Coupling Reactions and Coupling−Alkylations of Thiophenecarbaldehydes Promoted by Samarium Diiodide

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The coupling reactions of 2-thiophenecarbaldehyde with aromatic or aliphatic aldehydes were promoted by samarium diiodide in the presence of hexamethylphosphoramide to give C-5 hydroxyalkylation products. The coupling reactions of 3-thiophenecarbaldehyde occurred at C-2, and the subsequent alkylations occurred at the sulfur atom, accompanied by a concurrent opening of the thiophene ring to afford γ-lactols. Double hydroxyalkylations of 2- and 3-thiophenecarbaldehydes were also carried out under appropriate reaction conditions. Synthetic applications of these thiophenecarbonyl coupling products were demonstrated, for example, by elaboration to furans, butenolides, and thiophene-fused polycyclic compounds.

Introduction

Aromatic aldehydes usually undergo reductive carbonyl−carbonyl coupling reactions[1] to give pinacols by using SmI_2 or other suitable reducing agents. However, we have found that the coupling reactions of benzaldehydes or indole-3-carbaldehydes by using SmI_2/HMPA as the combined promoter proceed in a different mode to give aryl−carbonyl coupling products.[2] This new type of coupling reactions is further extended to the system of 2- and 3-thiophenecarbaldehydes.[3] Thiophenecarbaldehydes are generally reduced to the thienylmethanols by catalytic hydrogenation[4] or with $LiAlH_4$[5] or Fe/HOAc.[6] On treatment with Mg/MgI_2, thiophenecarbaldehydes undergo self-coupling reactions to give pinacols.[7] Electrochemical reductions of acetylthiophene or benzoylthiophene also give pinacols.[8] Reductions of alkanoylthiophenes with dissolving metals such as Li/NH_3 or Na/NH_3 give the corresponding 2,5-dihydro derivatives.[9] Reductions of thiophenes to tetrahydrothiophenes are achieved by using Et_3SiH/CF_3CO_2H.[10] We report herein the thiophenecarbonyl coupling reactions of 2- and 3-thiophenecarbaldehydes (**1** and **2**) by mediation of SmI_2/HMPA. Along this line, we also found a method for elaboration of thiophenecarbaldehydes to furans, α,β-unsaturated-γ-lactones, and various thiophene-fused polycyclic compounds including heterocyclic analogues of neolignans.

Table 1. SmI_2-Promoted Coupling Reactions of 2-Thiophenecarbaldehyde (1) in THF[a]

entry	substrates (RCHO)	additive	coupling products (% yield)[b]
1	**1**	none	**4a** (48)
2	**1**	none	**4a** (65)
3	**1**	HMPA	**3a** (45)
4	**1** + 3-thiophenecarbaldehyde	HMPA	**3b** (49)
5	**1** + 4-$MeOC_6H_4CHO$	HMPA	**3c** (45)
6	**1** + 1-methyl-2-pyrrolecarbaldehyde	HMPA	**3d** (36)
7	**1** + CH_3CH_2CHO	HMPA	**3a** (24) + **3e** (49)

[a] For entry 1, the molar ratio of **1**/SmI_2 = 1:1.8; for entry 2, the molar ratio of **1**/SmI_2 = 1:1.2; for entry 3, the molar ratio of **1**/SmI_2/HMPA = 1:1.8:8; for entries 4−7, the molar ratio of **1**/RCHO/SmI_2/HMPA = 1:1.2:3.6:16. The reactions were conducted by dropwise addition of **1** (or a mixture of **1** and RCHO) to the SmI_2 solution. The mixture was stirred at 0 °C to room temperature for 0.5−1.5 h. [b] The starting material **1** was recovered (13−25%).

Results and Discussion

We studied first the coupling reactions of 2-thiophenecarbaldehyde (**1**) promoted by SmI_2 (1.8 molar proportion) in THF solution (Table 1). In the presence of HMPA (8 M proportion), a thiophenecarbonyl coupling product **3a** was obtained in 45% yield. A significant amount (17%) of the starting material **1** was also recovered. No pinacolic coupling product was observed under such reaction conditions. The reaction was presumably initiated by sequential electron transfers from SmI_2 to 2-thiophenecarbaldehyde to form the C-3 organosamarium intermediate **A** or the C-5 organosamarium intermediate **B** (Scheme 1). The C-5 organosamarium **B** was presumably

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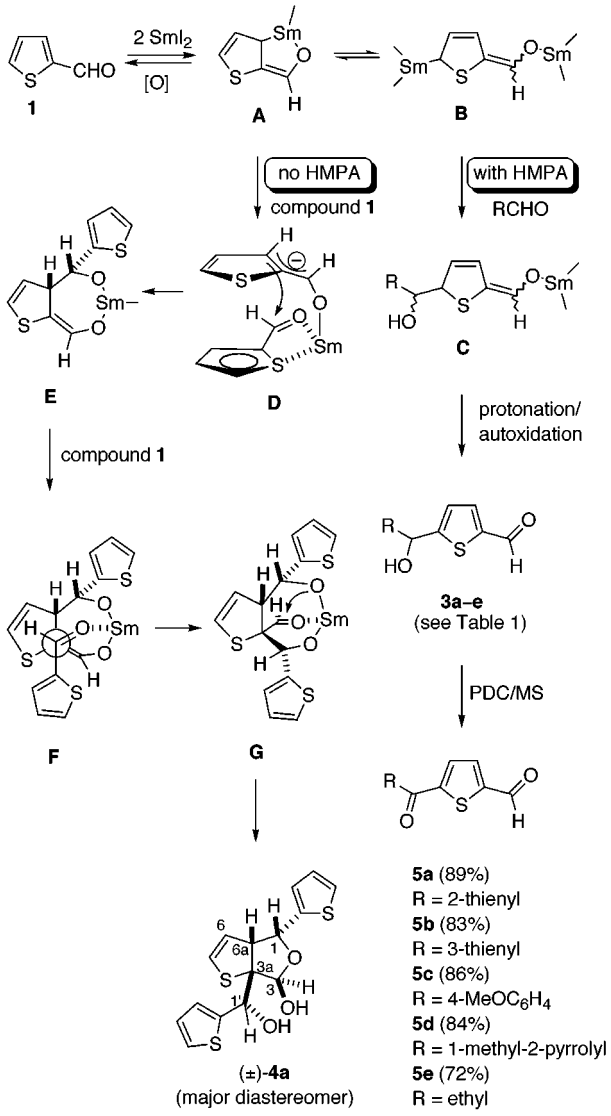
Scheme 1



favored due to the stabilizing effect of the adjacent sulfur atom.[11a] Theoretically, half of 2-thiophenecarbaldehyde would be converted to the samarium species to function as a donor and another half of 2-thiophenecarbaldehyde would act as an acceptor to furnish the coupling reaction. Thus, addition of **B** with a second molecule of 2-thiophenecarbaldehyde, giving **C**, followed by protonation and oxidative rearomatization upon workup, would give the thiophenecarbonyl coupling product **3a**. Otherwise, the unreacted intermediate **B** (or **A**) might revert to the aromatic starting material **1** upon autoxidation.[2]

