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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*-methyl-pyrrolidin-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.

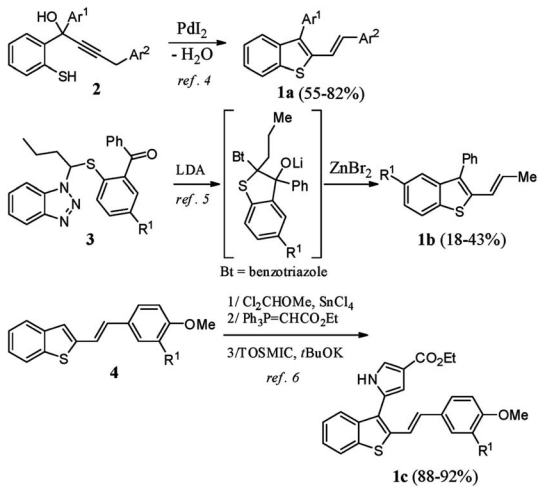
Introduction

2,3-Disubstituted benzothiophenes have been well studied by the scientific community in past decades, mainly for their numerous biological properties.[1] 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.[2] In contrast to the synthesis of 2,3-diarylbenzothiophenes, which is well reported,[3] the preparation of their stereo-defined 2-vinylogous analogues **1a–c** is poorly documented (Scheme 1).

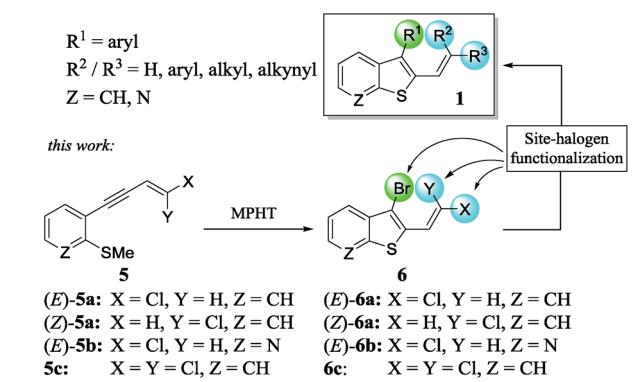
To our knowledge, these derivatives having (*E*)-double bonds have been prepared using three different strategies: (i) the Pd-catalyzed heterocyclodehydration of acyclic precursor **2**,[4] (ii) reaction of **3** with LDA followed by rearrangement in the presence of $ZnBr_2$,[5] and (iii) C3-functionalization 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.[6]

In a continuation of our work dedicated to the synthesis of functionalized heterocycles,[7] we described a new method to prepare a variety of stereo-defined polyhalogenated platforms **6** through the *N*-methyl-pyrrolidin-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[8] 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**.



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

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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.[9] We were pleased to observe that in the presence of MPHT, a mild and easy-to-handle brominating agent discovered in our lab,[10] (*E*)-**5a**[11] underwent bromocyclization[12] at rt in CH_2Cl_2 to provide the desired 2,3-disubstituted benzothiophene platform (*E*)-**6a** in a good (88%) yield[13] (Scheme 3).

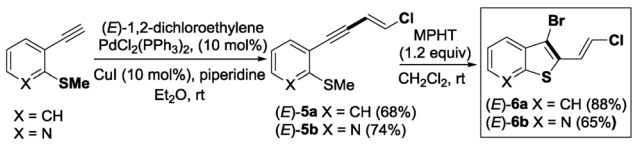
The scope of this bromocyclization was also demonstrated by the synthesis of (*E*)-**6b** (Scheme 3), which is suitable for the preparation of 7-aza-benzothiophene-containing scaffolds found in drug discovery.[14]

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 moity *vs.* a probably more reactive 3-bromine atom on a benzothiophene scaffold, we tested the conditions used for the coupling of chloroenynes[15] using $Pd(PPh_3)_4$ (5 mol%) as the catalyst, K_2CO_3 (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 $Pd(PPh_3)_4$ with other palladium sources such as $PdCl_2(PPh_3)_2$, $PdCl_2$(dppf) and $Pd(dba)_2$ (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[16] 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_2CO_3 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_3PO_4 gave a similar result to K_2CO_3 (entry 8). All other bases were unsuccessful in achieving efficient coupling reaction, leading to a complex mixture of by-products when using LiO*t*-Bu (entry 9) or to unchanged starting material (*E*)-**6a** in the presence of NEt_3 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_2CO_3 (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[17] 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%).

