Monodentate Chiral Spiro Phosphoramidites: Efficient Ligands for Rhodium-Catalyzed Enantioselective Hydrogenation of Enamides**

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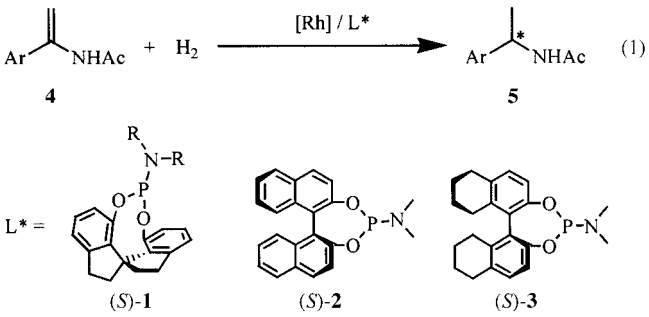
Optically active α-arylalkylamines are an important class of compounds that are widely used in organic and pharmaceutical synthesis, and much effort has been made to develop efficient asymmetric synthetic methods for them.[1] Asymmetric catalytic hydrogenation of enamides, initiated by Kagan et al.,[2] provides a direct and convenient route to chiral amine derivatives. However, many well-known chiral diphosphane ligands, such as DIOP, BINAP, and CHIRAPHOS, which are extremely successful in the asymmetric hydrogenation of dehydroamino acid derivatives, do not give high enantioselectivity in the hydrogenation of enamides.[3, 4] A breakthrough was achieved by Burk et al.[4a] with the introduction of BPE and DuPHOS ligands, which gave excellent enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of enamides. Lately, some other P ligands were also reported to be efficient in the hydrogenation of enamides.[4b, 5] However, all ligands that gave a high degree of enantiocontrol are bidentate. To our knowledge, no efficient chiral monodentate ligand has been reported for the asymmetric hydrogenation of enamides, although some monodentate P ligands were successfully used in the hydrogenation of dehydroamino acid derivatives.[6] Here we describe highly efficient monodentate chiral ligands **1** containing a 1,1′-spirobiindane backbone for the Rh-catalyzed asymmetric hydrogenation of α-arylethenylamine derivatives [Eq. (1)] with excellent enantioselectivities (up to 99.7% *ee*).



The chiral monodentate phosphoramidite ligands **1** (abbreviated SIPHOS) were conveniently synthesized in good yields from enantiomerically pure 1,1′-spirobiindane-7,7′-diol, which was easily prepared from 3-methoxybenzaldehyde by using the procedure described by Birman et al.[7] We demonstrated recently that the Rh complex of (*S*)-**1a** ($R = CH_3$) is a highly efficient catalyst in the asymmetric hydrogenation of dehydroamino acid and itaconic acid derivatives with up to 99.3% *ee*. Therefore, we were prompted to investigate the utility of this catalyst in the asymmetric hydrogenation of α-phenylenamide **4a** and an excellent enantioselectivity (up to 98.8% *ee*) was achieved. This showed, for the first time, that monodentate phosphorus ligands can be effective in the enantiocontrol of asymmetric hydrogenation of enamides.

The results in Table 1 show that the enantioselectivity of the reaction was sensitive to the solvent used, and toluene is the solvent of choice. In contrast, the hydrogen pressure has a negligible influence on the enantioselectivity. For example, in the hydrogenation of **4a** with Rh/(*S*)-**1a** catalyst in toluene, the *ee* values of product **5a** at 25 °C under 10 atm and 100 atm H_2 were 96% and 96.2%, respectively (Table 1, entries 1 and 2). The investigation of catalyst loading showed that 0.5 mol% catalyst was sufficient to give a high enantioselectivity, while the *ee* value of the product dropped drastically with 0.1 mol% catalyst.

