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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

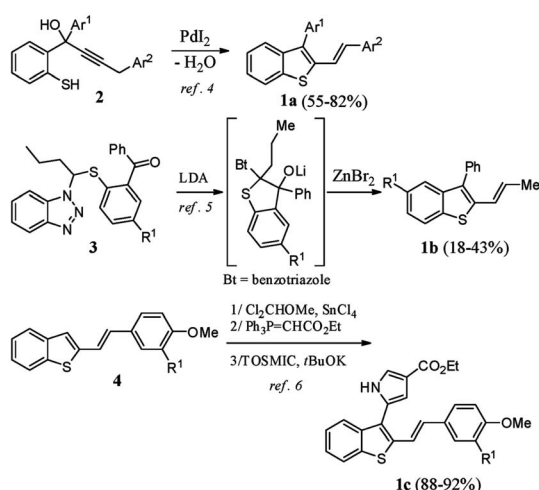
2,3-Disubstituted benzothiophenes have been well studied by the scientific community in past decades, mainly for their numerous biological properties.¹ For example, raloxifene (EvistaTM), an oral selective estrogen receptor modulator, is prescribed in the prevention and treatment of osteoporosis and 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-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**,⁴ (ii) reaction of **3** with LDA followed by rearrangement in the presence of ZnBr₂,⁵ 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*-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).

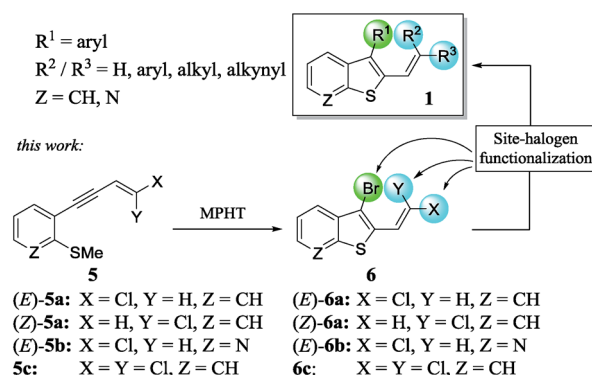
We choose a bromocyclization strategy instead of Larock's iodo heteroannulation⁸ since the site-selective Suzuki–Miyaura coupling of a C–Br vs. C–Cl bond is more challenging from our point of view than the coupling of C–I vs. C–Cl.



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.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 bromocyclization¹² at rt in CH₂Cl₂ to provide the desired 2,3-disubstituted benzothiophene platform (*E*)-**6a** in a good (88%) yield¹³ (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

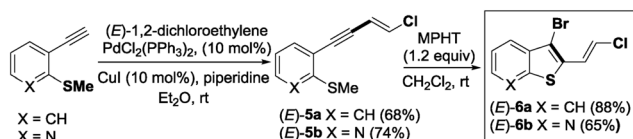
Next, we focus our attention on the identification of efficient experimental conditions for site-selective Suzuki–Miyaura coupling reactions between 3-bromobenzothiophene (*E*)-**6a** and arylboronic acid **7** (1.3 equiv.) as coupling partners (Table 1). Initially, to compare the reactivity of boronic acids towards a 2-vinylchlorine moiety *vs.* a probably more reactive 3-bromine atom on a benzothiophene scaffold, we tested the conditions used for the coupling of chloroenynes¹⁵ using Pd(PPh₃)₄ (5 mol%) as the catalyst, K₂CO₃ (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(PPh₃)₄ with other palladium sources such as PdCl₂(PPh₃)₂, PdCl₂(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 Ying¹⁶ 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 K₂CO₃ 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 K₃PO₄ gave a similar result to K₂CO₃ (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 NEt₃ 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%), K₂CO₃ (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 acids¹⁷ 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%).

