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Enantioselective hydroformylation of vinyl-aromatics using a rhodium complex with the (1*R*,2*R*,4*R*)-2-(2-diphenylphosphinyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl) pyridine

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Abstract

The rhodium complex of a pyridylphosphinite derived from (+)-camphor was prepared and assessed in the hydroformylation reaction of some vinyl-aromatic substrates. The complex exhibit good catalytic activity. The prevalent formation of the branched aldehyde was obtained with all examined substrates. The enantioselectivities were low to moderate (up to 45%).

Keywords: Hydroformylation; Pyridylphosphinite; Vinyl-aromatics; Rhodium catalysts

1. Introduction

The enantioselective hydroformylation of aromatic olefins is a very useful method to prepare optically active aldehydes which are precursors of biologically active molecules such as pharmaceuticals and agrochemicals [1–4]. In this contest promising results were obtained in the enantioselective hydroformylation using catalysts based on transition metal complexes modified with heterotopic P,N-chiral ligands [5,6]. Recently, Arena et al. [5] reported that the hydroformylation of 2-vinylnaphthene catalyzed by a chiral pyridylphosphinite–rhodium complex gave the corresponding aldehyde in good regio- and enantioselectivity (78% ee). This interesting result prompted us to develop new pyridylphosphinite ligands.

In the present paper we report the synthesis of the pyridylphosphinite **3** from the pyridylcarbinol derived from (+)-camphor **2** [7], the preparation of the corresponding cationic rhodium complex **1** and its use as a catalyst in the hydroformylation reaction of some vinyl-aromatic substrates (see Scheme 1).

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2. Experimental

2.1. General methods and chemicals

Diethylether, tetrahydrofuran (THF), and benzene were distilled from sodium under argon atmosphere. Synthesis gas (1:1 H_2/CO) was prepared directly in the autoclave using H_2 and CO flashes. Styrene and 2-vinylnaphthalene were purchased from Aldrich. $[Rh(COD)Cl]_2$ (COD = cyclooctadiene) was a Strem product. (1*R*,2*R*,4*R*)-2-(2-Hydroxy-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)pyridine [7], isobutylstyrene [8], 3-phenoxystyrene [9] and 2-vinyl-6-methoxynaphthalene [10] were prepared following literature procedures.

GLC analyses were performed using a Perkin-Elmer model 8500 gas chromatograph equipped with a DB5 30 mt column. Elemental analyses were performed using an elemental analyzer Perkin-Elmer Model 240C. NMR spectra were recorded using a Varian VXR 300s spectrometer. Optical rotations were measured on a Perkin-Elmer mod. 241 polarimeter in 1-dm tubes.

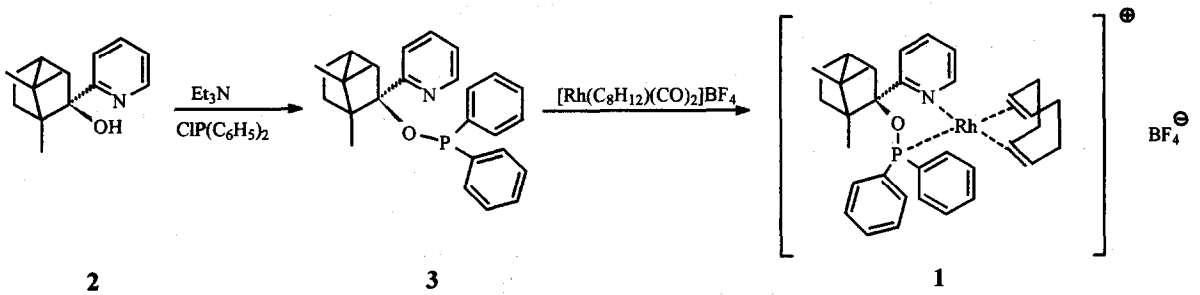
2.2. Synthesis of (1R,2R,4R)-2-(2-diphenylphosphinyl-1,7,7-trimethylbicyclo [2.2.1]hept-2-yl)pyridine (3)

A 1.6 molar solution of butyl lithium (0.9 ml, 1.46 mmol) was added slowly under argon to a cooled (0°C) solution of **2** (0.338 g, 1.46 mmol) in anhydrous THF (5 ml). After 1 h stirring at 0°C a solution of diphenylchlorophosphine (0.325 g) in anhydrous THF (2 ml) was added dropwise. After 5 h the solvent was evaporated under reduced pressure and the residue purified by flash chromatography (light petroleum ether/ethyl acetate = 7:3; the chromatography must be carried out quickly under argon because of the high tendency of **3** to hydrolyze) to give pure **3**: 0.450 mg (74%); ^{31}P NMR ($CDCl_3$) δ 112.10.

