CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000833

3rd EuCheMS Chemistry Congress

Asymmetric C–C Bond-Formation Reaction with Pd: How to Favor Heterogeneous or Homogeneous Catalysis?

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Abstract: The enantioselective allylic alkylation of (*E*)-1,3-diphenylallyl acetate was studied to clarify the heterogeneous or homogeneous character of the Pd/Al_2O_3–(*R*)-BINAP catalyst system. A combined approach was applied: the catalytic tests were completed with in situ XANES measurements to follow the oxidation state of Pd as a function of the reaction conditions. The study revealed that the oxidized Pd (after exposure to ambient air) is efficiently reduced by the solvents THF and dioxane, and by the nucleophile sodium dimethyl malonate, and thus these conditions prevent Pd leaching. The chiral modifier BINAP plays a dual role: a considerable coverage of the Pd surface by the bulky compound slows down the initial reduction of the surface oxides but BINAP itself may consume surface oxygen (through its conversion to BINAPO and $BINAPO_2$) and contribute to the maintenance of the active metal surface during the reaction. Carrying out the reaction under pressure in an inert gas atmosphere is important to minimize the oxygen diffusion into the reaction mixture and to avoid leaching. The (known) effect of temperature is critical as well: our catalyst system is inactive at room temperature, which is a clear deviation from the behavior of the corresponding homogeneous system. In contrast, halogenated solvents are easily dehalogenated on Pd/Al_2O_3 and thus they favor leaching of the metal and formation of soluble compounds, analogous to classical metal corrosion in the presence of halide ions. The frequently observed dissolution of Pd in the presence of halogenated substrates may be explained similarly.

Keywords: asymmetric synthesis · heterogeneous catalysis · metal leaching · palladium · X-ray diffraction

Introduction

C–C and C–N bond-forming reactions are a versatile tool in synthetic chemistry.[1] Such reactions are usually catalyzed by homogeneous complexes derived from palladium precursors, but for industrial applications heterogeneous catalysts are often preferred.[2] An important obstacle for any practical application of homogeneous or heterogeneous catalysts is the relocation of the active species, that is, reduction of the dissolved metal complex to Pd^0 (colloidal) particles or the oxidation of the Pd^0 surface sites and leaching into the liquid phase during the reaction. There are numerous examples on the extremely high activity of homogeneous complexes[3] that may be formed in situ from the solid catalyst,[4] and identification of 1–2 nm particles as being the real active sites or only spectator species is also a demanding task (for recent reviews see Refs. [4c] and [5]).

Every endeavor has been made to distinguish between homogeneous and heterogeneous catalysis. Several methods have been developed and refined in the past years for this purpose. Besides TEM analysis, filtration tests, and poisoning experiments, also more complex methods such as kinetic studies, the three-phase test, and the use of a membrane reactor belong to the available techniques.[5a] The great variety of the commonly used tests seems to be an indication that it is difficult to get an unambiguous conclusion from such experiments. Classical examples are the poisoning experiments

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000833.

with Hg and CS_2. Pd easily forms alloys with Hg even at room temperature,[6] and thus the observed reactivity and leaching behavior is characteristic of the bimetallic catalyst and not of the original catalyst. In addition, this unintended transformation may even open new reaction pathways.[7] Mercury may react with homogeneous Pd^0 complexes,[8] and incorporation of sulfur into the catalyst support can retard the dissolution of Pd.[9]

Another concept to discriminate homogeneous and heterogeneous catalysis is to look for conditions under which homogeneous catalysts are reduced and transformed to a solid by forming (nano)particles. It has been shown for the high-temperature Heck coupling reaction that actually none of the homogeneous catalyst precursors are stable under the applied conditions.[4c] A thoroughly investigated field is hydrogenation with soluble complexes at high temperature, in which in many cases the nature of the active species is still not clear.[5a] It seems to be a general trend that harsh reaction conditions, such as a reducing (hydrogen) atmosphere and high temperature, favor the formation of Pd nanoparticles.

As a result of the interplay of reaction components and conditions, already small changes may lead to an unexpected dislocation of the active species. This complexity makes it difficult to determine the factors that facilitate or prevent leaching when using ex situ techniques. Therefore, complementary in situ investigations are needed to track down the influences of the single reaction components on the catalytically active species and link them to the overall leaching behavior.

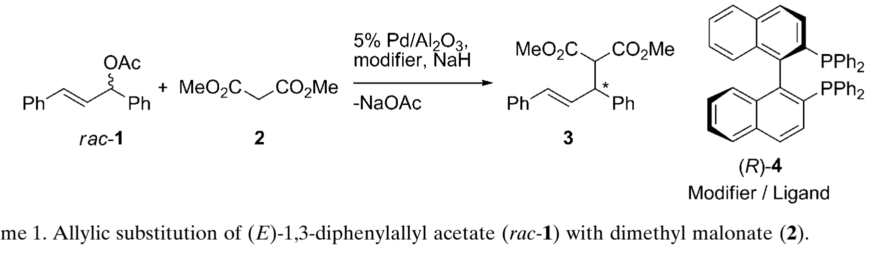
Here we used direct monitoring of the liquid and solid phases to analyze systematically what reaction components and conditions favor heterogeneous or homogeneous conditions in the Pd-catalyzed asymmetric allylic alkylation. The typical homogeneous catalytic cycle is initiated by an oxidative addition of the substrate to the Pd^0 catalyst, leading to the formation of a (η^3-allyl) Pd^{II} complex. The consecutive attack of a nucleophile on this complex leads to the formation of an unstable Pd^0-olefin complex from which the final product is readily released.[10] We chose a commonly used reaction, the transformation of (*E*)-1,3-diphenylallyl acetate (*rac*-**1**, Scheme 1), and the Pd/Al_2O_3–BINAP catalyst system. The oxidation state of Pd in the solid phase and the concentration of Pd in the liquid phase were analyzed by in situ X-ray adsorption spectroscopy (XAS). This report complements our previous studies that used a commercial supported Pd catalyst modified with various phosphines in the same reaction.[11] In contrast to other studies,[12] we concluded that truly heterogeneous catalysis was occurring based on separation experiments, TEM investigations, and kinetic comparisons with homogeneous catalysts. The current study allows us to shed more light into this discrepancy in the nature of the active species.

Results

Oxidation state of Pd during asymmetric allylic alkylation—X-ray absorption near edge structure (XANES) analysis: We followed the oxidation state of Pd by in situ XANES measurements through the catalyst bed of the XAS cell during allylic alkylation of *rac*-**1** (Scheme 1). In the first experiment, the original reaction mixture, consisting of *rac*-**1**, the sodium salt of **2**, and (*R*)-BINAP in THF, was added to the XAS cell containing the catalyst. The reduction of the Al_2O_3-supported Pd particles already started during heating of the reaction mixture to 60 °C and a steady state was reached at this temperature after 30–40 min. Measurements through the supernatant solution did not show any presence of leached Pd.

