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Review

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Recent developments in the synthesis of substituted benzo[*b*]thiophenes

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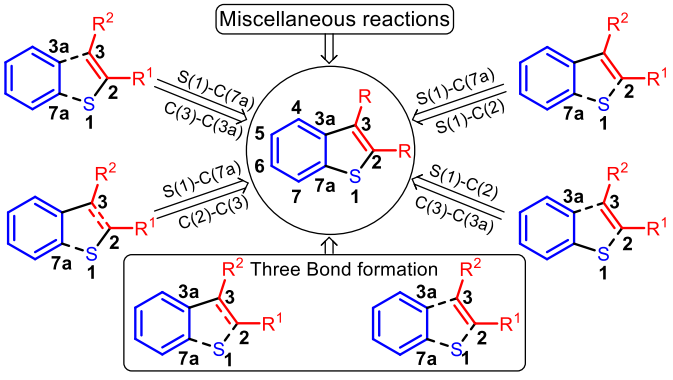
Abstract

Substituted-benzo[*b*]thiophenes are important heterocyclic frameworks which are present in several biologically-important natural products, medicinally-important molecules and commercially-available drugs. Benzo[*b*]thiophene-fused polycyclic (hetero)aromatics have also found applications in material science. Therefore, considerable attention has been drawn towards the development of new, efficient synthetic routes for this class of heterocycles. The present review focuses on recent syntheses of benzo[*b*]thiophene derivatives, directed towards the construction of the thiophene ring on substituted benzene derivatives, involving formation of at least two bonds in a one-pot operation. A few syntheses in which a thiophene ring is constructed by simultaneous formation of three bonds, in cascade fashion, are also discussed.



Keywords: Benzo[*b*]thiophene synthesis, sulfur surrogates, C–S bond formation, transition metal catalyzed syntheses, photoinduced synthesis, interrupted Pummerer reaction

Table of Contents

1. Introduction

Substituted-benzo[*b*]thiophenes are privileged frameworks, present in several natural products, bioactive molecules, clinically important small-molecule drugs.[1-3] They are also found in π-conjugated benzo[*b*]thiophenes, which are components of several functional materials, including light-emitting diodes (LEDs), field-effect transistors (FETs) and organic photovoltaics (OPVs).[4-6]

Raloxifene **1** is a selective estrogen-receptor modulator (SERM) used in the treatment of postmenopausal osteoporosis,[7,8] whereas arzoxifene **2** is used in the treatment of breast cancer (Figure 1).[9,10] Desketoraloxifene **3** is a much stronger activator of the Activator Protein-1 (AP-1) site through ERα and ERβ.[11] Zileuton **4**, a 5-lipoxygenase inhibitor, is a marketed drug, used in the treatment of asthma.[12,13] Sertaconazole **5** displays a broad range of antifungal activity against dermatophytes of the Trichophyton, Epidermophyton and Microsporum genera among others.[12,14] Compound **6** is an analog of naturally-occurring Combretastatin, acting as a tubulin-polymerization inhibitor (Figure 1).[15] Mitotenamine **7**[16] and Tienocarbine **8**[17] are shown to display antitumor activity.

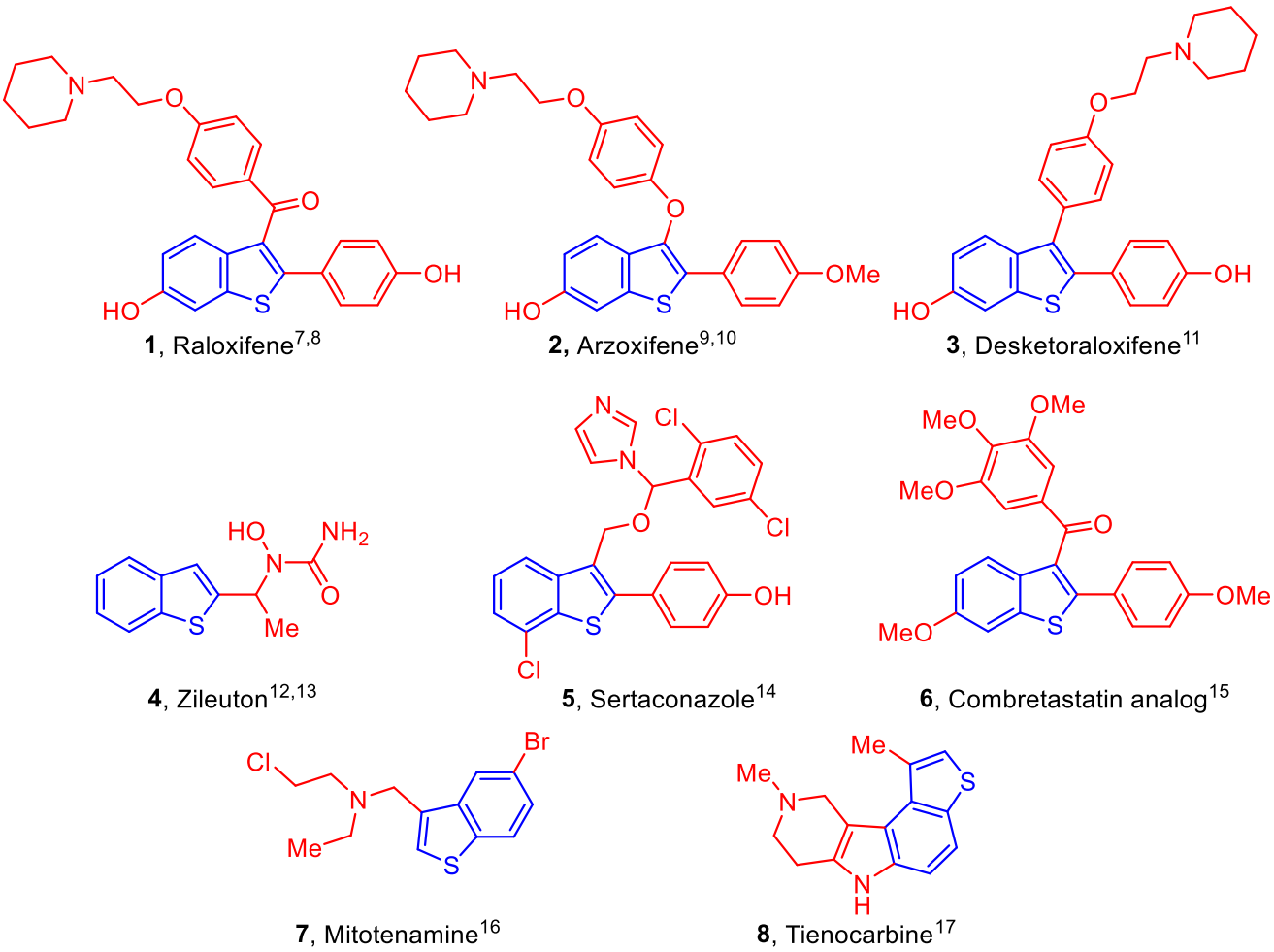


Figure 1. Selected benzo[*b*]thiophene-based drug molecules.

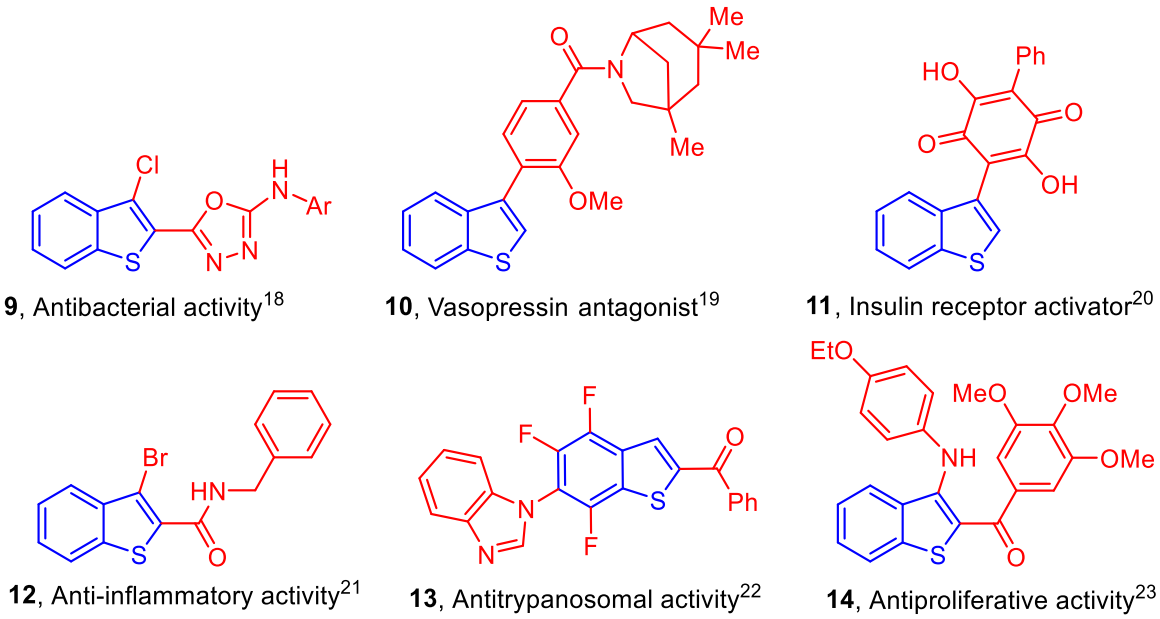


Figure 2. Selected benzo[*b*]thiophene analogues displaying various biological activities.

Other benzo[*b*]thiophenes such as **9**-**14**, display promising biological activities such as antibacterial,[18] vasopressin antagonist,[19] insulin receptor activator,[20] anti-inflammatory,[21] antitrypnasomal[22] and antiproliferative activities (Figure 2).[23]

Benzo[*b*]thiophene-fused polycyclic (hetero)aromatics are of great interest due to their excellent charge-transport properties, and their applications in the fields of organic conductors, OLEDs, field-effect transistors (OFETs), organic photovoltaics (OPVs) and as optoelectronic materials. In particular, acene-dithiophene systems, with two thiophene rings fused at the ends of a carbocyclic acene, such as benzodithiophenes (BDTs) **15,**[4,24] naphthodithiophenes (NDTs) **16**,[4,25,26] and other higher homologs, offer numerous advantages over other types of acenes, owing to the ease of functionalization at the α-position of thiophene ring (Figure 3). These dithiophene-fused acenes have been widely utilized as important π-cores, for the development of both high-performance, small molecule/oligomeric/polymeric semiconducting materials, and in co-polymers for solar cells. In addition, some of the conjugated benzo[*b*]thiophene cores such as **18-20** are found to be highly fluorescent (Figure 3)[4,27]

Because of the importance of bioactive benzo[*b*]thiophenes and its derivatives in medicinal chemistry, as well as their diverse applications in material science, considerable attention has been paid towards development of new and efficient synthetic methods for the construction of these privileged frameworks and their derivatives. In recent years, several new synthetic routes have been reported for the preparation of these heterocycles.

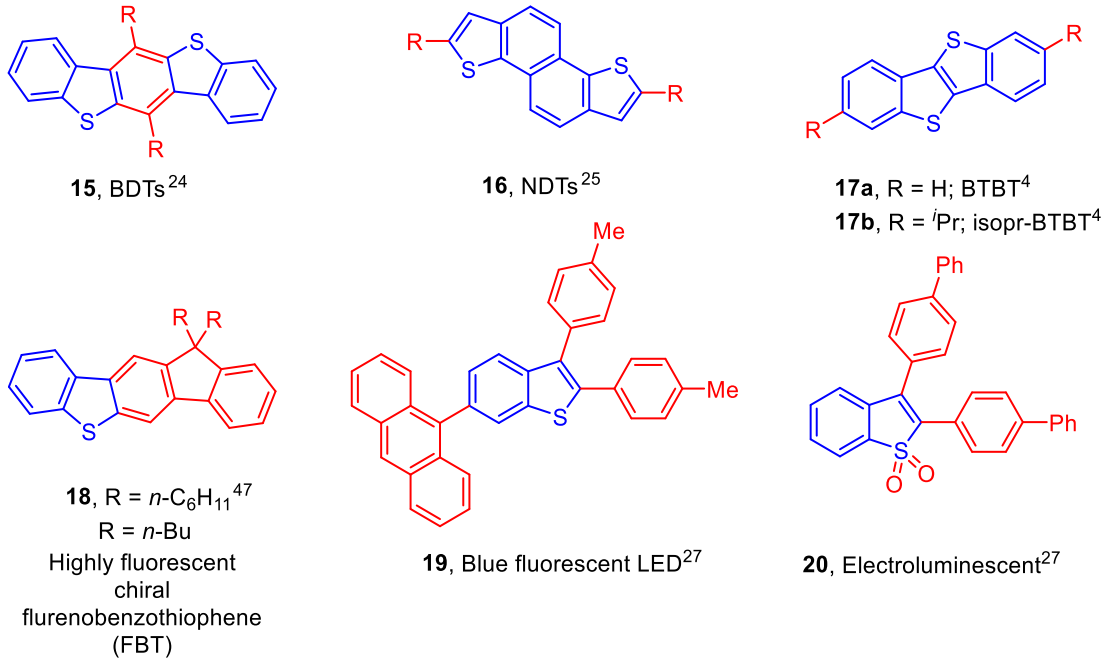


Figure 3. Selected examples of benzo[*b*]thiophene fused subunits in functional materials.

2. Synthesis of Substituted Benzo[*b*]thiophenes

Substituted-benzo[*b*]thiophenes are most commonly prepared through annulation reactions, wherein the sulfur heterocycle is constructed from a pre-functionalized benzene derivative. The most common methods include: (a) intramolecular electrophilic (or radical) 5-*endo*-*dig* cyclization of *o*-alkynylthioanisoles; (b)

intermolecular cyclization of thiol surrogates and *o*-haloalkynylbenzenes or their analogs, usually, promoted by transition-metal catalysts; (c) intermolecular cyclization of phenylthiols or phenylthiol surrogates with alkynes in the presence of transition-metal catalysts or radical initiators (Figure 4).

There are only a very few recent reviews dealing with the synthesis of benzo[*b*]thiophenes and their derivatives. The latest one, published in 2025 by Cai, highlights only benzo[*b*]thiophene syntheses *via* electrophilic and radical cyclization of *o*-alkynylthioanisoles[28] whereas another review by Duc (2020) describes various recent syntheses of benzo[*b*]thiophenes, [29] however, a detailed, systematic description of these reactions, along with their importance and mechanistic overview, have not been highlighted. The scope of two other reviews is rather limited, describing only the synthesis of benzo[*b*]thiophenes involving transition-metal-catalyzed cyclizations[30] and others deal mainly with either the biological activity of benzo[*b*]thiophene derivatives[31] or synthesis of benzo[*b*]thiophene-fused polycyclic compounds.[32]

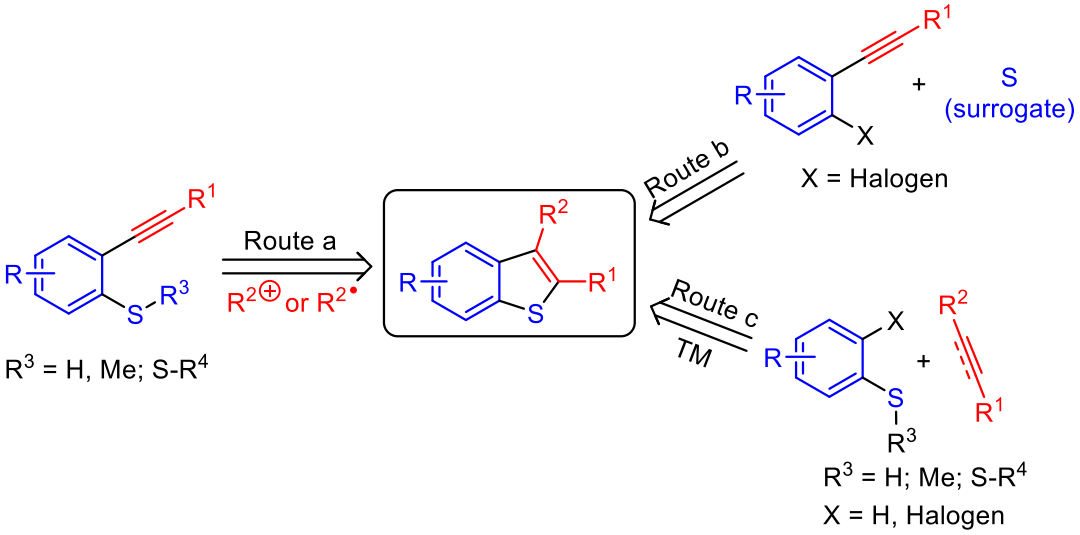


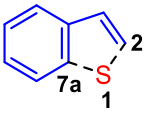
Figure 4. Common syntheses of substituted benzo[*b*]thiophenes.

The present review on benzo[*b*]thiophene synthesis focuses mainly on various synthetic approaches for the construction of the thiophene ring of benzo[*b*]thiophene from substituted benzene derivatives, involving formation of at least two bonds of the thiophene ring in a one-pot operation. A few syntheses in which the thiophene ring is constructed by simultaneous formation of three bonds in a cascade fashion, have also been included. The review is focused on various disconnection approaches for construction of the thiophene ring of benzo[*b*]thiophene derivatives. Some of the synthetic methods involving interesting mechanistic pathways have been discussed in detail. Some of the recent miscellaneous syntheses, which do not fall under any of these categories, have also been included. Since a detailed review on the synthesis of benzo[*b*]thiophenes *via* electrophilic or radical 5-*endo-dig* cyclization of *o*-alkynyl thiomethylethers have appeared only recently in 2025,[28] no discussion on this synthetic method has been included in the present review. Also, the alternative approaches for synthesis of benzo[*b*]thiophenes *via* benzoannulation of thiophene derivatives have not been described due to the length of review. Most of synthetic methods which appeared between 2010 to 2025 (with few exceptions) have been described, depending on their importance, mechanistic appeal of the reactions, and according to authors choice. The authors have attempted not to make it too descriptive, so as to maintain readers interest throughout the review, and young researchers may be stimulated to design some novel synthesis of benzo[*b*]thiophenes.

The review has been classified as follows:

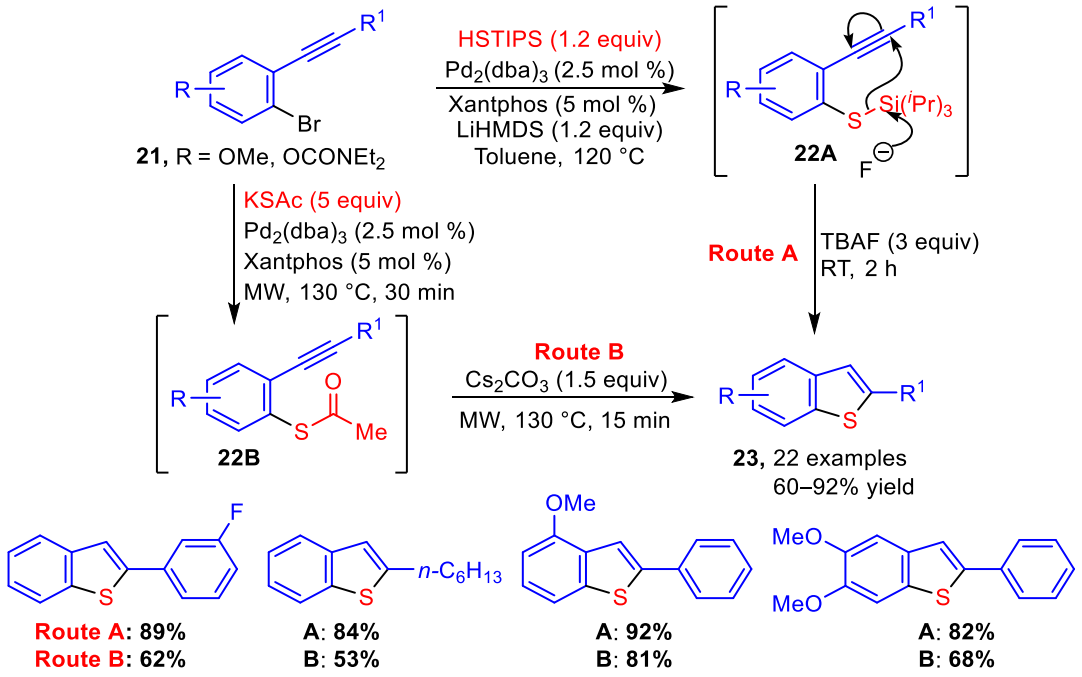
2.1. Benzo[*b*]thiophene synthesis involving S(1)-C(7a) and S(1)-C(2) bond formation
2.2. Benzo[*b*]thiophene synthesis involving S(1)-C(2) and C(3)-C(3a) bond formation
2.3. Benzo[*b*]thiophene synthesis involving S(1)-C(7a) and C(2)-C(3) bond formation
2.4. Benzo[*b*]thiophene synthesis involving S(1)-C(7a) and C(3)-C(3a) bond formation
2.5. Benzo[*b*]thiophene synthesis involving three bonds formation in one-pot operation
2.6. Miscellaneous synthesis of 2,3-substituted benzo[*b*]thiophenes

2.1. Synthesis of Benzo[*b*]thiophenes involving S(1)-C(7a) and S(1)-C(2) bonds formations



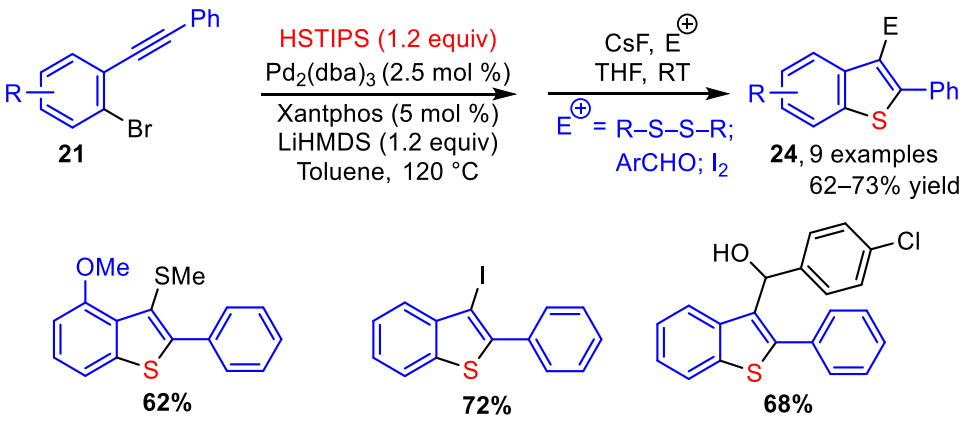
In this section, we have discussed efficient methodologies for 2- or 2,3-substituted benzo[*b*]thiophenes *via* tandem C–S coupling-heterocyclization of *o*-haloalkynyl/alkenylbenzenes or related precursors with various sulfur surrogates in the presence of palladium, copper or cobalt catalysts, or, in their absence, involving S(1)-C(7a) and S(1)-C(2) bond formations in one pot operation (Schemes 1-15).

Sashida and co-workers had previously reported the reaction of *o*-alkynylbromobenzenes with elemental sulfur upon lithium-halogen exchange to afford benzo[*b*]thiophenes in good yields.[33] Subsequently, Sanz and co-workers have developed a high-yield synthesis of 2-substituted-benzo[*b*]thiophenes **23** *via* tandem palladium catalyzed C–S bond formation-coupling/heteroannulation of *o*-bromo-2-(arylalkynyl)benzenes **21**, using triisopropylsilanethiol (HSTIPS) as sulfur surrogate, in the presence of LiHMDS as base at higher temperature (Scheme 1).[34]



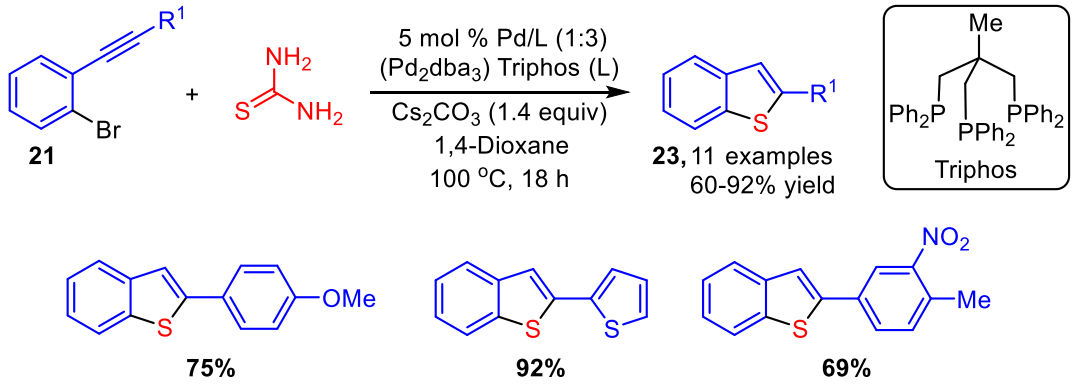
Scheme 1. Palladium-catalyzed **s**ynthesis of 2-aryl/alkylbenzo[*b*]thiophenes, using HSTIPS or KSAC as sulfur surrogates.

The intermediate silyl-substituted arenethiol **22A** was cleaved in situ with tetrabutylammonium fluoride (TBAF), yielding substituted-2-arylbenzo[*b*]thiophenes **23** in good yields (Route A, Scheme 1). Alternatively, in a second methodology, palladium catalyzed cross-coupling of **21** was carried out with potassium thioacetate, under microwave reaction conditions (Route B).[34] The product benzo[*b*]thiophenes **23** were obtained in excellent yields, in a one-pot protocol, by treatment of intermediate **22B** with cesium carbonate under microwave irradiation, thus, dramatically reducing the reaction time (Route B). In a further extension of the method, the same authors synthesized 2,3-disubstituted benzo[*b*]thiophenes **24** by adding an electrophile in a reaction sequence, using anhydrous cesium chloride as cleavage agent in the final step (Scheme 2). The electrophilic species employed were dialkyl/aryldisulfides, iodine and also aldehydes.[34]



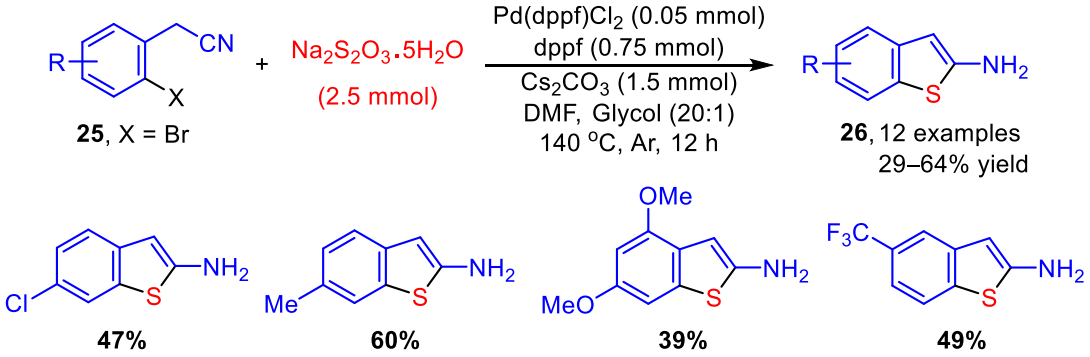
Scheme 2. Synthesis of 2,3 substituted benzo[*b*]thiophenes *via* in situ electrophilic substitution.

Paradies and co-workers have employed cheaper and easy-to-handle thiourea as a dihydrosulfide surrogate for domino-thiolation cyclization of *o*-bromo-2-(aryl)alkynes **21** in the presence of tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] catalyst and 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos) ligand at 100 °C, yielding 2-aryl substituted benzo[*b*]thiophenes **23** in high yields (Scheme 3).[35] Both electron-poor-and electron-rich substituents such as methoxy, nitrile, carbonyl and nitro groups were well tolerated on the 2-aryl group with good yields of benzo[*b*]thiophenes **23**.



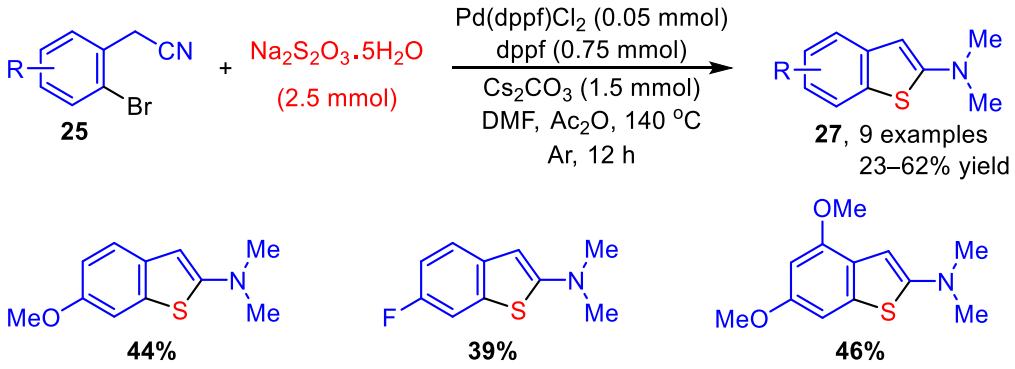
Scheme 3. Palladium-catalyzed synthesis of 2-substituted benzo[*b*]thiophenes employing thiourea as a thiolating agent.

Yang and co-workers have developed a one-step synthesis of 2-aminobenzo[*b*]thiophenes **26** *via* palladium catalyzed C–S bond formation on 2-bromoarylacetonitriles **25**, by using Na_2SO_3 as a cheaper and odorless sulfur surrogate, yielding **26** in moderate to good yields (Scheme 4).[36] A combination of Pd(dppf)Cl_2.dppf as a catalyst, and cesium carbonate, afforded best yields of **26** under optimized reaction conditions (Scheme 4).



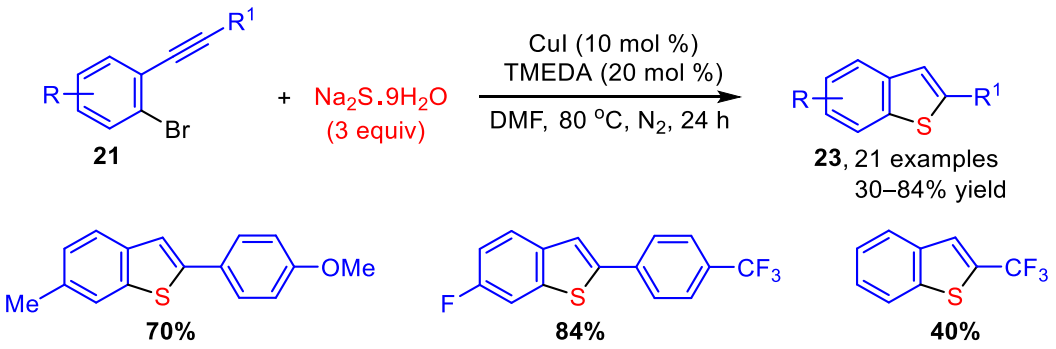
Scheme 4. Synthesis of 2-aminobenzo[*b*]thiophenes using Na_2SO_3 as sulfur surrogate.

