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Protecting Group Free Synthesis of 6-Substituted Naphthols and Binols

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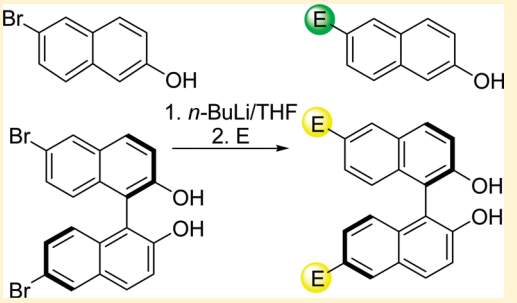
Supporting Information

ABSTRACT: A straightforward route for the preparation of 6-substituted naphthols and 6,6′-disubstituted binols (binol = 2,2′-dihydroxy-1,1′-binaphthyl) is presented. The synthesis has been accomplished by a one-step procedure starting from 6-bromo derivatives via direct lithiation with *n*-BuLi, followed by the addition of several electrophiles. This C−C functionalization has been successfully achieved with iodomethane, 3-methoxybenzaldehyde, benzophenone, methyl-2-methylbenzoate, methylbenzoate, dimethyl carbonate, ethyl 2-chloro-2-oxoacetate, and 2,2-dimethyloxirane (**E**). This reactivity offers a useful protecting group free synthetic protocol, toward chiral disubstituted 6,6′-binols with configuration retention of the binol moiety.



The functionalization of 2-naphthols and binols has been investigated for several years. Such an interest is due to the great versatility of binaphthyl derivatives, which has found a wide array of applications in many different areas of chemistry.[1] Due to their axial chirality with C_2 symmetry, and exhibiting a stable configuration in a broad range of conditions, binol derivatives have become important molecules in several fields, including asymmetric catalysis,[2] chiral supramolecular recognition,[3] crystal engineering,[4] electro-optic materials,[5] molecular electronics,[6] and DNA alkylation.[7] The binol core has been conveniently functionalized at both the 4,4′ and 3,3′ positions.[1,3−8] Furthermore, the access to the 6,6′ carbons has seldom been documented.[9] Recently, the functionalization at the C-6 position of 2-naphthol and binol has been carried out by a carbon halogen cleavage process, activated by photoexcitation of 6-bromo-2-naphthol[10] and 6,6′-dibromobinol.[11] With the exception of this example, all of the synthetic pathways for this type of functionalization require a protecting group strategy and a sequential lithiation reaction, resulting in multistep synthetic protocols. In this work, a free protecting group synthetic protocol has been exploited for the direct lithiation of 6-bromo-2-naphthol and the binol analogue, following a similar strategy described by Posner and co-workers.[12] They paved the route for the development of a general direct lithiation of unprotected phenols, showing the active role of lithium phenoxide as an *ortho*-directing moiety. More recently, direct lithiation has been exploited on several hydric and polyhydric aromatic compounds (monohydroxy polycyclic aromatics, naphthols,[13] *o*-hydroxybenzylamines,[14] and arenethiol[15]). Similar results have been achieved by direct lithiation of halo-substituted hydric derivatives, such as bromoarylalkonic acids and amides,[16] dihydric phenols,[17] and salicylic acids,[18] functionalized by lithium−halogen exchange reactions. Our group applied the latter synthetic strategy for the functionalization of both 2-naphthol and binol bromo derivatives, for which the above literature points away from this possibility. In a very recent example, 2-naphthol and binol derivatives, exploited as mono- and bis-alkylating agents of DNA, have been synthesized by our group through an efficient reductive amination protocol, starting from the aldehyde **1** and **2** (Scheme 1). The above have been prepared by a protecting group free lithiation.[19]

Our interest in binol derivatives, including binol amino acid (Binolams) and bis-hydroxymethyl binols, as DNA cross-linking agents,[19] further prompted us to develop a more general and straightforward synthetic pathway to achieve binol functionalization with configuration retention of the starting material. In this report, we describe the synthesis of both C-6-substituted 2-naphthols and binol analogues.

At the beginning, the synthetic protocol was explored for naphthol derivatives, which were used as a prototype system. Starting from 6-bromo-2-naphthol (**3**), the synthesis of all compounds proceed by lithiation at C-6, followed by addition/substitution reaction in the presence of several electrophiles, including iodomethane, 3-methoxybenzaldehyde, benzophenone, methyl 2-methylbenzoate, dimethylcarbonate, ethyl 2-chloro-2-oxoacetate, and 2,2-dimethyloxirane.

