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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

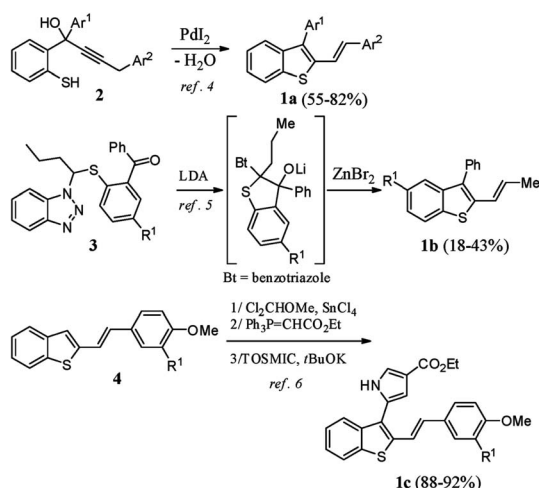
2,3-Disubstituted benzothiophenes have been well studied by the scientific community in past decades, mainly for their numerous biological properties.¹ For example, raloxifene (Evista™), an oral selective estrogen receptor modulator, is prescribed in the prevention and treatment of osteoporosis and is 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-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).

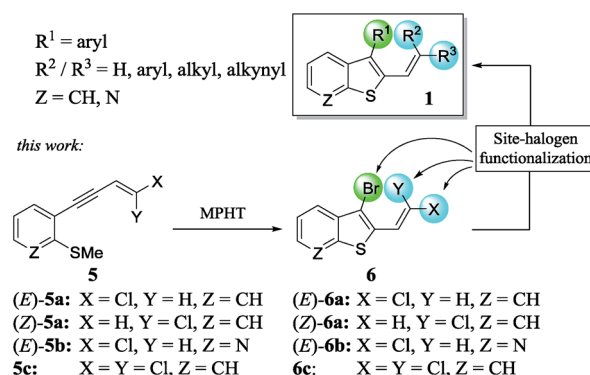
We choose a bromocyclization strategy instead of Larock's iodo heteroannulation⁸ since the site-selective Suzuki–Miyaura coupling of a C–Br vs. C–Cl bond is more challenging from our point of view than the coupling of C–I vs. C–Cl.



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*-5a¹¹ 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

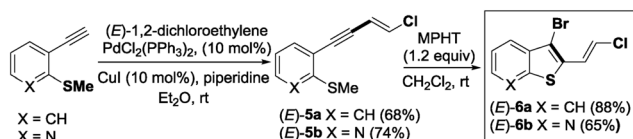
Next, we focus our attention on the identification of efficient experimental conditions for site-selective Suzuki–Miyaura coupling reactions between 3-bromobenzothiophene (*E*-6a and arylboronic acid 7 (1.3 equiv.) as coupling partners (Table 1). Initially, to compare the reactivity of boronic acids 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%).

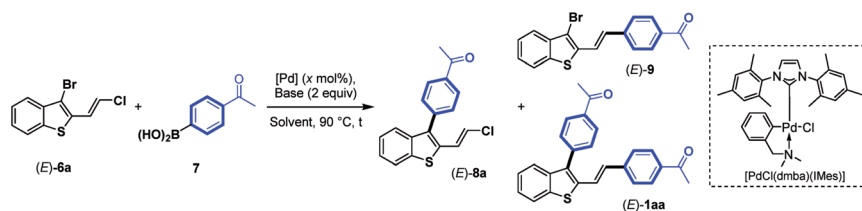
As the next logical extension, Suzuki–Miyaura coupling reactions at the remaining C–Cl bond of benzothiophene compounds (*E*-8a–d were attempted under the previous conditions reported for the couplings of arylboronic acids with chloroenynes.¹⁵ In the presence of Pd(PPh₃)₄ (5 mol%), K₂CO₃ (2 equiv.),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

