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General Platform for the Conversion of Isoxazol-5-ones to 3,5-Disubstituted Isoxazoles via Nucleophilic Substitutions and Palladium Catalyzed Cross-Coupling Strategies

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Abstract: A general platform for the conversion of isoxazol-5-ones to 3,5-disubstituted isoxazoles has been developed via a two-step strategy. The first step leads to the formation of 5-(pseudo)halogenated isoxazoles, while in the second, a variety of heteroalkyl-, heteroaryl-, alkyl-, alkenyl-, alkynyl- and aryl-chains can be installed via nucleophilic substitutions or palladium catalyzed cross-coupling reactions.

Introduction

Isoxazoles can be seen as versatile heterocycles having a plethora of applications. Indeed, in addition to the use of isoxazoles **1** as valuable intermediates for the development of new synthetic methods[1] and the preparation of natural products[2] (Figure 1a), they have been also recognized as important motifs in several biologically relevant molecules[3] (Figure 1b).

Among the methods available for the preparation of isoxazoles,[4] cycloadditions,[5] cycloisomerizations,[6] condensations[7] and cross-coupling/ functionalization reactions[8] can be arguably listed as the main synthetic routes (Scheme 1a).

In this context, we recognized that 3-substituted-5-(pseudo)halogenated isoxazoles **3** could be readily accessed from isoxazol-5-ones **2**,[9] and we became interested in further developing synthetic strategies to convert **3** into 3,5-disubstituted isoxazoles **4** via nucleophilic substitutions[10] and Pd-catalyzed cross-coupling reactions[11] (Scheme 1b).

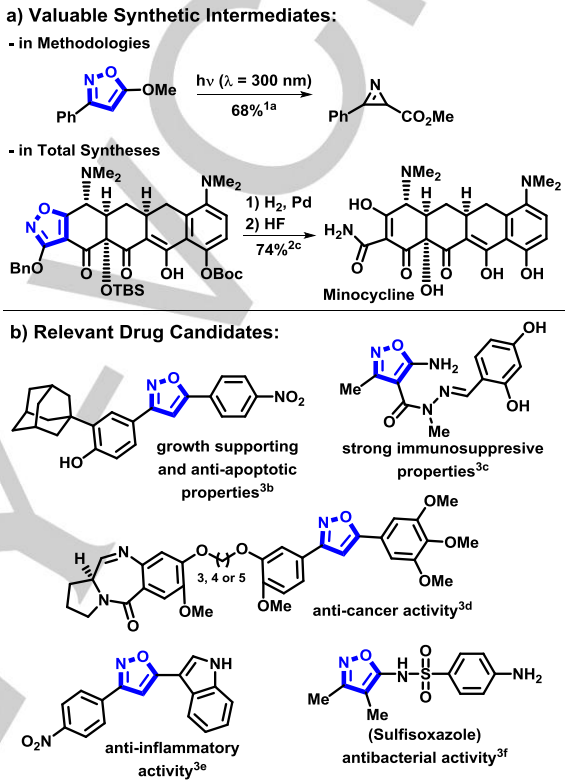

Figure 1. a) Examples of a synthetic method and a total synthesis employing isoxazoles as key intermediates. **b)** Examples of biologically relevant molecules containing the isoxazole heterocycle.

Results and Discussion

In order to investigate nucleophilic substitutions and cross-coupling strategies, 5-(pseudo)halogenated isoxazoles **3a**-**3f** were prepared as model substrates starting either from 3-phenylisoxazol-5(*4H*)-one **2a** or 4-benzyl-3-phenylisoxazol-5(*4H*)-one **2b** via Vilsmeier Haack-type reactions using $POCl_3$ and $POBr_3$;[12] or using Tf_2O (Scheme 2, see the experimental part for details). During this work, only derivatives from these two isoxazol-5-ones (**2a** and **2b**) have been employed based on the assumption that compounds **3a**-**3f** are representative scaffolds of the family.

Then, a brief screening of the reaction conditions using **3a** with varying amounts of benzyl alcohol **5a** and NaH, in THF, at different temperatures, reveals the use of 2 equiv. of both reagents, in refluxing THF, as optimal conditions (Table 1).

In addition, a comparison between isoxazoles **3a**, **3b** and **3c** under this reaction condition demonstrates that the chloro-derivative **3a** is the most reactive substrate for nucleophilic substitutions, as it is typically observed for other S_NAr-type processes.[13] Indeed, 5-benzyloxyisoxazole **4a** can be prepared from 5-chloroisoxazole **3a** and benzyl alcohol **5a** in 92% yield, while the use of 5-bromoisoxazole **3b** leads to 50% of **4a** and 5-trifluoromethanesulfonylisoxazole **3c** produces < 10% of **4a**.

When these previous reaction conditions were tested with phenols, the yields decreased significantly. As a consequence, more forcing conditions were evaluated; and the change of solvent to DMF, while heating the mixture at 100 °C proved to be the best choice for this class of nucleophiles.[14]

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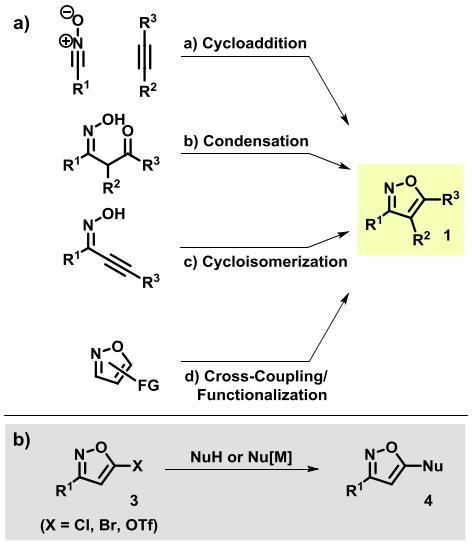
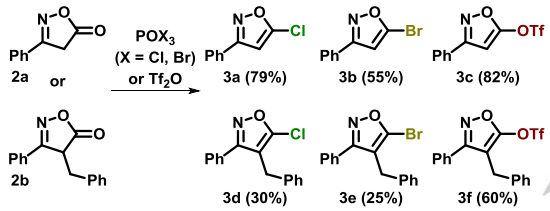


Scheme 1. a) General strategies for the preparation of isoxazoles **1**. b) Strategies developed in this work.



Scheme 2. 5-(pseudo)halogenated isoxazoles prepared in this study.

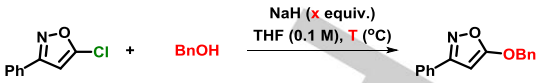
Having established two optimal reaction conditions for the nucleophilic substitution of alcohols **5** onto 5-chloroisoxazole **3a**, leading to the corresponding 5-alkoxy- or 5-aryloxy-3-substituted isoxazoles **4**, we turned our attention to the evaluation of the scope of this transformation.

In this regard, the use of primary, secondary and aromatic alcohols generally produce good yields, 50 - 91 % (**4a** - **4g** and **4i** - **4k**, Scheme 3), while 5-chloroisoxazole **3d** reacts with MeOH **5h** to produce 5-methoxyisoxazole **4h** in a moderate 45 % yield (Scheme 3).

In addition, we carried out a simple initial rate kinetic analysis of the model reaction involving **3a** and **5a** by measuring reaction yields in duplicates (using 1,3,5-trimethoxybenzene as internal standard) and using 1, 2 or 3 equivalents of one of the reactants, while keeping the concentration of the other partner constant (Figures 2a-b). Because the product yield (26% in 10 min) increases by a factor of two when doubling the [BnO^-] (53% in 10 min) and triplicates when [BnO^-] is increased three-fold (75% in 10 min), this analysis indicates a kinetic order of ~1 in respect to BnO^-.

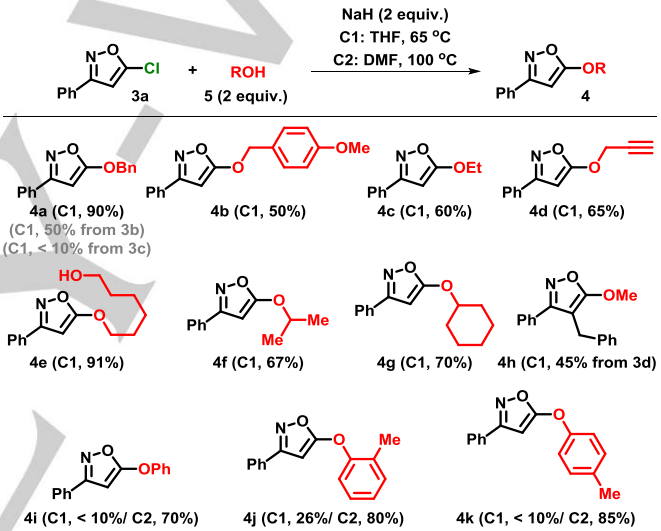
The rate obtained from the slope of the initial points (10-30 min of reaction) is shown in the Figure 2c. It exhibits an approximate two-fold increase (1.45/0.75 = 1.93) with the increase of [BnO^-] (It was not possible to determine the slope for a 3-fold excess of [BnO^-], because the reaction achieves 100% conversion before 20 min).

Table 1. Optimization for the addition of alcohols.



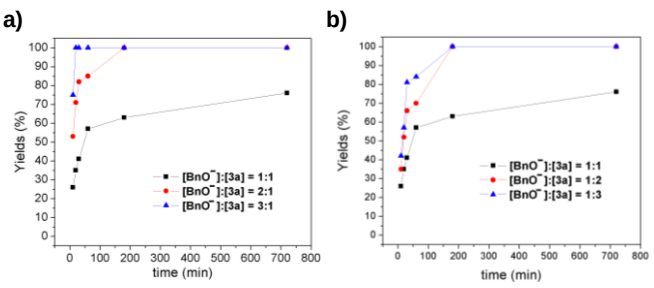
entry	x	T (°C)	yield (%)[a]
1	1	65	80
2	1.5	65	80
3	**2**	**65**	**quant.**
4	2	40	80
5	2	25	25

[a] Estimated by ^{1}H NMR from the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.



Scheme 3. Scope of nucleophilic substitutions using alcohols **5**.

In the same manner, the initial rate kinetic analysis indicates a kinetic order for **3a** in the range of ~0.86-1.03 (Figure 2d), because the 2-fold excess of [**3a**] increases the slope from 0.75 to 1.55 (1.55/0.75 = 2.06; 2.06/2 = 1.03) and the three-fold excess of [**3a**] increases the slope from 0.75 to 1.95 (1.95/0.75 = 2.60; 2.60/3 = 0.86).



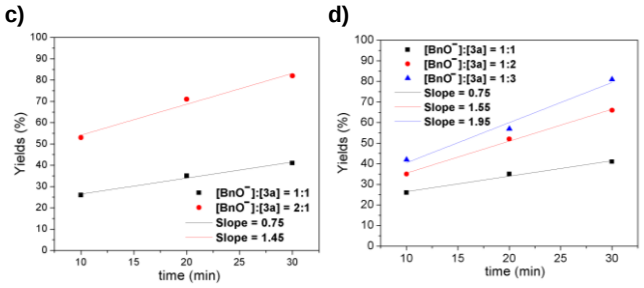
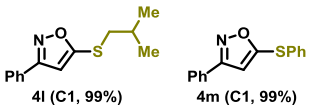


Figure 2. Plots of reaction yields vs time for **a)** 1-3-fold increase in [BnO^-] and **b)** 1-3-fold increase in [**3a**]. Slopes obtained for the initial rates of the reactions (10-30 min) with **c)** 1 and 2-fold excess of [BnO^-] and **d)** 1-3-fold excess of [**3a**].

Overall, this analysis showcases that the rate of this transformation depends on both reagents, **3a** and **5a**$^-$, in a somehow similar extent.

Then, aliphatic and aromatic thiol nucleophiles **6a** and **6b**, respectively, have been also employed under the same reaction conditions of Method C1 (NaH, THF, 65 °C). This time, the corresponding isoxazoles **4l** and **4m** are produced in quantitative yields, most likely as a consequence of the higher nucleophilicity of thiolates (Figure 3).



