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Research Article
doi.org/10.1002/slct.202200861

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Efficient Synthesis of 4-Bromo-*N*-(1-phenylethyl)benzamide, Arylation by Pd(0) Catalyst, Characterization and DFT Study

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The (*S*)-4-bromo-*N*-(1-phenylethyl)benzamide (**3**) was synthesized in excellent yield (93%) by the reaction of 4-bromobenzoic acid (**1**) and (*S*)-1-phenylethanamine (**2**) with the coupling reagent titanium tetrachloride ($TiCl_4$). Further, the Pd(0) catalyst was employed to form (*S*)-4-bromo-*N*-(1-phenylethyl)benzamide analogues (**5a-i**) by reacting various aryl boronic acids with 4-bromo-*N*-(1-phenylethyl)benzamide (**3**) in moderate to good yields (62-89%). Furthermore, DFT studies were carried out to compute optimized geometries, frontier molecular orbitals, polarizability (α), hyperpolarizability (β), MESP, reactivity descriptors, and NMR spectra. The measured NMR values matched the experimental NMR values well. In this series (**5a-i**), we predicted that the highest energy difference between the HOMO-LUMO of compound (**5a**) has 4.98 eV, resulting in a more stable compound, and compound (**5g**) has the lowest energy difference between the HOMO-LUMO 4.63 eV, resulting in the least stable compound. Compound (**5h**) has the highest hyperpolarizability (β) value, exhibits a better non-linear optical (NLO) behaviour compared as compare to other synthesized compounds in the series.

Introduction

Amide is an important class of compounds in the chemistry of peptides, agrochemicals, drug molecules and organic material.[1] The compounds containing a benzamide moiety possess a vast spectrum of biological activities such as anticancer, antimicrobial, antiinflammatory, antianalgesic, antimalarial, antiHIV and antidiabetic.[2–7] Traditionally, the majority of amide synthesis is based on the condensation of carboxylic acids or derivatives with amines or anilines.[8,9] Previously, it was developed the amidation of C–H bond by the reaction of 4-bromobenzamide with ethylbenzene to form (*S*)-4-bromo-*N*-(1-phenylethyl)benzamide (**3**).[10,11] Similarly, Gawande and his coworkers developed the synthesis of the compound (**3**) by the reaction of 1-phenylethanol and 4-bromobenzonitrile in the presence of nano-catalyst $FeOSO_3H$ in a solvent free environment.[12] In past, there is a lot of work in which amide is formed by the activated carboxylic acid like acid chloride or anhydride with amines or anilines.[13–16] The direct amidation is used to its low environmental impact by condensing non-activated carboxylic acid and amines or anilines. It was used metal based catalysis such as Zr(IV), Ti(IV) and Ta(V) instead of coupling reagents in direct amide preparations for excellent yields.[17,18] The researchers observed the oxophillic character of transition metal Titanium towards carboxylic acid and amine.[19] Our group has previously reported the synthesis of various amide arylated derivatives via Pd(0) catalyzed Suzuki-Miyaura cross-coupling, as well as computational studies on these derivatives.[20–25] Experimental studies have been computationally integrated with Density Functional Theory (DFT) calculations. Currently, density functional theory (DFT) is commonly used to examine the electronic structure of complex molecules. It meets the requirements of accuracy, ease of use and speed to allow the study of relatively large molecules.[26]

In this study, we did the synthesis of benzamide through the direct amidation of secondary amine and carboxylic acid in

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202200861

the presence of titanium (IV) chloride with 93% yield in the presence of pyridine. Furthermore, the arylation of synthesized amide was done by Pd(0) catalyzed Suzuki-Miyaura reaction. Subsequently, we elaborated the structural determination, reactivity descriptors, and NLO studies by computational approach.

Results and discussion

In the present study, we synthesized (*S*)-4-bromo-*N*-(1-phenylethyl)benzamide (**3**) by the reaction of 4-bromobenzoic acid (**1**) and (*S*)-1-phenylethanamine (**2**) in the presence of pyridine as a base also acts as solvent and $TiCl_4$ as a catalyst.

Previously, the activated acids were used for the amidation with amines or anilines.[14,27] Noteworthy, It is very useful to develop the direct amide linkage between inactivated carboxylic acids and amines or anilines as these are environment friendly.[18,28] So that coupling agents such as dicylohexyl carbodiimide (DCC) were also used for the reaction of carboxylic acids and amines or anilines and dimethyl aminopyridine (DMAP) as a catalyst.[29] It has been observed that acyl urea is produced as a side product and lower the yield of the compound.[30,31] Wilson and Weingarten developed $TiCl_4$ based amidation of a carboxylic acid with amines. There was no side product was observed like the amidation reactions in which coupling reagents were used.[32] Previously, it was investigated that carboxylic acid added in $TiCl_4$ in solvents like dichloromethane (DCM), hydrochloric acid (HCl) was produced which decreased the yield of amide. So, a base was employed in the reaction mixture to enhance the yield. It is not possible to use the tertiary alkyl amines as bases because of their possible reaction with $TiCl_4$. Thus, pyridine was selected as a base and a solvent.[33,34] In the current study, we decided to make amide by the reaction of carboxylic acid and amine in the presence of $TiCl_4$ and pyridine. We obtained an excellent yield of 93% of (*S*)-4-bromo-*N*-(1-phenylethyl)benzamide (**3**) due to the reaction between 4-bromobenzoic acid (**1**) and (*S*)-1-phenylethanamine (**2**) in the presence of pyridine and $TiCl_4$. Furthermore, we synthesized a series of compounds (**5a-i**) by the arylation of (*S*)-4-bromo-*N*-(1-phenylethyl)benzamide (**3**) via Suzuki-Miyaura cross-coupling reaction. The reaction was catalyzed by commercially available Palladium tetrakis at 90 °C in the presence of base K_3PO_4 and solvent 1,4-dioxane. The reaction was completed in 20–24 h under the inert atmosphere.

