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A Palladium-Catalyzed Approach to Polycyclic Sulfur Heterocycles

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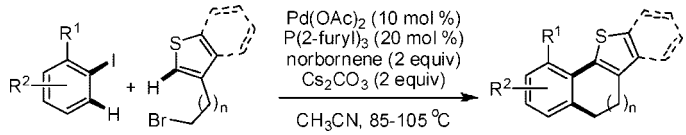

The synthesis of a variety of polycyclic thiophenes and benzothiophenes is accomplished via a palladium-catalyzed domino *ortho*-alkylation/direct arylation reaction. An examination of the intramolecular direct arylation of thiophenes suggests that an electrophilic metalation mechanism may be present. This method was further extended to include the synthesis of a (thieno)benzoxepine.

Introduction

Polycyclic thiophene-based heterocycles are key intermediates and relevant targets in the fields of synthetic, medicinal, and materials chemistry. Recently, numerous thiophenes and benzothiophenes have emerged as classes of molecules with synthetic utility[1] and a wide array of biological activities.[2] As such, an efficient and expedient method to synthesize a wide variety of this class of molecules would be highly desirable. Although numerous methods have been devised to generate these heterocycles, there are seldom, if any general, catalytic methods for their synthesis. With this in mind, we endeavored to extend the *ortho*-alkylation/C−C coupling methodology developed in our laboratories[3] to the synthesis of annulated polycyclic thiophene-based heterocycles. By combining the strategies of palladium-catalyzed aromatic *ortho*-alkylation derived from the Catellani reaction[4] with the direct arylation[5] of thiophene-based heterocycles,[6] we foresaw a method to generate polycyclic thiophenes from aryl iodides and 3-(bromoalkyl)thiophenes (Scheme 1).[7]

Results and Discussion

Thiophene-Based Heterocycles. In order to enable expedient access to polycyclic thiophenes, the bromoalkylthiophene component must be accessible through simple, straightforward chemistry (Scheme 2). From commercially available 3-formylthiophene, 3-(3-bromopropyl)thiophene **2a** is easily accessed through a Wittig/reduction/hydrogenation/bromination reaction sequence. Alternatively, (2*E*)-3-(3-thienyl)acrylic acid can be used as a precursor to **2a** to avoid the Wittig olefination step, although this route is much less cost-effective. To access **2b**, commercially available 2-(3-thienyl)ethanol is converted to the alkyl bromide with PBr_3. The aforementioned methods worked

(1) Carpino recently reported a polycyclic thiophene as an easily cleaved protecting group for amino acids; see: Carpino, L. A.; Abdel-Maksoud, A. A.; Ionescu, D.; Mansour, E. M. E.; Zewail, M. A. *J. Org. Chem.* **2007**, *72*, 1729–1736.

(2) As retinoic acid receptor antagonists for the treatment of leukemia and related carcinoma, see: (a) Yoshimura, H.; Nagai, M.; Hibi, S.; Kikuchi, K.; Abe, S.; Hida, T.; Higashi, S.; Hishinuma, I.; Yamanaka, T. *J. Med. Chem.* **1995**, *38*, 3163–3173. As PTP 1B modulators for antiobesity/antidiabetic treatments see: (b) Lee, J. et al. US2006135488. As DNA Topoisomerase II inhibitors in multidrug-resistant cells, see: (c) Zhu, H.; et al. *Mol. Cancer Therapeut.* **2007**, *6*, 484–495. As an intercalating agent and displaying cytotoxicity toward human lung carcinoma cells, see: (d) Xu, Y.; Qu, B.; Qian, X.; Li, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1139–1142.

(3) Selected examples: (a) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149. (b) Blaszykowski, C.; Aktoudianakis, V.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043–2045. (c) Jafarpour, F.; Lautens, M. *Org. Lett.* **2006**, *8*, 3601–3604. (d) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 1888–1897.

(4) (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119–122. (b) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336–4346. (c) Catellani, M. *Synlett* **2003**, 298–313.

