2,6-Difunctionalization of N-Substituted Dithienothiazines via Dilithiation

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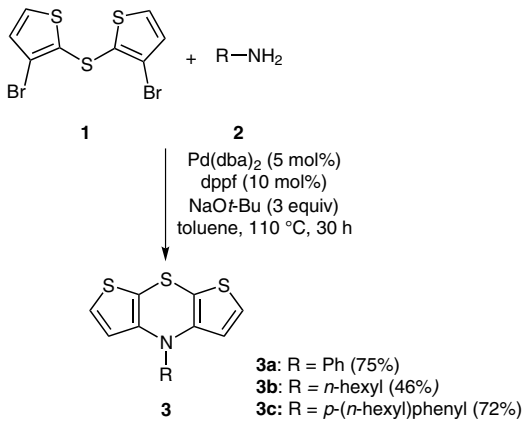
Abstract: The regioselective lithiation of dithienothiazines followed by electrophilic trapping in a one-pot fashion is an efficient route to 2-mono- and 2,6-difunctionalized dithienothiazines. A pseudo five-component dilithiation–diformylation–double-Wittig olefination sequence gives a dithienothiazine symmetrically functionalized with α,β-unsaturated ester side chains in excellent yield.

Key words: addition reactions, heterocycles, lithiation, multicomponent reactions, Wittig reactions

In recent years, interest in electroactive organic molecules has increased enormously because of their important technological applications, ranging from organic light-emitting diodes[1] through organic photovoltaic devices[2] to organic field-effect transistors.[3] The main advantages of using organic materials are their low production costs; their favorable properties, such as flexibility, transparency, and light weight; and their good processability.

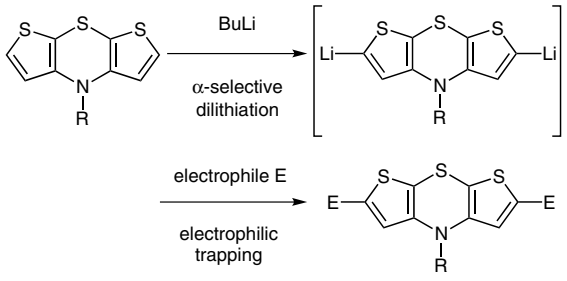
We recently described dithienothiazines as a new class of electron-rich heterocycles.[4] As a consequence of their unique electronic properties, which show two reversible oxidations with Nernstian behavior at low oxidation potentials, dithienothiazines are well suited, in principle, for use as hole conductors or as donor components in donor–acceptor compounds. Functionalization of the heterocyclic core of dithienothiazines represents a key step to achieving potential applications of these compounds, and is a major challenge. Most interestingly, annelation of thiophene offers an easy entry to typical thiophene transformations, such as lithiation in the α-position with respect to the sulfur atom;[5] furthermore, it is also amenable to sequential one-pot processing.[6] Here, we report a practical scale-up of the synthesis of three selected *N*-substituted dithienothiazines, together with the functionalization of this new class of electron-rich heterocycles through dilithiation and electrophilic trapping.

We examined the scale-up of the intermolecular/intramolecular Buchwald–Hartwig synthesis of 4-phenyl-4*H*-dithieno[2,3-*b*:3′,2′-*e*][1,4]thiazine (**3a**) from bis(3-bromo-2-thienyl) sulfide (**1**) and aniline (**2a**). Linear scale-up from 0.5 to 3 mmol was uneventful (Scheme 1). Furthermore, we were able to reduce the catalyst loading to 5 mol% and the ligand loading to 10 mol% without any decrease in yield. Besides aniline (**2a**), hexan-1-amine (**2b**) was successfully used as an amine component, albeit with a lower yield of the corresponding dithienothiazine **3b**. Nevertheless, the introduction of a solubilizing hexyl group is very attractive. Therefore, by combining a hexyl substituent with the higher yield of aniline derivatives, we successfully introduced a 4-hexylphenyl substituent in the dithienothiazine **3c**.



Scheme 1 Synthesis of selected dithienothiazines **3** by twofold Buchwald–Hartwig coupling

Next we tested several methods for functionalizing dithienothiazines by exploiting the inherent reactivity of thiophenes. However, attempted bromination with bromine or *N*-bromosuccinimide as brominating reagent[5a] to give 2,6-dibromodithienothiazines failed in a range of solvents and at various reaction temperatures. As a last resort, we attempted dual α-selective dilithiation, followed by dual electrophilic trapping (Scheme 2).



