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Diastereoselective hydrogenation of folic acid esters with the Daniphos ligand

Wolfgang Braun [a], Beatrice Calmuschi-Cula [a], Albrecht Salzer [a,*], Viola Groehn [b]

[a] *Institut für Anorganische Chemie, RWTH Aachen, Professor-Pirlet-Strasse 1, D 52074 Aachen, Germany*
[b] *Merck Eprova AG, Im Laternenacker 5, CH 8200 Schaffhausen, Switzerland*

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Abstract

Folic acid dimethylester benzenesulfonate was hydrogenated homogeneously in a rhodium-catalyzed diastereoselective reaction employing a set of the previously published planar-chiral "Daniphos" ligands, which are based on an arene chromium tricarbonyl scaffold. Diastereoselectivities of up to 42% *de* were achieved, almost matching the benchmark ligand BINAP. An X-ray structure of the most successful ligand P(*i*-Pr_2)/PPh_2 is presented and discussed.

Keywords: Rhodium; Diphosphines; Planar chirality; Asymmetric hydrogenation

1. Introduction

Asymmetric catalysis is undoubtfully the most powerful method for the synthesis of optically active compounds as it is possible to gain a maximum amount of enantiomerically enriched product at the expense of only catalytic amounts of a chiral catalyst which normally consists of a transition metal and an enantiomerically pure ligand. The nobel-prize winners Knowles, Noyori and Sharpless [1] layed the foundation of a modern transition-metal catalysis used on an industrial scale for the production of fine chemicals [2c], fragrances, agrochemicals and pharmaceutical intermediates (API, active pharmaceutical ingredients). Besides the well-known cases of the *Takasago*-process for the production of (−)-menthol [1b,1d] and the *Syngenta* herbicide (*S*)-Metolachlor [2a,2b], which involves an asymmetric hydrogenation employing the JOSIPHOS-ligand, more recent examples are *AstraZeneca*'s heartburn drug Esomeprazole by an asymmetric oxidation [3], *Novartis*' antihypertensive drug Valsartan [4] and *BASF*'s fungicide Boscalid (Nicobifen) [5] by *Suzuki*-coupling and the production of Ibuprofene by Pd-catalyzed carbonylation and the fragrance Civetone by Ru-catalyzed metathesis by *BASF* [5]. L-Tetrahydrofolic acid is a versatile intermediate for the manufacturing of different folates e.g., L-leucovorin [7], which is used in cancer therapy or Metafolin which is used as a vitamin in functional food. To our knowledge optically pure L-tetrahydrofolic acid is still obtained by repeated fractional crystallisation from an equimolar mixture of diastereoisomers formed by non-diastereoselective hydrogenation of folic acid. In order to increase the yield of L-tetrahydrofolic acid and to avoid recrystallisation steps, we checked the utility of our recently developed planar-chiral ligand, "Daniphos" [6] for the diastereoselective hydrogenation of folic acid dimethylester-benzenesulfonate. A sketch of the Daniphos ligand is given in Fig. 1.

2. Results and discussion

The hydrogenation of folic acid dimethyl ester benzenesulfonate is presented in Fig. 2. In this reaction the diazadiene system of the pteridine ring of the substrate is hydrogenated, giving a new stereogenic center at position

* Corresponding author. Tel.: +49 241 809 4646; fax: +49 241 809 2288.
E-mail address: albrecht.salzer@ac.rwth-aachen.de (A. Salzer).

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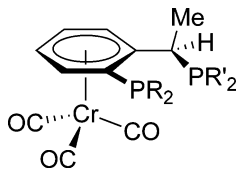

Fig. 1. The "Daniphos"-ligand.

6. The distance of the stereogenic center of the glutamic acid residue is too far from the newly formed chiral center and therefore it does not cause any measurable stereochemical induction in the hydrogenation and the outcome of the reaction is governed by the chiral ligand alone. Quite a number of experiments have been undertaken so far to reach a reasonable induction, but the best results achieved do not exceed some 40% *de*, in which the desired product is the (*S*,*S*)-diastereomer [8]. In the course of the reaction, a significant percentage of an undesired cleavage product is observed in varying amounts ($ABGAMe_2$, aminobenzoylgluamic acid dimethylester), depending on the ligand used, diminishing the yield of the valuable tetrahydrofolic acid dimethylester ($THFMe_2$).

A number of candidates from our ligand library has been employed in this survey, bearing aliphatic as well as aromatic substituents on the phosphorus donor atoms. They are summarized in Fig. 3, together with the benchmark ligands Josiphos and BINAP, which also were included in this examination for reasons of comparison (all ligands are configured (*R*) with respect to central as well as planar chirality except for ligand **1**, where also the (*S*,*S*)-enantiomer was employed). The results are collected in Table 1.

From the results achieved with ligand **1**, it can be seen that the use of the other enantiomer of the ligand results in a reversal of the configuration in the product together with (nearly) the same induction, as is to be expected. Moreover, it is remarkable that all derivatives that carry only aromatic substituents on the phosphorus donor atoms deliver preferably the undesired (6*R*,*S*) diastereomer. In contrast to this, the desired isomer is formed in excess when the ligands contain aliphatic side chains on the donor centers as well (it should be kept in mind that all ligands are configured (*R*,*R*)). Here, an especially high stereochemical induction and chemical yield of tetrahydrofolic acid ester is achieved in case of the P(*i*-Pr)$_2$/PPh$_2$ derivative **2**. So one might conclude that a sterically demanding, Lewis-basic group in the *ortho*-position influences the reaction in the desired direction. In case of the purely aromatic candidates the differences in optical yields are less pronounced: they range between 20% and 30% *de*. Better values are

