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Palladium-Catalyzed Domino C–S Coupling/Carbonylation Reactions: An Efficient Synthesis of 2-Carbonylbenzo[*b*]thiophene Derivatives

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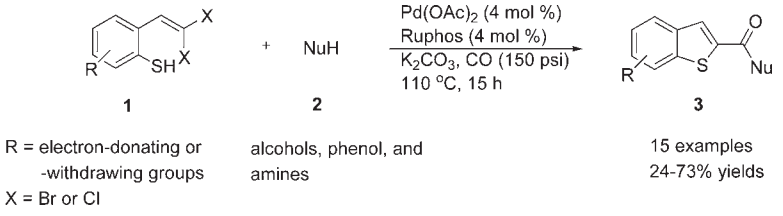
ABSTRACT



A facile and selective palladium-catalyzed domino procedure has been developed for the preparation of 2-carbonylbenzo[*b*]thiophene derivatives from 2-*gem*-dihalovinylthiophenols. This protocol involves intramolecular C–S coupling/intermolecular carbonylation cascade sequences and allows access to various highly functionalized benzo[*b*]thiophenes in moderate yields.

The transition-metal-catalyzed C–S coupling reaction has recently attracted considerable attention, as it can provide a more efficient, practical, and straightforward approach to valuable sulfur-containing compounds.[1] Since Migita and co-workers first reported the $Pd(PPh_3)_4$-catalyzed C–S coupling of stannyl sulfides and aryl bromides,[2] a number of catalytic systems based on transition metals, such as palladium,[3] nickel,[4] copper,[5] cobalt,[6] indium,[7] and iron,[8] have been developed for this purpose. In contrast to amination[9] and etherification[10] reactions of aryl and vinyl halides, this transformation still represents a challenge due to two main disadvantages: first, the sulfur-containing compounds may deactivate the catalysts owing to their strong coordination and absorption properties; second, thiols are prone to affording the corresponding

(1) For recent reviews on C–S coupling, see: (a) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335. (b) Kondo, T.; Mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *43*, 5400.

(2) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657.

(3) (a) Fernández-Rodríguez, M. A.; Hartwig, J. F. *Chem.—Eur. J.* **2010**, *16*, 2355. (b) Bryan, C.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064. (c) Lee, J.-Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 7413. (d) Fernández-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (e) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (f) Alvaro, E.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 7858.

(4) (a) Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484. (b) Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495. (c) Cristau, H. J.; Chabaud, B.; Chene, A.; Christol, H. *Synthesis* **1981**, 892.

(5) (a) Ma, D.; Lu, X.; Shi, L.; Zhang, H.; Jiang, Y.-G.; Liu, X.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1118. (b) Kabir, M. S.; Lorenz, M.; Van Linn, M. L.; Namjoshi, O. A.; Ara, S.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3626. (c) Firouzabadi, H.; Iranpoor, N.; Gholinejada, M. *Adv. Synth. Catal.* **2010**, *352*, 119. (d) Chen, C.-K.; Chen, Y.-W.; Lin, C.-H.; Lin, H.-P.; Lee, C.-F. *Chem. Commun.* **2010**, 282. (e) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222. (f) Jiang, Y.; Qin, Y.; Xie, S.; Zhang, X.; Dong, J.; Ma, D. *Org. Lett.* **2009**, *11*, 5250. (g) Bhadra, S.; Sreedhar, B.; Ranu, B. C. *Adv. Synth. Catal.* **2009**, *35*, 2369. (h) Gan, J.; Ma, D. *Org. Lett.* **2009**, *11*, 2788. (i) Kabir, M. S.; Van Linn, M. L.; Monte, A.; Cook, J. M. *Org. Lett.* **2008**, *10*, 3363. (j) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem.—Eur. J.* **2007**, *13*, 5100. (k) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583. (l) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (m) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517.

(6) Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5613.

(7) (a) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett.* **2009**, *11*, 1697. (b) Reddy, V. P.; Swapna, K.; Kumar, A. V.; Rao, K. R. *J. Org. Chem.* **2009**, *74*, 3189.

(8) (a) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880. (b) Qiu, J.-W.; Zhang, X.-G.; Tang, R.-Y.; Zhong, P.; Lia, J.-H. *Adv. Synth. Catal.* **2009**, *351*, 2319. (c) Wu, J.-R.; Lin, C.-H.; Lee, C.-F. *Chem. Commun.* **2009**, 4450. (d) Wu, W.-Y.; Wang, J.-C.; Tsai, F.-Y. *Green Chem.* **2009**, *11*, 326.

