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EXPEDIENT ROUTE TO 3- AND 3,3'-SUBSTITUTED 1,1'-BI-2-NAPHTHOLS BY DIRECTED ortho METALATION AND SUZUKI CROSS COUPLING METHODS

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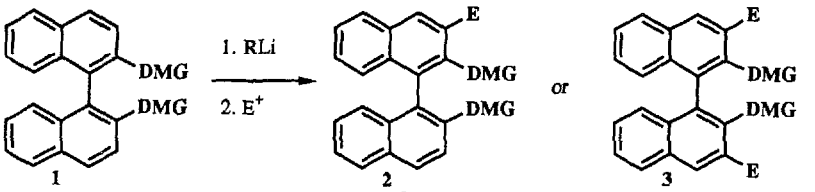
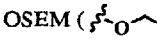
Abstract: A directed ortho metalation-based route to 3- and 3,3'-substituted binaphthols 2a-c and 3a-c, including chiral materials, is described. Using the Suzuki cross coupling process, dibromo system 3a (E = Br) has been transformed into 3,3'-diaryl binaphthols 5.

The C_2 symmetric[1] 2,2'-bis(diarylphosphino)-1,1'-binaphthyl (BINAP)[2] and 1,1'-bi-2-naphthol (BINOL)[1,3-5] ligands have emerged as important chiral auxiliaries and ligands for an increasing range of asymmetric organometallic transformations. Recently, chiral Lewis acid complexes of 3,3'-disubstituted 1,1'-bi-2-naphthols (BINOLs) have shown highly promising catalytic activity for asymmetric induction in Diels-Alder,[6] Claisen rearrangement,[7] and ene,[8] among other[3] reactions. In seminal host-guest complexation studies, Cram and coworkers prepared a series of symmetrical 3,3'-disubstituted BINOLs mainly via Mannich intermediates[5b] and, in two diaryl cases, by Grignard cross coupling of 3,3'-dibromo BINOL dimethyl ether obtained via bis ortho metalation of racemic or chiral BINOL dimethyl ether.[5c,6a] Symmetrical 3,3'-disilylated BINOLs are accessible[5b,6b] from the key 3,3'-dibromo-BINOL, most conveniently derived from enantiomerically pure BINOL,[9,10] Thus flexible, efficient routes to diversely substituted and unsymmetrical 3,3'-BINOLs and 3-BINOLs remain practically unexplored.[11] In our continuing efforts to expand the scope and utility of the directed ortho metalation strategy for the regiospecific construction of polysubstituted aromatics,[12] we now demonstrate a more direct and versatile method for 3- and 3,3'-functionalization of chiral and racemic substrates via 2,2'-oxygen-based directed metalation groups, **1** → **2** or **3** (**Scheme 1**). Products **2a-c** or **3a-c**, showing complementary deprotection properties, may be converted to a variety of potentially valuable BINOLs. Furthermore, we show that the Suzuki cross coupling reaction[13] on 3,3'-dibromo system **3a** (**Scheme 2**) provides an efficient, competitive[5c] route to new sterically encumbered 3,3'-diaryl BINOLs **5** whose potential in asymmetric catalysis has already been partially recognized.[6a]

