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Highly enantioselective copper-catalyzed allylic alkylation with atropos phosphoramidites bearing a D_2-symmetric biphenyl backbone

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ABSTRACT

A novel class of atropos dibridged biphenyl phosphoramidites bearing a D_2-symmetric biphenyl backbone was prepared and applied as chiral ligands in the copper-catalyzed allylic alkylation with Grignard reagent. The alkylation products were obtained in quantitative yields with high regioselectivities up to 94:6 of S_N2'/S_N2 ratio and enantiomeric excesses up to 91.1% for S_N2' products. The unique D_2-symmetric backbone ligands have the advantages of easy preparation and sufficient reusability of their key intermediates from the undesired isomers.

1. Introduction

Asymmetric allylic alkylation is a potentially powerful method for creating chiral centers in readily available starting materials.[1] In contrast to other metals,[2] copper allows harder nucleophiles, such as organozinc,[3] organoalumium[4] or Grigard reagents.[5-8] In 1995, Bäckvall and van Koten reported the first asymmetric Cu-catalyzed allylic alkylation using Grignard reagents with moderate enantioselectivity.[6] Since then, most efforts have been directed toward the development of new efficient ligands for allylic alkylation to control the chemo-, regio-, and enantioselectivities of the reaction produts.[9]

In 2002, Alexakis and co-workers introduced binaphthol and biphenol-based phosphoramidite ligands for the Cu-catalyzed asymmetric allylic alkylation with Grignard reagent, and moderate enantioselectivity and regioselectivity were obtained.[7] For obtaining higher enantioselectivity using this type of phosphoramidite ligands, they introduced methoxy groups at the *ortho*-position on the phenyl of the aryl amine groups, and provided excellent results in terms of both regio- and enantioselectivity.[8]

Recently, a family of axially achiral biaryls having four constitutionally identical substituents at the *ortho*-positions of the biphenyl axis caught our attention (Fig. 1).[10] This type of molecular has three C_2-symmetric factors in its structure, but no axial chirality due to the molecular symmetry. However, when the four identical substituents are linked pairwise by two bridges, the axial chirality of the molecule is induced and a pair of enantiomers is formed with axial chirality. To the best of our knowledge, this form of atropos scaffold remains unexplored in the design of chiral ligands.

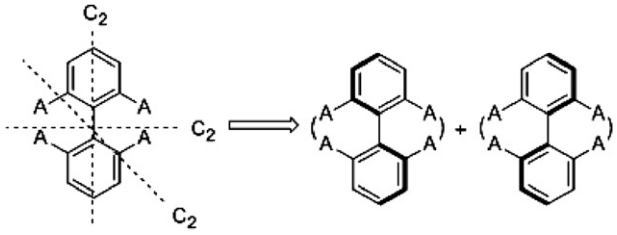

Figure 1. D_2-symmetric dibridged molecules.

Using the design concept of axial chiral ligands mentioned above, we here developed a novel class of atropos dibridged biphenyl phosphoramidite ligands **2a–c** (Scheme 1)[11] and applied them to the asymmetric allylic alkylation with good regio- and enantioselectivities.

For this new type of ligands **2**, there are four possible isomers with the configuration of a*R*/a*S* and *trans*/*cis*. We expected that one of the four isomers should dominate the others during the preparation due to the induction of the chiral amine segment, and the undesired isomers could be degraded to achiral tetrahydroxy biphenyls **1** with ease for recycle. Furthermore, it was expected that the ligands based on the D_2-symmetric backbone with more coordination sites and different chiral environments might provide higher enantioselectivities than those based on the C_2-symmetric backbone.

