Fast Ga(OTf)$_3$-catalyzed nucleophilic substitution of propargyl alcohols

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Abstract

Various nucleophiles (6-nitroindole, 6-chloroindole, phenol, anisole, and furan) underwent rapid alkylation with propargyl alcohols in the presence of 5 mol% gallium(III) triflate under mild conditions to produce the corresponding products. The reactions can be performed in an undried solvent under air atmosphere in short reaction times and provide good yields. In most cases, the reactions completed within 10 min.

Keywords: Ga(OTf)$_3$, catalyzed, fast, propargyl alcohol, nucleophile, nucleophilic substitution
Introduction

As versatile structural building blocks, propargyl alcohols are well-known carbon electrophiles capable of reacting with various nucleophiles for the construction of C–C or carbon–heteroatom bonds. Their ability to undergo nucleophilic substitution reactions contributes significantly to their synthetic value in organic chemistry. Further, the nucleophilic substitution of propargyl alcohols provides access to functionalized alkenes, which can be readily converted to a variety of other functional groups.\(^1\)

However, the direct nucleophilic substitution of propargyl alcohols generally requires the preactivation of the alcohols because the hydroxyl group is not a good leaving group. Thus, hydroxyl groups are typically transformed into better leaving groups, such as carbonates, phosphates, and halides.\(^2\) However, these processes inevitably produce stoichiometric amounts of salt waste, which limits their large-scale use. Therefore, the development of nucleophilic substitution reactions for propargyl alcohols without generating excess waste is highly required. Recently, methods for the substitution of propargyl alcohols using gold,\(^3\) cobalt,\(^4\) rhenium,\(^5\) and ruthenium,\(^6\) metal chlorides,\(^7\) Yb(O Tf)\(_3\),\(^8\) Al(O Tf)\(_3\),\(^9\) \(p\)-toluenesulfonic acid,\(^10\) HBF\(_4\),\(^11\) 4-nitrobenzenesulfonic acid,\(^12\) trifluoroacetic acid,\(^13\) trifluoromethanesulfonic acid,\(^14\) perchloric acid,\(^15\) phosphomolybdic acid,\(^16\) zeolite,\(^17\) Amberlyst-15,\(^18\) Amberlite IR-120H resin,\(^19\) iodine,\(^20\) InBr\(_3\),\(^21\) Ce(O Tf)\(_3\),\(^22\) and triflates in ionic liquids\(^23\) have been developed.

Continuing our interest in the catalytic nucleophilic substitution of propargyl alcohols,\(^24\) we report our results for the fast Ga(O Tf)\(_3\)-catalyzed nucleophilic substitution of propargyl alcohols with various nucleophiles to afford the corresponding products in good yields. Crucially, this method does not require expensive catalysts, explosive solvents, or extended reaction times. Furthermore, the reactions can be performed under mild conditions without the need for precautions to exclude moisture or air from the reaction system. In most cases, the reactions proceeded to completion within 10 min. Compared to previous reaction systems, our proposed method has the advantages of a short reaction time, water stability, and operational simplicity.

Results and Discussion

First, we attempted the nucleophilic substitution of 1-(3,4-dimethylphenyl)-3-phenylprop-2-yn-1-ol (1a) with 6-nitroindole as the nucleophile in acetonitrile in the presence of 10 mol\% of Ga(O Tf)\(_3\) at room temperature. However, there was no significant progress in the reaction for 1 h. Gratifyingly, when the temperature was increased to 60 °C, the reaction completed within 10 min, as confirmed by thin-layer chromatography (TLC) monitoring. After the work-up, the corresponding C-nucleophilic substitution product (2a) was isolated in good yield and characterized (Table 1; Entry 1). To determine the effectiveness of the catalyst, reactions were conducted with different concentrations of Ga(O Tf)\(_3\) (1, 5, 10 mol\%) in acetonitrile. The reaction progressed well at all concentrations tested. Thus, we determined that 5 mol % of Ga(O Tf)\(_3\) was the optimal concentration in terms of yield.

