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The use of monodentate phosphites and phosphoramidites as effective ligands for Rh-catalyzed asymmetric hydrogenation in supercritical carbon dioxide

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Abstract

Series of chiral monodentate phosphite-type ligands has been evaluated in the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate in both dichloromethane and supercritical CO_2. High reactivities (100% conversion in 1.5–3 h) and enantioselectivities (up to 90%) were obtained in the hydrogenation in $scCO_2$.

Keywords: Monodentate phosphites; Asymmetric hydrogenation; Rhodium; Supercritical carbon dioxide

1. Introduction

The asymmetric hydrogenation of prochiral olefins belongs to the most practical ways of producing many optically pure organic compounds, because it involves inexpensive molecular hydrogen and causes no side reactions. Rhodium-catalyzed asymmetric hydrogenation of prochiral olefins has generally been conducted using bidentate phosphines [1]. Recently, monodentate phosphites and phosphoramidites were shown to be inexpensive alternatives to the bidentate phosphine ligands, providing excellent enantioselectivity in the Rh-catalyzed hydrogenation [2–5]. In general, the main advantages of monodentate phosphite-type ligands include synthetic availability, high resistance to oxidative destruction and low cost. For example, BINOL-based monophosphites, which proved to be very efficient in asymmetric hydrogenation, are only about 2% of the price of the well-known diphosphine BINAP [6]. Despite the obvious advantages of monodentate phosphite-type ligands, high enantioselectivities often can be achieved in only a restricted range of solvents, many of which are environmentally hazardous [2–6]. Results obtained with chiral monodentate phosphite-type ligands in "green solvents", such as supercritical carbon dioxide ($scCO_2$), are much less impressive (with the highest ee 65% at 28% conversion), compared to bidentate phosphines (up to 99% ee, 100% conversion) [7]. Nevertheless, it is known that supercritical CO_2 can both retard and improve reaction rates and selectivity in comparison to conventional organic solvents [8,9]. Thus, an acceptable enantioselectivity (90% ee) was obtained only with amidophosphite MonoPhos in supercritical 1,1,1,2-tetraflouroetane, but this solvent is expensive [10]. Here, we report a successive application of monodentate phosphites and phosphoramidites in the Rh-catalyzed hydrogenation of dimethyl itaconate in $scCO_2$ and CH_2Cl_2, as conventional solvent.

2. Experimental

2.1. General methods

^{31}P, ^{13}C and ^{1}H spectra were recorded on a Bruker AV-400 instrument (162.0 MHz for ^{31}P, 100.6 MHz for ^{13}C and 400.13 MHz for ^{1}H). The complete assignment of all the resonances in ^{13}C NMR spectra was achieved using *J*-mod techniques. Chemical shifts (ppm) are given relative to Me_4Si (^{13}C NMR, ^{1}H NMR) and 85% H_3PO_4 in D_2O (^{31}P NMR). Elemental analyses were performed at the Laboratory of Micro-

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analysis (Institute of Organoelement Compounds, Moscow). Enantiomeric excesses of product **9** were determined using HPLC (Chiralcel OD-H column) according to the literature [11]. Conversion of substrate **8** was determined using ^{1}H NMR. All reactions were carried out under a dry argon atmosphere in freshly dried and distilled solvents. Asymmetric Rh-catalyzed hydrogenation of dimethyl itaconate in CH_2Cl_2 was performed according to the appropriate procedure [4].

*2.1.1. (R)-N-methyl-1-cymantrenylethanamine (**7**)*

(*R*)-1-cymantrenylethylamine [12] 2.47 g (0.01 mol) and $(BOC)_2O$ 2.5 g (0.0115 mol) were dissolved in THF and stirred for 0.5 h. THF was removed in vacuo and the residue was recrystallized from hexane. To a chilled (0 °C) solution of the product in 20 ml of DMF was added dropwise in a suspension of NaH 1.2 g (0.03 mol). The mixture was stirred for 1 h. After that, 5.04 ml (0.08 mol) MeI was added, and the mixture was stirred for additional 2 h. Water 50 ml was added dropwise to the obtained mixture. The organic layer was extracted with Et_2O and evaporated in vacuo. The obtained residue was purified by flash chromatography in benzene. Concentration in vacuo yielded an viscous yellow oil which was used without further characterization in the next step. Triflouracetic acid (20 ml) was added dropwise to the obtained yellow product in 20 ml of CH_2Cl_2, and the mixture was stirred for 1.5 h. Water 30 ml was added and the organic layer was separated and washed with 15 ml 2N HCl. The water layers were combined and pH was adjusted to 8 with 20% NaOH. (*R*)-*N*-methyl-1-cymantrenylethanamine was extracted with CH_2Cl_2 (3 × 30 ml), dried over Na_2SO_4 and the solvent was evaporated in vacuo.

