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Metal-Free Synthesis of Aryl Selenocyanates and Selenaheterocycles with Elemental Selenium

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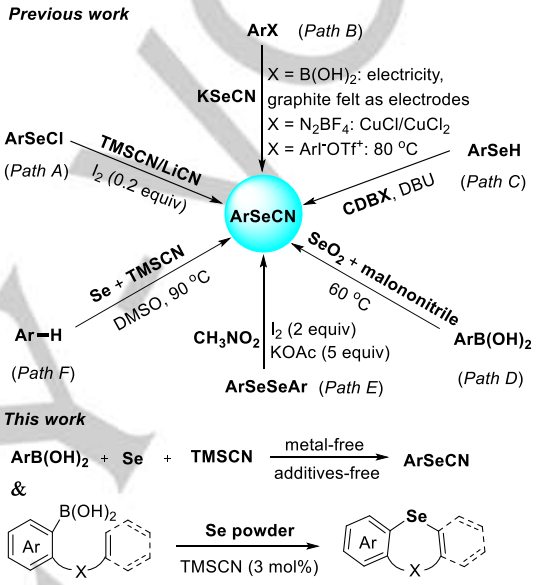
Abstract: We report a green method for the synthesis of aryl selenocyanates via a three-component reaction of arylboronic acids, Se powder and TMSCN under metal-free and additive-free conditions. Remarkably, TMSCN acts as not only the substrate, but also the catalyst. Various selenaheterocycles can be also accessed with a catalytic amount of TMSCN.

The organoselenium compounds represent a fundamentally important class of compounds because of their numerous applications in the field from pharmaceutical and agrochemical to catalysis, ligand and synthetic building blocks.[1] Over the past decade, aryl selenocyanates (ArSeCN) have attracted considerable attention since they displayed biological activity[2] and found wide applications in organic synthesis. For example, aryl selenocyanates have appeared as an important organoselenium reagent to construct various organic selenium compounds including monoselenides,[3a-3e] diselenides,[3f, 3g] trifluoromethyl (difluoromethyl) selenides,[3h,3i] selenoesters[3j] and selenium-containing ligands.[3k] In some cases, aryl selenocyanates could serve as a useful bifunctional reagent for the direct cyanoselenenylation of unsaturated C-C bonds.[4]

Such important roles in organic synthesis have encouraged chemists to develop more efficient methods to access aryl selenocyanates (Scheme 1). Initial approaches involving the use of PhSeCl as a selenium source allowed for the construction of aryl selenocyanates through a nucleophilic substitution reaction (Path A).[5] The most established methods based on the selenocyanation of arylboronic acids,[6] aryldiazonium salts[7] or aryliodonium salts[8] with KSeCN have been recently reported (Path B). Moreover, some examples included cyanation of selenophenol using cyanobenziodoxole hypervalent iodine reagent (CDBX) (Path C),[9] the reaction between diselenide and nitromethane (Path D)[10] as well as selenocyanation of arylboronic acids using malononitrile and selenium dioxide (Path E).[11] Despite these advances, the use of commercially unavailable reagents and the need for catalysts or additives eroded their overall appeal. From the perspectives of the atom economy, commercially availability and ease of handling, the use of selenium as selenium source would be a more attractive and promising alternative to previous organoselenium reagents undoubtedly. A recent work reported by Yan's group[12] that involved the oxidative C-H selenocyanation of electron-rich arenes with elemental selenium and TMSCN is highly attractive (Path F).



Scheme 1. Synthetic routes to aryl selenocyanates.

General, green and economical methods for the synthesis of organic selenocyanates are still lacking. Therefore, the development of a metal-free three-component reaction using Se powder as the selenium source with broad substrate scope would provide a complementary and alternative approach to aryl selenocyanates. In continuation of our efforts on the use of selenium powder in the construction of organoselenium compounds,[13] herein we report a three-component reaction of arylboronic acid,[14] selenium powder and TMSCN under metal-free conditions. This reaction features the use of commercially available raw materials, providing a facile route to aryl selenocyanates. Furthermore, it was first demonstrated that the presence of a catalytic amount of TMSCN can enable the radical cyclization of arylboronic acid with selenium powder to afford selenaheterocycles.