(5) Selected reviews: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253–1264. (c) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55–83. (d) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625–655. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1769. (f) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834. (g) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469. (h) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (i) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698–1712.

(6) Selected examples: (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951–1958. (b) Gozzi, C.; Lavenot, L.; Ilg, K.; Penalva, V.; Lemaire, M. *Tetrahedron Lett.* **1997**, *38*, 8867–8870. (c) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473. (d) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677–1680. (e) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301–304.

(7) Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827–4829.

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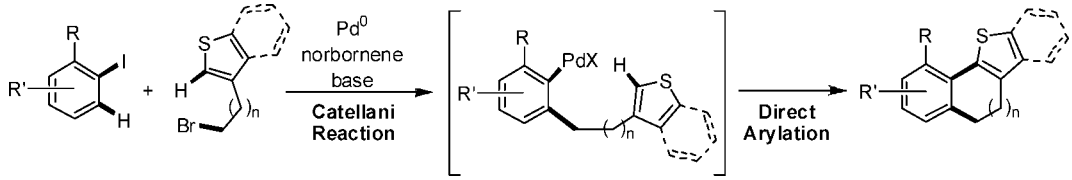
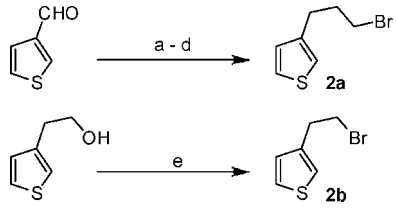
SCHEME 1. Our Approach toward Polycyclic Sulfur Heterocycles



SCHEME 2. Synthesis of 3-(Bromoalkyl)thiophenes[a]



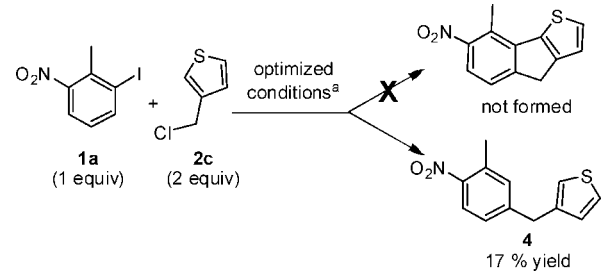
[a] Key: (a) $Ph_3P{=}CHCO_2Me$ (1.5 equiv), CH_2Cl_2, 84%; (b) $LiAlH_4$ (2 equiv), THF; (c) H_2, Pd/C, EtOH, 64% (two steps); (d) PPh_3 (1.1 equiv), Br_2 (1.1 equiv), CH_2Cl_2, 82%; (e) PBr_3 (1 equiv), benzene, 45%.

quite well on large scale, enabling access to gram-scale quantities of **2a** and **2b**.

With compounds **2a** and **2b** readily available, we sought to develop reaction conditions for the domino palladium-catalyzed *ortho*-alkylation/direct arylation sequence. Through the screening of reaction parameters such as palladium source, phosphines, solvents, bases, and concentration of each reagent, we arrived at the optimized reaction conditions shown in Table 1. From these optimized conditions, we were able to synthesize a variety of polycyclic thiophenes with central seven- and six-membered rings from aryl iodides which contained a pre-existing *ortho* functional group. A variety of *ortho* functional groups were tested under the reaction conditions; however, with only one exception (vide infra), a methyl group was the only *ortho* substitutent which could afford acceptable amounts of product. In addition, the electronic character of the aryl iodide was important to the success of the reaction, as only electron-deficient aryl iodides afforded acceptable amounts of product (Table 1, entries 1−14). When we tried to extend the scope to electroneutral or electron-rich aryl iodides, little to no desired product was formed. Although all aryl iodides containing solely electron-donating substituents afforded no desired product, when the aryl iodide contained both strongly electron-donating and electron-withdrawing substituents such as **1l**, the desired product **3o** was obtained. This product was crystalline and confirmed the structure of the products via X-ray crystallography.[7,8] We attempted to improve the yield with electroneutral aryl iodides such as 2-iodotoluene (**1m**) by screening a wide variety of conditions, including the use of additives such as silver salts to promote the direct arylation reaction. However, after screening, we were only able to isolate **3p** in 22% optimized isolated yield using microwave irradiation.