Interestingly, attempted in situ *N*-acetylation of 2-aminobenzo[*b*]thiophenes **26** by treatment of **25** with acetic anhydride in the absence of glycol, under identical conditions, afforded 2-(dimethylamino)benzo[*b*]thiophenes **27** in moderate yields, instead of the expected 2-(*N*-acetyl)benzo[*b*]thiophenes (Scheme 5).[36]



Scheme 5. Synthesis of 2-(dimethylamino)benzo[*b*]thiophenes.

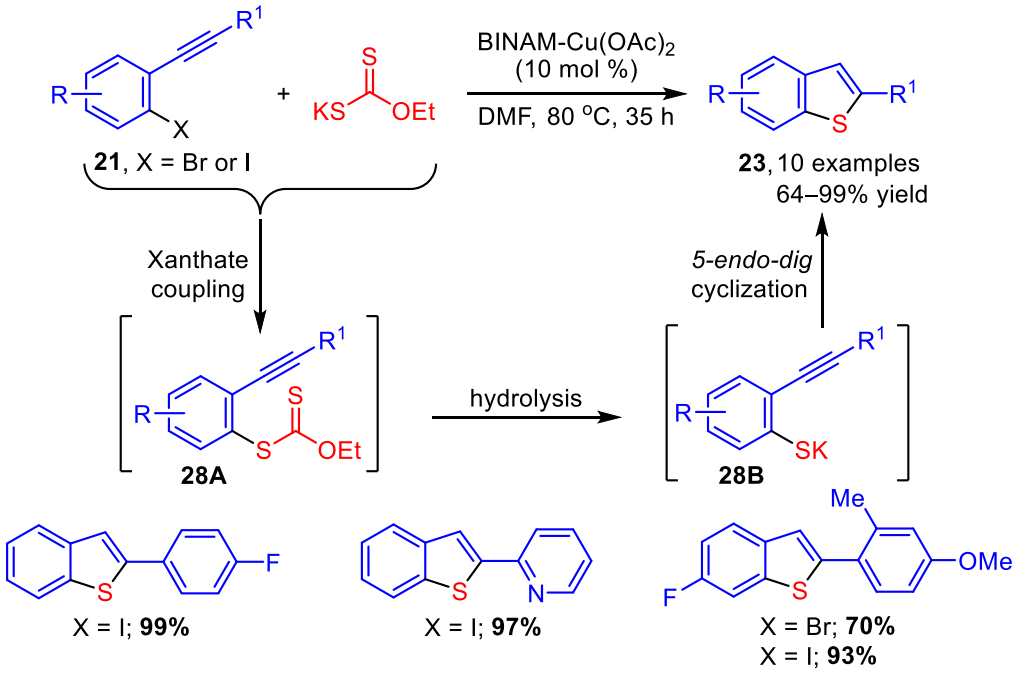
Zang and co-workers have reported a copper catalyzed thioannulation of 2-bromoalkynylbenzenes **21**, employing sodium sulfide as a thiolating agent in the presence of CuI/TMEDA in DMF at 80 °C, furnishing 2-arylbenzo[*b*]thiophenes **23** in moderate to good yields (Scheme 6).[37]



Scheme 6. Copper-catalyzed synthesis of 2-arylbenzo[*b*]thiophenes using sodium sulfide as thiolating agent.

It should be noted that, previously, Takimiya and co-workers had reported annulation of *o*-haloalkynylbenzenes using sodium sulfide, as a sulfur surrogate, for the synthesis of a few benzo[*b*]thiophenes, in the absence of any catalyst, however, requiring higher temperature (180 °C) (Scheme 11, pp 14).[38]

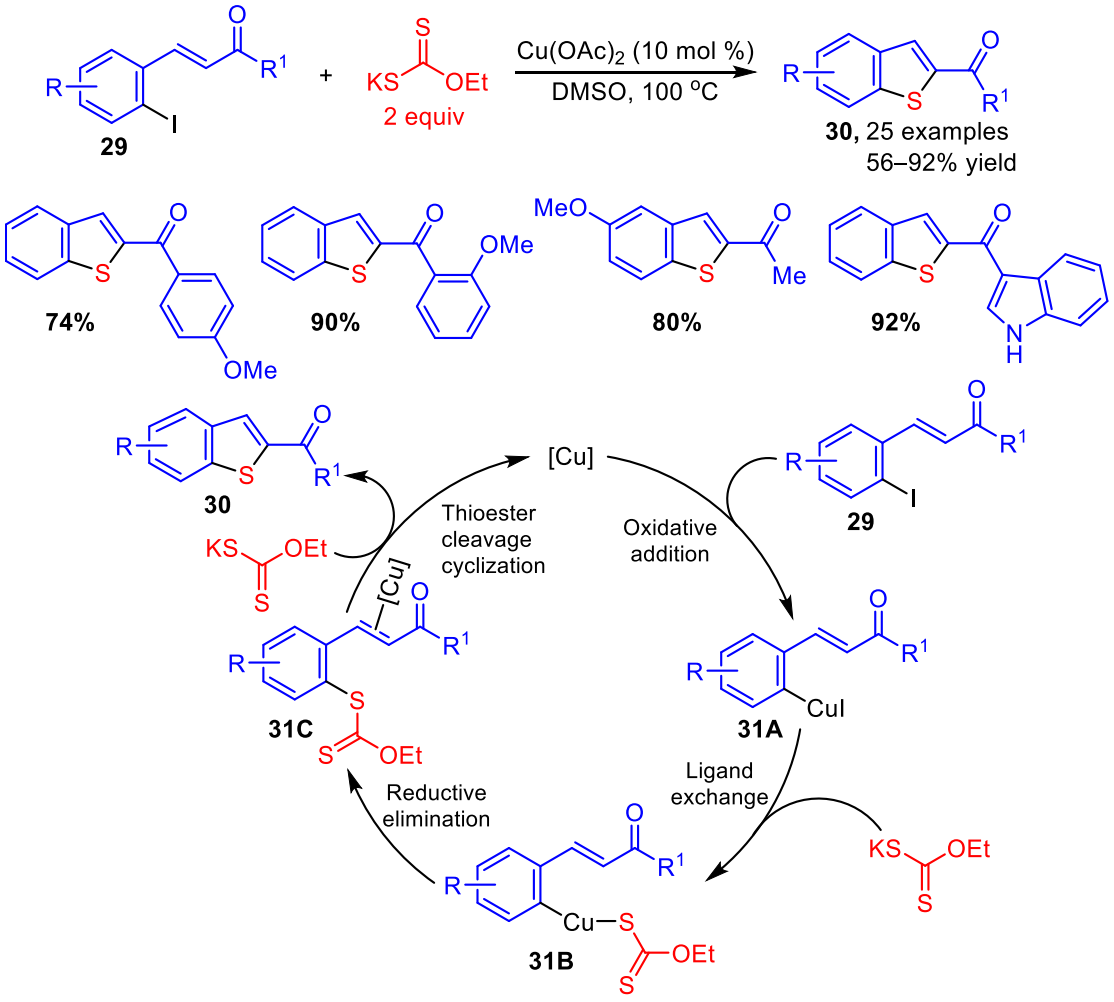
Sekar and co-workers have developed a domino synthesis of 2-(het)arylbenzo[*b*]thiophenes **23**, using xanthate as a thiolating agent, which reacts with *o*-iodoalkynylbenzenes, in the presence of copper catalyst and BINAM as a ligand, at 80 °C, to furnish products **23** in high yields.[39] The one-step reaction is shown to proceed *via* copper catalyzed Ullman C–S coupling (C–S bond formation) of xanthate with **21**, to give intermediate **28A**, which then undergoes in-situ hydrolysis to give the thiolate salt **28B**, followed by its intramolecular heterocyclization, yielding 2-(het)aryl benzo[*b*]thiophenes **23** (Scheme 7).[39]



Scheme 7. Copper-catalyzed synthesis of 2-(het)arylbenzo[*b*]thiophenes using xanthate as a thiol surrogate.

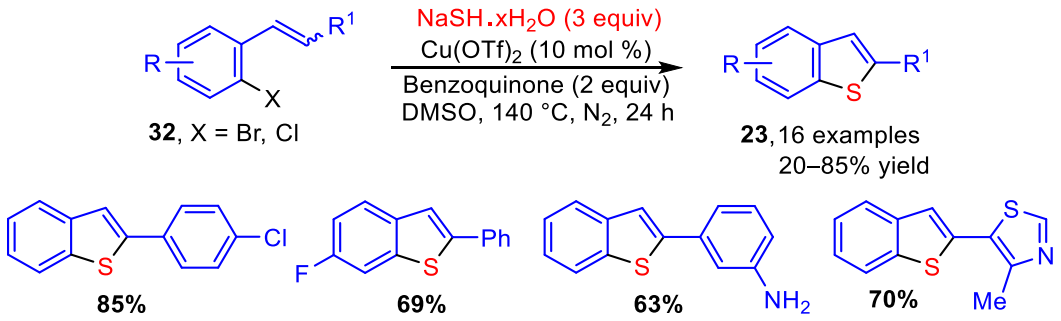
In a further extension of their work, Sekar and co-workers have reported a one-pot synthesis of 2-acylbenzo[*b*]thiophenes **30**, involving a copper catalyzed C–S bond formation-α-CH functionalization of 2-iodochalcones **29**, using xanthate as a thiol surrogate (Scheme 8).[40] The reaction was conducted in the

presence of cupric acetate as catalyst in DMSO, yielding 2-(acyl)benzo[*b*]thiophenes **30** in good yields. A broad range of benzo[*b*]thiophenes, bearing 2-aroyl, 2-acetyl and 2-het(aroyl) functionalities, could be synthesized in high yields using this procedure (Scheme 8). The probable mechanism involves oxidative addition of copper to **29**, and ligand exchange with xanthate, to give intermediate **31B** (*via* **31A**), which, on reductive elimination, affords intermediate xanthate **31C**, followed by hydrolysis and intramolecular heterocyclization of **31C**, in the presence of another molecule of xanthate, to yield 2-acylbenzo[*b*]thiophenes **30** in good yields (Scheme 8).[40]



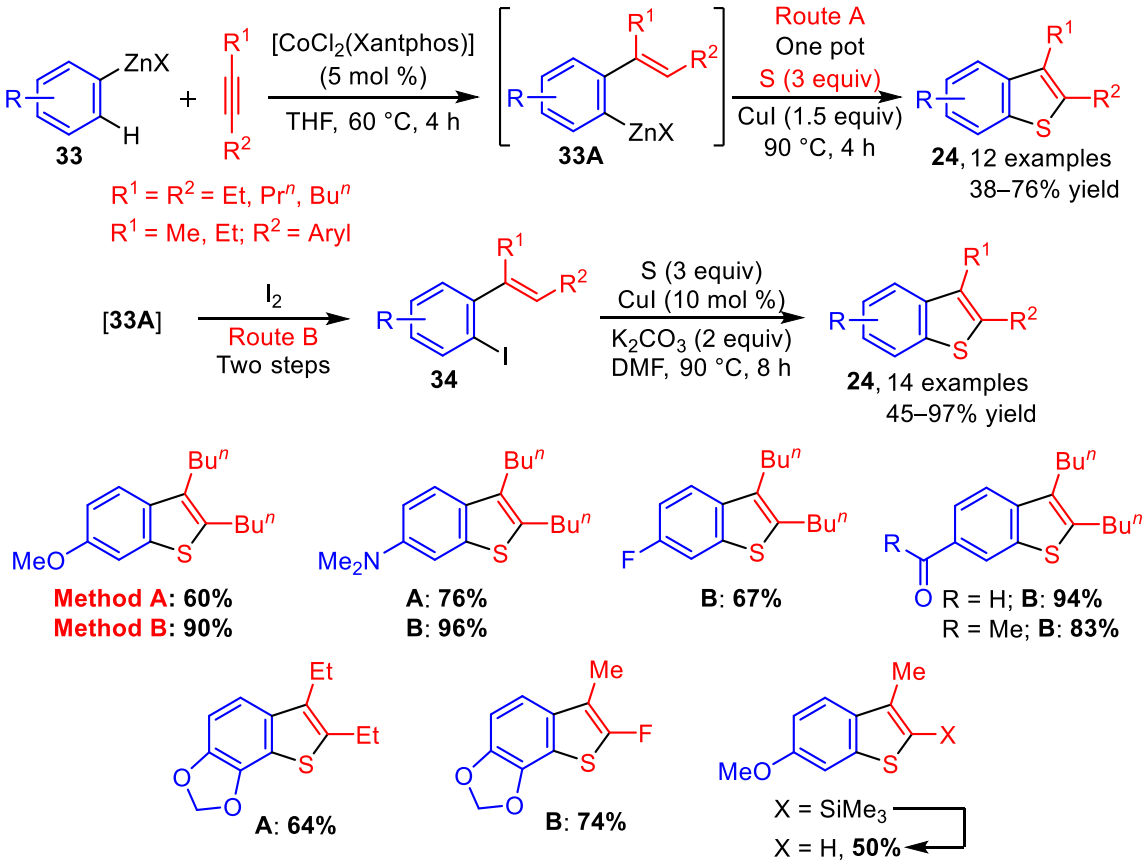
Scheme 8. Copper-catalyzed synthesis of 2-acylbenzo[*b*]thiophenes **30** using xanthate as thiol surrogate.

Chen and co-workers have successfully elaborated on a copper catalyzed thioannulation of commercially available *o*-bromostyrenes **32** with sodium hydrosulfide as thiol surrogate, in the presence of copper triflate as catalyst, and benzoquinone as dehydrogenating agent, in DMSO at 140 °C, to afford 2-(het)/arylbenzo[*b*]thiophenes **23** in moderate to good yields (Scheme 9).[41] The overall one-pot procedure involves oxidative dehydrogenation of initially formed dihydrobenzo[*b*]thiophene intermediates. A number of benzo[*b*]thiophenes with both electron-donating and withdrawing substituents on various positions of the aryl group could be synthesized through this method (Scheme 9).[41]



Scheme 9. Copper-catalyzed synthesis of 2-(het)arylbenzo[*b*]thiophenes *via* dehydrogenative thioannulation of *o*-bromostyrenes.

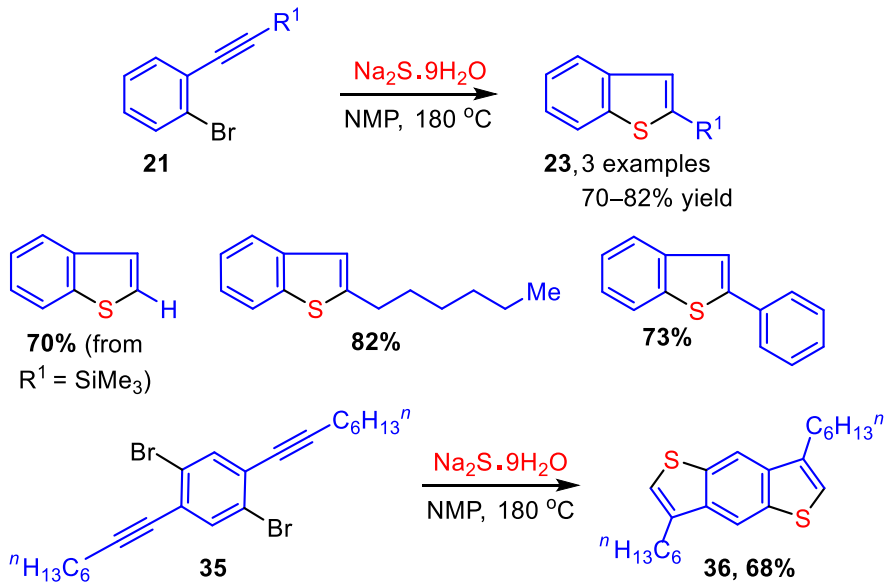
Most of the described syntheses of benzo[*b*]thiophenes above are usually applicable for the synthesis of 2-substituted benzo[*b*]thiophenes, despite their efficiency and reliability. Yoshikai and Wu have developed a versatile synthetic route for 2,3-substituted benzo[*b*]thiophenes **24** by reacting internal alkynes, sulfur, and arylzinc reagent **33** (prepared from arylmagnesium halide and $ZnCl_2$.TMEDA), in the presence of cobalt and copper catalysts, sequentially (Scheme 10).[42] The overall reaction involves intermediate *o*-alkenylzinc species **33A**, which were generated by the previously developed migratory aryl-zincation reaction of internal alkynes and arylzinc reagent **33** in the presence cobalt catalyst,[43] and their subsequent, either in situ or step-wise copper catalyzed thiolation and intramolecular heterocyclization, to afford 2,3-substituted-benzo[*b*]thiophenes **24** (Scheme 10). Thus, in a one-pot protocol, the key *ortho*-alkenylzinc reagent **33A** (prepared from arylzinc reagent **33** and internal alkynes, in the presence of cobalt catalyst) were in situ treated with CuI and elemental sulfur at 90 °C for 4 h, thus, affording 2,3-disubstituted benzo[*b*]thiophenes directly (Route A). Alternatively, the *ortho*-alkenylzinc reagent **33A** was first reacted with iodine, and the resulting *o*-alkenylaryl iodide **34** was subjected to copper catalyzed, thiolation-intramolecular-oxidative heterocyclization in the presence of CuI catalyst, S, and K_2CO_3 in DMF to afford benzo[*b*]thiophenes **24** in higher yields, in a two-step process (Route B) (Scheme 10).



Scheme 10. Sequential cobalt/copper-catalyzed one-pot synthesis of 2,3-substituted benzo[*b*]thiophenes.

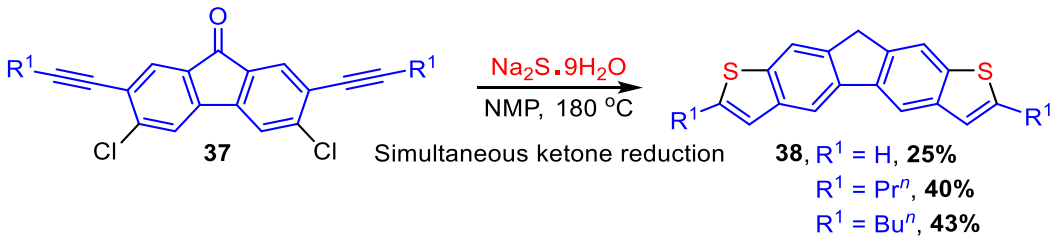
It should be noted that neither protocol required any particular external oxidant, suggesting that CuI, elemental sulfur or residual molecular oxygen served as an oxidant for the ring-closure-aromatization process. The study of various substituents showed that the one-pot protocol, route A, was applicable to electron-donating substituents, but fared poorly with electron-withdrawing substituents on the arylzinc reagent, while the step-wise protocol B furnished the desired benzo[*b*]thiophenes in high yields. These protocols are also applicable for the synthesis of benzo[*b*]thiophenes bearing different substituents on the C2 and C3 positions from a series of internal alkynes. It should be noted that the one-pot protocol A allows construction of three bonds, i.e., C(3)-C(3a), S(1)-C(7a) and S(1)-C(2) bond formation, in tandem fashion.[42] Thus, the present one-pot or two-step, three-component coupling route, allows the expedient synthesis of a wide variety of functionalized benzo[*b*]thiophenes, which are not accessible by the existing synthetic methods.

Takimiya and co-workers have first established a convenient transition-metal-free, one-pot procedure for the synthesis of benzo[*b*]thiophenes *via* thioannulation of *o*-haloethynylbenzenes by using sodium sulfide as a thiolating agent in refluxing *N*-methyl-2-pyrrolidones (NMP) at 180 °C (Scheme 11).[38] Using this procedure, they also synthesized a few benzo[*b*]dithiophenes (also benzo[*b*]trithiophenes), such as **36**, from acetylenic precursor **35** in overall good yields (57-82%) (Scheme 11).



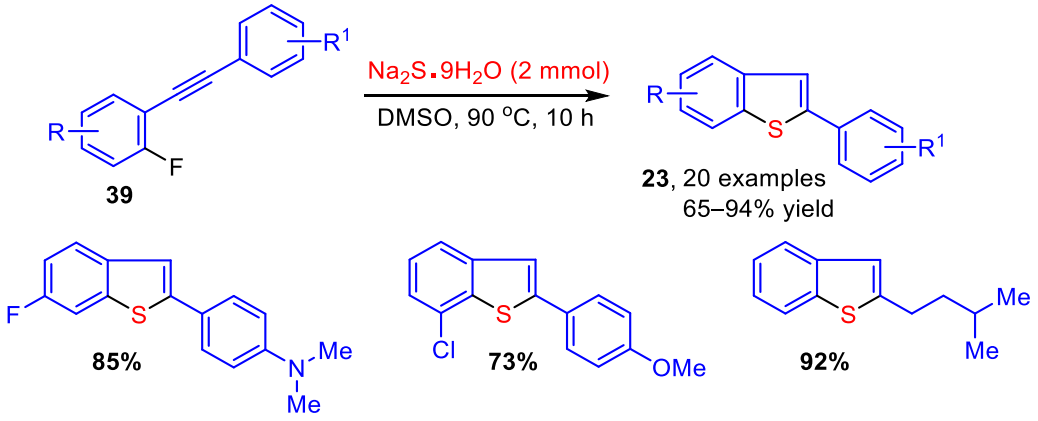
Scheme 11. Transition-metal-free synthesis of 2-substituted and condensed benzo[*b*]thiophenes with sodium sulfide as thiolating agent.

Using a similar procedure, Liu and co-workers developed an efficient synthesis of dithienofluorene **38** (Scheme 12). The key step involves tandem annulation–reduction of a 3,6-dichloro-2,7-di(alkynyl)fluorenone **37** using $Na_2S.9H_2O$, both as a thiolating agent and reductant, in refluxing NMP. The final dithiophene-fused fluorenes **38** are obtained in moderate yields (25–43%) (Scheme 12).[4,44]



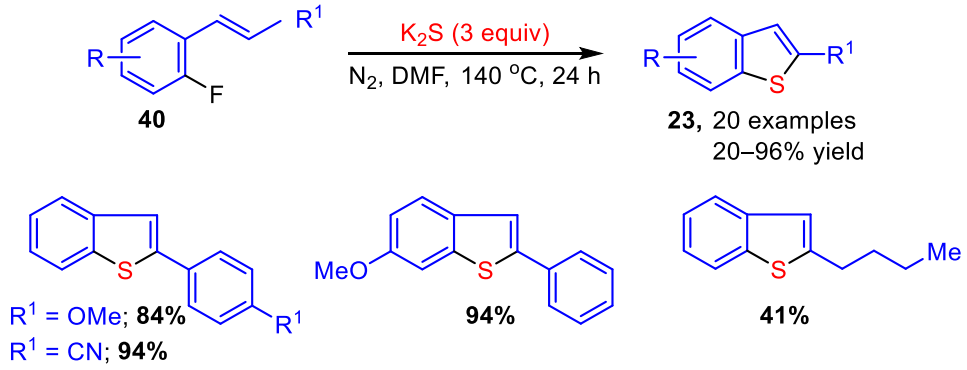
Scheme 12. Synthesis of dithienofluorenes involving a tandem thioannulation-reduction sequence of precursor **37**.

In a further extension of this method, Li and co-workers reported transition-metal-free synthesis of highly-functionalized benzo[*b*]thiophenes *via* thiolation-annulation of 2-fluorophenylacetylene derivatives **39** using $Na_2S.9H_2O$ as a thiolating agent, in DMSO, requiring lower temperature (90 °C). The method tolerates a broad range of functional groups, and a variety of benzo[*b*]thiophenes **23** could be synthesized using this procedure in moderate to good yields (Scheme 13).[45]



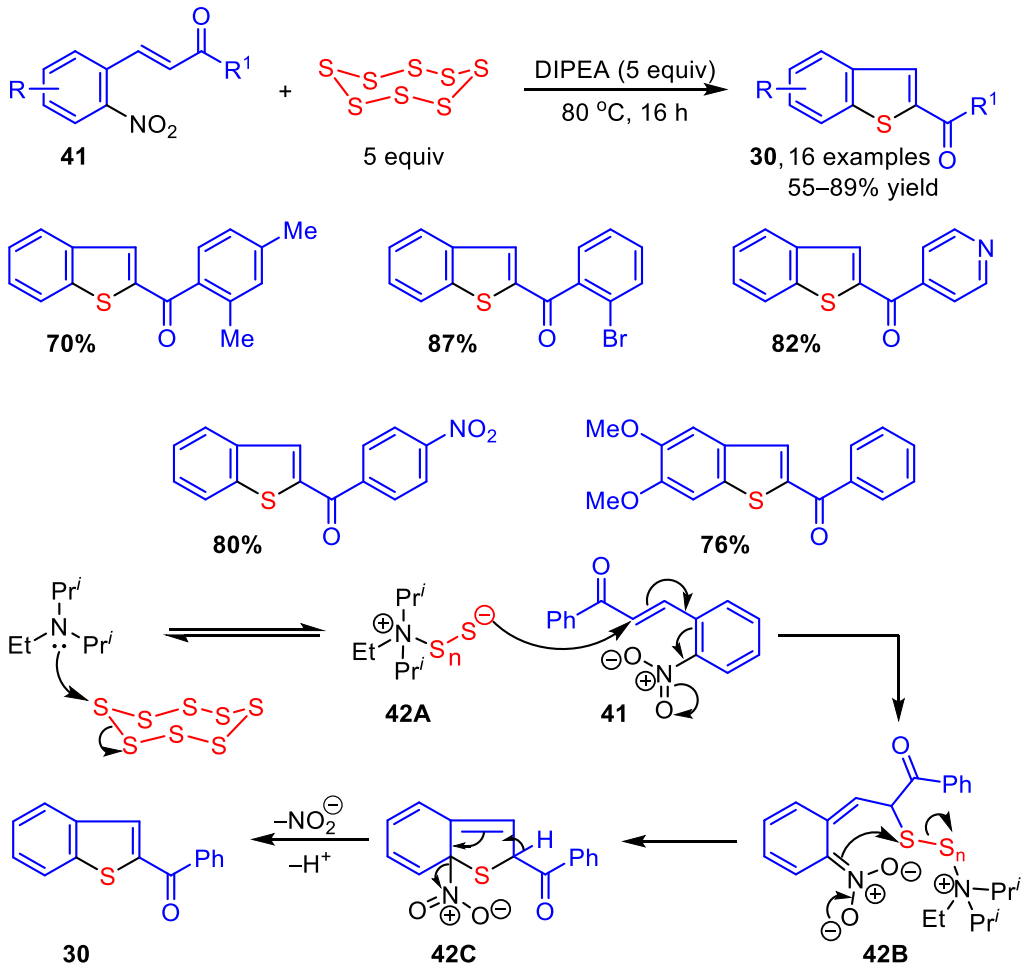
Scheme 13. Synthesis of 2-arylbenzo[*b*]thiophenes *via* thiolation-annulation of 2-fluorophenylacetylenes.

Liang and co-workers have reported a new, highly-efficient, transition-metal-free synthesis of 2-aryl-benzo[*b*]thiophenes from readily available *o*-halovinylbenzenes **40** and potassium sulfide in DMF at 140 °C under inert conditions (Scheme 14).[46-47]



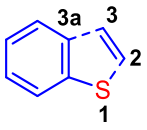
Scheme 14. Synthesis of 2-substituted-benzo[*b*]thiophenes *via* thioannulation of *o*-fluorovinylbenzenes.

Nguyen and co-workers have demonstrated a simple transition-metal-free synthesis of 2-benzoylbenzo[*b*]thiophenes **30** by simply heating 2-nitrochalcone **41** with elemental sulfur in diisopropylamine (DIPEA) (Scheme 15).[48] The reaction displays unusually diverse reactivities and selectivity of the nitro group, which acts as a leaving group instead of the *o*-halogen. A probable mechanism involves ring opening of cyclooctasulfur induced by DIPEA to give the zwitterionic polysulfide **42A** as the initial step (Scheme 15).[48] Nucleophilic attack of **42A** on the α-position of the highly activated double bond of nitrochalcone **41** affords intermediate **42B**, followed by its cyclization to intermediate **42C**, along with elimination of the polysulfide chain. Subsequently, an aromatic elimination of the nitro group in **42C** would yield benzo[*b*]thiophenes **30** (Scheme 15). Thus, the nitro group plays a unique role in the present reaction, both as activating and leaving group, without any transition metal. Similarly, the unusual role played by DIPEA, compared to other bases, is because of its highest steric hindrance around the basic nitrogen atom, which could attack only the most reachable electrophilic site, i.e., the cyclooctasulfur (instead of the nitrochalcone), because of the longer S–S distance and bivalent nature of the sulfur atom (Scheme 15).[48]



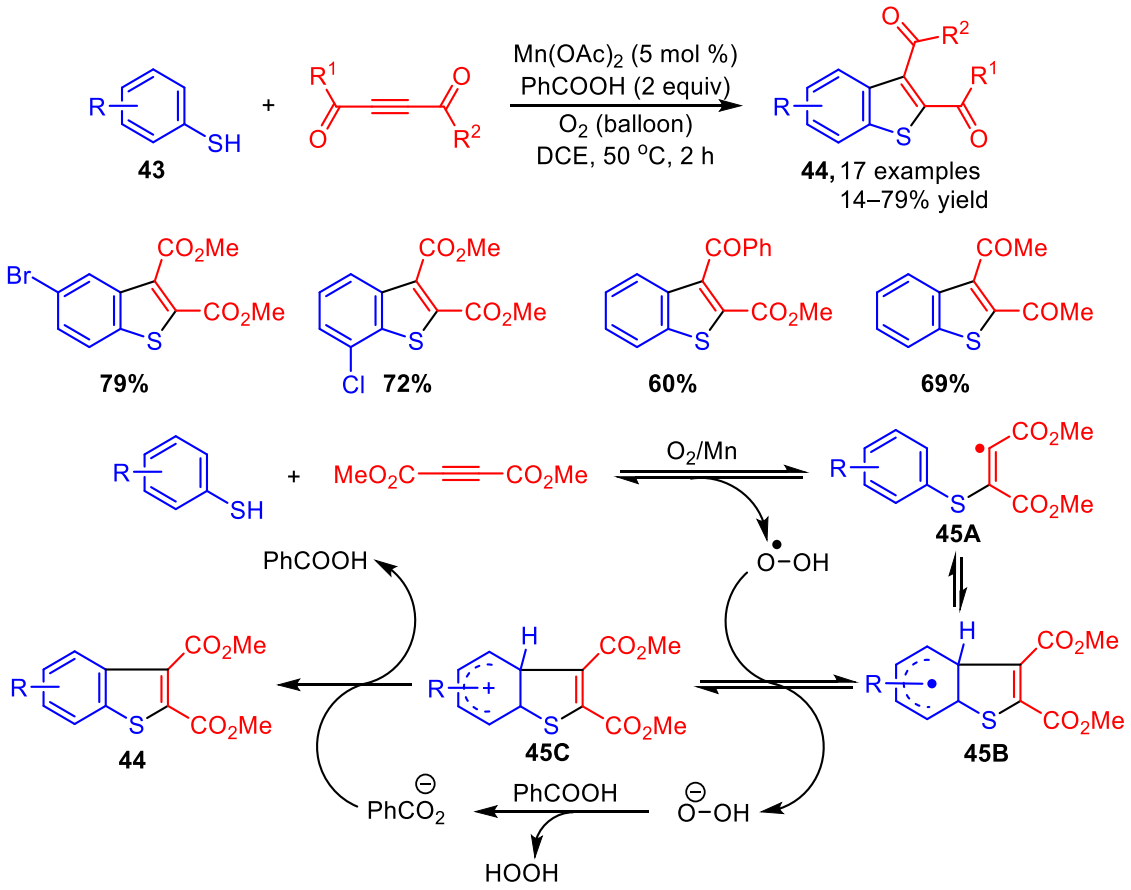
Scheme 15. Synthesis 2-acylbenzo[*b*]thiophenes *via* intermolecular heterocyclization of 2-nitrochalcones and elemental sulfur in diisopropylamine.

