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## Ligand Design

# Development of Axially Chiral Cyclo-Biaryldiol Ligands with Adjustable Dihedral Angles

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**Abstract:** A new type of axially chiral cyclo-[1,1′-biphenyl]-2,2′-diol (CYCNOL) ligands with adjustable dihedral angles have been developed by varying the bridge chain length. Eight-, nine- and ten-membered cyclo-ligands were prepared and evaluated by using two representative examples: enantioselective additions of diethylzinc to aldehydes and organometallic reagents to enones. The results revealed that the fine regulation of dihedral angles through variation of the bridge chain length was effective in the asymmetric synthesis.

## Introduction

Optically active compounds are widely found in biomolecules, natural products and drugs.[1] Preparation of high optical purity molecules is mainly through enzyme-promoted organic reactions,[2] organocatalysis,[3] and transition-metal-catalyzed asymmetric synthesis,[4] and their efficiency depends highly on the chiral inducers such as amino acid residues in enzymes, chiral organocatalysts, and chiral ligands of transition metals. In previous asymmetric organic syntheses, transition-metal-catalyzed asymmetric reactions and organocatalysis have been most commonly used. Therefore, the development of chiral ligands and organocatalysts has been a key issue for obtaining high reactivity and enantioselectivity. In the past decades, thousands of chiral ligands have been developed and successfully applied in academic research and industrial production,[5] and axially chiral ligands have found widespread applications in transition-metal-catalyzed asymmetric synthesis. It is well known that axially chiral biaryldiols constitute a key type of cores and their modification has provided a diverse range of excellent supporting ligands. The most prominent axially chiral ligand cores are [1,1′-naphenyl]-2,2′-diol (BINOL)[6] and 1,1′-spirobiindane-7,7′-diol (SPINOL; Figure 1 a).[7] BINOL[8] and SPINOL[9] derivatives such as mono- and diphosphine compounds have been extensively evaluated as versatile chiral ligands and catalysts in asymmetric transformations. However, the catalytic reactivity and enantioselectivity are generally substrate dependent, and no omnipotent ligand has yet been identified that can in deal with the many challenging transition-metal-catalyzed asymmetric transformations because subtle variations in geometric, steric, and/or electronic properties of chiral ligands can cause dramatic changes of reactivity and enantioselectivity. Conformationally rigid and adjustable chiral ligands can improve the enantioselectivity of a reaction. It is noted that the introduction of a chiral or achiral bridge with variable chain length can provide additional handles for fine-tuning the axially chiral ligand rigidity and the dihedral angles (and bite angles).[10] Unfortunately, previous bridges have been constructed through linkage of alkylaryl ethers, which does not favor further modification of ligands, so the diversity and application of tunable ligands has thus far been very limited. We realized that the introduction of a full-carbon bridge chain to biaryl diols may help to overcome such difficulties. In this paper, we report a new type of axially chiral cyclo-[1,1′-biphenyl]-2,2′-diol (CYCNOL) ligands with adjustable dihedral angles by varying the chain length of the full-carbon 6,6′-tether, and eight-, nine-, and ten-membered cyclo-ligands (Figure 1 b) were prepared and evaluated in asymmetric transformations.

## Results and Discussion

### Synthesis of axially chiral (*R*)-CYC-8-NOL and (*S*)-CYC-8-NOL

Racemic 6,6′-dimethoxybiphenyl-2,2′-dicarbaldehyde (*rac*-**1**) was prepared according to the previous procedures.[11] As shown in Scheme 1, reduction of *rac*-**1** in tetrahydrofuran (THF) with $NaBH_4$ provided the corresponding diol **2** in 99% yield, and bromination of **2** with triphenylphosphine dibromide ($Ph_3PBr_2$) in anhydrous dichloromethane ($CH_2Cl_2$) led to **3** in 96% yield in the presence of imidazole at 0 °C. Copper-catalyzed coupling of **3** with vinyl magnesium bromide in anhydrous THF afforded diallylbiphenyl **4** in 41% yield, and an intramolecular ring-closing metathesis using Grubbs' catalyst generated **5** in 86% yield.[12] Subsequently, hydrogenation with

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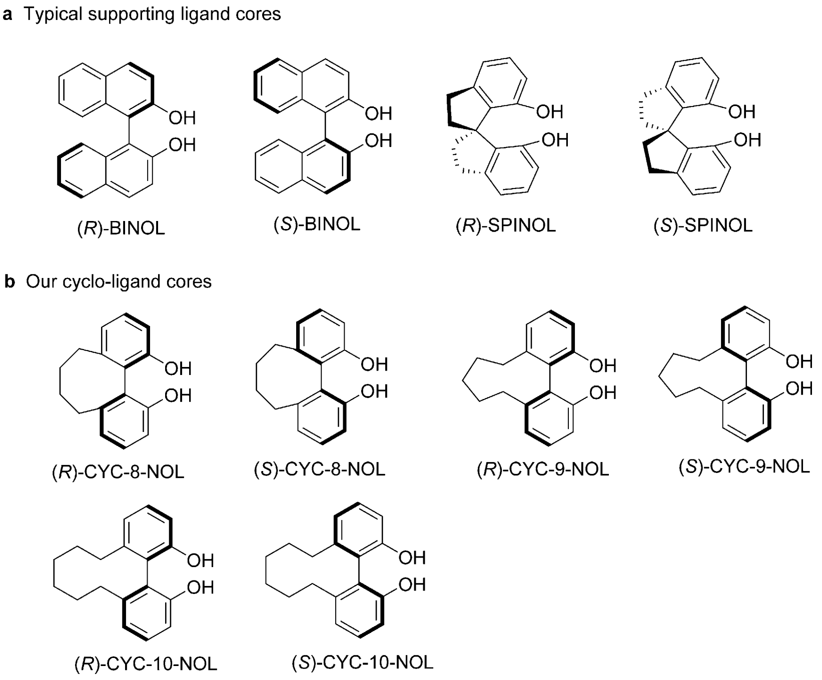