It was observed that the analogues of the compound (**3**) were produced in fair to excellent yields (**62–89%**). The synthesized (*S*)-4-bromo-*N*-(1-phenylethyl)benzamide (**3**) analogues (**5d**) and (**5g**) was obtained in a very good yield while (**5a–b**, **5e–f** and **5i**) in moderate to good yields (Figure 1). Our research group already reported the electronic effect of substituent present on the aryl boronic acids affected the yield of the compounds. It has been observed that aryl boronic acid with electron-donating groups gave more yield than the electron-withdrawing groups, the fluoro and chloro groups were responsible for the lesser yield of the synthesized compounds.[21,23]

Computational Study

All computer simulations of synthesis derivatives (**5a–i**) are done by using GaussView 6.0 and GAUSSIAN 09 W[35] program packages. Density functional theory (DFT)[23] were performed at B3LYP level of

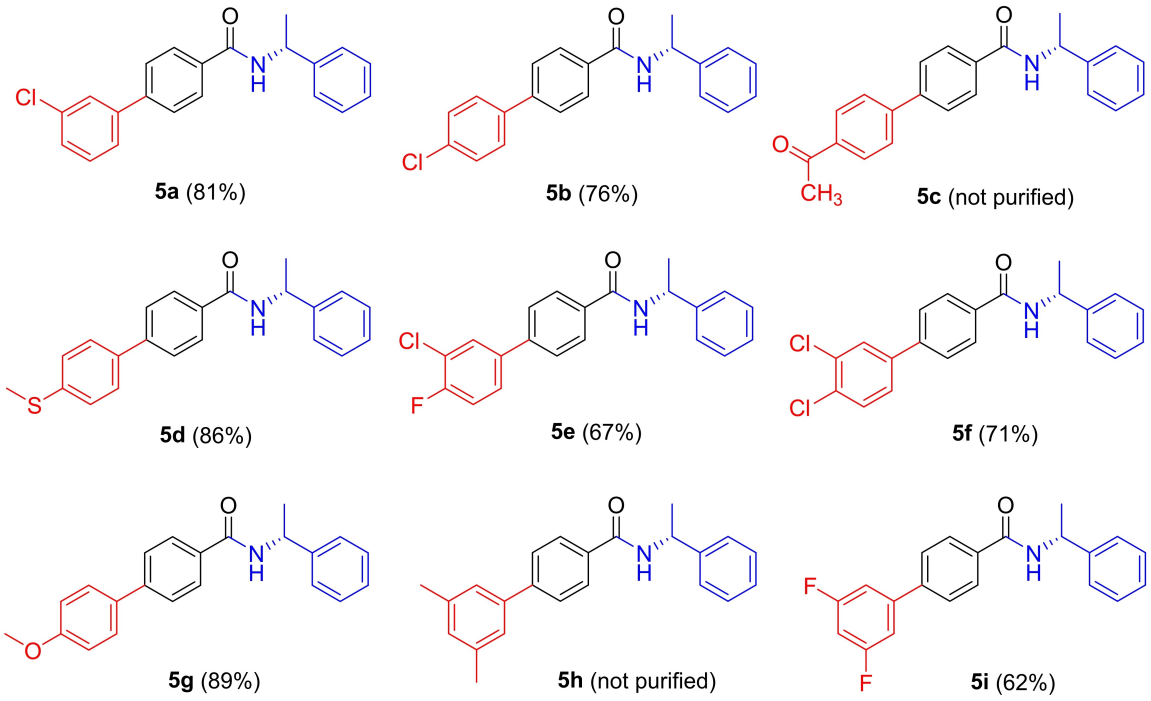


Figure 1. Derivatives of 4-bromo-*N*-(1-phenylethyl)benzamide (**5a–i**).

calculation with the basis set 6-311G (d, p). The 1,4-dioxane is used as a solvent for all the calculations.[36] Molecular electrostatic potential surfaces and frontier molecular orbital distributions were obtained, as well as various properties such as energies of the highest occupied molecular orbital (E_{HOMO}) and the lowest unoccupied molecular orbital (E_{LUMO}), HOMO-LUMO energy differences, and conceptual DFT reactivity descriptors like electrophilicity index (ω), electron-affinity (A), chemical hardness (η), ionization-energy (I) and chemical potential (μ) were also extracted. We may deduce the reactivity of the molecules from these properties.[21]

Optimized Geometries

Geometric optimization is a technique used by all computational scientists. This is a way to take rough geometric calculations and make them as correct as possible. This is a series of iterations achieved on the molecule until the energy of the molecule reaches to least.[37] Computational chemistry allows for more straightforward measurements of properties than wet laboratory work, like determining molecular energy and analysing intermolecular interactions.[38] The optimized geometries of (**5a**--**i**) are given in Figure 2.