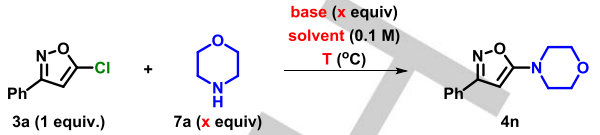
4l (C1, 99%) **4m (C1, 99%)** **(C1, 98% from 3b)** (C1, < 10% from 3c)

Figure 3. Examples of isoxazoles obtained using thiols **6** as nucleophiles.

Furthermore, amines **7** have been investigated as a third class of nucleophiles. In this case, optimization studies have been carried out using 5-chloroisoxazole **3a** and morpholine **7a** in the presence of different bases and solvents, at different temperatures (Table 2).

Initial interrogation of the reaction conditions using DMF as solvent, at 150 °C, in the absence of any base or in the presence of the weak bases $NaHCO_3$ or AcONa (2 equiv.) did not produce any conversion (Entries 1-3, Table 2). The use of NaOH leads to a poor 29% yield of isoxazole **4n** (Entry 4, Table 2), while K_2CO_3 affords **4n** in a significantly improved 80% yield (Entry 5, Table 2). A systematic evaluation of the reaction at lower temperatures (100, 80, 60 or 25 °C, Entries 6-9, Table 2) suggests that this protocol at 80 °C has the same efficiency as in 150 °C, also leading to 80% yield of **4n** (Entry 7, Table 2). Of note, the use of only 1 equiv of K_2CO_3 under these conditions provide a lower yield for **4n** (70%; Entry 10, Table 2). Different solvents have been considered and all of them, toluene, 1,2-DCE, THF, Dioxane, 1,2-DME, MeCN or DMSO (Entries 11-17, Table 2) produce lower yields than DMF (Entry 7, Table 2). With optimal reaction conditions in hand, the scope of this transformation was evaluated. Cyclic and linear amines perform generally well, thus providing the corresponding 5- aminoisoxazoles **4n** - **4r** in a range of good yields, 55-97% (Scheme 4).

Table 2. Optimization for the addition of amines.

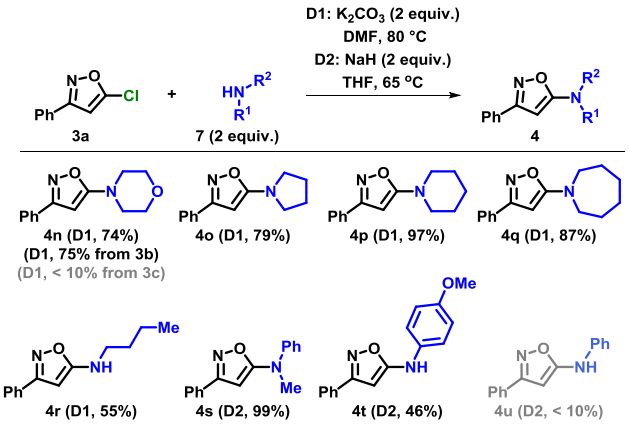


entry	base (x)	T (°C)	solvent	yield (%)[a]
1	-	150	DMF	0[b]
2	$NaHCO_3$ (2)	150	DMF	0[b]
3	AcONa (2)	150	DMF	0[b]
4	NaOH (2)	150	DMF	29
5	K_2CO_3 (2)	150	DMF	80
6	K_2CO_3 (2)	100	DMF	80
7	**K_2CO_3 (2)**	**80**	**DMF**	**80**
8	K_2CO_3 (2)	60	DMF	45
9	K_2CO_3 (2)	25	DMF	17
10	K_2CO_3 (1)	80	DMF	70
11	K_2CO_3 (2)	80	toluene	0[c]
12	K_2CO_3 (2)	80	1,2-DCE	0[c]
13	K_2CO_3 (2)	65	THF	14
14	K_2CO_3 (2)	80	Dioxane	22
15	K_2CO_3 (2)	80	1,2-DME	32
16	K_2CO_3 (2)	80	MeCN	42
17	K_2CO_3 (2)	80	DMSO	66

[a] Estimated by ^{1}H NMR from the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b]**3a** is fully consumed. Degradation is observed. [c] **3a** is recovered.

Some aromatic amines can also react in the presence of a stronger base; however, a number of them failed such as the isoxazole **4u**. For aromatic amines, the optimal conditions have been established as NaH (2 equiv) in THF, at 65 °C. In this case, *N*-methyl aniline **7f** and p-anisidine **7g** afford the corresponding isoxazoles **4s** and **4t**, in 99% and 46%, respectively. This difference in reactivity is presumably due to the higher nucleophilicity of secondary amines in respect to primary amines; and the higher nucleophilicity of alkylamines in respect to arylamines[15] (Scheme 4).

Initial rate kinetic analysis was also performed for the model reaction involving isoxazole **3a** and morpholine **7a**. Proceeding in the same manner as for the kinetic study using BnOH, the reaction yields were again measured in duplicates (using 1,3,5-trimethoxybenzene as internal standard), while varying [**7a**] or [**3a**] in relation to the other partner by 1-,2- and 3-fold (Figures 4a and 4b). The slopes of the initial rates



Scheme 4. Scope of nucleophilic substitutions using amines **7**.

(10-30 min, Figure 4c) increases from 0.08 to 0.10, and then to 0.13 when the number of equivalents of [**7a**] is increased from 1 to 2, then to 3 times, respectively. This indicates only a small increase in the rate of the reaction. Therefore, the reaction order in respect to **7a** ranges from 0.53 (0.13/0.08 = 1.63; 1.63/3 = 0.53) to 0.63 (0.10/0.08 = 1.25; 1.25/2 = 0.63). On the other hand, the initial rate kinetic analysis shows a zero-order reaction in respect to [**3a**], because the slope value is invariant with the increase in the concentration of **3a** (Figure 4d).

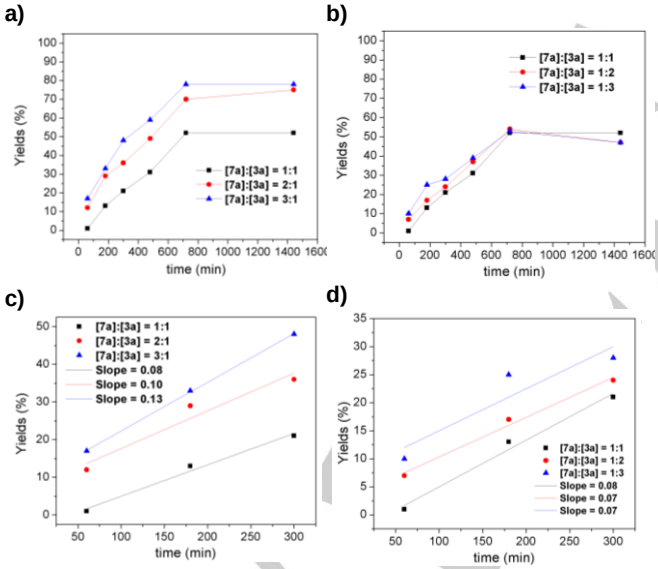


Figure 4. Plots of reaction yields vs time for **a)** 1-3-fold increase of [**7a**] and **b)** 1-3-fold increase of [**3a**]. Slopes obtained for the initial rates of the reactions (10-30 min) with **c)** 1-3 fold excess of [**7a**] and **d)** 1-3-fold excess of [**3a**].

For comparison purposes, in the reaction involving BnOH **5a**, its deprotonation by NaH is irreversible and the nucleophilic attack of the resulting anion **5a**$^-$ onto 5-chloroisoxazole **3a** seems to be the rate determining step (both reacting partners contribute to the rate of the reaction). In the case of morpholine, because K_2CO_3 is a much weaker base (in relation to NaH), the deprotonation of morpholine is a slow event and appears to be in this case the rate determining step. As a consequence, **3a** does not contribute to the reaction rate.

Next, the introduction of carbon chains at the C5 position of 5-(pseudo)halogenated isoxazoles **3** was investigated through cross-coupling approaches.

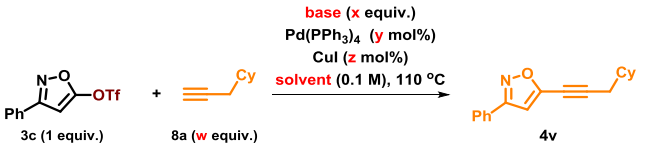
In this regard, a Sonogashira strategy was evaluated employing isoxazole **3c** and 3-cyclohexyl-1-propyne **8a** as model substrates, aiming at the preparation of isoxazole **4v**.

Initial screening of reaction conditions considered variation of the base, the amounts of CuI, $Pd(PPh_3)_4$ and alkyne **8a**, and the solvent employed, while heating at 110 °C (Table 3).

Comparing different bases (5 equiv; Et_3N, pyridine, 2,6-lutidine, DBU, *N,N*-DMA, piperidine, ^{i}PrNH, Na_2CO_3, TMEDA and DIPEA) in the presence of alkyne **8a** (2 equiv), $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), in DMF (Entries 1-10, Table 3) reveals the use of DIPEA as the best base, thus producing a 54% of the desired alkyne **4v** (Entry 10, Table 3). Variations in the amount of DIPEA (3, 1.5 or 1 equiv; Entries 11-13, Table 3) shows that 1.5 equiv is the optimal choice, this time producing a 80% yield of compound **4v** (Entry 12, Table 3). When employing $Pd(PPh_3)_4$ (10 mol%) in the absence of CuI, no convertion to **4v** is observed (Entry 14, Table 3). Inverting the previous amounts of CuI (5 mol%) and $Pd(PPh_3)_4$ (10 mol%) affords also an inferior result (9% yield; Entry 15, Table 3), which suggests that higher catalytic reactivity is obtained when the loading of Cu is higher than Pd. This time, when the catalysts amounts are increased, but taking into account this previous observation, *i.e.* using $Pd(PPh_3)_4$ (10 mol%) and CuI (20 mol%), a good yield (88%) is obtained (Entry 16, Table 3). Increasing the loading of CuI to 40 mol% does not improve the efficiency of this transformation, actually producing a virtually identical outcome (87% of **4v**; Entry 17, Table 3). Next, further evaluation of solvents involving DMSO, NMP, Dioxane, DIPEA, and toluene (Entries 18-22, Table 3) reveals the use of the latter as the optimal choice, this time producing **4v** in quantitative yield (Entry 22, Table 3). Finally, the use of 1 equiv of alkyne **8a** produces a lower yield of 95% (Entry 23, Table 3), while the use of 3 equiv of **8a** affords a quantitative yield for the desired alkyne **4v** (Entry 24, Table 3). Therefore, the use of 2 equiv of alkyne **8a** was chosen as the optimal amount.

Having established some of the optimal parameters for this Sonogashira cross-coupling protocol (Entry 22, Table 3), this allowed a second round of investigation, this time considering different temperatures and the nature of the Pd catalyst. The evaluation of temperatures (25, 60 and 80 °C; Entries 1-3, Table 4) using otherwise identical parameters to the previously established conditions indicates that 110 °C produces only a marginal increase in yields in relation to the reaction performed at lower temperatures, thus indicating that this protocol can also be efficiently carried out at r.t. (Entry 1, Table 4). In addition, interrogation of the most appropriate Pd source among $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$ and $PdCl_2(PPh_3)_2$ (Entries 4-7, Table 4) shows that $Pd(PPh_3)_4$ is actually the best option.

Table 3. First round for the optimization of the Sonogashira cross-coupling protocol.

