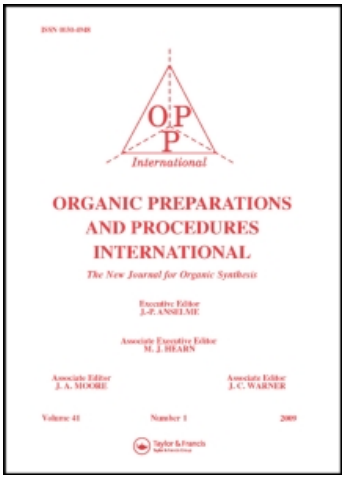

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SYNTHESES OF 3-AND 3,3'-SUBSTITUTED 1,1'-BI-2-NAPHTHOLS

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SYNTHESES OF 3- AND 3,3'-SUBSTITUTED 1,1'-BI-2-NAPHTHOLS

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(05/20/94)

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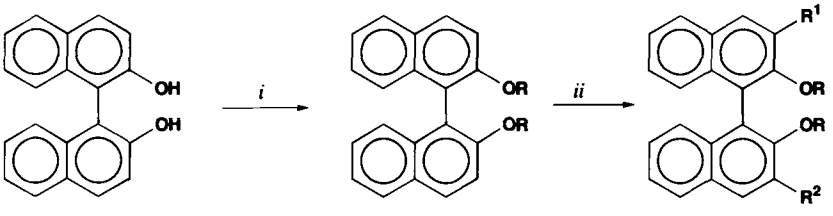
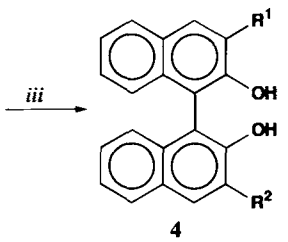
Chiral 1,1'-bi-2-naphthol (BINOL)[1a] is an important ligand of chiral catalysts endowed with a C_2-symmetric axis, useful in the synthesis of optically active compounds. Its high stereoselectivity stems from its flexible chiral axis which can rotate to adapt to the coordination requirements between various substrates and bidentate ligands. For example, its chiral Lewis acid complexes play important roles in asymmetric hydrogenations, alkylations, Grignard and Diels-Alder reactions.[1b] It has also been used in host-guest molecular complexation studies.[2] Some chiral 3,3'-substituted derivatives of BINOL have been applied to many asymmetric catalytic reactions because of its high enantioselectivity; in particular, the use of the sterically hindered BINOLS leads to excellent enantioselectivity.[3] Thus, it was thought that the introduction of oxygen-containing substituents at the *ortho*-position of BINOL would result in a favorable steric environment and the formation of chiral auxiliary bond which would be beneficial for the combination of ligand and substrate. Our aim was to synthesize a series of chiral 3- or 3,3'-BINOL ligands diversely substituted by oxygen or phosphoryl substituents, and to explore their influence on various catalytic reactions. Accordingly, we developed a convenient and direct *ortho*-lithiation strategy for the regiospecific construction of polysubstituted BINOL derivatives **2**. Products **3a-q** may be converted to a variety of potentially valuable BINOLS.



1 **2** a) R = Me b) R = CH_2OMe **3**



4

a) $R^1 = R^2 = CH_2OH$ b) $R^1 = CH_2OH$, $R^2 = H$
c) $R^1 = R^2 = CH_2OMe$ d) $R^1 = CH_2OH$, $R^2 = CH_2OMe$

i) $MeSO_4$, OH^-, heat or CH_3OCH_2Cl(MOMCl), K_2CO_3; *ii*) BuLi, 78°, E^+; *iii*) MeOH, HCl

Oxidative coupling of β-naphthol was followed by protection of the hydroxy group to give binaphthol ethers **2** (R = Me or R = CH_2OCH_3). Lithiation of the ethers and subsequent alkylation (**Table 1**) afforded a series of mono- or di-substituted BINOL derivatives **3a-q**. Dealkylation of **3n-q** gave several *ortho*-substituted BINOLS **4a-d** (*Scheme*); of the more than 30 compounds described, 22 were unreported previously. An improved procedure for the preparation of **1** from β-naphthol is also described.

