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Direct, metal-free C(sp^2)-H chalcogenation of indoles and imidazopyridines with dichalcogenides, catalysed by KIO_3

Jamal Rafique,[†] Sumbal Saba,[†] Marcelo S. Franco,[†] Luana Bettanin, Alex R. Schneider, Lais T. Silva, Antonio L. Braga*[a]

Abstract: Herein, we report a greener protocol for the synthesis of 3-Se/S-indoles and imidazo[1,2-*a*]pyridines through direct C(sp^2)-H bond chalcogenation of heteroarenes with half molar equiv. of different dichalcogenides, using KIO_3 as a non-toxic, easily handleable catalyst and stoichiometric amount of glycerol. The reaction features are high yields, based on atom economy, ease to gram scale, metal- and solvent-free approach as well as applicable to different types of *N*-heteroarenes.

Introduction

Functionalization of the indole and imidazo[1,2-*a*]pyridine (IP) cores are an important synthetic task, since they are well established as privileged scaffolds[1,2] and are widely used for pharmaceutical, biological and material applications.[3,4] These nuclei are frequently found in several commercially available pharmaceutical drugs,[5] e.g., alpidem **1a**, zolpidem **1b**, miroprofen **1c**, zolimidine **1d**, naratriptan **1e**, delavidine **1f** (Figure 1).

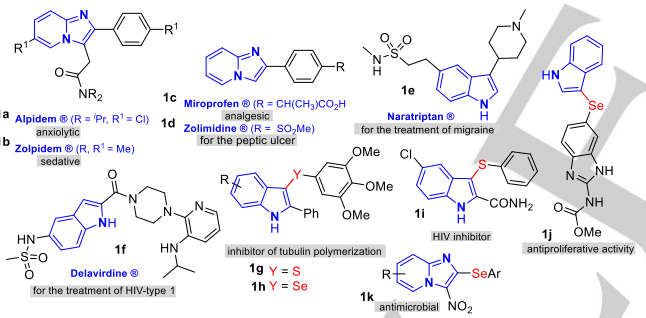


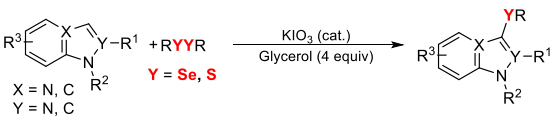
Figure 1. Indole and IP-based drugs and chalcogenated hybrids.

Similarly, the construction of C–S/Se bonds is becoming increasingly appreciated, due to their biological properties.[6,7] Reports in recent decades of antioxidant, anti-inflammatory, antitumor, and antiviral activities have led to increased interest in these compounds.[8]

Despite the wide spectrum of therapeutic properties associated with indole/IPs and the biological relevance of organochalcogen compounds, few synthetic methods for the construction of these hybrid structures, **1g-k** (Figure 1) in a single molecule, 3-Se/S-indoles/IPs, have been reported.[9] Several methods described in the literature offer interesting features,[10,11] but some have drawbacks which include the use of non-green solvents, pre-functionalized coupling partners, low atom economy, narrow substrate scope, transition-metal catalysts, malodorous reagents and elaborate multi-stepped processes.

In recent years, reactions catalysed by molecular iodine and iodine salts have emerged a versatile tool in the cross-coupling reaction for C-C and C-X bond formation.[12] Iodine catalysis represents a promising powerful approach to organic synthesis since it offers advantages over transition-metal catalysis including: greater atom economy; greener and milder reaction conditions; and broader substrate compatibility.[13] Furthermore, metal- and solvent-free reaction conditions have gained considerable attention from research groups and are widely applied in the functionalization of the C-H bond, which represents an important contribution to the development and prdogress of sustainable chemistry.[14]

Recently, we developed an I_2 catalysed C(sp^2)-H bond selenylation/sulfenylation of IPs using DMSO as oxidant under solvent free conditions.[11h] Now, considering our continuous interest in designing and developing eco-friendly processes as well as in the chalcogenation of biologically-relevant heterocycles,[11h,12b-c,15] we disclose a new alternative environmentally-benign protocol for the synthesis of 3-Se/S-Indoles and imidazo[1,2-*a*]pyridines through C(sp^2)-H functionalization using a KIO_3/glycerol catalytic system (Scheme 1). This new alternative and more sustainable approach uses KIO_3 as stable, non-toxic,easily handleable catalyst, allowing the use of glycerol in stiochimetric amount. Using this broader, regioselective, metal- and solvent-free approach worked effectively using indole/IP with a half-molar equivalent of diorganyl dichalcogenides (Se, S) as a non-malodorous source of chalcogens.



Scheme 1. KIO_3-catalysed 3-chalcogenyl-indole/IP.

Results and Discussion

To identify the best reaction conditions, we begin our studies using indole **2a** and diphenyl diselenide **3a** as model substrates (Table 1). Based on our previous experience of solvent-free systems,[11h,12a-c] the reactions were carried out under solvent-free conditions. The reaction in the absence of a catalyst was ineffective (entry 1). Transition metals and KI afforded the selenylated product in trace amounts only (entries 2,3,5), while

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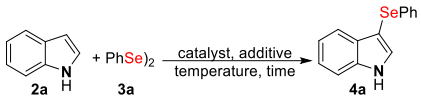
molecular iodine resulted in **4a** with 14% yield (entry 4). On switching from KI (entry 5) to KIO_3 (entry 6), the coupled product was isolated with 49% yield while its sodium analogue gave 40% yield (entry 7). Next, the type of additive was screened for this transformation (entries 8-11) and best results were obtained in glycerol (entry 9).

