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Ligand effects in the hydrogenation of methacycline to doxycycline and epi-doxycycline catalysed by rhodium complexes Molecular structure of the key catalyst [*closo*-3,3-($\eta^{2,3}$-$C_7H_7CH_2$)-3,1,2-$RhC_2B_9H_{11}$]

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Abstract

The catalytic reduction of the exocyclic methylene group of methacycline (**A**) leads to the formation of two diastereoisomers, doxycycline (**B**, the α-epimer) and 6-epi-doxycycline (**C**, the β-epimer), with a selectivity which markedly depends on the nature of hydrocarbon and carborane ligands of *closo*-(π-cyclodienyl)rhodacarborane catalysts. Neutral norbornadienyl complexes with unsubstituted carborane ligands [*closo*-3,3-($\eta^{2,3}$-$C_7H_7CH_2$)-3,1,2-$RhC_2B_9H_{11}$] (**1**) and [*closo*-2,2-($\eta^{2,3}$-$C_7H_7CH_2$)-2,1,7-$RhC_2B_9H_{11}$] (**7**) are more active and afford higher selectivity in the formation of doxycycline than those having mono- or di-substituents at the carborane cage, [*closo*-3,3-(cyclodienyl)-1-R-2-R′-3,1,2-$RhC_2B_9H_9$] (R = H, R′ = Me, $PhCH_2$; R = R′ = Me; cyclodienyl = $\eta^{2,3}$-$C_7H_7CH_2$ or η-$C_{10}H_{13}$) as well as those from the closely related series of η^5-cyclopentadienyl complexes [($\eta^{2,3}$-$C_7H_7CH_2$)Rh(η^5-C_5R_n)]$^+PF_6^-$ ($R_n = H_5$, Me_5, or H_2-1,2,4-Ph_3). Mechanistic aspects of the hydrogenation reaction of methacycline are sketched. The results of the X-ray diffraction study of the best catalyst **1** are reported. © 1997 Elsevier Science S.A.

Keywords: Rhodium; Boron; Hydrogenation; Methacycline; Doxycycline; Rhodacarboranes; X-ray diffraction study

1. Introduction

Stereoselective synthesis has been a focal point for much of the most interesting new organic chemistry developed over the past few years. With growing maturity of the topic, the realization of new opportunities offered by homogeneous transition metal catalysis [1] has been steadily increasing. Stereoselectivity in this case is induced by means of the catalytic entity and this is often achieved by selection of a suitable ligand environment of the central metal atom of the catalytically active complex.

Introduction of chirality in drugs in the course of their synthesis is of particular importance (for recent leading references on asymmetric hydrogenation, see Ref. [2]). Some of the recently discovered novel and potentially active metallacarborane systems based upon cyclodienyl-containing closo-rhodacarboranes [3] were found to be exceptionally effective for the stereoselective hydrogenation of methacycline (**A**) into doxycycline (**B**) (Scheme 1) [4], a potent tetracycline antibiotic extensively used in chemotherapy [5].

Among the series of different metallacarboranes previously tested as hydrogenation catalyst precursors for the title reaction [4,6], [*closo*-3,3-($\eta^{2,3}$-$C_7H_7CH_2$)-3,1,2-$RhC_2B_9H_{11}$] (**1**) proved to exhibit an excellent catalytic activity in the formation of doxycycline, with an efficiency equal or superior to that reported for patent systems [7,8]. Owing to the practical importance

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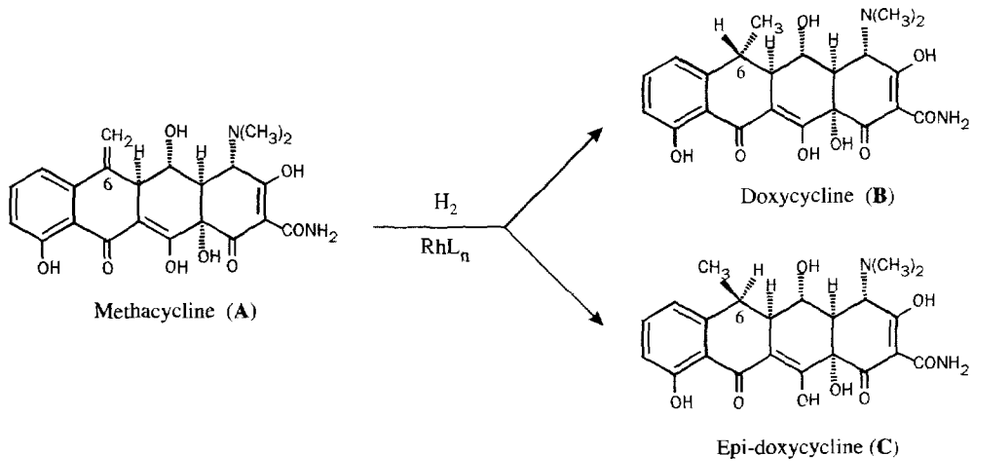


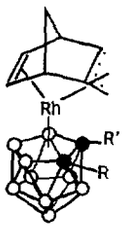
Scheme 1.

of this result, we decided to introduce some modifications in the ligand sphere of complex **1** (Scheme 2) in order to determine which characteristics of organic and carborane ligands attached to the rhodium centre control the stereoselectivity in this catalytic process.

