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Urea Hydrogen Peroxide and Ethyl Lactate, an Eco-Friendly Combo System in the Direct C(sp^2)−H Bond Selenylation of Imidazo[2,1-*b*]thiazole and Related Structures

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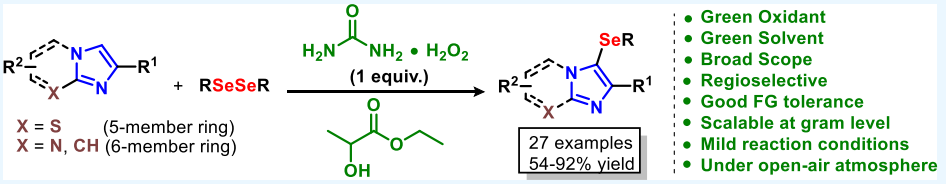

ABSTRACT: Herein, we describe a urea hydrogen peroxide-mediated sustainable protocol for the synthesis of selenylated imidazo[2,1-*b*]thiazole by using half molar equivalent diorganyl diselenides in ethyl lactate as a greener solvent. The reaction features high yields, easy performance on gram scale, metal-free conditions, as well as applicability to imidazopyridine and imidazopyrimidine.

INTRODUCTION

In the past few years, the functionalization of 5-membered N-heterocyclic privileged structures has been an emerging theme in organic synthesis,[1ab−c] medicinal chemistry,[1de−f] and material science.[1g,h] Among such structures, imidazole-containing heteroarenes, e.g., imidazo[2,1-*b*]thiazole (IT), imidazo[1,2-*a*]pyridine (IP), and imidazo[1,2-*a*]pyrimidine, are of interest among the scientific community.[2−4] These structures are widely used for biological and pharmaceutical applications (Figure 1). A vast number of commercially available drugs have imidazoheteroarenes in their core structure, e.g., alpidem **i** (as an anxiolytic),[3b] zolpidem **ii** (as a sedative),[3b] pifithrin-β **iii** (as a potent p53 inhibitor),[4f] miroprofen **iv** (as an analgesic),[4g] zolimidine **v** (for the treatment of peptic ulcer),[3b] and divaplon **vi** and fasiplon **vii** (as nonbenzodiazepine anxiolytic drugs)[4h] (Figure 1). Additionally, their derivatives are useful in the field of material sciences.[5] Therefore, their synthesis and functionalization have received considerable attention.[2−4]

Similarly, the construction of a C−Se bond is a very important transformation in organic synthesis, as structures with this linkage exhibit fascinating biological and medicinal properties.[6,7] Such compounds are renowned for their biological properties, mainly due to their anti-Alzheimer's, anti-inflammatory, antioxidant, and anticancer activities.[8−11] Besides, their role in modern organic chemistry and material science is undeniably very important.[12]

Considering the biological relevance of organoselenium compounds and therapeutic properties of imidazoheteroarenes, molecular hybridization of these structures could lead to molecules (e.g., compound **viii**−**xi**, Figure 1) with interesting biological properties.[13,14] There are several interesting methods in the literature to access such a hybrid structure. In this regard, different strategies are available in the literature for their synthesis, involving transition-metal catalysis, transition-metal-free catalytic approach, photoinduced transformation, solvent-free approach, etc.[6b,c,7,15] Therefore, continuous search for an alternative and greener approach involving benign solvents for the synthesis of such hybrid structure is a topic of interest.

Due to growing environmental concerns, application of biomass-derived solvents in cross-coupling reactions and C−H functionalization is gaining attention.[16−18] Among these solvents, ethyl lactate (EL) is a sustainable and economically viable alternative to traditional solvents.[19] Similarly, in organic transformations, urea hydrogen peroxide (UHP) is considered a safe, cheap, stable, and green oxidizing agent.[20]

As part of our wider research program aimed at developing and designing sustainable processes in the C(sp^2)−H bond functionalization and chalcogenation of biologically relevant

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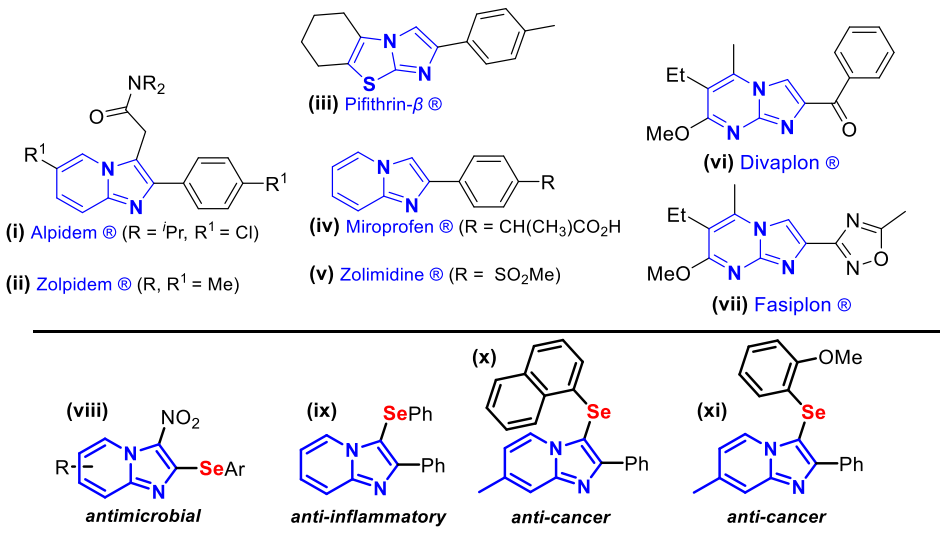


Figure 1. Imidazoheteroarenes-based drugs and their selenylated hybrids.

structures,[21,22] herein we report, for the first time, UHP-mediated, C(sp^2)−H bond seleno-functionalization of IT core in ethyl lactate as solvent. Our new regioselective, broader, and metal-free approach worked effectively using a half-molar equiv of diorganyl diselenides, without the need of any catalyst, under an air atmosphere. The reaction was also successfully extended to IP and imidazo[1,2-*a*]pyrimidine.

