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Development of Chiral Spiro Phosphoramidites for Rhodium-Catalyzed Enantioselective Reactions

Zhiyao Zheng,[b]† Yuxi Cao,[a, b]† Dongsheng Zhu,[a] Zheng Wang,* [b] and Kuiling Ding* [b, c, d]

Abstract: A series of 1,1'-spirobiindane-7,7'-diol (**SPINOL**) analogues bearing a 2,2'-dimethyl-, cyclopentyl-, or cyclohexyl-fused ring have been synthesized, and their distinct structural features were elucidated by X-ray crystallographic studies. On the basis of these scaffolds, an array of chiral monophosphoramidite ligands **6a-m** have been synthesized, which demonstrated excellent enantioselectivity in Rh(I) catalyzed asymmetric hydrogenation of a dehydroaminoacid methyl ester. Ligands **6a-m** have also been successfully applied in the Rh(I)-catalyzed enantioselective [4+2] cycloaddition of α, β-unsaturated imines with isocyanates, affording the corresponding pyrimidinones in good yields (60-92%) with high enantioselectivities (75-92% ee).

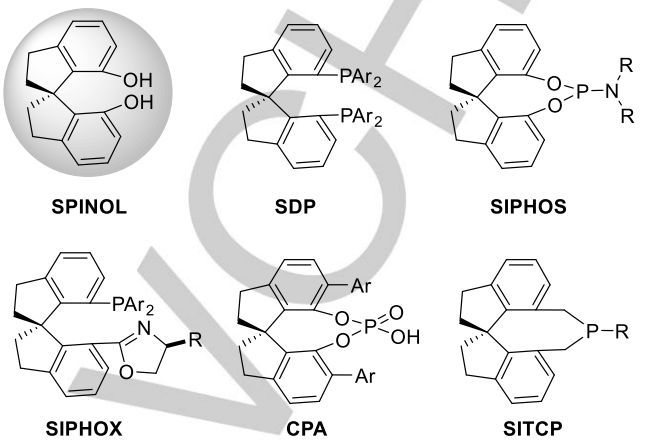

Figure 1. Selected chiral ligands and organocatalysts bearing a 1,1'-spirobiindane backbone.

INTRODUCTION

The development of new chiral ligands is of pivotal importance in the field of asymmetric catalysis and continues to attract intense research interests.[1] Owing to their sterically constrained features and structural stability, chiral spiro ligands have demonstrated high potency and great potential in asymmetric transformations.[2] Since the elegant studies by Chan, Jiang and Sasai et al.,[3] a variety of spirocyclic backbones have been used as building blocks for construction of chiral spiro ligands. In this context, Zhou and co-workers have made remarkable contributions to the development of chiral spiro ligands derived from 1,1'-spirobiindane-7,7'-diol (**SPINOL**),[4] which was first reported by Birman and co-workers.[5] A large family of chiral ligands (e.g., **SDP**, **SIPHOS**, **SIPHOX**, etc)[6] and organocatalysts (e.g., **CPA**, **SITCP**, etc)[7] based on **SPINOL** or its analogues have been developed (**Figure 1**), and have demonstrated extraordinary stereocontrol and high efficiencies in a broad range of asymmetric reactions, thus establishing the spirobiindane as a privileged building block for construction of chiral ligands and organocatalysts in asymmetric catalysis.

Recently, some efforts have also been devoted to the structural modulation of the **SPINOL** skeleton, with an aim to provide alternative chiral spirocyclic backbones featuring facile synthesis, unique properties and/or superior performance in catalysis. Tan and coworkers reported the use of chiral phosphoric acids as catalysts for enantioselective spirocyclization of achiral acetone derivatives, providing an efficient access to a range of 4,4'-disubstituted SPINOLs in high enantiopurities.[8] Nagorny et al. presented an expedient route to a new spiroketal-based SPINOL analogue, which served as spirocyclic scaffold for several chiral ligands that were successfully employed in some asymmetric transformations.[9] Yin, Zhang, and coworkers described a facile and column-free synthesis of a structurally unique O-SPINOL where one carbon atom of the **SPINOL** skeleton is replaced with a more electronegative oxygen atom, which has been transformed into a chiral tridentate ligand that was successfully applied in the iridium-catalyzed asymmetric hydrogenation of biaryl lactones.[10] Most recently, Lu, Hayashi, Dou and coworkers have developed the enantioselective synthesis of 3,3'-diaryl-SPINOLs, and showcased the superior enantioselectivities of the derived phosphoramidite ligands in several different types of reactions.[11] We envisioned that the spirobiindane backbone with a 2,2'-linker unit, sterically bulkier and conformationally more constrained than their regular spirobiindane counterparts, would be a promising candidate for chiral ligand construction. As an ongoing effort towards our development of chiral spiro ligands for asymmetric catalysis,[12] in a recent communication we have reported the practical synthesis, ligand development, and asymmetric catalytic applications of various chiral cyclohexyl-fused spirobiindanes, including some cyclohexyl-fused **SPINOL** analogues.[13] We expected that the systematic modification of such ring-fused **SPINOL** analogues with different 2,2'-substituent moieties or linker ring-sizes, although synthetically challenging, would be highly desirable for ligand development and catalytic structure-performance assessment. Herein, we disclose our results on the synthesis of **SPINOL** counterparts bearing a 2,2'-dimethyl-, cyclopentyl-, or cyclohexyl-fused ring, with distinct structural

