Journal of Organometallic Chemistry 693 (2008) 3689–3691

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Chiral carborane-derived thiophosphites: A new generation of ligands for Rh-catalyzed asymmetric hydrogenation

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ARTICLE INFO

Article history:
Received 16 July 2008
Received in revised form 19 September 2008
Accepted 22 September 2008
Available online 27 September 2008

Keywords:
Thiophosphite ligands
Carboranes
Asymmetric hydrogenation
Rhodium

ABSTRACT

A new class of chiral monodentate ligands – carborane-containing thiophosphites have been synthesized and tested in the Rh-catalyzed asymmetric hydrogenation of prochiral olefins with the result of up to 99% ee. The dependence of the enantioselectivity on the electronic properties of the carboranyl substituent has been studied.

1. Introduction

Transition metal-catalyzed hydrogenation of prochiral olefins belongs to the most practical ways of producing many optically active organic compounds including intermediates for the pharmaceutical industry [1,2], and a broad range of chiral hydrogenation catalysts has been developed, most of which rely on chiral bidentate phosphorus ligands [3,4]. In recent years, increasing attention has been directed to chiral monodentate phosphites and phosphoramidites, due to their ready accessibility and efficiency in the Rh-catalyzed hydrogenation [5–8] and references cited therein. Nevertheless, another type of chiral trivalent phosphorus derivatives – thiophosphites – has not been previously reported. Such compounds are promising as novel unexploited ligands for asymmetric metal complex catalysis.

Recently, we designed a novel class of chiral mono- and bidentate phosphite-type ligands containing sterically congested carborane fragments and showed their high efficiency for the Rh-catalyzed asymmetric hydrogenation of functionalized olefins (up to 99.8% ee) [9–11]. Encouraged by these results we have now prepared the first representatives of chiral thiophosphite ligands bearing bulky *ortho*- and *meta*-9-dicarba-*closo*-dodecaborane fragments for an application in the Rh-catalyzed asymmetric hydrogenation.

2. Results and discussion

The new monodentate thiophosphites **4** and **5** were synthesized by a convenient one-step phosphorylation of the corresponding *ortho*- and *meta*-9-mercapto-dicarba-*closo*-dodecaboranes (**2** and **3**, Scheme 1). The products **4**, **5** were characterized by ^{31}P, ^{1}H and ^{11}B NMR spectroscopy and by elemental analysis (see Section 3). They are white solids and are air stable under ambient conditions.

Reaction of the thiophosphites **4**, **5** with $[Rh(COD)_2]BF_4$ (COD = 1,5-cyclooctadiene) afforded the cationic rhodium complexes **6**, **7** (Scheme 2). These compounds are stable in air and have moderate solubility in common organic solvents (especially complex **7**). ^{31}P NMR data for complexes **6** and **7** showed chemical shifts and $J_{P,Rh}$ coupling constants (see Section 3) similar to those of rhodium complexes with monodentate phosphite and phosphoramidite ligands [6,12–14].

Ligands **4** and **5** were first used in the Rh-catalyzed hydrogenation of the benchmark substrate, dimethyl itaconate (**8**, Scheme 3). The catalysts were formed *in situ* by mixing $[Rh(COD)_2]BF_4$, with 2 equiv of the chiral ligand **4** or **5** in CH_2Cl_2 under argon (Table 1). The enantioselectivities are influenced by the donor/acceptor properties of the 9-*ortho*- and 9-*meta*-carboranyl substituents [11]. The rhodium catalyst with ligand **4**, which has a strongly electron-donating 9-*ortho*-carboranyl group (δ_i = - 0.23), exhibited excellent enantioselectivity (98% ee) and complete conversion. It should be noted that changes in H_2 pressure in this case had no