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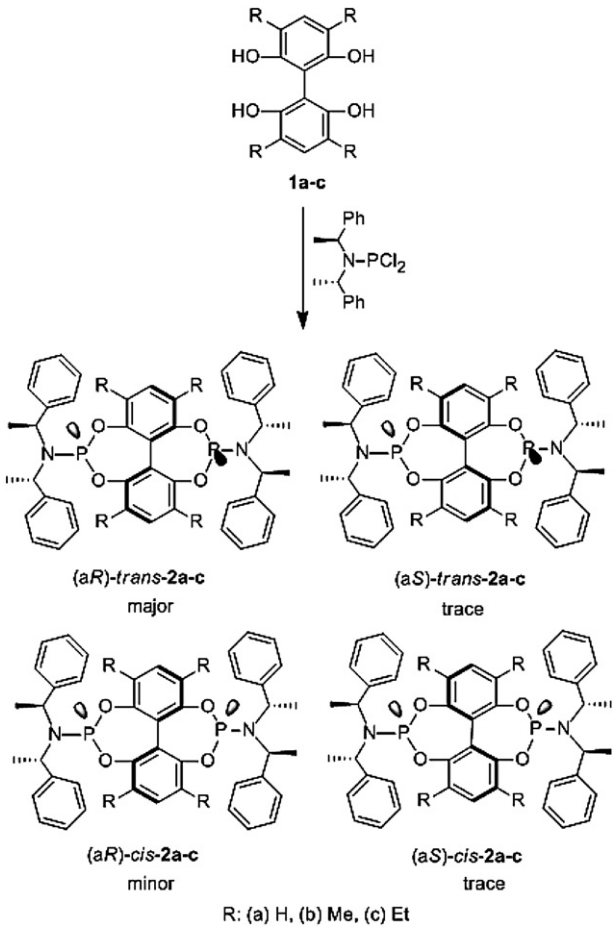


Scheme 1. Preparation of dibridged phosphoramidites with D_2-symmetric backbone.

2. Results and discussion

A series of atropos dibridged biphenyl phosphoramidite ligands could be synthesized with ease from achiral 3,3′,5,5′-tetrasubstituted-2,2′,6,6′-tetrahydroxy biphenyl **1a**–**c**[10] and chiral secondary amine (Scheme 1).

Firstly, bis[(*S*)-1-phenylethyl]amine[12] was reacted with purified PCl_3 in THF at room temperature for 3 h, then a solution of 2,2′,6,6′-tetrahydroxy biphenyl **1a** (0.5 equiv) in THF was added slowly at −78 °C to the above mixture. The reaction mixture was then gradually warmed to room temperature and kept stirring for another 6 h. As expected, a mixture of **2a** containing one major isomer, one minor isomer, and two trace isomers was obtained in 45% yield, and the ratio of the major isomer to the minor one was determined to be 3.8:1 by ^{31}P NMR analysis (Fig. 2). The major and minor isomers of **2a** were isolated by preparative HPLC and the other two trace isomers could not be obtained. The absolute configuration of the major isomer at 149.2 ppm in ^{31}P NMR was confirmed as (a*R*)-*trans*-**2a** by X-ray analysis (Fig. 3).

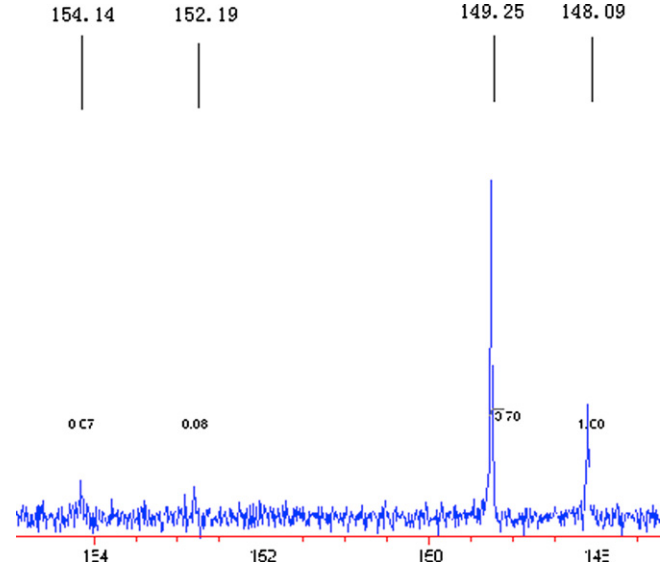


Figure 2. ^{31}P NMR data of the mixture of **2a**.