With the best catalyst and additive in hand, we then monitored the influence of the reaction temperature and time (entries 12-15) and ideal values of 100 °C and 6h were obtained. Subsequently, the catalyst loading and the stoichiometry of the additive were screened (entries 13-18). On using 5 mol% of KIO_3, **4a** was obtained in lower yield (entry 17). Increasing the catalyst loading to 15 mol% did not provide further improvement in the yield (entry 16). On decreasing the amount of glycerol from 5 to 4 equiv., **4a** was obtained in 87% yield (entry 18), while a further decrease in glycerol afforded a lower yield of **4a** (entries 18-19). The use of glycerol (2 mL) as the solvent did not provide any further positive influence on the yield of **4a** (entry 20 *vs* 18).

Table 1. Optimization of reaction conditions.[a]



Entry	catalyst [mol %]	additive [eq.]	*T* [°C]	*t* [h]	Yield [%][b]
1	-	PEG-400 (5)	100	8	NR
2	ZnI_2 (10)	PEG-400 (5)	100	8	traces
3	CuI (10)	PEG-400 (5)	100	8	traces
4	I_2 (10)	PEG-400 (5)	100	8	14
5	KI (10)	PEG-400 (5)	100	8	traces
6	KIO_3 (10)	PEG-400 (5)	100	8	49
7	$NaIO_3$ (10)	PEG-400 (5)	100	8	40
8	KIO_3 (10)	Et. lactate (5)	100	8	71
9	KIO_3 (10)	Glycerol (5)	100	8	87
10	KIO_3 (10)	DMSO (5)	100	8	11
11	KIO_3 (10)	toluene (5)	100	8	traces
12	KIO_3 (10)	Glycerol (5)	90	8	73
13	KIO_3 (10)	Glycerol (5)	110	8	85
14	KIO_3 (10)	Glycerol (5)	100	6	87
15	KIO_3 (10)	Glycerol (5)	100	4	65
16	KIO3 (15)	Glycerol (5)	100	8	87
17	KIO3 (5)	Glycerol (5)	100	8	61
18	KIO_3 (10)	Glycerol (4)	100	6	87
19	KIO_3 (10)	Glycerol (3)	100	6	70
20 [c]	KIO_3 (10)	Glycerol	100	6	86

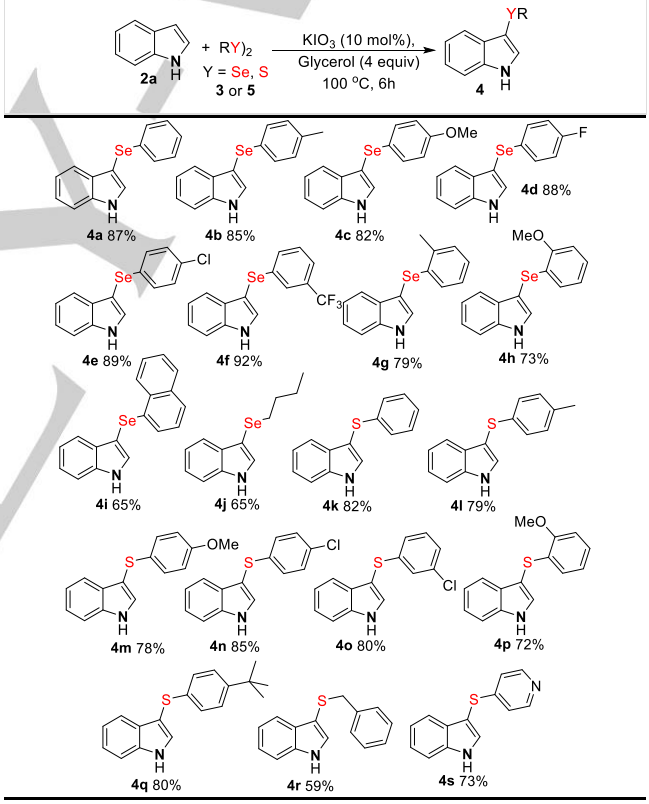
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.125 mmol), catalyst (mol %), additive (equivalent). [b] Isolated yields. [c] 2 mL Glycerol.

After ascertaining the best reaction parameters (Table 1, entry 16), the generality and scope of the C(sp^2)-H chalcogenylation of other indole **2** with various diorganyl dichalcogenides **3** were investigated (Schemes 1-2).

The reaction worked efficiently for structurally diverse diselenides **3**. This was tested through the use of different substituted diaryl diselenides with electron-donating (R = Me, OMe) and electron-withdrawing (R = F, Cl, CF_3) groups as well as sterically bulky groups (R = naphthyl). The results verified that the corresponding products were obtained in good to excellent yields (65−92%; **4a−i**). Notably, in general, good results were obtained in the case of electron-withdrawing groups (**4e-f** *vs* **4b-c**). In addition, there was a weaker influence of the steric hindrance of the *ortho*-substituted diselenides as compared to the respective para-derivatives (**4b-c** *vs* **4g-h**). By using a sterically bulkier substrate, the desired product **4i** was obtained in 65% yield. Furthermore, aliphatic diselenide **3j** afforded the respective product **4j** in 65% yield.

We further extended the scope of diorganyl dichalcogenides by using diorganyl disulfides **5a-i** as coupling partner (Scheme 1), affording the corresponding sulfenylated products **4k-s** in yields of 59% to 85%. The sulfenylation of indole **2a** showed similar electronic and steric effects to those observed during the selenylation. There was a small decrease in the yield of the sulfenylated product **4k-s** as compared with the corresponding selenylated indoles **4a-j**. The stronger S–S bond of the diaryl disulfides **5** in relation to the respective diselendies **3** offers a possible explanation in this regard.

