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Organocatalytic γ′[C(sp³)–H] Functionalization of Ynones: An Unusual Approach for the Cyclopentannulation of Benzothiophenes

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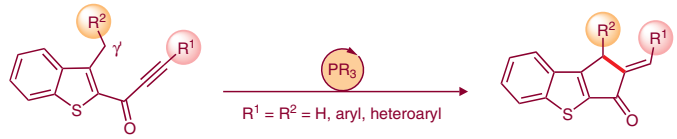

* Organocatalytic intramolecular hydroalkylation of ynones via γ′[C(sp³)–H] functionalization
* Unique access to cyclopenta[*b*]annulated benzothiophenes
* 12 examples; 60–92% yield

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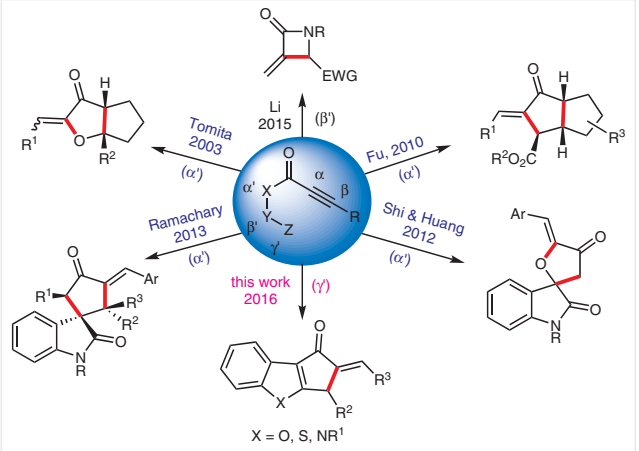
Abstract An efficient organocatalytic approach for the cyclopenta[*b*]annulation of benzothiophenes via γ′[C(sp³)–H] functionalization of ynones is described. Nucleophilic addition of an organophosphine to the designed ynones generates heteroaryl-based *ortho*-quinodimethanes (oQDMs), which undergo carbocyclization to provide a variety of cyclopenta-fused benzothiophenes. This approach also constitutes an unusual organophosphine-catalyzed intramolecular hydroalkylation of ynones.

Key words organophosphines, hydroalkylation, cyclopentannulation, ynones, benzothiophenes

Cyclopenta-annulated heterocycles have attracted the attention of synthetic chemists owing to their prevalence in several bioactive natural products and pharmaceutically pertinent compounds.[2] In addition, cyclopenta-fused heteroaromatics are widely employed in electronic devices such as organic photovoltaic devices (OPVs) and organic field-effect transistors (OFETs).[3] Consequently, several strategies were developed for the synthesis of cyclopenta[*b*]annulated heteroarenes.[4] However, the development of practical and efficient methods for this class of compounds from readily available compounds still remains an area of intense research.

Nucleophilic organophosphine catalysis has emerged as a versatile synthetic tool to rapidly assemble complex molecular architectures.[5] In 2003, Tomita discovered the organophosphine catalyzed α′[C(sp³)–H]-functionalization of ynones and successfully applied it for the synthesis of several bicyclic structures (Scheme 1).[6] Subsequently, the research groups of Fu,[7] Shi,[8] Huang,[9] and Ramachary[10] have extended the α′[C(sp³)–H]-functionalization strategy to obtain a variety of [3+2] and [4+2] cycloadducts (Scheme 1). In 2015, Li and co-workers have reported PPh_3-catalyzed β′[C(sp³)–H]-functionalization approach to access an interesting range of α-methylene-β-lactams (Scheme 1).[11] In this direction, we have recently described the first organophosphine-catalyzed γ′[C(sp³)–H] functionalization of ynones leading to the synthesis of an array of cyclopenta-fused heteroarenes (Scheme 1).[12] Herein, we wish to report a new organocatalyzed approach for the synthesis of a diverse set of cyclopenta-fused heterocycles via γ′[C(sp³)–H] functionalization of ynones.



Scheme 1 Phosphine-catalyzed C–H functionalization of ynones

Functionalization of C(sp³)–H has been the subject of active pursuit. This goal is primarily achieved by transition-metal-catalyzed functional-group-directed C–H activation.[13] However, metal-free and directing group-free activation of benzylic C(sp³)–H has been realized only recently through the pioneering trienamine-mediated organocatalytic approaches elucidated by Jørgensen, Chen, and Melchiorre (Scheme 2, a).[14] Further, Chi and Xu's N-heterocyclic carbene (NHC)-catalyzed benzylic C(sp³)–H functionaliza-