2.2. Synthesis of benzo[*b*]thiophenes *via* S(1)-C(2) and C(3)-C(3a) bond formation



The intermolecular cyclization of thiophenols and alkynes can be considered as one of the most simple and direct approaches for the construction of the benzo[*b*]thiophene ring. However, although catalytic and oxidative annulations of alkynes with phenols or anilines have been well investigated and reported in the literature for the synthesis of benzofurans and indoles, respectively, similar approaches were not known for benzo[*b*]thiophene synthesis, possibly because of poisoning of the catalyst by the thiol group, along with hydrothiolation of the triple bond with thiols to afford acyclic adducts. Undheim and co-workers had earlier reported a metal-free method for the formation of benzo[*b*]thiophene derivatives through cyclization of thiophenols and alkynes, requiring longer reaction times (5–22 days), with very low yields of benzo[*b*]thiophenes.[49] Subsequently, Li and co-workers have developed an efficient, high-yield, synthesis of benzo[*b*]thiophenes *via* direct intramolecular oxidative cyclization of thiophenols **43** and activated alkynes, mainly acetylenic diesters, catalyzed by manganese diacetate, in the presence of benzoic acid as an additive,

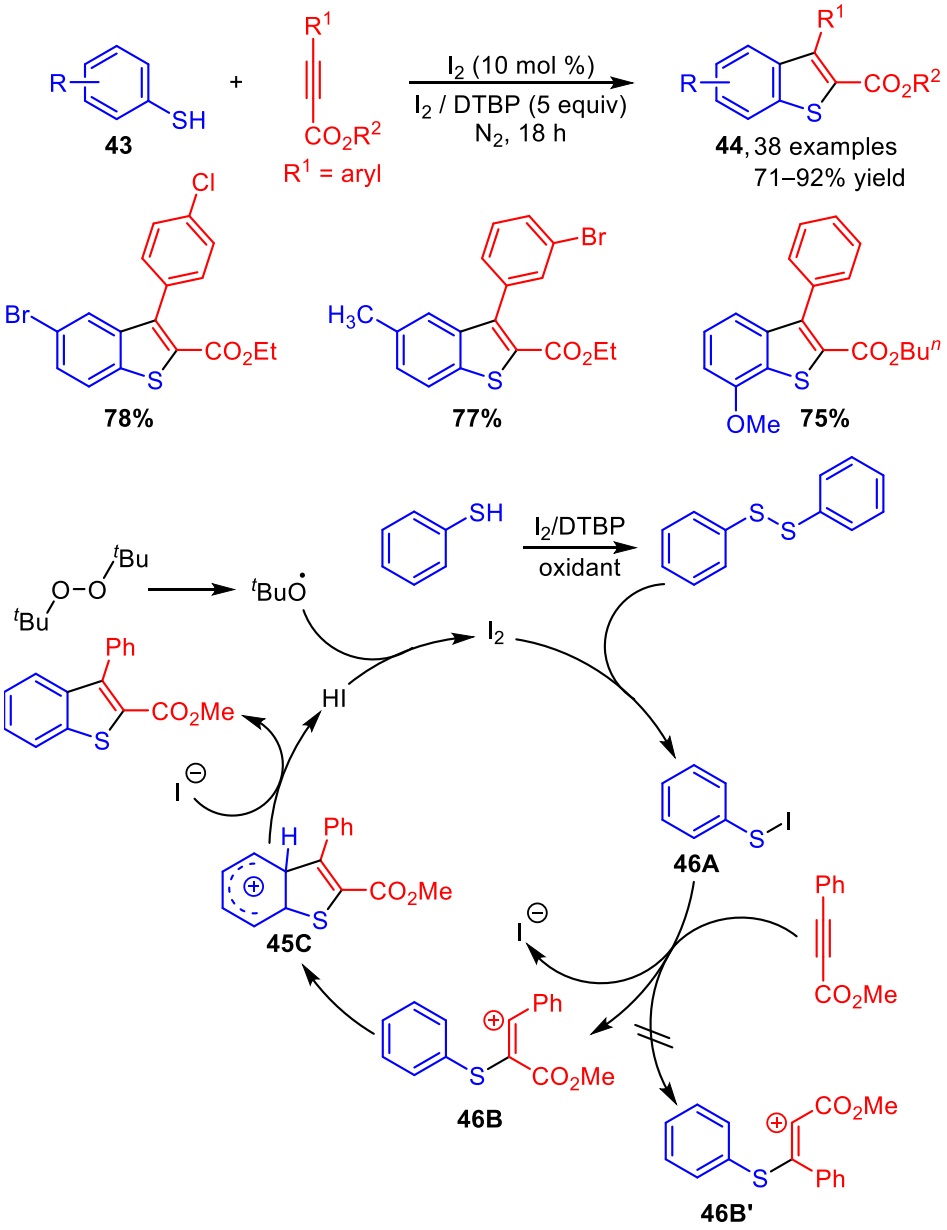
under oxygen atmosphere (Scheme 16).[50] The reaction could tolerate many substituents in *para* and *ortho* positions, although *m*-substituted thiophenols yielded a mixture of regioisomers. Similarly, lower yields of 2,3-*bis*-aroylbenzo[*b*]thiophenes **44** (R^1 = R^2 = Ph) were obtained when diaroylacetylenes were employed as a coupling partner, with the formation of side products (Scheme 16).



Scheme 16. Synthesis of 2,3-substituted-benzo[*b*]thiophenes *via* manganese-diacetate-catalyzed oxidative cyclization of thiophenols and activated alkynes.

The proposed mechanism involves the abstraction of hydrogen from the thiol to generate the benzenesulfanyl radical (along with release of a peroxyhydrogen radical), which then adds to an alkyne to generate the vinyl radical intermediate **45A**, followed by its intramolecular cyclization to benzo[*b*]thiophenes **44** *via* radical and cationic intermediates **45B**-**45C**, and involvement of a hydroperoxyl radical. The $Mn(OAc)_2$ catalyst appears to activate oxygen and stabilizes the peroxy radical (Scheme 16).

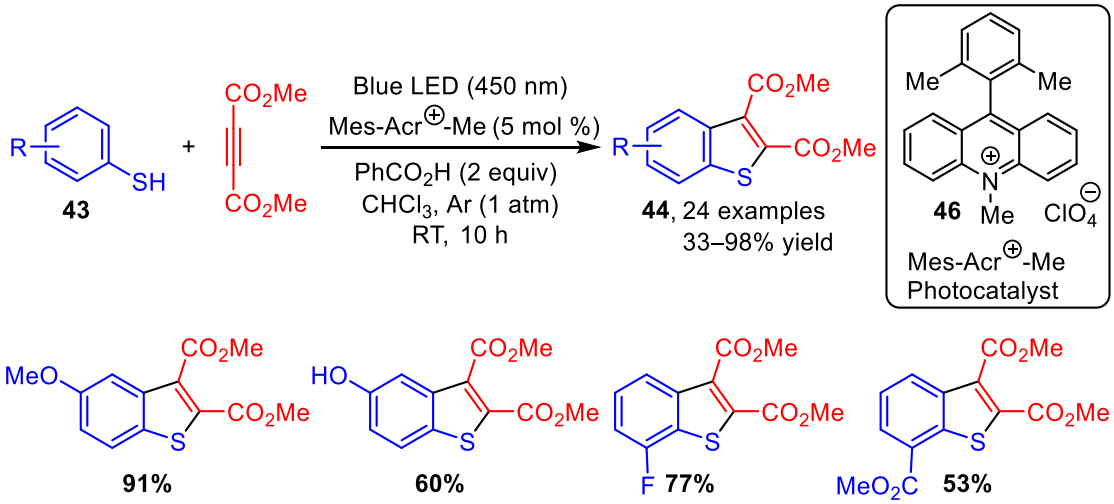
Wang and co-workers have demonstrated a metal- and solvent-free synthesis of benzo[*b*]thiophene derivatives, involving an iodine catalyzed tandem-oxidative cyclization of thiophenols with activated alkynes, such as 3-phenylpropiolate and dimethyl acetylene esters, yielding benzo[*b*]thiophenes **44** in moderate to good yields (Scheme 17).[51] The reaction displays excellent functional-group tolerance along with high regioselectivity with unsymmetrical alkynes, such as 3-phenylpropiolates, yielding only single regioisomers. A possible mechanism involves the oxidation of thiophenols to 1,2 diphenyldisulfane, which reacts with I_2 to give the electrophilic species PhSI **46A**, which is then attacked by 3-phenylpropiolate to give intermediate **46B**.



Scheme 17. Synthesis of 2,3-substituted benzo[*b*]thiophenes *via* iodine-catalyzed tandem-oxidative cyclization of thiophenols and activated alkynes.

Subsequent intramolecular arylation of **46B** affords intermediate **45C**, followed by loss of HI from the catalytic cycle. Finally, reaction of the *t*-butoxy radical with HI leads to the I_2 catalyst. The reason for the high regioselectivity with 3-phenylpropiolate is the preferred formation of the carbocation **46B** over **46B'** (Scheme 17).

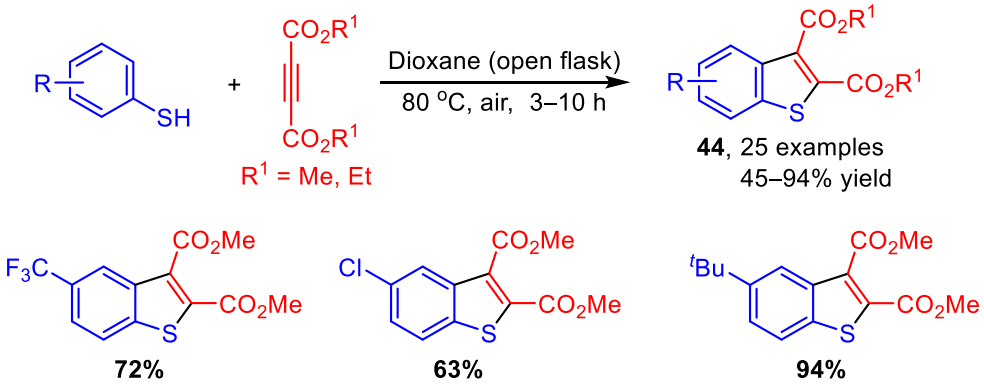
Xia and co-workers have developed an efficient, and general metal-free, visible light, photoredox-mediated synthesis of 2,3-substituted benzo[*b*]thiophene derivatives **44** *via* tandem addition/cyclization reactions of thiophenols with acetylenic diesters at room temperature, yielding **44** in good to excellent yields (Scheme 18).[52] Blue light irradiation of the organic dye, Mes-Acr-Me$^+$ **46**, was used as a photoredox catalyst, along with benzoic acid as an additive, by irradiating at 450 nm, in argon atmosphere. A series of functional groups could be tolerated under ambient conditions (Scheme 18).



Scheme 18. Synthesis of 2,3-substituted benzo[*b*]thiophenes *via* visible-light-photoredox-mediated cyclization of thiophenols and activated alkynes.

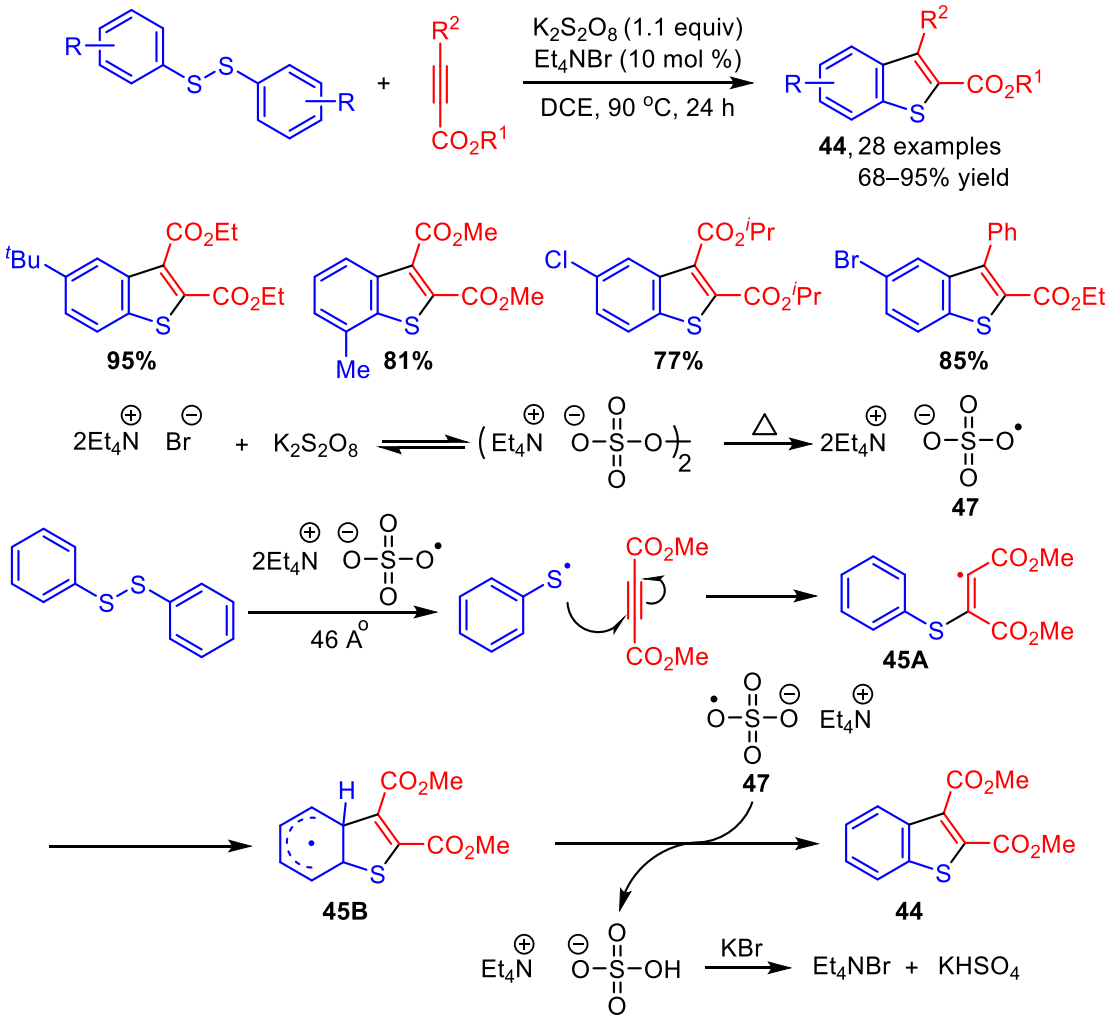
A catalyst-, oxidant- and additive-free, air-promoted intramolecular cyclization of thiophenols with activated alkynes in dioxane at 80 °C, leading to complex benzo[*b*]thiophenes, has been reported by Huo and co-workers (Scheme 19).[53] An auto-oxidation pathway (similar to Scheme 16) *via* oxidation of thiophenols with oxygen (*via* hydroperoxyl radical) to arylthiyl radical, which adds to an alkyne to give an intermediate radical, and its subsequent intramolecular annulation affording benzo[*b*]thiophenes, has been proposed (Scheme 19).[53] The method represents a powerful potential of auto-oxidation to construct complex bioactive heterocycles.

Diphenyl disulfides are frequently used as phenylthiol surrogates for benzo[*b*]thiophene synthesis. They are readily available, air-stable, odourless, and less toxic. The synthesis of benzo[*b*]thiophenes from diphenyl disulfides and alkynes was previously reported under drastic conditions (500–590 °C).[54] Later, Montevecchi and co-workers developed the preparation of benzo[*b*]thiophenes through the radical cyclization of disulfides and alkynes in the presence of radical initiators.[55] However, disulfides need to be prepared from aryl thiols, and two equivalents of thiophenols are generated from disulfide, and only one equivalent of thiophenol is usually utilized for the formation of benzo[*b*]thiophene framework.



Scheme 19. Catalyst- and oxidant-free, air-promoted synthesis of 2,3-disubstituted benzo[*b*]thiophenes *via* intramolecular cyclization of thiophenols and activated alkynes.

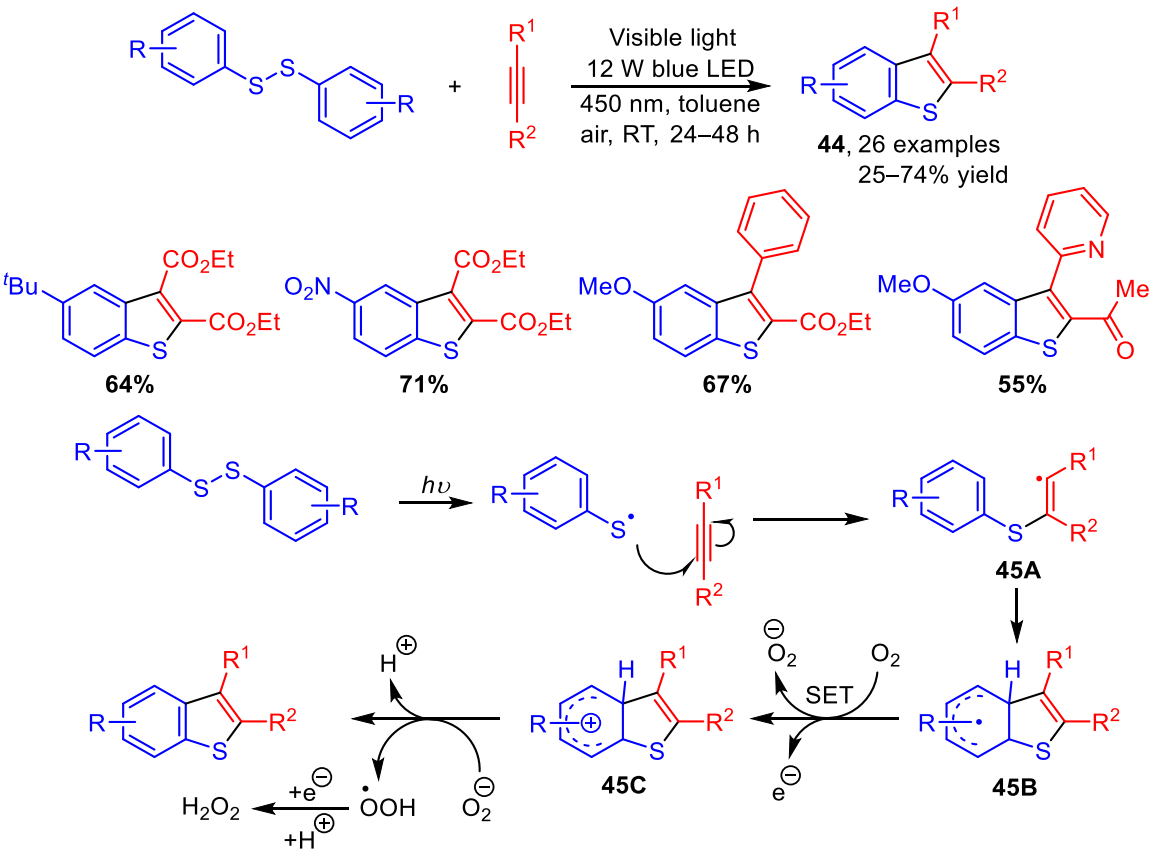
Wang and co-workers have previously developed a metal-free approach for benzo[*b*]thiophenes *via* tetraethylammonium bromide-catalyzed radical cyclization of disulfides and alkynes in the presence of potassium peroxysulphate (Scheme 20).[56] The yields of benzo[*b*]thiophenes are high and the reaction has high functional group tolerance. A possible mechanism involving reaction of Et_4NBr (TEAB) with peroxydisulfate to give tetraethylammonium sulfate radical anion **47**, which reacts with disulfide to form an arylthiyl radical, which adds to alkyne affording the alkenyl radical **45A** has been suggested (Scheme 20). The alkenyl radical **45A** undergoes intramolecular radical cyclization to give intermediate **45B** (cf Scheme 16). Finally, hydrogen abstraction of the radical intermediate **45B** by the tetraethylammonium sulfate radical anion **47** leads to benzo[*b*]thiophene derivatives **44** (Scheme 20).[56]



Scheme 20. Synthesis of 2,3-substituted-benzo[*b*]thiophenes *via* Et_4NBr-catalyzed oxidative cyclization of aryl disulfides and alkynes.

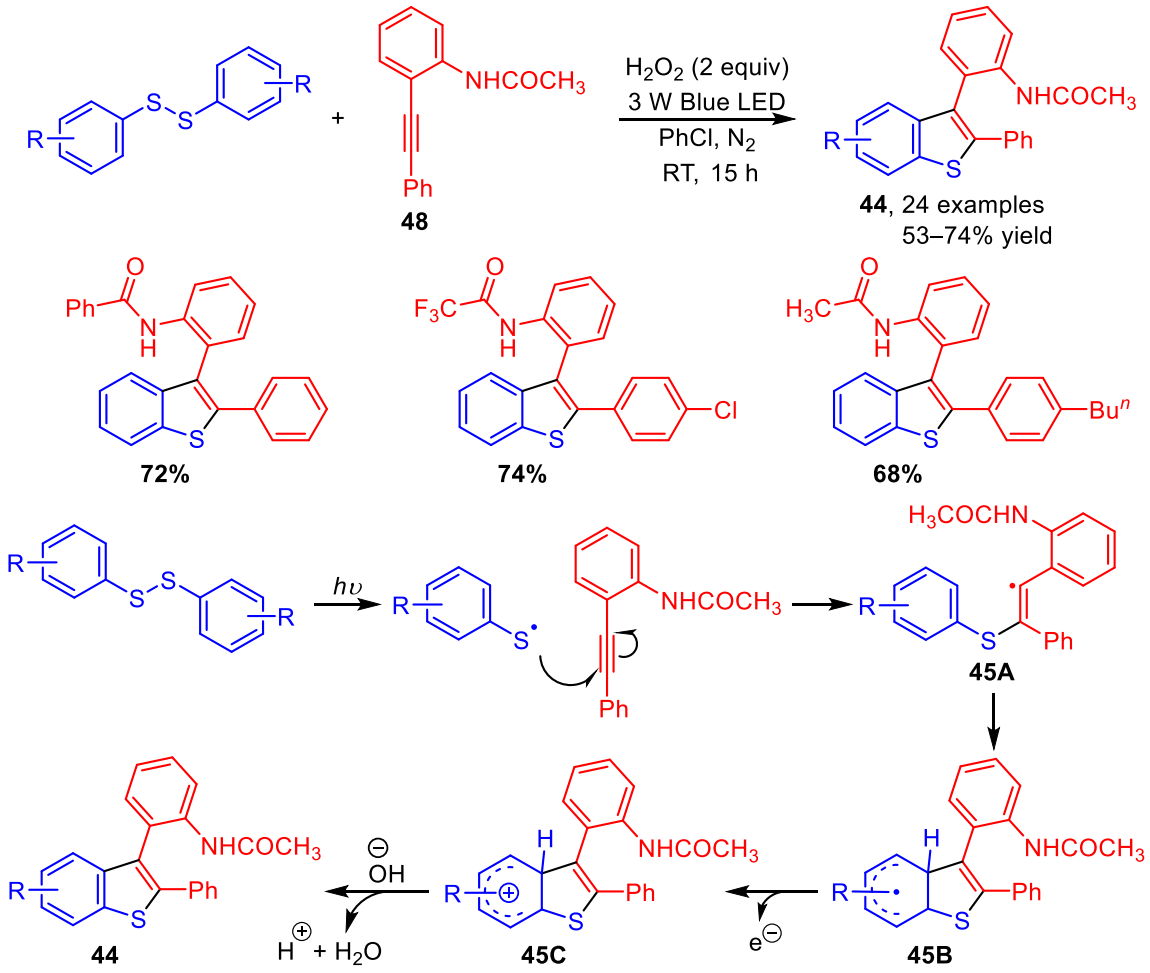
Yan and co-workers have reported a high yield, visible-light-promoted synthesis of benzo[*b*]thiophenes from disulfides and alkynes (Scheme 21).[57] The reaction was carried out in the absence of transition-metal catalysts; extra additives and oxygen was used as the only oxidant.[57] The reaction shows broad substrate scope and benzo[*b*]thiophenes bearing esters, ketones, aldehydes and aryl substituents were obtained in good yields. A reaction mechanism involving generation of a phenylthiyl radical *via* homolytic cleavage of disulfide, its addition to alkynes, and subsequent intramolecular cyclization of **45A** to give radical intermediate **45B** has

been suggested. The radical intermediate **45B** undergoes single-electron oxidation by oxygen to give the carbocationic intermediate **45C** and superoxide radical, which abstracts a proton from the carbocation to give benzo[*b*]thiophenes **44** (cf Scheme 16). The concurrently generated hydroperoxyl radical obtains an electron and a proton from **45C** to produce hydrogen peroxide (Scheme 21).



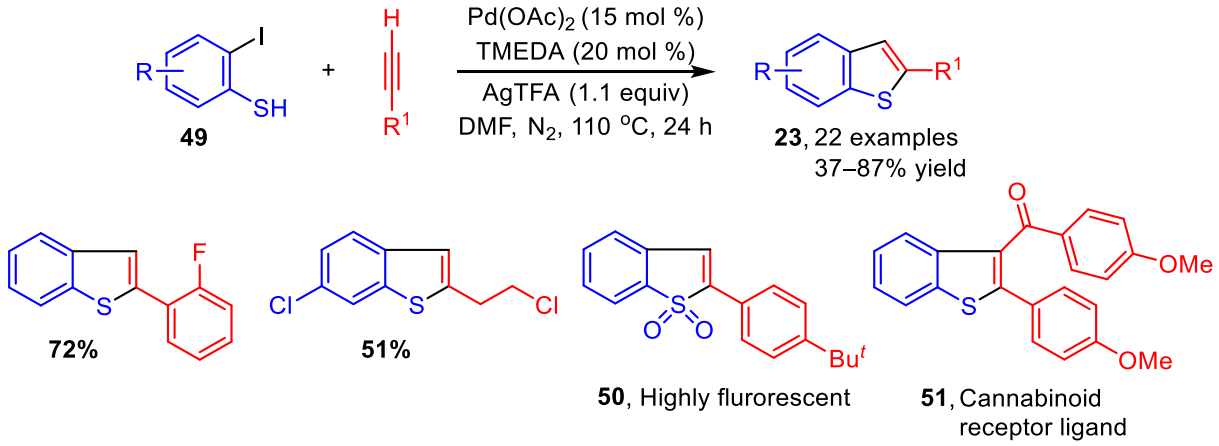
Scheme 21. Visible-light-promoted synthesis of 2,3-substituted benzo[*b*]thiophenes from disulfides and alkynes.

Wang and co-workers have reported an efficient route to benzo[*b*]thiophenes through visible light induced cyclization of disulfide and 2-alkynylanilines **48** (with 3W blue LED irradiation at room temperature) and H_2O_2 as an oxidant, under photocatalyst-free conditions (Scheme 22).[58] The important feature of this method is that, unlike other syntheses of benzo[*b*]thiophenes from either disulfides or thiophenols, requiring activated acetylenes bearing either carboethoxy or carbonyl groups, the present method is feasible with diarylalkynes bearing a sensitive acetylamino group. A plausible mechanism involving generation of arylthiyl radical from disulfide under LED irradiation, which reacts with dialrylalkynes, to afford vinyl radical **45A**, and its intramolecular cyclization to form radical intermediate **45B**, has been suggested. The radical intermediate **45B** transfers a single electron (SET) to a hydroxy radical (formed from hydrogen peroxide under irradiation) to give carbocationic intermediate **45C**, which loses a proton to give benzo[*b*]thiophenes (Scheme 22) (cf. Scheme 16).[58]



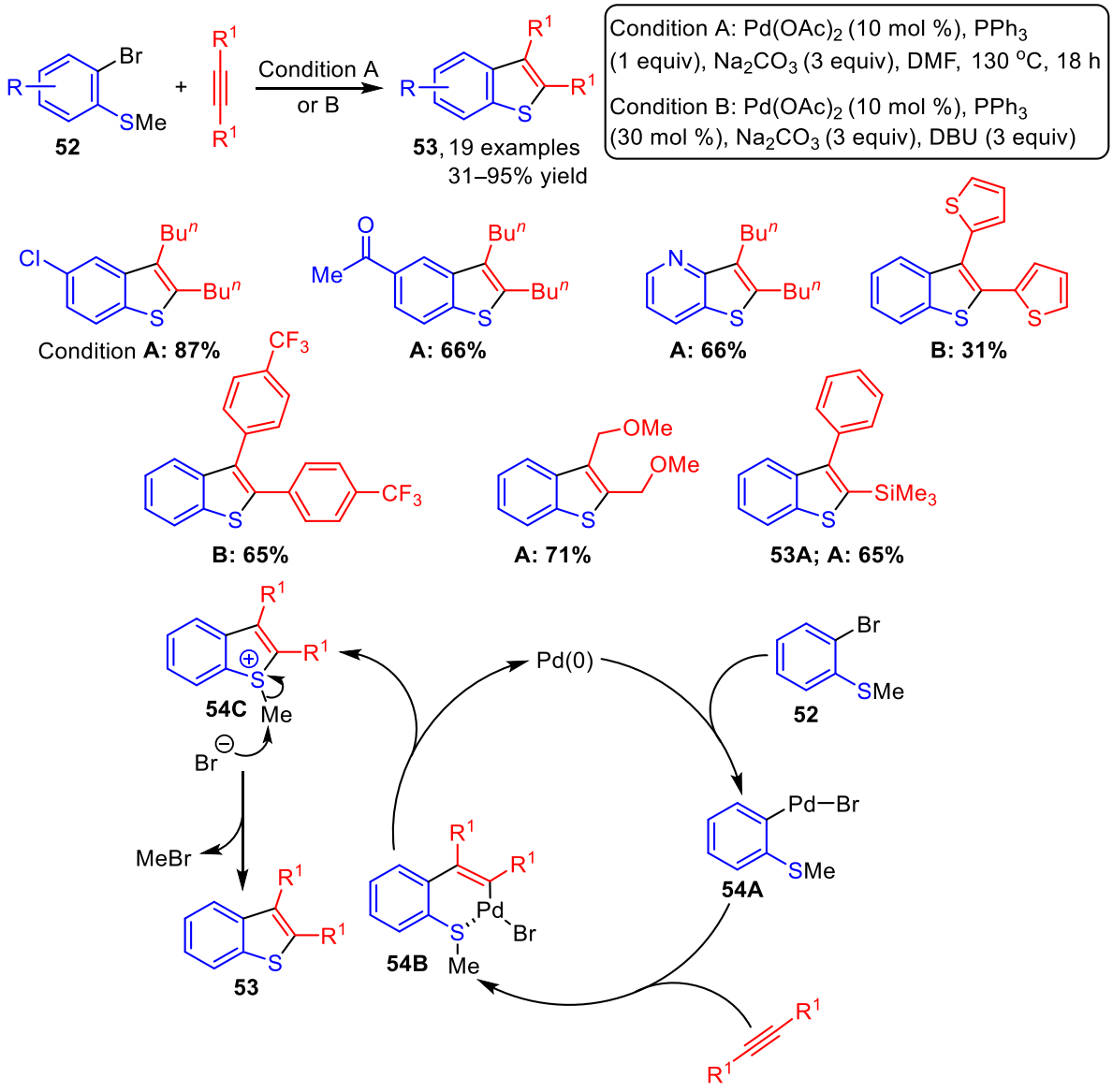
Scheme 22. Visible-light-promoted synthesis of 2,3-diarylbenzo[*b*]thiophenes *via* oxidative cyclization of disulfides and 2-alkynylanilines.

