Transition-Metal-Free Heterocyclization of 1,3-Diynes with Nitriles in the Presence of Aqueous Potassium Hydroxide: Synthesis of 2,4-Disubstituted 5-[(*E*)-2-Phenylethenyl]-1,3-oxazoles

Ling Ming, Jialiang Tang, Xiaoming Zhao*

Department of Chemistry, State Key Laboratory of Pollution Control and Resource Reuse, Tongji University, Siping Road 1239, Shanghai 200092, P. R. of China
Fax +86(21)65981376; E-mail: xmzhao08@mail.tongji.edu.cn
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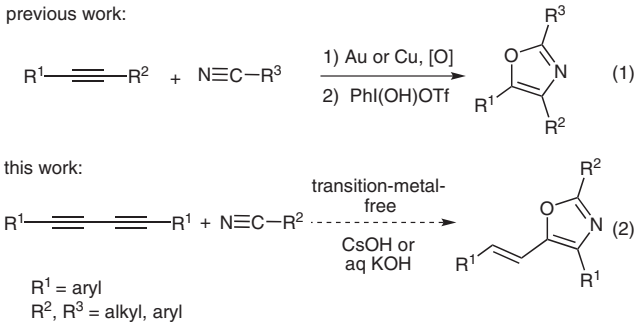
Abstract: A transition-metal-free heterocyclization of 1,3-diynes and nitriles in the presence of either aqueous potassium hydroxide or cesium hydroxide in 1,4-dioxane at 100 °C was realized. This method provided stereoselectively 2,4-disubstituted 5-[(*E*)-2-phenylethenyl]-1,3-oxazoles in moderate to good yields.

Key words: 1,3-diyne, nitrile, heterocyclization, cesium hydroxide, potassium hydroxide

Oxazole compounds are of great importance with regard to their uses as synthetic intermediates[1] and in pharmaceutical industry.[2] In addition, oxazole fragment can be found in some naturally occurring compounds.[3] Oxazole derivatives[4] are generally synthesized via four methods: 1) intramolecular cyclization of acyclic precursors;[5] 2) oxidative coupling reaction of amines and prefunctionalized aldehydes or ketones;[6] 3) oxidation of oxazolines;[7] and 4) other methods.[8] Heterocyclization (e.g., N,[9] O,[10] and S[11]) derived from various 1,3-diynes has received considerable attention during recent years.

Recently, gold(I)- and copper-catalyzed heterocyclization of alkynes and nitriles were disclosed.[12] In 2013, iodine(III)-mediated [2+2+1] annulation of alkynes, nitriles, and oxygen atoms was reported by Saito (Scheme 1, equation 1).[13] However, metal-free annulation of 1,3-diynes and nitriles with an alkali metal hydroxide in the absence of oxidant is not yet reported (Scheme 1, equation 2). In connection with our investigation on heterocyclization of 1,3-diynes,[14] we herein report the transition-metal-free heterocyclization of 1,3-diynes and nitriles in the presence of aqueous KOH or CsOH, which stereoselectively gives 2,4-disubstituted 5-[(*E*)-2-phenylethenyl]-1,3-oxazoles.

We began the investigation with a reaction of 1,4-diphenylbuta-1,3-diyne (**1a**), MeCN (**2a**), and KOH (**3a**) in the presence of water at 80 °C. Unexpectedly and interestingly, the formation of 2-methyl-4-phenyl-5-[(*E*)-2-phenylethenyl]-1,3-oxazole (**4a**) [(*E*)-2-methyl-4-phenyl-5-styryloxazole], which is both the oxidation and reduction product, was observed after the completion of this reaction by TLC monitoring (Table 1, entry 1). In this case, no *Z*-isomer of **4a** was observed. After examining various other alkali metal hydroxides, $CsOH·H_2O$ (**3b**) was found to give 34% yield of **4a** (Table 1, entry 2), and that NaOH (**3c**) and LiOH (**3d**) both led to only a trace amount of **4a** (Table 1, entries 3 and 4). KOH (**3a**) is cheaper than $CsOH·H_2O$ (**3b**), therefore, KOH (**3a**) was chosen for this investigation.



Scheme 1 Oxazoles are synthesized from alkynes and nitriles

The ratio of 1,3-diyne **1a**/KOH (**3a**) had a considerable impact on the results (Table 1, entries 1, 5, 6). Notably, MeCN (**2a**) served as not only reactant but also as solvent in these cases (entries 1–6). The reaction was carried out in a variety of solvents such as DMSO, toluene, 1,2-dichloroethane (DCE), and 1,4-dioxane. 1,4-Dioxane was the most effective medium for this cyclization, whereas other solvents were ineffective (entries 7–10). Variation of the reaction temperatures had a significant influence on the outcome of this reaction (entries 10–12). It was found that water plays an important role in this reaction (entries 11, 13–15). These results revealed that five equivalents of water were suitable, which gave an 80% yield of **4a**. In contrast, the reaction conducted in the absence of water gave only 10% yield of **4a** (entry 11 vs. entry 13). When this reaction was performed under argon, 78% yield of **4a** was obtained (entry 16). These results suggest that this reaction could proceed also in the absence of oxygen. Furthermore, no reaction occurred when 1,4-diphenylbuta-1,3-diyne (**1a**) was replaced with 1,2-diphenylethyne[12,13] under the optimized conditions presented in entry 17, since this reaction may require two triple bonds to be involved in the cyclization process.