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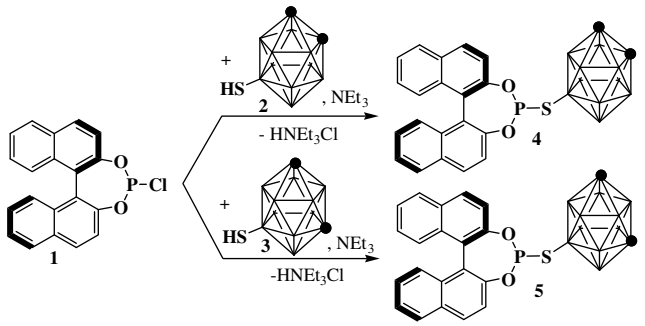
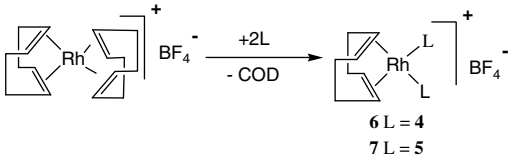
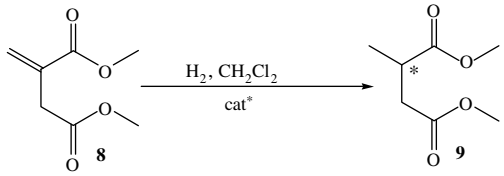
doi:10.1016/j.jorganchem.2008.09.032



Scheme 1. Synthesis of chiral carborane-containing thiophosphites.



Scheme 2. Synthesis of complexes **6** and **7**.



Scheme 3. Asymmetric hydrogenation of dimethyl itaconate.

Table 1
Asymmetric hydrogenation of **8**

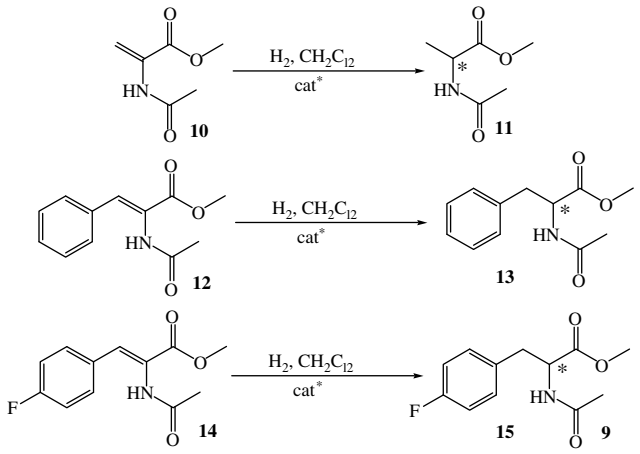
Entry	Catalyst	Substrate	*p* (atm)	*t* (h)	Conversion[a] (%)	ee[b] (%)
1	**4**/Rh	**8**	5	18	100	98 (*R*)
2	**4**/Rh	**8**	10	14	100	98 (*R*)
3	**6**	**8**	5	18	100	99 (*R*)
4	**5**/Rh	**8**	10	14	100	88 (*R*)
5	**7**	**8**	5	16	100	93 (*R*)

[a] Determined by ^{1}H NMR spectroscopy.
[b] Ee of **9** determined by HPLC (Daicel Chiralcel OD-H) 98/2 hexane/*i*-PrOH, 0.8 mL/min, 219 nm, $t(R)$ = 9.21 min, $t(S)$ = 16.14 min).

effect on the enantioselectivity (Table 1, entries 1 and 2). The less electron-donating 9-*meta*-carboranyl group ($\delta_i = -0.12$) in ligand **5** leads to a decrease in enantioselectivity (88% ee), compared to the isomeric ligand **4**. The use of the isolated cationic complexes **6** and **7** in the Rh-catalyzed hydrogenation of dimethyl itaconate showed some improvement in enantioselectivity (99% ee for complex **6** and 93% for **7**) compared to the catalytic systems formed *in situ*, when low (5 atm) hydrogen pressures were used.

To expand the utility of these ligands and further investigate the influence of the carborane component, we also examined the Rh-catalyzed enantioselective hydrogenation of α-dehydro amino acids esters: methyl 2-acetamidoacrylate (**10**), (*Z*)-methyl 2-acetamido-3-phenylacrylate (**12**) and (*Z*)-methyl 2-acetamido-3-(4-fluorophenyl)acrylate (**14**) (Scheme 4).

In the hydrogenation of **10**, for both ligands **4** and **5** complete conversion and high enantioselectivity (94% and 95% ee) was observed, independent of the hydrogen pressure (5 or 10 atm, Table 2, entries 1–4). Hydrogenation of the more sterically hindered substrate **12** with the electron-withdrawing phenyl substituent showed that ligand **4** (bearing a stronger electron-donating 9-*ortho*-carboranyl group) gave product **13** with better enantiomeric excess, compared to the catalytic system based on ligand **5** (Table 2, entries 5 and 6). Ligands **4**, **5** showed the same trend in the hydrogenation of the fluor-containing enamide **14** (Scheme 4, Table 2); the stronger electron-donating thiophosphite **4** showed better enantioselectivity. The ligand **5** bearing the weaker electron-donating 9-*meta*-carboranyl substituent gave not only lower ee, but also incomplete conversion in 18 h.