Scheme 2 General concept for functionalizing dithienothiazines by sequential dilithiation and electrophilic trapping in a one-pot reaction

On the basis of our previous findings on sequential desymmetrization by electrophilic trapping of various dili-

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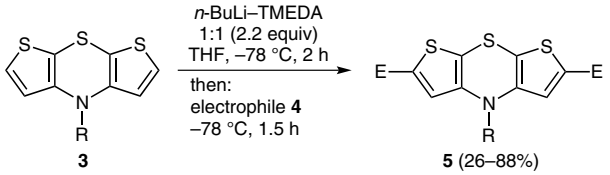
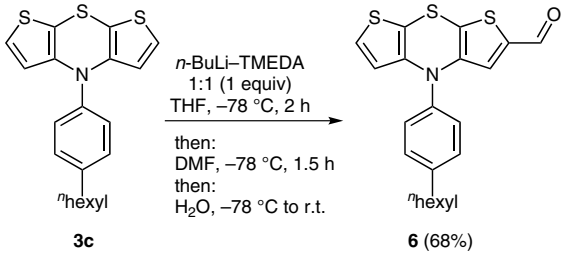
thiothiophenes, readily available by halogen–metal exchange,[6] we reasoned that dilithiation of dithienothiazines with butyllithium as a base might lead to a perfect entry to one-pot electrophilic trapping reactions.

Dithienothiazines **3** were deprotonated by inverse addition to two equivalents of butyllithium in dry tetrahydrofuran containing *N*,*N*,*N*′,*N*′-tetramethylethylenediamine at –78 °C under nitrogen to give the corresponding putative dilithio species, which were treated with two equivalents of a suitable electrophile **4** to give 2,6-disubstituted dithienothiazines **5** in moderate to good yields (Scheme 3 and Table 1). The structures of all the new compounds were unambiguously assigned by NMR, IR, and mass spectroscopy and by elemental analysis.



Scheme 3 Symmetrical functionalization of dithienothiazines **3** by sequential α-dilithiation and electrophilic trapping to give 2,6-disubstituted dithienothiazines **5**

Similarly, monolithiation was achieved by treating dithienothiazine **3c** with one equivalent of butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, with subsequent trapping by *N*,*N*-dimethylformamide. After aqueous workup, the monoaldehyde **6** was isolated in a good yield (Scheme 4).



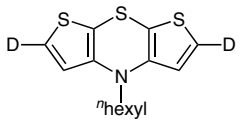
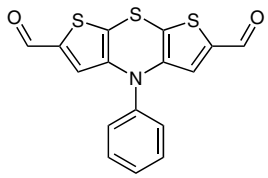
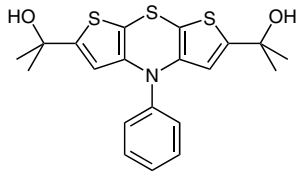
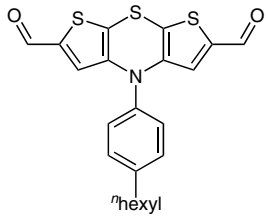
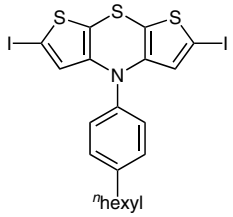
Scheme 4 Synthesis of 2-formyldithienothiazine **6**

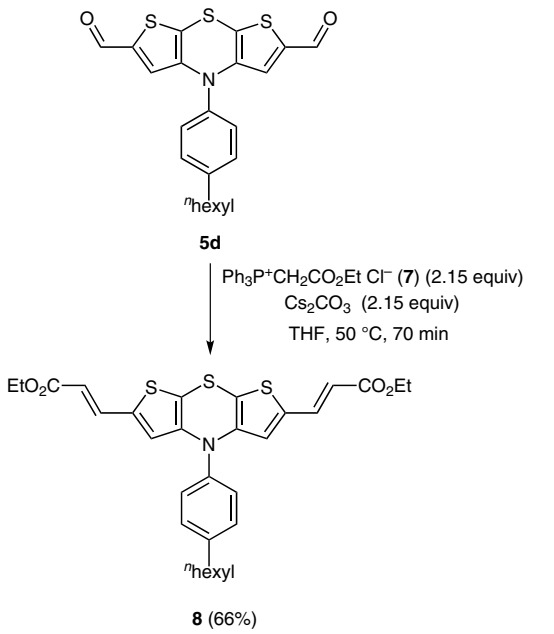
Further transformations of 2,6-diformyldithienothiazines are exemplified by a double-Wittig carbonyl olefination (Scheme 5). Wittig reaction of dialdehyde **5d** with (2-ethoxy-2-oxoethyl)(triphenyl)phosphonium chloride (**7**) in the presence of cesium carbonate as a base in tetrahydrofuran at 50 °C for 70 minutes gave the bis(α,β-unsaturated ester) **8** exclusively as the *E*,*E*-isomer in a yield of 66%.

