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Iron(III) Chloride/Diorganyl Diselenides: A Tool for Intramolecular Cyclization of Alkynone *O*-Methyloximes

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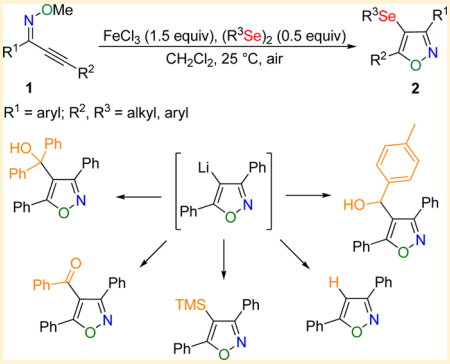
Supporting Information

ABSTRACT: This report describes the synthesis of 4-organoselenylisoxazoles via $FeCl_3$/RSeSeR-mediated intramolecular cyclization of alkynone *O*-methyloximes. The optimized conditions allowed the cyclization to proceed at room temperature under ambient atmosphere, and the reaction requires a short time to be completed. The reaction conditions tolerated neutral, electron-donating and electron-withdrawing groups present in both substrates, alkynone *O*-methyloximes and diorganyl diselenides. Treatment of 4-organoselenylisoxazoles with *n*-butyllithium, followed by trapping with electrophiles, furnished the functionalized isoxazoles in good yields. The obtained products also proved to be suitable substrates for the preparation of 4-bromoisoxazoles via Br/Se exchange reaction.



INTRODUCTION

Compounds containing one or more heterocyclic rings in their structures are widely studied principally in view of their important biological activities.[1] In particular, isoxazoles represent an interesting class of heterocycles that display a range of biological properties, such as anti-inflammatory,[2] antimicrobial,[3] anticancer,[4] and antinociceptive (Figure1).[5] In this way, the interest of the synthetic organic chemists in the development of alternative strategies to preparation of isoxazole derivatives is constant. Consequently, many synthetic approaches have been related to the construction of isoxazole moieties. Usually, these compounds have been prepared via reactions of hydroxylamine with α,β-unsaturated nitriles, carbonyl compounds, and 1,3-dicarbonyl substrates.[6] However, these classical protocols require the use of expensive transition-metal catalysts, strong acidic or base conditions, and sometimes high reaction temperatures. Alternatively, the electrophilic cyclization[7] of 2-alkynone *O*-methyloximes using different electrophilic sources was employed to synthesize highly substituted 4-halo-isoxazoles.[8] This method has some advantages when compared with classical methodologies, principally because 4-bromo- and 4-iodoisoxazoles are versatile precursors in many synthetic processes, such as palladium-catalyzed Sonogashira, Suzuki, and Heck cross coupling as well as carbonylative reactions.[9]

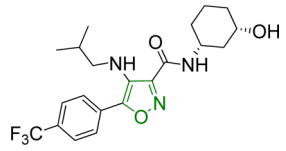


Figure 1. Biologically active isoxazole derivative.

In recent years, environmental concerns have directly influenced the development of new methodologies with high synthetic efficiency, atom economy, and employing mild reaction conditions. In this sense, iron species have emerged as a promising alternative, since most of them present low toxicity and have a small contribution to environmental pollution. Iron-based protocols have been employed for the synthesis of different organic compounds by forming carbon–carbon and carbon–heteroatom bonds.[10] In particular, iron-promoted cyclization reactions of alkyne derivatives consist of an important synthetic tool for the preparation of different heterocyclic units employing stoichiometric or catalytic amounts of the metal reagent.[11] Moreover, organic substances containing an organochalcogen group in their structures have drawn attention because a large number of them have pharmacological activities[12] and are quite useful as the reactive site in several different transformations.[13] Concerning the bad reputation related to the smell, toxicity, or instability of organoselenium compounds, recent studies about the pharmacological and toxicological aspects point out these compounds as promising pharmacological agents in view of their unique properties.[14,15] Regarding the use of organoselenium compounds in organic synthesis, recently others[16] and we[17] have described $FeCl_3$/RYYR (Y = S, Se or Te) as an efficient cyclization promoter of alkenyl and alkynyl substrates. This

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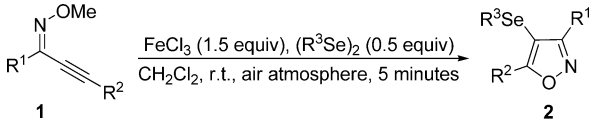
iron/dichalcogenide association is an alternative and useful tool for the synthesis of functionalized carbo- and heterocycles, such as cyclobutanes, benzo[*b*]furans, chromenones, isochromenones, selenophenes, and tellurophenes. Based on these previous aspects and considering that there is no protocol reporting the $FeCl_3$/RSeSeR-promoted synthesis of isoxazole heterocyclic units, in the present study we reported the synthesis of highly substituted 4-organoselenylisoxazoles **2** via intramolecular cyclization of alkynone *O*-methyloximes **1** using $FeCl_3$/RSeSeR as the promoter system by employing mild and environmentally benign reaction conditions (Scheme 1).

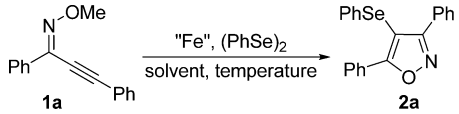
Scheme 1



RESULTS AND DISCUSSION

The alkynone *Z*-*O*-methyloxime derivatives **1** were prepared by reacting the corresponding alkynyl ketones with methoxylamine hydrochloride in the presence of pyridine and Na_2SO_4, using methanol as solvent at room temperature.[18] Since the alkynyl ketones have a bulky group directly bonded to the carbonyl function only the required *Z*-*O*-methyloxime derivatives were obtained.[8,9] In order to determine a general condition for the cyclization reaction of alkynone *O*-methyloximes **1**, the 1,3-diphenylprop-2-yn-1-one *O*-methyloxime **1a** was submitted to cyclization conditions in the presence of diphenyl diselenide by varying reaction parameters, such as solvent, temperature, reaction stoichiometry, and iron species, and the results are summarized in Table 1. In the first test, the alkynone *O*-methyloxime **1a** (0.25 mmol) was added to a solution of diphenyl diselenide (0.5 equiv) and $FeCl_3$ (1.5 equiv) in CH_2Cl_2 (2.5 mL), under argon atmosphere at room temperature. Under these conditions, the reaction delivered the 3,5-diphenyl-4-(phenylselenyl)isoxazole **2a** in 78% yield (Table 1, entry 1). Since these results, using 0.5 equiv of diphenyl diselenide, gave the cyclized product **2a** in higher than 50% yield, we concluded that both portions of phenylselenium (PhSe) from diphenyl diselenide (PhSeSePh) were incorporated in the final product. In fact, it represents the first advantage of this cyclization method in view of the atom economy, which is in agreement with the green chemistry concept. When the amount of diphenyl diselenide was increased from 0.5 to 1.0 equiv, a significant decrease in the reaction efficiency was observed, and the isoxazole **2a** was obtained in only 45% yield (Table 1, entry 2). With the goal of making our cyclization methodology more attractive, the $FeCl_3$/$(PhSe)_2$-mediated cyclization reaction of the oxime **1a** was carried out under ambient atmosphere (open to air) and the cyclized product **2a** in 76% yield (Table 1, entry 3). This is the second advantage of our methodology from a practical and economical standpoint. We observed that the amount of $FeCl_3$ affected the reaction behavior. By varying from catalytic (0.2 equiv) to equimolar ratio of $FeCl_3$, a decrease in the reaction yields was observed (Table 1, entries 7−9). The fact that the reactions do not take place by using a catalytic amount of iron salt suggests that $FeCl_3$ should be required not only to activate

Table 1. Effect of Different Reaction Parameters on the Iron-Mediated Cyclization of 1a[a]

