

*Supporting Information file... ...*

## **An Alkyne Linchpin Strategy for Drug:Pharmacophore Conjugation: Experimental and Computational Realization of a *meta*-selective Inverse Sonogashira Coupling**

Sandip Porey,<sup>1,†</sup> Xinglong Zhang,<sup>2,†</sup> Suman Bhowmick,<sup>1</sup> Vikas Kumar Singh,<sup>1</sup> Srimanta Guin,<sup>1,\*</sup> Robert S. Paton,<sup>2,3,\*</sup> and Debabrata Maiti<sup>1,\*</sup>

<sup>1</sup> Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

<sup>2</sup> Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK

<sup>3</sup> Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA

<sup>†</sup> These authors contributed equally to this work

Email: dmaiti@iitb.ac.in (DM)

Email: robert.paton@colostate.edu (RSP)

Email: srgnchem@gmail.com (SG)

## Table of Contents

Section	Title	Page No
1	General consideration	S3
2	Experimental section	S3
2.1	Preparation of starting materials	S3 – S11
2.2	Optimization details for <i>meta</i> -C–H alkynylation with (bromoethyl)triisopropylsilane	S12 – S19
	Screening of scaffolds	S20
2.3	General procedure for palladium catalyzed <i>meta</i> -selective C–H alkynylation of arene	S20
2.3.1.a	General procedure for palladium catalyzed <i>meta</i> -selective sequential hetero difunctionalization of arene	S21-S22
2.3.1.b	General procedure for gram scale synthesis of <i>meta</i> -alkynylated protocol	S23
2.3.1.c	General procedure for directing group removal of <i>meta</i> -alkynylated protocol	S23
2.3.1.d	General procedure for different application of <i>meta</i> -alkynylated product	S24-S25
2.4	Characterization data of <i>meta</i> - alkynylated products	S25 – S60
2.5	Mechanistic studies	S60 – S66
2.6	Computational methods	S67 – S115
3	References	S115 –S122
4	NMR spectra	S123 – S205

## 1. General Consideration:

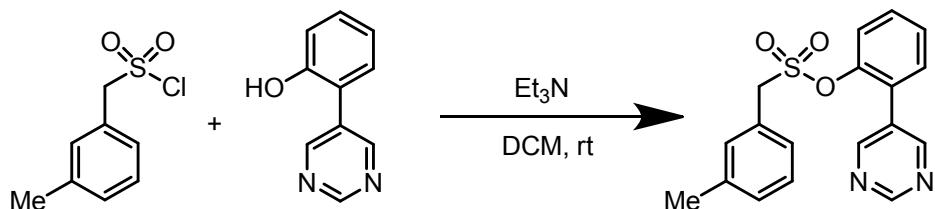
**Reagent Information.** All reactions were carried out in screw cap reaction tubes under aerobic condition, unless otherwise stated. All the chemicals were purchased from Sigma Aldrich, Alfa Aesar and TCI-India. Solvents were bought from commercial sources and were used without further purification. Silica gel (100–200 mesh) was used for column chromatography obtained from Merck. Petroleum ether and ethyl acetate mixture was used as a gradient elution for column chromatography.

**Analytical Information.** All isolated compounds were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR spectroscopy, and HRMS. Unless otherwise stated, all Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz and 500 MHz instrument. NMR spectra are reported in parts per million (ppm), and were measured relative to the signals for residual solvent (7.26 ppm for  $^1\text{H}$  NMR and 77.23 ppm for  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$ ) in the deuterated solvent, unless otherwise stated. All  $^{13}\text{C}$  NMR spectra were obtained with  $^1\text{H}$  decoupling. Chemical shift of  $^1\text{H}$  and  $^{13}\text{C}$  NMR are in ppm and IR in  $\text{cm}^{-1}$  unit. High-resolution mass spectra (HRMS) were recorded on a micro-mass ESI TOF (time of flight) mass spectrometer.

## 2. Experimental Section

### 2.1. Preparation of Starting materials

#### 2.1.1. Synthesis of sulfonyl ester scaffolds:



#### Step 1: Preparation of phenylmethanesulfonyl chloride

An oven dried clean round bottom flask was charged with magnetic stir-bar, 3-methyl benzyl chloride/bromide (10 mmol) and thiourea (10 mmol, 760 mg). 10 ml of absolute ethanol was added and refluxed at 96 °C. After 3 h the reaction was taken out and solvent was evaporated under reduced pressure to obtain white solid thiouric salt. The obtained solid salt was suspended in 14 ml of  $\text{CH}_3\text{CN}$  and 3 ml 2N HCl was added to it. The mixture was stirred at 0

°C for 15 min. N-chlorosuccinimide (NCS) (40 mmol; 5.34 g) was added in portion to the suspension in order to obtain a clear solution. The solution was stirred for another 30 min at room temperature. The solution was evaporated under reduced pressure to remove the CH<sub>3</sub>CN. The remaining aqueous portion was extracted with ethyl acetate. The organic portion was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the crude mixture was evaporated and purified by column chromatography using silica gel (100-200 mesh size) and ethyl acetate/petroleum ether as the eluent. Quantitative yield.

### **Step 2: Preparation of 2-(pyrimidin-5-yl)phenol**

2-(pyrimidin-5-yl)phenol was prepared by following Suzuki cross coupling reaction condition. A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with 5-bromopyrimidine (1 equiv.), 2-hydroxyphenyl boronic acid (1.2 equiv.), palladium (II) acetate (2 mol%), SPhos (4 mol%) and K<sub>3</sub>PO<sub>4</sub> (2 equiv.). The cap was fitted with a rubber septum and the reaction tube was evacuated and back filled with nitrogen and this sequence was repeated three additional times. Now under the positive flow of nitrogen 6 mL THF was added to the reaction mixture. The several reactions are carried out in different reaction tubes (2 mmol/reaction tube). The reaction mixture was vigorously stirred on an oil bath at 75 °C for 24 h. Now the reaction mixture was dried using rotary evaporator. The reaction mixture was extracted thrice with ethyl acetate (3 x 20 mL) and brine solution (3 x 10 mL). The organic layer was collected and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography using neutral alumina and ethyl acetate/petroleum ether (20/80, v/v) as the eluent; white solid, 72%.

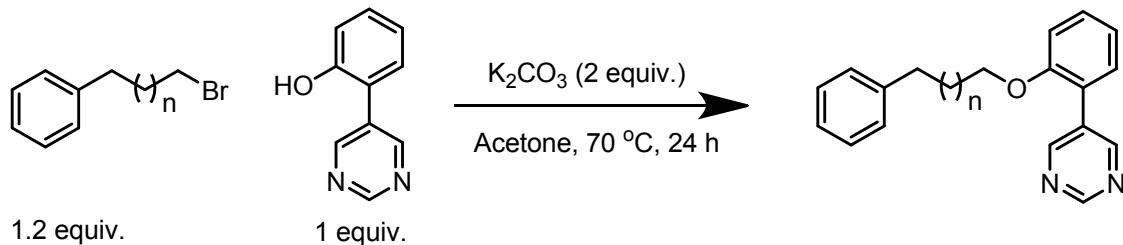
**Step 3:** To an ice-cold solution of 2-(pyrimidin-5-yl)phenol (5 mmol) and triethylamine (1.5 equiv, 1.04 mL) in 10 mL dichloromethane under nitrogen atmosphere, phenylmethanesulfonyl chloride was added portion wise. Stirring was continued for additional 20 minutes, after that the ice bath was removed and the reaction mixture was left for vigorous stirring at room temperature for overnight. CH<sub>2</sub>Cl<sub>2</sub> was removed under reduced pressure. The residual was diluted and extracted with ethyl acetate (3 x 20 mL) and brine solution (3 x 10 mL). The organic layer was collected and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent, the crude mixture was purified by column

chromatography using neutral alumina and petroleum-ether/ethyl acetate (85/15, v/v) as the eluent. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.21 (s, 1H), 8.81 (s, 2H), 7.46 – 7.39 (m, 3H), 7.36 – 7.32 (m, 1H), 7.22 (dd, *J* = 14.6, 7.5 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 4.29 (s, 2H), 2.34 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 158.0, 156.8, 146.2, 139.1, 131.5, 131.3, 131.1, 130.8, 130.4, 129.1, 128.8, 127.9, 127.9, 126.5, 123.4, 57.8, 21.5. HRMS (ESI): calcd. for C<sub>18</sub>H<sub>16</sub>KN<sub>2</sub>O<sub>3</sub>S [M+K]<sup>+</sup>: 379.0513, found: 379.0514.

All the sulfonyl esters were synthesized following the above procedures and characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, matched with our previous reports.<sup>1-2</sup>

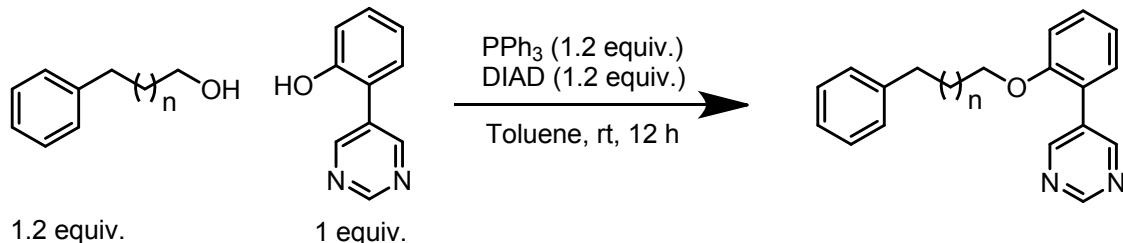
### 2.1.2. Synthesis of ether scaffolds:

#### General procedure A



A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with 2-(pyrimidin-5-yl)phenol (1 equiv, 2.4 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 equiv, 4 mmol). The cap was fitted with a rubber septum and the reaction tube was evacuated and back filled with nitrogen and this sequence was repeated three additional times. Now under the positive flow of nitrogen 6 mL acetone was added to the reaction mixture. Then, phenyl alkyl bromide (1.2 equiv, 2 mmol) was added by using syringe. The reaction mixture was vigorously stirred at 70 °C for 24 h. Reaction mixture was dried under rotary evaporator. The reaction mixture was extracted thrice with ethyl acetate (3 x 20 mL) and brine solution (3 x 10 mL). The organic layer was collected and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography using neutral alumina and ethyl acetate/ petroleum ether (5/95, v/v) as the eluent.

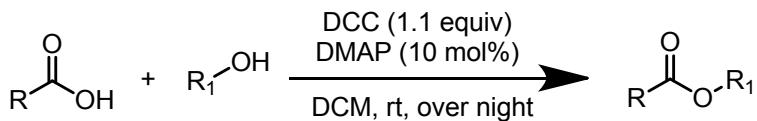
### General procedure B



To a 20 mL reaction tube, starting alcohol (1.2 equiv), 2-(pyrimidin-5-yl)phenol (1 equiv), triphenylphosphine (1.2 equiv), diisopropyl diazene-1,2-dicarboxylate (DIAD, 1.2 equiv) and toluene (2 mL) were added. The mixture was stirred at room temperature and monitored by TLC. Upon completion of the reaction, 5 mL water was added and the layers were separated. The aqueous phase was extracted twice with ethyl acetate (10 mL). The combined organic phase was washed with brine solution and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration and removal of solvent under vacuum, the residue was purified through column chromatography with hexane/ethyl acetate as an eluent. The target substrates were obtained generally in good to excellent yields.

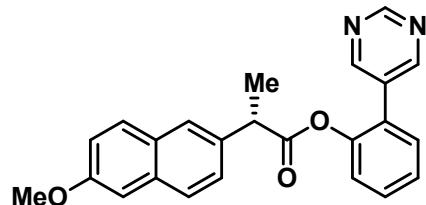
All the synthesized ether scaffolds were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and characterization data were matched with previous reports.<sup>3</sup>

#### 2.1.3. General Procedure for Synthesis of Carbonyl Ester:

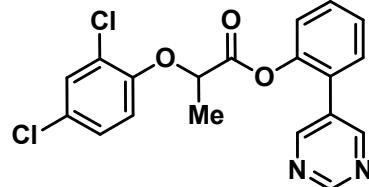


To a stirred solution of carboxylic acid (10 mmol) and DMAP (1 mmol) in 30 mL anhydrous  $\text{CH}_2\text{Cl}_2$ , alcohol (15 mmol) was added. After 15 minute of stirring, DCC (11 mmol) was added to the reaction mixture at 0°C, and then allowed to stir overnight at room temperature. Upon completion of reaction, precipitated urea is then filtered off. Filtrate is evaporated and

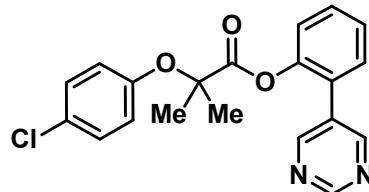
the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated NaHCO<sub>3</sub> solution, and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent is removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether) to give the desired ester.



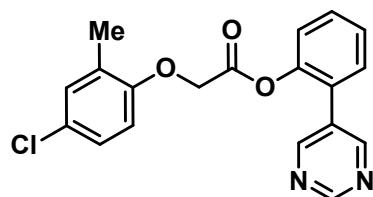
**(S)-2-(pyrimidin-5-yl)phenyl 2-(6-methoxynaphthalen-2-yl)propanoate:** Yellow <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.77 (s, 1H), 8.59 (s, 2H), 7.67 (s, 1H), 7.65 (s, 1H), 7.51 (d, *J* = 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.1, 7.3, 2.0 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.26 (s, 1H), 7.17 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.15 – 7.13 (m, 2H), 3.94 (d, *J* = 8.5 Hz, 4H), 1.52 (d, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 172.8, 158.0, 157.4, 156.3, 148.1, 134.3, 134.1, 131.0, 130.7, 130.4, 129.5, 129.1, 128.1, 127.7, 126.9, 126.1, 125.9, 123.3, 119.3, 105.7, 55.5, 45.5, 18.5. HRMS (ESI): calcd. for C<sub>24</sub>H<sub>20</sub>KN<sub>2</sub>O<sub>3</sub> [M+K]<sup>+</sup>: 423.1106, found: 423.1113.



**2-(pyrimidin-5-yl)phenyl 2-(2,4-dichlorophenoxy)propanoate:** 9.18 (s, 1H), 8.76 (s, 2H), 7.50 – 7.46 (m, 1H), 7.41 – 7.36 (m, 3H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.79 (q, *J* = 6.8 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.7, 157.9, 156.6, 152.0, 147.5, 131.1, 130.9, 130.7, 128.0, 127.8, 127.7, 127.5, 125.1, 123.0, 116.1, 74.3, 34.1, 18.4. HRMS (ESI): calcd. for C<sub>19</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 389.0454, found: 389.0454.

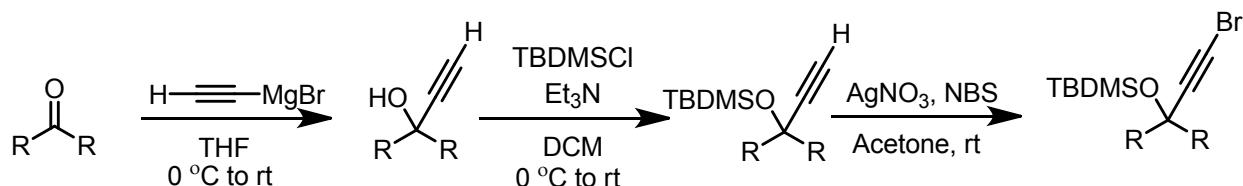


**2-(pyrimidin-5-yl)phenyl 2-(4-chlorophenoxy)-2-methylpropanoate:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.14 (s, 1H), 8.76 (s, 2H), 7.48 (ddd, *J* = 8.1, 6.5, 2.8 Hz, 1H), 7.39 (dd, *J* = 5.5, 1.8 Hz, 2H), 7.15 – 7.13 (m, 2H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.70 – 6.67 (m, 2H), 1.52 (s, 6H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 172.4, 157.9, 156.7, 153.7, 147.9, 131.1, 130.9, 130.6, 129.4, 128.1, 127.7, 127.3, 122.9, 120.5, 79.4, 25.3. HRMS (ESI): calcd. for C<sub>20</sub>H<sub>17</sub>ClN<sub>2</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 391.0820, found: 391.0829.



**2-(pyrimidin-5-yl)phenyl 2-(6-methoxynaphthalen-2-yl)propanoate:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.21 (s, 1H), 8.80 (s, 2H), 7.51 (ddd, *J* = 8.2, 5.8, 3.4 Hz, 1H), 7.42 (dd, *J* = 3.8, 2.1 Hz, 2H), 7.26 (s, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.04 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.42 (d, *J* = 8.7 Hz, 1H), 4.71 (s, 2H), 2.22 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 167.2, 158.0, 156.6, 154.4, 147.4, 131.3, 131.2, 130.9, 130.7, 129.5, 128.0, 127.6, 126.8, 126.6, 123.2, 112.1, 65.7, 16.3. HRMS (ESI): calcd. for C<sub>19</sub>H<sub>15</sub>ClN<sub>2</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 377.0663, found: 377.0666.

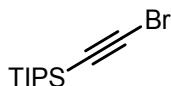
### 2.1.3. General Procedure for Synthesis of Alkynyl bromide:



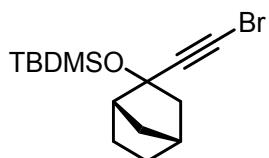
To a solution of ketone (10 mmol) in THF (15 mL) in ice bath, ethynylmagnesium bromide (0.5 M in THF, 30 mL, 15 mmol) was added slowly. Upon completion of addition, ice bath was removed and the mixture was stirred for 4 hours at room temperature. The reaction was quenched with 0.5 N HCl (20 mL). The aqueous layer was extracted with ethyl acetate (40 mL) for three times. Combined organic phases were dried with sodium sulfate and concentrated in vacuo. Desired propargyl alcohol was used directly without further purification.

To a solution of alcohol (10 mmol) and triethylamine (1.80 mL, 12.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) in ice bath was slowly added *tert*-Butyldimethylsilyl chloride (1.8 mL, 10 mmol). After completion of addition, the ice bath was removed. The reaction was stirred for 4 hours at room temperature. The reaction was quenched by sat. aqueous sodium bicarbonate (10 mL). The organic phase was collected and the aqueous layer was further extracted with  $\text{CH}_2\text{Cl}_2$  (10 mL) twice. The combined organic layers were dried with sodium sulfate and concentrated. Crude residue was purified by column chromatography (1% ether in hexane) to give desired silyl ether.

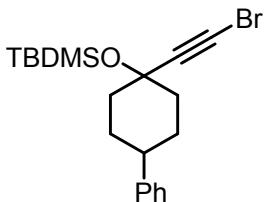
To a solution of alkyne (5 mmol) in acetone (25 mL) was added N-bromo succinimide (0.98 mg, 5.5 mmol) and silver nitrate (42.5 mg, 0.25 mmol) at room temperature. The solution was stirred for 4 hours at room temperature in darkness. The reaction was quenched with water (5 mL) and extracted with ethyl acetate (30 mL) for three times. The combined organic layers were dried with sodium sulfate and concentrated. Crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 100:1) to give desired alkynyl bromide.



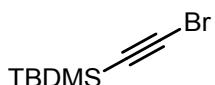
**(bromoethynyl)triisopropylsilane:**  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  1.07 (d,  $J$  = 1.5 Hz, 21H).  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  83.7, 61.9, 18.7, 11.5. HRMS (ESI): calcd. for  $\text{C}_{11}\text{H}_{22}\text{BrSi} [\text{M}+\text{H}]^+$ : 261.0667, found: 261.0668.



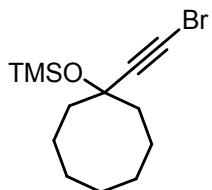
**((1S,4R)-2-(bromoethynyl)bicyclo[2.2.1]heptan-2-yl)oxy)(tert-butyl)dimethylsilane:**  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  2.37 (d,  $J$  = 10.4 Hz, 1H), 2.22 (s, 1H), 2.11 – 1.94 (m, 2H), 1.72 (d,  $J$  = 10.8 Hz, 1H), 1.59 – 1.50 (m, 1H), 1.37 – 1.23 (m, 4H), 0.92 – 0.88 (m, 9H), 0.16 (dd,  $J$  = 14.5, 9.8 Hz, 6H).  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  86.3, 75.6, 50.8, 49.4, 38.0, 37.0, 29.0, 26.1, 21.4, 18.3, -2.7, -3.1. HRMS (ESI): calcd. for  $\text{C}_{15}\text{H}_{26}\text{BrOSi} [\text{M}+\text{H}]^+$ : 329.0934, found: 329.0934.



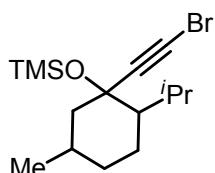
**((1-(bromoethynyl)-4-phenylcyclohexyl)oxy)(tert-butyl)dimethylsilane:** **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.20 (m, 3H), 2.56 – 2.46 (m, 1H), 2.09 (t, *J* = 9.4 Hz, 2H), 1.90 – 1.77 (m, 4H), 1.67 (td, *J* = 12.4, 4.5 Hz, 2H), 0.92 (s, 9H), 0.21 (s, 6H). **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)** δ 146.7, 128.6, 127.1, 126.3, 83.7, 71.5, 45.6, 43.4, 41.6, 31.6, 26.0, 18.2, -2.7. HRMS (ESI): calcd. for C<sub>20</sub>H<sub>30</sub>BrOSi [M+H]<sup>+</sup>: 393.1244, found: 393.1241.



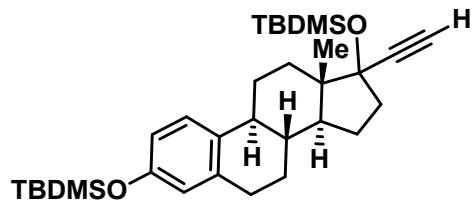
**(bromoethynyl)(tert-butyl)dimethylsilane:** **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 0.94 (s, 9H), 0.12 (s, 6H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 85.5, 61.7, 26.2, 16.9, -4.5. HRMS (ESI): calcd. for C<sub>8</sub>H<sub>15</sub>BrNaSi [M+Na]<sup>+</sup>: 241.0019, found: 241.0019.



**((1-(bromoethynyl)cyclooctyl)oxy)trimethylsilane:** **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 1.95 – 1.80 (m, 4H), 1.65 – 1.44 (m, 10H), 0.16 (d, *J* = 3.2 Hz, 9H). **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)** δ 85.2, 73.9, 43.9, 39.2, 28.2, 24.5, 21.9, 2.0. HRMS (ESI): calcd. for C<sub>13</sub>H<sub>23</sub>BrKOSi [M+K]<sup>+</sup>: 341.0333, found: 341.0325.



**((1-(bromoethynyl)-2-isopropyl-5-methylcyclohexyl)oxy)trimethylsilane:** **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 2.30 – 2.22 (m, 1H), 1.96 – 1.89 (m, 1H), 1.69 (dd, *J* = 7.9, 4.5 Hz, 2H), 1.42 (ddd, *J* = 11.4, 9.7, 3.1 Hz, 2H), 1.25 (dd, *J* = 16.4, 9.1 Hz, 1H), 1.18 – 1.14 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 1H), 0.91 (d, *J* = 7.1 Hz, 3H), 0.85 (dd, *J* = 12.9, 6.6 Hz, 6H), 0.16 (s, 9H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 85.2, 74.5, 52.0, 50.5, 35.1, 28.8, 27.3, 24.1, 22.1, 20.7, 18.5, 1.8. HRMS (ESI): calcd. for C<sub>15</sub>H<sub>28</sub>BrOSi [M+H]<sup>+</sup>: 331.1087, found: 331.1089.

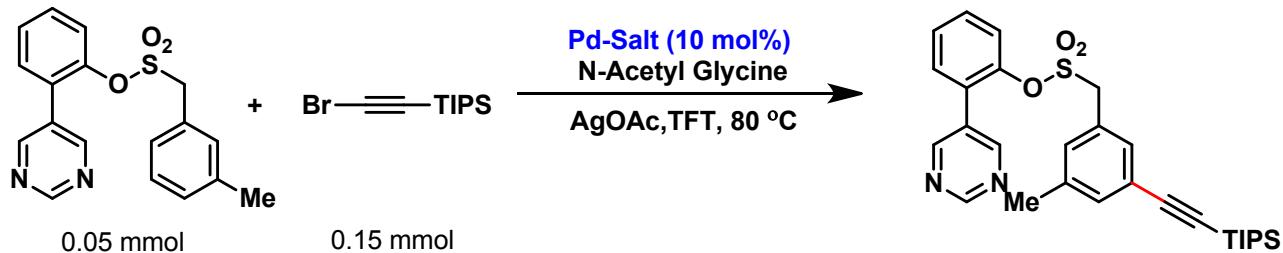


**((8R,9S,13S,14S)-17-ethynyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diyl)bis(tert-butyldimethylsilane):** **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.13 (d, *J* = 8.4 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.55 (d, *J* = 2.5 Hz, 1H), 2.79 (d, *J* = 4.6 Hz, 2H), 2.54 (s, 1H), 2.35 – 2.16 (m, 3H), 1.98 – 1.82 (m, 3H), 1.73 – 1.63 (m, 2H), 1.54 (s, 1H), 1.49 – 1.34 (m, 4H), 0.98 (s, 9H), 0.89 (s, 9H), 0.84 (s, 3H), 0.20 – 0.16 (m, 12H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 153.48, 138.11, 133.46, 126.40, 120.12, 117.32, 88.43, 80.84, 74.72, 48.50, 48.44, 43.94, 40.46, 39.69, 33.06, 29.92, 27.58, 26.65, 26.03, 25.94, 23.32, 18.48, 18.39, 13.38, -2.72, -2.85, -4.16. HRMS (ESI): calcd. for C<sub>32</sub>H<sub>53</sub>O<sub>2</sub>Si<sub>2</sub> [M+H]<sup>+</sup>: 525.3578, found: 525.3579.

**2.2.a Optimization details for *meta*-C–H alkynylation with (bromoethylanyl)triisopropylsilane:**

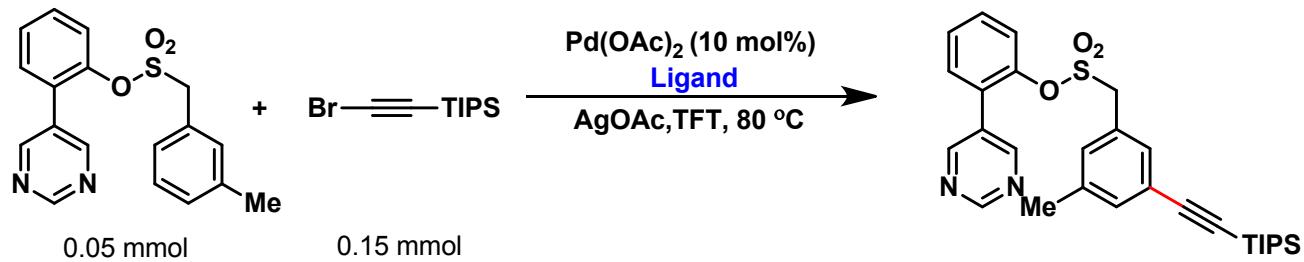
*Yield and selectivity are based on HPLC of the crude reaction mixture using acetophenone as internal standard.*

**Table S1. Optimization by varying different Palladium catalyst:**



Entry	Pd salt	Yield % ( <i>meta</i> :others) <sup>a</sup>
1	$\text{PdCl}_2$	20 (30:1)
2	$\text{PdO}$	0
<b>3</b>	$\text{Pd(OAc)}_2$	<b>23</b> (30:1)
4	$\text{PdCl}_2(\text{PPh}_3)_2$	6
5	$\text{Pd}(\text{acac})_2$	5
6	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	14
7	$[\text{Pd}(\pi\text{-cinnamyl})\text{Cl}]_2$	19 (30:1)
8	$\text{Pd}(\text{OPiv})_2$	5
9	$\text{Pd}(\text{dppf})\text{Cl}_2$	4
10	$\text{Pd}(\text{PhCN})_2\text{Cl}_2$	18 (30:1)
11	$\text{Pd}(\text{TFA})_2$	3
12	$\text{Pd}_2(\text{dba})_3$	8
13	$[\text{Pd}(\text{allyl})]_2\text{Cl}_2$	18 (30:1)

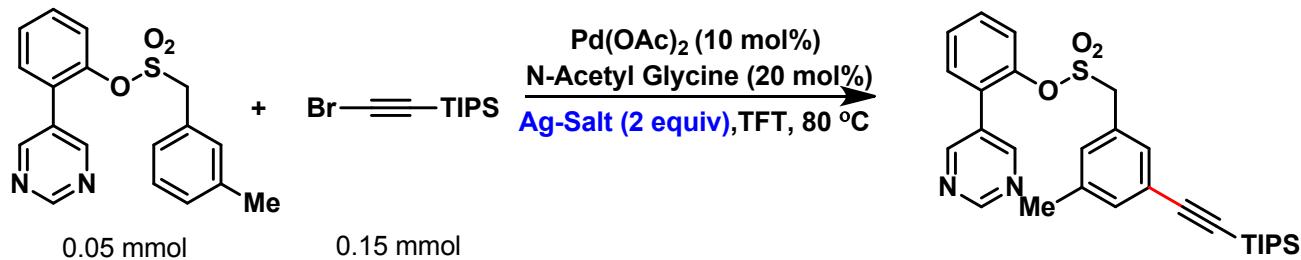
**Table S2. Optimization by varying different amino acid ligands:**



Entry	Ligand	Yield % (meta:others) <sup>a</sup>
1	N-Acetyl-Glycine	23 (30:1)
2	N-Ac-DL-2-Phenyl Glycine	1
3	N-Ac-L-leucine	7
4	N-Ac-DL-Norleucine	7
5	N-Ac-I-Valine	5
6	N-Ac-DL-Tryptophan	3
7	N-Ac-4-hydroxy-L-proline	5
8	N-Ac-DL-methionine	1
9	N-Ac-L-histidine monohydrate	11
10	N-Ac-Glycine Ethyl ester	9
11	N-Ac-L-Glutamic acid	3
12	N-Boc-D-Valine	4
13	N-Boc-L-Isoleucine	10
14	N-Boc-L- <i>tert</i> -leucine	3
15	N-Boc-L-Tyrosine	4
16	N-Boc-D-Serine	2
17	N-Boc-L-Aspartic acid	-
18	N-Boc-Glycine	2
19	N-Boc-4-Nitro phenyl glycine	4
20	N-Boc-L-Alanine	2
21	Fmoc-L-Leucine	4
22	Fmoc-L-Alanine	1
23	Fmoc-L-Methionine	3

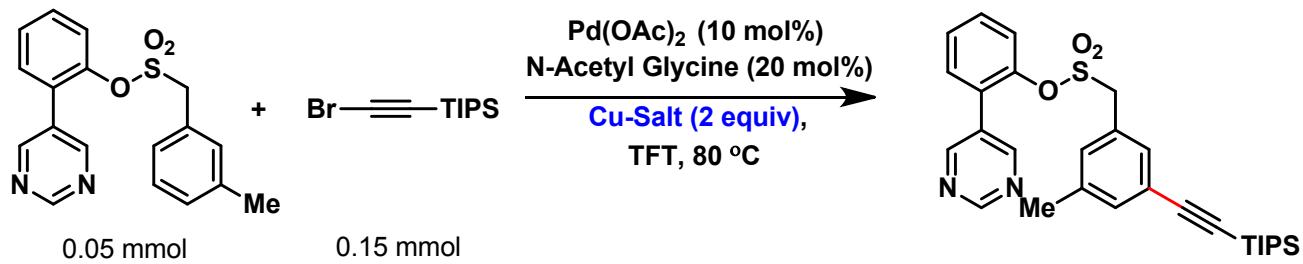
24	Fmoc-L-Glutamine	5
25	Fmoc-Glycine	1
26	Fmoc-L-Threonine	1
27	N-Boc-L-Phenyl alanine	4
28	N-Carbenzoxy-DL-valine	5
29	N-Carbenzoyl-DL-leucine	-
30	Glycine	4
31	Glycyl Glycine	1
32	N-Formyl Glycine	18 (30:1)
33	N-Benzoyl Histidine	3
34	N-Phthaloyl-L-Histidine	3
35	N- $\alpha$ -acetyl-L-Lysine	2

Table S3. Optimization by varying different Silver salt optimization:



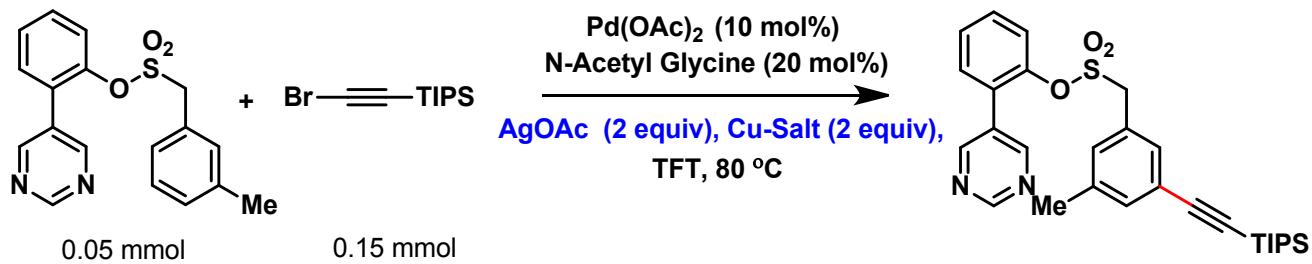
Entry	Ag-Salt	Yield % (meta:others) <sup>a</sup>
1	AgOAc	23 (30:1)
2	Ag <sub>2</sub> O	-
3	Ag <sub>2</sub> SO <sub>4</sub>	1
4	Ag <sub>2</sub> CO <sub>3</sub>	12
5	AgNO <sub>3</sub>	-
6	AgNO <sub>2</sub>	-
7	AgI	-
8	AgF	-
9	AgBF <sub>4</sub>	-
10	AgSbF <sub>6</sub>	-

**Table S4. Optimization by varying different Copper salt optimization:**



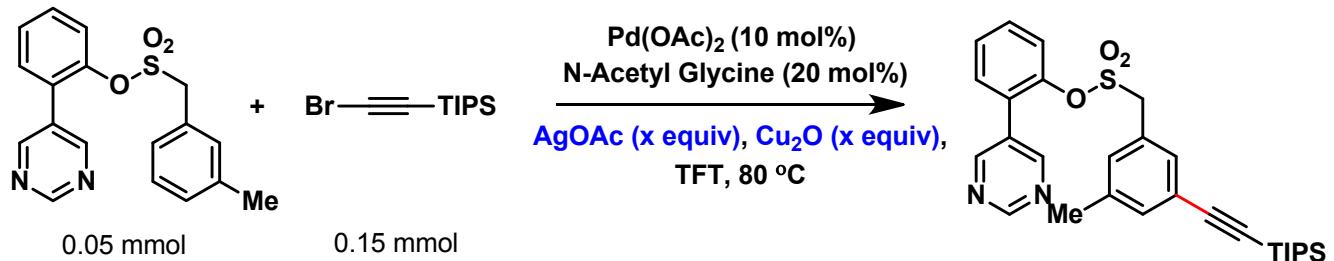
Entry	Ligand	Yield % (meta:others) <sup>a</sup>
1	CuCl	8
2	CuBr	-
3	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	6
4	$\text{Cu}(\text{TFA})_2$	-
5	$\text{CuCO}_3$	5
6	$\text{Cu}(\text{OAc})$	6
7	$\text{Cu}(\text{OTf})_2$	-
8	$\text{CuF}_2$	7
<b>9</b>	<b><math>\text{Cu}_2\text{O}</math></b>	<b>13 (30:1)</b>
10	CuO	8
11	$\text{CuBr}_2$	-
12	$\text{Cu}(\text{OAc})_2$	6
13	CuI	-
14	$\text{CuCl}_2$	5

**Table S5. Optimization by different Silver and Copper salt combination:**

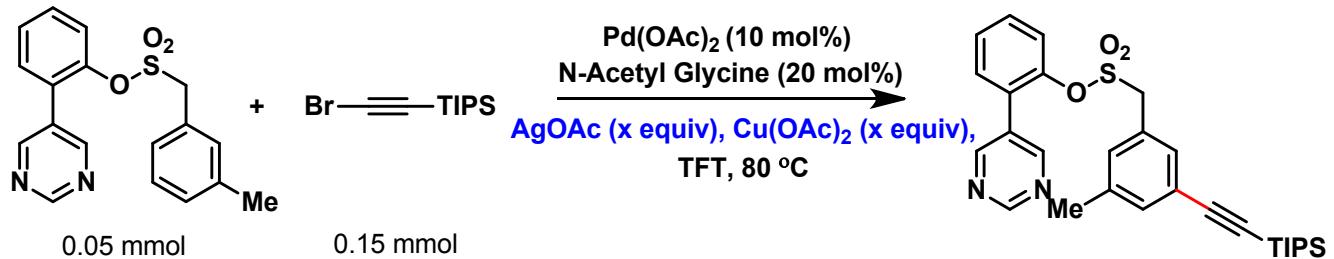


Entry	Copper Salt	Yield % ( <i>meta</i> :others) <sup>a</sup>
1	$\text{CuF}_2$	11
2	$\text{Cu}_2\text{O}$	15
<b>3</b>	$\text{Cu(OAc)}_2$	<b>18</b> (30:1)

**Table S6. Optimization of amount of different Silver and Copper salt combination:**

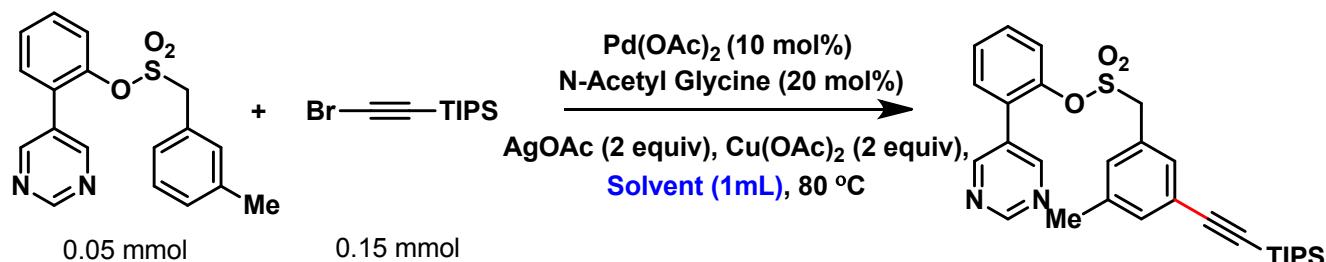


Entry	Cu-Ag Salt Combination	Yield % ( <i>meta</i> :others) <sup>a</sup>
1	$\text{AgOAc}$ (3 equiv) + $\text{Cu}_2\text{O}$ (3 equiv)	10
2	$\text{AgOAc}$ (3 equiv) + $\text{Cu}_2\text{O}$ (2 equiv)	8
3	$\text{AgOAc}$ (2 equiv) + $\text{Cu}_2\text{O}$ (3 equiv)	9
4	$\text{AgOAc}$ (2 equiv) + $\text{Cu}_2\text{O}$ (2 equiv)	9



Entry	Cu-Ag Salt Combination	Yield % ( <i>meta</i> :others) <sup>a</sup>
1	AgOAc (2 equiv) + Cu(OAc) <sub>2</sub> (2 equiv)	23 (30:1)
2	AgOAc (3 equiv) + Cu(OAc) <sub>2</sub> (2 equiv)	19
3	AgOAc (2 equiv) + Cu(OAc) <sub>2</sub> (3 equiv)	18
4	AgOAc (3 equiv) + Cu(OAc) <sub>2</sub> (3 equiv)	20

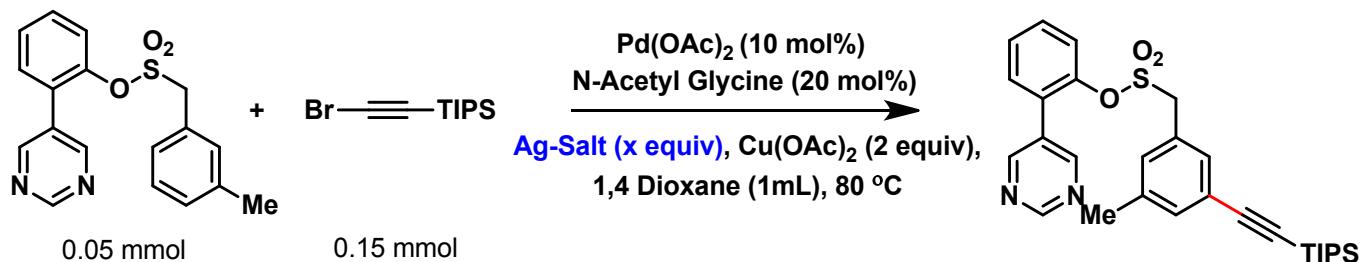
Table S7. Optimization of different Solvent:



Entry	Solvent	Yield % ( <i>meta</i> :others) <sup>a</sup>
1	TFT	9
2	Hexafluorobenzene	4
3	OctafluroToluene	2
4	TFE	1
5	DCE	37 (30:1)
6	CH <sub>2</sub> Cl <sub>2</sub>	26 (30:1)
7	MeCN	11
8	Toluene	7
9	1,4 Dioxane	80 (30:1)
10	TBME	13
11	Cyclopentyl methyl ether	7
12	THF	27 (30:1)
13	CH <sub>2</sub> Cl <sub>2</sub> (anhydrous)	16
14	1,4 Dioxane (anhydrous)	70 (30:1)
15	2-Methyl THF	11
16	MeOH	2

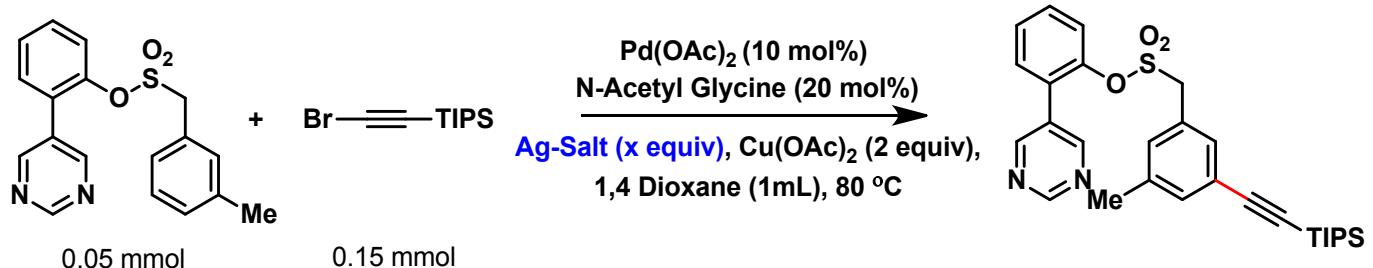
17	<chem>CHCl3</chem>	8
16	<i>tert</i> -Butanol	9
17	2-Propanol	1

Table S8. : Optimization by amount of Silver salt and Copper salt combination using 1,4-Dioxane as solvent:



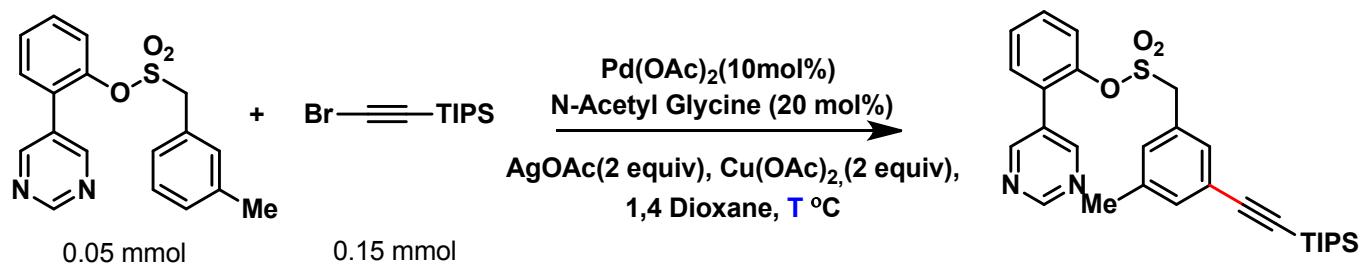
Entry	Solvent	Yield % ( <i>meta</i> :others) <sup>a</sup>
1	<chem>AgOAc</chem> (1 equiv)	57 (30:1)
<b>2</b>	<b><chem>AgOAc</chem> (2 equiv)</b>	<b>80</b> (30:1)
3	<chem>AgOAc</chem> (3 equiv)	78 (30:1)
4	<chem>Ag2CO3</chem> (1 equiv)	31 (30:1)
5	<chem>Ag2CO3</chem> (2 equiv)	71 (30:1)
6	<chem>Ag2CO3</chem> (3 equiv)	46 (30:1)

Table S9. Optimization of amount of alkyne:



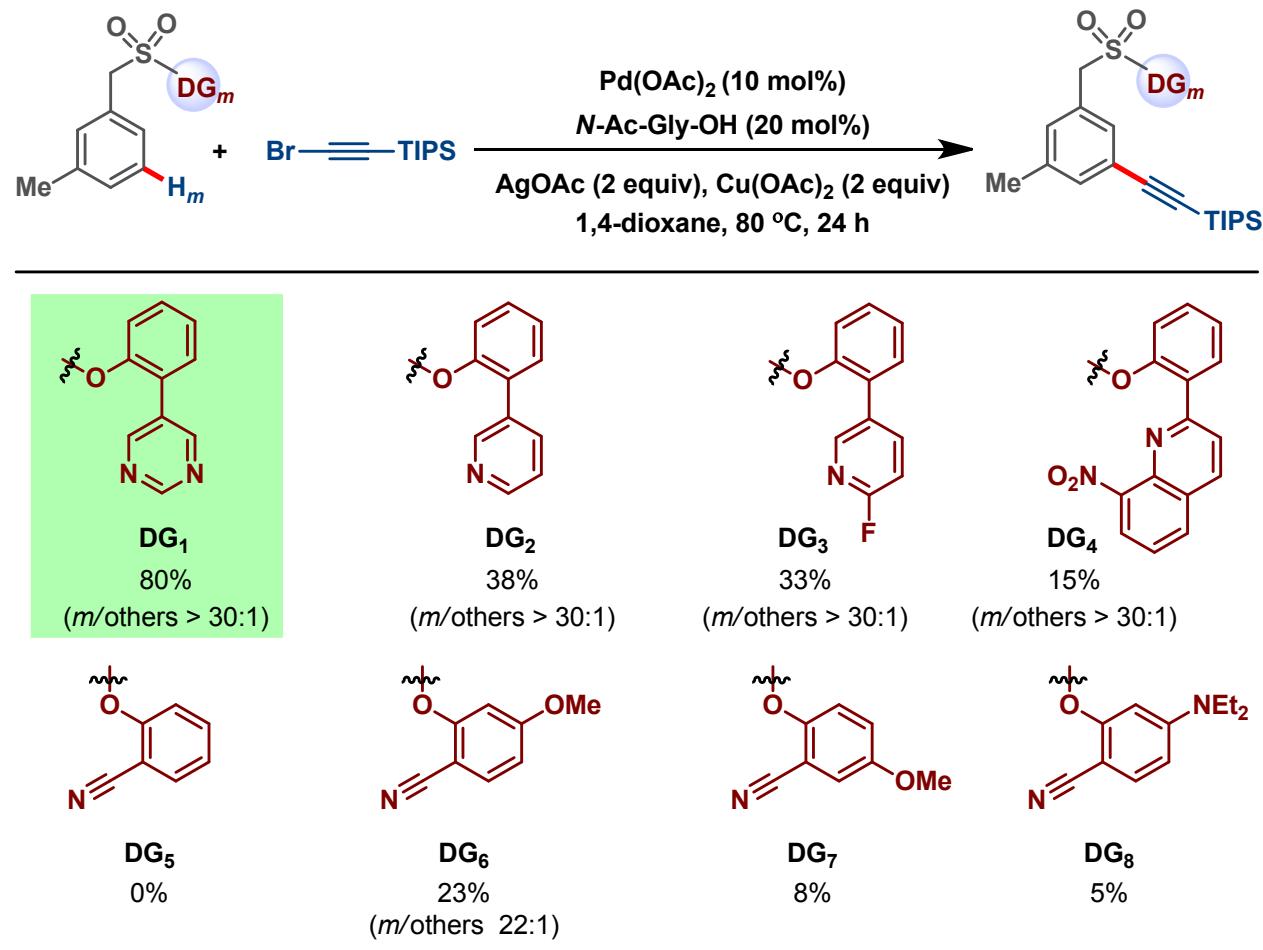
<b>Entry</b>	<b>Amount (equiv)</b>	<b>Yield % (<i>meta</i>:others)<sup>a</sup></b>
1	0.75	38 (30:1)
2	2	61 (30:1)
3	2.5	75 (30:1)
<b>4</b>	<b>3</b>	<b>80</b> (30:1)
5	4	90 (30:1)

**Table S10. Optimization of temperature:**



<b>Entry</b>	<b>Temperature °C</b>	<b>Yield % (<i>meta</i>:others)<sup>a</sup></b>
1	50	30 (30:1)
2	60	57 (30:1)
3	70	65 (30:1)
<b>4</b>	<b>80</b>	<b>80</b> (30:1)
5	90	66 (30:1)
6	100	73 (30:1)

## 2.2.b Screening of Scaffolds:



## 2.3. General procedure for palladium catalyzed *meta*-selective C–H alkynylation of arene:

To an oven-dried screw cap reaction tube charged with a magnetic stir-bar was added sulfonate ester / carboxylate ester / ether scaffold (0.1 mmol, 1 equiv), Pd(OAc)<sub>2</sub> (10 mol%), N-acetyl glycine (20 mol%), AgOAc (2 equiv) and Cu(OAc)<sub>2</sub> (2 equiv). After that (bromoethynyl)triisopropylsilane (2.5 equiv) was added with a microlitre pipette and 1 mL 1,4-dioxane was added with a disposable laboratory syringe under aerobic condition. The tube was placed in a preheated oil bath at 80 °C and the reaction mixture was stirred for 24 h. The reaction mixture was then cooled to room temperature and filtered through a celite pad with ethyl acetate. The filtrate was concentrated and the crude compound was purified by

column chromatography using silica gel (100-200 mesh size) and ethyl acetate/petroleum ether as the eluent (**1-66**).

### **2.3.1.a General procedure for palladium catalyzed *meta*-selective sequential hetero difunctionalization of arene**

#### **1. Olefination followed by alkynylation**

An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, , Pd(OAc)<sub>2</sub> (10 mol%), Ac-Gly-OH (20 mol%), Ag<sub>2</sub>CO<sub>3</sub> (2 equiv.), sulfonate ester / carboxylate ester / ether scaffold/silyl scaffold (0.2 mmol) and olefin (0.4 mmol). Solid reagents were weighed first followed by liquid reagents. 1.5 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was added. The reaction mixture was stirred vigorously on a preheated oil bath at 80 °C along. The reaction was taken out after 24 h and the reaction mixture was diluted with EtOAc and filtered through a celite pad. After filtration and evaporation of the solvent, the crude mixture was purified by column chromatography using silica gel (100-200 mesh size) and ethyl acetate/petroleum ether as the eluent.<sup>4</sup>

Compound (**67, 71, 73 & 74**) was prepared from the *m*-olefinated product following general by general procedure 2.3 using (bromoethynyl)triisopropylsilane as alkyne partner. Column chromatography: silica gel; Eluent: ethyl acetate/petroleum ether.

#### **2. Alkylation followed by alkynylation**

An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, Pd(OAc)<sub>2</sub> (10 mol%), Ac-Gly-OH (20 mol%), Ag<sub>2</sub>CO<sub>3</sub> (3.5 equiv.), sulfonate ester / carboxylate ester / ether scaffold/silyl scaffold (0.2 mmol). The reaction tube was evacuated and filled with oxygen. Then 2.5 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was added and followed by alkenyl alcohol (0.6 mmol) into the reaction tube by syringe. The reaction mixture was stirred vigorously on a preheated oil bath at 80 °C along. The reaction was carried out for 30 h and the reaction mixture was diluted with EtOAc and filtered through a celite pad. After filtration and evaporation of the solvent, the crude mixture was purified by column chromatography using neutral alumina and ethyl acetate/petroleum ether as the eluent.<sup>1</sup>

Compound (**68 & 75**) was prepared from the *m*-alkylated product following general procedure 2.3 using (bromoethynyl)triisopropylsilane as alkyne partner. Column chromatography: silica gel; Eluent: ethyl acetate/petroleum ether.

### 3. Cyanation followed by alkynytaion

An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, Pd(OAc)<sub>2</sub> (15 mol%), Ac-Gly-OH (30 mol%), Ag<sub>2</sub>CO<sub>3</sub>(2.0 equiv), CuCl (1 equiv.) benzylsulphonylester (0.2 mmol) and CuCN (0.6 mmol). Then 2.5 mL of DCE and 0.25 mL of 1,1,1,3,3-hexafluoro-2-propanol (HFIP) was added. The reaction mixture was stirred vigorously on a preheated oil bath at 90 °C along. The reaction was carried out for 30h and the reaction mixture was diluted with EtOAc and filtered through a celite pad. After filtration and evaporation of the solvent, the crude mixture was dissolved with 10 mL EtOAc and 5 mL H<sub>2</sub>O followed by aqueous ammonia solution was added dropwise until the aqueous part became blue color. Next, the mixture was extracted with ethyl acetate (3x10 mL) and the total organic part was collected and evaporated. The desired cyanation product was isolated by column chromatography using silica gel (100-200 mesh size) and ethyl acetate/petroleum ether as the eluent.<sup>2</sup>

Compound (**69**) was prepared from the *m*-cyanated product following general by general procedure 2.3 using (bromoethynyl)triisopropylsilane as alkyne partner. Column chromatography: silica gel; Eluent: ethyl acetate/petroleum ether (15/85, v/v); Yield: 53%.

### 4. Sequential hetero alkynylation

Compound (**70, 72 & 76**) was prepared by general procedure 2.3 using first (1-(bromoethynyl)-2-isopropyl-5-methylcyclohexyl)oxytrimethylsilane as the alkynye bromide and then (bromoethynyl)triisopropylsilane. Column chromatography: silica gel; Eluent: ethyl acetate/ petroleum ether.

### **2.3.1.b General procedure for gram scale synthesis of *meta*-alkynylated protocol**

An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, Pd(OAc)<sub>2</sub> (10 mol%, 67.2 mg for 3 mmol), Ac-Gly-OH (20 mol%, 70.2 mg for 3 mmol), AgOAc (2.0 equiv, 1.02 g for 3 mmol), Cu(OAc)<sub>2</sub> (2 equiv, 1.086 g for 3 mmol) benzylsulfonyl ester scaffold (1.0 g for 3 mmol) and (bromoethyl)triisopropylsilane (9 mmol, 2.3 g). Then 20 mL of 1,4-Dioxane was added. The reaction mixture was stirred vigorously on a preheated oil bath at 80°C along. The reaction was carried out for 24 h and the reaction mixture was diluted with EtOAc and filtered through a celite pad. After filtration and evaporation of the solvent, the desired alkynylated product was isolated by column chromatography using silica gel (100-200 mesh size) and ethyl acetate/petroleum ether (20/80, v/v); as the eluent.

### **2.3.1.c General procedure for directing group removal of *meta*-alkynylated protocol**

An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, the alkynylated product (**30**) (0.05 mmol) and 3 equiv LiOH·H<sub>2</sub>O. Then 1 mL of THF, 0.5 mL of MeOH and 0.5 mL of H<sub>2</sub>O were added. The reaction mixture was stirred vigorously at room temperature for 12 h. After the completion of the reaction the solvent was removed under reduced pressure. To the reaction mixture, 5 mL of water was added and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> followed by removal of solvent under reduced pressure. The desired phenylacetic acid (**77**) was isolated by preparative TLC.

An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, the alkynylated product (**38**) (0.05 mmol) and 1 mL of THF was added. Then 1.2 equiv TBAF was added to the reaction mixture. The reaction mixture was stirred vigorously at room temperature for 12 h. After the completion of the reaction the solvent was removed under reduced pressure. To the reaction mixture, 5 mL of water was added and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> followed by removal of solvent under reduced pressure the desired alkynylated product (**78**) was isolated by column chromatography using silica gel (100-200 mesh size) and ethyl acetate/petroleum ether (1/99, v/v); as the eluent.

### **2.3.1.d General procedure for different application of *meta*-alkynylated protocol**

#### **Desilylation of triisopropyl group from alkynylated product:**

An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, the alkynylated product (**1**) (0.05 mmol) and 4 equiv CsF. Then 1 mL of CH<sub>3</sub>CN was added. The reaction mixture was stirred vigorously for overnight at room temperature. After the completion of the reaction the solvent was removed under reduced pressure. To the reaction mixture, 5 mL of water was added and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> followed by removal of solvent under reduced pressure. The desired desilylated product (**79**) was isolated by column chromatography. Eluent: ethyl acetate/petroleum ether (10/90, v/v).

#### **1. Removal of –SO<sub>2</sub>-DG group (modified Julia olefination):**

To a dried r.b. flask equipped with a magnetic stir bar was added 0.3 mL of LDA solution (2M in THF) in 5 mL of dry THF solvent. The solution was cooled to -78° C. Then a solution in THF (20 mL) of benzaldehyde (0.4 mmol) and alkynylated product (**1**) (0.3 mmol) was added slowly to the LDA/THF solution around 1h at -78°C. The reaction mixture was stirred overnight while warming to room temperature. After the reaction mixture was quenched on saturated NH<sub>4</sub>Cl solution and extracted with ethylacetate. Combined organic portion was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The crude mixture was concentrated under reduced pressure and purified by column chromatography using silica gel (100-200 mesh size) and ethyl acetate/petroleum ether (2/98, v/v) as the eluent to give the disered product (**80**).

#### **2. Formation of acid by direct oxidation of alkynylated product:**

To a dried reaction tube solution of (**1**) (0.1 mmol) in a mixed solvent of CCl<sub>4</sub>, CH<sub>3</sub>CN and H<sub>2</sub>O (1.4mL, v/v/v 2:3:3) was added RuCl<sub>3</sub> (5 mol%) and sodium periodate (0.4 mmol), then the reaction was vigorously at 60°C for 2 h. After completion, the mixture was extracted with dichloromethane (3 x 5 mL).The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by column chromatography using silica gel (100-200 mesh size) and ethyl acetate/petroleum ether (10/90, v/v) as the eluent to give the disered product (**81**).<sup>5</sup>

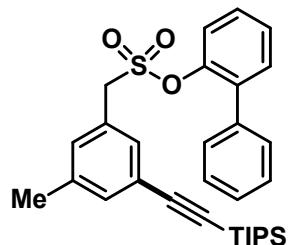
### 3. Synthesis of ketone derivative from alkynylated product:

To a dried reaction tube solution of (**1**) (0.1 mmol) in formic acid (2 mL) was added, then the reaction was stirred vigorously at 100°C for 1 h. After completion, the mixture was concentrated under reduced pressure. After that 5 mL of water was added and extracted with dichloromethane (3 x 5 mL). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>. Followed by removal of solvent under reduced pressure. The crude product was purified by column chromatography using silica gel (100-200 mesh size) and ethyl acetate/petroleum ether (10/90, v/v) as the eluent to give the desired product (**82**).<sup>6</sup>

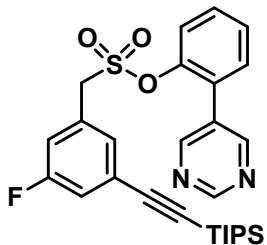
### 4. Synthesis of azoles from desilylated product:

To a solution of CuSO<sub>4</sub>.5H<sub>2</sub>O (0.018 mmol), sodium ascorbate (0.05 mmol), in water/*tert*-butanol mixture. of (1:1 v/v, 2.0 mL) was added a mixture of alkyne **79** (0.1 mmol) and tosyl azide (0.1 mmol) at room temperature. The mixture was stirred for 1 h. Then CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added to dissolve the crude product. The organic layer was washed with H<sub>2</sub>O followed by brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo. The desired product (**83**) was purified by a column chromatography. Eluent: ethyl acetate/petroleum ether (10/90, v/v).<sup>7</sup>

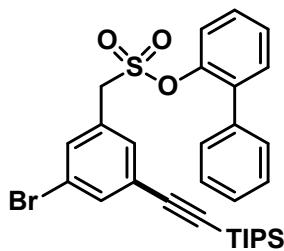
## 2.4 Characterization data of *meta*- alkynylated products



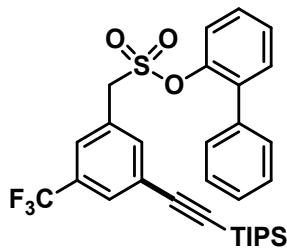
**3-(pyrimidin-5-yl)phenyl(3-methyl((triisopropylsilyl)ethynyl)phenyl)methanesulfonate (**1**):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 80%; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.25 (s, 1H), 8.86 (s, 2H), 7.48 – 7.37 (m, 4H), 7.32 (s, 1H), 7.20 (s, 1H), 7.07 (s, 1H), 4.24 (s, 2H), 2.31 (s, 3H), 1.12 (s, 21H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 156.8, 146.2, 139.1, 134.0, 131.4, 131.4, 131.3, 130.9, 128.9, 128.1, 126.7, 124.5, 123.5, 106.2, 91.8, 57.4, 21.2, 18.9, 11.5. **HRMS (ESI):** calcd. for C<sub>29</sub>H<sub>36</sub>N<sub>2</sub>O<sub>3</sub>SSi [M+H]<sup>+</sup>: 521.2289, found: 521.2286. **IR** 1002, 1098, 1156, 1194, 1261, 1308, 1361, 1412, 1462, 1552, 1598, 1734, 2155, 2865, 2943, 3043.



**2-(pyrimidin-5-yl)phenyl(3-fluoro-5((triisopropylsilyl)ethynyl)phenyl)methanesulfonate (2):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 75%; [meta/others = 14:1]. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.23 (s, 1H), 8.83 (s, 2H), 7.50 – 7.40 (m, 4H), 7.22 – 7.17 (m, 2H), 7.02 – 6.98 (m, 1H), 4.26 (s, 2H), 1.12 (s, 21H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 163.4, 161.4, 158.1, 156.8, 146.0, 131.4, 131.0, 130.9, 130.2, 130.1, 128.9, 128.9, 128.3, 123.5, 120.3, 120.2, 118.0, 117.9, 104.6, 93.9, 56.9, 18.9, 11.4. **HRMS (ESI):** calcd. for C<sub>28</sub>H<sub>34</sub>FN<sub>2</sub>O<sub>3</sub>SSi [M+H]<sup>+</sup>: 525.2038, found: 525.2039. **IR:** 1099, 1157, 1194, 1270, 1317, 1364, 1412, 1461, 1552, 1591, 1741, 2161, 2866, 2925, 3043.

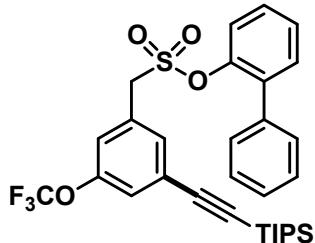


**2-(pyrimidin-5-yl)phenyl(3-bromo-5((triisopropylsilyl)ethynyl)phenyl)methanesulfonate (3):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish liquid; isolated yield: 74%; [meta/others = 17:1]. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.23 (s, J = 4.6 Hz, 1H), 8.83 (s, 2H), 7.64 – 7.62 (m, 1H), 7.49 – 7.39 (m, 5H), 7.32 (t, J = 1.4 Hz, 1H), 4.23 (s, 2H), 1.11 (d, J = 2.6 Hz, 21H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.1, 156.8, 146.0, 136.0, 133.4, 132.8, 131.4, 131.0, 130.9, 128.9, 128.7, 128.3, 126.4, 123.5, 122.7, 104.3, 94.3, 56.6, 18.8, 11.4. **HRMS (ESI):** calcd. for C<sub>28</sub>H<sub>34</sub>BrN<sub>2</sub>O<sub>3</sub>SSi [M+H]<sup>+</sup>: 585.1237, found: 585.1236. **IR:** 1098, 1156, 1194, 1246, 1364, 1412, 1462, 1491, 1564, 1742, 2157, 2866, 2943, 3043.

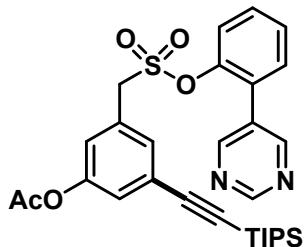


**2-(pyrimidin-5-yl)phenyl((triisopropylsilyl)ethynyl)phenyl)methanesulfonate (4):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 77%; [meta/others = 7:1]. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.23 (s, 1H), 8.83 (s, 2H), 7.73 (s, 1H), 7.57 (s, 1H), 7.52 – 7.40 (m, 5H), 4.32 (s, 2H), 1.13 (d, J = 2.8 Hz, 21H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 158.1, 156.8, 146.0,

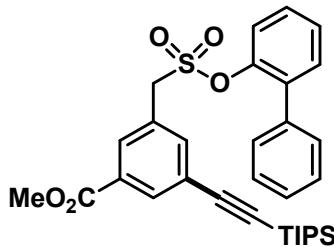
137.2, 132.2, 131.8, 131.5, 131.0, 130.0, 128.9, 128.4, 128.1, 127.0, 125.8, 123.6, 104.2, 94.9, 56.8, 18.8, 11.4. **HRMS (ESI)**: calcd. for  $C_{29}H_{34}F_3N_2O_3SSi$  [M+H]<sup>+</sup>: 575.2006, found: 575.2006. **IR**: 1104, 1134, 1158, 1179, 1230, 1349, 1412, 1459, 1492, 1552, 1580, 1745, 2158, 2867, 2944.



**2-(pyrimidin-5-yl)phenyl((triisopropylsilyl)ethynyl)phenylmethanesulfonate (5):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 71%; [*meta/others* = 5:1]. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.23 (s, 1H), 8.83 (s, 2H), 7.51 – 7.45 (m, 3H), 7.43 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.39 – 7.37 (m, 1H), 7.33 (d, *J* = 6.6 Hz, 1H), 7.15 (s, 1H), 4.28 (s, 2H), 1.12 (d, *J* = 3.2 Hz, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 169.1, 157.9, 156.6, 156.5, 148.0, 134.6, 133.0, 132.8, 131.3, 130.7, 130.6, 128.0, 127.3, 124.5, 123.3, 105.8, 92.2, 40.6, 19.4, 18.9, 18.5, 11.5. **HRMS (ESI)**: calcd. for  $C_{29}H_{34}F_3N_2O_3SSi$  [M+H]<sup>+</sup>: 591.1955, found: 591.1949. **IR**: 1073, 1115, 1194, 1219, 1258, 1413, 1463, 1552, 1588, 1765, 2151, 2867, 2943.

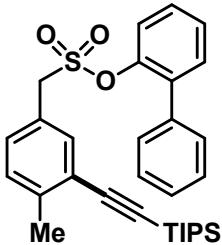


**3-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)-5-((triisopropylsilyl)ethynyl)phenyl acetate (6):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 58%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.23 (s, 1H), 8.83 (s, 2H), 7.50 – 7.44 (m, 2H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.38 (td, *J* = 8.1, 1.6 Hz, 1H), 7.25 (d, *J* = 3.1 Hz, 2H), 7.06 – 7.03 (m, 1H), 4.28 (s, 2H), 2.30 (s, 3H), 1.11 (s, 21H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 169.2, 158.1, 156.8, 150.8, 146.07, 131.69, 131.36, 131.05, 130.94, 128.91, 128.24, 128.20, 126.49, 126.00, 124.20, 123.58, 104.9, 93.6, 56.9, 21.3, 18.8, 11.4. **HRMS (ESI)**: calcd. for  $C_{30}H_{37}N_2O_5SSi$  [M+H]<sup>+</sup>: 565.2187, found: 565.2181. **IR**: 680, 727, 774, 860, 1020, 1099, 1157, 1195, 1262, 1306, 1366, 1412, 1457, 1491, 1552, 1587, 1771, 2159, 2865, 2927, 3043.

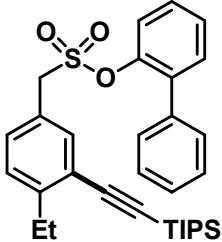


**methyl ((triisopropylsilyl)ethynyl)benzoate (7):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 63%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.21 (s, 1H), 8.82 (s,

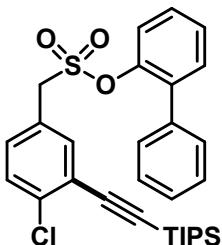
2H), 8.14 (d,  $J$  = 1.3 Hz, 1H), 7.91 (s, 1H), 7.58 (s, 1H), 7.51 – 7.39 (m, 4H), 4.32 (s, 2H), 3.93 (s, 3H), 1.13 (d,  $J$  = 2.6 Hz, 21H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  165.8, 158.1, 156.8, 146.0, 138.1, 134.3, 131.5, 131.4, 130.9, 128.9, 128.3, 127.5, 125.3, 123.6, 104.8, 93.8, 57.0, 52.7, 18.9, 11.4. HRMS (ESI): calcd. for  $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_5\text{SSi}$  [ $\text{M}+\text{H}]^+$ : 565.2187, found: 565.2191. IR: 1157, 1195, 1225, 1258, 1319, 1363, 1412, 1452, 1491, 1552, 1727, 2156, 2866, 2944, 3044.



**2-(pyrimidin-5-yl)phenyl ((triisopropylsilyl)ethynyl)phenyl methanesulfonate (8):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); brown solid; isolated yield: 62%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.23 (s, 1H), 8.85 (s, 2H), 7.44 (ddd,  $J$  = 25.6, 12.8, 4.9 Hz, 4H), 7.35 (s, 1H), 7.19 (d,  $J$  = 7.9 Hz, 1H), 7.14 (dd,  $J$  = 7.9, 1.3 Hz, 1H), 4.25 (s, 2H), 2.46 (s, 3H), 1.13 (s, 21H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  157.8, 156.8, 146.2, 142.4, 134.4, 131.3, 130.9, 130.4, 130.3, 128.7, 128.0, 124.6, 123.9, 123.5, 104.7, 96.2, 57.2, 20.9, 18.8, 11.5. HRMS (ESI): calcd. for  $\text{C}_{29}\text{H}_{37}\text{N}_2\text{O}_3\text{SSi}$  [ $\text{M}+\text{H}]^+$ : 521.2289, found: 521.2287. IR: 1099, 1157, 1192, 1215, 1261.125, 1362, 1412, 1452, 1492, 1552, 1734, 2150, 2866, 2944.

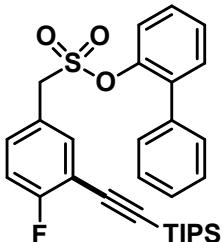


**2-(pyrimidin-5-yl)phenyl (4-ethyl-((triisopropylsilyl)ethynyl)phenyl) methanesulfonate (9):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 68%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.22 (s, 1H), 8.84 (s, 2H), 7.47 – 7.40 (m, 3H), 7.38 – 7.36 (m, 2H), 7.18 (d,  $J$  = 1.8 Hz, 2H), 4.25 (s, 2H), 2.84 (q,  $J$  = 7.6 Hz, 2H), 1.26 – 1.24 (m, 3H), 1.13 (d,  $J$  = 1.6 Hz, 21H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  158.0, 156.9, 148.3, 146.3, 134.9, 131.3, 130.9, 130.7, 128.9, 128.8, 128.0, 123.9, 123.9, 123.4, 104.5, 95.7, 57.2, 27.9, 18.9, 14.9, 11.5. HRMS (ESI): calcd. for  $\text{C}_{30}\text{H}_{39}\text{N}_2\text{O}_3\text{SSi}$  [ $\text{M}+\text{H}]^+$ : 535.2445, found: 535.2447. IR: 1099, 1156, 1187, 1260, 1362, 1412, 1462, 1491, 1552, 1579, 1725, 2150, 2865, 2927, 3041.

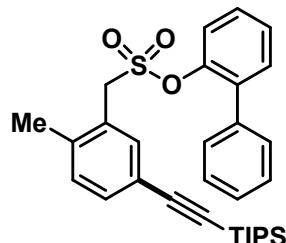


**2-(pyrimidin-5-yl)phenyl ((triisopropylsilyl)ethynyl)phenyl methanesulfonate (10):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 67%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.24 (s,

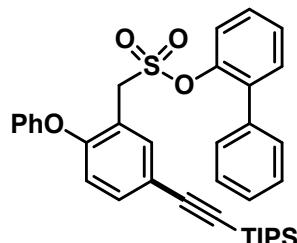
1H), 8.83 (s, 2H), 7.49 – 7.37 (m, 6H), 7.17 (dd,  $J$  = 8.3, 1.8 Hz, 1H), 4.25 (s, 2H), 1.14 (s, 21H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  146.0, 138.1, 135.7, 131.4, 131.3, 130.9, 130.1, 128.9, 128.2, 125.2, 124.6, 123.5, 102.2, 98.8, 56.7, 18.8, 11.5. HRMS (ESI): calcd. for  $\text{C}_{28}\text{H}_{34}\text{ClN}_2\text{O}_3\text{SSi}$  [ $\text{M}+\text{H}]^+$ : 541.1742, found: 541.1742. IR: 1057, 1099, 1157, 1195, 1262, 1363, 1412, 1470, 1552, 1580, 1721, 2157, 2866, 2927.



**2-(pyrimidin-5-yl)phenyl((triisopropylsilyl)ethynyl)phenylmethanesulfonate (11):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish liquid; isolated yield: 53%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.23 (s, 1H), 8.82 (s, 2H), 7.50 – 7.37 (m, 5H), 7.23 (ddd,  $J$  = 8.5, 4.7, 2.4 Hz, 1H), 7.06 (t,  $J$  = 8.6 Hz, 1H), 4.25 (s, 2H), 1.13 (d,  $J$  = 2.4 Hz, 21H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  165.0, 163.0, 158.0, 156.8, 146.0, 136.2, 132.3, 132.2, 131.4, 131.1, 130.9, 128.8, 128.2, 123.5, 122.5, 116.6, 116.4, 113.5, 113.4, 98.7, 56.7, 18.8, 11.4. HRMS (ESI): calcd. for  $\text{C}_{28}\text{H}_{34}\text{FN}_2\text{O}_3\text{SSi}$  [ $\text{M}+\text{H}]^+$ : 525.2038, found: 525.2033. IR: 1044, 1098, 1159, 1236, 1373, 1413, 1465, 1497, 1735, 2867, 2944, 2984, 3024.

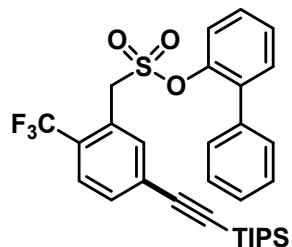


**2-(pyrimidin-5-yl)phenyl((triisopropylsilyl)ethynyl)phenylmethanesulfonate (12):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish liquid; isolated yield: 67%; [meta/others = 11:1].  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.22 (s, 1H), 8.85 (s, 2H), 7.48 – 7.38 (m, 4H), 7.35 (d,  $J$  = 8.1 Hz, 2H), 7.15 (d,  $J$  = 7.9 Hz, 1H), 4.34 (s, 2H), 2.30 (s, 3H), 1.11 (s, 21H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  158.0, 156.8, 146.1, 138.9, 135.3, 133.5, 131.3, 131.2, 130.9, 129.0, 128.1, 125.3, 123.6, 122.2, 106.1, 91.4, 55.0, 19.7, 18.9, 11.5. HRMS (ESI): calcd. for  $\text{C}_{29}\text{H}_{37}\text{N}_2\text{O}_3\text{SSi}$  [ $\text{M}+\text{H}]^+$ : 521.2289, found: 521.2293. IR: 1098, 1156, 1194, 1240, 1359, 1411, 1462, 1492, 1552, 1579, 1734, 2150, 2865, 2943, 3039.



**2-(pyrimidin-5-yl)phenyl((triisopropylsilyl)ethynyl)phenylmethanesulfonate (13):** Eluent: ethyl acetate/petroleum

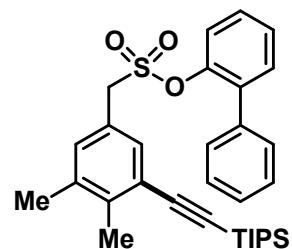
ether (20:80 v/v); yellowish solid; isolated yield: 57%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.22 (s, 1H), 8.83 (s, 2H), 7.50 – 7.40 (m, 5H), 7.31 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.13 (t, J = 1.4 Hz, 1H), 7.10 (dd, J = 2.3, 1.3 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 6.94 (d, J = 2.2 Hz, 1H), 6.92 – 6.89 (m, 1H), 4.23 (s, 2H), 1.11 (d, J = 2.6 Hz, 21H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.0, 157.4, 156.8, 155.1, 146.1, 131.4, 130.9, 130.2, 129.4, 129.3, 128.9, 128.6, 128.2, 126.3, 123.5, 123.1, 121.0, 120.6, 105.2, 93.4, 57.1, 18.8, 11.5. **HRMS (ESI)**: calcd. for C<sub>34</sub>H<sub>39</sub>N<sub>2</sub>O<sub>4</sub>SSi [M + H]<sup>+</sup>: 599.2394, found: 599.2391. **IR**: 1157, 1194, 1219, 1261, 1315, 1363, 1412, 1455, 1485, 1552, 1579, 1725, 2156, 2865, 2943, 3041.



### 2-(pyrimidin-5-yl)phenyl

### (2-(trifluoromethyl)-5-

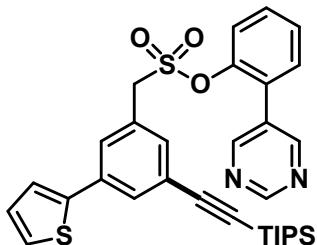
**((triisopropylsilyl)ethynyl)phenylmethanesulfonate (14):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 68%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.21 (s, 1H), 8.79 (s, 2H), 7.65 (d, J = 10.7 Hz, 2H), 7.58 (d, J = 8.2 Hz, 1H), 7.51 – 7.40 (m, 4H), 4.51 (s, 2H), 1.12 (d, J = 3.3 Hz, 21H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 158.0, 156.7, 145.9, 136.1, 133.2, 131.4, 131.0, 130.9, 129.1, 128.4, 128.3, 127.1, 127.0, 125.3, 123.7, 104.4, 96.1, 53.6, 18.8, 11.4. **HRMS (ESI)**: calcd. for C<sub>29</sub>H<sub>34</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>SSi [M+H]<sup>+</sup>: 575.2006, found: 575.2008. **IR**: 1123, 1158, 1187, 1311, 1368, 1413, 1463, 1491, 1552, 1579, 1609, 1729, 2157, 2867, 2945, 3042.



### 2-(pyrimidin-5-yl)phenyl

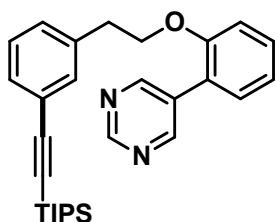
### (2,5-dimethyl-3-

**((triisopropylsilyl)ethynyl)phenylmethanesulfonate (15):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 71%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.23 (s, 1H), 8.86 (s, 2H), 7.49 – 7.41 (m, 3H), 7.37 (dd, J = 7.9, 1.3 Hz, 1H), 7.30 (s, 1H), 7.22 (s, 1H), 4.38 (s, 2H), 2.26 (s, 3H), 2.17 (s, 3H), 1.11 (s, 21H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 157.8, 156.9, 146.2, 145.8, 138.3, 137.8, 134.9, 133.3, 131.3, 131.0, 129.0, 128.1, 125.2, 123.7, 121.5, 106.3, 91.0, 55.6, 20.8, 18.9, 16.0, 11.5. **HRMS (ESI)**: calcd. for C<sub>30</sub>H<sub>38</sub>N<sub>2</sub>NaO<sub>3</sub>SSi [M+Na]<sup>+</sup>: 557.2265, found: 557.2264. **IR**: 1099, 1157, 1194, 1260, 1303, 1359, 1412, 1463, 1552, 1579, 1732, 2153, 2865, 2943, 3038.

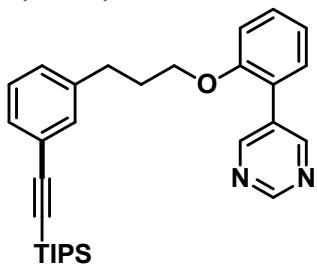


**2-(pyrimidin-5-yl)phenyl**

**((triisopropylsilyl)ethynyl)phenylmethanesulfonate (16):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 67%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.19 (s, 1H), 8.82 (s, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.64 (s, 1H), 7.41 (ddd, *J* = 18.4, 10.1, 5.1 Hz, 4H), 7.29 (dd, *J* = 9.9, 2.3 Hz, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 7.14 (d, *J* = 5.3 Hz, 1H), 4.36 (s, 2H), 1.08 (d, *J* = 3.4 Hz, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 158.0, 156.8, 146.3, 143.8, 136.3, 131.3, 130.8, 130.2, 129.9, 129.4, 129.2, 128.9, 128.0, 127.8, 126.9, 126.8, 123.5, 119.4, 99.6, 98.9, 57.8, 18.9, 11.5. **HRMS (ESI):** calcd. for C<sub>32</sub>H<sub>37</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub>Si [M + H]<sup>+</sup>: 589.2009, found: 589.2010. **IR:** 1156, 1200, 1261, 1360, 1412, 1462, 1490, 1552, 1580, 1727, 2138, 2865, 2943.

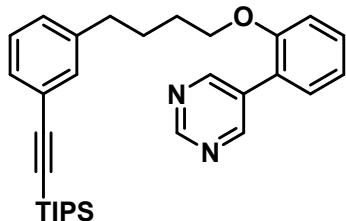


**5-(2-(3-((triisopropylsilyl)ethynyl)phenethoxy)phenyl)pyrimidine (17):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish liquid; isolated yield: 72%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.16 (s, 1H), 8.83 (s, 2H), 7.41 – 7.36 (m, 1H), 7.34 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.23 – 7.18 (m, 1H), 7.10 – 7.05 (m, 2H), 7.01 – 6.97 (m, 1H), 4.21 (t, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 1.12 (s, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 157.1, 155.9, 138.1, 132.3, 130.7, 130.6, 130.5, 129.5, 128.6, 124.0, 123.7, 121.6, 112.4, 107.1, 90.8, 69.2, 35.6, 18.9, 11.51. **HRMS (ESI):** calcd. for C<sub>29</sub>H<sub>37</sub>N<sub>2</sub>OSi [M+H]<sup>+</sup>: 457.2670, found: 457.2664. **IR:** 1113, 1163, 1241, 1272, 1383, 1411.591, 1462, 1496, 1551, 1579, 1600, 1726, 1783, 1884, 2150, 2865, 2925, 3040.

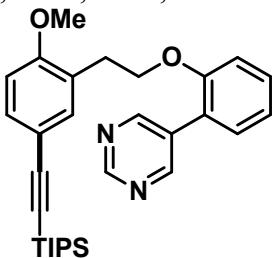


**5-(2-(3-(3-((triisopropylsilyl)ethynyl)phenyl)propoxy)phenyl)pyrimidine (18):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish liquid; isolated yield: 58%; [*meta/others* = 20:1]. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.16 (s, 1H), 8.95 (s, 2H), 7.39 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.32 – 7.29 (m, 1H), 7.25 (s, 1H), 7.19 (dd, *J* = 9.5, 5.8 Hz, 1H), 7.11 – 7.04 (m, 2H), 6.99 – 6.96 (m, 1H), 4.00 (t, *J* = 6.3 Hz, 2H), 2.67 (t, 2H), 2.10 – 2.02 (m, 2H), 1.12 (d, *J* = 2.0 Hz, 2H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 157.1, 156.1, 141.3,

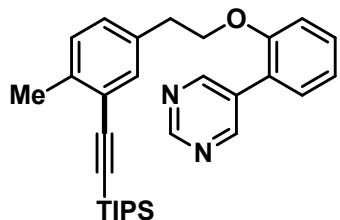
132.5, 132.4, 132.1, 130.7, 130.5, 130.1, 128.8, 128.5, 123.8, 123.7, 121.5, 112.5, 107.3, 90.5, 67.5, 32.1, 30.7, 18.9, 11.5. **HRMS (ESI)**: calcd. for: C<sub>30</sub>H<sub>38</sub>KN<sub>2</sub>Si [M+K]<sup>+</sup>: 493.2436, found: 493.2430. **IR**: 1112, 1163, 1192, 1243, 1271, 1411, 1454, 1495, 1551, 1579, 1600, 1721, 2151, 2865, 2942.



**5-(2-(4-(3-((triisopropylsilyl)ethynyl)phenyl)butoxy)phenyl)pyrimidine (19):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish liquid; isolated yield: 65%; [meta/others = 4:1]. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.15 (s, 1H), 8.93 (s, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.26 (s, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.10 – 7.06 (m, 2H), 6.99 (dd, J = 8.2, 4.4 Hz, 1H), 4.01 (t, J = 6.2 Hz, 2H), 2.60 (dd, J = 14.5, 7.1 Hz, 2H), 1.82 – 1.67 (m, 4H), 1.14 – 1.11 (m, 21H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 157.0, 156.2, 142.1, 133.2, 132.3, 132.1, 130.7, 130.5, 129.9, 128.7, 128.5, 123.7, 121.4, 112.5, 107.5, 90.3, 68.4, 35.4, 28.8, 27.8, 18.9, 11.5. **HRMS (ESI)**: calcd. for: C<sub>31</sub>H<sub>40</sub>N<sub>2</sub>NaOSi [M+Na]<sup>+</sup>: 507.2804, found: 507.2802. **IR**: 678, 728, 752, 795, 883, 909, 999, 1018, 1049, 1113, 1163, 1186, 1243, 1411, 1460, 1496, 1551, 1579, 1727, 2151, 2865, 2942, 3041.

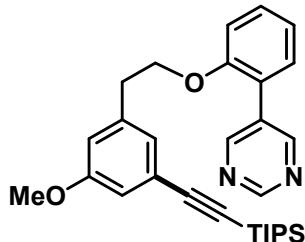


**5-(2-(2-methoxy-5-((triisopropylsilyl)ethynyl)phenethoxy)phenyl)pyrimidine (20)** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish liquid; isolated yield: 68%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.22 (s, 1H), 8.93 (s, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.30 (m, 1H), 7.23 (d, J = 1.8 Hz, 1H), 7.06 (dd, J = 14.3, 7.7 Hz, 2H), 6.78 (d, J = 8.5 Hz, 1H), 4.19 (t, J = 7.3 Hz, 2H), 3.81 (s, 3H), 3.04 (t, J = 7.3 Hz, 2H), 1.12 (s, 21H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.0, 156.9, 156.1, 134.5, 132.4, 130.6, 130.5, 126.1, 123.7, 121.4, 115.9, 112.6, 110.4, 107.2, 88.9, 67.9, 55.6, 30.26, 18.9, 11.6. **HRMS (ESI)**: calcd. for C<sub>30</sub>H<sub>39</sub>N<sub>2</sub>O<sub>2</sub>Si [M + H]<sup>+</sup>: 487.2775, found: 487.2778. **IR**: 1131, 1185, 1232, 1411, 1462, 1496, 1551, 1602, 2147, 2865, 2942.



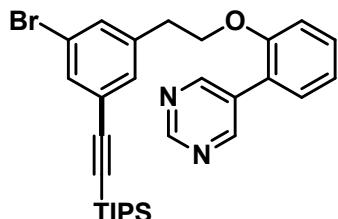
**5-(2-(4-methyl-3-((triisopropylsilyl)ethynyl)phenethoxy)phenyl)pyrimidine (21):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 65%; [meta/others = 12:1]. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.21 (s, 1H), 8.91 (s, 2H), 7.41 – 7.36 (m, 1H), 7.32 – 7.27 (m, 2H), 7.11 – 7.05 (m, 2H), 7.00 – 6.96 (m, 2H), 4.18 (t, J = 6.9 Hz, 2H), 2.97 (t, J =

6.9 Hz, 2H), 2.42 (s, 3H), 1.13 (s, 21H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 157.1, 156.0, 139.2, 135.2, 132.6, 130.7, 130.5, 129.7, 129.5, 123.8, 121.6, 112.5, 105.9, 94.8, 69.5, 35.2, 20.7, 18.9, 11.5. **HRMS (ESI)**: calcd. for C<sub>30</sub>H<sub>39</sub>N<sub>2</sub>OSi [M+H]<sup>+</sup>: 471.2826, found: 471.2825. **IR**: 1113, 1164, 1243, 1272, 1383, 1411, 1461, 1495, 1551, 1579, 1601, 1710, 1892, 2147, 2865.917, 2942, 3040.

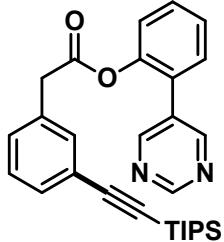


**5-(2-(3-methoxy-5-((triisopropylsilyl)ethynyl)phenethoxy)phenyl)pyrimidine (22):**

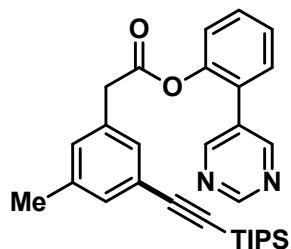
Eluent: ethyl acetate/petroleum ether (10:90 v/v); yellowish liquid; isolated yield: 65%; [meta/others = 6:1]. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.14 (s, 1H), 8.85 (s, 2H), 7.41 – 7.37 (m, 1H), 7.31 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.90 (s, 1H), 6.85 (s, 1H), 6.66 (s, 1H), 4.21 (t, *J* = 6.9 Hz, 2H), 3.76 (s, 3H), 2.98 (t, *J* = 6.9 Hz, 2H), 1.12 (s, 21H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 159.6, 157.0, 155.9, 139.6, 132.3, 130.7, 130.5, 125.0, 124.8, 123.7, 121.6, 116.0, 115.3, 112.5, 107.0, 90.6, 69.2, 55.5, 35.7, 18.9, 11.5. **HRMS (ESI)**: calcd. for C<sub>30</sub>H<sub>39</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup>: 487.2775, found: 487.2783. **IR**: 676, 728, 752, 810, 849, 882, 998, 1025, 1058, 1113, 1164, 1191, 1242, 1272, 1384, 1411, 1455, 1496, 1552, 1587, 1728, 2153, 2865, 2942, 3041.



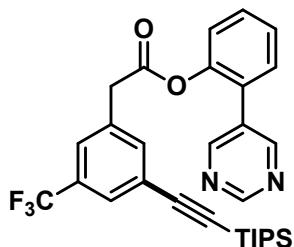
**5-(2-(3-bromo-5-((triisopropylsilyl)ethynyl)phenethoxy)phenyl)pyrimidine (23)** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 62%; [meta/others = 5:1]. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.17 (s, 1H), 8.85 (s, 2H), 7.46 – 7.45 (m, 1H), 7.38 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.31 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.20 (dd, *J* = 5.3, 1.5 Hz, 2H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 4.21 (t, 2H), 2.98 (t, *J* = 8.9, 4.5 Hz, 2H), 1.12 (s, 21H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 157.2, 157.0, 155.7, 140.2, 133.3, 132.3, 131.1, 130.7, 130.6, 125.7, 123.9, 123.1, 122.3, 121.8, 112.4, 105.4, 92.7, 68.8, 35.3, 18.9, 11.5. **HRMS (ESI)**: calcd. for C<sub>29</sub>H<sub>36</sub>BrN<sub>2</sub>OSi [M+H]<sup>+</sup>: 535.1775, found: 535.1760. **IR**: 1215, 1243, 1273, 1413, 1462, 1496, 1561, 1597, 1729, 2152, 2866, 2926, 3020.



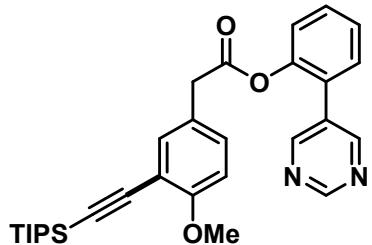
**2-(pyrimidin-5-yl)phenyl 2-(3-((triisopropylsilyl)ethynyl)phenyl)acetate (24):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 65%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.17 (s, 1H), 8.73 (s, 2H), 7.49 – 7.45 (m, 1H), 7.41 – 7.37 (m, 3H), 7.30 (s, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 3.67 (s, 2H), 1.13 (s, 21H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 169.4, 157.8, 156.5, 148.1, 132.8, 131.5, 131.4, 130.7, 130.6, 129.3, 128.9, 128.0, 127.2, 124.3, 123.3, 106.7, 91.3, 41.0, 18.9, 11.5. **HRMS (ESI):** calcd. for C<sub>29</sub>H<sub>35</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup>: 471.2462, found: 471.2462. **IR:** 676, 727, 754, 773, 803, 836, 882.834, 917, 960, 1000, 1114, 1194, 1231, 1344, 1410, 1462, 1551, 1580, 1760, 2153, 2865, 2942, 3041.



**2-(pyrimidin-5-yl)phenyl 2-(3-methyl-5-((triisopropylsilyl)ethynyl)phenyl)acetate (25):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 67%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.17 (s, 1H), 8.74 (s, 2H), 7.49 – 7.44 (m, 1H), 7.39 – 7.36 (m, 2H), 7.22 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.11 (s, 1H), 6.91 (s, 1H), 3.63 (s, 2H), 2.30 (s, 3H), 1.13 (s, 21H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 169.5, 157.7, 156.5, 148.1, 138.7, 132.7, 132.1, 131.4, 130.7, 130.5, 130.2, 123.0, 128.0, 127.1, 124.1, 123.4, 106.9, 90.8, 40.9, 21.3, 18.9, 11.5. **IR:** 675, 698, 728, 755, 829, 858, 883, 917, 997, 1114, 1194, 1229, 1293, 1345, 1410, 1462, 1492, 1551, 1597, 1760, 2155, 2865, 2943, 3041.

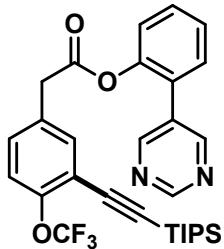


**2-(pyrimidin-5-yl)phenyl ((triisopropylsilyl)ethynyl)phenyl)acetate (26):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 73%. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.18 (s, 1H), 8.75 (s, 2H), 7.64 (s, 1H), 7.51 – 7.47 (m, 1H), 7.45 (s, 1H), 7.40 (dd, *J* = 8.2, 4.7 Hz, 3H), 7.21 (d, *J* = 8.0 Hz, 1H), 3.74 (s, 2H), 1.14 (d, *J* = 2.4 Hz, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 168.7, 157.9, 156.5, 147.9, 136.0, 133.8, 130.8, 130.7, 128.3 (q, *J* = 7.0 Hz, *J* = 298.8 Hz, CF<sub>3</sub>), 128.0, 127.4, 125.9 (q, *J* = 7.2 Hz, *J* = 298.8 Hz, CF<sub>3</sub>), 125.3, 123.3, 104.9, 93.7, 40.6, 18.9, 11.4. **HRMS (ESI):** calcd. for C<sub>30</sub>H<sub>34</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup>: 539.2336, found: 539.2341. **IR:** 1132, 1178, 1232, 1350, 1412, 1458, 1552, 1765, 2158, 2867, 2932.



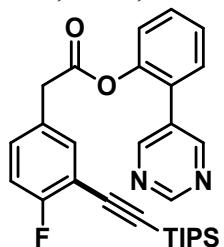
**2-(pyrimidin-5-yl)phenyl 2-(4-methoxy-3-((triisopropylsilyl)ethynyl)phenyl)acetate (27):**

Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish liquid; isolated yield: 71%.  **$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  9.18 (s, 1H), 8.74 (s, 2H), 7.49 – 7.44 (m, 1H), 7.37 (d,  $J = 4.2$  Hz, 2H), 7.25 (d,  $J = 2.3$  Hz, 1H), 7.18 (d,  $J = 8.0$  Hz, 1H), 7.05 (dd,  $J = 8.5, 2.2$  Hz, 1H), 6.79 (d,  $J = 8.5$  Hz, 1H), 3.86 (s, 3H), 3.60 (s, 2H), 1.14 (s, 21H).  **$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  169.8, 160.4, 157.8, 156.5, 148.1, 134.5, 130.7, 130.5, 130.5, 128.0, 127.1, 124.5, 123.4, 113.6, 111.5, 102.8, 95.7, 56.2, 40.2, 18.9, 11.6. **HRMS (ESI):** calcd. for  $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_3\text{Si} [\text{M}+\text{H}]^+$ : 501.2568, found: 501.2574. **IR:** 679, 753, 774, 818, 883, 918, 967, 1002, 1030, 1115, 1195, 1234, 1266, 1411, 1463, 1499, 1551, 1663, 1763, 2152, 2865, 2926, 3038.



**2-(pyrimidin-5-yl)phenyl ((triisopropylsilyl)ethynyl)acetate (28):**

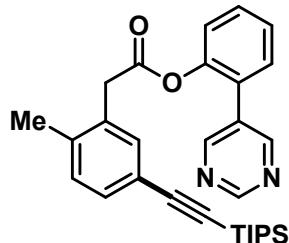
Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 68% ; [meta/others = 10:1].  **$^1\text{H NMR (400 MHz, CDCl}_3)$**   $\delta$  9.18 (s, 1H), 8.75 (s, 2H), 7.51 – 7.46 (m, 1H), 7.41 – 7.39 (m, 2H), 7.36 (d,  $J = 2.1$  Hz, 1H), 7.22 – 7.19 (m, 2H), 7.13 (dd,  $J = 8.5, 2.2$  Hz, 1H), 3.68 (s, 2H), 1.13 (d,  $J = 2.0$  Hz, 2H).  **$^{13}\text{C NMR (126 MHz, CDCl}_3)$**   $\delta$  169.0, 156.5, 148.0, 134.8, 131.4, 130.8, 130.7 (d,  $J = 18.9$  Hz, C-F), 130.6, 130.3, 128.0, 127.3, 123.3, 122.1, 121.8, 118.9, 100.1, 98.0, 40.3, 18.7, 11.4. **HRMS (ESI):** calcd. for  $\text{C}_{30}\text{H}_{33}\text{F}_3\text{N}_2\text{NaO}_3\text{Si} [\text{M}+\text{Na}]^+$ : 577.2105, found: 577.2107. **IR:** 1115, 1170, 1221, 1261, 1411, 1463, 1493, 1551, 1580.860, 1764, 2161, 2867, 2927, 3044.



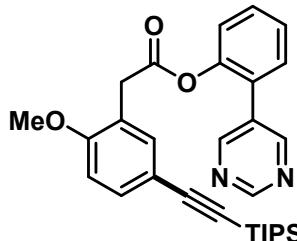
**2-(pyrimidin-5-yl)phenyl 2-(4-fluoro-3-((triisopropylsilyl)ethynyl)phenyl)acetate (29):**

Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 71%; [meta/others = 14:1].  **$^1\text{H NMR (400 MHz, CDCl}_3)$**   $\delta$  9.19 (s, 1H), 8.74 (s, 2H), 7.50 – 7.45 (m, 1H), 7.40 – 7.37 (m, 2H), 7.28 – 7.27 (m, 1H), 7.19 (d,  $J = 8.1$  Hz, 1H), 7.08 (ddd,  $J = 7.2, 4.8, 2.3$  Hz, 1H), 7.00 (t,  $J = 8.7$  Hz, 1H), 3.64 (s, 2H), 1.14 (s, 21H).  **$^{13}\text{C NMR (126 MHz, CDCl}_3)$**   $\delta$  169.8, 160.4, 157.8, 156.5, 148.1, 134.5, 130.7, 130.5, 130.5, 128.0, 127.1, 124.5, 123.4, 113.6, 111.5, 102.8, 95.7, 56.2, 40.2, 18.9, 11.6.

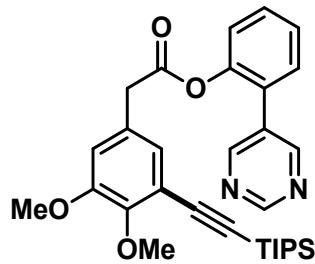
**MHz, CDCl<sub>3</sub>)** δ 169.3, 163.9, 161.9, 157.8, 156.5, 148.0, 134.6, 130.9, 130.8, 130.7, 130.6 (d, *J* = 20.5 Hz, C-F), 129.7 (d, *J* = 313.4 Hz, C-F), 128.4, 128.3, 128.0, 127.3, 123.3, 116.1, 116.0 (d, *J* = 21.4 Hz, C-F), 112.8, 112.7 (d, *J* = 16.8 Hz, C-F), 99.4, 97.6, 40.2, 18.8, 11.4. **HRMS (ESI):** calcd. for C<sub>29</sub>H<sub>34</sub>FN<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup>: 489.2368, found: 489.2367. **IR:** 1113, 1193, 1217, 1258, 1343, 1411, 1463, 1498, 1551.807, 1580.418, 1763, 2159, 2866, 2944., 3041.



