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Synthesis of C4-alkynylisoxazoles *via* a Pd-catalyzed Sonogashira cross-coupling reaction†

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A Pd-catalyzed Sonogashira cross-coupling reaction for the synthesis of C4-alkynylisoxazoles from 3,5-disubsitituted-4-iodoisoxazoles and terminal alkynes was described, which could afford the corresponding products with high yield (up to 98%). The results indicated that the steric effect from the group at the C3 position of the isoxazole had greater influence on the cross-coupling reaction than that from the group at the C5 position. In addition, the group at the C3 position of the isoxazole showed negligible electronic effects on the cross-coupling reaction. Furthermore, a gram-scale reaction of the Sonogashira coupling reaction was also investigated. Finally, a plausible mechanism for the Sonogashira coupling reaction was proposed.

Introduction

Isoxazole and its derivatives are important structural units of many molecules of biological interest.[1] As a result, numerous synthetic approaches have been made to access the isoxazole core, including the [3 + 2] cycloaddition between alkynes/alkenes and nitrile oxides,[2] intramolecular cyclo-isomerization of α,β-unsaturated oximes,[3] condensation between hydroxylamine and 1,3-dicarbonyl compounds or α,β-unsaturated carbonyls.[4] Many of the reported methods have two main limitations, (i) limitation to the preparation of disubstituted isoxazoles, and (ii) low regioselectivity.[5] In order to overcome these limitations, direct functionalization of isoxazoles or 4-haloisoxazoles has been developed by many research groups.[6]

Transition-metal-catalyzed cross-coupling reactions have become one of the most prominent and reliable methods for the formation of carbon–carbon bonds.[7] Among them, the Pd-catalyzed Sonogashira cross-coupling reaction between aromatic halides and terminal alkynes is very useful in the synthesis of carbo- and heterocycles, natural products, polymers, and molecular nanostructures.[8] Using this powerful reaction, some trisubstituted isoxazoles were synthesized. Yamanaka and co-workers first reported that the $Pd(PPh_3)Cl_2$ catalyzed Sonogashira cross-coupling reaction of 3-substituted-5-methyl-4-iodoisoxazoles with terminal alkynes, affording three examples of 3-substituted-5-methyl-4-alkynylisoxazole products in good yields (up to 86% yield).[6a] In 2001, Kromann and co-workers explored that $Pd(PPh_3)Cl_2$ catalyzed Sonogashira cross-coupling reaction of 3-ethoxy-5-methyl-4-iodoisoxazole with phenylacetylene, giving product of 3-ethoxy-5-methyl-4-phenylethynylisoxazole for only one example in 58% yield.[6c] Larock and co-workers chose 3-(3,4,5-trimethoxyphenyl)isoxazole-5-methyl-4-iodoisoxazole as a substrate to react with seven terminal alkynes, giving the targeted products with the yields between 30% and 83%.[6e] In 2005, a series of 3-carboxamide-5-(2,4-dihydroxy-5-isopropylphenyl)-4-alkynylisoxazoles were synthesized through $Pd(PPh_3)Cl_2$ catalyzed Sonogashira cross-coupling reaction of an alkynyl moiety and an isoxazole scaffold as novel HSP90 inhibitors by Zhang and co-works.[6l] Recently, Guo and co-workers reported that Sonogashira cross-coupling reaction of 3-trifluoromethyl-5-phenyl-4-iodoisoxazoles with phenylacetylene in the presence of $Pd(PPh_3)_2Cl_2$, affording the targeted product in 80% yield.[9] However, none of the above researches studied the impact of the groups at C3 position and C5 position of isoxazole core on the Sonogashira cross-coupling reaction. Because of the decreased symmetry in isoxazole, when compared to furan, pyrrole, and benzene, reaction channels which are equivalent in furan, pyrrole, and benzene will lead to the different results in isoxazole. For examples, Fall and co-workers discovered that 3-carboxylate-5-methylisoxazole reacted with 1-(4-bromophenyl)ethan-1-one to afford the targeted product, but 4-carboxylate-5-methylisoxazole did not afford desired product.[6f] Coffman and co-workers investigated the effects of the groups of 3,5-, 4,5-, and 3,4-bis(2-nitrophenyl) isoxazoles on the reaction.[10] Lately, Morita and co-workers reported intramolecular electrophilic aromatic substitution reaction only occurred at the 5-position of isoxazole rather than at the 3-position.[11]

Herein, we investigated the effect of the groups at C3 and C5 positions of the isoxazole on the Sonogashira cross-coupling reaction. Using 3,5-disubstituted-4-iodoisoxazoles and

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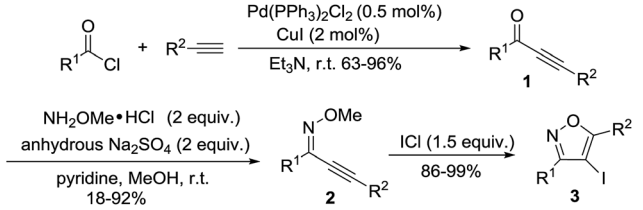
terminal alkynes as the substrates, we synthesized a series of 3,5-disubstituted-4-alkylnylisoxazole products.

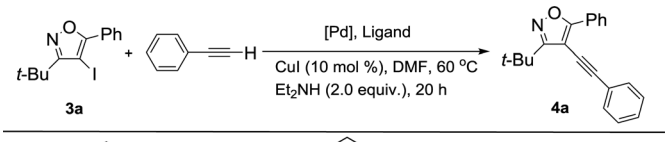
Results and discussion

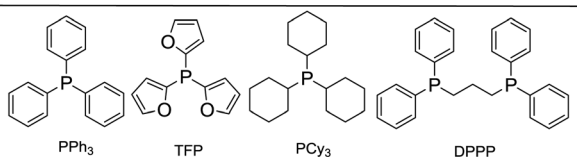
During our investigation, intermediate ynones **1** were prepared by the Sonogashira cross-coupling of an acid chloride and a terminal alkyne in the presence of $Pd(PPh_3)_2Cl_2$. The *O*-methyl oximes **2** were prepared by the reaction of ynones **1** with methoxylamine hydrochloride in the presence of pyridine and anhydrous Na_2SO_4. The substrates of 3,5-disubstituted-4-iodoisoxazoles **3** were prepared through the electrophilic cyclization of *O*-methyl oxime **2** in the presence of ICl (Scheme 1).



Scheme 1 Preparation of 3,5-disubstituted-4-iodoisoxazoles **3**.

Table 1 Effects of catalyst precursors, ligands and catalyst loadings[a]





Entry	Catalyst (mol%)	Ligand (mol%)	**3a** conv.[b] (%)	**4a** yield[b] (%)
1	$Pd(PPh_3)_2Cl_2$ (5)	—	47	26
2	$Pd(PPh_3)_2Cl_2$ (5)	PPh_3 (10)	49	30
3	$Pd(PPh_3)_2Cl_2$ (5)	PCy_3 (10)	48	28
4	$Pd(PPh_3)_2Cl_2$ (5)	DPPP (5)	35	20
5	$Pd(PPh_3)_4$ (5)	—	43	26
6	$Pd(OAc)_2$ (5)	PPh_3 (10)	52	31
7	$Pd(TFA)_2$ (5)	PPh_3 (10)	24	18
8	$Pd(MeCN)_2Cl_2$ (5)	PPh_3 (10)	50	29
9	**$Pd(acac)_2$ (5)**	**PPh_3 (10)**	**66**	**60**
10	$Pd(acac)_2$ (5)	PCy_3 (10)	42	26
11	$Pd(acac)_2$ (5)	TFP (10)	56	46
12	$Pd(acac)_2$ (5)	DPPP (5)	36	22
13	$Pd(acac)_2$ (3.5)	PPh_3 (7)	48	35
14	$Pd(acac)_2$ (7.5)	PPh_3 (15)	64	58

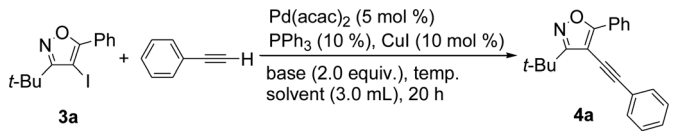
[a] Reaction condition: **3a** (0.3 mmol, 1 equiv.), phenylacetylene (0.6 mmol, 2 equiv.), [Pd], ligand, CuI (10 mol%), Et_2NH (2 equiv.), DMF (3 mL), 60 °C under N_2 protection. [b] Isolated yield.

