Design, synthesis and evaluation in enantioselective catalysis of diverse adjustable axially chiral biphenyl ligands and catalysts

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Abstract: Chiral compounds widely occur in biomolecules, natural products and drugs, and acquisition of chirality in the chiral molecules highly depends on chiral inducers including chiral ligands and chiral catalysts in asymmetric chemical synthesis. Therefore, development of highly efficient and practical chiral ligands and catalysts is an eternal theme in chemical field. In the past decades, various axially chiral biaryldiol ligands and catalysts have been developed, in which the typical axially chiral cores should be [1,1'-naphenyl]-2,2'-diol (BINOL) and 1,1'-spirobiindane-7,7'-diol (SPINOL). It is known to all that the catalytic reactivity and enantioselectivity are generally substrate-dependent, and the slight variations in steric, electronic and geometric properties of chiral ligands or catalysts can cause dramatic changes in reactivity of substrates and enantioselectivity of products, so no omnipotent ligand or catalyst has been found thus far. Here we report the design, synthesis and evaluation in enantioselective catalysis of a new kind of adjustable axially chiral biphenyl ligands and catalysts, in which six model reactions including asymmetric additions of diethylzinc or alkynes to aldehydes in the presence of axially chiral [1,1'-biphenyl]-2,2'-diol ligands, Pd-catalyzed asymmetric cycloadditions in the presence of phosphoramidite ligands, and chiral phosphoric acid-catalyzed asymmetric synthesis of 1,1'-spirobiindane-7,7'-diol (SPINOL) derivative and [4+3] cyclization were attempted. The results showed that variation of 2,2'-substituent groups could provide different types of ligands and catalysts, and adjustment of substituent groups at the 3, 3', 5, 5', 6, 6'-positions could make ligands and catalysts more efficient in the asymmetric catalytic synthesis. Therefore, our present researches should provide a new and useful strategy for development of diverse axially chiral ligands and catalysts.

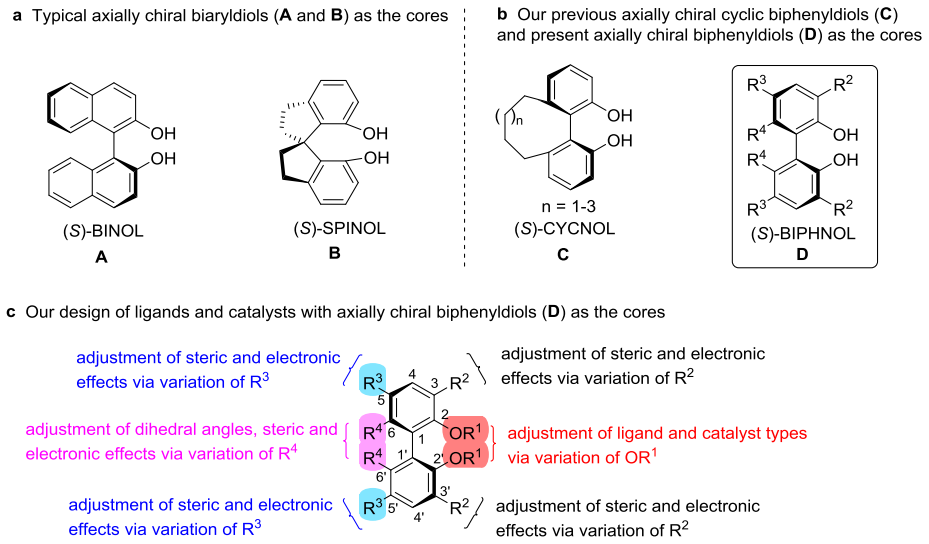


Fig. 1 | Axially chiral biaryldiol cores. a, Previous typical biaryldiols. **b**, Our previous cyclic biphenyldiols and present adjustable biphenyldiols. **c**, Our design of ligands and catalysts based on axially chiral biphenyldiols.

Chiral compounds widely occur in various fields, and they are often found in biomolecules, natural products and drugs[1-3]. Asymmetric chemical synthesis is an effective strategy for obtaining chiral molecules, and their efficiency highly depends on the chiral ligands[4-7] and catalysts[8-11]. Therefore, development of chiral ligands and catalysts is crucial in asymmetric synthesis. In the past decades, various chiral ligands and catalysts have been developed[12-14], in which the axially chiral ligands and catalysts have found widespread applications in areas of asymmetric synthesis. The representative axially chiral cores should be [1,1'-naphenyl]-2,2'-diol (BINOL)[15] and 1,1'-spirobiindane-7,7'-diol (SPINOL) (Fig. 1a)[16], and BINOL[17-22] and SPINOL[23,24] derivatives have been extensively evaluated as the useful chiral ligands and catalysts in asymmetric synthesis. However, there still is not an omnipotent chiral ligand or catalyst thus far because the slight changes in geometric, steric and electronic properties of chiral ligands or catalysts can cause dramatic variations of reactivity of substrates and enantioselectivity of products. Recently, we have developed a new kind of axially chiral cyclo-[1,1'-biphenyl]-2,2'-diol (CYCNOL) cores with adjustable dihedral angles by varying the chain length of the full-carbon 6,6'-tether (left one in Fig. 1b)[25], and CYCNOL-based phosphoramidite[26-29] and diphosphine[30] ligands and chiral phosphoric acid catalysts[31] were effectively developed. Here, we design a novel kind of adjustable axially chiral [1,1'-biphenyl]-2,2'-diol (BIPHNOL) cores (right one in Fig. 1b). As shown in Fig. 1c, our

imaginations are as follows: variation of 2,2'-substituent groups would adjust types of chiral ligands and catalysts, variation of substituent groups at the 3, 3', 5, 5'-positions would adjust steric and electronic properties of chiral ligands and catalysts, and variation of 6,6'-substituent groups would adjust dihedral angles, steric and electronic properties of chiral ligands and catalysts.

Results and discussion

1. Synthesis of diverse axially chiral (*S*)-biphenyldiols and crystal structures of representative axially chiral (*S*)-biphenyldiols

With our design above in hand, we first made the diverse biphenyldiols (see Supplementary Information for details).

1.1 Synthesis of four axially chiral (*S*)-biphenyldiol cores

Synthesis[32] and resolution[33] of racemic 6,6'-dimethoxybiphenyl-2,2'-dicarbaldehyde (*Rac*-**1**) were performed according to the previous procedures. (*S*)-6,6'-Dimethyl-[1,1'-biphenyl]-2,2'-diol ((*S*)-**L1**) was first prepared. As shown in Fig. 2a, reduction of (*S*)-**1** in ethanol with $NaBH_4$ provided the corresponding diol (*S*)-**2** in 99% yield, and bromination of (*S*)-**2** with phosphorus tribromide in anhydrous dichloromethane (CH_2Cl_2) led to (*S*)-**3** in 96% yield. Hydrogenation with Pd/C at atmospheric pressure provided (*S*)-**4** in 99% yield, and demethylation of the two ethers in (*S*)-**4** with BBr_3 in CH_2Cl_2 followed hydrolysis afforded (*S*)-**L1** in 95% yield.

