Advanced Synthesis & Catalysis

Accepted Article

Title: Palladium-Catalyzed Cascade Cyclization/Alkynylation and Alkenylation of Alkynone O-Methyloximes with Terminal Alkynes

Authors: Huanfeng Jiang, Jianxiao Li, Miao Hu, Chunsheng Li, Can Li, Jiawei Li, and Wanqing Wu

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800444

Link to VoR: http://dx.doi.org/10.1002/adsc.201800444

10.1002/adsc.201800444

FULL PAPER

DOI: 10.1002/adsc.200((will be filled in by the editorial sttaff**))**

Palladium-Catalyzed Cascade Cyclization/Alkynylation and Alkenylation of Alkynone *O*-Methyloximes with Terminal Alkynes

Jianxiao Li,[+a] Miao Hu,[+a] Chunsheng Li,[a] Can Li,[a] Jiawei Li,[a] Wanqing Wu[a] and Huanfeng Jiang[a,*]

[a] Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China.
Fax: (+86) 20-87112906; E-mail: jianghf@scut.edu.cn
[+] These authors contributed equally to this work.

Received: ((will be filled in by the editorial staff))

Abstract: A palladium-catalyzed cascade cyclization for the assembly of polyfunctionalized isoxazoles derivatives has been accomplished. This new protocol exhibits mild conditions, high efficiency, good functional group tolerance and broad substrate scope. Remarkably, the easy availability of starting materials along with the efficiency of the present strategy provides a new tool for the construction of structurally diverse isoxazole derivatives, becoming a promising application in synthetic and pharmaceutical chemistry.

Keywords: Palladium-catalyzed; alkynylation; alkenylation; alkynone *O*-methyloximes; terminal alkynes

Introduction

Heterocycles are ubiquitous building blocks in numerous biologically active natural products, functional materials molecules, agrochemicals, and pharmaceuticals.[1] Isoxazoles represent a privileged heteroaromatic motifs in pharmaceuticals and bioactive natural products.[2] In particular, highly substituted isoxazoles exhibit remarkable biological and therapeutic activities, such as antinociceptive, antimicrobial, antibiotic, anti-inflammatory, and anticancer activities.[3] As depicted in Figure 1, valdecoxib was established as a COX-2 inhibitor.[4] Leflunomide was reported as a antirheumatic drug.[5] Oxacillin was used as a β-lactam antibiotic.[6] In addition, these structural skeleton represent synthetically versatile intermediates for other chemical transformations.[7] Considerable efforts have been devoted to developing efficient synthetic methodologies for the assembly of functionalized isoxazole derivatives in the past few years. Undoubtedly, [3 + 2] cycloaddition reactions of alkynes with nitrile oxides represents the most straightforward and efficient methods in the construction of these important frameworks.[8] However, most of these excellent strategies required functionalized precursors, harsh conditions, and provided poor chemo- and regioselectivities, reducing their versatility and simplicity. Alternatively, electrophilic cyclization of alkynone *O*-methyloximes with a varieties of electrophilic agents have also been investigated for constructing 4-haloisoxazoles and 4-organoselenyl-isoxazoles.[9] However, the electrophilic reagents is limited to halogenated electrophilic species. As a consequence, the development of expeditious and practical synthetic route for the straightforward preparing these polyfunctionalized isoxazoles are still challenging.

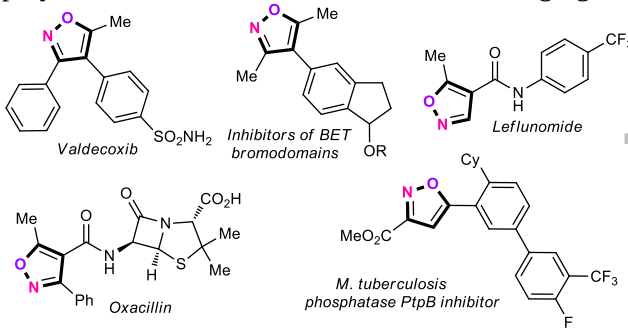
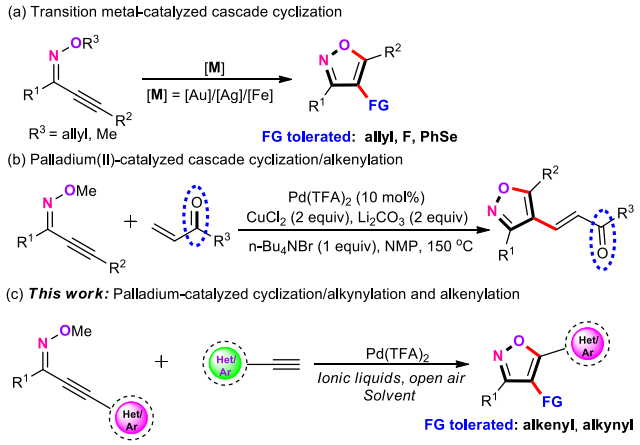


Figure 1. Selected examples of biologically active isoxazoles

In addition, transition-metal-catalyzed cascade approaches has been established as a powerful and efficient synthetic methodologies for the construction of complicated molecules with maximum atom and step economy.[10] In this regard, great achievements have been accomplished for the preparation of diversely isoxazole derivatives *via* metal-catalyzed cascade strategies of alkynyl oxime ethers (Scheme 1a). Using this strategy, Miyata and co-workers discovered an elegant method for the synthesis of trisubstituted isoxazoles through gold-catalyzed cyclization/ Claisen-type rearrangement process.[11] Subsequently, Ryu and co-workers developed an unprecedented gold-catalyzed cascade cyclization/fluorination of 2-alkynone *O*-methyloximes for the synthesis of 4-fluoroisoxazole derivatives in moderate to good yields under mild

reaction conditions.[12] Along these lines, Zeni and co-workers disclosed a iron-promoted intramolecular cyclization of alkynone *O*-methyloximes with diorganyl diselenides for synthesis of 4-organoselenylisoxazoles.[13] Especially, Chen and co-workers demonstrated a nice protocol of palladium-catalyzed cascade cyclization/alkenylation of alkynone *O*-methyloximes with activated alkenes (Scheme 1b).[14] Despite the undisputable significance, the direct and efficient synthetic methodologies to construct 4-alkynylisoxazole derivatives with excellent atom- and step-economy have not yet been reported. Recently, we reported a straightforward NHC-palladium-catalyzed cascade annulation/alkynylation of 2-alkynylanilines with terminal alkynes to afford 3-alkynylindoles in ionic liquids.[15] Very recently, we have also successfully developed a palladium-catalyzed regioselective three-component cascade bisthiolation of terminal alkynes using ionic liquids as the additive.[16] Inspired by the aforementioned background and our long-standing interest in Pd-catalyzed cross-coupling reactions in ionic liquids,[17] herein we describe an efficient and practical Pd-catalyzed cascade cyclization/ alkynylation and alkenylation of 2-alkynone *O*-methyloximes with terminal alkynes (Scheme 1c).

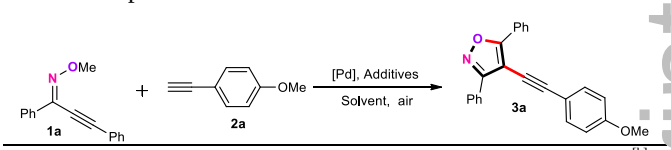


Scheme 1. Transition metal-catalyzed cascade cyclization of alkynyl oxime ethers

Results and Discussion

In our preliminary experiments, *O*-methyl oxime (**1a**) and 1-ethynyl-4-methoxybenzene (**2a**) were selected as the model system to screen the optimal conditions, and the results are summarized in Table 1. Initially, several additives were examined, and we found that *n*Bu$_4$NI was the best additive for this transformation (entries 1-5). Subsequently, different palladium salts were examined (entries 5-11), including Pd(OAc)$_2$, Pd(TFA)$_2$, Pd(PPh$_3$)$_2$Cl$_2$, Pd(MeCN)$_2$Cl$_2$, Pd(PhCN)$_2$Cl$_2$ and PdBr$_2$, and readily available Pd(TFA)$_2$ exhibited efficient catalytic activity (entry 7). Then, different solvents such as DMSO, Toluene, DME, NMP, [Bmim]Cl, [C$_2$OHmim]Cl, [C$_2$O$_2$mim]Cl were also investigated (entries 7, 12-18), and we found that [C$_2$O$_2$mim]Cl was the best solvent for this transformation. Strikingly, when using 2 equiv [C$_2$O$_2$mim]Cl as the additive and DMSO as the solvent, the corresponding product **3a** was detected in 78% GC yield (entry 20). It is noted that, when the reaction was performed at 80 °C, the desired product **3a** was detected in 82% GC yield (entry 21). Furthermore, when activated 4Å molecular sieves (MS) was added to the mixture, the desired product **3a** was detected in 88% yield by GC-MS (entry 23). Finally, the efficiency of this reaction was not changed when dry DMSO was used (entry 24).

Table 1. Optimization of the reaction conditions [a]



Entry	Catalyst	Additive	Solvent	Yield/% [b]
1	PdCl$_2$	-	DMF	N.D.
2	PdCl$_2$	LiCl	DMF	N.D.
3	PdCl$_2$	LiBr	DMF	N.D.
4	PdCl$_2$	*n*Bu$_4$NCl	DMF	N.D.
5	PdCl$_2$	*n*Bu$_4$NI	DMF	6
6	Pd(OAc)$_2$	*n*Bu$_4$NI	DMF	15
7	Pd(TFA)$_2$	*n*Bu$_4$NI	DMF	43
8	Pd(PPh$_3$)$_2$Cl$_2$	*n*Bu$_4$NI	DMF	trace
9	Pd(MeCN)$_2$Cl$_2$	*n*Bu$_4$NI	DMF	9
10	Pd(PhCN)$_2$Cl$_2$	*n*Bu$_4$NI	DMF	12
11	PdBr$_2$	*n*Bu$_4$NI	DMF	18
12	Pd(TFA)$_2$	*n*Bu$_4$NI	DMSO	48
13	Pd(TFA)$_2$	*n*Bu$_4$NI	Toluene	trace
14	Pd(TFA)$_2$	*n*Bu$_4$NI	DME	trace
15	Pd(TFA)$_2$	*n*Bu$_4$NI	NMP	17
16	Pd(TFA)$_2$	*n*Bu$_4$NI	[Bmim]Cl	26
17	Pd(TFA)$_2$	*n*Bu$_4$NI	[C$_2$OHmim]Cl	40
18	Pd(TFA)$_2$	*n*Bu$_4$NI	[C$_2$O$_2$mim]Cl	73
19	Pd(TFA)$_2$	-	[C$_2$O$_2$mim]Cl	73
20	Pd(TFA)$_2$	[C$_2$O$_2$mim]Cl	DMSO	78
21[c]	Pd(TFA)$_2$	[C$_2$O$_2$mim]Cl	DMSO	82
22[d]	Pd(TFA)$_2$	[C$_2$O$_2$mim]Cl	DMSO	79
23[e]	Pd(TFA)$_2$	[C$_2$O$_2$mim]Cl	DMSO	88 (80)
24[e], [f]	Pd(TFA)$_2$	[C$_2$O$_2$mim]Cl	DMSO	88

[a] Reactions were performed with **1a** (0.10 mmol), **2a** (0.12 mmol), catalyst (5 mol %), additive (2 equiv), solvent (1 mL) under air at 60 °C for 8 h. DME: 1,2-dimethoxyethane. NMP: *N*-methyl-2-pyrrolidone. [Bmim]Cl: 1-butyl-3-methylimidazolium chloride. [C$_2$OHmim]Cl: 1-hydroxyethyl-3-methylimidazolium chloride. [C$_2$O$_2$mim]Cl: 1-carboxymethyl-3-methylimidazolium chloride.

[b] Determined by GC using dodecane as the internal standard. N. D. = not detected.

[c] At 80 °C.

[d] At 100 °C.

