

Published in final edited form as:

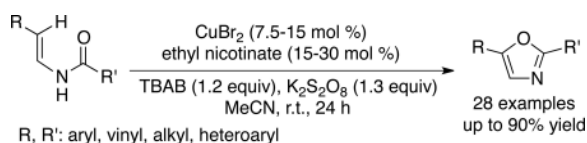
J Org Chem. 2012 September 7; 77(17): 7526–7537. doi:10.1021/jo301332s.

Room Temperature Copper(II)-Catalyzed Oxidative Cyclization of Enamides to 2,5-Disubstituted Oxazoles via Vinylic C-H Functionalization

Chi Wai Cheung and Stephen L. Buchwald

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, United States

Abstract



A copper(II)-catalyzed oxidative cyclization of enamides to oxazoles via vinylic C-H bond functionalization at room temperature is described. Various 2,5-disubstituted oxazoles bearing aryl, vinyl, alkyl, and heteroaryl substituents could be synthesized in moderate to high yields. This reaction protocol is complementary to our previously reported iodine-mediated cyclization of enamides to afford 2,4,5-trisubstituted oxazoles.

Introduction

Substituted oxazoles can be found in a wide variety of biologically active molecules of interest to the drug discovery community. Oxazole-containing biologically active natural products,¹ especially the diazonamide^{1b} and phorboxazole^{1c} families, exhibit anticancer properties, and a number of synthetic trisubstituted² and 2,5-disubstituted³ oxazoles have been evaluated to show activity against diabetes,^{2b} gram-positive and gram-negative bacterial infections,^{3a} breast cancer,^{3b} and pancreatic cancer^{3c} (Figure 1). Moreover, substituted oxazoles can be utilized in agrochemicals,⁴ fluorescent dyes,⁵ polymers,⁶ and also as ligands for transition-metal catalysis.⁷ Consequently, the development of synthetic methods to access functionalized oxazoles is of great importance to synthetic organic chemists.

To date, various synthetic methods have been developed for the synthesis of substituted oxazoles.⁸⁻¹⁰ In particular, a common strategy has been to convert an acyclic precursor to an oxazole ring.^{8a-d,8i,9,10} A versatile cyclization strategy is the Robinson-Gabriel condensation,^{8a-d} which has been utilized to prepare a range of highly substituted and complex oxazoles (Scheme 1A). However, this method requires the use of Brønsted acid catalysts or Lewis acid reagents which limits the overall functional group tolerance of the transformation. Alternatively, enamides can serve as stable and easily accessible starting materials to afford oxazoles.^{9,10} Enamides bearing the β -vinylic C—heteroatom bonds (C—Br,^{9a-d} C—I,^{9e,f} and C—S^{9g}) have been isolated or generated *in situ*, which undergo facile

Correspondence to: Stephen L. Buchwald.

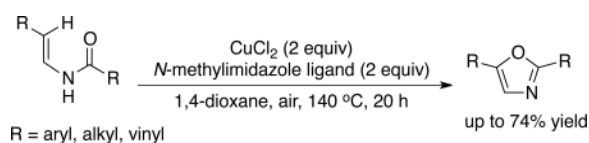
Corresponding sbuchwal@mit.edu.

Supporting Information Available. All spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

intramolecular vinylation of the amide oxygen to provide a broader range of oxazoles under milder conditions (Scheme 1B). While this strategy is effective, a method for the cyclization of enamides to oxazoles, without the need for further vinylic C-H functionalization, would be a more direct and convenient means of obtaining the same products (Scheme 1C).

Our group previously reported the development of a sequential synthesis of 2,4,5-trisubstituted oxazoles via initial copper-catalyzed amidation of vinyl halides to form enamides, followed by intramolecular cyclization promoted by iodine (Scheme 2).¹⁰ Unfortunately, the synthesis of mono- and disubstituted oxazoles still remained a limitation under the reported reaction conditions, and 2,5-disubstituted oxazoles were instead generated *via* a domino copper-catalyzed C-N/C-O coupling sequence starting from 1,2-dihaloalkenes and amides. Thus, the development of a direct cyclization of enamides to oxazoles without the need for a β -vinylic functional group remains an important challenge.

Recently, several examples of transition-metal-catalyzed methods for the direct vinylic C-H functionalization of enamides have been described.¹¹ Moreover, copper, as an inexpensive and readily available metal, has been widely utilized to facilitate C-O bond formation, via oxidative C-H functionalization, for the formation of various heterocycles.¹² We thus reasoned that a Cu-catalyzed direct oxidative cyclization of enamides to oxazoles via vinylic C-H functionalization might be plausible. In fact, during the preparation of this manuscript, Wendlandt and Stahl disclosed a similar method for the Cu-mediated oxidative cyclization of enamides to 2,5-disubstituted oxazoles (eq. 1).¹³ Their method is attractive as it uses oxygen as the oxidant, albeit with a stoichiometric quantity of copper(II) chloride, to promote this cyclization. Herein, we report a method for the synthesis of a broad range of 2,5-disubstituted oxazoles via stepwise Cu-catalyzed amidation of vinyl halides to form enamides, followed by subsequent Cu-catalyzed oxidative cyclization, promoted by potassium persulfate, of the enamide intermediates under ambient conditions (Scheme 3).



(1)

Results and Discussion

We began our studies by subjecting (*E*)-*N*-styrylbenzamide (**1a**) to a catalytic amount of copper(II) bromide, using potassium persulfate as an oxidant (Table 1, entry 1). Despite complete conversion of **1a**, 2,5-diphenyloxazole (**2a**) was only obtained in 14% yield.¹⁴ The use of tetrabutylammonium bromide (TBAB) as an additive,¹⁵ which probably aids in the regeneration of CuBr₂, led to a significant increase in yield (59%, Table 1, entry 2). Further, we found that the use of ethyl nicotinate (40 mol%) as a ligand for copper increased the yield up to 78% (Table 1, entry 3). A number of electronically varied substituted pyridine ligands were evaluated (Table 1, entries 3-7), and ethyl nicotinate was identified as the optimal ligand. In an attempt to reduce the loading of ethyl nicotinate, we found that by slightly increasing the amount of copper catalyst to 7.5 mol%, the amount of ethyl nicotinate could be lowered to 15 mol% while maintaining a high yield of product (Table 1, entry 9). The use of CuBr₂ was also found to be much more effective than the other transition metal salts (CuCl₂, FeBr₂, and FeCl₂) (Table 1, entries 11-13).¹⁶ In the absence of CuBr₂, only a trace of **2a** was obtained (Table 1, entry 14).

With good reaction conditions, we set out to examine the substrate scope for the process (Table 2). The process tolerates a range of *ortho*-, *meta*-, and *para*- substituents on either or both aromatic rings of the enamide intermediate to generally afford 2,5-diaryloxazoles in good yields. Notably, chloro- and bromo-substituted diaryloxazoles (**2d**, **2l**, and **2m**) could be prepared, which render them as suitable substrates for further functionalization via a range of cross-coupling methods. Moreover, these conditions described also provide access to 2,5-diaryloxazoles bearing fluoro and trifluoromethyl substituents (**2e**, **2f**, **2n**, and **2o**), which are often highly desirable in the synthesis of novel therapeutics.¹⁷ *Ortho*-substitution on the enamide aryl groups was also well-tolerated, affording the corresponding oxazoles in high yields (**2p**, **2q**). The presence of a highly electron-withdrawing nitro group on the benzamide region (**2g**, **2h**) or of a strongly π -donating methoxy group on the β -styryl region (**2i**)¹⁸ led to lower yields of the corresponding oxazoles.

Next, we sought to extend this methodology to include 2,5-disubstituted oxazoles bearing vinyl, alkyl, and heterocyclic substitution (Table 3). Enamides bearing the styryl groups could be cyclized to afford the styryloxazoles (**4a,b**), including the natural product annuloline (**4c**).¹⁹ Enamides bearing both cyclic and acyclic alkyl groups were also viable substrates (**4d-f**), although, interestingly, the cyclohexyl ring of oxazole **4f** was partially oxidized to 1-cyclohexenyl (**4f'**) during the course of the reaction. We were particularly pleased to discover that enamides bearing electron-rich 2-furyl, 2- and 3-thienyl, and *N*-benzoyl-5-indolyl groups survived the oxidizing conditions to afford the corresponding oxazoles in moderate to high yields (**4g-k**). Unfortunately, an oxazole containing an *N*-methyl-2-pyrrolyl group at the 2-position, as well as oxazoles bearing *N*-tosyl-2-pyrrolyl and 2-thienyl groups at the 5-position, could not be efficiently synthesized using the current conditions. Moreover, oxazoles with pyridyl groups, as well as an oxazole bearing an *N*-methyl-2-imidazolyl group at the 2-position, could only be generated in low yields.

Regarding the mechanism of copper(II)-catalyzed oxidative cyclization of enamides to oxazoles, Wendlandt and Stahl have proposed that CuCl_2 acts as a single-electron oxidant, triggering the cyclization via a radical pathway (eq. 1).¹³ We concur; in our case, CuBr_2 most likely serves as a single-electron oxidant, converting the electron-rich enamide **1a** to an enamide radical cation (Scheme 4, transformation i), which then cyclizes to radical intermediate **I** (Scheme 4, transformation ii).¹³ Subsequent oxidation of **I** by CuBr_2 provides the oxazole **2a** (Scheme 4, transformation iii). The reduced form of copper, CuBr , is then oxidized by $\text{K}_2\text{S}_2\text{O}_8$ and reacts with TBAB to regenerate the CuBr_2 catalyst (Scheme 4, transformation iv).

Conclusion

In summary, we have developed an efficient room temperature catalytic oxidative cyclization of enamides to generate 2,5-disubstituted oxazoles by using catalytic amounts of CuBr_2 in conjunction with $\text{K}_2\text{S}_2\text{O}_8$ as an oxidant. This reaction protocol can tolerate enamide substrates bearing aryl, heteroaryl, vinyl, and/or alkyl substituents to afford the corresponding oxazoles in moderate to high yields. This transformation is complementary to the iodine-promoted cyclization of enamides to 2,4,5-trisubstituted oxazoles previously reported by our group.

Experimental Section

General Information

Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument at ambient temperature. All ^1H NMR spectra were measured in parts per million (ppm) relative to the signals for tetramethylsilane (TMS) added into the deuterated chloroform (CDCl_3) (0

ppm), or the signals for residual dimethyl sulfoxide (DMSO) in deuterated DMSO (DMSO- d_6) (2.50 ppm). Data for ^1H NMR were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet, br = broad, $ovrlp$ = overlap), coupling constants, and integration. All ^{13}C NMR spectra were reported in ppm relative to CDCl_3 (77.16 ppm)²⁰ or DMSO- d_6 (25.12 ppm).²⁰ All ^{19}F NMR spectra were reported in ppm relative to a CFCl_3 external standard (0 ppm). Anhydrous acetonitrile (99.8%) was purchased from Alfa Aesar. Other commercial materials were used as received unless otherwise noted. Flash column chromatography was performed using Silicycle silica gel (ultra pure grade). (*E*)-(2-bromovinyl)benzene,²¹ (*E*)-1-(2-bromovinyl)-4-methoxybenzene,²¹ (*E*)-1-(2-bromovinyl)-4-methylbenzene,²¹ (*E*)-1-(2-bromovinyl)-4-chlorobenzene,²¹ (*E*)-1-iododec-1-ene,²² ((*E*)-4-bromobuta-1,3-dien-1-yl)benzene²³ ((3*Z*) : (3*E*) = 2.6 : 1.0), and (*E*)-3-(3,4-dimethoxyphenyl)acrylamide²⁴ were prepared according to the literature procedures.

General Procedure for the Preparation of β -Aryl-vinyl Bromides

Adapted from a previously reported procedure with some modification.²¹ A 250 mL round-bottom flask equipped with a Teflon-coated magnetic stir bar was charged with the cinnamic acid or its derivatives (1.0 equiv), *N*-bromosuccinimide (NBS) (1.05 equiv), and manganese(II) acetate tetrahydrate ($\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$) (20 mol%), followed by acetonitrile and water (1 : 1). The reaction mixture was stirred overnight at room temperature. The reaction mixture was then washed with excess water and ethyl acetate in a separation funnel. The aqueous fraction was further washed with ethyl acetate until most of the product has been extracted as judged by TLC analysis. The combined organic fraction was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate (EtOAc) : hexanes = 1 : 20) to afford the desired vinyl bromide. The ratio of (*E*) : (*Z*) isomers of vinyl bromide was determined by ^1H NMR spectroscopy.

(*E*)-4-(2-bromovinyl)phenyl acetate (S1)²⁵

((*E*) : (*Z*) > 99 : 1). Synthesized from *trans*-4-acetoxycinnamic acid (4.50 g, 21.8 mmol), $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (1.07 g, 4.36 mmol), and NBS (4.07 g, 22.9 mmol) in acetonitrile / water (50 mL / 50 mL). 3.23 g, 13.4 mmol, 61%; off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.31 (d, J = 8.4 Hz, 2H), 7.10-7.04 (ovrlp, 3H), 6.73 (d, J = 14.0 Hz, 1H), 2.30 (s, 3H).

(*E*)-1-bromo-4-(2-bromovinyl)benzene (S2)²⁶

((*E*) : (*Z*) > 99 : 1). Synthesized from *trans*-4-bromocinnamic acid (13.4 g, 59.0 mmol), $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2.89 g, 11.8 mmol), and NBS (11.0 g, 62.0 mmol) in acetonitrile / water (100 mL / 100 mL). 6.07 g, 23.2 mmol, 39%; off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 14.0 Hz, 1H), 6.78 (d, J = 14.0 Hz, 1H).

(*E*)-1-(2-bromovinyl)-4-fluorobenzene (S3)²⁷

((*E*) : (*Z*) > 99 : 1). Synthesized from *trans*-4-fluorocinnamic acid (12.0 g, 72.2 mmol), $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (3.54 g, 14.4 mmol), and NBS (13.5 g, 75.8 mmol) in acetonitrile / water (100 mL / 100 mL). 7.31 g, 36.4 mmol, 50%; off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.29 (dd, $^3J_{\text{HH}}$ = 8.4 Hz, $^4J_{\text{HF}}$ = 5.6 Hz, 2H), 7.08 (d, J = 14.0 Hz, 1H), 7.04 (dd, $^3J_{\text{HH}}$ = 8.4 Hz, $^3J_{\text{HF}}$ = 8.4 Hz, 2H), 6.71 (d, J = 14.0 Hz, 1H).

(*E*)-4-(2-bromovinyl)-1,2-difluorobenzene (S4)²⁸

((*E*) : (*Z*) ~ 95 : 5). Synthesized from *trans*-3,4-difluorocinnamic acid (10.0 g, 54.3 mmol), $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (2.66 g, 10.9 mmol), and NBS (10.2 g, 57.0 mmol). 2.45 g, 11.2 mmol,

21%; pale-yellow oil. $^1\text{H NMR}$ of (*E*)-isomer (400 MHz, CDCl_3) δ 7.14-7.08 (ovrlp, 2H), 7.02-6.99 (ovrlp, 2H), 6.72 (d, $J = 14.4$ Hz, 1H).

(*E*)-1-(2-bromovinyl)-2-methylbenzene (S5)²⁹

((*Z*) : (*E*) > 99 : 1). Synthesized from *trans*-2-methylcinnamic acid (4.00 g, 24.7 mmol), $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (1.21 g, 4.94 mmol), and NBS (4.62 g, 25.9 mmol) in acetonitrile / water (80 mL / 80 mL). 2.64 g, 13.4 mmol, 54%; pale-yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.30-7.27 (ovrlp, 2H), 7.21-7.12 (ovrlp, 3H), 6.60 (d, $J = 14.0$ Hz, 1H), 2.30 (s, 3H).