Subsequently, synthesis of (*S*)-6,6'-diethyl-[1,1'-biphenyl]-2,2'-diol ((*S*)-**L2**) was performed (Fig. 2b). The Wittig coupling of $Ph_3P^+MeBr^-$ with (*S*)-**1** in dry THF in the presence of ^{t}BuOK provided (*S*)-**5** in 95% yield, reduction of (*S*)-**5** with hydrogen in the presence of Pd/C at atmospheric pressure gave (*S*)-**6** in 99% yield, and demethylation of the two ethers in (*S*)-**6** with BBr_3 in CH_2Cl_2 followed hydrolysis led to (*S*)-**L2** in 94% yield.

Next, we prepared (*S*)-6,6'-diisopropyl-[1,1'-biphenyl]-2,2'-diol ((*S*)-**L3**). As shown in Fig. 2c, oxidation of (*S*)-**1** with $NaClO_2$ in the presence of NaH_2PO_4 in mixed solvent of H_2O and MeCN produced the corresponding dicarboxylic acid (*S*)-**7** in 99% yield, methyl esterification of (*S*)-**7** provided (*S*)-**8** in 98% yield, and reaction of (*S*)-**8** with 10 equiv of MeMgBr gave (*S*)-**9** in 89% yield. Dehydration of (*S*)-**9** in the presence of $SOCl_2$ and pyridine afforded (*S*)-**10** in 91% yield, hydrogenation with Pd/C at atmospheric pressure of (*S*)-**10** provided (*S*)-**11** in 99% yield, and demethylation of the two ethers in (*S*)-**11** with BBr_3 in CH_2Cl_2 followed hydrolysis gave (*S*)-**L3** in

90% yield.

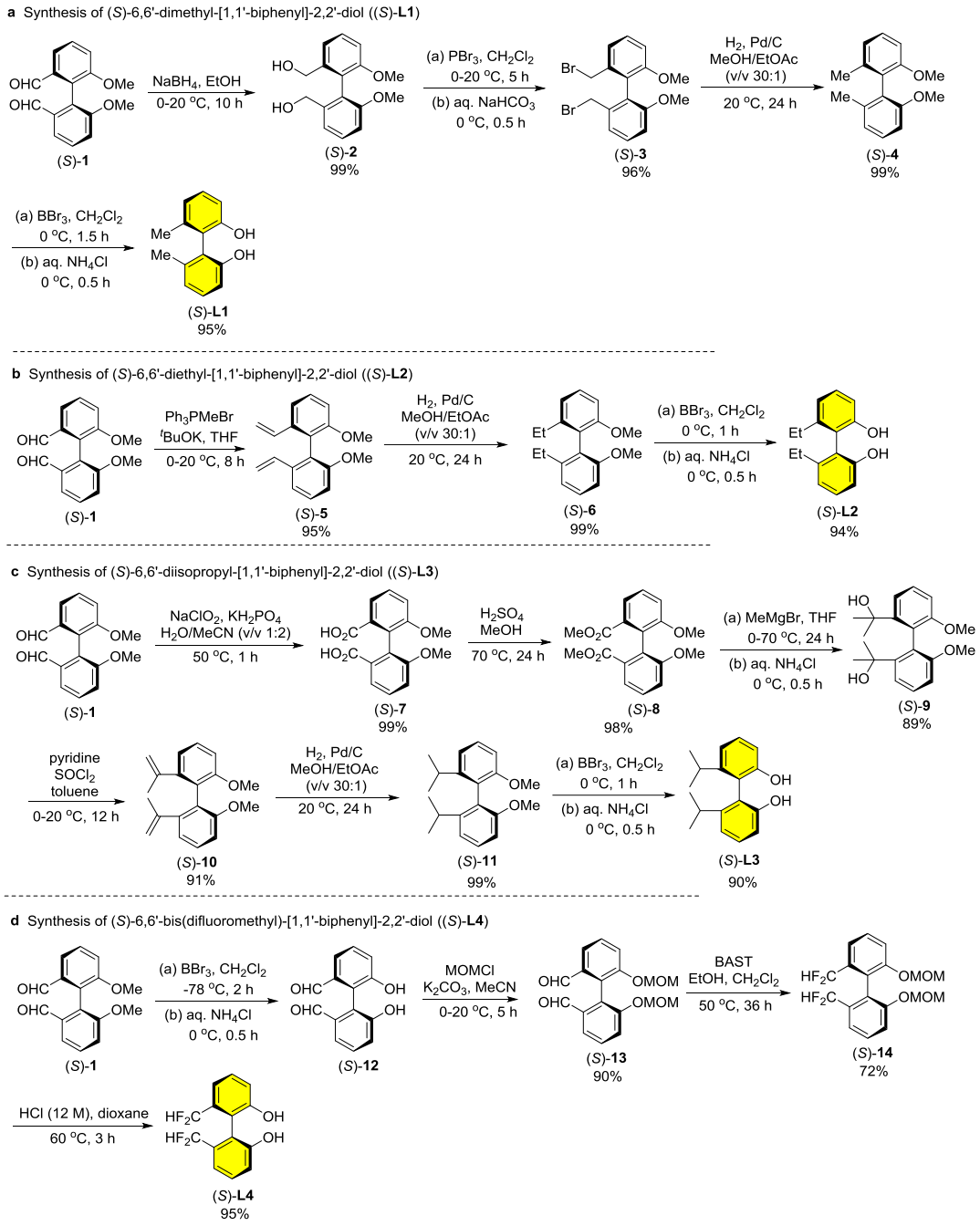


Fig. 2 | Synthesis of four axially chiral biphenyldiol cores, (*S*)-L1, (*S*)-L2, (*S*)-L3 and (*S*)-L4. **a**, Synthesis of (*S*)-**L1**. **b**, Synthesis of (*S*)-**L2**. **c**, Synthesis of (*S*)-**L3**. **d**, Synthesis of (*S*)-**L4**.

Finally, (*S*)-6,6'-bis(difluoromethyl)-[1,1'-biphenyl]-2,2'-diol ((*S*)-**L4**) was prepared (Fig. 2d). Demethylation of (*S*)-**1** with BBr_3 in CH_2Cl_2 followed hydrolysis gave (*S*)-**12**, then etherification of (*S*)-**12** with $MeOCH_2Cl$ (MOM-Cl) in the presence of K_2CO_3 led to (*S*)-**13** in 90% yield for the two step reactions, and the dialdehyde was transformed into the corresponding gemdifluorides

((*S*)-**14**) with bis(2-methoxyethyl)aminosulfur trifluoride (BAST)[34] in 72% yield. Desorption of MOM-protecting group with 12 M HCl in dioxane provided (*S*)-**L4** in 95% yield.