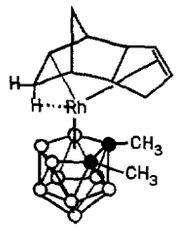
Since the π-dicarbollyl ligands, $[nido\text{-}C_2B_9H_{11}]^{2-}$, are known to resemble closely the π-R_n-cyclopentadienyl ligands $[C_5R_n]^-$, especially those with $R_n = Me_5$ [9,10], some of the related cationic π-($\eta^{2,3}$-norbornadienyl)cyclopentadienylrhodium derivatives have also been prepared and tested as catalyst precursors. The clearly crucial role of the nature of the ligands at the rhodium centre on the catalytic activity of the systems studied was confirmed.

2. Results and discussion

The rhodacarboranes [*closo*-3,3-($\eta^{2,3}$-$C_7H_7CH_2$)-3,1,2-$RhC_2B_9H_{11}$] (**1**) and [*closo*-2,2-($\eta^{2,3}$-$C_7H_7CH_2$)-2,1,7-$RhC_2B_9H_{11}$] (**7**) with unsubstituted isomeric dicarbollyl ligands have been found to be more active and to exhibit higher selectivity than their cage-substituted analogues **2**–**6** (Table 1).

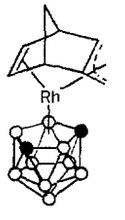


	R	R'
(1)	H	H
(2)	H	Me
(3)	Me	H
(4)	H	Bn
(5)	Bn	H
(6)	Me	Me

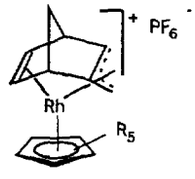


● C
O BH

(8)



(7) ● CH
O BH



	R_5
(9)	H_5
(10)	Me_5
(11)	H_2-1,2,4-Ph_3

Scheme 2.

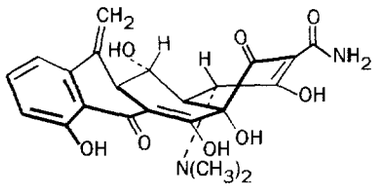
Table 1
Rhodium-catalysed hydrogenation of methacycline (**A**) to doxycycline (**B**) and epi-doxycycline (**C**) [a]

Catalyst	Conversion (%)	Yields (%)	
	A	**B**	**C**
1	99	96	2.5
2	45	37	4
3	35	31	2
4	27.5	26	1
5	15	13	0.5
6	84	30	39
7 [b]	98	95	2.5
(±)-**8**	78	39.5	29
(+)-**8**	68	37	16
(±)-**9**	99	12	71
(+)-**9**	95.5	12.5	71.5
10	51	45	5.5
11	98	12	79405–412

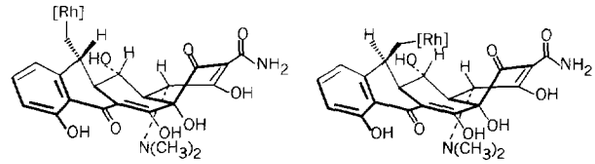
[a] Reaction conditions: 2 cm^3 of a 20 $mmol\,l^{-1}$ solution of methacycline hydrochloride in methanol; catalyst concentration, 2 $mmol\,l^{-1}$; P_{H_2}, 100 atm; temperature, 60 °C; reaction time, 4 h.
[b] A 'large'-scale hydrogenation reaction using 23 mg of **7** (instead of 1.4 mg in a typical run) afforded the same results. ^{1}H NMR analysis of the recovered catalyst precursor (7 mg, 30%) proved this species has retained its initial structure.

Both diastereoisomeric pairs of monomethyl- and monobenzyl-substituted closo-rhodacarboranes (**2**, **3** and **4**, **5**), with (*SS,RR*)- and (*SR,RS*)-configurations respectively [11], exhibited low conversions of methacycline (ca. 40%) but high selectivities for the pharmacologically important molecule (**B**); on the contrary, the dimethyl-substituted closo-rhodacarboranes, *closo*-3,3-($\eta^{2,3}$-$C_7H_7CH_2$)-1,2-Me_2-3,1,2-$RhC_2B_9H_9$ (**6**) and *closo*-3,3,3-(η-$C_{10}H_{13}$)-1,2-Me_2-3,1,2-$RhC_2B_9H_9$ (**8**), both in racemic and optically active forms [12], led to somewhat higher conversions of methacycline but with poor selectivity.