The nature of the electrophile biased the synthetic procedure applied for the preparation of the functionalized naphthols. Compound **3** was lithiated in dry THF at −78 °C using an excess of *n*-BuLi. At least 2.0 equiv of *n*-BuLi was required. Actually, the best results were achieved using a molar ratio **3**/*n*-BuLi = 1:4.4. After 5 h, the solution color turned from pale yellow to bright yellow due to the generation of the C-lithiated intermediate, and an excess of iodomethane was added. The solution was stirred for 45 min, keeping the temperature below −50 °C. Subsequent hydrolysis afforded the methylated product

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Scheme 1. Carbaldehydes 1 and 2 Used as Starting Materials in the Synthesis of Naphthol and Binol Amino Acids as Triggerable Photoalkylating Agents

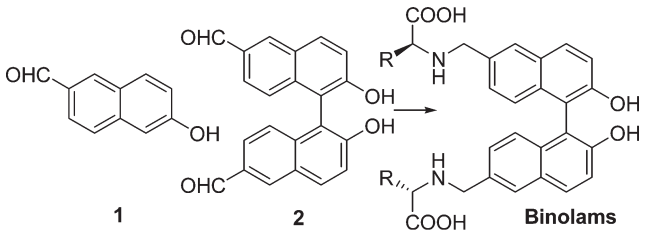
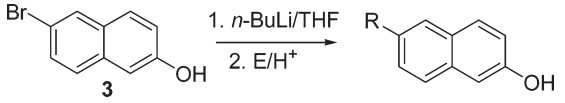
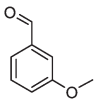
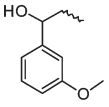
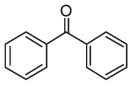
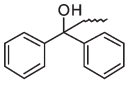
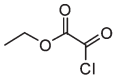


Table 1. Reactivity of 6-Bromo-2-naphthol (3) in the Presence of the Listed Electrophiles (E)



E	R	Products (% Yield)
CH_3I	CH_3	**4a** (80)[a]
		**4b** (67)[b]
		**4c** (68)[b]
		**4d** (47), **5** (10)[c]
		**4e** (65), **5** (10)[c]
		**4f** (44), **5** (15)[c]
		**4g** (60), **5** (5)[d]

Reaction conditions: 1 mmol of **3** reacts with 4.4 mmol of *n*-BuLi and 5 mmol of electrophile. After adding the electrophile, the temperature was kept under −50 °C and stirred for different times: [a] 45 min; [b] 1.5 h; [c] 2 h. [d] The reaction was carried out in presence of $BF_3 \cdot 2Et_2O$ (7.5 mmol, for 5 mmol electrophile), which was added after the electrophile and stirred for 2 h.

4a in a good yield (Table 1). A very similar procedure was followed for compounds **4b** and **4c**, shortening the reaction time, in the presence of the electrophile, to 1.5 h. The naphthols **4d**−**f** were synthesized following a slightly different procedure, as the resulting compounds could react further with a second equivalent of the lithiated naphthol. For this reason, the lithiated species was added to a solution of the electrophile in THF at −78 °C and stirred for 1.5 h below −40 °C. **4d**−**f** were obtained after aqueous workup (Table 1). These reactions required an excess of the electrophile, with best yields achieved using a molar ratio **3**/electrophiles = 1:5. The 2,2-dimethyloxirane, being less reactive as electrophile, required different reaction conditions for the synthesis of **4g**. In fact, the reaction of **3** in the presence of *n*-BuLi in THF and subsequent addition of 2,2-dimethyloxirane did not proceed with temperature ranging from −78 to 0 °C, even after a longer reaction time. A clean reaction took place in the presence of 2,2-dimethyloxirane with the addition of $BF_3 \cdot Et_2O$ at −78 °C[21] to give the corresponding product **4g** in fairly good yield (Table 1).

The best conversions (>65%) have been achieved for the most reactive and monofunctional electrophiles such as alkyl halides, aldehydes, and ketones. The lowest yields (40−50%) are typical for the reaction with esters and acyl halides, where 2-naphthol (**5**) has always been recovered as byproduct.

