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Chiroptical properties and enantioselectivity in hydrogenation with rhodium(I) complexes of chiral bis-diphenylphosphines derived from D-glucose and D-galactose

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Abstract

(2*R*,3*S*)-2-Diphenylphosphinomethyl-3-diphenylphosphinotetrahydropyran (**3**) has been prepared in 64% yield from the dimesylate **5**, derived from D-galactose. The surprisingly different reactivities of dimesylates **2** and **5** towards diphenylphosphide anion are considered and the conformational properties of **1**–**6** discussed in terms of their CD spectra. The rhodium(I) complexes **9** and **10** exhibit low to relatively high enantioselectivities in hydrogenation of *Z*-α-acetylaminocinnamic acid and α-acetylaminoacrylic acid. The chiroptical and conformational properties of the bidentate ligands (**3**, **6**), and their rhodium(I) complexes (**9**, **10**) are correlated with the observed enantioselectivities.

Introduction

Enantioselective catalytic hydrogenation in the presence of chiral phosphine-rhodium(I) complexes continues to attract attention [1–3]. Two main research lines in this area have been pursued by organometallic chemists in recent years. The first is directed towards the discovery of more active, stabilized or heterogenized chiral phosphine complexes, with the objective of preparing technologically useful catalytic systems [4–7]. The second is directed towards establishing details of the mechanism of homogeneous hydrogenation, and the relation between the stereoelectronic properties and enantioselectivity of the catalysts. The major contributions to

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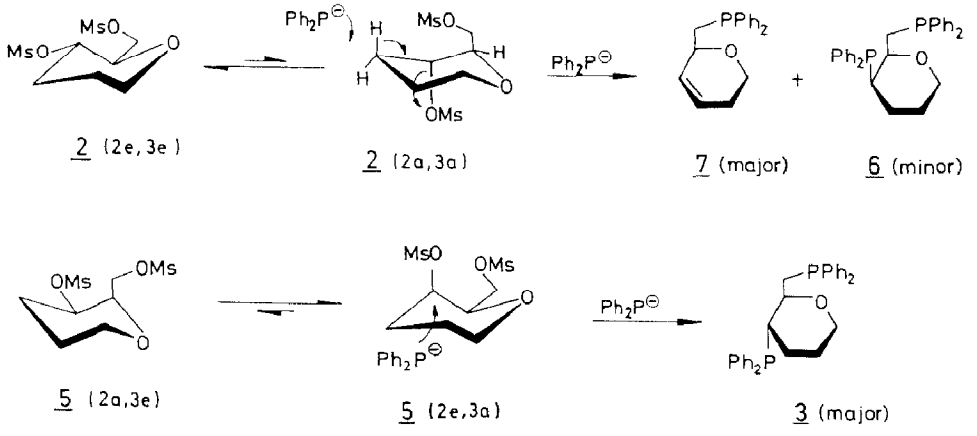
a detailed understanding of the mechanism have been by Halpern [8,9] and Brown [10,11], but some important stereochemical and structural studies have been made by other groups [12–16].

In continuation of our work on the preparation of chiral diphenylphosphinites [17,18] and diphenylphosphine [19] derived from the most common monosaccharides, we have now prepared and investigated the properties of the chiral complexes formed with diphosphines derived from D-galactose and D-glucose *.

Results and discussion

Recently we described [19] preparation in low yield (~ 8%) of diphosphine **6**, derived from D-glucose, diphenylphosphination of the corresponding dimesyl derivative (**2**) being performed at various temperatures. When the reaction was carried out with the dimesylate **5** derived from D-galactose, however, we were able to isolate the desired product **3** in ~ 65% yield, and this preparation was fully reproducible on the 10 g-scale. This result is particularly interesting in view of the difficulties we [19] and others [20,21] encountered in preparation of bis(diphenylphosphines) derived from cyclic secondary diols by nucleophilic substitution on their active esters, usually tosylates or mesylates.

In addition, when diphenylphosphination reaction was monitored by TLC, we found that **3** was formed much faster from **5**, than the elimination product **7** was formed from **2**. Different relative configurations in **2** and **5**, and consequently different relative conformations, obviously cause this difference in reactivity. As the CD-data of the corresponding dibenzoates **1** and **4** indicate [18], the latter is present predominantly in the chair conformation with a negative torsional angle between



Scheme 1.

