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SUPPORTING INFORMATION

Title: Sterics versus Electronics: Regioselective Cross-Coupling of Polybrominated Thiophenes
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Ref. No.: O200701148

General experimental details. Unless otherwise specified, all reactions were carried out under nitrogen atmosphere with reagent grade materials. 2,3,5-Tribromothiophene[1] and 3-hexyloxythiophene[2] were prepared as previously reported. THF and diethyl ether were distilled from sodium/benzophenone prior to use. Chromatographic separations were performed using standard column methods with silica gel (230-400 mesh). ^{1}H and ^{13}C NMR spectra were carried out on a 400 MHz spectrometer in $CDCl_3$. All NMR data was referenced to chloroform and peak multiplicity reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dq = doublet of quartets, ddd = doublet of doublet of doublets, m = multiplet.

2-Bromo-3-hexyloxythiophene. NBS (5.94 g, 33.4 mmol) was slowly added to 3-hexyloxy-thiophene (6.16 g, 33.4 mmol) in 100 mL DMF. This was stirred overnight in the absence of light. The solution was then poured into 150 mL water and extracted with hexanes (3 x 150 mL). The combined organic layers were then dried, concentrated to 50 mL, filtered through a plug of silica and evaporated to give 7.67 g (87%) of 2-bromo-3-hexyloxythiophene as a light yellow oil. (Note: this compound is unstable at room temperature for extended periods of time and can be stored at -20 in the dark.) ^{1}H NMR: δ 7.18 (d, J = 6.0 Hz, 1H), 6.74 (d, J = 6.0 Hz, 1H), 4.04 (t, J = 6.8 Hz, 2H), 1.76 (p, J = 6.8 Hz, 2H), 1.46 (m, 2H), 1.35 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR: δ 154.8, 124.3, 117.7, 91.8, 72.4, 31.7, 29.7, 25.7, 22.8, 14.2.

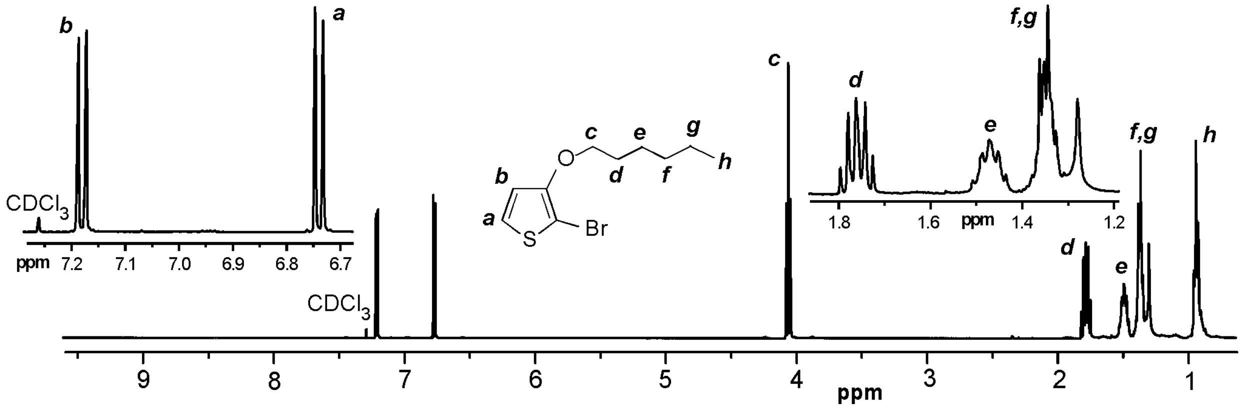


Figure S1. ^{1}H NMR spectrum of 2-bromo-3-hexyloxythiophene

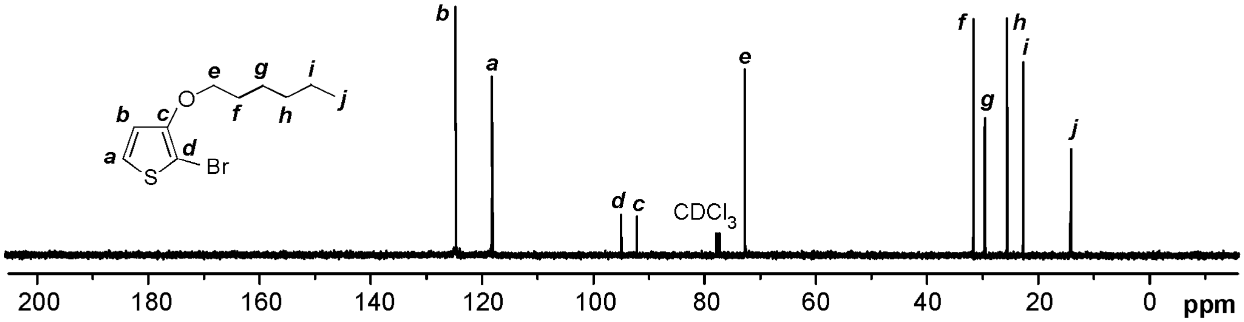


Figure S2. ^{13}C NMR spectrum of 2-bromo-3-hexyloxythiophene

2-Bromo-5-methylthiophene. To a solution of 2,5-dibromothiophene (24.18 g, 100 mmol) in 150 mL ether was added 40 mL of *n*-butyllithium (2.5 M in hexanes) at -78 ºC. This was stirred for one hour, after which MeI (20 mL, 321 mmol) was added via syringe. The mixture was then warmed and heated at reflux with stirring overnight. The solution was then cooled to room temperature, poured into 150 mL water, and extracted with ether (3 x 150 mL). To the combined organic extracts were added $MgSO_4$ and decolorizing carbon, and the mixture was stirred 30 min. This was then filtered, concentrated by rotary evaporation, and distilled (12.7 g, 71% yield). bp 66-71 ºC; ^{1}H NMR: δ 6.84 (d, *J* = 3.6 Hz, 1H), 6.53 (dq, *J* = 1.2, 3.6 Hz, 1H), 2.43 (d, *J* = 1.2, 3H); ^{13}C NMR: δ 141.5, 129.8, 125.8, 108.8, 15.6. ^{1}H NMR agree with previously reported values.[3]

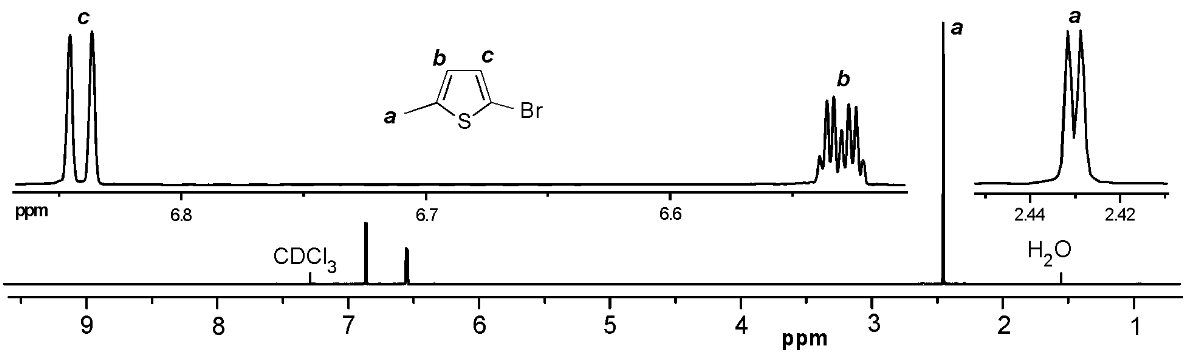


Figure S3. ^{1}H NMR spectrum of 2-bromo-5-methylthiophene

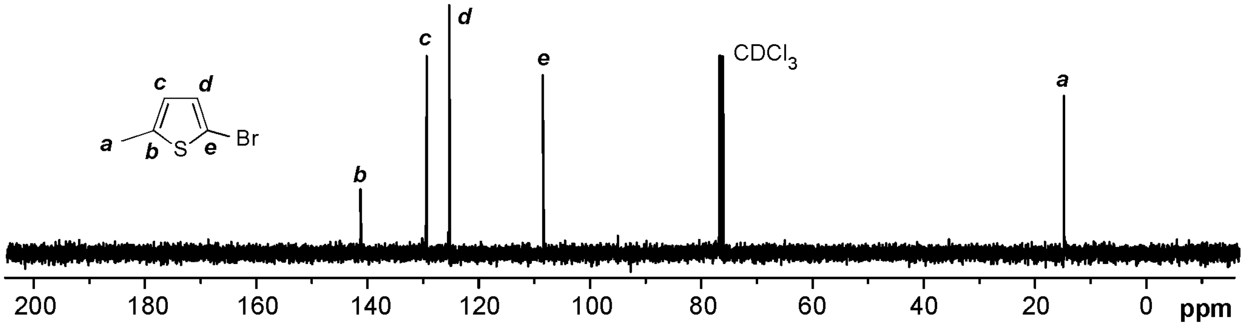


Figure S4. ^{13}C NMR spectrum of 2-bromo-5-methylthiophene

Investigation of the coupling of 2,3,5-tribromothiophene with 2-metallated thiophenes. Thiophene (6.0-7.5 mmol) was dissolved in 50 mL solvent and cooled in an ice bath. One equivalent of *n*-butyllithium (2.5 M in hexanes) was then added slowly via syringe. This mixture was stirred for one hour, after which one equivalent of anhydrous zinc chloride was added as a solid and the mixture stirred for another hour. 2,3,5-Tribromothiophene (1.60 g, 5.0 mmol) and catalyst (2.5 mol % for Pd(dppf)Cl_2; 5 mol % for Ni(PPh_3)$_2$$Cl_2$, Pd($PPh_3$)$_2$, and Pd(dppe)$Cl_2$) were then added as a solids. This mixture was allowed to stir overnight at RT. The mixture was then poured into 100 mL saturated NH_4Cl solution and extracted with ether (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, evaporated, and purified by silica gel chromatography (hexanes).