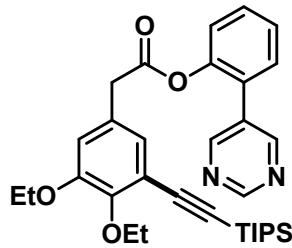
**2-(pyrimidin-5-yl)phenyl 2-(2-methyl-5-((triisopropylsilyl)ethynyl)phenyl)acetate (30):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 72%; [meta/others = 10:1]. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.22 (s, 1H), 8.76 (s, 2H), 7.49 – 7.45 (m, 1H), 7.39 – 7.37 (m, 2H), 7.32 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.24 (d, *J* = 1.5 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 3.68 (s, 2H), 2.11 (s, 3H), 1.13 (s, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 169.2, 157.8, 156.5, 148.1, 137.5, 133.8, 131.7, 131.6, 130.8, 130.7, 130.6, 128.7, 128.1, 127.2, 123.3, 121.7, 106.9, 90.4, 39.0, 19.5, 18.9, 11.5. **HRMS (ESI):** calcd. for C<sub>30</sub>H<sub>36</sub>N<sub>2</sub>NaO<sub>2</sub>Si [M+Na]<sup>+</sup>: 507.2438, found: 507.2436. **IR:** 1106, 1193, 1233, 1335, 1410, 1463, 1492, 1551, 1580, 1762, 2150, 2865, 2943.



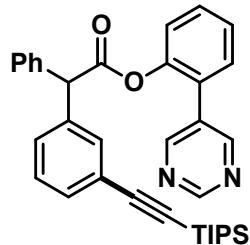
**2-(pyrimidin-5-yl)phenyl 2-(2-methoxy-5-((triisopropylsilyl)ethynyl)phenyl)acetate (31):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 72%; [meta/others = 10:1]. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.20 (s, 1H), 8.78 (s, 2H), 7.49 – 7.44 (m, 1H), 7.42 – 7.35 (m, 3H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 2H), 1.12 (s, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 169.7, 157.6, 156.6, 148.2, 134.8, 133.4, 131.2, 130.7, 130.5, 129.1, 127.8, 127.0, 123.5, 122.1, 116.0, 110.5, 106.9, 89.2, 55.8, 36.1, 18.9, 11.5. **HRMS (ESI):** calcd. for C<sub>30</sub>H<sub>37</sub>N<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup>: 501.2568, found: 501.2571. **IR:** 677, 728, 757, 815, 883, 918, 1002, 1028, 1113, 1186, 1236, 1261, 1289, 1339, 1411, 1463, 1499, 1552, 1606, 1765, 2018, 2148, 2865, 2942, 3044.



**2-(pyrimidin-5-yl)phenyl 2-(3,4-dimethoxy-5-((triisopropylsilyl)ethynyl)phenyl)acetate (32):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 77%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.17 (s, 1H), 8.74 (s, 2H), 7.49 – 7.46 (m, 1H), 7.39 (dd, *J* = 5.0, 0.9 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.66 (d, *J* = 2.0 Hz, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 3.61 (s, 2H), 1.14 (s, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 169.5, 157.8, 156.5, 153.0, 150.7, 148.1, 130.7, 130.6, 128.2, 128.1, 127.2, 126.2, 123.4, 118.6, 114.3, 113.8, 102.5, 95.9, 61.1, 56.2, 40.8, 18.9, 11.6. **HRMS (ESI):** calcd. for C<sub>31</sub>H<sub>39</sub>N<sub>2</sub>NaO<sub>4</sub>Si [M+Na]<sup>+</sup>: 553.2493, found: 553.2486. **IR:** 675, 696, 726, 754, 800, 882, 918, 1009, 1114, 1194, 1235, 1262.042, 1412, 1463, 1486, 1515, 1552, 1579, 1760, 2153, 2864, 2925.

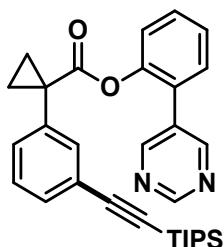


**2-(pyrimidin-5-yl)phenyl 2-(3,4-diethoxy-5-((triisopropylsilyl)ethynyl)phenyl)acetate (33):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 71%; [*meta/others* = 10:1]. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.19 (s, 1H), 8.78 (s, 2H), 7.50 – 7.45 (m, 1H), 7.39 (d, *J* = 4.5 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 1H), 6.86 (s, 1H), 6.66 (s, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.59 (s, 2H), 1.40 (dt, *J* = 16.6, 6.9 Hz, 6H), 1.14 (s, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 169.6, 157.9, 156.5, 152.6, 149.9, 148.2, 130.7, 130.6, 128.1, 127.9, 127.2, 126.2, 123.4, 119.1, 115.2, 103.1, 95.1, 69.4, 64.7, 40.8, 18.9, 15.9, 15.1, 11.6. **HRMS (ESI):** calcd. for C<sub>33</sub>H<sub>43</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup>: 559.2987, found: 559.2985. **IR:** 1113, 1193, 1226, 1261, 1410, 1464, 1510.274, 1551, 1578, 1667, 1759, 2153, 2865, 2941, 3042.

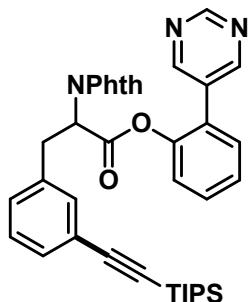


**2-(pyrimidin-5-yl)phenyl 2-(4-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-2-yl)acetate (34):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 63%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.07 (s, 1H), 8.65 (s, 2H), 7.50 – 7.45 (m, 1H), 7.37 (dd, *J* = 13.2, 4.3 Hz, 4H), 7.26 (s, 3H), 7.23 (s, 1H), 7.21 (s, 1H), 7.18 – 7.13 (m, 3H), 5.07 (s, 1H), 1.12 (s, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 170.4, 157.7, 156.5, 148.0, 137.6, 137.1, 132.1, 131.7, 130.8, 130.5, 129.1, 128.9, 128.5, 128.4, 128.2, 127.9, 127.2, 124.3, 123.3,

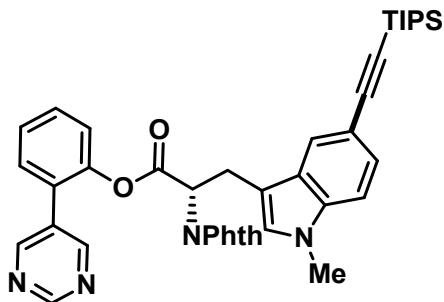
106.7, 91.4, 56.7, 18.8, 11.5. **HRMS (ESI)**: calcd. for  $C_{35}H_{39}N_2O_2Si$  [M + H]<sup>+</sup>: 547.2775, found: 547.2777. **IR**: 1110, 1185, 1261, 1308, 1410, 1454, 1550, 1579, 1763, 2152, 2865, 2942, 3036.



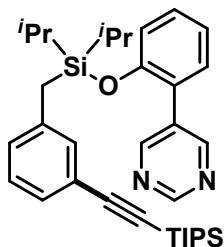
**2-(pyrimidin-5-yl)phenyl((triisopropylsilyl)ethynyl)cyclopropanecarboxylate (35):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellowish solid; isolated yield: 74%; [*meta/others* = 7:1]. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.24 (s, 1H), 8.65 (s, 2H), 7.46 – 7.39 (m, 3H), 7.34 (d, *J* = 4.3 Hz, 2H), 7.28 (t, *J* = 5.9 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 1.53 (dd, *J* = 7.0, 4.0 Hz, 2H), 1.24 (m, 2H), 1.14 (s, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 172.8, 157.8, 156.7, 148.4, 138.7, 133.9, 131.7, 131.0, 130.5, 130.4, 128.6, 127.9, 126.9, 123.9, 123.4, 106.8, 91.0, 29.9, 18.9, 17.6, 11.5. **HRMS (ESI)**: calcd. for  $C_{31}H_{36}N_2NaO_2Si$  [M+Na]<sup>+</sup>: 519.2438, found: 519.2441. **IR**: 1133, 1195, 1286, 1342, 1411, 1463, 1550, 1579.367, 1746, 2155, 2865, 2925, 3043.



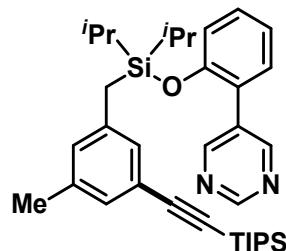
**2-(pyrimidin-5-yl)phenyl((triisopropylsilyl)ethynyl)propanoate (36):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); brown solid; isolated yield: 71%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.19 (s, 1H), 8.75 (s, 2H), 7.78 (dt, *J* = 7.0, 3.5 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.53 – 7.47 (m, 1H), 7.42 – 7.36 (m, 2H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.24 (s, 1H), 7.18 (s, 1H), 7.15 – 7.08 (m, 2H), 5.18 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.51 – 3.40 (m, *J* = 14.1, 6.1 Hz, 2H), 1.06 (d, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 167.5, 167.2, 156.5, 147.9, 136.3, 134.5, 132.7, 131.5, 131.0, 130.9, 130.6, 129.0, 128.7, 128.0, 127.4, 124.0, 123.9, 123.3, 106.7, 90.9, 53.0, 34.5, 18.9, 11.4. **HRMS (ESI)**: calcd. for  $C_{38}H_{39}N_3NaO_4Si$  [M+Na]<sup>+</sup>: 652.2602, found: 652.2599. **IR**: 1104, 1185, 1223, 1385, 1411, 1466, 1551, 1580, 1718, 1769, 2151, 2864, 2925, 3043.



**2-(pyrimidin-5-yl)phenyl ((triisopropylsilyl)ethynyl)-1H-indol-3-yl)propanoate (37):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 55%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.16 (s, 1H), 8.76 (s, 2H), 7.69 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.63 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.52 – 7.47 (m, 1H), 7.39 – 7.32 (m, 4H), 7.14 – 7.08 (m, 2H), 6.87 (t, *J* = 6.5 Hz, 1H), 5.38 (dd, *J* = 10.4, 4.9 Hz, 1H), 3.78 – 3.75 (m, 1H), 3.72 (s, 3H), 3.67 (d, *J* = 15.2 Hz, 1H), 1.13 (d, *J* = 2.3 Hz, 21H). **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)** δ 167.8, 167.2, 148.1, 136.9, 134.1, 131.8, 130.9, 130.5, 128.0, 127.2, 126.7, 123.7, 123.4, 121.8, 120.0, 119.0, 115.6, 109.5, 101.7, 96.8, 52.6, 30.9, 25.1, 18.9, 11.5. **HRMS (ESI):** calcd. for C<sub>41</sub>H<sub>43</sub>N<sub>4</sub>O<sub>4</sub>Si [M + H]<sup>+</sup>: 683.3048, found: 683.3048. **IR:** 724, 752, 882, 906, 955, 1000, 1105, 1185, 1387, 1411, 1466, 1552, 1718, 1770, 2148, 2865, 2942, 3021.

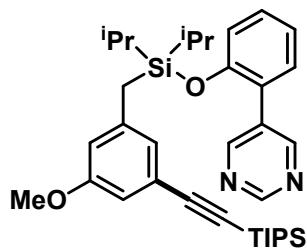


**5-((diisopropyl(3-((triisopropylsilyl)ethynyl)benzyl)silyl)oxy)phenyl)pyrimidine (38):** Eluent: ethyl acetate/petroleum ether (5:95 v/v); yellow liquid; isolated yield: 60%; [*meta/others* = 3:1]. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.11 (s, 1H), 8.77 (s, 2H), 7.26 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.06 (dd, *J* = 7.2, 5.4 Hz, 2H), 6.94 (d, *J* = 7.3 Hz, 1H), 6.87 – 6.81 (m, 2H), 2.28 (s, 2H), 1.08 (s, 21H), 0.94 – 0.88 (m, 14H). **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)** δ 157.0, 152.9, 138.3, 132.9, 132.3, 130.8, 130.5, 128.8, 128.6, 128.4, 125.8, 123.7, 122.3, 119.5, 107.4, 90.3, 21.1, 18.9, 17.5, 17.4, 13.1, 11.5. **HRMS (ESI):** calcd. for C<sub>34</sub>H<sub>48</sub>N<sub>2</sub>NaOSi<sub>2</sub> [M+Na]<sup>+</sup>: 579.3197, found: 579.3200. **IR:** 674, 728, 755, 882, 906, 997.476, 1073, 1109, 1169, 1246, 1276, 1409, 1462, 1491, 1551, 1577, 1740, 1884, 2151, 2866.139, 2943, 3040.

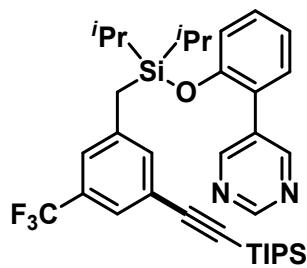


**5-((diisopropyl(3-((triisopropylsilyl)ethynyl)benzyl)silyl)oxy)phenyl)pyrimidine (39):**

Eluent: ethyl acetate/petroleum ether (5:95 v/v); yellow liquid; isolated yield: 75%; [meta/others = 15:1]. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.13 (s, 1H), 8.79 (s, 2H), 7.29 – 7.26 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.99 (s, 1H), 6.86 – 6.83 (m, 1H), 6.78 (s, 1H), 6.65 (s, 1H), 2.26 (s, 2H), 2.16 (s, 3H), 1.10 (s, 21H), 0.93 (dd, *J* = 10.4, 7.5 Hz, 14H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 157.1, 157.0, 153.0, 138.1, 138.0, 132.9, 130.7, 130.4, 129.9, 129.4, 129.2, 125.9, 123.5, 122.2, 119.6, 107.7, 89.8, 21.3, 21.0, 18.9, 17.5, 17.4, 13.1, 11.5. **HRMS (ESI)**: calcd. for C<sub>35</sub>H<sub>51</sub>N<sub>2</sub>OSi<sub>2</sub> [M+H]<sup>+</sup>: 571.3534, found: 571.3535. **IR**: 678, 728, 757, 859, 883, 916, 961, 1002, 1071, 1109, 1172, 1279, 1410, 1462, 1492, 1551, 1592, 1720, 2153.237, 2866, 2944, 3042.

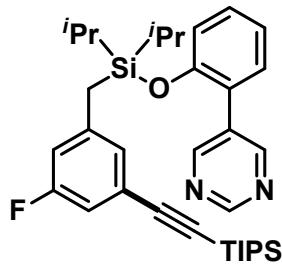


**5-(2-((diisopropyl(3-methoxy-5-((triisopropylsilyl)ethynyl)benzyl)silyloxy)phenyl)pyrimidine (40):** Eluent: ethyl acetate/petroleum ether (5:95 v/v); yellow liquid; isolated yield: 57%; [meta/others = 5:1]. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.13 (s, 1H), 8.81 (s, 2H), 7.29 – 7.26 (m, 2H), 7.09 – 7.05 (m, 1H), 6.85 (dd, *J* = 6.9, 2.5 Hz, 1H), 6.69 (s, 1H), 6.59 (s, 1H), 6.45 (s, 1H), 3.68 (s, 3H), 2.27 (s, 2H), 1.10 (s, 21H), 0.95 – 0.91 (m, 14H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 159.4, 157.1, 152.9, 139.77, 132.9, 130.8, 130.5, 125.9, 125.3, 124.5, 122.3, 119.6, 115.7, 113.2, 107.4, 90.2, 55.4, 21.3, 18.9, 17.5, 17.5, 13.1, 11.5. **HRMS (ESI)**: calcd. for C<sub>35</sub>H<sub>51</sub>N<sub>2</sub>O<sub>2</sub>Si<sub>2</sub> [M+H]<sup>+</sup>: 588.3496, found: 588.3484. **IR**: 676, 728, 757, 882, 917, 1000, 1058, 1109, 1163, 1194, 1248, 1279, 1325, 1409, 1453, 1492, 1551, 1584, 1714, 2154, 2867, 2944, 3040.



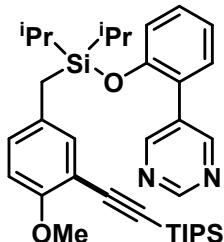
**5-(2-((diisopropyl(3-(trifluoromethyl)-5-((triisopropylsilyl)ethynyl)benzyl)silyloxy)phenyl)pyrimidine (41):** Eluent: ethyl acetate/petroleum ether (5:95 v/v); yellow liquid; isolated yield: 73%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.16 (s, 1H), 8.84 (s, 2H), 7.39 (s, 1H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.13 – 7.09 (m, 2H), 7.08 (s, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 2.37 (s, 2H), 1.10 (d, *J* = 2.0 Hz, 21H), 0.94 (t, *J* = 7.3 Hz, 14H). **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)** δ 156.8, 152.7, 139.7, 135.3, 130.9, 130.8, 125.4, 125.3 (q, *J* = 7.6 Hz, CF<sub>3</sub>), 125.2 (q, *J* = 9.6 Hz, CF<sub>3</sub>), 125.1, 125.0, 124.5, 122.6, 122.5, 119.4, 105.6, 92.7, 21.4, 18.9, 18.5, 17.5, 17.4, 13.1, 11.5. **HRMS (ESI)**: calcd. for C<sub>35</sub>H<sub>48</sub>F<sub>3</sub>N<sub>2</sub>OSi<sub>2</sub> [M+H]<sup>+</sup>: 625.3251, found: 625.3248.

**IR:** 680, 727, 756, 883, 918, 970, 998, 1131, 1177, 1233.987, 1273, 1345, 1411, 1453, 1492, 1553, 1600, 1712, 2157, 2867, 2944.



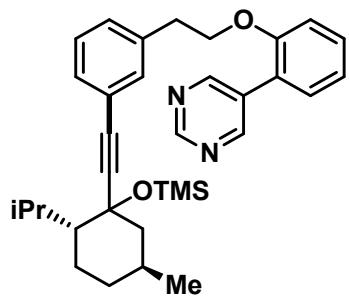
**5-((triisopropylsilyl)ethynyl)benzyl diisopropylsilyloxyphenyl pyrimidine (42):**

Eluent: ethyl acetate / petroleum ether (5:95 v/v); Yellow liquid; isolated yield: 65%; [meta/others = 15:1]. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.15 (s, 1H), 8.82 (s, 2H), 7.31 – 7.27 (m, 2H), 7.09 (t, J = 7.5 Hz, 1H), 6.85 (t, J = 7.7 Hz, 2H), 6.75 (s, 1H), 6.55 (d, J = 9.8 Hz, 1H), 2.29 (s, 2H), 1.13 – 1.11 (m, 2H), 1.10 (s, 2H), 0.93 (dd, J = 8.9, 7.6 Hz, 12H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 163.4, 161.4, 157.0, 152.8, 141.0, 140.9, 130.9, 130.7, 128.2, 125.2, 122.5, 119.5, 116.0, 115.9 (d, J = 21.6 Hz, C-F), 115.3 (d, J = 22.9 Hz, C-F), 115.2, 106.0, 91.8, 21.3, 18.8, 17.5, 17.4, 13.1, 11.5. **HRMS (ESI):** calcd. for C<sub>34</sub>H<sub>48</sub>FN<sub>2</sub>OSi<sub>2</sub> [M+H]<sup>+</sup>: 575.3284, found: 575.3276. **IR:** 680, 728, 757, 814, 882, 917, 979, 997, 1045, 1071, 1130, 1169, 1244, 1272, 1409, 1454, 1491, 1551, 1582, 1740, 2158, 2866, 2944, 3041.



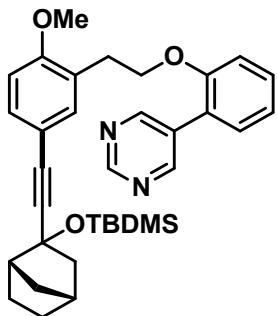
**5-((triisopropylsilyl)ethynyl)benzyl silyloxyphenyl pyrimidine (43):**

Eluent: ethyl acetate / petroleum ether (5:95 v/v); Yellow liquid; isolated yield: 63%; [meta/others = 3:1]. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.13 (s, 1H), 8.81 (s, 2H), 7.30 – 7.27 (m, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 2.1 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.63 (d, J = 8.5 Hz, 1H), 3.79 (s, 3H), 2.22 (s, 2H), 1.11 (s, 2H), 1.06 – 1.02 (m, 2H), 0.91 (dd, J = 15.6, 7.6 Hz, 12H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 158.4, 157.1, 153.0, 134.0, 132.9, 130.8, 130.5, 129.8, 129.7, 125.9, 122.2, 119.6, 114.1, 113.1, 111.4, 103.5, 94.9, 56.2, 19.8, 18.9, 17.5, 17.5, 13.0, 11.6. **HRMS (ESI):** calcd. for C<sub>35</sub>H<sub>51</sub>N<sub>2</sub>O<sub>2</sub>Si<sub>2</sub> [M+H]<sup>+</sup>: 587.3484, found: 587.3492.



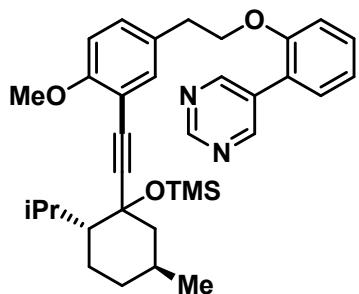
**5-(2-((2R,5S)-2-isopropyl-5-methyl-1-**

**((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenethoxyphenyl)pyrimidine (44):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); brown solid; isolated yield: 65% [*meta/others* = 20:1]. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.16 (s, 1H), 8.83 (s, 2H), 7.39 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.08 (td, *J* = 7.5, 1.0 Hz, 2H), 7.01 – 6.98 (m, 1H), 4.22 (t, *J* = 6.9 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H), 2.43 – 2.36 (m, 1H), 2.04 – 1.99 (m, 1H), 1.74 (d, *J* = 2.8 Hz, 1H), 1.52 – 1.31 (m, 5H), 1.28 – 1.26 (m, 1H), 0.95 – 0.93 (m, 3H), 0.87 (dd, *J* = 7.3, 5.0 Hz, 6H), 0.19 (s, 9H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 157.1, 157.0, 155.9, 138.2, 132.3, 131.6, 130.7, 130.6, 130.0, 129.2, 128.7, 123.9, 123.7, 121.6, 112.4, 94.9, 84.2, 73.7, 69.2, 52.2, 50.7, 35.6, 35.2, 28.8, 27.4, 24.3, 22.2, 20.8, 18.6, 2.0. **HRMS (ESI)**: calcd. for C<sub>33</sub>H<sub>42</sub>N<sub>2</sub>NaO<sub>2</sub>Si [M+Na]<sup>+</sup>: 549.2908, found: 549.2909. **IR**: 1037, 1071, 1246, 1375, 1412, 1453, 2254, 2293, 2930, 3023.

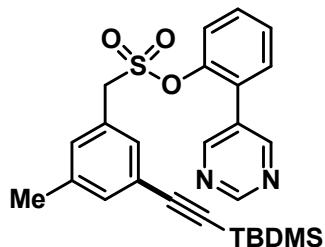


**5-(2-(2-methoxy-5-(((1S,4R)-2-((trimethylsilyl)oxy)bicyclo[2.2.1]heptan-2-**

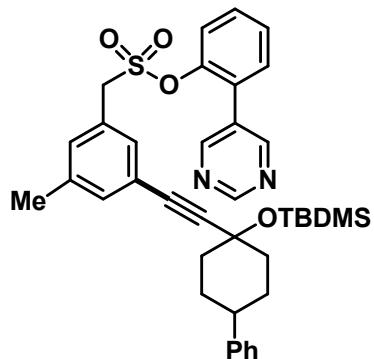
**yl)ethynyl)phenethoxyphenyl)pyrimidine (45):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 62%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.16 (s, 1H), 8.89 (s, 2H), 7.41 – 7.36 (m, 1H), 7.32 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 2H), 7.06 (dt, *J* = 14.7, 7.4 Hz, 2H), 6.80 (t, *J* = 8.4 Hz, 1H), 4.20 (t, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.44 (d, *J* = 3.3 Hz, 1H), 2.20 – 2.05 (m, 4H), 1.84 (d, *J* = 10.0 Hz, 1H), 1.56 – 1.52 (m, 2H), 1.37 – 1.33 (m, 2H), 0.90 (s, 9H), 0.18 (d, *J* = 12.0 Hz, 6H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 157.7, 157.0, 156.1, 133.7, 131.5, 130.7, 130.5, 126.2, 123.7, 121.4, 115.8, 112.5, 110.5, 94.6, 83.4, 74.9, 67.8, 55.6, 51.0, 50.0, 38.3, 37.1, 30.3, 29.1, 26.1, 25.9, 25.8, 21.5, 18.4. **HRMS (ESI)**: calcd. for C<sub>34</sub>H<sub>43</sub>N<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup>: 555.3037, found: 555.3039. **IR**: 1087, 1133, 1159, 1245, 1412, 1498.673, 1552, 1602, 1729, 2857, 2932, 2953.



**5-(2-(2-(3-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)-4-methoxyphenoxy)ethoxy)phenyl)pyrimidine (46):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 75%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.18 (s, 1H), 8.98 (s, 2H), 7.41 – 7.36 (m, 1H), 7.34 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.12 – 7.06 (m, 2H), 7.00 – 6.95 (m, 2H), 6.75 (d, *J* = 8.5 Hz, 1H), 3.99 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.49 – 2.43 (m, *J* = 12.9, 6.5 Hz, 1H), 2.01 (d, *J* = 5.9 Hz, 1H), 1.72 (d, *J* = 9.0 Hz, 1H), 1.51 – 1.28 (m, 5H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.90 – 0.85 (m, 7H), 0.19 (s, 9H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.9, 157.1, 157.0, 156.2, 133.1, 133.0, 130.7, 130.5, 129.4, 123.6, 121.5, 112.9, 112.5, 111.1, 98.7, 80.7, 73.8, 67.5, 55.9, 52.2, 50.7, 35.2, 31.2, 28.6, 27.5, 24.3, 22.2, 20.9, 18.6, 1.9. **HRMS (ESI):** calcd. for C<sub>35</sub>H<sub>46</sub>N<sub>2</sub>NaO<sub>3</sub>Si [M+Na]<sup>+</sup>: 593.3170, found: 593.3168. **IR:** 1112, 1143, 1173, 1246, 1412, 1454, 1497, 1552, 1602, 1725, 2869, 2927.

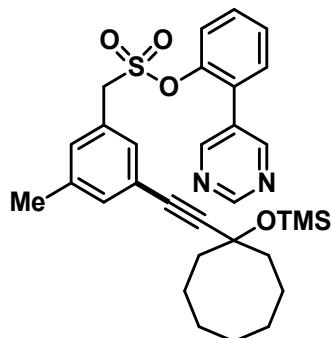


**2-(pyrimidin-5-yl)phenyl (3-((tert-butyldimethylsilyl)ethynyl)-5-methylphenyl)methanesulfonate (47):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 73%. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.23 (s, 1H), 8.84 (s, 2H), 7.49 – 7.41 (m, 3H), 7.37 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.31 (s, 1H), 7.20 (s, 1H), 7.07 (s, 1H), 4.23 (s, 2H), 2.31 (s, 3H), 0.99 (s, 9H), 0.18 (s, 6H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 158.0, 156.8, 146.2, 139.2, 133.9, 131.6, 131.4, 131.3, 130.9, 128.9, 128.1, 126.7, 124.3, 123.5, 104.9, 93.7, 57.4, 26.4, 21.3, 16.9, 1.2. **HRMS (ESI):** calcd. for C<sub>26</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub>SSi [M+H]<sup>+</sup>: 479.1819, found: 479.1819. **IR:** 1156, 1194, 1258, 1361, 1412, 1452, 1552, 1597, 1731, 2156, 2857, 2929, 2955.



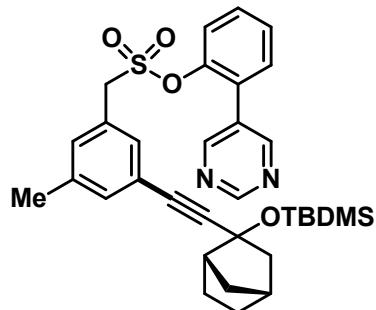
**2-(pyrimidin-5-yl)phenyl**

**(3-((1-((tert-butyldimethylsilyl)oxy)-4-phenylcyclohexyl)ethynyl)-5-methylphenyl)methanesulfonate (48):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 72%.  **$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  9.22 (s, 1H), 8.84 (s, 2H), 7.47 – 7.41 (m, 3H), 7.36 (d,  $J = 8.3$  Hz, 1H), 7.30 – 7.26 (m, 3H), 7.23 (d,  $J = 8.2$  Hz, 3H), 7.18 (d,  $J = 7.1$  Hz, 1H), 7.09 (s, 1H), 4.27 (s, 2H), 2.57 – 2.51 (m, 1H), 2.35 (s, 3H), 2.16 (d,  $J = 12.1$  Hz, 2H), 2.04 (dd,  $J = 14.2, 6.8$  Hz, 1H), 1.90 – 1.86 (m,  $J = 9.1, 6.7$  Hz, 3H), 1.73 (d,  $J = 5.0$  Hz, 2H), 0.89 (s, 9H), 0.21 (s, 6H).  **$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  158.0, 156.9, 146.8, 146.2, 139.4, 133.4, 131.4, 131.3, 130.9, 130.8, 128.9, 128.6, 128.1, 127.1, 126.9, 126.2, 124.2, 123.5, 114.3, 93.8, 85.4, 70.7, 57.4, 43.5, 41.8, 32.1, 31.8, 26.0, 22.9, 21.3, 18.2, 14.3. **HRMS (ESI):** calcd. for  $\text{C}_{38}\text{H}_{44}\text{N}_2\text{NaO}_4\text{SSi} [\text{M}+\text{Na}]^+$ : 675.2683, found: 675.2684.



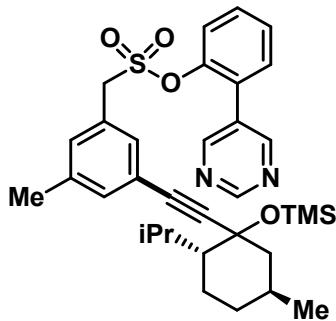
**2-(pyrimidin-5-yl)phenyl**

**((trimethylsilyl)oxy)cyclooctyl)ethynyl)-5-methylphenyl)methanesulfonate (49):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 62%; [meta/others = 12:1].  **$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  9.23 (s, 1H), 8.84 (s, 2H), 7.44 (ddt,  $J = 13.6, 7.5, 3.8$  Hz, 3H), 7.35 (dd,  $J = 7.9, 1.0$  Hz, 1H), 7.25 (s, 1H), 7.16 (s, 1H), 7.06 (s, 1H), 4.25 (s, 2H), 2.32 (s, 3H), 2.03 – 1.90 (m, 5H), 1.72 – 1.64 (m, 4H), 1.56 – 1.46 (m, 5H), 0.19 (s, 9H).  **$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  158.0, 156.9, 146.3, 139.2, 133.3, 131.3, 131.2, 131.1, 130.9, 128.9, 128.1, 126.8, 124.3, 123.5, 95.5, 83.4, 73.2, 57.5, 39.4, 28.2, 24.6, 22.0, 21.3, 2.2. **HRMS (ESI):** calcd. for  $\text{C}_{31}\text{H}_{39}\text{N}_2\text{O}_4\text{SSi} [\text{M}+\text{H}]^+$ : 563.2394, found: 563.2392. **IR:** 1099, 1157, 1195, 1261, 1361, 1413, 1450, 1557, 1599, 1723, 2855, 2925.

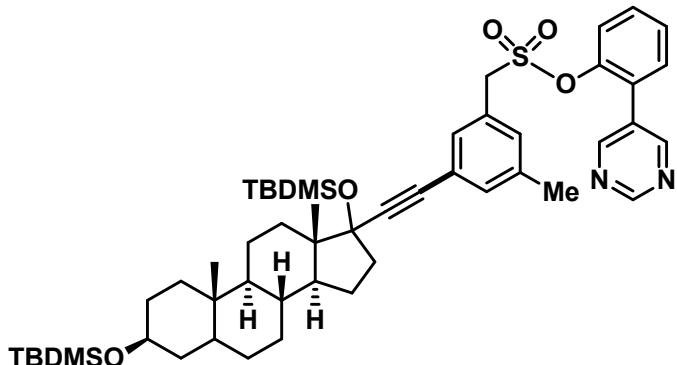


**2-(pyrimidin-5-yl)phenyl(3-((1S,4R)-2-((tert-butyldimethylsilyl)oxy)bicyclo[2.2.1]heptan-2-yl)ethynyl)methylphenylmethanesulfonate (50):**

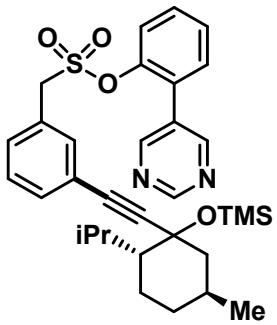
Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 75%; [meta/others = 12:1]. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.23 (s, 1H), 8.84 (s, 2H), 7.48 – 7.42 (m, 3H), 7.36 – 7.33 (m, 1H), 7.23 (s, 1H), 7.14 (s, 1H), 7.05 (s, 1H), 4.24 (s, 2H), 2.41 (dd, *J* = 15.3, 2.8 Hz, 1H), 2.32 (s, 3H), 2.24 (s, 1H), 2.19 – 2.15 (m, 1H), 2.08 – 2.02 (m, 2H), 1.80 (d, *J* = 9.9 Hz, 1H), 1.56 – 1.52 (m, 2H), 1.36 – 1.33 (m, 2H), 0.89 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.0, 156.9, 146.2, 139.2, 133.2, 131.3, 131.2, 131.1, 130.9, 130.7, 128.9, 128.1, 126.8, 124.5, 123.5, 96.8, 82.9, 74.9, 57.5, 51.0, 49.9, 38.3, 37.0, 29.1, 21.5, 21.3, 18.4, -2.9. **HRMS (ESI)**: calcd. for C<sub>33</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub>SSi [M+H]<sup>+</sup>: 589.2551, found: 589.2548. **IR**: 1158, 1189, 1215, 1253, 1362, 1413, 1453, 1553, 1599, 1727, 2857, 2928, 2954.



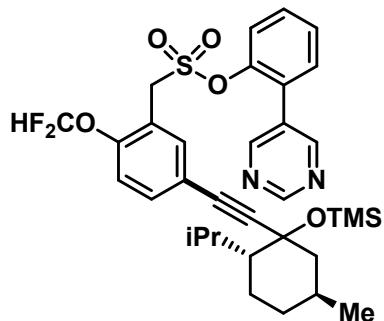
**2-(pyrimidin-5-yl)phenyl((3-((2R,5S)-2-isopropyl-5-methyl-1-(trimethylsilyl)oxy)cyclohexyl)ethynyl)-5-methylphenylmethanesulfonate (51):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 77%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.30 (s, 1H), 8.92 (s, 2H), 7.48 – 7.42 (m, 3H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 7.16 (s, 1H), 7.06 (s, 1H), 4.25 (s, 2H), 2.40 – 2.34 (m, 1H), 2.33 (s, 3H), 2.03 – 1.98 (m, 1H), 1.75 – 1.69 (m, 2H), 1.52 – 1.30 (m, 4H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.88 (dd, *J* = 13.1, 6.7 Hz, 7H), 0.18 (s, 9H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 146.3, 139.2, 133.2, 131.3, 131.2, 130.9, 130.8, 129.0, 128.1, 127.7, 126.8, 124.4, 123.5, 95.6, 83.5, 73.7, 57.5, 52.2, 50.6, 35.2, 28.8, 27.4, 24.3, 22.2, 21.3, 20.8, 18.6, 2.0. **HRMS (ESI)**: calcd. for C<sub>33</sub>H<sub>42</sub>N<sub>2</sub>NaO<sub>4</sub>SSi [M+Na]<sup>+</sup>: 613.2527, found: 613.2529. **IR**: 1099, 1156, 1196, 1215.443, 1249, 1362, 1412, 1453, 1491, 1552, 1598, 1735, 2870, 2928, 2953, 3022.



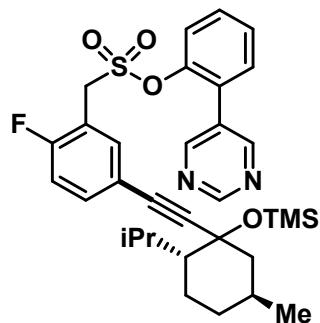
**2-(pyrimidin-5-yl)phenyl ((3-(((3S,8R,9S,10S,13S,14S)-3,17-bis((tert-butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethynyl)-5-methylphenyl)methanesulfonate (52):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow solid; isolated yield: 55%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.23 (s, 1H), 8.86 (s, 2H), 7.48 – 7.43 (m, 3H), 7.38 – 7.36 (m, 1H), 7.25 (s, 1H), 7.17 (s, 1H), 7.06 (s, 1H), 4.25 (s, 2H), 3.56 – 3.49 (m, 1H), 2.34 (s, 3H), 2.27 – 2.21 (m, 1H), 1.97 – 1.91 (m, 1H), 1.69 – 1.63 (m, 6H), 1.48 – 1.31 (m, 10H), 1.11 – 1.04 (m, 2H), 0.97 – 0.91 (m, 2H), 0.87 (d, J = 5.1 Hz, 18H), 0.81 (s, 6H), 0.15 (s, 3H), 0.13 (s, 3H), 0.04 (s, 6H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.0, 156.9, 146.3, 139.2, 133.3, 131.3, 131.1, 130.9, 130.8, 128.9, 128.1, 126.8, 124.6, 123.6, 95.1, 85.5, 81.3, 72.4, 57.5, 54.4, 49.9, 48.6, 45.3, 40.6, 39.0, 37.4, 36.5, 35.8, 33.4, 32.2, 28.9, 26.2, 26.0, 23.8, 22.9, 21.3, 18.5, 18.4, 14.3, 13.6, 12.6, -2.7, -4.3. **HRMS (ESI):** calcd. for C<sub>51</sub>H<sub>74</sub>N<sub>2</sub>NaO<sub>5</sub>SSi<sub>2</sub> [M+Na]<sup>+</sup>: 905.4749, found: 905.4751. **IR:** 1095, 1157, 1215, 1252, 1361, 1413, 1459, 1727, 2856, 2928, 3021.



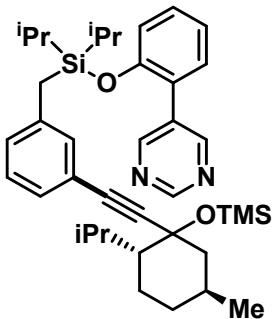
**2-(pyrimidin-5-yl)phenyl ((3-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)methanesulfonate (53):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 73%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.24 (s, 1H), 8.85 (s, 2H), 7.47 – 7.41 (m, 4H), 7.35 – 7.30 (m, 3H), 7.25 (d, J = 7.9 Hz, 1H), 4.29 (s, 2H), 2.36 (dq, J = 6.9, 5.6 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.75 – 1.68 (m, 1H), 1.51 – 1.26 (m, 5H), 0.94 (d, J = 7.0 Hz, 3H), 0.90 – 0.86 (m, 7H), 0.18 (s, 9H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.0, 156.8, 146.2, 133.6, 132.6, 131.3, 130.9, 130.3, 129.3, 128.9, 128.1, 127.0, 124.6, 123.5, 96.1, 83.3, 73.7, 57.5, 52.1, 50.6, 35.1, 27.4, 24.3, 22.2, 20.8, 18.6, 2.0. **HRMS (ESI):** calcd. for C<sub>32</sub>H<sub>40</sub>N<sub>2</sub>NaO<sub>4</sub>SSI [M+Na]<sup>+</sup>: 599.2370, found: 599.2368. **IR:** 1099, 1157, 1195, 1261, 1361, 1413, 1450, 1557, 1599.349, 1723, 2855, 2925.



**2-(pyrimidin-5-yl)phenyl (2-(difluoromethoxy)-5-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)methanesulfonate (54):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 70%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.22 (s, 1H), 8.85 (s, 2H), 7.49 – 7.40 (m, 6H), 7.17 – 7.13 (m, 1H), 6.49 (t, *J* = 77.7, 68.4 Hz, 1H), 4.42 (s, 2H), 2.34 (dtd, *J* = 13.8, 6.9, 1.4 Hz, 1H), 2.02 – 1.98 (m, 1H), 1.75 – 1.70 (m, 1H), 1.54 – 1.40 (m, 3H), 1.37 – 1.27 (m, 2H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.90 – 0.85 (m, 7H), 0.18 (s, 9H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.0, 156.8, 149.6, 146.0, 135.6, 134.4, 131.4, 130.9, 129.1, 128.3, 123.6, 121.6, 119.6, 119.2, 118.2, 116.1, 96.4, 82.3, 73.7, 52.1, 51.4, 50.5, 35.1, 28.9, 27.4, 24.2, 22.1, 20.8, 18.6, 2.0. **HRMS (ESI)**: calcd. for C<sub>33</sub>H<sub>40</sub>F<sub>2</sub>N<sub>2</sub>NaO<sub>5</sub>SSI [M+Na]<sup>+</sup>: 665.2287, found: 665.2284. **IR**: 1100, 1158, 1195, 1250, 1365, 1413, 1455, 1491, 1553, 1727, 2870, 2927.468, 2952.

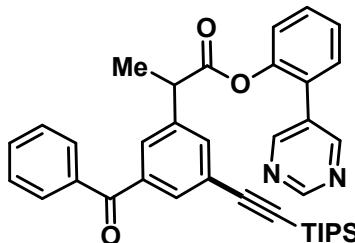


**2-(pyrimidin-5-yl)phenyl (2-fluoro-5-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)methanesulfonate (55):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 67%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.21 (s, 1H), 8.83 (s, 2H), 7.49 – 7.37 (m, 5H), 7.33 – 7.27 (m, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 4.43 (s, 2H), 2.42 – 2.34 (m, 1H), 2.05 – 2.00 (m, 1H), 1.76 – 1.70 (m, 1H), 1.49 – 1.34 (m, 5H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.88 (dd, *J* = 11.6, 6.7 Hz, 7H), 0.18 (s, 9H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.0, 156.8, 146.1, 135.0, 132.0, 131.4, 131.1, 130.9, 129.1, 128.2, 124.6, 124.5 (d, *J* = 4.5 Hz, C-F), 124.5, 123.4, 115.0, 101.3, 88.1, 73.9, 52.1, 50.7, 50.4, 35.1, 28.9, 27.4, 24.2, 22.2, 20.8, 18.6, 14.3, 1.90. **HRMS (ESI)**: calcd. for C<sub>32</sub>H<sub>39</sub>FN<sub>2</sub>NaO<sub>4</sub>SSI [M+Na]<sup>+</sup>: 617.2276, found: 617.2276. **IR**: 1075, 1158, 1194, 1250, 1294, 1366, 1412, 1462, 1552, 1579, 1730, 2854, 2924, 2924.

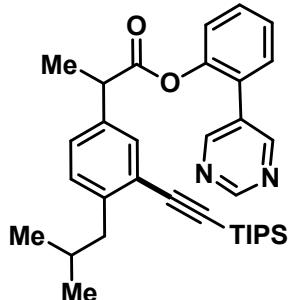


**5-((2-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)benzyl)silyloxyphenyl)pyrimidine (56):**

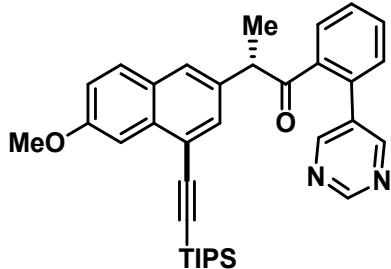
Eluent: ethyl acetate/petroleum ether (7:93 v/v); yellow liquid; isolated yield: 80%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.14 (s, 1H), 8.81 (s, 2H), 7.30 – 7.25 (m, 2H), 7.12 – 7.05 (m, 3H), 6.98 (s, 1H), 6.86 (d, *J* = 7.0 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 2.39 – 2.32 (m, 1H), 2.31 (s, 2H), 2.01 – 1.95 (m, 1H), 1.71 (dd, *J* = 7.8, 4.7 Hz, 1H), 1.52 – 1.26 (m, 5H), 1.10 (dq, *J* = 14.9, 7.5 Hz, 3H), 0.93 – 0.85 (m, 21H), 0.15 (s, 9H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 157.1, 157.0, 153.0, 138.4, 131.7, 130.7, 130.5, 128.5, 128.0, 125.9, 123.6, 122.3, 120.2, 119.6, 94.6, 84.5, 73.6, 52.2, 50.7, 35.2, 28.7, 27.4, 24.3, 23.0, 22.2, 21.2, 20.9, 18.7, 17.5, 17.4, 13.0, 2.0. **HRMS (ESI)**: calcd. for C<sub>38</sub>H<sub>54</sub>N<sub>2</sub>NaO<sub>2</sub>Si<sub>2</sub> [M+Na]<sup>+</sup>: 649.3616, found: 649.3619. **IR**: 1108, 1158, 1184, 1248, 1278, 1409, 1453, 1491, 1551, 1577, 1704, 2869, 2950, 3039.



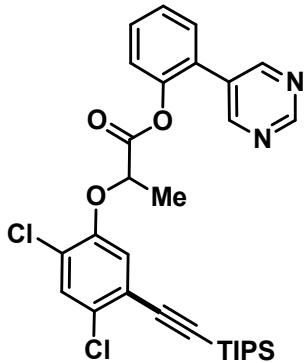
**2-(pyrimidin-5-yl)phenyl 2-(3-benzoyl-5-((triisopropylsilyl)ethynyl)phenyl)propanoate (57):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow solid; isolated yield: 82%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.11 (s, 1H), 8.67 (s, 2H), 7.85 – 7.82 (m, 2H), 7.79 (t, *J* = 1.5 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.52 – 7.44 (m, 4H), 7.40 – 7.35 (m, 1H), 7.15 – 7.12 (m, 2H), 3.86 (q, *J* = 7.2 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 2.1 Hz, 21H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 195.8, 172.0, 157.8, 156.4, 148.0, 139.8, 138.6, 137.2, 134.5, 133.0, 132.9, 131.1, 130.7, 130.5, 130.3, 128.9, 128.6, 128.1, 127.2, 124.7, 123.2, 105.6, 92.9, 45.3, 18.9, 18.4, 11.5. **HRMS (ESI)**: calcd. for C<sub>37</sub>H<sub>41</sub>N<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup>: 589.2881, found: 589.2878. **IR**: 1134, 1186, 1215, 1296, 1323.140, 1411, 1450, 1551, 1592, 1662, 1761, 2151, 2866, 2943, 3021.



**2-(pyrimidin-5-yl)phenyl 2-(4-isobutyl-3-((triisopropylsilyl)ethynyl)phenyl)propanoate (58):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 75%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.14 (s, 1H), 8.71 (s, 2H), 7.44 (ddd, *J* = 8.1, 5.4, 3.8 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.30 (d, *J* = 1.7 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.08 – 7.03 (m, 2H), 3.75 (q, *J* = 7.1 Hz, 1H), 2.67 (d, *J* = 7.3 Hz, 2H), 2.06 – 1.99 (m, *J* = 13.5, 6.8 Hz, 1H), 1.41 (d, 3H), 1.15 (s, 21H), 0.92 (d, *J* = 6.6 Hz, 6H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 172.7, 157.7, 156.5, 148.2, 143.7, 136.6, 132.0, 131.4, 130.7, 130.5, 130.4, 128.1, 127.1, 127.0, 124.0, 123.3, 105.8, 94.5, 45.1, 43.7, 29.6, 22.6, 19.0, 18.5, 11.6. **HRMS (ESI):** calcd. for C<sub>34</sub>H<sub>45</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup>: 541.3245, found: 541.3244. **IR:** 1069, 1132, 1193, 1261, 1330.648, 1383, 1410, 1463, 1491, 1551, 1580, 1761, 2147, 2866, 2926, 3024.

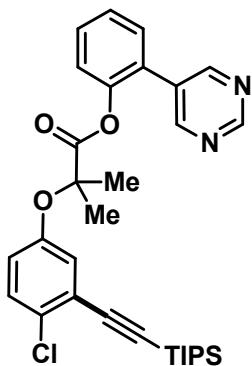


**(S)-2-(pyrimidin-5-yl)phenyl 2-(6-methoxy-4-((triisopropylsilyl)ethynyl)naphthalen-2-yl)propanoate (59):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 72%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 8.83 (s, 1H), 8.58 (s, 2H), 8.13 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.36 – 7.26 (m, 3H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 3.98 – 3.92 (m, 4H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 3.1 Hz, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 172.6, 157.4, 157.1, 156.3, 148.2, 135.3, 134.0, 130.7, 130.4, 129.5, 128.0, 126.9, 126.7, 124.7, 123.5, 123.4, 122.8, 107.5, 104.3, 96.5, 55.7, 45.8, 18.9, 18.2, 11.6. **HRMS (ESI):** calcd. for C<sub>35</sub>H<sub>40</sub>N<sub>2</sub>NaO<sub>3</sub>Si [M+Na]<sup>+</sup>: 587.2700, found: 587.2702. **IR:** 1132, 1195, 1289, 1338, 1410, 1462, 1551, 1598, 1762, 2151, 2865, 2926.

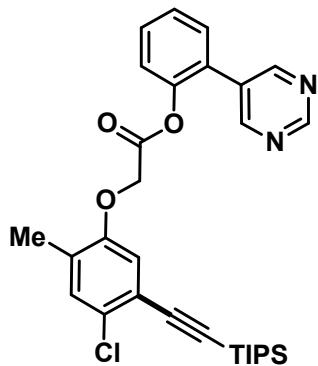


<b>2-(pyrimidin-5-yl)phenyl ((triisopropylsilyl)ethynyl)phenoxypropanoate (60):</b> Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 75%. <b><sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)</b> δ 9.20 (s, 1H), 8.79 (s, 2H), 7.50 – 7.45 (m, 1H), 7.44 – 7.40 (m, <i>J</i> = 6.0, 3.4 Hz, 3H), 7.16 (d, <i>J</i> = 7.8 Hz, 1H), 6.97 (s, 1H), 4.85 (q, <i>J</i> = 6.8 Hz, 1H), 1.52 (d, <i>J</i> = 6.8 Hz, 3H), 1.14 (d, <i>J</i> = 2.7 Hz, 21H). <b><sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)</b> δ 169.5, 158.0, 156.6, 151.6, 147.6, 131.2, 130.9, 130.8, 130.4, 128.1, 127.6, 125.4, 123.0, 122.7, 119.5, 102.1, 98.6, 74.5, 18.9, 18.2, 11.5. <b>HRMS (ESI):</b> calcd. for C <sub>30</sub> H <sub>34</sub> Cl <sub>2</sub> N <sub>2</sub> NaO <sub>3</sub> Si [M+Na] <sup>+</sup> : 591.1608, found: 591.1611. <b>IR:</b> 676, 722,	<b>2-(2,4-dichloro-5-</b>
---	---------------------------

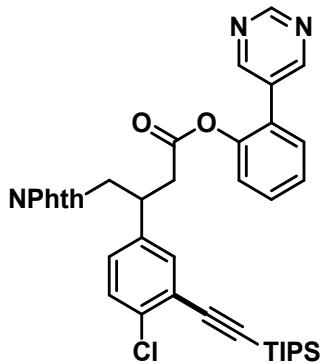
753, 803, 838, 882, 918, 1012, 1045, 1093, 1182, 1239, 1373, 1415, 1461, 1558, 1737, 2158.981, 2866, 2927.



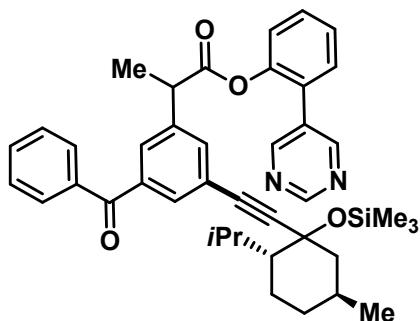
**2-(pyrimidin-5-yl)phenyl ((triisopropylsilyl)ethynyl)phenoxy-2-methylpropanoate (61):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 77%. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.20 (s, 1H), 8.81 (s, 2H), 7.50 – 7.46 (m, 1H), 7.41 (d, *J* = 6.1 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.02 (s, 1H), 6.68 – 6.65 (m, 1H), 1.50 (s, 6H), 1.14 (s, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 172.3, 158.0, 156.8, 153.4, 148.0, 130.9, 130.7, 130.2, 130.0, 128.2, 127.4, 124.3, 124.2, 122.9, 120.4, 102.9, 97.5, 79.7, 25.3, 22.9, 18.9, 14.3, 11.5. **HRMS (ESI)**: calcd. for C<sub>31</sub>H<sub>37</sub>ClN<sub>2</sub>NaO<sub>3</sub>Si [M+Na]<sup>+</sup>: 571.2154, found: 571.2154. **IR**: 882, 1017, 1107, 1168, 1260, 1410, 1466, 1551, 1591, 1759, 2158, 2865, 2926.



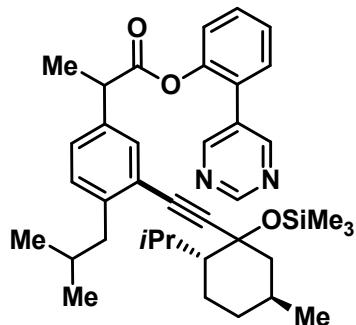
**2-(pyrimidin-5-yl)phenyl ((triisopropylsilyl)ethynyl)phenoxy-2-methyl-5-((triisopropylsilyl)ethynyl)phenoxy-propanoate (62):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 79%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.21 (s, 1H), 8.82 (s, 2H), 7.53 – 7.49 (m, 1H), 7.44 (d, *J* = 4.2 Hz, 2H), 7.28 (s, 1H), 7.17 (d, *J* = 0.7 Hz, 1H), 6.79 (s, 1H), 4.70 (s, 2H), 2.23 (s, 3H), 1.15 (d, *J* = 1.6 Hz, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 166.9, 158.0, 156.5, 154.0, 147.4, 131.7, 130.9, 130.7, 130.3, 129.5, 127.9, 127.6, 123.3, 121.3, 115.7, 103.2, 96.5, 65.8, 32.1, 18.9, 11.5. **HRMS (ESI)**: calcd. for C<sub>30</sub>H<sub>36</sub>ClN<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup>: 535.2178, found: 535.2182. **IR**: 1111, 1215, 1411, 1467, 1762, 2866, 2927.



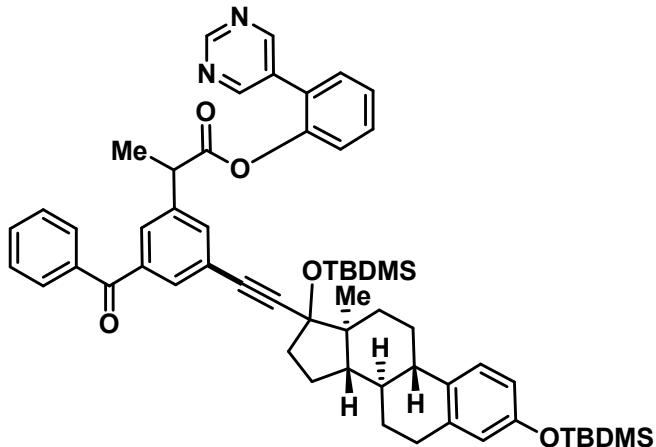
**2-(pyrimidin-5-yl)phenyl 3-(4-chloro-3-((triisopropylsilyl)ethynyl)phenyl)-3-(1,3-dioxoisooindolin-2-yl)propanoate (63):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 66%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.18 (s, 1H), 8.77 – 8.73 (m, 2H), 7.82 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.40 – 7.30 (m, 5H), 7.13 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 3.85 (dd, *J* = 7.5, 3.7 Hz, 2H), 3.69 – 3.60 (m, 1H), 2.84 – 2.77 (m, *J* = 11.6, 7.4 Hz, 2H), 1.13 (d, *J* = 1.6 Hz, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 169.7, 168.3, 157.8, 156.4, 147.8, 138.5, 135.8, 134.4, 133.1, 131.9, 130.6, 130.5, 129.8, 128.4, 127.9, 127.1, 123.9, 123.7, 123.3, 102.9, 97.5, 42.7, 40.1, 38.2, 18.9, 11.5. **HRMS (ESI):** calcd. for C<sub>39</sub>H<sub>40</sub>ClN<sub>3</sub>O<sub>4</sub>Si [M+H]<sup>+</sup>: 700.2369, found: 700.2368. **IR:** 1105, 1133, 1188, 1260, 1359, 1394, 1469, 1551, 1715.617, 1763, 2157, 2866, 2943.



**2-(pyrimidin-5-yl)phenyl 2-(3-benzoyl-5-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)-3-(1,3-dioxoisooindolin-2-yl)propanoate (64):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 82%. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.10 (s, 1H), 8.68 (s, 2H), 7.85 – 7.83 (m, 2H), 7.72 (s, 1H), 7.64 – 7.60 (m, 2H), 7.52 – 7.45 (m, 4H), 7.37 (dd, *J* = 6.9, 4.7 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 3.87 (q, *J* = 7.1 Hz, 1H), 2.36 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.03 (d, *J* = 12.9 Hz, 1H), 1.76 – 1.72 (m, 1H), 1.49 – 1.33 (m, 8H), 0.95 (dd, *J* = 7.0, 1.4 Hz, 3H), 0.91 – 0.86 (m, 7H), 0.19 (s, 9H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 195.7, 172.0, 157.8, 156.4, 148.0, 139.9, 138.6, 137.23, 133.9, 133.0, 132.5, 131.2, 130.8, 130.6, 130.4, 128.7, 128.6, 128.1, 127.2, 124.5, 123.2, 96.5, 83.1, 73.8, 52.1, 50.5, 45.3, 35.1, 28.9, 27.4, 24.3, 22.2, 20.8, 18.6, 18.4, 2.0. **HRMS (ESI):** calcd. for C<sub>41</sub>H<sub>46</sub>N<sub>2</sub>NaO<sub>4</sub>Si [M+Na]<sup>+</sup>: 681.3119, found: 681.3117. **IR:** 1073, 1138, 1193, 1215, 1249, 1327, 1378, 1411, 1450, 1551, 1596, 1665, 1763, 2855, 2925.

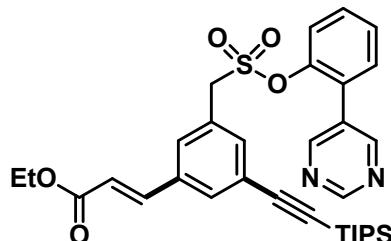


**2-(pyrimidin-5-yl)phenyl 2-(4-isobutyl-3-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl propanoate (65):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 77%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.14 (s, 1H), 8.72 (s, 2H), 7.46 – 7.42 (m, 1H), 7.36 (dd, *J* = 4.9, 0.8 Hz, 2H), 7.27 (s, *J* = 2.7 Hz, 1H), 7.12 – 7.04 (m, 3H), 3.75 (q, *J* = 7.2 Hz, 1H), 2.63 (d, *J* = 7.3 Hz, 2H), 2.50 – 2.44 (m, 1H), 1.99 (ddd, *J* = 20.5, 14.3, 7.8 Hz, 2H), 1.76 – 1.71 (m, 1H), 1.48 – 1.35 (m, 8H), 0.93 (ddd, *J* = 8.3, 6.8, 4.3 Hz, 13H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.20 (s, 9H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 172.7, 157.7, 156.6, 148.3, 143.1, 136.8, 131.4, 130.7, 130.5, 130.4, 129.0, 128.1, 127.0, 126.9, 123.8, 123.3, 98.5, 83.1, 74.0, 68.4, 52.5, 51.0, 45.1, 43.6, 35.2, 29.6, 28.9, 27.5, 24.3, 22.7, 22.2, 20.7, 18.5, 2.1. **HRMS (ESI)**: calcd. for C<sub>38</sub>H<sub>50</sub>N<sub>2</sub>NaO<sub>3</sub>Si [M+Na]<sup>+</sup>: 633.3483, found: 633.3481. **IR**: 1139, 1215, 1249, 1378, 1412, 1454, 1551, 1763, 2855, 2925.

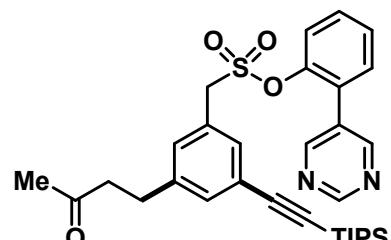


**2-(pyrimidin-5-yl)phenyl 2-(3-benzoyl-5-(((8R,9S,13S,14S)-3,17-bis((tert-butyldimethylsilyl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethynyl)phenyl propanoate (66):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 52%. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.10 (s, 1H), 8.68 (s, 2H), 7.84 (d, *J* = 7.7 Hz, 2H), 7.75 (s, 1H), 7.63 – 7.57 (m, 2H), 7.47 (dd, *J* = 19.2, 9.5 Hz, 4H), 7.37 (d, *J* = 6.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.62 – 6.59 (m, 1H), 6.55 (s, 1H), 3.87 (q, *J* = 14.3, 7.0 Hz, 1H), 2.81 (d, *J* = 15.9 Hz, 3H), 2.36 – 2.30 (m, 2H), 2.24 – 2.16 (m, 2H), 2.02 (dd, *J* = 16.6, 8.9 Hz, 2H), 1.93 – 1.80 (m, 4H), 1.72 (dd, *J* = 22.4, 11.9 Hz, 2H), 1.46 (dt, *J* = 13.0, 7.5 Hz, 6H), 0.97 (s, 9H), 0.89 (s, 9H), 0.18 (s, 12H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 195.8, 172.0, 156.4, 153.5, 148.0, 139.9, 138.6, 138.1, 137.2,

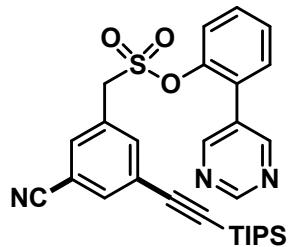
133.9, 133.4, 133.0, 132.5, 130.8, 130.6, 130.4, 128.6, 128.1, 127.2, 126.4, 124.6, 123.2, 120.1, 117.3, 114.3, 95.8, 85.3, 81.3, 49.0, 45.3, 44.0, 40.5, 39.7, 33.5, 32.1, 27.6, 26.7, 26.0, 25.9, 23.5, 22.9, 18.5, 18.4, 14.3, 13.5, -2.6, -4.2. **HRMS (ESI)**: calcd. for  $C_{58}H_{71}N_2O_5Si_2$   $[M+H]^+$ : 931.4896, found: 931.4897. **IR**: 1023, 1104, 1138, 1192, 1259, 1291, 1412, 1493.543, 1597, 1663, 1714.329, 1761, 2858, 2930.



**(E)-ethyl 3-((3-((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)-5-((triisopropylsilyl)ethynyl)phenyl)acrylate (67):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 64%.  **$^1H$  NMR** (500 MHz,  $CDCl_3$ )  $\delta$  9.23 (s, 1H), 8.84 (s, 2H), 7.64 (s, 1H), 7.59 (d,  $J$  = 16.0 Hz, 1H), 7.50 – 7.40 (m, 4H), 7.39 (s, 2H), 6.45 (d,  $J$  = 16.0 Hz, 1H), 4.29 – 4.24 (m,  $J$  = 12.8, 5.7 Hz, 4H), 1.33 (t,  $J$  = 7.1 Hz, 3H), 1.13 (d,  $J$  = 2.4 Hz, 21H).  **$^{13}C$  NMR** (101 MHz,  $CDCl_3$ )  $\delta$  166.6, 158.1, 156.8, 146.1, 142.6, 135.8, 135.3, 132.4, 131.4, 130.9, 130.0, 128.9, 128.3, 127.8, 125.5, 123.5, 120.6, 105.1, 93.5, 61.0, 57.1, 18.9, 14.5, 11.5. **HRMS (ESI)**: calcd. for  $C_{33}H_{41}N_2O_5SSi$   $[M+H]^+$ : 605.2500, found: 605.2505. **IR**: 681, 726, 759, 860, 1002.512, 1043, 1098, 1159, 1183, 1246, 1367, 1413, 1453, 1553, 1593, 1642, 1713, 2153, 2866, 2925.



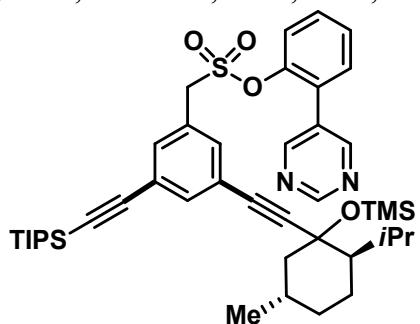
**2-(pyrimidin-5-yl)phenyl ((triisopropylsilyl)ethynyl)phenylmethanesulfonate (68):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 77%; [*meta/others* = 26:1].  **$^1H$  NMR** (400 MHz,  $CDCl_3$ )  $\delta$  9.29 (s, 1H), 8.91 (s, 2H), 7.49 – 7.41 (m, 3H), 7.37 (dd,  $J$  = 7.8, 1.4 Hz, 1H), 7.32 (s, 1H), 7.22 (s, 1H), 7.11 (s, 1H), 4.23 (s, 2H), 2.85 (t,  $J$  = 7.3 Hz, 2H), 2.75 (t,  $J$  = 7.2 Hz, 2H), 2.13 (s, 3H), 1.12 (s, 21H).  **$^{13}C$  NMR** (101 MHz,  $CDCl_3$ )  $\delta$  207.4, 146.3, 142.4, 133.2, 132.1, 131.4, 130.9, 130.8, 129.0, 128.1, 127.0, 124.9, 123.5, 106.0, 92.2, 57.4, 44.8, 30.2, 29.3, 18.9, 11.5. **HRMS (ESI)**: calcd. for  $C_{32}H_{41}N_2O_4SSi$   $[M+H]^+$ : 577.2551, found: 577.2545. **IR**: 1056, 1099, 1157, 1195, 1261, 1360, 1412, 1454, 1491, 1552, 1596, 1716, 2155, 2865, 2925, 3040.



**2-(pyrimidin-5-yl)phenyl**

**(3-cyano-5-**

**((triisopropylsilyl)ethynyl)phenyl)methanesulfonate (69):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 53%. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 9.26 (s, 1H), 8.83 (s, 2H), 7.77 (s, 1H), 7.59 (s, 1H), 7.53 (s, 1H), 7.52 – 7.41 (m, 4H), 4.28 (s, 2H), 1.12 (d, *J* = 3.3 Hz, 21H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 158.2, 156.8, 145.8, 138.0, 136.5, 133.2, 131.5, 131.0, 128.9, 128.7, 128.5, 126.3, 123.6, 117.3, 117.3, 114.0, 103.3, 96.2, 56.5, 18.8, 11.4. **HRMS (ESI):** calcd. for C<sub>29</sub>H<sub>34</sub>N<sub>3</sub>O<sub>3</sub>SSi [M+H]<sup>+</sup>: 532.2085, found: 532.2082. **IR:** 1158, 1214, 1264, 1365, 1413, 1457, 1553.549, 1593, 1723, 2163, 2234, 2865, 2927.

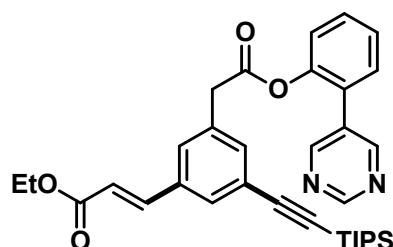


**2-(pyrimidin-5-yl)phenyl**

**(3-(((2R,5S)-2-isopropyl-5-methyl-1-**

**((trimethylsilyloxy)cyclohexyl)ethynyl)-5-**

**((triisopropylsilyl)ethynyl)phenyl)methanesulfonate (70):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 57% [*meta/others* = 12:1]. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 9.24 (s, 1H), 8.86 (s, 2H), 7.50 – 7.42 (m, 4H), 7.39 – 7.35 (m, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 4.24 (s, 2H), 2.38 – 2.31 (m, 1H), 2.05 – 2.01 (m, *J* = 8.6, 5.4 Hz, 1H), 1.75 – 1.71 (m, 1H), 1.45 – 1.34 (m, 5H), 1.12 (d, *J* = 2.4 Hz, 21H), 0.95 – 0.88 (m, 10H), 0.18 (d, *J* = 3.0 Hz, 9H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 158.1, 156.8, 146.2, 135.8, 133.5, 133.2, 131.3, 130.9, 129.0, 128.2, 127.3, 125.0, 124.8, 123.6, 114.3, 105.2, 96.8, 93.3, 82.6, 73.8, 57.0, 52.1, 50.5, 35.13, 28.9, 27.4, 24.3, 22.2, 20.8, 18.9, 14.3, 11.5, 2.0. **HRMS (ESI):** calcd. for C<sub>43</sub>H<sub>61</sub>N<sub>2</sub>O<sub>4</sub>SSi<sub>2</sub> [M+H]<sup>+</sup>: 757.3885, found: 757.3888. **IR:** 1158, 1215, 1249, 1366, 1413.755, 1455, 1552, 1590, 1726, 2155, 2866, 2926.

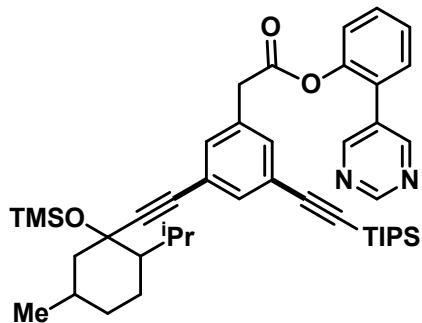


**ethyl**

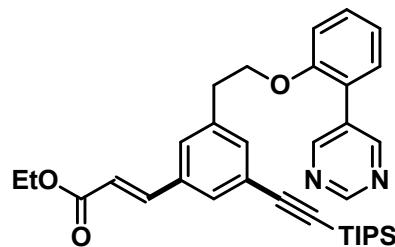
**(E)-3-(3-(2-oxo-2-(2-(pyrimidin-5-yl)phenoxy)ethyl)-5-**

**((triisopropylsilyl)ethynyl)phenyl)acrylate (71):** Eluent: ethyl acetate/petroleum ether

(20:80 v/v); yellow liquid; isolated yield: 59% [*meta*/others > 25:1]. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.17 (s, 1H), 8.73 (s, 2H), 7.60 (d, *J* = 16.0 Hz, 1H), 7.56 (s, 1H), 7.48 (ddd, *J* = 8.1, 5.6, 3.6 Hz, 1H), 7.40 – 7.38 (m, 2H), 7.29 (s, 1H), 7.26 (d, *J* = 1.4 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.14 (s, 2H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 169.1, 166.8, 157.9, 156.5, 148.0, 143.3, 135.4, 134.3, 133.6, 131.3, 130.8, 130.7, 130.6, 128.9, 128.0, 127.3, 125.0, 123.3, 119.9, 105.8, 92.4, 60.9, 40.8, 18.9, 14.5, 11.5. **HRMS (ESI)**: calcd. for C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup>: 569.2830, found: 569.2836. **IR**: 678, 728, 754, 858, 882, 918, 1038, 1115, 1180, 1231, 1254, 1306, 1367, 1410, 1463, 1551, 1592, 1641, 1711, 1761, 2151, 2865, 2943, 3044.

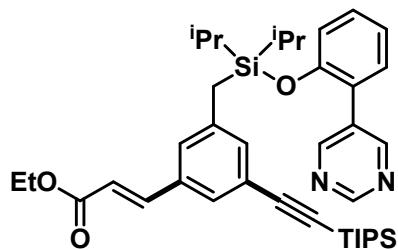


**2-(pyrimidin-5-yl)phenyl((trimethylsilyl)oxy)cyclohexyl)ethynyl)-5-((triisopropylsilyl)ethynyl)phenylacetate (72):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 51% [*meta*/others = 30:1]. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.21 (s, 1H), 8.79 (s, 2H), 7.49 – 7.44 (m, 1H), 7.41 (d, *J* = 3.8 Hz, 3H), 7.23 (s, 1H), 7.20 (d, *J* = 5.2 Hz, 2H), 3.65 (s, 2H), 2.38 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.02 (d, *J* = 13.3 Hz, 1H), 1.73 (d, *J* = 8.9 Hz, 2H), 1.52 – 1.44 (m, 2H), 1.35 (dd, *J* = 14.1, 10.6 Hz, 3H), 1.13 (s, 2H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 8.0 Hz, 6H), 0.19 (s, 9H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 169.1, 157.8, 156.5, 148.0, 134.2, 133.1, 132.4, 132.1, 130.7, 130.6, 128.0, 127.3, 124.6, 124.3, 123.3, 120.2, 105.9, 95.9, 92.2, 83.1, 73.8, 52.1, 50.6, 40.6, 35.1, 28.9, 27.4, 24.3, 22.2, 20.8, 18.9, 18.6, 11.5, 2.0. **HRMS (ESI)**: calcd. for C<sub>44</sub>H<sub>60</sub>KN<sub>2</sub>O<sub>3</sub>Si<sub>2</sub> [M+K]<sup>+</sup>: 759.3774, found: 759.3779. **IR**: 729, 754, 841, 883, 908, 994, 1073, 1113, 1195, 1249, 1297, 1382, 1412, 1456, 1552, 1588, 1711, 1765, 2156, 2867, 2926, 2952.

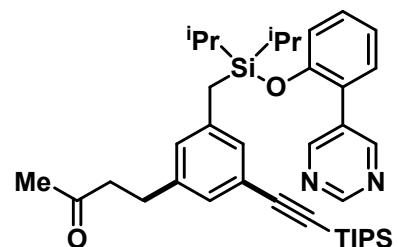


**(E)-ethyl ((triisopropylsilyl)ethynyl)phenylacrylate (73):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 66%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.19 (s, 1H), 8.86 (s, 2H), 7.57 (d, *J* = 16.0 Hz, 1H), 7.48 (s, 1H), 7.38 (dd, *J* = 12.5, 6.1 Hz, 1H), 7.30 (d, *J*

$\delta$  = 10.4 Hz, 2H), 7.21 (s, 1H), 7.08 (dd,  $J$  = 8.9, 5.4 Hz, 1H), 6.98 (t,  $J$  = 8.7 Hz, 1H), 6.40 (d,  $J$  = 16.0 Hz, 1H), 4.32 – 4.18 (m, 4H), 3.03 (t,  $J$  = 6.3 Hz, 2H), 1.35 (t,  $J$  = 7.1 Hz, 3H), 1.13 (s, 21H).  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  166.9, 155.8, 145.6, 143.6, 139.0, 138.5, 135.0, 133.8, 130.7, 130.6, 129.9, 129.1, 124.7, 123.8, 121.7, 119.5, 112.4, 106.2, 91.8, 69.0, 60.8, 35.6, 18.9, 14.5, 11.5, 1.2. **HRMS (ESI)**: calcd. for  $\text{C}_{34}\text{H}_{42}\text{N}_2\text{NaO}_3\text{Si} [\text{M}+\text{Na}]^+$ : 577.2857, found: 577.2863. **IR**: 663, 689, 729, 752, 798, 858, 882, 911, 999, 1029, 1113, 1179, 1241, 1272, 1306, 1412, 1462, 1496, 1552, 1639, 1716, 2153, 2866, 2942, 3520.

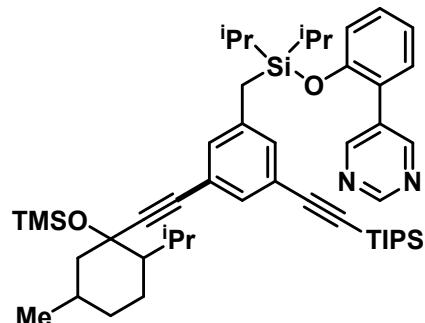


**(E)-ethyl 3-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)-5-((triisopropylsilyl)ethynyl)phenyl)acrylate (74):** Eluent: ethyl acetate/petroleum ether (10:90 v/v); yellow liquid; isolated yield: 70%.  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.21 (s, 1H), 8.91 (s, 2H), 7.47 (d,  $J$  = 16.0 Hz, 1H), 7.29 (dd,  $J$  = 14.3, 6.9 Hz, 3H), 7.10 (t,  $J$  = 7.3 Hz, 1H), 6.97 (s, 1H), 6.95 (s, 1H), 6.85 (d,  $J$  = 8.2 Hz, 1H), 6.24 (d,  $J$  = 16.0 Hz, 1H), 4.25 (q,  $J$  = 7.1 Hz, 2H), 2.32 (s, 2H), 1.33 (t,  $J$  = 7.1 Hz, 3H), 1.10 (s, 21H), 0.96 – 0.86 (m, 14H).  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  167.0, 152.8, 143.9, 139.2, 134.7, 133.8, 130.9, 130.5, 128.3, 128.1, 125.9, 124.4, 122.5, 119.5, 119.1, 106.5, 91.5, 60.8, 21., 18.9, 18.8, 17.5, 17.4, 14.5, 13.1, 11.5. **HRMS (ESI)**: calcd. for  $\text{C}_{39}\text{H}_{55}\text{N}_2\text{O}_3\text{Si}_2 [\text{M}+\text{H}]^+$ : 655.3746, found: 655.3748. **IR**: 670, 728, 754, 798, 858, 881, 906, 1016, 1016, 1094, 1176, 1260, 1367, 1409, 1462, 1491, 1551, 1586, 1639, 1713, 2156, 2866, 2944.

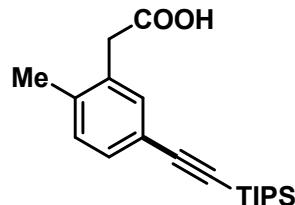


**4-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)-5-((triisopropylsilyl)ethynyl)butan-2-one (75):** Eluent: ethyl acetate/petroleum ether (10:90 v/v); yellow liquid; isolated yield: 52% [*meta/others* = 2.5:1].  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.12 (s, 1H), 8.79 (s, 2H), 7.28 (dd,  $J$  = 7.7, 1.8 Hz, 2H), 7.08 (dd,  $J$  = 9.7, 4.7 Hz, 1H), 6.98 (s, 1H), 6.82 (d,  $J$  = 9.4 Hz, 2H), 6.71 (s, 1H), 2.70 (t,  $J$  = 7.1 Hz, 2H), 2.62 (t,  $J$  = 7.1 Hz, 2H), 2.27 (s, 2H), 2.11 (s, 3H), 1.10 (s, 21H), 0.94 – 0.89 (m, 14H).  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  192.6, 157.0, 152.9, 141.3, 138.5, 134.8, 132.9, 130.8, 130.5, 130.2, 129.2, 128.4, 125.8, 123.8, 122.3, 119.6, 107.4, 90.2, 45.1, 30.2, 29.5, 21.1, 18.9, 17.5, 17.5, 13.1, 13.0, 11.5. **HRMS (ESI)**: calcd. for  $\text{C}_{38}\text{H}_{54}\text{N}_2\text{NaO}_2\text{Si}_2 [\text{M}+\text{Na}]^+$ : 649.3616, found: 649.3622.

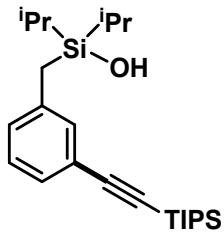
**IR:** 669, 728, 757, 882, 906, 969, 1001, 1071, 1108, 1161, 1187, 1246, 1278, 1365, 1409, 1452, 1491, 1551, 1591, 1717, 2154, 2725, 2866, 2944, 3038.



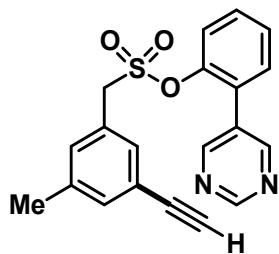
**5-((2-((diisopropyl(3-((2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)-5-((triisopropylsilyl)ethynyl)benzyl)silyl)oxy)phenyl)pyrimidine (76):** Eluent: ethyl acetate/petroleum ether (10:90 v/v); yellow liquid; isolated yield: 67% [*meta/others* > 20:1].  
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.14 (s, 1H), 8.82 (s, 2H), 7.28 (d, J = 7.4 Hz, 2H), 7.19 (s, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.95 (s, 1H), 6.90 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 2.35 – 2.26 (m, 3H), 2.00 – 1.94 (m, 1H), 1.71 (d, J = 13.1 Hz, 2H), 1.51 – 1.39 (m, 3H), 1.34 – 1.27 (m, 2H), 1.10 (s, 21H), 0.95 – 0.85 (m, 23H), 0.15 (s, 9H).  
**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 157.0, 152.8, 138.7, 131.9, 131.6, 131.3, 130.8, 130.5, 125.9, 123.9, 123.7, 122.4, 119.6, 106.5, 95.2, 91.2, 83.6, 73.7, 52.1, 50.6, 35.2, 29.9, 28.8, 27.4, 24.2, 22.2, 20.8, 18.9, 18.6, 17.4, 13.0, 11.5, 2.0, 1.2.  
**HRMS (ESI):** calcd. for C<sub>49</sub>H<sub>74</sub>N<sub>2</sub>NaO<sub>2</sub>Si<sub>3</sub> [M+Na]<sup>+</sup>: 829.4950, found: 829.4962. **IR:** 668, 755, 842, 882, 918, 994, 1042, 1072, 1107, 1185, 1249, 1410, 1462, 1492, 1552, 1582, 1730, 2158, 2867, 2946.



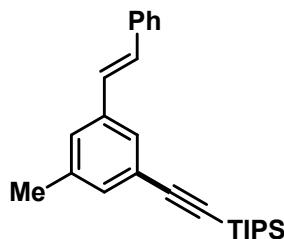
**2-(2-methyl-5-((triisopropylsilyl)ethynyl)phenyl)acetic acid (77):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 90%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.34 – 7.28 (m, 2H), 7.14 – 7.09 (m, 1H), 3.64 (s, 2H), 2.31 (s, 3H), 1.12 (d, J = 4.9 Hz, 21H).  
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 176.1, 137.8, 134.0, 132.3, 131.5, 130.5, 121.7, 107.0, 90.3, 38.7, 19.8, 18.9, 11.5. **HRMS (ESI):** calcd. for C<sub>20</sub>H<sub>30</sub>NaO<sub>2</sub>Si [M+Na]<sup>+</sup>: 353.1907, found: 353.1908. **IR:** 675, 725, 760, 792, 882, 919, 961, 997, 1017, 1072, 1094, 1160, 1216, 1259, 1412, 1463, 1498, 1711, 2151, 2866, 2943.



**diisopropyl(3-((triisopropylsilyl)ethynyl)benzyl)silanol (78):** Eluent: ethyl acetate/petroleum ether (1:99 v/v); yellow liquid; isolated yield: 71%. Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 71%. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.21 (d, *J* = 4.5 Hz, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 2.17 (s, 2H), 1.12 (s, 2H), 1.04 – 0.98 (m, 14H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 139.66, 131.98, 128.82, 128.46, 128.38, 123.78, 107.66, 90.31, 21.47, 18.89, 17.50, 17.44, 12.90, 11.56. **HRMS (ESI):** calcd. for C<sub>24</sub>H<sub>43</sub>OSi<sub>2</sub> [M+H]<sup>+</sup>: 403.2846, found: 403.2848. **IR:** 669, 772, 793, 818, 883, 936, 996, 1081, 1166, 1256, 1378, 1462, 1595, 2151, 2867, 2925.

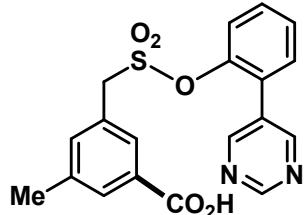


**2-(pyrimidin-5-yl)phenyl (3-ethynyl-5-methylphenyl)methanesulfonate (79):** Eluent: ethyl acetate/petroleum ether (10:90 v/v); yellow liquid; isolated yield: 78%. **NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.22 (s, 1H), 8.81 (s, 2H), 7.47 – 7.37 (m, 4H), 7.34 (s, 1H), 7.22 (s, 1H), 7.10 (s, 1H), 4.25 (s, 2H), 3.08 (s, 1H), 2.32 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 157.9, 156.8, 146.1, 139.3, 134.0, 132.0, 131.5, 131.3, 131.1, 130.9, 128.8, 128.1, 126.9, 123.5, 123.1, 82.9, 78.2, 57.3, 21.2. **HRMS (ESI):** calcd. for C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>NaO<sub>3</sub>S [M+Na]<sup>+</sup>: 387.0774, found: 387.0779. **IR:** 695, 726, 775, 857, 949, 1003, 1057, 1098, 1155, 1193, 1261, 1306, 1356, 1411, 1451, 1491, 1553, 1727, 2926, 3039, 3290.

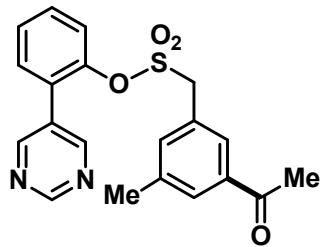


**(E)-triisopropyl((3-methyl-5-styrylphenyl)ethynyl)silane (80):** Eluent: ethyl acetate/petroleum ether (2:98 v/v); yellow liquid; isolated yield: 83%. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.46 (s, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 9.7 Hz, 2H), 7.23 (s, 1H), 7.12 (d, *J* = 16.3 Hz, 1H), 7.04 (d, *J* = 16.3 Hz, 1H), 2.36 (s, 3H), 1.18 (d, *J* = 2.1 Hz, 2H). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 138.4, 137.5, 137.4, 132.0, 129.4, 128.9,

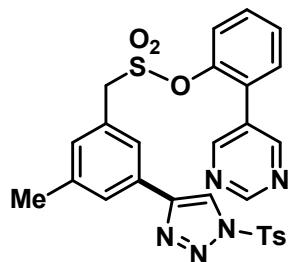
128.1, 127.9, 127.6, 127.5, 126.8, 125.7, 123.9, 107.4, 90.3, 21.4, 18.9, 11.6. **HRMS (ESI):** calcd. For  $C_{26}H_{34}NaSi$   $[M+Na]^+$ : 397.2322, found: 397.2326. **IR:** 661, 677, 715, 749, 837, 882, 919, 958, 996, 1017, 1073, 1161, 1232, 1382, 1462, 1590, 1751, 2153.388, 2865, 2942, 3028, 3644.



**3-methyl-5-((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methylbenzoic acid (81):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow liquid; isolated yield: 87%.  **$^1H$  NMR (500 MHz,  $CDCl_3$ )**  $\delta$  9.19 (s, 1H), 8.80 (s, 2H), 7.95 (s, 1H), 7.83 (s, 1H), 7.50 – 7.49 (m, 2H), 7.43 (ddd,  $J = 7.7, 5.6, 3.1$  Hz, 1H), 7.37 – 7.35 (m, 1H), 7.31 (s, 1H), 4.42 (s, 2H), 2.39 (s, 3H).  **$^{13}C$  NMR (126 MHz,  $CDCl_3$ )**  $\delta$  157.1, 156.6, 145.5, 139.5, 135.8, 131.9, 131.4, 131.2, 131.0, 129.5, 128.7, 128.1, 127.2, 123.7, 57.1, 21.4. **HRMS:** calcd. For  $C_{19}H_{16}N_2NaO_5S$   $[M+Na]^+$ : 407.0672, found 407.0669. **IR:** 690, 726, 783, 860, 1057, 1098, 1158, 1195, 1262, 1306, 1362, 1413, 1453, 1554, 1602, 1668, 1715, 2867, 2927.



**2-(pyrimidin-5-yl)phenyl (3-acetyl-5-methylphenyl)methanesulfonate (82):** Eluent: ethyl acetate/petroleum ether (10:90 v/v); yellow liquid; isolated yield: 63%.  **$^1H$  NMR (500 MHz,  $CDCl_3$ )**  $\delta$  9.19 (s, 1H), 8.79 (s, 2H), 7.78 (s, 1H), 7.68 (s, 1H), 7.49 – 7.39 (m, 4H), 7.32 (s, 1H), 4.33 (s, 2H), 2.59 (s, 3H), 2.41 (s, 3H).  **$^{13}C$  NMR (126 MHz,  $CDCl_3$ )**  $\delta$  197.6, 158.0, 156.8, 146.1, 139.7, 138.1, 135.8, 131.4, 130.9, 130.2, 128.9, 128.2, 127.9, 127.3, 123.5, 57.4, 26.9, 21.4. **HRMS (ESI):** calcd. for  $C_{20}H_{19}N_2O_4S$   $[M+H]^+$ : 383.1060, found: 383.1061. **IR:** 697, 727, 778, 860, 1056, 1098, 1157, 1208, 1261, 1309, 1358, 1412, 1451, 1491, 1553, 1603, 1684.223, 1719, 2854, 2924.



**2-(pyrimidin-5-yl)phenyl (3-methyl-5-(1-tosyl-1H-1,2,3-triazol-4-yl)phenyl)methanesulfonate (83):** Eluent: ethyl acetate/petroleum ether (20:80 v/v); yellow

liquid; isolated yield: 72%; [*meta*/others = 6:1]. **<sup>1</sup>H NMR** (**400 MHz, CDCl<sub>3</sub>**) δ 9.17 (s, 1H), 8.81 (s, 2H), 8.38 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.71 (s, 1H), 7.54 (s, 1H), 7.40 (dd, *J* = 7.6, 4.9 Hz, 6H), 7.13 (s, 1H), 4.30 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H). **<sup>13</sup>C NMR** (**126 MHz, CDCl<sub>3</sub>**) δ 158.0, 156.8, 147.7, 146.7, 146.1, 140.0, 133.2, 132.1, 131.4, 131.1, 130.9, 130.7, 139.9, 128.9, 128.8, 128.1, 128.0, 127.5, 125.6, 123.5, 119.7, 57.6, 22.1, 21.5. HRMS:calcd. For 600.0772 C<sub>27</sub>H<sub>23</sub>KN<sub>5</sub>O<sub>5</sub>S<sub>2</sub> [M+K]<sup>+</sup>: found 600.0781 IR: 672, 701, 726, 774, 774, 814, 861, 974, 1010, 1099, 1121, 1159, 1195, 1302, 1357, 1412, 1453, 1492, 1555, 1606, 1664, 2856, 2926.

## 2.5. Mechanistic studies

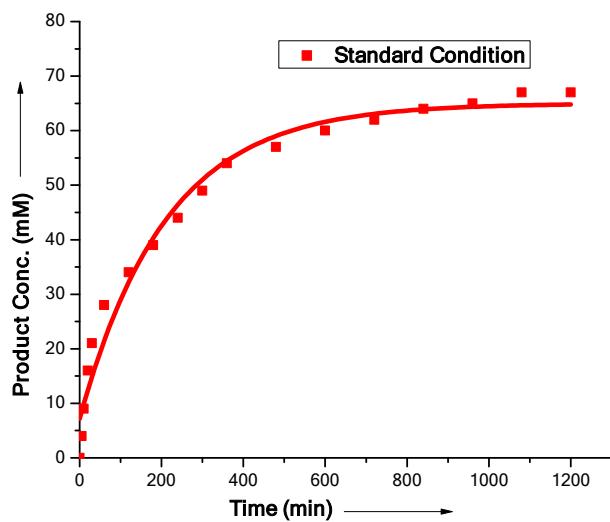
### 2.5.1. Kinetic experiments:

As *meta*-scaffold and alkynyl bromide were involved in this reaction, we can assume the rate of the reaction is only dependent on the concentration of scaffold and alkynyl bromide.

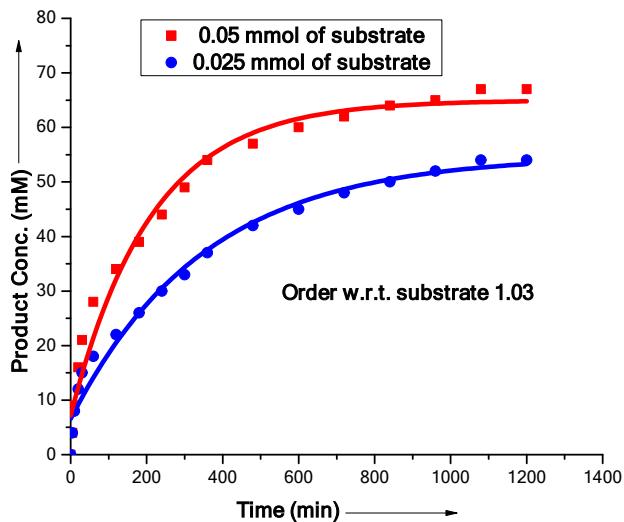
$$\text{So, Rate} = k \cdot [\text{scaffold}]^x [\text{alkynyl bromide}]^y [N\text{-Ac-Gly-OH}]^z \dots \dots \dots \quad (1)$$

Order determination with respect to sulfonyl ester **1a**

Run	<b>1a</b> substrate (mmol)	alkynyl bromide <b>(2a)</b> (mmol)	Pd(OAc) <sub>2</sub> (mmol)	<i>N</i> -Ac-Gly- OH (mmol)	AgOAc (mmol)	Cu(OAc) <sub>2</sub> (mmol)
1	0.05	0.15	0.005	0.01	0.1	0.1
2	0.025	0.15	0.005	0.01	0.1	0.1



**Figure S1.** Product formation plot in run 1



**Figure S2.** Product formation plot in run 1 and run 2

From the equation (1) we got, Rate =  $k \cdot [\text{substrate}]^x [\text{alkynyl bromide}]^y$

For run 1, initial rate = Rate 1

So, Rate 1 =  $k \cdot [\text{substrate}]^x [\text{alkynyl bromide}]^y$

$$\text{or, } 0.233 \text{ (mmol}^{-1} \cdot \text{min}^{-1}) = k \cdot [0.05]^x [0.15]^y \quad \dots \dots \dots (2)$$

For run 2, initial rate = Rate 2

So, Rate 2 =  $k \cdot [\text{substrate}]^x [\text{alkynyl bromide}]^y$

$$\text{or, } 0.114 \text{ (mmol}^{-1} \cdot \text{min}^{-1}) = k \cdot [0.025]^x [0.15]^y \quad \dots \dots \dots (3)$$

Hence from equation (2) and (3)

$$\text{We get, } [\text{Rate 1} / \text{Rate 2}] = [0.05 / 0.025]^x$$

$$\text{or, } x = [\log(\text{Rate 1}) - \log(\text{Rate 2})] / [\log(0.05) - \log(0.025)]$$

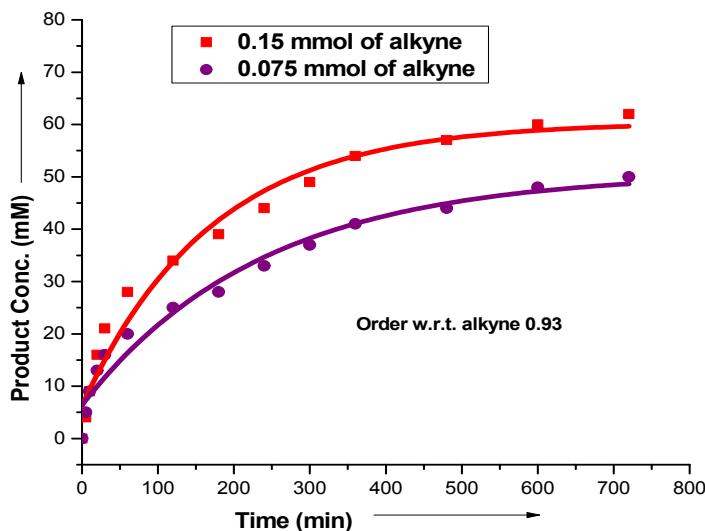
$$\text{or, } x = [\log(0.233) - \log(0.114)] / [\log(0.05) - \log(0.025)]$$

$$\text{or, } x = 1.03$$

**So, order with respect to scaffold (1a) is  $\sim 1$**

Order determination with respect to alkynyl bromide **2a**

Run	<b>1a</b> substrate (mmol)	alkynyl bromide <b>(2a)</b> (mmol)	Pd(OAc) <sub>2</sub> (mmol)	N-Ac-Gly- OH (mmol)	AgOAc (mmol)	Cu(OAc) <sub>2</sub> (mmol)
1	0.05	0.15	0.001	0.01	0.1	0.1
3	0.05	0.075	0.001	0.01	0.1	0.1



**Figure S3.** Product formation plot in (a) run 1 and (b) run 3

From the equation (1) we got, Rate = k. [substrate]<sup>x</sup> [alkynyl bromide]<sup>y</sup>

For run 1, initial rate = Rate 1

$$\text{So, Rate 1} = k \cdot [1\mathbf{a}]^x [2\mathbf{a}]^y$$

$$\text{or, } 0.233 \text{ (mmol}^{-1} \cdot \text{min}^{-1}) = k \cdot [0.05]^x [0.15]^y \quad \dots \dots \dots (2)$$

For run 3, initial rate = Rate 3

$$\text{So, Rate 3} = k \cdot [\text{substrate}]^x [\text{alkynyl bromide}]^y$$

$$\text{or, } 0.121 \text{ (mmol}^{-1} \cdot \text{min}^{-1}) = k \cdot [0.05]^x [0.075]^y \quad \dots \dots \dots (4)$$

Hence from equation (2) and (4)

$$\text{We get, } [\text{Rate 1} / \text{Rate 3}] = [0.15 / 0.075]^y$$

$$\text{or, } x = [\log(\text{Rate 1}) - \log(\text{Rate 3})] / [\log(0.15) - \log(0.075)]$$

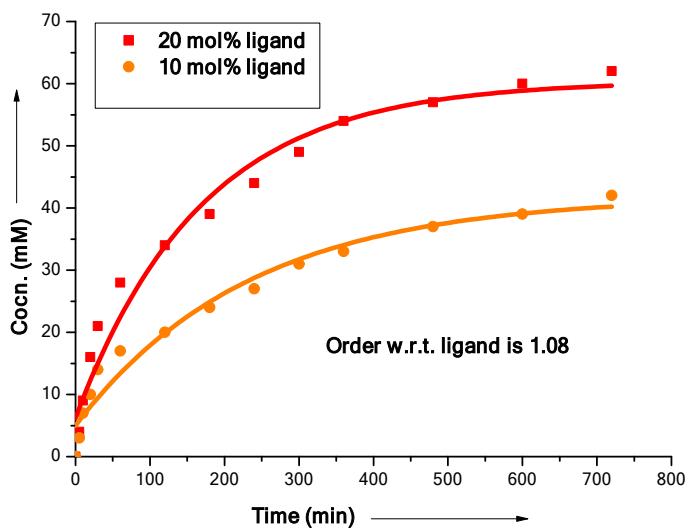
$$\text{or, } x = [\log(0.233) - \log(0.121)] / [\log(0.15) - \log(0.075)]$$

$$\text{or, } x = 0.93$$

**So, order with respect to alkynyl bromide (2a) is ~ 1**

Order determination with respect to *N*-Ac-Gly-OH

Run	<b>1a</b> substrate (mmol)	alkynyl bromide <b>(2a)</b> (mmol)	Pd(OAc) <sub>2</sub> (mmol)	<i>N</i> -Ac-Gly- OH (mmol)	AgOAc (mmol)	Cu(OAc) <sub>2</sub> (mmol)
1	0.05	0.15	0.001	0.01	0.1	0.1
4	0.05	0.15	0.001	0.005	0.1	0.1



**Figure S3.a** Product formation plot in (a) run 1 and (b) run 4

From intial rate equation we got, Rate = k. [substrate]<sup>x</sup> [*N*-Ac-Gly-OH]<sup>z</sup>

For run 1, initial rate = Rate 1

$$\text{So, Rate 1} = k \cdot [1\mathbf{a}]^x [N\text{-Ac-Gly-OH}]^z$$

$$\text{or, } 0.233 \text{ (mmol}^{-1} \cdot \text{min}^{-1}) = k \cdot [0.05]^x [0.01]^z \quad \dots \dots \dots (2)$$

For run 4, initial rate = Rate 4

$$\text{So, Rate 4} = k \cdot [1\mathbf{a}]^x [N\text{-Ac-Gly-OH}]^z$$

$$\text{or, } 0.110 \text{ (mmol}^{-1} \cdot \text{min}^{-1}) = k \cdot [0.05]^x [0.005]^z \quad \dots \dots \dots (5)$$

Hence from equation (2) and (5)

$$\text{We get, } [\text{Rate 1} / \text{Rate 4}] = [0.01 / 0.005]^z$$

$$\text{or, } x = [\log(\text{Rate 1}) - \log(\text{Rate 4})] / [\log(0.01) - \log(0.005)]$$

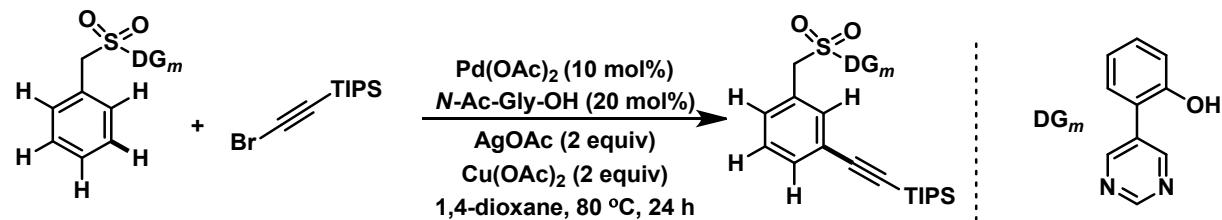
$$\text{or, } x = [\log(0.233) - \log(0.110)] / [\log(0.01) - \log(0.005)]$$

or,  $x = 1.08$

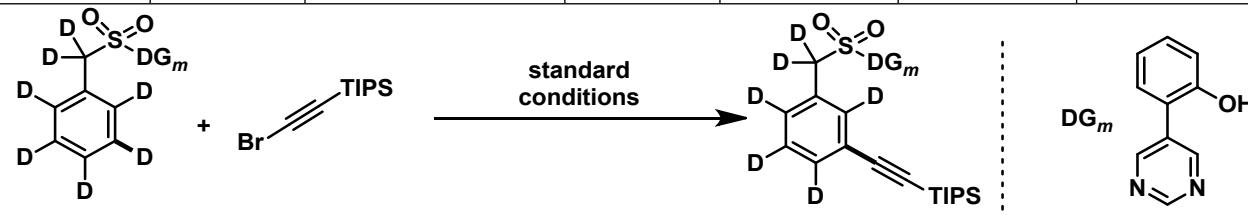
So, order with respect to *N*-Ac-Gly-OH is ~ 1

### $k_H/k_D$ determination:

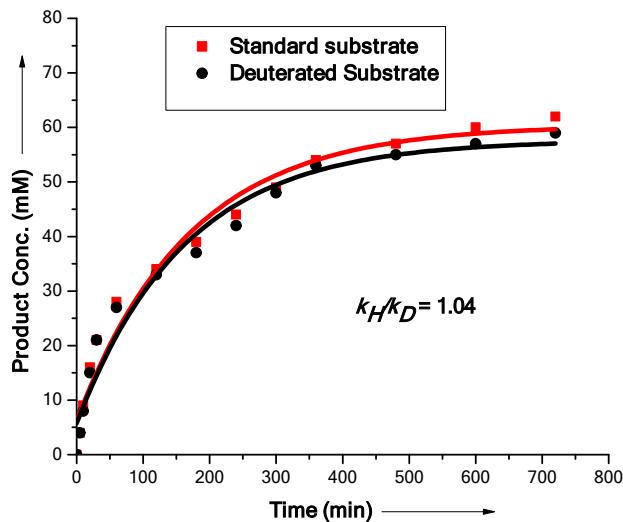
As mentioned in the manuscript, for **1a** we decided the total conversion of *meta*- alkynylated products for the labelling studies.



