Pergamon

0040-4020(94)01119-2

# The Regioselective Synthesis of Halophenols

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**Abstract:** The reactions of borates and borinates with zirconocene complexes of substituted benzynes lead regioselectively to heterodimetallic compounds which were, without isolation, converted to the corresponding halophenols.

## INTRODUCTION

For several years we have been involved in the synthesis of novel main group compounds employing zirconocene-mediated routes.[1] A number of reactions of main group compounds with benzyne, alkyne and butadiene complexes of zirconocene and hafnocene have been described in the literature,[2, 3] however the reactions of borates and borinates with these complexes have not been reported. In the course of studying the reaction of boron reagents with benzyne complexes of zirconocene (**1**), we have uncovered a regioselective synthesis of zirconium-boron heterodimetallic compounds **2** and **3**. Herein, we report on this discovery and on a method by which intermediates of the type **2** and **3** are used for the regioselective synthesis of halophenols.
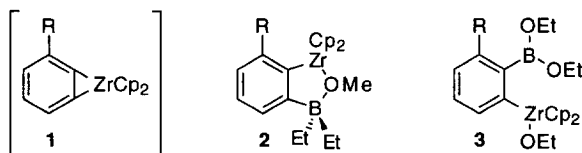


## RESULTS AND DISCUSSION

The reaction of methyl diethylborinate (MDEB) or triethylborate (TEB) with **1**, which is generated *in situ*[4] (Scheme 1), results in the insertion of a boron-oxygen bond into one of the zirconium-carbon bonds.[5] The most interesting and novel feature of these insertion reactions is that they are highly regioselective and the regioisomer obtained can in many instances be controlled by the boron reagent used. The reaction of MDEB with **1** leads to compounds **2** while, in most cases,[6] the reaction of TEB with **1** leads to compounds **3**. Compounds **2** and **3** were, without isolation, converted to iodo and bromophenols by iodination or bromination of the zirconacycle intermediates[7, 8] followed by oxidation of the aryl borate.[9]

The regioselective reaction of compounds containing boron-oxygen bonds with **1** is, to our knowledge, unknown. For reactions of compounds containing unsaturated functional groups, such as alkynes and nitriles with **1**, the insertion reaction is highly regioselective but only one regioisomer can be obtained.[4] We have attributed this regioselectivity to the notion that the unsaturated organic group approaches from the less hindered side of **1**.[7] In the reaction of MDEB with **1** the expected product **2**, where the borinate approaches

away from the substituent on the aromatic group (Scheme 2), is obtained. Interestingly in the reaction of TEB with **1**, the formation of the product **3** suggests that the approach of the boron reagent is from the more congested side of **1** (Scheme 2).

**Scheme 1**
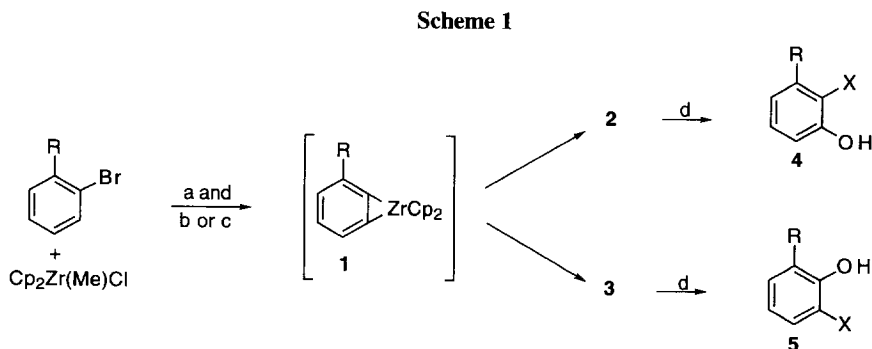


Reagents and conditions: all reactions were carried out in tetrahydrofuran as the solvent, (a) 1.5 equiv. *t*-butyllithium -78 °C, warm to room temperature. (b) 2 equiv. $Et_2BOMe$, 50-90 °C, 3 to 18 h. (c) 2 equiv. $(EtO)_3B$, 50-90 °C, 3 to 18 h. (d) $Br_2$ or $I_2$, 50 °C for 1 h, then excess 3M NaOH followed by excess 30% $H_2O_2$.