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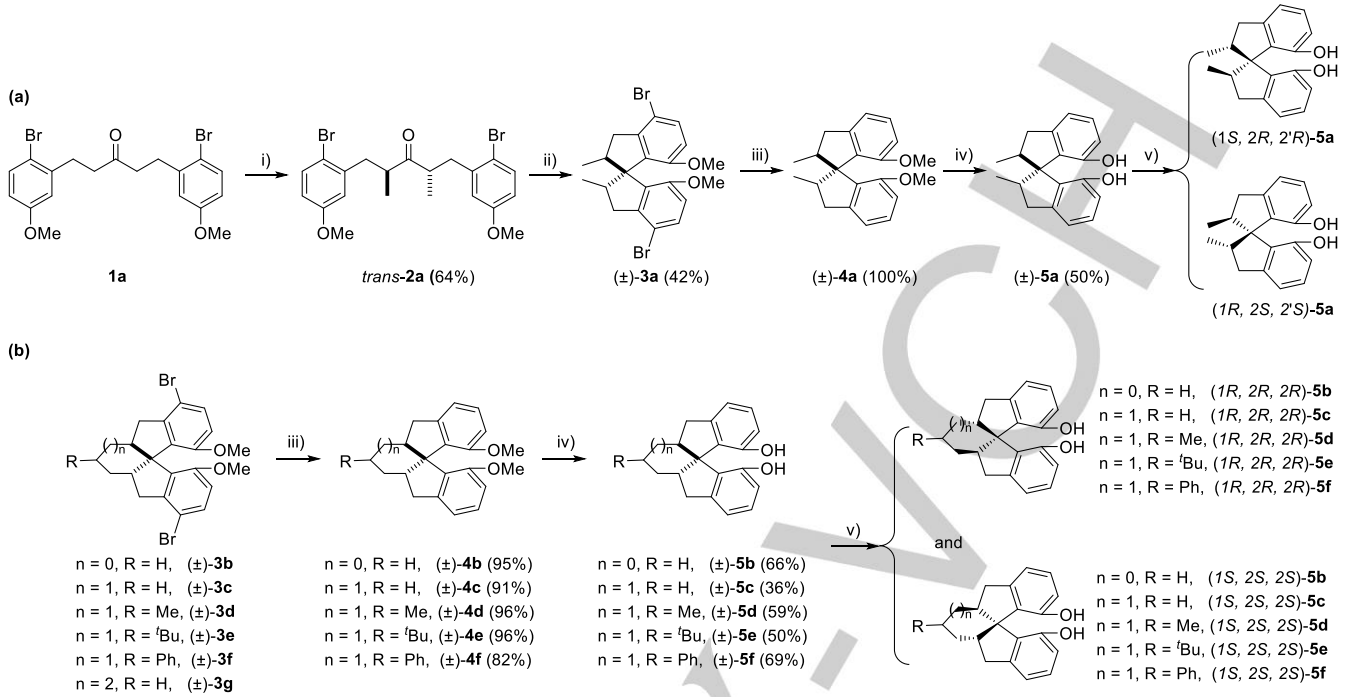


Scheme 1. (a) Synthesis of chiral 2,2'-dimethyl spirobiindanediols. (b) Synthesis of chiral cyclopentyl- or cyclohexyl-fused spirobiindanediols. Conditions: i) NaH (3.0 eq.), THF, 0 ℃, 1h, then MeI (3.0 eq.), 0 ℃-rt; ii) PPA, 105 ℃, 6 h; iii) ^{n}BuLi (3.0 eq.), THF, -78 ℃, 1 h; iv) BBr_3 (2.5 eq.), CH_2Cl_2, -78 ℃-rt, 12 h; v) optical resolution by semi-preparative HPLC on a chiral column.

features being unraveled by X-ray crystallographic studies. Based on these scaffolds, a large array of chiral monophosphoramidite ligands have been developed, which demonstrated excellent enantioselectivity in Rh(I) catalyzed asymmetric hydrogenation of a dehydroaminoacid methyl ester, and have been successfully applies in the Rh(I)-catalyzed enantioselective [4+2] cycloaddition of α, β-unsaturated imines with isocyanates.

