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Synthesis of 3 or 3,3′-substituted BINOL ligands and their application in the asymmetric addition of diethylzinc to aromatic aldehydes

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Abstract—Three new substituted BINOL ligands (*R*)-3-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-1,1′-bi-2-naphthol (*R*)-**1**, (*R*)-3,3′-bis[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-1,1′-bi-2-naphthol (*R*)-**2** and 2,4-bis(2,2′-dihydroxy-1,1′-binaphthalen-3-yl)-6-(*p*-tolyl)-1,3,5-triazine (*R*,*R*)-**3** have been obtained by directed *ortho*-lithiation or Suzuki cross-coupling process. Ligand (*R*)-**1** shows improved catalytic properties for the asymmetric diethylzinc addition to aromatic aldehydes.

1. Introduction

Application of 1,1′-bi-2-naphthol (BINOL) and its derivatives in asymmetric catalysis has been extensively studied.[1] Substituents at the 3-position of BINOL are normally introduced via a two-step protocol that involves treatment of a suitably protected BINOL with an organolithium reagent, followed by reaction with an electrophile. Cram et al. synthesized two enantiomerically pure 3,3′-diaryl-substituted BINOLs by a Grignard cross-coupling reaction of 3,3′-dibromo-BINOL-dimethyl ether and arylmagnesium bromides.[2] Snieckus et al. reported an expedient synthetic route to 3 or 3,3′-substituted-1,1′-bi-2-naphthols by directed *ortho*-metallation and Suzuki cross-coupling methods.[3]

BINOL ligands substituted by the introduction of heteroaromatic groups at the 3 or 3,3′-positions are less reported. Jørgensen et al. reported the synthesis of 3,3′-diaryl-BINOLs by reaction of 3,3′-diboronic acid of bis(methoxy)-BINOL with aromatic bromides using a Suzuki cross-coupling reaction. Heteroaromatic bromides, such as 2-bromopyridine and 2-bromothiophene, were also tried for the preparation of 3,3-bis(heteroaryl)-BINOLs; however, only low yields were obtained.[4] Ohta et al. prepared 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol

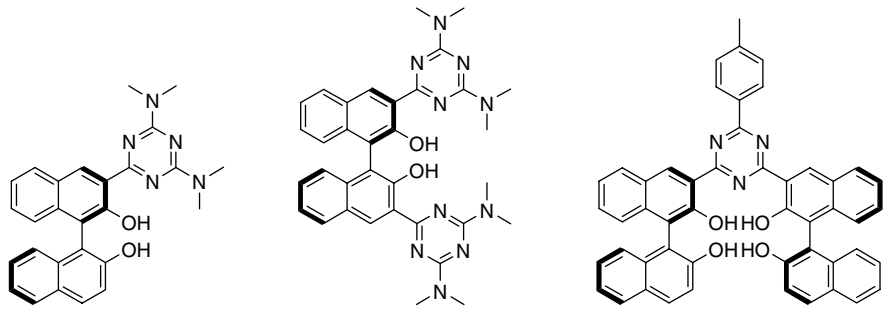

Figure 1.

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(BINOL-Box).[5] Gao et al. synthesized bis-binaphthyl units containing 2,2′-bipyridines via Suzuki cross-coupling reaction.[6]

