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A Highly Efficient Heterogeneous Copper-Catalyzed Oxidative Cyclization of Benzylamines and 1,3-Dicarbonyl Compounds To Give Trisubstituted Oxazoles

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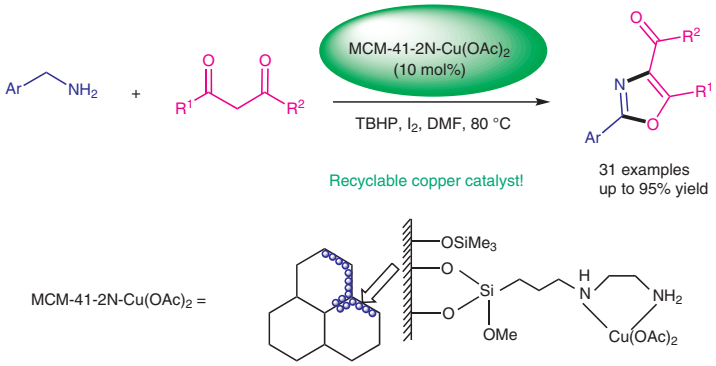

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Abstract The heterogeneous copper-catalyzed cascade oxidative cyclization between benzylamines and 1,3-dicarbonyl compounds was achieved by using the 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized copper(II) complex [MCM-41-2N-Cu(OAc)$_2$] as catalyst and *t*-BuOOH (TBHP) as oxidant, with iodine as additive, under mild conditions, yielding a wide variety of 2,4,5-trisubstituted oxazoles in mostly good to excellent yields. This heterogeneous copper catalyst can be facilely prepared via a simple two-step procedure from readily available and inexpensive reagents and exhibits a slightly higher activity than Cu(OAc)$_2$. MCM-41-2N-Cu(OAc)$_2$ is also easy to recover and can be recycled up to eight times with almost consistent activity. The reaction is the first example of heterogeneous copper-catalyzed intermolecular cyclization for the construction of polysubstituted oxazoles.

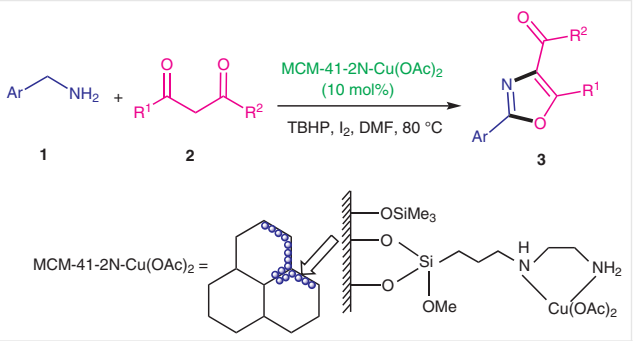
Key words copper, 2,4,5-trisubstituted oxazole, oxidative cyclization, heterogeneous catalysis, cascade reaction

The oxazole ring is a privileged five-membered heterocyclic motif found in many bioactive natural products, synthetic molecules, and pharmaceuticals.[1] In particular, 2,5-disubstituted and 2,4,5-trisubstituted oxazoles exhibit diverse and significant biological activities such as antibacterial, anticancer, antifungal, anti-inflammatory, and antiviral properties.[2] Additionally, oxazoles are frequently used as useful building blocks in the synthesis of natural products, pharmaceuticals, functional materials, and ligand frameworks.[3] As a result, the development of efficient synthetic routes to multisubstituted oxazoles is of great importance and various synthetic methodologies have been developed to construct these important frameworks.[4] Classical methods for the synthesis of oxazole derivatives include intramolecular cyclization of acyclic precursors,[5] oxidation of oxazolines,[6] and cross-coupling between prefunctionalized oxazoles and various organometallic reagents.[7] However, these methods often have limitations, such as the need for harsh conditions, tedious synthetic procedures, and inaccessible starting materials. In recent years, reactions catalyzed by transition metals such as gold,[8] palladium,[9] rhodium,[10] and ruthenium[11] have provided alternative routes to oxazoles, since they have overcome most of the disadvantages of the classical synthetic approaches; however, the use of expensive metal catalysts limits their utility. Therefore, the development of inexpensive metal-catalyzed construction of oxazole derivatives from readily available starting materials under mild conditions still represents a challenge.