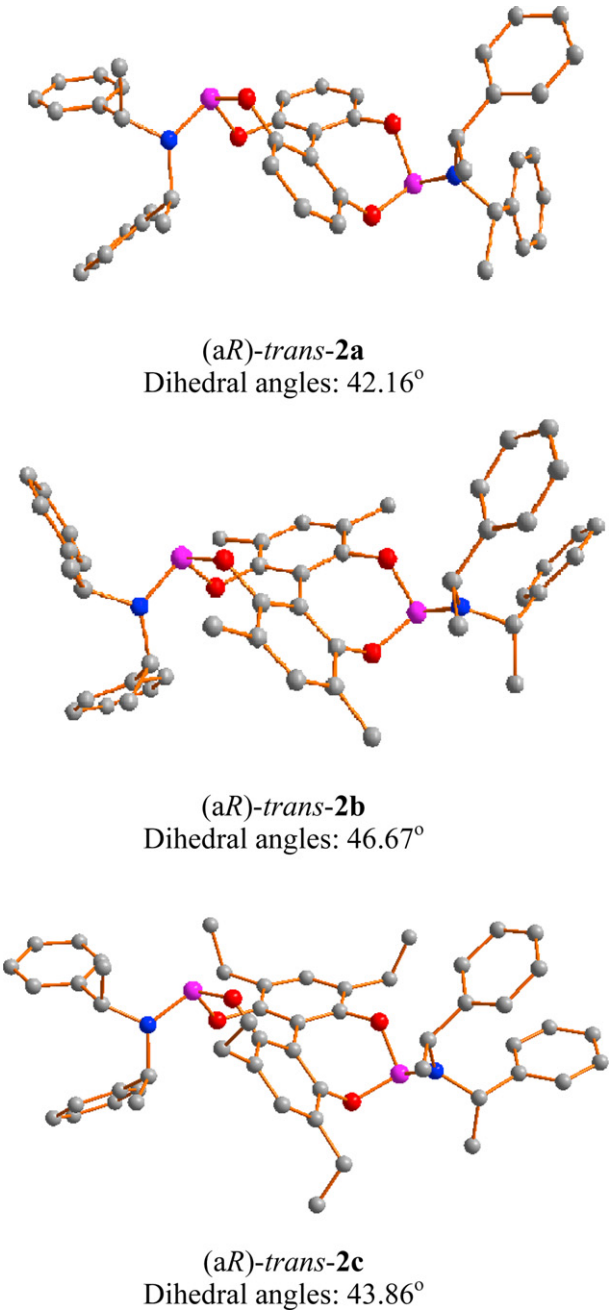


Figure 3. X-ray crystal structures of the dibridged ligands (a*R*)-*trans*-**2a**–**c**.[13]

Our attempted structural determination of the minor isomer by X-ray analysis was unsuccessful, and hence we tried to assign its absolute configuration by NMR analysis. Since it was reported that the ^{31}P NMR signals of the related biphenyl phosphoramidite

ligands (a*S*,*S*,*S*)-**3** and (a*R*,*R*,*R*)-**4** (Fig. 4) appeared at lower field compared with their corresponding diastereomers (a*R*,*S*,*S*)-**3** and (a*S*,*R*,*R*)-**4**,[14,15] the signal of (a*S*)-**2a** might appear at lower field than that of (a*R*)-*trans*-**2a** at 149.2 ppm. However, the minor isomer at 148.1 ppm is at higher field than (a*R*)-*trans*-**2a**. Therefore, it is suggested that the minor isomer at 148.1 ppm should be assigned as (a*R*)-*cis*-**2a**. This result showed that one of the two possible axial chiralities was induced by the chiral amine segment during the ligand preparation.

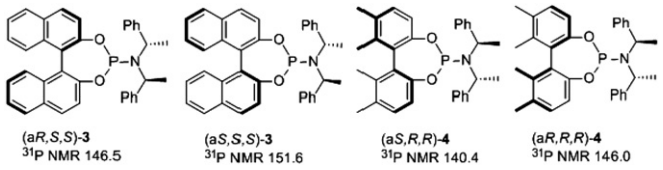
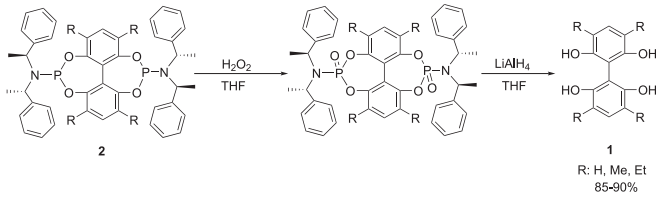


Figure 4. ^{31}P NMR data of the reported biphenyl phosphoramidite diastereomers.

Ligands **2b** and **2c** were obtained in a similar procedure with **2a**, but using Et_2O as the reaction solvent, and the addition temperature of **1b** and **1c** was −30 °C. Similarly, there were four isomers in the mixture, and one isomer dominated the others. Fortunately, the major isomers of **2a**–**c** could be easily separated by crystallization directly from the mixture with the isolated yield up to 32%. The (a*R*)-*trans* configurations of the major isomers of **2b** and **2c** could be further proved by the X-ray analysis (Fig. 3). It can be also seen that (a*R*)-*trans*-**2b** possesses the biggest dihedral angle of the biphenyl backbone among the three (a*R*)-*trans* ligands.