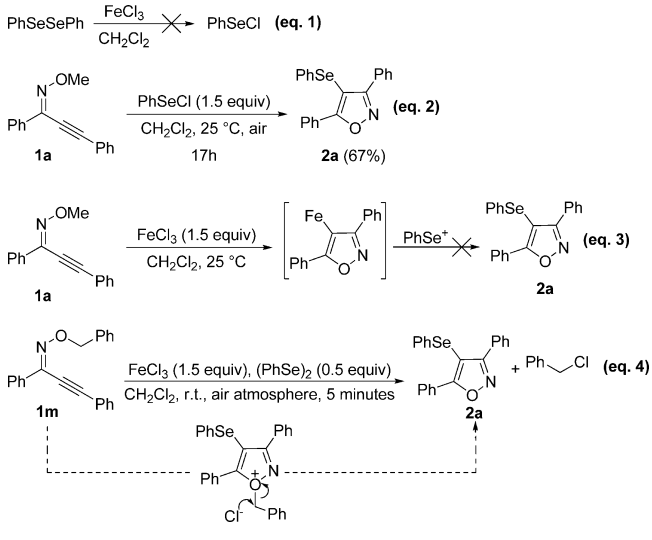


entry	[Fe] (equiv)	$(PhSe)_2$ (equiv)	solvent	yield[b] (%)
1	$FeCl_3$(1.5)	0.5	CH_2Cl_2	78[c]
2	$FeCl_3$(1.5)	1.0	CH_2Cl_2	45[c]
3	$FeCl_3$(1.5)	0.5	CH_2Cl_2	76
4	$FeCl_3$(1.5)	1.0	CH_2Cl_2	66
5	$FeCl_3$(1.5)		CH_2Cl_2	0
6		1.0	CH_2Cl_2	0
7	$FeCl_3$(0.2)	0.5	CH_2Cl_2	7
8	$FeCl_3$(0.5)	0.5	CH_2Cl_2	39
9	$FeCl_3$(1)	0.5	CH_2Cl_2	54
10	$FeCl_3$(2)	0.5	CH_2Cl_2	74
11	$FeCl_3$(1.5)	0.5	MeCN	50
12	$FeCl_3$(1.5)	0.5	$MeNO_2$	64
13	$FeCl_3$(1.5)	0.5	EtOH	0
14	$FeCl_3$(1.5)	0.5	DCE	68
15	$FeCl_3$(1.5)	0.5	THF	0
16	$FeCl_3$(1.5)	0.5	toluene	40
17	$FeCl_3$(1.5)	0.5	hexane	7
18	$FeCl_3$(1.5)	0.5	DMF	0
19	$FeCl_3{\cdot}6H_2O$(1.5)	0.5	CH_2Cl_2	39
20	$FeCl_2{\cdot}4H_2O$(1.5)	0.5	CH_2Cl_2	12
21	$Fe(acac)_3$(1.5)	0.5	CH_2Cl_2	0
22	Fe^0(1.5)	0.5	CH_2Cl_2	0
23	$Fe(SCN)_2$(1.5)	0.5	CH_2Cl_2	10
24	$FeCl_3$(1.5)	0.5	CH_2Cl_2	72[d]
25	Cu_2O	0.5	CH_2Cl_2	0[c]

[a]The reaction was performed in the presence of **1a** (0.25 mmol) under ambient atmosphere for 12 h. [b]Yields by GC analysis. [c]The reaction was carried out under argon atmosphere. [d]The reaction was performed at reflux temperature.

the triple bond to promote the cyclization but also as a nucleophile source (Cl^-) to remove the alkyl group directly bonded to the oxygen atom (see the mechanism discussion in Scheme 2). When the amount of $FeCl_3$ was increased from 1.5

Scheme 2



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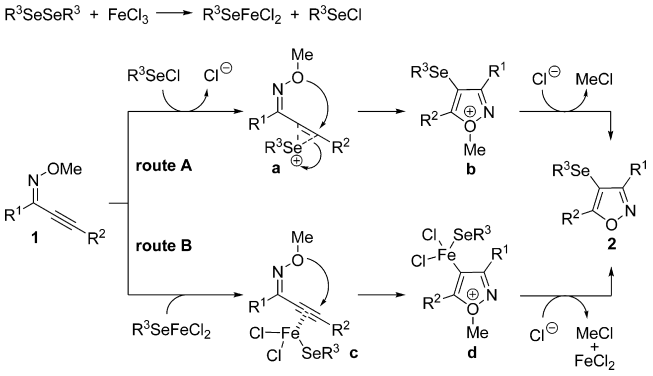
to 2.0 equiv, the desired isoxazole **2a** was obtained in comparable good yield (Table 1, entry 10). We have screened different experiments in order to verify the influence of solvent nature in the cyclization reaction. The use of polar aprotic solvents, such as MeCN, $MeNO_2$, and DCE, afforded a decrease in the reaction yields (Table 1, entries 11, 12, and 14). When EtOH, THF, and DMF were used, the PhSeSePh/$FeCl_3$ system was inefficient for the formation of **2a** (Table 1, entries 13, 15, and 18). We believe that affinity between solvents (Lewis bases) and $FeCl_3$ (Lewis acid) leads to an inactivation of the iron salt. Nonpolar solvents, such as toluene and hexane, furnished poor yields for the expected product because of the low solubility of the starting materials in these solvents (Table 1, entries 16 and 17). In addition, the yield could not be improved by using CH_2Cl_2 at reflux temperature (Table, entry 24). The iron source was also found to be important to the cyclization process. The hydrous iron species $FeCl_3{\cdot}6H_2O$ and $FeCl_2{\cdot}4H_2O$ proved to be somewhat effective for the formation of the cyclized product (Table 1, entries 19 and 20). These results suggest that chlorine atoms seem to play a key role in the cyclization process. This effect becomes more noticeable since iron reagents, such as $Fe(acac)_3$, $Fe(SCN)_2$, and Fe^0, were demonstrated to be ineffective as the cyclizing agent (Table 1, entries 21−23). We can infer that chlorine should act as a nucleophilic species in a substitution reaction to remove the methyl group bonded to the oxygen atom as detailed in the mechanism discussion (Scheme 2). According to Bolm and co-workers, in the metal-catalyzed/promoted transformations the trace metal impurities should work as the catalytic species.[19] In particular, $FeCl_3$ is known to present traces of Cu_2O.[20] In order to eliminate the possibility of a copper contaminant to be directly involved in the cyclization process, the alkynone *O*-methyloxime **1a** was submitted to reaction conditions using Cu_2O in absence of $FeCl_3$, and no trace of cyclized product was observed. These findings suggest that the iron salt is the active species in this transformation (Table 1, entry 25). Finally, monitoring the progress of a reaction by TLC, we observed that all alkynone *O*-methyloxime **1** was consumed after 5 min, and the increase of the reaction time to 30 min did not improve the yields. Based on these results, we concluded that the best reaction conditions to this cyclization approach were the use of the proper alkynone *O*-methyloxime **1** (0.25 mmol), $FeCl_3$ (1.5 equiv), and diorganyl diselenide (0.5 equiv), using CH_2Cl_2 as solvent, at room temperature, for 5 min under ambient atmosphere.

