Homogeneous Catalysis

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Palladium-Catalyzed Allylic Substitution: Reversible Formation of Allyl-Bridged Dinuclear Palladium(I) Complexes**

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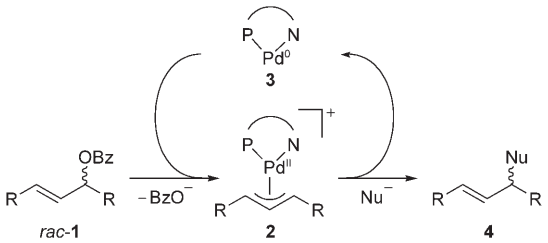
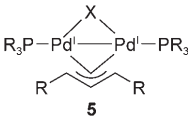
The mechanism of Pd-catalyzed allylic substitutions has been elucidated in detail (Scheme 1).[1] On the basis of this knowledge, we have recently developed a screening method



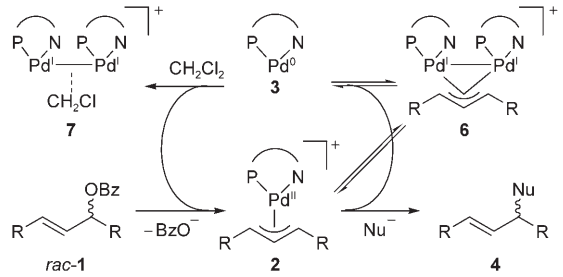
Scheme 1. Mechanism for the Pd-catalyzed allylic substitution. Bz = benzoyl; Nu = nucleophile.

for chiral catalysts that induce kinetic resolution of racemic allyl esters **1**.[2] Starting from a 1:1 mixture of quasi-enantiomeric substrates, the selectivity of chiral Pd catalysts could be determined by mass spectrometric quantification of the corresponding allyl–Pd intermediates **2**. Electrospray ionization mass spectrometry (ESI-MS) was used as an analytical tool, as this technique allows selective detection of charged species in the presence of a large excess of neutral compounds.[3]

Besides the expected signals of allyl–Pd complexes **2**, the spectra taken during the course of catalytic reactions showed additional peaks at higher *m*/*z* values, which we assigned to allyl-bridged dinuclear Pd^{I} complexes. A number of allyl-bridged dinuclear Pd^{I} complexes have been described in the past.[4] Most of them have the general structure **5**, containing two monodentate ligands and an additional bridging halide. Their chemistry has been studied in detail by Kurosawa and co-workers.[4b,c]



Herein we report our studies of the structure and reactivity of dinuclear Pd species that are present in significant quantities during the catalytic process. Our results show that dinuclear complexes **6** are formed reversibly and thus represent a reservoir of the active mononuclear catalysts **2** and **3** (Scheme 2). In our initial experiments, we investigated a typical allylic substitution reaction using a phosphanyl–oxazoline (phox) ligand and monitored the course of the reaction by ESI-MS and HPLC analysis (Figure 1).[6]



Scheme 2. Formation of dinuclear complexes during Pd-catalyzed allylic substitution.[5]

At the onset of the reaction we observed a dominant signal for the cationic precatalyst **2a** with the characteristic isotope distribution of Pd (*m*/*z* 520, Figure 1b). Complex **2a** is then activated by reaction with dimethyl malonate, leading to the reactive neutral Pd^{0} complex **3**. This complex rapidly reacts with substrate *rac*-**1** to produce the allyl complex **2b** (*m*/*z* 672). Subsequently, enantioselective attack of dimethyl malonate leads to the product and regenerates the nucleophilic Pd^{0} complex **3**.

Unexpectedly, the MS spectra also showed additional peaks of complexes to which we assigned structures **6a** (R = H, *m*/*z* 1001), **6b** (R = Ph, *m*/*z* 1153), and **7** (*m*/*z* 1009, Scheme 2). Complex **6a** was formed immediately after the reaction had started. As the reaction proceeded, its concentration decreased rapidly while concomitantly a heavier complex **6b** appeared at *m*/*z* 1153. Close to the end of the reaction, this signal vanished as well and a third complex **7** was observed, accounting for the dominant signal at *m*/*z* 1009. All three complexes showed the characteristic isotope pattern of dinuclear palladium species.