Zhou and co-workers have developed a new synthesis of 2-aryl/alkyl benzo[*b*]thiophenes *via* Pd(II)-catalyzed Sonogashira-type cross-coupling reaction between 2-iodothiophenol **49** and phenylacetylenes, yielding 2-arylbenzo[*b*]thiophenes **23** in moderate to good yields (Scheme 23).[59] The application of this method was further demonstrated by the synthesis of 2-(4-(*tert*-butyl)phenyl)benzo[*b*]thiophene 1,1-dioxide **50**, exhibiting a fluorescence quantum yield of up to 1 and (4-methoxyphenyl)(2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)methanone **51**, reported as a cannabinoid receptor ligand (Scheme 23).[59]



Scheme 23. Synthesis of 2-substituted benzo[*b*]thiophenes *via* palladium-catalyzed cross-coupling of 2-iodothiophenols and aryl/alkyl acetylenes.

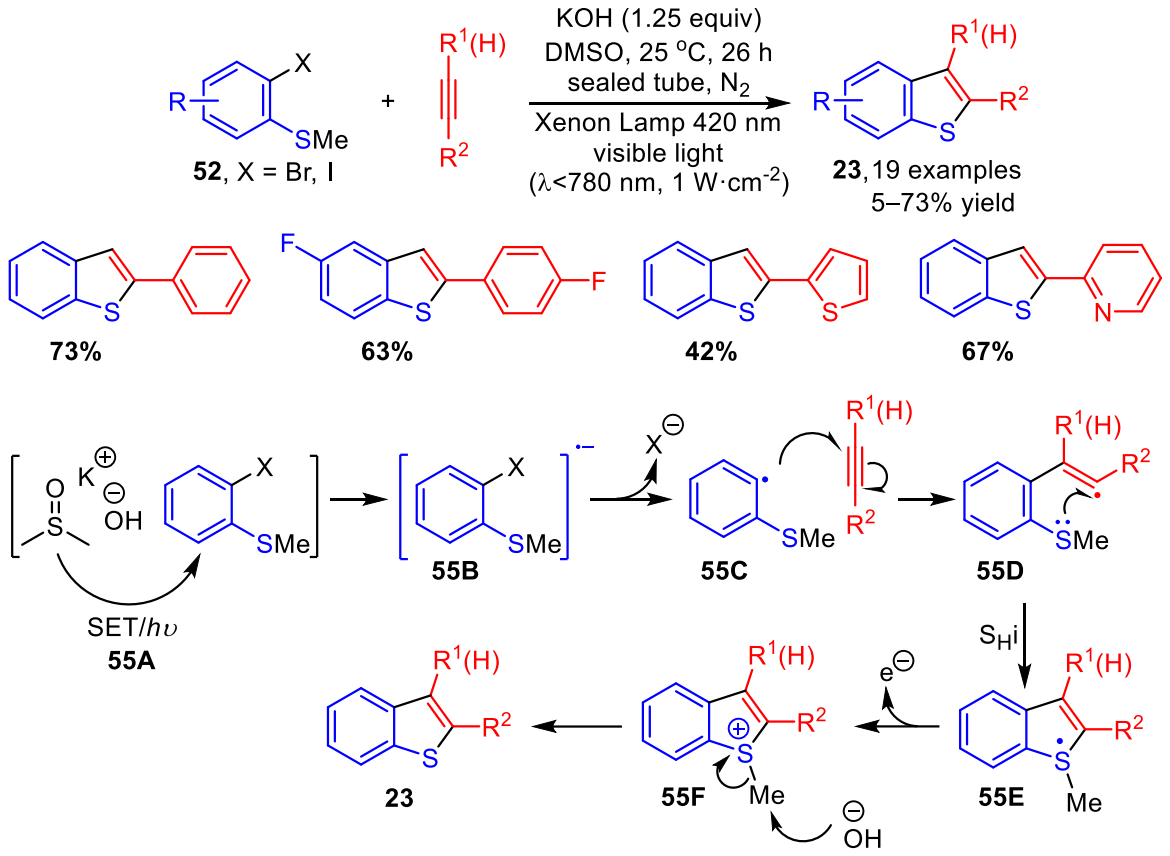
Most of the methods described (Schemes 16-22) involving sulfur-centered radical cyclization, were not applicable for the synthesis of 2,3-alkyl-substituted-benzo[*b*]thiophenes. Chatani's group was first to report a convergent synthesis of 2,3-dialkyl/aryl benzo[*b*]thiophenes **53**[60] (based on Larock's variant of indole synthesis, involving palladium catalyzed annulation of *o*-haloanilines with internal alkynes) (Scheme 24).[60] The present method involves palladium catalyzed annulation of *o*-haloarylsulfides **52** with internal alkynes, using two different sets of conditions (Scheme 24).[60] The method shows broad functional-group diversity, including chloride, cyano, and ketones, which were found to be compatible on the aromatic ring. In addition, the newly synthesized 2-silyl benzo[*b*]thiophenes **53A** could be further used for the synthesis of 2,3-unsuymmetrically-substituted benzo[*b*]thiophenes. A probable mechanism involving the oxidative insertion of Pd(0) species in the C–Br bond of **52** to give intermediate **54A**, which then adds an alkyne, affording a six-membered palladacycle intermediate **54B**, followed by its reductive elimination to give sulfonium salt **54C**, has been suggested. The sulfonium salt **54C** subsequently undergoes demethylation by some nucleophilic species present, to afford benzo[*b*]thiophenes **53** in good yields (Scheme 24).[60]



Scheme 24. Synthesis of 2,3-bisalkyl/aryl-benzo[*b*]thiophenes *via* palladium-catalyzed cycloannulation of *o*-haloarylsulfides and internal alkynes.

Yuan and co-workers have reported a transition-metal-free, KOH/DMSO super-base-promoted synthesis of 2-substituted-benzo[*b*]thiophenes, under visible light irradiation (Scheme 25).[61] The overall transformation involves photoinduced intermolecular annulation of 2-halothioanisoles with terminal alkynes at ambient temperature, yielding a wide range of 2-arylbenzo[*b*]thiophenes **23**, regioselectively, in moderate to good yields (Scheme 25). An aryl radical-chain pathway induced by a visible light driven SET process was shown to be involved in the cyclization of 2-halothioanisole and alkynes (Scheme 25).[61] The initially formed orange-red complex **55A** at the solid-liquid interface, resulting from interaction of KOH/DMSO superbase and 2-halothioanisole, was shown to be visible-light responsive. Thus, under visible light irradiation, KOH/DMSO superbase transfer a single electron to 2-halothioanisole **52** (SET process) to produce the corresponding aryl radical anion **55B**, which dissociates into aryl radical **55C** and halide anion (Scheme 25). The addition reaction of aryl radical **55C** with alkyne generates vinyl radical **55D**, which on intramolecular homolytic substitution gives radical intermediate **55E**. The radical intermediate **55E**, transfers an electron back to KOH/DMSO, thus

electron transfer cycle is accomplished, while S-methylsulfonium cation **55F** undergoes demethylation, in presence of some nucleophilic species to afford benzo[*b*]thiophene derivatives (Scheme 25).[61]



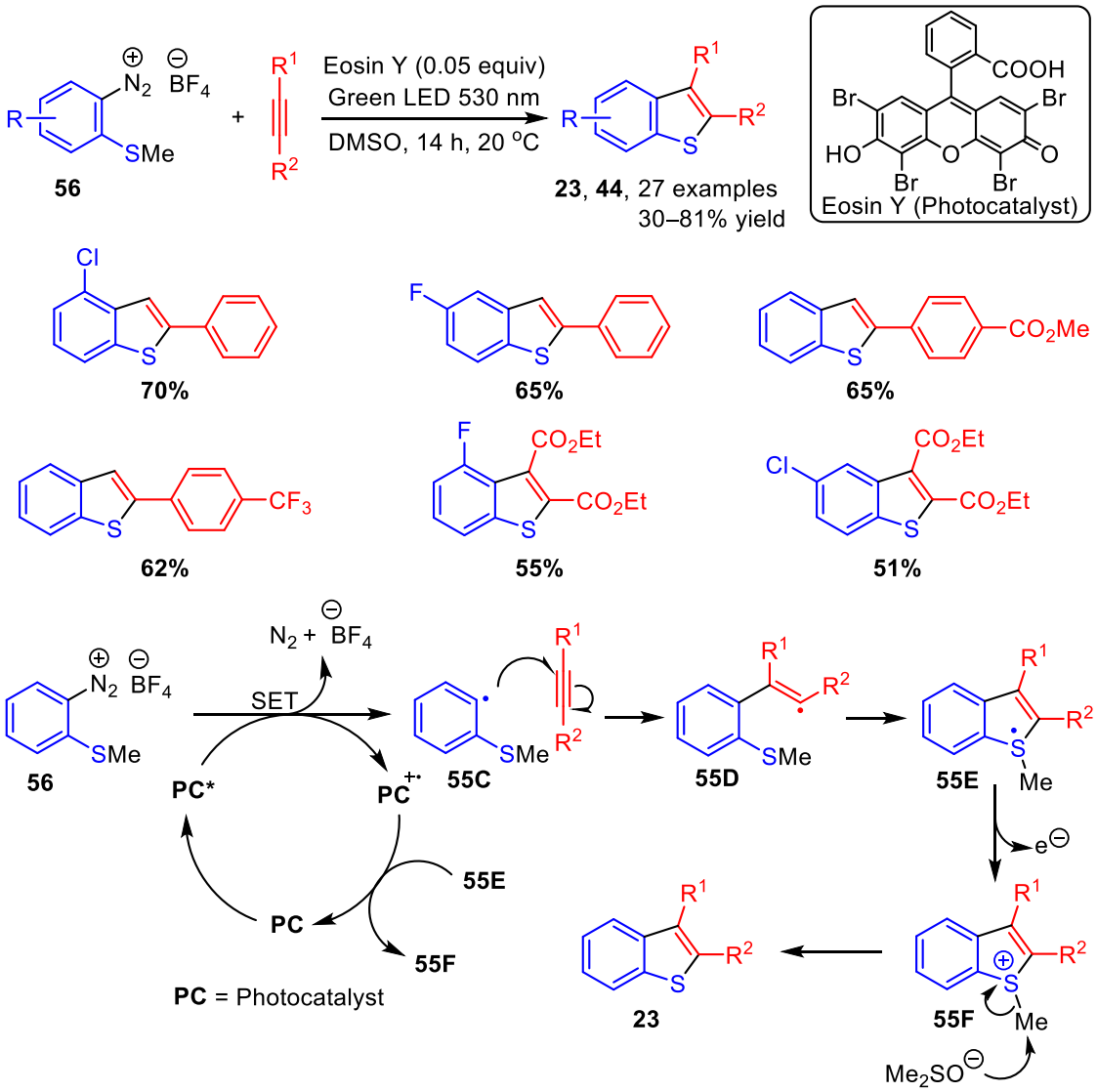
Scheme 25. KOH/DMSO superbase-promoted synthesis of 2-aryl benzo[*b*]thiophenes *via* photoinduced cyclization of 2-halothioanisole and terminal alkynes.

Zanardi's group was first to report the reaction of *o*-(methylthio)arendiazonium tetrafluoroborates **56** with alkynes, catalyzed by fresh copper or metal salts leading to selective formation of 2-aryl benzo[*b*]thiophenes [62] (Scheme 26). Subsequently, Huffman et al reported the synthesis of benzo[*b*]thiophenes from diazonium salts, with stoichiometric amounts of $FeSO_4$ and $TiCl_3$.[63] However, the instability and commercially unavailability of the *o*-methylthioarendiazonium tetrafluoroborates largely limit its practicality.

In 2012, the Konig's group reported a first photocatalytic reaction of *o*-(methylthio)-arenediazonium salts **56** with alkynes, yielding substituted benzo[*b*]thiophenes, regioselectively, under ambident conditions, *via* a radical annulation process (Scheme 26).[64] Green-light irradiation of Eosin Y initiates the photoredox catalysis. The scope of the reaction was investigated by using various substituted diazonium salts and different alkynes, yielding 2-arylbenzo[*b*]thiophenes in moderate to good yields. The method provides mild and efficient access to different types of benzo[*b*]thiophenes, avoiding metal catalysts and high temperatures. Instead, only green light, and a catalytic amount of organic dye as the catalyst, are employed at room temperature.[64]

The proposed mechanistic pathway involves initial formation of aryl radical **55C** by SET from the excited state of the photocatalyst to diazonium salt **56**. Addition of radical **55C** to the alkyne yields the corresponding vinyl radical **55D**, which then further cyclizes to give sulfuranyl radical **55E**. Radical **55E** is oxidized to cation **55F**, which undergoes demethylation by some nucleophile yielding product benzo[*b*]thiophenes (cf. Scheme

25). Radical **53E** is oxidized by either the cation radical of the photocatalyst to complete the electron transfer cycle or the diazonium salt in a chain-transfer mechanism (Scheme 26).[64]

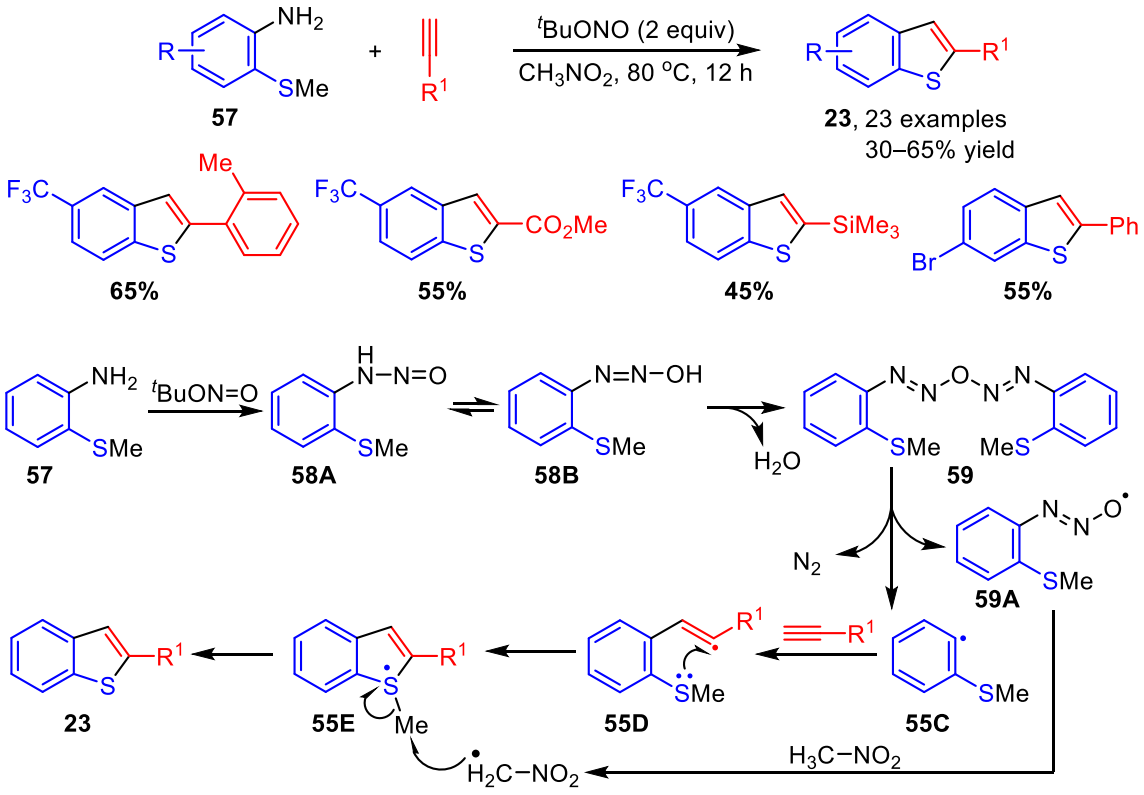


Scheme 26. Synthesis of 2,3-substituted-benzo[*b*]thiophenes *via* photocatalytic cyclization of 2-(methylthio)arenediazonium salts and alkynes.

In order to avoid preparation of unstable diazonium salts and to increase overall reaction efficiency, Li and Zhang have reported the syntheses of benzo[*b*]thiophenes by employing readily available *o*-(methylthio)arylamines **57** and alkynes in an intermolecular radical-cascade protocol (Scheme 27).[65] The reaction proceeds under simple conditions by reacting *o*-methylthioarylamines and alkynes with *t*-butyl nitrites in nitromethane at 80 °C for 12 h. This transformation occurs efficiently with complete regioselectivity, and the product benzo[*b*]thiophenes, bearing a variety of electron donating and withdrawing substituents, are obtained in moderate to good yields (Scheme 27).

A mechanistic study revealed that diazonium salts are not involved as intermediates in this reaction. Based on experimental studies, a plausible mechanism is proposed as shown in Scheme 27. First, *o*-methylthioarylamine is converted to the corresponding *N*-nitrosamine **58A**, which is in equilibrium with diazohydroxide **58B**. The diazohydroxide **58B** undergoes self-condensation to generate the diazoanhydride **59**.

Subsequent N–O homolysis of anhydride **59** affords the aryl radical **55C** along with the azoxy radical **59A** and nitrogen. Addition of aryl radical **55C** to alkyne leads to the vinyl radical **55D**, which reacts *via* intramolecular homolytic substitution at the sulfur atom to form the final products benzo[*b*]thiophenes *via* sulfur-centered radical **55E** (cf. Schemes 25-26). Further, the intermediate azoxy radical **59A** can abstract a hydrogen atom from the solvent to afford the diazo hydroxide **58B**, which can further react to generate the aryl radical **55C** .[65]

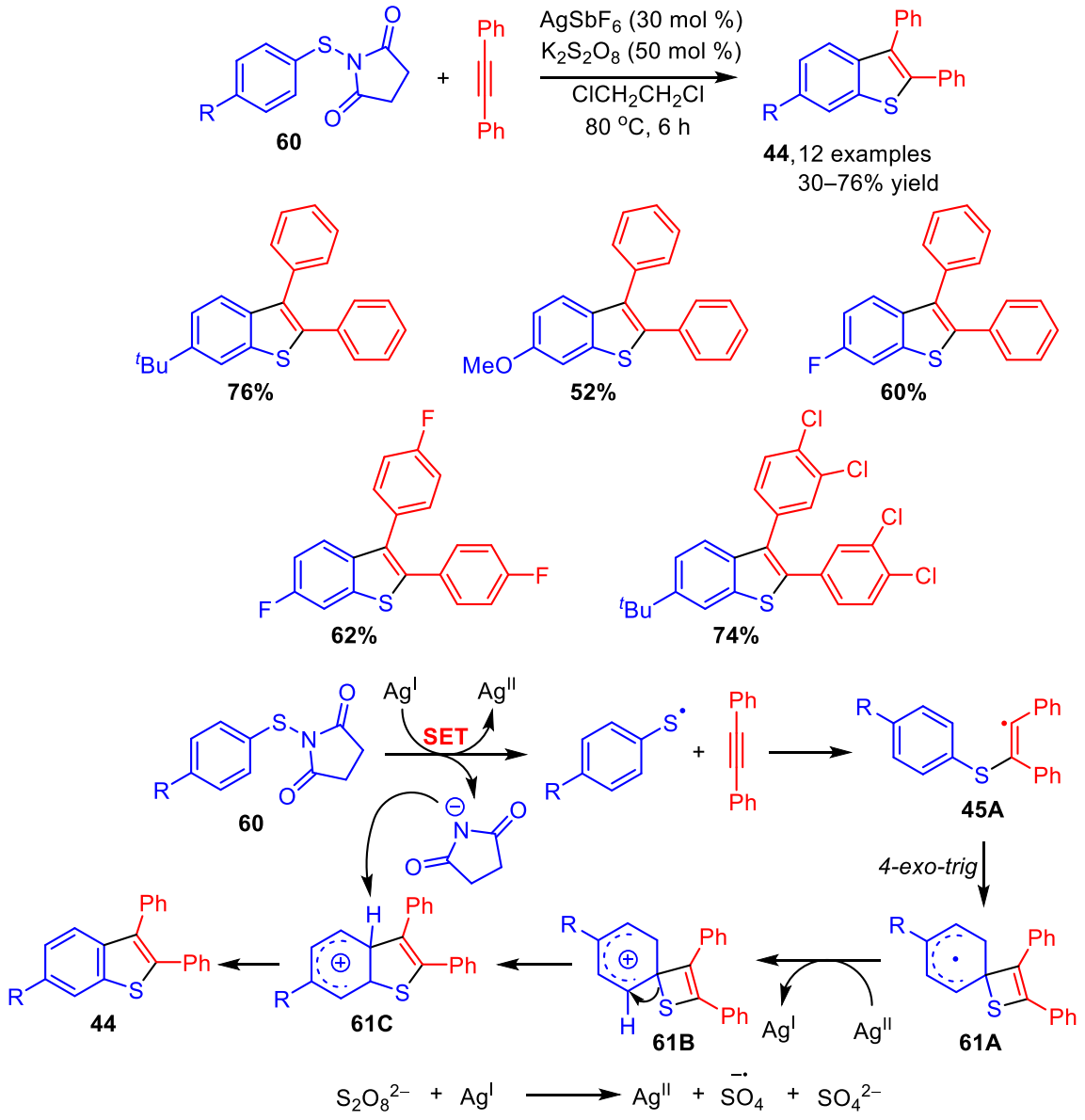


Scheme 27. Synthesis of 2-substituted-benzo[*b*]thiophenes *via* *t*-butyl-nitrite-mediated reaction of *o*-(methylthio)anilines and alkynes.

A convenient synthetic route to 2,3-diarylbenzo[*b*]thiophene derivatives *via* Ag catalyzed intermolecular oxidative cyclization of *N*-arylthiosuccinimides **60** and unactivated internal alkynes has been reported by Sahoo and co-workers (Scheme 28).[66] The reaction utilizes $AgSbF_6$ as catalyst along with $K_2S_2O_8$ as an oxidant. The reaction shows broad substrate scope, affording the diverse arrays of π-conjugated 2,3-diaryl substituted benzo[*b*]thiophenes. It is noteworthy that *p*-substituted *N*-arylsuccinimides furnished 6-substituted benzo[*b*]thiophenes **44**, displaying a 1,2-sulfur migration in the reaction. The reaction gave good yields of 2,3-diarylbenzo[*b*]thiophenes **44** with symmetrical unactivated diarylalkynes, whereas with unsymmetrically substituted alkynes, mixtures of regioisomers were obtained (Scheme 28).

On the basis of experimental studies, a plausible mechanistic pathway is proposed as shown in Scheme 28. The reaction begins with the single electron transfer from Ag(I) to **60** to produce arylthiyl radical, and a succinimide anion. A concomitant attack of arylthiyl radical on the alkyne, followed by the *ipso*-carbon attack of arene on the vinyl radical in **45A** leads to a highly strained spirocyclohexadienyl radical intermediate **61A.** Oxidation of **61A** leads to spirocyclohexadienyl arenium species **61B**, which rapidly undergoes ring expansion involving 1,2-S-migration to give the intermediate **61C**. Finally, deprotonation–aromatization of **61C** affords

substituted benzo[*b*]thiophenes **44**. Alternatively, 1,2-S-migration of the radical **61A**, followed by oxidation of intermediated radical may provide benzo[*b*]thiophenes (Scheme 28).[66]

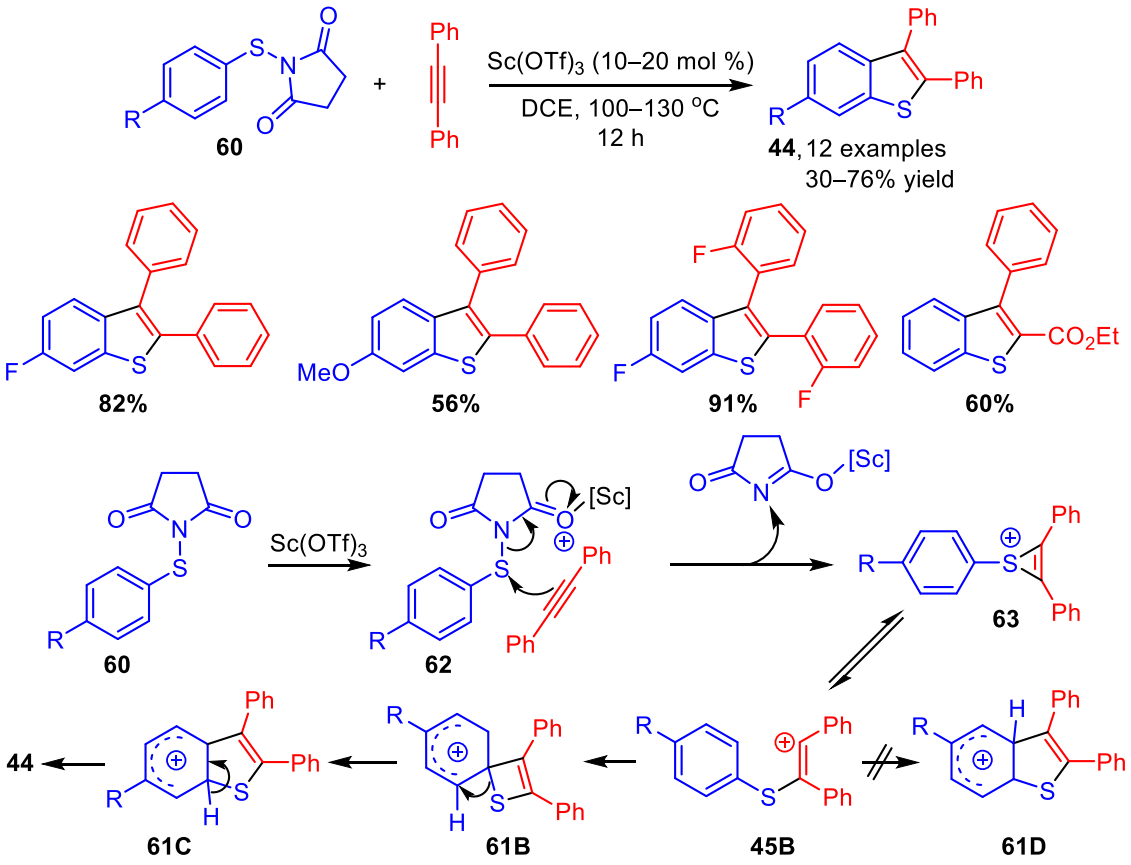


Scheme 28. Synthesis 2,3-bisarylbenzo[*b*]thiophenes *via* Ag-catalyzed intermolecular-oxidative cyclization of *N*-arylthiosuccinimide and internal alkynes.

In a parallel publication, Glorious and co-workers have developed a highly-selective and efficient synthesis of 6-substituted-2,3-*bis*arylbenzo[*b*]thiophenes using the metal-triflate [Sc(OTf)$_3$] Lewis Acid-catalyzed intermolecular cyclization of *p*-substituted-*N*-(arylthio)succinimides **60** with diarylalkynes (Scheme 29).[67] This method especially represents a highly useful and practical route to access 6-substituted-benzo[*b*]thiophenes, which are typically difficult to obtain with high regioselectivity from *meta*-substituted starting materials. The reaction involves a unique and unusual 1,2-sulfur migration. Both *para*-electron-donating and electron-withdrawing substituents on **60** gave the products resulting from sulfur migration with high selectivity (>93/7).

On the basis of these results and reports in the literature, a possible mechanism is suggested as shown in the Scheme 29.[67] Firstly, the succinimide moiety of the sulfenylating agent **60** coordinates with the Lewis acid,

$Sc(OTf)_3$, generating an electrophilic intermediate **62**, which then undergoes a nucleophilic attack by the alkyne to produce the thiirenium-ion intermediate **63**, which is in equilibrium with the vinyl cation **45B**. On the basis of DFT calculations, it has been suggested that the cyclization of the vinyl cation **45B** to the four-membered thiete intermediate **61B** is favored over the formation of the five-membered cation **61D,** due to the proximity of the *ipso*-C to the cation in **45B**, so very little structural distortion is required in the transition state.[67] A 1,2-shift of the sulfur atom in **61B** provides the cation **61C,** which, on subsequent deprotonation, affords the final product, 6-substituted-benzo[*b*]thiophenes **44**, resulting from formal aryl migration.

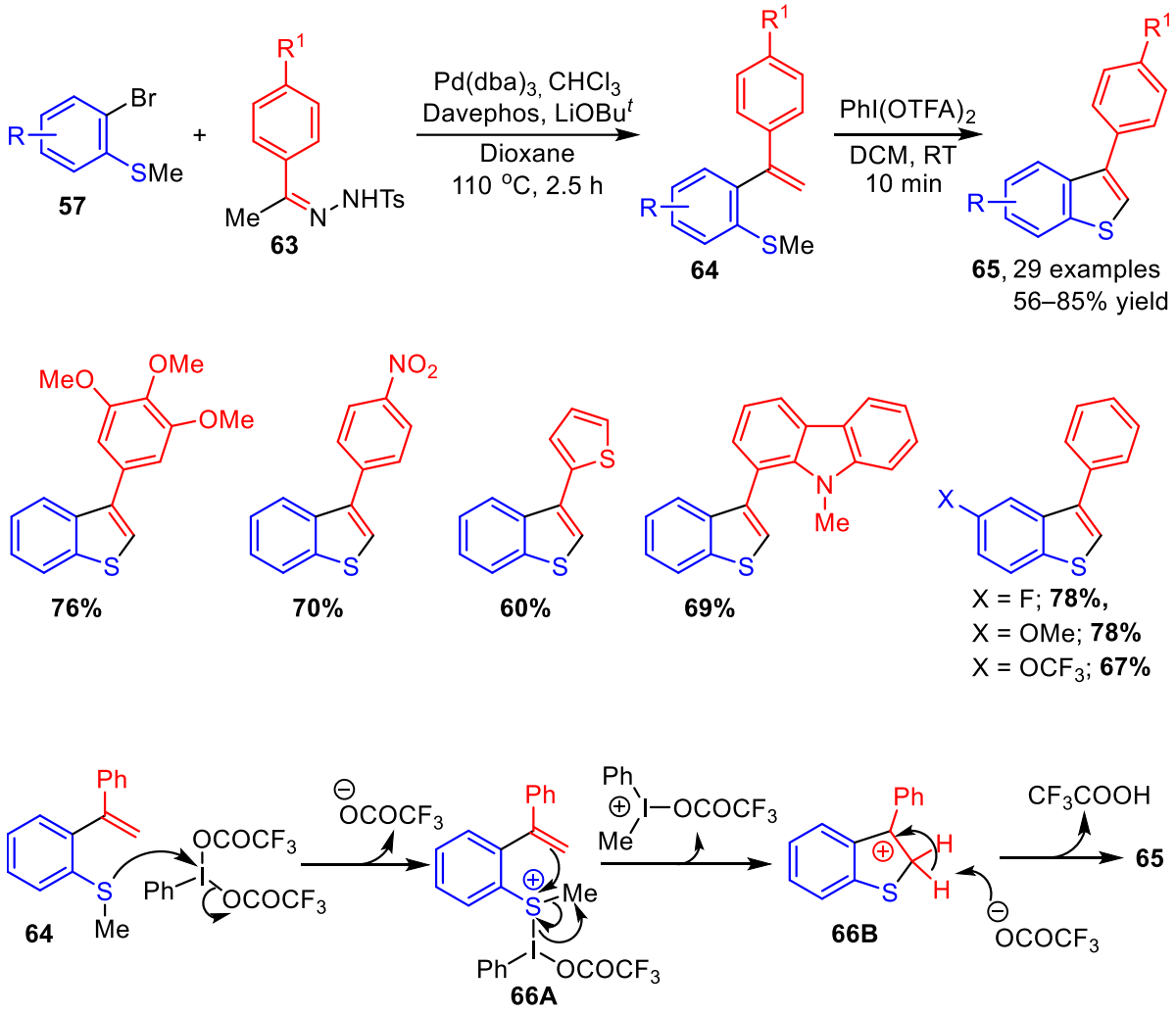


Scheme 29. Synthesis of 6-substituted-2,3-bisarylbenzo[*b*]thiophenes *via* $Sc(OTf)_3$-catalyzed intermolecular cyclization of *p*-substituted-*N*-arylthiosuccinimides and diarylalkynes.