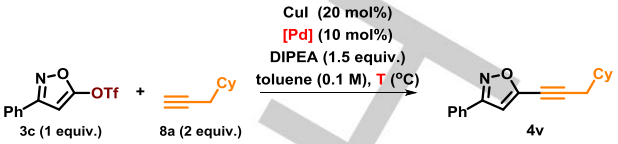


entry	w	base (x)	y	z	solvent	yield (%)[a][b]
1	2	Et_3N (5)	5	10	DMF	20
2	2	Pyridine (5)	5	10	DMF	0
3	2	2,6-Lutidine (5)	5	10	DMF	0
4	2	DBU (5)	5	10	DMF	0
5	2	N,N-DMA (5)	5	10	DMF	0
6	2	Piperidine (5)	5	10	DMF	0
7	2	^{i}PrNH (5)	5	10	DMF	27
8	2	Na_2CO_3 (5)	5	10	DMF	0
9	2	TMEDA (5)	5	10	DMF	0
10	2	DIPEA (5)	5	10	DMF	54
11	2	DIPEA (3)	5	10	DMF	68
12	2	DIPEA (1.5)	5	10	DMF	80
13	2	DIPEA (1)	5	10	DMF	72
14	2	DIPEA (1.5)	10	-	DMF	0
15	2	DIPEA (1.5)	10	5	DMF	9
16	2	DIPEA (1.5)	10	20	DMF	88
17	2	DIPEA (1.5)	10	40	DMF	87
18	2	DIPEA (1.5)	10	20	DMSO	0
19	2	DIPEA (1.5)	10	20	NMP	12
20	2	DIPEA (1.5)	10	20	Dioxane	93
21	2	-	10	20	DIPEA	46
22	**2**	**DIPEA (1.5)**	**10**	**20**	**Toluene**	**100**
23	1	DIPEA (1.5)	10	20	Toluene	90
24	3	DIPEA (1.5)	10	20	Toluene	100

[a]Estimated by ^{1}H NMR from the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b]**3c** is fully consumed. Degradation and Glaser-type diynes are observed.

Having in hand the optimal reaction conditions for this Sonogashira protocol, we turned our attention to the evaluation of its scope. In this regard, terminal alkynes **8** carrying aromatic and aliphatic chains or alcohol groups can be employed to produce the corresponding 3,5-disubstituted isoxazoles **4v – 4z**, which can be isolated in good yields, 61-94%.

Table 4. Second round for the optimization of the Sonogashira cross-coupling protocol.



entry	T (°C)	[Pd] (10 mol%)	yield (%)[a] [b]
1	25	$Pd(PPh_3)_4$	95
2	60	$Pd(PPh_3)_4$	94
3	80	$Pd(PPh_3)_4$	94
4	110	$PdCl_2$	<10
5	110	$Pd(OAc)_2$	<10
6	110	$Pd_2(dba)_3$	<10
7	110	$PdCl_2(PPh_3)_2$	45

[a]Estimated by ^{1}H NMR from the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b]**3c** is fully consumed. Degradation and Glaser-type diynes are observed.

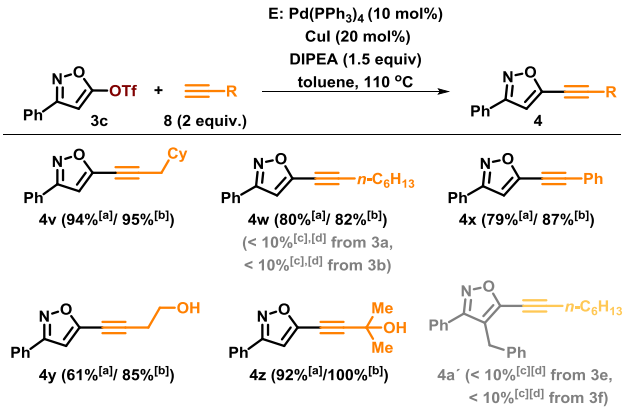
Remarkably, this protocol can be also employed at room temperature, without any sinificant change in yields (Scheme 5).

In addition, the reaction of isoxazoles **3a** or **3b** with *n*-octyne **8b** under the previously established conditions both fail to produce **4w**; as only formation of unidentifiable degradation products can be observed (Scheme 5).

These results confirm that the triflate derivative **3c** is the most appropriate starting isoxazole for this protocol. On the other hand, the reactions of isoxazoles **3e** or **3f** with 1-octyne **8b** also fail to produce the desired 4-benzyl-5-(oct-1-yn-1-yl)-3-phenylisoxazole **4a´** under the optimal conditions. Again, only complex mixtures are observed (Scheme 5).

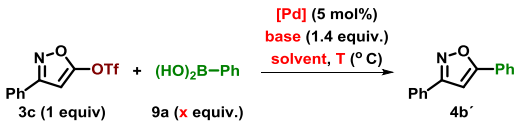
Finally, a Suzuki cross-coupling strategy has been also investigated for the preparation of 3,5-disubstituted isoxazoles **4**. The optimization of this transformation involved the reaction of triflate **3c** with phenylboronic acid **9a** aiming at the preparation of isoxazole **4b´** (Table 5). Initial screening of palladium catalysts in the presence of Na_2CO_3 and dioxane showed that $Pd_2(dba)_3$ and $Pd(OAc)_2$ produce only very poor yields (Entries 1 and 2, Table 5), while $PdCl_2(PPh_3)_2$ produces a higher yield of 66% (Entry 3, Table 5) and $PdCl_2$ and $Pd(PPh_3)_4$ afford quantitative yields of the desired isoxazole **4b´** (Entries 4 and 5, Table 5). Further investigation of bases (1.4 equiv), reveals an inferior result of 74% yield for the use of NaOH (Entry 6, Table 5), but both K_2CO_3 and $NaHCO_3$ afford **4b´** in quantitative yields (Entries 7 and 8, Table 5).

The use of 1 equiv. of boronic acid **9a** affords a slightly lower yield of 95% for **4b´** (Entry 9, Table 5), while 1.5 or 2 equiv. of **9a** produces isoxazole **4b´** in quantitative yields (Entries 10 and 11, Table 5). Based on these observations, the optimal amount considered for boronic acid **9a** was a slight excess of 1.2 equiv. Other solvents have been evaluated; DCM, EtOH, DMSO and



Scheme 5. Scope of the Sonogashira cross-coupling strategy. [a]Isolated yield. [b]Yield for reaction performed at r.t., estimated by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]Estimated by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [d]mass-balance: 0% starting isoxazole + degradation products.

Table 5. Optimization for the Suzuki cross-coupling protocol.



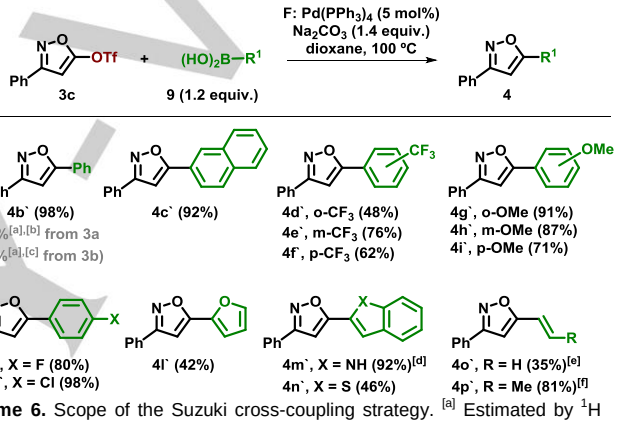
entry	[Pd] (5 mol%)	base (1.4 equiv)	x	solvent	T (°C)	Yield (%)[a]
1	$Pd_2(dba)_3$	Na_2CO_3	1.2	Dioxane	100	0[b]
2	$Pd(OAc)_2$	Na_2CO_3	1.2	Dioxane	100	6[b]
3	$PdCl_2(PPh_3)_2$	Na_2CO_3	1.2	Dioxane	100	66
4	$PdCl_2$	Na_2CO_3	1.2	Dioxane	100	100
5	**$Pd(PPh_3)_4$**	**Na_2CO_3**	**1.2**	**Dioxane**	**100**	**100**
6	$Pd(PPh_3)_4$	NaOH	1.2	Dioxane	100	74
7	$Pd(PPh_3)_4$	K_2CO_3	1.2	Dioxane	100	100
8	$Pd(PPh_3)_4$	$NaHCO_3$	1.2	Dioxane	100	100
9	$Pd(PPh_3)_4$	Na_2CO_3	1	Dioxane	100	95
10	$Pd(PPh_3)_4$	Na_2CO_3	1.5	Dioxane	100	100
11	$Pd(PPh_3)_4$	Na_2CO_3	2	Dioxane	100	100
12	$Pd(PPh_3)_4$	Na_2CO_3	1.2	DCM	40	0[b]
13	$Pd(PPh_3)_4$	Na_2CO_3	1.2	EtOH	80	0[c]
14	$Pd(PPh_3)_4$	Na_2CO_3	1.2	DMSO	100	0[c]
15	$Pd(PPh_3)_4$	Na_2CO_3	1.2	DMF	100	0[c]
16	$Pd(PPh_3)_4$	Na_2CO_3	1.2	Toluene	100	38

[a] Estimated by ^{1}H NMR from the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b]**3c** is recovered. [c]**3c** is fully consumed. Degradation is observed.

DMF fail to produce any isoxazole **4b´** (Entries 12-15, Table 4), while toluene affords only a modest yield of 38% (Entry 16, Table 5).

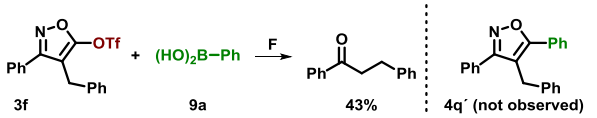
As a consequence of this investigation, the use of **9a** (1.2 equiv), Na_2CO_3 (1.4 equiv.), in dioxane at 100 °C, in the presence of $Pd(PPh_3)_4$ (5 mol%) was chosen as the optimal reaction condition for this Suzuki cross-coupling (Entry 5, Table 5).

Next, the scope of this transformation was evaluated and a number of 3,5-disubstituted isoxazoles **4** could be prepared in a range of good to excellent yields, 48-98% (Scheme 6). Exceptions to this general trend are observed only when a furan ring (42% for **4l´**, Scheme 6), a benzotiophene ring (46% for **4n`**, Scheme 6); or a vinyl chain (35 % for **4o´**, Scheme 6) are present, which might be a consequence of their sensitivity under the high temperature employed. (Scheme 6).



Scheme 6. Scope of the Suzuki cross-coupling strategy. [a] Estimated by ^{1}H NMR from the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b]mass-balance: 80% **3a** + degradation products. [c] mass-balance: 35% **3b** + degradation products. [d]Using pinacol ester as boron derivative. [e]Using 2.5 equiv of vinylboronic acid 2-methyl-2,4-pentanediol ester. [f]Using 2.5 equiv of boronic acid.

Finally, the reaction of isoxazoles **3e** with phenyl boronic acid **9a** fails (**3e** is fully recovered after 12h of reaction). On the other hand, isoxazole **3f** reacts with **9a** to produce 1,3-diphenylpropan-1-one as the major product in 43% yield, accompanied by other unidentified degradation products (Scheme 7).



Scheme 7. Reaction of the isoxazole **3f** under our standard Suzuki conditions leads to the formation of 1,3-diphenylpropan-1-one as the major product.

The formation of this ketone as a by-product can be attributed to a competing sequence of events involving N-O bond cleavage of the isoxazole ring, followed by hydrolysis promoted by adventitious water.

Conclusions

In summary, isoxazolones **2** can be readily transformed into 5-(pseudo)halogenated isoxazoles **3**. Then, chloroisoxazole **3a** can undergo nucleophilic substitutions using alcohols, amines and thiols; while triflate derivative **3c** is the optimal substrate for Sonogashira and Suzuki cross-coupling protocols. By using these methods, a straightforward and modular access to a large variety of 3,5-disubstituted isoxazoles **4** is obtained. The scope of the transformations reported herein suggest that these are general protocols.

Experimental Section

All reactions were carried out under air, in oven dried glassware with magnetic stirring, unless otherwise noted. All reagents employed in this work were purchased from Sigma-Aldrich and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. Organic solutions were concentrated under reduced pressure on a IKA rotary evaporator RV-10 Control. Reactions were monitored by thin-layer chromatography (TLC) on Silica gel 60 F_{254} aluminium plates (Merck). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using anisaldehyde solution. Flash column chromatography was performed using Merck silica gel 60 (particle size 35-70μm). ^{1}H and ^{13}C NMR spectra were recorded on either Bruker DPX-250, AV-400, AV-500 or AV-600 MHz spectrometers. Chemical shifts (δ) are given in parts per million, referenced to the residual peak of $CDCl_3$, δ = 7.24 (^{1}H NMR) and δ = 77.23 (^{13}C NMR) as internal references. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, sext. = sextuplet, sept. = septuplet, m = multiplet, br s = broad singlet. High-resolution mass spectra were recorded on Thermo Scientific LTQ FT Ultra and Q Exactive Orbitrap spectrometers working with an electronspray ionization (ESI).

