**Room Temperature Direct β-Arylation of Thiophenes and Benzo[b]thiophenes and Kinetic Evidence for a Heck-type Pathway**

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I. Experimental

**General Information.** Reagents were purchased from commercial sources and used without further purification. Column chromatography was carried out using a Biotage Isolera Four purification system, employing Biotage ZIP cartridges. Analytical thin layer chromatography was performed on pre-coated aluminium-backed silica gel F_{254} plates with visualization under UV light (λ = 254 nm). GC-MS analysis were carried out using a VARIAN 450-GC and 220-MS instrument or an AGILENT 7820A-GC and 5975-MS. Melting points were obtained using a Bibby or an SMP 11 Stuart Scientific apparatus. NMR spectra were recorded in CDCl$_3$ on Bruker AV–400 instrument at a constant temperature of 300 K (unless otherwise specified). Chemical shifts (δ) are reported in parts per million from low to high field and referenced to residual solvent (CDCl$_3$: δ 7.26/7.26/77.16, $^{1}$H/$^2$H/$^{13}$C NMR); $^{19}$F-NMR are referred to C$_6$F$_6$ (δ -164.9). Coupling constants (J) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: m = multiplet, q = quartet, t = triplet, d = doublet, s = singlet, br = broad. ATR-IR spectra were recorded using a Thermo-Scientific Nicolet iS5 machine and are quoted in cm$^{-1}$. High Resolution Mass Spectroscopy (HRMS) were recorded on Thermo Finnigan MAT95XP. Values of specific optical rotation were determined using a Rudolph Autopol I Automatic Polarimeter. High performance liquid chromatography was performed on Agilent Technologies chromatographs (Serie 1260; G1315D-1260 DAD VL) using Chiralpak IB column. Crystallographic data were obtained using Cu radiation on a Bruker Prospector Single Crystal X-Ray Diffractometer equipped with an APEX II detector.
II. Optimization of Reaction Conditions

II-1. Optimization of General Conditions

![Reaction Scheme](image)

**Table S.1:** Screening of Bases in H₂O.ᵃ

| Entry | Base                | Yield |
|-------|---------------------|-------|
| 1     | c-C₆H₁₁CO₂Ag        | 7%    |
| 2     | p-NO₂-C₆H₄CO₂Ag     | 14%   |
| 3     | 1-Ad-CO₂Ag          | 11%   |

ᵃ General conditions: 1a (0.25 mmol), 2a (1.5 equiv), base (1.5 equiv), Pd(OAc)₂ (5 mol %), H₂O (0.5 mL), 30 °C, 16 h. Yields were calculated by ¹H-NMR using an internal standard.

**Table S.2:** Screening of Bases in TFE.ᵇ

| Entry | Base       | Yield |
|-------|------------|-------|
| 1     | c-C₆H₁₁CO₂Ag | 15%   |
| 2ᵇ    | Ag₂CO₃     | 34%   |
| 3     | AgOPiv     | 9%    |
| 4ᵇ    | Ag₂O       | 7%    |

ᵇ General conditions: 1a (0.25 mmol), 2a (1.5 equiv), base (1.5-0.75ᵇ equiv), Pd(OAc)₂ (5 mol %), TFE (0.5 mL), 30 °C, 16 h. Yields were calculated by ¹H-NMR using an internal standard.
Table S.3: Screening of Fluorinated (Entry 1-6) and Non Fluorinated Solvents (Entry 7-14).\textsuperscript{a}

| Entry | Solvent                     | Yield |
|-------|-----------------------------|-------|
| 1     | 2,2,2-Trifluoroethanol      | 34%   |
| 2     | Tetrafluoro-1-propanol      | 17%   |
| 3     | Pentafluoro-1-pentanol      | Traces|
| 4     | Hexafluoro-2-propanol       | 72%   |
| 5     | Octafluoro-1-pentanol       | 25%   |
| 6     | Perfluoro-tert-butanol      | 65%   |
| 7     | EtOAc                       | -     |
| 8     | THF                         | -     |
| 9     | CHCl₃                       | 2%    |
| 10    | MeOH                        | 9%    |
| 11    | H₂O                         | -     |
| 12    | DMF                         | -     |
| 13    | 1,4-dioxane                 | Traces|
| 14    | CH₃CO₂H                     | 11%   |

\textsuperscript{a} General conditions: 1a (0.25 mmol), 2a (1.5 equiv), Ag₂CO₃ (0.75 equiv), Pd(OAc)\textsubscript{2} (5 mol %), solvent (0.5 mL), 24 °C, 16 h. Yields were calculated by \textsuperscript{1}H-NMR using an internal standard.

Table S.4: Screening of Bases in HFIP.\textsuperscript{a}

| Entry | Base                        | Yield |
|-------|-----------------------------|-------|
| 1     | Ag₂CO₃                      | 72%   |
| 2\textsuperscript{b} | c-C\textsubscript{6}H\textsubscript{11}CO₂Ag | 30%   |
| 3\textsuperscript{b} | AgOPiv                      | 34%   |
| 4     | Ag₂O                        | 67%   |
| 5\textsuperscript{b} | AgOTf                       | 8%    |
| 6\textsuperscript{c} | Ag₃PO₄                      | 14%   |

\textsuperscript{a} General conditions: 1a (0.25 mmol), 2a (1.5 equiv), base (0.75-1.5\textsuperscript{b}-0.5\textsuperscript{c} equiv), Pd(OAc)\textsubscript{2} (5 mol %), HFIP (0.5 mL), 24 °C, 16 h. Yields were calculated by \textsuperscript{1}H-NMR using an internal standard.
Table S.5: Screening of Palladium Catalysts.\textsuperscript{a}

| Entry | Catalyst           | Yield |
|-------|--------------------|-------|
| 1     | Pd(OAc)\(_2\)     | 72%   |
| 2     | PdCl\(_2\)        | 14%   |
| 3     | Pd(TFA)\(_2\)     | 58%   |
| 4     | Pd(NO\(_3\))\(_2\)\cdot H\(_2\)O | 89%   |
| 5     | PdI\(_2\)         | 89%   |
| 6     | Pd(dba)\(_2\)     | 63%   |
| 7     | Pd(PPh\(_3\))\(_4\) | 72%   |
| 8\textsuperscript{b} | Pd\(_2\)(dba)\(_3\)CHCl\(_3\) | 93%   |

\textsuperscript{a} General conditions: 1a (0.25 mmol), 2a (1.5 equiv), Ag\(_2\)CO\(_3\) (0.75 equiv), [Pd] catalyst (5-2.5\textsuperscript{b} mol %), HFIP (0.5 mL), 24 °C, 16 h. Yields were calculated by \(^1\)H-NMR using an internal standard.

Table S.6: Screening of Equivalents of HFIP.\textsuperscript{a}

| Entry | Catalyst | Yield |
|-------|----------|-------|
| 1     | 9.5      | 92%   |
| 2     | 6.5      | 90%   |
| 3     | 5        | 88%   |
| 4     | 4        | 86%   |
| 5     | 3        | 60%   |
| 6     | 2        | 38%   |

\textsuperscript{a} General conditions: 1a (0.25 mmol), 2a (1.5 equiv), Ag\(_2\)CO\(_3\) (0.75 equiv), Pd\(_2\)(dba)\(_3\)CHCl\(_3\) catalyst (2.5 mol %), HFIP, 24 °C, 16 h. Yields were calculated by \(^1\)H-NMR using an internal standard.
II-2. Optimization of Reaction Conditions Employing Electron-poor Iodoarenes

![Chemical structure][1]

**Table S.7:** Screening of Temperatures.\(^a\)

| Entry | Temperature | Yield |
|-------|-------------|-------|
| 1     | 24 °C       | 30%   |
| 2     | 40 °C       | 46%   |
| 3     | 60 °C       | 57%   |
| 4     | 80 °C       | 61%   |

\(^a\) General conditions: 1a (0.25 mmol), 2k (1.5 equiv), Ag₂CO₃ (0.75 equiv), Pd₂(dba)₃, CHCl₃ (2.5 mol %), HFIP (0.5 mL), 16 h. Yields were calculated by \(^1\)H-NMR using an internal standard.

**Table S.8:** Screening of Carboxylic Acids.\(^a\)

| Entry | RCO₂H                      | Yield |
|-------|----------------------------|-------|
| 1     | N-Boc-proline              | 31%   |
| 2     | N-acetyl-L-leucine         | traces|
| 3     | 2-chloroacetic acid        | 7%    |
| 4     | Cycloheptanecarboxylic acid| 8%    |
| 5     | 2-cyclohexylacetic acid    | 18%   |
| 6     | 3-methylbutanoic acid      | 11%   |

\(^a\) General conditions: 1a (0.25 mmol), 2k (1.5 equiv), Ag₂CO₃ (0.75 equiv), RCO₂H (1.5 equiv), Pd₂(dba)₃, CHCl₃ (2.5 mol %), HFIP (0.5 mL), 24 °C, 16 h. Yields were calculated by \(^1\)H-NMR using an internal standard.
Table S.9: Screening of Phosphines at Room Temperature (Entry 1-15) and at Higher Temperatures (Entry 16-19).^a

| Entry | Temperature (°C) | Phosphines                        | Yield |
|-------|------------------|-----------------------------------|-------|
| 1     | 24               | PCy₃                              | 49%   |
| 2     | 24               | (HPr-Bu₂Me)⁺ BF₄                  | 10%   |
| 3     | 24               | (HPCy₃)⁺ BF₄                      | 26%   |
| 4     | 24               | (HPrPr₃)⁺ BF₄                     | 8%    |
| 5     | 24               | PPh₃                              | 46%   |
| 6     | 24               | P(4-OMePh)₃                       | 49%   |
| 7     | 24               | P(4-FPh)₃                         | 31%   |
| 8     | 24               | P(2,4-MePh)₃                      | 26%   |
| 9     | 24               | BINAP                             | 6%    |
| 10    | 24               | dppe                              | 8%    |
| 11    | 24               | XPhos                             | 16%   |
| 12    | 24               | DavePhos                          | 9%    |
| 13    | 24               | JohnPhos                          | 23%   |
| 14    | 24               | Di(1-adamantyl)benzylphosphine    | 16%   |
| 15b   | 24               | P(4-OMePh)₃                       | 26%   |
| 16    | 40               | P(4-OMePh)₃                       | 73%   |
| 17    | 50               | P(4-OMePh)₃                       | 93%   |
| 18    | 60               | P(4-OMePh)₃                       | 97%   |
| 19    | 80               | P(4-OMePh)₃                       | 91%   |

^a General conditions: 1a (0.25 mmol), 2k (1.5 equiv), Ag₂CO₃ (0.75 equiv), phosphine (5-10⁶ mol%), Pd₂(dba)₃ CHCl₃ (2.5 mol %), HFIP (0.5 mL), 16 h. Yields were calculated by ¹H-NMR using an internal standard.
III. Experimental Details, Spectroscopic and Analytical Data

III-1. Experimental Details

*Synthesis of Pd$_2$(dba)$_3$·CHCl$_3$*

Pd$_2$(dba)$_3$·CHCl$_3$ was synthesized according to the procedure of Ananikov et al.$^1$ Pd(OAc)$_2$ (500 mg, 2.23 mmol, 1 equiv), sodium acetate trihydrate (3.08 g, 22.6 mmol, 10 equiv), dibenzylideneacetone (1.03 g, 4.46 mmol, 2 equiv) were weighted in a 250 mL round-bottom flask followed by the addition of 50 mL of MeOH. The reaction mixture was stirred at 40 °C for 3 hours. After completion of the reaction a brown solid was formed. The solid was filtered off and washed with MeOH (2 x 3 mL) and water (3 x 3 mL). The residue was washed with CHCl$_3$ and the solution was evaporated. The solid obtained was redissolved in a minimum amount of CHCl$_3$ and acetone (~ 20 mL) was slowly added to the solution. The mixture was kept overnight in the refrigerator. The crystals of Pd$_2$(dba)$_3$·CHCl$_3$ were filtered off, washed with cold acetone (~3 mL) and dried under vacuum at 40 °C. Pd$_2$(dba)$_3$·CHCl$_3$ was obtained in 72% yield (1.7 g, 1.6 mmol).

*General procedures*

**General procedure A.** Pd$_2$(dba)$_3$·CHCl$_3$ (2.5 mol %), silver carbonate (0.75 equiv), aryl iodide (1.50 equiv) and (benzo)thiophene (1.0 equiv) were stirred in hexafluoro-2-propanol at 24 °C for 16 h. After this time, the resultant mixture was diluted with EtOAc (5 mL) and filtered through a plug of silica. The silica plug was flushed with EtOAc (30 mL) and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by automated column chromatography using the specified eluent to afford the product.

**General procedure B.** Pd$_2$(dba)$_3$·CHCl$_3$ (2.5 mol %), silver carbonate (0.75 equiv), tris(4-methoxyphenyl)phosphine (5 mol %), aryl iodide (1.50 equiv) and (benzo)thiophene (1.0 equiv) were stirred in hexafluoro-2-propanol at 50 °C for 16 h. After this time, the resultant mixture was diluted with EtOAc (5 mL) and filtered through a plug of silica. The silica plug was flushed with EtOAc (30 mL)
and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by automated column chromatography using the specified eluent to afford the product.

**General procedure C.** Pd$_2$(dba)$_3$CHCl$_3$ (2.5 mol %), silver carbonate (0.75 equiv), aryl iodide (1.50 equiv) and (benzo)thiophene (1.0 equiv) were stirred in hexafluoro-2-propanol at 50 °C for 16 h. After this time, the resultant mixture was diluted with EtOAc (5 mL) and filtered through a plug of silica. The silica plug was flushed with EtOAc (30 mL) and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by automated column chromatography using the specified eluent to afford the product.

**General procedure D.** Pd$_2$(dba)$_3$CHCl$_3$ (2.5 mol %), silver carbonate (0.5 equiv), tris(4-methoxyphenyl)phosphine (5 mol %), aryl iodide (1.0 equiv) and (benzo)thiophene (3.0 equiv) were stirred in hexafluoro-2-propanol at 50 °C for 16 h. After this time, the resultant mixture was diluted with EtOAc (5 mL) and filtered through a plug of silica. The silica plug was flushed with EtOAc (30 mL) and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by automated column chromatography using the specified eluent to afford the product.

**General procedure E.** Pd$_2$(dba)$_3$CHCl$_3$ (2.5 mol %), silver carbonate or silver oxide (0.5 equiv), aryl iodide (1.0 equiv) and (benzo)thiophene (2.0 equiv) were stirred in hexafluoro-2-propanol at 24 °C for 16 h. After this time, the resultant mixture was diluted with EtOAc (5 mL) and filtered through a plug of silica. The silica plug was flushed with EtOAc (30 mL) and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using the specified eluent to afford the product.
III-2. Spectroscopic and Analytical Data

3-(p-tolyl)benzo[b]thiophene (3aa)

The product 3aa was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 4-iodotoluene 2a (245 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 88% yield (148 mg, 0.66 mmol).