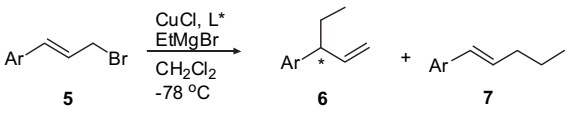
Furthermore, no racemization of these isomers was observed after refluxing in toluene under nitrogen atmosphere for 12 h, showing the high stability of the axial chirality of the ligands. In addition, the phosphoramidite ligands **2** could be readily degraded to achiral tetrahydroxy biphenyls **1** in 85–90% yields in one-pot on treatment with H_2O_2, followed by ring opening with $LiAlH_4$ (Scheme 2).[16] So, the key intermediates of the ligands could be recycled with ease from the undesired isomers.



Scheme 2. Ring opening of dibridged phosphoramidite.

These novel atropos dibridged biphenyl phosphoramidite ligands have already applied for enantioselective conjugate addition of four types of α,β-unsaturated substrates with $ZnEt_2$ and gave better or equal results compared with the best reports of the corresponding C_2-symmetric ligands.[11]

In order to broaden the application of the novel phosphoramidite ligands, we took notice of applying these new ligands to the copper-catalyzed asymmetric allylic alkylation with Grignard reagent (Scheme 3).



Scheme 3. Enantioselective copper-catalyzed allylic alkylation.

According to our previously research,[11] we found that the substituents on the biphenyl of the ligands had an apparent influence on the catalysis, and methyl-substituted (a*R*)-*trans* ligand was the best choice among those ligands. So, ligand (a*R*)-*trans*-**2b** was selected in our preliminary experiment to test the influence of the copper salts in the reaction.

The reaction using the simplest starting material cinnamyl bromide proceeded smoothly at −78 °C with CH_2Cl_2 as solvent in the presence of 2.0 mol % of copper salt and 2.0 mol % of the ligand. It was reported that the rate of the addition of the Grignard reagent was much more instructive, so addition of the EtMgBr was selected to last two hours in our reaction.[8b]

The reaction completed quantitatively and it was found that the copper salts had a little influence on the regioselectivities, but greatly influenced the enantioselectivities (Table 1). It could be seen that the highest enantiomeric excess of 88.1% was obtained using CuCl with an excellent regioselectivity (**6**/**7**=92/8) (entry 1). $Cu(OTf)_2$ gave a remarkable high regioselectivity, but moderate enantioselectivity for the major S_N2' product **6** (entry 5).

Table 1
Enantioselective allylic alkylation catalyzed by (a*R*)-*trans*-**2b**[a]

Entry	CuX	Conv.[b]	S_N2'/S_N2[b]	ee[c](%)
1	CuCl	100	92/8	88.1
2	CuBr	100	90/10	83.5
3	CuI	100	92/8	85.3
4	CuOTf	100	92/8	63.9
5	$Cu(OTf)_2$	100	96/4	59.3

[a] The reaction was carried out at −78 °C in CH_2Cl_2, with the ratio of **5**/(a*R*)-*trans*-**2b**/copper salt/EtMgBr=50/1.0/1.0/1.1.
[b] Determined by ^1H NMR spectra of crude product.
[c] The ee was determined by GC and the absolute configuration was assigned to be *R* by comparing with the literature.[3c]

Then, the effect of ligands was explored and all the ligands gave 100% conversion (Table 2). The introduction of sterically bulky 3,3′,5,5′-substituents on the biphenyl backbone of the ligands had great influence on both regioselectivity and enantioselectivity. Particularly, when the 3,3′,5,5′-positions were substituted by methyl, the enantioselectivity and regioselectivity were advanced dramatically compared with no substituents (entries 1 and 2). Ligand (a*R*)-*trans*-**2c** gave a lower ee than (a*R*)-*trans*-**2b** (entries 2 and 3). It seemed that the methyl was the appropriate group with the moderate hindrance.

Table 2
Enantioselective allylic alkylation catalyzed by different ligands[a]

Entry	Ligand	Dihedral angle (°)	Conv.[b]	S_N2'/S_N2[b]	ee[c](%)
1	(a*R*)-*trans*-**2a**	42.16	100	72/28	69.2
2	(a*R*)-*trans*-**2b**	46.67	100	92/8	88.1
3	(a*R*)-*trans*-**2c**	43.86	100	92/8	82.5
4	(a*R*)-*cis*-**2a**	—	100	65/35	61.2

[a] The reaction was carried out at −78 °C in CH_2Cl_2, with the ratio of **5**/Ligand/CuCl/EtMgBr=50/1.0/1.0/1.1.
[b] Determined by ^1H NMR spectra of crude product.
[c] The ee was determined by GC and the absolute configuration was assigned to be *R* by comparing with the literature.[3c]

It was reported that the dihedral angles of the ligands have significant influence on asymmetric control in some asymmetric reactions.[17] From Table 2, it can be known that the dihedral angles of our ligands also have a relationship with the enantioselectivity. That is, (a*R*)-*trans*-**2b** with the largest dihedral angles afforded the highest enantioselectivity (entry 2) and (a*R*)-*trans*-**2a** with the smallest dihedral angles gave the lowest enantioselectivity (entry 1).