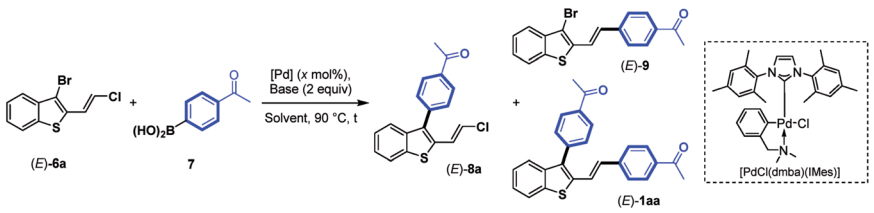
As the next logical extension, Suzuki–Miyaura coupling reactions at the remaining C–Cl bond of benzothiophene compounds (*E*)-**8a–d** were attempted under the previous conditions reported for the couplings of arylboronic acids with chloroenynes.[15] In the presence of $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (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 $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (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_2CO_3, 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_2CO_3 (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**[a]



Entry	[Pd]	*x*	Base	Time (h)	Solvent	Yield[b] of **8a** (%)	Yield[b] of **9** (%)	Yield[b] of **1aa** (%)
1	$Pd(PPh_3)_4$	5	K_2CO_3	7	Toluene/MeOH (2 : 1)	17	6	39
2	$PdCl_2(PPh_3)_2$	5	K_2CO_3	7	Toluene/MeOH (2 : 1)	0	0	0
3	$PdCl_2$(dppf)	5	K_2CO_3	7	Toluene/MeOH (2 : 1)	0[c]	0	0
4	$Pd(dba)_2$	5	K_2CO_3	7	Toluene/MeOH (2 : 1)	0[c]	0	0
5	**[PdCl(dbma)(IMes)]**	5	K_2CO_3	7	Toluene/MeOH (2 : 1)	38[d]	0	3
6	**[PdCl(dbma)(IMes)]**	5	K_2CO_3	**24**	Toluene/MeOH (2 : 1)	85	0	10
7	**[PdCl(dbma)(IMes)]**[f]	**10**	**K_2CO_3**	**24**	**Toluene/MeOH (2:1)**	**90**	**0**	7
8	[PdCl(dbma)(IMes)]	10	K_3PO_4	24	Toluene/MeOH (2 : 1)	85	0	8
9	[PdCl(dbma)(IMes)]	10	LiO*t*-Bu	24	Toluene/MeOH (2 : 1)	—[e]	—	—
10	[PdCl(dbma)(IMes)]	10	NEt_3	24	Toluene/MeOH (2 : 1)	0[c]	0	0
11	[PdCl(dbma)(IMes)]	10	KOAc	24	Toluene/MeOH (2 : 1)	0[c]	0	0
12	[PdCl(dbma)(IMes)]	10	K_2CO_3	24	DMF	0[c]	0	0
13	[PdCl(dbma)(IMes)]	10	K_2CO_3	24	THF	0[c]	0	0
14	[PdCl(dbma)(IMes)]	10	K_2CO_3	24	MeOH	72	0	17
15	[PdCl(dbma)(IMes)]	10	K_2CO_3	24	Toluene	21	0	4

[a] 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. [b] Yield of isolated product. [c] (*E*)-**6a** was recovered unchanged. [d] 45% of (*E*)-**6a** were recovered. [e] A complex mixture of unidentified products was obtained. [f] Replacing [PdCl(dbma)(IMes)] by Pd-PEPPSI™-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, $Pd(PPh_3)_4$ (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(dmba)(IMes)] (10–20 mol%) furnished (*E*)-**1ab** in low yield

Table 2 Suzuki coupling reactions of (*E*)-**6a**,**b** with a variety of arylboronic acids