Among the various transition metals, copper is particularly important in organic synthesis because of its low price and toxicity as well as its environmentally friendly features. Consequently, there are many reports on copper-catalyzed oxidative C–H bond activation[12] and C–N bond formation reactions.[13] Recently, copper-catalyzed or -mediated intermolecular cyclization reactions have provided attractive alternative methods for the synthesis of polysubstituted oxazoles owing to their high efficiency, the low price of the copper catalysts, the mild reaction conditions, and the ready availability of starting materials.[14] However, in all cases, homogeneous copper salts with high loadings (typically 0.1–1.5 equiv) were used to achieve high conversion, and they are difficult to separate from the reaction product and cannot be recycled. Moreover, homogeneous catalysis might result in copper contamination of the desired product due to the formation of complexes between the oxazoles and the copper salts, thereby limiting the application of such catalytic systems in the construction of drug molecules, which should not contain any residual metal. Immo-

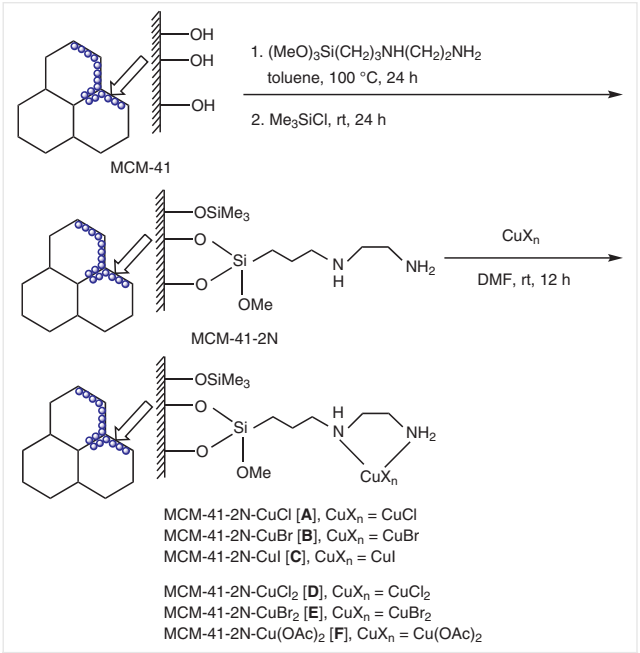
bilization of the existing copper catalysts on various solid supports appears to be an attractive solution to these problems of environmental and economic concern in chemical and pharmaceutical industries; employing heterogeneous catalysts could give rise to facile separation, recovery, and recyclability of the copper catalysts, thus minimizing both copper contamination of the target product and waste derived from reaction workup.[15] In recent years, supported copper complexes have been successfully applied in carbon–carbon[16] and carbon–heteroatom[17] bond-formation reactions. However, to the best of our knowledge, heterogeneous copper-catalyzed intermolecular cyclization for the construction of oxazole derivatives has not been explored until now.

The hexagonally ordered mesoporous MCM-41 material has recently emerged as a powerful support for the immobilization of homogeneous metal catalysts owing to its outstanding advantages such as ultrahigh surface area, large and defined pore size, big pore volume, and the existence of rich silanol groups in the inner walls, in comparison with other solid supports.[18] To date, MCM-41-anchored transition-metal complexes, including catalytic systems based on Pd,[19] Rh,[20] Mo,[21] Au,[22] and Cu,[16c,d,17f–h] have been successfully employed in many organic reactions as highly efficient and recyclable catalysts. Considering our continued interest in the development of economical and eco-friendly synthetic routes for organic transformations,[17f–h,19d–f,22e] herein we report a heterogeneous copper-catalyzed cascade oxidative cyclization between benzylamines and 1,3-dicarbonyl compounds leading to 2,4,5-trisubstituted oxazoles by using the 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized copper(II) complex [MCM-41-2N-Cu(OAc)$_2$] as catalyst and *t*-BuOOH (TBHP) as oxidant with iodine as additive (Scheme 1).



