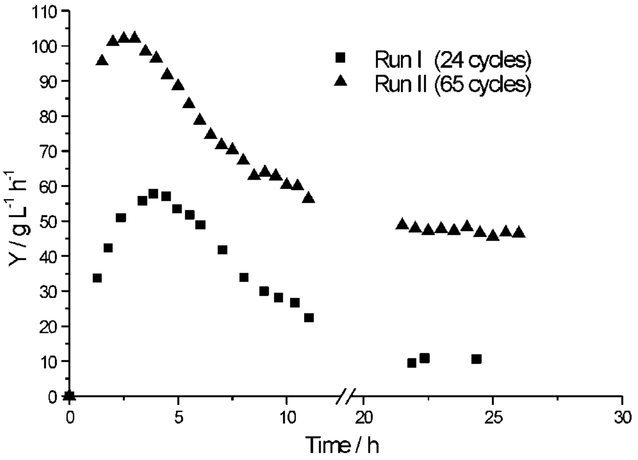


Figure 2. Two different continuous experiments; MPF-50 NF membrane; Run I: 1.6 mM [Pd], flow-rate = 12 mL h^{-1}, $\tau = 1$ (residence time in h), p = 20 bar; Run II: 4.2 mM [Pd], flow-rate = 30 mL h^{-1}, $\tau = 0.4$, p = 20 bar.

reported batch processes.[10b,14] Furthermore, the flow-rate was chosen such that the conversion never exceeded 85%. In this way, we were able to study the behavior of the catalyst in time.

Figure 2 shows the space-time yield Y (g L^{-1} h^{-1}) versus time for two different continuous catalytic runs. For Run I, a palladium concentration of 1.6 mM (= 0.13 mM of **4b**) and a flow-rate of 12 mL h^{-1} (= one reactor volume per hour) was used. In Run II, the palladium concentration and the flow-rate were both increased by a factor 2.5 to 4.2 mM (= 0.35 mM of **4b**) and 30 mL h^{-1} (= 2.5 reactor volumes per hour), respectively, allowing us to investigate the influence of these parameters on the catalytic process. Under these conditions the background reaction (thus without catalyst) is negligible ($<1\%$ conversion per hour). In both experiments, the space-time yield shows first a large increase, followed by a slow decrease in time until a more or less constant level is reached. While the reactor is filled with the catalyst solution in CH_2Cl_2 containing already some ethyl α-cyanoacetate necessary to completely solubilize **4b** before the start of the experiment (c = 0.39 M, see Experimental Procedure), the two substrate solutions are fed into the reactor independently. Under these circumstances steady state condition (a constant composition of all components in the reactor) is only reached after several residence times. The thus obtained curves (Figure 2) are typical examples of a startup behavior of a continuous stirred tank reactor[15] (CSTR). Furthermore, modeling the conversion using pseudo first-order kinetics, a space-time yield *versus* time diagram was obtained similar to the diagrams obtained for the catalysis experiments as depicted in Figure 2. For this modeling, the rate expression $r = k_{obs}$ [ethyl α-cyanoacetate] was used, with $k_{obs} = 8.1 \times 10^{-4}\ s^{-1}$, as determined in an earlier study.[14] Thus, only after a considerable number of residence times is a constant concentration of ethyl α-cyanoacetate reached.

For Run II, the percentage of [Pd] in both the retentate and the permeate was determined by ICP-AAS after reaction, revealing a catalyst retention of 99.5% under the reaction conditions. This is almost identical to the retention found for the isostructural platinum analogue **4c** (R = 99.9%).[10c] This minor leaching of the catalyst completely accounts for the slow decrease of the space-time yield at elongated reaction times (after 10 h). These results show that catalyst **4b** is stable under the continuous reaction conditions and exhibits a constant activity for prolonged times. This is of great importance in this research field, since catalyst stability, together with an efficient retention by NF membranes, determines the applicability of macromolecular homogeneous catalysts in continuous catalytic processes using membrane filtration technology.