1.2 Synthesis of axially chiral (*S*)-5,5'-dihalo-biphenyldiols

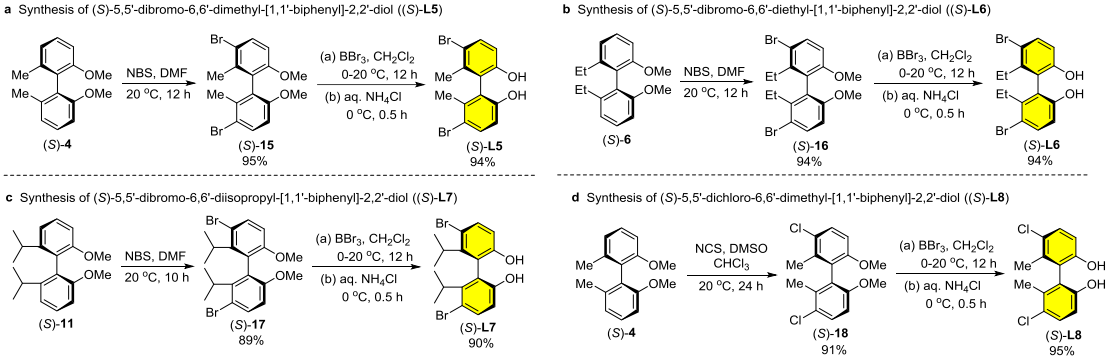


Fig. 3 | Synthesis of axially chiral (*S*)-5,5'-dihalo-biphenyldiols, (*S*)-L5, (*S*)-L6, (*S*)-L7 and (*S*)-L8. a, Synthesis of (*S*)-**L5**. **b**, Synthesis of (*S*)-**L6**. **c**, Synthesis of (*S*)-**L7**. **d**, Synthesis of (*S*)-**L8**.

Subsequently, we investigated synthesis of 5,5'-dihalo-biphenyldiols, (*S*)-**L5**, (*S*)-**L6**, (*S*)-**L7** and (*S*)-**L8** (Fig. 3). Brominations of (*S*)-**4**, (*S*)-**6** and (*S*)-**11** with *N*-bromosuccinimide (NBS) in DMF gave (*S*)-**15**, (*S*)-**16**, (*S*)-**17** in 95%, 94%, 89% yields, respectively, and their demethylations with BBr_3 in CH_2Cl_2 followed hydrolysis provided (*S*)-**L5**, (*S*)-**L6**, (*S*)-**L7** in 94%, 94%, 90% yields, respectively. Chlorination of (*S*)-**4** with *N*-chlorosuccinimide (NCS) in $CHCl_3$ formed (*S*)-**18** in 91% yield, and demethylation of (*S*)-**18** with BBr_3 in CH_2Cl_2 followed hydrolysis led to (*S*)-**L8** in 95% yield.

1.3 Synthesis of axially chiral (*S*)-5,5'-substituted biphenyldiols

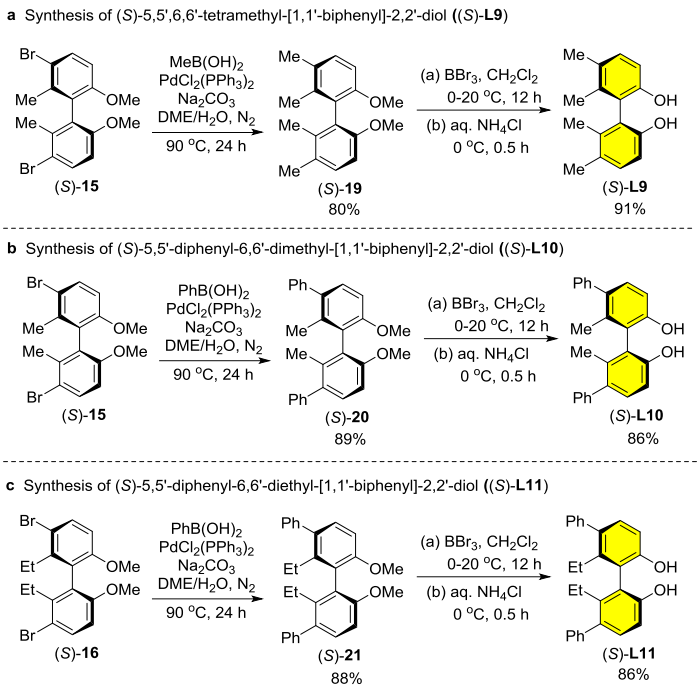


Fig. 4 | Synthesis of (*S*)-5,5'-substituted biphenyldiols (*S*)-L9, (*S*)-L10 and (*S*)-L11. a, Synthesis of (*S*)-**L9**. **b**, Synthesis of (*S*)-**L10**. **c**, Synthesis of (*S*)-**L11**.

Next, we investigated synthesis of 5,5'-dimethyl or 5,5'-diphenyl biphenyldiols, (*S*)-**L9**, (*S*)-**L10** and (*S*)-**L11** (Fig. 4). The Suzuki couplings of (*S*)-**15**, (*S*)-**16** with $MeB(OH)_2$ or $PhB(OH)_2$ led to the corresponding methylating or phenylating products (*S*)-**19**, (*S*)-**20** and (*S*)-**21** in 80%, 89% and 88% yields, respectively. Demethylation of the two ethers in (*S*)-**19**, (*S*)-**20** and (*S*)-**21** with BBr_3 in CH_2Cl_2 followed hydrolysis provided (*S*)-**L9**, (*S*)-**L10** and (*S*)-**L11** in 91%, 86% and 86% yields, respectively.