The π-(R_n)-cyclopentadienylrhodium complexes with $\eta^{2,3}$-norbornadienyl ligand [($\eta^{2,3}$-$C_7H_7CH_2$)Rh(η^5-C_5R_n)]$^+PF_6^-$ ($R_n = H_5$ (**9**), $R_n = Me_5$ (**10**), $R_n = H_2$-1,2,4-Ph_3 (**11**)) exhibited considerable differences in reactivity: complexes **9** and **11** were highly active and afforded mainly epi-doxycycline (**C**), while complex **10** was much less active but more selective in the formation of doxycycline (**B**). The contrary selectivity of complexes **9** and **11** compared with that of **10** and metallacarboranes **1**–**8** is in accordance with the well-known similarity of the steric and electronic requirements of the π-dicarbollyl and the π-C_5Me_5 ligands [10]. The similarity of the catalytic behaviour of complexes **9** and **11** is due to the fact that the introduction of the phenyl substituents in the cyclopentadienyl ligand changes mostly the steric characteristics of the ligand, but hardly influences its electronic properties. This idea is correlated to the results on comparative redox potentials of the first row transition metal complexes with C_5HPh_4 and C_5H_5 ligands [13].



Scheme 3.



Scheme 4.

Finally, comparison of the reactivity patterns of racemic complexes **8** and **9** with those of their optically active forms showed just some slight differences for complex **8** and no differences at all for complex **9**, thus raising some doubts concerning the possible influence of the chirality of the dicyclopentadienyl and 2-methyl-enenorbornadienyl ligands in the catalytic process.

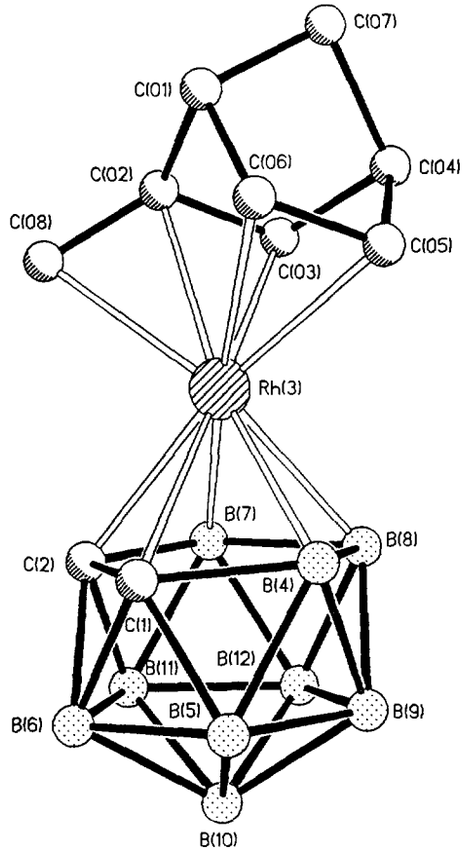


Fig. 1. Molecular structure of [*closo*-3,3-($\eta^{2,3}$-$C_7H_7CH_2$)-3,1,2-$RhC_2B_9H_{11}$] (**1**).

