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A new, efficient heterogeneous Pd catalyst for enantioselective allylic substitution

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Abstract

The enantioselective allylic substitution of (*E*)-1,3-diphenylallyl acetate with dimethyl malonate was studied on Pd/Al_2O_3 in the presence of optically active ferrocenyl phosphines as chiral modifiers. These catalyst systems offer 81–92% yield in 2–6 h, along with good enantioselectivity (45–88% ee) despite the elevated reaction temperature (60–120 °C) and the low modifier/substrate ratio (0.2 mol%). Addition of the modifiers to Pd leads to significant rate acceleration and some modifiers induce also kinetic resolution of the racemic allylic acetate substrate. The remarkably different behavior of heterogeneous and homogeneous Pd–(*R*)-(*S*)-Josiphos catalyst systems, and particularly the missing enantioselection after removal of Pd/Al_2O_3, indicate that the enantioselective transformation occurs at the chirally modified Pd surface.

Keywords: Asymmetric allylic substitution; Josiphos ligand; Chiral ferrocenyl phosphine; Palladium/alumina; Rate acceleration

1. Introduction

Enantioselective reactions catalyzed by chirally modified (supported) Pd metal are well known. Research to date has focused on the hydrogenation of C=C bonds [1–9], using mainly cinchona and vinca alkaloids and their simple derivatives as modifiers. Only a few examples on other reaction types have been reported [10–12]. In 2004, Jansat et al. described the enantioselective allylic substitution of (*E*)-1,3-diphenylallyl acetate (*rac*-**1**) with dimethyl malonate on Pd nanoparticles modified with a chiral diphosphite ligand [13]. The modifier, which was synthesized in four steps and used to stabilize the nanoparticles, afforded 97% ee, but the conversion was only 61%, even after a prolonged reaction time of 168 h. The enantioselectivity of this heterogeneous catalyst is excellent even when compared with the performance of the numerous soluble chiral complexes [14–16].

Later, allylic substitution of *rac*-**1** with diethyl malonate as nucleophile was catalyzed with a Pd/C–(*R*)-BINAP system [17]. The reaction in water at 70 °C gave 80% ee but only 21% yield after 12 h of reaction time. Interestingly, however, the good enantioselectivity could not be reproduced [18], and the absolute configuration of the product was not (*S*) but (*R*), as is typically observed for (*R*)-BINAP. Nevertheless, BINAP is a good chiral modifier of Pd/Al_2O_3; this catalyst system afforded 60% ee and 90% chemoselectivity at full conversion of *rac*-**1**, according to Scheme 1 [18]. Because other commonly used ligands that are structurally similar to BINAP did not lead to significantly better results, we explored the potential of commercially available chiral ferrocenyl phosphines [19], particularly the (*R*)-(*S*)-Josiphos ligand [20], in the allylic substitution of *rac*-**1**. The characteristics of Pd modified by these compounds are the topic of the present work.

2. Experimental

2.1. Materials

(*E*)-1,3-diphenylallyl acetate (*rac*-**1**) was synthesized from (*E*)-1,3-diphenylprop-2-en-1-ol (⩾98%, Fluka) as described previously [21] and was purified by column chromatography. The structure of *rac*-**1** was confirmed by ^1H and ^{13}C NMR, and the purity (>99%) was confirmed by GC. Tetrahydrofuran (THF, 99.99%, Acros) was dried and stored over acti-

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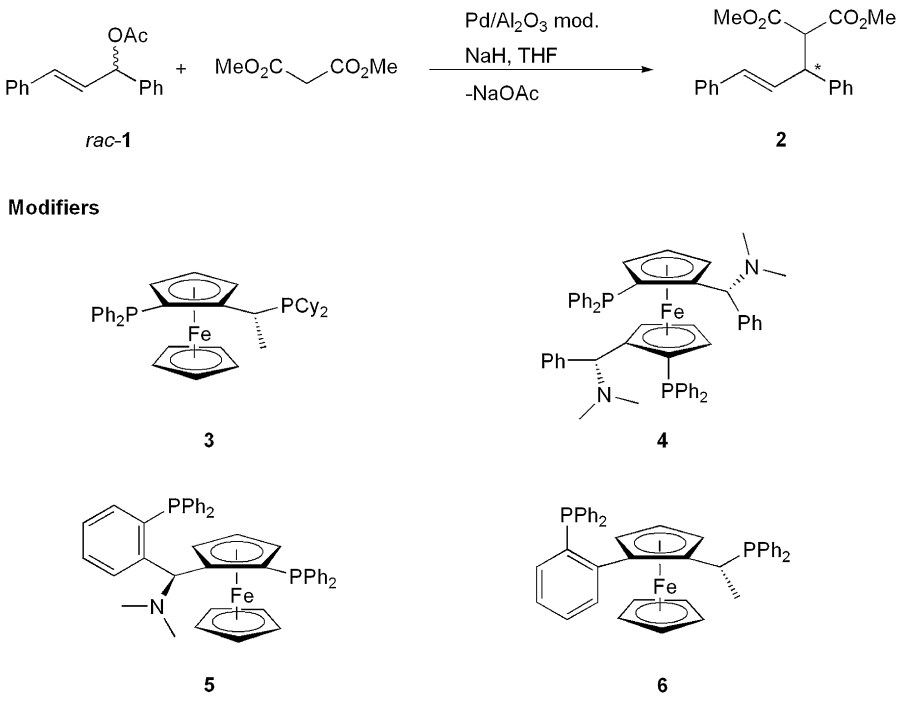