For comparison, the reduction in THF with hydrogen was also followed. The analysis of the normalized absorption intensity of the Pd K-edge whiteline of the spectra is shown in Figure 1 a. The spectra were additionally analyzed by a linear combination fit and this method gave very similar results (Figure 1 b). Note that owing to the high dispersion of the catalyst even the reduction of less than a monolayer of oxygen should be recordable because it is $>5\,\%$ (see also theoretical XANES spectra Ref.[13]). Unexpectedly, reduction with hydrogen led only to a slightly more reduced state than that with the reaction mixture. Another interesting observation is that THF alone could efficiently reduce Pd (Figure 1 a–c). Reduction by THF was slower but only a qualitative comparison was possible because of the probably less efficient mass transport in the XAS cell compared with that in the Parr reactor used for allylic alkylation. Nevertheless, the final reduction state of the catalyst in THF, the best solvent found for this reaction,[11] was similar to the level achieved in the presence of hydrogen.

The fact that the reduction of the catalyst proceeds faster in the presence of the reaction mixture than in pure THF implies that the solvent is not the only reducing agent. Therefore, reduction of Pd by every single component of the reaction mixture was followed in THF by XANES (Figure 2). The linear combination fit, by using PdO and hydrogen-reduced Pd/Al_2O_3 in THF as references, and analysis of the normalized absorption intensities of the Pd K-edge whiteline again gave very similar results.



Scheme 1. Allylic substitution of (*E*)-1,3-diphenylallyl acetate (*rac*-**1**) with dimethyl malonate (**2**).

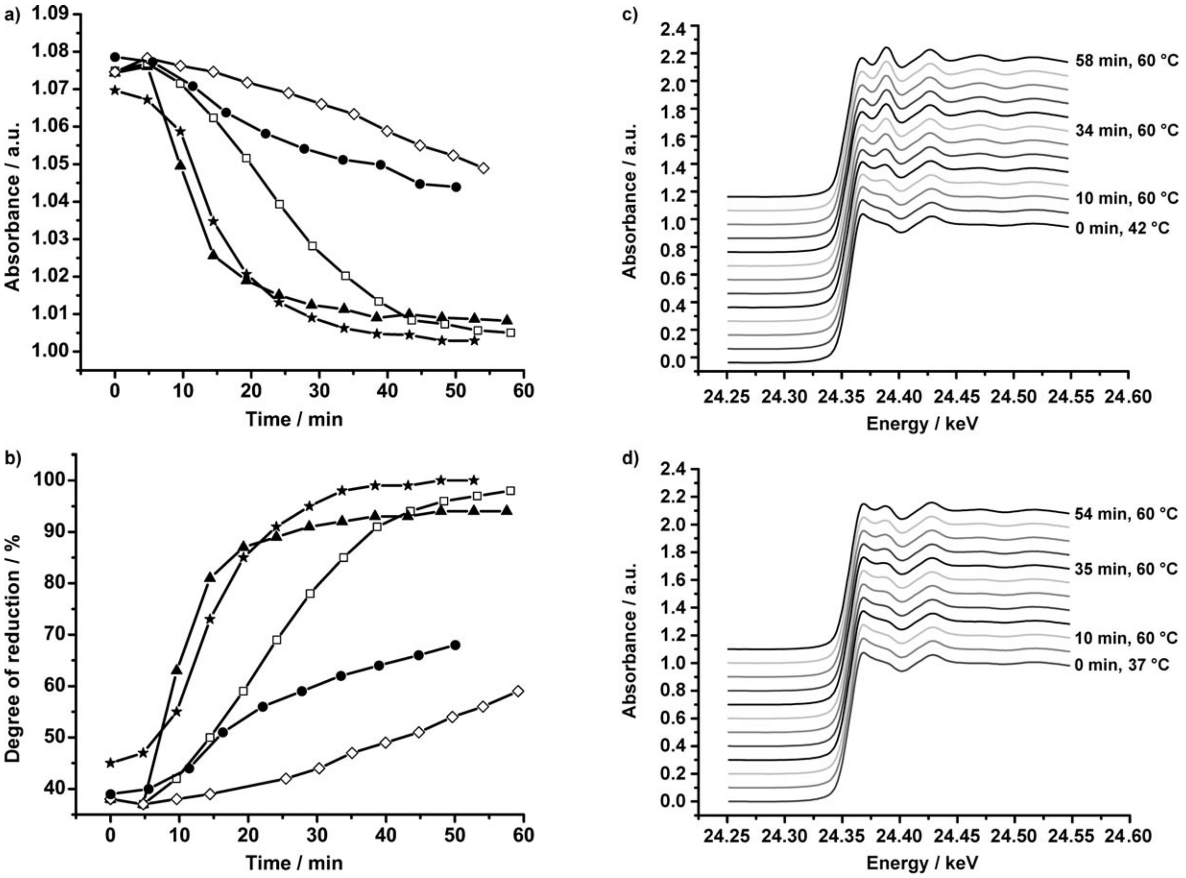


Figure 1. Reduction of 5% Pd/Al_2O_3 at 60°C and 10 bar N_2, as monitored by a) the analysis of the normalized absorption intensity of the Pd K-edge whiteline or b) linear-combination fit by using PdO and hydrogen-reduced Pd/Al_2O_3 in THF. The XANES spectra of the reduction of Pd/Al_2O_3 by THF and cyclohexane are shown in (c) and (d), respectively. Conditions: 5% Pd/Al_2O_3 (84 mg), *rac*-**1** (1.4 mmol), sodium salt of **2** (2.8 mmol), (*R*)-BINAP (6.4 μmol) in THF (6 mL) under N_2 (▲ = reaction mixture, □ = THF (neat), ◇ = cyclohexane (neat), ● = dichloromethane (neat), ★ = 5% H_2 in He, in THF (neat)). The reaction temperature was reached after 10 min.

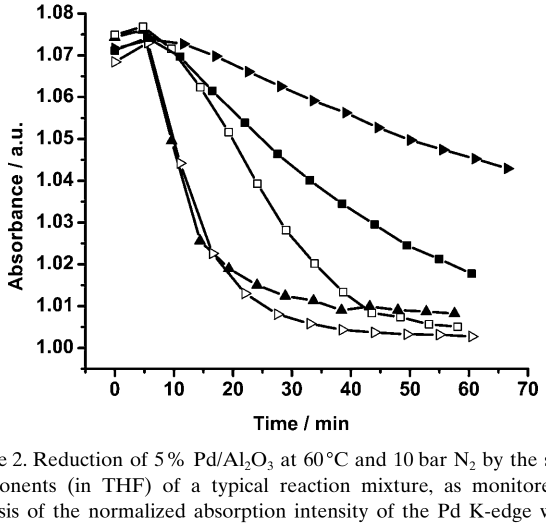


Figure 2. Reduction of 5% Pd/Al_2O_3 at 60°C and 10 bar N_2 by the single components (in THF) of a typical reaction mixture, as monitored by analysis of the normalized absorption intensity of the Pd K-edge whiteline. Conditions: 5% Pd/Al_2O_3 (84 mg), *rac*-**1** (1.4 mmol), sodium salt of **2** (2.8 mmol), (*R*)-BINAP (6.4 μmol), in THF (6 mL) under N_2 (▲ = reaction mixture, ▶ = *rac*-**1**, ▷ = sodium salt of **2**, ■ = (*R*)-BINAP, □ = THF (neat)). The reaction temperature was reached after 10 min.