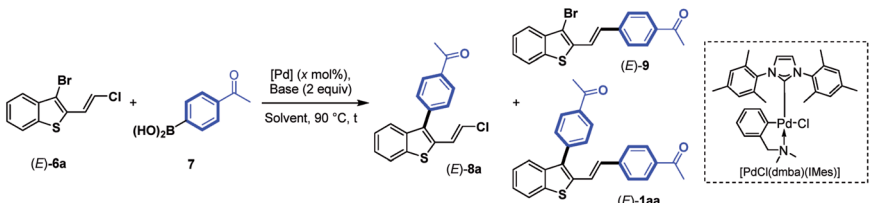
As the next logical extension, Suzuki–Miyaura coupling reactions at the remaining C–Cl bond of benzothiophene compounds (*E*)-**8a–d** were attempted under the previous conditions reported for the couplings of arylboronic acids with chloroenynes.¹⁵ In the presence of Pd(PPh₃)₄ (5 mol%), K₂CO₃ (2 equiv.), 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(PPh₃)₄ (10 mol%), K₂CO₃ (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 (K₂CO₃, 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 K₂CO₃ (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


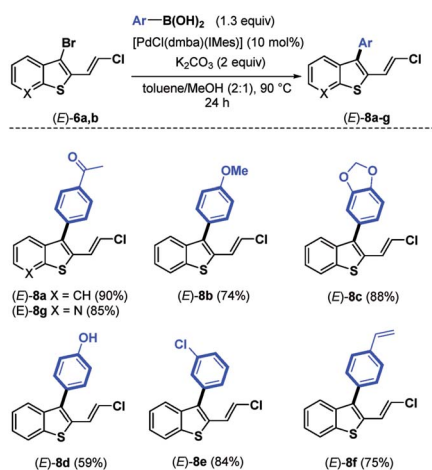
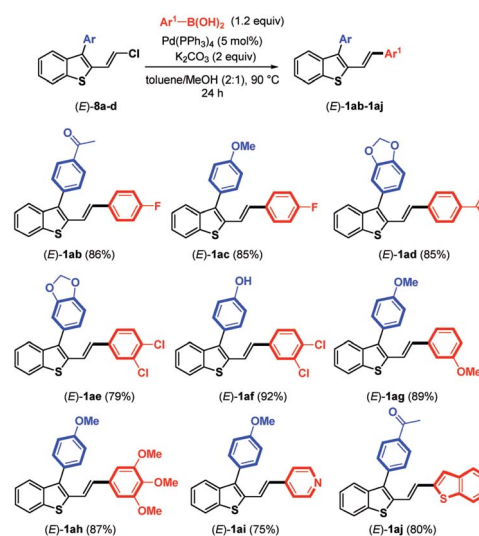
Entry	[Pd]	x	Base	Time (h)	Solvent	Yield ^b of 8a (%)	Yield ^b of 9 (%)	Yield ^b of 1aa (%)
1	Pd(PPh ₃) ₄	5	K ₂ CO ₃	7	Toluene/MeOH (2 : 1)	17	6	39
2	PdCl ₂ (PPh ₃) ₂	5	K ₂ CO ₃	7	Toluene/MeOH (2 : 1)	0	0	0
3	PdCl ₂ (dppf)	5	K ₂ CO ₃	7	Toluene/MeOH (2 : 1)	0 ^c	0	0
4	Pd(dba) ₂	5	K ₂ CO ₃	7	Toluene/MeOH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

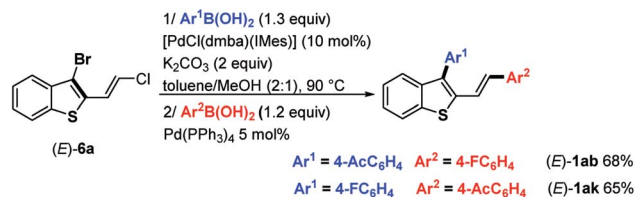
^a Conditions: (*E*)-6a (1 mmol), 7 (1.3 mmol), [Pd] (0.05 mmol or 0.1 mmol), base (2 equiv.) and solvent (18 mL) were heated in a sealed tube at 90 °C for time indicated in the table under argon atmosphere. ^b Yield of isolated product. ^c (*E*)-6a was recovered unchanged. ^d 45% of (*E*)-6a were recovered. ^e A complex mixture of unidentified products was obtained. ^f Replacing [PdCl(dbma)(IMes)] by Pd-PEPPSITM-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(PPh₃)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