Table 1. Ga(O Tf)\(_3\) catalyzed rapid nucleophilic substitution of propargyl alcohols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Propargyl alcohol</th>
<th>Nucleophile</th>
<th>Product</th>
<th>yield (%)</th>
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Having established the optimal reaction conditions, we investigated the scope and generality of the reaction by varying the R1 and R2 substituents on the propargyl alcohols and found that the reaction proceeded successfully to furnish the expected products (Table 1; Entries 2–6). Functional groups, such as methyl, benzyloxy, methoxy, and chloro did not affect the formation of sp3–sp3 carbon–carbon bonds. Further, the reaction proceeded successfully even when the alkyne substituent was changed from phenyl to n-pentyl (Table 1, Entries 5 and 6). Unfortunately, no reaction occurred when the alcohol substituent was changed from aryl to alkyl, leading us to speculate that aromatic substituents on the alcohol have a critical stabilizing effect on the propargylic carbocation in this reaction.

Next, we investigated various nucleophiles. Interestingly, other nucleophiles, such as 6-chloroindole, phenol, anisole, and furan reacted well with propargyl alcohols with high selectivity to give the corresponding products in good yields (Table 1; Entries 7–19). After all the nucleophiles had been tested, we determined that the substitution reaction resulted in a regioselective attack by the aromatic carbon with the highest electron density, that is, C-3 for indoles, C-4 for phenols, and C-2 for furans.12

To study the reaction mechanism, we performed the nucleophilic substitution of propargyl alcohol 1a with phenol under various reaction conditions. The addition of triethylamine inhibited the reaction, and no product was observed. When triflic acid was used instead of Ga(OTf)3, the reaction proceeded rapidly, however resulting in complex mixtures, as determined by TLC. Therefore, we believe that a basic environment is unfavorable for this reaction. We hypothesize that the hydroxyl group of the propargyl alcohol can be removed under acidic conditions only. Referring to previous studies,25 we assume that the reaction proceeds via a direct substitution of the hydroxyl group with a nucleophile through an SN1-type mechanism. In Scheme 1, we propose a possible mechanism for the synthesis of 2. Adduct I, formed by the ligand exchange of Ga(OTf)3 with a propargyl alcohol, can subsequently decompose into the intermediary propargylic carbocation II. The nucleophile then attacks the resulting propargylic carbocation II, which is immediately deprotonated, affording the corresponding product 2. Furthermore, the Ga(OTf)3 catalyst can be regenerated through the reversible equilibrium between adduct III and TfOH, thus restarting the catalytic cycle.
Conclusions

In conclusion, Ga(OTf)₃ is an effective catalyst for the nucleophilic substitution of propargyl alcohols with various nucleophiles, yielding good results and requiring short reaction times. The use of Ga(OTf)₃ simplifies this procedure simple, making it convenient, and practical for various applications.

Experimental Section

General Information. All chemicals and solvents were used as received without further purification and are commercially available. All manipulations were performed under an air atmosphere. Flash column chromatography was conducted on silica gel (200–300 mesh), and the reactions were monitored by TLC using UV light for visualization. Melting points were determined using a digital melting point apparatus and are uncorrected. ¹H-NMR (600 MHz) and ¹³C-NMR (150 MHz) spectra were recorded on a Bruker spectrometer using CDCl₃ as the solvent. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are reported in hertz. High-resolution mass spectrometry (HRMS) analyses were performed on an Agilent ESI-quadrupole mass spectrometer.

General procedure for the preparation of compounds 2a–s. To a solution of propargyl alcohol 1 (0.2 mmol) and the desired nucleophile (0.24 mmol, 1.1 equiv.) in acetonitrile (3 mL), Ga(OTf)₃ (0.01 mmol, 0.05 equiv.) was added at 60 °C. The reaction mixture was stirred at the same temperature for 10 min, and reaction progress was monitored by TLC. The reaction mixture was then quenched with a 10% aqueous Na₂CO₃ solution, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, 200–300 mesh, petroleum ether–EtOAc) to yield target product 2.