The success in synthesizing a variety of annulated six- and seven-membered rings prompted us to explore the analogous coupling to form five-membered rings. While benzylic bromides often give messy reaction mixtures under our reaction conditions, our recent success in the coupling of benzyl chlorides[9] led us to try 3-(chloromethyl)thiophene (**2c**) as a coupling partner (Scheme 3). Although we screened a variety of conditions for this reaction, we were not able to obtain the annulated product, but instead only observed **4**, the product of *ortho*-alkylation followed by arylpalladium(II) reduction.[10]

SCHEME 3. Attempt To Form a Five-Membered Ring Product



[a] See Table 1.

Our insight into the importance of the electronic character of the aryl iodide to product formation prompted us to study this effect on the direct arylation itself. While both electron-rich and electron-deficient aryl iodides have been effectively employed in numerous *ortho*-alkylation/coupling processes,[3] we proposed that the dramatic dependence of the isolated yield on electronic character relates specifically to the direct arylation step. In order to gain further insight, we synthesized several molecules of varying electronic character with a thiophene tethered to a pendant aryl iodide (Scheme 4, **5a**−**c**). We performed these experiments with two goals in mind: to gain further insight into the mechanism of the direct arylation reaction and to examine if our reaction conditions (i.e., the conditions above including norbornene, in the presence of an alkyl halide) enhance or hinder the terminal direct arylation reaction. Under our optimized conditions in the absence of norbornene, **5a**−**c** were reacted to form the corresponding annulated products **6a**−**c**. The conversion of nitro-substituted **5a** to **6a** occurred in 87% isolated yield, which is comparable to the yields obtained using nitro substituted aryl iodides. When we tried electroneutral compound **5b**, the yield of **6b** was an unexpectedly high 81%, recalling that in the domino reaction, a maximum yield of 22% was obtained with 2-iodotoluene. Furthermore, electron-deficient thiophene-containing compound **5c** only afforded product **6c** in 32% yield.

In terms of mechanistic insight into the intramolecular direct arylation of thiophenes, we initially proposed an electrophilic metalation mechanism[7,11] based upon the good yields of product with electron-deficient aryl iodides and lack of product with electron-rich ones. Our data from Scheme 4 suggest that the product yield is not directly proportional to the electron-richness

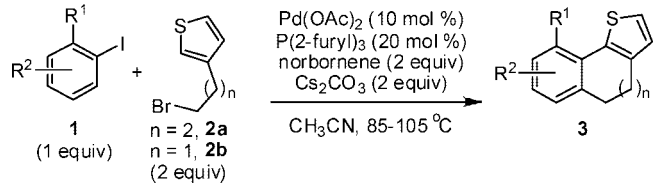
(8) The crystallographic information file (CIF) for this compound can also be found on the Cambridge Crystallographic Data Centre database (data_request@ccdc.cam.ac.uk) as CCDC 614852.

