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# Synthesis and functionalization of 3-bromo-2-(2-chlorovinyl)benzothiophenes as molecular tools†

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An efficient bromocyclization process of *ortho*-substituted arylmethyl sulfide promoted by *N*-methylpyrrolidin-2-one hydrotribromide led to the synthesis of 3-bromo-2-(2-(di)chlorovinyl)benzothiophene as a polyhalogenated platform. Various arylations on the C3 atom of such di-substituted benzothiophenes and further functionalizations at the chlorine atoms of the benzothiophenes afforded efficient and rapid access to a small library of stereo-defined 2,3-disubstituted benzothiophenes.

## Introduction

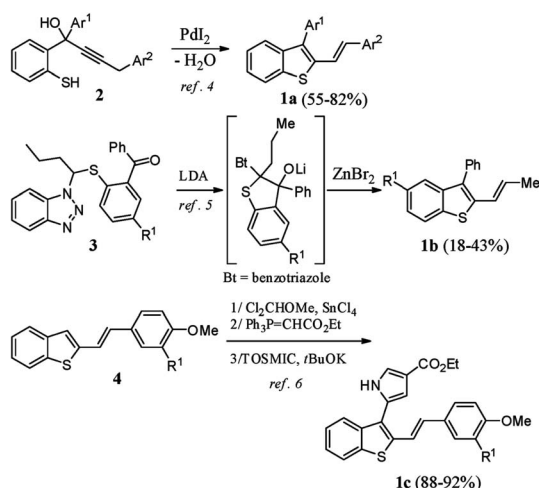
2,3-Disubstituted benzothiophenes have been well studied by the scientific community in past decades, mainly for their numerous biological properties.<sup>1</sup> For example, raloxifene (Evista™), an oral selective estrogen receptor modulator, is prescribed in the prevention and treatment of osteoporosis and is also given for postmenopausal women who are at high risk for invasive breast cancers.<sup>2</sup> In contrast to the synthesis of 2,3-diarylbenzothiophenes, which is well reported,<sup>3</sup> the preparation

of their stereo-defined 2-vinyllogous analogues **1a–c** is poorly documented (Scheme 1).

To our knowledge, these derivatives having (*E*)-double bonds have been prepared using three different strategies: (i) the Pd-catalyzed heterocyclodehydration of acyclic precursor **2**,<sup>4</sup> (ii) reaction of **3** with LDA followed by rearrangement in the presence of ZnBr<sub>2</sub>,<sup>5</sup> and (iii) C3-functionalization of 2-substituted benzothiophene **4** through a three-step sequence involving a Rieche formylation, a Wittig reaction, and a pyrrole ring construction under van Leusen reaction conditions.<sup>6</sup>

In a continuation of our work dedicated to the synthesis of functionalized heterocycles,<sup>7</sup> we described a new method to prepare a variety of stereo-defined polyhalogenated platforms **6** through the *N*-methylpyrrolidin-2-one hydrotribromide (MPHT)-promoted bromocyclization of (*Z*)- and (*E*)-chloroenynes **5** and subsequent site-selective Suzuki–Miyaura coupling reactions of **6** to prepare various 2,3-disubstituted benzothiophenes **1** (Scheme 2).

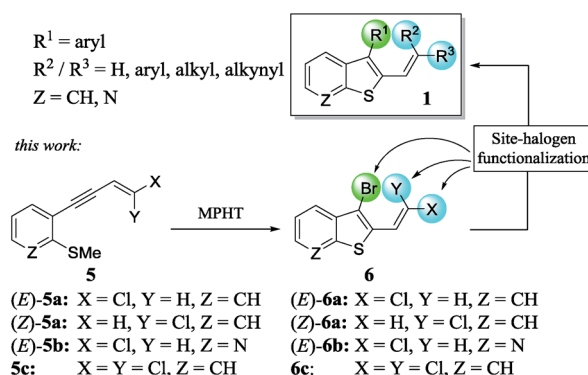
We choose a bromocyclization strategy instead of Larock's iodo heteroannulation<sup>8</sup> since the site-selective Suzuki–Miyaura coupling of a C–Br vs. C–Cl bond is more challenging from our point of view than the coupling of C–I vs. C–Cl.