Table 2
Bond lengths (Å) and selected bond angles (deg) for **1**

	A	B	C
Rh(3A)–C(03A)	2.132(11)	2.126(12)	2.133(12)
Rh(3A)–B(4A)	2.173(12)	2.191(14)	2.153(14)
Rh(3A)–C(05A)	2.190(11)	2.200(12)	2.161(13)
Rh(3A)–C(02A)	2.197(10)	2.203(12)	2.210(10)
Rh(3A)–C(2A)	2.213(12)	2.208(12)	2.232(11)
Rh(3A)–C(06A)	2.231(11)	2.216(13)	2.207(11)
Rh(3A)–B(7A)	2.235(13)	2.209(14)	2.223(12)
Rh(3A)–B(BA)	2.241(11)	2.244(13)	2.232(12)
Rh(3A)–C(1A)	2.243(12)	2.223(11)	2.232(15)
Rh(3A)–C(08A)	2.312(12)	2.281(14)	2.336(14)
C(1A)–C(2A)	1.58(2)	1.57(2)	1.59(2)
C(1A)–B(5A)	1.68(2)	1.68(2)	1.67(2)
C(1A)–B(6A)	1.71(2)	1.74(2)	1.68(2)
C(1A)–B(4A)	1.71(2)	1.69(2)	1.70(2)
C(2A)–B(11A)	1.68(2)	1.69(2)	1.68(2)
C(2A)–B(7A)	1.72(2)	1.73(2)	1.73(2)
C(2A)–B(6A)	1.73(2)	1.70(2)	1.72(2)
B(4A)–B(9A)	1.78(2)	1.79(2)	1.81(2)
B(4A)–B(5A)	1.81(2)	1.82(2)	1.82(2)
B(4A)–B(8A)	1.81(2)	1.83(2)	1.81(2)
B(5A)–B(9A)	1.76(2)	1.78(2)	1.78(2)
B(5A)–B(10A)	1.76(2)	1.76(2)	1.78(2)
B(5A)–B(6A)	1.77(2)	1.78(2)	1.75(2)
B(6A)–B(10A)	1.77(2)	1.77(2)	1.78(2)
B(6A)–B(11A)	1.77(2)	1.79(2)	1.79(2)
B(7A)–B(11A)	1.75(2)	1.80(2)	1.79(2)
B(7A)–B(12A)	1.79(2)	1.81(2)	1.78(2)
B(7A)–B(8A)	1.82(2)	1.82(2)	1.82(2)
B(8A)–B(12A)	1.78(2)	1.81(2)	1.81(2)
B(8A)–B(9A)	1.78(2)	1.81(2)	1.78(2)
B(9A)–B(10A)	1.76(2)	1.77(2)	1.79(2)
B(9A)–B(12A)	1.77(2)	1.79(2)	1.76(2)
B(10A)–B(12A)	1.78(2)	1.76(2)	1.76(2)
B(10A)–B(11A)	1.78(2)	1.78(2)	1.79(2)
B(11A)–B(12A)	1.79(2)	1.76(2)	1.77(2)
C(01A)–C(06A)	1.49(2)	1.52(2)	1.49(2)
C(01A)–C(07A)	1.51(2)	1.52(2)	1.54(2)
C(01A)–C(02A)	1.57(2)	1.59(2)	1.52(2)
C(02A)–C(08A)	1.37(2)	1.37(2)	1.40(2)
C(02A)–C(03A)	1.45(2)	1.43(2)	1.43(2)
C(03A)–C(04A)	1.52(2)	1.52(2)	1.54(2)
C(04A)–C(05A)	1.52(2)	1.45(2)	1.52(2)
C(04A)–C(07A)	1.58(2)	1.55(2)	1.56(2)
C(05A)–C(06A)	1.45(2)	1.37(2)	1.41(2)
C(2A)–C(1A)–B(4A)	110.4(9)	111.2(9)	111.6(11)
C(1A)–C(2A)–B(7A)	113.4(9)	114.0(10)	112.2(10)
C(1A)–B(4A)–B(8A)	106.8(9)	106.4(10)	106.6(10)
C(2A)–B(7A)–B(8A)	104.7(9)	103.7(10)	105.2(9)
B(4A)–B(SA)–B(7A)	104.4(9)	104.4(10)	104.0(9)
C(06A)–C(01A)–C(07A)	105.8(10)	101.7(11)	104.8(12)
C(06A)–C(01A)–C(02A)	98.1(9)	95.8(10)	99.1(10)
C(07A)–C(01A)–C(02A)	101.4(11)	97.4(11)	101.8(12)
C(08A)–C(02A)–C(03A)	125.6(12)	124.4(14)	125.5(12)
C(08A)–C(02A)–C(01A)	121.1(12)	120.2(14)	121.1(13)
C(03A)–C(02A)–C(01A)	104.8(10)	106.4(11)	104.6(10)
C(02A)–C(03A)–C(04A)	105.1(11)	105.0(11)	106.0(11)
C(05A)–C(04A)–C(03A)	97.9(9)	99.9(11)	96.6(11)
C(05A)–C(04A)–C(07A)	101.1(11)	102.8(11)	102.4(11)
C(03A)–C(04A)–C(07A)	102.4(10)	100.4(11)	100.9(11)
C(06A)–C(05A)–C(04A)	106.5(11)	107.7(12)	106.8(i2)
C(05A)–C(06A)–C(01A)	104.5(12)	107.5(12)	105.3(12)
C(01A)–C(07A)–C(04A)	93.7(9)	95.3(10)	92.9(10)

Elucidation of the reasons for selectivity of this catalytic process is by no means an easy task. It is clear-cut, however, that complexes with unsubstituted *ortho*- (**1**) or *meta*-carborane (**7**) ligands exhibit higher catalytic activity and selectivity than their substituted analogues, therefore indicating that severe steric requirements have to be met in this hydrogenation process.