**Figure 1.** Axially chiral biaryldiol ligand cores. a) Typical supporting ligand cores; b) Our cyclo-ligand cores.

Pd/C at atmospheric pressure produced the hydrogenated butyl-bridged biaryl ether (**6**) in almost quantitative yield. Demethylation of diethers with $BBr_3$ in $CH_2Cl_2$ followed by hydrolysis afforded *rac*-CYC-8-NOL in 95% yield. Treatment of *rac*-CYC-8-NOL with L-menthyl chloroformate (**7**) in the presence of $NEt_3$ and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) gave **8**, and separation of **8** by silica gel column chromatography provided ($R_a$)-**8** and ($S_a$)-**8**. Pure enantiomers, (*R*)-CYC-8-NOL and (*S*)-CYC-8-NOL, were obtained by hydrazinolysis of ($R_a$)-**8** and ($S_a$)-**8**, respectively. Their enantiomeric purity was determined by chiral HPLC (see the Supporting Information for details). The polarimeter analysis confirmed that the compounds were (*R*)-(−)-CYC-8-NOL and (*S*)-(+)-CYC-8-NOL. To ascertain absolute configuration of the newly synthesized (*R*)-(−)-CYC-8-NOL and (*S*)-(+)-CYC-8-NOL, a single crystal of (*S*)-(+)-CYC-8-NOL obtained from mixed solvent of hexane and dichloromethane was prepared, and its structure was unambiguously confirmed by X-ray diffraction analysis (Figure 2; see the Supporting Information for details).

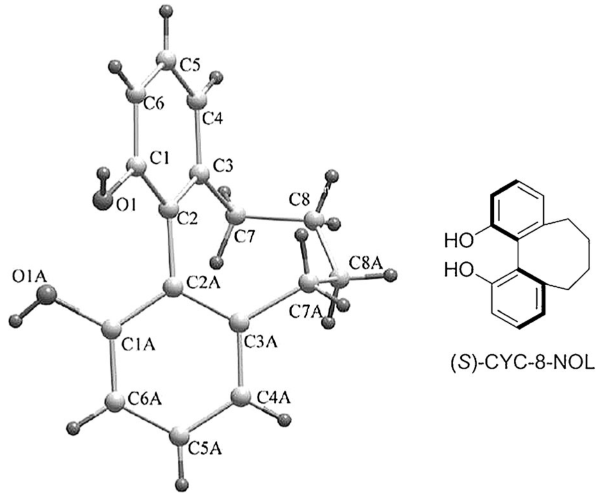
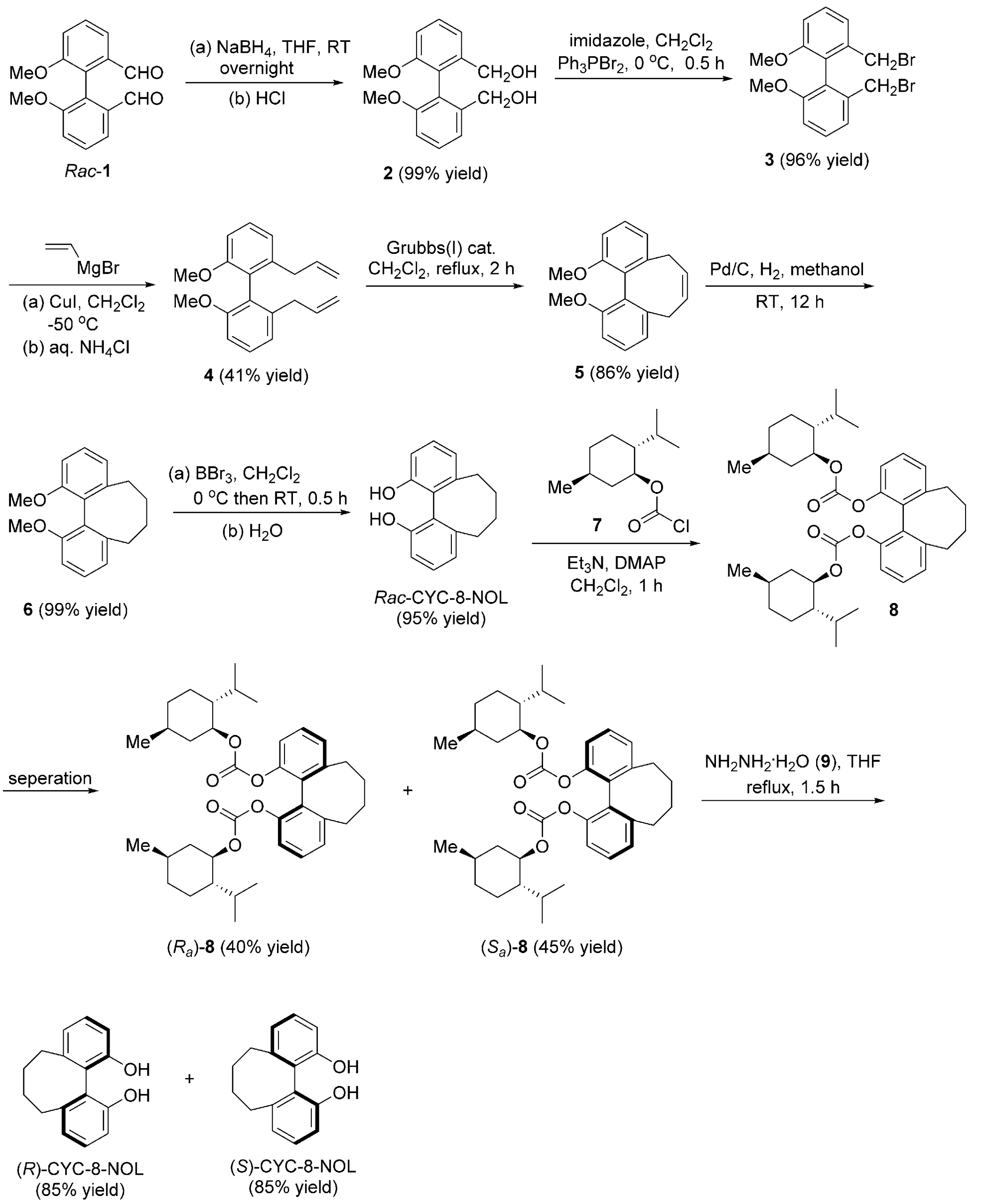