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[+] X-ray analyses

[#] NMR analyses

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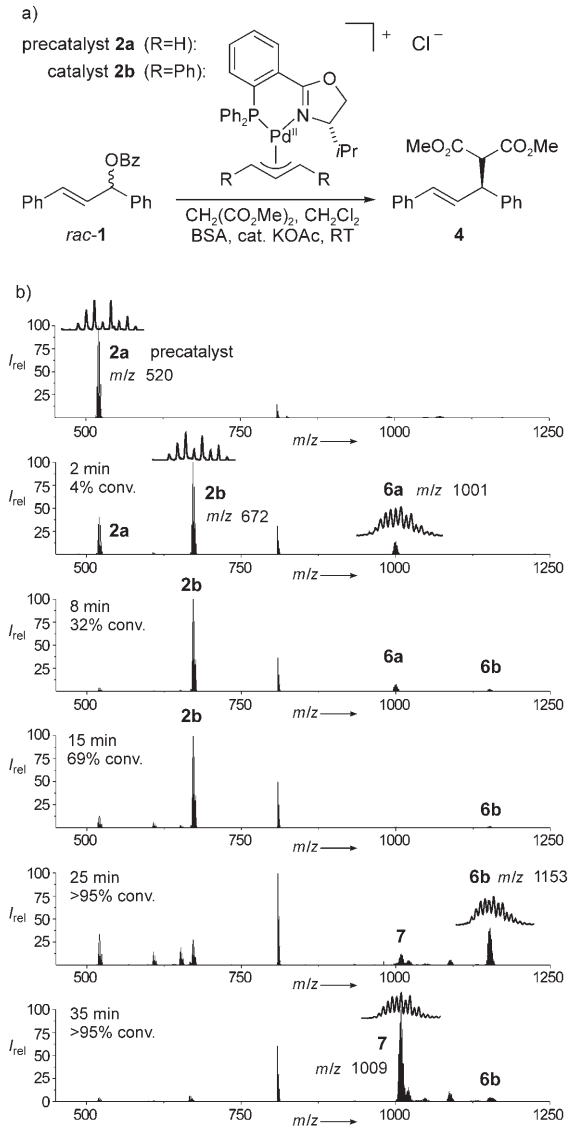
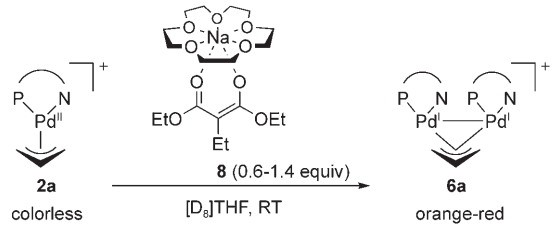


Figure 1. a) Allylic substitution reaction studied by ESI-MS;[6] BSA = *N*,*O*-bis(trimethylsilyl)acetamide. b) ESI-MS spectra of the reaction mixture with signals assigned to monomeric (**2a**,**b**) and dinuclear complexes (**6a**,**b** and **7**, see Scheme 2). The signal at *m*/*z* 809 originates from an impurity in the spectrometer and was identified as a Cu–phox complex.

Complex **6b** exhibited a revealing fragmentation pattern that was consistent with the assigned structure (Figure 2). The spectrum indicates loss of a diphenylallyl ligand (fragment at *m*/*z* 960) or a phox ligand (*m*/*z* 780). Dissociation into a neutral Pd^0–phox complex **3** and allyl complex **2b** is also observed, suggesting that during the catalytic process **6b** is formed by addition of a neutral Pd^0 complex **3** to the cationic allyl intermediate **2b**.[4b,c]

This hypothesis was probed in stoichiometric reactions of both monomeric complexes **2a** and **2b** with varying amounts of malonate **8**. ESI-MS and ^{31}P NMR spectroscopy revealed that about half an equivalent (0.6 equiv) of malonate is sufficient to cleanly transform the monomeric complexes **2** into the bimetallic complexes **6** (Scheme 3).[7]



Scheme 3. Stoichiometric transformation of precatalyst **2a** into dinuclear complex **6a**.

The reaction is accompanied by an impressive color change, which we attribute to the formation of a Pd^I–Pd^I bond. Both the solution of the monomeric complex **2a** and the malonate solution are colorless. Immediately after addition of malonate, an intense orange-red color appears, which corresponds to an absorption band at $\lambda_{max} = 352$ nm.

When we treated the monomeric complex **2b** with an excess of malonate **8** (1.4 equiv), we observed that the generated dinuclear complex **6b** remained stable for several hours. Apparently, the nucleophile rapidly attacks the monomeric Pd^{II} complex (**2b**), but not the dinuclear Pd^I complex (**6b**). This experiment demonstrates the significantly lower electrophilicity and reactivity of the dinuclear complex **6b** compared to **2b**. As nucleophilic attack is the turnover-limiting step in the catalytic cycle, we conclude that product formation from the dinuclear Pd^I complex **6b** is minimal.

