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Kinetic resolution in Pd-catalyzed allylic substitution using the helical PHelix ligand

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Abstract

The chiral helical diphosphine 2,15-bis(diphenylphosphino)-hexahelicene (PHelix) is an excellent ligand in palladium catalyzed kinetic resolution involving allylic substitution. Depending upon the substrate, enantioselectivities (ee) of up to 99% are observed. Although formally a diphosphine, PHelix appears not to undergo chelation, which means that it behaves as a chiral monophosphine. © 2000 Published by Elsevier Science S.A. All rights reserved.

Keywords: Pd-catalysis; Allylic substitution; Kinetic resolution; Helicity; Asymmetric catalysis

1. Introduction

Numerous chiral auxiliaries for use in transition metal catalyzed enantioselective reactions have been described; central, planar or axial symmetry traditionally being involved [1]. In many cases the ligands are chiral phosphines, although nitrogen-containing compounds and mixed phosphorus/nitrogen ligands have also emerged as useful auxiliaries. Oddly enough, the first case of asymmetric catalysis using a purely helical diphosphine was not reported until 1997 [2]. In that publication we described the synthesis and antipode separation of 2,15-bis(diphenylphosphino)-hexahelicene (**1**) [3], which was called PHelix. Using this novel ligand, the first application in catalysis was attempted, namely the Rh-catalyzed hydrogenation of itaconic acid dimethyl ester, resulting in an enantiomeric excess (ee) of only 39%. The X-ray structural analysis of PHelix (**1**) (Fig. 1) shows the twisted helical form of the carbon backbone [2], which is geometrically almost identical to the structure of the parent compound hexahelicene itself [4].

Importantly, the two phosphorus atoms span a distance of 6.481(1) Å [P1···P2]. This value is so large that the compound cannot be expected to behave in a chelating manner, unless considerable flexibility in the backbone is assumed which might bring the two P-atoms spatially closer to one another. Unfortunately, so far it has not been possible to obtain crystals of a 1:1 adduct with a transition metal which would show that either chelation does indeed enforce a smaller [P1···P2] distance, or that PHelix is actually behaving as a chiral monodentate ligand.

In the present paper we report on the use of palladium complexes of **1** as catalysts in allylic substitution, specifically in kinetic resolution of racemic allylic acetates. The enantioselective Pd-catalyzed substitution reaction of allylic acetates based on the use of chiral chelating ligands has emerged as a powerful synthetic method [1,5]. Generally, racemic substrates are employed. This means that both enantiomeric forms of the acetate lead to the same intermediate π-allylic Pd-species which then react enantioselectively with such nucleophiles as malonate anions (conversion: 100%). Many efficient ligands have been described, including chelating systems such as chiral diphosphines [5] and phosphino-oxazolines [6]. More recently, even a chiral monodentate phosphine (2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane) has been shown to lead to high ee-values in allylic substitution [7]. Less research

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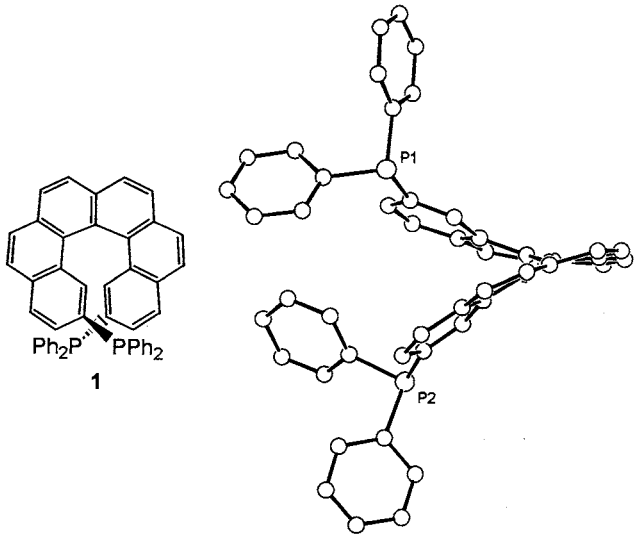