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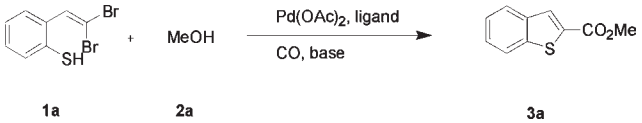
disulfides as accompanying products. Therefore, the development of new and efficient catalytic procedures to circumvent these limitations is a highly desirable goal.

2-Carbonylbenzo[*b*]thiophene derivatives are an important class of ring-fused compounds from both synthetic and biological points of view. For instance, they have good biological activities as anti-inflammatory,[11] antimitotic,[12] and antitumor[13] agents, FimH antagonists,[14] and PIM kinases inhibitors.[15] However, there are only a few efficient procedures which have been developed to synthesize them based on the oxidation of cinnamic acids and derivatives by a strong oxidant,[16] metalation at the C-2 position of benzo[*b*]thiophenes by organometallic reagents,[17] or cyclodehydration of *ortho*-formylphenylthioacetate and derivatives.[18] These procedures often suffer from harsh reaction conditions, poor availability of the requisite *o*-formylphenylthioacetate derivatives, and low yields. Transition-metal-catalyzed carbonylation, particularly palladium-catalyzed, is a fundamental, practical, and powerful transformation for the synthesis of carbonyl-containing compounds.[19] As part of our ongoing efforts to develop more efficient and environmentally benign strategies to synthesize carbonyl-containing heterocycles *via* carbonylation reactions,[20] we herein report a novel and straightforward domino protocol for the preparation of 2-carbonylbenzo[*b*]thiophene derivatives, which entails the consecutive formation of multiple new bonds in a single step, and potentially minimize the amounts of requisite reagents, separation steps, and chemical waste.

Table 1. Optimization of the Reaction Conditions Using 2-*gem*-Dibromovinylthiophenol and Methanol[a]



1a 2a 3a

entry	ligand	base	solvent	CO (psi)	yield (%)[b]
1	Johnphos	K_2CO_3	THF	500	36[c]
2	Johnphos	K_2CO_3	MeOH	500	45
3	Johnphos	K_2CO_3	THF/MeOH	500	58[d]
4	Johnphos	Et_3N	THF/MeOH	500	29[d]
5	Johnphos	$KHCO_3$	THF/MeOH	500	52[d]
6	Johnphos	K_3PO_4	THF/MeOH	500	42[d]
7	Johnphos	K_2CO_3	THF/MeOH	300	56[d]
8	Johnphos	K_2CO_3	THF/MeOH	150	58[d]
9	Johnphos	K_2CO_3	THF/MeOH	50	trace[d]
10	cyclohexyl Johnphos	K_2CO_3	THF/MeOH	150	40[d]
11	Ruphos	K_2CO_3	THF/MeOH	150	73[d]
12	Xphos	K_2CO_3	THF/MeOH	150	52[d]
13	Davephos	K_2CO_3	THF/MeOH	150	59[d]

[a] All reactions were carried out with 0.5 mmol of **1a**, 4 mol % of $Pd(OAc)_2$ and ligand, 3.0 equiv of base, and 6 mL of solvent, at 110 °C, for 15 h. [b] Isolated yield based on 2-*gem*-dibromovinylthiophenol. [c] 4.0 equiv of MeOH. [d] MeOH/THF (v/v = 1:1).

Initially, the 2-*gem*-dibromovinylthiophenol (**1a**) and methanol (**2a**) were chosen as model substrates to explore the feasibility and efficiency of the new domino protocol. Table 1 outlines the results of optimization experiments. Notably, the performance of this transformation significantly depended on the nature of solvents, and a 1:1 mixture of MeOH/THF was found to be the ideal solvent for the reaction providing thiophene **3a** in 58% yield, which is consistent with our previous report about the synthesis of 2-carboxylindoles (Table 1, entries 1−3).[20i] It should be mentioned that performing this reaction under the pressure of carbon monoxide as low as 50 psi only gave trace amounts of the desired product **3a** (Table 1, entry 9). The ligands employed in this process played an important role, and bulky electron-rich 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (Ruphos) was the most effective ligand, which furnished the anticipated product **3a** in 73% isolated yield. Other bulky electron-rich phosphine ligands, e.g., 2-di-*tert*-butylphosphinobiphenyl

(9) For reviews on catalytic amination, see: (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (c) Barluenga, J.; Valdés, C. *Chem. Commun.* **2006**, 4891. (d) Ley, S. V.; Thomas, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(10) (a) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321. (b) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146. (c) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770. (d) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718. (e) Gujadhur, R.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315.