General Procedure for the Preparation of β -Heteroaryl-vinyl Bromides

Adapted from a previously reported procedure.²³ A 250 mL round-bottom flask was charged with a Teflon-coated magnetic stir bar, (bromomethyl)triphenylphosphonium bromide³⁰ (1.0 equiv), and potassium *tert*-butoxide (KO^tBu) (1.05 equiv). The reaction vessel was evacuated and backfilled with argon (this sequence was repeated a total of 3 times) and then cooled to -78 °C. Anhydrous THF (80 mL) was added slowly into the reaction mixture to give a yellow suspension which was stirred at -78 °C for 1 h. A solution of carboxaldehyde (0.9 equiv) in anhydrous THF (10 mL) was then introduced via syringe. The resulting reaction mixture was stirred at -78 °C for 1 h, after which time it was gradually warmed to room temperature and further stirred for 4 hours. The mixture was diluted with hexanes (100 mL) and filtered under vacuum. The filtrate was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate (EtOAc) / hexanes) to afford the desired vinyl bromide. The ratio of (*Z*) : (*E*) isomers was determined by $^1\text{H NMR}$ spectroscopy.

3-(2-Bromovinyl)thiophene (S6)³¹

((*Z*) : (*E*) = 4.3 : 1.0). Synthesized from (bromomethyl)triphenylphosphonium bromide (12.1 g, 27.8 mmol), KO^tBu (3.15 g, 28.1 mmol), and thiophene-3-carboxaldehyde (2.80 g, 25.0 mmol); EtOAc / hexanes = 1 : 20. 1.96 g, 10.4 mmol, 41%; pale-yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 (d, $J = 2.8$ Hz, 1H), 7.47 (d, $J = 5.2$ Hz, 1H), 7.32-7.24 (ovrlp, 1.5H), 7.13-7.05 (ovrlp, 1.5H), 6.62 (d, $J = 14.0$ Hz, 0.23H), 6.22 (d, $J = 8.0$ Hz, 1H).

(5-(2-bromovinyl)-1H-indol-1-yl)(phenyl)methanone (S7)

((*Z*) : (*E*) = 20 : 1). Synthesized from (bromomethyl)triphenylphosphonium bromide (8.72 g, 20.0 mmol), KO^tBu (2.35 g, 21.0 mmol), and 1-benzoyl-1*H*-indole-5-carboxaldehyde³² (4.49 g, 18.0 mmol); EtOAc / hexanes = 1 : 12. 3.68 g, 11.3 mmol, 63%; white solid. **m.p.**: 66-68 °C. $^1\text{H NMR}$ of (*Z*) isomer (400 MHz, CDCl_3) 8.37 (d, $J = 8.8$ Hz, 1H), 8.01 (s, 1H), 7.73 (d, $J = 7.6$ Hz, 2H), 7.65-7.58 (ovrlp, 2H), 7.52 (t, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 3.6$ Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 1H), 6.62 (d, $J = 4.0$ Hz, 1H), 6.43 (d, $J = 8.0$ Hz, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 168.6, 135.7, 134.4, 132.6, 132.1, 130.8, 130.7, 129.3, 128.7, 128.3, 126.3, 121.4, 116.2, 108.8, 105.7. **IR** (neat cm^{-1}) 1673, 1468, 1444, 1371, 1323, 1184, 1065, 882, 825, 793, 771, 737, 720, 696, 606. **Anal.** Calcd. for $\text{C}_{17}\text{H}_{12}\text{BrNO}$: C, 62.60; H, 3.71. Found: C, 62.79; H, 3.83.

Preparation of Enamides via Cu-Catalyzed Amidations of Vinyl Halides

Adapted from a previously reported procedure with some modification.¹⁰ An oven-dried 25 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with vinyl halide (if solid), amide, CuI, and K_2CO_3 . The tube was then evacuated and backfilled with argon (this sequence was repeated a total of three times). Vinyl halide (if liquid) and *N,N*-dimethylethylenediamine (DMEDA) were added into the tube followed by anhydrous THF via syringe. The sealed tube was placed in a pre-heated oil bath (80 °C). After stirring at the same temperature for 18 h, the reaction mixture was allowed to cool to

room temperature. The reaction mixture was then extracted with ethyl acetate (EtOAc) (20 mL) and deionized water (100 mL) in a separation funnel. The aqueous fraction was further extracted with EtOAc (2 × 10 mL). The combined organic fractions were then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography using the indicated solvent system as an eluent to afford the enamide substrates.

(*E*)-*N*-styrylbenzamide (**1a**)³³

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (900 mg, 4.92 mmol, 1.0 equiv), benzamide (714 mg, 5.90 mmol, 1.2 equiv), K₂CO₃ (1.36 g, 9.84 mmol, 2.0 equiv), CuI (93.7 mg, 0.492 mmol, 10 mol%), DMEDA (212 μL, 1.97 mmol, 40 mol%), and THF (10.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 736 mg, 3.29 mmol, 67%; white solid. **m.p.**: 178-180 °C (lit.: 172-173 °C). ³¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.67 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 7.2 Hz, 2H), 7.70 (dd, *J* = 14.8 Hz, 8.0 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 14.8 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 164.1, 136.6, 133.4, 131.9, 128.8, 128.5, 127.7, 126.3, 125.3, 124.2, 113.0. **IR** (neat cm⁻¹) 3302, 1637, 1522, 1483, 1310, 1288, 1171, 1074, 953, 927, 746, 691.

(*E*)-4-methoxy-*N*-styrylbenzamide (**1b**)

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.28 g, 7.0 mmol, 1.0 equiv), 4-methoxybenzamide (1.27 g, 8.4 mmol, 1.2 equiv), K₂CO₃ (1.93 g, 14.0 mmol, 2.0 equiv), CuI (267 mg, 1.40 mmol, 20 mol%), DMEDA (301 μL, 2.80 mmol, 40 mol%), and THF (14.0 mL, 0.5 M); EtOAc / hexanes = 1:6, then 2:1. 1.09 g, 4.31 mmol, 62%; white solid. **m.p.**: 190-192 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.49 (d, *J* = 10.0 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.66 (dd, *J* = 14.8 Hz, 10 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 14.8 Hz, 1H), 3.84 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 163.5, 162.2, 136.8, 129.6, 128.7, 126.1, 125.5, 125.2, 124.4, 113.7, 112.3, 55.4. **IR** (neat cm⁻¹) 3336, 1665, 1636, 1603, 1524, 1486, 1288, 1252, 1179, 1028, 949, 844, 749, 694, 668. **Anal.** Calcd. for C₁₆H₁₅NO₂: C, 75.87; H, 5.97. Found: C, 75.61; H, 5.84.

(*E*)-4-methyl-*N*-styrylbenzamide (**1c**)³⁴

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.10 g, 6.0 mmol, 1.0 equiv), 4-methylbenzamide (973 mg, 7.2 mmol, 1.2 equiv), K₂CO₃ (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.20 mmol, 20 mol%), DMEDA (258 μL, 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 960 mg, 4.05 mmol, 67%; off-white solid. **m.p.**: 188-190 °C (lit.: 194-195 °C). ³¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.56 (d, *J* = 10.0 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.67 (dd, *J* = 14.8 Hz, 10.0 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.34-7.28 (ovrlp, 4H), 7.16 (t, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 14.8 Hz, 1H), 2.38 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 163.9, 142.0, 136.7, 130.5, 129.1, 128.7, 127.7, 126.2, 125.2, 124.2, 112.6, 21.0. **IR** (neat cm⁻¹) 3219, 1624, 1523, 1485, 1309, 1285, 1185, 961, 835, 761, 737, 693, 636.

(*E*)-4-chloro-*N*-styrylbenzamide (**1d**)

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.10 g, 6.0 mmol, 1.2 equiv), 4-chlorobenzamide (778 mg, 5.0 mmol, 1.0 equiv), K₂CO₃ (1.38 g, 10.0 mmol, 2.0 equiv), CuI (191 mg, 1.0 mmol, 20 mol%), DMEDA (215 μL, 2.0 mmol, 40 mol%), and THF (10.0 mL, 0.5 M). EtOAc / hexanes = 1:7, then 1:4. 821 mg, 3.18 mmol, 64%; pale-yellow solid. **m.p.**: 187-188 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.71 (d, *J* = 10.0 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.65 (dd, *J* = 14.8 Hz, 10.0 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 7.2

Hz, 2H), 7.70 (t, $J = 7.6$ Hz, 2H), 7.17 (t $J = 7.2$ Hz, 1H), 6.48 (d, $J = 14.8$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 163.0, 136.8, 136.5, 132.1, 129.6, 128.7, 128.6, 126.3, 125.3, 124.0, 113.3. IR (neat cm^{-1}) 3330, 1641, 1523, 1479, 1279, 1171, 1091, 1013, 941, 843, 747, 692, 670. Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{ClNO}$: C, 69.91; H, 4.69. Found: C, 69.91; H, 4.75.

(E)-4-fluoro-N-styrylbenzamide (1e)

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.32 g, 7.2 mmol, 1.2 equiv), 4-fluorobenzamide (835 mg, 6.0 mmol, 1.0 equiv), K_2CO_3 (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (258 μL , 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 813 mg, 3.37 mmol, 56%; off-white solid. **m.p.**: 181–183 °C. ^1H NMR (400 MHz, DMSO- d_6) δ : 10.66 (d, $J = 10.0$ Hz, 1H), 8.07 (dd, $^3J_{\text{HH}} = 8.4$ Hz, $^4J_{\text{HF}} = 5.6$ Hz, 2H), 7.67 (dd, $J = 14.4$ Hz, 10.0 Hz, 1H), 7.40–7.34 (ovrlp, 4H), 7.30 (t, $J = 8.0$ Hz, 2H), 7.17 (t, $J = 7.6$ Hz, 1H), 6.48 (d, $J = 14.8$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 164.3 (d, $^1J_{\text{CF}} = 248.1$ Hz), 163.0, 136.6, 130.4 (d, $^3J_{\text{CF}} = 9.1$ Hz), 129.8 (d, $^4J_{\text{CF}} = 2.7$ Hz), 128.7, 126.3, 125.3, 124.1, 115.5 (d, $^2J_{\text{CF}} = 21.7$ Hz), 113.1. ^{19}F NMR (376 MHz, DMSO- d_6) δ : -108.4. IR (neat cm^{-1}) 3343, 1642, 1599, 1525, 1483, 1286, 1222, 1158, 942, 846, 747, 692, 655, 624, 604. Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{FNO}$: C, 74.67; H, 5.01. Found: C, 74.85; H, 5.20.

(E)-N-styryl-4-(trifluoromethyl)benzamide (1f)

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (915 mg, 5.0 mmol, 1.5 equiv), 4-(trifluoromethyl)benzamide (630 mg, 3.33 mmol, 1.0 equiv), K_2CO_3 (921 mg, 6.67 mmol, 2.0 equiv), CuI (317 mg, 1.67 mmol, 50 mol%), DMEDA (215 μL , 2.0 mmol, 60 mol%), and THF (7.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 668 mg, 2.29 mmol, 69%; off-white solid. **m.p.**: 206–208 °C. ^1H NMR (400 MHz, DMSO- d_6) δ : 10.86 (d, $J = 10.0$ Hz, 1H), 8.18 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 8.4$ Hz, 2H), 7.68 (dd, $J = 14.8$ Hz, 10.0 Hz, 1H), 7.42 (d, $J = 7.6$ Hz, 2H), 7.31 (t, $J = 7.6$ Hz, 2H), 7.18 (t, $J = 7.2$ Hz, 1H), 6.52 (d, $J = 14.8$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 162.9, 137.1, 136.4, 131.7 (q, $^2J_{\text{CF}} = 31.7$ Hz), 128.8, 128.6, 126.5, 125.5 (q, $^3J_{\text{CF}} = 3.3$ Hz), 125.4, 123.91 (q, $^1J_{\text{CF}} = 270.6$ Hz), 123.88, 113.8. ^{19}F NMR (376 MHz, DMSO- d_6) δ : -61.7. IR (neat cm^{-1}) 3336, 1645, 1527, 1487, 1323, 1169, 1154, 1111, 1064, 1015, 941, 856, 770, 749, 688, 666. Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{NO}$: C, 65.98; H, 4.15; Found: C, 65.75; H, 4.20.

(E)-4-nitro-N-styrylbenzamide (1g)

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.10 g, 6.0 mmol, 1.0 equiv), 4-nitrobenzamide (1.20 g, 7.2 mmol, 1.2 equiv), K_2CO_3 (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (258 μL , 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:4, then 1:2. 609 mg, 2.27 mmol, 38%; yellow solid. **m.p.**: 224–225 °C. ^1H NMR (400 MHz, DMSO- d_6) δ : 10.93 (d, $J = 8.8$ Hz, 1H), 8.36 (dd, $J = 8.8$ Hz, 1.6 Hz, 2H), 8.20 (dd, $J = 8.8$ Hz, 2.0 Hz, 2H), 7.64 (dd, $J = 14.4$ Hz, 9.6 Hz, 1H), 7.41 (d, $J = 7.6$ Hz, 2H), 7.31 (t, $J = 7.6$ Hz, 2H), 7.18 (t, $J = 7.6$ Hz, 1H), 6.51 (d, $J = 14.8$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 162.4, 149.3, 138.9, 136.3, 129.1, 128.7, 126.6, 125.4, 123.8, 123.6, 114.2. IR (neat cm^{-1}) 3306, 1636, 1598, 1518, 1482, 1310, 1285, 1170, 1109, 937, 865, 852, 749, 685. Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3$: C, 67.16; H, 4.51; Found: C, 67.04; H, 4.46.

(E)-3-nitro-N-styrylbenzamide (1h)³⁵

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.54 g, 8.4 mmol, 1.4 equiv), 3-nitrobenzamide (997 mg, 6.0 mmol, 1.0 equiv), K_2CO_3 (1.66 g, 12.0 mmol, 2.0 equiv), CuI (572 mg, 3.0 mmol, 50 mol%), DMEDA (387 μL , 3.6 mmol, 60 mol%), and THF (12.0 mL,

0.5 M); EtOAc / hexanes = 1:5, then 1:2. 875 mg, 3.26 mmol, 54%; yellow solid. **m.p.**: 180-181 °C. (lit.: 178-179 °C). ³⁵¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.97 (d, *J* = 9.6 Hz, 1H), 8.81 (s, 1H), 8.43-8.39 (ovrlp, 2H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 14.4 Hz, 9.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 14.8 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 161.9, 147.8, 136.3, 134.7, 134.1, 130.3, 128.8, 126.5, 126.4, 125.4, 123.8, 122.3, 114.0. **IR** (neat cm⁻¹) 3301, 1638, 1524, 1348, 1177, 1074, 944, 909, 864, 818, 750, 714, 692, 666.

(*E*)-*N*-(4-methoxystyryl)benzamide (**1i**)³⁶

Synthesized from (*E*)-1-(2-bromovinyl)-4-methoxybenzene²¹ (1.53 g, 7.2 mmol, 1.2 equiv), benzamide (727 mg, 6.0 mmol, 1.0 equiv), K₂CO₃ (1.66 g, 12.0 mmol, 2.0 equiv), CuI (343 mg, 1.8 mmol, 30 mol%), DMEDA (387 μL, 3.6 mmol, 60 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:2, then 2:1. The isolated white solid was further purified by recrystallization from acetone / methanol / hexanes (~3:1:5) via slow evaporation with the aid of a rotary evaporator. 741 mg, 2.93 mmol, 49%; white solid. **m.p.**: 192-193 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.55 (d, *J* = 9.6 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 2H), 7.61-7.50 (ovrlp, 4H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 14.4 Hz, 1H), 3.74 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 163.9, 158.0, 133.5, 131.8, 129.0, 128.5, 127.6, 126.5, 122.4, 114.2, 112.8, 55.1. **IR** (neat cm⁻¹) 3319, 1636, 1605, 1504, 1484, 1285, 1244, 1177, 1031, 942, 846, 811, 690, 664.