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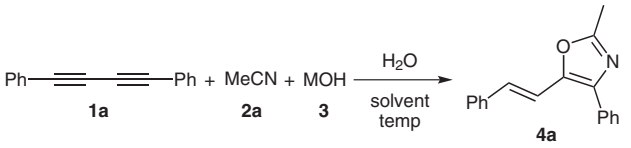
Table 1 Optimization for a Heterocyclization of 1,4-Diphenylbuta-1,3-diyne (**1a**) with Acetonitrile (**2a**) in the Presence of MOH **3**[a]



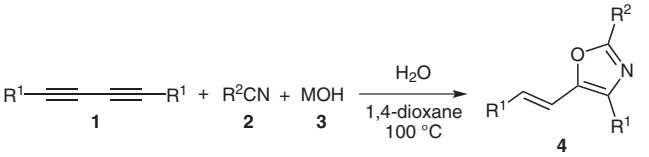
1a 2a 3 4a

Entry	MOH	H_2O (equiv)	Solvent	**1a**/**3**	Temp (°C)	Yield of **4a** (%)[b]
1	KOH	5.0	MeCN	1:10	80	41
2	$CsOH·H_2O$	–[c]	MeCN	1:10	80	34
3	NaOH	5.0	MeCN	1:10	80	trace
4	LiOH	5.0	MeCN	1:10	80	trace
5	KOH	5.0	MeCN	1:8	80	37
6	KOH	5.0	MeCN	1:5	80	33
7	KOH	5.0	DMSO	1:10	80	trace
8	KOH	5.0	toluene	1:10	80	trace
9	KOH	5.0	DCE	1:10	80	N.R.[d]
10	KOH	5.0	1,4-dioxane	1:10	80	53
11	KOH	5.0	1,4-dioxane	1:10	100	80
12	KOH	5.0	1,4-dioxane	1:10	120	43
13	KOH	–	1,4-dioxane	1:10	100	10
14	KOH	3.0	1,4-dioxane	1:10	100	52
15	KOH	10.0	1,4-dioxane	1:10	100	32
16[e]	KOH	5.0	1,4-dioxane	1:10	100	78
17[f]	KOH	5.0	1,4-dioxane	1:10	100	N.R.

[a] Reaction conditions: 1,4-diphenylbuta-1,3-diyne (**1a**; 0.2 mmol), MeCN (**2a**; 0.5 mL), and base (1.0–2.0 mmol) in solvent (1.5 mL) in a sealed tube.
[b] Isolated yield.
[c] Without the addition of H_2O.
[d] N.R. = No reaction.
[e] Under argon.
[f] 1,4-Diphenylbuta-1,3-diyne (**1a**) was replaced with 1,2-diphenylethyne in this case.

Using the optimized reaction conditions, the scope of symmetrical 1,3-diynes, nitriles, and alkali metal hydroxides was examined (Table 2). The heterocyclization of MeCN (**2a**), aqueous KOH (**3a**), and 1,3-diynes **1** containing phenyl or electron-donating (e.g., 4-Me) or electron-withdrawing groups (e.g., 4-F, 4-Cl, and 4-Br) on the phenyl ring occurred and they provided the corresponding oxazoles **4a**–**e** in fair to good yields (Table 2, entries 1–5). Moreover, the heterocyclization of 1,3-diynes **1**, $CsOH·H_2O$ (**3b**), and aryl- and alkyl-substituted nitriles **2** proceeded smoothly to afford the corresponding oxazoles **4f**–**q** in moderate to good yields (entries 6–17). Notably, the *Z*-isomers were not detected in these cases. A 5-fold excess of $CsOH·H_2O$ gave a superior result, which is similar to that of using 10-fold KOH. The reason for this is unclear, which is still under investigation. With respect to the benzonitrile substituent, the reaction showed broad substrate tolerance. Electron-rich benzonitriles gave better yields than the electron-deficient benzonitrile (entry 15 vs entry 17). Aryl halides were tolerated, enabling useful transformations through metal-catalyzed cross-coupling techniques (entries 4, 5, 16, and 17). The variety of functional groups on these oxazoles provides a great opportunity for further functionalization. Additionally, aliphatic 1,3-diynes such as tetradeca-6,8-diyne failed to afford the corresponding products under the optimized conditions.