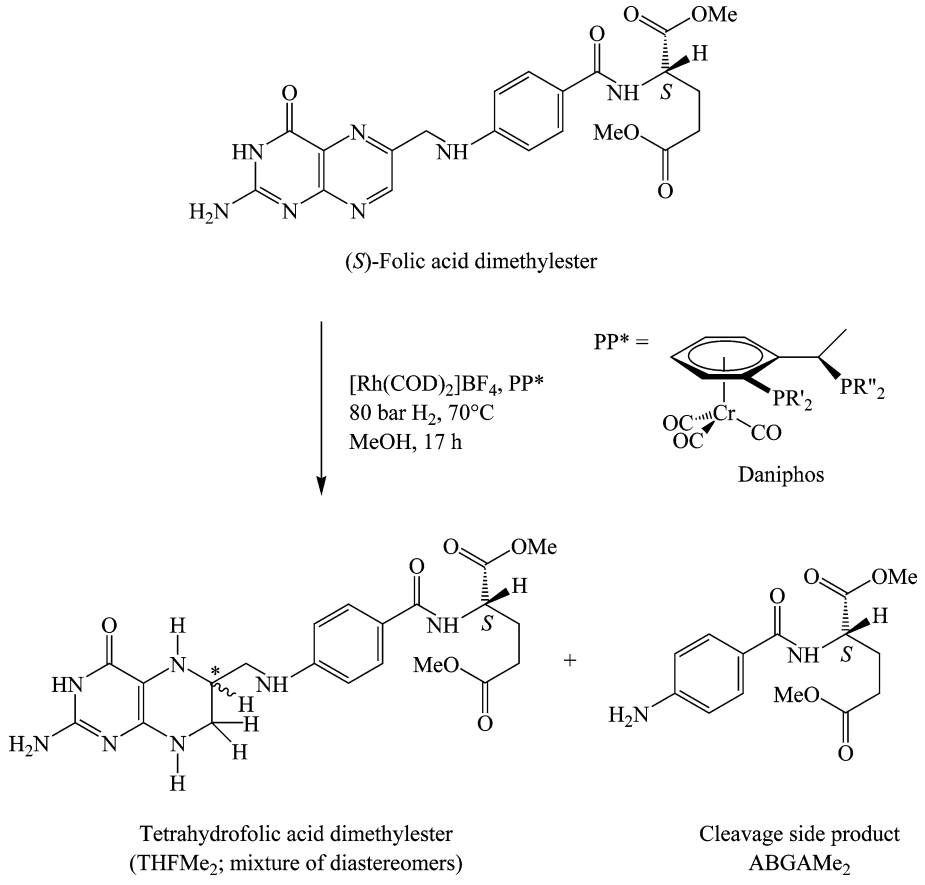

Fig. 2. Hydrogenation of folic acid dimethylester.