* After this manuscript was complete, a paper by Brunner et al. [25] came to our attention, in which the synthesis of an 1,3-bis(diphenylphosphine), bearing a hydroxy group at C(2) was described. Use of its Rh(COD) complex gave rise to 54% enantioselectivity in hydrogenation of *Z*-α-acetylaminocinnamic acid. The authors attributed the higher (83%) optical yield obtained with the mixture of 1,2- and 1,3-bis(diphenylphosphine) to the "1,2-component", thus confirming poorer efficacy of the "locally chiral" 1,3-structural isomer.

Table 1

Preparation of the diphenylphosphines **3** and **6**

Starting compound	Solvent	Temperature (°C)	Product (%) [a]			Ref.
			3	**6**	**7**	
2	THF	−50°	–	8.3	58.1	17
5	THF	−40°	63.7	–	–	

[a] After quantitative separation by chromatography on silica gel column.

Table 2

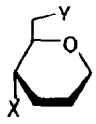
Enantioselective hydrogenation of *Z*-α-acetylaminocinnamic acid catalyzed by the rhodium(I) complexes **9** and **10** [a]

Run	Complex	Temperature (°C)	$p(H_2)$ (atm)	Chemical yield [b] (%)	e.e. [c] (%)	Configuration	Ref.
1	**9**	20	1.5	23.1	52.9	*S*	17
2		20	5.0	59.1	57.8	*S*	17
3		20	10.0	100	72.9	*S*	17
4	**10**	40	1.5	100	13.1	*S*	
5		60	1.5		13.3	*S*	
6		80	1.5		10.4	*S*	
7		20	10.0		17.9	*S*	
8		40	10.0		12.0	*S*	
9		60	10.0		11.7	*S*	
10		80	10.0		9.3	*S*	
11		20	20.0		17.7	*S*	
12		20	40.0		16.0	*S*	
13		20	60.0		15.7	*S*	

[a] Ratio catalyst-to-substrate was 1/100 and the solvent was ethanol/benzene (1/1). [b] Based on ^1H NMR spectra. [c] Enantiomeric excesses were calculated on the basis of $[\alpha]_D + 46.0$, $c = 1.0$ in EtOH for optically pure (*R*)-*N*-acetylphenylalanine.

the two chromophores (**4**,2e,3a). The former adopt the single energetically favourable conformation 2e,3e, with a positive torsional angle. If the same conformation distribution is assumed for **2** and **5** (Scheme 1), then the equatorially positioned leaving group in **2** is unreactive towards substitution by a bulky diphenylphosphide anion. As a result a slow E2 elimination occurs from the energetically unfavourable 2a,3a conformer of **2**, to yield the 3,4-*trans*-elimination product (**7**), however, not the higher substituted 2,3-elimination product **8**, since no *trans* (antiperiplanar) arrangement of the leaving groups is available. In the case of compound **5**, however, the axially positioned C(3) mesyl group reacts via a S_N2-type process to give diphosphine **3** in ~ 64% yield (Table 1).

Some information on enantioselective hydrogenation with the Rh^I-NBD (NBD = norbornadiene) complex **9** has been reported [19]. We present here the corresponding results obtained with the complexes **9** and **10**, Table 2.

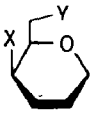


X, Y

1 OBz

2 OMs

3 PPh_2

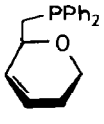


X, Y

4 OBz

5 OMs

6 PPh_2



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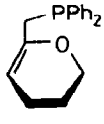

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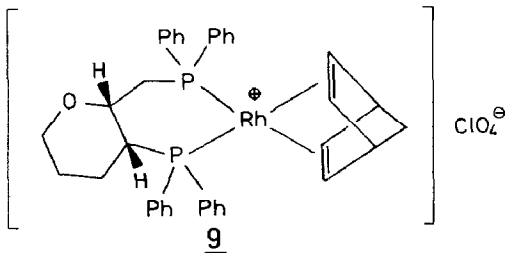

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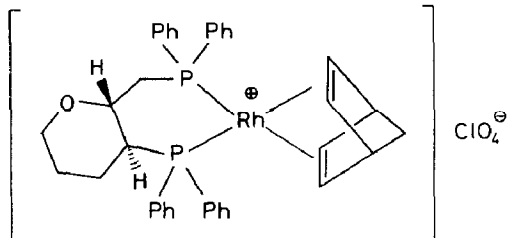

10

The enantioselectivity in hydrogenation of *Z*-α-acetylaminocinnamic acid with complex **10** was lower than that reported for complex **9** [19]. It was also almost independent of the temperature and pressure (Table 2).