Table 2 Scope of 1,3-Diynes, Nitriles, and MOH[a]



1 2 3 4

Entry	R^1	R^2	MOH	Yield of **4** (%)[b]
1	Ph	Me	KOH	**4a**, 80
2	4-MeC_6H_4	Me	KOH	**4b**, 73
3	4-FC_6H_4	Me	KOH	**4c**, 60
4	4-ClC_6H_4	Me	KOH	**4d**, 55
5	4-BrC_6H_4	Me	KOH	**4e**, 52
6[c]	4-$C_5H_{11}C_6H_4$	Me	$CsOH·H_2O$	**4f**, 80
7	4-$MeOC_6H_4$	Me	$CsOH·H_2O$	**4g**, 84
8	3-MeC_6H_4	Me	$CsOH·H_2O$	**4h**, 77
9	Ph	*n*-Bu	$CsOH·H_2O$	**4i**, 55
10	4-MeC_6H_4	*n*-Bu	$CsOH·H_2O$	**4j**, 67
11	4-$MeOC_6H_4$	*n*-Bu	$CsOH·H_2O$	**4k**, 71
12	Ph	Ph	$CsOH·H_2O$	**4l**, 81
13	4-$MeOC_6H_4$	Ph	$CsOH·H_2O$	**4m**, 70
14	4-FC_6H_4	Ph	$CsOH·H_2O$	**4n**, 58
15	Ph	4-MeC_6H_4	$CsOH·H_2O$	**4o**, 78
16	4-ClC_6H_4	4-MeC_6H_4	$CsOH·H_2O$	**4p**, 61
17[d]	Ph	4-BrC_6H_4	$CsOH·H_2O$	**4q**, 68

[a] Reactions conditions: 1,3-diyne **1** (0.2 mmol), KOH (**3a**) or $CsOH·H_2O$ (**3b**; 2.0 mmol), nitrile **2** (0.5 mL), and H_2O (1.0 mmol) in 1,4-dioxane (1.5 mL) at 100 °C for 24–36 h.
[b] Isolated yield.
[c] $CsOH·H_2O$ (1.0 mmol) was used instead of KOH and without the addition of H_2O.
[d] 4-BrC_6H_4CN (1.0 mmol) was used.

Furthermore, the molecular structure of **4b** has also been established by its X-ray crystallography analysis (Figure 1), which supports the results of these reactions.

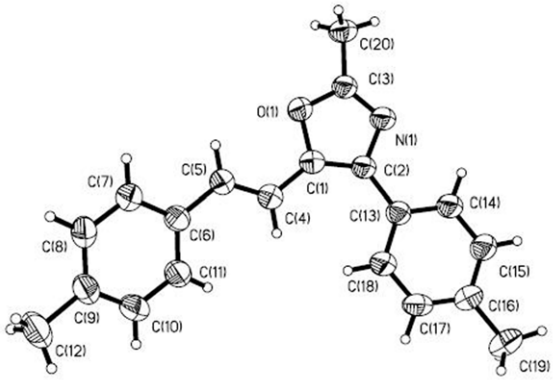
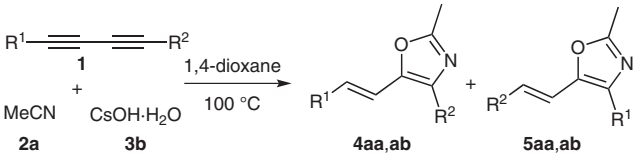


Figure 1 X-ray molecular structure of **4b**

The heterocyclization of unsymmetrical 1,3-diynes, acetonitrile (**2a**) in the presence of CsOH (**3b**) under the optimal conditions was also explored (Table 3). For example, the heterocylizations of nitrile **2a**, CsOH (**3b**), and 1,3-diynes **1** with either electron-donating (e.g., 4-$MeOC_6H_4$ and 4-$C_5H_{11}C_6H_4$) or electron-withdrawing groups (e.g., 4-FC_6H_4) on the phenyl ring resulted in the corresponding oxazoles **4aa**,**ab** and **5aa**,**ab** in a total yield of 72–73%, but with poor regioselectivity (Table 3, entries 1, 2). No isomer of **4aa**,**ab** or **5aa**,**ab** or the other 2,4,5-trisubstituted isomers were observed in these cases.

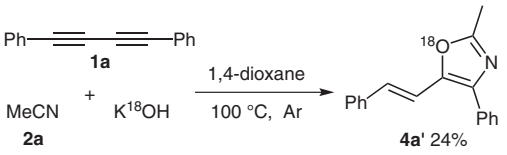
Table 3 The Heterocyclization of Unsymmetrical 1,3-Diynes, MeCN, and CsOH[a]



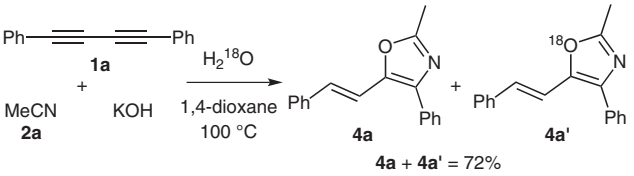
Entry	R^1	R^2	Yield of **4** (%)[b]	Yield of **5** (%)[b]
1	4-$MeOC_6H_4$	4-$C_5H_{11}C_6H_4$	**4aa**, 42	**5aa**, 31
2	4-$MeOC_6H_4$	4-FC_6H_4	**4ab**, 40	**5ab**, 32

[a] Reactions conditions: 1,3-diyne **1** (0.2 mmol), CsOH·H_2O (**3b**; 1.0 mmol), MeCN (**2a**; 0.5 mL), and 1,4-dioxane (1.5 mL) at 100 °C.
[b] Isolated yield.