Table 1. Syntheses of Mono- and Disubstituted BINOL Derivatives (**3**)[a]

	E^{+}[b]	R	R^1	R^2	Yield[c] (%)	mp. (°C)
3a	acetone	Me	-C $(CH_3)_2OH$	-C $(CH_3)_2OH$	37	140-142
3b	acetone	Me	-C $(CH_3)_2OH$	H	35	169-172
3c	ClP $(O)Ph_2$	Me	-P $(O)Ph_2$	-P $(O)Ph_2$	30	244-245.5
3d	ClP $(O)Ph_2$	Me	-P $(O)Ph_2$	H	35	224-226
3e	isopentanal	Me	R[d]	R[d]	82	64-66
3f	isopentanal	Me	R[d]	H	16	oil
3g	ethylene oxide	Me	-OH	H	—	172 -174
3h	acetone	CH_2OMe	-C $(CH_3)_2OH$	-C $(CH_3)_2OH$	10	148-151
3i	acetone	CH_2OMe	-C $(CH_3)_2OH$	H	27	oil
3j	ClP $(O)Ph_2$	CH_2OMe	-P $(O)Ph_2$	-P $(O)Ph_2$	14	—
3k	ClP $(O)Ph_2$	CH_2OMe	-P $(O)Ph_2$	H	20	146-148
3l	isopentanal	CH_2OMe	R[d]	R[d]	74	oil
3m	isopentanal	CH_2OMe	R[d]	H	20	90-93
3n	$(CH_2O)n$	CH_2OMe	$-CH_2OH$	$-CH_2OH$	35	oil
3o	$(CH_2O)n$	CH_2OMe	$-CH_2OH$	H	57	116-119
3p	ethylene oxide	CH_2OMe	$-CH_2CH_2OH$	$-CH_2CH_2OH$	33	oil
3q	ethylene oxide	CH_2OMe	$-CH_2CH_2OH$	H	23	105-108

a) All products were characterized by ^1H NMR, MS and IR analyses; b) If E^+ was $(CH_2O)_n$, the temperature should be maintained at -20 to -30° by means of an ice-salt bath; If E^+ was ethylene oxide, 50 mmol of E^+ was required; if E^+ was acetone, 20 mmol of E^+ was added; c) Both mono- and disubstituted products were obtained; d) R = -CH (OH)CH_2CH $(CH_3)_2$

EXPERIMENTAL SECTION

Melting points were determined on a Kofler hot stage and are uncorrected. Elemental analyses were carried out on a MOD-1106 elemental analyzer. IR spectra were recorded on a FT-5DX or a FT-170SX spectrometer. ^1H NMR spectra were determined in $CDCl_3$ at 80 MHz on a FT-80A or a AC-80 spectrometer and are reported in δ units with TMS as internal standard. Mass spectra were measured on a ZAB-HS spectrometer at 70 ev and signals given in *m/z* with relative intensity (%) in brackets. All anhydrous solvents were purified and dried by standard techniques just before use. Lithiation was

carried out under an inert atmosphere of Ar. All reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254}. Products were purified either by recrystallization or flash column chromatography (FCG) on silica gel (160-200 mesh) manufactured in *Qing Dao Marine Chemical Factory*, eluting with the solvent mixture of petroleum ether and ethyl acetate (v/v 8 : 1).