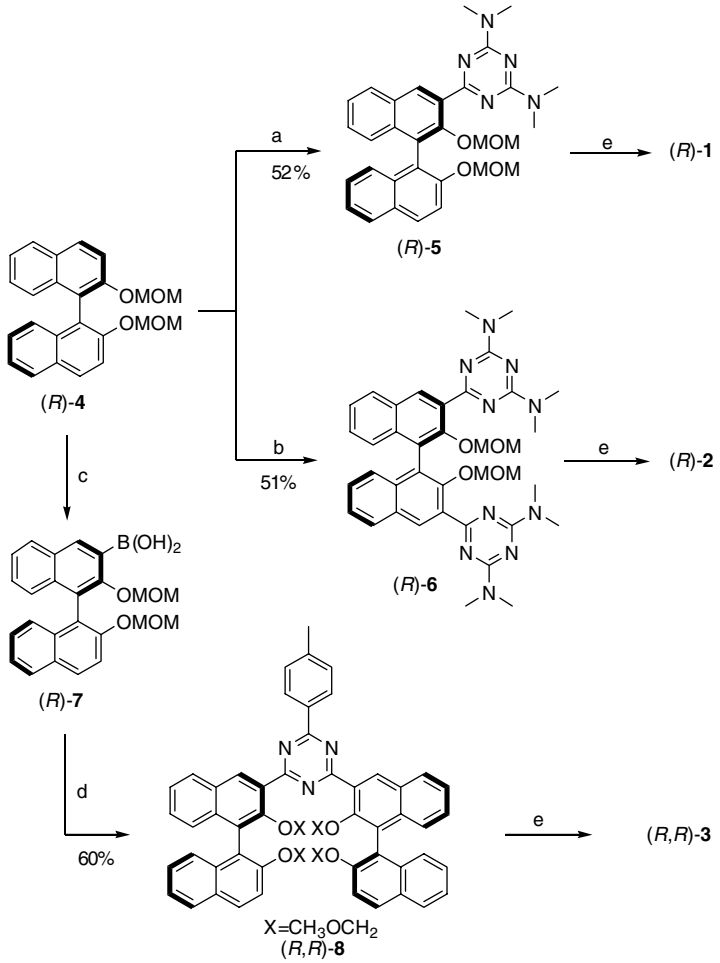
Herein, we report the synthesis of three modified BINOL ligands (*R*)-**1**, (*R*)-**2** and (*R*,*R*)-**3** via directed *ortho*-lithiation or Suzuki cross-coupling processes starting from (*R*)-BINOL and 2,4,6-trichloro-1,3,5-triazine (Fig. 1). We also tested their effectiveness in the titanium complex-catalyzed enantioselective addition of diethylzinc to aldehydes.

2. Results and discussion

The synthetic route to ligands (*R*)-**1**, (*R*)-**2** and (*R*,*R*)-**3** is outlined in Scheme 1. The hydroxy groups of (*R*)-BINOL were protected with methoxymethyl (MOM) groups to afford (*R*)-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (*R*)-**4**.[7] The lithium salt of (*R*)-**4** reacted with cyanuric chloride[8] to afford (*R*)-3-(4,6-dichloro-1,3,5-triazin-2-yl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene or (*R*)-3,3′-bis(4,6-dichloro-1,3,5-triazin-2-yl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene, which were treated with dimethylamine,[9] water and sodium hydroxide to produce (*R*)-3-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (*R*)-**5** or (*R*)-3,3′-bis[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (*R*)-**6**.

After deprotection of compounds (*R*)-**5** and (*R*)-**6**, ligands (*R*)-**1** and (*R*)-**2** were obtained. The Suzuki cross-coupling reaction was the general synthetic procedure used to introduce aromatic or heteroaromatic groups at the 3 or 3,3′-positions of BINOL. Herein, the direct coupling reaction was first used to prepare (*R*)-**5** and (*R*)-**6**.

The lithium salt of (*R*)-**4** reacted with $B(OMe)_3$ and the mixture was hydrolyzed with 2 M HCl to afford (*R*)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl-3-boronic acid (*R*)-**7**.[6] Suzuki coupling of (*R*)-**7** with 2,4-dichloro-6-*p*-tolyl-[1,3,5]-triazine[10] in the presence of aq Na_2CO_3 and $Pd(PPh_3)_4$ in THF at reflux for 36 h afforded 2,4-bis[2,2′-bis(methoxymethoxy)-1,1′-binaphthalen-3-yl]-6-(4-methylphenyl)-1,3,5-triazine (*R*,*R*)-**8**.[11] Deprotection of the MOM groups then afforded (*R*,*R*)-**3**.



