A Simple Synthetic Approach to 3,3′-Diaryl BINOLs

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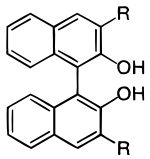
Introduction

Chiral auxiliaries and ligands with C_2 symmetry, such as binaphthyl[1] and bis(oxazolidine)[2] derivatives, have been widely employed as ligands in catalytic asymmetric Diels−Alder,[3] ene,[4] 1,3-dipolar cycloaddition,[5] and other reactions.[6] Although, chiral Lewis acid complexes of 3,3′-disubstituted 1,1′-bi-2-naphthol **1** (BINOL) have been used successfully for asymmetric induction in a variety of reactions,[7] general synthetic procedures to this important class of ligands are scarce. In 1981 Cram et al. synthesized two optical pure 3,3′-diaryl-substituted BINOLs by a Grignard cross-coupling reaction of 3,3′-dibromo-BINOL dimethyl ether and arylmagnesium bromides employing dichlorobis(triphenylphosphine)-nickel(II) as the catalyst.[8] The 3,3′-diphenyl BINOL has also been synthesized along with the 2-naphthyl derivative by a Suzuki cross-coupling reaction of the MOM-protected 3,3′-dibromo BINOL and phenyl- and 2-naphthylboronic acids followed by standard deprotection.[9,10]



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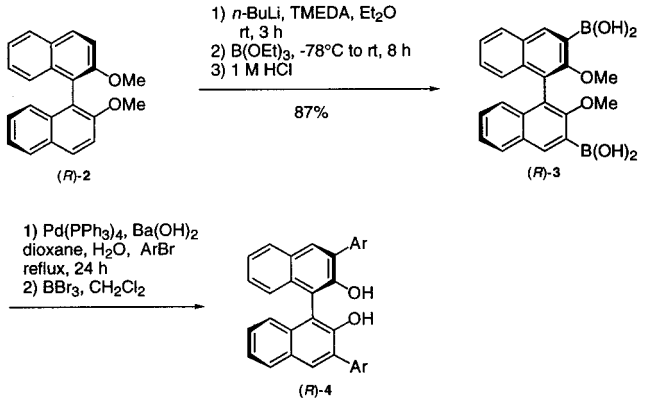
The main drawback in the above reactions is the in situ preparation of the Grignard compounds and the accessibility of the boronic acid derivatives. Thus, to screen a given reaction with a variety of 3,3′-diaryl-substituted BINOLs for asymmetric induction, a versatile and efficient procedure to 3,3′-diaryl-substituted BINOLs is needed. The approach for the synthesis of 3,3′-diaryl BINOLs (*R*)-**4** outlined in this paper presents an entry that makes 3,3′-diaryl BINOLs easy to prepare by reaction of the 3,3′-diboronic acid of BINOL ((*R*)-**3**) with commercially available aromatic bromides by a Suzuki cross-coupling reaction (Scheme 1).

Scheme 1



Results and Discussion

The reported Suzuki coupling reactions performed on BINOLs all involve either 3,3′-diiodo or 3,3′-dibromo BINOLs and an aromatic boronic acid.[10,11] The attention to this new approach is the introduction of two boronic acid substituents in the 3,3′ position of BINOL. The key diboronic acid (*R*)-**3** is prepared by treatment of (*R*)-2,2′-dimethoxy-1,1′-dinaphthyl ((*R*)-**2**) with *n*-BuLi (3.0 equiv) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 3.0 equiv) in dry Et_2O at room temperature for 3 h, generating the dilithiated compound, which reacts with $B(OEt)_3$ at −78 °C. During acidic workup the borate was hydrolyzed to give the corresponding diboronic acid (*R*)-**3** in 87% isolated yield after recrystallization. It should be noted that this reaction has been carried out on a 6 g scale without any difficulties.

Compound (*R*)-**3** and the appropriate aromatic bromide were refluxed for 24 h in 1,4-dioxane containing $Ba(OH)_2$, H_2O, and a catalytic amount of $Pd(PPh_3)_4$. Standard acidic workup gave the bis-coupled product 3,3′-diaryl-2,2′-dimethoxy-1,1′-dinaphthyl as a yellow semicrystalline oil. Demethylation was carried out on the crude material using BBr_3 in CH_2Cl_2 for 18 h. Chromatographic purification on silica gel afforded (*R*)-3,3′-diaryl BINOLs (*R*)-**4a**−**e** as white crystalline compounds in overall good yields. The results are presented in Table 1.