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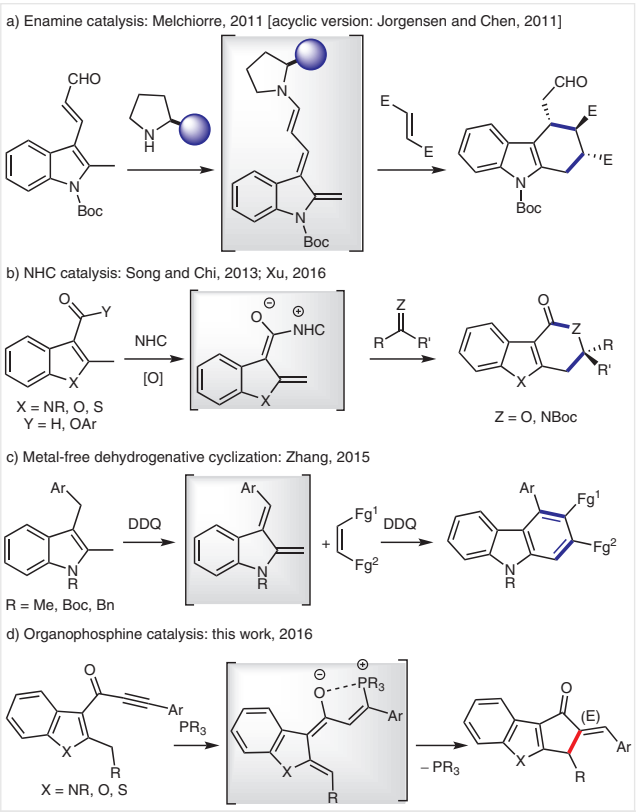
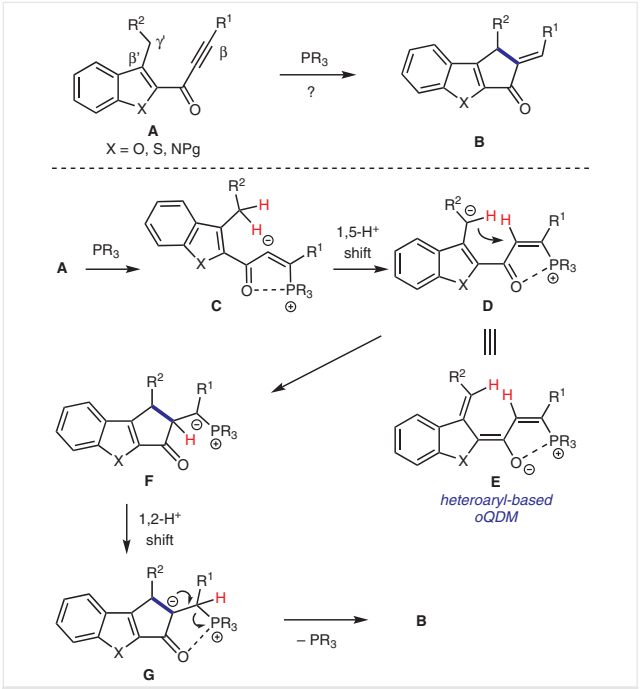
tions (Scheme 2, b),[15] and Zhang's metal-free dehydrogenative cyclization pathways (Scheme 2, c)[16] contributed enormously to the advancement of this area. The underlying concept in these studies is that the in situ generated heteroaryl-based *ortho*-quinodimethane (oQDM) intermediates undergo a typical [4+2] cycloaddition reaction to afford heteroarenes annulated with six-membered rings.[17] In contrast, our recent study deals with the generation of heteroaryl-based oQDMs under the influence of an organophosphine, and provides an efficient synthetic access to a variety of cyclopenta[*b*]annulated heteroarenes (Scheme 2, d).



Scheme 2 A comparison of the existing metal-free approaches involving heteroaryl-based oQDM intermediates

Against this background, and in continuation of our studies on the organophosphine-catalyzed annulation of heteroarenes,[12,18] we hypothesized whether the substrate design **A** could furnish the product **B** via phosphine-catalyzed γ′[C(sp^3)–H] functionalization (Scheme 3). It was expected that the conjugate addition of a phosphine to the ynone **A** could generate the zwitterionic intermediate **C**. Intramolecular 1,5-proton migration from the benzylic C(sp^3)–H could furnish heteroaryl-based oQDM **E**. Subsequent proton shifts can provide the expected product **B**.[12,19]

It can be anticipated that the reduced acidity of the γ′[C–H] in **A** renders the formation of the 3-heteroaryl-



Scheme 3 Our hypothesis for the cyclopentannulation of heteroarenes via γ′[C(sp^3)–H] functionalization

methyl anion **D** more demanding (unlike the 2-heteroarylmethyl anions); consequently, the prospects of formation of the respective oQDM **E** can be slim, and therefore the product formation can be challenging.

The aforementioned hypothesis was indeed verified through a pK_a study (Figure 1).[20,21] A comparison of the pK_a of the model substrates 2-methylbenzothiophene (**M-1**) and 3-methylbenzothiophene (**M-2**) with those of the respective ynone-appended benzothiophenes **M-3** to **M-6** clearly indicated the enhanced acidity of the γ′[C–H] (Figure 1, column 1 vs columns 2 and 3), which can be readily attributed to the presence of the ynone functionality. As expected, a substitution at the γ′-position marginally reduced the acidity of the C–H (Figure 1, column 2 vs column 3), but still significantly higher than even acetone (**M-10**). In addition, acidity of the benzylic C–H in 2-alkylated benzothiophenes **M-3** and **M-4** was found to be higher than the respective 3-alkylated benzothiophenes **M-5** and **M-6** (Figure 1, row 1 vs row 2). From these deliberations, we became aware of the benzylic C(sp^3)–H acidities of the 2- and 3-alkylated benzothiophenes and subsequently, the influence of ynone functionality on their acidities. Interestingly, the acidities of the benzylic C(sp^3)–H in benzothiophenes and benzofurans were comparable (**M-1** and **M-7**; **M-3** and **M-8**; **M-4** and **M-9**) and so the pK_a values for the respective benzofuran analogues of **M-2**, **M-5** and **M-6** were not estimated.

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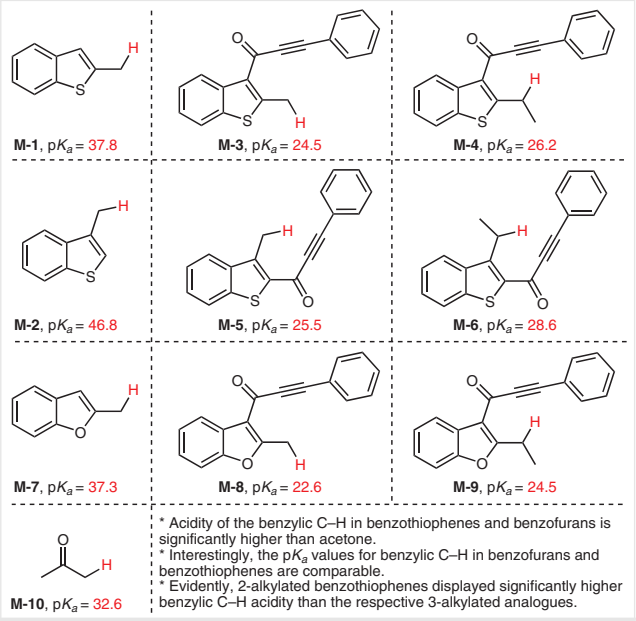
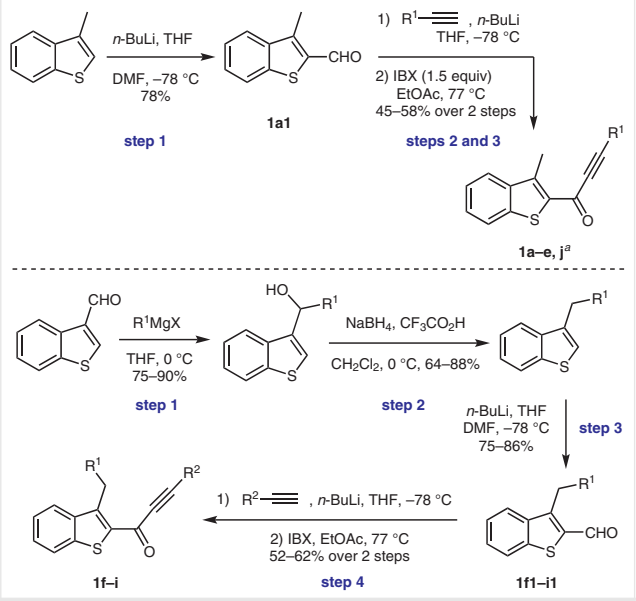