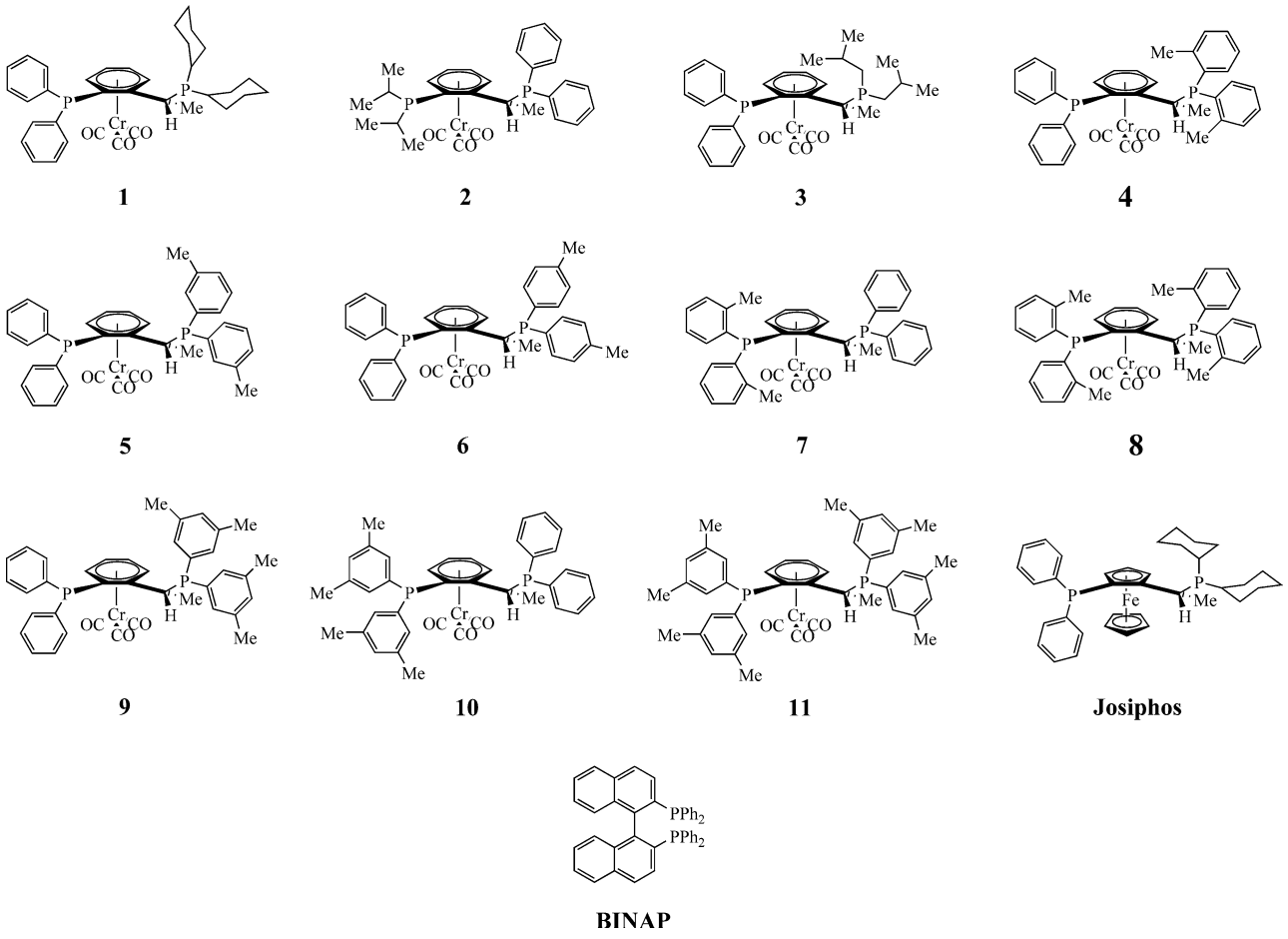

Fig. 3. Overview of the ligands employed in this investigation.

Table 1
Results of the hydrogenation of folic acid ester employing the Daniphos ligand

Ligand		Form	Stereoselectivity		Yield (%)	
No./R	R′		d.r.(6*S*,*S*):(6*R*,*S*)	de (%)[a]	$THFMe_2$	$ABGAMe_2$
1/Ph	Cy	*S*,*S*	43.0:57.0	−14.0	70.1	26.9
1/Ph	Cy	*R*,*R*	58.5:41.5	17.0	64.0	18.6
2/*i*-Pr	Ph	*R*,*R*	71.2:28.8	42.4	81.5	16.7
3/Ph	*i*-Bu	*R*,*R*	54.0:46.0	8.0	69.5	16.8
4/Ph	*o*-Tol	*R*,*R*	34.2:65.8	−31.6	87.9	7.2
5/Ph	*m*-Tol	*R*,*R*	39.2:60.8	−21.6	77.6	21.0
6/Ph	*p*-Tol	*R*,*R*	39.6:60.4	−20.8	80.6	9.9
7/*o*-Tol	Ph	*R*,*R*	37.2:62.8	−25.6	63.0	20.9
8/*o*-Tol	*o*-Tol	*R*,*R*	32.5:67.5	−35.0	76.1	21.7
9/Ph	*m*-Xyl	*R*,*R*	41.3:58.7	−17.4	71.3	14.9
10/*m*-Xyl	Ph	*R*,*R*	36.1:63.9	−27.8	83.1	14.2
11/*m*-Xyl	*m*-Xyl	*R*,*R*	34.0:66.0	−32.0	79.8	10.4
12 Josiphos		*S*,*S*	61:39	22	60	Unknown
13 BINAP		*R*	73:27	46	90	Unknown

[a] The *de* values were determined by HPLC analysis (see Section 4 for details).

obtained here if the *ortho*-group is quite bulky (*o*-Tol, *m*-Xyl versus Ph). This effect cannot be observed for the α-position, but it seems that the presence of a methyl group close to the phosphorus center has a benefitial effect here as well.

For the most successful ligand, $P(i\text{-}Pr)_2/PPh_2$ (**2**), we were able to obtain a single crystal suitable for X-ray diffraction measurements by slow evaporation of an etheral solution. The structure is depicted in Fig. 4, some selected bond lengths are given in Table 2. The experimental X-ray

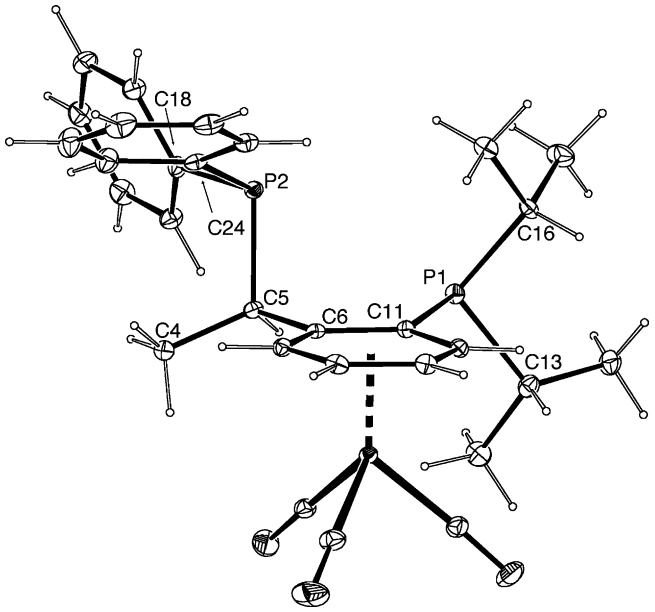

Fig. 4. Displacement elipsoids plot (30%) of **2**. The H atoms are shown with arbitrary radius.

Table 2
Selected distances (Å) and angles (°) for complex **2**

Distances (Å)			
P2–C5	1.876(2)	P1–C11	1.856(2)
P2–C18	1.831(2)	P1–C13	1.872(3)
P2–C24	1.832(3)	P1–C16	1.874(2)
C6–C5	1.514(3)	C5–C4	1.534(3)
Angles (°)			
C24–P2–C5	100.68(11)	C16–P1–C11	99.59(11)
C18–P2–C5	103.62(11)	C13–P1–C11	99.91(11)
C5–C6–C11	122.2(2)	P1–C11–C6	121.92(17)

diffraction parameters and the crystal data are summarized in Table 3. The structure exhibits the typical features that were found in numerous other examples of diphosphines of that kind [6d–i,6k]. The chromium tricarbonyl rotator shows the typical piano stool arrangement, staggered with regard to the chiral α-chain, causing this moiety to adopt a conformation in which the hydrogen atom on the stereogenic carbon atom points down towards the chromium atom to avoid steric hindrance. The diphenylphosphino group points upwards, exhibiting a dihedral angle of 78.1(2)° between the planes defined by P2–C5–C6 and C5–C6–C11. The disk-like shaped phenyl rings point away from the lone-pair, whereas the isopropyl groups of the other phosphine moiety can be regarded as rigid rotators, which presumably helps to create a chiral environment in the active catalyst and to force the substrate to coordinate facial-selectively, yielding a relatively high *de* value. A similar observation we made recently in the asymmetric ring opening of oxanorbornadiene, where a ligand bearing a bulky and rigid P(*t*-Bu)$_2$-group gave the best selectivities [6k].