Hamze and others have recently reported a concise synthesis of C3-arylated-benzo[*b*]thiophenes **65**, involving a PIFA-mediated cyclization of methyl(2-(1-phenylvinyl)phenyl)sulfane intermediates **64**[68] which were previously synthesized by the same workers by palladium catalyzed coupling of *N*-tosylhydrazones of acetophenones and 2-bromothioanisole partners (Scheme 30).[69] Thus, treatment of **64** with PIFA in DCM, at room temperature, furnished the 3-arylbenzo[*b*]thiophenes **65** within 10 minutes in excellent yields.

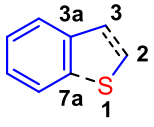
Based on the result of the control experiment and previous report on the cleavage of benzyl ethers with PIFA, a plausible mechanism was proposed as shown in Scheme 30.[68] Thus, the reaction proceeds by the nucleophilic attack of the sulfur atom of **64** on the iodine atom of PIFA, leading to the formation of the thionium complex **66A**. Subsequently, intramolecular attack of the double bond on the sulfur atom of the thionium salt **66A**, results in the formation of the carbocation **66B** and trivalent-iodine intermediate. Deprotonation of **66B** by the trifluoroacetate anion affords 3-phenylbenzo[*b*]thiophenes **65** in good yields. The trivalent-iodine intermediate decomposes into methyl trifluoroacetate and iodobenzene, which was isolated

and identified by ^{1}H NMR.[68] The present procedure involves synthesis of benzo[*b*]thiophenes by the stepwise formation of C(3)-C(3a) and (S1)-C(2) bonds.

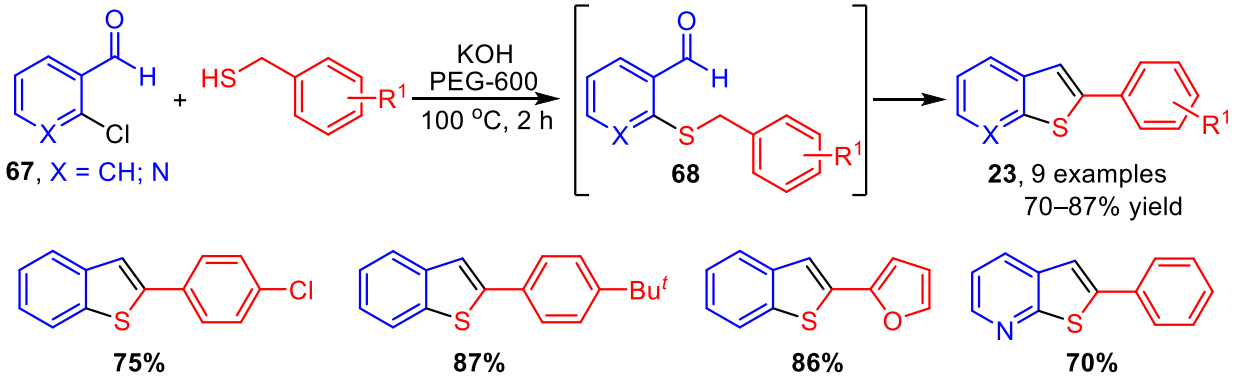


Scheme 30. Synthesis of C-3-arylated-benzo[*b*]thiophenes *via* PIFA-mediated intramolecular cyclization of methyl(2-((1-phenylvinyl)phenyl)sulfanes.

2.3. Synthesis of benzo[*b*]thiophenes *via* S(1)-C(7a) and C(2)-C(3) bond formation

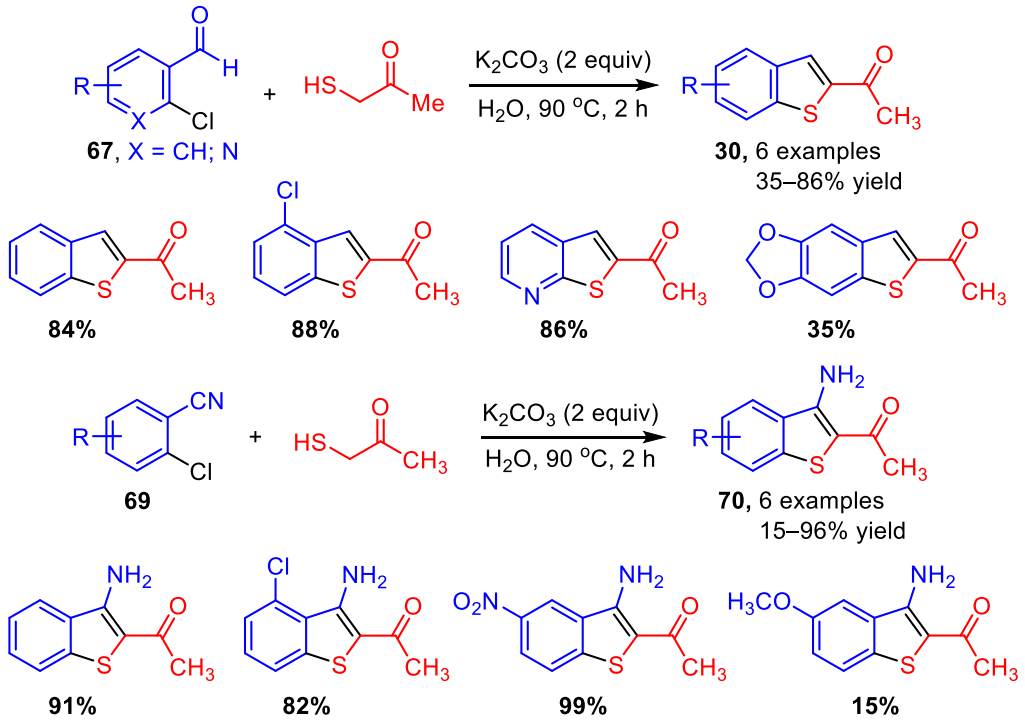


Liu and co-workers have reported a metal-free, cross-coupling reaction of 2-chlorobenzaldehyde **67** with benzylthiol derivatives in the presence of poly-(ethylene glycol)-600 (PEG-600) and potassium hydroxide (KOH) at higher temperature, yielding 2-arylbenzo[*b*]thiophenes **23** in excellent yields (Scheme 31).[70] The formation of 2-substituted benzo[*b*]thiophenes involves tandem C–S bond formation and base mediated intramolecular cyclocondensation process.



Scheme 31. Synthesis of 2-arylbenzo[*b*]thiophenes *via* coupling-intramolecular cyclocondensation of 2-chlorobenzaldehydes and benzyl thiol derivatives.

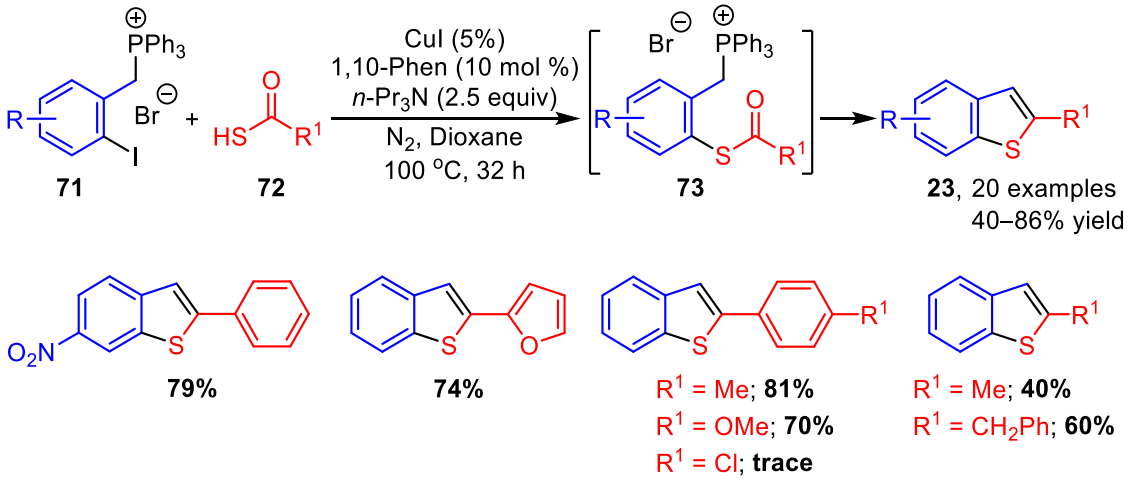
Popowycz and co-workers have developed a green, one-step, protocol for the preparation of 2-acetylbenzo[*b*]thiophenes **30** and 2-acetyl-3-aminobenzo[*b*]thiophenes **70** from commercially-available 2-chlorobenzaldehydes **67** or 2-chlorobenzonitriles **69** respectively (Scheme 32).[71] The overall strategy involves condensation of either 2-mercaptoacetone with either 2-chlorobenzaldehydes **67** or 2-chlorobenzonitrile **69** in the presence of potassium carbonate as a base, and water as reaction medium, yielding benzo[*b*]thiophenes **30** and **70**, respectively, in high yields. This method has the advantages of using water as the reaction medium, a short reaction time, and an easy purification process, resulting in high yields of pure cyclized products, which crystallized out directly from the reaction mixture. The reaction apparently proceeds *via* initial nucleophilic aromatic substitution of the chlorine atom by the mercapto group, followed by an aldol-type-cyclization dehydration.



Scheme 32. Synthesis of 2-acetyl- and 2-acetyl-3-aminobenzo[*b*]thiophenes *via* coupling-intramolecular cyclo-condensation of 2-chlorobenzaldehydes/2-chlorobenzonitriles with 2-mercaptoacetone.

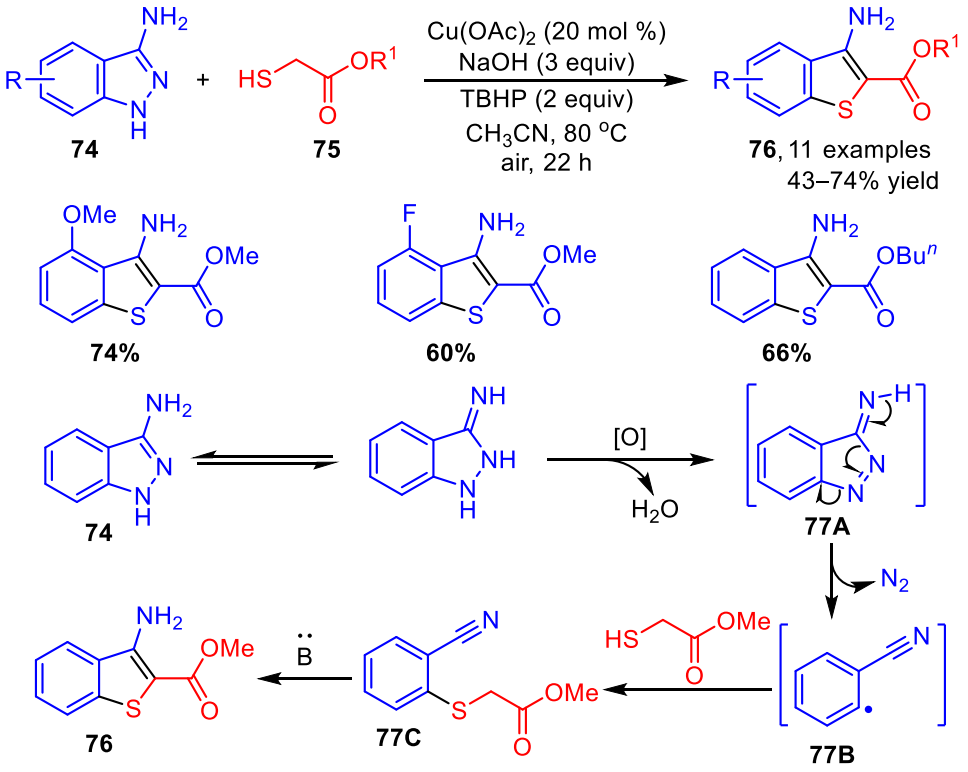
Yu and co-workers have reported an efficient, one-pot synthesis of 2-arylbenzo[*b*]thiophenes **23** by a combination of sequential copper catalyzed C–S bond formation (Ullman type C–S coupling) and an intramolecular Wittig condensation (Scheme 33).[72] Thus, thiocarboxylic acids **72** (as a sulfur source), and (2-iodobenzyl)triphenylphosphonium bromide **71** were reacted smoothly in the presence of CuI 1,10-phen, and *n*-Pr_3N as the base, at 100 °C, under nitrogen atmosphere to give benzo[*b*]thiophenes derivatives **23** in good yields.

A variety of substituted-thiobenzoic acids **72** were employed, and it was found that thiobenzoic acids with electron-donating groups displayed high reactivity under the present reaction conditions, in contrast, electron-deficient thiobenzoic acids were found to be less reactive under these reaction conditions, resulting in only trace amounts of the expected benzo[*b*]thiophenes being formed. Aliphatic acids, such as thioacetic acid and thiophenylacetic acid (R^1=$PhCH_2$), were also investigated, which provided the desired products in 40% and 60% yields, respectively, thus displaying the versatility of the reaction. A proposed mechanism involves Cu catalyzed cross coupling of ylid **71** with thioacids to give intermediate **73**, which underwent an intramolecular Wittig condensation to give the product benzo[*b*]thiophenes spontaneously.[72]



Scheme 33. Synthesis of 2-arylbenzo[*b*]thiophenes *via* sequential copper-catalyzed C–S bond formation and intramolecular Wittig cyclization.

Song and co-workers have reported for the first time, a novel Cu catalyzed denitrogenative transannulation of 3-aminoindazoles **74**, in the presence of mercaptoacetates **75**, to afford diversely-functionalized 3-aminobenzo[*b*]thiophenes **76** (Scheme 34).[73] The transformation proceeds *via* an "extrude-and-sew" strategy, with unprecedented radical reactivity of 3-amino-1*H*-indazoles **74**. Thus, when the reaction of 3-amino-1*H*-indazole **74** and mercaptoacetates **75** were performed in the presence of cupric acetate as catalyst, TBHP as oxidant, and NaOH as base, under air at 80 °C, a variety of diversely-functionalized 3-aminobenzo[*b*]thiophene derivatives **76** were obtained in good yields with wide substrate scope.



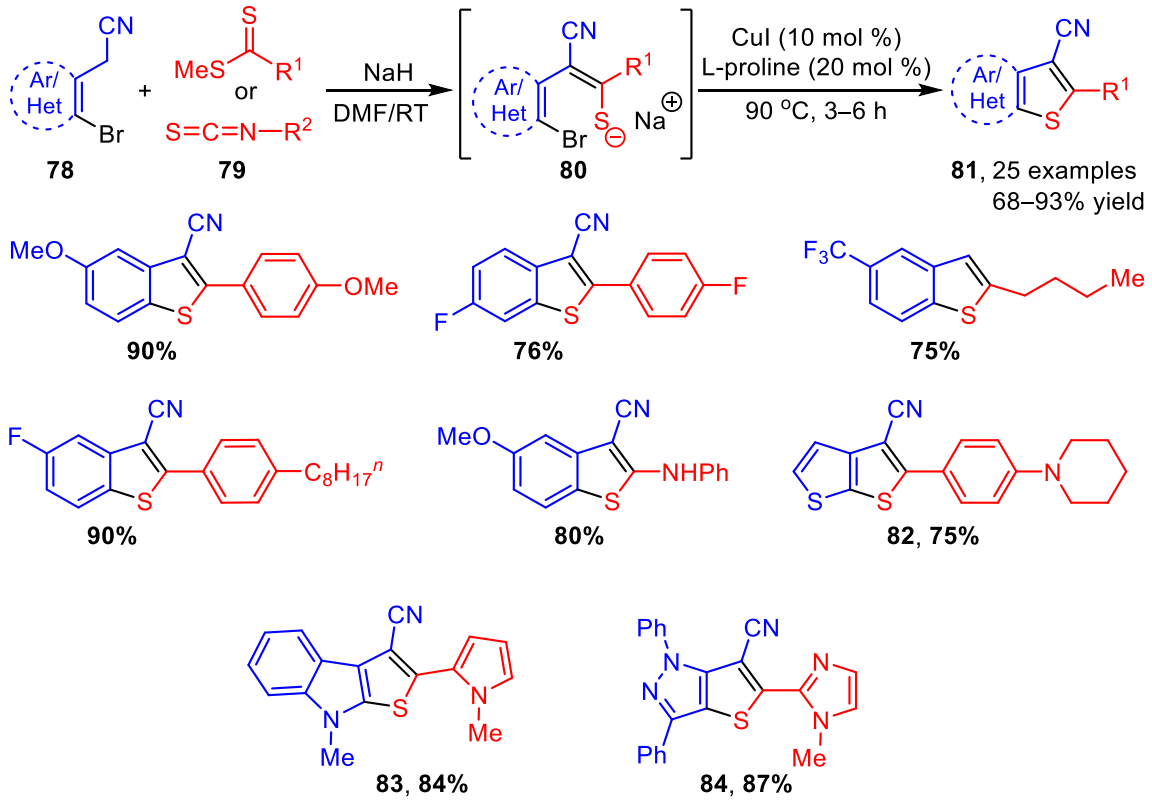
Scheme 34. Synthesis of 3-aminobenzo[*b*]thiophene-2-carboxylates *via* copper-catalyzed denitrogenative transannulation of 3-aminoindazoles and mercaptoacetate.

A possible reaction mechanism for this Cu catalyzed denitrogenative transannulation of 3-aminoindazoles **74**-**76**, is depicted in Scheme 34. First, 3-aminoindazole **74** undergoes oxidative dehydrogenation to afford intermediate **77A**, which successively undergoes extrusion of one molecule of nitrogen (initiated by abstraction of hydrogen by the *t*-butoxy radical generated in the reaction), to afford the aryl radical intermediate **77B**. Subsequent addition of **77B** to the mercaptoacetate yields the intermediate *o*-cyanoarylmercaptoacetate **77C**, which undergoes intramolecular base-induced condensation to give 3-aminobenzo[*b*]thiophene-2-carboxylates **76** in good yields.

The syntheses of benzo[*b*]thiophenes described above involve either crucial S(1)-C(2) and S(1)-C(7a) bond forming reaction (Schemes 1-15) or one-pot S1(C2) and C(3)-C(3a) bond formations (cf. Schemes 16-30). On the other hand, synthetic approaches to benzo[*b*]thiophenes involving the S(1)−C(7a) bond formation *via* intramolecular C−S coupling/cyclization of α-arylthioenol/enolate precursors are scarce in the literature. One of the oldest syntheses, which falls under this category, is iodine- or chlorine-mediated oxidative cyclization of β-aryl-α-mercaptoacrylic acids furnishing benzo[*b*]thiophene-2-carboxylic acids in good yields.[74]

Our research group has developed an efficient, and practical, one-pot synthesis of highly functionalized 2,3-substituted benzo[*b*]thiophenes **81** and hetero-fused thiophenes **82-84** from readily available 2-bromo-(het)arylacetonitriles **78** and (het)aryl/alkyldithioesters **79** and other thiocarbonyl precursors (Scheme 35).[75] The overall strategy involves sequential base mediated condensation of 2-bromohet(aryl)acetonitrile precursors **78** with (het)aryl/alkyl dithioesters **79** (intermolecular C(2)-C(3) bond formation), followed by intramolecular copper catalyzed arylthiolation of in situ generated enethiolate intermediates **80** [(S1)-C(7a) bond formation], in a one-pot sequence, furnishing a broad range of 2-functionalized 3-cyanobenzo[*b*]-and/hetero-fused thiophenes **81** in high yields. Further, this methodology could also be extended for the synthesis of hetero-fused thiophenes such as thieno[2,3-*b*]thiophenes **82**, indolo[2,3-*b*]thiophenes **83**, and

pyrazolo[3,2-*c*]thiophenes **84**, using appropriate 2-halo het(arene) precursors (Scheme 35). The new methodology allows direct access to a broad range of benzo/hetero-fused thiophenes with a variety of substitution patterns, making it a useful process for structure–activity relationship studies.

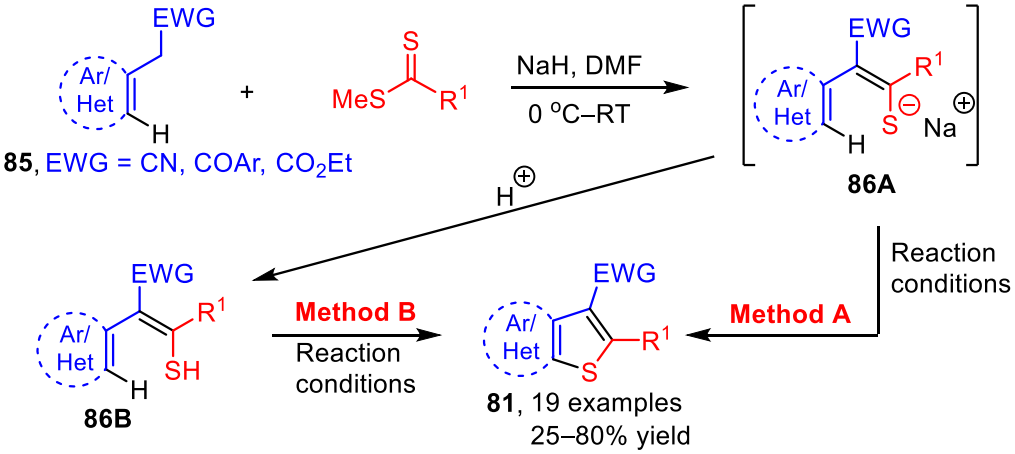


Scheme 35. Synthesis of 2-substituted-3-cyanobenzo[*b*]thiophenes and their hetero-fused analogs from 2-bromoarylacetonitriles and het(aryl)dithioesters.

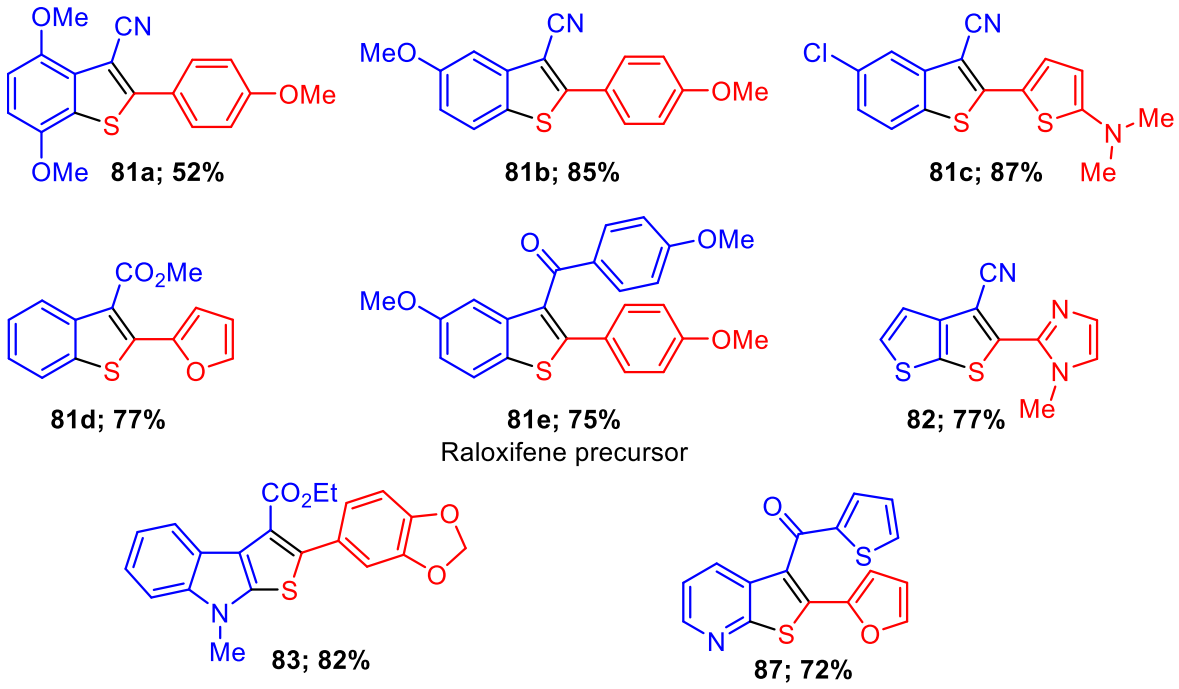
In a continuation of these studies, we further became intrigued with the idea of whether benzo[*b*]thiophenes **81** could be synthesized by an alternate strategy involving direct catalytic-oxidative intramolecular C–H functionalization-arylthiolation of thioenol precursors such as **86A**, which do not bear a 2-bromo substituent (obtained by condensation of active methylene precursors **85** with dithioesters) (Scheme 36). This would eliminate the requirement of *o*-bromo (or halo) substituents in **85**, thus opening up a much wider range of more readily accessible precursors for benzo[*b*]thiophene synthesis. In contrast to C–H amination and etherification reactions, catalytic C–H thiolation still represents a challenge because of the long-standing reputation of sulfur for catalyst poisoning. Inamoto and co-workers have previously described a direct synthesis of 2,3-bis(aryl)benzo[*b*]thiophenes through an intramolecular palladium ($PdCl_2$) catalyzed cyclization of 1,2,2-triarylethenethiols in the presence of dimethyl sulfoxide (DMSO). The reaction was shown to proceed through palladium catalyzed oxidative disulfide formation, and subsequent Pd catalyzed intramolecular cyclization to benzo[*b*]thiophenes, without involving a direct C–H functionalization. Besides, the generality and scope of the reaction was limited to the synthesis of only a few 1,2-diarylbenzo[*b*]thiophenes.[76]

We, therefore, developed a novel one-pot, two-step, diversity-oriented synthesis of highly-functionalized benzo[*b*]thiophenes and their hetero-fused analogs **81** by palladium catalyzed oxidative intramolecular C–H bond functionalization–arylthiolation of thioenolates **86,** generated in situ from substrates **85**.[77] Thus,

enethioates **86A**, obtained from arylacetonitriles, aryl acetates or desoxybenzoins **85** (EWG = CN, CO_2Et, COAr) and dithioesters, in the presence of sodium hydride in DMF, underwent smooth in situ intramolecular C–H bond functionalization/C–S bond formation in the presence of palladium acetate (20 mol %), cupric acetate (1 equiv) as an oxidant, and Bu_4NBr as an additive in DMF at 90 °C, within 4–6 hours to give benzo[*b*]thiophenes **81** (EWG = CN, CO_2Et, COAr) in high yields (Method A). In some cases, the yields of the benzo[*b*]thiophenes were better, using a two-step procedure by isolating the corresponding enethiols **86B** as substrates, under identical reaction conditions (Method B). In a few examples, $Pd(OAc)_2$ as the catalyst in the presence of oxygen was found to be more efficient than cupric acetate as a re-oxidant, furnishing benzo[*b*]thiophenes in improved yields by avoiding formation of side products.



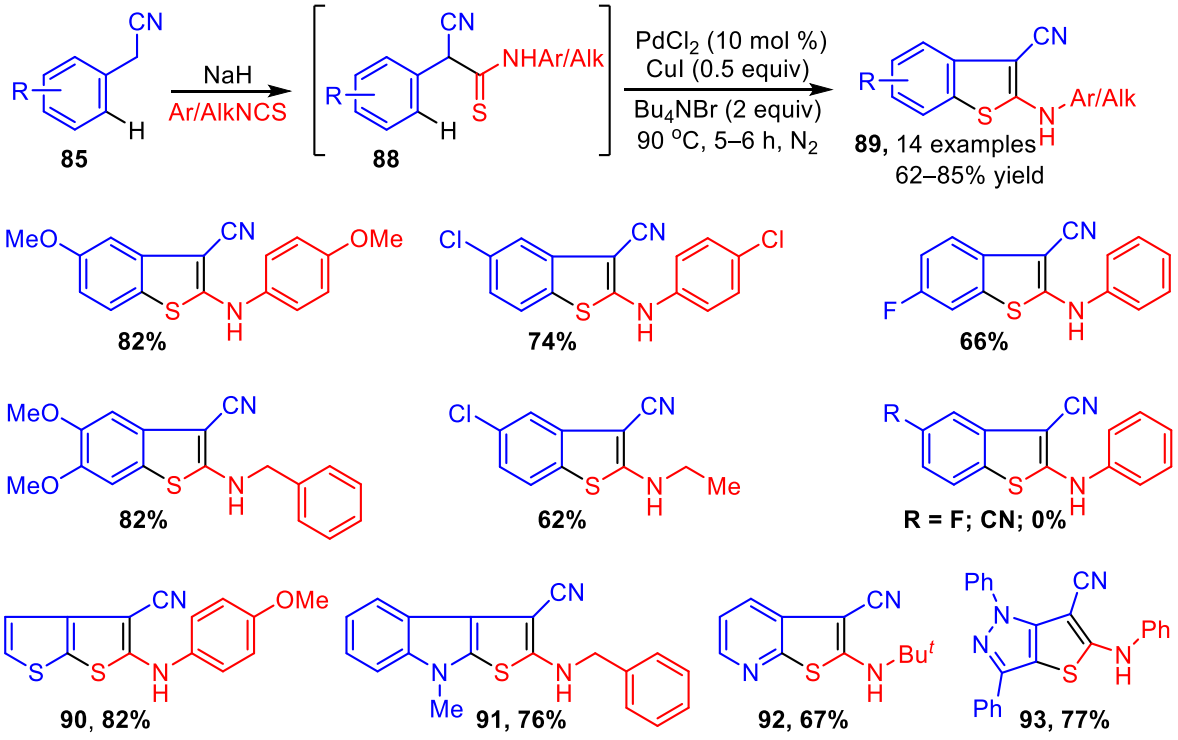
Reaction conditions: $Pd(OAc)_2$ (20 mol %); $Cu(OAc)_2$ (1 mol); Bu_4NBr (20 mol %); 90 °C, 4–6 h



Scheme 36. Synthesis of 2,3-substituted-benzo[*b*]thiophenes *via* palladium-catalyzed oxidative intramolecular C–H arylthiolation of thioenolate intermediates.

