





Density functional theory-supported studies of structural and electronic properties of substituted-phenol derivatives synthesized by efficient O- or C-arylation via Chan–Lam or Suzuki cross-coupling reactions

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Received: 18.01.2019

Accepted/Published Online: 25.07.2019

Final Version: 07.10.2019

Abstract: The present study reports the efficient synthesis and computational studies of the structural and electronic properties of some interesting substituted phenol derivatives. Efficient and versatile procedures to synthesize a series of diaryl ether derivatives (**2a–2c**, **4a–4h**) and bis-arylated products (**5a–5c**) are described. In this manuscript, using the commercially available starting material **1** and **3**, a 1-step approach was developed by means of Cu(II)-mediated Chan–Lam and Pd-catalyzed Suzuki cross-coupling reactions to synthesize diaryl ether and bis-arylated products with moderate to good yields. The starting substrates, 2-bromo-4-methylphenol **1** or 2,4-dibromophenol **3**, were both treated with several arylboronic acids, which led to the development of new carbon-oxygen bonds through Chan–Lam reactions. In addition, the hydroxyl group of 2,4-dibromophenol **3** was protected with isopropyl bromide to produce **4**, which was then treated with arylboronic acids to synthesize the corresponding bis-arylated products through Suzuki cross-coupling reactions. Density functional theory calculations provided insight into the structural and electronic properties of the synthesized compounds. An analysis of the frontier orbitals and other reactivity descriptors, including the ionization potential, electron affinity, chemical hardness, electronic chemical potential, and electrophilicity index, is presented, which shows that compound **4c** was the most reactive, while **4f** and **4h** were the most stable.

Key words: Diaryl ethers, bis-arylated derivatives, Chan–Lam reaction, Suzuki cross-coupling reaction, density functional theory

1. Introduction

Over the last few decades, transition metal-catalyzed coupling methods have been developed to make carbon-carbon and carbon-heteroatom connections [1–5]. In this regard, Cu-mediated cross-coupling reactions involving boronic acids are gaining attention [6–8]. Cu-promoted carbon-sulfur, carbon-oxygen, and carbon-nitrogen bond formations, via treatment of SH-, OH-, or NH- containing compounds and boronic acids (alkenyl or aryl) to produce the corresponding products (alkenylated or arylated), have been studied under Chan–Lam reactions [8]. Other Cu-mediated coupling reactions, such as the Ullmann–Goldberg reaction, required harsh conditions, like a strong base and very high temperature, to generate aryl ethers and aryl amines from aryl halides [9]. Among

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the other methods, the popularity of the Chan–Lam reaction has been due to the involvement of mild reaction conditions, such as a weak base, room temperature, or ambient atmosphere [10]. Moreover, in recent years, the palladium-promoted Suzuki cross-coupling reaction has also become an effective and powerful methodology to produce carbon-carbon bonds between arylboronic acids and aryl halides [11]. Both coupling methods are considered to be very useful due to mild reaction conditions, as well as the versatility and flexibility of the substrates, their ability to tolerate numerous functional groups, and good reaction yields [12].

It has been observed that polybrominated diphenyl ethers are widely used in industry as flame retardants in combustible things, such as building and textile materials, phone and computer sets, paints, electrical appliances, television sets, interior decoration in cars, plastics, and airplanes [13,14]. They are used to prevent the burning process of materials, with attention on minimizing losses and destruction due to fire. The bromine present in brominated diphenyl ethers reacts with oxidizing agents or free radicals and consequently prevents the ignition and burning process [15].

Based on the interesting and widely observed applications of diaryl ethers, the versatility of Chan–Lam reactions, and Suzuki cross-coupling reactions to generate O-arylated or bis-arylated products, the aim of the current study was to synthesize diaryl ether derivatives and bis-arylated products with moderate to good yields. Therefore, we report herein the facile synthesis of a series of diaryl ethers (**2a–2c**, **4a–4h**) and bis-arylated derivatives (**5a–5c**) via the treatment of 2-bromo-4-methylphenol or 2,4-dibromophenol with several arylboronic acids. In addition, density functional theory (DFT) calculations were performed to observe the structural and electronic properties of the synthesized compounds. The synthesized products were also characterized using spectroscopic techniques, such as ^1H NMR, ^{13}C NMR, and EI-MS.

2. Results and discussion

2.1. Chemistry

In 1998, Chan et al. described a novel and convenient methodology for the formation of diaryl ethers via the treatment of phenol with boronic acids, along with triethylamine as a base and copper(II) acetate as a catalyst in dichloromethane to obtain a good yield [10]. In the present research, applications of the Chan–Lam reaction were explored to synthesize new diaryl ether derivatives. First, synthesis commenced with commercially available 2-bromo-4-methylphenol **1** (1 equiv.), which was coupled with several arylboronic acids (1–2 equiv.) to afford the functionalized diaryl ether derivatives (**2a–2c**, Figure 1). To the best of our knowledge, Chan–Lam reactions of 2-bromo-4-methylphenol with arylboronic acids have not yet been reported. The reactions were carried out under mild conditions, such as at room temperature. These derivatives were synthesized as depicted in Scheme 1. These reactions were carried out in the presence of copper(II) acetate as a catalyst and triethylamine as a base in dichloromethane solvent. The newly synthesized diaryl ether products were obtained with good to excellent yields (Table 1). The synthesis of new derivatives was based on the procedure reported by Evans et al. [16]. As a result of these Cu-mediated 1-pot couplings, new C–O bonds were formed between the substituted phenol and arylboronic acids. The results of the present study have shown that the best yields of products were achieved when triethylamine was used as a base. Lam et al. reported that the yields of products are affected by the base, nature of the substrate, and arylboronic acids [17]. It was found here that the coupling reaction of electron-deficient 3-chloro-4-fluorophenylboronic acid with **1** resulted in corresponding product **2b** with the highest yield (92.0%).

