Hetero-Type Benzannulation Leading to Substituted Benzothio-Phenes

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Abstract: TiCl₄ (or SnCl₄)-promoted hetero-type benzannulation reactions using various (2,2-dichlorocyclopropyl)(thiophen-2-yl)methanols proceeded smoothly to produce uniquely substituted 4-chlorobenzothiophenes (five examples). The present approach involves the first distinctive thiophene formation from thiophene cores, in contrast to traditional methods of thiophene formation from benzene cores. The stereocongested (less reactive) Cl position in the obtained 4-chlorobenzothiophenes functioned successfully as the partners of three cross-coupling reactions: (i) a Suzuki–Miyaura cross-couplings using Pd(OAc)₂/SPhos/K₃PO₄ catalysis (seven examples; 63–91%), (ii) a hydroxylation using KOH/Pd(dba)₂/tBu-XPhos catalysis (85%), and (iii) a borylation using a B₂(pin)/Pd(dba)₂/XPhos/NaOAc catalysis-provided 4-(pin)B-benzothiophene (58%).

Keywords: thiophene; benzothiophene; benzannulation; gem-dichlorocyclopropane; Suzuki–Miyaura cross-coupling; hydroxylation; borylation; titanium tetrachloride; tin tetrachloride

1. Introduction

Benzothiophenes are well-recognized, basic sulfur-containing heterocycles as thiophene benzologues, and are utilized as key pharmacophores [1,2]. Raloxifene (an anti-cancer drug) [3], sertaconazole (an anti-fungal drug) [4], benocyclidine (a psychoactive recreational drug) [5], zileuton (a lipoxygenase inhibitor) [6], etc., are representative examples. Therefore, a number of syntheses have been developed to date [1,2]. Representative methods for the construction of simple, unsubstituted benzothiophenes are categorized into several approaches (Scheme 1): (i) Hinsberg-type annulations [7–9], (ii) Friedel–Crafts type annulations [10–13], (iii) Wittig-type condensations of phosphonium salts [14,15], (iv) Metal-catalyzed thiolation annulations [16–18], (v) Pd-catalyzed C-H arylations [19], and others [20–24].

These traditional syntheses consistently utilize thiophene formations from the benzene cores. Taking this background into account, we envisaged a unique synthetic approach for the construction of benzothiophenes from counter thiophene cores, which is one type of benzannulation strategy (Scheme 2). Our group previously investigated primary non-regioselective [25] and secondary regiocontrolled [26,27] benzannulation methodologies; symmetrical (diaryl)(2,2-dichloro-1-methylcyclopropyl)methanols (AAMC-1) and non-symmetrical and stereodefined (aryl-1)(aryl-2)(2,2-dichloro-1-methylcyclopropyl)methanols (AAMC-2) underwent the reactions to produce distinct 1-aryl-4-chloronaphthalene families bearing various substituents (Scheme 3). An ipso-variant of the regiocontrolled benzannulation for synthesizing uniquely substituted α-arylnaphthalenes and its application to the total synthesis of chaunaphthone was also disclosed [27]. Recently, Anilkumar and co-workers provided a comprehensive review of the synthetic application of 1,1-dihalocyclopropanes [28].
yield. Although the reaction of alcohol fully, affording the desired 4-chloro-6-methyl-7-(thiophen-2-yl)benzothiophene (1) with 2-thienylmagnesium bromide, whereas the reaction between the lithium salt of 2-methylthiophene and acid chloride (Scheme 4). Alcohol 3 was prepared from commercially and/or readily available methyl 2,2-dichloro-1-methylcyclopropanecarboxylate (1) with 2-thienylmagnesium bromide, whereas the reaction between the lithium salt of 2-methylthiophene and acid chloride 2 was applied for the preparation of 3 due to the less reactivity of the lithium salt of 2-methylthiophene.

**Scheme 1.** Representative synthetic methods for benzothiophenes.

**Scheme 2.** Annulation synthetic methods for benzothiophenes.

**Scheme 3.** Two types of benzannulation for naphthalene formation.

### 2. Results and Discussion

Our initial attempts were guided by the reaction using (2,2-dichloro-1-methylcyclopropyl) di(thiophen-2-yl)methanols 3 and 4 (Scheme 4). Alcohol 3 was prepared from commercially and/or readily available methyl 2,2-dichloro-1-methylcyclopropanecarboxylate (1) with 2-thienylmagnesium bromide, whereas the reaction between the lithium salt of 2-methylthiophene and acid chloride 2 was applied for the preparation of 3 due to the less reactivity of the lithium salt of 2-methylthiophene.
Scheme 4. Benzothiophene formations by a hetero-type benzannulation strategy.

The TiCl₄-promoted hetero-type benzannulation using alcohol 3 proceeded successfully, affording the desired 4-chloro-6-methyl-7-(thiophen-2-yl)benzothiophene (5) in 75% yield. Although the reaction of alcohol 4 using TiCl₄ unfortunately resulted in complex mixtures, a substitution with SnCl₄ successfully afforded the corresponding benzothiophene 6 in 54% yield.