Scheme 1 Heterogeneous copper-catalyzed synthesis of polysubstituted oxazoles

A series of 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized copper(I) or copper(II) complexes [MCM-41-2N-CuX$_n$] was easily prepared via a two-step procedure from commercially readily available and inexpensive[3-(2-aminoethylamino)propyl]trimethoxysilane according to our previous procedure, as shown in Scheme 2.[17f] The condensation of mesoporous MCM-41[18a] with [3-(2-aminoethylamino)propyl]trimethoxysilane in toluene under reflux for 24 h, followed by silylation with Me_3SiCl in toluene at room temperature for 24 hours gave the 3-(2-aminoethylamino)propyl-functionalized MCM-41 material (MCM-41-2N). The latter was then reacted with various copper salts in DMF at room temperature for 12 hours to afford a series of the MCM-41-2N-CuX$_n$ complexes as pale green powders.

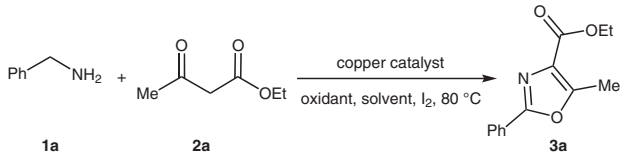


Scheme 2 Preparation of the MCM-41-2N-CuX$_n$ complexes

In our initial screening experiments, the cascade oxidative cyclization between benzylamine (**1a**) and ethyl acetoacetate (**2a**) was chosen as the model reaction to determine the optimal reaction conditions, and the results are summarized in Table 1. Firstly, various heterogeneous copper complexes **A**–**F** was examined by using a *t*-BuOOH (TBHP) solution in *n*-hexane as oxidant with iodine as additive at 80 °C in MeCN as solvent (entries 1–6). It was found that all the heterogeneous copper catalysts tested could catalyze the model reaction in moderate yields, but MCM-41-2N-Cu(OAc)$_2$ gave the best result (entry 6). The reaction afforded the desired product **3a** in a low yield of 15% in the absence of any copper catalyst (entry 7). Also, the reaction proceeded inefficiently without molecular iodine as additive, thereby providing the desired **3a** in a poor yield of 10% (entry 8). When other oxidants such as (*t*-BuO)$_2$, air, and oxygen were employed instead of TBHP, low yields of 11–30% were observed; therefore the use of TBHP solution in *n*-hexane as oxidant was the best choice (entries 6 and 9–11). Subsequently, the effect of solvents on the model reaction was checked and a significant solvent effect was observed.

Replacement of MeCN with THF or ethanol resulted in low yields (entries 12 and 13), whereas the use of DMF as solvent afforded **3a** in 81% yield (entry 14), while toluene and dioxane were ineffective (entries 15 and 16). Thus, DMF was found to be the most suitable solvent for this transformation. Lowering the reaction temperature to 30 °C led to a lower reaction rate and a lower yield was observed (entry 17). Finally, the amount of the catalyst was also screened. Reducing the amount of the catalyst to 5 mol% led to a decreased yield and required a longer reaction time (entry 18). Increasing the amount of the catalyst to 20 mol% could shorten the reaction time, but did not enhance the yield significantly (entry 19). When 10 mol% of $Cu(OAc)_2$ was used as catalyst, the desired oxazole was also isolated in 77% yield (entry 20), indicating that the MCM-41-2N-$Cu(OAc)_2$ complex exhibited a slightly higher catalytic activity than homogeneous $Cu(OAc)_2$. Therefore, the optimal reaction conditions were the use of MCM-41-2N-$Cu(OAc)_2$ (10 mol%) as catalyst, a TBHP solution in *n*-hexane (2 equiv) as oxidant, molecular iodine (1.2 equiv) as additive, and DMF as solvent, at 80 °C for 6 hours (entry 14).

