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Enantioselective allylic substitution on Pd/Al_2O_3 modified by chiral diphosphines

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Abstract

The allylic substitution of (*E*)-1,3-diphenylallyl acetate (**1a**) with dimethyl malonate was investigated on Pd/Al_2O_3 modified by (*R*)- and (*S*)-BINAP, (*S*,*S*)-Chiraphos, (*R*)-C_3-Tunephos, and (*R*)-Solphos. Stable performance of Pd/Al_2O_3 required its reduction in hydrogen before the allylic substitution reaction, which was carried out under Ar. The enantioselectivity of the Pd/Al_2O_3-BINAP system [58–60% ee to (*S*)-**2**] was independent of the reaction temperature (60 and 120 °C), and only 300 ppm BINAP related to **1a** was required. According to UV–vis analysis, only a small fraction of BINAP was adsorbed on Pd/Al_2O_3. At 120 °C, full conversion and 94% chemoselectivity were achieved in 6 h. For comparison, analogous soluble Pd–BINAP complexes were poorly efficient and afforded low ee to the opposite enantiomer of the product at 60 °C or above. Electron microscopy could detect no restructuring of Pd in Pd/Al_2O_3 during the reaction. Surprisingly, the addition of BINAP induced a significant rate acceleration (by a factor of almost 7 at 60 °C) and also improved the chemoselectivity of Pd/Al_2O_3. Among the diphosphine ligands tested, (*R*)-Solphos was the most effective (67% ee). An important advantage of the Pd/Al_2O_3–BINAP system is that it can transform not only the allyl acetate **1a**, but also the corresponding allyl alcohol **1b** without the application of any additive.

Keywords: Asymmetric; Allylic substitution; Palladium/alumina; Chiral modification; Diphosphines; BINAP; Rate acceleration

1. Introduction

Allylic substitution is a versatile reaction for the formation of new carbon–carbon and carbon-heteroatom bonds. After Tsuji reported the reaction of nucleophiles with π-allylpalladium chloride [1], Trost reported the first example of an asymmetric allylic substitution reaction in the 1970s [2]. Since then, the reaction has been investigated thoroughly, and numerous novel chiral catalysts have been developed that allow high yield and enantioselectivity [3–6]. A widely used test reaction is the allylic substitution of (*E*)-1,3-diphenylallyl acetate (**1a**, Scheme 1) with dimethyl malonate. Depending on the ligands and reaction conditions, >90% ee and good yields can be achieved. The reaction is usually carried out at room temperature in THF or CH_2Cl_2, and the nucleophile is added in the form of its salt or generated in situ by *N*,*O*-bis(trimethylsilyl) acetamide (BSA). The nucleophile has a large influence on the performance of the Pd–BINAP system; for example, 80% yield and 30% ee were achieved in 44 h when the sodium salt of dimethyl malonate was used in THF [7]. When the nucleophile was generated in situ in CD_2Cl_2, the yield (85%) and particularly the enantioselectivity (90%) increased, but the reaction time also doubled [8].

Intrigued by the well-known technical advantages of heterogeneous catalysts, Jansat et al. attempted the enantioselective allylic substitution of **1a** with Pd nanoparticles modified with a chiral diphosphite ligand [9]. The modifier, which had been synthesized in four steps, afforded excellent enantioselectivity (97% ee). Interestingly, it was not possible to increase the conversion beyond 61% even after a prolonged reaction time of 168 h. Instead, a high kinetic resolution (89%) was observed for the substrate. More recently, allylic substitution of **1a** with diethyl malonate (instead of dimethyl malonate) as a nucleophile was catalyzed with a Pd/C–(*R*)-BINAP system [10]. The reaction in water at 70 °C afforded an ee of 80% but a yield of only 21% after 12 h reaction time. Interestingly, the absolute config-

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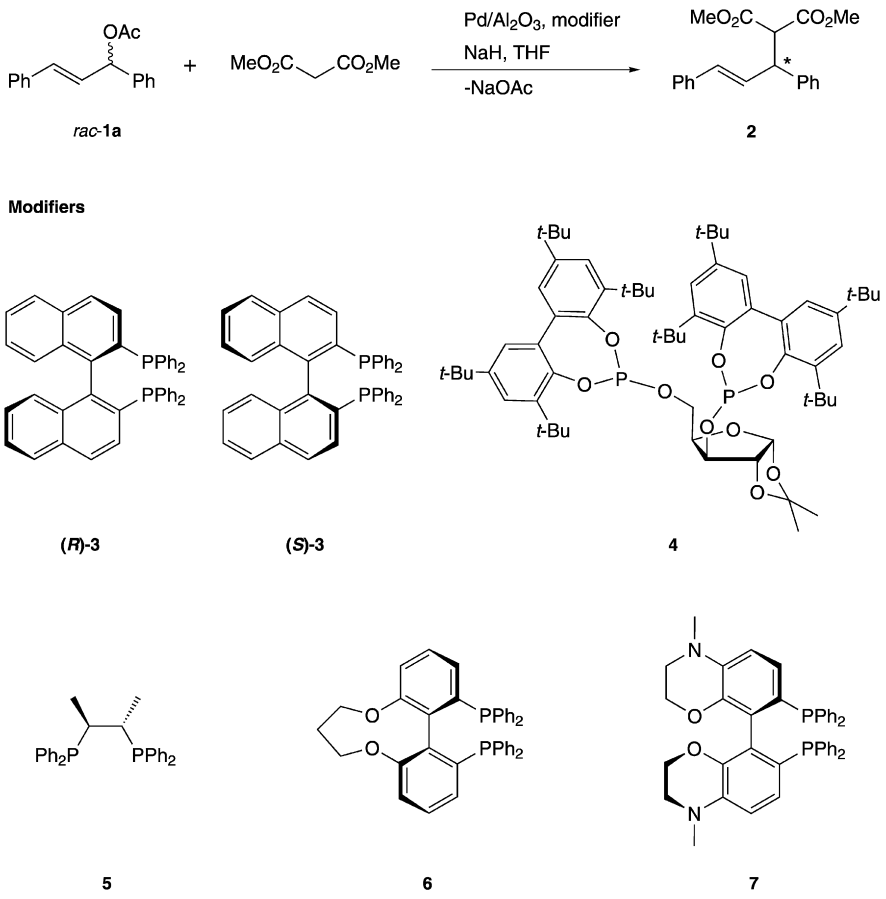