Table 3
Experimental X-ray diffraction parameters and the crystal data for compound **2**

Compound	**2**
Empirical formula	$C_{29}H_{32}CrO_3P_2$
Formula mass	542.49
Crystal habit, color	Rod, yellow
Crystal dimensions (mm)	$0.40 \times 0.13 \times 0.12$
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	9.7035(15)
b (Å)	13.995(2)
c (Å)	19.993(3)
V (Å^3)	2715.1(7)
Z	4
D_{calc} (g cm^{-1})	1.327
$F(000)$	1136
μ (Mo Kα) (cm^{-1})	0.567
Diffractometer	Bruker Smart CCD
T (K)	110(2)
θ Range (°)	2.33–27.45
Reflections collected	35642
Unique reflections	6213
R_{int}	0.0598
Reflections used	5663
Parameters refined	321
R_1	0.0378
wR_2	0.0887
Flack's parameter	−0.010(17)
Goodness-of-fit	1.001
Largest difference in peak/hole (e/Å^3)	0.50/−0.25

3. Conclusion

We have proved that the "Daniphos" class of ligands has indeed a high potential for the reaction under investigation and that with a suitable choice of the substitution pattern it is in fact competitive to the BINAP system and superior to the Josiphos ligand and its derivatives [9].

4. Experimental

The ligands were synthesized according to our published method [6d]. Analytical data are given below for those candidates that were not published previously (compounds **4**–**8** and **10**; for**1** see Ref. [6d], for **2**,**9** and **11** see Ref. [6j] and for **3** see Ref. [6k]). All substances were handled under argon atmosphere using standard inert gas techniques. NMR spectra were recorded on a Varian Unity 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz, ^{31}P: 200 MHz) spectrometer at ambient temperature. IR spectra were recorded on a Nicolet Avatar™ 360 E.S.P.™ spectrometer. Mass spectra were recorded on a Finnigan MAT 95 spectrometer using the chemical ionisation (CI) technique and isobutane as reactand gas. Solvents were purified applying standard procedures. Flash chromatography was performed using Merck grade silica gel 60 (0.04–0.063 mm).

4.1. General hydrogenation procedure

8.12 mg [Rh(COD)$_2$]BF$_4$ (20 μmol) and the diphosphine ligand (25 μmol) were degassed in a Schlenk tube and

suspended in 5 ml methanol. 1.25 g (2 mmol) of folic acid dimethylester benzenesulfonate were suspended in 25 ml methanol and added via a narrow tube to the catalyst. The suspension was added to a 100 ml autoclave flushed with nitrogen. The autoclave was sealed and the hydrogenation run at 70 °C at a constant pressure of 80 bar. After 17 h a sample for HPLC analysis was taken.

4.2. HPLC method for the separation of diastereoisomers of tetrahydrofolic acid dimethylester

The content and diastereomeric excess of tetrahydrofolic acid dimethylester was determined by using the following HPLC method: 6.8 g of β-cyclodextrine and 270 ml of 37% formaldehyde were dissolved in 1 L of water to give the sample dilution solution. 1 ml of this sample dilution solution was mixed with 15 mg of the hydrogenation mixture or 1 mg isolated product was dissolved in 100 ml of the sample dilution solution and analysed (flow rate 1 ml/min) on an OS column (Macherey and Nagel, Nucleosil, 240 × 4 mm) with UV detection at 300 nm. The eluent was prepared by mixing 6.8 g β-cyclodextrine, 8.5 ml triethylamine, 850 ml water and 150 ml acetonitrile. By addition of acetic acid the pH was adjusted to pH 7.5 and then 270 μl of 37% formaldehyde were added.

4.3. [η⁶-(R,R)-{(Po-Tol₂)CHMe}(C₆H₄PPh₂)]Cr(CO)₃ (4)

