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From C_2- to D_2-symmetry: atropos phosphoramidites with a D_2-symmetric backbone as highly efficient ligands in Cu-catalyzed conjugate additions

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ABSTRACT

Atropos phosphoramidites with the D_2-symmetric biphenyl backbone were diastereoselectively prepared with ease from achiral tetrahydroxy biphenyls. This type of ligands is proved to be highly efficient in the Cu-catalyzed conjugate additions of diethylzinc to α,β-unsaturated ketones and nitroalkenes. The unique D_2-symmetric backbone endows the ligands with an excellent chiral environment.

Axial chirality is considered to be the fundamental basis for useful reagents and catalysts in asymmetric synthesis because of its excellent chirality transfer property.[1] Chiral ligands based on the C_2-symmetric biaryl backbone are the most widely used axially chiral compounds,[2] and some of them have been successfully applied in industry.[3] In particular, phosphoramidites with a C_2-symmetric biaryl backbone have become a very important class of ligands in the last decade and are frequently employed in many catalytic asymmetric transformations.[4] Alexakis reported an efficient phosphoramidite ligand **1** with induced atropoisomerism on a flexible biphenol unit (Fig. 1).[5] The prominent role played by well-defined atropoisomerism of a binaphthol moiety[6] or a biphenol moiety[7] in efficient catalysis has been reported as well (compounds **2** and **3** in Fig. 1). However, for the latter cases, particularly in the case of compound **3**, it is often necessary to introduce resolution steps with limited yields to prepare the desired key intermediate enantiomers, atropos binaphthols, or biphenols, and the undesired enantiomers could not be used efficiently.[8] In addition, these ligands with different biaryl backbones do not always show high enantioselectivity in different catalyses and substrates.[5–7]

In order to develop efficient and widely applicable ligands possessing the characteristic features of both inherent and induced atropoisomerism,[5–7] and to make sufficient use of the key intermediate enantiomers of the ligands, we searched for an alternative approach in the development of efficient phosphoramidite ligands with a novel design concept.

Recently, a family of axially achiral biaryls having four constitutionally identical substituents at the ortho positions of the biphenyl axis caught our attention (Fig. 2). When the four identical substituents are linked pairwise by two bridges, a pair of D_2-symmetric enantiomers is formed with stable axial chirality.[9] To the best of our knowledge, this form of D_2-symmetric atropos scaffold remains unexplored in the design of chiral ligands.

Inspired by the axially chiral molecules mentioned above, we designed a new type of dibridged biphenyl phosphoramidites **5** with a D_2-symmetric backbone that can be prepared with ease from achiral tetrahydroxybiphenyls **4** (Scheme 1). For this new type of ligands **5**, four isomers with the configuration of a*R*/a*S* and trans/cis, respectively, are possible. 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 tetrahydroxybiphenyls **4** with ease for recycle.[10] Furthermore, it was expected that a ligand that is 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.

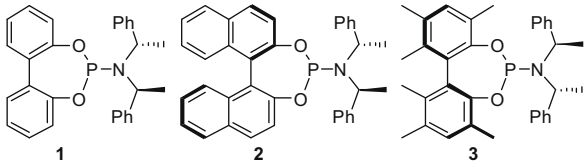

Figure 1. Phosphoramidites with C_2-symmetric backbone.

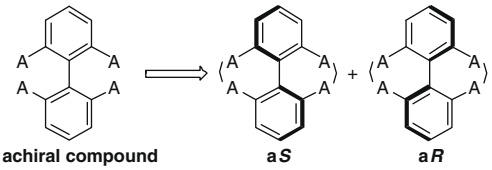

Figure 2. D_2-symmetric dibridged molecules.