The (*R*)-3,3′-diaryl BINOLs (*R*)-**4a**−**e** were pure by ^1H and ^{13}C NMR spectroscopy after chromatography and can be used as ligands without further purification. It appears from Table 1 that the (*R*)-3,3′-diaryl BINOLs (*R*)-**4a**,**c**−**e** are formed in good yields (entries 1, 3−5). The 3,3′-bis(2,6-dimethylphenyl) BINOL (*R*)-**4b** is formed in lower yield compared with the use of the other aromatic

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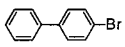
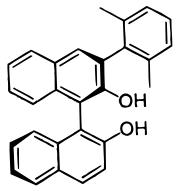
Table 1. Results for the Coupling of Diboronic Acid BINOL (*R*)-3 with Various Aromatic Bromides Catalyzed by $Pd(PPh_3)_4$ and Followed by Demethylation Leading to (*R*)-3,3′-Diaryl BINOLs (*R*)-4a−e

Entry	ArBr	Product	Yield[a] of (*R*)-4/%
1		**4a**	73
2		**4b**	22
3		**4c**	65
4		**4d**	68
5		**4e**	70

[a] Overall yield.

bromides (entry 2). The reason for the lower yield by use of 2,6-dimethylphenyl bromide via the coupling reaction is probably due to steric reasons, and the main (by-)product formed is the mono-arylated BINOL (*R*)-**5**. Furthermore, we have also tried to use heteroaromatic bromides, such as 2-bromopyridine and 2-bromothiophene, for the preparation of (*R*)-3,3′-bis(heteroaryl) BINOLs. However, the present approach gives only the BINOLs in low yields.



(*R*)-**5**

By reversing the reactants in the Suzuki coupling, we have been able to make a series of chiral (*R*)-3,3-diaryl BINOLs (*R*)-(**4**) in overall good yields in a two-step reaction starting from the 3,3′-diboronic acid BINOL (*R*)-**3** dimethyl ether and the appropriate aromatic bromide. Compound (*R*)-**3** represents a late common intermediate to several enantiopure 3,3′-disubstituted BINOLs in large batches employing standard reactions.

Experimental Section

General Methods. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. The chemical shifts are reported in ppm downfield with respect to tetramethylsilane (TMS). Plasma desorption mass spectrometry (PDMS) was recorded on a Bio-Ion 20K time-of-flight instrument on the basis of 500 000 fission events. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Et_2O and 1,4-dioxane were distilled from sodium and benzophenone prior to use. TMEDA was distilled form CaH_2 and stored over molecular sieves (4 Å).

Materials. (*R*)-BINOL was prepared by resolution of *rac*-BINOL (Aldrich) employing *N*-benzylcinchonidinium chloride (Aldrich)[12] and converted to 2,2′-dimethoxy-1,1′-dinaphthyl ((*R*)-**2**) according to the literature.[8] $B(OEt)_3$ (Aldrich) was distilled prior to use. $Pd(PPh_3)_4$ and the aromatic bromides were purchased from Aldrich and used without further purification.