The same reaction on a 20 mmol scale afforded 84% yield of product 3aa (3.77 g, 17 mmol) using 4 equivalent of hexafluoro-2-propanol (8.4 mL). Alternatively, product 3aa can be obtained in 89% yield using 0.5 mol% of Pd$_2$(dba)$_3$ CHCl$_3$ at 50 °C in 16 h (NMR yield determined against internal standard).

$R_f$ (hexane): 0.48; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 8.02-7.97 (m, 2H), 7.56 (d, $J = 8.0$ Hz, 2H), 7.47-7.44 (m, 2H), 7.42 (s, 1H), 7.36 (d, $J = 8.0$ Hz, 2H), 2.50 (s, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ (ppm) 140.9, 138.2, 138.2, 137.4, 133.3, 129.6, 128.7, 124.5, 124.4, 123.1, 123.1, 123.0, 21.2; HRMS: calcd for C$_{15}$H$_{12}$S, 225.0660 (M+H$^+$); found, 225.0730. Data is in accordance with the literature.$^{2,3,4}$

3-(4-methoxyphenyl)benzo[b]thiophene (3ab)

The product 3ab was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 4-idoanisole 2b (263 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane:EtOAc = 20:1) as a colorless oil in 88% yield (158 mg, 0.66 mmol).

$R_f$ (hexane:EtOAc = 20:1): 0.27; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.97-7.94 (m, 2H), 7.56 (d, $J = 8.9$ Hz, 2H), 7.44-7.40 (m, 2H), 7.37 (s, 1H), 7.07 (d, $J = 8.9$ Hz, 2H), 3.91 (s, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ (ppm) 159.3, 140.8, 138.2, 137.8, 129.9, 128.6, 124.4, 124.4, 123.0, 123.0, 122.7, 114.3, 55.4; HRMS: calcd for C$_{15}$H$_{12}$OS, 241.0609 (M+H$^+$); found, 241.0678. Data is in accordance with the literature.$^{2,3,4}$
3-phenylbenzo[b]thiophene (3ac)

The product 3ac was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and iodobenzene 2c (126 μl, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 90% yield (142 mg, 0.68 mmol).

Rf (hexane): 0.45; \(^{1}\)H-NMR (400 MHz, CDCl\(_3\)): δ (ppm) 8.05-7.98 (m, 2H), 7.68 (d, \(J = 7.5\) Hz, 2H), 7.58 (dd, \(J = 7.6, 7.6\) Hz, 2H), 7.49-4.47 (m, 4H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): δ (ppm) 140.8, 138.2, 138.0, 136.1, 128.8, 128.8, 127.7, 124.5, 124.4, 123.5, 123.0, 123.0; HRMS: calcd for C\(_{14}\)H\(_{10}\)S, 211.0503 (M+H\(^+\)); found, 211.0574. Data is in accordance with the literature.\(^{2,3,4}\)

Alternatively, product 3ac can be obtained in 75% yield using 0.5 mol% of Pd\(_2\)(dba)\(_3\) CHCl\(_3\) at 50 °C in 16 h (NMR yield determined against internal standard).

4-((benzo[b]thiophen-3-yl)phenyl)methanol (3ad)

The product 3ad was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and (4-iodophenyl)methanol 2d (263 mg, 1.12 mmol, 1.5 equiv) and isolated by column chromatography (hexane: EtOAc:Et\(_3\)N = 79:20:1) as a colorless oil in 86% yield (155 mg, 0.64 mmol).

Rf (hexane:EtoAc = 7:3): 0.44; \(^{1}\)H-NMR (400 MHz, CDCl\(_3\)): δ (ppm) 7.97-7.92 (m, 2H), 7.60 (d, \(J = 8.2\) Hz, 2H), 7.49 (d, \(J = 8.1\) Hz, 2H), 7.43-7.40 (m, 2H), 7.40 (s, 1H), 4.77 (s, 2H), 2.40 (br, 1H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): δ (ppm) 140.8, 140.3, 137.9, 137.8, 135.4, 128.9, 127.5, 124.5, 124.4, 123.5, 123.5, 122.9, 65.0; IR: ν = 3272, 2860, 1915, 1528, 1492, 1456, 1424, 1342, 1259, 1204, 1060, 1031, 1021, 1008, 938, 842, 822, 802, 783, 760, 731, 702, 619 cm\(^{-1}\); HRMS: calcd for C\(_{15}\)H\(_{12}\)OS, 241.0609 (M+H\(^+\)); found, 241.0678.
4-(benzo[b]thiophen-3-yl)benzaldehyde (3ae)

The product 3ae was obtained via the general procedure B using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 4-iodobenzaldehyde 2e (260.4 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane:EtOAc = 20:1) as a colorless oil in 96% yield (172 mg, 0.72 mmol).

R_f (hexane:EtOAc = 20:1): 0.25; ^1H-NMR (400 MHz, CDCl_3): δ (ppm) 10.10 (s, 1H), 8.00 (d, J = 8.3 Hz, 2H), 7.97-7.95 (m, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.52 (s, 1H), 7.48-7.45 (m, 2H); ^13C-NMR (101 MHz, CDCl_3): δ (ppm) 191.6, 141.9, 140.8, 137.2, 136.7, 135.3, 130.1, 129.0, 125.2, 124.8, 124.7, 123.0, 122.5; IR: ν = 3090, 2837, 1907, 1698, 1602, 1528, 1493, 1456, 1424, 1335, 1303, 1207, 1167, 1103, 1032, 900, 765, 817, 759, 734,666, 614 cm\(^{-1}\); HRMS: calcd for C_{15}H_{10}OS, 239.0472 (M+H\(^{+}\)); found, 239.0524.

3-(4-acetylphenyl)benzo[b]thiophene (3af)

The product 3af was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 4-iodoacetophenone 2f (278 mg, 1.13 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane:EtOAc = 20:1) as a white solid in 88% yield (167 mg, 0.66 mmol).

R_f (hexane:EtOAc = 20:1): 0.10; ^1H-NMR (400 MHz, CDCl_3): δ (ppm) 8.08 (d, J = 8.5 Hz, 2H), 7.95-7.90 (m, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.48 (s, 1H), 7.43-7.41 (m, 2H), 2.66 (s, 3H); ^13C-NMR (101 MHz, CDCl_3): δ (ppm) 197.7, 140.9, 140.8, 137.5, 137.0, 136.2, 128.9, 128.8, 124.9, 124.8, 124.8, 123.2, 122.8, 26.7; HRMS: calcd for C_{16}H_{12}OS, 253.0609 (M+H\(^{+}\)); found, 253.0685; Mp: 89-90°C.

Data is in accordance with the literature.\(^3\) Alternatively, product 3af can be obtained in 90% yield using 0.5 mol% of Pd\(_2\)(dba)_3 CHCl_3 at 50 °C in 16 h (NMR yield determined against internal standard).
Methyl 4-(benzo[b]thiophen-3-yl)benzoate (3ag)

The product 3ag was obtained via the general procedure A using benzo[b]thiophene 1a (100 mg, 0.75 mmol, 1.0 equiv) and methyl-4-iodobenzoate 2g (305 mg, 1.16 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane:EtOAc = 20:1) as a white solid in 88% yield (177 mg, 0.66 mmol).

R<sub>f</sub> (hexane:EtOAc = 20:1): 0.16; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.17 (d, <i>J</i> = 8.2 Hz, 2H), 7.94-7.91 (m, 2H), 7.67 (d, <i>J</i> = 8.3 Hz, 2H), 7.46 (s, 1H), 7.41-7.39 (m, 2H), 3.96 (s, 3H); <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>): δ (ppm) 166.9, 140.8, 140.6, 137.5, 137.0, 130.1, 129.2, 128.6, 124.7, 124.7, 124.6, 123.1, 122.7, 52.2; HRMS: calcd for C<sub>16</sub>H<sub>12</sub>O<sub>2</sub>S, 269.0558 (M+H<sup>+</sup>); found, 269.0633; Mp: 60-61°C. Data is in accordance with the literature.<sup>2</sup>

Alternatively, product 3aa can be obtained in 83% yield using 0.5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub>CHCl<sub>3</sub> at 50 °C in 16 h (NMR yield determined against internal standard).

3-(4-fluorophenyl)benzo[b]thiophene (3ah)

The product 3ah was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 1-iodo-4-fluorobenzene 2h (130 μl, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 89% yield (153 mg, 0.67 mmol).

R<sub>f</sub> (hexane): 0.45; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 7.97-7.95 (m, 1H), 7.90-7.89 (m, 1H), 7.57 (dd, <i>J</i> = 8.8, 5.8 Hz, 2H), 7.44-7.43 (m, 2H), 7.39 (s, 1H), 7.21 (dd, <i>J</i> = 8.8, 8.8 Hz, 2H); <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>): δ (ppm) 162.5 (d, <i>J</i> = 251.8 Hz), 140.8, 138.0, 137.1, 132.0 (d, <i>J</i> = 3.3 Hz), 130.4 (d, <i>J</i> = 8.1 Hz), 124.6, 124.6, 123.6, 123.0, 122.8, 115.8 (d, <i>J</i> = 22.2 Hz); <sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>): δ (ppm)
HRMS: calcd for C_{14}H_{9}FS, 229.0409 (M+H^+); found, 229.0484. Data is in accordance with the literature.\(^3\)

3-(4-chlorophenyl)benzo[b]thiophene (3ai)

The product 3ai was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 1-iodo-4-chlorobenzene 2i (268 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 61% yield (112 mg, 0.46 mmol).

R\(_f\) (hexane): 0.50; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.97-7.94 (m, 1H), 7.93-7.89 (m, 1H), 7.54 (d, \(J= 8.4\) Hz, 2H), 7.49 (d, \(J= 8.4\) Hz, 2H), 7.46-7.43 (m, 2H), 7.40 (s, 1H); \(^13\)C-NMR (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 140.8, 137.7, 136.9, 134.5, 133.6, 130.0, 129.0, 124.7, 124.6, 123.9, 123.1, 122.7; HRMS: calcd for C\(_{14}\)H\(_9\)ClS, 245.0113 (M+H\(^+\)) ; found, 245.0184. Data is in accordance with the literature.\(^3\)^4

3-(4-bromophenyl)benzo[b]thiophene (3aj)

The product 3aj was obtained via the general procedure A using benzo[b]thiophene 1a (100 mg, 0.75 mmol, 1.0 equiv) and 1-iodo-4-bromobenzene 2j (326 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 35% yield (76 mg, 0.26 mmol).

R\(_f\) (hexane): 0.52; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.96-7.92 (m, 1H), 7.89-7.85 (m, 1H), 7.63 (d, \(J= 8.4\) Hz, 2H), 7.47 (d, \(J= 8.4\) Hz, 2H), 7.43-7.39 (m, 3H); \(^13\)C-NMR (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 140.8, 137.7, 136.9, 135.0, 132.0, 130.4, 124.7, 124.6, 123.9, 123.1, 122.8, 121.8; HRMS: calcd for C\(_{14}\)H\(_9\)BrS, 288.9608 (M+H\(^+\)) ; found, 288.9684. Data is in accordance with the literature.\(^3\)^4

S-14
3-(4-nitrophenyl)benzo[b]thiophene (3ak)

The product 3ak was obtained via the general procedure B using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 1-iodo-4-nitrobenzene 2k (280 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane:DCM = 75:25) as a yellow solid in 89% yield (171 mg, 0.67 mmol).

Rf (hexane:DCM = 75:25): 0.27; 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.34 (d, J= 8.8 Hz, 2H), 7.95 (m, 1H), 7.89 (m,1H), 7.75 (d, J= 8.9 Hz, 2H), 7.55 (s, 1H), 7.47-7.42 (m, 2H); 13C-NMR (101 MHz, CDCl3): δ (ppm) 147.2, 142.7, 140.9, 137.1, 135.9, 129.3, 125.9, 125.1, 125.0, 124.2, 123.3, 122.5; IR: ν = 3105, 1595, 1521, 1456, 1423, 1336, 1261, 1215, 1144, 1109, 1058, 941, 869, 854, 839, 781, 755, 725, 695, 635 cm⁻¹; HRMS: calcd for C14H9NO2S, 256.0354 (M+H⁺); found, 256.0426; Mp: 108-109°C.

3-(4-(trifluoromethyl)phenyl)benzo[b]thiophene (3al)

The product 3al was obtained via the general procedure B using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 1-iodo-4-(trifluoromethyl)benzene 2l (165 μl, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 89% yield (185 mg, 0.66 mmol).

Rf (hexane): 0.52; 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.00-7.96 (m, 1H), 7.94-7.92 (m, 1H), 7.80 (d, J= 8.2 Hz, 2H), 7.72 (d, J= 8.1 Hz, 2H), 7.48 (s, 1H), 7.47-7.46 (m, 2H); 13C-NMR (101 MHz, CDCl3): δ (ppm) 140.9, 139.7, 137.6, 136.8, 129.7 (q, J = 31.4 Hz), 129.0, 125.8 (q, J = 4.1 Hz), 124.8, 124.8, 124.7, 124.4 (q, J = 272.1 Hz), 123.2, 122.7; 19F-NMR (376 MHz, CDCl3) δ (ppm) -62.3; HRMS: calcd for C15H13F3S, 279.0377 (M+H⁺); found, 279.0450. Data is in accordance with the literature.3,4
3-(m-tolyl)benzo[b]thiophene (3am)

The product 3am was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 3-iodotoluene 2m (144 μl, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 83% yield (140 mg, 0.62 mmol).

Rf (hexane): 0.45; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ (ppm) 8.04-7.98 (m, 2H), 7.50-7.44 (m, 6H), 7.31 (d, \(J = 7.7\) Hz, 1H), 2.53 (s, 3H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): δ (ppm) 140.8, 138.4, 138.3, 138.1, 136.1, 129.6, 128.7, 128.4, 125.9, 124.5, 124.4, 123.4, 123.1, 123.0, 21.6; HRMS: calcd for C\(_{15}\)H\(_{12}\)S, 225.0660 (M+H\(^+\)); found, 225.0733. Data is in accordance with the literature.\(^2\)

3-(3-methoxyphenyl)benzo[b]thiophene (3an)

The product 3an was obtained via the general procedure B using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 1-iodo-3-methoxybenzene 2n (187 μl, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane:EtOAc = 95:5) as an inseparable mixture C3:C2 = 91:9 in 72% yield (130 mg, 0.54 mmol).

