Organic LETTERS
Letter
pubs.acs.org/OrgLett

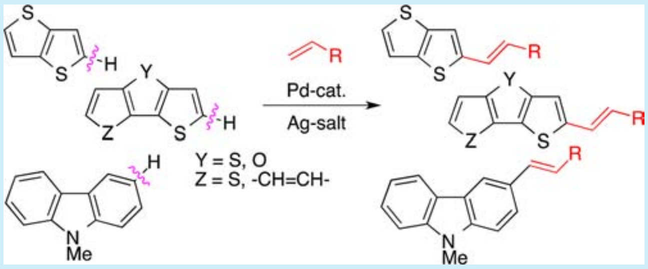
Palladium(II)-Catalyzed Direct C−H Alkenylation of Thienothiophene and Related Fused Heteroarenes

Tomohiro Morita,[†] Tetsuya Satoh,*[,†,‡,§] and Masahiro Miura*[,†]

[†]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan
[‡]ACT-C, JST, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan
[§]Department of Chemistry, Graduate School of Science, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan

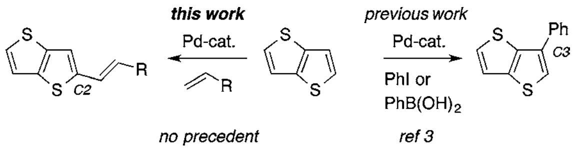
Ⓢ *Supporting Information*

ABSTRACT: The palladium-catalyzed direct alkenylation of thieno[3,2-*b*]thiophene takes place regioselectively at C2. Symmetrically and unsymmetrically 2,5-dialkenylated thienothiophene derivatives can be prepared by the catalytic procedure. Related fused thienyl and carbazole derivatives also undergo regioselective direct alkenylation.



Thienothiophene and related π-conjugated motifs are among important frameworks in organic materials, especially because of their utility as key cores of organic semiconductors.[1] Therefore, the development of synthetic methods for the introduction of π-conjugated substituents on the thienothiophene nucleus has attracted attention. From the atom- and step-economy points of view, direct C−H functionalization appears to be promising for the derivatization.[2] However, such direct functionalization reactions of thienothiophene derivatives have been less explored. As a rare example, the palladium-catalyzed phenylation of thieno[3,2-*b*]thiophene itself has recently been reported by Itami's group (Scheme 1).[3] The reaction took place at C3 regioselectively.

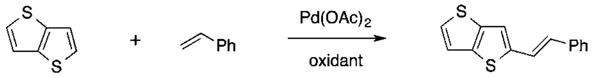
Scheme 1. Direct Functionalization of Thienothiophene



There is to our knowledge no report on the direct C−H alkenylation of thienothiophenes. In the context of our continuous study of the Fujiwara−Moritani-type C−H alkenylation,[4,5] we have succeeded in finding that the direct alkenylation of thieno[3,2-*b*]thiophene and related fused thiophenes can be conducted effectively under palladium catalysis.[6] This reaction has been found to take place at C2 regioselectively, in contrast to the previous phenylation. Under similar conditions, unprecedented C3-selective alkenylation of a carbazole derivative has also been achieved. These new findings are described herein.

In an initial attempt, thieno[3,2-*b*]thiophene (**1a**) (0.2 mmol) was treated with styrene (**2a**) (0.4 mmol) in the presence of Pd(OAc)$_2$ (0.02 mmol) and AgOAc (0.4 mmol) as the catalyst and oxidant, respectively, under N$_2$ in TFE at room temperature for 24 h. As a result, C2-selective alkenylation proceeded smoothly to produce (*E*)-2-styrylthieno[3,2-*b*]thiophene (**3aa**) in 68% yield (Table 1, entry 1). It should be noted that no dialkenylation product was detected even under conditions using excess **2a**. Other oxidants such as

Table 1. Reaction of Thieno[3,2-*b*]thiophene (1a) with Styrene (2a)[a]



1a **2a** **3aa**

entry	oxidant (mmol)	yield (%)[b]
1	AgOAc (0.4)	68 (66)
2	AgOCOCF$_3$ (0.4)	8
3	Ag$_2$CO$_3$ (0.2)	13
4	Ag$_2$O (0.2)	16
5	Cu(OAc)$_2$·H$_2$O (0.4)	5
6[c]	AgOAc (0.4)	62
7[d]	AgOAc (0.4)	49