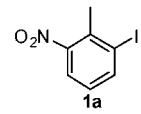
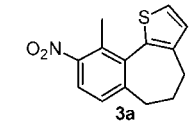
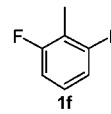
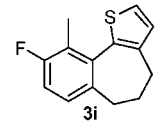
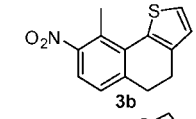
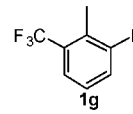
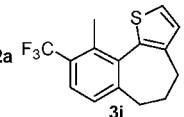
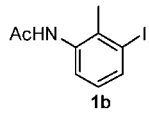
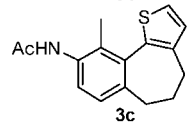
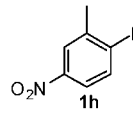
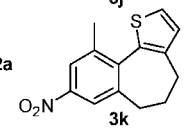
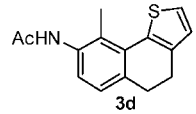
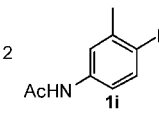
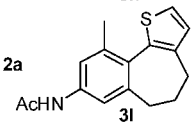
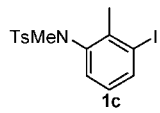
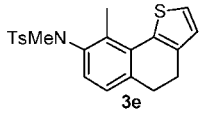
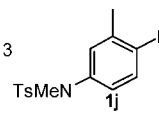
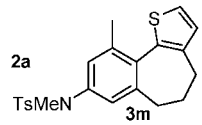
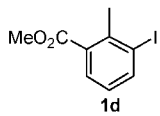
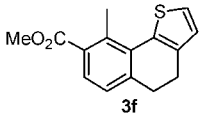
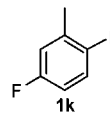
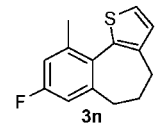
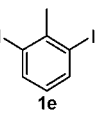
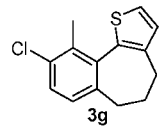
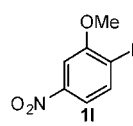
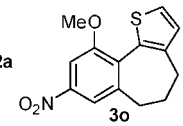
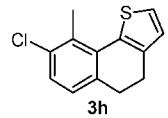
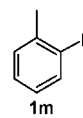
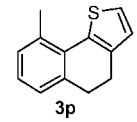
(9) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372–15379.

(10) Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053–4056.

(11) (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057. (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159–1162. (c) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835–4837.

TABLE 1. Domino *ortho*-Alkylation/Direct Arylation of Thiophenes[a]



Entry	1	2	product	yield (%)	Entry	1	2	product	yield (%)
1	 **1a**	**2a**	 **3a**	89	9	 **1f**	**2a**	 **3i**	69
2	**1a**	**2b**	 **3b**	73	10	 **1g**	**2a**	 **3j**	48
3	 **1b**	**2a**	 **3c**	76	11	 **1h**	**2a**	 **3k**	87
4	**1b**	**2b**	 **3d**	82	12	 **1i**	**2a**	 **3l**	39
5	 **1c**	**2b**	 **3e**	66	13	 **1j**	**2a**	 **3m**	56
6	 **1d**	**2b**	 **3f**	71	14	 **1k**	**2a**	 **3n**	32
7	 **1e**	**2a**	 **3g**	57	15	 **1l**	**2a**	 **3o**	52
8	**1e**	**2b**	 **3h**	77	16	 **1m**	**2b**	 **3p**	22[a]

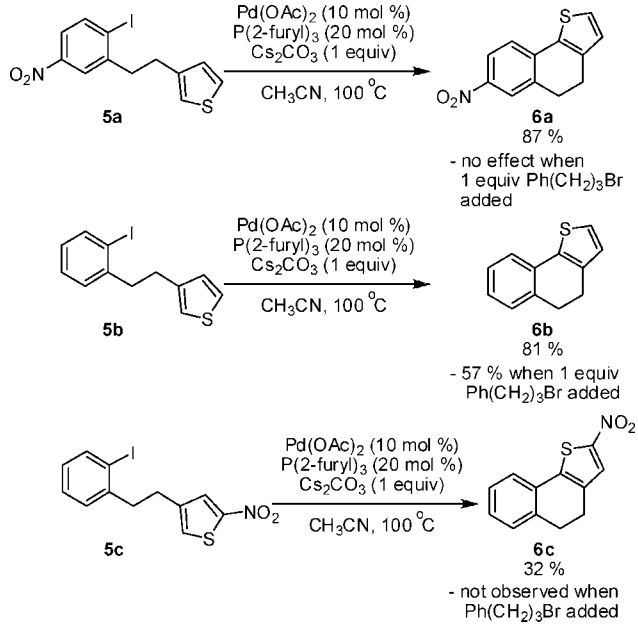
[a] μwave, 150 °C, 30 min.