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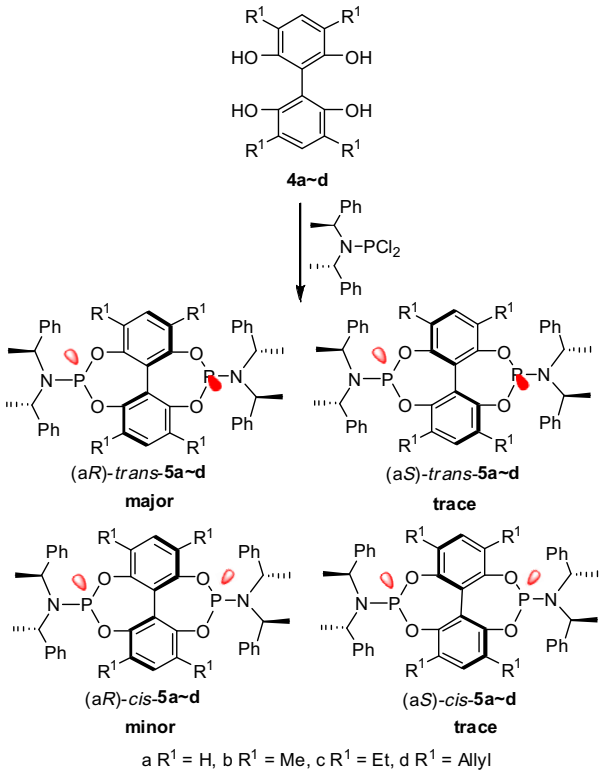


Scheme 1. Preparation of dibridged phosphoramidites with D_2-symmetric backbone.

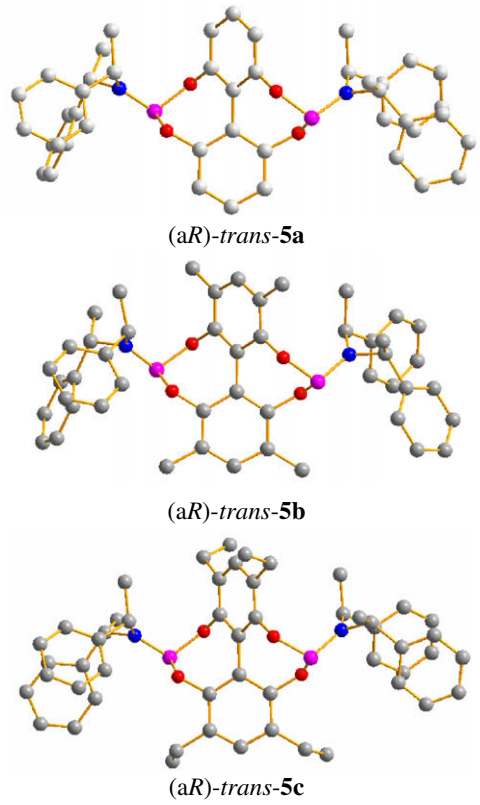
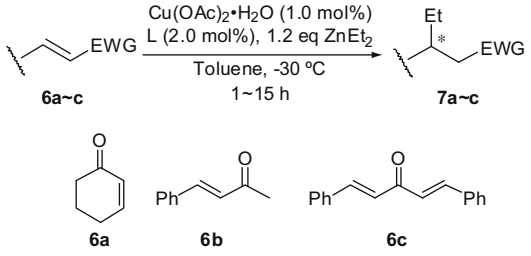


Figure 3. Crystal structures of the dibridged ligands.

First, we attempted to synthesize ligand **5a** from achiral 2,2′,6,6′-tetrahydroxybiphenyl **4a** and (*S*,*S*)-dichlorophosphino-(bis(1-phenylethyl))amine (Scheme 1). As expected, a mixture 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 ones was determined to be 3.8:1 by ^{31}P NMR.[11] The major and minor isomers were isolated by preparative HPLC. The configuration of the major isomer was assigned as (a*R*)-*trans* by X-ray analysis[12] (Fig. 3, (a*R*)-*trans*-**5a**), and that of the minor isomer was assigned as (a*R*)-*cis* by ^{31}P NMR determination.[13] This result shows that one of the two possible axial chiralities was induced by the chiral amine segment during the ligand preparation. Similarly, ligands **5b**–**d** were prepared from **4b**–**d**[14] as a mixture of four isomers with one isomer dominating the others. It was found that the major isomers of **5b**–**d** could be easily separated by crystallization directly from the mixture in up to 35% yield.[15] The (a*R*)-*trans* configuration of the major isomers could be further proved by the X-ray analysis of **5b** and **5c**[12] (Fig. 3, (a*R*)-*trans*-**5b**, (a*R*)-*trans*-**5c**). 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, as expected, all the ligands **5a**–**d** could be readily degraded to achiral tetrahydroxybiphenyls **4** in 85–90% yields in one-pot on treatment with H_2O_2, followed by ring opening with $LiAlH_4$.[10] This result indicates that key intermediates **4** of the undesired isomers can be recovered.

