Enantiomerically pure bicyclo[3.3.1]nona-2,6-diene as the sole source of enantioselectivity in BIPHEP-Rh asymmetric hydrogenation†

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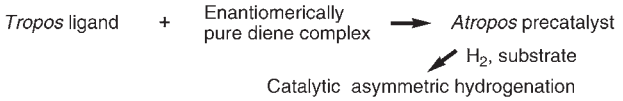
***In situ* resolution of the rapidly racemising diphosphine BIPHEP and its relatives with the cationic Rh complex of (*S*,*S*)-bicyclonona-2,6-diene permits the asymmetric hydrogenation of dehydroamino esters.**

Following the first results from Hayashi's and Carreira's laboratories, the use of enantiomerically pure dienes as ligands in asymmetric catalysis has expanded rapidly.[1,2] By contrast, the application of such dienes as templates for *in situ* ligand enantioselection has rarely been explored.[3] Experiments that demonstrate the principle shown in Scheme 1 are presented here.

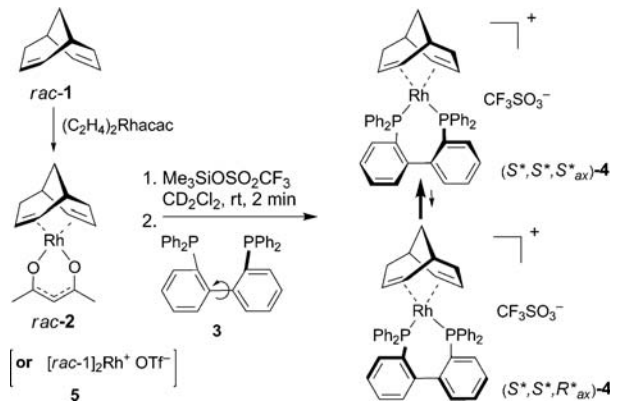
Soon after the first demonstration of [diene]RhBINAP$^+$ complexes as catalysts for asymmetric hydrogenation of enamides,[4] the preparation and application of the simpler atropisomeric but dynamic 2,2′-bis(diphenylphosphino)-biphenyl (BIPHEP) system was claimed.[5] This work was later refuted.[6] Interest had however been stimulated in applying readily racemised (*tropos* as opposed to *atropos*) ligands to asymmetric catalysis.[7] Since then, Mikami, Gagné and others have provided pioneering examples.[8,9]

The availability of Rh complexes derived from enantiomerically pure (*S*,*S*)- or *rac*-bicyclo[3.3.1]nona-2,6-diene **1** provided the basis for further work.[10] Equivalents of BIPHEP **3** and complex *rac*-**2** were mixed in CD_2Cl_2, and the reaction was monitored by ^{1}H and ^{31}P NMR. Two diastereomeric Rh complexes **4** were observed, whose ratio changed over time; only one was present after *ca.* 60 h (Scheme 2). Likewise, the bis-alkene complex **5** gave a single racemic diastereomer of product **4** after reaction with ligand **3** in CD_2Cl_2 for 20 h. When complex *rac*-**2** was activated and then treated with BIPHEP **3** in CD_3OD, the process was complete within 30 min at RT. Again, a single diastereomer was observed at equilibrium (>98%).

In prior work,[3] Faller and Wilt demonstrated 3 : 1 diastereoselectivity between equilibrating diastereomers of complex **6**, derived from Carreira's diene;[1b] the major complex was structurally characterised after recrystallisation. Isolation and crystallisation of our racemic product for X-ray analysis ($CDCl_3$–CH_2Cl_2; pentane layering) indicated that the stable form of complex **4** had the (*S**,*S**)-alkene and (*S**$_{ax}$)-BIPHEP configurations (Fig. 1). Stereoselectivity must arise from more favourable H–H van der Waals' interactions between diene and ligand in the preferred form. Accordingly, the related



Scheme 1 Principle of the hydrogenation experiment.