It is normally considered that the shape of the substrate and the presence of proximate functional groups are of paramount importance in deciding which face of the molecule is coordinated to the catalyst. It has been shown by an X-ray diffraction study [14] that methacycline has a definite U-shape (Scheme 3), typical of tetracyclines.

According to Heggie [14], on the basis of the X-ray structure, one could predict that the convex α-face of the molecule was less hindered than the concave β-face, and hence the preferred approach would give rise to the β-methyl isomer. One could also invoke the fact that a proximate homoallylic hydroxyl group can participate in the coordination of the substrate on the catalyst. Both these effects could probably be operating. This simplistic approach may account for the formation of an excess of epi-doxycycline with complexes **9** and **11**. This approach, however, does not explain the stereoselectivity of the synthesis of the α-isomer in the presence of complexes **1–5, 7**, or **10**. One objection that could be raised is that methacycline hydrochloride was used instead of the neutral methacycline whose X-ray structure is known, and that the shape of the substrate coordinated on the catalyst is very different from that given in the X-ray analysis. Another possible objection may lie in the fact that it is not the initial approach of the substrate, nor the stability of the intermediate alkene–rhodium complex which makes the difference here but, rather, the stability of the alkyl–rhodium species (Scheme 4). The equatorial-type organo-rhodium species could be more stable than the axial-type species, even though this is formed from the probably less stable complex resulting from the coordination of the most hindered β-face of the substrate to rhodium. Furthermore, this less favoured coordination mode should not benefit from the additional stabilization from complexation with the homoallylic proximate alcohol. If we admit that the hydrogen insertion reaction is reversible and that the rate determining step is the insertion of the second hydrogen atom, then our prediction would be that the α-epimer would be formed preferably [14].

Further studies should be undertaken to elucidate the mechanism of the hydrogenation of methacycline into doxycycline. Research continues with the objectives to improve the level of stereocontrol and also to understand the nature of the interactions which control the stereoselectivity in this process.

Among the metallacarborane complexes **1–8**, the least substituted closo-rhodacarboranes **1** and **7** proved to be the most effective catalyst precursors for hydrogenation of methacycline into doxycycline. In order to examine the structural peculiarities of complex **1**, its X-ray diffraction study has been undertaken (Fig. 1, Table 2). Although the molecule of complex **1** is chiral due to the asymmetry of the dienyl ligand, the centrosymmetric crystal is naturally racemic and contains both enantiomers. In the crystal structure there are three independent molecules of **1** exhibiting quite similar geometry. All three molecules show the same orientation of the dienyl ligand relative to the coordinating C_2B_3 open face, so that allylic C(03)–C(02)–C(08) fragment of the hydrocarbon ligand projects over C(2)–B(7) bond of the carborane cage. It is noteworthy that almost the same orientation of norbornadienyl ligand was found earlier in the solid state structure of the dimethyl-substituted analogue (**6**) [15]. These results, as well as those of preliminary molecular mechanics calculations of molecules **1** and **6** [11], indicate that the steric effects in these complexes are of minor importance. The similarity of the orientations of the dienyl ligand relative to the pentagonal face of the carborane cage in molecule **6** and in all three independent molecules in the structure of **1** suggests that such orientation is primarily determined by the electronic factors. The bond lengths involving carbon atoms of the dienyl ligand in the structure of **1** are close to those found in a number of neutral or cationic rhodium complexes with $\eta^{2,3}$-allylolefinic ligands [15,16]. The geometry of the dicarbollyl ligands is unexceptional [17,18].

3. Experimental section

3.1. General methods

^1H and ^{13}C NMR spectra of complexes **10** and **11** were recorded in CD_2Cl_2 solution with TMS as an internal standard on a Bruker AM-400 spectrometer. Elemental analyses were carried out in the Analytical Laboratory of the Institute of Organoelement Compounds of the Russian Academy of Sciences.

3.2. Synthesis of rhodacarboranes 1–8

Complexes **1–7** [15] and **8** [12,19] were synthesized according to the literature. Further studies on diastereoisomeric complexes **4** and **5** in the individual forms, including their full characterization by spectroscopy and by X-ray diffraction studies, will be published in due course [11]. Complexes **9**, both in racemic and optically active forms, were prepared as described in Ref. [20] and Ref. [21] respectively.