Two controlled experiments were conducted in order to figure out the source of oxygen on the oxazole ring. Under the optimal conditions, $K^{18}OH$ was used in this reaction in the absence of H_2O. The structure of the product **4a′** obtained was supported by NMR and HRMS analyses (Scheme 2). When $H_2{}^{18}O$ (5 equiv) was employed in this annulation, the formation of **4a** and **4a′** was observed (Scheme 3). Scheme 2 suggested that the source of oxygen may derive from $K^{18}OH$. The results shown in Scheme 3 revealed that the source of oxygen may derive from both $H_2{}^{18}O$ and KOH in this process.

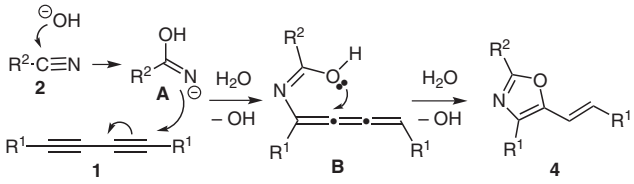


Scheme 2 Controlled experiment 1 with $K^{18}OH$



Scheme 3 Controlled experiment 2 with $H_2{}^{18}O$

A plausible mechanism is proposed in Scheme 4. The addition of a hydroxide ion to nitrile **2** forms a nucleophile **A** at 100 °C, which attacks a triple bond of 1,3-diyne **1** in the presence of 1,4-dioxane and H_2O to give the intermediate **B**. The intermediate **B** then undergoes an intramolecular cyclization to produce the 2,4-disubstituted 5-[(*E*)-2-phenylethenyl]-1,3-oxazoles **4**.[15]



Scheme 4 Possible mechanism for the cyclization of 1,3-diynes with nitriles in the presence of aqueous potassium hydroxide

In conclusion, we have developed for the first time a transition-metal-free heterocyclization of 1,3-diynes and nitriles in the presence of aqueous KOH or CsOH·H_2O, which stereoselectively provided 2,4-disubstituted 5-[(*E*)-2-phenylethenyl]-1,3-oxazoles in fair to good yields.

^1H and ^{13}C NMR spectra were recorded using Bruker AM 400 spectrometer in $CDCl_3$ with TMS as an internal standard. ^{19}F NMR spectra were obtained at 376 MHz. High-resolution mass spectra (HRMS) were obtained by using a MicroTOF mass spectrometer. Melting points were recorded using a WRS-2A micro melting point apparatus and are uncorrected. A Nicolet AVATAR 360 FT-IR spectrophotometer was used for IR spectra. Analytical TLC was performed using glass plates precoated with GF 254 silica gel impregnated with fluorescent indicator. All manipulations were carried out under air atmosphere using standard Schlenk techniques. All glassware was oven or flame dried immediately prior to use. All solvents were purified and dried according to standard methods prior to use, unless otherwise stated. Petroleum ether (PE) used refers to the fraction boiling in the range 60–90 °C. The 1,3-diynes were prepared according to the known procedures.[16]

2,4-Disubstituted 5-[(*E*)-2-Phenylethenyl]-1,3-oxazoles 4a–e; General Procedure

1,3-Diyne **1** (0.2 mmol), KOH (**3a**; 112 mg, 2 mmol), H_2O (18 mg, 1 mmol), nitrile **2** (0.5 mL) were dissolved in 1,4-dioxane (1.5 mL) in a sealed tube. The reaction mixture was stirred at 100 °C until the

consumption of substrate as monitored by TLC analysis (eluent: PE–EtOAc, 10:1). The mixture was diluted with brine (40 mL) and extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4). After concentration of the filtrate to dryness, purification of the residue by silica gel column chromatography (PE–EtOAc, 90:10) gave the desired product **4**.

2,4-Disubstituted 5-[(*E*)-2-Phenylethenyl]-1,3-oxazoles 4f–q, 4aa,ab, and 5aa,ab; General Procedure

1,3-Diyne **1** (0.2 mmol), CsOH·H_2O (**3b**; 168 mg, 1 mmol), and nitrile **2** (0.5 mL) were dissolved in 1,4-dioxane (1.5 mL) in a sealed tube. The reaction mixture was stirred at 100 °C until the consumption of substrate as monitored by TLC analysis (eluent: PE–EtOAc, 10:1). After concentration of the filtrate to dryness, purification of the residue by silica gel column chromatography (PE–EtOAc, 90:10) gave the desired product **4** or **5**.

(*E*)-2-Methyl-4-phenyl-5-styryloxazole (4a)

Yield: 41.8 mg (80%); yellow oil.