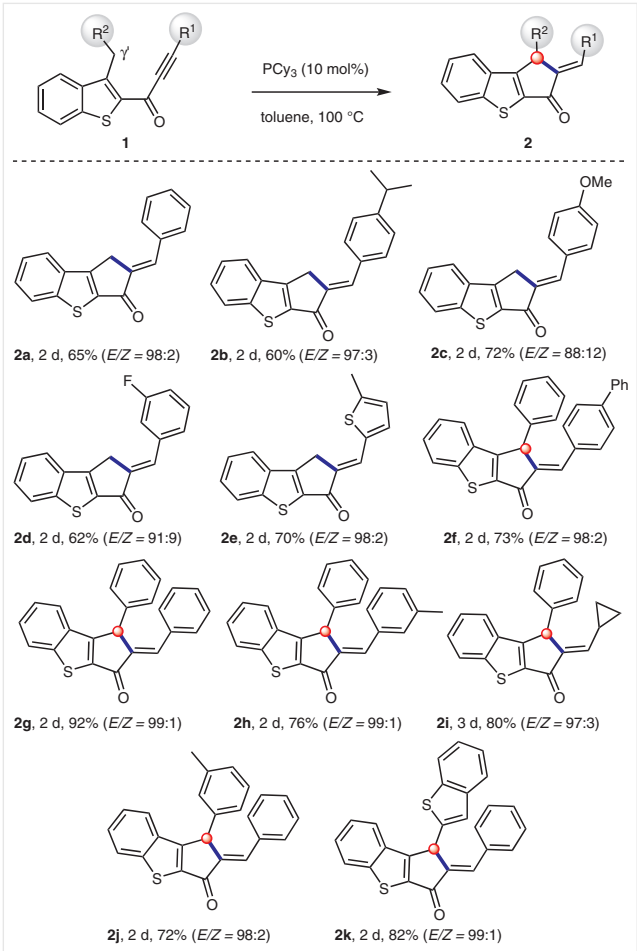
Figure 1 Estimation of the pK_a of the selected benzothiophene and benzofuran derivatives by computational methods

At the beginning of our investigation, we devoted our efforts to establish general and high-yielding methods for the synthesis of ynones required to validate the hypothesis presented in Scheme 3. The ynones **1a–j** with benzothiophene as a backbone that were employed in the study were prepared by following the protocols described in Scheme 4.



Scheme 4 Synthesis of the ynones appended to 3-alkylated benzothiophenes employed in this study. [a] Ethynylmagnesium bromide was employed in step 2 for the synthesis of **1j**.

The ynone **1a** was subjected to the reaction conditions described in our earlier work concerning the synthesis of cyclopenta[*b*]heteroarenes.[12] However, as speculated, the reaction of **1a** did not proceed under the prototypical conditions (cat. PCy_3, CH_2Cl_2, r.t.). But, to our delight, a brief optimization led to the identification of suitable conditions for achieving the desired outcome. The reaction of the ynone **1a** with PCy_3 in toluene at 100 °C successfully furnished the respective product **2a** in excellent yield with remarkable stereoselectivity (Scheme 5).



Scheme 5 Substrate scope. Isolated yields after column chromatography are shown. *E*/*Z* ratios were determined by ^{1}H NMR analysis of the purified sample.

To illustrate the generality of the protocol, a variety of ynones tethered to benzothiophene backbone were examined under the optimized conditions. The results of this investigation are summarized in Scheme 5. The reaction of the ynones **1b–e** with PCy_3 in toluene at 100 °C successfully furnished the respective products **2b–e** in good to excellent yields with remarkable stereoselectivities. Noteworthy feature of the reaction is its flexibility towards electron-rich as

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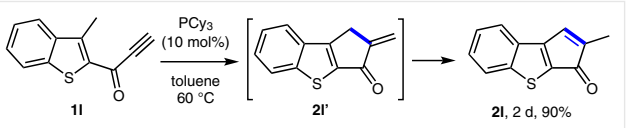
well as electron-poor arenes, and heteroarenes on the alkyne.

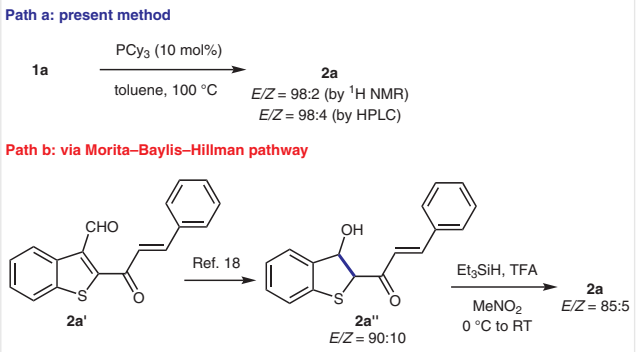
With this success, our attention was turned towards exploring the effect of γ′-branching on the annulation process. We envisaged that γ′-branching can provide an opportunity to explore an enantioselective variant of this reaction, since the reaction leads to the generation of a new stereogenic center in the products. In addition, it significantly enhances the scope of the reaction. Accordingly, the ynones **1f–k** were subjected to the optimized conditions. Gratifyingly, the reaction appeared to be quite general with respect to the substrate designs tested, providing the respective cyclopenta-annulated benzothiophenes **2f–k** in consistent yields and high stereoselectivities (Scheme 5). In particular, ynones possessing electron-donating aryl groups (**2h**), and alkyl groups (**2i**), and substrates bearing γ′-aryl (**2f–j**) and heteroaryl groups (**2k**) turned out to be equally efficient, thereby highlighting the versatility of this protocol.