(11) Radwan, M. A. A.; Shehab, M. A.; El-Shenawy, S. M. *Monatsh. Chem.* **2009**, *140*, 445.

(12) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Lopez Cara, C.; Preti, D.; Fruttarolo, F.; Pavani, M. G.; Tabrizi, M. A.; Tolomeo, M.; Grimaudo, S.; Di Antonella, C.; Balzarini, J.; Hadfield, J. A.; Brancale, A.; Hamel, E. *J. Med. Chem.* **2007**, *50*, 2273.

(13) Valderrama, J. A.; Espinozaa, O.; Rodriguezb, J.; Theoduloz, C. *Lett. Org. Chem.* **2009**, *6*, 278.

(14) Han, Z.; Pinker, J. S.; Ford, B.; Obermann, R.; Nolan, W.; Wildman, S. A.; Hobbs, D.; Ellenberger, T.; Cusumano, C. K.; Hultgren, S. J.; Janetka, J. W. *J. Med. Chem.* **2010**, *53*, 4779.

(15) Tao, Z.-F.; Hasvold, L. A.; Leverson, J. D.; Han, E. K.; Guan, R.; Johnson, E. F.; Stoll, V. S.; Stewart, K. D.; Stamper, G.; Soni, N.; Bouska, J. J.; Luo, Y.; Sowin, T. J.; Lin, N.-H.; Giranda, V. S.; Rosenberg, S. H.; Penning, T. D. *J. Med. Chem.* **2009**, *52*, 6621.

(16) (a) Campaigne, E.; Cline, R. E. *J. Org. Chem.* **1956**, *21*, 39. (b) Higa, T.; Krubsack, A. *J. Org. Chem.* **1976**, *41*, 3399.

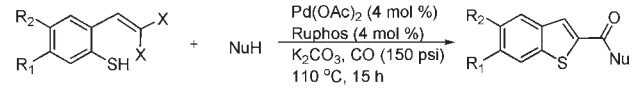
(17) (a) Kudo, H.; Castle, R. N.; Lee, M. L. *J. Heterocycl. Chem.* **1985**, *22*, 215. (b) Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008**, *10*, 2697.

(18) Hirota, T.; Tashima, Y.; Sasaki, K.; Namba, T.; Hayakawa, S. *Hetercycles* **1987**, *26*, 2717.

(19) (a) Negishi, E., de Meijere, A., Eds. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: New York, 2002; Vol. 2, p 2309. (b) Skoda-Foldes, R.; Kollar, L. *Curr. Org. Chem.* **2002**, *6*, 1097. (c) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A* **1995**, *104*, 17. (d) Tsuji, J. *Palladium Reagents and Catalysis: Innovation in Organic Synthesis*; John Wiley & Sons: Chichester, U.K., 1995. (e) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation, Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991.

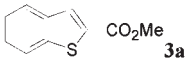
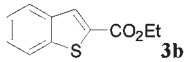
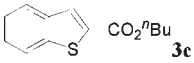
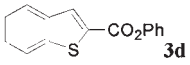
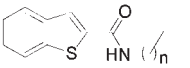
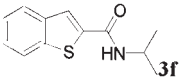
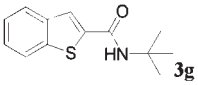
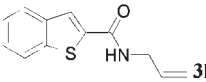
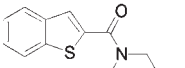
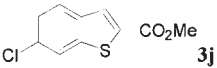
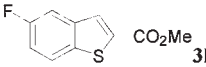
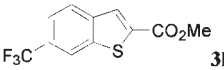
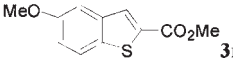
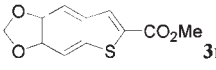
(20) (a) Cao, H.; Vieira, T. O.; Alper, H. *Org. Lett.* **2011**, *13*, 11. (b) Zeng, F. L.; Alper, H. *Org. Lett.* **2010**, *12*, 5567. (c) Zeng, F. L.; Alper, H. *Org. Lett.* **2010**, *12*, 3642. (d) Zeng, F. L.; Alper, H. *Org. Lett.* **2010**, *12*, 1188. (e) Chouhan, G.; Alper, H. *Org. Lett.* **2010**, *12*, 192. (f) Cao, H.; Alper, H. *Org. Lett.* **2010**, *12*, 4126. (g) Chouhan, G.; Alper, H. *J. Org. Chem.* **2009**, *74*, 6181. (h) Zheng, Z.; Alper, H. *Org. Lett.* **2009**, *11*, 3278. (i) Vieira, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899. (j) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 829. (k) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 4903. (l) Chouhan, G.; Alper, H. *Org. Lett.* **2008**, *10*, 4987.