Scheme 4. Asymmetric hydrogenation of α-dehydro amino acids esters **10**, **12**, **14**.

Table 2
Asymmetric hydrogenation of α-dehydro amino acids esters

Entry	Catalyst	Substrate	*p* (atm)	*t* (h)	Conversion[a] (%)	Ee[b] (%)
1	**4**/Rh	**10**	5	18	100	94 (*S*)
2	**4**/Rh	**10**	10	14	100	94 (*S*)
3	**5**/Rh	**10**	5	16	100	95 (*S*)
4	**5**/Rh	**10**	10	12	100	95 (*S*)
5	**4**/Rh	**12**	10	16	100	88 (*S*)
6	**5**/Rh	**12**	10	18	100	70 (*S*)
7	**4**/Rh	**14**	10	18	100	75 (*S*)
8	**5**/Rh	**14**	10	18	85	50 (*S*)
9	**5**/Rh	**14**	10	22	100	50 (*S*)

[a] Determined by ^{1}H NMR spectroscopy.
[b] Ee of **11** determined by HPLC (Daicel Chiralcel OJ-H) 95/5 hexane/*i*-PrOH, 1.0 mL/min, 219 nm, $t(R)$ = 14.01 min, $t(S)$ = 16.01 min). Ee of **13** determined by HPLC (Daicel Chiralcel OD-H) 9/1 hexane/*i*-PrOH, 0.9 mL/min, 219 nm, $t(R)$ = 11.8 min, $t(S)$ = 15.8 min). Ee of **15** determined by HPLC (Daicel Chiralcel OD-H) 9/1 hexane/*i*-PrOH, 0.9 mL/min, 219 nm, $t(R)$ = 12.2 min, $t(S)$ = 15.2 min), *t* **14** = 18 min).

In summary, we have designed and synthesized the first examples of sterically congested carborane-containing chiral thiophosphite ligands for use in asymmetric catalysis. Initial studies of the monodentate carboranylthiophosphite ligands resulted in excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of prochiral olefins (up to 99% ee). These ligands can also be regarded as attractive candidates for other asymmetric transition metal-catalyzed reactions in traditional and alternative 'green' solvents, such as $scCO_2$ [8–9].

3. Experimental

All reactions were carried out under dry argon atmosphere in freshly dried and distilled solvents. ^{1}H (400.13 MHz), ^{11}B (128.38 MHz) and ^{31}P (161.98 MHz) NMR spectra were recorded

with an Avance 400 instrument. Chemical shifts (ppm) are given relative to Me_4Si (^1H), $BF_3(OEt_2)$ (^{11}B NMR) and 85% H_3PO_4 (^{31}P NMR). Elemental analyses were performed at the Laboratory of Microanalysis (Institute of Organoelement Compounds, Moscow). (*R*)-2-Chloro-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2] dioxaphosphine (**1**) [15], *ortho*- and *meta*-9-mercapto-dicarba-*closo*-dodecarboranes **2** and **3** were prepared as published [16].

3.1. Preparation of ligands **4**, 5 (general technique)

ortho- or *meta*-9-mercapto-dicarba-*closo*-dodecaborane (**2** or **3**) (0.176 g, 1 mmol) was added to a vigorously stirred solution of (*R*)-2-chloro-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2] dioxaphosphine (0.350 g, 1 mmol) and NEt_3 (0.135 mL, 1 mmol) in benzene (25 mL). The mixture was stirred for 10 min. The reaction mixture was then heated at reflux for 20 min, cooled and filtered. Benzene was removed under reduced pressure (40 torr) and the crude products **4** or **5** were purified by flash column chromatography (silica gel, toluene) to give the desired thiophosphites as white powders after evaporation of the solvent. Yield: 84% for **4** and 88% for **5**.

