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Copper-Catalyzed One-Pot Synthesis of Chalcogen-Benzothiazoles/Imidazo[1,2-*a*]pyridines with Sulfur/Selenium Powder and Aryl Boronic Acids

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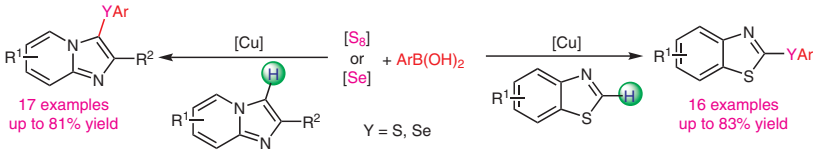

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Abstract An efficient and convenient copper-catalyzed oxidative chalcogenation of benzothiazoles and imidazo[1,2-*a*]pyridines with sulfur/selenium powder and aryl boronic acids was developed. This procedure allows access to a wide range of structurally diverse arylchalcogen-substituted benzothiazoles/imidazo[1,2-*a*]pyridines in good yields and with good functional group tolerance. A biological evaluation revealed that some of the obtained products exhibited in vitro antiproliferative activities on human-derived lung, stomach, esophageal, and breast cancer cell lines.

Key words benzothiazoles, imidazoheterocycles, chalcogenation, C–H activation, copper

Heterocyclic compounds are important structural motifs in a number of bioactive compounds and are used as crucial intermediates in the pharmaceutical industry.[1] Among various heterocycles, benzothiazoles and imidazo[1,2-*a*]pyridines have received considerable research attention due to the diverse pharmacological profile including their use as antitumor agents, RSK2 inhibitors, anti-inflammatory, antiviral agent, and SIRT1 agonist.[2] Moreover, these heterocycles are essential building blocks in the synthesis of functional materials such as charge transporters, industrial dyes and plant growth regulators.[3] Owing to the merits of benzothiazole and imidazo[1,2-*a*]pyridine derivatives, there is a strong incentive to develop new synthetic strategies geared towards these heterocyclic classes.[4]

Additionally, the nature of the substituent at either the 2- or 3-position of benzothiazoles and imidazo[1,2-*a*]pyridines has a profound influence on the biological and physical properties. Considering the importance of organochalcogenides (S, Se), scientific progress in the direct chalcogenation of both benzothiazoles and imidazo[1,2-*a*]pyridines has been made using chalcogen agents such as ArSH, ArSSAr, $ArSO_2Cl$, $ArSO_2Na$, $ArSO_2H$, and ArSeSeAr (Scheme 1a and b).[5] For example, the Zeni group reported a copper oxide nanoparticle-catalyzed synthesis of 2-(organochalcogen)thiazoles through direct C–H bond activation of benzothiazoles.[6] Subsequently, Braga reported a novel iodine-catalyzed chalcogenation of imidazo[1,2-*a*]pyridines with diaryl disulfides and diselenides.[7] Additionally, Wang developed an Eosin B-catalyzed direct sulfenylation of imidazo[1,2-*a*]pyridines with sulfinic acids through a photoredox process at room temperature.[8] However, the use of the above chalcogen agents has some drawbacks including unpleasant fumes, volatility, toxicity, cost, and moisture sensitivity. In contrast, a more straightforward and attractive alternate is to employ sulfur and selenium powder as stable and easily handled cross-coupling partners to construct C–S/C–Se bonds, avoiding the need for substrate pre-activation (Scheme 1c).[9] For example, Adimurthy and co-workers developed a facile approach to arylthio-substituted imidazo[1,2-*a*]pyridine derivatives from aryl halide and sulfur using catalytic copper(I) iodide.[10] Subsequently, Wu reported a protocol to access 2-arylselanyl-benzothiazoles from aryl halides and Se powder using $CuCl_2$ as a catalyst.[11] However, the need for an inert environment limits its usage and the synthetic compounds are rarely applied to biological activity estimation.