Scheme 1. Scope of diorganyl dicalcogenides **3** and **5**.[a]



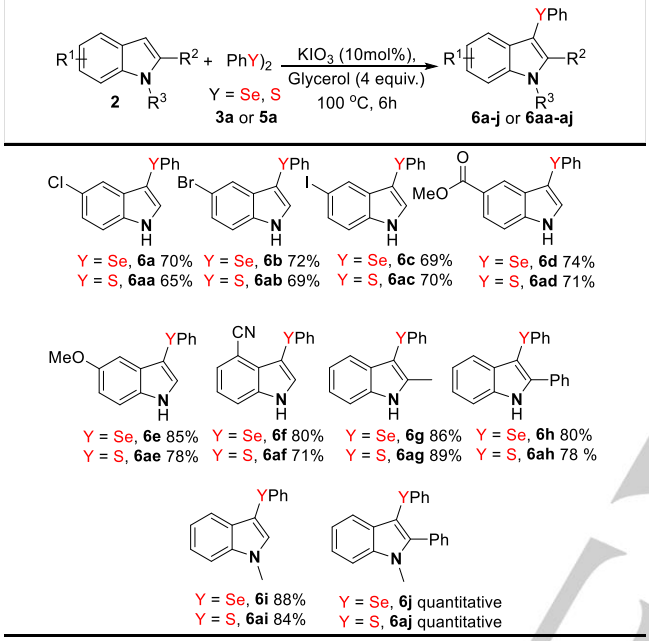
[a] Isolated yields.

To further broaden the scope in relation to the substrate, the influence of the indoles **2** moiety was evaluated with **3a** and **5a** (Scheme 2). The indole nucleus was tested with different functionalities, e.g. halogen, ester, nitrile, and methyl groups, attached at the aryl moiety.

The system tolerated the electronic effects of the substituents on the phenyl group and both electron-withdrawing and electron-donating groups were found to be suitable substrates, affording the corresponding products **6a-f** and **6aa-af**

in 65% to 88% yields. In this case, electron-donating groups showed superiority over electron-withdrawing groups. Substituents at the 1- and 2-positions of the indole also influenced the performance of this transformation. For example, 1-methyl and 1-phenyl derivatives gave the desired products **6g-h** and **6ag-ah** in 78% to 89% yield, respectively. Interestingly, 2-methyl substituted indoles resulted in the corresponding products **6i-j** and **6ai-aj** in 80% to 99% (yields, respectively).

Scheme 2. Scope of Indoles **2**.[a]

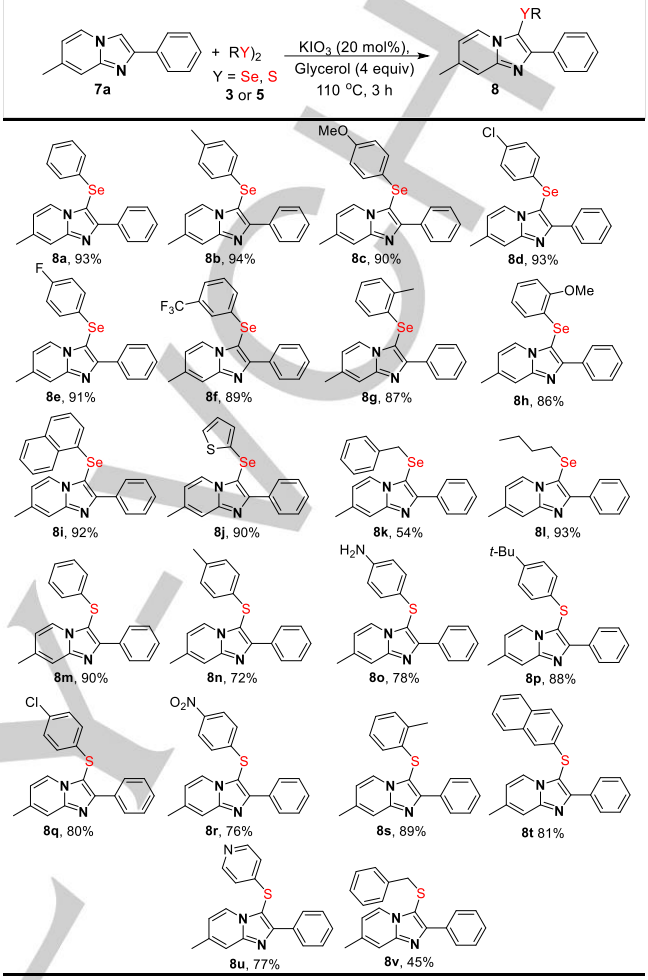


[a] Isolated yields.

Following the success in the KIO_3-catalyzed C(sp^2)–H bond chalcogenation of indole **2a**, this method was extended to imidazo[1,2-*a*]pyridine **7** and diorganyl dichalcogenides (**3**, **5**) as the coupling partner (Scheme 3-4). In this case, however, 20 mol% of catalyst loading for a duration of 3 h at 110 °C (for diselenides **3**) or 130 °C (for disulfides **5**) were found to be ideal. In general, all of the tested diorganyl dichalcogenides (**3**, **5**) against 7-methyl-2-phenylimidazo[1,2-*a*]pyridine **7a** reacted well, and afforded the selenylated-IPs (**8a-l**) and sulfenylated-IPs (**8m-v**) in good to excellent yields (Scheme 3). The reaction tolerated the electronic (electron-donating and electron-withdrawing substituents) as well as steric effects. Notably, aliphatic and heterocycle dichalcogenides led to the corresponding products (**8j-l,u-v**) equally well.