Later, only the normalized absorption intensity at 24.352 keV is shown in Figure 2 and other similar figures.

A solution of sodium dimethyl malonate in THF reduced the catalyst completely within a few minutes. The rate and the final state of reduction are comparable to those achieved by hydrogen in THF (see also Figure 1 a) and slightly exceed those of the reaction mixture, leading to the conclusion that sodium dimethyl malonate is probably the main reducing agent in the reaction mixture. This assumption is supported by our former catalytic study in which a 100% excess compared to the stoichiometric amount of malonate was necessary to achieve full conversion of the substrate.[11a] Reduction of the catalyst by pure THF was faster than in the presence of (*R*)-BINAP and addition of the substrate slowed down the reduction even more. Retardation of the reduction process by these two reaction components can explain why the reduction of the catalyst by the reaction mixture is less efficient than with the malonate solution in THF.

To exclude misinterpretation owing to beam damage by the X-ray beam itself, we repeated a typical experiment shown above by heating the catalyst in THF to 60°C while the X-ray beam was switched off. Subsequent XANES measurements after 30 min showed that Pd/Al_2O_3 was reduced to the same extent as in the case when the X-ray beam was on. Another important confirmation, that the in situ spectroscopic measurements are not distorted, is the similar catalytic performance observed here and in previous studies. After 3 h reaction time at 60 °C, a conversion of 3–4 % with an *ee* of 57 % was achieved in the in situ reactor cell, which are typical values at this temperature[11a] and demonstrate that the reaction conditions chosen for the in situ XANES measurements were close to those in the catalytic reactor.

Reduction of Pd by the solvent: Reduction of Pd by solvents is rarely described in the literature, with the important exception of alcohols,[13–14] the dehydrogenation of which on Pt-group metals is widely used as the source of hydrogen in transfer hydrogenation reactions. Therefore, we studied here in more detail the effect of different solvents.

Replacement of THF by cyclohexane resulted in a sluggish and incomplete reduction of Pd/Al_2O_3 (Figure 1 a, b, and d). Toluene was even less reactive: no significant reduction occurred at 60 °C, and even at 100 °C Pd remained partly oxidized (Figure 3). In the popular solvent dichloromethane the rate of reduction was between those observed in THF and cyclohexane (Figure 1). In general, increasing the temperature to 100–120 °C enhanced the rate and extent of the reduction of Pd in all these solvents, as expected; an illustration is shown for toluene in Figure 3.

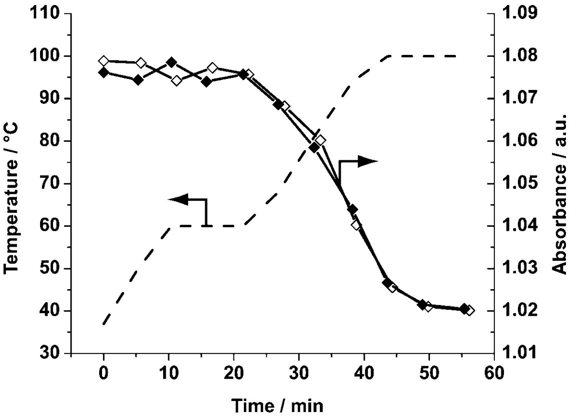


Figure 3. Effect of temperature on the reduction of 5 % Pd/Al_2O_3 by toluene with (◆) and without (◇) *rac*-BINAP. Analysis of the normalized absorption intensity of the Pd K-edge whiteline. Conditions: 5 % Pd/Al_2O_3 (84 mg) in toluene (6 mL) under N_2 (10 bar), and *rac*-BINAP (12.8 μmol).

In the Pd/Al_2O_3-catalyzed allylic alkylation of *rac*-**1** the best yield of **3** was achieved in THF.[11] The suitability of this solvent is partly attributed to the good solubility of the sodium salt of **2**. Hence, we extended the study to dioxane, which is chemically similar to THF. A comparative study revealed that replacing THF by dioxane diminished the reaction rate (conversion) to about one half but the chemo- and enantioselectivities were barely affected (Table 1). In both solvents, addition of BINAP enhanced the reaction rate and the chemoselectivity as compared with the unmodified reaction (in the absence of BINAP).

Table 1. Allylic substitution of *rac*-**1** in cyclic ethers.[a]

Entry	Solvent	Modifier	*t* [h]	Conv. [%]	Chemosel. [%]	*ee* [%]
1[b]	THF	(*R*)-BINAP	3	73	95	60
2[b]	THF	–	6	64	60	0
3	dioxane	(*R*)-BINAP	3	33	90	55
4	dioxane	–	6	30	58	0

[a] Conditions: 5 % Pd/Al_2O_3 (42 mg), 3.2 μmol of modifier, *rac*-**1** (1.4 mmol), sodium salt of **2** (2.8 mmol), solvent (18 mL), 120 °C, N_2 (20 bar). Conv. = conversion, chemosel. = chemoselectivity. [b] Taken from Ref. [11a].

According to XANES analysis, pure dioxane reduces the catalyst somewhat faster than pure THF, but after 40–50 min the oxidation states of Pd are very similar in the two cyclic ethers (Figure 4). The negative effect of BINAP on the rate of Pd reduction in dioxane is similar to that observed in THF (Figure 2). However, if the original reaction mixture including the modifier was present, the reduction behavior of the catalyst in these two solvents was different.

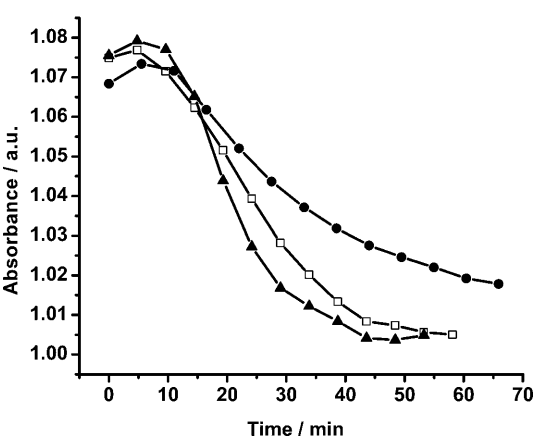
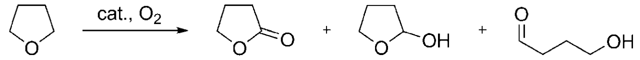


Figure 4. Reduction of 5 % Pd/Al_2O_3 in dioxane at 60 °C with (●) and without (▲) (*R*)-BINAP monitored by analysis of the normalized absorption intensity of the Pd K-edge whiteline. Neat THF (□) is shown for comparison. Conditions: 5 % Pd/Al_2O_3 (84 mg) in solvent (6 mL) under N_2 (10 bar), and (*R*)-BINAP (6.4 μmol). The reaction temperature of 60 °C was reached after 10 min.

