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Synthesis of Novel Diastereomeric Diphosphine Ligands and Their Applications in Asymmetric Hydrogenation Reactions

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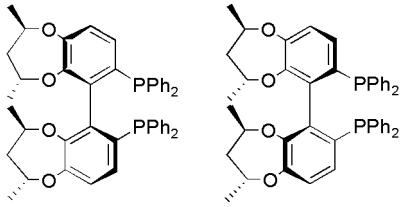
ABSTRACT



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Diastereomeric biaryl diphosphine ligands 10 and 11 with added chiral centers on the backbone were synthesized. Substrate-directed asymmetric synthesis occurred in the coupling step of the preparation of the diastereomeric diphosphine oxides. The diastereomeric diphosphine oxides were easily separated by column chromatography with silica gel. Ruthenium catalysts containing these ligands were highly effective in the hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid and β-ketoesters. The additional chiral centers had a significant influence on the enantioselectivity and activity of the catalysts.

Chiral bidentate phosphines are among the most important auxiliaries in enantioselective catalysis.[1] Although many effective chiral diphosphine ligands such as BINAP,[2] BIPHEMP,[3] MeO-BIPHEP,[3] P-phos,[4] tetraMe-bitianp,[5a] bitinap,[5b] bimip,[5c] biscap,[5c] SEG-PHOS,[6] BIFAP,[7] bisbenzodioxanPhos,[8] and TangPhos[9] have been developed, it is important and necessary to develop new classes of chiral ligands with novel features to probe new concepts and facilitate practical applications. An important reason for the need of develop-

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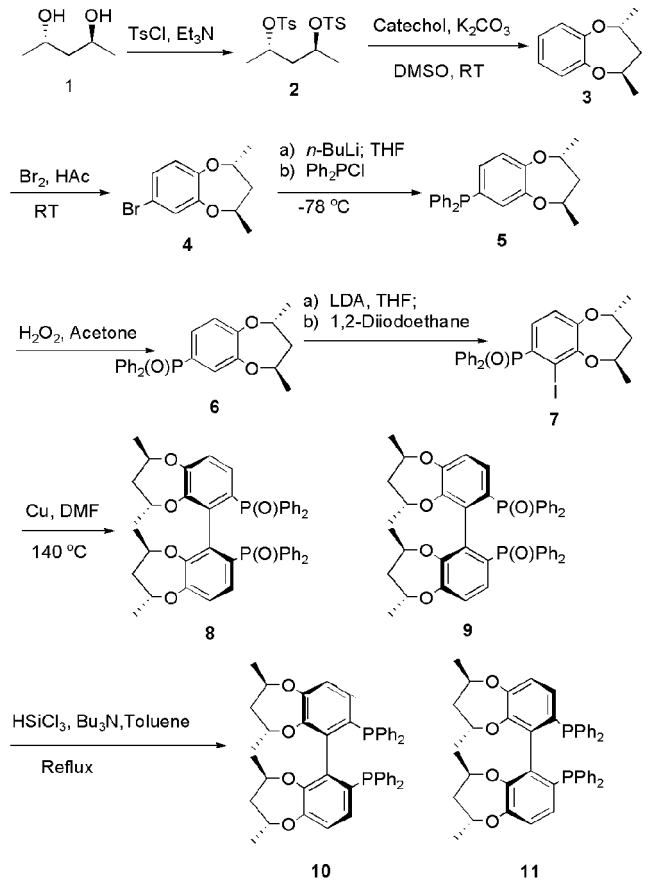
Scheme 1. Synthesis of Ligands.



ment in this field is that the substrates for asymmetric catalysis are highly diverse and have different demands for chiral ligands and corresponding catalysts. As the atropisomeric BINAP type ligands are effective for the easy sp_2-sp_2 axis rotation to change conformation in catalysis,[1b] much effort was made to systematically adjust the electronic and steric effects of the substituents on BINAP or its analogues to tune their capability of chiral recognition. Chiral diphosphine ligand H_8−BINAP has been shown to be superior to BINAP in a series of asymmetric catalytic reactions, due possibly to the more bulky structure of H_8−BINAP.[10] Recently, TunaPhos ligands were designed to change the dihedral angles of the ligands and high ees in the hydrogenation of β-ketoesters were obtained.[11] In this communication we report the development of two novel biaryl ligands with added chiral centers on the backbone and with high steric hindrance, namely, (*S*)-[5,5′,6,6′-bis(2*R*,4*R*-pentadioxy)]-(2,2′)-bis(diphenylphosphino)-(1,1′)-biphenyl **10** and (*R*)-[5,5′,6,6′-bis(2*R*,4*R*-pentadioxy)]-(2,2′)-bis(diphenylphosphino)-(1,1′)-biphenyl **11**. The ligands are highly effective in the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)-propenoic acid and β-ketoesters.