The asymmetric Cu-catalyzed conjugate addition of dialkylzinc reagents to α,β-unsaturated ketones has become a powerful carbon-carbon bond-forming method, and axially chiral phosphoramidite was found to be one of the most useful ligands for this reaction.[16] Thus, our axially chiral dibridged biphenyl phosphoramidite ligands **5** were preliminarily applied to the Cu-catalyzed asymmetric 1,4-addition reaction with substrates **6a**–**c** (Table 1). First, we tested both (a*R*)-*trans*-**5a** and (a*R*)-*cis*-**5a** to see how the *cis* and *trans* configurations influence the catalysis. As a result, both

Table 1
Cu-catalyzed conjugate addition reactions of enones with dibridged phosphoramidites



Entry	Substrate	Ligand	Yield[a] (%)	ee[b] (%)
1	**6a**	(a*R*)-*cis*-**5a**	85	96 (*R*)
2	**6b**	(a*R*)-*cis*-**5a**	80	83 (*S*)
3	**6c**	(a*R*)-*cis*-**5a**	79	82 (*R*)
4	**6a**	(a*R*)-*trans*-**5a**	82	97 (*R*)
5	**6b**	(a*R*)-*trans*-**5a**	85	86 (*S*)
6	**6c**	(a*R*)-*trans*-**5a**	76	87 (*R*)
7	**6a**	(a*R*)-*trans*-**5b**	86	98 (*R*)
8	**6b**	(a*R*)-*trans*-**5b**	90	97 (*S*)
9	**6c**	(a*R*)-*trans*-**5b**	84	96 (*R*)
10	**6a**	(a*R*)-*trans*-**5c**	78	94 (*R*)
11	**6b**	(a*R*)-*trans*-**5c**	90	93 (*S*)
12	**6c**	(a*R*)-*trans*-**5c**	82	99 (*R*)
13	**6a**	(a*R*)-*trans*-**5d**	74	91 (*R*)
14	**6b**	(a*R*)-*trans*-**5d**	91	87 (*S*)
15	**6c**	(a*R*)-*trans*-**5d**	77	93 (*R*)

[a] Isolated yields.
[b] Determined by HPLC and GC analyses.

cis and *trans* isomers gave excellent enantioselectivities for 2-cyclohexenone (**6a**) with 96% and 97% ee, respectively (entries 1 and 4). For other substrates **6b–c**, (a*R*)-*trans*-**5a** afforded good enantioselectivities, while (a*R*)-*cis*-**5a** afforded slightly lower enantioselectivities (entries 2, 3, 5, and 6). The substituents on the ligands apparently had an influence on the catalysis. Methyl-substituted (a*R*)-*trans*-**5b** was the best choice among these ligands. It is noteworthy that all substrates **6a–c** afforded enantioselectivities that were equal to or higher than 96% ee when (a*R*)-*trans*-**5b** was used (entries 7–9). Ethyl-substituted (a*R*)-*trans*-**5c** and allyl-substituted (a*R*)-*trans*-**5d** also provided good to excellent enantioselectivities (entries 10–15).