Fig. 1. Side-view of the crystal structure of PHelix (**1**) [2].

has been invested in the possibility of kinetic resolution in these systems in which conversion is stopped at about 50% [8]. This has no influence on the ee of the product, but the starting substrate (acetate) can be isolated theoretically in the enantiomerically enriched form. Thus, this type of kinetic resolution is quite different from the usual form [9], an aspect that has not always been emphasized in the past. Indeed, two enantiodifferentiating processes occur which are independent of one another. In the present study we focus our attention on the kinetic resolution of racemic allylic acetates using Pd-complexes of PHelix (**1**). Evidence is presented which indicates that PHelix is in fact performing as a chiral monodentate phosphine.

2. Experimental

All reactions were performed using standard Schlenck tubes under an atmosphere of argon. All starting materials and products are known compounds and were compared with authentic samples.

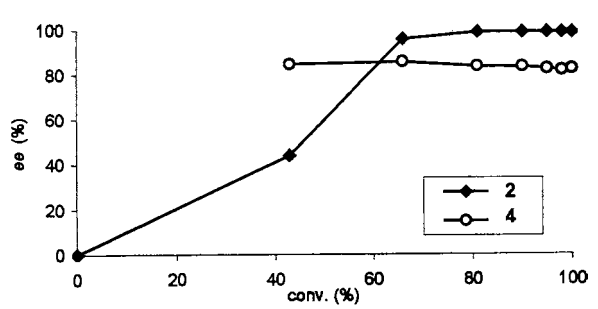


Fig. 2. Conversion dependence of the ee-values of substrate **2** and product **4**.

2.1. Typical procedure for allylic substitution

A solution of 1.22 mg (1.75 μmol; 1.00 mol%) of (+)-bis(diphenylphosphino)-hexahelicene (PHelix) (**1**) [2] in 0.35 ml of methylene chloride was added to a solution of 0.16 mg (0.44 μmol; 0.25 mol%) of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ in 1.00 ml of methylene chloride. The solution was stirred for 1 h at room temperature (r.t.). The yellow solution was treated successively with a solution of 44 mg (0.18 mmol) of *rac*-1,3-diphenylpropenylacetate (**2**) in 1.50 ml of methylene chloride, 69 mg (0.53 mmol) of dimethylmalonate (**3**), 107 mg (0.53 mmol) of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of anhydrous potassium acetate. The yellow solution was degassed three times by freeze–thaw cycles. The reaction mixture, which turned bright yellow, was stirred 5 h at r.t. until conversion was complete by TLC analysis. The pale yellow reaction mixture was diluted with 10 ml of diethyl ether and washed twice with saturated aqueous NH_4Cl-solution. The organic phase was dried over $MgSO_4$, concentrated in vacuum and filtered through SiO_2. The residual yellow oil was analyzed by HPLC. Instrument: Varian 5560; column: 250 mm Chiralpak OD-H, 4.6 mm i.d.; mobile phase: *n*-heptane–2-propanol = 99:1; temperature: 298 K; velocity: 0.5 ml min^{-1}; pressure: 3.2 MPa; detection: UV, 220 nm.