Inspired by the successful conversion of dialdehyde **5d** by a double-Wittig olefination and by Schlosser's sequential *N*,*N*-dimethylformamide trapping of aryllithium derivatives and their subsequent olefination in a one-pot fashion,[7] we envisioned a novel pseudo five-component process starting from dithienothiazine **3c**. The one-pot reaction began with the dilithiation of **3c**, which was followed by trapping with *N*,*N*-dimethylformamide, treatment with water, and subsequent addition of the phosphonium salt **7** to give the double-olefination product **8** in 79% yield (Scheme 6). Most interestingly, no addition of base in the terminal olefination step was necessary, and the overall yield of the one-pot sequence was considerably higher than that of the stepwise process with intermediate isolation of the dialdehyde **5d**.

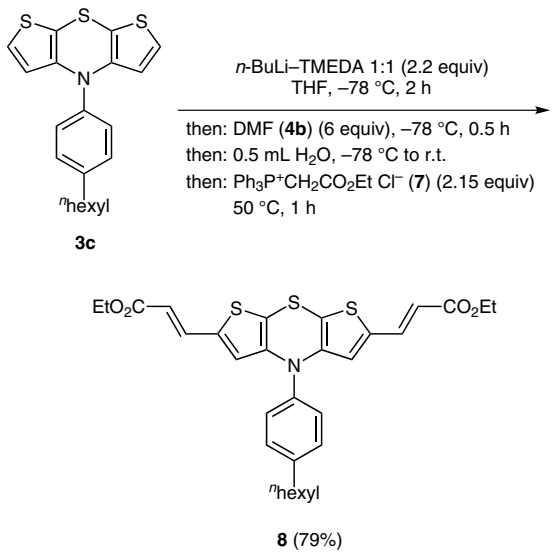
In conclusion, we have developed a straightforward and efficient one-pot route to 2-monofunctionalized and 2,6-difunctionalized dithienothiazines by site-selective lithiation of dithienothiazines followed by trapping with an electrophile. Synthetically valuable diiodides and dialdehydes might be obtained in moderate to very good yields by this method. Furthermore, the potential of one-pot

Table 1 Synthesis of 2,6-Disubstituted Dithienothiazines **5**

Entry	Electrophile	Product	Yield (%)
1	D_2O (**4a**)	 **5a**	63
2	DMF (**4b**)	 **5b**	66
3	acetone (**4c**)	 **5c**	26
4	DMF (**4b**)	 **5d**	88
5	I_2 (**4d**)	 **5e**	73



Scheme 5 Synthesis of the bis(α,β-unsaturated ester) **8**



Scheme 6 Pseudo five-component synthesis of the bis(α,β-unsaturated ester) **8** in a one-pot fashion

transformations through dilithiodithienothiazines was illustrated by an efficient pseudo five-component synthesis of a diacrylate derivative. Further studies directed towards dithienothiazines as substrates in cross-coupling reactions and investigations of the electronic properties of the derivatives are currently underway.