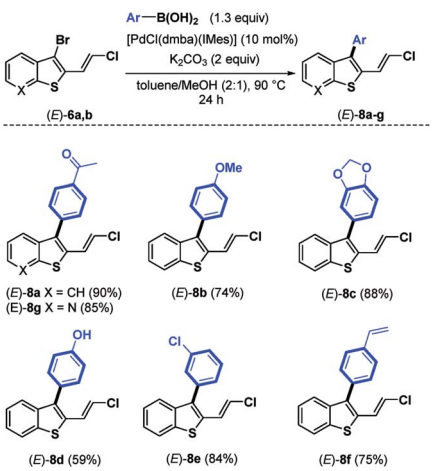
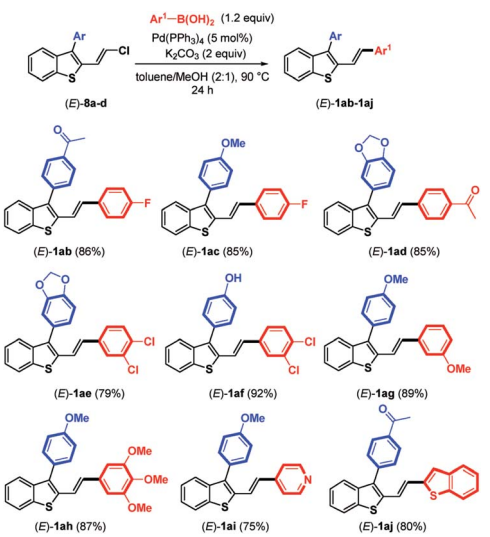
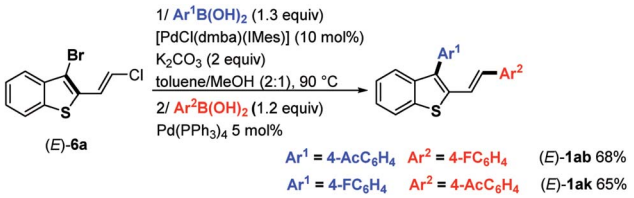
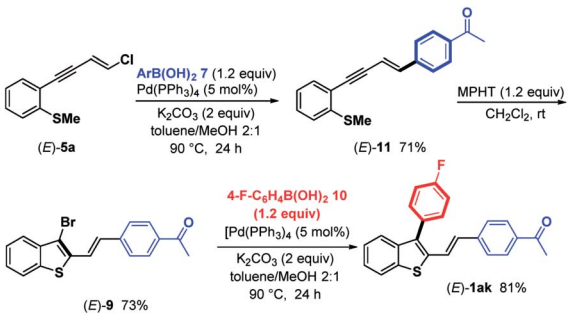


Table 3 Suzuki coupling reactions of (*E*)-**8a–d** with a variety of arylboronic acids





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

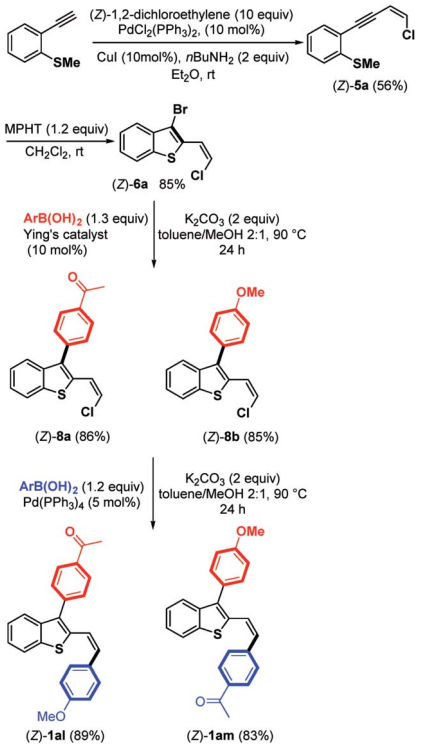


Scheme 5 Synthesis of (*E*)-**1ak**.

(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 inversing the MPHT-bromo-cyclization process followed by the arylation of the resulting 3-bromoposition of the thiophene backbone (Scheme 5).

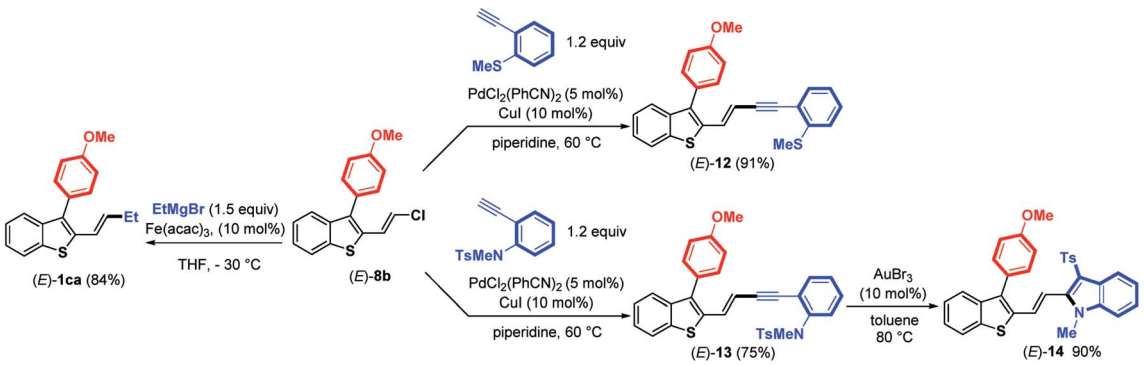
In detail, chloroenyne (*E*)-**5a** was initially coupled with (4-acetylphenyl)boronic acid **7** in the presence of $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2 equiv.) in toluene/MeOH (2 : 1) at 90 °C to give the expected 1,4-diarylenyne (*E*)-**11** in 71% yield.[15] (*E*)-**11** then undergoes MPHT-promoted 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 $Pd(PPh_3)_4$ (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.