Scheme 1. Pd-catalyzed allylic substitution of **1a** with dimethyl malonate and the structure of chiral modifiers.

uration of the product was (*R*), not (*S*) as is usually observed for (*R*)-BINAP.

Considering these heterogeneous catalysts from a broader perspective, enantioselective reactions on chirally modified (supported) Pd metal are well known. With only a few exceptions [11–13], research has focused on the hydrogenation of C=C bonds [14–22], using mainly cinchona and vinca alkaloids and their simple derivatives as modifiers. A fundamental deviation from the homogeneous metal–ligand systems is that on the metal surface, the substrate cannot interact with the same metal atom that is blocked by the chiral modifier due to steric limitations; this deviation is expected to lead to different reaction characteristics and mechanisms.

Here we report the allylic substitution of **1a** using a conventional Pd/Al_2O_3 catalyst modified with various chiral biphosphines (Scheme 1). A detailed analysis of the reaction revealed some unprecedented characteristics of this chirally modified Pd catalyst.

2. Experimental

2.1. Materials

(*E*)-1,3-diphenylallyl acetate (*rac*-**1a**) was synthesized from (*E*)-1,3-diphenylprop-2-en-1-ol (*rac*-**1b**, ⩾98%, Fluka) as described previously [23]. The diphosphite ligand **4** was prepared by reacting the corresponding diol [24] with 2 equivalents of 4,4′,6,6′-tetra-*t*-butyl-2,2′-bisphenoxyphosphorus chloride [25] in the presence of a base [26]. All synthesized compounds were purified by column chromatography. The structures of **1a** and **4** were confirmed by ^1H and ^{13}C NMR. Ligand **4** was also characterized by HR-MALDI-MS. The purity (>99%) of **1a** was confirmed by GC. Tetrahydrofuran (THF, 99.99%, Acros) was dried and stored over activated molecular sieve (water content: 0.012 wt%). $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (⩾98%, Fluka), $Pd(OAc)_2$ (>99%, Merck), (*R*)-(+)- and (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene ((*R*)- and (*S*)-BINAP ((*R*)-and (*S*)-**3**), puriss., Fluka), (2*S*,3*S*)-(−)-bis(diphenylphosphino)butane ((*S*,*S*)-Chiraphos (**5**), Aldrich), (*R*)-(6,6′-*O*-(1,3-propylene)-oxylbiphenyl-2,2′-diyl)bis(diphenyl)-phosphine ((*R*)-C_3-Tunephos (**6**), Aldrich), (*R*)-7,7′-bis(diphenylphosphino)-3,3′,4,4′-tetrahydro-4,4′-dimethyl-8,8′-bi-(2H-1,4-benzoxazine) ((*R*)-Solphos (**7**), >97%, Aldrich), dimetyl malonate (>99%, Aldrich), *N*,*O*-bis(trimetylsilyl) acetamide (BSA, 95%, Acros), and NaH (60% dispersion in mineral oil, Fluka) were used without further purification. The 5 wt% Pd/Al_2O_3 (No. 40692) catalyst was purchased from Engelhard.

2.2. Catalytic experiments

The commercial 5 wt% Pd/Al_2O_3 catalyst was stored in air and prereduced in solution or in gas phase before use. For the pretreatment in solution, the catalyst was stirred in 5 ml of THF

for 5 min under Ar at 60 °C, after which the Ar was replaced by H_2 for 30 min. The ligand was added to the solution, and the system was flushed again for 10 min with Ar before the substrate and the solution of sodium dimetyl malonate were added. The gas-phase catalyst pretreatment was carried out in a fixed-bed reactor in flowing H_2 for 60 min at different temperatures. After cooling to room temperature in H_2 (30 min), the catalyst was flushed with Ar for 10 min and transferred to the reactor used for allylic substitution. If not mentioned otherwise, the pretreatment in gas phase at 200 °C was used as the standard method.