The synthetic route is shown in Scheme 1.

(2*S*,4*S*)-Pentanediol di-*p*-tosylate **2** was prepared in 80.2% yield via the reaction of (2*S*,4*S*)-pentanediol **1** with *p*-toluenesulfonyl chloride in the presence of triethylamine. The further reaction of compound **2** with catechol in the presence of K_2CO_3 in DMSO solvent at room temperature for 72 h gave (2*R*,4*R*)-2,4-dimethyl-3,4-dihydro-2*H*-1,5-benzodioxepine **3** in 41.7% yield. (2*R*,4*R*)-7-Bromo-2,4-dimethyl-3,4-dihydro-2*H*-1,5-benzodioxepine **4** was subsequently prepared quantitatively via the bromination of **3** at room temperature for 24 h. For the preparation of **5**, *n*-butyllithium was added dropwise to a THF solution containing **4** at −78 °C over 1 h, followed by the addition of chlorodiphenylphosphine to the resulting mixture. The reaction was continued at room-temperature overnight to afford 95.5% yield of phosphine **5** that was further oxidized to phosphine oxide **6** with H_2O_2 in acetone solution at 0 °C in 97.0% yield. A sequence of *ortho*-lithiation/iodination with lithiumdiisopropylamide via a thermodynamically controlled process gave iododiphosphine oxide **7** with 59% conversion and 100% selectivity. Diastereomers **8** and **9** were then obtained via Ullmann coupling of oxide **7** in a combined yield of 80.9%. The molecular structure of **8** was confirmed by single-crystal X-ray diffraction (Figure 1). Ligands **10** and **11** were obtained in 89.5

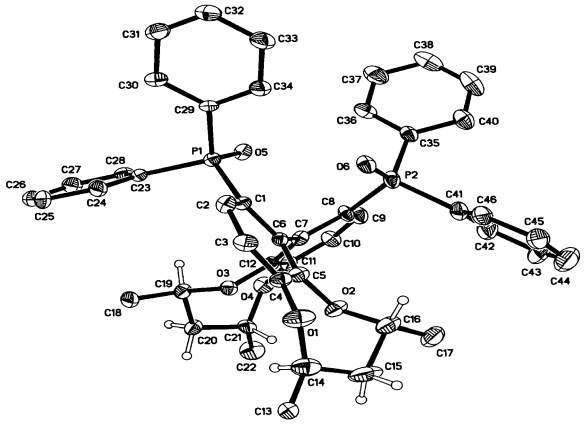


Figure 1. ORTEP drawing of S_{ax}-**8**.

and 92.0% yields, respectively, by reducing **8** and **9** with trichlorosilane and tributylamine in toluene at reflux temperature. Two characteristics of the Ullmann coupling were noted. First, the coupling reaction was moderately diastereoselective, giving the two diastereomers in unequal amounts. The S_{ax}-form diastereomer **8** was obtained as the major product, and its ratio to the R_{ax}-form diasteromer **9** was 7:2.

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Table 1. Asymmetric Hydrogenation of 2-(6′-Methoxy-2′-naphthyl)propenoic Acid with [RuL(*p*-cymene)Cl]Cl

entry[a]	ligand	P_{H2} (psi)	T (°C)	time (h)	conversion (%)	% ee[b] (config)
1	**10**	500	rt	4	100	83 (*S*)
2	*S*-BINAP	500	rt	4	100	87 (*S*)
3	**11**	500	rt	4	100	90 (*R*)
4	**10**	800	rt	4	100	85 (*S*)
5	*S*-BINAP	800	rt	4	100	87 (*S*)
6	**11**	800	rt	4	100	91 (*R*)
7	**10**	1000	rt	4	100	86 (*S*)
8	*S*-BINAP	1000	rt	4	100	89 (*S*)
9	**11**	1000	rt	4	100	93 (*R*)
10	**10**	1600	rt	4	100	88 (*S*)
11	*S*-BINAP	1600	rt	4	100	90 (*S*)
12	**11**	1600	rt	4	100	93 (*R*)
13	**10**	1000	0	24	100	93 (*S*)
14	*S*-BINAP	1000	0	24	100	94 (*S*)
15	**11**	1000	0	24	100	96 (*R*)
16	**10**	2000	0	24	100	94 (*S*)
17	**11**	1750	0	24	100	97 (*R*)
18	**10**	1000	rt	0.5	46	87 (*S*)
19	*S*-BINAP	1000	rt	0.5	90	90 (*S*)
20	**11**	1000	rt	0.5	36	94 (*R*)

[a] Reaction conditions: solvent = MeOH (2.5 mL); substrate/catalyst = 100:1 (mol/mol); substrate concentration = 2.0 mg/mL. [b] The ee values were determined by chiral HPLC with a Sumichiral OA-2500 column.