(*E*)-4-(2-benzamidovinyl)phenyl acetate (**1j**)

Synthesized from (*E*)-4-(2-bromovinyl)phenyl acetate (**S1**) (1.86 g, 7.7 mmol, 1.1 equiv), benzamide (848 mg, 7.0 mmol, 1.0 equiv), K₂CO₃ (1.26 g, 9.1 mmol, 1.3 equiv), CuI (400 mg, 2.1 mmol, 30 mol%), DMEDA (452 μL, 4.2 mmol, 60 mol%), and THF (14.0 mL, 0.5 M); EtOAc / hexanes = 1:6, then 2:3. The isolated white solid was further purified by recrystallization from EtOAc / methanol (~3:1) via slow evaporation with the aid of a rotary evaporator. 474 mg, 1.69 mmol, 24%; white solid. **m.p.**: 205-207 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.66 (d, *J* = 10.0 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 2H), 7.65 (dd, *J* = 14.8 Hz, 10.0 Hz, 1H), 7.61-7.51 (ovrlp, 3H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 14.4 Hz, 1H), 2.26 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 169.3, 164.1, 148.9, 134.3, 133.3, 132.0, 128.5, 127.7, 126.2, 124.3, 122.1, 112.1, 20.9. **IR** (neat cm⁻¹) 3304, 1755, 1639, 1505, 1371, 1331, 1226, 1016, 949, 915, 796, 694. **Anal.** Calcd. for C₁₇H₁₅NO₃: C, 72.58; H, 5.37. Found: C, 72.39; H, 5.27.

(*E*)-*N*-(4-methylstyryl)benzamide (**1k**)¹³

Synthesized from (*E*)-1-(2-bromovinyl)-4-methylbenzene²¹ (1.38 g, 7.0 mmol, 1.0 equiv), benzamide (1.02 mg, 8.4 mmol, 1.2 equiv), K₂CO₃ (1.93 g, 14.0 mmol, 2.0 equiv), CuI (267 mg, 1.4 mmol, 20 mol%), DMEDA (300 μL, 2.8 mmol, 40 mol%), and THF (14.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 1.18 g, 4.98 mmol, 71%; off-white solid. **m.p.**: 174-176 °C (lit.: 178-179 °C). ¹³¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.61 (d, *J* = 9.6 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 2H), 7.66-7.57 (ovrlp, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.45 (d, *J* = 14.8 Hz, 1H), 2.27 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 164.0, 135.5, 133.7, 133.4, 131.9, 129.4, 128.5, 127.6, 125.2, 123.4, 113.0, 20.8. **IR** (neat cm⁻¹) 3301, 1638, 1531, 1506, 1309, 1285, 1170, 956, 925, 794, 692. **Anal.** Calcd. for C₁₆H₁₅NO: C, 80.98; H, 6.37. Found: C, 80.71; H, 6.41.

(*E*)-*N*-(4-chlorostyryl)benzamide (**1l**)

Synthesized from (*E*)-1-(2-bromovinyl)-4-chlorobenzene (1.31 g, 6.0 mmol, 1.0 equiv), benzamide (872 mg, 7.2 mmol, 1.2 equiv), K₂CO₃ (1.66 g, 12.0 mmol, 2.0 equiv), CuI (286 mg, 1.5 mmol, 25 mol%), DMEDA (322 μL, 3.0 mmol, 50 mol%), and THF (12.0 mL, 0.5

M); EtOAc / hexanes = 1:7, then 1:3. 987 mg, 3.83 mmol, 64%; pale yellow solid. **m.p.**: 181–183 °C. **¹H NMR** (400 MHz, DMSO-*d*₆) δ: 10.68 (d, *J* = 10.0 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.68 (dd, *J* = 14.8 Hz, 10.0 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.45 (d, *J* = 14.8 Hz, 1H). **¹³C NMR** (100 MHz, DMSO-*d*₆) δ: 164.1, 135.7, 133.3, 132.0, 130.4, 128.6, 128.5, 127.7, 126.9, 125.0, 111.6. **IR** (neat cm⁻¹) 3338, 1634, 1516, 1479, 1326, 1298, 1275, 1166, 1091, 1010, 945, 852, 808, 716, 692, 657. **Anal.** Calcd. for C₁₅H₁₂ClNO: C, 69.91; H, 4.69. Found: C, 69.82; H, 4.69.

(*E*)-4-bromo-*N*-(4-bromostyryl)benzamide (1m)

Synthesized from (*E*)-1-bromo-4-(2-bromovinyl)benzene (**S2**) (2.20 g, 8.4 mmol, 1.4 equiv), 4-bromobenzamide (1.20 g, 6.0 mmol, 1.0 equiv), K₂CO₃ (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (258 μL, 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:6, then 2:5. The isolated off-white solid was further purified by recrystallization from acetone / EtOAc / hexanes (~1:1:2) via slow evaporation with the aid of a rotary evaporator. 1.02 g, 2.67 mmol, 45%; off-white solid. **m.p.**: 227–230 °C. **¹H NMR** (400 MHz, DMSO-*d*₆) δ: 10.74 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.67 (dd, *J* = 14.0 Hz, 10.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 6.43 (d, *J* = 14.8 Hz, 1H). **¹³C NMR** (100 MHz, DMSO-*d*₆) δ 163.1, 135.9, 132.3, 131.5, 129.7, 127.3, 125.8, 124.9, 118.9, 112.0. **IR** (neat cm⁻¹) 3309, 1639, 1588, 1521, 1477, 1334, 1274, 1170, 1072, 1008, 946, 938, 839, 804, 753, 700, 679. **Anal.** Calcd. for C₁₅H₁₁Br₂NO: C, 47.28; H, 2.91. Found: C, 47.03; H, 2.85.

(*E*)-4-(*tert*-butyl)-*N*-(4-fluorostyryl)benzamide (1n)

Synthesized from (*E*)-1-(2-bromovinyl)-4-fluorobenzene (**S3**) (1.21 g, 6.0 mmol, 1.0 equiv), 4-(*tert*-butyl)benzamide (1.28 g, 7.2 mmol, 1.2 equiv), K₂CO₃ (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (258 μL, 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 755 mg, 2.54 mmol, 42%; off-white solid. **m.p.**: 181–182 °C. **¹H NMR** (400 MHz, DMSO-*d*₆) δ: 10.55 (d, *J* = 9.6 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.62 (dd, *J* = 14.4 Hz, 9.6 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.43 (dd, ³*J*_{HH} = 8.8 Hz, ⁴*J*_{HF} = 5.6 Hz, 2H), 7.12 (dd, ³*J*_{HH} = 8.8 Hz, ³*J*_{HF} = 8.8 Hz, 2H), 1.30 (s, 9H). **¹³C NMR** (100 MHz, DMSO-*d*₆) δ: 163.9, 160.8 (d, ¹*J*_{CF} = 241.5 Hz), 154.8, 133.2 (d, ⁴*J*_{CF} = 3.1 Hz), 130.6, 127.5, 126.9 (d, ³*J*_{CF} = 8.7 Hz), 125.2, 124.2, 115.5 (d, ²*J*_{CF} = 21.4 Hz), 111.6, 34.7, 30.9. **¹⁹F NMR** (376 MHz, DMSO-*d*₆) δ: -115.9. **IR** (neat cm⁻¹) 3243, 2968, 1633, 1532, 1495, 1319, 1302, 1283, 1233, 1171, 1155, 962, 852, 816, 749, 700. **Anal.** Calcd. for C₁₉H₂₀FNO: C, 76.74; H, 6.78. Found: C, 76.55; H, 6.91.

(*E*)-*N*-(3,4-difluorostyryl)-3,4,5-trimethoxybenzamide (1o)

Synthesized from (*E*)-4-(2-bromovinyl)-1,2-difluorobenzene (**S4**) (1.84 g, 8.4 mmol, 1.2 equiv), 3,4,5-trimethoxybenzamide (1.48 g, 7.0 mmol, 1.0 equiv), K₂CO₃ (1.93 g, 14.0 mmol, 2.0 equiv), CuI (400 mg, 2.1 mmol, 30 mol%), DMEDA (451 μL, 4.2 mmol, 60 mol %), and THF (14.0 mL, 0.5 M); EtOAc / hexanes = 1:6, then 2:5. 1.27 g, 3.64 mmol, 52%; white solid. **m.p.**: 158–159 °C. **¹H NMR** (400 MHz, DMSO-*d*₆) δ: 10.55 (d, *J* = 9.6 Hz, 1H), 7.66 (dd, *J* = 14.8 Hz, 9.6 Hz, 1H), 7.53–7.48 (m, 1H), 7.35–7.28 (ovrlp, 3H), 7.23 (br, 1H), 6.41 (d, *J* = 14.8 Hz, 1H), 3.87 (s, 6H), 3.73 (s, 3H). **¹³C NMR** (100 MHz, DMSO-*d*₆) δ: 163.6, 152.7, 149.9 (dd, ¹*J*_{CF} = 243.1 Hz, ²*J*_{CF} = 12.7 Hz), 148.0 (dd, ¹*J*_{CF} = 243.5 Hz, ²*J*_{CF} = 12.8 Hz), 140.7, 134.7 (dd, ³*J*_{CF} = 6.2 Hz, ⁴*J*_{CF} = 3.6 Hz), 128.3, 125.7, 122.0 (dd, ³*J*_{CF} = 6.2 Hz, ⁴*J*_{CF} = 2.9 Hz), 117.6 (d, ²*J*_{CF} = 17.2 Hz), 113.7 (d, ²*J*_{CF} = 17.5 Hz), 110.9, 105.3, 60.1, 56.1. **¹⁹F NMR** (376 MHz, DMSO-*d*₆) δ: -138.3, -141.4. **IR** (neat cm⁻¹) 3286, 1638, 1581, 1493, 1413, 1337, 1234, 1124, 995, 942, 868, 847, 814, 754, 708, 674. **Anal.** Calcd. for C₁₈H₁₇F₂NO₄: C, 61.89; H, 4.91. Found: C, 61.91; H, 5.00.

(E)-2-methyl-N-(2-methylstyryl)benzamide (1p)

Synthesized from (*E*)-1-(2-bromovinyl)-2-methylbenzene (**S5**) (1.18 g, 6.0 mmol, 1.0 equiv), 2-methylbenzamide (973 mg, 7.2 mmol, 1.2 equiv), K_2CO_3 (1.66 g, 12.0 mmol, 2.0 equiv), CuI (343 mg, 1.8 mmol, 30 mol%), DMEDA (397 μ L, 3.6 mmol, 60 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:7; then 1:4. 890 mg, 3.54 mmol, 59%; white solid. **m.p.**: 184-185 °C. 1H NMR (400 MHz, DMSO- d_6) δ : 10.57 (d, J = 10.0 Hz, 1H), 7.54-7.47 (ovrlp, 3H), 7.40 (t, J = 7.2 Hz, 1H), 7.31-7.28 (ovrlp, 2H), 7.18-7.15 (ovrlp, 2H), 7.09 (t, J = 7.2 Hz, 1H), 6.56 (d, J = 14.8 Hz, 1H), 2.41 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 166.5, 135.9, 135.6, 135.1, 134.1, 130.7, 130.2, 130.0, 127.4, 126.2, 126.2, 125.6, 124.3, 124.0, 110.3, 19.5. **IR** (neat cm^{-1}) 3263, 1637, 1517, 1471, 1322, 1281, 1170, 1098, 946, 782, 742, 729, 703, 663. **Anal.** Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82. Found: C, 81.02; H, 6.81.

(E)-N-(2-methylstyryl)-2-naphthamide (1q)

Synthesized from (*E*)-1-(2-bromovinyl)-2-methylbenzene (**S5**) (1.66 g, 8.4 mmol, 1.2 equiv), 2-naphthamide (1.20 g, 7.0 mmol, 1.0 equiv), K_2CO_3 (1.93 g, 14.0 mmol, 2.0 equiv), CuI (400 mg, 2.1 mmol, 30 mol%), DMEDA (452 μ L, 4.2 mmol, 60 mol%), and THF (14.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:3. 1.23 g, 4.27 mmol, 61%; off-white solid. **m.p.**: 179-181 °C. 1H NMR (400 MHz, DMSO- d_6) δ : 10.87 (d, J = 9.6 Hz, 1H), 8.64 (s, 1H), 8.10-8.04 (ovrlp, 3H), 8.01 (d, J = 8.4 Hz, 1H), 7.68-7.60 (ovrlp, 3H), 7.51 (d, J = 7.6 Hz, 1H), 7.18-7.15 (ovrlp, 2H), 7.10 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 14.4 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 164.0, 135.3, 134.4, 134.2, 132.1, 130.7, 130.3, 129.0, 128.2, 128.1, 128.0, 127.7, 126.9, 126.3, 124.7, 124.2, 124.0, 110.6, 19.6. **IR** (neat cm^{-1}) 3275, 1636, 1521, 1478, 1327, 1286, 1239, 1089, 951, 822, 741, 718. **Anal.** Calcd. for $C_{20}H_{17}NO$: C, 83.59; H, 5.96. Found: C, 83.41; H, 6.04.

N-((E)-styryl)cinnamamide (3a)³³

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.32 g, 7.2 mmol, 1.2 equiv), *trans*-cinnamamide (883 mg, 6.0 mmol, 1.0 equiv), K_2CO_3 (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (258 μ L, 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:4, then 2:1. 1.31 g, 5.26 mmol, 88%; yellow solid. **m.p.**: 196-198 °C. 1H NMR (400 MHz, DMSO- d_6) δ : 10.50 (d, J = 10.0 Hz, 1H), 7.65-7.57 (ovrlp, 4H), 7.46-7.38 (ovrlp, 5H), 7.29 (t, J = 7.6 Hz, 2H), 7.15 (t, J = 7.2 Hz, 1H), 6.74 (d, J = 16.0 Hz, 1H), 6.28 (d, J = 14.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 162.6, 140.6, 136.5, 134.6, 129.9, 129.0, 128.7, 127.8, 126.2, 125.2, 123.8, 120.9, 112.2. **IR** (neat cm^{-1}) 3373, 3159, 3027, 1635, 1606, 1520, 1341, 1234, 1195, 983, 957, 748, 679.

N-((1E,3E)-4-phenylbuta-1,3-dien-1-yl)benzamide (3b)

Synthesized from ((1*E*)-4-bromobuta-1,3-dien-1-yl)benzene ((3*Z*) : (3*E*) = 2.6 : 1.0)²³ (3.76 g, 18.0 mmol, 3.0 equiv), benzamide (727 mg, 6.0 mmol, 1.0 equiv), K_2CO_3 (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (258 μ L, 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 1.13 g, 4.53 mmol, 70%; yellow solid. **m.p.**: 179-181 °C. 1H NMR (400 MHz, DMSO- d_6) δ : 10.62 (d, J = 10.0 Hz, 1H), 7.97 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.2 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.36 (dd, J = 13.6 Hz, 10.4 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 7.03 (dd, J = 15.2 Hz, 11.2 Hz, 1H), 6.49 (d, J = 15.6 Hz, 1H), 6.36 (dd, J = 13.2 Hz, 11.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 163.8, 137.6, 133.3, 131.9, 128.6, 128.5, 128.4, 128.1, 128.0, 127.6, 126.7, 125.8, 114.3. **IR** (neat cm^{-1}) 3328, 3060, 1634, 1510, 1485, 1444, 1340, 1300, 1264, 1150, 1072, 968, 908, 795, 744, 688. **HRMS** (ESI) calcd for $C_{17}H_{15}NO$ [M+H]: 250.1226; found 250.1235.

(E)-3-(3,4-dimethoxyphenyl)-N-((E)-4-methoxystyryl)acrylamide (3c)

Synthesized from (*E*)-1-(2-bromovinyl)-4-methoxybenzene²¹ (1.41 g, 6.6 mmol, 1.1 equiv), (*E*)-3-(3,4-dimethoxyphenyl)acrylamide²⁴ (1.24 g, 6.0 mmol, 1.0 equiv), K₂CO₃ (1.66 g, 12.0 mmol, 2.0 equiv), CuI (343 mg, 1.8 mmol, 30 mol%), DMEDA (387 μL, 3.6 mmol, 60 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1: 4, then 4:1. The isolated yellow solid was further purified by recrystallization from acetone / EtOAc / hexanes (~1:1:2) via slow evaporation with the aid of a rotary evaporator. 1.31 g, 3.87 mmol, 64%; yellow solid. **m.p.**: 195-197 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.29 (d, *J* = 10.4 Hz, 1H), 7.54 (d, *J* = 15.6 Hz, 1H), 7.45 (dd, *J* = 14.8 Hz, 10.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 1.6 Hz, 1H), 7.18 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.59 (d, *J* = 15.6 Hz, 1H), 6.20 (d, *J* = 14.8 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 162.7, 157.9, 150.5, 148.9, 140.4, 129.1, 127.5, 126.4, 122.1, 121.7, 118.6, 114.2, 111.8, 111.7, 110.2, 55.5, 55.4, 55.0. **IR** (neat cm⁻¹) 3260, 1640, 1622, 1503, 1440, 1339, 1240, 1190, 1137, 1020, 964, 947, 845, 807, 691, 585. **Anal.** Calcd. for C₂₀H₂₁NO₄: C, 70.78; H, 6.24. Found: C, 70.48; H, 6.13.

