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Directed *ortho* Metalation Reactions. Expedient Synthesis of 3,3'-Disubstituted 1,1'-Bi-(2-Phenols) (BIPOLS)†

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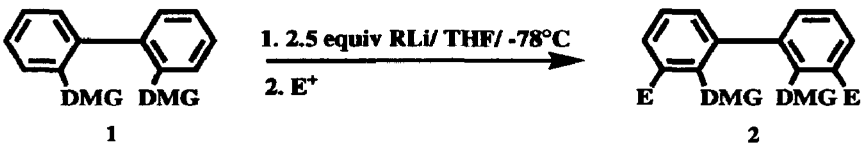
Abstract: Metalation-electrophile quench of the 1,1'-bi-(2-biphenol) bis $OCONEt_2$ and OMOM derivatives **1a-b** provides a general route to 3,3'-disubstituted products **2a-b**; dianionic *ortho*-Fries rearrangement of **1a** furnishes, after acetylation, the 3,3'-bisamide **4** while Suzuki and Negishi cross coupling of **2a** (E = I and ZnBr) affords 3,3'-diaryl derivatives **5a-b** in good yields.

In an ongoing program aimed at devising new ligands for enantioselective organometallic reactions,[1] we recently reported a new general route to 3,3'-disubstituted 1,1'-bi(2-naphthols) (BINOLs) by application of the Directed *ortho* Metalation (DoM) reaction.[2] As a sequel, we now describe the utility of this continuously advancing protocol[3] as a direct and versatile route for the preparation of 3,3'-disubstituted 1,1'-bi-(2-phenols) (BIPOLS) **2** from the readily accessible biphenols **1** bearing carbamate and methoxymethoxy directed metalation groups (DMGs) (**Scheme 1**).[4] The design and synthesis of new BIPOLs is currently witnessing a surge of activity in connection with their use as building blocks for crown ethers,[5] azacrown ethers,[6] spherands,[7] enzyme mimics,[8] siderophores[9] and, most recently, catalysts in asymmetric transformations.[10] Consequently, the described methodology and its ramifications (**Scheme 2**) may find useful application.

Scheme 1



DMG = Directed Metalation Group

a: DMG = $OCONEt_2$; b: DMG = OMOM

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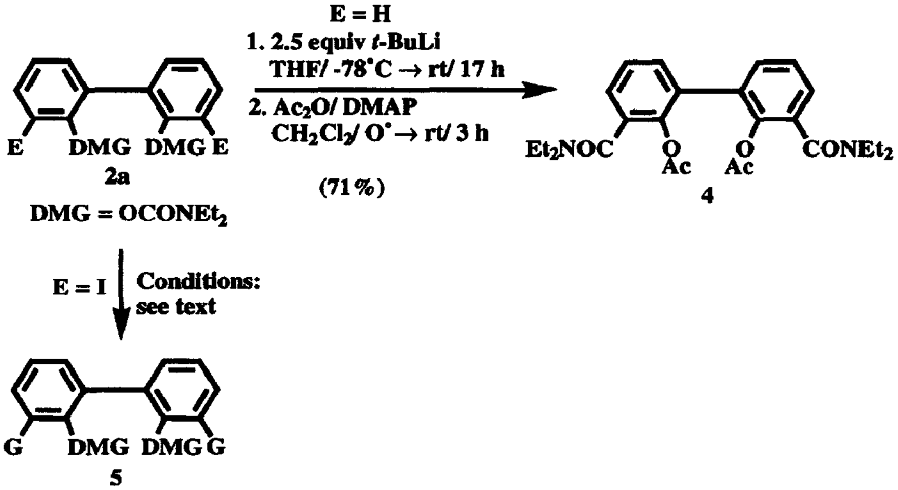
† Dedicated to the memory of Melvin S. Newman.

Metalation (2.5 equiv *s*-BuLi) of the bis-O-carbamate **1a** followed by quench with representative electrophiles (2.5-3 equiv/-78°C → rt/ 15 h) furnished a variety of carbon- and heteroatom-substituted products **2a** in acceptable yields (**Table**). For reactions with aldehydes (entries 4, 5), Et_2O is the solvent of choice over THF since the latter leads to aldehyde reduction products.[11] The protected bis(salicylaldehyde) (entry 2) was obtained by quenching with 6 equiv of HOAc before workup.[12] If a MeOH quench is applied for this as well as the reaction with PhCHO, anchimerically assisted hydrolysis of dicarbamates occurs,[4b,13] to give products **3a-b** respectively. The high-yield synthesis of the"bis-salicaldehyde" **3a** may have value in view of the recent intense interest in the use of chiral salen metal complexes as catalysts in a number of asymmetric transformations.[14,15] The interesting and highly polar 3,3'-diamino and -dihydroxy derivatives (entries 7, 8) were conveniently isolated via their diacetyl derivatives. The product from the reaction of the dimetalated diOMOM BIPOL **1b** with CO_2 unavoidably afforded, upon acidic work up, the corresponding deprotected dicarboxylic acid **3c**. When **1a** was subjected to the conditions of the anionic Fries rearrangement,[13] followed by standard acetylation, the 3,3'-diamide **4** was isolated in good yield.[16]