Recently, a system of $ArB(OH)_2$ and S_8 was used as an ideal and useful sulfanylation method for C–S bond formation.[12] Inspired by our longstanding interest in the development and application of imidazo[1,2-*a*]pyridine derivatives in medicinal chemistry,[13] herein we disclose an efficient and concise route to access 2-chalcogen-benzothiazoles and 3-chalcogen-imidazo[1,2-*a*]-pyridines via copper-cata-

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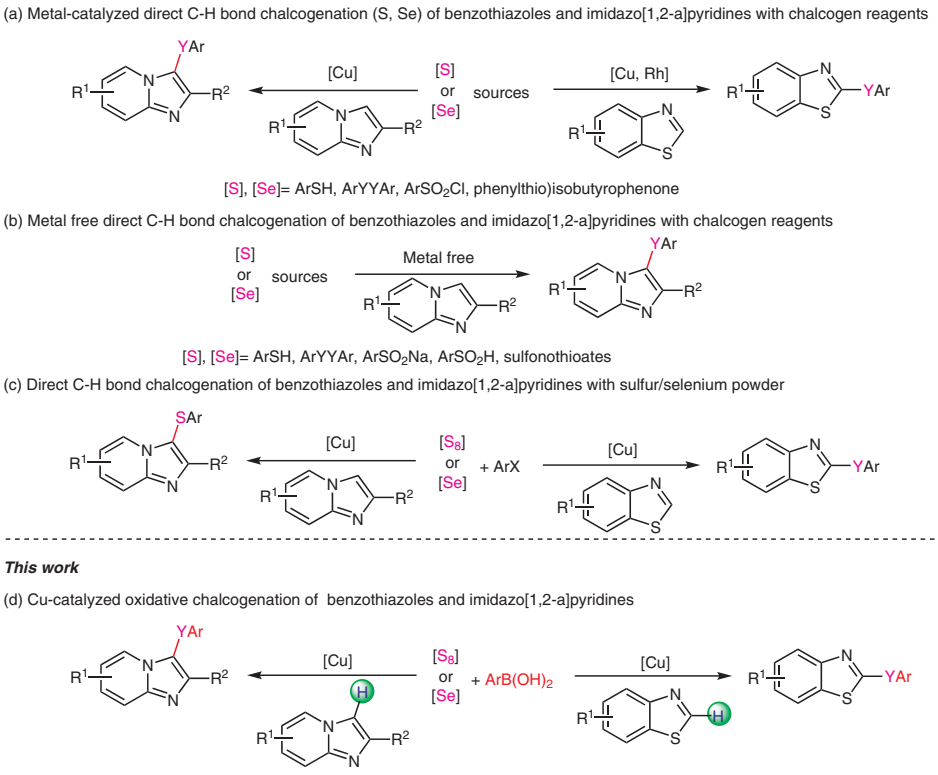
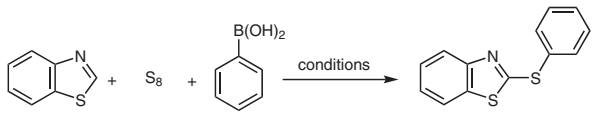


Scheme 1 Representative methods for the chalcogenation of benzothiazoles and imidazo[1,2-*a*]pyridines

lyzed oxidative chalcogenation of imidazo[1,2-*a*]pyridines/benzothiazoles with sulfur/selenium powder and aryl boronic acids (Scheme 1d).