RESULTS AND DISCUSSION

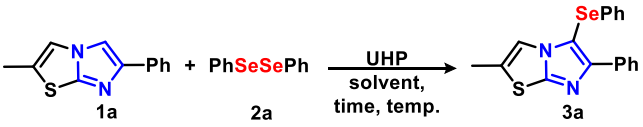
To identify the optimum reaction conditions, IT **1a** and half molar equiv of diphenyl diselenide **2a** were used as model substrates. These substrates were then tested under various conditions (Table 1). Initial screening was performed using only CH_3CN as solvent (Table 1, entry 1) for 3 h at 60 °C, which was completely ineffective. When 1 molar equiv of UHP was used, the desired product **4a** was obtained in a 90% yield (Table 1, entry 2).

In the next step, the effect of solvent on the reaction was screened (Table 1, entries 3−12). It was observed that THF, DMSO, and water were not very effective solvents (entries 3,4,5 respectively). Afterward, we planned to test biomass-derived solvents, e.g., 2-methyl THF, EtOH, glycerol, PEG-200, PEG-400, EL, and dimethyl carbonate (Table 1, entries 6−12). Among them, EL presented better results (Table 1, entry 11). Considering the greener effect of EL than CH_3CN,[23] we decided to perform further screening in EL. Subsequently, the influence of time (entries 13, 14), temperature (Table 1, entries 15, 16), and the stoichiometric quantity of UHP on the reaction system was explored (entries 17, 18). Any variation in time, temperature, or amount of UHP resulted in the selenylated product 3a in a lower yield (Table 1, entry 11 vs 12−17).

After ascertaining the best reaction condition (Table 1, entry 11), the applicability of various diorganyl diselenides and other IT as well as other imidazole-containing *N*-heteroarenes, e.g., IP and imidazo[1,2-*a*]pyrimidine, were screened (Schemes 1−3).

The selenylation of IT worked effectively for structurally diverse diselenides **2** (Scheme 1). Diaryl diselenides **2** with electron-donating (R = Me, OMe) and electron-withdrawing (R = F, Cl) at the *p*-position successfully afforded the corresponding products in good to excellent yields (81−88%; **3b−e**). Similarly, *m*-CF_3-substituted diselenide was also effective (**3f**).

Table 1. Optimization of Reaction Conditions[a]



entry	solvents (1 mL)	time (h)	tempt. (°C)	UHP (equiv)	yield (%)[b]
1	CH_3CN	3	60		N.R.
2	CH_3CN	3	60	1	91
3	DMSO	3	60	1	N.R.
4	THF	3	60	1	55
5	H_2O	3	60	1	35
6	2-Me THF	3	60	1	60
7	EtOH	3	60	1	40
8	glycerol	3	60	1	52
9	PEG-200	3	60	1	60
10	PEG-400	3	60	1	68
11	**ethyl lactate**	**3**	**60**	**1**	**92**
12	dimethyl carbonate	3	60	1	78
13	ethyl lactate	4	60	1	90
14	ethyl lactate	2	60	1	72
15	ethyl lactate	3	50	1	79
16	ethyl lactate	3	70	1	91
17	ethyl lactate	3	60	0.8	78
15	ethyl lactate	3	60	1.2	88
16	CH_3CN	3	60		N.R.
17	CH_3CN	3	60	1	91
18	DMSO	3	60	1	N.R.

[a]Reaction conditions: **2a** (0.20 mmol), **3a** (0.11 mmol), solvent (1 mL), under open-air atmosphere. [b]Isolated yields.

It was observed that the steric hindrance of the *o*-substituted diselenides showed a weaker negative influence on the yields as compared to the respective *p*-derivatives (**3g−h** vs **3b−c**). However, 1,2-di(naphthalen-1-yl)diselenide **2i** (a sterically bulkier substrate) resulted in the desired selenylated product **3i** in a 75% yield. To our delight, it was observed that C-2 heteroaryl diselenide **2j** provided the desired selenide **3j** with a 70% yield. In the case of dibenzyl diselenide **2k**, the benzylated