Run	<b>1a</b> (mmol)	alkynyl bromide <b>2a</b> (mmol)	Pd(OAc) <sub>2</sub> (mmol)	<i>N</i> -Ac-Gly- OH (mmol)	AgOAc (mmol)	Cu(OAc) <sub>2</sub> (mmol)
1	0.05	0.15	0.005	0.01	0.1	0.1



Run	Deuterated substrate (mmol)	alkynyl bromide (mmol)	Pd(OAc) <sub>2</sub> (mmol)	<i>N</i> -Ac-Gly- OH (mmol)	AgOAc (mmol)	Cu(OAc) <sub>2</sub> (mmol)
4	0.05	0.15	0.005	0.01	0.1	0.1



**Figure S4.** Determination of kinetic isotope effect

Now, Rate =  $k \cdot [\text{substrate}]^x [\text{alkynyl bromide}]^y$

For run 1, initial rate = Rate 1

So, Rate =  $k_H \cdot [\text{substrate}]^x [\text{alkynyl bromide}]^y$

or,  $0.233 \text{ (mmol-1.min-1)} = k_H \cdot [0.05]^x [0.15]^y$

For run , initial rate = Rate 4

So, Rate =  $k_D \cdot [\text{deuterated substrate}]^x [\text{alkynyl bromide}]^y$

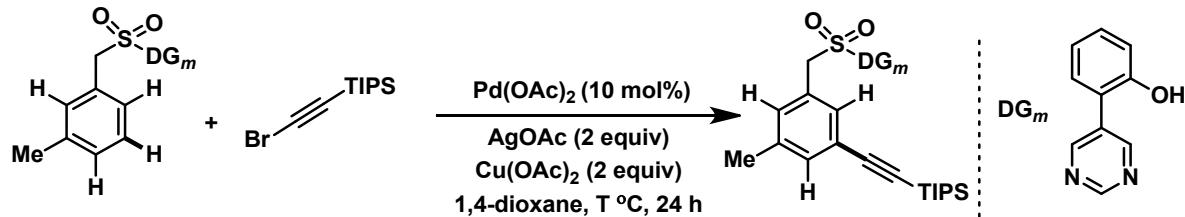
or,  $0.224 \text{ (mmol-1.min-1)} = k_D \cdot [0.05]^x [0.15]^y$

So,  $k_H / k_D = \text{Rate 1} / \text{Rate 4}$

or,  $k_H / k_D = 0.233 \text{ (mmol-1.min-1)} / 0.224 \text{ (mmol-1.min-1)}$

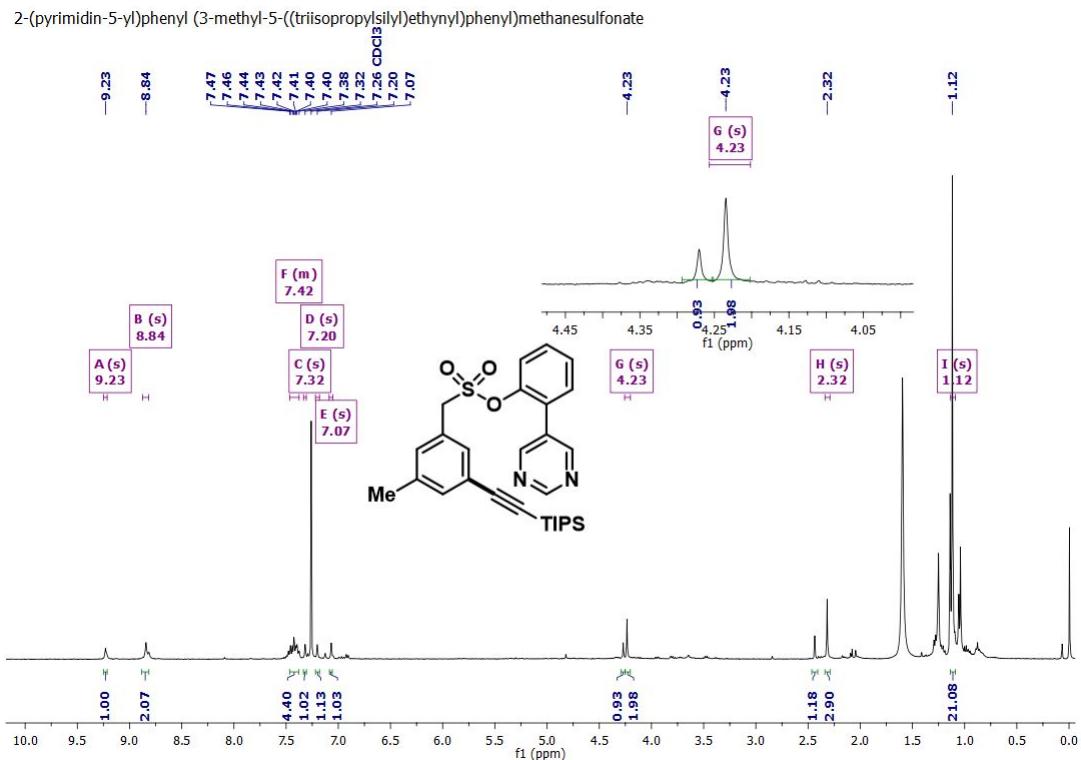
or,  $\mathbf{k_H / k_D = 1.04}$

***meta*-alkynylation reaction without N-Ac-Gly-OH:**



Entry	Temperature °C	Yield % ( <i>meta</i> :others) <sup>a</sup>
1	80	17 (2:1)
2	100	28 (2:1)
3	120	34 (2:1)

**<sup>1</sup>H NMR of *meta*-alkynylated product at 80 °C without N-Ac-Gly-OH:**



## 2.6. Computational methods

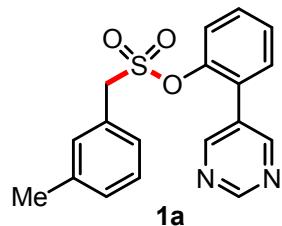
Density functional theory (DFT) calculations were performed with Gaussian 16 rev. A.03.<sup>8</sup> Geometry optimisations were carried out using recently developed global-hybrid meta-NGA (nonseparable gradient approximation) MN15 functional<sup>9</sup> with a mixed Karlsruhe-family basis set of triple- $\zeta$  valence def2-TZVPPD (where ‘D’ indicates diffuse basis functions) for Br<sup>10</sup>, Pd<sup>10,11</sup> and Ag<sup>10,11</sup> atoms and def2-SVP<sup>12,13</sup> for all other atoms (BS1). This functional was chosen as it performs much better than many other functionals (e.g.  $\omega$ B97X-D and TPSS) in predicting transition metal (TM) reaction barrier heights and better geometry for both TM complexes and organic molecules.<sup>9</sup> MN15 has also been employed to study similar Pd-catalytic systems with excellent agreement with experimental results.<sup>14–19</sup> Minima and transition structures on the potential energy surface (PES) were confirmed as such by harmonic frequency analysis, showing respectively zero and one imaginary frequency, at the same level of theory. Where appropriate, intrinsic reaction coordinate (IRC) analyses<sup>20,21</sup> were performed to confirm that the said TSs connect to the right reactants and products. Single point (SP) corrections were performed separately with either MN15 or  $\omega$ B97X-D<sup>22</sup> functional and def2-QZVPP<sup>12</sup> basis set for all atoms. The SMD continuum solvation model<sup>23</sup> was used to include the effect of 1,4-dioxane solvent on the computed Gibbs energy profile. Gibbs energies were evaluated at the reaction temperature of 353.15 K, using a quasi-RRHO treatment of vibrational entropies.<sup>24,25</sup> Vibrational entropies of frequencies below 100 cm<sup>-1</sup> were obtained according to a free rotor description, using a smooth damping function to interpolate between the two limiting descriptions. The free energies were further corrected using standard concentration of 1 mol/L, which were used in solvation calculations. SMD(1,4-dioxane)- $\omega$ B97X-D/def2-QZVPP//MN15/BS1 Gibbs energies were given with SMD(1,4-dioxane)-MN15/def2-QZVPP//MN15/BS1 Gibbs energies given in brackets throughout. Unless otherwise stated, the former set of Gibbs energy values are used for discussion. All Gibbs energy values in the text and figures are quoted in kcal mol<sup>-1</sup> throughout.

Non-covalent interactions (NCIs) were analysed using NCIPLLOT<sup>26</sup> calculations. The .wfn files for NCIPLLOT were generated at MN15/DGDZVP<sup>27,28</sup> level of theory. NCI indices calculated with NCIPLLOT were visualised at a gradient isosurface value of s = 0.5 au. These

are coloured according to the sign of the second eigenvalue ( $\lambda_2$ ) of the Laplacian of the density ( $\nabla^2\rho$ ) over the range of -0.1 (blue = attractive) to +0.1 (red = repulsive). Molecular orbitals are visualised using an isosurface value of 0.05 throughout. All molecular structures and molecular orbitals were visualized using PyMOL software.<sup>29</sup> Geometries of all optimized structures (in .xyz format with their associated energy in Hartrees) are included in a separate folder named alkynylation\_structures\_xyz with an associated README file. All these data have been deposited with this Supporting Information and uploaded to zenodo.org (DOI:[10.5281/zenodo.3376707](https://doi.org/10.5281/zenodo.3376707)). All Python scripts used for data analysis have been made available - <https://github.com/bobbypaton> - under a creative commons CC-BY license.

### 2.6.1 Conformational considerations for starting materials

The starting material for computational modelling, sulfonyl arene, **1a**, was first conformationally sampled. The possible rotamers for sulfonyl arene, **1a**, were generated by systematically varying a combination of key dihedral angles shown in red (Scheme S1) and optimising the structures. The lowest energy conformer was used for subsequent calculations.

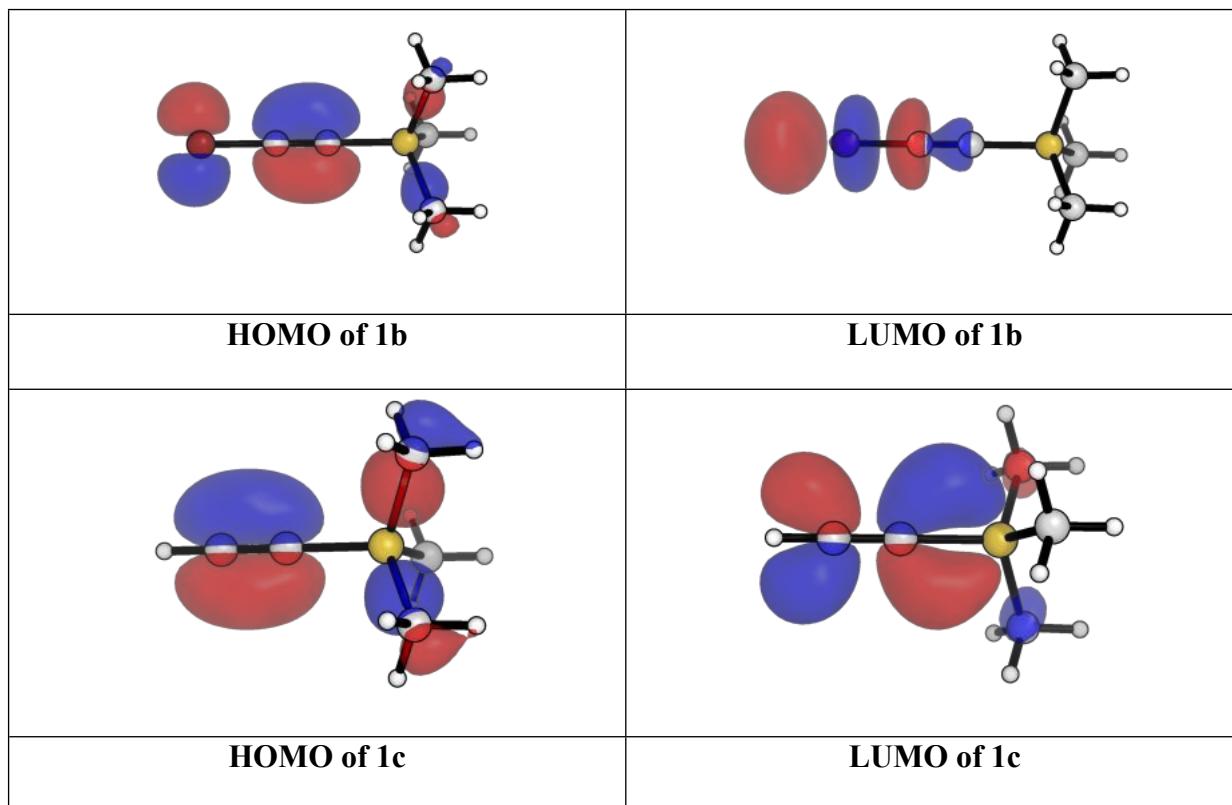


**Scheme S1.** Rotamers were generated by varying the dihedral angles in red in conformational sampling of the most stable conformer used for reaction modelling.

### 2.6.2 Frontier molecular orbitals (FMOs) of starting materials

Figure S5 shows the FMOs for the starting material bromoethynyltrimethylsilane **1b** (hereafter bromoalkyne) and ethynyltrimethylsilane **1c** (hereafter TMS-alkyne). In **1b**, the HOMO arises predominantly from the  $\pi$ -electrons from the alkyne triple bond. This electron-rich  $\pi$ -bond can be donated to a vacant d-orbital on the electrophilic Pd(II) centre, giving rise to  $\pi$ -complexes with the transition metal before further transformations. Interestingly, the LUMO of **1b** is  $\sigma_{\text{CBr}}^*$  instead of  $\pi_{\text{CC}}^*$ . These have implications on the reactivity of bromoalkyne **1b**, suggesting that oxidative insertion of **1b** breaking the C–Br bond could be possible.

However, it seems that **1b** acts predominantly as a  $\pi$ -donor rather than  $\pi$ -acceptor, as seen in the HOMO for both oxidative insertion and 1,2-migratory insertion of **1b**, where the major contribution comes from the  $\pi$ -electrons from the alkyne triple bond (Figure S8). FMOs for TMS-alkyne **1c** are also shown in Figure S5. The HOMO is  $\pi_{CC}$  and the LUMO is  $\pi_{CC}^*$ . These are rather different from FMOs in **1b**, implicating different reactivity (see section 2.6.10 for a discussion of the reactivity with **1c** as a substrate).

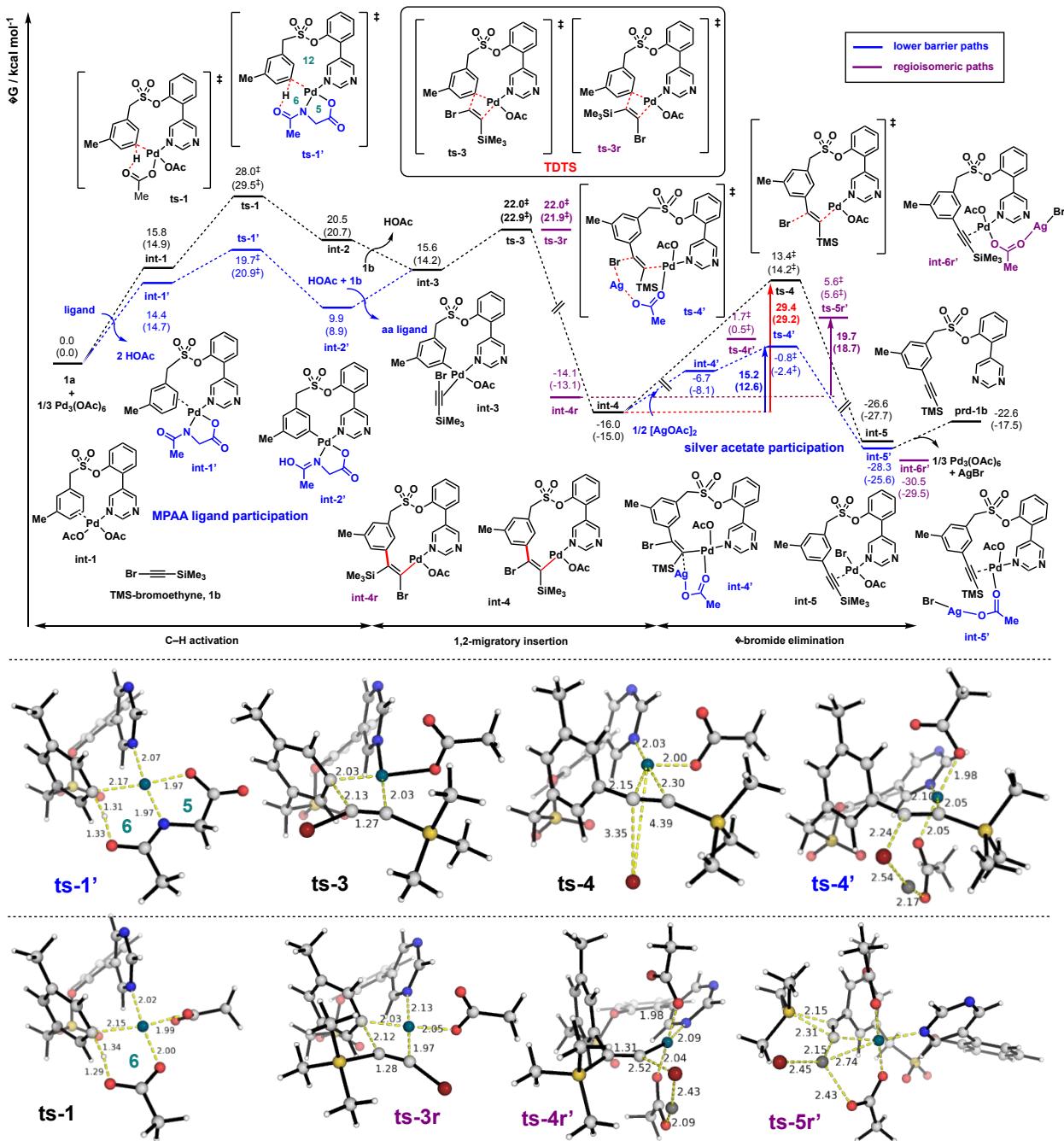


**Figure S5.** FMOs for bromoethynyltrimethylsilane **1b** and ethynyltrimethylsilane **1c** at an isosurface value of 0.05.

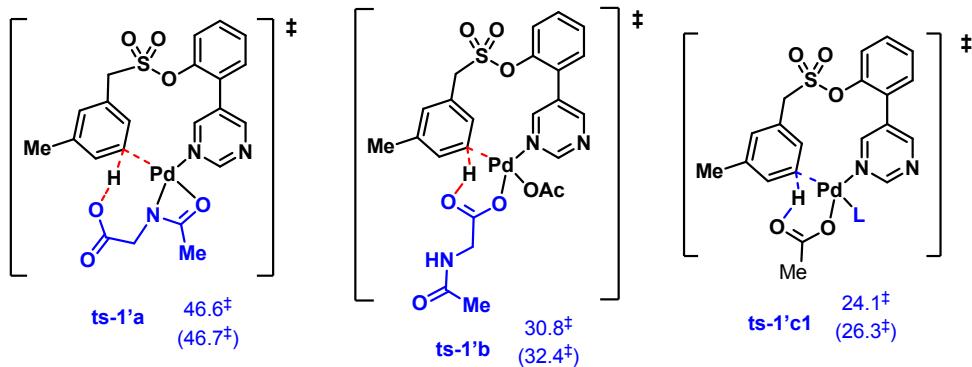
### 2.6.3 C–H activation in the presence and the absence of ligand

The full energy profile for the reaction is given in Figure S6, with key optimised geometries. For the C–H activation step, in the absence of the absence of mono-protected amino acid (MPAA) ligand, *N*-acetylglycine, the reaction has a high barrier of 28.0 kcal mol<sup>-1</sup>. In the presence of the ligand, the TS is lowered in activation barrier by forming a [5,6]-membered palladacycle (**ts-1'** at 19.7<sup>‡</sup> (20.9<sup>‡</sup>) kcal mol<sup>-1</sup>). Other possible arrangements of this ligand,

following ref.<sup>10</sup>, were found to have higher activation barriers than **ts-1'** (Scheme S2) and are thus not competitive.



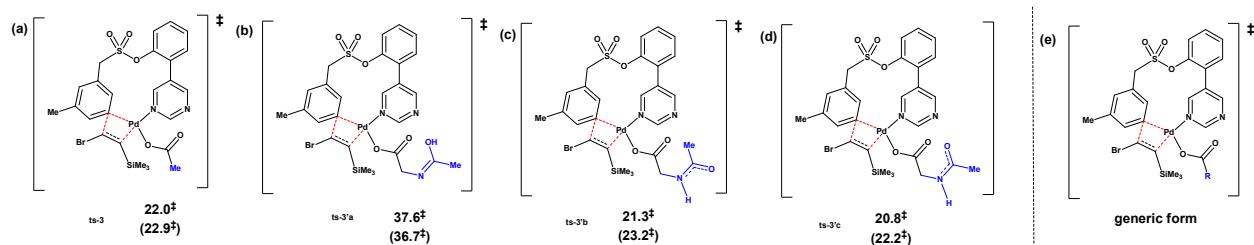
**Figure S6.** Full Gibbs energy profile for the reaction and selected optimized TS structures.



**Scheme S2.** Other possible arrangements of the ligand for C–H activation step.

#### 2.6.4 Replacement of a.a. ligand by acetate ligand in migratory insertion step

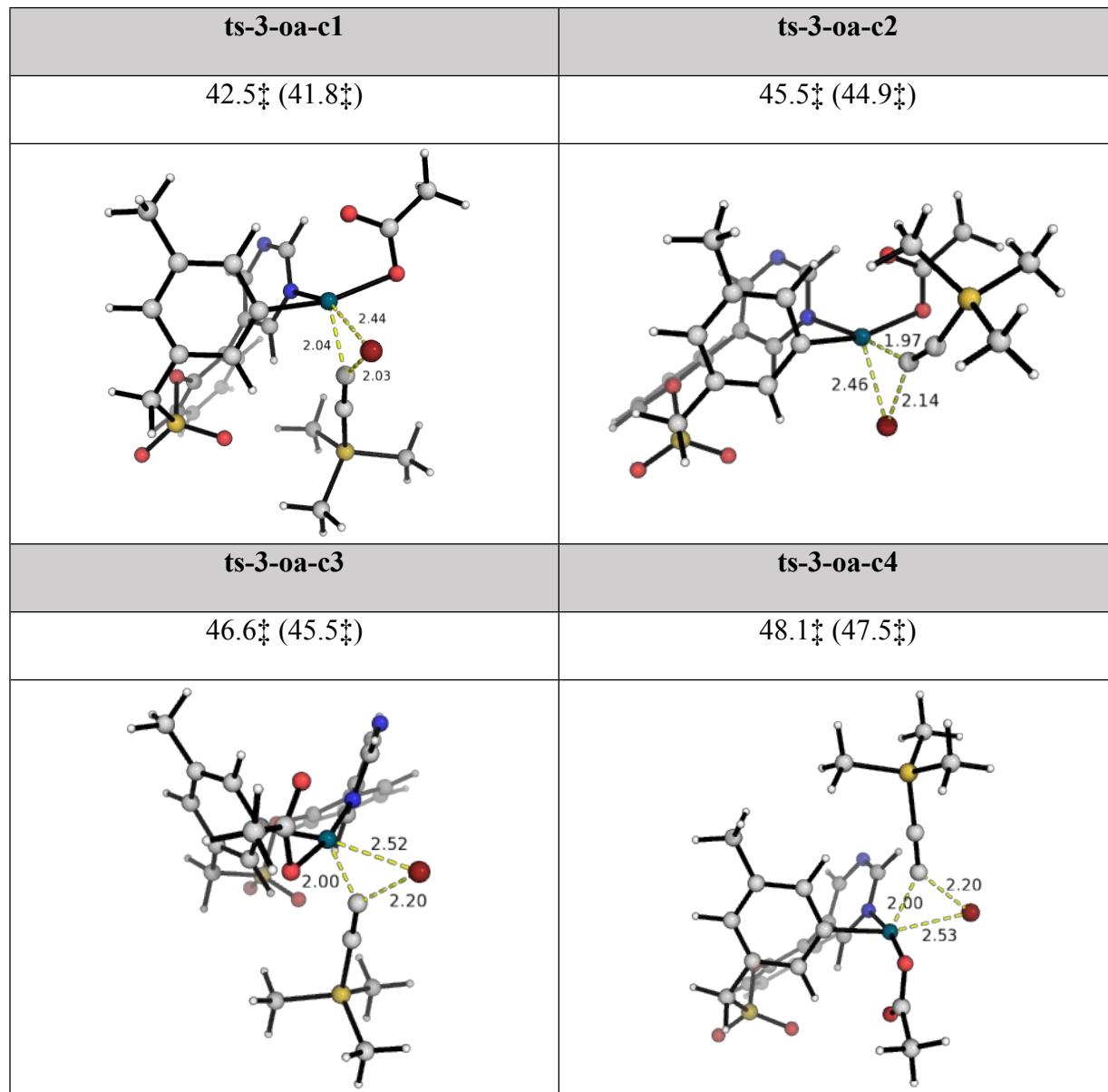
The turnover frequency-determining transition state (TDTS) for the reaction is the 1,2-migratory insertion of bromoalkyne. We investigated the effect of using acetate ligand in replacement of the amino acid (a.a.) ligand for this step since all these forms have the generic form shown in Scheme S3(e) with variable R-group. We note that the energies are rather close (Scheme S3), without complete conformational sampling. Following the approach adopted in ref.<sup>19</sup> where complete conformational samplings were performed, showing that using acetate ligand instead of full a.a. ligand for this step does not affect the overall energy profile, we used, for simplicity, acetate ligand for the modelling of all steps subsequent to C–H activation. The a.a. ligand's main role in this reaction is to lower the C–H activation barrier significantly, making this step reversible. Its subsequent coordination to Pd-center is monodentate in fashion, similar to the coordination mode of acetate ligand. This Pd–N interactions would dominate over other possible non-covalent interactions (or unfavorable sterics) in the side chains.



**Scheme S3.** Comparison of rate-determining 1,2-migratory insertion step using different ligands.

## 2.6.5 Alternative mechanism: oxidative addition of bromoethynyltrimethylsilane **1b**

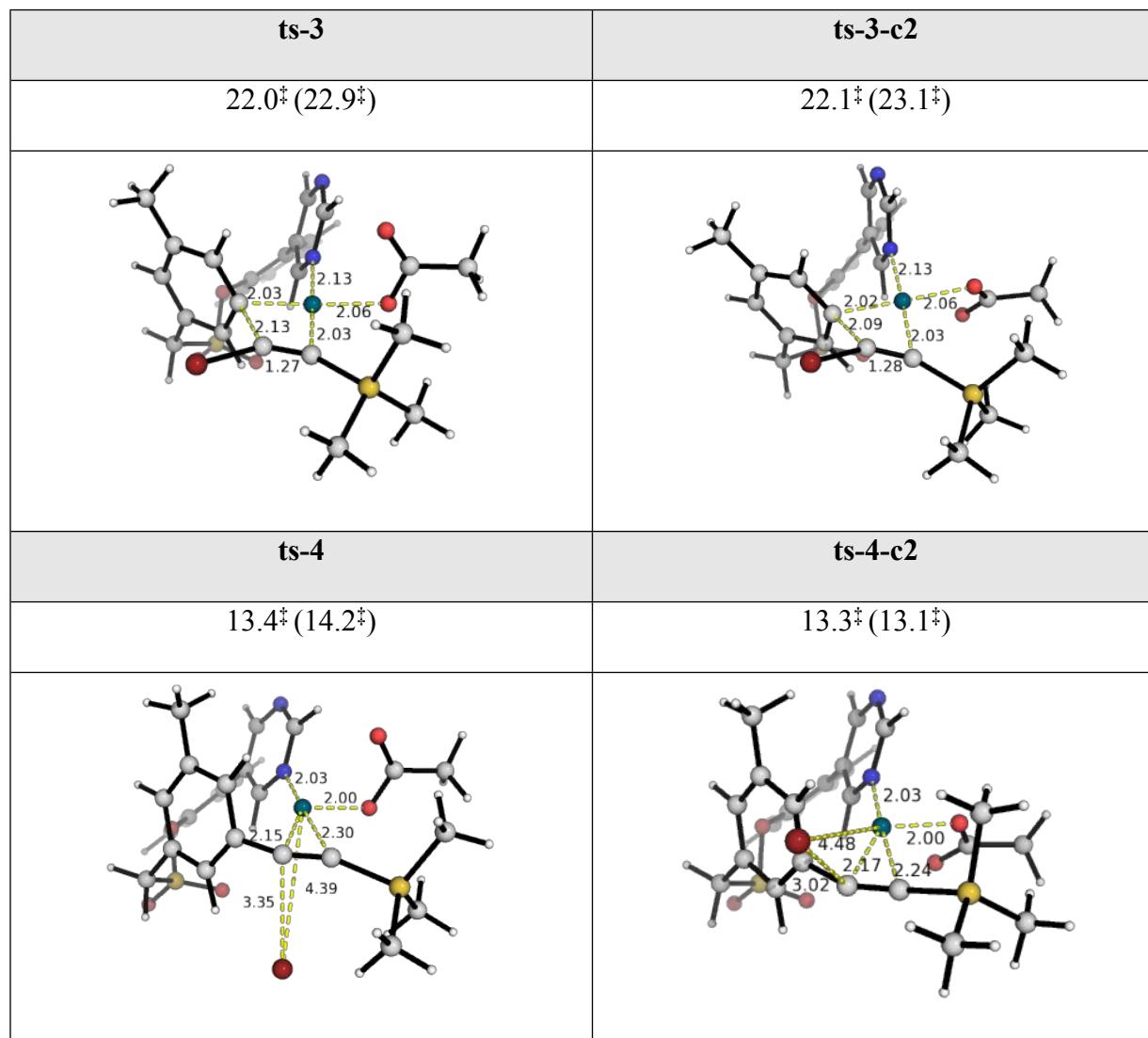
The oxidative addition (OA) of bromoethynyltrimethylsilane **1b** was investigated as Pd(II) were known to cycle through Pd(II)/Pd(IV) manifold.<sup>30</sup> All possible arrangements of OA of **1b** were investigated (Figure S7). These all have activation barriers > 40 kcal mol<sup>-1</sup>, making this mechanistic path inaccessible; the alternative path of 1,2-migratory insertion, as discussed in the main text, with a barrier of 22.0 kcal mol<sup>-1</sup>, is much more feasible.



**Figure S7.** Oxidative addition of bromoethynyltrimethylsilane **1b**.

## 2.6.6 Conformers for 1,2-migratory insertion and $\beta$ -bromide elimination

Transition state (TS) conformers for 1,2-migratory insertion and  $\beta$ -bromide elimination are shown in Figure S8. These differ in the orientations of the acetate ligand and the side in which  $\beta$ -bromide elimination occurs. They are found to be very close in energy, indicating that the conformational flexibility in the ligand does not change the TS energies very much.



**Figure S8.** Optimised geometries for 1,2-migratory insertion and  $\beta$ -bromide elimination transition state conformers.

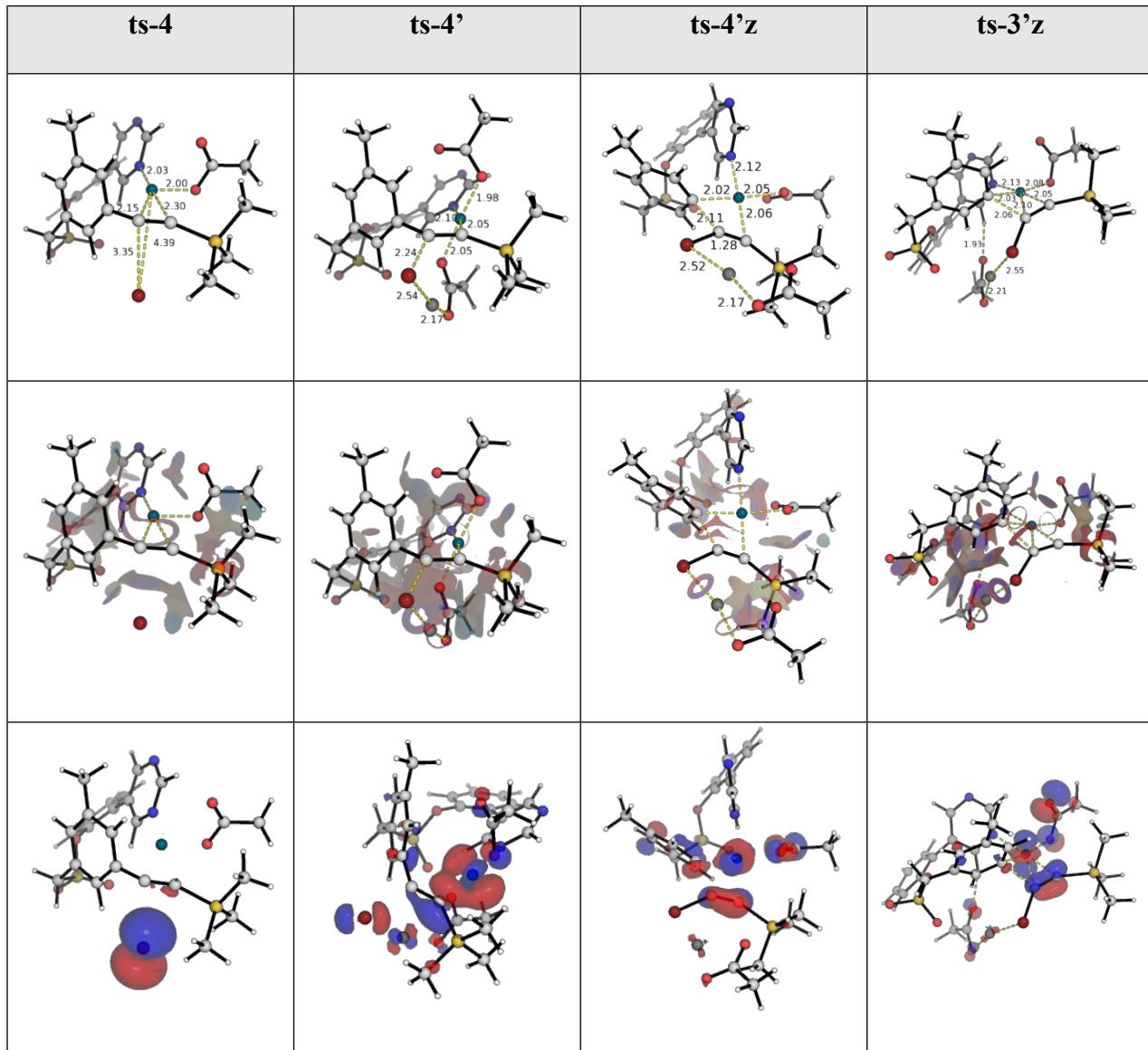
## 2.6.7 Role of silver acetate additive

Silver carboxylate salts are commonly employed as additives in Pd-catalysed C–H activation.<sup>31–35</sup> In many systems, silver salt plays an essential role in enhancing the reaction rate and/or yields. Various roles of silver carboxylate AgCOOR salts in such reactions have been proposed: (1) they serve as a source of carboxylate for the Pd(II) metal-centre, participating in carboxylate-assisted concerted metalation deprotonation (CMD) in the C–H activation step;<sup>35–39</sup> (2) they act as a terminal oxidant to regenerate Pd(II) catalyst;<sup>40–42</sup> (3) they form heterometallic Pd–Ag complexes that facilitate C–H activation;<sup>40,43,44</sup> (4) they directly activate C–H bond forming Ag–C intermediate;<sup>45,46</sup> (5) they act as halide scavengers in PdX (X = halide) complex after the reductive elimination step.<sup>47</sup> The experimental work to establish the exact role of these silver additives are rare and an understanding of their exact roles in the mechanistic picture is rather incomplete.

Silver carboxylates are known to exist in dimeric form.<sup>47–50</sup> We computed the energy differences in the thermodynamic stabilities of both the monomeric and dimeric form of silver acetate and found that the dimeric form  $[\text{AgOAc}]_2$  is more stable; the formation of  $[\text{AgOAc}]_2$  from AgOAc monomers is -16.7 (-19.9) kcal mol<sup>-1</sup> downhill. This enhanced stability in the dimer has been attributed to Ag–Ag interactions.<sup>35,49</sup> The more stable dimer (or in fact,  $\frac{1}{2} [\text{AgOAc}]_2$ ) is used in the Gibbs energy calculations of silver additive participation throughout (the use of AgOAc monomer would artificially lower the activation barrier of **ts-4'** since AgOAc monomer is already high in energy).

In the absence of silver salt, the  $\beta$ -bromide elimination step has a very high activation barrier (**ts-4**, 29.4 kcal mol<sup>-1</sup>, Figure S6). For the present transformation, silver cation plays a role in assisting  $\beta$ -bromide elimination step by forming silver bromide salt. An initial TS search placing the Ag<sup>+</sup> ion adjacent to the leaving Br<sup>-</sup> as the former pulls off the latter yielded a TS that is higher in activation barrier than that without silver acetate (Figure S9, **ts-4'z**); only in **ts-4'** where not only Ag<sup>+</sup> interacts with the leaving Br<sup>-</sup> but also the acetate coordinates to Pd(II) was the transition state lower in activation barrier. In the presence of silver acetate, the HOMO shows that there is predominant electron donation from bromoalkyne  $\pi$ -electrons to the vacant d-orbital on Pd(II) centre, this enhanced interaction is favourable to product formation as the bromide ion leaves (Figure S9). Although there seems to be more steric

strain due to non-covalent interactions (NCIs) in **ts-4'**, the formation of Ag–Br bond is enthalpically favoured and more dominant over NCIs, thus lowering the activation barrier of this transition state.



**Figure S9.** Optimised structures, NCI plots and HOMOs for  $\beta$ -bromide elimination without (**ts-4**) and with (**ts-4'** and **ts-4'z**) silver acetate co-ligand and for 1,2-migratory insertion with silver acetate co-ligand (**ts-3'z**).

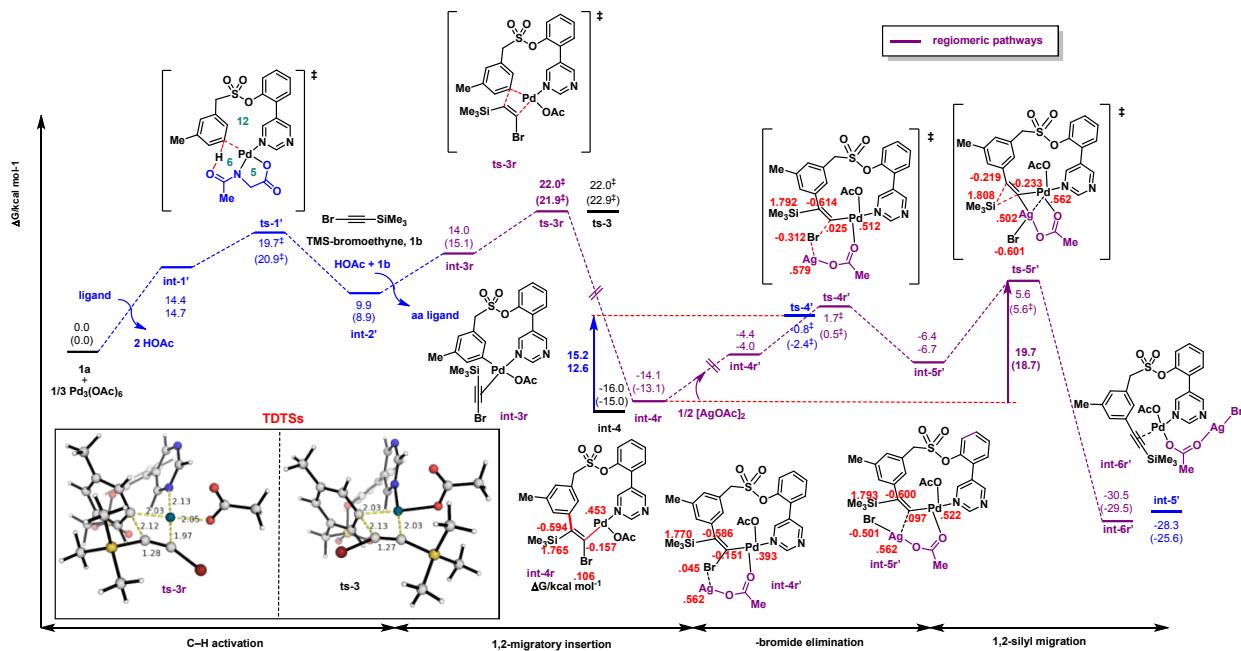
For completeness, we went further to ascertain the role, if any, of silver acetate in affecting the 1,2-migratory insertion step. We found that, introducing AgOAc (**ts-3'z**) increased the

activation barrier to 40.0 kcal mol<sup>-1</sup>, which is much higher than **ts-3** without any AgOAc participation at 22.0 kcal mol<sup>-1</sup>. The acetate ligand from silver could not coordinate to Pd-centre (despite the initial geometry guess as so) in the optimised structure as Pd(II) is tetra-coordinating and all coordination sites have been occupied (Figure S9).

## 2.6.8 Regioselectivity in 1,2-migratory insertion of bromoethynyltrimethylsilane **1b**

Figure S10 shows the energy profile for the regioconvergent formation of alkynylated product. All activation barriers are thermally accessible at the reaction temperature of 80°C. TS structures are shown in Figure S11.

It was found that the regiosomeric 1,2-migratory insertions of **1b** (**ts-3** and **ts-3r**, Figure S10) have almost identical barrier, at 22.0 kcal mol<sup>-1</sup>, suggesting unselective 1,2-migratory insertion.

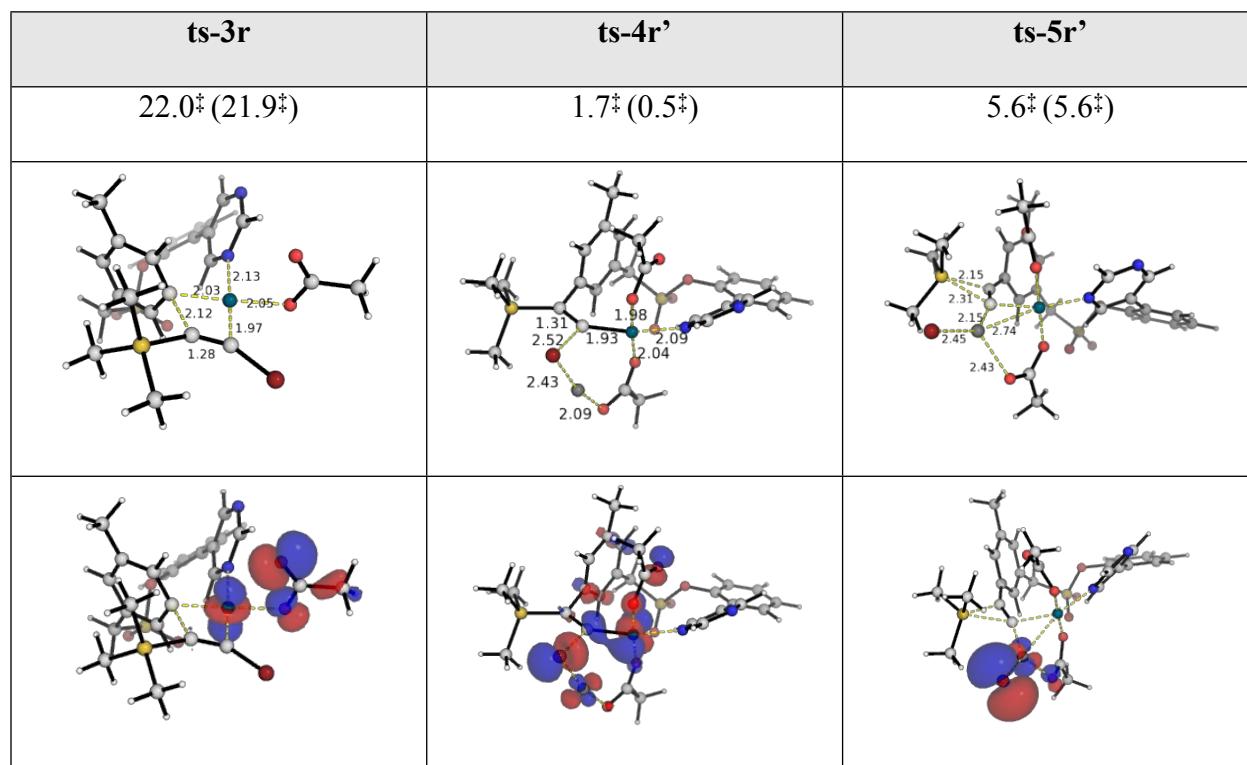


**Figure S10.** Gibbs energy profile for the regioisomeric insertion of bromoalkyne **1b** and its subsequent β-Br elimination and 1,2-silyl migration to regioconverge on the alkynylated product. Gibbs energies for the key structures from Figure S6 are included for comparison.

Both insertion products are highly exergonic and irreversible. In the latter case, the regiosomeric insertion of **1b** affords a highly stabilized intermediate **int-4r** (at -14.1 kcal

$\text{mol}^{-1}$ ) that further undergoes stepwise loss of bromide (**ts-4r'**) and 1,2-silyl shift (**ts-5r'**) to give regiospecifically the observed alkynylated product. 1,2-silyl shift occurs as the bromide leaves, gaining negative charge (NBO charge (Figure S10, numbers in red) from +0.106 in **int-4r** and +0.045 in **int-4r'** to -0.312 in **ts-4r'** and -0.501 in **int-5r'** and -0.601 in **ts-5r'**), while the carbon atom that it is attached gains carbocationic character (NBO charge at this site that is -0.157 in **int-4r** and -0.151 in **int-4r'** that goes to +0.025 in **ts-4r'** and +0.097 in **int-5r'**). This resembles the anionic 1,n-silyl migration observed in some organocopper-catalysed chemical systems.<sup>34–36</sup>

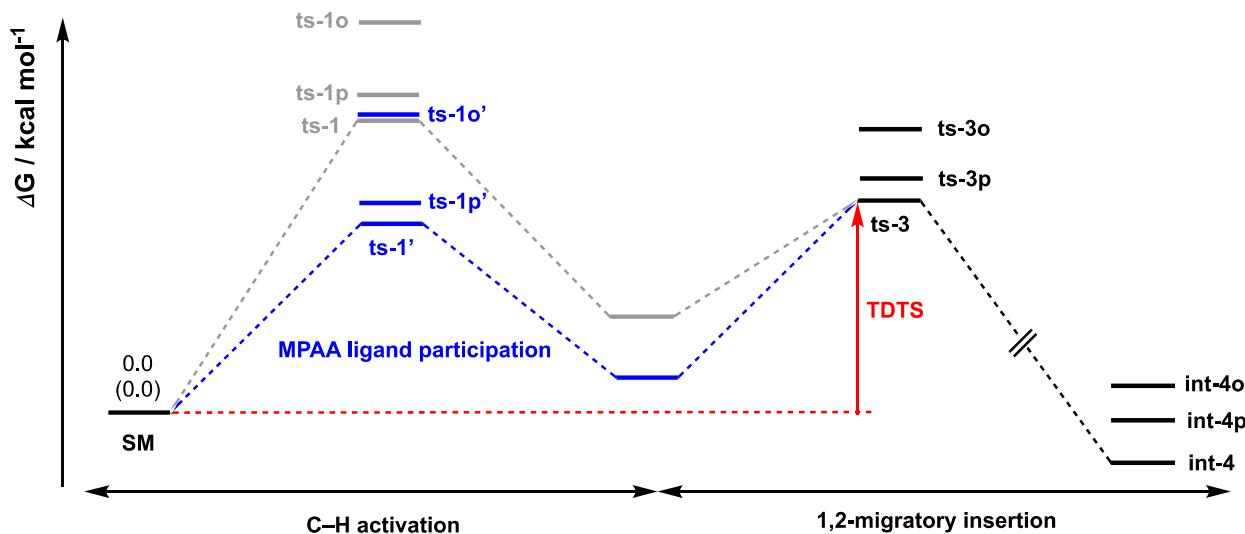
The rate-limiting step after the insertion product is 1,2-silyl migration **ts-5r'** at 19.7  $\text{kcal mol}^{-1}$ , which, although is higher than the barrier of **ts-4r'** at 15.2  $\text{kcal mol}^{-1}$ , can still occur thermodynamically at the reaction temperature of 80°C, especially given that the overall TDTs of this regioisomeric pathway is the 1,2-migratory insertion step **ts-3r** at 22.0  $\text{kcal mol}^{-1}$ .



**Figure S11.** Optimised structures and HOMOs for TSs in Figure S10.

## 2.6.9 C–H activation site selectivity studies

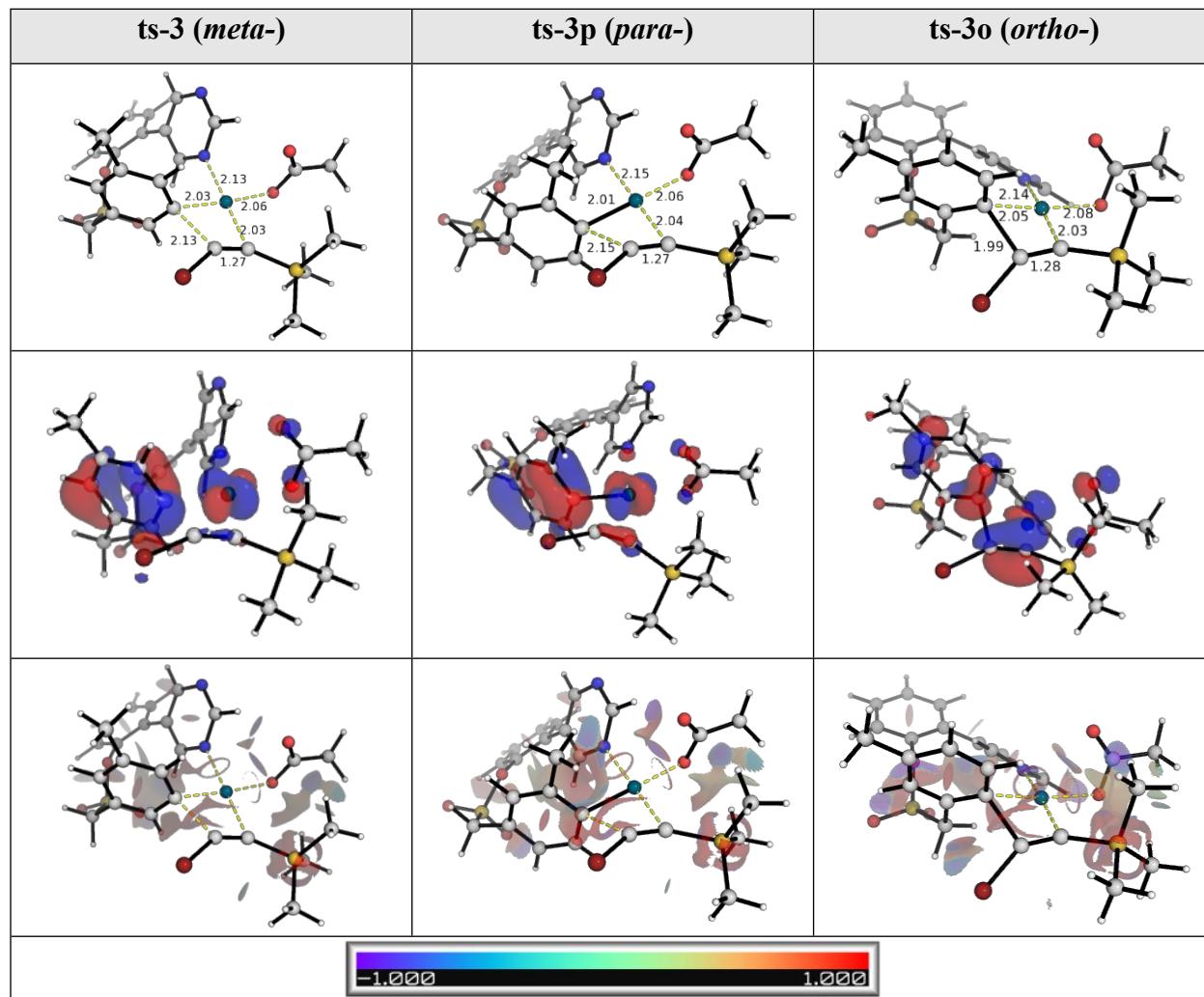
The site-selectivity of arene activation was then investigated. The *ortho-/para*-positions on the arene for potential activation were compared to *meta*-activation (Table S11). The C–H activation and the 1,2-migratory insertion steps were studied. 1,2-migratory insertion was the TDTS for *meta*- and *para*-activation, whereas C–H activation was the TDTS for *ortho*-activation. Application of simple transition state theory (TST) suggests that the *para*-alkynylated product would be disfavoured by 1 in 41, and that the *ortho*-alkynylated product 1 in ~8000.



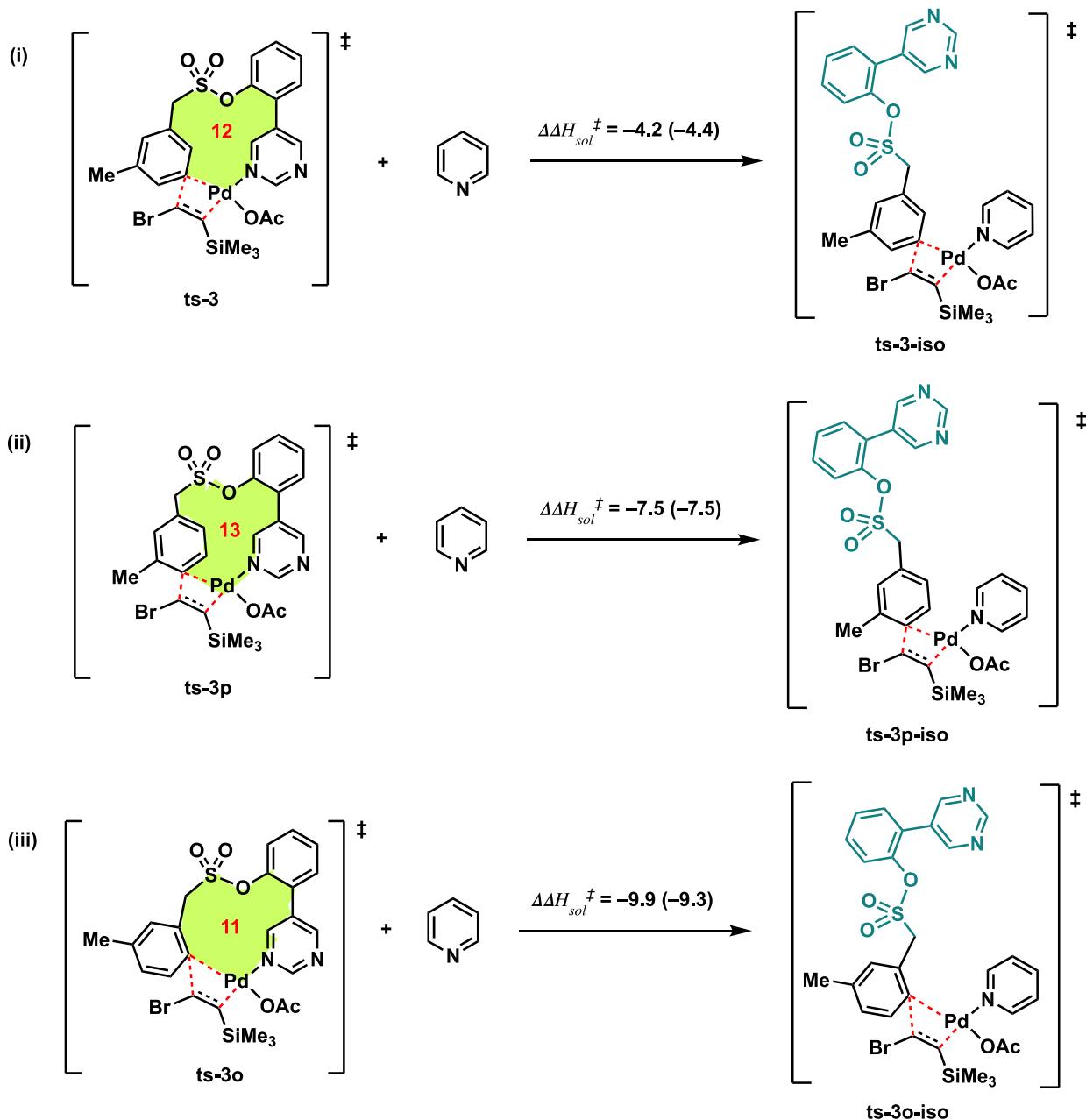
C–H activation site	ts-1x	ts-1x'	ts-3x	int-4x	Overall barrier
<i>meta</i> - (x=nil)	28.0‡ (29.5‡)	19.7‡ (20.9‡)	<b>22.0‡</b> <b>(22.9‡)</b>	-16.0 (-15.0)	<b>22.0‡</b> <b>(22.9‡)</b>
<i>para</i> - (x=p)	29.4‡ (29.4‡)	22.2‡ (21.6‡)	<b>24.6‡</b> <b>(23.3‡)</b>	-9.9 (-10.1)	<b>24.6‡</b> <b>(23.3‡)</b>
<i>ortho</i> - (x=o)	36.2‡ (35.2‡)	<b>28.3‡</b> <b>(28.8‡)</b>	26.8‡ (26.1‡)	-4.5 (-4.4)	<b>28.3‡</b> <b>(28.8‡)</b>

**Table S11.** Site selectivity study for alkynylation. The highest activation barriers (TDTS) were given in bold.

The optimised structures, HOMOs and non-covalent interaction (NCI) plots for 1,2-migratory insertion are given in Figure S12. We observed that the NCIs are rather similar in all 3 TSs. In earlier studies of a similar system,<sup>10</sup> the ring strain in *ortho*-selective TS is much higher than either *meta*- or *para*-activation. Herein, the *ortho*-selective TS **ts-3o** seemed to undergo a relatively early TS forming C–C bond and thereby relieving the ring strain, as the C–C bond distance is much shorter, at 1.99 Å, than either *meta*- or *para*-selective TS, at 2.13 Å and 2.15 Å, respectively.



**Figure S12.** Optimised structures, HOMOs and NCI plots for 1,2-migratory insertion step in arene site-selectivity studies.



**Scheme S4.** Computed ring strain involving a hypothetical pyridine ligand for 1,2-migratory insertion step. The enthalpies of the reactions were corrected with SMD solvation model:  
 $\Delta\Delta H_{sol}^{\ddagger} = \Delta H_{gas}^{\ddagger} - \Delta E_{gas}^{\ddagger} + \Delta E_{sol}^{\ddagger}$ .

The differences in the ring strain in these 3 TSs were further verified via isodesmic studies,<sup>51,52</sup> (see refs.<sup>19,53</sup> for an example) which confirmed this conclusion (Scheme S4). Specifically, a hypothetical pyridine ligand was used for TS searches to release the ring strain where the directing group (DG) got uncoordinated. Note that in an isodesmic reaction, the

total number and type of all bonds in the reactants and the products are preserved. The starting conformation for the DG (in green, Scheme S4) in all 3 cases was made the same in a linear form for subsequent

TS searches. The enthalpies of the reactions were further corrected with SMD solvation model:

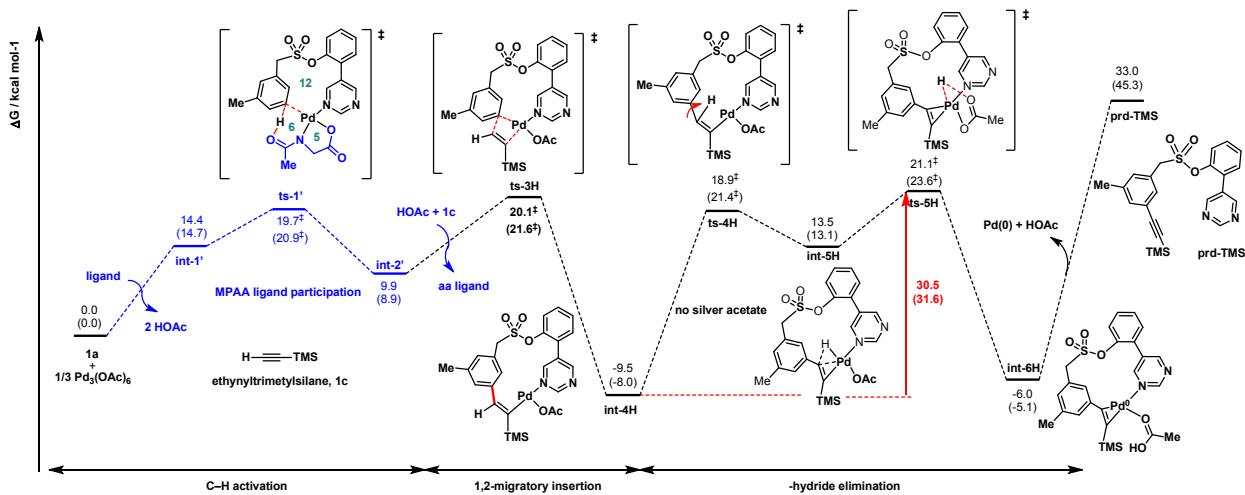
$$\Delta\Delta H_{\text{sol}}^{\ddagger} = \Delta\Delta H_{\text{gas}}^{\ddagger} - \Delta\Delta E_{\text{gas}}^{\ddagger} + \Delta\Delta E_{\text{sol}}^{\ddagger}$$

where  $\Delta H_{\text{gas}}^{\ddagger}$  is the enthalpy change of the reaction in the gas phase at low level of theory for computation,  $\Delta E_{\text{gas}}^{\ddagger}$  is the energy change of the reaction in the gas phase at low level of theory for computation and  $\Delta E_{\text{sol}}^{\ddagger}$  is the energy change of the reaction in the solvent phase at high level of theory for computation.

From the enthalpic changes, we can see that there is 4.2 kcal mol<sup>-1</sup> ring strain in **ts-3** as compared to 7.5 kcal mol<sup>-1</sup> in **ts-3p** and 9.9 kcal mol<sup>-1</sup> in **ts-3o**. Their ring strain energy differences are similar to the differences in their activation barriers for this step, as shown in Table S11. The 12-membered *meta*-selective TOF-determining palladacycle (**ts-3**) has the least strain, followed by 13-membered *para*-selective palladacycle (**ts-3p**) and then by 11-membered *ortho*-selective palladacycle (**ts-3o**).

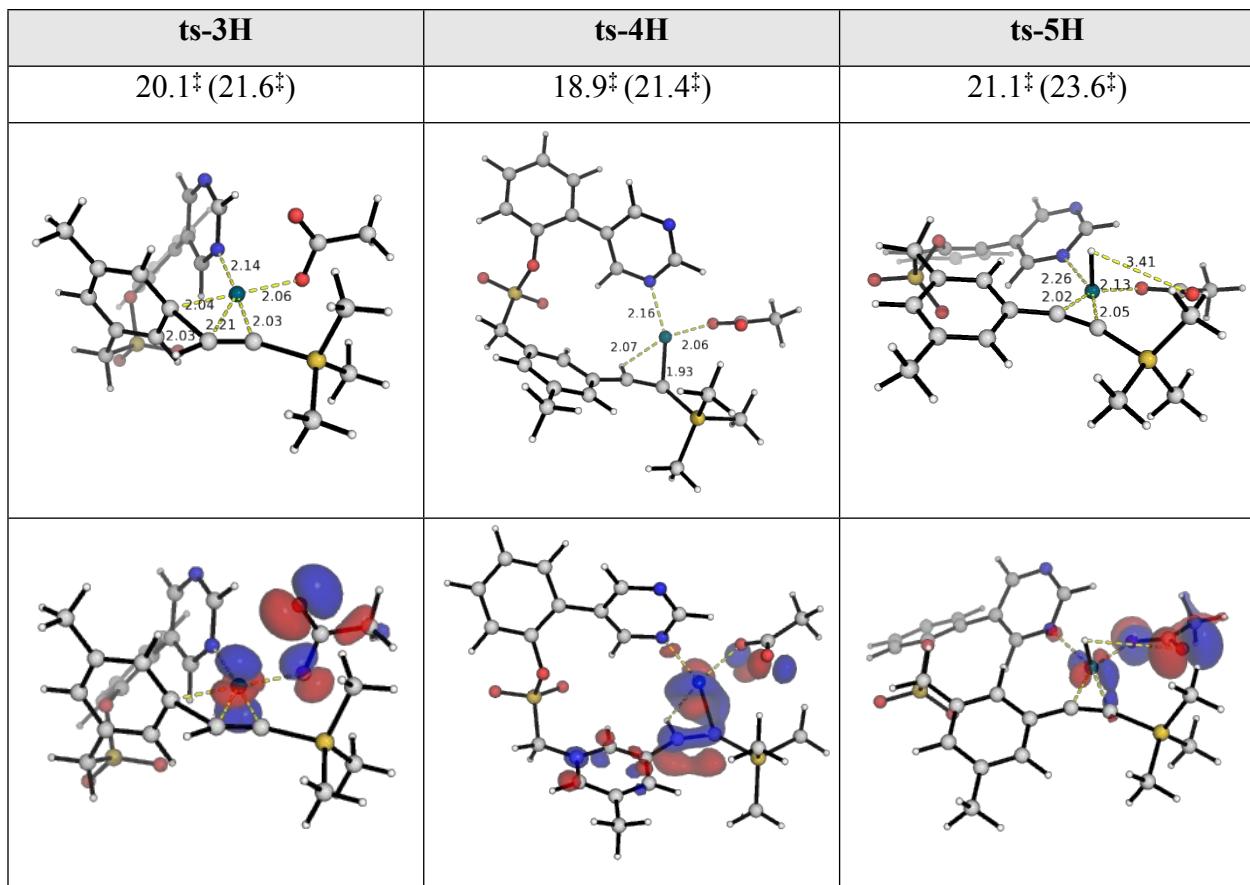
### 2.6.10 Reaction involving substrate ethynyltrimethylsilane **1c**

Experimentally, when the reaction was carried out using ethynyltrimethylsilane **1c** instead of **1b**, the reaction did not occur; the substrate was recovered. Detailed TS searches showed that silver could not participate in the beta-H elimination step, perhaps unsurprising since silver cation cannot interact with a leaving hydride. The full Gibbs energy profile in Figure S13 suggests that, as a result, beta-H elimination giving a Pd–H (**ts-4H**, Figure S14) and the subsequent reductive elimination of acetic acid to generate Pd(0) (**ts-5H**, Figure S14, overall barrier of 30.5 kcal mol<sup>-1</sup>) are high in energy barrier, thus being kinetically unfavourable. In fact, the TDI for the reaction is **int-4H**, making the overall barrier for subsequent catalytic cycles to be > 50.0 kcal mol<sup>-1</sup>, thus not thermally accessible at the reaction temperature.



**Figure S13.** Gibbs energy profile for the reaction involving ethynyltrimethylsilane **1c**.

In addition, the overall reaction gives endergonic intermediates relative to the 1,2-migratory insertion intermediate **int-4H**, making this reaction thermodynamically unfavourable. The potentially poor orbital overlap between the  $\sigma_{\text{CH}}$  of the beta-hydride and the d-orbital of Pd in **ts-4H** and that between lone pair orbital of acetate and  $\sigma^*_{\text{Pd-H}}$  of the metal-hydride in **ts-5H** could be the reason for this unfavourability; the ring strains in the palladacycle (distorted geometries) potentially contribute to the high activation barriers too (Figure S14). In addition, the release of product **prd-TMS** from the end Pd(0) species is highly unfavourable thermodynamically. Therefore, both steric and electronic factors disfavour the reaction of substrate **1c** in this alkynylation reaction. Experimentally, it is also possible that homocoupling of terminal alkynes occurs due to the presence of copper additives,<sup>54–59</sup> rendering this substrate incompetent.

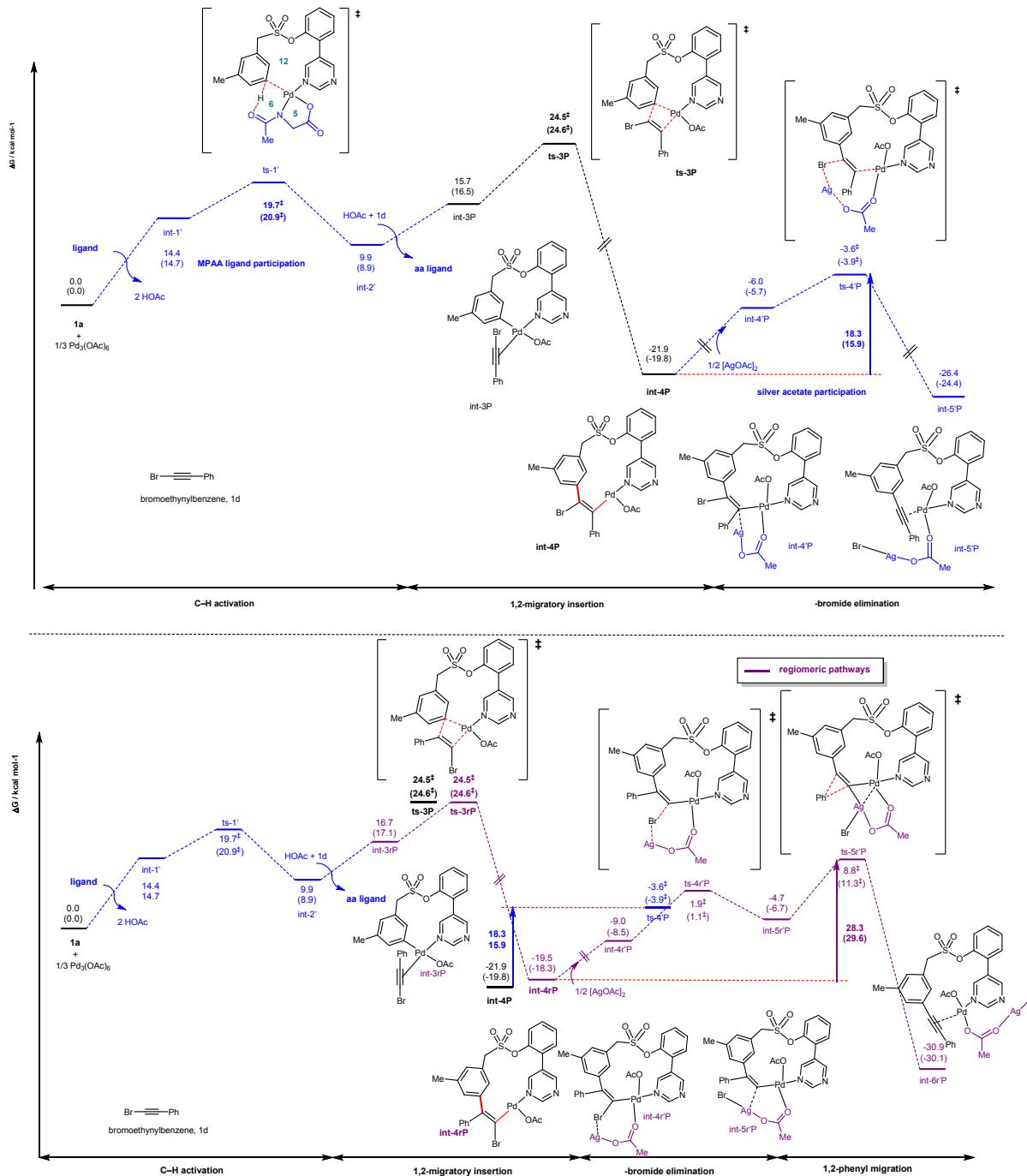


**Figure S14.** Optimised structures and HOMOs for TSs in Figure S12.

### 2.6.11 Reactivity for substrate bromoethynylbenzene **1d**

When bromoethynylbenzene **1d** was used experimentally, the reaction has a poor yield; the majority of the substrate was recovered unreacted. The full Gibbs energy profiles for the reaction using substrate bromoethynylbenzene **1d** are shown in Figure S15. These energy profiles indicate that the irreversible 1,2-migratory insertion steps occurred unselectively (**ts-3P** and **ts-3rP** have the same activation barrier, at 24.5 kcal mol<sup>-1</sup>), where either carbon of the acetylene functional group of the substrate can form C–C bond with the activated arene. This is similar to the reaction using silylated alkynylbromide **1b** (**ts-3** and **ts-3r**, Figure S10). However, for the regioisomeric insertion, the subsequent 1,2-phenyl shift (**ts-5r'P**, at 28.3 kcal mol<sup>-1</sup>) for one of the regioisomeric paths had a much higher barrier than 1,2-silyl shift (**ts-5r'**, Figures S10 and S11) using substrate **1b**. The 1,2-silyl migration on carbon atoms can

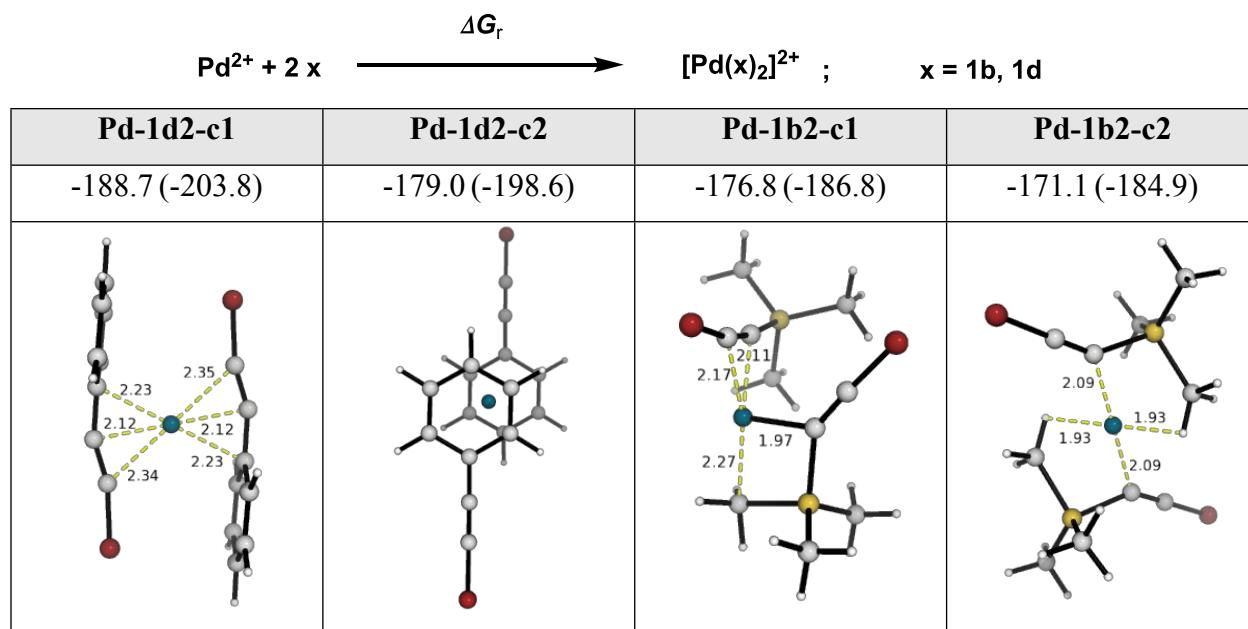
occur much more readily than 1,2-aryl migration on carbon atoms. Similar 1,2-silyl migration reactions have been previously reported.<sup>60,61</sup>



**Figure S15.** Gibbs energy profiles (two regioisomer pathways) for the reaction involving bromoethynylbenzene **1d**.

Nevertheless, computations seem to suggest that the reaction is at least kinetically and thermodynamically feasible as that using substrate **1b**, though the selectivity/regioconvergency of the product formation might not be as good (barrier of 28.3 kcal mol<sup>-1</sup>, Figure S15) as using substrate **1b** (barrier of 19.7 kcal mol<sup>-1</sup>, Figure S10), perhaps unsurprising as the phenyl group has a higher difficulty than the trialkylsilyl group in carrying out 1,2-migration.

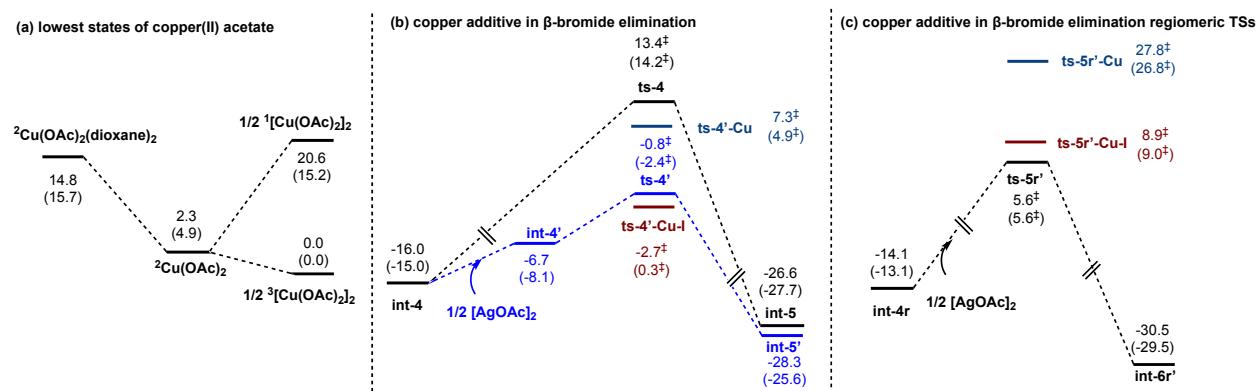
The reactivity could potentially be hindered due to the propensity of bromoethynyl-benzene **1d** to form favourable  $\pi$ - $\pi$  stacking<sup>62-64</sup> within themselves and with arene starting material; it can also form cation- $\pi$  interactions<sup>64,65</sup> with Pd(II), making them less available for reaction. This is possible as the relative comparison of  $[Pd(\text{substrate})_2]^{2+}$  complexes showed that Pd(II) coordination with two bromoethynylbenzene **1d** molecules  $[Pd(\mathbf{1d})_2]^{2+}$  is 11.9 (15.3) kcal mol<sup>-1</sup> more stabilised than with two bromoethynyl-trimethylsilane **1b** molecules  $[Pd(\mathbf{1b})_2]^{2+}$  (Figure S16).



**Figure S16.** Gibbs energy of reaction ( $\Delta G_r$ , in kcal mol<sup>-1</sup>) for the coordination complexes of substrates **1b** and **1d** with Pd(II) cation.

## 2.6.12 Possible role of copper according to computational studies

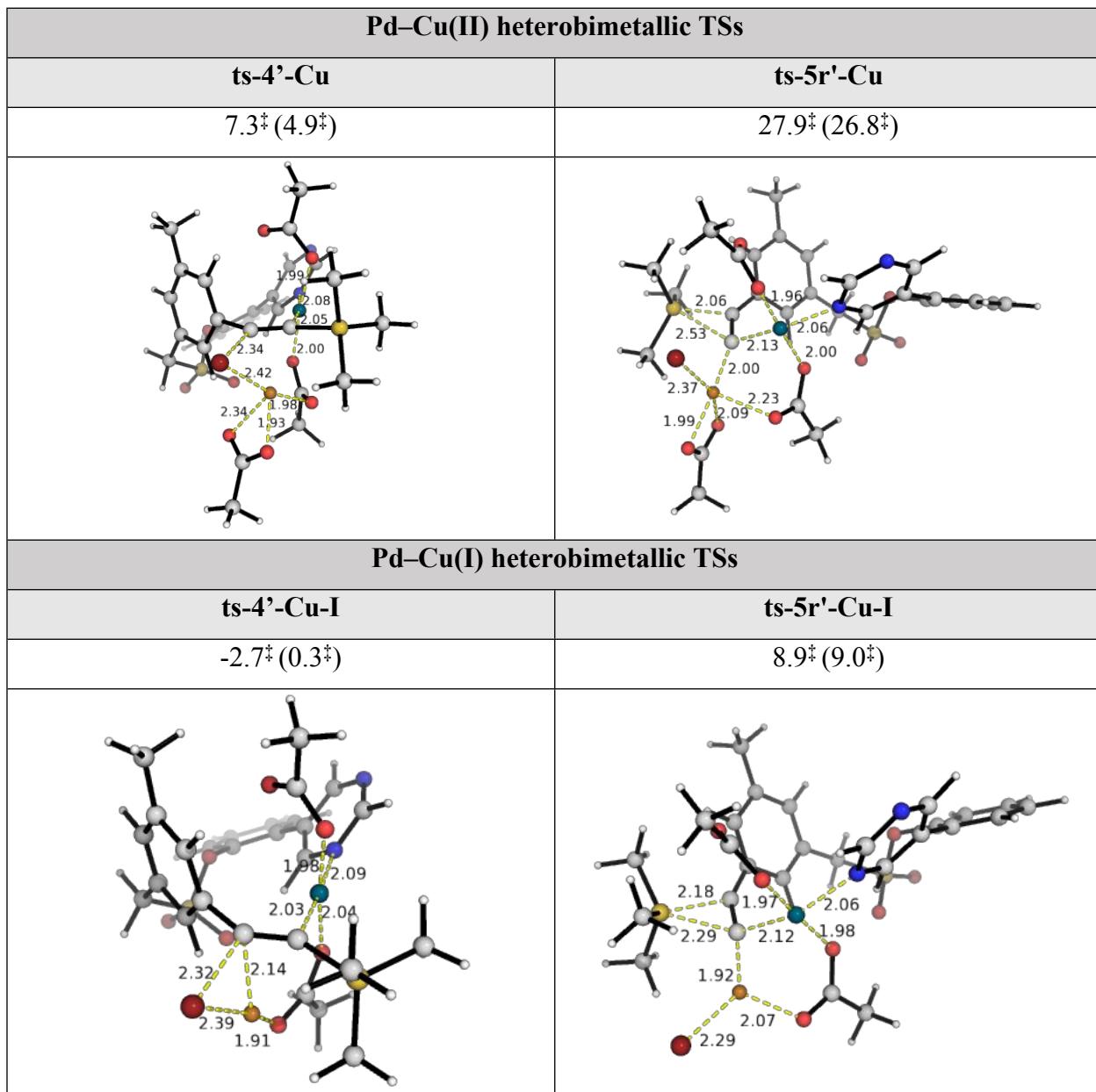
Experimentally, it was shown that the yield of the reaction is augmented by the addition of copper(II) acetate salt. The role of this copper additive was explored computationally. The most stable form of  $\text{Cu(OAc)}_2$  is in triplet spin state (Figure S17 (a)), thus, we take  $\frac{1}{2}$  of triplet copper(II) acetate dimer as the reference species. Normally, any copper additive is assumed to play a role as a co-oxidant to regenerate the main catalyst or as a source of acetate ions; computational studies of these reactions do not normally consider its explicit role in the catalytic cycle and its exact roles in the catalytic cycle are poorly understood.<sup>66–68</sup> The explicit role of  $\text{Cu(OAc)}_2$  salt was demonstrated in one study by Funes-Ardoiz and Maseras, who show that copper additive can act as a cooperative catalyst in the reductive coupling of a C–O bond in isocoumarin formation through a Rh–Cu heterobimetallic TS.<sup>69</sup> We wonder if  $\text{Cu(OAc)}_2$  plays a similar role as AgOAc in the present reaction in forming a heterometallic complex in the  $\beta$ -bromide elimination step, potentially forming  $\text{CuBr}_2$  as a side product.



**Figure S17.** (a) Stability of mononuclear and dinuclear (singlet vs triplet) copper(II) acetate species. (b) TSs with copper additive in  $\beta$ -bromide elimination step, and (c) TSs with copper additive in  $\beta$ -bromide elimination step for the regioisomeric reaction.

We found that the Pd–Cu(II) heterobimetallic TS (**ts-4'-Cu**, 7.3 kcal mol<sup>-1</sup>, Figure S18) gives an overall barrier of 23.3 kcal mol<sup>-1</sup>; this is 8.1 kcal mol<sup>-1</sup> higher than the Pd–Ag heterobimetallic TS (**ts-4'**, -0.8 kcal mol<sup>-1</sup>), although it is 6.1 kcal mol<sup>-1</sup> lower in activation

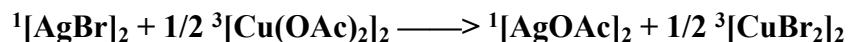
barrier than the  $\beta$ -bromide elimination TS without any metal additive (**ts-4**, 13.4 kcal mol<sup>-1</sup>) (Figure S17 (b)). The Pd–Cu(II) heterobimetallic TS for the regioisomeric rate-determining 1,2-silyl group migration (**ts-5r'-Cu**, 27.9 kcal mol<sup>-1</sup>, Figure S18) also has a higher barrier than the Pd–Ag heterobimetallic TSs (**ts-5r'**, 5.6 kcal mol<sup>-1</sup>) (Figure S17 (c)).



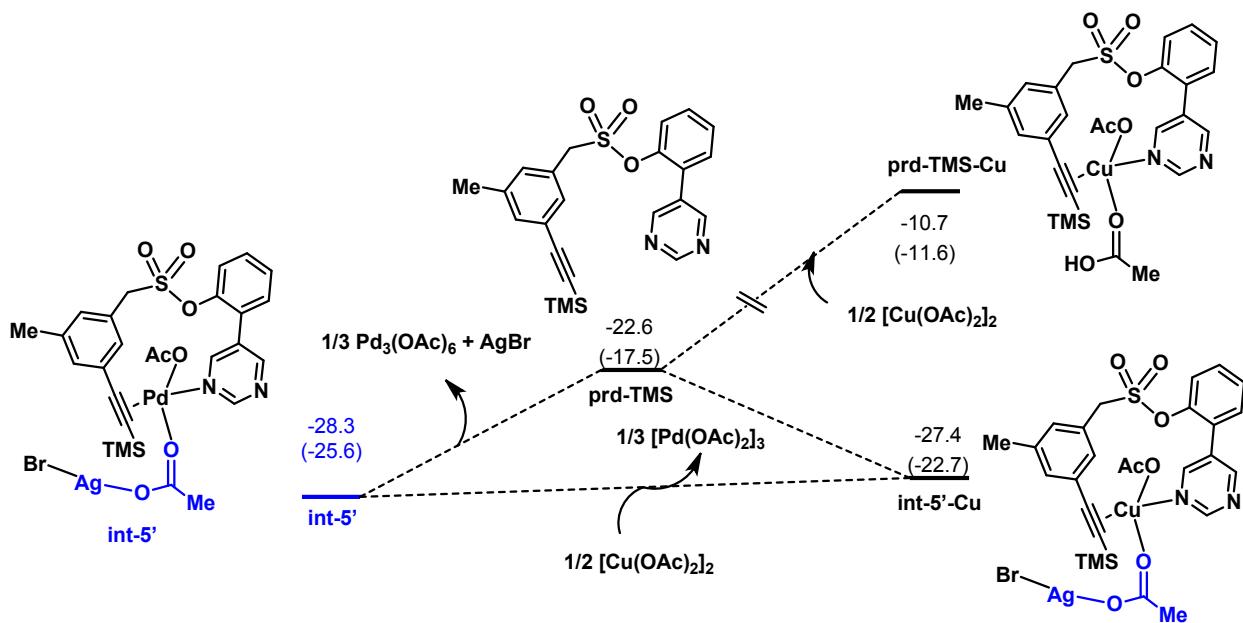
**Figure S18.** Optimised structures for Pd–Cu(II) and Pd–Cu(I) heterobimetallic TSs using Cu(OAc)<sub>2</sub> and CuOAc additive respectively.

As the Cu(II) additive also acts as an oxidant, we considered if the reduced form Cu(I) had any effect on the activation barriers for the β-bromide elimination step. We found that the use of CuOAc gives a Pd–Cu(I) heterobimetallic TS for the β-bromide elimination step (**ts-4'-Cu-I**, -2.7 kcal mol<sup>-1</sup>, Figure S17) with a lower activation barrier than the use of AgOAc (**ts-4'**, -0.8 kcal mol<sup>-1</sup>). For the regiometric pathway, the use of AgOAc has lower activation barrier (**ts-5r'**, 5.6 kcal mol<sup>-1</sup>, Figure S10) than CuOAc (**ts-5r'-Cu-I**, 8.9 kcal mol<sup>-1</sup>). Cu(I) additive give lower barriers than Cu(II) additive for both heterobimetallic TSs.

We wondered if Cu(OAc)<sub>2</sub> helps to regenerate the silver salt. This is unlikely as 2 equivalents each of Cu(OAc)<sub>2</sub> and AgOAc were used in the reaction. We calculated the thermodynamics of the following reaction:



and found that this reaction has an uphill Gibbs energy of reaction of 16.4 (17.1) kcal mol<sup>-1</sup>, thus ruling out this possibility.



**Figure S19.** Transmetallation in the product release to free up palladium catalyst.

Next, we checked if the copper salt helps in the release of palladium catalyst from its coordination to the alkynylated product, so that it can undergo the next catalytic cycle. Coordination of  $\frac{1}{2} [\text{Cu}(\text{OAc})_2]_2$  to the product releases the palladium catalyst for the next cycle. This transmetallation is more thermodynamically favourable than the direct release of product from **int-5'** (Figure S19), suggesting that it could possibly increase the yield by making palladium catalyst more available after each catalytic cycle.

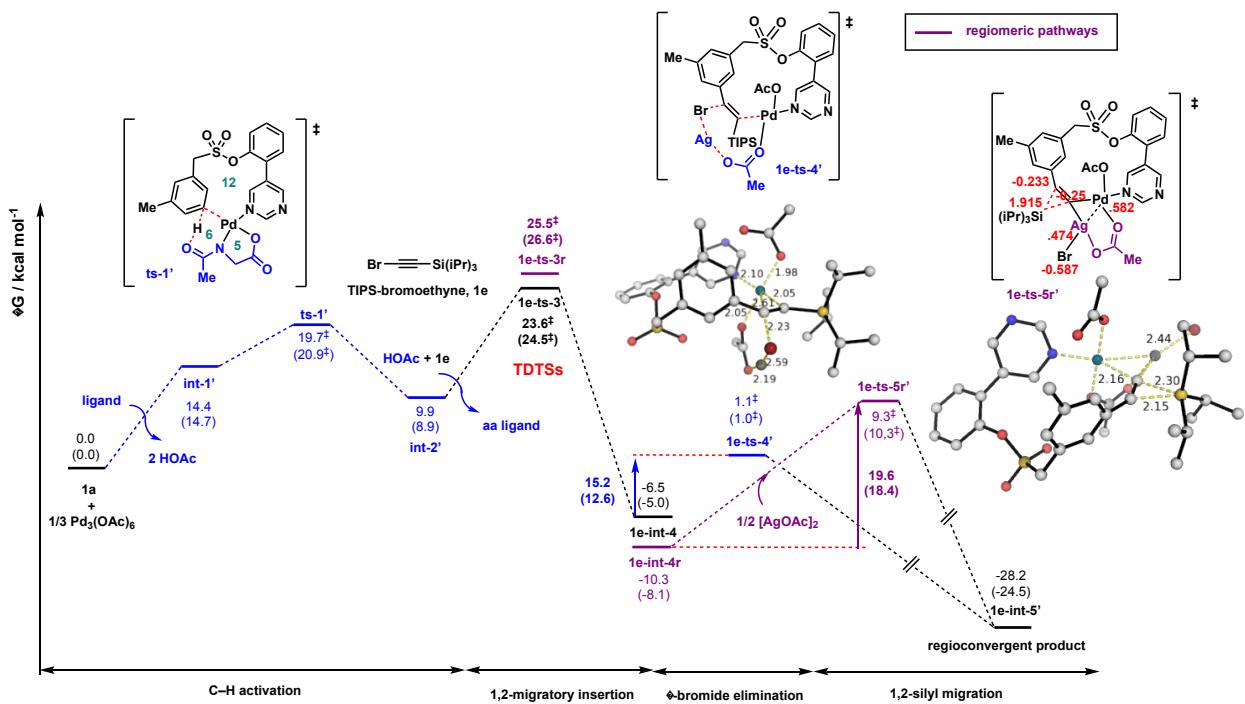
### 2.6.13 Comparative study of other trialkylsilyl and siloxy-substituted substrates

We compared the chemical reactivity and selectivity of the other substrates used in the present transformation, namely that of (bromoethynyl)triisopropylsilane, or hereafter TIPS-bromoalkyne **1e**; (bromoethynyl)tritert-butylidemethylsilane or TBDMS-bromoalkyne **1f**; (bromoethynyl)triethylsilane or TES-bromoalkyne **1g**; and siloxy-substituted substrate ((1-(bromoethynyl)cyclohexyl)oxy)trimethylsilane **1h**. The optimised structures are named as per TMS-bromoalkyne, except where the substrate name is added to the front of the structures, for example, **1e-ts-3** gives the “normal” 1,2-migratory insertion TS for substrate **1e**.

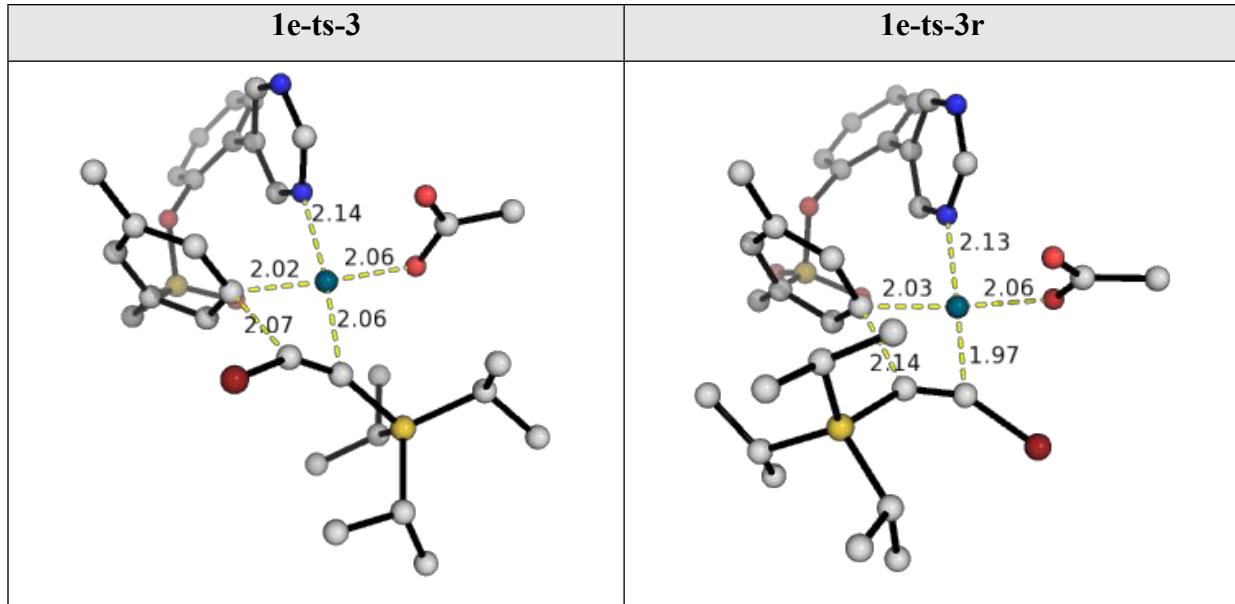
The energy profile for TIPS-bromoalkyne **1e** is shown in Figure S20. As we can see, the regioselectivity can be controlled in this case, where the bulky TIPS-group favours the “normal” 1,2-migratory insertion **1e-ts-3** over the other one **1e-ts-3r** by 1.9 kcal mol<sup>-1</sup>. This is likely due to the unfavourable steric clashes between the triisopropylsilyl group and the arene in the regiosomeric 1,2-migratory insertion TS **1e-ts-3r**, as shown by the NCI plots in Figure S21. This finding is in accordance with the steric control of regioselective of migratory insertion of C–H alkynylation observed by Sarpong, Musaev, and co-workers.<sup>56</sup>

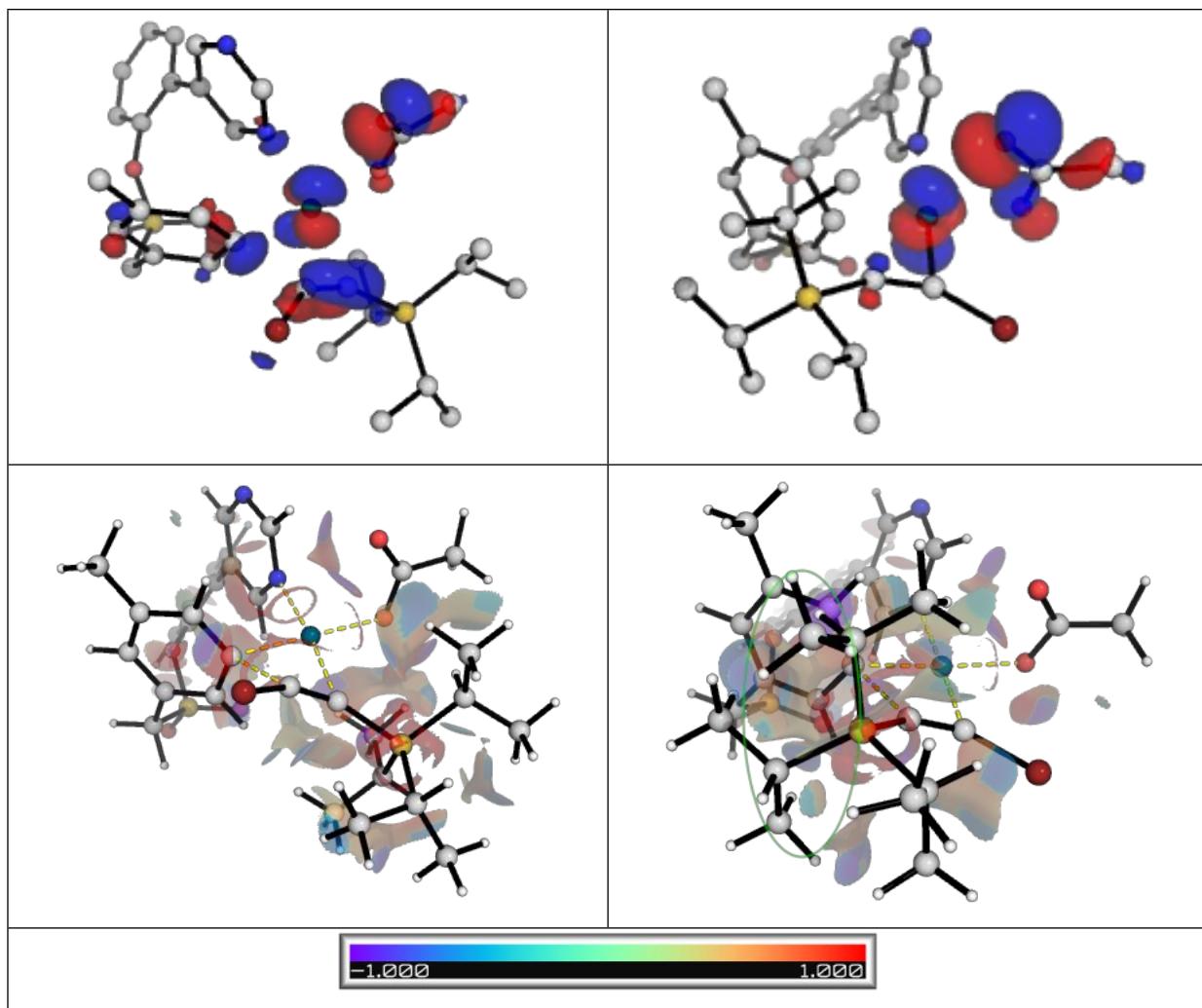
NBO second-order perturbation theory calculations were used to study the potential for a  $\beta$ -Pd effect as observed by Musaev and Sarpong, whereby a filled  $\sigma(\text{Pd}-\text{C})$  donates electron density to the  $\sigma^*(\text{C}-\text{Br})$  orbital. Although we do not observe such an interaction in the carbopalladation TS, it was apparent in the resulting intermediate: in int4 the computed delocalization energy from the  $\sigma(\text{Pd}-\text{C})$  to  $\sigma^*(\text{C}-\text{Br})$  is 22.5 kcal/mol. In contrast, in int4r we found a  $\sigma(\text{Pd}-\text{C})$  to  $\sigma^*(\text{C}-\text{Si})$  delocalization of 6.9 kcal/mol, along with a  $\sigma(\text{C}-\text{C})$  to  $\sigma^*(\text{C}-\text{Br})$  delocalization of 11.0 kcal/mol. These results are consistent with hyperconjugation playing a role in stabilizing int4 over int4r.