(*R*)-3,3′-Bis(dihydroxyborane)-2,2′-dimethoxy-1,1′dinaphthyl ((*R*)-3). In a 500 mL flame-dried three-necked round-bottomed flask equipped with a N_2-inlet were placed dry Et_2O (300 mL) and TMEDA (6.3 g, 54 mmol). To this solution was added 1.6 M *n*-BuLi in hexane (35 mL, 56 mmol). The solution was stirred for 30 min at room temperature**,** solid (*R*)-**2** (5.9 g, 19 mmol) was added in one portion, and the reaction mixture was stirred for 3 h. The resulting light brown suspension was cooled to −78 °C, and $B(OEt)_3$ (17.1 g, 117 mmol) was added via syringe over a period of 10 min. The solution was allowed to warm to room temperature and was left stirring overnight. The reaction mixture was cooled to 0 °C, 1 M HCl (150 mL) was added, and the reaction mixture was stirred for 2 h. The phases were separated, and the organic phase was washed twice with 1 M HCl (100 mL) and saturated aqueous NaCl (100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting white solid was recrystallized from toluene to give (*R*)-**3** (6.53 g, 87%) as white crystals: mp >250 °C; $[\alpha]_D = -153.4°$ ($c = 1$, $CHCl_3$). ^1H NMR (acetone-d_6): δ 3.41 (s, 6H), 7.11 (dd, $J = 8.1$, 1.1 Hz, 2H), 7.34 (td, $J = 7.5$, 1.2 Hz, 2H), 7.46 (td, $J = 7.4$, 1.2 Hz, 2H), 8.05 (d br, $J = 7.1$ Hz, 2H), 8.56 (s, 2H). ^{13}C (acetone-d_6): δ 61.8, 124.2, 125.7, 126.3, 128.2, 129.7, 131.4, 136.6, 139.1, 161.2. MS(PDMS) *m*/*z*: 402 (M^+), calcd for $C_{22}H_{20}B_2O_6$ 402.0.

General Procedure for the Suzuki Cross-Coupling Reaction. In a 50 mL two-necked flask equipped with a condenser were placed (*R*)-**3** (0.75 g, 1,9 mmol), $Ba(OH)_2 \cdot 8H_2O$ (1.74 g, 5.5 mmol), and $Pd(PPh_3)_4$ (0.116 g, 0.1 mmol), and the flask was evacuated and filled with N_2 three times. 1,4-Dioxane (12 mL), H_2O (4 mL), and the appropriate bromoarene (6.0 mmol) were added. The reaction mixture was refluxed for 24 h under N_2 and cooled to room temperature. The dioxane was removed, and the resulting phase was redissolved in CH_2Cl_2 (75 mL), washed with 1 M HCl (2 × 50 mL) and saturated aqueous NaCl (75 mL), and dried over Na_2SO_4. The solvent was removed to give the crude product as a yellow semicrystalline oil. The crude product was dissolved in dry CH_2Cl_2 (75 mL) and cooled to 0 °C, BBr_3 (1 mL) was added over a period of 10 min, and the reaction mixture was stirred for 18 h at room temperature. The pale yellow solution was cooled to 0 °C, and H_2O (150 mL) was carefully added. The phases were separated, and the organic phase was washed with H_2O (2 × 100 mL) and saturated aqueous NaCl (100 mL), dried over Na_2SO_4, and concentrated. The resulting yellow solid was chromatographed on silica to give (*R*)-**4** as white crystalline solids.

(*R*)-3,3′-Diphenyl-2,2′-dihydroxy-1,1′-dinaphthyl ((*R*)-4a). Chromatography (silica, hexane:EtOAc 19:1, $R_f = 0.4$): yield 73%; mp 202−204 °C (CH_2Cl_2/hexane, lit.[8] 197−198 °C); $[\alpha]_D = 69.1°$ ($c = 1$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 5.36 (s, 2H), 7.25−7.52 (m, 12 H), 7.45 (m, 4H), 7.93 (d, $J = 7.7$ Hz, 2H), 8.03 (s, 2H). ^{13}C ($CDCl_3$): δ 112.4, 124.3, 124.4, 127.4, 127.8, 128.5, 128.5, 129.5, 129.6, 130.7, 131.4, 133.0, 137.5, 150.2. MS(PDMS) *m*/*z*: 438.7 (M^+), calcd for $C_{32}H_{20}O_2$ 438.5.

(*R*)-3,3′-Bis(2,6-dimethylphenyl)-2,2′-dihydroxy-1,1′-dinaphthyl ((*R*)-4b). Chromatography (silica, CH_2Cl_2:hexanes 1:1, $R_f = 0.3$): yield 22%; mp 153−156 °C; $[\alpha]_D = 46.3°$ ($c = 1$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.14 (s, 6), 2.22 (s, 6H), 5.01 (s, 2H), 7.15−7.54 (m, 14 H), 7.78 (s, 2H), 7.91 (d, $J = 8.7$ Hz, 2H).^{13}C ($CDCl_3$): δ 20.6, 20.7, 113.0, 124.0, 124.5, 127.0, 127.6, 127.7, 128.1, 128.3, 129.5, 130.5, 133.4, 136.0, 137.2, 137.3, 149.9. MS(PDMS) *m*/*z*: 494.6 (M^+), calcd for $C_{36}H_{30}O_2$ 494.6.