The probable explanation for the reduction of Pd in the most suitable solvents, THF and dioxane, is the consumption of surface oxygen by the oxidation at the α-carbon atom of the ether.[15] Palladium complexes[16] as well as supported Pd,[17] Rh,[17] and Pt[18] are proven catalysts for the oxidation of ethers to the corresponding lactones by using molecular oxygen as the oxidant. In the specific case of THF, γ-butyrolactone (main product), tetrahydrofuran-2-ol, and 4-hydroxybutanal are formed (Scheme 2).

When a (supported) Pd catalyst is stored under air, the outer surface layers of the metal particles are transformed to metal oxide and reduction of this oxide layer is slow. This

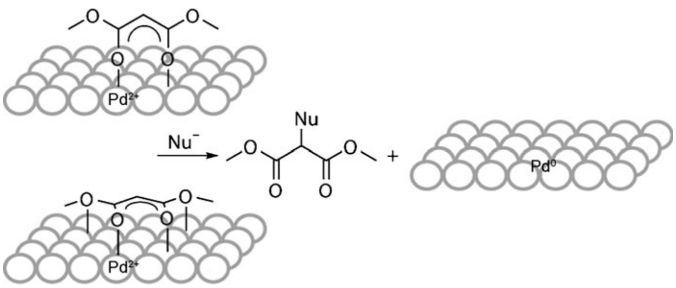


Scheme 2. Products formed by catalytic oxidation of THF with molecular oxygen.

slow reduction is seen in Figures 1–3. Before the use in allylic alkylation, the catalyst was always reduced in a fixed-bed reactor in flowing hydrogen at 200 °C, which increased the reaction rate and the chemoselectivity, and also the reproducibility of the results.[11] Note that the pretreatment did not lead to a change of the mean Pd particle size (typically 3 nm).[11a] During transferring the catalyst to the slurry reactor, the surface of the Pd particles were reoxidized, but this freshly formed oxide layer was thinner and more easy to reduce, which explains the improved catalytic performance. This explanation is supported by XPS measurements (see the Supporting Information). Reduction of the surface by THF regenerates the active metal surface, and the solvent being present in large excess allows maintaining the reduced state during the slow allylic alkylation reaction, despite of the possible oxygen diffusion into the reactor.

The slow reduction of oxidized Pd by cyclohexane (Figure 1) and toluene (Figure 3) was attributed to dehydrogenation of the solvents and reduction of the Pd surface by the hydrogen produced in situ. The Pd-catalyzed dehydrogenation of cyclohexane and toluene was accompanied by the formation of benzene[19] and carbonaceous species on the surface, respectively.[20] A control experiment with cyclohexene and Pd/Al_2O_3 in THF led, as expected, to dehydrogenation as well as hydrogenation of cyclohexene to benzene and cyclohexane, respectively.[21] An analogous mechanism for the cyclic ethers might also seem a possible reaction pathway. However, significant dehydrogenation of the ethers and the formation of surface hydrogen is unlikely to occur because during allylic alkylation of *rac*-**1** in ether solvents no hydrogenation of the double bond in the substrate was observed, even at 120 °C.[11]

Interaction of the nucleophile and the substrate with the Pd surface: It is shown in Figure 2 that reduction of Pd in THF occurs at similar rates with sodium dimethyl malonate or hydrogen. We assume that reduction of the oxidized surface Pd sites by sodium dimethyl malonate occurs analogously to the arylation of malonate anions via reductive elimination from aryl Pd complexes.[22] A nucleophilic attack on the malonate anion coordinated to the Pd surface leads to the reduction of Pd^{II} to Pd^0 and the release of the corresponding addition product of malonate (Scheme 3). Potential nucleophilic species are another malonate anion and alcohols formed during reduction of the catalyst by the solvent (Scheme 2). During allylic alkylation the acetate ion released by the substrate (Scheme 1) may as well react with the adsorbed malonate to form the corresponding acetoxy malonate. The reaction is usually carried out with homogeneous complexes, but an example of a heterogeneously catalyzed reaction is also described.[23]



Scheme 3. Possible mechanism for the reduction of surface Pd^{II} species to Pd^0 by dimethyl malonate anions.

The negative influence of the substrate on the reduction of Pd may be attributed to a partial coverage of the surface by the strongly adsorbing electron-rich molecule that slows down the reduction by the solvent. Alternatively, some competing reactions such as oxidative additions, analogous to those described in homogeneous catalysis, may play a role.[10b,24]

Interaction of the modifier with Pd: We have shown by UV/Vis spectroscopy[11a] that BINAP adsorbs strongly on the surface of alumina-supported Pd particles, which is a key characteristic of a chiral modifier being present in trace amounts.[25] The XANES analysis revealed that BINAP slows down the reduction of Pd in THF (Figure 2) and dioxane (Figure 4), the two most suitable solvents for our test reaction. In toluene the influence is negligible (Figure 3) but this solvent proved to be the least effective in reducing the oxidized Pd surface. The retardation by BINAP is, however, less pronounced when the whole reaction mixture is present, as monitored by the Pd K-edge XANES during allylic alkylation in the presence and absence of the modifier in THF (Figure 5a) and dioxane (Figure 5b). Note that in these cases, the analysis of the normalized absorption intensities of the Pd K-edge whiteline gave a more distinct picture than the linear-combination fit (not shown). In both cyclic ether solvents, the rate of reduction of Pd and the steady state during the reaction were similar with and without BINAP at 60 °C (Figure 5a and b, respectively) and also at 100 °C (not shown). Interestingly, in THF Pd was even more reduced in the presence of a modifier, although the differences were small. A feasible explanation is that the solvent adsorbs relatively weakly on Pd and the presence of BINAP disturbs the Pd–solvent interaction. In contrast, the electron-rich dimethyl malonate anion is assumed to be adsorbed strongly on the metal surface and BINAP does not hinder this interaction significantly. As discussed previously, the nucleophile is the strongest reducing agent in the reaction mixture; hence the effect of BINAP in the reaction mixture is minor.

