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Asymmetric catalysis 87*. Enantioselective allylation of 1,5-dimethylbarbituric acid with Pd catalysts and new optically active PN ligands

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Abstract

The new PN ligands **5**, **6** and **7** were prepared by Schiff base condensation of 2-formylphenyl(diphenyl)phosphine (**1**) with the optically active amines (*R*)-(−)-2-aminobutanol (**2**), (*S*)-(+)-2-aminobutanol (**3**) and (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol (**4**). These new ligands were used in the Pd catalysed allylation of 1,5-dimethylbarbituric acid with allylacetate. 5-Allyl-1,5-dimethylbarbituric acid was obtained with an optical induction of up to 12.7% ee.

Key words: Catalysis; Asymmetric catalysis; Palladium complexes; Barbituric acid; Allylation

Introduction

The palladium catalysed allylation of CH acidic substrates is a well established method of C–C bond formation. In enantioselective catalysis the asymmetric centre usually is built up at one of the carbon atoms of the allylic system. In particular, soft nucleophiles such as the anions of 1,3-dicarbonyl compounds and prochiral allylic systems give high enantiomeric excesses [2–5]. However, there are only a few examples for the formation of an asymmetric centre on the α-C atom of the nucleophile [2, 6]. In this case, it is much more difficult to obtain optical inductions, because the attack of the nucleophile on the allylic system occurs from the *exo*-side opposite to the Pd atom. Due to these stereochemical facts enantioselectivity in the Pd-catalysed allylation will depend on the development of new ligands. These new ligands should be able to influence the incoming nucleophile because of their expansion, for example via a long side chain with a polar end group.

Unsymmetrical barbiturates with a quarternary asymmetric carbon atom in 5-position play a significant role in pharmacy. Pharmacological examination showed that the (*R*) and (*S*) enantiomers or barbituric acids can display different effects in the body. At present, the synthesis of optically active barbituric acids is carried out by basic condensation of urea derivatives with substituted cyanoacetates, which have to be optically resolved [7–9]. Therefore, it is of interest to examine the synthesis of barbituric acids by way of enantioselective catalysis.

In this paper we report the synthesis of new optically active PN ligands and the Pd catalysed allylation of 1,5-dimethylbarbituric acid with allylacetate.

Preparation of new optically active PN ligands

In addition to the biphosphines, chelating PN ligands play an important part in enantioselective transition metal catalysis. Ligands of this type can be prepared starting from 2-formylphenyl(diphenyl)phosphine (**1**) [10–12], which is easily accessible in a multi-step synthesis. The Schiff base condensation of optically active primary amines and **1** leads to PN ligands, which on coordination to a metal centre form six-membered chelate rings.

The condensation of 2-formylphenyl(diphenyl)-phosphine (**1**) with the optically active amines (*R*)-(−)-2-aminobutanol (**2**), (*S*)-(+)-2-aminobutanol (**3**) and (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol (**4**) in methanol gives the Schiff bases **5**–**7** (Scheme 1).

*For Part 86 see ref. 1.

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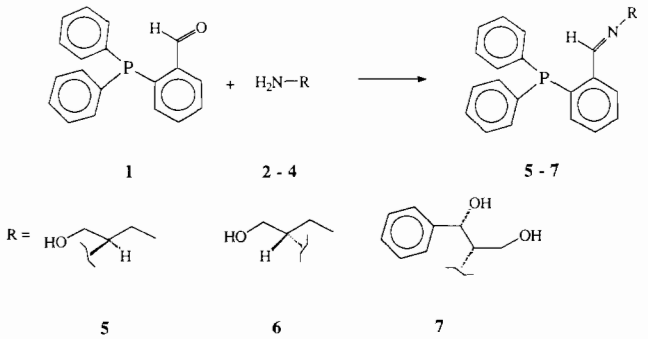
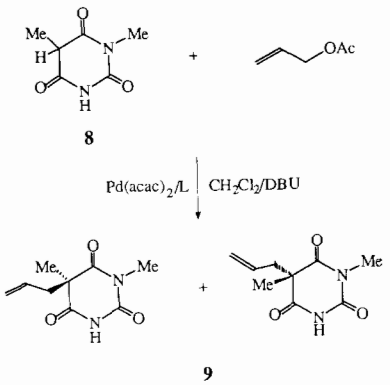


Scheme 1.



Scheme 2.

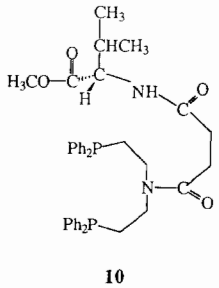
The mass spectra of the phosphineimines contain the molecular ions (**5**, **6** (EI) 361 *m/z*; **7** (FD) 439.3 *m/z*).

The ^{1}H NMR spectra of compounds **5–7** show a doublet resulting from the coupling of the methine proton of the azomethine group with the phosphorus atom. The coupling constants are 3.9 Hz for **5** and **6** and 3.1 Hz for **7**.