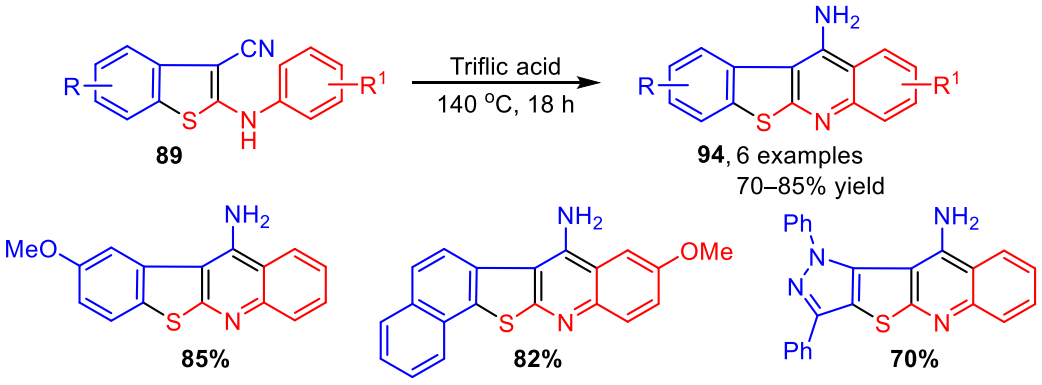
The method is compatible with a diverse range of heteroaromatic substituents, as well as with various substituents on the aromatic ring, besides ester and aroyl substituents could also be introduced at the 3-position of the benzo[*b*]thiophenes. The versatility of this method was further demonstrated by extending it to the synthesis of thieno-fused heterocycles such as thieno[2,3-*b*]thiophenes **82**, thieno[2,3-*b*]indoles **83**, pyrazolo[3,2-*c*]thiophene **84**, and thieno[2,3-*b*]pyridines **87** with cyano-(**81a-c**, **82**), carboethoxy (**81d**, **83**) and (het)aroyl substituents (**81e**, **87**). The protocol could also be extended to the synthesis of compound **81e**, a precursor of raloxifene, a selective estrogen receptor modulator.[78] A probable mechanism involving intramolecular electrophilic arylthiolation *via* either a Pd–S adduct or palladacycle intermediate has been proposed on the basis of experimental studies.[78]

In subsequent studies, we extended this methodology to the synthesis of 2-amino-substituted benzo[*b*]thiophenes **89** and their hetero-fused analogs such as **90**-**93** (Scheme 37-38).[79] This was achieved by employing palladium catalyzed intramolecular oxidative C–H functionalization/arylthiolation of in situ-generated *N*-(alkyl/aryl)thioamides **88**, obtained by base-mediated condensation of readily available (heteroaryl)acetonitriles **85** and alkyl/aryl isothiocyanates (Scheme 37).



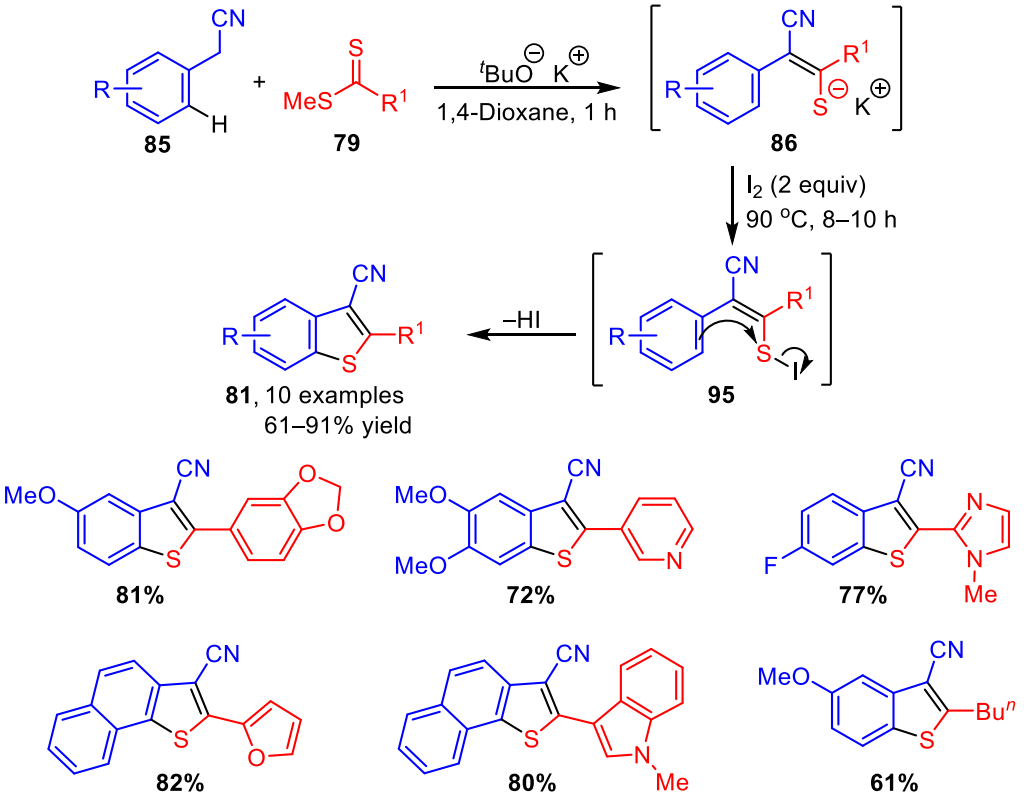
Scheme 37. Synthesis of 2-aryl/alkylamino-3-cyanobenzo[*b*]thiophenes *via* palladium-catalyzed intramolecular oxidative C–H arylthiolation of in situ-generated *N*-(alkyl/aryl)thioamides.

This protocol was further elaborated for the synthesis of a few amino-substituted-benzo[*b*]thieno[2,3-*b*]quinolines **94** by employing a triflic-acid-mediated cyclocondensation of the newly prepared 2-arylamino-3-cyanobenzo[*b*]thiophenes **89** (Scheme 38).



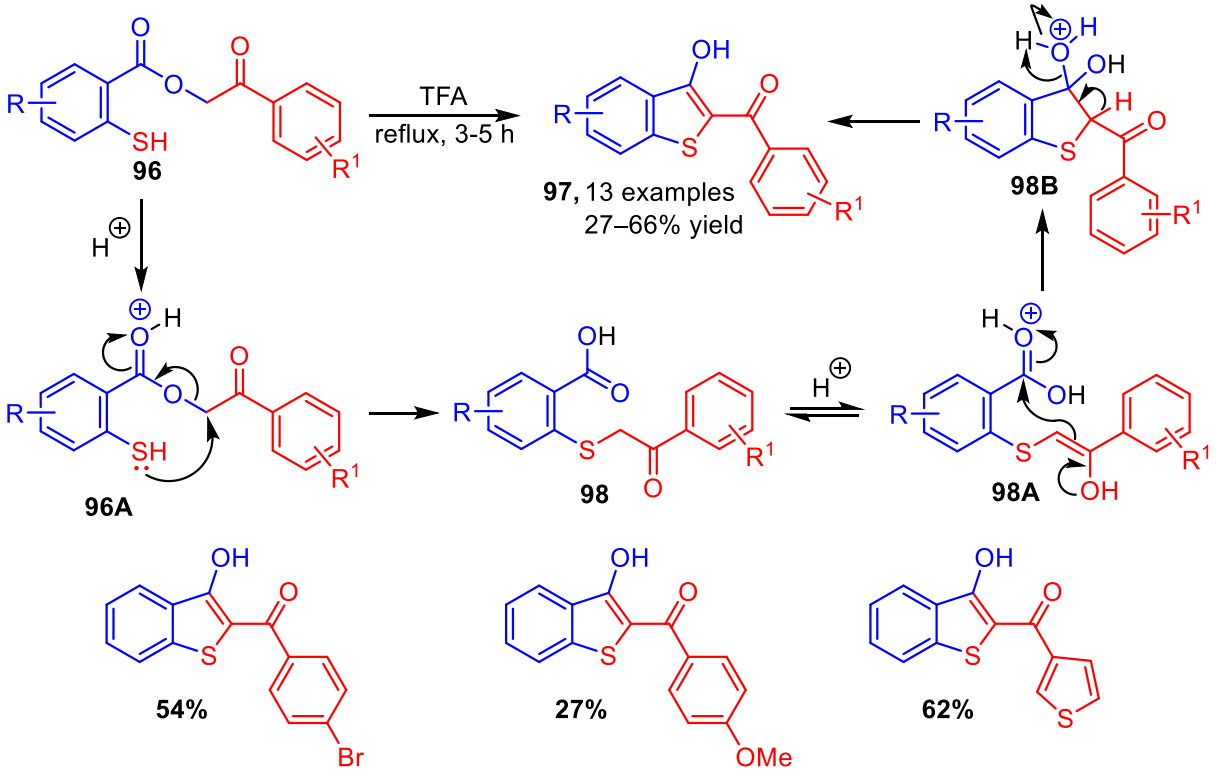
Scheme 38. Synthesis of amino-substituted-benzo[*b*]thieno[2,3-*b*]quinolines *via* triflic-acid-mediated cyclo-condensation of 2-arylamino-3-cyanobenzo[*b*]thiophenes.

In a further extension of this work, we also developed a metal-free, one-pot synthesis of 2-substituted-3-cyanobenzo[*b*]thiophenes **81** by iodine-mediated intramolecular cyclization of enethiolate intermediates **86** (Scheme 39).[80] Thus, under optimized reaction conditions, the enethiolates **86** were generated from arylacetonitriles **85** and dithioesters **79** in the presence of potassium *t*-butoxide as the base, and 1,4-dioxane as the solvent. Subsequent iodine-mediated intramolecular arylthiolation of enethiolates **86** at 90 °C for 8–10 h, afforded the substituted benzo[*b*]thiophenes **81** and their hetero analogs in good yields. Based on experimental studies, a probable mechanism involving intramolecular electrophilic cyclization of the sulfenyl iodide intermediate **95**, formed by nucleophilic displacement of thioenolate **86** with iodine, was suggested.



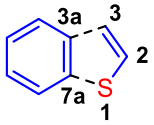
Scheme 39. Metal-free, one-pot synthesis of 2-(het)aryl-3-cyanobenzo[*b*]thiophenes *via* iodine-mediated intramolecular heterocyclization of thioenolate intermediates.

In a miscellaneous report, phenacyl thiosalicylate **96** was unexpectedly shown to give 2-aroyl-3-hydroxythiophenes **97** in good yields when refluxed in TFA for 3-5 h (Scheme 40).[81] The applicability of the reaction using different phenacyl thioesters was tested. A probable mechanism involving formation of intermediate **98** *via* intramolecular rearrangement of the protonated phenacylthiosalicylate **96A** was suggested. The intermediate **98**, again, undergoes intramolecular cyclocondensation in the presence of triflic acid to give 3-hydroxy-2-aroylbenzo[*b*]thiophenes **97** in good yields *via* intermediates **98A**-**B**. The present rearrangement, in fact, involves benzo[*b*]thiophene synthesis *via* intramolecular formation of S(1)-C(2) and C(2)-C(3) bonds. This category has not been included separately because of only one example.



Scheme 40. Unexpected synthesis of 2-aroyl-3-hydroxybenzo[*b*]thiophenes *via* TFA-mediated rearrangement of phenacyl thiosalicylates.

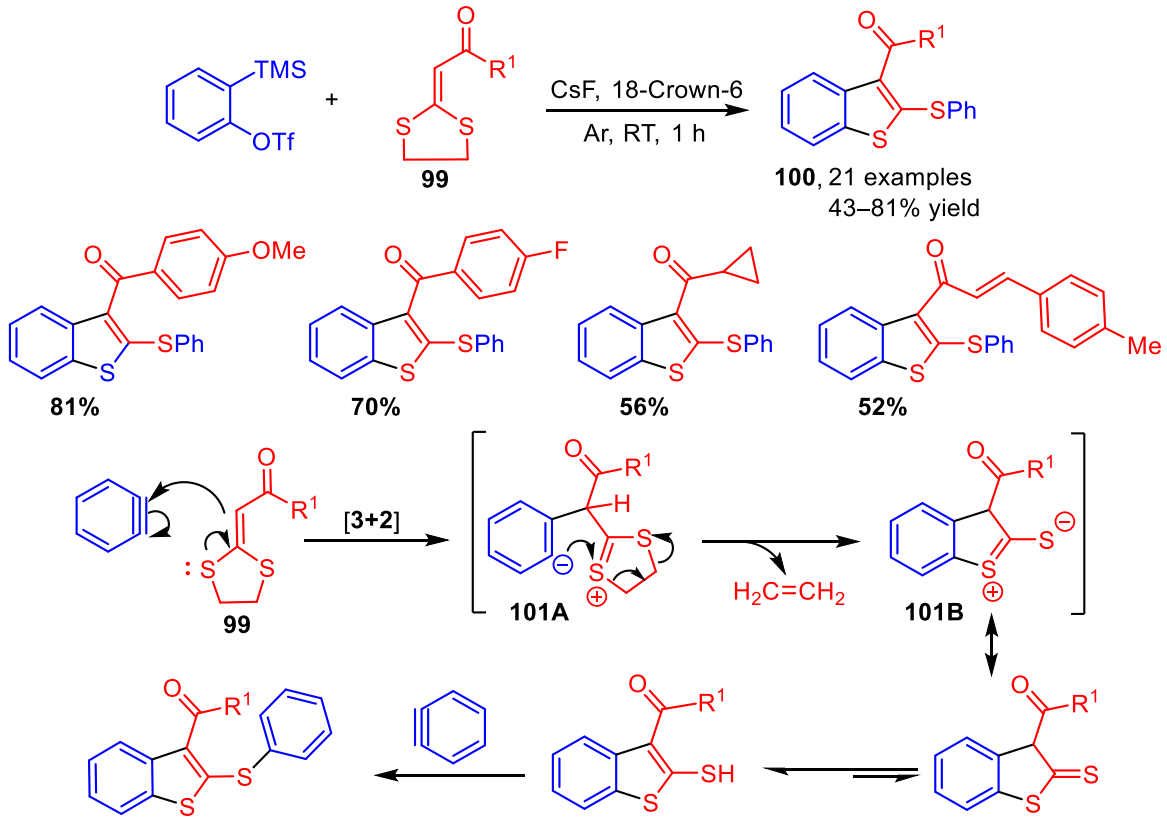
2.4. Benzo[*b*]thiophenes synthesis *via* S(1)-C(7a) and C(3)-C(3a) bond formation



Singh and co-workers have recently demonstrated formation of 2,3-substituted-benzo[*b*]thiophenes **100** by generation of an aryne in the presence of acyl ketene dithioacetals **99**, through a cascade reaction involving [3+2] cycloaddition and a dealkylative-arylation of the thioether moiety (Scheme 41).[82] The reaction represents a new approach to benzo[*b*]thiophenes, employing the acyl ketene dithioacetals as dipoles. The reaction displays broad substrate scope, and a diverse variety of 3-acyl-2-arylthiobenzo[*b*]thiophenes could be obtained in moderate to excellent yields.

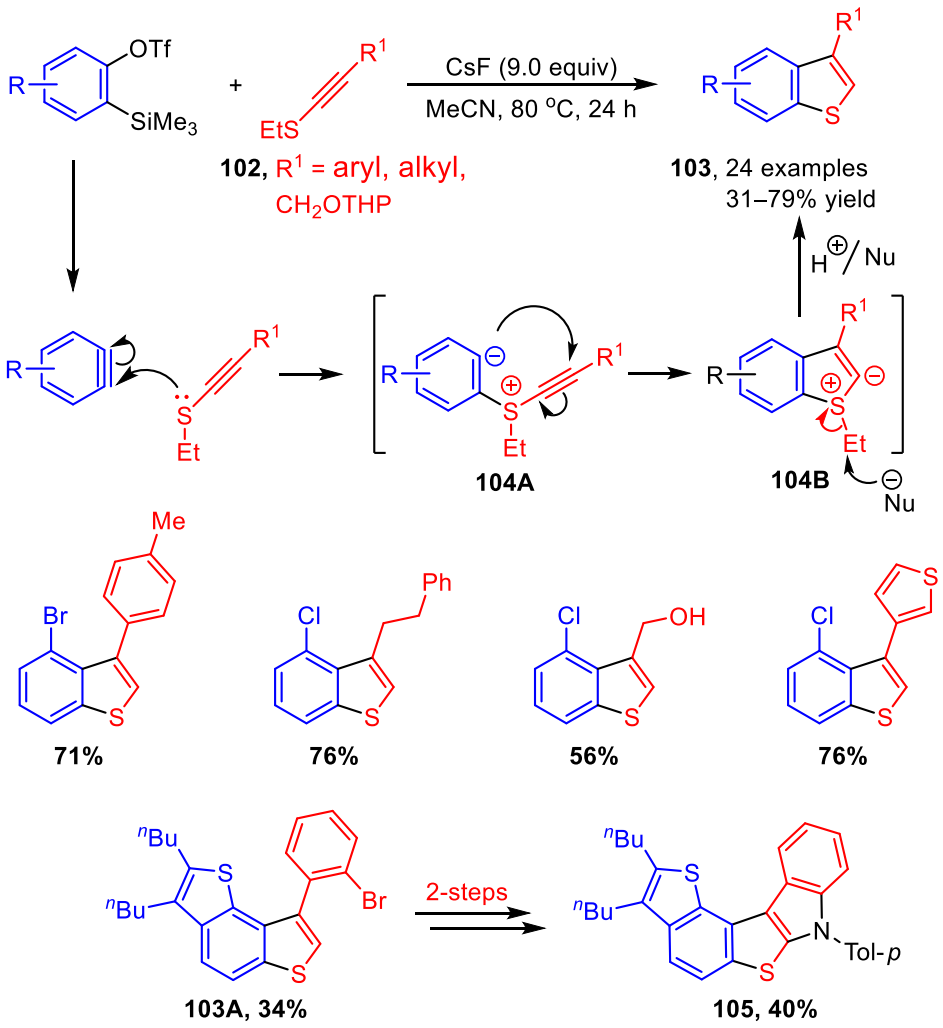
A plausible mechanism involving a concurrent [3+2] cycloaddition of benzyne and the ketene dithioacetal **99** followed by fragmentation of ethylene (*via* intermediate **101A**) to give benzo[*b*]thiophene-2(3*H*)-thioate anion adduct **101B** has been suggested. The subsequent insertion of another molecule of benzyne to intermediate **101B** affords the product benzo[*b*]thiophenes **100**.

Yoshida and co-workers have recently developed a versatile synthesis of 3-functionalized-benzo[*b*]thiophenes **103** by reaction of *o*-silyl triflates and alkynethioethers **102** in the presence of cesium fluoride in acetonitrile at 80 °C, involving the cycloannulation of benzyne with alkynethioethers **102** *via* intermediates **104A**-**B** (Scheme 42).[83]



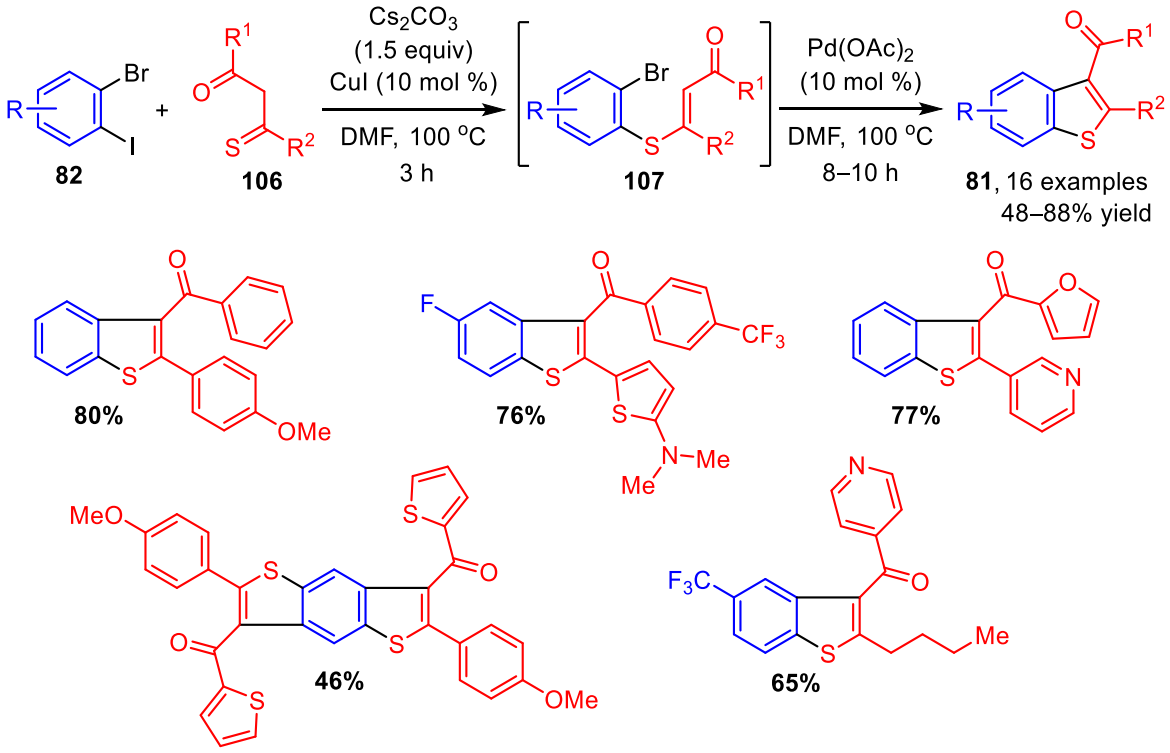
Scheme 41. Synthesis of 2-arylthio-3-acylbenzo[*b*]thiophenes *via* cascade [3+2] cycloaddition-dealkylative-arylthiolation between benzyne and cyclic-oxoketene dithioacetals.

A wide range of multisubstituted benzo[*b*]thiophenes, which are difficult to synthesize by conventional methods, could be obtained in good yields, following this one-step intermolecular protocol. The synthesis of diverse multisubstituted benzo[*b*]thiophene derivatives such as **103A**, with extended π conjugation bearing sensitive functionalities like *o*-bromo group, could also be achieved *via* this route. The benzo[*b*]thiophene **103A** could be transformed, subsequently, into pentacyclic-fused-benzo[*b*]thiophene derivative **105** in good yield (Scheme 42).[83]



Scheme 42. Synthesis of 3-functionalized-benzo[*b*]thiophenes *via* cycloannulation of benzynes and alkynylthioethers.

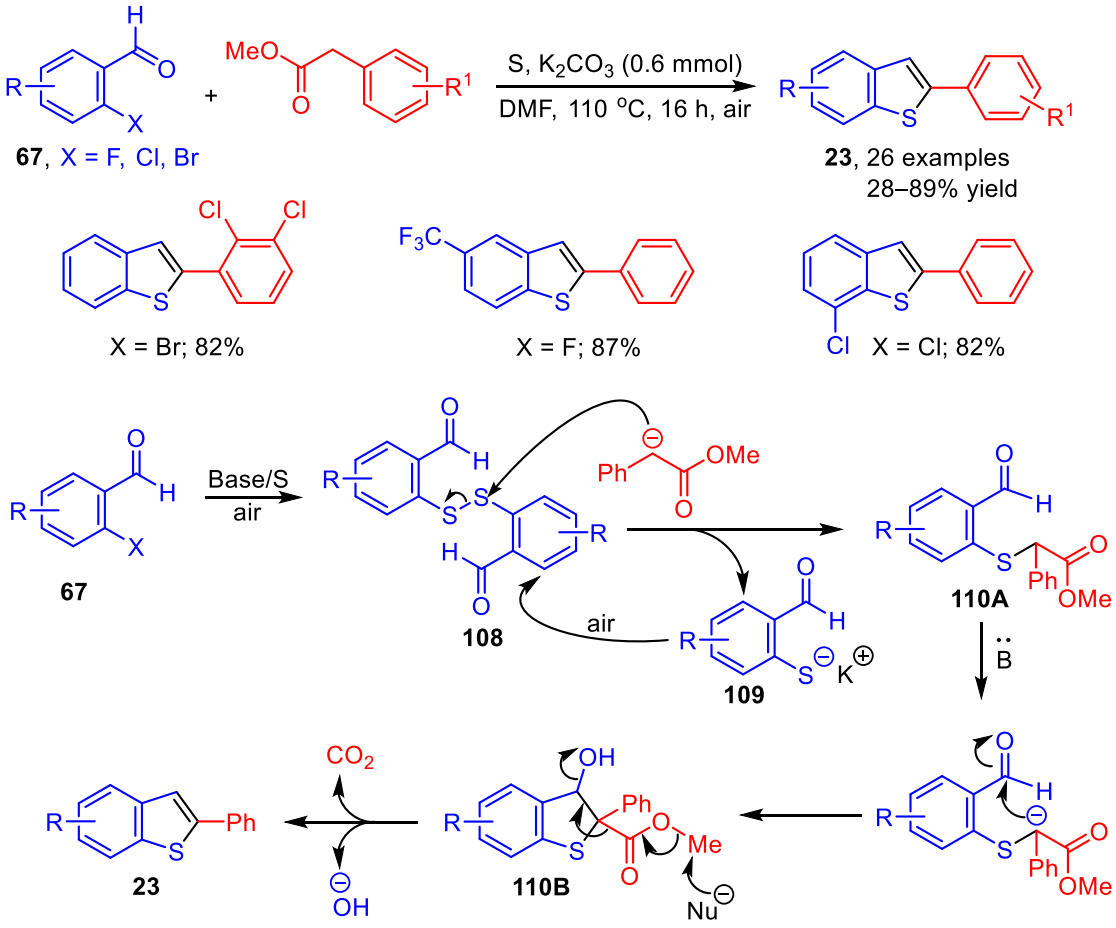
We have recently developed a novel convergent approach for 2,3-disubstituted benzo[*b*]thiophenes **81** *via* the sequential one-pot copper catalyzed intermolecular Ullman-type C–S coupling of 1,3-monothiodiketones **106** and 2-bromoiodoarenes, followed by subsequent palladium catalyzed intramolecular Heck-type coupling of the resulting β-aryl(2-bromoarylthio)enones intermediates **107** (Scheme 43).[84] Thus when 1,3-monothioketones **106** were subjected to copper catalyzed intermolecular C–S coupling with 2-bromoiodoarenes **82**, in the presence of 10 mol % of CuI and Cs_2CO_3 as the base, in DMF at 100 °C for 3 h, β-aryl(2-bromoarylthio)enones intermediates **107** was formed. The intermediates **107** was subjected in situ to palladium catalyzed intramolecular arene–alkene coupling, in a two-step, one-pot protocol, affording the corresponding 2-(het)aryl-3-(het)aroyl benzo[*b*]thiophenes **81** in moderate to excellent yields (Scheme 43).[84] These optimized one-pot reaction conditions were effective with an array of substituted *o*-bromoiodoarenes, bearing electron-withdrawing or electron-donating groups, and with 1,3-monothioketones with diverse (het)aryl substituents, including alkyl groups adjacent to either the carbonyl or thiocarbonyl moieties, thus affording the corresponding 2-(het)aryl/alkyl-3-(het)aroylbenzo[*b*]thiophenes **81** in excellent yields (Scheme 43).[84]



Scheme 43. Synthesis of 2,3-substituted benzo[*b*]thiophenes *via* tandem copper catalyzed intermolecular C–S bond formation and intramolecular palladium catalyzed C–C bond formation between 1,3-monothioketones and 1,2-bromoiodoarenes.

2.5. Benzo[*b*]thiophene synthesis involving three bonds formation in one-pot operation

Huang and Deng have reported a novel, three-component approach for 2-arylbenzo[*b*]thiophene synthesis from 2-halobenzaldehydes **67**, benzylic esters and sulfur under transition metal-free conditions, in the presence of potassium carbonate as a base, at higher temperature (Scheme 44). Functional groups such as halogen, trifluoromethyl and nitro were well tolerated under these reaction conditions.[85]



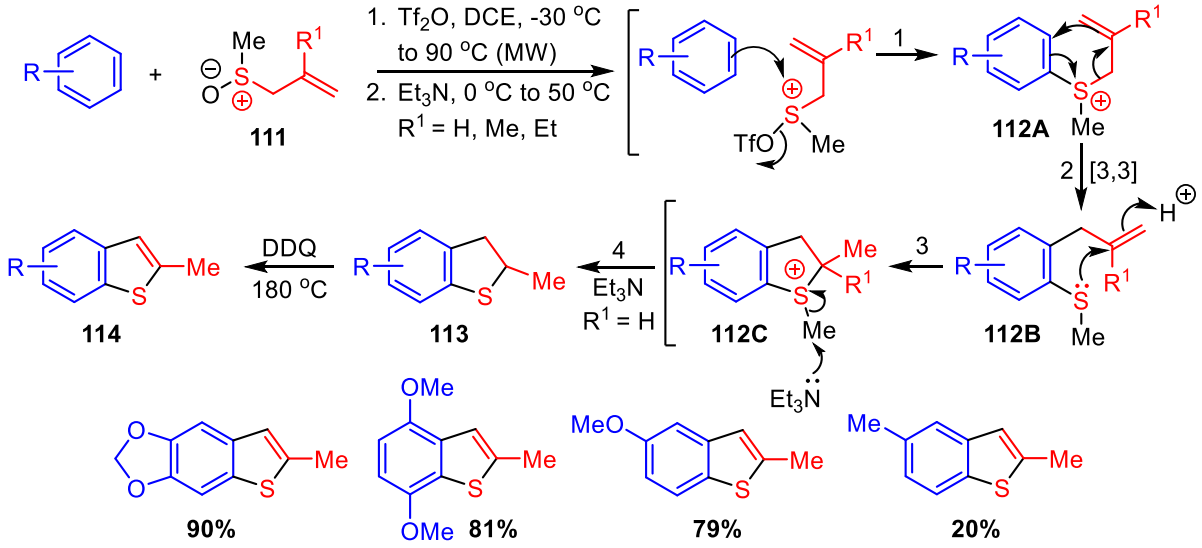
Scheme 44. Transition-metal-free, three-component synthesis of 2-arylbenzo[*b*]thiophenes from 2-halobenzaldehydes, benzylic esters and sulfur.