Preliminary results,[10] indicate that this reagent directed regioselectivity may be due to kinetic control leading to **2** and thermodynamic control leading to **3** (Scheme 2). We postulate that in intermediate **6**, the boron atom is sufficiently electron deficient that the reaction with the adjacent zirconium-carbon bond occurs before equilibration between **6** and **7** can occur. In the case of TEB, complexation with **1** through an ethoxy group leaves two ethoxy groups which can π-donate to the boron atom; this stabilization allows equilibration between **8** and **9** to occur and, thus, the thermodynamic isomer **3** is the predominant product.

**Scheme 2**
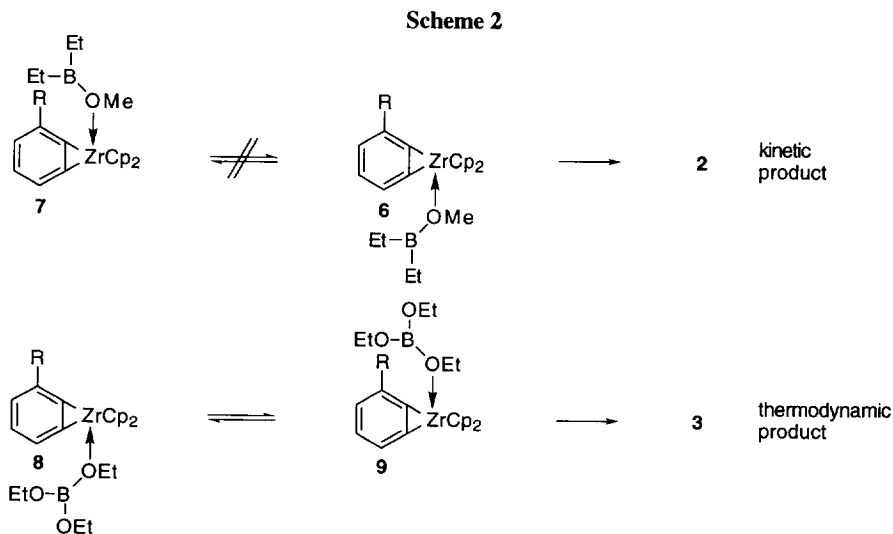
A list of the halophenols prepared by this method is given in Table 1. The yields are for the conversion of the aryl bromide substrate to the isolated product. The variety of methods reported for the synthesis of halophenols highlights the difficulty in making substituted halophenols in a regioselective fashion.[11a-g] A strong feature of our method is its generality, ease of use, readily available starting materials and excellent control of the regiochemistry.

In summary, in our search for synthetic routes to main group complexes, we have discovered that the reaction of 1 with MDEB and TEB results in the regioselective insertion of boron-oxygen bonds into zirconium-carbon bonds. The intermediates so formed serve as vehicles for the regioselective preparation of bromo and iodophenols. Cleavage of the zirconium-carbon bond in 2 or 3 with reagents other than halides [12a-d] or reactions of the aryl borate bond other than oxidation,[13a, b] should lead to other useful substituted aromatics. Research is currently underway directed toward understanding the regioselectivity of the reactions of MDEB and TEB with 1. Additionally, we are exploring the reactions of other main group complexes containing metal-oxygen bonds with 1 in hopes of discovering other useful heterodimetallic compounds.