Considering that the chemistry involving iron salts and diorganyl dichalcogenides is recent, it must be accepted that knowledge of the mechanistic pathways of the transformations promoted by these systems is still limited.[21] In this context, we have worked to propose a possible mechanism to these reactions; however, at this moment to draw a mechanistic picture would be a speculative exercise. However, the following experimental data obtained in this study can contribute to the best understanding of the reaction mechanisms. During our studies, it became clear that a typical electrophilic cyclization mechanism, which could involve the PhSeCl[22] as electrophilic source, is improbable. This hypothesis is supported by the fact that when $FeCl_3$ and diphenyl diselenide reacted, under the optimized cyclization conditions, in the absence of the alkynone *O*-methyloxime **1**, no PhSeCl was detected by GC/MS analysis of the crude reaction mixture (Scheme 2, eq 1). However, the in situ formation of the PhSeCl cannot be totally discarded. This idea could be supported by the fact that when the oxime **1a** was submitted to the electrophilic cyclization, by using PhSeCl as a cyclization agent, the isoxazole **2a** was obtained in 67% yield after 17 h (Scheme 2, eq 2). This expected result is in agreement with those obtained by the Larock's previous cyclization protocol, in which PhSeBr is employed as the electrophilic reagent.[8] When the oxime **1a** was submitted to $FeCl_3$-mediated reaction in the absence of diphenyl diselenide, and likewise when the same substrate reacted with diphenyl diselenide in the absence of $FeCl_3$, no cyclized product was obtained in both reactions (Table 1, entries 5 and 6). The analysis of these results indicates a dependence of the cyclization process to simultaneous presence of $FeCl_3$ and diphenyl diselenide into the reaction mixture. Based on these experimental data, we supposed that the formation of a mixed iron/diselenide complex is the species responsible for the cyclization process. In addition, the result shown in Table 1, entry 5, also suggests that the cyclization promoted by $FeCl_3$ and a subsequent replacement of the Csp^2−Fe bond by the electrophilic organoselenyl motif could not occur (Scheme 2, eq 3). Finally, when the reaction was carried out using the alkynone *O*-benzyloxime **1m** as substrate, we obtained a mixture of desired isoxazole **2a** and benzyl chloride (Scheme 2, eq 4). This implies that the chlorine anion is acting as a nucleophile in a S_N2 reaction to remove the alkyl group directly bonded to the oxygen atom.

Based on the above experiments, we believe that a plausible mechanism for this cyclization reaction could involve two concomitant mechanistic routes, as demonstrated in Scheme 3.

Scheme 3



First, the mixture of $FeCl_3$ and diorganyl diselenide $(R^3Se)_2$ would furnish the reactive species $R^3SeFeCl_2$ and R^3SeCl. The reaction of the carbon−carbon triple bond with the electrophilic R^3SeCl leads to the selenonium intermediate **a**, and a subsequent nucleophilic *anti* attack from the oxygen atom into the activated Csp affords the cationic species **b**, which gives the desired product **2** with the elimination of methyl chloride (route A). Conversely, the coordination of the carbon−carbon triple bond and the iron(III) specie ($R^3SeFeCl_2$) affords the intermediate **c**; a nucleophilic *anti* attack of the oxygen lone pair into the activated triple bond furnishes the isoxazolyliron species **d**, which suffers a reductive elimination process to generate the desired isoxazole **2** with simultaneous formation of methyl chloride. These two concomitant pathways could explain the incorporation of the two portions of R^3Se in the final product.

Once determined the ideal reaction parameters, we examined the generality of our cyclization methodology (Table 2).

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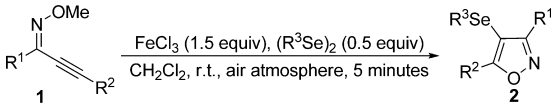
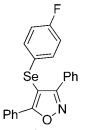
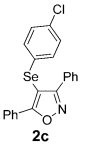
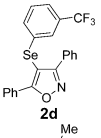
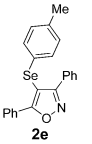
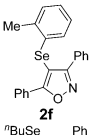
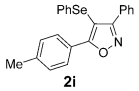
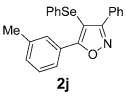
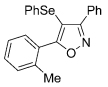
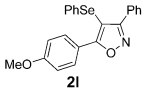
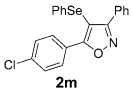
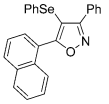
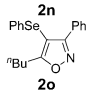
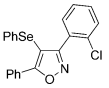
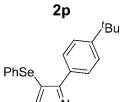
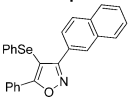
Table 2. Scope and Generality of the Cyclization Reaction[a]



entry	substrate	$(R^3Se)_2$	product	yield (%)
1	**1a** R^1 = Ph; R^2 = Ph	$(PhSe)_2$	 **2a**	70
2	**1a**	$(p\text{-}FC_6H_4Se)_2$	 **2b**	65
3	**1a**	$(p\text{-}ClC_6H_4Se)_2$	 **2c**	70
4	**1a**	$(m\text{-}CF_3C_6H_4Se)_2$	 **2d**	50
5	**1a**	$(p\text{-}MeC_6H_4Se)_2$	 **2e**	67
6	**1a**	$(o\text{-}MeC_6H_4Se)_2$	 **2f**	70
7	**1a**	$(^nBuSe)_2$	 **2g**	55
8	**1a**	$(EtSe)_2$	 **2h**	56
9	**1b** R^1 = Ph; R^2 = *p*-MeC_6H_4	$(PhSe)_2$	 **2i**	59
10	**1c** R^1 = Ph; R^2 = *m*-MeC_6H_4	$(PhSe)_2$	 **2j**	65
11	**1d** R^1 = Ph; R^2 = *o*-MeC_6H_4	$(PhSe)_2$	 **2k**	60
12	**1e** R^1 = Ph; R^2 = *p*-$MeOC_6H_4$	$(PhSe)_2$	 **2l**	55
13	**1f** R^1 = Ph; R^2 = *p*-ClC_6H_4	$(PhSe)_2$	 **2m**	65
14	**1g** R^1 = Ph; R^2 = 1-naphthyl	$(PhSe)_2$	 **2n**	67
15	**1h** R^1 = Ph; R^2 = ^{n}Bu	$(PhSe)_2$	 **2o**	57
16	**1i** R^1 = *o*-ClC_6H_4; R^2 = Ph	$(PhSe)_2$	 **2p**	56
17	**1j** R^1 = *p*-^{t}BuC_6H_4; R^2 = Ph	$(PhSe)_2$	 **2q**	51
18	**1k** R^1 = 2-naphthyl; R^2 = Ph	$(PhSe)_2$	 **2r**	62

[a]Reaction performed in the presence of **1** (0.25 mmol), diorganyl diselenide (0.5 equiv), and $FeCl_3$ (1.5 equiv) using CH_2Cl_2 (2.5 mL) as solvent, under ambient atmosphere, at room temperature for 5 min.

Notably, the cyclization reaction was shown to be tolerant to several different substituents. Different diaryl diselenides bearing neutral, electron-withdrawing, and electron-donating groups in the aromatic rings afforded the expected products in moderate to good yields (Table 2, entries 1−6). Gratifyingly, the reaction also worked well by using dialkyl diselenides giving the corresponding 4-butylselenylisoxazole **2g** and 4-ethylselenylisoxazole **2h** in 55 and 56% yields, respectively (Table 2, entries 7 and 8). These results are significant since the alkyl group directly bonded to the selenium atom could undergo *β*-selenoxide elimination giving the isoxazole without the selenium group incorporated in the structure. Next, we tested the influence of steric and electronic effects of different substituents in the aromatic rings directly bonded to the triple bond of the alkynone *O*-methyloximes **1** (Table 2, entries 9−15). The experiments showed that the cyclization reaction was not influenced by electronic effects since electron-poor and electron-rich groups furnished the expected products in similar yields (Table 2, entries 9−13). It is worth noting that the protocol was tolerant to the presence of a sterically hindered naphthalene as well as an alkyl group into the triple bond, providing the products **2n** and **2o** in reasonable yields (Table 2, entries 14 and 15). In addition, the presence of electron-withdrawing, -donating, and bulky naphthyl groups in the R^1 position proved it does not have significant influence in the reaction behavior. Using the same reaction conditions, the cyclization of oximes **1i−k** led to the formation of the expected products **2p−r** in moderate yields (Table 2, entries 16−18). Finally, when the optimized conditions were extended to diorganyl disulfides and ditellurides only traces of the expected cyclized products were obtained.