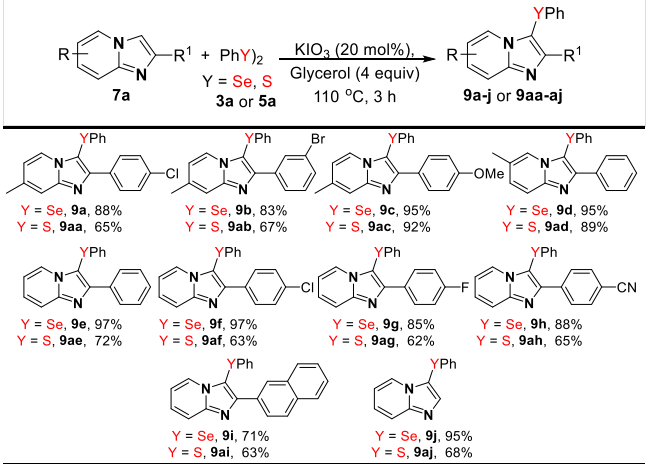
The scope of the reaction regarding the IP **7** was explored next (Scheme 4). Using diphenyl selenide **3a** and disulfide **5a** as the substrate, the corresponding C-3 selenyl- and sulfenyl-IP (**9a-j** and **9aa-aj**, respectively), were obtained in 62-97% yields. Interestingly, the method presented high regioselectivity (like indole **2**) because when the IP with no substituent at the C-2 position was used, the reaction exclusively afforded chalcogenated products at C-3 (**9j** and **9aj**) in very good yields.

Scheme 3. Scope of diorganyl dicalcogenides **3** and **5**.[a],[b]



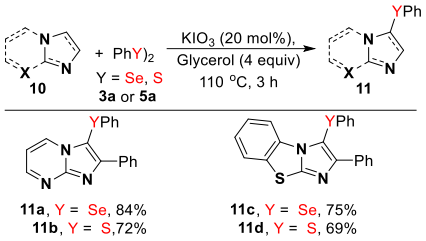
[a] In the case of $PhS)_2$, reaction temperature: 130 °C. [b] Isolated yields.

Scheme 4. Scope of imidazo[1,2-*a*]pyridines **7** [a],[b]



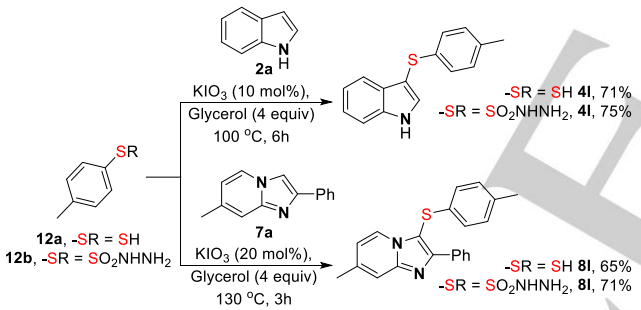
[a] In the case of $PhS)_2$, reaction temperature: 130 °C. [b] Isolated yields.

To further demonstrate the synthetic value of this new catalytic system, imidazo[1,2-*a*]pyrimidine **10a** and benzo[*d*]imidazo[2,1-*b*]thiazole **10b** were tested as an alternate *N*-heterocyclic nucleus for the chalcogenation under the optimal reaction conditions. The reaction furnished the desired selenylated **11a,c** and sulfenylated **11b,d** products in good yields, respectively (Scheme 5).



Scheme 5. Scope of *N*-heterocyclic core **10**.

To extend the versatility of this method, other sulfenylating agents were also employed. The use of 1 equiv. of thiol **12a** and sulfonyl hydrazide **12b** as thiolating agents afforded the respective thiolated products **4l** and **8l** in good yields (Scheme 6). However, since diorganyl dichalcogenides are odorless and inexpensive they appear to be better options as chalcogenylating agents.



Scheme 6. Thiolation using other sulfenylating agents.

To further demonstrate the synthetic utility of this new coupling protocol, scale-up reactions at 10 mmol were carried out (Scheme 7). Indole **2a,** diphenyl diselenide **3a** and disulfide **5a** were selected as the reagents to be tested under optimized conditions, affording **4a** and **4l** with no major decrease in the yields. Thus, this procedure could be used as a robust method for the larger scale synthesis of 3-chalcogenyl indoles and IPs, which are precursors for some important bioactive molecules.
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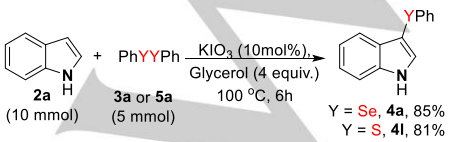
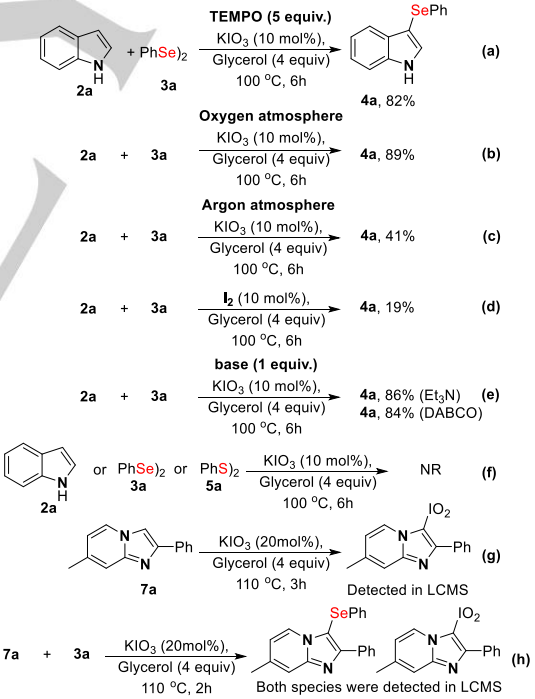


Scheme 7. Reaction at gram scale.

