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Synthesis of Spiro Diphosphines and Their Application in Asymmetric Hydrogenation of Ketones

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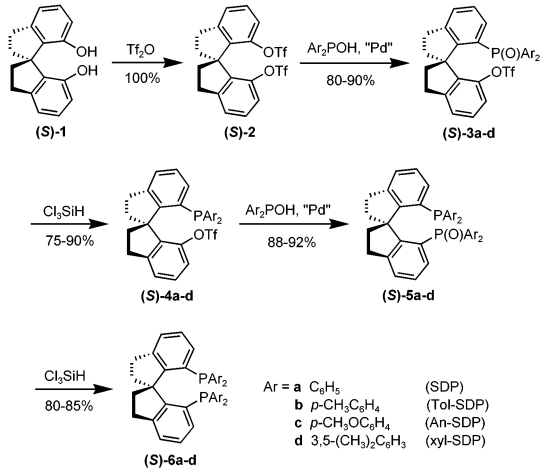
The design of new chiral ligands is the key in the development of transition metal catalyzed asymmetric synthesis.[1] Many chiral diphosphine ligands have been prepared and applied in asymmetric catalytic reactions with excellent enantioselectivities.[1,2] Among the chiral diphosphine ligands that have been reported, the atropisomeric C_2-symmetric phosphines with a biaryl scaffold initiated by Noyori and co-workers[3] with BINAP were found to have the widest application in the transition metal catalyzed reactions.[4] Planar chiral diphosphines based on ferrocene or paracyclophane backbones have also been applied to a number of reactions with a remarkable degree of success.[5] However, the spiro diphosphine compounds, another type of axially chiral ligands, have not been synthesized until now.[6] Recently, we designed chiral phosphoramidite ligands (SIPHOS)[7] containing a 1,1′-spirobiindane backbone and demonstrated that these ligands can be highly efficient for the Rh-catalyzed asymmetric hydrogenation of functionalized olefins. Especially, in the case of asymmetric hydrogenation of α-arylethenylamines, the spiro monophosphoramidite ligands provided a significantly higher level of enantiocontrol compared to that of the monophosphoramidite ligands derived from BINOL.[7b] We now describe the synthesis of spiro diphosphines **6** (SDP) containing 1,1′-spirobiindane as a new chiral scaffold and their application in the ruthenium-catalyzed asymmetric hydrogenation of simple ketones with high activity (*S*/*C* up to 100 000) and excellent enantioselectivity (ee up to 99.5%).

Chiral spiro diphosphines (*S*)-**6** were easily prepared from enantiomerically pure (*S*)-1,1-spirobiindane-7,7-diol (**1**)[8] (Scheme 1). The diol (*S*)-**1** was converted into triflate (*S*)-**2** in quantitative yield. Monophosphinylation of triflate (*S*)-**2** with diarylphosphine oxide in the presence of Pd catalyst, followed by reduction with trichlorosilane, generated (*S*)-7-(diarylphosphino)-7′-trifluoromethanesulfonyl)oxy-1,1′-spirobiindanes ((*S*)-**4**).[9] Phosphinylation and reduction of compounds (*S*)-**4** provided desired diphosphines (*S*)-**6** in high yields. Using the same procedure, the diphosphines (*R*)-**6** were also synthesized from (*R*)-1,1-spirobiindane-7,7-diol.[10]

The catalytic asymmetric hydrogenation of prochiral ketones appears to be the most facile route to produce enantiomerically enriched secondary alcohols. A number of efficient catalysts have been developed for the asymmetric hydrogenation of functionalized ketones.[4j,11] In contrast, only a few catalysts have been reported in the asymmetric hydrogenation of simple ketones.[12] Recently, a significant breakthrough was achieved by Noyori and co-workers by using diphosphine−ruthenium−diamine complexes as catalysts in the hydrogenation of ketones.[13] The most effective catalyst was *trans*-[((*S*)-Xyl-BINAP)Ru((*S*)-DAIPEN)Cl_2][14] which has extremely high activity and enantioselectivity in the hydrogenation of a wide range of ketones.[13e,f] To date, only two other chiral diphosphine ligands, PhanePhos[15] and P-Phos,[16] have been reported to approach the utility of Noyori's Xyl-BINAP in this important reaction.[17] We are delighted to find that the ruthenium complexes of spiro diphosphine ligands **6** serve as excellent catalysts for the asymmetric

Scheme 1



hydrogenation of aromatic, heteroaromatic, and α,β-unsaturated ketones.

The catalysts **7** (Figure 1) were prepared by reacting ligands **6** with $[(C_6H_6)RuCl_2]_2$ in DMF at 100 °C, followed by the treatment of the resulting reddish brown solution with 1 equiv of DPEN[14] at room temperature. The complexes, thus obtained, were used directly in the catalytic reactions. Initial tests with catalyst [((*S*)-SDP)Ru((*R*,*R*)-DPEN)Cl_2] ((*S*,*RR*)-**7a)** in the asymmetric hydrogenation of acetophenone in 2-propanol in the presence of *t*-BuOK (*S*/*B* = 70) at room temperature provided (*S*)-1-phenylethanol in quantitative yield and 90% ee over 1.5 h at *S*/*C* = 5000 (Table 1, entry 1). This result is slightly better than that obtained with [((*R*)-BINAP)Ru((*R*,*R*)-DPEN)Cl_2] (87% ee).[13a] A systematical investigation on the effect of substituents in the ligands **6** indicated that the introduction of 3,5-dimethyl groups to *P*-pheny rings, (*S*,*RR*)-**7d**, dramatically increased the enantioselectivity to 99% ee (entry 4).[18] The enantioselectivity remained to be 98% ee even when the ratio of substrate to catalyst (*S*/*C*) was increased to 100 000 (entry 5).