Red oil, 0.8 g (30% yield). $[\alpha]_D = +22.4$ (c 2.0; EtOH). ^{1}H NMR (C_6D_6): 0.38 (s, 1H, NH), 1.05 (d, $J = 5.5$ Hz, 3H, $CHCH_3$), 2.15 (s, 3H, NCH_3), 3.01 (m, 1H, $CHCH_3$), 3.95 (m, 2H, Cp), 4.32 (m, 1H, Cp), 4.35 (m, 1H, Cp). Anal. Calc. for $C_{16}H_{20}NO_5Mn$ (%): C 50.59, H 4.63, N 5.36. Found: C 50.62, H 4.76, N 5.76.

*2.1.2. Synthesis of ligands **4** and **5** general procedure*

A solution of Et_3N (0.1 ml, 0.7 mmol) and the amine **7** (0.183 g, 0.7 mmol) in benzene (3 ml) was added to a vigorously stirred solution of (*S*a) or (*R*a)-2-chloro-dinaphtho[2,1-d:1′,2′f] [1,2,3] dioxaphosphepine **7** [13] (0.245 g, 0.7 mmol) in benzene (7 ml). The mixture was heated up on stirring to be boiled and then cooled down to 20 °C. Solid HEt_3NCl was filtered off. The resulting solution was filtered through a short silica gel plug and the solvent evaporated at reduced pressure (40 Torr).

*2.1.2.1. N-methyl-N-[(R)-1-cymantrenylethyl]-(R)-dinaphtho[2,1-d:1′,2′-f] [1,2,3] dioxaphosphepine (**4**).* Yellow solid, 0.388 g (96% yield); mp, 47–48 °C; ^{31}P NMR ($CDCl_3$); δ_P: 148.3. ^{13}C NMR ($CDCl_3$): δ_C, ($J_{C,P}$, Hz): 18.7 (d, $J = 4.4$ Hz, Me), 25.8 (d, $J = 3.6$ Hz, NMe), 50.3 (d, $J = 52.0$ Hz, CH), 79.3, 82.7, 83.0, 83.3, 105.8 (*Cp* all), 121.5, 121.7, 122,4, 123.6 (d, $J = 4.8$ Hz), 124.5, 124.6, 126.0, 126.0, 126.6, 126.7, 128.1, 128.2, 129.9, 130.2, 130.6, 131.2, 132.4, 132.6, 149.0, 149.6 (d, $J = 5.6$ Hz) (Ar all), 224.5 (CO). Anal. Calc. for $C_{31}H_{23}NMnO_5P$ (%): C 64.70, H 4.03, N 2.43. Found: C 64.87, H 4.11, N 2.36.

*2.1.2.2. N-methyl-N-[(R)-1-cymantrenylethyl]-(S)-dinaphtho[2,1-d:1′,2′-f] [1,2,3] dioxaphosphepine (**5**).* Yellow solid, 0.35 g (87% yield); mp, 42–43 °C; ^{31}P NMR ($CDCl_3$); δ_P: 147.2. ^{13}C NMR ($CDCl_3$): δ_C, ($J_{C,P}$, Hz): 17.3 (d, $J = 6.1$ Hz, Me), 26.3 (d, $J = 7.2$ Hz, NMe), 49.6 (d, $J = 38.9$ Hz, CH), 78.6, 83.1, 83.5, 84.0, 105.5 (*Cp* all), 121.4, 121.7, 122,3, 123.8 (d, $J = 5.2$ Hz), 124.5, 124.7, 126.0, 126.0, 126.8, 126.9, 128.0, 128.2, 129.8, 130.2, 131.3, 131.2, 132.5, 132.6, 149.0, 149.6 (d, $J = 5.2$ Hz) (Ar all), 224.4 (CO). Anal. Calc. for $C_{31}H_{23}NMnO_5P$ (%): C 64.70, H 4.03, N 2.43. Found: C 64.85, H 4.16, N 2.32.