Enantioselective allylation of 1,5-dimethylbarbituric acid and allylacetate

The Pd catalysed allylation of 1,5-dimethylbarbituric acid (**8**) [13] with allylacetate gives 5-allyl-1,5-dimethylbarbituric acid (**9**) with a quarternary carbon atom in 5-position (Scheme 2). In the first step of the reaction, an equimolar amount of DBU withdraws a proton from the CH acidic 1,5-dimethylbarbituric acid. After addition of $Pd(acac)_2$, ligand and allylacetate the catalytic cycle starts. The Pd/ligand/substrate ratio is 1:2.2:100.

In the standard procedure, 1,5-dimethylbarbituric acid (**8**) is stirred under nitrogen with an equimolar amount of DBU in methylene chloride. **8** dissolves with formation of its anion. To this solution $Pd(acac)_2$, ligand and allylacetate is added. Then, the reaction mixture is



Scheme 3.

TABLE 1. Enantioselective allylation of 0.96 mmol of 1,5-dimethylbarbituric acid (**8**) with 1.2 mmol of allylacetate in 10 ml of CH_2Cl_2 at 25 °C in presence of 9.6 μmol of $Pd(acac)_2$ and 22.0 μmol of ligand

Ligand	Reaction time (h)	Yield (%)	% ee	No. of experiments
(−)-Norphos	24	75	0	1
(−)-Diop	24	78	0	1
(−)-Prophos	24	75	0	1
10	24	72/72	11.9/11.8(−)	2
5	48	69/69	9.7/9.7(−)	2
6	48	70/70	9.9/9.9(+)	2
7	48	68/68	12.7/12.6(−)	2

stirred at room temperature. The reaction is stopped by addition of HCl. The organic layer is washed with water and evaporated. The excess of allylacetate is removed under reduced pressure. The enantiomeric excess of the product **9** is determined by gas chromatography on a Chirasil-L-Val column. The chemical yield is also determined by gas chromatography using the internal standard octadecane.

The reaction was first set up for the ligand triphenylphosphine. Then, optically active ligands were tested. We used the conventional phosphines (−)-Diop, (−)-Prophos, (−)-Norphos, the anchor-ligand **10** (Scheme 3) [14] and the newly synthesised PN ligands **5–7**. The results of the allylation are shown in Table 1.

Under the conditions of the standard procedure the conventional ligands do not give enantioselectivity. With the anchor-ligand **10** an enantiomeric excess of 11.9% ee is obtained, showing its ability to influence the incoming nucleophile with the long side chain. The newly synthesised PN ligands **5–7** induce enantioselectivities in the same range as the anchor-ligand **10**. The highest enantiomeric excess of 12.7% ee is achieved with the new PN ligand **7**.

Experimental

^{1}H NMR and ^{31}P NMR spectra were recorded on a Bruker WM 250 spectrometer and were referenced

to internal TMS and external H_3PO_4, respectively. FD mass spectra were obtained on a Finnigan MAT 95 spectrometer, and for EI mass spectra a Varian MAT 311 A spectrometer was used. Gas chromatography measurements were carried out on a Varian-Aerograph, model 1800.

2-Formylphenyl(diphenyl)phosphine [10–12] and 1,5-dimethylbarbituric acid [13] were prepared as described in the literature. The optically active aminoalcohols, (*R*)- and (*S*)-2-aminobutanol, and (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol were bought and used without purification.

Synthesis of iminophosphines 5–7

Gencral proccdure: 5 g (17.2 mmol) of **1** and 17.2 mmol of the corresponding aminoalcohol **2–4** were dissolved in 100 ml of MeOH and refluxed for 3 h. After cooling the solvent was evaporated and the residue recrystallised from petroleum ether 40/60. The products were obtained as colourless crystals.

(−)-2-[N-(R)-1'-Hydroxy-2'-butylcarbaldimino]-phenyl(diphenyl)phosphine (5)

Yield 91%, m.p. 83.5–84.5 °C. $[\alpha]_D^{25} -52.3$ ($c=1$, EtOH). IR (KBr): 3500–3100 (OH), 3060 (=CH), 2950, 2920, 2860, 2820 (CH), 1630 (C=N). EI MS: $m/z=361$ (M^+). ^{1}H NMR ($CDCl_3$): 8.68 (d, $J_{PH}=3.9$, 1H, azomethine), 7.80–7.78 (m, 1H, Ar–H), 7.41–7.23 (m, 12H, Ar–H), 6.91–6.86 (m, 1H, Ar–H), 3.51 (d, $^3J=5.4$, 2H, CH_2–OH), 3.10–3.05 (m, 1H, C*H*–N), 1.91 (d, 1H, OH), 1.42–1.30 (m, 2H, CH–CH_2–CH_3), 0.62 (t, $^3J=7.5$, CH–CH_2–CH_3). ^{31}P{^{1}H} NMR ($CDCl_3$:$CHCl_3$ 1/1): −9.6 (s).