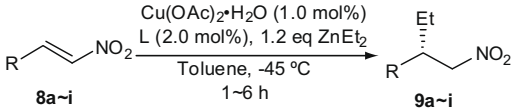
Nitroalkenes are very important substrates for the asymmetric Cu-catalyzed conjugate addition reaction with dialkylzinc reagents to prepare chiral amines.[17] Several ligands have shown good to excellent enantioselectivities for this kind of substrate.[17f,g,18b] But for the axially chiral ligands, no good enantioselectivity was reported with a wide scope of substrates. It was reported that the catalysis with phosphoramidite ligands was strongly affected by the steric and electronic elements of the substrate.[18] Therefore, we also applied our ligands **5** to this important reaction (Table 2). First, we used **8a** as the substrate to examine the effect of the ligands. It was found that (a*R*)-*trans*-**5b** afforded the highest enantioselectivity (96%) (entries 1–5). Then, we applied (a*R*)-*trans*-**5b** to several other typical nitroalkene substrates. To our delight, the ligand was widely applicable; most of the substrates reacted in excellent enantioselectivities (entries 6–13). In particular, for *meta*- and *ortho*-substituted substrates **8c** and **8d**, much higher enantioselectivity was obtained with (a*R*)-*trans*-**5b** than the reported ones with ligand **3** (entries 7 and 8). This ligand was effective also for the reactions of heteroaromatic nitroalkenes (**8h** and **8i**) to give the addition products with 96% ee and 99% ee, respectively (entries 12 and 13). For aliphatic nitroalkene (**8j**), however, only moderate enantioselectivity was obtained (entry 14).

Comparing the results of (a*R*)-*trans*-**5b** with those of the reported biaryl phosphoramidites **1–3** (Table 3), it can be seen that ligand (a*R*)-*trans*-**5b** is a highly efficient and widely applicable ligand in Cu-catalyzed conjugate additions for the above-mentioned three types of enones and nitroalkene.

A reaction model was proposed for rationalizing the high efficiency and wide applicability of ligand (a*R*)-*trans*-**5b** based on its crystal structure (Fig. 4). From the top view of the crystal structure of (a*R*)-*trans*-**5b**, it is reasonable to speculate that when the Cu ion was coordinated to one phosphine atom of the ligand, the benzyl amine group attached to the other phosphine atom of the ligand might provide a strong steric hindrance with the reaction field of the catalytic transition states (Fig. 4, the left). However, the steric hindrance for ligands **1–3** between the binaphthyl or biphenyl backbone and the reaction field might be weaker than that for (a*R*)-*trans*-**5b** (Fig. 4, the right for ligand **2**). This might give a possible explanation for the apparent enantioselectivity increase and wide applicability of (a*R*)-*trans*-**5b** compared with the reported ligands **1–3**.

In conclusion, we have developed a novel class of atropos dibridged biphenyl phosphoramidite ligands with the D_2-symmetric backbone, which can be diastereoselectively prepared from achiral tetrahydroxy biphenyls. Preliminary application of this type of ligands shows that (a*R*)-*trans*-**5b** is a highly efficient and widely applicable ligand in the Cu-catalyzed conjugate addition of diethylzinc to several kinds of α,β-unsaturated ketones and disubstituted nitroalkenes, the enantioselectivities being comparable or superior to those obtained with reported corresponding C_2-symmetric ligands. The unique D_2-symmetric backbone endows the ligands with an excellent chiral environment and the advantage of sufficient reusability of their key intermediates 2,2′,6,6′-tetrahydroxybiphenyls. Further applications of the phosphoramidite ligands are in progress in our laboratory.

