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Novel monodentate spiro phosphorus ligands for rhodium-catalyzed hydrogenation reactions

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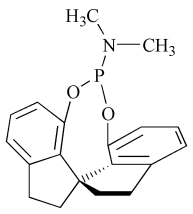
Novel monodentate phosphorus ligands containing the 1,1′-spirobiindane backbone have been synthesized and applied in the asymmetric rhodium-catalyzed hydrogenation of functionalized olefins, providing excellent enantioselectivities (up to 99.3% ee).

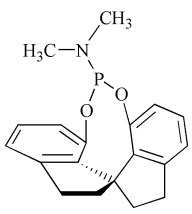
The homogeneous catalytic asymmetric hydrogenation of functionalized prochiral olefins is one of the most developed and most useful transition metal-catalyzed reactions. In the rhodium-catalyzed asymmetric hydrogenation of prochiral enamines, the use of chiral phosphorus ligands has been found to be extremely successful and those that are bidentate have been the most effective.[1–3] However, the development of monodentate chiral phosphorus ligands for asymmetric hydrogenation has been less successful even though the earliest chiral ligand used by Knowles and Sabacky in this reaction was monodentate phosphine.[4] Very recently, chiral monodentate phosphines, phosphonites, phosphites and phosporamidites have been reported to be excellent ligands in the rhodium-catalyzed asymmetric hydrogenation of dehydroamino acid and itaconic acid derivatives.[5–9] It is noteworthy that all the reported monodentate ligands that induced high enantioselectivity are phosphorus derivatives of binaphthol.[10]

In the ligand design for asymmetric synthesis, C_2-symmetric biaryls, like 1,1′-binaphthalene derivatives, occupy a prominent position. By contrast, spiranes, another class of C_2-symmteric molecules which also possess axial chirality, have received much less attention. The rigidity of the spirocyclic framework should decrease the flexibility of these ligands and their related complexes and consequently benefit selectivity in asymmetric catalysis. The chiral spiro compounds which have been employed in asymmetric synthesis include spiro bis(phosphinite) and spiro bis(isoxazoline).[11,12] Both of them are bidentate ligands. In this paper, we report the synthesis of novel and highly effective chiral monodentate phosphoramidite ligands containing a 1,1′-spirobiindane backbone and their application in the rhodium-catalyzed asymmetric hydrogenation of functionalized olefins, which provides the first example of monodentate chiral ligands with a spiro structure in asymmetric catalysis.

The chiral spiro phosphoramidite ligands **1** (SIPHOS) were conveniently synthesized in high yields from enantiomerically pure (*S*)- and (*R*)-1′1-spirobiindane-7,7′-diol[13] and hexamethyl phosphoramide (HMPT). Compounds **1** have been characterized by elemental analysis, ^{1}H and ^{31}P NMR spectroscopy. They are white solids and are very stable in the atmosphere.[14]



(*S*)-**1**

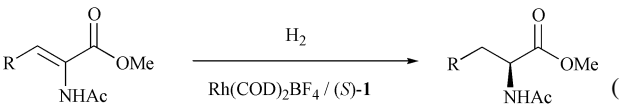


(*R*)-**1**

Ligands **1** were found to be highly efficient in the rhodium-catalyzed hydrogenation of dehydroamino esters. The hydrogenation of methyl 2-acetamidocinnamate was performed at room temperature under ambient H_2 pressure in the presence of 1 mol% catalyst formed *in situ* from $[Rh(COD)_2BF_4]$ and the phosphoramidite ligand (*S*)-**1** (1:2.1). Excellent enantioselectivities (95.6–97.4% ee) were achieved in nonprotic solvents such as CH_2Cl_2, toluene, EtOAc, THF and acetone, although the reaction in methanol gave a slightly lower enantioselectivity (93.9% ee). The pre-generation of the active catalyst was found to be unnecessary.

The influence of H_2 pressure and the Rh : substrate ratio on the rate and enantioselectivity in the hydrogenation of methyl 2-acetamidocinnamate was examined in CH_2Cl_2. A higher pressure of H_2 accelerated the hydrogenation reaction, but gave almost no difference in the enantiomeric excess compared with the reaction under ambient H_2 pressure (Table 1, entry 1–3). When the Rh : substrate ratio was changed from 1 : 20 to 1 : 200, the change in catalyst amount had no obvious effect on the level of enantio-control, although the hydrogenation with less catalyst needed a longer reaction time (Table 1, entry 3–5). However, when the Rh : substrate ratio was decreased to 1 : 1000 the reaction conversion was only 25% after 48 h under 20 atm H_2 pressure. A slightly higher enantioselectivity was obtained when the hydrogenation reaction was carried out at 0 °C (Table 1, entry 6).