Scheme 1. Reagents and conditions: (a) (i) 1.1 equiv *n*-BuLi, −78 °C, (ii) 1.0 equiv cyanuric chloride, −78 °C–rt, (iii) $HNMe_2$, NaOH, H_2O; (b) (i) 2.0 equiv *n*-BuLi, −78 °C, (ii) 2.0 equiv cyanuric chloride, −78 °C–rt, (iii) $HNMe_2$, NaOH, H_2O; (c) (i) 1.1 equiv *n*-BuLi, −78 °C, (ii) $B(OMe)_3$, −78 °C, (iii) 2 M HCl, 0 °C; (d) 0.5 equiv 2,4-dichloro-6-*p*-tolyl-[1,3,5]-triazine, $Pd(PPh_3)_4$, aq Na_2CO_3, THF/reflux; (e) CH_2Cl_2, CH_3OH, 6 M HCl, rt.

The colourless crystals of *rac*-**1** were obtained from a CH_2Cl_2–petroleum ether solution. The crystal structure of *rac*-**1** was determined by X-ray diffraction (Fig. 2).[12] The dihedral angle of C(18)–C(19)–C(21)–N(3) is 9.5°, and the dihedral angle between the two naphthalene systems is 98°.

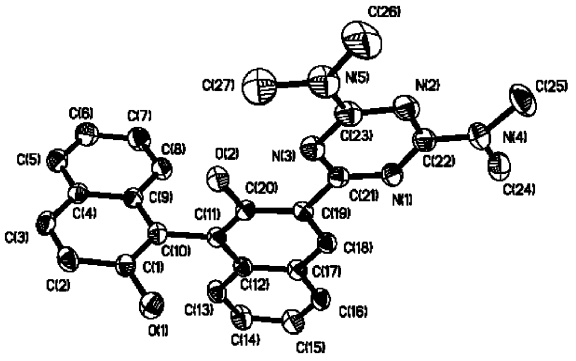
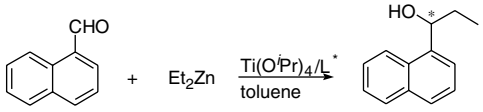


Figure 2. The molecular structure of *rac*-**1**. Hydrogen atoms are excluded for clarity.

The effectiveness of the three new ligands in the titanium complex-catalyzed enantioselective addition of diethylzinc to 1-naphthaldehyde was tested.[13] The active catalyst was formed in situ by mixing the ligand with titanium tetraisopropoxide in toluene.[14] In this reaction, the molar ratio of (*R*)-**1** or (*R*)-**2**/Ti(O^{i}Pr)$_4$/Et_2Zn/1-naphthaldehyde was set up to be 0.2:1.4:3:1 and (*R*,*R*)-**3**/Ti(O^{i}Pr)$_4$/Et_2Zn/1-naphthaldehyde was 0.1:1.4:3:1. The three ligands exhibited very different catalytic properties from each other. Compound (*R*)-**1** showed improved catalytic properties in this reaction (94.7% ee). The increasing steric effects of (*R*)-**2** and (*R*,*R*)-**3** probably led to their much lower enantioselectivity than (*R*)-**1**. In addition, reducing the amount of (*R*)-**1** catalyst from 20% to 5% led to a large decrease in the enantioselectivity. The results are shown in Table 1.

Table 1. Catalytic asymmetric addition of diethylzinc (1 M in toluene) to 1-naphthaldehyde

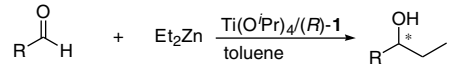


Entry	Ligand[a]	Yield[b] (%)	$[\alpha]_D$ (*c*, solvent)	ee[c] (%)
1	(*R*)-**1**	99	+55.4 (1.6, $CHCl_3$)	90.1 (94.7)
2	(*R*)-**2**	99	+32.5 (2.0, $CHCl_3$)	52.9 (50.8)
3	(*R*,*R*)-**3**[d]	82	+16.1 (1.4, $CHCl_3$)	26.3
4	(*R*)-**1**[e]	85	+49.2 (0.72, $CHCl_3$)	77.5
5	(*R*)-**1**[f]	87	+38.9 (0.74, $CHCl_3$)	61.3