Table 1. Asymmetric hydrogenation of **4a** (Ar = Ph) with $[Rh(cod)_2]BF_4$/(*S*)-**1a**.[a]

Entry	Solvent	Cat. [mol%]	*ee*[b] [%]	Config.[c]
1	toluene	1	96	*S*
2[d]	toluene	1	96.2	*S*
3[e]	toluene	1	98.7	*S*
4	EtOAc	1	89.8	*S*
5	acetone	1	83.3	*S*
6	CH_2Cl_2	1	82.5	*S*
7	THF	1	80.5	*S*
8	CH_3OH	1	50	*S*
9[e]	toluene	0.5	98.8	*S*
10[d]	toluene	0.1	84	*S*

[a] The reaction was performed at 25 °C with 0.5 mmol of substrate in 5 mL of solvent, $P_{H_2} = 10$ atm, $[Rh(cod)_2]BF_4$/(*S*)-**1a** = 1/2.2 unless otherwise mentioned. Complete conversions were achieved within 12 h. Yields were quantitative. [b] Determined by chiral capillary GC on a Varian Chirasil-L-Val column (25 m). [c] Determined by comparing the optical rotation with the reported value.[4a] [d] $P_{H_2} = 100$ atm. [e] $T = 5$ °C, $P_{H_2} = 50$ atm.

Catalysts prepared in situ from cationic Rh complexes were active in the asymmetric hydrogenation of enamide **4a** and provided a similar level of enantiocontrol, although the catalyst with a bulkier counteranion needed a longer time for completion of the reaction (Table 2, entries 1, 4, 5). In sharp contrast, the catalyst prepared from the neutral complex $[\{RhCl(cod)\}_2]$ was completely inert under the same conditions (entry 6). This might imply that the difficult dissociation of chloride hindered the coordination of the substrate to Rh.[5d, 5e] The influence of ligand structure on the enantioselectivity of the catalysts was also examined in the hydrogenation of **4a**. When the alkyl groups on the nitrogen atom of ligands **1** was changed from methyl ((*S*)-**1a**) to ethyl ((*S*)-**1b**) and isopropyl ((*S*)-**1c**), the enantioselectivity of the

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Table 2. Asymmetric hydrogenation of **4a**: influence of the structure of the catalyst.[a]

Entry	Catalyst	T [°C]	t [h][b]	*ee* [%]	Config.
1	$[Rh(cod)_2]BF_4$/(*S*)-**1a**	25	12	96	*S*
2[c]	$[Rh(cod)_2]BF_4$/(*S*)-**1a**	5	12	98.7	*S*
3	$[Rh(cod)_2]BF_4$/(*R*)-**1a**	25	12	96.2	*R*
4	$[Rh(cod)_2]PF_6$/(*S*)-**1a**	25	20	96.4	*S*
5	$[Rh(cod)_2]SbF_6$/(*S*)-**1a**	25	48	95.3	*S*
6	$[\{Rh(cod)Cl\}_2]$/(*S*)-**1a**	25	no reaction		
7	$[Rh(cod)_2]BF_4$/(*S*)-**1b**	25	20	57	*S*
8	$[Rh(cod)_2]BF_4$/(*S*)-**1c**	25	24	38	*S*
9[c]	$[Rh(cod)_2]BF_4$/(*S*)-**2**	5	12	93	*R*
10[c]	$[Rh(cod)_2]BF_4$/(*S*)-**3**	5	12	96	*R*

[a] Reaction conditions: substrate/catalyst (S/C) = 100; P_{H_2} = 10 atm unless otherwise mentioned. [b] Time for 100% conversion. [c] P_{H_2} = 50 atm.

catalysts was greatly decreased (entries 7 and 8). For comparison, ligand (*S*)-**2**, which was developed by Feringa et al. and was highly efficient in the asymmetric hydrogenation of dehydroamino acid derivatives,[6d] was investigated, and 93% *ee* was obtained (entry 9). A difference between (*S*)-**1a** and (*S*)-**2** is that the dihedral angle of the two aromatic planes is larger in the former than in the latter. This might be one of the reasons that (*S*)-**1a** provides a more efficient steric effect around the Rh atom, which improves the enantioselectivity of the catalyst. This rationale is supported by the utility of ligand (*S*)-**3** prepared from H_8-BINOL.[8] The dihedral angle of the two aromatic planes in (*S*)-**3** should be larger than that in (*S*)-**2**, but smaller than that in (*S*)-**1a**. When the Rh complex of (*S*)-**3** catalyzed the asymmetric hydrogenation of enamide **4a**, 96% *ee* was achieved (entry 10). This *ee* value lies between those with (*S*)-**1a** (98.7% *ee*) and (*S*)-**2** (93% *ee*).