Compound **4** was prepared according to the method published in Ref. [6d] from the corresponding chloro derivative [η⁶-(*R*,*R*)-{(Cl)CHMe}($C_6H_4PPh_2$)]$Cr(CO)_3$ (0.85 g, 1.85 mmol), di-(2-methylphenyl)-phosphine (0.396 g, 1.85 mmol) and $TlPF_6$ (0.612 g, 1.75 mmol). It was purified by column chromatography (first pentane, then ether). Yield: 0.91 g (1.43 mmol, 76%). IR ($CHCl_3$): ν_{max} 1968, 1899 (CO) cm^{-1}. MS (CI): $m/z = 639.0$ ($M+1^{+\cdot}$). ^{31}P NMR (200 MHz, C_6D_6) $\delta = 13.21$ (d, $J_{PP} = 30.5$ Hz, α-P), −9.00 (d, $J_{PP} = 30.5$ Hz, *ortho*-P) ppm. ^1H NMR (500 MHz, C_6D_6) $\delta = 7.61$ (m, 3H, ar-*H*(PPh_2) and ar-*H*($PTol_2$)), 7.32 (trm, 2H, ar-*H*(PPh_2) and ar-*H*($PTol_2$)), 7.12 (trm 2H, ar-*H*(PPh_2) and ar-*H*($PTol_2$)), 7.06–6.94 (m, 8H, ar-*H*(PPh_2) and ar-*H*($PTol_2$)), 6.88 (dd, 1H, $J_{PH} = 3.1$ Hz, $J_{PH} = 1.2$ Hz, ar-*H*(PPh_2) and ar-*H*($PTol_2$)), 6.82 (trm, 1H, ar-*H*(PPh_2) and ar-*H*($PTol_2$)), 6.75 (trm, 1H, ar-*H*(PPh_2) and ar-*H*($PTol_2$)), 4.97 (m, 2H, ar-*H*), 4.54 (tr, 1H, $J = 6.4$ Hz, ar-*H*), 4.28 (m, 1H, $PTol_2CHMe$), 2.05 (s, 3H, *Me*-Tol), 1.64 (d, 3H, $J_{PH} = 1$–5 Hz, *Me*-Tol), 1.35 (dd, 3H, $J = 7.0$ Hz, $J_{PH} = 4.6$ Hz, $PTol_2CHMe$) ppm. ^{13}C NMR (125 MHz, C_6D_6) $\delta = 232.88$ (CO), 143.84 (d, $J_{CP} = 31.8$ Hz, ar-C_{ipso}Me-Tol), 141.20 (d, $J_{CP} = 24.6$ Hz, ar-C_{ipso}Me-Tol), 136.10 (dd, $J_{CP} = 6.9$ Hz, $J_{CP} = 3.0$ Hz, ar-C_{ipso}P-Tol or ar-C_{ipso}(PPh_2)), 135.83 (dd, $J_{CP} = 13.5$ Hz, $J_{CP} = 2.5$ Hz, ar-C_{ipso}P-Tol or ar-C_{ipso}(PPh_2)), 135.69 (d, $J_{CP} = 19.2$ Hz, ar-C_{ipso}P-Tol or ar-C_{ipso}(PPh_2)), 135.54 (d, $J_{CP} = 1.5$ Hz, ar-*C*(PAr_2)), 134.97 (ar-*C*(PAr_2)), 134.81 (ar-*C*(PAr_2)), 134.53 (d, $J_{CP} = 2.2$ Hz, ar-*C*(PAr_2)), 134.38 (d, $J_{CP} = 2.2$ Hz, ar-*C*(PAr_2)), 132.99 (dd, $J_{CP} = 23.0$ Hz, $J_{CP} = 1.1$ Hz, ar-C_{ipso}P-Tol or ar-C_{ipso}-(PPh_2)), 130.72 (d, $J_{CP} = 3.3$ Hz, ar-*C*(PAr_2)), 130.64 (ar-*C*(PAr_2)), 130.14 (d, $J_{CP} = 6.1$ Hz, ar-*C*(PAr_2)), 129.61–125.93 (10C, ar-*C*(PAr_2)), 124.26 (dd, $J_{CP} = 25.8$ Hz, $J_{CP} = 22.4$ Hz, ar-C_{ipso}), 104.32 (dd, $J_{CP} = 22.4$ Hz, $J_{CP} = 3.2$ Hz, ar-C_{ipso}), 99.21 (d, $J_{CP} = 2.2$ Hz, ar-*C*), 94.04 (ar-*C*), 89.75 (ar-*C*), 88.74 (dd, $J_{CP} = 4.2$ Hz, $J_{CP} = 4.2$ Hz, ar-*C*), 31.53 (dd, $J_{CP} = 24.7$ Hz, $J_{CP} = 21.9$ Hz, $PTol_2CHMe$), 22.46 (d, $J_{CP} = 23.5$ Hz, *Me*-Tol)21.70 (d, $J_{CP} = 20.3$ Hz, *Me*-Tol), 15.75 ($PTol_2CHMe$) ppm.

4.4. [η⁶-(R,R)-{(Pm-Tol₂)CHMe}(C₆H₄PPh₂)]Cr(CO)₃ (5)

Compound **5** was prepared according to the method published in Ref. [6d] from the corresponding chloro derivative [η⁶-(*R*,*R*)-{(Cl)CHMe}($C_6H_4PPh_2$)]$Cr(CO)_3$ (0.50 g, 1.09 mmol), di-(3-methylphenyl)-phosphine (0.26 g, 1.09 mmol) and $TlPF_6$ (0.36 g, 1.03 mmol). It was purified by column chromatography (first pentane, then ether). Yield: 0.51 g (0.80 mmol, 73%). IR ($CHCl_3$): ν_{max} 1967, 1895 (CO) cm^{-1}. MS (CI): $m/z = 696.0$ ($M+58^{+\cdot}$), 639.0 ($M+1^{+\cdot}$). ^{31}P NMR (200 MHz, C_6D_6) $\delta = 9.81$ (d, $J_{PP} = 20.4$ Hz, α-P), −18.1 (d, $J_{PP} = 20.4$ Hz, *ortho*-P) ppm. ^1H NMR (500 MHz, C_6D_6) $\delta = 7.46$–6.80 (m, 18H, ar-*H*(PPh_2) and ar-*H*($PTol_2$)), 5.31 (mbr, 1H, ar-*H*), 5.12 (mbr, 1H, ar-*H*), 5.02 (mbr, 1H, ar-*H*), 4.60 (mbr, 1H, $PTol_2CHMe$), 4.55 (mbr, 1H, ar-*H*), 2.31 (s, 3H, *Me*-Tol), 2.28 (s, 3H, *Me*-Tol), 1.27 (tr, 3H, J = 5.7 Hz, $PTol_2CHMe$) ppm. ^{13}C NMR (125 MHz, C_6D_6) $\delta = 232.48$ (*C*O), 137.68 (d, $J_{CP} = 5.5$ Hz, ar-C_{ipso}Me-Tol), 137.50 (d, $J_{CP} = 7.7$ Hz, ar-C_{ipso}Me-Tol), 136.49–127.84 (22C) (ar-*C*(PPh_2) and ar-*C*($PTol_2$)), 123.79 (ar-C_{ipso}), 104.09 (d, $J_{CP} = 21.4$ Hz, ar-C_{ipso}), 98.57 (ar-*C*), 97.44 (ar-*C*), 90.25 (ar-*C*), 89.24 (br, ar-*C*), 33.47 (tr, $J_{CP} = 23.9$ Hz, $PTol_2CHMe$), 21.53 (*Me*-Tol), 21.44 (*Me*-Tol), 15.98 ($PTol_2CHMe$) ppm.