4-Phenyl-4*H*-dithieno[2,3-*b*:3′,2′-*e*][1,4]thiazine (3a); Typical Procedure

A screw-cap Schlenk vessel was charged with anhydrous toluene (15 mL) under N_2 then sulfide **1** (1.07 g, 3.00 mmol), $PhNH_2$ (**2a**; 321 mg, 3.45 mmol), bis(dibenzylideneacetone)palladium (5 mol%, 86 mg, 0.15 mmol), 1,1′-bis(diphenylphosphino)ferrocene (166 mg, 0.30 mmol), and *t*-BuONa (865 mg, 9.00 mmol) were successively added. The mixture was stirred in an oil bath at 100 °C for 40 h and then allowed to cool to r.t. When conversion was complete (TLC), H_2O (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was adsorbed on Celite and purified by chromatography (silica gel, 2.5% Et_3N–hexane) to give yellow crystals; yield: 673 mg (78%); mp 93 °C, R_f = 0.26. IR (ATR): 513 (m), 521 (w), 533 (w), 606 (m), 629 (m), 683 (s), 687 (s), 722 (m), 795 (m), 835 (m), 853 (m), 916 (w), 993 (s), 1007 (w), 1072 (w), 1098 (m), 1221 (m), 1275 (m), 1375 (m), 1398 (m), 1444 (w), 1487 (s), 1512 (m), 1555 (m), 2852 (w), 2924 (w), 3119 (w) cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ = 6.19 (d, *J* = 5.5 Hz, 2 H), 7.23 (d, *J* = 5.5 Hz, 2 H), 7.38–7.43 (m, 3 H), 7.53–7.57 (m, 2 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 104.9 (C_{quat}), 121.0 (CH), 125.0 (CH), 128.3 (CH), 128.7 (CH), 131.2 (CH), 144.9 (2 C_{quat}). MS (EI+, 70 eV), *m/z* (%) = 287 (6) [$C_{14}H_9NS_3$], 198 (30), 197 (16), 196 (100), 153 (13), 152 (23), 151 (10), 120 (14). UV/Vis (CH_2Cl_2): λ_{max} (ε) = 248 (19400), 319 nm (5650). Anal. Calcd for $C_{14}H_9NS_3$ (287.4): C, 58.50; H, 3.16; N, 4.87. Found: C, 58.55; H, 3.33; N, 4.59.

4-(4-Hexylphenyl)-4*H*-dithieno[2,3-*b*:3′,2′-*e*][1,4]thiazine-2,6-dicarbaldehyde (5d); Typical Procedure

In a flame-dried Schlenk flask, TMEDA (0.17 mL, 1.20 mmol) was dissolved in anhydrous THF (5 mL) under N_2. The solution was then cooled to –78 °C and BuLi (1.6 M in hexane; 0.72 mL, 1.2 mmol) was added. Dithienothiazine **3c** (186 mg, 0.50 mmol) was then added in portions and the solution was stirred at –78 °C for 2 h. DMF AcroSeal (0.1 mL, 1.3 mmol) was then added and stirring was continued for another 1.5 h. At –78 °C, the reaction was quenched with H_2O (25 mL) and the mixture was allowed to warm to r.t. The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was adsorbed on Celite and purified by chromatography [silica gel, hexane–EtOAc (20:1) + 2% Et_3N)] to give a dark-red viscous oil; yield: 188 mg (88%); R_f = 0.14. IR (ATR): 621 (w), 667 (m), 733 (w), 770 (w), 789 (w), 835 (m), 1007 (m), 1059 (m), 1115 (w), 1169 (s), 1198 (w), 1236 (m), 1275 (m), 1358 (s), 1389 (m), 1423 (w), 1508 (m), 1562 (m), 1655 (s), 2770 (w), 2816 (w), 2924 (w), 2953 (w) cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ = 0.90 (t, *J* = 7.0 Hz, 3 H), 1.29–1.45 (m, 6 H), 1.63–1.74 (m, 2 H), 2.69–2.78 (m, 2 H), 6.81 (s, 2 H), 7.37–7.58 (m, 4 H), 9.62 (s, 2 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 14.4 (CH_3), 23.3 (CH_2), 29.9 (CH_2), 32.3 (CH_2), 32.5 (CH_2), 36.3 (CH_2), 114.9 (C_{quat}), 126.8 (CH), 129.7 (CH), 131.9 (CH), 140.6 (C_{quat}), 141.8 (C_{quat}), 144.9 (C_{quat}), 145.0 (C_{quat}), 182.6 (CH). MS (EI+, 70 eV): *m/z* (%) = 429 (17), 428 (27), 427 (100) [M^+], 356 (20) [$C_{17}H_{10}NO_2S_3$], 266 (16) [$C_{10}H_4NO_2S_3$]. UV/Vis (CH_2Cl_2): λ_{max} (ε) 291 (40550), 448 (5050), 502 nm (5500). Anal. Calcd for $C_{22}H_{21}NO_2S_3$ (427.6): C, 61.79; H, 4.95; N, 3.28. Found: C, 61.90; H, 5.11; N, 3.51.