Hetero-type benzannulation using diastereoisomeric (2,2-dichloro-1,3-dimethylcyclopropyl) di(thiophen-2-yl)methanols 9 and 10 afforded intriguing results (Scheme 5). Alcohol 9 was prepared from methyl angelate by the addition of stereospecific syn-dichlorocarbene and the subsequent addition of the two molar 1-lithiated thiophene through methyl ester 7. In a similar procedure, isomeric methyl tiglate was converted to alcohol 10 through methyl ester 8. The identical TiCl₄-mediated and SnCl₄-mediated reactions using 9, however, yielded only complex mixtures. To our delight, 10 successfully underwent hetero-benzannulation to afford 11 in 48% yield. This outcome is in clear contrast to the benzannulations for naphthalene formation, wherein methyl angelate was employed as a starting compound [9,10]. The reason for the contrast switching results using diastereomeric substrates is not clear at present.

Scheme 5. Stereochemical features of the hetero-type benzannulation.

Next, the regiocontrol aspect of the present hetero-benzannulation is discussed (Scheme 6). Following the reported procedure for the preparation of AACM-2 (Scheme 3) [10], the sequential introduction of Ar groups and a 1-thienyl group to acid chloride 2 provided stereodefined alcohols 13a and 13b in good yield with excellent stereoselectivity through ketones 12a [26] and 12b, respectively. The stereochemical course of the diastereoselective addition accounts for the reported mechanistic speculation based on the Cram rule [25–27]; the thienyl anion attacks the less hindered side of the more stable s-trans conformer of ketones 12 to afford stereodefined alcohols 13 with >95:5 de.
Scheme 6. Regiocontrolled hetero-type benzannulation.

The distinctive hetero-type benzannulation procedure using 13a and 13b successfully produced 6-arylbenzothiophenes 14a and 14b in 47% and 58% yields, respectively, with high regiocontrol (Electronic Supporting Information of Free Energy Calculations: see SI).

With these successful results in hand, we investigated the functionalization of the obtained benzothiophenes 5, 11, and 14a to demonstrate the utility for synthesizing seven 4-aryl-substituted benzothiophene derivatives 15–21. As depicted in Figure 1, the Suzuki–Miyaura cross-couplings proceeded smoothly at the congested (less reactive) 4-Cl-position using Pd(OAc)$_2$/SPhos/K$_3$PO$_4$ catalysis to produce a variety of uniquely substituted benzothiophenes 15–21 in good to excellent yield. The use of K$_3$PO$_4$ was superior to that of K$_2$CO$_3$ (70%) and i-Pr$_2$NEt (65%).

Figure 1. Suzuki–Miyaura cross-coupling of 4-chlorobenzothiophenes.
As a further distinctive extension, a couple of heteroatom groups [OH- and (pin)B-] were successfully introduced into benzothiophene 5 using recently developed cross-coupling methods; KOH/Pd(dbad₂)/tBu-XPhos catalysis [29] provided 4-hydroxybenzothiophene 22, whereas B₂(pin)₂/Pd(dbad₂)/XPhos/NaOAc catalysis [30] provided 4-(pin)B-benzothiophene 23 (Scheme 7).

![Scheme 7. Two types of cross-couplings leading to 4-heteroatom-substituted benzothiophenes.](image)

**3. Materials and Methods**

((1S*,3S*)-2,2-Dichloro-1,3-dimethylcyclopropyl)di(thiophen-2-yl)methanol (3)

2-Bromothiophene (2.45 g, 15.0 mmol) was added to a stirred suspension of Mg (365 mg, 15.0 mmol) in THF (15 mL) at 20–25 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Methyl (1S*,3S*)-2,2-dichloro-1-methylcyclopropane carboxylate (commercially available or prepared by the reported method [9]) (1, 549 mg, 3.0 mmol) in THF (3.0 mL) was added to the mixture at 0–5 °C, and was stirred at 20–25 °C for 3 h. Sat. NH₄Cl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na₂SO₄) and concentrated. The obtained crude oil was purified by SiO₂ column chromatography (hexane/AcOEt = 50:1) to give the desired product 3 (739 mg, 77%).

Pale yellow oil; Rf = 0.49 (hexane/AcOEt = 10:1); 1H NMR (500 MHz, CDCl₃): δ = 1.35 (d, 1H, J = 7.5 Hz), 1.36 (s, 3H), 2.48 (d, 1H, J = 7.5 Hz), 3.24 (s, 1H), 6.72–6.74 (m, 1H), 6.88–6.91 (m, 1H), 7.06–7.09 (m, 1H), 7.29–7.32 (m, 1H), 7.33–7.35 (m, 1H), 7.40–7.42 (m, 1H); 13C NMR (125 MHz, CDCl₃): δ = 22.3, 28.7, 39.1, 67.4, 77.2, 125.6, 125.9, 126.2, 126.6, 126.9, 127.3, 146.7, 149.8; IR (neat): ν max = 3545, 3103, 3000, 1663, 1319, 1020, 667 cm⁻¹; HRMS (DART): m/z calc for C₁₃H₁₂Cl₂O₃S₂ [M − OH]+ 328.9992; found: 328.9965.