3-(1-(3,4-Dimethylphenyl)-3-phenylprop-2-yn-1-yl)-6-nitro-1H-indole (2a). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1a (47 mg, 0.2 mmol), 6-nitroindole (39 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2a (73 mg, 96%) as a yellow solid: Decomposed over 170 °C; IR(KBr): 3313, 3077, 2918,
3-(1-(4-Benzoyloxy)phenyl)-3-phenylprop-2-yn-1-yl)-6-nitro-1H-indole (2b). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1b (63 mg, 0.2 mmol), 6-nitroindole (39 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2b (84 mg, 92%) as a yellow solid: Decomposed over 140 °C; IR(KBr): v: 3344, 2928, 2857, 1610, 1598, 1456, 1323, 1244, 1172 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 8.52 (s, 1H), 8.32 (s, 1H), 7.96 (d, J 8.4 Hz, 1H), 7.67 (d, J 9.0 Hz, 1H), 7.50-7.40 (m, 3H), 7.32-7.27 (m, 3H), 7.25 (s, 1H), 7.22 (d, J 7.8 Hz, 1H), 7.10 (d, J 7.8 Hz, 1H), 5.40 (s, 1H), 2.24 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ: 143.5, 137.8, 137.0, 135.6, 135.2, 131.7, 130.8, 130.0, 129.0, 128.3, 128.1, 125.1, 123.4, 119.7, 118.5, 115.2, 108.2, 89.9, 83.7, 34.9, 19.9, 19.4; HRMS (ESI) Calcd for C₃₂H₂₂N₂O₂: M+H⁺ = 381.1598; Found: 381.1598.

3-(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-yl)-6-nitro-1H-indole (2c). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1c (54 mg, 0.2 mmol), 6-nitroindole (39 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2c (71 mg, 86%) as a yellow solid: Decomposed over 180 °C; IR(KBr): v: 3401, 1607, 1507, 1457, 1338, 1248, 1175 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 8.52 (s, 1H), 8.34 (s, 1H), 7.97 (d, J 9.0 Hz, 1H), 7.62 (d, J 7.8 Hz, 1H), 7.45-7.40 (m, 3H), 7.37 (d, J 7.8 Hz, 2H), 7.31 (d, J 7.8 Hz, 2H), 6.83 (d, J 7.8 Hz, 2H), 5.42 (s, 1H), 3.81 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ: 159.6, 143.7, 139.2, 135.3, 132.8, 131.7, 130.7, 128.9, 128.6, 128.3, 128.2, 128.1, 128.0, 127.5, 123.3, 119.7, 118.6, 115.2, 115.1, 108.2, 89.7, 83.8, 70.1, 34.5; HRMS (ESI) Calcd for C₃₀H₂₃N₂O₃: M+H⁺ = 459.1703; Found: 459.1704.

3-(1-(3,4-Dimethoxyphenyl)-3-phenylprop-2-yn-1-yl)-6-nitro-1H-indole (2d). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1d (53 mg, 0.2 mmol), 6-nitroindole (39 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to afford compound 2d (73 mg, 90%) as a yellow solid: Decomposed over 197 °C; IR(KBr): v: 3375, 2362, 1607, 1512, 1457, 1340, 1230, 1136 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 8.63 (s, 1H), 8.34 (s, 1H), 7.98 (d, J 8.4 Hz, 1H), 7.68 (d, J 8.4 Hz, 1H), 7.45 (d, J 3.0 Hz, 2H), 7.41 (s, 1H), 7.31 (m, 3H), 7.05 (s, 2H), 6.85 (d, J 6.0 Hz, 1H), 5.42 (s, 1H), 3.88 (s, 1H), 3.85 (s, 1H); ¹³C NMR (150 MHz, CDCl₃) δ: 149.2, 148.3, 143.6, 135.3, 132.9, 131.7, 130.7, 128.3, 128.2, 128.1, 123.3, 120.0, 119.7, 118.4, 115.2, 111.2, 108.2, 89.7, 83.9, 56.0, 34.9; HRMS (ESI) Calcd for C₃₂H₂₃N₂O₃: M+H⁺ = 417.1000; Found: 417.1000.

3-(1-(4-Benzoyloxy)phenyl)oct-2-yn-1-yl)-6-nitro-1H-indole (2e). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1e (61 mg, 0.2 mmol), 6-nitroindole (39 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2e (83 mg, 93%) as a yellow solid: M.p. 91-92 °C; IR(KBr): v: 3344, 2928, 2857, 1610, 1508, 1456, 1323, 1244, 1098 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 8.52 (s, 1H), 8.30 (s, 1H), 7.94 (d, J 9.0 Hz, 1H), 7.58 (d, J 8.4 Hz, 1H), 7.45-7.30 (m, 8H), 6.93 (d, J 7.2 Hz, 2H), 5.17 (s, 1H), 5.04 (s, 2H), 2.25 (t, J 6.6 Hz, 2H), 1.54 (t, J 6.6 Hz, 2H), 1.40-1.25 (m, 4H), 0.88 (t, J 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ: 157.8, 143.4, 137.0, 135.2, 133.6,
130.7, 128.8, 128.6, 128.1, 128.0, 127.5, 119.8, 119.3, 115.0, 114.9, 108.1, 84.1, 80.2, 70.1, 34.0, 31.2, 28.6, 22.2, 18.9, 14.0; HRMS (ESI) Calcd for C_{29}H_{29}N_{2}O_{2}: M+H^+ = 453.2173, Found: 453.2173.