Scheme 1. Pd-catalyzed allylic substitution of *rac*-**1** with dimethyl malonate and the structure of the chiral modifiers.

vated molecular sieves. The modifiers **3** (⩾97.0% Aldrich), **4** (⩾97.0% Aldrich), **5** (⩾97.0% Aldrich), **6** (⩾97.0% Aldrich), $[Pd(C_3H_5)Cl]_2$ (98%, 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. Heterogeneous catalytic experiments

The sodium salt solution of dimethyl malonate was prepared from equimolar amounts of dimethyl malonate and NaH and was filtered before use. If not otherwise stated, the commercial 5 wt% Pd/Al_2O_3 catalyst was prereduced 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 Ar for 10 min and transferred to the batch reactor used for allylic substitution. The stirring speed for all catalytic experiments was set to 750 rpm. 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 condenser and an oil bath. For a typical experiment, 1.4 mmol of sodium salt of dimethyl malonate in 3 mL of THF was added into the flask containing 5 mL of THF, 42 mg of catalyst, 3.2 μmol of modifier, and 1.4 mmol of substrate (condition I). For reactions at higher temperature, a magnetically stirred stainless steel autoclave equipped with a glass liner (Parr; condition II), or a parallel reactor system from Equilabo equipped with 6 magnetically stirred reactors containing PTFE liners (condition III) were used. For standard experiments under condition II, the glass liner was filled with 12 mL of THF and 42 mg of catalyst, 3.2 μmol of 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). With the nitrogen pressure set to 20 bar, the reactor was heated to 120 °C by immersing it in a preheated oil bath. Under condition III, the PTFE liner was filled with 3 mL of solvent and 18.6 mg of catalyst, 1.4 μmol of modifier, 0.62 mmol of substrate, and 1.24 mmol of sodium salt of dimethyl malonate in 5 mL of THF (added in that order). The nitrogen pressure was set to 20 bar, and the reactor was heated to 120 °C.

2.3. Homogeneous catalytic experiments

The homogeneous catalytic experiments at 20 °C and 60 °C were carried out under Ar in a 50-mL triple-necked flask equipped with a condenser. First the catalyst (1.6 μmol) dissolved in 2.5 mL of THF and then the substrate (1.4 mmol) and the dimethyl malonate salt (2.8 mmol) dissolved in 6 mL of THF were added to the flask containing 9.5 mL of THF. For a reaction temperature of 60 °C, the reaction mixture was heated to 60 °C before addition of the substrate and the malonate solution (also preheated to 60 °C).

A magnetically stirred stainless steel autoclave (Parr), equipped with a glass liner, was used for the experiments at 120 °C. A high-pressure injection unit consisting of an HPLC injection valve with a 2-mL sample loop and a HPLC pump was connected to the autoclave. The catalyst (1.6 μmol) dissolved in 2.5 mL of THF, was added to the glass liner containing 7.5 mL of THF. The autoclave was pressurized to 20 bar with N_2 and then heated to 120 °C by immersing it in a preheated oil bath. Finally, the substrate (1.4 mmol) in 2 mL of THF and the dimethyl malonate salt (2.8 mmol) in 6 mL of THF were added to the reactor via the high-pressure injection unit. The stock solution of the catalyst was prepared as described previously [20] from $[Pd(C_3H_5)Cl]_2$ (3.2 μmol) and (*R*)-(*S*)-Josiphos (**3**) (6.4 μmol) in 10 mL of THF.

