

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

Tharmalingam Punniyamurthy,*‡, Monika Mayr, Alexander S. Dorofeev, Carole J. R. Bataille, Silvia Gosiewska, Bao Nguyen, Andrew R. Cowley and John M. Brown*

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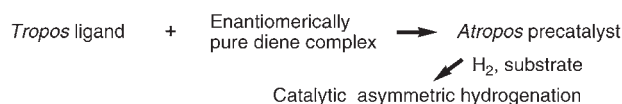
In situ resolution of the rapidly racemising diphosphine BIPHEP and its relatives with the cationic Rh complex of (*S,S*)-bicyclonona-2,6-diene permits the asymmetric hydrogenation of dehydroamino esters.

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.

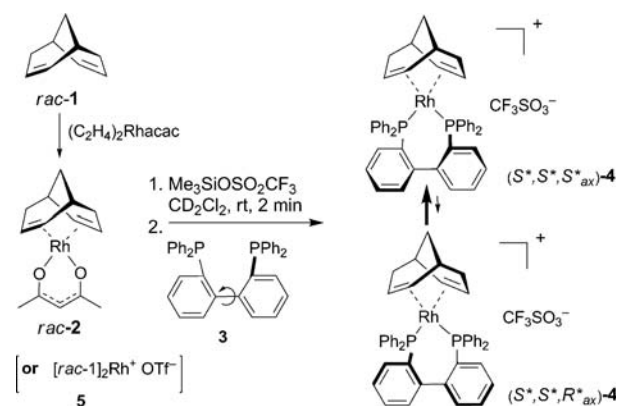
Soon after the first demonstration of [diene]RhBINAP⁺ complexes as catalysts for asymmetric hydrogenation of enamides,⁴ the preparation and application of the simpler atropisomeric but dynamic 2,2'-bis(diphenylphosphino)-biphenyl (BIPHEP) system was claimed.⁵ This work was later refuted.⁶ Interest had 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 CD₂Cl₂, and the reaction was monitored by ¹H and ³¹P 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 CD₂Cl₂ for 20 h. When complex *rac-2* was activated and then treated with BIPHEP **3** in CD₃OD, 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



Scheme 1 Principle of the hydrogenation experiment.



Scheme 2 Equilibration of diphosphine dialkene rhodium diastereomers.

and crystallisation of our racemic product for X-ray analysis (CDCl₃–CH₂Cl₂; 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

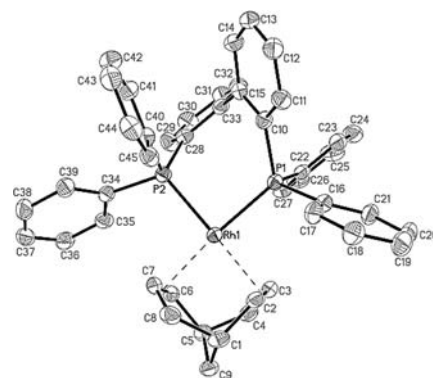


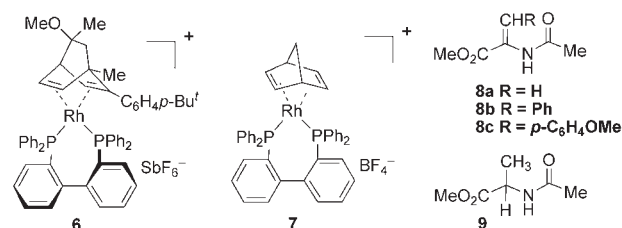
Fig. 1 ORTEP diagram of the X-ray structure of the cationic component of complex (*S*^{*},*S*^{*},*S*_{ax}^{*})-**4**; CCDC 686878. See ESI for full details.†

Chemical Research Laboratory, 12 Mansfield Rd, Oxford, UK OX1 3TA.
 E-mail: john.brown@chem.ox.ac.uk; Fax: +44 (0)1865 285002