Scheme 1 Previous syntheses of 3-aryl-2-alkenyl-benzothiophenes **1a–c**.

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Scheme 2 Synthesis of polyhalogenated platforms **6**.



## Results and discussion

The required 1,3-chloroenynes (*E*-**5a**) with an *ortho* nucleophilic methyl sulfide was prepared *via* Pd-catalyzed Sonogashira–Linstrumelle coupling reaction.<sup>9</sup> We were pleased to observe that in the presence of MPHT, a mild and easy-to-handle brominating agent discovered in our lab,<sup>10</sup> (*E*-**5a**)<sup>11</sup> underwent bromocyclization<sup>12</sup> at rt in CH<sub>2</sub>Cl<sub>2</sub> to provide the desired 2,3-disubstituted benzothiophene platform (*E*-**6a**) in a good (88%) yield<sup>13</sup> (Scheme 3).

The scope of this bromocyclization was also demonstrated by the synthesis of (*E*-**6b**) (Scheme 3), which is suitable for the preparation of 7-aza-benzothiophene-containing scaffolds found in drug discovery.<sup>14</sup>

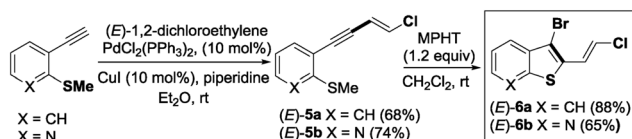
Next, we focus our attention on the identification of efficient experimental conditions for site-selective Suzuki–Miyaura coupling reactions between 3-bromobenzothiophene (*E*-**6a**) and arylboronic acid **7** (1.3 equiv.) as coupling partners (Table 1). Initially, to compare the reactivity of boronic acids towards a 2-vinylchlorine moiety *vs.* a probably more reactive 3-bromine atom on a benzothiophene scaffold, we tested the conditions used for the coupling of chloroenynes<sup>15</sup> using Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) as the catalyst, K<sub>2</sub>CO<sub>3</sub> (2 equiv.) as the base, and toluene/MeOH (2 : 1) as the solvent at 90 °C. However, no selectivity was observed, and the expected C-3 monoarylated benzothiophene (*E*-**8a**) was isolated in 17% yield accompanied with (*E*-**9**) (6%) and significant amounts (39%) of the diarylated product (*E*-**1aa**) (entry 1). This result clearly highlighted that the selective introduction of an aryl substituent at the C-3 position of (*E*-**6a**) is far from trivial, although the C–Br bond is more reactive than the C–Cl bond. It should be noted that 2,3-disubstituted benzothiophene derivatives (*E*-**8a**, (*E*-**9**) and (*E*-**1aa**) can be easily separated by column chromatography on silica gel.

Next, we continued our study by exploring the influence of the palladium- and ligand-controlled site-selective Suzuki–Miyaura cross couplings. No reaction occurred by replacing Pd(PPh<sub>3</sub>)<sub>4</sub> with other palladium sources such as PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>(dppf) and Pd(dba)<sub>2</sub> (entries 2–4), even when increasing the amount of the catalyst from 5 to 20 mol%. By using the N-heterocyclic carbene palladacycle precatalyst [PdCl(dmba)(IMes)] (Pd–NHC) developed in 2008 by Ying<sup>16</sup> for Heck- and Suzuki-coupling reactions, we were pleased to observe the formation of the desired C-3 monoarylated benzothiophene (*E*-**8a**) in a moderate but promising yield of 38% after 7 h of reaction (entry 5). In this case, (*E*-**9**) was not detected, and a trace amount (3%) of the diarylated product (*E*-**1aa**) was isolated along with significant amounts (45%) of unreacted (*E*-**6a**). Increasing the reaction time from 7 to 24 h (entry 6) improved