Relative selectivities were also determined for hydrogenation of α-acetylaminoacrylic acid, Table 3. Again complex **9** was the more selective, and **10** exhibited only a very low selectivity. Both gave an excess of the *R* enantiomer, however. The lower enantioselectivity in hydrogenation of α-acetylaminoacrylic acid than in that of the cinnamic acid derivative observed for both **9** and **10** is not surprising, and has been noted for many other complexes [10,11,22]. The observations were recently rationalized by Koenig [23], who defined a cross section of functionalities required for efficient enantioselective hydrogenation.

Table 3

Enantioselective hydrogenation of *Z*-acetylaminoacrylic acid catalysed by the rhodium(I) complexes **9** and **10** [a]

Run	Complexes	Temperature (°C)	$p(H_2)$ (atm)	Chemical yield [b] (%)	e.e. [c]	Configuration
1	**9**	40	1.2	100	27.5	*R*
2		20	10.0	100	32.5	*R*
3	**10**	40	1.5	100	8.4	*R*
4		40	1.5	100	8.9	*R*
4		20	10	100	7.3	*R*

[a] Ratio catalyst-to-substrate was 1/100; the solvent was ethanol/benzene (1/1). [b] Based on ^{1}H NMR spectra. [c] Enantiomeric excesses were calculated on the basis of $[\alpha]_D + 66.3$, $c = 2.0$ in water for optically pure (*R*)-*N*-acetylalanine.

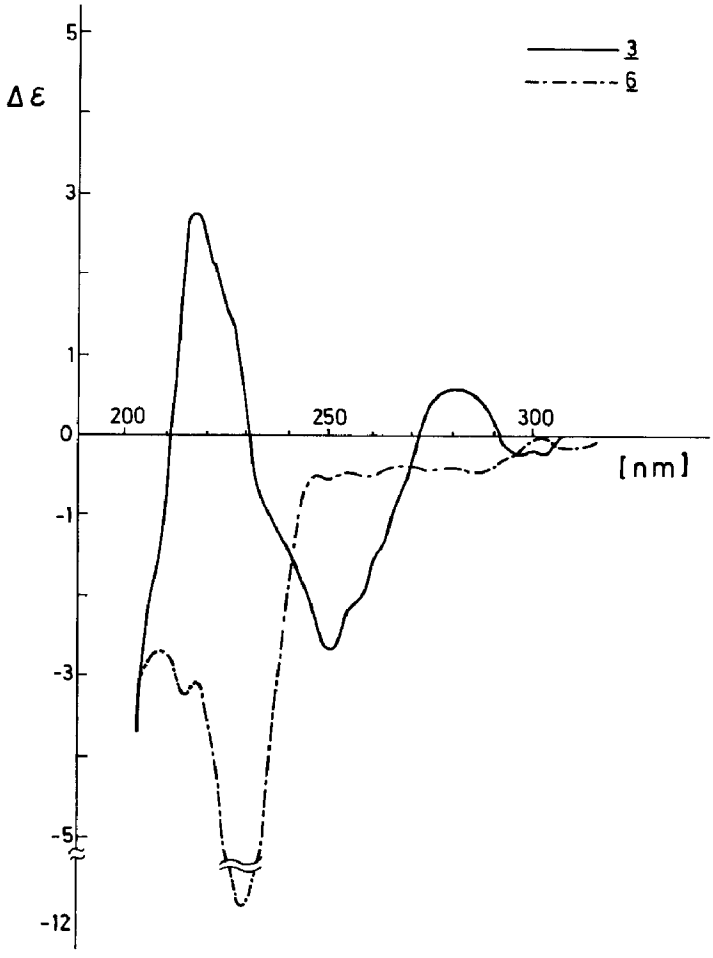

Fig. 1. CD-Spectra of diphosphines **3** (———) and **6** (·–·–·).