2.3. Preparation of [Rh(COD)(1R,2R,4R)-2-(2-Diphenylphosphinyl-1,7,7-trimethylbicyclo [2.2.1]hept-2-yl)pyridine]BF_4 (1) [11]

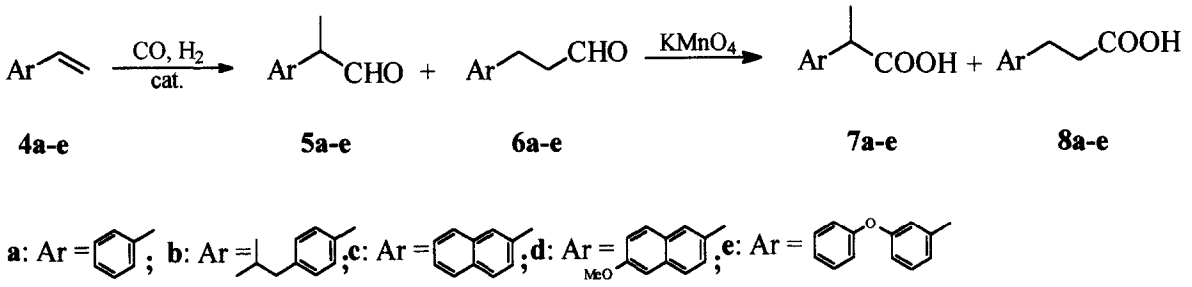
(a) Preparation of $[Rh(COD)_2]BF_4$ *(4).* 1,5-Cyclooctadiene (0.86 ml, 7 mmol) and $AgBF_4$ (0.31 g, 1.6 mmol) were added in sequence to a solution of $[Rh(COD)Cl]_2$ (0.25 g, 0.64 mmol) in CH_2Cl_2 (2 ml) under inert atmosphere. After 30 minutes stirring cold ether (5 ml) was added to the clear solution obtained after filtration through Celite under inert atmosphere. The formed orange solid was filtered, dried under *vacuo* and used in the next step without further purification.

(b) Reaction of **4** *with the (1R,2R,4R)-2-(2-diphenylphosphinyl-1,7,7-trimethyl-bicyclo-[2.2.1]hept-2-yl)pyridine (3).* A solution of **3** (0.6 mmol) in CH_2Cl_2 (2 ml) was added to a solution of **4** (0.64 mmol) in CH_2Cl_2 (2 ml). After 1 h stirring, the light yellow solution was concentrated under reduced pressure (residue volume ca. 1 ml) and degassed ether (20 ml) was added. The formed orange-yellow solid was collected by filtration to give pure **1** in almost



2 3 1

Scheme 1.



Scheme 2.

quantitative yield. Elemental analysis, for $C_{35}H_{42}BF_4NOPRh$ calcd. % H, 5.93; C, 58.89; N, 1.96. Found % H, 6.02; C, 58.52, N, 1.89. ^{31}P NMR ($CDCl_3$) δ + 142.12 ($^1J_{Rh-P}$ 164.12 Hz). $[\alpha]_D^{25}$ − 12.78 (C = 1, CH_3OH).

2.4. General procedure for the hydroformylation experiments

In a typical run a mixture of the olefin (6.0 mmol) and the rhodium complex **1** (0.02 mmol) in benzene (20 ml) was introduced in a 0.15 L stainless steel reaction vessel and pressurized to the desired atmosphere with synthesis gas (CO/H_2 = 1:1). After 24 h at 80°C the reaction was cooled and vented. The crude reaction mixture (conversion and composition of the reaction products were determined by GLC) was oxidated by $KMnO_4$ in the presence of potassium phosphate buffer following a literature procedure [12]. After usual work up a mixture of 3-aryl- and 2-arylpropanoic acid was recovered. The enantiomeric excess was determined by recording the optical rotatory power of the mixture acids. In the case of runs 2 and 4 the ee % was confirmed by GLC analyses carried out on a 30 mt Beta dex-120 column (Supelco) [13]. The acids were identified by ^1H NMR spectra [2].

7a: ^1H NMR ($CDCl_3$) δ7.22–7.08 (m, 5H), 3.63–3.55 (q, 1H), 1.44–1.38 (d, 3H). **8a**: ^1H NMR ($CDCl_3$) δ 7.22–7.10 (m, 5H), 2.98–2.85 (t, 2H), 2.78–2.65 (t, 2H).