1.4 Crystal structures of representative axially chiral (*S*)-biphenyldiols

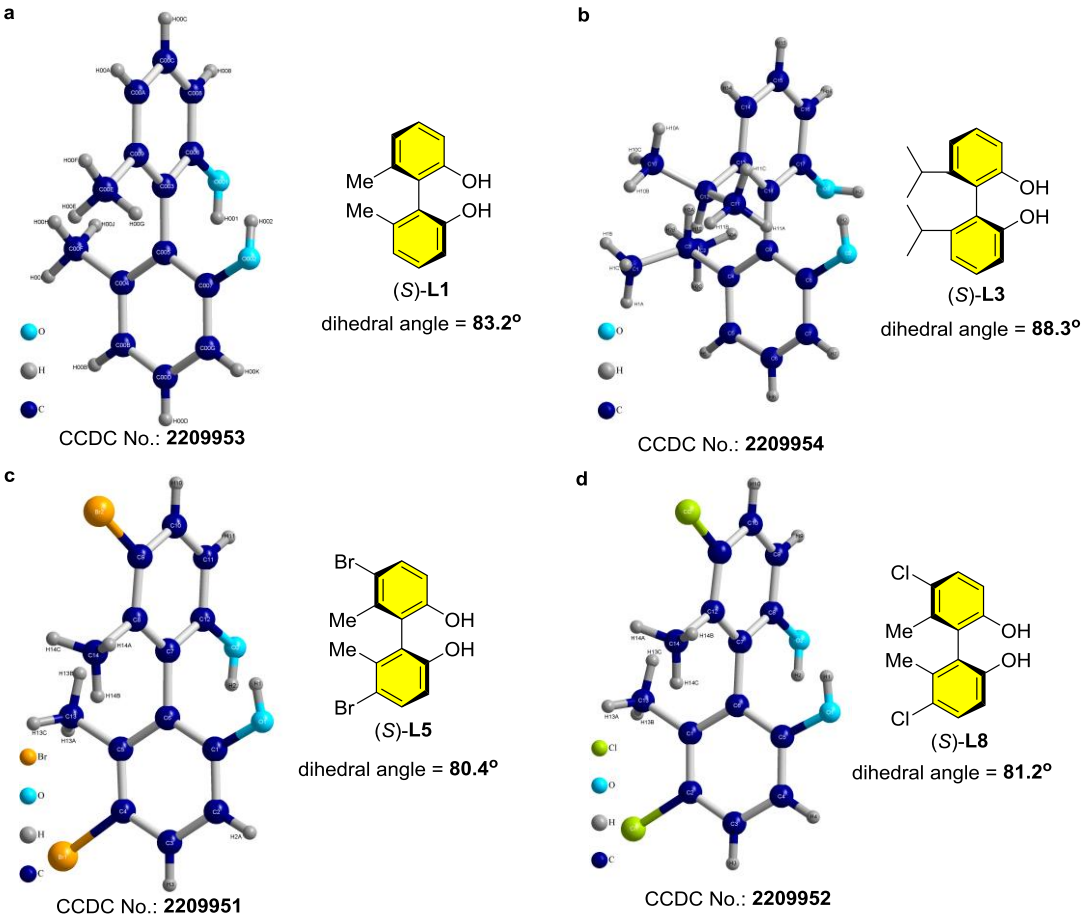


Fig. 5 | Crystal structures of (*S*)-L1, (*S*)-L3, (*S*)-L5 and (*S*)-L8. a, Crystal structure of (*S*)-**L1** (Reference number: CCDC 2209953). **b**, Crystal structure of (*S*)-**L3** (Reference number: CCDC 2209954). **c**, (*S*)-**L5** (Reference number: CCDC 2209951). **d**, Crystal structure of (*S*)-**L8** (Reference number: CCDC 2209952).

Several representative biphenyldiols, (*S*)-**L1**, (*S*)-**L3,** (*S*)-**L5** and (*S*)-**L8**, were chose as the examples, their single crystals from mixed solvent of hexane and diethyl ether were prepared, and the corresponding structures were unambiguously confirmed by X-ray diffraction analysis (Fig. 5) (see Supplementary Information for details). According to their X-ray diffraction data, dihedral angles of (*S*)-**L1**, (*S*)-**L3,** (*S*)-**L5** and (*S*)-**L8** are 83.2°, 88.3°, 80.4° and 81.2°, respectively. The results show that introduction of substituents with bigger steric hindrance at 6, 6'-positions leads to bigger dihedral angles. Interestingly, introduction of halos at 5, 5'-positions makes dihedral angles of the axially chiral biphenyldiols become smaller. It is well known that the dihedral angles for the axially chiral ligands and catalysts are a key factor for reactivity of substrates and enantioselectivity of products in asymmetric synthesis.

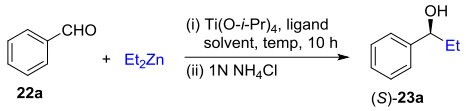
2. Evaluation of BIPHNOL-based axially chiral ligands and catalysts

Subsequently, we chose six model reactions to evaluate reactivity and enantioselectivity in asymmetric catalysis in the presence of BIPHNOL-based axially chiral ligands or catalysts including additions of diethylzinc or alkynes to aldehydes in the presence of axially chiral [1,1'-biphenyl]-2,2'-diol ligands, Pd-catalyzed asymmetric cycloadditions in the presence of phosphoramidite ligands, and chiral phosphoric acid-catalyzed asymmetric synthesis of 1,1'-spirobiindane-7,7'-diol (SPINOL) derivative and [4+3] cyclization.

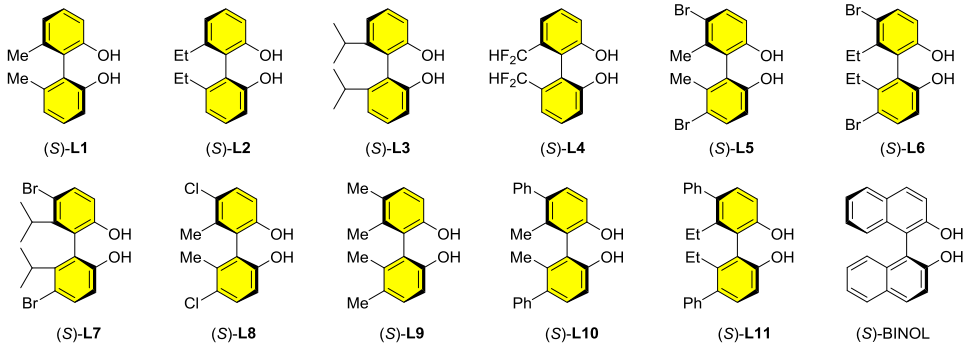
2.1 Addition of diethylzinc to aldehydes in the presence of chiral biphenyldiols

It is well known that the enantioselective addition of diethylzinc to aldehydes with biaryldiol ligands is a standard reaction to evaluate the reactivity and enantioselectivity of newly developed chiral ligands[35-38]. We chose addition of diethylzinc to benzaldehyde (**22a**) as the model reaction to test ligands including our newly developed (*S*)-**L1** ~ (*S*)-**L11** and previous (*S*)-BINOL using titanium tetraisopropoxide as the Lewis acid, dry dichloromethane (DCM) as the solvent at -3 ºC or room temperature. As shown in Table 1, every ligand showed high reactivity, but the enantioselectivity was different (entries 1-12), and (*S*)-**L2** (entry 2), (*S*)-**L5** (entry 5) and (*S*)-**L8** (entry 8) provided higher ee values (>90% ee). Effect of solvents was investigated (13-17), and toluene was the best solvent for the reaction (entry 13). Subsequently, the substrate scope on the enantioselective addition of diethylzinc to aldehydes (**22**) was investigated. As shown in Fig. 6, most of the tested aldehydes afforded excellent yields and good to excellent ee values. An aliphatic aldehyde, 3-phenylpropanal was used as the substrate, and it gave 84% yield and 87% ee (see (*S*)-**23n**). We found that several aldehydes provided poor ee values with (*S*)-**L2** as the ligand, for example, 50% ee was afforded for 4-methoxybenzaldehyde. When (*R*)-**L4** replaced (*S*)-**L2** as the ligand, higher enantioselectivity (-91% ee) was observed (see (*S*)-**23o**). Similarly, ligands (*R*)-**L1**, (*R*)-**L6** and (*S*)-**L3** instead of (*S*)-**L2** were used in the addition reactions of diethylzinc to 2-chlorobenzaldehyde, thiophene-2-carbaldehyde and cinnamaldehyde, respectively, and the corresponding ee values were obviously improved (see (*S*)-**23p**, **23q** and **23r**). The results show that our diverse adjustable chiral biphenyldiol ligands are very useful for enantioselective regulation of different substrates. The reaction above can tolerate various functional groups including ether, cyano, CF_3, C-F, C-Cl, C-Br bonds and *S*-heterocycle.