Table 2
Cu-catalyzed conjugate addition of nitroalkenes

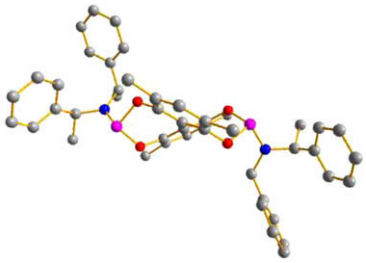


Entry	Substrate (R)	Ligand	Yield[a] (%)	ee[b] (%)
1	**8a** (Ph)	(a*R*)-*cis*-**5a**	92	61
2	**8a** (Ph)	(a*R*)-*trans*-**5a**	92	74
3	**8a** (Ph)	(a*R*)-*trans*-**5b**	89	96
4	**8a** (Ph)	(a*R*)-*trans*-**5c**	83	83
5	**8a** (Ph)	(a*R*)-*trans*-**5d**	90	90
6	**8b** (p-MeOC$_6$H$_4$)	(a*R*)-*trans*-**5b**	87	97
7	**8c** (m-MeOC$_6$H$_4$)	(a*R*)-*trans*-**5b**	88	92
8	**8d** (o-MeOC$_6$H$_4$)	(a*R*)-*trans*-**5b**	77	85
9	**8e** (p-MeC$_6$H$_4$)	(a*R*)-*trans*-**5b**	80	94
10	**8f** (p-ClC$_6$H$_4$)	(a*R*)-*trans*-**5b**	89	92
11	**8g** (2-Naphthyl)	(a*R*)-*trans*-**5b**	86	85
12	**8h** (2-Furyl)	(a*R*)-*trans*-**5b**	86	96
13	**8i** (2-Thienyl)	(a*R*)-*trans*-**5b**	91	99
14	**8j** (Cyclohexanyl)	(a*R*)-*trans*-**5b**	77	62

[a] Isolated yields.
[b] Determined by HPLC and GC analyses.

Table 3
Comparison of **5b** with reported biaryl phosphoramidites in Cu-catalyzed conjugate additions

Entry	Substrate	ee (%)			
		1[4c]	**2**[4c,16j]	**3**[8,18a]	(a*R*)-*trans*-**5b**
1	**6a**	96	97	99	**98**
2	**6b**	82	93	—	**97**
3	**6c**	—	92	—	**96**
4	**8a**	66	82	94	**96**



top view of (a*R*)-*trans*-**5b**

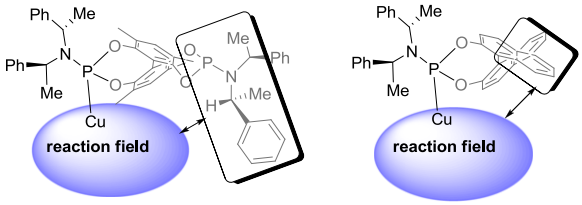


Figure 4. Plausible chiral environment in catalysis.

Acknowledgments

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Foundation of China (20972095) and Science and Technology Commission of Shanghai Municipality (09JC1407800), and Nippon Chemical Industrial Co., Ltd.