[a] L*/Ti(O^{i}Pr)$_4$/Et_2Zn/1-naphthaldehyde = 0.2:1.4:3:1; reaction temperature: 0 °C; reaction time: 5 h.
[b] Isolated yield.
[c] Based on the reported value of $[\alpha]_D$ = +45.5 (*c* 0.8, $CHCl_3$) in 74% ee for (*R*)-1-(1′-naphthyl)-1-propanol.[15] Data in brackets were determined by GC analysis using a chiral column (Chrompack Chirasil-DEX-CB column).[16]
[d] (*R*,*R*)-**3**/Ti(O^{i}Pr)$_4$/Et_2Zn/1-naphthaldehyde = 0.1:1.4:3:1.
[e] 10 mol % of catalyst was used.
[f] 5 mol % of catalyst was used.

The high enantioselectivity of ligand (*R*)-**1** for the addition of diethylzinc to 1-naphthaldehyde prompted us to examine its use for the reaction of various aromatic aldehydes. These results are summarized in Table 2.

Table 2. Enantioselective addition of diethylzinc to aldehydes with (*R*)-**1**[a]



Entry	R	Yield[b] (%)	$[\alpha]_D$ (*c*, solvent)	ee[c] (%)
1	Ph	99	+40.8 (3.75, $CHCl_3$)	85.6
2	*p*-ClC_6H_4	99	+18.8 (1.4, PhH)	74.5
3	*p*-BrC_6H_4	77	+15.8 (1.49, PhH)	90.3
4	*p*-$MeOC_6H_4$	65	+31.9 (1.0, PhH)	83 (87)
5	*o*-$MeOC_6H_4$	94	+47.2 (1.15, Ph–CH_3)	87.3
6	1-Naphthyl	99	+55.4 (1.6, $CHCl_3$)	90.1 (94.7)

[a] (*R*)-**1**/Ti(O^{i}Pr)$_4$/Et_2Zn/aldehyde = 0.2:1.4:3:1; solvent: toluene; reaction temperature: 0 °C; reaction time: 5 h.
[b] Isolated yield.
[c] Based on the reported value of $[\alpha]_D$ = +45.6 (*c* 3.5, $CHCl_3$) for (*R*)-1-phenyl-1-propanol;[17] $[\alpha]_D$ = −28.2 (*c* 5.01, PhH) in 100% ee for (*S*)-1-(4′-chlorophenyl)-1-propanol;[18] $[\alpha]_D$ = +13.3 (*c* 1.0, PhH) in 76% ee for (*R*)-1-(4′-bromophenyl)-1-propanol;[19] $[\alpha]_D$ = −34.6 (*c* 5.0, PhH) in 90% ee for (*S*)-1-(4′-methoxyphenyl)-1-propanol;[20] $[\alpha]_D$ = −44.9 (*c* 1, toluene) in 83% ee for (*S*)-1-(2′-methoxyphenyl)-1-propanol;[21] $[\alpha]_D$ = +45.5 (*c* 0.8, $CHCl_3$) in 74% ee for (*R*)-1-(1′-naphthyl)-1-propanol.[15] Data in brackets were determined by GC analysis using a chiral column (Chrompack Chirasil-DEX-CB column).[16]

3. Conclusion

We have synthesized three new modified-BINOL ligands (*R*)-**1**, (*R*)-**2** and (*R*,*R*)-**3** from (*R*)-BINOL and 2,4,6-trichloro-1,3,5-triazine. In particular, ligands (*R*)-**1** and (*R*)-**2** can be synthesized by a direct coupling reaction rather than Suzuki cross-coupling reaction. The titanium complex of (*R*)-**1** was found to be an effective catalyst in the asymmetric addition of diethylzinc to a variety of aromatic aldehydes.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument in $CDCl_3$ solution with TMS as internal standard. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. IR spectra were recorded as KBr plates on a Bruker Equinox 55 spectrometer. Elemental analysis was performed with a Yanaco CHN Corder MT-3 elemental analyzer. All experiments, which are sensitive to moisture or air, were carried out under an argon atmosphere using standard Schlenk techniques. Diethylzinc (1.0 M solution in toluene), cyanuric chloride and $Pd(PPh_3)_4$ were purchased from

Aldrich. All anhydrous solvents were purified and dried by standard techniques just before use.