We chose 3-(*tert*-butyl)-4-iodo-5-phenylisoxazole (**3a**) with phenylacetylene as a model substrate to identify the feasibility of our process. When **3a** reacted with phenylacetylene in anhydrous DMF at 60 °C in the presences of $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), and Et_2NH (2 equiv.) under nitrogen atmosphere, the desired product **4a** was obtained in 26% yield after 20 h and the conversion of starting material **3a** was 47% (Table 1, entry 1). To improve the reaction efficiency, three kinds of phosphine ligands, such as PPh_3, PCy_3 and DPPP, were examined for this reaction under similar condition (Table 1 entries 2–4). Unfortunately, the yield of targeted product **4a** could only be up to 30% (Table 1, entry 2). Then, different palladium catalysts were screened for the reaction (Table 1, entries 5–9). Among them, **3a** reacted with phenylacetylene to afford the corresponding product **4a** in 60% yield and the conversion of **3a** could be increased to 66% in the presence of $Pd(acac)_2$ (Table 1, entry 9). Encouraged by this result, a series of phosphine ligands, such as PPh_3, TFP, PCy_3 and DPPP, were tested for this reaction under similar condition (Table 1, entries 9–12). The general trends in yields of product **4a** related to different phosphine ligands were as followed: PPh_3 > TFP > PCy_3 > DPPP. The impact of the catalyst loading on the reaction was also investigated, and the yield of **4a** was strongly influenced by the amount of catalyst loading (Table 1, entries 13 and 14). The yield of **4a** was decreased with the amount of catalyst loading decreased to 3.5 mol% (Table 1, entry 13). However, a further increase the amount of catalyst loading did not improve the yield of **4a** (Table 1, entry 14).

The effects of bases, solvents and temperatures were then examined (Table 2). No reaction took place without bases (not shown in Table 2). Moderate yields were obtained when Et_2NH and Et_3N were used as bases (Table 2, entries 1 and 2). As we added the base *n*-butylamine or DIPEA (*N*,*N*-diisopropylethylamine) to this reaction system, the reaction proceeded to give the targeted product **4a** with low yields (25% and 18%, respectively) (Table 2, entries 3 and 4). The selection of solvents proved to have a dramatic influence on the reaction (Table 2, entries 1, 5–8). When the reaction was carried out in anhydrous DMF, a dipolar aprotic solvent, targeted product **4a** could be obtained in 60% yield (Table 2, entry 1). Other solvents, such as anhydrous THF, MeCN, toluene and DCE, resulted in low yields (30%, 25%, 22% and 20%, respectively) (Table 2, entries 5–8). At last, the effects of temperatures on the reaction were investigated (Table 2, entries 1 and 9 and 10). The results showed that the optimum reaction temperature was 60 °C in terms of yield (Table 2, entry 1).

With the above optimized reaction condition in hand (5 mol% $Pd(acac)_2$, 10 mol% PPh_3, 10 mol% CuI, and 2 equiv. Et_2NH in anhydrous DMF at 60 °C under N_2 atmosphere), the effects of the substituent at 3 and 5 position of the isoxazole were examined (Table 3). We used the substrate **3a** to react with three different kinds of terminal alkynes, affording the corresponding targeted products (**4a**, **4b**, and **4c**) with the yields of 60%, 61%, and 63%, respectively (Table 3). For these reactions, the substrate **3a** couldn't be completely transferred, and its conversion was 66%, 68%, and 69%, respectively.

Table 2 Effects of bases, solvents and temperatures[a]



Entry	Base	Solvent	Temp. (°C)	**3a** conv.[b] (%)	**4a** yield[b] (%)
1	Et_2NH	DMF	60	66	60
2	Et_3N	DMF	60	63	58
3	*n*-Butylamine	DMF	60	38	25
4	DIPEA	DMF	60	25	18
5	Et_2NH	THF	60	41	30
6	Et_2NH	MeCN	60	46	35
7	Et_2NH	Toluene	60	33	22
8	Et_2NH	DCE	60	26	20
9	Et_2NH	DMF	30	38	22
10	Et_2NH	DMF	90	82	40

[a] The reaction was carried out with **3a** (0.3 mmol, 1 equiv.), phenylacetylene (0.6 mmol, 2 equiv.), CuI (10 mol%), base (2.0 equiv.) in the solvent at the stated temperature in the presence of $Pd(acac)_2$ (5 mol%) and PPh_3 (10 mol%) under N_2 atmosphere. [b] Isolated yield.

When we used **3b** as the substrate, with a phenyl group at the 3 position and a *tert*-butyl group at the 5 position to react with three kinds of terminal alkynes, the targeted products (**4d–4f**) were obtained in high yields (up to 97%) and almost full conversion of **3b** was gained within 8 h. Such phenomena were very interesting, which encouraged us to investigate the impact of the groups at the 3 and 5 positions of 4-iodoisoxazoles on the reaction. First, we studied the impact of the group at the 5 position of 4-iodoisoxazoles on the reaction. When we used the substrate **3c** (5 position was cyclopropyl group) or **3d** (5 position was *n*-pentyl group) to react with the three kinds of terminal alkynes, all of the products (**4g–4l**) could be obtained in high yields, accompanied by almost full conversation of **3c** or **3d** within 8 h. Second, we examined the effect of the group at the 3 position of 4-iodoisoxazole on the reaction. We chose the substrate **3e**, with an isopropyl group at the 3 position, to react with the three kinds of terminal alkynes, affording the targeted products (**4m**, **4n**, and **4o**) in high yields (90%, 91%, and 93%, respectively), and **3e** was almost transferred in the three reactions. As the steric hindrance from the *tert*-butyl group is greater than that from the isopropyl group, this implied that 4-iodoisoxazoles containing large steric hindrance functional groups at the 3 position was poor for this type Sonogashira cross-coupling reaction. Then, we further investigated the electronic effects of the group at the 3 position of 4-iodoisoxazoles. We chose **3f** containing strong electron donor group (OCH_3) and **3g** containing strong electron-withdrawing group (CF_3) to test the electronic effects on the reaction. To our delight, all of the targeted products (**4p–4u**) could be obtained with high yields and the starting materials (**3f** and **3g**) could be completely transferred with 8 h. The results implied that the steric effect rather than the electronic effect of the group at the 3 position affected the efficiency of the cross-coupling reactions.

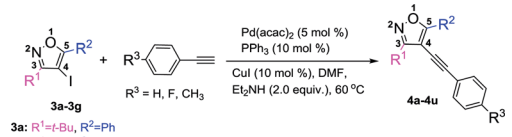
Based on the above results (Table 3), 3,5-diphenyl-4-iodoisoxazole **3h** was chosen as a substrate to react with a variety of terminal alkynes in the presence of $Pd(acac)_2/PPh_3$ complex (Table 4). The results showed that both electron-donating and electron-withdrawing substituents on the phenyl groups of the terminal alkynes were well accommodated, achieving the desired products (**5a–5g**) in high yields. The 4-ethynyl-1,1′-biphenyl could also be converted into **5h** in 53% yield. Furthermore, R^3 = thiophenyl was also afforded the targeted product **5i** in 91% yield. Both 1-ethynylcyclohexene and 1-ethynylcyclohexane could be component coupling partner for this transformation (**5j–5k**). And 3-methoxyprop-1-yne could achieve the desired product **5l** in 80% yield as well.

To further demonstrate the synthetic application of the developed protocol, a gram-scale reaction was tested using substrates **3h** to react with phenylacetylene, and it could proceed smoothly, affording the targeted product **5a** in high yields (Scheme 2).