The stirring speed for all catalytic experiments was set to 750 rpm. The sodium salt solution of dimethyl malonate was prepared from equimolar amounts of dimethyl malonate and NaH and filtered before use. The experiments with 5 wt% Pd/Al_2O_3 at 60 °C were carried out in a 50-ml double-necked flask equipped with a cooler and an oil bath. For a typical experiment, 1.4 mmol sodium salt of the dimethyl malonate in 3 ml of THF was added to the flask containing 5 ml of THF, 42 mg of catalyst, 3.2 μmol of modifier, and 1.4 mmol of substrate (conditions I). For reactions at higher temperature, a magnetically stirred stainless steel autoclave equipped with a glass liner (Parr, conditions II), or a parallel reactor system from Equilabo equipped with 6 magnetically stirred reactors containing PTFE liners (conditions III) were used. For standard experiments under conditions II, the glass liner was filled with 12 ml of THF, 42 mg of catalyst, 3.2 μmol of the modifier, 1.4 mmol of substrate, and 1.4 mmol of sodium salt of dimethyl malonate in 6 ml of THF (added in that order). After the nitrogen pressure was set to 20 bar, the reactor was heated to 120 °C in a preheated oil bath. Under conditions III, the PTFE liner was filled with 3 ml of solvent, 18.6 mg of catalyst, 1.4 μmol of the modifier, 0.62 mmol of the substrate, and 1.24 mmol of sodium salt of dimethyl malonate in 5 ml THF (added in that order). The nitrogen pressure was set to 20 bar, and the reactor was heated to 120 °C.

The homogeneous catalytic experiments were carried out in a 20-ml Schlenk tube following a previously reported procedure with slight modifications [27]. The corresponding ligand (12.8 μmol) was dissolved in 5 ml of THF under Ar atmosphere at room temperature. Then the catalyst precursor $\{[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (6.4 μmol) or $Pd(OAc)_2$ (12.8 μmol)$\}$ was added to the solution. After 10 min, the substrate (1.28 mmol) was added to the solution. Subsequently, 2.56 mmol of sodium salt of dimethyl malonate in 3 ml of THF was added dropwise over 5 min to the reaction mixture. When the catalytic experiment was carried out at temperatures above room temperature, the catalyst precursor and the corresponding ligand were stirred together for 10 min at room temperature before the solution was heated to the desired temperature. To avoid a temperature drop in the system on the addition of the sodium salt solution of dimethyl malonate, the latter was also warmed and then slowly added to the reaction mixture.

2.3. Analytics

The NMR spectra were recorded on a Bruker Avance 200 or Avance 500 spectrometer, and the signals were referenced to TMS. HR-MALDI mass spectra were recorded on an IonSpec Ultima FTMS-spectrometer. The crude reaction mixture was filtered before analysis. The conversion of **1a** and **1b** was determined using a Thermo Finningan gas chromatograph equipped with an HP-5 (30 m × 0.32 mm × 0.25 μm) capillary column and diethyl phthalate (>99%, Merck) as an internal standard. The following GC parameters were used: carrier gas flow, 1.1 ml/min; start temperature, 150 °C (1 min); end temperature, 300 °C (5 min); heating rate, 25 °C/min. The retention times for **1a**, **1b**, and **2** were 4.7, 4.4, and 6.1 min, respectively. Structural identification of **2** was done by GC/MS using an HP-6890 gas chromatograph coupled with a HP-5973 mass spectrometer, and by ^1H and ^{13}C NMR measurements of the isolated product **2**. Product **2** was isolated as described previously [28]. The side products were analyzed by GC-MS. The major side product **1b** was also identified by comparison with an authentic sample.

The kinetic resolution of **1a** and the ee of **2** were followed by HPLC (Merck LaChrom). The analysis of **1a** [(*S*)-enantiomer, 9.3 min; (*R*)-enantiomer, 10.2 min] was carried out on a Chiracel OD (240 mm × 4.6 mm i.d., 10 μm particle size) chiral column at 25 °C with a liquid flow rate of 0.9 ml/min and a 99/1 *n*-hexane/isopropanol mixture as the eluent. The assignment of the peaks was made by comparison with literature data [29]. For the analysis of **2** [(*R*)-enantiomer, 19.1 min; (*S*)-enantiomer, 27.7 min], a Chiralpak AD (240 mm × 4.6 mm i.d., 10 μm particle size) chiral column was used at 10 °C with a liquid flow rate of 0.5 ml/min and a 6/4 hexane/isopropanol mixture as the eluent. The absolute configuration of **2** was verified by comparing the sign of the optical rotation with literature data [30]. 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).

UV–vis measurements were carried out in a homemade in situ UV–vis cell (path length, 4 mm) equipped with a magnetic stirrer and heating. The cell was connected to the light source (HD-2000 BAL, Mikropack) and the detector (USB2000, Ocean Optics) via optic fibers.

The scanning transmission electron microscopic (STEM) investigation was performed on a Tecnai 30F field emission transmission electron microscope (SuperTwin lens with $C_s = 1.2$ mm), operated at 300 kV. The samples were suspended in ethanol, and some droplets were deposited on a holey carbon foil supported on a copper grid. The mean particle size (d_{av}) was calculated from the particle size histogram derived from the STEM pictures [31].