[e] 25 mg 4Å MS was used

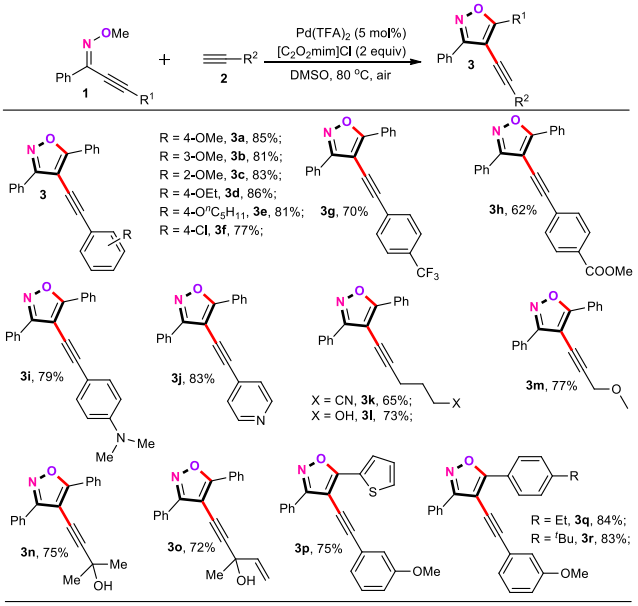
[f] Dry DMSO was added

Having established the optimum reaction conditions, we next investigated the substrate scopes and limitations of the present protocol.

10.1002/adsc.201800444

Representative results are summarized in Table 2. Satisfactorily, both electron-donating and electron-withdrawing substituents on the phenyl ring of alkynes were well accommodated, generating the desired products in moderate to good yields (**3a**-**3i**). Gratifyingly, aryl alkynes with strong electron-withdrawing groups, such as CF_3 and CO_2Me groups, were amenable to this transformation, and furnished the expected products **3g** and **3h** in 70% and 62% yields, respectively. More importantly, *N*, *N*-dimethyl substituted aryl alkyne was well tolerated, and afforded the desired product **3i** in 79% yield. As for the synthetically attractive heteroaromatic alkyne, such as 4-ethynylpyridine, could be successfully converted into **3j** in 83% yield. Prominently, various structurally diverse aliphatic alkynes were compatible with the current reaction conditions, furnishing the corresponding products in satisfied yields (**3k**-**3o**).

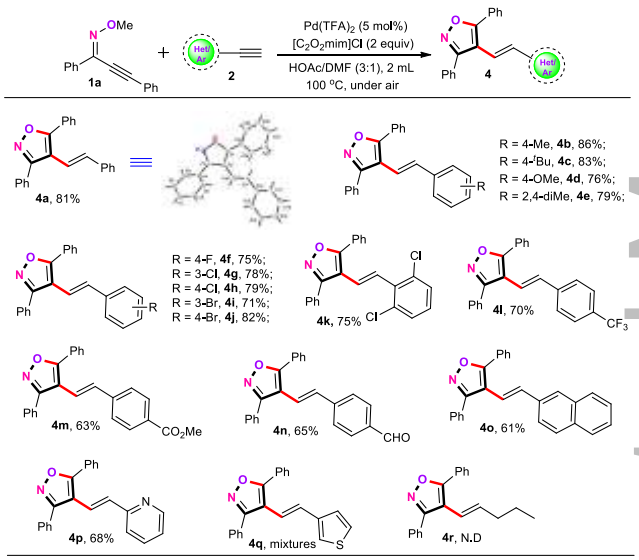
Table 2. Substrate scope of *O*-methyl oxime **1** with alkynes derivatives [a]



[a] Reaction conditions: **1** (0.20 mmol), **2a** (1.2 equiv), $Pd(TFA)_2$ (5 mol %), 50 mg 4Å MS, $[C_2O_2mim]Cl$ (2 equiv) and DMSO (2 mL) at 80 °C for 8 h. Yields referred to isolated yield.

Noteworthy, 4-vinyl substituted isoxazole derivatives could be obtained in a similar reaction conditions. We optimized the alkenylation of alkynone *O*-methyloximes with terminal alkynes reaction as follows: alkynone *O*-methyloximes **1** (0.20 mmol), terminal alkynes **2** (0.24 mmol), $Pd(TFA)_2$ (5 mol %), $[C_2O_2mim]Cl$ (0.4 mmol), HOAc (1.5 mL) and DMF (0.5 mL) at 100 °C for 12 h.[18] As illustrated in Table 3, the position of the substituents on the phenyl ring has a very limited effect on the reaction efficiency (**4a**-**4k**). The *E*-configuration of the product **4a** was confirmed unambiguously by an X-ray crystallographic analysis.[19] Moreover, disubstituted substrates such as 1-ethynyl-2,4-dimethylbenzene (**1e**) and 1,3-dichloro-2-ethynylbenzene (**1k**) were also suitable substrates, and the corresponding products **4e** and **4k** were obtained in 79% and 75% yields, respectively. Particularly, halo substituents, such as F, Cl, and Br, were all nicely tolerated, thus providing the possibility for further manipulation by transition metal-catalyzed coupling reactions (**4f**-**4k**). Furthermore, aryl alkynes bearing strong electron-withdrawing groups, such as trifluoromethyl, ester, and aldehyde groups were also successfully participated in the current cascade reaction, albeit with somewhat reduced yields were observed (**4l**-**4n**). 2-Ethynylnaphthalene proved to be amenable substrate under the reported conditions, and provided the target product **4o** in 61% yield. Particularly noteworthy was the functional group tolerance of this protocol, such as 2-ethynylpyridine was also perfectly accommodated, furnishing the corresponding product **4p** in 68% yield. However, when 3-ethynylthiophene was used as the substrate under the standard conditions, only a complex mixtures was obtained. Unfortunately, aliphatic alkyne was not amenable to this protocol and failed to convert to the desired product **4r**.

Table 3. Substrate scope of **1a** with various aryl alkynes derivatives [a]



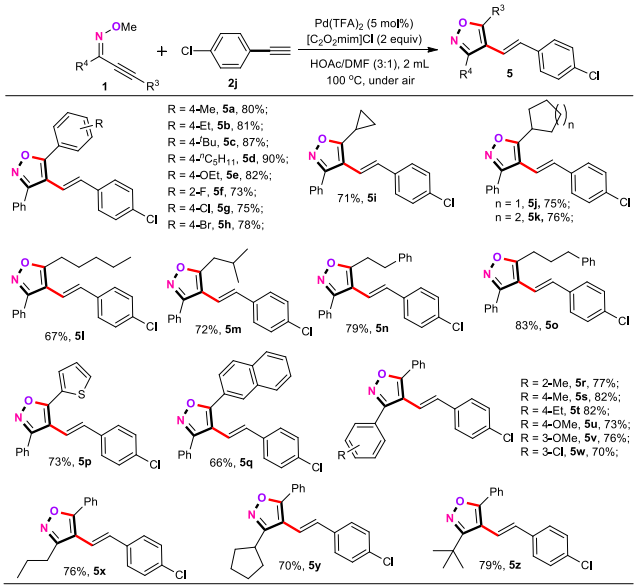
[a] Reaction conditions: **1a** (0.20 mmol), **2** (1.2 equiv), $Pd(TFA)_2$ (5 mol %), $[C_2O_2mim]Cl$ (2 equiv), HOAc (1.5 mL) and DMF (0.5 mL) at 100 °C for 12 h. Yields referred to isolated yield.

With the positive results above, the scopes and limitations of alkynone *O*-methyloxime derivatives were further investigated. The results are summarized in Table 4. Generally, aryl substituted (R^3) alkynone *O*-methyloximes with either an electron-donating or electron-withdrawing group on the benzene ring were well tolerated, delivering the desired products in moderate to excellent yields (**5a**-**5h**). Additionally, substrates containing three-, five- or six-membered-ring-substituted aliphatic alkynes were good candidates to deliver the corresponding products in satisfactory yields (**5i**-**5k**). Similarly, linear chain alkynes such as 1-pentyne, 1-hexyne, 3-methylbut-1-yne, but-3-yn-1-ylbenzene, and pent-4-yn-1-ylbenzene were compatible with the optimized

10.1002/adsc.201800444

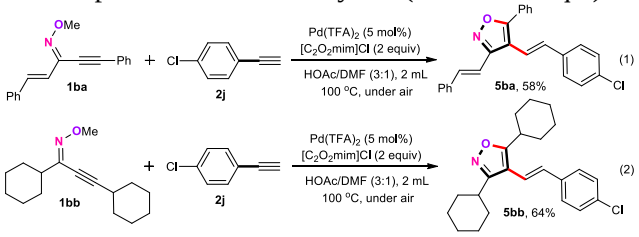
conditions, furnishing the expected products in moderate to good yields (**5l**-**5o**). Notably, the heteroaromatic alkyne 2-ethynylthiophene could be tolerated in this protocol, giving the expected product **5p** in 73% yield. Gratifyingly, 2-ethynylnaphthalene also proceeded smoothly to afford the corresponding product **5q** in satisfied yield. In addition, substituted alkynone *O*-methyloxime derivatives bearing alkyl, methoxyl, and halides groups survived the standard conditions, producing the desired products in synthetically useful yields (**5r**-**5w**). Satisfactorily, several alkyl substituted *O*-methyloxime also proved suitable for this transformation, giving the corresponding products in moderate yields (**5x**-**5z**).

Table 4. Substrate scope of alkynone *O*-methyloximes **1** with **2j** [a]



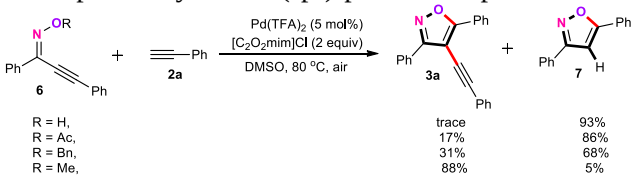
[a] Reaction conditions: **1** (0.20 mmol), **2j** (1.2 equiv), $Pd(TFA)_2$ (5 mol %), $[C_2O_2mim]Cl$ (2 equiv), HOAc (1.5 mL) and DMF (0.5 mL) at 100 °C for 12 h. Yields referred to isolated yield.

Satisfactorily, styryl substituted *O*-methyloxime framework (**1ba**) was well tolerable under the optimized conditions, furnishing functionalized isoxazole **5ba** in 58% yield (Scheme 2, eq 1). Double alkyl substituted *O*-methyloxime, such as 1,3-dicyclohexylprop-2-yn-1-one *O*-methyl oxime (**1bb**), could also be applied for this reaction to give the desired product **5bb** in 64% yield (Scheme 2, eq 2).



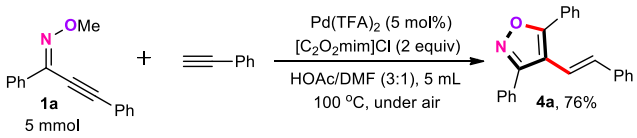
Scheme 2. Palladium-catalyzed cascade cyclization/ alkenylation for the synthesis of **5ba** and **5bb**

Additionally, we turned our attention to the influence of OR of alkynone oxime ethers for the cascade cyclization/alkynylation (Scheme 3). Examination of various R revealed that methyl is well tolerated to afford the corresponding **3a** in 88% yield. For other substituents of alkynone oxime ethers with low yields, the major byproduct was 3,5-diphenylisoxazole (**7**), which was generated *via* the direct protonolysis of $C(sp^2)$-palladium species.



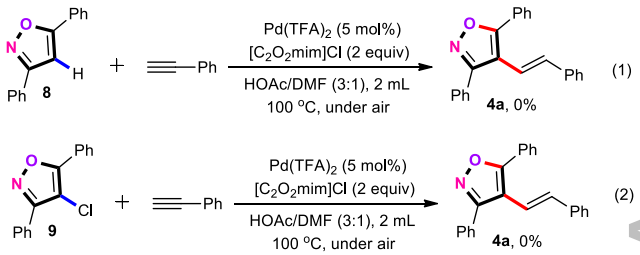
Scheme 3. Evaluating different substituents of alkynone oximes

To demonstrate the efficiency and practicability of this methodology, a gram-scale synthesis of **4a** was performed, as shown in Scheme 4. The reaction of 1.17 g of alkynone *O*-methyloxime **1a** with ethynylbenzene in the presence of 5 mol % $Pd(TFA)_2$ catalyst provided 1.23g of the corresponding 4-vinyl substituted isoxazole **4a** in 76% yield.



Scheme 4. Scale-up synthesis of **4a**

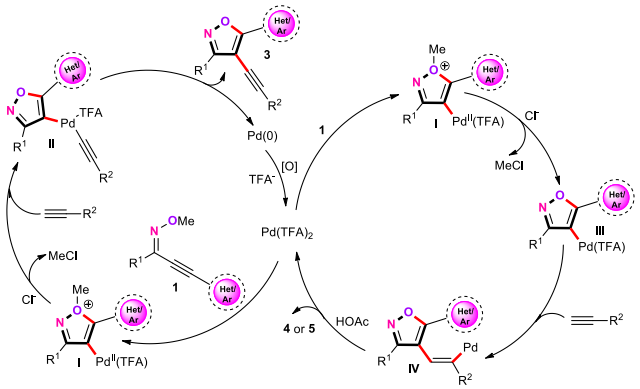
In addition, to gain some insight into the mechanism of this cascade protocol, two control experiments have been also conducted (Scheme 5). When 3,5-diphenylisoxazole (**8**) was employed to react with ethynylbenzene under the standard conditions, unfortunately, no desired product **4a** was detected by GC-MS (eq 1). Similarly, when 4-chloro-3,5-diphenylisoxazole (**9**) was subjected to the same reaction conditions, no desired product was observed as well (eq 2). All of these results described above indicated that neither **8** nor **9** was a possible intermediate in this current chemical transformation.



