Synthetic Methods

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Versatile Synthesis of Benzothiophenes and Benzoselenophenes by Rapid Assembly of Arylzinc Reagents, Alkynes, and Elemental Chalcogens**

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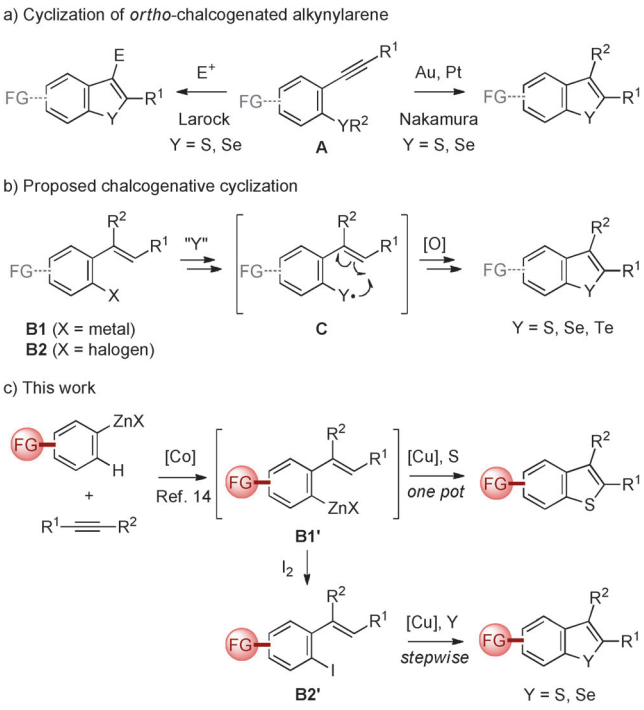
Benzothiophene is frequently found as a core structure of biologically active compounds such as raloxifene, sertaconazole, and SB-271046,[1] as well as materials for organic electronics applications.[2] The selenium analogue, benzoselenophene, has also attracted increasing attention in the fields of medicinal chemistry[3] and materials science.[4] Approaches to their synthesis often involve cyclization of an alkynylarene bearing an *ortho*-chalcogen functional group (**A**, Scheme 1 a).



Scheme 1. Synthetic approaches to benzothiophenes and benzoselenophenes. FG = functional group.

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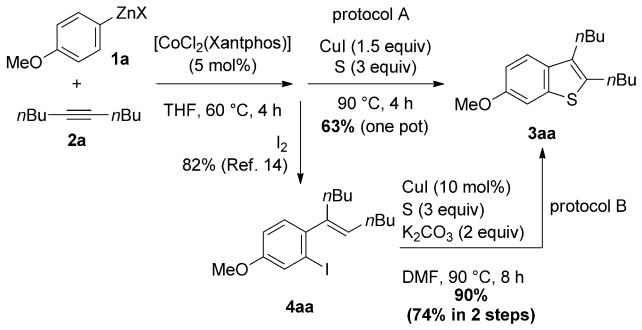
For example, Larock's electrophile (I_2, *N*-bromosuccinimide (NBS), RSCl) mediated cyclization[5,6] and Nakamura's alkynophilic metal (Au or Pt) catalyzed cyclization reactions[7,8] represent efficient and complementary routes to benzothiophenes and benzoselenophenes. A sequence comprising lithiation of an *ortho*-alkynylaryl bromide, electrophilic trapping with elemental sulfur or selenium (or tellurium), and cyclization of the resulting chalocogenide anion also allows preparation of the corresponding benzochalcogenophene.[9–12] Regardless of their efficiency and reliability, these and other intramolecular cyclization approaches usually have difficulty in diversifying the benzene ring moiety of benzothiophene and benzoselenophene, because preparation of the starting material such as **A** becomes increasingly tedious with additional substituents on the benzene ring. We report here an alternative synthetic approach based on the assembly of arylzinc reagents, alkynes, and elemental sulfur or selenium with the aid of cobalt and copper catalysts (Scheme 1 b,c). The modular nature of this approach allows facile access to diversely functionalized benzothiophenes and benzoselenophenes that are laborious to synthesize by the existing synthetic methods.