6,6′-Dibromobinol (**6**) is a much more interesting reactant than **3** because it is widely used as a precursor in the synthesis of both 6,6′-disubstituted chiral ligands[19,20] and helicates with different cavity sizes and chemical properties.[1,2] These important applications prompted us to explore the bisfunctionalization of the binol at the C-6 and C-6′ by direct lithiation. The application of our protecting group free protocol can reduce the reaction step number from four to two. In fact, it has already been shown that the compound **2**[19] can be prepared in fairly good yield through a four-step synthesis, including protection/deprotection of both the binol hydroxyl moieties.[22] The reactivity of **6** in the presence of electrophiles has been investigated for the synthesis of 6,6′-bisfunctionalized binols as described in Table 2. Therefore, the very same protocol optimized for the functionalization of **3** was applied. The synthetic protocol was tested in the presence of several electrophiles, such as iodomethane, benzophenone, methylbenzoate, dimethylcarbonate, ethyl 2-chloro-2-oxoacetate, and 2,2-dimethyloxirane.

As described above, compound **6** was dissolved in anhydrous THF and the solution purged with argon and cooled to −78 °C. To the vigorously stirred solution was added *n*-BuLi in hexane. A high excess of *n*-BuLi was required for the reaction. The higher reaction yields were achieved using a **6**/*n*-BuLi = 1:8 molar ratio. The color change of the reaction is very helpful, clearly indicating the end of the lithiation process. In fact, at the beginning, the solution became bright yellow and the lithium phenolate precipitated. The bis-lithiation at both the positions 6 and 6′ increased the solubility in THF, and after 5.5−6 h at −78 °C, a clear brownish-orange solution was obtained. The electrophile was added in the same way as described for compound **3**, with the molar ratio **6**/electrophiles = 1:8.8. After stirring at −50 °C, the solution was warmed to 0°C, and the products were recovered after workup in HCl/ice.

The reaction has been optimized with different electrophiles in order to improve the reaction yields of the bifunctional products (Table 2). The 6,6′-bis-substituted binols (**7a**, **7c**−**e**, and **7g**) obtained from this synthetic procedure are listed in Table 2. The reaction carried out in presence of ethyl 2-chloro-2-oxoacetate gave a complex reaction mixture, and no further isolation of the resulting products was performed.

As displayed in Table 2, the higher yields were obtained for the monofunctional electrophiles. Lower yields were achieved for methyl benzoate and dimethyl carbonate, from which binol **8** was formed in a sizable amount (∼25% yields) as byproduct. Longer reaction time (2 h) and higher temperatures (−40 °C) were required.

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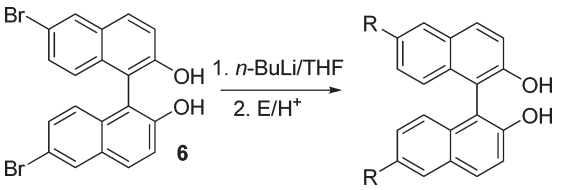
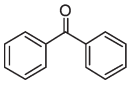
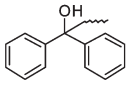
Table 2. Reactivity of 6,6′-Dibromobinol (6) in the Presence of the Listed Electrophiles (E)



E	R	Products (% Yield)
CH_3I	CH_3	**7a** (84)[a,e]
		**7c** (67)[b,e]
		**7d** (45), **8** (25)[c]
		**7e** (32), **8** (20)[c,e]
		**7g** (82), **8** (5)[d]

Reaction conditions: 1 mmol of **6** reacts with 8 mmol of *n*-BuLi and 8.8 mmol of electrophile. After adding the electrophile, the temperature was kept under −50 °C and stirred for different times: [a] 45 min; [b] 1.5 h; [c] 2 h. [d] The reaction was carried out in the presence of $BF_3 \cdot 2Et_2O$ (13.2 mmol, for 8.8 mmol electrophile) stirring for 2 h. [e] The reaction was carried out on enantiopure binol **6** and the preservation of the chirality evaluated by HPLC chromatography, using a chiral column.

The reactivity pattern appeared to be fairly similar to that of 6-bromo-2-naphthol (**3**). The main difference was the formation of sloppy reaction mixtures with polyfunctional electrophiles such as 2-chloro-2-oxoacetate.