Scheme 5. Control Experiments

Based on the above experiments, a plausible reaction mechanism is proposed in Scheme 6. The left pathway is initiated by *trans*-oxypalladation of alkynone *O*-methyloximes (**1**), generating an oxonium intermediate **I**.[12, 14] Subsequently, **I** could undergo the elimination of methyl chloride.[13, 14] Simultaneously, in a weak acidity reaction medium, the terminal alkynes coordinate with $C(sp^2)$-

palladium species affords intermediate **II**.[20] Finally, a reductive elimination gives the target products **3** and Pd(0). The oxidation of Pd(0) to Pd(II) by air completes the catalytic cycle.[21] For the right pathway, intermediate **III** may undergo alkynes insertion to generate vinylpalladium intermediate **IV**.[22] Then, protonolysis of vinylpalladium species **IV** gives the desired products **4** and **5** in the presence of an acid (HOAc) with regeneration of the palladium(II) species to complete the catalytic cycle.[23] Thus, all these observations indicated that the acidity of the reaction medium plays an important role for the reaction selectivity control for this type of cascade cyclization.



Scheme 6. Proposed mechanism

Conclusion

In conclusion, we have successfully accomplished an alternative and efficient approach for the synthesis of 4-alkynylation and 4-alkenylation isoxazole derivatives *via* palladium-catalyzed cascade cyclization of alkynone *O*-methyloximes with terminal alkynes. The acidic ionic liquid $[C_2O_2mim]Cl$ as additive makes this transformation green and high efficiency. Moreover, the present methodology demonstrates excellent functional group compatibility, excellent atom- and step-economy, and mild reaction conditions. Notably, this synthetic protocol provides a new tool for the construction of diversely isoxazole derivatives, becoming a promising application in synthetic and pharmaceutical chemistry.

Experimental Section

All reagents and catalysts were purchased as analytical reagent grade and used without further purification. ^1H and ^{13}C NMR spectra were recorded using a Bruker DRX-400 spectrometer using $CDCl_3$ or Acetone-d_6 as solvent and TMS as an internal standard. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm, respectively. GC analyses were performed on a GC-7900 chromatograph with an FID and equipped with an AT.SE-30 capillary column (internal diameter: 0.32 mm, length: 30 m). Mass spectra were recorded on a Thermo Scientific ISQ gas chromatograph-mass spectrometer at an ionization voltage of 70 eV and equipped with a DB-WAX capillary column (internal diameter: 0.25 mm, length: 30 m). The data of HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). IR spectra were recorded in KBr disks with a Bruker TENSOR 27 spectrometer. Melting points were determined with a Büchi Melting Point B-545 instrument.

Typical procedure for the preparation of 4-alkynylisoxazoles: A mixture of *O*-methyl oxime **1** (0.20 mmol), $Pd(TFA)_2$ (5 mol %), $[C_2O_2mim]Cl$ (2.0 equiv), and DMSO (2 mL) was added to an Schlenk tube equipped with a stir-bar. Then, terminal alkynes (0.24 mmol) were quickly added to the tube under air atmosphere and stirred at 80 °C for 8 h. After the reaction was finished, the mixture was quenched by water and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to afford the desired products **3**.

4-((4-Methoxyphenyl)ethynyl)-3,5-diphenylisoxazole (3a): Yield: 85% (59.7 mg) as a yellow solid; mp = 115.2 - 116.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.6 Hz, 2H), 8.14 (dd, J = 6.8, 2.8 Hz, 2H), 7.59 - 7.42 (m, 8H), 6.90 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 162.5, 160.1, 132.9, 130.7, 130.2, 128.9, 128.7, 127.9, 127.5, 126.4, 114.9, 114.3, 97.7, 96.6, 78.4, 55.4 ppm; ν_{max}(KBr)/cm^{-1} 3058, 2927, 2217, 1605, 1505, 1247, 691; MS (EI) m/z 77, 105, 176, 220, 246, 309, 337, 351; HRMS-ESI (m/z): calcd for $C_{24}H_{17}NNaO_2$, $[M+Na]^+$: 374.1151, found 374.1155.

4-((3-Methoxyphenyl)ethynyl)-3,5-diphenylisoxazole (3b): Yield: 81% (56.9 mg) as a yellow solid; mp = 77.5 - 78.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 8.0, 1.6 Hz, 2H), 8.14 (dd, J = 6.8, 3.2 Hz, 2H), 7.58 - 7.47 (m, 6H), 7.30 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 6.94 (dd, J = 8.4, 2.4 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 162.6, 159.5 130.8, 130.2, 129.7, 128.9, 128.7, 128.5, 127.9, 127.3, 126.5, 123.9, 123.7, 116.6, 115.1, 97.3, 96.4, 79.6, 55.4 ppm; ν_{max}(KBr)/cm^{-1} 3060, 2924, 2214, 1646, 1579, 1451, 686; MS (EI) m/z 77, 105, 176, 220, 246, 283, 351; HRMS-ESI (m/z): calcd for $C_{24}H_{17}NNaO_2$, $[M+Na]^+$: 374.1151, found 374.1155.

4-((2-Methoxyphenyl)ethynyl)-3,5-diphenylisoxazole (3c): Yield: 83% (58.3 mg) as a yellow solid; mp = 85.3 - 86.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 7.2 Hz, 2H), 8.25 (dd, J = 6.8, 2.8 Hz, 2H), 7.58 - 7.48 (m, 6H), 7.45 (dd, J = 7.6, 1.2 Hz, 1H), 7.35 (dd, J = 11.6, 4.4 Hz, 1H), 6.95 (dd, J = 14.2, 7.6 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 162.3, 160.4, 132.8, 130.6, 130.2, 130.1, 128.8, 128.6, 128.6, 128.0, 127.4, 126.5, 120.6, 112.2, 110.7, 97.7, 93.6, 83.7, 55.8 ppm; ν_{max}(KBr)/cm^{-1} 3059, 2923, 2210, 1646, 1584, 1452, 1249, 697; MS (EI) m/z 77. 105, 191, 219, 246, 322, 351; HRMS-ESI (m/z): calcd for $C_{24}H_{17}NNaO_2$, $[M+Na]^+$: 374.1151, found 374.1148.

4-((4-Ethoxyphenyl)ethynyl)-3,5-diphenylisoxazole (3d): Yield: 86% (62.8 mg) as a yellow solid; mp = 107.4 - 108.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 6.8 Hz, 2H), 8.14 (dd, J = 6.8, 3.0 Hz, 2H), 7.60 - 7.48 (m, 6H), 7.45 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.05 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 162.5, 159.5, 132.9, 130.6, 130.2, 128.9, 128.7, 127.9, 127.5, 126.4, 114.8, 114.7, 97.7, 96.7, 78.3, 63.7, 14.7 ppm; ν_{max}(KBr)/cm^{-1} 3053, 2921, 2216, 1606, 1503, 1450, 1250, 689; MS (EI) m/z 77, 105, 206, 234, 281, 336, 368; HRMS-ESI (m/z): calcd for $C_{25}H_{19}NNaO_2$, $[M+Na]^+$: 388.1308, found 388.1310.

4-((4-(Pentyloxy)phenyl)ethynyl)-3,5-diphenylisoxazole (3e): Yield: 81% (65.9 mg) as a yellow solid; mp = 94.1 -

95.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 6.8 Hz, 2H), 8.15 (dd, J = 6.4, 2.8 Hz, 2H), 7.51 (tt, J = 8.0, 4.2 Hz, 6H), 7.45 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.97 (t, J = 6.8 Hz, 2H), 1.90 - 1.72 (m, 2H), 1.51 - 1.34 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 162.5, 159.7, 132.9, 130.6, 130.2, 128.9, 128.7, 127.9, 127.5, 126.4, 114.8, 114.6, 97.7, 96.7, 78.3, 68.2, 28.9, 28.2, 22.5, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 3061, 2930, 2218, 1604, 1510, 1467, 1250, 690; MS (EI) m/z 115, 167, 210, 228, 300, 334, 407; HRMS-ESI (m/z): calcd for $C_{28}H_{26}NO_2$, $[M+H]^+$: 408.1958, found 408.1957.

4-((4-Chlorophenyl)ethynyl)-3,5-diphenylisoxazole (3f): Yield: 77% (54.7 mg) as a yellow solid; mp = 109.3 - 110.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 8.0, 1.6 Hz, 2H), 8.11 (dd, J = 6.8, 3.0 Hz, 2H), 7.58 - 7.49 (m, 6H), 7.44 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 162.6, 1345.0, 132.6, 130.9, 130.3, 129.0, 128.9, 128.7, 128.6, 127.9, 127.3, 126.5, 121.2, 97.1, 95.2, 80.8 ppm; ν_{max}(KBr)/cm^{-1} 3061, 2919, 2210, 1645, 1486, 1408, 687; MS (EI) m/z 77, 105, 189, 207, 281, 355; HRMS-ESI (m/z): calcd for $C_{23}H_{14}ClNNaO$, $[M+Na]^+$: 378.0656, found 378.0660.

3,5-Diphenyl-4-((4-(trifluoromethyl)phenyl)ethynyl)-isoxazole (3g): Yield: 70% (54.5 mg) as a yellow solid; mp = 105.1 - 106.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 7.8, 2.0 Hz, 2H), 8.10 (dd, J = 6.8, 3.0 Hz, 2H), 7.63 (q, J = 8.8 Hz, 4H), 7.57 - 7.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 162.7, 131.6, 131.1, 130.4, 129.0, 128.9, 128.8, 128.4 (q, J = 32.8 Hz), 128.3, 127.9, 127.1, 126.5, 125.5 (q, J = 3.8 Hz), 125.1 (q, J = 253.9 Hz), 96.8, 94.8, 82.3 ppm; ν_{max}(KBr)/cm^{-1} 3056, 2922, 2216, 1604, 1495, 1446, 1406, 691; MS (EI) m/z 77, 105, 189, 258, 284, 370, 389; HRMS-ESI (m/z): calcd for $C_{24}H_{15}F_3NO$, $[M+H]^+$: 390.1100, found 390.1104.

Methyl 4-((3,5-diphenylisoxazol-4-yl)ethynyl)benzoate (3h): Yield: 62% (47.0 mg) as a yellow solid; mp = 148.5 - 149.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, J = 8.0, 1.6 Hz, 2H), 8.11 (dd, J = 6.8, 3.0 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 7.64 - 7.49 (m, 8H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 166.4, 162.6, 131.2, 131.0, 130.4, 130.1, 129.7, 129.0, 128.7, 128.4, 127.9, 127.3, 127.2, 126.6, 96.9, 95.5, 82.8, 52.3 ppm; ν_{max}(KBr)/cm^{-1} 3052, 2922, 2217, 1640, 1407, 1275, 691; MS (EI) m/z 65, 91, 129, 188, 281, 341, 379; HRMS-ESI (m/z): calcd for $C_{25}H_{17}NNaO_3$, $[M+Na]^+$: 402.1101, found 402.1109.

4-((3,5-Diphenylisoxazol-4-yl)ethynyl)-*N*, *N*-dimethyl-aniline (3i): Yield: 79% (57.5 mg) as a yellow solid; mp = 142.7 - 144.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 7.2 Hz, 2H), 8.18 (d, J = 7.6 Hz, 2H), 7.60 - 7.44 (m, 6H), 7.40 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 8.8 Hz, 21H), 2.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.4, 150.5, 133.7, 132.6, 130.4, 130.1, 128.8, 128.6, 127.9, 127.6, 126.3, 111.9, 109.4, 98.2, 98.0, 77.6, 40.2 ppm; ν_{max}(KBr)/cm^{-1} 3062, 2921, 2209, 1607, 1521, 1446, 1235, 694; MS (EI) m/z 77, 105, 231, 280, 364; HRMS-ESI (m/z): calcd for $C_{25}H_{21}N_2O$, $[M+H]^+$: 365.1648, Found 365.1651.