Rf (hexane:EtOAc = 95:5): 0.57; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ (ppm) 8.03-7.97 (m, 2H), 7.97-7.91 (m, 1H), 7.48-7.39 (m, 4H), 7.23-2.16 (m, 2H), 7.01-6.98 (ddd, \(J = 8.3, 2.6, 1.0\) Hz, 1H), 3.88 (s, 3H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): δ (ppm) 160.0, 140.8, 138.1, 138.0, 137.4, 129.8, 124.5, 124.4, 123.6, 123.1, 123.0, 121.3, 114.4, 113.2, 55.4; HRMS: calcd for C\(_{15}\)H\(_{12}\)O\(_{5}\), 241.0609 (M+H\(^+\)); found, 241.0681. Data is in accordance with the literature.\(^2\)
3-(3,5-dimethylphenyl)benzo[b]thiophene (3ao)

The product 3ao was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 1,3,5-dimethylbenzene 2o (162 μl, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 81% yield (145 mg, 0.61 mmol).

Rf (hexane): 0.36; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.99-7.93 (m, 2H), 7.45-7.39 (m, 3H), 7.26 (s, 2H), 7.10 (s, 1H), 2.45 (s, 6H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 140.8, 138.5, 138.4, 138.2, 136.1, 129.4, 126.7, 124.4, 124.3, 123.2, 123.2, 123.0, 21.5; IR: \(\nu = 2918, 2853, 1600, 1519, 1459, 1426, 1376, 1348, 1315, 1253, 1164, 1065, 1023, 939, 900, 844, 792, 758, 732, 702, 688, 630 \text{ cm}^{-1}\); HRMS: calcd for C\(_{16}\)H\(_{14}\)S, 239.0816 (M+H\(^+\)); found, 239.0888.

3-(o-tolyl)benzo[b]thiophene (3ap)

The product 3ap was obtained via the general procedure C using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 2-iodotoluene 2p (144 μl, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 80% yield (134 mg, 0.60 mmol).

Rf (hexane): 0.48; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.95 (d, \(J = 7.9\) Hz, 1H), 7.49 (d, \(J = 7.9\) Hz, 1H), 7.42-7.30 (m, 7H), 2.22 (s, 3H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 140.1, 139.2, 137.2, 136.1, 130.6, 130.4, 128.0, 125.8, 124.4, 124.3, 123.8, 123.3, 122.8, 20.3; HRMS: calcd for C\(_{15}\)H\(_{12}\)S, 225.0660 (M+H\(^+\)); found, 225.0734. Data is in accordance with the literature.\(^3\)\(^,\)\(^4\)
3-(2-fluorophenyl)benzo[b]thiophene (3aq)

The product 3aq was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 1-fluoro-2-iodobenzene 2q (132 μl, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 88% yield (151 mg, 0.66 mmol).

Rf (hexane): 0.31; \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): δ (ppm) 7.94-7.92 (m, 1H), 7.76-7.75 (m, 1H); 7.54-7.50 (m, 2H), 7.41-7.36 (m, 3H), 7.27-7.21 (m, 2H); \textsuperscript{13}C-NMR (101 MHz, CDCl\textsubscript{3}): δ (ppm) 160.1 (d, J = 251.8 Hz), 140.2, 138.2, 131.5 (d, J = 5.5 Hz), 131.4, 129.5 (d, J = 7.9 Hz), 125.6 (d, J = 2.4 Hz), 124.6, 124.5, 124.3, 124.3, 123.5 (d, J = 15.2 Hz), 123.2 (d, J = 2.4 Hz), 116.2 (d, J = 23.1 Hz); \textsuperscript{19}F-NMR (376 MHz, CDCl\textsubscript{3}) δ (ppm) -113.8; HRMS: calcd for C\textsubscript{14}H\textsubscript{9}FS, 229.0409 (M+H\textsuperscript{+}); found, 229.0481. Data is in accordance with the literature.

3-(naphthalene-1-yl)benzo[b]thiophene (3ar)

The product 3ar was obtained via the general procedure C using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and 1-iodonaphthalene 2r (164 μl, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 80% yield (156 mg, 0.60 mmol).

Rf (hexane): 0.34; \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): δ (ppm) 8.03 (d, J= 8.1 Hz, 1H), 8.01-7.98 (m, 2H), 7.80 (d, J= 8.5 Hz, 1H), 7.64-7.51 (m, 4H), 7.50-7.38 (m, 3H), 7.36-7.29 (m, 1H); \textsuperscript{13}C-NMR (101 MHz, CDCl\textsubscript{3}): δ (ppm) 140.1, 139.7, 136.5, 133.9, 133.9, 132.6, 128.4, 128.4, 128.0, 126.3, 126.2, 126.1, 125.6, 125.1, 124.6, 124.3, 123.6, 122.8; HRMS: calcd for C\textsubscript{14}H\textsubscript{12}S, 261.0660 (M+H\textsuperscript{+}); found, 261.0732. Data is in accordance with the literature.
3-(thiophen-2-yl)benzo[b]thiophene (3as)

The product 3as was obtained via the general procedure D using benzo[b]thiophene 1a (302 mg, 2.25 mmol, 3.0 equiv) and 2-iodothiophene 2s (83 μl, 0.75 mmol, 1.0 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 57% yield (92 mg, 0.43 mmol).

Rf (hexane): 0.41; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.15 (d, J= 7.6 Hz, 1H), 7.91 (d, J= 7.7 Hz, 1H), 7.51 (s, 1 H), 7.48-7.40 (m, 2H), 7.37-7.35 (m, 2H), 7.17 (dd, J= 3.8, 5.2 Hz, 1H); ¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 140.6, 137.4, 137.4, 130.6, 127.7, 125.3, 124.9, 124.8, 124.7, 124.0, 123.1, 123.0; HRMS: calcd for C₁₂H₈S₂, 216.0062 (M⁺); found, 216.0064. Data is in accordance with the literature.⁶

3-(thiophen-3-yl)benzo[b]thiophene (3at)

The product 3at was obtained via the general procedure D using benzo[b]thiophene 1a (302 mg, 2.25 mmol, 3.0 equiv) and 3-iodothiophene 2t (76 μl, 0.75 mmol, 1.0 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 63% yield (102 mg, 0.47 mmol).

Rf (hexane): 0.42; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.07 (m, 1H), 7.98 (m, 1H), 7.55 (dd, J= 3.3, 5.8 Hz, 1H), 7.51-7.43 (m, 5H); ¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 140.5, 137.9, 136.3, 132.7, 128.0, 126.0, 124.6, 124.5, 123.3, 123.0, 123.0, 122.1; HRMS: calcd for C₁₂H₈S₂, 216.0062 (M⁺); found, 216.0063. Data is in accordance with the literature.⁷
5-(benzo[b]thiophene-3-yl)-1-tosyl-1H-indole (3au)

The product 3au was obtained via the general procedure B using benzo[b]thiophene 1a (70 μl, 0.75 mmol, 1.0 equiv) and 5-iodo-1-tosyl-1H-indole 2u (447 mg, 1.12 mmol, 1.5 equiv), previously synthesized in 95% yield according to the procedure reported in Chem. Pharm. Bull. 2009, 57, 591. The product was isolated by column chromatography (hexane:DCM = 8:2) in 61% yield as a white solid (186 mg, 0.46 mmol).

Rf (hexane: DCM = 8:2): 0.20; 1H NMR (400 MHz, CDCl3): δ (ppm) 8.08 (d, J = 8.5 Hz, 1H), 7.91-7.84 (m, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 1.2 Hz, 1H), 7.61 (d, J = 3.8 Hz, 1H), 7.50 (dd, J = 8.5, 1.7 Hz, 1H), 7.38-7.33 (m, 2H), 7.33 (s, 1H), 7.21 (d, J = 8.2 Hz, 2H), 6.68 (dd, J = 3.7, 0.7 Hz, 1H), 2.3 (s, 3H); 13C NMR (101 MHz, CDCl3): δ (ppm) 145.2, 140.7, 138.1, 138.0, 135.4, 134.3, 131.4, 131.3, 130.1, 127.1, 127.0, 125.6, 124.5, 124.4, 123.4, 123.0, 123.0, 121.5, 113.8, 109.2, 21.7; IR: ν = 2922, 1595, 1514, 1493, 1451, 1423, 1368, 1284, 1263, 1222, 1188, 1169, 1141, 1129, 1091, 1059, 1019, 995, 886, 812, 761, 749, 732, 702, 679, 659, 614 cm⁻¹; HRMS: calcd for C23H17O2NS2, 403.0695 (M⁺); found, 403.0693; Mp: 61-62 °C.

Methyl (S)-3-(4-(benzo[b]thiophene-3-yl)phenyl)-2-(( tert-butoxycarbonyl)amino)propanoate ((S)-3av)

The product (S)-3av was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate (S)-2v (455 mg, 1.12 mmol, 1.5 equiv), previously synthesized enantiomerically pure in 90% yield according to the procedure reported in Org. Lett. 2002, 4, 4171. The product was isolated by automated column chromatography (hexane:AcOEt = 90:10) as a white solid in 82% yield (253 mg, 0.62 mmol).
**Rf** (hexane:AcOEt = 90:10): 0.21; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.90 (m, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.38 (m, 2H), 7.37 (s, 1H), 7.63 (d, J = 7.7 Hz, 2H), 5.10 (m, 0.85H, conformer 1), 4.85 (m, 0.15H, conformer 2), 4.67 (m, 0.85H, conformer 1), 4.48 (m, 0.15H, conformer 2), 3.76 (s, 3H), 3.17 (m, 1.7H, conformer 1), 3.05 (m, 0.3H, conformer 2), 1.46 (s, 9H); ¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 172.4, 155.2, 140.7, 137.9, 137.7, 135.5, 134.8, 129.8, 128.9, 124.5, 124.4, 123.5, 123.0, 122.9, 80.1, 54.5, 52.4, 38.2, 28.4; IR: ν = 3368, 2975, 1742, 1711, 1495, 1435, 1391, 1248, 1248, 1161, 1059, 1092, 760, 733; HRMS: calcd for C₂₃H₂₅O₄N₁S₁ (M+Na⁺) 434.1397; found, 434.1385. Mp: 48-49°C; [α]²⁶D: -0.061 (c = 0.10, CH₃OH).

The enantiomeric excess of compound (S)-3av was determined by HPLC with a Chiralpack IB column, hexane-isopropanol 98:2, 1 mL·min⁻¹, 254-220-210 nm): tᵣ = 17.05 min [ee >99%].

Methyl (R)-3-(4-(benzo[b]thiophene-3-yl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate ((R)-3av)

The product (R)-3av was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and methyl (R)-2-((tert-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate (R)-2v (455 mg, 1.12 mmol, 1.5 equiv), previously synthesized enantiomerically pure in 91% yield according to the procedure reported in Org. Lett. 2002, 4, 4171. The product was isolated by automated column chromatography (hexane:AcOEt = 90:10) as a white solid in 84% yield (259 mg, 0.63 mmol).

For characterization see the enantiomeric compound (S)-3av; [α]²⁶D: +0.060 (c = 0.09, CH₃OH). The enantiomeric excess of compound (R)-3av was determined by HPLC with a Chiralpack IB column, hexane-isopropanol 98:2, 1 mL·min⁻¹, 254-220-210 nm): tᵣ = 19.15 min [ee >99%].
N-(4-(benzo[b]thiophene-3-yl-phenyl)acetamide (3ax)

The product 3ax was obtained via the general procedure A using benzo[b]thiophene 1a (101 mg, 0.75 mmol, 1.0 equiv) and N-(4-iodophenyl)acetamide 2x (294 mg, 1.12 mmol, 1.5 equiv), previously synthesized in 48% yield according to the procedure reported in *J. Am. Chem Soc.* 1996, 47, 11720. The product was isolated by automated column chromatography (hexane:AcOEt = 65:35) as a white solid in 84% yield (169 mg, 0.63 mmol).

**Rf** (hexane:AcOEt = 65:35): 0.26; **1H-NMR** (400 MHz, (CD₃)₂CO): δ (ppm) 9.38 (br, 1H), 8.00 (m, 1H), 7.94 (m, 1H), 7.82 (d, J = 8.53, 2H), 7.60 (s, 1H), 7.56 (d, J = 8.53, 2H), 7.41 (m, 2H), 2.14 (s, 3H); **13C-NMR** (101 MHz, (CD₃)₂CO): δ (ppm) 169.0, 141.5, 139.9, 138.6, 138.3, 131.5, 129.6, 125.3, 125.2, 124.0, 123.8, 123.5, 120.1, 24.3; **IR**: ν = 3296, 3183, 3117, 3063, 1688, 1663, 1603, 1544, 1495, 1454, 1425, 1401, 1371, 1342, 1320, 1293, 1263, 1178, 1060, 1013, 967, 938, 848, 835, 759, 734 cm⁻¹; **HRMS**: calcd for C₁₆H₁₃O₁N₁S₁, 267.0710 (M⁺); found, 267.0712. **Mp**: 132-133°C.

3-methyl-4-(p-tolyl)thiophene (3ba)

The product 3ba was obtained via the general procedure A using 3-methylthiophene 1b (73 μl, 0.75 mmol, 1.0 equiv) and 4-iodotoluene 2a (245 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 77% yield (109 mg, 0.58 mmol).

**Rf** (hexane): 0.57; **1H-NMR** (400 MHz, CDCl₃): δ (ppm) 7.30 (d, J= 8.0 Hz, 2H), 7.22 (d, J= 8.0 Hz, 2H), 7.16 (d, J= 3.3 Hz, 1H), 7.02-7.00 (m, 1H), 2.40 (s, 3H), 2.28 (s, 3H); **13C-NMR** (101 MHz, CDCl₃): δ (ppm) 143.2, 136.7, 136.3, 134.3, 129.1, 128.6, 122.7, 122.0, 21.3, 15.7; **HRMS**: calcd for C₁₂H₁₂S, 189.0660 (M+H⁺); found, 189.0731. Data is in accordance with the literature.⁴
3-bromo-4-(p-tolyl)thiophene (3ca)

The product 3ca was obtained via the general procedure A using 3-bromothiophene 1c (141 μl, 1.5 mmol, 2.0 equiv) and 4-iodotoluene 2a (245 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in yield 48% (91 mg, 0.36 mmol).

Rf (hexane): 0.51; ^1H-NMR (400 MHz, CDCl3): δ (ppm) 7.46 (d, J= 8.1 Hz, 2H), 7.40 (d, J= 3.5 Hz, 1H), 7.31-7.26 (m, 3H), 2.46 (s, 3H); ^13C-NMR (101 MHz, CDCl3): δ (ppm) 142.2, 137.7, 132.5, 129.1, 129.0, 124.1, 123.1, 111.4, 21.4. HRMS: calcd for C_{11}H_{9}BrS, 252.9608 (M+H^+); found, 252.9679. Data is in accordance with the literature.9

3-chloro-4-(p-tolyl)thiophene (3da)

The product 3da was obtained via the general procedure A using 3-chlorothiophene 1d (70 μl, 0.75 mmol, 1.0 equiv) and 4-iodotoluene 2a (246 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 56% yield (87 mg, 0.42 mmol).

