General, mild and metal-free functionalization of indole and its derivatives through direct C3-selenylation

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TOC text:

Nature mimicking synthetic route allow for the preparation of C-3 indoyl selenoethers bearing labile functionalized alkyl substituents on selenium atom.

Key Topics: Indole chemistry, selenium, electrophilic substitution

ABSTRACT

A very mild method for the introduction of functionalized alkylselenyl group at C-3 position of the indole ring was developed. Proposed procedure consists of an electrophilic substitution of indole and its derivatives with bis(O,O-diisopropoxyphosphorothioyl) diselenide and subsequent cleavage of the P-Se bond with tetrabutylammonium fluoride in the presence of various electrophilic reagents. These method can be successfully applied, inter alia, for the preparation of amino acid and glucoside derivatives of 3-selenoindole.

INTRODUCTION

The indole ring is a structural motif that is widely distributed among the naturally occurring and synthetic bioactive compounds.**[1]** By way of example, indole-based natural anticarcinogens can be isolated from cruciferous vegetables or deep water plants **[2-3]** while its derivatives obtained synthetically are commonly used as pharmaceuticals of diverse biological activities. For instance, oxindoles **[4]** are used as an antimicrobial agents, while 2-arylindoles are COX-2 inhibitors, reducing the inflammation and pain.**[5]** Among them, 3-sulfenylated and 3-selenylated indoles are found to exhibit anticancer and anti-HIV activity. **[6-10].** This ubiquity of indole across pharmaceuticals and natural products qualifies it as an attractive scaffold for novel drug development.

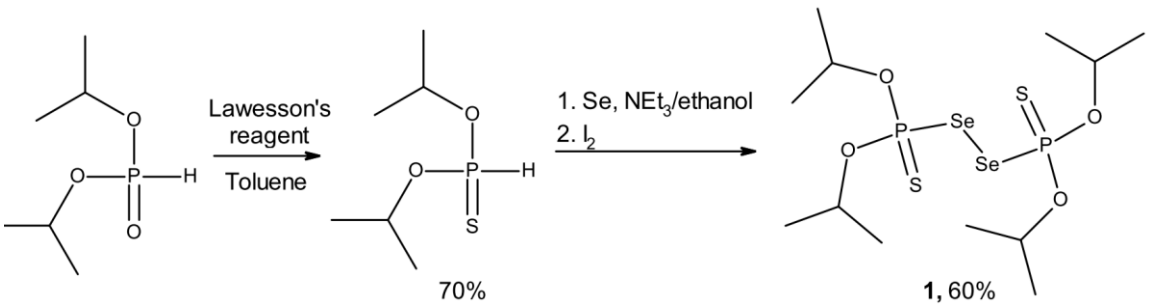
Various synthetic methods for indole selenylation have been reported. Over the past few years, synthetic methods for the preparation indoyl selenides have been drastically improved, but the reaction of indole with diorganyl diselenide in the basic conditions remains the most common pathway. **[11]** Other commonly used selenylation methods are electrophilic substitution with organoselenium halides or phthalimides **[12-15]** and copper-catalyzed reaction with diorganyl diselenides **[16]**. However, despite of their advantages, this methods have one common drawback: all methods require the usage of diaryl or dialkyl diselenides, and especially the preparation of the latter might be the major challenge of the synthetic procedure. Most of these reported procedures focus on the usage of diaryl diselenides, among which diphenyl diselenide is being the one most commonly used, **[17-22]** and thus omit the discussion of the difficulties related to the diselenide preparation. An alternative method of the synthesis involves the reaction of indole with *in-situ* prepared cyanogen triselenide, which is highly toxic. Obtained 3-selenocyanatoindole can be further reduced using

$NaBH_4$, finally forming sodium selenolate that can be used in the reaction with electrophiles (eg. alkyl halides) to form indoyl selenoethers. **[23]** Finally, metal-catalyzed indole and 5-deazapurine selenylation reactions were reported, although harsh conditions of the processes (temperature ~110 °C) limit their application in the synthesis. **[24-27]**

As stated before, great deal of attention has been lately paid to synthesis of indoyl thio- and selenoethers due to their potent therapeutic value. The most prominent (and well known bioactive) group of indoyl thio- and selenoethers contain aryl substituents on the chalcogen atom, eg. tubulin polymerization inhibitors or PPAR gamma agonists.**[28,29]** The popularity of these scaffold is due to the simplicity of the synthesis of aryl diselenides, which are used to incorporate thio- and selenoaryl substituent into indole ring.**[16]** The recently developed anti-HIV agents **[10]** composed of an indole ring bearing alkylselenyl substituents shows that there is an urgent need to develop a simple and general path for the synthesis of these potentially bioactive compounds.

According to the known metabolic pathway, the selenium incorporation into bioorganic compounds takes place with the participation of the selenophosphate **[30]**. Inspired by nature, we decided to examine the selenylation efficiency of indoles by selenophosphate analogue, namely, bis(O,O-diisopropoxyphosphorothioyl) diselenide **1**. In present work we report easy, selective and efficient method for introduction of protected selenole group into indole scaffold. The formed indole O,O-diisopropoxyphosphorothioylselenyl derivatives possess hydrolyzable Se-P bond, which can be selectively deprotected in the presence of electrophilic substrate. Thus, our synthetic route offers an efficient method to synthesize various alkyl selenoindoles, such as

alkyl, aryl or acyl. The most prominent advantage of our method is mild reaction conditions, which allow us to obtain susceptible selenoindole derivatives, such as *Se*-(3-indolyl)-L-selenocysteine, an example of unnatural tryptophan-alike derivatives which are of a broad interest,**[31-33]** or 3-indolyl β-selenoglycosides that can be used as a glycosidase inhibitors.**[34]** The preparation of mentioned compounds would be difficult or even impossible with currently known methods of the selenoindole derivative synthesis. We also examine the scope of our synthetic procedure, showing that our method is suitable to efficiently introduce selenoether group not only into indole rings with various substituents, but also into 7-deazapurine derivatives, which are known to exhibit a significant cytostatic effect.**[35]** Bis(O,O-diisopropoxyphosphorothioyl) diselenide **1** used as selenium source is a crystalline, non hygroscopic, moisture, temperature and light stable solid with a long shelf life (it can be stored on shelf for 10 years without significant traces of degradation). It is also easy to prepare from readily available O,O-diisopropyl *H*-phosphonate (Scheme 1). **[36]**



Scheme 1. Preparation of bis(O,O-diisopropoxyphosphorothioyl) diselenide **1**

RESULTS AND DISCUSSION

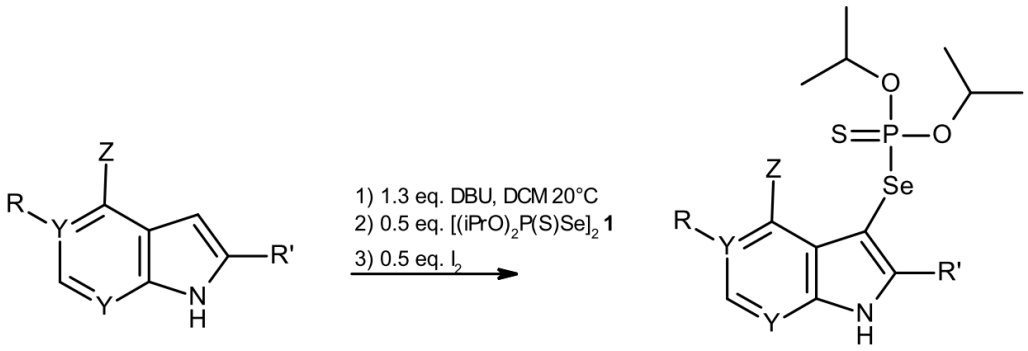
Our research was focused on the development of an effective method for electrophilic selenylation of indole rings. For this purpose we used bis(O,O-diisopropoxyphosphorothioyl) diselenide **1**, which we have previously shown to

be an easy to handle and stable source of electrophilic selenium. The initial reactions were performed using O,O-diisopropoxyphosphorothioylselenyl bromide generated *in-situ* in the reaction of **1** with bromide at -78 ^{o}C in DCM followed by its reaction with indole. This method led us to obtain the desired product **2a**, however, in poor yields (12-15%). Suspecting that low yields were caused by a low nucleophilicity of indole moiety, we decided to increase indole nucleophilicity by the deprotonation of pyrrole ring instead of increasing the selenide electrophilicity. Treatment of indole with 1 in the presence of DBU in DCM at room temperature gave 3-selenylated indole **2a** in an almost quantitative yield. Addition of iodine allowed us to reduce the amount of **1** to 0.5 eq. and thereby increase selenium atom economy to 100%.