As an extension of the γ′-functionalization strategy, reaction of the ynone bearing terminal alkyne (**1l**) was planned (Scheme 6). Interestingly, reaction of **1l** under the reaction conditions afforded 2-methyl-3*H*-benzo[*b*]cyclopenta[*d*]thiophen-3-one (**2l**), presumably via the isomerization of the initially formed **2l′**. Thus, an approach for the synthesis of cyclopentenone-fused benzothiophene was also established.



Scheme 6 Synthesis of cyclopentenone-fused benzothiophene

Considering the excellent stereoselective nature of the reaction, we planned to confirm the stereochemistry of the major isomer by a parallel synthetic route. For this, we planned to synthesize the compound **2a** in a known method starting from **2a′** (Scheme 7).[18] The HPLC chromatogram



Scheme 7 Confirmation of the stereochemistry of the major isomer

of **2a** obtained via path b was compared with **2a** obtained via the present method (path a) and accordingly *E*/*Z* ratios were estimated. The results confirmed the high stereoselective cyclopentannulation of ynones to deliver *E*-isomer in major quantities (see the Supporting Information). This result is also consistent with the proposed mechanism in Scheme 3.

While exploring the substrate scope, we have realized certain limitations of the present protocol. Several of our attempts to develop a catalytic enantioselective version were unsuccessful. In addition, no product formation could be observed with the benzothiophenes bearing γ′-alkyl substituents (**1m**) (but the reaction works efficiently with the substrates having γ′-aryl substitution, see **2f–k**), and substrates possessing either indole (**3a**) or benzofuran backbones **4a** and **4b** (Figure 2), though the reasons are not completely understood at this stage. But it can be attributed to the acidity requirements of the benzylic C(sp^3)–H. For example, a facile reaction of the benzothiophene-based ynones **1**, and no reaction of the ynones possessing indole or benzofuran backbones **3** and **4** potentially indicate a narrow pK_a requirement for a successful transformation (see Figure 1).

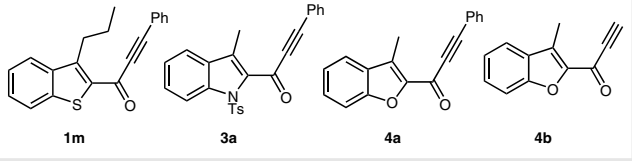


Figure 2 A few non-working examples

In summary, we have presented our efforts towards the development of organophosphine-catalyzed γ′[C(sp^3)–H] functionalization/intramolecular hydroalkylation of ynones leading to the synthesis of diverse cyclopenta[*b*]annulated benzothiophenes. This method also establishes a new means of generating heteroaryl-based oQDMs and their unprecedented carbocyclization. Noteworthy features of this method are its display of excellent levels of efficiency and consistency with regard to yield and stereoselectivity. We believe that the present study can have implications on the development of newer organocatalytic C(sp^3)–H-functionalization pathways. Efforts to extend this novel synthetic tool for the synthesis of other privileged scaffolds is in progress and the results will be communicated in due course.

All the starting compounds and catalysts employed in this study were procured from commercial sources and were used without further purification. For TLC, aluminum-backed silica gel sheets with fluorescent indicator 254 nm were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), concd H_2SO_4 (35 mL), and AcOH (10 mL) in

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EtOH (900 mL) followed by heating. Column chromatography was performed using 100–200 mesh silica gel (approximately 15–20 g per 1 g of the crude product). Anhydrous THF was obtained by distillation over Na and stored over Na wire. IR spectra were recorded on a FT-IR spectrometer as thin films or KBr pellet in cm^{-1}. Melting points were recorded on a digital melting point apparatus. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz FT-NMR spectrometer. NMR shifts are reported as δ units in ppm and coupling constants *J* are reported in hertz (Hz). Standard abbreviations are utilized to describe peak patterns. Proton chemical shifts are given in δ relative to TMS (δ = 0.00) in $CDCl_3$. Carbon chemical shifts are internally referenced to the deuterated solvent signals in $CDCl_3$ (δ = 77.1). High-resolution mass spectra were recorded on a QTOF mass spectrometer.

The compounds **1a–e** were prepared as described in Scheme 4 starting from 3-methylbenzothiophene **1a1**.

3-Methylbenzo[*b*]thiophene-2-carbaldehyde (1a1); Typical Procedure for Step 1 (Scheme 4)

To a solution of 3-methylbenzothiophene (1.00 g, 7.45 mmol) in anhydrous THF (35 mL) cooled at –78 °C was added dropwise *n*-BuLi (5.12 mL, 1.6 M in hexane, 8.20 mmol). After stirring for 1 h at –78 °C, DMF (1.15 mL, 14.90 mmol) was added dropwise and the reaction continued for 1 h. The reaction mixture was quenched by the addition of sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc and the organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The purification of the residue by column chromatography (hexane/EtOAc, 95:5) afforded **1a1** as a pale yellow solid;[22] yield: 853 mg (78%); mp 87–89 °C; R_f = 0.7 (hexane/EtOAc 8:2).

IR (KBr): 2915, 1651, 1529, 1377, 1265, 1212, 1074, 936 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.36 (s, 1 H), 7.92–7.88 (m, 2 H), 7.54 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.49–7.45 (m, 1 H), 2.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.0, 143.0, 142.0, 140.0, 137.5, 128.4, 124.8, 123.9, 123.3, 12.1.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{10}H_9OS$: 177.0374; found: 177.0349.

Benzothiophenes 1a–e; Steps 2 and 3 (Scheme 4)

These compounds were prepared by following the literature procedures.[12]

1-(3-Methylbenzo[*b*]thiophen-2-yl)-3-phenylprop-2-yn-1-one (1a)

Pale yellow solid; mp 98–100 °C; R_f = 0.7 (hexane/EtOAc 8:2).