Computation of NMR Data

The basic 6–311G and GIAO method of DFT theoretical level were used to optimize the chemical shifts of ^{1}H NMR of all the studied compounds (**5a–5i**).[39] Table 1. shows the experimental and theoretical chemical shifts of ^{1}H of compound (**5a**). The experimental and theoretical chemical shift of ^{1}H of all the other compounds has been given in the supporting information. It can be seen that the performance of the NMR calculation method is very good, and the average absolute error (MAE) is only 0.42 ppm. Therefore, it has been predicted with great confidence that the NMR data of compounds whose experimental NMR cannot be obtained in a good yield, and can be used as a guide for these synthesized compounds.

Frontier Molecular Orbitals and Non-linear optics

The HOMO and LUMO are called frontier molecular orbitals. The HOMO shows the ability of molecules to donate electrons, and LUMO shows the ability of molecules to gain electrons. Both the HOMO and LUMO and the energy gap help to calculate optical and electronic properties. Smaller HOMO-LUMO energy gap represents poor molecular stability and higher activity and vice versa.[40,41] In this serious, we observe that compound (**5a**) have the highest energy gap of HOMO-LUMO 4.98 eV which lead to kinetically more stable and least reactive and the compound (**5g**) has lowest energy gap of HOMO-LUMO 4.63 eV which lead to kinetically least stable and more reactive. The HOMO-LUMO gaps of the remaining compounds are lie in the range 4.63–4.98 eV. The iso-density surfaces of all the compounds are almost the same behaviour at the amide group which attached benzene ring but further attached benzene rings are disturbed due to the presence of different substituents such as –F, –Cl, $-SCH_3$, $-OCH_3$, $-COCH_3$. The HOMO-LOMO gap is expressed in Figure 3.

Nonlinear optics (NLO) materials play an important role in the field of photonics, including data storage, sensor protector application and optical information processing etc. Some organic compound exhibits a large NLO response, in many cases, the amplitude is several orders of magnitude larger than the wide range of known inorganic materials.[42,43] The phenyl rings in the compounds under investigation (**5a–5i**) serve as electron donors, while the amide

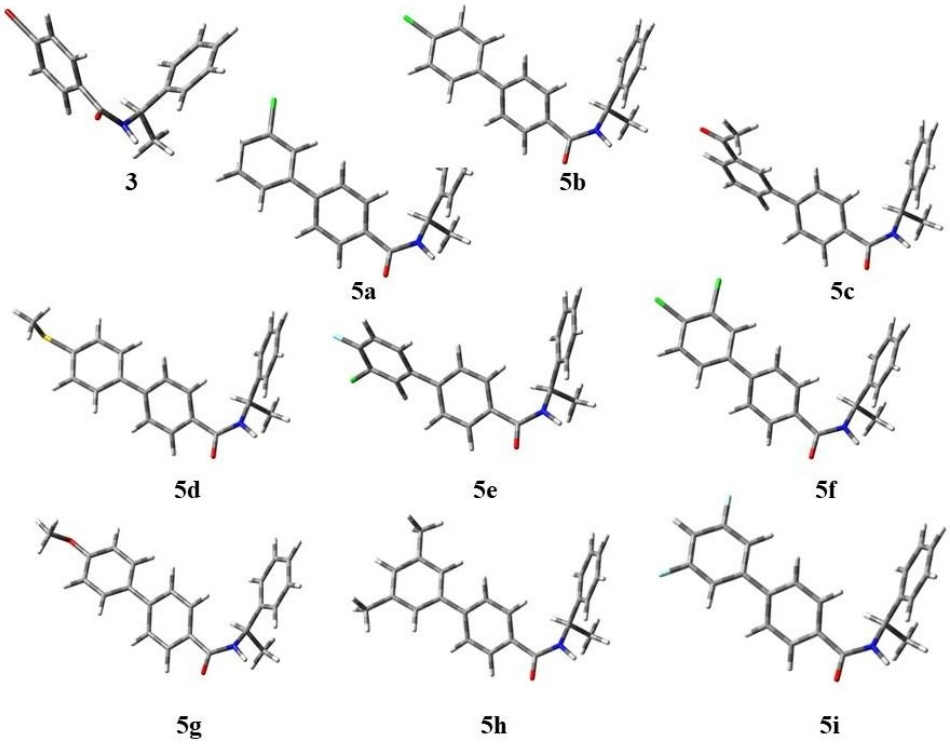


Figure 2. Optimized geometries of (**3**,**5a–i**) calculated at the B3LYP/6-311G (d,p)/$SMD_{1,4\text{-dioxane}}$level of theory.