We then proceed to examine the suitability of this procedure (Table 1) for selenylation of substituted indoles. All tested compounds underwent selenylation at 3-position exclusively. We also successfully applied our selenylation procedure for 7-deazapurines, which are structurally similar to nucleobases, but share the same structure of the pyrrole ring with indole. Here we also observed only one product with the selenophosphate group attached to 7-position. The reaction yields of obtained products **2a-h** are shown in Table 1. To further examine the scope of our method, we performed the same procedure for other activated aromatic systems, such as carbazole, dibenzazepine, pyrrole, furan, thiophene and benzotriazole. In most cases we either observed only trace amount of product (furan and thiophene) or did not observe formation of any product at all (carbazole and dibenzazepine). On the other hand, reaction with pyrrole anion led to multiple products, and in case of benzotriazole the reaction went through N-phosphorothioylation accompanied with a loss of selenium to

give benzotriazol-1-yl-phosphonothioic acid O,O-diisopropyl ester as the sole product. The reaction of **1** with indole also did not proceed in the absence of DBU. These results further emphasize that additional activation of electron-rich aromatic ring is indispensable for the reaction with poorly electrophilic diselenide **1** and provide that our procedure leads selectively to C-selenylation of a pyrrole ring.

Table 1. Synthesis of 3-[(O,O-diisopropoxyphosphorothioyl)seleno]indoles 2a-2h using bis(O,O-diisopropoxyphosphorothioyl) diselenide **1**

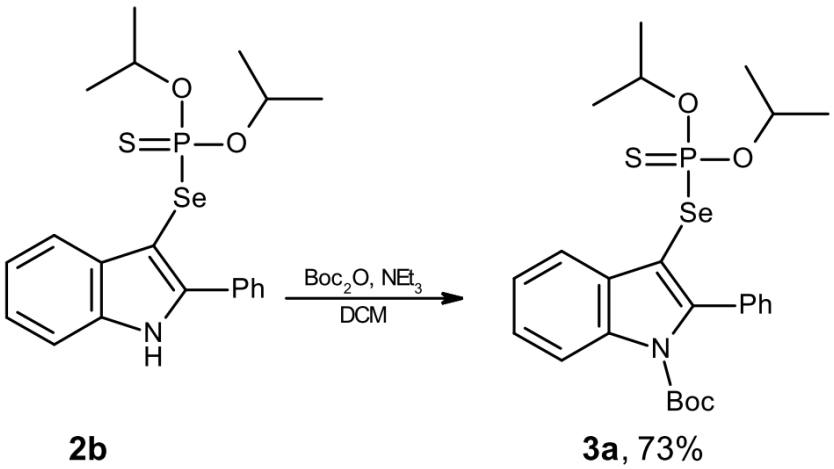


products **2a-h**
50 - 80% yield

	R	**R'**	**Y**	**Z**	**yield**
2a	H	H	C	H	75%
2b	H	Ph	C	H	78%
2c	Br	H	C	H	56%
2d	Cl	H	C	H	66%
2e	F	H	C	H	80%
2f	CN	H	C	H	60%
2g	-	H	N	Cl	50%
2h	-	H	N	OMe	67%

*Yields are given for isolated products.

Encouraged by the efficacy of the selenylation process we tried to deprotect the selenide **2b [37]** through the selective cleavage of P-Se bond. To select an appropriate nucleophilic agent for this reaction, we examined the efficiency of the thiophosphate removal from *S*-(2,4-dinitrophenyl) phosphorodithioic acid *O*,*O*-diisopropyl ester as a model compound. Our model compound reacted with nucleophiles, forming colorful 2,4-dinitrobenzenethiolate as a product. We examined the cleavage of P-S bond with ammonium fluoride, tetrabutylammonium hydroxide (TBAOH), tetrabutylammonium fluoride (TBAF), ammonia, dimethylamine, sodium methanolate, DBU, potassium hydroxide, potassium trimethylsilanolate, *N*-methylmorpholine *N*-oxide and sodium propionaldehyde oximate. Similarly as in case of phosphoroselenoic acid Se-esters,**[38]** here also only TBAF caused the rapid appearance of the intensive color of the thiolate.



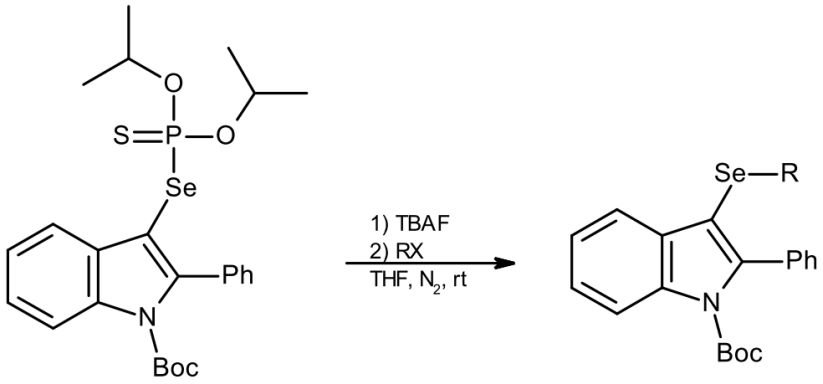
2b **3a**, 73%

Scheme 2. *Tert*-butoxycarbonylation of **2b**

However, it turned out that the reaction of TBAF with **2b** in DCM in the presence of methyl iodide led to the formation of multiple products. We assumed that the side reactions could be initiated by the removal of the acidic N-H proton from

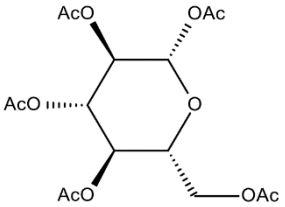
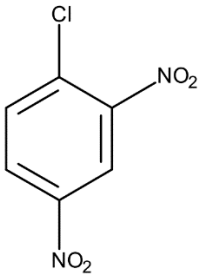
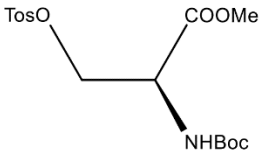
pyrrole ring under the basic reaction conditions. Therefore we decided to protect the pyrrole nitrogen atom with Boc group. After *N*-Boc protection of **2b** (Scheme 2) the reaction with TBAF proceeded to give exclusively the product of P-Se cleavage. We determined the amount of TBAF needed for the full and rapid deprotection of selenole to be 1.8 eq by TLC analysis of the reaction mixtures (Table S1). When reaction was performed in DCM in the presence of methyl iodide as the terminating electrophile only desired product **4a** was formed. Surprisingly, the same reaction with benzyl bromide led to the mixture of **4c** and chloromethylated derivative. Moreover when n-butyl bromide was used as an electrophile, generated selenolate reacted with DCM exclusively to give *Se*-chloromethylated product instead of **4d**. Thus, to suppress the unwanted side reaction caused by the solvent, we changed reaction environment to THF, what allowed us to perform reactions with other less reactive electrophilic agents. In case of compounds **4i** and **4k** the yield was poor and we observed multiple products formation, including diselenides and N-Boc dehydroalanine methyl ester as selenolates oxidation and *O*-tosyl serine elimination products, respectively. To avoid this undesired side-reactions, we added ascorbic acid to buffer the reaction mixture and ensure reducing conditions. This procedures (Procedure A and B in experimental part) allowed us to obtain products **4a-4l** (Table 2) in yields from 71% to 93%.

Table 2 Synthesis of *Se*-substituted *N-tert*butoxycarbonyl-3-selenoindoles **4a**-**4l**



3a

products **4a-4l**
71 - 93% yield

	RX	yield		RX	yield
4a	CH_3I	80%	4g	$Cl(CH_2)_4Br$	77%
4b	$(CH_3)_2CHI$	79%	4h	$ClCH_2COOCH_2CH_3$	78%
4c	BnBr	86%	4i*		85%
4d	n-BuBr	93%	4j		78%
4e	$CH_2=CHCH_2Br$	71%	4k *		90%
4f	$ClCH_2(CH_2)_2CN$	76%	4l	$BrCH_2C(O)CH_3$	75%

***** compounds 4i and 4k were prepared according to procedure B, other compounds were prepared following the procedure A.

CONCLUSIONS

In summary, we have developed an efficient method for the C(3) selenylation of indole and its analogues using bis(O,O-

diisopropoxyphosphorothioyl) diselenide 1 as selenium source and TBAF as nucleophilic reagent for P-Se bond cleavage, followed by treating the resulting selenolate with a variety of electrophiles. Due to a mild conditions, this selenylation can be successfully performed in the presence of a simple functional groups, such as halides, nitriles and ethers. We show that this procedure is also suitable to functionalize 7-deazapurines, allowing to synthesize a novel purine analogues. Reaction products were obtained under mild reaction conditions, with high yields and under short reaction times. Finally, we were able to obtain selenoindoyl derivatives of amino acid and glycoside which can be used as a scaffold for a new class of bioactive compounds.