Nevertheless, BINAP may play a role in the surface (redox) processes by 1) modifying the electronic state of Pd, 2) displacement of surface-blocking species, and 3) stabilization of the reduced state of the Pd surface. Based on the

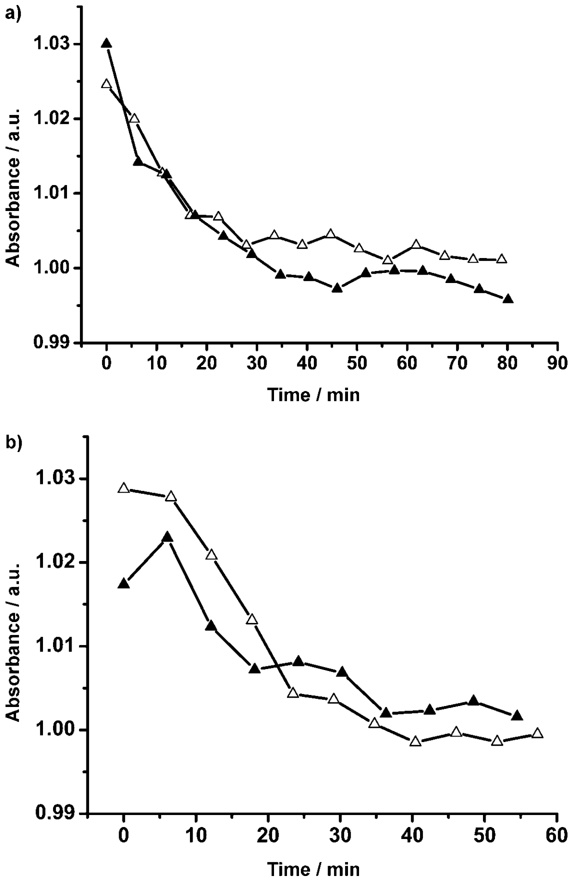


Figure 5. Reduction of 5% Pd/Al_2O_3 by the reaction mixture in a) THF or b) dioxane with (▲) and without (△) (*S*)-BINAP at 60°C; analysis of the normalized absorption intensity of the Pd K-edge whiteline. Conditions: 5% Pd/Al_2O_3 (84 mg), *rac*-**1** (1.4 mmol), sodium salt of **2** (2.8 mmol), (*S*)-BINAP (6.4 µmol), in THF (6 mL) under N_2 (10 bar). The reaction temperature of 60°C was reached after 15 min.

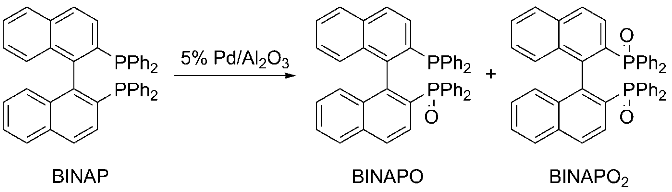
pertinent literature, BINAP is probably not inert on the Pd surface. The facile transformation of the Pd^{II}/P^{III} system to Pd^0/P^V is well-known and plays an important role, for example in Heck coupling reactions.[26] The phosphine is thereby transformed into the corresponding phosphine oxide and residual water or acetate is speculated to be the source of oxygen.[27] In addition, phosphines are easily oxidized with O_2.[28]

To confirm the possibility that BINAP is a potential reducing agent for the oxidized Pd surface, transformation of the modifier under nitrogen atmosphere was followed by quantitative ^{31}P NMR spectroscopy (Table 2). BINAP monoxide (BINAPO) and BINAP dioxide ($BINAPO_2$) were identified as products (Scheme 4). In a control experiment the catalyst was activated in hydrogen at elevated temperature prior to use. Although the catalyst was reoxidized upon exposure to ambient air during transfer to the reactor, the formation of $BINAPO_2$ was enhanced compared to the non-activated catalyst, and without catalyst this product did not form at all. The results show that the formation of $BINAPO_2$ requires Pd as a catalyst.

Table 2. Oxidation of *rac*-BINAP under nitrogen in the presence and absence of 5% Pd/Al_2O_3.[a]

Catalyst	Prereduction[b]	*T* [°C]	BINAP/BINAPO/$BINAPO_2$ molar ratio
5% Pd/Al_2O_3	+	60	100:12:20
5% Pd/Al_2O_3	+	120	100:16:46
5% Pd/Al_2O_3	–	120	100:13:18
no catalyst	–	120	100:22:0

[a] Conditions: 84 mg of catalyst, *rac*-BINAP (16 µmol) in THF (10 mL), N_2 atmosphere, 20 bar, 3 h. [b] The catalyst was prereduced in hydrogen at 200°C in a continuous flow reactor prior to use (+) or used as received (–).



Scheme 4. Oxidation of BINAP leading to BINAP monoxide (BINAPO) and BINAP dioxide ($BINAPO_2$).

Next, the importance of the oxidation of BINAP during allylic alkylation of *rac*-**1** was investigated. The reactions, carried out with different mixtures of (*R*)-BINAP and (*R*)-$BINAPO_2$, revealed that the influence of the oxidized modifier is small as long as BINAP is present in the reaction mixture (Table 3). When, however, only $BINAPO_2$ was applied as a modifier, no enantioselection was observed and the reaction rate and chemoselectivity decreased. For comparison, attempts to use $BINAPO_2$ as a ligand for $Pd(OAc)_2$ failed, and only traces of the racemic product were formed.

Table 3. Allylic substitution of *rac*-**1** by using (*R*)-BINAP/(*R*)-$BINAPO_2$ mixtures as modifiers.[a]

Entry	(*R*)-BINAP/(*R*)-$BINAPO_2$ molar ratio	*t* [h]	Conv. [%]	Chemosel. [%]	*ee* [%]
1	1:0	3	61	96	59
2	1:1	3	62	95	57
3	1:10	3	57	96	56
4	1:20	3	59	96	55
5	0:1	6	27	36	0
6[b]	0:0	6	64	60	0

[a] Conditions: 5% Pd/Al_2O_3 (42 mg), modifier (3.2 µmol), *rac*-**1** (1.4 mmol), sodium salt of **2** (2.8 mmol), solvent (18 mL), 120°C, 20 bar N_2. Conv. = conversion, chemosel. = chemoselectivity. [b] Taken from Ref. [11a].

We can conclude from the results in Tables 2 and 3 that BINAP may provide some protection of the active, metallic Pd catalyst during allylic alkylation by consuming the surface oxygen. This process is, however, detrimental to the enantioselection as the co-product $BINAPO_2$ is ineffective as a chiral modifier. Oxidation of the P atoms of BINAP probably weakens its adsorption on the Pd surface and the molecule is replaced by an intact modifier from the solution phase. This also explains the negligible effect of $BINAPO_2$ on the alkylation reaction as long as BINAP is present. In the light of these observations it seems essential to keep the metal surface in a reduced state by the solvent and the nucleophile that are present in large excess and thus protect BINAP from oxidation and avoid the loss of enantioselection.

Palladium leaching in chlorinated solvents: Chlorinated solvents, such as dichloromethane and chloroform, are commonly used in allylic alkylation reactions.[1a,c] These solvents are useful in the chemical transformation but represent a potential source of corrosion of the metal catalyst. Supported Pd is a highly active dehalogenation catalyst[29] that can be applied also without hydrogen.[30] Interaction of the chlorinated solvent with the metal surface may lead to the formation of Cl^-,[31] which accelerates the metal corrosion by shifting the redox potentials[32] and stabilizing the leached Pd species as a chloro complex. A commonly neglected point is that not only the metal but also the support can contribute to the degradation of chlorinated hydrocarbons. It has been found that methyl chloride interact with the surface hydroxyl groups of Al_2O_3 to form adsorbed methoxy species already below 100 °C and the formation of HCl accelerates at above approximately 125 °C .[33] In addition, the generation of HCl from chloroform can occur via an α,α-elimination and the formation of dichlorocarbene in the presence of a base[34] such as sodium dimethyl malonate.