Table 1 | Optimization of conditions on enantioselective addition of diethylzinc to benzaldehyde (22a)*



22a (*S*)-**23a**



entry	ligand	solvent	temp	yield (%)†	ee (%)‡
1	(*S*)-**L1**	CH_2Cl_2	-3 °C	97	86
2	(*S*)-**L2**	CH_2Cl_2	-3 °C	97	93
3	(*S*)-**L3**	CH_2Cl_2	rt	96	84
4	(*S*)-**L4**	CH_2Cl_2	-3 °C	93	81
5	(*S*)-**L5**	CH_2Cl_2	-3 °C	97	93
6	(*S*)-**L6**	CH_2Cl_2	-3 °C	90	83
7	(*S*)-**L7**	CH_2Cl_2	rt	91	80
8	(*S*)-**L8**	CH_2Cl_2	-3 °C	95	91
9	(*S*)-**L9**	CH_2Cl_2	rt	92	85
10	(*S*)-**L10**	CH_2Cl_2	rt	91	81
11	(*S*)-**L11**	CH_2Cl_2	rt	89	83
12	(*S*)-BINOL	CH_2Cl_2	-3 °C	95	86
13	(*S*)-**L2**	**toluene**	**-3 °C**	**97**	**94**
14	(*S*)-**L2**	THF	-3 °C	75	42
15	(*S*)-**L2**	Et_2O	-3 °C	97	92
16	(*S*)-**L5**	toluene	-3 °C	96	91
17	(*S*)-**L5**	Et_2O	-3 °C	92	92

*Conditions: **22a**:Et_2Zn:$Ti(O^iPr)_4$:ligand = 1:3:1.6:0.1 (molar ratio), **22a** (0.2 mmol), $ZnEt_2$ (0.6 mmol), $Ti(O^iPr)_4$ (0.32 mmol), ligand (0.02 mmol), solvent (2.0 mL), temperature (-3 °C or rt), time (10 h), 1N HCl (2.0 mL). †Isolated yield. ‡Absolute configurations known, determined or assigned by analogy (see Supplementary Information), ee values determined by HPLC analysis using a chiral stationary phase (Chiralpak® OD-H column) (*n*-hexane: *i*-PrOH= 96:4).

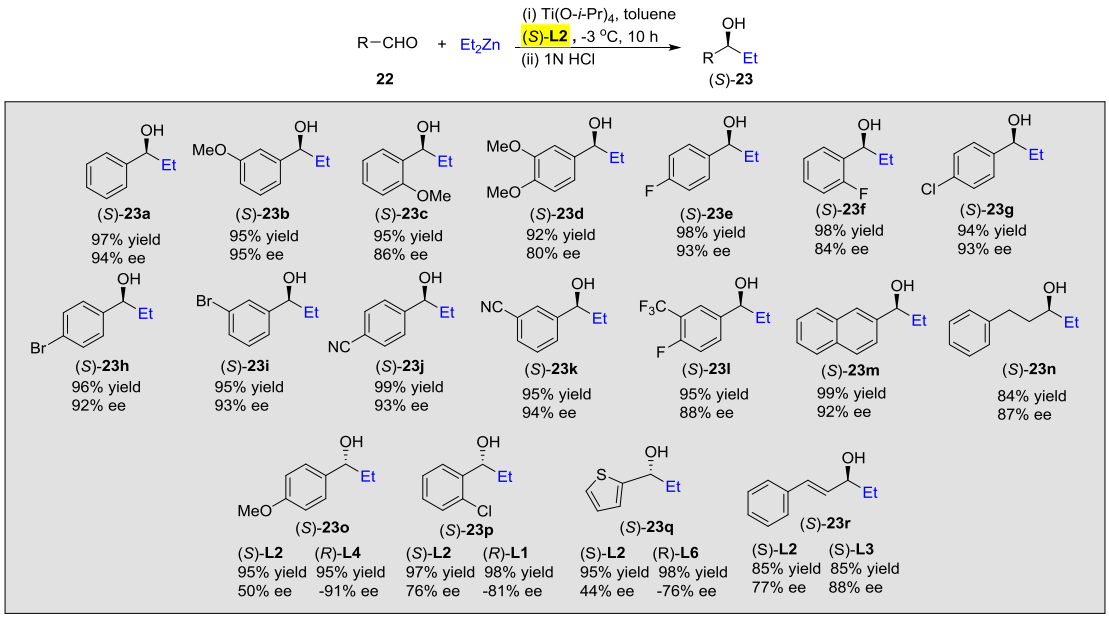


Fig. 6 | Enantioselective addition of diethylzinc to different aldehydes (22) leading to 23.

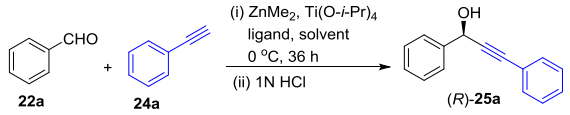
Conditions: **22**:$ZnEt_2$:$Ti(O^iPr)_4$:ligand = 1:1.6:3:0.1 (molar ratio), aldehyde (**22**) (0.2 mmol), $ZnEt_2$ (0.6 mmol), $Ti(O^iPr)_4$ (0.32 mmol), lignad (0.02 mmol), toluene (2.0 mL), temperature (-3 °C), time (10 h), 1N HCl (2.0 mL). †Absolute configurations known, determined or assigned by analogy (see Supplementary Information). ‡Isolated yield. ¶ee values determined by HPLC analysis (see Supplementary Information).

2.2 Addition of alkynes to aldehydes in the presence of $ZnMe_2$ and chiral biphenyldiols

To further explore application of our diverse adjustable chiral biphenyldiol ligands, we investigated Ti(O-*i*-Pr)$_4$-catalyzed addition of alkynes to aldehydes in the presence of $ZnMe_2$. Chiral propargylic alcohols are versatile synthons in organic chemistry, and catalytic asymmetric alkynylzinc addition to aldehydes can provide various chiral propargylic alcohols with high enantioselectivity[39-42]. As shown in Table 2, Ti(O-*i*-Pr)$_4$-catalyzed addition of phenylacetylene (**24a**) to benzaldehyde (**22a**) was selected as the model reaction to test our ligands and (*R*)-BINOL in the presence of $ZnMe_2$ using dry dichloromethane (DCM) as the solvent at 0 °C (entries 1-12)), and (*S*)-**L5** provided higher yield (85%) and highest ee value (93% ee) (entry 5). Other solvents, toluene, diethyl ether and THF, were attempted (entries 13-15), and they were inferior to DCM (entry 5). Subsequently, we surveyed substrate scope on the enantioselective addition of alkynes (**25**) to aldehydes (**22**). As shown in Fig. 7, most of the tested aldehydes (**22**) and alkynes (**25**) afforded high yields and good to excellent ee values. During our screening, we found that addition of phenylacetylene (**24a**) to 3-bromobenzaldehyde only afforded 74% ee with (*S*)-**L5** as the ligand.

When (*S*)-**L10** and (*S*)-**L11** instead of (*S*)-**L5** were used as the ligands, and 85% ee and 90% ee were obtained, respectively (see (*R*)-**25t**). The results also show that our diverse adjustable chiral biphenyldiol ligands are very useful for enantioselective regulation of different substrates. The reaction above can tolerate various functional groups including ether, cyano, CF_3, NO_2, C-F, C-Cl, C-Br bonds and *S*-heterocycle.