EXPERIMENTAL SECTION

General information:

The products were purified using column chromatography on silica gel (60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer, operating at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR), 160 MHz (^{31}P NMR) and 80 MHz (^{77}Se NMR) in $CDCl_3$ as a solvent. All NMR spectra are included in supporting information. Multiplicities were marked as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), hept (heptet), m (multiplet), app. t (apparent triplet). High resolution mass spectra were recorded on a Waters XEVO-G2 XS Q-TOF mass spectrometer equipped with an electrospray ion source.

General procedure for thiophosphoselenylation of indoles, compounds 2a-h

To a solution of indole (0.2 g, 1.71 mmol) in 10 ml of dry DCM was added DBU (335 µl, 2.24 mmol). To the resulting solution was added bis(O,O-diisopropoxyphosphorothioyl) diselenide **1** (0.447 g, 0.86 mmol) in DCM (2 ml). The reaction mixture was then stirred for 5 min at room temperature and 0.6M solution of iodine in DCM (1.45 ml, 0.87 mmol) was added. After complete consumption of the starting material, as monitored by TLC, the reaction mixture was diluted with 40 ml of DCM and washed with a 5% citric acid solution (20 ml), a 10% sodium thiosulfate solution (20 ml) and water (20 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography (hexane:EtOAc; 10:1) to give compounds **2a-h** as white solids.

Procedure for the synthesis of N-tertbutoxycarbonyl-3-[(O,O-diisopropoxyphosphorothioyl)seleno]-2-phenylindole, compound 3a

To a solution of **2b** (3 g, 7 mmol) in 30 ml of dry DCM was added di-*tert*-butyl dicarbonate (4.8 g, 22 mmol) and DMAP (0.086g, 0.7 mmol). The reaction mixture was stirred for 5 hours at room temperature under nitrogen atmosphere. The product was purified by silica gel column chromatography (hexane:EtOAc; 25:1) to give compound **3a** as slightly yellow oil which solidified upon standing.

General procedure for the synthesis of *Se*-substituted (Procedure A) N-*tert*butoxycarbonyl-3-seleno-2-phenylindole, compounds 4a-h, 4j, 4l

Compound **3a** (100 mg, 0.18 mmol) was diluted in 2 ml of anhydrous THF under nitrogen atmosphere. Electrophilic reagent (0.198 mmol) was placed into a reaction flask and then was added 0.1M tetrabutylammonium fluoride (330 µl,

0.33 mmol). The reaction mixture was stirred for 10 minutes and monitored by TLC. The product was purified by silica gel column chromatography (hexane:chloroform; 5:1) to give compounds **4a-h, 4j, 4l**.

General procedure for the synthesis of *Se*-substituted (Procedure B) N-*tert*butoxycarbonyl-3-seleno-2-phenylindole, compounds 4i, 4k

Compound **3a** (100 mg, 0.18 mmol) was dissolved in anhydrous THF (1 ml) under nitrogen atmosphere and 0.1M tetrabutylammonium fluoride (330 µl, 0.33 mmol) was added. The reaction mixture turned yellow immediately and, after 5 min of stirring, a suspension of finely grinded ascorbic acid (32 mg, 0.18 mmol) in 1 ml of anhydrous THF was added. After stirring for 1 min a solution of electrophilic reagent (0.198 mmol) in 1 ml of anhydrous THF was added. The reaction mixture was stirred for 30 minutes and monitored by TLC. The product was purified by silica gel column chromatography (1:1 n-hexane/chloroform) to give pure compound **4k**.

In case of compound **4i**, the crude product was dissolved in 15 ml of ethyl acetate and the solution was filtered through thin silica pad (2g of SiO2). The silica pad was additionally washed with 5 ml of ethyl acetate and washings were concentrated. The resulting residue was dissolved in acetone (3 ml) and 80 mg of thiourea was added to remove unreacted 2,3,4,6-Tetra-O-acetyl-a-D-glucopyranosyl bromide. The mixture was heated to reflux for 5 min, cooled to rt and concentrated in vacuo. The product was purified by silica gel column chromatography (1:1 n-hexane/chloroform) to give compound **4i** with a purity of approximately 90% (as determined by 1H NMR).

Caution: Special care should be taken during operating and disposal of chromatographic fractions containing $(iPrO)_2PSF$ due to its potential neurotoxic effects. For this reason, fractions not containing products **4** were collected and neutralized by passing through a short pad of silica gel pretreated with Cu-TMEDA complex. **[39,40]**

3-[(O,O-diisopropoxyphosphorothioyl)seleno]indole (2a)

δH(400 MHz; $CDCl_3$; Me_4Si) 8.50 (1H, br s), 7.73-7.76 (1H, m), 7.37-7.47 (2H, m), 7.18-7.27 (2H, m), 4.80-4.93 (2H, hpt, J = 6 Hz, OCH), 1.28 (12H, 2 x d, J = 6 Hz, CH_3). δC(100 MHz; $CDCl_3$; Me_4Si) 135.9, 130.9, 130.9, 129.9, 129.8, 122.8, 122.0, 120.75, 120.7, 120.5, 119.8, 111.3, 96.6 (d, $^2J_{CP}$ = 8.4 Hz, C3), 73.8, 73.6, 23.8, 23.7, 23.5, 23.4. δP(160 MHz; $CDCl_3$; H_3PO_4) 79.2 (s, and Se satellites: $^1J_{PSe}$ = 498 Hz). HRMS (ESI): calcd for $C_{14}H_{21}NO_2PSSe$ $[M+H]^+$: 378.0190, found: 378.0218.

3-[(O,O-diisopropoxyphosphorothioyl)seleno]-2-phenylindole (2b)

Colourless crystals, mp: 111 °C (from ethyl acetate/n-hexane). δH(400 MHz; $CDCl_3$; Me_4Si) 11.00 (1H, br s), 8.00 (2H, m), 7.80 (1H, m), 7.41-7.53 (4H, m), 7.17-7.25 (2H, m), 4.65-4.75 (2H, hpt, J = 6 Hz, OCH), 1.15 (12H, 2 x d,J = 6 Hz, CH_3). δC(100 MHz; $CDCl_3$; Me_4Si) 142.5, 142.4, 135.9, 132.2, 132.1,129.2, 129.1, 128.6, 128.5, 123.0, 121.5, 121.0, 111.0, 95.2 (d, $^2J_{CP}$ = 8.3 Hz, C3), 73.5, 73.4, 23.7, 23.6, 23.4, 23.3. δP(160 MHz; $CDCl_3$; H_3PO_4) 79.4 (s, and Se satellites: $^1J_{PSe}$ = 504 Hz). δSe(80 MHz; $CDCl_3$; $(PhSe)_2$) 272.2 (d, $^1J_{SeP}$ = 507 Hz). HRMS (ESI): calcd for $C_{20}H_{25}NO_2PSSe$ $[M+H]^+$: 454.0503, found: 454.0528.

5-Bromo-3-[(O,O-diisopropoxyphosphorothioyl)seleno]indole (2c)

δH(400 MHz; $CDCl_3$; Me_4Si) 8.50 (1H, br s, H1), 7.90 (1H, m), 7.45 (1H, m), 7.27-7.35 (2H, m), 4.82-4.94 (2H, hpt,J = 6 Hz, OCH), 1.29 (12H, 2 x d, J = 6 Hz, CH_3). δC(100 MHz; $CDCl_3$; Me_4Si) 134.6, 132.0 (d, $^3J_{CP}$ = 5 Hz, C2), 131.7 (d, $^3J_{CP}$ = 1 Hz, C9), 125.8, 123.4,114.1, 112.6, 96.6 (d, $^2J_{CP}$ = 8.4 Hz, C3), 73.8, 73.6, 23.8, 23.7, 23.5, 23.4. HRMS (ESI): calcd for $C_{14}H_{20}BrNO_2PSSe$ $[M+H]^+$: 455.9295, found: 455.9290.

5-Chloro-3-[(O,O-diisopropoxyphosphorothioyl)seleno]indole (2d)

δH(400 MHz; $CDCl_3$; Me_4Si) 8.50 (1H, br s), 7.75 (1H, m), 7.45-7.48 (1H, dd, ^1J = 3.8 Hz, ^2J = 2.7 Hz), 7.32-7.35 (1H, d, J = 9 Hz), 7.19-7.23 (1H, dd, ^1J = 2 Hz, ^2J = 8.6 Hz), 4.82-4.94 (2H, hpt, J = 6 Hz, OCH), 1.29 (12H, 2 x d, J = 6 Hz, CH_3). δC(100 MHz; $CDCl_3$; Me_4Si) 134.3, 132.2 (d, $^3J_{CP}$ = 5 Hz, C2), 131.1, 126.6, 123.3, 120.3, 112.4, 96.5 (d, $^2J_{CP}$ = 8.3 Hz, C3), 73.9, 73.8, 23.8, 23.7, 23.5, 23.4.