3-Phenylisoxazol-5(*4H*)-one **2a**[16] and 4-benzyl-3-phenylisoxazol-5(*4H*)-one **2b**[17] have been prepared according to the literature.

General Procedure A: *Preparation of 5-Chloro or 5-Bromo Isoxazoles*

A round bottom flask is charged with isoxazol-5-one **2** (1 equiv.) and dissolved in POX_3, X = Cl (7 equiv.) or Br (5 equiv.). Next, the reaction is cooled to 0 ºC and Et_3N (1 equiv.) is added. Then, the reaction is allowed to warm up to room temperature and is heated to reflux (100 ºC). Upon complete consumption of the starting isoxazolone **2** (TLC), the reaction is allowed to cool to rt, and ice is added. The pH is adjusted to 8 employing a 2M aqueous NaOH solution. Finally, the crude reaction mixture is diluted in DCM, washed with H_2O, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the crude reaction mixture by flash column chromatography affords the 5-halogenated isoxazole in the stated yields.

5-chloro-3-phenylisoxazole (3a): General procedure A is employed using isoxazol-5-one **2a** (7.14 mmol, 1.15 g), $POCl_3$ (50 mmol, 4.7 mL) and Et_3N (7.14 mmol, 1 mL). *Reaction time: 6 h.* Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:DCM – 8:2 Hex:DCM – 7:3 Hex:DCM – 6:4 Hex:DCM) affords the title compound as a white solid (930 mg, 79%). **^{1}H (500 MHz, $CDCl_3$) δ:**[1a] 7.75-7.70 (m, 2H), 7.46-7.45 (m, 3H), 6.47 (s, 1H). **^{13}C (100 MHz, $CDCl_3$) δ:** 164.2, 155.1, 130.6, 129.1, 128.2, 126.6, 99.7. **M. P.:** 44-46 ^{o}C. **IR (ATR, cm^{-1}):** 1558, 1460, 1402, 1132, 815, 765, 689, 506. **HRMS (ESI+)**: Calcd. for $[C_9H_6ClNO+H]^+$: 180.0211, found 180.0211.

5-bromo-3-phenylisoxazole (3b): General procedure A is employed using isoxazol-5-one **2a** (2 mmol, 400 mg), $POBr_3$ (10 mmol, 2.8 g) and Et_3N (2 mmol, 278 μL). *Reaction time: 6 h*. Purification by flash column chromatography (SiO_2, gradient: Hex – 9:1 Hex:DCM – 8:2 Hex:DCM) affords the title compound as a white solid (308 mg, 55%). **^{1}H (400 MHz, $CDCl_3$) δ:**[18] 7.75-7.73 (m, 2H), 7.46-7.44 (m, 3H), 6.57 (s, 1H). **^{13}C (100 MHz, $CDCl_3$) δ:** 164.4, 141.9, 130.8, 129.3, 128.2, 126.9, 104.6. **^{19}F (235 MHz, $CDCl_3$) δ:** -71.8. **M.P.:** 40 - 41 ^{o}C. **IR (ATR, cm^{-1}):** 1551, 1458,1398, 1115, 955, 886, 769, 692. **HRMS (ESI+)**: Calcd. for $[C_9H_6BrNO+H]^+$: 223.9706, found: 223.9706.

4-benzyl-5-chloro-3-phenylisoxazole (3d): General procedure A is employed using 4-benzyl-3-phenylisoxazol-5(4H)-one **2b** (0.5 mmol, 125 mg), $POCl_3$ (3.5 mmol, 196 μL) and Et_3N (0.5 mmol, 70 μL). *Reaction time: 6 h*. Purification by flash column chromatography (SiO_2, gradient: Hex – 9:1 Hex:DCM – 8:2 Hex:DCM) affords the title compound as an yellow liquid (40 mg, 30%). **^{1}H (400 MHz, $CDCl_3$) δ:** 7.42-7.30 (m, 5H), 7.22-7.12 (m, 3H), 7.23-7.0 (m, 2H), 3.8 (s, 2H). **^{13}C (125 MHz, $CDCl_3$) δ:** 164.6, 153.4, 137.8, 130.3, 129.0, 128.9, 128.8, 128.3, 128.1, 126.9, 111.8, 28.4. **IR (ATR, cm^{-1}):** 1605, 1579, 1497, 1445, 1393, 1177, 972, 897, 728, 765, 728, 694, 461. **HRMS (ESI+)**: calcd. for $[C_{16}H_{12}ClNO+H]^+$: 270.0680, found 270.0681.

4-benzyl-5-bromo-3-phenylisoxazole (3e): General procedure A is employed using benzyl-3-phenylisoxazol-5(4H)-one **2b** (0.5 mmol, 125 mg), $POBr_3$ (2.5 mmol, 716 mg) and Et_3N (0.5 mmol, 70 μL). *Reaction time: 6 h*. Purification by flash column chromatography (SiO_2, gradient: Hex – 9:1 Hex:DCM – 8:2 Hex:DCM) affords the title compound as an yellow liquid (39 mg, 25%). **^{1}H (400 MHz, $CDCl_3$) δ:** 7.42-7.30 (m, 5H), 7.23-7.15 (m, 3H), 7.00-7.0 (m, 2H), 3.81 (s, 2H). **^{13}C (125 MHz, $CDCl_3$) δ:** 164.4, 142.0, 137.9, 130.2, 129.0, 128.9, 128.7, 128.4, 128.2, 126.9, 116.0, 28.9. **IR (ATR, cm^{-1}):** 1598, 1573, 1497, 1454, 1441, 1385, 1169, 1078, 964, 886, 765, 726, 694. **HRMS (ESI+)**: calcd. for $[C_{16}H_{12}BrNO+H]^+$: 314.0175, found 314.0173.

General Procedure B: *Synthesis of Isoxazol-5-yl Trifluoromethanesulfonates*

A round bottom flask is charged with the isoxazol-5-one **2** (1 equiv.), DCM (0.25 M), and Et_3N (1.2 equiv.). The reaction mixture is cooled to -78 ºC and stirred for 10 min. Then, Tf_2O (1.5 equiv.) is added, stirred for 10 min, warmed up to r.t. and stirred at this temperature for additional 30 min. Finally, the reaction is quenched with H_2O, extracted with DCM (3x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The title compound is purified by flash column chromatography to afford the corresponding triflate in the stated yield.

3-phenylisoxazol-5-yl trifluoromethanesulfonate (3c): General procedure B is employed using isoxazol-5-one **2a** (10 mmol, 1.73 g), Tf_2O (15 mmol, 2.51 mL) and Et_3N (20 mmol, 2.7 mL) and DCM (2 mL). *Reaction time: 50 min.* Purification by flash column chromatography (SiO_2, gradient: Hex – 9:1 Hex:DCM – 8:2 Hex:DCM) affords the title

compound as a white solid (1.42 g, 82%). **^{1}H (400 MHz, $CDCl_3$) δ:**[11c] 7.76-7.74 (m, 2H), 7.48-7.44 (m, 3H), 6.36 (s, 1H). **^{13}C (100 MHz, $CDCl_3$) δ:** 164.9, 161.7, 131.2, 129.3, 128.0, 126.8, 119.1 (q, *J* = 322.0 Hz), 89.0. **M. P.:** 38-40 °C. **IR (ATR, cm^{-1}):** 1620, 1585, 1471, 1480, 1221, 1124, 1015, 1080, 938, 770. **HRMS (ESI+)**: calcd. for $[C_{10}H_6F_3NO_4S+H]^+$: 294.0042, found: 294.0042.

4-benzyl-3-phenylisoxazol-5-yl trifluoromethanesulfonate (3f): General procedure B is employed using benzyl-3-phenylisoxazol-5(4H)-one **2b** (1 mmol, 375 mg), Tf_2O (1.5 mmol, 425 µL) and Et_3N (2 mmol, 420 µL) and DCM (5 mL). *Reaction time: 50 min.* Purification by flash column chromatography (SiO_2, gradient: Hex – 9:1 Hex:DCM – 8:2 Hex:DCM – 7:3 Hex:DCM – 6:4 Hex:DCM) affords the title compound as a white solid (150 mg, 60%). **^{1}H (400 MHz, $CDCl_3$) δ:** 7.56-7.54 (m, 2H), 7.49-7.42 (m, 3H), 7.33-7.25 (m, 3H), 7.14-7.12 (m, 2H), 3.94 (s, 2H). **^{13}C (100 MHz, $CDCl_3$) δ:** 165.6, 159.0, 136.6, 130.6, 129.1, 129.0, 128.4, 128.3, 128.3, 127.3, 118.5 (q, *J* = 320.0 Hz), 103.8, 27.5. **^{19}F (235 MHz, $CDCl_3$) δ:** -72.0. **M. P.:** 38 - 40 °C. **IR (ATR, cm^{-1}):** 1655, 1432, 1400, 1221, 1205, 1128, 1097, 990, 914, 832, 674, 618. **HRMS (ESI+)**: calcd. for $[C_{17}H_{12}F_3NO_4S+H]^+$: 384.0512, found 384.0509.

General Procedure C1: *Preparation of 5-Alkoxy-3-Substituted Isoxazoles*

A reaction vessel is charged with the 5-chloro-3-phenylisoxazole **3a** (1 equiv.), NaH (2 equiv.), and THF (0.1M). Then, ROH **5** (2 equiv.) is added. The reaction is heated at 65 ºC overnight. Then, the reaction is quenched with an aqueous saturated solution of NH_4Cl, extracted with AcOEt (3x), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography affords the title compounds in the stated yields.

General Procedure C2: *Preparation of 5-Aryloxy-3-Substituted Isoxazoles*

A reaction vessel is charged with the 5-chloro-3-phenylisoxazole **3a** (1 equiv.), NaH (2 equiv.), and DMF (0.1 M). Then, ArOH **5** (2 equiv.) is added. The reaction is heated at 100 °C overnight. Then, the reaction is quenched with an aqueous saturated solution of NH_4Cl, diluted in AcOEt, washed with H_2O (5x), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography affords the title compounds in the stated yields.

5-(benzyloxy)-3-phenylisoxazole (4a): This compound is prepared employing the general procedure C1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), benzyl alcohol **5a** (0.2 mmol, 22 mg) and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as an yellow oil (23 mg, 90%). **^{1}H (400 MHz, $CDCl_3$) δ:**[19] 7.75-7.73 (m, 2H), 7.46-7.39 (m, 8H), 5.56 (s, 1H), 5.29 (s, 2H). **^{13}C (100 MHz, $CDCl_3$) δ:** 173.6, 164.4, 134.6, 130.3, 129.8, 129.2, 129.0 (x2), 128.2, 126.7, 76.9, 73.8. **IR (ATR, cm^{-1}):** 1577, 1450, 1387, 892, 676, 690. **M. P.:** 137-138 °C. **HRMS (ESI+):** Calcd. for $[C_{16}H_{13}NO_2+H]^+$: 252.1019, found: 252.1018.

5-((4-methoxybenzyl)oxy)-3-phenylisoxazole (4b): This compound is prepared employing the general procedure C1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), (4-methoxyphenyl)methanol **5b** (0.2 mmol, 28 mg), and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt – 8:2 Hex:AcOEt) affords the title compound as a white solid (14 mg, 50%). **^{1}H (500 MHz, $CDCl_3$) δ:** 7.72-7.69 (m, 2H), 7.42-7.39 (m, 3H), 7.38-7.35 (m, 2H), 6.91-6.89 (m, 2H) 5.51 (s, 1H), 5.19 (s, 2H), 3.80 (s, 3H). **^{13}C (125 MHz, $CDCl_3$) δ:** (1C cannot be unambiguously assigned) 173.6, 164.4, 160.4, 130.2, 129.8, 129.0, 126.7, 126.6, 114.4, 76.8, 73.9, 55.5. **M. P.:** 126-128 °C. **IR (ATR, cm^{-1}):** 2900, 2890, 1610, 1580, 1500, 1489, 1430, 1360, 1230, 1150, 1006, 817, 789, 687. **HRMS (ESI+):** Calcd. for $[C_{17}H_{15}NO_3+H]^+$: 282.1125, found: 282.1121.