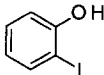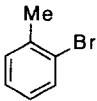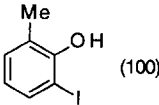## EXPERIMENTAL SECTION

*General Considerations:*
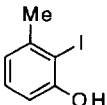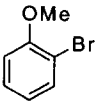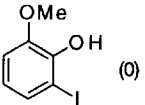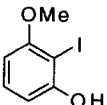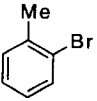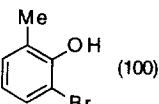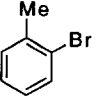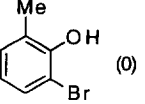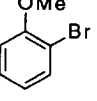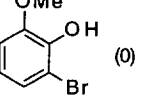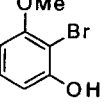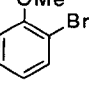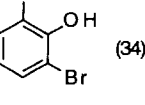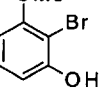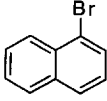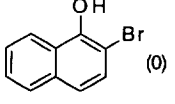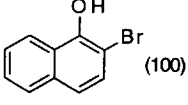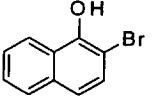
All reactions were carried out under an atmosphere of purified argon or nitrogen using standard Schlenk and glove box techniques. [1]H Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity-300 or a Varian XL-300 Fourier transform spectrometer. Gas chromatography (GC) analyses were performed on a Hewlett-Packard model 5890 gas chromatograph with a flame ionization detector and a model 3392A integrator using a 25 meter capillary column with polymethylsiloxane (Hewlett-Packard) as a stationary phase. Melting points were determined with a Haake Buchler melting point apparatus and are uncorrected.

Tetrahydrofuran (THF) was dried and deoxygenated by refluxing and distilling from sodium / benzophenone ketyl under an argon atmosphere. Preparative flash chromatography was performed on silica gel (E. M. Science Kieselgel 60, 230-400 mesh). All reagents were prepared according to published procedures or were commercially available and used without further purification. Yields in Table 1 refer to isolated yields of products of greater than 95% purity as determined by capillary GC and ^{1}H NMR spectrometry.

*General procedure for the preparation of iodo and bromophenols:*

A dry sealable Schlenk flask was charged with zirconocene(methyl)chloride (0.272 g, 1 mmol) in a glove box. The flask was removed from the glove box and attached to a Schlenk line, and THF (10 mL) was added. The flask was then charged with the aryl bromide (1 mmol) and cooled to -78 °C. Using a gas-tight syringe, *tert*-butyllithium (0.9 mL, 1.7 M in pentane) was added. After 15 min, the flask was removed from the -78 °C bath and allowed to warm to room temperature over 1 h (warm to 0 °C over 20 min in the case of the na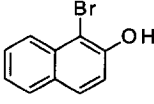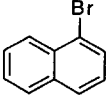phthalene derivative). The triethylborate (0.34 mL, 2 mmol) or diethyl methylborinate (0.26 mL, 2 mmol) was added *via* syringe. The flask was sealed and was then heated in an oil bath for 18 h at 80 °C (heated for 3 h at 50 °C in the case of the naphthalene derivative). After allowing the reaction mixture to

F. M. G. DE REGE and S. L. BUCHWALD

Table 1. Results for the Synthesis of Halophenols from Substituted Aromatic Bromides

| Substrate | Boron reagent | Halogen | Regioisomer A[a] | Regioisomer B[a] | Isolated Yield |
|---|---|---|---|---|---|
| Cp₂ZrPh₂ | (EtO)₃B | I₂ |  | | 72 |
|  | (EtO)₃B | I₂ |  (100) |  (0) | 61 |
|  | Et₂BOMe | I₂ |  (0) |  (100) | 51[b] |
|  | (EtO)₃B | Br₂ |  (100) |  (0) | 74 |
|  | Et₂BOMe | Br₂ |  (0) |  (100) | 58 |
|  | Et₂BOMe | Br₂ |  (0) |  (100) | 61[b] |
|  | (EtO)₃B | Br₂ |  (34) |  (66) | 53 |
|  | Et₂BOMe | Br₂ |  (0) |  (100) | 70 |
|  | (EtO)₃B | Br₂ |  (100) |  (0) | 71 |