To evaluate the potential application of our functionalization protocol for synthetic purposes, we had to clarify if the chirality of the binol moiety was preserved in the lithiation process. Therefore, we decided to investigate the lithiation of both (*S*)- and (*R*)-**6** following the same procedure described above. The subsequent alkylation/acylation of the resulting lithiated binol by iodomethane, benzophenone, and dimethylcarbonate afforded the chiral adducts (*S*)-**7a**, (*S*)-**7c**, and (*R*)-**7e**, respectively, with retention of the binol moiety configuration (Table 3). The structural and configuration assignment of (*S*)-**7a**, (*S*)-**7c**, and (*R*)-**7e** has been achieved by chiral HPLC chromatography, comparing the retention time of the resulting chiral products to those of the racemic adducts arising from the same reaction carried out on the racemic reactant **6** (Supporting Information Figures S2−S4).

The enantiomeric excess of the products (ee) was affected by the nature of the electrophile since, with the less reactive ones, a higher reaction temperature was required. In more detail, product ee was lowered by the rising of the reaction temperature above −50 °C but was not significantly affected by the reaction time. Indeed, the slight reduction of the reaction ee using reactive electrophiles affording products such as (*S*)-**7c** has to be mainly ascribed to the bromination reaction of the chiral binol rather than to the lithiation step (Supporting Information Figure S1).

Table 3. Reaction Yields and Temperature, Together with Retention Times and Enantiomeric Excess (ee), Measured by Chiral HPLC[a]

adduct	yield (%)	*T* (°C)	t_r (min)	ee %
(*S*)-**7a**	84	−50	9.7	99.7[b]
(*S*)-**7c**	67	−50	10.9	97.0[c]
(*R*)-**7e**	32	−40	17.4	88.4[c]

[a] Concentration of **6** = 1×10^{-3} M in IPA (isopropyl alcohol). [b] CHIRALCEL OD-H column: *n*-heptane/IPA 90:10. [c] Kromasil KR100-5CHI-DMB column: *n*-heptane/IPA 80:20.

In conclusion, we have described the alkylation and acylation of 6-bromo-2-naphthol and 6,6′-dibromobinol, through the generation of mono- and bis-lithiated intermediates and further "one-pot" functionalization following a protecting group free protocol. The above offers a straightforward and general strategy for the synthesis of 6,6′-disubstituted binols as chiral DNA cross-linking agents since it has been shown that chirality of the binol moiety is preserved.

EXPERIMENTAL SECTION

3[23] and **6**[24] have been synthesized via standard published procedures. The substituted naphthols, **4a**,[25] **4c**,[26] and **4e**,[27] together with the binol **7a**[28] are known products.

6-(Hydroxy(3-methoxyphenyl)methyl)naphthalen-2-ol (4b). **3** (0.200 g, 9.06×10^{-4} mol) was dissolved in 10.8 mL of dry THF under argon. The stirred solution was cooled to −78 °C, and 2.50 mL of *n*-BuLi in *n*-hexane (1.6 M) (3.98×10^{-3} mol) was added at such a rate to keep the temperature at −70 °C. Temperature was measured using an internal probe in the reaction flask. After 5 h, 3-methoxybenzaldehyde (0.617 g, 0.552 mL, 4.53×10^{-3} mol) was added, keeping the temperature below −50 °C. The solution was stirred at −50 °C for 1.5 h. The reaction mixture was poured into HCl/ice under vigorous stirring and allowed to reach room temperature overnight. The reaction mixture was extracted three times with CH_2Cl_2, and the combined organic phases were washed twice with water and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude was purified by column chromatography cyclohexane/ethyl acetate = 7/3 to give 0.170 g of **4b** (67%, yield): white solid, mp 168−169 °C; ^{1}H NMR (DMSO) δ 3.72 (s, 3H), 5.76 (d, J = 3.8 Hz, 1H), 5.91 (d, J = 3.8 Hz, 1H), 6.77 (dd, J = 8.1, 1.6 Hz, 1H), 6.96 (d, J = 7.7 Hz, 1H), 7.00 (d, J = 1.1 Hz, 1H), 7.05−7.07 (m, 1H), 7.18−7.23 (m, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR (DMSO) δ 21.4, 109.3, 117.6, 126.1, 126.4, 126.6, 128.7, 129.0, 132.6, 133.0, 152.6. Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75; O, 17.12. Found: C, 77.09; H, 5.77.