A probable mechanism involving a base-promoted coupling of 2-halobenzaldehyde **67** with elemental sulfur, as the first step, leading to the formation of disulfide as intermediate **108** (through air oxidation), has been suggested as the initial step. Subsequently, the nucleophilic attack of the carbanion, generated from benzylic ester, on disulfide **108** gives intermediate **110A**, followed by its Intramolecular aldol-type condensation, affording the intermediate **110B**. Subsequent concurrent demethoxylative-decarboxylation and dehydration of the intermediate **110B**, promoted by base, generates the product benzo[*b*]thiophenes **23** in good yields. The overall reaction releases 2-formylbenzenethiolate **109**, which could then be readily oxidized into the disulfide **108** under air. The reaction also proceeds with o-fluorobenzaldehydes furnishing similar yields. The overall reaction involves three bonds, i.e., S(1)-C(7a), S(1)-C(2) and C(2)-C(3) bond formations in a one-pot operation .[85]

Proctor and co-workers have developed a novel metal-free direct procedure for the construction of benzo[*b*]thiophenes, involving two-fold vicinal C-H functionalization of arenes, with a suitable coupling partner, without requiring pre-functionalization (Scheme 45-46).[86] The overall process of constructing a thiophene ring on the edge of aromatic ring involves an intermolecular interrupted Pummerer reaction (step 1), [3,3]-sigmatropic rearrangement (step 2), H^+ promoted cyclization (step 3) and demethylation (step 4) in a one-pot sequence, to give dihydrobenzo[*b*]thiophene products **113** directly from arenes (Scheme 45).[86]

Thus, an intermolecular, interrupted Pummerer reaction between an activated sulfoxide **111** and an arene, in the presence of triflic anhydride, yields intermediate **112A** (step 1, Scheme 45). Subsequently, on heating

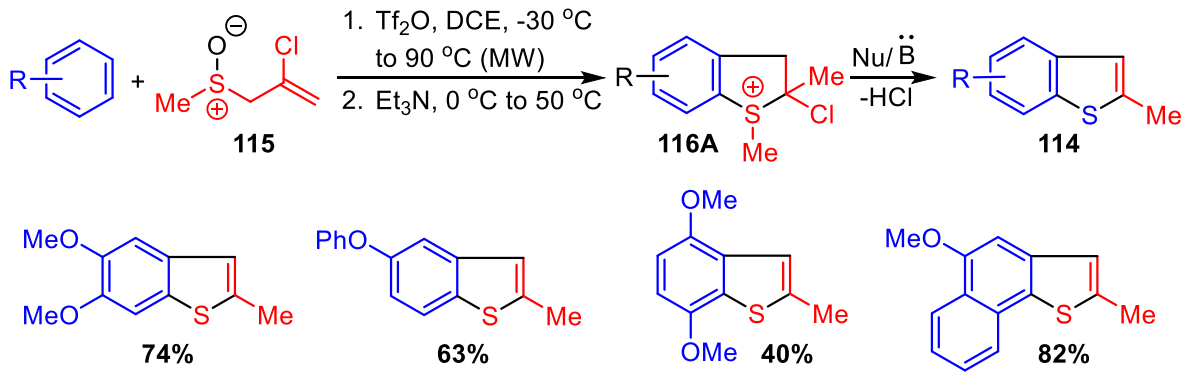
the reaction mixture, the desired [3,3]-sigmatropic rearrangement of intermediate **112A** to **112B** takes place (step 2), followed by spontaneous in situ, acid-promoted cyclization of **112B** to sulfonium salt **112C** (step 3). Addition of a nucleophilic base like NEt_3 in the same reaction pot led to demethylation of the sulfonium salt **112C**, to give the desired 2,3-dihydrobenzo[*b*]thiophene product **113** in overall good yields (step 4). Subsequently, treatment of dihydrobenzo[*b*]thiophene **113** with DDQ, afforded benzo[*b*]thiophene products **114** in high yields. It should be noted that overall transformation of the arene and **111** into **114** can be accomplished in a one-pot synthesis, without need for isolation of intermediates.[86]



Scheme 45. One pot synthesis of substituted benzo[*b*]thiophenes from arenes *via* interrupted Pummerer reaction, 3,3-sigmatropic rearrangement, acid promoted intramolecular cyclization.

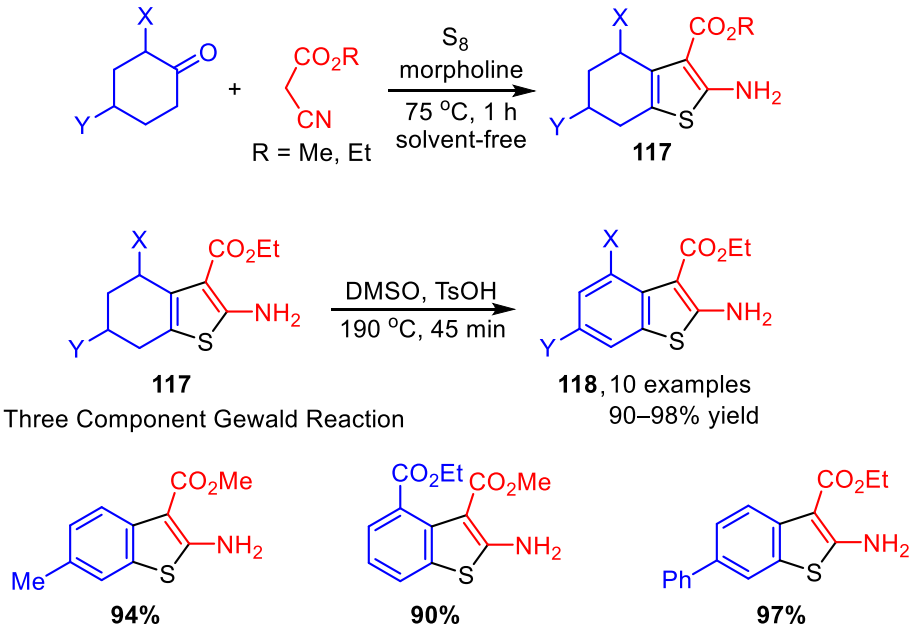
A study of generality of reaction revealed, that the best yields of benzo[*b*]thiophenes were obtained with electron-donating substituents on the benzene ring; as the electron-donating ability of the aryl substituent was reduced, the overall yield of the process decreased. Thus, toluene gave benzo[*b*]thiophene in very low yield, whereas benzene was found to be unreactive under the present conditions.[86] Halogen substituents were tolerated under the reaction conditions, but with reduced yields of benzo[*b*]thiophenes.[86] Polyaromatic hydrocarbons (PAHs) such as naphthalene, fluoranthrene and triphenylene afforded condensed thiophenes such as naptho-fused dihydrobenzo[*b*]thiophenes and other polycyclic dihydrobenzo[*b*]thiophenes in good yields.[86] The overall reaction involves formation of S(1)-C(7a), C(3)-C(3a) and S(1)-C(2) bonds in a one -pot sequence.

In a further improved modification, Proctor and co-workers developed a more direct one-pot approach to benzo[*b*]thiophenes from simple arenes by employing chloro-containing sulfoxide **115** (Scheme 46).[86] The reaction of readily-available sulfoxide **115** and an arene, under the standard reaction conditions, afforded the intermediate **116A**, which then undergoes simultaneous dealkylative-elimination on treatment with base, to give benzo[*b*]thiophene products **114** directly, in a one-pot operation, thus, avoiding an additional dehydrogenation step for the formation of benzo[*b*]thiophenes (Scheme 46). The methodology was found to be useful for the annulative π-extension of a range of polyaromatic hydrocarbons, such as naphthalene, fluoranthrene, pyrene and corannulene, yielding, directly, a range of interesting polyaromatic benzo[*b*]thiophene products.[86]



Scheme 46. One-pot synthesis of benzo[*b*]thiophenes employing chloroallylsuphoxide **115**.

In an extension of Gewald reaction, Adib and co-workers have reported an efficient oxidant-free dehydrogenative aromatization of the Gewald product, i.e., alkyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylates **117** (obtained by a three-component condensation of cyclohexanones, alkyl cyanoacetate and sulfur in morpholine), to the corresponding alkyl 2-aminobenzo[*b*]thiophene-3-carboxylates **118**, in dimethylsulfoxide, in the presence of *p*-toluenesulphonic acid catalyst at 190 °C within 45 minutes (Scheme 47).[87] Previously, the same workers have reported dehydrogenation of tetrahydrobenzo[*b*]thiophenes **117** and **118** in benzonitrile, at 200 °C, in air, requiring 24 h (Scheme 47).[88]

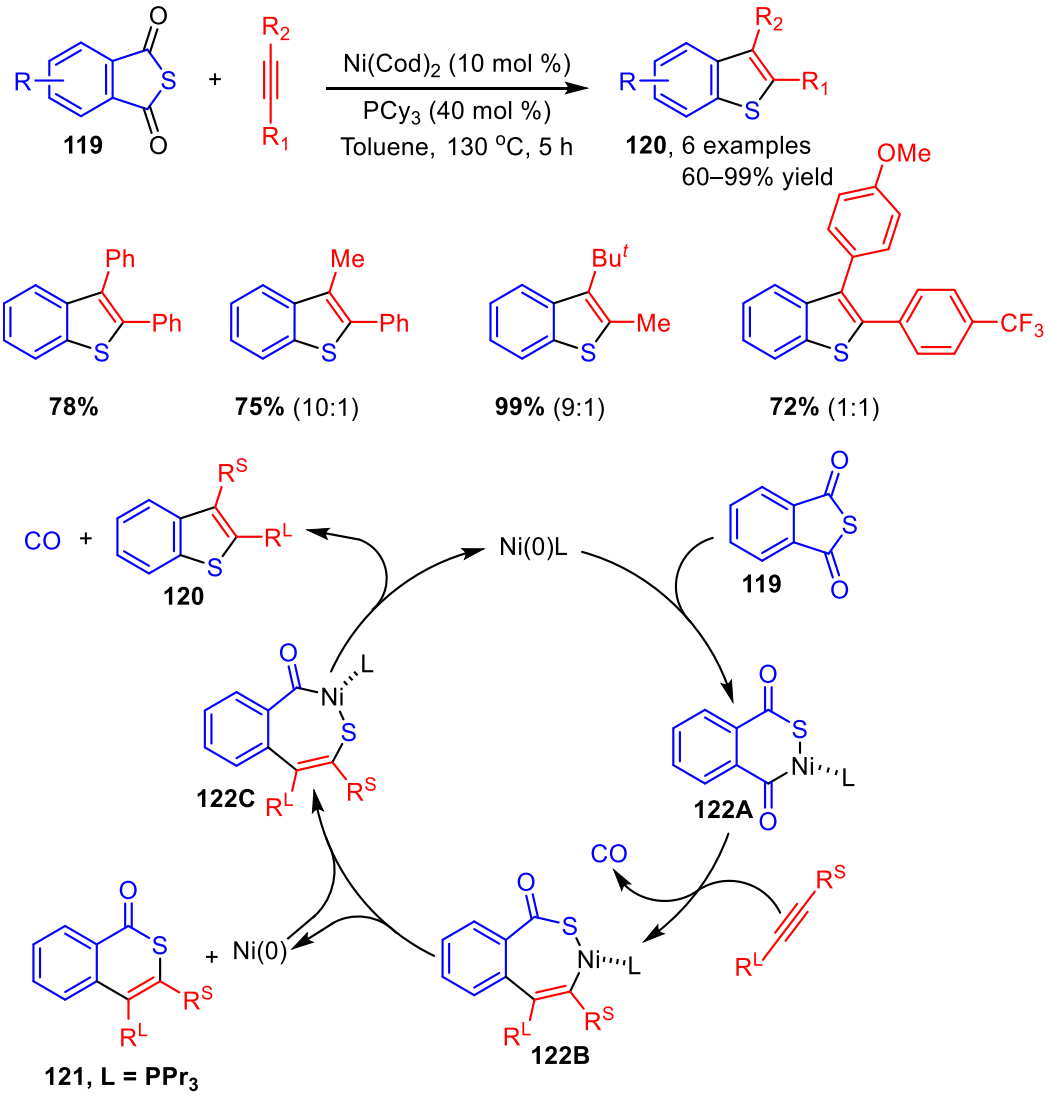


Scheme 47. Synthesis of 2-aminobenzo[*b*]thiophene-3-carboxylates *via* oxidant-free dehydrogenative aromatization of Gewald products.

Kurahashi and Matsubara have elegantly demonstrated nickel catalyzed cycloadditions of thiophthalic anhydride **119** with alkynes, affording three types of sulfur-containing heterocyclic compounds depending on the reaction conditions employed. Thus, the use of Ni(0)/PPr_3 catalyst in combination with a Lewis acid,

yielded thioisocoumarin **121,** whereas by employing sterically crowded ligand Ni(0)/PCy_3 catalyst, benzo[*b*]thiophenes **120** were obtained selectively in good yields (Scheme 48).[89]

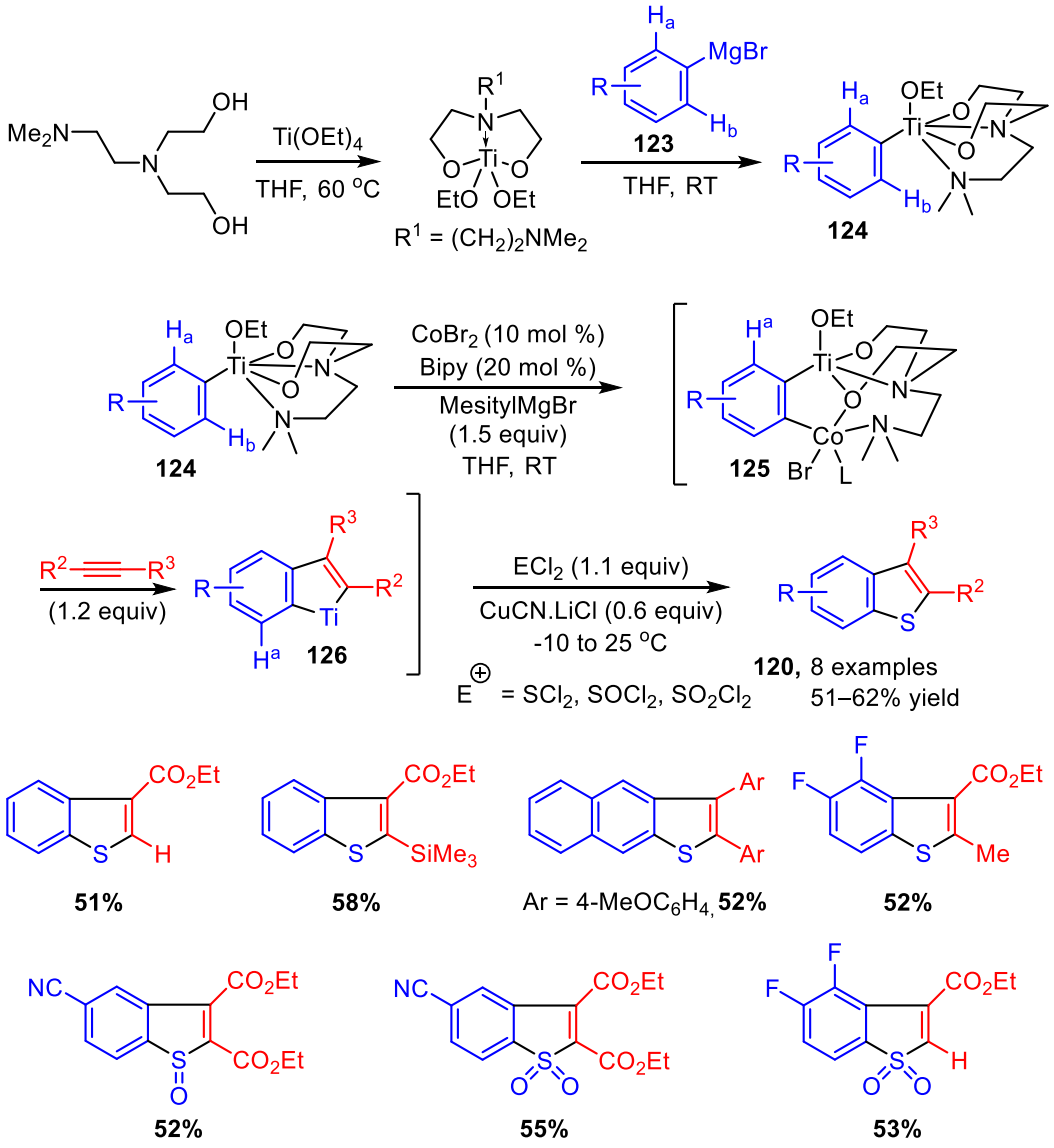
Examination of the scope of reaction showed that the reaction proceeded well with symmetrically-substituted alkynes, yielding benzo[*b*]thiophenes in high yields.[89] Unsymmetrical alkynes, such as 1-phenyl-1-propyne, also reacted with thiophthalic anhydride **119** to afford the correspondingly substituted regioisomeric benzo[*b*]thiophenes with good regioselectivity. The reaction of **119** to unsymmetrical alkynes containing sterically-hindered substituents such as the *t*-Bu group, gave adducts benzo[*b*]thiophene in 99% yields, with good regioselectivity. The reaction with not sterically, but electronically differentiated diaryl-substituted alkynes, afforded benzo[*b*]thiophene in 72% yield, consisting of regioisomers in a ratio of 1:1.[89]



Scheme 48. Synthesis of 2,3-substituted-benzo[*b*]thiophene *via* nickel-catalyzed cycloaddition of thiophthalic anhydride and internal alkynes.

A proposed reaction pathway for the formation of benzo[*b*]thiophenes **120**, based on the observed results, is shown in Scheme 48.[89] The catalytic cycle consists of the oxidative addition of S–CO bond of thiophthalic anhydride to Ni(0) to give the nickelacycle **122A**. The use of bulky ligand PCy_3 inhibits insertion of an alkyne to a nickelacycle **122A**, and decarbonylation occurs prior to alkyne insertion to give intermediate **122B**.

Subsequent reductive elimination of intermediate **122B** gives the thioisocoumarin **121**, which undergoes reoxidative addition in the catalytic cycle to afford the intermediate nickelacycle **122C**. Subsequent reductive decarbonylative elimination of **122C** provides benzo[*b*]thiophenes **120**, and regenerates starting Ni(0) catalyst. The regioselectivity of the reaction can be rationalized due to the direction of alkyne insertion, in which the steric repulsive interaction is minimal between the bulkier R^L substituent on the alkyne in the nickel-ligand complex **122B**.[89]

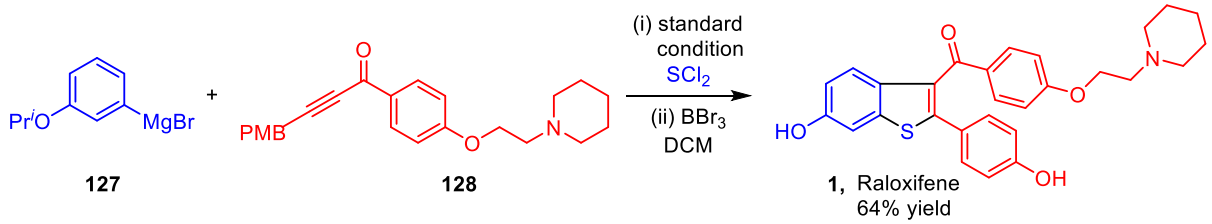


Scheme 49. Co/Ti-hetero-bimetallic-arylene-complex-catalyzed synthesis of 2,3-substituted benzo[*b*]thiophenes.

Duan and co-workers have reported a novel, modular and regioselective methodology to access five membered benzoheterocycles such as indoles and benzo[*b*]thiophenes, which were synthesized by reacting alkynes and an electrophilic reagent under the catalysis of $CoBr_2$/bipyridine and aryl titanates (Scheme 49).[90] The overall process involves generation of an unprecedented 1,2-Co/Ti heterobimetallic arylene complex **125**, by reacting the titanate complex **124** in situ with $CoBr_2$/2,2-bipyridine and mesityl magnesium bromide.[90] The intermediate **125** was reacted in situ with alkynes to form the Ti-aryne complex intermediates **126**

(benzotitanol comlex), which were reacted in situ with sulfur electrophiles at room temperature in THF to give benzo[*b*]thiophenes in moderate yields, in a highly regioselective manner. The reaction proceeds at room temperature in THF. These Co/Ti bimetallic reagents **125** proved to be effective for the synthesis of benzo[*b*]thiophenes, benzo[*b*]thiophene-1-oxide, and benzo[*b*]-thiophene-1,1-dioxide by employing electrophiles such as SCl_2, $SOCl_2$ and SO_2Cl_2, respectively.[90]

Furthermore, raloxifene **1**, recognized as a medication for breast cancer and osteoporosis (as an estrogen-receptor ligand),[7-8] was synthesized in a straightforward manner through regioselective annulation of the Co/Ti bimetallic reagent **125** with alkyne **128** under identical conditions (Scheme 50).[90]

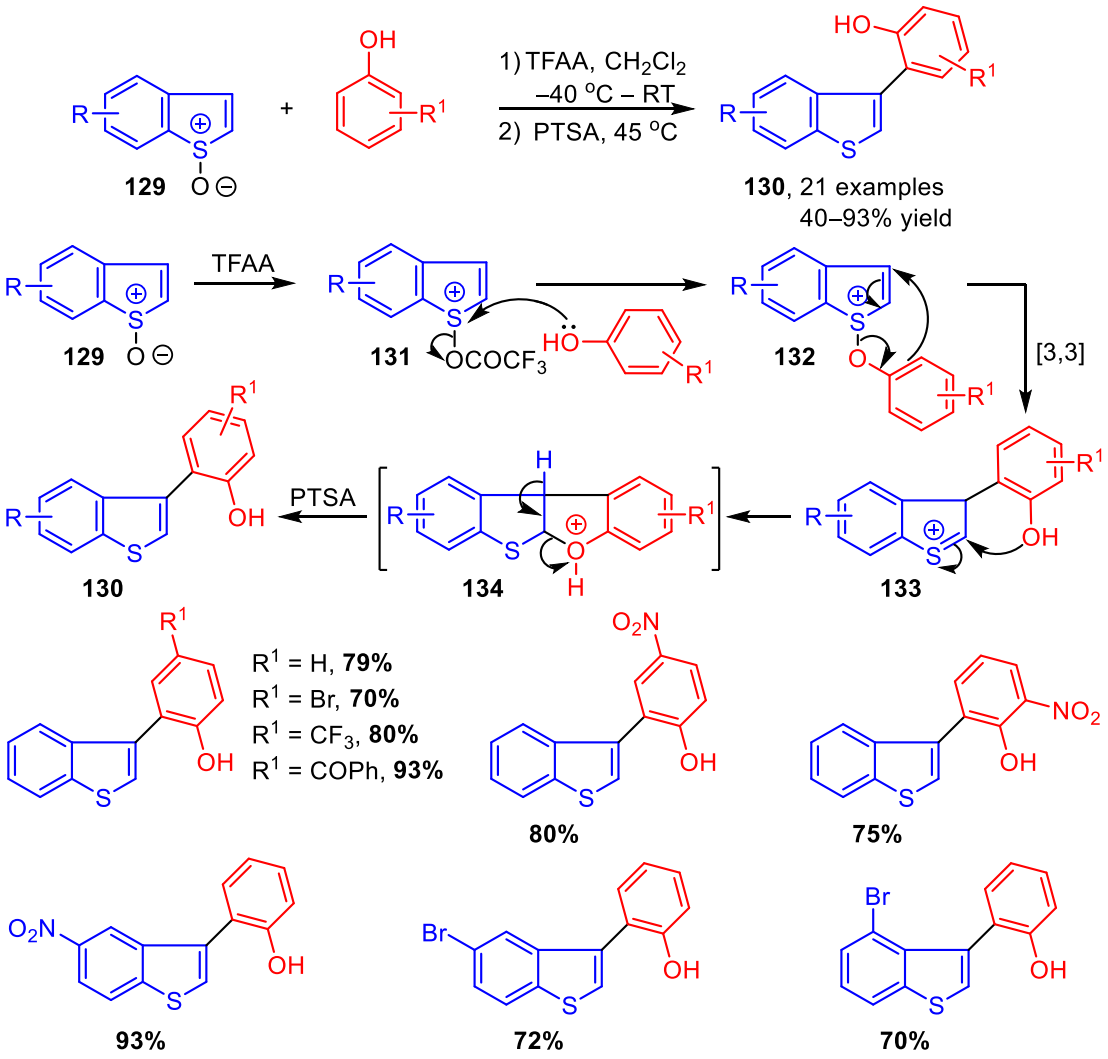


Scheme 50. Synthesis of raloxifene *via* regioselective annulation Co/Ti-bimetallic complex with alkyne and SCl_2.

2.6. Miscellaneous: synthesis of 2- and 3- substituted benzo[*b*]thiophenes

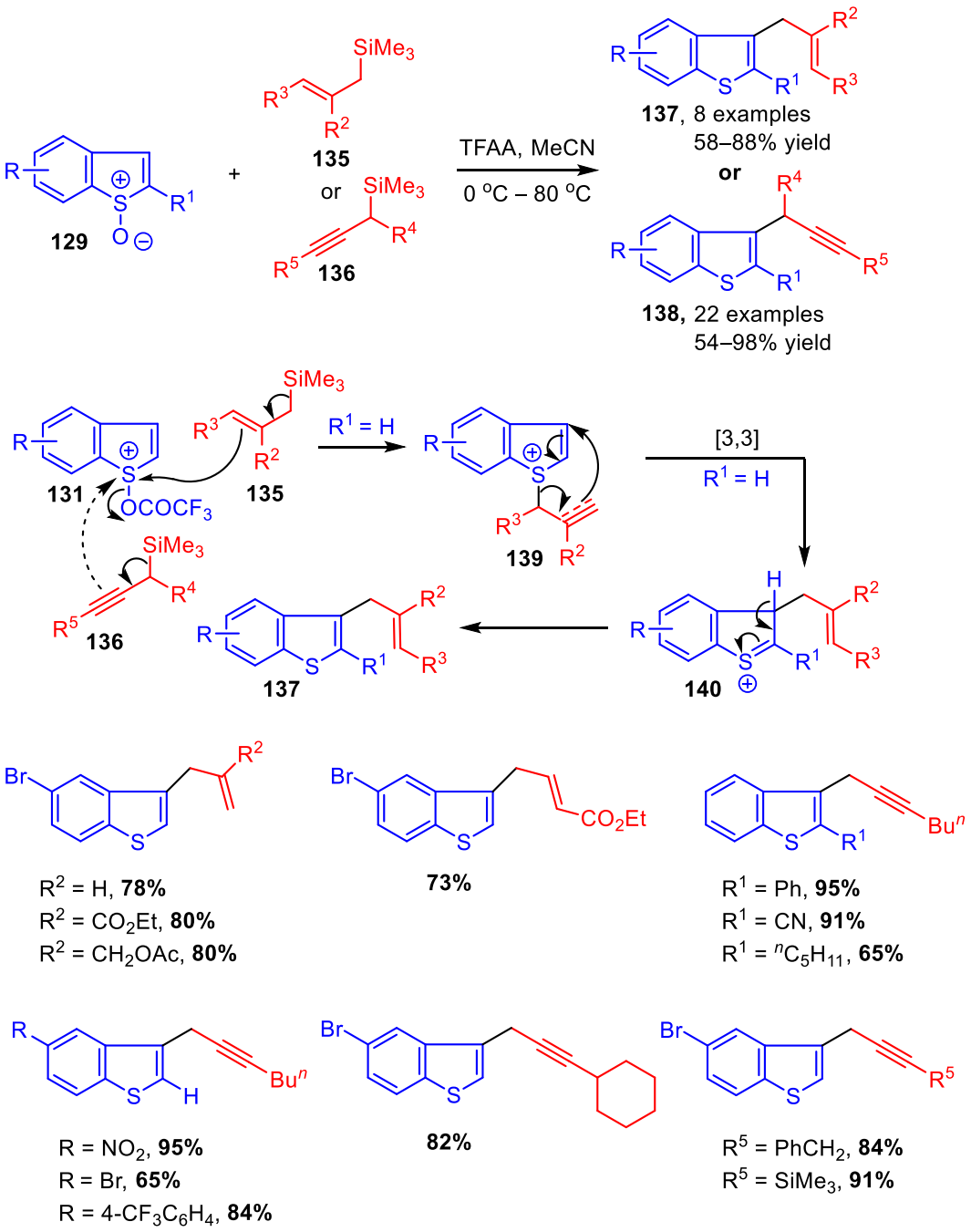
Proctor and co-workers have also shown recently that benzo[*b*]thiophene S-oxides **129**, readily prepared from the corresponding benzo[*b*]thiophenes by treatment with *m*-CPBA/BF_3.OEt_2, serve as useful precursors for highly-regioselective, metal-free synthesis of C3-arylated- and C-3 alkylated benzo[*b*]thiophenes **130** and **137-138**, respectively, under mild conditions (Schemes 51-52).[91] The overall strategy involves activation of the S–O bond of benzo[*b*]thiophene S-oxides **129** with trifluoroacetic anhydride (TFAA) for an interrupted Pummerer reaction with phenols (Scheme 51) or allyl-/propargyl-silanes **135-136** (Scheme 52) to form the intermediates **132**.

The **132** intermediates (with phenol) (Scheme 51) undergo spontaneous charge accelerated [3,3]-sigmatropic rearrangement, resulting in C–C bond formation, leading to the coupling products **130** *via* intermediates **133**-**134**, in a perfectly site-selective manner.[91] Thus, benzo[*b*]thiophene S-oxides **129**, when treated with trifluoroacetic acid anhydride (TFAA), and reacted with the phenol-coupling partner, the interrupted Pummerer reaction and, surprisingly, the resulting [3,3]-sigmatropic rearrangement occurred at or below ambient temperature. [91] After rearomatization of the phenol ring, thioacetal **134** was formed in 67% yield *via* intermediate **133**. Upon warming the reaction mixture to 45 °C in the presence of *p*-toluenesulfonic acid, thioacetal **134** opened to form the desired C3-arylated benzo[*b*]thiophenes **130** in high isolated yields, and complete control over regiochemistry with respect to both C3 of the benzo[*b*]thiophenes **130** and the *ortho* position of the phenol. The reaction tolerates several substituents, including both electron withdrawing and donating, at various position of the phenols as well as on the benzene ring of benzo[*b*]thiophene (Scheme 51).[91]



Scheme 51. One-pot tandem synthesis of 3-arylbenzo[*b*]thiophenes from benzothiophene-S-oxide.