IR (KBr): 2924, 2196, 1622, 1589, 1513, 1302, 1193, 1086 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.1 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.73–7.71 (m, 2 H), 7.54–7.51 (m, 2 H), 7.48–7.44 (m, 3 H), 2.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 141.5, 140.9, 140.6, 137.4, 133.0 (2 × CH), 130.9, 128.7 (2 × CH), 128.0, 124.8, 124.4, 122.8, 120.0, 92.9, 88.7, 13.8.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{18}H_{13}OS$: 277.0687; found: 277.0699.

3-(4-Isopropylphenyl)-1-(3-methylbenzo[*b*]thiophen-2-yl)prop-2-yn-1-one (1b)

Yellow oil; R_f = 0.6 (hexane/EtOAc 8:2).

IR (neat): 2961, 2192, 1622, 1595, 1513, 1283, 1195, 1086, 834 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.90 (m, 1 H), 7.88–7.86 (m, 1 H), 7.67–7.65 (m, 2 H), 7.54–7.44 (m, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 2.98 (quint, *J* = 6.9 Hz, 1 H), 2.93 (s, 3 H), 1.30 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 152.5, 141.5, 140.74, 140.72, 137.6, 133.2 (2 × CH), 128.0, 126.9 (2 × CH), 124.8, 124.4, 122.8, 117.2, 93.7, 88.6, 34.3, 23.7 (2 × CH_3), 13.8.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{21}H_{19}OS$: 319.1157; found: 319.1143.

3-(4-Methoxyphenyl)-1-(3-methylbenzo[*b*]thiophen-2-yl)prop-2-yn-1-one (1c)

Pale yellow solid; mp 118–120 °C; R_f = 0.5 (hexane/EtOAc 7:3).

IR (KBr): 2929, 2188, 1600, 1509, 1305, 1255, 1170, 1085, 940 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.6 Hz, 1 H), 7.89 (d, *J* = 7.9 Hz, 1 H), 7.70–7.67 (m, 2 H), 7.55–7.45 (m, 2 H), 6.98–6.96 (m, 2 H), 3.89 (s, 3 H), 2.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 161.8, 141.4, 140.7, 140.5, 137.6, 135.0 (2 × CH), 127.9, 124.7, 124.3, 122.8, 114.4 (2 × CH), 111.7, 94.1, 88.8, 55.5, 13.8.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{19}H_{15}O_2S$: 307.0793; found: 307.0780.

3-(3-Fluorophenyl)-1-(3-methylbenzo[*b*]thiophen-2-yl)prop-2-yn-1-one (1d)

Pale yellow solid; mp 97–99 °C; R_f = 0.7 (hexane/EtOAc 7:3).

IR (KBr): 2925, 2201, 1626, 1604, 1581, 1514, 1356, 1210, 1087, 972 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.93 (m, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.57–7.39 (m, 5 H), 7.24 (tdd, *J* = 8.4, 2.6, 1.0 Hz, 1 H), 2.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 162.3 (d, *J* = 246.5 Hz, 1 C), 141.5 (d, *J* = 30.8 Hz, 1 C), 140.6, 137.1, 130.5 (d, *J* = 8.5 Hz, 1 C), 128.94, 128.91, 128.2, 124.9, 124.5, 122.9, 121.8 (d, *J* = 9.4 Hz, 1 C), 119.6 (d, *J* = 23.2 Hz, 1 C), 118.4 (d, *J* = 21.0 Hz, 1 C), 90.7 (d, *J* = 3.5 Hz, 1 C), 88.8, 13.8.

^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –111.5.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{18}H_{12}FOS$: 295.0593; found: 295.0581.

1-(3-Methylbenzo[*b*]thiophen-2-yl)-3-(5-methylthiophen-2-yl)prop-2-yn-1-one (1e)

Pale yellow solid; mp 104–106 °C; R_f = 0.5 (hexane/EtOAc 8:2).

IR (KBr): 2923, 2178, 1614, 1592, 1513, 1285, 1213, 1160, 914 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.8 Hz, 1 H), 7.87 (d, *J* = 7.9 Hz, 1 H), 7.54–7.46 (m, 2 H), 7.45–7.44 (m, 1 H), 6.81–6.79 (m, 1 H), 2.92 (s, 3 H), 2.57 (d, *J* = 0.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 147.7, 141.4, 140.7, 140.5, 137.5, 137.4, 127.9, 126.5, 124.7, 124.3, 122.8, 117.2, 93.3, 88.3, 15.7, 13.7.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{17}H_{13}OS_2$: 297.0408; found: 297.0395.

Benzothiophenes 1f–i; General Procedure

Compounds **1f–i** were prepared as described in Scheme 4 starting from commercially available benzo[*b*]thiophene-3-carbaldehyde. Literature procedures were followed for the Grignard reaction (step 1),[23] for dehydroxylation (step 2),[24] and for steps 3 and 4, the procedures described for the preparation of **1a–e** were followed.

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3-Benzylbenzo[*b*]thiophene-2-carbaldehyde (1f1)

Pale yellow solid; mp 99–101 °C; R_f = 0.7 (hexane/EtOAc 8:2).

IR (KBr): 2920, 1660, 1524, 1494, 1452, 1206, 764 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.36 (s, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.86 (d, *J* = 8.1 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.42–7.38 (m, 1 H), 7.33–7.31 (m, 3 H), 7.25–7.21 (m, 2 H), 4.66 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.1, 144.6, 142.4, 139.9, 138.8, 138.4, 128.8 (2 × CH), 128.3, 128.1 (2 × CH), 126.8, 125.0, 124.5, 123.4, 32.2.

HRMS (ESI): *m*/*z* (M + Na)$^+$ calcd for $C_{16}H_{12}OSNa$: 275.0507; found: 275.0495.

3-([1,1′-Biphenyl]-4-yl)-1-(3-benzylbenzo[*b*]thiophen-2-yl)prop-2-yn-1-one (1f)

Pale yellow solid; mp 161–163 °C; R_f = 0.6 (hexane/EtOAc 8:2).

IR (KBr): 2923, 2190, 1621, 1598, 1510, 1485, 1288, 1208, 1178, 1077, 841 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.1 Hz, 1 H), 7.89 (d, *J* = 8.2 Hz, 1 H), 7.64–7.62 (m, 4 H), 7.59–7.57 (m, 2 H), 7.54–7.48 (m, 3 H), 7.45–7.39 (m, 2 H), 7.34–7.28 (m, 4 H), 7.25–7.20 (m, 1 H), 4.94 (s, 2 H).