It was further found that the 1,2-silyl migratory following regiosomeric insertion TS **1e-ts-3r** has a low activation barrier of 19.6 kcal mol<sup>-1</sup>, which is much lower than the barrier for the turnover-limiting 1,2-insertion step, indicating that the regioconvergency of product will still be achieved regardless of the regioselectivity step. The proposed 1,2-silyl migration in **1e-ts-5r'** is the same as for the TMS-alkynylbromide case as discussed in the main manuscript. As before, following the 1,2-migratory insertion step, the AgOAc ligand-assisted heterobimetallic  $\beta$ -bromide elimination TS **1e-ts-4'** has a lower activation barrier (15.2 kcal mol<sup>-1</sup>) than the TDTS **1e-ts-3** with a barrier of 23.6 kcal mol<sup>-1</sup>. The final alkynylated product is once again energetically very downhill and thermodynamically favourable.



**Figure S20.** Gibbs energy profile for the present transformation using substrate TIPS-alkynylbromide **1e**.

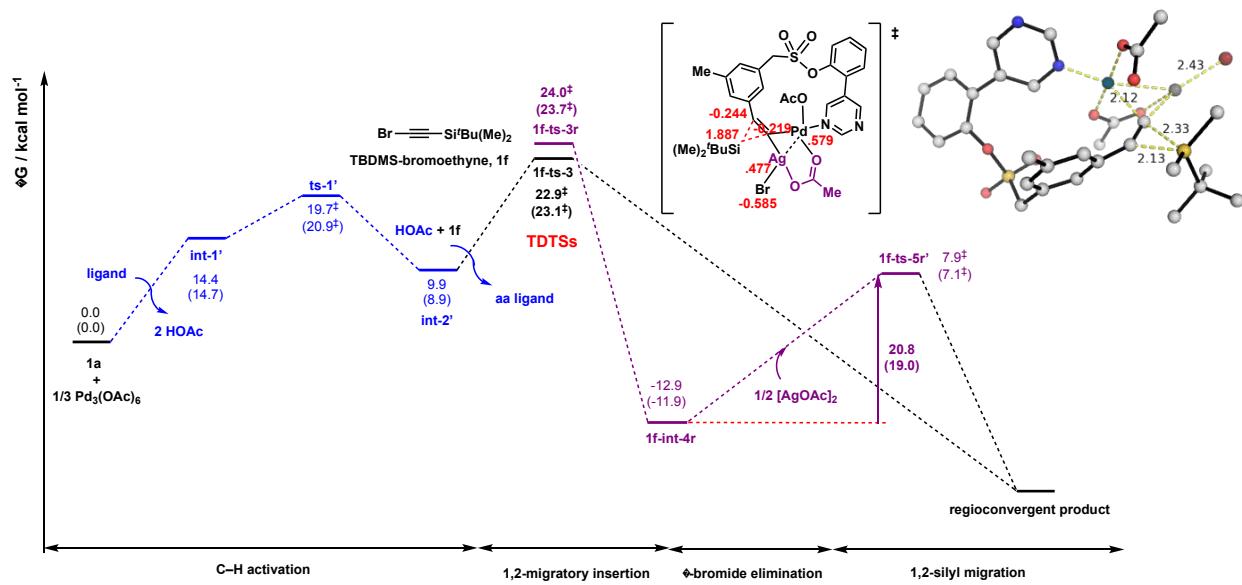




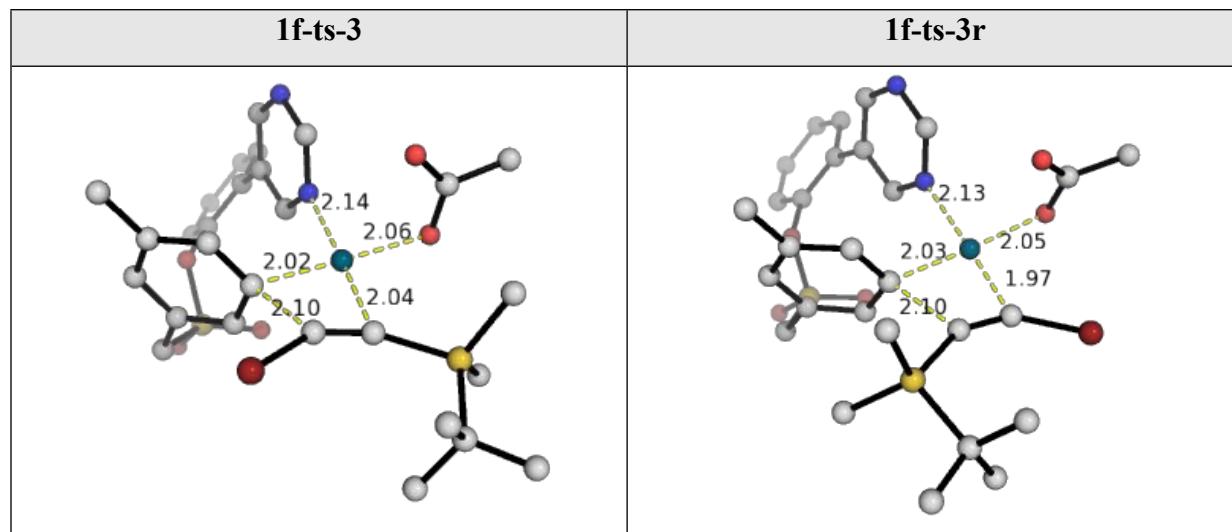
**Figure S21.** Optimised structures, HOMOs and NCI plots for the regioisomeric 1,2-migratory insertion steps for substrate TIPS-alkynylbromide **1e**.

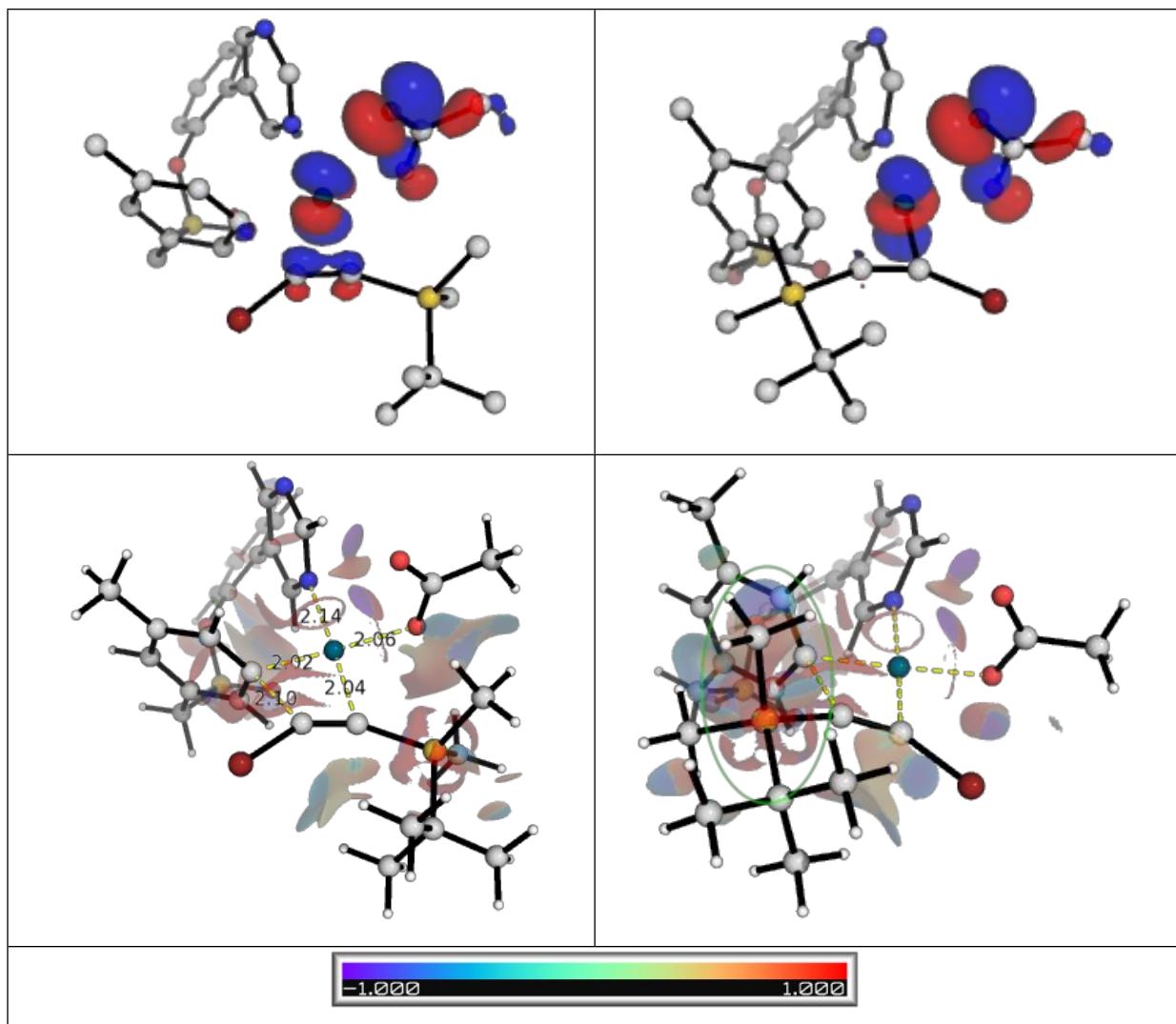
The reaction using the other trialkylsilyl bromoalkyne substrates TBDMS-bromoalkyne **1f** and TES-bromoalkyne **1g** are similarly considered; the results are shown in Figures S22 to S25. We can see that for all trialkylsilyl bromoalkynes, the 1,2-migratory insertion is the TDTS. The regioselectivity is in favour of one over the other due to possible larger steric constraints in one of the TS (**ts-3r**) than the other (**ts-3**). We can see that **1f-ts-3** is favoured by 1.1 kcal mol<sup>-1</sup> than the regioisomeric pathway **1f-ts-3r** (Figure S22) and that **1g-ts-3** is favoured by 2.2 kcal mol<sup>-1</sup> than the regioisomeric pathway **1g-ts-3r** (Figure S24). However, in all these cases, the 1,2-silyl migration following one of the regioisomeric pathways has lower

activation barrier than the TDTS, indicating that the regioconvergency of product will be observed regardless of the regioselectivity at the turnover-limiting insertion step.

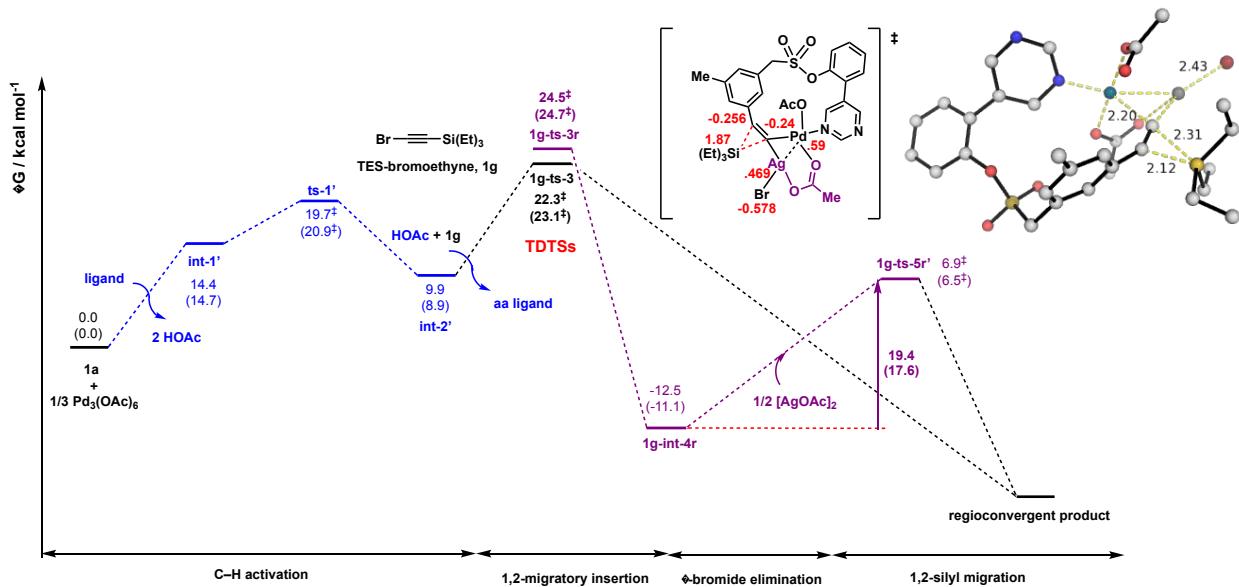


**Figure S22.** Gibbs energy profile for the present transformation using substrate TBDMS-alkynylbromide **1f**.

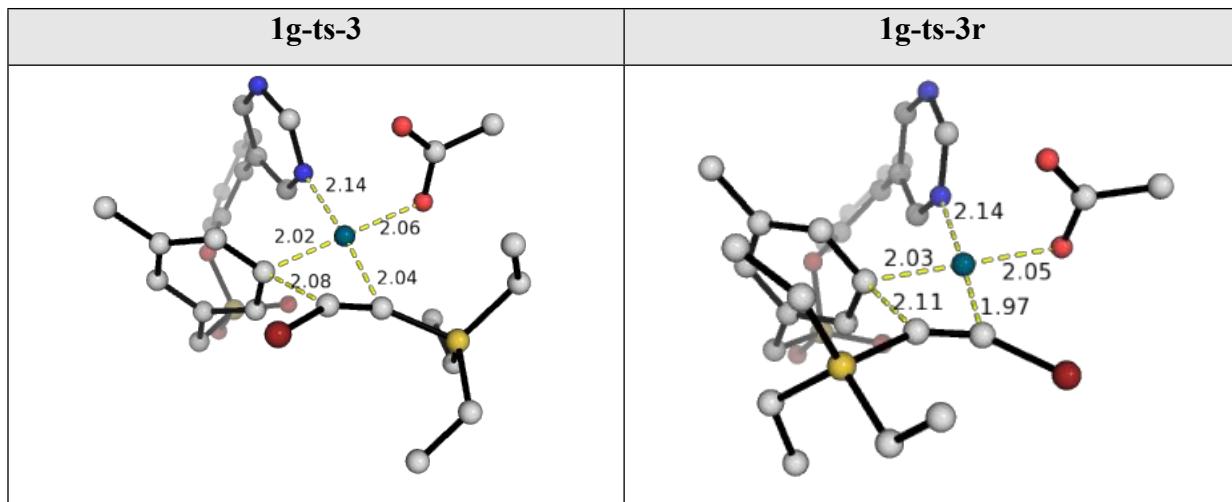


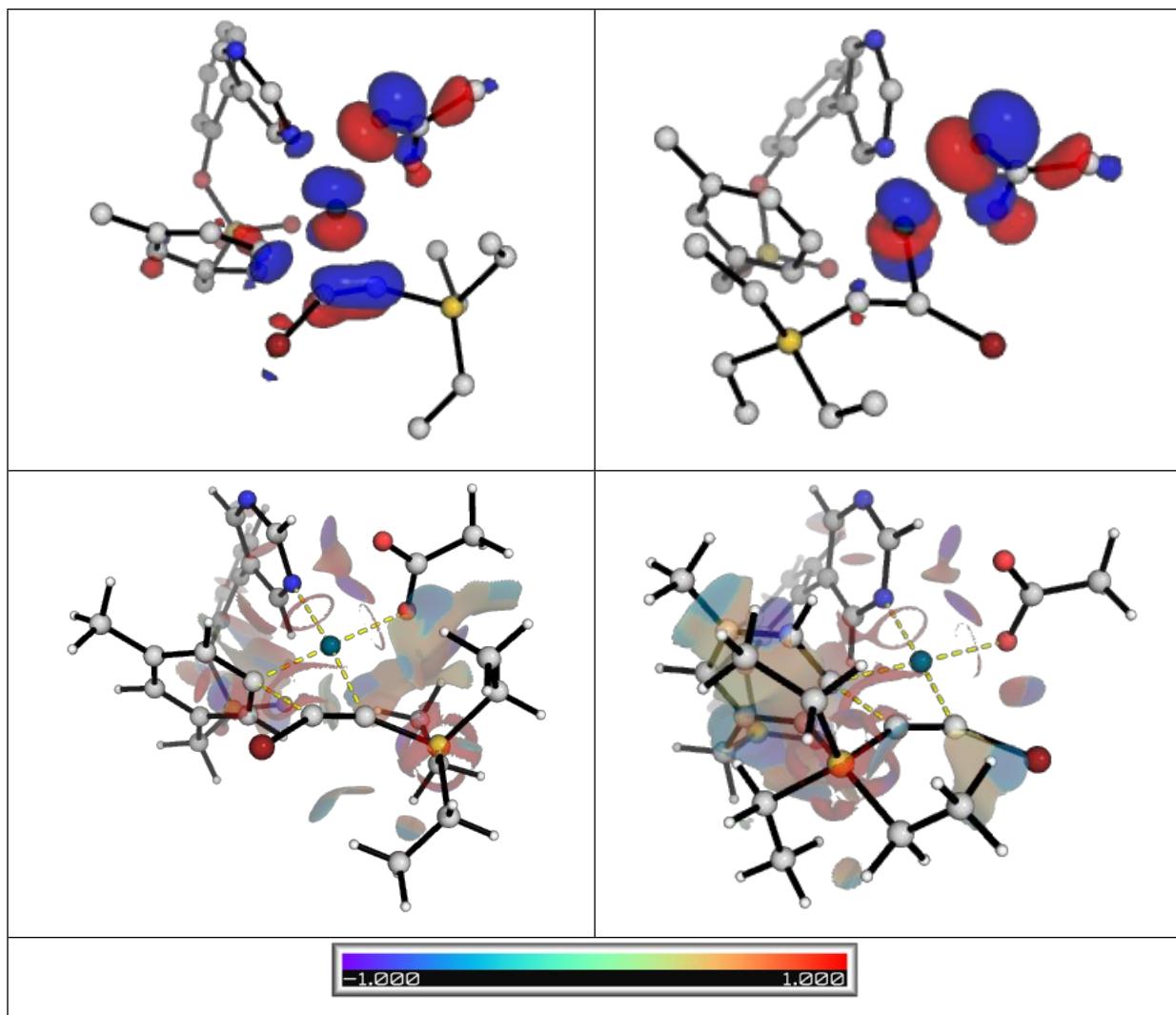


**Figure S23.** Optimised structures, HOMOs and NCI plots for the regioisomeric 1,2-migratory insertion steps for substrate TBDMS-alkynylbromide **1f**.



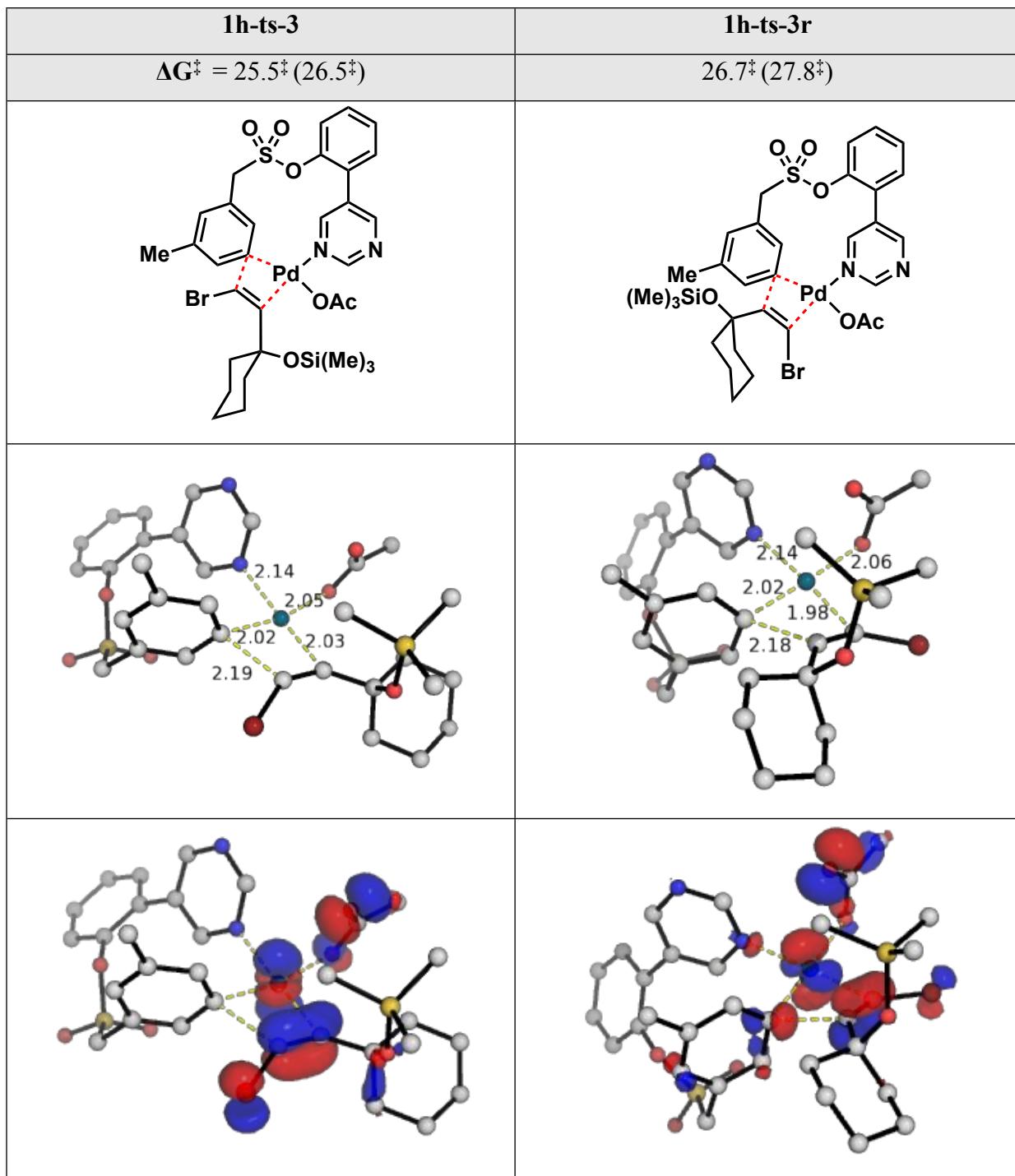
**Figure S24.** Gibbs energy profile for the present transformation using substrate TES-alkynylbromide **1g**.

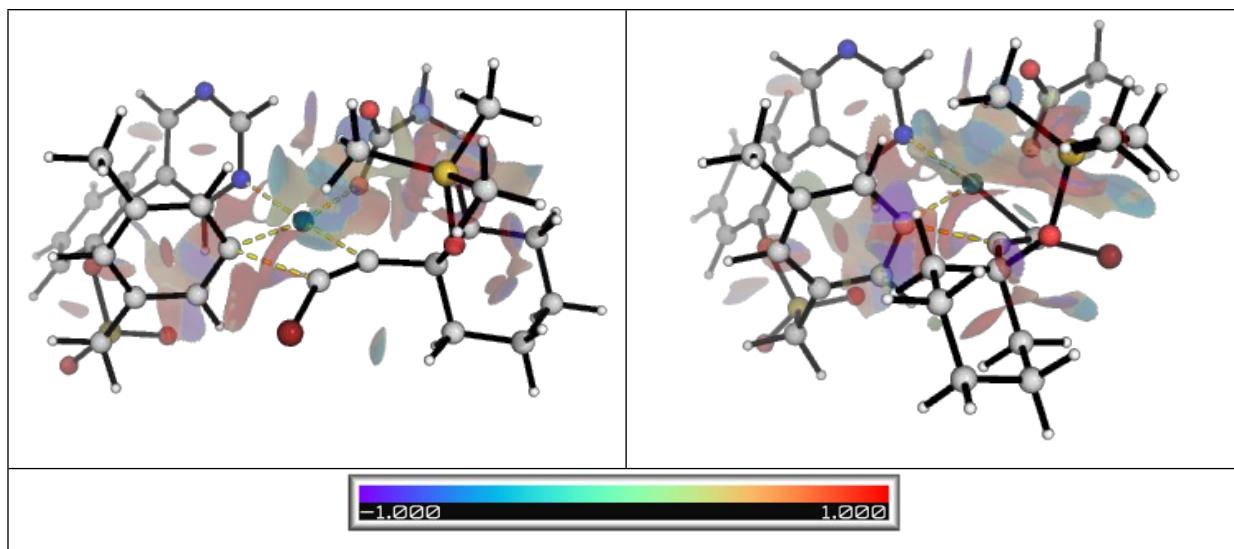




**Figure S25.** Optimised structures, HOMOs and NCI plots for the regioisomeric 1,2-migratory insertion steps for substrate TES-alkynylbromide **1g**.

For the siloxy-substituted substrate ((1-(bromoethynyl)cyclohexyl)oxy)trimethylsilane **1h**, we compared the TDTS 1,2-migratory insertion step for regioselectivity. The results are given in Figure S26. We can see that the TS for the “correct” regioselectivity is favoured by slightly better sterics (as evidenced by the NCI plots) as the bulky siloxy group is kept away from the C–C bond formation centre. This is in agreement with the steric control of regioselectivity observed in similar reactions reported by Sarpong, Musaev, and co-workers,<sup>56</sup> as noted previously.





**Figure S26.** Optimised structures, HOMOs and NCI plots for the regiosomeric 1,2-migratory insertion steps for the siloxy-substituted substrate **1h**.

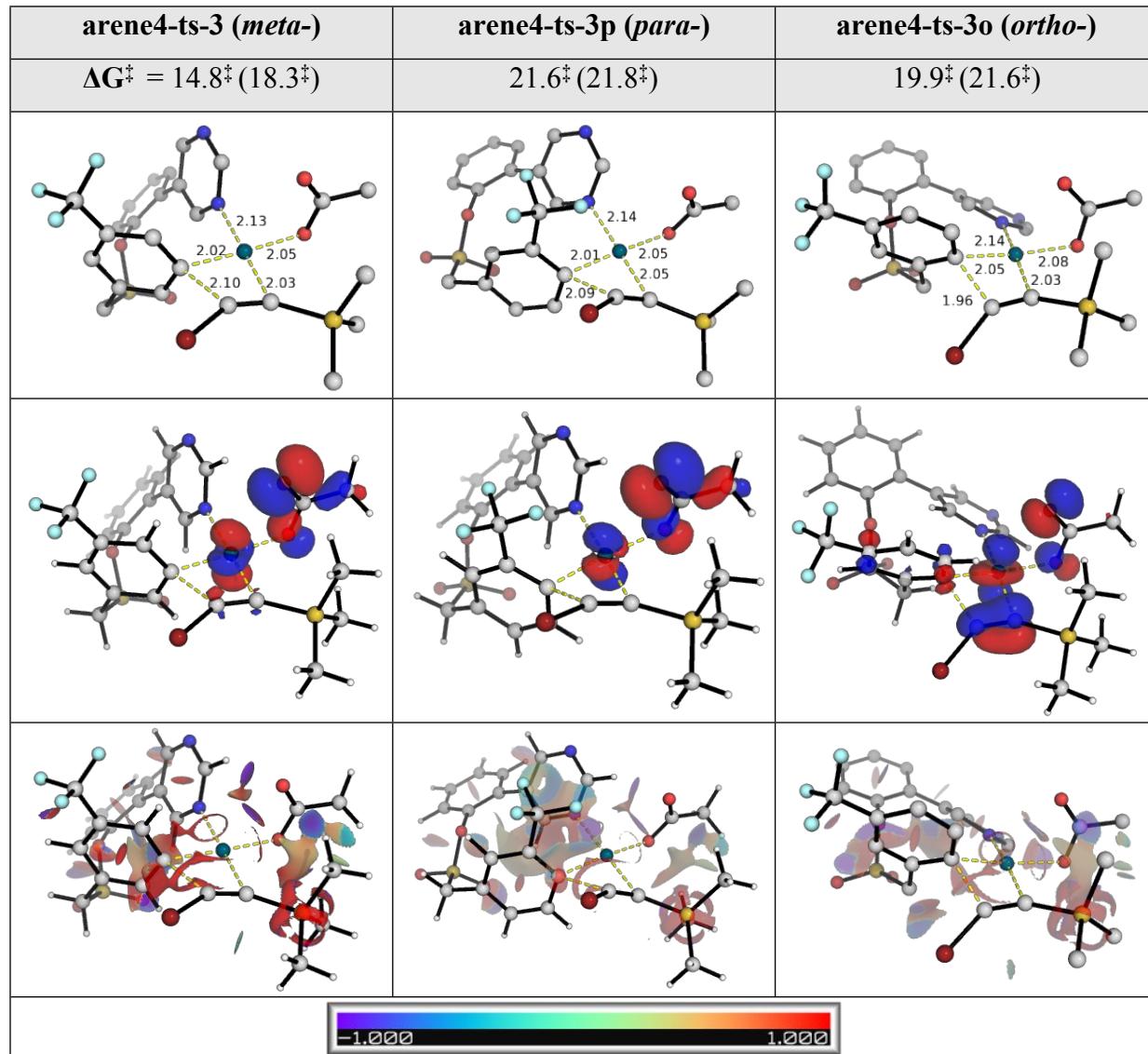
#### 2.6.14 Comparative study of other arenes with varying substituents

We compared the arene site-selectivity for the other arene substrates used in the present transformation, namely that giving products **4**, **5** and **12**. These substrates differ from substrate **1a** (methyl group on *meta*-position of arene) used in the computational study in that for products **4**, the substituent is *meta*-CF<sub>3</sub>; for **5**, it is *meta*-OCF<sub>3</sub>; for **12**, it is *ortho*-CH<sub>3</sub>.

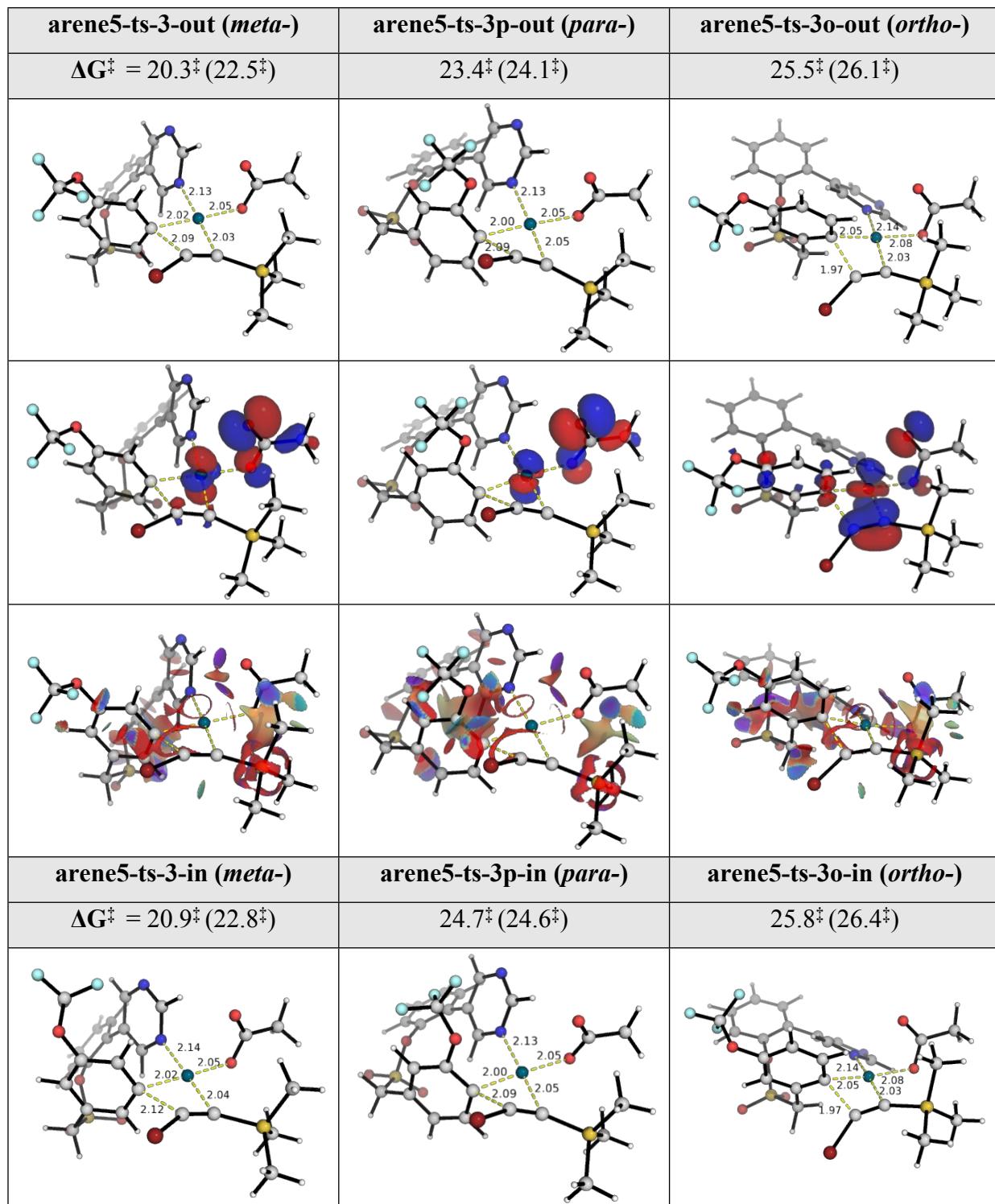
For product **4**, the optimized structures, the HOMO and the NCI plots for the 1,2-migratory insertion step at different arene sites are given in Figure S27. *Meta*-selectivity is favored as for substrate **1a**. Our calculations show that *meta*-functionalization will be favoured by a factor of 10<sup>3</sup>, although experimentally, it is favoured only by 7 times. There seems to be a balancing effect between the sterics and electronics for the meta-selectivity, although it is difficult to see the molecular origins from the HOMO and NCI plots.

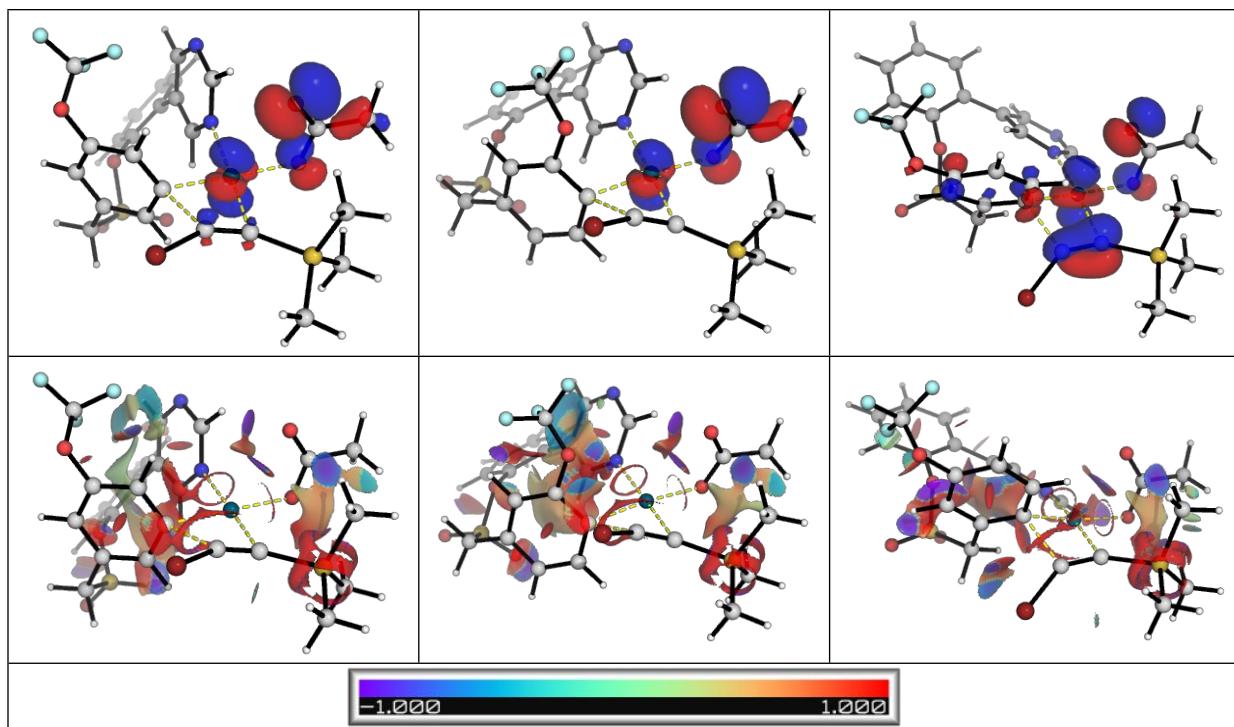
For product **5**, a similar analysis was performed and the results were shown in Figure S28. Two conformers for the –OCF<sub>3</sub> substituent on the arene can be distinguished, with this group either pointing into or away from the palladacycle. We found that the ones pointing away from the palladacycle has the lower barrier (albeit only slightly), possibly due to more

favourable sterics. Once again, for this substrate, the *meta*-functionalization was computationally found to be more favourable than either the *ortho*- or *para*-functionalization.



**Figure S27.** Optimised structures, HOMOs and NCI plots for 1,2-migratory insertion step in site-selectivity studies for arene giving product 4.

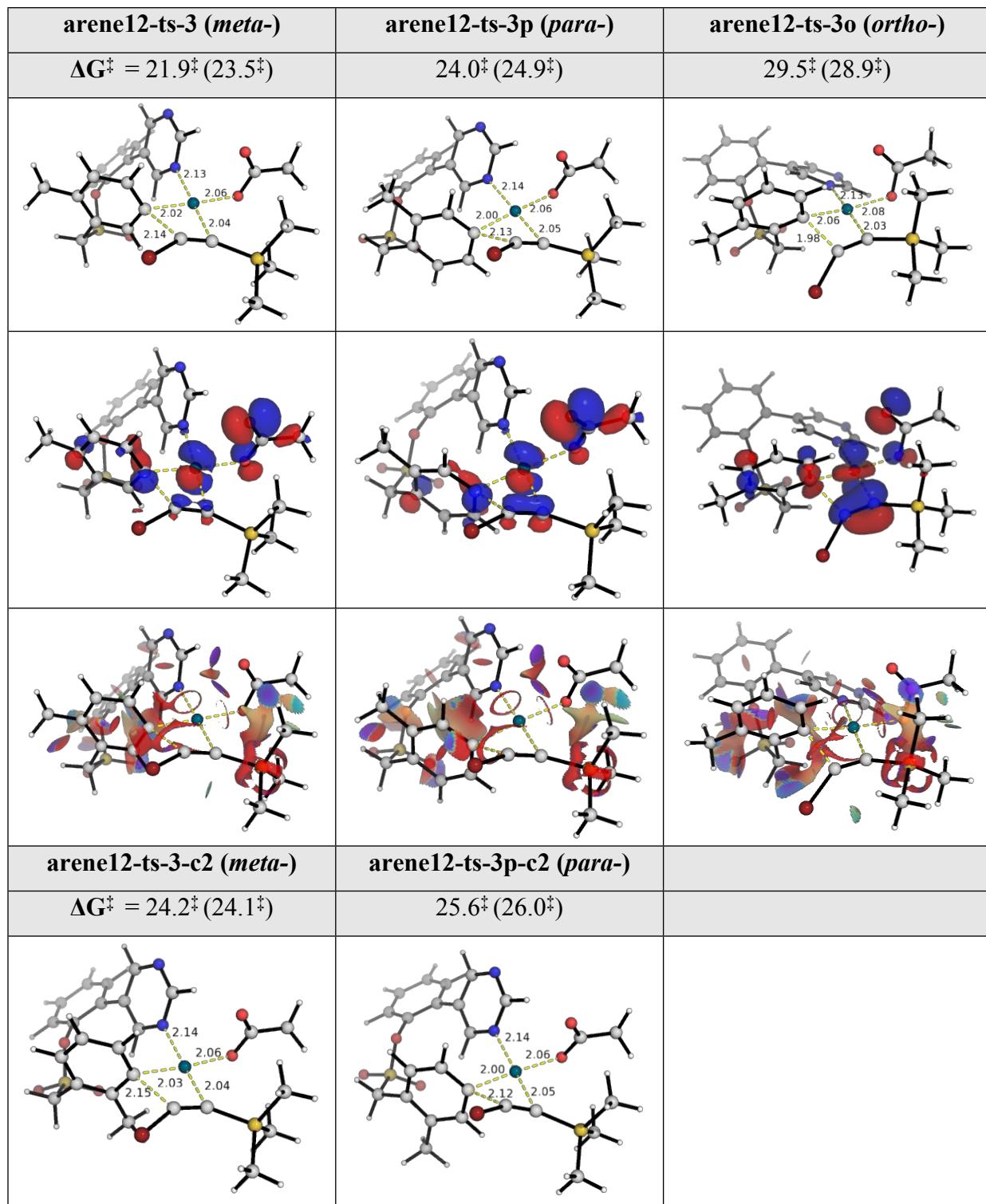


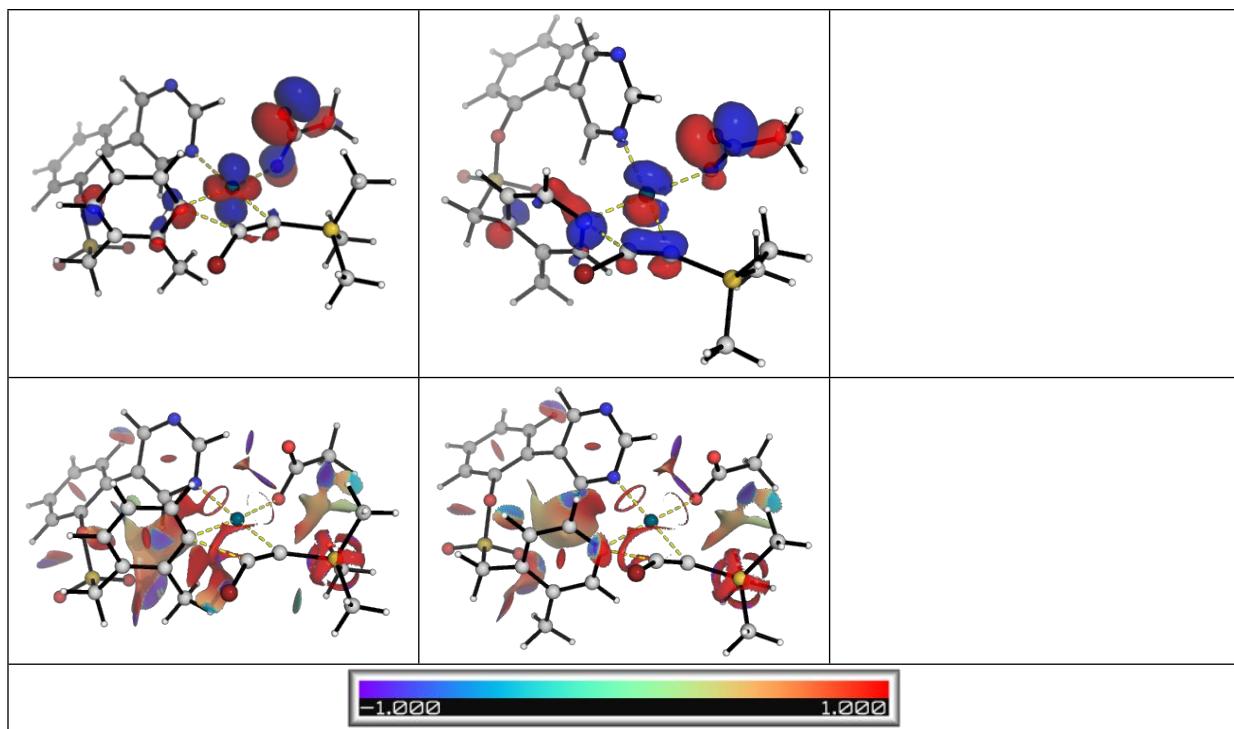


**Figure S28.** Optimised structures, HOMOs and NCI plots for 1,2-migratory insertion step in site-selectivity studies for arene giving product **5**. The suffix “-out” and “-in” in the TS names indicate the conformation of the  $-\text{OCF}_3$  group with respect to the palladacycle.

The results for product **12** is shown in Figure S29. The same *meta*-selectivity is observed, as for substrate **1a**. This is again likely due to the ring strain control in the different membered palladacycle for these TSs. For *meta*- and *para*-functionalization, the TSs have two different conformers with the methyl group on the arene in different orientation. It was found that the TS with the methyl group pointing away from the palladacyclic ring is lower in activation barrier, as would be expected for substrate **1a**.

For all these arene substrates, we have shown that the *meta*-selectivity is obtained in all cases. This shows our computational model of arene site-selectivity via ring strain control by the palladacycle is general and widely applicable to a range of substrates. In addition, it shows that this sterics control is dominant over electronic variations in the substituents in the arene substrates.



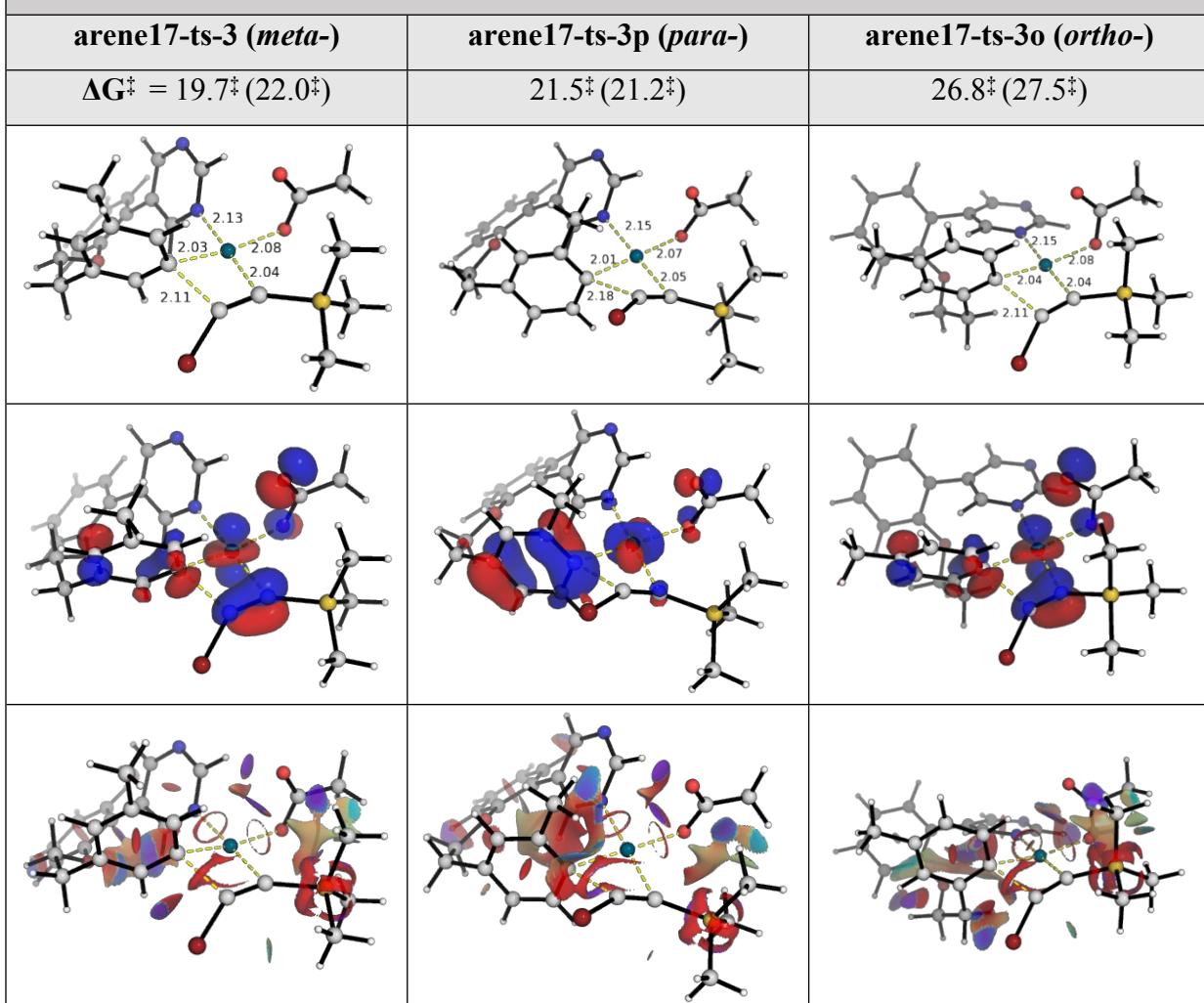


**Figure S29.** Optimised structures, HOMOs and NCI plots for 1,2-migratory insertion step in site-selectivity studies for arene giving product **12**.

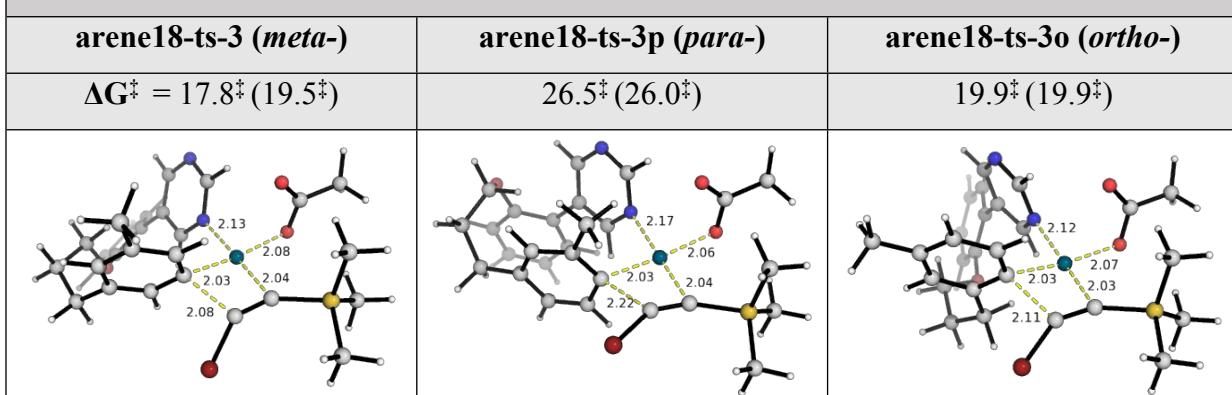
#### 2.6.15 Comparative study of directing group with varying alkyl chain lengths (products 17-19)

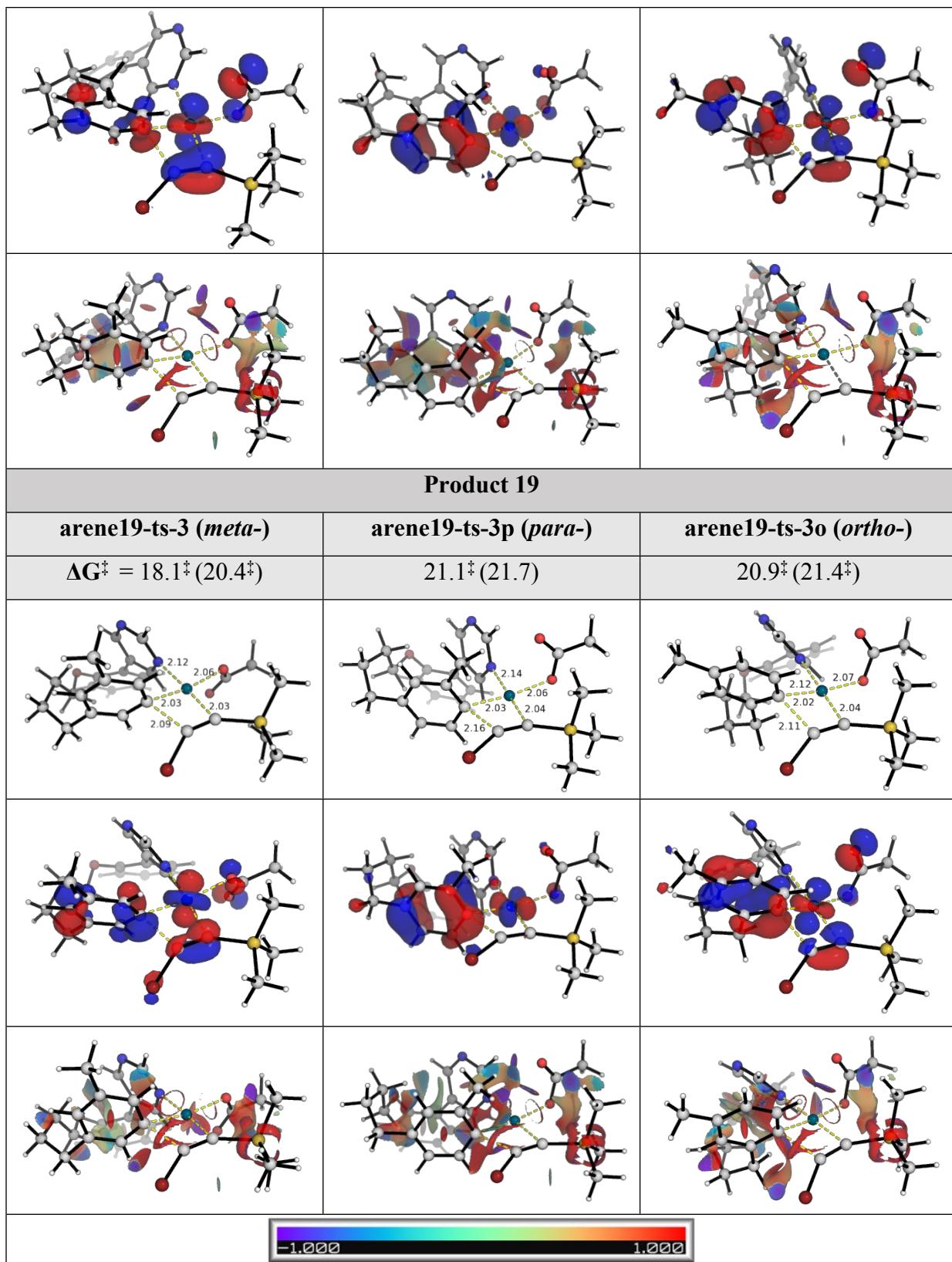
Our computational model of site-selectivity control via differing ring strains in the palladacyclic TS predicts that as the length of the directing group increases, this site-selectivity control will diminish. Indeed, this is what was observed experimentally for products **17**, **18** and **19**, that *meta*-selective product formation diminishes. Computationally herein, we show that *meta*-site is favored in the turnover frequency determining 1,2-insertion step for all these substrates. The results are shown in Figure S30. The discrepancy in the quantitative selectivity / product ratio could result from incomplete conformational sampling since with greater chain length in the directing groups, the corresponding possible conformers also increase. Nevertheless, our model successfully predicts selective *meta*-functionalization for all these three substrates.

### Product 17



### Product 18





**Figure S30.** Optimised structures, HOMOs and NCI plots for comparison of regioselctivity in product **17-19**.

### 2.6.16 Absolute energies, zero-point energies

Absolute values (in Hartrees) for SCF energy, zero-point vibrational energy (ZPE), enthalpy and quasi-harmonic Gibbs free energy (at 363K) for optimised structures are given below. Single point corrections in SMD 1,4-dioxane using  $\omega$ B97X-D and MN15 functionals are also included. Each sub-heading corresponds to a subfolder inside the *alkynylation\_structures\_xyz* folder where all optimised structural coordinates are given in *.xyz* format, along with the corresponding (gas-phase) energy, *E*.

Structure	E/au	ZPE/au	H/au	G/au	qh-G/au	SP $\omega$ B97X-D (1,4-dioxane)	SP MN15 (1,4- dioxane)
<b>0_sm (starting materials):</b>							
<b>1a</b>	-1426.5229	0.311509	-1426.1822	-1426.271357	-1426.2667	-1429.04845440	-1428.6786329
<b>1b</b>	-3059.2496	0.12121	-3059.1129	-3059.171373	-3059.1703	-3059.73136747	-3059.9403307
<b>1c</b>	-485.35706	0.130012	-485.21303	-485.265131	-485.26489	-486.0681293	-485.9084379
<b>1d</b>	-2881.6333	0.101851	-2881.5201	-2881.570127	-2881.5693	-2882.07267838	-2882.3366382
<b>HOAc</b>	-228.64453	0.062197	-228.57532	-228.611767	-228.61143	-229.13351888	-229.0668662
<b>Nacetylglycin e</b>							
<b>HBr</b>	-2575.0853	0.006123	-2575.0752	-2575.098797	-2575.0988	-2574.87712744	-2575.2352612
<b>CuOA monomer</b>							
<b>c2_monomer_si</b>	-2096.9448	0.103478	-2096.8259	-2096.887377	-2096.884	-2097.7220570	-2097.862484
<b>CuOA singlet</b>							
<b>c2_dimer_si</b>	-4193.9145	0.2089	-4193.6748	-4193.770684	-4193.7642	-4195.41435355	-4195.7209312
<b>CuOA triplet</b>							
<b>c2_dimer_tr</b>	-4193.9647	0.210384	-4193.7241	-4193.819467	-4193.8132	-4195.48133	-4195.770429

<b>CuOA</b>							
<b>c_dim</b>	-3737.8511	0.105272	-3737.7284	-3737.7944	-3737.7912	-3738.42516828	-3738.851
<b>er_sin</b>							
<b>glet</b>							
<b>CuOA</b>							
<b>c_dim</b>	-3737.7103	0.104279	-3737.5884	-3737.6552	-3737.6524	-3738.29887073	-3738.7162
<b>er_trip</b>							
<b>let</b>							
<b>CuBr2</b>							
<b>_mono</b>	-6789.8301	0.001703	-6789.8214	-6789.860471	-6789.8594	-6789.22792048	-6790.217605
<b>mer</b>							
<b>CuBr2</b>							
<b>_dime</b>	-13579.701	0.004317	-13579.682	-13579.74594	-13579.743	-13578.47209	-13580.47502
<b>r_singl</b>							
<b>et</b>							
<b>CuBr2</b>							
<b>_dime</b>	-13579.72	0.003987	-13579.702	-13579.76965	-13579.764	-13578.50789	-13580.49347
<b>r_tripl</b>							
<b>et</b>							
<b>AgBr_</b>							
<b>mono</b>	-2721.2253	0.000564	-2721.2202	-2721.251781	-2721.2518	-2721.36119518	-2721.3856319
<b>mer</b>							
<b>AgBr_</b>							
<b>dimer</b>	-5442.5245	0.001782	-5442.5131	-5442.563924	-5442.5627	-5442.77059613	-5442.8311465
<b>AgOA</b>							
<b>c_mon</b>	-374.7487	0.050645	-374.68909	-374.734768	-374.73318	-375.57469470	-375.1751886
<b>omer</b>							
<b>AgOA</b>							
<b>c_dim</b>	-749.614	0.104042	-749.49181	-749.561524	-749.55757	-751.22801036	-750.4392581
<b>er</b>							
<b>PdOA</b>							
<b>c2_tri</b>	-1751.5873	0.317868	-1751.2239	-1751.355928	-1751.3441	-1755.20433723	-1754.0362117
<b>mer</b>							
<b>1_alkynylation_of_1b:</b>							
<b>int-1</b>	- 2010.361021	0.417336	-2009.8989	-2010.025439	-2010.0157	-2014.09960593	-2013.3417185
<b>ts-1</b>	-2010.33609	0.411975	-2009.8797	-2010.005994	-2009.9958	-2014.07504621	-2013.3134469

<b>int-2</b>	-2010.35148	0.417256	-2009.8891	-2010.01868	-2010.0072	-2014.0909700	-2013.3314472
<b>int-1'</b>	-1989.299016	0.40982	-1988.8469	-1988.96541	-1988.9582	-1992.99638924	-1992.242002
<b>ts-1'</b>	-1989.285298	0.404477	-1988.8388	-1988.957426	-1988.9496	-1992.98274427	-1992.226918
<b>int-2'</b>	-1989.308364	0.410403	-1988.8556	-1988.975621	-1988.9672	-1993.00391157	-1992.251518
<b>int-3</b>	-4840.971216	0.475881	-4840.4416	-4840.587747	-4840.5761	-4844.70115850	-4844.219901
<b>ts-3</b>	-4840.954399	0.475297	-4840.4262	-4840.571417	-4840.5599	-4844.69041408	-4844.205339
<b>int-4</b>	-4841.020565	0.477956	-4840.49	-4840.632214	-4840.6224	-4844.75555636	-4844.269364
<b>ts-4</b>	-4840.959972	0.476549	-4840.4307	-4840.573444	-4840.5632	-4844.70633991	-4844.221584
<b>int-5</b>	-4841.03872	0.477823	-4840.5075	-4840.652789	-4840.6415	-4844.77052705	-4844.288776
<b>ts-3-c2</b>	-4840.953808	0.475018	-4840.4258	-4840.570625	-4840.5593	-4844.69020998	-4844.205156
<b>ts-4-c2</b>	-4840.959568	0.476335	-4840.4304	-4840.57422	-4840.5633	-4844.70609086	-4844.222823
<b>int-4'</b>	-5215.84045	0.530066	-5215.2484	-5215.412349	-5215.4	-5220.36794079	-5219.492117
<b>ts-4'</b>	-5215.832056	0.529735	-5215.2409	-5215.402897	-5215.3907	-5220.35928688	-5219.483928
<b>int-5'</b>	-5215.865795	0.530375	-5215.2726	-5215.440323	-5215.4261	-5220.4013	-5219.519246
<b>ts-3'z</b>	-5215.75066	0.527466	-5215.1604	-5215.327817	-5215.3139	-5220.28972195	-5219.408864
<b>ts-4'z</b>	-5215.740197	0.526905	-5215.1501	-5215.322905	-5215.3057	-5220.28632879	-5219.406788
<b>int-3r</b>	-4840.966352	0.475466	-4840.4367	-4840.586257	-4840.5731	-4844.70196831	-4844.216596
<b>ts-3r</b>	-4840.95523	0.47543	-4840.4271	-4840.570658	-4840.5596	-4844.69151480	-4844.208097
<b>int-4r</b>	-4841.015859	0.477568	-4840.4854	-4840.629472	-4840.6187	-4844.75055601	-4844.265451
<b>prd-TMS</b>	-1910.712531	0.422586	-1910.2474	-1910.369467	-1910.36	-1913.930509	-1913.409386
<b>1_alkynylation_of_1b (regioconvergence):</b>							
<b>int-4r'</b>	-	0.530422	-5215.2395	-5215.405033	-5215.3917	-5220.36410756	-5219.485658

	5215.832104							
<b>ts-4'r'</b>	- 5215.821896	0.529437	-5215.2308	-5215.394645	-5215.3817	-5220.35427898	-5219.47812	
<b>int-5'r'</b>	- 5215.829729	0.529865	-5215.2374	-5215.403028	-5215.3898	-5220.36688210	-5219.489466	
<b>ts-5'r'</b>	- 5215.800846	0.528577	-5215.2093	-5215.37938	-5215.3637	-5220.34501888	-5219.467047	
<b>int-6'r'</b>	- 5215.871336	0.530833	-5215.2777	-5215.445362	-5215.4312	-5220.40546946	-5219.525982	
<b>2_alkynylation_of_1b_aa_ligand:</b>								
<b>ts-1'a</b>	- 1989.241518	0.404846	-1988.7947	-1988.914288	-1988.9057	-1992.93996133	-1992.185971	
<b>ts-1'b</b>	- 2217.946095	0.468797	-2217.4274	-2217.567499	-2217.5552	-2222.12071512	-2221.297634	
<b>ts-1'c</b>	- 2217.950755	0.467665	-2217.4326	-2217.575045	-2217.5616	-2222.1295546	-2221.3056348	
<b>ts3'a</b>	- 5048.547111	0.531403	-5047.9573	-5048.114495	-5048.1014	-5052.71629339	-5052.172854	
<b>ts3'b</b>	- 5048.564282	0.531205	-5047.9743	-5048.134568	-5048.1203	-5052.74047130	-5052.192636	
<b>ts3'c</b>	- 5048.571284	0.532029	-5047.9809	-5048.13779	-5048.1249	-5052.74364579	-5052.196485	
<b>3_alkynylation_of_1b_copper:</b>								
<b>prd-</b>								
<b>TMS-</b>								
<b>Cu</b>	- 4007.706141	0.528899	-4007.1194	-4007.27282	-4007.2619	-4011.68135651	-4011.302816	
<b>int-5'-</b>								
<b>Cu</b>	- 6728.989054	0.529306	-6728.3963	-6728.565912	-6728.5517	-6733.07561264	-6732.724159	
<b>ts-4'-</b>								
<b>Cu</b>	- 6937.993403	0.582236	-6937.3431	-6937.519912	-6937.5065	-6942.47112391	-6942.135956	
<b>ts-5r'-</b>								
<b>Cu</b>	- 6937.944999	0.581394	-6937.2949	-6937.474663	-6937.4599	-6942.43658511	-6942.099334	
<b>ts-4'-</b>								
<b>Cu-I</b>	- -6709.9488	0.529478	-6709.3577	-6709.5201	-6709.508	-6713.95378711	-6713.688	
<b>ts-5r'-</b>								
<b>Cu-I</b>	- -6709.9194	0.530303	-6709.3274	-6709.4906	-6709.4778	-6713.94078388	-6713.6704	

#### 4\_arene\_site\_selectivity\_ortho\_para:

<b>ts-1o</b>	- 2010.327235	0.412335	-2009.8706	-2009.996525	-2009.9864	-2014.06251681	-2013.3048429
<b>ts-1'o</b>	- 1989.275333	0.40504	-1988.8284	-1988.945718	-1988.9386	-1992.97006819	-1992.21543
<b>ts-3o</b>	- 4840.950848	0.475039	-4840.4227	-4840.567922	-4840.5564	-4844.68267726	-4844.2002067
<b>int-4o</b>	- 4841.005502	0.478328	-4840.4746	-4840.615898	-4840.6066	-4844.73707307	-4844.253322
<b>ts-1p</b>	- 2010.335874	0.412169	-2009.8794	-2010.004978	-2009.9953	-2014.07305762	-2013.3139172
<b>ts-1'p</b>	- 1989.285331	0.405046	-1988.8386	-1988.955232	-1988.9485	-1992.97998020	-1992.2270019
<b>ts-3p</b>	- -4840.95513	0.47566	-4840.4269	-4840.568977	-4840.5592	-4844.68772197	-4844.2061858
<b>int-4p</b>	- 4841.014183	0.478097	-4840.4835	-4840.625278	-4840.6157	-4844.74520831	-4844.2619844
<b>pyridine</b>	- -247.762761	0.089473	-247.66632	-247.703094	-247.7031	-248.30299639	-248.2171106
<b>ts-3-iso</b>	- 5088.733157	0.565521	-5088.1063	-5088.273417	-5088.2574	-5093.00230034	-5092.431749
<b>ts-3o-iso</b>	- 5088.739269	0.566537	-5088.1119	-5088.273959	-5088.2602	-5093.00429760	-5092.43484
<b>ts-3p-iso</b>	- 5088.737798	0.566374	-5088.1105	-5088.27522	-5088.2607	-5093.00522025	-5092.437843

#### 5\_alternative\_oxidative\_addition\_TSs:

<b>ts-3- oa-c1</b>	- 4840.926859	0.475106	-4840.3986	-4840.542395	-4840.5316	-4844.65853300	-4844.176038
<b>ts-3- oa-c2</b>	- 4840.916281	0.474524	-4840.3882	-4840.535615	-4840.5231	-4844.65155100	-4844.168891
<b>ts-3- oa-c3</b>	- 4840.920333	0.475375	-4840.3919	-4840.536547	-4840.5252	-4844.65176600	-4844.169894
<b>ts-3- oa-c4</b>	- 4840.913291	0.475415	-4840.3848	-4840.530401	-4840.5186	-4844.64899900	-4844.166361

#### 6\_ethyltrimethylsilane\_1c:

<b>ts-3H</b>	- 2267.064352	0.484575	-2266.5286	-2266.667859	-2266.6578	-2271.02940120	-2270.174764
<b>int-4H</b>	- 2267.117887	0.487514	-2266.5796	-2266.716169	-2266.7075	-2271.08034834	-2270.225851

<b>ts-4H</b>	-	2267.065965	0.485481	-2266.5297	-2266.667975	-2266.6581	-2271.03263981	-2270.176345
<b>int-5H</b>	-	2267.080525	0.486262	-2266.5432	-2266.682216	-2266.6722	-2271.04173857	-2270.19011
<b>ts-5H</b>	-	2267.058347	0.482448	-2266.5243	-2266.666613	-2266.655	-2271.02464274	-2270.168419
<b>int-6H</b>	-	2267.112587	0.487541	-2266.5733	-2266.716186	-2266.7043	-2271.07262933	-2270.218973
<b>ts-3rH</b>	-	2267.059619	0.484192	-2266.5242	-2266.663393	-2266.653	-2271.02667613	-2270.173159
<b>int-4rH</b>	-	2267.110337	0.487008	-2266.5722	-2266.71284	-2266.7017	-2271.07618079	-2270.220442

**7\_bromoethylbenzene\_1d:**

<b>int-3P</b>	-	4663.348539	0.45632	-4662.8422	-4662.982617	-4662.97	-4667.04108395	-4666.611194
<b>ts-3P</b>	-	4663.334882	0.455895	-4662.8302	-4662.966822	-4662.9556	-4667.02770871	-4666.598967
<b>int-4P</b>	-	4663.410381	0.458554	-4662.9032	-4663.037486	-4663.0277	-4667.10511821	-4666.673142
<b>int-4'P</b>	-	5038.220005	0.511025	-5037.6508	-5037.806846	-5037.7944	-5042.70847151	-5041.885059
<b>ts-4'P</b>	-	5038.213948	0.50998	-5037.6461	-5037.802513	-5037.7894	-5042.70363654	-5041.881219
<b>int-5'P</b>	-	5038.246678	0.510894	-5037.677	-5037.836798	-5037.8225	-5042.73960204	-5041.913369
<b>int-3rP</b>	-	4663.348567	0.456396	-4662.8424	-4662.981827	-4662.9697	-4667.03983832	-4666.610208
<b>ts-3rP</b>	-	4663.334352	0.45606	-4662.8295	-4662.965766	-4662.9546	-4667.02827091	-4666.599432
<b>int-4rP</b>	-	4663.408013	0.458631	-4662.9007	-4663.035552	-4663.0254	-4667.10120678	-4666.670752
<b>int-4r'P</b>	-	5038.221148	0.51122	-5037.6518	-5037.809372	-5037.796	-5042.71271368	-5041.888975
<b>ts-4r'P</b>	-	5038.203812	0.510319	-5037.6359	-5037.791775	-5037.7788	-5042.69533863	-5041.873737
<b>int-5r'P</b>	-	5038.208472	0.51074	-5037.6393	-5037.798524	-5037.7844	-5042.70482600	-5041.88134

<b>ts-5r'P</b>	-	5038.179023	0.508913	-5037.6113	-5037.773914	-5037.7576	-5042.68075194	-5041.853769
<b>int-6r'P</b>	-	5038.253672	0.510711	-5037.6836	-5037.846764	-5037.8306	-5042.74558486	-5041.921402
<b>Pd-1d2-c1</b>	-	5890.364189	0.205082	-5890.1328	-5890.219516	-5890.2141	-5891.64277896	-5891.906803
<b>Pd-1d2-c2</b>	-	5890.359886	0.205108	-5890.1286	-5890.218338	-5890.2113	-5891.62582953	-5891.89701
<b>Pd-1b2-c1</b>	-	6245.565123	0.242534	-6245.2867	-6245.39694	-6245.3888	-6246.93689409	-6247.085401
<b>Pd-1b2-c2</b>	-	-6245.56809	0.242148	-6245.292	-6245.39765	-6245.3897	-6246.92986787	-6247.081794
<b>8_other_substrates:</b>								
<b>1e</b>	-3294.59	0.292704	-3294.2712	-3294.3534	-3294.35	-3295.634897	-3295.721341	
<b>1e-ts-3</b>	-5076.2974	0.646681	-5075.5873	-5075.7523	-5075.7398	-5080.593801	-5079.986219	
<b>1e-int-4</b>	-	-5076.3526	0.649515	-5075.64	-5075.803	-5075.7916	-5080.645143	-5080.03672
<b>1e-ts-4'</b>	-	-5451.1723	0.70129	-5450.3991	-5450.5815	-5450.5684	-5456.261713	-5455.261447
<b>1e-int-5'</b>	-	-5451.2102	0.702589	-5450.4347	-5450.6222	-5450.6067	-5456.308062	-5455.301817
<b>1e-ts-3r</b>	-	-5076.2924	0.64712	-5075.5819	-5075.7473	-5075.7345	-5080.591088	-5079.983186
<b>1e-int-4r</b>	-	-5076.3522	0.649212	-5075.6394	-5075.8049	-5075.7925	-5080.649833	-5080.040274
<b>1e-ts-5r'</b>	-	-5451.1408	0.700775	-5450.3667	-5450.5561	-5450.5398	-5456.2458	-5455.243674
<b>1f</b>	-3176.924	0.205792	-3176.6972	-3176.7683	-3176.7656	-3177.686636	-3177.835616	
<b>1f-ts-3</b>	-4958.6302	0.559899	-4958.0119	-4958.1676	-4958.1552	-4962.645778	-4962.101901	
<b>1f-ts-3r</b>	-	-4958.6289	0.560226	-4958.0107	-4958.1647	-4958.1529	-4962.645048	-4962.101922
<b>1f-int-4r</b>	-	-4958.6908	0.562524	-4958.0702	-4958.2244	-4958.2128	-4962.705875	-4962.160724
<b>1f-ts-5r'</b>	-	-5333.4774	0.613627	-5332.7958	-5332.9756	-5332.9591	-5338.298815	-5337.362075
<b>1g</b>	-3176.9162	0.207853	-3176.6874	-3176.7601	-3176.7565	-3177.680792	-3177.827112	
<b>1g-ts-3</b>	-4958.624	0.561729	-4958.0041	-4958.1605	-4958.1475	-4962.640979	-4962.093565	

<b>1g-ts-</b>							
<b>3r</b>	-4958.6197	0.562476	-4957.9995	-4958.1535	-4958.1419	-4962.638822	-4962.092373
<b>1g-int-</b>							
<b>4r</b>	-4958.6825	0.564508	-4958.0601	-4958.2153	-4958.203	-4962.699377	-4962.151008
<b>1g-ts-</b>							
<b>5r'</b>	-5333.4697	0.615664	-5332.7861	-5332.9672	-5332.9502	-5338.294293	-5337.354334
<b>1h</b>	-3368.5384	0.275855	-3368.2375	-3368.3177	-3368.3143	-3369.708772	-3369.79762
<b>1h-ts-3</b>	-5150.2455	0.631166	-5149.5526	-5149.7138	-5149.7016	-5154.666852	-5154.061617
<b>1h-ts-</b>							
<b>3r</b>	-5150.2426	0.630357	-5149.5501	-5149.7127	-5149.6998	-5154.663669	-5154.058248
rct4	-1723.7941	0.290043	-1723.4729	-1723.5664	-1723.5616	-1726.834042	-1726.446171
<b>arene4</b>							
<b>-ts-3</b>	-5138.2315	0.453342	-5137.7229	-5137.8746	-5137.8618	-5142.486279	-5141.979126
<b>arene4</b>							
<b>-ts-3o</b>	-5138.2273	0.453186	-5137.7188	-5137.8705	-5137.8577	-5142.478066	-5141.973756
<b>arene4</b>							
<b>-ts-3p</b>	-5138.2327	0.45348	-5137.7243	-5137.8715	-5137.8611	-5142.47737	-5141.975429
<b>rct5</b>	-1798.8924	0.294448	-1798.5655	-1798.6645	-1798.6575	-1802.07487	-1801.676443
<b>arene5</b>							
<b>-ts-3 -</b>							
<b>in</b>	-5213.3278	0.45795	-5212.8135	-5212.9666	-5212.9538	-5217.719327	-5217.204019
<b>arene5</b>							
<b>-ts-3-</b>							
<b>out</b>	-5213.3268	0.457935	-5212.8125	-5212.9672	-5212.9537	-5217.71939	-5217.203736
<b>arene5</b>							
<b>--ts-</b>							
<b>3o-in</b>	-5213.3225	0.457925	-5212.8082	-5212.9611	-5212.9484	-5217.711578	-5217.198451
<b>arene5</b>							
<b>-ts-3o-</b>							
<b>out</b>	-5213.3222	0.457813	-5212.808	-5212.962	-5212.9488	-5217.711411	-5217.198334
<b>arene5</b>							
<b>-ts-3p-</b>							
<b>in</b>	-5213.3285	0.458439	-5212.8141	-5212.9645	-5212.9532	-5217.71457	-5217.202591
<b>arene5</b>							
<b>-ts-3p-</b>							
<b>out</b>	-5213.3269	0.458125	-5212.8125	-5212.9665	-5212.9533	-5217.714939	-5217.201559
<b>rct12</b>	-1426.5206	0.311768	-1426.1798	-1426.2688	-1426.264	-1429.045799	-1428.678001

<b>arene1</b>							
<b>2-ts-3</b>	-4840.9551	0.475883	-4840.4268	-4840.5694	-4840.5591	-4844.688978	-4844.204842
<b>arene1</b>							
<b>2-ts-3 -</b>							
<b>c2</b>	-4840.9558	0.476203	-4840.4273	-4840.568	-4840.5587	-4844.686417	-4844.205075
<b>arene1</b>							
<b>2-ts-3p</b>	-4840.9516	0.475861	-4840.4233	-4840.5655	-4840.5554	-4844.685907	-4844.202936
<b>arene1</b>							
<b>2-ts-</b>							
<b>3p-c2</b>	-4840.951	0.475834	-4840.4228	-4840.5643	-4840.5545	-4844.683508	-4844.201388
<b>arene1</b>							
<b>2-ts-3o</b>	-4840.9485	0.475274	-4840.4206	-4840.5627	-4840.5527	-4844.676657	-4844.196173
<b>rct17</b>	-917.69754	0.329967	-917.34115	-917.42361	-917.41975	-919.6751142	-919.3624192
<b>arene1</b>							
<b>7-ts-3</b>	-4332.1279	0.493298	-4331.584	-4331.7241	-4331.713	-4335.319402	-4334.889262
<b>arene1</b>							
<b>7-ts-3o</b>	-4332.1213	0.493222	-4331.5775	-4331.7169	-4331.7061	-4335.308496	-4334.881006
<b>arene1</b>							
<b>7-ts-3p</b>	-4332.1323	0.494036	-4331.5882	-4331.7242	-4331.7154	-4335.318613	-4334.892731
<b>rct18</b>	-956.91929	0.358325	-956.53275	-956.61915	-956.61514	-958.991959	-958.6575218
<b>arene1</b>							
<b>8-ts-3</b>	-4371.3551	0.52194	-4370.781	-4370.9237	-4370.9127	-4374.640464	-4374.189512
<b>arene1</b>							
<b>8-ts-3o</b>	-4371.3554	0.521749	-4370.7814	-4370.924	-4370.9132	-4374.636954	-4374.188736
<b>arene1</b>							
<b>8-ts-3p</b>	-4371.3496	0.522566	-4370.7754	-4370.9147	-4370.9054	-4374.62844	-4374.181094
<b>rct19</b>	-996.14608	0.38758	-995.72869	-995.81932	-995.81428	-998.3137032	-997.9588521
<b>arene1</b>							
<b>9-ts-3</b>	-4410.5805	0.55009	-4409.9763	-4410.1237	-4410.1118	-4413.960342	-4413.488137
<b>arene1</b>							
<b>9-ts-3o</b>	-4410.5796	0.550033	-4409.9755	-4410.1217	-4410.1105	-4413.956386	-4413.486858
<b>arene1</b>							
<b>9-ts-3p</b>	-4410.5823	0.55073	-4409.978	-4410.1224	-4410.1122	-4413.957052	-4413.487479

## 2.6.17 Optimised geometries

All optimized geometries (in .xyz format with their associated energy in Hartrees) are included in a separate folder named *alkynylation\_structures\_xyz* with an associated README file. All these data have been uploaded to zenodo.org (DOI:[10.5281/zenodo.3550223](https://doi.org/10.5281/zenodo.3550223)) and are freely available.

## 3. References:

Full reference for Gaussian 16 software:

*Gaussian 16*, Revision A.01, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., Sonnenberg, J. L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery Jr., J. A.; Peralta, J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, J. M., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R. L., Morokuma, K., Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, Ö., Foresman, J. B., Ortiz, J. V, Cioslowski, J., Fox, D. J. Gaussian, Inc. & Wallingford CT. (2016).

- (1) Bag, S., Jayarajan, R., Mondal, R. & Maiti, D. Template-assisted *meta*-C–H alkylation and alkenylation of arenes. *Angew. Chem. Int. Ed.* **56**, 3182–3186 (2017).
- (2) Bag, S., Jayarajan, R., Dutta, U., Chowdhury, R., Mondal, R. & Maiti, D. Remote *meta*-C–H cyanation of arenes enabled by a pyrimidine based auxiliary. *Angew. Chem. Int. Ed.* **56**, 12538–12542 (2017).
- (3) Jayarajan, R., Das, J., Bag, S., Chowdhury, R. & Maiti, D. Diverse *meta*-C–H functionalization of arenes across different linker lengths. *Angew. Chem. Int. Ed.* **57**, 7659 –7663 (2018).

- (4) Bera, M., Maji, A., Sahoo, S.K. & Maiti, D. Palladium(II)-catalyzed *meta*-C–H olefination: constructing multisubstituted arenes through homo-diolefination and sequential hetero-diolefination. *Angew. Chem. Int. Ed.* **54**, 8515–8519 (2015).
- (5) Griffith, W. P., Shoair, A. G. & Suriaatmaja, M. Ruthenium-catalysed cleavage of alkenes and alkynes to carboxylic acids. *Synth. Commun.* **30**, 3091–3095 (2000).
- (6) Xu, G., Hartman, T. L., Wargo, H., Turpin, J. A., Buckheit, R.W. & Cushman, M. Synthesis of alkenyldiarylmethane (ADAM) non-nucleoside HIV-1 reverse transcriptase inhibitors with non-identical aromatic rings. *Bioorg. Med Chem.* **10**, 283–90 (2002).
- (7) Himo, F., Lovell, T., Hilgraf, R., Rostovtsev, V. V., Noddleman, L., Sharpless, K. B. & Fokin, V. V. Copper(I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates. *J. Am. Chem. Soc.* **127**, 210–216 (2005).
- (1) Rappoport, D.; Furche, F. Property-Optimized Gaussian Basis Sets for Molecular Response Calculations. *J. Chem. Phys.* **2010**, 133 (13), 134105.
- (2) Andrae, D.; Häußermann, U.; Dolg, M.; Stoll, H.; Preuß, H. Energy-Adjustedab Initio Pseudopotentials for the Second and Third Row Transition Elements. *Theor. Chim. Acta* **1990**, 77 (2), 123–141.
- (3) Weigend, F.; Ahlrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **2005**, 7 (18), 3297–3305.
- (4) Weigend, F. Accurate Coulomb-Fitting Basis Sets for H to Rn. *Phys. Chem. Chem. Phys.* **2006**, 8 (9), 1057–1065.
- (5) Guin, S.; Dolui, P.; Zhang, X.; Paul, S.; Singh, V. K.; Pradhan, S.; Chandrashekhar, H. B.; Anjana, S. S.; Paton, R. S.; Maiti, D. Iterative Arylation of Amino Acids and Aliphatic Amines via  $\delta$ -C(Sp<sup>3</sup>)–H Activation: Experimental and Computational Exploration. *Angew. Chemie - Int. Ed.* **2019**, 58 (17), 5633–5638.
- (6) Landstrom, E. B.; Handa, S.; Aue, D. H.; Gallou, F.; Lipshutz, B. H. EvanPhos: A Ligand for Ppm Level Pd-Catalyzed Suzuki–Miyaura Couplings in Either Organic

- Solvent or Water. *Green Chem.* **2018**, *20* (15), 3436–3443.
- (7) Dandu, N. K.; Reed, J. A.; Odoh, S. O. Performance of Density Functional Theory for Predicting Methane-to-Methanol Conversion by a Tri-Copper Complex. *J. Phys. Chem. C* **2018**, *122* (2), 1024–1036.
- (8) Zhou, T.; Malakar, S.; Webb, S. L.; Krogh-Jespersen, K.; Goldman, A. S. Polar Molecules Catalyze CO Insertion into Metal-Alkyl Bonds through the Displacement of an Agostic C-H Bond. *Proc. Natl. Acad. Sci. U. S. A.* **2019**, *116* (9), 3419–3424.
- (9) Luconi, L.; Demirci, U. B.; Peruzzini, M.; Giambastiani, G.; Rossin, A. Ammonia Borane and Hydrazine Bis(Borane) Dehydrogenation Mediated by an Unsymmetrical (PNN) Ruthenium Pincer Hydride: Metal–Ligand Cooperation for Hydrogen Production. *Sustain. Energy Fuels* **2019**.
- (10) Achar, T. K.; Zhang, X.; Mondal, R.; Shanavas, M. S.; Maiti, S.; Maity, S.; Pal, N.; Paton, R. S.; Maiti, D. Palladium-Catalyzed Directed Meta -Selective C–H Allylation of Arenes: Unactivated Internal Olefins as Allyl Surrogates. *Angew. Chemie Int. Ed.* **2019**, *58*, 2–10.
- (11) Fukui, K. Formulation of the Reaction Coordinate. *J. Phys. Chem.* **2005**, *74* (23), 4161–4163.
- (12) Fukui, K. The Path of Chemical Reactions - The IRC Approach. *Acc. Chem. Res.* **1981**, *14* (12), 363–368.
- (13) Grimme, S. Supramolecular Binding Thermodynamics by Dispersion-Corrected Density Functional Theory. *Chem. - A Eur. J.* **2012**, *18* (32), 9955–9964.
- (14) Funes-Ardoiz, I.; Paton, R. S. GoodVibes v1.0.1 <http://doi.org/10.5281/zenodo.56091>.
- (15) Sosa, C.; Andzelm, J.; Elkin, B. C.; Wimmer, E.; Dobbs, K. D.; Dixon, D. A. A Local Density Functional Study of the Structure and Vibrational Frequencies of Molecular Transition-Metal Compounds. *J. Phys. Chem.* **1992**, *96* (16), 6630–6636.
- (16) Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E. Optimization of Gaussian-Type Basis Sets for Local Spin Density Functional Calculations. Part I. Boron through

Neon, Optimization Technique and Validation. *Can. J. Chem.* **1992**, *70* (2), 560–571.

- (17) Dang, Y.; Qu, S.; Nelson, J. W.; Pham, H. D.; Wang, Z. X.; Wang, X. The Mechanism of a Ligand-Promoted C(Sp<sub>3</sub>)-H Activation and Arylation Reaction via Palladium Catalysis: Theoretical Demonstration of a Pd(II)/Pd(IV) Redox Manifold. *J. Am. Chem. Soc.* **2015**, *137* (5), 2006–2014.
- (18) Weibel, J.-M.; Blanc, A.; Pale, P. Ag-Mediated Reactions: Coupling and Heterocyclization Reactions. *Chem. Rev.* **2008**, *108* (8), 3149–3173.
- (19) Daugulis, O.; Do, H. Q.; Shabashov, D. Palladium- and Copper-Catalyzed Arylation of Carbon-Hydrogen Bonds. *Acc. Chem. Res.* **2009**, *42* (8), 1074–1086.
- (20) Chen, X.; Engle, K. M.; Wang, D. H.; Jin-Quan, Y. Palladium(II)-Catalyzed C-H Activation/C-C Cross-Coupling Reactions: Versatility and Practicality. *Angew. Chemie - Int. Ed.* **2009**, *48* (28), 5094–5115.
- (21) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions. *Chem. Rev.* **2010**, *110* (2), 1147–1169.
- (22) Lotz, M. D.; Camasso, N. M.; Canty, A. J.; Sanford, M. S. Role of Silver Salts in Palladium-Catalyzed Arene and Heteroarene C–H Functionalization Reactions. *Organometallics* **2017**, *36* (1), 165–171.
- (23) Masui, K.; Ikegami, H.; Mori, A. Palladium-Catalyzed C–H Homocoupling of Thiophenes: Facile Construction of Bithiophene Structure. *J. Am. Chem. Soc.* **2004**, *126* (16), 5074–5075.
- (24) Stuart, D. R.; Villemure, E.; Fagnou, K. Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene Cross-Coupling. *J. Am. Chem. Soc.* **2007**, *129* (40), 12072–12073.
- (25) Hull, K. L.; Sanford, M. S. Catalytic and Highly Regioselective Cross-Coupling of Aromatic C–H Substrates. *J. Am. Chem. Soc.* **2007**, *129* (39), 11904–11905.
- (26) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. Oxidant-Controlled Regioselectivity in the Oxidative Arylation of N-

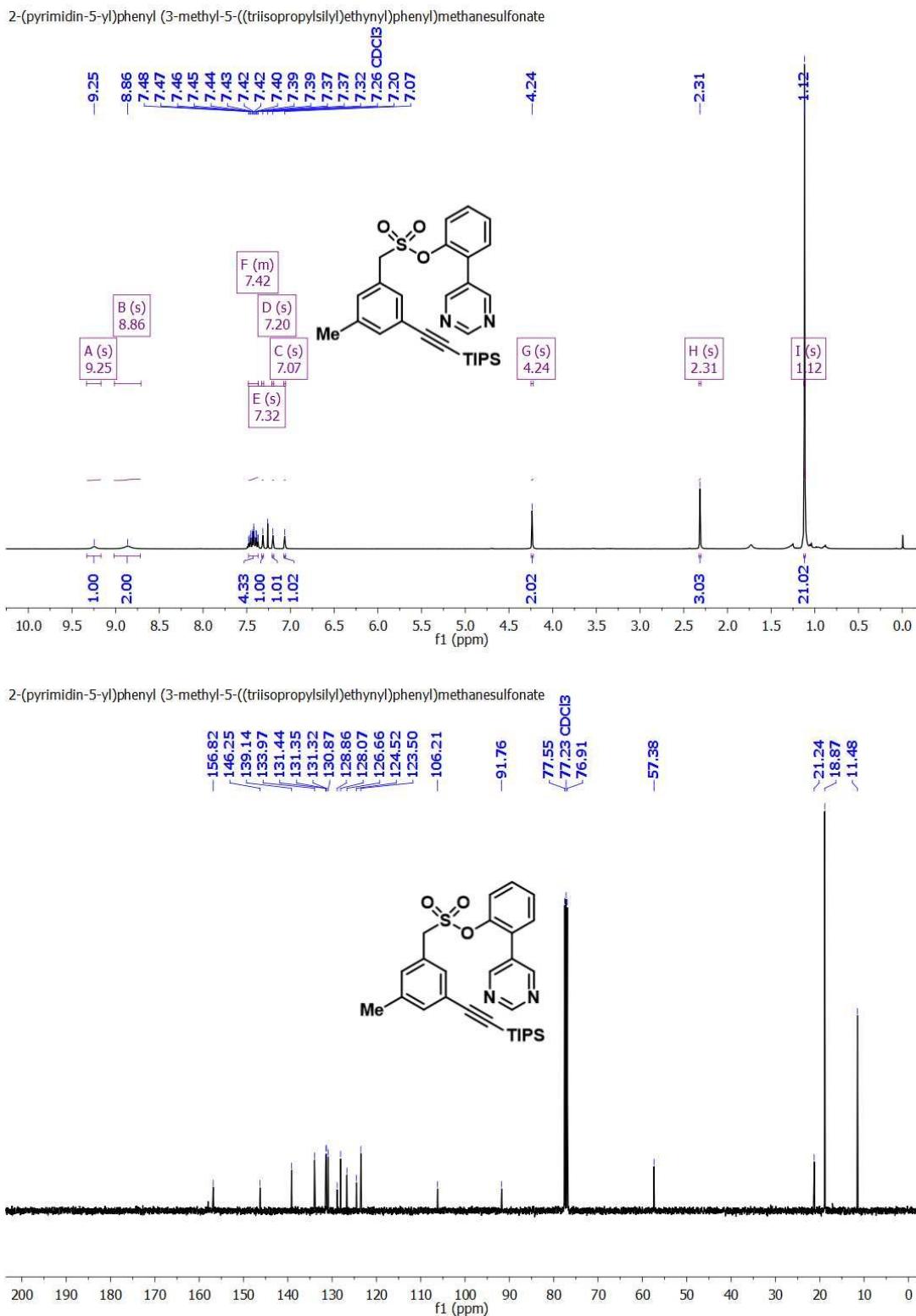
- Acetylindoles. *Tetrahedron Lett.* **2008**, *49* (25), 4050–4053.
- (27) Anand, M.; Sunoj, R. B.; Schaefer, H. F. Non-Innocent Additives in a Palladium(II)-Catalyzed C–H Bond Activation Reaction: Insights into Multimetallic Active Catalysts. *J. Am. Chem. Soc.* **2014**, *136* (15), 5535–5538.
- (28) Li, H.; Liu, J.; Sun, C. L.; Li, B. J.; Shi, Z. J. Palladium-Catalyzed Cross-Coupling of Polyfluoroarenes with Simple Arenes. *Org. Lett.* **2011**, *13* (2), 276–279.
- (29) Wang, G. W.; Zhou, A. X.; Li, S. X.; Yang, S. D. Regio- and Stereoselective Allylic C-H Arylation with Electron-Deficient Arenes by 1,1'-Bi-2-Naphthol-Palladium Cooperation. *Org. Lett.* **2014**, *16* (11), 3118–3121.
- (30) Preciado, S.; Mendive-Tapia, L.; Albericio, F.; Lavilla, R. Synthesis of C-2 Arylated Tryptophan Amino Acids and Related Compounds through Palladium-Catalyzed C-H Activation. *J. Org. Chem.* **2013**, *78* (16), 8129–8135.
- (31) Paramonov, S. E.; Mychlo, E. V.; Troyanov, S. I.; Kuz'mina, N. P. Synthesis and Thermal Stability of Silver Carboxylates: Crystal Structure of Silver Pivalate. *Russ. J. Inorg. Chem.* **2000**, *45* (12), 1852–1856.
- (32) Olson, L. P.; Whitcomb, D. R.; Rajeswaran, M.; Blanton, T. N.; Stwertka, B. J. The Simple yet Elusive Crystal Structure of Silver Acetate and the Role of the Ag - Ag Bond in the Formation of Silver Nanoparticles during the Thermally Induced Reduction of Silver Carboxylates. *Chem. Mater.* **2006**, *18* (6), 1667–1674.
- (33) Schmidbaur, H.; Schier, A. Argentophilic Interactions. *Angew. Chemie - Int. Ed.* **2015**, *54* (3), 746–784.
- (34) Taguchi, H.; Miyashita, H.; Tsubouchi, A.; Takeda, T. First Anionic Silyl Migration from Sp<sub>2</sub> Carbon to Carbonyl Oxygen. Stereospecific Allylation of (Z)-β-Trimethylsilyl-α,β-Unsaturated Ketones. *Chem. Commun.* **2002**, *2* (19), 2218–2219.
- (35) Tsubouchi, A.; Sasaki, N.; Enatsu, S.; Takeda, T. Regio- and Stereoselective Preparation of (Z)-Silyl Enol Ethers by Three-Component Coupling Using α,β-Unsaturated Acylsilanes as Core Building Blocks. *Tetrahedron Lett.* **2013**, *54* (10), 1264–1267.