Scheme 2 Equilibration of diphosphine dialkene rhodium diastereomers.

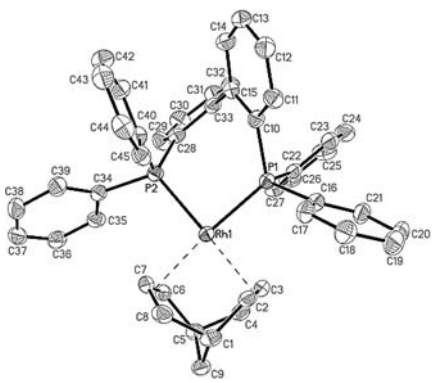


Fig. 1 ORTEP diagram of the X-ray structure of the cationic component of complex (*S**,*S**,*S*$_{ax}$*)-**4**; CCDC 686878. See ESI for full details.†

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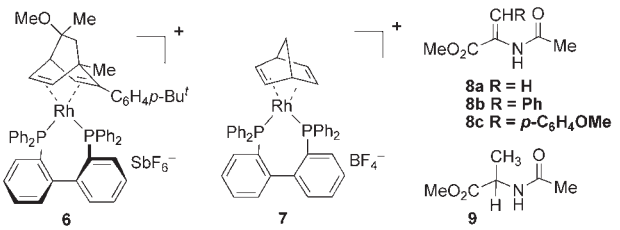
complex cation [NBD]RhBIPHEP$^+$ **7** shows longer H_{ortho}–H_{alkene} distances between the P–aryl groups and the vinylic C–H of the less bulky bicyclo[2.2.1]heptadiene.[11]



Enantiomerically enriched (S,S,S_{ax})-**4** was prepared in this way from 99% ee (S,S)-**1**. Hydrogenation of enamide **8a** was carried out in MeOH, and was very slow under standard conditions (2.5 mol% catalyst, 1.5 atm H_2, 0 °C, 16 h, 50% completion) giving product (R)-**9** in 23% ee. Adding LiCl permitted complete reaction at RT, but modest ee's were still observed, up to 42% (S). The corresponding NBD or COD complexes of ligand **3** effected complete hydrogenation within 10 min under the same conditions. Enantiomerically pure complex **6** had previously been found to resist hydrogenation, and is not an active catalyst.[3]

Stoichiometric hydrogenation of equilibrated and non-equilibrated complexes **4** was carried out at 0 °C on a 12 μmolar scale (0.5 mL MeOH) in the absence of substrate. For the initially formed mixed diastereomers of **4** this was biphasic, the first phase being fast and the second very slow, accompanied by a Rh mirror. After equilibration to the single stable (S,S,S_{ax})-**4** diastereomer, only the slow phase was observed. Further stoichiometric hydrogenation, followed by ^{31}P NMR, corroborated this (Fig. 2). There is a correspondence between the rate of hydrogen uptake and the rate of (S_{ax})–(R_{ax}) interconversion, implying that the diene dissociates in both processes, and free diene arising mainly from the (R_{ax})-diastereomer is hydrogenated. The BIPHEPRh$^+$ solvate complex is formed concurrently under H_2, but not under Ar.

The modest results in hydrogenation encouraged a change of tack. Keay *et al.* had found that 3,3′-dialkoxy-derivatives of BINAP gave greatly superior enantioselectivities to the parent ligand in simple Rh-catalysed hydrogenations, with enantioselectivities of 99% for **8a** → **9**.[12] Synthesis of the corresponding