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‡ On leave 2007 from the Indian Institute of Technology, Department of Chemistry, Guwahati 781039, India, tpunni@iitg.ernet.in

complex cation $[\text{NBD}]\text{RhBIPHEP}^+$ **7** shows longer $\text{H}_{\text{ortho}}-\text{H}_{\text{alkene}}$ 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** \rightarrow **9**.¹² Synthesis of the corresponding

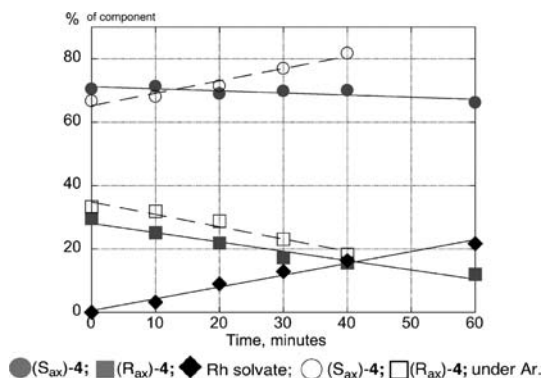
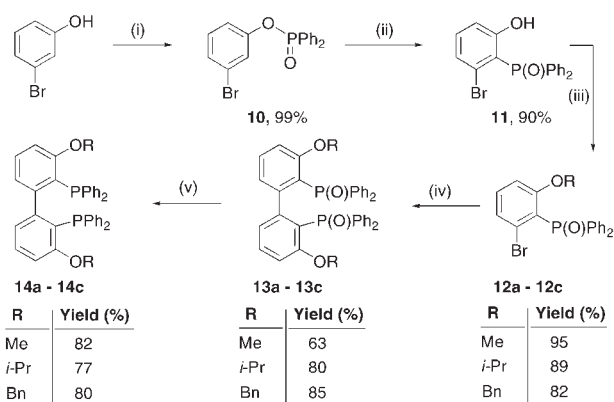


Fig. 2 Hydrogen uptake for complex **4** in CD_3OD , 0 °C by ^{31}P NMR; $t = 0$ follows several minutes' equilibration at 0 °C.



Scheme 3 (i) $\text{Ph}_2\text{P}(\text{O})\text{Cl}$, 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 $\text{P}=\text{O}$ 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

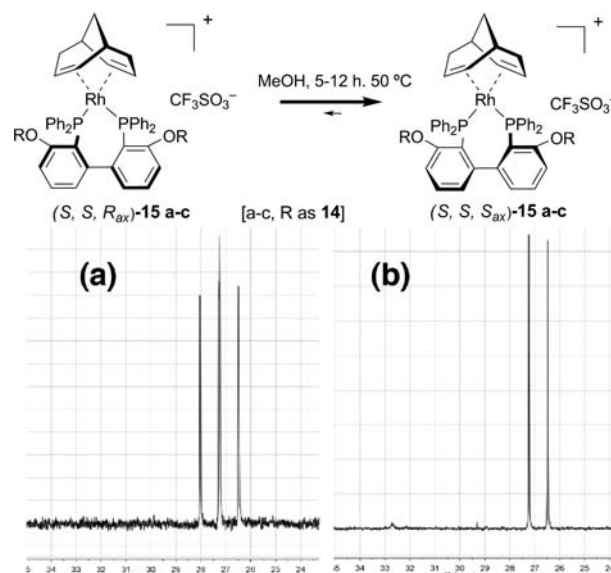
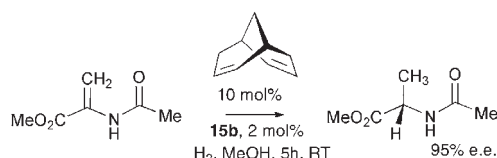


Fig. 3 ^{31}P NMR spectra of complex **15a** in CD_3OD ; (a) before, and (b) after 5 h at 50 °C [$(\text{R}_{\text{ax}})-\delta_{\text{P}} = 27.65$, $(\text{S}_{\text{ax}})-\delta_{\text{P}} = 26.87$ ppm].

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 Chiralcel-Val GC. ^b DPPBRh⁺ complex of (S,S)-**1**. ^c At 0 °C, 85% ee also by chiral shift analysis. ^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 OPrⁱ 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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