of the aryl iodide. In addition, the electron-deficient thiophene **5c** which would react poorly as a nucleophile (in an electrophilic metalation reaction) but would react well via a Heck-type mechanism[6e] (due to lowering of the LUMO energy by the presence of an electron-withdrawing group) fared poorly, suggesting an electrophilic mechanism. We were unable to obtain conclusive rate data on the annulation reactions; however, we can say that the conversion of **5a** to **6a** was complete within 4 h, the conversion of **5b** to **6b** was complete within 10 h, and the conversion of **5c** to **6c** was complete within 18 h, suggesting that an electrophilic mechanism is still a possibility for the direct arylation reaction.

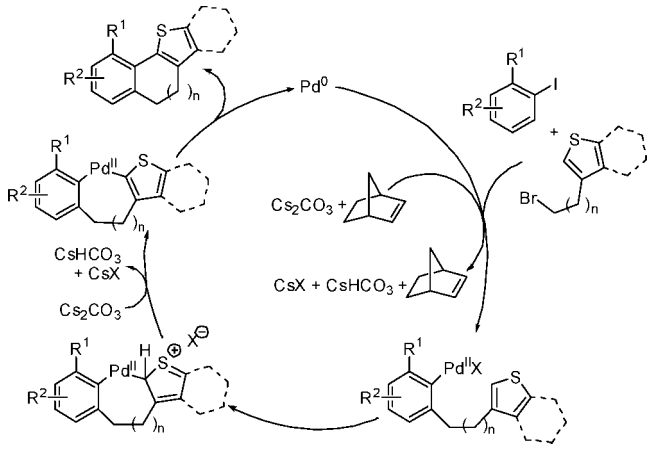
Our next goal was to determine whether the reaction conditions of the domino reaction enhance or hinder the yield of the direct arylation reaction. As the domino reaction is performed in the presence of norbornene and excess 3-(bromoalkyl)thiophene, we decided to mimic the reaction conditions after *ortho*-alkylation to observe the effect on the direct arylation. As the presence of norbornene would initiate palladacycle formation (which is not possible in the domino reaction due to the presence of a pre-existing *ortho* substitutent) it was omitted from the reaction. To approximate the additional 1 equiv of 3-(bromoalkyl)thiophene, we chose 1-bromo-3-phenylpropane, which does not undergo direct arylation reactions under the reaction conditions. When this reagent was added to the reactions converting **5a**−**c** to **6a**−**c**, the yield of **6a** was unchanged, **6b** was dramatically reduced to 57%, and **6c** was not observed. These results suggest that the presence of alkyl halides initiates an unproductive reaction pathway, which is competitive with the direct arylation reaction for the slower-reacting substrates **5b** and **5c**.

As the data obtained in Scheme 4 demonstrated that an electron-deficient thiophene is a poor substrate for the reaction, we supposed that an electron-rich thiophene would be a suitable

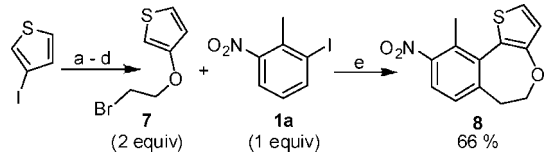
SCHEME 4. Intramolecular Direct Arylation of Thiophenes



SCHEME 5. Possible Electrophilic Mechanism for Direct Arylation



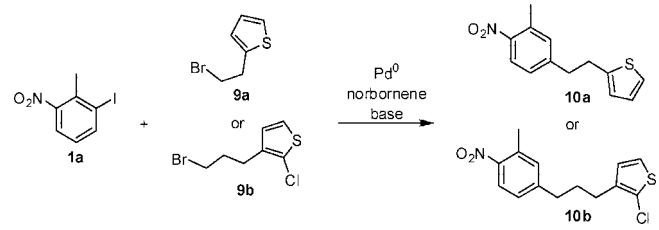
SCHEME 6. Access to (Thieno)benzoxepine[a]