6-(2-Hydroxy-2-methylpropyl)naphthalen-2-ol (4g). **3** (0.200 g, 9.06×10^{-4} mol) was dissolved in 10.8 mL of dry THF under argon. The solution vigorously stirred was cooled to −78 °C, and 2.50 mL of *n*-BuLi in *n*-hexane (1.6 M) (3.98×10^{-3} mol) was added, keeping the temperature below −70 °C. After 5 h of stirring at this temperature, 2,2-dimethyloxirane (0.327 g, 0.400 mL, 4.53×10^{-3} mol^3 mol) was added, keeping the temperature at −50 °C. After stirring for 30 min, $BF_3 \cdot 2Et_2O$ (0.964 g, 0.839 mL, 6.80×10^{-3} mol) was added very slowly to the solution. After stirring for an additional 1.5 h at this

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temperature, the reaction mixture was poured into HCl/ice (pH < 1) under vigorous stirring. The mixture was allowed to reach room temperature overnight and extracted three times with CH_2Cl_2. The combined organic phases were washed twice with water and dried over $MgSO_4$. Then, the solvent was removed under reduced pressure to give the crude as oil, which was purified by column chromatography (cyclohexane/ethyl acetate = 7/3) to give 0.118 g of **4g** (60% yield): white solid, mp 117−119 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 6H), 1.58 (s, 1H), 2.93 (s, 2H), 5.50 (br s, 1H), 7.09−7.14 (m, 2H), 7.33 (d, J = 9.4 Hz, 1H), 7.61−7.64 (m, 2H), 7.70 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.1, 49.5, 71.3, 109.2, 118.0, 126.1, 128.6, 129.4, 129.5, 132.6, 133.3, 153.3. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46; O, 14.80. Found: C, 77.71; H, 7.50.

(2,2′-Dihydroxy-1,1′-binaphthyl-6,6′-diyl)bis(phenyl methanone) (7d). A 0.200 g sample of **6** (4.66×10^{-4} mol) was dissolved in 5.59 mL of dry THF under argon. After cooling at −78 °C, 2.33 mL of *n*-BuLi in *n*-hexane (1.6 M) (3.73×10^{-3} mol) was added at such a rate in order to keep the temperature just below −70 °C. After 5 h of stirring at this temperature, the bis-lithiated compound was transferred dropwise to a solution of 0.489 mL of methyl benzoate (0.558 g, 4.10×10^{-3} mol) in 5 mL of dry THF cooled at −78 °C. The reaction mixture was added controlling the temperature below −40 °C. After stirring for 2 h at the same temperature, the reaction mixture was poured into HCl/ice (pH < 1) under vigorous stirring. The solution was allowed to reach room temperature overnight and extracted twice with CH_2Cl_2. The combined organic phases were washed with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give an oily residue. The crude was purified by column chromatography (cyclohexane/ethyl acetate = 8/2) to give 0.104 g of **7d** (45% yield) as colorless oil: ^{1}H NMR (acetone-d_6) δ 7.26 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.9 Hz, 2H), 7.56−7.61 (m, 4H), 7.67 (d, J = 7.3 Hz, 2H), 7.74 (dd, J = 8.8, 1.7 Hz, 2H), 7.84−7.86 (m, 4H), 8.14 (d, J = 8.9 Hz, 2H), 8.37 (d, J = 1.7 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 115.6, 120.9, 126.0, 127.4, 129.0, 129.6, 130.9, 133.0, 133.3, 133.5, 138.0, 139.6, 157.4, 196.6. Anal. Calcd for $C_{34}H_{22}O_4$: C, 82.58; H, 4.48; O, 12.94. Found: C, 82.54; H, 4.50.

■ ASSOCIATED CONTENT

Supporting Information. General experimental methods, synthetic procedure for naphthols **4a**, **4c**, **4d**, **4e**, and **4f**, and binols **7a**, **7c**, **7e**, and **7g** and compound **4a**, **4c**, **4d**, **4e**, **4f**, **7a**, **7c**, **7e**, and **7g** characterization data. ^{1}H NMR and ^{13}C NMR for the adducts **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, **7a**, **7c**, **7d**, **7e**, and **7g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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