3. Results and discussion

3.1. Development of the catalyst system

In the allylic substitution of **1a** with dimethyl malonate (Scheme 1), Jansat et al. applied Pd nanoparticles of ca. 4 nm diameter stabilized by a chiral xylofuranoside diphosphite **4** [9]. We found that their results could be closely reproduced, but that replacement of the colloidal Pd with conventional supported Pd was not straightforward. Various commercial catalysts con-

Table 1
Influence of catalyst pretreatment on the allylic substitution of **1a** with 1 equivalent of dimethyl malonate over 5 wt% Pd/Al_2O_3 modified by (*R*)-**3** (conditions I, 60 °C, 24 h)[a]

Pretreatment method	Temp. (°C)	Conv. (%)	Chemosel. (%)	ee (%)
a	60	26	75	55 (*S*)
b	60	25	80	58 (*S*)
c	60	25	90	60 (*S*)
d	200	34	81	59 (*S*)
e	400	34	87	59 (*S*)

[a] Pretreatments: reduction of the catalyst in THF at 60 °C in the presence (a) or absence (b) of modifier, and prereduction in the gas phase (c–e).

taining 5 wt% Pd on carbon, silica, and alumina were tested using the same ligand **4** as the chiral modifier. Some catalysts were barely active, but a 5 wt% Pd/Al_2O_3 offered acceptable rates and yields. Next, we tested some P-containing ligands to replace **4**, which is highly efficient but time-consuming to synthesize; the allylic substitution of **1** was very slow even on Pd/Al_2O_3. In this screening, the commercially available ligand (*R*)- and (*S*)-BINAP (**3**) emerged as a promising candidate. (Note that several attempts to reproduce the good results reported for the Pd/C–(*R*)-BINAP system in aqueous medium failed [10].)

We experienced another complication when tuning the reaction conditions to supported Pd: The widely used base precursor BSA with a small amount of KOAc [32] did not lead to conversion. This hurdle was overcome, and reproducible results were obtained by direct addition of the nucleophile, in the form of its sodium salt, to the reaction mixture. In a control experiment, we found no conversion when BSA was also added along with the sodium salt of the malonate. The missing reactivity in the presence of one equivalent BSA might be explained by blocking of the Pd surface by BSA or one of its decomposition products.

Pd/Al_2O_3 could be used in allylic substitution without any pretreatment, but the results were poorly reproducible. The poor reproducibility could be eliminated by reductive pretreatment of the catalyst in hydrogen before the allylic substitution of *rac*-**1a**, which transfers the surface oxides to Pd^0 active sites. Table 1 shows the influence of catalyst pretreatment in solution and in the gas phase at different temperatures. Prereduction in flowing hydrogen at elevated temperature enhanced the reaction rate and the chemoselectivity, but afforded only a minor improvement in enantioselectivity.

We assume that an important role of catalyst pretreatment in hydrogen is the transformation of surface oxides to metallic Pd, the active sites for the allylic substitution reaction, and the reduction may not be complete at 60 °C (Table 1). Note that Pd/Al_2O_3 was stored in air, and its surface was covered by an oxide layer. The elevated temperature likely is necessary for the complete removal of some surface impurities, such as organic residues originating from the catalyst preparation. Both processes lead to an increased number of free surface Pd^0 sites. This interpretation was supported indirectly by STEM investigation. As shown in Fig. 1, there was no significant deviation in the average particle size or size distribution after the reductive heat treatment of Pd/Al_2O_3 at 200 °C, and even after the substitution reaction at 120 °C. Interestingly, the average particle size of Pd/Al_2O_3 (3.3 nm) is similar to that of

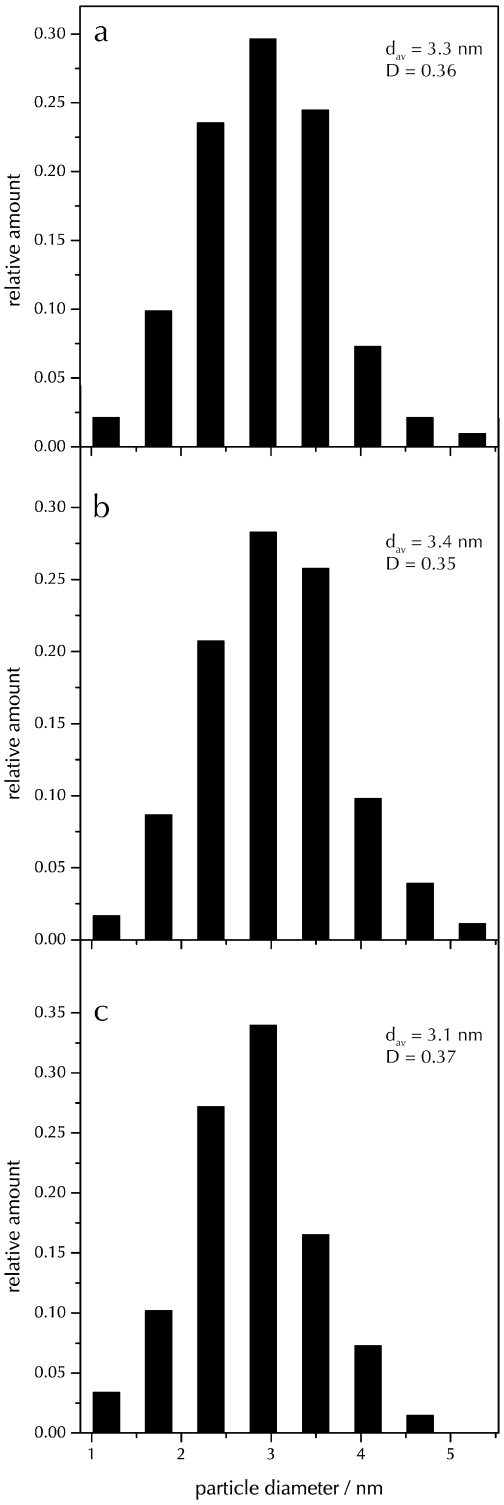


Fig. 1. Metal particle size distributions calculated from the electron micrographs of the 5 wt% Pd/Al_2O_3 catalyst (number of particles measured >300). (a) without any pretreatment, (b) catalyst pretreated in the gas-phase in H_2 at 200 °C for 1 h, (c) the pretreated catalyst after the allylic substitution reaction carried out at 120 °C for 2 h.