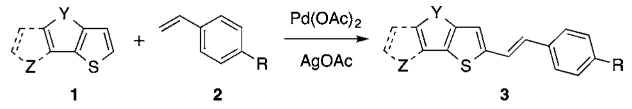
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), and Pd(OAc)$_2$ (0.02 mmol) in TFE (1 mL) under N$_2$ at rt for 24 h, unless otherwise noted. [b] GC yields based on the amount of **1a** used. The value in parentheses indicates the yield after purification. [c] With Pd(OAc)$_2$ (0.01 mmol). [d] With **2a** (0.2 mmol).

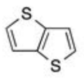
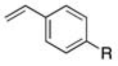
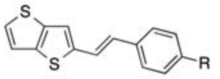
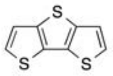
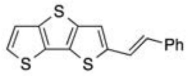
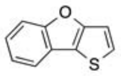
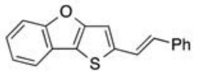
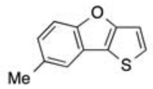
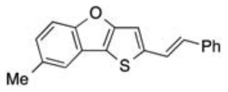
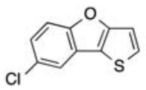
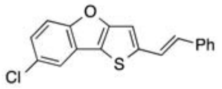
Received: August 2, 2015
Published: August 18, 2015

$AgOCOCF_3$, Ag_2CO_3, Ag_2O, and $Cu(OAc)_2{\cdot}H_2O$ were less effective than AgOAc (entries 2–5). In each case using a decreased amount of $Pd(OAc)_2$ or **2a**, the yield of **3aa** was slightly reduced (entries 6 and 7).

We next examined the reactions of a number of fused thiophenes **1** with styrenes **2** under the conditions used in Table 1, entry 1 (Table 2). Among the *para*-substituted styrenes employed, electron-deficient styrenes **2b–d** reacted with **1a** efficiently to afford the corresponding C2-styrylated products **3ab–ad** in 74–76% yield (entries 1–3). Contrastingly, the reactions of styrenes possessing an electron-donating group, **2e** and **2f**, were relatively sluggish, producing **3ae** and **3af** in moderate yields even at 50 °C (entries 4 and 5). These electron-rich styrenes had a tendency to undergo unidentified dimerization under the present reaction conditions. Tricyclic dithieno[3,2-*b*:2′,3′-*d*]thiophene (**1b**) also underwent C2-alkenylation to give (*E*)-2-styryldithieno[3,2-*b*:2′,3′-*d*]-thiophene (**3ba**) in 62% yield (entry 6). It should be noted that dithieno[3,2-*b*:2′,3′-*d*]thiophene derivatives are also of importance in organic materials because of their optical and electronic properties.[7]

Table 2. Reaction of Fused Thiophenes 1 with Styrenes 2[a]



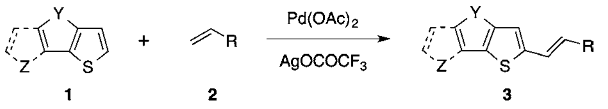
entry	1	2	product	% yield[b]
				
1	**1a**	**2b**: R = F	**3ab**: R = F	76
2		**2c**: R = Cl	**3ac**: R = Cl	74
3		**2d**: R = CF_3	**3ad**: R = CF_3	75
4		**2e**: R = Me	**3ae**: R = Me	59[c]
5		**2f**: R = OMe	**3af**: R = OMe	34[c]
				
6	**1b**	**2a**	**3ba**	62
				
7	**1c**	**2a**	**3ca**	66
				
8	**1d**	**2a**	**3da**	74
				
9	**1e**	**2a**	**3ea**	45

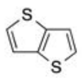
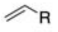
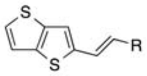
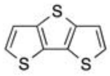
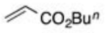
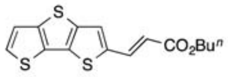
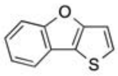
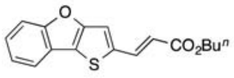
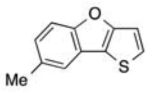
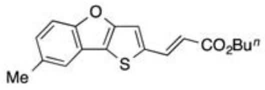
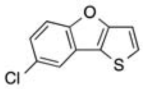
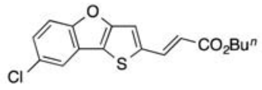
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), and AgOAc (0.4 mmol) in TFE (1 mL) under N_2 at rt for 24 h. [b]Isolated yields based on the amount of **1** used. [c]At 50 °C.