4,5-Dibromo-2,2'-bithiophene (2): mp 82.8-83.9 ºC; ^{1}H NMR: δ 7.27 (dd, *J* = 1.2, 5.0 Hz, 1H), 7.13 (dd, *J* = 1.0, 3.6 Hz, 1H), 7.03 (dd, *J* = 3.6, 5.0 Hz, 1H), 6.97 (s, 1H); ^{13}C NMR: δ 138.9, 135.5, 128.2, 126.1, 125.9, 124.8, 114.6, 109.7.

4'-Bromo-2,2';5',2"-terthiophene (3). Faint yellow liquid (literature reports it as either a colorless liquid,[4] or a low melting solid,[5] 40.5-41.5 ºC); ^{1}H NMR: δ 7.45 (dd, *J* = 1.5, 4.5 Hz, 1H), 7.36 (dd, *J* = 1.5, 6.0 Hz, 1H), 7.26 (dd, *J* = 1.5, 6.0 Hz, 1H), 7.19 (dd, *J* = 1.5, 4.5 Hz, 1H), 7.10 (s, 1H), 7.10 (dd, *J* = 4.5, 6.0 Hz, 1H), 7.04 (dd, *J* = 4.5, 6.0 Hz, 1H); ^{13}C NMR: δ 135.9, 134.5, 131.0, 128.3, 127.9, 127.6, 126.9, 126.4, 125.6, 124.6, 108.2. All NMR agree with previously reported values.[4,5]

2,2'-bithiophene (4). mp 32-33 °C (lit[6] 32-33 °C); ^{1}H NMR: δ 7.02 (2H, dd, *J* = 5.1, 3.6 Hz), 7.18 (2H, dd, *J* = 3.6, 1.2 Hz), 7.21 (2H, dd, *J* = 5.1, 1.2 Hz); ^{13}C NMR: δ 124.0, 124.5, 128.0, 137.6. All NMR agree with previously reported values.[6]

4,4',5,5'-Tetrabromo-2,2'-bithiophene (5). mp 178.5-180.4 ºC (lit[7] 182-183 ºC); ^{1}H NMR: δ 6.93 (s); ^{13}C NMR: δ 136.6, 127.0, 115.0, 111.4; All NMR agree with previously reported values.[7]

2,4-dibromothiophene (6). ^{1}H NMR: δ 7.15 (d, *J* = 1.6, 1H), 6.98 (d, *J* = 1.6, 1H); ^{13}C NMR: δ 132.1, 124.5, 113.3, 109.7. All NMR agree with previously reported values.[8]

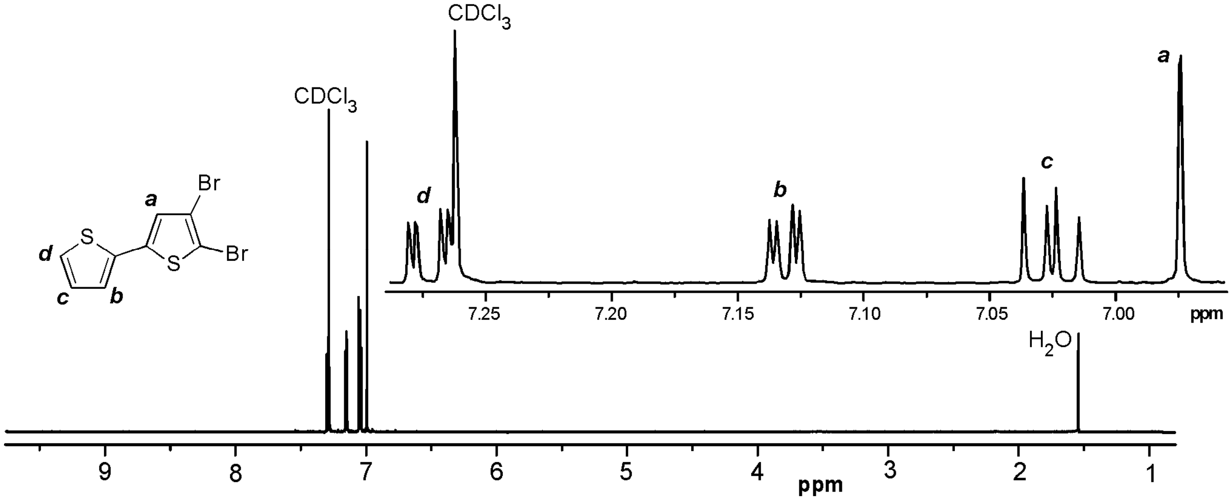


Figure S5. ^{1}H NMR spectrum of **4**

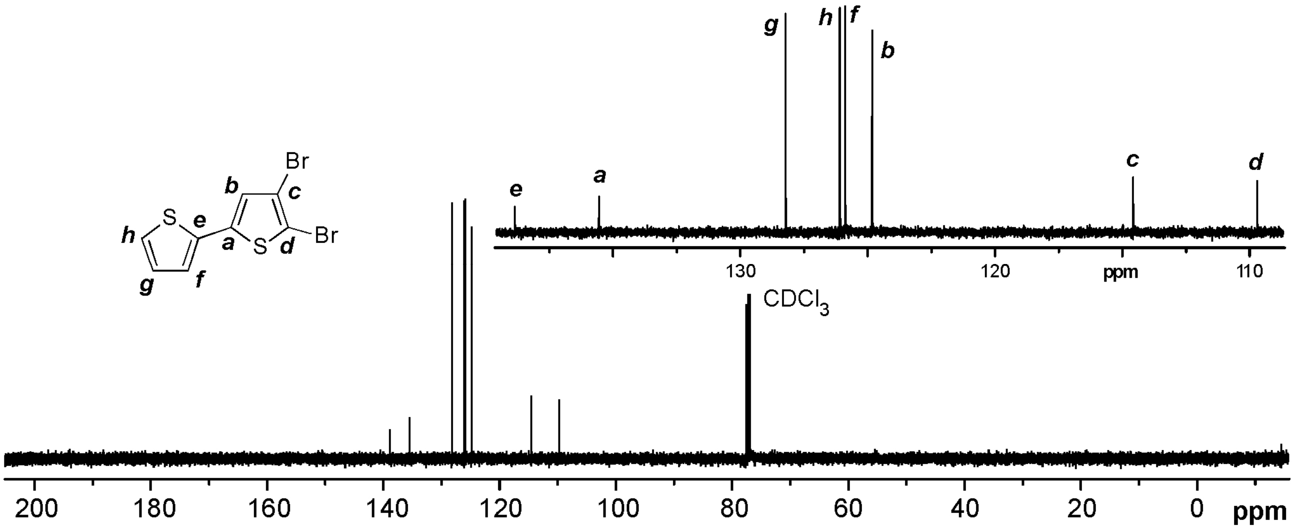


Figure S6. ^{13}C NMR spectrum of **2**

Procedure for generating arylzinc chlorides. Phenyl-, 5-methyl-2-thienyl-, 4-bromophenyl-, and 4-methyoxyphenyl-zinc chloride were generated by adding 7.1 mL of a *t*-butyllithium solution (1.7 M in pentane, 12 mmol) to the bromoaryl (6.0 mmol) in 50 mL ether at -78 ºC. The solution was then stirred for 1 hour and warmed to room temperature. Anhydrous zinc chloride (0.81g, 6.0 mmol) was then added and stirring continued for 1 hour.

3-Hexyloxy-2-thienylzinc chloride was generated by adding 2.4 mL *n*-butyllithium (2.5 M in hexanes, 6.0 mmol) to a solution of 2-bromo-3-hexyloxythiophene (1.57 g, 6.0 mmol) in 50 mL ether at -78 ºC. The mixture was stirred for 1 hour, after which anhydrous zinc chloride (0.81 g, 6.0 mmol) was added, the solution allowed to warm to room temperature and stirred another hour.

2-Thienylzinc chloride was generated by addition of 2.4 mL *n*-butyllithium (2.5 M in hexanes, 6.0 mmol) to a solution of thiophene (6.0 mmol) at 0 ºC and stirring 1 hour. Anhydrous zinc chloride (0.81g, 6.0 mmol) was then added and stirred another hour.

4-Trifluoromethylzinc chloride was generated by the addition of anhydrous zinc chloride (0.81g, 6.0 mmol) to a solution of 4-trifluoromethylphenyllithium[10] (6.0 mmol) in 50 mL ether at room temperature and stirred for one hour.