Preparation of 1,1'-bi-2-Naphthol (1).- To a stirred solution of β-naphthol (15.0 g, 100 mmol) in boiling water (2000 mL) was added dropwise a solution of $FeCl_3 \cdot 6H_2O$ (28.5 g , 105 mmol) in water (200 mL) at 100° over 1.5 hr. After the addition, the reaction mixture was stirred for another 30 min at 100°, then filtered warm. The solid collected was washed with boiling water and then dissolved in 80 mL of 10% NaOH. The solution was filtered and then neutralized to pH 7 with 2N HCl acid. The crude product was collected and recrystallized from 95% EtOH to give 11.0 g (77%) of white needles, mp. 213.5-216°, lit.[1a] mp. 207-209°; ^{1}H NMR: δ 7.75-7.95 (m, 4 H), 7.00-7.36 (m, 8 H), 5.00 (s, 2 H, OH) *ppm*; *m/z* (EIMS): 286 (M^+, 100%), 268 (M-H_2O, 15%), 257 (25), 239 (30), 115 (70); IR (KBr): 3484 (OH), 3402, 1617, 1215 cm^{-1}.

2,2'-Dimethoxy-1,1'-binaphthalene (2a).- To a solution of binaphthol **1** (14 g, 50 mmol) and dimethyl sulfate (13 mL, 135 mmol) in 95% EtOH (200 mL) was added dropwise a solution of NaOH (25 g) in water (40 mL). After the addition, the reaction mixture was refluxed for another 3 hrs and then cooled. The precipitate solid was collected and washed with 10% NaOH and recrystallized from toluene to give 12.2 g (78%) white prisms, mp. 202-203°, lit.[4] mp. 198-202°; ^{1}H NMR: δ 7.77-8.00 (m, 4 H, ArH), 7.10-7.50 (m, 8 H, ArH), 3.70 (s, 6 H, OCH_3) *ppm*; *m/z* (EIMS): 314 (M^+, 100%), 284 (15), 268 (75), 239 (25)

2,2'-Dimethoxylmethyl-1,1'-binaphthalene (2b).- To a suspension of binaphthol **1** (8.6 g, 30 mmol) and dry powdered K_2CO_3 (25 g , 20 mmol) in anhydrous acetone (400 mL) was added dropwise a solution of MOMCl (8 mL , 105 mmol) in anhydrous acetone (50 mL). After the addition was completed, stirring was continued for 1 hr and the reaction mixture was then filtered. Evaporation of the solvent followed by recrystallization of the residue from solvent mixture of acetone-pet. ether afforded 10.3 g (92%) white prisms, mp. 93-94°, lit.[5] mp. 93-94°; ^{1}H NMR: δ 7.20-8.06 (m, 12 H, ArH), 4.96-5.19 (q, 4 H, OCH_2O), 3.18 (s, 6 H, OCH_3) *ppm*; *m/z* (EIMS): 374 (M^+, 100%), 311 (10), 298 (65), 270 (70), 239 (25)

General Procedure for the *ortho* Lithiation and Subsequent Electrophilic Substitution of Binaphthyl Ethers 2a and 2b.- To a stirred solution of binaphthol ether **2a** or **2b** (3.5 mmol) in anhydrous tetrahydrofuran (20 mL) was added dropwise at room temperature *n*-BuLi (1.29 N, 7.7 mL, 10 mmol) in hexane. Upon completion of the addition, the reaction mixture was stirred for another 3 hrs and then cooled to -78° in an acetone-dry ice bath. To this reaction mixture was added dropwise *via* a syringe a solution of the electrophile (E^+) (9.6 mmol) in tetrahydrofuran (2 mL). The reaction mixture was stirred for an additional 1 hr at -78° and then allowed to warm to room temperature gradually overnight. Saturated aqueous NH_4Cl solution (10 mL) and ethyl ether (20 mL) were added to the reaction mixture to quench the reaction. The organic phase was separated and the aqueous layer was extracted with ethyl ether (2 x 20 mL) and the combined organic phases were washed successively

with water and brine prior to being dried ($MgSO_4$). Evaporation of the solvent in vacuum was followed by purification of the residue by flash column chromatography to give mono- and/or disubstituted binaphthol ethers **3a-3q**.