Table 1 Optimization of the Reaction Conditions[a]



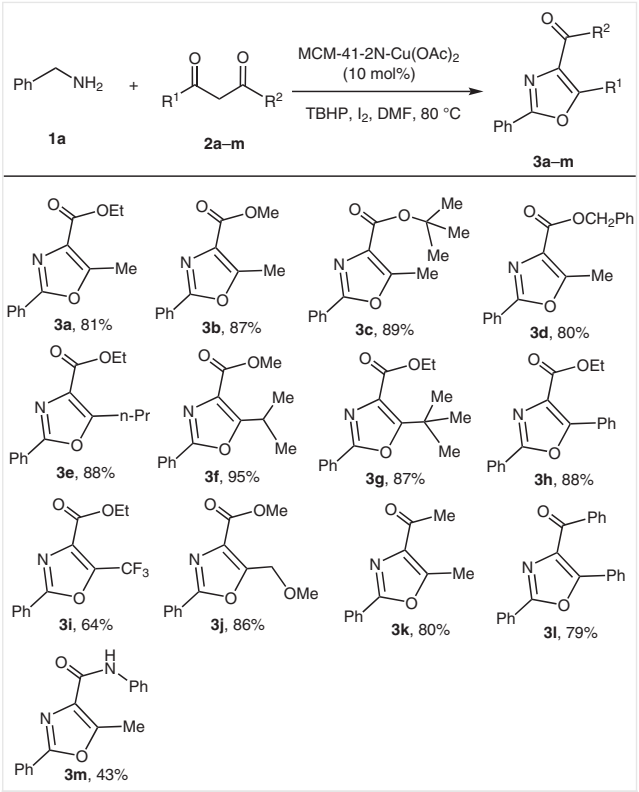
1a **2a** **3a**

Entry	Copper catalyst (mol%)	Oxidant	Solvent	Yield (%)[b]
1	**A** (10)	TBHP	MeCN	45
2	**B** (10)	TBHP	MeCN	49
3	**C** (10)	TBHP	MeCN	50
4	**D** (10)	TBHP	MeCN	44
5	**E** (10)	TBHP	MeCN	46
6	**F** (10)	TBHP	MeCN	58
7	–	TBHP	MeCN	15
8[c]	**F** (10)	TBHP	MeCN	10
9	**F** (10)	$(t\text{-BuO})_2$	MeCN	30
10	**F** (10)	air	MeCN	11
11	**F** (10)	O_2	MeCN	12
12	**F** (10)	TBHP	THF	28
13	**F** (10)	TBHP	EtOH	40
14	**F** (10)	TBHP	DMF	81
15	**F** (10)	TBHP	toluene	0
16	**F** (10)	TBHP	dioxane	0
17[d]	**F** (10)	TBHP	DMF	54
18[e]	**F** (5)	TBHP	DMF	64
19[f]	**F** (20)	TBHP	DMF	82
20	$Cu(OAc)_2$ (10)	TBHP	DMF	77