Scheme 1



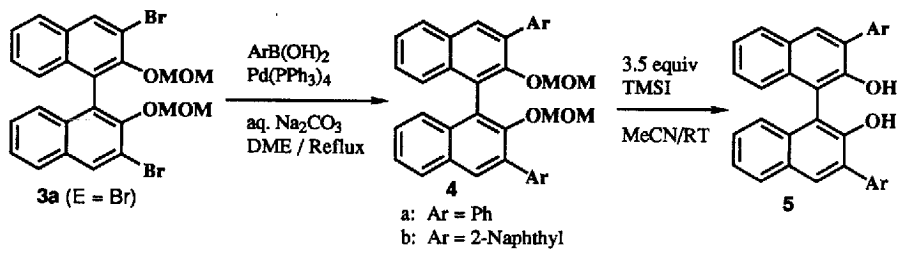
1 2 3

a: DMG = OMOM; **b**: DMG = OSEM (); **c**: DMG = $OCONEt_2$

Selected results of ortho lithiation - electrophile quench reactions are collected in the **Table**. Unexpectedly, 2.2 equiv of t-BuLi (THF/-78°C/1h) proved to be the optimum conditions[14] for the preparation of 3-substituted BINOLs **2a** (entries 1-4). Using similar conditions and range of electrophiles on **1b** led to the formation of several SEM-protected BINOLs (entries 5-7). The generation of the dianion of MOM-BINOL **1a** was optimally achieved[15] using 3.0 equiv of n-BuLi (Et_2O/RT) (entry 8), conditions which were then employed for the preparation of diverse 3,3'-disubstituted MOM-BINOLs (entries 9-15). To establish complementarity with other work,[5c,6a] (*S*)-(+)-3,3'-dimethyl-(entry 9) and (*S*)-(-)-3,3'-dibromo-(entry 14) MOM-BINOLs were show to be available in high yields. Furthermore, to show retention of configuration, the (*S*)-(+)-3,3'-dimethyl derivative was converted (3.5 equiv TMSI/MeCN/RT) into the known (*S*)-(-)-BINOL.[16,17] Using excess base but otherwise under previously reported[18] protocol (2.5 equiv n-BuLi/Et_2O/RT) on **1b** led to a series of 3,3'-disubstituted SEM-BINOLs (entries 16-21), one of which (entry 16) was likewise deprotected to confirm retention of enantiomeric purity.[16,17] Dideprotonation of carbamate BINOL **1c** under 2.5 equiv s-BuLi/TMEDA/THF/-78°C conditions followed by electrophile quench gave good yields of 3,3'-disubstituted products (entries 22-25); **3c** (E = Me) (entry 22) was deprotected (10 equiv MeLi/Et_2O/RT) to give (±)-3,3'-dimethyl BINOL.

The preparation of differentially 3,3'-disubstituted derivatives was achieved with 3-substituted MOM-BINOL. Thus metalation/chlorination or bromination of **2a** (E = SPh) led to 3-chloro or 3-bromo-3'-thiophenyl products in good yields (entries 26, 27).

Scheme 2



For the preparation of 3,3'-diaryl BINOLs, the dibromo **3a**, E = Br (**Scheme 2**) was treated with phenyl and 2-naphthyl boronic acids under modified Suzuki cross coupling conditions[13b] to furnish **4a** and **4b** respectively which, without isolation, were converted into the BINOLs **5a** (87%) and **5b** (83%) under the TMSI deprotection conditions. Optically active **4a**, derived from (*S*)-(-)-**3a** (E = Br), was deprotected to give (*S*)-(-) **5a** with essentially complete retention of chirality.[17,19]

In summary, this work provides efficient and convenient access to 3- and 3,3'-substituted BINOL derivatives, including chiral systems, through the expediency of directed ortho metalation and cross coupling tactics. Both the method and the products may have timely utility in the expanding and innovative use of axial chirality for asymmetric induction of organometallic processes.[20-22]