General procedure for the regioselective cross-coupling of 2,3,5-tribromothiophene. To a solution of 6.0 mmol arylzinc chloride was added 1.60 g (5.0 mmol) 2,3,5-tribromothiophene and 0.10 g (2.5 mol%) Pd(dppf)Cl_2, and the resulting mixture stirred overnight at room temperature. The mixture was then poured into 150 mL sat. ammonium chloride, and extracted with ether (3 x 150 mL). The combined organic phases were dried over $MgSO_4$, filtered, and purified by silica gel chromatography. To obtain analytically pure samples of **9-11** and **13** required additional recrystallization from acetonitrile.

4,5-Dibromo-2,2'-bithiophene (2): 63%. *See above for characterization data.*

4,5-Dibromo-5'-methyl-2,2'-bithiophene (7). 58%; mp 106.2-107.6 ºC; ^{1}H NMR: δ 6.91 (d, *J* = 3.6 Hz, 1H), 6.87 (s, 1H), 6.66 (dq, *J* = 0.08, 3.6 Hz, 1H), 1.48 (d, *J* = 0.08 Hz, 3H); ^{13}C NMR: δ 140.9, 139.3, 133.2, 126.4, 125.2, 124.7, 114.4, 108.9, 15.6.

4,5-Dibromo-3'-hexyloxy-2,2'-bithiophene (8). 65%; mp 59.4-60.5 ºC; ^{1}H NMR: δ 7.10 (d, *J* = 5.6 Hz, 1H), 6.94, (s, 1H), 6.81 (d, *J* = 5.6 Hz, 1H), 4.11 (t, *J* = 6.4 Hz, 2H), 1.83 (m, 2H), 1.51 (m, 2H), 1.37 (m, 4H), 0.93 (t, *J* = 6.8 Hz); ^{13}C NMR: δ 153.9, 137.1, 123.7, 122.9, 117.2, 113.8, 113.7, 109.0, 72.3, 31.7, 29.7, 25.8, 22.8, 14.2.

2,3-Dibromo-5-(4-methoxyphenyl)thiophene (9). 57%; mp 105.7-106.9 ºC (lit[9] 108-110 ºC); ^{1}H NMR: δ 7.40 (d, *J* = 9.2 Hz, 2H), 6.98 (s, 1H), 6.91 (d, *J* = 9.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR: δ 160.2, 145.6, 127.1, 125.7, 124.7, 114.7, 114.6, 109.0, 55.7. All NMR agree with previously reported values.[9]

2,3-Dibromo-5-phenylthiophene (10). 51%; mp 76.6-77.8 ºC; ^{1}H NMR: δ 7.49 (m, 2H), 7.39 (m, 2H), 7.34 (m, 1H), 7.10 (s, 1H); ^{13}C NMR: δ 145.6, 132.9, 129.4, 128.8, 125.8, 125.7, 114.8, 110.3.

2,3-Dibromo-5-(4-bromophenyl)thiophene (11). 38%; mp 113.7-115.0 ºC; ^{1}H NMR: δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.08 (s, 1H); ^{13}C NMR: δ 144.2, 132.5, 131.8, 127.1, 126.2, 122.8, 115.0, 110.8.

2,3-Dibromo-5-(4-trifluoromethylphenyl)thiophene (12). 31%; mp 100.9-102.3 ºC (lit[9] 103-104 °C); ^{1}H NMR: δ 7.61 (AB, 4H), 7.18 (s, 1H); ^{13}C NMR: δ 143.6, 136.1, 130.5 (q, *J* = 32 Hz), 128.1, 127.0, 126.4 (*q*, J = 3.7 Hz), 124.1 (q, *J* = 270), 115.3, 112.0. All NMR agree with previously reported values.[9]

3,5-Dibromo-2-(4-methoxyphenyl)thiophene (14). 6.3%; mp 52.2-53.1 ºC; ^{1}H NMR: δ 7.51, (d, *J* = 9.2 Hz, 2H), 7.00 (s, 1H), 6.95 (d, *J* = 9.2 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR: δ 140.9, 139.3, 133.1, 126.3, 125.2, 124.7, 114.4, 108.9.