4.5. [η⁶-(R,R)-{(Pp-Tol₂)CHMe}(C₆H₄PPh₂)]Cr(CO)₃ (6)

Compound **6** was prepared according to the method published in Ref. [6d] from the corresponding chloro derivative [η⁶-(*R*,*R*)-{(Cl)CHMe}($C_6H_4PPh_2$)]$Cr(CO)_3$ (0.63 g, 1.50 mmol), di-(4-methylphenyl)-phosphine (0.32 g, 1.50 mmol) and $TlPF_6$ (0.48 g, 1.37 mmol). It was purified by column chromatography (first pentane, then ether). Yield: 0.56 g (0.88 mmol, 64%). IR ($CHCl_3$): ν_{max} 1961, 1892 (CO) cm^{-1}. MS (CI): $m/z = 696.0$ ($M+58^{+\cdot}$), 639.0 ($M+1^{+\cdot}$). ^{31}P NMR (200 MHz, C_6D_6) $\delta = 7.38$ (d, $J_{PP} = 25.6$ Hz, α-P), −20.12 (d, $J_{PP} = 23.8$ Hz, *ortho*-P) ppm. ^1H NMR (500 MHz, C_6D_6) $\delta = 7.47$–7.05 (m, 18H, ar-*H*(PPh_2) and ar-*H*($PTol_2$)), 5.31 (tr, 1H, J = 6.1 Hz, ar-*H*), 5.11 (tr, 1H, $J = 6.1$ Hz, ar-*H*), 5.02 (tr, 1H, J = 6.1 Hz, ar-*H*), 4.58 (m, 1H, $PTol_2CHMe$), 4.55 (d,

1H, $J = 6.4$ Hz, ar-*H*), 2.36 (s, 3H, *Me*-Tol), 2.32 (s, 3H, *Me*-Tol), 1.26 (tr, 3H, $J = 6.1$ Hz, $PTol_2CHMe$) ppm. ^{13}C NMR (125 MHz, C_6D_6) $\delta = 232.51$ (*C*O), 139.85 (ar-C_{ipso}Me-Tol), 137.41 (ar-C_{ipso}Me-Tol), 135.89–128.18 (22C) (ar-*C*(PPh_2) and ar-*C*($PTol_2$)), 123.81 (ar-C_{ipso}), 104.19 (d, $J_{CP} = 21.3$ Hz, ar-C_{ipso}), 99.56 (ar-*C*), 93.74 (ar-*C*), 90.22 (ar-*C*), 89.28 (br, ar-*C*), 33.59 (d, $J_{CP} = 24.2$ Hz, $PTol_2CHMe$), 21.40 (*Me*-Tol), 21.22 (*Me*-Tol), 15.89 ($PTol_2CHMe$) ppm.

4.6. [η^6-(*R,R*)-{(*PPh*$_2$)*CHMe*}(*C*$_6$*H*$_4$*Po-Tol*$_2$)]*Cr*(*CO*)$_3$ (*7*)