Rf (hexane): 0.54; ^1H-NMR (400 MHz, CDCl3): δ (ppm) 7.42 (d, J= 8.0 Hz, 2H), 7.26-7.21 (m, 4H), 2.40 (s, 3H); ^13C-NMR (101 MHz, CDCl3): δ (ppm) 140.5, 137.7, 131.8, 129.2, 128.8, 125.0, 123.0, 121.3, 21.4; HRMS: calcd for C_{11}H_{9}ClS, 209.0113 (M+H^+); found, 209.0185. Data is in accordance with the literature.4

S-23
2-methyl-4-(p-tolyl)thiophene (3ea)

The product 3ea was obtained via the general procedure A using 2-methylthiophene 1e (73 μl, 0.75 mmol, 1.0 equiv) and 4-iodotoluene 2a (245 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in yield 65% (92 mg, 0.49 mmol).

Rf (hexane): 0.41; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.45 (d, J= 8.1 Hz, 2H), 7.18 (d, J= 8.1 Hz, 2H), 7.14 (d, J= 1.4 Hz, 1H), 7.04 (s, 1H), 2.52 (s, 3H), 2.36 (s, 3H); ¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 142.2, 140.4, 136.7, 133.5, 129.5, 126.2, 124.7, 117.5, 21.2, 15.5; HRMS: calcd for C₁₂H₁₂S, 189.0660 (M+H⁺); found, 189.0731. Data is in accordance with the literature.³,⁴

2-bromo-4-(p-tolyl)thiophene (3fa)

The product 3fa was obtained via the general procedure A using 2-bromothiophene 1f (73 μl, 0.75 mmol, 1.0 equiv) and 4-iodotoluene 2a (245 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a white solid in 52% yield (98 mg, 0.39 mmol).

Rf (hexane): 0.64; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.41 (d, J= 8.1 Hz, 2H), 7.32 (d, J= 1.6 Hz, 1H), 7.27 (d, J= 1.6 Hz, 1H), 7.20 (d, J= 8.0 Hz, 2H), 2.38 (s, 3H); ¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 142.9, 137.6, 132.3, 129.7, 129.3, 126.2, 120.9, 112.9, 21.3; HRMS: calcd for C₁₁H₉BrS, 252.9608 (M+H⁺); found, 252.9683; Mp: 97-98 °C. Data is in accordance with the literature.⁴
2-chloro-4-(p-tolyl)thiophene (3ga)

The product 3ga was obtained via the general procedure A using 2-chlorothiophene 1g (72 μl, 0.75 mmol, 1.0 equiv) and 4-iodotoluene 2a (246 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a white solid in 80% yield (125 mg, 0.60 mmol).

Rf (hexane): 0.52; 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.32 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 1.9 Hz, 1H), 7.06 (d, J = 1.8 Hz, 1H), 2.28 (s, 3H); 13C-NMR (101 MHz, CDCl3): δ (ppm) 148.1, 137.6, 132.5, 130.7, 129.7, 126.1, 125.6, 118.0, 21.3; HRMS: calcd for C11H9ClS, 209.0113 (M+H+); found, 209.0186; Mp: 117-118 °C. Data is in accordance with the literature.4

3-bromo-2-chloro-4-(p-tolyl)thiophene (3ha)

The product 3ha was obtained via the general procedure C using 3-bromo-2-chlorothiophene 1h (82 μl, 0.75 mmol, 1.0 equiv) and 4-iodotoluene 2a (246 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a colorless oil in 77% yield (165 mg, 0.57 mmol).

Rf (hexane): 0.52; 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.37 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.08 (s, 1H), 2.41 (s, 3H); 13C-NMR (101 MHz, CDCl3): δ (ppm) 141.8, 138.2, 132.6, 129.1, 128.8, 127.5, 120.1, 112.2, 21.4; IR: ν = 3098, 2919, 1903, 1598, 1495, 1423, 1335, 1305, 1217, 1203, 1183, 1104, 1032, 900, 859, 815, 744, 670 cm⁻¹; HRMS: calcd for C11H8BrClS, 285.9213 (M⁺); found, 285.9208.
3-bromo -4-(p-tolyl)thiophene (3ia)

The product 3ia was obtained via the general procedure A using 2-(thiophen-2-y1)ethan-1-ol 1i (84 μl, 0.75 mmol, 1.0 equiv) and 4-iodotoluene 2a (245 mg, 1.12 mmol, 1.5 equiv) and isolated by column chromatography (hexane:AcOEt = 80:20) as a white solid in yield 65% (106 mg, 0.49 mmol).

Rf (hexane:AcOEt = 80:20): 0.24; \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.46 (d, \(J = 8.0\) Hz, 2H), 7.27-7.13 (m, 4H), 3.89 (br, 2H), 3.09 (t, \(J = 6.1\) Hz, 2H), 2.37 (s, 3H), 1.77 (br, 1H); \(^{13}\text{C-NMR}\) (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 142.3, 141.6, 137.0, 133.2, 129.6, 126.3, 125.2, 118.4, 63.5, 33.7, 21.3; IR: \(\nu = 3330, 2912, 2854, 1515, 1478, 1454, 1373, 1215, 1202, 1122, 1047, 895, 855, 839, 816, 801, 747, 707, 635, 618\) cm\(^{-1}\); HRMS: calcd for C\(_{13}\)H\(_{14}\)OS, 218.0760 (M\(^+\))\(^\dagger\); found, 218.0758; Mp: 75-76 °C.

Trimethyl(4-(p-tolyl)thiophene-2-yl)silane (3ja)

The product 3ja was obtained via the general procedure A using 2-chlorothiophene 1j (126 μl, 0.75 mmol, 1.0 equiv) and 4-iodotoluene 2a (246 mg, 1.12 mmol, 1.5 equiv) and isolated by automated column chromatography (hexane) as a white solid in 46% yield (85 mg, 0.34 mmol).

Rf (hexane): 0.35; \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.63 (d, \(J = 0.9\) Hz, 1H), 7.53-7.47 (m, 3H), 7.20 (d, \(J = 7.8\) Hz, 2H), 2.37 (s, 3H), 0.37 (s, 9H); \(^{13}\text{C-NMR}\) (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 143.9, 141.4, 136.8, 133.3, 133.2, 129.6, 126.6, 125.3, 21.3, 0.1; IR: \(\nu = 2955, 1538, 1501, 1395, 1339, 1248, 1206, 1002, 894, 833, 816, 761, 695, 624\) cm\(^{-1}\); HRMS: calcd for C\(_{14}\)H\(_{18}\)SSi, 246.0893 (M\(^+\))\(^\dagger\); found, 246.0895; Mp: 35-36 °C.
2-(5-(4-methoxyphenyl)benzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3kb)

The product 3kb was obtained via the general procedure E using 2-(benzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 1k (390, 1.5 mmol, 2.0 equiv) and 4-iodoanisole 2b (176 mg, 0.75 mmol, 1.0 equiv) and silver carbonate as additive (104 mg, 0.38 mmol, 0.5 equiv). The product was isolated as a white solid in 50% yield (138 mg, 0.38 mmol) by column chromatography using impregnated silica gel with boric acid and hexane:CHCl₃ = 60:40 as eluent.¹⁰

Rᶠ (hexane:CHCl₃ = 60:40) = 0.33; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.34 (s, 1H), 7.94 (dd, J= 8.1, 0.7 Hz, 1H), 7.92 (dd, J= 8.1, 0.7 Hz, 1H), 7.54 (d, J= 8.8 Hz, 2H), 7.31 (s, 1H), 7.03 (d, J= 8.8 Hz, 2H), 3.90 (s, 3H), 1.28 (s, 12H); ¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 159.3, 143.9, 138.3, 137.8, 130.1, 130.0, 129.9, 128.7, 126.2, 122.4, 114.4, 83.9, 55.5, 25.0; IR: ν = 2978, 2920, 2835, 1596, 1528, 1495, 1441, 1354, 1324, 1244, 1173, 1137, 1085, 1031, 967, 846, 815, 789, 695 cm⁻¹; HRMS: calcd for C₂₁H₂₃BO₃S, 367.1534 (M+H⁺); found, 367.1534; Mp: 183-184 °C.

5-(p-tolyl)benzo[b]thiophene (4)

The product 4 was obtained via the general procedure E using 2-(benzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 1k (390, 1.5 mmol, 2.0 equiv) and 4-iodotoluene 2a (163 mg, 0.75 mmol, 1.0 equiv) and silver oxide as additive (87 mg, 0.38 mmol, 0.5 equiv). The product was isolated by column chromatography (hexane) as a white solid in 77% yield (129 mg, 0.58 mmol).

Rᶠ (hexane) = 0.27; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.10 (d, J= 1.4 Hz, 1H), 7.99 (d, J= 8.4 Hz, 1H), 7.66 (m, 3H), 7.53 (d, J= 5.4, 1H), 7.44 (dd, J= 5.4, 0.6 Hz, 1H), 7.36 (d, J= 8.0, 2H), 2.50 (3H); ¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 140.3, 138.6, 138.5, 137.7, 137.0, 130.0, 127.3, 127.0, 124.2,
124.0, 122.8, 121.8, 21.2; **HRMS**: calcd for C_{15}H_{12}S, 225.0660 (M+H^+); found, 225.0733; **Mp**: 119-120 °C. Data is in accordance with the literature.\textsuperscript{11}

### IV. Mechanistic Studies

#### IV.1 Competition Experiments

**Competition Experiment between 4-iodotoluene 2a and 1-iodo-4-nitrobenzene 2k**

Pd\textsubscript{2}(dba)\textsubscript{3}CH\textsubscript{3} (6.5 mg, 6.25 \(\mu\)mol, 2.5 mol %), silver carbonate (52 mg, 0.19 mmol, 0.75 equiv), 4-iodotoluene 2a (82 mg, 0.38 mmol, 1.50 equiv), 1-iodo-4-nitrobenzene 2k (93 mg, 0.38 mmol, 1.50 equiv) and benzo[b]thiophene 1a (34 mg, 0.25 mmol, 1.0 equiv) were stirred in hexafluoro-2-propanol at 24 °C for 16 h. The resultant mixture was diluted with EtOAc (5 mL) and filtered through a plug of silica. The silica plug was flushed with EtOAc (30 mL) and the filtrate was evaporated to dryness under reduced pressure. Yields were calculated by \textsuperscript{1}H-NMR using an internal standard.

\[
\begin{align*}
\text{1a} & \quad \text{2a} & \quad \text{2k} \\
(1.0 \text{ equiv}) & \quad (1.5 \text{ equiv}) & \quad (1.5 \text{ equiv})
\end{align*}
\]

![Reaction Scheme](attachment:image.png)

**Competition Experiment between 2-methylthiophene 1e and 2-chlorothiophene 1g**

Pd\textsubscript{2}(dba)\textsubscript{3}CH\textsubscript{3} (6.5 mg, 6.25 \(\mu\)mol, 1.7 mol %), silver carbonate (52 mg, 0.19 mmol, 0.5 equiv), 4-iodotoluene 2a (82 mg, 0.38 mmol, 1.0 equiv), 2-methylthiophene 1e (184 \(\mu\)L, 1.9 mmol, 5 equiv) and 2-chlorothiophene 1g (175 \(\mu\)L, 1.9 mmol, 5.0 equiv) were stirred in hexafluoro-2-propanol at 24 °C for 16 h. The resultant mixture was diluted with EtOAc (5 mL) and filtered through a plug of silica. The
silica plug was flushed with EtOAc (30 mL) and the filtrate was evaporated to dryness under reduced pressure. Yields were calculated by $^1$H-NMR using an internal standard.

IV-2. H/D Scrambling Experiments

Pd$_2$(dba)$_3$CHCl$_3$ (6.5 mg, 6.25 µmol, 2.5 mol%), silver carbonate (52 mg, 0.19 mmol, 0.75 equiv), and benzo[b]thiophene 1a-d-3 (34 mg, 0.25 mmol, 1.0 equiv) or benzo[b]thiophene 1a-d-2 (34 mg, 0.25 mmol, 1.0 equiv) with and without 4-iodotoluene 2a (82 mg, 0.38 mmol, 1.50 equiv) were stirred in hexafluoro-2-propanol at 24 °C for 3 h. The resultant mixture was diluted with EtOAc (5 mL) and filtered through a plug of silica. The silica plug was flushed with EtOAc (30 mL) and the filtrate was evaporated to dryness under reduced pressure. H/D scrambling was calculated by $^1$H-NMR in C$_6$D$_6$ using an internal standard.
IV-3. Determination of KIEs

Synthesis of Benzo[b]thiophenes-d for $^2$H KIEs Experiment

Benzo[b]thiophene-3-d (1a-d-3)

Benzothiophene-3-d was synthesized according to the procedure by Glorius et al.\(^2\) \(n\)-BuLi (1.6 M in hexane, 8.8 mL, 15.5 mmol, 1.1 equiv) was added dropwise over 10 minutes with vigorous stirring to 3-bromobenzo[b]thiophene (3.0 g, 14.1 mmol, 1.0 equiv) in Et\(_2\)O (35 mL) at -78 °C. The reaction mixture was quenched with MeOH-\(d_4\) (5 mL) at -78 °C and then allowed to warm to room temperature. D\(_2\)O (10 mL) was added to the reaction mixture prior to removal of organic solvents in vacuo. The aqueous residue was extracted with Et\(_2\)O, the combined organic phases then dried over anhydrous MgSO\(_4\), and concentrated in vacuo. Purification by flash column chromatography (pentane) gave the product as a white solid in 69% yield (1.3 g, 9.6 mmol, 97% deuteration). \(R_f\) (pentane): 0.53; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.91-7.89 (m, 1H), 7.85-7.83 (m, 1H); 7.45 (s, 1H), 7.40-7.34 (d, 2H); \(^2\)H-NMR (77 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.47; \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 139.9, 139.7, 126.3, 124.3, 124.3, 123.8 (t, J = 26 Hz, CD), 123.7, 122.6; \(M_p\): 32-33°C. Data is in accordance with the literature.\(^2\)

Benzo[b]thiophene-2-d (1a-d-2)