- (36) Tsubouchi, A.; Matsuda, H.; Kira, T.; Takeda, T. Silyl Migration in Conjunction with Substitution on Silicon in Copper(I) t -Butoxide-Promoted Coupling between o -Silylphenyl Ketones and Organic Halides. *Chem. Lett.* **2009**, *38* (12), 1180–1181.
- (37) Wheeler, S. E.; Houk, K. N.; Schleyer, P. V. R.; Allen, W. D. A Hierarchy of Homodesmotic Reactions for Thermochemistry. *J. Am. Chem. Soc.* **2009**, *131* (7), 2547–2560.
- (38) Wheeler, S. E. Homodesmotic Reactions for Thermochemistry. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2012**, *2* (2), 204–220.
- (39) Zhang, X.; Lu, G.; Sun, M.; Mahankali, M.; Ma, Y.; Zhang, M.; Hua, W.; Hu, Y.; Wang, Q.; Chen, J.; et al. A General Strategy for Synthesis of Cyclophane-Braced Peptide Macrocycles via Palladium-Catalysed Intramolecular Sp 3 C-H Arylation. *Nat. Chem.* **2018**, *10* (5), 540–548.
- (40) Holganza, M. K.; Trigoura, L.; Elfarra, S.; Seo, Y.; Oiler, J.; Xing, Y. Copper (II) Catalyzed Homocoupling and Heterocoupling of Terminal Alkynes. *Tetrahedron Lett.* **2019**, *60* (17), 1179–1181.
- (41) Bai, R.; Zhang, G.; Yi, H.; Huang, Z.; Qi, X.; Liu, C.; Miller, J. T.; Kropf, A. J.; Bunel, E. E.; Lan, Y.; et al. Cu(II)-Cu(I) Synergistic Cooperation to Lead the Alkyne C-H Activation. *J. Am. Chem. Soc.* **2014**, *136* (48), 16760–16763.
- (42) Zuidema, E.; Bolm, C. Sub-Mol % Catalyst Loading and Ligand-Acceleration in the Coppercatalyzed Coupling of Aryl Iodides and Terminal Alkyenes. *Chem. - A Eur. J.* **2010**, *16* (14), 4181–4185.
- (43) Zou, L. H.; Johansson, A. J.; Zuidema, E.; Bolm, C. Mechanistic Insights into Copper-Catalyzed Sonogashira-Hagihara-Type Cross-Coupling Reactions: Sub-Mol % Catalyst Loadings and Ligand Effects. *Chem. - A Eur. J.* **2013**, *19* (25), 8144–8152.
- (44) He, C.; Ke, J.; Xu, H.; Lei, A. Synergistic Catalysis in the Sonogashira Coupling Reaction: Quantitative Kinetic Investigation of Transmetalation. *Angew. Chemie - Int. Ed.* **2013**, *52* (5), 1527–1530.
- (45) Zhang, G.; Yi, H.; Zhang, G.; Deng, Y.; Bai, R.; Zhang, H.; Miller, J. T.; Kropf, A. J.;

- Bunel, E. E.; Lei, A. Direct Observation of Reduction of Cu(II) to Cu(I) by Terminal Alkynes. *J. Am. Chem. Soc.* **2014**, *136* (3), 924–926.
- (46) Shimizu, T.; Morisako, S.; Yamamoto, Y.; Kawachi, A. 1,2-Silyl Migration in 1-Halonaphthalenes Catalyzed by I<sub>2</sub>. *Heteroat. Chem.* **2018**, *29* (4), e21434.
- (47) Barczak, N. T.; Rooke, D. A.; Menard, Z. A.; Ferreira, E. M. Stereoselective Synthesis of Tetrasubstituted Olefins through a Halogen-Induced 1,2-Silyl Migration. *Angew. Chemie Int. Ed.* **2013**, *52* (29), 7579–7582.
- (48) Zhao, R.; Zhang, R. Q. A New Insight into  $\pi$ - $\pi$  Stacking Involving Remarkable Orbital Interactions. *Phys. Chem. Chem. Phys.* **2016**, *18* (36), 25452–25457.
- (49) Zhao, R.; Zhang, R. Q. Intermolecular Orbital Interaction in  $\pi$  Systems. *Mol. Phys.* **2018**, *116* (7–8), 978–986.
- (50) Neel, A. J.; Hilton, M. J.; Sigman, M. S.; Toste, F. D. Exploiting Non-Covalent  $\pi$  Interactions for Catalyst Design. *Nature* **2017**, *543* (7647), 637–646.
- (51) Yamada, S. Cation- $\pi$  Interactions in Organic Synthesis. *Chem. Rev.* **2018**, *118* (23), 11353–11432.
- (52) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. Palladium(II)-Catalyzed Oxidative C-H/C-H Cross-Coupling of Heteroarenes. *J. Am. Chem. Soc.* **2010**, *132* (6), 1822–1824.
- (53) Martínez, Á. M.; Alonso, I.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. Rhodium-Catalyzed Copper-Assisted Intermolecular Domino C–H Annulation of 1,3-Diynes with Picolinamides: Access to Pentacyclic  $\Pi$ -Extended Systems. *Chem. – A Eur. J.* **2019**, *25* (22), 5733–5742.
- (54) Funes-Ardoiz, I.; Maseras, F. Computational Characterization of the Mechanism for the Oxidative Coupling of Benzoic Acid and Alkynes by Rhodium/Copper and Rhodium/Silver Systems. *Chem. - A Eur. J.* **2018**, *24* (47), 12383–12388.
- (55) Funes-Ardoiz, I.; Maseras, F. Cooperative Reductive Elimination: The Missing Piece in the Oxidative-Coupling Mechanistic Puzzle. *Angew. Chemie - Int. Ed.* **2016**, *55* (8),

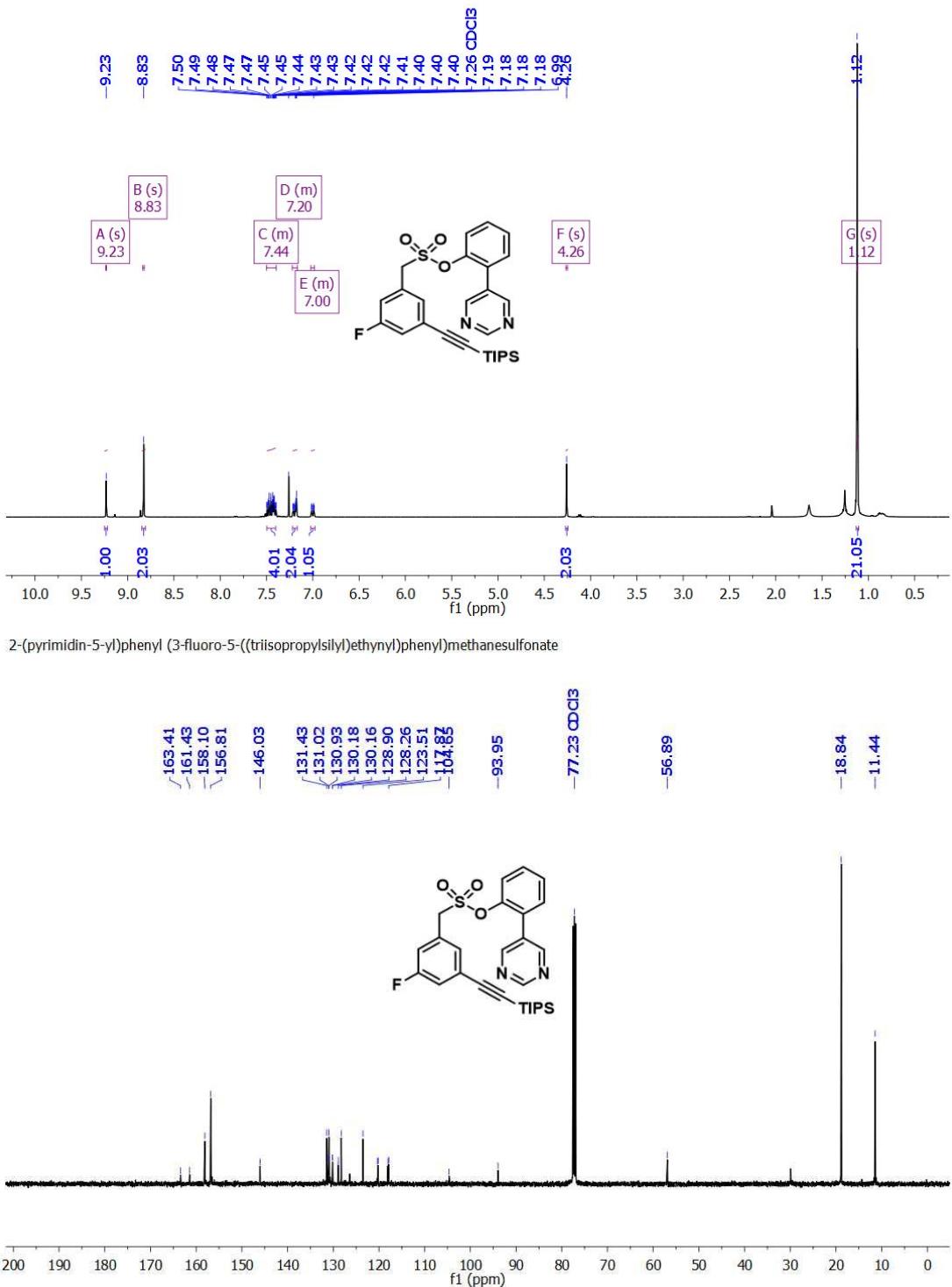
2764–2767.

- (56) Usui, K.; Haines, B. E.; Musaev, D. G.; Sarpong, R. Understanding Regiodivergence in a Pd(II)-Mediated Site-Selective C-H Alkynylation. *ACS Catal.* **2018**, *8* (5), 4516–4527.



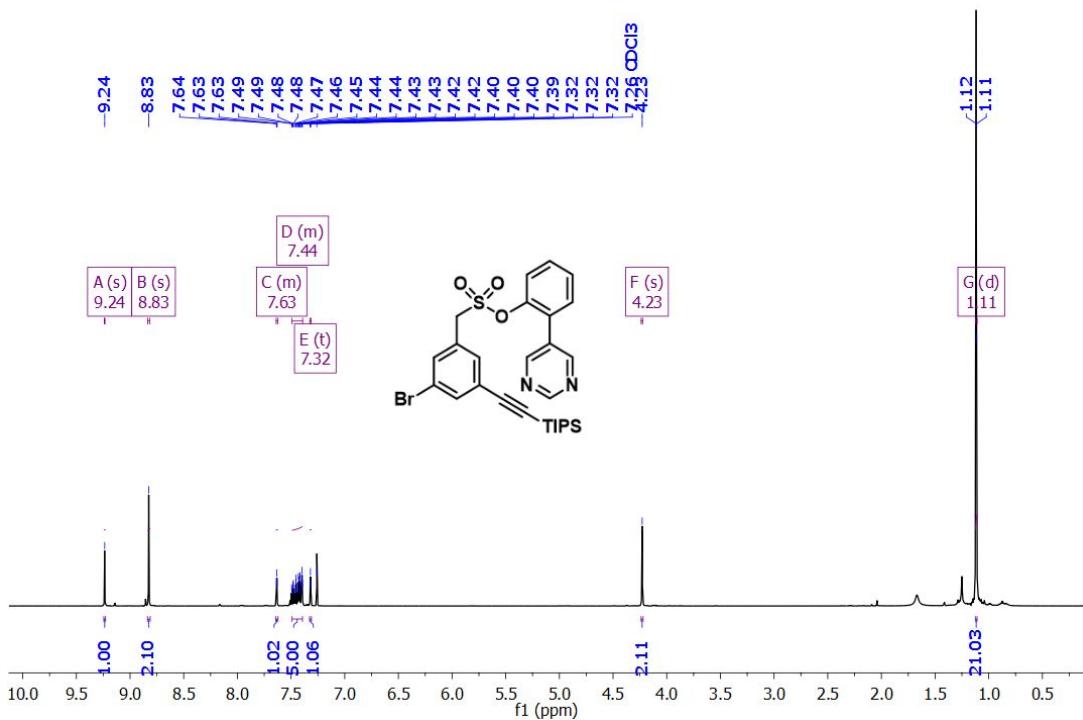
**Figure S31.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **1**

2-(pyrimidin-5-yl)phenyl (3-fluoro-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

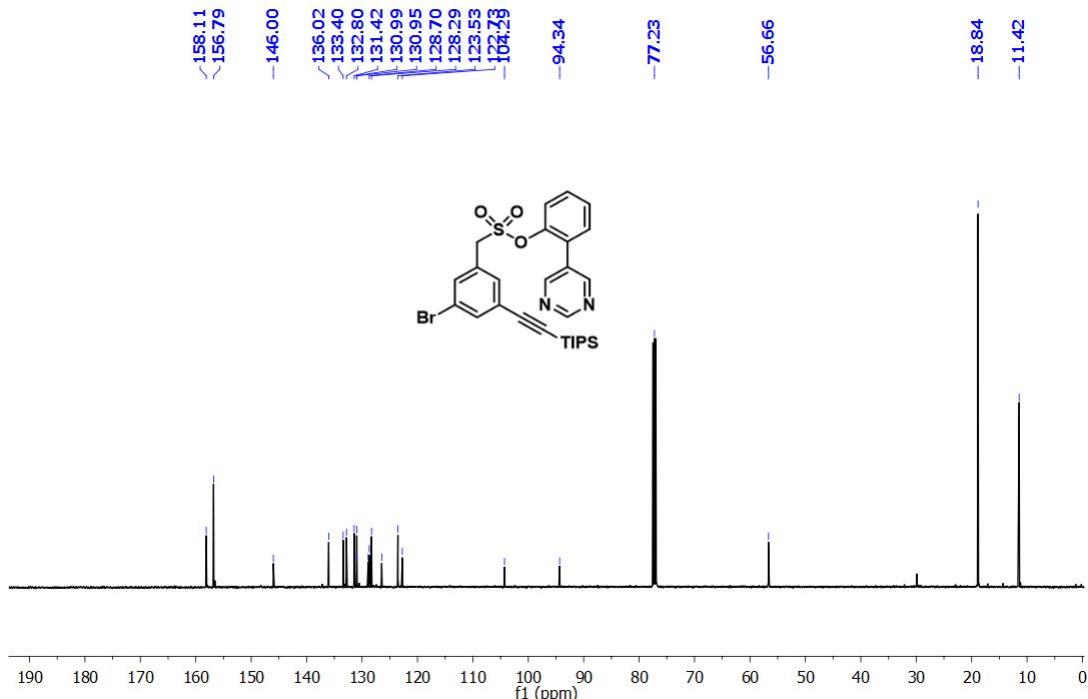


**Figure S32.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **2**

2-(pyrimidin-5-yl)phenyl (3-bromo-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

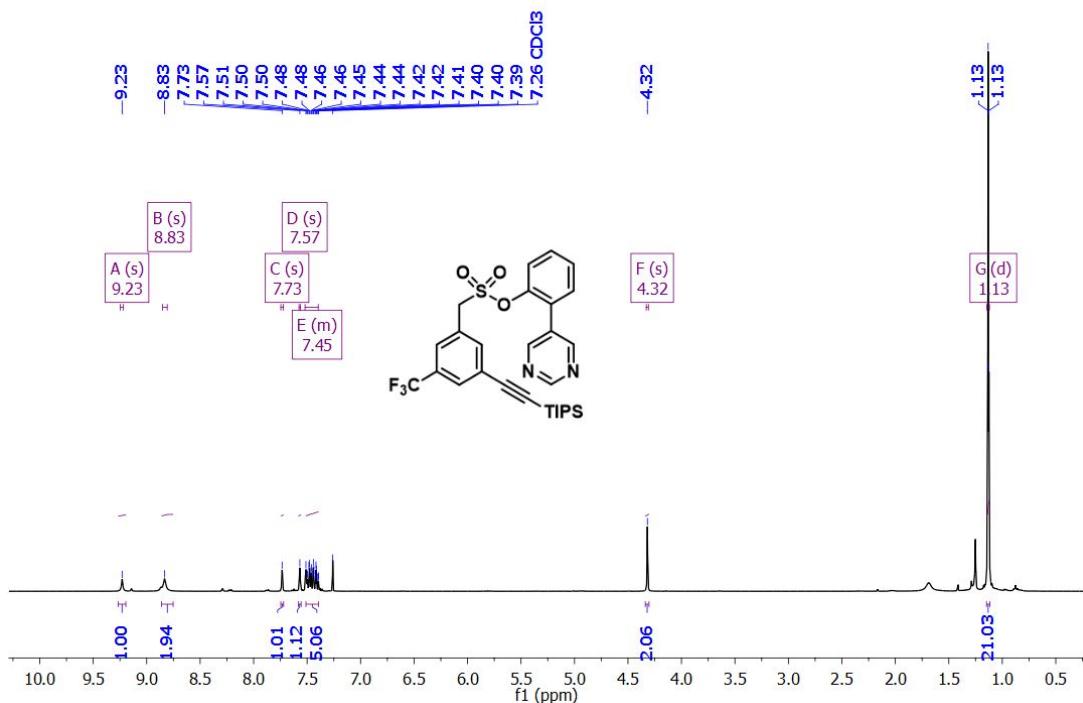


2-(pyrimidin-5-yl)phenyl (3-bromo-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

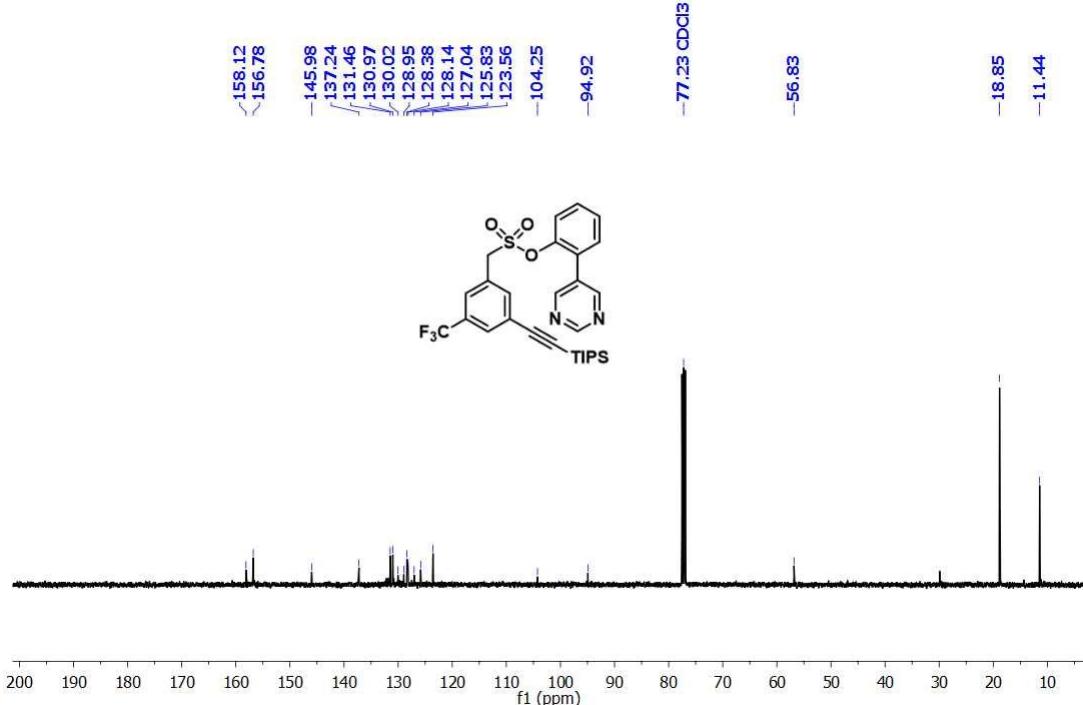


**Figure S33.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **3**

2-(pyrimidin-5-yl)phenyl (3-(trifluoromethyl)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

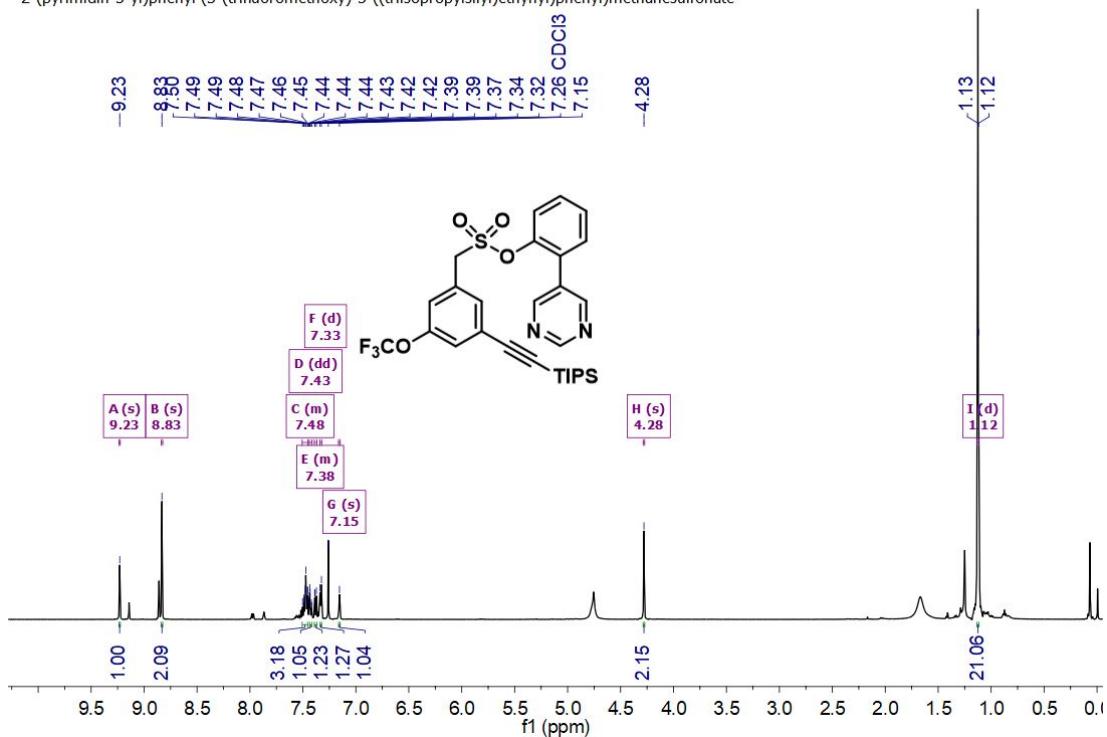


2-(pyrimidin-5-yl)phenyl (3-(trifluoromethyl)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

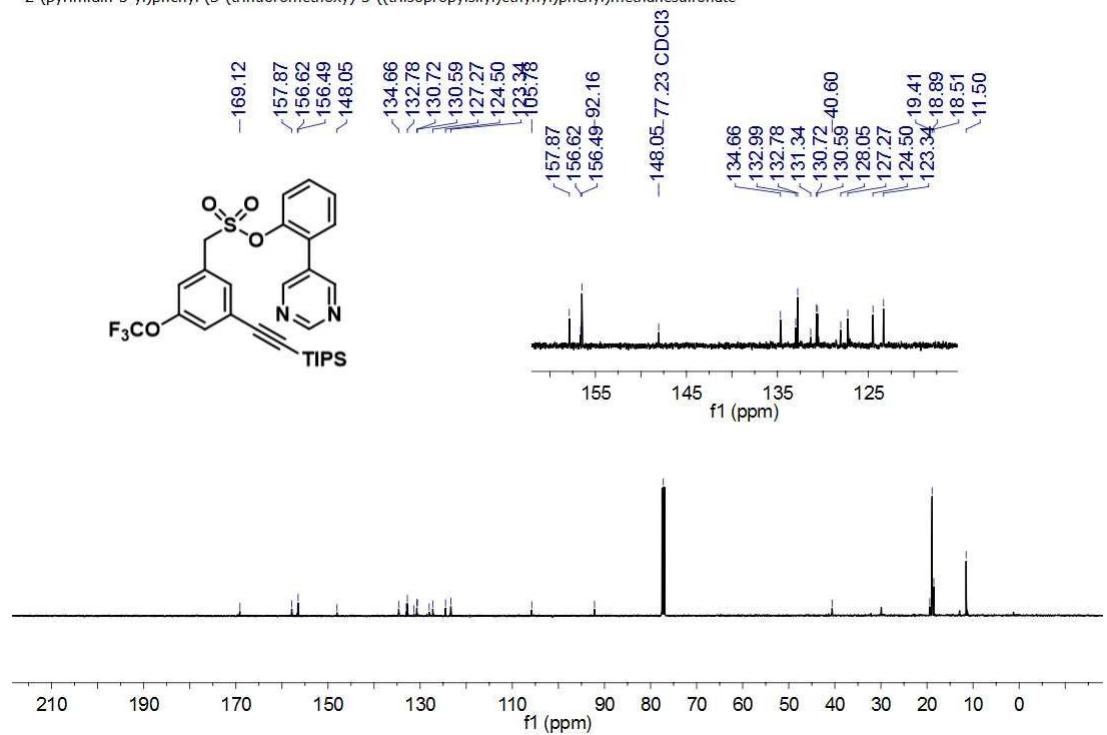


**Figure S34.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of 4

2-(pyrimidin-5-yl)phenyl (3-(trifluoromethoxy)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

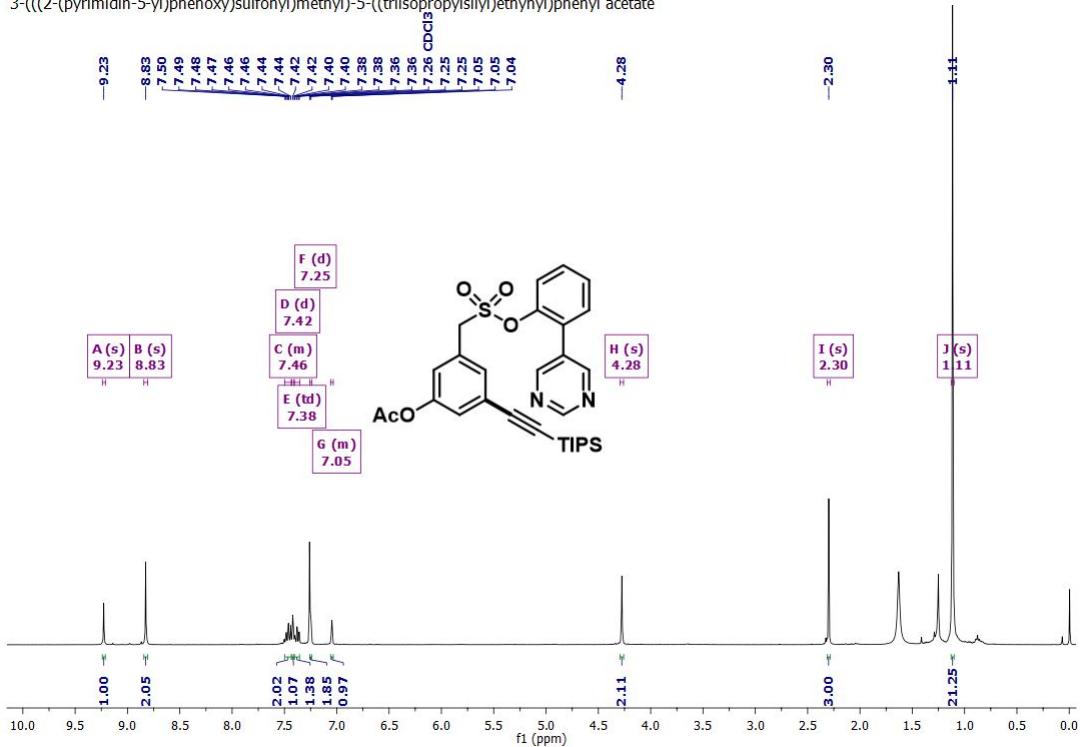


2-(pyrimidin-5-yl)phenyl (3-(trifluoromethoxy)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

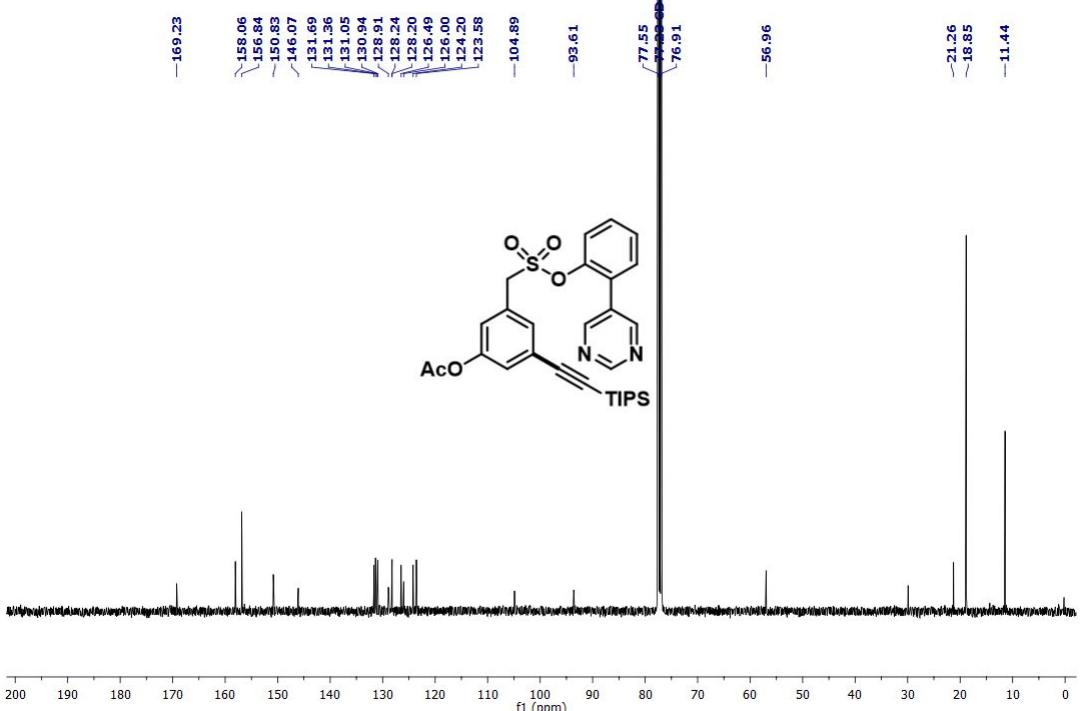


**Figure S35.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **5**

3-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)-5-((triisopropylsilyl)ethynyl)phenyl acetate

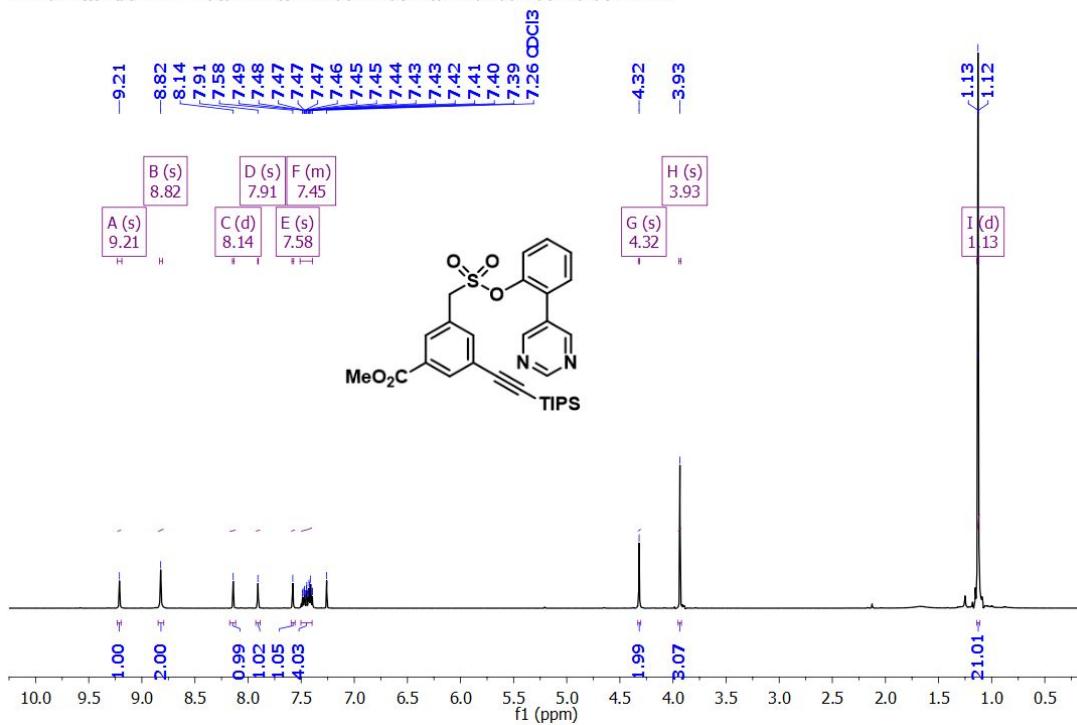


3-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)-5-((triisopropylsilyl)ethynyl)phenyl acetate



**Figure S36.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **6**

methyl 3-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)-5-((triisopropylsilyl)ethynyl)benzoate



methyl 3-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)-5-((triisopropylsilyl)ethynyl)benzoate

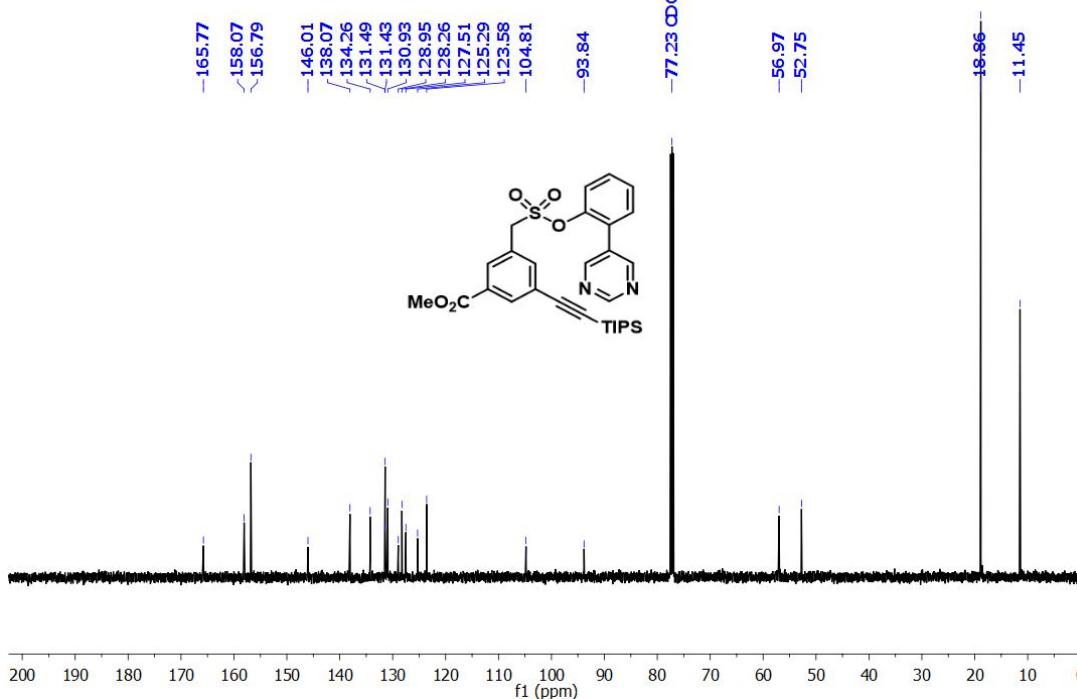
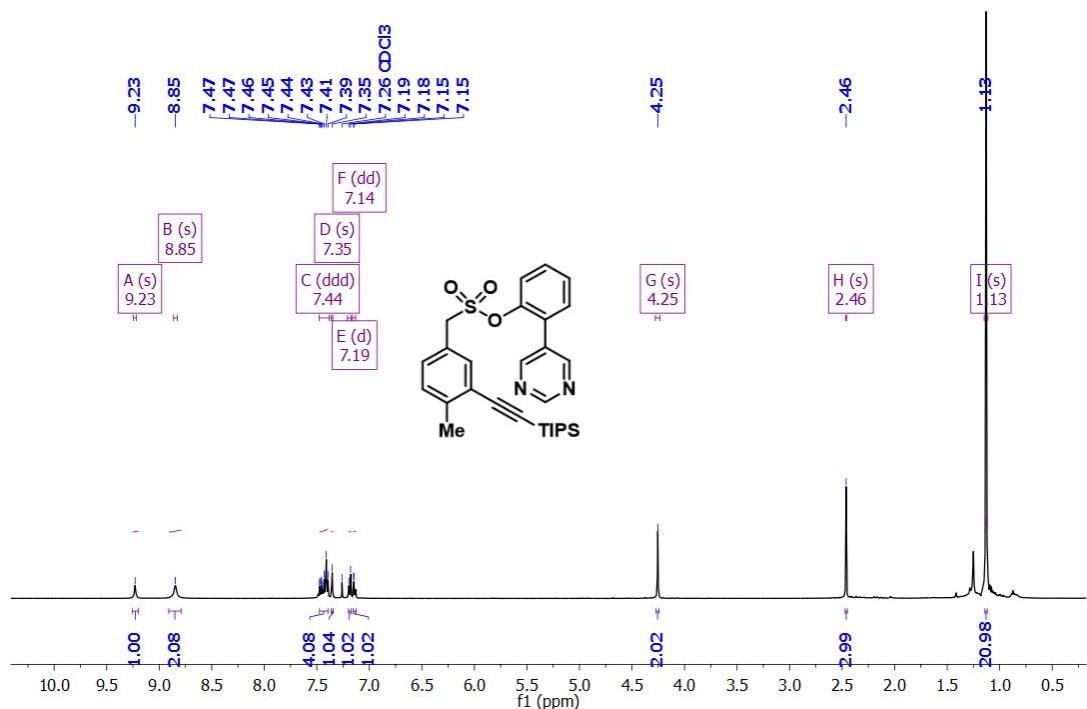
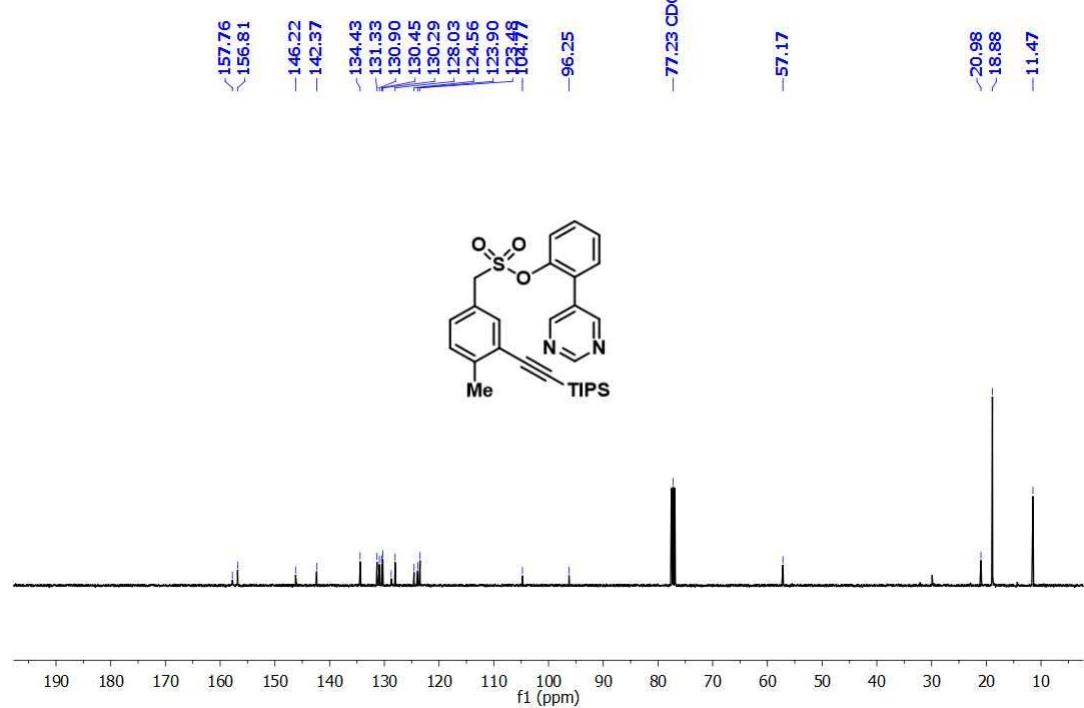


Figure S37. <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of 7

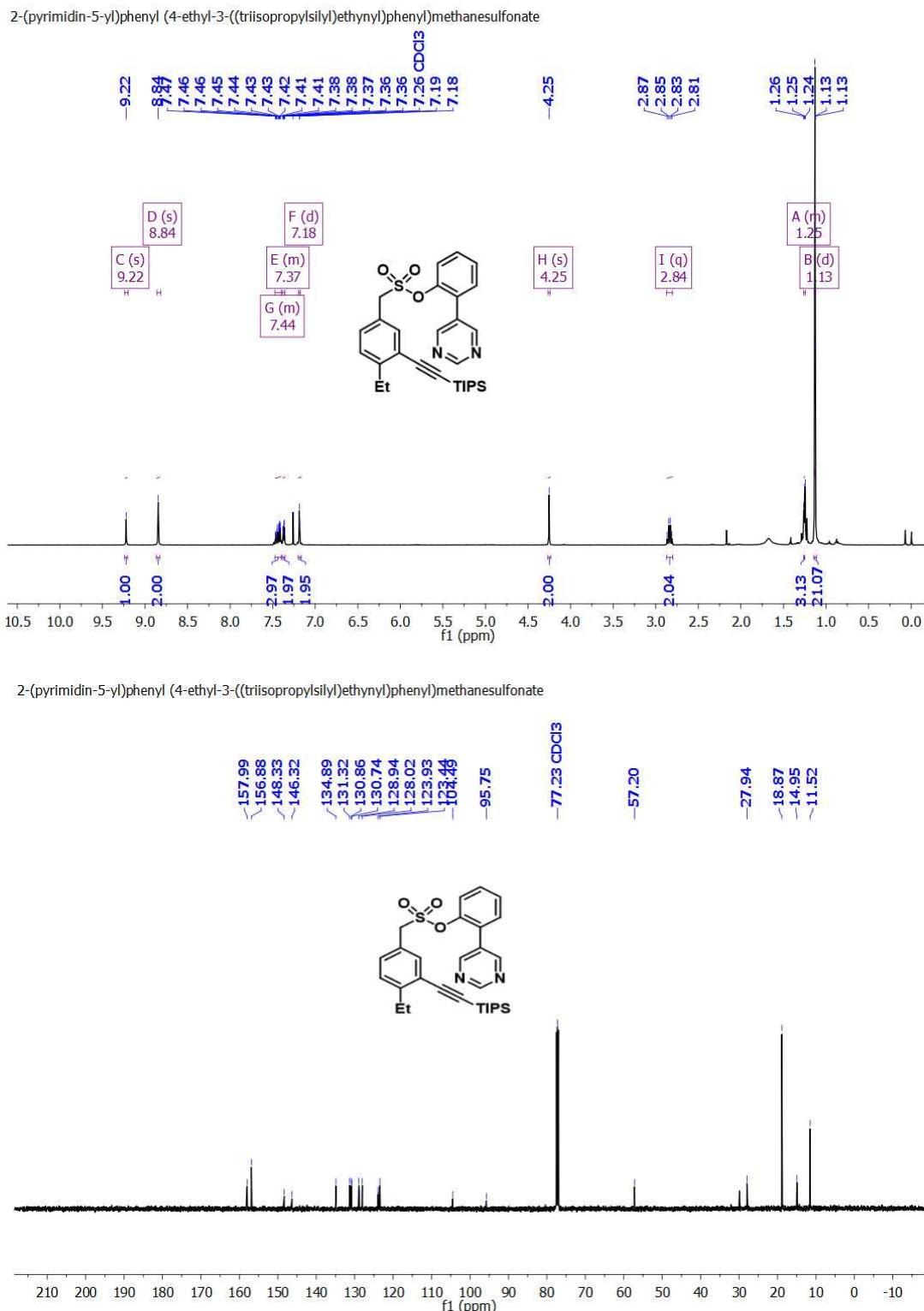
2-(pyrimidin-5-yl)phenyl (4-methyl-3-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate



2-(pyrimidin-5-yl)phenyl (4-methyl-3-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

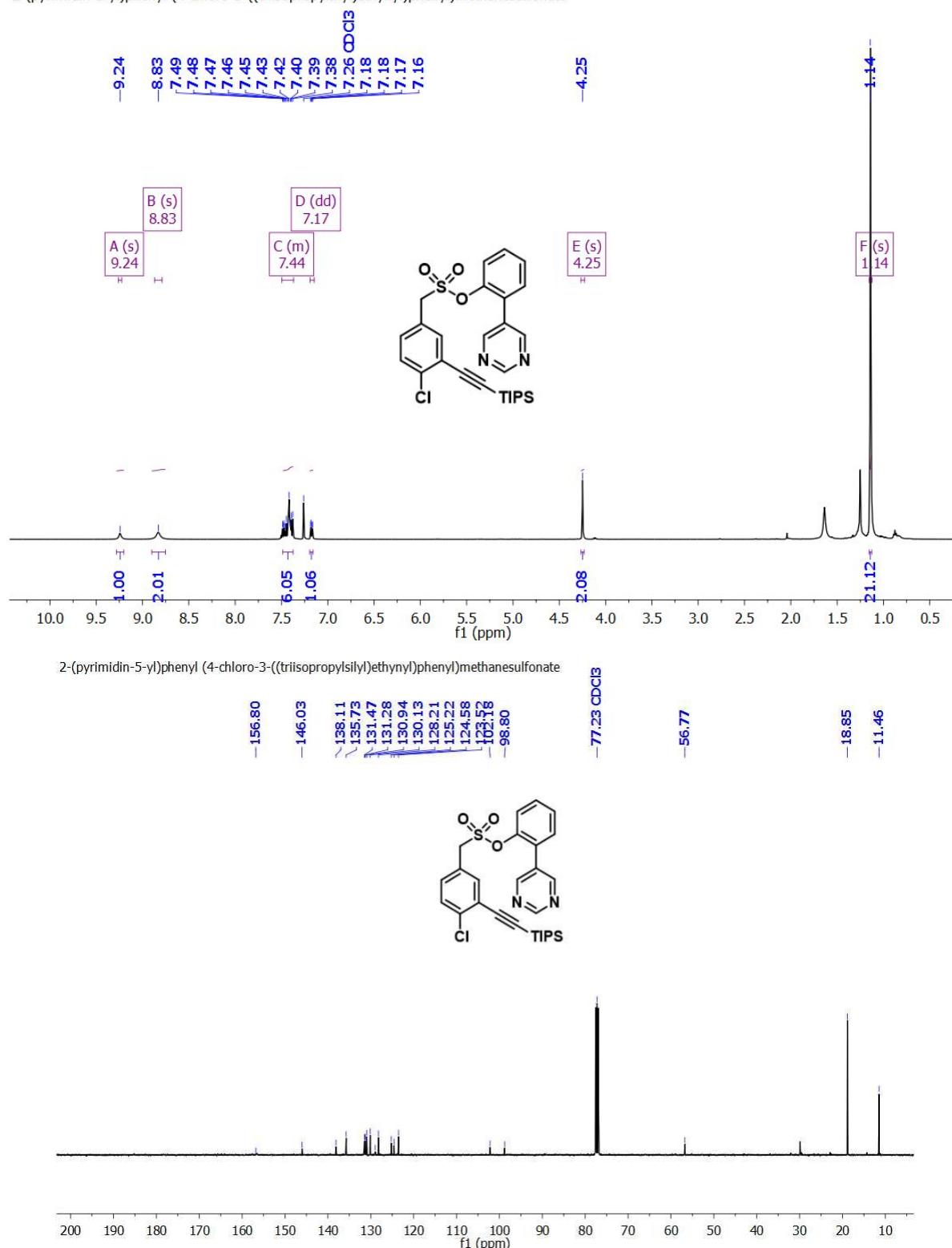


**Figure S38.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **8**



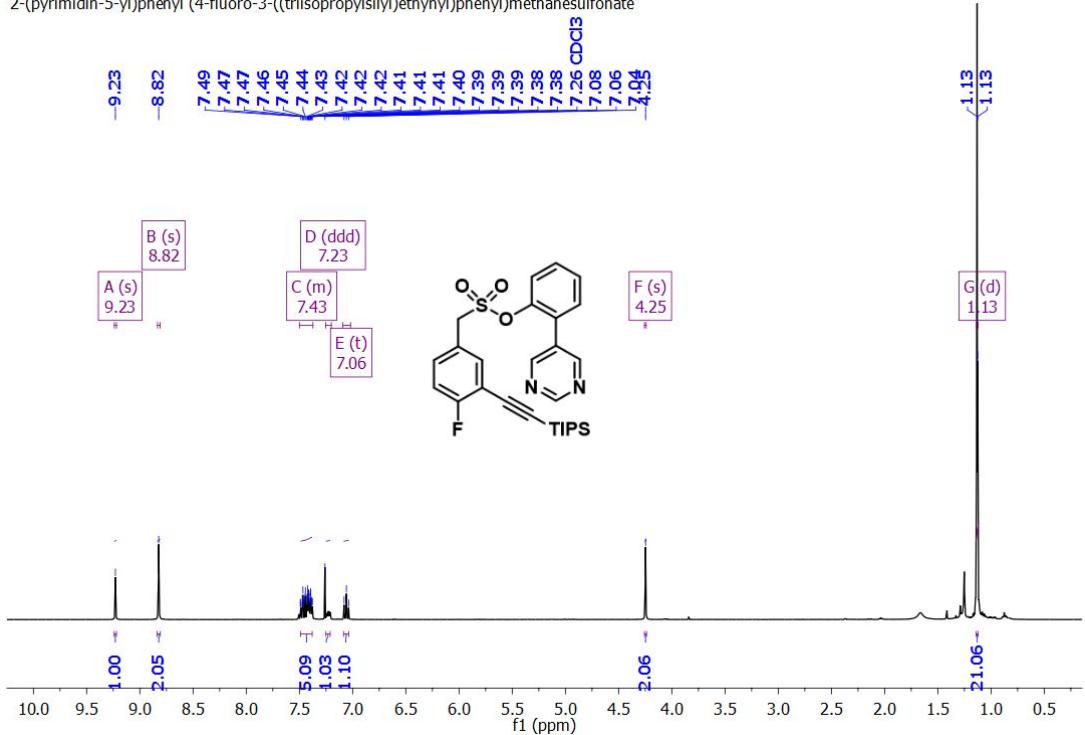
**Figure S39.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **9**

2-(pyrimidin-5-yl)phenyl (4-chloro-3-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

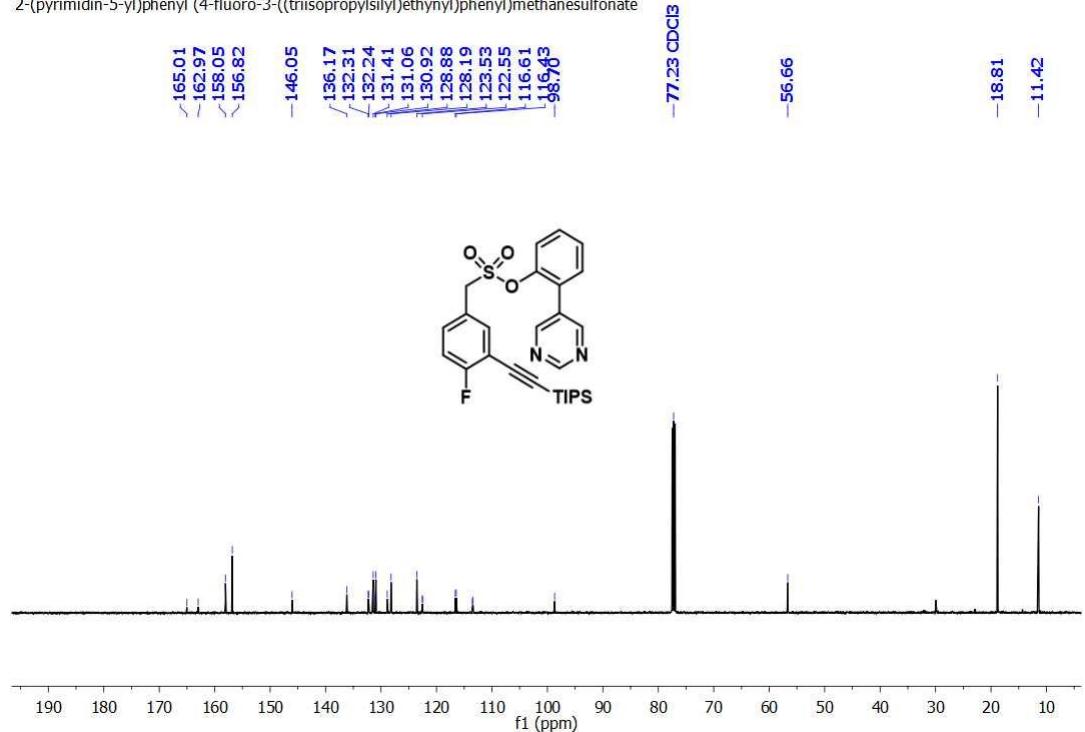


**Figure S40.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **10**

2-(pyrimidin-5-yl)phenyl (4-fluoro-3-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

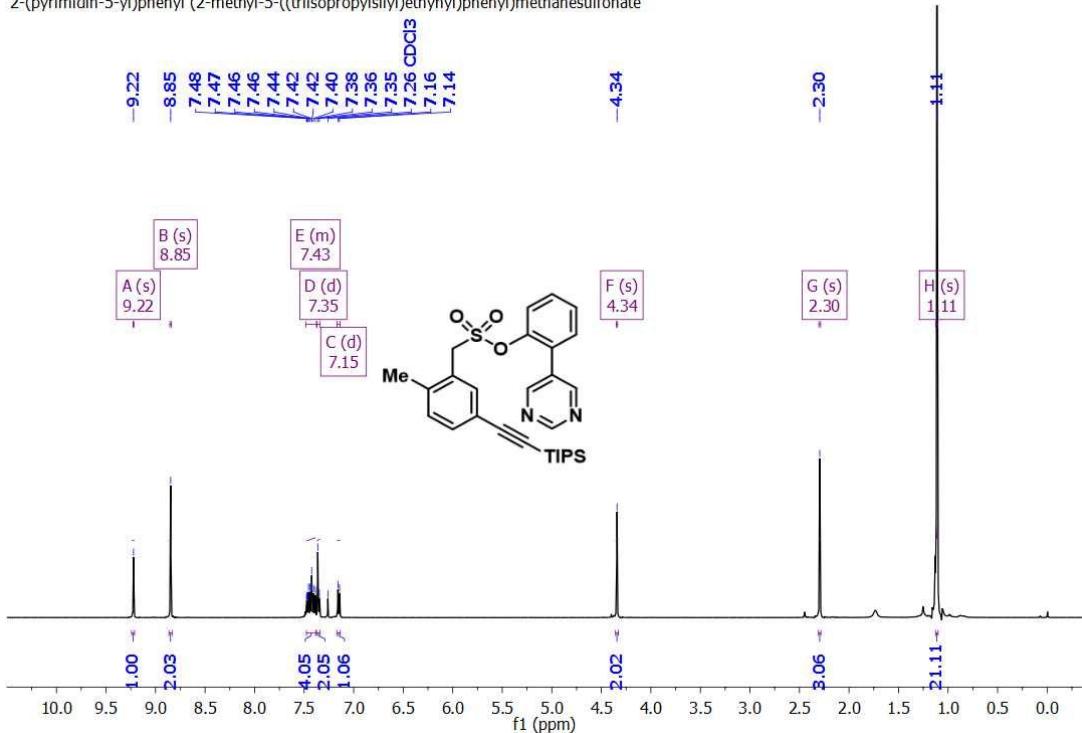


2-(pyrimidin-5-yl)phenyl (4-fluoro-3-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

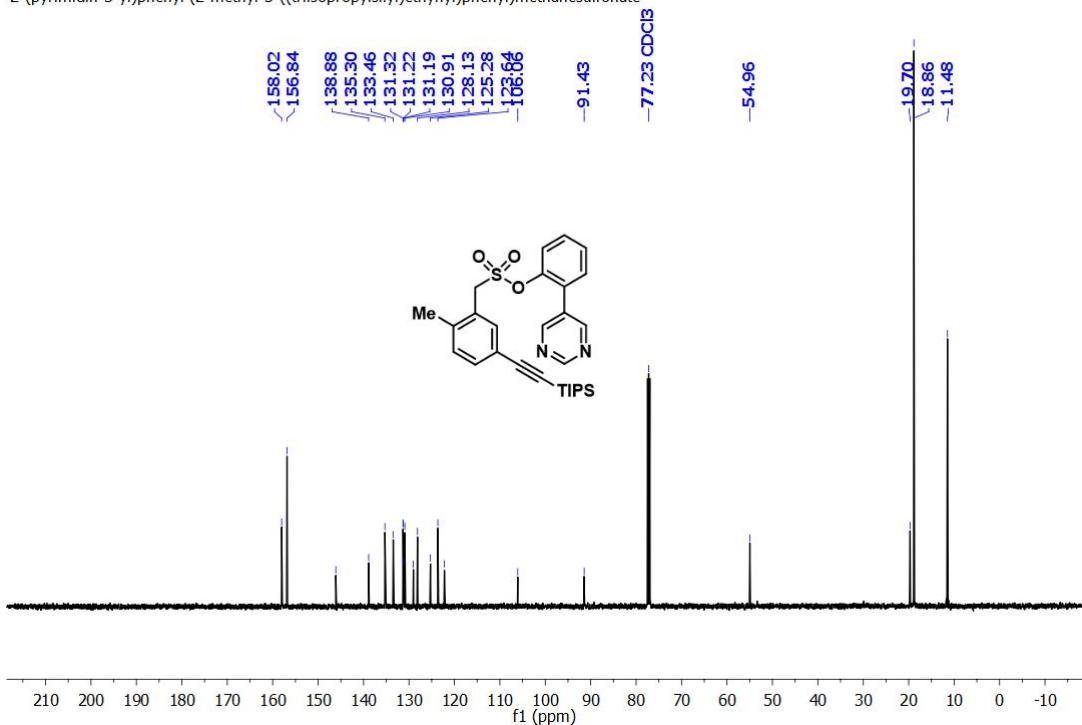


**Figure S41.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **11**

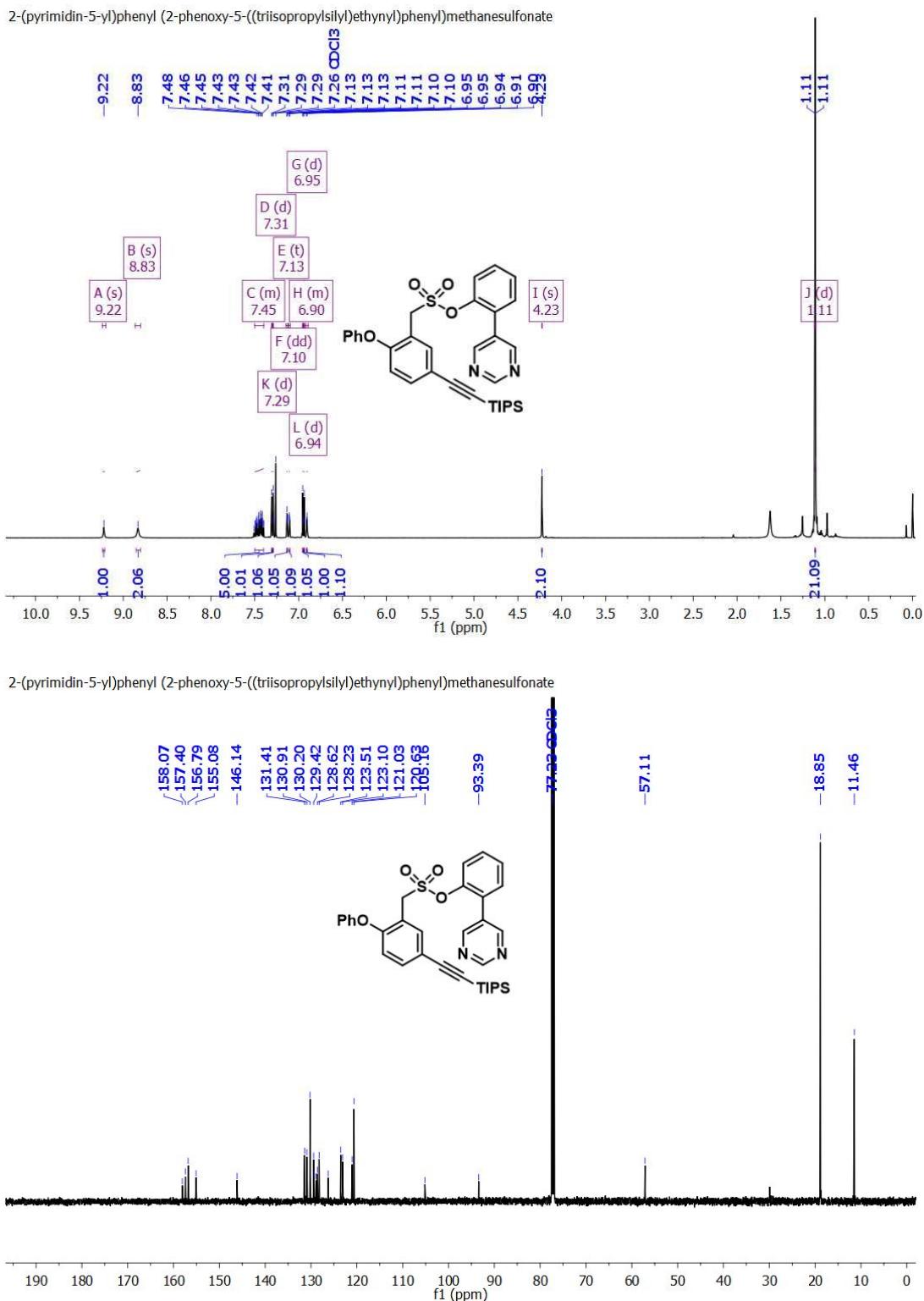
2-(pyrimidin-5-yl)phenyl (2-methyl-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate



2-(pyrimidin-5-yl)phenyl (2-methyl-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

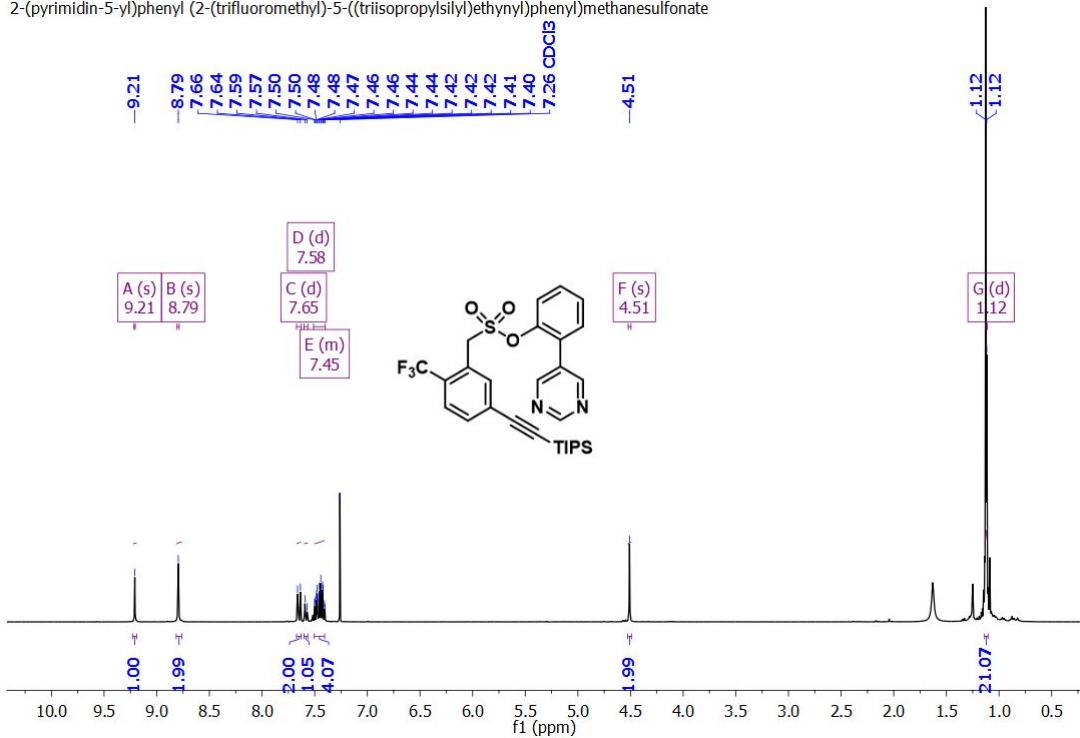


**Figure S42.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **12**

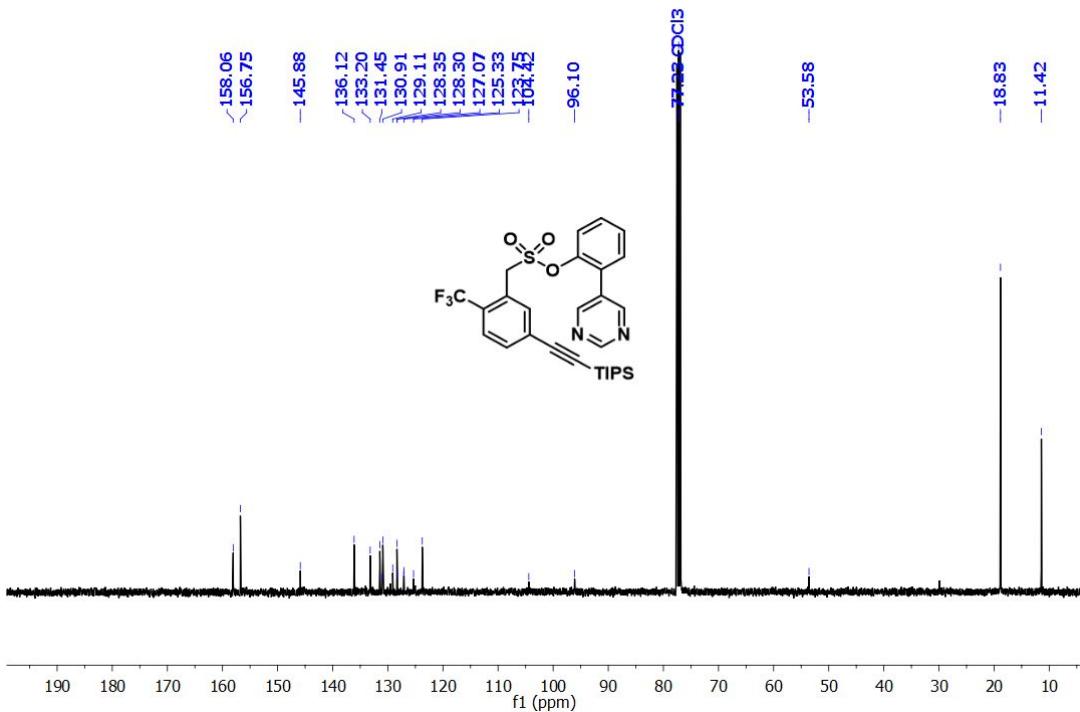


**Figure S43.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **13**

2-(pyrimidin-5-yl)phenyl (2-(trifluoromethyl)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

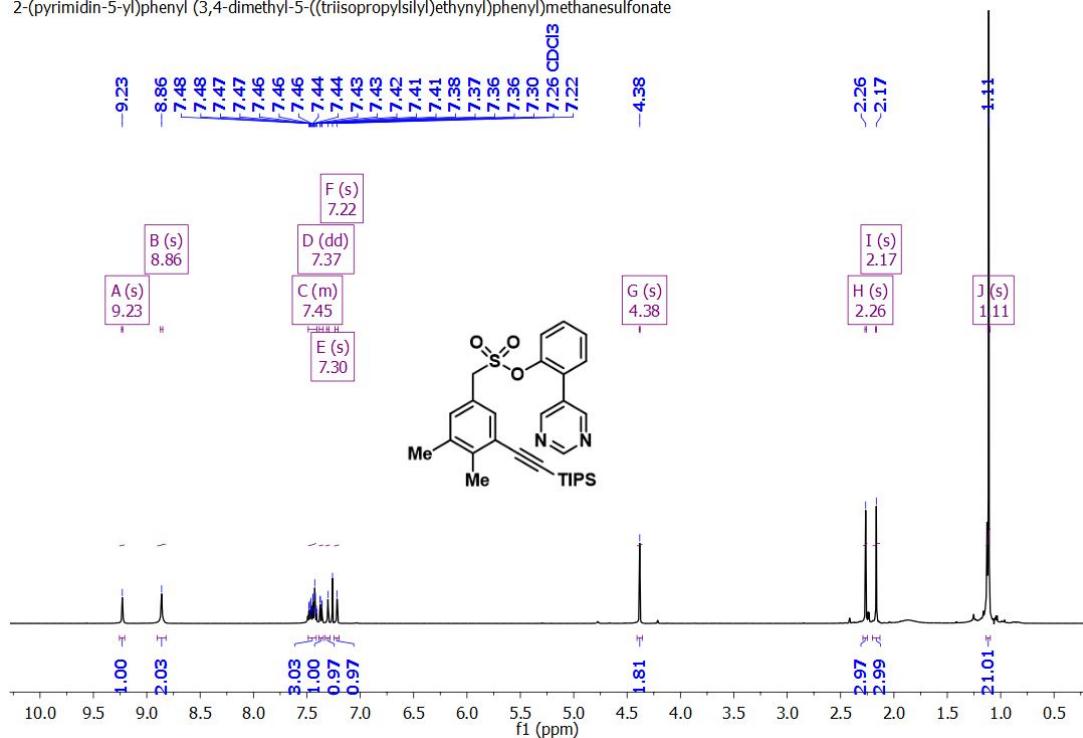


2-(pyrimidin-5-yl)phenyl (2-(trifluoromethyl)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

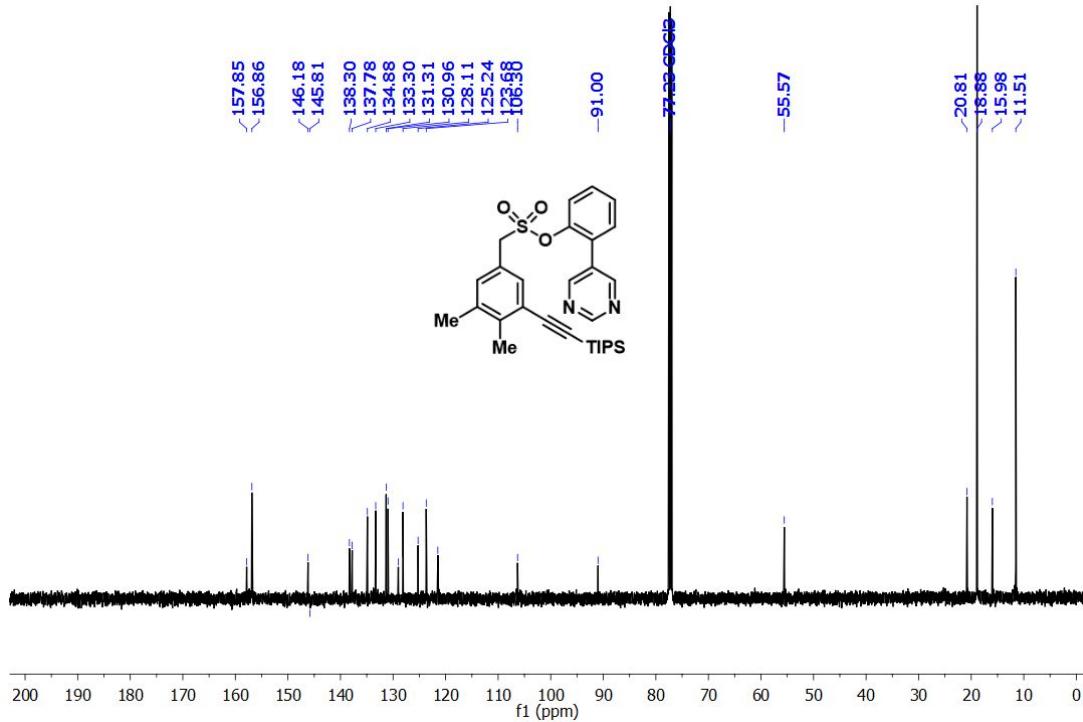


**Figure S44.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **14**

2-(pyrimidin-5-yl)phenyl (3,4-dimethyl-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

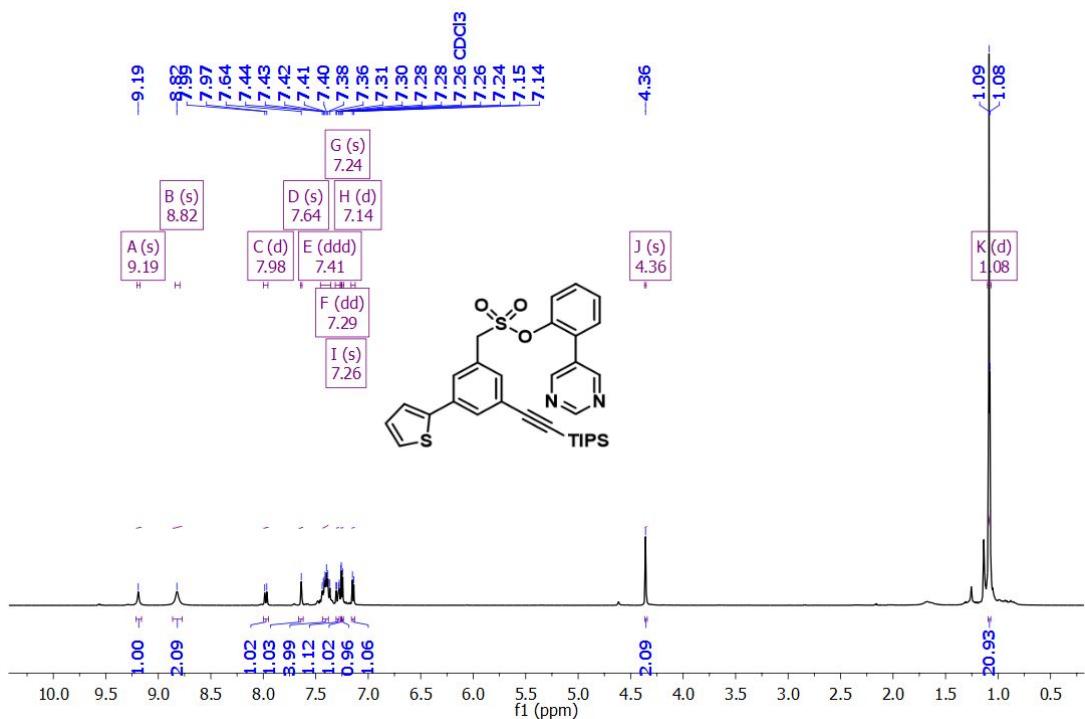


2-(pyrimidin-5-yl)phenyl (3,4-dimethyl-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

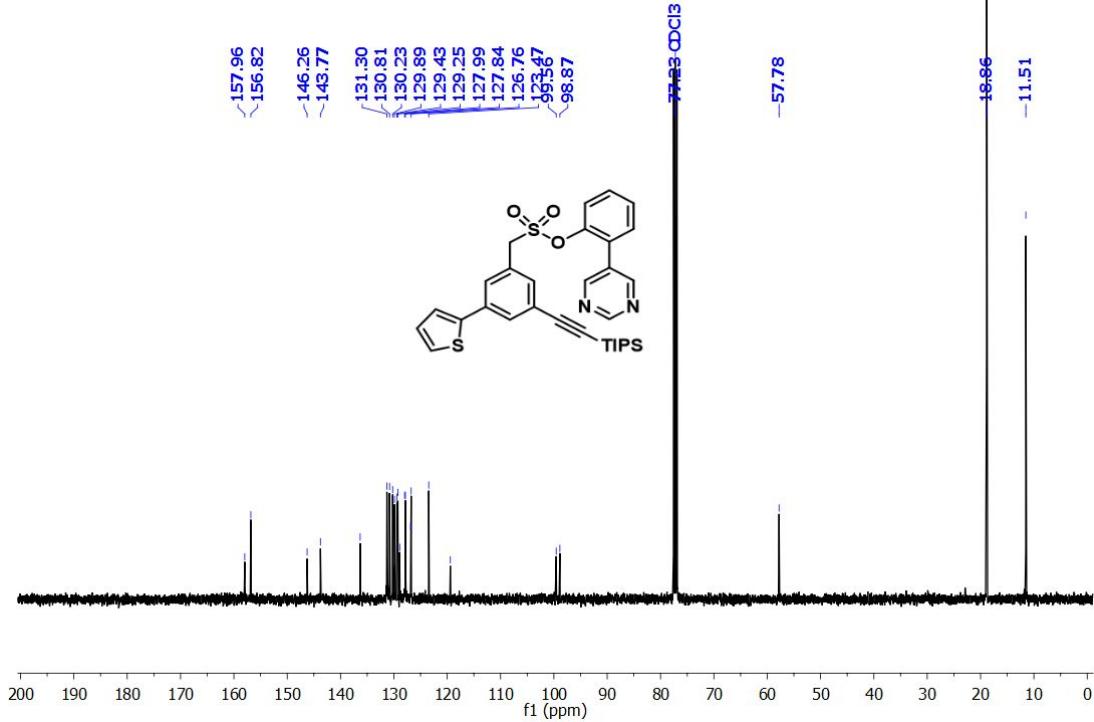


**Figure S45.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **15**

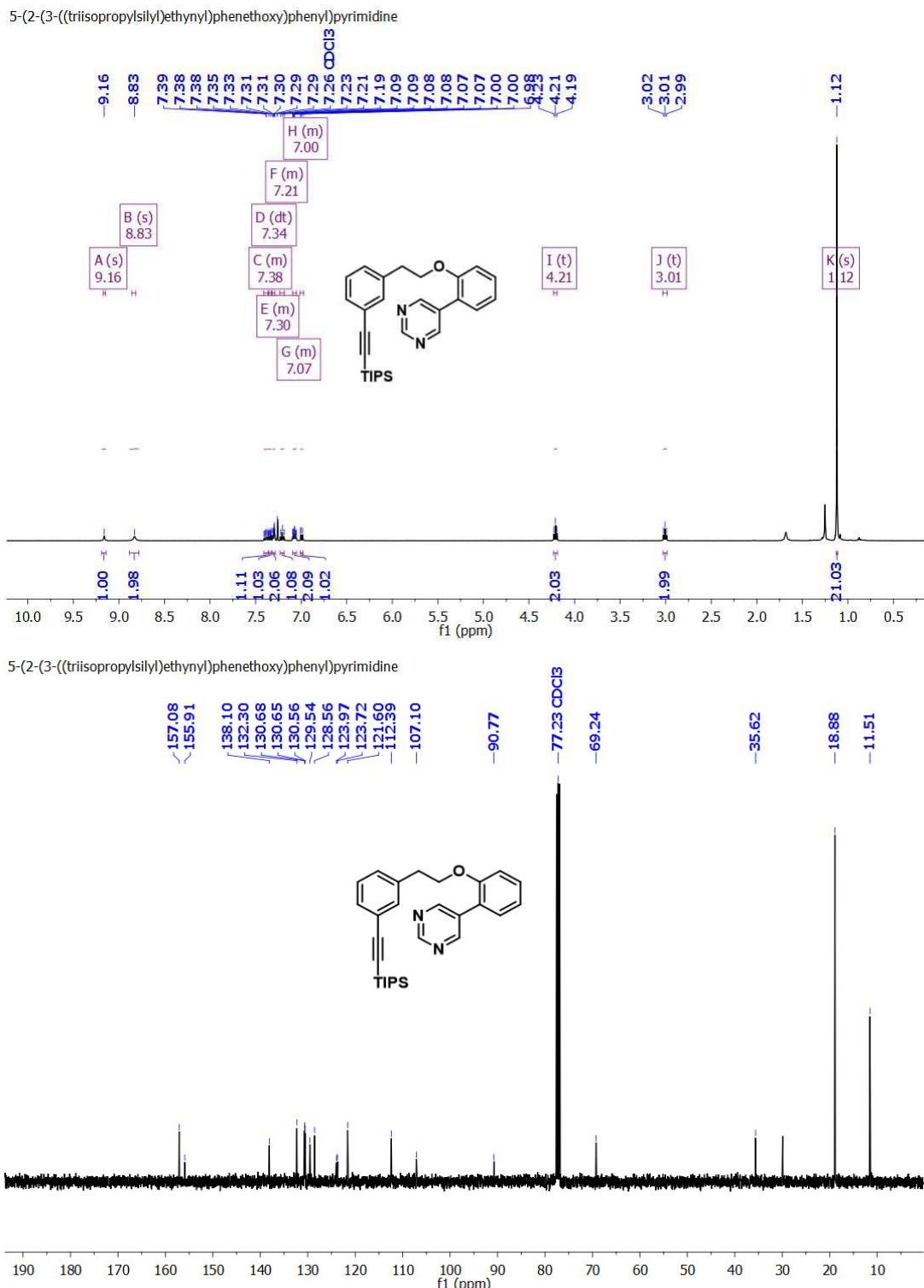
2-(pyrimidin-5-yl)phenyl (3-(thiophen-2-yl)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate



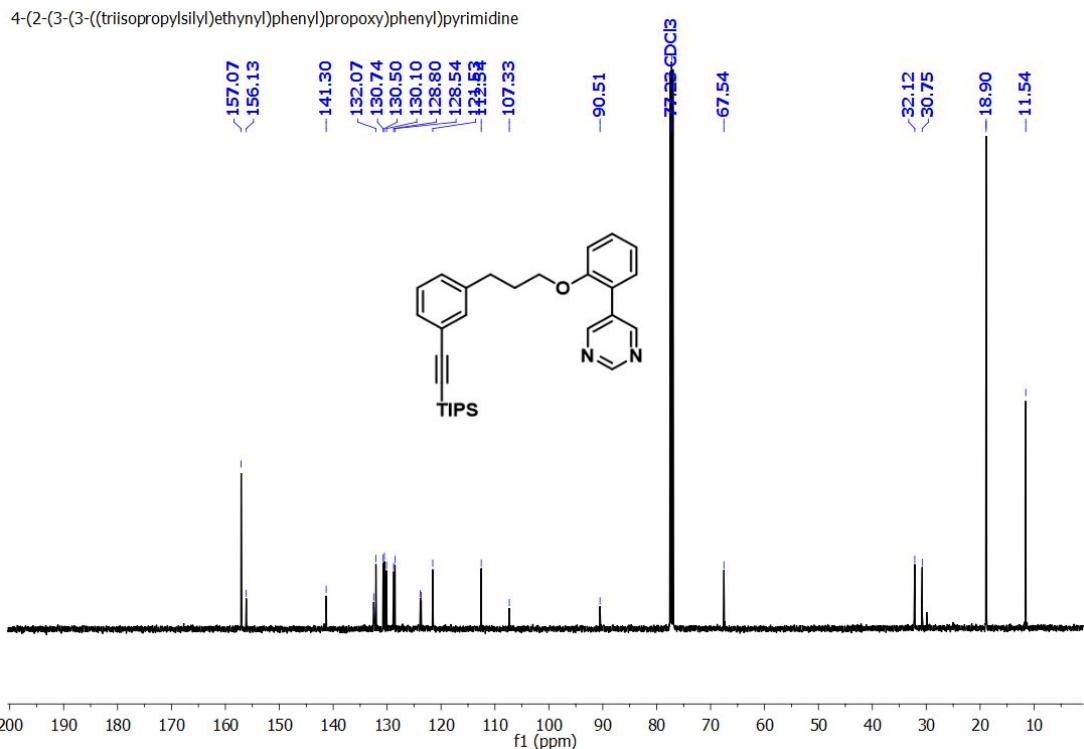
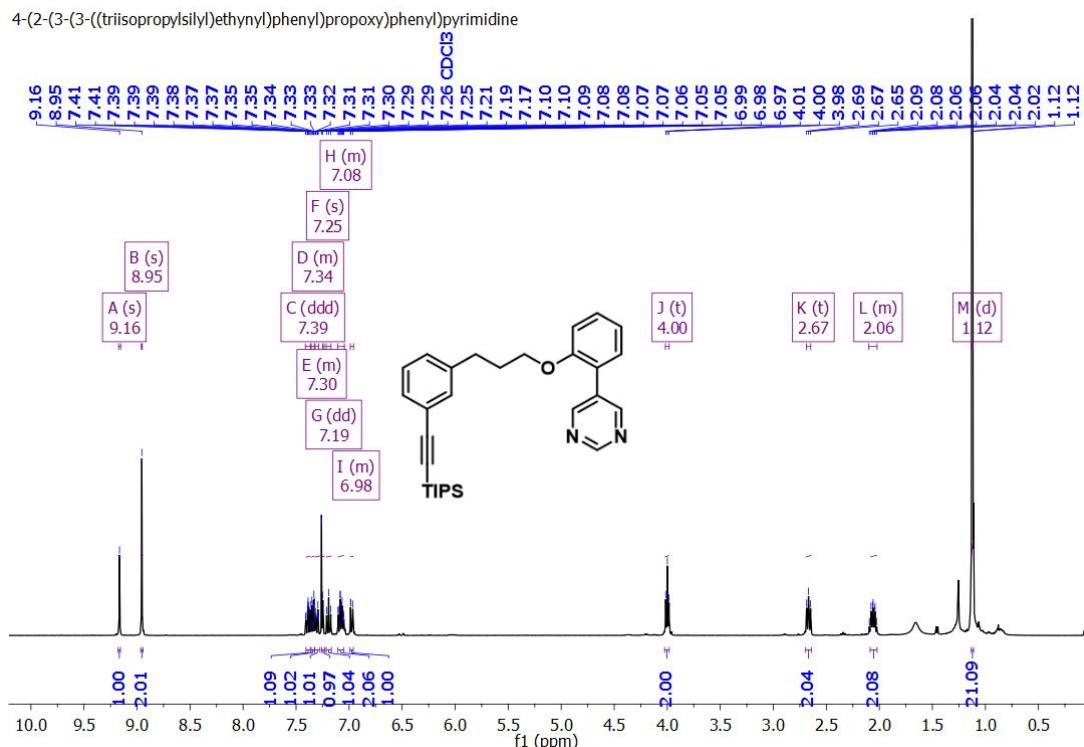
2-(pyrimidin-5-yl)phenyl (3-(thiophen-2-yl)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate



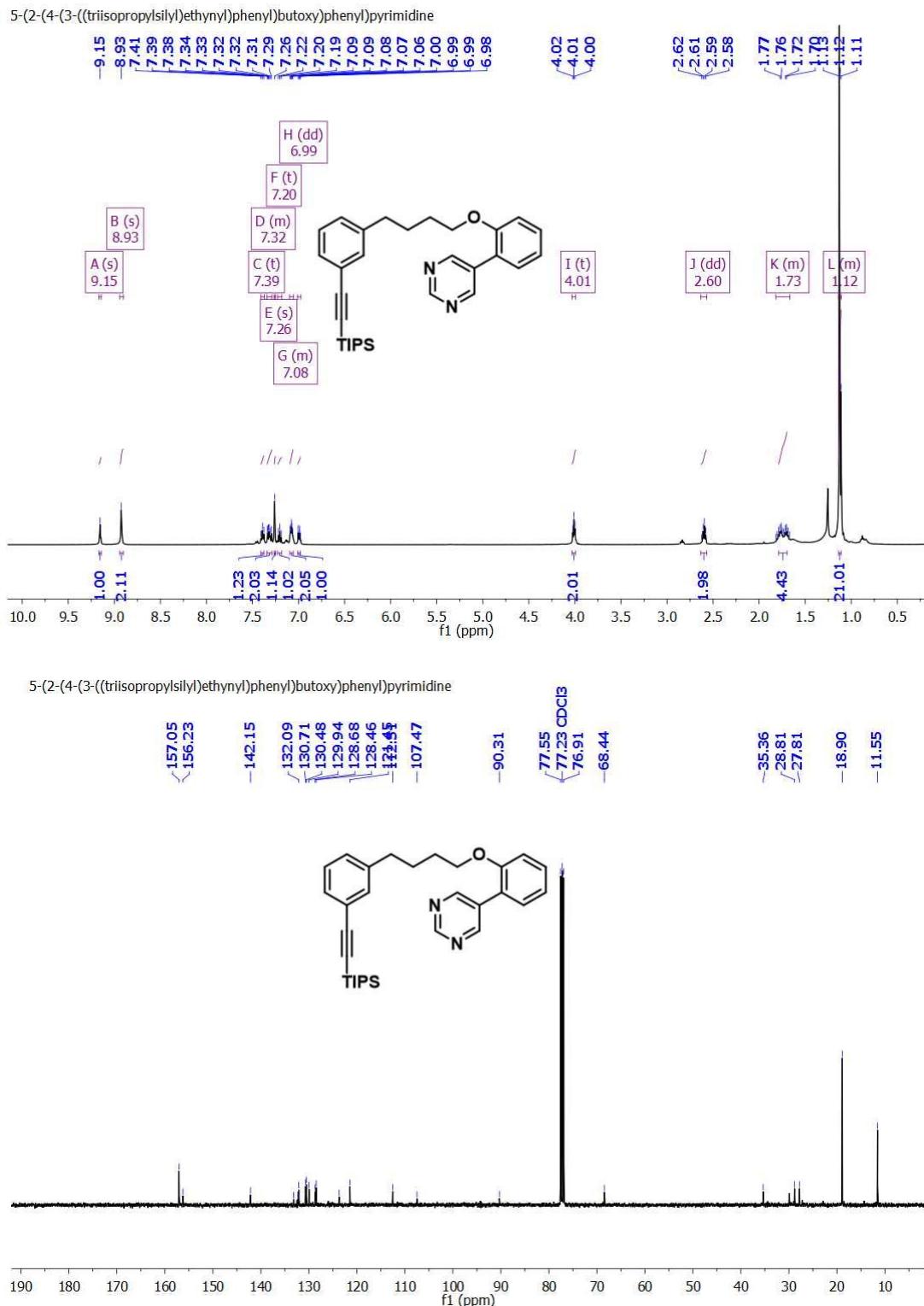
**Figure S46.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **16**



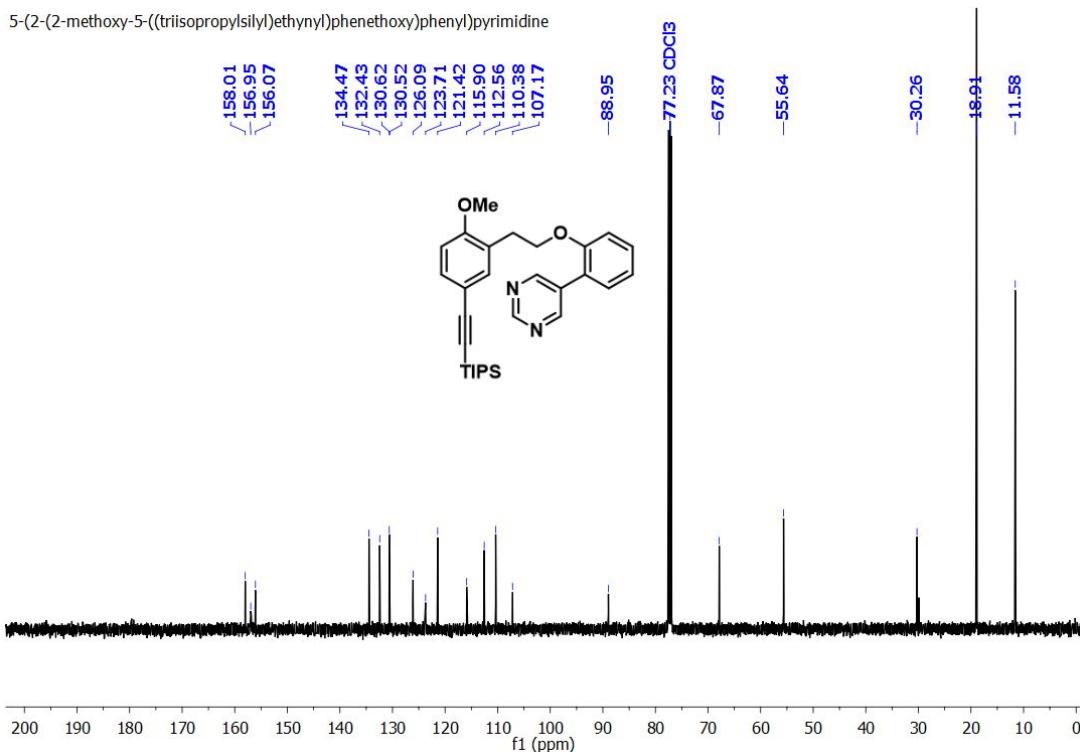
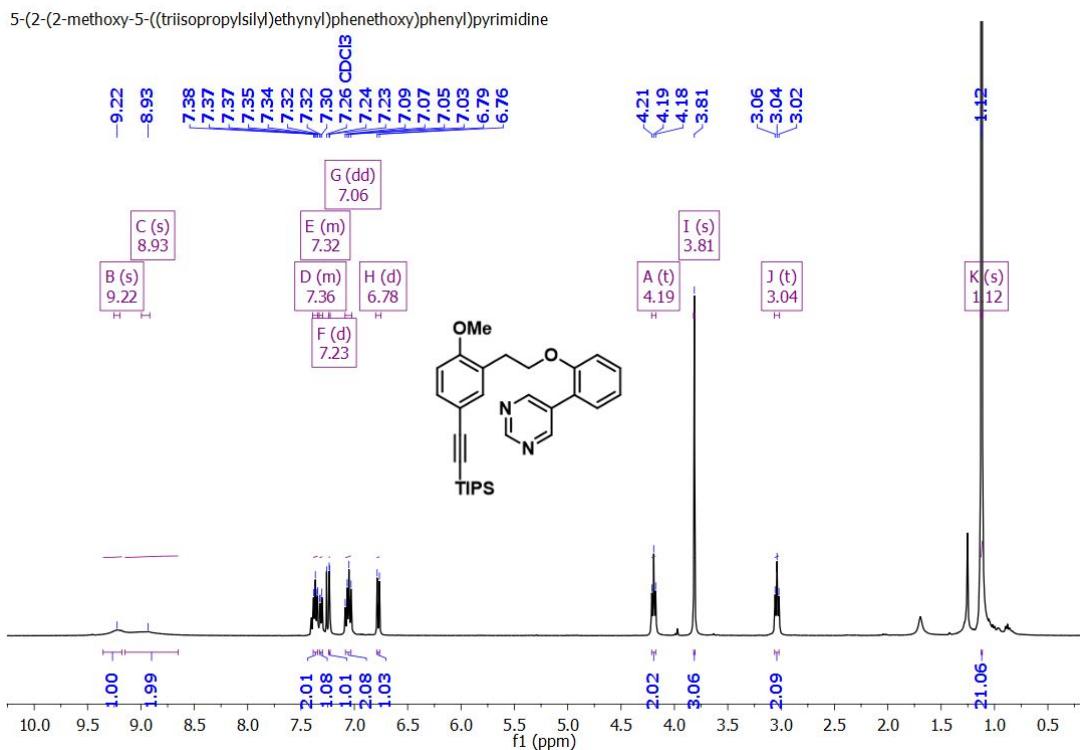
**Figure S47.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **17**



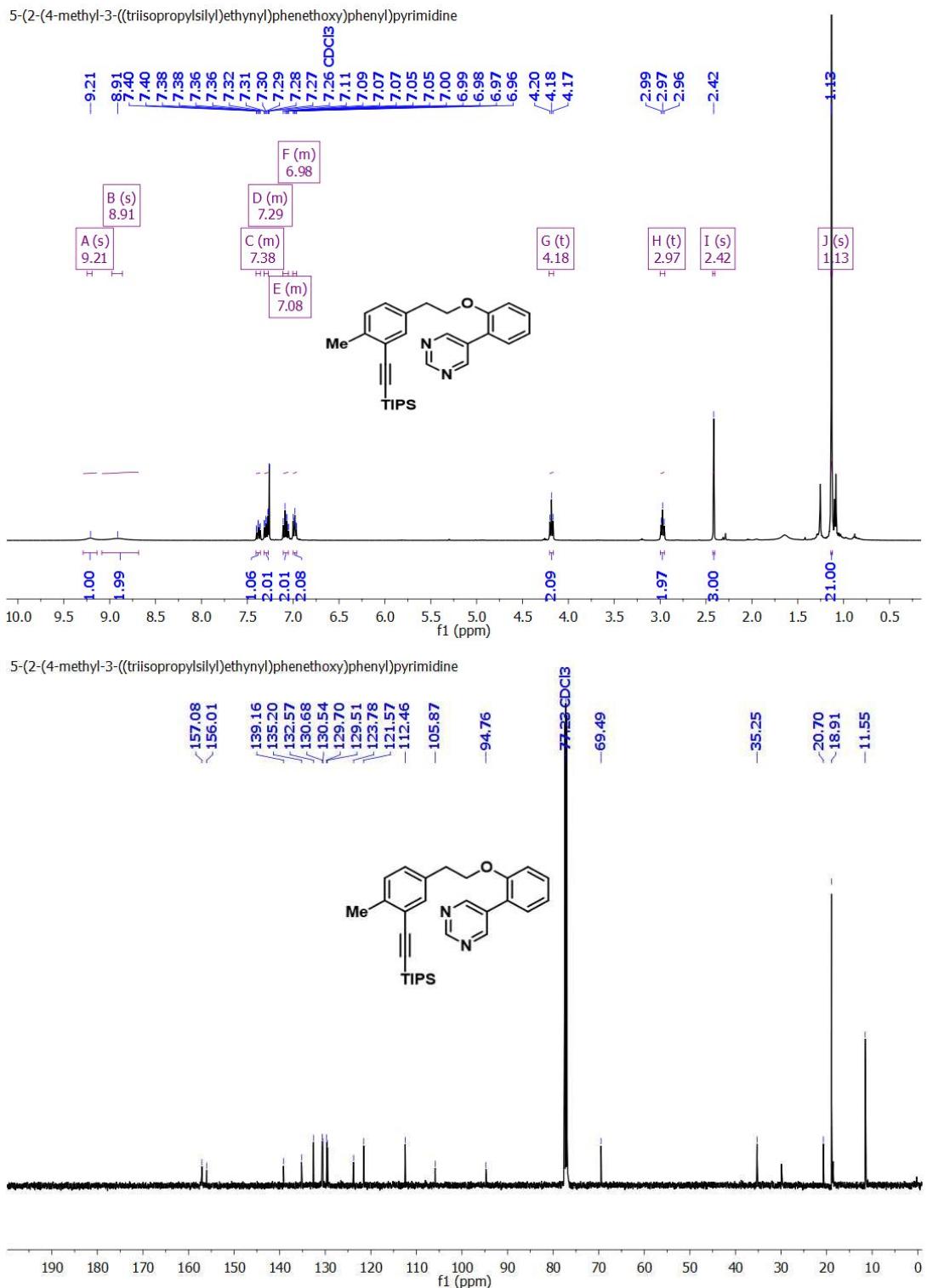
**Figure S48.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **18**