3-(1-(4-Chlorophenyl)oct-2-yn-1-yl)-6-nitro-1H-indole (2f). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1f (47 mg, 0.2 mmol), 6-nitroindole (39 mg, 0.24 mmol), and Ga(OTF)_3 (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2f (66 mg, 88%) as a yellow solid: M.p. 98-99 °C; IR(KBr): 3401, 2927, 2856, 1587, 1502, 1458, 1338, 1088 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ: 8.55 (s, 1H), 8.33 (s, 1H), 7.95 (d, J 9.0 Hz, 1H), 7.55 (d, J 8.4 Hz, 1H), 7.38-7.34 (m, 3H), 7.28 (d, J 7.8 Hz, 2H), 5.19 (s, 1H), 2.26 (t, J 6.6 Hz, 2H), 1.54 (t, J 6.6 Hz, 2H), 1.40-1.28 (m, 4H), 0.88 (t, J 6.6 Hz, 3H); \(^13\)C NMR (150 MHz, CDCl\(_3\)) δ: 143.4, 139.8, 135.3, 132.8, 130.6, 129.1, 128.7, 128.4, 119.6, 118.4, 115.1, 108.4, 84.8, 79.5, 34.2, 31.1, 28.6, 22.2, 18.8, 14.0; HRMS (ESI) Calcd for C_{22}H_{22}Cl_{2}N_{2}O_{2}: M+H^+ = 381.1364, Found: 381.1365.

6-Chloro-3-(1-(3,4-dimethylphenyl)-3-phenylprop-2-yn-1-yl)-1H-indole (2g). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1a (47 mg, 0.2 mmol), 6-chloroindole (36 mg, 0.24 mmol), and Ga(OTF)_3 (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to afford compound 2g (66 mg, 90%) as a light yellow oil: IR(KBr): 3424, 3060, 3015, 2922, 2860, 1617, 1495, 1450, 1334, 1275, 1130 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ: 7.95 (s, 1H), 7.51 (d, J 9.0 Hz, 1H), 7.45-7.42 (m, 2H), 7.30-7.24 (m, 5H), 7.22 (d, J 7.8 Hz, 1H), 7.10 (d, J 1.8 Hz, 1H), 7.08 (d, J 7.8 Hz, 1H), 7.02 (dd, J 1.8, 7.8 Hz, 1H), 5.34 (s, 1H), 2.22 (s, 6H); \(^13\)C NMR (150 MHz, CDCl\(_3\)) δ: 138.4, 137.1, 136.8, 135.3, 131.7, 129.8, 129.1, 128.2, 128.1, 127.9, 125.2, 124.8, 123.7, 123.2, 120.6, 120.4, 117.5, 111.2, 90.6, 83.3, 35.1, 19.9, 19.4; HRMS (ESI) Calcd for C_{23}H_{23}ClN\(_2\)Na: M+Na^+ = 392.1176, Found: 392.1181.

3-(1-(4-Benzoxyl)phenyl)-3-phenylprop-2-yn-1-yl)-6-chloro-1H-indole (2h). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1b (63 mg, 0.2 mmol), 6-chloroindole (36 mg, 0.24 mmol), and Ga(OTF)_3 (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to afford compound 2h (81 mg, 90%) as a white solid: M.p. 137-138 °C; IR(KBr): 3425, 3062, 3034, 2930, 2868, 1608, 1507, 1451, 1242, 1175 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ: 11.15 (d, J 1.8 Hz, 1H), 7.53 (d, J 9.0 Hz, 1H), 7.49-7.34 (m, 13H), 7.31 (t, J 7.2 Hz, 1H), 7.00-6.96 (m, 3H), 5.54 (s, 1H), 5.06 (s, 2H); \(^13\)C NMR (150 MHz, CDCl\(_3\)) δ: 157.6, 137.6, 134.2, 131.8, 129.1, 129.0, 128.9, 128.7, 128.3, 128.1, 126.5, 124.8, 124.7, 123.4, 120.8, 119.4, 116.2, 115.2, 111.8, 91.7, 83.1, 69.7, 34.1; HRMS (ESI) Calcd for C_{30}H_{25}ClNO: M+H^+ = 448.1463, Found: 448.1451.