Meanwhile, we also tested the effect of (a*R*)-*cis*-**2a** to see how the cis and trans configurations influenced the catalysis. As a result, the decreased regioselectivity and enantionselectivity were obtained comparing with (a*R*)-*trans*-**2a** (entries 1 and 4). This result suggested that the trans isomer gave much better enantioselectivity and regioselectivity than the cis one.

With the optimized reaction conditions in hand, we applied our methodology to different substrates to generalize the scope of the reaction. The results are summarized in Table 3.

Table 3
Enantioselective allylic alkylation with different substrates[a]

Entry	Ar	Conv.[b]	S_N2'/S_N2[b]	ee[c](%)
1	Ph (**6a**)	100	92:8	88.1
2	4-CH_3–Ph (**6b**)	100	92:8	81.0
3	3-CH_3–Ph (**6c**)	100	91:9	84.0
4	4-F–Ph (**6d**)	100	92:8	83.1
5	2-F–Ph (**6e**)	100	88:12	59.9
6	4-Cl–Ph (**6f**)	100	94:6	85.6
7	4-CF_3-Ph (**6g**)	100	94:6	91.1

[a] The reaction was carried out at −78 °C in CH_2Cl_2, with the ratio of **5**/(a*R*)-*trans*-**2b**/CuCl/EtMgBr=50/1.0/1.0/1.1.
[b] Determined by ^{1}H NMR spectra of crude product.
[c] The ee was determined by GC and the absolute configuration was assigned to be *R* by comparing with the literature.[3c]

It was observed that for all substrates, the conversion and regioselectivity were excellent, whatever the electron demand of the substituent on the aromatic group. And all the substrates afforded very good enantioselectivities except **6e**, which possesses an *ortho*-fluoro group on the phenyl unit (entry 5). The best results of 91.1% ee and 94:6 of S_N2'/S_N2 ratio were obtained when the 4-position on the phenyl group of the cinnamyl bromide was substituted by trifluoromethyl group (entry 7).

3. Conclusion

We have developed a novel class of atropos dibridged biphenyl phosphoramidite ligands. The stable axial chirality of the molecule can be induced when the four identical substituents are linked pairwise by two bridges. Compared with the traditional C_2-symmetric biaryl backbone ligands, which need resolution and the undesired enantiomers of which could not be used efficiently, the unique D_2-symmetric backbone ligands have the advantages of easy preparation and sufficient reusability of their key intermediates from the undesired isomers. Furthermore, it was found that these novel ligands were efficient for the copper-catalyzed allylic alkylation with Grignard reagents. 3,3′,5,5′-Tetrasubstituted groups on the phosphoramidite ligands showed remarkable effect on both enantioselectivity and regioselectivity and tetramethyl substituted ligand (a*R*)-*trans*-**2b** afforded the best results with 100% conversion, 94:6 of S_N2'/S_N2 ratio and 91.1% ee.

4. Experimental section

4.1. General comments

All solvents were reagent grade and were dried and distilled before use. All reactions were carried out under nitrogen atmosphere using dried glassware (standard schlenk procedures). Column chromatography was run on silica gel (200–300 mesh). ^{1}H NMR, ^{13}C NMR, ^{31}P NMR spectra were recorded on a Varian MECURY plus-400 spectrometer in $CDCl_3$. Optical rotations were measured with SPSI SGW-1 polarimeter. Melting points were determined on a XT-5 microscopic melting point apparatus without corrected. HRMS were performed on a micromass LCTTM at the Analysis and Research Center of East China University of Science and Technology.