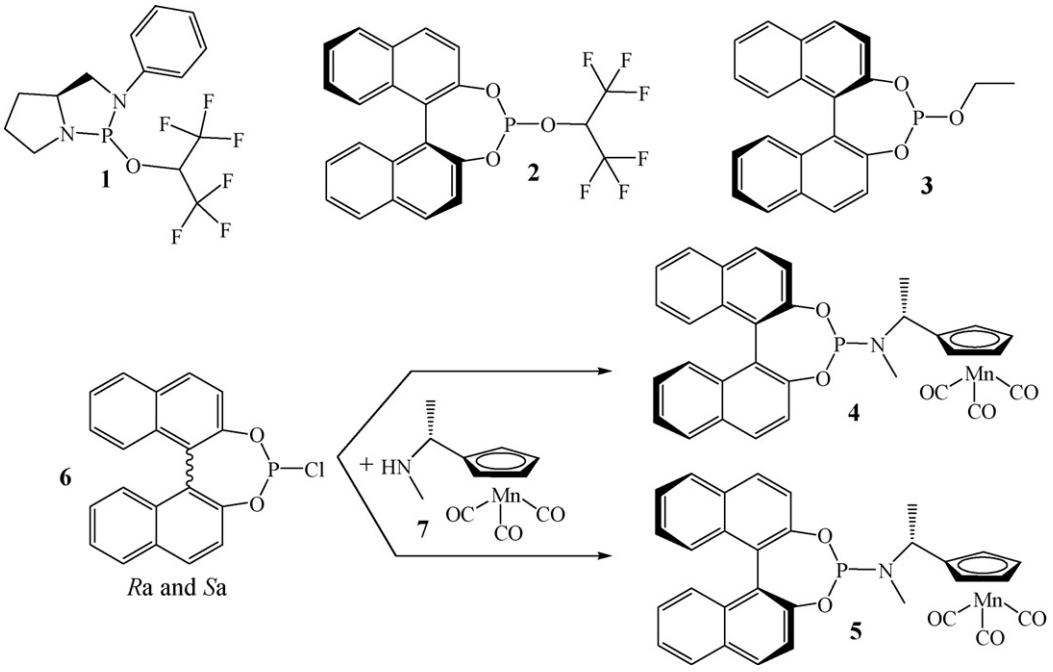
2.2. General procedure for hydrogenation experiments in $scCO_2$

The catalysts were prepared by adding the corresponding monodentate ligand (0.012 mmol) to a solution of $[Rh(cod)_2]BF_4$ (2.4 mg, 0.006 mmol) in CH_2Cl_2 (1 ml). The solution was stirred for 10 min before the solvent was removed in vacuo. The pre-formed catalysts (0.006 mmol) and substrate (0.6 mmol) were placed open to air into a 5 ml autoclave. The vessel was pressurized to 100 atm with hydrogen and then filled with $scCO_2$ by means of a syringe-press to a total pressure of 200 atm. The mixture was allowed to equilibrate to the reaction temperature of 35–36 °C (5 min) and stirred for 1.5–3 h. After stirring, the vessel was slowly depressurized. The reaction mixture was dissolved in CH_2Cl_2 (3 ml), the catalyst removed via a short silica gel column. The filtrate was concentrated in vacuo to afford the target product **9**.

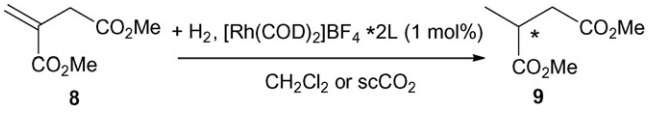
3. Result and discussion

Rh-catalyzed hydrogenation was examined using a short series of monodentate phosphite and phosphoramidite ligands **1**–**5** (Scheme 1). As initially shown, perfluorinated substituents can act as solubilizers for the P-ligands making the corresponding metal complexes sufficiently 'CO_2-philic' for a successful catalysis [7,14]. Based on these findings, we have chosen chiral ligands **1**, **2** with hexaflourisopropyl exocyclic substituents, synthesized by us previously [15,16] and the ligand **3** without fluorous ponytails to compare its catalytic properties [17]. Additionally, we prepared new diastereomeric phosphoramidite ligands **4**, **5** due to the known good solubility of cymantrene in $scCO_2$ [18].

The rhodium catalysts were formed with ligands **1**–**5** in situ by mixing a cationic Rh complex, $[Rh(COD)_2]BF_4$, with 2 equivalents of the chiral ligands in CH_2Cl_2 under argon. All complexes were first used in hydrogenation of dimethyl itaconate **8** in CH_2Cl_2 (Scheme 2), which is the conventional solvent for this reaction and usually gives better enantioselectivity and conversion for this substrate [2–6]. We also examined the effect of H_2 pressure on the reaction. The results, summarized in Table 1, show, that complete conversion may be obtained for all ligands **1**–**5** at 20 atm of hydrogen. Changes in H_2 pressure had



Scheme 1. Monodentate phosphite-type ligands.