HRMS (ESI): calcd for $C_{14}H_{20}ClNO_2PSSe$ $[M+H]^+$: 411.9801, found: 411.9802.

3-[(O,O-diisopropoxyphosphorothioyl)seleno]-5-fluoroindole (2e)

δH(400 MHz; $CDCl_3$; Me_4Si) 8.50 (1H, br s), 7.28-7.52 (3H, m), 6.95-7.05 (1H, m), 4.82-4.94 (2H, hpt, J = 6 Hz, OCH), 1.29 (12H, 2 x d, J = 6 Hz, CH_3). δC(100 MHz; $CDCl_3$; Me_4Si) 158.6 (d, ^{1}JCF = 236 Hz, C5), 132.7 (d, $^4J_{CP}$ = 5 Hz, C2), 132.4 (C8), 131.2 (dd, $^3J_{CF}$ = 5Hz, $^3J_{CP}$=1Hz, C9), 112.2 (d, $^3J_{CF}$ = 10 Hz, C7), 111.4 (d, $^2J_{CF}$ = 27 Hz, C4), 105.5 (d, $^2J_{CF}$ = 24 Hz, C6), 96.5 (dd, $^2J_{CP}$ = 8.4 Hz,

$^4J_{CF}$ = 5.0 Hz, C3), 73.8, 73.6, 23.8, 23.7, 23.5, 23.4. HRMS (ESI): calcd for $C_{14}H_{19}FNO_2PSSe$ $[M+H]^+$: 396.0096, found: 396.0120.

5-Cyano-3-[(O,O-diisopropoxyphosphorothioyl)seleno]indole (2f)

δH(400 MHz; $CDCl_3$; Me_4Si) 8.90 (1H, br s), 8.14 (1H, s), 7.55 (1H, dd, ^1J = 2.5 Hz, ^2J = 3 Hz), 7.49 (2H, d, J = 1Hz), 4.82-4.94 (2H, hpt, J = 6 Hz, OCH), 1.29 (12H, 2 x d,J = 6 Hz, CH_3). δC(100 MHz; $CDCl_3$; Me_4Si) 137.7, 133.0 (d, $^3J_{CP}$ = 5.5 Hz, C2), 129.9, 126.4 125.7, 120.2, 112.4, 104.0, 97.9 (d, $^2J_{CP}$ = 8.4 Hz, C3), 73.8, 73.6, 23.8, 23.7, 23.5, 23.4. HRMS (ESI): calcd for $C_{15}H_{19}N_2O_2PSSeNa$ $[M+Na]^+$: 424.9962, found: 424.9980.

6-Chloro-3-[(O,O-diisopropoxyphosphorothioyl)seleno]-7-deazapurine (2g)

δH(400 MHz; $CDCl_3$; Me_4Si) 11.30 (1H, br s), 8.80 (1H, s), 7.75 (1H, d, J = 3.5 Hz), 4.87-4.97 (2H, hpt, J = 6 Hz, OCH), 1.33 (12H, 2 x d, J = 6 Hz, CH_3). δC(100 MHz; $CDCl_3$; Me_4Si) 153.2, 152.3, 150.55, 133.7 (d, $^3J_{CP}$ = 5.65 Hz, C2), 117.6 (d, $^3J_{CP}$ = 1.7 Hz, C9), 95.6 (d, $^2J_{CP}$ = 8.6 Hz, C3), 74.3, 74.2, 23.8, 23.7, 23.5, 23.4. δP(160 MHz; $CDCl_3$; H_3PO_4) 78.5 (s, and Se satellites: $^1J_{PSe}$ = 469 Hz). HRMS (ESI): calcd for $C_{12}H_{17}ClN_3O_2PSSe$ $[M+H]^+$: 413.9705, found: 413.9714.

6-Methoxy-3-[(O,O-diisopropoxyphosphorothioyl)seleno]-7-deazapurine (2h)

δH(400 MHz; $CDCl_3$; Me_4Si) 12.30 (1H, br s), 8.50 (1H, s), 7.49 (1H, d, J = 3.5 Hz), 4.85-4.95 (2H, hpt, J = 6 Hz, OCH), 4.15 (3H, s, OCH_3), 1.32 (12H, 2 x d,J = 6 Hz, CH_3). δC(100 MHz; $CDCl_3$; Me_4Si) 163.7, 152.2, 150.6, 129.6 (d, $^3J_{CP}$ =

5.77 Hz, C2), 107.1 (d, $^{3}J_{CP}$ = 2.0 Hz, C9), 94.2 (d, $^{2}J_{CP}$ = 8.4 Hz, C3), 73.8, 73.7, 53.8, 23.8, 23.7, 23.4, 23.3. δP(160 MHz; $CDCl_3$; H_3PO_4) 78.8 (s, and Se satellites: $^{1}J_{PSe}$ = 484 Hz). HRMS (ESI): calcd for $C_{13}H_{20}N_3O_3PSSe$ $[M+H]^+$: 410.0201, found: 410.0187.

_N_-tertbutoxycarbonyl-3-[(O,O-diisopropoxyphosphorothioyl)seleno]-2-phenylindole (3a)

δH(400 MHz; $CDCl_3$; Me_4Si) 8.26 (1H, m), 7.8 (1H, m), 7.34-7.54 (7H, m), 4.55-4.6 (2H, hpt, J = 6 Hz, OCH), 1.25 (9H, s, CH_3C), 1.2 (12H, 2 x d, J = 6 Hz, CH_3CH). δC(100 MHz; $CDCl_3$; Me_4Si) 149.6, 146.7, 144.6 (d, $^{2}J_{CP}$ = 8.06 Hz, C9), 136.6, 133.8 (d, $^{4}J_{CP}$ = 3 Hz, C10), 131.4, 130.65, 130.6, 128.0, 127.4, 125.1, 123.0, 121.3, 115.0, 106.5 (d, $^{2}J_{CP}$ = 8.86 Hz, C3), 85.2, 83.8, 73.4, 73.3, 27.5, 27.4, 23.7, 23.6, 23.4, 23.3. δP(160 MHz; $CDCl_3$; H_3PO_4) 80.5 (s, and Se satellites: $^{1}J_{PSe}$ = 477 Hz). HRMS (ESI): calcd for $C_{25}H_{33}N_3O_4PSSe$ $[M+H]^+$: 554.1028, found: 554.1031.

***N-tert*butoxycarbonyl-3-methylseleno-2-phenylindole (4a)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.26 (1H, m), 7.8 (1H, m), 7.37-7.54 (7H, m), 2.06 (3H, s, and Se satellites: $^{2}J_{HSe}$ = 16 Hz), 1.25 (9H, s, CH_3C). δC(100 MHz; $CDCl_3$; Me_4Si) 149.7, 142.3, 136.7, 134.5, 131.2, 130.0, 128.0, 127.6, 126.0, 125.0, 123.2, 120.6, 115.2, 108.1, 83.6, 27.4, 8.3 (s, and Se satellites: $^{1}J_{CSe}$ = 62 Hz, CH_3Se). δSe(80 MHz; $CDCl_3$; $(PhSe)_2$) 248.3 (t, $^{2}J_{HSe}$ = 16 Hz). HRMS (ESI): calcd for $C_{20}H_{22}NO_3Se$ $[M+OH]^+$: 404.0759, found: 404.0759.

***N-tert*butoxycarbonyl-3-isopropylseleno-2-phenylindole (4b)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.26 (1H, m), 7.80 (1H, m), 7.34-7.49 (7H, m), 3.17-3.28 (1H, hpt, J = 6.8 Hz, and Se satellites: $^2J_{HSe}$ = 20 Hz), 1.25 (9H, s), 1.22 (6H, d, J = 6.8 Hz). δC(100 MHz; $CDCl_3$; Me_4Si) 149.7, 143.4, 136.6, 134.5, 132.2, 130.3, 127.8, 127.5, 124.9, 123.2, 121.0, 115.1, 107.7, 83.5, 33.7 (s, and Se satellites: $^1J_{CSe}$ = 56.5 Hz, SeCH), 27.4, 24.3 (s, $^2J_{CSe}$ = 13.5 Hz, $SeCHCH_3$). HRMS (ESI): calcd for $C_{22}H_{26}NO_3Se$ $[M+OH]^+$: 432.1072, found: 432.1080.