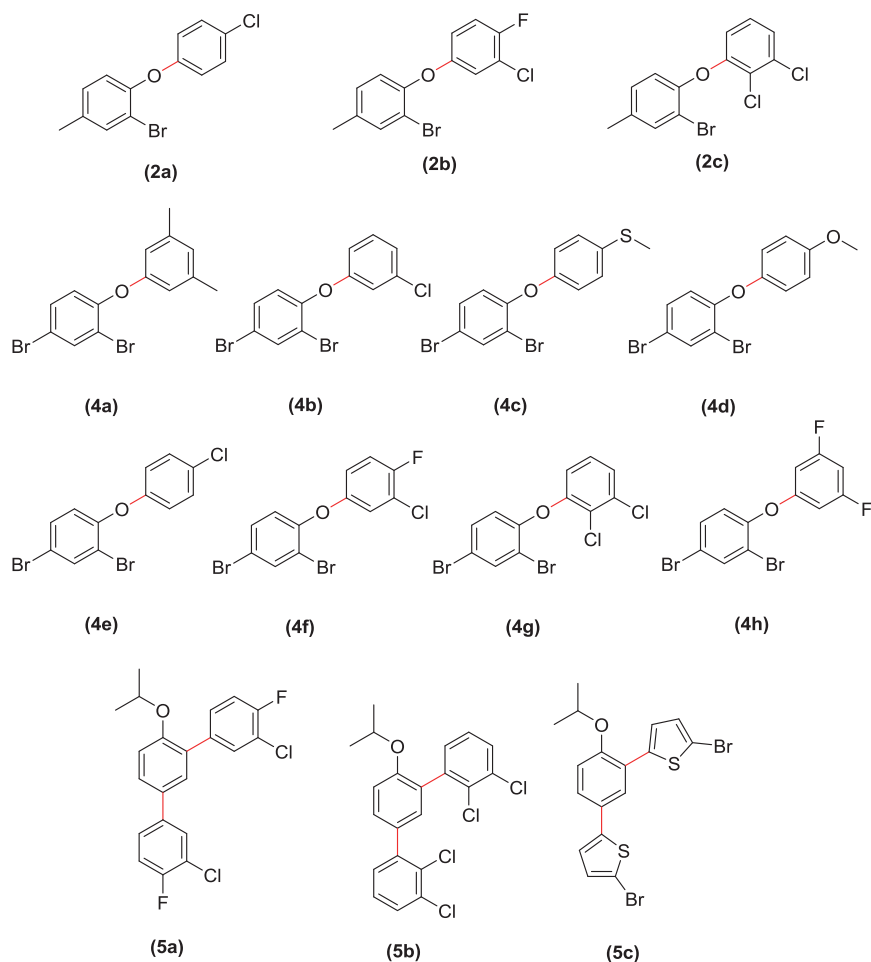
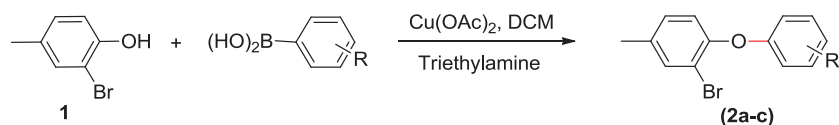


Figure 1. Synthesis of the diaryl ether derivatives (**2a–2c**, **4a–4h**) and bis-arylated derivatives (**5a–5c**).



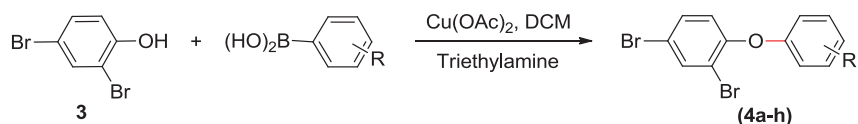
Scheme 1. Synthesis of the diaryl ether derivatives (**2a–2c**): **1** (1 equiv.), copper(II) acetate (1–1.5 equiv.), arylboronic acid (1–2 equiv.), Et_3N as a base (1–2 equiv.), DCM (10–12 mL), 24–72 h reflux, 25 °C.

Table 1. Synthesis of the diaryl ether derivatives (**2a–2c**).

Entry	Arylboronic acid	Product	Yield (%)
1	4-Chlorophenylboronic acid	2a	89.2
2	3-Chloro-4-fluorophenylboronic acid	2b	92.0
3	2,3-Dichlorophenylboronic acid	2c	86.4

Commercially available starting material 2,4-dibromophenol (**3**) was also utilized to synthesize new diaryl ether derivatives. Therefore, the Chan–Lam reactions of **3** with various arylboronic acids to synthesize the corresponding diaryl ether products (**4a–4h**, Figure 1) were employed. The reactions were carried out in

the presence of copper(II) acetate as a catalyst and triethylamine as a base to afford a series of novel diaryl ether derivatives. These coupling reactions were produced as illustrated in Scheme 2. These Chan–Lam reactions were carried out in a dichloromethane solvent at room temperature. Consequently, the desired diaryl ether derivatives were achieved in moderate to good yields. The arylboronic acids utilized for this coupling and the corresponding newly synthesized products are listed in Table 2. The results of the present study have shown that compound **4f** was obtained in excellent yield (90.3%) as a result of the coupling reaction between **3** and electron-deficient 3-chloro-4-fluorophenylboronic acid.



Scheme 2. Synthesis of the diaryl ether derivatives (**4a–4h**): **3** (1 equiv.), copper(II) acetate (1–1.5 equiv.), arylboronic acid (1–2 equiv.), Et₃N as base (1–2 equiv.), DCM (10–12 mL), 24–72 h reflux, 25 °C.

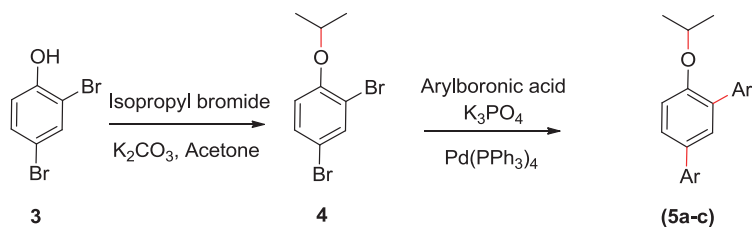
Table 2. Synthesis of the diaryl ether derivatives (**4a–4h**).