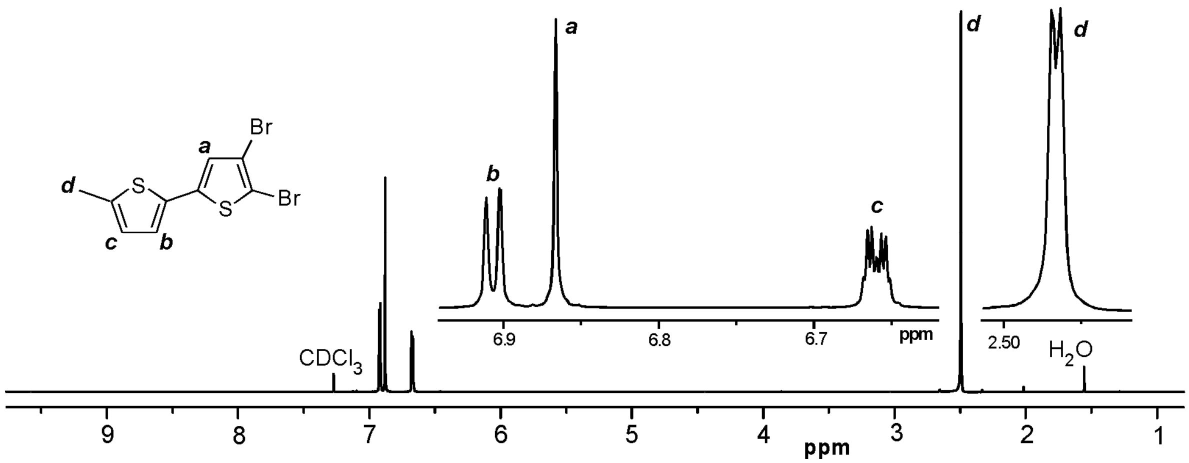


Figure S7. ^{1}H NMR spectrum of **7**

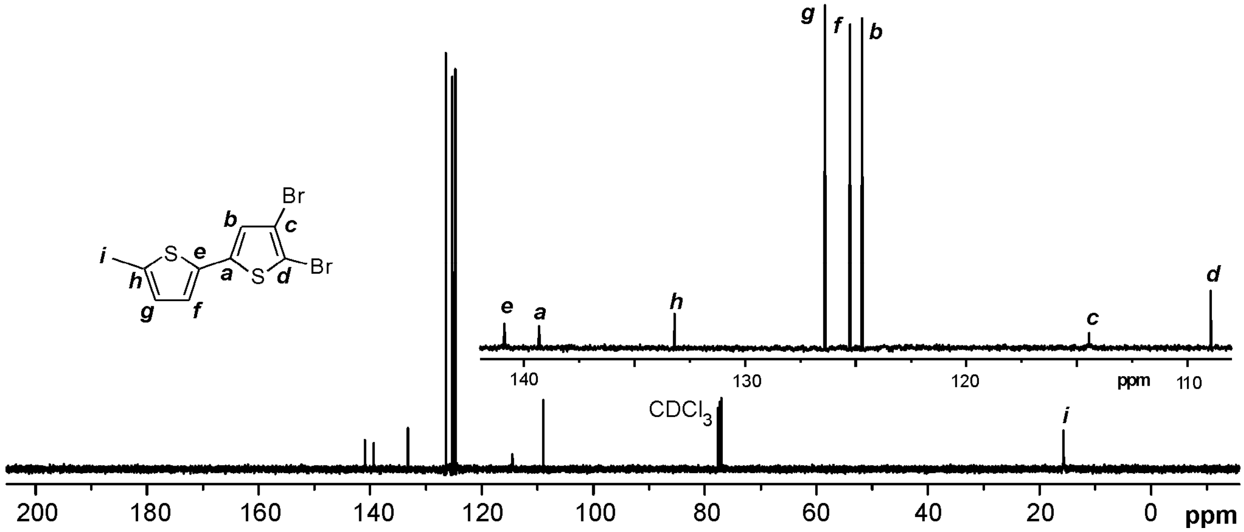


Figure S8. ^{13}C NMR spectrum of **7**

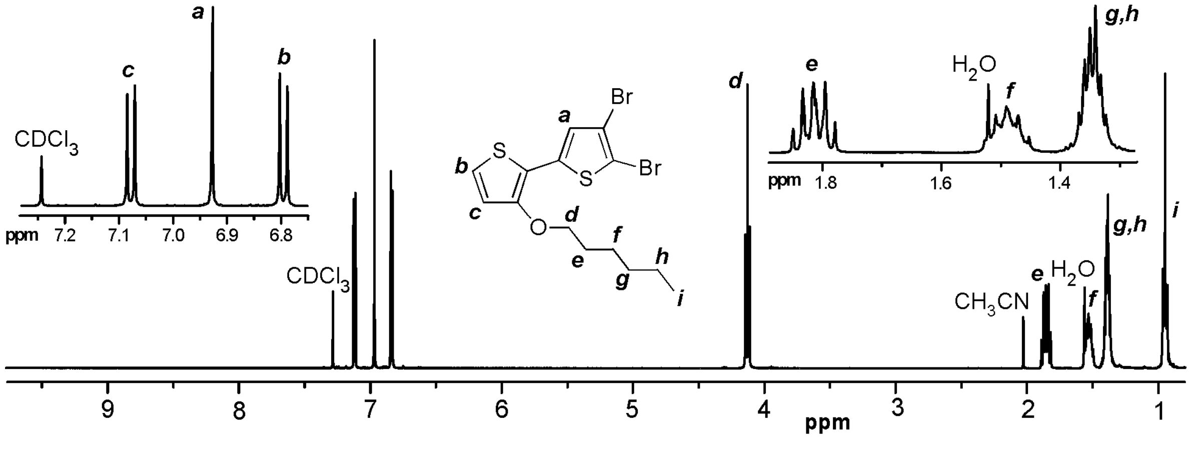


Figure S9. ^{1}H NMR spectrum of **8**

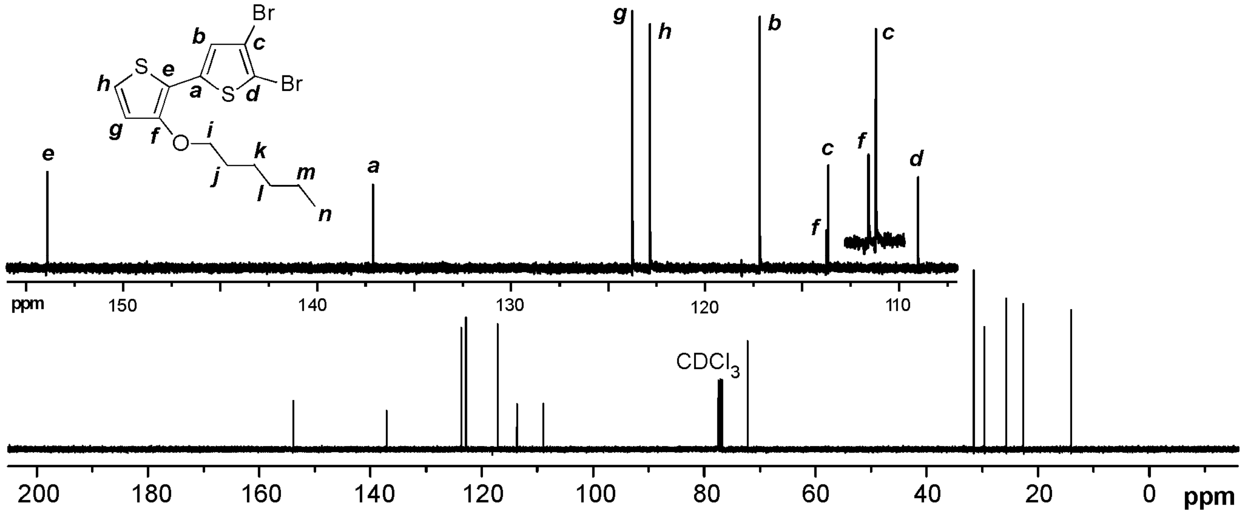


Figure S10. ^{13}C NMR spectrum of **8**

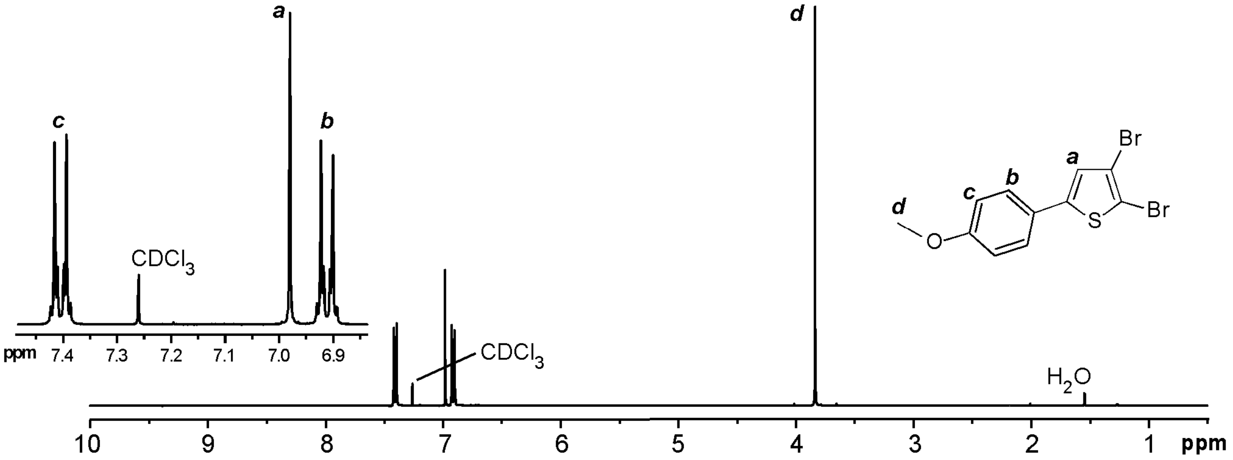


Figure S11. ^{1}H NMR spectrum of **9**

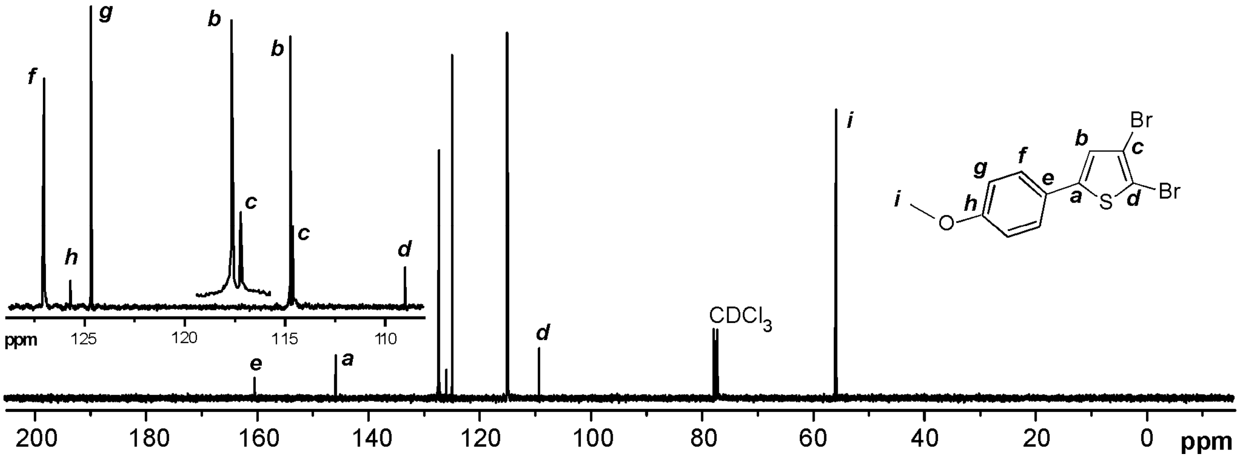


Figure S12. ^{13}C NMR spectrum of **9**

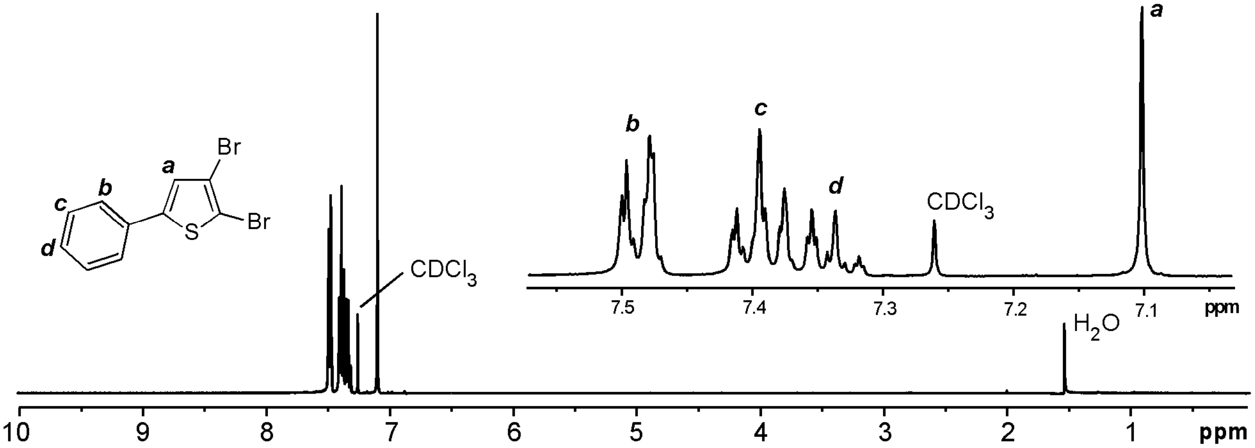


Figure S13. ^{1}H NMR spectrum of **10**

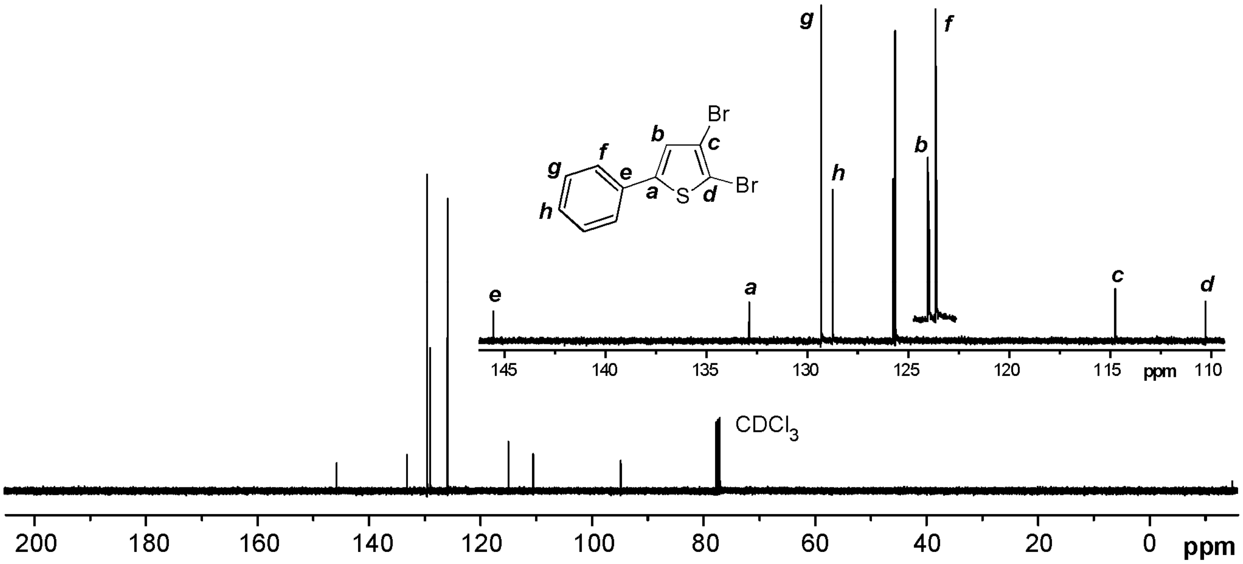


Figure S14. ^{13}C NMR spectrum of **10**

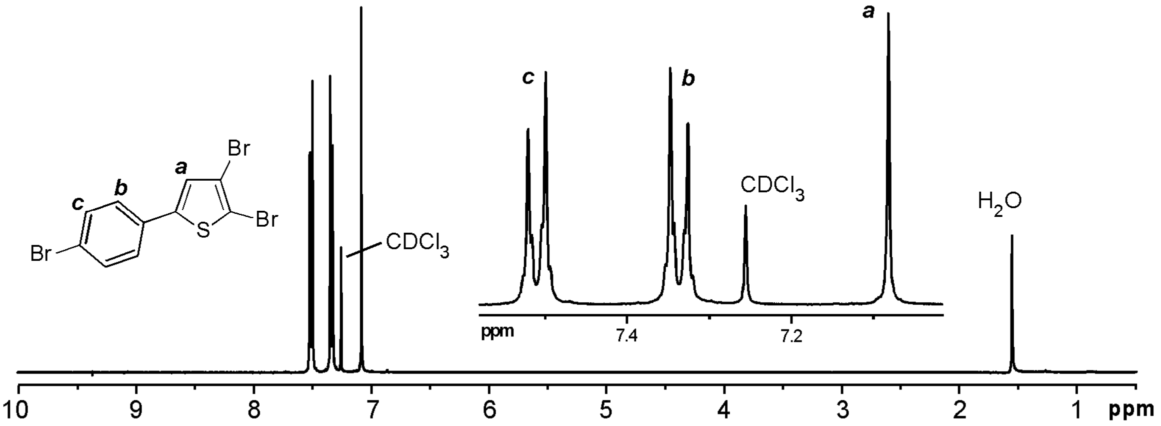


Figure S15. ^{1}H NMR spectrum of **11**

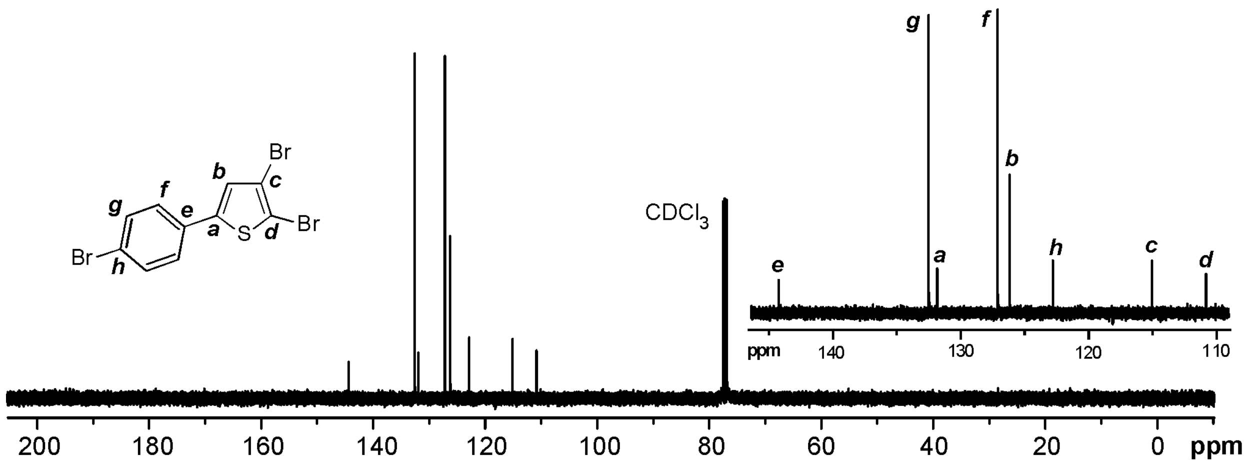


Figure S16. ^{13}C NMR spectrum of **11**

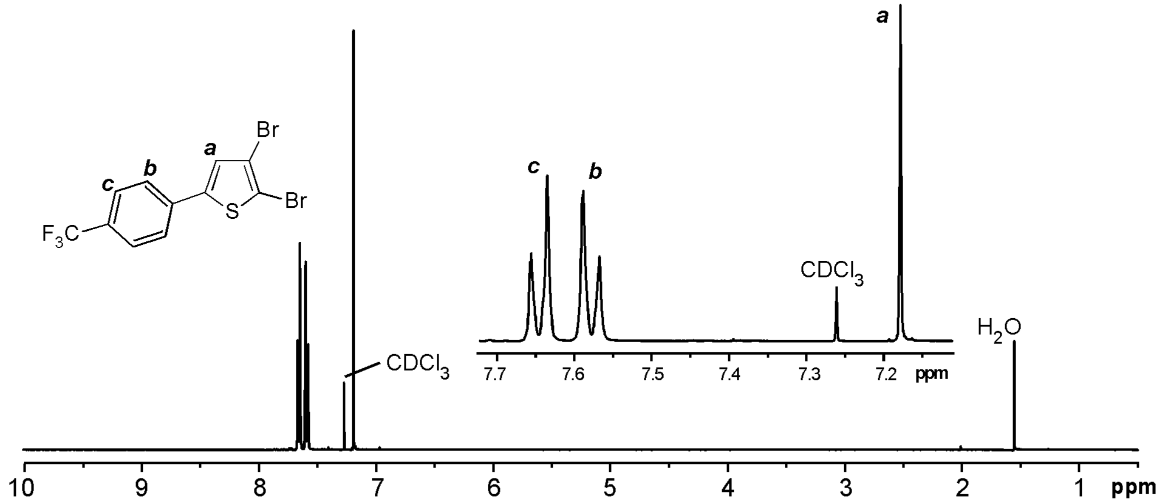


Figure S17. ^{1}H NMR spectrum of **12**

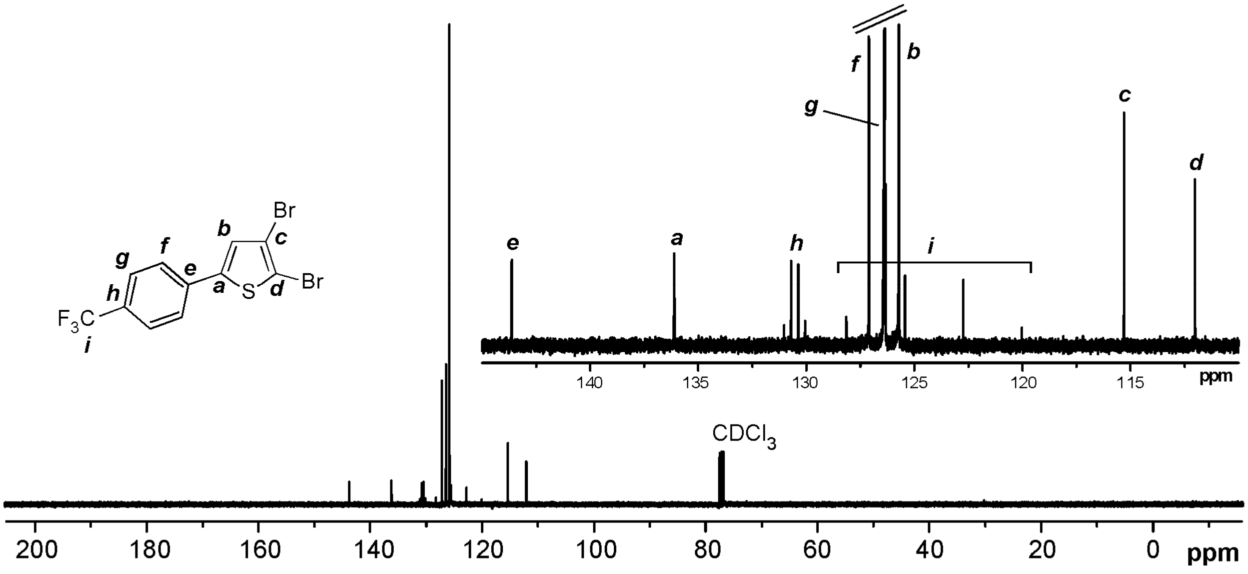


Figure S18. ^{13}C NMR spectrum of **12**

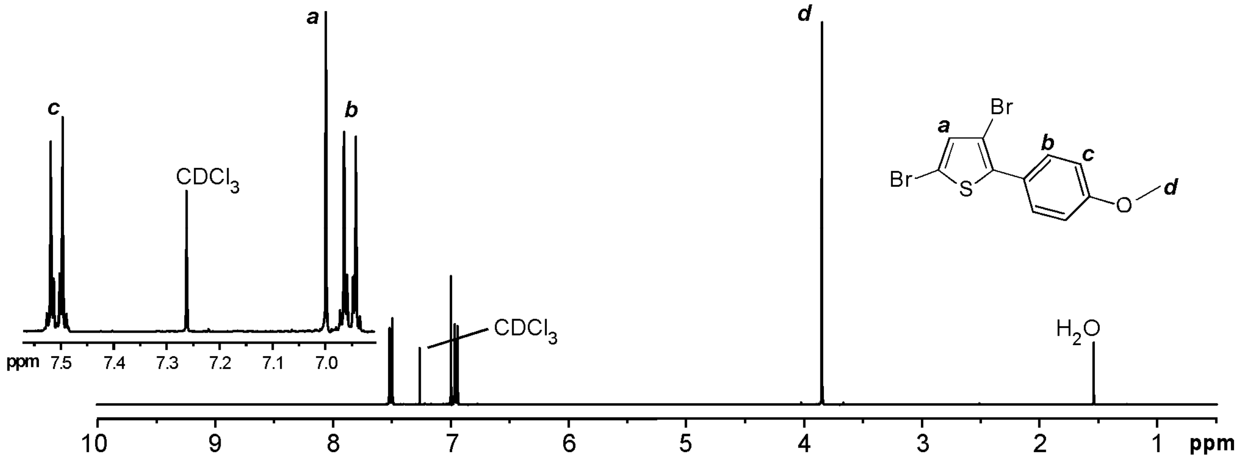


Figure S19. ^{1}H NMR spectrum of **14**

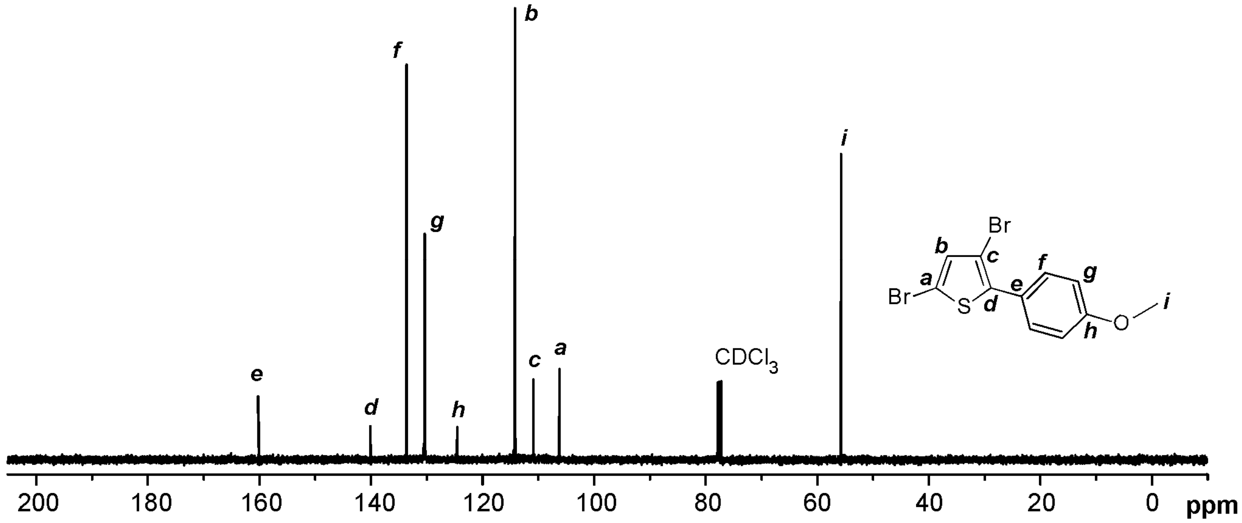


Figure S20. ^{13}C NMR spectrum of **14**

X-ray Crystallography. X-ray quality crystals of **2** were grown by the slow evaporation of acetonitrile solutions, respectively. The X-ray intensity data of the crystals were measured at 293 K on a Bruker SMART 1000 CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube (λ = 0.71073 Å) operated at 2000 W of power. The detector was placed at a distance of 5.047 cm from the crystal. Frames were collected with a scan width of 0.3° in ω and exposure time of 10 s/frame and then integrated