3.3. Synthesis of complexes **10** and **11**

3.3.1. $[Rh(\eta^5\text{-}C_7H_7CH_2)(\eta^5\text{-}C_5(CH_3)_5]^+PF_6^-$ (**10**)

To a solution of dimeric complex $[Rh(\eta^4\text{-}C_7H_7CH_2OH)Cl]_2$ (100 mg, 0.19 mmol) in dry THF, slightly more than two-fold excess of Cp^*Na (solution in THF, 65 mg, 10.5 cm^3) was added dropwise at room temperature (24 °C) under argon. After stirring for 2 h the reaction was quenched with water (1 cm^3), the solvent was evaporated to dryness, and the residue treated with ether (20 cm^3). The ethereal solution of $Cp^*Rh(\eta^4\text{-}C_7H_7CH_2OH)$ was then washed with brine (2 × 10 cm^3) and dried over anhydrous Na_2SO_4 overnight. After filtration, several drops of concentrated H_2SO_4 were added to the ether solution. The semi-solid precipitate was extracted by water (2 × 5 cm^3) and added to a solution of slight excess of $NaPF_6$ in water. The amorphous yellow precipitate was filtered off to give crude **10** (70 mg, 72%). An analytically pure complex **10** was obtained by recrystallization from CH_2Cl_2–*n*-hexane. Anal. Found: C, 44.60; H, 5.18. $C_{18}H_{24}F_6PRh$. Calc.: C, 44.26; H, 4.92%. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.11 (s, 1H, $H_{8\text{-syn}}$), 3.81 (m, 1H, $H_{4(1)}$), 3.70 (q-like, 1H, $H_{5(6)}$), 3.54 (q-like, 1H, $H_{6(5)}$), 3.35 (m, 1H, H_3), 3.31 (m, 1H, $H_{1(4)}$), 2.94 (s, 1H, $H_{8\text{-anti}}$), 1.94 (s, 15H, Me), 1.70 (d, J_{AB} = 10.3 Hz, $H_{7\alpha(\beta)}$), 1.59 (dt, J_{AB} = 10.3 Hz, J_t = 1.6 Hz, $H_{7\beta(\alpha)}$); ^{13}C NMR [3] (100.6 MHz, CD_2Cl_2) δ 103.9 (d, J_{C-Rh} = 5.4 Hz, C-Cp), 99.3 (d, J_{C-Rh} = 2.1 Hz, C_2), 74.8 (d, J_{C-Rh} = 7.3 Hz, C_8), 56.81 (d, J_{C-Rh} = 7.2 Hz, $C_{5(6)}$), 55.7 (d, J_{C-Rh} = 6.4 Hz, $C_{6(5)}$), 54.4 (d, J_{C-Rh} = 2.4 Hz, C_7), 46.9 (s, $C_{1(4)}$), 43.2 (s, $C_{4(1)}$), 42.8 (d, J_{C-Rh} = 8.2 Hz, C_3), 10.3 (s, Me).

3.3.2. $[Rh(\eta^5\text{-}C_7H_7CH_2)(\eta^5\text{-}1,2,4\text{-}(C_6H_5)_3\text{-}C_5H_2]^+PF_6^-$ (**11**)

By an analogous method, complex **11** was obtained in 68% yield using a freshly prepared solution of 1,2,4-$Ph_3C_5H_2Li$ and the dimeric complex $[Rh(\eta^4\text{-}C_7H_7CH_2OH)Cl]_2$. Anal. Found: C, 57.84; H, 4.00. $C_{31}H_{26}F_6PRh$. Calc.: C, 57.58; H, 4.02%. ^{1}H NMR [4] (400 MHz, CD_2Cl_2) δ 7.6–7.3 (m, 15H, Ph), 6.80 (dd, 1H, J_{AB} = 2.1 Hz, J_d = 0.9 Hz, $H_{3(5)}$-Cp), 6.66 (dd, 1H, J_{AB} = 2.1 Hz, $J_d \sim$ 0.5 Hz, $H_{5(3)}$-Cp), 5.40 (s, 1H, $H_{8\text{-syn}}$), 3.96 (q-like, 1H, H_5), 3.87 (m, 1H, H_4), 3.83 (m, 1H, H_3), 3.70 (q-like, 1H, H_6), 3.38 (m, 1H, H_1), 3.09 (s, 1H, $H_{8\text{-anti}}$), 1.75 ($d_{br.}$, 1H, J_{AB} = 10.6 Hz, $H_{7\alpha(\beta)}$), 1.64 (dt, 1H, J_{AB} = 10.6 Hz, J_t = 1.7 Hz, $H_{7\beta(\alpha)}$). ^{13}C NMR [5] (100.6 MHz, CD_2Cl_2) δ 131.0, 130.7, 130.4, 130.32, 130.25, 129.85, 129.74, 129.71, 129.67, 128.7, 127.0 (s, Ph), 111.3, 111.0, 109.2 (d, J_{C-Rh} = 4.2 Hz, 1,2,4-C-Cp), 98.1 (d, J_{C-Rh} = 3.3 Hz, C_2), 87.50, 86.43 (d, J_{C-Rh} = 5.2 Hz, 3,5-C-Cp), 76.3 (d, J_{C-Rh} = 9.8 Hz, C_8), 59.4 (d, J_{C-Rh} = 7.4 Hz, $C_{5(6)}$), 57.3 (d, J_{C-Rh} = 6.7 Hz, $C_{6(5)}$), 55.2 (d, J_{C-Rh} = 3.0 Hz, C_7), 48.1 (d, J_{C-Rh} = 8.3 Hz, C_3), 47.5 (s, $C_{1(4)}$), 43.0 (s, $C_{4(1)}$).