Recently, Larock and co-workers reported a competitive cyclization using halogen and selenium electrophiles on a wide variety of functionally substituted alkynes. The results indicated that the nucleophilicity of the competing functional groups is one of the most important factors in determining the outcome of these reactions.[23] In this context, aiming to study the regioselectivity of this method to the synthesis of isoxazoles, the compound **1l** was submitted to the cyclization conditions. This substrate could give both benzo[*b*]furan **2s′** and isoxazole

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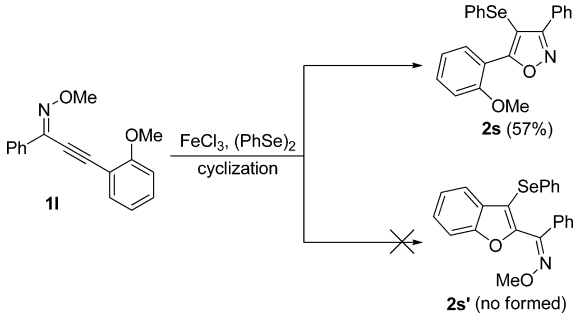
derivative **2s**; however, by using our cyclization conditions, 5-(4-methoxyphenyl)-3-phenyl-4-(phenylselenyl)isoxazole **2s** was obtained as the unique regioisomer (Scheme 4). This result is in agreement with those obtained by the Larock's competitive cyclization, in which the electronic factors play a crucial role in these reactions.

Scheme 4



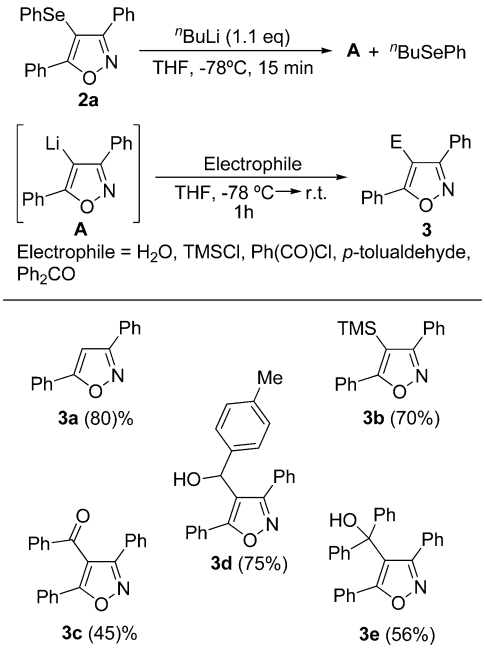
The chalcogen−lithium exchange consists of a useful synthetic tool since the corresponding organolithium species[24] are able to react with a number of different electrophiles providing grossly functionalized organic molecules.[25] Further, as a PhSe group is a good precursor for the selenium−lithium exchange reaction, we have carried out this reaction employing the isoxazole **2a** with *n*-butyllithium. In the first experiment, the generation of the organolithium intermediate **A** from selenide **2a** was attempted by the addition of *n*-butyllithium (1.1 equiv) to a solution of 3,5-diphenyl-4-(phenylselenyl)isoxazole **2a** (0.5 mmol) in THF (4 mL) at −78 °C. The resulting solution was stirred for 15 min at this temperature and quenched in H_2O. Under these conditions, the corresponding 4-hydrogenated product **3a** was isolated in 80% yield (Scheme 4). After this result, we extended this method by trapping the corresponding lithium intermediate **A** with different electrophilic sources, such as aldehyde, benzoyl chloride, ketone, and trimethylsilyl chloride. Through this method, the 4-organoselenylisoxazoles synthesized proved to be convenient precursors for the preparation of isoxazole derivatives bearing different functional groups, furnishing the target compounds in moderate to good yields (Scheme 5).

The transition-metal-catalyzed cross-coupling reaction using 4-haloisoxazoles as substrate is a desirable transformation for the construction of new carbon−carbon bonds.[26] For this reason, we decided to examine the selenium−halogen exchange reaction of 4-phenylselenylisoxazole **2a** in an attempt to directly access the 4-bromoisoxazole. In this way, the reaction of **2a** with molecular bromine in $CHCl_3$, for 1 h, at room temperature afforded the expected halogenated isoxazole **3f** in 85% yield (Scheme 6).

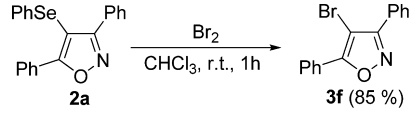
CONCLUSION

In conclusion, we have developed an alternative and efficient approach to 4-organoselenylisoxazoles from alkynone *O*-methyloximes via $FeCl_3$-mediated intramolecular cyclization in the presence of substituted diorganyl diselenides. The cyclization protocol is straightforward and allows for the construction of highly functionalized isoxazole derivatives in moderate to good yields. We consider that there are three main advantages of our methodology; a short reaction time was required, and the reactions were carried out under ambient

Scheme 5



Scheme 6



atmosphere and had atom economy (the two PhSe groups from PhSeSePh are incorporated into the isoxazole ring). To our knowledge, this is the first example of $FeCl_3$/RSeSeR-mediated isoxazole synthesis. In addition, the 4-organoselenylisoxazole obtained in the course of this work proved to be convenient as substrate for the preparation of more functionalized isoxazole derivatives, becoming a promising alternative to the construction of heterocycle libraries.

EXPERIMENTAL SECTION

General Procedure for the $FeCl_3/(R^3Se)_2$ Cyclization. In a Schlenk flask, under ambient atmosphere, containing CH_2Cl_2 (1.5 mL) were added $FeCl_3$ (0.061 g, 1.5 equiv) and the appropriate diorganyl diselenide (0.5 equiv). The reaction mixture was stirred for 20 min at room temperature. After this time, the corresponding alkynone *O*-methyloxime (0.25 mmol) was added, diluted in CH_2Cl_2 (1 mL), and the reaction was stirred at room temperature for 5 min. After that, the reaction mixture was diluted with dichloromethane (20 mL) and washed with a saturated aqueous solution of NH_4Cl (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography, using hexane/acetate (95:5) as eluent. *3,5-Diphenyl-4-(phenylselenyl)isoxazole* (***2a***). Obtained as a pale yellow solid. Mp = 86−87 °C. Yield: 0.066 g (70%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.13−8.05 (m, 2H), 7.79−7.69 (m, 2H), 7.48−7.31 (m, 6H), 7.20−7.07 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 165.7, 131.5, 130.7, 129.7, 129.4, 128.8, 128.7, 128.6, 128.5, 128.3, 127.8, 127.3, 126.5, 96.3. MS (relative intensity) *m*/*z*: 377 (11), 207 (4), 169 (33), 105 (100), 77 (59), 51 (12). FTIR (neat) 4060, 3406, 3032, 2956, 2929, 2854, 2370, 1550, 1373, 1070, 690, 667 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NOSe$: C, 67.03; H, 4.02; N, 3.72. Found: C, 67.30; H, 4.09; N, 3.80.

4-(4-Fluorophenylselenyl)-3,5-diphenylisoxazole (***2b***). Obtained as a pale yellow solid. Mp = 114−115 °C. Yield: 0.064 g (65%). ^{1}H

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NMR ($CDCl_3$, 200 MHz): δ 8.15−8.05 (m, 2H), 7.77−7.70 (m, 2H), 7.54−7.36 (m, 6H), 7.18−7.05 (m, 2H), 6.93−6.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.1, 165.5, 162.0 (d, $^1J_{CF}$ = 251.0 Hz), 131.4 (d, $^3J_{CF}$ = 8.0 Hz), 130.8, 129.8, 128.8, 128.7, 128.6, 128.4, 127.9, 127.4, 125.7 (d, $^4J_{CF}$ = 2.9 Hz), 116.6 (d, $^2J_{CF}$ = 21.9 Hz), 97.2. MS (relative intensity) *m*/*z*: 395 (4), 187 (7), 105 (100), 77 (80), 51 (14). HRMS: calcd for $C_{21}H_{14}FNOSe$ [ESI, M + H^+] 396.0304, found 396.0311. FTIR (neat): 3059, 1884, 1556, 1485, 1377, 1219, 821, 761, 692, 570 cm^{-1}.