The dipolar cosolvent HMPA is known to alter the regioselectivity in the reactions of allylmetals.[11] Interestingly, the reaction of **1** with SmI_2 (1.2 M proportion) in the absence of HMPA gave a mixture of the trimeric product **4a** and its diastereomers, as indicated by the ^{1}H NMR analysis. The major diastereomer **4a** (40% yield) was isolated by trituration of the reaction mixture with EtOAc/hexane. A recrystallized sample was subjected to X-ray diffraction to reveal the (1*R**,1′*R**,3*R**,3a*S**,6a*R**) configuration of this major diastereomer. To account for the formation of this product, the chelate organosamarium species **A** was considered to dominate over **B** in the absence of HMPA. The C-3 organosamarium intermediate **A** could add to a second molecule of 2-thiophenecarbaldehyde via a transition state **D** having two stacked thiacycles (Scheme 1). The resulting samarium enolate **E** was then trapped by a third molecule of 2-thiophenecarbaldehyde, presumably following the favored chelate form **F**, to give an aldehyde **G**. The subsequent intramolecular hemiacetalization would occur in a stereoselective manner to furnish (1*R**,1′*R**,3*R**,3a*S**,6a*R**)-**4a**.

A cross-coupling reaction between 2-thiophenecarbaldehyde (1.0 equiv) and 3-thiophenecarbaldehyde (1.2 equiv) was effected by SmI_2 (3.6 equiv) in the presence of HMPA (16 equiv) to afford a single product **3b** (49%). This result indicated that 2-thiophenecarbaldehyde was more reactive toward SmI_2 to form organosamarium species. Thus, 2-thiophenecarbaldehyde functioned as a donor, whereas 3-thiophenecarbaldehyde functioned as an acceptor in this cross-coupling reaction. Under similar reaction conditions, the cross-coupling reactions of 2-thiophenecarbaldehyde with other aldehydes were also carried out (Table 1). The self-coupling of **1** was diminished except for the reaction with propionaldehyde, a relatively unreactive substrate toward SmI_2 reduction. The coupling products **3a**−**e** were oxidized by PDC to give the corresponding thiophene-2,5-dicarbonyl compounds **5a**−**e** in high yields. These compounds are potentially useful for the preparation of macrocycles and tris-1,3-dithiole photoelectric material.[12]

We then studied the coupling reactions of 3-thiophenecarbaldehyde (**2**) by using SmI_2 in THF solution (Table 2). Unlike the coupling reactions of **1**, the thiophenecarbonyl coupling reaction of **2** was complicated by a pinacolic coupling reaction. In the absence of HMPA (entries 1 and 2), the SmI_2-promoted reaction afforded pinacols **6**, dimer **7a**, and trimeric products **8** in variable yields (Scheme 2). In the presence of HMPA (entry 3), the thiophenecarbonyl coupling product **7a** became the major product (40−46%). However, the trimeric products **8** (50%) and **9** (9%) predominated (entry 4) when 3-thiophenecarbaldehyde (1 equiv) was treated with SmI_2 (1.8 equiv) and HMPA (8 equiv) in THF solution for 10 min at 0 °C followed by addition of another 0.6 equiv of 3-thiophenecarbaldehyde.

According to the ^{1}H NMR spectral analysis, pinacols **6** existed as a mixture of two diastereomers (1:2). Compound **8** also existed as a mixture of hemiacetals, which was subjected to oxidation with PDC to give a lactone **10**. Compound **9** was isolated as a single isomer; it was presumably derived by a hydride transfer from the hemiacetal **8** to 3-thiophenecarbaldehyde. This deduction was supported by isolation of 3-thienylmethanol in a nearly equal amount. The coupling constants $J_{3,3a}$ of **9** and **10** were 7.6 and 7.8 Hz, respectively. By comparison

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Table 2. SmI_2-Promoted Coupling Reactions of 3-Thiophenecarbaldehyde (2) in THF[a]

entry	substrates (RCHO)	additive	coupling products (% yield)[b]
1	**2**	none	**6** (20)[c] + **7a** (20) + **8**[c] (<5)
2	**2**	none	**6** (25)[c] + **7a** (15) + **8**[c] (19)
3[d]	**2**	HMPA	**6** (9)[c] + **7a** (46)
4[e]	**2** + **2**	HMPA	**6** (5)[c] + **7a** (10) + **8** (50)[c] + **9** (9)
5	**2** + 4-$MeOC_6H_4CHO$	HMPA	**7a** (18) + **7b** (43)
6	**2** + 4-$CH_3C_6H_4CHO$	HMPA	**7a** (17) + **7c** (37)
7[f]	**2** + 1-methyl-2-pyrrolecarbaldehyde	HMPA	**7a** (27) + **7d** (21)
8	**2** + CH_3CH_2CHO	HMPA	**7a** (22) + **7e** (43)