with the Bruker SAINT software package using an arrow-frame integration algorithm. The unit cell was determined and refined by least-squares upon the refinement of *XYZ*-centeroids of reflections above $20\sigma(I)$. The structure was refined using the Bruker SHELXTL (Version 5.1) Software Package. The S2-C5-C6-C7-C8 ring is positionally disordered due to the free rotation along C4-C5 bond. The crystal data, data collection parameters, and refinement statistics are listed in Table S1. CCDC-667707 contains the full supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

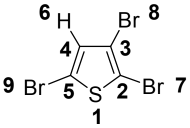
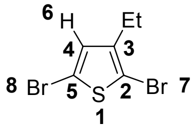
Table S1. Crystal data, collection parameters, and refinement statistics for 4,5-Dibromo-2,2'bithiophene (**2**).

	2
Formula	$C_8H_4Br_2S_2$
Formula Weight	324.05
Temperature (K)	293(2)
Crystal System	monoclinic
Space Group	P21/n
a (Å)	15.1471(2)
b (Å)	4.03870(10)
c (Å)	15.8942(2)
α (°)	90.00
β (°)	90.6440(10)
γ (°)	90.00
V (Å^3)	972.26(3)
Z	4
d_{calc} (g cm^{-3})	2.214
μ (mm^{-1})	8.705
Reflections collected	13061
Unique reflections	2124 [R_{int} = 0.0436]
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0369$ $wR_2 = 0.1023$
R indices (all data)[a]	$R_1 = 0.0492$ $wR_2 = 0.1113$
Goodness-of-fit on F^2	1.028

[a] $R_1 = \Sigma(\| F_o \| - |F_c \|) / \Sigma|F_o|$, $wR_2 = [\Sigma(w(F_o^2 - F_c^2)^2) / \Sigma(F_o^2)^2]^{1/2}$, Goodness-of-fit on $F^2 = [\Sigma(w(F_o^2 - F_c^2)^2 / (n-p)]^{1/2}$, where n is the number of reflections and p is the number of parameters refined.