6-Chloro-3-(1-(3,4-dimethoxyphenyl)-3-phenylprop-2-yn-1-yl)-1H-indole (2i). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1d (53 mg, 0.2 mmol), 6-chloroindole (36 mg, 0.24 mmol), and Ga(OTF)_3 (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2i (75 mg, 95%) as a white solid: M.p. 167-168 °C; IR(KBr): 2415, 3354, 3060, 3000, 2958, 2936, 2836, 1597, 1512, 1457, 1262, 1139 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ: 8.22 (s, 1H), 7.51 (d, J 8.4 Hz, 1H), 7.46-7.42 (m, 2H), 7.31 (s, 1H), 7.30-7.26 (m, 3H), 7.08 (s, 1H), 7.06-7.01 (m, 3H), 6.82 (d, J 7.8 Hz, 1H), 5.37 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H); \(^13\)C NMR (150 MHz, CDCl\(_3\)) δ: 149.0, 148.0, 137.2, 133.6, 131.7, 128.3, 128.2, 128.0, 124.7, 123.6, 123.3, 120.6, 120.3, 120.0, 117.2, 111.3, 111.2, 111.1, 90.4, 83.5, 56.0, 55.9, 35.1; HRMS (ESI) Calcd for C_{25}H_{20}ClN\(_2\)O\(_2\): M+Na^+ = 424.1075, Found: 424.1079.

4-(1-(3,4-Dimethylphenyl)-3-phenylprop-2-yn-1-yl)phenol (2j). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1a (47 mg, 0.2 mmol), phenol (23
mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2j (53 mg, 83%) as a light yellow oil: IR(KBr): 3378, 3054, 3022, 2922, 1603, 1508, 1446, 1265, 1172 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.48-7.44 (m, 2H), 7.32-7.27 (m, 5H), 7.16 (s, 1H), 7.14 (d, J 7.8 Hz, 1H), 7.08 (d, J 7.8 Hz, 1H), 6.77 (d, J 8.4 Hz, 1H), 5.09 (s, 1H), 2.23 (s, 3H), 2.22 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ: 154.4, 139.5, 136.8, 135.1, 134.4, 131.7, 129.9, 129.1, 128.2, 127.9, 125.2, 123.7, 115.4, 90.8, 84.5, 42.5, 19.9, 19.4; HRMS (ESI) Calcd for C₂₃H₂₂O₃: M+H⁺ = 313.1587, Found: 313.1587.

4-(1-(4-(Benzyloxy)phenyl)-3-phenylprop-2-yn-1-yl)phenol (2k). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1b (63 mg, 0.2 mmol), phenol (23 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2k (67 mg, 86%) as a light yellow oil: IR(KBr): 3397, 3061, 3032, 2930, 2869, 1606, 1508, 1448, 1241, 1174 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.47-7.44 (m, 2H), 7.41 (d, J 7.2 Hz, 2H), 7.38-7.34 (m, 2H), 7.33-7.26 (m, 8H), 6.92 (d, J 9.0 Hz, 2H), 6.76 (d, J 8.4 Hz, 2H), 5.10 (s, 1H), 5.03 (s, 2H); ¹³C NMR (150 MHz, CDCl₃) δ: 157.8, 154.5, 137.1, 134.6, 134.4, 131.7, 129.1, 128.9, 128.6, 128.3, 128.0, 127.9, 127.5, 123.6, 115.5, 115.0, 90.8, 84.6, 70.1, 42.1; HRMS (ESI) Calcd for C₂₂H₂₂NaO₂: M+Na⁺ = 413.1512, Found: 413.1516.

4-(1-(3,4-Dimethoxyphenyl)-3-phenylprop-2-yn-1-yl)phenol (2l). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1d (53 mg, 0.2 mmol), phenol (23 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2l (53 mg, 78%) as a light yellow oil: IR(KBr): 3432, 3059, 3006, 2958, 2937, 1597, 1511, 1445, 1264, 1234 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.48-7.44 (m, 2H), 7.32-7.26 (m, 5H), 6.98-6.93 (m, 2H), 6.82 (d, J 7.8 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H), 5.10 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ: 154.6, 149.0, 147.9, 134.7, 134.1, 131.7, 129.0, 128.3, 128.0, 123.6, 120.0, 115.4, 111.3, 111.2, 90.7, 84.7, 56.0, 55.9, 42.5; HRMS (ESI) Calcd for C₂₃H₂₄O₃: M+H⁺ = 345.1485, Found: 345.1484.