((S*)-(2,2-Dichloro-1-methylcyclopropyl)di(thiophen-2-yl)methanol (4)

nBuLi (1.57 M in hexane, 5.73 mL, 9.0 mmol) was added to a stirred solution of 2-methylthiophene (883 mg, 9.0 mmol) in THF (6.75 mL) at −78 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. 2,2-Dichloro-1-methylcyclopropanecarbonyl chloride [9] (2; 562 mg, 3.0 mmol) in THF (2.25 mL) was added to the mixture at the same temperature, and gradually warmed up to 20–25 °C for...
3 h. Sat. NH₄Cl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na₂SO₄) and concentrated. The obtained crude oil was purified by SiO₂ column chromatography (hexane/AcOEt = 30:1) to give the desired product 4 (571 mg, 67%).

Pale yellow oil; Rf = 0.65 (hexane/AcOEt = 10:1); ¹H NMR (500 MHz, CDCl₃): δ = 1.31 (d, 1H, J = 7.5 Hz), 1.36 (s, 3H), 2.43 (d, 1H, J = 7.5 Hz), 2.45 (s, 3H), 2.51 (s, 3H), 3.10 (s, 1H), 6.52–6.56 (m, 2H), 6.68–7.01 (m, 1H), 7.08–7.09 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 15.3, 15.4, 22.6, 28.7, 38.8, 67.4, 77.2, 123.7, 124.3, 126.7, 127.2, 140.4, 141.1, 143.9, 147.3; IR (neat): νmax = 3555, 2920, 1449, 1231, 1018, 907 cm⁻¹; HRMS (DART): m/z calc for C₁₅H₁₆Cl₂OS₂ [M − OH]+: 328.9992; found: 328.9965.

((15⁰,3⁰)-2,2-Dichloro-1,3-dimethylcyclopropyl)(phenyl)(thiophen-2-yl)methanol (9)

Following the procedure for the preparation of 4, the reaction using methyl (15⁰,3⁰)-2,2-dichloro-1,3-dimethylcyclopropane-1-carboxylate [9] 7 (591 mg, 3.0 mmol) derived from methyl angelate, nBuLi (1.55 M in hexane, 9.68 mL, 15.0 mmol), and thiophene (1.26 g, 15.0 mmol) in THF (18 mL) gave the crude oil, which was purified by SiO₂ column chromatography (hexane/AcOEt = 30:1) to give the desired product 9 (468 mg, 47%).

Pale yellow oil; Rf = 0.35 (hexane/AcOEt = 10:1); ¹H NMR (500 MHz, CDCl₃): δ = 1.35 (s, 3H), 1.59 (q, 1H, J = 6.9 Hz), 1.73 (d, 3H, J = 6.9 Hz), 3.22 (s, 1H), 6.75–6.77 (m, 1H), 6.89–6.91 (m, 1H), 7.04–7.07 (m, 1H), 7.31–7.34 (m, 2H), 7.38–7.40 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 10.7, 26.3, 37.1, 39.5, 73.0, 80.0, 125.6, 126.0, 126.2, 126.4, 127.0, 127.4, 148.5, 150.0; IR (neat): νmax = 3557, 3107, 2932, 2361, 1450, 1405, 700 cm⁻¹; HRMS (DART): m/z calc for C₁₄H₁₄Cl₂OS₂ [M − OH]+: 314.9836; found: 314.9814.

((15⁰,3⁰)-2,2-Dichloro-1,3-dimethylcyclopropyl)(thiophen-2-yl)methanol (10)

Following the procedure for the preparation of 4, the reaction using methyl (15⁰,3⁰)-2,2-dichloro-1,3-dimethylcyclopropane-1-carboxylate [9] 8 (985 mg, 5.0 mmol) derived from methyl tiglate, nBuLi (1.57 M in hexane, 15.9 mL, 25.0 mmol), and thiophene (2.10 g, 25.0 mmol) in THF (30 mL) gave the crude oil, which was purified by SiO₂ column chromatography (hexane/AcOEt = 30:1) to give the desired product 10 (1.13 g, 68%).

Pale yellow oil; Rf = 0.47 (hexane/AcOEt = 10:1); ¹H NMR (500 MHz, CDCl₃): δ = 1.13 (s, 3H), 1.18 (d, 3H, J = 6.9 Hz), 2.61 (q, 1H, J = 6.9 Hz), 3.25 (s, 1H), 6.70–6.72 (m, 1H), 6.85–6.88 (m, 1H), 7.05–7.08 (m, 1H), 7.28–7.33 (m, 2H), 7.39–7.42 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 9.0, 16.5, 27.4, 40.1, 71.7, 77.7, 125.5, 126.0, 126.2, 126.5, 126.8, 127.3, 146.8, 149.9; IR (neat): νmax = 3547, 3105, 2934, 2361, 1236, 835, 700 cm⁻¹; HRMS (DART): m/z calc for C₁₄H₁₄Cl₂OS₂ [M − OH]+: 314.9836; found: 314.9833.