(E)-N-(dec-1-en-1-yl)benzamide (3d)

Synthesized from (*E*)-1-iododec-1-ene²² (2.24 g, 8.4 mmol, 1.2 equiv), benzamide (848 mg, 7.0 mmol, 1.0 equiv), K₂CO₃ (1.93 g, 14.0 mmol, 2.0 equiv), CuI (267 mg, 1.4 mmol, 20 mol%), DMEDA (301 μL, 2.80 mmol, 40 mol%), and THF (14.0 mL, 0.5 M) at 70 °C; EtOAc / hexanes = 1:10, then 1:7. 1.19 g, 4.6 mmol, 66%; white solid. **m.p.**: 69-70 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.14 (d, *J* = 9.6 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 2H), 6.83 (dd, *J* = 14.4 Hz, 9.6 Hz, 1H), 5.46 (dt, *J* = 14.4 Hz, 7.2 Hz, 1H), 2.02 (td, *J* = 6.9 Hz, 6.8 Hz, 2H), 1.35-1.25 (ovrlp, 12H), 0.85 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 163.5, 133.7, 131.5, 128.3, 127.4, 123.6, 113.3, 31.3, 29.61, 29.56, 28.9, 28.7, 28.6, 22.1, 13.9. **IR** (neat cm⁻¹) 3322, 2922, 2850, 1636, 1518, 1488, 1326, 1294, 1260, 1185, 961, 857, 795, 725, 692, 638. **Anal.** Calcd. for C₁₇H₂₅NO: C, 78.72; H, 9.71. Found: C, 78.91; H, 9.62.

(E)-N-styrylpivalamide (3e)³⁷

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.10 g, 6.0 mmol, 1.0 equiv), pivalamide (728 mg, 7.2 mmol, 1.2 equiv), K₂CO₃ (1.70 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (259 μL, 2.4 mmol, 40 mol%), and THF (6.0 mL, 1.0 M); EtOAc / hexanes = 1:10. 974 mg, 4.79 mmol, 80%; white solid. **m.p.**: 146-147 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.65 (d, *J* = 10.0 Hz, 1H), 7.45 (dd, *J* = 14.8 Hz, 10.0 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.33 (d, *J* = 14.8 Hz, 1H), 1.18 (s, 9H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 175.6, 136.9, 128.7, 125.9, 125.0, 124.4, 111.4, 38.3, 27.0. **IR** (neat cm⁻¹) 3279, 2973, 1632, 1524, 1474, 1398, 1303, 1285, 1235, 1183, 952, 746, 718, 691.

(E)-N-styrylcyclohexanecarboxamide (3f)³⁵

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.10 g, 6.0 mmol, 1.0 equiv), cyclohexanecarboxamide (916 mg, 7.2 mmol, 1.2 equiv), K₂CO₃ (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (258 μL, 2.4 mmol, 40 mol%), and THF (6.0 mL, 1.0 M); EtOAc / hexanes = 1: 10, then 1:7. 869 mg, 3.79 mmol, 63%; white solid. **m.p.**: 151-152 °C. (lit.: 148-150 °C). ³⁵¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.04 (d, *J* = 10.4 Hz, 1H), 7.41 (dd, *J* = 14.8 Hz, 10.4 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.15 (d, *J* = 14.8 Hz, 1H), 2.23 (m, 1H), 1.77-1.72 (ovrlp, 4H), 1.63 (d, *J* = 8.8 Hz, 1H), 1.43-1.35 (m, 2H), 1.29-1.12 (ovrlp, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 173.3, 136.8, 128.6, 125.9, 125.0, 123.9, 111.0, 43.9, 29.0, 25.4, 15.2.

IR (neat cm^{-1}) 3262, 2933, 2850, 1665, 1634, 1536, 1444, 1252, 1227, 1194, 956, 748, 718, 688.

(*E*)-*N*-(2-(thiophen-3-yl)vinyl)benzamide (**3g**)

Synthesized from 3-(2-bromovinyl)thiophene (**Z**) : (**E**) = 4.3 : 1.0 (**S6**) (1.96 g, 10.4 mmol, 2.1 equiv), benzamide (606 mg, 5.0 mmol, 1.0 equiv), K_2CO_3 (1.38 g, 10.0 mmol, 2.0 equiv), CuI (191 mg, 1.0 mmol, 20 mol%), DMEDA (215 μL , 2.0 mmol, 40 mol%), and THF (10.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 821 mg, 3.58 mmol, 72%; off-white solid. **m.p.**: 147-149 °C. **$^1\text{H NMR}$** (400 MHz, $\text{DMSO}-d_6$) δ : 10.54 (d, J = 10.0 Hz, 1H), 7.97 (d, J = 7.2 Hz, 2H), 7.61-7.49 (ovrlp, 5H), 7.36 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 4.8 Hz, 1H), 6.52 (d, J = 14.8 Hz, 1H). **$^{13}\text{C NMR}$** (100 MHz, $\text{DMSO}-d_6$) δ : 164.0, 138.5, 133.5, 131.8, 128.5, 127.6, 126.7, 124.7, 124.1, 120.1, 108.3. **IR** (neat cm^{-1}) 3308, 1638, 1539, 1506, 1485, 1316, 1250, 1200, 952, 926, 771, 726, 672, 627. **Anal.** Calcd. for $\text{C}_{13}\text{H}_{11}\text{NOS}$: C, 68.09; H, 4.84. Found: C, 67.81; H, 4.72.

(*E*)-*N*-styrylthiophene-3-carboxamide (**3h**)

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.32 g, 7.2 mmol, 1.2 equiv), thiophene-3-carboxamide (763 mg, 6.0 mmol, 1.0 equiv), K_2CO_3 (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (258 μL , 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 990 mg, 4.32 mmol, 72%; off-white solid. **m.p.**: 166-167 °C. **$^1\text{H NMR}$** (400 MHz, $\text{DMSO}-d_6$) δ : 10.48 (d, J = 9.6 Hz, 1H), 8.35 (dd, J = 2.4 Hz, 1.6 Hz, 1H), 7.66-7.60 (ovrlp, 3H), 7.39 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H), 6.42 (d, J = 14.8 Hz, 1H). **$^{13}\text{C NMR}$** (100 MHz, $\text{DMSO}-d_6$) δ : 159.6, 136.63, 136.60, 130.2, 128.8, 127.2, 127.0, 126.2, 125.2, 123.9, 112.5. **IR** (neat cm^{-1}) 3230, 1619, 1531, 1486, 1304, 1283, 1262, 1165, 1071, 956, 853, 813, 721, 691. **Anal.** Calcd. for $\text{C}_{13}\text{H}_{11}\text{NOS}$: C, 68.09; H, 4.84. Found: C, 67.88; H, 4.75.

(*E*)-*N*-styrylthiophene-2-carboxamide (**3i**)

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.32 g, 7.2 mmol, 1.2 equiv), thiophene-2-carboxamide (763 mg, 6.0 mmol, 1.0 equiv), K_2CO_3 (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (258 μL , 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 856 mg, 3.73 mmol, 62%; off-white solid. **m.p.**: 154-155 °C. **$^1\text{H NMR}$** (400 MHz, $\text{DMSO}-d_6$) δ : 10.66 (d, J = 9.6 Hz, 1H), 7.99 (d, J = 3.6 Hz, 1H), 7.86 (d, J = 4.8 Hz, 1H), 7.60 (dd, J = 14.8 Hz, 9.6 Hz, 1H), 7.39 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 7.23 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 6.44 (d, J = 14.8 Hz, 1H). **$^{13}\text{C NMR}$** (100 MHz, $\text{DMSO}-d_6$) δ : 158.8, 138.8, 136.5, 132.2, 129.3, 128.7, 128.2, 126.3, 125.3, 123.7, 112.7. **IR** (neat cm^{-1}) 3223, 1615, 1526, 1487, 1413, 1353, 1307, 1288, 1171, 958, 850, 757, 719, 690. **Anal.** Calcd. for $\text{C}_{13}\text{H}_{11}\text{NOS}$: C, 68.09; H, 4.84. Found: C, 67.83; H, 4.81.

(*E*)-*N*-styrylfuran-2-carboxamide (**3j**)

Synthesized from (*E*)-(2-bromovinyl)benzene²¹ (1.10 g, 6.0 mmol, 1.0 equiv), furan-2-carboxamide (800 mg, 7.2 mmol, 1.2 equiv), K_2CO_3 (1.66 g, 12.0 mmol, 2.0 equiv), CuI (229 mg, 1.2 mmol, 20 mol%), DMEDA (259 μL , 2.4 mmol, 40 mol%), and THF (12.0 mL, 0.5 M); EtOAc / hexanes = 1:7, then 1:4. 843 mg, 3.95 mmol, 66%; off-white solid. **m.p.**: 184-185 °C. **$^1\text{H NMR}$** (400 MHz, $\text{DMSO}-d_6$) δ : 10.62 (d, J = 9.6 Hz, 1H), 7.94 (s, 1H), 7.59 (dd, J = 14.8 Hz, 10.0 Hz, 1H), 7.38-7.27 (ovrlp, 5H), 7.15 (t, J = 7.2 Hz, 1H), 6.69 (m, 1H), 6.48 (d, J = 14.8 Hz, 1H). **$^{13}\text{C NMR}$** (100 MHz, $\text{DMSO}-d_6$) δ : 155.2, 147.0, 146.0, 136.5, 128.7, 126.3, 125.3, 123.1, 115.1, 113.1, 112.3. **IR** (neat cm^{-1}) 3205, 1628, 1584, 1519, 1486, 1465, 1308, 1263, 1177, 1018, 961, 863, 739, 689. **Anal.** Calcd. for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: C, 73.23; H, 5.20. Found: C, 72.95; H, 5.06.

(E)-N-(2-(1-benzoyl-1*H*-indol-5-yl)vinyl)thiophene-3-carboxamide (3k)

Synthesized from 5-(2-bromovinyl)-1*H*-indol-1-yl(phenyl)methanone ((*Z*) : (*E*) = 20 : 1) (**S7**) (1.17 g, 3.59 mmol, 1.2 equiv), thiophene-3-carboxamide (380 mg, 2.99 mmol, 1.0 equiv), K₂CO₃ (826 mg, 5.98 mmol, 2.0 equiv), CuI (171 mg, 0.90 mmol, 30 mol%), DMEDA (194 μL, 1.8 mmol, 60 mol%), and THF (6.0 mL, 0.5 M); EtOAc / hexanes = 1:5, then 1:2. 310 mg, 0.83 mmol, 28%; pale yellow solid. **m.p.**: 208-210 °C. **¹H NMR** (400 MHz, DMSO-*d*₆) δ: 10.49 (d, *J* = 10.0 Hz, 1H), 8.36 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.71-7.66 (ovrlp, 5 H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 3.6 Hz, 1H), 6.71 (d, *J* = 3.6 Hz, 1H), 6.55 (d, *J* = 14.8 Hz, 1H). **¹³C NMR** (100 MHz, DMSO-*d*₆) δ: 168.0, 159.6, 136.7, 134.1, 134.0, 132.6, 132.0, 131.2, 130.1, 129.0, 128.7, 128.6, 127.1, 127.0, 123.4, 122.1, 117.6, 116.1, 112.8, 108.6. **IR** (neat cm⁻¹) 3274, 1679, 1633, 1527, 1459, 1367, 1335, 1285, 1190, 1067, 945, 881, 806, 766, 697. **Anal.** Calcd. for C₂₂H₁₆N₂O₂S: C, 70.95; H, 4.33. Found: C, 70.65; H, 4.59.

General Procedure for the Optimization of Cu(II)-Catalyzed Oxidative Cyclization of Enamide (Table 1)

A oven-dried 20 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with (*E*)-*N*-styrylbenzamide (**1a**) (0.2 mmol, 1.0 equiv), tetrabutylammonium halide (TBAB or TBAC) (0.24 mmol, 1.2 equiv), potassium persulfate (K₂S₂O₈) (0.26 mmol, 1.3 equiv), metal catalyst (5-20 mol%), and ligand (0-40 mol%) (if solid). The tube was then evacuated and backfilled with argon (this sequence was repeated a total of three times). Ligand (0-40 mol%) (if liquid) was added into the tube followed by anhydrous acetonitrile (2.0 mL, 0.1 M) via syringe. The sealed tube was then vigorously stirred at room temperature for 24 h. After completion, *n*-dodecane (20 μL, 0.088 mol) was added into the reaction mixture. The reaction mixture was extracted with ethyl acetate (3 mL) and deionized water (10 mL). Aliquots from the organic fractions were filtered through silica gel for GC analysis to determine the reaction conversion and the GC-yield of 2,5-diphenyloxazole **2a** using *n*dodecane as an internal standard. The aqueous fraction was further washed with ethyl acetate (2 × 3 mL). The combined organic fractions were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography using ethyl acetate (EtOAc) / hexanes (1:12) as an eluent to afford **2a** to determine the isolated yield.

General Procedure for Synthesis of Oxazoles via Cu(II)-Catalyzed Oxidative Cyclization of Enamides (Tables 2 and 3)

Unless otherwise noted, an oven-dried 25 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with enamide (**1a-q**, **3a-k**) (1.0 mmol, 1.0 equiv), copper(II) bromide (CuBr₂) (16.8 mg, 0.075 mmol, 7.5 mol%), tetrabutylammonium bromide (TBAB) (387 mg, 1.2 mmol, 1.2 equiv), and potassium persulfate (K₂S₂O₈) (351 mg, 1.3 mmol, 1.3 equiv). The tube was then evacuated and backfilled with argon (this sequence was repeated a total of three times). Ethyl nicotinate (20.5 μL, 0.15 mmol, 15 mol %) was added into the tube followed by anhydrous acetonitrile (10.0 mL, 0.1 M) via syringe. The sealed tube was then vigorously stirred at room temperature for 24 h. After completion, the reaction mixture was extracted with ethyl acetate (10 mL) and deionized water (20 mL). The aqueous fraction was further washed with ethyl acetate (2 × 5 mL). The combined organic fractions were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography using ethyl acetate (EtOAc) / hexanes as an eluent to afford the oxazole products.

2,5-Diphenyloxazole (2a)³⁸

Synthesized from (*E*)-*N*-styrylbenzamide (**1a**) (233 mg); EtOAc / hexanes = 1 : 12. 175 mg, 79%; white solid. **m.p.**: 70-71 °C (lit: 70-71 °C). ³⁸¹H NMR (400 MHz, CDCl₃) δ: 8.08 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.46-7.36 (ovrlp, 6H), 7.28 (t, *J* = 7.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 161.1, 151.2, 130.3, 128.9, 128.8, 128.4, 128.0, 127.5, 126.3, 124.2, 123.5. **IR** (neat cm⁻¹) 1480, 1446, 1133, 1058, 952, 822, 775, 759, 705, 684. **Anal.** Calcd. for C₁₅H₁₁NO: C, 81.43; H, 5.01. Found: C, 81.39; H, 5.10.