Entry	Arylboronic acid	Product	Yield (%)
1	3,5-Dimethylphenylboronic acid	4a	53.7
2	3-Chlorophenylboronic acid	4b	75.1
3	4-(Methylthio)phenyl boronic acid	4c	87.3
4	4-Methoxybenzeneboronic acid	4d	82.0
5	4-Chlorophenylboronic acid	4e	83.6
6	3-Chloro-4-fluorophenylboronic acid	4f	90.3
7	3,4-Dichlorophenylboronic acid	4g	85.9
8	3,5-Difluorophenylboronic acid	4h	72.6

In an attempt to investigate the Suzuki cross-coupling reactions of 2,4-dibromophenol (**3**) with arylboronic acids, the hydroxyl group of 2,4-dibromophenol was made to protect with isopropyl bromide to form 2,4-dibromo-1-isopropoxybenzene (**4**) through a previously reported method [18]. After protection, **4** was made to react with different arylboronic acids by application of the Suzuki cross-coupling reaction to obtain bis-arylated products (**5a–5c**), as shown in Figure 1. These reactions were accomplished in the presence of K₃PO₄, which was taken as a base, and Pd(PPh₃)₄ as a catalyst (Scheme 3). The newly synthesized products were obtained in moderate to good yields (Table 3). The catalyst Pd(PPh₃)₄ proved to be very important and effective in the Suzuki cross-coupling reaction. Its combination with the solvent, as well as the base, was extremely important for synthesizing the desired products. Hence, the reactions were carried out in 1,4-dioxane (solvent) with K₃PO₄ as the base at 90 °C [19,20].

2.2. Computational methods

Gaussian 09 software (Revision D.01; Gaussian Inc., Wallingford, CT, USA) [21] was used for all of the computations. DFT was implemented for all of the calculations by employing Adamo's hybrid version [22] of the Perdew, Burke, and Ernzerhof functional (PBE0) [23,24], together with the application of Grimme's empirical D3 correction with Becke–Johnston damping (D3BJ) [25–27]. All of the calculations were performed



Scheme 3. Synthesis of the bis-arylated derivatives (**5a–5c**): **4** (0.1 g, 0.340 mmol), Pd(PPh₃)₄ (5 mol%), arylboronic acid (2.5 equiv.), K₃PO₄ (2 equiv.), 1,4-dioxane (4 mL) : water (1 mL), 12 h reflux, 90 °C.

Table 3. Synthesis of the bis-arylated products (**5a–5c**).

Entry	Arylboronic acid	Product	Yield (%)
1	3-Chloro-4-fluorophenylboronic acid	5a	43.7
2	2,3-Dichlorophenylboronic acid	5b	46.2
3	5-Bromo-2-thienylboronic acid	5c	65.8

with Ahlrich's triplet ζ basis set Def2-TZVP [28] aided by the polarizable continuum model (PCM) with the integral equation formalism variant (IEFPCM) [29–35] for solvation modeling. The solvent used for the diaryl ethers (**2a–2c**, **4a–4h**) was dichloromethane, while for the bis-arylated derivatives (**5a–5c**), it was 1,4-dioxane, whose effects were modeled with the SMD parameter set of Cramer and Truhlar [36] (as implemented in Gaussian 09) [21]. All of the optimized structures were confirmed to be minima on the potential energy surface at the PBE0-D3BJ/def2-TZVP/SMD_{1,4-dioxane} level by calculating the harmonic force constants, which showed the absence of imaginary frequencies. Frontier molecular orbital (FMO) calculations were performed at the same level of theory as the optimizations. The 3D images of optimized molecules were drawn using GaussView 5.0.9 (Gaussian Inc.) and CYLview software[37].

2.3. Results and discussion

All of the structures, including the diaryl ether derivatives (**2a–2c**, **4a–4h**, Figure 2) and bis-arylated derivatives (**5a–5c**, Figure 3), were subjected to optimizations at the PBE0-D3BJ/def2-TZVP/SMD_{1,4-dioxane} level of theory followed by frequency calculations to confirm the structures as true minima on the PES with no imaginary frequencies.

2.4. FMO analysis

With the advancements in DFT, FMO analysis serves as a very important tool to explain the electronic properties of molecules and their reactivity [38]. FMOs (HOMO/LUMO) are mainly responsible for electronic transitions and the HOMO-LUMO energy gap explains the reactivity and kinetic stability of the compounds [39]. The lower this energy gap is, the more reactive the compound is, and vice versa. The FMO analysis was performed at the same level of theory as the optimizations of the molecules and the plots of these orbitals are shown in Figures 4 and 5.

Table 4 lists the HOMO-LUMO gap values (ΔE) of all of the compounds under study. The ΔE values of the molecules ranged from 6.54 to 7.40 eV. This narrow range of ΔE values with high values showed that most of these compounds were generally quite stable and less reactive. Compounds 4f and 4h had the highest ΔE values of all the compounds, which made them highly stable compounds when compared to the others. On

the other hand, 4c and 4a had the lowest ΔE values, which showed that these would be the most reactive in the series under study.

The isodensity dispersion in the frontier orbitals showed a more or less similar trend for all of the compounds, except for 4c. For all of the other compounds, the isodensity was located on the phenyl rings. For 4c, where the SMe group was attached on the phenyl ring, the HOMO isodensity was shifted onto the SMe group at the phenyl ring. That also explained it having the lowest ΔE value and more reactivity than the rest of the molecules in the series, which was evident from the other reactivity descriptor values.

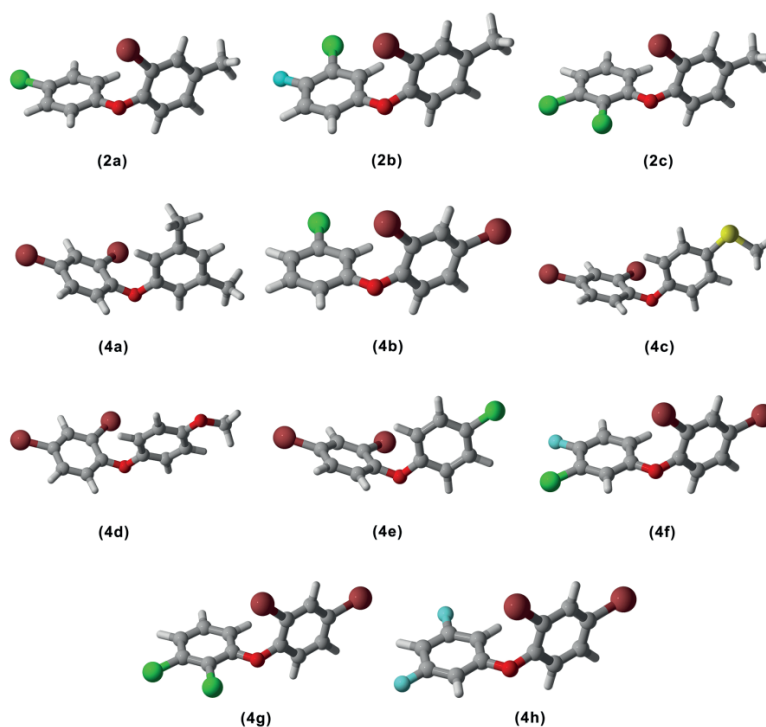


Figure 2. Optimized structures of the diaryl ethers (2a–2c, 4a–4h) at the PBE0-D3BJ/def2-TZVP/SMD_{1,4-dioxane} level of theory. In the 3D models, the color gray represents carbon, white represents hydrogens, green is for the chlorine atoms, brown represents the bromine atoms, red is for oxygen, and light blue shows the fluorine atoms.