4-(4-Chlorophenylselenyl)-3,5-diphenylisoxazole (**2c**). Obtained as a pale yellow solid. Mp = 124−125 °C. Yield: 0.072 g (70%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.12−8.03 (m, 2H), 7.76−7.68 (m, 2H), 7.53−7.35 (m, 6H), 7.18−7.04 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 165.5, 132.8, 130.9, 130.2, 129.9, 129.7, 129.6, 128.7, 128.5, 128.4, 127.8, 127.2, 96.2. MS (relative intensity) *m*/*z*: 411 (4), 281 (4), 207 (11), 165 (4), 105 (100), 77 (48), 51 (10). FTIR (neat): 3061, 2926, 1558, 1473, 1442, 1373, 1087, 810, 688, 482 cm^{-1}. Anal. Calcd for $C_{21}H_{14}ClNOSe$: C, 61.41; H, 3.44; N, 3.41. Found: C, 61.27; H, 3.19; N, 3.38.

3,5-Diphenyl-4-(3-trifluoromethyl)phenylselenyl)isoxazole (**2d**). Obtained as a white solid. Mp = 70−71 °C. Yield: 0.055g (50%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.12−7.82 (m, 2H), 7.73−7.60 (m, 2H), 7.52−7.15 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 165.5, 132.4, 132.2 (*J* = 1.4 Hz), 131.7 (*J* = 32.2 Hz), 130.9, 129.9, 129.7, 128.8, 128.7, 128.4, 127.8, 127.1, 126.8, 125.9 (*J* = 3.6 Hz), 125.8 (*J* = 272.9 Hz), 123.5 (*J* = 3.6 Hz), 95.9. MS (relative intensity) *m*/*z*: 445 (4), 281 (11), 207 (30), 105 (100), 77 (37), 51 (9). HRMS: calcd for $C_{22}H_{14}F_3NOSe$ [ESI, M + Na^+] 468.0097, found 468.0108. FTIR (neat): 3061, 2924, 1556, 1487, 1413, 1325, 1176, 1122, 1068, 769, 690, 570 cm^{-1}.

3-Phenyl-4-(phenylselenyl)-5-(p-tolyl)isoxazole (**2e**). Obtained as a white solid. Mp = 112−113 °C. Yield: 0.057 g (59%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.78−7.71 (m, 2H), 7.44−7.35 (m, 3H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.19−7.13 (m, 5H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6, 165.7, 141.1, 131.7, 129.7, 129.4, 129.3, 129.0, 128.9, 128.8, 128.3, 127.8, 126.5, 124.8, 95.9, 21.4. MS (relative intensity) *m*/*z*: 391 (7), 207 (7), 169 (14), 119 (100), 91 (46), 65 (13). FTIR (neat): 3059, 2941, 1554, 1487, 1444, 1377, 1114, 937, 798, 765, 692, 569, 482 cm^{-1}. Anal. Calcd for $C_{22}H_{17}NOSe$: C, 67.69; H, 4.39; N, 3.59. Found: C, 67.81; H, 4.75; N, 3.62.

4-(2-Methoxyphenylselenyl)-3,5-diphenylisoxazole (**2f**). Obtained as a pale yellow solid. Mp = 89−90 °C. Yield: 0.068 g (70%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.09−8.01 (m, 2H), 7.75−7.67 (m, 2H), 7.50−7.32 (m, 6H), 7.16−6.93 (m, 4H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.0, 165.9, 136.6, 132.3, 130.7, 130.3, 129.7, 128.8, 128.7, 128.6, 128.3, 128.0, 127.8, 127.4, 127.1, 126.4, 99.9, 21.2. MS (relative intensity) *m*/*z*: 391 (5), 207 (5), 183 (12), 105 (100), 77 (48), 51 (8). HRMS: calcd for $C_{22}H_{17}NOSe$ [ESI, M + H^+] 392.0554, found 392.0568. FTIR (neat): 3053, 1554, 1444, 1373, 935, 918, 750, 692, 56 cm^{-1}9.

4-(Butylselenyl)-3,5-diphenylisoxazole (**2g**). Obtained as a yellow oil. Yield: 0.049 g (55%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.20−8.14 (m, 2H), 7.95−7.88 (m, 2H), 7.56−7.43 (m, 6H), 2.45 (t, *J* = 7.2 Hz, 2H), 1.33 (quint, *J* = 7.3 Hz), 1.13 (sext, *J* = 7.2 Hz, 2H), 0.66 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 165.2, 130.3, 129.6, 129.2, 128.8, 128.5, 128.3, 127.9, 127.8, 96.8, 31.5, 28.9, 22.3, 13.2. MS (relative intensity) *m*/*z*: 357 (1), 207 (8), 169 (3), 105 (100), 77 (38), 51 (8). HRMS: calcd for $C_{19}H_{19}NOSe$ [ESI, M + H^+]: 358.0711, found 358.0714. FTIR (neat): 3059, 2956, 2927, 2860, 1554, 1489, 1444, 1375, 1257, 937, 773, 692, 487 cm^{-1}.

4-(Ethylselenyl)-3,5-diphenylisoxazole (**2h**). Obtained as a pale yellow solid. Mp = 56−57 °C. Yield: 0.046 g (56%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.24−8.14 (m, 2H), 7.96−7.88 (m, 2H), 7.52−7.44 (m, 6H), 2.48 (quart, *J* = 7.3 Hz, 2H), 1.11 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 165.3, 130.3, 129.7, 129.3, 128.8, 128.5, 128.4, 127.8, 126.5, 99.9, 22.6, 14.9. MS (relative intensity) *m*/*z*: 329 (10), 327 (7), 281 (6), 207 (17), 135 (4), 117 (11), 105 (100), 77 (54), 51 (12). FTIR (neat): 3055, 2958, 2926, 1560, 1485, 1442, 1373, 1226, 767, 690, 574 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NOSe$: C, 62.20; H, 4.61; N, 4.27. Found: C, 62.41; H, 4.82; N, 4.31.

3-phenyl-4-(phenylselenyl)-5-(p-tolyl)isoxazole (**2i**). Obtained as a white solid. Mp = 112−113 °C. Yield: 0.057 g (59%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.78−7.71 (m, 2H), 7.44−7.35 (m, 3H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.19−7.13 (m, 5H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6, 165.7, 141.1, 131.7, 129.7, 129.4, 129.3, 129.0, 128.9, 128.8, 128.3, 127.8, 126.5, 124.8, 95.9, 21.4. MS (relative intensity) *m*/*z*: 391 (7), 207 (7), 169 (14), 119 (100), 91 (46), 65 (13). FTIR (neat): 3055, 2920, 2854, 2173, 1570, 1554, 1375, 827, 727, 694, 561, 480 cm^{-1}. Anal. Calcd for $C_{22}H_{17}NOSe$: C, 67.69; H, 4.39; N, 3.59. Found: C, 67.81; H, 4.75; N, 3.62.