Results and Discussion

Synthesis of SPINOL analogues with a 2,2'-linker unit

The study was initiated by the synthesis of **5a**-**f**, the 2,2'-dimethyl-, cyclopentyl- or cyclohexyl-fused counterparts of the prototype **SPINOL**. The enantiopure 2,2'-dimethyl-substituted **SPINOL** derivatives (*1S*, *2R*, *2'R*)-**5a** and (*1R*, *2S*, *2'S*)-**5a** were obtained via the synthetic sequence shown in **Scheme 1a**. Deprotonation of the α- and α'- positions on ketone **1a** with NaH followed by double methylation with MeI afforded a good yield of *trans*-α,α'-dimethylketone **2a**, which underwent a polyphosphoric acid (PPA) promoted spirocyclization, following a procedure similar to that reported by Venugopal et al.,[14] affording dibrominated spirobiindane (±)-**3a** as a racemic compound. (±)-**3a** was treated with ^{n}BuLi to afford an excellent yield of debrominated product (±)-**4a**, which was transformed to (±)-**5a** by demethylation using BBr_3. Both enantiomers (*1S*, *2R*, *2'R*)-**5a** and (*1R*, *2S*, *2'S*)-**5a** were easily accessed as the enantiopure chiral antipodes by optical resolution of (±)-**5a** using a semi-preparative HPLC on a ChiralPak AD-H column (Scheme 1. (a)). Using a similar procedure, enantiopure **SPINOL** analogues **5b**-**f**, featured by a cyclopentyl- or cyclohexyl-fused spirobiindane scaffold, were also synthesized in moderate to good overall yields (**Scheme 1b**, For details, see SI). However, the dibrominated spirobiindane analogue (±)-**3g**, key precursor for synthesis of cycloheptyl-fused **SPINOL** analogue, was only obtained in poor yield (8%) in the PPA promoted spirocyclization. Since no improvements were observed for (±)-**3g** synthesis after an extensive screening of acidic catalysts and other reaction conditions (see SI), no further synthetic manipulations were performed on this compound. The optically pure chiral spirobiindane-diols **5** were fully characterized and their absolute configurations were deduced from or established by X-ray single crystallographic studies (*vide infra*).

X-ray crystal structural studies of the SPINOL analogues

The solid-state structures of spirobiindane-diols (1*S*, 2*R*, 2'*R*)-**5a,** *rac*-5b, (1*R*, 2*R*, 2'*R*)-**5c,** (1*R*, 2*R*, 2'*R*)-**5d**, (1*R*, 2*R*, 2*R*)-**5f**, and dibrominated spirobiindane (±)-**3g**, have been elucidated by X-ray crystallographic analysis. Indeed, introduction of a 2,2'-linker moiety into the indanyl rings of **SPINOL** led to significant structural variations in resulting spirobiindane-diols **5**, as shown in **Figure 2**. A close examination of the structural features of **5a-d** and **5f**, also revealed remarkable differences from their regular prototype compound **SPINOL**. **Table 1** listed some relevant structural parameters of these compounds, including the dihedral angles between the two indanol phenyl rings and the distances between the phenolic oxygen atoms O1 and O2. In

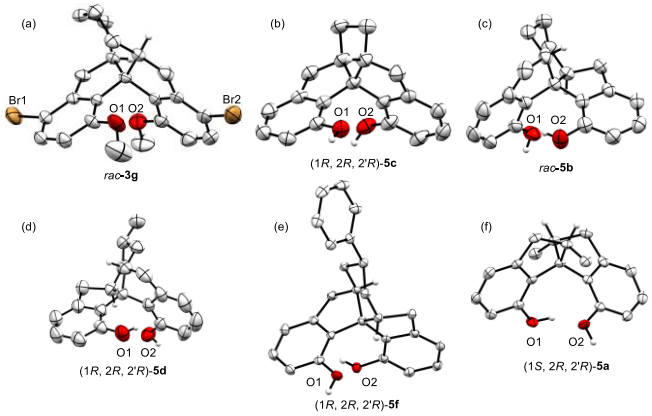


Figure 2. X-ray crystallographic structures of the spirobiindanediol derivatives *rac*-**3g** (a), (1*R*, 2*R*, 2'*R*)-**5c** (b)**,** *rac*-**5b** (c), (1*R*, 2*R*, 2'*R*)-**5d** (d), (1*R*, 2*R*, 2'*R*)-**5f** (e), and (1*S*, 2*R*, 2*R*)-**5a** (f). Part of the H atoms in each molecule are removed for clarity. The thermal ellipsoids are shown at 50% probability.