In an attempt to rationalise the results obtained with the complexes **9** and **10** we examined their chiroptical properties. The large difference in the appearance of the CD curves of the ligands **3** and **6** we ascribe to the interactions of the exciton type between two phenyl groups of two different Ph_2P moieties in the same molecule (Fig. 1).

Since four such pairwise interactions between individual phenylchromophores can be envisaged, it is impossible to deduce the preferred conformation of **3** or **6** from CD. Although the tetrahydropyran ring of **6**, in contrast to that in **3**, can adopt two different chair conformations, since one of the substituents is always axial [18], the strong 229 nm CD band indicates a strong preference for one single conformation of **6** in solution.

Bosnich et al. [11] described a detailed study of the chiral chelating six-membered ring diphosphines, i.e. of the complexes of two acyclic 1,3-diphosphines of the same chelate ring size as in **9** and **10**. Those authors provided convincing evidence that the chiral 6-membered ring conformation of these complexes is of decisive importance in determining the optical yields. They demonstrated that the stronger Cotton effect above 300 nm in the CD spectrum of a 2,4-bis(diphenylphosphine)pentane

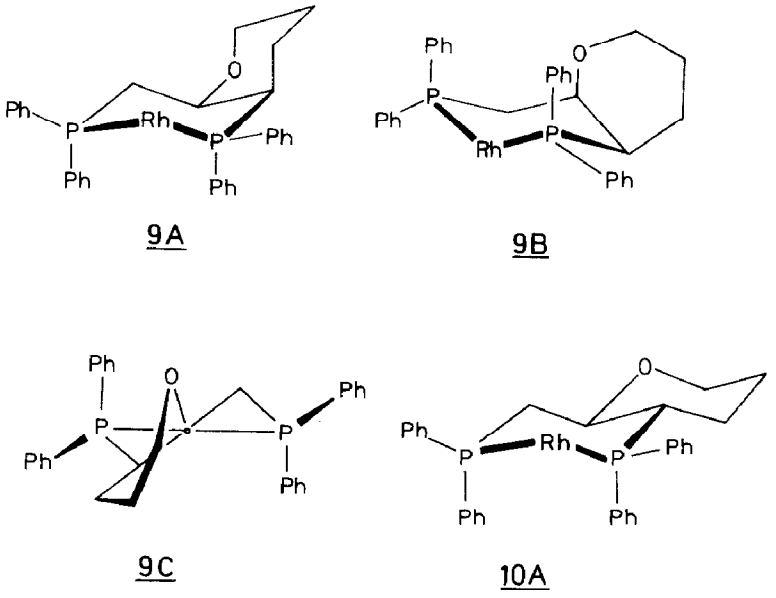

Fig. 2. A selection of possible conformations of **9** and **10**.

("skewphos") is associated with the predominant skew conformation of the chelate ring, the CD spectrum of 1,3-bis(diphenylphosphino)butane ("chairphos") exhibited a weaker Cotton effect at the same wavelength. Since only the skew conformation is chiral, and the phenyl groups are in a chiral array, the former complex exhibited a 10–20 times higher enantioselectivity in hydrogenation of a series of α,β-unsaturated α-acylamino carboxylic acids.

We ascribe the higher enantioselectivity of **9** than of **10** to a similar effect, i.e. to higher chiral distortion of the chelating 6-membered ring by the *cis*-annulated pyran ring in the former. *cis*-Annulation in **9** forces one of the bonds on the chelating ring into the axial position, Fig. 2.

To avoid strong non-bonding interaction between phenyl groups and the annulated ring, the chair conformations (**9A** or **9B**) have to addopt skew-like conformation (**9C**). In complex **10** two rings are *trans*-annulated, with both bonds on the chelating ring in the equatorial position, with a minimum of non-bonding interactions. Therefore **10A** tends to maintain the locally achiral chair conformation of the chelate ring. This conformation can also be deduced from the CD spectra. The chiral skew conformation of **9** is indicated by the stronger long-wave CD band at 333 nm (−1.25), whereas for **10**, a very weak band at 384 nm (−0.12) is observed (Fig. 3).