The more challenging metal-free syntheses of C3-alkylated benzo[*b*]thiophenes **137**-**138,** were achieved by coupling the benzothiophene S-oxide **129** with either allyl silanes **135** or propargyl silanes **136,** respectively, furnishing a range of C3-allylated and C3-propargylated benzo[*b*]thiophenes **137** and **138**, with total regiocontrol. This involved a [3,3]-sigmatropic rearrangement of the intermediate **139**, and subsequent aromatization of intermediate **140** (Scheme 52).[91] Thus allylation proceeded smoothly with unsubstituted allylsilanes **135**, β-methyl substituted, as well as, with those bearing reactive functional groups including β-chloromethyl, β-methylacetate, β-bromo substituents and more. The propargylic silane coupling partner **136,** was also amenable to variation, with various primary silanes containing primary alkyl halide, secondary alkyl, phenyl and silyl substituents at the terminal position, as well as unsubstituted propargyl silanes, all undergoing efficient metal-free cross coupling, to afford 3-alkylated benzo[*b*]thiophenes **138** in high yields (Scheme 52).[91]



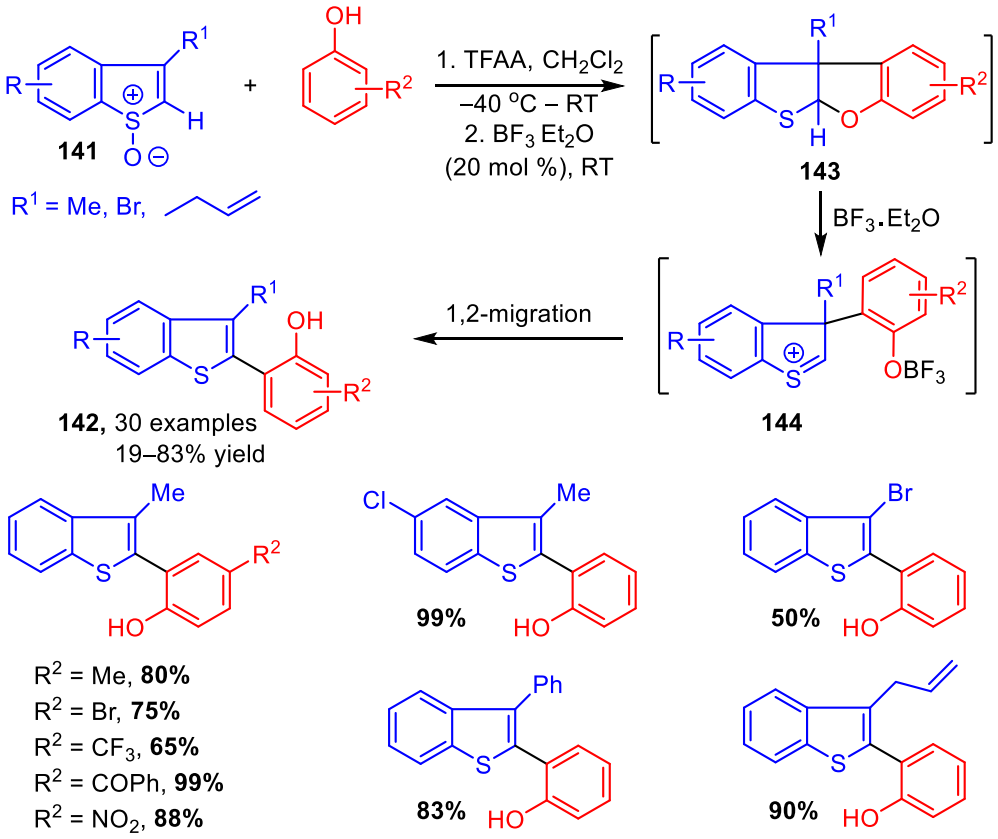
Scheme 52. One-pot tandem synthesis of 3-alkenyl/alkynyl benzo[*b*]thiophenes from benzothiophene S-oxide.

Subsequently, Proctor and group have reported a metal-free, regioselective synthesis of C2-functionalized benzo[*b*]thiophenes using readily available, 3-substituted benzothiophene S-oxides **141**, as precursors (Scheme 53-54).[92] By engaging phenols, and allyl/propargyl silanes **135**-**136** (cf. Scheme 52) as coupling partners in this strategy, C2-substituted benzo[*b*]thiophenes **142** (Scheme 53) and **147**-**148** (Scheme 54) were obtained under mild conditions, in good yields, and with complete regioselectivity with respect to the benzo[*b*]thiophene core and the coupling partners.

Thus, in a general procedure, treatment of C3-substituted benzothiophene-S-oxides **141** and phenols with TFAA in CH_2Cl_2 at low temperature, yielded first thioacetals **143**, which underwent $BF_3.Et_2O$-induced ring

opening and selective 1,2- migration of aryl group (*via* intermediate **144**) to yield C-2 arylbenzo[*b*]thiophenes **142** in good yields (Scheme 53).[92]

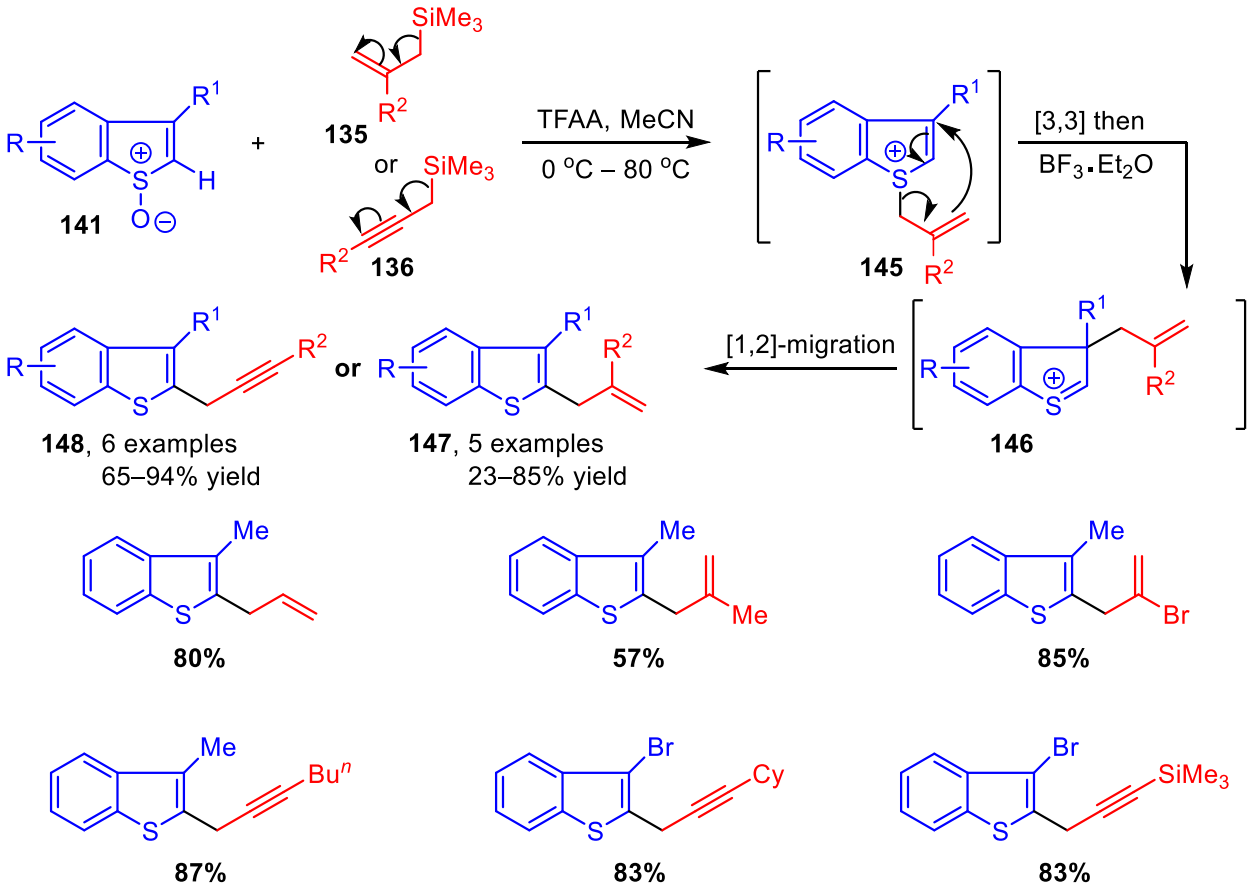
Subsequently, the coupling of S-oxide and phenols could be carried out in one-pot procedures directly leading to benzo[*b*]thiophenes **142** in good yields. The scope of this C2–CH arylation was demonstrated by varying the substituents on the phenols and benzothiophene S-oxides which resulted in various functional groups such as bromo, trifluoromethyl, keto, and nitro were well tolerated in the phenol-coupling partner with complete selectivity. Similarly, the reaction could tolerate many substitution patterns and functional groups like alkyl, bromo, propargyl, allyl and aryl groups at various positions of benzothiophene-S-oxide, including the C-3 substituent (allyl, Br, aryl, alkoxy, etc.).[92] Notably, in all of the cases, the phenol-coupling partner exclusively migrated from C3 to C2 in the 3,3-disubstituted benzothiophenium intermediate **144** formed after [3,3]-sigmatropic rearrangement, even when the existing C3 substituent had a comparable migratory aptitude.[92]



Scheme 53. Synthesis of 2- aryl-substituted benzo[*b*]thiophene *via* interrupted Pummerer reaction.

Procter et al. also investigated the coupling of allyl- and propargyl silanes **135**-**136** with 3-substituted benzothiophene-S-oxides **141**, in the interrupted Pummerer/[3,3]-sigmatropic rearrangement/1,2-migration cascade (*via* intermediates **145** and **146**) for the synthesis of C2-alkylated benzo[*b*]thiophenes **147**-**148**, respectively (Scheme 54). Thus, upon treating intermediate **145** with $BF_3{\cdot}OEt_2$, the [3,3]-sigmatropic rearrangement to C-3-allylated intermediate **146**, and its 1,2-shift to benzo[*b*]thiophene **147**, proceeded smoothly, even when the allyl silane **135** bore reactive functional groups such as β-bromo-, β -chloromethyl, and y-ester. Similarly, propargyl silanes **136** containing alkyl-, and silyl- and sterically hindered substituents at

the terminal position underwent efficient metal-free cross coupling to afford 2-alkyl benzo[*b*]thiophenes **148** in good yields (Scheme 54).[92]



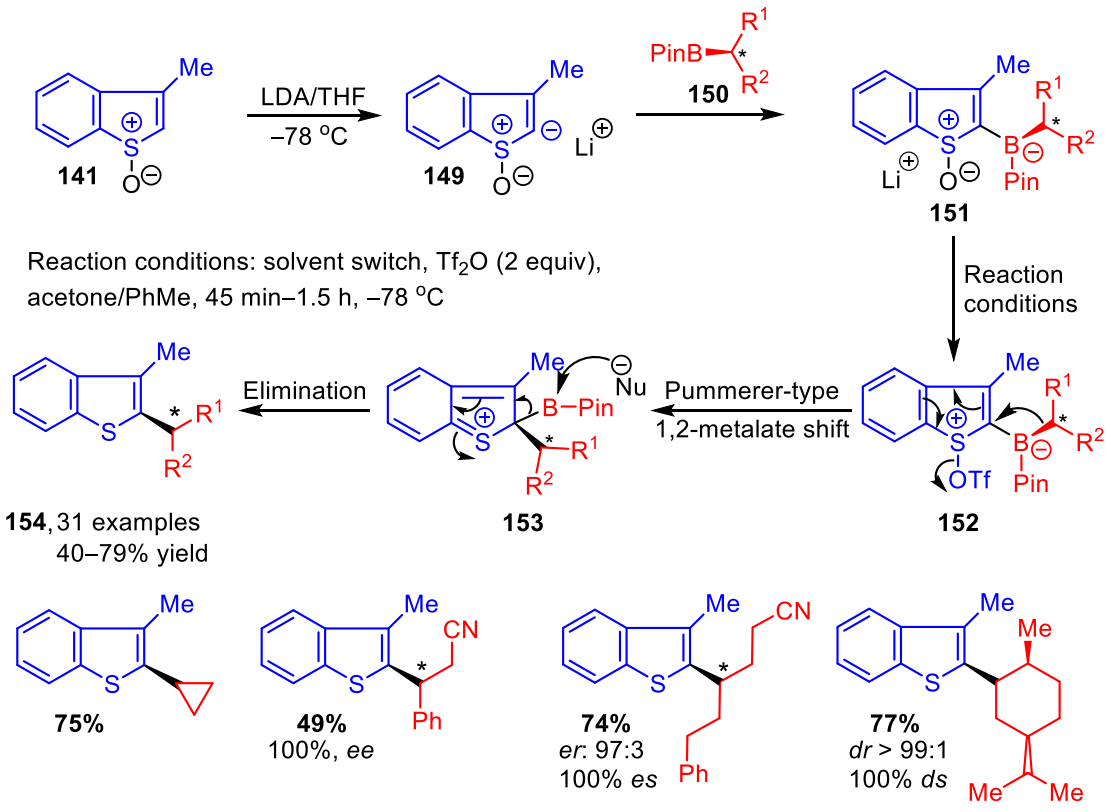
Scheme 54. Synthesis of 2-alkylated-benzo[*b*]thiophenes *via* interrupted Pummerer reaction.

Aggarwal and co-workers have reported a general method for the synthesis of enantioenriched 2,3-disubstituted-benzo[*b*]thiophenes **154**, utilizing coupling of C2-lithiated-benzothiophene-S-oxide **149** with boronic esters **150** to give the intermediate arylboronate complexes **151**, and subsequent Tf_2O-promoted S-O bond cleavage of arylboronate complexes **151** to trigger a Pummerer-type 1,2-metalate shift (**151**→**152**→**153**), yielding the coupled products **154** with complete enantiospecificity (Scheme 55).[93-94]

Lithiation of sulfoxide **141** at C2 was achieved by treatment with LDA at 78 °C, and subsequent borylation with boronic ester **150**, yielding the intermediate boronate complexes **151**. However, the success of the transformation depended on the identification of trifluoromethanesulphonic anhydride (Tf_2O), as an effective activator of the SO bond of the benzothiophene S-oxide boronate complexes **151**, which induced a stereospecific Pummerer-type 1,2-metalate shift.[93] The choice of solvent was also found to be important for the reaction efficiency and side-product formation; a toluene/acetone combination proved to be the best, providing higher yields of products.[93]

A range of structurally-diverse primary, secondary, and tertiary alkylboronic esters were successfully coupled with benzothiophene S-oxide **141**. Various synthetically-useful functional groups were tolerated, including alkenes, nitriles, carbamates, ethers, and perfluoroalkyl groups. The coupling of chiral secondary boronic esters, including both benzylic- and non-benzylic, afforded the corresponding chiral benzo[*b*]thiophenes in good yields and with complete enantiospecificity (Scheme 55).[93] Diastereospecific

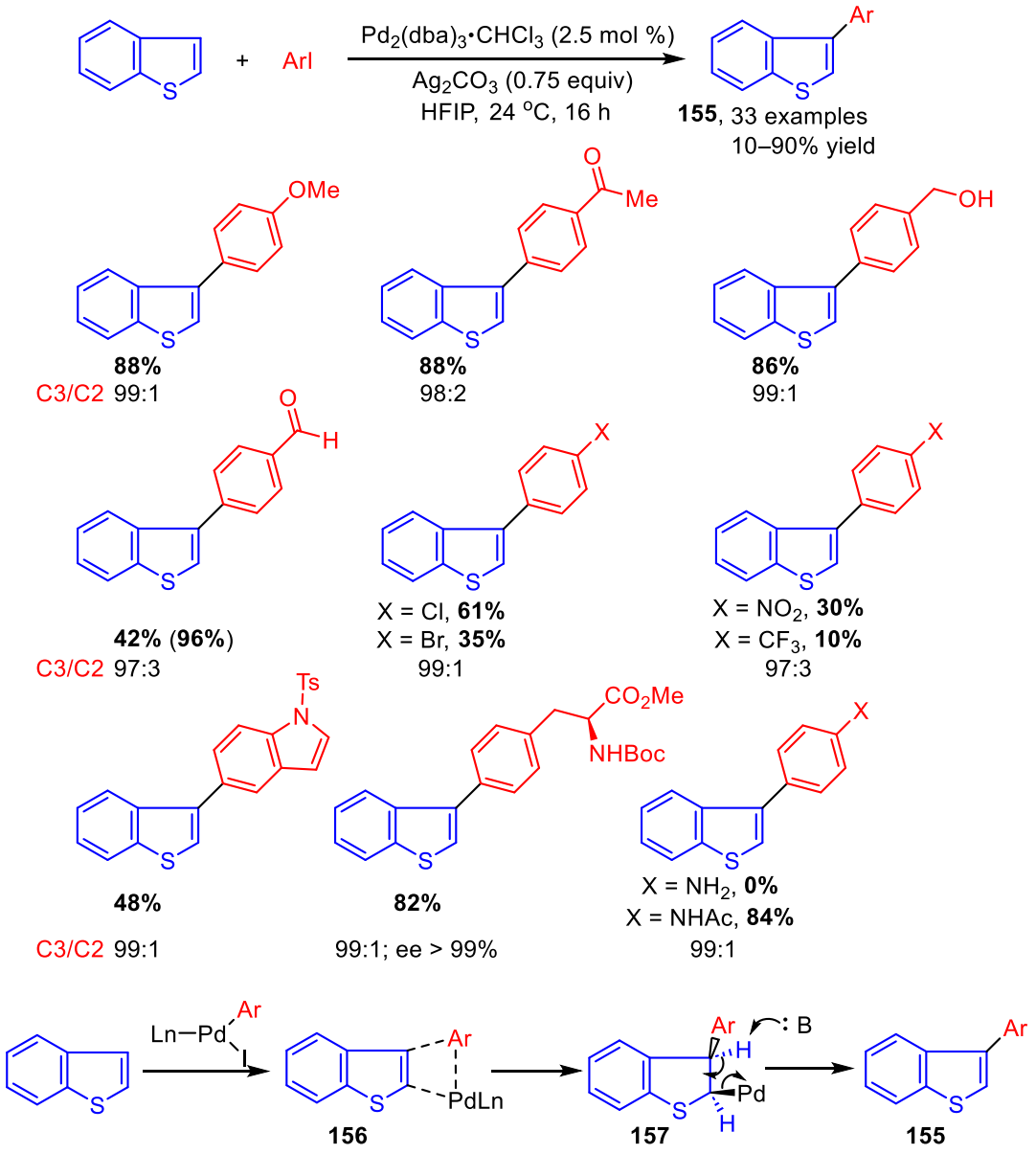
coupling of natural-product-derived boronic esters such as norbornene, the sterically-hindered terpenes menthol, pinene, and cholesteryl chloride, also reacted in good yields and with complete diastereospecificity (*ds*). Similarly, the benzo[*b*]thiophene-substrate scope was also found to be broad, and a variety of functional groups such as methyl, aryl and halide were tolerated at the C5 position.[93]



Scheme 55. Synthesis of enantio-enriched-2,3-substituted-benzo[*b*]thiophenes *via* rearrangement of 2-lithiated-benzothiophene-S-oxide and boronic esters.

The direct arylation of thiophenes and benzo[*b*]thiophenes is an important area of research, and, over the past few years, several methodologies allowing the direct arylation of benzo[*b*]thiophenes at the most acidic α-position have been developed. However, direct β-arylation of benzo[*b*]thiophenes has been found to be more challenging, and only a few examples, in the absence of directing groups, are reported. Larrosa and co-workers have recently reported, for the first time, β-arylation of thiophenes and benzo[*b*]thiophenes at room temperature (Scheme 56).[95] Previously, in 2010, Itami and co-workers have reported a methodology for the highly regioselective β-arylation of thiophenes with iodoarenes in the presence of $PdCl_2/P[OCH(CF_3)_2]_3$ as catalytic system.[96] Subsequently, a few reports were published employing arylboronic acids, aryltrimethyl silanes, aryl chlorides, and benzenesulfonyl chlorides as aryl donors.[95] However, all of these methods suffer from some limitations, requiring either high temperatures (80−150 °C) or TFA as solvent, thus limiting functional-group compatibility. Besides, some of these methods afford lower yields with electron-deficient aryl donors, requiring a large excess of this coupling partner, and/or suffer from moderate C-3/C-2 regioselectivity. Recently, Glorius and co-workers have reported a milder method that uses diaryliodineTrip(III) salt, (TRIP = 2,4,6-triisopropylphenyl) as coupling partners, allowing the selective β-arylation to proceed at 60 °C.[97]

Larrosa and co-workers have employed iodoarenes as coupling partners, and a combination of $Pd_2(dba)_3{\cdot}CHCl_3$ as a pre-catalyst and silver carbonate/ hexafluoroisopropan-2-ol (HFIP) as the most effective catalytic system. The reaction proceeded at 24 °C within 24 h, and displayed, in most cases, >99:1 regioselectivity (Scheme 56).[95] This methodology stands out for its operational simplicity, requiring no pre-functionalization of either starting materials. In addition, the reaction is insensitive to air and moisture, and proceeds at room temperature.



Scheme 56. Synthesis of 3-aryl benzo[*b*]thiophenes *via* room-temperature, regioselective palladium-catalyzed C-3- arylation of benzo[*b*]thiophenes.

The method tolerates a variety of substituents on the iodobenzene, including *para*-electron-donating- and withdrawing groups. Also, the method is compatible with benzylic alcohol and aldehyde and ketone functionalities. Chloro- and bromo- substitution was also tolerated, although with somewhat decreased yields. Highly electron-withdrawing *para*-substituents, such as nitro and trifluoromethyl groups, gave lower yields of products. Heteroiodoarenes, such as 1- and 2-iodothiophene and *N*-tosyl-5-iodoindole, could also be

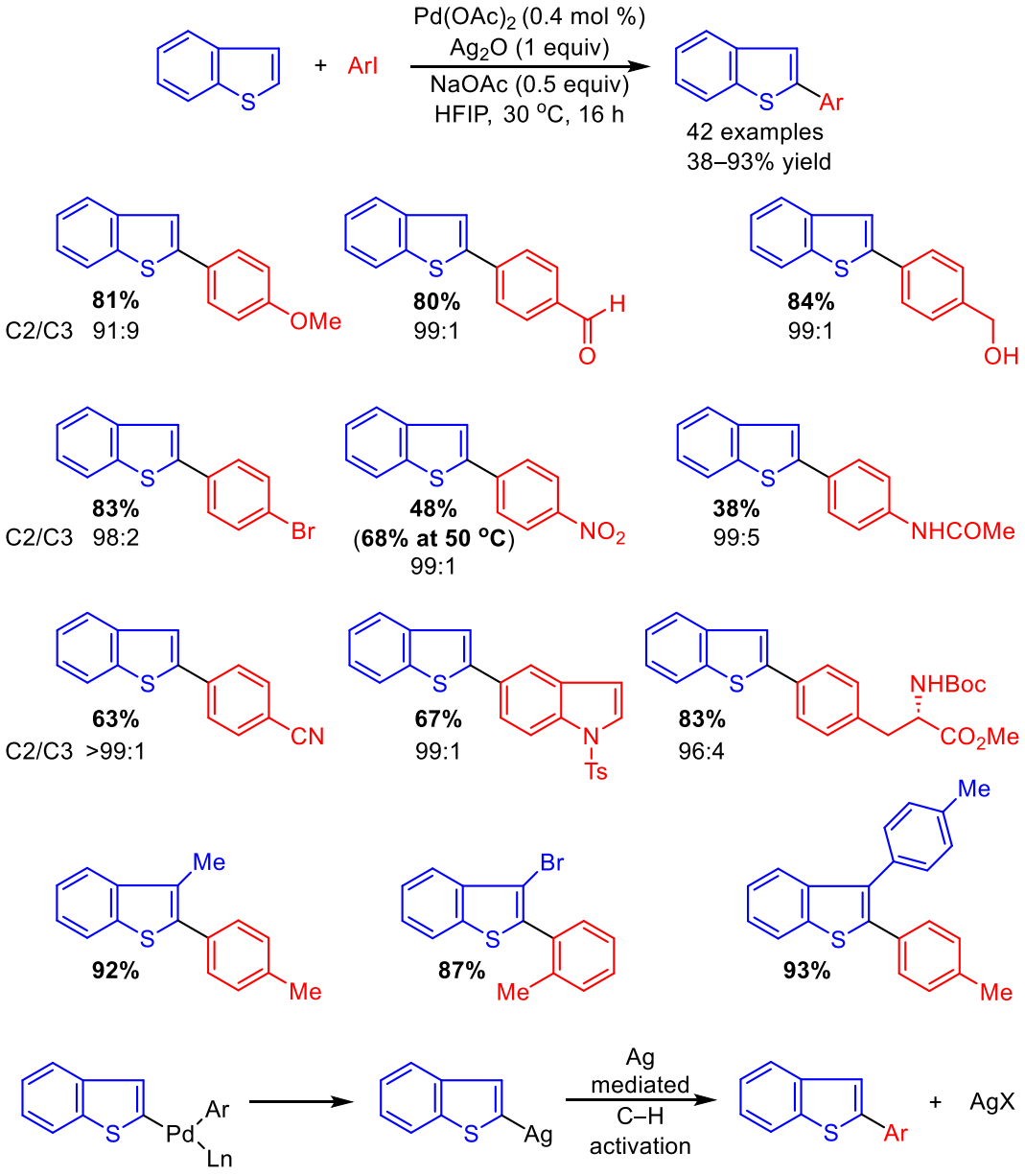
successfully employed as coupling partners. The methodology could be employed for the synthesis of non-natural amino acids, thus, coupling between benzo[*b*]thiophene and (S)-*N*-Boc-4-iodo-phenylalanine, yielding the desired product in high yield with 99% enantiomeric excess. 4-Iodoaniline was found not to be compatible under the reaction conditions; however, acetamide substitution gave the desired product in 84% yield.[95]

Preliminary mechanistic studies, including ^{13}C and kinetic evidence, suggest that this reaction proceeds *via* a concerted carbo-palladation across the thiophene double bond, followed by a base-assisted *anti*-elimination [**156**→**157**→**155**].[95]

The direct C2-arylation of benzo[*b*]thiophene was first demonstrated by Ohta in 1990.[98] Over the past decade, several more examples have been reported using Pd, Cu, or Ir as catalysts.[99] However, all the methods usually require the use of higher temperatures (100−150 °C), and high catalytic loading, which limits their functional-group compatibility. Larrosa and co-workers also reported recently, the first near-room-temperature C2-arylation of benzo[*b*]thiophenes using Pd/Ag salt catalyst, with only 0.4 mol % catalyst loading (Scheme 57).[100]

A combination of palladium (II) acetate/Ag_2O and sodium acetate in HFIP was found to be the most optimal catalytic system to obtain 2-arylated benzo[*b*]thiophenes selectively (Scheme 57). This methodology displays broad functional-group tolerance. Iodoarenes, bearing either electron-donating or electron-withdrawing groups in *para*-position, reacted to give excellent yields.[100] Alcohol, aldehyde, and ketone functionalities were also found to be compatible, along with halogen substituents, with the possibility to further functionalize the products *via* cross-coupling reactions. Highly electron-poor iodoarenes gave lower yields, although higher yields could be obtained by increasing the temperature to 50 °C. Similarly, amide and cyano-substituted iodoarenes afforded the 2-arylated products in 38% and 63%, respectively, while 4-iodoaniline was incompatible under these reaction conditions. Heterocyclic arenes such as *N*-tosyl-5-iodoindole afforded the desired α-functionalized product in 67% yield with excellent regioselectivity. The versatility of this protocol was further evidenced by coupling between benzo[*b*]thiophene and (*S*)-*N*-boc-4-iodophenylalanine, furnishing the desired product in 83% yield without any racemization. The 3-substituted-benzo[*b*]thiophenes bearing 3-bromo, 3-methyl or 3-aryl substituents also coupled with 4-iodotoluene, yielding 2-aryl-3-substituted-benzo[*b*]thiophenes (Scheme 57).[100]

The probable mechanism involves initial Ag(I) promoted C2-selective C−H activation, before trans-metalation to the Pd complex, and subsequent C−C bond formation. The use of very low concentrations of the Pd catalyst is possible due to the key role played by Ag. D/H scrambling, competition experiments, KIE, and kinetic studies support a mechanism involving Ag(I)−C−H activation.[100]



Scheme 57. Synthesis of 2-arylated-benzo[*b*]thiophenes *via* regioselective room temperature palladium catalyzed C-2 arylation of benzo[*b*]thiophenes.

3. Conclusion

The present article highlights some of the remarkable progress made in the syntheses of benzo[*b*]thiophenes in last 15 years, which makes benzo[*b*]thiophenes readily accessible to a large community of organic and medicinal chemists. The key advancement reported in the past include (a) development of a range of one-pot tandem reactions for construction of the thiophene ring of benzo[*b*]thiophene, (b) development of new metal-catalyzed approaches, (c) development of novel thiol surrogates, and (d) development of several useful photochemical methods, involving also photoredox catalysis in a few cases. Also noteworthy are the development of several curiosity-driven protocols for benzo[*b*]thiophenes, which focus on fundamental synthetic organic chemistry research exploring new reactivity, thus, advancing our mechanistic knowledge,

which may not have immediate (industrial) uses, but will find applications in the future. Nonetheless, the remaining long-standing challenges still include the need for more efficient, versatile, users-friendly, economically-viable methods for benzo[*b*]thiophenes, with improved functional-group diversity, employing non-thiophenolic precursors. Also, more environmentally sustainable methods such as transition-metal-free syntheses, shorter reaction-duration reactions, performed at ambient conditions, with minimal product purification, are also needed, including the application of electrochemistry, flow chemistry and more photochemistry. Application of synthetic methods for the syntheses of commercially-important benzo[*b*]thiophene-based drugs, related biologically-important benzo[*b*]thiophenes, and their large-scale syntheses is also a more challenging area, which needs further attention. We anticipate additional new developments, and creative and unconventional new approaches, towards the substituted-benzo[*b*]thiophenes core in the coming years.

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Authors' Biographies

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Hiriyakkanavar Ila received her Ph.D. from IIT Kanpur (1968). After a postdoctoral stay with Prof. R. L. Whistler at Purdue University, USA (1969), she joined the Central Drug Research Institute, Lucknow (1970), as a research scientist. In 1977, together with her husband, Prof. H. Junjappa, also a chemistry professor, she moved to North Eastern Hill University, Shillong to establish a School of Chemistry there. She became a professor in 1986, and joined the Department of Chemistry at IIT Kanpur, her alma mater, in 1995. After her superannuation (2007), she moved to Bangalore and joined Jubilant Biosys as a 'Principal Advisor, medicinal chemistry' (2007–2009). In January 2010, she moved to the New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bangalore, as an INSA Senior Scientist (2010–2014), where she is currently the 'Hindustan Lever Research Professor' (2015-2013). Presently she is INSA Honorary Scientist in JNCASR Bangalore. Prof. Ila was elected as a Fellow of the Indian Academy of Science, Bangalore (FASc) in 1990 and Fellow of the Indian National Science Academy (FNA) in 2001. She was awarded the Chemical

Research Society of India, Lifetime Achievement Award Gold Medal in 2019 and Silver Medal in 2001, the AV Ramarao Foundation Prize in Chemistry, and the Indian Chemical Society Medal. She has been an Alexander von Humboldt Fellow (1984–1985, with Prof. R. Gompper, Munich; 1998, 2000, 2001, 2003, and 2016 with Prof. L. F. Tietze, Gottingen; 2004, 2005, 2010, 2011, and 2015 with Prof. Paul Knochel, LMU, Munich), a Marie Curie Visiting Fellow at the University of Cambridge, UK (1995), an INSA exchange visitor to the UK and France (1993 and 1996), a visiting professor at Sevilla, Spain (1999), USC, Los Angeles (2002), and the University of Sendai, Japan (2012). She has delivered several plenary and invited lectures in various l international conferences as well as national conferences. She has co-authored more than 265 research publications in international journals, and her research activities revolve around the design and development of efficient new synthetic methods for biologically important molecules, especially heterocycles. Prof. Ila has been Scientific Editor of *Arkivoc* journal from India (2006-2013). Her biography was published in 'Lilawati's Daughters', a book published by the Indian Academy of Science, Bangalore (2008) on Indian Women Scientists, and recently in 'Vigyan Vidushi', a book published by Vigyan Prasar DST (2023), New Delhi on Indian women scientists to celebrate 'Azadi ka Amrut Mahotsav'.