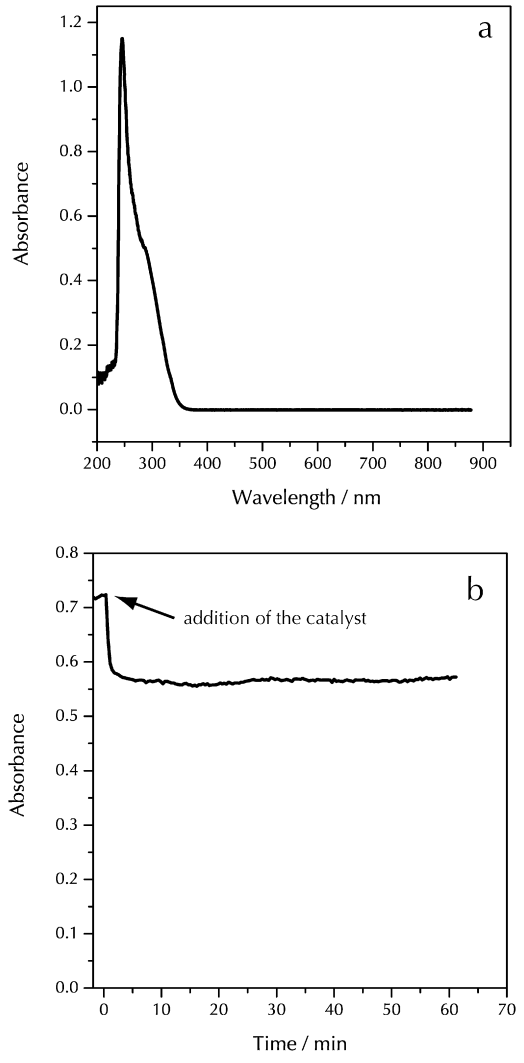


Fig. 2. UV–vis spectrum of 0.8 μmol (*R*)-BINAP in 10 ml THF at 60 °C (a) and the changes in the solution concentration, derived from the absorption at 270 nm, upon addition of 42 mg 5 wt% Pd/Al_2O_3 (b).

the colloidal Pd used previously by Jansat et al. (4 nm) [9]. Clearly, the difference in the particle size alone cannot explain the significantly different characteristics of the two catalysts.

UV–vis measurements showed very rapid adsorption of (*R*)-BINAP on the catalyst (Fig. 2). The conditions chosen correspond to conditions I of the allylic substitution reactions (see Section 2), except with a fourfold lower BINAP/catalyst ratio to increase the sensitivity of the method. After addition of Pd/Al_2O_3, the concentration of BINAP dropped sharply within a few seconds and reached a stable level after a few minutes. Only a fraction of the modifier was adsorbed on the catalyst surface, even though the BINAP/catalyst ratio was lower than that applied under conditions I. Considering that the reactants were adsorbed on Pd during reaction and that a fraction of BINAP, which disappeared from the solution, was adsorbed on the high-surface area support, we can conclude that BINAP was present in large excess during allylic substitution, related to the number of surface Pd atoms.

Table 2
Rate acceleration induced by (*R*)-**3** as chiral modifier. The 5 wt% Pd/Al_2O_3 was prereduced in H_2 at 200 °C and the reactions were carried out under conditions I at 60 °C, or conditions II at 120 °C

Entry	Mod.	Time (h)	Temp. (°C)	Conv. (%)	Chemosel. (%)	ee (%)
1	–	24	60	5	30	0
2	(*R*)-**3**	6	60	20	70	57 (*S*)
3	(*R*)-**3**	24	60	34	81	59 (*S*)
4	–	6	120	16	62	0
5	(*R*)-**3**	6	120	47	95	58 (*S*)

3.2. The influence of reaction conditions

Variation of the reaction rate and selectivity in the presence and absence of BINAP ((*R*)-**3**) at two different temperatures is given in Table 2. To minimize the distortion of the results by partial evaporation of the solvent, the reactions at 120 °C were carried out under pressure in nitrogen (conditions II). Interestingly, not only the conversion, but also the chemoselectivity, improved significantly at higher temperature. GC analysis revealed the formation of two byproducts. The major byproduct was identified as the alcohol **1b** (Scheme 2), the formation of which is attributed to base-catalyzed hydrolysis of **1a**. The minor byproduct was formed only in traces, except when the reaction was carried out in the absence of the chiral modifier. On the basis of the GC-MS data, the minor byproduct was (*E*)-methyl-3,5-diphenylpent-4-enoate, which probably was formed from **2**.

The enantioselectivity did not change at higher temperature (Table 2). This observation is surprising, because there is only one known chirally modified metal—the Ni-tartaric acid system—that gives reasonably high ee even at 60–100 °C [33–35]; all other metals, including Pd, perform at best at around room temperature or below [21,36–39].

Another interesting observation is that the chirally modified catalyst is considerably more active than the unmodified catalyst at both reaction temperatures studied (compare entries 1 and 3 and entries 4 and 5 in Table 2). This correlation is unprecedented with chirally modified Pd; modification by cinchona or vinca alkaloids always leads to lower reaction rates [13,21,40–42], which is understandable because a fraction of the active Pd sites are covered by the bulky, strongly adsorbing modifier.