2-(4-Methoxyphenyl)-5-phenyloxazole (2b)¹³

Synthesized from (*E*)-4-methoxy-*N*-styrylbenzamide (**1b**) (253 mg); EtOAc / hexanes = 1:10, then 1:8. 181 mg, 72%; white solid. **m.p.**: 100-101 °C (lit: 94-96 °C). ¹³¹H NMR (400 MHz, CDCl₃) δ: 8.01 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.41-7.37 (ovrlp, 3H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 161.3, 161.2, 150.7, 128.9, 128.2, 127.9, 124.0, 123.3, 120.3, 114.2, 55.3. **IR** (neat cm⁻¹) 1610, 1495, 1303, 1250, 1173, 1135, 1024, 828, 762, 736, 687, 615. **Anal.** Calcd. for C₁₆H₁₃NO₂: C, 76.48; H, 5.21. Found: C, 76.29; H, 5.33.

5-Phenyl-2-(*p*-tolyl)oxazole (2c)³⁸

Synthesized from (*E*)-4-methyl-*N*-styrylbenzamide (**1c**) (237 mg); EtOAc / hexanes = 1:10. 171 mg, 73%; white solid. **m.p.**: 73 °C (lit: 72-73 °C). ³⁸¹H NMR (400 MHz, CDCl₃) δ: 7.97 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.41-7.37 (ovrlp, 3H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 161.3, 150.9, 140.6, 129.5, 128.9, 128.3, 128.1, 126.2, 124.8, 124.1, 123.3, 21.5. **IR** (neat cm⁻¹) 1495, 1134, 950, 822, 760, 730, 703, 688. **Anal.** Calcd. for C₁₆H₁₃NO: C, 81.68; H, 5.57. Found: C, 81.79; H, 5.69.

2-(4-Chlorophenyl)-5-phenyloxazole (2d)³⁹

Synthesized from (*E*)-4-chloro-*N*-styrylbenzamide (**1d**) (258 mg); EtOAc / hexanes = 1:10. 187 mg, 73%; white solid. **m.p.**: 116-118 °C (lit: 115-117 °C). ³⁹¹H NMR (400 MHz, CDCl₃) δ: 7.96 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.41-7.33 (ovrlp, 5H), 7.23 (t, *J* = 7.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 160.1, 151.4, 136.3, 129.1, 128.9, 128.6, 127.8, 127.5, 125.9, 124.2, 123.5. **IR** (neat cm⁻¹) 1477, 1403, 1132, 1087, 1009, 950, 824, 761, 731, 689. **Anal.** Calcd. for C₁₅H₁₀ClNO: C, 70.46; H, 3.94. Found: C, 70.17; H, 3.82.

2-(4-Fluorophenyl)-5-phenyloxazole (2e)³⁸

Synthesized from (*E*)-4-fluoro-*N*-styrylbenzamide (**1e**) (241 mg). EtOAc / hexanes = 1:10. 170 mg, 71%; off-white solid. **m.p.**: 84-85 °C (lit: 81-82 °C). ³⁸¹H NMR (400 MHz, CDCl₃) δ: 8.04 (dd, ³*J*_{HH} = 8.8 Hz, ⁴*J*_{HF} = 5.2 Hz, 2H), 7.64 (d, ³*J*_{HH} = 7.2 Hz, 2H), 7.41-7.37 (ovrlp, 3H), 7.29 (t, ³*J*_{HH} = 7.2 Hz, 1H), 7.11 (dd, ³*J*_{HH} = 8.8 Hz, ³*J*_{HF} = 8.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ: 164.0 (d, *J*_{CF} = 249.4 Hz), 160.3, 151.3, 128.9, 128.5, 128.3 (d, ³*J*_{CF} = 8.6 Hz), 127.9, 124.1, 123.8 (d, ⁴*J*_{CF} = 3.0 Hz), 123.4, 116.0 (d, ²*J*_{CF} = 21.9 Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ: -109.8. **IR** (neat cm⁻¹) 1608, 1494, 1414, 1220, 1134, 952, 842, 756, 732, 685, 614. **Anal.** Calcd. for C₁₅H₁₀FNO: C, 75.30; H, 4.21. Found: C, 75.08; H, 4.32.

5-Phenyl-2-(4-(trifluoromethyl)phenyl)oxazole (2f)³⁹

Synthesized from (*E*)-*N*-styryl-4-(trifluoromethyl)benzamide (**1f**) (233 mg, 0.80 mmol, 1.0 equiv), CuBr₂ (13.4 mg, 0.06 mmol, 7.5 mol%), TBAB (310 mg, 0.96 mmol, 1.2 equiv), K₂S₂O₈ (281 mg, 1.04 mmol, 1.3 equiv), ethyl nicotinate (16.4 μL, 0.12 mmol, 15 mol%), and acetonitrile (8.0 mL, 0.1 M). EtOAc / hexanes = 1:10. 166 mg, 0.57 mmol, 72%; white

solid. **m.p.**: 110-111 °C (lit. = 109-111 °C). ³⁹**H NMR** (400 MHz, CDCl₃) δ: 8.14 (d, *J* = 8.0 Hz, 2H), 7.69-7.65 (ovrlp, 4H), 7.43-7.39 (ovrlp, 3H), 7.32 (t, *J* = 7.6 Hz, 1H). ¹³**C NMR** (100 MHz, CDCl₃) δ: 159.7, 152.1, 131.8 (q, ²*J*_{CF} = 32.6 Hz), 130.6, 129.0, 128.9, 127.7, 126.4, 125.9 (q, ³*J*_{CF} = 3.5 Hz), 124.4, 124.0 (q, ¹*J*_{CF} = 270.7 Hz), 123.8. ¹⁹**F NMR** (376 MHz, CDCl₃) δ: -63.3. **IR** (neat cm⁻¹) 1485, 1414, 1324, 1168, 1102, 1055, 951, 843, 762, 750, 709, 691, 594. **Anal.** Calcd. for C₁₆H₁₀F₃NO: C, 66.44; H, 3.48. Found: C, 66.19; H, 3.50.

2-(4-Nitrophenyl)-5-phenyloxazole (2g)⁴⁰

Synthesized from (*E*)-4-nitro-*N*-styrylbenzamide (**1g**) (268 mg); EtOAc / hexanes = 1:9. 58 mg, 22%; yellow solid. **m.p.**: 201-203 °C (lit: 207-208 °C). ⁴⁰**H NMR** (400 MHz, CDCl₃) δ: 8.35 (d, *J* = 8.8 Hz, 2H), 8.27 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.54 (s, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H). ¹³**C NMR** (100 MHz, CDCl₃) δ: 159.1, 153.0, 148.7, 133.0, 129.33, 129.25, 127.5, 127.0, 124.7, 124.44, 124.41. **IR** (neat cm⁻¹) 1537, 1514, 1339, 1103, 951, 853, 822, 765, 709, 690. **Anal.** Calcd. for C₁₅H₁₀N₂O₃: 67.67; H, 3.79. Found: C, 67.26; H, 4.10.

2-(3-Nitrophenyl)-5-phenyloxazole (2h)⁴¹

Synthesized from (*E*)-3-nitro-*N*-styrylbenzamide (**1h**) (268 mg); EtOAc / hexanes = 1:9. 116 mg, 44%; pale yellow solid. **m.p.**: 148-149 °C (lit: 148-150 °C). ⁴¹**H NMR** (400 MHz, CDCl₃) δ: 8.89 (t, *J* = 1.6 Hz, 1H), 8.40 (dt, *J* = 7.6 Hz, 1.6 Hz, 1H), 8.28 (ddd, *J* = 8.0 Hz, 2.4 Hz, 1.2 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.48-7.45 (ovrlp, 3H), 7.38 (t, *J* = 7.2 Hz, 1H). ¹³**C NMR** (100 MHz, CDCl₃) δ: 158.8, 152.4, 148.7, 131.8, 130.1, 129.11, 129.07, 129.00, 127.4, 124.6, 124.4, 123.9, 121.1. **IR** (neat cm⁻¹) 1519, 1352, 1135, 940, 816, 768, 742, 710. **Anal.** Calcd. for C₁₅H₁₀N₂O₃: C, 67.67; H, 3.79. Found: C, 67.39; H, 4.02.

5-(4-Methoxyphenyl)-2-phenyloxazole (2i)³⁹

Synthesized from (*E*)-*N*-(4-methoxystyryl)benzamide (**1i**) (253 mg); EtOAc / hexanes = 1:10. 108 mg, 43%; off-white solid. **m.p.**: 80-81 °C (lit.: 78-79 °C). ³⁹**H NMR** (400 MHz, CDCl₃) δ: 8.07 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.46-7.38 (ovrlp, 3H), 7.29 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H). ¹³**C NMR** (100 MHz, CDCl₃) δ: 160.5, 159.8, 151.3, 130.1, 128.8, 127.6, 126.1, 125.7, 121.9, 120.8, 114.4, 55.3. **IR** (neat cm⁻¹) 1618, 1502, 1255, 1175, 1058, 1026, 951, 822, 813, 770, 713, 690. **Anal.** Calcd. for C₁₆H₁₃NO₂: C, 76.48; H, 5.21. Found: C, 76.19; H, 5.35.

4-(2-Phenyloxazol-5-yl)phenyl acetate (2j)

Synthesized from (*E*)-4-(2-benzamidovinyl)phenyl acetate (**1j**) (281 mg); EtOAc / hexanes = 1:10, then 1:5. 226 mg, 81%; off-white solid. **m.p.**: 113-115 °C. ¹**H NMR** (400 MHz, CDCl₃) δ: 8.09 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.50-7.43 (ovrlp, 3H), 7.41 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 2.32 (s, 3H). ¹³**C NMR** (100 MHz, CDCl₃) δ: 169.4, 161.3, 150.7, 150.6, 130.5, 128.9, 127.4, 126.3, 125.9, 125.4, 123.6, 122.3, 21.2. **IR** (neat cm⁻¹) 1748, 1500, 1485, 1373, 1225, 1207, 1167, 1136, 1016, 953, 915, 844. **HRMS** (ESI) calcd for C₁₇H₁₃NO₃ [M+H]⁺: 280.0968; found 280.0966.

2-Phenyl-5-(*p*-tolyl)oxazole (2k)¹³

Synthesized from (*E*)-*N*-(4-methylstyryl)benzamide (**1k**) (237 mg). EtOAc / hexanes = 1:10. 124 mg, 53%; off-white solid. **m.p.**: 77-78 °C (lit: 77-78 °C). ¹³**H NMR** (400 MHz, CDCl₃) δ: 8.08 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.46-7.40 (ovrlp, 3H), 7.35 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 3H). ¹³**C NMR** (100 MHz, CDCl₃) δ: 160.8, 151.4, 138.4,

130.2, 129.6, 128.8, 127.6, 126.2, 125.3, 124.1, 122.8, 21.4. **IR** (neat cm^{-1}) 1543, 1500, 1476, 1446, 1133, 1055, 952, 817, 775, 709, 693, 504, 490. **Anal.** Calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}$: C, 81.68; H, 5.57. Found: C, 81.43; H, 5.81.

5-(4-Chlorophenyl)-2-phenyloxazole (2l)¹³

Synthesized from (*E*)-*N*-(4-chlorostyryl)benzamide (**1l**) (258 mg); EtOAc / hexanes = 1:10. 175 mg, 69%; pale yellow solid. **m.p.**: 104-105 °C (lit: 102-104 °C). **¹H NMR** (400 MHz, CDCl_3) δ : 8.04 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.45-7.39 (ovrlp, 3H), 7.36 (s, 1H), 7.33 (d, J = 8.4 Hz, 2H). **¹³C NMR** (100 MHz, CDCl_3) δ : 161.3, 150.2, 134.1, 130.4, 129.1, 128.8, 127.2, 126.5, 126.3, 125.3, 123.8. **IR** (neat cm^{-1}) 1480, 1448, 1132, 1091, 1011, 951, 818, 772, 705, 686. **Anal.** Calcd. for $\text{C}_{15}\text{H}_{10}\text{ClNO}$: C, 70.46; H, 3.94. Found: C, 70.76; H, 3.84.

2,5-Bis(4-bromophenyl)oxazole (2m)

Synthesized from (*E*)-4-bromo-*N*-(4-bromostyryl)benzamide (**1m**) (381 mg). EtOAc / hexanes = 1:10. 287 mg, 76%; white solid. **m.p.**: 176-178 °C. **¹H NMR** (400 MHz, CDCl_3) δ : 7.95 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.57 (s, 4H), 7.44 (s, 1H). **¹³C NMR** (100 MHz, CDCl_3) δ : 160.7, 150.7, 132.34, 132.29, 127.9, 126.9, 126.3, 125.8, 125.1, 124.2, 122.7. **IR** (neat cm^{-1}) 1474, 1404, 1133, 1073, 1051, 1006, 950, 821, 730, 697. **Anal.** Calcd. for $\text{C}_{15}\text{H}_9\text{Br}_2\text{NO}$: C, 47.53; H, 2.39. Found: C, 47.17; H, 2.35.

2-(4-(*tert*-Butyl)phenyl)-5-(4-fluorophenyl)oxazole (2n)

Synthesized from (*E*)-4-(*tert*-butyl)-*N*-(4-fluorostyryl)benzamide (**1n**) (297 mg); EtOAc / hexanes = 1:10. 230 mg, 78%; off-white solid. **m.p.**: 76-77 °C. **¹H NMR** (400 MHz, CDCl_3) δ : 8.00 (d, J = 8.8 Hz, 2H), 7.62 (dd, $^3J_{\text{HH}} = 9.6$ Hz, $^4J_{\text{HF}} = 5.2$ Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.33 (s, 1H), 7.08 (dd, $^3J_{\text{HH}} = 8.8$ Hz, $^3J_{\text{HF}} = 8.8$ Hz, 2H), 1.34 (s, 9H). **¹³C NMR** (100 MHz, CDCl_3) δ : 162.6 (d, $^1J_{\text{CF}} = 247.2$ Hz), 161.3, 153.8, 150.1, 126.1, 125.9 (d, $^3J_{\text{CF}} = 8.1$ Hz), 125.8, 124.6, 124.5 (d, $^4J_{\text{CF}} = 3.1$ Hz), 123.0, 116.0 (d, $^2J_{\text{CF}} = 21.8$ Hz), 34.9, 31.2. **¹⁹F NMR** (376 MHz, CDCl_3) δ : -112.7. **IR** (neat cm^{-1}) 2951, 1499, 1227, 1140, 951, 827, 750, 708, 615. **Anal.** Calcd. for $\text{C}_{19}\text{H}_{18}\text{FNO}$: C, 77.27; H, 6.14. Found: C, 77.29; H, 6.14.

5-(3,4-Difluorophenyl)-2-(3,4,5-trimethoxyphenyl)oxazole (2o)

Synthesized from (*E*)-*N*-(3,4-difluorostyryl)-3,4,5-trimethoxybenzamide (**1o**) (349 mg). EtOAc / hexanes = 1:2, then 1:1. 310 mg, 90%; white solid. **m.p.**: 145-146 °C. **¹H NMR** (400 MHz, CDCl_3) δ : 7.54-7.50 (m, 1H), 7.46-7.42 (m, 1H), 7.39 (s, 1H), 7.32 (s, 2H), 7.28-7.22 (m, 1H), 3.98 (s, 6H), 3.93 (s, 3H). **¹³C NMR** (100 MHz, CDCl_3) δ : 161.4, 153.6, 150.8 (dd, $^1J_{\text{CF}} = 244.6$ Hz, $^2J_{\text{CF}} = 10.2$ Hz), 150.3 (dd, $^1J_{\text{CF}} = 248.4$ Hz, $^2J_{\text{CF}} = 10.1$ Hz), 149.3, 140.4, 125.1 (dd, $^3J_{\text{CF}} = 6.5$ Hz, $^4J_{\text{CF}} = 4.1$ Hz), 124.0, 122.4, 120.5 (dd, $^3J_{\text{CF}} = 6.3$ Hz, $^4J_{\text{CF}} = 4.0$ Hz), 118.2 (d, $^2J_{\text{CF}} = 17.9$ Hz), 113.4 (d, $^2J_{\text{CF}} = 19.2$ Hz), 103.6, 61.0, 56.3. **¹⁹F NMR** (376 MHz, CDCl_3) δ : -136.9, -137.4. **IR** (neat cm^{-1}) 2945, 2838, 1592, 1506, 1496, 1457, 1416, 1354, 1272, 1235, 1181, 1129, 1001, 841, 773, 728. **Anal.** Calcd. for $\text{C}_{18}\text{H}_{15}\text{F}_2\text{NO}_4$: C, 62.25; H, 4.35. Found: C, 62.44; H, 4.35.