Table 2. One-Step Synthesis of Benzo[*b*]thiophene-2-carboxylates and Benzo[*b*]thiophene-2-carboxamides[a]



1a $R_1 = R_2 = H$, X = Br
1b R_1 = Cl, R_2 = H, X = Br
1c R_1 = H, R_2 = F, X = Br
1d $R_1 = CF_3$, R_2 = H, X = Br
1e R_1 = H, R_2 = OMe, X = Br
1f R_1, $R_2 = OCH_2O$, X = Br
1g $R_1 = R_2$ = H, X = Cl

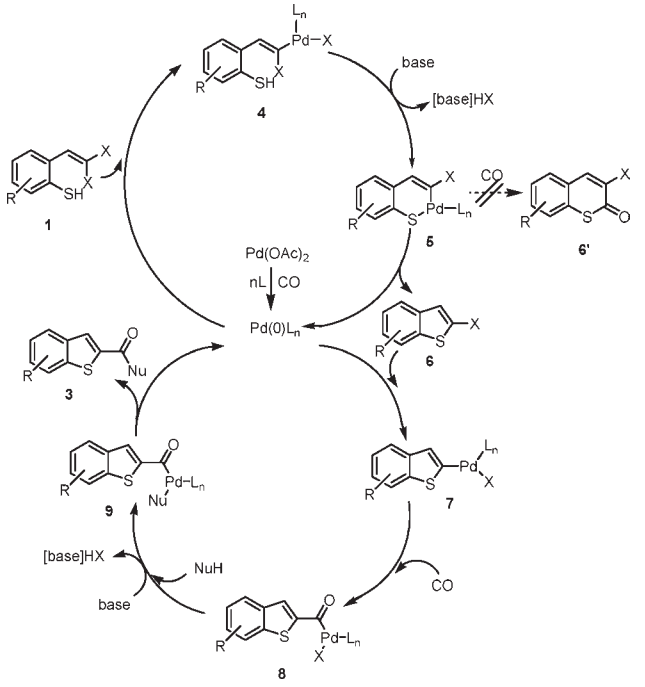
2 **3**

entry	1	NuH	product	yield (%)[b]
1	**1a**	MeOH	 **3a**	73
2	**1a**	Ethanol	 **3b**	65[c]
3	**1a**	*n*-butanol	 **3c**	51
4	**1a**	PhOH	 **3d**	24[d]
5	**1a**	*n*-hexylamine	 n = 5 **3e**	54[e]
6	**1a**	i-propylamine	 **3f**	50[e]
7	**1a**	*t*-butylamine	 **3g**	58[e]
8	**1a**	Allylamine	 **3h**	64[e]
9	**1a**	diethylamine	 **3i**	44[e]
10	**1b**	MeOH	 **3j**	44
11	**1c**	MeOH	 **3k**	57
12	**1d**	MeOH	 **3l**	trace
13	**1e**	MeOH	 **3m**	68
14	**1f**	MeOH	 **3n**	70
15	**1g**	MeOH	**3a**	52

[a] All reactions were carried out with 0.5 mmol of **1**, 4 mol % of $Pd(OAc)_2$ and Ruphos, 3.0 equiv of base, and 6 mL of MeOH/THF (v/v = 1:1), at 110 °C, 150 psi, for 15 h. [b] Isolated yield based on **1**. [c] 6 mL of EtOH/dioxane (v/v = 1:1). [d] 2.0 equiv of phenol, 6 mL of THF. [e] 4.0 equiv of amine, 6 mL of THF.