Under conditions I at 60 °C, we applied only one equivalent of nucleophile (Tables 1 and 2). Doubling this ratio more than doubled the reaction rate at 120 °C, whereas the effect at 60 °C was minor (Table 3, entries 3–6). For comparison, in the homogeneously catalyzed allylic substitution, it is common to use two equivalents of the nucleophile [29]. The addition of three instead of two equivalents of malonate did not result in any improvement (Table 3, entries 7 and 8) and the chemoselectivity and enantioselectivity were not affected by the nucleophile concentration. The fact that the nucleophile concentration has a strong influence on the reaction rate only at higher temperature may indicate a change in the rate determining step of the reaction.

Table 3
Influence of the nucleophile (Nu, malonate salt) concentration on the outcome of the allylic substitution of **1a** (conditions II, catalyst prereduction at 200 °C)

Entry	Mod.	Nu/**1a** (mol/mol)	Time (h)	Temp. (°C)	Conv. (%)	Chemosel. (%)	ee (%)
1	–	1	6	120	16	62	0
2	–	2	6	120	64	60	0
3	(*R*)-**3**	1	24	60	34	81	59 (*S*)
4	(*R*)-**3**	2	24	60	40	74	56 (*S*)
5	(*R*)-**3**	1	6	120	47	95	58 (*S*)
6	(*R*)-**3**	2	6	120	100	94	58 (*S*)
7	(*R*)-**3**	2	3	120	73	95	60 (*S*)
8	(*R*)-**3**	3	3	120	67	95	59 (*S*)
9[a]	(*R*)-**3**	2	6	120	0	0	0
10[a]	–	2	6	120	0	0	0

[a] Reaction without Pd/Al_2O_3.

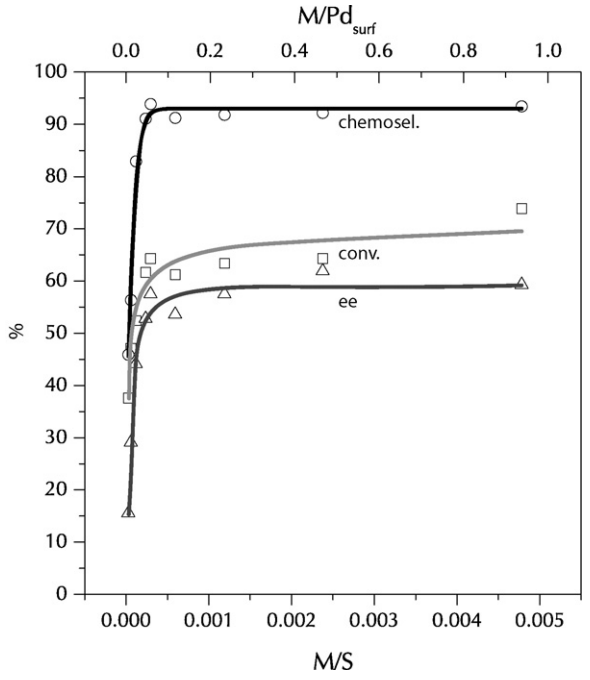


Fig. 3. Influence of the modifier/substrate (M/S) and modifier/surface Pd atoms (M/Pd_{surf}) molar ratios on the conversion (□), chemoselectivity (○) and ee (△) in the allylic substitution of **1a** with sodium salt of dimethyl malonate (Scheme 1) under conditions III with a reaction time of 2 h.

Although transition metal-free allylic substitution reactions are possible [43], no conversion was observed in the absence of Pd/Al_2O_3, independent of the presence or absence of (*R*)-**3** (Table 3, entries 9 and 10).

The influence of the modifier/substrate molar ratio (M/S) was investigated by varying the concentration of (*R*)-**3** at a constant Pd/**1** ratio (Fig. 3). The chemoselectivity and enantioselectivity reached their highest values already at an M/S molar ratio of 300 ppm, after which the changes leveled off. A further increase in the M/S ratio from 0.005 to 0.02 decreased the ee to 52% (not shown). Considering the M/Pd_{surf} molar ratio, the stable range for conversion, chemoselectivity and enantioselectivity started at a (nominal) (*R*)-**3** to Pd_{surf} ratio of 1 to 17.

The curves in Fig. 3 visualize the dramatic influence of the modifier on the outcome of the reaction. Besides inducing enantioselection, trace amounts of the modifier improved the reaction rate and chemoselectivity (see also Tables 2 and 3). A similar but smaller rate acceleration was observed in the allylic substitution on Pd/C modified with triphenylphosphine [10]. This phenomenon, termed *ligand-accelerated reaction*, was first described by Jacobsen et al. [44]. They proposed a two-cycle mechanism in which a slow nonselective reaction (on the unmodified catalyst) and a fast enantioselective reaction (on the modified catalyst) occurred in parallel. Rate acceleration in heterogeneous asymmetric catalysis was first observed with cinchonidine-modified Pt/Al_2O_3 in the hydrogenation of ethyl pyruvate [45,46]. Note that the term "ligand acceleration" is misleading in heterogeneous catalysis. On addition of a chiral ligand, the number of active sites does not change in homogeneous catalysis with metal complexes, whereas in the case of a chirally modified metal surface, a considerable number of the active sites are covered by the bulky modifier; these sites are not available for the adsorption of the substrate. Thus, the intrinsic rate acceleration at the molecular level cannot be quantitatively determined from the observed (overall) rate acceleration [47].