We began our study by examining the reaction between benzothiazole (**1a**), phenylboronic acid (**2a**), and elemental sulfur (S_8) in *N*,*N*-dimethylacetamide (DMAc) by using CuI as catalyst at 130 °C (Table 1). Initially, various oxidants were investigated and the choice of oxidant was crucial. Only a trace amount of product was observed when H_2O_2 and O_2 were used (entries 1 and 2). When the reaction was carried out with TBHP and $Mn(OAc)_2$, no product **3a** was obtained (entries 3 and 4). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was also an inefficient catalyst for this transformation (entry 5). Among the various silver salts examined, Ag_2CO_3 was the most effective, and its use afforded **3a** in 70% yield (entries 6–9). Furthermore, the effects of various copper sources were examined. CuI was the optimal catalyst. Notably, other catalysts such as $Cu(OTf)_2$, $CuBr_2$, $Cu(OAc)_2$, and $CuCl_2$ led to significantly lower reaction yields (entries 10–13). Next, different solvents were tested using CuI as the catalyst and Ag_2CO_3 as the oxidant. There was no advantage when dimethyl sulfoxide (DMSO) was used as the solvent (entry 14). Shifting the solvent system to *N*,*N*-dimethylformamide (DMF), **3a** was isolated in 75% yield under the same conditions (entry 15). Furthermore, no improvements were observed when other solvents such as *N*-methyl-2-pyrrolidinone (NMP), xylenes, or 1,4-dioxane were employed (entries 16–18). Efforts to further enhance the yield by changing the base and ligand produced little improvements. Notably, ligands and bases commonly used in Cu-catalyzed reactions such as bpy, 4,5-diazafluoren-9-one, K_2CO_3, and K_3PO_4, led to lower yields under the current reaction conditions (entries 19–24). Further modifications of reaction concentration and temperature did not improve the yield of **3a**. Therefore, the conditions employed in entry 15 were chosen as the optimized reaction conditions.

Table 1 Optimization of the Reaction Conditions



1a **2a** **3a**

Entry[a]	Catalyst	Oxidant	Base	Solvent	Yield (%)[b]
1	CuI	O_2	Cs_2CO_3	DMAc	trace
2	CuI	H_2O_2	Cs_2CO_3	DMAc	trace
3	CuI	TBHP	Cs_2CO_3	DMAc	NR
4	CuI	$Mn(OAc)_2$	Cs_2CO_3	DMAc	NR
5	CuI	DDQ	Cs_2CO_3	DMAc	11
6	CuI	Ag_2CO_3	Cs_2CO_3	DMAc	70

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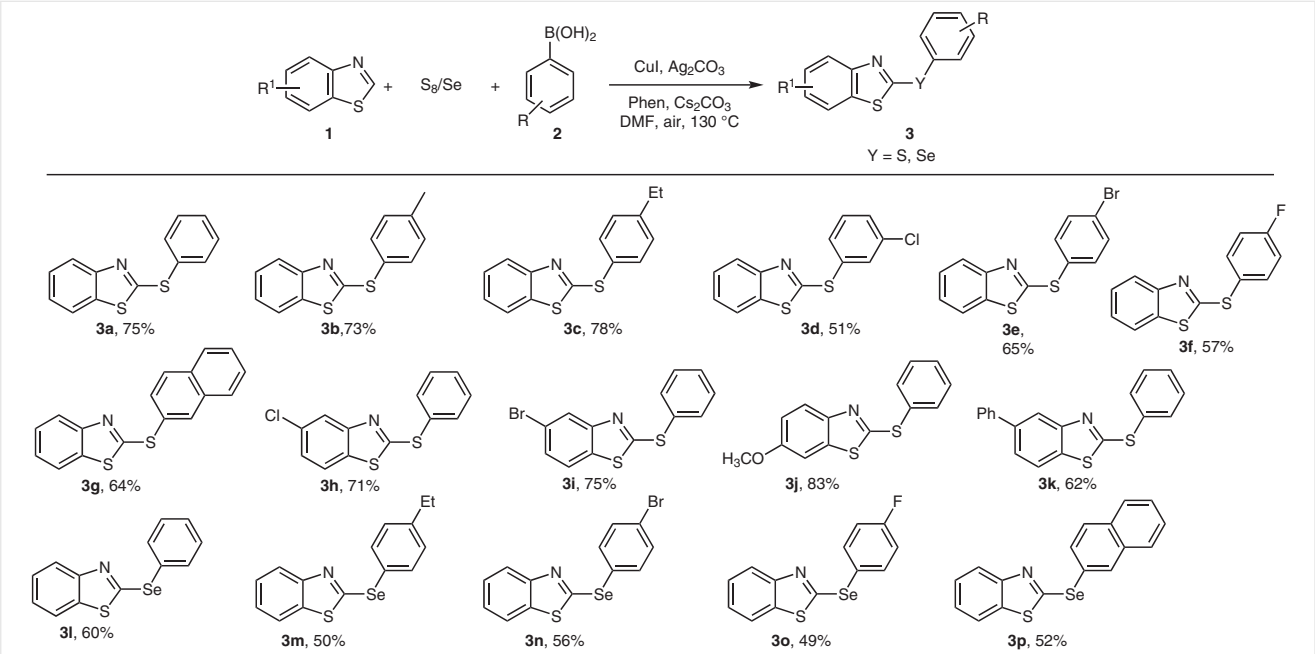
Entry[a]	Catalyst	Oxidant	Base	Solvent	Yield (%)[b]
7	CuI	$AgNO_3$	Cs_2CO_3	DMAc	33
8	CuI	AgOAc	Cs_2CO_3	DMAc	NR
9	CuI	AgOTf	Cs_2CO_3	DMAc	trace
10	$Cu(OTf)_2$	Ag_2CO_3	Cs_2CO_3	DMAc	21
11	$CuBr_2$	Ag_2CO_3	Cs_2CO_3	DMAc	40
12	$Cu(OAc)_2$	Ag_2CO_3	Cs_2CO_3	DMAc	62
13	$CuCl_2$	Ag_2CO_3	Cs_2CO_3	DMAc	55
14	CuI	Ag_2CO_3	Cs_2CO_3	DMSO	52
15	CuI	Ag_2CO_3	Cs_2CO_3	DMF	75
16	CuI	Ag_2CO_3	Cs_2CO_3	NMP	15
17	CuI	Ag_2CO_3	Cs_2CO_3	xylenes	trace
18	CuI	Ag_2CO_3	Cs_2CO_3	1,4-dioxane	NR
19	CuI	Ag_2CO_3	K_2CO_3	DMF	61
20	CuI	Ag_2CO_3	K_3PO_4	DMF	68
21	CuI	Ag_2CO_3	$KHCO_3$	DMF	NR
22[c]	CuI	Ag_2CO_3	Cs_2CO_3	DMF	NR
23[d]	CuI	Ag_2CO_3	Cs_2CO_3	DMF	65
24[e]	CuI	Ag_2CO_3	Cs_2CO_3	DMF	trace