Pseudo Five-Component Synthesis of Diethyl (2*E*,2′*E*)-3,3′-[4-(4-Hexylphenyl)-4*H*-dithieno[2,3-*b*:3′,2′-*e*][1,4]thiazine-2,6-diyl]bisacrylate (8); Typical Procedure

TMEDA (0.17 mL, 1.20 mmol) was dissolved in anhydrous THF (5 mL) in a flame-dried Schlenk flask under N_2.The solution was then cooled to –78 °C and BuLi (1.6 M in hexane; 0.72 mL, 1.2 mmol was added, followed by portionwise addition of dithienothiazine **3c** (186 mg, 0.50 mmol). The solution was stirred at –78 °C for 2 h, DMF AcroSeal (0.1 mL, 1.3 mmol) was added, and stirring was continued at –78 °C for another 0.5 h. H_2O (0.5 mL) was then added and the mixture was allowed to warm to r.t. Phosphonium chloride **7** (231 mg, 0.6 mmol) was added at –78 °C and the temperature was raised to 50 °C for 1 h. The mixture was then cooled to r.t. and subjected to aqueous workup with brine and CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was adsorbed on Celite and purified by flash chromatography [silica gel, hexane–EtOAc (30:1 + 2% Et_3N) to give a dark-red viscous oil; yield: 225 mg (79%); R_f = 0.17. IR

(ATR): 619 (w), 640 (w), 669 (w), 721 (w), 758 (w), 820 (m), 851 (w), 962 (m), 1003 (w), 1034 (m), 1094 (m), 1152 (s), 1209 (w), 1260 (s), 1300 (m), 1364 (m), 1379 (w), 1427 (m), 1508 (m), 1524 (m), 1557 (w), 1614 (s), 1703 (m), 2855 (w), 2062 (w), 2955 (w), 2978 (w) cm^{-1}. ^1H NMR (600 MHz, acetone-d_6): δ = 0.90 (t, *J* = 7.0 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 6 H), 1.32–1.42 (m, 6 H), 1.65–1.71 (m, 2 H), 2.69–2.73 (m, 2 H), 4.14 (q, *J* = 7.1 Hz, 4 H), 6.02 (d, *J* = 15.6 Hz, 2 H), 6.43 (s, 2 H), 7.34–7.37 (m, 2 H), 7.41–7.44 (m, 2 H), 7.51 (d, *J* = 15.6 Hz, 2 H). ^{13}C NMR (150 MHz, acetone-d_6): δ = 14.4 (CH_3), 14.6 (CH_3), 23.3 (CH_2), 29.8 (CH_2), 32.2 (CH_2), 32.5 (CH_2), 36.3 (CH_2), 60.9 (CH_2), 106.9 (C_{quat}), 117.0 (CH), 123.2 (CH), 129.4 (2 CH), 131.5 (CH), 136.7 (2 C_{quat}), 137.9 (C_{quat}), 144.9 (C_{quat}), 166.6 (C_{quat}). MS (MALDI-TOF): *m/z* = 567.1 [M^+]. UV/Vis (CH_2Cl_2): λ_{max} (ε) 312 (38000), 492 nm (5450). Anal. Calcd for $C_{30}H_{33}NO_4S_3$ (567.8): C, 63.46; H, 5.86; N, 2.47; S 16.94. Found: C, 63.28; H, 6.14; N, 2.45; S, 16.83.

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References

(1) For excellent reviews, see for example: (a) Farinola, G. M.; Ragni, R. *Chem. Soc. Rev.* **2011**, *40*, 3467. (b) Hu, L.; Xu, G. *Chem. Soc. Rev.* **2010**, *39*, 3275. (c) Qian, G.; Zhong, Z.; Luo, M.; Yu, D.; Zhang, Z.; Wang, Z. Y.; Ma, D. *Adv. Mater. (Weinheim, Ger.)* **2009**, *21*, 111. (d) Shinar, J.; Shinar, R. *J. Phys. D: Appl. Phys.* **2008**, *41*, 133001. (e) Williams, J. A. G.; Wilkinson, A. J.; Whittle, V. L. *Dalton Trans.* **2008**, 2081. (f) *Organic Light Emitting Devices: Synthesis, Properties and Applications*; Müllen, K.; Scherf, U., Eds.; Wiley-VCH: Weinheim, **2006**. (g) Veinot, J. G. C.; Marks, T. J. *Acc. Chem. Res.* **2005**, *38*, 632. (h) Hughes, G.; Bryce, M. R. *J. Mater. Chem.* **2005**, *15*, 94. (i) Tang, C. W.; VanSlyke, S. A. *Appl. Phys. Lett.* **1987**, *51*, 913.