2,5-Di-*o*-tolylloxazole (2p)

Synthesized from (*E*)-2-methyl-*N*-(2-methylstyryl)benzamide (**1p**) (251 mg); EtOAc / hexanes = 1:12, then 1:10. 199 mg, 80%; white solid. **m.p.**: 77-79 °C. **¹H NMR** (400 MHz, CDCl_3) δ : 8.09 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.38 (s, 1H), 7.37-7.28 (ovrlp, 6H), 2.76 (s, 3H), 2.53 (s, 3H). **¹³C NMR** (100 MHz, CDCl_3) δ : 161.3, 150.4, 137.4, 134.9, 131.8, 131.3, 130.1, 128.9, 128.4, 127.5, 126.9, 126.5, 126.4, 126.2, 126.1, 22.3, 22.1. **IR**

(neat cm^{-1}) 2956, 2921, 1489, 1451, 1152, 1127, 1053, 774, 758, 724, 714. **Anal.** Calcd. for $\text{C}_{17}\text{H}_{15}\text{NO}$: C, 81.90; H, 6.06. Found: C, 81.94; H, 6.09.

2-(Naphthalen-2-yl)-5-(*o*-tolyl)oxazole (2q)

Synthesized from (*E*)-*N*-(2-methylstyryl)-2-naphthamide (**1q**) (287 mg); EtOAc / hexanes = 1:15, then 1:10. 221 mg, 78%; off-white solid. **m.p.**: 108-110 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.46 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.84-7.71 (ovrlp, 4H), 7.42-7.40 (ovrlp, 2H), 7.29 (s, 1H), 7.27-7.23 (m, 1H), 7.18-1.17 (ovrlp, 2H), 2.42 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 160.7, 150.7, 134.6, 134.0, 132.9, 131.2, 128.6, 128.5, 128.2, 127.8, 127.11, 127.06, 126.61, 126.57, 126.3, 126.1, 126.0, 124.5, 123.1, 22.0. **IR** (neat cm^{-1}) 3057, 2953, 1721, 1463, 1375, 1277, 1195, 1130, 942, 859, 818, 752, 473. **HRMS** (ESI) calcd for $\text{C}_{20}\text{H}_{15}\text{NO}$ [M+H]: 286.1226; found 286.1231.

(*E*)-5-Phenyl-2-styryloxazole (4a)¹³

Synthesized from *N*-((*E*)-styryl)cinnamamide (**3a**) (249 mg); EtOAc / hexanes = 1:12. 138 mg, 56%; off-white solid. **m.p.**: 98-100 °C (lit.: 97-100 °C). $^{13}\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.70 (d, J = 7.2 Hz, 2H), 7.59-7.55 (ovrlp, 3H), 7.46-7.32 (ovrlp, 7H), 6.99 (d, J = 16.4 Hz, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 161.2, 151.0, 135.9, 135.7, 129.3, 129.1, 129.0, 128.6, 128.1, 127.3, 124.3, 123.9, 114.0. **IR** (neat cm^{-1}) 1520, 1480, 1133, 971, 942, 830, 753, 688. **Anal.** Calcd. for $\text{C}_{17}\text{H}_{13}\text{NO}$: C, 82.57; H, 5.30. Found: C, 82.19; H, 5.16.

(*E*)-2-Phenyl-5-styryloxazole (4b)⁴²

Synthesized from *N*-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)benzamide (**3b**) (249 mg), with CuBr_2 (33.5 mg, 15 mol%) and pyridine (48 μL , 60 mol%); EtOAc / hexanes = 1:14. 99 mg, 40%; off-white solid. **m.p.**: 81-82 °C (lit.: 82 °C). $^{42}\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.09 (d, J = 7.6 Hz, 2H), 7.49-7.44 (ovrlp, 5H), 7.35 (t, J = 7.2 Hz, 2H), 7.27 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.6 Hz, 2H), 6.90 (d, J = 16.4 Hz, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 161.1, 150.4, 136.4, 130.5, 129.5, 128.9, 128.3, 127.4, 126.62, 126.57, 126.4, 113.1. **IR** (neat cm^{-1}) 1478, 1447, 1128, 961, 752, 824, 707, 693, 682. **Anal.** Calcd. for $\text{C}_{17}\text{H}_{13}\text{NO}$: C, 82.57; H, 5.30. Found: C, 82.28; H 5.46.

(*E*)-2-(3,4-Dimethoxystyryl)-5-(4-methoxyphenyl)oxazole (Annuloline) (4c)³⁸

Synthesized from (*E*)-3-(3,4-dimethoxyphenyl)-*N*-((*E*)-4-methoxystyryl)acrylamide (**3c**) (339 mg), with CuBr_2 (33.5 mg, 15 mol%) and ethyl nicotinate (41.0 μL , 30 mol%). EtOAc / hexanes = 1:4, then 1:2. A yellow oily product was obtained, then recrystallized from CH_2Cl_2 / hexanes (~1:2) by slow evaporation with the aid of a rotary evaporator. 192 mg, 57%; yellow solid. **m.p.**: 104-106 °C (lit.: 104-107 °C). $^{38}\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.61 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 16.4 Hz 1H), 7.27 (s, 1H), 7.11-7.08 (ovrlp, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.88-6.82 (ovrlp, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 160.7, 159.7, 150.6, 150.0, 149.2, 135.0, 128.7, 125.6, 122.1, 121.1, 120.8, 114.3, 112.0, 111.1, 108.8, 55.9, 55.8, 55.3. **IR** (neat cm^{-1}) 1599, 1518, 1444, 1263, 1233, 1131, 1021, 972, 823, 800, 768, 613.

5-Octyl-2-phenyloxazole (4d)

Synthesized from (*E*)-*N*-(dec-1-en-1-yl)benzamide (**3d**) (259 mg); EtOAc / hexanes = 1:15. 107 mg, 42%; pale-yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.00 (d, J = 7.2 Hz, 2H), 7.44-7.37 (ovrlp, 3H), 6.83 (s, 1H), 2.69 (t, J = 7.6 Hz, 2H), 1.68 (qu, J = 7.2 Hz, 2H), 1.38-1.27 (ovrlp, 10H), 0.88 (t, J = 7.2 Hz, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 160.6, 153.3, 129.9, 128.7, 127.9, 126.0, 123.6, 31.9, 29.31, 29.25, 29.2, 27.7, 25.7, 22.7, 14.2. **IR**

(neat, cm^{-1}) 2928, 2856, 1597, 1551, 1490, 1449, 1354, 1123, 1066, 1025, 982, 825, 775, 711, 691. **Anal.** Calcd. for $\text{C}_{17}\text{H}_{23}\text{NO}$: C, 79.33; H, 9.01. Found: C, 79.32; H, 9.11.

2-(*tert*-Butyl)-5-phenyloxazole (4e)^{9d}

Synthesized from (*E*)-*N*-styrylpivalamide (**3e**) (203 mg), with CuBr_2 (33.5 mg, 15 mol%) and ethyl nicotinate (41.0 μL , 30 mol%); EtOAc / hexanes = 1:10. 121 mg, 60%; pale-yellow oil. **¹H NMR** (400 MHz, CDCl_3) δ : 7.60 (d, $J = 7.6$ Hz, 2H), 7.38 (t, $J = 7.6$ Hz, 2H), 7.27 (t, $J = 7.6$ Hz, 1H), 7.20 (s, 1H), 1.44 (s, 9H). **¹³C NMR** (100 MHz, CDCl_3) δ : 170.8, 150.6, 128.8, 128.4, 128.0, 124.0, 121.5, 33.8, 28.6. **IR** (neat cm^{-1}) 2971, 1549, 1447, 1367, 1244, 1145, 1121, 1060, 961, 822, 762, 747, 688. **Anal.** Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}$: C, 77.58; H, 7.51. Found: C, 77.34; H, 7.71.

2-Cyclohexyl-5-phenyloxazole (4f) and 2-(1-cyclohexenyl)-5-phenyloxazole (4f') (10 : 1)

Synthesized from (*E*)-*N*-styrylcyclohexanecarboxamide (**3f**) (229 mg), with CuBr_2 (33.5 mg, 15 mol%) and ethyl nicotinate (41 μL , 30 mol%); EtOAc / hexanes = 1:20. **4f** and **4f'** were isolated as an inseparable, white product mixture (142 mg). The formation of **4f'** was further confirmed by GC-MS analysis ($[\text{M}]^+$ of **4f**: 227; $[\text{M}]^+$ of **4f'**: 225). The isolated yields of **4f** and **4f'** were estimated to be 54% (123 mg, 0.54 mmol) and 6% (14 mg, 0.06 mmol), respectively, by comparing the ratio of the proton signals of **4f** and **4f'** by ¹H NMR spectroscopy. The product mixture was recrystallized from CH_2Cl_2 / acetonitrile (~2:1) by slow evaporation with the aid of a rotary evaporator to afford a pure **4f** as a white solid. **¹H NMR of an inseparable mixture of 4f and 4f'** (400 MHz, CDCl_3) δ : 7.63-7.58 (ovrlp, 2.2 H), 7.39-7.35 (ovrlp, 2.2 H), 7.30-7.25 (ovrlp, 1.1 H), 7.21 (ovrlp, 1.1 H), 6.85 (br, 0.1 H), 2.83 (tt, $^3J = 11.2$ Hz, $^3J = 3.6$ Hz, 1H), 2.52 (br, 0.2 H), 2.25 (br, 0.2 H), 2.13-2.10 (m, 2H), 1.85-1.81 (m, 2H), 1.76-1.59 (ovrlp, 3.2H), 1.44-1.25 (ovrlp, 3.2H). **¹³C NMR of an inseparable mixture of 4f and 4f'** (100 MHz, CDCl_3) (1) **4f**: δ : 167.8, 150.5, 128.8, 128.4, 128.0, 123.9, 121.6, 37.6, 30.6, 25.8, 25.6. (2) **4f'**: δ : 162.4, 150.1, 131.4, 128.3, 128.1, 126.1, 124.0, 122.8, 25.5, 24.5, 22.1, 21.8. **m.p. of pure 4f**: 88-90 °C. **¹H NMR of pure 4f** (400 MHz, CDCl_3) δ : 7.61 (d, $J = 7.8$ Hz, 2H), 7.40 (t, $J = 7.6$ Hz, 2H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.21 (s, 1H), 2.86 (tt, $^3J = 11.2$ Hz, $^3J = 3.6$ Hz, 1H), 2.15-2.11 (m, 2H), 1.87-1.82 (m, 2H), 1.75-1.60 (ovrlp, 3H), 1.46-1.26 (ovrlp, 3H). **¹³C NMR of pure 4f** (100 MHz, CDCl_3) δ : 168.0, 150.6, 128.9, 128.5, 128.1, 124.1, 121.7, 37.7, 30.8, 25.9, 25.8. **IR of pure 4f** (neat cm^{-1}) 2922, 2854, 1551, 1448, 1117, 895, 835, 757, 705, 689. **Anal.** Calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}$ (**4f**): C, 79.26; H, 7.54. Found: C, 78.94; H, 7.57.

2-Phenyl-5-(thiophen-3-yl)oxazole (4g)^{8f}

Synthesized from (*E*)-*N*-(2-(thiophen-3-yl)vinyl)benzamide (**3g**) (229 mg), with CuBr_2 (33.5 mg, 15 mol%) and ethyl nicotinate (41 μL , 30 mol%); EtOAc / hexanes = 1:15, then 1:12. 134 mg, 59%; off-white solid. **m.p.**: 73-74 °C. **¹H NMR** (400 MHz, CDCl_3) δ : 8.07 (d, $J = 8.0$ Hz, 2H), 7.56 (dd, $J = 2.8$ Hz, 1.2 Hz, 1H), 7.47-7.39 (ovrlp, 3H), 7.35 (dd, $J = 5.2$ Hz, 2.8 Hz, 1H), 7.32 (dd, $J = 5.2$ Hz, 1.2 Hz, 1H), 7.26 (s, 1H). **¹³C NMR** (100 MHz, CDCl_3) δ : 160.5, 148.1, 130.3, 129.2, 128.8, 127.4, 126.9, 126.2, 124.5, 123.0, 120.6. **IR** (neat cm^{-1}) 3107, 1611, 1500, 1447, 1396, 1130, 1066, 1022, 973, 849, 820, 772, 706, 689, 603. **Anal.** Calcd. for $\text{C}_{13}\text{H}_9\text{NOS}$: C, 68.70; H, 3.99. Found: C, 68.46; H, 3.94.

5-Phenyl-2-(thiophen-3-yl)oxazole (4h)⁴³

Synthesized from (*E*)-*N*-styrylthiophene-3-carboxamide (**3h**) (229 mg); EtOAc / hexanes = 1:10. 171 mg, 75%; off-white solid. **m.p.**: 71-72 °C. **¹H NMR** (400 MHz, CDCl_3) δ : 7.94 (dd, $J = 2.8$ Hz, 1.2 Hz, 1H), 7.65-7.63 (ovrlp, 3H), 7.40-7.33 (ovrlp, 4H), 7.38 (t, $J = 7.6$ Hz, 1H). **¹³C NMR** (100 MHz, CDCl_3) δ : 158.1, 150.5, 129.5, 128.9, 128.3, 127.9, 126.7, 125.9, 125.2, 124.1, 123.1. **IR** (neat cm^{-1}) 1592, 1493, 1132, 852, 787, 761, 717, 695.

5-Phenyl-2-(thiophen-2-yl)oxazole (4i)³⁸

Synthesized from (*E*)-*N*-styrylthiophene-2-carboxamide (**3i**) (229 mg); EtOAc / hexanes = 1:20, then 1:15. 106 mg, 47%; off-white solid. **m.p.**: 63-65 °C (lit.: 59-61 °C). ³⁸¹H NMR (400 MHz, CDCl₃) δ: 7.70 (d, *J* = 4.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.41-7.37 (ovrlp, 3H), 7.36 (s, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 4.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 157.3, 150.8, 130.0, 128.9, 128.4, 128.3, 128.0, 127.7, 127.6, 124.1, 123.3. IR (neat cm⁻¹) 3102, 1575, 1489, 1448, 1420, 1128, 1063, 945, 853, 823, 762, 718, 687.

2-(Furan-2-yl)-5-phenyloxazole (4j)³⁸

Synthesized from (*E*)-*N*-styrylfuran-2-carboxamide (**3j**) (211 mg); EtOAc / hexanes = 1:10. 110 mg, 53%; off-white solid. **m.p.**: 66-67 °C (lit.: 61-63 °C). ³⁸¹H NMR (400 MHz, CDCl₃) δ: 7.67 (d, *J* = 7.6 Hz, 2H), 7.57-7.56 (m, 1H), 7.42-7.39 (ovrlp, 3H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 3.2 Hz, 1H), 6.54 (dd, *J* = 3.2 Hz, 1.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 154.0, 150.9, 144.4, 143.0, 128.9, 128.6, 127.7, 124.2, 123.3, 111.9, 111.4. IR (neat cm⁻¹) 1519, 1452, 1171, 1135, 1008, 939, 895, 749, 720, 685, 643, 592.