Table 1. Comparison of Experimental and Computed NMR data for compound (**5a**).

Carbon No.	Carbon Type	^{1}H-NMR (δ, ppm) Experimental	^{1}H-NMR (δ, ppm) Computed	Δδ, ppm
1	C	–	–	–
2	CH	7.82	7.09	0.73
3	CH	8.09	6.97	1.12
4	C	–	–	–
5	CH	8.09	7.12	0.97
6	CH	7.82	7.09	0.73
1′	C	–	–	–
2′	CH	8.01	6.91	1.10
3′	C	–	–	–
4′	CH	7.45	7.09	0.36
5′	CH	7.45	8.21	-0.76
6′	CH	7.40	6.95	0.45
1″	C	–	–	–
1″-CH	CH	4.97	2.69	2.28
1″-CH-CH_3	CH3	1.84	1.33	0.51
2″	CH	7.29	7.09	0.20
3″	CH	7.40	7.23	0.17
4″	CH	7.27	7.07	0.20
5″	CH	7.40	7.10	0.30
6″	CH	7.29	6.98	0.31

[a] Mean absolute error (MAE) = 0.42, [b] Root mean Square error (RMSE) = 0.68.

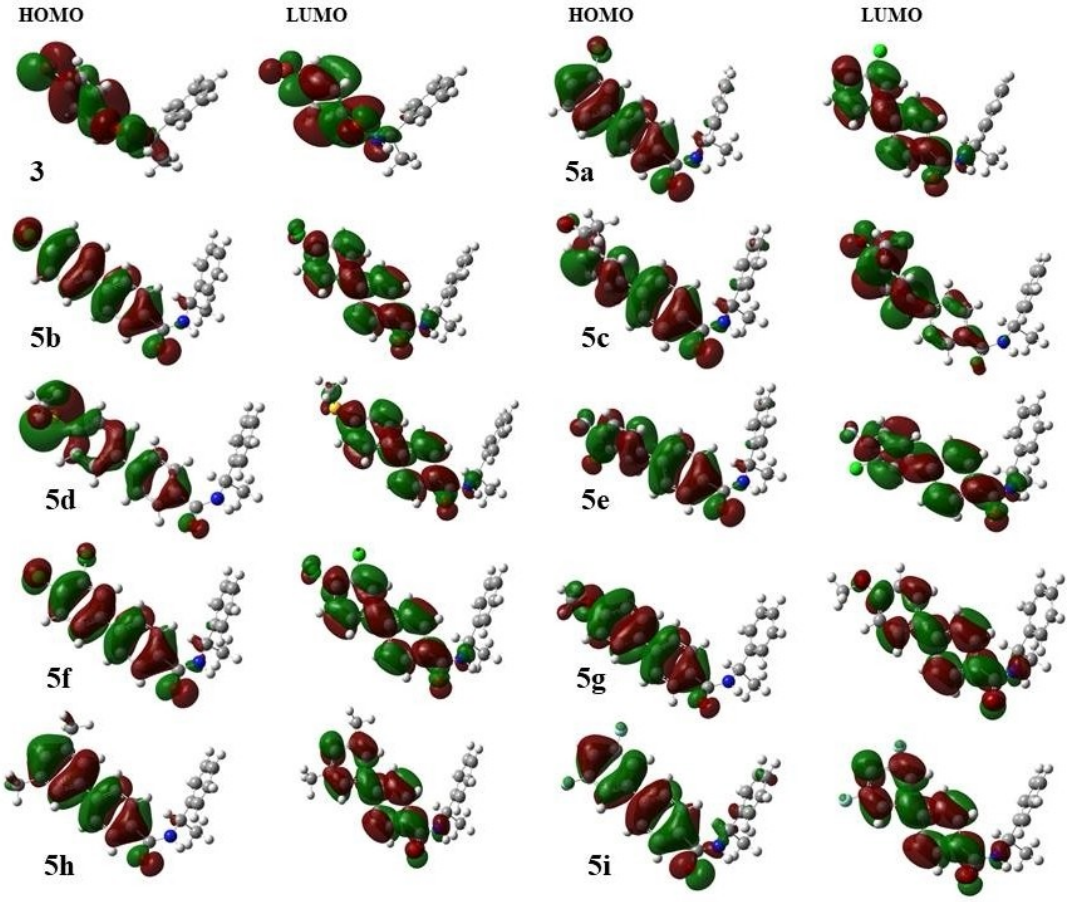


Figure 3. Frontier Molecular Orbitals (**3**, **5a**–**5i**) calculated at the B3LYP/6-311G (d,p)/$SMD_{1,4\text{-dioxane}}$level of theory.

group acts as an electron acceptor. The electron push-pull mechanism is effective when there are electron donor groups on the phenyl rings, and the hyperpolarizability (β) values are higher. Since both ends of the phenyl moiety become electron acceptors

when an electronwithdrawing group is present, there is no electron push-pull mechanism, resulting in a less NLO response. In this series of compounds (**5a–5i**), the compound (**5h**) has the highest hyperpolarizability (β) values 1096.57 Hartree, indicating the highest NLO response, while compound (**5b**) has the lowest 202.52 Hartree, indicating the lowest NLO response as show in Table 2.