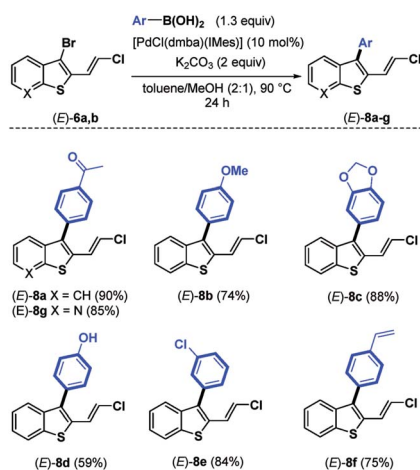
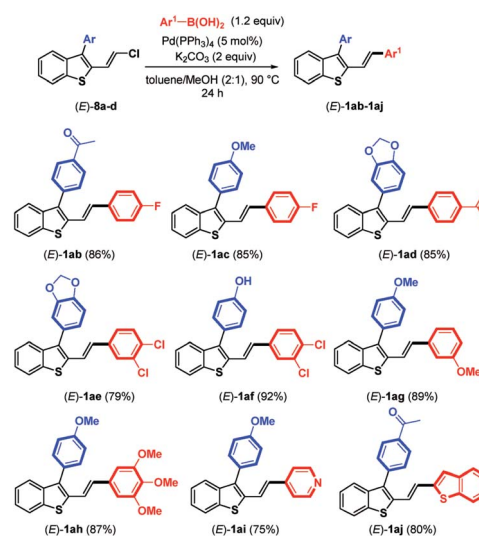
Entry	[Pd]	x	Base	Time (h)	Solvent	Yield ^b of 8a (%)	Yield ^b of 9 (%)	Yield ^b of 1aa (%)
1	Pd(PPh ₃) ₄	5	K ₂ CO ₃	7	Toluene/MeOH (2 : 1)	17	6	39
2	PdCl ₂ (PPh ₃) ₂	5	K ₂ CO ₃	7	Toluene/MeOH (2 : 1)	0	0	0
3	PdCl ₂ (dppf)	5	K ₂ CO ₃	7	Toluene/MeOH (2 : 1)	0 ^c	0	0
4	Pd(dba) ₂	5	K ₂ CO ₃	7	Toluene/MeOH (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)]	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

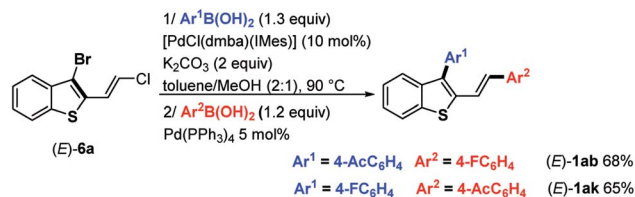
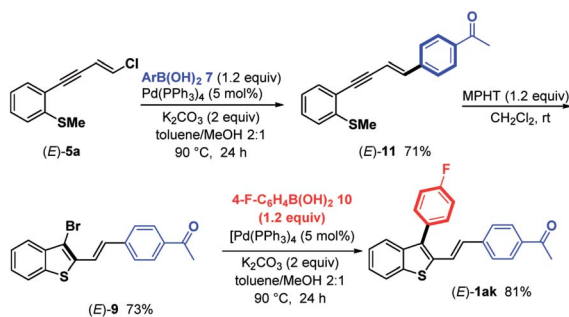
^a Conditions: (*E*)-6a (1 mmol), 7 (1.3 mmol), [Pd] (0.05 mmol or 0.1 mmol), base (2 equiv.) and solvent (18 mL) were heated in a sealed tube at 90 °C for time indicated in the table under argon atmosphere. ^b Yield of isolated product. ^c (*E*)-6a was recovered unchanged. ^d 45% of (*E*)-6a were recovered. ^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

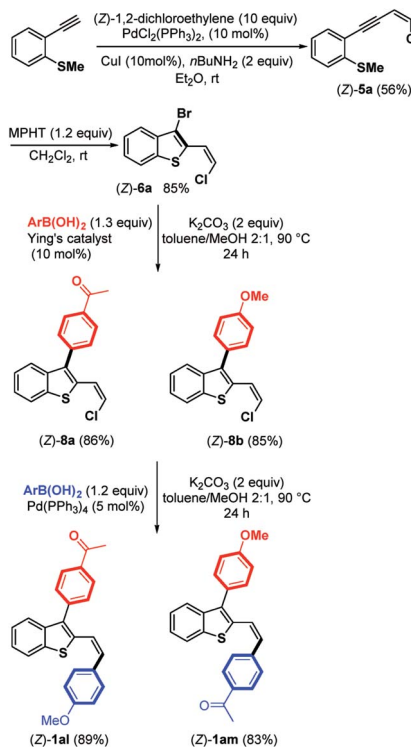
Table 2 Suzuki coupling reactions of (*E*)-6a,b with a variety of arylboronic acidsTable 3 Suzuki coupling reactions of (*E*)-8a–d with a variety of arylboronic acids

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.