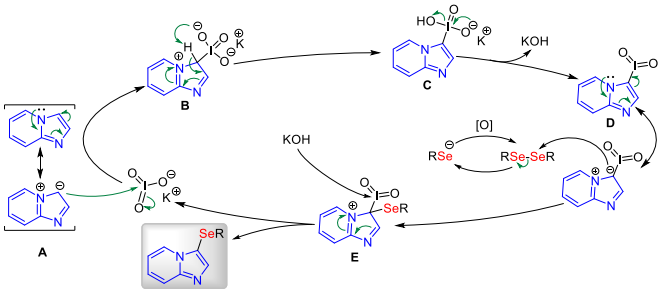
In view of the unique features observed in this new coupling reaction and to gain some insight into the mechanism involved in the KIO_3-catalyzed chalcogenation of indoles/IPs through C(sp^2)−H functionalization, some control experiments were conducted (Scheme 8). A radical inhibitor did not hamper the reaction and **4a** was obtained in 82% yield (Scheme 8a). Thus, the possibility of a radical pathway was neglected. We have also observed that the reaction under oxygen atmosphere had no negative effect (Scheme 8b), while under argon atmosphere an abrupt decrease was perceived (Scheme 8c). These results signify the importance of reaction under open atmosphere. When iodine was used as the catalyst (Scheme 8d), the reaction afforded **4a** in low yield, indicating that this specie most probably is not involved in the catalytic process, as observed in our previous research. When the standard reaction was performed in the presence of tertiary amines as the base (Scheme 8e), the reaction showed complete tolerance. These excludes the possibility of any acidic species, as observed in our previous work.[10i],[11h] There was no reaction when indole **2a** or diselenide **3a** or disulfide **5a** was used alone under the standard conditions (Scheme 8f). Notably, when IP **7a** was used without dichacogenide, the iodate specie of IP was detected in LCMS (Scheme 8g, S.I.-s34). This motivated us to try the reaction of **7a** with diselenide **3a** (Scheme 8h, S.I.-s35). Interestingly, selenylated product **8a** as well as iodate intermediate were also detected in LCMS. Considering the role of glycerol in this transformation, we are not ascertain about its contribution and a more comprehensive study is needed.



Scheme 8. Controlled experiments.

Based on these results, a plausible mechanism for this transformation could be proposed (Scheme 9). Initially, a nucleophilic attack of specie **A** on hypervalent iodate afford the specie **B**. This specie **B**, through intramolecular proton transfer (IPT) leads to specie **C**, which on releasing KOH forms the

intermediate **D** (captured in LCMS). A nucleophilic attack of **D** on diorganyl diselenide results in selenylated specie **E** and selenolate anion. The selenolate anion suffer oxidation by air resulting in the diselenide (for this reason only half molar equiv. of dichalcogenide was needed). Finally, the specie **E** in the presence of KOH forms the desired product with the subsequent regeneration of the catalyst in the reaction medium.



Scheme 9. Plausible mechanism.

Conclusions

We have developed a synthetically attractive, robust and greener approach for the synthesis of 3-Se/S-indole and IP derivatives in good to excellent yields. This is an important contribution considering the potential therapeutic application of these compounds. The procedure provided good results in the presence of the KIO_3 as non-toxic, easily handleable and stable catalyst combining with stoichiometric amount of glycerol with a half molar equivalent of diorganyl dichalcogenides. The reaction showed tolerance for various substituents with different electronic and steric effects using an odourless source of chalcogens and without the need of the exclusion of air and moisture. Moreover, this method could be applied in the large-scale synthesis of 3-chalcogenyl indoles.

The key features of this benign and robust protocol are: (1) metal-free and solvent-free; (2) open to the air; (3) atom-economic; (4) gram-scalable; (5) non-toxic and easily handleable catalyst; (6) regioselective; and (7) applicable to different sources of organochalcogenides as well as a wide range of indoles, IPs and other *N*-heterocycles.

Experimental Section

General

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 200 MHz and 400 MHz on Bruker AC-200 or Varian AS-400 spectrometers, respectively. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, 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. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained either at 50 MHz or 101 MHz on Bruker AC-200 NMR or Varian AS-400 spectrometers spectrometer, respectively. Spectra were recorded in $CDCl_3$ solutions. 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), quint (quintet), sext (sextet) and m (multiplet). High resolution mass spectra were recorded on a Bruker microTOF-Q II ESI mass spectrometer equipped with an automatic syringe pump for sample injection. The LC-MS analyzes were performed on system consisted of a high performance liquid chromatograph equipped with a mass spectrometer (Shimadzu LC-20A-MS-2020) with a source of ionization electrospray (ESI). The mobile phase was an acetonitrile and water (70:30 v/v) that has been filtered and degassed with a flow rate of 0.2 mL/min. The separation was performed under isocratic conditions. Infrared analyzes were performed on an Agilent Cary 600 Series FTIR infrared equipment. 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.

Unless otherwise stated, all reactions were carried out in Schlenk tube; all reagents and solvents were obtained from commercial sources and used without any further purification.

General procedure for the KIO_3-catalyzed chalcogenation of Indoles 2 using Diorganyl Chalcogenides 3 or 5

A mixture of appropriate indole 2 (0.25 mmol), diorganyl dichalcogenide 3 or 5 (0.125 mmol), KIO_3 (10 mol %, 6 mg), and 4 equiv. of glycerol (1 mmol, 92 mg) were charged in a Schlenck tube. The reaction was heated to 100 ºC in an oil bath for 6 h. After this, the reaction mixture was dissolved in ethyl acetate (10 mL), and washed with 2 x 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.