Molecular Electrostatic Potential Surfaces

Mapping of molecular electrostatic potential (MEP) for chemical structure has become a key concern. Molecules are most likely to move through this chemical addition, electrophilic or nucleophilic addition since it can clarify useful details about interactions, active sites, and determining the type of chemical additions.[44,45] On surfaces, the red colour indicates the electronrich site where the electrophilic species is easily attacked. On the other hand, the blue colour indicates the electron-deficient site where nucleophilic species is easily attacked. The MEP surfaces of (**5a–i**) are given in Figure 4.

Conceptual DFT Reactivity Descriptors

Molecular properties related to selectivity and reactivity, such as ionization energy (I) and electron affinity (A), were calculated using Koopman's theorem,[46] which was derived from the HOMO and LUMO energies.

Ionization energies (I) are calculated through the following equation.

Table 2. Theoretically calculated energies of HOMO-LUMO, HOMO-LUMO gap Polarizability (α) and Hyperpolarizability (β)at the B3LYP/6-311G (d,p)/$SMD_{1,4\text{-dioxane}}$ level of theory. The unit of Polarizability (α) and Hyperpolarizability (β) in Hartree.

Comp.	E_{HOMO} (eV)	E_{LUMO} (eV)	△E (eV)	Polarizability (α)	Hyperpolarizability (β)
3	−6.74	−1.21	5.52	210.63	648.29
5a	−6.50	−1.51	4.98	283.52	489.37
5b	−6.38	−1.50	4.87	284.17	202.52
5c	−6.50	−1.74	4.75	301.25	774.31
5d	−6.28	−1.52	4.75	309.63	424.12
5e	−6.49	−1.53	4.96	282.96	439.99
5f	−6.53	−1.65	4.88	297.50	432.23
5g	−5.88	−1.25	4.63	288.33	289.92
5h	−6.18	−1.31	4.87	312.97	1096.57
5i	−6.57	−1.62	4.94	281.33	439.24

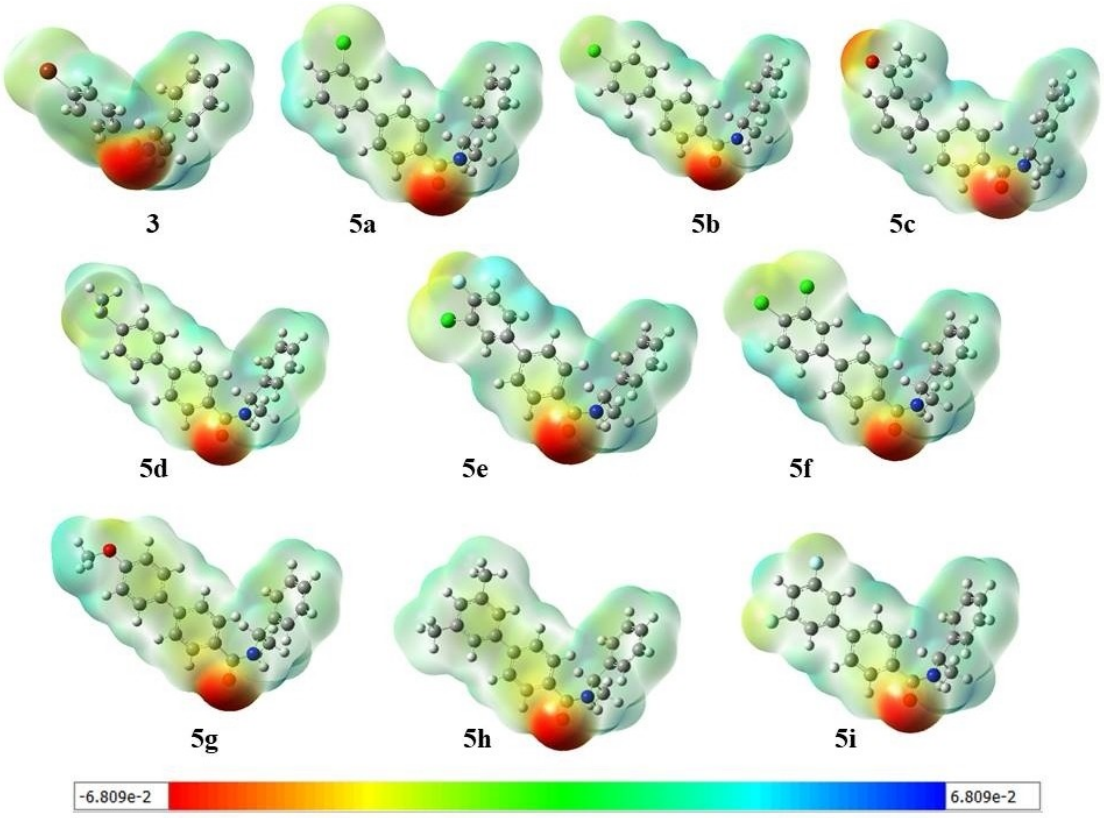


Figure 4. Molecular electrostatic potential surfaces calculated at the B3LYP/6-311G (d,p)/$SMD_{1,4\text{-dioxane}}$level of theory.