the yield of (*E*-**8a**) from 38 to 85%, but also increased the quantity of the diarylated product (*E*-**1aa**) from 3% to 10%. Finally, using 10 mol% of this Pd–NHC precatalyst with 2 equiv. of K<sub>2</sub>CO<sub>3</sub> in a hot mixture of toluene/MeOH (2 : 1) for 24 h led to the selective C-3 monoarylation of (*E*-**6a**), thus providing (*E*-**8a**) in 90% yield together with 7% of (*E*-**1aa**) (entry 7). Due to the σ-donation and steric bulk around the metal, this Pd complex with a carbene ligand instead of phosphine ligands facilitates the oxidative addition and the reductive elimination in the palladacycle. Thereby, the selectivity between a C–Br *vs.* a C–Cl bond was increased in the presence of a boronic acid. This result was confirmed by replacing [PdCl(dmba)(IMes)] by PEPPSI™-IPr precatalyst, and the reaction furnished mainly the mono-coupling product (*E*-**8a**) (82% yield). The effect of the base was next investigated, and K<sub>3</sub>PO<sub>4</sub> gave a similar result to K<sub>2</sub>CO<sub>3</sub> (entry 8). All other bases were unsuccessful in achieving efficient coupling reaction, leading to a complex mixture of by-products when using LiOt-Bu (entry 9) or to unchanged starting material (*E*-**6a**) in the presence of NEt<sub>3</sub> or KOAc (entries 10 and 11). The effect of the solvent was studied, but no improvement was noted when toluene/MeOH was replaced by DMF, THF, MeOH or toluene (entries 12–15). A mixture of toluene associated with MeOH was found to be the best solvent combination, likely for solubility reasons. The conditions used in entry 7 ([PdCl(dmba)(IMes)] (10 mol%), K<sub>2</sub>CO<sub>3</sub> (2 equiv.), and arylboronic acid (1.3 equiv.) in toluene/MeOH (2 : 1) in a sealed tube at 90 °C for 24 h) were then used for other coupling reactions using a variety of boronic acids to demonstrate the versatility and the chemoselectivity of the present protocol (Table 2). As expected, using the experimental conditions depicted in entry 7 of Table 1, a variety of arylboronic acids<sup>17</sup> bearing electron-donating and electron-withdrawing groups were introduced at the C-3 position of (*E*-**6a**,**b**), leading to (*E*-**8a**–**g**) in good to excellent yields (59–90%).

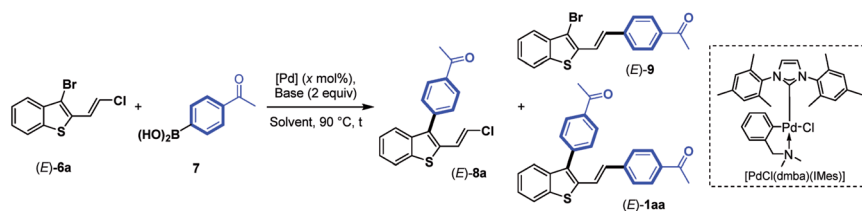
As the next logical extension, Suzuki–Miyaura coupling reactions at the remaining C–Cl bond of benzothiophene compounds (*E*-**8a**–**d**) were attempted under the previous conditions reported for the couplings of arylboronic acids with chloroenynes.<sup>15</sup> In the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%), K<sub>2</sub>CO<sub>3</sub> (2 equiv.), and arylboronic acid (1.2 equiv.) in a hot mixture of toluene/MeOH, we were pleased to observe the successful replacement of the chlorine atom by various aromatic and heteroaromatic rings (Table 3). The reactions proceeded in good yields (75–92%) with electron-poor and electron-rich arylboronic acids used as coupling partners for (*E*-3-aryl-2-(2-chlorovinyl)benzothiophenes (*E*-**8a**–**d**). It should be noted that using Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol%), K<sub>2</sub>CO<sub>3</sub> (2 equiv.) and 4-acetylboronic acid in a slight excess (2.2 equiv.) furnished (*E*-**1aa**) (see Table 1), in which the boronic acid replaced both the bromine and chlorine atoms of (*E*-**6a**) (83%).