A variety of aromatic, heteroaromatic, and α,β-unsaturated ketones can be hydrogenated by catalyst (*S*,*RR*)-**7d** with excellent enantioselectivities. The results summarized in Table 1 are better than or comparable to those achieved with Xyl-BINAP−Ru−DAIPEN,[13e] Xyl-PhanePhos−Ru−DPEN,[15] and Xyl-P-Phos−Ru−DPEN[16] systems. It deserves commendation that the hydrogenation of acetylferrocene with (*S*,*RR*)-**7d** produced (*S*)-1-ferrocenylethanol in 98% ee at *S*/*C* = 5000.[19] The enantiomerically enriched 1-ferrocenylethanol is a crucial starting material in the synthesis of many chiral ferrocene compounds such as ferrocenylethylamines and ferrocenylphosphines.[20] Our study provides a practical method to the synthesis of ferrocenylethanol and related compounds.

In conclusion, we have developed novel chiral diphosphine ligands with spiro biindane as a new chiral scaffold, which are highly effective for the asymmetric hydrogenation of ketones. The extremely high activity and enantioselectivity of their ruthenium

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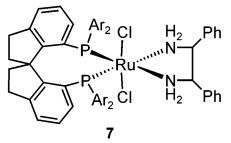
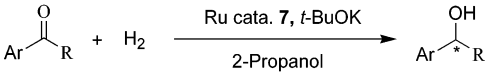


(*S*,*RR*)-**7a**, [((*S*)-SDP)Ru((*R*,*R*)-DPEN)Cl_2]
(*R*,*SS*)-**7b**, [((*R*)-Tol-SDP)Ru((*S*,*S*)-DPEN)Cl_2]
(*R*,*SS*)-**7c**, [((*R*)-An-SDP)Ru((*S*,*S*)-DPEN)Cl_2]
(*S*,*RR*)-**7d**, [((*S*)-Xyl-SDP)Ru((*R*,*R*)-DPEN)Cl_2]

7

Figure 1.

Table 1. Asymmetric Hydrogenation of Ketones[a]



		ketone				
entry	cat.	Ar	R	time (h)	convn[b] (%)	ee[c] (%)
1	**7a**	C_6H_5	CH_3	1.5	100	90 (*S*)
2	**7b**	C_6H_5	CH_3	3	99	89 (*S*)
3	**7c**	C_6H_5	CH_3	2.5	100	92 (*S*)
4	**7d**	C_6H_5	CH_3	1.5	100	99 (*S*)
5[d]	**7d**	C_6H_5	CH_3	72	98	98 (*S*)
6	**7d**	*o*-ClC_6H_4	CH_3	3.5	99	98 (*S*)
7	**7d**	*o*-BrC_6H_4	CH_3	6.5	100	99.2 (*S*)
8	**7d**	*m*-BrC_6H_4	CH_3	3	99	99.2 (*S*)
9	**7d**	*m*-$CF_3C_6H_4$	CH_3	2	99	99 (*S*)
10	**7d**	*p*-$CH_3C_6H_4$	CH_3	1.5	100	99.2 (*S*)
11	**7d**	*p*-$OCH_3C_6H_4$	CH_3	4.5	100	98 (*S*)
12	**7d**	*p*-ClC_6H_4	CH_3	1.5	100	99 (*S*)
13	**7d**	*p*-BrC_6H_4	CH_3	3	100	99 (*S*)
14	**7d**	C_6H_5	C_2H_5	3.5	99	99.5 (*S*)
15	**7d**	C_6H_5	$PhCH_2$	46	100	98 (*S*)
16	**7d**	2-naphthyl	CH_3	4	98	99.2 (*S*)
17[e]	**7d**	ferrocenyl	CH_3	5	100	98 (*S*)
18	**7d**	2-furyl	CH_3	5	99	98 (*S*)
19	**7d**	2-thienyl	CH_3	5	98	98 (*S*)
20[f]	**7d**	*trans*-PhCH=CH	CH_3	3	100	96 (*S*)

[a] Reactions were conducted at 20−25 °C under 50 atm of H_2 pressure using a 2.0−2.5 M solution in 2-propanol containing (*S*,*RR*)-**7d** (*S*/*C* = 5000) and *t*-BuOK (*S*/*B* = 70). [b] Determined by GC or ^1H NMR. [c] The ee were determined by chiral GC or HPLC. The absolute configuration was determined by comparison of the sign of optical rotation or retention time with 1iterature data. [d] *S*/*C* = 100 000, at 40 °C. [e] Using a 1.0 M solution in 2-propanol, *S*/*B* = 50. [f] *S*/*B* = 50.

complexes for the hydrogenation of a variety of prochiral ketones indicated a good potential for wide application of these spiro diphosphine ligands. Studies of these spiro ligands in other transition metal catalyzed asymmetric reactions are in progress.

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Supporting Information Available: Preparations and properties of compounds **2**−**6** and **7**, procedures for asymmetric hydrogenation of ketones, GC behavior of chiral alcohols (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) PhanePhos = 4,12-bis(diphenylphospino)-[2,2]paracyclophane. Xyl-PhanePhos = 4,12-bis(di-3,5-xylylphospino)-[2,2]paracyclophane. See: Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173.

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(18) With the catalyst (*S*,*SS*)-**7d**, which represents a mismatch in chirality between SDP and DPEN, (*S*)-1-phenylethanol was produced in 28% ee.

(19) [((*S*)-Tol-BINAP)Ru((*S*)-DAIPEN)Cl_2] (87% ee) and [((*S*)-Xyl-PhanePhos)Ru((*R*,*R*)-DPEN)Cl_2] (92% ee) were also used in the hydrogenation of acetylferrocene, see refs 13f and 15.

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