Table 2. Elemental Analyses and Spectral Data of Compounds **3a-3k**

	Elemental Analysis Calcd. (Found) C	H	IR (cm^{-1})	EIMS (*m/z* (%))	^1H NMR (δ)
3a	78.11 (78.06)	7.02 (7.05)	3595 1616	430 (M^+) 397 (100)	1.80-1.90 (d, 12H,Me); 3.20 (s, 6H, OMe); 4.40 (s, 2H, OH); 7.25-8.05 (m, 10H, ArH)
3b	80.62 (80.51)	6.49 (6.52)	3595 2924 1616	372 (M^+) 357 (100) 314 (35)	1.85-1.90 (d, 6H, Me); 3.40 (s, 3H, OMe); 3.90 (s, 3H, OMe); 4.50 (brs, 1H, OH); 7.20-8.15 (m, 11H, ArH)
3c[a]	77.30 (77.42)	5.08 (5.03)	1433 1187	499 (5) 201 (100)	2.45 (s, 6H, OMe); 7.20-8.60 (m, 30H,ArH)
3d[b]	79.36 (79.29)	5.29 (5.33)	1433 1187	514 (M^+) 201 (100)	2.60 (s, 3H, OMe); 3.80 (s, 3H, OMe); 7.20-8.60 (m, 21H, ArH)
3e	78.98 (78.84)	7.87 (7.91)	3450 2953 1595 1145	486 (M^+) 411 (100) 355 (95) 343 (95)	0.90-1.10 (d, 12H, Me);1.30-1.60 (m, 2H, $CHMe_2$); 1.75-1.90 (m, 4H, CH_2); 2.50 (br s, 2H,OH); 3.25 (s, 6H, OMe); 5.10 (t, 2H, CHOH); 6.90-8.20 (m, 10H, ArH)
3f	80.97 (80.83)	7.05 (7.09)	3430 2952 1616 1588 1152	400 (M^+) 343 (100) 328 (20) 268 (17) 126 (25)	1.05-1.15 (d, 6H, Me); 1.50-1.70 (m, 1H, $CHMe_2$); 1.80-2.10 (m, 2H, CH_2); 2.30-2.40 (m, 1H, OH); 3.40 (s, 3H, OMe); 3.85 (s, 3H, OMe); 5.20-5.40 (m, 1H, CHOH); 7.10-8.20 (m, 11H, ArH)
3g	79.98 (79.82)	5.49 (5.55)		330 (M^+) 89 (100)	3.40 (s, 3H, OMe); 3.85 (s, 3H, OMe); 6.15 (s,1H,OH); 7.05-8.10 (m,11H, ArH)
3h	73.45 (73.56)	6.99 (6.96)		490 (M^+) 366 (100)	1.80 (s, 12H, Me); 3.15 (s, 6H, OMe); 3.95-4.40 (q, 4H, OCH_2O); 7.15-7.95 (m, 10H, ArH)
3i	74.98 (75.14)	6.52 (6.45)	3501 2959 1616	432 (M^+) 370 (80) 338 (85)	1.80 (s, 6H, Me); 3.10 (s, 3H, OMe); 3.20 (s, 3H, OMe); 4.25-4.55 (q, 2H, OCH_2O); 5.00 (s, 2H, OCH_2O); 7.05-7.95 (m, 11H, ArH)
3j	74.41 (74.33)	5.20 (5.23)		353 (100) 201 (100)	2.35 (s, 6H, OMe); 4.10-4.50 (q, 4H, OCH_2O); 7.20-8.10 (m, 30H, ArH)
3k	75.25 (75.39)	5.44 (5.38)	1588 1434 1194	574 (M^+) 483 (70) 201 (70)	2.35 (s, 3H, OMe); 3.15 (s, 3H, OMe); 4.25-4.45 (q, 2H, OCH_2O); 5.00 (s, 2H, OCH_2O); 7.15-8.15 (m, 21H, ArH)

a) ^{31}P NMR ($CDCl_3$, 32.4 MHz): δ 25.32 (s); b) ^{31}P-NMR ($CDCl_3$, 32.4 MHz): δ 24.71 (s)