[a] The numbers in parentheses refer to ratios of products.
[b] Contained 3 to 4 % 2-methoxyphenol as an impurity.

cool to room temperature, the volatiles were removed *in vacuo* and the yellowish boron-zirconium complex was dissolved in THF (10 mL). A dry round bottom Schlenk flask equipped with a stirbar was attached to the Schlenk line. The round bottom flask was charged with iodine (0.254 g, 1 mmol) or bromine (0.2 mL, excess) and THF (10 mL). The boron-zirconium complex was added quickly to the halogen solution *via* cannula at room temperature with vigorous stirring. After this addition was complete, the cannula was removed and the flask was heated to 50 °C for 1 h. The flask was then cooled in an ice bath. Using a syringe, aqueous sodium hydroxide (2.6 mL, 3 M) was added dropwise immediately followed by dropwise addition of 30% hydrogen peroxide (3 mL). The flask was removed from the ice bath and was allowed to warm up for 15 min after which time the reaction mixture was quenched by the addition of excess saturated aqueous sodium thiosulfate solution. Some ammonium chloride was added at this time to ensure the pH of the solution was close to 7. The product was extracted in ether (3 x 70 mL), dried over magnesium sulfate and the solvents removed by rotary evaporation. The products were purified using preparative flash chromatography to afford the pure halophenols.

In the case of the synthesis of 2-Iodophenol, diphenyl zirconocene was used instead of the zirconocene(methyl)chloride and an aryl bromide substrate.

The spectral data for 2-bromo-6-methylphenol[11a] and 2-bromo-6-methoxyphenol[11b] have been reported in the literature. Spectral data of both 2-iodophenol and 1-bromo-2-napthol were compared with spectral data of material purchased from Aldrich Chemical Co., Inc. and Lancaster Synthesis, Inc. Spectral data of the 2-Bromo-1-naphthol was compared with spectral data of material prepared by literature methods.[11c] While all of the compounds in Table 1 are known,[11a-g] the ^{1}H NMR and IR spectral data which were not available in the literature are listed below.

*2-Iodo-6-methylphenol*[11d]
^{1}H NMR (300 MHz, $CDCl_3$): $\delta$ 2.30 (s, 3H), 5.28 (s, 1H), 6.57 (t, $J$ =7.8 Hz, 1H), 7.07 (d, $J$ =7.8 Hz, 1H), 7.47 (d, $J$ =7.8 Hz, 1H). IR (KBr): 3484 cm$^{-1}$.

*2-Iodo-3-methoxyphenol*[11e]
^{1}H NMR (300 MHz, $CDCl_3$): $\delta$ 3.87 (s, 3H), 5.48 (s, 1H), 6.39 (d, $J$ =8.2 Hz, 1H), 6.67 (d, $J$ =8.2 Hz, 1H), 7.18 (t, $J$ =8.2 Hz, 1H). IR (KBr): 3463 cm$^{-1}$.

*2-Bromo-3-methylphenol*[11f]
^{1}H NMR (300 MHz, $CDCl_3$): $\delta$ 2.39 (s, 3H), 5.60 (s, 1H), 6.80 (d, $J$ =7.7 Hz, 1H), 6.87 (d, $J$ =7.7 Hz, 1H), 7.10 (t, $J$ =7.7 Hz, 1H). IR (KBr): 3396 cm$^{-1}$.

*2-Bromo-3-methoxyphenol*[11g]
^{1}H NMR (300 MHz, $CDCl_3$): $\delta$ 3.879 (s, 3H), 5.68 (s, 1H), 6.47 (d, $J$ =8.2 Hz, 1H), 6.67 (d, $J$=8.2 Hz, 1H), 7.16 (t, $J$ =8.2 Hz, 1H). IR (KBr): 3489 cm$^{-1}$.

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6. An exception to this regioselectivity was found for the anisole derivative (R = MeO), where intermediate **3** was not obtained as a single isomer when TEB was used as the boron reagent.

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