We commenced our work by evaluating the three-component reaction of [1,1'-biphenyl]-4-ylboronic acid, selenium powder and TMSCN (Table 1). After preliminary evaluation of reaction conditions, we found that this reaction conducted in DMSO at 90 °C for 24 h under air atmosphere provided the desired product **1b** in 92% yield in the absence of catalysts or additives (entry 1). Increasing the temperature properly could improve reaction efficiency, but more than 120 °C is counterproductive (entries 2-5). Interestingly, the employment of other solvents such as DMA, C_2H_5OH, toluene, THF and dioxane resulted in no formation of

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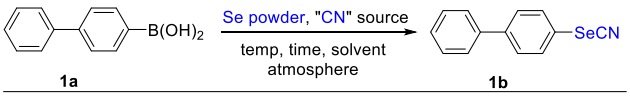
Table 1. Identification of the optimal reaction conditions[a]



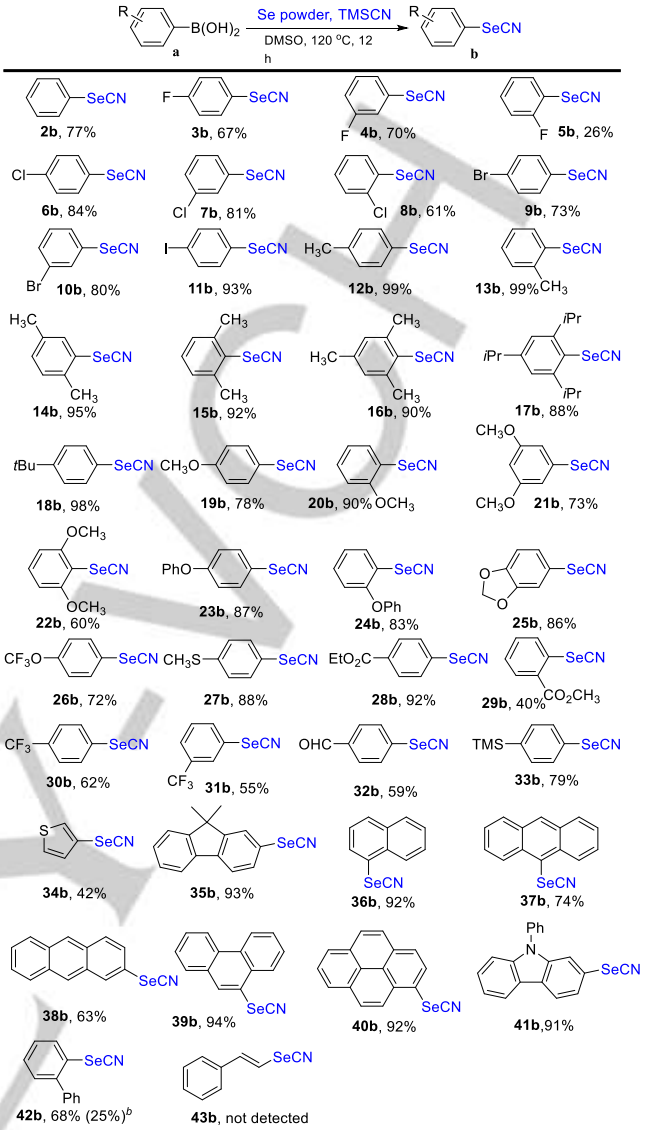
1a 1b

Entry	Temp (°C)	Solvent	"CN" source	Yield (%)
1	90	DMSO	TMSCN	92
2	100	DMSO	TMSCN	94
3	110	DMSO	TMSCN	95
4	120	DMSO	TMSCN	99
5	130	DMSO	TMSCN	79
6	120	DMA	TMSCN	0
7	120	ethanol	TMSCN	0
8	120	toluene	TMSCN	0
9	120	THF	TMSCN	0
10	120	dioxane	TMSCN	0
11	120	DMSO	acetonitrile	0
12	120	DMSO	tetrabutylammonium cyanide	0
13	120	DMSO	malononitrile	91
14	120	DMSO	potassium ferricyanide	37
15[b]	120	DMSO	TMSCN	99
16[c]	120	DMSO	TMSCN	92
17[d]	120	DMSO	TMSCN	96
18[e]	120	DMSO	TMSCN	92

[a]Reaction conditions: **1a** (0.2 mmol), Se powder (3 equiv), TMSCN (2 equiv), solvent (2 mL), 24 h, air, isolated yield. [b]Se powder (2.5 equiv). [c]Se powder (1.5 equiv). [d]O_2 atmosphere. [e]N_2 atmosphere.