4-(1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-yl)phenol (2m). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1g (48 mg, 0.2 mmol), phenol (23 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2m (52 mg, 82%) as a light yellow oil: IR(KBr): 3357, 3056, 1599, 1510, 1489, 1442, 1234, 1173, 1093 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.48-7.44 (m, 2H), 7.34 (d, J 8.4 Hz, 2H), 7.32-7.24 (m, 7H), 6.78 (d, J 9.0 Hz, 2H), 5.12 (s, 1H), 4.91 (s, 1H); ¹³C NMR (150 MHz, CDCl₃) δ: 154.6, 140.6, 133.6, 132.7, 131.7, 129.1, 129.2, 128.7, 128.3, 128.2, 123.3, 115.6, 89.9, 85.1, 42.3; HRMS (ESI) Calcd for C₂₃H₁₅ClNaO: M+Na⁺ = 341.0704, Found: 341.0707.

4-(3-Phenyl-1-(3-trifluoromethyl)phenyl)prop-2-yn-1-yl)phenol (2n). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1h (55 mg, 0.2 mmol), phenol (23 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford compound 2n (56 mg, 80%) as a yellow oil: IR(KBr): 3371, 3061, 2931, 1605, 1511, 1444, 1330, 11238, 1167, 1126, 1074 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.70 (s, 1H), 7.60 (d, J 7.2 Hz, 1H), 7.50 (d, J 7.8 Hz, 1H), 7.44-7.43 (m, 2H), 7.43 (t, J 7.8 Hz, 1H), 7.32-7.30 (m, 3H), 7.28 (d, J 8.4 Hz, 2H), 6.80 (d, J 8.4 Hz, 2H), 5.20 (s, 1H); ¹³C NMR (150 MHz, CDCl₃) δ: 154.8, 143.1, 133.2, 131.7, 131.3, 130.9 (q, J²=32.6 Hz), 129.2, 129.1, 128.3, 128.2, 124.6 (q, J²=3.3 Hz), 124.1 (q, J²=270.9 Hz), 123.8 (q, J²=3.3 Hz), 123.2, 115.7, 89.4, 85.5, 42.8; HRMS (ESI) Calcd for C₂₂H₁₆F₃O: M+H⁺ = 353.1148, Found: 353.1147.
1-(Benzylxoy)-4-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)benzene (2o). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1b (63 mg, 0.2 mmol), anisole (26 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (petroleum ether) to afford compound 2o (73 mg, 90%) as a colorless oil: IR(KBr): 3032, 2932, 2836, 1606, 1508, 1459, 1248, 1176 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.48-7.45 (m, 2H), 7.42 (d, J 7.8 Hz, 2H), 7.39-7.35 (m, 2H), 7.35-7.27 (m, 8H), 6.93 (d, J 8.4 Hz, 2H), 6.85 (d, J 8.4 Hz, 2H), 5.04 (s, 2H), 3.78 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ: 158.5, 157.7, 137.1, 134.6, 134.3, 132.3, 131.7, 128.9, 128.6, 128.2, 128.0, 127.9, 127.5, 123.6, 114.9, 114.0, 90.8, 84.6, 70.1, 55.3, 42.1; HRMS (ESI) Calcd for C₁₉H₁₈O₂N: M+H⁺ = 345.1484, Found: 345.1483.

1,2-Dimethoxy-4-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)benzene (2p). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1d (53 mg, 0.2 mmol), anisole (26 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (1% EtOAc in petroleum ether) to afford compound 2p (58 mg, 82%) as a colorless oil: IR(KBr): 3060, 3002, 2956, 2935, 1599, 1511, 1460, 1256, 1175 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.48-7.45 (m, 2H), 7.34 (d, J 8.4 Hz, 2H), 7.32-7.28 (m, 3H), 6.98-6.94 (m, 2H), 6.86 (d, J 8.4 Hz, 2H), 6.82 (d, J 8.4 Hz, 1H), 5.12 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ: 158.5, 149.0, 148.0, 134.7, 134.1, 131.7, 128.8, 128.3, 123.6, 119.9, 114.0, 111.2, 90.7, 84.6, 55.94, 55.89, 55.3, 42.5; HRMS (ESI) Calcd for C₁₉H₁₈O₃: M+H⁺ = 359.1642, Found: 359.1636.