IR (film): 3535, 3473, 3416, 3238, 1637, 620 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.6 Hz, 2 H), 7.46 (dd, *J* = 13.6, 7.6 Hz, 4 H), 7.36 (t, *J* = 7.6 Hz, 3 H), 7.29–7.24 (m, 1 H), 7.15 (d, *J* = 16.4 Hz, 1 H), 7.09 (d, *J* = 15.6 Hz, 1 H), 2.56 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 145.0, 137.1, 136.7, 132.2, 129.5, 128.8, 128.8, 128.0, 127.9, 127.5, 126.6, 113.5, 14.09.

ESI-MS: *m*/*z* = 261 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{15}NO$ + Na: 284.1051; found: 284.1054.

(*E*)-2-Methyl-5-(4-methylstyryl)-4-(*p*-tolyl)oxazole (4b)

Yield: 42.2 mg (73%); yellow solid; mp 102–104 °C.

IR (KBr): 3538, 3473, 3413, 3229, 1640, 620 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.07 (s, 2 H), 2.53 (s, 3 H), 2.39 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.1, 144.8, 137.9, 137.7, 136.71 (s), 134.1, 129.5, 129.5, 1294, 129.1, 127.4, 126.4, 112.7, 21.3, 14.1.

ESI-MS: *m*/*z* = 289 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}NO$ + Na: 312.1361; found: 312.1342.

(*E*)-4-(4-Fluorophenyl)-5-(4-fluorostyryl)-2-methyloxazole (4c)

Yield: 35.6 mg (60%); yellow solid; mp 125–127 °C.

IR (KBr): 3553, 3488, 3458, 3467, 3232, 1637, 623 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 5.6, 5.6 Hz, 2 H), 7.44 (dd, *J* = 5.6, 5.6 Hz, 2 H), 7.15 (t, *J* = 8.8 Hz, 2 H), 7.09 (d, *J* = 11.2 Hz, 1 H), 7.05 (t, *J* = 6.0 Hz, 2 H), 6.96 (d, *J* = 16.0 Hz, 1 H), 2.54 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8 (d, *J* = 6.5 Hz), 161.3 (d, *J* = 6.0 Hz), 160.4, 144.6, 136.1, 132.8 (d, *J* = 3.3 Hz), 129.2 (d, *J* = 8.1 Hz), 128.44, 128.2 (d, *J* = 3.2 Hz), 128.1 (d, *J* = 8.0 Hz), 115.9, 115.7, 112.9 (d, *J* = 2.3 Hz), 14.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –113.1 (s), –113.4 (s).

ESI-MS: *m*/*z* = 297 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{14}F_2NO$: 298.1038; found: 298.1018.

(*E*)-4-(4-Chlorophenyl)-5-(4-chlorostyryl)-2-methyloxazole (4d)

Yield: 36.2 mg (55%); yellow solid; mp 134–136 °C.

IR (KBr): 3503, 3470, 3416, 3232, 1631, 602 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.07 (d, *J* = 16.0 Hz, 1 H), 7.01 (d, *J* = 16.0 Hz, 1 H), 2.54 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 144.9, 136.3, 135.1, 133.9, 133.8, 130.5, 129.0, 128.7, 128.6, 127.7, 113.5, 14.0.

ESI-MS: *m*/*z* = 329 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{13}Cl_2NO$ + Na: 352.0272; found: 352.0239.

(*E*)-4-(4-Bromophenyl)-5-(4-bromostyryl)-2-methyloxazole (4e)

Yield: 43.3 mg (52%); yellow solid; mp 147–149 °C.

IR (KBr): 3550, 3476, 3413, 3229, 1640, 623 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.8 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.06 (d, *J* = 16.0 Hz, 1 H), 7.02 (d, *J* = 16.0 Hz, 1 H), 2.54 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 144.9, 136.4, 135.4, 131.9, 131.9, 130.9, 128.9, 128.7, 128.0, 122.1, 122.0, 113.6, 14.1.

ESI-MS: *m*/*z* = 417 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{14}Br_2NO$: 417.9437; found: 417.9451.

(*E*)-2-Methyl-4-(4-pentylphenyl)-5-(4-pentylstyryl)oxazole (4f)

Yield: 64.2 mg (80%); yellow oil.

IR (film): 3550, 3470, 3413, 3227, 1640, 620 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.0 Hz, 2 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.06 (s, 2 H), 2.67–2.57 (m, 4 H), 2.53 (s, 3 H), 1.63 (tt, *J* = 14.8, 7.6 Hz, 4 H), 1.34 (dd, *J* = 8.4, 5.6 Hz, 8 H), 0.90 (dd, *J* = 10.0, 6.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 144.8, 143.1, 142.8, 136.7, 134.3, 129.6, 129.1, 128.8, 128.8, 127.3, 126.5, 112.8, 35.7, 31.5, 31.5, 31.1, 22.6, 14.1, 14.1, 14.0.