Compound **7** was prepared according to the method published in Ref. [6d] from the corresponding chloro derivative [η^6-(*R,R*)-{(Cl)CHMe}(C_6H_4Po-Tol_2)]$Cr(CO)_3$ (0.92 g, 1.88 mmol), diphenylphosphine (0.40 g, 2.16 mmol) and $TlPF_6$ (0.66 g, 1.88 mmol). It was purified by column chromatography (first pentane, then ether). Yield: 0.82 g (1.28 mmol, 68%). IR ($CHCl_3$): ν_{max} 1968, 1897 (CO) cm^{-1}. MS (CI): $m/z = 639.1$ ($M+1^{+\cdot}$). ^{31}P NMR (200 MHz, C_6D_6) $\delta = 10.04$ (d, $J_{PP} = 34.6$ Hz, α-P), −40.37 (d, $J_{PP} = 32.0$ Hz, *ortho*-P) ppm. ^1H NMR (500 MHz, C_6D_6) $\delta = 7.51$ (m, 1H), 7.21–7.12 (m, 6H), 7.11–6.94 (m, 9H), 6.90–6.85 (tm, 1H), 6.77–6.74 (tm, 1H) (ar-*H*(PAr_2)), 4.83 (dq, 1H, $J = 7.0$ Hz, $J_{PH} = 8.5$ Hz, C*H*Me), 4.73 (t, 1H, $J = 6.4$ Hz), 4.15 (td, 1H, $J = 6.4$ Hz, $J_{PH} = 1.2$ Hz), 4.11 (m, 1H) (ar-*H*), 3.08 (s, 3H, Ph–*Me*), 2.04 (d, 3H, $J_{PH} = 1.8$ Hz, ar-*H*), 1.30 (dd, 3H, $J = 7.6$ Hz, $J_{PH} = 4.3$ Hz, CH*Me*) ppm. ^{13}C NMR (125 MHz, C_6D_6) $\delta = 232.84$ (*C*O), 145.07 (d, $J_{CP} = 30.9$ Hz, ar-C_{ipso}Me-Tol), 141.68 (d, $J_{CP} = 26.9$ Hz, ar-C_{ipso}Me-Tol), 136.97 (dd, $J_{CP} = 7.4$ Hz, $J_{CP} = 2.5$ Hz, ar-C_{ipso}PAr), 136.78 (d, $J_{CP} = 19.8$ Hz, ar-C_{ipso}PAr), 136.00, 135.82, 135.10, 134.42 (d, $J_{CP} = 5.2$ Hz) (ar-*C*(PAr_2)), 134.26 (d, $J_{CP} = 1.9$ Hz, ar-C_{ipso}PAr), 132.84 (dd, $J_{CP} = 11.8$ Hz, $J_{CP} = 2.5$ Hz, ar-C_{ipso}PAr), 131.68, 131.56, 130.50 (d, $J_{CP} = 4.9$ Hz), 130.15, 129.65, 128.90, 128.61, 128.58, 128.29, 127.89, 126.18, 125.60 (ar-*C*(PAr_2), 125.39 (dd, $J_{CP} = 23.0$ Hz, $J_{CP} = 23.0$ Hz, ar-C_{ipso}), 101.00 (ar-*C*), 99.69 (dd, $J_{CP} = 22.0$ Hz, $J_{CP} = 3.3$ Hz, ar-C_{ipso}), 96.31, 87.66, 87.43 (dd, $J_{CP} = 3.8$ Hz, $J_{CP} = 3.8$ Hz) (ar-*C*), 34.12 (dd, $J_{CP} = 24.0$ Hz, $J_{CP} = 24.0$ Hz, *C*HMe), 22.30 (d, $J_{CP} = 24.9$ Hz, *Me*-Ph), 21.09 (d, $J_{CP} = 23.0$ Hz, *Me*-Ph), 15.24 (CH*Me*) ppm.

4.7. [η^6-(*R,R*)-{(*Po-Tol*$_2$)*CHMe*}(*C*$_6$*H*$_4$*Po-Tol*$_2$)]*Cr*(*CO*)$_3$ (*8*)

Compound **8** was prepared according to the method published in Ref. [6d] from the corresponding chloro derivative [η^6-(*R,R*)-{(Cl)CHMe}(C_6H_4Po-Tol_2)]-$Cr(CO)_3$ (0.68 g, 1.39 mmol), di-(2-methylphenyl)-phosphine (0.34 g, 1.59 mmol) and $TlPF_6$ (0.49 g, 1.39 mmol). It was purified by column chromatography (ethyl acetate/pentane = 1/8). Yield: 0.62 g (0.93 mmol, 67%). IR ($CHCl_3$): ν_{max} 1969, 1900 (CO) cm^{-1}. MS (CI): $m/z = 667.1$ ($M+1^{+\cdot}$). ^{31}P NMR (200 MHz, C_6D_6) $\delta = -12.12$ (d, $J_{PP} = 46.9$ Hz, α-P), −41.74 (d, $J_{PP} = 44.3$ Hz, *ortho*-P) ppm. ^1H NMR (500 MHz, C_6D_6) $\delta = 7.33$ (d, 1H, $J = 7.3$ Hz), 7.47 (dd, 1H, $J = 7.6$ Hz, $J_{PH} = 3.9$ Hz), 7.14 (m, 1H), 7.11–6.95 (m, 8H), 6.84 (m, 3H), 6.73 (m, 2H) (ar-*H*(PAr_2)), 5.40 (dt, 1H, $J = 6.0$ Hz, $J_{PH} = 1.2$ Hz, ar-*H*), 4.86 (ddq, 1H, $J = 7.3$ Hz, $J_{PH} = 7.3$ Hz, $J_{PH} = 2.8$ Hz, C*H*Me), 4.78 (t, 1H, $J = 6.4$ Hz, ar-*H*), 4.24 (m, 1H, ar-*H*), 4.17 (td, 1H, $J = 6.4$ Hz, $J_{PH} = 0.9$ Hz, ar-*H*), 3.02 (s, 3H, Ph–*Me*), 2.14 (s, 3H, Ph–*Me*), 1.83 (d, 3H, $J_{PH} = 2.1$ Hz, Ph–*Me*), 1.60 (d, 3H, $J_{PH} = 1.2$ Hz, Ph–*Me*), 1.32 (dd, 3H, $J = 7.0$ Hz, $J_{PH} = 4.3$ Hz, CH*Me*) ppm. ^{13}C NMR (125 MHz, C_6D_6) $\delta = 232.87$ (CO), 145.71 (d, $J_{CP} = 31.3$ Hz), 145.15 (d, $J_{CP} = 31.2$ Hz), 141.91 (d, $J_{CP} = 22.0$ Hz), 141.70 (d, $J_{CP} = 19.2$ Hz) (ar-C_{ipso}Me–Ph), 136.99 (dd, $J_{CP} = 7.2$ Hz, $J_{CP} = 3.3$ Hz, ar-C_{ipso}P–Ph), 135.64 (d, $J_{CP} = 18.6$ Hz, ar-C_{ipso}P–Ph), 135.18, 134.39 (d, $J_{CP} = 4.8$ Hz) (ar-*C*(PAr_2), 133.65 (dd, $J_{CP} = 25.2$ Hz, $J_{CP} = 2.8$ Hz, ar-C_{ipso}P–Ph), 132.65 (dd, $J_{CP} = 12.6$ Hz, $J_{CP} = 3.2$ Hz, ar-C_{ipso}P–Ph)), 131.43 (d, $J_{CP} = 5.5$ Hz), 130.59 (d, $J_{CP} = 3.8$ Hz), 130.36 (d, $J_{CP} = 3.2$ Hz), 130.26 (d, $J_{CP} = 5.5$ Hz), 130.13 (d, $J_{CP} = 5.5$ Hz), 130.07, 129.22, 128.67, 128.33, 128.29 (ar-*C*(PAr_2), 126.50 (d, $J_{CP} = 20.3$ Hz, ar-C_{ipso}P), 126.35, 126.07, 125.98, 125.24 (ar-C_{ipso}(PAr_2)), 101.29 (ar-*C*), 99.77 (dd, $J_{CP} = 22.5$ Hz, $J_{CP} = 3.9$ Hz, ar-C_{ipso}C), 96.22, 87.46, 87.15 (dd, $J_{CP} = 3.9$ Hz, $J_{CP} = 3.9$ Hz) (ar-*C*), 31.71 (dd, $J_{CP} = 23.3$ Hz, $J_{CP} = 23.3$ Hz, *C*HMe), 22.60 (d, $J_{CP} = 23.6$ Hz, Ph–*Me*), 22.21 (d, $J_{CP} = 24.7$ Hz, Ph–*Me*), 20.95 (d, $J_{CP} = 22.0$ Hz, Ph–*Me*), 20.70 (d, $J_{CP} = 24.0$ Hz, Ph–*Me*), 15.80 (CH*Me*) ppm.