(*R*)-3-(2,6-Dimethylphenyl)-2,2′-dihydroxy-1,1′-dinaphthyl ((*R*)-5). Chromatography (silica, CH_2Cl_2:hexanes 1:1, $R_f = 0.15$) gave (*R*)-**5** as a semicrystalline solid: yield 48%; $[\alpha]_D = 91.3°$ ($c = 1$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.17 (s, 6H), 2.18 (s, 6H), 5.03 (br. s, 2H), 7.15−7.45 (m, 10 H), 7.83 (s, 1H), 7.92 (d, $J = 8.4$ Hz, 2H), 8.00 (d, $J = 8.7$ Hz, 1H). ^{13}C ($CDCl_3$): δ 20.6, 20.8, 111.6, 112.4, 117.7, 123.8, 124.2, 124.4, 127.2, 127.3, 127.7, 128.2, 128.4, 128.5, 129.5, 129.6, 129.6, 131.0, 131.1, 133.3, 133.5, 135.8, 137.1, 137.3, 150.4, 152.2. MS(PDMS) *m*/*z*: 390.3 (M^+), calcd for $C_{28}H_{22}O_2$ 390.0.

(*R*)-3,3′-Bis(3,5-dimethylphenyl)-2,2′-dihydroxy-1,1′-dinaphthyl ((*R*)-4c). Chromatography (silica, hexane:EtOAc 19:1, $R_f = 0.4$): yield 65%; mp >250 °C; $[\alpha]_D = 75.6°$ ($c = 1$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.55 (s, 6H), 2.63 (s, 6H), 4.43 (s, 2H), 7.15−7.45 (m, 10H), 8.04 (d, $J = 8.2$ Hz, 2H). 8.16 (s, 2H), 8.80 (s, 2H). ^{13}C ($CDCl_3$): δ 22,1, 22.9, 120.3, 120.8, 123.2, 123.8, 124.2, 125.6, 126.3, 128.5, 129.5, 131.2, 133.4, 141.3, 141.5, 146.2, 146.9. MS(PDMS) *m*/*z*: 494.6 (M^+), calcd for $C_{36}H_{30}O_2$ 494.6.

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(*R*)-3,3′-Bis(4-biphenyl)-2,2′-dihydroxy-1,1′-dinaphthyl ((*R*)-4d). Chromatography (silica, CH_2Cl_2:hexane 1:1, R_f = 0.3): yield 68%; mp 220−222 °C; $[\alpha]_D = -70.3°$ (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.43 (s, 2H), 7.29−7.54 (m, 12 H), 7.69 (d, J = 7.1 Hz, 4H), 7.75 (d, J = 8.2 Hz, 4H), 7.86 (d, J = 8.8 Hz, 4H), 7.97 (d, J = 7.8 Hz, 2H), 8.11 (s, 2H).^{13}C ($CDCl_3$): δ 112.4, 124.3, 124.5, 127.2, 127.3, 127.5, 128.5, 128.9, 129.6, 130.1, 130.3, 131.5, 133.0, 136.5, 140.6, 140.8, 150.3. MS(PDMS) m/z: 590.8 (M^+), calcd for $C_{44}H_{30}O_2$ 590.7.

(*R*)-3,3′-Bis(2-naphthyl)-2,2′-dihydroxy-1,1′-dinaphthyl ((*R*)-4e). Chromatography (silica, CH_2Cl_2:hexane 1:1, R_f = 0.4): yield 70%; mp 248−249 °C; $[\alpha]_D = -40.2°$ (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.50 (s, 2H), 7.31−7.62 (m, 10 H), 7.88−7.97 (m, 10 H), 8.16 (s, 2H), 8.24 (s, 2H).^{13}C ($CDCl_3$): δ 112.5, 124.4, 124.4, 126.3, 126.3, 127.5, 127.7, 128.0, 128.2, 128.5, 129.6, 130.7, 131.7, 132.8, 133.1, 133.5, 135.0, 150.3. MS(PDMS) m/z: 539.0 (M^+), calcd for $C_{40}H_{26}O_2$ 538.6.

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