[a] Reaction conditions: **1a** (0.25 mmol), S_8 (0.75 mmol), **2a** (0.5 mmol), catalyst (20 mol%), phen (20 mol%), oxidant (0.5 mmol), base (0.5 mmol) and solvent (1 mL) in air reacted for 10 h.
[b] Isolated yield.
[c] Without ligand.
[d] bpy (20 mol%) was used.
[e] 4,5-Diazafluoren-9-one (20 mol%) was used.

With the optimized reaction conditions in hand, the scope and generality of the chalcogenation reaction was investigated by using several structurally diverse benzothiazoles, arylboronic acids, and sulfur/selenium powder. The results, summarized in Scheme 2, demonstrate that the reaction has a high degree of functional group tolerance with a broad substrate scope. Generally, aryl boronic acid bearing both electron-donating (Me, Et) and electron-withdrawing (F, Cl, Br) groups with *meta* and *para* substitution were transformed into the 3-sulfanyl-benzothiazole derivatives with yields ranging from 51 to 78%. Fortunately, 2-naphthylboronic acid could also undergo this transformation to furnish the corresponding product **3g** using the CuI/Ag_2CO_3 system. Next, the effect of various benzothiazole components on the reactions with aryl boronic acids were examined. As demonstrated from the yields of products **3h–k**, both electron-withdrawing and electron-donating functionalities on the benzothiazole ring had little influence on the reaction efficiency. Most importantly, the reactions of benzothiazole, aryl boronic acid, and Se powder permitted the efficient synthesis of selenation products **3l–p** in 49–60% yield. Unfortunately, aliphatic boronic acids such as *n*-hexaneboronic acid were not suitable for the developed transformation.

Having established a simple approach for the copper-catalyzed C–S/C–Se bond formation via C–H bond activation, we next investigated whether valuable 3-chalcogen-imidazo[1,2-*a*]pyridines could be obtained using imidazo[1,2-*a*]pyridines as the coupling partner (Scheme 3).