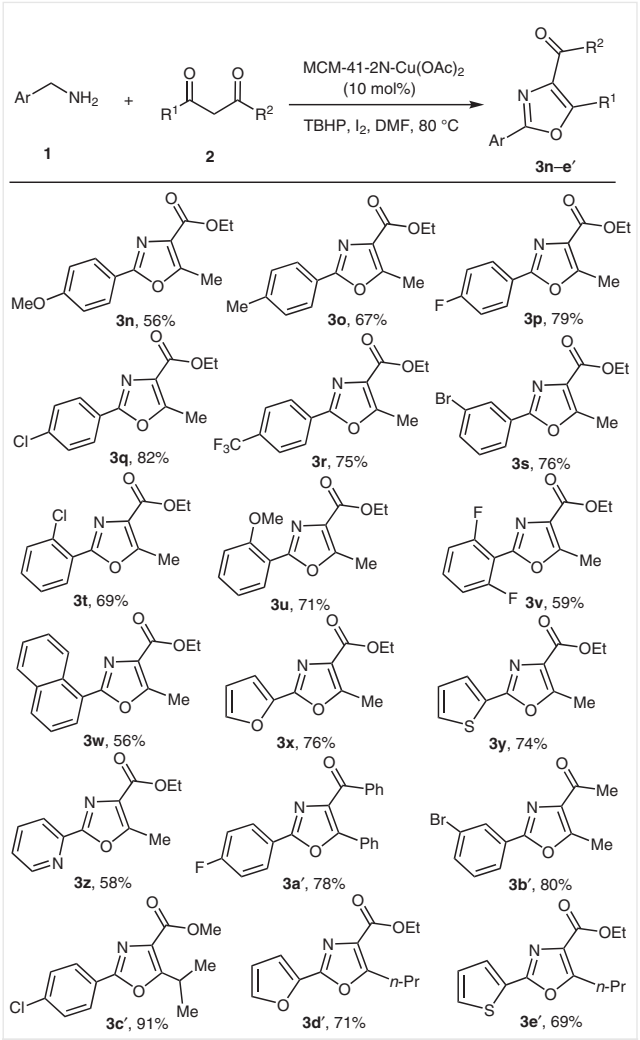
[a] Reaction conditions: **1a** (1.0 mmol, addition in two portions), **2a** (0.5 mmol), oxidant (1.0 mmol), I_2 (0.6 mmol), solvent (3 mL), 80 °C, 6 h.
[b] Isolated yield.
[c] Without I_2 as additive.
[d] Reaction was conducted at 30 °C for 24 h.
[e] For 16 h.
[f] For 4 h.

With the optimized reaction conditions in hand, we started to investigate the scope of this heterogeneous copper-catalyzed intermolecular oxidative cyclization reaction. First, a series of 1,3-dicarbonyl compounds were examined by using benzylamine (**1a**) as the substrate. As shown in Scheme 3, the reactions of a range of 1,3-dicarbonyl compounds **2a–m** with benzylamine (**1a**) afforded the corresponding 2,4,5-trisubstituted oxazoles in good to excellent yields. For example, the reaction of various acetoacetates **2a–d** with **1a** proceeded smoothly to give the desired products **3a–d** in 80–89% yield. Other β-keto esters bearing different alkyl or aryl substituents **2e–h**, regardless of the steric and electronic effects of the substituent, could furnish the corresponding oxazoles **3e–h** in 87–95% yield. It is noteworthy that CF_3-substituted β-keto ester **2i** was compatible with the standard conditions and afforded the CF_3-substituted oxazole **3i** in 64% yield. In addition, 4-methoxymethyl-substituted methyl acetoacetate **2j** was also a suitable substrate and provided the expected product **3j** in 86% yield. When the reaction substrates were changed from β-keto esters to β-diketones (**2k** and **2l**), the reaction also worked well, giving the expected products **3k** and **3l** in high yields. However, β-keto amide **2m** displayed a lower reactivity than the β-keto esters or β-diketones and produced the target product **3m** in a lower yield of 43%.