3-Phenyl-4-(phenylselenyl)-5-(m-tolyl)isoxazole (**2j**). Obtained as a pale orange solid. Mp = 59−60 °C. Yield: 0.063 g (65%). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.92−7.85 (m, 2H), 7.77−7.72 (m, 2H), 7.45−7.22 (m, 6H), 7.21−7.12 (m, 5H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 165.6, 138.7, 131.7, 131.4, 129.7, 129.4, 129.2, 128.9, 128.8, 128.5, 128.3, 127.4, 126.6, 125.1, 96.6, 21.3. MS (relative intensity) *m*/*z*: 391 (7), 207 (19), 169 (17), 119 (100), 91 (57), 73 (24), 51 (6). FTIR (neat): 3410, 3051, 2924, 1573, 1548, 1436, 1381, 1018, 920, 794, 738, 696, 453 cm^{-1}. Anal. Calcd for $C_{22}H_{17}NOSe$: C, 67.69; H, 4.39; N, 3.59. Found: C, 67.81; H, 4.42; N, 3.62.

3-Phenyl-4-(phenylselenyl)-5-(o-tolyl)isoxazole (**2k**). Obtained as an orange oil. Yield: 0.058 g (60%). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.93−7.84 (m, 2H), 7.43−7.20 (m, 7H), 7.17−7.07 (m, 5H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.4, 164.1, 138.0, 131.3, 130.6, 130.5, 130.4, 129.8, 129.5, 129.2, 128.7, 128.5, 128.4, 127.0, 126.6, 125.5, 99.3, 20.1. MS (relative intensity) *m*/*z*: 391 (11), 207 (13), 179 (9), 169 (18), 119 (100), 103 (11), 91 (70), 65 (18), 51 (10). FTIR (neat): 3057, 2926, 1606, 1577, 1477, 1375, 1255, 1118, 939, 773, 731, 690, 503 cm^{-1}. Anal. Calcd for $C_{22}H_{17}NOSe$: C, 67.69; H, 4.39; N, 3.59. Found: C, 67.85; H, 4.43; N, 3.61.

5-(4-Methoxyphenyl)-3-phenyl-4-(phenylselenyl)isoxazole (**2l**). Obtained as a pale yellow solid. Mp = 130−131 °C. Yield: 0.056 g (55%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.12−8.05 (m, 2H), 7.77−7.69 (m, 2H), 7.44−7.36 (m, 3H), 7.21−7.13 (m,5H), 7.00−6.93 (m, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 165.8, 161.5, 131.8, 129.7, 129.5, 129.4, 128.9, 128.8, 128.7, 128.3, 126.5, 120.1, 114.1, 100.0, 55.3. MS (relative intensity) *m*/*z*: 407 (3), 327 (7), 281 (21), 253 (13), 207 (68), 191 (15), 135 (100), 103 (30), 73 (43). HRMS: calcd for $C_{22}H_{17}NO_2Se$ [ESI, M + H^+] 408.0504, found 408.0516. FTIR (neat): 2956, 2926, 2837, 1734, 1604, 1496, 1375, 1249, 1024, 831, 734, 688, 559 cm^{-1}.

5-(4-Chlorophenyl)-3-phenyl-4-(phenylselenyl)isoxazole (**2m**). Obtained as a pale yellow solid. Mp = 113−114 °C. Yield: 0.068 g (66%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.12−8.02 (m, 2H), 7.77−7.68 (m, 2H), 7.47−7.34 (m, 5H), 7.20−7.10 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 165.8, 136.9, 131.2, 129.9, 129.5, 129.1, 129.0, 128.8, 128.7, 128.4, 128.3, 126.7, 125.7, 96.7. MS (relative intensity) *m*/*z*: 411 (14), 402 (28), 326 (15), 298 (15), 207 (9), 180 (9), 105 (100), 77 (54), 51 (6). FTIR (neat): 3446, 2924, 1600, 1575, 1544, 1475, 1253, 1016, 935, 831, 729, 698 cm^{-1}. Anal. Calcd for $C_{21}H_{14}ClNOSe$: C, 61.41; H, 3.44; N, 3.41. Found: C, 61.62; H, 3.50; N, 3.46.

5-(Naphthalen-1-yl)-3-phenyl-4-(phenylselenyl)isoxazole (**2n**). Obtained as a pale orange solid. Mp = 106−107 °C. Yield: 0.071 g (67%). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.00−7.86 (m, 5H), 7.62−7.40 (m, 7H), 7.10−7.03 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.5, 164.4, 133.5, 131.5, 131.2, 131.1, 129.9, 129.8, 129.2, 129.1, 128.8, 128.6, 128.5, 128.4, 127.1, 126.6, 126.4, 125.3, 124.8, 124.7, 100.7. MS (relative intensity) *m*/*z*: 427 (11), 230 (9), 215 (12), 167 (29), 155 (94), 127 (100), 105 (9), 89 (12), 77 (21), 51 (8). FTIR (neat): 3064, 1573, 1490, 1436, 1371, 1062, 1018, 800, 731, 729, 698. cm^{-1} Anal. Calcd for $C_{25}H_{17}NOSe$: C, 70.42; H, 4.02; N, 3.29. Found: C, 70.66; H, 4.08; N, 3.37.

5-Butyl-3-phenyl-4-(phenylselenyl)isoxazole (**2o**). Obtained as a yellow oil. Yield: 0.051 g (57%). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.84−7.77 (m, 2H), 7.44−7.32 (m, 3H), 7.22−7.12 (m, 5H), 2.93 (t, *J* = 7.8 Hz, 2H), 1.69 (quint, *J* = 7.6 Hz, 2H), 1.35 (sext, *J* = 7.6 Hz,

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2H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.6, 163.8, 131.8, 129.6, 129.4, 129.3, 129.2, 128.5, 128.3, 126.5, 97.4, 29.6, 26.4, 22.2, 13.4. MS (relative intensity) m/z: 357 (44), 193 (38), 169 (100), 144 (28), 116 (54), 89 (46), 77 (68), 57 (45), 51 (28). HRMS: calcd for $C_{19}H_{19}NOSe$ [ESI, M + H^+] 358.0705, found 358.0657. FTIR (neat): 3059, 2929, 2870, 1577, 1477, 1382, 1022, 734, 690, 491 cm^{-1}.

3-(2-Chlorophenyl)-5-phenyl-4-(phenylselenyl)isoxazole (**2p**). Obtained as a pale yellow solid. Mp = 87−88 °C. Yield: 0.057 g (56%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.22−8.13 (m, 2H), 7.50−7.22 (m, 7H), 7.14−7.03 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 165.8, 134.1, 131.6, 130.8, 130.7, 130.6, 130.0, 129.6, 129.2, 128.7, 128.3, 127.6, 127.2, 126.8, 126.4, 99.1. MS (relative intensity) m/z: 411 (5), 281 (10), 207 (25), 169 (22), 105 (100), 77 (60), 51 (13). FTIR (neat): 3446, 3064, 1575, 1558, 1475, 1373, 1022, 756, 729, 686, 453 cm^{-1}. Anal. Calcd for $C_{21}H_{14}ClNOSe$: C, 61.41; H, 3.44; N, 3.41. Found: C, 61.55; H, 3.48; N, 3.49.

3-(4-tert-Butylphenyl)-5-phenyl-4-(phenylselenyl)isoxazole (**2q**). Obtained as a pale orange solid. Mp = 124−125 °C. Yield: 0.045 g (51%) ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.11−8.05 (m, 2H), 7.75−7.66 (m, 2H), 7.48−7.37 (m, 5H), 7.22−7.13 (m, 5H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 165.5, 153.0, 131.8, 130.7, 129.5, 128.7, 128.6, 128.4, 127.4, 126.5, 125.7, 125.3, 96.1, 34.7, 31.2. MS (relative intensity) m/z: 433 (7), 281 (5), 207 (15), 169 (49), 144 (7), 105 (100), 89 (13), 77 (57), 51 (5). FTIR (neat): 3446, 3055, 2929, 2866, 1575, 1475, 1375, 837, 734, 688, 586 cm^{-1}. Anal. Calcd for $C_{25}H_{23}NOSe$: C, 69.44; H, 5.36; N, 3.24. Found: C, 69.62; H, 5.41; N, 3.30.