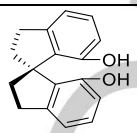
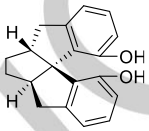
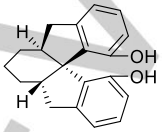
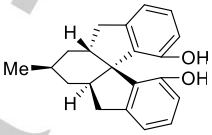
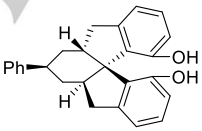
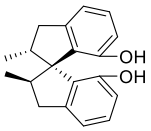
comparison with **SPINOL**, the spirobiindane-diol **5c** demonstrated a smaller dihedral angle (80.057(69)° vs 86.247(122)°) between the two indanol phenyl rings and a longer O1…O2 distance (4.7013(27) vs 4.1004(30) Å), presumably caused by the strain imposed by the cyclopentyl-fused ring (entry 2 vs 1). Similarly, the cyclohexyl-fused spirobiindane-diols **5b**,**5d** and **5f** also exhibited different phenyl-phenyl dihedral angles (87.216(247)-89.985(6)°) and O1…O2 distances (3.9665(14)-4.2590(22) Å) from those of **SPINOL** (entries 3-5 vs 1), hence demonstrating the effectiveness of 2,2'-bridging units in fine-tuning the spirobiindane structure. Remarkably, introduction of two methyl groups onto the 2,2'-positions of the **SPINOL** core gave rise to spirobiindane-diol **5a** (entry 6), which exhibited a much smaller phenyl-phenyl dihedral angle (60.732(61)°) and a largely reduced O1…O2 distance (2.9708(14) Å). The structurally diversified spirobiindane-diols **5a**-**f** can provide a convenient platform for further synthetic transformations to various chiral ligands, and their subtle differences may lead to interesting consequences in their catalytic applications.

Synthesis of chiral monodentate phosphoramidite ligands

These results set the stage for facile access to a series of new chiral monodentate phosphoramidites **6a-m**, started from the enantiopure 2,2'-dimethyl-substituted, cyclopentyl-fused, or cyclohexyl-fused spirobiindane-diols **5a**-**f**. Owing to their modular structure and facile synthesis, a variety of mono-phosphoramidites have been established as highly versatile chiral ligands in transition metal catalysis, with widespread applications being achieved in numerous asymmetric transformations in these two decades.[15] Since it is well known that the amino moiety can substantially influence the catalytic performance of the resulting phosphoramidite ligand, hence several types of amines with distinct stereoelectronic features were used in combination with spirobiindane-diols **5a**-**f** to building the phosphoramidite ligands for fine-tune the catalysis.

As shown in **Scheme 2**, treatment of the enantiopure diols **5a-f** with an aminophosphorus dichloride (Cl_2PNR_2) in the presence of triethylamine, led to ready formation of the corresponding chiral spiro mono-phosphoramidite ligands **6a-m**, respectively, in a single step. It is notable that using this procedure, this class of ligands, bearing a dimethylamino (**6a**-**f**), morpholine (**6g**), piperidine (**6h**), pyrrolidine (**6i**), or a chiral amine moiety (**6j**, **6k**, **6l** and **6m**), were obtained in good to excellent yields (49-91%, see SI for details).

Table 1 Structural comparison of the spirobiindanediols[a]