Given the propensity of chalcogenide anions and chalcogen–H bonds to be oxidized and form chalcogenide radicals, we conceived that *ortho*-alkenylaryl metal **B1** and halide **B2** would serve as viable precursors to benzochalcogenophenes (Scheme 1 b). Thus, electrophilic or nucleophilic chalcogenation of **B1** or **B2**, respectively, would be followed by the formation of a radical species **C**, which would readily undergo cyclization onto the alkenyl moiety to afford the desired product upon oxidation. The apparent simplicity notwithstanding, this approach cannot be an attractive option without a convenient method to access starting materials **B1** or **B2** with diverse substitution patterns and has not been explored practically.[13] However, we recently developed a cobalt-catalyzed migratory arylzincation reaction of an internal alkyne to afford *ortho*-alkenylarylzinc species **B1′** (or its iodinated product **B2′**).[14] Thus, we envisioned that a combination of this reaction and the proposed chalcogenative cyclization would allow divergent synthesis of benzochalcogenophenes containing flexibility with respect to the functional group on the benzene ring as well as the chalcogen element (Scheme 1 c).

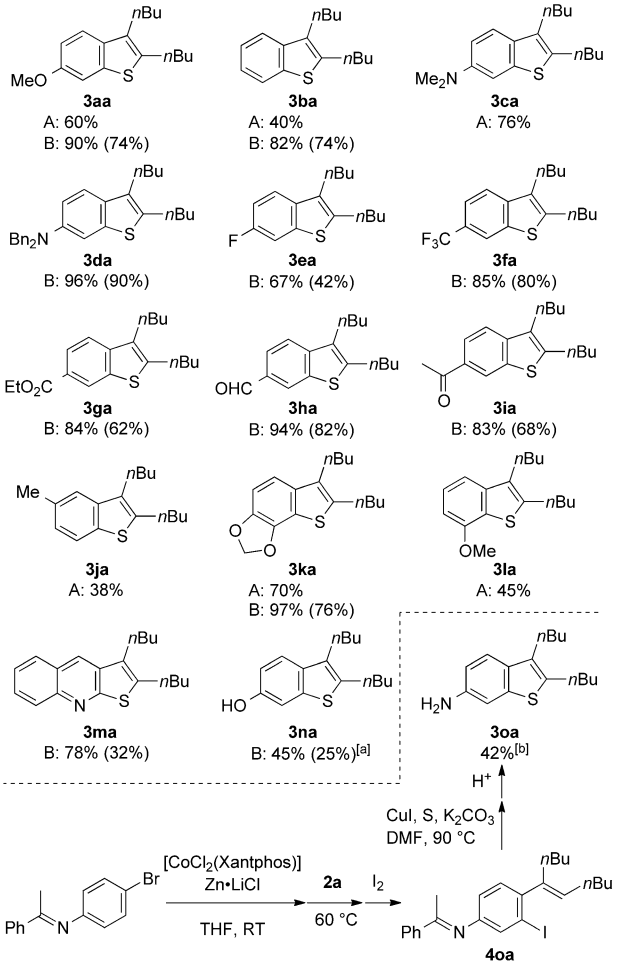
Along with the above idea, our initial study was focused on the construction of benzothiophene from *ortho*-alkenylarylzinc species generated by [$CoCl_2$(Xantphos)]-catalyzed addition of 4-methoxyphenylzinc reagent **1a** to 5-decyne **2a** (Scheme 2). After extensive screening of reaction conditions,



Scheme 2. One-pot and stepwise constructions of benzothiophene **3aa** from 4-methoxyphenylzinc reagent, 5-decyne, and elemental sulfur. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

we managed to establish two independent protocols (see the Supporting Information for the optimization study). In one protocol, the generation of the key arylzinc intermediate from **1a** (prepared from $ZnCl_2$·TMEDA and 4-methoxyphenylmagnesium bromide) was followed by treatment with CuI and elemental sulfur at 90 °C for 4 h, thereby affording the desired benzothiophene **3aa** in 63% yield in a one-pot manner (protocol A). Although **3aa** was obtained even in the absence of CuI, the Zn-to-Cu transmetalation significantly improved the yield. Alternatively, the *ortho*-alkenylarylzinc intermediate (prepared in a one-pot manner from 4-iodoanisole, Zn·LiCl, and 5-decyne with the Co-Xantphos catalyst)[15] was first quenched with iodine, and the resulting *ortho*-alkenylaryl iodide **4aa** was subjected to copper-catalyzed thiolation using CuI, S, and K_2CO_3 in DMF to afford the product **3aa** cleanly in 90% yield (protocol B).[16] Note that neither protocol required any particular external oxidant, thus suggesting that CuI, elemental sulfur, or residual molecular oxygen served as oxidants for the ring-closure/aromatization process. Alternatively, oxidation may take place during the workup.