We were able to obtain a crystal structure of complex **6b** that reveals two Pd–phox moieties oriented in an almost C_2-symmetrical arrangement (Figure 3). The configuration of the phenyl substituents at the allyl ligand is *syn*–*anti*,[9] which is rather unexpected as this configuration is disfavored in the related monomeric allyl–Pd^{II} complex **2b**. DFT calculations

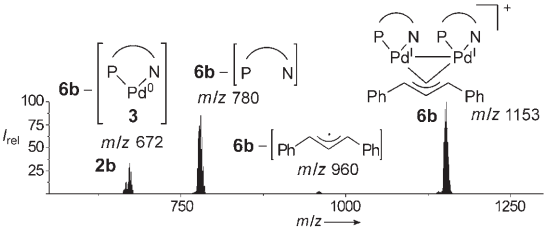


Figure 2. ESI-MS spectrum of dinuclear complex **6b**.

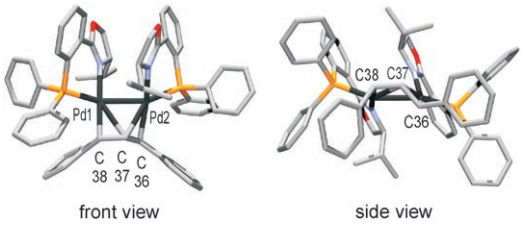


Figure 3. Crystal structure of dinuclear palladium complex **6b**.[8] Note the *syn*–*anti* configuration of the substituents at the allyl ligand.[9] The counterion $[SbF_6]^-$ and solvent molecules are omitted for clarity.

showed that the observed *syn–anti* isomer is thermodynamically favored by more than 11 kcal mol^{-1} over the alternative *syn–syn* isomer (see the Supporting Information). A detailed NMR analysis of complex **6a** including ^{1}H NOESY spectra indicated that its solution structure is very similar to the solid-state structure of **6b**.

We next investigated the reactivity of the isolated crystallized Pd^{I} complex **6b** with substrate **1** in [D$_8$]THF by time-resolved NMR spectroscopy (Figure 4). At 0 °C the signals of the dinuclear complex slowly decreased while concomitantly

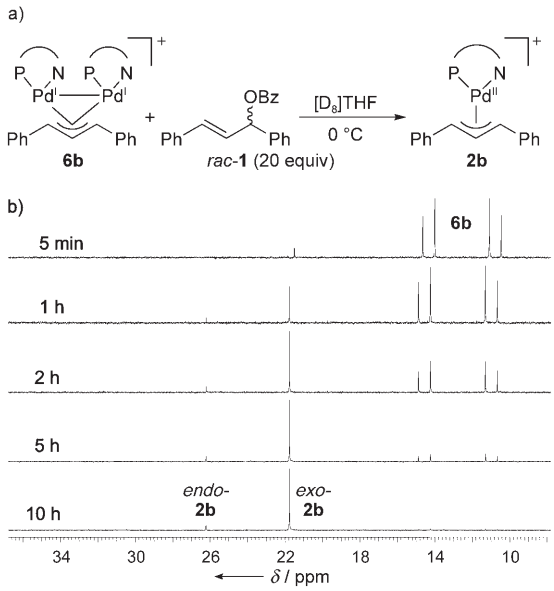
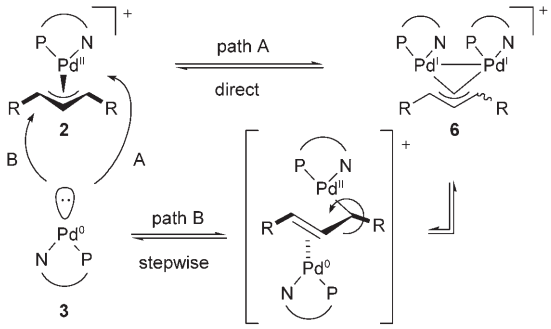


Figure 4. a) Reaction of complex **6b** with substrate **1**. b) Time-resolved ^{31}P NMR spectra. The regenerated mononuclear complex **2b** exists as a 1:9 mixture of *endo* and *exo* conformers.[1]

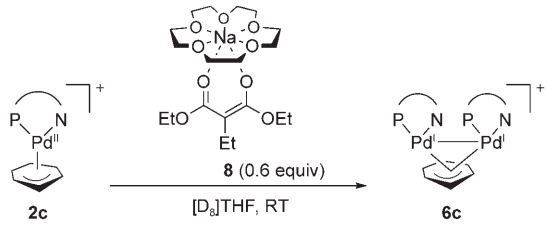
the signals of the monomeric complex **2b** appeared. Towards the end of the reaction, the deep red solution of complex **6b** had turned into a bright yellow solution of the mononuclear Pd^{II} complex **2b**. It seems that complex **6b** reversibly disproportionates and that the equilibrium is shifted toward the mononuclear complex by reaction with substrate **1**. In a catalytic reaction, two molecules of the active mononuclear catalyst **2b** are regenerated this way.