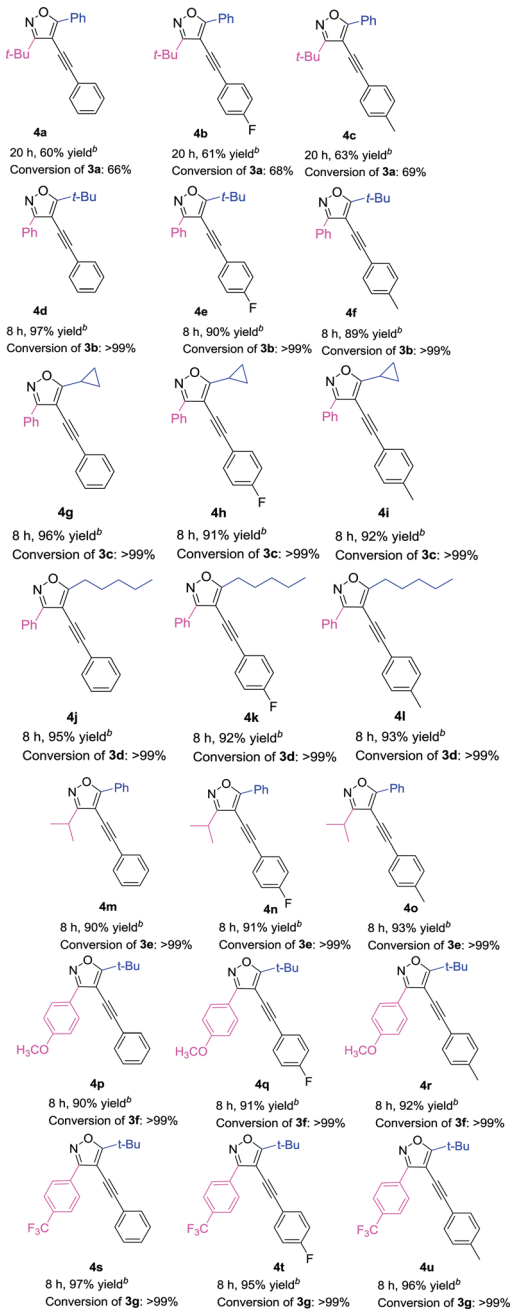
In addition, to gain insight into the mechanism of the Sonogashira coupling reaction, a control experiment had been conducted (Scheme 3). The yield of targeted product **4a** was slightly decreased when run in the presence of radical inhibitor (2.0 equiv. TEMPO). The result excluded the possible involvement of radical species.

Based on the above experiments and classical description of the Sonogashira coupling reaction, a plausible mechanism for the reaction was depicted in Scheme 4, involving two connected catalytic cycles (cycle A and cycle B).[8,12] In the cycle A, the catalytically active species $Pd[0](PPh_3)_2$ **D** was formed by reduction of $Pd[II](PPh_3)_2(acac)_2$ **C** (activation) which was produced *in situ* by combination two equivalents of triphenylphosphine with a $Pd(II)(acac)_2$. Oxidative addition of palladium[0] catalyst **D** to 4-iodoisoxazoles **3** produced intermediate **E**, followed by

Table 3 Pd-catalyzed Sonogashira cross-coupling between 3,5-disubstituted-4-iodoisoxazoles **3a–3g** and terminal alkynes[a]



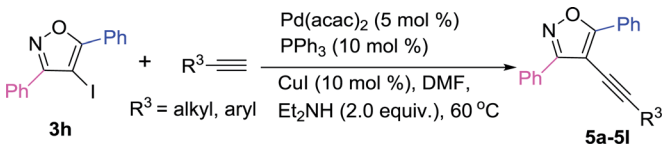
3a: R^1=*t*-Bu, R^2=Ph
3b: R^1=Ph, R^2=*t*-Bu
3c: R^1=Ph, R^2=Cyclopropyl
3d: R^1=Ph, R^2=*n*-Pentyl
3e: R^1=Isopropyl, R^2=Ph
3f: R^1=4-CH_3OPh, R^2=*t*-Bu
3g: R^1=4-CF_3Ph, R^2=*t*-Bu

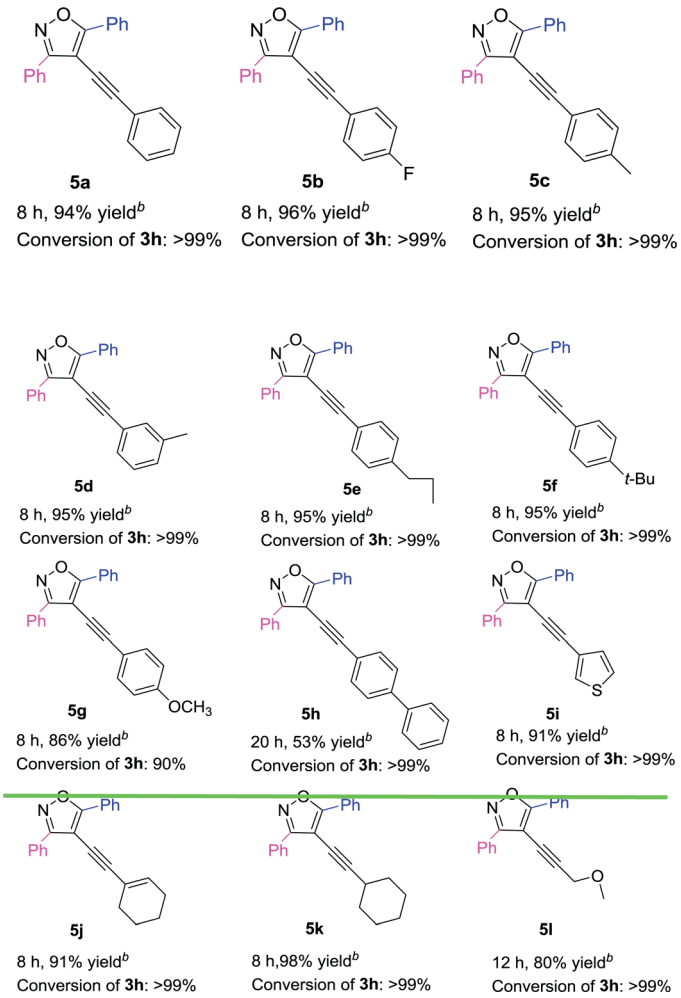


4a — 20 h, 60% yield[b]; Conversion of **3a**: 66%
4b — 20 h, 61% yield[b]; Conversion of **3a**: 68%
4c — 20 h, 63% yield[b]; Conversion of **3a**: 69%
4d — 8 h, 97% yield[b]; Conversion of **3b**: >99%
4e — 8 h, 90% yield[b]; Conversion of **3b**: >99%
4f — 8 h, 89% yield[b]; Conversion of **3b**: >99%
4g — 8 h, 96% yield[b]; Conversion of **3c**: >99%
4h — 8 h, 91% yield[b]; Conversion of **3c**: >99%
4i — 8 h, 92% yield[b]; Conversion of **3c**: >99%
4j — 8 h, 95% yield[b]; Conversion of **3d**: >99%
4k — 8 h, 92% yield[b]; Conversion of **3d**: >99%
4l — 8 h, 93% yield[b]; Conversion of **3d**: >99%
4m — 8 h, 90% yield[b]; Conversion of **3e**: >99%
4n — 8 h, 91% yield[b]; Conversion of **3e**: >99%
4o — 8 h, 93% yield[b]; Conversion of **3e**: >99%
4p — 8 h, 90% yield[b]; Conversion of **3f**: >99%
4q — 8 h, 91% yield[b]; Conversion of **3f**: >99%
4r — 8 h, 92% yield[b]; Conversion of **3f**: >99%
4s — 8 h, 97% yield[b]; Conversion of **3g**: >99%
4t — 8 h, 95% yield[b]; Conversion of **3g**: >99%
4u — 8 h, 96% yield[b]; Conversion of **3g**: >99%

[a] Reaction condition: **3** (0.3 mmol, 1 equiv.), terminal alkynes (0.6 mmol, 2 equiv.), Pd(acac) (5 mol%), PPh_3 (10 mol%), CuI (10 mol%), Et_2NH (2 equiv.), and DMF (3 mL) under N_2 protection. [b] Isolated yield.