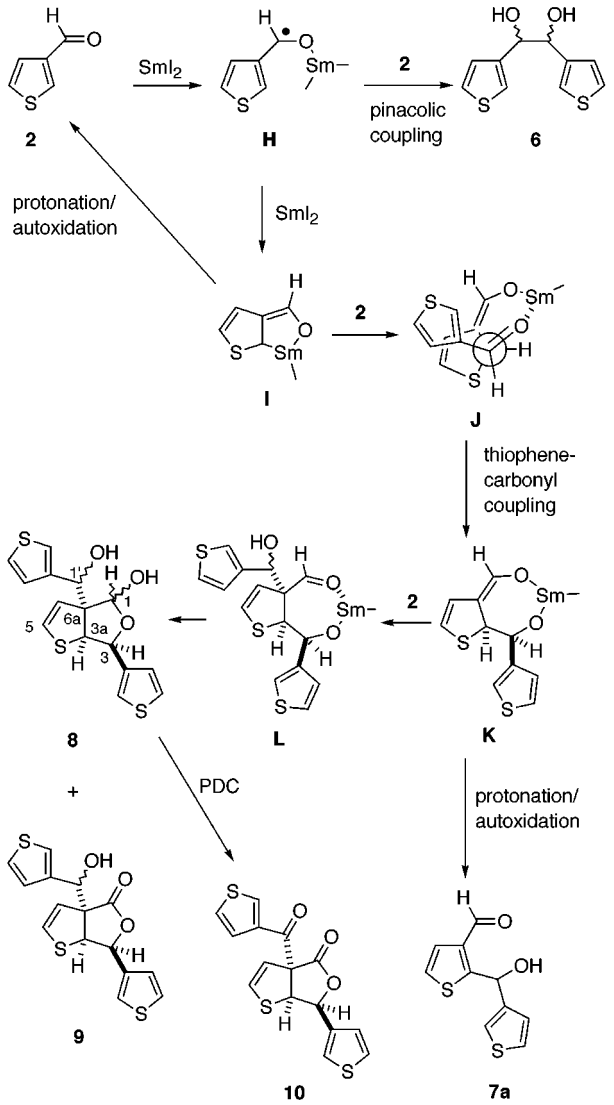
[a] For entry 1, the molar ratio of **2**/SmI_2 = 1:1.8; for entry 2, the molar ratio of **2**/SmI_2 = 1:1.2; for entry 3, the molar ratio of **2**/SmI_2/HMPA = 1:1.8:8; for entries 5−8, the molar ratio of **2**/RCHO/SmI_2/HMPA = 1:1.2:3.6:16. The reactions were conducted by dropwise addition of **2** (or a mixture of **2** and RCHO) to the SmI_2 solution. The mixture was stirred at 0 °C to room temperature for 0.5−2 h. [b] The starting material **2** was recovered (14−38%). [c] The products consisted of diastereomers. [d] If **2** was added in one portion to the SmI_2/HMPA solution, the reaction gave **6** (21%) and **7a** (40%). If the SmI_2/HMPA solution was added to the 3-thiophenecarbaldehyde solution, the reaction gave **6** (26%) and **7a** (46%). [e] Another 0.6 equiv of **2** was added after the mixture of **2**/SmI_2/HMPA (1:1.8:8) was stirred at 0 °C for 10 min. The reaction also gave a 13% of 3-thienylmethanol. [f] The side products were 3-thienylmethanol (14%) and 2-hydroxy-1-(1-methylpyrrol-2-yl)-2-(3-thienyl)ethanone (16%).

with the coupling constant of 7.0 Hz for H_1−H_{6a} of (1*R**,1′*R**,3*R**,3a*S**,6a*R**)-**4a**, the H-3 and H-3a of **9** and **10** also likely had the cis relationship. This result could also account for a chelate transition state **J** having two stacked thiacycles (Scheme 2). Addition of 3-thiophenecarbaldehyde to the enolate **K** should occur on the less hindered face, giving the aldehyde **L**, which formed the hemiacetal **8** intramolecularly. The relative configuration of C-1′ remained unknown, though it was likely *R** according to the mechanistic consideration.

By the promotion of SmI_2/HMPA, 3-thiophenecarbaldehyde reacted with aromatic and aliphatic aldehydes to give the thiophenecarbonyl coupling products **7b**−**e** (entries 5−8, Table 2). Nonetheless, the self-coupling of **2** (giving **7a**) also competed with these cross-couplings. The reaction with 1-methyl-2-pyrrolecarbaldehyde also yielded 3-thienylmethanol and 2-hydroxy-1-(1-methylpyrrol-2-yl)-2-(3-thienyl)ethanone in nearly equal amounts (ca. 15% each). This result indicated that a side reaction of crossed pinacolic coupling between **2** and 1-methylpyrrole-2-carbaldehyde occurred and the resulting pinacol could transfer a hydride to the remaining aldehyde **2**.

The key intermediate **M** (Scheme 3) in the coupling reactions of 3-thiophenecarbaldehyde was also trapped by alkylating agents. The alkylations occurred exclusively at the sulfur atom to effect a concurrent opening of the thiophene ring, giving the hemiacetals **11a**−**d** (Table 3). The double bonds of **11a**−**d** retained the (*Z*) configuration as indicated by the coupling constants (ca. 10.5 Hz) of the two adjacent vinyl protons. As trapping of the intermediate by alkylating agents drove the coupling reaction through the last irreversible step, the yields of **11a**−**d** (55−74%) were higher than those of dimers **7a**−**d** (21−46%). The hemiacetals **11a**−**d** were oxidized by PDC to give 70−82% yields of the corresponding lactones **12a**−**d** with cis double bonds. It was noted that the hemiacetals were unstable in $CDCl_3$ solution containing

Scheme 2



a small amount of DCl. Indeed, an acid-catalyzed dehydration of **11b** was carried out to give a quantitative yield of the furan **13a** with a cis double bond. (*Z*)-**13a** isomerized in part to (*E*)-**13a** when it was subjected to chromatography on a silica gel column. The hemiacetal **11c** was similarly converted to the furan **13b** by acid catalysis. This sequential thiophenecarbonyl coupling−alkylation method thus provides a convenient route to furans and butenolides, which often exhibit important biological activities.[13]

This method is also applicable to the synthesis of thiophene-fused polycyclic compounds. The coupling products **7a**,**b** were similarly oxidized by PDC to give thiophene-2,3-dicarbonyl compounds **14a**,**b**, which reacted further with hydrazine to give thieno[2,3-*d*]pyridazines **15a**,**b** (Scheme 4). The thienopyriazones related to **15a**,**b** have been used as antiasthmatic drugs.[14] The coupling products **7a**−**c** were treated with Lawesson's