Consequently, the different enantioselectivities in hydrogenations with **9** and **10**, which have a bicyclic system bound to the rhodium(I) atom, and a formally vicinally substituted chelating 6-membered ring, can be accounted for in terms of the reasoning of Bosnich et al. [10,11] applied to the behaviour of monocyclic chelating six-membered ring diphosphines.

To rationalize the observation that both catalytic complexes have the same enantiomeric bias it is necessary to know the most preferred conformations of the four phenyl rings. In general, the most preferred conformations of a substituted benzene along the sp^2–sp^3 bond are those in which either one of the three benzylic

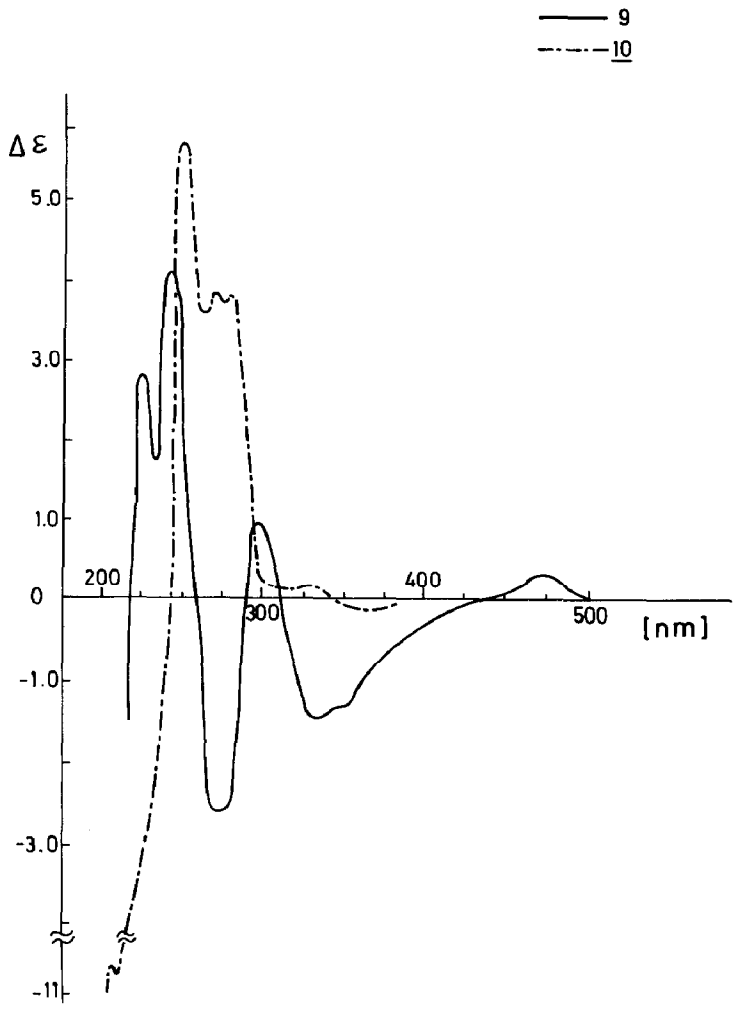

Fig. 3. CD-Spectra of rhodium(I) complexes **9** (———) and **10** (· – · – ·).

bonds is coplanar with the ring, or one in which the torsional angle of one of the benzylic bonds is 90°; six-fold barrier arises from the latter [24]. Of the two equatorially arranged P-phenyl groups, the one next to the tertiary ring–carbon atom will be sterically more restricted than the other. For the first one, molecular models indicate that the energetically preferred one seems to be rather similar for **9** and **10**, and is the one with a torsional angle of ca. 90° between P–C(3) bond and the equatorial phenyl group. By the "gear-effect" the preferred torsional angles of the other three phenyls are then automatically determined [24].