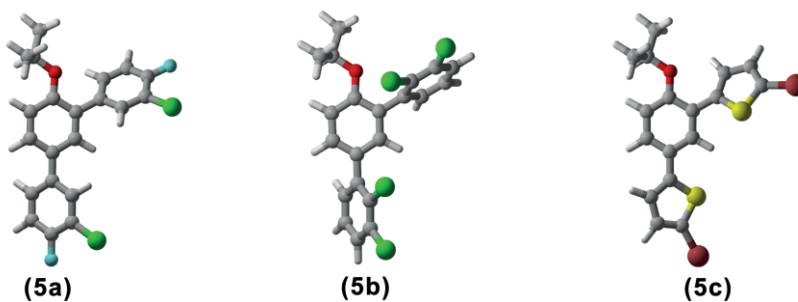


Figure 3. Optimized structures of the bis-arylated derivatives (5a–5c) at the PBE0-D3BJ/def2-TZVP/SMD_{1,4-dioxane} level of theory. In the 3D models, gray represents carbon, white represents hydrogens, green is for the chlorine atoms, red is for oxygen, brown represents the bromine atoms, yellow represents sulfur, and light blue shows the fluorine atoms.

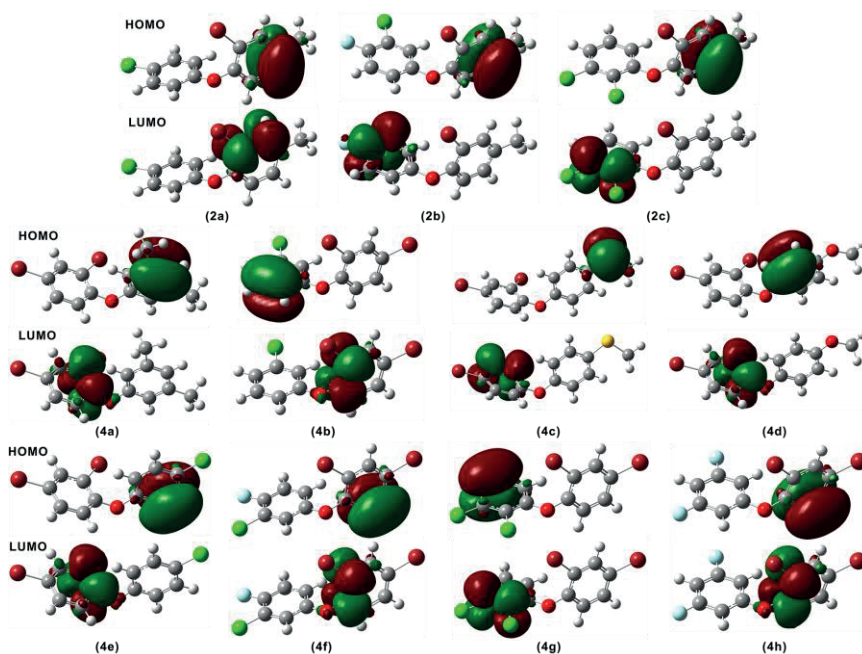


Figure 4. A plot of the frontier orbitals of molecules (2a–2c, 4a–4h) calculated at the PBE0-D3BJ/def2-TZVP/SMD_{1,4-dioxane} level of theory.

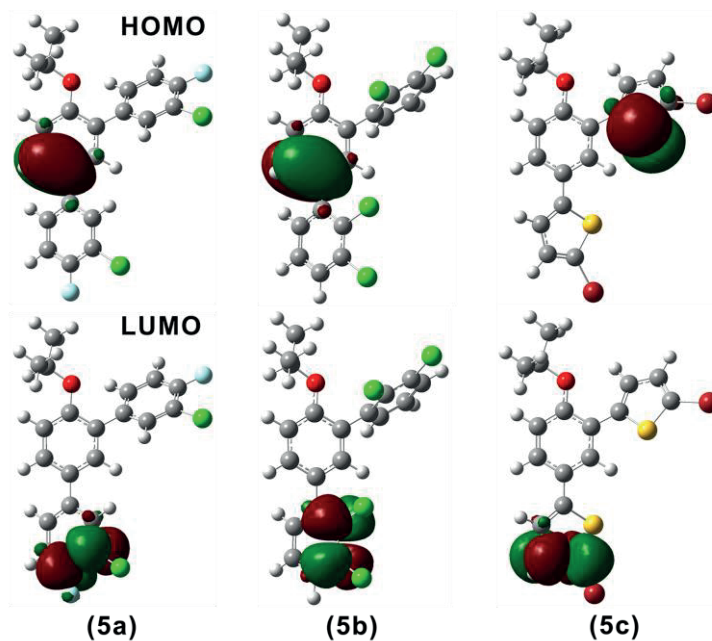


Figure 5. Plot of the frontier orbitals of molecules (5a–5c) calculated at the PBE0-D3BJ/def2-TZVP/SMD_{1,4-dioxane} level of theory.

2.5. Conceptual DFT reactivity descriptors

The conceptual DFT reactivity descriptors are very important for explaining the reactivity of a compound. These include the ionization potential (I), electron affinity (A), chemical hardness (η), electronic chemical

Table 4. Energies of HOMO, LUMO, and the gap between HOMO-LUMO. All energies are given in eV.