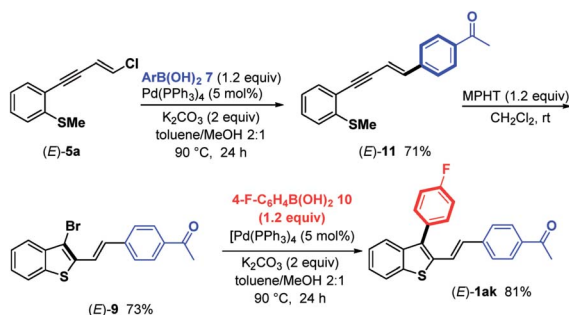
order of boronic acids (first 4-fluoroboronic acid followed by 4-acetylboronic acid).

However, it should be noted that attempts to achieve one-pot coupling in the presence of only one catalyst [PdCl(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.

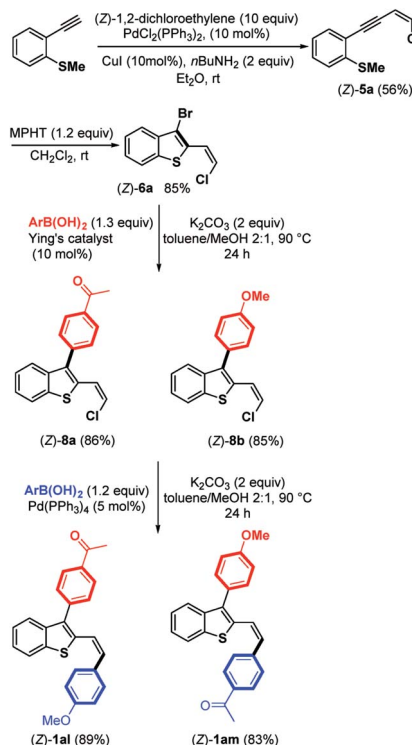


Scheme 5 Synthesis of (E)-1ak.

(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).

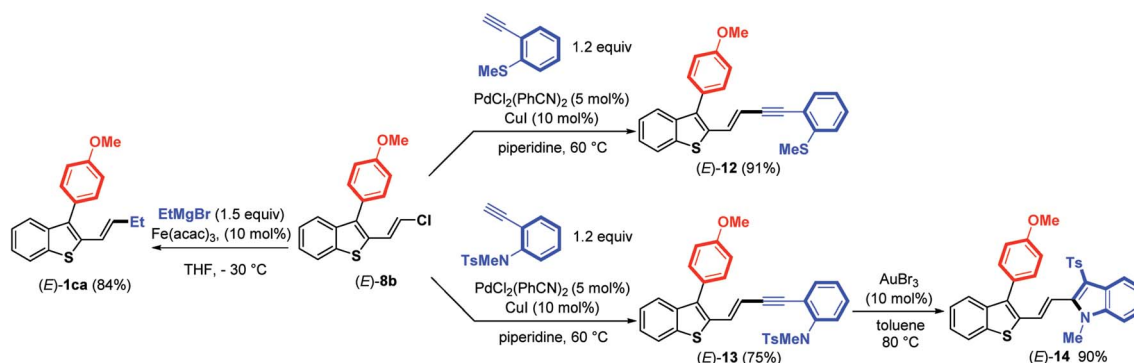
In detail, chloroenyne (E)-5a was initially coupled with (4-acylphenyl)boronic acid 7 in the presence of $\text{Pd}(\text{PPh}_3)_4$ (5 mol%), K_2CO_3 (2 equiv.) in toluene/MeOH (2 : 1) at 90 °C to give the expected 1,4-diarylene (E)-11 in 71% yield.¹⁵ (E)-11 then undergoes MPHT-promoted bromo-cyclization to furnish the 3-bromo-benzothiophene (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.