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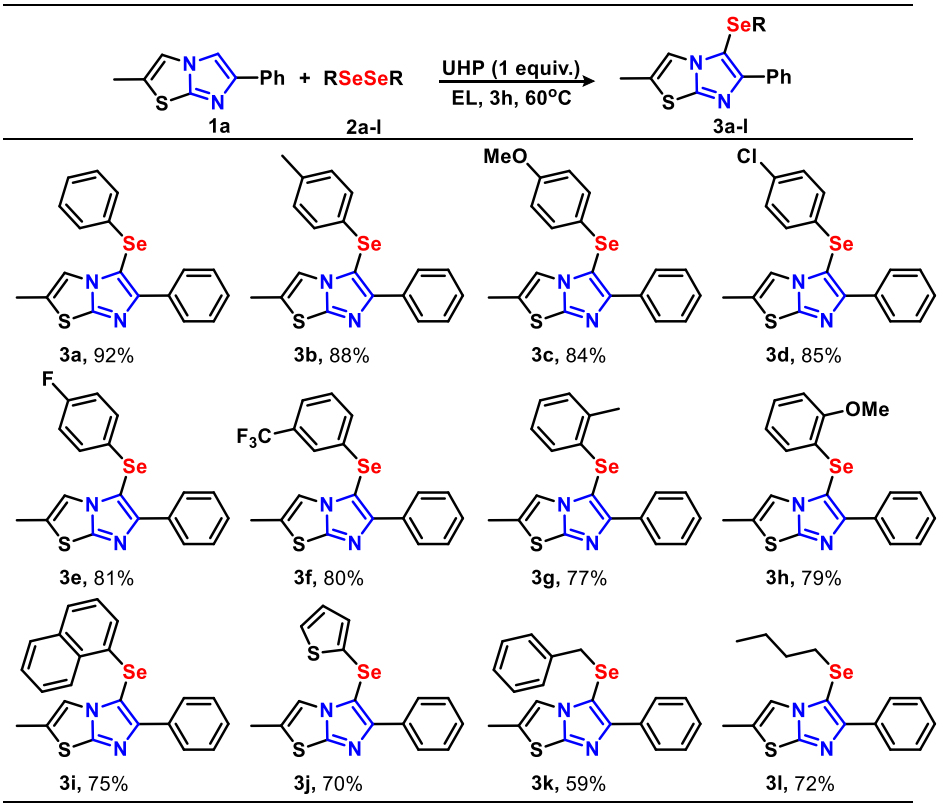
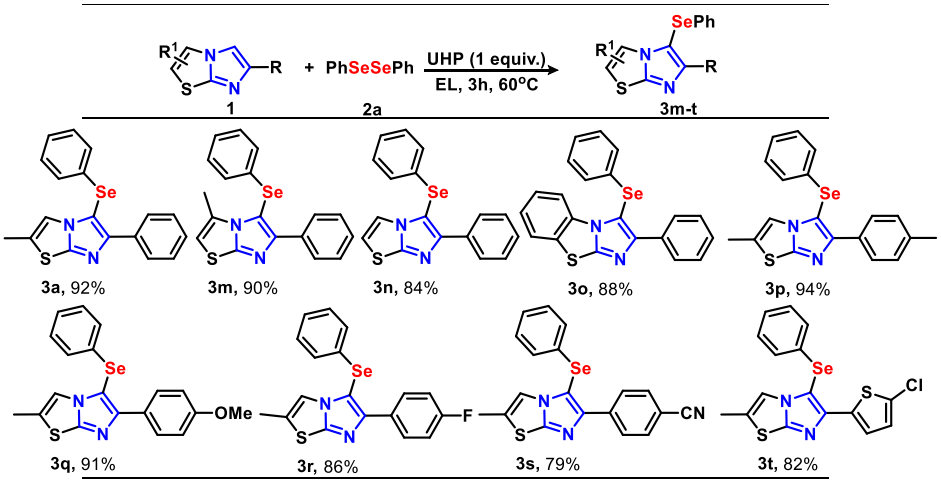
Scheme 1. Scope of Diorganyl Diselenides 2[a,b]



[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.11 mmol), UHP (1 molar equiv), EL (1 mL) for 3h at 60 °C, under open-air atmosphere. [b]Isolated yields.

Scheme 2. Scope of IT 1[a,b]



[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.11 mmol), UHP (1 molar equiv), EL (1 mL) for 3 h at 60 °C, under open-air atmosphere. [b]Isolated yields.

product **3k** was isolated in a 58% yield. Last, considering the importance of butylated organoselenides in organic synthesis,[24] the reaction was applied to dibutyl diselenide **2l**, which furnished the corresponding product **3l** in a 72% yield.

To check the usefulness of this methodology and expand its scope in relation to the substrate, the influence of substituted IT moiety **1** was evaluated with diselenide **2a** (Scheme 2). The corresponding coupled selenylated IT products **3m−t** were successfully obtained in 79−94% yields. There was no significant variation in yield when substitution at the thiophene moiety was tested (**3a** vs **3m−o**). Similarly, the *p*-substituted phenyl group at the C-6 position of IT was also tested. It was observed that electron-donating groups (R = Me, Ome) **1e−f** were more effective than electron-withdrawing groups (R = F, CN) **1g−h**, furnishing **3p−q** and **3r−s**, respectively. Last, thiophene-bearing IT **1i** was also screened for the selenylation reaction. To our delight, the reaction afforded the desired selenylated product **3t** in an 82% yield.

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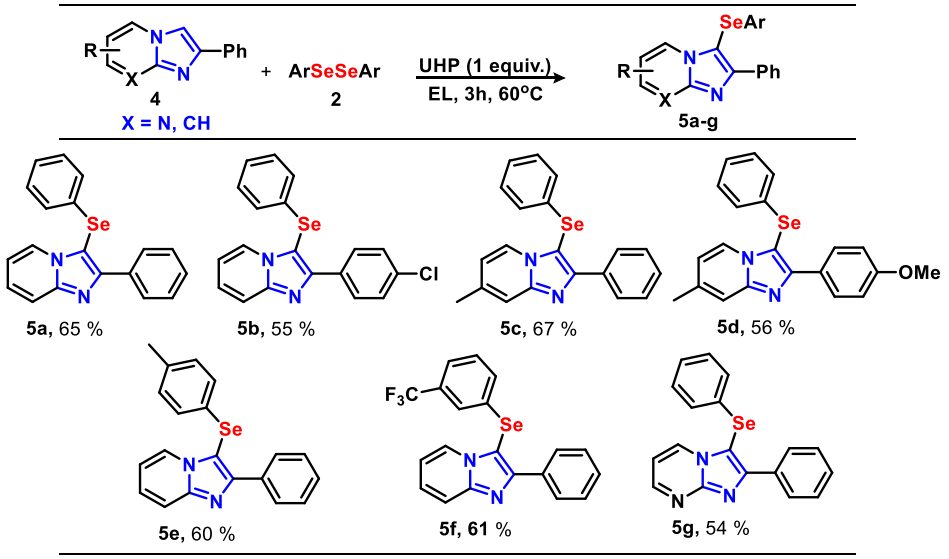
Scheme 3. Synthesis of Selenylated IP and Imidazo[1,2-*a*]pyrimidine 5a−g[a,a]

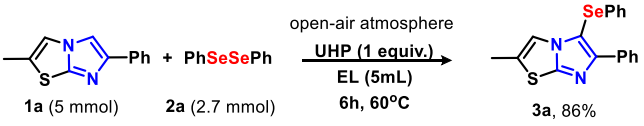


[a]Reaction conditions: **4** (0.20 mmol), **2a** (0.11 mmol), UHP (1 molar equiv), EL (1 mL) for 3h at 60 °C, under open-air atmosphere. [a]Isolated yields.