Anal. Calc. for $C_{23}H_{24}NOP$ (361.1): C, 76.49; H, 6.69; N, 3.87. Found: C, 76.51; H, 6.55; N, 4.05%.

(+)-2-[N-(S)-1'-Hydroxy-2'-butylcarbaldimino]-phenyl(diphenyl)phosphine (6)

Yield 90%, m.p. 83.5–84.5 °C. $[\alpha]_D^{25} +52.3$ ($c=1$, EtOH). IR (KBr): 3500–3100 (OH), 3060 (=CH), 2950, 2920, 2860, 2820 (CH), 1630 (C=N). EI MS: $m/z=361$ (M^+). ^{1}H NMR ($CDCl_3$): 8.68 (d, $J_{PH}=3.9$, 1H, azomethine), 7.80–7.78 (m, 1H, Ar–H), 7.41–7.23 (m, 12H, Ar–H), 6.91–6.86 (m, 1H, Ar–H), 3.51 (d, $^3J=5.4$, 2H, CH_2–OH), 3.10–3.05 (m, 1H, C*H*–N), 1.91 (d, 1H, OH), 1.42–1.30 (m, 2H, CH–CH_2–CH_3), 0.62 (t, $^3J=7.5$, CH–CH_2–CH_3). ^{31}P{^{1}H} NMR ($CDCl_3$:$CHCl_3$ 1/1): −9.6 (s).

Anal. Calc. for $C_{23}H_{24}NOP$ (361.1): C, 76.49; H, 6.69; N, 3.87. Found: C, 76.48; H, 6.65; N, 4.03%.

(+)-2-[N-(1S,2S)-1',3'-Dihydroxy-1'-phenyl-2'-propylcarbaldimino]phenyl(diphenyl)phosphine (7)

Yield 55%, m.p. 95 °C. $[\alpha]_D^{25} +100$ ($c=1$, EtOH). IR (KBr): 3600–3100 (OH), 3050 (=CH), 2950, 2910, 2860 (CH), 1635 (C=N). FD MS (acetone): $m/z=439.3$ (M^+). ^{1}H NMR ($CDCl_3$): 8.30 (d, $J_{PH}=3.1$, 1H, azomethine), 7.64–6.91 (m, 19H, Ar–H), 4.66 (d, $^3J=5.2$, 1H, N=CH–C*H*Ph), 3.60–3.30 (m, 3H, C*H*–CH_2–OH), 3.15–2.20 (broad, 2H, OH). ^{31}P{^{1}H} NMR ($CDCl_3$:$CHCl_3$ 1/1): −4.1 (s).

Anal. Calc. for $C_{28}H_{24}NO_2P$ (439.5): C, 76.52; H, 5.96; N, 3.19. Found: C, 76.16; H, 6.16; N, 3.39%.

Enantioselective Pd catalysed allylation of 8 with allylacetate

150 mg (0.96 mmol) of **8** were stirred with 0.15 ml (0.96 mmol) of DBU in 10 ml of CH_2Cl_2 for 2 min at room temperature. Then, in the following order were added: 3 mg (9.6 μmol) of $Pd(acac)_2$, 22.0 μmol of ligand and 0.12 ml (1.2 mmol) of allylacetate. The solution was stirred for 24 h at room temperature. Then, the reaction mixture was washed with 5 ml of 0.1 N HCl and three times with 5 ml of water. The organic layer was dried over Na_2SO_4, filtered and evaporated. The excess of allylacetate was removed under reduced pressure. The residue was recrystallised from water.

5-Allyl-1,5-dimethylbarbituric acid (9)

Colourless crystals, m.p. 131 °C. IR (KBr): 3215, 3100 (N–H), 1710 (C=O). EI MS: $m/z=196$ (M^+). ^{1}H NMR ($CDCl_3$): 8.59 (s, 1H, N–H), 5.96–5.51 (m, 2H, olefin), 5.17–5.13 (m, 1H, olefin), 3.27 (s, 3H, N–CH_3), 2.70 (d, $^3J=7.5$, 2H, CH_2), 1.57 (s, 3H, C–CH_3).

Anal. Calc. for $C_9H_{12}N_2O_3$ (196.2): C, 55.10; H, 6.16; N, 14.27. Found: C, 55.21; H, 6.13; N, 14.23%.

GC analysis

An exactly determined amount of about 50 mg of octadecane was added to the crude product. The solution obtained after adding 5 ml of CH_2Cl_2 was used for the gas chromatographic measurement.

GC data: Chirasil-L-Val glass capillary column 25 m; gas H_2; pressure 0.85 bar; column temperature 130 °C; injector temperature 250 °C; detector temperature 250 °C (flame ionisation). Retention times: standard (octadecane) 14.8 min (correlation factor 3.2 ± 0.1), (−)-enantiomer 21.2 min, (+)-enantiomer 22.7 min.

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