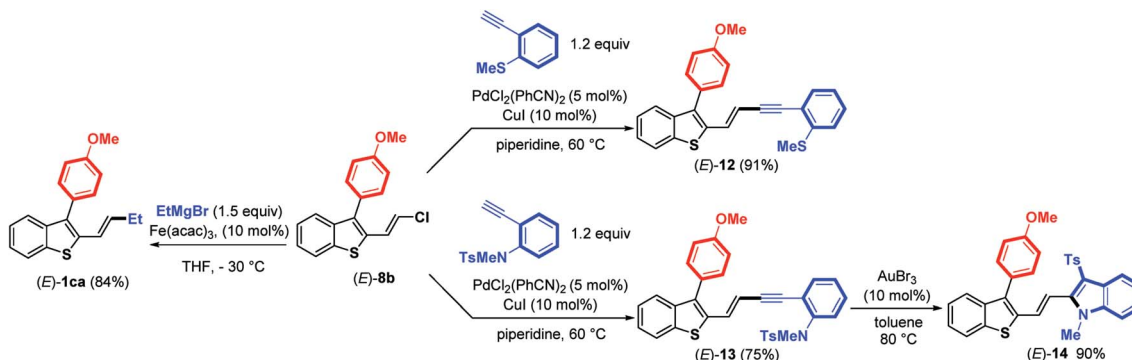
2,3-Disubstituted benzothiophenes (*E*)-1ak were also accessed by inverting the MPHT-bromo-cyclization process followed by the arylation of the resulting 3-bromoposition of the thiophene backbone (Scheme 5).

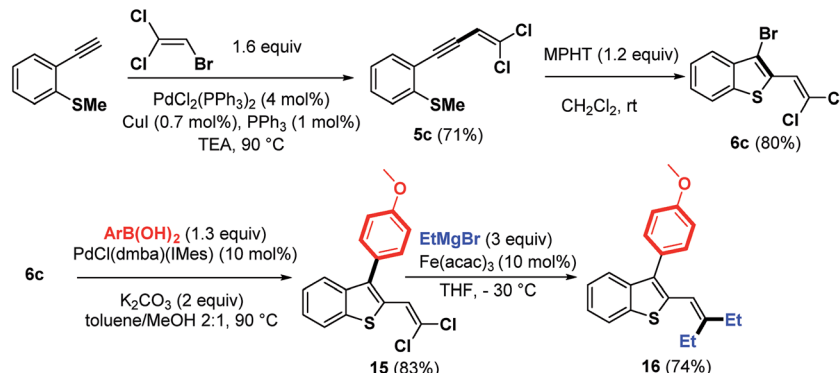
In detail, chloroenyne (*E*)-5a was initially coupled with (4-acylphenyl)boronic acid 7 in the presence of $\text{Pd}(\text{PPh}_3)_4$ (5 mol%), K_2CO_3 (2 equiv.) in toluene/MeOH (2 : 1) at 90 °C to give the expected 1,4-diarylene (*E*)-11 in 71% yield.¹⁵ (*E*)-11 then undergoes MPHT-promoted bromo-cyclization to furnish the 3-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 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 (Csp³), arylboronic acids (Csp²) 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 PdCl₂(PPh₃)₂ and CuI.

Interestingly, the reaction conditions used for the synthesis of (*E*)-**6a** (MPHT, CH₂Cl₂) 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*)-Csp²–Cl bond can be accomplished by arylboronic acids in the presence of Pd(PPh₃)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).

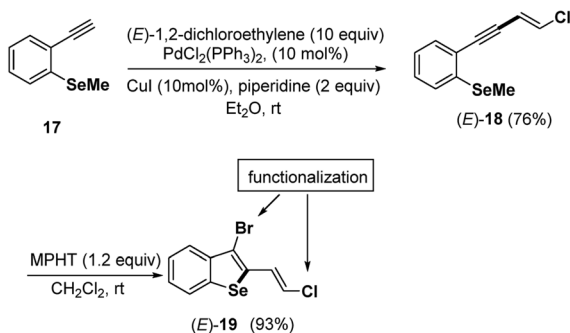
As expected, the bromocyclization process of **5c** promoted by MPHT furnished **6c** in 80% yield. An illustration of its synthetic potential is shown in Scheme 8. Trihalogenated benzothiophene **6c** was first monoarylated at the C-3 position using Pd–NHC pre-catalyst as a palladium source to give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

Finally, under the mild conditions (MPHT 1.2 equiv., CH₂Cl₂, 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

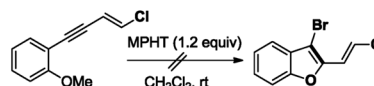
There are no conflicts to declare.

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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. Salian, 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. Danilkina, 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. Sleeb, 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.