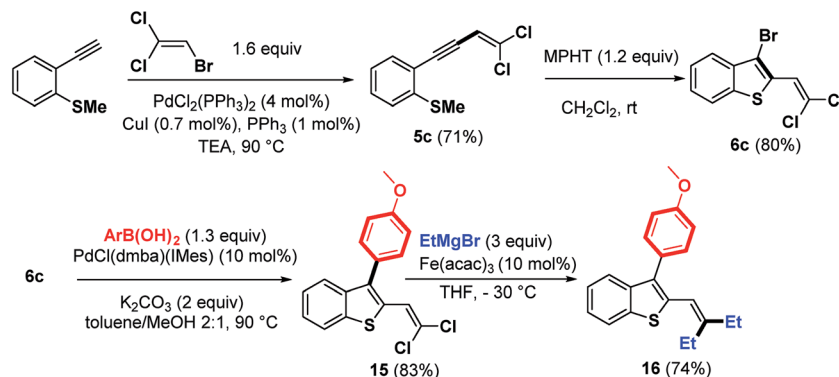


Scheme 7 Bromocyclization of (Z)-5a into (Z)-6a and subsequent Suzuki-Miyaura coupling reactions.

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 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 cyclization¹⁹ 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 $\text{Fe}(\text{acac})_3$ (ref. 20) to introduce an alkyl substituent, thus providing 2-

Scheme 6 Coupling reactions of vinylchloride (E)-8b with terminal *ortho*-substituted arylalkynes and 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 bond²¹ 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*BuNH₂ as the base,⁹ 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-dichloroethylene in the presence of catalytic amounts of $\text{PdCl}_2(\text{PPh}_3)_2$ 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–NHC¹⁶ 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 $\text{Pd}(\text{PPh}_3)_4$ 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).

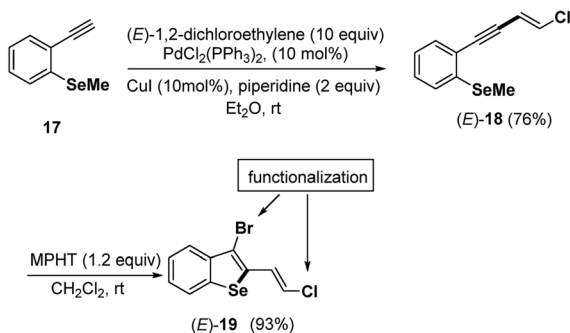
As expected, the bromocyclization process of **5c** promoted by MPHT furnished **6c** in 80% yield. An illustration of its synthetic potential is shown in Scheme 8. Trihalogenated benzothiophene **6c** was first monoarylated at the C-3 position using Pd–NHC precatalyst as a palladium source to give **15** (83%). This product was then coupled with EtMgBr (3 equiv.) in the presence of a catalytic amount of $\text{Fe}(\text{acac})_3$ (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 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

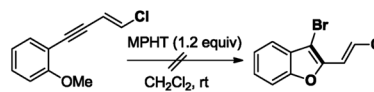
There are no conflicts to declare.