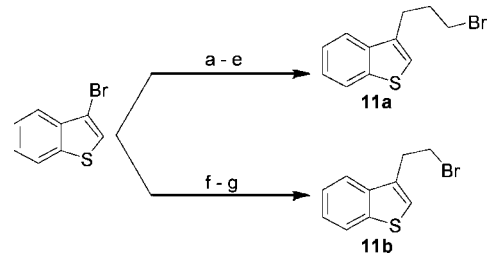
[a] Key: (a) glyoxaldehyde dimethyl acetal (2 equiv), CuI (10 mol %), 1,10-phenanthroline (20 mol %), Cs_2CO_3 (2 equiv), toluene, 110 °C, 88−91%; (b) HCl/acetone, then (c) $NaBH_4$, MeOH, 24% (two steps); (d) PPh_3 (1.1 equiv), Br_2 (1.05 equiv), CH_2Cl_2, 54%; (e) $Pd(OAc)_2$ (10 mol %), P(2-furyl)$_3$ (20 mol %), norbornene (2 equiv), Cs_2CO_3 (2 equiv), CH_3CN, 95 °C, 66%.

substrate, prompting us to synthesize compound **7**. This compound was accessible via the CuI-catalyzed coupling of aryl iodides with aliphatic alcohols developed by Buchwald[12] and subsequent synthetic transformations listed in Scheme 6. When compound **7** was subjected to the optimized reaction conditions in the presence of **1a**, the (thieno)benzoxepine product **8** was

SCHEME 7. Attempts To Cyclize onto the 3-Position of Thiophene



SCHEME 8. Synthesis of 3-(Bromoalkyl)benzothiophenes[a]



[a] Key: (a) *n*-BuLi (1 equiv), Et_2O, −78 °C, then DMF (1.5 equiv), 87%; (b) $Ph_3P{=}CHCO_2Me$ (1.5 equiv), CH_2Cl_2, 82%; (c) H_2, Pd/C, EtOAc, 96%; (d) $LiAlH_4$ (2 equiv), THF, 83%; (e) PPH_3 (1.1 equiv), Br_2 (1.1 equiv), CH_2Cl_2, 83%; (f) *n*-BuLi (1.1 equiv), Et_2O, −78 °C, then ethylene oxide (excess), 39%; (g) PPh_3 (1.05 equiv), Br_2 (1.05 equiv), CH_2Cl_2, 79%.

obtained in 66% yield. This result demonstrates the utility and potential of the domino reaction to generate an interesting class of heterocyclic compounds.

Our success in developing an efficient domino *ortho*-alkylation/direct arylation at the 2-position of thiophene prompted us to explore the analogous terminal coupling at the 3-position of thiophene. While intramolecular cyclizations upon the 3-position of thiophene have been reported,[13] they typically employ the use of Ag_2CO_3 to generate cationic palladium(II) species to promote the cyclization. We synthesized **9a** and **9b** and subjected them to the optimized reaction conditions and a variety of other conditions (including variation of solvent, temperature, conventional versus microwave heating, and using Ag_2CO_3 as base) in the presence of **1a** (Scheme 7). We were only able to obtain traces of impure product, with varying amounts of the *ortho*-alkylation/reduction products **10a** and **10b**.

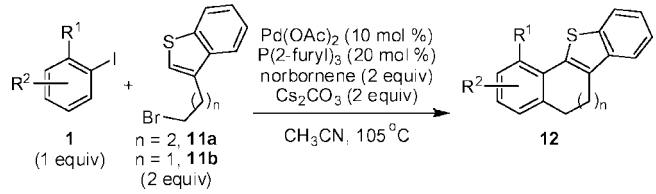
Benzothiophene-Based Heterocycles. Our study of the *ortho*-alkylation/direct arylation of thiophenes led us to also study 3-(bromoalkyl)benzothiophenes as bifunctional substrates. Both 3-(bromopropyl)benzothiophene **11a** and 2-(bromoethyl)benzothiophene **11b** are accessible from commercially available 3-bromobenzothiophene (Scheme 8). The synthetic route toward **11a** involves lithium−halogen exchange of 3-bromobenzothiophene, followed by formylation, Wittig olefination, hydrogenation, reduction, and bromination. Compound **11b** is accessible via lithium−halogen exchange followed by addition to ethylene oxide and bromination. As with the synthetic routes toward **2a** and **2b**, gram-scale quantities of these compounds were accessible.