(5⁰)-[2,2-Dichloro-1-methylcyclopropyl(phenyl)methanone (9) (12a)

(5⁰)-(4-Chlorophenyl)(2,2-dichloro-1-methylcyclopropyl)methanone (12b)

1-Bromo-4-chlorobenzene (1.15 g, 6.0 mmol) was added to a stirred suspension of Mg (146 mg, 6.0 mmol) in THF (5 mL) at 20–25 °C under Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Acid chloride 2 (937 mg, 5.0 mmol) in THF (5.0 mL) was added to the mixture at 0–5 °C, which was stirred at 20–25 °C for 3 h. Sat.NH₄Cl aqueous solution was added to the mixture, which was extracted twice
with AcOEt. The combined organic phase was washed with water, brine, dried (Na₂SO₄) and concentrated. The obtained crude oil was purified by SiO₂ column chromatography (hexane/AcOEt = 30:1) to give the desired product 12b (1.06 g, 80%).

Colorless oil; Rf = 0.63 (hexane/AcOEt = 10:1); 1H NMR (500 MHz, CDCl₃): δ = 1.50 (d, 1H, J = 7.5 Hz), 1.63 (s, 3H), 2.29 (d, 1H, J = 7.5 Hz), 7.49–7.55 (m, 2H), 7.87–7.92 (m, 2H); 13C NMR (125 MHz, CDCl₃): δ = 20.6, 30.0, 39.6, 62.2, 129.1 (2C), 131.0 (2C), 132.8, 139.9, 194.3; IR (neat): νmax = 3090, 2936, 1684, 1587, 1091, 986, 773 cm⁻¹; HRMS (DART): m/z calcd for C₁₅H₁₄Cl₂OS [M + H⁺]⁺ 262.9797; found: 262.9790. (S*)-(4-Chlorophenyl)((S*)-2,2-dichloro-1-methylcyclopropyl)methanone (13b)

Following the procedure for the preparation of 2a, the reaction using ketone 12b (1.05 g, 4.0 mmol), nBuLi (1.55 M in hexane, 5.16 mL, 8.0 mmol), and thiophene (676 mg, 8.0 mmol) in the THF (8.0 mL) gave the crude oil, which was purified by SiO₂ column chromatography (hexane/AcOEt = 50:1) to give the desired product 13b (766 mg, 57%).

Pale yellow oil; Rf = 0.40 (hexane/AcOEt = 30:1); 1H NMR (500 MHz, CDCl₃): δ = 1.26 (s, 3H), 1.32 (d, 1H, J = 7.5 Hz), 2.48 (d, 1H, J = 7.5 Hz), 2.96 (s, 1H), 6.44–6.46 (m, 1H), 6.83–6.88 (m, 1H), 7.28–7.31 (m, 1H), 7.37–7.48 (m, 3H), 7.62–7.66 (m, 2H); 13C NMR (125 MHz, CDCl₃): δ = 23.0, 28.0, 37.3, 68.0, 79.7, 125.5, 125.6, 126.7, 128.2 (2C), 128.5, 128.9 (2C), 142.0, 150.9; IR (neat): νmax = 3563, 3296, 3088, 2941, 1024, 704 cm⁻¹; HRMS (DART): m/z calcd for C₁₅H₁₄Cl₂OS [M − OH]⁻ 295.0115; found: 295.0109. (S*)-(4-Chlorophenyl)((S*)-2,2-dichloro-1-methylcyclopropyl)(thiophen-2-yl)methanol (13a)

TiCl₄ (1.0 M in 1,2-dichloroethane, 4.1 mL, 4.1 mmol) was added to a solution of alcohol 3 (1.32 g, 4.1 mmol) in 1,2-dichloroethane (83 mL) at 80 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 0.5 h. After cooling down to room temperature, sat. NaHCO₃ aqueous solution was added to the mixture, which was...
extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na2SO4) and concentrated. The obtained crude oil was purified by SiO2 column chromatography (hexane) to give the desired product 5 (822 mg, 75%).

Colorless crystals; RF = 0.34(hexane); 1H NMR (500 MHz, CDCl3): δ = 2.35 (s, 3H), 7.00–7.02 (m, 1H), 7.13–7.18 (m, 2H), 7.28–7.31 (m, 1H), 7.39–7.41 (m, 1H), 7.44–7.46 (m, 1H); 13C NMR (125 MHz, CDCl3): δ = 20.1, 124.7, 126.0, 126.1, 127.1, 127.3, 127.4, 127.7, 127.8, 135.3, 136.4, 139.3, 142.0; IR (neat): νmax = 3105, 2920, 1450, 1231, 826, 696 cm−1; HRMS (DART): m/z calcd for C13H9ClS2 [M + H]+ 293.0225; found: 293.0223.