Encouraged by the results of this UHP-EL combo system for the selenylation of IT, we extended this method to other similar imidazole-containing *N*-heteroarenes 4 under ideal reaction conditions (Scheme 3). For this purpose, we extended our studies to IP, and imidazo[1,2-*a*]pyrimidine. IP resulted in the corresponding selenylated products 5a-f in 55−67% yields. Imidazo[1,2-*a*]pyrimidine **4g** was also tested, furnishing the coupled product **5g** in a 54% yield.

To demonstrate the synthetic utility and potential of this new selenylating methodology, a scale-up reaction at the gram scale was carried out. For this, IT **1a** and diselenide **2a** were selected as the test materials (Scheme 4). To our delight, the

Scheme 4. Reaction at Gram Scale



corresponding product **3a** was obtained in an 86% yield. This is very significant from a synthesis point of view, since this protocol could be used to synthesize biologically relevant compounds in bulk quantities.

Last, in order to gain some insight into the mechanism of this new approach, few control experiments were performed (Scheme 5). Standard reaction under an oxygen atmosphere had no negative effect (Scheme 5a), while under an argon atmosphere a decrease in yield was perceived (Scheme 5b). These results signify the importance of the reaction under an open atmosphere. In the case of radical inhibitors, TEMPO and BHT (Scheme 5c,d), the reaction suffers some inhibition, indicating a possible involvement of radical species. To further develop our understanding of the reaction mechanism, the reaction was performed in the presence of tertiary amines as the base (Scheme 5e−g). Use of DABCO, Hünig's base, and Et_3N resulted in an abrupt decrease in yields. These results indicate the possible presence of acid species.

In order to check the reactivity of substrates with UHP, test reactions were performed with individual substrates **1a** and **2a** (Scheme 5h,i). In the case of diselenide **2a**, formation of seleninic acid ($PhSeO_2H$) was observed in ^{77}Se NMR (95 MHz) at δ = 1175 ppm (Figure S1, ESI). This result motivated us to perform a separate standard reaction for 1h to study the formation of the product **3a** using 77Se NMR spectroscopy (Scheme 5j). In the ^{77}Se NMR spectrum, besides the formation of selenylated product **3a**, a ^{77}Se NMR signal for $PhSeO_2H$ was also observed at δ = 1175 ppm (Figure S2).

Based on these results (Scheme 5) and on the previous literature,[25] a possible mechanism can be proposed (Scheme 6). The diselenide **2** was initially oxidized to the organoseleninic acid **I** by UHP. The acid **I** on further oxidation, results in the corresponding peroxyseleninic acid **II**, which could generate organoselenenic acid **III**. Selenenic acid **III** after the protonation converted into the strong reactive species **IV**. In the subsequent step, imidazoheteroarene undergoes electrophilic aromatic substitution via species **V**, to afford the selenylated product.

EXPERIMENTAL SECTION

Materials and Methods. ^1H NMR spectra were obtained at 300 MHz on a Bruker DPX 300 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million, referenced to the solvent peak of $CDCl_3$ or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz, and integrated intensity. ^{13}C NMR were obtained at 75 MHz on a Bruker DPX 300 NMR spectrometer. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Spectra were recorded in $CDCl_3$ solutions. Selenium-77 nuclear magnetic resonance spectra (^{77}Se NMR) were obtained at 95 MHz on a Bruker Avance Neo 500 spectrometer. The chemical shifts are reported in ppm, referenced to diphenyl diselenide as the external reference (454 ppm). High-resolution mass spectra

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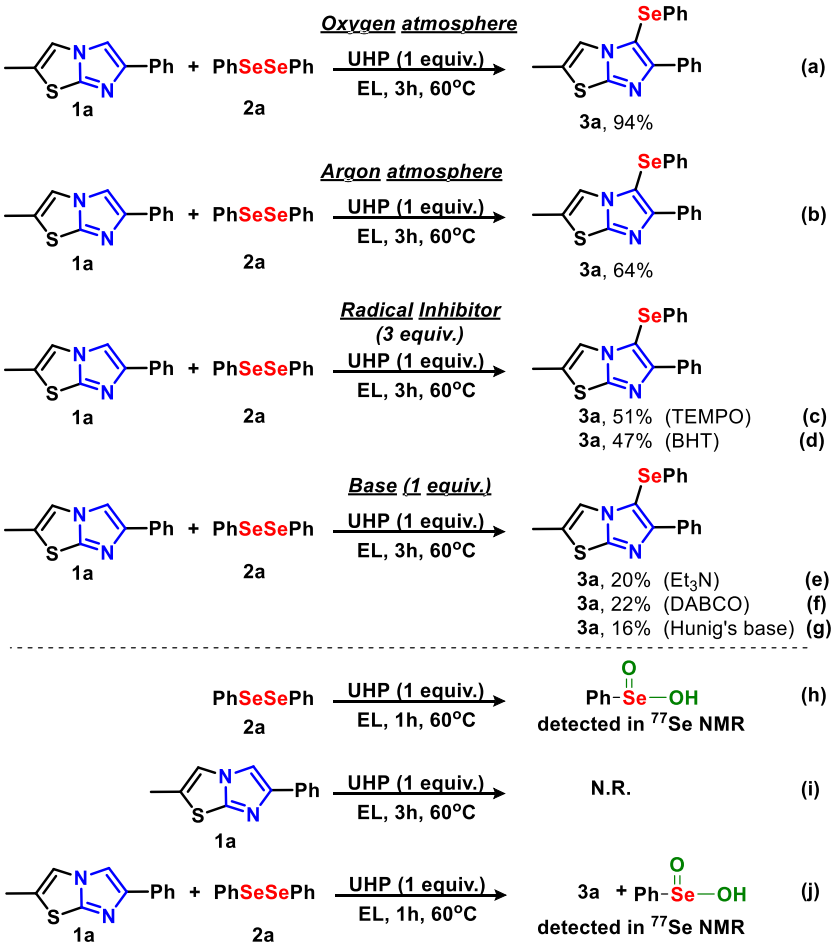
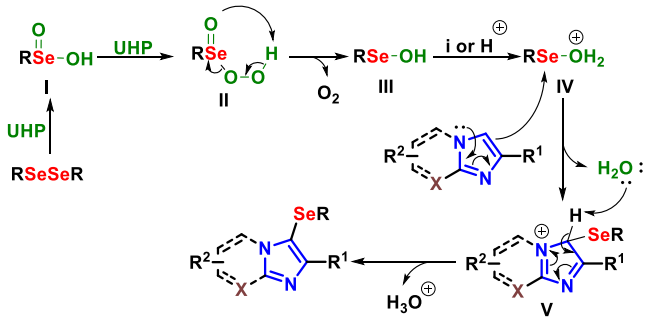
Scheme 5. Controlled Experiments