3.4. X-ray diffraction study

Although a number of solvents appeared to be suitable for crystallization of **1**, our numerous attempts to find the appropriate solvents and conditions to grow high quality crystals for X-ray diffraction study were unsuccessful. The more-or-less suitable crystals were finally obtained by very slow crystallization of **1** from a solution of 1,2-dichloroethane–*n*-hexane in 3:2 ratio.

3.4.1. Crystal data for complex **1**

$C_{10}H_{20}B_9Rh$, M = 340.46, monoclinic, at −125 °C a = 18.042(10), b = 9.197(4), c = 26.686(11) Å, β = 105.21(4)° (by least squares refinement for 24 reflections in the range $20 < 2\theta < 22$, λ = 0.71073 Å), space group $P2_1/c$, Z = 12, D_x = 1.588 g cm^{-3}, μ = 1.17 mm^{-1}.

3.4.2. Data collection and processing

Siemens P3/PC diffractometer, θ–2θ scan mode, graphite-monochromated Mo Kα radiation; 10455 reflections measured ($2 < \theta < 28$, $+h, +k, \pm l$), 9753 unique (no absorption correction was applied) giving 4670 with $I > 2\sigma(I)$.

3.4.3. Structure analysis and refinement

All calculations were carried out with the SHELXTL PLUS 5 (gamma version) programs using an IBM PC. Direct methods. Full matrix least squares refinement on F^2 for 9703 independent reflections (about 50 reflections with low θ obviously severely affected by absorption were excluded) with all non-hydrogen atoms anisotropic. All carborane hydrogen atoms were located in the difference syntheses and refined in the isotropic approximation, other H atoms were placed geometrically and were included in the final refinement in the riding model approximation, their temperature factors being kept 20% higher than the equivalent isotropic factors of the corresponding carbon atom. Weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0815P)^2 + 1.0229P]$, where $P = (F_o^2 + 2F_o^2)/3$. Final $R1$ factor is equal to 0.0929 (on F for $I > 2\sigma(I)$ reflections), $wR2$ = 0.2234 (on F^2 for all reflections used in the refinement). Rather low accuracy of the data is obviously due to the low quality of the crystals, all of which were diffracting very poorly even at −125 °C. The final atomic coordinates and thermal displacement parameters are given in Table 3. Tables of anisotropic thermal parameters and hydrogen atom coordinates, and a complete list of bond

[3] The assignment of proton and carbon signals was made by using standard methods, including 2D ^{1}H-COSY and DEPT.

[4] See footnote 3.

[5] See footnote 3.