Scheme 2. Asymmetric Rh-catalyzed hydrogenation of dimethyl itaconate.

little effect on the enantioselectivity (1–2%) in all cases, the only exception being ligand **2** that gave 56% ee with low conversion (28%) at 1.1 atm H_2, as we reported previously [15]. It should be noted that maximum enantioselectivity in CH_2Cl_2 among this series of chiral ligands was obtained with the cheap phosphite **3** (Table 1, entries 8 and 9). The diastereomeric cymantrene-derived ligands **4**, **5** afforded the product **9** in opposite absolute configuration and different enantioselectivity, the ligand **4** representing the matched case.

Hydrogenation of dimethyl itaconate in $scCO_2$ led to an exciting result (Table 2). A complete conversion of **8** was already achieved in 1.5–3 h with all the catalysts used (**1**–**4**/Rh), compared to 14–24 h in CH_2Cl_2. Enantioselectivities in all cases were comparable to those obtained in CH_2Cl_2. The catalysts with fluorinated ligands (**1**–**2**) gave from moderate to good ees in $scCO_2$, with a small (8–10%) decrease in ee, compared to CH_2Cl_2. The catalytic systems based on ligands **3** and **4** prove to be more effective. The maximum enantioselectivity (90% ee) in $scCO_2$ was obtained with phosphite **4**. Despite the small loss in ee (by 7%), the increase of the reaction rate by a factor of seven, compared to CH_2Cl_2, deserves special attention. It should be noted, that cymantren-based phosphoramidite **4** showed equal asymmetric induction in $scCO_2$ and in CH_2Cl_2, but in the case of $scCO_2$ the reaction rate again was much higher (1.5 h rather than 14 h for complete conversion). The high reaction rates in this case may be attributed not only to the high concentration of H_2 (100 atm), that is known to increase enantioselectivity and conversion in asymmetric hydrogenation in $scCO_2$, but also to the high diffusivity of gaseous hydrogen in the supercritical medium [19].

Table 1
Asymmetric Rh-catalyzed hydrogenation of dimethyl itaconate in CH_2Cl_2

Entry	Catalyst[a]	P_{H_2} (atm)	t (h)	Conversion (%)	ee (%)
1	**1**/Rh	5	36	98	54 (*S*)
2	**1**/Rh	20	24	100	52 (*S*)
3	**2**/Rh	1.1	24	26	56 (*S*)[b]
4	**2**/Rh	5	20	97	81 (*S*)
5	**2**/Rh	20	18	100	79 (*S*)
6	**3**/Rh	5	16	100	**97** (*R*)
7	**3**/Rh	20	14	100	95 (*R*)
8	**4**/Rh	5	20	100	80 (*R*)
9	**4**/Rh	20	16	100	79 (*R*)
10	**5**/Rh	5	24	87	14 (*S*)
11	**5**/Rh	20	18	100	13 (*S*)

[a] L/Rh = 2/1, 1 mol%, room temperature.
[b] Ref. [15].

Table 2
Asymmetric Rh-catalyzed hydrogenation of dimethyl itaconate in $scCO_2$

Entry	Catalyst[a]	P_{H_2} (atm)	t (h)	Conversion (%)	ee (%)
1	**1**/Rh	100	2	100	46 (*S*)
2	**2**/Rh	100	3	100	70 (*S*)
3	**3**/Rh	100	2	100	**90** (*R*)
4	**4**/Rh	100	1.5	100	81 (*R*)

[a] L/Rh = 2/1, 1 mol%.

4. Conclusions

In summary, we have demonstrated that high enantioselectivity (up to 90% ee) and complete conversion in the hydrogenation

of dimethyl itaconate may be obtained in $scCO_2$ with easily accessible monodentate phosphite-type ligands. The high reaction rates are attributed to the higher miscibility and higher diffusivity of gaseous hydrogen in the supercritical medium when compared to that in CH_2Cl_2. Since the present ligands (**1**–**4**) and CO_2 are unusually cheap and the reaction rates in $scCO_2$ are exceptionally high, the process may constitute an industrially viable approach to the asymmetric synthesis of 2-alkyl succinates, which were found to be potential pharmaceuticals [20,21].

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