Table 2 | Optimization of conditions on enantioselective addition of phenylacetylene (24a) to benzaldehyde (22a)[*]



entry	ligand	solvent	yield (%)[†]	ee (%)[‡]
1	(*S*)-**L1**	CH_2Cl_2	82	81
2	(*S*)-**L2**	CH_2Cl_2	82	91
3	(*S*)-**L3**	CH_2Cl_2	89	79
4	(*S*)-**L4**	CH_2Cl_2	89	57
5	(*S*)-**L5**	**CH_2Cl_2**	**85**	**93**
6	(*S*)-**L6**	CH_2Cl_2	84	84
7	(*S*)-**L7**	CH_2Cl_2	87	60
8	(*S*)-**L8**	CH_2Cl_2	81	91
9	(*S*)-**L9**	CH_2Cl_2	88	28
10	(*S*)-**L10**	CH_2Cl_2	80	10
11	(*S*)-**L11**	CH_2Cl_2	86	9
12	(*R*)-BINOL	CH_2Cl_2	82	-90
13	(*S*)-**L5**	toluene	84	84
14	(*S*)-**L5**	THF	81	29
15	(*S*)-**L5**	Et_2O	77	91

[*]Conditions: **22a** (0.2 mmol), **24a** (0.5 mmol), $ZnMe_2$ (0.4 mmol), $Ti(O^iPr)_4$ (0.05 mmol), ligand (0.04 mmol), solvent (2.0 mL), temperature (0℃), time (36 h), 1N HCl (2.0 mL). [†]Isolated yield. [‡]Absolute configurations known, determined or assigned by analogy (see Supplementary Information), and ee values determined by HPLC analysis using a chiral stationary phase (Chiralpak® OD-H) (*n*-hexane: *i*-PrOH= 90:10).

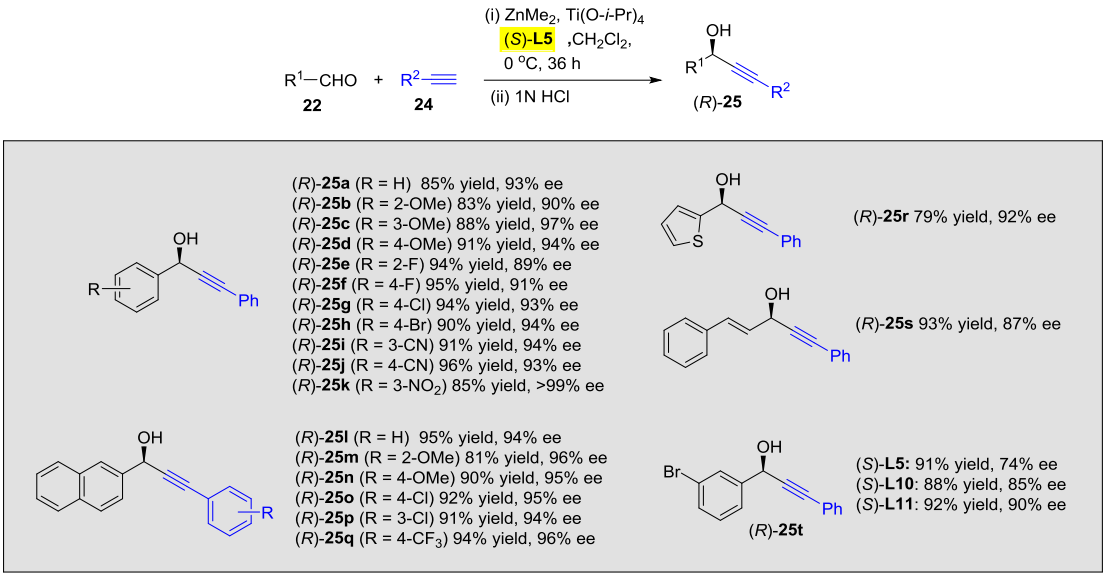


Fig. 7 | Enantioselective addition of alkynes (24) to aldehydes (22) leading to 25.

Conditions: **22** (0.5 mmol), **24** (1.25 mmol), $ZnMe_2$ (1.0 mmol), $Ti(O^iPr)_4$ (0.125 mmol), ligand (0.1 mmol), solvent (2.0 mL), temperature (0 °C), time (36 h), 1N HCl (2.0 mL). †Isolated yield. ‡Absolute configurations known, determined or assigned by analogy (see Supplementary Information), and ee values determined by HPLC analysis using a chiral stationary phase (see Supplementary Information).

2.3 Pd-catalyzed asymmetric cycloadditions in the presence of chiral phosphoramidites

Next, we investigated derivatization of our newly developed axially chiral biphenyldiol cores. It is well known that the phosphoramidites of axially chiral biaryldiols are the privileged ligands in the asymmetric synthesis[43-48]. At first, we prepared the BIPHNOL-derived phosphoramidite ligands according to previous procedures[43-48]. As shown in Fig. 8a, reaction of chiral secondary amine **26** with PCl_3 in dry toluene provided **27**, and treatment of **27** with our axially chiral biphenyldiols ((*S*)-**L1**, **L2** or **L3**) gave the corresponding phosphoramidite ligands (*S*)-**L14**, **L15** or **L16** in 90%, 83% and 71% yields, respectively, for the two step reactions. Subsequently, we prepared chiral phosphoramidite ligand (*S*)-**L18** in 56% yield via the similar procedures.