Compound	E_{HOMO}	E_{LUMO}	HOMO-LUMO gap
2a	-7.26	-0.20	7.06
2b	-7.28	-0.19	7.09
2c	-7.30	-0.45	6.86
4a	-6.85	-0.19	6.66
4b	-7.38	-0.34	7.04
4c	-6.66	-0.12	6.54
4d	-7.22	-0.19	7.03
4e	-7.45	-0.34	7.11
4f	-7.80	-0.39	7.40
4g	-7.51	-0.55	6.97
4h	-7.80	-0.41	7.39
5a	-7.12	-0.23	6.89
5b	-7.11	-0.40	6.71
5c	-7.08	-0.01	7.07

potential (μ), and electrophilicity index (ω) [40], which were calculated for the given compounds. According to Koopman's theorem for closed-shell compounds, the ionization potential (I) and electron affinity (A) correspond to the negativity of E_{HOMO} and E_{LUMO} , respectively [40,41]. The rest of the above stated properties can easily be calculated from these 2, as follows:

$$\eta = (E_{HOMO} - E_{LUMO})/2 \quad (1)$$

$$\mu = -(E_{HOMO} + E_{LUMO})/2 \quad (2)$$

$$\omega = \mu^2/2\eta \quad (3)$$

Here, Eq. (1) shows the calculation of the chemical hardness, which is expressed as half of the HOMO-LUMO energy gap, while the electronegativity or electronic chemical potential of the compounds is the average of I and A shown in Eq. (2). Next, Eq. (3) is used to calculate the electrophilicity index from the former 2 properties. The values of all of the important reactivity descriptors of the compounds under study are given in Table 5.

By looking at Table 5 in detail, it becomes clear that different reactivity descriptors support each other and thus strengthen the findings. According to the ΔE values discussed in the previous section, compounds **4f** and **4h** were the most stable compounds, which was supported by their highest ionization potential, chemical hardness, and electrophilicity index values. On the other hand, compound **4c** had the lowest ionization potential, chemical hardness, and electrophilicity index values, while having the highest electronegativity value. This showed that **4c** should be the most reactive compound in the series, which was also in line with the findings from the FMO analysis. Thus, the speed of reaction for compound **4c** should be much greater than that of **4f** and **4h**, which would react slowly due to the larger HOMO-LUMO gap.

Table 5. Ionization potential (I), electron affinity (A), chemical hardness (η), electronic chemical potential (μ), and electrophilicity index (ω) of the compounds under study.

Compound	Ionization potential, I (eV)	Electron affinity, A (eV)	Chemical hardness, η (eV)	Electronic chemical potential, μ (eV)	Electrophilicity index, ω (eV)
2a	7.26	0.20	3.53	-3.73	1.97
2b	7.28	0.19	3.55	-3.73	1.96
2c	7.30	0.45	3.43	-3.87	2.19
4a	6.85	0.19	3.33	-3.52	1.86
4b	7.38	0.34	3.52	-3.86	2.12
4c	6.66	0.12	3.27	-3.39	1.76
4d	7.22	0.19	3.51	-3.70	1.95
4e	7.45	0.34	3.56	-3.90	2.13
4f	7.80	0.39	3.70	-4.09	2.26
4g	7.51	0.55	3.48	-4.03	2.33
4h	7.80	0.41	3.70	-4.11	2.28
5a	7.12	0.23	3.44	-3.68	1.96
5b	7.11	0.40	3.36	-3.75	2.10
5c	7.08	0.01	3.54	-3.54	1.78

3. Experimental

All of the reagents were purchased from Sigma Aldrich (Sigma, St. Louis, MO, USA), Alfa Aesar (Alfa Aesar Chemicals, Ward Hill, MA, USA), and Merck (Merck KGaA, Darmstadt, Germany). They were utilized as received, without any purification. A Büchi B-540 melting point apparatus (Merck KGaA) was used to measure the melting points of the newly synthesized derivatives. The ^{13}C and ^1H NMR data were obtained using a CDCl_3 on a Bruker Aspect AM-400 spectrometer (Bruker Corp., Billerica, MA, USA) at 500 MHz, and TMS was taken as the internal standard. The coupling constant values were given in Hz. EI-MS data were obtained using a JMS-HX-110 spectrometer (JEOL Ltd., Akishima, Tokyo, Japan). The newly synthesized products were examined with an ultraviolet lamp at a wavelength ranging from 254 to 365 nm. The newly synthesized products were monitored with an ultraviolet lamp at wavelengths from 254 to 365 nm.

3.1. General procedure for the synthesis of compounds 2a–2c

The weighed amount of starting substrate 2-bromo-4-methylphenol **1** (1 equiv.) and arylboronic acids (1–2 equiv.) was placed into a dried round-bottomed flask (250 mL). To the above mixture was added $\text{Cu}(\text{OAc})_2$ (1–1.5 equiv.) and triethylamine (1–2 equiv.), along with a magnetic stirrer and 4 Å molecular sieves (MSs). The solvent dichloromethane (10–12 mL) was mixed with the reaction mixture at 25 °C for about 24–72 h. Over time, thin-layer chromatography (TLC) was applied to examine the reaction progress. After completion of the reaction, the above mixture was filtered, and the desired diaryl ethers were separated and purified using column chromatography [16].

3.1.1. 2-Bromo-1-(chlorophenoxy)-4-methylbenzene (2a)

A colorless crystalline solid. Yield: 89%; mp 242 °C. C₁₃H₁₀BrClO (requires: C, 52.47; H, 3.41; found: C, 52.35; H, 3.38%). ¹H NMR (CDCl₃) δ = 7.57 (d, *J* = 7.21, 2H-Ph), 7.49 (d, *J* = 7.32, 2H-Ph), 7.34 (d, *J* = 7.49, 1H-Ph), 7.13 (d, *J* = 7.51, 1H-Ph), 6.91 (d, *J* = 7.45, 1H-Ph), 2.29 (s, 3H-Me). ¹³C NMR (CDCl₃) δ = 155.54, 150.57, 137.40, 133.27, 128.91, 127.65, 121.55, 119.17, 117.98, 113.56, 20.13. EI-MS *m/z*(+ion mode): 297.96: [M - Br]⁺ = 218.06: [M - CH₃]⁺ = 203.06: [M - C₆H₃O]⁺ = 110.86: [M - Cl]⁺ = 75.05.