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Notes and references

- See for examples: (a) L. H. Li, M. C. Mathieu, D. Denis, A. G. Therien and Z. Y. Wang, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 734–737; (b) L. H. C. Berthelette, A. Chateaufneuf, M. Ouellet, C. F. Sturino and Z. Y. Wang, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7440–7443; (c) R. Romagnoli, P. G. Baraldi, C. L. Cara, E. Hamel, G. Basso, R. Bortolozzi and G. Viola, *Eur. J. Med. Chem.*, 2010, **45**, 5781–5791; (d) L. N. Li, L. Chang, S. Pellet-Rostaing, F. Liger, M. Lemaire, R. Buchet and Y. Q. Wu, *Bioorg. Med. Chem.*, 2009, **17**, 7290–7300; (e) M. Aleksić, B. Bertoša, R. Nhili, L. Uzelac, I. Jarak, S. Depauw, M. H. David-Cordonnier, M. Kralj, S. Tomić and G. Karminski-Zamola, *J. Med. Chem.*, 2012, **55**, 5044–5060; (f) C. Yang, K. Cross, G. J. Myatt, P. E. Blower and J. F. Rathman, *J. Med. Chem.*, 2004, **47**, 5984–5994.
- F. X. Li, J. L. Dou, L. J. Wei, S. X. Li and J. T. Liu, *Cancer Chemother. Pharmacol.*, 2016, **77**, 895–903.
- For recent papers concerning the synthesis of 2,3-diarylbenzothiophenes, see for examples: (a) D. Y. Wan, Y. D. Yang, X. Y. Liu, M. L. Li, S. L. Zha and J. S. You, *Eur. J. Org. Chem.*, 2016, 55–59; (b) T. Yamauchi, F. Shibahara and T. Murai, *Tetrahedron Lett.*, 2016, **57**, 2945–2948; (c) Y. Masuya, M. Tobisu and N. Chatani, *Org. Lett.*, 2016, **18**, 4312–4315; (d) I. Smari, H. Ben Ammar, B. Ben Hassine, J. F. Soulé and H. Doucet, *Synthesis*, 2015, **47**, 3354–3362; (e) K. Nobushige, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2014, **16**, 1188–1191; (f) L. Q. Zhao, C. Bruneau and H. Doucet, *Tetrahedron*, 2013, **69**, 7082–7089; (g) J. Yin, Y. Zhou, T. Lei and J. Pei, *Angew. Chem., Int. Ed.*, 2011, **50**, 6320–6323; (h) C. C. McAtee, P. S. Riehl and C. S. Schindler, *J. Am. Chem. Soc.*, 2017, **139**, 2960–2963; (i) P. R. Likhar, S. M. Salián, S. Roy, M. L. Kantam, B. Sridhar, K. V. Mohan and B. Jagadeesh, *Organometallics*, 2009, **28**, 3966–3969; (j) M. S. Subhas, S. S. Racharlawar, B. Sridhar, P. K. Kennady, P. R. Likhar, M. L. Kantam and S. K. Bhargava, *Org. Biomol. Chem.*, 2010, **8**, 3001–3010.
- B. Gabriele, R. Mancuso, E. Lupinacci, L. Veltri, G. Salerno and C. Carfagna, *J. Org. Chem.*, 2011, **76**, 8277–8286.
- A. R. Katritzky, K. Kirichenko, D. Hür, X. M. Zhao, Y. Ji and P. J. Steel, *ARKIVOC*, 2004, **6**, 27–44.
- P. Raju and A. K. Mohanakrishnan, *Eur. J. Org. Chem.*, 2016, 4361–4371.
- (a) M. Jacubert, O. Provot, J. F. Peyrat, A. Hamze, J. D. Brion and M. Alami, *Tetrahedron*, 2010, **66**, 3775–3787; (b) B. Tréguier, E. Rasolofonjatovo, A. Hamze, O. Provot, J. Wdzieczac-Bakala, J. Dubois and M. Alami, *Eur. J. Org. Chem.*, 2011, 4868–4876; (c) G. Le Bras, A. Hamze, S. Messaoudi, O. Provot, P. B. Le Calvez, J. D. Brion and M. Alami, *Synthesis*, 2008, 1607–1611; (d) G. K. Zhao, L. Z. Yuan, M. Roudier, J. F. Peyrat, A. Hamze, J. D. Brion, O. Provot and M. Alami, *Synthesis*, 2016, **48**, 3382–3392.
- For a recent review on the synthesis of iodoheterocycles by iodocyclization, see: (a) B. Gabriele, R. Mancuso and R. C. Larock, *Curr. Org. Chem.*, 2014, **18**, 341–358; (b) B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937–2980 and references herein; (c) T. Kesharwani, S. A. Worlikar and R. C. Larock, *J. Org. Chem.*, 2006, **71**, 2307–2312; (d) D. W. Yue and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 1905–1909; (e) C. H. Cho, D. I. I. Jung, B. Neuenwander and R. C. Larock, *ACS Comb. Sci.*, 2011, **13**, 501–510; (f) S. Mehta, J. P. Waldo and R. C. Larock, *J. Org. Chem.*, 2009, **74**, 1141–1147; (g) N. A. Danalkina, A. E. Kulyashova, A. F. Khlebnikov, S. Brase and I. A. Balova, *J. Org. Chem.*, 2014, **79**, 9018–9045; (h) S. Mehta and R. C. Larock, *J. Org. Chem.*, 2010, **75**, 1652–1658; (i) C. H. Cho, B. Neuenwander and R. C. Larock, *J. Comb. Chem.*, 2010, **12**, 278–285; (j) C. H. Cho, D. I. I. Jung and R. C. Larock, *Tetrahedron Lett.*, 2010, **51**, 6485–6488; (k) G. Ferrara, T. Jin, M. Akhtaruzzaman, A. Islam, L. Y. Han and H. Yamamoto, *Tetrahedron Lett.*, 2012, **53**, 1946–1950; (l) N. A. Danilina, S. Bräse and I. A. Balova, *Synlett*, 2011, **4**, 517–520.
- For the Pd-coupling of (Z)-1,2-dichloroethylene with terminal alkynes, we have demonstrated that *n*BuNH₂ is superior to piperidine as base, see: (a) M. Alami, S. Gueugnot, E. Domingues and G. Linstrumelle, *Tetrahedron*, 1995, **51**, 1209–1220; (b) M. Alami, J. F. Peyrat and J. D. Brion, *Synthesis*, 2000, 1499–1518.
- (a) J. F. Berrien, O. Provot, D. Joseph and A. Bekaert, *J. Chem. Educ.*, 2004, **81**, 1348–1349; (b) A. Bekaert, O. Provot, O. Rasolohajona, M. Alami and J. D. Brion, *Tetrahedron Lett.*, 2005, **46**, 4187–4191.
- Switching from (E)-**5a** to substrate (E)-1-(4-chlorobut-3-en-1-yn-1-yl)-2-methoxybenzene having a less nucleophile *ortho* OMe substituent, no bromocyclization occurred in the presence of MPHT to give the expected 3-bromo-2-chlorovinyl-benzofuran derivative.