**Figure 2.** Crystal structure of (*S*)-CYC-8-NOL. CCDC 1493466 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

### Synthesis of axially chiral (*R*)-CYC-9-NOL, (*S*)-CYC-9-NOL, (*R*)-CYC-10-NOL, and (*S*)-CYC-10-NOL

We investigated the preparation of (*R*)-CYC-9-NOL, (*S*)-CYC-9-NOL, (*R*)-CYC-10-NOL, and (*S*)-CYC-10-NOL. As shown in Scheme 2a, optical resolution of racemic 6,6′-dimethoxybiphenyl-2,2′-dicarbaldehyde (*rac*-**1**) performed well using enantiomeric *tert*-butanesulfinamide as the resolving agent according to the previous reference.[13] We prepared single crystals of (*R*)-**1** and (*S*)-**1** from mixed solvent of hexane and dichloromethane, and their structures were unambiguously confirmed by X-ray diffraction analysis (see the Supporting Information for details). Here, the synthesis of (*R*)-CYC-9-NOL and (*R*)-CYC-10-NOL is reported as an example. Wittig coupling of (*R*)-**1** with $Ph_3P{=}CHCH_2CH{=}PPh_3$ (from treatment of propane-1,3-diylbis-(triphenylphosphonium) bromide with *n*BuLi) in anhydrous THF led to (*R*)-**10** in 30% yield, and reduction with hydrogen under catalysis of Pd/C provided (*R*)-**11** in 98% yield. Finally, demethylation of (*R*)-**11** followed by hydrolysis generated the desired axially chiral (*R*)-(−)-CYC-9-NOL (Scheme 2b). (*S*)-(+)-CYC-9-NOL was prepared by using the same procedures (see the Supporting Information for details). Their enantiomeric purity was determined by chiral HPLC (see the Supporting Informa-



**Scheme 1.** Synthesis and separation of axially chiral (*R*)-CYC-8-NOL and (*S*)-CYC-8-NOL.

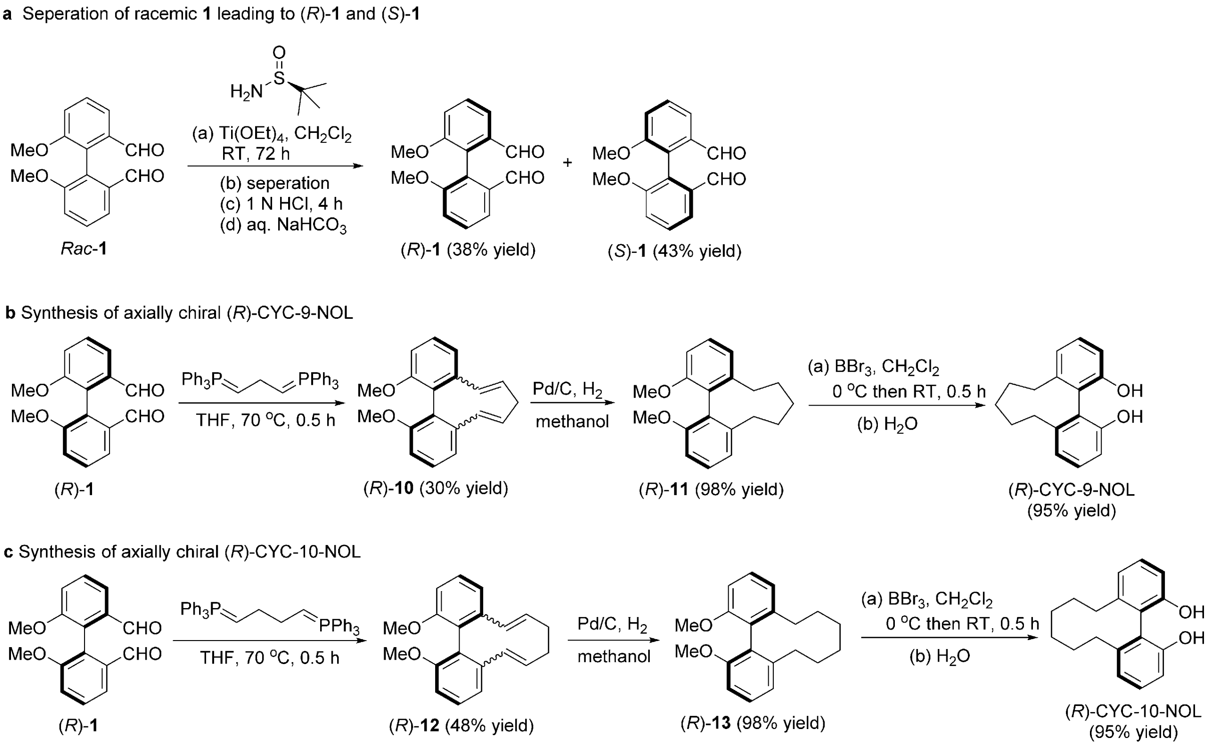
tion for details). Optical rotations of (*R*)-(−)-CYC-9-NOL and (*S*)-(+)-CYC-9-NOL were determined, and the corresponding absolute configurations were unambiguously indentified by X-ray diffraction analysis (Figure 3; see the Supporting Information for details). Similarly, preparation of (*R*)-CYC-10-NOL and (*S*)-CYC-10-NOL were also investigated. Fortunately, (*R*)-(+)-CYC-10-NOL and (*S*)-(−)-CYC-10-NOL were obtained (Scheme 2c), and their structures were confirmed by X-ray diffraction analysis (Figure 3; see the Supporting Information for details).