3.1.2. 2-Bromo-1-(3-chloro-4-fluorophenoxy)-4-methylbenzene (2b)

A yellowish solid. Yield: 92%; mp 251–253 °C. C₁₃H₉BrClFO (requires: C, 49.48; H, 2.87; found: C, 49.39; H, 2.75%). ¹H NMR (CDCl₃) δ = 7.34 (d, *J* = 7.49, 1H-Ph), 7.32 (dd, *J* = 7.48, 1.52, 1H-Ph), 7.31 (dd, *J* = 5.0, 1.54, 1H-Ph), 7.14 (dd, *J* = 7.99, 7.49, 1H-Ph), 7.13 (d, *J* = 7.43, 1H-Ph), 7.11 (d, *J* = 7.52, 1H-Ph), 2.30 (s, 3H-Me). ¹³C NMR (CDCl₃) δ = 154.21, 151.96, 150.57, 137.40, 133.27, 128.90, 121.55, 120.05, 119.15, 118.45, 116.71, 113.56, 20.13. EI-MS *m/z*(+ion mode): 315.95: [M - Br]⁺ = 237.03: [M - CH₃]⁺ = 222.01: [M - C₆H₃O]⁺ = 130.99.

3.1.3. 1-(2-Bromo-4-methylphenoxy)-2,3-dichlorobenzene (2c)

A white crystalline solid. Yield: 86.4%; mp 264 °C. C₁₃H₉BrCl₂O (requires: C, 47.03; H, 2.70; found: C, 46.90; H, 2.59%). ¹H NMR (CDCl₃): δ = 7.49 (dd, *J* = 7.48, 1.49, 1H-Ph), 7.29 (d, *J* = 7.49, 1H-Ph), 7.23 (t, *J* = 7.47, 1H-Ph), 7.13 (d, *J* = 7.44, 1H-Ph), 6.96 (dd, *J* = 7.48, 1.46, 1H-Ph), 6.88 (d, *J* = 7.54, 1H-Ph), 2.28 (s, 3H-Me). ¹³C NMR (CDCl₃): δ = 152.79, 150.75, 137.40, 134.94, 133.30, 128.86, 128.00, 126.25, 125.19, 121.58, 118.18, 113.58, 20.13. EI-MS *m/z*(+ion mode): 331.92: [M - Br]⁺ = 251.0: [M - CH₃]⁺ = 235.98: [M - C₆H₃O]⁺ = 144.96: [M - 2Cl]⁺ = 75.02.

3.2. General procedure for the synthesis of compounds 4a–4h

A weighed amount of 2,4-dibromophenol **3** (1 equiv.) and arylboronic acids (1–2 equiv.) were added to a 250-mL round-bottomed flask. Copper(II) acetate (1–1.5 equiv.), triethylamine (1–2 equiv.), a magnetic stirrer, and 4 Å MSs were also added to the above mixture. The dichloromethane (10–12 mL) solvent was then mixed with it at 25 °C for about 24–72 h. TLC was applied to monitor the progress of the reaction. The reaction mixture was filtered and the diaryl ether products were separated and purified using column chromatography [16].

3.2.1. 2,4-Dibromo-1-(3,5-dimethylphenoxy)benzene (4a)

A colorless solid. Yield: 53.7%; mp 271–273 °C. C₁₄H₁₂Br₂O (requires: C, 47.19; H, 3.39; found: C, 47.13; H, 3.29%). ¹H NMR (CDCl₃): δ = 7.96 (s, 1H-Ph), 7.45 (dd, *J* = 7.41, 1.46, 1H-Ph), 7.11 (d, *J* = 1.49, 1H-Ph), 6.97 (s, 1H-Ph), 6.89 (d, *J* = 7.49, 1H-Ph), 2.31 (s, 6H-Me). ¹³C NMR (CDCl₃): δ = 155.36, 152.17, 139.55, 136.26, 131.86, 125.97, 121.84, 116.19, 115.25, 21.34. EI-MS *m/z*(+ion mode): 356.05: [M - 2Br]⁺ = 196.09: [M - C₆H₃O]⁺ = 105.07: [M - 2CH₃]⁺ = 75.03.

3.2.2. 2,4-Dibromo-1-(3-chlorophenoxy)benzene (4b)

A colorless crystalline solid. Yield: 75%; mp 273 °C. C₁₂H₇Br₂ClO (requires: C, 39.77; H, 1.95; found: C, 39.66; H, 1.86%). ¹H NMR (CDCl₃): δ = 7.96 (s, 1H-Ph), 7.51 (dd, *J* = 7.4, 1.45, 1H-Ph), 7.43 (s, 1H-Ph), 7.40 (m, 1H-Ph), 7.19 (t, *J* = 7.5, 1H-Ph), 7.02 (m, 1H-Ph), 6.92 (d, *J* = 7.47, 1H-Ph). ¹³C NMR (CDCl₃): δ = 156.87, 152.0, 136.26, 135.21, 131.86, 130.54, 122.36, 118.13, 117.09, 115.95, 114.05, 112.11. EI-MS *m/z*(+ion mode): 361.85: [M - 2Br]⁺ = 202.02: [M - C₆H₃O]⁺ = 122.0: [M - Cl]⁺ = 76.02.

3.2.3. 4-(2,4-Dibromophenoxy)phenyl(methyl)sulfane (4c)

A yellowish crystalline solid. Yield: 87%; mp 278 °C. C₁₃H₁₀Br₂OS (requires: C, 41.69; H, 2.71; found: C, 41.66; H, 2.58%). ¹H NMR (CDCl₃): δ = 7.96 (s, 1H-Ph), 7.53 (d, *J* = 7.4, 1H-Ph), 7.29 (d, *J* = 7.5, 2H-Ph), 7.27 (d, *J* = 7.48, 2H-Ph), 6.92 (d, *J* = 7.45, 1H-Ph), 2.53 (s, 3H-Me). ¹³C NMR (CDCl₃): δ = 155.08, 151.59, 134.89, 134.01, 131.86, 128.10, 121.62, 120.46, 116.19, 115.84, 15.72. EI-MS *m/z*(+ion mode): 373.88: [M - 2Br]⁺ = 214.05: [M - C₆H₃O]⁺ = 123.20: [M - SCH₃]⁺ = 76.03.