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11. ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): 149.2 ppm as a major isomer and 148.1 ppm as a minor isomer, and 152.8 ppm and 154.1 ppm as isomers in trace.
(*S*,*S*,a*R*,*S*,*S*)-*trans*-Dibridged biphenyl phosphoramidite ((a*R*)-*trans*-**5a**) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.39 (m, 2H, ArH), 7.22–7.15 (m, 22H, ArH), 7.04–7.06 (m, 2H, ArH), 4.85–4.89 (m, 4H, CH), 1.79 (d, J = 7.2 Hz, 12H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.08, 153.96, 151.5, 143.0, 129.9, 128.8, 128.19, 128.17, 128.1, 126.9, 119.3, 117.5, 52.50, 52.38; ^{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 133–135 °C; $[\alpha]_D^{27}$ −113 (c 0.10, $CHCl_3$).
(*S*,*S*,a*R*,*S*,*S*)-*cis*-Dibridged biphenyl phosphoramidite ((a*R*)-*cis*-**5a**) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.41 (m, 2H, ArH), 7.03–7.14 (m, 22H, ArH), 7.01–7.03 (m, 2H, ArH), 4.60–4.82 (m, 4H, CH), 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, 151.6, 143.0, 129.5, 128.23, 128.18, 128.16, 128.13, 128.11, 128.10, 128.07, 127.03, 126.97, 118.6, 118.0, 52.6, 52,5; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ = 146.7; 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, $CHCl_3$).
12. Crystallographic data for (a*R*)-*trans*-**5a**: $C_{44}H_{42}N_2O_4P_2$, M_r = 724.74, T = 293(2) K, Orthorhombic, $P2(1)2(1)2(1)$, a = 12.4525(8) Å, b = 12.8410(9) Å, c = 24.4382(16) Å, β = 90.00(2), V = 3907.7(5) Å^3, Z = 4, ρ_{calcd} = 1.232 Mg m^{-3}, μ = 0.156 mm^{-1}, 21,675 reflections collected, 7684 independent reflections (R_{int} = 0.0767), Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0487, wR_2 = 0.0702. (a*R*)-*trans*-**5b**: $C_{48}H_{49}N_2O_4P_2$, M_r = 779.83, T = 293(2) K, Orthorhombic, $P2(1)2(1)2(1)$, a = 11.227(4) Å, b = 14.464(5) Å, c = 26.709(9) Å, β = 90, V = 4337(2) Å^3, Z = 4, ρ_{calcd} = 1.194 Mg m^{-3}, μ = 0.145 mm^{-1}, 21,174 reflections collected, 9387 independent reflections (R_{int} = 0.0822), Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0551, wR_2 = 0.1130. (a*R*)-*trans*-**5c**: $C_{52}H_{58}N_2O_4P_2$, M_r = 836.94, T = 293(2) K, orthorhombic, $P2(1)2(1)2(1)$, a = 11.3264(9) Å, b = 12.6123(11) Å, c = 33.148(3) Å, β = 90.00, V = 4735.26(70) Å^3, Z = 4, ρ_{calcd} = 1.174 Mg m^{-3}, μ = 0.137 mm^{-1}, 25,989 reflections collected, 9272 independent reflections (R_{int} = 0.0647), Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0640, wR_2 = 0.1531. CCDC 750221 (a*R*)-*trans*-**5a**, 753649 (a*R*)-*trans*-**5b**, and 750222 (a*R*)-*trans*-**5c** contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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15. (*S*,*S*,a*R*,*S*,*S*)-*trans*-3,3′,5,5′-Tetramethyl-dibridged biphenyl phosphoramidite ((a*R*)-*trans*-**5b**) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.07 (m, 22H, ArH), 4.85–4.52 (m, 4H, CH), 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 = 148.8, 148.7, 147.37, 147.35, 132.1, 131.9, 128. 2, 128.16, 128.13, 127.96, 127.86, 126.7, 126.24, 126.22, 124.2, 52.2, 52.1, 17.7, 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, $CHCl_3$).
(*S*,*S*,a*R*,*S*,*S*)-*trans*-3,3′,5,5′-Tetraethyl dibridged biphenyl phosphoramidite ((a*R*)-*trans*-**5c**) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04–7.26 (m, 22H, ArH), 4.52–4.73 (m, 4H, CH), 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, 146.9, 132.7, 132.6, 130.9, 129.8, 128.4, 128.1, 127.9, 126.7, 52.3, 52.2, 24.9, 23.6, 15,50, 15.47, 15.1; ^{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, $[\alpha]_D^{27}$ 264 (c 0.10, $CHCl_3$).
(*S*,*S*,a*R*,*S*,*S*)-*trans*-3,3′,5,5′-Tetraallylic dibridged biphenyl phosphoramidite ((a*R*)-*trans*-**5d**) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04–7.14 (m, 22H, ArH), 5.81–6.02 (m, 4H), 4.86–5.04 (m, 8H), 4.62–4.66 (m, 4H), 3.91–3.97 (m, 2H), 3.43–3.48 (m, 2H), 3.14–3.28 (m, 4H), 1.39–2.06 (m, 12H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 148.7, 147.4, 137.02, 137.00, 136.9, 131.4, 130.4, 128.7, 128.4, 128.24, 128.19, 128.17, 127.9, 127.8, 127.2, 126.9, 126.7, 115.9, 115.8, 52.3, 52.2, 35.7, 34.4, 34.3; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ = 146.3; HRMS (ES) calcd for $C_{56}H_{58}N_2O_4P_2$ [M+H]$^+$ 885.3933, found: 885.3949; mp 108–110 °C, $[\alpha]_D^{27}$ −234 (c 0.10, $CHCl_3$).
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