Calculation of atomic charges in polybrominated thiophenes. Calculations were performed using the Gaussian 03 software package. Optimized geometries were calculated using DFT methods utilizing a 6-311G(d) basis set, the B3LYP correlation functional, and very tight SCF convergence criteria, followed by frequency calculations. Single point energy calculations were performed using the same methods as the geometry optimization. Mulliken atomic charges were used to determine charges on individual atoms.

Table S2. Mulliken atomic charges for 2,3,5-tribromo- and 2,5-dibromo-3-ethyl-thiophene

2,3,5-tribromothiophene:		**2,5-tribromo-3-ethylthiophene:**	
Atom	**Atomic Charge**	**Atom**	**Atomic Charge**
S1	0.393801	S1	0.376130
C2	-0.307744	C2	-0.336256
C3	-0.078000	C3	0.109859
C4	-0.104850	C4	-0.147974
C5	-0.319120	C5	-0.319058
H6	0.241608	H6	0.223218
Br7	0.081337	Br7	0.035121
Br8	0.032026	Br8	0.039930
Br9	0.060941	C9 (Et α-C)	-0.447989
		C10 (Et β-C)	-0.651380

2,3-Dibromo-5-(2-pyridyl)thiophene (15). To a 2-pyridyllithium[11] solution (6.0 mmol in 50 mL ether) at -60 ºC was added either anhydrous $ZnCl_2$ (0.81 g, 6.0 mmol) or $MgBr_2$ etherate (1.5 g, 6.0 mmol) and stirred for one hour with warming to room temperature. 2,3,5-Tribromothiophene (1.60 g, 5.0 mmol) and 0.10 g (2.5 mol%) Pd(dppf)Cl_2 were then added. The remaining reaction conditions and workup are as described in the general coupling description above. No reaction from pyridylzinc chloride; 6% from pyridylmagnesium bromide; mp 68.9-70.3 ºC; ^{1}H NMR: δ 8.57 (ddd, J = 4.8, 1.6, 1.2 Hz, 1H), 8.27 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 7.75 (dt, J = 7.6, 1.6 Hz, 1H), 7.23 (ddd, J = 7.6, 4.8, 1.6 Hz, 1H), 7.03 (s, 1H); ^{13}C NMR: δ 150.9, 149.8, 141.1, 136.8, 134.8, 123.0, 120.4, 115.6, 106.7.