2.2. Typical procedure for kinetic resolution

A solution of 3.66 mg (5.25 μmol; 1.00 mol%) of (+)-bis(diphenylphosphino)-hexahelicene (PHelix) (**1**) [2] in 1.00 ml of methylene chloride was added to a solution of 0.96 mg (1.31 μmol; 0.25 mol%) of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ in 2.60 ml of methylene chloride. The solution was stirred for 1 h at r.t. The yellow solution was treated successively with a solution of 132 mg (0.53 mmol) of *rac*-1,3-diphenylpropenylacetate (**2**) in 4.50 ml of methylene chloride, 180 mg (1.58 mmol) of dimethylmalonate (**3**), 390 mg (1.58 mmol) of *N*,*O*-bis(trimethylsilyl)acetamide and a catalytic amount of anhydrous potassium acetate. The yellow solution was degassed three times by freeze–thaw cycles. The reaction mixture, which turned bright yellow, was stirred at r.t. Samples of 0.5 ml of the reaction mixture were taken every 15 min with a syringe, diluted with 2 ml of methylene chloride and filtered through SiO_2. The filtrates were analyzed directly by HPLC. Enantiomeric excess of the substrate and the product can be measured in one run. Sample: 20 μl of the solutions with 0.5 ml *n*-heptane and 0.2 ml CH_2Cl_2; instrument: Shimadzu LC 10AVP; column: 250 mm Chiralcel OD-H, 4.6 mm i.d.; mobile phase: *n*-heptane–2-propanol = 99:1; temperature: 298 K; velocity: 0.5 ml min^{-1}; pressure: 3.4 MPa; detection: UV, 220 nm.

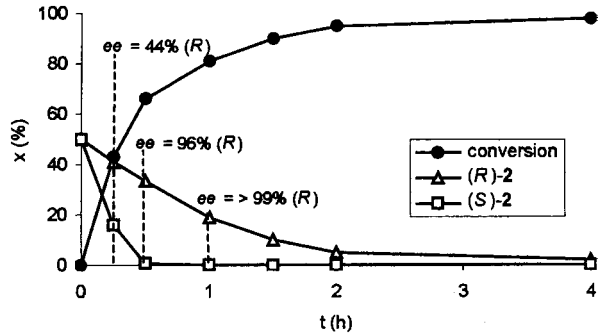


Fig. 3. Proportions of (*R*)- and (*S*)-**2** during the Pd-catalyzed allylic substitution (HPLC-determination).

Table 1
Results of the Pd-catalyzed allylic substitution of 1,3-diphenylpropenylacetate (**2**)

Time (h)	Conversion **2** (%)	ee **2** (%)	ee **4** (%)
0.25	43	44.0 (*R*)	84.7 (*R*)
0.5	66	96.0 (*R*)	85.7 (*R*)
1.0	81	>99 (*R*)	83.7 (*R*)
1.5	90	>99 (*R*)	83.4 (*R*)
2.0	98	>99 (*R*)	82.7 (*R*)
4.0	100	–	81.6 (*R*)

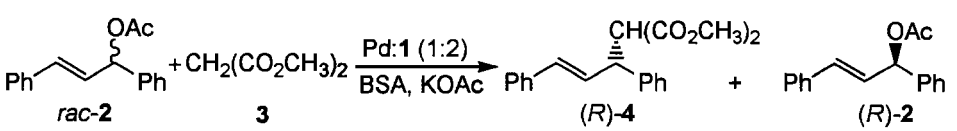
The details of the results concerning the kinetic resolution of **2** (Figs. 2 and 3) are summarized in Table 1.

3. Results and discussion

In an exploratory experiment, substitution at complete conversion was first studied employing the standard substrate **2** in conjunction with malonate (**3**) as the nucleophile, leading to product **4**. Using 0.5 mol% of a catalyst prepared in situ by adding the ligand (+)-**1** (one part) to $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (one part) with (formal) formation of the π-allyl complex $\eta^3\text{-}C_3H_5PdCl$–**1**, relatively slow substitution was observed. After 3 days conversion was 60–64%, the ee-value of the product **4** being 84–88% in favor of the *R*-enantiomer. Upon using 0.5 mol% palladium with a ligand–metal ratio of 2:1, the reaction turned out to be considerably faster: in several runs quantitative conversion to the *R*-product was observed within 4 h, the ee-values being in the same range as previously (Scheme 1).