Table 2. Elemental Analyses and Spectral Data of Compounds **3l-3q**

	Elemental Analysis Calcd. (Found) C	H	IR (cm^{-1})	EIMS (*m/z* (%))	^1H NMR (δ)
3l	74.70 (74.58)	7.74 (7.81)	3356 3058 2952 1152 1068	546 (M^+) 484 (40) 422 (100) 395 (30) 195 (25)	1.00-1.10 (d, 12H, Me); 1.25-1.60 (m, 2H, $CHMe_2$); 1.75-1.95 (m, 4H, CH_2); 3.10 (s, 6H, OMe); 4.25-4.45 (m, 4H, OCH_2O); 5.10-5.30 (m, 2H, **CH**OH); 7.00-8.05 (m, 10H, ArH)
3m	75.63 (75.74)	7.00 (6.92)	3592 2945 1595 1152 1011	460 (M^+) 398 (100) 354 (100) 327 (50) 239 (35)	0.95-1.05 (d, 6H, Me); 1.10-1.50 (m, 1H, $CHMe_2$); 1.75-1.95 (m, 2H, CH_2); 3.10-3.15 (d, 6H, OMe); 4.35-4.55 (q, 2H, OCH_2O); 5.00 (s, 2H, OCH_2O); 5.10-5.30 (m, 1H, **CH**OH); 7.10-8.00 (m, 11H, ArH)
3n	71.87 (71.75)	6.03 (6.11)	3409 2938 1588	434 (M^+) 328 (65) 253 (50)	3.11-3.17 (d, 6H, OMe); 4.41-4.46 (d, 4H, OCH_2O); 4.89 (s, 4H, **CH_2**OH); 7.14-8.02 (m, 10H, ArH)
3o	74.24 (74.38)	5.98 (5.92)	3486 2903 1623 1588	404 (M^+) 298 (100) 269 (75) 239 (30)	3.10 (s, 3H, OMe); 3.20 (s, 3H, OMe); 4.35-4.65 (q, 2H, OCH_2O); 4.90 (s,2H,**CH_2**OH); 5.00-5.05 (d, 2H,OCH_2O); 7.10-8.00 (m, 11H, ArH)
3p	72.71 (72.59)	6.54 (6.60)	3430 2991 1623	462 (M^+) 386 (70) 356 (60)	2.90 (s,6H, OMe); 3.13-3.36 (t, 4H, CH_2); 3.90-4.10 (t, 4H, CH_2); 4.38-4.60 (q, 4H, OCH_2O); 7.15-7.87 (m, 10H, ArH)
3q	74.62 (74.74)	6.26 (6.22)	3438 2952 1616 1152	418 (M^+) 342 (90) 312 (100) 252 (20)	3.00 (s, 3H, OMe); 3.15 (s, 3H, OMe); 3.05-3.25 (t, 2H, CH_2); 3.90-4.05 (t, 2H, CH_2); 4.35-4.60 (q, 2H, OCH_2O); 5.00 (s, 2H, OCH_2O); 7.05-7.95 (m, 11H, ArH)

3,3'-Dihydroxylmethyl-1,1'-binaphthalene (4a) and 3-Hydroxylmethyl-1,1'-binaphthalene (4b).- To a solution of **3n** or **3o** (1 mmol) in methanol (2 mL) was added 10% HCl aqueous solution (2.5 mmol) with stirring . After the stirring was continued for 3 hrs , the reaction mixture was evaporated in vacuum . The resulting residue was diluted with ethyl ether and washed with water , brine, dried over $MgSO_4$. After evaporation of the solvent in vacuum, the resulting residue was purified by flash column chromatography to give **4a** or **4b**.