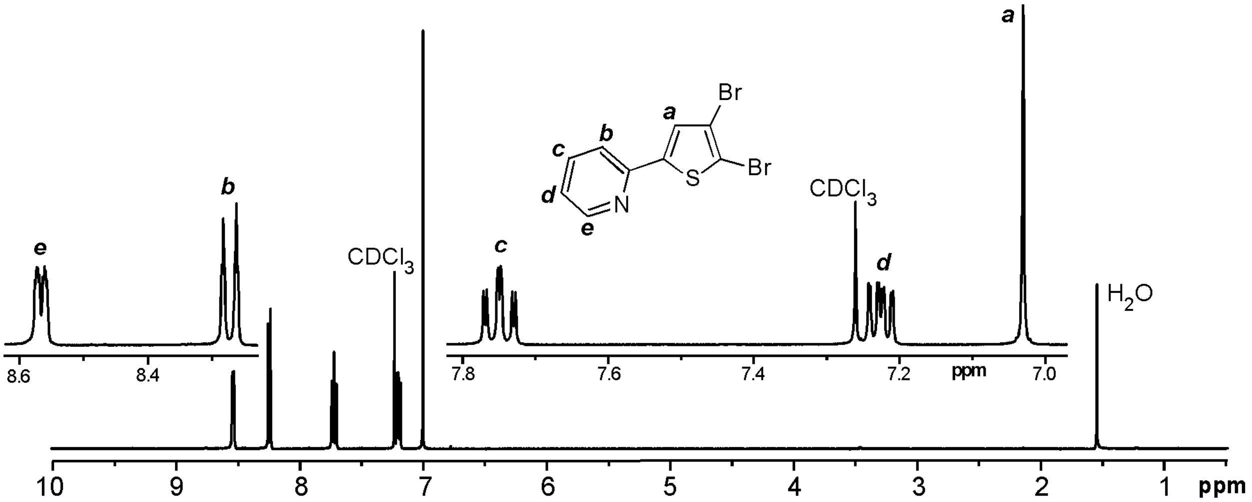


Figure S21. ^{1}H NMR spectrum of **15**

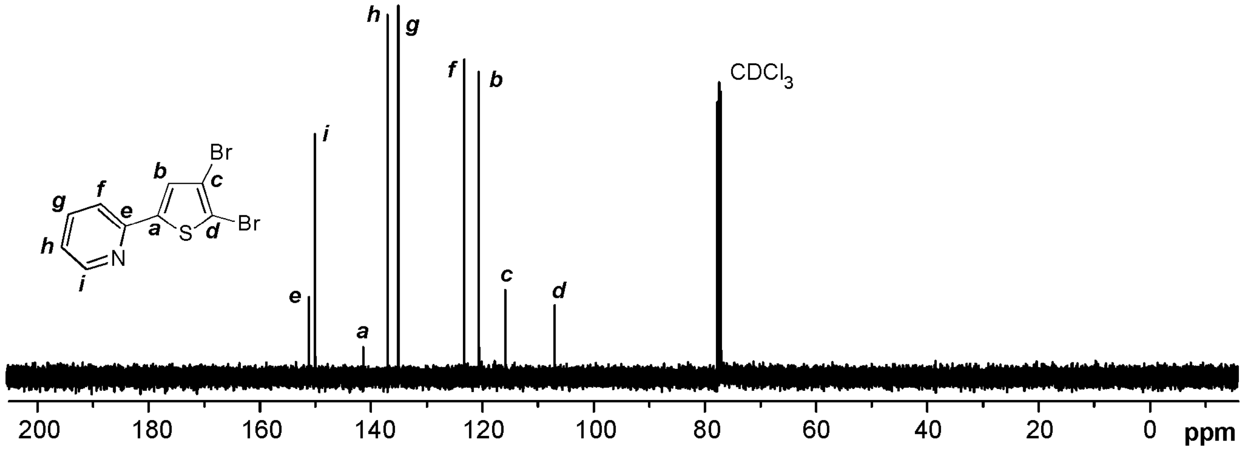


Figure S22. ^{13}C NMR spectrum of **15**

4’-Bromo-5-methyl-2,2’;5',2"-terthiophene (16). To a solution of 2-methyl-5-thienylmagnesium bromide (6.0 mmol, details above) in 50 mL ether was added bithiophene **4** (1.62 g, 5.0 mmol) and Pd(dppf)Cl$_2$ (0.1g, 2.5 mol %). This mixture was stirred 30 hours at room temperature, poured into sat. ammonium chloride, and extracted with ether (3 x 150 mL). The combined organic fractions were then dried over MgSO$_4$ and purified by silica gel chromatography to give 1.37 g (80%) of a yellow solid. mp 32.4-33.7 ºC; ^{1}H NMR: δ 7.25 (dd, J = 1.2 Hz, 5.2 Hz, 1H), 7.23 (dq, J = 3.6 Hz, 0.4 Hz, 1H), 7.17 (dd, J = 3.6, 1.2, 1H), 7.06 (s, 1H), 7.03 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 6.74 (dq, J = 3.6 Hz, 1.2 Hz, 1H), 2.52 (dd, J = 1.2 Hz, 0.4 Hz); ^{13}C NMR: δ 141.3, 136.0, 135.3, 132.0, 131.4, 125.2, 127.8, 126.9, 125.8, 125.4, 124.4, 107.3, 15.5.