3-(Naphthalen-2-yl)-5-phenyl-4-(phenylselenyl)isoxazole (**2r**). Obtained as a pale orange solid. Mp = 106−108 °C. Yield: 0.066 g (62%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.27 (s, 1H), 8.18−8.10 (m, 2H), 7.88−7.72 (m, 4H), 7.55−7.43 (m, 5H), 7.26−7.13 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6, 165.6, 133.7, 132.8, 131.6, 130.8, 129.5, 128.9, 128.8, 128.7, 128.6, 128.0, 127.9, 127.6, 127.3, 126.9, 126.6, 126.3, 126.0, 125.7, 96.5. MS (relative intensity) m/z: 427 (11), 322 (4), 230 (5), 169 (17), 153 (7), 127 (8), 105 (100), 77 (50), 51 (7). FTIR (neat): 3051, 1575, 1546, 1494, 1438, 1382, 860, 819, 686, 466 cm^{-1}. Anal. Calcd for $C_{25}H_{17}NOSe$: C, 70.42; H, 4.02; N, 3.29. Found: C, 70.61; H, 4.09; N, 3.35.

5-(2-Methoxyphenyl)-3-phenyl-4-(phenylselenyl)isoxazole (**2s**). Obtained as a pale yellow solid. Mp = 95−96 °C. Yield: 0.058 g (57%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.85−7.79 (m, 2H), 7.50−7.31 (m, 5H), 7.15−6.94 (m, 7H), 3.73 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 164.1, 157.5, 132.2, 131.7, 131.2, 129.6, 129.4, 129.0, 128.9, 128.5, 128.3, 126.2, 120.3, 116.7, 111.3, 99.9, 55.3. MS (relative intensity) m/z: 407 (9), 207 (8), 169 (8), 135 (100), 105 (9), 92 (12), 77 (36), 51 (7). HRMS: calcd for $C_{22}H_{17}NO_2Se$ [ESI, M] 407.0425, found 407.0429. FTIR (neat): 3412, 2929, 1614, 1575, 1373, 1282, 1093, 914, 754, 677, 532 cm^{-1}.

General Procedure for the Reaction of (3,5-Diphenylisoxazol-4-yl)lithium Intermediate with Different Electrophiles. To a two-necked round-bottomed flask, under argon, containing a solution of **2a** (0.5 mmol) in THF (4 mL) at −78 °C was added dropwise *n*-BuLi (0.55 mmol, of a 2.5 M solution in hexane). The reaction mixture was stirred for 15 min and then was gradually added a solution of the appropriate electrophilic specie (0.55 mmol) in THF (2 mL), at −78 °C. The reaction mixture was allowed to stir at 25 °C for 1 h. After this time, the mixture was diluted in ethyl acetate (20 mL) and washed with a saturated aqueous solution of NH_4Cl (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. *3,5-Diphenylisoxazole* (**3a**). Obtained as a white solid. Mp = 138−139 °C. Yield: 0.088 g (80%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.89−7.78 (m, 4H), 7.55−7.40 (m, 6H), 6.83 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 162.9, 130.1, 129.9, 129.3, 128.9, 128.8, 127.6, 126.8, 125.8, 108.4, 97.4. MS (relative intensity) m/z: 221 (36), 193 (8), 165 (6), 144 (14), 105 (100), 89 (12), 77 (61), 51 (20). FTIR (neat): 3113, 3047, 1570, 1462, 1400, 819, 763, 690 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6,33. Found: C, 81.71; H, 5.12; N, 6.40.

3,5-Diphenyl-4-(trimethylsilyl)isoxazole (**3b**). Purified by flash chromatography using hexane as eluent. Obtained as a white solid. Mp = 156−157 °C. Yield: 0.102 g (70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65−7.63 (m, 2H), 7.60−7.57 (m, 2H), 7.53−7.47 (m, 6H), −0.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.0, 168.2, 131.6, 130.1, 129.7, 129.2, 129.1, 129.0, 128.3, 108.4, 0.27. MS (relative intensity) m/z: 293 (43), 278 (100), 204 (74), 135 (72), 105 (22), 77 (72), 51 (11). HRMS: calcd for $C_{18}H_{19}NOSi$ [ESI, M]: 293.1236. Found: 293.1240. FTIR (neat): 3462, 3055, 2935, 1552, 1454, 1369, 1249, 1139, 1070, 761, 634 cm^{-1}.

(3,5-Diphenylisoxazol-4-yl)phenylmethanone (**3c**). Purified by flash chromatography using ethyl acetate/hexane (5:95) as eluent. Obtained as a pale yellow solid. Mp = 116−117 °C. Yield: 0.036g (45%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81−7.78 (m, 2H), 7.71−7.67 (m, 2H), 7.60−7.57 (m, 2H), 7.45−7.24 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.8, 169.0, 162.2, 136.8, 133.9, 130.8, 129.8, 129.7, 128.8, 128.7, 128.6, 128.2, 128.1, 127.5, 126.6, 114.1. MS (relative intensity) m/z: 325 (29), 296 (7), 180 (16), 105 (100), 77 (74), 51 (13). FTIR (neat): 3061, 1593, 1492, 1404, 1325, 1242, 1136, 902, 742, 688 cm^{-1}. Anal. Calcd for $C_{22}H_{15}NO_2$ C, 81.21; H, 4.65; N, 4.30. Found: C, 81.40; H, 4.71; N, 4.37.

(3,5-Diphenylisoxazol-4-yl)-p-tolylmethanol (**3d**). Purified by flash chromatography using ethyl acetate/hexane (20:80) as eluent. Obtained as a white solid. Mp = 135−136 °C. Yield: 0.128 g (75%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.75−7.63 (m, 2H), 7.50−7.23 (m, 8H), 7.18 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.00 (s, 1H), 2.62 (s, 1H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.9, 163.4, 138.7, 137.2, 130.1, 129.4, 129.3, 129.1, 129.0, 128.6, 128.4, 128.2, 127.8, 126.1, 116.0, 67.0, 20.9. MS (relative intensity) m/z: 341 (26), 248 (16), 220 (11), 119 (29), 105 (100), 91 (25), 77 (73), 51 (12). FTIR (neat): 3307, 1593, 1566, 1450, 1276, 1159, 1060, 781, 686 cm^{-1}. Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 81.22; H, 5.69; N, 4.15.

(3,5-Diphenylisoxazol-4-yl)diphenylmethanol (**3e**). Purified by flash chromatography using ethyl acetate/hexane (20:80) as eluent. Obtained as a white solid. Mp = 148−149 °C. Yield: 0.113 g (56%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25−7.03 (m, 20H), 2.79 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.8, 163.3, 144.9, 130.1, 129.2, 129.0, 128.9, 128.8, 128.5, 128.1, 127.9, 127.8, 127.7, 127.6, 120.9, 77.8. MS (relative intensity) m/z: 403 (14), 402 (28), 326 (15), 298 (15), 207 (9), 180 (9), 105 (100), 77 (54), 51 (6). HRMS: calcd for $C_{28}H_{21}NO_2$ [ESI, M] 403.1572, found 403.1579. FTIR (neat): 3460, 1570, 1490, 1448, 1334, 1161, 875, 694 cm^{-1}.