The origin of rate acceleration in allylic substitution on Pd is not yet clear. There are several feasible explanations to rationalize this phenomenon:

(i) It is possible that the interaction between the modifier and the metal surface generates new active sites [10]. The formation of these new active sites may occur via modifier-induced changes in the electronic and/or surface structure of the metal. The feasibility of this process is well demonstrated for Cu and Ni single-crystal surfaces by STM analysis [48–51].

(ii) Another probable role of the strongly adsorbing (*R*)-**3** is the displacement of site-blocking (deactivating) species from the metal surface. A decrease of the size of active site ensembles by adsorption of the bulky modifier also may lead to suppression of some demanding side reactions that produce strongly adsorbing byproducts.

(iii) We assume that the most important contribution of the chiral diphosphine modifier is that it keeps the Pd surface in a reduced state during reaction. The Pd/Al_2O_3 catalyst is stored in air and its surface is oxidized. Reduction of the catalyst in hydrogen before reaction generates active Pd^0 surface sites, but even traces of oxygen in the reactor can reoxidize and deactivate Pd during the long reaction time. Application of small amounts of hydrogen during allylic substitution to maintain the reduced state of the Pd surface led to saturation of the double bond in the substrate and thus to lower chemoselectivity. Suppression of the reoxidation of Pd by (*R*)-**3** during allylic substitution may be linked to the modifier-induced changes in the electronic structure of the metal [see point (i)].

3.3. Heterogeneous versus homogeneous catalysis

The allylic substitution of *rac*-**1a** (Scheme 1) also was carried out with a homogeneous Pd-catalyst, which was generated

Table 4
Temperature dependence of the enantioselectivity in the homogeneously catalyzed allylic substitution of **1a**, using (*R*)-**3** as ligand

Entry	Precursor	Temp. (°C)	Yield (%)	ee (%)
1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	25	100	30 (*S*)
2	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	50	100	20 (*S*)
3	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	60	100	4 (*R*)
4	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	66[a]	100	5 (*R*)
5	$Pd(OAc)_2$	66[a]	97	9 (*R*)

[a] Refluxing THF.

in situ from a $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ precursor and (*R*)-**3** ligand (Table 4). At room temperature, 30% ee was achieved at full conversion after only 1 h reaction time, which value is in good agreement with the literature data [52]. Since the reaction temperature of the heterogeneously catalyzed reaction is at least 60 °C, the characteristics of the homogeneous catalyst were investigated also at higher temperatures. As shown in Table 4, the ee decreased with increasing temperature, and from 60 °C on, even the absolute configuration of the major enantiomer changed from (*S*) to (*R*). Application of $Pd(OAc)_2$ as a catalyst precursor led to similar results, indicating that the observed changes in enantioselectivity are independent of the catalyst precursor (Table 4, entries 4 and 5). For comparison, an inversion of the major enantiomer with increasing temperature also was observed in the Pd-catalyzed asymmetric allylic substitution of butadiene monoepoxide using (*R*)-C4-Tunephos as a ligand [53] and in the hydroformylation of styrene with a homogeneous $PtCl_2$((*S*)-BINAP) complex [54]. In the latter case, NMR studies indicated that the change in the conformational behavior of (*S*)-BINAP at different temperatures might be at the origin of the inversion [54].

Clearly, the stereochemical outcome of the allylic substitution catalyzed by (*R*)-BINAP-modified Pd/Al_2O_3 is completely different from that of the homogeneous counterparts. Considering the enantioselectivity, the heterogeneous catalyst system was twice as efficient as the homogeneous catalyst (Tables 3 and 4), and its performance was independent of the reaction temperature (Table 2, entries 3 and 5). The deviations between the properties of the homogeneous and heterogeneous systems are probably due to the strong interaction of the modifier with the metal surface. This interaction may cause considerable constraints to the conformational flexibility of the modifier itself and to its interaction with the substrate. Another obvious difference is that in the soluble metal complex, the substrate and the modifier (ligand) coordinate to the same metal center during enantioselection, whereas on the metal surface, this geometry is not possible. We assume that the adsorption of the modifier on the metal surface induces some restriction in the degrees of freedom of the modifier, and the higher conformational rigidity of the adsorbed diphosphine may explain the better enantioselection even at elevated temperatures.

An important consequence of the remarkably different properties of the homogeneous and heterogeneous Pd–BINAP catalyst systems is that metal leaching and the contribution of homogeneous catalysis during the heterogeneously catalyzed allylic substitution can be excluded. Jansat et al. arrived at the same conclusion when they compared the behavior of Pd nanoparticles modified with the diphosphite **4** and the corresponding homogeneous system [9]. A high kinetic resolution was observed for the substrate with the colloidal Pd-**4** system, and complete conversion could never be reached. In contrast, the homogeneous (soluble) catalyst system offered full conversion within less than 2 h, but no kinetic resolution was detectable. The heterogeneity of the colloidal Pd-**4** system was proved by poisoning experiments (Hg and CS_2) as well.