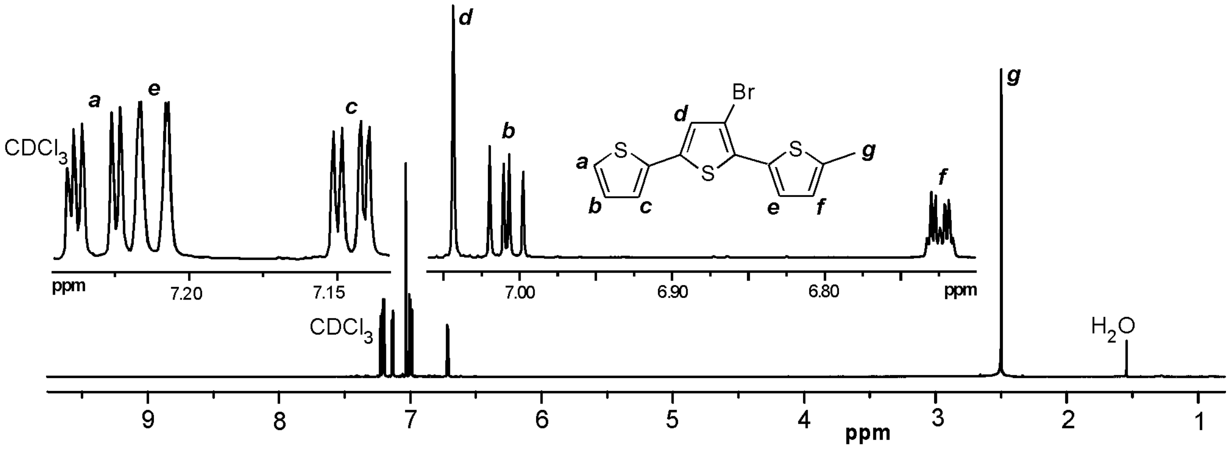


Figure S23. ^{1}H NMR spectrum of **16**

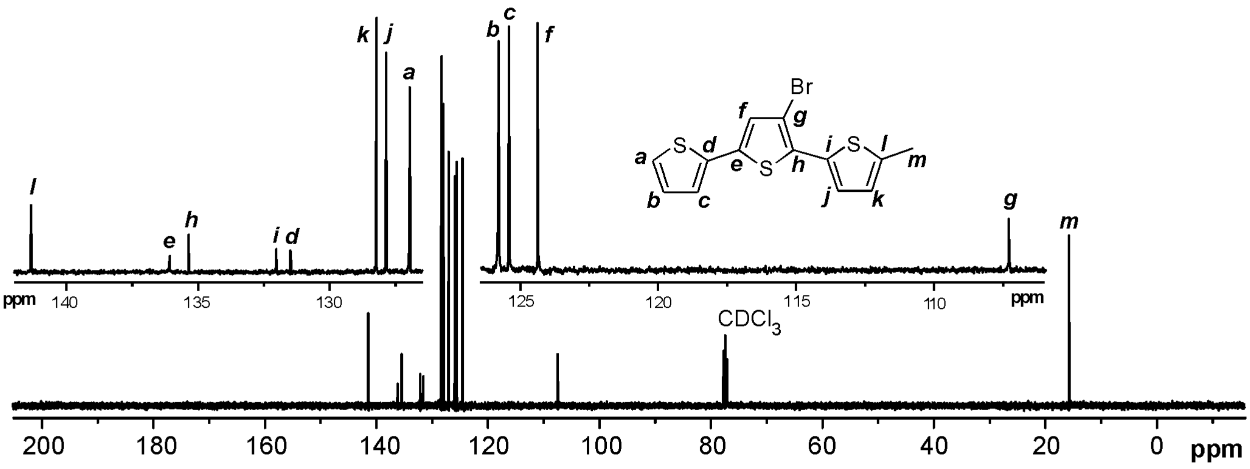


Figure S24. ^{13}C NMR spectrum of **16**

3’-(4-methoxyphenyl)-5-methyl-2,2’;5',2"-terthiophene (17). A 25 mL schlenk tube was charged with *p*-methoxyphenylboronic acid[12] (0.18 g, 1.2 mmol), **3** (0.34 g, 1.0 mmol), K_3PO_4-n$H_2$0 (0.636 g, ~3 mmol), Ni(dppp)Cl_2 (0.027g, 0.05 mmol), and triphenylphosphine (0.026 g, 0.10 mmol). The tube was then evacuated and backfilled with nitrogen three times, and 5.0 mL toluene was added. The mixture was stirred at 90 ºC for 18 hours. The mixture was poured into water, extracted with ether (3 x 75 mL), dried, and purified by silica gel chromatography (hexanes) to give 0.25 g (68%) of a yellow oil. ^{1}H NMR: δ 7.39 (d, *J* = 8.8 Hz, 2H), 7.24 (m, 2H), 7.16 (s, 1H), 7.06 (dd, *J* = 5.2 Hz, 4.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.87 (dd, *J* = 3.6, 0.4 Hz, 1H), 6.63 (dd, *J* = 3.6, 1.2 Hz, 1H), 3.88 (s, 3H), 2.45 (d, *J* = 1.2 Hz); ^{13}C NMR: δ 159.3, 140.6, 138.7, 137.2, 134.8, 133.7, 130.7, 130.6, 128.7, 128.1, 127.3, 126.5, 125.6, 124.7, 123.9, 114.1, 55.5, 15.5.

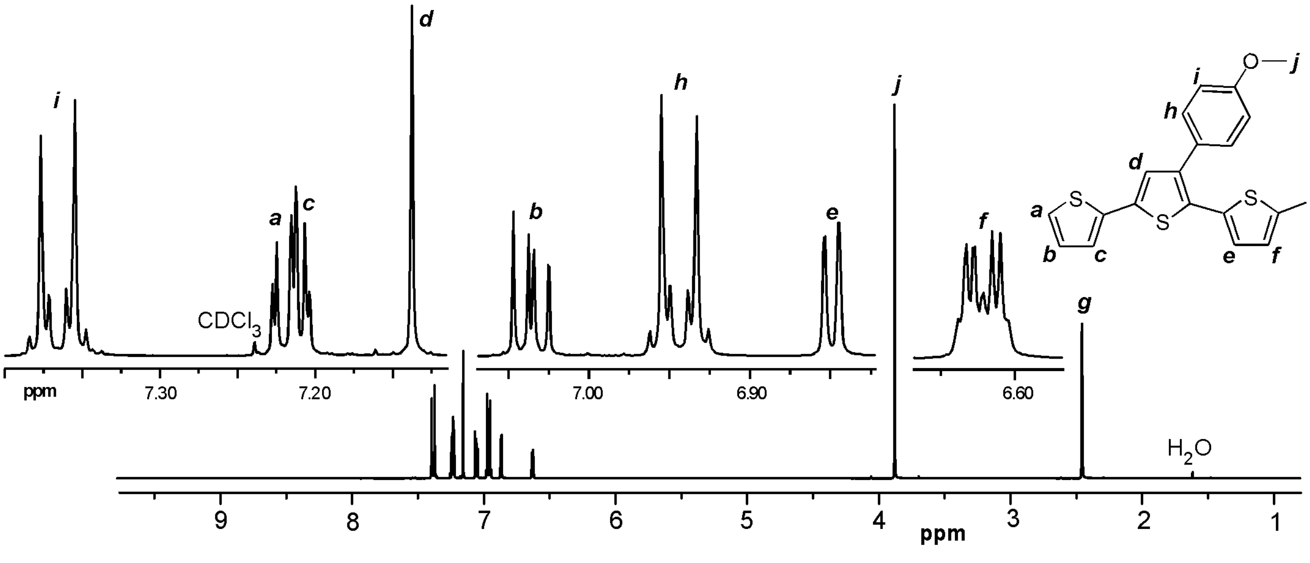


Figure S25. ^{1}H NMR spectrum of **17**

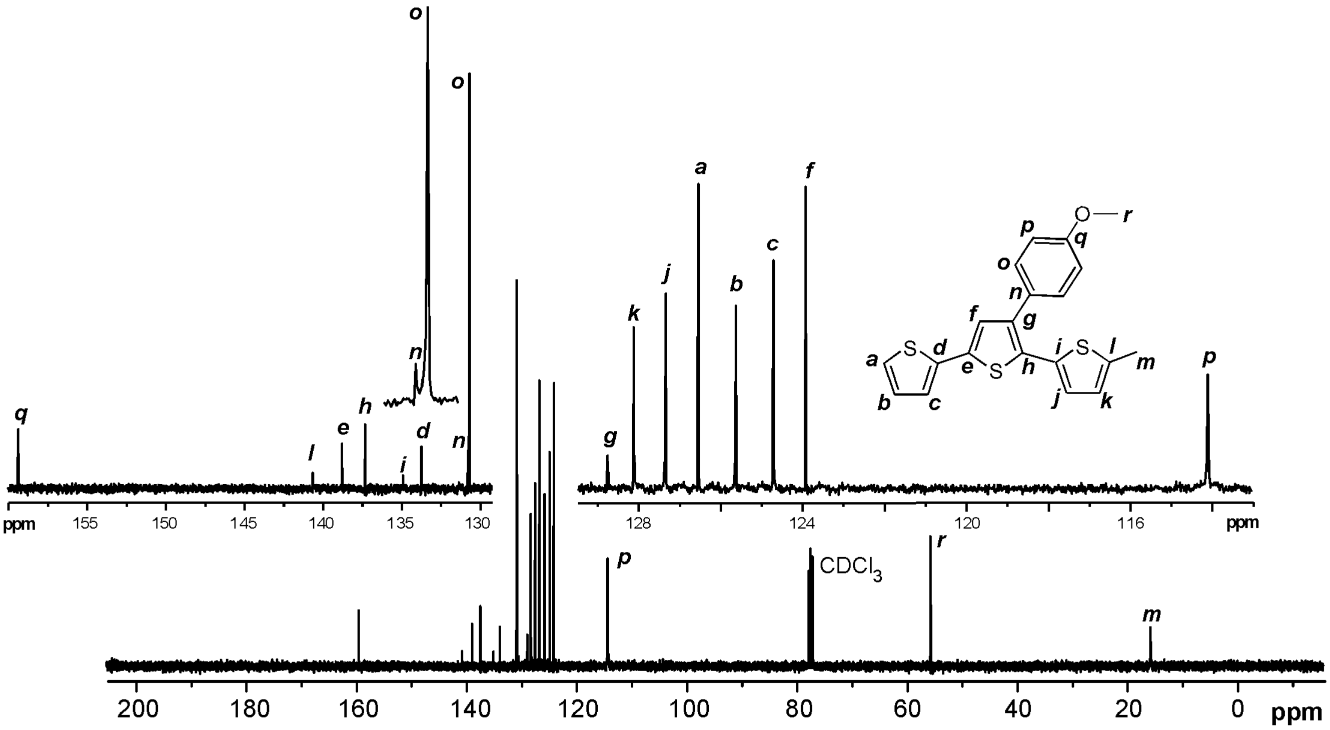


Figure S26. ^{13}C NMR spectrum of **17**

REFERENCES

1. Brandsma, L.; Verkruijsse, H. D. *Synth. Commun.* 1988, **18**, 1763.
2. Sheina, E. E.; Khersonsky, S. M.; Jones, E. G.; McCullough, R. D. *Chem. Mater.* **2005**, *17*, 3317.
3. Gestblom, B.; Mathiasson, B. *Acta Chem. Scan.* **1964**, *18*, 1905.
4. Collard, D. M.; Inaoka, S. *Langmuir* **1999**, *15*, 3752.
5. Carpita, A.; Rossi, R. *Gazz. Chim. Ital.* **1985**, *115*, 575.
6. Rasmussen, S. C.; Pickens, J. C.; Hutchison, J. E. *Chem. Mater.* **1998**, *10*, 1990.
7. Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930.
8. Sauter, F.; Frohlich, H.; Kalt, W. *Synthesis* **1989**, 771.
9. Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005,** *7*, 5083.
10. Clark, T. J.; Rodezno, J. M.; Clendenning, S. B.; Aouba, S.; Brodersen, P. M. Lough, A. J.; Ruda, H.E.; Manners, I. *Chem. Eur. J.* **2005**, *11*, 4526.
11. Uchida, Y.; Echikawa, N.; Oae, S. *Heteroatom. Chem.* **1994**, *5*, 409.
12. Steele, M.; Watkinson, M.; Whiting, A. J. Chem. Soc., Perkin Trans. 1, 2001, 588–598