(Johnphos), 2-dicyclohexylphosphinobiphenyl (cyclohexyl Johnphos), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos), and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (Davephos) were effective as well, albeit giving lower yields (Table 1, entries 8, 10, 12, and 13). Further studies showed that the organic base Et_3N was much less useful than inorganic bases, such as K_2CO_3, $KHCO_3$, and K_3PO_4 (Table 1, entries 3–6).

Scheme 1. Possible Reaction Mechanism



With the optimized reaction conditions in hand, the generality of the present domino strategy was explored, and the results are summarized in Table 2. First, the reactions of 2-*gem*-dibromovinylthiophenol (**1a**) with methanol, ethanol, and *n*-butanol generated the corresponding target products **3a**–**3c** in 73%, 65%, and 51% yields, respectively, which indicates increasing the chain length of alcohols reduces the efficiency of this transformation (Table 2, entries 1–3). Using phenol as the nucleophile, the desired product **3d** was isolated in low yield (24%), owing to the weaker nucleophilicity of the phenols relative to aliphatic alcohols. When primary amines, including *n*-hexylamine, isopropylamine, *tert*-butylamine, and allylamine, were employed as the nucleophiles, the anticipated amides **3e**–**3h** were obtained in moderate yields (Table 2, entries 5–8). However, the reaction of diethylamine using the standard conditions afforded the desired amide **3i** in 44% yield, demonstrating the steric hindrance of two ethyl groups modestly affects the outcome of this process. The influence of substituents on the aryl groups of the thiophenol derivatives was also investigated, and the electronic properties of the substituents had a significant effect on the efficiency of this reaction. The thiophenols with electron-donating groups (**1e** and **1f**) gave similar results to that of the unfunctionalized substrate **1a** (Table 2, entries 13 and 14). The thiophenols with mildly electron-withdrawing groups,

i.e., chloride and fluoride, furnished the corresponding products, but in slightly reduced yields (Table 2, entries 10 and 11). In contrast, the thiophenol **1d** with a strongly electron-withdrawing CF_3 group only gave trace amounts of the target product **3l**. We were pleased to find that our synthetic strategy was also suitable for 2-*gem*-dichlorovinylthiophenol (**1g**), providing the corresponding benzothiophene **3a** in 52% yield.

A possible mechanism for the formation of 2-carbonylbenzo[*b*]thiophenes **3** is depicted in Scheme 1. Oxidative addition of **1** to the *in situ* formed palladium(0) species[21] gives the palladium complex **4**, which is followed by the formation of the palladacycle **5** *via* base-catalyzed intramolecular cyclization. Reductive elimination of **5** affords the intermediate 2-halobenzo[*b*]thiophene **6** and releases the palladium(0) species. Oxidative addition of **6** to palladium(0) leads to complex **7**, followed by CO insertion into the carbon−palladium bond to provide **8**. Base-catalyzed intermolecular nucleophilic attack on the aroylpalladium complex **8** then gives the intermediate **9**. Reductive elimination of **9** furnishes the product **3** and regenerates the active palladium(0) species.

(21) (a) Amatore, C.; Jutand, A.; M'Barki, M. *Organometallics* **1992**, *11*, 3009. (b) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. *Organometallics* **1995**, *14*, 1818.

(22) For instance, the reactions of **1a** with methanol and hexylamine gave the intermediate 2-bromobenzo[*b*]thiophene in 8% and 14% yields, respectively. The reaction of **1b** with methanol furnished 2-bromo-6-chlorobenzo[*b*]thiophene in 15% yield.

Under a CO atmosphere, the intermediate **5** has the potential to form the six-membered thiolactone **6′** *via* CO insertion into the carbon−palladium bond. However the thiolactone **6′** was not detected in all cases, which may be because the seven-membered transition state is unfavorable relative to the formation of five-membered 2-halobenzo[*b*]thiophene **6**. The conversion of 2-halobenzo[*b*]thiophene **6** to the product **3** was not quantitative, and the corresponding compound **6** was detected as a byproduct,[22] which provides insight to the mechanism of this process.

In summary, a novel strategy for the synthesis of 2-carbonylbenzo[*b*]thiophene derivatives has been developed based on a one-pot palladium-catalyzed intramolecular C−S coupling/intermolecular carbonylation reaction sequence. This procedure tolerates significant variation of both nucleophiles and the thiophenol backbone and provides a general, straightforward, and practical approach to benzo[*b*]thiophene-2-carboxylates and benzo[*b*]thiophene-2-carboxamides.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for the starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.