Scheme 2 Chalcogenation of benzothiazoles with aryl boronic acids. *Reaction conditions*: **1** (0.25 mmol), S_8/Se (0.75 mmol), **2** (0.5 mmol), CuI (20 mol%), phen (20 mol%), Cs_2CO_3 (0.5 mmol), Ag_2CO_3 (0.5 mmol) and DMF (1 mL) in air reacted for 10 h at 130 °C. Isolated yields are given.

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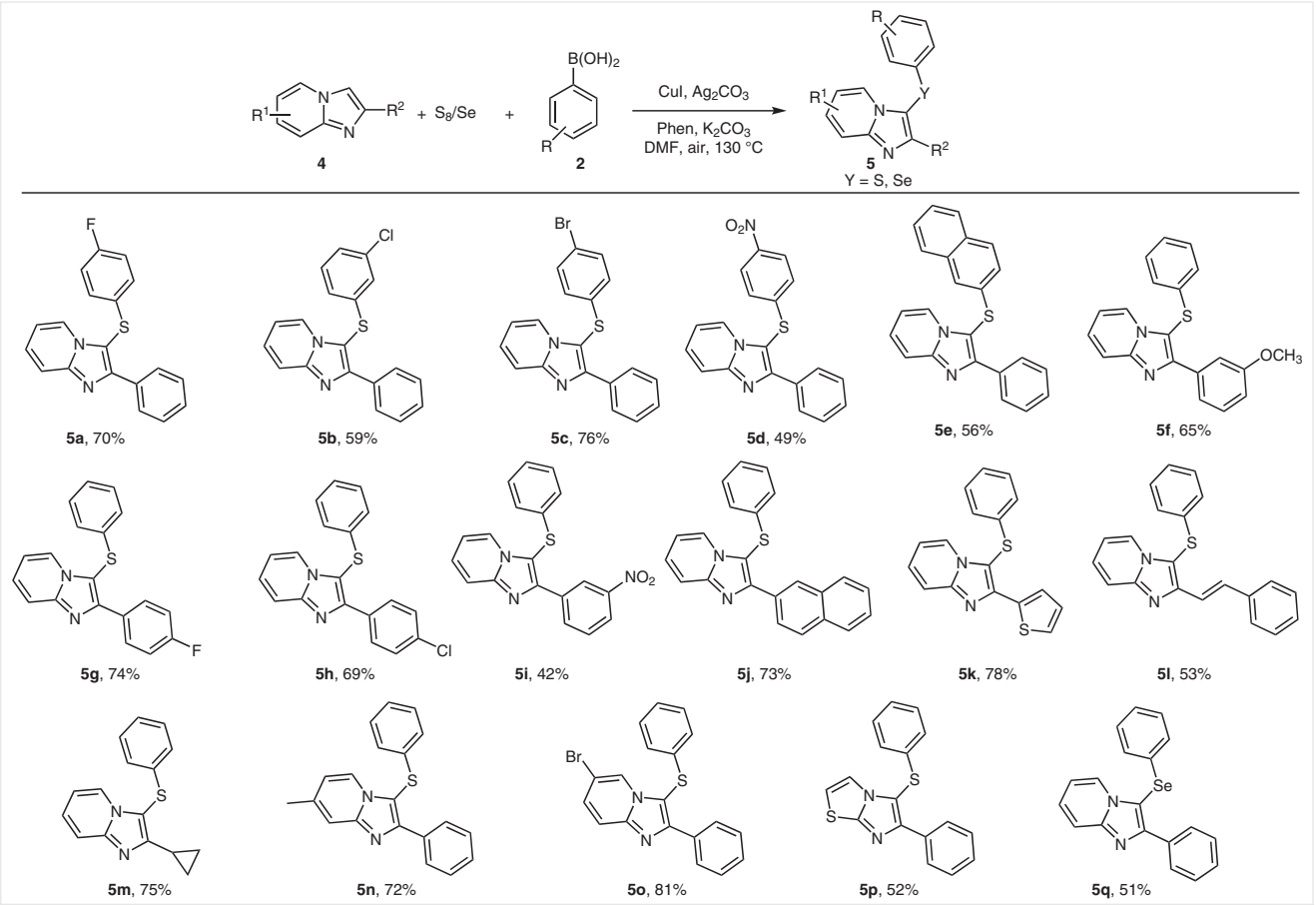
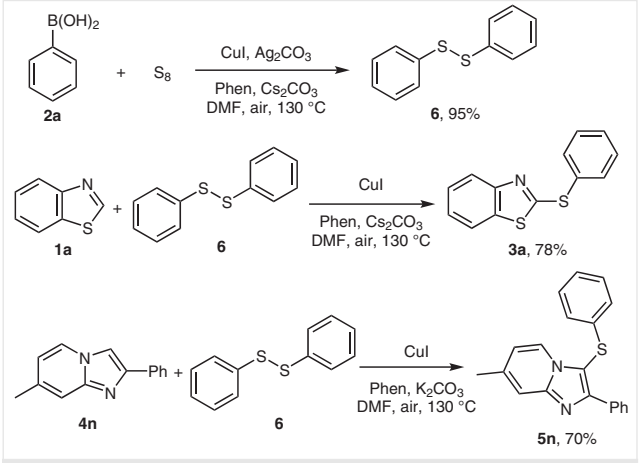