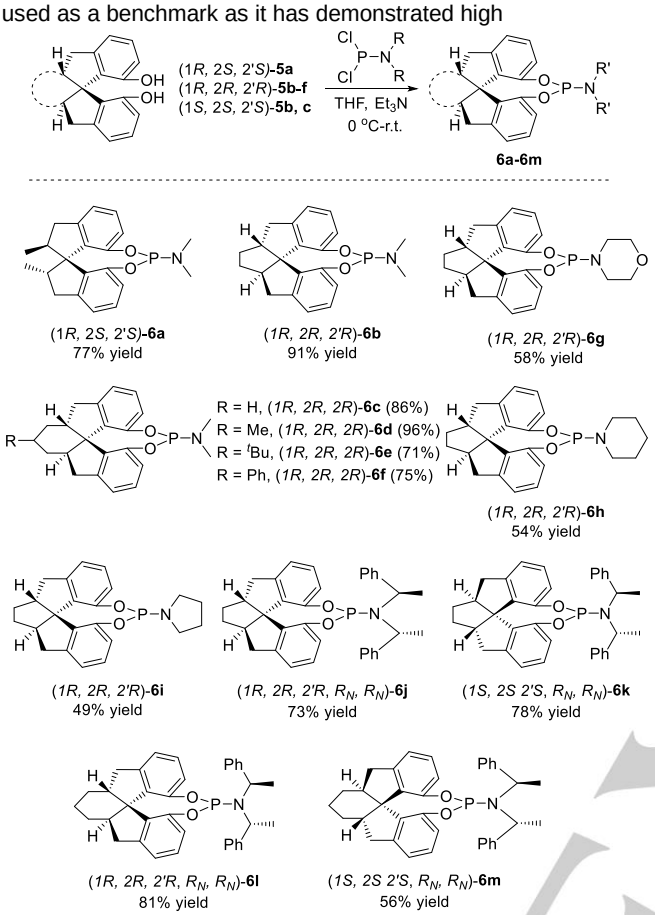
Entry	Spirobiindane-diols	Dihedral angles (°)[c]	O1...O2 Distances (Å)[d]
1[b]	 (*S*)-**SPINOL**	86.247(122)	4.1004(30)
2	 (*1R, 2R, 2'R*)-**5c**	80.057(69)	4.7013(27)
3	 *rac*-**5b**	89.985(6)	4.0909(26)
4	 (*1R, 2R, 2'R*)-**5d**	87.216(247)	4.2590(22)
5	 (*1R, 2R, 2'R*)-**5f**	88.133(61)	3.9665(14)
6	 (*1S, 2R, 2'R*)-**5a**	60.732(61)	2.9708(14)

[a] Unless otherwise noted, all data are taken from X-ray crystallography. [b] Data taken from ref 5b. [c] Dihedral angles between indanyl phenyl rings (°). [d] See Figure 2.

Preliminary assessment of the chiral monodentate phosphoramidite ligands in Rh-catalyzed asymmetric hydrogenation

As a preliminary evaluation of these new chiral mono-phosphoramidite ligands **6**, we proceeded to examine their stereoinduction capabilities in Rh-catalyzed asymmetric hydrogenation of dehydroaminoacid methyl ester **7**. The results

are summarized in **Table 2**, whereby Zhou's **SIPHOS-Me** was used as a benchmark as it has demonstrated high



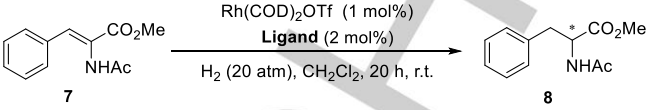
Scheme 2. Synthesis of chiral monophosphoramidite ligands **6a-m**.

enantioselectivity for this reaction (96% ee, entry 1).[4d] Under the otherwise identical conditions, a slightly enhanced ee value was obtained for hydrogenation product **8** using **6a** as ligand (97% ee, entry 2), while equally excellent enantioselectivities were also achieved with the cyclopentyl- or cyclohexyl-fused ligands **6b** and **6c** (96% ee, entries 3 and 4). For the monophosphoramidite ligands **6d-f** with a substituent group on the cyclohexyl backbones (e.g., Me, *t*-Bu, or Ph), intriguing differences in the enantioselectivities were shown in this reaction. Whereas **6d** and **6f** with a methyl or phenyl substituent still retained the excellent enantioselectivity in the reaction (95-96% ee, entries 5 and 7), **6e** bearing a bulkier *t*-butyl group on the cyclohexyl backbone led to a distinctively lower ee values in the product (76% ee, entry 6), indicating significant effect of structural modification of the ligand spirobiindane backbone on the stereochemical control in the reaction.

Rh-catalyzed asymmetric [4 + 2] cycloaddition of α,β-unsaturated imines and isocyanates

Subsequently, the ligands **6a-m** were further surveyed in Rh-catalyzed [4 + 2] cycloaddition reaction of α,β-unsaturated imines and isocyanates. Catalytic systems based on Rh(I) complexes, owing to their versatile reactivities and broad functional group tolerance, have been extensively studied

Table 2. Ligand assessment in the Rh(I) catalyzed asymmetric hydrogenation of a dehydroaminoacid methyl ester[a]