Because the reaction conditions for the two-step Suzuki–Miyaura couplings are similar (K<sub>2</sub>CO<sub>3</sub>, toluene/MeOH, 90 °C), we investigated whether the two-step coupling reactions could be carried out in a one-pot fashion directly from (*E*-**6a**), avoiding the isolation of the monocoupling products (*E*-**8**). Reactions were conducted using K<sub>2</sub>CO<sub>3</sub> (2 equiv.) in toluene/MeOH (2 : 1) as the solvent at 90 °C. In the first step, (4-acetylphenyl)boronic



Scheme 3 MPHT promoted the cyclization of 1,3-chloro-enyne (*E*-**5a**,**b**).



Table 1 Optimization of the site-selective coupling reaction between (*E*)-6a and arylboronic acid 7<sup>a</sup>

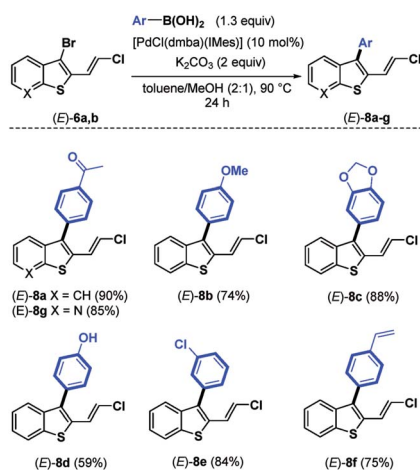
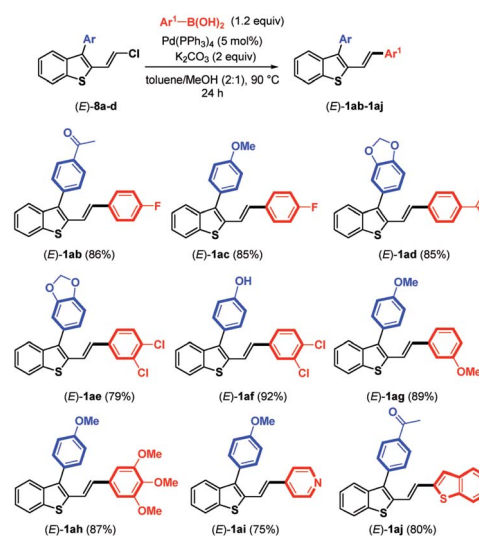
Entry	[Pd]	x	Base	Time (h)	Solvent	Yield <sup>b</sup> of 8a (%)	Yield <sup>b</sup> of 9 (%)	Yield <sup>b</sup> of 1aa (%)
1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	5	K <sub>2</sub> CO <sub>3</sub>	7	Toluene/MeOH (2 : 1)	17	6	39
2	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	5	K <sub>2</sub> CO <sub>3</sub>	7	Toluene/MeOH (2 : 1)	0	0	0
3	PdCl <sub>2</sub> (dppf)	5	K <sub>2</sub> CO <sub>3</sub>	7	Toluene/MeOH (2 : 1)	0 <sup>c</sup>	0	0
4	Pd(dba) <sub>2</sub>	5	K <sub>2</sub> CO <sub>3</sub>	7	Toluene/MeOH (2 : 1)	0 <sup>c</sup>	0	0
5	[PdCl(dbma)(IMes)]	5	K <sub>2</sub> CO <sub>3</sub>	7	Toluene/MeOH (2 : 1)	38 <sup>d</sup>	0	3
6	[PdCl(dbma)(IMes)]	5	K <sub>2</sub> CO <sub>3</sub>	24	Toluene/MeOH (2 : 1)	85	0	10
7	[PdCl(dbma)(IMes)] <sup>f</sup>	10	K <sub>2</sub> CO <sub>3</sub>	24	Toluene/MeOH (2:1)	90	0	7
8	[PdCl(dbma)(IMes)]	10	K <sub>3</sub> PO <sub>4</sub>	24	Toluene/MeOH (2 : 1)	85	0	8
9	[PdCl(dbma)(IMes)]	10	LiOt-Bu	24	Toluene/MeOH (2 : 1)	— <sup>e</sup>	—	—
10	[PdCl(dbma)(IMes)]	10	NEt <sub>3</sub>	24	Toluene/MeOH (2 : 1)	0 <sup>c</sup>	0	0
11	[PdCl(dbma)(IMes)]	10	KOAc	24	Toluene/MeOH (2 : 1)	0 <sup>c</sup>	0	0
12	[PdCl(dbma)(IMes)]	10	K <sub>2</sub> CO <sub>3</sub>	24	DMF	0 <sup>c</sup>	0	0
13	[PdCl(dbma)(IMes)]	10	K <sub>2</sub> CO <sub>3</sub>	24	THF	0 <sup>c</sup>	0	0
14	[PdCl(dbma)(IMes)]	10	K <sub>2</sub> CO <sub>3</sub>	24	MeOH	72	0	17
15	[PdCl(dbma)(IMes)]	10	K <sub>2</sub> CO <sub>3</sub>	24	Toluene	21	0	4