5-ethoxy-3-phenylisoxazole (4c): This compound is prepared employing the general procedure C1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), ethanol **5c** (0.2 mmol, 12 µL) and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as an yellow oil (12 mg, 60%). **^{1}H (400 MHz, $CDCl_3$) δ:**[20] 7.74-7.72 (m, 2H), 7.42-7.40 (m, 3H), 5.48 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H). **^{13}C (100 MHz, $CDCl_3$) δ:** 173.9, 164.3, 130.2, 129.8, 129.0, 126.6, 75.9, 68.5, 14.7. **IR (ATR, cm^{-1}):** 1611, 1585, 1398, 1018, 990, 672, 555. **M. P.:** 76-78 °C. **HRMS (ESI+):** Calcd. for $[C_{11}H_{11}NO_2+H]^+$: 190.0863, found: 190.0866.

3-phenyl-5-(prop-2-yn-1-yloxy)isoxazole (4d): This compound is prepared employing the general procedure C1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), prop-2-yn-1-ol **5d** (0.2 mmol, 12 µL), and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt – 8:2 Hex:AcOEt) affords the title compound as a brown solid (13 mg, 65%). **^{1}H (400 MHz, $CDCl_3$) δ:** 7.75-7.73 (m, 2H), 7.44-7.42 (m, 3H), 5.67 (s, 1H), 4.88-4.87 (m, 2H), 2.64-6.63 (m, 1H). **^{13}C (100 MHz, $CDCl_3$) δ:** 172.8, 164.5, 130.4, 129.6, 129.0, 126.7, 77.7, 77.6, 76.2, 59.5. **M. P.:** 59 - 60 °C. **IR (ATR, cm^{-1}):** 1630, 1610, 1600, 1589, 1480, 1447, 1387, 1189, 1100, 980, 768, 689. **HRMS (ESI+):** Calcd. for $[C_{12}H_9NO_2+H]^+$: 200.0706, found: 200.0704.

3-phenylisoxazol-5-yl-oxy-hexan-1-ol (4e): This compound is prepared employing the general procedure C1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), hexane-1,6-diol **5e** (0.2 mmol, 24 mg) and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt). affords the title compound as a white solid (24 mg, 91%). **^{1}H (400 MHz, $CDCl_3$) δ:** 7.73-7.71 (m, 2H), 7.42-7.40 (m, 3H), 5.47 (s, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 3.64 (t, *J* = 6.7 Hz, 2H), 1.83 (quint, *J* = 6.7 Hz, 2H), 1.58 (quint, *J* = 6.7 Hz, 2H), 1.51-1.43 (m, 5H). **^{13}C (100 MHz, $CDCl_3$) δ:** 174.0, 163.4, 130.2, 129.8, 129.0, 126.6, 75.9, 72.6, 62.9, 32.7, 29.0, 25.7, 25.6. **M. P.:** 83 - 85 °C. **IR (ATR, cm^{-1}):** 3100, 2900, 1590, 1580, 1490, 1476, 1340, 1260, 1100, 1000, 908,765 678. **HRMS (ESI+):** Calcd. for $[C_{15}H_{19}NO_3+H]^+$: 262.1438, found: 262.1434.

5-isopropoxy-3-phenylisoxazole (4f): This compound is prepared employing the general procedure C1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), propan-2-ol **5f** (0.2 mmol, 15 µL), and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex: AcOEt – 9:1 Hex:AcOEt – 8:2 Hex:AcOEt) affords the title compound as a white solid (14 mg, 67%). **^{1}H (400 MHz, $CDCl_3$) δ:** 7.74-7.72 (m, 2H), 7.43-7.40 (m,

3H), 5.47 (s, 1H), 4.70 (sept, *J* = 6.0 Hz, 1H), 1.43 (d, *J* = 6.0 Hz, 6H). **^{13}C (100 MHz, CDCl$_3$) δ:** 173.4, 164.4, 130.1, 129.9, 129.0, 126., 76.9, 76.6, 21.1. **M. P.:** 39 - 40 °C. **IR (ATR, cm^{-1}):** 1601, 1579, 1482, 1419, 1354, 1343, 1106, 1026, 901, 758, 692, 510. **HRMS (ESI+):** Calcd. for $[C_{12}H_{13}NO_2+H]^+$: 204.1019, found: 204.1024.

5-(cyclohexyloxy)-3-phenylisoxazole (4g): This compound is prepared employing the general procedure C1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), cyclohexanol **5g** (0.2 mmol, 21 µL) and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt – 8:2 Hex:AcOEt). affords the title compound as a white solid (17 mg, 70%). **^{1}H (500 MHz, CDCl$_3$) δ:** 7.74-7.72 (m, 2H), 7.41-7.40 (m, 3H), 5.47 (s, 1H), 4.43 (sept, *J* = 3.9 Hz, 1H), 2.03-2.01 (m, 1H), 1.83-1.80 (m, 2H), 1.70-1.61 (m, 2H), 1.55-1.56 (m, 2H), 1.43-1.32 (m, 3H). **^{13}C (100 MHz, CDCl$_3$) δ:** 173.4, 164.4, 130.1, 130.1, 128.9, 126.6, 81.7, 76.6, 31.7, 25.4, 23.6. **M. P.:** 100 - 101 °C. **IR (ATR, cm^{-1}):** 2939, 2857, 1603, 1581, 1562, 1421, 1218, 1043, 1026, 949, 905, 890, 582. **HRMS (ESI+):** Calcd. for $[C_{15}H_{17}NO_2+H]^+$: 244.1332, found: 244.1336.

4-benzyl-5-methoxy-3-phenylisoxazole (4h): This compound is prepared employing the general procedure C1 with 4-benzyl-5-chloro-3-phenylisoxazole **3d** (0.1 mmol, 27 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), methanol **5h** (0.2 mmol, 8 µL) and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid (12 mg, 45%). **^{1}H (400 MHz, CDCl$_3$) δ:**[1e] 7.49-7.47 (m, 2H), 7.39-7.34 (m, 3H), 7.26-7.22 (m, 2H), 7.18-7.16 (m, 1H), 7.12-7.10 (m, 2H), 4.11 (s, 3H), 3.71 (s, 2H). **^{13}C (100 MHz, CDCl$_3$) δ:** 170.5, 165.4, 139.9, 130.1, 129.8, 128.8, 128.7, 128.2, 128.1, 126.4, 90.3, 58.2, 27.2. **M.P.:** 42 - 44 °C. **IR (ATR, cm^{-1}):** 1639, 1488, 1449, 1413, 1011, 966, 933, 769, 665. **HRMS (ESI+):** Calcd. for $[C_{17}H_{15}NO_2+H]^+$: 266.1176, found: 266.1175.

5-phenoxy-3-phenylisoxazole (4i): This compound is prepared employing the general procedure C2 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), phenol **5i** (0.2 mmol, 18 mg), and DMF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex: AcOEt – 9:1 Hex:AcOEt). affords the title compound as a white solid (24 mg, 70%). **^{1}H (400 MHz, CDCl$_3$) δ:** 7.68-7.65 (m, 2H), 7.40-7.36 (m, 5H), 7.22-7.18 (m, 3H), 5.51 (s, 1H). **^{13}C (125 MHz, CDCl$_3$) δ:** 172.7, 164.4, 154.8, 130.4, 130.3, 129.5, 129.0, 126.7, 126.2, 119.4, 79.7. **M. P.:** 55 - 56 °C. **IR (ATR, cm^{-1}):** 2950, 2870, 1680, 1630, 1480, 1410, 1300, 1208, 1124, 1000, 908, 820, 710, 598. **HRMS (ESI+):** Calcd. for $[C_{15}H_{11}NO_2+H]^+$: 238.0863, found: 238.0862.

3-phenyl-5-(o-tolyloxy)isoxazole (4j): This compound is prepared employing the general procedure C2 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), *o*-cresol **5j** (0.2 mmol, 22 mg) and DMF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt). affords the title compound as a white solid (20 mg, 80%). **^{1}H (400 MHz, CDCl$_3$) δ:** 7.75-7.74 (m, 2H), 7.45-7.44 (m, 3H), 7.34-7.21 (m, 4H), 5.45 (s, 1H), 2.35 (s, 3H). **^{13}C (125 MHz, CDCl$_3$) δ:** 172.9, 164.4, 153.0, 132.1, 130.3, 129.7, 129.5, 128.9, 127.7, 126.6 (x2), 119.8, 78.7, 16.0. **M. P.:** 63 - 64 °C. **IR (ATR, cm^{-1}):** 1610, 1600, 1580, 1490, 1400, 1390, 1310, 1170, 1108, 1000, 930, 850, 648. **HRMS (ESI+):** Calcd. for $[C_{16}H_{13}NO_2+H]^+$: 252.1019, found: 252.1016.

3-phenyl-5-(p-tolyloxy)isoxazole (4k): This compound is prepared employing the general procedure C2 with the 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), *p*-cresol **5k** (0.2 mmol, 22 mg) and DMF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex - 95:5 Hex:AcOEt – 9:1 Hex:AcOEt). affords the title compound as a white solid (21 mg, 85%). **^{1}H (400 MHz, CDCl$_3$) δ:** 7.71-7.69 (m, 2H), 7.41-7.40 (m, 3H), 7.22-7.20 (m, 2H), 7.14-7.11 (m, 2H), 5.50 (s, 1H), 2.36 (s, 3H). **^{13}C (125 MHz, CDCl$_3$) δ:** 173.2, 164.4, 152.6, 136.1, 130.8, 130.3, 129.5, 129.0, 126.7, 119.3, 79.2, 21.0. **M. P.:** 61 - 62 °C. **IR (ATR, cm^{-1}):** 1616, 1598, 1574, 1474, 1443, 1415, 1294, 1206, 1162, 1078, 1018, 832, 750, 692, 500. **HRMS (ESI+):** Calcd. for $[C_{16}H_{13}NO_2+H]^+$: 252.1019, found: 252.1016.

5-(isobutylthio)-3-phenylisoxazole (4l): This compound is prepared employing the general procedure C1 with the 5-chloro-3-phenylisoxazole **3a** (0.2 mmol, 36 mg), NaH (60% in mineral oil, 0.4 mmol, 16 mg), 2-mehtyl-1-propanethiol **6a** (0.4 mmol, 50 µL) and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as an yellow oil: 47 mg, 99%. **^{1}H (400 MHz, CDCl$_3$) δ:** 7.76-7.74 (m, 2H), 7.44-7.42 (m, 3H), 6.41 (s, 1H), 2.95 (d, *J* = 6.8 Hz, 2H), 1.94 (sept, *J* = 6.8 Hz, 1H), 1.03 (d, *J* = 6.8 Hz, 6H). **^{13}C (100 MHz, CDCl$_3$) δ:** 167.5, 163.2, 130.3, 129.1, 129.0, 126.9, 101.9, 42.2, 29.1, 21.9. **IR (ATR, cm^{-1}):** 3049, 2958, 2870, 1541, 1457, 1394, 1248, 760, 687. **HRMS (ESI+):** Calcd. for $[C_{13}H_{15}NOS+H]^+$: 234.0953, found: 234.0950.