4.2. Typical procedure for the preparation of phosphoramidite ligands

A solution of bis[(*S*)-1-phenylethyl]amine (8.0 mmol) in THF (2.0 mL) was added slowly to a mixture of PCl_3 (8.0 mmol) and NEt_3 (32 mmol) in THF (40 ml) at 0 °C under a N_2 atmosphere. After stirred for 3 h at room temperature, a solution of 2,2′,6,6′-tetrahydroxy biphenyl **1a** (4.0 mmol) in THF (5.0 mL) was added slowly at −78 °C to the mixture. The reaction mixture was then gradually warmed to room temperature and kept stirring for another 6 h. The resulting suspension was directly filtered through a pad of Celite. The filtrate was concentrated and the residue was passed through a short silica gel column (hexane/ethyl acetate=1:50) to give a mixture containing four isomers in the yield of 45%. After crystallization from a mixed solvent of hexane and ethyl acetate (25/1, v/v), the major isomer was obtained as a white crystal. The major and minor isomers of **2a** could be also separated by preparative HPLC using a Daicel Chiralpak IC column.

*4.2.1. (S,S,aR,S,S)-trans-Dibridged biphenyl phosphoramidite ((aR)-trans-**2a**).* Recrystallization yield: 20%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.39 (m, 2H, Ar*H*), 7.15–7.22 (m, 22H, Ar*H*), 7.04–7.06 (m, 2H, Ar*H*), 4.85–4.89 (m, 4H, C*H*), 1.79 (d, *J*=7.2 Hz, 12H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.96, 153.08, 151.51, 143.03, 129.90, 128.83, 128.19, 128.17, 128.10, 126.92, 119.34, 117.51, 52.48, 52.37; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ 149.2; HRMS (EI) calcd for $C_{44}H_{42}N_2O_4P_2$ $[M-H]^+$ 723.2551, found: 723.2545; mp 133–135 °C; $[\alpha]_D^{27}$ −113 (*c* 0.10, $CHCl_3$).

*4.2.2. (S,S,aR,S,S)-cis-Dibridged biphenyl phosphoramidite ((aR)-cis-**2a**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.41 (m, 2H, Ar*H*), 7.03–7.14 (m, 22H, Ar*H*), 7.01–7.03 (m, 2H, Ar*H*), 4.60–4.82 (m, 4H, C*H*), 1.82 (d, *J*=7.2 Hz, 12H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.94, 152.92, 152.84, 152.82, 151.61, 143.03, 129.52, 128.23, 128.18, 128.16, 128.13, 128.11, 128.10, 128.07, 127.03, 126.97, 118.64, 118.01, 52.61, 52.50; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ 148.1; HRMS (EI) calcd for $C_{44}H_{42}N_2O_4P_2$ $[M-H]^+$ 723.2551, found: 723.2545; mp 113–116 °C; $[\alpha]_D^{27}$ −171 (*c* 0.10, $CHCl_3$).

*4.2.3. (S,S,aR,S,S)-trans-3,3′,5,5′-Tetramethyl dibridged biphenyl phosphoramidite ((aR)-trans-**2b**).* Similar to the preparation of (a*R*)-*trans*-**2a**, (a*R*)-*trans*-**2b** was obtained in 32% isolated yield after recrystallization. Et_2O was used as the reaction solvent and the addition temperature of **1b** was −30 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07–7.20 (m, 22H, Ar*H*), 4.52–4.85 (m, 4H, C*H*), 2.49 (s, 6H, CH_3), 2.14 (s, 6H, CH_3), 1.79 (m, 12H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.83, 148.74, 147.37, 147.35, 132.08, 131.89, 128.21, 128.16, 128.13, 127.96, 127.86, 126.70, 126.24, 126.22, 124.23, 52.22, 52.14, 17.73, 16.23, 16.22; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ 143.7; HRMS (ES) calcd for $C_{48}H_{50}N_2O_4P_2$ $[M+H]^+$ 781.3324, found: 781.3318; mp 106–109 °C; $[\alpha]_D^{27}$ −137 (*c* 0.10, $CHCl_3$).

*4.2.4. (S,S,aR,S,S)-trans-3,3′,5,5′-Tetraethyl dibridged biphenyl phosphoramidite ((aR)-trans-**2c**).* Similar to the preparation of (a*R*)-*trans*-**2b**, (a*R*)-*trans*-**2c** was obtained in 28% isolated yield after recrystallization. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04–7.26 (m, 22H, Ar*H*), 4.52–4.73 (m, 4H, C*H*), 3.16–3.25 (m, 2H, CH_2), 2.67–2.76 (m, 2H, CH_2), 2.43–2.57 (m, 4H, CH_2), 1.49–1.95 (m, 12H, CH_3), 1.19–1.24 (m, 6H, CH_3), 1.06–1.13 (m, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.04, 147.96, 146.91, 132.56, 130.88, 129.81, 128.35, 128.11, 127.85, 126.73, 52.34, 52.22, 24.94, 23.65, 15.51, 15.47, 15.08; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ 145.9; HRMS (ES) calcd for $C_{52}H_{58}N_2O_4P_2$ $[M+H]^+$ 837.3950, found: 837.3944; mp 101–103 °C; $[\alpha]_D^{27}$ +263 (*c* 0.10, $CHCl_3$).