Scheme 3 Chalcogenation of imidazoheterocycles with aryl boronic acids. *Reaction conditions*: **4** (0.25 mmol), S_8/Se (0.75 mmol), **2** (0.5 mmol), CuI (20 mol%), phen (20 mol%), K_2CO_3 (0.5 mmol), Ag_2CO_3 (0.5 mmol) and DMF (1 mL) in air reacted for 10 h at 130 °C. Isolated yields are given.

The reactions of imidazo[1,2-*a*]pyridine with different substituted aryl boronic acids containing F, Cl, Br, NO_2 substituents afforded the desired products **5a–e** in 49–76% yields. It should be noted that the boronic acids with a strongly electron-withdrawing group (NO_2) gave the desired product **5d** in a markedly reduced yield of 49%. For the substituted imidazopyridines, both the electron-donating and the electron-withdrawing substituents were well tolerated, showing no obvious electronic effect for this transformation. Additionally, when naphthyl, thienyl, and (*E*)-2-styryl-substituted imidazo[1,2-*a*]pyridines were used, the desired products **5j–l** were obtained in 73, 78, and 53% isolated yields, respectively. Cyclopropylimidazo[1,2-*a*]-pyridine was also suitable for the present protocol, affording the aliphatic products **5m** in 75% yield. Additionally, the copper-induced sulfenylation protocol was applied to other imidazoheterocycles, such as imidazo[2,1-*b*]thiazoles. To our delight, the reaction proceeded smoothly, providing **5p** in 52% yield. Moreover, it was gratifying to find that the selenation reaction was viable in this protocol and provided 3-phenylselanyl-imidazo[1,2-*a*]pyridine **5q** in 51% yield.



Scheme 4 Control experiments

To further understand the possible mechanism of this novel reaction, a series of control experiments were performed (Scheme 4). Treatment of phenylboronic acid **2a** with S_8, under the standard conditions, gave diphenyl disul-