4.2. Synthesis of (*R*)-3-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (*R*)-5

To a solution of (*R*)-**4** (3.74 g, 10 mmol) in anhydrous THF (80 mL) was added *n*-BuLi (7.0 mL, 11 mmol, 1.57 M solution in hexane) at −78 °C under argon and the reaction mixture allowed to warm to room temperature and stirred for 2 h. The resulting solution was slowly added to a solution of cyanuric chloride (1.845 g, 10 mmol) in THF (30 mL) at −78 °C. The mixture was then warmed to room temperature and stirred for another 9 h. A 33% aqueous solution of dimethylamine (10 mL, 70 mmol) and NaOH (0.8 g, 20 mmol) in water (20 mL) were added to the mixture and refluxed for 6 h. After cooling to room temperature, the organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$. After removal of the solvent, the residue was submitted to column chromatographic separation on silica gel with petroleum ether/ethyl acetate (5/1) as eluent to give (*R*)-**5** (2.81 g, 52% yield) as a pale yellow foam: $[\alpha]_D^{25} = +88.2$ (*c* 0.51, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, δ): 2.36 (s, 3H), 3.19 (s, 12H), 3.24 (s, 3H), 4.84 (d, $J = 5.4$ Hz, 1H), 4.87 (d, $J = 5.4$ Hz, 1H), 5.06 (d, $J = 6.6$ Hz, 1H), 7.21–7.39 (m, 6H), 7.59 (d, $J = 9.3$ Hz, 1H), 7.83 (d, $J = 7.2$ Hz, 1H), 7.93 (d, $J = 9.3$ Hz, 2H), 8.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 36.22, 55.80, 56.02, 94.73, 99.56, 116.34, 121.00, 123.99, 124.98, 125.76, 126.07, 126.46, 126.87, 127.00, 127.71, 128.71, 129.54, 129.60, 130.64, 131.82, 133.79, 134.36, 134.51, 150.78, 153.10, 165.44, 171.82; IR (KBr): 2925, 1556, 1509, 1394, 808, 749 cm^{-1}. Anal. Calcd for $C_{31}H_{33}N_5O_4$: C, 69.00; H, 6.16; N, 12.98. Found: C, 69.06; H, 6.11; N, 12.90.

4.3. Synthesis of (*R*)-3,3′-bis[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (*R*)-6

To a solution of (*R*)-**4** (1.87 g, 5 mmol) in anhydrous THF (100 mL) was added *n*-BuLi (6.4 mL, 10 mmol, 1.57 M solution in hexane) at 0 °C under argon and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The resulting solution was added slowly to a solution of cyanuric chloride (1.845 g, 10 mmol) in THF (40 mL) at −78 °C. The mixture was then warmed to room temperature and stirred for another 9 h. A 33% aqueous solution of dimethylamine (10 mL, 70 mmol) and NaOH (0.8 g, 20 mmol) in water (20 mL) were added to the mixture and then refluxed for 6 h. After cooling to room temperature, the organic layer was separated and the aqueous layer extracted with AcOEt. The combined organic phases were dried over $MgSO_4$. After removal of the solvent, the residue was submitted to column chromatographic separation on silica gel with petroleum ether/ethyl acetate (4/1) as eluent to give (*R*)-**6** (1.8 g, 51% yield) as a pale yellow foam: $[\alpha]_D^{25} = +16.7$ (*c* 0.52, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, δ): 2.50 (s, 6H), 3.19 (s, 24H), 4.85 (d, $J = 4.8$ Hz, 2H), 4.97 (d, $J = 4.5$ Hz, 2H), 7.23–7.41 (m, 6H), 7.92 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 36.17, 56.04, 99.34, 124.92, 126.49, 126.83, 126.99, 128.41, 130.29, 131.76, 133.74, 134.80, 151.14, 165.46, 171.78; IR (KBr): 2930, 1569, 1512, 1393, 818, 752 cm^{-1}. Anal. Calcd for $C_{38}H_{44}N_{10}O_4$: C, 64.76; H, 6.29; N, 19.87. Found: C, 64.56; H, 6.42; N, 19.87.