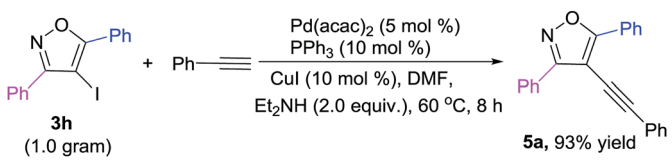
Table 4 Pd-catalyzed Sonogashira cross-coupling between 3,5-diphenyl-4-iodoisoxazole **3h** and various terminal alkynes[a]



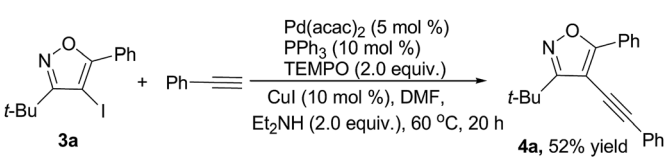


[a] Reaction condition: **3h** (0.3 mmol, 1 equiv.), terminal alkynes (0.6 mmol, 2 equiv.), $Pd(acac)_2$ (5 mol%), PPh_3 (10 mol%), CuI (10 mol%), Et_2NH (2 equiv.), and anhydrous DMF (3 mL) under N_2 protection. [b] Isolated yield.

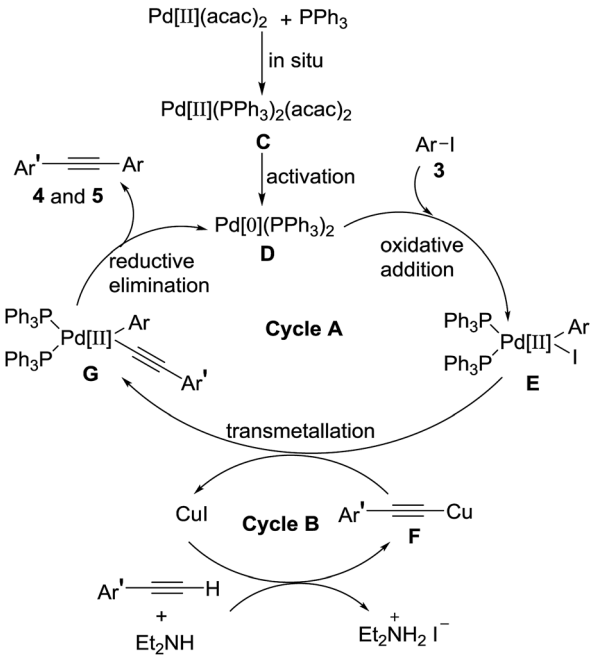
a transmetallation reaction of intermediate **E** with alkynyl copper **F** to give intermediate **G**. Reductive elimination of intermediate **G** to give the targeted product **4** and **5**. Meanwhile, the generating $Pd[0](PPh_3)_2$ **D** promoted the next catalytic cycle. In the cycle **B**, terminal alkyne reacted with Et_2NH and CuI to form alkynyl copper **F**, followed *via* transmetallation with intermediate **E** to afford intermediate **G** and regenerate CuI for the next catalytic cycle.



Scheme 2 A gram-scale reaction.



Scheme 3 The control experiment.



Scheme 4 Plausible reaction mechanism.

Conclusions

In summary, we report herein the $Pd(acac)_2/PPh_3$ complex catalyzed Sonogashira cross-coupling reaction of 3,5-disubstituted-4-iodoisoxazoles with terminal alkynes, which affords 3,5-disubstituted-4-alkynylisoxazole products in excellent yields. The effects of the groups at C3 and C5 positions of the isoxazole on the Sonogashira cross-coupling reaction were investigated. The group at C3 position of the isoxazole has great influence on the reaction due to steric effect, whereas the electric effect of the group at C3 position was negligible. Furthermore, a gram-scale reaction demonstrated potential synthetic application of this protocol.

Experimental section

General procedure (I) for the preparation of intermediate ynones (1)

Intermediates **1** were prepared according to a literature.[3d] To a 50 mL round-bottomed flask were added CuI (19 mg, 0.1 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), and triethylamine (10 mL). The flask was flushed with nitrogen atmosphere, and the terminal acetylene (5.0 mmol) was added to the stirred suspension, followed by immediately dropwise addition of acyl chloride (6.5 mmol). The resulting mixture was allowed to stir at room temperature overnight. Water (10 mL) was added to the reaction mixture to work up. The resulting mixture was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed under a vacuum, and the residue was purified by column chromatography on silica gel (200–300 mesh) using ethyl acetate/petroleum ether as the eluent to afford the desired products **1**.

4,4-Dimethyl-1-phenylpent-1-yn-3-one (1a). Prepared according to general procedure (I). Intermediate **1a** was obtained as yellow oil (753.7 mg, 81% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[13]

4,4-Dimethyl-1-phenylpent-2-yn-1-one (1b). Prepared according to general procedure (I). Intermediate **1b** was obtained as yellow oil (770.8 mg, 77% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[14]

3-Cyclopropyl-1-phenylprop-2-yn-1-one (1c). Prepared according to general procedure (I). Intermediate **1c** was obtained as yellow oil (646.4 mg, 76% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[15]

1-Phenyloct-2-yn-1-one (1d). Prepared according to general procedure (I). Intermediate **1d** was obtained as yellow oil (900.5 mg, 90% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[16]

4-Methyl-1-phenylpent-1-yn-3-one (1e). Prepared according to general procedure (I). Intermediate **1e** was obtained as yellow oil (602.3 mg, 70% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[17]

1-(4-Methoxyphenyl)-4,4-dimethylpent-2-yn-1-one (1f). Prepared according to general procedure (I). Intermediate **1f** was obtained as a yellow oil (780.9 mg, 73% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[18]

4,4-Dimethyl-1-(4-(trifluoromethyl)phenyl)pent-2-yn-1-one (1g). Prepared according to general procedure (I). Intermediate **1g** was obtained as yellow oil (889.4 mg, 70% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 1.39 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2, 139.7, 135.5, 133.7 (q, J = 31.5 Hz), 129.9, 125.8 (q, J = 3.0 Hz), 123.8 (q, J = 271.5 Hz), 105.6, 78.1, 30.2, 28.3. ^{19}F NMR (564 MHz, $CDCl_3$) δ −63.10. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{14}H_{14}F_3O$: 255.0997; found: 255.0995.

1,3-Diphenylprop-2-yn-1-one (1h). Prepared according to general procedure (I). Intermediate **1h** was obtained as yellow oil (927.3 mg, 90% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[16]

General procedure (II) for the preparation of intermediate ynone *O*-methyl oximes (2)

Intermediates **2** were prepared according to a literature procedure.[3d] To a 50 mL round-bottomed flask were added the alkynones (3.5 mmol), methoxylamine hydrochloride (7.0 mmol, 579 mg), anhydrous Na_2SO_4 (7.0 mmol, 994 mg), pyridine (1.0 mL), and anhydrous methanol (10 mL). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with water (25 mL) and extracted with ethyl acetate (3 × 25 mL). The organic layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed under a vacuum, and the residue was purified by flash column chromatography on silica gel (200–300 mesh) using ethyl acetate/petroleum ether as the eluent to afford the desired products **2**.