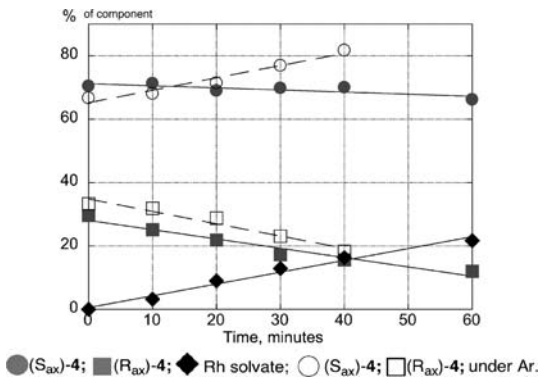
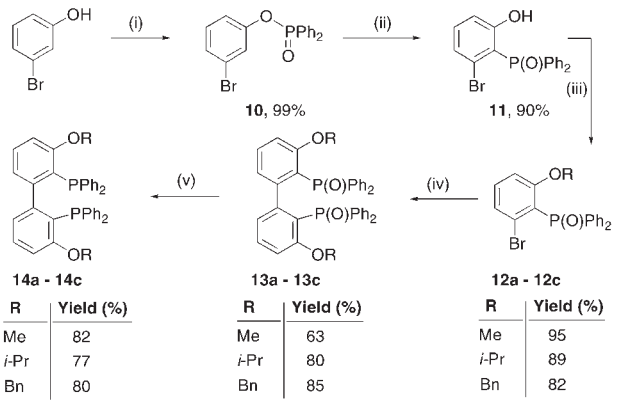


Fig. 2 Hydrogen uptake for complex **4** in CD_3OD, 0 °C by ^{31}P NMR; t = 0 follows several minutes' equilibration at 0 °C.



Scheme 3 (i) $Ph_2P(O)Cl$, NEt_3, DMAP, CH_2Cl_2, 0 °C to RT; (ii) LDA, THF, −78 °C to RT; (iii) RX (X = Br, I), Cs_2CO_3–Me_2CO, RT, 12 h; (iv) Cu 35 μ, py, 120 °C, 12 h; (v) $HSiCl_3$, Bu_3N, *m*-xylene, 120 °C, 14 h.

3,3′-dialkoxy BIPHEP derivatives was carried out through the anionic phospho-Fries rearrangement of **10** to **11**,[13] conversion to the ethers **12a–c**, Ullmann coupling to give **13a–c**,[14] and P=O reduction to **14a–c**,[15] as shown in Scheme 3.

In contrast to the BIPHEP complex **4**, the analogous Rh complexes **15a–c** derived from (S,S)-**1** were all stable as 1 : 1 diastereomeric pairs in CD_3OD at ambient temperature. In the case of **15a** and **15b**, their interconversion required ≥ 5 h heating at 50 °C before it was demonstrably complete, the second diastereomer then being undetectable by ^{31}P NMR (Fig. 3). The equilibration of **15c** was only 97% complete after 12 h at this temperature. Complexes **15a–c** were isolated as stable orange solids in each case. The samples, including assigned (S,S,S_{ax})-**4**, had similar CD curves (positive ε_{max}, 465–485 nm), requiring that each one is the (S_{ax})-biaryl diastereomer.

A series of hydrogenations of alkene **8** was carried out under standardised conditions (Table 1). It was verified that the Rh complex of (S,S)-**1** with an achiral ligand did not lead to

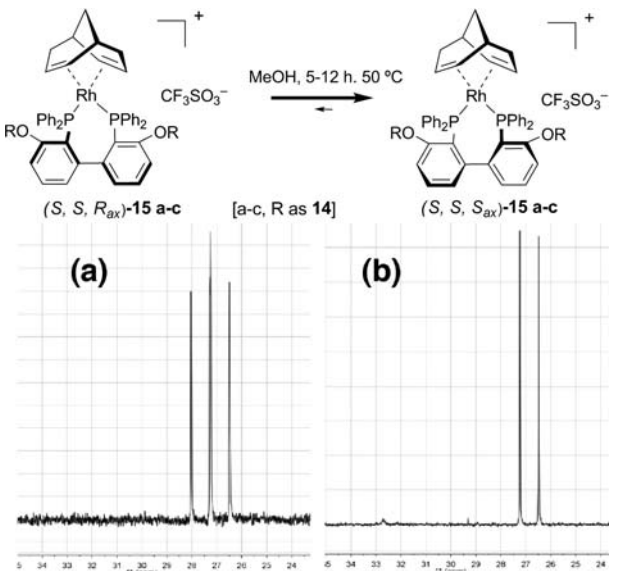


Fig. 3 ^{31}P NMR spectra of complex **15a** in CD_3OD; (a) before, and (b) after 5 h at 50 °C [(R_{ax})-δ_P = 27.65, (S_{ax})-δ_P = 26.87 ppm].