4.4. Synthesis of 2,4-bis[2,2′-bis(methoxymethoxy)-1,1′-binaphthalen-3-yl]-6-(*p*-tolyl)-1,3,5-triazine (*R*,*R*)-8

Under argon, (*R*)-**7** (1.73 g, 4.14 mmol) was combined with 2,4-dichloro-6-*p*-tolyl-[1,3,5]-triazine (0.497 g, 2.07 mmol), $Pd(PPh_3)_4$ (0.09 g, 0.078 mmol), THF (40 mL), H_2O (18 mL) and Na_2CO_3 (1.75 g, 16.5 mmol). The resulting mixture was heated at reflux for 36 h. The organic layer was separated and the aqueous layer extracted with AcOEt. The combined organic phases were dried over $MgSO_4$. After removal of the solvent, the residue was submitted to column chromatography on silica gel with petroleum ether/ethyl acetate (4/1) as eluent to give (*R*,*R*)-**8** (1.13 g, 60% yield) as a yellow powder. $[\alpha]_D^{25} = +158.6$ (*c* 0.57, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, δ): 2.44 (s, 6H), 2.46 (s, 3H), 3.27 (s, 6H), 4.95 (d, $J = 5.4$ Hz, 2H), 4.99 (d, $J = 4.8$ Hz, 2H), 5.12 (d, $J = 7.8$ Hz, 2H), 5.22 (d, $J = 6.6$ Hz, 2H), 7.27–7.41 (m, 12H), 7.47 (t, $J = 6.6$ Hz, 2H), 7.65 (d, $J = 9.0$ Hz, 2H), 7.90 (d, $J = 7.2$ Hz, 2H), 8.01 (d, $J = 9.0$ Hz, 2H), 8.06 (d, $J = 8.4$ Hz, 2H), 8.62 (d, $J = 8.1$ Hz, 2H), 8.84 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 21.80, 56.07, 94.79, 100.08, 116.32, 120.57, 124.15, 125.51, 125.83, 125.97, 126.75, 127.72, 127.80, 127.88, 129.14, 129.30, 129.59, 129.65, 129.88, 130.66, 132.00, 133.50, 133.55, 134.29, 135.33, 143.29, 151.22, 153.14, 171.59, 173.45; IR (KBr): 3433, 3053, 1514, 1351, 817, 750 cm^{-1}. Anal. Calcd for $C_{58}H_{49}N_3O_8$: C, 76.05; H, 5.39; N, 4.59. Found: C, 76.19; H, 5.60; N, 4.92. ESI-MS (*m*/*z*): $[M+H]^+$ 916.1.

4.5. (*R*)-3-[4,6-Bis(dimethylamino)-1,3,5-triazin-2-yl]-1,1′-bi-2-naphthol (*R*)-1: deprotection of the MOM groups; typical procedure

To a solution of (*R*)-**5** (2.81 g, 5.21 mmol) in CH_2Cl_2 (35 mL) and MeOH (35 mL) was added 6 M HCl (15 mL) and the mixture was stirred at room temperature for 12 h. The mixture was poured into water (80 mL), extracted with CH_2Cl_2, washed with water and then saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated in vacuo.