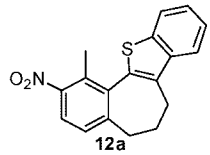
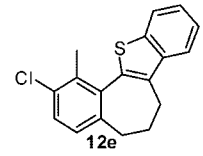
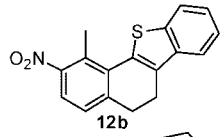
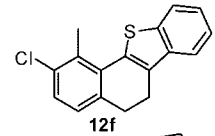
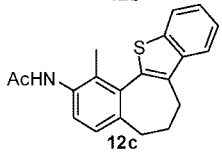
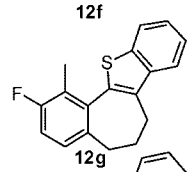
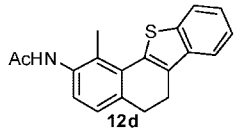
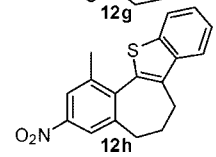
We explored the scope of the domino coupling reaction of **11a** and **11b** with a variety of aryl iodides (Table 2). A similar trend with respect to the electronic character of the aryl iodide was observed in that only electron-deficient aryl

(12) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973–976.

(13) (a) Joucla, L.; Putey, A.; Joseph, B. *Tetrahedron Lett.* **2005**, *46*, 8177–8179. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Paladino, G.; Zoni, C. *Eur. J. Org. Chem.* **2005**, 2091–2096. (c) Putey, A.; Joucla, L.; Picot, L.; Besson, T.; Joseph, B. *Tetrahedron* **2007**, *63*, 867–869.

TABLE 2. Domino *ortho*-Alkylation/Direct Arylation of Benzothiophenes



Entry	1	11	product	yield (%)	Entry	1	11	product	yield (%)
1	1a	11a	 12a	77	5	1e	11a	 12e	45
2	1a	11b	 12b	42	6	1e	11b	 12f	26
3	1b	11a	 12c	61	7	1f	11a	 12g	41
4	1b	11b	 12d	70	8	1h	11a	 12h	63

iodides afforded the desired products. In comparison to the domino reaction with 3-(bromoalkyl)thiophenes, the analogous coupling with 3-(bromoalkyl)benzothiophenes generally required higher reaction temperatures and afforded lower yields of product.

Conclusion

In summary, we have developed a route to a variety of polycyclic sulfur heterocycles based upon a palladium-catalyzed *ortho*-alkylation/direct arylation reaction sequence. The method works well with electron-deficient aryl iodides, allowing efficient domino annulation of six- and seven-membered rings. An examination of the intramolecular direct arylation of thiophenes lends support to an electrophilic metalation mechanism.

Experimental Section

The following represents experimental procedures toward the synthesis of products **3i** and **12b**. This includes experimental details and characterization data for the aforementioned compounds. The information for all other compounds can be found in the Supporting Information.

General Procedure for the Domino Reaction. To a 2.5−5 mL microwave reaction vial with a magnetic stir bar were added sequentially Cs_2CO_3 (2 equiv, 0.400 mmol), $Pd(OAc)_2$ (10 mol %, 0.020 mmol), P(2-furyl)$_3$ (20 mol %, 0.040 mmol), and norbornene (2 equiv, 0.400 mmol). In a separate vial, aryl iodide (1 equiv, 0.200 mmol) and 3-(bromoalkyl)heteroaryl (2 equiv, 0.400 mmol) were combined and added to the reaction vial. CH_3CN (0.1 M of Ar−I, 2 mL) was added and the vial capped, sealed, and flushed with $N_{2(g)}$. The vial was then heated in an oil bath until the reaction was complete (appearance of Pd-black usually signifies completion of reaction). The vial was then removed from the oil bath and cooled and H_2O (3 mL) added. The mixture was then washed with Et_2O (3 × 5 mL), and the organic extracts were combined, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then purified by column chromatography on silica gel to afford product.