7b: ^1H NMR ($CDCl_3$) δ 7.30–7.05 (m, 4H), 3.65–3.48 (q, 1H), 2.51–2.40 (t, 2H), 1.98–1.80 (h, 1H), 1.45–1.40 (d, 3H), 1.00–0.82 (d, 6H). **8b**: ^1H NMR ($CDCl_3$) δ 7.30–7.05 (m, 4H), 2.98–2.91 (t, 2H), 2.80–2.71 (t, 2H), 2.51–2.40 (t, 2H), 1.98–1.80 (h, 1H), 1.00–0.82 (d, 6H).

7c: ^1H NMR ($CDCl_3$) δ 8.00–7.41 (m, 7H), 3.98–3.83 (q, 1H), 1.58–1.45 (d, 3H). **8c**: ^1H NMR ($CDCl_3$) δ 8.00–7.41 (m, 7H), 3.17–3.05 (t, 2H), 2.91–2.80 (t, 2H).

7d: ^1H NMR ($CDCl_3$) δ 7.78–7.02 (m, 6H), 3.92–3.85 (s, 3H), 3.55–3.43 (q, 1H), 1.60–1.52 (d, 3H). **8d**: ^1H NMR ($CDCl_3$) δ 7.78–7.02 (m, 6H), 3.92–3.85 (s, 3H), 3.11–3.02 (t, 2H), 2.80–2.71 (t, 2H).

7e: ^1H NMR ($CDCl_3$) δ 8.25–7.30 (m, 9H), 3.91–3.82 (q, 1H), 1.62–1.58 (d, 3H). **8e**: ^1H NMR ($CDCl_3$) δ 8.25–7.30 (m, 9H), 3.12–3.00 (t, 2H), 2.79–2.67 (t, 2H).

3. Results and discussion

The complex **1** was assessed in the enantioselective hydroformylation of some vinylaromatics on account of the increasing interest that aromatic branched aldehydes are find as precursors of non-steroidal antiinflammatory drugs (NSAI) [1–4] (see also Scheme 2).

The reaction conditions and yields are reported in Table 1. For the determination of the enantioselectivity the crude aldehydes were

[2] Compound **7a**: $[\alpha]_{D\,max}^{25}$ 77.0° (C = 2.38, $CHCl_3$) [14]; Compound **7b**: $[\alpha]_{D\,max}^{25}$ 60.0° (C = 2, EtOH) [15]; Compound **7c**: $[\alpha]_{D\,max}^{25}$ 71.2° (C = 1, $CHCl_3$) [14]; Compound **7d**: $[\alpha]_{D\,max}^{25}$ 66.1° (C = 1, $CHCl_3$) [14]; Compound **7e**: $[\alpha]_{D\,max}^{25}$ 57.1° (C = 0.76, CH_2Cl_2) [16].

Table 1
Hydroformylation of vinylaromatics catalyzed by the complex **1** [a]

Run	Substrate	Conv. (%)	Hydr. (%)	Aldh. yields (%)	*b/n*	Acid $[\alpha]_D^{25}$ [b]	o.p. [c]	Conf.
1	Styrene	95	–	95	80/20	+6.7	8.7	(*S*)
2	4-Isobutylstyrene	98	2	96	60/40	+11.3	18.8	(*S*)
3	2-Vinylnaphthalene	98	2	96	72/28	+32.1	45.1	(*S*)
4	6-Methoxy-2-vinylnaphthalene	93	5	88	78/22	+8.9	14.0	(*S*)
5	*m*-Phenoxystyrene	97	7	70 [d]	54/46	+3.8	6.6	(*S*)

[a] Reaction temp. = 80°C, reaction time 24 h, substrate/catalyst = 300/1.[b] Obtained by $KMnO_4$ oxidation of aldehydes.[c] Calculated on the maximum rotatory power of the acids [14].[d] Presence of unidentified products was detected.

oxydated immediately to the corresponding acids with the aim to avoid racemization.

An examination of Table 1 shows that in all cases excellent conversions and yields of *oxo*-products were obtained. Moderate regioselectivities were observed with the branched isomers prevailing. Low enantioselectivities were obtained and only with the 2-vinylnaphthalene a moderate enantiodifferentiation was achieved (45% ee). It should be noted that the enantioselectivities obtained in the hydroformylation reaction could be better to that reported in Table 1 owing to racemization phenomena which probably takes place during the relatively long time required to obtain high substrate conversion [8]a, [17].

In conclusion, the synthesis of a new pyridylphosphinite ligand has been achieved and the catalytic activity of the corresponding rhodium complex demonstrates. The results clearly indicate the enantioface discriminating ability of the catalyst **1** in the enantioselective hydroformylation reaction.

Further studies aimed to the synthesis of new P–N ligands are in progress.

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