Meanwhile, we recently reported that thieno[3,2-*b*]-benzofuran frameworks can be readily constructed by the palladium-catalyzed dehydrogenative cyclization of 3-phenoxythiophenes.[8] A series of thienobenzofurans **1c–e** prepared by our method could be employed as the substrates in the present alkenylation. Thus, the corresponding 2-styrylthienobenzofurans **3ca–ea** were obtained under the standard room-temperature conditions (Table 2, entries 7–9).

Besides styrenes, acrylic acid derivatives could also be employed as coupling partners for the C2-alkenylation of fused thiophenes **1** (Table 3). Treatment of **1a** with butyl acrylate (**2g**) under the same conditions as those in the reactions with styrenes gave butyl (*E*)-3-(thieno[3,2-*b*]-thiophen-2-yl)acrylate (**3ag**) in 31% yield (entry 1). At 50 °C, **3ag** was obtained in 55% yield (entry 2). In AcOH or PivOH, the yield of **3ag** decreased (entries 3 and 4). Using $AgOCOCF_3$ and $EtCO_2H$ as the oxidant and solvent, respectively, improved the product yield to 63% (entry 5). Under similar conditions, various acrylates **2h–l** and *N*,*N*-dimethylacrylamide (**2m**) coupled with **1a** to produce **3ah–am** (entries 6–11). Dithienothiophene **1b** and thienobenzofurans

Table 3. Reaction of Fused Thiophenes 1 with Alkenes 2[a]



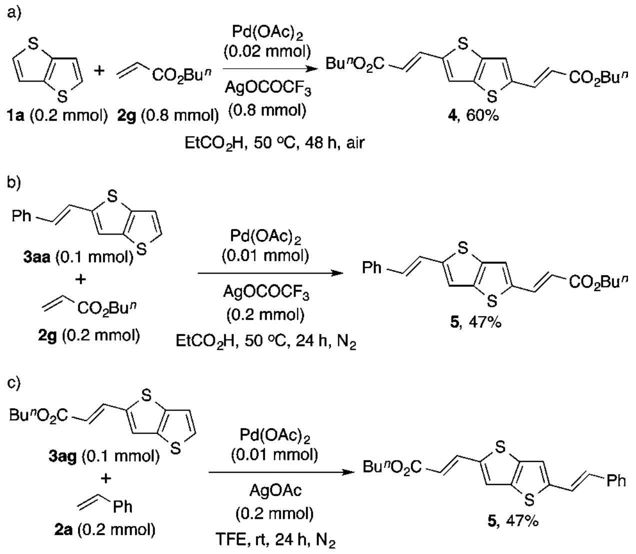
entry	1	2	product	% yield[b]
				
1[c,d,e]	**1a**	**2g**: R = CO_2Bu^n	**3ag**: R = CO_2Bu^n	(31)
2[d,e]		**2g**: R = CO_2Bu^n	**3ag**: R = CO_2Bu^n	(55)
3[d,f]		**2g**: R = CO_2Bu^n	**3ag**: R = CO_2Bu^n	(36)
4[d,g]		**2g**: R = CO_2Bu^n	**3ag**: R = CO_2Bu^n	(38)
5		**2g**: R = CO_2Bu^n	**3ag**: R = CO_2Bu^n	60 (63)
6		**2h**: R = CO_2Bu^i	**3ah**: R = CO_2Bu^i	58
7		**2i**: R = CO_2Bu^t	**3ai**: R = CO_2Bu^t	54
8[h]		**2j**: R = CO_2Cy	**3aj**: R = CO_2Cy	60
9		**2k**: R = CO_2Et	**3ak**: R = CO_2Et	52
10		**2l**: R = CO_2Me	**3al**: R = CO_2Me	51
11		**2m**: R = $CONMe_2$	**3am**: R = $CONMe_2$	45
				
12	**1b**	**2g**	**3bg**	56
				
13	**1c**	**2g**	**3cg**	74
				
14	**1d**	**2g**	**3dg**	81
				
15	**1e**	**2g**	**3eg**	71

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), and $AgOCOCF_3$ (0.4 mmol) in $EtCO_2H$ (1 mL) under N_2 at 50 °C for 24 h. [b]Isolated yields based on the amount of **1** used. Values in parentheses are GC yields. [c]At rt. [d]Using AgOAc in place of $AgOCOCF_3$. [e]In TFE. [f]In AcOH. [g]In PivOH. [h]Cy = cyclohexyl.