9-Fluoro-10-methyl-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*b*]-thiophene (3i). Following the domino general procedure, 2-iodo-6-fluorotoluene **1f** (47.0 mg, 0.200 mmol) and 3-(3-bromopropyl)-thiophene **2a** (82.0 mg, 0.400 mmol) were reacted at 105 °C for 18 h. The crude mixture was purified by flash chromatography on silica gel (R_f 0.68 in 2% Et_2O/hexane) using 1% Et_2O/hexane to afford **3i** as a clear colorless oil: yield 32 mg (69%). At 95 °C, the yield was 52%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07−2.18 (m, 2H), 2.36 (t, 2H), 2.40 (d, J = 2.6 Hz, 3H), 2.47 (br t, J = 7.0 Hz, 2H), 6.92 (t, J = 8.5 Hz, 1H), 6.96 (d, J = 5.3 Hz, 1 H), 7.06 (dd, J = 8.2, 5.9 Hz, 1H), 7.33 (d, J = 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1 (d, J = 5.5 Hz), 25.4, 32.5, 34.4 (d, J = 1.6 Hz), 113.9 (d, J = 23.2 Hz), 123.2 (d, J = 16.6 Hz), 124.9, 127.5 (d, J = 8.8 Hz), 128.1, 134.3 (d, J = 3.3 Hz), 136.2 (d, J = 4.4 Hz), 136.9 (d, J = 3.3 Hz), 141.6, 160.5 (d, J = 241.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −118.5; IR thin film, ν (cm^{-1}) 818 (m), 1102 (m), 1241 (m), 1255 (m), 1382 (w), 1448 (m), 1473 (s), 1581 (m), 2856 (m), 2932 (s); HRMS (EI) calcd for $C_{14}H_{13}FS$ 232.0722 (M^+), found 232.0726.

1-Methyl-2-nitro-5,6-dihydrobenzo[*b*]naphtho[2,1-*d*]thiophene (12b). Following the domino general procedure, 2-iodo-6-nitrotoluene **1a** (52.0 mg, 0.200 mmol) and 3-(2-bromoethyl)-benzothiophene **11b** (96.0 mg, 0.400 mmol) were reacted at 105 °C for 24 h. The crude mixture was purified by flash chromatography on silica gel (R_f 0.17 in 5% Et_2O/hexane) using 5% Et_2O/hexane to afford **12b** as a viscous yellow oil: yield 25 mg (42%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (s, 3H), 2.99−3.05 (m, 4H), 7.25 (d, J = 8.2 Hz, 1H), 7.35−7.46 (m, 2H), 7.55 (d, J = 7.9 Hz, 1H), 7.76−7.80 (m, 1H), 7.86−7.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 21.6, 30.7, 121.9, 122.1, 124.5, 125.1, 126.2, 127.1, 128.0, 132,8 133.1, 133.6, 134.8, 137.1,

140.0, 142.1; IR neat, ν (cm^{-1}) 729 (m), 754 (m), 831 (m), 1155 (w), 1248 (w), 1346 (m), 1519 (s), 1589 (w), 1736 (w), 2931 (m); HRMS (EI) calcd for $C_{17}H_{13}NO_2S$:295.0667 (M^+), found 295.0662.

Acknowledgment. We thank the National Science and Engineering Research Council of Canada and Merck Frosst Canada & Co. for financial support in the form of an Industrial Research Chair and the University of Toronto for additional support. We also wish to thank Dr. Dino Alberico for preliminary work and helpful discussions.

Supporting Information Available: Experimental details and characterization data for compounds all compounds listed above and their precursors. This information is available free of charge via the Internet at http://pubs.acs.org.

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