3,5-Diphenyl-4-(pyridin-4-ylethynyl)isoxazole (3j): Yield: 83% (53.5 mg) as a yellow solid; mp = 146.5 - 147.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 4.0 Hz, 2H), 8.23 (dd, J = 7.6, 2.4 Hz, 2H), 8.13 - 7.92 (m, 2H), 7.56 (ddd, J = 9.2, 6.4, 4.0 Hz, 6H), 7.38 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 162.7, 149.8, 131.3, 131.0, 130.5, 129.0, 128.8, 128.2, 127.9, 126.9, 126.6, 125.2, 96.4, 93.4, 84.8 ppm; ν_{max}(KBr)/cm^{-1} 3057, 2922, 2217, 1654, 1575, 1408, 696; MS (EI) m/z 77, 105, 135, 207, 281, 322; HRMS-ESI (m/z): calcd for $C_{22}H_{15}N_2O$, $[M+H]^+$: 323.1179, found 323.1180.

6-(3,5-Diphenylisoxazol-4-yl)hex-5-ynenitrile (3k): Yield: 65% (40.6 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.6 Hz, 2H), 8.01 (dd, J = 6.8, 2.4 Hz, 2H), 7.62 - 7.41 (m, 6H), 2.72 (t, J = 6.8 Hz, 2H), 2.48 (t, J = 7.2 Hz, 2H), 1.97 (p, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 162.9, 130.8, 130.3, 128.9, 128.7, 128.5, 127.8, 127.3, 126.3, 118.8, 97.2, 94.5, 72.8, 24.3, 18.9, 16.2 ppm; ν_{max}(KBr)/cm^{-1} 3054, 2923, 2215, 1639, 1540, 1404, 1267, 686; MS (EI) m/z 77, 105, 152, 207, 258, 284, 312; HRMS-ESI (m/z): calcd for $C_{21}H_{16}N_2NaO$, $[M+Na]^+$: 335.1155, found 335.1159.

5-(3,5-Diphenylisoxazol-4-yl)pent-4-yn-1-ol (3l): Yield: 73% (44.2 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 7.2 Hz, 2H), 8.05 (dd, J = 6.4, 2.8 Hz, 2H), 7.55 - 7.43 (m, 6H), 3.79 (t, J = 6.4 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 1.90 (p, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 162.8, 130.6, 130.1, 128.8, 128.6, 128.6, 127.8, 127.4, 126.2, 97.7, 97.1, 71.2, 61.5, 31.2, 16.4 ppm; ν_{max}(KBr)/cm^{-1} 3064, 2930, 2214, 1639, 1444, 1407, 1260, 688; MS (EI) m/z 77, 105, 219, 246, 274, 303; HRMS-ESI (m/z): calcd for $C_{20}H_{17}NNaO_2$, $[M+Na]^+$: 326.1151, found 326.1155.

4-(3-Methoxyprop-1-yn-1-yl)-3,5-diphenylisoxazole (3m): Yield: 77% (44.5 mg) as a yellow solid; mp = 68.0 - 69.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 - 8.15 (m, 2H), 8.05 (dd, J = 6.4, 2.8 Hz, 2H), 7.63 - 7.44 (m, 6H), 4.40 (s, 2H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 162.8, 130.9, 130.2, 128.9, 128.7, 128.4, 127.8, 127.2, 126.4, 96.7, 92.7, 76.8, 60.6, 57.9 ppm; ν_{max}(KBr)/cm^{-1} 3066, 2923, 2214, 1562, 1445, 1090, 690; MS (EI) m/z 77, 105, 153, 184, 230, 258, 289; HRMS-ESI (m/z): calcd for $C_{19}H_{15}NNaO_2$, $[M+Na]^+$: 312.0995, found 312.0996.

4-(3,5-Diphenylisoxazol-4-yl)-2-methylbut-3-yn-2-ol (3n): Yield: 75% (45.4 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 7.6, 2.0 Hz, 2H), 8.12 - 7.93 (m, 2H), 7.56 - 7.43 (m, 6H), 2.02 (s, 1H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 162.6, 130.8, 130.2, 128.8, 128.6, 128.4, 127.8, 127.2, 126.3, 101.1, 96.7, 72.9, 65.9, 31.1 ppm; ν_{max}(KBr)/cm^{-1} 3062, 2923, 2226, 1560, 1445, 1414, 1096, 696; MS (EI) m/z 77, 105, 166, 246, 288, 303; HRMS-ESI (m/z): calcd for $C_{20}H_{18}NO_2$, $[M+H]^+$: 304.1332, found 304.1335.

5-(3,5-Diphenylisoxazol-4-yl)-3-methylpent-1-en-4-yn-3-ol (3o): Yield: 72% (45.3 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 6.4, 3.0 Hz, 2H), 8.05 (dd, J = 6.8, 3.0 Hz, 2H), 7.60 - 7.36 (m, 6H), 6.07 (dd, J = 17.2, 10.4 Hz, 1H), 5.55 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 10.4 Hz, 1H), 2.29 (s, 1H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 162.6, 141.5, 130.9, 130.3, 128.9, 128.6, 128.3, 127.8, 127.1, 126.4, 114.2, 98.4, 96.6, 75.3, 69.0, 29.8 ppm; ν_{max}(KBr)/cm^{-1} 3064, 2926, 2220, 1562, 1446, 1406, 1098, 699; MS (EI) m/z 77, 105, 141, 165, 210, 272, 300, 315; HRMS-ESI (m/z): calcd for $C_{21}H_{18}NO_2$, $[M+H]^+$: 316.1332, found 316.1337.

4-((3-Methoxyphenyl)ethynyl)-3-phenyl-5-(thiophen-2-yl)isoxazole (3p): Yield: 75% (53.6 mg) as a yellow solid; mp = 79.7 - 80.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 2.8 Hz, 1H), 8.14 (dd, J = 6.4, 3.0 Hz, 2H), 7.87 (d, J = 5.2 Hz, 1H), 7.56 - 7.49 (m, 3H), 7.47 (dd, J = 5.2, 3.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.06 (s, 1H), 6.95 (dd, J = 8.4, 2.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 162.1, 159.5, 130.3, 129.7, 128.7, 128.5, 128.5, 127.8, 126.7, 126.1, 125.4, 124.0, 123.7, 116.6, 115.1, 96.5, 96.4, 79.4, 55.4 ppm; ν_{max}(KBr)/cm^{-1} 3062, 2924, 2222, 1581, 1449, 1413, 1092, 687; MS (EI) m/z 73, 111, 186, 207, 281, 328, 357; HRMS-ESI (m/z): calcd for $C_{22}H_{16}NO_2S$, $[M+H]^+$: 358.0896, found 358.0899.

5-(4-Ethylphenyl)-4-((3-methoxyphenyl)ethynyl)-3-phenylisoxazole (3q): Yield: 84% (63.7 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 2H), 8.14 (dd, J = 6.8, 3.0 Hz, 2H), 7.60 - 7.46 (m, 3H), 7.36 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.04 (s, 1H), 6.93 (dd, J = 8.4, 2.4 Hz, 1H), 3.82 (s, 3H), 2.72 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 162.5, 159.5, 147.5, 130.2, 129.7, 128.7, 128.6, 128.4, 127.9, 126.5, 124.9, 123.9, 123.8, 116.6, 115.0, 96.7, 96.2, 79.8, 55.4, 29.0, 15.3 ppm; ν_{max}(KBr)/cm^{-1} 3062, 2927, 2217, 1674, 1584, 1450, 1413, 1042, 690; MS (EI) m/z 77, 105, 133, 189, 207, 248, 307, 379; HRMS-ESI (m/z): calcd for $C_{26}H_{22}NO_2$, $[M+H]^+$: 380.1645, found 380.1647.

5-(4-(*tert*-Butyl)phenyl)-4-((3-methoxyphenyl)ethynyl)-3-phenylisoxazole (3r): Yield: 83% (67.6 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 2H), 8.14 (dd, J = 6.4, 3.0 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.51 (dd, J = 5.2, 1.8 Hz, 3H), 7.30 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.06 (s, 1H), 6.94 (dd, J = 8.4, 2.4 Hz, 1H), 3.83 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 162.5, 159.5, 154.4, 130.2, 129.7, 128.7, 128.6, 127.9, 126.3, 125.9, 124.6, 124.0, 123.9, 116.6, 115.0, 96.7, 96.2, 79.8, 55.4, 35.1, 31.2 ppm; ν_{max}(KBr)/cm^{-1} 3063, 2928, 2211, 1583, 1461, 1411, 1040, 691; MS (EI) m/z 73, 135, 207, 282, 343, 372, 407; HRMS-ESI (m/z): calcd for $C_{28}H_{25}NNaO_2$, $[M+Na]^+$: 430.1778, found 430.1773.

Typical procedure for the preparation of 4-alkenylisoxazoles: A mixture of *O*-methyl oxime **1** (0.20 mmol), $Pd(TFA)_2$ (5 mol %), $[C_2O_2mim]Cl$ (2.0 equiv), HOAc (1.5 mL), and DMSO (0.5 mL) was added to an Schlenk tube equipped with a stir-bar. Then, terminal alkynes (0.24 mmol) were quickly added to the tube under air atmosphere and stirred at 100 ºC for 12 h. After the reaction was finished, the mixture was quenched by water and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to afford the desired products **4** and **5**.

(*E*)-3,5-Diphenyl-4-styrylisoxazole (4a): Yield: 81% (52.3 mg) as a yellow solid; mp = 162.3 - 163.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.6, 1.6 Hz, 2H), 7.70 (dd, J = 6.4, 2.4 Hz, 2H), 7.57 - 7.45 (m, 6H), 7.35 - 7.28 (m, 4H), 7.25 (dd, J = 10.8, 6.4 Hz, 1H), 6.97 (d, J = 16.8 Hz, 1H), 6.65 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 162.3, 136.9, 134.4, 130.1, 129.6, 129.5, 129.0, 128.9, 128.8, 128.7, 128.3, 128.1, 127.7, 126.3, 115.9, 112.4 ppm; ν_{max}(KBr)/cm^{-1} 3058, 2923, 1579, 1450, 1408, 694; MS (EI) m/z 77, 105, 207, 246, 294, 306, 323; HRMS-ESI (m/z): calcd for $C_{23}H_{17}NNaO$, $[M+Na]^+$: 346.1202, found 346.1197.

(*E*)-4-(4-Methylstyryl)-3,5-diphenylisoxazole (4b): Yield: 86% (57.9 mg) as a yellow solid; mp = 121.6 - 123.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 8.0, 1.6 Hz, 2H), 7.72 - 7.66 (m, 2H), 7.55 - 7.41 (m, 6H), 7.21 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 16.8 Hz, 1H), 6.62 (d, J = 16.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 162.3, 138.1, 134.3, 134.1, 130.0, 129.6, 129.4, 129.2, 128.9, 128.9, 128.7, 128.4, 127.6, 126.3, 114.9, 112.5, 21.2 ppm; ν_{max}(KBr)/cm^{-1} 3052, 2922, 1577, 1493, 1448, 1268, 696; MS (EI) m/z 77, 105, 128, 217, 260, 308, 337; HRMS-ESI (m/z): calcd for $C_{24}H_{19}NNaO$, $[M+Na]^+$: 360.1359, found 360.1352.

(*E*)-4-(4-(*tert*-Butyl)styryl)-3,5-diphenylisoxazole (4c): Yield: 83% (62.9 mg) as a yellow solid; mp = 119.3 - 120.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.0, 1.6 Hz, 2H), 7.71 (dd, J = 6.4, 3.0 Hz, 2H), 7.54 - 7.45 (m, 6H), 7.35 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 16.8 Hz, 1H), 6.64 (d, J = 16.8 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 162.3, 151.4, 134.2, 134.1, 129.9, 129.6, 129.5, 128.9, 128.8, 128.7, 128.3, 127.6, 126.1, 125.7, 115.1, 112.5, 34.7, 31.3 ppm; ν_{max}(KBr)/cm^{-1} 3054, 2927, 1578, 1495, 1450, 1027, 696; MS (EI) m/z 77, 105, 210, 271, 322, 379; HRMS-ESI (m/z): calcd for $C_{27}H_{25}NNaO$, $[M+Na]^+$: 402.1828, found 402.1822.