3.2.4. 2,4-Dibromo-1-(4-methoxyphenoxy)benzene (4d)

A colorless crystalline solid. Yield: 82%; mp 275 °C. C₁₃H₁₀Br₂O₂ (requires: C, 43.61; H, 2.82; found: C, 43.53; H, 2.73%). ¹H NMR (CDCl₃): δ = 7.96 (s, 1H-Ph), 7.55 (dd, *J* = 7.4, 1.47, 1H-Ph), 7.35 (d, *J* = 7.5, 2H-Ph), 7.27 (d, *J* = 7.51, 2H-Ph), 6.92 (d, *J* = 7.48, 1H-Ph), 2.83 (s, 3H-Me). ¹³C NMR (CDCl₃): δ = 157.03, 153.01, 152.62, 136.26, 131.86, 121.62, 119.20, 116.19, 115.84, 115.05, 55.35. EI-MS *m/z*(+ion mode): 357.90: [M - 2Br]⁺ = 198.07: [M - C₆H₃O]⁺ = 107.05: [M - OCH₃]⁺ = 76.01.

3.2.5. 2,4-Dibromo-1-(4-chlorophenoxy)benzene (4e)

A crystalline yellowish solid. Yield: 83.6%; mp 280 °C. C₁₂H₇Br₂ClO (requires: C, 39.77; H, 1.95; found: C, 39.65; H, 1.85%). ¹H NMR (CDCl₃): δ = 7.96 (s, 1H-Ph), 7.56 (dd, *J* = 7.41, 1.48, 1H-Ph), 7.53 (dd, *J* = 7.49, 1.45, 2H-Ph), 7.50 (dd, *J* = 7.4, 1.46, 2H-Ph), 6.92 (d, *J* = 7.52, 1H-Ph). ¹³C NMR (CDCl₃): δ = 155.54, 149.62, 135.26, 130.86, 129.51, 121.63, 119.17, 116.19, 115.84, 112.11. EI-MS *m/z*(+ion mode): 361.85: [M - 2Br]⁺ = 202.02: [M - C₆H₃O]⁺ = 111.0: [M - Cl]⁺ = 76.03.

3.2.6. 2,4-Dibromo-1-(3-chloro-4-fluorophenoxy)benzene (4f)

A yellowish crystalline solid. Yield: 90.35%; mp 286 °C. C₁₂H₆Br₂ClFO (requires: C, 37.86; H, 1.57; found: C, 37.73; H, 1.45%). ¹H NMR (CDCl₃): δ = 7.96 (s, 1H-Ph), 7.54 (dd, *J* = 7.4, 1.45, 1H-Ph), 7.32 (d, *J* = 5.15, 2H-Ph), 7.29 (dd, *J* = 7.51, 1.49, 1H-Ph), 7.19 (d, *J* = 7.90, 1H-Ph), 6.92 (d, *J* = 7.48, 1H-Ph). ¹³C NMR (CDCl₃): δ = 155.01, 153.9, 151.1, 136.41, 129.67, 123.21, 119.4, 118.38, 116.67, 115.99, 115.01, 113.89. EI-MS *m/z*(+ion mode): 379.84: [M - 2Br]⁺ = 219.03: [M - C₆H₃O]⁺ = 128.53.

3.2.7. 1,2-Dichloro-3-(2,4-dibromophenoxy)benzene (4g)

An orange-colored solid. Yield: 85.9%; mp 290–292 °C. C₁₂H₆Br₂Cl₂O (requires: C, 36.29; H, 1.49; found: C, 36.18; H, 1.38%). ¹H NMR (CDCl₃): δ = 7.96 (s, 1H-Ph), 7.50 (dd, *J* = 7.42, 1.49, 1H-Ph), 7.43 (dd, *J* = 7.47, 1.48, 1H-Ph), 7.23 (t, *J* = 7.5, 1H-Ph), 6.96 (dd, 7.47, 1.46, 1H-Ph), 6.92 (d, *J* = 7.49, 1H-Ph).

^{13}C NMR (CDCl_3): $\delta = 152.79, 152.26, 135.97, 134.94, 132.82, 128.00, 126.25, 125.19, 121.30, 118.18, 116.19, 115.73$. EI-MS m/z (+ion mode): 395.82: $[\text{M} - 2\text{Br}]^+ = 235.96$: $[\text{M} - \text{C}_6\text{H}_3\text{O}]^+ = 144.91$: $[\text{M} - 2\text{Cl}]^+ = 75.03$.

3.2.8. 2,4-Dibromo-1-(3,5-difluorophenoxy)benzene (4h)

A colorless crystalline solid. Yield: 72.6%; mp 270 °C. $\text{C}_{12}\text{H}_6\text{Br}_2\text{F}_2\text{O}$ (requires: C, 39.57; H, 1.64; found: C, 39.49; H, 1.55%). ^1H NMR (CDCl_3): $\delta = 8.40$ (d, $J = 1.49$, 1H-Ph), 7.96 (s, 1H-Ph), 7.51 (dd, $J = 7.43, 1.47$, 1H-Ph), 7.42 (d, $J = 1.5$, 2H-Ph), 6.92 (d, $J = 7.51$, 1H-Ph). ^{13}C NMR (CDCl_3): $\delta = 164.25, 160.31, 152.17, 136.26, 131.86, 121.84, 116.19, 115.44, 101.31, 97.89$. EI-MS m/z (+ion mode): 363.84: $[\text{M} - 2\text{Br}]^+ = 204.01$: $[\text{M} - \text{C}_6\text{H}_3\text{O}]^+ = 113.01$: $[\text{M} - 2\text{F}]^+ = 75.01$.

3.3. General procedure for the synthesis of compound 4

2,4-Dibromophenol **3** (0.1 g or 1 equiv.) and isopropyl bromide (1.2–2.7 equiv.) were placed into a dried Schlenk flask. K_2CO_3 (2–4 equiv.) and acetone (3 mL) were also added to it. The above mixture was refluxed while the temperature of the flask was maintained at 80 °C until completion of the reaction. TLC was used to examine the progress of the reactions. After lowering the temperature to about 25 °C, the excess amount of solvent was removed through vacuum distillation. The residue obtained was mixed with distilled water and the extraction was done via the addition of methylene chloride. Anhydrous magnesium sulfate was used to dry the separated organic layer. After filtration and evaporation, flash chromatography was employed to purify the desired product [18].