2.4. Analysis

The NMR spectra were recorded on a Bruker Avance 200 or Avance 500 spectrometer, and the signals were referenced to TMS. The conversion of *rac*-**1** 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 the internal standard. Structural identification of **2** was performed by GC/MS using an HP-6890 gas chromatograph coupled with a HP-5973 mass spectrometer, and by ^{1}H and ^{13}C NMR measurements of the isolated product **2**. The byproducts were analyzed by GC-MS. The major byproduct, (*E*)-1,3-diphenylprop-2-en-1-ol, also was identified via comparison with an authentic sample.

The kinetic resolution of **1** and the ee of **2** were followed by HPLC (Merck LaChrom). The analysis of **1** 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/iso-propanol mixture as the eluent. The assignment of the peaks was made by comparison with literature data [22]. For the analysis of **2**, 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/iso-propanol mixture as the eluent. The configuration of **2** was verified by comparing the sign of the optical rotation with data in the literature [23]. Optical rotations were measured on a Perkin–Elmer 241 polarimeter using a 1-dm cell at room temperature in chloroform (λ = 589 nm, Na D-line).

Table 1
Influence of catalyst pretreatment on the allylic substitution of *rac*-**1** with one equivalent of dimethyl malonate over 5 wt% Pd/Al_2O_3 modified by **3**. Pretreatments: reduction of the catalyst in THF at 60 °C in the presence of modifier (a) or without modifier (b); prereduction of the catalyst in gas-phase at 60 °C (c), 200 °C (d), and 400 °C (e) prior to addition of the other reaction components. The subsequent reaction was carried out at 60 °C under Ar, for 24 h (conditions I)

Entry	Pretreatment method	Modifier	Conversion (%)	Chemoselectivity (%)	Yield (%)	ee (%)
1	a	**3**	20	77	15.4	82 (*S*)
2	b	**3**	27	78	21.1	82 (*S*)
3	c	**3**	14	68	9.5	80 (*S*)
4	d	**3**	19	70	13.3	88 (*S*)
5	d	–	5	30	1.5	0
6	e	**3**	20	73	14.6	87 (*S*)

3. Results and discussion

3.1. Characteristics of the Pd/Al_2O_3-Josiphos system

The 5 wt% Pd/Al_2O_3 catalyst was stored in air, and consequently the metal surface was covered by an oxide layer. Preliminary experiments revealed that transformation of the surface oxides to metallic Pd by a hydrogen treatment improved the reproducibility of the allylic substitution of **1**, as well as the enantioselectivity of the reaction. Pretreatment in flowing hydrogen at 200 °C allowed up to 88% ee in the presence of **3** as a chiral modifier, although the conversion at 60 °C was low (Table 1, entry 4). Prehydrogenation of the catalyst in solution, or in the gas phase but at lower temperature, was less favorable for enantioselectivity, and application of higher temperatures for catalyst pretreatment demonstrated no advantage. The higher enantioselectivity of the prereduced catalyst is likely due to the complete transformation of surface oxides to metallic Pd and/or to a more efficient cleaning of organic impurities from the metal surface. It has been shown that reductive heat treatment does not cause a significant restructuring of the Pd particles [18].

The reaction rate could be enhanced by increasing the nucleophile concentration from one to two equivalents and the reaction temperature from 60 °C to 120 °C (Table 2). Under these conditions, full conversion was achieved within 6 h, and the chemoselectivity improved to 92%, although the enantioselectivity decreased to 82% (entry 5). Similar trends in conversion and chemoselectivity as functions of reaction temperature and nucleophile concentration was observed in the absence of the chiral modifier (entries 1 and 2). Note that it is common in allylic substitution reactions to use an excess of the nucleophile [20].

The dramatic effect of chiral modification on the reaction rate and chemoselectivity is illustrated by the two experiments conducted after the standard catalyst pretreatment method at 200 °C (Table 1, entries 4 and 5). Under otherwise identical conditions, the yield to **2** increased by a factor of almost nine due to the addition of **3**. A similar but somewhat smaller effect of **3** is shown in Table 2, at different temperature and nucleophile concentration. A more systematic analysis on the effect of modifier **3** is presented in Fig. 1. The chiral phosphine has a strong effect on the conversion as well as on chemoselectivity and enantioselectivity at low modifier/substrate (M/S) molar ratios, but the effect levels off at around 0.1–0.2 mol%. In

Table 2
Influence of the nucleophile (Nu., malonate salt) concentration on the outcome of the allylic substitution of *rac*-**1** (conditions II). The 5 wt% Pd/Al_2O_3 was prereduced at 200 °C in a H_2 flow for 1 h before use

Entry	Modifier	Nu./*rac*-**1**	Time (h)	Temperature (°C)	Conversion (%)	Chemoselectivity (%)	Yield (%)	ee (%)
1	–	1	6	120	16	62	9.9	0
2	–	2	6	120	64	60	38.4	0
3[a]	**3**	2	6	120	47	22	10.3	0
4	**3**	1	6	120	51	90	45.9	82 (*S*)
5	**3**	2	6	120	100	92	92.0	82 (*S*)
6	**3**	2	24	60	26	74	19.2	83 (*S*)

[a] Reaction without catalyst.