General procedure for the KIO_3-catalyzed chalcogenation of Imidazo[1,2-*a*]pyridines 7 using Diorganyl Chalcogenides 3 or 5

A mixture of appropriate indole 2 (0.25 mmol), diorganyl dichalcogenide 3 or 5 (0.125 mmol), KIO_3 (10 mol %, 6 mg), and 4 equiv. of glycerol (1 mmol, 92 mg) were charged in a Schlenck tube. The reaction was heated to 100 ºC in an oil bath for 6 h. After this, the reaction mixture was dissolved in ethyl acetate (10 mL), and washed with 2 x 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.

3-(Naphthalen-1-ylselanyl)-1*H*-indole (4i) [New compound]: Yield: 65% (52.6 mg); white solid; mp: 116-118 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.33 – 8.22 (m, 2H), 7.79 (d, J = 7.5 Hz, 1H), 7.61 – 7.07 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 136.5, 133.9, 132.6, 132.4, 131.5, 130.0, 128.6, 127.0, 126.3, 126.1, 125.7, 123.0, 120.9, 120.4, 111.5, 97.4. HRMS (APCI$^+$) *m/z* calculated for $C_{18}H_{13}NSe$ $[M + H]^+$ 324.0287, found 324.0292.

5-Chloro-3-(phenylselanyl)-1*H*-indole (**6a**) [New compound]: Yield: 70% (53.5 mg); yellow solid; mp: 112−115ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.43 (s, 1H), 7.60 (d, J = 1.9 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.23 – 7.10 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 134.8, 133.4, 132.6, 131.3, 129.2, 128.9, 126.9, 125.9, 123.5, 119.9,

112.6, 98.1. HRMS (APCI$^+$) *m/z* calculated for $C_{14}H_{10}NClSe$ $[M]^+$ 306.9659, found 306.9659.

5-Iodo-3-(phenylselanyl)-1*H*-indole (6c) [New compound]: Yield: 69% (68.8 mg); white solid; mp: 124-127 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.46 (s, 1H), 7.98 (s, 1H), 7.51 – 7.12 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 135.6, 133.4, 132.6, 132.1, 131.5, 129.2, 129.2, 128.8, 125.9, 113.4, 97.6, 84.7; HRMS (APCI$^+$) *m/z* calculated for $C_{14}H_{10}NISe$ $[M]^+$ 398.9018, found 398.9019.

5-Iodo-3-(phenylthio)-1*H*-indole (6ac) [New compound]: Yield: 70% (61.4 mg); white solid; mp: 111-113 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (s, 1H), 7.96 (s, 1H), 7.53 – 7.09 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 138.8, 135.7, 131.7, 131.5, 128.9, 128.5, 126.0, 125.1, 113.6, 102.6, 84.9; HRMS (APCI$^+$) *m/z* calculated for $C_{14}H_{10}NIS$ $[M]^+$ 350.9573, found 350.9575.

3-(Phenylthio)-1*H*-indole-4-carbonitrile (6af) [New compound]: Yield: 71% (44.4 mg); yellow solid; mp: 166-167 ºC; ^{1}H NMR (200 MHz, DMSO-d_6) δ = 12.40 (s, 1H), 8.09 (d, *J* = 2.6 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.40 – 7.06 (m, 6H); ^{13}C NMR (50 MHz, DMSO-d_6) δ = 139.5, 137.1, 136.4, 128.8, 127.7, 127.4, 125.5, 124.9, 122.0, 117.7, 117.6, 101.1, 99.4; HRMS (APPI$^+$) *m/z* calculated for $C_{15}H_{10}N_2S$ $[M]^+$ 250.0565, found 250.0568.

3-(Benzylselanyl)-7-methyl-2-phenylimidazo [1,2-*a*] pyridine (8k) (New compound): Yield: 54% (103 mg); yellow liquid; ($C_{21}H_{18}N_2Se$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 – 8.08 (m, 2H), 8.15 – 8.07 (m, 1H), 7.94 (d, *J* = 7.0 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.36 – 7.30 (m, 2H), 7.06 – 6.95 (m, 3H), 6.89 – 6.81 (m, 2H), 6.45 (dd, *J* = 7.0, 1.4 Hz, 1H), 3.79 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 150.9, 147.6, 138.1, 136.9, 134.3, 128.6, 128.5, 128.4, 128.1, 128.0, 127.0, 124.5, 115.7, 114.8, 103.3, 33.1, 21.3; IR (KBr) $\overline{\nu}$ (cm^{-1}): 3062, 3027, 2978, 2915, 1951, 1890, 1810, 1646, 1495, 1464, 1440, 1348, 1232, 855, 775, 759, 696; HRMS (APCI, *m/z*) calculated for $C_{21}H_{19}N_2Se$ $[M+H]^+$: 379.0709, found: 379.0705.

4-((7-Methyl-2-phenylimidazo [1,2-*a*] pyridin-3-yl)thio) aniline (8o) (New compound): Yield: 78% (129 mg); yellow solid; mp: 240-242 °C; ($C_{20}H_{17}N_3S$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.31 – 8.20 (m, 2H), 8.17 (dd, *J* = 7.2, 0.7 Hz, 1H), 7.46 – 7.33 (m, 3H), 7.29 – 7.16 (m, 1H), 6.94 – 6.79 (m, 2H), 6.66 (dd, *J* = 7.2, 1.9 Hz, 1H), 6.57 – 6.48 (m, 2H), 3.59 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 150.5, 147.2, 145.5, 137.6, 134.0, 133.9, 129.6, 128.6, 128.6, 128.5, 128.4, 128.4, 123.8, 122.9, 116.2, 116.2, 115.5, 115.5, 107.9, 21.5; IR (KBr) $\overline{\nu}$ (cm^{-1}): 3404, 3327, 3210, 3051, 3025, 1965, 1945, 1873, 1794, 1733, 1624, 1601, 1495, 1352, 1301, 1171, 816, 775, 699; HRMS (APCI, *m/z*) calculated for $C_{20}H_{18}N_3S$ $[M+H]^+$: 332.1216, found: 332.1216.