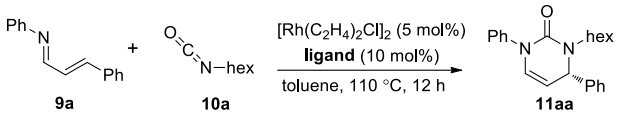
Entry	Ligand	Yield (%)[b]	Ee (%)[c]
1[d]	(*S*)-**SIPHOS-Me**	>99	96
2	(*1R, 2R, 2'R*)-**6a**	>99	97
3	(*1R, 2R, 2'R*)-**6b**	>99	96
4	(*1R*, *2R*, *2'R*)-**6c**	>99	96
5	(*1R*, *2R*, *2'R*)-**6d**	>99	96
6	(*1R*, *2R*, *2'R*)-**6e**	>99	76
7	(*1R*, *2R*, *2'R*)-**6f**	>99	95

[a] Reaction conditions: 7 (0.25 mmol), $Rh(COD)_2OTf$ (0.0025 mmol), ligand (0.005 mmol), CH_2Cl_2 (2.5 mL), rt, 12 h. [b] Yield of the isolated product 8. [c] Determined by HPLC analysis on a chiral column. [d] 1 h.

in heterocycle syntheses.[16] In 2011, Oberg and Rovis demonstrated that a monodentate phosphoramidite can serve as a competent ligand for Rh catalyzed [4 + 2] cycloaddition of α,β-unsaturated imines and isocyanates,[17] affording highly enantioenriched pyrimidinones with a substitution pattern complementary to that of Biginelli adducts.[18] Given the remarkable biological and pharmaceutical relevance of the 3,4-dihydropyrimidin-2-ones, we subsequently explored the phosphoramidite ligands **6a-m** in this cycloaddition reaction, using 1,4-diphenyl-1-azabuta-1,3-diene (**9a**) and *n*-hexyl isocyanate (**10a**) as the model substrates and chlorobis(ethylene)rhodium(I) dimer as the Rh(I) precursor. The reactions were generally conducted in toluene at 110°C for 12 h in the presence of the catalyst generated *in situ* from 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% phosphoramidite **6** (molar ratio Rh/L = 1:1), and the results were summarized **Table 2**. While it has been reported that the rhodium complex of (*R*)-**SIPHOS-Me** furnished the pyrimidinone product **11aa** in moderate catalytic performance,[17] the use of either **6b** or **6c** as the ligand under otherwise identical conditions led to a significant enhancement in both yield and enantioselectivity (entries 3, 4 *vs* 1), suggesting that modification of the spirobiindane backbone of the ligand with a 2,2'-alkylene linker can indeed result in beneficial consequences on this catalytic reaction. For the reactions involving the use of cyclopentyl-fused (1*R*, 2*R*, 2'*R*)-spirobiindane-based monophosphoramidite ligands, moderate to good enantioselectivities for pyrimidinone **11aa** were obtained with ligands bearing morpholinyl (**6g**), piperidyl (**6h**), or pyrrolidyl moieties (**6i**) (72-79% ee, entries 4, 5 and 8), while switching to ligand (1*R*, 2*R*, 2'*R*, R_N, R_N)-**6j** bearing a chiral amino group led to a remarkable boost of the enantioselectivity to 92% ee (entry 11). In contrast, the reaction using (1*S*, 2*S*, 2'*S*,

R_N, R_N)-**6k**, the diastereomer of **6j** with different configuration at the ligand backbone, afforded the enantiomer of **11aa** with only 76% ee and inverse chiral induction (entry 12). This observation indicated that for Rh(I)/**6** catalyzed reaction of **9a** and **10a**, the absolute configuration of the product **11aa** was predominated by the chirality of the spirobiindane backbone, while (1*R*, 2*R*, 2'*R*, R_N, R_N)-configuration in **6j** was apparently the matched pair of chiralities on ligand skeleton and its amino functionality. Similar results were obtained with cyclohexyl-fused ligands **6l** and **6m** (entries 13 and 14), with the former being optimal among the ligand **6a-m** series in terms of both yield (74%) and enantioselectivity (92% ee). Somehow less satisfactory results were observed with the non-fused ligand analogue **SIPHOS-PE** (**Figure 1**) (entries 15 vs 13), further attesting the beneficial role in the ligand backbone mofication. Finally, the catalyst loading could be reduced substantially (5 mol% with respect to both Rh and ligand **6l**) without loss of either product yield or ee value (entry 16), and hence this set of reaction conditions were used in subsequent studies.