It is remarkable that in this homogeneously catalyzed reaction the average space-time yield can be increased considerably (Run I *vs.* Run II) just by increasing both the flow rate and the catalyst concentration. This results in a more efficient catalytic process. In all cases, no Pd black formation or precipitation, suggesting decomposition or deactivation processes, was observed as was established by inspection of the reactor content after completion of the experiment. Applying nanofiltration techniques, the turnover number per palladium center of **4b** could be increased more than 40-fold from 80 mol/mol Pd comparing the batch experiment (batch: 4.2 mM [Pd] = 0.35 mM **4b**, 0.32 M ethyl α-cyanoacetate, 1.0 M methyl vinyl ketone, 0.032 M diisopropylethylamine, 5 mL CH_2Cl_2), to over 3000 mol/mol Pd in Run II. Even after more than 65 residence times (Run II), the catalytic system is still able to produce more than 45 grams of product per liter and hour. This is not so easy to obtain by other homogeneous catalyst recycling methods. In biphasic systems, a continuous operating process is often complicated since the catalyst has to be separated in an additional step, e.g., phase separation or extraction. Hybrid heterogenized homogeneous catalysts, on the other hand, suffer from mass-transfer limitations and often possess a lower activity than the homogeneous catalyst caused by narrow channels or entanglement in the heterogeneous supports. Furthermore, the dispersion and local environment of the catalytic centers are often unknown, making direct comparison with the corresponding homogeneous system impossible. Applying nanofiltration membranes in homogeneous catalyst recycling overcomes these limitations, since the catalyst is homogeneously dissolved and does not suffer from mass-transfer limitations and the separation is accomplished in the same phase. This makes this approach ideal for continuous processes. An additional advantage of this technology is the relative ease of obtaining higher space-time yields by simply adjusting the continuous reaction conditions, such as catalyst loading, residence time and substrate concentrations.

Conclusions

The first example of a shape-persistent multi(pincer-metal) complex as a homogeneous catalyst under continuously operating conditions in a nanofiltration membrane reactor is described. Based on earlier studies in a membrane reactor, the dodecakis[NCN-Pd^{II}-aqua]$(BF_4)_{12}$ complex **4b** was selected for this purpose since this complex showed excellent retentions by the MPF-60 and MPF-50 nanofiltration membranes. Applying this technology, the efficiency of **4b** as a Lewis acid catalyst in the double Michael reaction between methyl vinyl ketone and ethyl α-cyanoacetate was significantly enhanced, as the turnover number was increased by a factor greater than 40. In addition, after prolonged reaction times only a minor decrease in activity in time was observed, which could be completely ascribed to very slow leaching of the catalyst (R = 99.5%). This means that the catalyst shows very little decomposition or deactivation even after prolonged reaction times, an absolute prerequisite when applying these complexes as homogeneous catalysts under continuous reaction conditions. In conclusion, we have shown that with a number of important conditions fulfilled, i.e., high retention rates, high catalyst stability and resistant membranes, membrane technology is very promising for the application of homogeneous catalysts in industrial processes. For a broader application of homogeneous catalysts under continuous reaction conditions in a membrane reactor, both improvement of the membrane technology (especially more resistant membranes) and finding more catalytic systems which possess the required properties are of crucial importance.

Experimental Section

Procedure

The continuous catalytic experiments were performed in CH_2Cl_2 in a nanofiltration membrane cell (12 mL) using the Koch MPF-50 flat-membrane.[11] Prior to the continuous experiments, the membranes were first stored overnight in a methanol bath, followed by 1 h in a CH_2Cl_2 bath. Finally, CH_2Cl_2 was flushed through the membrane in the membrane reactor in order to remove residual traces of methanol. In a typical experiment (Run II), catalyst **4b** (MW = 5701.2; 24.1 mg, 4.2 μmol) was suspended in 3 mL of CH_2Cl_2 and ethyl α-cyanoacetate (0.5 mL) was added, affording a clear solution. This solution was transferred into the reactor. Subsequently, a solution of MVK (2 M) and diisopropylethylamine (0.064 M) in CH_2Cl_2 (500 mL), as well as a solution of ethyl α-cyanoacetate (0.64 M) and n-decane (0.4 M, internal standard) in CH_2Cl_2 (500 mL) were pumped simultaneously with equal flow rates (15 mL h^{-1}) into the reactor. Resulting flow rate = 30 mL h^{-1}, $\tau = 0.4$ h, T = 23 °C, p = 20 bar. Samples of the solution leaving the reactor were taken continuously, quenched with Et_2O and analyzed by GC spectroscopy.

Acknowledgements

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