4-Chloro-2,6-dimethyl-7-(5-methylthiophen-2-yl)benzo[b]thiophene (6)

Following the procedure for the preparation of 5, the reaction using alcohol 4 (65 mg, 0.18 mmol) in 1,2-dichloroethane (20 mL) with SnCl4 (1.0 M in dichloromethane, 0.18 mL, 0.18 mmol) in the place of TiCl4, gave the crude oil, which was purified by SiO2 column chromatography (hexane) to give the desired product 6 (28 mg, 53%).

Colorless oil; RF = 0.77(hexane); 1H NMR (500 MHz, CDCl3): δ = 2.32 (s, 3H), 2.52 (s, 3H), 2.55 (s, 3H), 2.57–2.60 (m, 1H), 6.74–6.76 (m, 1H), 6.77–6.80 (m, 1H), 7.17–7.19 (m, 1H); 13C NMR (125 MHz, CDCl3): δ = 15.3, 16.2, 20.2, 21.2, 122.5, 125.1, 125.2, 126.5, 127.2, 127.4, 135.1, 135.9, 137.2, 140.3, 142.0, 142.7; IR (neat): νmax = 3063, 2918, 2857, 1574, 1219, 1001, 802 cm−1; HRMS (DART): m/z calcd for C15H13ClS2 [M + H]+ 293.0225; found: 293.0223.

4-Chloro-5,6-dimethyl-7-(thiophen-2-yl)benzo[b]thiophene (11)

Following the procedure for the preparation of 5, the reaction using alcohol 10 (666 mg, 2.0 mmol) and TiCl4 (1.0 M in 1,2-dichloroethane, 2.0 mL, 2.0 mmol) in 1,2-dichloroethane (100 mL) gave the crude oil, which was purified by SiO2 column chromatography (hexane) to give the desired product 11 (266 mg, 48%).

Colorless crystals; RF = 0.66 (hexane/AcOEt = 30:1); mp 81–82 °C; 1H NMR (500 MHz, CDCl3): δ = 2.29 (s, 3H), 2.52 (s, 3H), 6.97–6.99 (m, 1H), 7.01–7.04 (m, 1H), 7.14–7.17 (m, 1H), 7.29–7.32 (m, 1H), 7.43–7.45 (m, 1H); 13C NMR (125 MHz, CDCl3): δ = 17.1, 18.4, 124.8, 125.9, 126.0, 127.0, 127.5, 127.6, 127.7, 131.1, 134.8, 137.0, 139.5, 140.4; IR (neat): νmax = 3017, 2920, 2949, 1323, 1229, 771 cm−1; HRMS (DART): m/z calcd for C14H11ClS2 [M + H]+ 279.0069; found: 279.0054.

4-Chloro-6-methyl-7-phenylbenzo[b]thiophene (14a)

Following the procedure for the preparation of 5, the reaction using alcohol 13a (157 mg, 0.5 mmol) and TiCl4 (1.0 M in 1,2-dichloroethane, 0.5 mL, 0.5 mmol) in 1,2-dichloroethane (5.0 mL) gave the crude oil, which was purified by SiO2 column chromatography (hexane) to give the desired product 14a (61 mg, 47%).

Pale yellow oil; RF = 0.55(hexane); 1H NMR (500 MHz, CDCl3): δ = 2.25 (s, 3H), 6.93–6.96 (m, 1H), 7.27–7.32 (m, 3H), 7.34–7.43 (m, 2H), 7.44–7.52 (m, 2H); 13C NMR (125
Following the procedure for the preparation of 5, the reaction using alcohol 13b (174 mg, 0.5 mmol) and TiCl₄ (1.0 M in 1,2-dichloroethane, 0.5 mL, 0.5 mmol) in 1,2-dichloroethane (5.0 mL) gave the crude oil, which was purified by SiO₂ column chromatography (hexane) to give the desired product 14b (83 mg, 57%).

Colorless oil; Rf = 0.50 (hexane); ¹H NMR (500 MHz, CDCl₃): δ = 2.24 (s, 3H), 6.91–6.93 (m, 1H), 7.22–7.25 (m, 2H), 7.29–7.31 (m, 1H), 7.37–7.39 (m, 1H), 7.44–7.47 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ = 19.8, 124.2, 126.2, 127.3, 128.7 (2C), 129.1, 130.6, 131.0 (2C), 133.2, 133.4, 134.1, 137.5, 140.8; IR (neat): νmax = 3103, 2922, 2361, 1558, 1491, 1015, 826 cm⁻¹; HRMS (DART): m/z calcd for C₁₇H₁₂S₃ [M + H]⁺ 307.0615; found: 307.0600.