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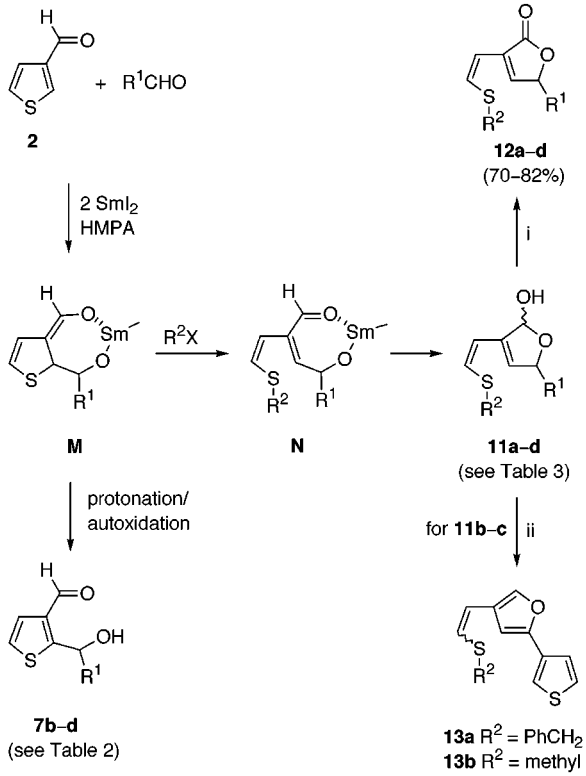
Scheme 3



[a] Reagents and conditions: (i) PDC, CH_2Cl_2, sieves, 3−7 h, **12a** 77%, **12b** 79%, **12c** 82%, **12d** 70%; (ii) cat. HCl in $CHCl_3$, **13a** 100%, **13b** 100%.

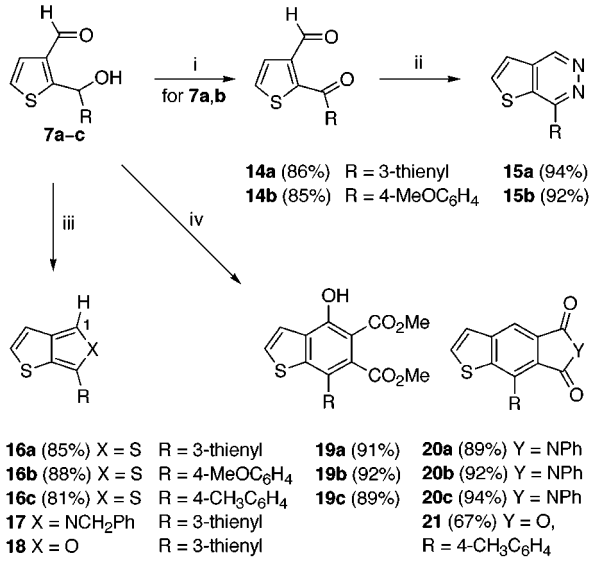
Table 3. Sequential Coupling−Alkylations of 3-Thiophenecarbaldehyde (2)[a]

entry	substrates (R^1CHO)	R^2X (equiv)	products (% yield)
1	**2**	allyl bromide (1)	**6**[b] (18) + **7a** (38) + **11a**[b] (20)
2	**2**	allyl bromide (2)	**6**[b] (5) + **11a**[b] (55)
3	**2**	benzyl bromide (1)	**6**[b] (15) + **11b**[b] (46)
4	**2**	benzyl bromide (2)	**6**[b] (13) + **11b**[b] (65)
5	**2**	dimethyl sulfate (2.5)	**6**[b] (7) + **7a** (29) + **11c**[b] (29)
6	**2**	methyl iodide (2.5)	**6**[b] (8) + **11c**[b] (74)
7	**2** + 4-$MeOC_6H_4CHO$	benzyl bromide (2)	**11b**[b] (22) + **11d**[b] (63)

[a] Refer to Scheme 3 for these sequential reactions. [b] The products existed as diastereomeric mixtures.

reagent to give thieno[2,3-*c*]thiophenes **16a**−**c** in 81−88% yields. Compound **7a** was heated with benzylamine in the presence of *p*-TsOH to give an unstable product of thieno[2,3-*c*]pyrrole **17**, which displayed a characteristic signal at δ_H 5.40 (2 H, s) for the *N*-benzyl group in addition to other signals for aromatic protons. The acid-catalyzed dehydration of **7a** also led to an unstable thieno[2,3-*c*]furan **18** of which H-1 occurred at δ 7.73 (s). Compounds **16a**−**c**, **17**, and **18** can serve as the equivalents of thiophene-2,3-quinodimethane employed as the diene substrates in Diels−Alder reactions.[15] Thus, condensation of **7a**−**c** with dimethyl acetylenedicarboxylate was carried out by the catalysis of PPTS to give benzothiophenes **19a**−**c** in 89−92% yields. Cycloadditions of

Scheme 4



[a] Reagents and conditions: (i) PDC, CH_2Cl_2, rt, 2.5 h; (ii) N_2H_4, EtOH, rt (10 min) then reflux (20 min); (iii) For **16a**−**c**, Lawesson's reagent, 1,4-dioxane, reflux, 3 h; for **17**, $PhCH_2NH_2$, cat. PTSA, PhH; for **18**, cat. PPTS, PhH; (iv) For **19a**−**c**, dimethyl acetylenedicarboxylate, cat. PPTS, PhH, 1−2 h; for **20a**−**c**, *N*-phenylmaleimide, cat. PPTS, PhH, 2 h; for **21**, maleic anhydride, cat. PPTS, PhH, 2 h.

7a−**c** with *N*-phenylmaleimide or maleic anhydride were also realized by similar procedures. Compounds **19a**,**b** are heterocyclic analogues of 1-arylnaphthalene lignans with antihyperlipidemic activity.[16]

A previous method[17] for alkylation of thiophenecarbaldehydes requires sequential treatments with amine (such as *N*-methylpiperazine) and BuLi (several molar proportions) at low temperatures to generate α-aminoalkoxide intermediates. This procedure is tedious and the reaction shows variable regioselectivities depending on the reaction substrates and conditions. On the other hand, our present method using SmI_2/HMPA as the promoter is relatively simple and gives the thiophenecarbonyl coupling products with predictable regiochemistry. The thiophenecarbonyl coupling products are versatile building blocks for the synthesis of thiophene-fused polycyclic compounds such as **15**−**21**. Furthermore, we have demonstrated a novel way for the ring-opening of 3-thiophenecarbaldehyde by sequential coupling−alkylation to culminate in the formation of furans and α,β-unsaturated γ-lactones such as **12** and **13**.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded at 200, 300, or 400 MHz; ^{13}C NMR spectra were recorded at 50, 75, or 100 MHz. Tetramethylsilane and $CDCl_3$ were used as internal standards in the ^1H and ^{13}C NMR spectra, respectively. Mass spectra were recorded at an ionizing voltage of 70 or 20 eV. High-resolution mass spectra were taken using an internal PFK reference followed by a computer

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(17) (a) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104. (b) Comins, D. L. *Synlett* **1992**, 615.

search for the mass that best fit an elemental formula. Merck silica gel 60F sheets were used for analytical thin-layer chromatography. Column chromatography was performed on SiO_2 (70−230 mesh); gradients of EtOAc and *n*-hexane were used as eluents. High-pressure liquid chromatography was carried out on a liquid chromatograph equipped with a refractive index detector. The samples were analyzed and/or separated on a Hibar Lichrosorb Si 60 (7 μm) column (25 cm × 1 cm) with the indicated eluent with a 5 mL/min flow rate. THF was distilled from sodium benzophenone ketyl under N_2.