4a: yield 90%, pale yellow prism, mp.126-128°; ^1H NMR: δ 7.15-7.90 (m, 10 H, ArH), 6.00 (br m, 2 H, phenol OH), 5.00 (s, 4 H, **CH_2**OH), 2.00-2.30 (br m, 2 H, OH) *ppm*; *m/z* (EIMS): 346 (M^+, 45%), 326 (30), 297 (40), 269 (35), 253 (100), 239 (80), 215 (25), 128 (20).

Anal. Calcd for $C_{22}H_{18}O_4$, Calcd: C, 76.29; H, 5.24, Found: C, 76.16; H, 5.28

4b: yield 90%, pale yellow prism, mp. 87-90°; ^1H NMR: δ 7.00-8.00 (m, 11 H, ArH), 5.00 (s, 2 H, **CH_2**OH) *ppm*; *m/z* (EIMS): 316 (M^+, 60%), 298 (50, M^+-H_2O), 269 (70), 253 (100), 239 (100), 226 (35), 115 (40).

Anal. Calcd for $C_{21}H_{16}O_3$, Calcd: C, 79.73; H, 5.10; Found: C, 79.89; H, 5.05

3,3'-Dimethoxylmethyl-1,1'-binaphthalene (4c) and 3-Methoxylmethyl-3'-hydroxylmethyl-1,1'-binaphthalene (4d).-To a solution of **3n** (600 mg , 1.3 mmol) in pet. ether (60-90°, 20 mL), was added 50% NaOH (3 mL) with efficient stirring in the presence of a catalytical amount of $(n\text{-}C_4H_9)_4N^+I^-$. The reaction mixture was stirred for 20 min, then dimethyl sulfate (3 mL , 30 mmol) was added. After being stirred for another 30 min, the mixture was diluted with ethyl ether, washed with 10% NaOH, water, brine, dried over $MgSO_4$. The solvent was evaporated in vacuum and the residue was purified by flash column chromatography to obtain methyl ether of **3n** , which was then dissolved in methanol (25 mL) and followed by addition of 10% HCl acid (1.5 mL). After being stirred for 3 hrs, the reaction mixture was evaporated in vacuum to remove the solvent and the residue was taken in ethyl ether, washed with water, brine, dried over $MgSO_4$. After evaporation of the solvent in vacuum, the resulting residue was purified by flash column chromatography to give **4c** and **4d**.

4c: yield 54 % , white prism, mp. 114-116°; IR (KBr): 3500 (s), 3043 (Ar C-H), 2924 (s), 1616, 1588 (m), 1215 (s) cm^{-1}; ^1H NMR: δ 7.19-7.88 (m, 10 H, ArH), 6.60 (s, 2 H, OH), 4.87 (s, 4 H, CH_2OMe), 3.54 (s, 6 H, OMe) *ppm*; *m/z* (EIMS): 374 (M^+, 75%), 342 (100), 310 (45), 97 (20), 282 (40), 266 (25), 253 (85), 155 (40).

Anal. Calcd for $C_{24}H_{22}O_4$, Calcd: C, 76.99, H, 5.92; Found: C, 76.83; H, 5.97

4d: yield 21% , yellow oil, ^1H NMR: δ 7.15-7.89 (m, 10 H, ArH), 6.00-7.00 (br m, 2 H, OH), 4.88 (s, 2 H, CH_2OMe), 4.79 (s, 2 H, CH_2OH), 3.49-3.60 (s, 3 H, OMe), 2.57 (s, 1 H, OH) *ppm*; *m/z* (EIMS): 360 (M^+, 100%), 342 (20), 328 (90), 310 (30), 282 (35), 253 (95), 239 (45), 149 (35), 126 (50).

Anal. Calcd for $C_{23}H_{20}O_4$, Calcd: C, 76.65, H, 5.59; Found: C, 76.77; H, 5.53

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