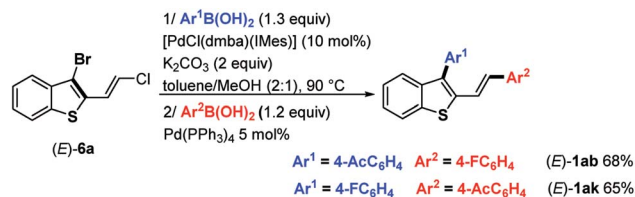
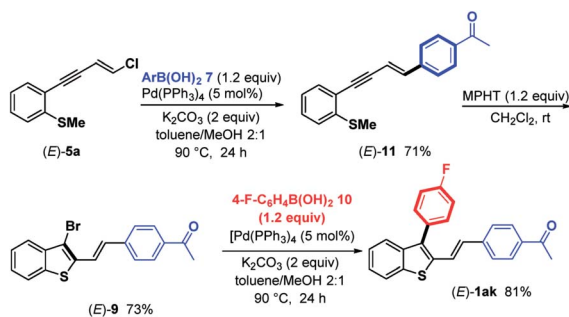
<sup>a</sup> Conditions: (*E*)-6a (1 mmol), 7 (1.3 mmol), [Pd] (0.05 mmol or 0.1 mmol), base (2 equiv.) and solvent (18 mL) were heated in a sealed tube at 90 °C for time indicated in the table under argon atmosphere. <sup>b</sup> Yield of isolated product. <sup>c</sup> (*E*)-6a was recovered unchanged. <sup>d</sup> 45% of (*E*)-6a were recovered. <sup>e</sup> A complex mixture of unidentified products was obtained. <sup>f</sup> Replacing [PdCl(dbma)(IMes)] by Pd-PEPPSI<sup>TM</sup>-IPr furnished 8a in a slightly lower yield of 82%.

acid (1.3 equiv.) reacted with (*E*)-6a. When consumption of the substrate was complete according to TLC, Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) and 4-fluoroboronic acid were added to the reaction mixture. Accordingly, we were pleased to isolate (*E*)-1ab containing two different aryl groups in a good overall yield of 68% (Scheme 4). One can also note that the one-pot synthesis of (*E*)-1ak (65%) was successfully achieved from (*E*)-6a by inverting the addition

order of boronic acids (first 4-fluoroboronic acid followed by 4-acetylboronic acid).

However, it should be noted that attempts to achieve one-pot coupling in the presence of only one catalyst [PdCl(dbma)(IMes)] (10–20 mol%) furnished (*E*)-1ab in low yield

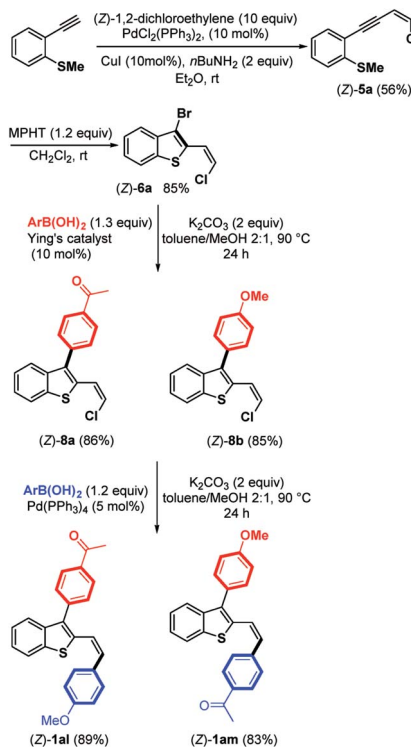
Table 2 Suzuki coupling reactions of (*E*)-6a,b with a variety of arylboronic acidsTable 3 Suzuki coupling reactions of (*E*)-8a–d with a variety of arylboronic acids

Scheme 4 One-pot synthesis of (*E*)-1ab and (*E*)-1ak from (*E*)-6a.Scheme 5 Synthesis of (*E*)-1ak.