Table 3. Ligand screening for asymmetric [4 + 2] cycloaddition of **9a** and **10a**[a]



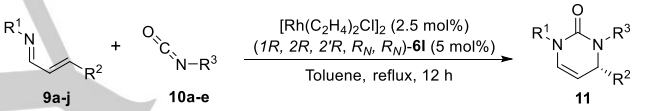
9a **10a** **11aa**

Entry	Ligand	Yield (%)[b]	Ee (%)[c]
1[d]	(*R*)-**SIPHOS-Me**	21	52 (*S*)
2	(*1R, 2S, 2'S*)-**6a**	24	56 (*S*)
3	(*1R, 2R, 2'R*)-**6b**	56	75 (*S*)
4	(*1R, 2R, 2'R*)-**6c**	56	75 (*S*)
5	(*1R, 2R, 2'R*)-**6d**	54	75 (*S*)
6	(*1R, 2R, 2'R*)-**6e**	36	67 (*S*)
7	(*1R, 2R, 2'R*)-**6f**	50	71 (*S*)
8	(*1R*, *2R*, *2'R*)-**6g**	56	72 (*S*)
9	(*1R*, *2R*, *2'R*)-**6h**	64	73 (*S*)
10	(*1R, 2R, 2'R*)-**6i**	62	79 (*S*)
11	(*1R*, *2R*, *2'R, R_N, R_N*)-**6j**	68	92 (*S*)
12	(*1S*, *2S*, *2'S, R_N, R_N*)-**6k**	56	76 (*R*)
13	(*1R*, *2R*, *2'R, R_N, R_N*)-**6l**	74	92 (*S*)
14	(*1S*, *2S*, *2'S, R_N, R_N*)-**6m**	60	76 (*R*)
15	(*R, R_N, R_N*)-**SIPHOS-PE**	72	85 (*S*)
16[e]	(*1R*, *2R*, *2'R, R_N, R_N*)-**6l**	74	92 (*S*)

[a] Reaction conditions: **9a** (0.15 mmol), **10a** (0.19 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.0075 mmol), ligand (0.015 mmol), toluene (1.5 mL), 110 °C, 12 h. [b] Yield of the isolated product **11aa**. [c] Determined by HPLC analysis on a chiral column. Absolute configurations assigned by comparison of specific rotations of **11aa** with that reported in literature (ref 17). [d] Data from ref 17. [e] The conditions are identical to those shown in footnote [a], except for a lower catalyst loading: $[Rh(C_2H_4)_2Cl]_2$ (0.00375 mmol, 2.5 mol%) and **6l** (0.0075 mmol, 5 mol%).

Having established the optimized reaction conditions, we proceeded to explore the substrate scope of this reaction with respect to both α,β-unsaturated imines (**9a-j**) and isocyanates (**10a-e**). As shown in Table 3, the catalyst generated in situ from $[Rh(C_2H_4)_2Cl]_2$ and **6l** proved to be generally enantioselective for various combinations of α,β-unsaturated imines and isocyanates, affording the corresponding pyrimidinones in high yields (60-92%) with good to excellent enantioselectivities (75-92% ee). For the reactions with *n*-hexyl isocyanate **10a**, 4-diphenyl-α,β-unsaturated imines **9a**-**g** with different *N*-substituent patterns (aryl or alkyl) reacted similarly to give their corresponding cycloadducts **11aa**-**11ga** with good yields and ee values exceeding or equal to 90% (entries 1-7). The imine with a *ortho*-methoxy group at R^2 led to the formation of **11ha** in good yield and 90% ee (entry 8), while its analogue with a *para*-methoxy substituent at R^2 gave **11ia** in a higher yield albeit with a slightly decreased ee value (entry 9). The reaction also proceeded smoothly for the imine with a furyl substituent, providing the

Table 4. Asymmetric [4 + 2] cycloaddition of α,β-unsaturated imines with isocyanates[a]



9a-j **10a-e** **11**

Entry	R^1	R^2	R^3	Product	Yield (%)[b]	ee (%)[c]
1	Ph	Ph	$^nC_6H_{13}$	**11aa**	74	92
2	4-$MeOC_6H_4$	Ph	$^nC_6H_{13}$	**11ba**	83	92
3	4-$CF_3C_6H_4$	Ph	$^nC_6H_{13}$	**11ca**	92	91
4	4-FC_6H_4	Ph	$^nC_6H_{13}$	**11da**	80	92
5	4-BrC_6H_4	Ph	$^nC_6H_{13}$	**11ea**	68	91
6	Bn	Ph	$^nC_6H_{13}$	**11fa**	72	90
7	$PhCH_2CH_2$	Ph	$^nC_6H_{13}$	**11ga**	66	91
8	Ph	2-$MeOC_6H_4$	$^nC_6H_{13}$	**11ha**	76	90
9	Ph	4-$MeOC_6H_4$	$^nC_6H_{13}$	**11ia**	81	83
10	Ph	2-furyl	$^nC_6H_{13}$	**11ja**	81	86
11	Ph	Ph	Bn	**11ab**	87	92
12	Ph	Ph	4-$MeOC_6H_4$	**11ac**	91	89
13	Ph	Ph	4-$CF_3C_6H_4$	**11ad**	78	75
14	Ph	Ph	CH_2CO_2Et	**11ae**	60	85