4.3. Stereochemistry stability test of atropisomeric dibridged biphenyl phosphoramidites

A 5 mL two-necked flask with a magnetic stirring bar and a reflux condenser was charged with (a*R*)-*trans*-**2a** (0.1 mmol) in dry and degassed toluene (2.5 mL) under N_2 atmosphere. After

stirring at reflux overnight (12 h), the solvent was removed and $CDCl_3$ was added for ^{31}P NMR measurement. No other stereoisomers of the dibridged phosphoramidte ligand were detected in the ^{31}P NMR spectrum. In a similar manner, stereochemical stability of ligands (a*R*)-*trans*-**2b**, (a*R*)-*trans*-**2c** were examined, and we confirmed on the basis of ^{31}P NMR measurements that no stereomutation occurred under the conditions.

4.4. Ring opening of dibridged phosphoramidite 2c

Hydrogen peroxide (30%, 1.0 mL) was added dropwise to a solution of **2c** (0.84 g, 1.0 mmol) in THF (25 mL). The oxidation process was finished within 15 min. The resulting mixture was concentrated under vacuum and the residue was dissolved in THF (40 mL). Then $LiAlH_4$ (0.18 g, 4.1 mmol) was added in portions with vigorous stirring. After stirring for 4 h, a diluted NaOH solution was cautiously added to the mixture till the pH turned to slightly basic. The reaction mixture was extracted with CH_2Cl_2 (30 mL×3) and the combined extracts were dried over Na_2SO_4. The solvent was evaporated and the residue was purified by silica gel column chromatography to give 3,3′,5,5′-tetraethyl-2,2′,6,6′-tetrahydroxy biphenyl **1c** (0.30 g) in 90% yield.

4.5. Typical procedure for the copper-catalyzed allylic alkylation

A dried Schlenk tube was charged with copper salt (2 mol %) and the chiral ligand (2 mol %). Dichloromethane (1 mL) was added and the mixture was stirred at room temperature for 30 min. The allylic bromide (1 mmol) was introduced dropwise and the reaction mixture was stirred at room temperature for a further 5 min before being cooled to −78 °C in an acetone-dry ice cold bath. EtMgBr (3 M in hexane, 1.2 equiv) diluted in dichloromethane (0.5 mL) was added over 2 h. Once the addition was completed, the reaction mixture was quenched by addition of aqueous hydrochloric acid (3 N, 10 mL). Dichloromethane (10 mL) was added and the aqueous phase was separated and exacted further with dichloromethane (10 mL×2). The combined organic fractions were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The conversion and the ratio of S_N2' and S_N2 were determined by ^1H NMR. Gas chromatography showed the enantiomeric excess of S_N2' products.

*4.5.1. (R)-3-(4′-Phenyl)-1-pentene (**6a**)*[3c]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21–7.37 (m, 5H, Ar*H*), 5.96–6.05 (m, 1H, CH_2=C*H*), 5.08–5.11 (m, 1H, CH_2=CH), 5.05–5.06 (m, 1H, CH_2=CH), 3.16–3.22 (m, 1H, C*H*Ph), 1.75–1.83 (m, 2H, CH_2CH_3), 0.92 (t, *J*=7.6 Hz, 3H, CH_2CH_3). Determination of the ee of **6a** was performed by GC on a CP-Chiralsil-DEX-CB column, 25 m×0.25 mm column, oven temp 75 °C, retention time: t_R=38.51 min (major), 39.27 min (minor).

*4.5.2. (R)-3-(4′-Methylphenyl)-1-pentene (**6b**)*[3c]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J*=7.2 Hz, 2H, Ar*H*), 7.09 (d, *J*=7.2 Hz, 2H, Ar*H*), 5.87–5.97 (m, 1H, CH_2=C*H*), 4.98–5.04 (m, 2H, CH_2=CH), 3.06–3.14 (m, 1H, C*H*Ph), 2.33 (s, 3H, CH_3), 1.69–1.76 (m, 2H, CH_2CH_3), 0.88 (t, *J*=7.6 Hz, 3H, CH_2CH_3). Determination of the ee of **6b** was performed by GC on a Supelco β-DEX-120 column, 30 m×0.25 mm ID column, initially at 50 °C, isotherm 15 min, then increase at the rate of 5 °C/min to 90 °C, isotherm 30 min, then increase at the rate of 5 °C/min to 120 °C, retention time: t_R=55.84 min (major), 56.34 min (minor).