A mixture of 5 (132 mg, 0.50 mmol), PhB(OH)₂ (91 mg, 0.75 mmol), K₃PO₄ (212 mg, 1.00 mmol), Pd(OAc)₂ (3.4 mg, 0.015 mmol), and SPhos (12 mg, 0.030 mmol) in toluene (1 mL) was stirred at 80–85 °C for 2 h. After cooling down, water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na₂SO₄) and concentrated. The obtained crude oil was purified by SiO₂ column chromatography (hexane) to give the desired product 15 (139 mg, 91%).

Colorless crystals; Rf = 0.17 (hexane); ¹H NMR (500 MHz, CDCl₃): δ = 2.42 (s, 3H), 7.06–7.08 (m, 1H), 7.17–7.22 (m, 2H), 7.31–7.33 (m, 1H), 7.37–7.39 (m, 1H), 7.41–7.47 (m, 2H), 7.49–7.54 (m, 2H), 7.74–7.78 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ = 20.2, 124.3, 125.8, 126.7, 126.9, 127.0, 127.5, 128.0, 128.1, 128.2 (2C), 128.8 (2C), 134.3, 136.3, 136.4, 140.2, 140.4, 141.5; IR (neat): νmax = 3028, 2922, 2359, 1576, 1443, 1360, 906 cm⁻¹; HRMS (DART): m/z calcd for C₁₉H₁₃Cl₂OS [M + H]⁺ 307.0615; found: 307.0600.

Following the procedure for the preparation of 15, the reaction of 5 (79 mg, 0.30 mmol) with 4-MeOC₆H₄B(OH)₂ (68 mg, 0.45 mmol), K₃PO₄ (127 mg, 0.60 mmol), Pd(OAc)₂ (2.2 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) in toluene (1 mL) and the successive purification by SiO₂ column chromatography (hexane/AcOEt = 30:1) gave the desired product 16 (85 mg, 82%).

Colorless crystals; Rf = 0.44 (hexane/AcOEt = 10:1); mp 105–106 °C; ¹H NMR (500 MHz, CDCl₃): δ = 2.41 (s, 3H), 3.89 (s, 3H), 7.03–7.08 (m, 3H), 7.16–7.22 (m, 2H),
7.27–7.30 (m, 1H), 7.36–7.39 (m, 1H), 7.44–7.47 (m, 1H), 7.68–7.71 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 20.2, 55.3, 114.2 (2C), 124.3, 125.7, 126.6, 126.7, 127.0, 127.5, 129.3 (2C), 132.9, 134.3, 136.1, 136.3, 140.3, 141.4, 159.4; IR (neat): $\nu_{\max}$ = 2955, 2359, 1611, 1514, 1246, 1179, 906 cm$^{-1}$; HRMS (DART): $m/z$ calcd for C$_{20}$H$_{16}$O$_3$S$_2$ [M + H]$^+$ 337.0721; found: 337.0706.

6-Methyl-4,7-di(thiophen-2-yl)benzo[b]thiophene (17)

Following the procedure for the preparation of 15, the reaction of 14a (79 mg, 0.30 mmol) with 2-thienylboronic acid (58 mg, 0.45 mmol), K$_3$PO$_4$ (127 mg, 0.60 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) in toluene (1 mL) and successive purification by SiO$_2$ column chromatography (hexane) gave the desired product 17 (85 mg, 85%, 89%).

Colorless crystals; Rf = 0.28 (hexane); mp 123–124 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 2.40 (s, 3H), 7.04–7.06 (m, 1H), 7.16–7.21 (m, 3H), 7.39–7.42 (m, 2H), 7.43–7.47 (m, 1H), 7.49–7.51 (m, 1H), 7.62–7.64 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 20.2, 124.4, 125.4, 125.5, 125.8, 126.4, 126.7, 127.0, 127.6, 127.8, 128.5, 129.1, 134.2, 135.1, 140.0, 141.8, 142.3; IR (neat): $\nu_{\max}$ = 3103, 2922, 2359, 1576, 1456, 906 cm$^{-1}$; HRMS (DART): $m/z$ calcd for C$_{17}$H$_{12}$S$_2$ [M + H]$^+$ 312.0101; found: 312.0091.

5,6-Dimethyl-4-phenyl-7-(thiophen-2-yl)benzo[b]thiophene (18)

Following the procedure for the preparation of 15, the reaction of 11 (84 mg, 0.30 mmol) with PhB(OH)$_2$ (55 mg, 0.45 mmol), K$_3$PO$_4$ (127 mg, 0.60 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) in toluene (1 mL) and successive purification by SiO$_2$ column chromatography (hexane) gave the desired product 18 (85 mg, 89%).