**Figure S49.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **19**



**Figure S50.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **20**



**Figure S51.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **21**

5-(2-(3-methoxy-5-((trisopropylsilyl)ethynyl)phenethoxy)phenyl)pyrimidine

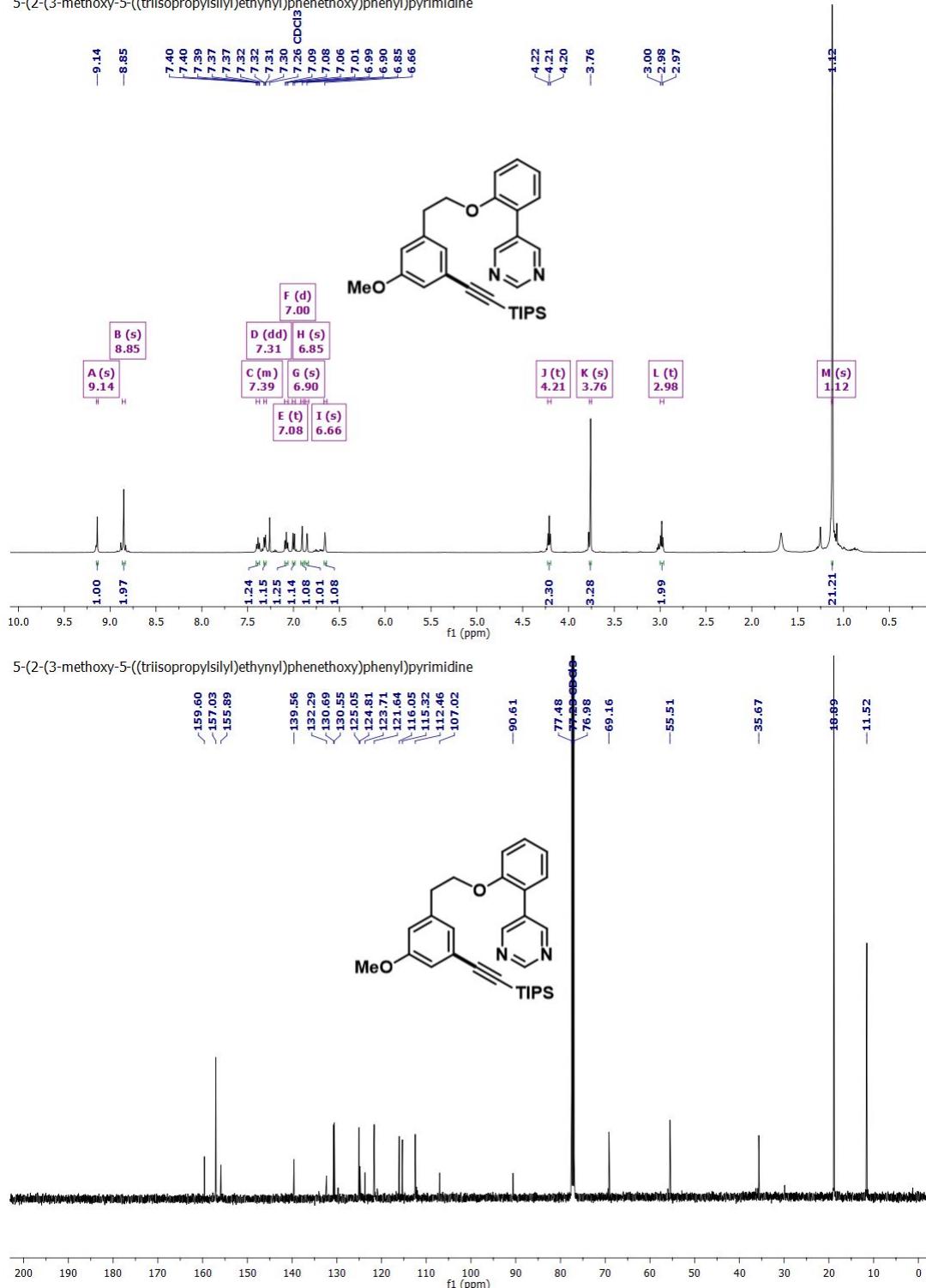
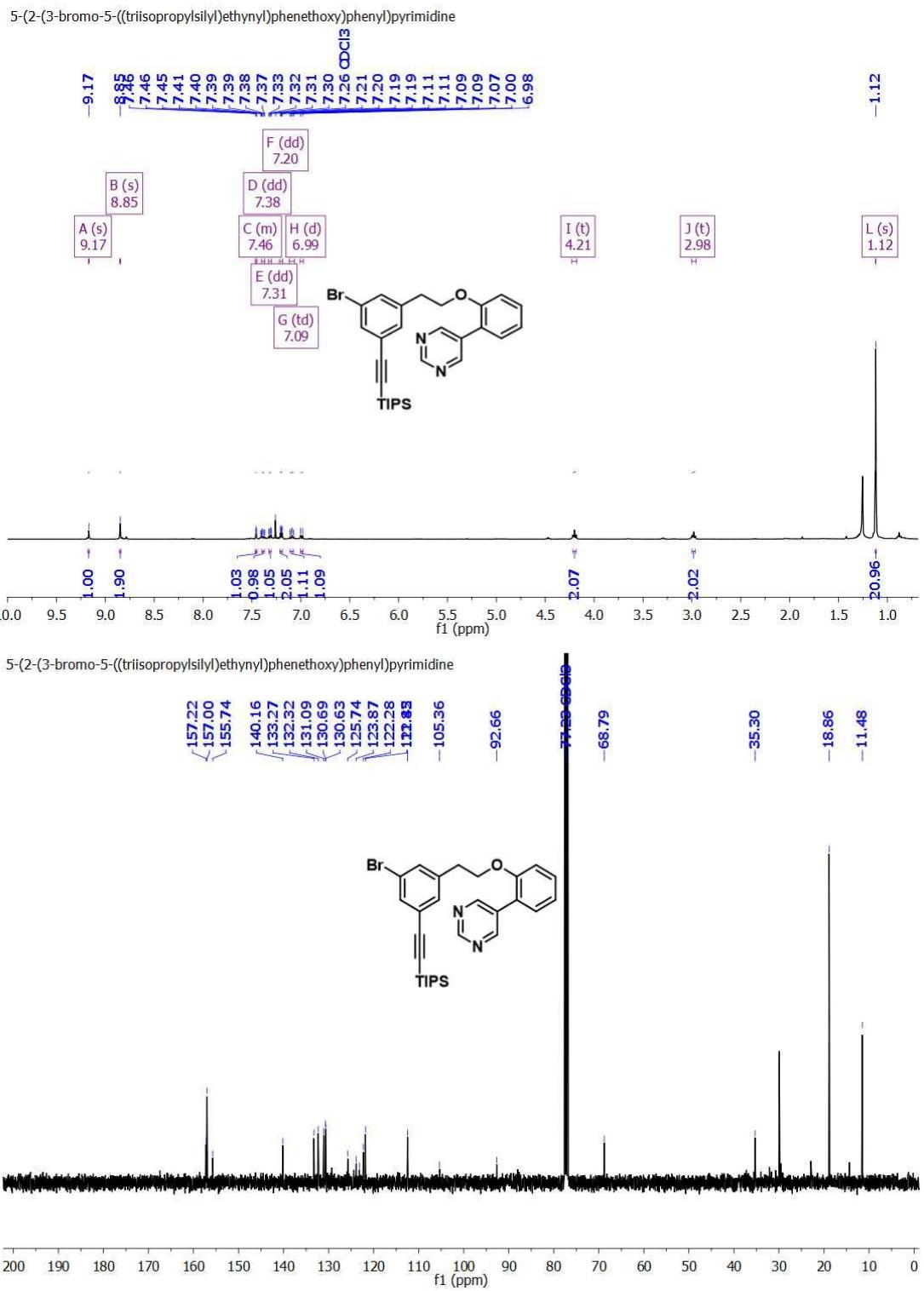
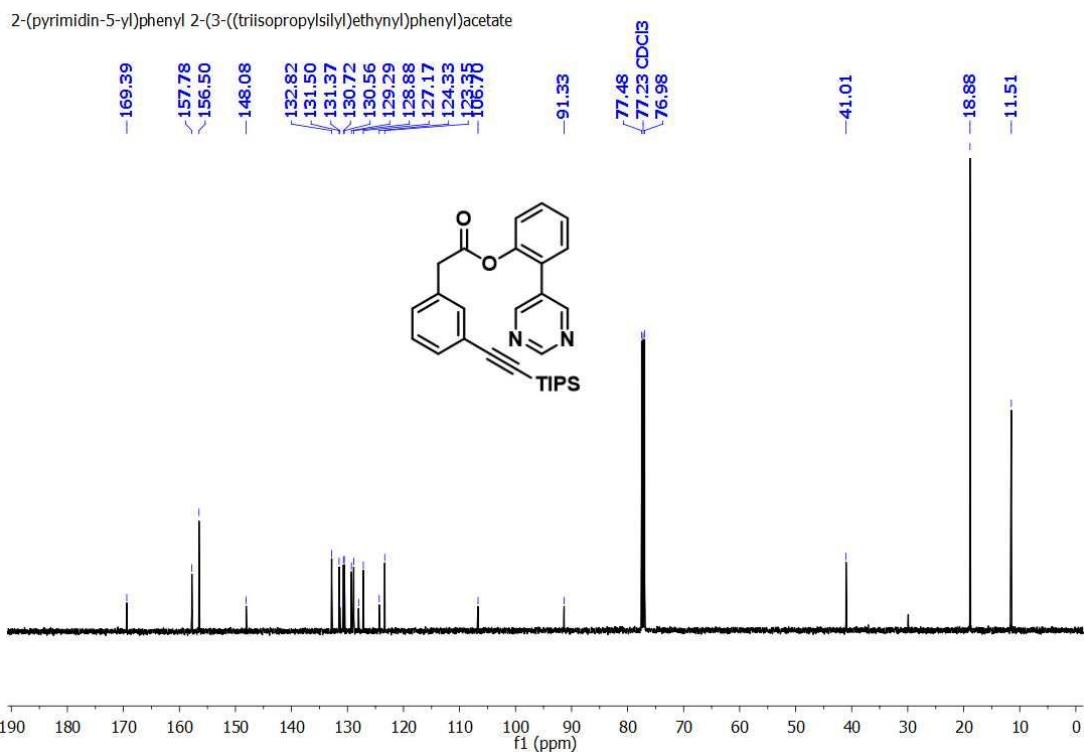
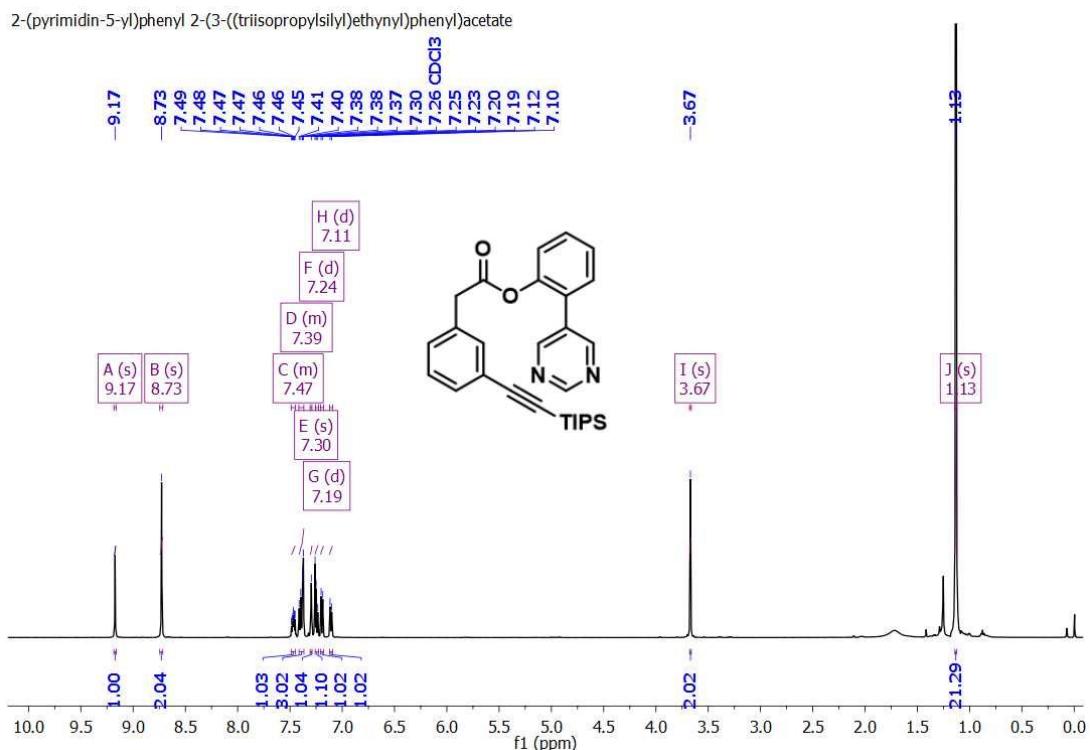


Figure S52. <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of 22

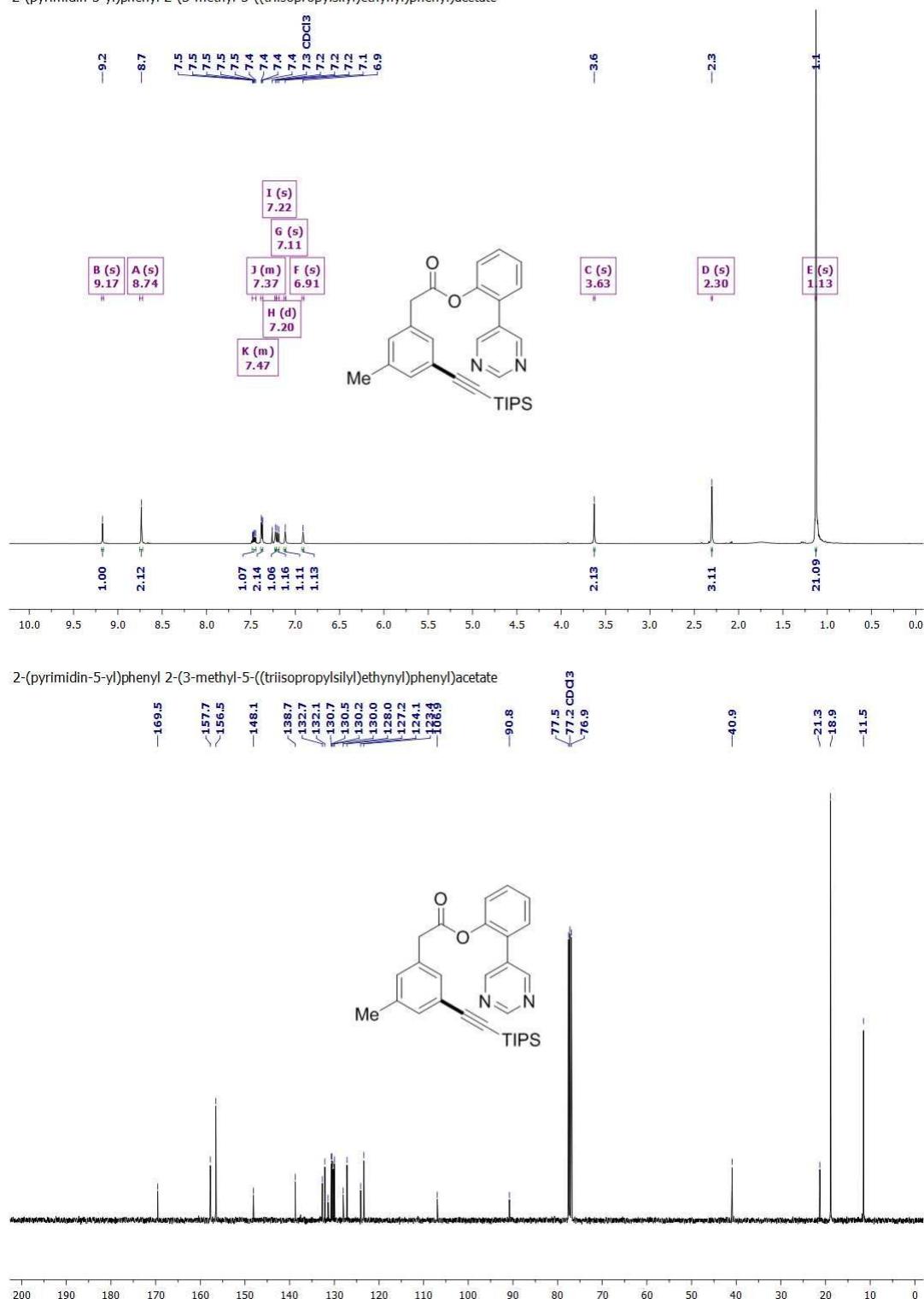


**Figure S53.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **23**



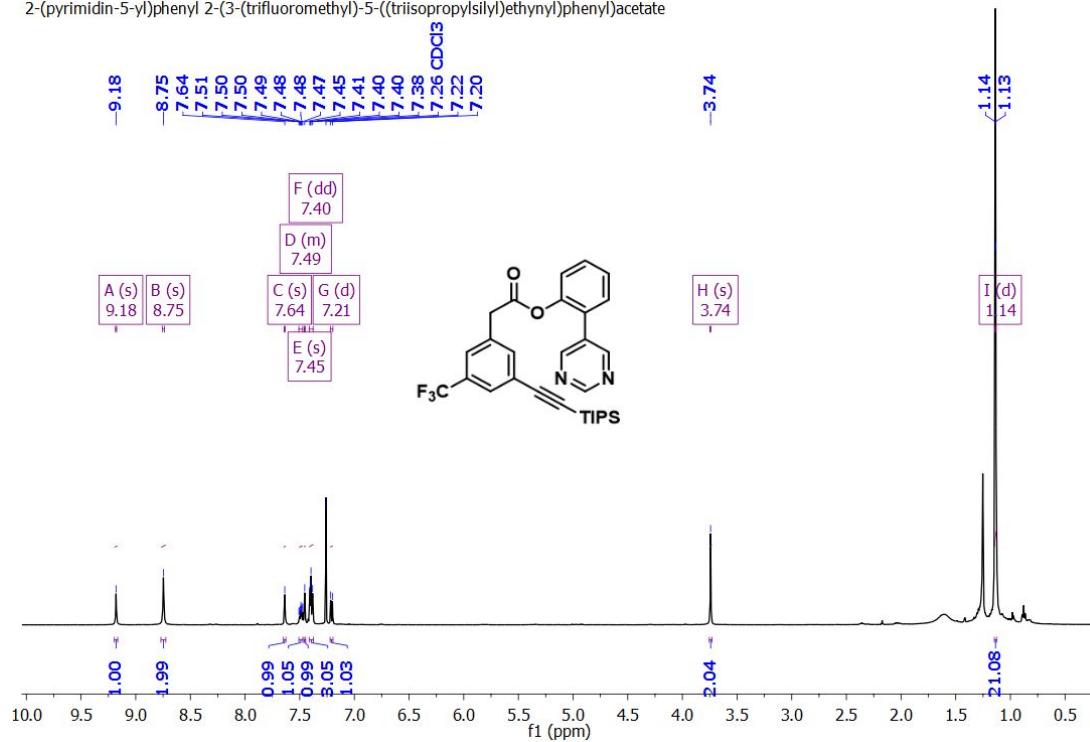
**Figure S54.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **24**

2-(pyrimidin-5-yl)phenyl 2-(3-methyl-5-((triisopropylsilyl)ethynyl)phenyl)acetate

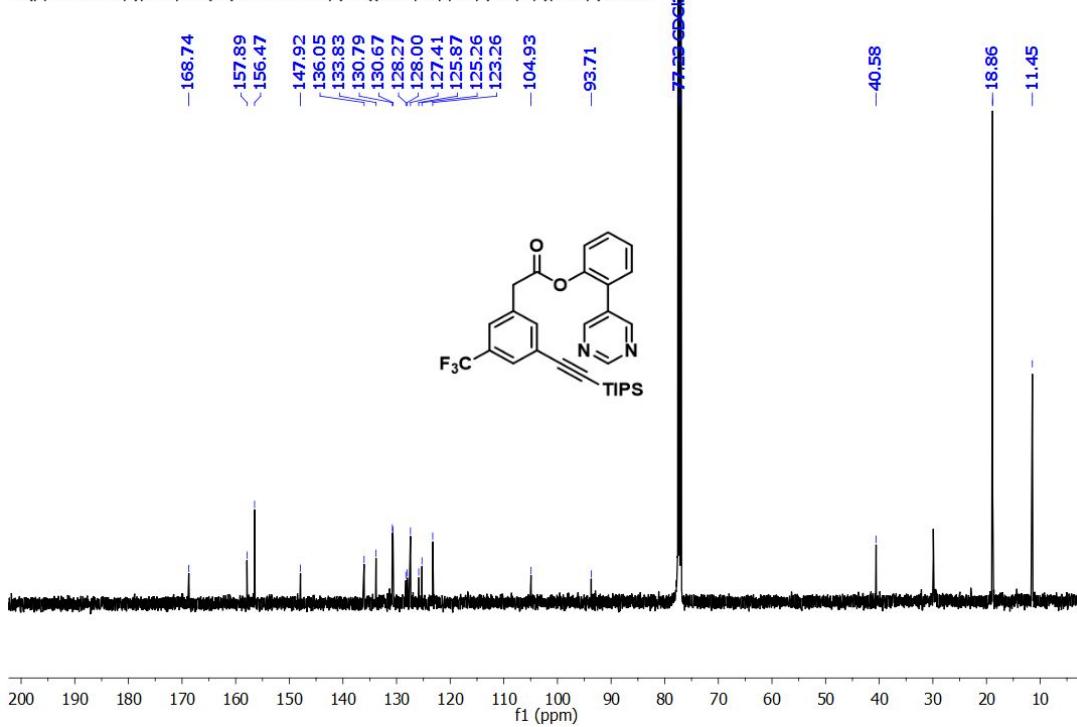


**Figure S55.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **25**

2-(pyrimidin-5-yl)phenyl 2-(3-(trifluoromethyl)-5-((triisopropylsilyl)ethynyl)phenyl)acetate

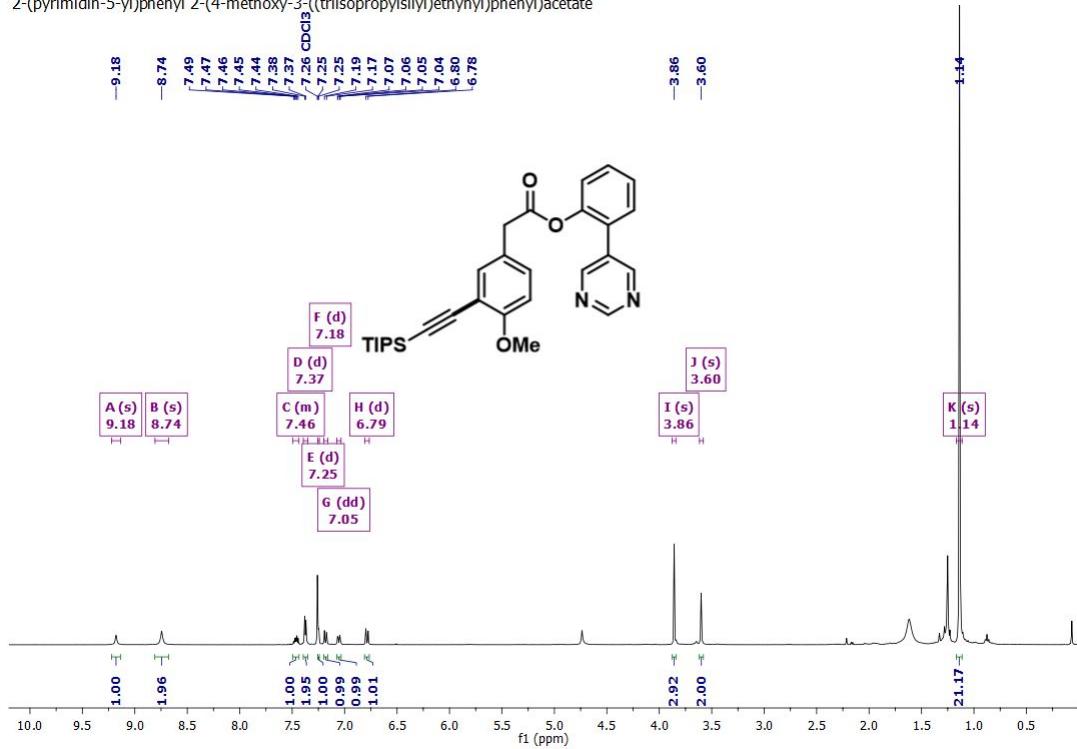


2-(pyrimidin-5-yl)phenyl 2-(3-(trifluoromethyl)-5-((triisopropylsilyl)ethynyl)phenyl)acetate

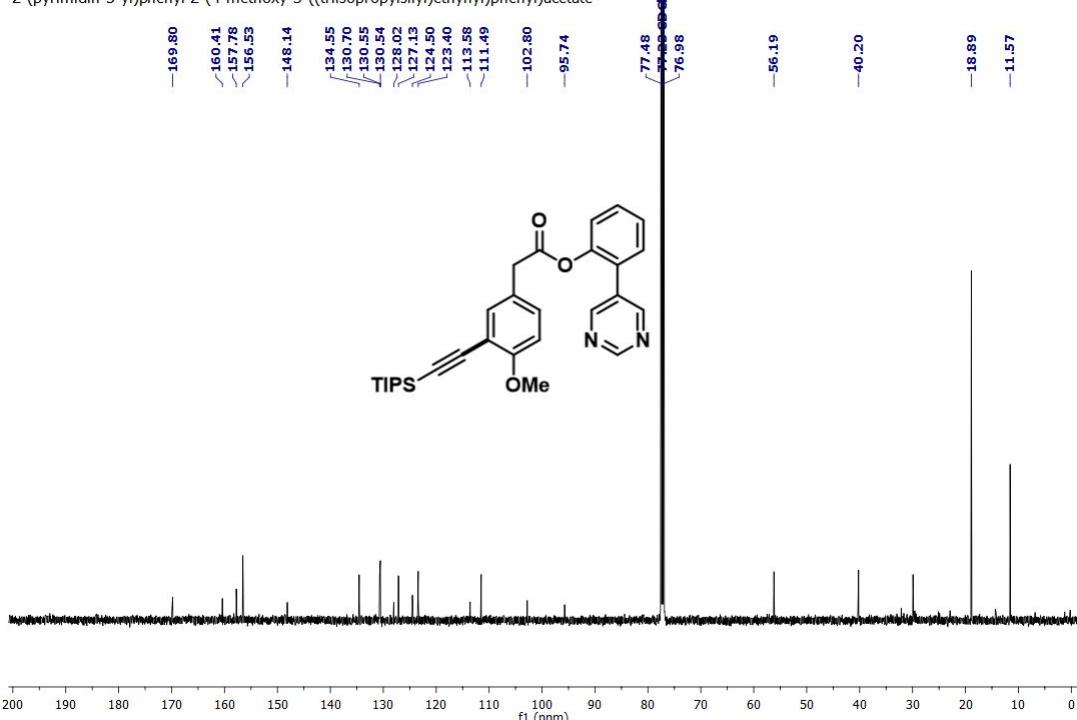


**Figure S56.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **26**

2-(pyrimidin-5-yl)phenyl 2-(4-methoxy-3-((trisopropylsilyl)ethynyl)phenyl)acetate

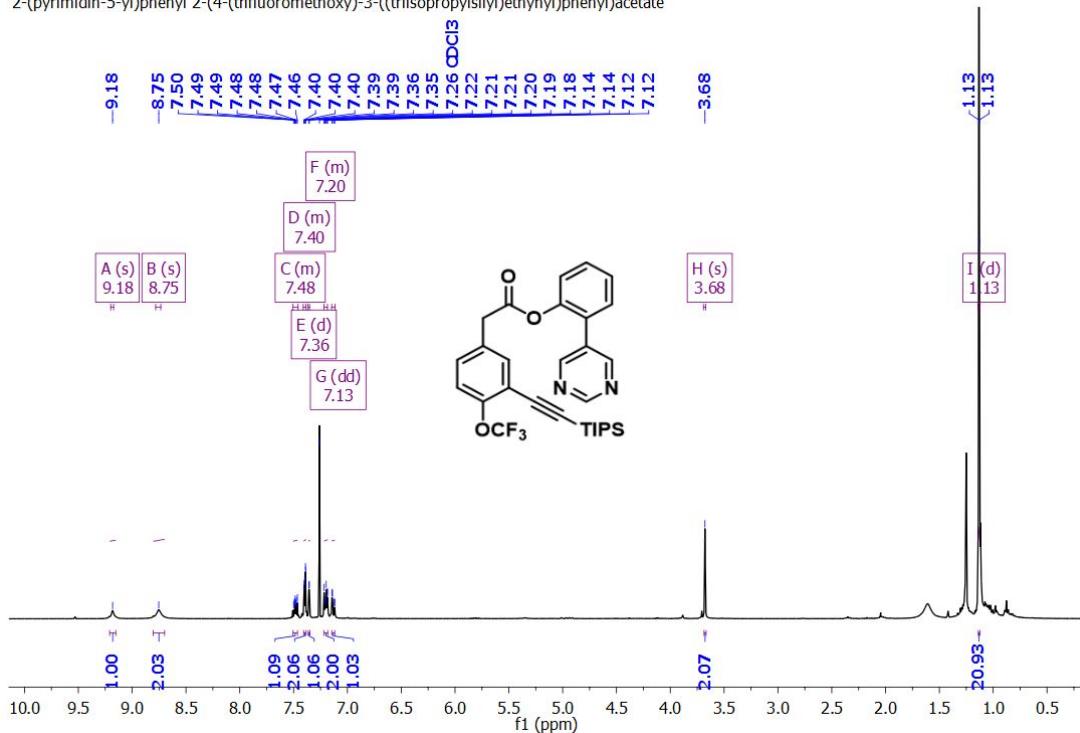


2-(pyrimidin-5-yl)phenyl 2-(4-methoxy-3-((trisopropylsilyl)ethynyl)phenyl)acetate

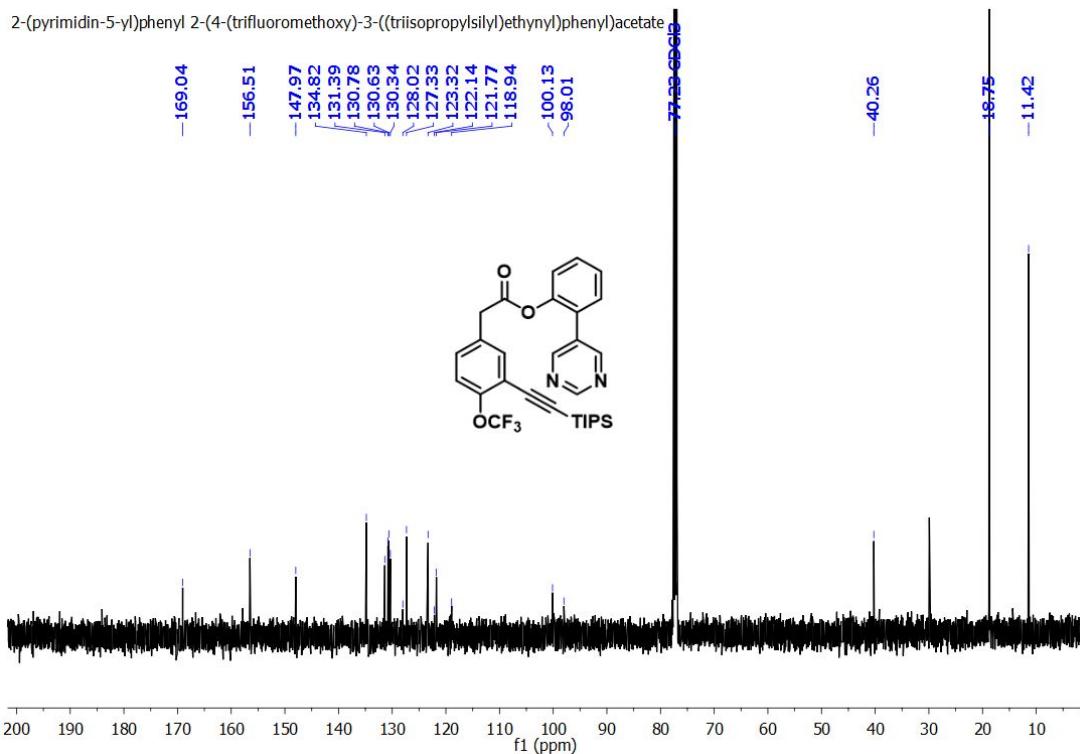


**Figure S57.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **27**

2-(pyrimidin-5-yl)phenyl 2-(4-(trifluoromethoxy)-3-((trisopropylsilyl)ethynyl)phenyl)acetate

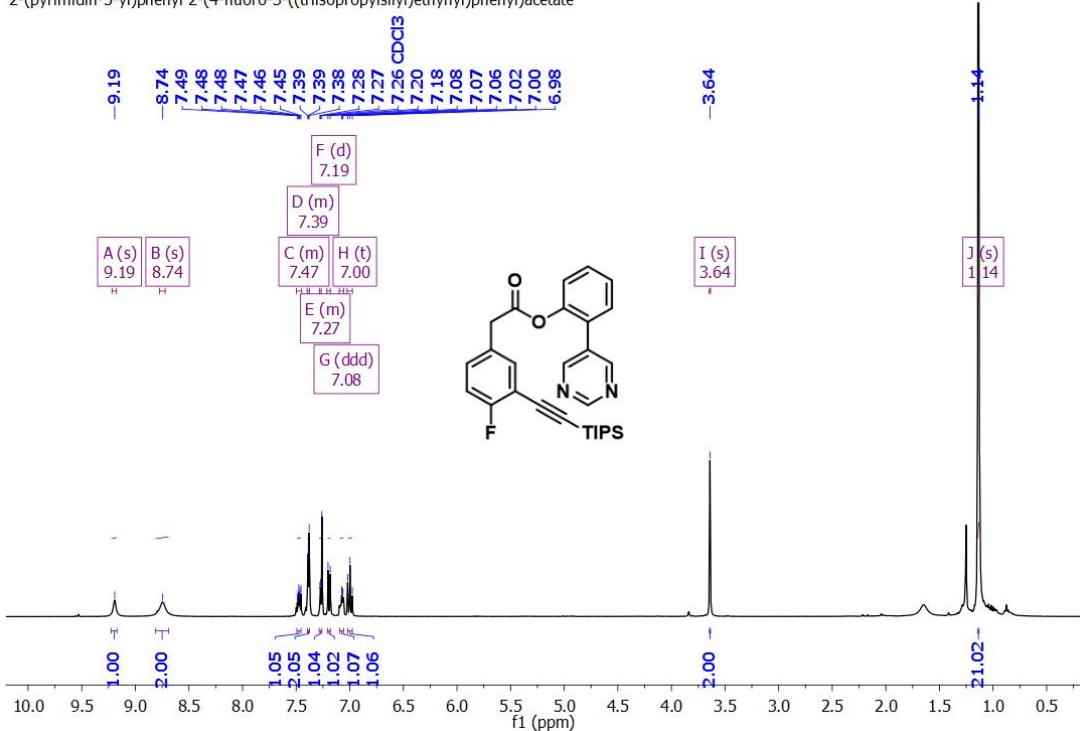


2-(pyrimidin-5-yl)phenyl 2-(4-(trifluoromethoxy)-3-((trisopropylsilyl)ethynyl)phenyl)acetate

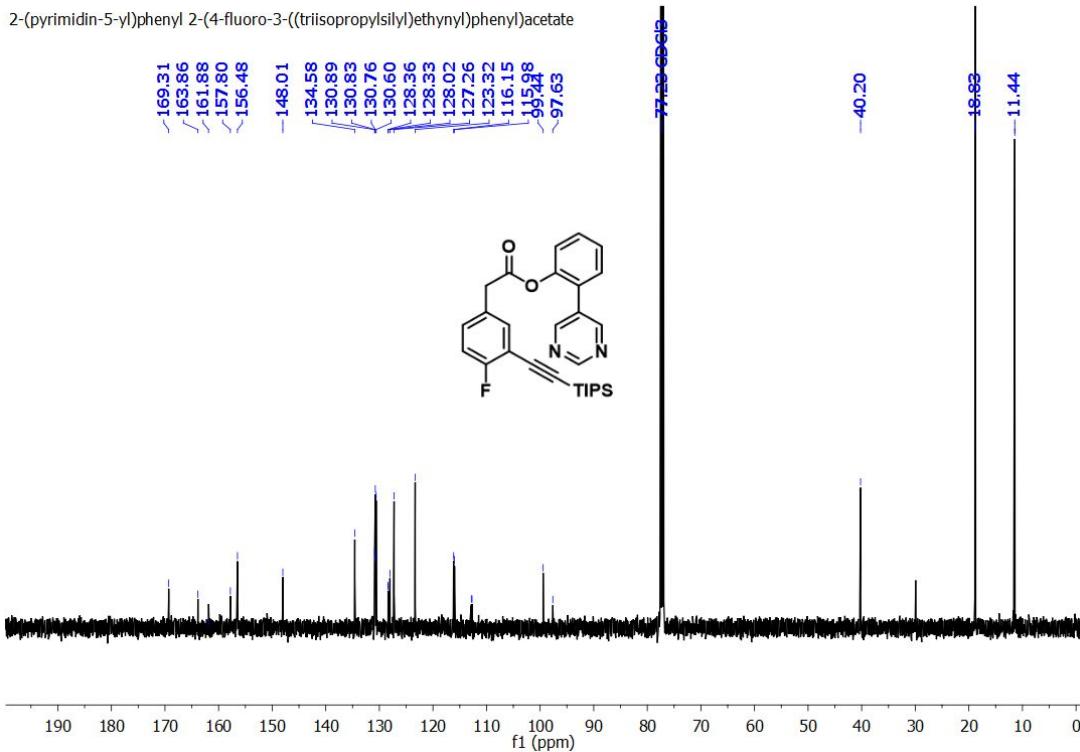


**Figure S58.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **28**

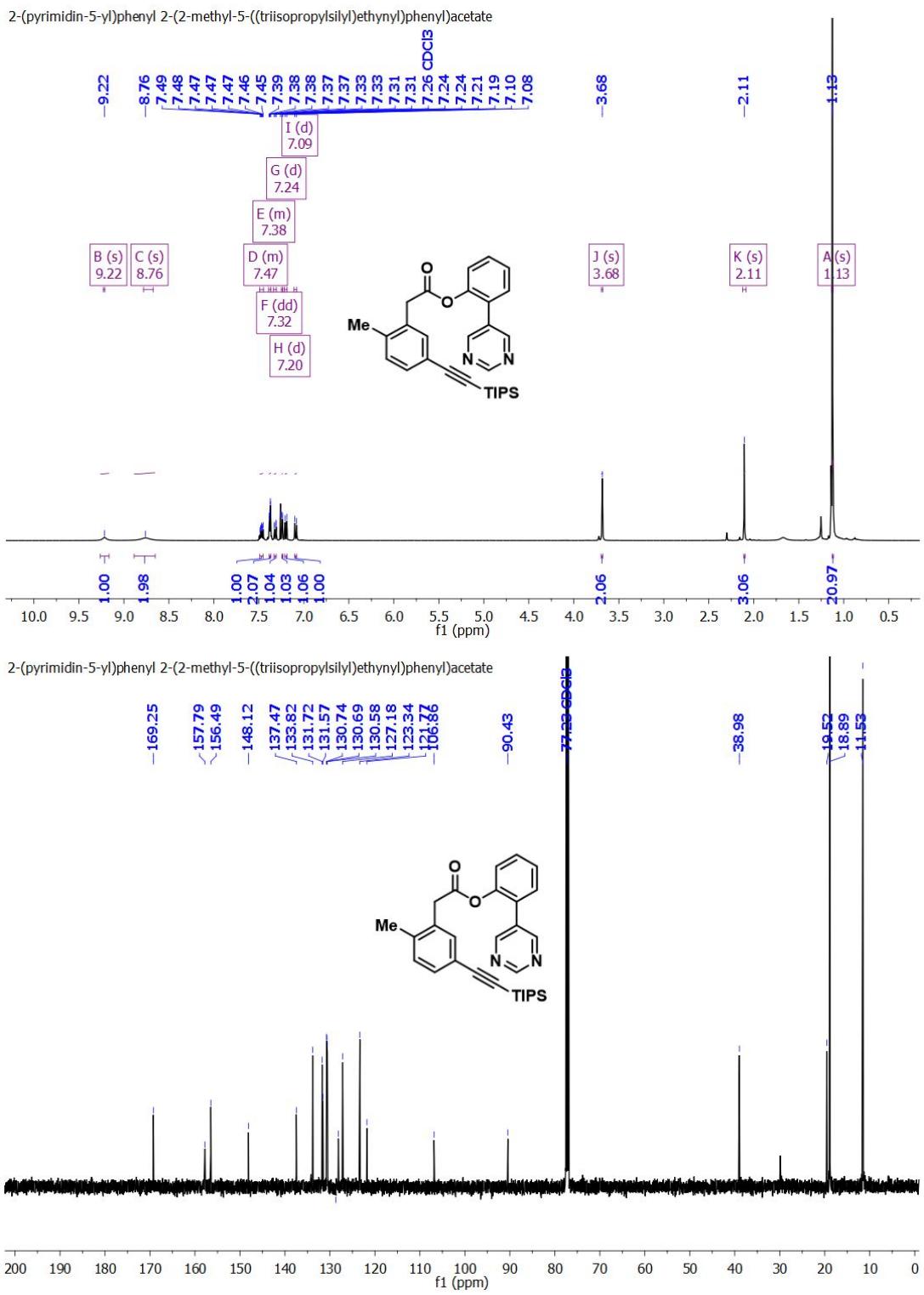
2-(pyrimidin-5-yl)phenyl 2-(4-fluoro-3-((triisopropylsilyl)ethynyl)phenyl)acetate



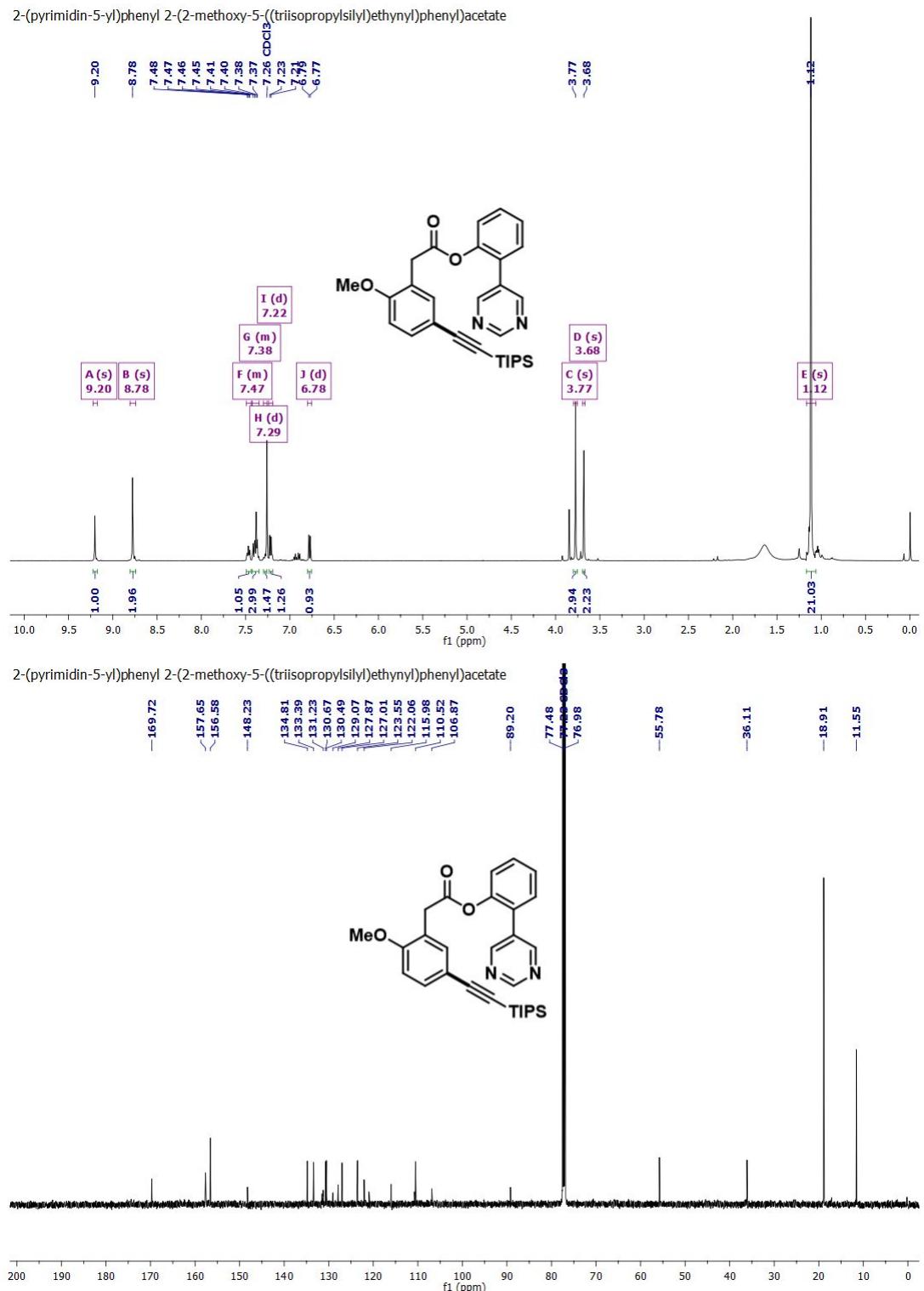
2-(pyrimidin-5-yl)phenyl 2-(4-fluoro-3-((triisopropylsilyl)ethynyl)phenyl)acetate



**Figure S59.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **29**

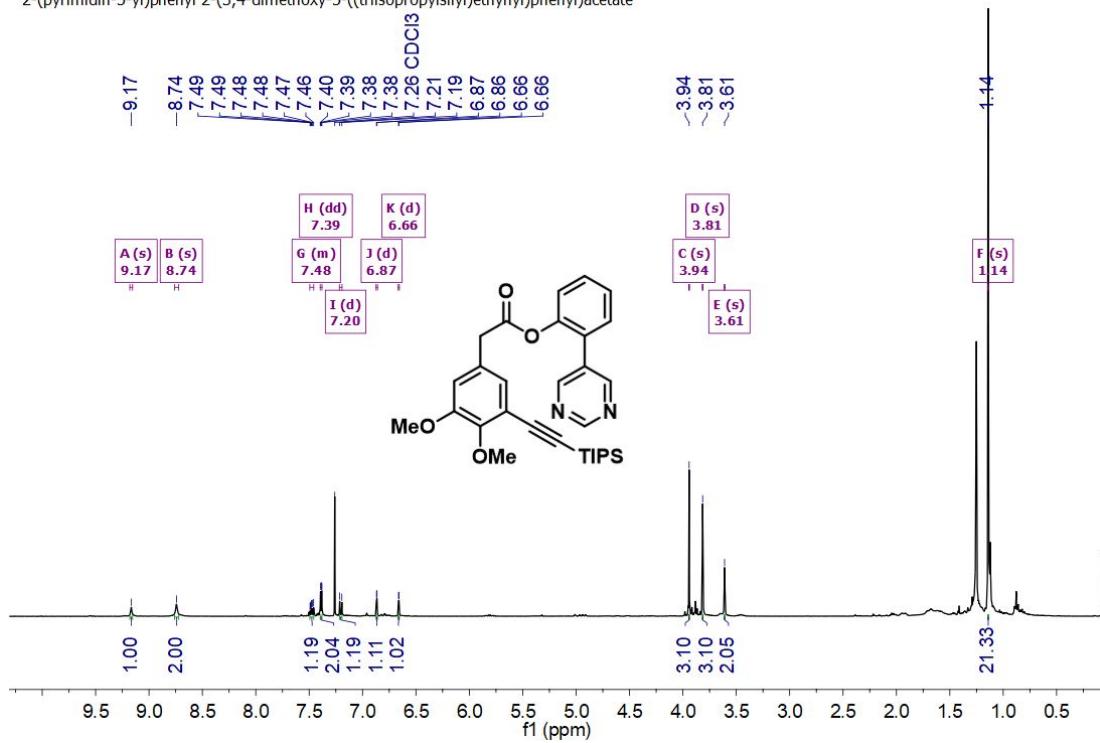


**Figure S60.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **30**

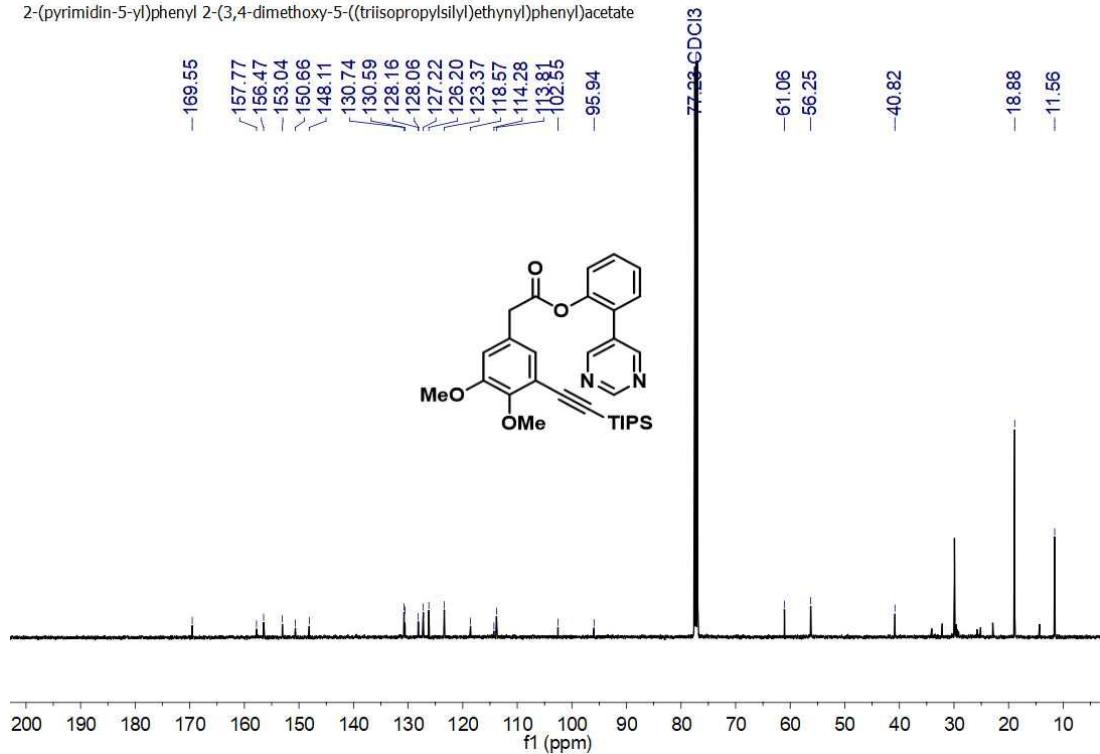


**Figure S61.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **31**

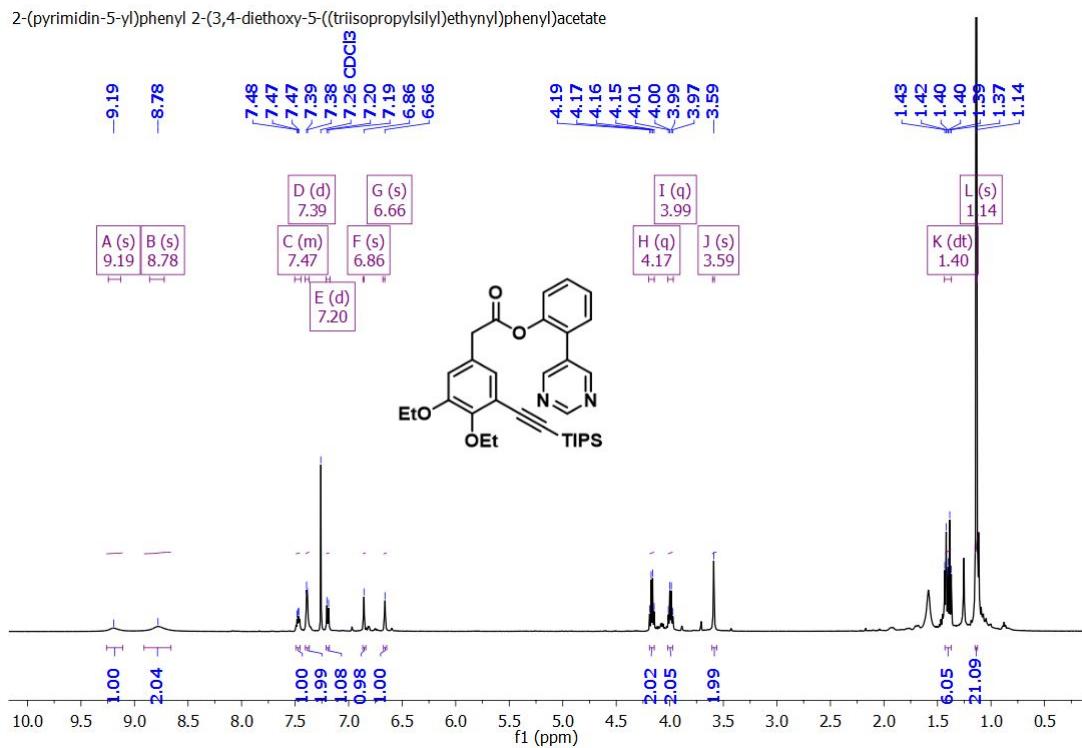
2-(pyrimidin-5-yl)phenyl 2-(3,4-dimethoxy-5-((triisopropylsilyl)ethynyl)phenyl)acetate

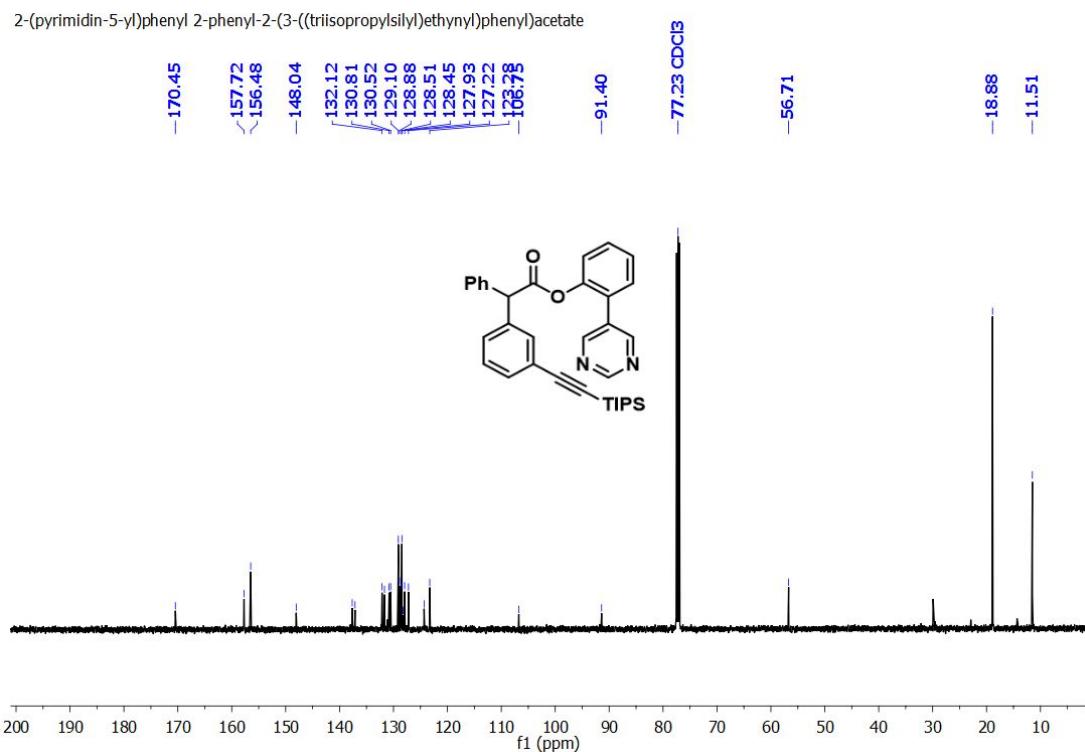
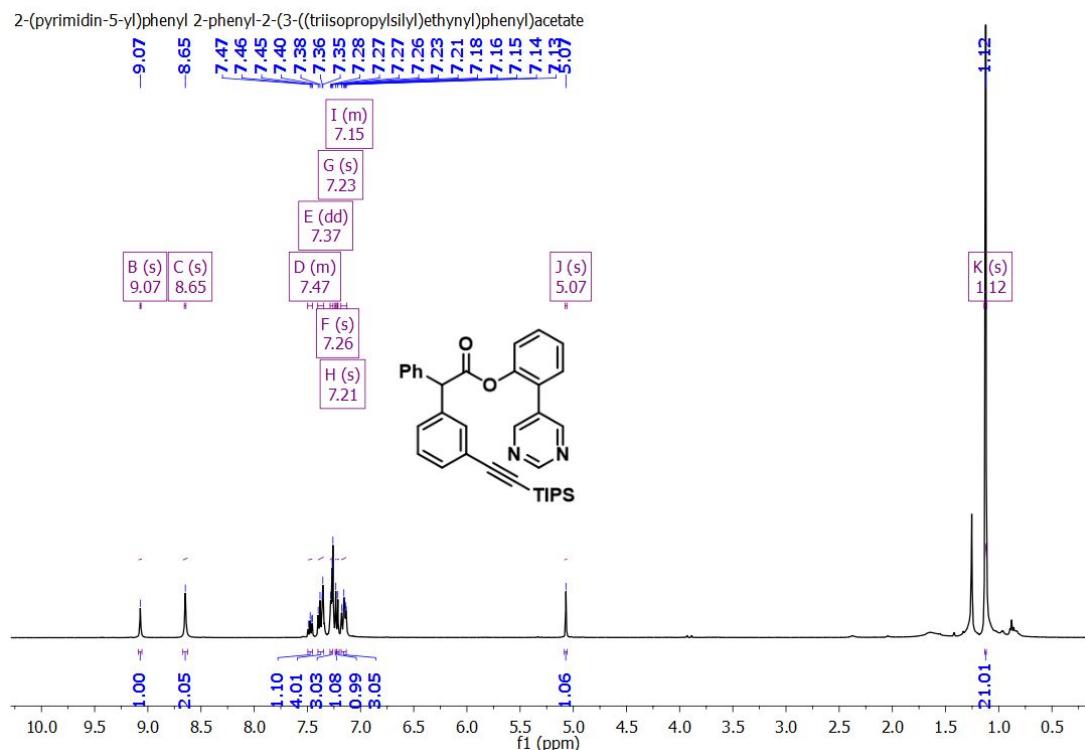


2-(pyrimidin-5-yl)phenyl 2-(3,4-dimethoxy-5-((triisopropylsilyl)ethynyl)phenyl)acetate

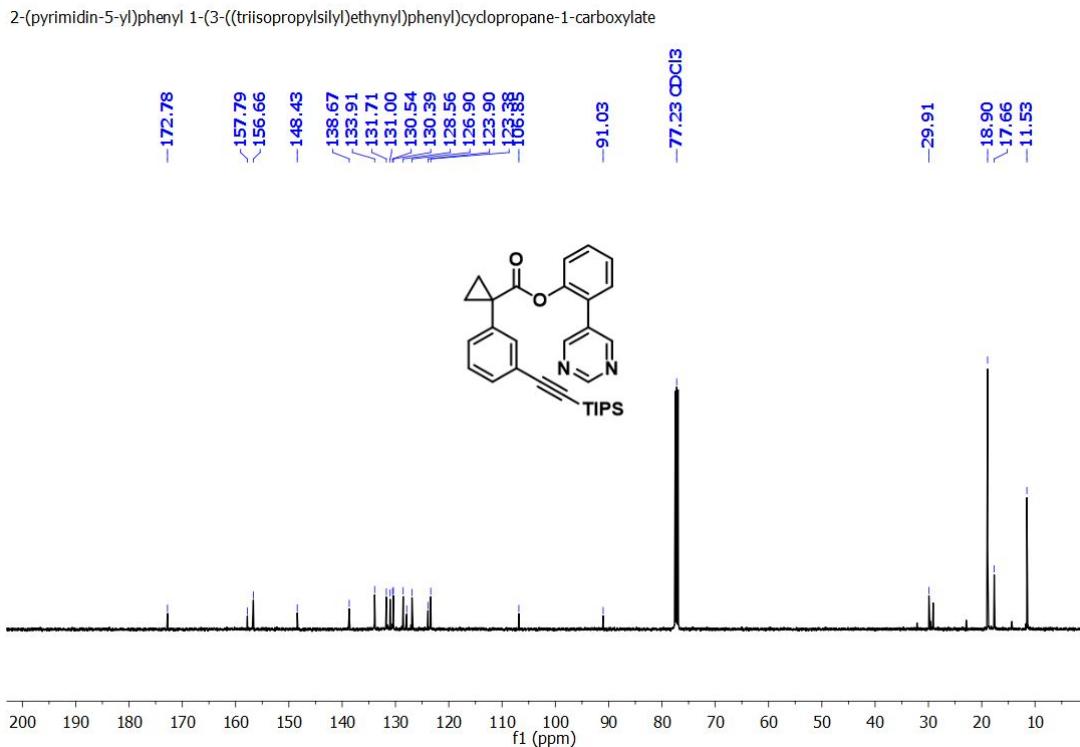
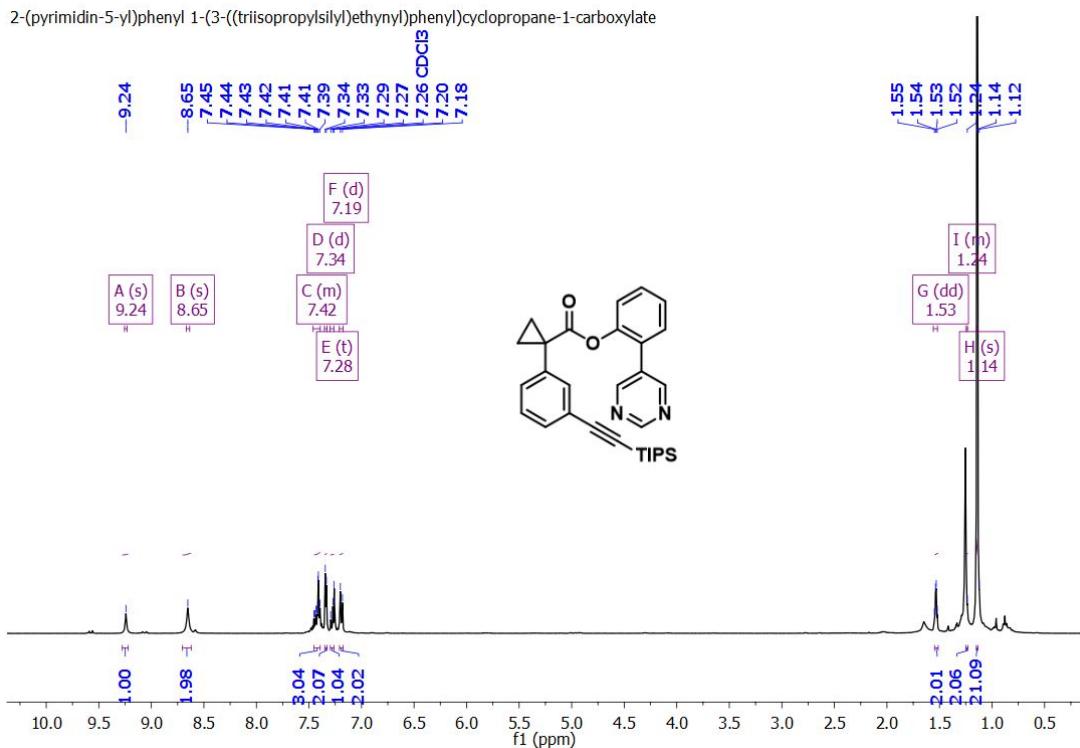


**Figure S62.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of 32

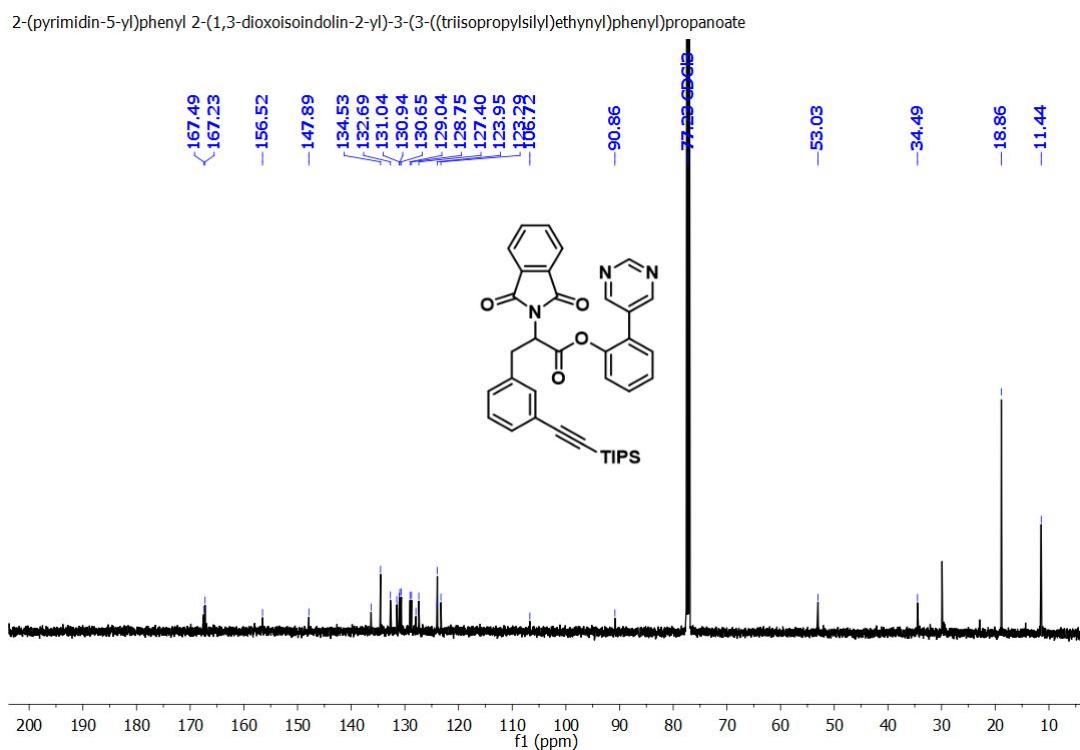
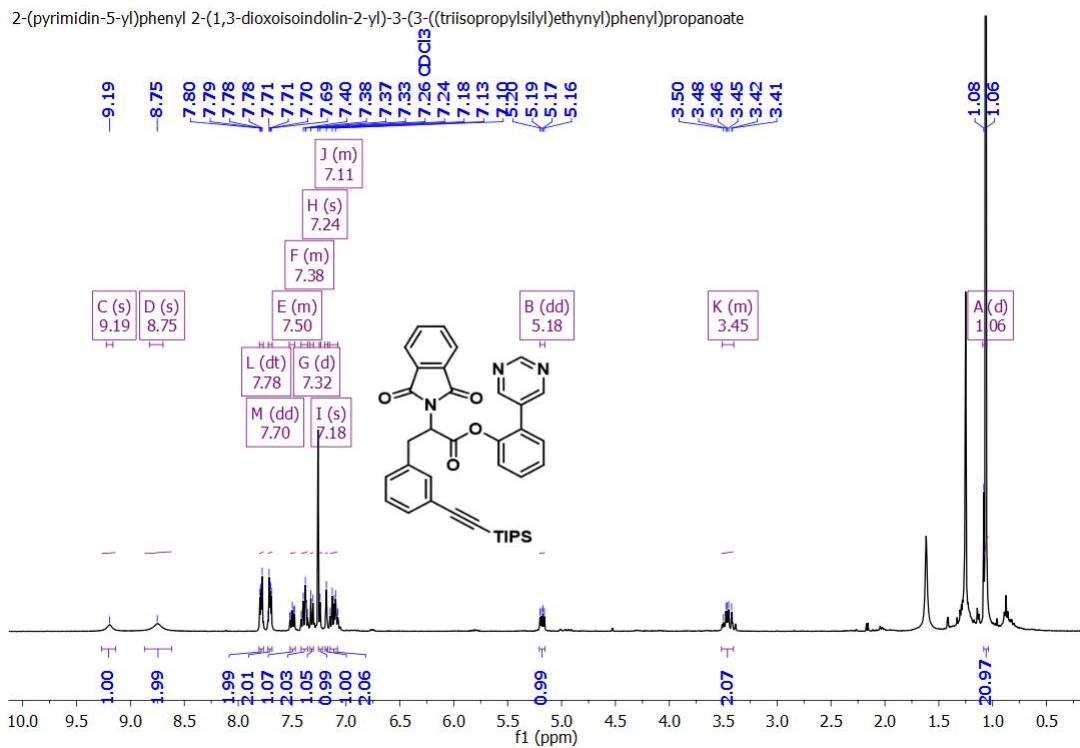




**Figure S64.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **34**

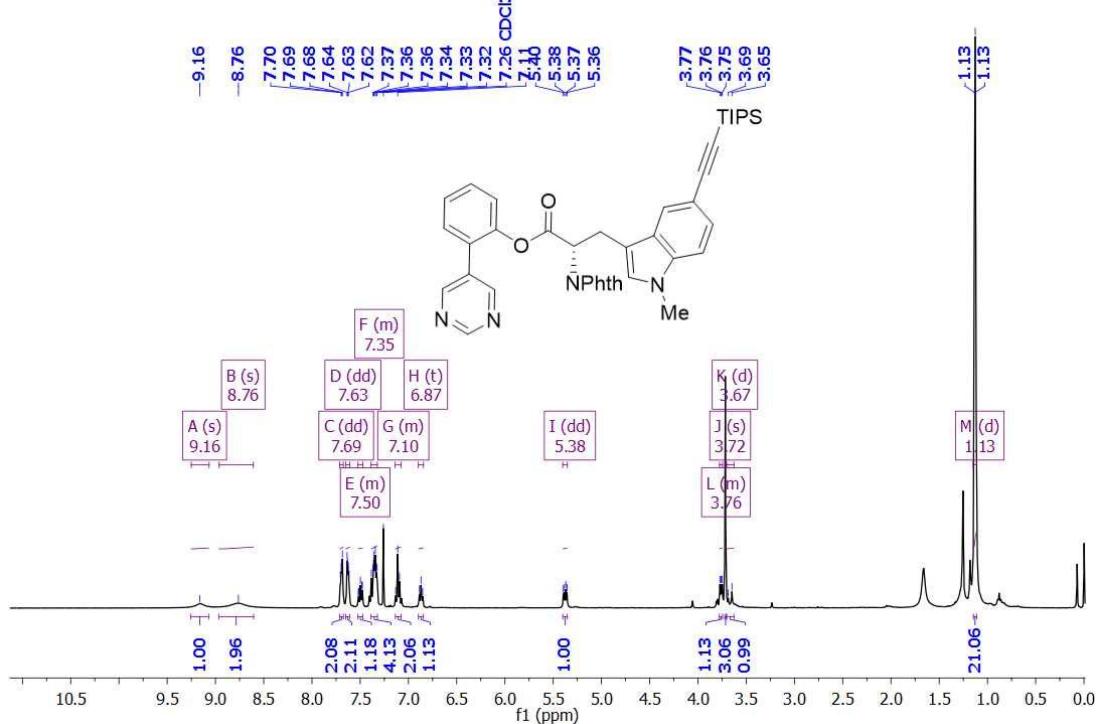


**Figure S65.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **35**

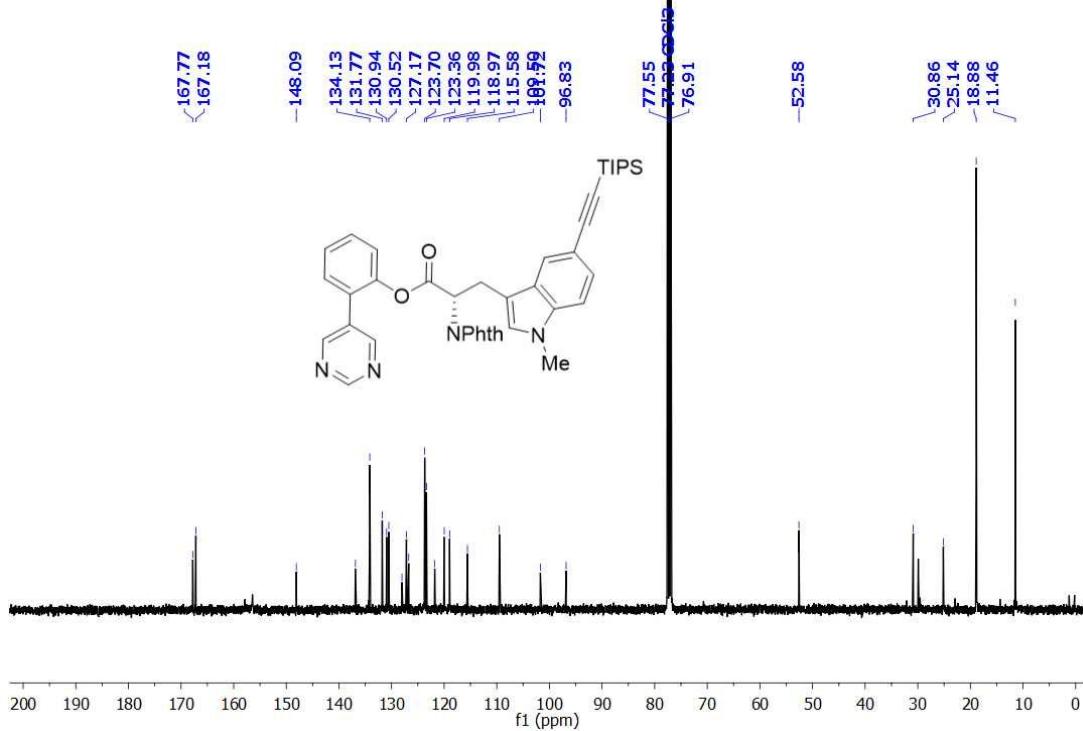


**Figure S66.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **36**

2-(pyrimidin-5-yl)phenyl (5)-2-(1,3-dioxoisindolin-2-yl)-3-(1-methyl-5-((triisopropylsilyl)ethynyl)-1H-indol-3-yl)propanoate

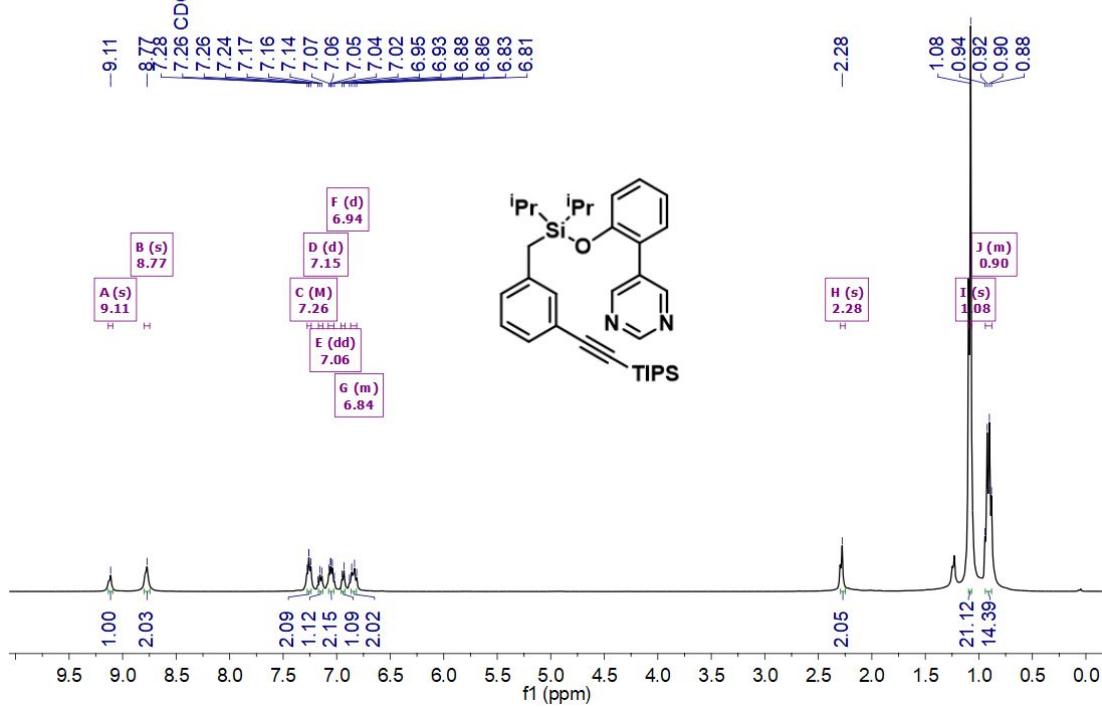


2-(pyrimidin-5-yl)phenyl (5)-2-(1,3-dioxoisindolin-2-yl)-3-(1-methyl-5-((triisopropylsilyl)ethynyl)-1H-indol-3-yl)propanoate

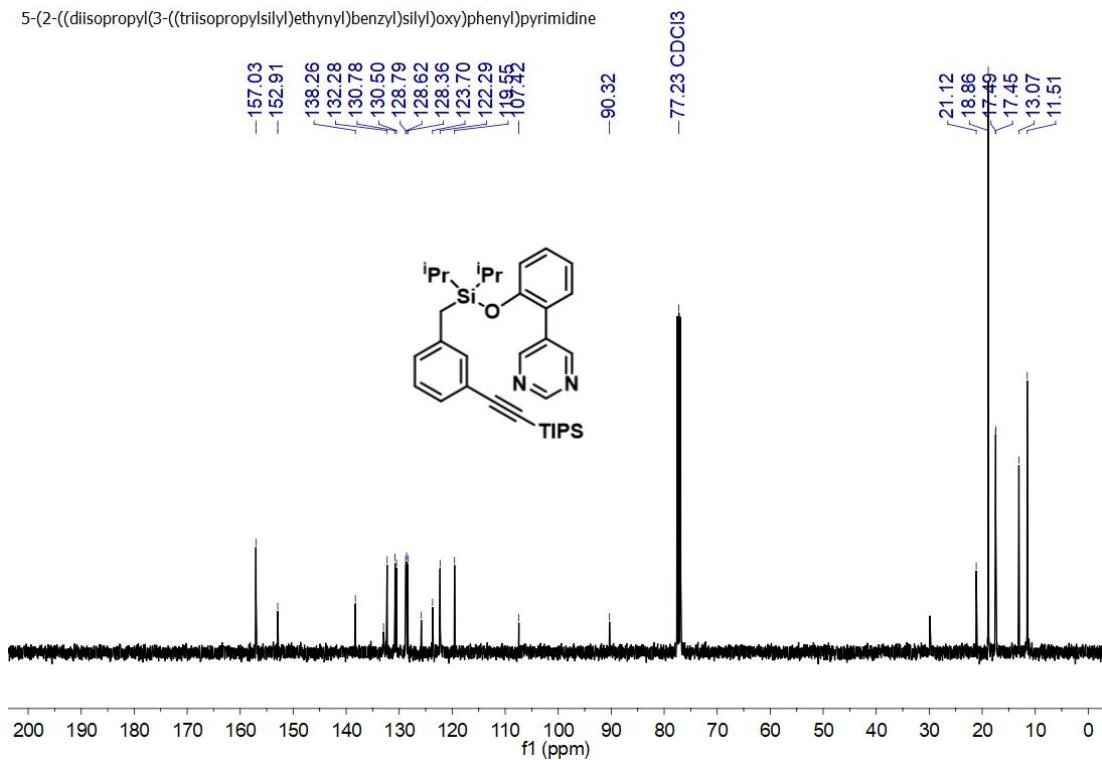


**Figure S67.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **37**

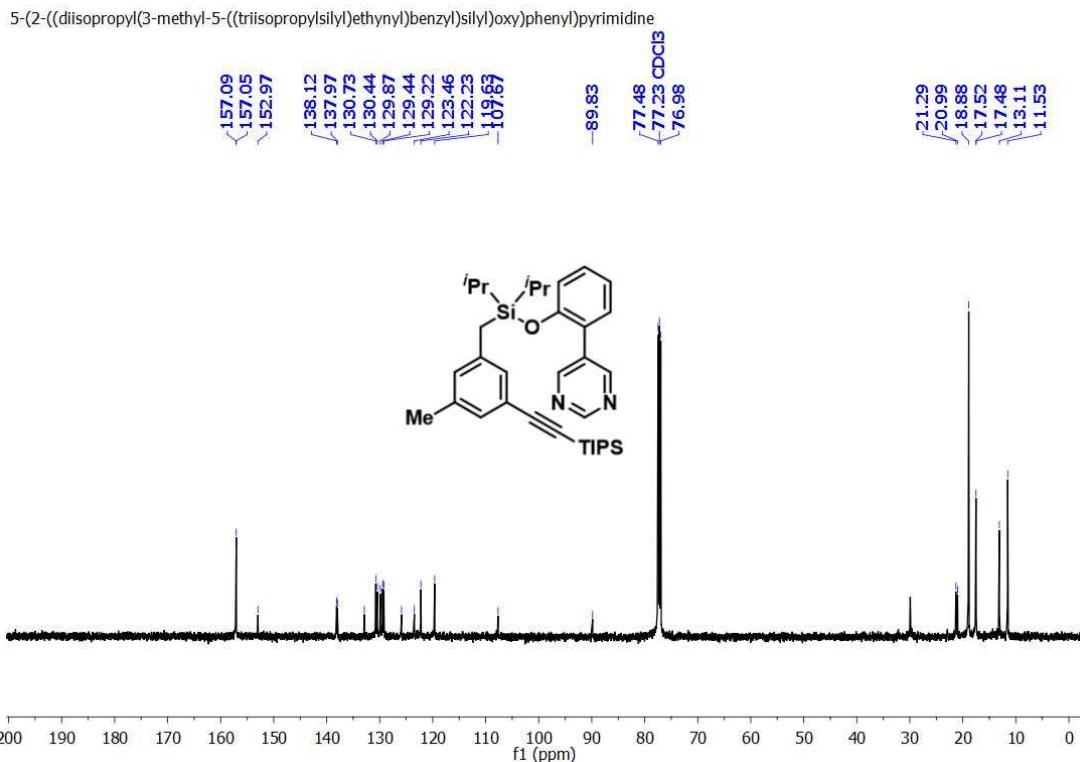
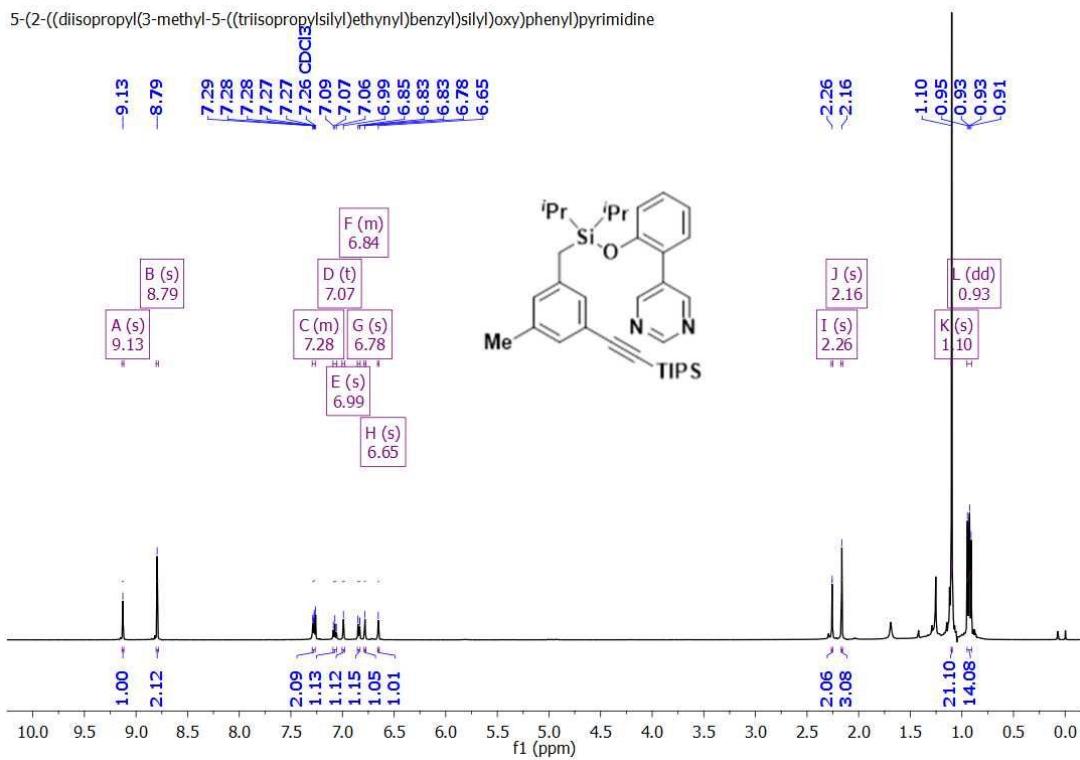
5-(2-((diisopropyl(3-((triisopropylsilyl)ethynyl)benzyl)silyloxy)phenyl)pyrimidine



5-(2-((diisopropyl(3-((triisopropylsilyl)ethynyl)benzyl)silyloxy)phenyl)pyrimidine

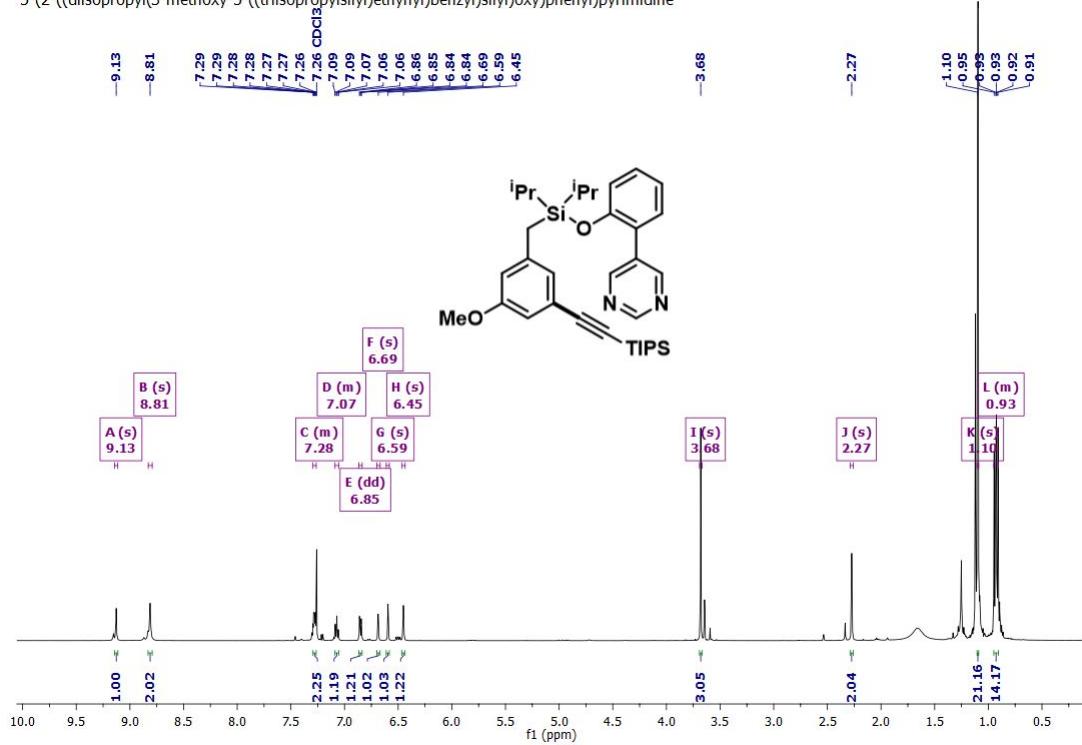


**Figure S68.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **38**

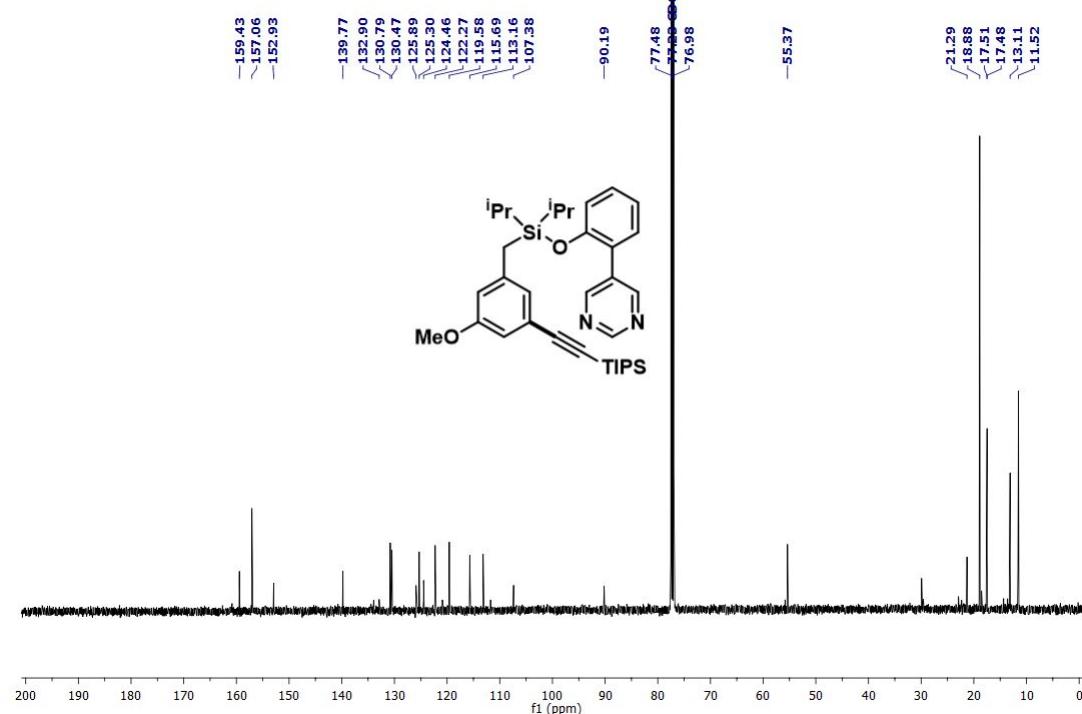


**Figure S69.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **39**

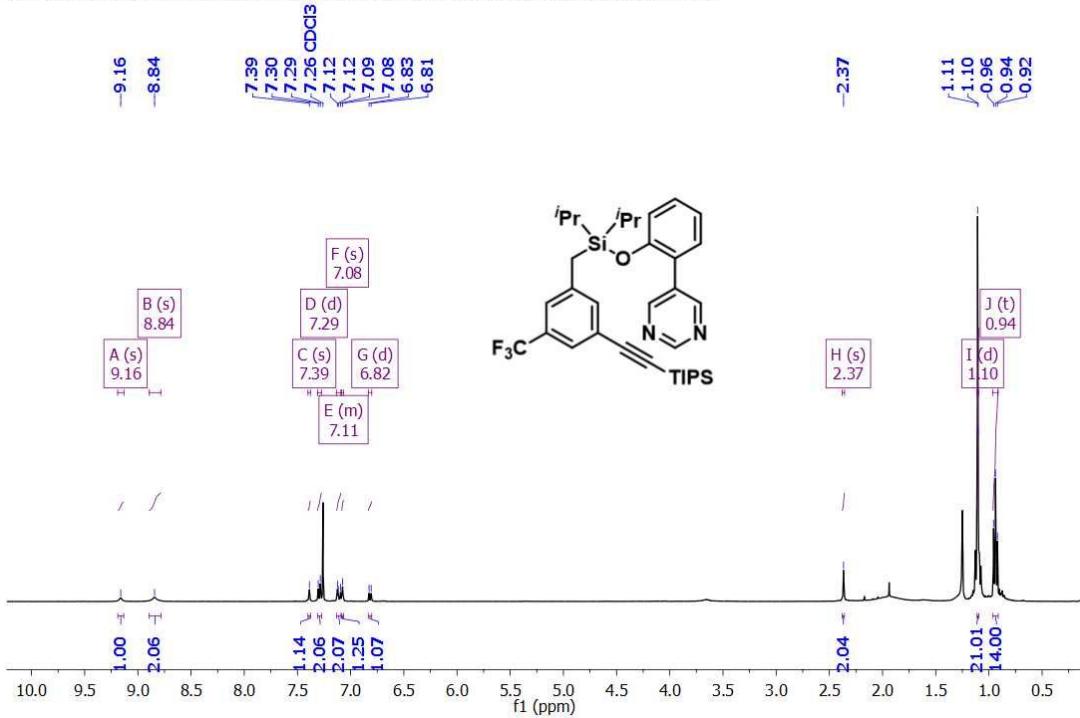
5-(2-((diisopropyl(3-methoxy-5-((trisopropylsilyl)ethynyl)benzyl)silyloxy)phenyl)pyrimidine



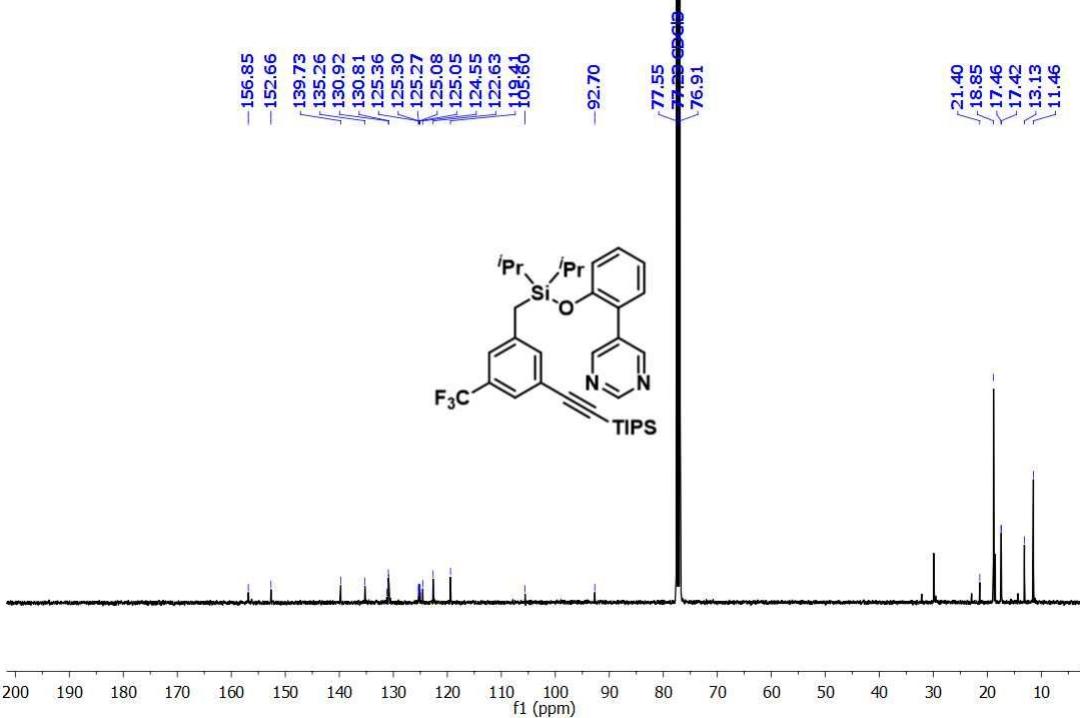
5-(2-((diisopropyl(3-methoxy-5-((trisopropylsilyl)ethynyl)benzyl)silyloxy)phenyl)pyrimidine



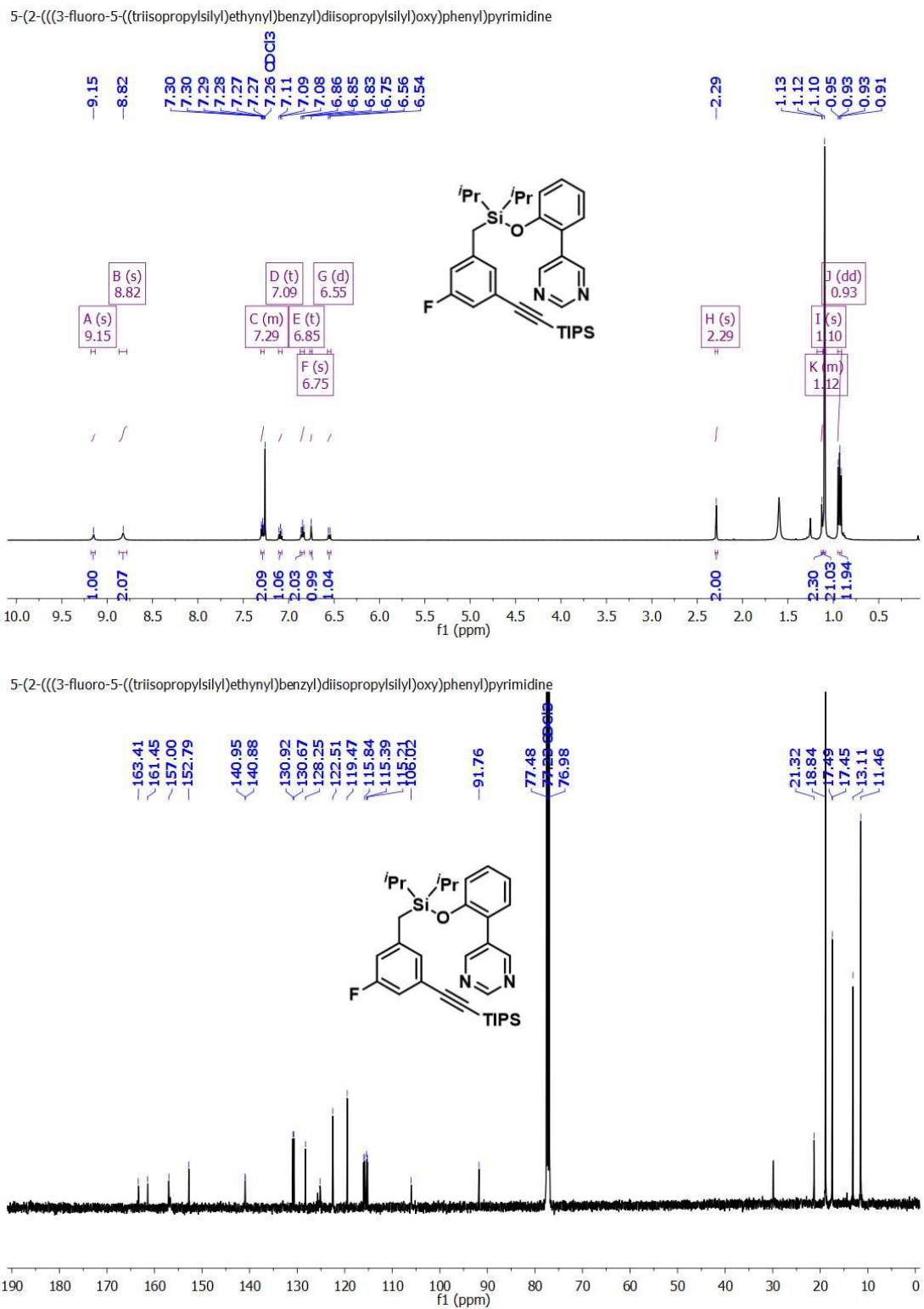
5-(2-((diisopropyl(3-(trifluoromethyl)-5-((triisopropylsilyl)ethynyl)benzyl)silyloxy)phenyl)pyrimidine



5-(2-((diisopropyl(3-(trifluoromethyl)-5-((triisopropylsilyl)ethynyl)benzyl)silyloxy)phenyl)pyrimidine



**Figure S71.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **41**



**Figure S72.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **42**

5-(2-((diisopropyl(4-methoxy-3-((triisopropylsilyl)ethynyl)benzyl)silyloxy)phenyl)pyrimidine

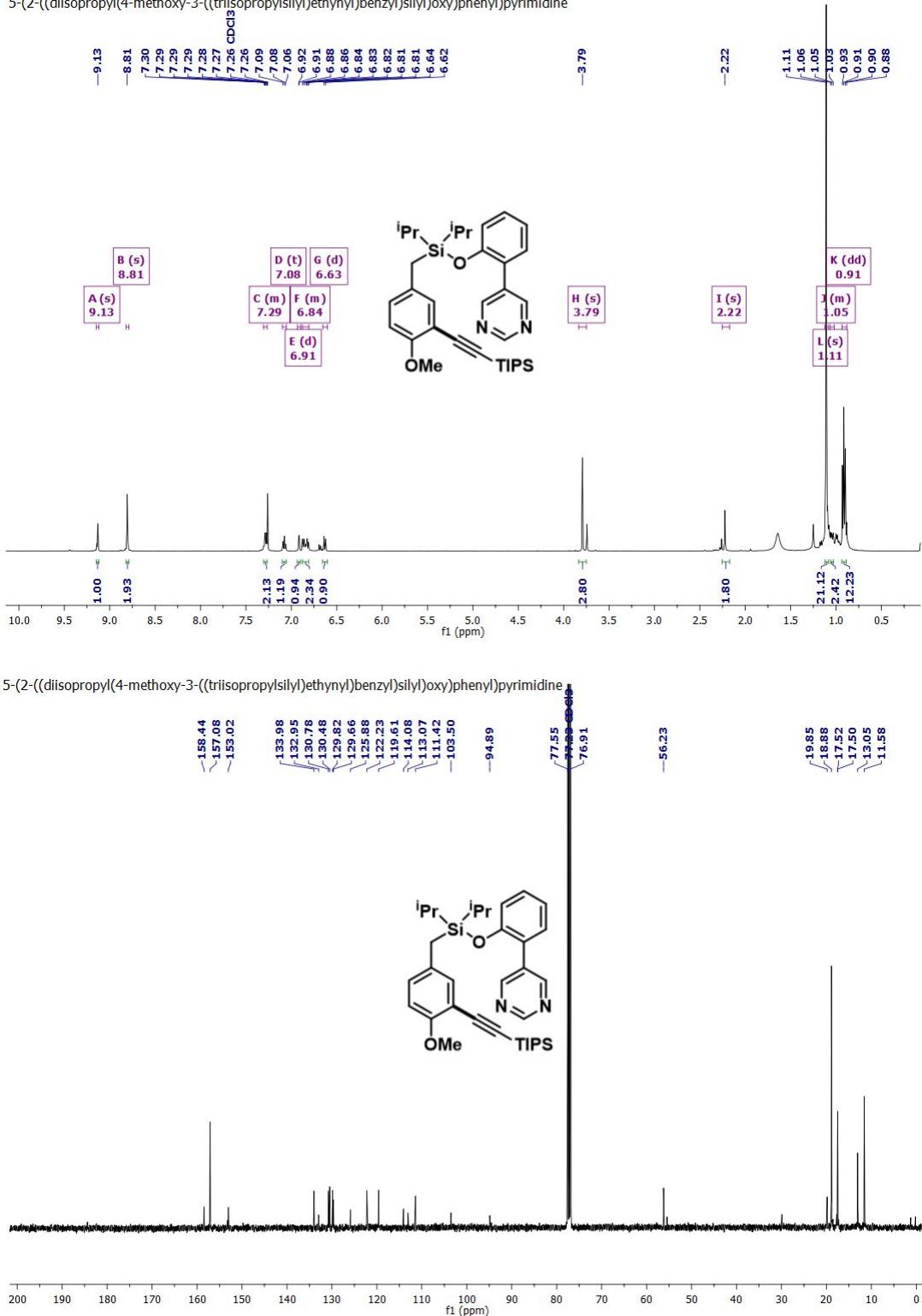
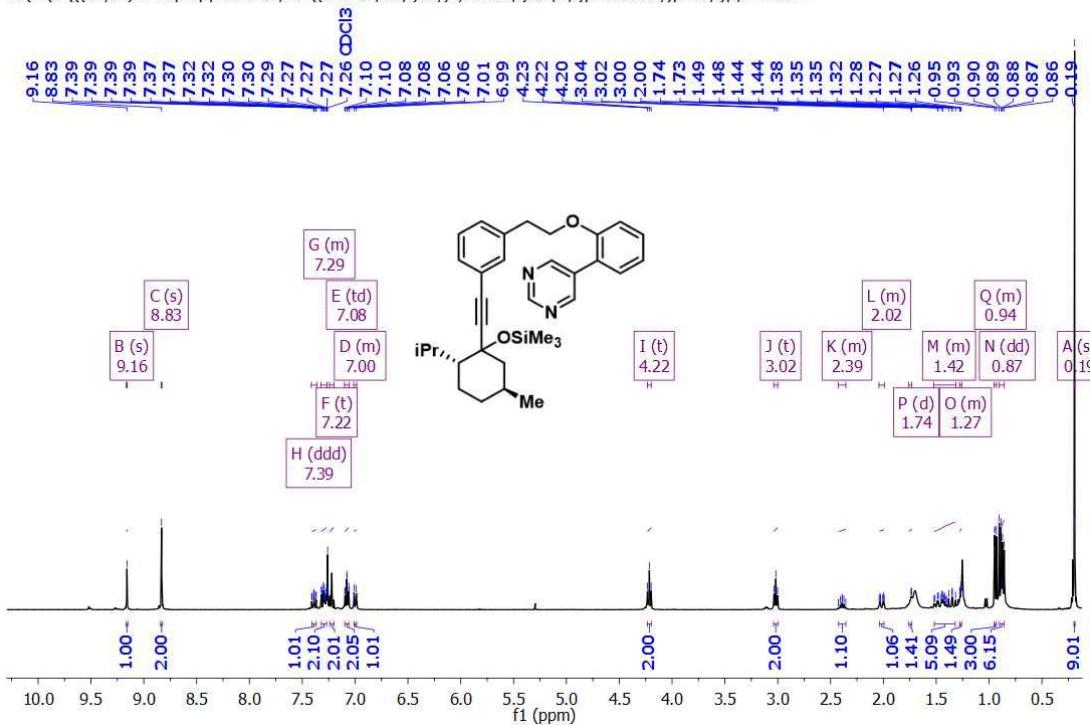
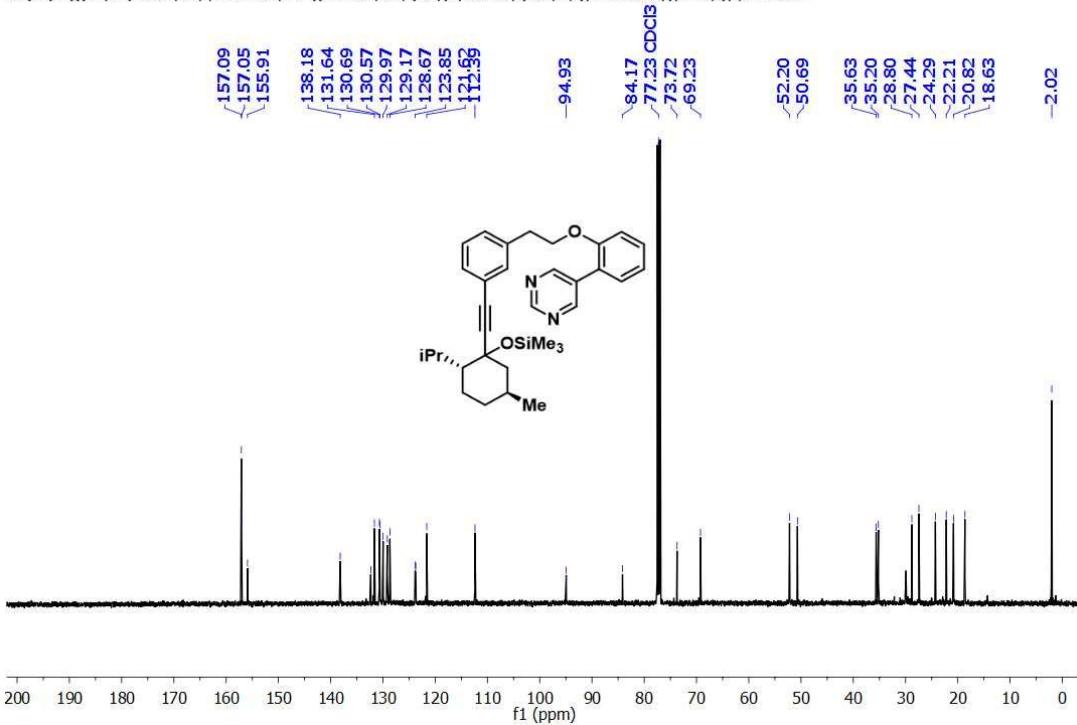