Benzothiophene-2-d was synthesized according to the procedure by Glorius et al.\(^1\)\(^2\) \(n\)-BuLi (1.6 M solution in hexane, 23.3 mL, 37.2 mmol, 1.5 equiv) was added dropwise to a solution of benzo[b]thiophene (3.3 g, 24.8 mmol, 1 equiv) in dry THF (67 mL) at -78 °C. The resulting mixture was stirred for 2 h at -78 °C and D\(_2\)O (17 mL) was added. The white suspension was warmed to room temperature and stirred for an additional hour. H\(_2\)O was added (20 mL) and the product was extracted with Et\(_2\)O (3 x 30 mL). The combined organic phases were washed with brine, dried over MgSO\(_4\) and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (eluent: pentane) gave the benzo[b]thiophene-2-d as a white crystalline solid in 84% yield (2.8 g,
20.7 mmol, >99% deuteration). R_{f} (pentane): 0.54; ^1H-NMR (400 MHz, CDCl₃): δ (ppm) 7.82 (m, 1H), 7.76 (m, 1H), 7.34-7.24 (m, 3H); ^2H-NMR (77 MHz, CDCl₃): δ (ppm) 7.55; ^13C-NMR (101 MHz, CDCl₃): δ (ppm) 139.9, 139.8, 126.3 (t, J = 28.3 Hz, CD), 124.4, 124.4, 123.9, 123.8, 122.7; Mp: 32-33°C. Data is in accordance with the literature.¹²

**Synthesis of Standard for \(^2H\) KIEs Experiment**

![Chemical Structure](attachment:image.png)

1-methoxy-3-nitro-4-deuterobenzene was synthesized according to the procedure by Larrosa et al.¹³ A mixture of 4-methoxy-2-nitrobenzoic acid (197 mg, 1 mmol, 1 equiv), silver carbonate (27 mg, 0.1 mmol, 0.1 equiv) and D₂O (1 mL, 50 mmol, 50 equiv) in dry DMSO (5 mL) was stirred for 16 h at 120 °C in a sealed vessel. After this time the reaction was partitioned with Et₂O (15 mL) and saturated aqueous NaHCO₃ (15 mL). The two layers were separated and the aqueous re-extracted with Et₂O (2 x 15 mL). The organic extracts were combined and washed with saturated aqueous NaHCO₃ (2 x 30 mL) and brine (2 x 30 mL). The ethereal layer was dried over anhydrous MgSO₄, filtered and evaporated to dryness under reduced pressure affording a pale yellow solid in 93% yield (144 mg, 0.93 mmol, 95% deuteration). R_{f} (hexane): 0.37; ^1H-NMR (400 MHz, CDCl₃): δ (ppm) 7.77 (m, 0.05 H), 7.67 (d, J = 2.3 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1.04 H), 7.20 (dd, J = 8.2, 2.2 Hz, 1H), 3.86 (s, 3H); ^2H-NMR (77 MHz, CDCl₃): δ (ppm) 7.93; ^13C-NMR (101 MHz, CDCl₃): δ (ppm) 160.1, 149.1, 129.9, 121.3, 115.5 (J = 26.3), 108.1, 55.7. Data is in accordance with the literature.¹³
Formulas for the Determination of KIEs

The formulas applied for the determination of KIEs and their errors were reported by Saunders\textsuperscript{13} and Singleton\textsuperscript{14} and here are summarized:

\( F = \) conversion of starting material

\( R/R_0 = \) proportion of the minor isotopic component (\(^{13}\)C or \(^2\)H) in recovered material compared to the original starting material

\[ \Delta(R/R_0) = R/R_0 \left( (\Delta \text{Int sample}/\text{Int sample})^2 + (\Delta \text{Int standard}/\text{Int standard})^2 \right)^{1/2} \]

\[ \text{KIE} = \frac{\log(1-F)}{\log\left(\frac{1-(1-F)R}{R_0}\right)} \]

\[ \Delta\text{KIE}_F = \frac{\partial \text{KIE}}{\partial F} \Delta F = \frac{-\log(R/R_0)}{(1-F)\log^2(1-F)R/R_0} \Delta F \]

\[ \Delta\text{KIE}_R = \frac{\partial \text{KIE}}{\partial (R/R_0)} \Delta (R/R_0) = \frac{-\log(1-F)}{(R/R_0)\log^2(1-F)R/R_0} \Delta (R/R_0) \]

\[ \Delta\text{KIE} = \text{KIE} \left( (\Delta\text{KIE}_R/\text{KIE})^2 + (\Delta\text{KIE}_F/\text{KIE})^2 \right)^{1/2} \]

IV-3.1. Determination of \(^{13}\)C KIEs via Competition Experiment at Natural Abundance\textsuperscript{14,15}

Experimental Procedure for Large Scale Reactions

Pd\(_2\)(dba\(_3\))CHCl\(_3\) (129 mg, 0.125 mol, 2.5 mol %), silver carbonate (1.034 g, 3.75 mmol, 0.75 equiv), 4-iodotoluene (1.635 g, 7.5 mmol, 1.5 equiv) and benzo[b]thiophene (671 mg, 5 mmol, 1 equiv) were stirred in 5 mL of hexafluoro-2-propanol at 24 °C for 8 h. The resultant mixture was diluted with EtOAc and filtered through a plug of silica. The silica plug was flushed with EtOAc and the filtrate was evaporated to dryness under reduced pressure. The crude mixture was transferred to a 5 mL conical flask. Six aliquots were then taken from the reaction mixture and analyzed by \(^1\)H-NMR in order to determine the conversion. In order to ensure the complete relaxation of atoms, the \(^1\)H spectra were recorded at 500 MHz using 40 s delays between calibrated \(\pi/2\) pulses, 6.5 s acquisition time and 16
scans obtaining a conversion of 72.4 ± 3.1% for the first sample and of 70.8 ± 0.4% for the second sample. The remaining crude was purified by flash column chromatography using hexane as eluent, affording ~70 mg of recovered benzo[b]thiophene.

**Quantitative $^{13}$C NMR**

All NMR samples were prepared using benzo[b]thiophene (50 mg) in 0.5 mL of CDCl$_3$. The $^{13}$C spectra were recorded at 125.81 MHz using inverse gated decoupling, 51 s delays between calibrated $\pi$/2 pulses, 1.4 s acquisition time and 64 scans collecting 32768 complex points. Six spectra were recorded for each sample. A zero order baseline correction was generally applied, but in no case a first or higher correction was tested. Integrations were numerically determined using a constant region for each peak corresponding to a multiple of the peak widths at half height (± 5w$_{1/2}$) and referred to C7 of benzo[b]thiophene, which was set with an integration of 1000.
Determination of $^{13}$C KIEs via Competition Experiment at Natural Abundance (1st sample)

Table S.10: Conversion of benzo[b]thiophene (%)

| fid1 | fid2 | fid3 | fid4 | fid5 | fid6 | average (F) | stddev (ΔF) |
|------|------|------|------|------|------|-------------|-------------|
| 76.7 | 73.1 | 73.6 | 69.4 | 73.3 | 68.3 | 72.4        | 3.1         |

Table S.11: $^{13}$C-NMR integrations of benzo[b]thiophene starting material

| ppm peaks | fid1 | fid2 | fid3 | fid4 | fid5 | fid6 | average | stddev |
|-----------|------|------|------|------|------|------|---------|--------|
| 126.4 = C2 | 988.7 | 991.1 | 993.8 | 994.4 | 996.3 | 997.6 | 993.65 | 3.292871 |
| 123.9 = C3 | 1002.3 | 1002.1 | 1002.4 | 1000.3 | 1003 | 998.5 | 1001.433 | 1.701372 |
| 123.7 = C4 | 996.9 | 987.3 | 990.8 | 997.4 | 999.2 | 994.0 | 994.2667 | 4.510285 |
| 122.6 = C7 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 0 |

Table S.12: $^{13}$C-NMR integrations of recovered benzo[b]thiophene from 72.4 ± 3.1% conversion reaction

| ppm peaks | fid1 | fid2 | fid3 | fid4 | fid5 | fid6 | average | stddev |
|-----------|------|------|------|------|------|------|---------|--------|
| 126.4 = C2 | 1016.1 | 1007 | 1021.4 | 1017.6 | 1002.3 | 1013.7 | 1013.017 | 7.103638 |
| 123.9 = C3 | 1054.2 | 1052.1 | 1061.7 | 1059.9 | 1048.5 | 1052.8 | 1054.867 | 4.998666 |
| 123.7 = C4 | 994.9 | 987.7 | 997.9 | 997.6 | 986.6 | 992.9 | 992.9333 | 4.854139 |
| 122.6 = C7 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 0 |

Table S.13: Determination $^{13}$C KIEs

| ppm peaks | R/R₀ | Δ(R/R₀) | KIE | ΔKIE | ΔKIEᵣ | ΔKIEᵣ | ΔKIEᵣastics |
|-----------|------|---------|-----|------|--------|--------|--------------|
| 126.4 = C2 | 1.01949 | 0.0079071 | 1.015222 | 0.006351 | -0.00133 | 0.006210 |
| 123.9 = C3 | 1.053357 | 0.0053026 | 1.042078 | 0.005689 | -0.00379 | 0.004246 |
| 123.7 = C4 | 0.998659 | 0.0066602 | 0.998958 | 0.00517 | 8.98E-05 | 0.005170 |
| 122.6 = C7 | 1 | 0 | 1 | 0 | 0 | 0 |
Determination of $^{13}$C KIEs via Competition Experiment at Natural Abundance (2$^{nd}$ sample)

Table S.14: Conversion of benzo[b]thiophene (%)

| fid1 | fid2 | fid3 | fid4 | fid5 | fid6 | average (F) | stddev (ΔF) |
|------|------|------|------|------|------|-------------|-------------|
| 71.5 | 70.9 | 70.7 | 70.1 | 70.8 | 70.7 | 70.8        | 0.4         |

Table S.15: $^{13}$C-NMR integrations of benzo[b]thiophene starting material

| ppm peaks | fid1 | fid2 | fid3 | fid4 | fid5 | fid6 | average | stddev |
|-----------|------|------|------|------|------|------|---------|--------|
| 126.4 = C2 | 988.7 | 991.1 | 993.8 | 994.4 | 996.3 | 997.6 | 993.65 | 3.292871 |
| 123.9 = C3 | 1002.3 | 1002.1 | 1002.4 | 1000.3 | 1003 | 998.5 | 1001.433 | 1.701372 |
| 123.7 = C4 | 996.9 | 987.3 | 990.8 | 997.4 | 999.2 | 994.0 | 994.2667 | 4.510285 |
| 122.6 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 0 |

Table S.16: $^{13}$C-NMR integrations of recovered benzo[b]thiophene from 70.8 ± 0.4% conversion reaction

| ppm peaks | fid1 | fid2 | fid3 | fid4 | fid5 | fid6 | average | stddev |
|-----------|------|------|------|------|------|------|---------|--------|
| 126.4 = C2 | 1001.6 | 1006.7 | 1011.1 | 1011.4 | 1016.9 | 1015.1 | 1010.467 | 5.60238 |
| 123.9 = C3 | 1056.1 | 1054.8 | 1048.7 | 1047.9 | 1062.6 | 1055.4 | 1054.25 | 5.401759 |
| 123.7 = C4 | 996.4 | 1005.4 | 984.8 | 993.2 | 1002.4 | 995.3 | 996.25 | 7.250862 |
| 122.6 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 0 |

Table S.17: Determination $^{13}$C KIEs

| ppm peaks | R/R$_0$ | Δ(R/R$_0$) | KIE | ΔKIE | ΔKIE$_F$ | ΔKIE$_R$ |
|-----------|---------|---------|-----|------|----------|----------|
| 126.4 = C2 | 1.016924 | 0.0065686 | 1.013828 | 0.005399 | -0.00018 | 0.005396 |
| 123.9 = C3 | 1.052741 | 0.0056828 | 1.043593 | 0.004812 | -0.00057 | 0.004778 |
| 123.7 = C4 | 1.001995 | 0.0085932 | 1.001622 | 0.006993 | -2E-05 | 0.006993 |
| 122.6 | 1 | 0 | 1 | 0 | 0 | 0.000000 |
IV-3.2. Determination of $^2$H KIEs via Competition Experiment in Enriched Substrates$^{14,15}$

**Experimental Procedure for Large Scale Reactions**

In order to measure the $^2$H KIEs using the same analytic technique, we partially deuterated the benzothiophene starting material at C-2 and C-3 (ca 1% each). The same procedure described for the $^{13}$C KIEs determination was applied in the following reactions, in this case in the presence of an internal standard (1-methoxy-3-nitro-4-deuterobenzene). A conversion of 66.7 ± 0.7% was obtained for the first sample and 68.2 ± 0.6% for the second sample.

**Quantitative $^2$H NMR**

All NMR samples were prepared using benzo[b]thiophene (60 mg) in 0.25 mL of CHCl$_3$. 150 µl of a solution of 456 mg of 1-methoxy-3-nitro-4-deuterobenzene in 10 mL of CHCl$_3$ were then added to each sample as external standard for the integration. The $^2$H($^{13}$C) spectra were recorded at 77 MHz using inverse gated decoupling, 6.2 s delays between calibrated $\pi/2$ pulses, 2.7 s acquisition time and 256 scans collecting 8192 complex points. Each spectrum was obtained by taking the sum of five subspectra; six spectra were recorded for each sample. A zero order baseline correction was generally applied, but in no case a first or higher correction was tested. Integrations were numerically determined using by fitting the data to a Lorenztian function using the line shape fitting tool of Bruker’s Topspin v.3.2 software.
**Determination of $^2\text{H}$ KIEs via Competition Experiment in Enriched Substrate (1st sample)**

\[
\begin{array}{ccc}
5 & 4 & 3 \\
\text{S} & - & \text{37} \\
\end{array}
\]

*Table S.18:* Conversion of benzo[b]thiophene (%)

| fid1 | fid2 | fid3 | fid4 | fid5 | fid6 | average (F) | stddev (ΔF) |
|------|------|------|------|------|------|-------------|--------------|
| 67.1 | 66.7 | 66.1 | 67.3 | 65.7 | 67.5 | 66.7        | 0.7          |

*Table S.19:* $^2\text{H}$-NMR integrations of benzo[b]thiophene starting material

| ppm peaks | fid1     | fid2     | fid3     | fid4     | fid5     | fid6     | average | stddev |
|-----------|----------|----------|----------|----------|----------|----------|---------|--------|
| 7.55 = D-2| 1108.404 | 1093.657 | 1084.546 | 1107.548 | 1121.458 | 1102.198 | 1102.969 | 12.79867 |
| 7.47 = D-3| 1160.268 | 1156.808 | 1152.354 | 1135.146 | 1139.702 | 1150.299 | 1149.096 | 9.78962  |
| 7.93 = Standard | 1000     | 1000     | 1000     | 1000     | 1000     | 1000     | 1000    | 0      |