## Dihedral angles of axially chiral (*S*)-CYC-8-NOL, (*S*)-CYC-9-NOL, and (*S*)-CYC-10-NOL

According to data from X-ray diffraction analysis of (*S*)-CYC-8-NOL, (*S*)-CYC-9-NOL, and (*S*)-CYC-10-NOL, dihedral angles of the axially chiral cyclo-biaryldiols show remarkable difference with variation of the ring sizes (Table 1). It is well known that the dihedral angles for the axially chiral ligands are a key factor for reactivity and enantioselectivity in asymmetric synthesis.

## Enantioselective addition of diethylzinc to aldehydes using biaryldiol ligands

Applications of the obtained axially chiral cyclo-biaryldiols in asymmetric synthesis were investigated. It is known that the enantioselective addition of diethylzinc to aldehydes using biaryldiol ligands is one of the most reliable protocols for synthesis of chiral *sec*-alcohols and also a standard reaction to test the reactivity and enantioselectivity of newly developed chiral ligands.[14] As shown in Table 2, enantioselective addition of diethylzinc to 2-naphthaldehyde (**14m**) was chosen as the



**a** Seperation of racemic **1** leading to (*R*)-**1** and (*S*)-**1**

**b** Synthesis of axially chiral (*R*)-CYC-9-NOL

**c** Synthesis of axially chiral (*R*)-CYC-10-NOL

**Scheme 2.** Synthesis of axially chiral (*R*)-**1**, (*S*)-**1**, (*R*)-CYC-9-NOL, (*S*)-CYC-9-NOL, (*R*)-CYC-10-NOL, and (*S*)-CYC-10-NOL. a) Separation of axially chiral (*R*)-**1** and (*S*)-**1**. b) Synthesis of axially chiral (*R*)-CYC-9-NOL. c) Synthesis of axially chiral (*R*)-CYC-10-NOL.

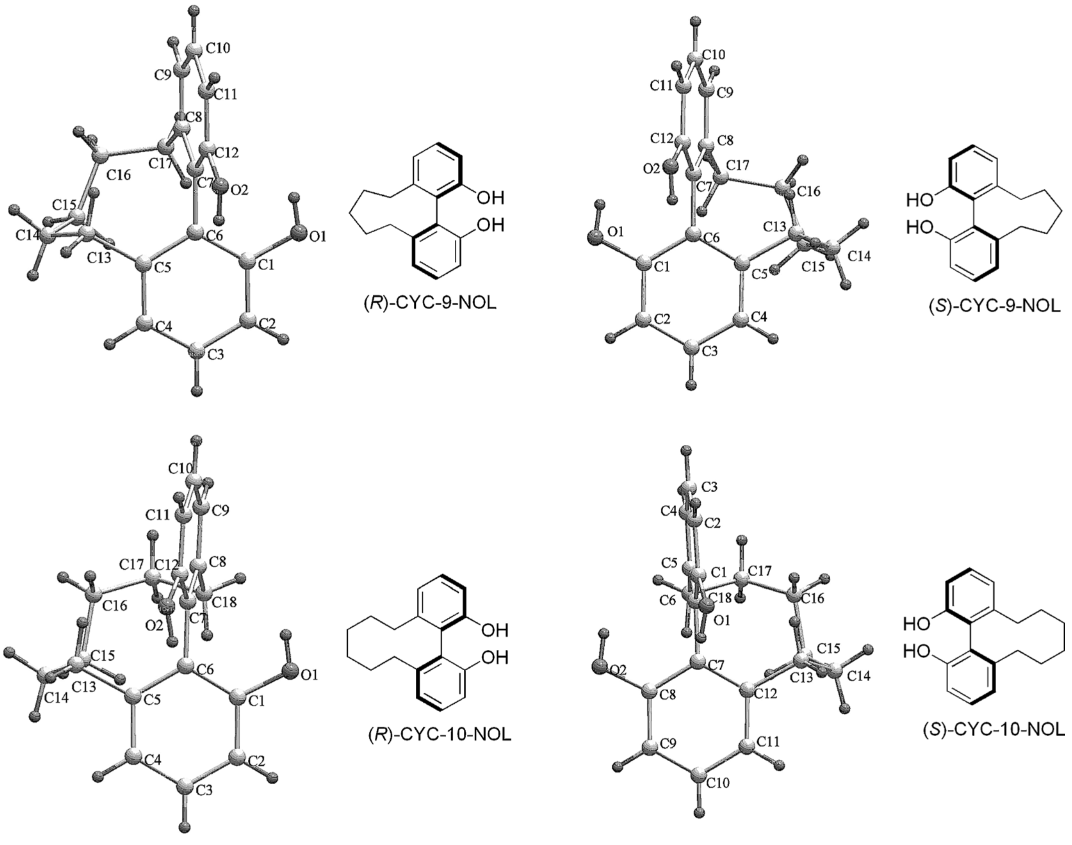


**Figure 3.** Crystal structures of (*R*)-CYC-9-NOL, (*S*)-CYC-9-NOL, (*R*)-CYC-10-NOL and (*S*)-CYC-10-NOL. CCDC 1476688 ((*R*)-CYC-9-NOL), 1475886 ((*S*)-CYC-9-NOL), 1475890 ((*R*)-CYC-10-NOL), and 1475888 ((*S*)-CYC-10-NOL) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