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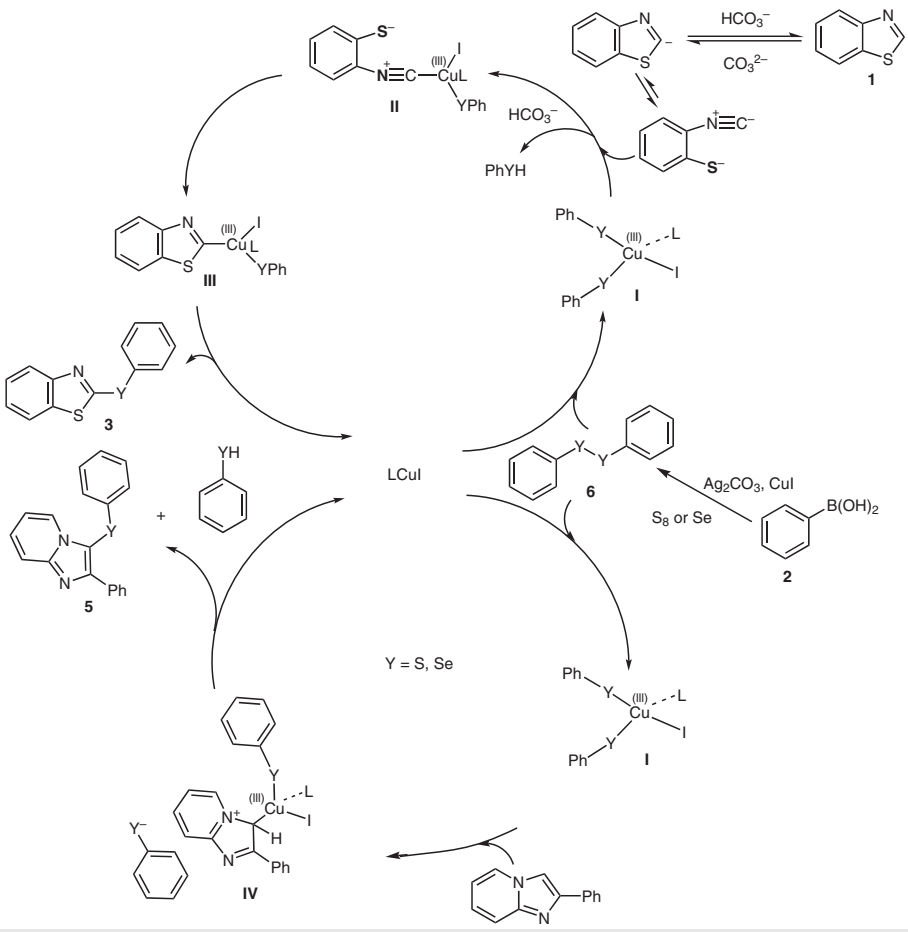
fide **6** in 95% yield. Furthermore, the reaction of **6** with **1a** or **4n** gave the desired products **3a** and **5n** in 78 and 70% yield, respectively. Based on the above experimental results and on previous reports,[10,12,14] two plausible mechanistic pathways are proposed (Scheme 5). For the 2-chalcogenbenzothiazole synthesis, initial deprotonation of benzothiazole produces a carbanion, which is in equilibrium with 2-isocyanothiolate.[15] The reactions of aryl boronic acids with S_8 and Se generate the disulfide and the diselenide **6**,[16] which further react with CuI to provide a Cu(III)-tetracoordinated square planar sulfate I. Then, 2-isocyanothiolate reacts with the copper species to form key intermediate II. Subsequent, intramolecular nucleophilic attack of the thiolate sulfur on the activated isocyanide carbon of I affords 2-benzothiazole-copper III. Finally, reductive elimination of intermediate III furnishes the desired product **3** and regenerates the Cu(I) catalyst. The mechanism for the synthesis of 3-chalcogen-imidazo[1,2-*a*]pyridines has also been investigated and matched the proposed pathway up to the electrophilic attack of imidazoheterocycles, which affords intermediate IV. Elimination and aromatization of IV gives the corresponding product **5**, CuI, and the thiol/selenol, which can be oxidized to the dichalcogenides **6**.

The antiproliferative activities for some of the compounds were evaluated in vitro against a panel of five human-derived tumor cell lines using a conventional MTT assay. Compound 5-fluorouracil, a widely used clinical cancer drug, was chosen as the positive control. The results show that compounds **5a** and **5k** displayed antiproliferative activities against PC-9 and H1975 with IC_{50} values of 6.68±0.82 and 15.30±1.18 μM, respectively, which was better than the positive control (Table 2). These results support our approach to devise novel antiproliferative drugs based on the framework of 3-chalcogen-imidazo[1,2-*a*]pyridines.

In summary, we report a new, effective, straightforward, and promising synthetic route to develop bioactive compounds such as 2-chalcogen-benzothiazoles and 3-chalcogen-imidazo[1,2-*a*]pyridines, with good yields under mild reaction conditions.[17] This method uses odorless and stable S_8/Se as the sulfur/selenium source and aryl boronic acids as reactants with functional group compatibility and a



Scheme 5 Proposed mechanism.