product **1b** (entries 6-10). The combination of these results with previous work[12] implied that DMSO functions as not only the solvent but also the oxidant. Switching the nitrile source to acetonitrile or tetrabutylammonium cyanide led to no reaction (entries 11 and 12). In the case of malononitrile and potassium ferricyanide, product **1b** was isolated albeit in inferior yield (entries 13 and 14). The excellent yield was also observed when the transformation was performed under the O_2 atmosphere (entry 15). In contrast, the use of the N_2 atmosphere provided a decreased yield of **1b** (entry 16). Lowering the amount of selenium powder also decreased the yield of the desired product **1b** (entries 17 and 18).

Having established optimal reaction conditions, we next explored the scope with respect to arylboronic acids (Scheme 2). Arylboronic acids bearing halogen substituents proved to be very amenable to our protocol (**3b**-**11b**). Analogues with electron-neutral alkyl groups such as methyl, isopropyl and tertiary butyl reacted smoothly to provide the corresponding products (**13b**-**18b**) in excellent yields. The reactions showed the insensitivity towards sterically hindrance, as exemplified by substrates **13a**-**17a**. Either electron-rich or electron-withdrawn arylboronic acids were susceptible to the reaction conditions, furnishing the desired products (**19b**-**32b**) in moderate to excellent yields. A heterocyclic system was tried and a 42% yield of product **34b** was isolated. This reaction was also operable with a series of polycyclic boric acids, affording the desired products (**35b**-**41b**) in 63%-94% yields. In the case of vinylboronic acid, the reaction didn't take place (**43b**).



Scheme 2. Substrate scope for the synthesis of aryl selenocyanates. Reaction conditions: arylboronic acids (0.2 mmol), Se powder (3 equiv), TMSCN (2 equiv), DMSO (2 mL), 120 °C, 24 h, isolated yields. [b]The yield of byproduct dibenzo[*b*,*d*]selenophene (**1d**).

More and more efforts have been devoted to the development of the synthetic approaches to selenaheterocycles due to their wide applications.[15] However, most of the existing methods[16] suffered from tedious synthetic steps, narrow substrate scope and the use of unfavorable selenium reagents as well as transition metals. It was found that the treatment of [1,1'-biphenyl]-2-ylboronic acid with standard conditions resulted in a 25% yield of an unexpected byproduct **1d** (dibenzo[*b*,*d*]selenophene) aside from the desired product **42b**. Systematical examination of reaction parameters showed that the use of 3 mol% of TMSCN was essential and sufficient for the full conversion of [1,1'-biphenyl]-2-ylboronic acid to yield product **1d** in 98% yield (Scheme S4). Next, we examined the substrate scope for the synthesis of selenaheterocycles (Scheme 3). It was found that the presence of halogen and alkyl groups on ring B led to excellent yields of the desired products (**2d**-**4d**). Both electron-rich and electron-withdrawn groups were well tolerated (**5d**-**8d**). The substrate carrying a methyl or methoxyl group on ring A gave a different isolated yield (**4d** and **5d**) from the one carrying the same