**Table 1.** Dihedral angles of axially chiral cyclo-biaryldiols determined from X-ray diffraction analysis.

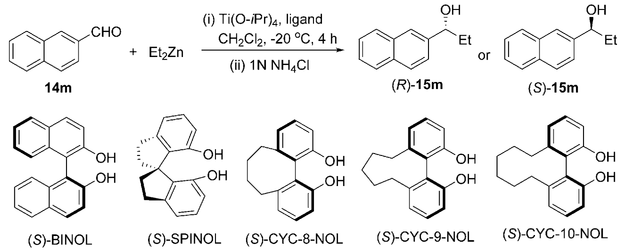
| Ligand | (*S*)-CYC-8-NOL | (*S*)-CYC-9-NOL | (*S*)-CYC-10-NOL |
|---|---|---|---|
| dihedral angle [°] | 61.4 | 82.9 | 100.8 |

model to screen ligands including known (*S*)-BINOL, (*S*)-SPINOL, and our newly developed (*S*)-CYC-8-NOL, (*S*)-CYC-9-NOL, and (*S*)-CYC-10-NOL; the reaction was performed in anhydrous $CH_2Cl_2$ at $-20\,^{\circ}C$ using titanium tetraisopropoxide as the Lewis acid. All ligands exhibited high reactivity, but the enantioselectivity showed remarkable difference (entries 1–5). (*S*)-CYC-8-NOL and (*S*)-CYC-10-NOL afforded similar enantioselectivity as (*S*)-BINOL, and (*S*)-CYC-9-NOL gave an excellent *ee* value (94% *ee*). The results indicated that the fine regulation of dihedral angles by varying bridge chain length was effective in asymmetric synthesis. When the amount of (*S*)-CYC-9-NOL was changed from 10 to 5 mol%, a 90% *ee* was recorded (entry 6). Further reduction of the amount of (*S*)-CYC-9-NOL led to reduction in enantioselectivity (entries 7 and 8). After obtaining the optimal ligand, (*S*)-CYC-9-NOL, we investigated the substrate scope for the enantioselective addition of diethylzinc to aldehydes **14**, and found that the examined aldehydes all provided excellent yields and high to excellent *ee* values (Table 3). Aryl aldehydes containing *ortho*-halogens exhibited slightly lower enantioselectivity (see (*S*)-**15 f**, (*S*)-**15 g**, and (*S*)-**15 k** in Table 3), and aliphatic aldehyde (see (*S*)-**15 o** in Table 3) provided lower *ee* value than aromatic aldehydes. The reaction can tolerate various functional groups including ether, C–F bond, C–Cl bond, C–Br bond, and *S*-heterocycle. The results confirm that the axially chiral cyclo-biaryldiol ligands are very useful in asymmetric synthesis.

### Enantioselective addition of organometallic reagents 17 to enones 18 using phosphoramidite ligands

We surveyed derivatization of our axially chiral cyclo-biaryldiols. Given that phosphoramidites of axially chiral biaryldiols are privileged ligands in asymmetric catalysis,[15] we prepared twenty phosphoramidite ligands (Table 4) according to the previous procedures (see the Supporting Information for details).[16] An interesting reaction, copper-catalyzed asymmetric carbon–carbon bond formation using alkenes as alkylmetal equivalents, developed by Fletcher and co-workers[16] was selected as the model to evaluate the effects of the known ligands and our newly developed biaryldiol phosphoramidites. As shown in Table 4, treatment of phosphoramidite ligand with $(CuOTf)_2PhH$ led to the formation of their respective complex (ligand-Cu) at room temperature under argon atmosphere; meanwhile, reaction of alkene **16 a** with $Cp_2ZrHCl$ gave addition product **17 a** in another flask under the similar conditions. The reaction of **17 a** with **18 a** was then performed under catalysis of ligand-Cu at room temperature under argon atmosphere. Here, some representative phosphoramidite ligands were selected as examples to evaluate their reactivity (Table 4; see the Supporting Information for more data). Phos-

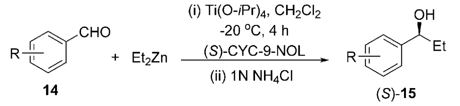
**Table 2.** Enantioselective addition of diethylzinc to 2-naphthaldehyde (**14 m**).[a]