[a] Reaction conditions: **9** (0.15 mmol), **10** (0.19 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.00375 mmol) and **6l** (0.0075 mmol), toluene (1.5 mL), 110 °C, 12 h. [b] Yield of the isolated product **11**. [c] Determined by HPLC analysis on a chiral column.

target product **11ia** in a similar level of enantioselection (entry 10). Notably, isocyanates **10a-e** with varying substitution patterns (alkyl, aryl, CH_2CO_2Et) and distinct electronic properties (MeO or CF_3 on the phenyl moiety) were also well tolerated in the reactions with **9a**, affording the pyrimidinones **11aa**-**11ae** in 60-92% yields with 75-92% ee (entries 1 and 11-14).

Conclusions

In summary, a series of 1,1'-spirobiindane-7,7'-diol analogues **5a-f** bearing a 2,2'-dimethyl-, cyclopentyl-, or cyclohexyl-fused ring have been synthesized, and their structural features were compared on the basis of X-ray crystallographic studies. Based on these scaffolds, a new class of chiral spiro monophosphoramidite ligands **6a-m** have been developed, which demonstrated excellent enantioselectivity in Rh(I) catalyzed asymmetric hydrogenation of a dehydroaminoacid methyl ester. Ligands **6a-m** have also been successfully evaluated in the Rh(I)-catalyzed enantioselective [4+2] cycloaddition of α, β-unsaturated imines with isocyanates, affording the corresponding pyrimidinones in good yields (60-92%) with high enantioselectivities (75-92% ee). Further studies on the ligand development and synthetic applications of these new spirobiindane-type skeletons are underway.

Experimental Section

Synthesis of chiral monophosphoramidite ligands 6a-m, general procedure:

To a 25-mL Schlenk tube under argon were added the diol **5** (0.55 mmol), THF (5 mL), and triethylamine (0.40 mL). The resulting mixture was cooled to 0 °C, followed by dropwise addition of the THF solution of the pre-prepared aminophosphorus dichloride (3.4 mmol). The reaction mixture was allowed to warm to rt, and was left under stirring for 12 h. The solvent removed under reduced pressure, and the residue was purified by column chromatography on silica gel (pretreated with PE/Et_3N = 20/1) using PE/Et_3N (20/1 v/v) as the eluent, to afford the target chiral monophosphoramidite ligand as an analytically pure product.

Asymmetric [4+2] cycloaddition of 9 and 10, general procedure:

To a 15-mL Schlenk tube under argon were added $[Rh(C_2H_4)_2Cl]_2$ (1.45 mg, 0.00375 mmol), ligand (1*R*, 2*R*, 2'*R*, R_N, R_N)-**6l** (0.0075 mmol), and toluene (1.5 mL). The resulting solution was stirred at rt for 15 min, followed by addition of **9** (0.15 mmol) and **10** (0.188 mmol). The mixture was heated to 110 ºC and kept refluxing at this temperature for 12 h, then cooled to rt, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography with n-Hexane/CH_2Cl_2 (v/v 2/1) as the eluent, to afford 3,4-dihydropyrimidin-2(1*H*)-one **11** as an analytically pure product.

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Keywords: Asymmetric Catalysis • Spiro Ligand • Phosphoramidite • Cycloaddtion • Pyrimidinone

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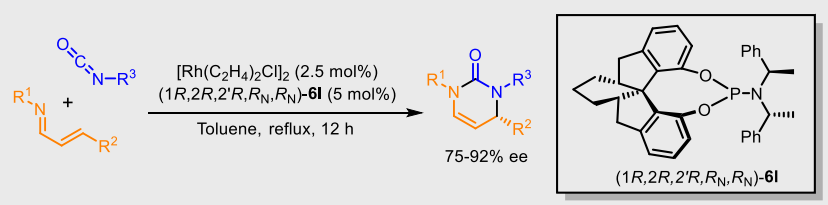

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Page No. – Page No.

Development of Chiral Spiro Phosphoramidites for Rhodium-Catalyzed Enantioselective Reactions

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