Table 3
Allylic substitution of **1** on Pd/Al_2O_3 modified with different derivatives of **3** (conditions III)

Modifier	Time (h)	Conversion (%)	Chemoselectivity (%)	Yield (%)	ee (%)	Kin. res. of **1** (%)
3	0.25	25	79	19.8	80 (*S*)	<1 (*R*)
3	1	89	89	79.2	76 (*S*)	3 (*R*)
3	2	97	87	84.4	77 (*S*)	–[a]
4	0.25	49	87	42.6	44 (*R*)	11 (*S*)
4	1	88	95	83.6	45 (*R*)	23 (*S*)
4	2	98	96	94.1	44 (*R*)	–[a]
5	0.25	8	41	3.3	28 (*S*)	<1 (*R*)
5	1	67	87	58.3	36 (*S*)	37 (*R*)
5	2	91	89	81.0	35 (*S*)	–[a]
6	0.25	40	90	36.0	68 (*R*)	32 (*S*)
6	1	92	95	87.4	63 (*R*)	42 (*S*)
6	2	98	94	92.1	62 (*R*)	–[a]

[a] Could not be determined.

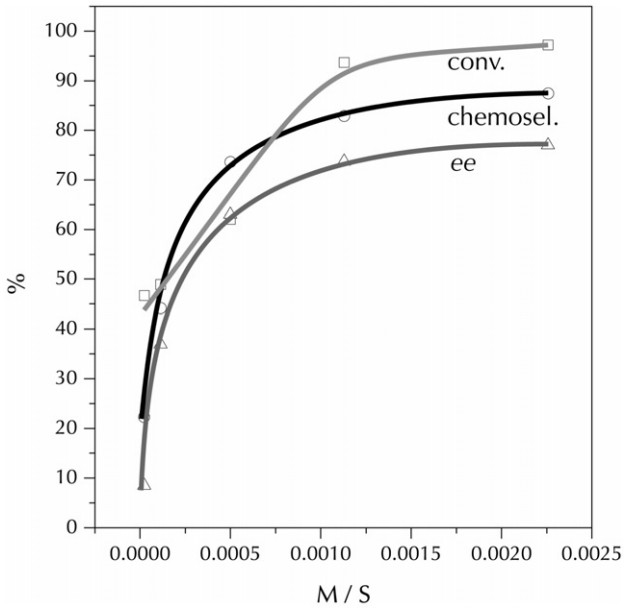

Fig. 1. Influence of the modifier/substrate (M/S) ratio on the conversion (□), chemoselectivity (○), and ee (△) in the allylic substitution of *rac*-**1** with sodium salt of dimethyl malonate (Scheme 1) under conditions III with a reaction time of 2 h. **3** was used as modifier.

comparison, only 0.03 mol% (*R*)-BINAP related to *rac*-**1** was sufficient to reach the plateau under the same conditions [18]. A common feature of both chiral phosphine modifiers is their significant rate acceleration effect. We speculate that not only the catalyst prereduction at elevated temperature, but also the phosphine modifier, contribute to keeping the Pd surface in a reduced state during reaction, which may be at the root of improved catalyst performance. Note that the reactions were carried out under nitrogen, but traces of oxygen could not be excluded from the system. Addition of hydrogen in even trace amounts keeps Pd in a reduced state but also leads to significant hydrogenation of the substrate and product.

Two byproducts were observed in the asymmetric allylic substitution of *rac*-**1**. GC-MS identified (*E*)-1,3-diphenylprop-2-en-1-ol as the major byproduct. The second byproduct, identified by GC-MS as (*E*)-methyl-3,5-diphenylpent-4-enoate, was found only in traces except when the reaction was carried out in the absence of chiral modifier. Because (*E*)-1,3-diphenylprop-2-en-1-ol is also transformed to **2**, although very slowly [18], the chemoselectivity would be expected to increase with the reaction time [18]. This assumption was confirmed by the experimental data given in Table 3 and Fig. 1.