(*Z*)-4,4-Dimethyl-1-phenylpent-1-yn-3-one *O*-methyl oxime (2a). Prepared according to general procedure (II). Intermediate **2a** was obtained as yellow oil (617.5 mg, 82% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

(*Z*)-4,4-Dimethyl-1-phenylpent-2-yn-1-one *O*-methyl oxime (2b). Prepared according to general procedure (II). Intermediate **2b** was obtained as yellow oil (492.7 mg, 70% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

(*Z*)-3-Cyclopropyl-1-phenylprop-2-yn-1-one *O*-methyl oxime (2c). Prepared according to general procedure (II). Intermediate **2c** was obtained as a yellow oil (383.3 mg, 55% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[20]

(*Z*)-1-Phenyloct-2-yn-1-one *O*-methyl oxime (2d). Prepared according to general procedure (II). Intermediate **2d** was obtained as yellow oil (641.7 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.82 (m, 2H), 7.40–7.35 (m, 3H), 4.09 (s, 3H), 2.55 (t, J = 7.2 Hz, 2H), 1.72–1.65 (m, 2H), 1.51–1.34 (m, 4H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 134.1, 129.6, 128.4, 126.6, 104.1, 71.6, 63.1, 31.2, 28.1, 22.3, 19.9, 14.1. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1545; found: 230.1540.

(*Z*)-4-Methyl-1-phenylpent-1-yn-3-one *O*-methyl oxime (2e). Prepared according to general procedure (II). Intermediate **2e** was obtained as yellow oil (492.7 mg, 70% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[21]

(*Z*)-1-(4-Methoxyphenyl)-4,4-dimethylpent-2-yn-1-one *O*-methyl oxime (2f). Prepared according to general procedure (II). Intermediate **2f** was obtained as yellow oil (642.1 mg, 80% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.05 (s, 3H), 3.82 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.8, 139.9, 128.0, 126.9, 113.8, 111.3, 70.2, 62.8, 55.4, 30.8, 28.6. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$: 246.1494; found: 246.1488.

(*Z*)-4,4-Dimethyl-1-(4-(trifluoromethyl)phenyl)pent-2-yn-1-one *O*-methyl oxime (2g). Prepared according to general procedure (II). Intermediate **2g** was obtained as yellow oil (792.7 mg, 80% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 4.11 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1, 137.6, 131.3 (q, J = 31.5 Hz), 126.9, 125.4 (q, J = 3.0 Hz), 126.9, 124.3 (q, J = 270.0 Hz), 112.6, 69.8, 63.3, 30.8, 28.8. ^{19}F NMR (564 MHz, $CDCl_3$) δ −62.70. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{15}H_{17}F_3NO$: 284.1262; found: 284.1258.

(*Z*)-1,3-Diphenylprop-2-yn-1-one *O*-methyl oxime (2h). Prepared according to general procedure (II). Intermediate **2h** was obtained as yellow oil (501.9 mg, 61% yield). The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

General procedure (III) for iodocyclization using ICl as a catalyst (3)

To a stirred solution of the appropriate *O*-methyl oxime (3.0 mmol) in CH_2Cl_2 (30 mL), ICl (1 M in CH_2Cl_2, 1.2 equiv.) was added by dropwise, and then the solution was allowed to stir at room temperature. The reaction was monitored by TLC to establish completion. The excess ICl was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel (200–300 mesh) using ethyl acetate/petroleum ether as the eluent to afford the desired products **3**.

3-(*tert*-Butyl)-4-iodo-5-phenylisoxazole (3a). Following general procedure (III), the substrate **3a** was obtained as a colourless solid (961.4 mg, 98% yield). Mp 80–82 °C. The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

5-(*tert*-Butyl)-4-iodo-3-phenylisoxazole (3b). Following general procedure (III), the substrate **3b** was obtained as a yellow solid (971.3 mg, 99% yield). Mp 91–93 °C. The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

5-Cyclopropyl-4-iodo-3-phenylisoxazole (3c). Following general procedure (III), the substrate **3c** was obtained as a yellow solid (914.3 mg, 98% yield). Mp 73–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dt, J = 7.4, 3.2 Hz, 2H), 7.51–7.45 (m, 3H), 2.18 (dq, J = 8.4, 5.1 Hz, 1H), 1.25–1.20 (m, 2H), 1.14 (ddd, J = 11.5, 6.9, 4.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 163.1, 130.1, 128.9, 128.8, 128.7, 56.5, 9.4, 8.8. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{12}H_{11}INO$: 311.9885; found: 311.9880.

4-Iodo-5-pentyl-3-phenylisoxazole (3d). Following general procedure (III), the substrate **3d** was obtained as yellow oil (992.4 mg, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.79 (m, 2H), 7.49–7.44 (m, 3H), 2.91–2.83 (m, 2H), 1.82–1.72 (m, 2H), 1.39 (td, J = 7.2, 3.6 Hz, 4H), 0.98–0.89 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 162.6, 129.9, 128.9, 128.6, 128.5, 57.3, 31.2, 27.1, 26.9, 22.3, 13.9. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{14}H_{17}INO$: 342.0355; found: 342.0341.

4-Iodo-3-isopropyl-5-phenylisoxazole (3e). Following general procedure (III), the substrate **3e** was obtained as a white solid (901.5 mg, 96% yield). Mp 70–72 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (dd, J = 5.2, 2.8 Hz, 2H), 7.52–7.46 (m, 3H), 3.05 (dt, J = 13.9, 6.9 Hz, 1H), 1.40 (d, J = 7.0 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 167.6, 130.6, 128.8, 127.7, 127.5, 56.8, 28.1, 20.9. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{12}H_{12}INO$: 314.0042; found: 314.0040.

5-(*tert*-Butyl)-4-iodo-3-(4-methoxyphenyl)isoxazole (3f). Following general procedure (III), the substrate **3f** was obtained as a yellow solid (1017.6 mg, 95% yield). Mp 75–77 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66–7.61 (m, 2H), 7.02–6.98 (m, 2H), 3.85 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.8, 164.5, 160.9, 130.6, 121.4, 114.1, 55.4, 34.5, 28.4. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{14}H_{17}INO$: 358.0304; found: 358.0304.

5-(*tert*-Butyl)-4-iodo-3-(4-(trifluoromethyl)phenyl)isoxazole (3g). Following general procedure (III), the substrate **3g** was obtained as a yellow solid (1019.1 mg, 86% yield). Mp 99–101 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 1.55 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2, 132.9, 131.9 (q, J = 31.5 Hz), 129.8, 125.6 (q, J = 4.5 Hz), 126.9, 124.1 (q, J = 271.5 Hz), 53.4, 34.7, 28.5. ^{19}F NMR (564 MHz, $CDCl_3$) δ −62.80. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{14}H_{14}F_3INO$: 396.0072; found: 396.0070.

4-Iodo-3,5-diphenylisoxazole (3h). Following general procedure (III), the substrate **3h** was obtained as a colourless solid (739.1 mg, 71% yield). Mp 176–178 °C. The ^{1}H NMR spectral data are in good agreement with the literature data.[22]

General procedure (IV) for the synthesis of C4-alkynyl isoxazoles (4 or 5)

A 10 mL two-neck round-bottomed flask with a reflux condenser was flame-dried under a stream of nitrogen and cooled to room temperature. **3** (0.3 mmol, 1.0 equiv.), $Pd(acac)_2$ (4.7 mg,

5 mol%), PPh_3 (7.9 mg, 10 mol%), CuI (5.8 mg, 10 mol%), and Et_2NH (43.9 mg, 2 equiv.) were added, followed by the addition of anhydrous DMF (2.5 mL). The flask was flushed with nitrogen and the terminal acetylene (1.0 M in DMF, 2.0 equiv.) was added gradually by a syringe. The resulting solution was allowed to stir at 60 °C until completion as monitored by thin layer chromatography. After cooling to room temperature, the reaction was poured into 10 mL ethyl acetate and washed three times (3 × 10 mL) with water. The organic layers were combined, dried with anhydrous $MgSO_4$, and then filtered. The filtrate was concentrated in vacuum, and the resulting residue was purified on silica gel column (200–300 mesh) using ethyl acetate/petroleum ether as eluent to afford the desired products **4** or **5**.

3-(*tert*-Butyl)-5-phenyl-4-(phenylethynyl)isoxazole (4a). Following general procedure (IV), the product **4a** was obtained as yellow oil (54.2 mg, 60% yield). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.14–8.11 (m, 2H), 7.60 (dddd, J = 6.3, 5.7, 3.3, 1.7 Hz, 5H), 7.49–7.46 (m, 3H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 170.7, 169.0, 131.2, 130.9, 129.3, 129.0, 126.5, 125.9, 121.7, 96.8, 96.2, 79.4, 33.0, 27.8. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{21}H_{20}NO$: 302.1545; found: 302.1542.