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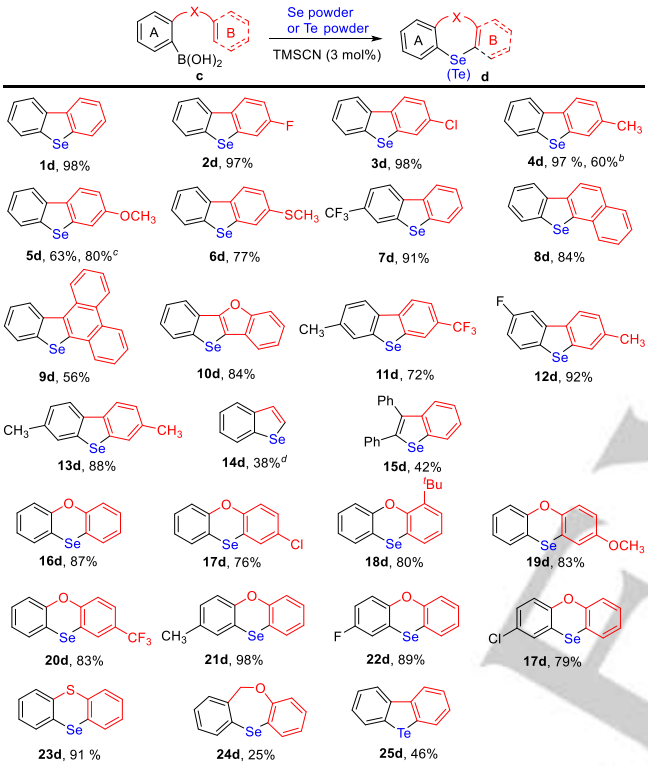
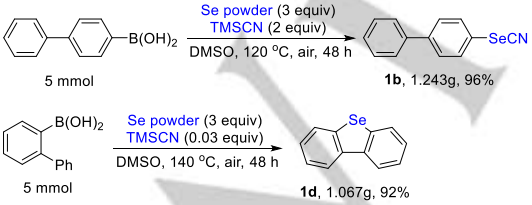
group on ring B. Ring B could be a fused ring or a heterocycle, providing the corresponding products (**8d**-**10d**) in 56%-84% yields. The substrates bearing two functionalized ring were also amenable to reaction conditions to afford the desired products (**11d**-**13d**) in good yields. Construction of the benzo[*b*]selenophene products (**14d** and **15d**) was achieved under the optimal conditions. Phenoxaselenines (**16d**-**22d**) and dibenzo[*b*,*e*][1,4]thiaselenine (**23d**) could be also accessed with this strategy. It was worth to note that this protocol provided a facile route to seven-membered selenaheterocycle (**24d**). In addition to Se powder, the reaction between [1,1'-biphenyl]-2-ylboronic acid and Te powder proceeded well to provide the dibenzo[*b*,*d*]tellurophene (**25d**).



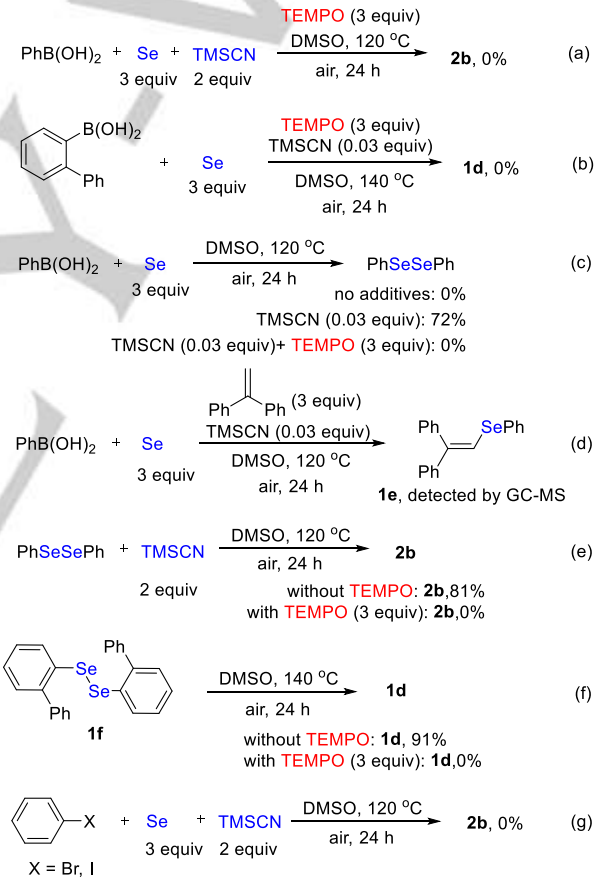
Scheme 3. Substrate scope for the synthesis of selenaheterocycles. [a]Reaction conditions: arylboronic acids (0.2 mmol), Se powder (3 equiv), TMSCN (0.03 equiv), DMSO (2 mL), 140 °C, 24 h, isolated yields. [b]Using (4-methyl-[1,1'-biphenyl]-2-yl)boronic acid as the substrate. [c]Using (4-methoxy-[1,1'-biphenyl]-2-yl)boronic acid as the substrate. [d]120 °C.



Scheme 4. Gram-Scale reactions.

It was found that gram-scale reactions for 48h afforded the products (**1b** and **1d**) in 96% and 92% yields that were comparable to those obtained in small-scale reactions, demonstrating the potential practicability of the protocol (Scheme 4).