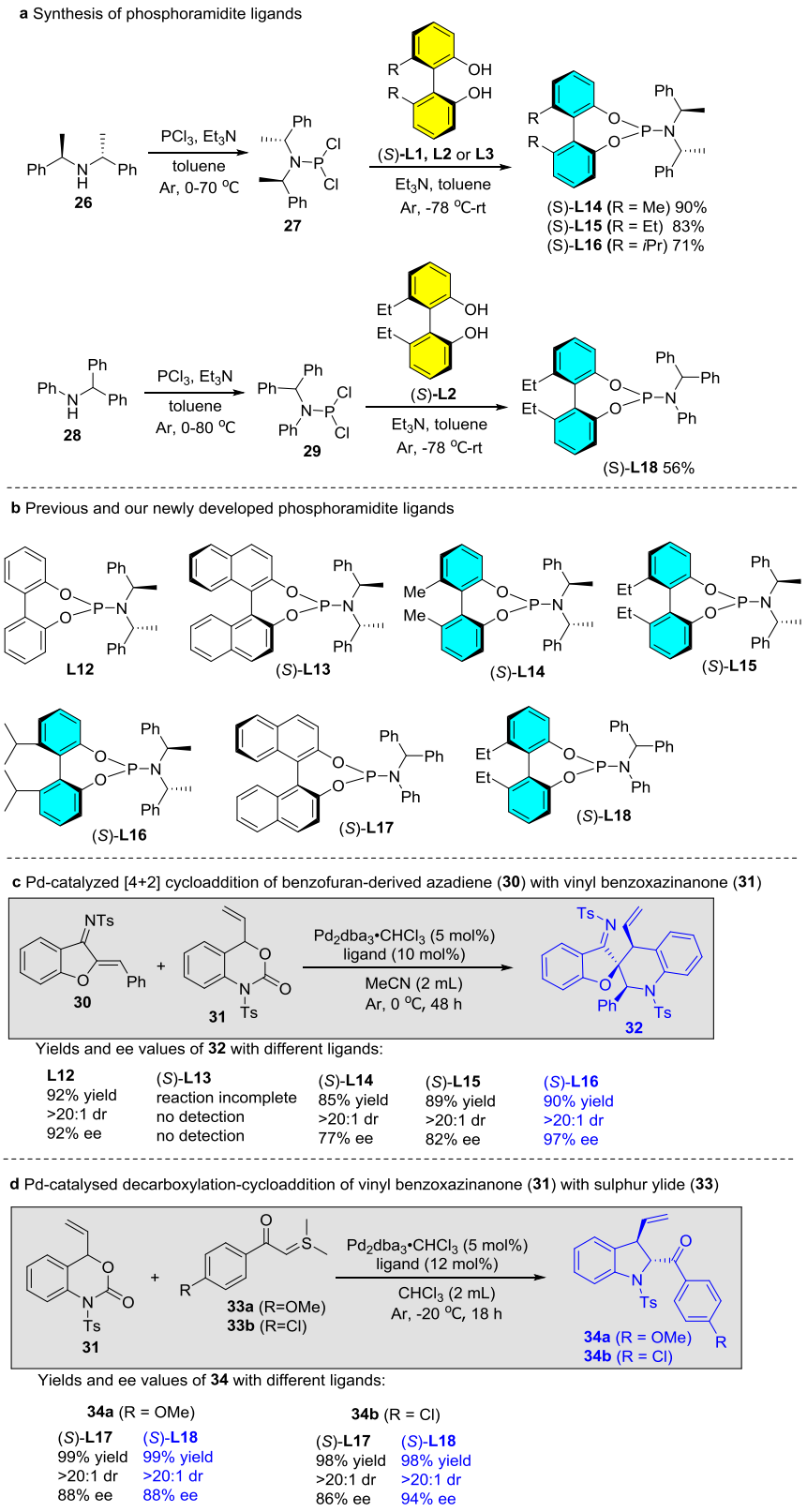


Fig. 8 | Synthesis and applications of phosphoramidite ligands. a, Synthesis of phosphoramidite ligands. **b**, Previous and our newly developed phosphoramidite ligands. **c**, Pd-catalyzed [4+2] cycloaddition of benzofuran-derived azadiene (**30**) with vinyl benzoxazinanone (**31**). **d**, Pd-catalysed decarboxylation-cycloaddition of vinyl benzoxazinanone (**31**) with sulphur ylide (**33**).

To evaluate reactivity and enantioselectivity of our newly developed chiral phosphoramidite ligands in asymmetric catalysis, two reactions were selected as the examples. Yang and Zhao reported the Pd-catalyzed [4+2] cycloaddition of benzofuran-derived azadienes with vinyl benzoxazinanones, and they found that cycloaddition of **30** with **31** in the presence of phosphoramidite ligand **L12** provided high yield (92%) and ee value (92% ee). However, the reaction was incomplete when (*S*)-**L13** was used as the ligand (Fig. 8c)[49]. We attempted the cycloaddition of **30** with **31** in the presence of our chiral phosphoramidite ligands (*S*)-**L14**, **L15** or **L16**. Inspiringly, (*S*)-**L16** provided excellent diastereo- and enantioselectivity (>20:1 dr, 97% ee) (Fig. 8c). Subsequently, another example was surveyed. In 2014, Lu and Xiao developed the Pd-catalyzed asymmetric decarboxylation-cycloaddition of vinyl benzoxazinanones with sulphur ylides[50]. We investigated efficiency of the previous (*S*)-**L17** and our newly developed (*S*)-**L18** by using asymmetric decarboxylation-cycloaddition of **31** and **33**, and the results showed that (*S*)-**L18** was better than (*S*)-**L17** in asymmetric reaction of **31** and **33b** (Fig. 8d).

2.4 Chiral phosphoric acid-catalyzed asymmetric synthesis of 1,1'-spirobiindane-7,7'-diol (SPINOL) derivative and [4+3] cyclization

Since the pioneering researches from the groups of Akiyama[51] and Terada[52] in 2004, chiral phosphoric acids are widely used as the organocatalysts in the asymmetric synthesis[53-56], in which the previous chiral phosphoric acid catalysts usually are BINOL and SPINOL-based derivatives. Here, we first performed synthesis of BIPHNOL-based chiral phosphoric acids. As shown in Fig. 9a, the Suzuki couplings of (*S*)-**16** with alkyl boric acids (**35**) led to (*S*)-**36-39** in 84-88% yields, and demethylation of the two ethers in (*S*)-**21** and (*S*)-**36-38** with BBr_3 in CH_2Cl_2 followed hydrolysis provided (*S*)-**39**, (*S*)-**L11**, (*S*)-**40** and (*S*)-**41** in 86-90% yields. Diiodization of (*S*)-**39**, (*S*)-**L11**, (*S*)-**40** and (*S*)-**41** at 3, 3'-position with iodine in CH_2Cl_2 in the presence of morpholine gave (*S*)-**42-45** in 90-98% yields, and couplings of (*S*)-**42-45** with chloro (methoxy) methane (MOM-Cl) using NaH as the base afforded the corresponding diethers ((*S*)-**46-49**) in 92-95% yields. The Suzuki couplings of (*S*)-**46-49** with (3,5-bis(trifluoromethyl)phenyl)boronic acid (**35d**) formed (*S*)-**50-53** in 75-81% yields, and deprotection of (*S*)-**50-53** with conc. HCl in dioxane provided substituted biphenyldiols (*S*)-**54-57** in 60-72% yields. Finally, couplings of (*S*)-**54-57** with $POCl_3$ followed hydrolysis provided the corresponding chiral phosphoric acids (*S*)-**CPA-2**,

(*S*)-**CPA-3**, (*S*)-**CPA-4** and (*S*)-**CPA-5** in 69-80% yields. Similarly, chiral phosphoric acids (*S*)-**CPA-1** was obtained in 81% yield using (*S*)-**47** as the material (Fig. 9b).