4.8. [η^6-(*R,R*)-{(*PPh*$_2$)*CHMe*}*C*$_6$*H*$_4$*Pm-Xyl*$_2$)]*Cr*(*CO*)$_3$ (*10*)

Compound **10** was prepared according to the method published in Ref. [6d] from the corresponding chloro derivative [η^6-(*R,R*)-{(Cl)CHMe}C_6H_4Pm-Xyl_2)]$Cr(CO)_3$ (0.46 g, 0.89 mmol), diphenylphosphine (0.25 g, 1.34 mmol) and $TlPF_6$ (0.30 g, 0.85 mmol). It was purified by column chromatography (first pentane, then ether:pentane = 1:3). Yield: 0.12 g (0.18 mmol, 20%). IR ($CHCl_3$): ν_{max} 1964, 1895 (CO) cm^{-1}. MS (CI): $m/z = 667.0$ ($M+1^{+\cdot}$).^{31}P NMR (200 MHz, C_6D_6) $\delta = 7.39$ (d, $J_{PP} = 16.5$ Hz, α-P), −18.17 (d, $J_{PP} = 14.7$ Hz, *ortho*-P) ppm. ^1H NMR (500 MHz, C_6D_6) $\delta = 7.67$ (trd, 2H, $J = 8.1$ Hz, $J = 1.7$ Hz, ar-H_{ortho}-Xyl), 7.45 (trd, 2H, $J = 7.6$ Hz, $J = 1.7$ Hz, ar-H_{ortho}-Xyl), 7.11–6.99 (m, 10H, ar-*H*(PPh_2)), 6.77 (s, 1H, ar-H_{para}-Xyl), 6.62 (s, 1H, ar-H_{para}-Xyl), 5.12–5.06 (mbr, 1H, ar-*H*), 5.00 (dtr, 1H, $J = 6.4$ Hz, $J = 1.2$ Hz, ar-*H*), 4.58–4.53 (mbr, 1H, ar-*H*), 4.35–4.30 (mbr, 1H, ar-*H*), 4.26 (trd, 1H, $J = 6.1$ Hz, $J = 1.5$ Hz, ar-*H*), 2.02 (s, 6H, *Me*-Xyl), 1.96 (s, 6H, *Me*-Xyl), 1.49 (d, 3H, $J = 7.1$ Hz, CH*Me*) ppm. ^{13}C NMR (125 MHz, C_6D_6) $\delta = 233.02$ (*C*O), 136.05 (d, $J_{CP} = 23.0$ Hz, ar-C_{ipso}Xyl–Me), 135.55 (ar-C_{ipso}Xyl–Me), 135.50 (ar-C_{ipso}Xyl–Me), 135.46 (ar-

C_{ipso}Xyl–Me), 127.12–131.65 (20C, ar-*C*(PPh_2 and $PXyl_2$)), 100.26 (ar-*C*), 88.05 (ar-*C*), 95.81 (ar-*C*), 88.05 (ar-*C*), 87.90 (ar-*C*), 33.68 (tr, $J_{CP} = 24.7$ Hz, PPh_2CHMe), 21.78 (d, $J_{CP} = 23.6$ Hz, Xyl–*Me*), 21.37 (Xyl–*Me*), 20.94 (Xyl–*Me*), 20.76 (d, $J_{CP} = 23.1$ Hz, Xyl–*Me*), 15.89 (PPh_2CH*Me*) ppm.

4.9. X-ray structure determination

Crystal data and details of the structure determination are listed in Table 3. Data collection was performed with a Bruker Smart CCD (Mo Kα radiation, $\lambda = 0.71073$ Å, graphite monochromator) area detector. The unit cell parameters were obtained by the least-squares refinement of a maximum of 8096 reflections. The structure was solved by direct methods (SHELXS-97) [10] and refined by full-matrix least-squares procedures based on F^2 with all measured reflections (SHELXL-97) [11]. The SADABS [12] program was used for absorption correction of the structures. All non-hydrogen atoms were refined anisotropically. All H atom were introduced at their idealized positions (d(CH) = 0.98Å) and were refined using a riding model. The absolute configuration was confirmed by refining the Flack's [13] parameter.

5. Supplementary material

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-262406. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21 EZ, UK (fax: int. code +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk; web, www: http://www.ccdc.cam.ac.uk).

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