$$I = -E_{HOMO} \quad (1)$$

Electron affinity (A) is calculated through the following equation:

$$A = -E_{LUMO} \quad (2)$$

When the values of **I** and **A** are known, one can determine the global hardness (η) chemical potential (μ), electrophilicity index (ω) from the equation 3,4,5[47] respectively.

$$\eta = (I-A)/2 \quad (3)$$

$$\mu = -(I+A)/2 \quad (4)$$

$$\omega = \mu^2/2\eta \quad (5)$$

The values in Table 3. shows the measured values for electrophilicity index (ω), ionization energy (I), chemical hardness (η), and electron affinity (A) chemical potential (μ).

Conclusion

We synthesized (*S*)-4-bromo-*N*-(1-phenylethyl)benzamide in an excellent yield (93%) via Titanium tetrachloride ($TiCl_4$) and arylated in moderate to good yields. It was observed that the electron-donating groups favour the Suzuki-Miyaura cross-coupling reaction as compared to electron-withdrawing groups. It was observed that fluoro and chloro groups were responsible for lesser yields. The thermochemical properties like frontier molecular orbitals, polarizability (α), hyperpolarizability (β), MESP, and reactivity descriptors such as electron-affinity (A), ionization energy (I), global hardness (η), chemical potential(μ), electrophilicity index(ω) and NMR spectra were calculated using the DFT model. The determined NMR values for all of the compounds were in good agreement with the experimental NMR values due to the experimental and theoretical chemical shift of ^{1}H. In this serious (**5a–5i**), the compound (**5a**) has highest energy gap between HOMO-LUMO 4.98 eV which lead to less reactive and the compound (**5g**) lowest energy gap between HOMO-LUMO 4.63 eV which lead to more reactive. The Hyperpolarizability (β) value of compound (**5h**) is highest which showed the compound (**5h**) a good NLO material.

Materials and methods

Chemical and Reagents

All the chemicals were purchased from IS Chemical Technology, Shanghai, China and Sigma Aldrich. The reactions were done in an inert media. The progress of the reactions was checked by the thin layer chromatography (TLC) (Merck silica-gel PF_{254}) and visualized by an ultraviolet lamp having wavelength ranges from 254–365 nm. The solvent is evaporated by a Rota evaporator (Buchii R-210). The synthesized compounds were analyzed with the help of IR (PerkinElmer Spectrum-2 FT-IR spectrometer), ^{1}HNMR and ^{13}CNMR with BRUKER Aspect AM-600 instrument.

General procedure of the synthesis of (S)-4-bromo-N-(1-phenylethyl)benzamide (3)

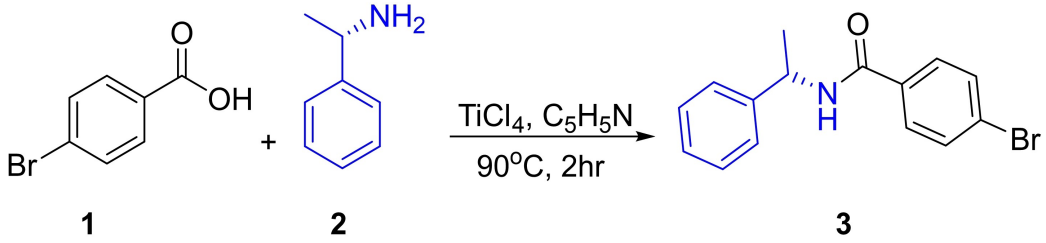
The 4-bromobenzoic acid (1 g, 4.94 mmol) was added to a schlenk flask containing 20 ml of pyridine and stirred for 30 minutes, followed by the addition of TiCl4 (1.638 ml, 5.54 mmol). After that, (*S*)-1-phenylethanamine (0.648 ml, 5 mmol) was added to the reaction media, which was then heated to 90 °C and stirred for 2 hours. TLC was used to monitor the progress of the reaction. After the reaction completion, the pyridine present in the reaction mixture was removed by adding 20 ml of 1 N HCl, followed by 20 ml of dichloromethane (DCM) in the separating funnel. Then the concentrated aqueous solution of sodium bicarbonate was added to the reaction mixture. The DCM layer was separated followed by the addition of toluene in the same amount as the product. The reaction mixture was dried by rotary evaporator. Column chromatography is used to separate the components of the reaction mixture (Scheme 1). The ^{1}H NMR, ^{13}C NMR used to elucidate the structure of the synthesized product.[14,48,49]

General procedure for the synthesis of (S)-4-aryl-N-(1-phenylethyl)benzamide (5a-i)