(28%) along with (*E*)-8a (42%) after 48 h of reaction, clearly indicating that the Pd–NHC precatalyst was not efficient to introduce an aryl substituent on the C–Cl bond of (*E*)-8a.

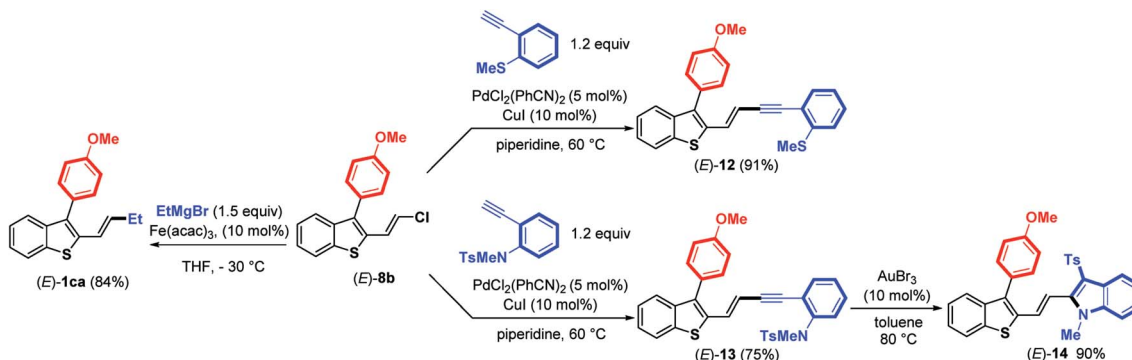
2,3-Disubstituted benzothiophenes (*E*)-1ak were also accessed by inverting the MPHT-bromo-cyclization process followed by the arylation of the resulting 3-bromoposition of the thiophene backbone (Scheme 5).

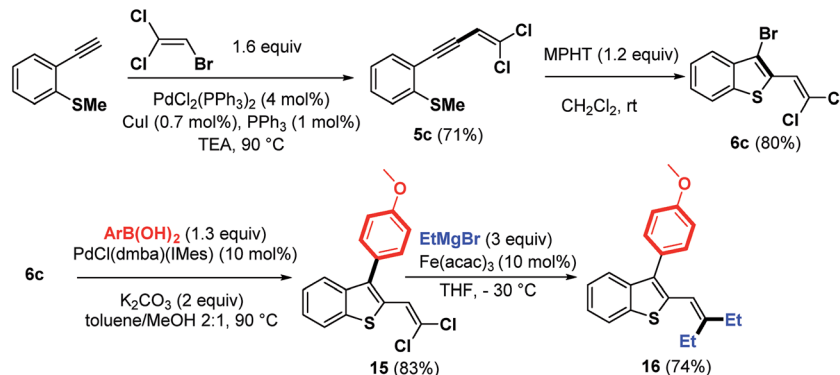
In detail, chloroenyne (*E*)-5a was initially coupled with (4-acylphenyl)boronic acid 7 in the presence of  $\text{Pd}(\text{PPh}_3)_4$  (5 mol%),  $\text{K}_2\text{CO}_3$  (2 equiv.) in toluene/MeOH (2 : 1) at 90 °C to give the expected 1,4-diarylene (*E*)-11 in 71% yield.<sup>15</sup> (*E*)-11 then undergoes MPHT-promoted bromo-cyclization to furnish the 3-bromobenzothiophene (*E*)-9 (73%). Further Suzuki–Miyaura coupling between (*E*)-9 and (4-fluoro-phenyl)boronic acid 10 in the presence of  $\text{Pd}(\text{PPh}_3)_4$  (5 mol%) led to (*E*)-1ak in a good (81%) yield. The comparison of the two strategies, bromocyclization/Suzuki/Suzuki to prepare (*E*)-1ab–aj and Suzuki/bromocyclization/Suzuki to obtain (*E*)-1ak, shows that they are equivalent in terms of overall yield and ease of implementation.