^{13}C NMR (100 Hz, $CDCl_3$): δ = 171.4, 143.8, 142.3, 141.8, 140.3, 139.7, 138.8, 138.7, 133.6 (2 × CH), 129.0 (2 × CH), 128.6 (2 × CH), 128.4 (2 × CH), 128.2, 128.0, 127.3 (2 × CH), 127.1 (2 × CH), 126.3, 125.07, 125.05, 122.9, 118.4, 93.2, 89.2, 33.0.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{30}H_{21}OS$: 429.1313; found: 429.1295.

1-(3-Benzylbenzo[*b*]thiophen-2-yl)-3-phenylprop-2-yn-1-one (1g)

Pale yellow solid; mp 122–124 °C; R_f = 0.7 (hexane/EtOAc 8:2).

IR (KBr): 2926, 2193, 1622, 1510, 1281, 1204, 1077, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.87 (m, 2 H), 7.54–7.47 (m, 4 H), 7.42–7.38 (m, 3 H), 7.31–7.28 (m, 4 H), 7.23–7.19 (m, 1 H), 4.92 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 142.3, 141.8, 140.3, 138.7, 138.6, 133.1 (2 × CH), 131.0, 128.6 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.0, 126.3, 125.06, 125.04, 122.9, 119.7, 93.1, 88.5, 33.0.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{17}OS$: 353.1000; found: 353.1010.

1-(3-Benzylbenzo[*b*]thiophen-2-yl)-3-(*m*-tolyl)prop-2-yn-1-one (1h)

Pale yellow solid; mp 111–113 °C; R_f = 0.6 (hexane/EtOAc 8:2).

IR (KBr): 2926, 2192, 1623, 1601, 1511, 1213, 1078, 1041, 867 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (dd, *J* = 8.1, 0.8 Hz, 1 H), 7.89–7.87 (m, 1 H), 7.51 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1 H), 7.42–7.28 (m, 8 H), 7.26–7.22 (m, 2 H), 4.93 (s, 2 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 142.2, 141.8, 140.3, 138.9, 138.7, 138.5, 133.6, 132.0, 130.3, 128.6 (2 × CH), 125.58, 128.50 (2 × CH), 128.0, 126.3, 125.07, 125.04, 122.9, 119.5, 93.6, 88.3, 33.0, 21.2.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{25}H_{19}OS$: 367.1157; found: 367.1140.

1-(3-Benzylbenzo[*b*]thiophen-2-yl)-3-cyclopropylprop-2-yn-1-one (1i)

Pale yellow solid; mp 97–99 °C; R_f = 0.7 (hexane/EtOAc 8:2).

IR (KBr): 2923, 2205, 1623, 1599, 1512, 1283, 1243, 1183, 1030, 877 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.1 Hz, 1 H), 7.83 (dd, *J* = 8.2, 0.9 Hz, 1 H), 7.48 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1 H), 7.37 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1 H), 7.30–7.24 (m, 4 H), 7.22–7.18 (m, 1 H), 4.83 (s, 2 H), 1.46 (tt, *J* = 8.2, 5.0 Hz, 1 H), 1.02–0.97 (m, 2 H), 0.90–0.86 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 141.7 (2 × CH), 141.6, 140.2, 138.8, 128.5 (2 × CH), 128.3 (2 × CH), 127.8, 126.3, 124.96, 124.91, 122.8, 101.4, 77.2, 32.8, 9.9 (2 × CH_2), 0.08.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{21}H_{17}OS$: 317.1000; found: 317.0990.

1-[3-(3-Methylbenzyl)benzo[*b*]thiophen-2-yl]-3-phenylprop-2-yn-1-one (1j)

Pale yellow oil; R_f = 0.6 (hexane/EtOAc 9:1).

IR (neat): 2924, 2194, 1623, 1511, 1427, 1361, 1300, 1283, 1202, 1077, 1040, 944, 759, 745, 687 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.82 (m, 2 H), 7.48–7.41 (m, 4 H), 7.35–7.32 (m, 3 H), 7.08 (m, 2 H), 7.03 (d, *J* = 7.8 Hz, 1 H), 6.97 (d, *J* = 7.4 Hz, 1 H), 4.83 (s, 2 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 142.5, 141.8, 140.3, 138.6 (2 C), 138.1, 133.1 (2 C), 131.0, 129.2, 128.6 (2 C), 128.4, 128.0, 127.1, 125.4, 125.1, 125.0, 122.8, 119.8, 93.1, 88.5, 32.9, 21.4.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{25}H_{19}OS$: 367.1157; found: 367.1172.

1-[3-(Benzo[*b*]thiophen-2-ylmethyl)benzo[*b*]thiophen-2-yl]-3-phenylprop-2-yn-1-one (1k)

Pale yellow viscous oil; R_f = 0.5 (hexane/EtOAc 9:1).

IR (neat): 2924, 2190, 1621, 1511, 1430, 1384, 1303, 1277, 1190, 1074, 1037, 742, 687 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.1 Hz, 1 H), 7.87 (d, *J* = 8.1 Hz, 1 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 7.60–7.57 (m, 3 H), 7.50–7.34 (m, 5 H), 7.26–7.18 (m, 2 H), 7.05 (s, 1 H), 5.06 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 142.4, 141.8, 140.8, 139.9, 139.8, 139.5, 138.3, 133.2 (2 C), 131.1, 128.7 (2 C), 128.2, 125.3, 124.7, 124.2, 123.8, 123.0 (2 C), 122.1, 121.9, 119.7, 93.3, 88.5, 28.4.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{26}H_{17}OS_2$: 409.0721; found: 409.0704.

1-(3-Methylbenzo[*b*]thiophen-2-yl)prop-2-yn-1-one (1l)

Pale yellow solid; mp 100–102 °C; R_f = 0.5 (hexane/EtOAc 8:2).