Under the optimized conditions, we next examined the scope of benzylamine derivatives **1** by using ethyl acetoacetate **2a** as the substrate; the results are listed in Scheme 4. The reactions of *para*- or *meta*-substituted benzylamines **1b–g** with **2a** provided the corresponding products **3n–s** in 56–82% yield. The electron-rich benzylamines showed a lower reactivity than the electron-deficient ones. For instance, 4-methoxybenzylamine **1b** furnished the desired **3n** in only 56% yield. The sterically hindered *ortho*-substituted benzylamines **1h–j** also displayed a relatively lower reactivity and produced the expected products **3t–v** in 59–71% yield. In addition, bulky (naphthalen-1-yl)methanamine **1k** also gave the desired oxazole **3w** in moderate yield. Notably, heteroaryl-substituted methanamines **1l–n** were compatible with the standard conditions and afforded the 2-heteroaryl-substituted oxazoles **3x–z** in moderate to good yields. The reactions of substituted benzylamines **1d** and **1g** with β-diketones also worked well to give the desired products **3a′** and **3b′** in good yields. Under the optimized reaction conditions, substituted benzylamines or heterocyclic amines were allowed to react with various β-keto esters, providing the corresponding products **3c′–e′** in 69–91% yield. We also performed the reaction of butylamine with **2a**, but the desired product was not detected, which may



Scheme 3 Heterogeneous copper-catalyzed oxidative cyclization between benzylamine and various 1,3-dicarbonyl compounds. *Reagents and conditions*: **1a** (1.0 mmol, addition in two portions), **2** (0.5 mmol), TBHP (1.0 mmol), I_2 (0.6 mmol), MCM-41-2N-Cu(OAc)$_2$ (10 mol%), DMF (3 mL), 80 °C, 6 h; isolated yields.

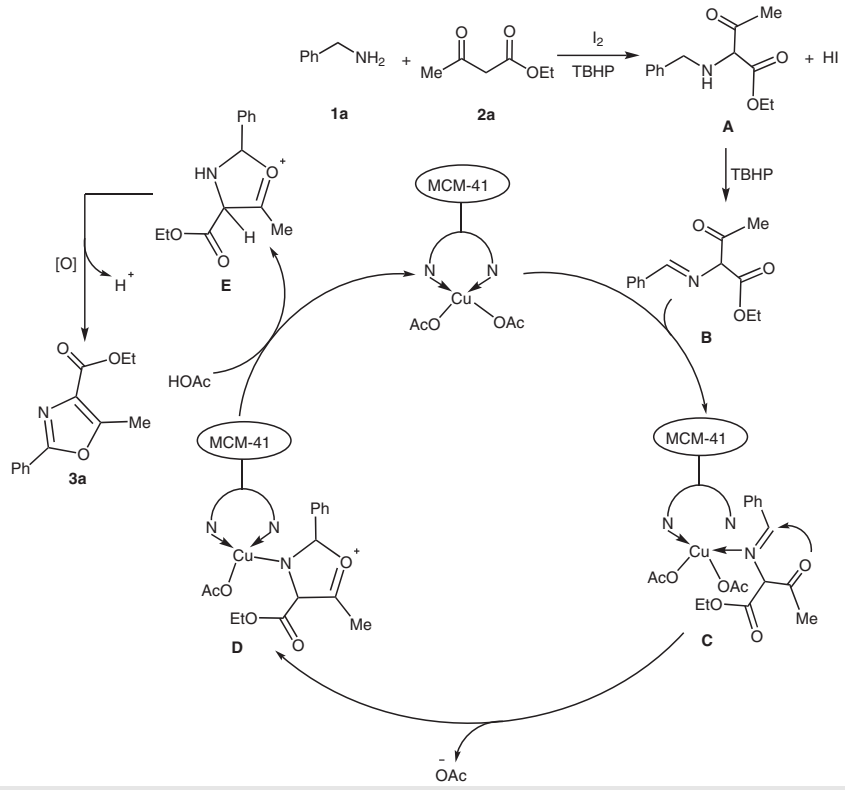


Scheme 4 Heterogeneous copper-catalyzed oxidative cyclization between various benzylamines and β-keto esters or β-diketones. *Reagents and conditions*: **1** (1.0 mmol, addition in two portions), **2** (0.5 mmol), TBHP (1.0 mmol), I_2 (0.6 mmol), MCM-41-2N-Cu(OAc)$_2$ (10 mol%), DMF (3 mL), 80 °C, 6 h; isolated yields.