***N-tert*butoxycarbonyl-3-benzylseleno-2-phenylindole (4c)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.26 (1H, m), 7.80 (1H, m), 7.3-7.45 (5H, m), 6.9-7.15 (7H, m), 3.79 (2H, s, and Se satellites: $^2J_{HSe}$ = 14 Hz), 1.25 (9H, s). δC(100 MHz; $CDCl_3$; Me_4Si) 149.7, 143.7, 138.9, 136.6, 134.1, 131.5, 130.0, 128.7, 128.2, 127.7, 127.4, 126.6, 125.0, 123.2, 120.6, 115.2, 107.2, 83.5, 31.2 (s, and Se satellites: $^1J_{CSe}$ = 58.5 Hz, $SeCH_2$). HRMS (ESI): calcd for $C_{26}H_{26}NO_3Se$ $[M+OH]^+$: 480.1072, found: 480.1113.

***N-tert*butoxycarbonyl-3-butylseleno-2-phenylindole (4d)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.26 (1H, m), 7.80 (1H, m), 7.37-7.52 (7H, m), 2.58 (2H, t, J = 7.4 Hz, and Se satellites: $^2J_{HSe}$ = 13 Hz), 1.35-1.45 (4H, m), 1.25 (9H, s), 0.75 (3H, t, J = 7.3 Hz). δC(100 MHz; $CDCl_3$; Me_4Si) 149.7, 142.9, 136.7, 134.5, 131.8, 130.2, 127.8, 127.5, 125.0, 123.2, 120.8, 115.0, 107.2, 83.5, 32.2, 27.8 (s, and Se satellites: $^1J_{CSe}$ = 60 Hz, $SeCH_2$), 27.4, 22.5, 13.5. HRMS (ESI): calcd for $C_{23}H_{28}NO_3Se$ $[M+OH]^+$: 446.1229, found: 446.1243.

***N-tert*butoxycarbonyl-3-allylseleno-2-phenylindole (4e)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.27 (1H, m), 7.76 (1H, m), 7.34-7.50 (7H, m), 5.70 (1H, ddt, ^1J = 17 Hz, ^2J = 10 Hz, ^3J = 7 Hz), 4.76 (1H, dd, ^1J = 1.5 Hz, ^2J = 10 Hz), 4.71 (1H, dd, ^1J = 1.4 Hz, ^2J = 17 Hz), 3.22 (2H, d, J = 7.5 Hz, and Se satellites: $^2J_{HSe}$ = 13.6 Hz), 1.25 (9H, s). δC(100 MHz; $CDCl_3$; Me_4Si) 149.7, 143.6, 136.6, 134.5, 134.3, 131.6, 130.4, 127.9, 127.5, 125.0, 123.2, 120.7, 116.5, 115.1, 107.0, 83.6, 30.2 (s, and Se satellites: $^1J_{CSe}$ = 56 Hz, CCH_2), 27.4. HRMS (ESI): calcd for $C_{22}H_{24}NO_3Se$ $[M+OH]^+$: 430.0916, found: 430.0948.

***N-tert*butoxycarbonyl-3-[3-(cyanopropyl)seleno]-2-phenylindole (4f)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.28 (1H, m), 7.74 (1H, m), 7.34-7.53 (7H, m), 2.65 (2H, t, J = 6.7 Hz, and Se satellites: $^1J_{HSe}$ = 16.3 Hz), 2.07 (2H, t, J = 7 Hz), 1.63 (2H, quint, J = 6.6 Hz), 1.25 (9H, s). δC(100 MHz; $CDCl_3$; Me_4Si) 149.5, 143.7, 136.7, 134.1, 131.2, 130.2, 128.2, 127.8, 125.3, 123.5, 120.3, 119.0, 115.3, 105.6, 83.9, 27.4, 25.8 (s, and Se satellites: $^1J_{CSe}$ = 65 Hz, CH_2Se), 25.2, 16.2. HRMS (ESI): calcd for $C_{22}H_{23}N_2O_3Se$ $[M+H]^+$: 441.1076, found: 441.1004.

***N-tert*butoxycarbonyl-3-(4-chlorobutyl)seleno-2-phenylindole (4g)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.26 (1H, m), 7.80 (1H, m), 7.32-7.5 (7H, m), 3.30 (2H, t, J = 6.6 Hz), 2.50 (2H, t, J = 7Hz, and Se satellites: $^1J_{HSe}$ = 14 Hz), 1.60-1.70 (2H, m), 1.5-1.6 (2H, m), 1.25 (9H, s). δC(100 MHz; $CDCl_3$; Me_4Si) 149.6, 143.2, 136.7, 134.3, 131.6, 130.2, 127.9, 127.5, 125.1, 123.3, 120.5, 115.2, 106.7, 83.7, 44.3, 32.0, 27.4, 27.2, 26.9. HRMS (ESI): calcd for $C_{23}H_{27}ClNO_3Se$ $[M+OH]^+$: 480.0839, found: 480.0844.

***N-tert*butoxycarbonyl-3-(ethoxycarbonylmethylseleno-2-phenylindole (4h)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.26 (1H, m), 7.74 (1H, m), 7.37-7.52 (7H, m), 3.91 (2H, q, J = 7 Hz), 3.16 (2H, s, and Se satellites: $^1J_{HSe}$ = 14.8 Hz), 1.25 (9H, s), 1.05 (3H, t, J = 7 Hz). δC(100 MHz; $CDCl_3$; Me_4Si) 170.6, 149.6, 143.9, 136.6, 134.0, 131.2, 130.2, 128.1, 127.6, 125.1, 123.4, 120.5, 115.2, 106.2, 83.8, 61.1, 27.4, 26.7 (s, and Se satellites: $^1J_{CSe}$ = 69.40 Hz, CH_2Se), 13.8. HRMS (ESI): calcd for $C_{23}H_{26}NO_5Se$ $[M+OH]^+$: 476.0971, found: 476.0993.

***N-tert*butoxycarbonyl-3-(2,3,4,6-*tetra*-*O*-acetyl-D-glucopyranosylseleno) -2-phenylindole (4i)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.26 (1H, m), 7.72 (1H, m), 7.34-7.52 (7H, m), 5.10 (1H, dd, app. t, J = 9.0 Hz), 5.03 (1H, dd, app. t, J = 9.5), 4.98 (1H, dd, app. t, J = 9.0 Hz), 4.70 (1H, d, J = 10.3 Hz, H-1'), 4.15 (1H, dd, ^1J = 5.3 Hz, ^2J = 12.2 Hz, H-6'), 4.08 (1H, dd, ^1J = 2.2 Hz, ^2J = 12.2 Hz, H-6'), 3.49 (1H, ddd, ^1J = 2.2 Hz, ^2J = 5.3 Hz, ^3J = 10.0 Hz, H-5'), 2.05, 2.00, 1.99 and 1.83 (12H, 4 x s, $CH_3C=O$), 1.25 (9H, s, CH_3C). δC(100 MHz; $CDCl_3$; Me_4Si) 170.65, 170.17, 169.47, 169.35, 149.53, 143.73, 136.65, 133.78, 131.44, 130.37, 128.07, 127.54, 125.25, 123.37, 121.01, 115.05, 105.96, 86.56, 83.92, 82.75, 73.66, 70.77, 68.27, 62.34, 27.09, 20.77, 20.60, 20.59, 20.56. δSe(80 MHz; $CDCl_3$; $(PhSe)_2$) 238.1. HRMS (ESI): calcd for $C_{33}H_{38}NO_{11}Se$ $[M+H]^+$: 704.1605, found: 704.1607.

***N-tert*butoxycarbonyl-3-(2,4-dinitrophenylseleno)-2-phenylindole (4j)**

δH(400 MHz; $CDCl_3$; Me_4Si) 9.15 (1H, d, J = 2.4 Hz), 8.35 (1H, d, ^1J = 8.4 Hz), 8.06 (1H, dd, ^1J = 2.4 Hz, ^2J = 8.9 Hz), 7.37-7.5 (5H, m), 7.28-7.35 (4H, m), 1.25 (9H, s). δC(100 MHz; $CDCl_3$; Me_4Si) 149.2, 146.0, 145.5, 145.3, 144.5, 137.0, 132.9, 131.2, 130.0, 129.4, 128.8, 128.0, 126.7, 126.0, 124.1, 121.6, 120.1,

115.6, 105.5, 84.7, 27.4. δSe(80 MHz; $CDCl_3$; $(PhSe)_2$) 347.2. HRMS (ESI): calcd for $C_{24}H_{22}N_3O_6SeK$ $[M+K]^+$:578.0227, found: 578.0270.