*Table S.20:* $^2\text{H}$-NMR integrations of recovered benzo[b]thiophene from 66.7 ± 0.7% conversion reaction

| ppm peaks | fid1     | fid2     | fid3     | fid4     | fid5     | fid6     | average | stddev |
|-----------|----------|----------|----------|----------|----------|----------|---------|--------|
| 7.55 = D-2| 1122.183 | 1129.096 | 1118.575 | 1110.191 | 1132.582 | 1121.465 | 1122.349 | 7.913178 |
| 7.47 = D-3| 978.5681 | 987.5299 | 968.7239 | 974.3194 | 965.7251 | 956.453  | 971.8865 | 10.78365 |
| 7.93 = Standard | 1000     | 1000     | 1000     | 1000     | 1000     | 1000     | 1000    | 0      |

*Table S.21:* Determination $^2\text{H}$ KIEs

| ppm peaks | R/R₀ | Δ(R/R₀) | KIE   | ΔKIEF  | ΔKIER  |
|-----------|------|---------|-------|--------|-------|
| 7.55 = D-2| 1.017571 | 0.013816 | 1.01608 | -0.00032 | 0.012737 |
| 7.47 = D-3| 0.845784 | 0.011832 | 0.86792 | 0.009828 | 0.00222 | 0.009574 |
| 7.93 = Standard | 1 | 0 | 1 | 0 | 0 | 0.000000 |
Determination of $^2$H KIEs via Competition Experiment in Enriched Substrate (2nd sample)

Table S.22: Conversion of benzo[b]thiophene (%)

| fid1 | fid2 | fid3 | fid4 | fid5 | fid6 | average (F) | stddev (ΔF) |
|------|------|------|------|------|------|-------------|-------------|
| 67.3 | 67.9 | 69.1 | 68.7 | 67.8 | 68.2 | 68.2        | 0.6         |

Table S.23: $^2$H-NMR integrations of benzo[b]thiophene starting material

| ppm peaks | fid1     | fid2     | fid3     | fid4     | fid5     | fid6     | average | stddev |
|-----------|----------|----------|----------|----------|----------|----------|---------|--------|
| 7.55 = D-2| 1108.404 | 1093.657 | 1084.546 | 1107.548 | 1121.458 | 1102.198 | 1102.969 | 12.79867 |
| 7.47 = D-3| 1160.268 | 1156.808 | 1152.354 | 1135.146 | 1139.702 | 1150.299 | 1149.096 | 9.78962  |
| 7.93 = Standard | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 0       |

Table S.24: $^2$H-NMR integrations of recovered benzo[b]thiophene from 68.2 ± 0.6% conversion reaction

| ppm peaks | fid1     | fid2     | fid3     | fid4     | fid5     | fid6     | average | stddev |
|-----------|----------|----------|----------|----------|----------|----------|---------|--------|
| 7.55 = D-2| 1110.513 | 1118.182 | 1107.938 | 1112.704 | 1094.404 | 1102.479 | 1107.703 | 8.329566 |
| 7.47 = D-3| 987.4436 | 985.3003 | 985.1250 | 985.3551 | 979.6736 | 988.1606 | 985.1764 | 2.979146 |
| 7.93 = Standard | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 0       |

Table S.25: Determination $^2$H KIEs

| ppm peaks | $R/R_0$ | $\Delta(R/R_0)$ | KIE | $\Delta$KIE | $\Delta$KIE$_F$ | $\Delta$KIE$_R$ |
|-----------|---------|-----------------|-----|-------------|-----------------|-----------------|
| 7.55 = D-2| 1.004293| 0.013887        | 1.003756 | 0.012171 | -0.00007        | 0.012171        |
| 7.47 = D-3| 0.857349| 0.007751        | 0.881477 | 0.006413 | 0.00186         | 0.006137        |
| 7.93 = S. | 1       | 0               | 1   | 0           | 0               | 0.000000        |
V. Computational Studies

Computational details

Density functional theory calculations were performed using Gaussian 09,\textsuperscript{16} with spin-restricted method. All optimisations and single point calculations were performed using the B3LYP functional\textsuperscript{17} with the LanL2DZ basis set for Pd and 6-31G(d) for all other atoms (C, H, S, F and O). In optimisations, frequency calculations were used to determine the nature (minimum or transition state of all stationary points) and intrinsic reaction coordinate (IRC)\textsuperscript{18} calculations were used to characterise the transition states. Gibbs free energies were evaluated at 298 K and 1 atm.

Olefin insertion

The olefin insertion was modeled starting from benzo[\textit{b}]thiophene and a proposed Pd[Ph(OCH(CF\textsubscript{3})\textsubscript{2})(HOCH(CF\textsubscript{3})\textsubscript{2})] complex. IRC calculations in the gas phase from the determined transition state showed that a C2,C3-olefin π-complex can be initially formed, followed by the insertion step. The resulting overall energy diagram is shown below:

\begin{center}
Scheme 1. Energies measured in kcal/mol for DFT modelling in the gas phase
\end{center}
Coordinates and energies of computed structures

**Benzo[b]thiophene** (minimum)

No imaginary frequencies

E = $-706.653622$ a.u.

G = $-706.570263$ a.u.

Solvent correction (TFE) = $-0.003895$ a.u.

Solvent correction (tBuOH) = $-0.003731$ a.u.

| Atom | X  | Y  | Z  | 
|------|----|----|----|
| C    | 0.06164800 | -0.55437800 | 0.00003700 |
| C    | -0.11140200 | 0.85287100 | -0.00005700 |
| C    | -1.41878900 | 1.37367400 | 0.00002600 |
| C    | -2.50326000 | 0.50751200 | 0.00019600 |
| C    | -2.31065200 | -0.88614300 | 0.00028700 |
| C    | -1.03005300 | -1.42835600 | 0.00020900 |
| C    | 2.21858200 | 0.71276500 | -0.00026400 |
| C    | 1.15000300 | 1.54993100 | -0.00023100 |
| H    | -1.57163700 | 2.44993100 | -0.00004500 |
| H    | -3.51314300 | 0.90821300 | 0.00026000 |
| H    | -3.17188200 | -1.54850500 | 0.00042100 |
| H    | -0.88302500 | -2.50462000 | 0.00028000 |
| H    | 3.26750300 | 0.97943600 | -0.00038200 |
| H    | 1.23604300 | 2.63147100 | -0.00032400 |
| S    | 1.76873000 | -0.98019900 | -0.00008900 |

**Pd[Ph(OCH(CF$_3$)$_2$)(HOCH(CF$_3$)$_2$)] complex** (minimum)

No imaginary frequencies

E = $-1937.341786$ a.u.

G = $-1937.200357$ a.u.

Solvent correction (TFE) = $-0.019754$ a.u.

Solvent correction (tBuOH) = $-0.018810$ a.u.
| Atom | X         | Y         | Z         |
|------|-----------|-----------|-----------|
| Pd   | -0.6937300| -1.1360980| -0.5988830|
| C    | -2.5549320| -1.3985990| -0.1162640|
| C    | -2.8355850| -2.4163040|  0.8015110|
| C    | -3.5790260| -0.7148000| -0.7784490|
| C    | -4.1663640| -2.8024890|  1.0012580|
| H    | -2.0385370| -2.9016200|  1.3596760|
| C    | -4.9041250| -1.1100160| -0.5654220|
| H    | -3.3527490|  0.1041960| -1.4549600|
| C    | -5.1963210| -2.1514160|  0.3191790|
| H    | -4.3930830| -3.5991620|  1.7050050|
| H    | -5.7062770| -0.5979630| -1.0906770|
| H    | -6.2285470| -2.4453360|  0.4883690|
| O    | -0.2934880|  0.5985050|  0.4060550|
| C    | -1.0726130|  1.7363410|  0.3390970|
| H    | -2.1447410|  1.5435960|  0.4847320|
| C    | -0.9335650|  2.4297560| -1.0281430|
| C    | -0.6399170|  2.6539820|  1.5001350|
| F    | -1.6204700|  3.5838800| -1.0969300|
| F    | -1.4215440|  1.6162140| -2.0024540|
| F    |  0.3514300|  2.6843920| -1.3316840|
| F    | -1.3759170|  3.7841060|  1.5388680|
| F    |  0.6546420|  3.0053620|  1.4014160|
| F    | -0.8111780|  2.0149890|  2.6693410|
| O    |  1.5487600| -0.4597780| -1.0246060|
| C    |  2.7585970| -1.0537120| -0.6232900|
| H    |  3.0826470| -1.7236230| -1.4239430|
| C    |  3.8348170|  0.0317430| -0.4609070|
| C    |  2.5705800| -1.9166940|  0.6356750|
Benzo[\textit{b}]thiophene-Pd intermediate complex (minimum)

No imaginary frequencies

\[ E = -2644.026708 \text{ a.u.} \]
\[ G = -2643.778477 \text{ a.u.} \]

Solvent correction (TFE) = −0.013665 a.u.

Solvent correction (tBuOH) = −0.013072 a.u.

C                  -1.02171600  -2.81718200  -0.15855400
C                  -0.48805200  -2.79543600  1.13821200
C                  -2.40716100  -2.37584500  -0.18596500
S                  -1.66567200  -2.29606400  2.34953700
H                  0.38886600  -3.33633500  1.47038800
C                  -2.88855200  -2.04508500  1.10375100
H                  -0.56176000  -3.36501900  -0.97339000
C                  -3.26454000  -2.25007400  -1.29155100
C                  -4.56643100  -1.80200200  -1.09956200
H                  -5.23451300  -1.70524500  -1.95006900
C                  -5.02535000  -1.46504200  0.18648400
H                  -6.04486800  -1.11412800  0.31823400
C                  -4.19184200  -1.57659900  1.29749200
H                  -4.54958600  -1.31463800  2.28856800
H                  -2.90489000  -2.49602900  -2.28653300
Pd                  0.35811400  -1.02856800  0.03760800
**Olefin insertion transition state** (maximum)

One imaginary frequency: \(i337.82\) cm\(^{-1}\)

\[
E = -2643.989676 \text{ a.u.}
\]

\[
G = -2643.742683 \text{ a.u.}
\]

Solvent correction (TFE) = \(-0.016534\) a.u.

Solvent correction (\(t\)BuOH) = \(-0.015835\) a.u.

\[
\begin{align*}
\text{C} & & -2.97118100 & & 0.21142100 & & -1.34754500 \\
\text{C} & & -2.04456100 & & -0.85481700 & & -1.66108200 \\
\text{C} & & -4.06080500 & & -0.25471600 & & -0.48958800 \\
\text{S} & & -2.53763700 & & -2.38796300 & & -0.87465900 \\
\text{H} & & -1.64463900 & & -0.96139600 & & -2.66966600 \\
\text{C} & & -3.93270800 & & -1.61239300 & & -0.12737000 \\
\text{H} & & -3.17477500 & & 0.96073900 & & -2.10383000 \\
\text{C} & & -5.15625000 & & 0.48465300 & & -0.01795400 \\
\text{C} & & -6.09555200 & & -0.12928200 & & 0.80154200 \\
\text{H} & & -6.94896200 & & 0.43569900 & & 1.16421300 \\
\text{C} & & -5.94344900 & & -1.47656200 & & 1.17198600 \\
\text{H} & & -6.68103200 & & -1.94221500 & & 1.81948900 \\
\text{C} & & -4.86289600 & & -2.22724300 & & 0.71841600 \\
\text{H} & & -4.75170100 & & -3.26871700 & & 1.00413100 \\
\text{H} & & -5.25644100 & & 1.53268100 & & -0.28601100 \\
Pd & & -0.51344600 & & 0.04664700 & & -0.61729800 \\
\text{C} & & -1.87288800 & & 1.58101100 & & -0.24685200 \\
\text{O} & & 1.23608800 & & 0.79426700 & & 0.38026500 \\
\text{O} & & 1.33976700 & & -1.33161800 & & -0.80251900 \\
\text{C} & & -2.22948300 & & 1.66612200 & & 1.11045700 \\
\text{C} & & -1.66638700 & & 2.76024300 & & -0.98596800 
\end{align*}
\]
C  1.79178700  2.04095000  0.25765100
C  1.61315000 -2.57048400 -0.20699600
H  1.72220600 -0.52814400 -0.27628600
C  -2.31213700  2.91143900  1.73228800
H  -2.43347500  0.76289200  1.67804600
C  -1.76152900  4.00362300 -0.35912100
H  -1.41958900  2.70739500 -2.04258100
H  1.07342300  2.85491600  0.45056800
C  2.32967800  2.28769600 -1.16488300
C  2.89943500  2.19769400  1.31631500
H  0.95517300 -3.32247100 -0.65225300
C  3.05908500 -2.97331800 -0.54609000
C  1.33379300 -2.57915500  1.30652900
C  -2.08051900  4.08077300  0.99992900
H  -2.56228800  2.96968400  2.78812200
H  -1.58995500  4.91037300 -0.93310200
F  2.85788700  3.51873000 -1.31854900
F  1.31530900  2.18090200 -2.06406800
F  3.26474700  1.38652200 -1.51823600
F  3.48546900  3.41595600  1.26282700
F  3.86644300  1.27299600  1.17295100
F  2.37458400  2.05959700  2.54825900
F  3.18401100 -3.11634900 -1.87716100
F  3.39328500 -4.14508600  0.02828200
F  3.93272900 -2.03903000 -0.14056100
F  0.07712400 -2.14637300  1.54408800
F  2.18092500 -1.79080400  1.98188600
F  1.43031600 -3.82890400  1.79943100
H  -2.15904600  5.04967500  1.48512400
Product of olefin insertion (minimum)

No imaginary frequencies

\[ E = -2644.021764 \text{ a.u.} \]

\[ G = -2643.772745 \text{ a.u.} \]

Solvent correction (TFE) = −0.016088 a.u.