imply that it is necessary for a weak C–H bond to be adjacent to the amino group for this reaction. The present method provides a quite general, simple, and practical route for the synthesis of a variety of 2,4,5-trisubstituted oxazoles from readily available benzylamine derivatives and β-keto esters or β-diketones. A range of functional groups were easily tolerated, including methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, bulky 1-naphthyl and *tert*-butyl groups, furyl, thienyl, and pyridinyl groups.

To verify whether the MCM-41-2N-Cu(OAc)$_2$ catalyst is actually functioning in a heterogeneous manner, or whether the observed catalysis is due to a leached copper species in solution, the heterogeneity of MCM-41-2N-Cu(OAc)$_2$ was checked by the hot filtration experiment.[23] For this, the oxidative cyclization reaction of benzylamine (**1a**) with ethyl acetoacetate (**2a**) was conducted until an approximately 40% conversion of **2a**. Then MCM-41-2N-Cu(OAc)$_2$ was removed from the solution by filtration at 80 °C and the resulting catalyst-free filtrate was allowed to stir at 80 °C for another 5 hours. It was found that no increase in the conversion of ethyl acetoacetate **2a** was observed, indicating that the soluble Cu species leached from MCM-41-2N-Cu(OAc)$_2$ (if any) are not responsible for the observed activity. It was also confirmed by ICP-AES analysis on the filtrate that no detectable copper species was found (below 0.2 ppm), which indicates negligible copper leaching. These results indicate that the copper(II) complex remains on the support at elevated temperature during the oxidative cyclization reaction and MCM-41-2N-Cu(OAc)$_2$ is actually functioning in a heterogeneous manner.

A plausible mechanism for the heterogeneous copper(II)-catalyzed oxidative cyclization reaction between benzylamine (**1a**) and ethyl acetoacetate (**2a**) is shown in Scheme 5. First, ethyl acetoacetate (**2a**) reacts with iodine in the presence of TBHP to give ethyl 2-iodoacetoacetate,[24] which undergoes a nucleophilic substitution reaction with benzylamine **1a** to form intermediate **A**. The latter can be further oxidized by TBHP to produce imine intermediate **B**.



Scheme 5 Plausible mechanism for the heterogeneous copper(II)-catalyzed synthesis of oxazole derivatives

Subsequent coordination of the imine intermediate **B** with MCM-41-2N-Cu(OAc)$_2$ provides an MCM-41-anchored Schiff base copper(II) complex intermediate **C**, which undergoes an intramolecular cyclization via an oxygen atom attacking the C=N double bond to give an MCM-41-anchored amino copper(II) complex intermediate **D** along with release of an acetate anion. Subsequently, the protonolysis of the N–Cu bond in intermediate **D** with HOAc affords intermediate **E** and regenerates the MCM-41-2N-Cu(OAc)$_2$ to complete the catalytic cycle. Finally, intermediate **E** undergoes further oxidation to furnish the target product **3a**.

From an economic and environmental point of view, the recovery and recycling of a catalyst is a major sustainability concern for a transition-metal-catalyzed organic reaction. The recyclability of MCM-41-2N-Cu(OAc)$_2$ was then investigated by using the cyclization reaction of benzylamine (**1a**) with methyl 4-methyl-3-oxopentanoate (**2f**) (Figure 1). After completion of the first reaction cycle, the reaction mixture was diluted with ethyl acetate and filtered. The washing of the resulting solid with acetone followed by drying at 60 °C under vacuum allowed the easy recovery of MCM-41-2N-Cu(OAc)$_2$. As shown in Figure 1, the recovered catalyst could be reused at least seven times with a slight decrease in the catalytic activity. In addition, the copper content of the recovered catalyst after the eighth reaction run was found to be 0.57 mmol·g^{-1} by ICP-AES analysis, indicating negligible copper leaching. The high catalytic activity and stability of the MCM-41-2N-Cu(OAc)$_2$ catalyst may be mainly due to the efficient active site isolation and the optimal dispersion of the active sites on the inner channel walls of MCM-41 with ultrahigh surface area as well as to the relatively strong coordination action between the 2-aminoethylamino bidentate ligand and the copper center anchored on the support.