***N-tert*butoxycarbonyl-3-[{2-[(*tert*butoxycarbonyl)amino]-3-methoxy-3-oxopropyl}seleno]-2-phenylindole (4k)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.24 (1H, m), 7.73 (1H, m), 7.33-7.46 (7H, m), 4.99 (1H, d, J= 8.8 Hz, NH), 4.99 (1H, d, J = 10.3 Hz), 4.45 (1H, dt, ^1J = 5.0 Hz, ^2J = 8.8 Hz, Hα), 3.37 (3H, s, OCH_3), 3.11 (1H, dd, ^1J = 5.0 Hz, ^2J = 13.2 Hz), 2.99 (1H, dd, ^1J = 5.0 Hz, ^2J = 13.2 Hz), 1.34 (9H, s), 1.25 (9H, s). δC(100 MHz; $CDCl_3$; Me_4Si) 170.8, 154.7, 149.5, 143.1, 136.6, 134.1, 131.1, 130.1, 128.1, 127.7, 125.1, 123.4, 120.4, 115.3, 105.7, 83.7, 79.7, 53.4, 52.1, 28.1, 27.4; δSe(80 MHz; $CDCl_3$; $(PhSe)_2$) 60.2. HRMS (ESI): calcd for $C_{28}H_{35}N_2O_7Se$ $[M+OH]^+$: 591.1604, found: 591.1629.

***N-tert*butoxycarbonyl-3-(2-oxopropylseleno)-2-phenylindole (4l)**

δH(400 MHz; $CDCl_3$; Me_4Si) 8.28 (1H, m), 7.74 (1H, m), 7.34-7.53 (7H, m), 3.23 (2H, s, $^1J_{HSe}$ = 15Hz), 1.96 (3H, s), 1.25 (9H, s). δC(100 MHz; $CDCl_3$; Me_4Si) 203.1, 149.5, 144.2, 136.7, 133.8, 130.9, 130.4, 128.1, 127.5, 125.3, 123.5, 120.2, 115.4, 105.8, 83.9, 35.9 (s, and Se satellites: $^1J_{CSe}$ = 66. Hz, CH_2Se), 27.5, 27.4. HRMS (ESI): calcd for $C_{22}H_{23}NO_3Se$ $[M+H]^+$: 430.0916, found: 430.0904.

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors would like to thank

Polpharma S.A.(dr Paweł Olszowy) for providing HRMS analysis and prof. Jarosław Chojnacki for carrying out single-crystal X-ray diffraction analysis for compound **2b**.