The asymmetric hydrogenation of various dehydroamido acid derivatives [eqn. (1)] was investigated in CH_2Cl_2 at room



2 **3** (1)

temperature under ambient H_2 pressure and the results are summarized in Table 2. For all the methyl esters, the conversions are quantitative and the enantioselectivities (95.6–99.3% ee) are higher than or comparable to those achieved with other monodentate phosphorus ligands and bidentate phosphorus ligands (*e.g.* DIOP 64–84%,[1] BINAP 67–100%,[2] DuPHOS 99–99.4%,[3] MonoPHOS, 93.2–99.8%.[8])

Under similar conditions, the asymmetric hydrogenation reactions of itaconic acid derivatives **4** were also performed and

Table 1 Asymmetric hydrogenation of methyl 2-acetamidocinnamate with different catalyst loading and H_2 pressure[a]

Entry	pH_2/atm	Rh : substrate **1**	Time/h[b]	% ee[c]
1	20	1 : 100	1	96.2
2	5	1 : 100	4	96.7
3	1	1 : 100	10	96.6
4	1	1 : 20	4	97.1
5	1	1 : 200	16	96.4
6[d]	1	1 : 100	20	97.8

[a] The reaction was performed at room temperature with 0.5 mmol of substrate and 1 mol% of catalyst {$[Rh(COD)_2BF_4]$: (*S*)-**1** = 1 : 2.1} in 5 mL of solvent unless stated otherwise. [b] Time taken for 100% conversion of substrate. [c] Determined by chiral HPLC using a CHIRACEL-OJ column. The configurations of product are *S*. [d] Reaction temperature was 0 °C.

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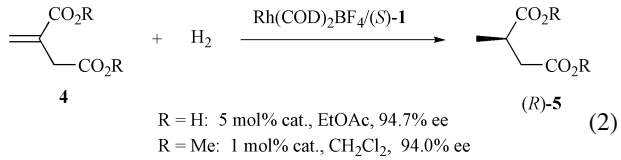
excellent enantioselectivities were obtained [eqn. (2)], although



(2)

the reaction with acid needed more catalyst to go to completion.

In conclusion, novel and highly effective monodentate chiral spiro ligands have been developed for the catalytic asymmetric hydrogenation of dehydroamino acid and itaconic acid derivatives. The remarkably high enantioselectivity and stability indicate a high potential for wide application of these chiral spiro ligands in asymmetric catalysis, and such studies are in progress.

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Table 2 Asymmetric hydrogenation of dehydroamino acid derivatives[a]

Entry	Substrate (**2**)	% ee[b]	Config.[c]
1	(R = Ph)	96.6 (97.8)[d]	*S*
2[e]	(R = Ph)	96.1	*R*
3	(R = 4-CH_3Ph)	98.2	ND[f]
4	(R = 4-CH_3OPh)	95.6	*S*
5	(R = 2-ClPh)	97.2	*S*
6	(R = 4-ClPh)	98.5	*S*
7	(R = 3-NO_2Ph)	99.3	*S*
8	(R = 4-NO_2Ph)	99.1	*S*
9	(R = Me)	98.6	*S*
10	(R = H)	97.1	*S*

[a] The reaction was performed with 1 mol% catalyst at room temperature under ambient H_2 pressure unless stated otherwise; 100% conversion (*ca.* 100% yield) was observed within 24 h in all cases. [b] Determined by chiral GC using a Supelco γ-DEX-225 column or chiral HPLC using a CHIRACEL-OJ column. [c] Assigned by comparing the optical rotation with reported values. [d] Ee value in parentheses is that achieved from reaction at 0 °C. [e] (*R*)-**1** was used. [f] Not determined.

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14 Mp 84.5–85.5 °C, $[\alpha]_D^{20}$ −519 (c = 0.92 × 10^{-2}, $CHCl_3$) for (*S*)-**1**, and mp 84–85 °C, $[\alpha]_D^{20}$ +525 (c = 1.14 × 10^{-2}, $CHCl_3$) for (*R*)-**1**.