Table. Synthesis of 3-Substituted and 3,3'-Disubstituted Binaphthol Derivatives

Entry	Substrate	Conditions[a]	E^+	Product (E)	Yield (%)[b]	m.p.(C°)
1	**1a**	A	MeI	**2a** (Me)	71	87-89
2	**1a**	A	PhCHO	**2a** (CH(OH)Ph)	58	146-148/oil[c]
3	**1a**	A	PhSSPh	**2a** (SPh)	68	74-76
4	**1a**	A	BrF_2CCF_2Br	**2a** (Br)	72	91-92
5	**1b**	B	MeI	**2b** (Me)	63	oil
6	**1b**	B	Cl_3CCCl_3	**2b** (Cl)	71	72.5-74.5
7	**1b**	B	BrF_2CCF_2Br	**2b** (Br)	61	62-64
8	**1a**	C	D_2O	**3a** (D)	93[d]	89-91
9	**S-(-) 1a**	C	MeI	**S-(+) 3a** (Me)	82	90.5-91.5
10	**1a**	C	TMSCl	**3a** (TMS)	79	78-81
11	**1a**	C	Ph_3SiCl	**3a** ($SiPh_3$)	51[e]	264-266.5
12	**1a**	C	PhSSPh	**3a** (SPh)	89	90-92
13	**1a**	C	Cl_3CCCl_3	**3a** (Cl)	86	105-107.5
14	**S-(-) 1a**	C	BrF_2CCF_2Br	**S-(-) 3a** (Br)	84	122-123
15	**1a**	D	I_2	**3a** (I)	71	127-128
16	**S-(-) 1b**	D	MeI	**S-(+) 3b** (Me)	88	oil
17	**1b**	D	TMSCl	**3b** (TMS)	90	93-96
18	**1b**	D	PhSSPh	**3b** (SPh)	77	oil
19	**1b**	D	Cl_3CCCl_3	**3b** (Cl)	95	74-75
20	**1b**	D	BrF_2CCF_2Br	**3b** (Br)	83	62-64
21	**1b**	D	I_2	**3b** (I)	51	75-78
22	**1c**	E	MeI	**3c** (Me)	60	114-115
23	**1c**	E	TMSCl	**3c** (TMS)	66	128-130
24	**1c**	E	PhSSPh	**3c** (SPh)	88	139-141
25	**1c**	E	Cl_3CCCl_3	**3c** (Cl)	96	123-124
26	**2a** (E=SPh)	F	Cl_3CCCl_3	**3a** (SPh, Cl)	84	115-116
27	**2a** (E=SPh)	F	BrF_2CCF_2Br	**3a** (SPh, Br)	72	139-140

[a] A: 2.2 equiv t-BuLi/THF/-78°C; B: 2.7 equiv t-BuLi/THF/-78°C; C: 3 equiv n-BuLi/Et_2O/RT/3h; D: 2.5 equiv n-BuLi/Et_2O/RT/3h; E: 2.5 equiv t-BuLi/TMEDA/THF/-78°C/1h; F: 2 equiv n-BuLi/Et_2O/RT/3h. [b] Yield of chromatographed and recrystallized material. [c] Diastereomeric mixture (1.7 : 1). [d] > 95% d_2 content by MS. [e] Polar co-solvent HMPA was used.

References and Footnotes

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14. Under these conditions, quenching with MeOD gave a mixture of mono- and di-deuterated products (68% d_1, 27% d_2 by MS).
15. The use of a similar substrate:base stoichiometry for mono- and di-anion generation of **1a** may be due to the di-OMOM functions playing the role of "internal solvent" to complex 1 equiv of RLi in its less aggregated state in THF solution (see ref 12).
16. (*S*)-(-)-3,3'-dimethyl-1,1'-bi-2-naphthol: from entry 9: $[\alpha]^{25}_{546}$ = -42.9° (c 1.0, $CHCl_3$); from entry 16: $[\alpha]^{25}_{546}$ = -43.5° (c 1.0, $CHCl_3$); lit[5b] $[\alpha]^{25}_{546}$ = -45.1° (c 1.0, $CHCl_3$).
17. Determination of enantiomeric purity by chiral HPLC of this and a series of new BINOL chiral auxiliaries is in progress
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19. (*S*)-(-)-3,3'-diphenyl-1,1'-bi-2-naphthol: $[\alpha]^{25}_{546}$ = -139.1°(c 1.0, THF), lit[5c] (*R*)-(+)-isomer $[\alpha]^{25}_{546}$ = +132.4° (c 1.0, THF).
20. Representative procedure: To a solution of **1a** (1 mmol) in anhydrous Et_2O (17 mL) was added n-BuLi (3 mmol, 2 mL of 1.5 M solution) at room temperature under nitrogen and the reaction mixture was stirred for 3 h. The mixture was cooled to 0°C and sequentially treated with THF (10 mL) and electrophile (3.5 mmol). The reaction mixture was allowed to warm to room temperature over 4 h and quenched with saturated aqueous NH_4Cl solution. The THF was removed in vacuo and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and evaporated to dryness to give product **3a** which was purified by flash chromatography.
21. All new compounds show spectroscopic (^1H and ^{13}C NMR, HRMS) and analytical properties in concert with the assigned structures.
22. We are grateful to Professor S. Collins for a sample of (*R*)-(+)-BINOL and to Professor R. Kazlauskas for a sample of (*S*)-(-)-BINOL and a detailed procedure for its resolution. We acknowledge with gratitude NSERC Canada for financial support.

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