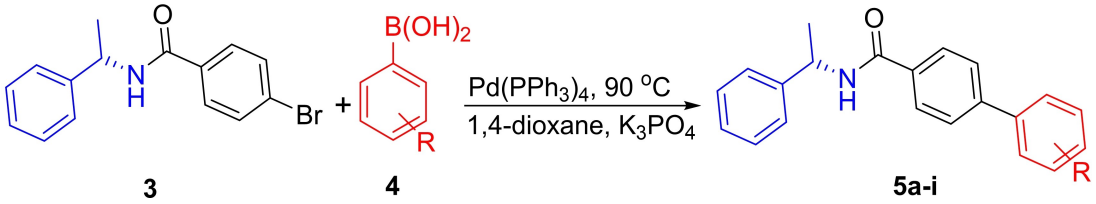
This reaction was carried out in the presence of argon (*S*)-4-bromo-*N*-(1-phenylethyl)benzamide (0.2 g, 0.6 mmol), 6 ml 1,4-dioxane, and tetrakis(triphenylphosphine)palladium (0.0455 g, 0.3937 mmol) were added to the schlenk tube (Scheme 2). After stirring these reagents at room temperature for half an

Table 3. Theoretical calculated electrophilicity index (ω), ionization-energy (I), chemical hardness (η), and electron-affinity (A) chemical-potential (μ) at the B3LYP/6-311G (d,p)/$SMD_{1,4\text{-dioxane}}$ level of theory.

Compounds	I (eV)	A (eV)	η (eV)	μ (eV)	ω (eV)
3	6.74	1.21	2.76	−3.98	2.86
5a	6.50	1.51	2.49	−4.00	3.22
5b	6.38	1.50	2.43	−3.94	3.19
5c	6.50	1.74	2.37	−4.12	3.58
5d	6.28	1.52	2.37	−3.90	3.21
5e	6.49	1.53	2.48	−4.015	3.24
5f	6.53	1.65	2.44	−4.09	3.42
5g	5.88	1.25	2.31	−3.56	2.74
5h	6.18	1.31	2.43	−3.74	2.88
5i	6.57	1.62	2.47	−4.09	3.39



Scheme 1. Synthesis of 2-(4-bromophenyl)-N-(1-phenylethyl)acetamide.



Scheme 2. Arylated derivatives (**5 a–i**) of 4-bromo-*N*-(1-phenylethyl)benzamide.

hour, K_3PO_4 (0.2793 g, 1.31578 mmol), aryl boronic acid (0.7236 mmol), and 0.5 ml distilled water were added, and the temperature was set to 90 °C for 24–36 hours. The reaction was keenly monitored by TLC. After the reaction completion, the reaction mixture was washed with solvent ethyl acetate. The reaction was dried by rotary evaporator. N-hexane and ethyl acetate are used to separate the components of the reaction mixture through column chromatography. The ^{1}H NMR, ^{13}C NMR used to elucidate the structure of the synthesized product.[50–53]

Characterization Data

4-bromo-N-(1-phenylethyl)benzamide (3)

Off solid, 93 % yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.5, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.28-7.25 (m, 4H), 7.17 (t, *J* = 6.8 Hz, 1H), 6.42 (d, *J* = 7.0 Hz, 1H), 5.22-5.20 (m, 1H), 1.49 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.64, 141.91, 132.39, 130.70 (2 C), 127.74 (2 C), 127.54 (2 C), 126.50 (2 C), 125.21, 125.07, 48.38, 20.64. Analysis calculated for $C_{15}H_{14}BrNO$: C, 59.23; H, 4.64; N, 4.60. Found: C, 59.21; H, 4.63; N, 4.58.

3-chloro-N-(1-phenylethyl)biphenyl-4-carboxamide (5 a)

White solid, 81 % yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.98 Hz, 2H), 7.56-7.50 (m, 3H), 7.39 (d, *J* = 7.44 Hz, 2H), 7.34-7.27 (m, 5H), 7.21 (t, *J* = 7.14 Hz, 1H), 6.30 (d, *J* = 6.96 Hz, 1H), 5.31-5.28 (m, 1H), 1.53 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.06, 143.05, 142.87, 141.86, 134.86, 133.85, 131.78, 130.14, 128.79, 128.54, 127.98 (2 C), 127.57, 127.32, 127.22, 126.27, 126.12 (2 C), 125.35, 49.40, 21.70. Analysis calculated for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.08; H, 5.42; N, 4.13.

4-chloro-N-(1-phenylethyl)biphenyl-4-carboxamide (5 b)

White solid, 76 % yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.34-7.32 (m, 4H), 7.26 (t, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 6.38 (d, *J* = 7.6 Hz, 1H), 5.29-5.27 (m, 1H), 1.53 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.11, 142.09, 141.97, 137.42, 133.17, 132.55, 128.06 (2 C), 127.77 (2 C), 127.57, 127.39, 126.57 (2 C), 126.47 (2 C), 126.01 (2 C), 125.25 48.29, 20.71. Analysis calculated for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.08; H, 5.42; N, 4.13.