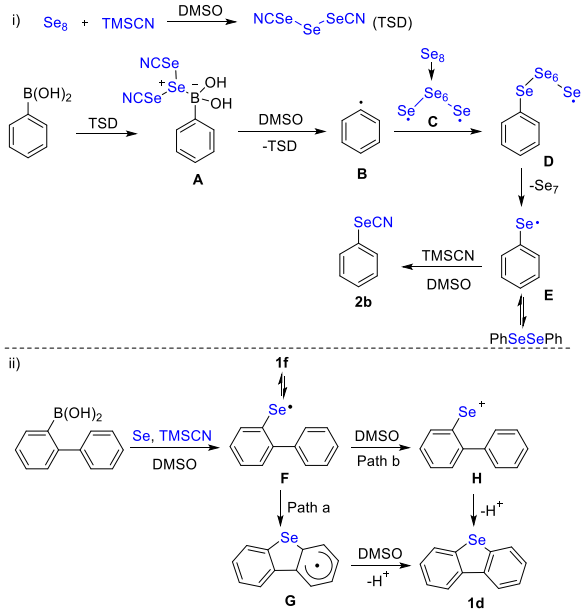
Several control experiments were performed to investigate how the TMSCN-promoted C-Se forming reaction occurs (Scheme 5). The presence of TEMPO inhibited the formation of products **2b** and **1d**, suggesting a radical way (Scheme 5a and 5b). The reaction between $PhB(OH)_2$ and selenium powder gave diphenyl diselenide in the presence of 3 mol% of TMSCN, and proceeded via a radical way as confirmed by the control experiment with the addition of TEMPO (Scheme 5c). Product **1e** was detected by GC-MS upon addition of ethene-1,1-diyldibenzene into the reaction between $PhB(OH)_2$ and selenium powder, supporting a PhSe radical intermediate (Scheme 5d). Control experiments showed biphenyl diselenide could be converted into the corresponding products **2b** via a radical way, providing further evidences for the selenium-centred radical acting as the key intermediate in the reaction (Scheme 5e). Even in the absence of TMSCN, diselenide **1f** could be converted into product **1d** (Scheme 5f). Finally, the replacement of arylboronic acids with aryl halides failed to furnish the desired aryl selenocyanates (Scheme 5g).



Scheme 5. Control experiments.

Based on these results and related literatures,[11,17] the reaction mechanism involving the formation of selenocyanatobenzene (**2b**) and dibenzo[*b*,*d*]selenophene (**1d**) was proposed in Scheme 6. i) Initially, triselenium dicyanide (TSD) could be generated from the reaction of selenium powder with TMSCN in DMSO. The reaction of pheylboronic acid with TSD forms intermediate **A**, followed by the oxidation of DMSO to give phenyl radical **B**. The radical **B** reacts with selenium biradical **C**, followed by the release of a Se_6 moiety to furnish PhSe radical **E**. The radical **E** then

reacts with TMSCN to provide product **2b**. ii) Similarly, a selenium-centred radical **F** is in-situ generated from [1,1'-biphenyl]-2-ylboronic acid and selenium powder. The radical cyclization of **F** offers intermediate **G** followed by oxidation to produce **1d** (Path a). Alternatively, **F** can be further oxidized to generate **H** followed by electrophilic cyclization to provide **1d** (Path b). Moreover, both **E** and **F** can undergo homocoupling to furnish diselenides in a reversible way.



Scheme 6. Possible reaction pathways.

In conclusion, we report the metal-free tandem synthesis of aryl selenocyanates and selenaheterocycles from arylboronic acids in the presence of elemental selenium. The investigations on the substrate scope reveal that both the steric hindrance and the electronic nature of substituents had little influence on the reaction efficiency, enabling wide substrate scope and excellent functional group compatibility. Preliminary mechanistic studies support the important role of TMSCN and the presence of a selenium-centred radical as the key intermediate.

Acknowledgements

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Keywords: selenocyanates • selenaheterocycles • selenium • metal-free • cyclization

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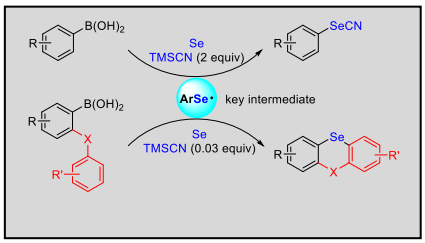

A facile method for the synthesis of aryl selenocyanates and selenaheterocycles under metal-free and additive-free conditions is developed.

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