3-((4-(tert-Butyl)phenyl) thio)-7-methyl-2-phenylimidazo [1,2-*a*]pyridine (8p) (New compound): Yield: 88% (164 mg); colorless liquid; ($C_{24}H_{24}N_2S$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.25 – 8.19 (m, 2H), 8.13 – 8.02 (m, 1H), 7.49 – 7.46 (m, 1H), 7.44 – 7.28 (m, Hz, 3H), 7.21 – 7.16 (m, 2H), 6.93 – 6.89 (m, 2H), 6.64 – 6.56 (m, 1H), 2.37 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 151.1, 149.2, 147.4, 137.7, 133.6, 134.0, 128.4, 128.4, 128.3, 126.4, 125.5, 123.7, 116.1, 115.5, 106.0, 34.4, 31.2, 21.3; IR (KBr) $\overline{\nu}$ (cm^{-1}): 3068, 2957, 2866, 1946, 1887, 1805, 1754, 1640, 1493, 1440, 1352, 1269, 1236, 1169, 1118, 1010, 816, 795, 775, 691; HRMS (APCI, *m/z*) calculated for $C_{24}H_{25}N_2S$ $[M+H]^+$: 373.1733, found: 373.1731.

3-((4-Chlorophenyl)thio)-7-methyl-2-phenylimidazo[1,2-*a*] pyridine (8q) (New compound): Yield: 80% (140 mg); white solid; mp: 169-171 °C; ($C_{20}H_{15}N_2SCl$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 – 8.14 (m, 2H), 8.05 (d, *J* = 6.9 Hz, 1H), 7.47 (s, 1H), 7.44 – 7.39 (m, 2H), 7.37 – 7.31 (m, 1H), 7.16 – 7.09 (m, 2H), 6.91 – 6.85 (m, 2H), 6.65 (dd, *J* = 7.0, 1.2 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 151.5, 147.6, 138.0, 134.1, 133.4, 132.0, 129.5, 128.6, 128.4, 128.3, 126.8, 123.4, 116.3, 115.8, 104.9, 21.3; IR (KBr) $\overline{\nu}$ (cm^{-1}): 3072, 3053, 3023, 1930, 1880, 1798, 1745, 1646, 1493, 1473, 1440, 1085, 1006, 809, 771, 689; HRMS (APCI, *m/z*) calculated for $C_{20}H_{16}N_2SCl$ $[M+H]^+$: 351.0717, found: 351.0721.

7-Methyl-3-((4-nitrophenyl)thio)-2-phenylimidazo [1,2-*a*] pyridine (8r) (New compound): Yield: 76% (137 mg); yellow solid; mp: 197-198 °C; ($C_{20}H_{15}N_3SO_2$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 – 8.07 (m, 2H), 8.06 – 7.99 (m, 3H), 7.52 (s, 1H), 7.43 – 7.33 (m, 3H), 7.07 – 7.01 (m, 2H), 6.74 (dd, *J* = 7.0, 1.6 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 152.2, 148.0, 146.0, 145.3, 138.6, 133.0, 128.9, 128.5, 128.2, 125.2, 124.5, 123.3, 116.6, 116.3, 115.5, 102.8, 21.4; IR (KBr) $\overline{\nu}$ (cm^{-1}): 3088, 3051, 2915, 1947, 1830, 1805, 1646, 1575, 1509, 1336, 1105, 1081, 857, 771, 742, 698; HRMS (APCI, *m/z*) calculated for $C_{20}H_{16}N_3SO_2$ $[M+H]^+$: 362.0958, found: 362.0959.

7-Methyl-3-(naphthalen-2-ylthio)-2-phenylimidazo [1,2-*a*] pyridine (8t) (New compound): Yield: 81% (148 mg); white solid; mp: 162-163 °C; ($C_{24}H_{18}N_2S$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.25 – 8.17 (m, 2H), 8.14 – 8.09 (m, 1H), 7.74 – 7.69 (m, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.52 – 7.47 (m, 1H), 7.43 – 7.31 (m, 6H), 7.15 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.61 (dd, *J* = 7.0, 1.6 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 151.6, 147.7, 138.0, 134.0, 133.7, 133.1, 131.9, 129.3, 128.6, 128.5, 128.4, 127.8, 127.1, 126.8, 125.8, 123.9, 123.8, 123.5, 116.4, 115.8, 105.5, 21.4; IR (KBr) $\overline{\nu}$ (cm^{-1}): 3049, 2972, 2917, 1956, 1888, 1843, 1752, 1699, 1646, 1593, 1440, 1352, 1234, 806, 773, 744, 700; HRMS (APCI, *m/z*) calculated for $C_{24}H_{19}N_2S$ $[M+H]^+$: 367.1263, found: 367.1264.