(2) For excellent reviews, see for example: (a) Huang, X.; Han, S.; Huang, W.; Liu, X. *Chem. Soc. Rev.* **2013**, *42*, 173. (b) Liang, M.; Chen, J. *Chem. Soc. Rev.* **2013**, *42*, 3453. (c) Schlenker, C. W.; Thompson, M. E. *Chem. Commun.* **2011**, *47*, 3702. (d) Delgado, J. L.; Bouit, P.-A.; Filippone, S.; Herranz, M. A.; Martin, N. *Chem. Commun.* **2010**, *46*, 4853. (e) Mishra, A.; Fischer, M. K. R.; Bäuerle, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 2474. (f) Cheng, Y.-J.; Yang, S.-H.; Hsu, C.-S. *Chem. Rev.* **2009**, *109*, 5868. (g) Thompson, B. C.; Fréchet, J. M. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 58. (h) Günes, S.; Neugebauer, H.; Sariciftci, N. S. *Chem. Rev.* **2007**, *107*, 1324. (i) *Organic Photovoltaics: Concept and Realization*; Brabec, C. J.; Dyakonov, V.; Parisi, J.; Sariciftci, N. S., Eds.; Springer: Berlin, **2003**. (j) Peumans, P.; Yakimov, A.; Forrest, S. R. *J. Appl. Phys.* **2003**, *93*, 3693.

(3) For excellent reviews, see for example: (a) Wu, W.; Liu, Y.; Zhu, D. *Chem. Soc. Rev.* **2010**, *39*, 1489. (b) Klauk, H. *Chem. Soc. Rev.* **2010**, *39*, 2643. (c) Dong, H.; Wang, C.; Hu, W. *Chem. Commun.* **2010**, *46*, 5211. (d) Anthony, J. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 452. (e) Briseno, A. L.; Mannsfeld, S. C. B.; Jenekhe, S. A.; Bao, Z.; Xia, Y. *Mater. Today* **2008**, *11*, 38. (f) Facchetti, A. *Mater. Today* **2007**, *10*, 28. (g) Murphy, A. R.; Fréchet, J. M. J. *Chem. Rev.* **2007**, *107*, 1066. (h) Mas-Torrent, M.; Rovira, C. *Chem. Soc. Rev.* **2008**, *37*, 827. (i) Mas-Torrent, M.; Rovira, C. *J. Mater. Chem.* **2006**, *16*, 433. (j) Sun, Y.; Liu, Y.; Zhu, D. *J. Mater. Chem.* **2005**, *15*, 53. (k) Dimitrakopoulos, C. D.; Malenfant, P. R. L. *Adv. Mater. (Weinheim, Ger.)* **2002**, *14*, 100. (l) Horowitz, G. *Adv. Mater. (Weinheim, Ger.)* **1998**, *10*, 365.

(4) Dostert, C.; Wanstrath, C.; Frank, W.; Müller, T. J. J. *Chem. Commun.* **2012**, *48*, 7271.

(5) (a) Gronowitz, S.; Hörnfeldt, A.-B. *Thiophenes: Best Synthetic Methods*; Elsevier: Oxford, **2004**. (b) Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887. (c) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, **1974**. (d) Mallan, J. M.; Bebb, R. L. *Chem. Rev.* **1969**, *69*, 693. (e) Gilman, H.; Shirley, D. *J. Am. Chem. Soc.* **1949**, *71*, 1870.

(6) (a) Muschelknautz, C.; Dostert, C.; Müller, T. J. J. *Synlett* **2010**, 415. (b) Shu, W.; Pellegatti, L.; Oberli, M. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 10665.

(7) Wang, Q.; Wei, H.; Schlosser, M. *Eur. J. Org. Chem.* **1999**, 3263.