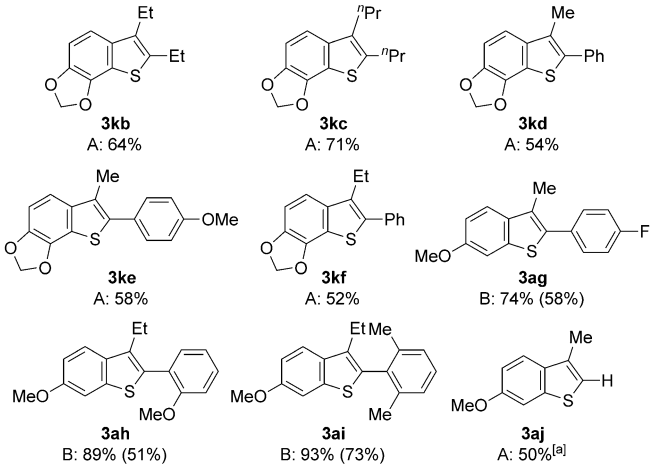
The scope of the benzothiophene synthesis was explored first using different arylzinc reagents and 5-decyne (Scheme 3). Benzothiophenes **3aa**–**3ia** bearing various functional groups at the C6-position could be prepared in moderate to good yields with either protocol A or B. The one-pot protocol A was applicable to arylzinc reagents bearing electron-donating substituents (**3aa** and **3ca**). On the other hand, protocol A worked poorly with an electron-withdrawing substituent on the zinc reagent and produced a significant amount of the corresponding protonation product, while the stepwise protocol B cleanly furnished the desired benzothiophene (**3ea**–**3ia**). Note that the synthesis of **3ha** could be performed on a 2 mmol scale in 85% yield. Regioselective migratory addition of *meta*-substituted arylzinc reagents, controlled either by steric hindrance or by coordination,[14] was applied to the regioselective synthesis of 6-methyl-, 6,7-methylenedioxy-, and 7-methoxybenzothiophenes **3ja**–**3la**. The low yield of **3ja** was not due to formation of its regioisomer, but because of the sluggish reaction of the *m*-tolylzinc reagent. Thieno[2,3-*b*]quinoline **3ma** was also synthesized with exclusive regioselectivity. 6-Hydroxybenzothiophene **3na** was obtained from a Boc-protected precursor iodide, where removal of the Boc group



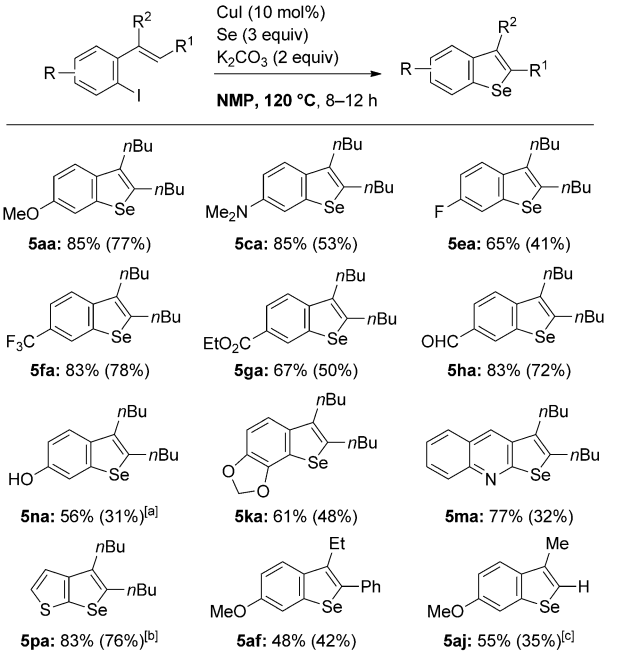
Scheme 3. Benzo[*b*]thiophenes synthesized from different arylzinc reagents and 5-decyne (0.5 mmol and 0.2 mmol scales for protocols A and B, respectively). The yields for protocols A and B are based on 5-decyne and the *ortho*-alkenylaryl iodide (**4**), respectively. The two-step yields for protocol B (based on 5-decyne) are shown in parentheses. [a] The starting material was protected with a Boc group, which was removed during the reaction. [b] Yield is based on 5-decyne (**2a**). Boc = *tert*-butoxycarbonyl.