1c–e also underwent the C2-alkenylation with **2g** to yield **3bg–eg** in 56–81% yield (entries 12–15).

The C2-alkenylation of thienothiophenes appears to proceed in a similar manner as the Fujiwara–Moritani-type C–H alkenylation[5c,d] through C2-selective palladation,[9] alkene insertion, and *β*-hydrogen elimination. It appears possible that, once formed, C2-alkenylated thienothiophenes undergo the second alkenylation at the reactive 5-position. To confirm the hypothesis, **1a** was treated with excess amounts of **2g** and $AgOCOCF_3$ under air (Scheme 2a). As expected, 2,5-dialkenylated product **4** was obtained predominantly in 60% yield after a prolonged reaction time of 48 h, along with a minor amount of monoalkenylated **3ag** (14%).

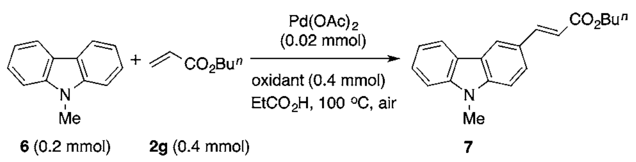
Scheme 2. Synthesis of Dialkenylated Thienothiophenes



An unsymmetrically dialkenylated thienothiophene could also be prepared by the present procedure. Thus, treatment of 2-styrylthienothiophene **3aa** with **2g** gave **5** in 47% yield (Scheme 2b). The same compound **5** could be obtained in the reaction of **3ag** with **2a** (Scheme 2c). However, the reaction of **3aa** with another styrene molecule did not occur. The reason is obscure at the present stage.

Finally, we attempted to apply the C–H alkenylation procedure to substrates other than thiophenes. As an example, we succeeded in conducting the alkenylation of 9-methyl-9*H*-carbazole (**6**) regioselectively (Scheme 3). Thus, the reaction of **6** with **2g** using $AgOCOCF_3$ as the oxidant in $EtCO_2H$ at 100 °C under air gave 3-alkenylated 9-methylcarbazole **7** as a single major product[9] in 44% isolated yield along with minor amounts of removable isomers (less than 10%). Using $Cu(OAc)_2{\cdot}H_2O$ in place of the Ag salt as the oxidant improved the yield of **7** to 51%.

Scheme 3. Reaction of 6 with 2g



oxidant	time (h)	yield (%)
$AgOCOCF_3$	4	44
$Cu(OAc)_2{\cdot}H_2O$	20	51

In summary, we have demonstrated that C2-selective direct alkenylation of thieno[3,2-*b*]thiophene and related fused thiophene derivatives can be achieved under palladium catalysis. This procedure provides simple synthetic routes toward various *π*-conjugated molecules containing a fused thiophene core, which are of importance in the field of organic materials. By the present means, C3-alkenylation of the carbazole framework can also be conducted. Further work is now ongoing to extend the substrate scope.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02246.

Experimental procedures and characterization data for the products (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: satoh@chem.eng.osaka-u.ac.jp.
*E-mail: miura@chem.eng.osaka-u.ac.jp.

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was partly supported by Grants-in-Aid from MEXT, JSPS, and JST, Japan.