Colorless crystals; Rf = 0.29 (hexane); mp 143–144 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 2.22 (s, 3H), 2.31 (s, 3H), 7.03–7.08 (m, 2H), 7.15–7.19 (m, 1H), 7.20–7.24 (m, 1H), 7.39–7.46 (m, 4H), 7.48–7.54 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 19.9, 55.3, 114.1 (2C), 124.2, 125.6, 125.8, 126.9, 127.4, 127.7, 128.1, 128.7 (2C), 129.3 (2C), 131.1, 133.8, 136.0, 138.4, 138.9, 140.6, 141.3; IR (neat): $\nu_{\max}$ = 3069, 2922, 1601, 1441, 1211, 986, 907 cm$^{-1}$; HRMS (DART): $m/z$ calcd for C$_{20}$H$_{16}$O$_3$S$_2$ [M + H]$^+$ 321.0772; found: 321.0778.

5,6-Dimethyl-4,7-di(thiophen-2-yl)benzo[b]thiophene (19)

Following the procedure for the preparation of 15, the reaction of 11 (84 mg, 0.30 mmol) with 2-thienylboronic acid (58 mg, 0.45 mmol), K$_3$PO$_4$ (127 mg, 0.60 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) in toluene (1 mL) and successive purification by SiO$_2$ column chromatography (hexane) gave the desired product 19 (81 mg, 82%).

Colorless crystals; Rf = 0.29 (hexane); mp 207–208 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 2.30 (s, 3H), 2.33 (s, 3H), 7.02–7.05 (m, 2H), 7.13–7.15 (m, 1H), 7.16–7.21 (m, 2H),
7.24–7.25 (m, 1H), 7.44–7.46 (m, 1H), 7.47–7.49 (m, 1H); \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta = 17.9, 18.0, 124.2, 125.7, 126.0, 126.1, 127.0, 127.2, 127.5, 128.5, 129.1, 133.3, 133.8, 138.4, 140.4, 140.8, 141.0; IR (neat): \( \nu_{\max} = 3103, 2924, 1798, 1734, 1433, 1366, 1240, 1207 \text{ cm}^{-1}; \) HRMS (DART): \( m/z \) calcd for C\(_{19}\)H\(_{17}\)BO\(_2\)S\(_2\) \([M + H]^+\) 327.0336; found: 327.0337.

6-Methyl-4,7-diphenylbenzo[b]thiophene (20)

Following the procedure for the preparation of 15, the reaction of 14a (104 mg, 0.40 mmol) with PhB(OH)\(_2\) (73 mg, 0.60 mmol), K\(_2\)PO\(_4\) (170 mg, 0.80 mmol), Pd(OAc)\(_2\) (2.7 mg, 0.012 mmol) and SPhos (8.2 mg, 0.020 mmol) in toluene (1 mL), and the successive purification by SiO\(_2\) column chromatography (hexane) gave the desired product 20 (81 mg, 68%).

Colorless crystals; Rf = 0.36 (hexane); mp 171–172 °C; \(^1H\) NMR (500 MHz, CDCl\(_3\)): \( \delta = 2.32 \) (s, 3H), 6.99–7.02 (m, 1H), 7.31–7.34 (m, 2H), 7.35–7.39 (m, 2H), 7.40–7.45 (m, 2H), 7.47–7.54 (m, 4H), 7.76–7.79 (m, 2H); \(^{13}C\) NMR (125 MHz, CDCl\(_3\)): \( \delta = 19.9, 124.2, 126.2, 126.8, 127.1, 127.8, 128.2(2C), 128.3(2C), 128.7(2C), 129.7(2C), 132.1, 135.4, 135.9, 136.3, 139.9, 140.3, 140.7; IR (neat): \( \nu_{\max} = 3053, 2924, 2357, 1599, 1443, 1358, 1213, 1016 \text{ cm}^{-1}; \) HRMS (DART): \( m/z \) calcd for C\(_{21}\)H\(_{16}\)S \([M + H]^+\) 301.1051; found: 301.1053.

4-(4-Methoxyphenyl)-6-methyl-7-phenylbenzo[b]thiophene (21)

Following the procedure for the preparation of 15, the reaction of 14a (78 mg, 0.30 mmol) with 4-MeOC\(_6\)H\(_4\)B(OH)\(_2\) (68 mg, 0.45 mmol), K\(_2\)PO\(_4\) (127 mg, 0.60 mmol), Pd(OAc)\(_2\) (2.2 mg, 0.010 mmol) and SPhos (8.2 mg, 0.020 mmol) in toluene (1 mL), and the successive purification by SiO\(_2\) column chromatography (hexane/AcOEt = 30:1) gave the desired product 21 (79 mg, 80%).

Colorless crystals; Rf = 0.56 (hexane/AcOEt = 10:1); mp 155–156 °C; \(^1H\) NMR (500 MHz, CDCl\(_3\)): \( \delta = 2.31 \) (s, 3H), 3.90 (s, 3H), 6.99–7.01 (m, 1H), 7.04–7.07 (m, 2H), 7.28–7.52 (m, 7H), 7.70–7.73 (m, 2H); \(^{13}C\) NMR (125 MHz, CDCl\(_3\)): \( \delta = 19.9, 55.3, 114.1(2C), 124.2, 126.2, 126.8, 127.1, 128.3(2C), 129.3(2C), 129.8(2C), 132.1, 133.1, 135.1, 135.5, 136.3, 140.0, 140.2, 159.3; IR (neat): \( \nu_{\max} = 3034, 2930, 2835, 1609, 1502, 1244, 1034 \text{ cm}^{-1}; \) HRMS (DART): \( m/z \) calcd for C\(_{22}\)H\(_{18}\)OS \([M + H]^+\) 331.1157; found: 331.1158.