Scheme 2



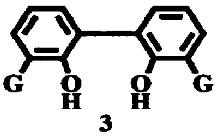
a: G = Ph (82%)
b: G = 2-pyridyl (76%)

To probe cross coupling reactivity of BIPOLs, the 3,3'-diiodo dicarbamate **2a** (E = I) (**Scheme 2**) was treated with phenyl boronic acid under typical cross coupling conditions[17] [$Pd(PPh_3)_4$ 5 mol%/2M aq Na_2CO_3/DME/reflux/62 h] and led to the corresponding 3,3'-diphenyl product **5a** in good yield. Standard dimetalation followed by modification of the Negishi protocol,[18] (2.8 equiv $ZnBr_2$/THF/-78°C/1 h; 3 equiv 2-bromopyridine/$Pd(PPh_3)_4$ (5 mol%/reflux/15 h) furnished a comparable yield of the 3,3'-bipyridyl derivative **5b**.

Table. Synthesis of 3,3'-Disubstituted 1,1'-Bi(2-Phenol) (BIPOL) Derivatives

Entry	Substrate	Conditions[a]	E^+	Product (E)	Yield, %[b]
1	**1a**	A	MeI	**2a** (Me)	87
2	**1a**	A	DMF	**2a** (CHO)	48
3	**1a**	A	DMF	**3a**	67
4	**1a**	B	PhCHO	**3b**	82
5	**1a**	B	Py-2-CHO	**2a** (CH(OH)Py)	50
6	**1a**	A	CO_2	**2a** (CO_2H)	68
7	**1a**	A	TsN_3, $Na_4P_2O_7$ PPh_3, H_2O[c]	**2a** (NH_2)[d]	25
8	**1a**	A	$B(OMe)_3/H_2O_2$, HOAc	**2a** (OH)[d]	29
9	**1a**	A	MeSSMe	**2a** (SMe)	49
10	**1a**	A	TMSCl	**2a** (TMS)	61
11	**1a**	A	TMSCl	**2a** (TES)	58
12	**1a**	A	I_2	**2a** (I)	81
13	**1b**	C	DMF	**2b** (CHO)	65
14	**1b**	C	CO_2	**3c**	70

[a] A: 2.5 equiv *s*-BuLi/THF/-78°C/1 h; 2.8 equiv E^+. B: 2.5 equiv *s*-BuLi/Et_2O/-78°C/1 h; 2.8 equiv E^+. C: 3 equiv *t*-BuLi /Et_2O/O°C/2 h; 2.8 equiv E^+. [b] Yield of purified (chromatographed) material. [c] Iwao, M.; Reed, J.N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531; Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763. [d] Product isolated as its diacetyl derivative.



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a: G = CHO
b: G = CH(OMe)Ph
c: G = CO_2H

In summary, a general and convenient route to 3,3'-disubstituted 1,1'-bi-(2-phenols) (BIPOLS) has been devised using the directed *ortho* metalation protocol. The functional diversity in the derived systems and the demonstration of cross coupling possibilities suggest considerable synthetic utility, especially in context of current interests in molecular recognition and catalysis.[19,20,21]

References and Footnotes

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15. For the preparation of bis-salen-like systems from **3a**, see ref 8.
16. The dimethyl diamide corresponding to the diphenol of **4** has been prepared by a lengthy route that incorporates dibenzofuran DoM chemistry, see ref 9.
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19. *Representative procedure:* To a stirred solution of TMEDA (1.25 mmol) in anhydrous THF (10 mL) was added *s*-BuLi (1.25 mmol, 1.1 mL of 1.1 M solution) at -78°C under nitrogen. After 15 min, a solution of **1a** (0.50 mmol) in anhydrous THF (5 mL) was added dropwise by cannula over 10 min, and the pale yellow solution was stirred for 1 h. Electrophile (1.4 mmol) was added dropwise over 5 min and the reaction mixture was allowed to warm to rt over 12 h, whereupon the solvent was evaporated *in vacuo*. The product was dissolved in saturated NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined extract was dried ($MgSO_4$), evaporated *in vacuo*, and the residue was subjected to flash chromatography (hexane/ acetone mixtures as eluent) to give **2a**.
20. All new compounds show spectroscopic (^{1}H, ^{13}C NMR and HRMS) and analytical data in accordance with their assigned structures.
21. We are grateful to NSERC Canada for financial support through Operating and Industrial Research Chair programs. ASP is grateful to the South African Foundation for Research Development (FRD) and JMG to the Spanish Ministerio de Educación y Ciencia for postdoctoral awards. We thank Dr. Poh Lee Wong for early experimental work.

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