Scheme 7 Bromocyclization of (*Z*)-5a into (*Z*)-6a and subsequent Suzuki–Miyaura coupling reactions.

Next, the reactivity of 3-aryl-2-(2-chlorovinyl)benzothiophene (*E*)-8b in Pd-catalyzed couplings was examined to demonstrate the usefulness of such molecular tools. Gratifyingly, the use of  $\text{PdCl}_2(\text{PhCN})_2$  (5 mol%) and  $\text{CuI}$  (10 mol%) as the catalysts in piperidine at 60 °C (ref. 18) allowed the coupling to proceed efficiently between (*E*)-8b and *ortho*-substituted arylalkynes to provide (*E*)-enynes 12 and 13 in good yields (Scheme 6).

Taking advantage of the structure of enyne (*E*)-13 having an *ortho*-*N*-tosyl-*N*-methylaniline function, we achieved a gold-catalyzed cyclization<sup>19</sup> to give, after tosyl migration, 2-alkenyl-3-sulfonylindole (*E*)-14 in 90% yield. We further demonstrated that the C–Cl bond in (*E*)-8b can react with a Grignard reagent ( $\text{EtMgBr}$ ) in the presence of a catalytic amount of  $\text{Fe}(\text{acac})_3$  (ref. 20) to introduce an alkyl substituent, thus providing 2-

Scheme 6 Coupling reactions of vinylchloride (*E*)-8b with terminal *ortho*-substituted arylalkynes and  $\text{EtMgBr}$ .



Scheme 8 Synthesis of substituted-3-bromobenzothiophenes **6c** and its functionalization.

benzothiophene (*E*)-**1ca** in a good (84%) yield with no trace of (*E*)-double bond isomerization. Altogether, these results clearly highlight that it is possible to create various C–C bonds through the coupling of alkyl Grignard reagents ( $Csp^3$ ), arylboronic acids ( $Csp^2$ ) or terminal alkynes ( $Csp$ ) with the C–Cl bond of benzothiophenes (*E*)-**8**, demonstrating the synthetic potential of these molecular tools.

Due to the biological interest in benzothiophenes containing a (*Z*)-double bond<sup>21</sup> at the C-2 position as tubulin polymerization inhibitors, we investigated the preparation of (*Z*)-**6a** and explored its coupling to provide stereoselectively (*Z*)-2,3-disubstituted benzothiophene derivatives (Scheme 7). Thus, by replacing piperidine with *n*BuNH<sub>2</sub> as the base,<sup>9</sup> we were able to synthesize the expected chloroenyne (*Z*)-**5a** (56%) through the Sonogashira–Linstremelle coupling of (2-ethynylphenyl)(methyl)sulfane with (*Z*)-1,2-dichloroethene in the presence of catalytic amounts of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and CuI.

Interestingly, the reaction conditions used for the synthesis of (*E*)-**6a** (MPHT, CH<sub>2</sub>Cl<sub>2</sub>) also allowed us to selectively prepare (*Z*)-**6a** (85%) through the bromo-cyclization of (*Z*)-**5a** (Scheme 7).

Further Suzuki–Miyaura monoarylation reactions of (*Z*)-**6a** with electron-poor phenylboronic acid **7** or the electron-rich (4-methoxyphenyl)boronic acid in the presence of Pd–NHC<sup>16</sup> led to the expected coupling products (*Z*)-**8a** and (*Z*)-**8b** in good yields of 86% and 85%, respectively. Further arylation of the (*Z*)- $Csp^2$ –Cl bond can be accomplished by arylboronic acids in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> as a palladium source. Push-pull

benzothiophene derivatives (*Z*)-**1al** and (*Z*)-**1am** were synthesized in excellent yields from (*Z*)-**8a** and (*Z*)-**8b**, respectively, with no trace of (*Z*)-double bond isomerization (Scheme 7).