Table 1 Hydrogenation of dehydroaminoesters with $P_2Rh^+OTf^-$ complexes; all reactions went to completion[a]

Entry	MeOH/mL	Catalyst	Reactant	Time/h	Ee (%) (*S*)
1	5	[b]	**8a**	2.0	<1
2	5.0	**4**	**8a**	3	20
3	5.0	**15a**	**8a**	0.8	27
4	6.0	**15b**	**8a**	2.0	84
5[c]	5.0	**15b**	**8a**	12	85
6[d]	2.5	**15b**	**8b**	19	17
7[e]	1.5	**15b**	**8a**	3.1	6
8[f]	5.0	**15c**	**8a**	3.0	80

[a] Conditions: alkene (0.23 mmol), catalyst (0.0046 mmol), H_2 1.8 atm, RT, save run 5; assay by Chiralsil-Val GC. [b] $DPPBRh^+$ complex of (*S*,*S*)-**1**. [c] At 0 °C, 85% ee also by chiral shift analysis.[16] [d] Half-scale; ee was determined by HPLC with Chiralcel OD-H, 1 : 19 isopropanol : hexane. **8c** gave similar result. [e] No equilibration of the catalyst diastereomers before reaction. [f] Ligand is 93% ee.

Scheme 4 Improved conditions for asymmetric hydrogenation with catalyst **15b**; as Table 1, entry 4 with 0.023 mmol (*S*,*S*)-**1** added.

enantioselectivity (entry 1). Hydrogenation with the OMe-BIPHEP complex **15a** gave a disappointing ee (entry 3). Much more promising results were obtained with the OPr^i analogue **15b**, improved only slightly at 0 °C and not extended to the more slowly hydrogenating aromatic dehydroamino ester (entries 4–6; see below for a more detailed discussion). Starting from non-equilibrated catalyst **15b** (mixture of R_{ax} and S_{ax}-diastereomers) a low ee was obtained (entry 7). The corresponding OBn complex **15c**, which was only 93% enantiomerically pure, also looked promising (entry 8).

It was found that the enantioselectivity observed in hydrogenation of **8** by catalyst **15b** was strongly concentration dependent. The ee in 0.5 mL MeOH was 46% (cf. Table 1, entry 4); see ESI for details.†This implied that high concentrations of catalyst and substrate were detrimental. Higher concentrations of reactant **8a**, known to bind strongly to rhodium during hydrogenation, could be responsible for promoting partial or complete phosphine dissociation. Since the ligand racemises easily this offers a possible explanation for the unusual ee dependency.

Helpful insights came when the reaction of entry 4, Table 1 was repeated, but with *in situ* NMR monitoring. This demonstrated that the original diene complex (*S*,*S*,S_{ax})-**15b** remained largely intact on completion of hydrogenation! With this evidence in hand, hydrogenation was now repeated in the presence of excess (*S*,*S*)-**1**. A strong improvement in the ee of the product was observed (Scheme 4). Hence free diene provides an important additional function in regulating the catalyst configuration and suppressing free ligand racemisation,[17] or the formation of a catalytically active but less enantioselective by-product.

These results demonstrate the viability of a simple 2,2′-diphosphinated biphenyl as the sole active ligand in an asymmetric hydrogenation catalyst. The only previous example involved BIPHEP and its sulfonated analogues operating in an (L)-proline-derived ionic liquid solvent, giving **9** in up to 69% ee.[18] With access to a range of BIPHEP derivatives feasible now,[19] these results extend the potential for their practical application in asymmetric hydrogenation.

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