Phenyl(5-(2-(thiophen-3-yl)oxazol-5-yl)-1H-indol-1-yl)methanone (4k)

Synthesized from (*E*)-*N*-(2-(1-benzoyl-1*H*-indol-5-yl)vinyl)thiophene-3-carboxamide (**3k**) (186 mg, 0.50 mmol, 1.0 equiv), CuBr₂ (8.4 mg, 0.038 mmol, 7.5 mol%), TBAB (193 mg, 0.60 mmol, 1.2 equiv), K₂S₂O₈ (176 mg, 0.65 mmol, 1.3 equiv), ethyl nicotinate (10.2 μL, 0.075 mmol, 15 mol%), and acetonitrile (5.0 mL, 0.1 M). EtOAc / hexanes = 1:5. 109 mg, 0.29 mmol, 59%; pale yellow solid. **m.p.**: 148-149 °C. ¹H NMR (400 MHz, CDCl₃) δ: 8.46 (d, *J* = 8.8 Hz, 1H), 8.02 (dd, *J* = 3.2 Hz, 1.2 Hz, 1H), 7.95 (d, *J* = 1.2 Hz, 1H), 7.77-7.70 (ovrlp, 4H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 2H), 7.43-7.41 (ovrlp, 2H), 7.35 (d, *J* = 3.6 Hz, 1H), 6.67 (d, *J* = 4.0 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 168.5, 158.0, 151.0, 135.8, 134.2, 132.1, 131.2, 129.5, 129.3, 128.7, 126.7, 126.0, 125.1, 123.9, 122.6, 121.3, 116.9, 116.6, 108.6. IR (neat cm⁻¹) 1686, 1598, 1457, 1367, 1336, 1191, 877, 724, 713. **Anal.** Calcd. for C₂₂H₁₄N₂O₂S: C, 71.33; H, 3.81. Found: C, 71.04; H, 3.97.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (NIH) for financial support (Grant GM58160). C.W.C. thanks the Croucher Foundation (Hong Kong) for a Postdoctoral Fellowship. We thank Dr. Meredith A. McGowan (Massachusetts Institute of Technology) for help with preparation of this manuscript.

References and Footnotes

1. For examples, see: Jin Z. Nat. Prod. Rep. 2011; 28:1143. [PubMed: 21472175] Zhang J, Ciufolini MA. Org. Lett. 2011; 13:390. [PubMed: 21174393] Wang B, Hansen TM, Weyer L, Wu D, Wang T, Christmann M, Lu Y, Ying L, Engler MM, Cink RD, Lee C-S, Ahmed F, Forsyth CJ. J. Am. Chem. Soc. 2011; 133:1506. [PubMed: 21190384]
2. For examples, see: Hashimoto H, Imamura K, Haruta J, Wakitani K. J. Med. Chem. 2002; 45:1511. [PubMed: 11906292] Momose Y, Maekawa T, Yamano T, Kawada M, Odaka H, Ikeda H, Sohta T. J. Med. Chem. 2002; 45:1518. [PubMed: 11906293]
3. For examples, see: Brown P, Davies DT, O'Hanlon PJ, Wilson JM. J. Med. Chem. 1996; 39:446-457. [PubMed: 8558513] Yang WS, Shimada K, Delva D, Patel M, Ode E, Skouta R, Stockwell BR. ACS Med. Chem. Lett. 2012; 3:35. [PubMed: 22247791] Shaw AY, Henderson MC, Flynn G, Samulitis B, Han H, Stratton SP, Chow H-HS, Hurley LH, Dorr RT. J. Pharmacol. Exp. Ther. 2009; 331:636. [PubMed: 19657049] Giddens AC, Boshoff HIM, Franzblau SG, Barry CE III, Copp BR.

- Tetrahedron Lett. 2005; 46:7355. Bey E, Marchais-Oberwinkler S, Kruchten P, Frotscher M, Werth R, Oster A, Algül O, Neugebauer A, Hartmann RW. *Bioorg. Med. Chem.* 2008; 16:6423. [PubMed: 18514529]
- For examples, see: Zhao Q, Liu S, Li Y, Wang Q. *J. Agric. Food Chem.* 2009; 57:2849–2855. [PubMed: 19271709]
 - For examples, see: Min J, Lee JW, Ahn Y-H, Chang Y-T. *J. Comb. Chem.* 2007; 9:1079. [PubMed: 17902630] Grotkopp O, Ahmad A, Frank W, Müller TJ. *J. Org. Biomol. Chem.* 2011; 9:8130. Iliashenko RY, Gorobets NY, Doroshenko AO. *Tetrahedron Lett.* 2011; 52:5086.
 - For examples, see: Maier G, Schneider JM. *Macromolecules.* 1998; 31:1798. Gong Z-H, Leu C-M, Wu F-I, Shu C-F. *Macromolecules.* 2000; 33:8527.
 - For examples, see: Luo Q, Eibauer S, Reiser O. *J. Mol. Catal. A: Chem.* 2007; 268:65. Mazuela J, Paptchikhine A, Pàmies O, Andersson PG, Diéguez M. *Chem. Eur. J.* 2010; 16:4567. [PubMed: 20229536] Mazuela J, Tolstoy P, Pàmies O, Andersson PG, Diéguez M. *Org. Biomol. Chem.* 2011; 9:941. [PubMed: 21152643]
 - For the classical synthetic methods to oxazoles, see: Turchi IJ, Dewar MJS. *Chem. Rev.* 1975; 75:389. Turchi IJ. *Ind. Eng. Chem. Prod. Res. Dev.* 1981; 20:32. Revuelta J, Machetti F, Cicchi S, Alvarez-Builla J, Vaquero JJ, Barluenga J. *Modern Heterocyclic Chemistry.* 2011; 2Wiley-VCH Verlag & Co. Weinheim, Germany For the recent examples of synthetic methods to oxazoles, see: Shi B, Blake AJ, Lewis W, Campbell IB, Judkins BD, Moody CJ. *J. Org. Chem.* 2010; 75:152. [PubMed: 19954177] He W, Li C, Zhang L. *J. Am. Chem. Soc.* 2011; 133:8482. [PubMed: 21563762] Cano I, Álvarez E, Nicasio MC, Pérez PJ. *J. Am. Chem. Soc.* 2011; 133:191. Xie J, Jiang H, Cheng Y, Zhu C. *Chem. Commun.* 2012; 48:979. Xue W-J, Li Q, Zhu Y-P, Wang J-G, Wu A-X. *Chem. Commun.* 2012; 48:3485. Weyrauch JP, Hashmi ASK, Schuster A, Hengst T, Schetter S, Littmann A, Rudolph M, Hamzic M, Visus J, Rominger F, Frey W, Bats JW. *Chem. Eur. J.* 2010; 16:956. [PubMed: 19938017] Verrier C, Fiol-Petit C, Hoarau C, Marsais F. *Org. Biomol. Chem.* 2011; 9:6215. [PubMed: 21796283] Li Z, Ma L, Xu J, Kong L, Wu X, Yao H. *Chem. Commun.* 2012; 48:3763.
 - For the cyclization of enamides bearing β -vinylic carbon-heteroatom bonds, see: (i) C-Br bond: Shin C, Sato Y, Sugiyama H, Nanjo K, Yoshimura J. *Bull. Chem. Soc. Jpn.* 1977; 50:1788. Das J, Reid JA, Kronenthal DR, Singh J, Pansegrau PD, Mueller RH. *Tetrahedron Lett.* 1992; 33:7835. Chattopadhyay SK, Kempson J, McNeil A, Pattenden G, Reader M, Rippon DE, Waite D. *J. Chem. Soc. Perkin Trans. 1.* 2000:2415. Schuh K, Glorius F. *Synthesis.* 2007; 15:2297. (ii) C-I bond: Ferreira PMT, Monteiro LS, Pereira G. *Eur. J. Org. Chem.* 2008:4676. Ferreira PMT, Castanheira EMS, Monteiro LS, Pereira G, Vilaça H. *Tetrahedron.* 2010; 66:8672. (iii) C-S bond: Misra NC, Ila H. *J. Org. Chem.* 2010; 75:5195. [PubMed: 20670028]
 - Martin R, Cuenca A, Buchwald SL. *Org. Lett.* 2007; 9:5521. [PubMed: 18020351]
 - For recent reported examples, see: Zhou H, Chung W-J, Xu Y-H, Loh T-P. *Chem. Commun.* 2009:3472. Yang L, Lei C-H, Wang D-X, Huang Z-T, Wang M-X. *Org. Lett.* 2010; 12:3918. [PubMed: 20698503] Xu Y-H, Chok YK, Loh T-P. *Chem. Sci.* 2011; 2:1822. Besset T, Kuhl N, Patureau FW, Glorius F. *Chem. Eur. J.* 2011; 17:7167. [PubMed: 21618301] Zhang H-J, Bolm C. *Org. Lett.* 2011; 13:3900. [PubMed: 21739949] Hesp KD, Bergman RG, Ellman JA. *J. Am. Chem. Soc.* 2011; 133:11430. [PubMed: 21714533]
 - For recent reviews, see: Wendlandt AE, Suess AM, Stahl SS. *Angew. Chem. Int. Ed.* 2011; 50:11062. Shi Z, Zhang C, Tang C, Jiao N. *Chem. Soc. Rev.* 2012; 41:3381. [PubMed: 22358177] For recent reported examples, see: Ueda S, Nagasawa H. *Angew. Chem. Int. Ed.* 2008; 47:6411. Ueda S, Nagasawa H. *J. Org. Chem.* 2009; 74:4272. [PubMed: 19382756] Guru MM, Ali MA, Punniyamurthy T. *J. Org. Chem.* 2011; 76:5295. [PubMed: 21598946] Xiao B, Gong T-J, Liu Z-J, Liu J-H, Luo D-F, Xu J, Liu L. *J. Am. Chem. Soc.* 2011; 133:9250. [PubMed: 21609019]
 - Wendlandt AE, Stahl SS. *Org. Biomol. Chem.* 2012; 10:3866. [PubMed: 22526327]
 - Most of the enamide substrate **1a** has been decomposed since it was not observed by GC analysis.
 - TBAB has been used as an additive to promote the yields in CuBr₂-catalyzed reactions. For example, see: Ye F, Shi Y, Zhou L, Xiao Q, Zhang Y, Wang J. *Org. Lett.* 2011; 13:5020. [PubMed: 21875127]
 - ^a During the initial optimization of copper(II) catalyst in the oxidative cyclization of **1a** to **2a** in acetonitrile, CuBr₂ was found to be superior to other copper(II) salts (CuCl₂, CuF₂, Cu(OAc)₂,

Cu(OTf)₂, CuCO₃, CuSO₄) in promoting the yield of **2a**.^b During the initial optimization of solvent in the CuBr₂-catalyzed oxidative cyclization of **1a** to **2a** at room temperature, acetonitrile was found to be the best solvent to provide highest yield of **2a**.^c Refer to Tables S1 and S2 in the Supporting Information for details of the optimizations of catalyst and solvent.

17. For the recent reviews on the applications of organofluorine compounds in medicinal chemistry, see: Müller K, Faeh C, Diederich F. *Science*. 2007; 317:1881. [PubMed: 17901324] Purser S, Moore PR, Swallow S, Gouverneur V. *Chem. Soc. Rev.* 2008; 37:320. [PubMed: 18197348] Kirk KL. *Org. Process. Res. Dev.* 2008; 12:305. Tomashenko OA, Grushin VV. *Chem. Rev.* 2011; 111:4475. [PubMed: 21456523] Roy S, Gregg BT, Gribble GW, Le V-D, Roy S. *Tetrahedron*. 2011; 67:2161.
18. Other strong π -electron-rich groups (3,4-dimethoxyphenyl and 3,4-methylenedioxyphenyl) on the β -vinyl carbons of enamides also led to the formation of oxazoles in modest yields.
19. (i) For the isolation of natural product annuloline, see: Axelrod B, Belzile JR. *J. Org. Chem.* 1958; 23:919. (ii) For the examples of the synthesis of annuloline, see: Karimoto RS, Axelrod B, Wolinsky J, Schall ED. *Phytochemistry*. 1964; 3:349. Doyle MP, Buhro WE, Davidson JG, Elliott RC, Hoekstra JW, Oppenhuizen M. *J. Org. Chem.* 1980; 45:3657. Besselièvre F, Piguel S, Mahuteau-Betzer F, Grierson DS. *Org. Lett.* 2008; 10:4029. [PubMed: 18720988]
20. Fulmer GR, Miller AJM, Sherden NH, Gottlieb HE, Nudelman A, Stoltz BM, Bercaw JE, Goldberg KI. *Organometallics*. 2010; 29:2176.
21. Chowdhury S, Roy S. *Tetrahedron Lett.* 1996; 37:2623.
22. Furuyama T, Yonehara M, Arimoto S, Kobayashi M, Matsumoto Y, Uchiyama M. *Chem. Eur. J.* 2008; 14:10348. [PubMed: 18816554]
23. Matsumoto M, Kuroda K. *Tetrahedron Lett.* 1980; 21:4021.
24. Linder J, Blake AJ, Moody CJ. *Org. Biomol. Chem.* 2008; 6:3908. [PubMed: 18931796]
25. Telvekar VN, Chettiar SN. *Tetrahedron Lett.* 2007; 48:4529.
26. Pawluć P, Hreczycho G, Szudkowska J, Kubicki M, Marciniak B. *Org. Lett.* 2009; 11:3390. [PubMed: 19572730]
27. Bull JA, Mousseau JJ, Charette AB. *Org. Lett.* 2008; 10:5485. [PubMed: 18975954]
28. Janssen Pharmaceutica NV, Anzalone L, Feibush P, Dorziotis IK, Li X, Villani FJ. *PCT Int. Appl.* May 06. 2010 2010051372.
29. Sinha J, Layek S, Mandal GC, Bhattacharjee M. *Chem. Commun.* 2001:1916.
30. Li C-W, Lin G-Y, Liu R-S. *Chem. Eur. J.* 2010; 16:5803. [PubMed: 20379977]
31. Rahman SMA, Sonoda M, Ono M, Miki K, Tobe Y. *Org. Lett.* 2006; 8:1197. [PubMed: 16524302]
32. Guillon R, Giraud F, Logé C, Borgne ML, Picot C, Pagniez F, Pape PL. *Bioorg. Med. Chem. Lett.* 2009; 19:5833. [PubMed: 19762235]
33. Bolshan Y, Batey RA. *Angew. Chem. Int. Ed.* 2008; 47:2109.
34. Katritzky AR, Ignatchenko AV, Lang H. *Synth. Commun.* 1995; 25:1197.
35. Fürstner A, Brehm C, Cancho-Grande Y. *Org. Lett.* 2001; 3:3955. [PubMed: 11720578]
36. Gooßen LJ, Salih KSM, Blanchot M. *Angew. Chem. Int. Ed.* 2008; 47:8492.
37. Alonso DA, Alonso E, Nájera C, Yus M. *Synlett.* 1997; 5:491.
38. Wan C, Gao L, Wang Q, Zhang J, Wang Z. *Org. Lett.* 2010; 12:3902. [PubMed: 20681600]
39. Jiang H, Huang H, Cao H, Qi C. *Org. Lett.* 2010; 12:5561. [PubMed: 21058706]
40. Beletskii EV, Kuznetsov MA. *Russ. J. Org. Chem.* 2009; 45:1229.
41. Besselièvre F, Lebrequier S, Mahuteau-Betzer F, Piguel S. *Synthesis*. 2009; 20:3511.
42. Kuznetsov MA, Voronin VV. *Chem. Heterocycl. Compd.* 2011; 47:173.
43. Flegeau EF, Popkin ME, Greaney MF. *Org. Lett.* 2008; 10:2717. [PubMed: 18540631]