The scope of this strategy involving bromocyclization followed by Pd-catalyzed coupling reactions was also extended to the synthesis of polyhalogenated platform **6c**, suitable for the elaboration of benzothiophenes containing a trisubstituted double bond at the C-2 position (Scheme 8).

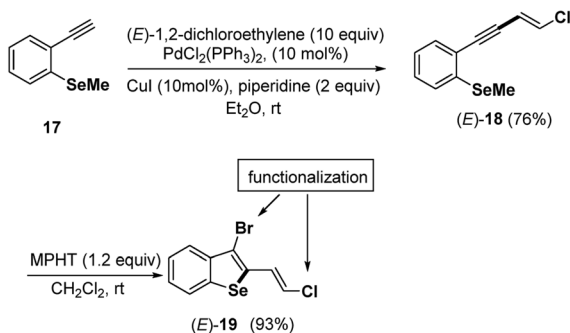
As expected, the bromocyclization process of **5c** promoted by MPHT furnished **6c** in 80% yield. An illustration of its synthetic potential is shown in Scheme 8. Trihalogenated benzothiophene **6c** was first monoarylated at the C-3 position using Pd–NHC pre-catalyst as a palladium source to give **15** (83%). This product was then coupled with EtMgBr (3 equiv.) in the presence of a catalytic amount of Fe(acac)<sub>3</sub> (ref. 20) at –30 °C to give benzothiophene **16** in 74% yield.

Finally, under the mild conditions (MPHT 1.2 equiv., CH<sub>2</sub>Cl<sub>2</sub>, rt) described above for the bromocyclization of chloroenynes **5** having an *ortho*-methyl sulfide group on the aromatic moiety, we successfully transformed the *ortho*-SeMe-aryl chloroenyne (*E*)-**18** into a 2,3-disubstituted benzoselenophene **19** (93%), which is possibly useful for further chemical transformations (Scheme 9).

Efforts are in progress in our lab to develop satisfactory coupling conditions at both the bromine and chlorine atoms of (*E*)-**19** and (*Z*)-**19** benzoselenophenes.

## Conclusion

In summary, we have demonstrated that MPHT is a mild and efficient brominating agent useful for the room-temperature bromocyclization of *ortho*-alkynylaryl methyl sulfides **5**. The resulting 3-bromo-2-(2-(di)chlorovinyl)benzothiophenes **6** may serve as di- or tri-halogenated benzothiophene platforms useful for chemoselective and successive coupling reactions (Suzuki, Sonogashira, *etc.*) leading to rapid and convergent access to a series of 2,3-disubstituted benzothiophenes. We have also demonstrated that it is possible to access to these benzothiophene targets using a complementary strategy involving the arylation of stereo-defined chloroenynes **5a** followed by bromocyclization and a second C-3 functionalization on the resulting 3-



Scheme 9 Synthesis of (*E*)-**19**.



bromo-benzothiophene (arylation, alkynylation, or alkylation). Finally, we have shown that this bromocyclization process is also efficient for arylselenomethyl ether **18**, which was transformed into the novel and potentially functionalizable 2-chlorovinyl-3-bromobenzo selenophene platform **19**. We believe that these novel methodologies will find broad applications in synthetic organic chemistry and in pharmaceutical sciences.

## Conflicts of interest

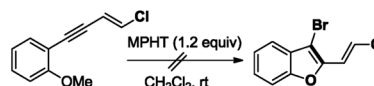
There are no conflicts to declare.

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- 12 It is also possible to prepare a 3-iodo-2-(chlorovinyl) benzothiophene using  $I_2$  and chloroenyne (*E*)-**5a** (82%).
- 13 When NBS (1.2 equiv.) was used in place of MPHT, (*E*)-**6a** was obtained in a poor yield of 20%. Using  $Br_2$ , the reaction furnished (*E*)-**6a** in 80%. Solid MPHT is more convenient to handle than  $Br_2$  particularly when small quantities were used (1.2 equiv., 61  $\mu$ L).
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