3-(*tert*-Butyl)-4-((4-fluorophenyl)ethynyl)-5-phenylisoxazole (4b). Following general procedure (IV), the product **4b** was obtained as a white solid (58.4 mg, 61% yield). Mp 81–83 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 7.5 Hz, 2H), 7.50 (dt, J = 15.9, 7.1 Hz, 5H), 7.09 (t, J = 8.5 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 169.8, 163.9, 161.9, 133.3, 133.2, 130.7, 129.0, 127.7, 126.5, 119.3, 119.2, 116.2, 116.1, 96.9, 96.0, 80.2, 33.6, 28.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ −109.90. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{21}H_{19}FNO$: 320.1451; found: 320.1443.

3-(*tert*-Butyl)-5-phenyl-4-(*p*-tolylethynyl)isoxazole (4c). Following general procedure (IV), the product **4c** was obtained as a white solid (59.6 mg, 63% yield). Mp 77–79 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, J = 8.1, 0.8 Hz, 2H), 7.52–7.42 (m, 5H), 7.21 (d, J = 7.9 Hz, 2H), 2.40 (s, 3H), 1.56 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 169.5, 139.2, 131.3, 130.6, 129.5, 128.9, 127.8, 126.5, 120.1, 97.4, 97.3, 79.8, 33.6, 28.4, 21.8. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{22}H_{22}NO$: 316.1701; found: 316.1694.

5-(*tert*-Butyl)-3-phenyl-4-(phenylethynyl)isoxazole (4d). Following general procedure (IV), the product **4d** was obtained as a white solid (87.6 mg, 97% yield). Mp 58–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 6.5, 3.1 Hz, 2H), 7.51–7.45 (m, 5H), 7.39–7.33 (m, 3H), 1.58 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2, 162.3, 131.1, 130.1, 128.9, 128.8, 128.7, 128.6, 128.0, 123.2, 96.8, 95.9, 79.6, 34.8, 28.5. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{21}H_{20}NO$: 302.1545; found: 302.1539.

5-(*tert*-Butyl)-4-((4-fluorophenyl)ethynyl)-3-phenylisoxazole (4e). Following general procedure (IV), the product **4e** was obtained as yellow oil (86.2 mg, 90% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06–8.01 (m, 2H), 7.48 (d, J = 4.0 Hz, 3H), 7.43 (dd, J = 8.1, 5.7 Hz, 2H), 7.05 (t, J = 8.5 Hz, 2H), 1.56 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.2, 163.6, 162.4, 162.0, 133.1, 133.0, 132.7, 130.2, 129.4, 128.9, 128.7, 128.6, 128.0, 119.4, 119.3, 116.0, 115.9, 96.6, 94.8, 79.3, 34.8, 28.5. ^{19}F NMR (564 MHz, $CDCl_3$) δ −110.30. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{21}H_{19}FNO$: 320.1451; found: 320.1449.

5-(*tert*-Butyl)-3-phenyl-4-(*p*-tolylethynyl)isoxazole (4f). Following general procedure (IV), the product **4f** was obtained as a white solid (84.2 mg, 89% yield). Mp 81–83 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09–8.04 (m, 2H), 7.49–7.47 (m, 3H), 7.36 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 2.38 (s, 3H), 1.56 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.0, 162.3, 138.9, 132.7, 131.1, 130.1, 129.4, 129.0, 128.7, 128.6, 128.0, 120.2, 96.9, 96.1, 78.9, 34.8, 28.5, 21.7. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{22}H_{22}NO$: 316.1701; found: 316.1694.

5-Cyclopropyl-3-phenyl-4-(phenylethynyl)isoxazole (4g). Following general procedure (IV), the product **4g** was obtained as yellow oil (82.1 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dt, J = 9.3, 2.8 Hz, 2H), 7.55–7.43 (m, 4H), 7.32 (dd, J = 5.0, 3.0 Hz, 1H), 7.18 (dd, J = 5.0, 1.0 Hz, 1H), 2.37–2.27 (m, 1H), 1.38–1.32 (m, 2H), 1.21–1.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 161.6, 131.4, 130.2, 128.9, 128.8, 128.7, 128.6, 127.8, 123.1, 97.5, 94.8, 78.6, 9.0, 8.9. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{21}H_{18}NO$: 300.1388; found: 300.1386.

5-Cyclopropyl-4-((4-fluorophenyl)ethynyl)-3-phenylisoxazole (4h). Following general procedure (IV), the product **4h** was obtained as a yellow solid (82.8 mg, 91% yield). Mp 85–87 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11–8.03 (m, 2H), 7.48 (dd, J = 7.4, 6.0 Hz, 5H), 7.06 (t, J = 8.5 Hz, 2H), 2.37–2.27 (m, 1H), 1.40–1.34 (m, 2H), 1.22–1.15 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 163.8, 161.8, 161.6, 133.4, 133.3, 130.2, 128.8, 128.7, 127.8, 119.3, 119.2, 116.0, 115.8, 97.4, 93.7, 78.3, 9.0, 8.9. ^{19}F NMR (564 MHz, $CDCl_3$) δ −109.90, −109.91. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{20}H_{15}FNO$: 304.1138; found: 304.1130.

5-Cyclopropyl-3-phenyl-4-(*p*-tolylethynyl)isoxazole (4i). Following general procedure (IV), the product **4i** was obtained as yellow oil (82.6 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.06 (m, 2H), 7.53–7.45 (m, 3H), 7.41 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 2.39 (s, 3H), 1.40–1.34 (m, 2H), 1.23–1.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 161.5, 138.9, 131.3, 130.2, 129.3, 128.8, 128.7, 127.7, 120.0, 97.6, 94.9, 77.8, 21.7, 8.9, 8.8. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{21}H_{18}NO$: 300.1388; found: 300.1386.

5-Pentyl-3-phenyl-4-(phenylethynyl)isoxazole (4j). Following general procedure (IV), the product **4j** was obtained as yellow oil (89.9 mg, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14–8.06 (m, 2H), 7.52–7.45 (m, 5H), 7.10–7.03 (m, 2H), 2.96 (t, J = 7.5 Hz, 2H), 1.86 (p, J = 7.3 Hz, 2H), 1.41 (dd, J = 7.2, 3.6 Hz, 4H), 0.93 (t, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 163.8, 161.8, 161.3, 133.5, 133.4, 130.2, 128.8, 127.7, 119.1, 116.1, 115.9, 98.7, 93.9, 78.3, 31.3, 26.9, 26.7, 22.4, 14.1. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{22}H_{22}NO$: 316.1701; found: 316.1690.

4-((4-Fluorophenyl)ethynyl)-5-pentyl-3-phenylisoxazole (4k). Following general procedure (IV), the product **4k** was obtained as yellow oil (91.9 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (td, J = 4.2, 2.5 Hz, 2H), 7.51–7.48 (m, 4H), 7.37 (dd, J = 4.2, 2.3 Hz, 3H), 3.01–2.91 (m, 2H), 1.87 (p, J = 7.3 Hz, 2H), 1.42 (dd, J = 4.2, 3.1 Hz, 4H), 0.94 (dt, J = 7.0, 3.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 161.3, 131.5, 130.2, 128.9, 128.8, 128.7, 128.6, 127.8, 123.1, 98.9, 95.0, 78.6, 31.4, 27.0, 26.7, 22.4, 14.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ −110.30. HRMS (ESI-ion trap): m/z [M + H]$^+$ calcd for $C_{22}H_{21}FNO$: 334.1607; found: 334.1599.