To clarify the role of chlorinated solvents, we repeated the experiment in Table 1 (entry 1) by replacing a small fraction of THF with chloroform. The remarkable loss in reaction rate (conversion) and the lower selectivities, shown in Table 4, demonstrate that the chlorinated solvent is detrimental to the performance of the heterogeneous catalyst. The "poisoning" effect of chloroform increased with its amount. The analysis of pure chloroform by argentometric titration showed no presence of free chloride anions. In the reaction mixture, however, the dehalogenation of chloroform proceeded already in the absence of the catalyst, probably by the action of the nucleophile **2** (Table 4, entry 4), and free Cl^- ions were detected. With the catalyst present, the amount of free Cl^- ions doubled.

Table 4. The influence of $CHCl_3$ on the allylic alkylation of **1**.[a]

Entry	Catalyst	$CHCl_3$ [mL]	Cl^- [mmol]	Conv. [%]	Chemosel. [%]	*ee* [%]
1	5 % Pd/Al_2O_3[b]	0	0	73	95	60
2	5 % Pd/Al_2O_3[c]	0.11	n.d.[d]	22	86	55
3	5 % Pd/Al_2O_3	1	0.23	5	74	35
4	–	1	0.11	2	0	0

[a] Conditions: 5 % Pd/Al_2O_3 (42 mg, prereduced), *rac*-**1** (1.4 mmol), sodium salt of **2** (2.8 mmol), (*R*)-BINAP (3.2 µmol), in THF (17 mL), 3 h, 120 °C, under N_2 (20 bar). Conv. = conversion, chemosel. = chemoselectivity. [b] 18 mL THF, taken from Ref. [11a]; [c] 2 h reaction time; [d] Not determined.

In control experiments, the catalyst was removed by centrifugation under N_2 after the reactions in Table 4, entries 1 and 3. After the addition of fresh sodium malonate, the filtrate was allowed to react further at room temperature. After 18 h reaction time no further conversion was observed in the case of pure THF as the solvent (reaction according to Table 4, entry 1). However, when chloroform was present during the catalytic reaction, a small conversion of additional 4 % was observed (reaction according to Table 4, entry 3). This is an indication to the presence of soluble active species in the filtrate.

In the allylic alkylation reaction two equivalents of nucleophile **2** were used. In the experiment in Table 4, entry 2, the amount of free chloride (0.23 mmol), and therefore the amount of HCl that could deactivate the nucleophile by protonation, was much lower than the amount of nucleophile (2.8 mmol). Therefore, deactivation of the nucleophile through protonation with in situ formed HCl may have only a small effect on the reaction (Table 4). Additionally, it may be possible that the reaction is slower because the nucleophile is consumed by the reduction of leached Pd^{II} ions. Other reasons for the deactivation could be the degradation of chloroform on the Pd surface similar to that of dichloromethane, leading to the formation of carbonaceous species and site blocking.[35] Considering the large number of surface sites necessary to accommodate the bulky modifier BINAP, this site blocking can easily explain the dramatic loss of catalytic performance. Already the adsorption of chloroform on the Pd surface may diminish the activity by blocking the surface and/or changing the electronic properties of the metal.[36]

Next, the role of chloroform in leaching of palladium and the formation of a homogeneous active species was investigated. The prereduced Pd/Al_2O_3 catalyst was shaken for 72 h in the presence of (*R*)-BINAP and chloroform at room temperature under an inert atmosphere. After removal of the solid catalyst and addition of the reaction components *rac*-**1** and **2** to the filtrate, the alkylation reaction proceeded smoothly, even at room temperature (Table 5, entry 1). The high reaction rate and chemoselectivity but moderate *ee* are typical for the corresponding homogeneous catalyst.[11a,37] When the catalyst was not prereduced prior to the leaching period, the conversion in the subsequent alkylation reaction decreased (Table 5, entry 2). As mentioned previously, after prereduction in hydrogen at 200 °C, the catalyst was reoxidized during transferring into the slurry reactor, but prereduction diminishes the amount of surface oxide developed during storage in open air and activates the noble metal particles for restructuring.[38] Upon increasing the amount of (*R*)-BINAP, the conversion increased only in the case of the prereduced catalyst (Table 5, entries 1 and 4, 2 and 5). Increasing the amount of chloroform led to higher conversion (Table 5, entries 1 and 3) even when the catalyst was not prereduced (Table 5, entries 5 and 7). In a control experiment without chloroform, no conversion was detectable (Table 5, entry 8).

Table 5. Leaching experiments with chloroform at room temperature.[a]

Entry	Prereduction[b]	(*R*)-BINAP [μmol]	$CHCl_3$/THF volume ratio	*t* [h]	Conv. [%]	Chemosel. [%]	*ee* [%]
1	+	6.4	1:4	1	52	100	21
				20	100	100	27
2	–	6.4	1:4	1	20	100	23
				20	73	100	26
3	+	6.4	1:0	1	100	100	30
				20	100	100	30
4	+	16	1:4	1	91	100	25
				20	100	100	26
5	–	16	1:4	1	15	100	17
				20	53	100	22
6	+	16	1:0	1	93	100	25
				20	100	100	27
7	–	16	1:0	2	60	100	24
				20	93	98	28
8	+	6.4	0:1	1	0	–	–
				24	0	–	–

[a] Preleaching: 5% Pd/Al_2O_3 (42 mg) was shaken for 72 h in the solvent mixture (THF/$CHCl_3$, 5 mL) under N_2 at 1 bar. Then *rac*-**1** (0.7 mmol), sodium salt of **2** (1.4 mmol), and THF (9 mL) were added to the filtrate for the allylic alkylation at RT. Conv. = conversion, chemosel. = chemoselectivity. [b] The catalyst was prereduced in hydrogen at 200 °C in a continuous flow reactor prior to use (+) or used as received (–).

All these observations indicate that addition of chloroform favors homogeneous catalysis and is detrimental to the heterogeneous route.

Discussion

It is a demanding task to obtain convincing evidence for homogeneous or heterogeneous catalysis in the Pd-catalyzed C–C and C–N bond-forming reactions, as illustrated by the lively debate on the nature of active species in the past decade.[4c,5b,d] Instead of using the common (and frequently unreliable) heterogeneity tests, we considered the classical metal corrosion in inorganic systems as an analogy to metal leaching during allylic alkylation with a supported Pd catalyst. Based on this analogy, we assumed that by choosing the appropriate conditions and reaction components it is possible to favor either homogeneous ("molecular") or heterogeneous ("surface") catalysis. Here we tested this approach by in situ monitoring of the oxidation state in the Pd-catalyzed asymmetric allylic alkylation of *rac*-**1** with Pd/Al_2O_3 by using BINAP as the chiral modifier (Scheme 1).