3-phenyl-5-(phenylthio)isoxazole (4m): This compound is prepared employing the general procedure C1 with 5-chloro-3-phenylisoxazole **3a** (0.2 mmol, 36 mg), NaH (60% in mineral oil, 0.4 mmol, 16 mg), thiophenol **6b** (0.4 mmol, 41 µL) and THF (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as an yellow solid: 51 mg, 99%. **^{1}H (400 MHz, CDCl$_3$) δ:**[19] 7.75-7.72 (m, 2H), 7.52-7.50 (m, 2H), 7.43-7.35 (m, 6H), 6.46 (s, 1H). **^{13}C (125 MHz, CDCl$_3$) δ:** 166.3, 163.3, 132.4, 130.8, 130.4, 129.8, 129.1 (2x), 128.8, 127.0, 104.8. **M. P.:** 50 - 52 °C. **IR (ATR, cm^{-1}):** 3141, 2917, 1534, 1455, 1386, 1021, 768, 686. **HRMS (ESI+):** Calcd. for $[C_{15}H_{11}NOS+H]^+$: 254.0640, found: 254.0634.

General Procedure D1: *Preparation of 5-Amino-3-Substituted Isoxazoles using Aliphatic Amines*

A reaction vessel is charged with 5-chloro-3-substituted isoxazole **3a** (1 equiv.), K_2CO_3 (2 equiv.), and DMF (0.25 M). Then, R^2R^3NH **7** (2 equiv.) is added. The reaction is heated at 80 °C overnight. Then, the reaction is cooled to room temperature, quenched with a saturated aqueous solution of NH_4Cl, extracted with AcOEt (3x), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography affords the title compounds in the stated yields.

4-(3-phenylisoxazol-5-yl)morpholine (4n): This compound is prepared employing the general procedure D1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), K_2CO_3 (0.2 mmol, 28 mg), morpholine **7d** (0.2 mmol, 17 µL) and DMF (0.4 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 17 mg, 74%. **^{1}H (500 MHz, CDCl$_3$) δ:**[21] 7.74-

7.71 (m, 2H), 7.41-7.40 (m, 3H), 5.33 (s, 1H), 3.82-3.80 (m, 4H), 3.37-3.35 (m, 4H). **^{13}C (125 MHz, $CDCl_3$) δ:** 171.5, 163.8, 130.0 (2x), 128.9, 126.8, 77.1, 66.2, 47.0. **M. P.:** 87 - 89 °C. **IR (ATR, cm^{-1}):** 3129, 3053, 2967, 2853, 1595, 1578, 1476, 1276, 1112, 1070. **HRMS (ESI+):** Calcd. for $[C_{13}H_{14}N_2O_2+H]^+$: 231.1128, found: 231.1128.

3-phenyl-5-(pyrrolidin-1-yl)isoxazole (4o): This compound was prepared employing the general procedure D1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), K_2CO_3 (0.2 mmol, 28 mg), pyrrolidine **7a** (0.2 mmol, 16 µL) and DMF (0.4 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 17 mg, 79%. **^{1}H (500 MHz, $CDCl_3$) δ:**[22] 7.74-7.71 (m, 2H), 7.41-7.37 (m, 3H), 5.11 (s, 1H), 3.44-3.41 (m, 4H), 2.00-1.98 (m, 4H). **^{13}C (125 MHz, $CDCl_3$) δ:** 169.4, 163.8, 130.5, 129.6, 128.8, 126.8, 74.3, 48.0, 25.8. **M. P.:** 98 - 100 °C. **IR (ATR, cm^{-1}):** 3118, 2917, 2850, 1625, 1584, 1422, 1353, 1161. **HRMS (ESI+):** Calcd. for $[C_{13}H_{14}N_2O+H]^+$: 215.1179, found: 215.1177.

3-phenyl-5-(piperidin-1-yl)isoxazole (4p): This compound was prepared employing the general procedure D1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), K_2CO_3 (0.2 mmol, 28 mg), piperidine **7b** (0.2 mmol, 20 µL) and DMF (0.4 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as an yellow solid: 22 mg, 97%. **^{1}H (400 MHz, $CDCl_3$) δ:** 7.73-7.72 (m, 2H), 7.39-7.38 (m, 3H), 5.25 (s, 1H), 3.34-3.32 (m, 4H), 1.64-1.63 (m, 6H). **^{13}C (100 MHz, $CDCl_3$) δ:** 171.8, 163.8, 130.4, 129.7, 128.8, 126.8, 76.1, 47.9, 25.1, 24.1. **M. P.:** 80 - 83 °C. **IR (ATR, cm^{-1}):** 2932, 2852, 1593, 1577, 1480, 1288, 1118. **HRMS (ESI+):** Calcd. for $[C_{14}H_{16}N_2O+H]^+$: 229.1335, found: 229.1338.

5-(azepan-1-yl)-3-phenylisoxazole (4q): This compound is prepared employing the general procedure D1 with 5-chloro-3-phenylisoxazole **3a** (0.2 mmol, 36 mg), K_2CO_3 (0.4 mmol, 55 mg), hexamethyleneimine **7c** (0.4 mmol, 45 µL) and DMF (0.8 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as an yellow oil: 42 mg, 87%. **^{1}H (500 MHz, $CDCl_3$) δ:** 7.74-7.72 (m, 2H), 7.41-7.36 (m, 3H), 5.12 (s, 1H), 3.47-3.45 (m, 4H), 1.78-1.76 (m, 4H), 1.58-1.56 (m, 4H). **^{13}C (125 MHz, $CDCl_3$) δ:** 170.6, 163.8, 130.5, 129.6, 128.7, 126.7, 73.6, 48.9, 28.3, 27.7. **IR (ATR, cm^{-1}):** 2924, 2853, 1597, 1422, 1170, 1068. **HRMS (ESI+):** Calcd. for $[C_{15}H_{18}N_2O+Na]^+$: 265.1317, found: 265.1415.

***N*-butyl-3-phenylisoxazol-5-amine (4r):** This compound was prepared employing the general procedure D1 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), K_2CO_3 (0.2 mmol, 28 mg), butylamine **7e** (0.2 mmol, 20 µL) and DMF (0.4 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a brown oil: 12 mg, 55%. **^{1}H (400 MHz, $CDCl_3$) δ:** 7.74-7.72 (m, 2H), 7.42-7.38 (m, 3H), 5.26 (s, 1H), 4.50 (m, 1H), 3.21 (q, *J* = 6.0 Hz, 2H), 1.64-1.58 (m, 2H), 1.41 (sex, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.6 Hz, 3H). **^{13}C (100 MHz, $CDCl_3$) δ:** 170.7, 163.8, 130.2, 129.8, 128.9, 126.9, 75.2, 44.7, 31.8, 20.2, 13.9. **IR (ATR, cm^{-1}):** 3284, 3055, 2926, 2870, 1610, 1582, 1413, 1066. **HRMS (ESI+):** Calcd. for $[C_{13}H_{16}N_2O+H]^+$: 217.1335, found: 217.1340.

General Procedure D2: *Preparation of 5-Amino-3-Substituted Isoxazoles using Aromatic Amines*

A reaction vessel is charged with the 5-chloro-3-substituted isoxazole **3a** (1 equiv.), NaH (2 equiv.), and THF (0.25 M). Then, $ArNH_2$ **7** (2 equiv.) is added. The reaction is heated at 65 ºC overnight. Then, the reaction is cooled to room temperature, quenched with a saturated aqueous solution of NH_4Cl, extracted with AcOEt (3x), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography affords the corresponding product.

***N*-methyl-*N*,3-diphenylisoxazol-5-amine (4s):** This compound was prepared employing the general procedure D2 with 5-chloro-3-phenylisoxazole **3a** (0.2 mmol, 36 mg), NaH (60% in mineral oil, 0.4 mmol, 16 mg), *N*-methylaniline **7f** (0.4 mmol, 43 µL) and THF (0.8 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a brown solid: 50 mg, quantitative. **^{1}H (500 MHz, $CDCl_3$) δ:**[21] 7.72-7.71 (m, 2H), 7.41-7.37 (m, 5H), 7.34-7.32 (m, 2H), 7.20-7.17 (m, 1H), 5.47 (s, 1H), 3.48 (s, 3H). **^{13}C (125 MHz, $CDCl_3$) δ:** 169.8, 163.8, 145.0, 130.1, 129.9, 129.6, 128.9, 126.8, 125.4, 123.0, 78.8, 38.5. **M. P.:** 76 - 77 °C. **IR (ATR, cm^{-1}):** 2921, 2852, 1593, 1487, 1312, 1094. **HRMS (ESI+):** Calcd. for $[C_{16}H_{14}N_2O+Na]^+$: 273.1004, found: 273.1097.

***N*-(4-methoxyphenyl)-3-phenylisoxazol-5-amine (4t):** This compound was prepared employing the general procedure D2 with 5-chloro-3-phenylisoxazole **3a** (0.1 mmol, 18 mg), NaH (60% in mineral oil, 0.2 mmol, 8 mg), *p*-anisidine **7g** (0.2 mmol, 25 mg) and THF (0.4 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a brown solid: 12 mg, 46%. **^{1}H (400 MHz, $CDCl_3$) δ:** 7.75-7.71 (m, 2H), 7.41-7.40 (m, 3H), 7.16-7.12 (m, 2H), 6.91-6.88 (m, 2H), 6.48 (s, 1H), 5.65 (s, 1H), 3.80 (s, 3H). **^{13}C (100 MHz, $CDCl_3$) δ:** 167.3, 163.9, 156.4, 132.6, 130.0, 129.9, 129.0, 126.9, 121.1, 115.1, 78.2, 55.8. **M. P.:** 137 - 139 °C. **IR (ATR, cm^{-1}):** 3204, 2995, 2915, 2850, 1636, 1603, 1578, 1478, 1252, 1178, 1029. **HRMS (ESI+):** Calcd. for $[C_{16}H_{14}N_2O_2+H]^+$: 267.1128, found: 267.1128.

General Procedure E: *Preparation of 3-Substituted-5-(Alk-1-yn-1-yl)isoxazoles*

A reaction vessel is charged with 3-substitutedlisoxazol-5-yl trifluoromethanesulfonate **3c** (1 equiv.), $Pd(PPh_3)_4$ (10 mol%), CuI (20 mol%) and toluene (0.1 M). Then, DIPEA (1.5 equiv.) and the alkyne **8** (2 equiv.) are added. The reaction is heated at 110 °C overnight. Then, the reaction mixture is concentrated under reduced pressure. Purification by flash column chromatography affords the title compounds in the stated yields.

5-(3-cyclohexylprop-1-yn-1-yl)-3-phenylisoxazole (4v): General procedure E is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 30 mg), $Pd(PPh_3)_4$ (0.01 mmol, 12 mg), CuI (0.02 mmol, 4 mg), DIPEA (0.15 mmol, 26 µL), prop-2-yn-1-ylcyclohexane **8a** (0.2 mmol, 30 µL) and toluene (1 mL). *Reaction time: 12 h.* Purification by flash column chromatography (SiO_2, gradient: Hex – 9:1 Hex:DCM – 8:2 Hex: DCM – 7:3 Hex:DCM – 6:4 Hex:DCM) affords the title compound as an yellow oil (25 mg, 94%). **^{1}H (500 MHz, $CDCl_3$) δ:** 7.78-7.76 (m, 2H), 7.44-7.43 (m, 3H), 6.61 (s, 1H), 2.37 (d, *J* = 6.7 Hz, 2H), 1.86-1.72 (m, 4H), 1.68-1.65 (m, 1H), 1.30-1.02 (m, 6H). **^{13}C (100**

MHz, $CDCl_3$) δ: 162.7, 154.7, 130.3, 129.2, 128.9, 127.0, 105.1, 100.4, 68.8, 37.2, 33.0, 27.5 26.3, 26.2. **IR (ATR, cm^{-1}):** 2922, 2853, 1577, 1443, 1423, 1395, 933, 884, 802, 769, 689. **HRMS (ESI+):** Calcd. for $[C_{18}H_{19}NO+H]^+$: 266.1539, found: 266.1539.