4.6. (*R*)-3-[4,6-Bis(dimethylamino)-1,3,5-triazin-2-yl]-1,1′-bi-2-naphthol [(*R*)-1]

Mp > 300 °C; $[\alpha]_D^{25} = +61.1$ (*c* 0.61, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, δ): 3.21 (s, 12H), 5.27 (s, 1H), 7.08 (d, $J = 8.1$ Hz, 1H), 7.15–7.33 (m, 5H), 7.39 (d, $J = 9.0$ Hz, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.91 (d, $J = 9.3$ Hz, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 9.21 (s, 1H), 14.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 36.35, 36.65, 113.35, 121.03, 123.20, 123.43, 124.53, 125.19, 126.38, 127.59, 128.21, 128.58, 129.34, 129.70, 129.80, 132.16, 133.86, 136.40, 151.61, 156.77, 163.49, 169.60;

IR (KBr): 3525, 3374, 2927, 1574, 1509, 1386, 810, 746 cm^{-1}. Anal. Calcd for $C_{27}H_{25}N_5O_2$: C, 71.82; H, 5.58; N, 15.51. Found: C, 71.75; H, 5.40; N, 15.42. ESI-MS (*m*/*z*): $[M+H]^+$ 452.3.

4.7. (*R*)-3,3′-Bis[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-1,1′-bi-2-naphthol (*R*)-2

Mp > 300 °C; $[\alpha]_D^{25} = +79.15$ (*c* 0.47, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, δ): 3.20 (s, 24H), 7.14–7.26 (m, 6H), 7.94 (d, $J = 9.0$ Hz, 2H), 9.17 (s, 2H), 13.78 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 36.48, 117.50, 120.81, 122.73, 124.84, 127.41, 127.79, 129.53, 130.95, 136.50, 155.70, 163.57, 170.12; IR (KBr): 3448, 2926, 1583, 1513, 1395, 826, 744 cm^{-1}. Anal. Calcd for $C_{34}H_{36}N_{10}O_2$: C, 66.22; H, 5.88; N, 22.71. Found: C, 66.21; H, 5.83; N, 22.19.

4.8. 2,4-Bis(2,2′-dihydroxy-1,1′-binaphthalen-3-yl)-6-(*p*-tolyl)-1,3,5-triazine [(*R*,*R*)-3]

Mp > 300 °C; $[\alpha]_D^{25} = +202.2$ (*c* 0.81, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, δ): 2.45 (s, 6H), 5.22 (s, 2H), 7.22–7.49 (m, 16H), 7.94 (d, $J = 8.1$ Hz, 2H), 8.01 (d, $J = 8.4$ Hz, 2H), 8.17 (d, $J = 8.1$ Hz, 2H), 8.35 (d, $J = 8.4$ Hz, 2H), 9.53 (s, 2H), 13.17 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 21.89, 114.68, 115.13, 117.88, 119.06, 123.53, 124.46, 124.76, 126.76, 127.82, 128.39, 129.29, 129.35, 130.08, 130.21, 130.27, 130.30, 130.36, 133.66, 133.94, 137.70, 145.61, 151.57, 155.99, 169.29, 171.35; IR (KBr): 3537, 3494, 3438, 3060, 1522, 1353, 818, 745 cm^{-1}. Anal. Calcd for $C_{50}H_{33}N_3O_4$: C, 81.17; H, 4.50; N, 5.68. Found: C, 80.83; H, 4.72; N, 5.71. ESI-MS (*m*/*z*): M^+ 739.

4.9. A typical procedure for the asymmetric addition of diethylzinc to benzaldehyde

Titanium tetraisopropoxide (0.43 mL, 1.24 mmol) was added to a solution of (*R*)-**1** (0.08 g, 0.177 mmol) in 3 mL of toluene at room temperature and stirred for 15 min followed by the addition of diethylzinc (2.7 mL, 1.0 M solution in toluene) with continued stirring for 15 min. The solution was cooled to 0 °C and benzaldehyde (0.09 mL, 0.88 mmol) was introduced with a syringe. The reaction mixture was stirred at 0 °C for 5 h. The reaction was quenched with 20 mL of saturated NH_4Cl solution. The mixture was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated to solvent free. The residue was purified by column chromatography on silica gel to afford 1-phenyl-1-propanol as a colourless liquid. The specific rotation was then measured.

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