In analogy to metal corrosion we assumed that the key requirements for metal dissolution are the oxidation of the surface metal atoms and the presence of an appropriate anion or ligand that stabilizes the oxidized state in solution. An important point in our considerations is that in the usual laboratory reactor applied for organic synthesis, the conditions cannot be considered as oxygen free. At the beginning, the metal surface is in an oxidized state owing to storage of the catalyst in ambient air. In addition, the reaction usually starts with a certain level of oxygen concentration in the system and there is continuous oxygen diffusion into the reactor during reaction. Obviously, working under an inert atmosphere at elevated pressure minimizes the oxygen diffusion rate into the reaction mixture and thus favors the maintenance of the active, reduced state of the Pd surface.

Another important factor is the presence of a "reducing agent" in the reaction mixture. This component can reduce the oxidized (supported) metal catalyst and restore the active M^0 sites at the early stage of the reaction and avoid the reoxidation of the metal during reaction by, for example, oxygen diffusion into the reactor. It is also important that the amount of the reducing agent is high enough to keep Pd in a reduced state throughout the reaction.

The combined catalytic, in situ XANES study confirmed our previous result that the enantioselective allylic alkylation of *rac*-**1** with the Pd/Al_2O_3–BINAP catalyst system is a truly heterogeneous reaction. We could show unambiguously that the original reaction mixture is able to reduce the Pd surface and maintain this reduced state during reaction (Figure 1 a), and no leached Pd was detected in the reaction mixture by in situ XANES measurements. By using various combinations of the reaction components, it was indicated that sodium dimethyl malonate (**2**) is probably the main reducing agent (Figure 2). The necessity of using more than a stoichiometric amount of **2** to achieve high conversion had already been recognized earlier but could not be rationalized at that time.[11a]

The proper choice of solvent is critical. The two best solvents of the reaction, THF and dioxane, are strong reducing agents of oxidized Pd (Figures 1 a and 4). They reduced the catalyst almost as fast as hydrogen, although the difference in favor of hydrogen would probably have been significantly higher under better mass-transfer conditions than those allowed by the tiny XANES reactor cell (Figure 1 a). In contrast, halogenated solvents such as chloroform promote metal dissolution and homogeneous catalysis. Taking the example of chloroform, the first step is probably the decomposition and formation of chloride ions, catalyzed by Pd and also by the support Al_2O_3 (Table 4). Halide ions are excellent catalysts of metal corrosion in inorganic systems (leading to rate acceleration and stabilization of the M^{n+} species), and the same is assumed for the complex organic–inorganic reaction mixture during allylic alkylation in the presence of chloroform. Note also that the corrosion effect of halides increases in the order $Cl^- < Br^- < I^-$.[32,39] The effect of halogenated substrates on the heterogeneity of Pd can probably be explained similarly, and this speculation is supported by the numerous papers reporting Pd leaching and homogeneous catalysis in the transformation of aryl bromides and iodides.[4c]

The role of the chiral modifier BINAP is more complex. It is present only in minor amounts. Because of the strong adsorption on Pd, its effect on the oxidation state is important. Coverage of the surface sites by the bulky modifier slows down the redox processes and also modifies the electronic properties of the Pd surface (Figure 1 a). On the other hand, it is easily oxidized to BINAPO and $BINAPO_2$ by Pd in the presence of surface oxygen even in inert atmosphere (Table 2). Although this transformation contributes to the maintenance of the reduced state of Pd, the oxidized modifier probably adsorbs weaker and loses its role as the source of chiral information in the transformation of *rac*-**1** (Table 3). This process is assumed to be the reason for the necessity of applying relatively high BINAP/surface Pd atoms ratio (typically 0.2–0.4) to obtain the optimum enantioselectivity in the slow transformation of *rac*-**1**.[11a] It was shown that under these conditions only a small fraction of BINAP was actually adsorbed on the catalyst and the rest was present in the solution phase functioning as a “reservoir” for the replacement of the oxidized modifier in the course of the reaction.

Finally, the reaction temperature should be considered. It has already been described in the literature that high reaction temperatures usually lead to reduction of the soluble active complex and to the formation of Pd nanoparticles.[5a] This parameter is particularly important in our case because the potential homogeneous catalyst is not stable at elevated temperature.

Conclusion

There are only very few reports on heterogeneous asymmetric allylic alkylation reactions. Jansat et al. reported for the first time the high activity and enantioselectivity of Pd nanoparticles in the addition of dimethyl malonate to *rac*-**1** (Scheme 1).[12b] The nanoparticles were stabilized by a chiral xylofuranoside diphosphite ligand. Some years later the authors admitted that in fact the active species was a soluble Pd complex formed during the reaction.[12a] Our present investigation supports this conclusion because chlorinated solvents (in that case CH_2Cl_2) favor dissolution of metallic Pd, and the high activity of the catalyst system under ambient conditions is also a strong indication to homogeneous catalysis.

In contrast, all observations of the present study corroborate the heterogeneity of the Pd/Al_2O_3–BINAP–sodium dimethyl malonate–THF (dioxane) system. We hope that the presented systematic approach of investigating directly the effect of reaction conditions and reaction components on the oxidation state and stability of the active metal species will help discriminating between heterogeneous and homogeneous catalysis also in other cases.

Experimental Section

Materials: Tetrahydrofuran (THF, 99.99%, Acros), dioxane (99.5%, Acros) dichloromethane (99.5%, J. T. Baker), and chloroform (99%. J. T. Baker) were dried and stored over activated molecular sieves. (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphtalene ((*R*)-BINAP; >99.5%, Fluka), *rac*-BINAP (≥98%, Fluka), dimetyl malonate (>99%, Aldrich), and NaH (60% dispersion in mineral oil, Fluka) were used without further purification. The 5 wt% Pd/Al_2O_3 (N° 40692) catalyst was purchased from Engelhard. The BET surface of the catalyst was 130 $m^2 g^{-1}$ according to the data sheet provided by the manufacturer. The mean particle size was determined to be 3.3 nm and the corresponding metal dispersion was calculated to be 0.36, as described elsewhere.[11a]

(*E*)-1,3-diphenylallyl acetate (*rac*-**1**) was synthesized from (*E*)-1,3-diphenylprop-2-en-1-ol (≥ 98%, Fluka) and acetic anhydride (>98%, Acros) in dichloromethane and was purified by column chromatography (cyclohexane/ethyl acetate 9:1).[40] The structure of *rac*-**1** was confirmed by ^1H and ^{13}C NMR spectroscopy and its purity (>99%) was determined by GC analysis. (*R*)-$BINAPO_2$ was synthesized by oxidizing (*R*)-BINAP with H_2O_2 and identified by ^1H and ^{31}P NMR spectroscopy.[41]

Catalytic experiments: The allylic alkylation reactions were carried out in a magnetically stirred stainless steel autoclave (Parr) equipped with a glass liner. For a typical experiment, the glass liner was filled with solvent (12 mL), 5 wt% Pd/Al_2O_3 (42 mg), (*R*)-BINAP (0.002 g, 3.2 μmol), *rac*-**1** (0.353 g 1.4 mmol), and a solution of the sodium salt of **2** in the corresponding solvent (0.47 M, 6 mL). The malonate salt solution was always freshly prepared from equimolar amounts of NaH and **2** and filtered carefully before use. The reactor was pressurized with N_2 (20 bar) and heated to the desired reaction temperature (typically 120 °C) by immerging it into an oil bath. The catalyst was prereduced prior to its use in a fixed bed reactor in flowing H_2 at 200 °C for 60 min. After cooling to room temperature in H_2 (30 min), the catalyst was flushed with N_2 for 10 min and transferred to the autoclave.