Figure S73. <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of 43

5-(2-(3-(((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenethoxy)phenyl)pyrimidine

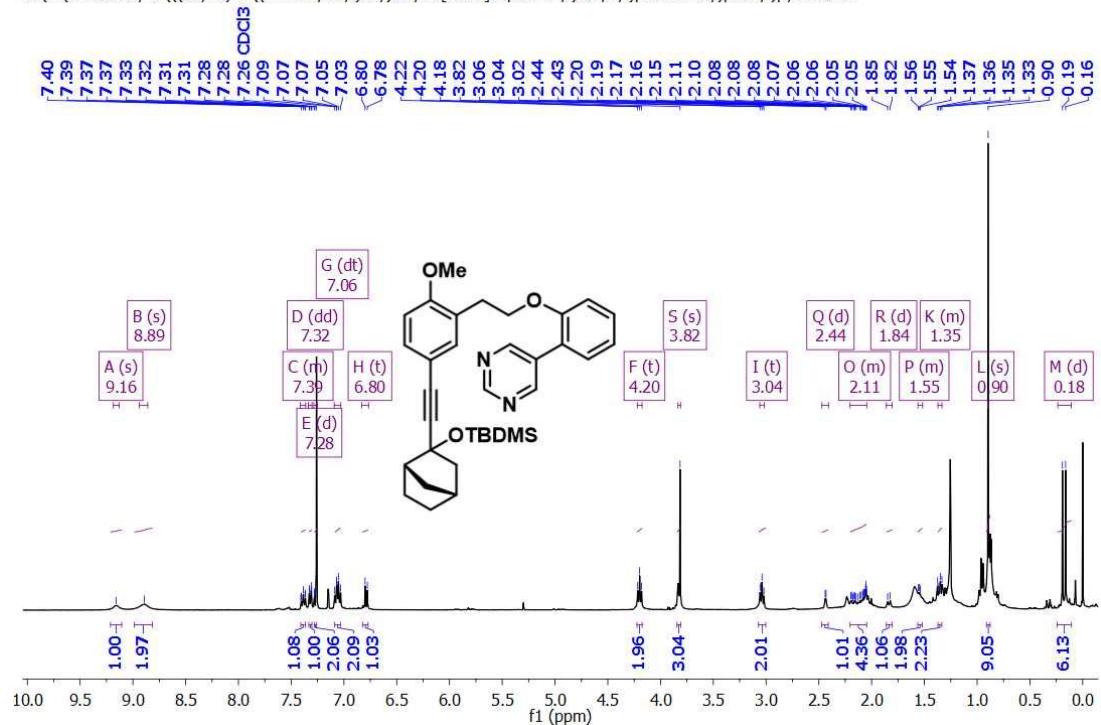


5-(2-(3-(((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenethoxy)phenyl)pyrimidine



**Figure S74.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **44**

5-(2-(2-methoxy-5-(((1S,4R)-2-((trimethylsilyl)oxy)bicyclo[2.2.1]heptan-2-yl)ethynyl)phenethoxy)phenyl)pyrimidine



5-(2-((5-(((1S,4R)-2-((tert-butyldimethylsilyl)oxy)bicyclo[2.2.1]heptan-2-yl)ethynyl)-2-methoxyphenethoxy)phenyl)pyrimidine

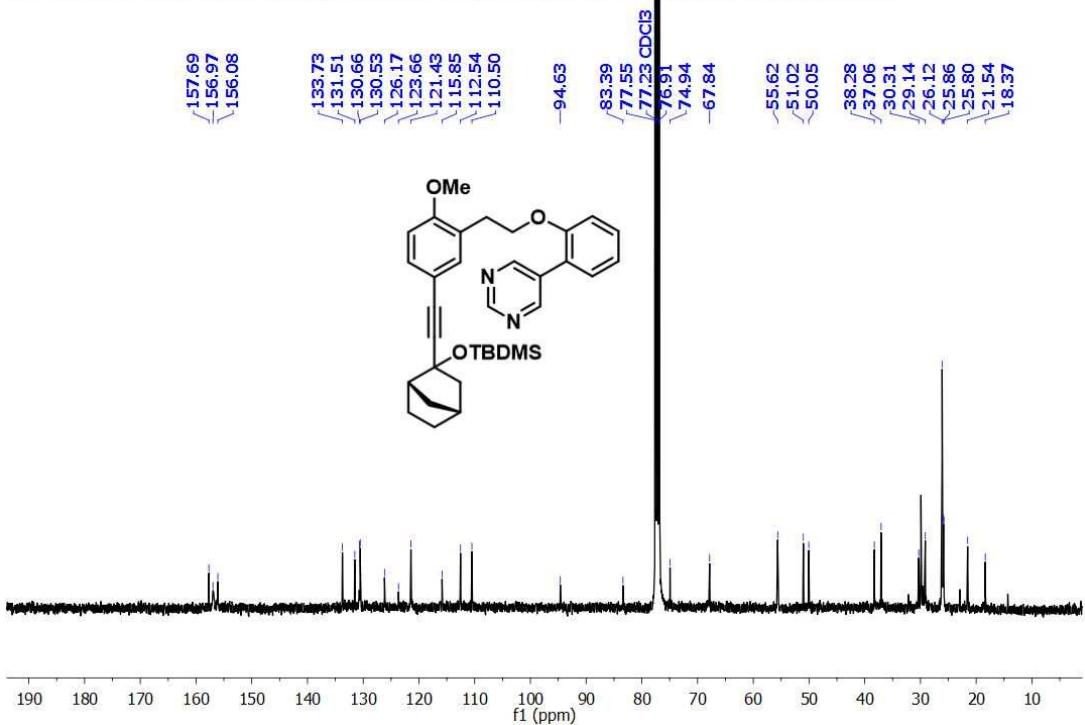
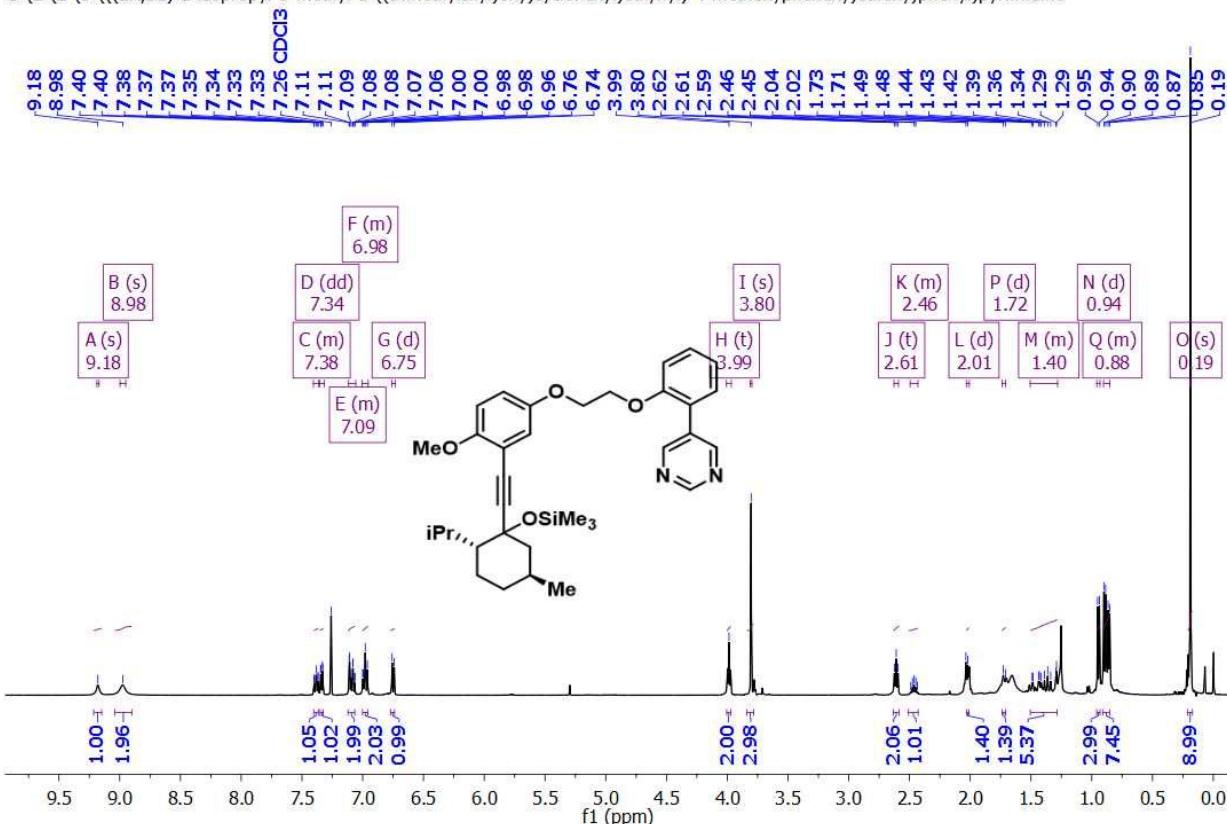
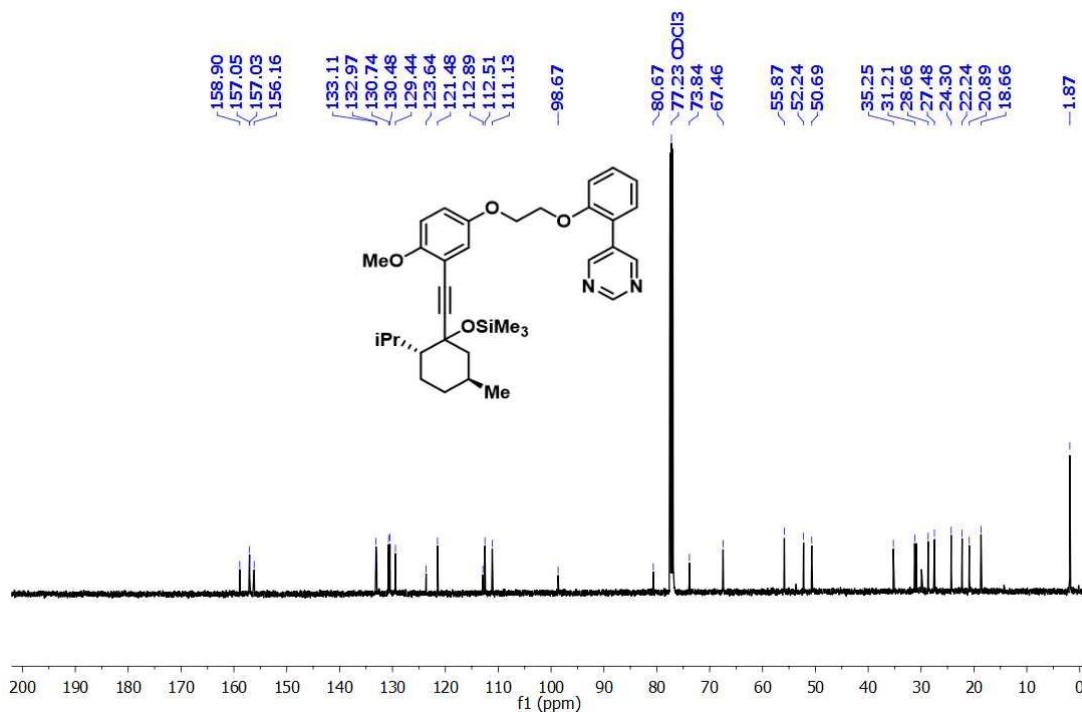


Figure S75.  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **45**

5-(2-(2-(3-(((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)-4-methoxyphenoxy)ethoxy)phenyl)pyrimidine

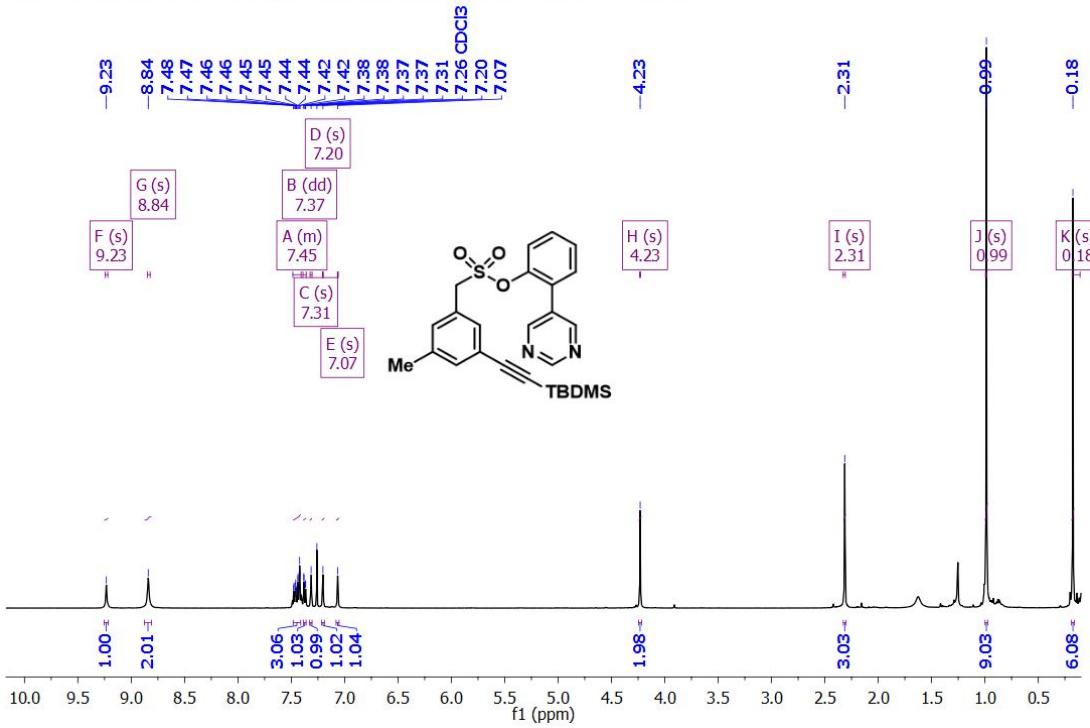


5-(2-(2-(3-(((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)-4-methoxyphenoxy)ethoxy)phenyl)pyrimidine

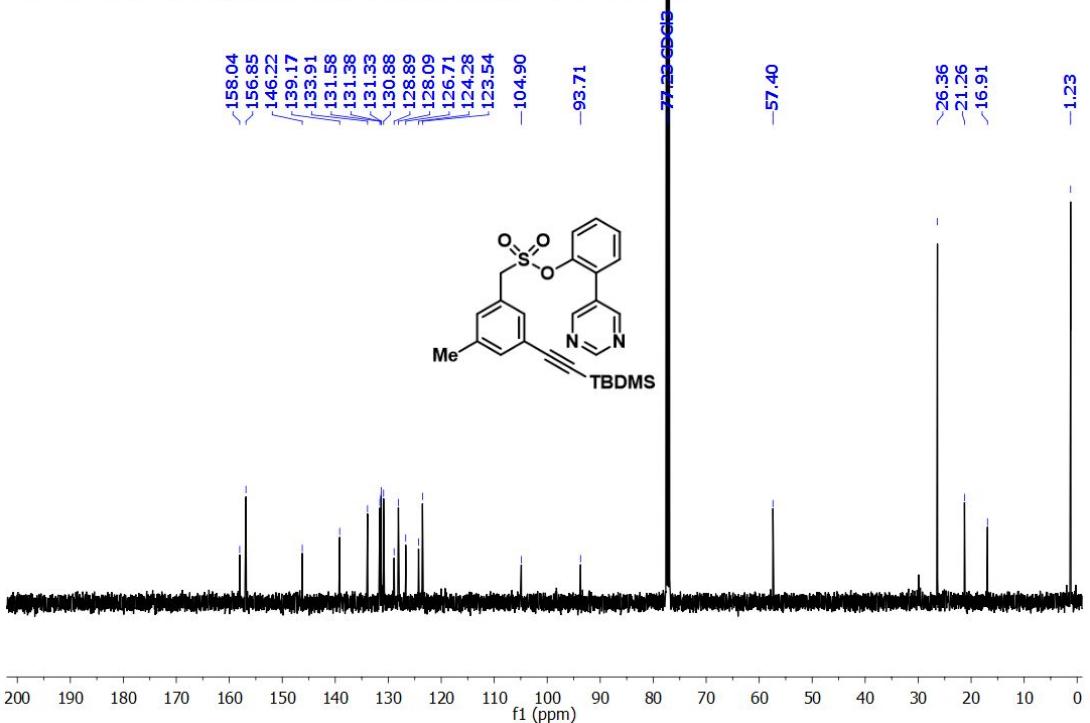


**Figure S76.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **46**

2-(pyrimidin-5-yl)phenyl (3-((tert-butyldimethylsilyl)ethynyl)-5-methylphenyl)methanesulfonate

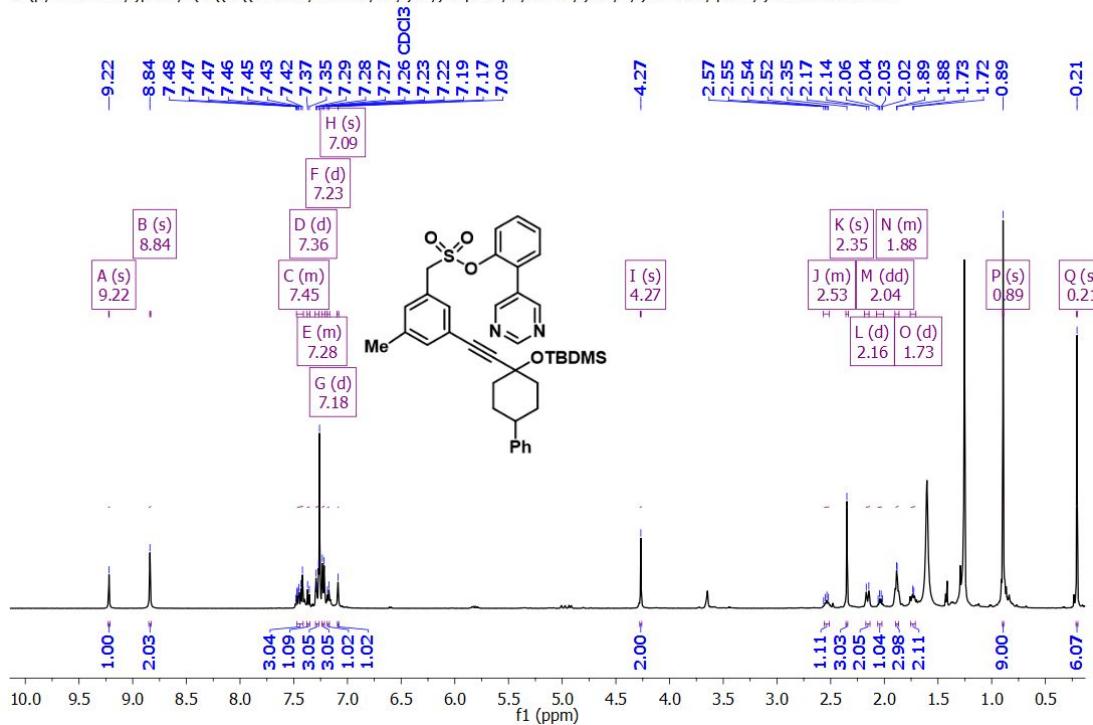


2-(pyrimidin-5-yl)phenyl (3-((tert-butyldimethylsilyl)ethynyl)-5-methylphenyl)methanesulfonate

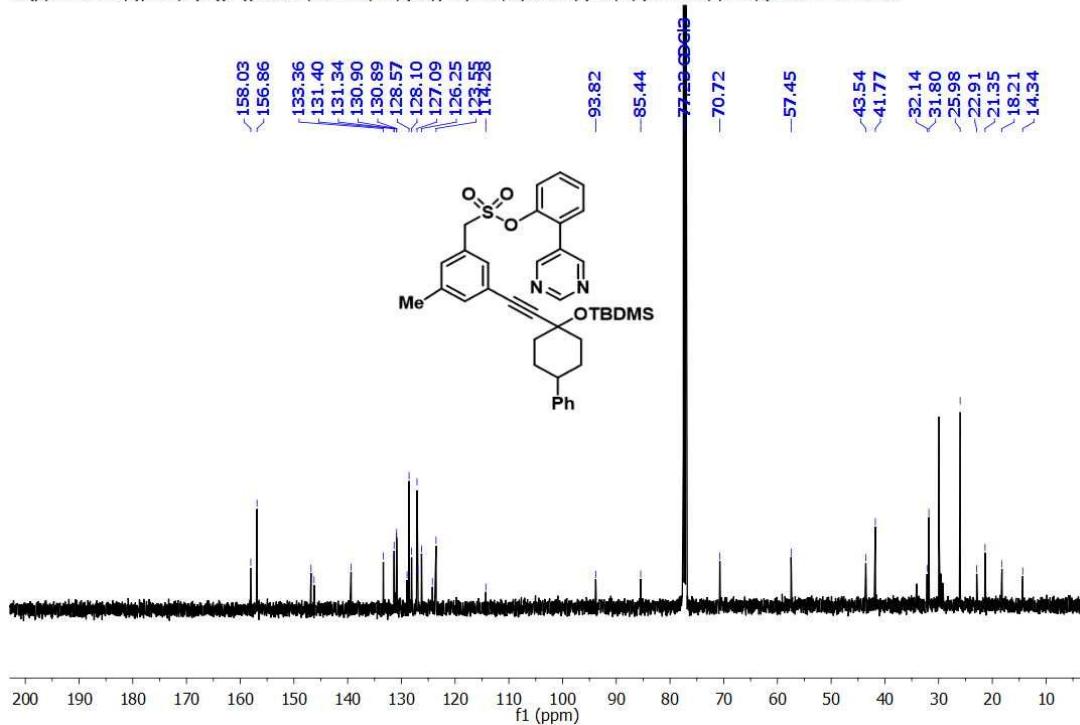


**Figure S77.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **47**

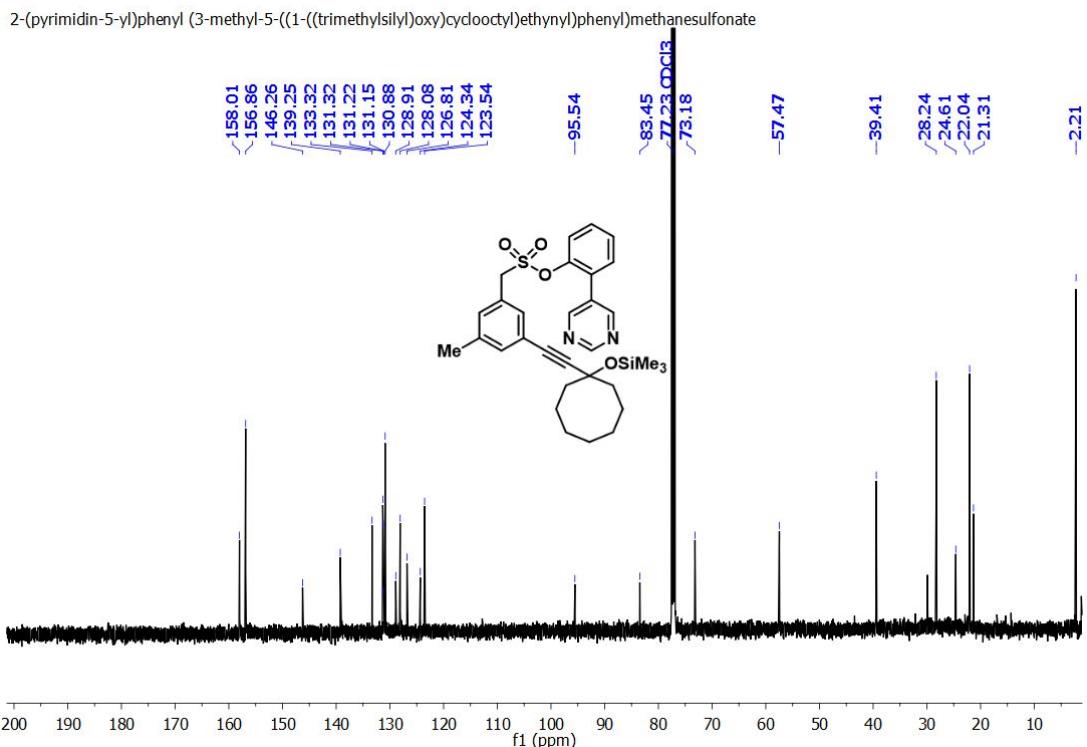
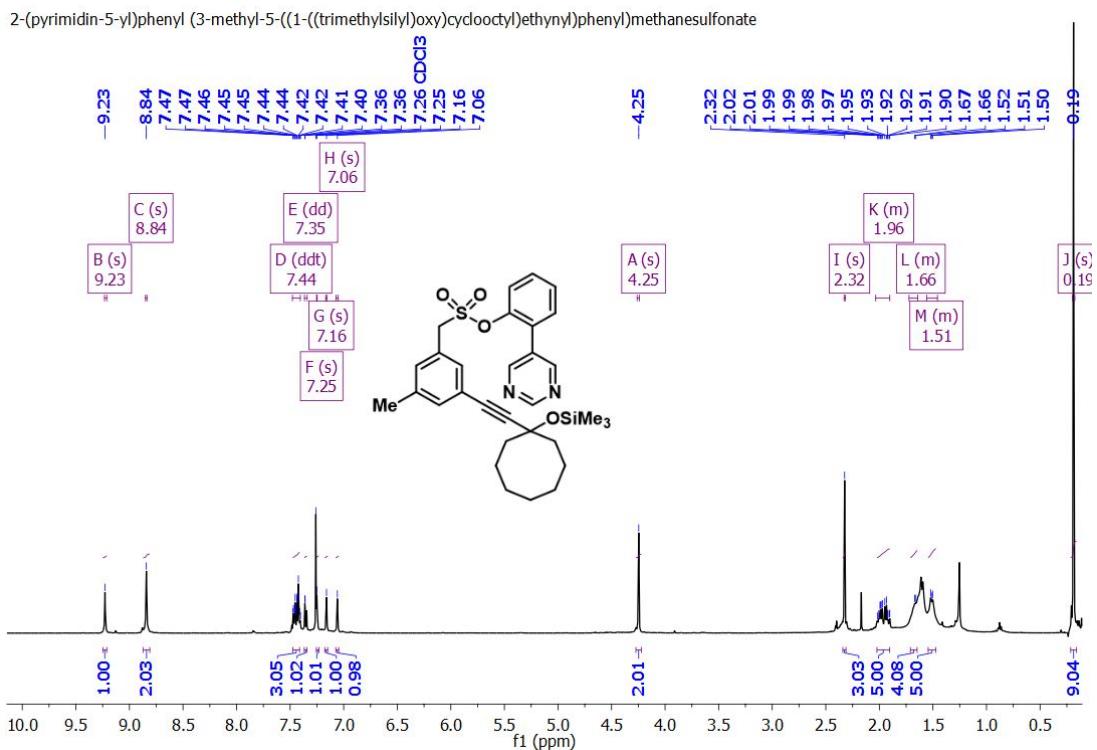
2-(pyrimidin-5-yl)phenyl (3-((1-((tert-butyldimethylsilyl)oxy)-4-phenylcyclohexyl)ethynyl)-5-methylphenyl)methanesulfonate



2-(pyrimidin-5-yl)phenyl (3-((1-((tert-butyldimethylsilyl)oxy)-4-phenylcyclohexyl)ethynyl)-5-methylphenyl)methanesulfonate

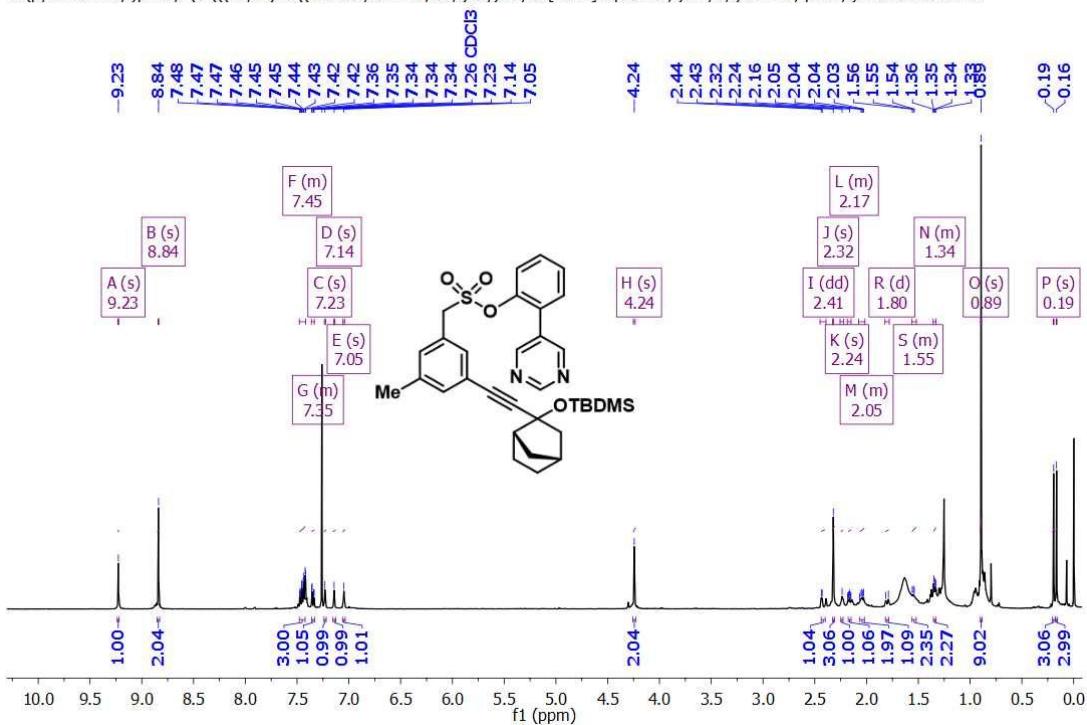


**Figure S78.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **48**

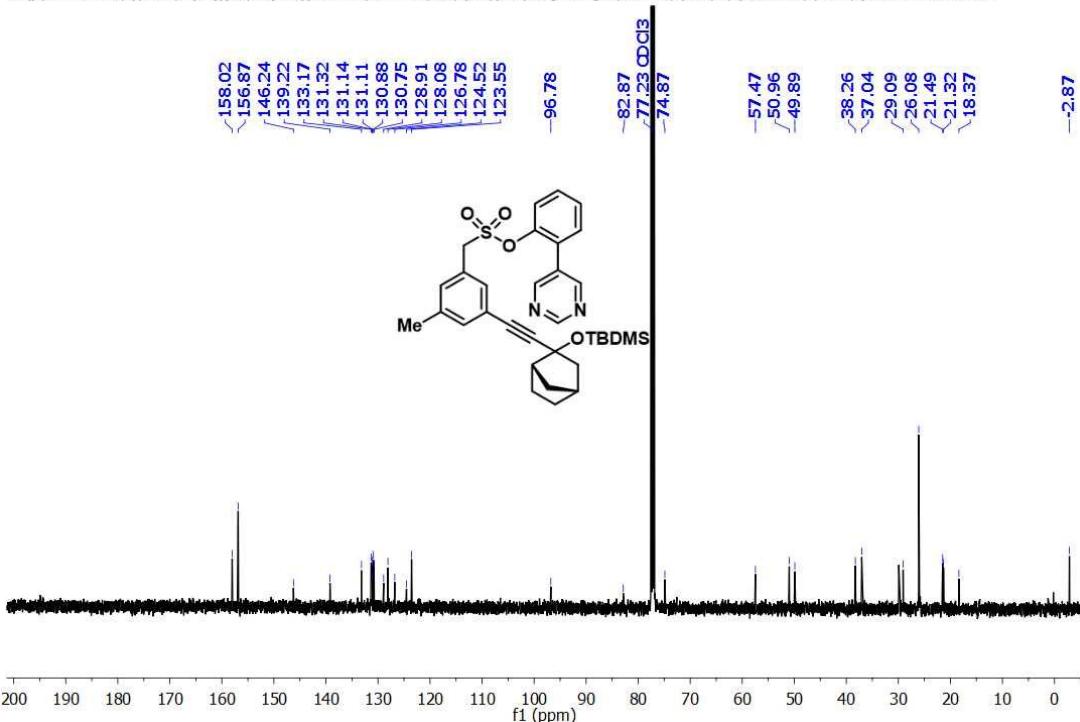


**Figure S79.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **49**

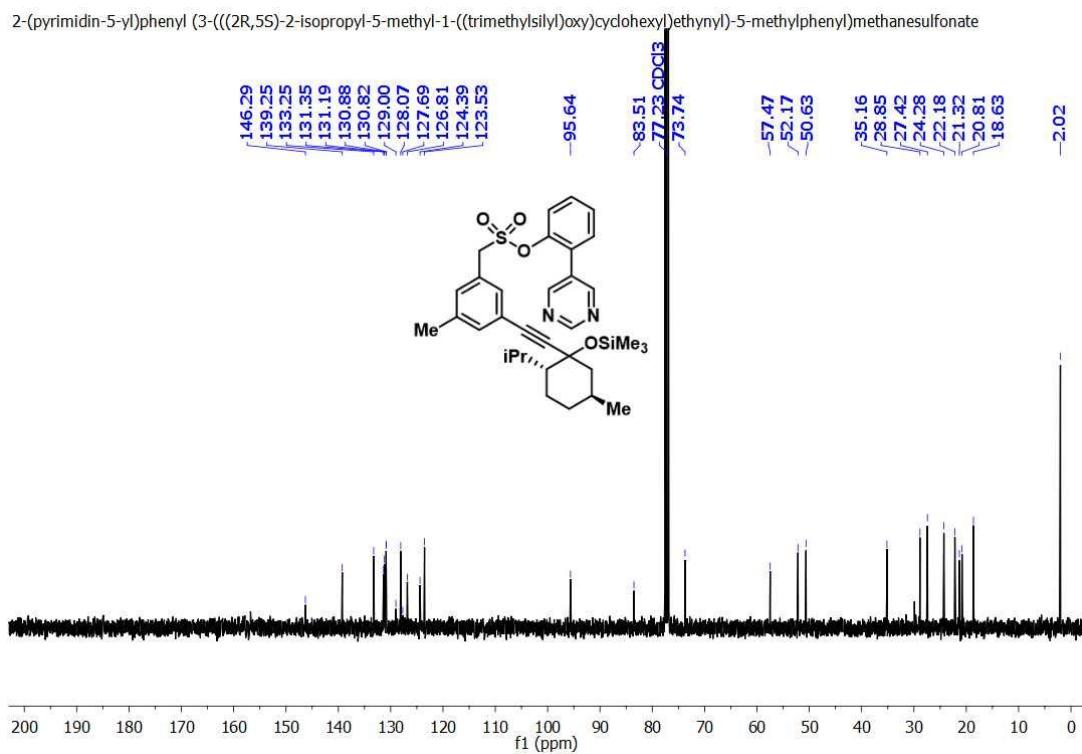
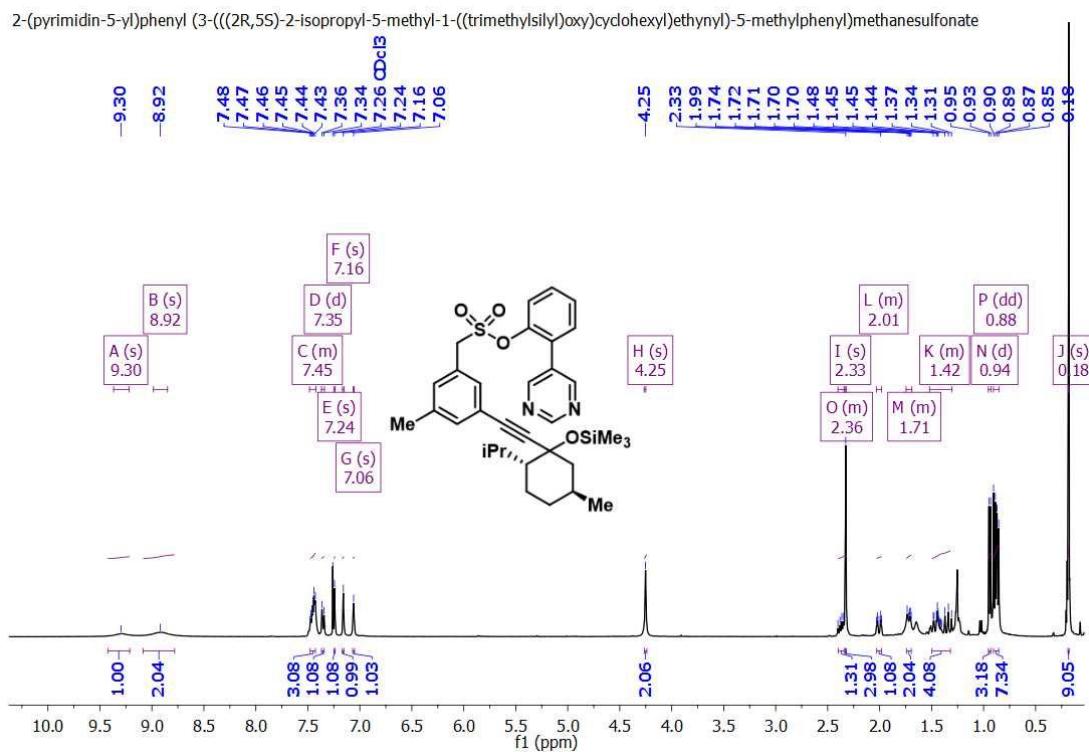
2-(pyrimidin-5-yl)phenyl (3-(((1*S*,4*R*)-2-((tert-butyldimethylsilyl)oxy)bicyclo[2.2.1]heptan-2-yl)ethynyl)-5methylphenyl)methanesulfonate



2-(pyrimidin-5-yl)phenyl (3-(((1*S*,4*R*)-2-((tert-butyldimethylsilyl)oxy)bicyclo[2.2.1]heptan-2-yl)ethynyl)-5-methylphenyl)methanesulfonate

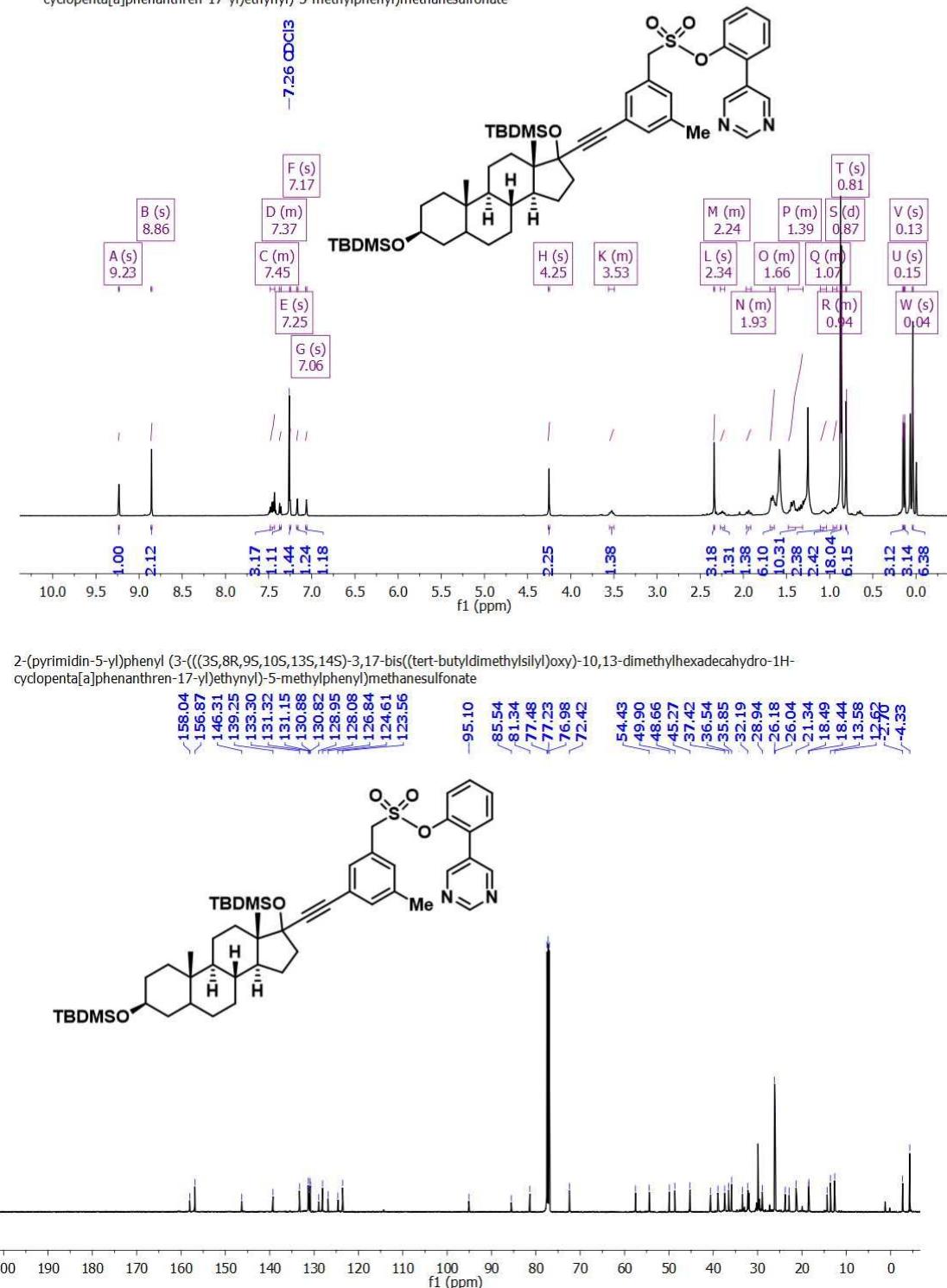


**Figure S80.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **50**



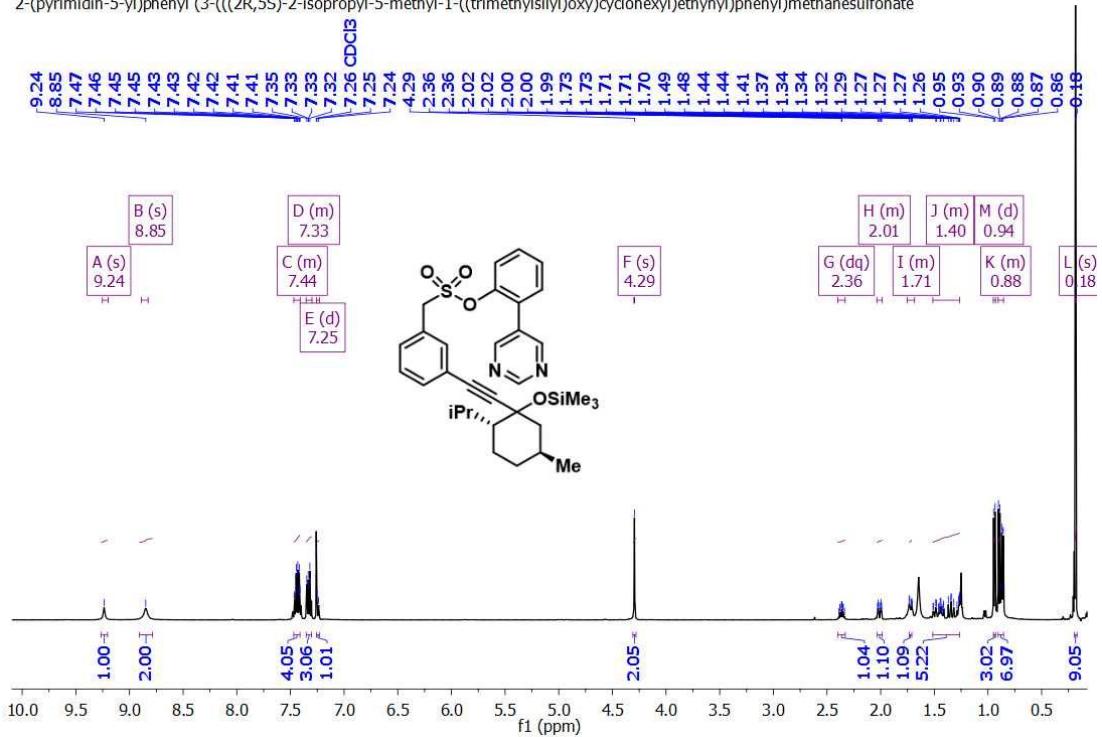
**Figure S81.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **51**

2-(pyrimidin-5-yl)phenyl (3-(((3S,8R,9S,10S,13S,14S)-3,17-bis((tert-butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethynyl)-5-methylphenyl)methanesulfonate

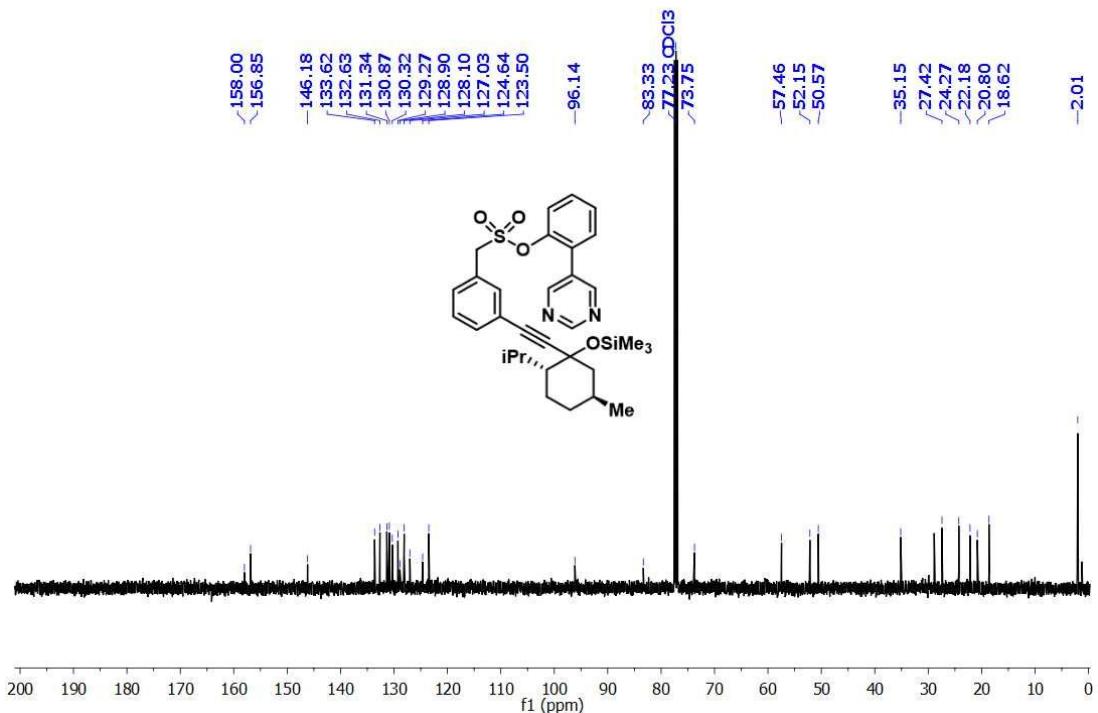


**Figure S82.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **52**

2-(pyrimidin-5-yl)phenyl (3-(((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)methanesulfonate

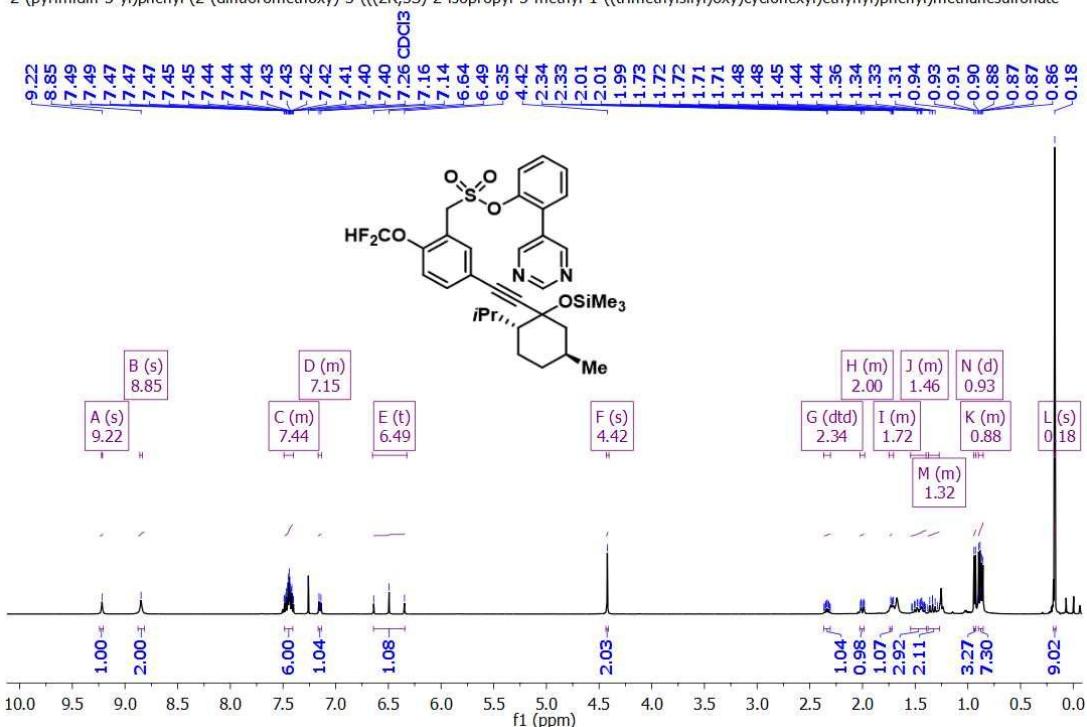


2-(pyrimidin-5-yl)phenyl (3-(((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)methanesulfonate

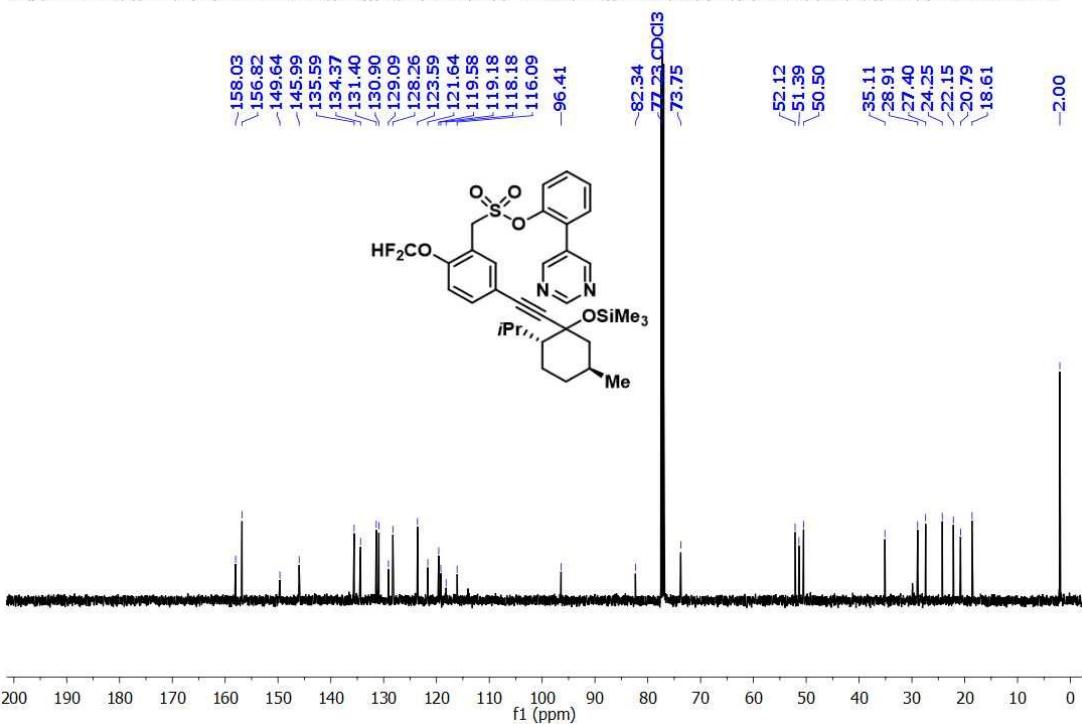


**Figure S83.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **53**

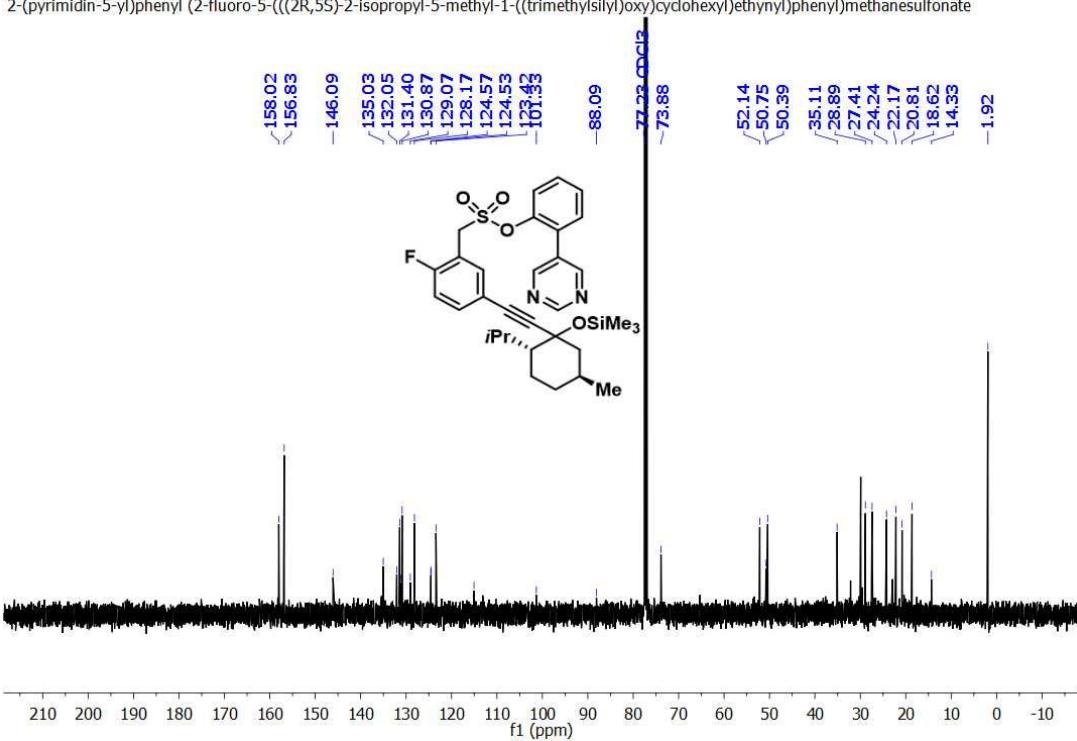
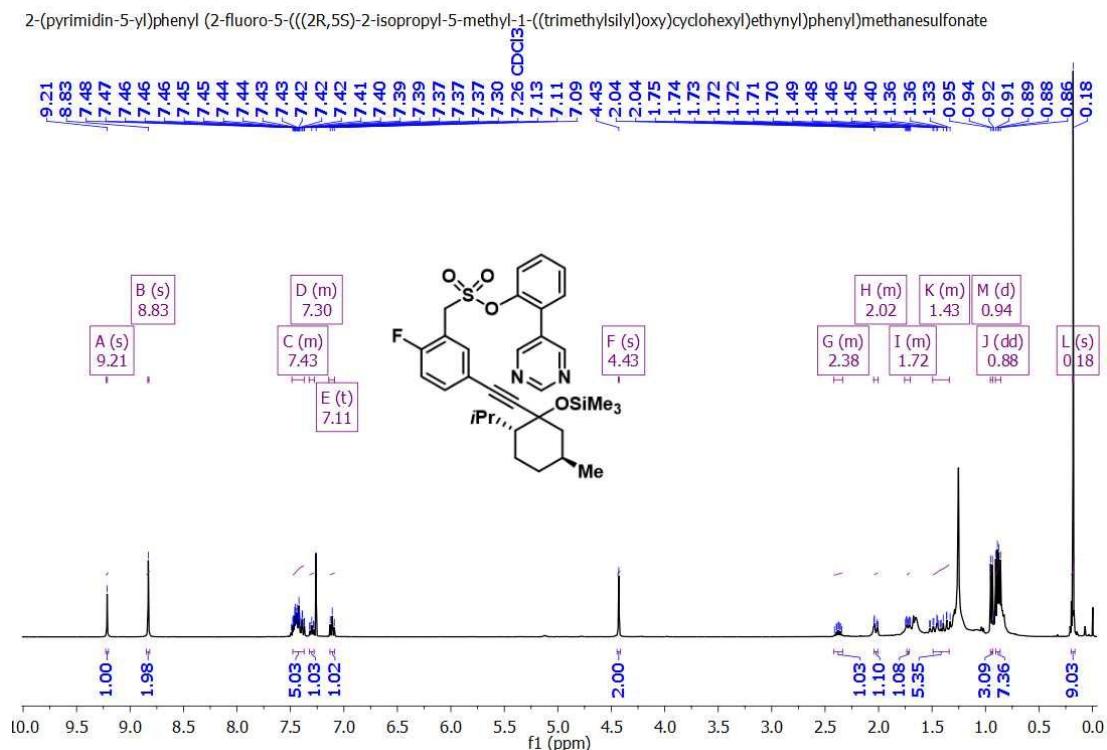
2-(pyrimidin-5-yl)phenyl (2-(difluoromethoxy)-5-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)methanesulfonate



2-(pyrimidin-5-yl)phenyl (2-(difluoromethoxy)-5-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)methanesulfonate

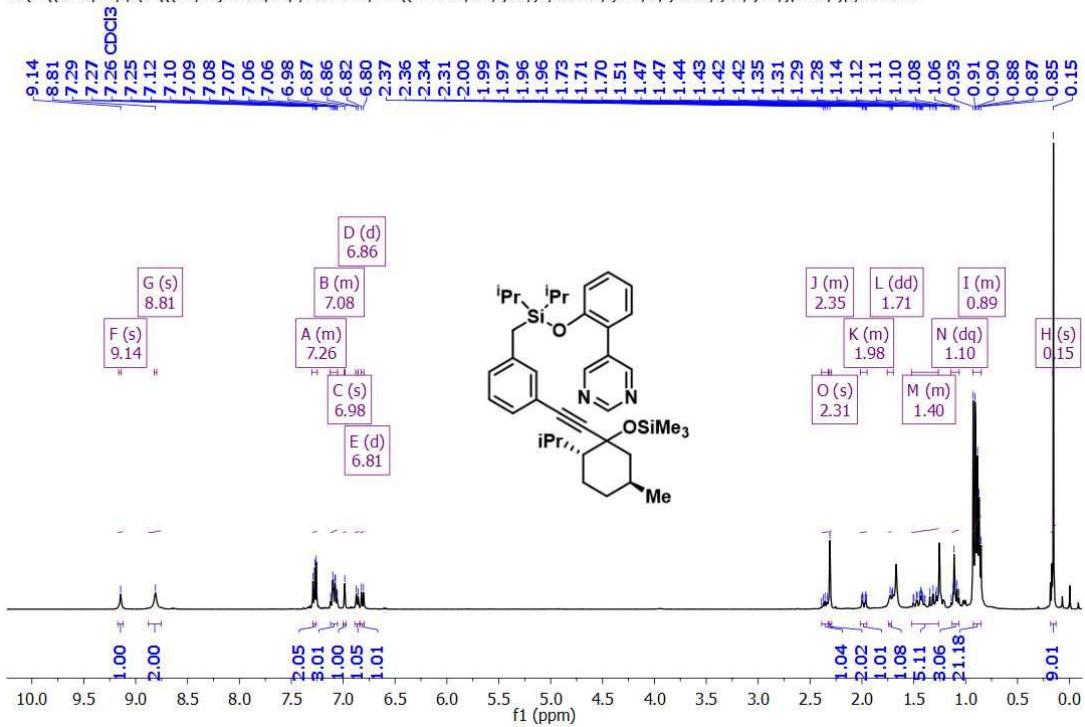


**Figure S84.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **54**

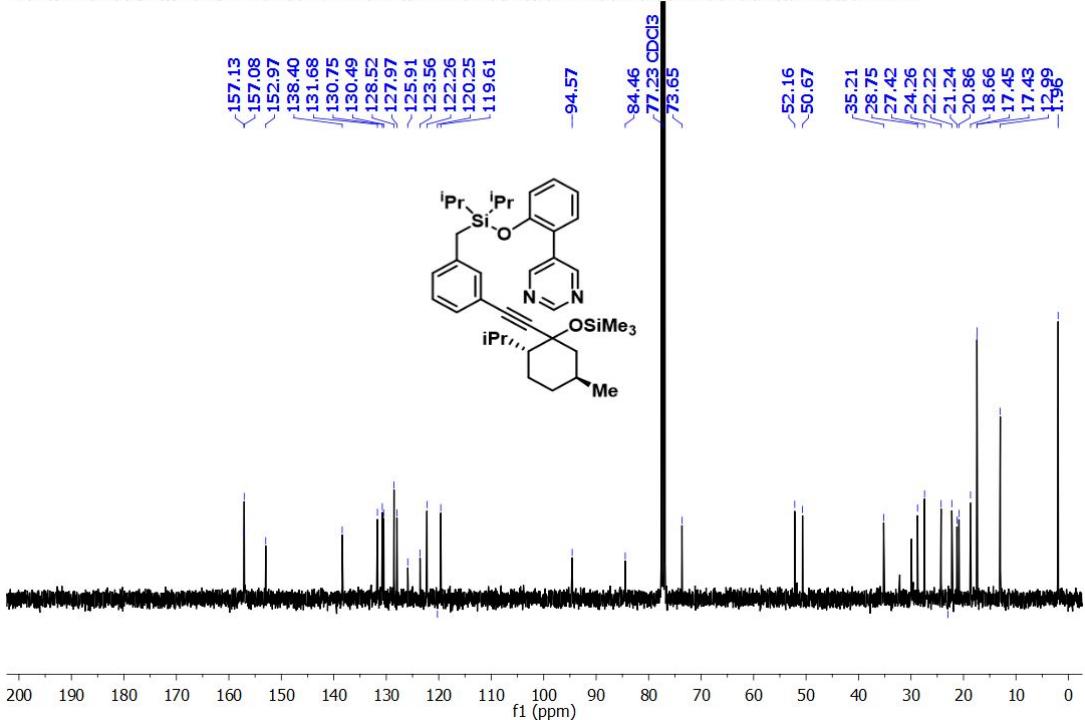


**Figure S85.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **55**

5-(2-((diisopropyl(3-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)benzyl)silyl)oxy)phenyl)pyrimidine

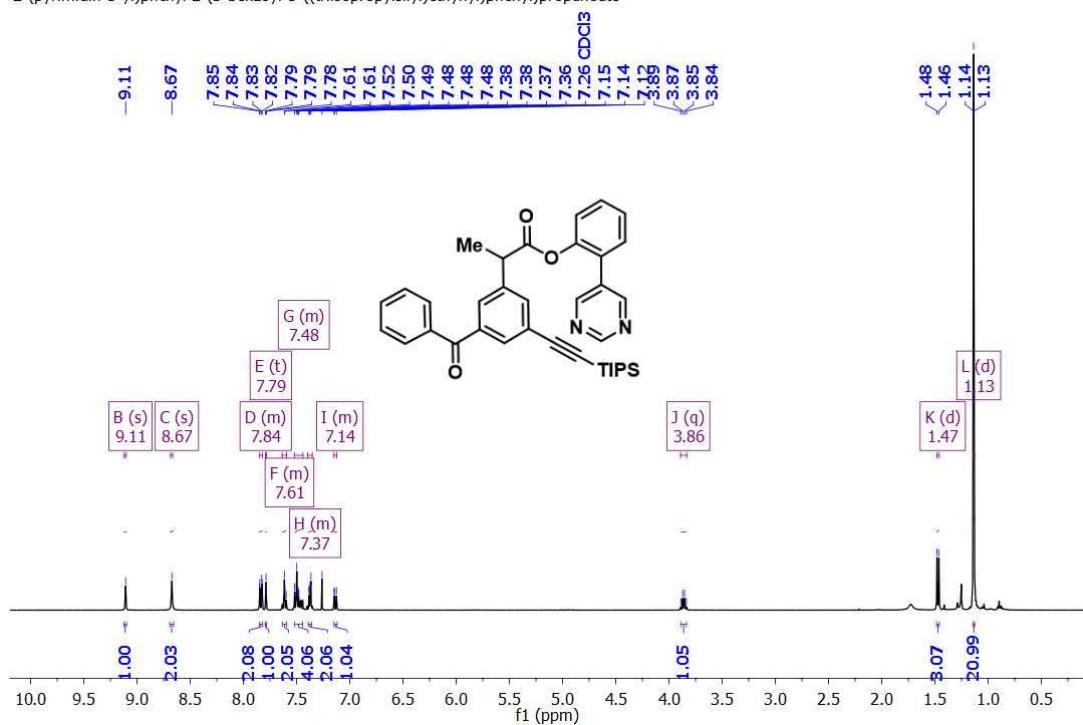


5-(2-((diisopropyl(3-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)benzyl)silyl)oxy)phenyl)pyrimidine

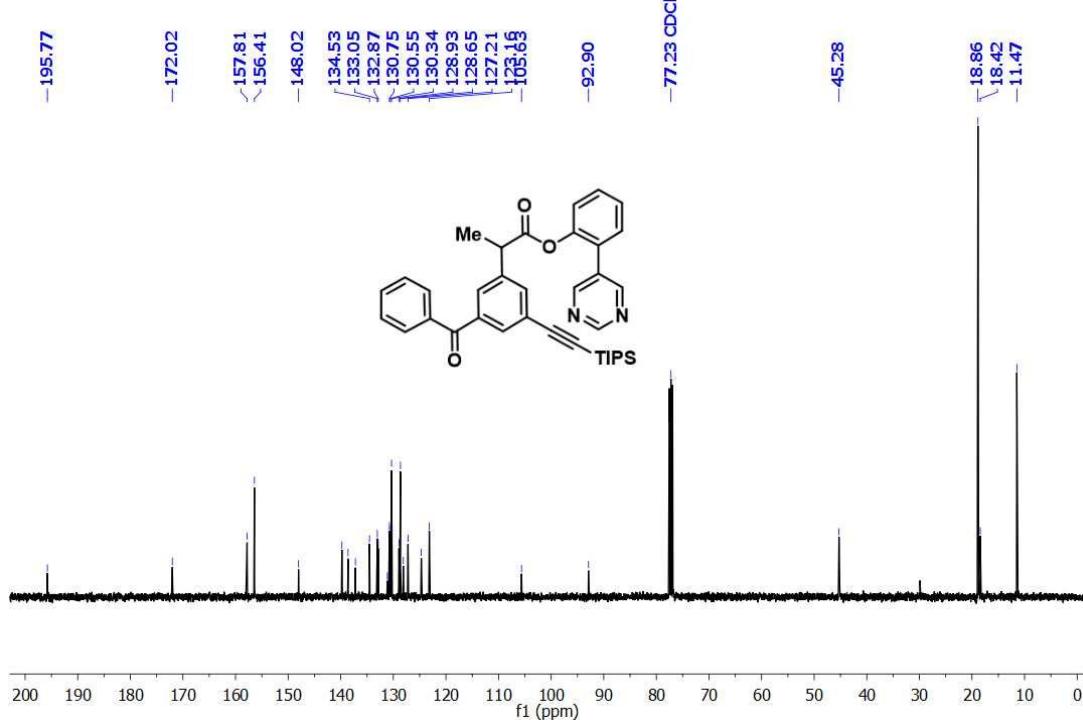


**Figure S86.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **56**

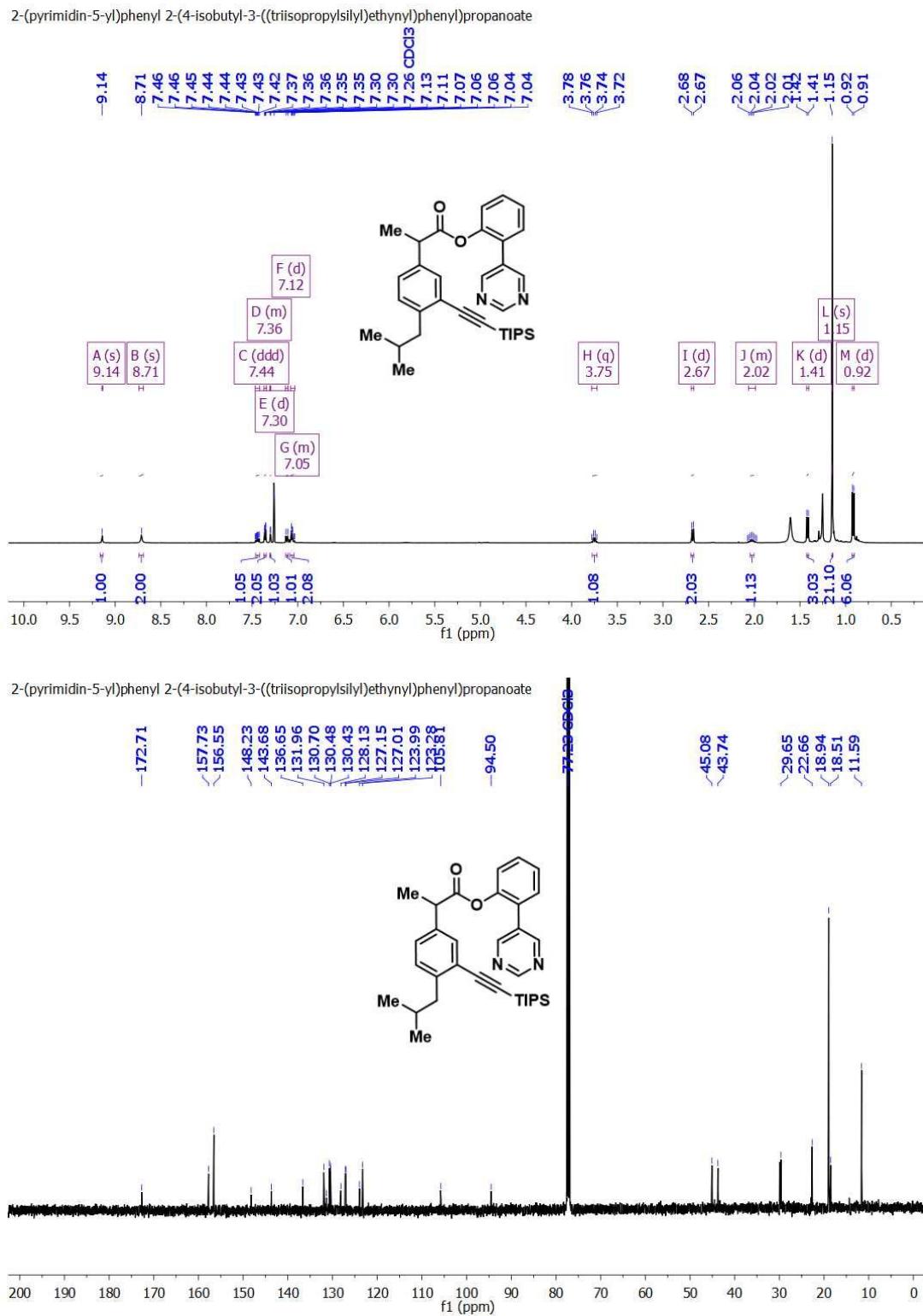
2-(pyrimidin-5-yl)phenyl 2-(3-benzoyl-5-((triisopropylsilyl)ethynyl)phenyl)propanoate



2-(pyrimidin-5-yl)phenyl 2-(3-benzoyl-5-((triisopropylsilyl)ethynyl)phenyl)propanoate

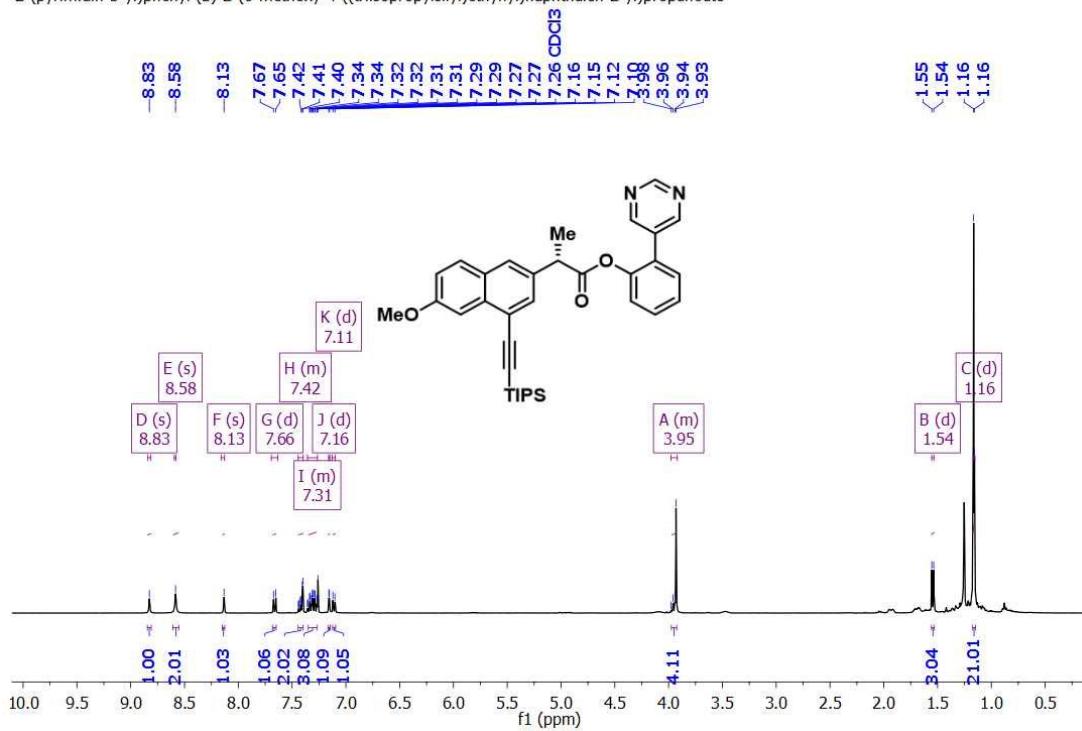


**Figure S87.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **57**

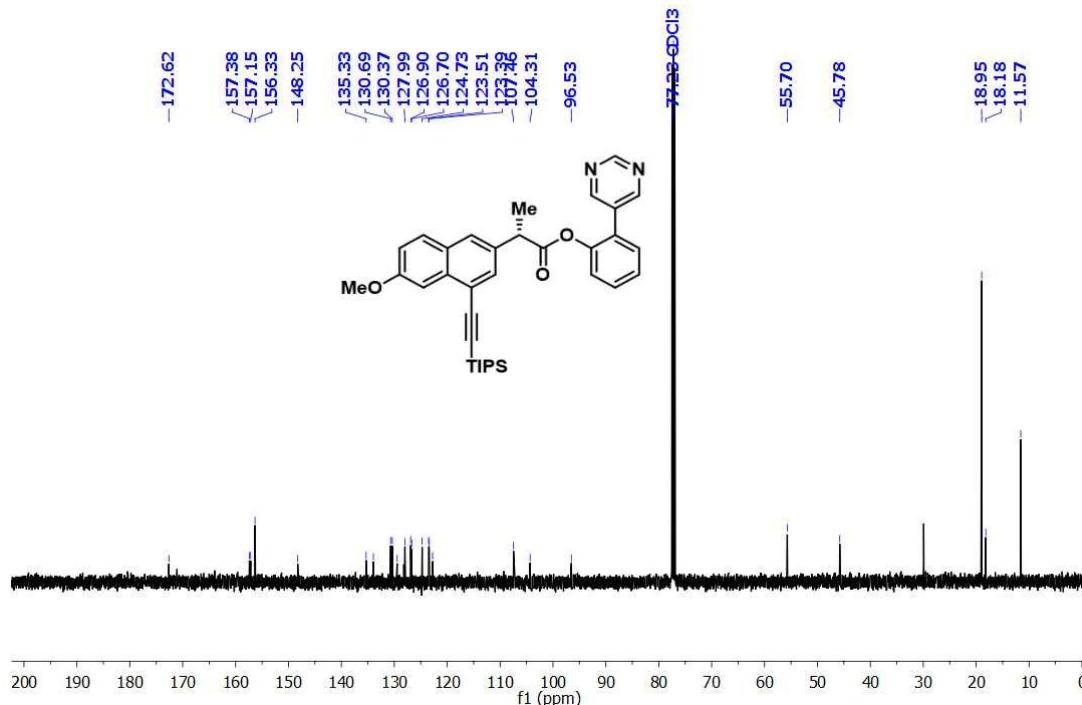


**Figure S88.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **58**

2-(pyrimidin-5-yl)phenyl (S)-2-(6-methoxy-4-((triisopropylsilyl)ethynyl)naphthalen-2-yl)propanoate

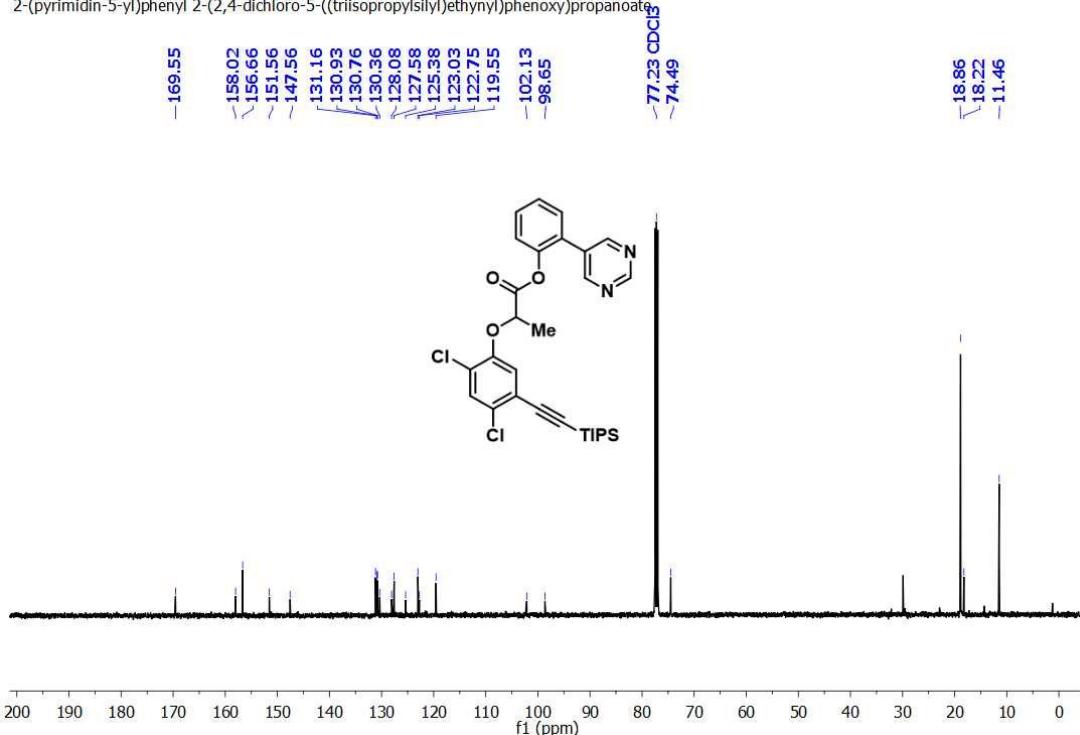
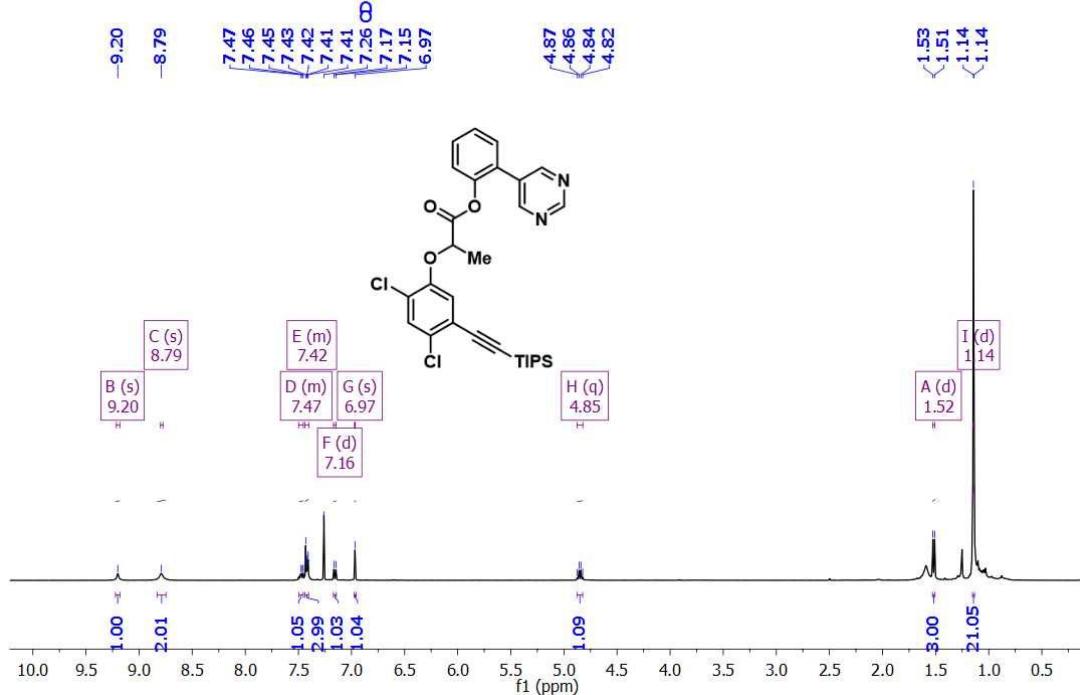


2-(pyrimidin-5-yl)phenyl (S)-2-(6-methoxy-4-((triisopropylsilyl)ethynyl)naphthalen-2-yl)propanoate



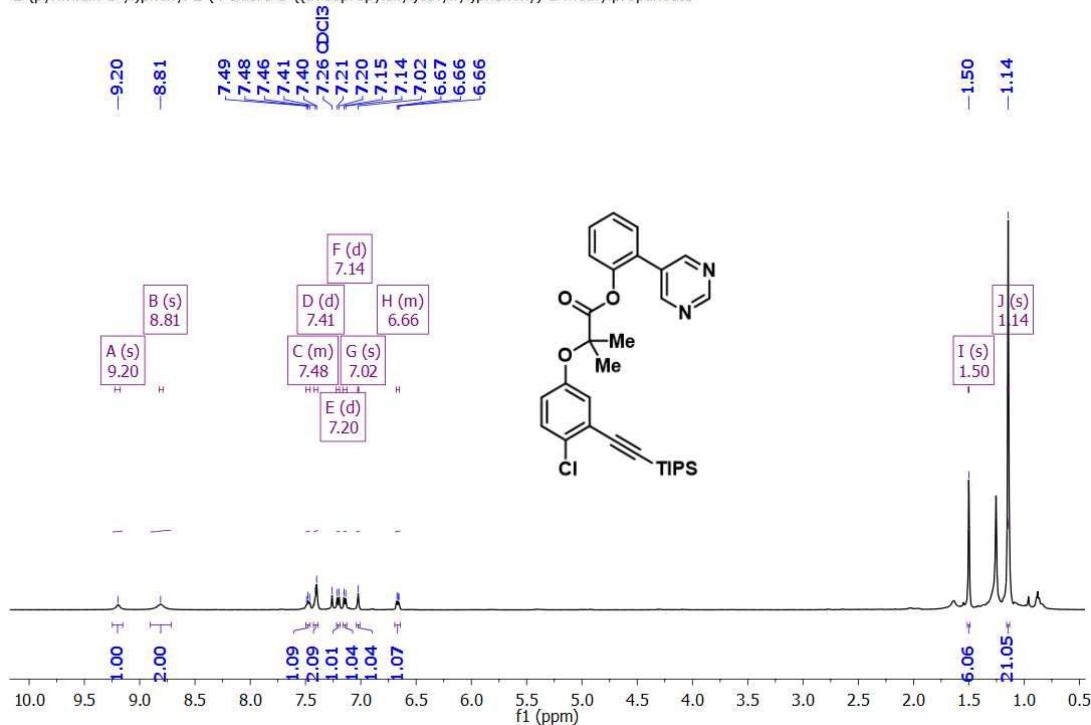
**Figure S89.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **59**

2-(pyrimidin-5-yl)phenyl 2-(2,4-dichloro-5-((triisopropylsilyl)ethynyl)phenoxy)propanoate

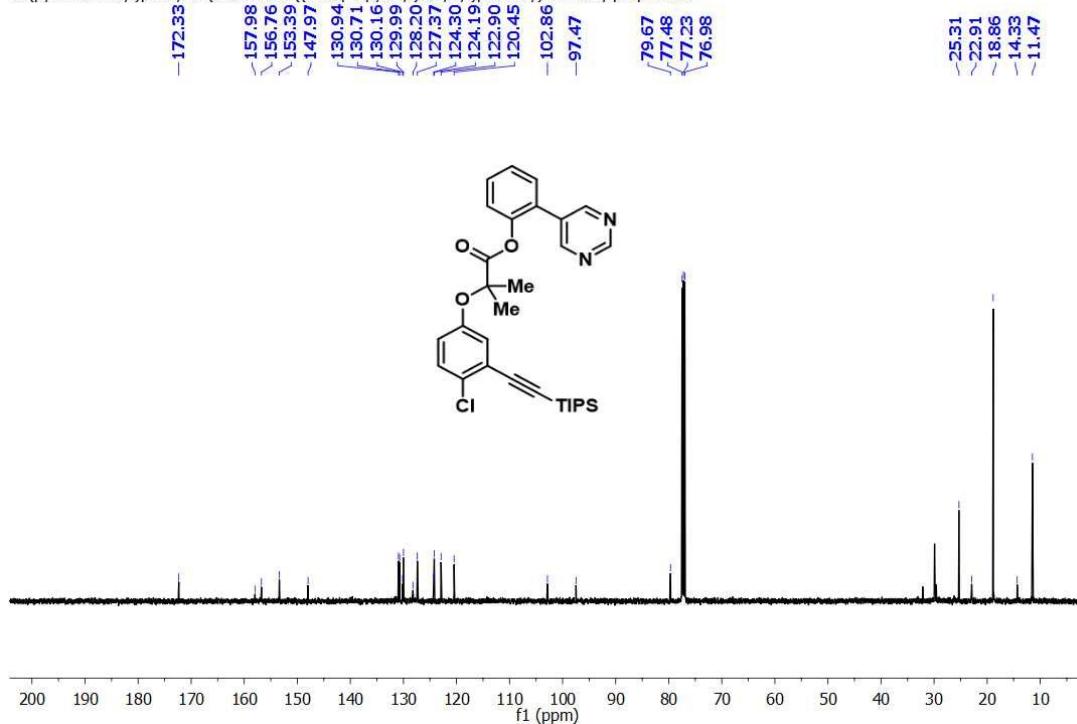


**Figure S90.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **60**

2-(pyrimidin-5-yl)phenyl 2-(4-chloro-3-((trisopropylsilyl)ethynyl)phenoxy)-2-methylpropanoate

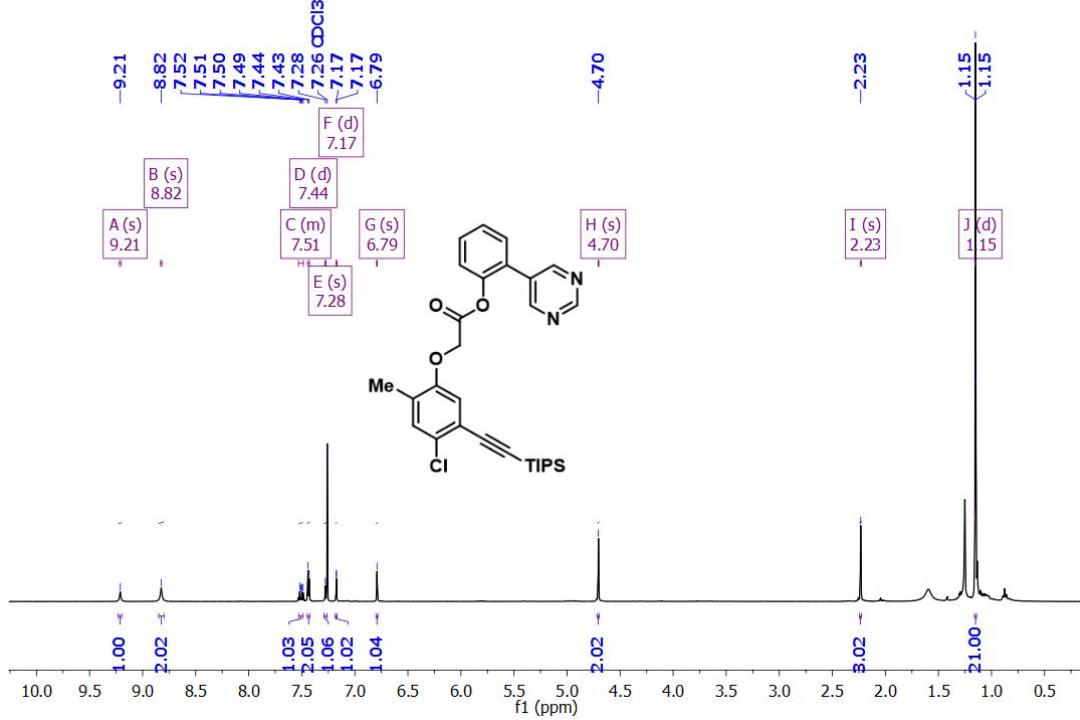


2-(pyrimidin-5-yl)phenyl 2-(4-chloro-3-((trisopropylsilyl)ethynyl)phenoxy)-2-methylpropanoate

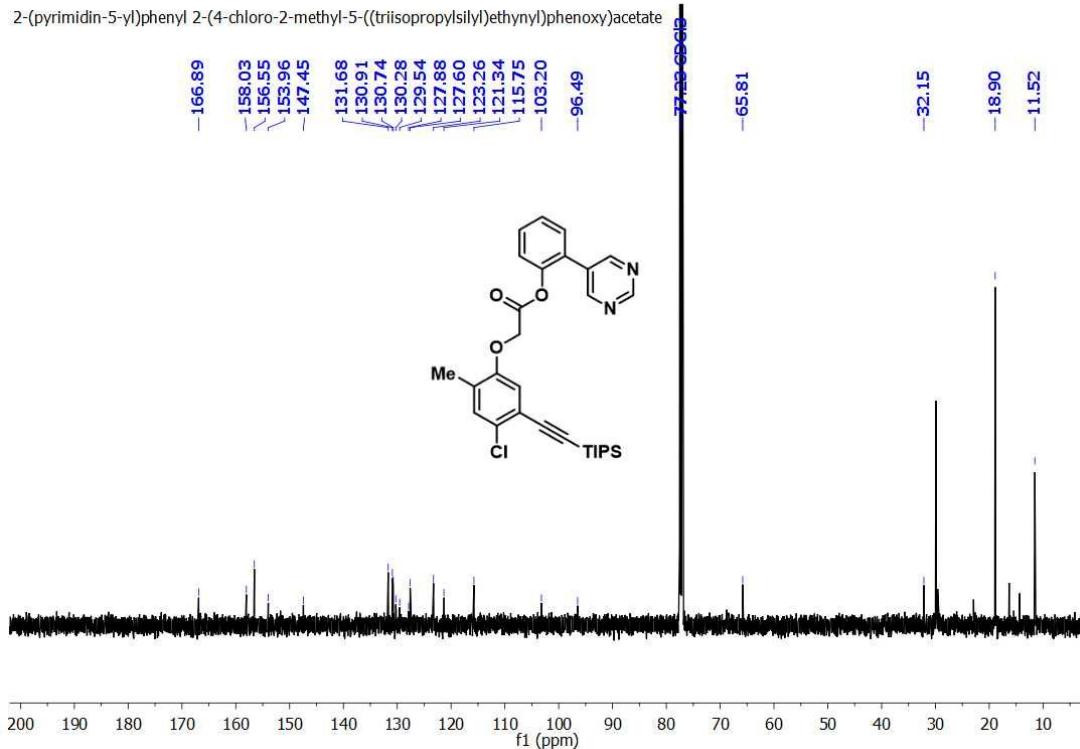


**Figure S91.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **61**

2-(pyrimidin-5-yl)phenyl 2-(4-chloro-2-methyl-5-((triisopropylsilyl)ethynyl)phenoxy)acetate

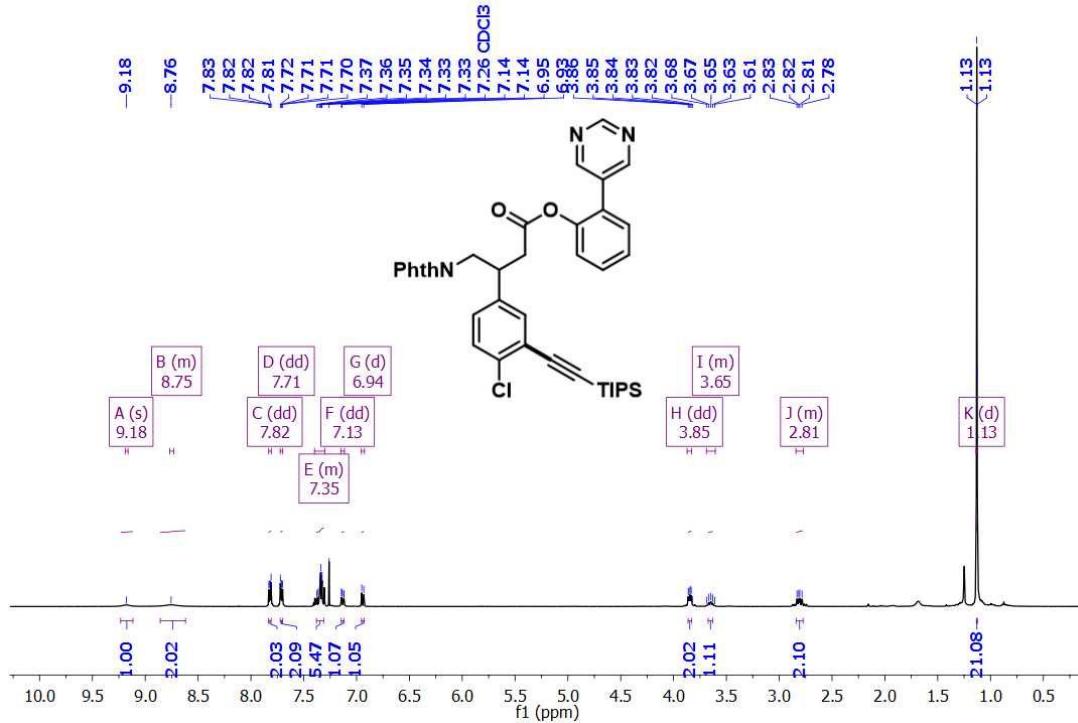


2-(pyrimidin-5-yl)phenyl 2-(4-chloro-2-methyl-5-((triisopropylsilyl)ethynyl)phenoxy)acetate

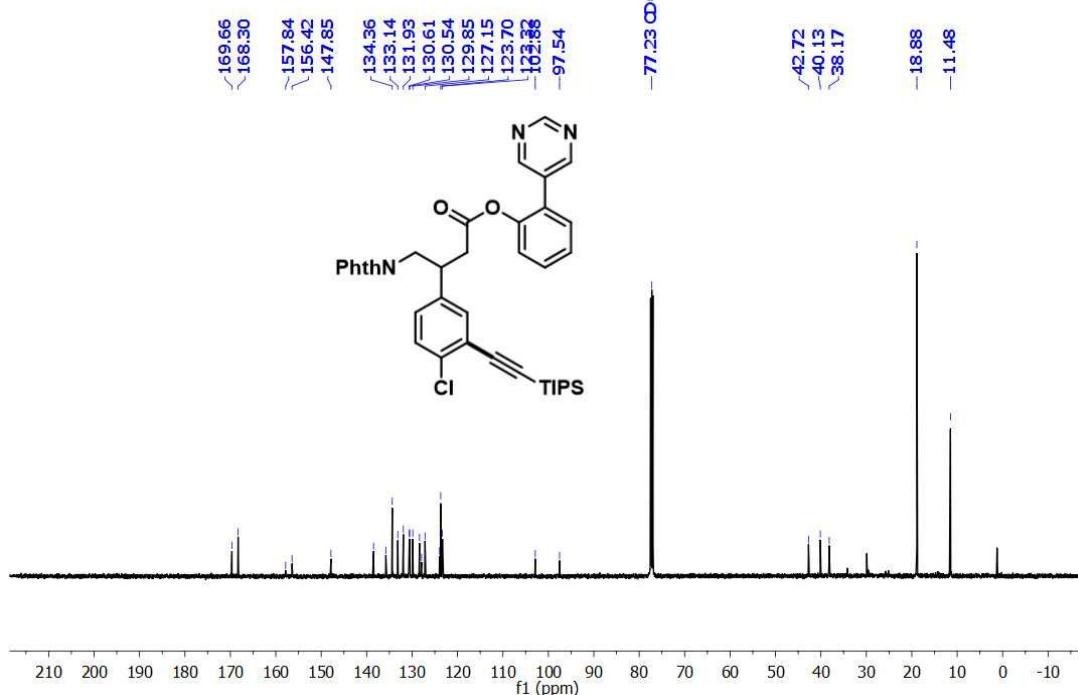


**Figure S92.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **62**

2-(pyrimidin-5-yl)phenyl 3-(4-chloro-3-((triisopropylsilyl)ethynyl)phenyl)-3-(1,3-dioxoisindolin-2-yl)propanoate

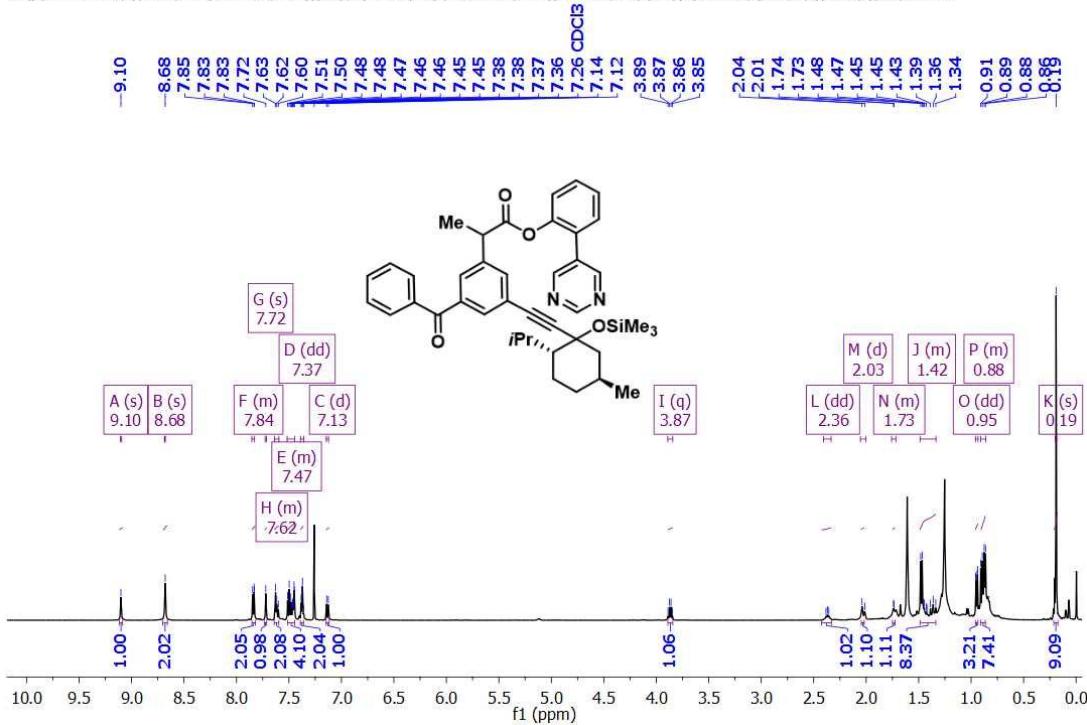


2-(pyrimidin-5-yl)phenyl 3-(4-chloro-3-((triisopropylsilyl)ethynyl)phenyl)-3-(1,3-dioxoisindolin-2-yl)propanoate