5-(oct-1-yn-1-yl)-3-phenylisoxazole (4w): General procedure E is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 30 mg), $Pd(PPh_3)_4$ (0.01 mmol, 12 mg), CuI (0.02 mmol, 4 mg), DIPEA (0.15 mmol, 26 µL), oct-1-yne **8b** (0.2 mmol, 31 µL) and toluene (1 mL). *Reaction time: 12 h.* Purification by flash column chromatography (SiO_2, gradient: Hex – 9:1 Hex:DCM – 8:2 Hex:DCM – 7:3 Hex:DCM – 6:4 Hex:DCM) affords the title compound as a brown oil (20 mg, 80%). **^{1}H (400 MHz, $CDCl_3$) δ:** 7.78-7.76 (m, 2H), 7.44-743 (m, 3H), 6.61 (s, 1H), 2.47 (t, *J* = 7.0 Hz, 2H), 1.63 (q, *J* = 7.0 Hz, 2H), 1.48-1.40 (m, 2H), 1.32-1.31 (m, 4H), 0.91-0.87 (m, 3H). **^{13}C (100 MHz, $CDCl_3$) δ:** 162.7, 154.7, 130.3, 129.2, 128.9, 127.0, 105.1, 101.4, 67.9, 31.5, 28.8, 28.1, 22.7, 19.8, 14.2. **IR (ATR, cm^{-1}):** 2955, 2928, 2857, 2240, 1594, 1577, 1467, 1441, 1398, 1300, 1084, 951, 767, 690. **HRMS (ESI+):** Calcd. for $[C_{17}H_{19}NO+H]^+$: 254.1539, found: 254.1537.

3-phenyl-5-(phenylethynyl)isoxazole (4x): General procedure E is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 30 mg), $Pd(PPh_3)_4$ (0.01 mmol, 12 mg), CuI (0.02 mmol, 4 mg), DIPEA (0.15 mmol, 26 µL), phenylacetylene **8c** (0.2 mmol, 22 µL) and toluene (1 mL). *Reaction time: 12 h.* Purification by flash column chromatography (SiO_2, gradient: Hex – 9:1 Hex:DCM – 8:2 Hex:DCM – 7:3 Hex:DCM – 6:4 Hex:DCM) affords the title compound as an orange solid (19 mg, 79%). **^{1}H (400 MHz, $CDCl_3$) δ:**[11a] 7.82-7.80 (m, 2H), 7.59-7.57 (m, 2H), 7.48-7.44 (m, 3H), 7.43-7.36 (m, 3H). 6.79 (s, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 162.8, 154.2, 132.1, 130.5, 130.1, 129.2, 128.8, 128.7, 127.0, 121.1, 106.1, 98.7, 75.8. **M. P.** 103-105 °C. **IR (ATR, cm^{-1}):** 2918, 2851, 2100, 1575, 1441, 1398, 1262, 1072, 1050, 1026, 804, 758, 690. **HRMS (ESI+):** Calcd. for $[C_{17}H_{11}NO+H]^+$: 246.0913, found: 246.0912.

4-(3-phenylisoxazol-5-yl)but-3-yn-1-ol (4y): General procedure E is employed using 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 30 mg), $Pd(PPh_3)_4$ (0.01 mmol, 12 mg), CuI (0.02 mmol, 4 mg), DIPEA (0.15 mmol, 26 µL), but-3-yn-1-ol **8d** (0.2 mmol, 15 µL) and toluene (1 mL). *Reaction time: 12 h.* Purification by flash column chromatography (SiO_2, gradient, Hex - 9:1 Hex:DCM – 8:2 Hex:DCM) affords the title compound as a colorless oil (13 mg, 61%). **^{1}H (250 MHz, $CDCl_3$) δ:** 7.78-7.74 (m, 2H), 7.46-742 (m, 3H), 6.65 (s, 1H), 3.86 (t, *J* = 6.3 Hz, 2H), 2.76 (t, *J* = 6.3 Hz, 2H). **^{13}C (62.5 MHz, $CDCl_3$) δ:** 162.7, 154.1, 130.4, 129.2, 128.7, 127.0, 105.6, 97.8, 69.4, 60.6, 24.1. **IR (ATR, cm^{-1}):** 3369, 2920, 2888, 2242, 1576, 1397, 1049, 767, 690. **HRMS (ESI+):** Calcd. for $[C_{13}H_{11}NO_2+H]^+$: 214.0863 Found: 214.0858

2-methyl-4-(3-phenylisoxazol-5-yl)but-3-yn-2-ol (4z): General procedure E is employed using 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 30 mg), $Pd(PPh_3)_4$ (0.01 mmol, 12 mg), CuI (0.02 mmol, 4 mg), DIPEA (0.15 mmol, 26 µL), 2-methylbut-3-yn-2-ol **8e** (0.2 mmol, 20 µL) and toluene (1 mL). *Reaction time: 12 h.* Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt – 85:15 Hex:AcOEt – 8:2 Hex:AcOEt) affords the title compound as a brown oil (21 mg, 92%). **^{1}H (250 MHz, $CDCl_3$) δ:** 7.78-7.74 (m, 2H), 7.45-7.42 (m, 3H), 6.68 (s, 1H), 2.46 (br s, 1H), 1.63 (s, 6H). **^{13}C (62.5 MHz, $CDCl_3$) δ:** 162.7, 153.8, 130.5, 129.2, 128.5, 127.0, 106.1, 103.6, 69.3, 65.8, 31.0. **IR (ATR, cm^{-1}):** 3373, 2983, 2929, 1575, 1465, 1398, 1378, 1253, 1164, 951, 767, 692, 685, 549. **HRMS (ESI+):** Calcd. for $[C_{14}H_{13}NO_2+H]^+$: 228.1019, found: 228.1018.

General Procedure F: *Preparation of 3,5-Disubstituted Isoxazolones*

A reaction vessel is charged with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (1 equiv.), boronic acid derivative **9** (1.2 equiv.), Na_2CO_3 (1.4 equiv.), $Pd(PPh_3)_4$ (5 mol%) and dioxane (0.1 M). The reaction is heated at 100 ºC overnight. Then, the reaction mixture is allowed to cool to rt, then being concentrated under reduced pressure. Purification by flash column chromatography affords the title compounds in the stated yields.

3,5-diphenylisoxazole (4b´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), phenylboronic acid **9a** (0.12 mmol, 15 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as an yellow solid: 22 mg, 98%. **^{1}H (500 MHz, $CDCl_3$) δ:**[23] 7.87-7.82 (m, 4H), 7.49-7.44 (m, 6H), 6.82 (s, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 170.6, 163.2, 130.4, 130.2, 129.3, 129.2, 129.1, 127.7, 127.0, 126.0, 97.7. **M. P.:** 140 - 141 ºC. **IR (ATR, cm^{-1}):** 3114, 3049, 2922, 1612, 1571, 1487, 1450, 1399, 1322, 1285, 1257, 1071, 1025. **HRMS (ESI+):** Calcd. for $[C_{15}H_{11}NO+H]^+$: 222.0913, found: 222.0912.

5-(naphthalen-2-yl)-3-phenylisoxazole (4c´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), naphthalen-2-ylboronic acid **9b** (0.12 mmol, 21 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg,) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 25 mg, 92%. **^{1}H (500 MHz, $CDCl_3$) δ:**[24] 8.35 (s, 1H), 7.94-7.85 (m, 6H), 7.56-7.52 (m, 2H), 7.50-7.46 (m, 3H), 6.93 (s, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 170.6, 163.3, 134.2, 133.3, 130.3, 129.4, 129.2, 129.1, 128.9, 128.1, 127.6, 127.2, 127.1, 125.8, 124.9, 123.1, 96.1. **M. P.:** 161 - 163 ºC **IR (ATR, cm^{-1}):** 3106, 3054, 2922, 1611, 1561, 1509, 1458, 1401, 1366, 1213, 1165, 1090, 1026, 978. **HRMS (ESI+):** Calcd. for $[C_{19}H_{13}NO+H]^+$: 272.1070, found: 272.1069.

3-phenyl-5-(2-(trifluoromethyl)phenyl)isoxazole (4d´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), (2-(trifluoromethyl)phenyl)boronic acid **9c** (0.12 mmol, 24 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as an yellow oil: 14 mg, 48%. **^{1}H (500 MHz, $CDCl_3$) δ:** 7.87-7.82 (m, 4H), 7.69-7.66 (m, 1H), 7.60-7.7.58 (m, 1H), 7.50-7.45 (m, 3H), 6.85 (s, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 167.6, 163.1, 132.3, 131.19, 130.4, 130.4, 129.2, 129.8, 128.3 (q, *J* = 31.4 Hz), 127.1, 126.9 (q, *J* = 5.2 Hz), 126.6 (q, *J* = 1.4 Hz), 123.5 (q, *J* = 273.7 Hz), 102.7 (q, *J* = 3.7 Hz). **^{19}F (235 MHz, $CDCl_3$) δ:** -59.2. **IR (ATR, cm^{-1}):** 3129, 3067, 2927, 1578, 1491, 1449, 1401, 1312, 1291, 1243, 1111, 1063, 1035, 950. **HRMS (ESI+):** Calcd. for $[C_{16}H_{10}F_3NO+H]^+$: 290.0787, found: 290.0796.

3-phenyl-5-(3-(trifluoromethyl)phenyl)isoxazole (4e´): General procedures F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), (3-(trifluoromethyl)phenyl)boronic acid **9d** (0.12 mmol, 24 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 22 mg, 76%. **^{1}H (500 MHz, $CDCl_3$) δ:** 8.05 (m, 1H), 8.02-8.00 (m, 1H), 7.97-7.85 (m, 2H), 7.70-7.69 (m, 1H), 7.63-7.60 (m, 1H), 7.49-7.46 (m, 3H) 6.91 (s, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 170.0, 163.4, 131.9 (q, *J* = 35.2 Hz), 130.5, 129.9, 129.2, 129.1 (x2), 128.4, 127.1, 126.9 (q, *J* = 3.2 Hz), 123.9 (q, *J* = 272.8 Hz), 122.9 (q, *J* = 3.8 Hz), 98.8. **^{19}F (235 MHz, $CDCl_3$) δ:** -62.9. **M. P.:** 119 - 121 ºC. **IR (ATR, cm^{-1}):** 2925, 2323, 1621, 1446, 1327, 1250, 1220, 1167, 1103, 1069, 1048, 949. **HRMS (ESI+):** Calcd. for $[C_{16}H_{10}F_3NO+H]^+$: 290.0787, found: 290.0791.

3-phenyl-5-(4-(trifluoromethyl)phenyl)isoxazole (4f´): General procedures F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), (4-(trifluoromethyl)phenyl)boronic acid **9e** (0.12 mmol, 24 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 9:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 18 mg, 62 %. **^{1}H (500 MHz, $CDCl_3$) δ:**[25] 7.96-7.94 (m, 2H), 7.87-7.85 (m, 2H), 7.75-7.73 (m, 2H), 7.50-7.47 (m, 3H), 6.92 (s, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 169.0, 163.4, 132.2 (q, *J* = 32.7 Hz), 130.8, 130.5, 129.3, 129.0, 127.1, 126.4, 126.3, 123.4 (q, *J* = 272.8 Hz), 99.2. **^{19}F (235 MHz, $CDCl_3$) δ:** -62.9. **M.P.:** 191 - 193 ºC. **IR (ATR, cm^{-1}):** 3110, 2922, 2852, 2643, 2305, 2103, 1663, 1600, 1569, 1502, 1465, 1441, 1416, 1321, 1263, 1064, 1108, 1016, 948, 915. **HRMS (ESI+):** Calcd. for $[C_{16}H_{10}F_3NO+H]^+$: 290.0787 Found: 290.0784.

5-(2-methoxyphenyl)-3-phenylisoxazole (4g´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), (2-methoxyphenyl)boronic acid **9f** (0.12 mmol, 19 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 23 mg, 91%. **^{1}H (500 MHz, $CDCl_3$) δ:** 8.02-8.01 (m, 1H), 7.90-7.88 (m, 2H), 7.48-7.39 (m, 4H), 7.09-7.06 (m, 2H), 7.02-7.08 (m, 1H), 3.98 (s, 3H). **^{13}C (125 MHz, $CDCl_3$) δ:** 166.5, 163.2, 158.4, 131.4, 130.0, 129.8, 129.0, 128.0, 127.1, 121.1, 116.7, 111.4, 101.7, 55.8. **M. P.:** 65 - 67 ºC. **IR (ATR, cm^{-1}):** 3125, 2940, 2838, 1609, 1570, 1494, 1452, 1399, 1285, 1251, 1180, 1028, 1084, 1052, 947. **HRMS (ESI+):** Calcd. for $[C_{16}H_{13}NO_2+H]^+$: 252.1019, found: 252.1018.