Scheme 6. Proposed Mechanism



were recorded on a Bruker MicroTOF-Q III mass spectrometer equipped with an automatic syringe pump for sample injection. The melting points were determined in a Microquimica MQRPF-301 digital model equipment with heating plate. Column chromatography was performed using Silica Gel (230−400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF_{254}, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light or stained with iodine vapor and acidic vanillin. Most reactions were monitored by TLC for the disappearance of starting material.

Unless otherwise stated, all reactions were carried out in a borosilicate glass test tube (1.6 cm × 10 cm); all reagents and solvents were obtained from commercial sources and used without any further purification. Reactions under an inert or oxygen atmosphere were conducted in a flame-dried Schlenk tube equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon/dry oxygen. Reagents and solvents were handled by using standard syringe techniques. Temperatures above room temperature were maintained by the use of a mineral oil bath. The yields are based on isolated compounds after purification.

General Procedure for the UHP-Mediated Selenylation of Imidazoheteroarenes. A mixture of appropriate imidazoheteroarenes 1 or 4 (0.2 mmol), diorganyl diselenide 2 (0.11 mmol), UHP (1 molar equiv, 18.8 mg), and 1 mL of ethyl lactate was charged in a test tube. The reaction mixture was heated to 60 °C for 6 h. After this, the reaction mixture was dissolved in ethyl acetate (10 mL), and the mixture was washed with 2 × 5 mL of brine. The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using hexane or a mixture of hexane/ethyl acetate (9:1) as the eluent.

2-Methyl-6-phenyl-5-(phenylselanyl)imidazo[2,1-b]-thiazole (***3a***). Yield: 92%; beige solid; mp: 134−136 °C (lit. = 141−143 °C);[26a] purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 (d, J = 7.0 Hz, 2H), 7.49−7.23 (m, 3H), 7.22−7.08 (m, 6H), and 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.7, 151.0, 134.0, 131.7, 129.6, 128.3, 128.3, 127.8, 127.6, 126.6, 115.3, 102.0, and 14.1; ^{77}Se NMR (95 MHz, $CDCl_3$) δ: 245.65.

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*2-Methyl-6-phenyl-5-(p-tolylselanyl)imidazo[2,1-b]-thiazole (**3b**).* Yield: 88%; white solid; mp: 117−119 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, J = 7.1 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.33−7.23 (m, 1H), 7.15 (d, J = 1.5 Hz, 1H), 7.08 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H), 2.35 (s, 3H), and 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.4, 150.8, 136.6, 134.1, 130.4, 128.7, 128.2, 127.9, 127.7, 127.6, 126.5, 115.3, 102.4, 21.0, and 14.1; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{19}H_{17}N_2SSe$, 384.0199; found, 384.0136.

*5-((4-Methoxyphenyl)selanyl)-2-methyl-6-phenylimidazo-[2,1-b]thiazole (**3c**).* Yield: 84%; beige solid; mp: 51−153 °C; purification was performed via silica gel flash chromatography (100% hexane and 75% hexane: 25% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, J = 7.0 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.32−7.23 (m, 1H), 7.20−7.09 (m, 3H), 6.72 (d, J = 8.9 Hz, 2H), 3.68 (s, 3H), and 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.0, 150.9, 150.6, 134.1, 131.0, 128.2, 127.7, 127.7, 126.5, 121.3, 115.3, 115.3, 103.3, 55.3, and 14.1; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{19}H_{17}N_2OSSe$, 400.0148; found, 400.0083.

*5-((4-Chlorophenyl)selanyl)-2-methyl-6-phenylimidazo-[2,1-b]thiazole (**3d**).* Yield: 85%; yellow solid; mp: 139−141 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (d, J = 7.1 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.32−7.23 (m, 1H), 7.19−7.01 (m, 5H), and 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.8, 151.1, 133.8, 132.8, 129.9, 129.7, 129.6, 128.3, 128.0, 127.6, 126.9, 115.1, 101.5, and 14.1; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{18}H_{14}N_2ClSSe$, 403.9653; found, 403.9591.

*5-((4-Fluorophenyl)selanyl)-2-methyl-6-phenylimidazo-[2,1-b]thiazole (**3e**).* Yield: 81%; beige solid; mp: 99−101 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, J = 7.0 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.33−7.26 (m, 1H), 7.20−7.08 (m, 2H), 6.90 (t, J = 8.8 Hz, 2H), and 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0 (d, J_F = 246.5 Hz), 151.5, 151.0, 133.9, 130.5 (d, J_F = 7.7 Hz), 128.3, 127.9, 127.6, 126.8, 125.9 (d, J_F = 3.4 Hz), 116.8 (d, J_F = 21.9 Hz), 115.1, 102.3, and 14.1; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{18}H_{14}N_2FSSe$, 387.9948; found, 387.9837.