Solvent correction (tBuOH) = −0.015434 a.u.

\[
\begin{align*}
C & \quad 3.16992400 \quad -0.75361500 \quad -1.16024100 \\
C & \quad 2.12709900 \quad 0.34402600 \quad -1.42599700 \\
C & \quad 4.27164500 \quad -0.15914900 \quad -0.30674700 \\
S & \quad 2.72773600 \quad 1.94303700 \quad -0.86030200 \\
H & \quad 1.75460600 \quad 0.39933100 \quad -2.45269700 \\
C & \quad 4.14368200 \quad 1.21672800 \quad -0.06664900 \\
H & \quad 3.57874000 \quad -1.14899700 \quad -2.09980800 \\
C & \quad 5.35564300 \quad -0.84932700 \quad 0.23620800 \\
C & \quad 6.30025400 \quad -0.16703900 \quad 1.00729400 \\
H & \quad 7.14489100 \quad -0.70495900 \quad 1.42755300 \\
C & \quad 6.15808900 \quad 1.20420400 \quad 1.24116500 \\
H & \quad 6.89258200 \quad 1.73038900 \quad 1.84432600 \\
C & \quad 5.07617600 \quad 1.90829200 \quad 0.70882700 \\
H & \quad 4.96446900 \quad 2.97243600 \quad 0.89371400 \\
H & \quad 5.46134100 \quad -1.91733600 \quad 0.06118600 \\
Pd & \quad 0.52029800 \quad -0.31731100 \quad -0.38441500 \\
C & \quad 2.34475400 \quad -1.85722300 \quad -0.47046900 \\
O & \quad -1.42450600 \quad -0.70916900 \quad 0.55881900 \\
O & \quad -1.09630300 \quad 1.24917100 \quad -0.81253600 \\
C & \quad 1.97901700 \quad -1.71979900 \quad 0.89503800 \\
C & \quad 1.96552500 \quad -3.03356600 \quad -1.15985000 \\
C & \quad -2.22437200 \quad -1.81423300 \quad 0.44389000 \\
C & \quad -1.16187900 \quad 2.56511200 \quad -0.33453000 \\
H & \quad -1.61642700 \quad 0.55133800 \quad -0.22583900 
\end{align*}
\]
C  1.26554300 -2.75090000  1.54142900
H  2.37956800 -0.89756100  1.48182800
C  1.27797100 -4.04438300 -0.50539700
H  2.23960100 -3.14595300 -2.20571000
H  -1.74103000 -2.73528000  0.81347200
C  -2.59387400 -2.10768000 -1.02258200
C  -3.47749400 -1.61900100  1.31758800
H  -0.30952800  3.12710900 -0.72879400
C  -2.43717200  3.22363800 -0.88922300
C  -1.07168600  2.64809100  1.19993200
C  0.92605700 -3.90443500  0.84943900
H  0.99900600 -2.63485200  2.58730300
H  1.01153100 -4.94984500 -1.04273200
F  -3.32757500 -3.23013000 -1.16239800
F  -1.45848700 -2.28606100 -1.74864400
F  -3.27146200 -1.09320700 -1.59062100
F  -4.31786900 -2.67673400  1.24792400
F  -4.16908400 -0.52163600  0.96155700
F  -3.11449500 -1.47986400  2.60700200
F  -2.37789100  3.25338500 -2.23233200
F  -2.56468600  4.49224200 -0.45308300
F  -3.53629100  2.54214200 -0.53273300
F  0.02447600  1.98966300  1.63383700
F  -2.14327400  2.11126600  1.80031000
F  -0.95825500  3.92883300  1.59968400
H  0.39424100 -4.70564200  1.35461200
Computed values of $^{13}$C and $^2$H KIEs for a Heck-type pathway

$^{13}$C and $^2$H KIEs related to the insertion of Pd[Ph(OCH(CF$_3$)$_2$)(HOCH(CF$_3$)$_2$)] complex into the double bond of benzo[b]thiophene were determined using ISOEFF.$^{19}$

![Diagram of benzo[b]thiophene]

| Position of benzothiophene | Computed $^{13}$C KIEs | Computed $^2$H KIEs | Experimental $^{13}$C KIEs | Experimental $^2$H KIEs |
|----------------------------|------------------------|----------------------|-----------------------------|-------------------------|
| 2                          | 1.014                  | 1.00                 | $1.015 \pm 0.006$           | $1.02 \pm 0.01$         |
|                            |                        |                      | $1.014 \pm 0.005$           | $1.00 \pm 0.01$         |
| 3                          | 1.032                  | 0.88                 | $1.042 \pm 0.006$           | $0.87 \pm 0.01$         |
|                            |                        |                      | $1.044 \pm 0.005$           | $0.88 \pm 0.01$         |
| 4                          | 1.000                  | not determined       | $0.999 \pm 0.005$           | not determined          |
|                            |                        |                      | $1.002 \pm 0.007$           |                         |

*Table S.26:* Computed and experimental values of $^{13}$C KIEs and $^2$H KIEs
**C-H activation via concerted metalation deprotonation process**

The C-H activation via CMD process was modeled starting from benzo[b]thiophene and a proposed Pd[Ph(OCO₂H)(HOCH(CF₃)₂)] complex. The resulting overall energy diagram is shown below:

![Energy Diagram](image)

**Scheme 2.** Energies measured in kcal/mol for DFT modelling in the gas phase

**Coordinates and energies of computed structures**

**Pd[Ph(OCO₂H)(HOCH(CF₃)₂)] complex (minimum)**

No imaginary frequencies

E = −1412.573640 a.u.

G = −1412.444273 a.u.

Solvent correction (TFE) = −0.016930 a.u.

Solvent correction (tBuOH) = −0.017642 a.u.

| Atom | X      | Y      | Z      |
|------|--------|--------|--------|
| Pd   | 1.27902900 | -0.34216500 | -0.35082900 |
| C    | 3.30058700  | -1.80318600  | -0.21509000  |
O                  3.31158600   -0.54417800    0.02224400
O                  2.25416900   -2.42205500   -0.54776100
C                  1.11931200    1.59951500   -0.02354500
C                  0.18981900    2.38098000   -0.72028900
C                  1.96712400    2.18796400    0.92032400
C                  0.09355600    3.75217300   -0.44790800
H                  -0.45287000    1.94249400   -1.47901600
C                  1.85942700    3.55644700    1.18821700
H                  2.71424700    1.58826000    1.43177200
C                  0.92289400    4.33924400    0.50806400
H                  -0.62598300    4.35731900   -0.99454600
H                  2.51548200    4.01044300    1.92699900
H                  0.84684500    5.40313200    0.71630000
O                  4.47326900   -2.44225300   -0.09011600
H                  4.29771700    -3.37628700   -0.30064300
O                  -0.87814600   -0.54669000   -0.80204400
C                  -1.91073700   -0.15530600    0.09673900
H                  -1.61145000    0.80487900    0.51895100
C                  -3.20001800    0.04323400   -0.71467100
C                  -2.03585400   -1.18957000    1.22551500
H                  -1.06009500   -1.44971700   -1.12272800
F                  -2.21774800   -2.42173000    0.69999000
F                  -0.90996700   -1.21347200    1.95272300
F                  -3.06295500   -0.91377100    2.03706600
F                  -4.21642600    0.42863400    0.06609500
F                  -3.54370400   -1.10269500   -1.33881000
F                  -3.00285600    0.98209200   -1.65280500

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Benzo[b]thiophene-Pd intermediate complex (minimum)

No imaginary frequencies
E = $-2119.229531$ a.u.
G = $-2118.997804$ a.u.
Solvent correction (TFE) = $-0.018514$ a.u.
Solvent correction ($t$BuOH) = $-0.017765$ a.u.

| Atom | X     | Y     | Z     |
|------|-------|-------|-------|
| Pd   | -0.34720900 | 0.42255700 | 0.12821800 |
| C    | -0.29553700  | -3.76439700  | 0.70930100 |
| C    | -0.21215300  | -2.37892000  | 0.89447700 |
| C    | -0.73280100  | -1.51467700  | -0.07636400 |
| C    | -1.34011900  | -2.03101800  | -1.22276600 |
| C    | -1.41869400  | -3.41783500  | -1.40010800 |
| C    | -0.89943000  | -4.28477600  | -0.43686700 |
| O    | 0.67765100   | 2.36700100   | 0.27888700 |
| O    | -0.88286800  | 3.76620400   | -0.60109600 |
| H    | 0.25878500   | -1.98707400  | 1.79250200 |
| H    | -1.88738200  | -3.81586000  | -2.29685300 |
| H    | -0.96550100  | -5.36022000  | -0.57824300 |
| H    | 0.10704800   | -4.43186600  | 1.46753900 |
| H    | -1.75413200  | -1.37068000  | -1.97950600 |
| H    | -2.13446900  | 2.19896600   | -0.41597600 |
| O    | 1.78184200   | 0.29304400   | -0.63471800 |
| C    | 2.86207000   | -0.46801300  | -0.14630100 |
| H    | 2.54560500   | -1.51350000  | -0.11816400 |
| C    | 3.23609800   | -0.05163900  | 1.28403300 |
| C    | 4.03080900   | -0.34922000  | -1.13875000 |
| F    | 4.21224200   | -0.82437400  | 1.78020100 |
| F    | 3.63970100   | 1.23153500   | 1.32826100 |
| F    | 2.16022600   | -0.17147200  | 2.09095400 |
| F    | 3.65921200   | -0.84008500  | -2.32982600 |
**CMD transition state** (maximum)

One imaginary frequency: \( i1072.64 \) cm\(^{-1} \)

\[ E = -2119.203362 \text{ a.u.} \]

\[ G = -2118.975151 \text{ a.u.} \]

Solvent correction (TFE) = -0.014838 a.u.

Solvent correction (tBuOH) = -0.014201 a.u.

Pd  -0.14393300  -0.35384400  0.04199000
C   0.21328600  3.70542000  -1.14461600
C   0.23165600  2.30495200  -1.12546900

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| Element | X      | Y      | Z      |
|---------|--------|--------|--------|
| C       | -0.44575700 | 1.60117300 | -0.11737700 |
| C       | -1.17389200 | 2.31457700 | 0.84358100 |
| C       | -1.18656500 | 3.71352800 | 0.82088600 |
| C       | -0.49397800 | 4.41205600 | -0.17068500 |
| O       | 0.52270100  | -2.46531100 | 0.30292300 |
| O       | -1.40991600 | -3.22086800 | -0.59777100 |
| H       | 0.77939400  | 1.77023300 | -1.89758400 |
| H       | -1.74515200 | 4.25659600 | 1.57986100 |
| H       | -0.51236600 | 5.49862000 | -0.18877100 |
| H       | 0.74458500  | 4.23946600 | -1.92945300 |
| H       | -1.73237900 | 1.78707700 | 1.61149100 |
| H       | -1.71719300 | -1.95492000 | -0.60981800 |
| O       | 2.01947400  | -0.27239900 | 0.77871300 |
| C       | 3.09772700  | 0.43127800 | 0.19921600 |
| H       | 2.74652000  | 1.44517900 | -0.00549000 |
| C       | 3.50734800  | -0.21809100 | -1.13079900 |
| C       | 4.24525600  | 0.51144500 | 1.21866000 |
| F       | 4.56792600  | 0.38806400 | -1.67875800 |
| F       | 3.80499400  | -1.52136300 | -0.94397000 |
| F       | 2.48778800  | -0.15610400 | -2.00873300 |
| F       | 3.81353300  | 1.10816900 | 2.33787600 |
| F       | 5.28005600  | 1.21710400 | 0.73495100 |
| F       | 4.68410100  | -0.72163700 | 1.54207400 |
| H       | 2.17093700  | -1.24008700 | 0.75419600 |
| C       | -4.36918000 | 0.15083200 | -0.24685100 |
| C       | -3.24194300 | -0.44668600 | 0.36354100 |
| C       | -3.31645100 | -0.75873600 | 1.73197100 |
| C       | -4.47260900 | -0.46683100 | 2.44692700 |
Product of CMD process (minimum)

No imaginary frequencies

E = −2119.222175 a.u.

G = −2118.989955 a.u

Solvent correction (TFE) = −0.015895 a.u.

Solvent correction (tBuOH) = −0.015183 a.u.
| Element | X          | Y          | Z          |
|---------|------------|------------|------------|
| H       | 1.09606000 | 1.57617600 | -2.06412400|
| H       | -0.75713800| 4.83263100 | 1.18924600 |
| H       | 0.65221500 | 5.62869200 | -0.70149400|
| H       | 1.56727200 | 3.98200300 | -2.32909400|
| H       | -1.24648300| 2.43125400 | 1.45614900 |
| H       | -1.98451700| -2.08176000| -0.86180500|
| O       | 1.97377400 | -0.42591900| 0.80713800 |
| C       | 3.12250000 | 0.11176000 | 0.18343000 |
| H       | 2.86797100 | 1.12774000 | -0.12719400|
| C       | 3.47247700 | -0.70768700| -1.06637900|
| C       | 4.26220400 | 0.18246000 | 1.21083100 |
| F       | 4.59445800 | -0.27799000| -1.65460500|
| F       | 3.63066800 | -2.01121400| -0.73830700|
| F       | 2.47121900 | -0.63708600| -1.96251800|
| F       | 3.88776200 | 0.94023600 | 2.24970100 |
| F       | 5.37331100 | 0.71267000 | 0.67709400 |
| F       | 4.55956800 | -1.04968300| 1.67618500 |
| H       | 2.06803000 | -1.39040600| 0.91694100 |
| C       | -4.49670800| 0.10434800 | -0.19237000|
| C       | -3.22938200| 0.09531400 | 0.44617400 |
| C       | -3.18812300| 0.19064700 | 1.85061400 |
| C       | -4.36834200| 0.29396300 | 2.57550700 |
| C       | -5.61345900| 0.29916000 | 1.92087100 |
| C       | -5.68805900| 0.20135100 | 0.53549500 |
| C       | -2.57615100| -0.09809000| -1.77974800|
| C       | -2.12121400| -0.02322100| -0.49183100|
| H       | -2.22402500| 0.18553700 | 2.35289300 |
| H       | -4.33177100| 0.37107100 | 3.65878100 |
Computed values of $^{13}$C and $^2$H KIEs for a CMD pathway

$^{13}$C and $^2$H KIEs related to the CMD process of Pd[Ph(OCO$_2$H)(HOCH(CF$_3$)$_2$)] complex at the C-3 position of benzo[b]thiophene were determined using ISOEFF.$^{19}$

![Diagram of benzo[b]thiophene](image)

| Position of benzothiophene | Computed $^{13}$C KIES | Computed $^2$H KIES | Experimental $^{13}$C KIES | Experimental $^2$H KIES |
|-----------------------------|------------------------|---------------------|---------------------------|------------------------|
| 2                           | 1.003                  | 0.98                | $1.015 \pm 0.006$         | $1.02 \pm 0.01$        |
|                             |                        |                     | $1.014 \pm 0.005$         | $1.00 \pm 0.01$        |
| 3                           | 1.018                  | 5.15                | $1.042 \pm 0.006$         | $0.87 \pm 0.01$        |
|                             |                        |                     | $1.044 \pm 0.005$         | $0.88 \pm 0.01$        |
| 4                           | 0.998                  | *not determined*   | $0.999 \pm 0.005$         | *not determined*       |
|                             |                        |                     | $1.002 \pm 0.007$         |                        |

*Table S.27:* Computed and experimental values of $^{13}$C KIES and $^2$H KIES
VI. References

1. Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* 2012, 31, 2302.