IR (KBr): 3207, 3054, 2095, 1621, 1594, 1511, 1356, 1281, 1237, 916, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.1 Hz, 1 H), 7.86 (d, *J* = 8.1 Hz, 1 H), 7.53 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.48–7.44 (m, 1 H), 3.53 (s, 1 H), 2.87 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 142.0, 141.7, 140.5, 136.3, 128.3, 124.9, 124.5, 122.9, 81.8, 80.6, 13.8.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_9OS$: 199.0218; found: 199.0220.

Cyclopenta-Fused Benzothiophenes 2a–j; General Procedure

An oven dried 5 mL round-bottom flask was charged with ynone **1** (0.1 mmol), toluene (1 mL) and PCy_3 (0.01 mmol) at r.t. under N_2 atmosphere and the contents were stirred at 100 °C until the ynone **1** had disappeared as monitored by TLC. All the volatiles were removed

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under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography using hexane/EtOAc as eluent, to afford the respective product **2**.

(*E*)-2-Benzylidene-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2a)

Yield: 19 mg (65%); colorless solid; mp 183–185 °C; R_f = 0.5 (hexane/EtOAc 8:2).

IR (KBr): 2924, 1688, 1629, 1467, 1288, 1175, 1150, 1055, 921 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 2 H), 7.69 (d, *J* = 7.3 Hz, 2 H), 7.63 (s, 1 H), 7.54–7.49 (m, 4 H), 7.46–7.42 (m, 1 H), 4.10 (d, *J* = 1.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.4, 158.6, 147.8, 142.9, 137.0, 135.0, 134.0, 133.1, 130.5 (2 × CH), 129.6, 129.0 (2 × CH), 128.3, 125.2, 124.5, 123.6, 29.7.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{18}H_{13}OS$: 277.0687; found: 277.0699.

(*E*)-2-(4-Isopropylbenzylidene)-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2b)

Yield: 18 mg (60%); yellow semi-solid; R_f = 0.4 (hexane/EtOAc 8:2).

IR (neat): 2960, 1687, 1631, 1516, 1383, 1274, 1094, 923 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.93 (m, 2 H), 7.65–7.62 (m, 3 H), 7.55–7.49 (m, 2 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 4.10 (d, *J* = 1.7 Hz, 2 H), 3.0 (dt, *J* = 13.8, 6.9 Hz, 1 H), 1.32 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.5, 158.4, 151.0, 147.7, 143.0, 136.1, 134.1, 133.2, 132.6, 130.7 (2 × CH), 128.2, 127.1 (2 × CH), 125.2, 124.5, 123.6, 34.1, 29.7, 23.8 (2 × CH_3).

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{21}H_{19}OS$: 319.1157; found: 319.1147.

(*E*)-2-(4-Methoxybenzylidene)-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2c)

Yield: 18 mg (72%); colorless solid; mp 234–236 °C; R_f = 0.4 (hexane/EtOAc 7:3).

IR (KBr): 2925, 1682, 1624, 1601, 1513, 1256, 1177, 1096, 1029, 923 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.95 (m, 2 H), 7.68 (d, *J* = 8.8 Hz, 2 H), 7.61 (s, 1 H), 7.56–7.50 (m, 2 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 4.11 (d, *J* = 1.3 Hz, 2 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.6, 160.8, 158.1, 147.7, 143.1, 134.7, 134.1, 133.0, 132.3 (2 × CH), 128.1, 127.8, 125.2, 124.5, 123.5, 114.5 (2 × CH), 55.4, 30.9.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{19}H_{15}O_2S$: 307.0793; found: 307.0782.

(*E*)-2-(3-Fluorobenzylidene)-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2d)

Yield: 19 mg (62%); colorless solid; mp 167–169 °C; R_f = 0.5 (hexane/EtOAc 7:3).

IR (KBr): 2926, 1691, 1633, 1582, 1278, 1247, 1150, 966, 902 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 13.7, 7.4 Hz, 2 H), 7.60–7.47 (m, 5 H), 7.40 (d, *J* = 10.0 Hz, 1 H), 7.16 (d, *J* = 6.8 Hz, 1 H), 4.13 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.1, 162.9 (d, *J* = 245.1 Hz, 1 C), 158.6, 147.9, 142.8, 138.1, 133.9, 131.7 (d, *J* = 2.3 Hz, 1 C), 130.58, 130.50, 128.4, 126.5 (d, *J* = 2.6 Hz, CH), 125.3, 124.6, 123.7, 116.6 (d, *J* = 9.3 Hz, CH), 116.4 (d, *J* = 10.1 Hz, CH), 29.6.

^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –112.1.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{18}H_{12}FOS$: 295.0593; found: 295.0583.

(*E*)-2-[(5-Methylthiophen-2-yl)methylene]-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2e)

Yield: 14 mg (70%); colorless solid; mp 183–185 °C; R_f = 0.4 (hexane/EtOAc 8:2).

IR (KBr): 2924, 1681, 1620, 1515, 1461, 1383, 1270, 1097, 909 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.92 (m, 2 H), 7.72 (s, 1 H), 7.53–7.48 (m, 2 H), 7.24 (d, *J* = 3.4 Hz, 1 H), 6.83 (d, *J* = 2.8 Hz, 1 H), 3.93 (s, 2 H), 2.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.0, 157.4, 147.6, 146.1, 143.3, 137.2, 134.1, 133.7, 133.6, 128.0, 126.7, 126.3, 125.1, 124.4, 123.5, 29.4, 15.8.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{17}H_{13}OS_2$: 297.0408; found: 297.0414.

(*E*)-2-([1,1′-Biphenyl]-4-ylmethylene)-1-phenyl-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2f)

Yield: 15 mg (73%); pale yellow solid; mp 188–190 °C; R_f = 0.5 (hexane/EtOAc 8:2).

IR (KBr): 2923, 1685, 1624, 1601, 1514, 1272 1373, 1074, 935 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.2 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.59–7.56 (m, 4 H), 7.54–7.52 (m, 2 H), 7.47–7.43 (m, 6 H), 7.38–7.32 (m, 2 H), 7.29–7.25 (m, 2 H), 7.16–7.14 (m, 1 H), 5.55 (d, *J* = 0.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.8, 161.9, 148.1, 142.1, 141.9, 141.8, 140.0, 139.1, 133.5, 133.4, 132.7, 131.5 (2 × CH), 128.9 (2 × CH), 128.8 (2 × CH), 128.2 (2 × CH), 128.1, 127.8, 127.4, 127.0 (2 × CH), 126.9 (2 × CH), 125.2, 124.5, 124.2, 47.4.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{30}H_{21}OS$: 429.1313; found: 429.1294.