*2-Methyl-6-phenyl-5-((3-(trifluoromethyl)phenyl)selanyl)-imidazo[2,1-b]thiazole (**3f**).* Yield: 80%; beige solid; mp: 108−110 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 7.3 Hz, 2H), 7.50 (s, 1H), 7.43−7.12 (m, 7H), and 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.3, 151.4, 133.7, 133.1, 131.8 (q, J_F = 32.5 Hz), 131.3, 130.0, 128.3, 128.0, 127.6, 127.1, 124.8 (q, J_F = 3.8 Hz), 123.6 (q, J_F = 272.9 Hz), 123.5 (q, J_F = 3.6 Hz), 115.1, 100.8, and 14.1; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{19}H_{14}N_2F_3SSe$, 437.9916; found, 437.9797.

*2-Methyl-6-phenyl-5-(o-tolylselanyl)imidazo[2,1-b]-thiazole (**3g**).* Yield: 77%; white solid; mp: 168−170 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 7.0 Hz, 2H), 7.36 (t, J = 7.3 Hz, 2H), 7.32−7.24 (m, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.13−7.03 (m, 2H), 6.94 (t, J = 7.6 Hz, 1H), 6.76 (d, J = 6.6 Hz, 1H), 2.41 (s, 3H), and 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.2, 151.2, 136.2, 134.0, 132.3, 130.5, 128.3, 127.8, 127.6, 127.3, 127.2, 126.6, 126.4, 115.3, 100.9, 21.1, and 14.1; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{19}H_{17}N_2SSe$, 384.0199; found, 384.0105.

*5-((2-Methoxyphenyl)selanyl)-2-methyl-6-phenylimidazo-[2,1-b]thiazole (**3h**).* Yield: 79%; beige solid; mp: 196−198 °C; purification was performed via silica gel flash chromatography (100% hexane and 75% hexane: 25% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 7.0 Hz, 2H), 7.34 (t, J = 7.3 Hz, 2H), 7.31−7.23 (m, 1H), 7.20−7.08 (m, 2H), 6.84 (d, J = 9.4 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 3.90 (s, 3H), and 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.3, 152.4, 151.2, 134.0, 128.2, 127.7, 127.6, 127.5, 127.4, 126.5, 122.1, 120.8, 115.5, 110.5, 100.2, 55.8, and 14.1; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{19}H_{17}N_2OSSe$, 400.0148; found, 400.0118.

*2-Methyl-5-(naphthalen-1-ylselanyl)-6-phenylimidazo-[2,1-b]thiazole (**3i**).* Yield: 75%; yellow solid; mp: 113−116 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15−8.03 (m, 3H), 7.83 (dd, J = 6.3, 3.3 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.53 (dt, J = 6.1, 2.9 Hz, 2H), 7.42−7.25 (m, 3H), 7.20 (t, J = 7.7 Hz, 1H), 7.11−7.04 (m, 2H), and 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.4, 151.3, 134.2, 134.0, 132.1, 130.2, 128.8, 128.3, 127.9, 127.7, 127.2, 126.7, 126.6, 126.45, 126.4, 126.1, 125.2, 115.4, 100.8, and 14.1; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{22}H_{17}N_2SSe$, 420.0199; found, 420.0094.

*2-Methyl-6-phenyl-5-(thiophen-2-ylselanyl)imidazo[2,1-b]thiazole (**3j**).* Yield: 70%; yellow solid; 105−106 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.2 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.37−7.22 (m, 3H), 7.17−7.09 (m, 1H), 6.90 (dd, J = 5.2, 3.6 Hz, 1H), and 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.5, 150.5, 134.0, 133.0, 130.0, 128.2, 128.0, 128.0, 127.8, 126.6, 125.0, 115.2, 104.3, and 14.2; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{16}H_{13}N_2S_2Se$, 375.9607; found, 375.9524.

*5-(Benzylselanyl)-2-methyl-6-phenylimidazo[2,1-b]-thiazole (**3k**).* Yield: 59%; beige solid; mp: 119−120 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J = 7.1 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.30 (t, J = 6.0 Hz, 1H), 7.15−7.04 (m, 3H), 6.99−6.87 (m, 2H), 6.58 (s, 1H), 3.84 (s, 2H), and 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.8, 150.2, 138.6, 134.4, 128.7, 128.4, 128.1, 127.5, 126.9, 125.3, 115.2, 102.9, 33.7, and 13.8; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{19}H_{17}N_2SSe$, 384.0199; found, 384.0156.

*5-(Butylselanyl)-2-methyl-6-phenylimidazo[2,1-b]thiazole (**3l**).* Yield: 72%; beige solid; mp: 87−88 °C; purification was performed via silica gel flash chromatography (100% hexane and 85% hexane: 15% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (d, J = 8.3 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.32−7.21 (m, 2H), 2.65 (t, J = 7.3 Hz, 2H), 2.36 (s, 3H), 1.47 (p, J = 7.7 Hz, 2H), 1.27 (h, J = 7.2 Hz, 2H), and 0.75 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.1, 149.8, 134.5, 128.1, 127.5, 127.4, 126.1, 115.4, 103.1, 32.1, 29.9, 22.6, 14.2, and 13.4; HRMS (ESI$^+$) m/z: $[M + H]^+$ calcd. for $C_{16}H_{19}N_2OSSe$, 350.0355; found, 350.0241.

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*3-Methyl-6-phenyl-5-(phenylselanyl)imidazo[2,1-b]-thiazole (**3m**).* Yield: 90%; brown solid; mp: 119−121 °C (lit. = 145−146 °C);[26a] purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, J = 6.8 Hz, 2H), 7.48−7.31 (m, 3H), 7.29−7.06 (m, 5H),6.37 (s, 1H), and 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.6, 154.6, 153.8, 134.5, 134.0, 131.5, 129.7, 128.4, 128.1, 128.0, 127.6, 126.3, 107.7, 102.7, and 15.0.