ESI-MS: *m*/*z* = 401 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{35}NO$ + Na: 424.2611; found: 424.2585.

(*E*)-4-(4-Methoxyphenyl)-5-(4-methoxystyryl)-2-methyloxazole (4g)

Yield: 53.9 mg (84%); yellow solid; mp 97–99 °C.

IR (KBr): 3550, 3473, 3413, 3241, 1637, 623 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 2 H), 7.04 (d, *J* = 16.0 Hz, 1 H), 6.98 (d, *J* = 6.8 Hz, 2 H), 6.95 (d, *J* = 14.0 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 2.52 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 159.6, 159.3, 144.5, 136.0, 129.7, 128.7, 128.5, 127.7, 124.9, 114.2, 114.2, 111.6, 55.31, 14.0.

ESI-MS: *m*/*z* = 321 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}NO_3$ + Na: 344.1263; found: 344.1256.

(*E*)-2-Methyl-5-(3-methylstyryl)-4-(*m*-tolyl)oxazole (4h)

Yield: 44.5 mg (77%); yellow oil.

IR (film): 3350, 3473, 3407, 3232, 1634, 614 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.27 (s, 2 H), 7.24 (m, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 7.08 (d, *J* = 9.6 Hz, 3 H), 2.54 (s, 3 H), 2.41 (s, 3 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 145.1, 138.5, 138.3, 137.0, 136.7, 132.1, 129.5, 128.9, 128.7, 128.7, 128.6, 128.2, 127.3, 124.6, 123.7, 113.4, 21.5, 21.4, 14.1.

ESI-MS: *m*/*z* = 289 $[M]^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}NO$ + Na: 312.1364; found: 312.1321.

(*E*)-2-Butyl-4-phenyl-5-styryloxazole (4i)
Yield: 33.3 mg (55%); yellow oil.

IR (film): 3550, 3476, 3410, 3235, 1631, 623 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.6 Hz, 2 H), 7.47 (dd, *J* = 16.0, 8.0 Hz, 4 H), 7.37 (d, *J* = 1.6 Hz, 1 H), 7.35 (d, *J* = 7.6 Hz, 2 H), 7.29–7.24 (m, 1 H), 7.13 (s, 2 H), 2.85 (t, *J* = 7.6 Hz, 2 H), 1.89–1.80 (m, 2 H), 1.48 (dd, *J* = 15.6, 7.6 Hz, 2 H), 0.99 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 144.8, 137.0 (s), 136.8, 132.3, 129.4, 128.8, 128.7, 128.0, 127.8, 127.6, 126.5, 113.6, 29.3, 28.1, 22.4, 13.7.

ESI-MS: *m*/*z* = 303 [M]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{21}NO$ + Na: 326.1515; found: 326.1509.

(*E*)-2-Butyl-5-(4-methylstyryl)-4-(*p*-tolyl)oxazole (4j)
Yield: 44.3 mg (67%); yellow oil.

IR (film): 3711, 3565, 3232, 1643, 626 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.07 (s, 2 H), 2.88–2.79 (m, 2 H), 2.39 (s, 3 H), 2.35 (s, 3 H), 1.88–1.79 (m, 2 H), 1.46 (dt, *J* = 14.8, 7.4 Hz, 2 H), 0.98 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 144.6, 137.9, 137.6, 136.6, 134.1, 129.5, 129.4, 129.0, 127.4, 126.4, 112.8, 29.3, 28.1, 22.4, 21.3, 13.8.

ESI-MS: *m*/*z* = 331 [M]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{25}NO$ + Na: 354.1828; found: 354.1808.

(*E*)-2-Butyl-4-(4-methoxyphenyl)-5-(4-methoxystyryl)oxazole (4k)
Yield: 51.7 mg (71%); yellow oil.

IR (KBr): 3749, 3550, 3461, 3416, 3238, 1640 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.8 Hz, 2 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.04 (d, *J* = 16.0 Hz, 1 H), 6.97 (dd, *J* = 16.0, 8.8 Hz, 3 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 2.82 (t, *J* = 7.6 Hz, 2 H), 1.82 (dd, *J* = 15.2, 7.6 Hz, 2 H), 1.47 (dd, *J* = 15.2, 7.6 Hz, 2 H), 0.98 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 159.5, 159.3, 144.2, 136.0, 129.7, 128.7, 128.4, 127.7, 125.0, 114.2, 114.2, 111.7, 55.3, 29.3, 28.1, 22.4, 13.7.

ESI-MS: *m*/*z* = 363 [M]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{25}NO_3$ + Na: 387.1727; found: 386.1703.

(*E*)-2,4-Diphenyl-5-styryloxazole (4l)
Yield: 52.3 mg (81%); yellow solid; mp 107–109 °C.