3.2. (Ra)-2-(ortho-Carboran-9-ylthio)-dinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine (**4**)

$^{31}P\{H\}$ NMR ($CDCl_3$): 223.3 (q, $J_{P,B}$ = 18 Hz). ^{11}B NMR ($CDCl_3$): 4.3 (s, 1B), −1.7 (d, J = 148 Hz, 1B), 8.4 (d, J = 153 Hz, 2B), −14.1 (m, 6B). ^1H NMR ($CDCl_3$): 1.14–3.34 (m, 9H, carborane), 3.40 (s, 1H, CH carborane), 3.54 (s, 1H, CH carborane), 7.23–7.52 (m, 8H, aryl), 7.91–7.98 (m, 4H, aryl). Anal. Calc. for $C_{22}H_{23}B_{10}O_2PS$: C, 53.86; H, 4.73; B, 22.04. Found: C, 53.98; H, 4.80; B, 22.11%.

3.3. (Ra)-2-(meta-Carboran-9-ylthio)-dinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine (**5**)

$^{31}P\{H\}$ NMR ($CDCl_3$): 223.6 (q, $J_{P,B}$ = 14 Hz). ^{11}B NMR ($CDCl_3$): −2.5 (s, 1B), −5.6 (d, J = 164 Hz, 2B), −9.3 (d, J = 152 Hz, 1B), −10.9 to 15.5 (m, 4B), −17.5 (d, J = 182 Hz, 1B), −20.8 (d, J = 182 Hz, 1B). ^1H NMR ($CDCl_3$): 1.33–3.65 (m, 9H, carborane), 3.04 (s, 2H, CH carborane), 7.21–7.56 (m, 8H, aryl), 7.89–8.02 (m, 4H, aryl). Anal. Calc. for $C_{22}H_{23}B_{10}O_2PS$: C, 53.86; H, 4.73; B, 22.04. Found: C, 53.95; H, 4.86; B, 22.16.

3.4. General procedure for the synthesis of rhodium complexes **6**, 7

A solution of compound **4** or **5** (0.029 g, 0.06 mmol) in CH_2Cl_2 (6 mL) was added dropwise during 15 min to a vigorously stirred solution of $[Rh(COD)_2]BF_4$ (0.012 g, 0.03 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred for additional 15 min and concentrated at reduced pressure to a volume of ca. 0.5 mL, and diethyl ether (12 mL) was added. The precipitated solid was separated by centrifugation and dried in vacuo (1 mm Hg) for 0.5 h.

3.5. $[Rh(COD)(4)_2]BF_4$ (**6**)

Yellow solid, poorly soluble in organic solvents, m.p. 112–114 °C (dec), $^{31}P\{H\}$ NMR ($CDCl_3$): 184.4 (br d, $J_{P,Rh}$ = 240 Hz). Anal. Calc. for $C_{52}H_{58}B_{21}F_4O_4P_2RhS_2$: C, 48.83; H, 4.57; B, 17.75. Found: C, 48.96; H, 4.65; B, 17.70.

3.6. $[Rh(COD)(5)_2]BF_4$ (**7**)

Yellow solid, moderately soluble in organic solvents, m.p. 120–124 °C (dec), $^{31}P\{H\}$ NMR ($CDCl_3$): 182.6 (br d, $J_{P,Rh}$ = 238 Hz). Anal. Calc. for $C_{52}H_{58}B_{21}F_4O_4P_2RhS_2$: C, 48.83; H, 4.57; B, 17.75. Found: C, 48.92; H, 4.68; B, 17.86.

3.7. General procedure for asymmetric hydrogenation

$[Rh(COD)_2]BF_4$ (2.4 mg, 0.006 mmol), ligand (**4** or **5**, 5.8 mg, 0.012 mmol) or the corresponding complex **6** or **7** (0.006 mmol), the appropriate substrate (**8**, **10**, **12**, **14**, 0.6 mmol) and CH_2Cl_2 (5 mL) were placed in a 25-mL autoclave. The autoclave was closed and flushed three times with argon, and then the hydrogenation was performed at room temperature under H_2 pressure of 5 or 10 atm during 12–22 h. After releasing the hydrogen gas, the reaction mixtures were diluted with hexane, passed through a short silica gel plug using hexane as the eluent and analysed by HPLC and ^1H NMR spectroscopy.

Acknowledgement

This work was supported by INTAS Open Call Grant No. 05-1000008-8064.

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