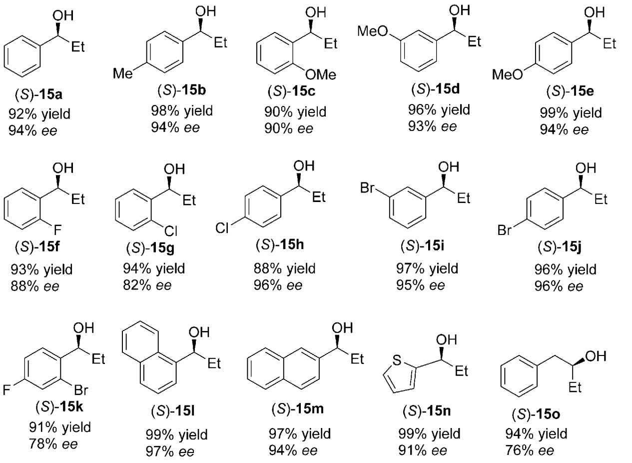


| Entry | Ligand | Product[b] | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|
| 1 | (*S*)-BINOL | (*S*)-**15 m** | 97 | 86 |
| 2 | (*S*)-SPINOL | (*R*)-**15 m** | 94 | 75 |
| 3 | (*S*)-CYC-8-NOL | (*S*)-**15 m** | 97 | 84 |
| 4 | (*S*)-CYC-9-NOL | (*S*)-**15 m** | 97 | 94 |
| 5 | (*S*)-CYC-10-NOL | (*S*)-**15 m** | 95 | 86 |
| 6[e] | (*S*)-CYC-9-NOL | (*S*)-**15 m** | 96 | 90 |
| 7[f] | (*S*)-CYC-9-NOL | (*S*)-**15 m** | 93 | 81 |
| 8[g] | (*S*)-CYC-9-NOL | (*S*)-**15 m** | 88 | 62 |

[a] Reaction conditions: **14 m**/ligand/Ti(O*i*Pr)$_4$/$Et_2Zn$ = 1:0.1:1.4:3 (molar ratio), **14 m** (0.125 mmol), ligand (12.5 μmol), Ti(O*i*Pr)$_4$ (0.175 mmol), $Et_2Zn$ (0.375 mmol), $CH_2Cl_2$ (1.0 mL), $-20\,^{\circ}C$, 4 h, 1 N $NH_4Cl$ (2.0 mL). [b] Absolute configurations known, determined or assigned by analogy (see the Supporting Information). [c] Isolated yield. [d] The *ee* values were determined by HPLC analysis using a chiral stationary phase (Chiralpak® OD-H). [e] Using 6.25 μmol of (*S*)-CYC-9-NOL as the ligand. [f] Using 2.5 μmol of (*S*)-CYC-9-NOL as the ligand. [g] Using 1.25 μmol of (*S*)-CYC-9-NOL as the ligand.

**Table 3.** Enantioselective addition of diethylzinc to aldehydes **14** leading to **15**.[a–d]





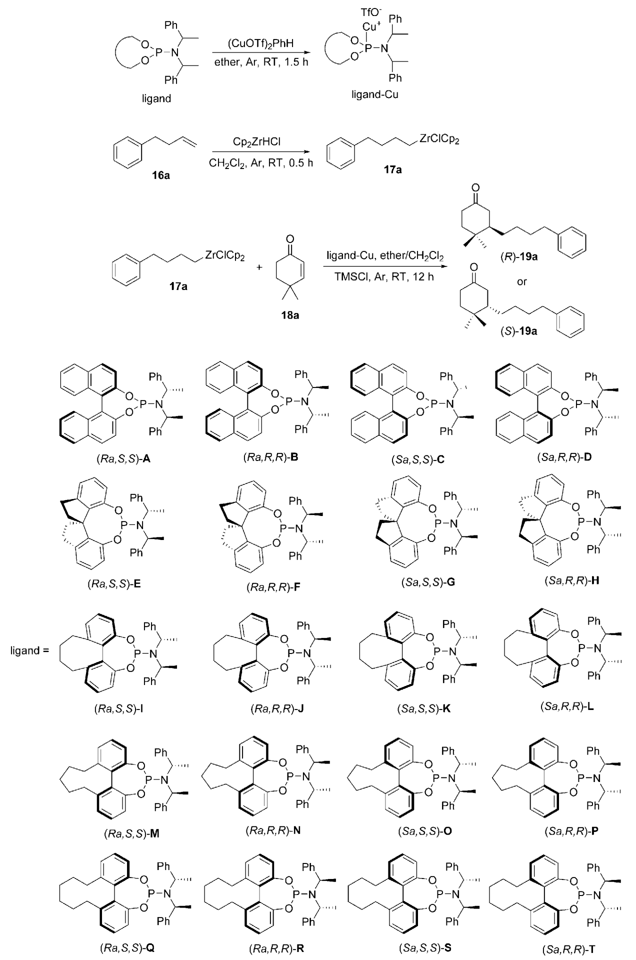
(*S*)-**15a** 92% yield 94% *ee*
(*S*)-**15b** 98% yield 94% *ee*
(*S*)-**15c** 90% yield 90% *ee*
(*S*)-**15d** 96% yield 93% *ee*
(*S*)-**15e** 99% yield 94% *ee*
(*S*)-**15f** 93% yield 88% *ee*
(*S*)-**15g** 94% yield 82% *ee*
(*S*)-**15h** 88% yield 96% *ee*
(*S*)-**15i** 97% yield 95% *ee*
(*S*)-**15j** 96% yield 96% *ee*
(*S*)-**15k** 91% yield 78% *ee*
(*S*)-**15l** 99% yield 97% *ee*
(*S*)-**15m** 97% yield 94% *ee*
(*S*)-**15n** 99% yield 91% *ee*
(*S*)-**15o** 94% yield 76% *ee*

[a] Reaction conditions: aldehyde/ligand/Ti(O*i*Pr)$_4$/$Et_2Zn$ = 1:0.1:1.4:3 (molar ratio), aldehyde **14** (0.125 mmol), (*S*)-CYC-9-NOL (12.5 μmol), Ti(O*i*Pr)$_4$ (0.175 mmol), $Et_2Zn$ (0.375 mmol), $CH_2Cl_2$ (1.0 mL), $-20\,^{\circ}C$, 4 h, 1 N $NH_4Cl$ (2.0 mL). [b] Absolute configurations known, determined or assigned by analogy (see the Supporting Information). [c] Isolated yield. [d] The *ee* values were determined by HPLC analysis using a chiral stationary phase (see the Supporting Information).

phoramidites of (*S*)-CYC-8-NOL (entries 5 and 6) displayed similar reactivity and enantioselectivity to those of known ligands (entries 1–4). Interestingly, ligands ($S_a$,*R*,*R*)-**P**, with nine-membered ring (entry 8), and ($S_a$,*R*,*R*)-**T**, with ten-membered ring (entry 10), exhibited excellent enantioselectivity. The results showed that the fine regulation of dihedral angles by varying the bridge chain length could change the level of enantioselectivity. The reactivity and enantioselectivity decreased when amount of ligand-Cu was reduced (entries 11 and 12).