5-(3-methoxyphenyl)-3-phenylisoxazole (4h´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), (3-methoxyphenyl)boronic acid **9g** (0.12 mmol, 19 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as an yellow oil: 22 mg, 87%. **^{1}H (400 MHz, $CDCl_3$) δ:**[24] 7.87-7.84 (m, 2H), 7.49-7.36 (m, 6H), 7.00-6.68 (m, 1H), 6.80 (s, 1H), 3.87 (s, 3H). **^{13}C (100 MHz, $CDCl_3$) δ:** 170.5, 163.2, 160.2, 130.3, 130.2, 129.3, 129.1, 128.8, 127.0, 118.6, 116.4, 111.2, 97.9, 55.6. **IR (ATR, cm^{-1}):** 3125, 3057, 2936, 2836, 2290, 2109, 1572, 1492, 1466, 1450, 1399, 1320, 1273, 1235, 1203, 1170, 1036. **HRMS (ESI+):** Calcd. for $[C_{16}H_{13}NO_2+H]^+$: 252.1019, found: 252.1019.

5-(4-methoxyphenyl)-3-phenylisoxazole (4i´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), (4-methoxyphenyl)boronic acid **9h** (0.12 mmol, 19 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 18 mg, 71%. **^{1}H (500 MHz, $CDCl_3$) δ:**[26] 7.85-7.84 (m, 2H), 7.76-7.75 (m, 2H), 7.46-7.43 (m, 3H), 6.98-6.97 (m, 2H), 6.69 (s, 1H), 3.84 (s, 3H). **^{13}C (125 MHz, $CDCl_3$) δ:** 170.6, 163.1, 161.3, 130.1, 129.5, 129.1, 127.6, 127.0, 120.5, 114.6, 96.3, 55.6. **M. P.:** 128 - 130 ºC**. IR (ATR, cm^{-1}):** 3061, 2916, 2838, 2297, 1612, 1581, 1518, 1500, 1462, 1399, 1306, 1246, 1176, 1118, 948, 926, 839. **HRMS (ESI+):** Calcd. for $[C_{16}H_{13}NO_2+H]^+$: 252.1019, found: 252.1018.

5-(4-fluorophenyl)-3-phenylisoxazole (4j´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), (4-fluorophenyl)boronic acid **9i** (0.12 mmol, 18 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a white solid: 19 mg, 80%. **^{1}H (500 MHz, $CDCl_3$) δ:** 7.85-7.80 (m, 4H), 7.49-7.45 (m, 3H), 7.18-7.14 (m, 2H), 6.76 (s, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 169.7, 164.0 (d, *J* = 251.6 Hz), 163.3, 130.3, 129.2, 129.1, 128.1 (d, *J* = 8.5 Hz), 127.0, 124.1 (d, *J* = 3.3 Hz), 116.4 (d, *J* = 22.1 Hz), 97.5. **^{19}F (235 MHz, $CDCl_3$) δ:** -109.4. **M. P.:** 168 -170 ºC. **IR (ATR, cm^{-1}):** 3111, 3058, 1613, 1497, 1460, 1416, 1394, 1305, 1225, 1157, 1089, 1014. **HRMS (ESI+):** Calcd. for $[C_{15}H_{10}FNO+H]^+$: 240.0819, found: 240.0817.

5-(4-chlorophenyl)-3-phenylisoxazole (4k´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), (4-chlorophenyl)boronic acid **9j** (0.12 mmol, 20 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 25 mg, 98%. **^{1}H (500 MHz, $CDCl_3$) δ:**[24] 7.85-7.83 (m, 2H), 7.77-7.75 (m, 2H), 7.48-7.44 (m, 5H), 6.81 (s, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 169.5, 163.3, 136.5, 130.4, 129.6, 129.2, 129.1, 127.3, 127.0, 126.1, 96.0. **M. P.:** 179 – 180 ºC. **IR (ATR, cm^{-1}):** 3105, 1611, 1485, 1458, 1409, 1258, 1305, 1156, 1089, 1014, 949. **HRMS (ESI+):** Calcd. for $[C_{15}H_{10}ClNO+H]^+$: 256.0524, found: 256.0524.

5-(furan-2-yl)-3-phenylisoxazole (4l´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), furan-2-ylboronic acid **9k** (0.12 mmol, 14 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a brown solid: 9 mg, 42%. **^{1}H (400 MHz, $CDCl_3$) δ:**[27] 7.85-7.83 (m, 2H), 7.56-7.54 (m, 1H), 7.48-7.44 (m, 3H), 6.94-6.93 (m, 1H), 6.74 (s, 1H), 6.55-6.53 (m, 1H). **^{13}C (100 MHz, $CDCl_3$) δ:** 162.9, 162.3, 144.3, 143.5, 130.3, 129.2, 129.0, 127.1, 112.2, 110.7, 97.3. **M. P.:** 75 - 77 ºC. **IR (ATR, cm^{-1}):** 3117, 3064, 2920, 1621, 1553, 1490, 1439, 1399, 1273, 1240, 1216, 1157, 1014, 964. **HRMS (ESI+):** Calcd. for $[C_{13}H_9NO_2+H]^+$: 212.0706, found: 212.0705.

5-(1H-indol-2-yl)-3-phenylisoxazole (4m´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), indole-2-boronic acid pinacol ester **9l** (0.12 mmol, 29 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a brown solid: 24 mg, 92%. **^{1}H (500 MHz, $CDCl_3$) δ:** 8.75 (s, 1H), 7.87-7.85 (m, 2H), 7.68-7.66 (m, 1H), 7.49-7.43 (m, 4H), 7.30-7.27 (m, 1H), 7.18-7.14 (m, 1H), 7.02-7.02 (m, 1H), 6.82 (s, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 164.0, 163.2, 137.0, 130.4, 129.2, 129.0, 128.4, 127.1, 125.3, 124.5, 121.8, 121.2, 111.7, 103.8, 97.6. **M. P.:** 191 -193 ºC. **IR (ATR, cm^{-1}):** 3414, 3102, 3054, 1620, 1577, 1490, 1440, 1395, 1343, 1287, 1249, 1090. **HRMS (ESI+):** Calcd. for $[C_{17}H_{12}N_2O+H]^+$: 261.1022, found: 261.1018.

5-(benzo[b]thiophen-2-yl)-3-phenylisoxazole (4n´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg,), benzo[b]thiophen-2-ylboronic acid **9m** (0.12 mmol, 23 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 13 mg, 46%. **^{1}H (400 MHz, $CDCl_3$) δ**: 7.89-7.84 (m, 4H), 7.79 (s, 1H), 7.50-7.45 (m, 3H), 7-42-7.7.34 (m, 2H), 6.80 (s, 1H). **^{13}C (100 MHz, $CDCl_3$) δ:** 165.5, 163.3, 140.4, 139.7, 130.4, 129.3, 129.2, 129.0, 127.1, 126.1, 125.3, 124.9, 123.9, 122.7, 99.0. **M. P.:** 157 -159 ºC. **IR (ATR, cm^{-1}):** 3117, 3054, 1602, 1498, 1463, 1439, 1396, 1331, 1254, 1201, 1072, 1023. **HRMS (ESI+):** Calcd. for $[C_{17}H_{10}NOS+H]^+$: 278.0634, found: 278.0630.

3-phenyl-5-vinylisoxazole (4o´): General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), vinylboronic acid 2-methyl-2,4-pentanediol ester **9n** (95%, 0.25 mmol, 41 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex - 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as an yellow solid: 6 mg, 35%. **^{1}H (500 MHz, $CDCl_3$) δ:**[28] 7.80-7.78 (m, 2H), 7.45-7.42 (m, 3H), 6.65 (dd, *J* = 11.4 Hz, *J* = 17.8 Hz, 1H), 6.50 (s, 1H), 6.05 (d, *J* = 17.8 Hz, 1H), 5.58 (d, *J* = 11.4 Hz, 1H). **^{13}C (125 MHz, $CDCl_3$) δ:** 169.0, 162.9, 130.2, 129.3, 129.1, 127.0, 122.6, 120.9, 99.7. **M. P.:** 37 - 38 ºC. **IR (ATR, cm^{-1}):** 2850, 1664, 1564, 1509, 1466, 1403, 1297, 1227, 1260, 1081, 1027, 999, 961. **HRMS (ESI+):** Calcd. for $[C_{11}H_9NO+H]^+$: 172.0757, found: 172.0757.

***(E)*-3-phenyl-5-(prop-1-en-1-yl) isoxazole (4p´):** General procedure F is employed with 3-phenylisoxazol-5-yl trifluoromethanesulfonate **3c** (0.1 mmol, 29 mg), *trans*-prop-1-en-1-ylboronic acid **3o** (0.25 mmol, 22 mg), Na_2CO_3 (0.14 mmol, 15 mg), $Pd(PPh_3)_4$ (0.005 mmol, 6 mg) and dioxane (1 mL). Purification by flash column chromatography (SiO_2, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt) affords the title compound as a white solid: 15 mg, 81%. **^{1}H (500 MHz, $CDCl_3$) δ:** 7.79-7.77 (m, 2H), 7.44-7.41 (m, 3H), 6.61-6.54 (m, 1H), 6.37-66.34 (m, 1H), 6.65 (s, 1H), 1.93 (dd, *J* = 6.8 Hz, *J* = 1.6 Hz, 3H). **^{13}C (125 MHz, $CDCl_3$) δ:** 169.3, 162.7, 134.0, 130.0, 129.5, 129.0, 127.0, 117.3, 97.9, 18.9. **M. P.:** 60 - 61 ºC. **IR (ATR, cm^{-1}):** 2850, 1664, 1564, 1509, 1466, 1403, 1297, 1227, 1260, 1081, 1027, 999, 961. **HRMS (ESI+):** Calcd. for $[C_{12}H_{11}NO+H]^+$: 186.0913, found: 186.0912.

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Keywords: Heterocycles • Isoxazoles • Isoxazolones • Nucleophilic Substitutions • Cross-Coupling

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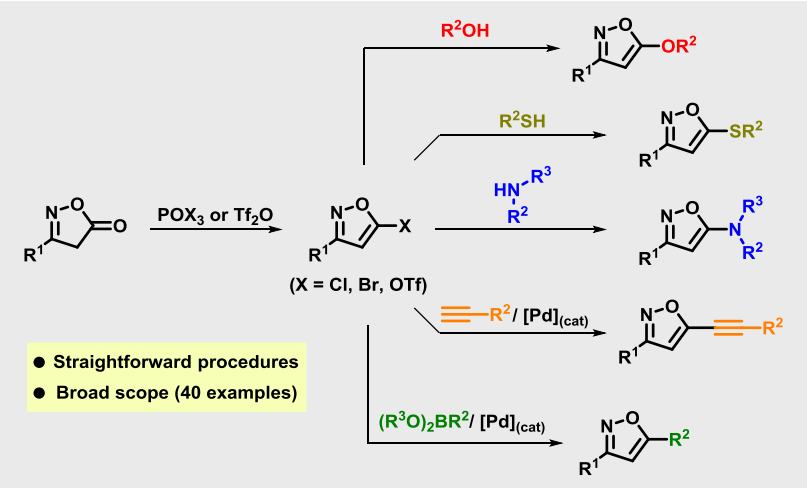

Heterocycles

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General Platform for the Conversion of Isoxazol-5-ones to 3,5-Disubstituted Isoxazoles via Nucleophilic Substitutions and Palladium Catalyzed Cross-Coupling Strategies

A general platform for the conversion of isoxazol-5-ones to 3,5-disubstituted isoxazoles has been developed via a two-step strategy. The first step leads to the formation of 5-(pseudo)halogenated isoxazoles, while in the second, a variety of heteroalkyl-, heteroaryl-, alkyl-, alkenyl-, alkynyl- and aryl-chains can be installed via nucleophilic substitutions or palladium catalyzed cross-coupling reactions.