2. Tang, D.-T. D.; Collins, K. D.; Glorius, F. *J. Am. Chem. Soc.* 2013, 135, 7450.

3. Funaki, K.; Sato, T.; Oi, S. *Org. Lett.* 2012, 14, 6186.

4. Yuan, K.; Doucet, H. *Chem. Sci.* 2014, 5, 392.

5. Anbarasan, P.; Neumann, H.; Beller, M. *Chem. Asian J.* 2010, 5, 1775.

6. Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* 2007, 13, 150.

7. Lipshutz, B. H.; Abela, A. R. *Org. Lett.* 2008, 10, 5329.

8. Katritzky, A. R.; Kirichenko, K.; Ji, Yu; Prakash, I. *Chem. Heterocycl. Compd.* 2002, 51, 3066.

9. Merck and Co., Inc. Patent: US5177074 A1, 1993.

10. Hitosugi, S.; Tanimoto, D.; Nakanishi, W.; Isobe. *Chem. Lett.* 2012, 41, 972.

11. Qui, Y.; Ma, D.; Fu, C.; Ma, S. *Tetrahedron* 2013, 69, 6305.

12. Kuhl, N.; Hopkinson, M. N.; Glorius, F. *Angew. Chem. Int. Ed.* 2012, 51, 8230.

13. Grainger, R.; Nikmal, A.; Cornella, J.; Larrosa, I. *Org. Biomol. Chem.* 2012, 10, 3172.

14. *Reactions Rates of Isotopic Molecules*; Melander, L.; Saunders, W. H.; Wiley: New York, 1980; pp 95-102.

15. Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* 1995, 117, 9357.

16. Gaussian 09, Revision A.1, 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, 2009.
17 (a) Becke, A. D. *J. Chem. Phys.* 1993, 98, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* 1988, 37, 785.

18 (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* 1989, 90, 2154. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* 1990, 94, 5523.

19 V. Anisinov, P. Paneth, ISOEFF98, Lodz, Poland, 1998. For reference and example see: (a) Anisimov, V.; Paneth, P. *J. Math. Chem.* 1999, 26, 75. (b) Cen, Y.; Sauve, A. A. *J. Am. Chem. Soc.* 2010, 132, 12286.
VII. Crystallographic data of 3ak

The crystal structure was deposit at the Cambridge Crystallographic Data Centre.

**CCDC**: 1422785.

**Table S.28: Crystal data and structure refinement for 3ak**

| Property                        | Value                                      |
|---------------------------------|--------------------------------------------|
| Empirical formula               | C_{14}H_{9}NO_{2}S                         |
| Formula weight                  | 255.28                                     |
| Temperature/K                   | 100(2)                                     |
| Space group                     | P2_12_2_1                                  |
| a/Å                             | 7.2320(7)                                  |
| b/Å                             | 10.7011(10)                                |
| c/Å                             | 14.8484(13)                                |
| α/°                            | 90.00                                      |
| β/°                            | 90.00                                      |
| γ/°                            | 90.00                                      |
| Volume/ Å³                      | 1149.12(18)                                |
| Z                               | 4                                          |
| \( \rho_{\text{calc}} \)/g/cm³ | 1.476                                      |
| \( \mu \)/mm⁻¹                  | 2.442                                      |
| F(000)                          | 528.0                                      |
| Crystal size/mm³                | 0.26 x 0.15 x 0.09                        |
| Radiation                       | CuKα (\( \lambda = 1.54178 \))            |
| 2Θ range for data collection/°  | 10.18 to 144.5                             |
| Index ranges                    | -8 ≤ h ≤ 6, -12 ≤ k ≤ 13, -18 ≤ l ≤ 18   |
| Reflections collected           | 7101                                       |
| Independent reflections         | 2175 [R_{int} = 0.0288]                    |
| Data/restraints/parameters      | 2175/0/163                                 |
| Goodness-of-fit on F²           | 1.059                                      |
| Final R indexes [I>=2σ (I)]     | R₁ = 0.0243, wR₂ = 0.0638                 |
| Final R indexes [all data]      | R₁ = 0.0251, wR₂ = 0.0643                 |
| Largest diff. peak/hole / e Å⁻³ | 0.20/-0.15                                 |
| Flack parameter                 | 0.032(14)                                  |

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Table S.29: Fractional Atomic Coordinates ($\times10^4$) and Equivalent Isotropic Displacement Parameters (Å$^2\times10^3$) for 3ak. $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$ tensor.

| Atom | $x$    | $y$          | $z$          | $U_{eq}$ |
|------|--------|--------------|--------------|----------|
| C1   | 1614(2)| -184.3(14)   | 3564.9(9)    | 19.7(3)  |
| C2   | 2082(2)| -1444.7(14)  | 3464.7(11)   | 24.6(3)  |
| C3   | 2646(3)| -2097.2(14)  | 4216.7(11)   | 28.5(4)  |
| C4   | 2730(2)| -1513.1(14)  | 5061.0(11)   | 26.0(3)  |
| C5   | 2263(2)| -267.0(14)   | 5155.8(10)   | 20.1(3)  |
| C6   | 1693(2)| 427.3(13)    | 4405.6(9)    | 16.5(3)  |
| C7   | 1213(2)| 1742.3(13)   | 4320.3(9)    | 16.1(3)  |
| C8   | 812(2) | 2051.6(14)   | 3453.9(9)    | 18.5(3)  |
| C9   | 1225(2)| 2669.4(13)   | 5052.8(9)    | 14.9(3)  |
| C10  | 682(2) | 2350.9(13)   | 5930.5(9)    | 16.1(3)  |
| C11  | 706(2) | 3221.3(13)   | 6616.6(9)    | 17.2(3)  |
| C12  | 1308(2)| 4417.9(13)   | 6426.0(9)    | 18.3(3)  |
| C13  | 1819(2)| 4782.5(13)   | 5563(1)      | 19.4(3)  |
| N1   | 1413.3(19)| 5328.9(12) | 7157.9(9)    | 24.2(3)  |
| O1   | 1004.5(19)| 4976.8(12) | 7920.2(7)    | 33.1(3)  |
| S1   | 967.7(5) | 825.2(4)   | 2704.3(2)    | 22.2(11) |

Table S.30: Anisotropic Displacement Parameters (Å$^2\times10^3$) for 3ak

The Anisotropic displacement factor exponent takes the form: -2π$^2$h$^2$ a$^*$$^2$ $U_{11}$ + 2hk a$^*$ b$^*$ $U_{12}$ + ...

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|------|----------|----------|----------|----------|----------|----------|
| C1   | 14.4(8)  | 25.5(7)  | 19.3(7)  | -4.2(6)  | 2.2(5)   | -2.6(6)  |
| C2   | 21.7(9)  | 24.5(7)  | 27.5(8)  | -12.0(6)| 4.3(6)   | -3.4(6)  |
| C3   | 30.4(10)| 16.9(7)  | 38.1(9)  | -5.7(6)  | 4.4(7)   | -1.0(6)  |
| C4   | 29(1)    | 19.5(7)  | 29.6(8)  | 0.7(6)   | 2.1(7)   | -0.1(6)  |
| C5   | 19.8(8)  | 21.5(7)  | 19.1(6)  | -1.7(6)  | 1.5(5)   | -0.9(6)  |
| C6   | 12.1(7)  | 18.7(6)  | 18.7(6)  | -3.4(5)  | 1.6(5)   | -2.4(5)  |
| C7   | 11.4(8)  | 20.7(7)  | 16.2(6)  | -0.2(5)  | 1.2(5)   | -2.5(5)  |
| C8   | 15.3(8)  | 24.1(7)  | 16.0(6)  | -1.4(5)  | 1.8(6)   | -1.5(6)  |
| C9   | 10.2(7)  | 19.2(7)  | 15.4(6)  | 0.1(5)   | -0.1(5)  | 1.3(5)   |
| C10  | 13.8(7)  | 18.3(6)  | 16.2(6)  | 0.6(5)   | 0.4(5)   | 0.1(5)   |
| C11  | 14.0(7)  | 23.3(7)  | 14.4(6)  | -0.7(5)  | -0.1(5)  | 2.6(6)   |
| C12  | 15.0(7)  | 20.4(6)  | 19.4(6)  | -6.6(5)  | -3.2(5)  | 3.8(5)   |
| C13  | 14.4(8)  | 15.7(6)  | 28.1(7)  | 1.5(6)   | -0.9(6)  | 0.5(6)   |
| C14  | 14.1(7)  | 20.5(7)  | 17.7(6)  | 2.7(5)   | 1.2(5)   | 1.7(5)   |
| N1   | 19.2(7)  | 25.0(6)  | 28.4(7)  | -11.4(5)| -4.2(5)  | 4.0(5)   |
| O1   | 37.7(8)  | 38.8(7)  | 22.9(5)  | -13.9(5)| 0.4(5)   | 1.6(6)   |
| O2   | 39.0(8)  | 21.7(6)  | 43.1(7)  | -12.4(5)| -5.1(5)  | -1.2(5)  |
| S1   | 21.3(2)  | 31.56(19)| 13.85(15)| -5.29(14)| -0.24(13)| -0.93(15)|
Table S.31: Bond Lengths for 3ak

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|------|------|----------|------|------|----------|
| C1   | C2   | 1.399(2) | C8   | S1   | 1.7245(14) |
| C1   | C6   | 1.4106(18)| C9   | C14  | 1.401(2)   |
| C1   | S1   | 1.7373(15)| C9   | C10  | 1.4033(18) |
| C2   | C3   | 1.379(2) | C10  | C11  | 1.3805(19) |
| C3   | C4   | 1.402(2) | C11  | C12  | 1.382(2)   |
| C4   | C5   | 1.383(2) | C12  | C13  | 1.389(2)   |
| C5   | C6   | 1.401(2) | C12  | N1   | 1.4618(17) |
| C6   | C7   | 1.455(2) | C13  | C14  | 1.3787(19) |
| C7   | C8   | 1.3595(19)| N1   | O2   | 1.2229(18) |
| C7   | C9   | 1.4721(18)| N1   | O1   | 1.2290(18) |

Table S.32: Bond Angles for 3ak

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|------|------|------|---------|------|------|------|---------|
| C2   | C1   | C6   | 122.12(14)| C14  | C9   | C10  | 118.26(13) |
| C2   | C1   | S1   | 125.91(12)| C14  | C9   | C7   | 120.35(12) |
| C6   | C1   | S1   | 111.92(11)| C10  | C9   | C7   | 121.38(13) |
| C3   | C2   | C1   | 118.29(14)| C11  | C10  | C9   | 121.20(13) |
| C2   | C3   | C4   | 120.74(14)| C10  | C11  | C12  | 118.55(12) |
| C5   | C4   | C3   | 120.69(16)| C11  | C12  | C13  | 122.20(13) |
| C4   | C5   | C6   | 120.16(14)| C11  | C12  | N1   | 118.82(12) |
| C5   | C6   | C1   | 118.00(13)| C13  | C12  | N1   | 118.98(13) |
| C5   | C6   | C7   | 130.72(13)| C14  | C13  | C12  | 118.41(13) |
| C1   | C6   | C7   | 111.23(12)| C13  | C14  | C9   | 121.31(12) |
| C8   | C7   | C6   | 111.63(12)| O2   | N1   | O1   | 123.61(13) |
| C8   | C7   | C9   | 122.43(12)| O2   | N1   | C12  | 118.51(13) |
| C6   | C7   | C9   | 125.88(12)| O1   | N1   | C12  | 117.88(12) |
| C7   | C8   | S1   | 114.31(11)| C8   | S1   | C1   | 90.92(7) |
### Table S.33: Torsion Angles for 3ak

| A   | B   | C   | D   | Angle/° |   A   | B   | C   | D   | Angle/° |
|-----|-----|-----|-----|--------|-------|-----|-----|-----|--------|
| C6  | C1  | C2  | C3  | -0.3(2) | C8    | C7  | C9  | C10 | 146.22(15) |
| S1  | C1  | C2  | C3  | 177.05(13) | C6    | C7  | C9  | C10 | -36.8(2)  |
| C1  | C2  | C3  | C4  | 0.6(3)  | C14   | C9  | C10 | C11 | -1.2(2)   |
| C2  | C3  | C4  | C5  | -0.5(3) | C7    | C9  | C10 | C11 | 179.62(13) |
| C3  | C4  | C5  | C6  | 0.2(3)  | C9    | C10 | C11 | C12 | -1.0(2)   |
| C4  | C5  | C6  | C1  | 0.0(2)  | C10   | C11 | C12 | C13 | 2.6(2)    |
| C4  | C5  | C6  | C7  | -176.98(16) | C10   | C11 | C12 | N1  | -177.37(12) |
| C2  | C1  | C6  | C5  | 0.0(2)  | C11   | C12 | C13 | C14 | -1.7(2)   |
| S1  | C1  | C6  | C5  | -177.69(12) | N1    | C12 | C13 | C14 | 178.21(13) |
| C2  | C1  | C6  | C7  | 177.60(15) | C12   | C13 | C14 | C9  | -0.6(2)   |
| S1  | C1  | C6  | C7  | -0.12(16) | C10   | C9  | C14 | C13 | 2.1(2)    |
| C5  | C6  | C7  | C8  | 177.08(16) | C7    | C9  | C14 | C13 | -178.75(13) |
| C1  | C6  | C7  | C8  | -0.08(18) | C11   | C12 | N1  | O2  | -178.76(15) |
| C5  | C6  | C7  | C9  | -0.2(3)  | C13   | C12 | N1  | O2  | 1.3(2)    |
| C1  | C6  | C7  | C9  | -177.38(13) | C11   | C12 | N1  | O1  | 1.9(2)    |
| C6  | C7  | C8  | S1  | 0.25(17)  | C13   | C12 | N1  | O1  | -178.02(15) |
| C9  | C7  | C8  | S1  | 177.65(11) | C7    | C8  | S1  | C1  | -0.27(13) |
| C8  | C7  | C9  | C14 | -32.9(2) | C2    | C1  | S1  | C8  | -177.40(15) |
| C6  | C7  | C9  | C14 | 144.09(16) | C6    | C1  | S1  | C8  | 0.22(12)  |

### Table S.34: Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 3ak

| Atom | x     | y     | z     | U(eq) |
|------|-------|-------|-------|-------|
| H2   | 2013  | -1841 | 2893  | 29    |
| H3   | 2981  | -2952 | 4162  | 34    |
| H4   | 3111  | -1978 | 5573  | 31    |
| H5   | 2330  | 119   | 5731  | 24    |
| H8   | 475   | 2874  | 3277  | 22    |
| H10  | 290   | 1521  | 6055  | 19    |
| H11  | 316   | 3002  | 7207  | 21    |
| H13  | 2197  | 5616  | 5444  | 23    |
| H14  | 2096  | 4143  | 4289  | 21    |
VIII. $^1$H-NMR and $^{13}$C-NMR Spectra