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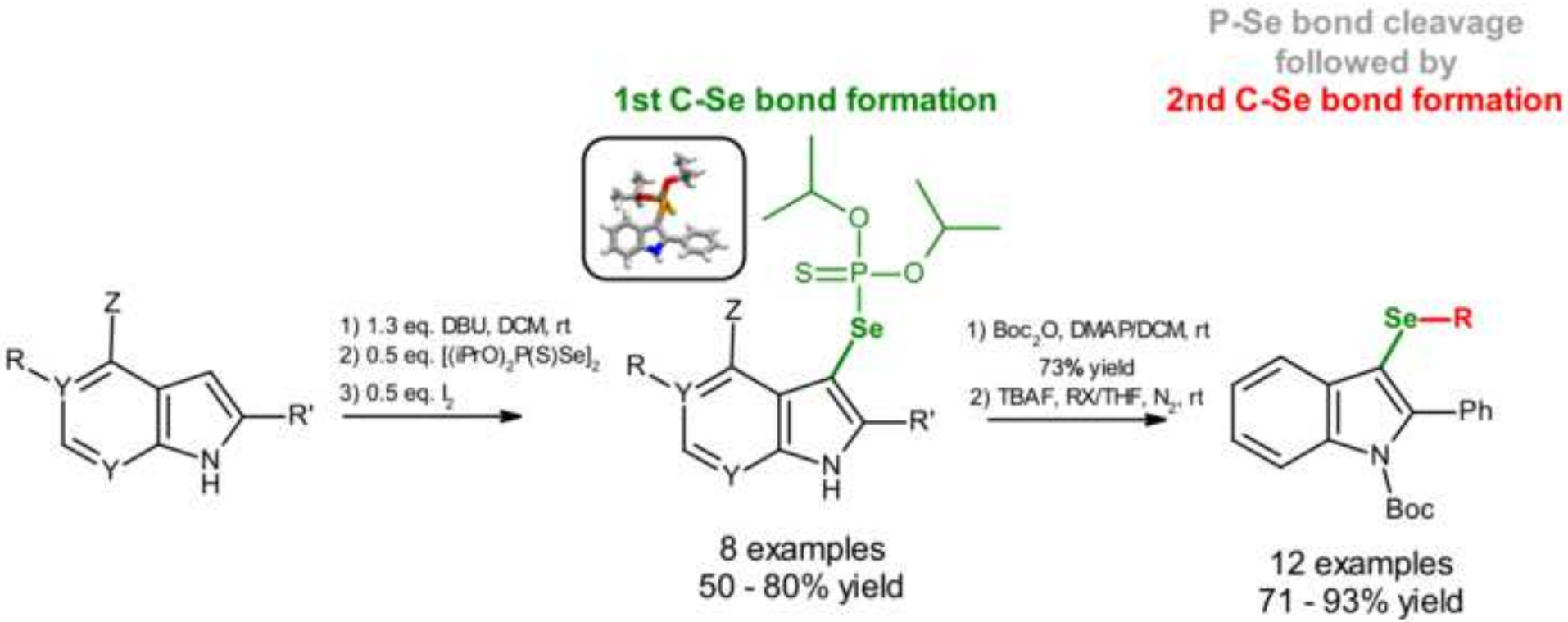
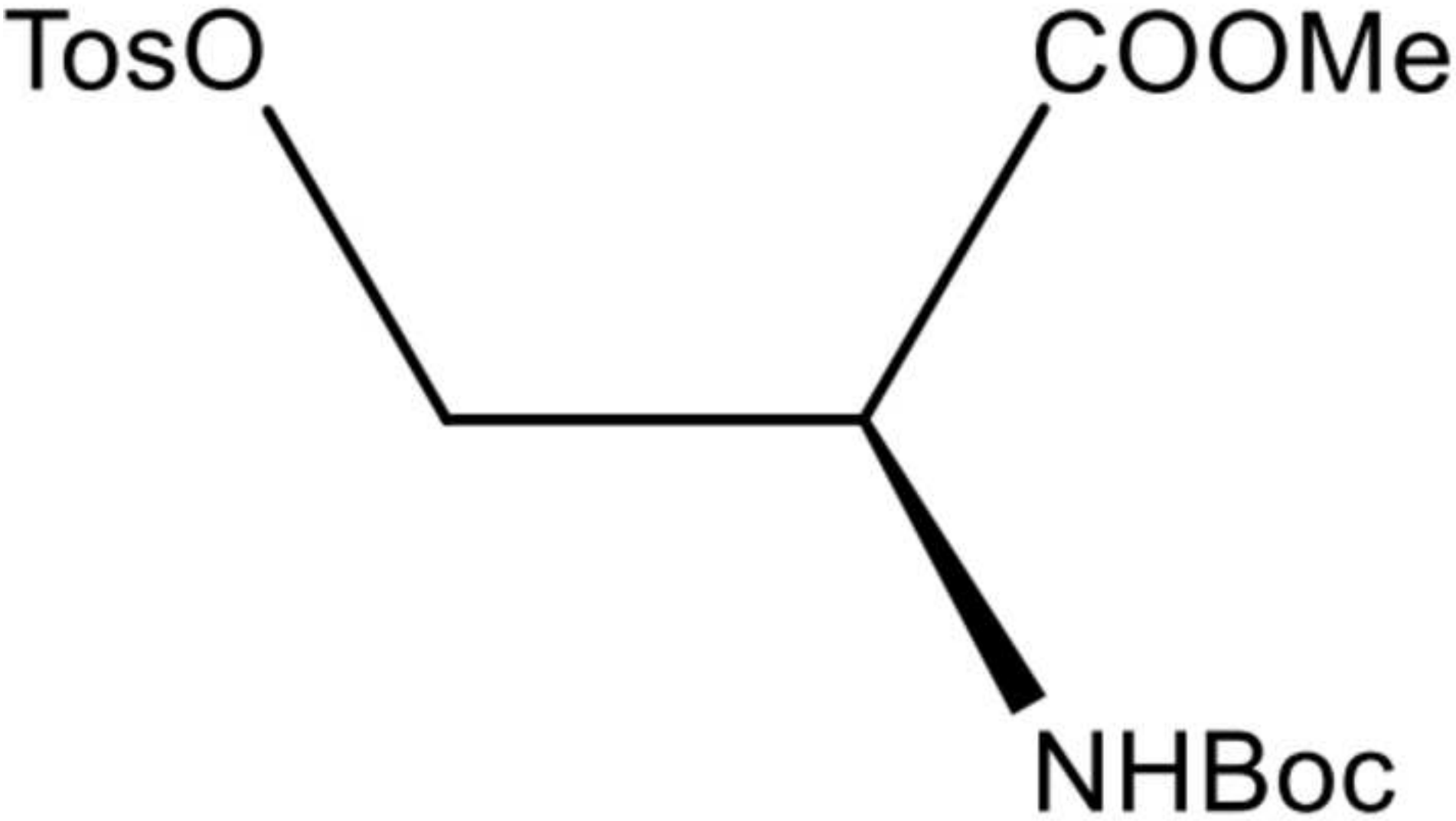
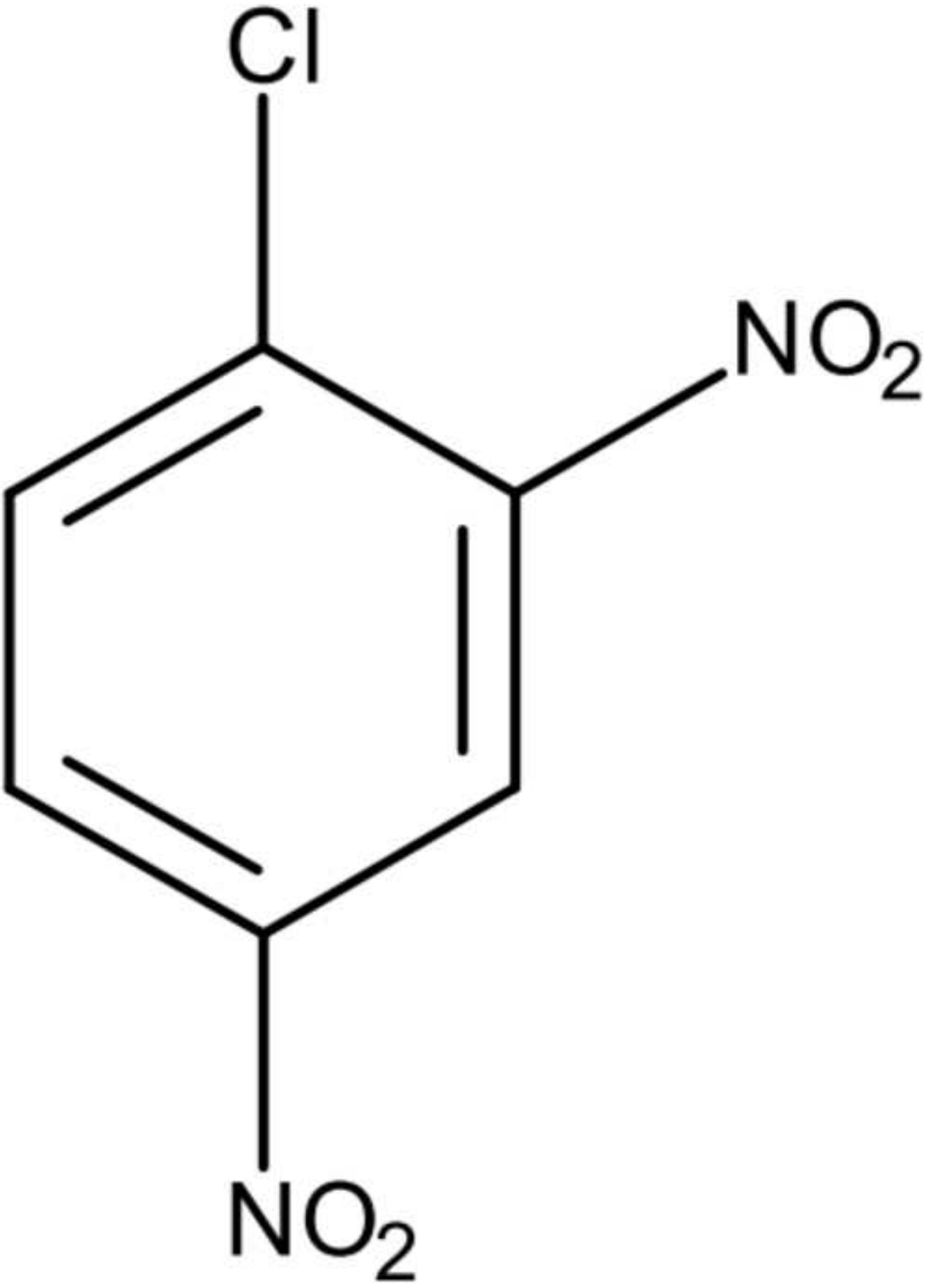
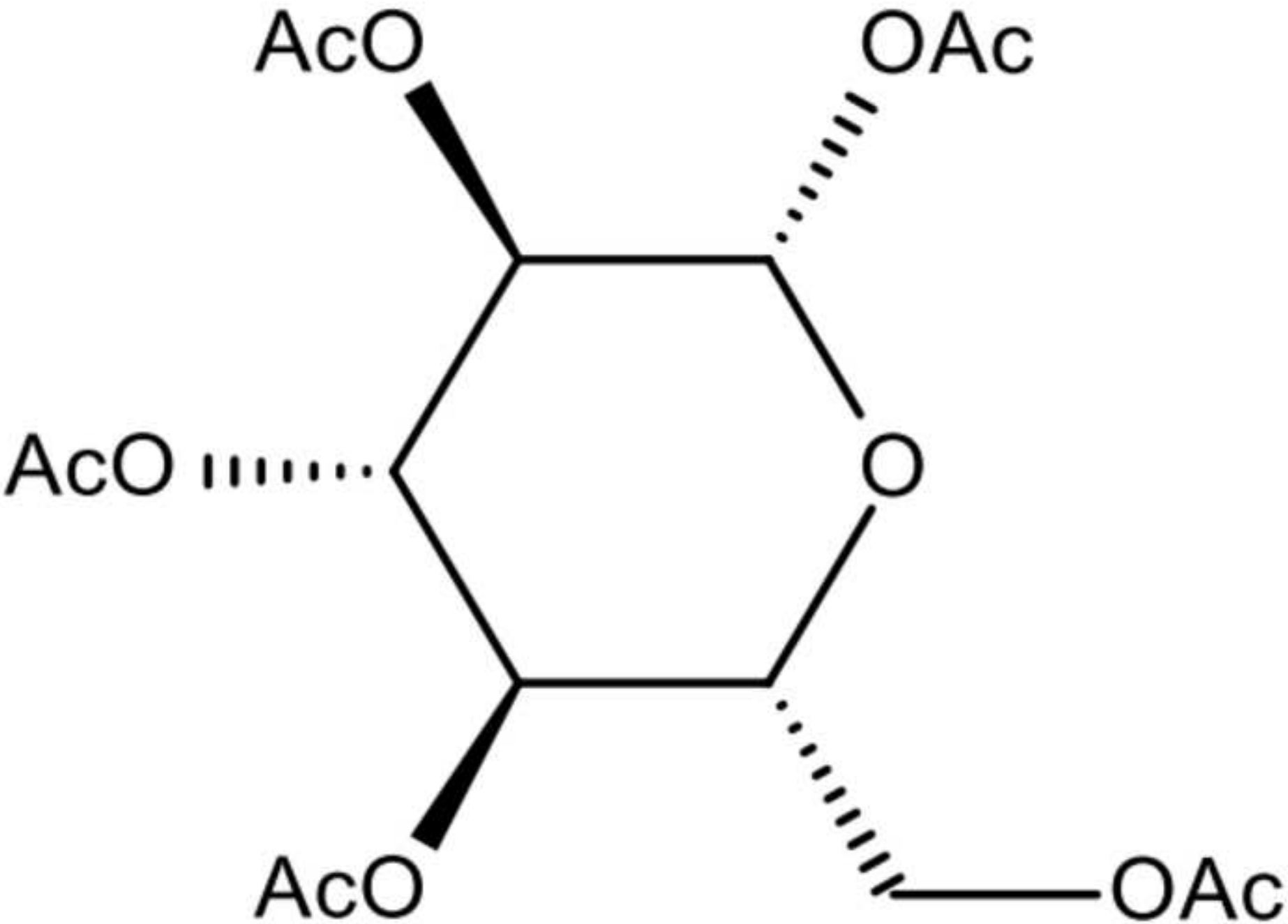
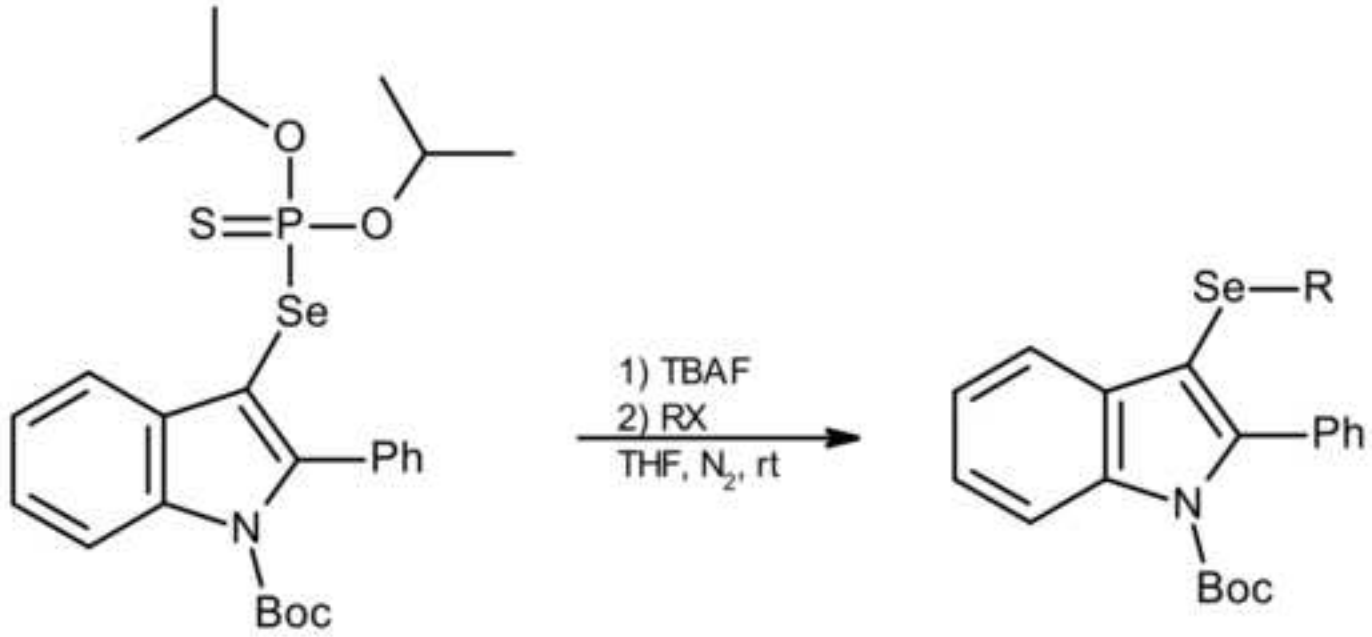