We have so far been unable to obtain crystals of **9** or **10** suitable for X-ray structure determination.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Jeol FX 90Q FT spectrometer, and the IR spectra on a Perkin–Elmer M137 spectrometer. TLC was performed on

silica gel 60F (Merck) column, and column chromatography involved use of granular silica gel (0.05–0.2 mm, Merck). Optical rotations were determined with a Perkin–Elmer 141 polarimeter in 1 dm cells. CD spectra were measured at room temperature with a Jobin–Yvon-ISA dichrograph Mark III for 1–2 m*M* solutions in acetonitrile. Data were collected on-line with a PDP/8-e (5 or 10 data points per nm), and curve smoothing was by use of the Golay–Savitzky algorithm.

The preparations of the compounds **1** and **4** (starting from the corresponding diols) were described in ref. 18, and those of compounds **2**, **6**, **7** and **9** in ref. 19. *Z*-α-*N*-Acetylaminocinnamic acid and α-*N*-acetylaminoacrylic acid were purchased from Aldrich and recrystallized before use.

(2R,3R)-2-Methanesulfonyloxymethyl-3-methanesulfonyloxy-tetrahydropyran (5)

The diol [18] (2.74 g, 20.7 mmol) and methanesulfonyl chloride (4.9 ml, 7.13 g, 62 mmol) were mixed in pyridine (15 ml), and the crude product (5.2 g, 80.8%) was isolated after usual work-up. Recrystallisation from methanol afforded pure **5**, m.p. 70.72 °C. IR (KBr): 3040, 2970, 2950, 2870, 1350, 1320, 1220, 1180, 1170, 1090, 1080, 1000, 955, 946, 905, 875, 840, 820, 805 cm^{-1}. NMR data. ^1H: δ 1.7–1.95 (m, 1H), 2.0–2.4 (m, 1H), 3.18 and 3.20 (two s, 2xCH_3), 3.3–3.6 (m, 1H), 3.8–4.0 (m, 2H), 4.18 (s, 3H), 4.49 (s, 1H), 4.55 (d, *J* 1.2 Hz, 1H). ^{13}C: δ 20.09 (C(5)), 28.51 (C(4)), 37.25 (CH_3SO_2O on C(2′)), 38.49 (CH_3SO_2O on C(3)), 67.72 (C(6)), 69.81 (C(2′)), 74.95 (C(2)), 75.96 (C(3)). Anal. Found: C, 33.57; H, 5.59. $C_8H_{16}O_7S_2$ (288.34) calcd.: C, 33.43; H, 5.59%.

(2R,3S)-2-Diphenylphosphinomethyl-3-diphenylphosphino-tetrahydropyran (3)

Lithium diphenylphosphide was prepared from 53.25 g (20.3 mmol) of triphenylphosphine and freshly-cut lithium strips (2.82 g, 40.6 mmol) in anhydrous THF (150 ml). The solution was cooled to room temperature, t-butyl chloride (18.8 g, 203 mmol) was added, and stirring was continued as the temperature was raised to 60 °C. Then compound **5** (11.7 g, 40.6 mmol) was added at −40 °C and stirring continued at −15 °C for 24 h. Monitoring by TLC (chloroform/light petroleum ether/ether 10/30/1) revealed that the reaction was almost complete after 2–3 h. After the usual work-up [17] the crude product was subjected to chromatography on 250 g of silica gel, with light petroleum/chloroform/ether (30/10/1) as eluant. From fractions 55–133 (10 ml per fraction) 12.1 g (63.7%) of chromatographically pure **3** were obtained. After recrystallisation from ethyl acetate it had m.p. 136–137 °C $[\alpha]_D = +127.2$ ($c = 1.11$ in $CHCl_3$). IR (KBr): 3070, 3050, 2900–2980 (multiplet), 2840, 1480, 1435, 1355, 1110, 1025, 950, 855, 745, 700 cm^{-1}. NMR data. ^1H: δ 1.9–1.2 (m, 3H), 2.0–3.9 (m, 2H), 4.0–4.4 (m, 2H), 5.8–5.9 (m, 1H), 7.2–7.6 (m, 20H). ^{13}C: δ 26.27 (d, *J* 3.8 Hz, C(5)), 26.61 (d, *J* 3.8 Hz, C(4)), 35.44 and 35.07 (2xd, J_1 10.2 Hz, J_2 8.8 Hz, C(2′)), 40.60 and 39.81 (2xd, $J_1 = J_2 = 6.4$ Hz, C(3)), 67.89 (s, C(6)), 77.93 (t, J_1 26.7 Hz, J_2 10.2 Hz, C(2)), 127.77,127.88, 128.11, 128.33, 128.61, 128.84, 131.72, 132.51, 133.19, 135.35, 134.03, 134.88, 135.67, 136.35, 136.85, 138.21, 138.88, 139.56, 140.13. Anal. Found: C, 79.84; H, 6.30; P, 12.72. $C_{30}H_{30}OP_2$ (468.52) calcd.: C, 79.91; H, 6.45; P, 13.22%.