In the enantioselective addition of organometallic reagent **17a** to 4,4-dimethylcyclohex-2-enone (**18a**) above, the phosphoramidite ligands ($S_a$,*R*,*R*)-**P**, with nine-membered ring, and ($S_a$,*R*,*R*)-**T**, with ten-membered ring, provided higher enantioselectivity than that of ($S_a$,*R*,*R*)-**L**, with eight-membered ring, as shown in Table 4. However, the catalytic reactivity and enantioselectivity are generally substrate-dependent. To further determine the effect of ligands with different dihedral angles in the asymmetric synthesis, alkenes **16b** and **16c** were used as the partner of **18a**. Interestingly, ($R_a$,*S*,*S*)-**I** and ($S_a$,*R*,*R*)-**L**, with eight-membered ring, and ($R_a$,*S*,*S*)-**M** and ($S_a$,*R*,*R*)-**P**, with nine-membered ring, afforded higher enantioselectivity than ($R_a$,*S*,*S*)-**Q** and ($S_a$,*R*,*R*)-**T**, with ten-membered ring (Table 5, entries 1–6). According to the results above, ($R_a$,*S*,*S*)-**M** and ($S_a$,*R*,*R*)-**P**, with nine-membered ring, are optimal ligands. Subsequently, we used ($S_a$,*R*,*R*)-**P** as the ligand to investigate the substrate scope on the enantioselective addition of organometallic reagents **17** to enones **18** leading to **19**; the examined alkenes **16** and enones **18** afforded moderate yields and high to excellent *ee* values (Table 5). For alkenes **16**, aliphatic terminal alkenes gave higher *ee* values than aromatic alkenes. For enones **18**, 4,4-dimethylcyclohex-2-enone (**18a**) provided higher enantioselectivity than cyclohex-2-enone (**18b**) and cyclopent-2-enone (**18c**), and cyclohept-2-enone also was a good Michael acceptor. Interestingly, the reaction could tolerate the presence of a C–Cl bond, which is usually difficult for reactions of other organometallic reagents. The method exhibits some advantages including the ready availability of alkenes and enones as the starting materials, application of alkylmetal agents generated in situ from alkenes, room temperature conditions, and high levels of enantioselectivity. The results show that our newly developed axially chiral cyclo-biaryldiols have significant potential in asymmetric synthesis.

**Table 4.** Ligand screening for enantioselective addition of organometallic reagent **17a** to 4,4-dimethylcyclohex-2-enone (**18a**).[a]



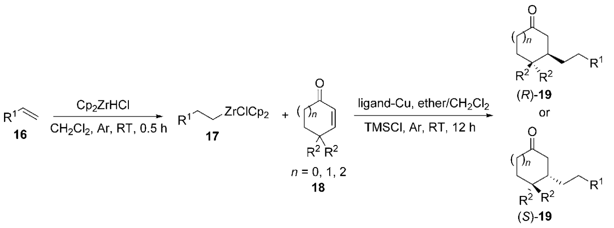
| Entry | Ligand | Product[b] | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|
| 1 | ($S_a$,*S*,*S*)-**C** | (*R*)-**19a** | 68 | 85 |
| 2 | ($S_a$,*R*,*R*)-**D** | (*R*)-**19a** | 64 | 85 |
| 3 | ($S_a$,*S*,*S*)-**G** | (*S*)-**19a** | 66 | 82 |
| 4 | ($S_a$,*R*,*R*)-H | (*S*)-**19a** | 65 | 86 |
| 5 | ($S_a$,*S*,*S*)- **K** | (*R*)-**19a** | 73 | 81 |
| 6 | ($S_a$,*R*,*R*)- **L** | (*R*)-**19a** | 72 | 88 |
| 7 | ($S_a$,*S*,*S*)-**O** | (*R*)-**19a** | 70 | 86 |
| 8 | ($S_a$,*R*,*R*)-**P** | (*R*)-**19a** | 75 | 92 |
| 9 | ($S_a$,*S*,*S*)-**S** | (*R*)-**19a** | 60 | 67 |
| 10 | ($S_a$,*R*,*R*)-**T** | (*R*)-**19a** | 77 | 91 |
| 11[e] | ($S_a$,*R*,*R*)-**P** | (*R*)-**19a** | 53 | 79 |
| 12[f] | ($S_a$,*R*,*R*)-**P** | (*R*)-**19a** | 40 | 27 |