REFERENCES

(1) For recent reviews, see: (a) Cinar, M. E.; Ozturk, T. *Chem. Rev.* **2015**, *115*, 3036. (b) Takimiya, K.; Nakano, M.; Kang, M. J.; Miyazaki, E.; Osaka, I. *Eur. J. Org. Chem.* **2013**, *2013*, 217. (c) Mei, J.; Diao, Y.; Appleton, A. L.; Fang, L.; Bao, Z. *J. Am. Chem. Soc.* **2013**, *135*, 6724. (d) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev.* **2012**, *112*, 2208. (e) Takimiya, K.; Shinamura, S.; Osaka, I.; Miyazaki, E. *Adv. Mater.* **2011**, *23*, 4347. (f) Murphy, A. R.; Fréchet, J. M. J. *Chem. Rev.* **2007**, *107*, 1066. For applications as organic dyes, see: (g) Diac, A.; Demeter, D.; Allain, M.; Grosu, I.; Roncali, J. *Chem. - Eur. J.* **2015**, *21*, 1598. (h) Fuse, S.; Sugiyama, S.; Maitani, M. M.; Wada, Y.; Ogomi, Y.; Hayase, S.; Katoh, R.; Kaiho, T.; Takahashi, T. *Chem. - Eur. J.* **2014**, *20*, 10685. (i) Xu, M.; Li, R.; Pootrakulchote, N.; Shi, D.; Guo, J.; Yi, Z.; Zakeeruddin, S. M.; Grätzel, M.; Wang, P. *J. Phys. Chem. C* **2008**, *112*, 19770. (j) Li, G.; Jiang, K.-J.; Li, Y.-F.; Li, S.-L.; Yang, L.-M. *J. Phys. Chem. C* **2008**, *112*, 11591.

(2) For selected recent reviews of C–H functionalization, see: (a) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (b) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751. (c) Jin, T.; Zhao, J.; Asao, N.; Yamamoto, Y. *Chem. - Eur. J.* **2014**, *20*, 3554. (d) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461. (e) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (f) Shi, G.; Zhang, Y. *Adv. Synth. Catal.* **2014**, *356*, 1419. (g) Bonin, H.; Sauthier, M.; Felpin, F.-X. *Adv. Synth. Catal.* **2014**, *356*, 645. (h) Engle, K. M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927. (i) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (j) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (k) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (l) Mitchell, E. A.; Peschiulli, A.;

Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. - Eur. J.* **2012**, *18*, 10092. (m) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (n) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (o) Kuninobu, Y.; Takai, K. *Chem. Rev.* **2011**, *111*, 1938. (p) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (q) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (r) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (s) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (t) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (u) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (v) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (w) Satoh, T.; Miura, M. *Synthesis* **2010**, *2010*, 3395. (x) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (y) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (z) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (aa) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (bb) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, *2008*, 3013. (cc) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987. (dd) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (ee) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (ff) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (gg) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (hh) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(3) (a) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387. (b) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946.

(4) (a) Takeda, D.; Hirano, K.; Satoh, T.; Miura, M. *Heterocycles* **2014**, *88*, 275. (b) Miyasaka, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 5421. (c) Maehara, A.; Satoh, T.; Miura, M. *Tetrahedron* **2008**, *64*, 5982.

(5) For early work on the Fujiwara–Moritani reaction, see: (a) Fujiwara, Y.; Noritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. (b) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. Also see the following reviews: (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (d) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170.

(6) A number of palladium-catalyzed functionalization reactions of thiophene derivatives have been reported. For example, see: Mitsudo, K.; Thansandote, P.; Wilhelm, T.; Mariampillai, B.; Lautens, M. *Org. Lett.* **2006**, *8*, 3939.

(7) For recent examples, see: (a) Marco, A. B.; Andreu, R.; Franco, S.; Garín, J.; Orduna, J.; Villacampa, B.; Alicante, R. *Tetrahedron* **2013**, *69*, 3919. (b) Huang, J.-D.; Wen, S.-H.; Han, K.-L. *Chem. - Asian J.* **2012**, *7*, 1032.

(8) Kaida, H.; Satoh, T.; Hirano, K.; Miura, M. *Chem. Lett.* **2015**, *44*, 1125.

(9) Usual electrophilic attack on thienothiophenes is known to take place at C2. For an example of the typical C2-bromination, see: (a) Jung, S.-H.; Kim, H. K.; Kim, S.-H.; Kim, Y. H.; Jeoung, S. C.; Kim, D. *Macromolecules* **2000**, *33*, 9277. In addition, the bromination of 9-methyl-9*H*-carbazole predominantly takes place at C3. See: Ponce, M. B.; Cabrerizo, F. M.; Bonesi, S. M.; Erra-Balsells, R. *Helv. Chim. Acta* **2006**, *89*, 1123.

DOI: 10.1021/acs.orglett.5b02246
Org. Lett. 2015, 17, 4384–4387