IR (KBr): 3548, 3493, 3472, 3236, 1640, 623 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.15 (m, 2 H), 7.79 (d, *J* = 7.6 Hz, 2 H), 7.49 (dd, *J* = 14.4, 7.2 Hz, 7 H), 7.37 (dd, *J* = 14.8, 7.6 Hz, 3 H), 7.30–7.24 (m, 2 H), 7.18 (d, *J* = 16.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 145.3, 138.7, 136.7, 132.2, 130.5, 130.1, 129.4, 128.9, 128.8, 128.8, 128.2, 128.1, 127.8, 127.3, 126.7, 113.5.

ESI-MS: *m*/*z* = 323 [M]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{17}NO$ + Na: 346.1202; found: 346.1176.

(*E*)-4-(4-Methoxyphenyl)-5-(4-methoxystyryl)-2-phenyloxazole (4m)
Yield: 53.3 mg (70%); yellow solid; mp 134–136 °C.

IR (KBr): 3546, 3474, 3415, 3234, 1635, 630 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 7.6, 1.6 Hz, 2 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 5 H), 7.19 (d, *J* = 16.0 Hz, 1 H), 7.06–6.99 (m, 3 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 3.86 (s, 3 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 159.5, 144.84, 137.7, 130.3, 129.7, 129.2, 128.9, 128.7, 127.9, 127.4, 126.5, 124.9, 114.3, 114.3, 111.5, 55.4, 55.3.

ESI-MS: *m*/*z* = 383 [M]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{21}NO_3$ + Na: 406.1414; found: 406.1386.

(*E*)-4-(4-Fluorophenyl)-5-(4-fluorostyryl)-2-phenyloxazole (4n)
Yield: 41.6 mg (58%); yellow solid; mp 149–150 °C.

IR (KBr): 3549, 3477, 3413, 3236, 1635, 637 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.12 (m, 2 H), 7.75 (dd, *J* = 8.8, 5.6 Hz, 2 H), 7.48 (m, 5 H), 7.24 (d, *J* = 15.6 Hz, 1 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 7.08 (d, *J* = 8.6 Hz, 2 H), 7.01 (d, *J* = 16.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 161.5, 160.1, 144.9, 137.7, 132.8 (d, *J* = 3.3 Hz), 130.6, 129.5, 129.4, 129.0, 128.8, 128.2 (d, *J* = 8.0 Hz), 127.1, 126.6, 115.9 (d, *J* = 2.8 Hz), 115.9 (d, *J* = 2.8 Hz), 112.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –112.85 (s), –113.16 (s).

ESI-MS: *m*/*z* = 359 [M]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{15}F_2NO$ + Na: 382.1014; found: 382.0993.

(*E*)-4-Phenyl-5-styryl-2-(*p*-tolyl)oxazole (4o)
Yield: 52.4 mg (78%); yellow solid; mp 139–140 °C.

IR (KBr): 3551, 3475, 3419, 3233, 1639, 632 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 7.6 Hz, 2 H), 7.49 (dd, *J* = 15.2, 7.6 Hz, 4 H), 7.37 (dd, *J* = 13.6, 6.8 Hz, 4 H), 7.28 (d, *J* = 7.6 Hz, 2 H), 7.24 (d, *J* = 15.6 Hz, 2 H), 7.18 (d, *J* = 16.0 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 145.0, 140.9, 138.6, 136.8, 132.3, 129.8, 129.5, 128.8, 128.8, 128.1, 128.1, 127.8, 124.6, 113.5, 21.6.

ESI-MS: *m*/*z* = 337 [M]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{20}NO$ + Na: 338.1539; found: 338.1525.

(*E*)-4-(4-Chlorophenyl)-5-(4-chlorostyryl)-2-(*p*-tolyl)oxazole (4p)
Yield: 49.2 mg (61%); yellow solid; mp 191–192 °C.

IR (KBr): 3547, 3475, 3411, 3239, 1637, 635 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.48–7.41 (m, 4 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 16.0 Hz, 1 H), 7.09 (d, *J* = 16.0 Hz, 1 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 144.8, 141.2, 137.8, 135.1, 134.1, 133.9, 130.6, 129. 6, 129.0, 129.0, 128.9, 128.8, 127.8, 126.6, 124.3, 113. 6, 21.6.

ESI-MS: *m*/*z* = 405 [M]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{17}Cl_2NO$ + Na: 428.0585; found: 428.0586.

(*E*)-2-(4-Bromophenyl)-4-phenyl-5-styryloxazole (4q)
Yield: 54.5 mg (68%); yellow solid; mp 169–170 °C.

IR (KBr): 3547, 3476, 3413, 3238, 1637, 637 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 7.2 Hz, 2 H), 7.60 (d, *J* = 8.4 Hz, 2 H), 7.48 (dd, *J* = 12.0, 7.6 Hz, 4 H), 7.42–7.33 (m, 3 H), 7.29 (d, *J* = 7.2 Hz 1 H), 7.40 (d, *J* = 16.0 Hz, 1 H), 7.15 (d, *J* = 16.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 145.5, 138.7, 136.6 132.1 132.0, 130.4, 128.9, 128.3, 128.2, 128.1, 127.7, 126.7, 126.2, 125.0, 113.3.