A variety of α-arylenamides can be hydrogenated with Rh/(*S*)-**1a** catalyst to produce the corresponding α-arylamine derivatives with high *ee* values (Table 3). The electronic nature of the phenyl ring of the enamide had little influence on the enantioselectivity of the reaction, while substitution at the *ortho* or *meta* position of the phenyl ring led to a lower *ee* value.

Although several rhodium complexes with monodentate phosphorus ligands have been successfully applied in the asymmetric hydrogenation of dehydroamino acid and itaconic acid derivatives, the structures of the catalysts are still unknown.[9] We were able to grow a single crystal of the Rh complex of (*S*)-**1a** suitable for X-ray crystallography. The structure of $[Rh(cod)\{(S)\text{-}\mathbf{1a}\}_2]^+$ is shown in Figure 1.[10, 11] The complex contains two phosphoramidite ligands **1a**, coordinated to Rh through the P atom. To minimize the steric repulsion, the two ligands have an orientation in which the angle of the two Rh-P-N planes is 43.6°. The Rh–P bond lengths (2.286 Å) in the crystal of $[Rh(cod)\{(S)\text{-}\mathbf{1a}\}_2]^+$ are close to those reported in the Rh complexes of bidentate phosphane ligands.[12] However, the P-Rh-P angle (95.6°) is distinctly larger than those in Rh complexes of bis-phosphanes.[12] This may cause the chiral spiro frameworks of the ligands in the transition state to be closer to the substrate coordinated to Rh and enhance the enantiodiscrimination of the catalyst.

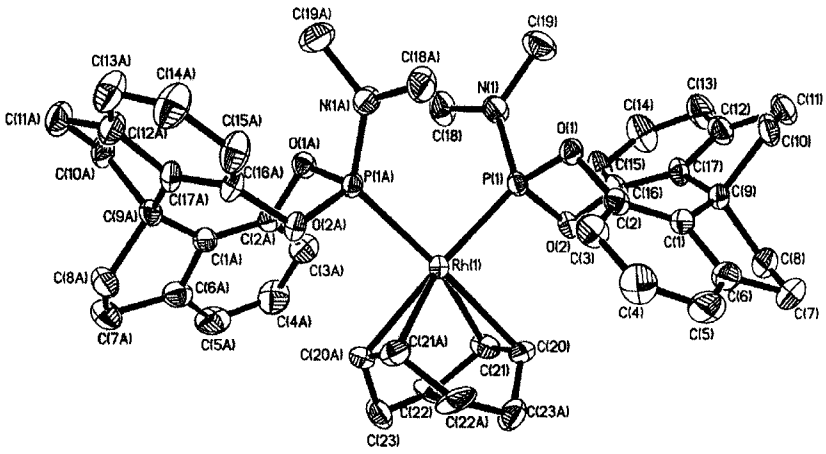

Figure 1. Structure of $[Rh(cod)\{(S)\text{-}\mathbf{1a}\}_2]^+$.

In conclusion, we have developed novel and easily prepared chiral spiro phosphorus ligands that provide the first examples of highly efficient monodentate chiral ligands for the asymmetric hydrogenation of enamides. The applications of these ligands in other asymmetric transformations are currently under investigation.

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Table 3. Asymmetric hydrogenation of **4** with catalysis by Rh/(*S*)-**1a**.[a]

Entry	Ar	*ee* [%][b]	Config.[c]
1	C_6H_5 (**4a**)	98.7	*S*
2	p-$CH_3C_6H_4$ (**4b**)	99.7	*S*
3	m-$CH_3C_6H_4$ (**4c**)	91.6	*S*
4	p-$CF_3C_6H_4$ (**4d**)	98.9	*S*
5	p-FC_6H_4 (**4e**)	99.1	*S*
6	o-FC_6H_4 (**4f**)	91.1	*S*
7	p-ClC_6H_4 (**4g**)	99.3	*S*
8	p-BrC_6H_4 (**4h**)	99.5	*S*
9	2-furanyl (**4i**)	98.7	*S*
10	2-thienyl (**4j**)	95.8	*S*

[a] Reaction condition: S/C = 100, T = 5 °C, P_{H_2} = 50 atm. [b] Determined by chiral capillary GC on a Varian Chirasil-L-Val column (25 m). [c] Determined by comparing the optical rotation with the reported value.[4a]