- 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 μ L).
- 14 B. E. Sleebs, A. Levit, I. P. Street, H. Falk, T. Hammonds, A. C. Wong, M. D. Charles, M. F. Olson and J. B. Baell, *Med. Chem. Commun.*, 2011, **2**, 977–981.
- 15 A. Tikad, A. Hamze, O. Provot, J. D. Brion and M. Alami, *Eur. J. Org. Chem.*, 2010, 725–731.
- 16 (a) E. A. B. Kantchev, G. R. Peh, C. Zhang and J. Y. Ying, *Org. Lett.*, 2008, **10**, 3949–3952; (b) G. R. Peh, E. A. B. Kantchev, J. C. Er and J. Y. Ying, *Chem.–Eur. J.*, 2010, **14**, 4010–4017.
- 17 Experimental conditions found to prepare 3-arylated benzothiophenes (*E*)-**8a–g** (see Table 1, entry 7) failed with heterocyclic boronic acids such as 3-pyridineboronic acid, 4-pyridine boronic acid and benzo[*b*]thiophen-2-ylboronic acid and starting material (*E*)-**6a** was recovered unchanged.
- 18 (a) M. Alami and G. Linstrumelle, *Tetrahedron Lett.*, 1991, **32**, 6109–6112; (b) M. Alami, B. Crousse and F. Ferri, *J. Organomet. Chem.*, 2001, **624**, 114–123.
- 19 I. Nakamura, U. Yamagishi, D. Song, S. Konta and Y. Yamamoto, *Chem.–Asian J.*, 2008, **3**, 285–295.
- 20 (a) G. Cahiez and H. Avedissian, *Synthesis*, 1998, 1199–1205; (b) M. Seck, X. Frank, R. Hocquemiller, B. Figadère, J. F. Peyrat, O. Provot, J. D. Brion and M. Alami, *Tetrahedron Lett.*, 2004, **45**, 1881–1884; (c) M. Dos Santos, X. Frank, R. Hocquemiller, B. Figadère, J. F. Peyrat, O. Provot, J. D. Brion and M. Alami, *Synlett*, 2004, **15**, 2697–2700.
- 21 T. T. B. Nguyen, T. Lomberget, N. C. Tran, E. Colomb, L. Nachtergaele, S. Thoret, J. Dubois, J. Guillaume, R. Abdayem, M. Haftek and R. Barret, *ACS Med. Chem. Lett.*, 2012, **22**, 7227–7231.