(*E*)-4-(4-Methoxystyryl)-3,5-diphenylisoxazole (4d): Yield: 76% (53.6 mg) as a yellow solid; mp = 80.2 - 81.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.0, 1.6 Hz, 2H), 7.77 - 7.66 (m, 2H), 7.52 - 7.43 (m, 6H), 7.25 (d, J = 4.8 Hz, 2H), 6.84 (dd, J = 12.6, 10.2 Hz, 3H), 6.59 (d, J = 16.8 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 162.3, 159.7, 133.9, 129.9, 129.7, 129.6, 129.5, 128.9, 128.9, 128.7, 128.4, 127.6, 114.2, 113.6, 112.6, 55.4 ppm; ν_{max}(KBr)/cm^{-1} 3050, 2922, 1603, 1508, 1448, 1249, 696; MS (EI) m/z 77, 105, 145, 207, 276, 353; HRMS-ESI (m/z): calcd for $C_{24}H_{19}NNaO_2$, $[M+Na]^+$: 376.1308, found 376.1300.

(*E*)-4-(2,4-Dimethylstyryl)-3,5-diphenylisoxazole (4e): Yield: 79% (55.5 mg) as a yellow solid; mp = 134.2 - 135.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.0, 1.6 Hz, 2H), 7.69 (dd, J = 6.4, 3.0 Hz, 2H), 7.55 - 7.44 (m, 6H), 7.41 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 6.84 (s, 2H), 2.29 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 162.4, 137.9, 135.8, 133.0, 131.9, 131.3, 130.0, 129.7, 129.5, 129.0, 128.9, 128.8, 128.4, 127.6, 127.0, 124.8, 115.7, 113.0, 21.1, 19.4 ppm; ν_{max}(KBr)/cm^{-1} 3053, 2922, 1605, 1499, 1448, 1252, 1029, 696; MS (EI) m/z 77, 105, 143, 231, 274, 322, 351; HRMS-ESI (m/z): calcd for $C_{25}H_{21}NNaO$, $[M+Na]^+$: 374.1515, found 374.1517.

(*E*)-4-(4-Fluorostyryl)-3,5-diphenylisoxazole (4f): Yield: 75% (51.2 mg) as a yellow solid; mp = 133.0 - 134.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 8.0, 1.6 Hz, 2H), 7.76 - 7.62 (m, 2H), 7.50 (ddd, J = 10.2, 5.2, 3.2 Hz, 6H), 7.28 (d, J = 2.8 Hz, 1H), 7.25 (d, J = 5.2 Hz, 1H), 7.06 - 6.96 (m, 2H), 6.88 (d, J = 16.8 Hz, 1H), 6.60 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9 (d, J = 226.9 Hz), 162.3, 161.4, 133.1 (d, J = 3.3 Hz), 133.0, 130.1, 129.7, 129.5, 128.9, 128.9 (d, J = 23.0 Hz), 128.2, 127.9 (d, J = 8.0 Hz), 127.6, 115.8, 115.6 (d, J = 2.4 Hz), 115.6, 112.3 ppm; ν_{max}(KBr)/cm^{-1} 3055, 2923, 1600, 1504, 1448, 1228, 697; MS (EI) m/z 77, 105, 133, 207, 264, 312, 341; HRMS-ESI (m/z): calcd for $C_{23}H_{16}FNNaO$, $[M+Na]^+$: 364.1108, found 364.1109.

(*E*)-4-(3-Chlorostyryl)-3,5-diphenylisoxazole (4g): Yield: 78% (55.7 mg) as a yellow solid; mp = 118.6 - 119.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.77 (m, 2H), 7.68 (dd, J = 6.4, 2.8 Hz, 2H), 7.56 - 7.45 (m, 6H), 7.27 (s, 1H), 7.24 - 7.19 (m, 2H), 7.16 - 7.11 (m, 1H), 6.97 (d, J = 16.8 Hz, 1H), 6.57 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 162.3, 138.7, 134.7, 132.6, 130.2, 129.9, 129.7, 129.4, 129.1, 128.9, 128.8, 128.1, 127.9, 127.7, 126.2, 124.5, 117.4, 112.0 ppm; ν_{max}(KBr)/cm^{-1} 3054, 2924, 1600, 1503, 1447, 1406, 695; MS (EI) m/z 77, 105, 149, 217, 280, 328, 357; HRMS-ESI (m/z): calcd for $C_{23}H_{16}ClNNaO$, $[M+Na]^+$: 380.0813, found 380.0820.

(*E*)-4-(4-Chlorostyryl)-3,5-diphenylisoxazole (4h): Yield: 79% (56.4 mg) as a yellow solid; mp = 124.2 - 125.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.6, 1.8 Hz, 2H), 7.68 (dd, J = 6.4, 3.0 Hz, 2H), 7.57 - 7.42 (m, 6H), 7.27 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 16.8 Hz, 1H), 6.58 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 162.2, 135.3, 133.7 132.8, 130.2, 129.7, 129.4, 129.0, 128.9, 128.8, 128.2, 127.7, 127.5, 116.5, 112.2 ppm; ν_{max}(KBr)/cm^{-1} 3055, 2923, 1597, 1492, 1448, 1402, 696; MS (EI) m/z 77, 105, 165, 217, 280, 328, 357; HRMS-ESI (m/z): calcd for $C_{23}H_{17}ClNO$, $[M+H]^+$: 358.0993, found 358.0995.

(*E*)-4-(3-Bromostyryl)-3,5-diphenylisoxazole (4i): Yield: 71% (56.9 mg) as a yellow solid; mp = 123.8 - 125.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.6, 1.8 Hz, 2H), 7.67 (dd, J = 6.8, 3.0 Hz, 2H), 7.50 (ddd, J = 10.2, 5.6, 3.2 Hz, 6H), 7.42 (s, 1H), 7.35 (dt, J = 7.2, 1.6 Hz, 1H), 7.22 - 7.11 (m, 2H), 6.95 (d, J = 16.8 Hz, 1H), 6.55 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 162.3, 139.0, 132.5, 130.9, 130.3, 130.2, 129.8, 129.4, 129.1, 129.0, 128.9, 128.8, 128.1, 127.7, 124.9, 123.0, 117.4,

112.0 ppm; ν_{max}(KBr)/cm^{-1} 3056, 2922, 1597, 1496, 1408, 695; MS (EI) m/z 77, 105, 189, 217, 293, 372, 401; HRMS-ESI (m/z): calcd for $C_{23}H_{17}BrNO$, $[M+H]^+$: 402.0488, found 402.0484.

(*E*)-4-(4-Bromostyryl)-3,5-diphenylisoxazole (4j): Yield: 82% (65.7 mg) as a yellow solid; mp = 123.0 - 124.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.6, 1.6 Hz, 2H), 7.68 (dd, J = 6.8, 2.8 Hz, 2H), 7.58 - 7.46 (m, 6H), 7.42 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 16.8 Hz, 1H), 6.56 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 162.2, 135.8, 132.8, 131.8, 130.2, 129.7, 129.4, 129.0, 128.9, 128.8, 128.1, 127.8, 127.7, 121.9, 116.6, 112.1 ppm; ν_{max}(KBr)/cm^{-1} 3054, 2922, 1593, 1488, 1407, 696; MS (EI) m/z 77, 105, 193, 271, 321, 345, 401; HRMS-ESI (m/z): calcd for $C_{23}H_{17}BrNO$, $[M+H]^+$: 402.0488, found 402.0485.

(*E*)-4-(2,6-Dichlorostyryl)-3,5-diphenylisoxazole (4k): Yield: 75% (58.7 mg) as a yellow solid; mp = 115.3 - 116.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.0, 1.6 Hz, 2H), 7.80 - 7.71 (m, 2H), 7.50 (ddd, J = 11.6, 7.2, 2.4 Hz, 6H), 7.28 (d, J = 8.0 Hz, 2H), 7.11 - 7.00 (m, 2H), 6.67 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 162.4, 134.4, 134.4, 130.2, 129.6, 129.3, 129.2, 128.9, 128.8, 128.6, 128.5, 128.0, 127.9, 127.9, 124.7, 112.0 ppm; ν_{max}(KBr)/cm^{-1} 3057, 2923, 1645, 1569, 1492, 1411, 698; MS (EI) m/z 77, 105, 148, 246, 293, 356, 391; HRMS-ESI (m/z): calcd for $C_{23}H_{16}Cl_2NO$, $[M+H]^+$: 392.0603, found 392.0605.

(*E*)-3,5-Diphenyl-4-(4-(trifluoromethyl)styryl)isoxazole (4l): Yield: 70% (54.7 mg) as a yellow solid; mp = 132.8 - 134.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.6, 2.0 Hz, 2H), 7.68 (dd, J = 6.8, 3.0 Hz, 2H), 7.57 - 7.45 (m, 8H), 7.38 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 16.8 Hz, 1H), 6.65 (d, J = 16.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 162.3, 140.3, 132.4, 130.3, 129.8, 129.7 (q, J = 32.5 Hz), 129.3, 129.1, 128.9, 128.8, 128.0, 127.7, 126.4, 125.7 (q, J = 3.8 Hz), 124.1 (q, J = 271.9 Hz), 118.5, 112.0 ppm; ν_{max}(KBr)/cm^{-1} 3058, 2924, 1608, 1494, 1409, 1323, 697; MS (EI) m/z 77, 105, 183, 245, 345, 391; HRMS-ESI (m/z): calcd for $C_{24}H_{17}F_3NO$, $[M+H]^+$: 392.1257, found 392.1261.

(*E*)-Methyl 4-(2-(3,5-diphenylisoxazol-4-yl)vinyl)-benzoate (4m): Yield: 63% (48.0 mg) as a yellow solid; mp = 153.6 - 155.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 2H), 7.81 (dd, J = 7.6, 2.0 Hz, 2H), 7.69 (dd, J = 6.8, 2.8 Hz, 2H), 7.59 - 7.39 (m, 6H), 7.34 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 16.8 Hz, 1H), 6.66 (d, J = 16.8 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 166.7, 162.3, 141.2, 132.7, 130.3, 130.0, 129.8, 129.4, 129.3, 129.1, 128.9, 128.8, 128.0, 127.8, 126.1, 118.5, 112.1, 52.1 ppm; ν_{max}(KBr)/cm^{-1} 3056, 2926, 1604, 1495, 1413, 1276, 1116, 700; MS (EI) m/z 77, 105, 207, 262, 283, 322, 381; HRMS-ESI (m/z): calcd for $C_{25}H_{19}NNaO_3$, $[M+Na]^+$: 404.1257, found 404.1262.

(*E*)-4-(2-(3,5-Diphenylisoxazol-4-yl)vinyl)benzaldehyde (4n): Yield: 65% (45.6 mg) as a yellow solid; mp = 99.5 - 100.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.81 (d, J = 8.0 Hz, 4H), 7.68 (dd, J = 6.8, 3.0 Hz, 2H), 7.53 (qd, J = 5.5, 2.8 Hz, 6H), 7.42 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 16.8 Hz, 1H), 6.68 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 166.9, 162.2, 142.8, 135.6, 132.3, 130.4, 130.2, 129.8, 129.3, 129.1, 128.9, 128.9, 127.9, 127.8, 126.7, 119.4, 112.0 ppm; ν_{max}(KBr)/cm^{-1} 3055, 2923, 1693, 1596, 1494, 1405, 696; MS (EI) m/z 77, 105, 135, 207, 281, 322, 351; HRMS-ESI (m/z): calcd for $C_{24}H_{17}NNaO_2$, $[M+Na]^+$: 374.1151, found 374.1157.

(*E*)-4-(2-(Naphthalen-2-yl)vinyl)-3,5-diphenylisoxazole (4o): Yield: 61% (45.5 mg) as a yellow solid; mp = 145.2 - 147.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.0, 1.6 Hz, 2H), 7.82 - 7.72 (m, 5H), 7.63 - 7.54 (m, 2H), 7.53 - 7.46 (m, 6H), 7.45 - 7.39 (m, 2H), 7.08 (d, J = 16.8 Hz, 1H), 6.80 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 162.3, 134.3, 134.2, 133.6, 133.2, 130.1, 129.7, 129.0, 128.9, 128.8, 128.5, 128.3, 128.0, 127.8, 127.7, 126.7, 126.5, 126.2, 1240, 123.0, 116.2, 112.5 ppm; ν_{max}(KBr)/cm^{-1} 3054, 2924, 1693, 1596, 1497, 1446, 1406, 697; MS (EI) m/z 77, 105, 165, 207, 281, 355, 373; HRMS-ESI (m/z): calcd for $C_{27}H_{19}NNaO$, $[M+Na]^+$: 396.1359, found 396.1363.