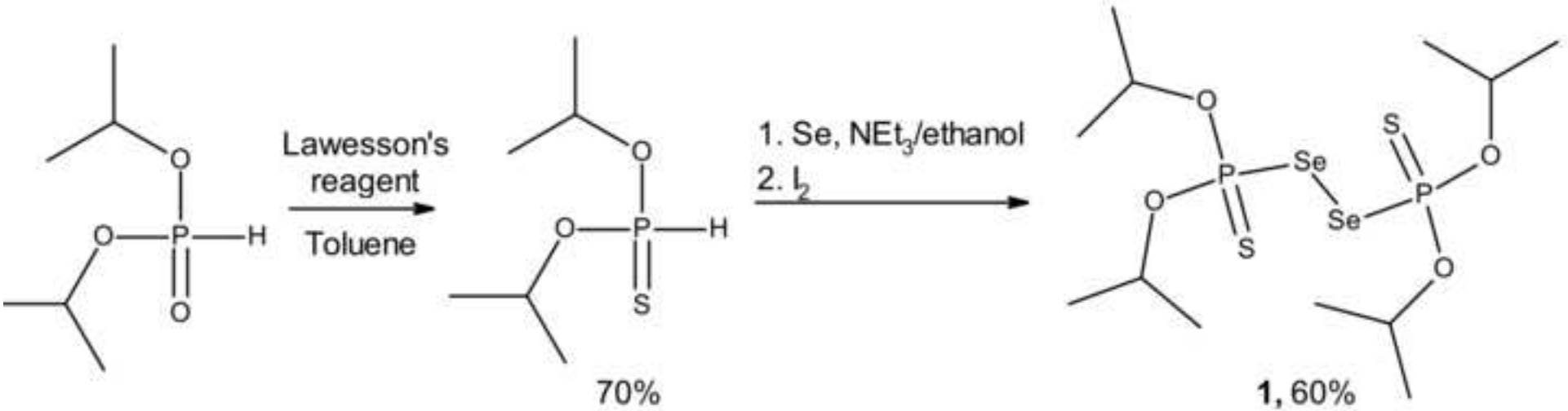


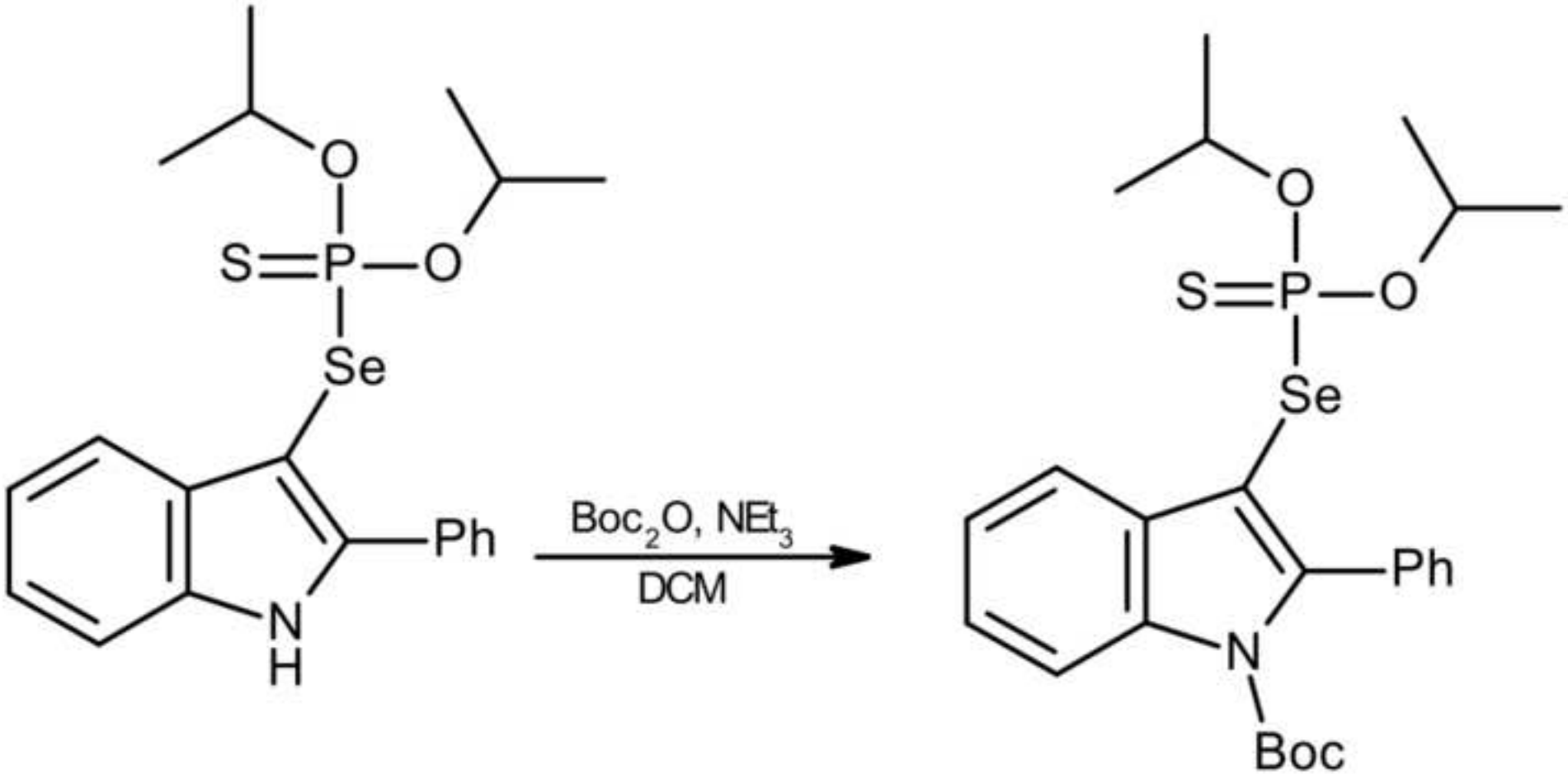




3a

products **4a-4l**
71 - 93% yield





2b

3a, 73%