7-Methyl-2-phenyl-3-(pyridin-4-ylthio) imidazo [1,2-a] pyridine (8u) (New compound): Yield: 77% (122 mg); pale yellow solid; mp: 160-161 °C; ($C_{19}H_{15}N_3S$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.35 – 8.32 (m, 2H), 8.11 – 8.07 (m, 2H), 8.02 (d, *J* = 7.0 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.43 – 7.38 (m, 2H), 7.36 – 7.32 (m, 1H), 6.85 – 6.82 (m, 2H), 6.70 (dd, *J* = 7.0, 1.6 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 152.1, 149.8, 147.8, 147.3, 138.3, 133.0, 128.7, 128.4, 128.1, 123.2, 119.7, 116.4, 116.0, 102.1, 21.2; IR (KBr) $\overline{\nu}$ (cm^{-1}): 3043, 2919, 1939, 1842, 1731, 1696, 1646, 1571, 1468, 1403, 1356, 1240, 808, 771, 691; HRMS (APCI, *m/z*) calculated for $C_{19}H_{16}N_3S$ $[M+H]^+$: 318.1059, found: 318.1058.

2-(Naphthalen-2-yl)-3-(phenylselanyl) imidazo [1,2-*a*] pyridine (9i) (New compound): Yield: 71% (142 mg); pale yellow solid; mp: 142-143 °C; ($C_{23}H_{16}N_2Se$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (d, *J* = 1.0 Hz, 1H), 8.35 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.28 (dt, *J* = 6.9, 1.0 Hz, 1H), 7.88 – 7.85 (m, 2H), 7.79 (dd, *J* = 6.1, 3.4 Hz, 1H), 7.70 (dd, *J* = 9.0, 0.9 Hz, 1H), 7.42 (dd, *J* = 6.3, 3.2 Hz, 2H), 7.23 – 7.19 (m, 1H), 7.09 (s, 5H), 6.72 (td, *J* = 6.8, 1.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 151.5, 147.8, 133.3, 131.3, 130.9, 129.7, 128.6, 128.4, 128.2, 127.8, 127.6, 126.7, 126.5, 126.4, 126.3, 126.0, 125.5, 117.4, 113.0, 103.4; IR (KBr) $\overline{\nu}$ (cm^{-1}): 3066, 3027, 1930, 1809, 1705, 1628, 1573, 1489, 1473, 818, 763, 734, 685, 663; HRMS (APPI, *m/z*) calculated for $C_{23}H_{17}N_2Se$ $[M+H]^+$: 401.0553, found: 401.0550.

2-(Naphthalen-2-yl)-3-(phenylthio) imidazo [1,2-*a*] pyridine (9ai) (New compound): Yield 63% (111 mg); pale yellow solid; mp: 129-130 °C; ($C_{23}H_{16}N_2S$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.73 (s, 1H), 8.39 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.23 (d, *J* = 6.8 Hz, 1H), 7.89 – 7.85 (m, 2H), 7.82 – 7.77 (m, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.27 – 7.23

(m, 1H), 7.18 – 7.13 (m, 2H), 7.10 – 7.05 (m, 1H), 7.03 – 6.97 (m, 2H), 6.76 (td, J = 6.8, 0.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 151.2, 147.2, 135.2, 133.41, 130.9, 128.7, 128.0, 127.9, 127.6, 126.7, 126.4, 126.2, 126.1, 126.0, 125.8, 124.5, 117.6, 113.1, 106.9; IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3096, 3068, 2957, 2925, 1941, 1909, 1874, 1850, 1815, 1791, 1630, 1581, 1475, 1230, 818, 765, 734, 685; HRMS (APPI, *m/z*) calculated for $C_{23}H_{17}N_2S$ $[M+H]^+$: 353.1107, found: 353.1105.

2-Phenyl-3-(phenylselanyl)benzo[*d*]imidazo[2,1-*b*]thiazole (11c) (New compound): Yield: 75% (152 mg); pale yellow solid; mp: 141-142 °C; ($C_{21}H_{14}N_2SSe$) ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.56 – 8.43 (m, 1H), 8.12 – 7.95 (m, 2H), 7.66 – 7.57 (m, 1H), 7.44 – 7.11 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 154.2, 151.5, 133.9, 133.7, 132.5, 130.3, 129.9, 128.4, 128.3, 128.3, 128.2, 126.8, 126.2, 125.0, 124.0, 114.6, 104.2; IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3066, 2921, 1942, 1893, 1577, 1479, 1436, 1369, 1314, 1261, 1122, 1069, 1020, 771, 734, 689, 665, 628, 569, 461; HRMS (APCI, *m/z*) calculated for $C_{21}H_{15}N_2SSe$ $[M+H]^+$: 407.0116, found: 407.0119.

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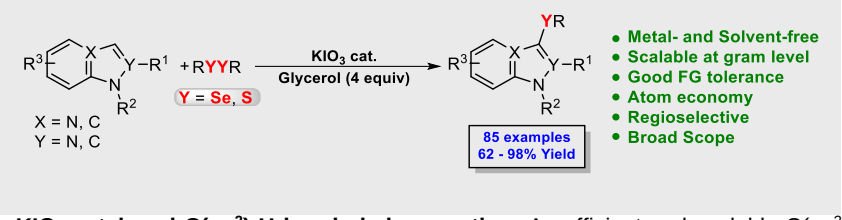

KIO_3 catalysed C(sp^2)-H bond chalcogenation: An efficient and scalable C(sp^2)-H bond chalcogenation (Se/S) of 5-membered *N*-heterocyclic arenes, using KIO_3 as a stable and easily handleable catalyst under solvent free conditions, has been developed. Compared to other chalcogenation methods, this alternate sustaible system has significantly increased the substrate scope and avoids the use of non-stable and toxic catalyst.

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Direct, metal-free C(sp^2)-H chalcogenation of indoles and imidazopyridines with dichalcogenides, catalysed by KIO_3