General Procedure for the Preparation of the 4-Bromo-3,5-diphenylisoxazole. A solution of bromine (0.32 g, 2 mmol) in $CHCl_3$ (2 mL) was added dropwise to a solution of 3,5-diphenyl-4-(phenylselenyl)-isoxazole **2a** (0.188 g, 0.5 mmol) in $CHCl_3$ (10 mL) at 25 °C. After complete addition, the reaction was stirred under reflux for 3 h. After this time, the reaction mixture was diluted in CH_2Cl_2 (10 mL) and washed with brine solution (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by chromatography on silica gel using hexane as eluent. *4-Bromo-3,5-diphenylisoxazole* (**3f**). Obtained as a pale yellow solid. Mp = 128−129 °C. Yield: 0.127 g (85%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.13−8.05 (m, 2H), 7.89−7.81 (m, 2H), 7.57−7.48 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.7, 162.1, 130.6, 130.1, 128.8, 128.6, 128.5, 127.8, 127.0, 126.7, 89.5. MS (relative intensity) m/z: 299 (12), 220 (17), 180 (14), 105 (100), 77 (60), 51 (17). HRMS: calcd for $C_{15}H_{10}BrNO$ [ESI, M + H^+] 300.0019, found 299.9979. FTIR (neat): 3446, 3055, 1489, 1446, 1388, 1072, 927, 765, 705 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, additional experimental details for the preparation of all compounds, and ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Topics in Heterocyclic Chemistry, Bioactive Heterocycles VII. Flavonoids and Anthocyanins in Plants and Latest Bioactive Heterocycles. Noboru, M., Ed.; Springer: Weinheim, 2009.

(2) Daidone, G.; Raffa, D.; Maggio, B.; Plescia, F.; Cutuli, V. M. C.; Mangano, N. G.; Caruso, A. *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 50.

(3) Al-Tel, T. H.; Al-Qawasmeh, R. A.; Zaarour, R. *Eur. J. Med. Chem.* **2011**, *46*, 1874.

(4) Li, W.-T.; Hwang, D.-R.; Chen, C.-P.; Shen, C.-W.; Huang, C.-L.; Chen, T.-W.; Lin, C.-H.; Chang, Y.-L.; Chang, Y.-Y.; Lo, Y.-K.; Tseng, H.-Y.; Lin, C.-C.; Song, J.-S.; Chen, H.-C.; Chen, S.-J.; Wu, S.-H.; Chen, C.-T. *J. Med. Chem.* **2003**, *46*, 1706.

(5) Ratcliffe, P.; Maclean, J.; Abernethy, L.; Clarkson, T.; Dempster, M.; Easson, A.-M.; Edwards, D.; Everett, K.; Feilden, H.; Littlewood, P.; McArthur, D.; McGregor, D.; McLuskey, H.; Nimz, O.; Nisbet, L.-A.; Palin, R.; Tracey, H.; Walker, G. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2559.

(6) (a) Cuadrado, P.; Gonzalez-Nogal, A. M.; Valero, R. *Tetrahedron* **2002**, *58*, 4975. (b) Bandiera, T.; Grünanger, P.; Albini, F. M. *J. Heterocycl. Chem.* **1992**, *29*, 1423. (c) Vicentini, C. B.; Verones, A. C.; Poli, T.; Guarneri, M.; Giori, P.; Ferretti, V. *J. Hetercycl. Chem.* **1990**, *27*, 1481.

(7) (a) Worlikar, S. A.; Kesharwani, T.; Yao, T. L.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347. (b) Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 2307.

(8) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203.

(9) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643 and references therein.

(10) (a) Ortega, N.; Feher-Voelger, A.; Brovetto, M.; Padrón, J. I.; Martín, V. S.; Martín, T. *Adv. Synth. Catal.* **2011**, *353*, 963. (b) Carballo, R. M.; Valdomir, G.; Purino, M.; Martín, V. S.; Padrón, J. I. *Eur. J. Org. Chem.* **2010**, 2304. (c) Carballo, R. M.; Purino, M.; Ramírez, M. A.; Martin, V. S.; Padrón, J. I. *Org. Lett.* **2010**, *12*, 5334. (d) Miranda, P. O.; Carballo, R. M.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2009**, *11*, 357. (e) Bistri, O.; Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 586. (f) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880. (g) Bonnamour, J.; Bolm, C. *Org. Lett.* **2008**, *10*, 2665. (h) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (i) Fürstner, A.; Schlecker, A.; Lehmann, C. W. *Chem. Commun.* **2007**, 4277. (j) Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8862. (k) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934. (l) Diaz, D. D.; Miranda, P. O.; Padron, J. I.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 457. (m) Seidel, G.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950. (n) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (o) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609.

(11) (a) Li, Z.; Hong, J.; Weng, L.; Zhou, X. *Tetrahedron* **2012**, *68*, 1552. (b) Yeh, M.-C. P.; Fang, C.-W.; Lin, H.-H. *Org. Lett.* **2012**, *14*, 1830. (c) Cao, H.; Zhan, H.; Wu, J.; Zhong, H.; Lin, Y.; Zhang, H. *Eur. J. Org. Chem.* **2012**, 2318. (d) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, *5*, 1979.

(12) (a) Jamier, V.; Ba, L. A.; Jacob, C. *Chem.—Eur. J.* **2010**, *16*, 10920. (b) Giles, G. I.; Fry, F. H.; Tasker, K. M.; Holme, A. L.; Peers, C.; Green, K. N.; Klotz, L. O.; Sies, H.; Jacob, C. *Org. Biomol. Chem.* **2003**, *1*, 4317.

(13) (a) Santi, C.; Santoro, S.; Battistelli, B. *Curr. Org. Chem.* **2012**, *14*, 2442. (b) Santi, C.; Battistelli, B.; Testaferri, L.; Tiecco, M. *Green Chem.* **2012**, *14*, 1277. (c) Yu, L.; Huang, X. *Synlett* **2007**, 1371. (d) Murai, T.; Nonoyama, T. *Tetrahedron* **2012**, *68*, 10489. (e) Kamiya, I.; Nishinaka, E.; Ogawa, A. *J. Org. Chem.* **2005**, *70*, 696.

(14) Nogueira, C. W.; Rocha, J. B. T. *Arch. Toxicol.* **2011**, *85*, 1313.

(15) (a) Ba, L. A.; Doring, M.; Jamier, V.; Jacob, C. *Org. Biomol. Chem.* **2010**, *8*, 4203. (b) Nogueira, C. W.; Rocha, J. B. T. *J. Braz. Chem. Soc.* **2010**, *21*, 2055.

(16) Yu, L.; Ren, L.; Yi, R.; Wu, Y.; Chen, T.; Guo, R. *J. Organomet. Chem.* **2011**, *696*, 2228.

(17) Godoi, B.; Sperança, A.; Bruning, C. A.; Back, D. F.; Menezes, P. H.; Nogueira, C. W.; Zeni, G. *Adv. Synth. Catal.* **2011**, *353*, 2042.

(18) Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016.

(19) Thomé, I.; Nijs, A.; Bolm, C. *Chem. Soc. Rev.* **2012**, *41*, 979.

(20) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586.

(21) (a) Wang, M.; Ren, K.; Wang, L. *Adv. Synth. Catal.* **2009**, *351*, 1586. (b) Taher, D.; Pritzkow, H.; Walfort, B.; Lang, H. *J. Organomet. Chem.* **2006**, *691*, 793.

(22) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936.

(23) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141.

(24) The C−Zn bond generated directly from 2-alkynylphenol; see: (a) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944. (b) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803. (c) Najera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255. (d) Najera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867.

(25) (a) Reich, H. J.; Bevan, M. J.; Gudmundsson, B. O.; Puckett, C. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3436. (b) Reich, H. J.; Bowe, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 8994. (c) Seebach, D.; Peleties, N. *Chem. Ber.* **1972**, *105*, 511. (d) Seebach, D.; Peleties, N. *Angew. Chem., Int. Ed.* **1969**, *8*, 450.

(26) (a) Williams, D. R.; Fu, L. *Org. Lett.* **2010**, *12*, 808. (b) Martin, T.; Laguerre, C.; Hoarau, C.; Marsais, F. *Org. Lett.* **2009**, *11*, 3690.