coincided with C–S coupling/cyclization. 6-Aminobenzothiophene **3oa** was obtained from *p*-bromoaniline protected in the form of the acetophenone imine in a respectable yield of 42% (based on 5-decyne) through a sequence comprising cobalt-catalyzed zinc insertion,[15] migratory arylzincation to 5-decyne, iodination, copper-catalyzed C–S coupling/cyclization, and acidic hydrolysis.

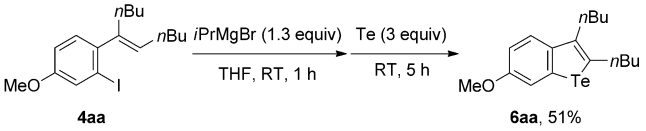
Benzothiophenes bearing different substituents on the C2- and C3-positions were also synthesized from a series of internal alkynes (Scheme 4). The one-pot protocol A was applicable to the condensation of the 3,4-methylenedioxyphenylzinc reagent, dialkyl- or alkylarylalkyne, and elemental sulfur to afford the corresponding benzothiophenes **3kb**–**3kf** in reasonable yield. With alkylarylalkynes bearing sterically hindered aryl groups, protocol B allowed synthesis of benzothiophenes **3ah** and **3ai** in excellent yields. The reaction of 1-trimethylsilyl-1-propyne by using protocol A resulted in partial loss of the trimethylsilyl group, which was completely removed by further treatment of the crude product with KOH



Scheme 4. Benzo[*b*]thiophenes synthesized from different alkynes (0.5 mmol and 0.2 mmol scales for protocols A and B, respectively). The yields for protocols A and B are based on the alkyne and the *ortho*-alkenylaryl iodide (**4**), respectively. The two-step yields for protocol B (based on the alkyne) are shown in parentheses. [a] The reaction was performed using 1-trimethylsilyl-1-propyne, and the $SiMe_3$ group was removed by treatment with KOH/MeOH.



Scheme 5. Synthesis of benzo[*b*]selenophenes through copper-catalyzed C–Se coupling/cyclization (0.2 mmol scale). The two-step yields based on the alkyne are shown in parentheses. [a] The starting material had an OBoc group as the R group, which was removed after the reaction. [b] The reaction time was 36 h. [c] The starting material had a $SiMe_3$ group as the R^1 group, which was removed during the reaction. NMP = *N*-methyl-2-pyrrolidone.



Scheme 6. Synthesis of benzo[*b*]tellurophene through iodine–magnesium exchange/trapping with tellurium.

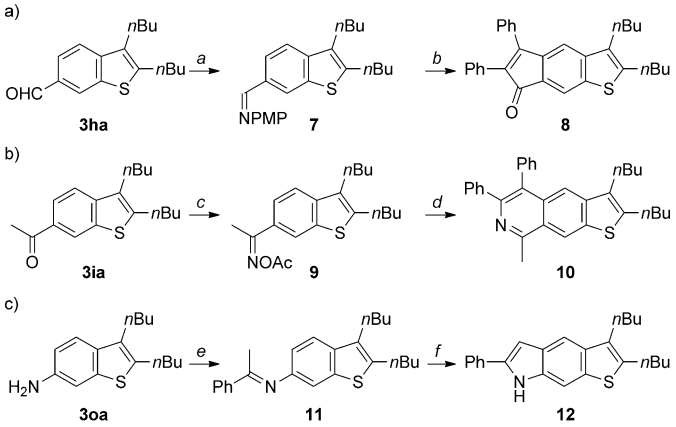
in MeOH to afford 3-methylbenzothiophene **3aj** in 50% yield.