(*E*)-3,5-Diphenyl-4-(2-(pyridin-2-yl)vinyl)isoxazole (4p): Yield: 68% (44.1 mg) as a yellow solid; mp = 135.0 - 136.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.0 Hz, 1H), 7.84 (dd, J = 7.6, 1.2 Hz, 2H), 7.76 - 7.68 (m, 2H), 7.63 (d, J = 16.0 Hz, 1H), 7.57 (dd, J = 7.6, 1.6 Hz, 1H), 7.54 - 7.45 (m, 6H), 7.12 (dd, J = 7.2, 5.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.4, 154.8, 149.7, 136.6, 132.6, 130.2, 129.7, 129.4, 129.1, 129.0, 128.8, 128.1, 127.9, 122.4, 120.2, 112.1 ppm; ν_{max}(KBr)/cm^{-1} 3055, 2924, 1692, 1644, 1577, 1411, 699; MS (EI) m/z 77, 105, 144, 193, 221, 295, 324; HRMS-ESI (m/z): calcd for $C_{22}H_{16}N_2NaO$, $[M+Na]^+$: 347.1155, found 347.1157.

(*E*)-4-(4-Chlorostyryl)-3-phenyl-5-(p-tolyl)isoxazole (5a): Yield: 80% (59.4 mg) as a yellow solid; mp = 125.0 - 126.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 - 7.63 (m, 4H), 7.50 - 7.44 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 6.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 16.8 Hz, 1H), 6.57 (d, J = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 162.2, 140.5, 135.4, 133.6, 132.4, 129.7, 129.7, 129.5, 128.9, 128.9, 128.8, 127.6, 127.5, 125.4, 116.7, 111.7, 21.6 ppm; ν_{max}(KBr)/cm^{-1} 3041, 2922, 1634, 1491, 1408, 1091, 697; MS (EI) m/z 91, 119, 149, 165, 280, 342, 371; HRMS-ESI (m/z): calcd for $C_{24}H_{18}ClNNaO$, $[M+Na]^+$: 394.0969, found 394.0975.

(*E*)-4-(4-Chlorostyryl)-5-(4-ethylphenyl)-3-phenyl-isoxazole (5b): Yield: 81% (62.4 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.70 - 7.63 (m, 2H), 7.48 (dd, J = 6.4, 3.6 Hz, 3H), 7.33 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 16.8 Hz, 1H), 6.57 (d, J = 16.8 Hz, 1H), 2.72 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMP (100 MHz, $CDCl_3$) δ 166.6, 162.2, 146.7, 135.4, 133.6, 132.4, 129.6, 129.5, 128.9, 128.9, 128.8, 128.5, 127.7, 127.5, 125.6, 116.7, 111.7, 28.9, 15.3 ppm; ν_{max}(KBr)/cm^{-1} 3044, 2926, 1609, 1490, 1446, 1408, 1092, 698; MS (EI) m/z 73, 135, 207, 253, 283, 327, 385; HRMS-ESI (m/z): calcd for $C_{25}H_{20}ClNNaO$, $[M+Na]^+$: 408.1126, found 408.1123.

(*E*)-5-(4-(tert-Butyl)phenyl)-4-(4-chlorostyryl)-3-phenyl -isoxazole (5c): Yield: 87% (71.8 mg) as a yellow solid; mp = 134.8 - 136.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 2H), 7.68 (dd, J = 6.8, 3.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.50 - 7.43 (m, 3H), 7.27 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 16.4 Hz, 1H), 6.58 (d, J = 16.4 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 162.2, 153.6, 135.4, 133.6, 132.5, 129.6, 129.6, 128.9, 128.9, 128.7, 127.5, 127.4, 126.0, 125.3, 116.8, 111.7, 35.0, 31.2 ppm; ν_{max}(KBr)/cm^{-1} 3049, 2961, 1640, 1489, 1409, 1092, 698; MS (EI) m/z 77, 118, 161, 217, 280, 328, 398, 413; HRMS-ESI (m/z): calcd for $C_{27}H_{25}ClNO$, $[M+H]^+$: 414.1619, found 414.1622.

(*E*)-4-(4-Chlorostyryl)-5-(4-pentylphenyl)-3-phenyl-isoxazole (5d): Yield: 90% (76.9 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 2H), 7.67 (dd, J = 6.8, 3.0 Hz, 2H), 7.48 (dd, J = 6.4, 3.6 Hz, 3H), 7.31 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 16.4 Hz, 1H), 6.57 (d, J = 16.8 Hz, 1H), 2.73 - 2.62 (m, 2H), 1.67 (dt, J = 14.8, 7.2 Hz, 2H), 1.45 - 1.29 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 162.2, 145.5, 135.4, 133.6, 132.4, 129.6, 129.6, 129.1, 128.9, 128.8, 128.7, 127.6, 127.4, 125.5, 116.8, 111.7, 35.9, 31.5, 30.9, 22.6, 14.1 ppm; ν_{max}(KBr)/cm^{-1} 3040, 2929, 1606, 1490, 1450, 1092, 699; HRMS-ESI (m/z): calcd for $C_{28}H_{27}ClNO$, $[M+H]^+$: 428.1776, found 428.1775.

(*E*)-4-(4-Chlorostyryl)-5-(4-ethoxyphenyl)-3-phenyl-isoxazole (5e): Yield: 82% (65.7 mg) as a yellow solid; mp = 115.3 - 117.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 2H), 7.71 (dd, J = 6.4, 2.8 Hz, 2H), 7.57 - 7.45 (m, 3H), 7.30 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 16.4 Hz, 1H), 6.61 (d, J = 16.8 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 162.2, 160.5, 135.5, 133.6, 132.2, 129.6, 129.2, 128.9, 128.9, 128.7, 127.4, 120.5, 116.9, 114.9, 111.0, 63.7, 14.8 ppm; ν_{max}(KBr)/cm^{-1} 3050, 2928, 1610, 1497, 1408, 1253, 1095, 699; MS (EI) m/z 73, 135, 207, 281, 372, 401; HRMS-ESI (m/z): calcd for $C_{25}H_{20}ClNNaO_2$, $[M+Na]^+$: 424.1075, found 424.1078.

(*E*)-4-(4-Chlorostyryl)-5-(2-fluorophenyl)-3-phenyl-isoxazole (5f): Yield: 73% (54.7 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 - 7.68 (m, 2H), 7.66 (dd, J = 7.2, 1.6 Hz, 1H), 7.50 (dt, J = 5.6, 2.8 Hz, 4H), 7.31 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 8.4 Hz, 3H), 7.16 (d, J = 8.8 Hz, 2H), 6.83 (dd, J = 16.4, 1.2 Hz, 1H), 6.48 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 161.9, 159.4 (d, J = 253.6 Hz), 135.4, 133.6, 132.4 (d, J = 8.3 Hz), 131.8 (d, J = 1.3 Hz), 130.9 (d, J = 2.3 Hz), 129.8, 129.2, 129.0, 128.9, 128.8, 127.5, 124.7 (d, J = 3.7 Hz), 116.7 (d, J = 21.3 Hz), 116.4, 116.3 (d, J = 3.6 Hz), 114.6 ppm; ν_{max}(KBr)/cm^{-1} 3055, 2928, 1609, 1492, 1409, 700; MS (EI) m/z 95, 149, 207, 300, 358, 375; HRMS-ESI (m/z): calcd for $C_{23}H_{15}ClFNNaO$, $[M+Na]^+$: 398.0718, found 398.0727.

(*E*)-5-(4-Chlorophenyl)-4-(4-chlorostyryl)-3-phenyl-isoxazole (5g): Yield: 75% (58.7 mg) as a yellow solid; mp = 148.0 - 149.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.8 Hz, 2H), 7.67 (dd, J = 6.4, 3.0 Hz, 2H), 7.55 - 7.44 (m, 5H), 7.28 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 16.4 Hz, 1H), 6.59 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 162.3, 136.3, 135.1, 133.9, 133.3, 129.8, 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 127.5, 126.6, 116.1, 112.5 ppm; ν_{max}(KBr)/cm^{-1} 3056, 2920, 1580, 1475, 1438, 1087, 737; MS (EI) m/z 77, 111, 139, 217, 280, 355, 391; HRMS-ESI (m/z): calcd for $C_{23}H_{15}Cl_2NNaO$, $[M+Na]^+$: 414.0423, found 414.0426.

(*E*)-5-(4-Bromophenyl)-4-(4-chlorostyryl)-3-phenyl-isoxazole (5h): Yield: 78% (67.8 mg) as a yellow solid; mp = 126.2 - 127.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.88 (m, 1H), 7.71 - 7.62 (m, 3H), 7.56 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 4.8, 1.4 Hz, 3H), 7.42 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.93 - 6.81 (m, 1H), 6.62 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 162.4, 134.9, 134.5, 134.0, 133.6, 131.1, 129.8, 129.3, 129.0, 128.9, 128.8, 127.9, 127.6, 126.5, 115.7, 113.2 ppm; ν_{max}(KBr)/cm^{-1} 3056, 2926, 1602, 1485, 1406, 697; MS (EI) m/z 91, 175, 202, 328, 370, 435; HRMS-ESI (m/z): calcd for $C_{23}H_{16}BrClNO$, $[M+H]^+$: 436.0098, found 436.0096.

(*E*)-4-(4-Chlorostyryl)-5-cyclopropyl-3-phenylisoxazole (5i): Yield: 71% (49.4 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.59 (m, 2H), 7.55 - 7.44 (m, 3H), 7.36 - 7.26 (m, 4H), 6.82 (d, J = 16.4 Hz, 1H), 6.77 (d, J = 16.4 Hz, 1H), 2.25 - 2.13 (m, 1H), 1.33 - 1.22 (m, 2H), 1.20 - 1.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 161.9, 135.7, 133.4, 130.7, 129.6, 129.4, 128.9, 128.8, 128.7, 127.4, 117.2, 112.3, 8.3, 8.2 ppm; ν_{max}(KBr)/cm^{-1} 3055, 2926, 1603, 1487, 1410, 1091, 698; MS (EI) m/z 59, 77, 103, 149, 253, 292, 321; HRMS-ESI (m/z): calcd for $C_{20}H_{16}ClNNaO$, $[M+Na]^+$: 344.0813, found 344.0814.

(*E*)-4-(4-Chlorostyryl)-5-cyclopentyl-3-phenylisoxazole (5j): Yield: 75% (52.4 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.58 (m, 2H), 7.55 - 7.40 (m, 3H), 7.32 - 7.26 (m, 4H), 6.77 (d, J = 16.4 Hz, 1H), 6.57 (d, J = 16.4 Hz, 1H), 3.50 - 3.32 (m, 1H), 2.15 - 2.04 (m, 2H), 1.97 (ddd, J = 20.4, 14.8, 7.6 Hz, 4H), 1.82 - 1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 161.5, 135.6, 133.5, 130.9, 129.7, 129.6, 128.9, 128.8, 128.7, 127.4, 117.3, 111.4, 37.1, 31.9, 26.0 ppm; ν_{max}(KBr)/cm^{-1} 3052, 2955, 1645, 1489, 1447, 1413, 1090, 697; MS (EI) m/z 55, 69, 149, 217, 253, 280, 349; HRMS-ESI (m/z): calcd for $C_{22}H_{21}ClNO$, $[M+H]^+$: 350.1306, found 350.1310.

(*E*)-4-(4-Chlorostyryl)-5-cyclohexyl-3-phenylisoxazole (5k): Yield: 76% (55.2 mg) as a yellow solid; mp = 93.2 - 94.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 5.6, 2.4 Hz, 2H), 7.52 - 7.42 (m, 3H), 7.37 - 7.27 (m, 4H), 6.76 (d, J = 16.8 Hz, 1H), 6.53 (d, J = 16.8 Hz, 1H), 3.13 - 2.93 (m, 1H), 1.94 (dd, J = 24.0, 12.4 Hz, 4H), 1.85 - 1.72 (m, 3H), 1.52 - 1.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 161.4, 135.6, 133.5, 130.7, 129.7, 129.6, 129.5, 128.9, 128.7, 127.4, 117.2, 110.7, 36.7, 30.9, 26.2, 25.7 ppm; ν_{max}(KBr)/cm^{-1} 3052, 2933, 1642, 1489, 1449, 1091, 696; MS (EI) m/z 77, 149, 217, 253, 280, 334, 363; HRMS-ESI (m/z): calcd for $C_{23}H_{22}ClNNaO$, $[M+Na]^+$: 386.1282, found 386.1288.