General Procedure for the Reactions of Thiophenecarbaldehydes with SmI_2. Samarium metal (0.66 g, 4.4 mmol) and 1,2-diiodoethane (1.02 g, 3.6 mmol) in anhydrous THF (40 mL) were stirred at room temperature under an argon atmosphere for 1 h to give a deep-blue solution. HMPA (2.8 mL, 16 mmol) was added in most cases. Precaution should be taken as HMPA is a toxic cancer suspect agent. The mixture was cooled to 0 °C in an ice bath, and a THF solution (2 mL) of thiophenecarbaldehyde (2.0 mmol) (for self-coupling reactions) or a mixture of thiophenecarbaldehyde (1 mmol) and an appropriate aldehyde (1.2 mmol) (for cross-coupling reactions) was added dropwise over a period of 2 min. The light-yellow mixture was stirred at 0 °C for 10 min and warmed to room temperature over a period of 0.5−2 h. Saturated $NH_4Cl_{(aq)}$ (0.1 mL) was added. The mixture was filtered through a pad of silica gel and rinsed with EtOAc/hexane (1:1). The organic phase was concentrated under reduced pressure and chromatographed on a silica gel column with elution of EtOAc/hexane to give products.

5-[1-Hydroxy-(2-thienyl)methyl]thiophene-2-carbaldehyde (3a) and 5-(Thiophene-2-carbonyl)thiophene-2-carbaldehyde (5a). According to the general procedure, treatment of 2-thiophenecarbaldehyde (224 mg, 2 mmol) with SmI_2 (3.6 mmol) in the presence of HMPA (16 mmol) gave the self-coupling product **3a** (100 mg, 45%). By a procedure similar to that for **10**, treatment of **3a** (75 mg, 0.33 mmol) with PDC (376 mg, 1.0 mmol) and molecular sieves (4 Å, 2 g) in CH_2Cl_2 (10 mL) at 25 °C for 2 h gave **5a** (66 mg, 89%). **3a**: oil; TLC (EtOAc/hexane (3:7)) R_f = 0.2; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.74 (1H, s, CHO), 7.58 (1 H, d, J = 3.8 Hz), 7.27−7.20 (1 H, m), 7.03−6.90 (3 H, m), 6.22 (1 H, d, J = 3.6 Hz), 3.95 (1 H, br s, OH). **5a**: solid; mp 102−103 °C; TLC (EtOAc/hexane, 3:7) R_f = 0.26; IR (KBr) 2802 (CHO), 1670 (C=O), 1599 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.98 (1 H, s, CHO), 7.90 (1 H, dd, J = 3.8, 1.0 Hz), 7.88 (1 H, d, J = 3.9 Hz), 7.79 (1 H, d, J = 3.9 Hz), 7.75 (1 H, dd, J = 4.8, 1.0 Hz), 7.19 (1 H, dd, J = 4.8, 3.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.3 (d), 178.5 (s), 148.9 (s), 147.7 (s), 142.1 (s), 135.0 (d), 134.9 (d), 134.1 (d), 132.5 (d), 128.3 (d); MS *m*/*z* (rel intensity) 222 (10, M$^+$), 57 (100); HRMS calcd for $C_{10}H_6O_2S_2$ 221.9809, found 221.9813.

1,3,6a-Trihydro-3-hydroxy-3a-[1-hydroxy-(2-thienyl)-methyl]-1-(2-thienyl)thieno[2,3-*c*]furan (4a). According to the general procedure, treatment of 2-thiophenecarbaldehyde (336 mg, 3.0 mmol) with SmI_2 (3.6 mmol) gave the trimeric product **4a** and its diastereomers (220 mg, 65%). The mixture was triturated with EtOAc/hexane (1:4) and filtered to give the major (1*R**,1′*R**,3*R**,3a*S**,6a*R**)-**4a** isomer (136 mg, 40%). The configuration was established by an X-ray diffraction analysis of a sample recrystallized from $CHCl_3$/cyclohexane. **4a**: solid; mp 157.5−158.5 °C; TLC (EtOAc/hexane, 3:7) R_f = 0.23; IR (KBr) 3481, 3381 cm^{-1}; ^{1}H NMR (CD_3COCD_3, 200 MHz) δ 7.33 (2 H, dd, J = 4.7, 1.2 Hz), 7.17 (1 H, dd, J = 2.5, 0.8 Hz), 7.01−6.88 (3 H, m), 6.29 (1 H, d, J = 3.3 Hz), 5.92 (1 H, dd, J = 6.0, 1.5 Hz), 5.80 (1 H, d, J = 7.0 Hz), 5.73 (1 H, d, J = 3.3 Hz), 5.57 (1 H, d, J = 5.3 Hz), 4.83 (1 H, d, J = 5.3 Hz), 4.59 (1 H, dd, J = 6.0, 3.1 Hz), 3.74 (1 H, ddd, J = 7.0, 3.1, 1.5 Hz); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 146.1 (s), 142.5 (s), 127.4 (d, C-5), 126.9 (d), 126.8 (d), 126.7 (d), 126.0 (d), 125.5 (d), 125.2 (d), 121.4 (d, C-6), 104.6 (d, C-3), 78.9 (s, C-3a), 78.6 (d, C-1), 72.7 (d, C-1′), 60.9 (d, C-6a); MS *m*/*z* (rel intensity) 338 (31, M$^+$), 113 (100). Anal. Calcd for $C_{15}H_{14}O_3S_3$: C, 53.25; H, 4.17. Found: C, 52.78; H, 4.17.