5-Pentyl-3-phenyl-4-(*p*-tolylethynyl)isoxazole (4l). Following general procedure (IV), the product **4l** was obtained as yellow oil (91.9 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18–8.11 (m, 2H), 7.53–7.46 (m, 3H), 7.42 (d, J = 8.0 Hz, 2H), 7.19 (d, J =

7.9 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.39 (s, 3H), 1.86 (dd, J = 14.7, 7.3 Hz, 2H), 1.46–1.39 (m, 4H), 0.95 (dd, J = 10.0, 4.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 161.2, 138.9, 131.4, 130.1, 129.3, 128.9, 128.7, 127.7, 120.0, 99.0, 95.2, 77.8, 31.3, 26.9, 26.6, 22.4, 21.6, 14.0. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{23}H_{24}NO$: 330.1858; found: 330.1852.

3-Isopropyl-5-phenyl-4-(phenylethynyl)isoxazole (4m). Following general procedure (IV), the product **4m** was obtained as yellow oil (77.6 mg, 90% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23–8.18 (m, 2H), 7.57–7.55 (m, 2H), 7.53–7.46 (m, 3H), 7.42–7.38 (m, 3H), 3.27 (dt, J = 14.0, 7.0 Hz, 1H), 1.49 (d, J = 7.0 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 168.8, 131.5, 130.7, 129.0, 128.9, 128.7, 127.6, 126.4, 123.0, 97.6, 96.6, 79.2, 27.1, 20.7. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{20}H_{18}NO$: 288.1388; found: 288.1385.

4-((4-Fluorophenyl)ethynyl)-3-isopropyl-5-phenylisoxazole (4n). Following general procedure (IV), the product **4n** was obtained as yellow oil (83.3 mg, 91% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20–8.14 (m, 2H), 7.54–7.47 (m, 5H), 7.12–7.06 (m, 2H), 3.25 (dt, J = 14.0, 7.0 Hz, 1H), 1.48 (d, J = 7.0 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 168.9, 163.7, 162.1, 133.5, 133.4, 130.7, 130.6, 129.0, 128.8, 127.6, 127.5, 126.4, 119.2, 119.1, 116.1, 116.0, 97.5, 95.4, 78.9, 27.1, 20.9, 20.6. ^{19}F NMR (564 MHz, $CDCl_3$) δ −109.90. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{20}H_{17}FNO$: 306.1294; found: 306.1288.

3-Isopropyl-5-phenyl-4-(*p*-tolylethynyl)isoxazole (4o). Following general procedure (IV), the product **4o** was obtained as yellow oil (84.1 mg, 93% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26–8.17 (m, 2H), 7.52–7.44 (m, 5H), 7.21 (d, J = 7.9 Hz, 2H), 3.27 (dt, J = 13.9, 7.0 Hz, 1H), 2.40 (s, 3H), 1.49 (dd, J = 7.0, 1.7 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 168.6, 139.1, 131.4, 130.6, 129.4, 128.9, 127.68, 126.4, 119.9, 97.8, 96.8, 78.5, 27.1, 21.7, 20.6. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{21}H_{20}NO$: 302.1545; found: 302.1539.

5-(*tert*-Butyl)-3-(4-methoxyphenyl)-4-(phenylethynyl)isoxazole (4p). Following general procedure (IV), the product **4p** was obtained as yellow oil (89.4 mg, 90% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 8.8 Hz, 2H), 7.49–7.45 (m, 2H), 7.36 (dd, J = 5.1, 1.9 Hz, 3H), 7.01 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 1.56 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.1, 161.9, 161.1, 131.1, 129.4, 128.6, 123.3, 121.4, 114.1, 96.5, 95.8, 79.9, 55.5, 34.8, 28.4. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{22}H_{22}NO_2$: 332.1651; found: 332.1647.

5-(*tert*-Butyl)-4-((4-fluorophenyl)ethynyl)-3-(4-methoxyphenyl) isoxazole (4q). Following general procedure (IV), the product **4q** was obtained as yellow oil (95.3 mg, 91% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, J = 8.7 Hz, 2H), 7.47–7.41 (m, 2H), 7.06 (t, J = 8.6 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 3.86 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.1, 163.6, 161.9, 161.1, 133.1, 133.0, 129.3, 121.3, 119.4, 119.3, 116.0, 115.9, 114.1, 96.3, 94.7, 79.6, 55.5, 34.8, 28.4. ^{19}F NMR (564 MHz, $CDCl_3$) δ −110.34, −110.35, −110.36, −110.37, −110.38, −110.39, −110.40. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{22}H_{22}FNO_2$: 350.1556; found: 350.1552.

5-(*tert*-Butyl)-3-(4-methoxyphenyl)-4-(*p*-tolylethynyl)isoxazole (4r). Following general procedure (IV), the product **4r** was obtained as yellow oil (95.3 mg, 92% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07–8.01 (m, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.01–6.98 (m, 2H), 3.86 (s, 3H), 2.38 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.8, 161.9, 161.1, 138.8, 131.1, 129.5, 129.4, 121.5, 120.2, 114.1, 96.6, 95.9, 79.2, 55.5, 34.7, 28.4, 21.7. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{23}H_{24}NO_2$: 346.1807; found: 346.1798.

5-(*tert*-Butyl)-4-(phenylethynyl)-3-(4-(trifluoromethyl)phenyl) isoxazole (4s). Following general procedure (IV), the product **4s** was obtained as yellow oil (107.5 mg, 97% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.51–7.45 (m, 2H), 7.41–7.34 (m, 3H), 1.58 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.8, 161.1, 132.5, 132.1, 131.8, 131.2, 129.7, 129.0, 128.7, 128.3, 125.7 (q, J = 4.5 Hz), 125.1, 123.2, 122.9, 96.9, 96.4, 78.9, 34.9, 28.5. ^{19}F NMR (564 MHz, $CDCl_3$) δ −62.80. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{22}H_{19}F_3NO$: 370.1419; found: 370.1416.

5-(*tert*-Butyl)-4-((4-fluorophenyl)ethynyl)-3-(4-(trifluoromethyl) phenyl)isoxazole (4t). Following general procedure (IV), the product **4t** was obtained as a yellow solid (110.4 mg, 95% yield). Mp 77–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.44 (dd, J = 8.7, 5.4 Hz, 2H), 7.07 (t, J = 8.6 Hz, 2H), 1.57 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.8, 163.8, 162.2, 161.1, 133.2, 133.1, 132.4, 132.1, 131.9, 128.3, 127.2, 125.7 (q, J = 3 Hz), 125.1, 123.2, 119.0, 118.9, 116.2, 116.0, 96.7, 95.3, 78.7, 34.9, 29.0, 28.4. ^{19}F NMR (564 MHz, $CDCl_3$) δ −62.80, −109.80. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{22}H_{19}F_4NO$: 388.1325; found: 388.1319.

5-(*tert*-Butyl)-4-(*p*-tolylethynyl)-3-(4-(trifluoromethyl)phenyl) isoxazole (4u). Following general procedure (IV), the product **4u** was obtained as a yellow solid (111.4 mg, 97% yield). Mp 83–85 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 2.39 (s, 3H), 1.58 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.5, 161.1, 139.2, 132.5, 132.2, 132.0, 131.8, 131.6, 131.1, 129.5, 128.3, 126.8, 125.7 (q, J = 3 Hz), 123.2, 121.4, 119.8, 97.1, 96.6, 78.3, 34.9, 28.4, 21.7. ^{19}F NMR (564 MHz, $CDCl_3$) δ −62.80. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{23}H_{21}F_3NO$: 384.1575; found: 384.1571.

3,5-Diphenyl-4-(phenylethynyl)isoxazole (5a). Following general procedure (IV), the product **5a** was obtained as a yellow solid (90.6 mg, 94% yield). Mp 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, J = 8.1, 1.4 Hz, 2H), 8.21–8.14 (m, 2H), 7.61–7.51 (m, 8H), 7.41 (dd, J = 6.4, 2.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 162.6, 131.5, 130.9, 130.4, 129.1, 129.0, 128.8, 128.7, 128.6, 128.0, 127.4, 126.5, 122.8, 97.5, 96.6, 79.9. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{23}H_{16}NO$: 322.1232; found: 322.1229.