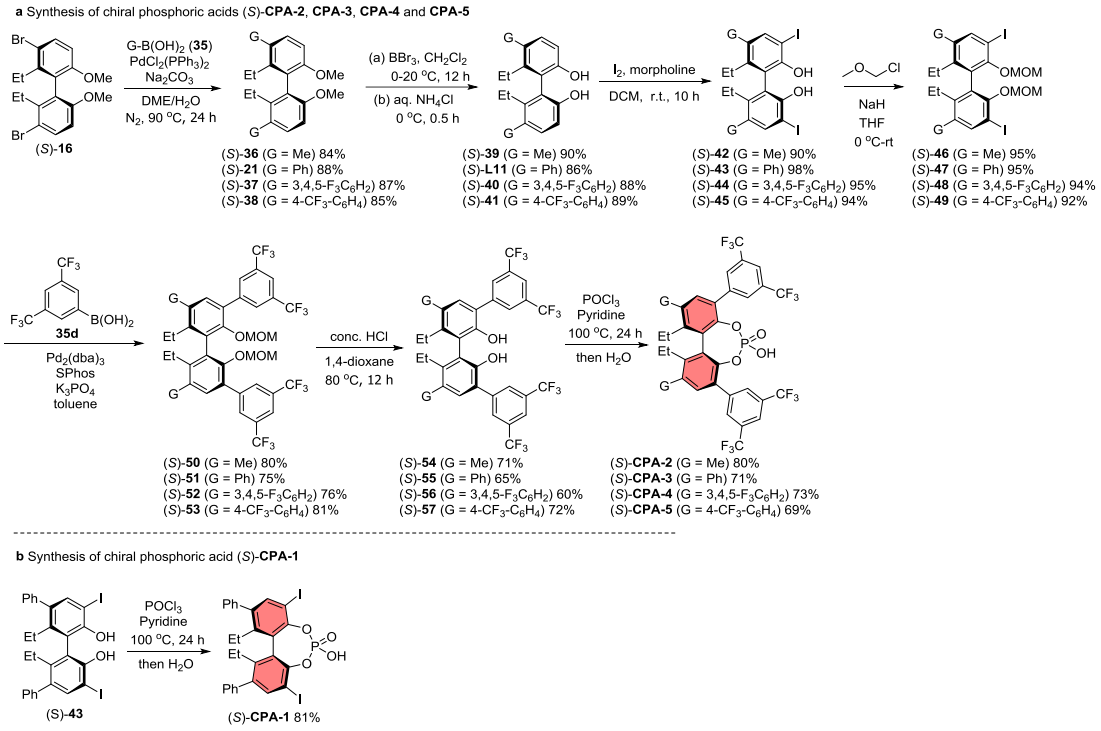


Fig. 9 | Synthesis and applications of chiral phosphoric acid catalysts. a, Synthesis of chiral phosphoric acids (*S*)-**CPA-2**, **CPA-3**, **CPA-4** and **CPA-5**. **b**, Synthesis of chiral phosphoric acid (*S*)-**CPA-1**.

To evaluate reactivity and enantioselectivity of our newly developed chiral phosphoric acids in asymmetric catalysis, we selected two reactions as the examples. In 2016, Tan and co-workers developed chiral phosphoric acid-catalyzed asymmetric synthesis of 1,1'-spirobiindane-7,7'-diol (SPINOL) derivatives (Fig. 10b)[57]. When they used **59** as the substrate, the SPINOL-based chiral phosphoric acid-catalyzed reaction for five days only provided 19% yield with 93% ee. We attempted our chiral phosphoric acids to perform the same reaction, fortunately, (*S*)-**CPA-4** afforded 26% yield with 98% ee (Fig. 10b). In 2019, Shi and co-workers reported chiral phosphoric acid-catalyzed asymmetric [4+3] cyclizations of *in situ* generated *ortho*-quinonemethides from *o*-hydroxybenzylalcohols with 2-indolylmethanols, and 90% ee was provided when reaction of **61** with **62** was performed with (*R*)-8H-BINOL-based chiral phosphoric acid (Fig. 10c)[58]. We chose the reaction to evaluate our chiral phosphoric acids, and the results showed that (*S*)-**CPA-4** provided higher enantioselectivity (93% ee) than (*R*)-8H-BINOL-based chiral phosphoric acid (Fig. 10c).

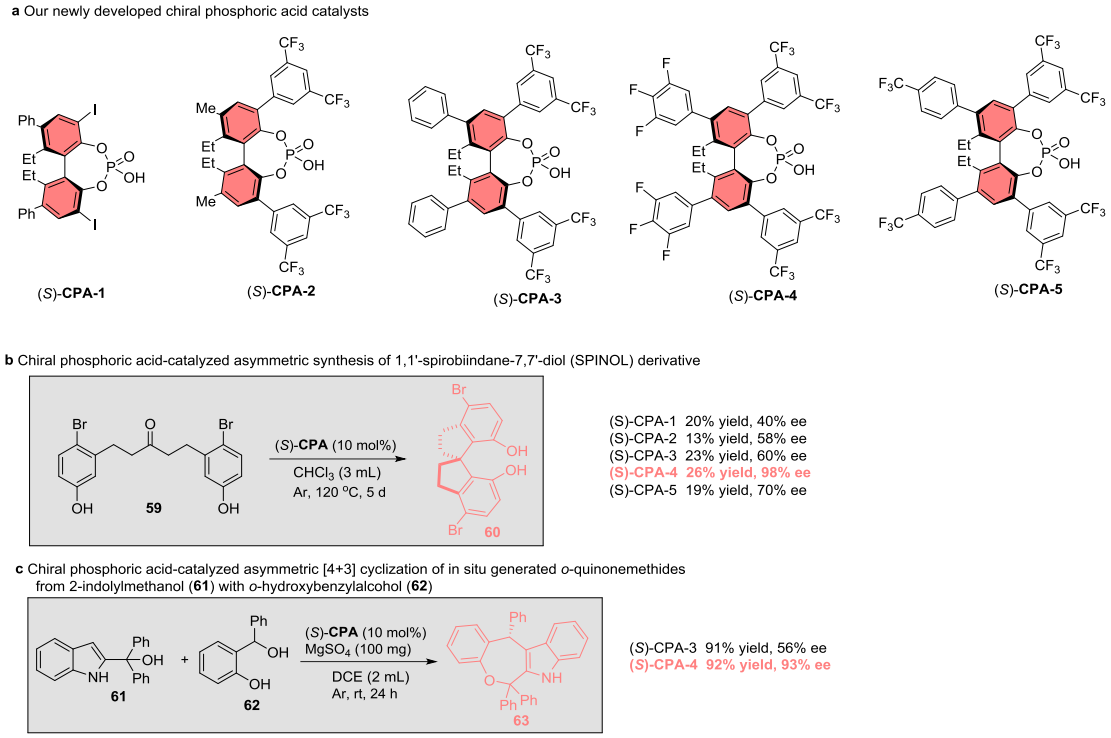


Fig. 10 | Applications of chiral phosphoric acid catalysts. a, Our newly developed chiral phosphoric acid catalysts. **b**, Chiral phosphoric acid-catalyzed asymmetric synthesis of 1,1'-spirobiindane-7,7'-diol (SPINOL) derivative. **c**, Chiral phosphoric acid-catalyzed asymmetric [4+3] cyclization of in situ generated *o*-quinonemethides from 2-indolylmethanol (**61**) with o-hydroxybenzylalcohol (**62**).

Conclusion

We have developed a new kind of diverse adjustable axially chiral biphenyl ligands and catalysts. Six model reactions were performed including asymmetric additions of diethylzinc or alkynes to aldehydes in the presence of axially chiral BIPHNOL ligands, Pd-catalyzed asymmetric cycloadditions in the presence of chiral phosphoramidite ligands, and chiral phosphoric acid-catalyzed asymmetric synthesis of 1,1'-spirobiindane-7,7'-diol (SPINOL) derivative and [4+3] cyclization to evaluate reactivity and enantioselectivity of our biphenyl ligands and catalysts. We found that variation of 2,2'-substituent groups could provide different types of ligands and catalysts, and variation of substituent groups at the 3, 3', 5, 5', 6, 6'-positions could make ligands and catalysts more efficient in the asymmetric catalytic synthesis. We believe that our newly developed diverse adjustable axially chiral biphenyldiols will find wide applications in enantioselective catalysis.

Data availability

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information, or from the authors on reasonable request.

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Author contributions

J.J. and H.F. conceived this subject, J.J. conducted the experimental work, J.J., H.Y., Y.Z. and H.F. analyzed the results, J.J. and H.F. co-wrote the manuscript.

Competing financial interests

The authors declare no competing financial interests.

Additional information

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