4-(methylthio)-N-(1-phenylethyl)biphenyl-4-carboxamide (5 d)

Light brown solid, 86 % yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.83 (d, *J* = 9.8 Hz, 3H), 7.54 (d, *J* = 9.7 Hz, 4H), 7.39 (d, *J* = 8.9 Hz, 3H), 7.29 (t, *J* = 9.3 Hz, 2H), 7.20 (t, *J* = 8.6 Hz, 1H), 5.29-5.23 (m, 1H), 3.26 (s, 3H), 1.55 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.00, 143.02, 132.41, 129.84, 129.80 (2 C), 129.76 (4 C), 128.15, 126.96 (2 C), 125.47 (2 C), 124.93 (2 C), 124.89, 124.01, 47.57, 21.35, 14.39. Analysis calculated for $C_{22}H_{21}NOS$: C, 76.04; H, 6.09; N, 4.03. Found: C, 76.01; H, 6.12; N, 3.98.

3-chloro-4′-fluoro-N-(1-phenylethyl)biphenyl-4-carboxamide (5 e)

Off White solid, 67 % yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.22 Hz, 2H), 7.53 (dd, *J* = 2.23, 2.3 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.37-7.35 (m, 3H), 7.28 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.16–7.13 (m, 1H), 6.32 (d, *J* = 7.5 Hz, 1H), 5.30-5.28 (m, 1H), 1.55 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.00, 157.22, 143.03, 141.98, 137.29, 137.26, 133.81, 129.34, 128.79, 127.65, 127.53, 127.07, 126.90, 126.86, 126.27, 121.62, 121.50,

117.08, 116.94 49.34, 21.71. Analysis calculated for $C_{21}H_{17}ClFNO$: C, 71.29; H, 4.84; N, 3.96. Found: C, 71.25; H, 4.87; N, 3.95.

3,4-dichloro-N-(1-phenylethyl)biphenyl-4-carboxamide (5f)

White solid, 71% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (d, J= 8.2 Hz, 2H), 7.55 (d, J=2.0 Hz, 1H), 7.45 (d, J=8.04 Hz, 2H), 7.41 (d, J=8.3 Hz, 1H), 7.32-7.30 (m, 3H), 7.26 (t, J=7.8 Hz, 2H), 7.18 (t, J=7.3 Hz, 1H), 6.47 (s, 1H), 5.28-5.25 (m, 1H), 1.53 (d, J= 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.01, 143.09, 141.67, 139.98, 134.11, 133.09, 132.26, 130.85, 128.97, 128.78 (2 C), 127.74 (2 C), 127.51, 127.02 (2 C), 126.37 (2 C), 126.28, 49.37, 21.74. Analysis calculated for $C_{21}H_{17}Cl_2NO$: C, 68.12; H, 4.63; N, 3.78. Found: C, 68.09; H, 4.67; N, 3.75.

4-methoxy-N-(1-phenylethyl)biphenyl-4-carboxamide (5g)

Off white solid, 89% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, J=8.3 Hz, 2H), 7.51 (d, J=8.3 Hz, 2H), 7.46 (d, J=8.8 Hz, 2H), 7.33 (d, J=7.4 Hz, 2H), 7.28 (t, J=7.9 Hz, 2H), 7.20 (t, J=7.3 Hz, 1H), 6.90 (d, J=6.9 Hz, 2H), 6.28 (d, J=7.4 Hz, 1H), 5.30-5.28 (m, 1H), 3.78 (s, 3H), 1.54 (d, J=6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.31, 159.74, 143.92, 143.18, 132.57, 132.47, 128.76 (2 C), 128.25 (2 C), 127.46 (2 C), 127.43, 126.67 (2 C), 126.27 (2 C), 114.38 (2 C), 55.38, 49.23, 21.75. Analysis calculated for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.69; H, 6.41; N, 4.21.

3,5-difluoro-N-(1-phenylethyl)biphenyl-4-carboxamide (5i)

Brown solid, 62% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 (d, J= 8.34 Hz, 2H), 7.52 (d, J=6.7 Hz, 2H), 7.33 (d, J=15.6 Hz, 2H), 7.29 (t, J=2.1 Hz, 2H), 7.23 (t, J=1.3 Hz, 1H), 7.02 (d, J=2.6 Hz, 2H), 6.77–6.73 (m, 1H), 6.29 (d, J=7.4 Hz, 1H), 5.31-5.28 (m, 1H), 1.53 (d, J=6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.89, 164.23, 143.36, 142.98, 141.86, 134.41, 131.78, 128.80, 128.54 (2 C), 127.67, 127.56 (2 C), 127.16 (2 C), 126.27, 110.14 (2 C), 103.21, 49.40, 21.68. Analysis calculated for $C_{21}H_{17}F_2NO$: C, 74.76; H, 5.08; N, 4.15. Found: C, 74.73; H, 5.11; N, 4.11.

Supporting Information Summary Paragraph

The experimental details including detailed protocol descriptions on instruments used, product characterization, physical data, NMR spectra and computational details are given in supporting information.

Acknowledgements

This research is the part of Ali Raza Shah thesis. M. Imran M.A.A. appreciates the support of the Research Center for Advanced Materials Science (RCAMS) at King Khalid University Abha, Saudi Arabia, through grant KKU/RCAMS/22.

Conflict of Interest

The authors is no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: arylation · cross-coupling · density functional theory · one-pot amidation · Suzuki-Miyaura

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Submitted: March 2, 2022
Accepted: July 12, 2022