2-[1-Hydroxy-(3-thienyl)methyl]thiophene-3-carbaldehyde (7a). According to the general procedure, treatment of 3-thiophenecarbaldehyde (224 mg, 2 mmol) with SmI_2 (3.6 mmol) in the presence of HMPA gave pinacol **6** (47 mg, 21%) and the self-coupling product **7a** (102 mg, 46%) (40%). **7a**: oil; TLC (EtOAc/hexane, 1:4) R_f = 0.18; IR (neat) 3378 (OH), 1658 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.92 (1 H, s, CHO), 7.43 (1 H, d, J = 5.1 Hz, H-5), 7.27 (2 H, m), 7.20 (1 H, d, J = 5.1 Hz, H-4), 7.08 (1 H, dd, J = 4.4, 1.9 Hz, H-4′), 6.42 (1 H, d, J = 4.9 Hz), 4.43 (1 H, d, J = 4.9 Hz, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 186.1 (d), 158.3 (s), 142.8 (s), 136.1 (s), 129.8 (d), 126.1 (d), 126.0 (d), 124.3 (d), 122.4 (d), 66.9 (d); MS *m*/*z* (rel intensity) 224 (100, M$^+$); HRMS calcd for $C_{10}H_8O_2S_2$ 223.9966, found 223.9961. Anal. Calcd for $C_{10}H_8O_2S_2$: C, 53.57; H, 3.60. Found: C, 53.56, H, 3.49.

3,3a-Dihydro-6a-(1-hydroxy-(3-thienyl)methyl)-3-(3-thienyl)thieno[2,3-*c*]furan-1-one (9) and 3,3a-Dihydro-3-(3-thienyl)-6a-(thiophene-3-carbonyl)thieno[2,3-*c*]furan-1-one (10). According to the general procedure, 3-thiophenecarbaldehyde (224 mg, 2 mmol) was added to the SmI_2 (3.6 mmol)/HMPA (16 mmol) solution. The mixture was stirred for 10 min at 0 °C, and a second portion of 3-thiophenecarbaldehyde (135 mg, 1.2 mmol) was added. The mixture was stirred at room temperature for 10 h to give **8** (166 mg, 50%), **9** (28 mg, 9%), and 3-thienylmethanol (45 mg, 13%). Compound **9** existed as a single isomer: oil; TLC (EtOAc/hexane, 3:7) R_f = 0.36; IR (neat) 3468, 1756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37−7.31 (2 H, m), 7.24−7.20 (2 H, m), 7.04−7.00 (2 H, m), 6.28 (1 H, d, J = 5.6 Hz, H-5), 5.66 (1 H, d, J = 5.6 Hz, H-6), 5.25 (1 H, d, J = 5.0 Hz, H-1), 5.22 (1 H, d, J = 7.4 Hz, H-3), 4.18 (1 H, d, J = 7.4 Hz, H-3a), 3.16 (1 H, d, J = 5.0 Hz, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5 (s), 139.8 (s), 138.3 (s), 130.7 (d), 127.4 (d), 126.3 (d), 125.3 (d), 125.1 (d), 123.6 (d), 122.7 (d), 119.5 (d), 84.9 (d), 72.0 (s), 70.6 (d), 54.2 (d); MS *m*/*z* (rel intensity) 336 (33, M$^+$), 224 (100), 206 (73), 179 (46), 113 (65); HRMS calcd for $C_{15}H_{12}O_3S_3$ 335.9949, found 335.9946.

Compound **8** existed as a mixture of two isomers (3:2). The diastereomeric mixture of **8** (38 mg, 0.11 mmol) was treated with PDC (138 mg, 0.37 mmol) and molecular sieves (4 Å, 2 g) in CH_2Cl_2 (10 mL) at 25 °C for 1 h. The mixture was filtered through a pad of silica gel and rinsed with EtOAc/hexane (3:7). The organic phase was concentrated under reduced pressure and chromatographed on a silica gel column with elution of EtOAc/hexane (1:9) to give the product **10** (22 mg, 59%). **10**: solid; mp 109−111 °C; TLC (EtOAc/hexane, 1:9) R_f = 0.17; IR (neat) 1773, 1664, 1247, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.44 (1 H, dd, J = 2.7, 1.2 Hz), 7.65 (1 H, dd, J = 5.1, 1.2 Hz), 7.42−7.40 (2 H, m), 7.32 (1 H, dd, J = 5.1, 2.7 Hz), 7.16 (1 H, dd, J = 4.2, 2.1 Hz), 6.49 (1 H, d, J = 5.5 Hz), 5.96 (1 H, d, J = 5.5 Hz), 5.38 (1 H, d, J = 7.9 Hz), 4.96 (1 H, d, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.4 (s), 170.7 (s), 138.0 (s), 137.4 (s), 135.3 (d), 130.8 (d), 128.5 (d), 127.6 (d), 126.0 (d), 125.0 (d), 123.5 (d), 119.0 (d), 83.9 (s), 76.9 (d), 56.8 (d); MS *m*/*z* (rel intensity) 334 (31, M$^+$), 257 (7), 223 (10), 206 (13), 111 (100); HRMS calcd for $C_{15}H_{10}O_3S_3$ 333.9792, found 333.9798.

General Procedure for Sequential Coupling−Alkylation. The THF solution (40 mL) of SmI_2 (3.6 mmol) and HMPA (2.8 mL, 16 mmol) was prepared by the described general procedure and cooled to 0 °C in an ice bath. A THF solution (2 mL) of 3-thiophenecarbaldehyde (224 mg, 2 mmol) (for self-coupling reactions) or a mixture of 3-thiophenecarbaldehyde (112 mg, 1.0 mmol) and an appropriate aldehyde (1.2 mmol) in THF (2 mL) (for cross-coupling reactions) was added dropwise over a period of 2 min. The mixture was stirred for 10 min, and an alkylating agent (1−2.5 mmol) was added. The mixture was stirred at room temperature for a period of 21−27 h and quenched by addition of saturated $NH_4Cl_{(aq)}$ (0.1 mL). The mixture was filtered through a pad of silica gel and rinsed with EtOAc/hexane (1:1). The organic phase was concentrated under reduced pressure and chromatographed on a silica gel column with elution of EtOAc/hexane to give the γ-lactols **11a**−**d**.