On the basis of this observation, this reaction can be regarded as a substrate-directed asymmetric synthesis. Second, the two diastereomers could be easily separated by silica gel column chromatography using a mixed eluent (100:100:10 $CHCl_3$/EA/MeOH). This simple separation avoided the generally tedious and sometimes difficult resolution step.

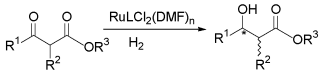
The reaction of Ru(cymene)Cl_2 with ligands **10**, *S*-BINAP, or ligand **11** gave the corresponding chiral catalysts [RuL(*p*-cymene)Cl]Cl (L = **10**, BINAP, or **11**). The asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid for the preparation of naproxen,[8,12] a popular antiinflammatory drug, was carried out as a model reaction. The preliminary results are summarized in Table 1.

It was found that [RuCl(*p*-cymene)**11**]Cl was more enantioselective than [RuCl(*p*-cymene)(*S*-BINAP)]Cl, which was in turn better than [RuCl(*p*-cymene)**10**]Cl in the reaction. These results clearly reveal that the additional chiral centers on the ligand backbone have a significant effect on the catalytic enantioselectivity and activity (entries 18, 20). In addition, naproxen was obtained in 96% ee using [RuCl(*p*-cymene)**11**]Cl as a catalyst at 0 °C under 1000 psi H_2, which was an improvement over the Ru[(*S*)-BINAP] catalyst system (94% ee) (entries 14, 15). The enantioselectivity was further improved slightly by increasing the reaction pressure. Up to 97% ee was obtained by using [RuCl(*p*-cymene)**11**]Cl as a catalyst at 0 °C under 1750 psi H_2 (entry 17).

When $RuLCl_2(DMF)_n$ (L = **10** or **11**) catalysts were applied to the asymmetric hydrogenation of β-ketoesters,[5b,8,13] the enantioselectivities for the corresponding products were also very high and compared favorably with the Ru[(*S*)-BINAP]$Cl_2(DMF)_n$ system (Table 2). These results clearly showed the great potential of these new ligands in a variety of useful asymmetric catalytic reactions.

In conclusion, two novel diastereomeric biaryl diphosphine ligands possessing both added chiral centers on the backbone and high steric hindrance were synthesized. A substrate-directed asymmetric synthesis occurred in the coupling step of the diastereomeric diphosphine oxides. In addition, the results of our asymmetric hydrogenation reactions exhibited

Table 2. Asymmetric Hydrogenation of β-Ketoesters Catalyzed by $RuLCl_2(DMF)_n$



				% ee (config)		
entry[a]	R^1	R^2	R^3	S_{ax}-**10**	R_{ax}-**11**	(*S*)-BINAP
1[b]	Me	H	Me	99.4 (*S*)	99.3 (*R*)	97.7 (*S*)
2[b]	Me	H	Et	99.2 (*S*)	99.4 (*R*)	98.0 (*S*)
3[b]	Me	H	Bn	99.7 (*S*)	99.4 (*R*)	96.1 (*S*)
4[b]	$ClCH_2$	H	Et	95.1 (*R*)	96.7 (*S*)	94.2 (*R*)
5[c]	Ph	H	Et	97.7 (*R*)	82.4 (*S*)	89.3 (*R*)
6[c]	Ph	Cl	Et	84.4 (2*S*,3*S*) (13.6% anti)	98.7 (2*R*,3*R*) (34.0% anti)	16.3 (2*S*,3*S*) (10.4% anti)
				7.4 (2*R*,3*S*) (86.4% syn)	53.4 (2*S*,3*R*) (66.0% syn)	9.8 (2*S*,3*R*) (89.6% syn)

[a] Reaction conditions: solvents = 12.5 μL CH_2Cl_2 + 987.5 μL MeOH or EtOH; time = 24 h except for entry 6 (45 h); substrate/[Ru] = 667:1 (mol/mol) except for entry 6 (100:1); substrate concentration = 0.5 mmol/mL; T = 70 °C except for entry 6 (rt); P = 50 psi H_2 except for entry 6 (1000 psi H_2); complete conversions were obtained in all cases. [b] The ee values were determined by chiral GC with a WCOT fused silica CP Chirasil-DEX CB column (25 m × 0.25 mm) after converting the products to the corresponding acetyl derivatives. [c] The ee values were determined by chiral HPLC with a Daicel Chiralcel OD column; ratio of anti to syn products was determined by ^1H NMR.

a significant influence of the additional chiral centers on the enantioselectivity and activity of the catalysts. These findings accordingly offer a good handle for the development of new chiral ligands. Further explorations of other applications of these ligands in asymmetric catalytic reactions are in progress.

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Supporting Information Available: Experimental details, spectroscopic data, and analytical data for **2**−**4** and **6**−**11** and crystallographic data for compound **8** (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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