The dinuclear species **6** can be formed either directly by nucleophilic attack of the Pd^{0} complex **3** at the metal center of the electrophilic allyl complex **2** (path A, Scheme 4) or stepwise by addition of **3** to the allyl ligand and subsequent formation of the Pd–Pd bond (path B).[4b] Path B would require C–C bond rotation in the intermediate Pd$_2$ σ,π complex to bring both Pd atoms into proximity for metal–metal bond formation.[10]

In analogous experiments with complex **2c**, which cannot react along path B because its cyclic structure prevents C–C bond rotation, rapid formation of complex **6c** was observed (Scheme 5). This observation implies that at least in this case, the reaction proceeds by direct Pd–Pd bond formation (path A).



Scheme 4. Possible mechanisms for the reaction of Pd^{0} complex **3** with Pd^{II} complexes **2**.



Scheme 5. Formation of dinuclear Pd^{I} complex **6c**.

The structure of complex **7**, which was formed at the end of the catalytic reaction (Figure 1), could not be fully established. However, on the basis of the *m*/*z* values and the isotope distribution, its composition was determined to be $[(phox)_2Pd_2(CH_2Cl)]^+$. An analogous experiment in CD_2Cl_2, which showed the signals of the corresponding dideuterated complex, confirmed this formula (Figure 5). The dinuclear complex **7** obviously results from a reaction with the solvent, most likely by reductive C–Cl bond activation by Pd^{0} complex **3** or another low-valent Pd species present in the solution. The possibility that this complex was formed in the spectrometer and not in solution was ruled out by diluting the CD_2Cl_2 solution with CH_2Cl_2 before MS analysis.

Our findings demonstrate that dinuclear allyl-bridged Pd^{I} complexes are generated reversibly during allylic substitution

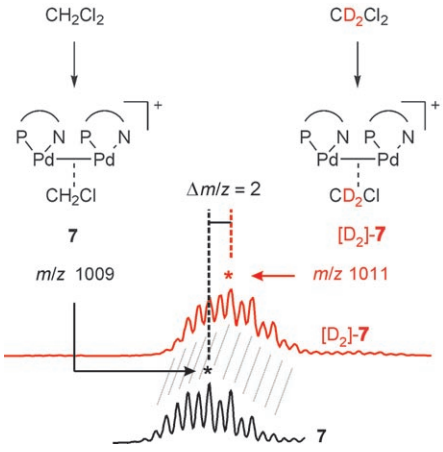


Figure 5. ESI-MS spectra of the dinuclear complex **7** formed in CH_2Cl_2 and CD_2Cl_2.

reactions. Evidence for the formation of dinuclear complexes of this type was previously obtained from in situ X-ray absorption fine structure (XAFS) studies, but no detailed structural assignments could be made.[4d] Trinuclear complexes and higher aggregates were also detected in that study, and it was proposed that the dinuclear complexes undergo association with additional Pd^0 complexes to form polynuclear clusters and eventually metallic Pd, resulting in catalyst deactivation. Under the conditions used in this study, the observed dinuclear complexes proved to be remarkably stable and did not show any tendency to form higher aggregates. Thus, these complexes represent a reservoir, from which catalytically active mononuclear complexes can be released under the reaction conditions. In the presence of excess substrate, mononuclear allyl–Pd^{II} complexes are the dominating species. However, when the concentration of substrate diminishes toward the end of the reaction, addition of the Pd^0 catalyst to the allyl–Pd^{II} intermediate becomes a competing process and, consequently, the concentration of the resulting dinuclear complex increases. The nature of the unusual reaction with CH_2Cl_2 and the structure of the resulting dinuclear complex **7** are still unclear and deserve further investigation.

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[5] The unsaturated Pd^0 complex **3** is most likely stabilized by a weakly coordinated olefin. The structure of complex **7** is still unknown. Formula **7** is based on ESI-MS data and analogy to complex **6**.

[6] Samples for ESI-MS analysis were diluted with CH_2Cl_2 and injected into a mass spectrometer without further purification. A second aliquot of the reaction mixture was filtered through silica gel and analyzed by HPLC to determine the conversion.

[7] In the ^{31}P NMR spectra, the two diastereotopic phosphorus atoms couple with each other (**6a**: $^3J_{PP} = 150$ Hz; **6b**: $^3J_{PP} = 129$ Hz). ^{31}P signals of **6b** were previously observed by G. Helmchen and co-workers. However, no unambiguous structural assignment could be made at that time: H. Steinhagen, M. Reggelin, G. Helmchen, *Angew. Chem.* **1997**, *109*, 2199 – 2202; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2108 – 2110.

[8] CCDC-634865 (**6b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] The *syn* notation refers to a *cis* relationship between the terminal substituent and the central C–H bond.

[10] Such a stepwise mechanism would resemble the allyl transfer mechanism proposed by Bosnich and co-workers: P. B. Mackenzie, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2046 – 2054; see also references [4b,c].