ESI-MS: *m*/*z* 401 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{16}BrNO$ + Na: 424.0307; found: 424.0283.

(*E*)-4-(4-Methoxystyryl)-2-methyl-5-(4-pentylphenyl)oxazole (4aa)
Yield: 30.3 mg (42%); yellow oil.

IR (film): 3557, 3467, 3443, 3413, 3226, 2917, 1613, 623 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.28–7.23 (m, 2 H), 7.06 (d, *J* = 16.0 Hz, 1 H), 7.00 (d, *J* = 16.0 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 3.82 (s, 3 H), 2.67–2.60 (m, 2 H), 2.54 (s, 3 H), 1.69–1.60 (m, 2 H), 1.38–1.31 (m, 4 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 159.6, 144.9, 142.7, 136.3, 129.7, 129.6, 128.8, 128.7, 127.8, 127.3, 114.2, 111.7, 55.3, 35.7, 31.5, 31.1, 22.6, 14.1, 14.0.

ESI-MS: *m*/*z* = 361 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{27}NO_2$ + Na: 384.1934; found: 384.1912.

(*E*)-4-(4-Pentylstyryl)-5-(4-methoxyphenyl)-2-methyloxazole (5aa)
Yield: 22.4 mg (31%); yellow oil.

IR (KBr): 3553, 3494, 3416, 3229, 2357, 1640, 626 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.8 Hz, 2 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.06 (s, 2 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H), 2.63–2.57 (m, 2 H), 2.53 (s, 3 H), 1.66–1.56 (m, 2 H), 1.36–1.30 (m, 3 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 159.4, 144.4, 143.0, 136.5, 134.3, 128.9, 128.8, 128.7, 126.4, 124.8, 114.2, 112.7, 55.3, 35.7, 31.7, 30.8, 22.6, 14.1, 14.0.

ESI-MS: *m*/*z* = 361 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{27}NO_2$ + Na: 384.1934; found: 384.1913.

(*E*)-4-(4-Methoxystyryl)-5-(4-fluorophenyl)-2-methyloxazole (4ab)
Yield: 21.7 mg (40%); yellow solid; mp 84–86 °C.

IR (KBr): 3561, 3484, 3412, 3229, 2348, 1645, 629 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 8.8, 5.6 Hz, 2 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.13 (t, *J* = 8.8 Hz, 2 H), 7.08 (d, *J* = 16.0 Hz, 1 H), 6.94 (d, *J* = 15.2 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 3.82 (s, 3 H), 2.53 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 161.2, 160.0, 159.7, 145.1, 135.2, 129.4 (d, J = 3.9 Hz), 129.1 (d, *J* = 8.1 Hz), 128.5 (d, *J* = 3.3 Hz), 127.8, 115.8, 115.6, 114.3, 111.1, 55.3, 14.0.

ESI-MS: *m*/*z* = 309 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{16}FNO_2$ + Na: 332.1063; found: 332.1056.

(*E*)-4-(4-Fluorostyryl)-5-(4-methoxyphenyl)-2-methyloxazole (5ab)
Yield: 19.8 mg (32%); yellow solid; mp 92–94 °C.

IR (KBr): 3559, 3491, 3419, 3232, 2355, 1644, 626 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.8 Hz, 2 H), 7.43 (dd, *J* = 8.4, 5.6 Hz, 2 H), 7.08–6.96 (m, 6 H), 3.86 (s, 3 H), 2.54 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 161.2, 160.2, 159.5, 144.1, 136.9, 133.1 (d, *J* = 3.4 Hz), 128.7, 127.9 (d, *J* = 8.0 Hz), 127.5, 124.7, 115.8, 115.6, 114.3, 113.4 (d, *J* = 2.3 Hz), 55.3, 14.1.

ESI-MS: *m*/*z* = 309 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{16}FNO_2$ + Na: 332.1063; found: 332.1056.

Procedure for the Controlled Experiment 1
$K^{18}OH$ generated from KH (2 mmol, 10 equiv, 30% dispersion in mineral oil) and $H_2{}^{18}O$ (2 mmol, 10 equiv), **1a** (0.2 mmol), MeCN (0.5 mL), and 1,4-dioxane (1.5 mL) were charged in a sealed tube under argon. The reaction mixture was stirred at 100 °C. After completion, the purification of the residue by silica gel column chromatography (PE–EtOAc, 90:10) gave the desired product **4a′**; yield: 12.6 mg (24%); yellow oil.

IR (KBr): 3535, 3473, 3416, 3238, 1637, 620 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.68 (m, 2 H), 7.48–7.43 (m, 4 H), 7.35 (t, *J* = 7.20 Hz, 3 H), 7.28–7.24 (m, 1 H), 7.12 (s, 2 H), 2.54 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 144.9, 137.0, 136.7, 132.1, 129.4, 128.8, 128.7, 128.0, 127.8, 127.4, 126.5, 113.4, 14.0.

ESI-MS: *m*/*z* = 263 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{15}N^{18}O$ + Na: 286.1088; found: 286.1090.

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