Table 4
Allylic substitution of **1** using a homogeneous palladium catalyst with **3** as ligand

Temperature (°C)	Reaction time (h)	Conversion (%)	Chemoselectivity (%)	ee (%)	Kin. res. of **1** (%)
20	3	60	100	92 (*S*)	12 (*R*)
20	23	100	100	92 (*S*)	0
60	1	63	100	85 (*S*)	3 (*S*)
60	7	100	100	85 (*S*)	0
120	2	65	89	55 (*S*)	12 (*S*)

3.2. *Heterogeneity of the Pd/Al_2O_3-Josiphos system*

An intriguing question is whether the Pd-ferrocenyl phosphine catalyst system is truly heterogeneous, or whether leaching of Pd and homogeneous catalysis also contributes to the results. To answer this question, we carried out some control reactions commonly used in the literature to distinguish between homogeneous and heterogeneous catalysis [24,25]. First, we repeated the transformation of *rac*-**1** to **2** in the presence of a homogeneous Pd catalyst with **3** as the ligand (Table 4). Increasing the reaction temperature led to a decrease in ee from 92% at room temperature to 55% at 120 °C. In comparison, the Pd/Al_2O_3-catalyzed reaction showed no temperature dependence of enantioselectivity in the same temperature range and gave >80% ee even at elevated temperature (Table 2). In addition, the homogeneous catalyst produced a significant kinetic resolution of the substrate, and the absolute configuration of the major enantiomer changed with increasing reaction temperature (Table 4), whereas the reaction catalyzed by the Pd/Al_2O_3-**3** system did not lead to detectable kinetic resolution in the substrate at any temperature.

The lower activity of the homogeneous catalyst at 120 °C may be explained by the partial decomposition of the catalyst, also resulting in lower chemoselectivity. This explanation is supported by the observation that the reaction in the presence of the dissolved ligand alone leads mainly to the formation of side products at 120 °C (Table 2). It seems that at 120 °C, the preferred process is not the oxidation and leaching of Pd^0, but rather the opposite process, the reduction of the metal ion and metal deposition. Also note the recently reported simple method for preparing monodisperse Pd nanoparticles by thermal decomposition of various Pd-phosphine complexes [26,27].

In another series of experiments, after the allylic alkylation reaction (with **3** as chiral modifier, at 120 °C for 6 h), the catalyst was removed by centrifugation, fresh substrate and nucleophile (2 equivalents) were added to the solution, and the reaction was continued for another 6 h at 120 °C. In the first

step, 81% yield and 76% ee were achieved. In the second step, in the absence of catalyst, the additional yield was only 19%, and the substrate was converted mainly to byproducts, as would be expected based on the "blank" experiment results given in Table 2, entry 3. Most importantly, no enantioselection occurred in the absence of the solid catalyst. This result, along with the clear differences between the characteristics of the heterogeneous system and its homogeneous counterpart, suggest that in the Pd/Al_2O_3-**3** system, the reaction occurs on the metal surface, and the contribution of metal leaching and homogeneous catalysis can be ignored.

3.3. Comparison of various ferrocenyl diphosphines as chiral modifiers

Finally, the efficiency of **3** as a chiral modifier of Pd was compared with the efficiencies of three other commercially available chiral ferrocenyl diphosphines (Table 3). Unfortunately, none of these offered higher enantioselectivity, but the reaction was faster in the presence of **4** and **6**, based on the yields achieved in 2 h. Interestingly, the modifiers **4**, **5**, and **6** induced some kinetic resolution of the substrate during the reaction, whereas modifier **3** did not. Note that Jansat et al. reported a high kinetic resolution of 89% when using Pd nanoparticles modified with a chiral diphosphite ligand [13].

4. Conclusion

Our search for efficient phosphine-type chiral modifiers of Pd was fruitful; the commercially available (*R*)-(*S*)-Josiphos ligand [20] offered up to 88% ee in the enantioselective allylic alkylation of *rac*-**1**, although at only low conversion (Table 1). The reaction rate could be enhanced by increasing the temperature and the nucleophile concentration, which allowed 97% conversion in only 2 h (Table 3). Under (partly) optimized conditions, 82% ee and 92% yield were achieved (Table 2). Unfortunately, structural variations in the ligand (modifier) did not lead to higher enantioselectivity, but these phosphines induced some kinetic resolution in the racemic substrate (Table 3).

The characteristics of phosphine-modified Pd are remarkably different from those of the cinchona- and vinca-modified Pd commonly used for enantioselective hydrogenation reactions. The most intriguing deviation is the rate acceleration induced by addition of the modifier (Fig. 1). The rate enhancement by a factor of almost nine (Table 1) is striking considering that a considerable fraction of the Pd surface sites is covered by the strongly adsorbing chiral phosphine, a well-known poison of noble metal hydrogenation catalysts [28]. Clarification of the origin of rate acceleration needs further investigation.

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