NMR studies of $\eta^3\text{-}C_3H_5PdCl$–**1** showed that a single discrete species is not involved. For example, the ^{31}P-NMR spectrum revealed the presence of more than one peak, indicating the existence of several species. Specifically, the main peak appeared at 33.6 ppm next to somewhat smaller signals at 24.1, 27.2, 27.9 and 28.0 ppm, respectively. It was not possible to identify these species structurally. Variation of the ligand–metal ratio also failed to produce a single discrete Pd-complex. Thus, these results coupled with the observation that the ligand–metal ratio has no significant effect on enantioselectivity constitute strong evidence that catalysis is not mediated by a Pd-chelate of PHelix. It is much more likely that the diphosphine **1** is behaving as a monodentate ligand, which means that the difunctional compound forms oligomers with transition metal salts.

Although the catalyst system is not well defined structurally, it was tested in the kinetic resolution of substrate **2** using a Pd–ligand ratio of 1:2. The results show that the product ee stays approximately constant over the entire reaction, whereas the ee-value of the educt **2** in favor of (*R*)-configuration increases as the reaction proceeds reaching a plateau at >97% ee after about 60% conversion, i.e. when about 40% of the starting material is still present (Fig. 2). Fig. 3 shows the proportion of (*R*)- and (*S*)-**2** as the reaction proceeds. The complete data is summarized in Table 1. This behavior is to be expected of efficient enantiodiscriminating systems. Indeed such a trend, as shown in Fig. 3, has been observed using other ligand systems [8]. Thus, if an additive were to be introduced into the system, which causes the rapid racemization of the starting material **2**, then at 50% conversion, no enantioselectivity would be observed, while the product **4** would have the same ee as before. In the present reaction, enantioselectivity is almost optimal, comparing well with the best systems based on chelating ligands described previously [8a–e]. As already pointed out, two independent chirally discriminating processes are involved: enantioselective formation of the π-allyl-Pd-intermediate, which is responsible for the observed kinetic resolution, and asymmetric nucleophilic addition to this species leading to the observed ee-value of the product. Very few previous ligand systems allow for kinetic resolution in the efficiency range described here. In fact, some systems known to result in high ee-values in allylic substitution products show essentially no enantiodifferentiaton whatsoever in kinetic resolution (ee = 0–5%), as for example in the case of BINAP or 2,2′-isopropylidenebis[(4*S*)-4-*t*-butyl-2-oxazoline] [10].



Scheme 1.

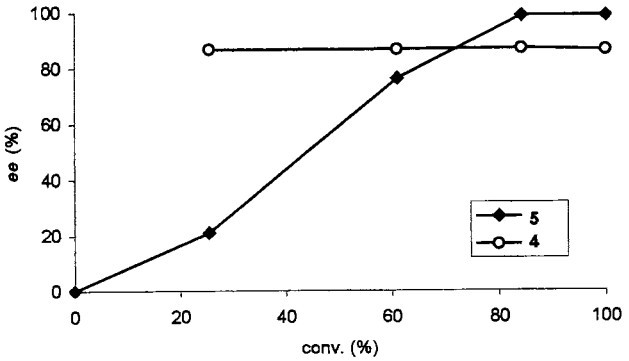


Fig. 4. Conversion dependence of the ee-values of substrate **5** and product **4**.

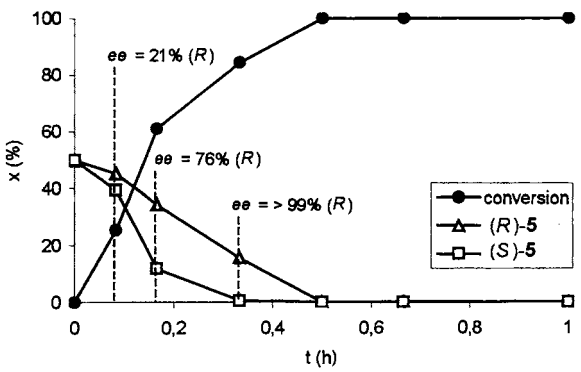


Fig. 5. Proportions of (*R*)- and (*S*)-**5** during the Pd-catalyzed allylic substition (HPLC-determination).