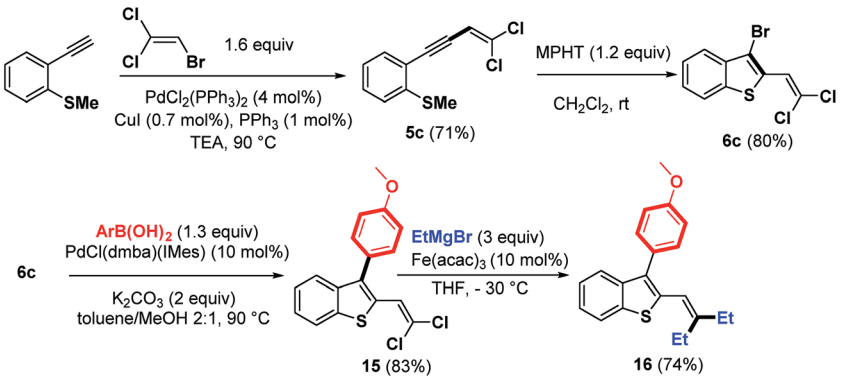
Scheme 7 Bromocyclization of (*Z*)-**5a** into (*Z*)-**6a** and subsequent Suzuki–Miyaura coupling reactions.

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 $PdCl_2(PhCN)_2$ (5 mol%) and 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[19] 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 (EtMgBr) in the presence of a catalytic amount of $Fe(acac)_3$ (ref. 20) to introduce an alkyl substituent, thus providing 2-



Scheme 6 Coupling reactions of vinylchloride (*E*)-**8b** with terminal *ortho*-substituted arylalkynes and 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[21] 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 nBuNH$_2$ as the base,[9] we were able to synthesize the expected chloroenyne (*Z*)-**5a** (56%) through the Sonogashira–Linstrumelle coupling of (2-ethynylphenyl)(methyl)-sulfane with (*Z*)-1,2-dichloroethylene in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI.

Interestingly, the reaction conditions used for the synthesis of (*E*)-**6a** (MPHT, CH_2Cl_2) also allowed us to selectively prepare (*Z*)-**6a** (85%) through the bromo-cyclization of (*Z*)-**5a** (Scheme 7).

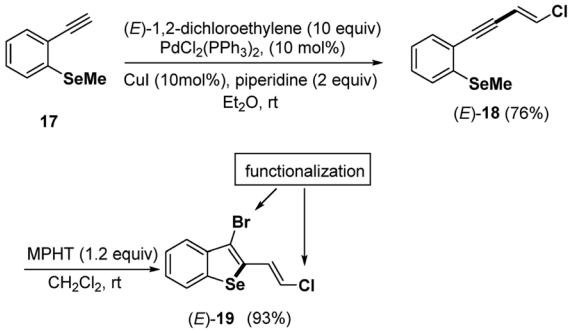
Further Suzuki–Miyaura monoarylation reactions of (*Z*)-**6a** with electron-poor phenylboronic acid **7** or the electron-rich (4-methoxyphenyl)boronic acid in the presence of Pd–NHC[16] led to the expected coupling products (*Z*)-**8a** and (*Z*)-**8b** in good yields of 86% and 85%, respectively. Further arylation of the (*Z*)-Csp^2–Cl bond can be accomplished by arylboronic acids in the presence of $Pd(PPh_3)_4$ 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 precatalyst 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 $Fe(acac)_3$ (ref. 20) at −30 °C to give benzothiophene **16** in 74% yield.

Finally, under the mild conditions (MPHT 1.2 equiv., CH_2Cl_2, rt) described above for the bromocyclization of chloroenynes **5** having an *ortho*-methyl sulfide group on the aromatic moity, we successfully transformed the *ortho*-SeMe-aryl chloro enyne (*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.



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

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-

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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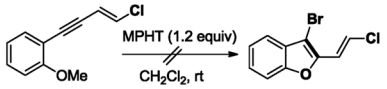

12 It is also possible to prepare a 3-iodo-2-(chlorovinyl) benzothiophene using I_2 and chloroenyne (*E*)-**5a** (82%).
13 When NBS (1.2 equiv.) was used in place of MPHT, (*E*)-**6a** was obtained in a poor yield of 20%. Using Br_2, the reaction furnished (*E*)-**6a** in 80%. Solid MPHT is more convenient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