*6-Phenyl-5-(phenylselanyl)imidazo[2,1-b]thiazole (**3n**).* Yield: 84%; brown solid; mp: 84−86 °C (lit. = 109−111 °C);[26a] purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, J = 7.1 Hz, 2H), 7.46−7.30 (m, 4H), 7.18 (s, 5H), and 6.80 (d, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.9, 151.6, 133.9, 131.4, 129.7, 128.5, 128.3, 128.0, 127.8, 126.7, 118.7, 112.5, and 102.5.

*2-Phenyl-3-(phenylselanyl)benzo[d]imidazo[2,1-b]-thiazole (**3o**).* Yield: 88%; beige solid; mp: 138−140 °C (lit. = 140−143 °C);[26a] purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50 (d, J = 9.5 Hz, 1H), 8.03 (d, J = 6.9 Hz, 2H), 7.63 (dd, J = 7.5, 1.9 Hz, 1H), and 7.45−7.07 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.2, 151.4, 133.8, 133.6, 132.5, 130.3, 129.8, 128.3, 128.2, 128.2, 126.7, 126.1, 124.9, 124.0, 114.5, and 104.1.

*2-Methyl-5-(phenylselanyl)-6-(p-tolyl)imidazo[2,1-b]-thiazole (**3p**).* Yield: 94%; brown solid; mp: 109−111 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 9.1 Hz, 7H), and 2.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.9, 150.9, 137.6, 131.8, 131.2, 129.6, 129.0, 128.3, 127.5, 126.5, 126.4, 115.3, 101.6, 21.3, and 14.1; HRMS (ESI$^+$) m/z: [M + H]$^+$ calcd. for $C_{19}H_{17}N_2SSe$, 384.0199; found, 384.0060.

*6-(4-Methoxyphenyl)-2-methyl-5-(phenylselanyl)imidazo-[2,1-b]thiazole (**3q**).* Yield: 91%; brown solid; mp: 91−94 °C; purification was performed via silica gel flash chromatography (100% hexane and 75% hexane: 25% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (d, J = 9.1 Hz, 2H), 7.27−7.08 (m, 6H), 6.90 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), and 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.4, 151.7, 150.8, 131.9, 129.6, 128.9, 128.2, 126.7, 126.5, 126.3, 115.3, 113.7, 101.0, 55.2, and 14.1; HRMS (ESI$^+$) m/z: [M + H]$^+$ calcd. for $C_{19}H_{17}N_2OSSe$, 400.0148; found, 400.0083.

*6-(4-Fluorophenyl)-2-methyl-5-(phenylselanyl)imidazo-[2,1-b]thiazole (**3r**).* Yield: 86%; beige solid; 121−122 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (s, 1H), 7.70 (dd, J = 6.2, 2.6 Hz, 1H), 7.32−7.16 (m, 6H), 7.11−7.03 (m, 2H), 7.01−6.91 (m, 1H), and 3.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.6 (d, J_F = 247.0 Hz), 150.9 (d, J_F = 12.6 Hz), 131.5, 130.1, 129.7, 129.3 (d, J_F = 8.1 Hz), 128.3, 126.7, 115.2 (d, J_F = 21.0 Hz), 101.7, and 14.1; HRMS (ESI$^+$) m/z: [M + H]$^+$ calcd. for $C_{18}H_{14}N_2FSSe$, 384.9948; found, 384.9827.

*4-(2-Methyl-5-(phenylselanyl)imidazo[2,1-b]thiazol-6-yl)-benzonitrile (**3s**).* Yield: 79%; beige solid; mp: 181−183 °C; purification was performed via silica gel flash chromatography (100% hexane and 70% hexane: 30% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.24 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 7.29−7.11 (m, 6H), and 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.4, 149.1, 138.4, 132.1, 130.8, 129.8, 128.5, 127.7, 127.0, 119.1, 115.2, 110.8, 103.6, and 14.2; HRMS (ESI$^+$) m/z: [M + H]$^+$ calcd. for $C_{19}H_{14}N_3FSSe$, 394.9995; found, 394.9883.

*6-(5-Chlorothiophen-2-yl)-2-methyl-5-(phenylselanyl)-imidazo[2,1-b]thiazole (**3t**).* Yield: 82%; orange solid; mp: 123−125 °C; purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (d, J = 3.9 Hz, 1H), 7.17 (d, J = 17.0 Hz, 6H), 6.84 (d, J = 3.9 Hz, 1H), and 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.1, 146.3, 135.5, 130.9, 129.9, 129.7, 128.7, 127.1, 127.0, 126.5, 124.1, 115.1, 101.4, and 14.1; HRMS (ESI$^+$) m/z: [M + H]$^+$ calcd. for $C_{16}H_{12}N_2ClS_2Se$, 409.9217; found, 409.9132.

*2-Phenyl-3-(phenylselanyl)imidazo[1,2-a]pyridine (**5a**).* Yield: 65%; yellow solid; mp: 136−138 °C (lit. = 137−138 °C);[26b] purification was performed via silica gel flash chromatography (100% hexane and 85% hexane: 15% ethyl acetate gradient); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.32 (d, J = 6.9 Hz, 1H), 8.16 (d, J = 6.9 Hz, 2H), 7.70 (d, J = 9.0 Hz, 1H), 7.40 (dt, J = 15.1, 7.0 Hz, 4H), 7.22−7.04 (m, 5H), and 6.80 (t, J = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.8, 147.7, 133.8, 130.9, 129.7, 128.8, 128.5, 128.3, 128.2, 126.7, 126.5, 125.6, 117.5, 113.0, and 102.9.