3-(2-Allylsulfanyl)ethenyl-2-hydroxy-5-(3-thienyl)-2,5-dihydrofuran (11a) and 3-(2-Allylsulfanyl)ethenyl-5-(3-thienyl)-5*H*-furan-2-one (12a). According to the general procedure, coupling of 3-thiophenecarbaldehyde (224 mg, 2 mmol) followed by alkylation with allyl bromide (0.173 mg,

2.0 mmol) gave the γ-lactol **11a** (145 mg, 55%) as a mixture of two isomers (62:38). Oxidation of **11a** (45 mg, 0.17 mmol) with PDC (188 mg, 0.5 mmol) at 25 °C for 3 h by a procedure similar to that for **10** gave **12a** (35 mg, 77%). **11a**: oil; TLC (EtOAc/hexane (3:7)) R_f = 0.31; IR (neat) 3402, 1570, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28−7.21 (2 H, m), 7.09 (0.62 H, dd, J = 4.2, 2.0 Hz), 7.00 (0.38 H, dd, J = 4.8, 1.1 Hz), 6.38 (1 H, d, J = 10.7 Hz), 6.26 (1 H, s), 6.08 (0.38 H, s), 6.20−6.00 (1 H, m), 5.98 (1 H, d, J = 10.7 Hz), 5.84 (0.62 H, s), 5.89−5.72 (1 H, m), 5.24−5.13 (2 H, m), 3.38 (2 H, d, J = 7.0 Hz), 3.11 (1 H, d, J = 7.8 Hz, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 142.5 (s), 141.5 (s), 136.8 (s), 136.5 (s), 133.5 (d, 2 C), 131.5 (d), 131.4 (d), 130.1 (d), 130.0 (d), 126.4 (d, 2 C), 126.2 (d), 126.1 (d), 122.2 (d, 2 C), 118.2 (t, 2 C), 115.5 (d, 2 C), 103.9 (d), 103.7 (d), 82.8 (d), 82.5 (d), 37.4 (t, 2 C); MS m/z (rel intensity) 266 (10, M$^+$), 141 (100); HRMS calcd for $C_{13}H_{14}O_2S_2$ 266.0435, found 266.0421. **12a**: oil; TLC (EtOAc/hexane, 1:9) R_f = 0.12; IR (neat) 3498 (overtone), 1747, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.47 (1 H, d, J = 2.0 Hz), 7.35−7.32 (2 H, m), 7.01 (1 H, dd, J = 4.0, 2.2 Hz), 6.64 (1 H, d, J = 10.7 Hz), 6.29 (1 H, d, J = 10.7 Hz), 6.07 (1 H, d, J = 2.0 Hz), 5.90−5.73 (1 H, m), 5.28−5.17 (2 H, m), 3.45 (2 H, dd, J = 7.1, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.6 (s), 145.9 (d), 136.0 (s), 134.8 (d), 133.0 (d), 128.0 (s), 127.0 (d), 125.7 (d), 123.9 (d), 118.8 (t), 112.8 (d), 78.6 (d), 37.6 (t); MS m/z (rel intensity) 264 (35, M$^+$), 111 (100); HRMS calcd for $C_{13}H_{12}O_2S_2$ 264.0279, found 264.0283.

3-(2-Benzylsulfanyl)ethenyl-5-(3-thienyl)furan (13a). Compound **11b** (85 mg, 0.27 mmol) was treated with 0.01 N HCl in $CHCl_3$ (5 mL) for 5 min. The solution was concentrated under reduced pressure to give (*Z*)-**13a** (80 mg, 100%), which isomerized in part (Z/E = 2:3) on filtration through a pad of silica gel. (*Z*)-**13a**: oil; TLC (EtOAc/hexane, 1:19) R_f = 0.37; IR (neat) 3104, 1493, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (1 H, s), 7.45−7.44 (1 H, m), 7.37−7.24 (7 H, m), 6.69 (1 H, s), 6.22 (1 H, d, J = 10.4 Hz), 6.13 (1 H, d, J = 10.4 Hz), 4.00 (2 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.8 (s), 140.4 (d), 137.4.(s), 132.3 (s), 128.9 (d, 2 C), 128.7 (d, 2 C), 127.4 (d), 126.1 (d), 124.8 (d), 124.7 (d), 124.2 (s), 119.2 (d), 116.4 (d), 105.5 (d), 38.8 (t); MS m/z (rel intensity) 298 (87, M$^+$), 91 (100); HRMS calcd for $C_{17}H_{14}OS_2$ 298.0486, found 298.0481. (*E*)-**13a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (1 H, s), 7.45−7.27 (8 H, m), 6.51 (1 H, s), 6.47 (1 H, d, J = 15.4 Hz), 6.39 (1 H, d, J = 15.4 Hz), 3.97 (2 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.6 (s), 138.1 (d), 137.2 (s), 132.2 (s), 128.7 (d, 2 C), 128.6 (d, 2 C), 127.2 (d), 126.2 (d), 125.4 (s), 124.5 (d), 123.3 (d), 119.4 (d), 118.7 (d), 102.0 (d), 37.4 (t).

2-(Thiophene-3-carbonyl)thiophene-3-carbaldehyde (14a). By a procedure similar to that for **10**, oxidation of **7a** (120 mg, 0.53 mmol) with PDC (414 mg, 1.1 mmol) and molecular sieves (4 Å, 2 g) in CH_2Cl_2 (15 mL) at 25 °C for 2.5 h gave **14a** (101 mg, 86%). **14a**: solid; mp 111.5−112.0 °C; TLC (EtOAc/hexane, 3:17) R_f = 0.24; IR (KBr) 1675, 1614 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.21 (1 H, s, CHO), 8.13−8.11 (1 H, m), 7.66−7.61 (2 H, m), 7.50 (1 H, d, J = 4.8 Hz), 7.42−7.38 (1 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 186.0 (d, CHO), 180.6 (s), 146.8 (s), 144.6 (s), 142.0 (s), 134.7 (d), 129.8 (d), 128.1 (d), 127.9 (d), 127.0 (d); MS m/z (rel intensity) 222 (100, M$^+$); HRMS calcd for $C_{10}H_6O_2S_2$ 221.9809, found 221.9810.