3.4. General procedure for the synthesis of compounds 5a–5c

Added to a 250-mL dried Schlenk flask were 2,4-dibromo-1-isopropoxybenzene **4** (0.1 g or 0.340 mmol), tetrakis(triphenylphosphine)palladium(0) (5 mol%) along with a magnetic stirrer, and 1,4-dioxane (4 mL). The mixture was enclosed with a Teflon septum and stirred at about room temperature for 30 min. Arylboronic acid (2.5 equiv.), potassium phosphate (2 equiv.), and 1 mL of distilled water were also added to the above mixture under an inert argon atmosphere for 12 h at approximately 90 °C. After completion of the reaction, the resulting crude mixture was cooled to about 25 °C and diluted with $\text{C}_2\text{H}_5\text{COOCH}_3$, and the organic layer was separated. The impure product was purified using column chromatography [42–45].

3.4.1. 3,3''-Dichloro-4,4''difluoro-4'-isopropoxy-1,1',3',1''-terphenyl (5a)

A colorless crystalline solid. Yield: 43.7%; mp 287 °C. $\text{C}_{21}\text{H}_{16}\text{Cl}_2\text{F}_2\text{O}$ (requires: C, 64.12; H, 4.11; found: C, 64.03; H, 4.02%). ^1H NMR (CDCl_3): $\delta = 7.95$ (s, 1H-Ph), 7.90 (s, 1H-Ph), 7.64 (d, $J = 7.48$, 1H-Ph), 7.59 (s, 1H-Ph), 7.30 (d, $J = 7.52$, 1H-Ph), 7.27 (d, $J = 7.45$, 1H-Ph), 7.23 (dd, $J = 8.02, 7.49$, 1H-Ph), 7.20 (dd, $J = 7.95, 7.41$, 1H-Ph), 7.11 (d, $J = 7.49$, 1H-Ph), 4.69 (m, 1H-CH), 1.35 (d, $J = 6.79$, 6H-Me). ^{13}C NMR (CDCl_3): $\delta = 157.51, 153.13, 137.22, 133.35, 129.91, 129.04, 128.31, 126.62, 125.90, 121.61, 117.21, 115.73, 76.21, 22.76$. EI-MS m/z (+ion mode): 392.02: $[\text{M} - \text{C}_3\text{H}_7\text{O}]^+ = 333.0$: $[\text{M} - \text{C}_6\text{H}_3\text{ClF}]^+ = 204.05$: $[\text{M} - \text{C}_6\text{H}_3\text{ClF}]^+ = 75.07$.

3.4.2. 2,2'',3,3''-Tetrachloro-4-isopropoxy-1,1',3',1''-terphenyl (5b)

A colorless crystalline solid. Yield: 46.2%; mp 298 °C. C₂₁H₁₆Cl₄O (requires: C, 59.17; H, 3.77; found: C, 59.06; H, 3.67%). ¹H NMR (CDCl₃): δ = 7.78 (d, *J* = 7.47, 1H-Ph), 7.71 (d, *J* = 7.48, 1H-Ph), 7.64 (d, *J* = 7.46, 1H-Ph), 7.63 (d, *J* = 7.41, 1H-Ph), 7.59 (d, *J* = 7.51, 1H-Ph), 7.54 (s, 1H-Ph), 7.36 (t, *J* = 7.49, 1H-Ph), 7.30 (t, *J* = 7.47, 1H-Ph), 4.61 (m, 1H-CH), 1.31 (d, *J* = 6.70, 6H-Me). ¹³C NMR (CDCl₃): δ = 153.45, 142.62, 138.39, 133.68, 131.38, 129.61, 128.20, 127.97, 127.01, 126.79, 126.02, 115.71, 76.30, 22.11. EI-MS *m/z*(+ion mode): 425.96: [M - C₃H₇O]⁺ = 366.91: [M - 4Cl]⁺ = 225.02: [M - 2C₆H₃]⁺ = 75.03.

3.4.3. 5,5'-(4-Isopropoxy-1,3-phenylene)bis(2-bromothiophene) (5c)

A yellowish crystalline solid. Yield: 65.8%; mp 305 °C. C₁₇H₁₄Br₂OS₂ (requires: C, 44.54; H, 3.05; found: C, 44.48; H, 3.01%). ¹H NMR (CDCl₃): δ = 7.58 (d, *J* = 7.47, 1H-Ph), 7.55 (s, 1H-Ph), 7.49 (d, *J* = 7.47, 1H-thiophene), 7.41 (d, *J* = 7.45, 1H-thiophene), 7.23 (d, *J* = 7.45, 1H-thiophene), 7.18 (d, *J* = 7.49, 1H-thiophene), 7.06 (d, *J* = 7.44, 1H-Ph), 4.59 (m, 1H-CH), 1.33 (d, *J* = 6.71, 6H-Me). ¹³C NMR (CDCl₃): δ = 153.91, 140.69, 131.33, 129.12, 128.23, 126.12, 125.89, 122.39, 115.62, 111.91, 76.51, 22.3. EI-MS *m/z*(+ion mode): 457.85: [M - C₃H₇O]⁺ = 398.81: [M - 2Br]⁺ = 239.1: [M - 2Thiophene]⁺ = 75.04.

4. Conclusion

A series of Chan–Lam reactions of 2-bromo-4-methylphenol **1** and 2,4-dibromophenol **3** with various arylboronic acids were studied at 25 °C in the presence of a copper(II) acetate Cu(OAc)₂ catalyst, Et₃N as a base, and dichloromethane as a solvent to form diaryl ether derivatives (**2a–2c**, **4a–4h**). The newly synthesized products were obtained in moderate to good yields. A series of Suzuki cross-coupling reactions were also performed to produce bis-arylated products. In order to synthesize the desired bis-arylated products, 2,4-dibromophenol was protected with isopropyl bromide using acetone and K₂CO₃. The protected substrate was made to react with different arylboronic acids utilizing Pd (PPh₃)₄ as catalyst and K₃PO₄ as base. The synthesized derivatives were obtained in moderate yields. DFT calculations provided insight into the structural and electronic properties of the synthesized compounds. An analysis of the frontier orbitals and other reactivity descriptors, including the ionization potential, electron affinity, chemical hardness, electronic chemical potential, and electrophilicity index, showed that compound **4c** was the most reactive, while **4f** and **4h** were the most stable.

Acknowledgments

The present data were a part of the M.Phil. thesis research work of Muhammad Arfan Anjum. Additional computer time was provided by the Victoria University of Wellington High Performance Computer Facilities SciFacHPC and Heisenberg.

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