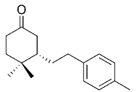
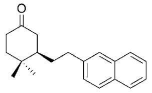
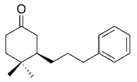
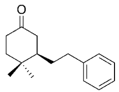
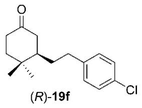
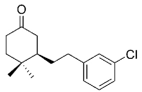
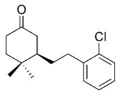
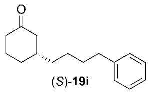
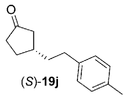
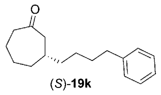
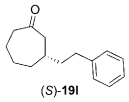
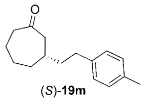
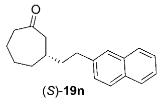
[a] Reaction conditions: alkene **16a** (1.0 mmol, 2.5 equiv), $Cp_2ZrHCl$ (0.80 mmol, 2 equiv), enone **18a** (0.40 mmol, 1 equiv), ligand (0.04 mmol, 0.1 equiv), $(CuOTf)_2PhH$ (0.02 mmol, 0.05 equiv), trimethylsilylchloride (TMSCl; 2.0 mmol, 0.25 mL, 5.0 equiv), ether (2.0 mL), $CH_2Cl_2$ (1.0 mL). [b] Absolute configurations known, determined or assigned by analogy (see the Supporting Information). [c] Isolated yield. [d] The *ee* values were determined by HPLC using a chiral stationary phase (Chiralpak® AY-H). [e] $(CuOTf)_2PhH$ (0.01 mmol, 0.025 equiv), ligand (0.02 mmol, 0.05 equiv). [f] $(CuOTf)_2PhH$ (0.004 mmol, 0.01 equiv), ligand (0.008 mmol, 0.02 equiv).

## Conclusions

We have developed a new type of axially chiral cyclo-[1,1′-biphenyl]-2,2′-diol (CYCNOL) ligands with dihedral angles that can be adjusted by varying the chain length of the full-carbon 6,6′-tether, and eight-, nine-, and ten-membered cyclo-ligands were obtained. The enantioselective addition of diethylzinc to aldehydes was conducted in the presence of the axially chiral cyclo-ligands, and the systems provided good to excellent reactivity and enantioselectivity, in which the ligands with different dihedral angles exhibited remarkable differences. Furthermore, the phosphoramidites of the axially chiral biaryldiols were used as ligands in the enantioselective addition of organometallic reagents to enones. The results showed that fine regulation of the dihedral angles by varying the bridge chain length was effective in the asymmetric synthesis. We believe that our newly developed axially chiral biaryldiols will find wide applications in synthesis of chiral molecules.

**Table 5.** Substrate scope for enantioselective addition of organometallic reagents **17** to enones **18** leading to **19**.[a]



| Entry | Ligand | Product[b] | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|
| 1 | $(R_a,S,S)$-**I** |  (*S*)-**19b** | 51 | 92 |
| 2 | $(R_a,S,S)$-**M** | (*S*)-**19b** | 63 | 93 |
| 3 | $(R_a,S,S)$-**Q** | (*S*)-**19b** | 56 | 86 |
| 4 | $(S_a,R,R)$-**L** |  (*R*)-**19c** | 57 | 91 |
| 5 | $(S_a,R,R)$-**P** | (*R*)-**19c** | 56 | 93 |
| 6 | $(S_a,R,R)$-**T** | (*R*)-**19c** | 50 | 88 |
| 7 | $(S_a,R,R)$-**P** |  (*R*)-**19d** | 66 | 84 |
| 8 | $(S_a,R,R)$-**P** |  (*R*)-**19e** | 69 | 90 |
| 9 | $(S_a,R,R)$-**P** |  (*R*)-**19f** | 80 | 86 |
| 10 | $(S_a,R,R)$-**P** |  (*R*)-**19g** | 79 | 92 |
| 11 | $(S_a,R,R)$-**P** |  (*R*)-**19h** | 75 | 82 |
| 12 | $(S_a,R,R)$-**P** |  (*S*)-**19i** | 61 | 82 |
| 13 | $(S_a,R,R)$-**P** |  (*S*)-**19j** | 30 | 83 |
| 14 | $(S_a,R,R)$-**P** |  (*S*)-**19k** | 76 | 90 |
| 15 | $(S_a,R,R)$-**P** |  (*S*)-**19l** | 81 | 93 |
| 16 | $(S_a,R,R)$-**P** |  (*S*)-**19m** | 76 | 85 |
| 17 | $(S_a,R,R)$-**P** |  (*S*)-**19n** | 74 | 84 |

[a] Reaction conditions: alkene **16** (1.0 mmol, 2.5 equiv), $Cp_2ZrHCl$ (0.80 mmol, 2 equiv), enone **18** (0.40 mmol, 1 equiv), ligand (0.04 mmol, 0.1 equiv), $(CuOTf)_2PhH$ (0.02 mmol, 0.05 equiv), trimethylsilylchloride (TMSCl; 2.0 mmol, 0.25 mL, 5.0 equiv), ether (2.0 mL), $CH_2Cl_2$ (1.0 mL). [b] Absolute configurations known, determined or assigned by analogy (see the Supporting Information). [c] Isolated yield. [d] The *ee* values were determined by HPLC (see the Supporting Information).

## Acknowledgements

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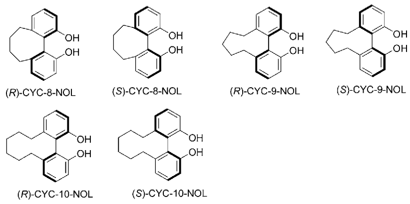
# FULL PAPER

**Adjustable ligands**: A new type of axially chiral cyclo-[1,1′-biphenyl]-2,2′-diol (CYCNOL) ligands with adjustable dihedral angles were developed (see figure). Eight-, nine-, and ten-membered cycloligands were prepared and evaluated by using two representative examples: enantioselective additions of diethylzinc to aldehydes and organometallic reagents to enones. The results revealed that the fine regulation of dihedral angles through variation of the bridge chain length was effective in the asymmetric synthesis.



**Ligand Design**

*P. Zhang, J. Yu, F. Peng, X. Wu, J. Jie, C. Liu, H. Tian, H. Yang, H. Fu**

■■–■■

**Development of Axially Chiral Cyclo-Biaryldiol Ligands with Adjustable Dihedral Angles**