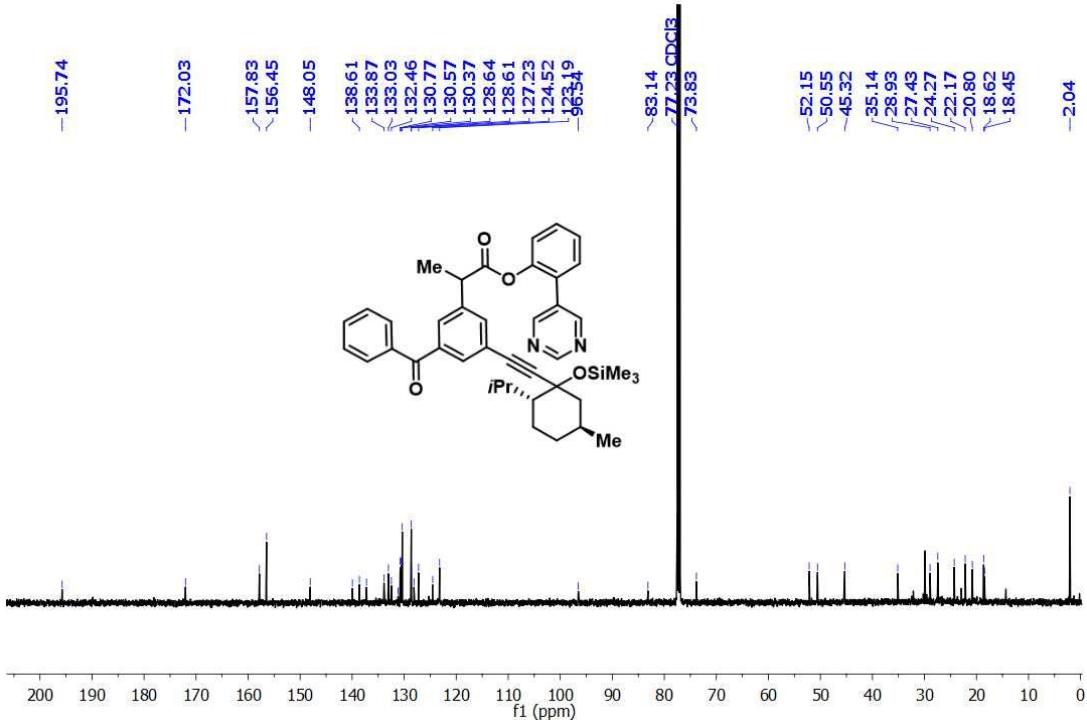


**Figure S93.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **63**

2-(pyrimidin-5-yl)phenyl 2-(3-benzoyl-5-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)propanoate



2-(pyrimidin-5-yl)phenyl 2-(3-benzoyl-5-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)phenyl)propanoate



**Figure S94.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **64**

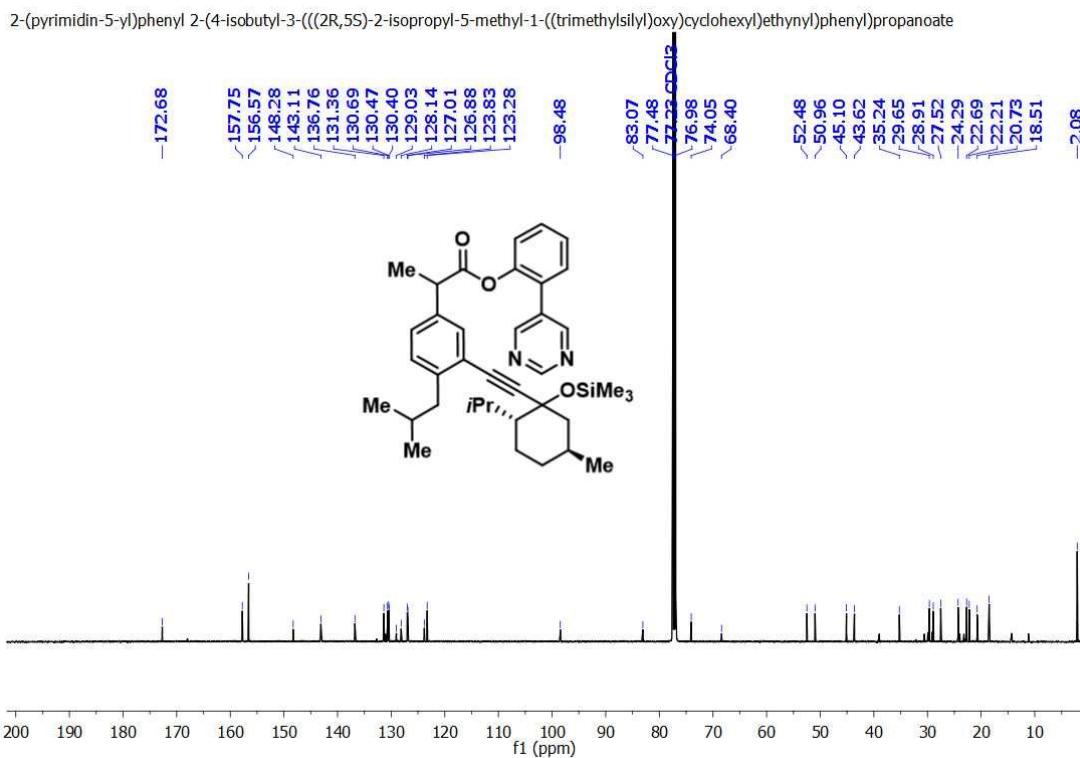
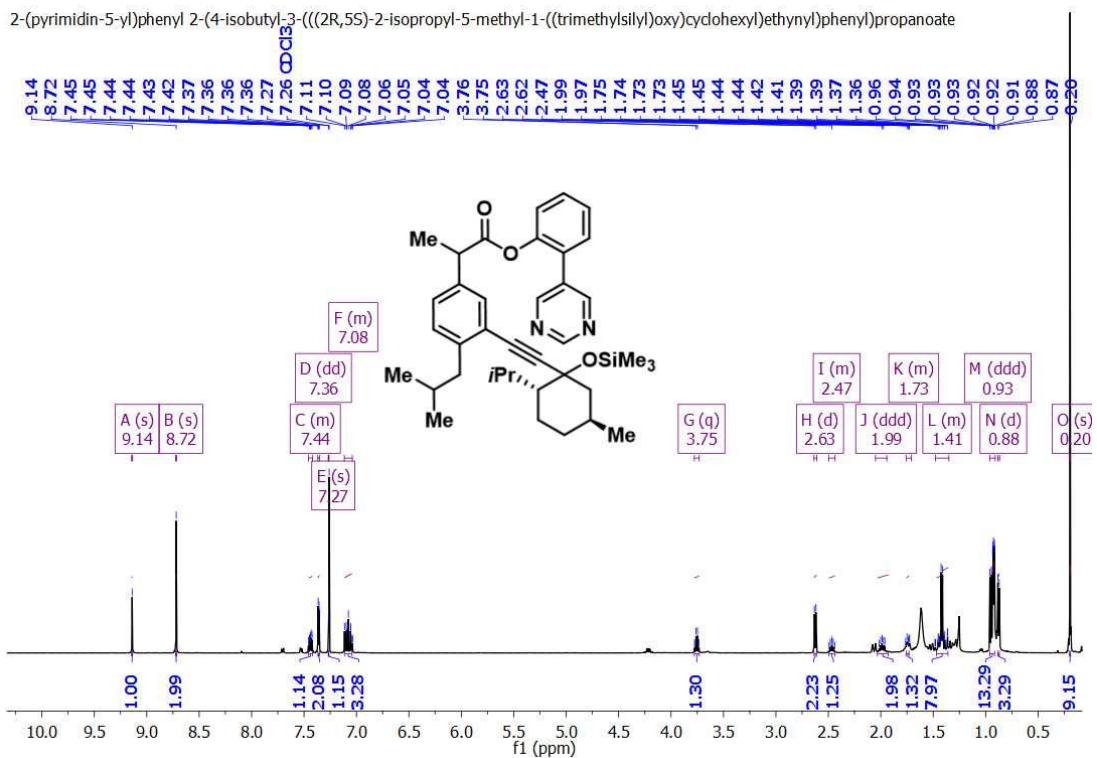
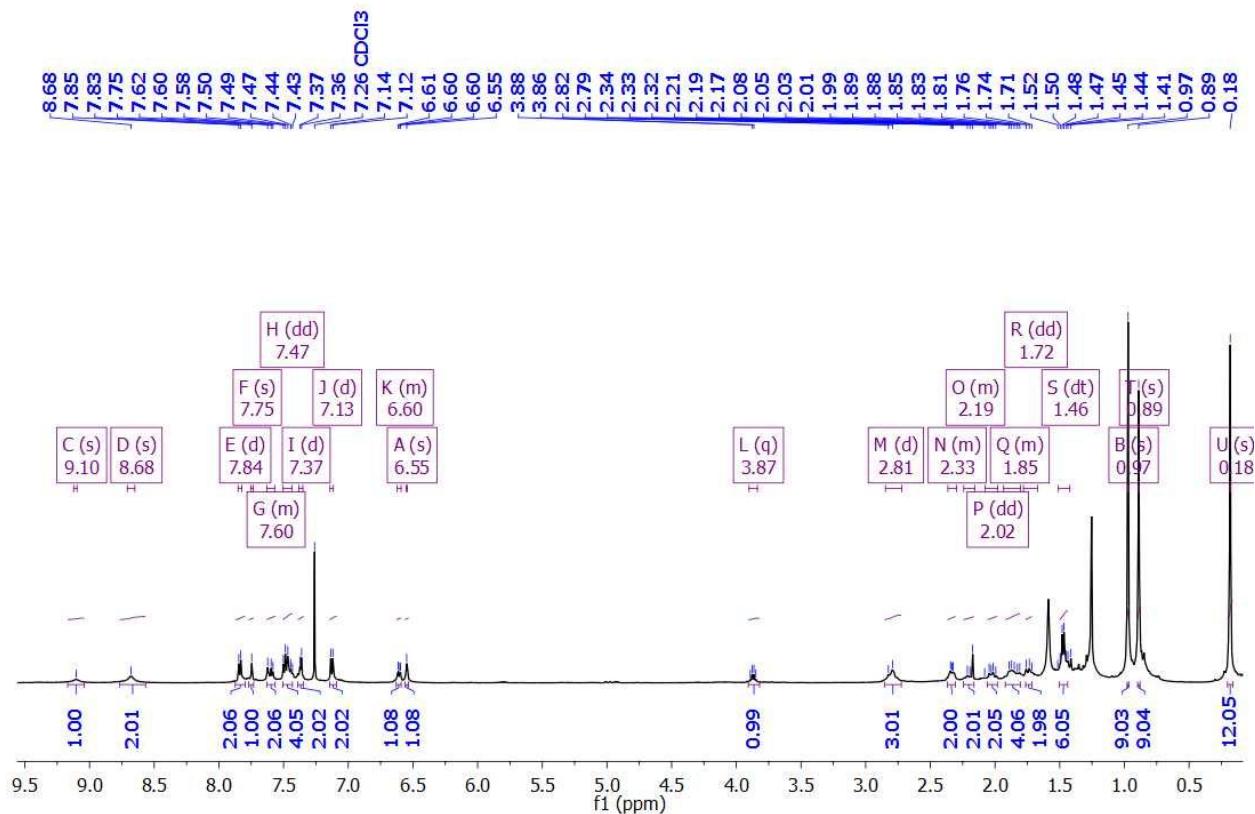
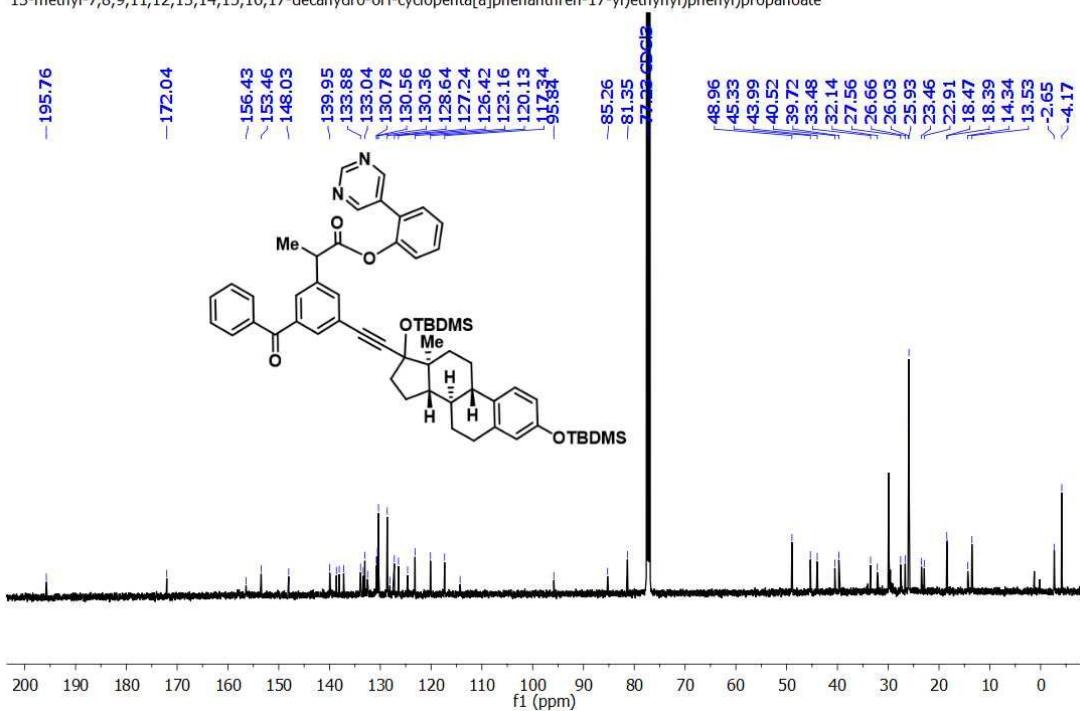


Figure S95. <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of 65

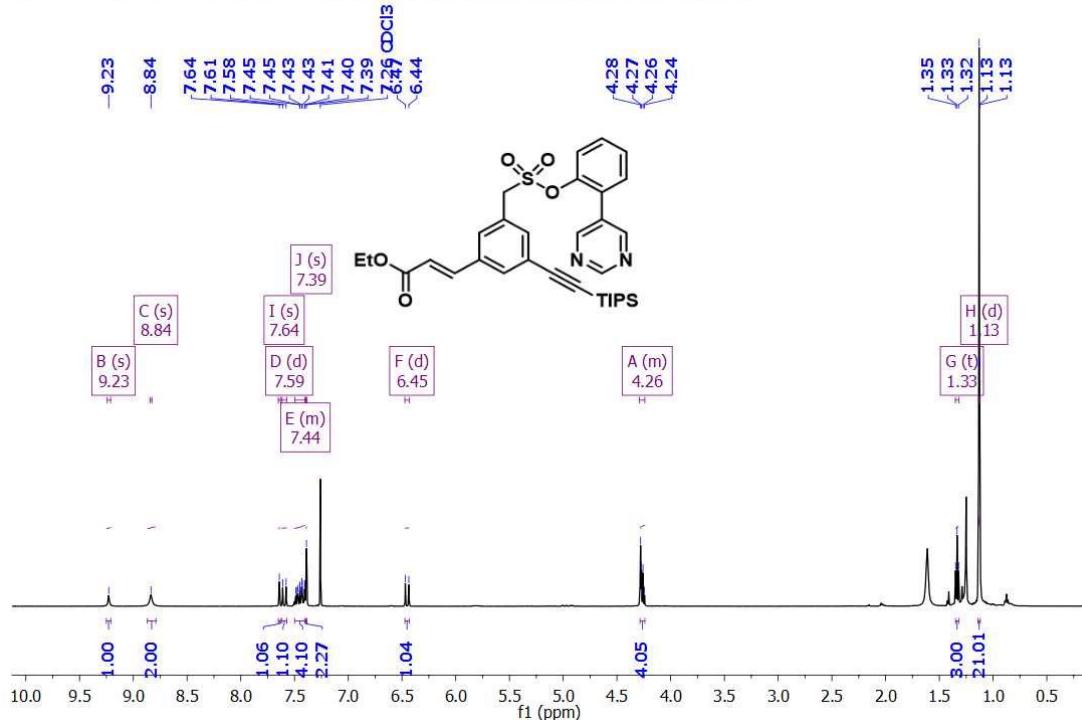


2-(pyrimidin-5-yl)phenyl 2-(3-benzoyl-5-(((8R,9S,13S,14S)-3,17-bis((tert-butyldimethylsilyl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethynyl)phenyl)propanoate

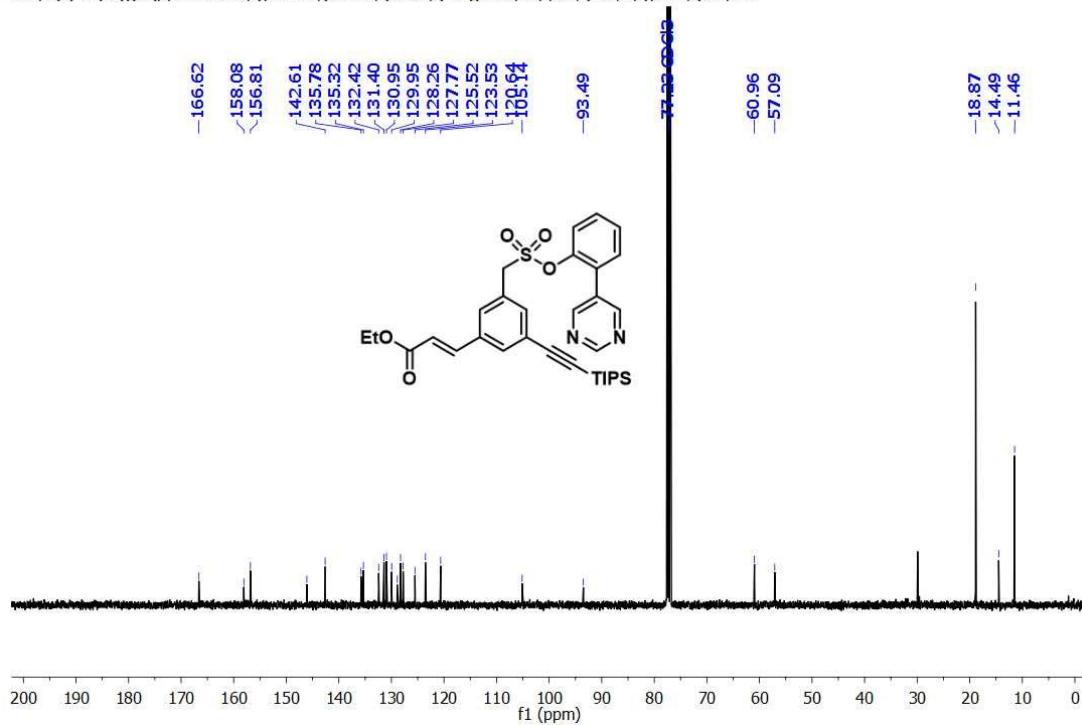


**Figure S96.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **66**

ethyl (E)-3-((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)-5-((triisopropylsilyl)ethynyl)phenylacrylate

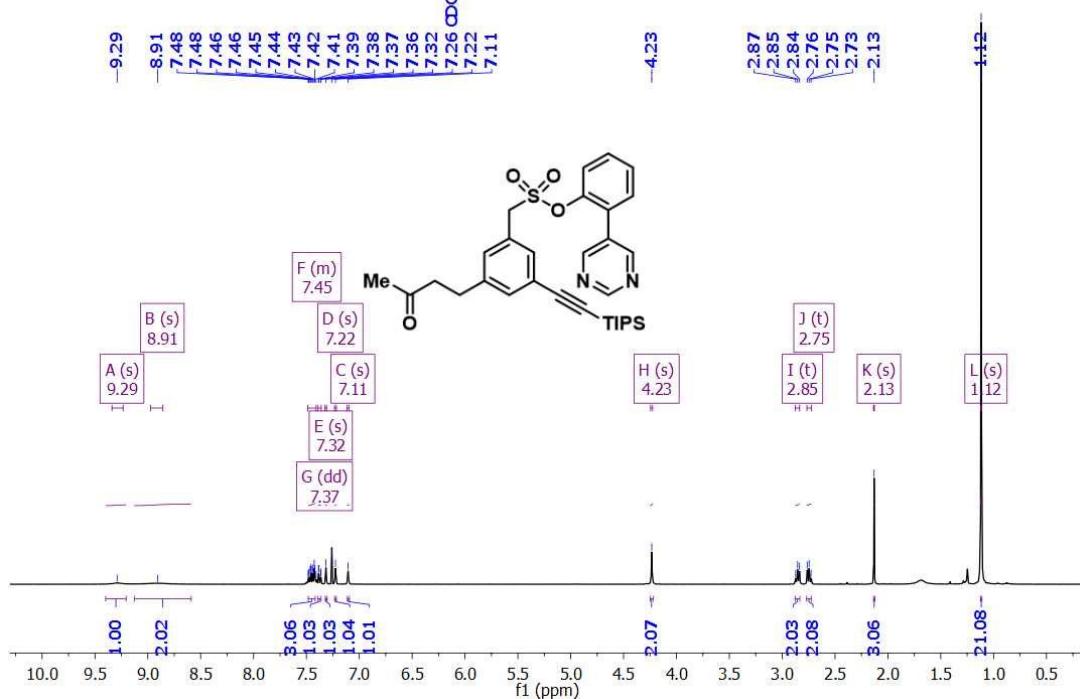


ethyl (E)-3-((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)-5-((triisopropylsilyl)ethynyl)phenylacrylate

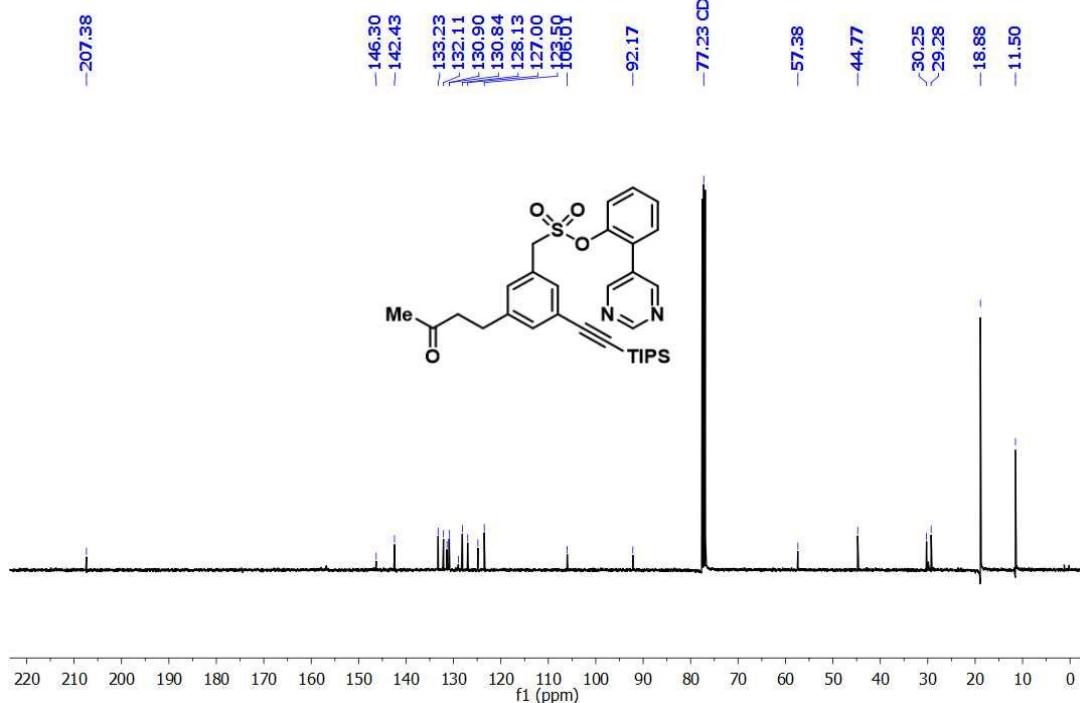


**Figure S97.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **67**

2-(pyrimidin-5-yl)phenyl (3-(3-oxobutyl)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

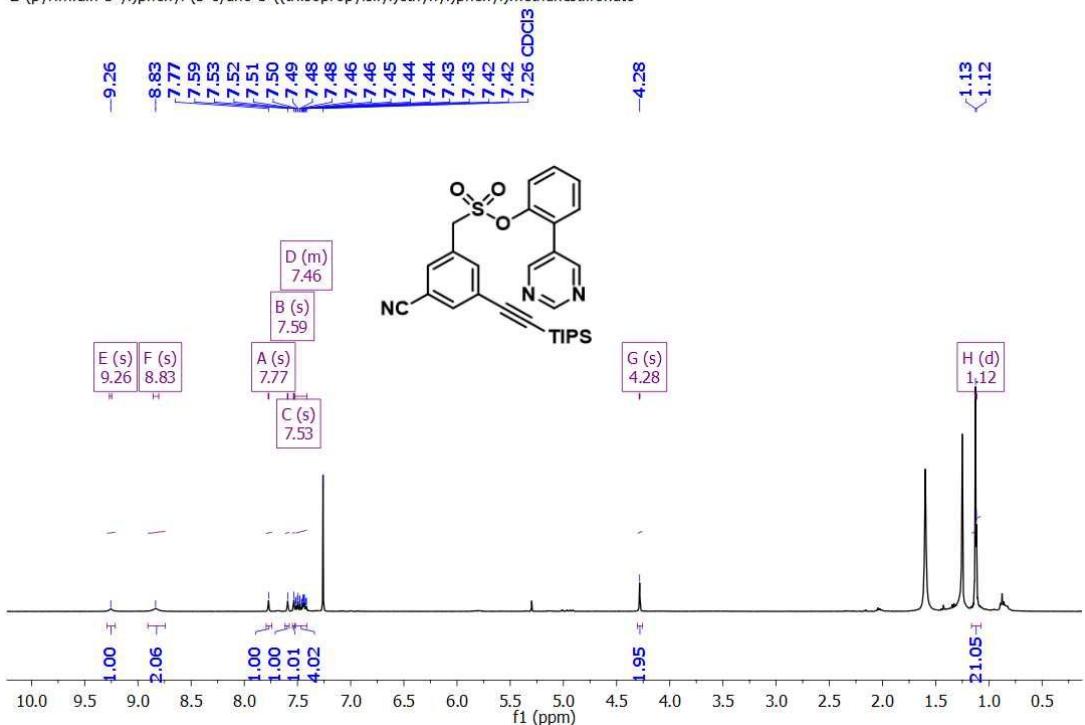


2-(pyrimidin-5-yl)phenyl (3-(3-oxobutyl)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

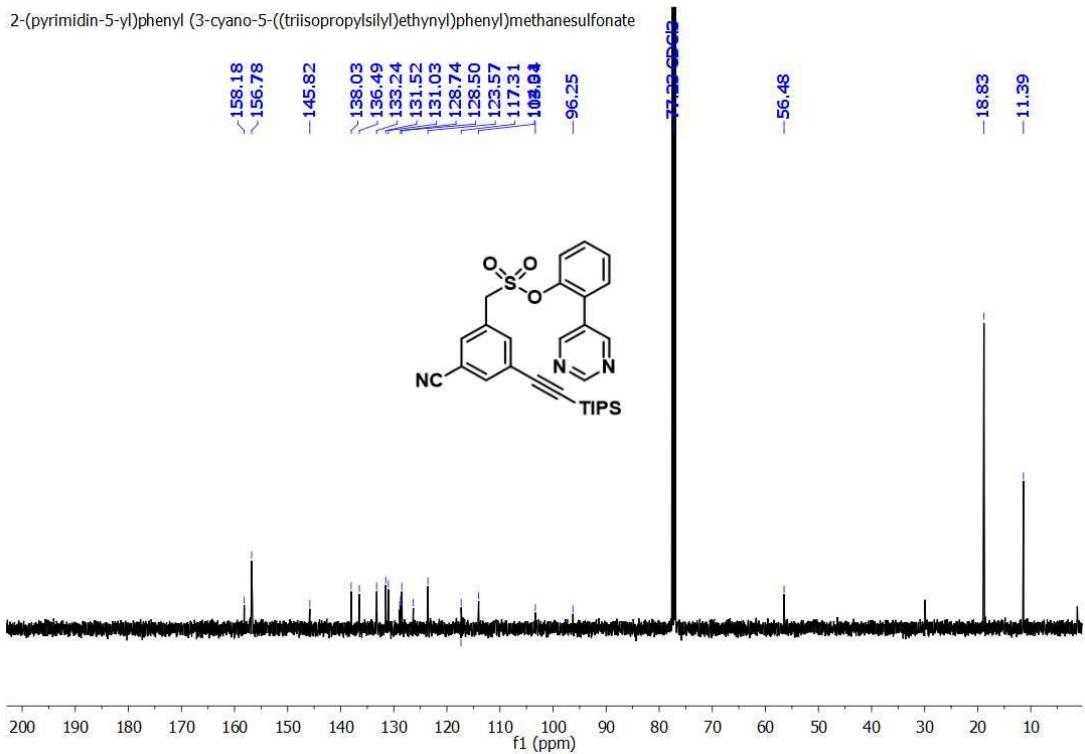


**Figure S98.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **68**

2-(pyrimidin-5-yl)phenyl (3-cyano-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

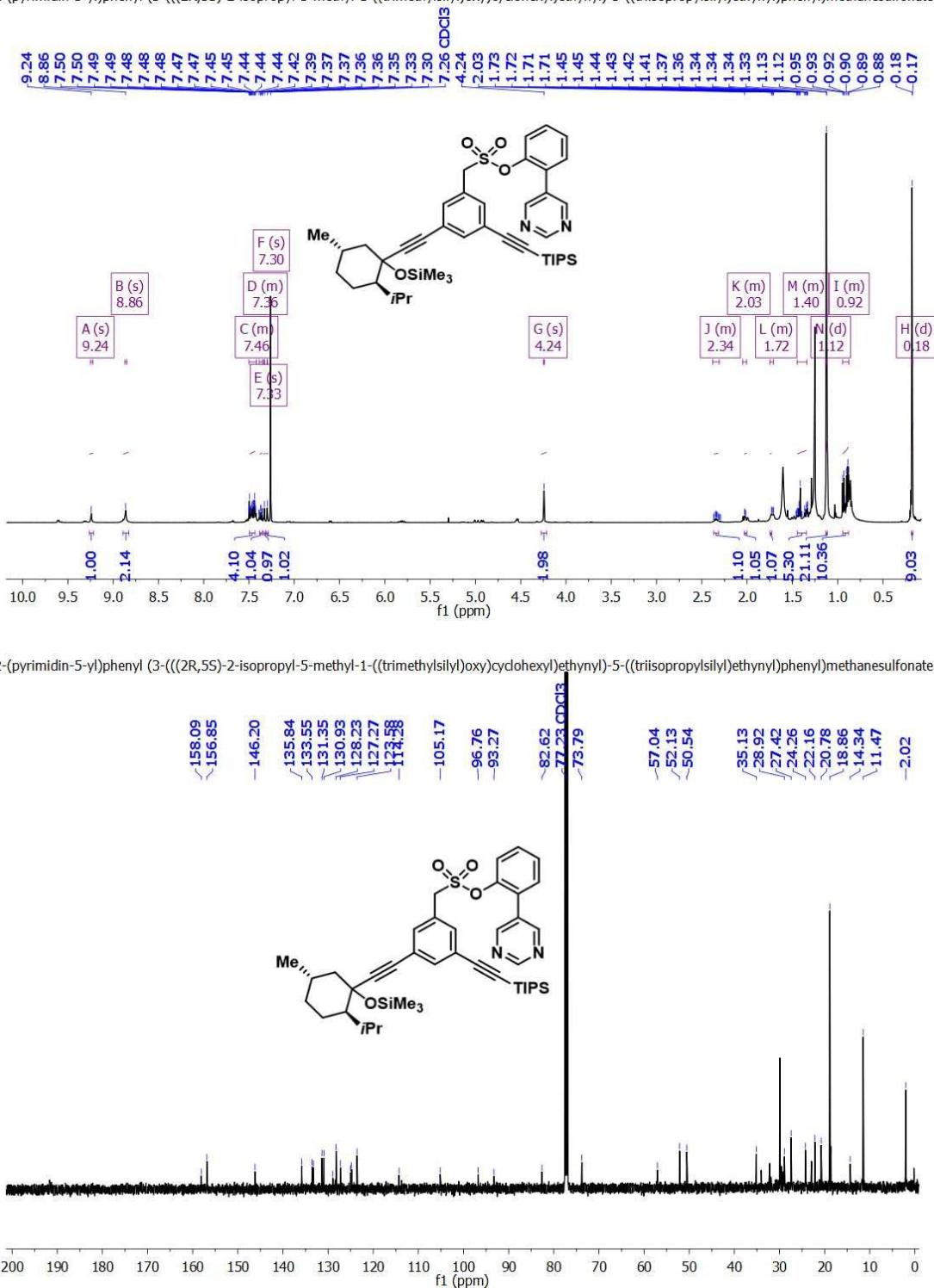


2-(pyrimidin-5-yl)phenyl (3-cyano-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate



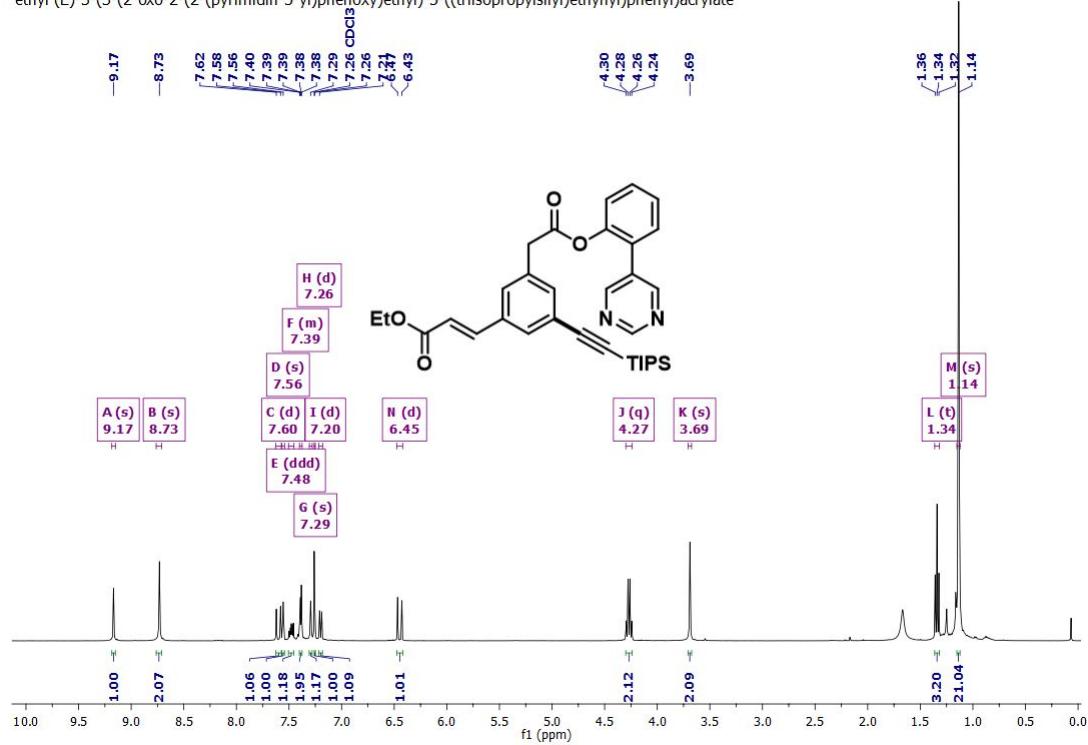
**Figure S99.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **69**

2-(pyrimidin-5-yl)phenyl (3-(((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)-5-((triisopropylsilyl)ethynyl)phenyl)methanesulfonate

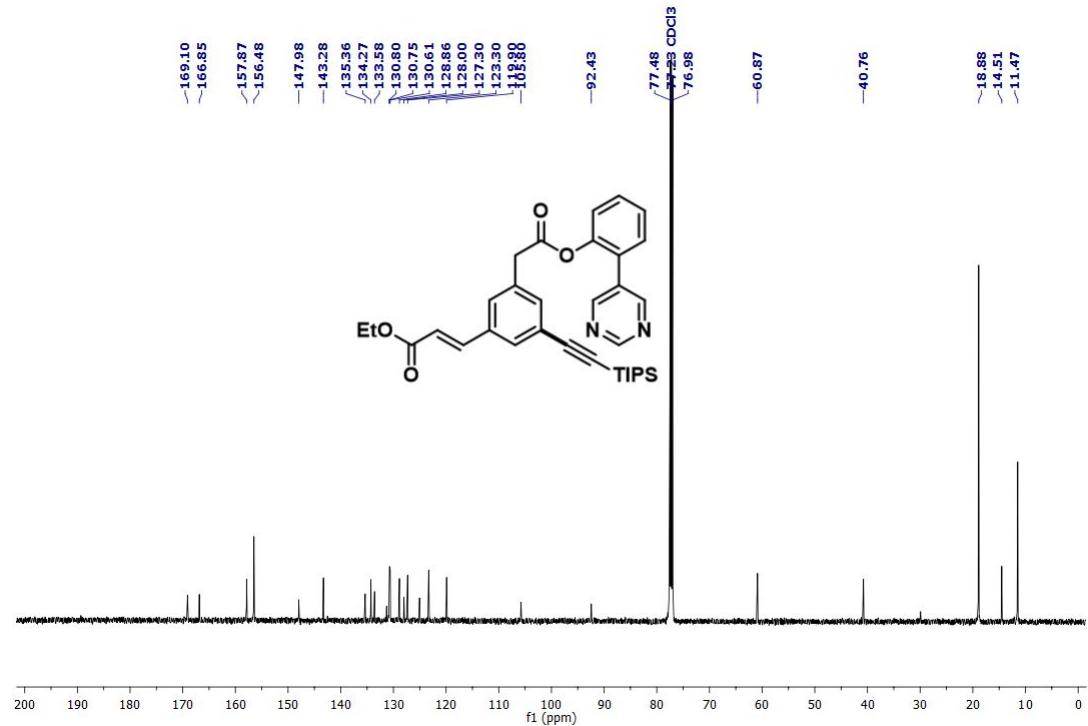


**Figure S100.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **70**

ethyl (E)-3-(3-(2-oxo-2-(2-(pyrimidin-5-yl)phenoxy)ethyl)-5-((triisopropylsilyl)ethynyl)phenyl)acrylate

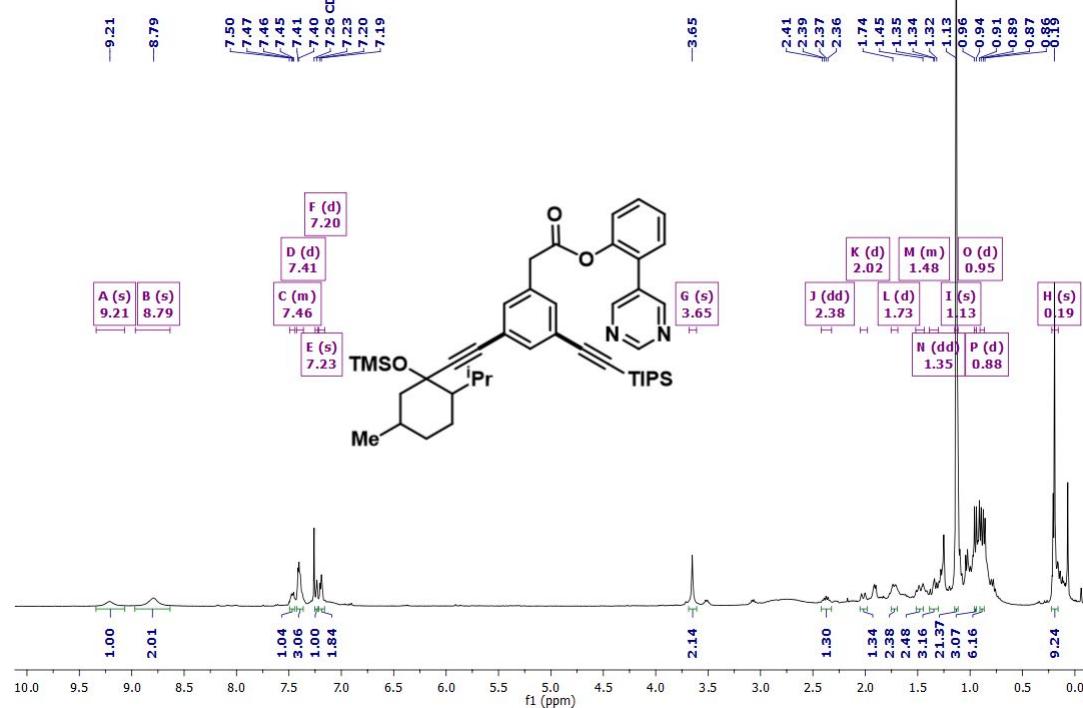


ethyl (E)-3-(3-(2-oxo-2-(2-(pyrimidin-5-yl)phenoxy)ethyl)-5-((triisopropylsilyl)ethynyl)phenyl)acrylate

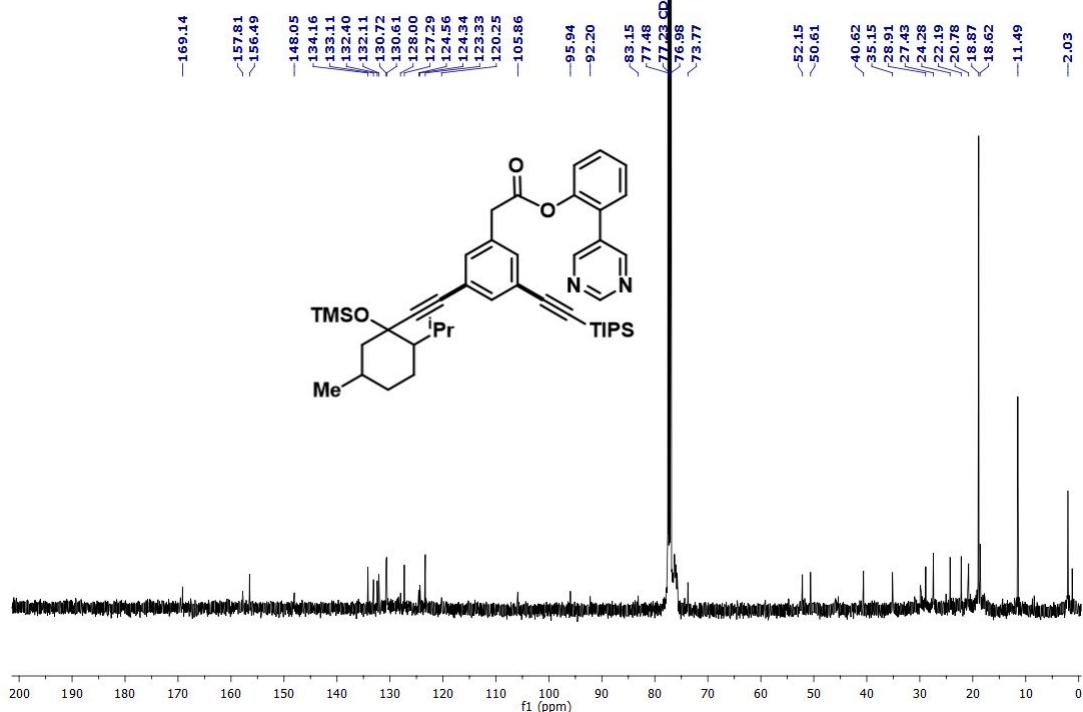


**Figure S101.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of 71

2-(pyrimidin-5-yl)phenyl 2-(3-((2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)-5-((triisopropylsilyl)ethynyl)phenyl)acetate

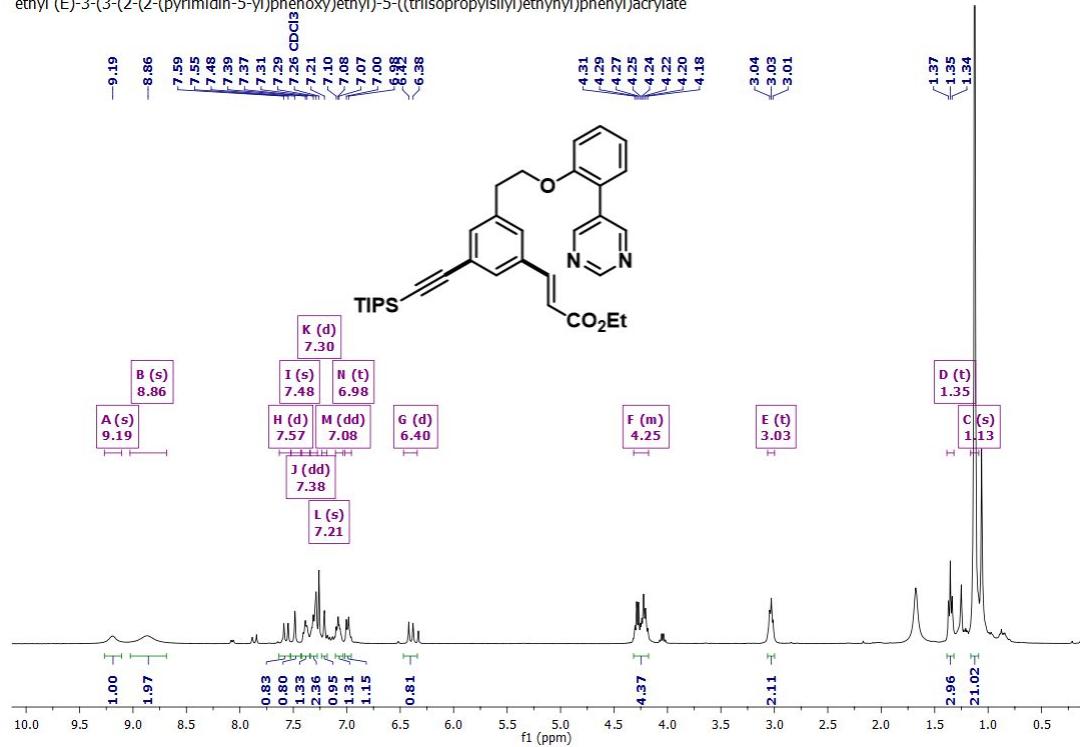


2-(pyrimidin-5-yl)phenyl 2-(3-((2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)-5-((triisopropylsilyl)ethynyl)phenyl)acetate

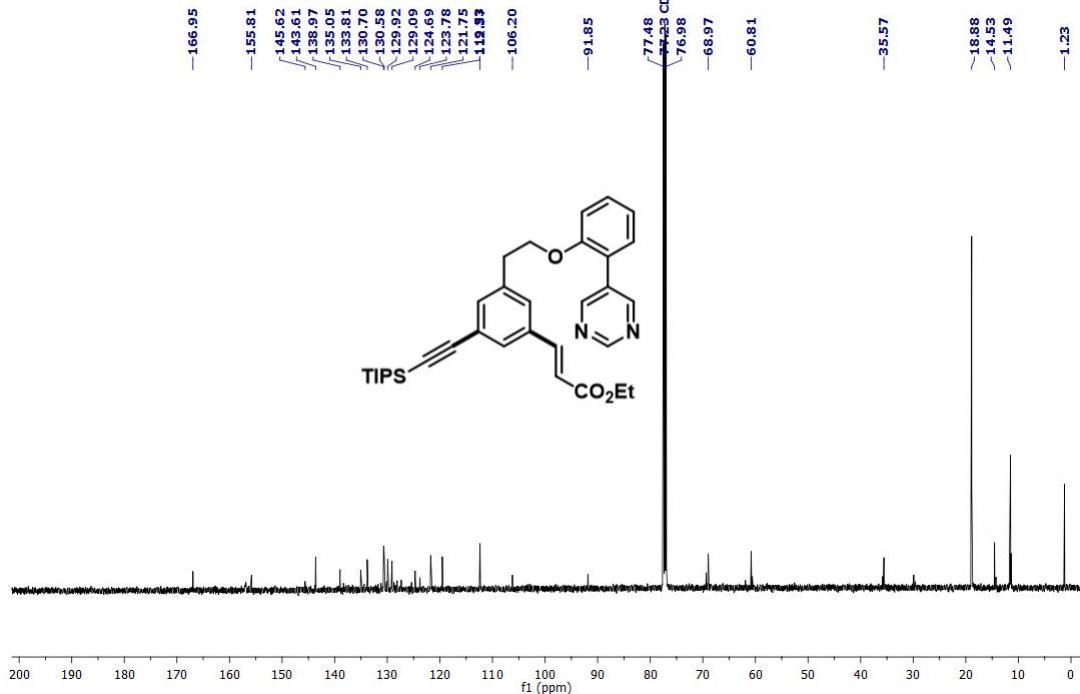


**Figure S102.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of 72

ethyl (E)-3-(3-(2-(pyrimidin-5-yl)phenoxy)ethyl)-5-((trisopropylsilyl)ethynyl)phenyl)acrylate

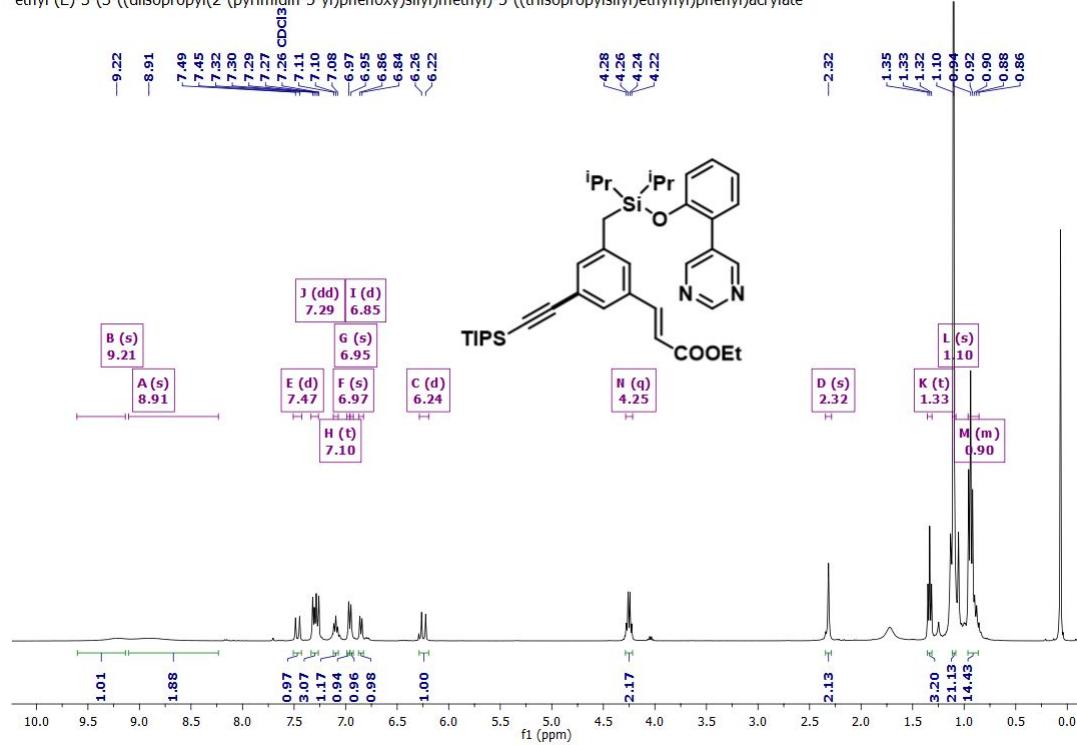


ethyl (E)-3-(3-(2-(pyrimidin-5-yl)phenoxy)ethyl)-5-((trisopropylsilyl)ethynyl)phenyl)acrylate

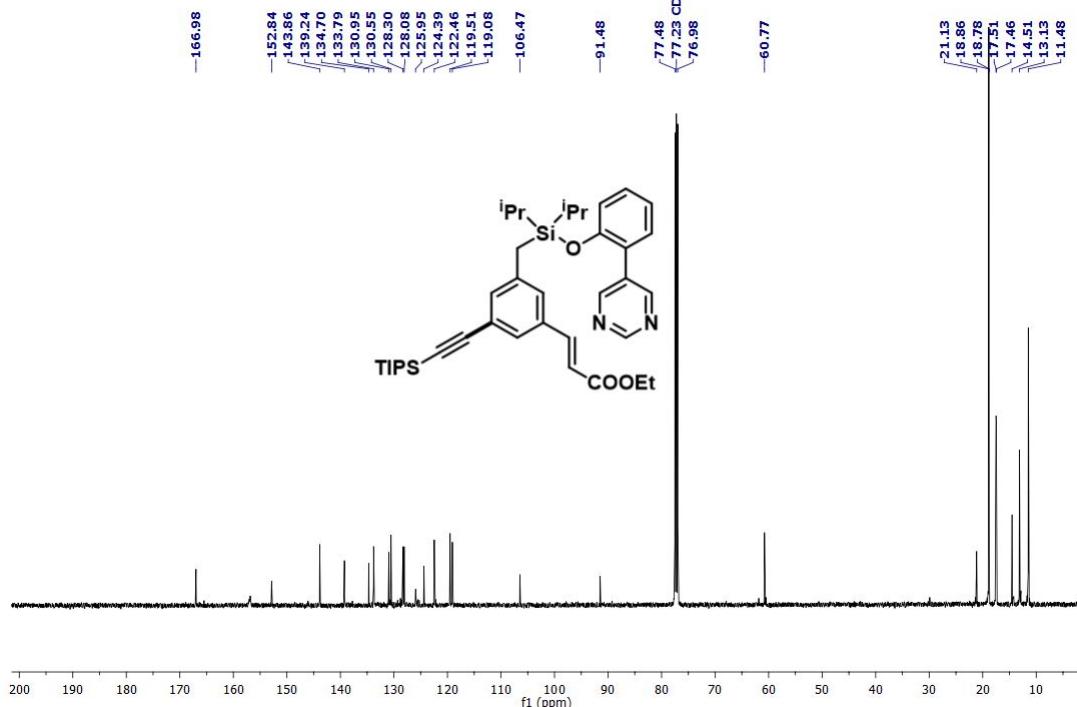


**Figure S103.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of 73

ethyl (E)-3-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)-5-((triisopropylsilyl)ethynyl)phenyl)acrylate

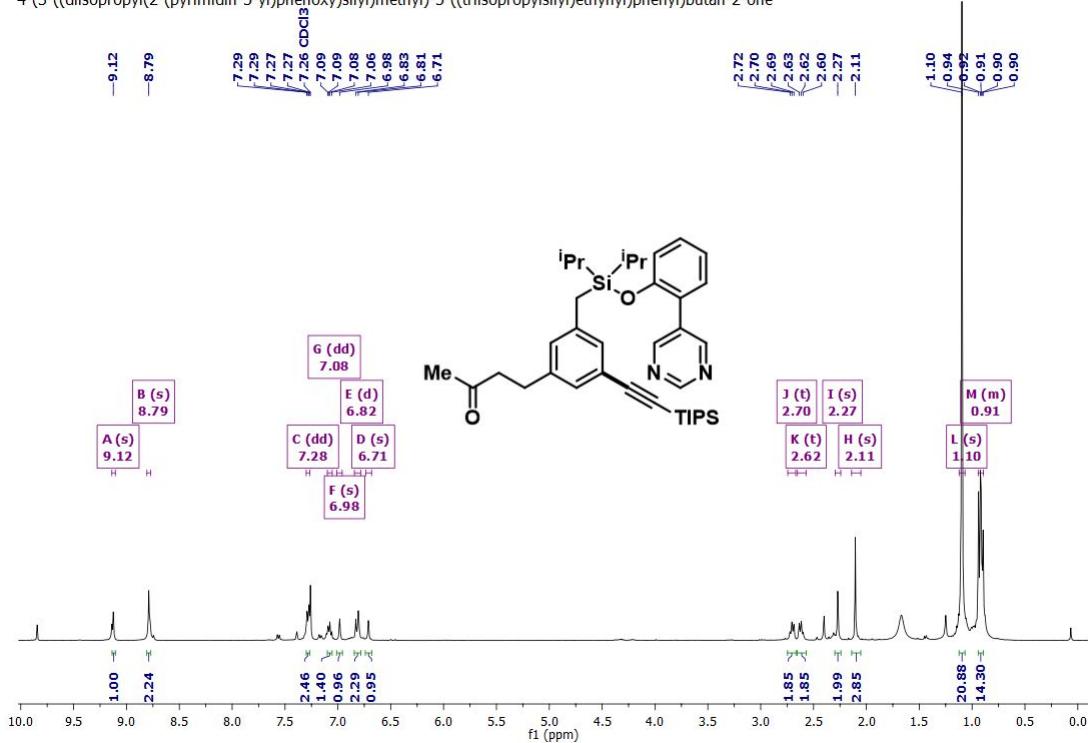


ethyl (E)-3-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)-5-((triisopropylsilyl)ethynyl)phenyl)acrylate

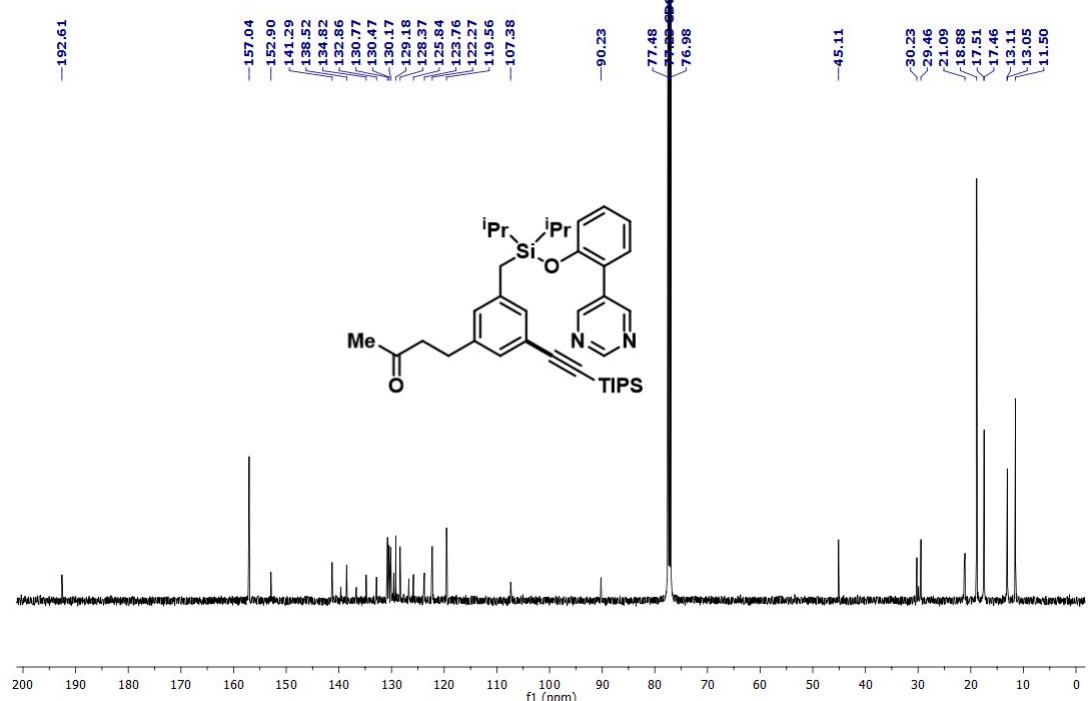


**Figure S104.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **74**

4-(3-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)-5-((triisopropylsilyl)ethynyl)phenyl)butan-2-one

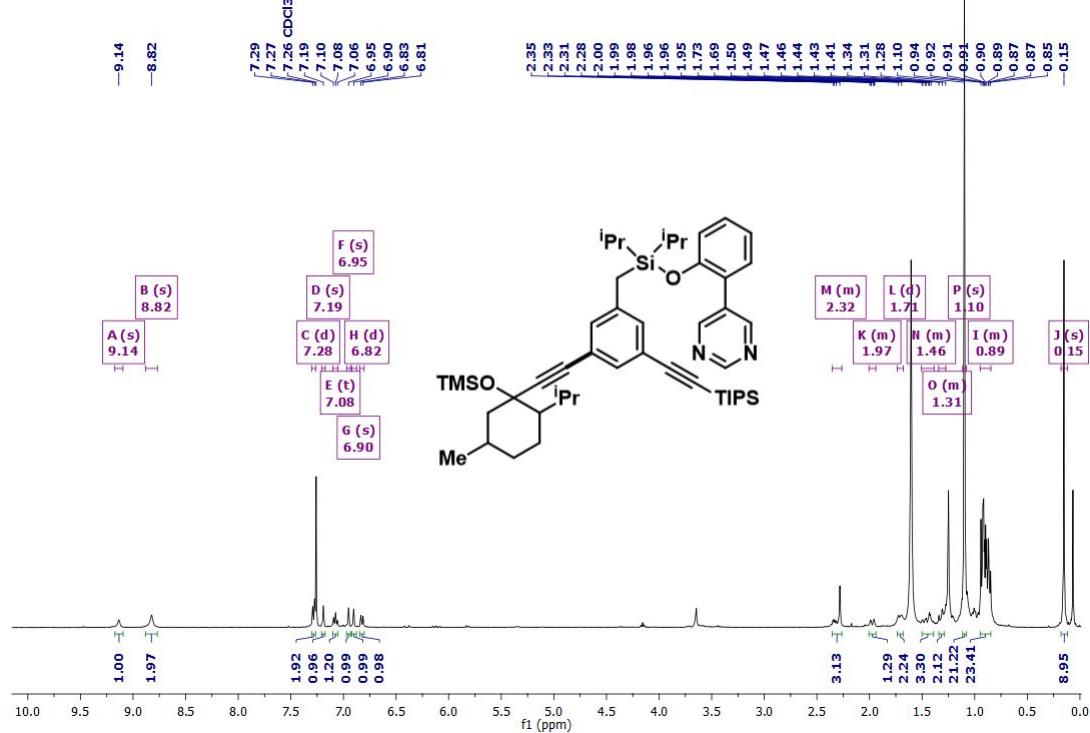


4-(3-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)-5-((triisopropylsilyl)ethynyl)phenyl)butan-2-one

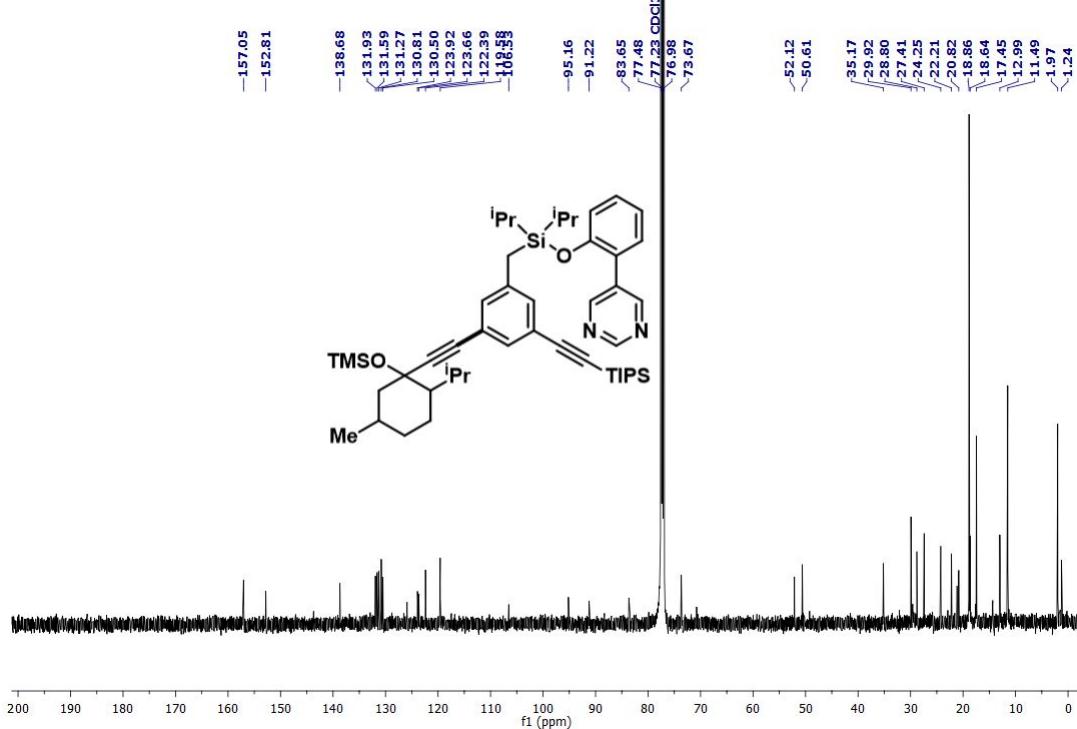


**Figure S105.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **75**

5-(2-((diisopropyl(3-((2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)-5-((triisopropylsilyl)ethynyl)benzyl)silyl)oxy)phenyl)pyrimidine

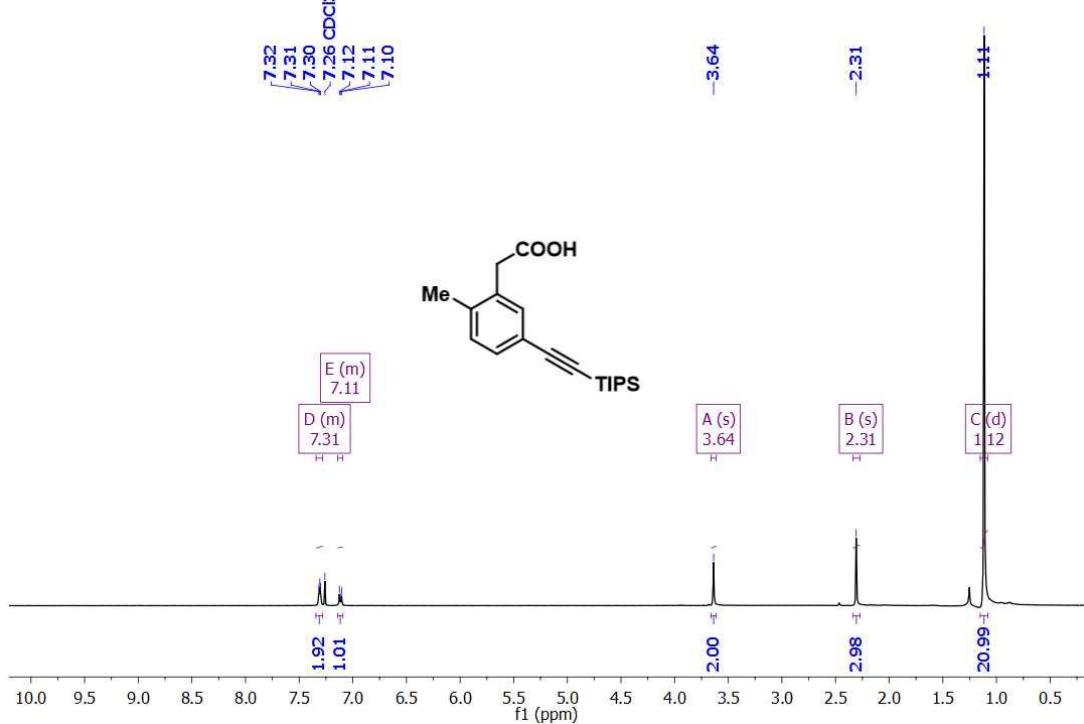


5-(2-((diisopropyl(3-((2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)-5-((trisopropylsilyl)ethynyl)benzyl)silyl)oxy)phenyl)pyrimidine

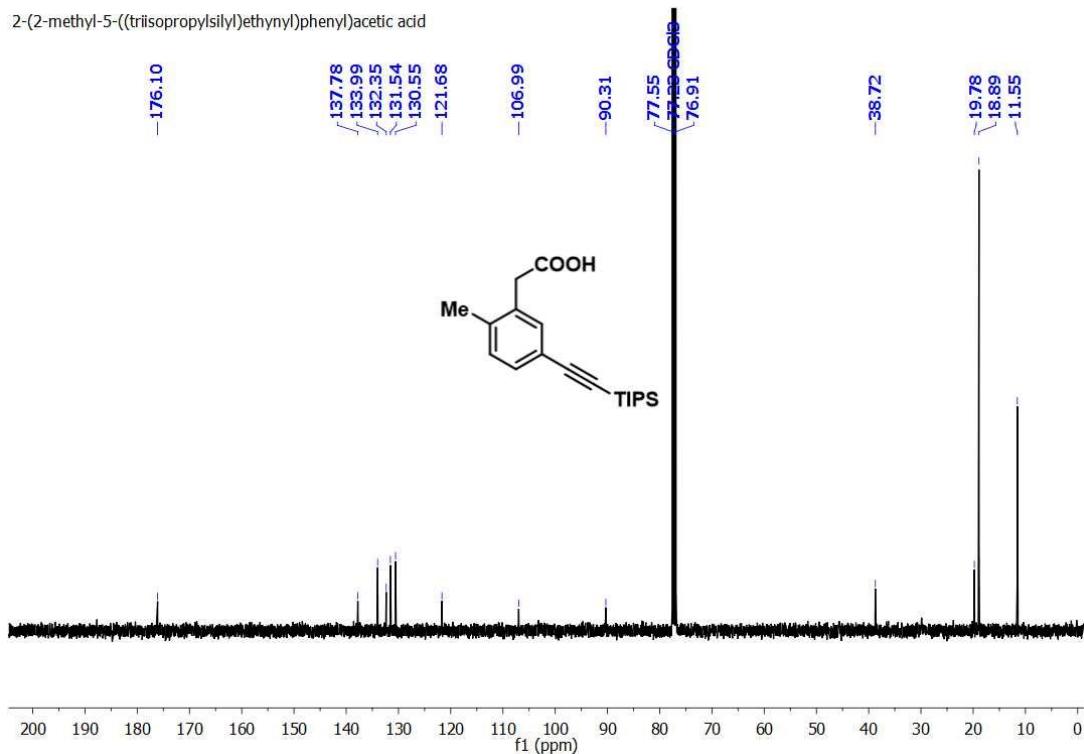


**Figure S106.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **76**

2-(2-methyl-5-((triisopropylsilyl)ethynyl)phenyl)acetic acid

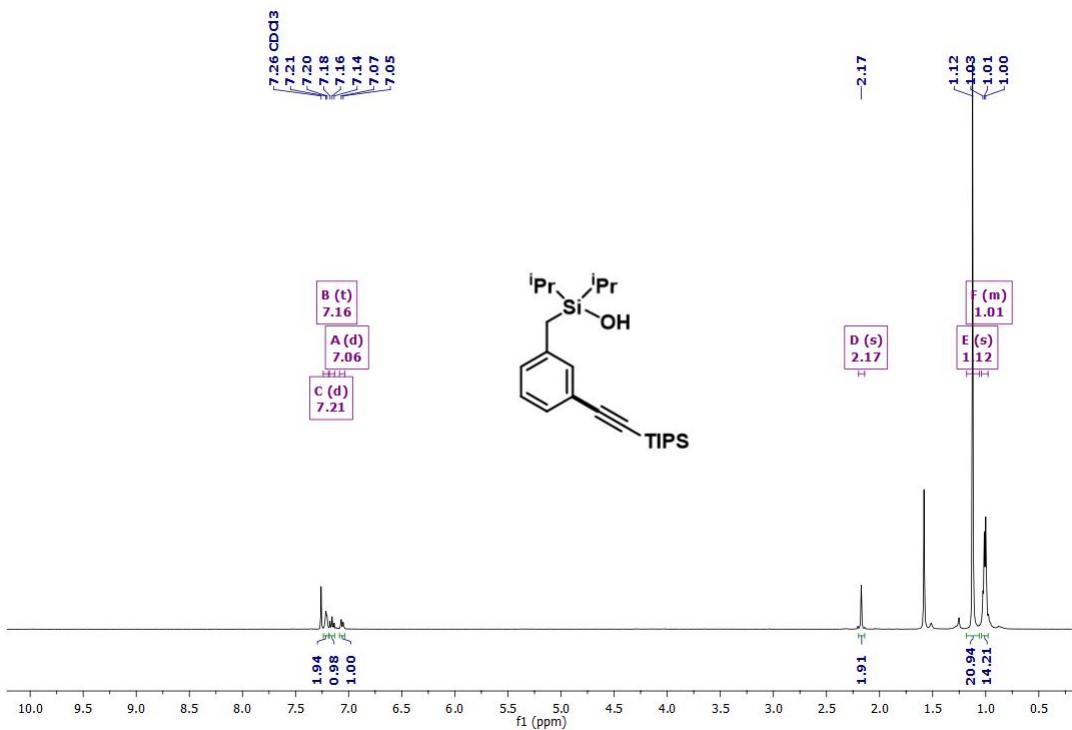


2-(2-methyl-5-((triisopropylsilyl)ethynyl)phenyl)acetic acid

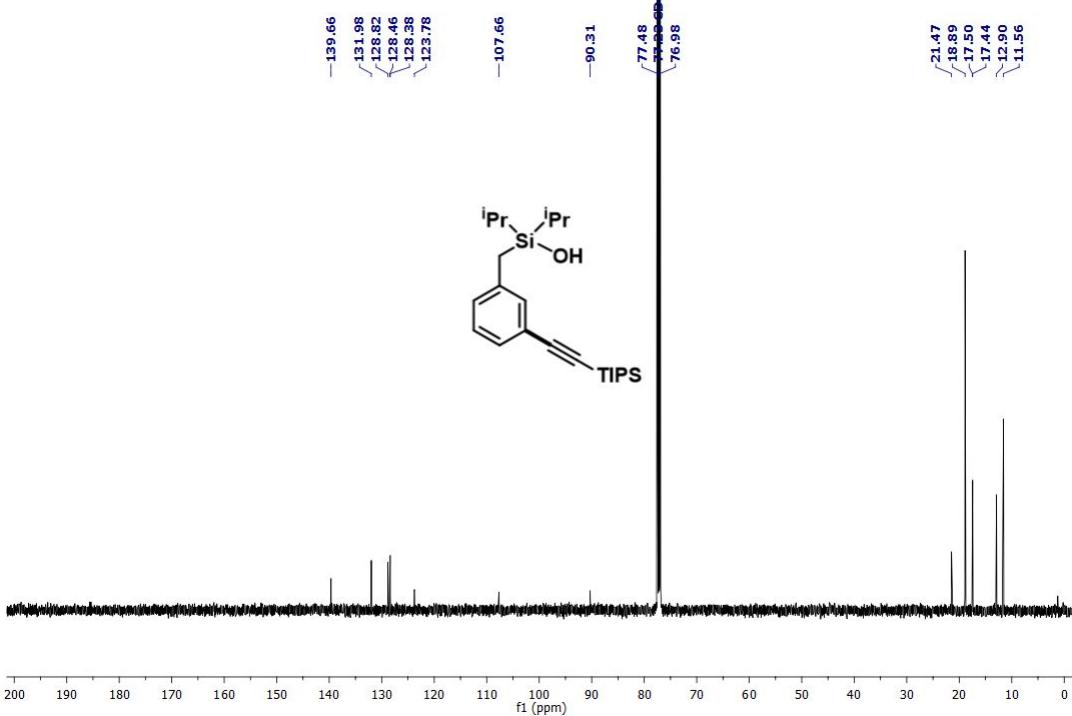


**Figure S107.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of 77

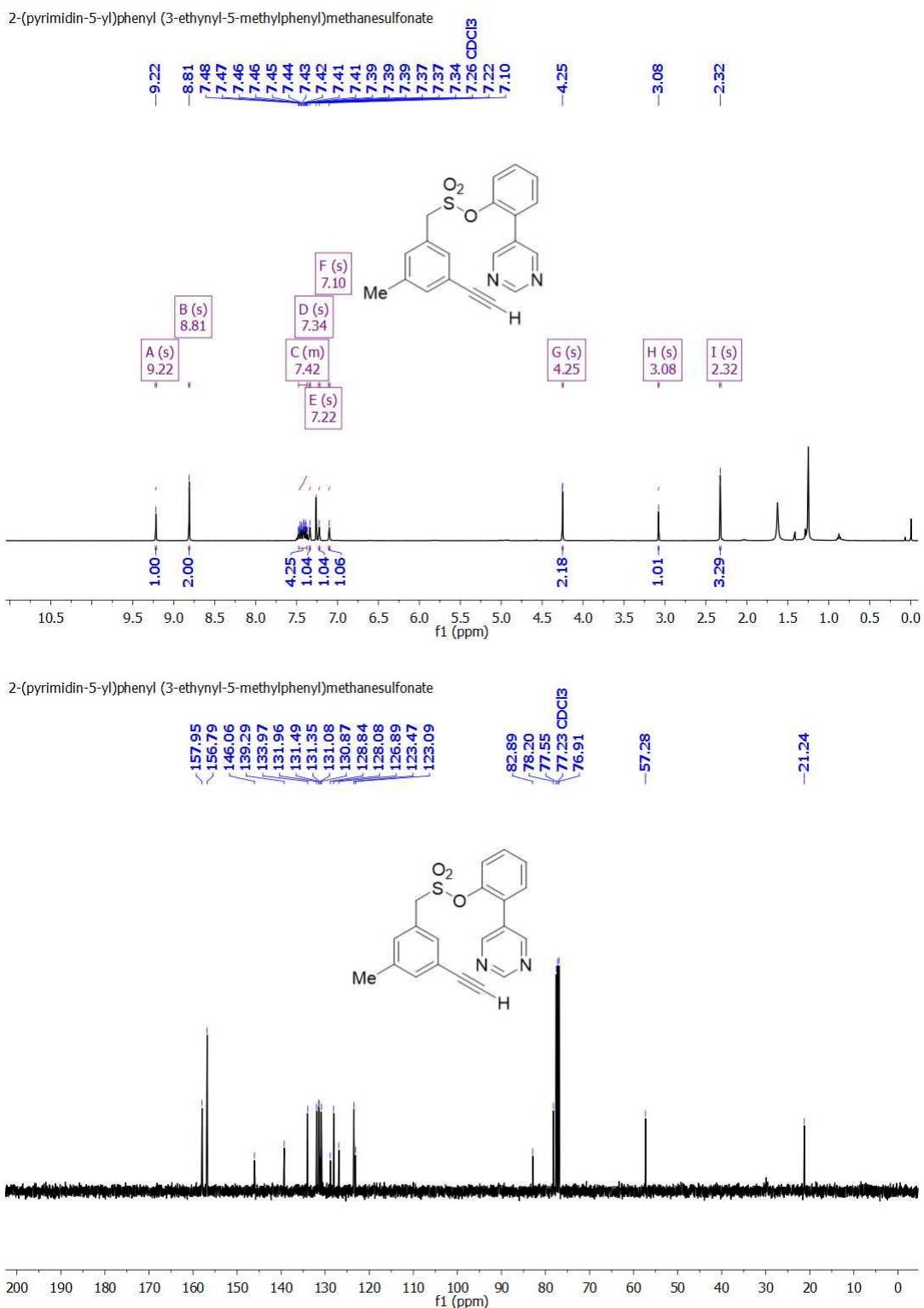
diisopropyl(3-((triisopropylsilyl)ethynyl)benzyl)silanol



diisopropyl(3-((triisopropylsilyl)ethynyl)benzyl)silanol

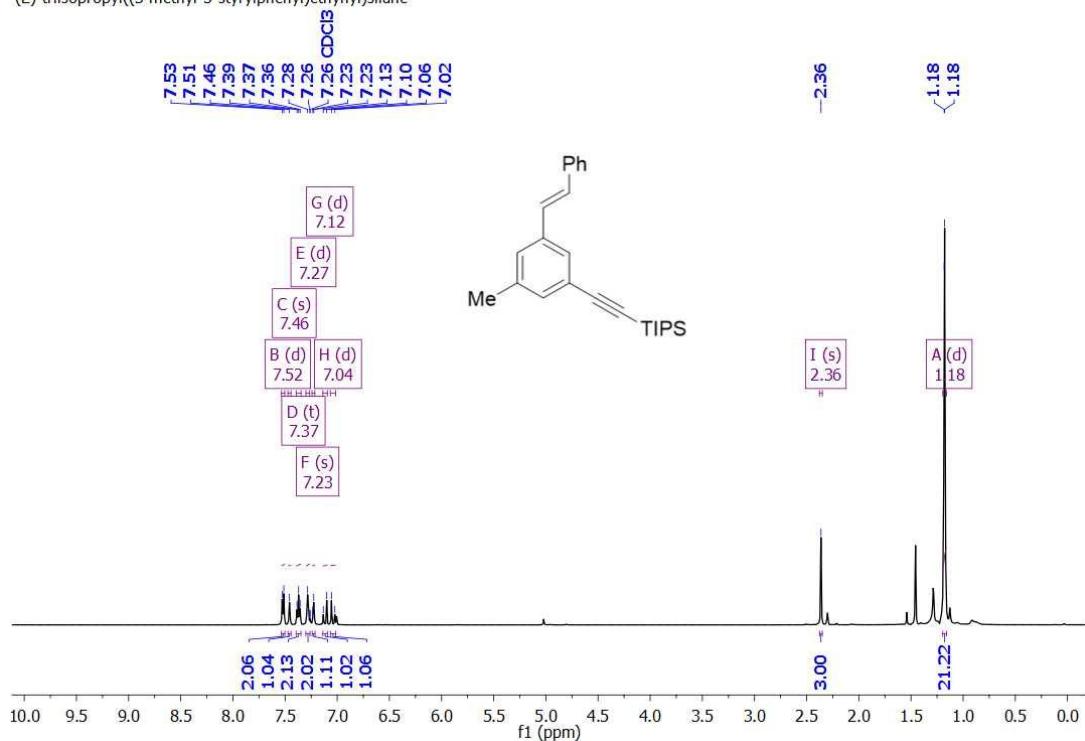


**Figure S108.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **78**

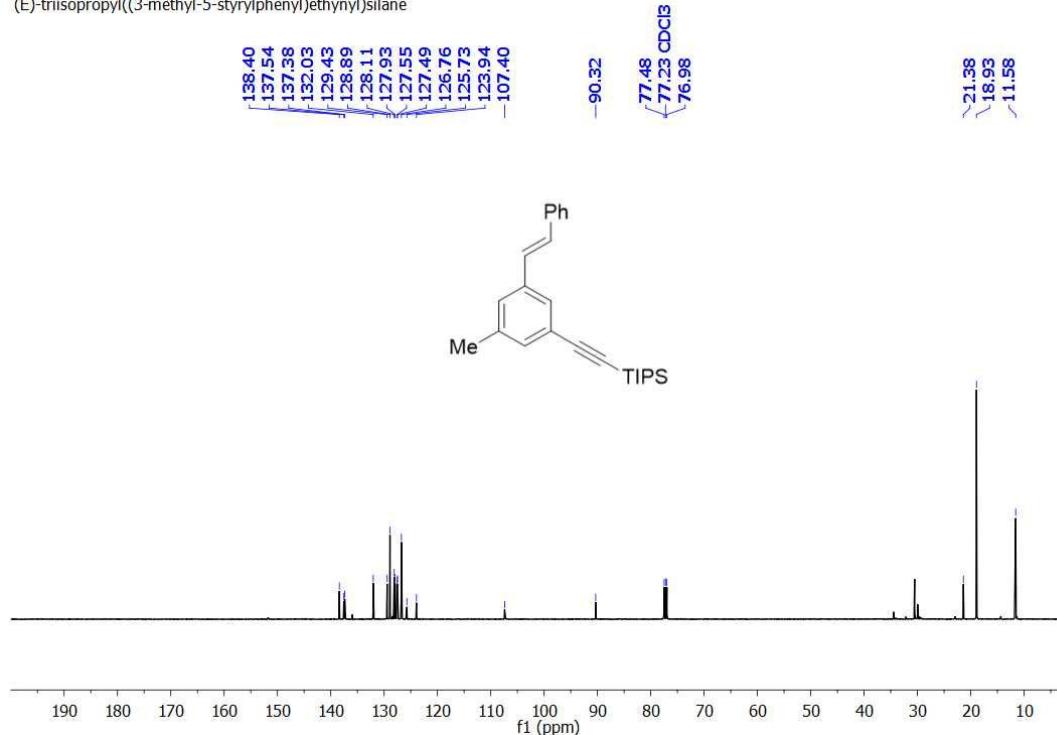


**Figure S109.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **79**

(E)-triisopropyl((3-methyl-5-styrylphenyl)ethynyl)silane

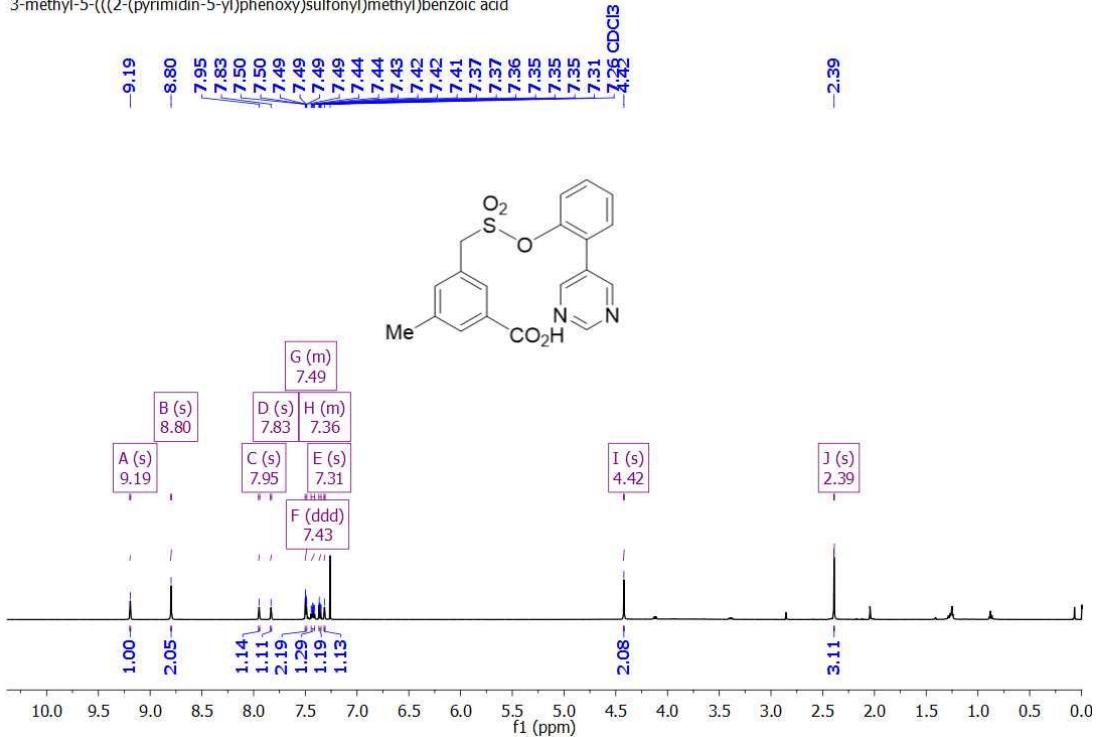


(E)-triisopropyl((3-methyl-5-styrylphenyl)ethynyl)silane

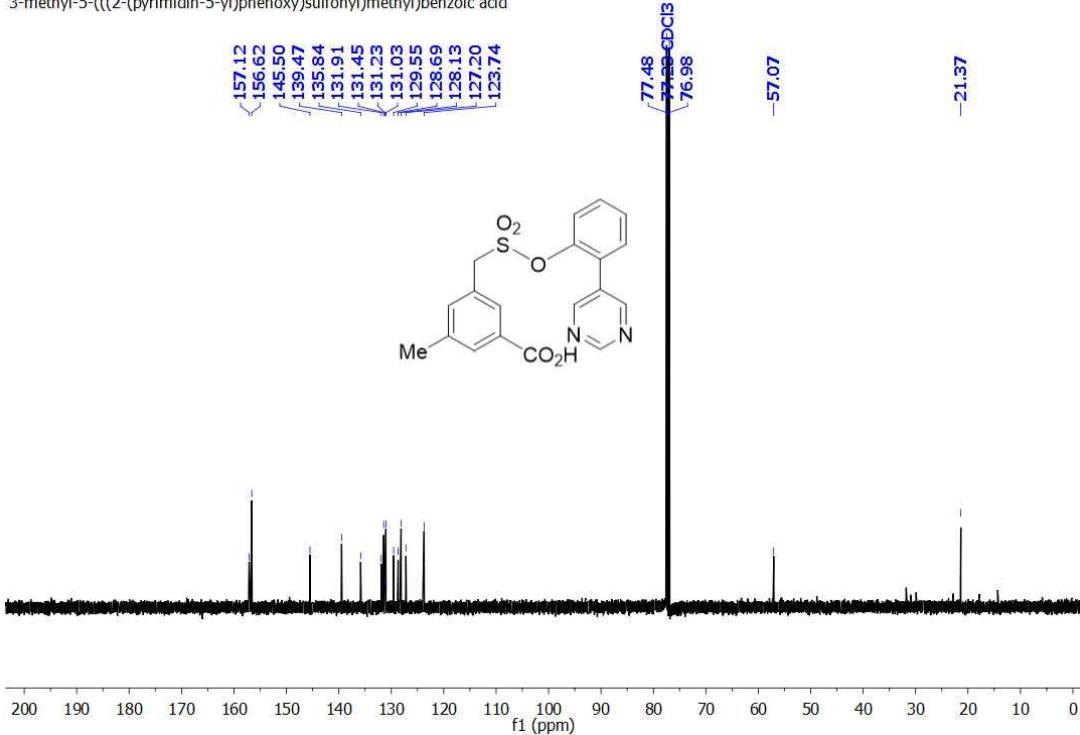


**Figure S110.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR of **80**

3-methyl-5-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)benzoic acid

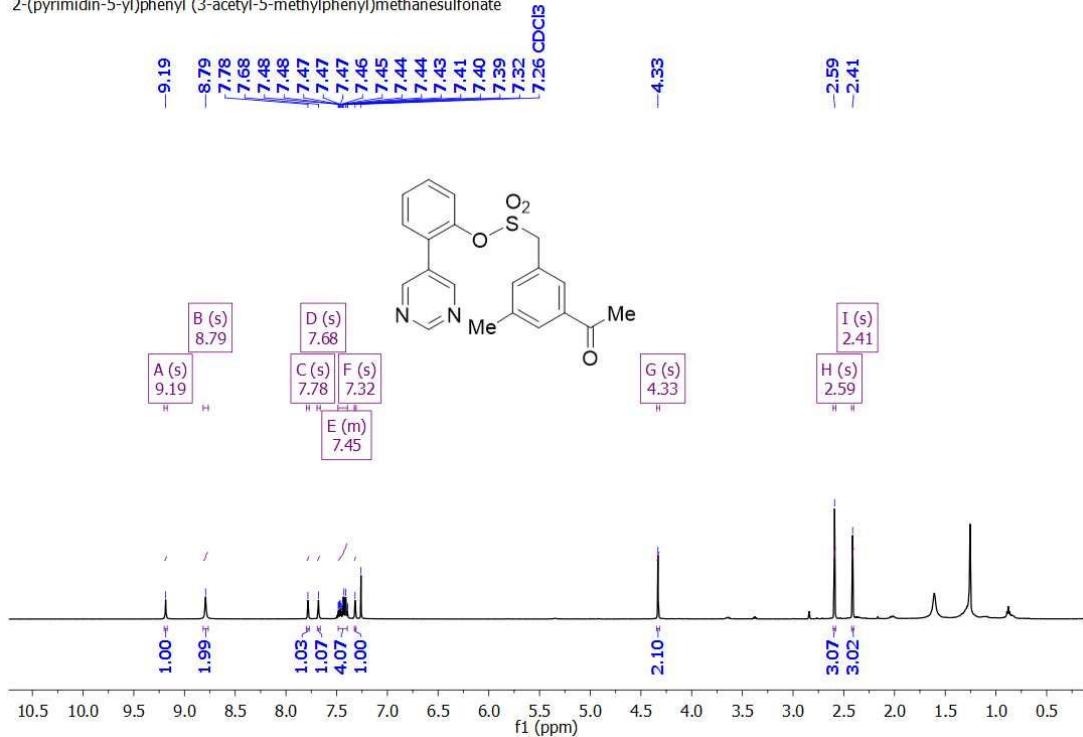


3-methyl-5-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)benzoic acid

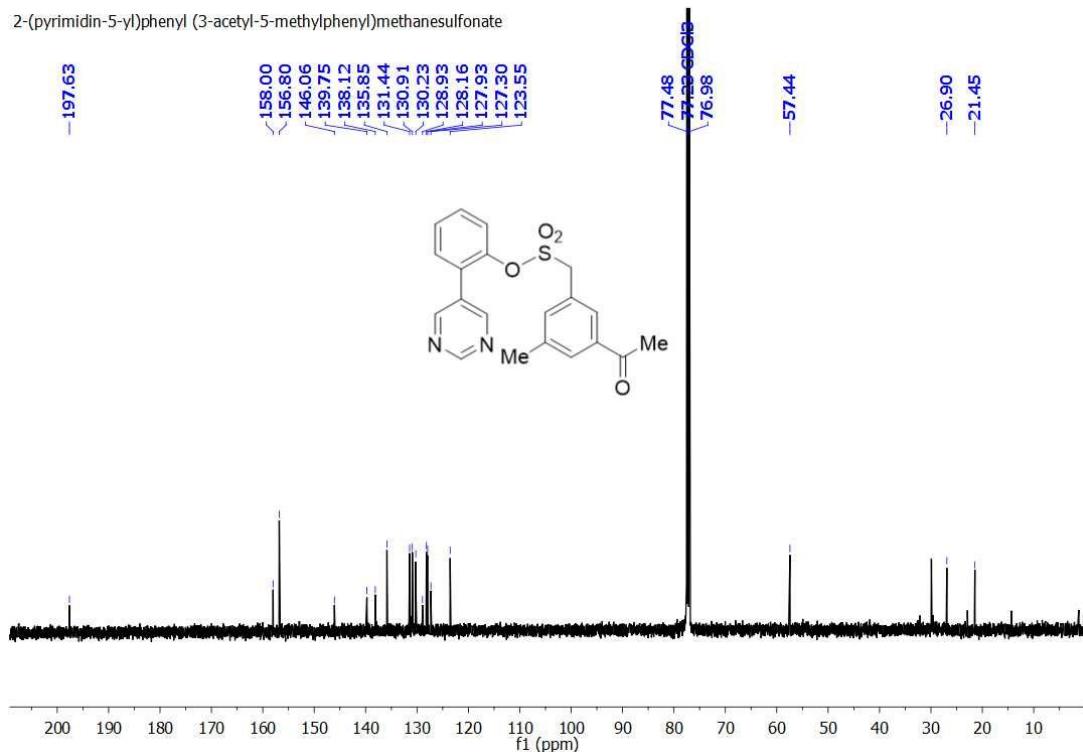


**Figure S111.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **81**

2-(pyrimidin-5-yl)phenyl (3-acetyl-5-methylphenyl)methanesulfonate

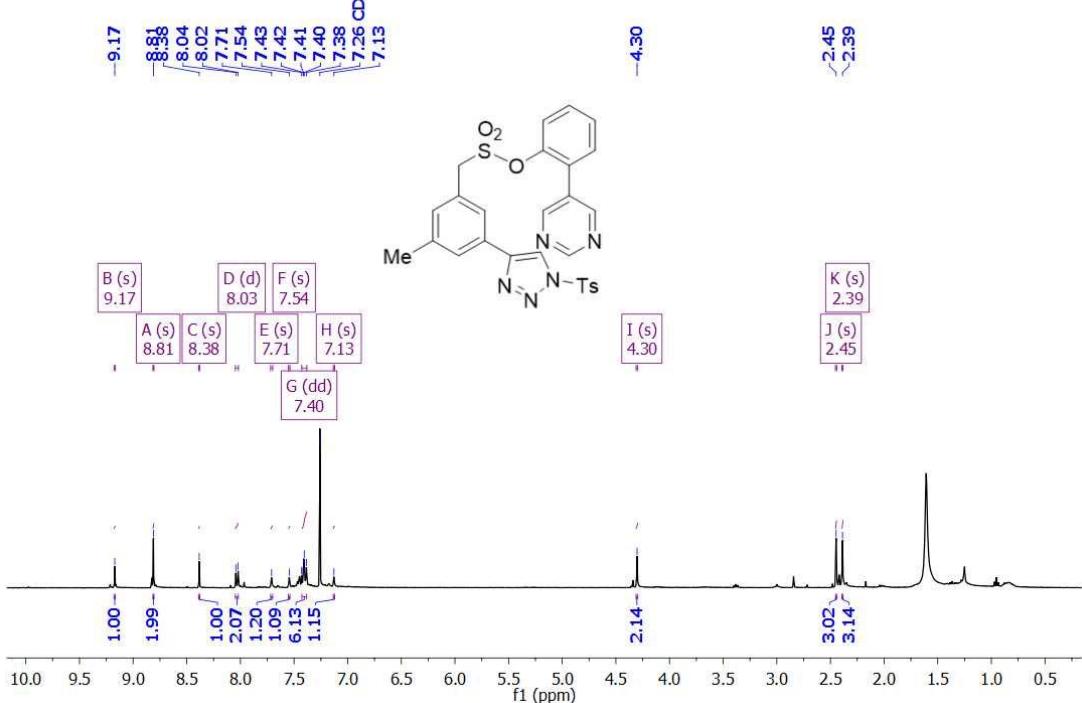


2-(pyrimidin-5-yl)phenyl (3-acetyl-5-methylphenyl)methanesulfonate

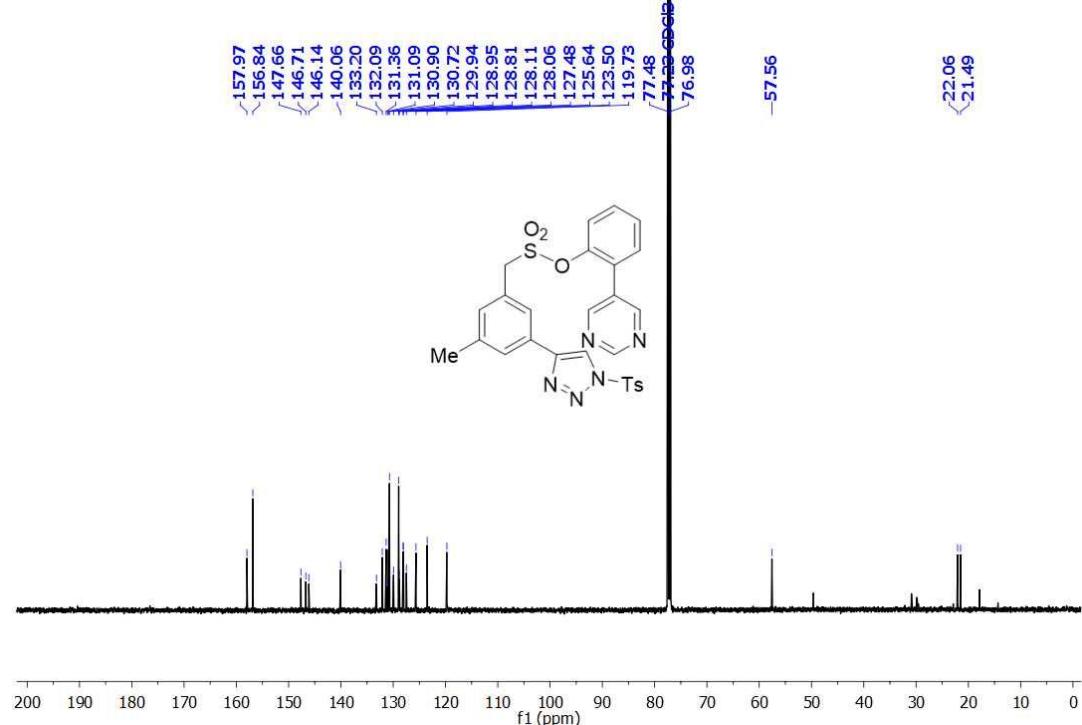


**Figure S112.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of **82**

2-(pyrimidin-5-yl)phenyl (3-methyl-5-(1-tosyl-1H-1,2,3-triazol-4-yl)phenyl)methanesulfonate



2-(pyrimidin-5-yl)phenyl (3-methyl-5-(1-tosyl-1H-1,2,3-triazol-4-yl)phenyl)methanesulfonate



**Figure S113.** <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR of 83