Table 3
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **1**

	x	y	z	U_{eq} [a]
Rh(3A)	104(1)	−6435(1)	1185(1)	20(1)
C(1A)	−880(7)	−5725(11)	1494(5)	25(3)
C(2A)	−90(6)	−5668(12)	1926(5)	24(3)
B(4A)	−805(7)	−4833(12)	945(5)	21(3)
B(5A)	−1309(8)	−4089(13)	1389(6)	29(3)
B(6A)	−849(9)	−4668(14)	2027(6)	32(3)
B(7A)	606(8)	−4666(14)	1746(5)	25(3)
B(5A)	141(8)	−4016(12)	1096(5)	22(3)
B(9A)	−671(8)	−2997(14)	1158(6)	32(3)
B(10A)	−679(8)	−2908(13)	1816(5)	28(3)
B(11A)	103(8)	−3987(13)	2173(5)	27(3)
B(12A)	208(8)	−2879(13)	1645(5)	23(3)
C(01A)	433(8)	−9118(13)	721(5)	40(3)
C(02A)	898(7)	−8263(12)	1211(5)	33(3)
C(03A)	1158(7)	−6952(13)	1005(5)	33(3)
C(04A)	877(8)	−7103(12)	418(5)	37(3)
C(05A)	28(8)	−6859(12)	365(5)	35(3)
C(06A)	−247(9)	−8143(12)	575(4)	40(4)
C(07A)	897(10)	−8801(12)	339(6)	54(4)
C(08A)	715(8)	−8371(14)	1676(5)	44(3)
Rh(3B)	3441(1)	1525(1)	−564(1)	23(1)
C(1B)	2474(7)	758(12)	−1211(5)	25(3)
C(2B)	3261(7)	641(12)	−1357(5)	25(3)
B(4B)	2517(9)	−71(14)	−638(6)	29(3)
B(5B)	2032(8)	−862(13)	−1263(5)	26(3)
B(6B)	2524(8)	−341(13)	−1730(5)	27(3)
B(7B)	3968(9)	−269(14)	−900(5)	28(3)
B(5B)	3476(8)	−882(15)	−423(6)	31(3)
B(9B)	2658(8)	−1942(13)	−775(5)	27(3)
B(10B)	2681(9)	−2078(14)	−1434(6)	36(4)
B(11B)	3479(9)	−1055(14)	−1515(6)	34(3)
B(12B)	3553(9)	−2073(15)	−947(6)	37(4)
C(01B)	3677(9)	4313(15)	−18(6)	50(4)
C(02B)	4195(8)	3413(16)	−305(5)	48(4)
C(03B)	4450(7)	2158(14)	7(5)	40(3)
C(04B)	4109(8)	2310(14)	467(5)	43(3)
C(05B)	3309(7)	2035(13)	213(5)	32(3)
C(06B)	3036(9)	3200(15)	−101(6)	51(4)
C(07B)	4131(9)	3987(14)	534(5)	52(4)
C(08B)	4041(10)	3441(15)	−834(6)	61(4)
Rh(3C)	3194(1)	−3645(1)	−3273(1)	24(1)
C(1C)	4194(8)	−4407(13)	−2642(6)	35(4)
C(2C)	3428(7)	−4449(12)	−2457(4)	27(3)
B(4C)	4080(9)	−5246(13)	−3226(6)	32(3)
B(5C)	4614(9)	−6032(14)	−2612(6)	33(3)
B(6C)	4205(8)	−5444(14)	−2122(6)	31(3)
B(7C)	2704(8)	−5398(12)	−2884(5)	21(3)
B(8C)	3128(10)	−6049(13)	−3390(6)	34(4)
B(9C)	3933(10)	−7113(15)	−3063(7)	42(4)
B(10C)	3999(8)	−7226(13)	−2384(6)	30(3)
B(11C)	3240(7)	−6125(12)	−2274(5)	23(3)
B(12C)	3096(9)	−7188(13)	−2844(6)	32(3)
C(01C)	2809(10)	−962(14)	−3825(5)	57(5)
C(02C)	2380(8)	−1817(13)	−3500(5)	38(3)
C(03C)	2119(7)	−3102(13)	−3798(5)	36(3)
C(04C)	2371(9)	−2941(13)	−4302(5)	46(4)
C(05C)	3224(9)	−3170(13)	−4060(5)	45(4)
C(06C)	3494(9)	−1922(13)	−3761(5)	42(4)
C(07C)	2318(10)	−1263(14)	−4379(5)	57(4)
C(08C)	2593(9)	−1731(15)	−2958(6)	56(4)

lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre.

3.5. Hydrogenation of methacycline

In a stainless steel autoclave, 2 cm^3 of a 20 mmol l^{-1} solution of methacycline hydrochloride in methanol (LAB-SCAN, H.P.L.C. grade), containing the catalyst (2 mmol l^{-1}) was magnetically stirred and heated at 60 °C for 4 h under 100 atm of hydrogen.

3.6. H.P.L.C. analysis of the reaction mixtures

The reaction mixture was thereafter analysed by H.P.L.C. (Merck–Hitachi, equipped with an L-6000 pump and an L-4000 UV detector) using a Macherey–Nagel column (ET 125-8-4 Nucleosil 100-5 C18 AB). The mobile phase was a mixture of 500 cm^3 of 0.1 M sodium phosphate buffer containing 0.01 M EDTA, 500 cm^3 methanol H.P.L.C. and 6 cm^3 *N,N*-dimethyloctylamine adjusted to pH 8 with 20% aqueous NaOH. Samples from the reaction mixtures and authentic samples were diluted with the mobile phase before injection. Flow rate, 0.7 cm^3 min^{-1}; temperature, 38 °C; wavelength, 280 nm. The amounts of methacycline, doxycycline, and epi-doxycycline in the reaction mixtures were determined by H.P.L.C., using authentic samples.

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Notes to Table 3:
[a] U_{eq} is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

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