1-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)-3-(trifluoromethyl)benzene (2q). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1h (55 mg, 0.2 mmol), anisole (26 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (petroleum ether) to afford compound 2q (65 mg, 89%) as a colorless oil: IR(KBr): 2961, 2840, 2361, 1601, 1510, 1447, 1330, 1256, 1172, 1126, 1073 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.71 (s, 1H), 7.60 (d, J 7.2 Hz, 1H), 7.50 (d, J 7.8 Hz, 1H), 7.48-7.46 (m, 2H), 7.42 (t, J 7.8 Hz, 1H), 7.33 (d, J 8.4 Hz, 2H), 7.32-7.29 (m, 3H), 6.87 (d, J 9.0 Hz, 2H), 5.21 (s, 1H), 3.78 (s, 1H); ¹³C NMR (150 MHz, CDCl₃) δ: 158.8, 143.1, 133.0, 131.7, 131.3, 130.9 (q, J = 32.6 Hz), 129.1, 129.0, 128.3, 128.2, 124.6 (q, J = 3.2 Hz), 124.1 (q, J = 270.9 Hz), 123.8 (q, J = 3.2 Hz), 123.2, 114.2, 89.5, 85.4, 55.3, 42.8; HRMS (ESI) Calcd for C₂₃H₁₈F₃O: M+H⁺ = 367.1304, Found: 367.1305.

2-{1-(3,4-Dimethylphenyl)-3-phenylprop-2-yn-1-yl}furan (2r). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1a (47 mg, 0.2 mmol), furan (17 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (petroleum ether) to afford compound 2r (39 mg, 68%) as a colorless oil: IR(KBr): 3054, 3016, 2922, 2860, 2362, 1603, 1595, 1497, 1448, 1176 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.48-7.45 (m, 2H), 7.33 (s, 1H), 7.30-7.27 (m, 3H), 7.22 (s, 1H), 7.20 (d, J 7.8 Hz, 1H), 7.11 (d, J 7.8 Hz, 1H), 6.31-6.29 (m, 1H), 6.28 (d, J 3.0 Hz, 1H), 5.19 (s, 1H), 2.25 (s, 3H), 2.23 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ: 154.2, 142.2, 136.9, 136.4, 135.7, 131.8, 130.0, 129.1, 128.3, 128.1, 125.3, 123.4, 110.3, 106.5, 87.8, 83.7, 37.6, 19.9, 19.4; HRMS (ESI) Calcd for C₁₃H₁₂NaO: M+Na⁺ = 309.1250. Found: 309.1258.

2-{1-(3,4-Dimethoxyphenyl)-3-phenylprop-2-yn-1-yl}furan (2s). The title compound was synthesized according to the above general procedure by stirring a mixture of propargyl alcohol 1d (53 mg, 0.2 mmol), furan (17 mg, 0.24 mmol), and Ga(OTf)₃ (5 mg, 0.05 equiv.) in acetonitrile (3 mL) at 60 °C for 10 min. The crude product was purified by silica gel column chromatography (1% EtOAc in petroleum ether) to afford compound 2s (47 mg, 75%) as a light yellow oil: IR(KBr): 3059, 3001, 2957, 2936, 2836, 1597, 1513, 1460, 1264, 1179 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ: 7.59 (s, 1H), 7.50-7.46 (m, 2H), 7.40-7.37 (m, 3H), 7.04 (s, 1H), 6.97 (dd, J 7.8, 18.6 Hz, 1H), 6.41 (s, 1H), 6.31 (s, 1H), 5.47 (s, 1H), 3.74 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ: 154.0, 149.2,
148.6, 143.1, 131.9, 131.7, 129.2, 129.0, 122.8, 120.2, 112.5, 112.0, 111.0, 106.9, 88.9, 83.5, 56.1, 56.0, 36.6; HRMS (ESI) Calcd for C\textsubscript{21}H\textsubscript{19}O\textsubscript{3}: M+H\textsuperscript{+} = 319.1329, Found: 319.1327.

Supplementary Material

Copies of the \textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR and HRMS spectra are provided in the supplementary material file.

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