4-(3-Thienyl)thieno[2,3-*d*]pyridazine (15a). A mixture of **14a** (12 mg, 0.054 mmol) and hydrazine monohydrate (0.1 mL, 2 mmol) in EtOH (10 mL) was stirred at 25 °C for 10 min and then heated at reflux for 20 min. The mixture was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:1) to give **15a** (11 mg, 94%). **15a**: solid; mp 78−79 °C; TLC (EtOAc/hexane, 1:1) R_f = 0.13; IR (KBr) 1527, 1461, 1312, 863, 782, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.44 (1 H, s), 8.17 (1 H, dd, J = 2.8, 1.3 Hz), 7.99 (1 H, dd, J = 5.0, 1.3 Hz), 7.84 (1 H, d, J = 5.4 Hz), 7.52 (1 H, d, J = 5.4 Hz), 7.49 (1 H, dd, J = 5.0, 2.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 151.1 (s), 144.9 (d), 138.2 (s), 137.1 (s), 136.6 (s), 132.9 (d), 127.3 (d), 126.5 (d), 126.4 (d), 122.8 (d); MS m/z (rel intensity) 218 (100, M$^+$); HRMS calcd for $C_{10}H_6N_2S_2$ 217.9973, found 217.9975.

3-(3-Thienyl)thieno[2,3-*c*]thiophene (16a). Compound **7a** (80 mg, 0.357 mmol) was treated with Lawesson's reagent (289 mg, 0.714 mmol) in refluxing 1,4-dioxane (10 mL) for 3 h. The mixture was cooled, concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane (1:19) to give **16a** (67 mg, 85%). **16a**: oil; TLC (EtOAc/hexane, 1:9) R_f = 0.64; IR (neat) 1367, 1092, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.44−7.39 (3H, m), 7.35 (1 H, d, J = 5.5 Hz), 7.22 (1 H, s), 6.90 (1 H, d, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.9 (s), 134.6 (s), 134.4 (s), 132.1 (d), 126.5 (d), 125.8 (d), 124.2 (s), 119.5 (d), 117.3 (d), 109.9 (d); MS m/z (rel intensity) 222 (100, M$^+$); HRMS calcd for $C_{10}H_6S_3$ 221.9632, found 221.9635.

4-Hydroxy-5,6-bis(methoxycarbonyl)-7-(3-thienyl)benzo[*b*]thiophene (19a). A mixture of **7a** (79 mg, 0.352 mmol) and dimethyl acetylenedicarboxylate (DMAD, 50 mg, 0.352 mmol) was treated with 20 mol % PPTS (18 mg, 0.071 mmol) in refluxing benzene (30 mL) for 2 h. A Dean−Stark apparatus was equipped for the removal of water. The mixture was cooled, filtered through a pad of silica gel, and rinsed with EtOAc/hexane (1:1). The organic phase was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:4) to give **19a** (112 mg, 91%). **19a**: solid; mp 108−110 °C (lit.[16a] 107−109 °C); TLC (EtOAc/hexane, 1:4) R_f = 0.26; IR (neat) 1733, 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.88 (1 H, s), 7.63 (1 H, d, J = 5.4 Hz), 7.40−7.37 (3 H, m), 7.20 (1 H, dd, J = 5.0, 1.2 Hz), 3.91 (3 H, s), 3.64 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1 (s), 168.8 (s), 157.7 (s), 147.9 (s), 136.8 (s), 130.1 (s), 129.3 (s), 128.3 (d), 127.5 (d), 125.6 (d), 124.8 (d), 122.0 (d), 121.3 (s), 103.8 (s), 52.9 (q), 52.1 (q); MS m/z (rel intensity) 348 (90, M$^+$), 316 (100).

***N*-Phenyl-7-(3-thienyl)benzo[*b*]thiophene-5,6-dicarboximide (20a).** By a procedure similar to that for **19a**, a mixture of **7a** (79 mg, 0.352 mmol) and *N*-phenylmaleimide (61 mg, 0.352 mmol) was treated with 20 mol % PPTS (18 mg, 0.071 mmol) in refluxing benzene (30 mL) for 2 h to give **20a** (113 mg, 89%). **20a**: solid; mp 250−252 °C; TLC (EtOAc/hexane, 3:7) R_f = 0.31; IR (neat) 1762, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.33 (1 H, s), 7.79−7.75 (2 H, m), 7.59 (1 H, d, J = 5.5 Hz), 7.50−7.32 (7 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.0 (s), 166.7 (s), 146.9 (s), 143.4 (s), 134.4 (s), 132.6 (d), 131.8 (s), 131.7 (s), 129.1 (s), 129.0 (d, 3 C), 128.0 (d), 126.7 (d, 2 C), 126.5 (d), 125.6 (d), 125.4 (d), 121.8 (s), 118.5 (d); MS m/z (rel intensity) 361 (100, M$^+$); HRMS calcd for $C_{20}H_{11}NO_2S_2$ 361.0231, found 361.0242. Anal. Calcd for $C_{20}H_{11}NO_2S_2$: C, 66.48; H, 3.07; N, 3.88. Found: C, 65.85; H, 2.99; N, 3.80.

7-(4-Methylphenyl)benzo[*b*]thiophene-5,6-dicarboxylic anhydride (21). By a procedure similar to that for **19a**, a mixture of **7c** (90 mg, 0.388 mmol) and maleic anhydride (38 mg, 0.388 mmol) was treated with 20 mol % PPTS (20 mg, 0.078 mmol) in refluxing benzene (30 mL) for 2 h to give **21** (76 mg, 67%). **21**: solid; mp 170−172 °C; TLC (EtOAc/hexane, 3:7) R_f = 0.40; IR (neat) 1838, 1772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (1 H, s), 7.87 (1 H, d, J = 5.3 Hz), 7.63 (1 H, d, J = 5.3 Hz), 7.50 (2 H, d, J = 8.0 Hz), 7.35 (2 H, d, J = 8.0 Hz), 2.46 (3 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.2 (s), 162.1 (s), 148.2 (s), 144.5 (s), 140.1 (s), 138.8 (s), 134.6 (d), 130.6 (s), 129.4 (d, 2 C), 128.9 (d, 2 C), 127.9 (s), 125.4 (d), 120.7 (s), 120.0 (d), 21.5 (q); MS m/z (rel intensity) 294 (100, M$^+$); HRMS calcd for $C_{17}H_{10}O_3S$ 294.0351, found 294.0348.

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Supporting Information Available: Additional experimental procedures, ORTEP drawing and crystal data of compound **4a**, and spectral data of new compounds (52 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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