Table 5
A comparison of **3** and **4** as modifiers of Pd/Al_2O_3 in the allylic substitution of **1a** (conditions I at 60 °C, and conditions II at 120 °C)

Modifier	Temp. (°C)	Time (h)	Nu/**1a**	Conv. (%)	Chemosel. (%)	ee (%)	Kinetic res. (%)
4	60	24	1	7	46	84 (*S*)	2 (*S*)
(*R*)-**3**	60	24	1	34	81	59 (*S*)	–
4	120	6	2	76	89	73 (*S*)	82 (*S*)
(*R*)-**3**	120	6	2	100	94	58 (*S*)	–

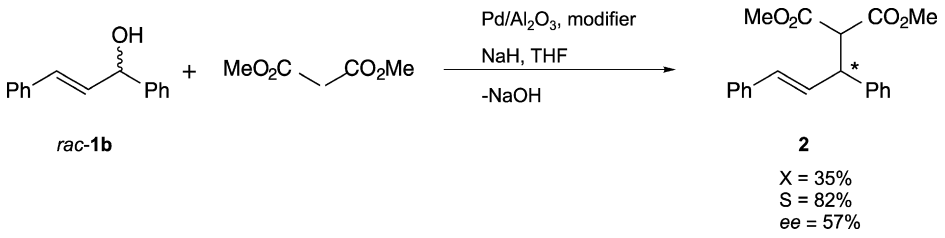
Table 6
Allylic substitution of **1a** on Pd/Al_2O_3 modified with different chiral diphosphines (conditions III, 2 h)

Mod.	Conv. (%)	Chemosel. (%)	ee (%)
(*S*)-**3**	52	95	58 (*R*)
5	17	75	33 (*R*)
6	47	95	59 (*S*)
7	41	93	67 (*S*)

3.4. Extension to other modifiers and substrate

As mentioned in Section 1, Jansat et al. achieved up to 97% ee in the allylic substitution of *rac*-**1a** using Pd nanoparticles that were stabilized and modified with the diphosphite **4** [9]. We compared the synthesized modifier **4** with the commercially available (*R*)-**3** using Pd/Al_2O_3 under two different conditions. As shown in Table 5, the reaction rate and the chemoselectivity were higher but the enantioselectivity was lower in the presence of modifier (*R*)-**3** at both reaction temperatures. In addition, only the diphosphite **4** induced kinetic resolution, and the enantioselectivity with this modifier decreased with increasing temperature.

We extended the study to some other commercially available diphosphines as modifiers of Pd/Al_2O_3 (Table 6). Replacement of (*R*)-**3** by (*S*)-**3** led to an inversion of the major enantiomer of the product from (*S*) to (*R*), as expected. Whereas (*S*,*S*)-Chiraphos (**5**) afforded considerably lower conversion, chemoselectivity, and ee, (*R*)-C3-Tunephos (**6**) led to chemoselectivity and ee similar to those achieved with (*R*)-**3**. The most selective diphosphine-type modifier in this study was (*R*)-Solphos (**7**), which afforded 67% ee. Comparing the structurally related modifiers **3**, **6**, and **7** (Scheme 2) demonstrates that the additional functional groups in the latter two diphosphines influenced their enantiodifferentiating ability only slightly.



Scheme 2. Allylic substitution of *trans*-1.3-diphenyl-2-propen-1-ol (**1b**) with two equivalents of the sodium salt of dimethyl malonate, using (*R*)-**3**-modified Pd/Al_2O_3 (conditions III, 3 h).

In the literature, most of the Pd-catalyzed allylic substitution reactions focus on substrates that have good leaving groups, such as carbonates [55], carboxylates [56], halides [57], and phosphates [58]. However, from both an economic and environmental standpoint, the direct transformation of allylic alcohols would be desirable. The conversion of allylic alcohols to the corresponding substitution product is generally possible when the OH group is activated by BEt_3 [59], $SnCl_2$ [60], $Ti(O^iPr)_4$ [61], As_2O_3 [62], or CO_2 [63]. Using the Pd/Al_2O_3–(*R*)-**3** catalyst system, we could transform the alcohol (**1b**) instead of the acetate (**1a)** to the desired product **2** (Scheme 2). The reaction rate and the chemoselectivity were lower than with **1a**, as expected, but the enantioselectivity barely decreased.

Because the allylic alcohol **1b** is also the major side product in the allylic substitution of **1a**, we may assume a two-cycle reaction pathway for the transformation of **1a** into product **2**. One cycle includes the fast direct alkylation of the allylic acetate **1a**, whereas the allylic alcohol **1b** is transformed in a slower second cycle to **2**. According to this two-cycle mechanism, the chemoselectivity of the overall reaction can increase even after full conversion of **1a**. Formation of **1b** can be avoided by working under water-free conditions.

4. Conclusion

We have investigated various diphosphines as chiral modifiers of Pd/Al_2O_3 in the allylic substitution of **1a** and **1b** with dimethyl malonate (Schemes 1 and 2). In the presence of BINAP, full conversion and 94% chemoselectivity were obtained at 120 °C, although the ee [58–60% to (*S*)-**2**] was lower than that achieved with (*R*)-Solphos [67% to (*S*)-**2**]. From a synthetic standpoint, the fact that a BINAP/substrate ratio of only 300 ppm was sufficient to achieve the highest enantioselectivity is desirable. The low modifier/substrate ratio, the reasonably high enantioselectivity even at 120 °C, and the significant rate acceleration induced by addition of the modifier are unprecedented phenomena in heterogeneous asymmetric catalytic hydrogenation over chirally modified Pd [14–22].

The low enantioselectivity to the opposite enantiomer provided by the analogous homogeneous Pd–BINAP system, along with the very similar Pd particle size distribution before and after the substitution reaction at 120 °C, indicate that the BINAP-modified Pd/Al_2O_3 is truly heterogeneous, in good agreement with an earlier study on a diphosphite (**4**)-modified colloidal Pd [9].

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