(*E*)-2-Benzylidene-1-phenyl-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2g)

Yield: 18 mg (92%); light yellow solid; mp 202–204 °C; R_f = 0.6 (hexane/EtOAc 8:2).

IR (KBr): 2926, 1687, 1624, 1513, 1370, 1273, 1070, 934 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.2 Hz, 1 H), 7.76–7.74 (m, 2 H), 7.50–7.43 (m, 3 H), 7.37–7.34 (m, 3 H), 7.32–7.28 (m, 3 H), 7.26–7.22 (m, 2 H), 7.17–7.12 (m, 1 H), 5.55 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.8, 162.0, 148.1, 142.2, 141.7, 139.0, 134.0, 133.8, 133.4, 130.9 (2 × CH), 129.4, 128.8 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.1, 127.3, 125.2, 124.4, 124.2, 47.3.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{17}OS$: 353.1000; found: 353.1008.

(*E*)-2-(3-Methylbenzylidene)-1-phenyl-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2h)

Yield: 19 mg (76%); pale yellow solid; mp 171–173 °C; R_f = 0.5 (hexane/EtOAc 8:2).

IR (KBr): 2923, 1687, 1625, 1514, 1371, 1276, 1074, 898 cm^{-1}.

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^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.2 Hz, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 7.71 (d, *J* = 1.4 Hz, 1 H), 7.43 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.38–7.33 (m, 3 H), 7.30–7.27 (m, 3 H), 7.25–7.24 (m, 1 H), 7.20–7.13 (m, 2 H), 7.09 (d, *J* = 7.6 Hz, 1 H), 5.51 (d, *J* = 1.5 Hz, 1 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.9, 162.0, 148.1, 141.9, 141.8, 139.2, 137.8, 134.2, 133.6, 133.4, 131.5, 130.3, 128.8 (2 × CH), 128.34, 128.32 (2 × CH), 128.2, 128.0, 127.3, 125.1, 124.4, 124.2, 47.4, 21.2.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{25}H_{19}OS$: 367.1157; found: 367.1142.

(*E*)-2-(Cyclopropylmethylene)-1-phenyl-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2i)

Yield: 24 mg (80%); pale yellow solid; mp 180–182 °C; R_f = 0.6 (hexane/EtOAc 8:2).

IR (KBr): 2926, 1690, 1638, 1512, 1304, 1266, 1052, 899 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.2 Hz, 1 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.43 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.36–7.31 (m, 4 H), 7.29–7.24 (m, 2 H), 6.25 (dd, *J* = 11.0, 1.5 Hz, 1 H), 5.29 (d, *J* = 1.5 Hz, 1 H), 1.46–1.39 (m, 1 H), 1.00–0.95 (m, 1 H), 0.74–0.66 (m, 2 H), 0.56–0.51 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.5, 160.8, 147.9, 143.8, 142.5, 141.7, 140.2, 133.6, 128.9 (2 × CH), 128.1 (2 × CH), 127.8, 127.2, 125.0, 124.4, 124.0, 46.7, 11.8, 9.2, 9.1.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{21}H_{17}OS$: 317.1000; found: 317.0987

(*Z*)-2-Benzylidene-1-(*m*-tolyl)-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2j)

Yield: 36 mg (72%); pale yellow solid; mp 192–194 °C; R_f = 0.4 (hexane/EtOAc 9:1).

IR (KBr): 2919, 1687, 1624, 1514, 1447, 1384, 1369, 1271, 1040, 933, 771, 736, 698, 687 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.2 Hz, 1 H), 7.73 (d, *J* = 8 Hz, 1 H), 7.68 (d, *J* = 1.5 Hz, 1 H), 7.48–7.45 (m, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.33–7.25 (m, 4 H), 7.20 (d, *J* = 7.7 Hz, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.02 (s, 1 H), 6.91 (d, *J* = 7.5 Hz, 1 H), 5.45 (s, 1 H), 2.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.0, 162.3, 148.2, 142.3, 141.7, 139.0, 138.6, 133.9 (2 C), 133.5, 131.0 (2 C), 129.5, 128.7, 128.6, 128.4 (2 C), 128.1 (2 C), 125.6, 125.2, 124.5, 124.3, 47.3, 21.4.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{25}H_{19}OS$: 367.1157; found: 367.1141.

(*Z*)-1-(Benzo[*b*]thiophen-2-yl)-2-benzylidene-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one (2k)

Yield: 39 mg (82%); pale white solid; mp 224–226 °C; R_f = 0.2 (hexane/EtOAc 9:1).

IR (KBr): 2924, 1682, 1621, 1514, 1384, 1320, 1274, 1123, 1057, 936, 872, 765, 742, 725, 684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.1 Hz, 1 H), 7.87 (d, *J* = 8.1 Hz, 1 H), 7.75 (s, 1 H), 7.63–7.57 (m, 4 H), 7.44–7.17 (m, 8 H), 5.92 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.7, 160.3, 148.1, 143.1, 142.2, 140.8, 139.4, 139.3, 134.9, 133.7, 133.2, 131.1 (2 C), 129.9, 128.6 (2 C), 128.3, 125.4, 124.6, 124.3 (2 C), 124.2, 123.3, 122.9, 122.3, 42.6.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{26}H_{17}OS_2$: 409.0721; found: 409.0704.

2-Methyl-3*H*-benzo[*b*]cyclopenta[*d*]thiophen-3-one (2l)

Yield: 18 mg (90%); colorless solid; mp 211–213 °C; R_f = 0.4 (hexane/EtOAc 5:5).

IR (KBr): 2919, 1660, 1524, 1494, 1452, 1206, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (s, 1 H), 7.93–7.91 (m, 1 H), 7.89–7.86 (m, 1 H), 7.55–7.47 (m, 2 H), 2.70 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.4, 141.0, 140.8, 140.2, 140.1, 133.7, 133.1, 127.7, 124.9, 124.1, 122.7, 14.4.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_9OS$: 199.0218; found: 199.0220.

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Supporting Information

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