(*E*)-5-Butyl-4-(4-chlorostyryl)-3-phenylisoxazole (5l): Yield: 67% (45.2 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 - 7.60 (m, 2H), 7.58 - 7.45 (m, 3H), 7.38 - 7.29 (m, 4H), 6.79 (d, J = 16.4 Hz, 1H), 6.63 (d, J = 16.4 Hz, 1H), 2.95 (t, J = 7.6 Hz, 2H), 1.93 - 1.77 (m, 2H), 1.52 - 1.32 (m, 4H), 0.96 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 161.5, 135.6, 133.5, 130.7, 129.6, 129.5, 128.9, 128.8, 128.7, 127.4, 117.2, 112.0, 31.5, 27.2, 26.5, 22.3, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 3049, 2931, 1603, 1489, 1422, 1090, 695; MS (EI) m/z 77, 121, 149, 217, 253, 280, 351; HRMS-ESI (m/z): calcd for $C_{22}H_{22}ClNNaO$, $[M+Na]^+$: 374.1282, found 374.1286.

(*E*)-4-(4-Chlorostyryl)-5-*iso*butyl-3-phenylisoxazole (5m): Yield: 72% (48.5 mg) as a yellow solid; mp = 95.5 - 97.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 6.8, 3.0 Hz, 2H), 7.46 - 7.32 (m, 3H), 7.27 - 7.16 (m, 4H), 6.66 (d, J = 16.4 Hz, 1H), 6.50 (d, J = 16.4 Hz, 1H), 2.71 (d, J = 7.2 Hz, 2H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 161.4, 135.6, 133.5, 130.8, 129.6, 129.5, 128.9, 128.8, 128.7, 127.4, 117.2, 112.7, 35.3, 28.0, 22.6 ppm; ν_{max}(KBr)/cm^{-1} 3048, 2953, 1598, 1486, 1414, 1270, 1090, 698; MS (EI) m/z 57, 77, 114, 217, 280, 304 337; HRMS-ESI (m/z): calcd for $C_{21}H_{20}ClNNaO$, $[M+Na]^+$: 360.1126, found 360.1130.

(*E*)-4-(4-Chlorostyryl)-5-phenethyl-3-phenylisoxazole (5n): Yield: 79% (60.8 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 6.4, 3.0 Hz, 2H), 7.51 - 7.40 (m, 3H), 7.33 - 7.24 (m, 4H), 7.19 (dd, J = 12.0, 5.6 Hz, 5H), 6.57 (d, J = 16.4 Hz, 1H), 6.30 (d, J = 16.4 Hz, 1H), 3.21 (dd, J = 11.4, 4.8 Hz, 2H), 3.12 (dd, J = 11.4, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 161.5, 140.2, 135.4, 133.6, 131.0, 129.7, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 127.5, 126.6, 116.9, 112.9, 33.7, 28.7 ppm; ν_{max}(KBr)/cm^{-1} 3042, 2941, 1599, 1487, 1415, 1089, 698; MS (EI) m/z 77, 91, 149, 217, 280, 342, 385; HRMS-ESI (m/z): calcd for $C_{25}H_{21}ClNO$, $[M+H]^+$: 386.1306, found 386.1304.

(*E*)-4-(4-Chlorostyryl)-3-phenyl-5-(3-phenylpropyl)-isoxazole (5o): Yield: 83% (66.2 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 6.4, 2.8 Hz, 2H), 7.54 - 7.45 (m, 3H), 7.36 - 7.25 (m, 4H), 7.20 (dd, J = 12.4, 5.6 Hz, 5H), 6.68 (d, J = 16.4 Hz, 1H), 6.49 (d, J = 16.45 Hz, 1H), 2.93 (t, J = 7.6 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H), 2.17 (p, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 161.6, 141.1, 135.5, 133.5, 130.8, 129.7, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 127.4, 126.2, 117.0, 112.2, 35.2, 28.8, 25.7 ppm; ν_{max}(KBr)/cm^{-1} 3035, 2932, 1600, 1489, 1415, 1264, 1091, 698; MS (EI) m/z 77, 91, 149, 207, 294, 355, 399; HRMS-ESI (m/z): calcd for $C_{26}H_{23}ClNO$, $[M+H]^+$: 400.1463, found 400.1460.

(*E*)-4-(4-Chlorostyryl)-3-phenyl-5-(thiophen-2-yl)-isoxazole (5p): Yield: 73% (53.1 mg) as a yellow solid; mp = 111.3 - 112.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 2.8, 1.2 Hz, 1H), 7.68 (dd, J = 6.8, 3.0 Hz, 2H), 7.55 (dd, J = 5.2, 1.2 Hz, 1H), 7.46 (tt, J = 5.2, 3.2 Hz, 4H),

7.31 - 7.27 (m, 3H), 7.24 - 7.21 (m, 1H), 6.94 (d, *J* = 16.4 Hz, 1H), 6.64 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 162.1, 135.2, 133.8, 133.1, 129.7, 129.3, 129.0, 128.9, 128.8, 128.7, 127.5, 126.9, 126.0, 125.7, 116.5, 111.7 ppm; ν_{max}(KBr)/cm^{-1} 3026, 2925, 1598, 1488, 1437, 696; MS (EI) m/z 83, 111, 149, 214, 267, 330, 363; HRMS-ESI (m/z): calcd for $C_{21}H_{14}ClNNaOS$, $[M+Na]^+$: 386.0377, found 386.0369.

(*E*)-4-(4-Chlorostyryl)-5-(naphthalen-2-yl)-3-phenylisoxazole (5q): Yield: 66% (53.7 mg) as a yellow solid; mp = 132.8 - 134.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.98 - 7.82 (m, 4H), 7.76 - 7.66 (m, 2H), 7.61 - 7.44 (m, 5H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 16.8 Hz, 1H), 6.63 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 162.4, 135.3, 133.8, 133.8, 133.1, 132.9, 129.7, 129.4, 128.9, 128.8, 128.7, 127.9, 127.8, 127.5, 127.5, 127.0, 125.5, 124.3, 116.6, 112.5 ppm; ν_{max}(KBr)/cm^{-1} 3054, 2924, 1595, 1489, 1408, 753; MS (EI) m/z 77, 105, 207, 310, 387, 407; HRMS-ESI (m/z): calcd for $C_{27}H_{18}ClNNaO$, $[M+Na]^+$: 430.0969, found 430.0973.

(*E*)-4-(4-Chlorostyryl)-5-phenyl-3-(*o*-tolyl)isoxazole (5r): Yield: 77% (57.1 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.78 (m, 2H), 7.61 - 7.49 (m, 3H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 16.4 Hz, 1H), 6.26 (d, *J* = 16.4 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 162.2, 137.3, 135.5, 133.5, 130.5, 130.4, 130.2, 130.0, 129.8, 129.3, 129.1, 128.8, 128.1, 127.8, 127.4, 126.1, 116.5, 112.9, 19.8 ppm; ν_{max}(KBr)/cm^{-1} 3055, 2926, 1590, 1488, 1410, 1090, 696; MS (EI) m/z 65, 105, 194, 266, 354, 371; HRMS-ESI (m/z): calcd for $C_{24}H_{18}ClNNaO$, $[M+Na]^+$: 394.0969, found 394.0973.

(*E*)-4-(4-Chlorostyryl)-5-phenyl-3-(*p*-tolyl)isoxazole (5s): Yield: 82% (60.8 mg) as a yellow solid; mp = 137.5 - 138.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.53 - 7.44 (m, 3H), 7.34 - 7.24 (m, 3H), 7.22 (d, *J* = 8.8 Hz, 3H), 6.93 (d, *J* = 16.4 Hz, 1H), 6.61 (d, *J* = 16.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 162.2, 139.7, 135.4, 133.7, 132.7, 130.1, 129.5, 129.0, 128.9, 128.8, 128.2, 127.7, 127.5, 126.4, 116.7, 112.1, 21.5 ppm; ν_{max}(KBr)/cm^{-1} 3052, 2927, 1592, 1489, 1412, 1090, 696; MS (EI) m/z 77, 105, 149, 194, 294, 342, 371; HRMS-ESI (m/z): calcd for $C_{24}H_{18}ClNNaO$, $[M+Na]^+$: 394.0969, found 394.0975.

(*E*)-4-(4-Chlorostyryl)-3-(4-ethylphenyl)-5-phenylisoxazole (5t): Yield: 82% (63.1 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.76 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.55 - 7.44 (m, 3H), 7.29 (dd, *J* = 14.8, 8.2 Hz, 4H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 16.4 Hz, 1H), 6.62 (d, *J* = 16.4 Hz, 1H), 2.72 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 162.2, 146.0, 135.4, 133.7, 132.7, 130.1, 129.0, 128.9, 128.8, 128.3, 128.3, 127.7, 127.5, 126.6, 116.7, 112.1, 28.8, 15.4 ppm; ν_{max}(KBr)/cm^{-1} 3053, 2934, 1605, 1487, 1416, 1270, 1089, 698; MS (EI) m/z 77, 105, 149, 208, 280, 321, 385; HRMS-ESI (m/z): calcd for $C_{25}H_{20}ClNNaO$, $[M+Na]^+$: 408.1126, found 408.1124.

(*E*)-4-(4-Chlorostyryl)-3-(4-methoxyphenyl)-5-phenylisoxazole (5u): Yield: 73% (56.5 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.55 - 7.39 (m, 3H), 7.24 (t, *J* = 8.2 Hz, 4H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 16.4 Hz, 1H), 6.63 (d, *J* = 16.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 161.9, 160.8, 135.4, 133.7, 132.7, 130.2, 130.1, 129.0, 128.9, 128.3, 127.6, 127.5, 121.6, 116.8, 114.3, 112.1, 55.4 ppm; ν_{max}(KBr)/cm^{-1} 3051, 2934, 1607, 1487, 1429, 1251, 1091, 696; MS (EI) m/z 77, 105, 207, 281, 327, 387; HRMS-ESI (m/z): calcd for $C_{24}H_{19}ClNO_2$, $[M+H]^+$: 388.1099, found 388.1103.

(*E*)-4-(4-Chlorostyryl)-3-(3-methoxyphenyl)-5-phenylisoxazole (5v): Yield: 76% (58.8 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.58 - 7.50 (m, 3H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 12.4, 5.6 Hz, 6H), 7.15 - 7.03 (m, 1H), 6.98 (d, *J* = 16.4 Hz, 1H), 6.66 (d, *J* = 16.4 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 162.1, 159.8, 135.3, 133.7, 132.8, 130.6, 130.2, 129.9, 129.0, 128.9, 128.2, 127.7, 127.5, 121.3, 116.5, 115.9, 113.9, 112.2, 55.4 ppm; ν_{max}(KBr)/cm^{-1} 3051, 2929, 1606, 1489, 1413, 1252, 694; MS (EI) m/z 77, 105, 149, 207, 283, 358, 387; HRMS-ESI (m/z): calcd for $C_{24}H_{19}ClNO_2$, $[M+H]^+$: 388.1099, found 388.1098.

(*E*)-3-(3-Chlorophenyl)-4-(4-chlorostyryl)-5-phenylisoxazole (5w): Yield: 70% (54.7 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 - 7.69 (m, 2H), 7.63 (s, 1H), 7.52 - 7.37 (m, 5H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 16.4 Hz, 1H), 6.50 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 161.0, 135.1, 134.8, 133.9, 133.3, 131.2, 130.3, 130.0, 129.8, 129.1, 129.0, 128.9, 127.9, 127.6, 127.5, 127.0, 116.1, 112.0 ppm; ν_{max}(KBr)/cm^{-1} 3056, 2929, 1598, 1488, 1438, 694; MS (EI) m/z 77, 105, 149, 251, 328, 362, 391; HRMS-ESI (m/z): calcd for $C_{23}H_{16}Cl_2NC$, $[M+H]^+$: 392.0603, found 392.0602.

(*E*)-4-(4-Chlorostyryl)-5-phenyl-3-propylisoxazole (5x): Yield: 76% (49.1 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 - 7.64 (m,2H), 7.57 - 7.46 (m, 3H), 7.44 - 7.28 (m, 4H), 6.80 (d, *J* = 16.4 Hz, 1H), 6.64 (d, *J* = 16.4 Hz, 1H), 2.95 (t, *J* = 7.2 Hz, 2H), 1.98 - 1.82 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 161.5, 135.6, 133.5, 130.8, 129.6, 129.5, 128.9, 128.8, 128.7, 127.4, 117.2, 112.1, 28.4, 21.0, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 3044, 2957, 1638, 1482, 1089, 773, 698; MS (EI) m/z 77, 114, 149, 217, 253, 280, 323; HRMS-ESI (m/z): calcd for $C_{20}H_{19}ClNO$, $[M+H]^+$: 324.1150, found 324.1152.