*2-(4-Chlorophenyl)-3-(phenylselanyl)imidazo[1,2-a]-pyridine (**5b**).* Yield: 55%; yellow solid; mp: 102−104 °C (lit. = 101−102 °C);[26b] purification was performed via silica gel flash chromatography (100% hexane and 85% hexane: 15% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.35 (d, J = 6.9 Hz, 1H), 8.12 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 9.0 Hz, 1H), 7.46−7.02 (m, 8H), and 6.86 (t, J = 6.2 Hz, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ: 150.5, 147.7, 134.4, 132.2, 130.6, 129.9, 129.7, 128.5, 128.2, 126.8, 126.7, 125.6, 117.5, 113.2, and 103.0.

*7-Methyl-2-phenyl-3-(phenylselanyl)imidazo[1,2-a]-pyridine (**5c**).* Yield: 67%; beige solid; mp: 50−52 °C (lit. = 52−53 °C);[26b] purification was performed via silica gel flash chromatography (100% hexane and 85% hexane: 15% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21−8.09 (m, 3H), 7.49−7.27 (m, 4H), 7.17−7.04 (m, 5H), 6.62 (d, J = 6.9 Hz, 1H), and 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.7, 148.1, 137.6, 133.9, 131.2, 129.6, 128.7, 128.3, 128.3, 128.1, 126.6, 124.7, 116.0, 115.6, 102.0, and 21.3.

*2-(4-Methoxyphenyl)-7-methyl-3-(phenylselanyl)imidazo-[1,2-a]pyridine (**5d**).* Yield: 56%; yellow solid; mp: 112−114 °C (lit. = 117−119 °C);[26b] purification was performed via silica gel flash chromatography (100% hexane and 75% hexane: 25% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (d, J = 6.9 Hz, 1H), 8.08 (d, J = 9.0 Hz, 2H), 7.42 (s, 1H), 7.18−7.02 (m, 5H), 6.93 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 6.9 Hz, 1H), 3.79 (s, 3H), and 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.8, 151.4, 148.0, 137.6, 131.3, 129.9, 129.6, 128.0, 126.5, 126.4, 124.6, 115.7, 115.4, 113.7, 101.1, 55.2, and 21.3.

*2-Phenyl-3-(p-tolylselanyl)imidazo[1,2-a]pyridine (**5e**).* Yield: 60%; yellow solid; mp: 134−116 °C (lit. = 135−137 °C);[26b] purification was performed via silica gel flash chromatography (100% hexane and 85% hexane: 15% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.32 (d, J = 6.9 Hz, 1H), 8.16 (d, J = 6.9 Hz, 2H), 7.69 (d, J = 9.0 Hz, 1H), 7.49−7.33 (m, 3H), 7.26 (t, J = 7.9 Hz, 1H), 7.05−6.91 (m,

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4H), 6.80 (t, J = 6.2 Hz, 1H), and 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.5, 147.6, 136.7, 133.8, 130.5, 128.8, 128.5, 128.4, 128.3, 126.9, 126.3, 125.6, 117.5, 112.9, 103.3, and 20.9.

*2-Phenyl-3-((3-(trifluoromethyl)phenyl)selanyl)imidazo-[1,2-a]pyridine (**5f**).* Yield: 61%; yellow solid; mp: 101−102 °C (lit. = 100−102 °C);[26b] purification was performed via silica gel flash chromatography (100% hexane and 85% hexane: 15% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: δ 8.32 (d, J = 6.9 Hz, 1H), 8.11 (dd, J = 8.3, 1.5 Hz, 2H), 7.74 (d, J = 9.0 Hz, 1H), 7.57−7.28 (m, 6H), 7.23 (t, J = 7.3 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), and 6.89 (td, J = 6.8, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.4, 147.9, 133.5, 132.4, 131.9 (q, J_F = 32.6 Hz), 131.1, 130.0, 129.6, 128.9, 128.7, 128.7, 128.4, 126.8, 125.4, 123.5 (q, J_F = 3.6 Hz), 123.5 (q, J = 3.6 Hz), 121.7, 123.6 (q, J = 273.0 Hz), 117.7, 113.3, and 101.8.

*2-Phenyl-3-(phenylselanyl)imidazo[1,2-a]pyrimidine (**5g**).* Yield: 54%; yellow solid; mp: 120−122 °C (lit. 120−121 °C);[26b] purification was performed via silica gel flash chromatography (100% hexane and 80% hexane: 20% ethyl acetate gradient); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.63−8.51 (m, 2H), 8.27 (d, J = 6.6 Hz, 2H), 7.49−7.31 (m, 3H), 7.27−7.04 (m, 5H), and 6.88 (dd, J = 6.8, 4.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.0, 151.4, 150.7, 133.1, 130.0, 129.8, 129.0, 128.9, 128.5, 128.4, 127.1, 109.3, and 101.6.

Gram-Scale Reaction. A mixture of appropriate IT **1a** (5 mmol, 1.07 g), diphenyl diselenide **2a** (2.7 mmol, 0.84 g), UHP (1 molar equiv, 470 mg), and 5 mL of ethyl lactate were charged in a test tube. The reaction was heated to 60 °C for 6 h. After this, the reaction mixture was dissolved in ethyl acetate (20 mL) and washed 3 × with 10 mL of brine. The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using a mixture of hexane/ethyl acetate (9:1) as the eluent.

CONCLUSIONS

In conclusion, we have developed an alternative, synthetically attractive, environmentally benign, robust, and safe scalable protocol for the synthesis of a selenylated imidazo[2,1-*b*]thiazole (IT) via C(sp^2)−H bond selenylation, with interest for therapeutic applications. This regioselective procedure afforded the desired products in good to excellent yields by using 1 M equiv of UHP and ethyl lactate (EL) as sustainable solvents, in the presence of half molar equiv of diselenides without the exclusion of air and moisture, at 60 °C for 3 h. Furthermore, the reaction was applicable to imidazo[1,2-*a*]pyridine (IP) and imidazo[1,2-*a*]pyrimidine.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c05338.

Spectra data for all compounds (PDF)

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Notes

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