*(Norbornadiene)rhodium (2R,3S)-2-diphenylphosphinomethyl-3-diphenylphosphino-tetrahydropyran perchlorate (**10**)*

To a solution of bis(diphenylphosphine) **3** (940 mg, 2.0 mmol) n 20 ml of degassed THF, $[Rh(NBD)_2]ClO_4$ (77.7 mg, 2.0 mmol) was added with stirring. After

1 h stirring at ambient temperature, 50 ml of n-hexane were added, and stirring was continued for 1 h at 0 °C. The product was filtered off, and washed with cold n-hexane (3 × 10 ml) to leave 1.55 g (100%) of orange-red crystals which had m.p. 216–218 °C (dec.). UV (EtOH) nm (log ε); 336 (3.63), 273 (3.26). IR (KBr) 2970, 2860, 1440, 1100 (broad), 925, 850, 755, 740, 705, 700 cm^{-1}. NMR data. ^1H: δ 1.3–1.5 ppm (m, 2H), 1.5–1.6 (m, CH_2 of NBD), 1.7–1.9 (m, 4H), 2.8–3.0 (m, 4H), 3.7–4.2 (m, 2xCH of NBD), 4.3–5.0 (m, 2xCH=CH of NBD), 7.3–7.9 (m, 20H). ^{13}C: δ 24.94 (d, J 6.3 Hz, C(5)), 26.93 (d, J 5.5 Hz, C(2′)), 31.52 and (2d, J_1 29.6 Hz, J_2 29 Hz, C(4)), 39.28 and 39.32 (2xd, J_1 18.9 Hz, J_2 19.5 Hz, C(4)), 54.82, 53.51 (2s, CH of NBD), 67.91 (s, C(6)), 70.0 (s, CH_2 of NBD), 73.93 and 73.85 (2d, $J_1 = J_2 = 10.8$ Hz, C(2)), 91.82, 89.30, 87.39, 85.66 (4 broad s, 2xCH=CH of NBD) 125.77, 126.17, 127.21, 127.65, 128.69, 129.01, 129.11, 129.21, 129.31, 129.43, 129.53, 129.74, 129.84, 130.48, 130.76, 130.88, 130.93, 131.50, 131.60, 131.93, 132.09, 133.27, 133.39, 135.66, 135.79. Anal. Found: C, 58.12; H, 5.29. $C_{37}H_{38}O_5P_2ClRh$ (763.02) calcd.: C, 58.24; H, 5.02%.

Hydrogenation experiments. A 25 ml tube attached to a three-way glass stopcock, so that it could be connected either to a respiratory pump or nitrogen source was used. The solvent (8 ml) was placed in this tube and dearated by alternate evacuation and flushing with nitrogen. The catalyst (0.1 mmol) was then added, the yellow-orange solution was stirred for 30 minutes under nitrogen, and, diethylamine (0.015 mmol) and either *Z*-α-*N*-acetylaminocinnamic or *Z*-α-*N*-acetylaminoacrylic acid were added. The mixture was stirred and repeatedly flushed with hydrogen. The probe tube was then placed in a Parr-hydrogenation bomb (40 ml), and the hydrogen pressure maintained at the chosen value. The crude *N*-acetyl-α-amino acids were purified by preparative thick layer chromatography on freshly prepared plates cooled with Kieselgel 60 PF_{254} (Merck) and activated at 120 °C before use. This removed completely the coloured impurities; which was not possible with flash-chromatography as used in our previous work [17–19]. ^1H NMR monitoring of the degree of conversion and the e.e. values determined (%) as described previously [17]. The results are listed in Tables 2 and 3.

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