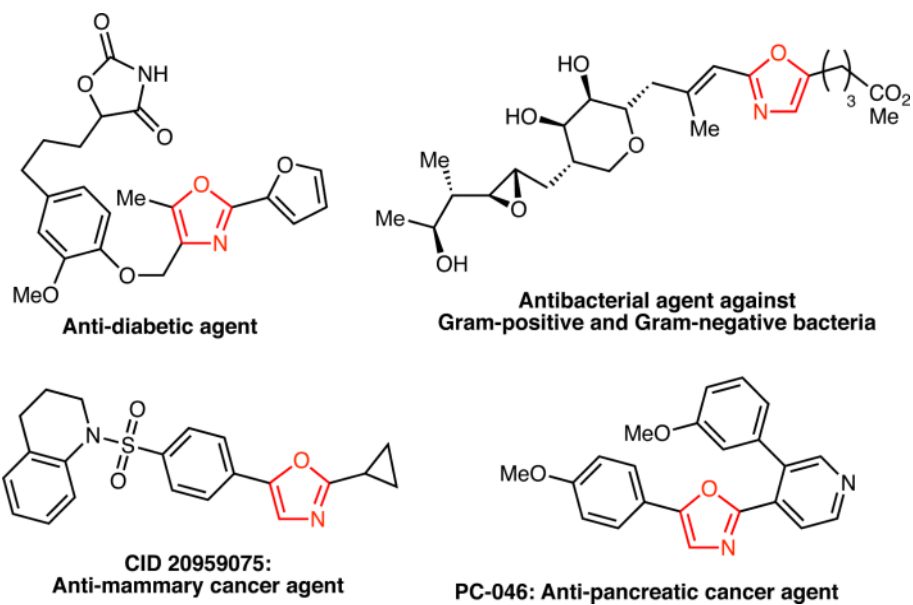
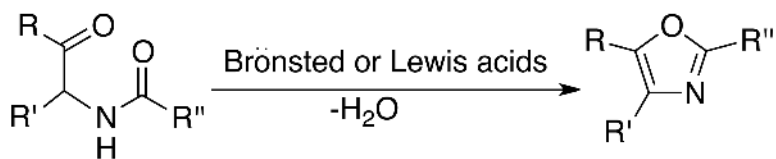
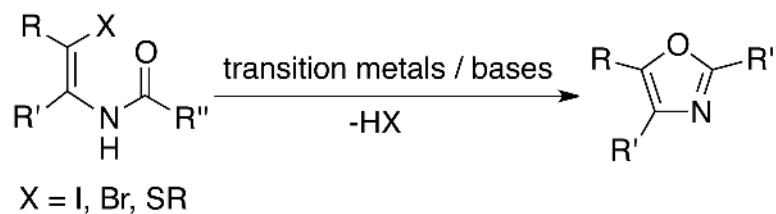
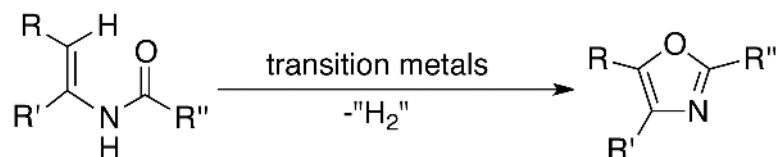
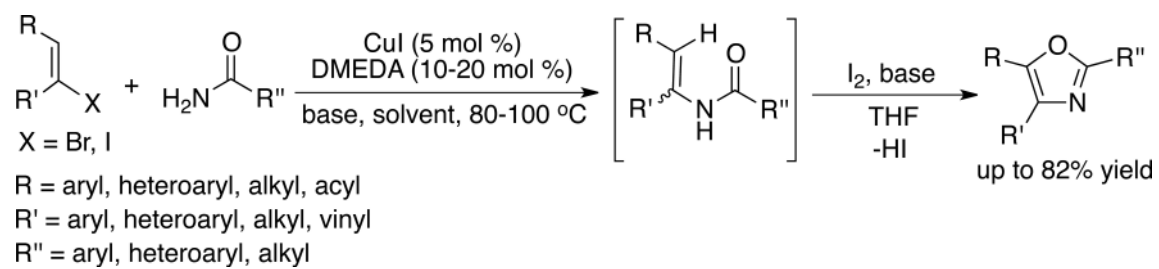


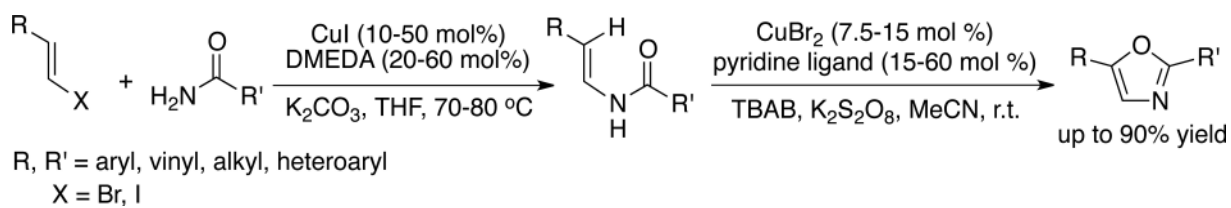
Figure 1.
Selected Biologically Active Oxazoles.

(A) Robinson-Gabriel Condensation**(B) Cyclization of Pre-activated Enamides****(C) Direct Cyclization of Enamides**

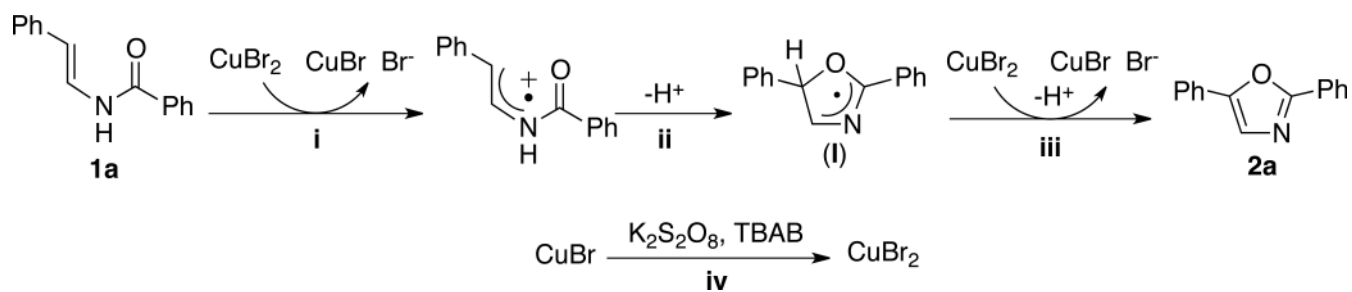
Scheme 1.
Approaches of Oxazole Synthesis via Cyclization



Scheme 2.
Sequential Synthesis of Trisubstituted Oxazoles via Coupling and Cyclization

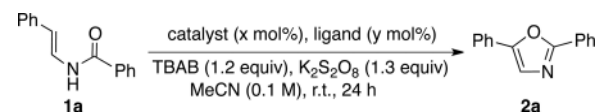
**Scheme 3.**

Improved Cu-Catalyzed Oxidative Cyclization of Enamides to 2,5-Disubstituted Oxazoles



Scheme 4.
Proposed Mechanism for Cu(II)-Catalyzed Oxidative Cyclization of **1a** to **2a**

Table 1

Optimization of Oxidative Cyclization of Enamide^a


entry	catalyst (x mol %)	ligand (y mol %)	conversion (%) ^b	yield of 2a (%) ^c
1 ^d	CuBr ₂ (5)	none	100	14 ^e
2	CuBr ₂ (5)	none	100	59
3	CuBr ₂ (5)	ethyl nicotinate (40)	100	78
4	CuBr ₂ (5)	3-nitropyridine (40)	100	62
5	CuBr ₂ (5)	3-cyanopyridine (40)	100	59
6	CuBr ₂ (5)	2-fluoropyridine (40)	100	64
7	CuBr ₂ (5)	pyridine (40)	100	54
8	CuBr ₂ (5)	ethyl nicotinate (10)	100	66
9	CuBr ₂ (7.5)	ethyl nicotinate (15)	100	84
10	CuBr ₂ (10)	ethyl nicotinate (20)	100	80
11	CuCl ₂ (5) ^f	ethyl nicotinate (10)	39	2 ^e
12	FeBr ₂ (20)	ethyl nicotinate (40)	75	24 ^e
13	FeCl ₂ (20) ^f	ethyl nicotinate (40)	49	0
14	none	ethyl nicotinate (15)	50	2 ^e

^aReaction conditions: enamide (0.2 mmol), tetrabutylammonium bromide (TBAB) (0.24 mmol), K₂S₂O₈ (0.26 mmol), CuBr₂ (x mol%), ligand (y mol%), acetonitrile (2 mL), r.t., 24 h, argon atmosphere.

^bDetermined by GC.

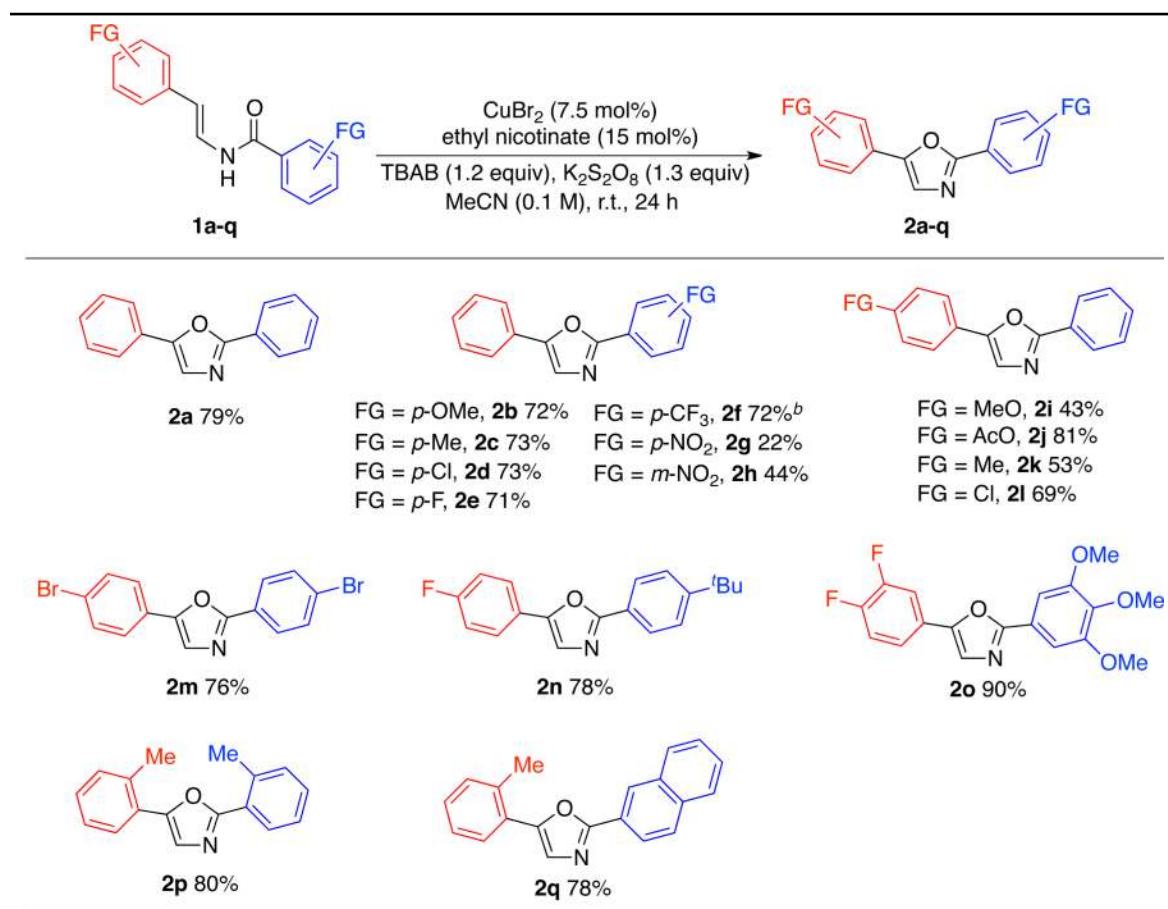
^cIsolated yield.

^dNo TBAB was added.

^eGC yield using *n*-dodecane as an internal standard.

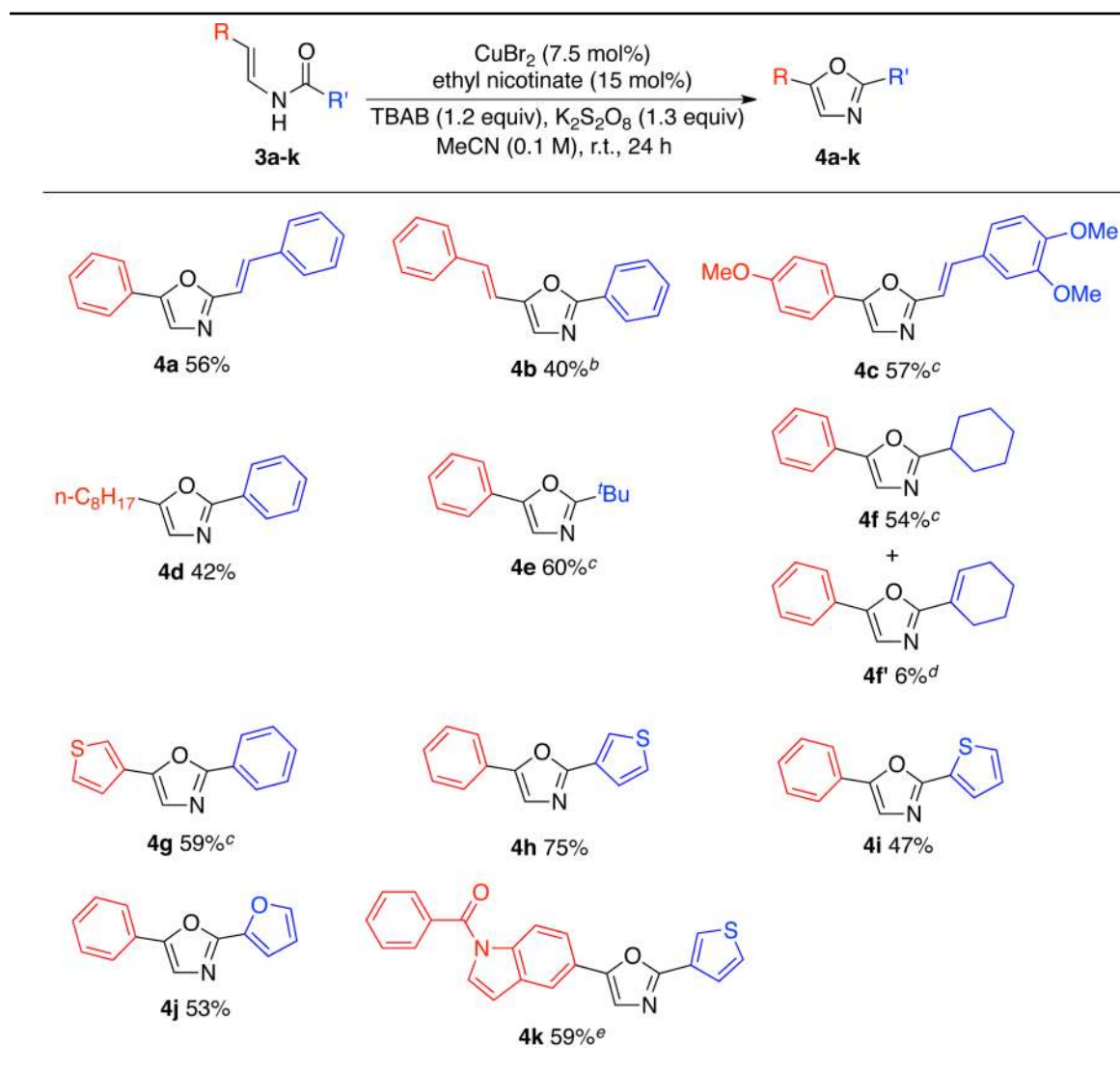
^fTetrabutylammonium chloride (TBAC) (1.2 equiv) was used.

Table 2

Scope of Enamides bearing Aryl Groups^a

^a Reaction conditions: Enamide (1 mmol), CuBr₂ (7.5 mol%), ethyl nicotinate (15 mol%), TBAB (1.2 mmol), K₂S₂O₈ (1.3 mmol), acetonitrile (10 mL), r.t., 24 h, argon atmosphere; isolated yields based on an average of two runs. ^b Enamide (0.8 mmol).

Table 3

Scope of Enamides bearing Vinyl, Alkyl, and Heteroaryl Groups^a

^a Reaction conditions: Enamide (1 mmol), CuBr₂ (7.5 mol%), ethyl nicotinate (15 mol%), TBAB (1.2 mmol), K₂S₂O₈ (1.3 mmol), acetonitrile (10 mL), r.t., 24 h, argon atmosphere; isolated yields based on an average of two runs. ^b CuBr₂ (15 mol%), pyridine (60 mol%). ^c CuBr₂ (15 mol%), ethyl nicotinate (30 mol%). ^d An inseparable dehydrogenated co-product was isolated; ratio of **4f** : **4f'** was determined by ¹H NMR spectroscopy. ^e Enamide (0.5 mmol).