The leaching experiments at room temperature were carried out in a glass vial under a N_2 atmosphere. The proper amount of (*R*)-BINAP was dissolved in a mixture of the solvent (5 mL) and catalyst (42 mg), which was then sealed and shaken for 72 h. The solid catalyst was then removed by centrifugation under N_2, and the supernatant solution was transferred into a N_2 flushed 50 mL Schlenk flask. Finally, *rac*-**1** (0.177 g, 0.7 mmol) and a freshly prepared and filtered solution of the sodium salt of **2** in THF (0.16 M, 9 mL) were added to the reaction mixture. At the end of the reaction, the reaction mixture was filtered and the filtrate was analyzed by GC and HPLC.

The typical leaching experiments at 120 °C were carried out according to the procedure described previously for the standard catalytic experiments. At the end of the reaction, the reactor was cooled down in an ice bath and the solid catalyst was removed by centrifugation under N_2. The supernatant solution was transferred into a N_2 flushed Schlenk flask, and a freshly prepared and filtered solution of the sodium salt of **2** (0.47 M, 6 mL) was added to the reaction mixture. After the desired reaction time the reaction mixture was filtered and the filtrate was analyzed by GC and HPLC.

The oxidation of *rac*-BINAP by 5 wt% Pd/Al_2O_3 was carried out in a 50 mL flask equipped with a cooler (60 °C) or in the reactor described above (120 °C). In both cases, 5 wt% Pd/Al_2O_3 (84 mg) and *rac*-BINAP (0.010 g, 16 μmol) in THF (10 mL) under a N_2 atmosphere (1 bar at 60 °C, 20 bar at 120 °C) were used. The reaction time was set to 3 h.

Analysis: The ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker Avance 200 or Avance 500 spectrometer and the signals were referenced to TMS. The quantitative ^{31}P NMR spectra were recorded on a Bruker Avance 700 spectrometer using inverse gated decoupling.

The conversion of *rac*-**1** was determined by using a Thermo Finningan gas chromatograph equipped with an HP-5 capillary column (30 m × 0.32 mm × 0.25 μm) and diethyl phthalate (>99%, Merck) as the internal standard. The following conditions were used: 1.1 mL min^{-1} carrier gas flow, 150 °C initial temperature (1 min), 300 °C final temperature (5 min), 25 °C min^{-1} heating rate. The retention times for **1** and **3** were 4.7 min and 6.1 min, respectively. Structural identification of **3** was made by GC–MS by using an HP-6890 gas chromatograph coupled with an HP-5973 mass spectrometer, and by ^1H and ^{13}C NMR measurements. Product **3** was isolated according to a known procedure.[42] The side products were analyzed by GC–MS.

The *ee* of **3** ((*R*) enantiomer: 12.3 min, (*S*) enantiomer: 13.2 min) was determined by HPLC (Merck LaChrom). The analysis was carried out on a Chiracel OD chiral column (240 mm × 4.6 mm i.d., 10 μm particle size) at 25 °C with a liquid flow rate of 0.9 mL min^{-1} and a 99:1 *n*-hexane/isopropanol mixture as the eluent. The assignment of the peaks was made by comparison with literature data.[43] The absolute configuration of **3** was verified by comparing the sign of the optical rotation with literature data.[44] Optical rotations were measured on a Perkin–Elmer 241 polarimeter using a 1 dm cell at room temperature in chloroform ($\lambda = 589$ nm, Na D-line).

Before the argentometric determination of free Cl^-, the reaction mixture was washed twice with water (15 mL). The combined water phases were washed with cyclohexane (15 mL). The water phase was then diluted to a volume of 60 mL. For a single measurement, 10 mL of the sample solution was again diluted to a volume of 50 mL. After adding a few drops of $K_2CrO_4/K_2Cr_2O_7$ indicator the solution was titrated with a 0.01 M aqueous solution of $AgNO_3$. For each sample the measurement was repeated six times.

XANES measurements: In situ XANES experiments were carried out in a specially designed XAS batch reactor cell possessing two paths for X-ray adsorption measurements at the bottom and in the middle of the reactor to measure the solid/liquid interface at the catalyst bed and the liquid phase, respectively, at temperatures up to 220 °C and pressures up to 250 bar. The reactor was equipped with inlet and outlet lines to compressed liquids and gases, and magnetic stirring of the solution facilitated mass transport. A polyetheretherketone (PEEK) inset in the 10 mL stainless steel reactor allowed corrosive materials to be used. The details of the cell are described elsewhere.[45]

For a typical experiment, 5 wt% Pd/Al_2O_3 (84 mg; used as received, without prereduction) was placed in the reactor followed by *rac*-**1** (0.353 g, 1.4 mmol) and a solution of (*R*)-BINAP (0.004 g, 6.4 μmol) in solvent (1 mL). Then a freshly prepared and filtered solution of the sodium salt of **2** in the corresponding solvent (0.56 M, 5 mL) was added. After setting a N_2 pressure of typically 10 bar, the cell was heated to the desired temperature. For the measurements of a single reaction component, the amounts described above in 6 mL of solvent were used. The raw data were energy calibrated at the Pd K-edge by using the Pd K-edge energy of a Pd foil, background corrected and normalized by using the WINXAS 3.1 software;[46] in this way a difference in variation with less than 5% could be analyzed. The linear-combination fit was also carried out by using the WINXAS 3.1 software. As references, the XANES spectra of PdO and the catalyst reduced by H_2 in THF at 60 °C were used.

Acknowledgements

We thank Dr. Adam Webb and Dr. Maarten Nachtegaal for their assistance during XANES measurements, Dr. Wolfgang Kleist for the XPS measurements and HASYLAB at DESY (Germany) and the SLS at PSI (Switzerland) for beam time. Financial support by the Swiss National Foundation and the European Community (through the Integrated Infrastructure Initiative "Integrating Activity on Synchrotron and Free Electron Laser Science", Contract RII3-CT-2004-506008) is kindly acknowledged.

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Received: April 1, 2010