(*E*)-4-(4-Chlorostyryl)-3-cyclopentyl-5-phenylisoxazole (5y): Yield: 70% (48.9 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.66 (m, 2H), 7.54 - 7.42 (m, 3H) 7.34 (q, *J* = 8.8 Hz, 4H), 6.91 (d, *J* = 16.4 Hz, 1H), 6.83 (d, *J* = 16.4 Hz, 1H), 3.32 (p, *J* = 7.6 Hz, 1H), 2.12 (td, *J* = 11.8, 6.8 Hz, 2H), 1.99 (td, *J* = 14.4, 7.2 Hz, 2H), 1.93 1.81 (m, 2H), 1.78 - 1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.8, 135.6, 133.6, 131.4, 129.9, 129.0, 128.9, 128.4, 127.6, 127.5, 117.6, 112.3, 37.0, 31.6, 25.6 ppm; ν_{max}(KBr)/cm^{-1} 3044, 2942, 1642, 1574, 1484, 1238, 1086, 763, 692; MS (EI) m/z 77, 105, 191, 253, 280, 308, 349; HRMS-ESI (m/z): calcd for $C_{22}H_{21}ClNO$, $[M+H]^+$: 350.1306, found 350.1309.

(*E*)-3-(*tert*-Butyl)-4-(4-chlorostyryl)-5-phenylisoxazole (5z): Yield: 79% (53.4 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.46 - 7.36 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 16.4 Hz, 1H), 6.28 (d, *J* = 16.4 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 162.1, 135.4, 133.5, 133.1, 129.9, 129.4, 128.9, 128.8, 128.6, 127.4, 117.3, 110.6, 34.4, 29.2 ppm; ν_{max}(KBr)/cm^{-1} 3053, 2964, 1643, 1479, 1282, 1086, 764, 694; MS (EI) m/z 77, 114, 149, 245, 280, 322, 337; HRMS-ESI (m/z): calcd for $C_{21}H_{21}ClNO$, $[M+H]^+$: 338.1306, found 338.1309.

4-((*E*)-4-Chlorostyryl)-5-phenyl-3-((*E*)-styryl)isoxazole (5ba): Yield: 58% (44.5 mg) as a yellow solid; mp = 113.2 - 114.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.52 (dt, *J* = 12.8, 10.6 Hz, 6H), 7.43 - 7.32 (m, 7H), 7.03 (d, *J* = 11.2 Hz, 1H), 6.99 (d, *J* = 11.6 Hz, 1H), 6.87 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 159.5, 136.1, 135.4, 133.9, 133.1, 133.0, 130.1, $^{-1}$ 3057, 2931, 1591, 1486, 1445, 1408, 694129.1, 129.0, 128.9, 128.8, 128.0, 127.6, 127.5, 127.2, 117.1, 114.5, 112.5 ppm; ν_{max}(KBr)/cm; MS (EI) m/z 77, 105, 149, 292, 354, 383; HRMS-ESI (m/z): calcd for $C_{25}H_{18}ClNNaO$, $[M+Na]^+$: 406.0969, found 406.0972.

(*E*)-4-(4-Chlorostyryl)-3,5-dicyclohexylisoxazole (**5bb**): Yield: 64% (47.3 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 6.75 (d, J = 16.4 Hz, 1H), 6.62 (d, J = 16.4 Hz, 1H), 2.92 (t, J = 10.6 Hz, 1H), 2.78 (t, J = 10.4 Hz, 1H), 2.03 (d, J = 12.4 Hz, 2H), 1.93 – 1.81 (m, 6H), 1.70 (dd, J = 24.8, 11.2 Hz, 4H), 1.64 - 1.53 (m, 1H), 1.49 - 1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 165.8, 135.9, 133.3, 129.3, 128.9, 127.4, 117.5, 110.1, 36.5, 36.2, 31.4, 30.9, 26.4, 26.2, 26.1, 25.7 ppm; ν_{max}(KBr)/cm^{-1} 3052, 2928, 1594, 1443, 1093; MS (EI) m/z 83, 125, 149, 204, 244, 286, 301, 369; HRMS-ESI (m/z): calcd for calcd for $C_{23}H_{29}ClNO$, $[M+H]^+$: 370.1932, found 370.1937.

Supporting Information

Copies of the ^{1}H NMR and ^{13}C NMR spectra for all compounds are available in the supporting Information.

Acknowledgements

This work was supported by the financial support from the National Key Research China and Development Program of China (2016YFA0602900), the National Natural Science Foundation of China (21502055, 21490572 and 21420102003), and the Fundamental Research Funds for the Central Universities (2015ZM150 and 2015ZY001).

References

[1] For recent reviews, a) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Acc. Chem. Res*. **2016**, *49*, 1911-1923; b) J.-J. Feng, J. Zhang, *ACS Catal*. **2016**, *6*, 6651-6661; c) G. Albano, L. A. Aronica, *Eur. J. Org. Chem*. **2017**, 7204-7221; d) X. Wang, A. Studer, *Acc. Chem. Res.* **2017**, *50*, 1712-1724; e) Q.-Q. Cheng, Y. Yu, J. Yedoyan, M. P. Doyle, *ChemCatChem* **2018**, *10*, 488-496.

[2] For review, T. M. V. D. Pinho e Melo, *Curr. Org. Chem*. **2005**, *9*, 925-958.

[3] For selected reviews, a) B. J. Wakefield, in: *Science of Synthesis*: *Houben-Weyl Methods of Molecular Transformations*, Vol. 11, (Ed.: E. Schaumann), Georg Thieme Verlag, Stuttgart, New York, **2004**, pp 229-288; b); A. M. S. Silva, A. C. Tome, T. M. V. D. Pinho e Melo, J. Elguero, in: *Modern Heterocyclic Chemistry*, (Eds.: J. Alvarez-Builla, J. J. Vaquero, J. Barluenga), Wiley-VCH, Weinheim, **2011**, pp 727-808.

[4] a) J. J. Talley, *Prog. Med. Chem*. **1999**, *36*, 201-234; b) J. J. Talley, D. L. Brown, J. S. Carter, M. J. Graneto, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, R. S. Rogers, A. F. Shaffer, Y. Y. Zhang, B. S. Zweifel, K. Seibert, *J. Med. Chem*. **2000**, *43*, 775-777.

[5] M. Dougados, P. Emery, E. M. Lemmel, C. A. F. Zerbini, S. Brin, P. van Rie, *Ann. Rheum. Dis*. **2005**, *64*, 44-51.

[6] a) R. G. Micetich, R. Raap, *J. Med. Chem*. **1968**, *18*, 159-160; b) A. Severin, K. Tabei, F. Tenover, M. Chung, N. Clarke, A. Tomasz, *J. Biol. Chem*. **2004**, *279*, 3398-3407; c) K.-Y. Dong, H.-T. Qin, X.-X. Bao, F. Liu, C. Zhu, *Org. Lett*. **2014**, *16*, 5266-5268.

[7] a) P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, D. Simon, *Synthesis* **1987**, 857-869; b) B. Heasley, *Angew. Chem. Int. Ed*. **2011**, *50*, 8474-8477.

[8] a) N. T. Patil, Y. Yamamoto, *Chem. Rev*. **2008**, *108*, 3395-3442; b) T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2010**, 3363-3376; c) F. Heaney, *Eur. J. Org. Chem*. **2012**, 3043-3048; d) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev*. **2013**, *113*, 3084-3213.

[9] For selected reviews, a) F. Hu, M. Szostak, *Adv. Synth. Catal*. **2015**, *357*, 2583-2614; b) P. Vitale, A. Scilimati, *Adv. Heterocycl. Chem*. **2017**, *122*, 1-41; For selected examples, c) J. P. Waldo, R. C. Larock, *Org. Lett*. **2005**, *7*, 5203-5205; d) J. P. Waldo, R. C. Larock, *J. Org. Chem*. **2007**, *72*, 9643-9647; e) L. Zhang, Q. Zeng, A. Mao, Z. Wu, T. Luo, Y. Xiao, J. Zhang, *Org. Biomol. Chem*. **2014**, *12*, 8942-8946; f) W. Kaewsri, C. Thongsornkleeb, J. Tummatorn, S. Ruchirawat, *RSC Adv*. **2016**, *6*, 48666-48675.

[10] For selected reviews, a) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev*. **2011**, *111*, 1417-1492; b) Y. Xia, Y. Zhang, J. Wang, *ACS Catal*. **2013**, *3*, 2586-2598; c) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev*. **2013**, *113*, 3084-3213; d) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev*. **2013**, *113*, 1-35; e) J.-R. Chen, X.-Q. Hu, W.-J. Xiao, *Angew. Chem. Int. Ed*. **2014**, *53*, 4038-4040; f) X.-H. Yang, R.-J. Song, Y.-X. Xie, J.-H. Li, *ChemCatChem* **2016**, *8*, 2429-2445.

[11] M. Ueda, A. Sato, Y. Ikeda, T. Miyoshi, T. Naito, O. Miyata, *Org. Lett*. **2010**, *12*, 2594-2597.

[12] Y. Jeong, B.-I Kim, J. K. Lee, J.-S. Ryu, *J. Org. Chem*. **2014**, *79*, 6444-6455.

[13] A. Sperança, B. Godoi, G. Zeni, *J. Org. Chem*. **2013**, *78*, 1630-1637.

[14] Z. She, D. Niu, L. Chen, M. A. Gunawan, X. Shanja, W. H. Hersh, Y. Chen, *J. Org. Chem*. **2012**, *77*, 3627-3633.

[15] J. Li, C. Li, L. Ouyang, C. Li, W. Wu, H. Jiang, *Org. Biomol. Chem*. **2017**, *15*, 7898-7908.

[16] J. Li, C. Li, L. Ouyang, C. Li, S. Yang, W. Wu, H. Jiang, *Adv. Synth. Catal*. **2018**, *360*, 1138-1150.

[17] a) J. Li, W. Yang, S. Yang, L. Huang, W. Wu, Y. Sun, H. Jiang, *Angew. Chem., Int. Ed*. **2014**, *53*, 7219-7222; b) J. Li, S. Yang, W. Wu, H. Jiang, *Chem. Commun*. **2014**, *50*, 1381-1383; c) J. Li, C. Li, S. Yang, Y. An, W Wu, H. Jiang, *J. Org. Chem*. **2016**, *81*, 2875-2887; d) J. Li, C. Li, S. Yang, Y. An, W. Wu, H. Jiang, *J. Org. Chem*. **2016**, *81*, 7771-7783; e) J. Li, W. Hu, C. Li, S. Yang, W. Wu, H. Jiang, *Org. Chem. Front*. **2017**, *4*, 373-376. For reviews, f) W. Wu, H. Jiang, *Acc. Chem. Res*. **2014**, *47*, 2483-2504; g) J. Li, S. Yang, W. Wu, H. Jiang, *Eur. J. Org. Chem*. **2018**, 1284-1306.

[18] For details of optimization of the reaction conditions for the synthesis of 4-vinyl substituted isoxazoles derivatives, see the Supporting Information.

[19] CCDC 1821824 (**4a**) contains the supplementary crystallographic data for this paper.

[20] a) B. Yao, Q. Wang, J. Zhu, *Angew. Chem., Int. Ed*. **2012**, *51*, 12311-12315; b) C. M. R. Volla, J.-E. Bäckvall, *Angew. Chem. Int. Ed*. **2013**, *52*, 14209-14213.

[21] a) K. M. Gligorich, M. S. Sigman, *Angew. Chem. Int. Ed*. **2006**, *45*, 6612-6615; b) W. Wu, H. Jiang, *Acc. Chem. Res*. **2012**, *45*, 1736-1748; c) J. Wang, S. Luo, J. Li, Q. Zhu, *Org. Chem. Front*. **2014**, *1*, 1285-1288; d) L. Ouyang, W. Wu, *Curr. Opin. Green Sustain. Chem*. **2017**, *7*, 46-55.

[22] a) J. Li, H. Jiang, M. Chen, *J. Org. Chem*. **2001**, *66*, 3627-3629; b) J. Huang, L. Zhou, H. Jiang, *Angew. Chem. Int. Ed*. **2006**, *45*, 1945-1949.

[23] a) L. Zhao, X. Lu, *Org. Lett*. **2002**, *4*, 3903-3906; b) L. Zhao, X. Lu, W. Xu, *J. Org. Chem*. **2005**, *70*, 4059-4063.

10.1002/adsc.201800444

FULL PAPER

Palladium-Catalyzed Cascade Cyclization/Alkynylation and Alkenylation of Alkynone *O*-Methyloximes with Terminal Alkynes

Adv. Synth. Catal. **2018**,

Jianxiao Li,[+a] Miao Hu,[+a] Chunsheng Li,[a] Can Li,[a] Jiawei Li,[a] Wanqing Wu[a] and Huanfeng Jiang[a,*]