We then proceeded to study the possible influence of the leaving group. Specifically, the benzoate **5** was subjected to the same conditions of kinetic resolution used previously for the acetate **2**. The results (Figs. 4 and 5) show a similar trend as in the reaction of substrate **2**, except that asymmetric induction in the enantioselective addition of palladium to the substrate with formation of the π-allyl Pd-complex is slightly less efficient. This means that in this step of the kinetic resolution, acetate is a more efficient leaving group than benzoate, whereas in the substitution process no significant differences are observed (Scheme 2).

Finally, the unsymmetrically substituted substrate **6** was tested in kinetic resolution. The results, as summarized in Figs. 6 and 7, demonstrate clearly that the phenomenon of kinetic resolution operates here as well, albeit with a lower degree of enantiodifferentiation. The

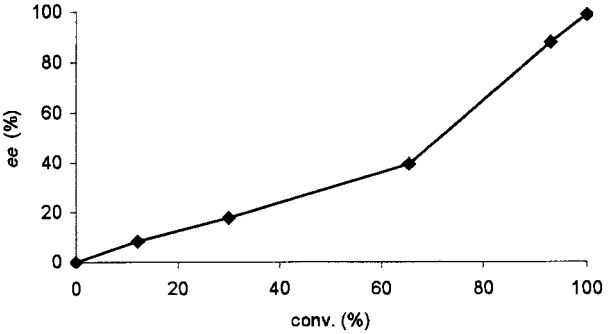


Fig. 6. Conversion dependence of the ee-values of substrate **6**.

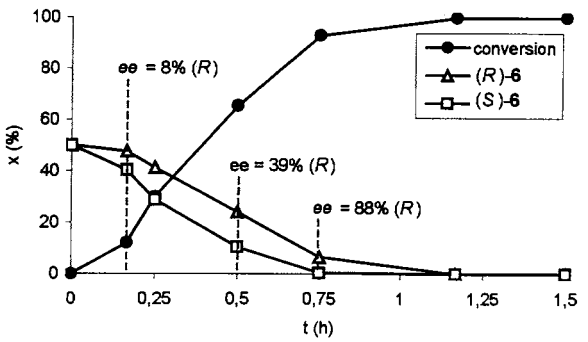
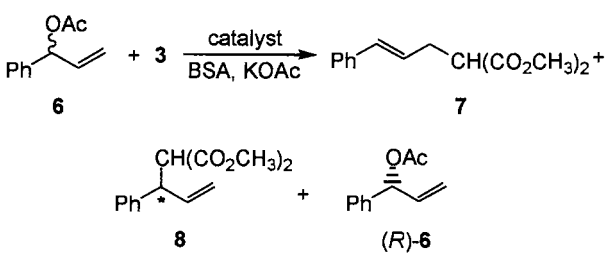


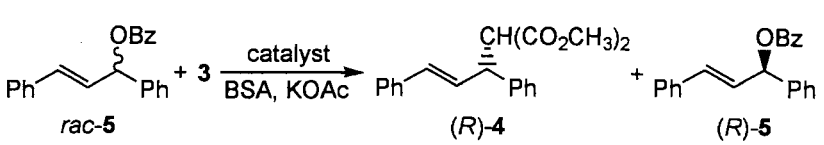
Fig. 7. Proportions of (*R*)- and (*S*)-**6** during the Pd-catalyzed allylic substition (HPLC-determination).



Scheme 3.

absolute configuration of compound **8** was not determined because of its low yield (< 5%) (Scheme 3).

In summary, the diphosphine **1** behaves as a monodentate ligand. In Pd-catalyzed allylic substitution, enantioselectivity is below the standard high values reached by the best systems described in the literature [1,5,6]. In contrast, enantiodiscrimination in kinetic resolution of such substrates as **2** is highly efficient, ee-values of > 98% being possible when 30–40% of the starting material is still present.



Scheme 2.

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