Attempts to expand the above benzothiophene synthesis to benzoselenophenes met with a challenge. The one-pot approach through copper-mediated reaction of *ortho*-alkenylarylzinc species with selenium powder resulted in a complex mixture with no indication of benzoselenophene formation. Nevertheless, careful examination of the stepwise route allowed us to establish suitable reaction conditions for the copper-catalyzed C–Se coupling/cyclization of *ortho*-alkenylaryl iodide, where the choice of NMP as the solvent and an elevated temperature of 120 °C were crucial (Scheme 5).[17] Thus, selenium analogues of many of the benzothiophenes presented in Schemes 3 and 4 could be synthesized in moderate to good yields. Selenopheno[2,3-*b*]thiophene **5pa** is a notable additional example, as preparation of its sulfur analogue was unsuccessful for unknown reasons.

We encountered difficulty in further extension of the present approach to benzotellurophene synthesis. As was the case with benzoselenophene, the one-pot approach was not successful. Furthermore, copper-catalyzed C–Te coupling/cyclization reactions of *ortho*-alkenylaryl iodide under various conditions produced the desired benzotellurophene, however, as an inseparable mixture with a substantial amount of a deiodination product.[18] As a compromise to these problems, benzotellurophene **6aa** was synthesized in moderate yield from the iodide **4aa** through iodine–magnesium exchange[19] followed by electrophilic trapping with tellurium powder (Scheme 6).

The functional groups on the cyclization products offer us diverse opportunities for the extension of the π-conjugated system through C–H bond functionalization (Scheme 7). First, condensation of benzothiophene-6-carbaldehyde **3ha** with *p*-anisidine was followed by rhodium(III)-catalyzed, aldimine-directed oxidative annulation with diphenylacetylene[20] to afford, upon hydrolysis, 7*H*-indeno[5,6-*b*]thiophen-7-one **8** (Scheme 7a). Second, *O*-acetyloxime **9** derived from 6-acetylbenzothiophene **3ia** was subjected to rhodium(III)-catalyzed redox-neutral annulation with diphenylacetylene[21] to afford thieno[3,2-*g*]isoquinoline **10** (Scheme 7b). Finally, imine **11** derived from 6-aminobenzothiophene **3oa** and acetophenone participated in a palladium-catalyzed dehydrogenative cyclization reaction[22] to afford 7*H*-thieno[3,2-*f*]indole **12**. In all of these examples, C–H functionalization took place at the less hindered position.

In summary, we have established versatile and flexible synthetic methods for benzothiophenes and benzoselenophenes through the combination of cobalt-catalyzed migratory arylzincation and copper-mediated or -catalyzed chalcogenative cyclization reactions. The present one-pot or two-step, three-component coupling approach allows expedient synthesis of a wide variety of functionalized benzothiophenes and benzoselenophenes, which are not easily accessible by the existing synthetic methods, with minimum synthetic labor. Further studies on the use of *ortho*-alkenylarylzinc compounds and *ortho*-alkenylaryl iodides as reagents for the construction of benzo-fused heterocycles are ongoing in our laboratory, in light of growing interest in nonconventional



Scheme 7. Transformation of functionalized benzothiophenes through C–H bond functionalization. Reaction conditions: a) *p*-anisidine, 4 Å MS, toluene, 80%; b) diphenylacetylene, $[\{Cp^*RhCl_2\}_2]$ (5 mol%), $Cu(OAc)_2{\cdot}H_2O$, DMF, 80°C, then 3 N HCl, 55%; c) $NH_2OH{\cdot}HCl$, pyridine, EtOH, 60°C then Ac_2O, DMAP, pyridine, RT, 65%; d) diphenylacetylene, $[\{Cp^*RhCl_2\}_2]$ (5 mol%), $Cu(OAc)_2$ (10 mol%), DMF, 80°C, 48%; e) acetophenone, 4 Å MS, toluene; f) $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$, DMSO, 60°C, 36% (2 steps). PMP = *p*-methoxyphenyl, $Cp^* = C_5Me_5$, DMAP = 4-dimethylaminopyridine, MS = molecular sieves.

benzoheteroles containing silicon,[23] phosphorus,[24] and other hetroatom elements.

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