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[10] Crystal data for $[Rh(cod)\{(S)\text{-}\mathbf{1a}\}_2](OH)\cdot CH_2Cl_2$: $C_{47}H_{55}N_2Cl_2O_5P_2Rh$, $M_r = 963.68$, $T = 293$ K, tetragonal, space group $P4_12_12$, $a = 10.495(2)$, $b = 10.495(2)$, $c = 42.528(12)$ Å, V4684.1(19) Å^3, $Z = 4$, 4099 unique reflections, $R1 = 0.0519$. CCDC 179716 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[11] The salt of the Rh$^{\text{I}}$ complex obtained as a single crystal was $[Rh(cod)\{(S)\text{-}\mathbf{1a}\}_2](OH)$, instead of expected $[Rh(cod)\{(S)\text{-}\mathbf{1a}\}_2]BF_4$. This might be because the $[Rh(cod)_2]BF_4$ used in the preparation of catalyst contained water of crystallization [Aldrich 33498-7 (2000–2001)]. The single crystal of $[Rh(cod)\{(S)\text{-}\mathbf{1a}\}_2](OH)$ was also tested in the catalytic hydrogenation of **4a**, and 97.6% *ee* (at 10 °C) was obtained.

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Gas-Phase Detection of the Elusive Benzoborirene Molecule**

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The cyclic delocalization of π electrons, responsible for the important concepts of aromaticity and antiaromaticity,[1] has been fascinating ever since the discovery of benzene by Michael Faraday almost 200 years ago.[2] The π system of benzene can be ported to the five- and seven-membered rings by removing or introducing a CH^+ unit to result in the cyclopentadienyl anion ($C_5H_5^-$) and tropylium cation ($C_7H_7^+$ (**1a**),[3] Scheme 1), respectively. Volpin et al. suggested that it

Scheme 1. Structures of (potentially) π aromatic compounds.

is possible to generate heteroaromatic homologues of aromatic hydrocarbons by substitution of a CH^+ unit by an isoelectronic BH group.[4] Borirene **2b**[5] and 1*H*-borepin **1b**,[6] first synthesized in a low-temperature argon matrix and in solution, thus resemble the 2π-electron cyclopropenylium **2a**[7] and the 6π-electron tropylium cation **1a**, respectively (Scheme 1). Extension of the 6π-electron system onto a second ring results in benzocyclopropenylium **3a** and benzoborirene **3b** as the simplest systems (Scheme 1). Although studied theoretically,[8] **3a** and **3b** have not yet been observed experimentally.

How could the elusive benzoborirene **3b** be "made" in the laboratory? Ground-state boron and carbon atoms are known to react with a variety of unsaturated systems in crossed-beam experiments by an atom addition–hydrogen elimination mechanism.[9, 10] This protocol was used very recently to produce **2b** from atomic boron and ethene in the gas phase through reaction (1).[9a] Here we extend this novel concept and report on the formation of the hitherto unknown benzoborirene **3b**, the isoelectronic boron analogue of the elusive **3a**, through the atom–molecule reaction (2).

$$^{11}B + C_2H_4 \rightarrow \underset{(\mathbf{2b})}{^{11}BC_2H_3} + H \qquad (1)$$

$$^{11}B + C_6D_6 \rightarrow \underset{([D5]\text{-}\mathbf{3b})}{^{11}BC_6D_5} + D \qquad (2)$$

This reaction was studied in the gas phase at the molecular level by employing a crossed molecular beam setup.[11] We prepared a pulsed boron beam by laser ablation of a boron rod and by entraining the ablated atoms in helium gas; this beam perpendicularly crossed a beam of benzene seeded in argon in a scattering chamber at a collision energy of (23.1 ± 0.8) kJ mol^{-1}. The reaction products were detected with a rotatable quadrupole mass spectrometer after electron ionization (EI); the ionizer was suited in an ultra-high-vacuum chamber. Velocity distributions of the product were collected with the time-of-flight (TOF) technique, that is, recording the arrival time of a distinct mass-to-charge ratio (m/z) of the ionized product, at different scattering angles (Figure 1).[11] Integrating these TOF spectra leads to the laboratory angular distribution.

TOF spectra were recorded at m/z 93 ($^{11}BC_6D_5^+$) and 91 ($^{11}BC_6D_4^+$). At both mass-to-charge ratios, superimposable spectra were obtained suggesting that the signal at m/z 91 originates from cracking of the parent molecule (m/z 93) in

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