6-Methyl-7-(thiophen-2-yl)benzo[b]thiophene-4-ol (22)

A mixture of 5 (140 mg, 0.53 mmol), Pd(dbu\(_2\)) (5.8 mg, 0.01 mmol), iBu-XPhos (17 mg, 0.04 mmol) and KOH (140 mg, 2.50 mmol) in 1,4-dioxane (0.50 mL) and H\(_2\)O (0.50 mL) was stirred at 100–105 °C for 14 h. After cooling down, 1M HCl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The organic phase was washed with
water, brine, dried (Na$_2$SO$_4$), and concentrated. The obtained crude product was purified by SiO$_2$ column chromatography (hexane/AcOEt = 5:1) to give the desired product 22 (105 mg, 80%).

Colorless crystals; mp 114–115 °C; Rf = 0.34 (hexane/AcOEt = 5:1); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 2.31 (s, 3H), 6.68 (s, 1H), 6.97–6.99 (m, 1H), 7.10–7.12 (m, 1H), 7.13–7.15 (m, 1H), 7.34–7.36 (m, 1H), 7.39–7.42 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 20.2, 111.4, 121.8, 124.4, 124.7, 125.5, 126.5, 126.9, 127.5, 135.4, 140.4, 143.0, 149.9; IR (neat): $\nu_{\text{max}}$ = 3491, 3103, 2959, 2338, 1574, 1352, 1242, 1072 cm$^{-1}$; HRMS (DART): $m/z$ calcd for C$_{13}$H$_{10}$OS$_2$ [M + H]$^+$ 247.0251; found: 247.0261.

4,4,5,5-Tetramethyl-2-(6-methyl-7-(thiophen-2-yl)benzo[b]thiophen-4-yl)-1,3,2-dioxaborolane (23)

A mixture of 5 (66 mg, 0.25 mmol), bis(pinacolato)diborane (76 mg, 0.30 mmol), NaOAc (31 mg, 0.38 mmol), Pd(dba)$_2$ (6.9 mg, 0.012 mmol), and XPhos (11.9 mg, 0.025 mmol) in 1,4-dioxane (0.50 mL) was heated at 95–100 °C for 14 h. After cooling down, water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na$_2$SO$_4$) and concentrated. The obtained crude oil was purified by SiO$_2$ (neutral, Kanto Chemical, 60N) column chromatography (hexane/AcOEt = 30:1) to give the desired product 22 (52 mg, 58%).

Pale yellow crystals; mp 93–94 °C; 0.59 (hexane/AcOEt = 10:1); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 1.42 (s, 12H), 2.37 (s, 3H), 7.02–7.03 (m, 1H), 7.12–7.14 (m, 1H), 7.15–7.17 (m, 1H), 7.38–7.40 (m, 1H), 7.43–7.45 (m, 1H), 7.76 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 19.9, 24.9 (4C), 84.3 (2C), 123.2, 125.7, 126.5, 126.9, 127.4 (2C), 132.0, 132.7, 134.3, 140.2, 140.4, 143.3; IR (neat): $\nu_{\text{max}}$ = 3103, 2976, 2926, 1609, 1502, 1244, 1034 cm$^{-1}$; HRMS (DART): $m/z$ calcd for C$_{13}$H$_{21}$BO$_2$S$_2$ [M + H]$^+$ 331.1157; found: 331.1158.

4. Conclusions

We achieved regiocontrolled hetero-type benzannulations of various (2,2-dichlorocyclopropyl)(thiophen-2-yl)methanols to produce uniquely substituted benzothiophenes. This wide variety of hetero-type benzannulations and functionalizations will contribute to synthetic studies, especially for medicinal and material chemistries.

Furthermore, three types of cross-coupling derivatizations of the obtained stereo-congested (less reactive) 4-chlorobenzothiophenes were performed: (i) Suzuki–Miyaura cross-couplings affording various 4-arylbenzothiophenes, (ii) hydroxylation leading to a 4-hydroxybenzothiophene, and (iii) borylation leading to a 4-(pin)B-benzothiophene. This wide variety of hetero-type benzannulations and functionalizations will contribute to synthetic studies, especially for medicinal and material chemistries.

Supplementary Materials: The following are available online, $^1$H NMR, $^{13}$C NMR spectra for compounds 3–23 (Figure S1–S44), Electronic Supporting Information (S24).

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Sample Availability: Samples of all the compounds 1–23 are available from the authors.

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