4-((4-Fluorophenyl)ethynyl)-3,5-diphenylisoxazole (5b). Following general procedure (IV), the product **5b** was obtained as a white solid (96.6 mg, 96% yield). Mp 100–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 7.3 Hz, 2H), 8.17–8.11 (m, 2H), 7.56–7.49 (m, 8H), 7.09 (t, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 163.9, 162.7, 162.0, 133.5, 133.4, 130.9, 130.4, 129.1, 128.8, 128.6, 128.0, 127.5, 126.6, 119.0, 118.9, 116.2, 116.0, 97.3, 95.5, 79.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ −109.62. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{23}H_{15}FNO$: 340.1138; found: 340.1130.

3,5-Diphenyl-4-(*p*-tolylethynyl)isoxazole (5c). Following general procedure (IV), the product **5c** was obtained as a white solid (95.5 mg, 95% yield). Mp 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.31 (d, J = 6.9 Hz, 2H), 8.23–8.15 (m, 2H), 7.58–7.43 (m, 8H), 7.22 (d, J = 7.9 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 162.6, 139.2, 131.4, 130.8, 130.3, 129.4, 129.0, 128.8, 128.7, 128.0, 127.5, 126.5, 119.8, 97.6, 96.8, 79.2, 21.7. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{24}H_{18}NO$: 336.1388; found: 336.1382.

3,5-Diphenyl-4-(*m*-tolylethynyl)isoxazole (5d). Following general procedure (IV), the product **5d** was obtained as a yellow solid (92.5 mg, 92% yield). Mp 95–97 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J = 7.5 Hz, 2H), 8.22–8.12 (m, 2H), 7.57–7.51 (m, 6H), 7.36 (d, J = 5.9 Hz, 2H), 7.29 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 162.7, 138.5, 132.1, 130.9, 130.4, 129.9, 129.1, 128.8, 128.7, 128.6, 128.1, 127.5, 126.6, 122.7, 97.6, 96.9, 79.5, 21.5. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{24}H_{18}NO$: 336.1388; found: 336.1381.

3,5-Diphenyl-4-((4-propylphenyl)ethynyl)isoxazole (5e). Following general procedure (IV), the product **5e** was obtained as a yellow solid (102.4 mg, 94% yield). Mp 97–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 6.8 Hz, 2H), 8.19 (dd, J = 6.4, 2.8 Hz, 2H), 7.53 (ddd, J = 25.3, 12.3, 7.4 Hz, 8H), 7.22 (d, J = 8.0 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 1.68 (dd, J = 15.0, 7.5 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 162.6, 144.0, 131.4, 130.8, 130.3, 129.0, 128.9, 128.8, 128.7, 128.0, 127.5, 126.5, 120.1, 97.7, 96.9, 79.2, 38.1, 24.5, 13.9. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{26}H_{22}NO$: 364.1701; found: 364.1690.

4-((4-(*tert*-Butyl)phenyl)ethynyl)-3,5-diphenylisoxazole (5f). Following general procedure (IV), the product **5f** was obtained as a yellow solid (105.3 mg, 93% yield). Mp 115–117 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J = 7.8 Hz, 2H), 8.17 (d, J = 7.6 Hz, 2H), 7.52 (dd, J = 14.2, 7.5 Hz, 8H), 7.43 (d, J = 8.2 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 162.7, 152.5, 131.4, 130.9, 130.8, 130.4, 130.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.1, 127.9, 127.6, 126.6, 125.8, 119.9, 97.7, 96.9, 79.2, 35.1, 31.4. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{27}H_{24}NO$: 378.1858; found: 378.1849.

4-((4-Methoxyphenyl)ethynyl)-3,5-diphenylisoxazole (5g). Following general procedure (IV), the product **5g** was obtained as a white solid (90.6 mg, 89% yield). Mp 114–116 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32–8.26 (m, 2H), 8.21–8.13 (m, 2H), 7.56–7.45 (m, 8H), 6.92 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 162.6, 160.2, 133.1, 130.8, 130.4, 129.1, 128.9, 128.8, 128.1, 127.6, 126.5, 115.1, 114.4, 97.8, 96.7, 78.6, 55.6. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{22}H_{19}F_4NO$: 352.1338; found: 352.1334.

4-([1,1′-Biphenyl]-4-ylethynyl)-3,5-diphenylisoxazole (5h). Following general procedure (IV), the product **5h** was obtained as a white solid (59.6 mg, 50% yield). Mp 120–122 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33–8.29 (m, 2H), 8.18 (dd, J = 7.7, 1.8 Hz, 2H), 7.65–7.60 (m, 6H), 7.55 (qdd, J = 6.6, 4.2, 2.2 Hz, 6H), 7.48 (dd, J = 10.5, 4.9 Hz, 2H), 7.41–7.38 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 162.7, 141.8, 140.3, 132.1, 131.0, 130.4, 129.2, 129.1, 128.9, 128.7, 128.1, 128.0, 127.5, 127.4, 127.2, 126.6, 121.7, 97.6, 96.5, 80.6. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{29}H_{20}NO$: 398.1545; found: 398.1540.

3,5-Diphenyl-4-(thiophen-3-ylethynyl)isoxazole (5i). Following general procedure (IV), the product **5i** was obtained as a white solid (89.3 mg, 91% yield). Mp 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 7.9, 1.4 Hz, 2H), 8.15 (dd, J = 6.6, 3.1 Hz, 2H), 7.60–7.48 (m, 7H), 7.36 (dd, J = 4.9, 3.0 Hz, 1H), 7.23 (dd, J = 5.0, 0.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 162.7, 130.9, 130.3, 129.7, 129.3, 129.2, 129.1, 128.9, 128.6, 128.0, 127.4, 126.9, 126.5, 125.9, 121.8, 97.4, 91.9, 79.3. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{21}H_{14}NOS$: 328.0796; found: 328.0790.

4-(Cyclohex-1-en-1-ylethynyl)-3,5-diphenylisoxazole (5j). Following general procedure (IV), the product **5j** was obtained as yellow oil (88.8 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27–8.20 (m, 2H), 8.12 (dd, J = 6.2, 2.7 Hz, 2H), 7.56–7.44 (m, 6H), 6.28–6.21 (m, 1H), 2.30–2.24 (m, 2H), 2.21–2.15 (m, 2H), 1.74–1.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 162.5, 136.1, 130.6, 130.2, 128.9, 128.8, 128.7, 127.9, 127.6, 126.4, 120.7, 98.7, 97.9, 28.8, 25.9, 22.3, 21.6. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{23}H_{20}NO$: 326.1545; found: 326.1540.

4-(Cyclohexylethynyl)-3,5-diphenylisoxazole (5k). Following general procedure (IV), the product **5k** was obtained as a white solid (96.2 mg, 98% yield). Mp 97–99 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27–8.23 (m, 2H), 8.12 (dd, J = 6.6, 3.0 Hz, 2H), 7.50 (dd, J = 8.2, 5.1 Hz, 5H), 2.83–2.63 (m, 1H), 1.97–1.90 (m, 2H), 1.78 (dt, J = 12.8, 5.2 Hz, 2H), 1.65–1.57 (m, 3H), 1.45–1.37 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 162.7, 130.6, 130.2, 129.1, 128.8, 128.6, 127.9, 127.7, 126.3, 102.2, 98.0, 71.0, 32.4, 30.2, 26.0, 24.9. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{23}H_{22}NO$: 328.1701; found: 328.1696.

4-(3-Methoxyprop-1-yn-1-yl)-3,5-diphenylisoxazole (5l). Following general procedure (IV), the product **5l** was obtained as a white solid (69.4 mg, 80% yield). Mp 68–70 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (dd, J = 7.9, 1.5 Hz, 2H), 8.09–8.03 (m, 2H), 7.56–7.46 (m, 6H), 4.41 (s, 2H), 3.46 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 162.9, 131.1, 130.4, 129.1, 128.8, 128.5, 128.1, 127.3, 126.6, 96.8, 92.8, 76.9, 60.7, 58.1. HRMS (ESI-ion trap): m/z $[M + H]^+$ calcd for $C_{19}H_{16}NO_2$: 290.1181; found: 290.1180.

Conflicts of interest

There are no conflicts to declare.

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