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Table 2 In Vitro Antiproliferative Activity of Products on H1975 (lung), PC-9 (lung), HGC-27 (stomach), EC-109 (esophageal), and MCF-7 (breast)

Compound	IC_{50} (μM)				
	H1975	PC-9	HGC-27	EC-109	MCF-7
3a	>80	>80	>80	>80	>80
3e	>80	>80	>80	61.68±1.79	>80
3f	>80	>80	>80	>80	>80
3g	>80	>80	>80	55.18±1.74	>80
3k	>80	>80	>80	>80	>80
3n	50.66±1.70	>80	>80	42.00±1.62	>80
3p	>80	>80	>80	45.72±1.66	>80
5a	>80	6.68±0.82	35.53±1.55	31.32±1.36	68.48±1.84
5c	>80	>80	72.71±1.86	>80	>80
5g	16.50±1.21	49.26±1.69	13.22±1.12	19.48±1.29	32.99±1.52
5h	17.20±1.23	22.38±1.35	15.62±1.98	27.26±1.44	46.43±1.67
5j	53.92±1.73	57.25±1.76	44.34±1.65	40.63±1.61	15.44±1.19
5k	15.30±1.18	44.03±1.64	46.57±1.68	33.88±1.53	17.07±1.23
5-Fluorouracil	43.31±1.63	47.96±1.68	6.04±0.78	6.49±0.81	13.78±1.13

broad substrate scope. Importantly, some synthesized compounds displayed antitumor activity by a MTT assay, supporting the value of this method.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609758.

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(17) **General procedure**: DMF (1 mL) was added into a flask charged with benzothiazole (**1**; 0.25 mmol), S_8 or Se (0.75 mmol), aryl boronic acid (**2**; 0.5 mmol), CuI (0.05 mmol), phen (0.05 mmol), Cs_2CO_3 (0.5 mmol), and Ag_2CO_3 (0.5 mmol). The mixture was stirred at 130 °C in air for 10 h. Then, the reaction was cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with H_2O (10 mL). The aqueous layer was extracted twice with ethyl acetate (5 mL) and the combined organic phase was dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by flash column chromatography (silica gel, PE–EtOAc, 15: 1 to 10: 1) to afford the desired products.
2-(Phenylthio)benzo[*d*]thiazole (3a): Purified by using a flash chromatography column (PE/EtOAc, 15: 1); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.4 Hz, 1 H), 7.75–7.73 (m, 2 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.52–7.46 (m, 3 H), 7.42–7.38 (m, 1 H), 7.28–7.24 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 154.1, 135.7, 135.5, 130.6, 130.1, 130.1, 126.3, 124.5, 122.1, 120.9; IR (KBr): 2922, 1581, 1456, 1425, 1309, 1236, 1080, 1007, 752 cm^{-1}; HRMS *m*/*z* [M$^+$+H] calcd. for $C_{13}H_{10}NS_2^+$: 244.02492; found: 244.02441
3-((4-Fluorophenyl)thio)-2-phenylimidazo[1,2-*a*]pyridine (5a): Purified by using a flash chromatography column (PE/EtOAc, 5:1); white solid; mp 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 7.0 Hz, 1 H), 8.20 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 9.0 Hz, 1 H), 7.46–7.31 (m, 4 H), 6.99–6.86 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7 (d, J_{C-F} = 244.9 Hz), 151.5, 147.2, 133.4, 130.2 (d, J_{C-F} = 3.6 Hz), 128.8, 128.6, 128.5, 127.7 (d, J_{C-F} = 7.8 Hz), 126.9, 124.5, 117.9, 116.7 (d, J_{C-F} = 21.0 Hz), 113.3, 106.7; IR (KBr): 2924, 2852, 1489, 1346, 1219, 1080, 735 cm^{-1}; HRMS: *m*/*z* [M$^+$+H] calcd. for $C_{19}H_{14}FN_2S^+$: 321.08562; found: 321.08527.

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