*4.5.3. (R)-3-(3′-Methylphenyl)-1-pentene (**6c**)*[3c]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.98–7.26 (m, 4H, Ar*H*), 5.90–5.98 (m, 1H, CH_2=C*H*), 5.01–5.06 (m, 2H, CH, CH_2=CH), 3.06–3.13 (m, 1H, C*H*Ph), 2.34 (s, 3H, CH_3), 1.69–1.76 (m, 2H, CH_2CH_3), 0.87 (t, *J*=7.6 Hz, 3H, CH_2CH_3). Determination of the ee of **6c** was performed by GC on a Supelco β-DEX-120 column, 30 m×0.25 mm ID column, oven temp 75 °C, retention time: t_R=37.39 min (major), 39.42 min (minor).

*4.5.4. (R)-3-(4′-Flurophenyl)-1-pentene (**6d**)*[3c]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.96–7.15 (m, 4H, Ar*H*), 5.87–5.96 (m, 1H, CH_2=C*H*), 4.97–5.04 (m, 2H, CH_2=CH), 3.10–3.15 (m, 1H, C*H*Ph), 1.66–1.79 (m, 2H, CH_2CH_3), 0.86 (t, *J*=7.6 Hz, 3H, CH_2CH_3). Determination of the ee of **6d** was performed by GC on a Supelco β-DEX-120 column, 30 m×0.25 mm ID column, initially at 50 °C, isotherm 30 min, then increase at the rate of 5 °C/min to 60 °C, isotherm 30 min, then increase at the rate of 5 °C/min to 150 °C, retention time: t_R=64.62 min (major), 65.28 min (minor).

*4.5.5. (R)-3-(2′-Flurophenyl)-1-pentene (**6e**)*[3c]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.98–7.26 (m, 4H, Ar*H*), 5.93–6.02 (m, 1H, CH_2=C*H*), 5.04–5.08 (m, 2H, CH_2=CH), 3.49–3.55 (m, 1H, C*H*Ph), 1.69–1.82 (m, 2H, CH_2CH_3), 0.88 (t, *J*=7.6 Hz, 3H, CH_2CH_3). Determination of the ee of **6e** was performed by GC on a Supelco β-DEX-120 column, 30 m×0.25 mm ID column, initially at 50 °C, isotherm 5 min, then increase at the rate of 5 °C/min to 75 °C, isotherm 20 min, then increase at the rate of 5 °C/min to 150 °C, retention time: t_R=36.53 min (major), 36.87 min (minor).

*4.5.6. (R)-3-(4′-Chlorophenyl)-1-pentene (**6f**)*[3c]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J*=8.4 Hz, 2H, Ar*H*), 7.12 (d, *J*=8.4 Hz, 2H, Ar*H*), 5.87–5.97 (m, 1H, CH_2=C*H*), 5.00–5.07 (m, 2H, CH_2=CH), 3.10–3.16 (m, 1H, C*H*Ph), 1.63–1.78 (m, 2H, CH_2CH_3), 0.86 (t, *J*=7.6 Hz, 3H, CH_2CH_3). Determination of the ee of **6f** was performed by GC on a Supelco β-DEX-120 column, 30 m×0.25 mm ID column, oven temp 80 °C, retention time: t_R=48.49 min (major), 50.79 min (minor).

*4.5.7. (R)-3-(4′-(Trifluoromethyl)phenyl)-1-pentene (**6g**)*[3c]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J*=8.0 Hz, 2H, Ar*H*), 7.31 (d, *J*=8.4 Hz, 2H, Ar*H*), 5.90–5.97 (m, 1H, CH_2=C*H*), 5.04–5.10 (m, 2H, CH_2=CH), 3.20–3.26 (m, 1H, C*H*Ph), 1.70–1.83 (m, 2H, CH_2CH_3), 0.89 (t, *J*=7.6 Hz, 3H, CH_2CH_3). Determination of the ee of **6g** was performed by GC on a CP-Chiralsil-DEX-CB column, 25 m×0.25 mm column, initially at 50 °C, then increase at the rate of 5 °C/min to 120 °C, retention time: t_R=14.07 min (major), 14.76 min (minor).

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