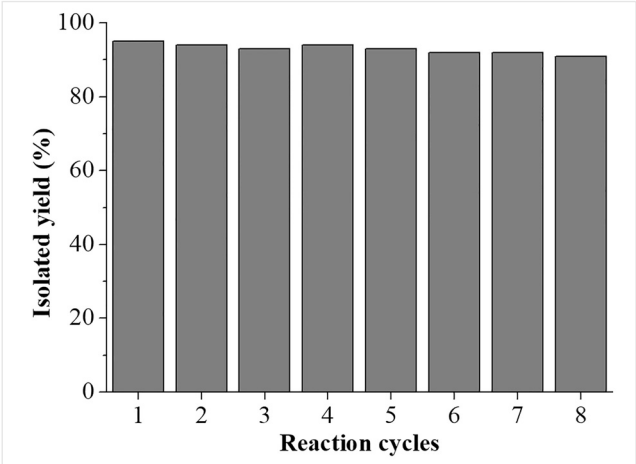


Figure 1 Recycling of the MCM-41-2N-Cu(OAc)$_2$ catalyst

In conclusion, we have developed a facile and efficient heterogeneous copper(II)-catalyzed tandem oxidative cyclization between benzylamines and 1,3-dicarbonyl compounds for the construction of polysubstituted oxazoles, which are found in a variety of drug-relevant natural and synthetic compounds. In contrast to the traditional synthetic route to oxazoles, this heterogeneous tandem oxidative cyclization strategy has some attractive features, such as: (a) the starting materials are readily available, and a wide range of benzylamine derivatives and 1,3-dicarbonyl compounds can be used; (b) a wide variety of 2,4,5-trisubstituted oxazoles can be obtained in mostly good to excellent yields; (c) the reaction conditions are mild; and (d) the MCM-41-2N-Cu(OAc)$_2$ catalyst can be easily prepared via a simple two-step procedure from readily available and inexpensive reagents and recovered from the reaction mixture by filtration, and recycled up to eight times with almost consistent activity. Thus, the present method is an attractive alternative to construct polysubstituted oxazoles.

All reagents were obtained from commercial sources and used as received without further purification. All solvents were dried and distilled prior to use. The products were purified by flash column chromatography on silica gel. A mixture of light petroleum ether and ethyl acetate was generally employed as eluent. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz or 100 MHz, respectively) by using $CDCl_3$ as solvent and with TMS as internal reference. Melting points were determined on a Beijing Tech Instrument Co., LTD X-6 melting point apparatus and are uncorrected. Copper content was determined on a Jarrell-Ash 1100 ICP. HRMS spectra were obtained on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer in the electrospray mode (ES). Mesoporous material MCM-41 was easily prepared according to a literature method.[18a]

MCM-41-2N-Cu(OAc)$_2$ (F)[17f]

A mixture of MCM-41 (2.22 g) and [3-(2-aminoethylamino)propyl]trimethoxysilane (1.561 g) in anhyd toluene (160 mL) was stirred at 100 °C under argon for 24 h. The product was filtered and washed with $CHCl_3$ (30 mL) and dried under vacuum at 150 °C for 5 h. The dried solid product was then soaked in a solution of Me_3SiCl (3.8 g) in anhyd toluene (120 mL) at 25 °C with stirring under argon for 24 h. Then the product was filtered, washed with acetone (3 × 20 mL), and dried under vacuum at 100 °C for 5 h to provide modified material MCM-41-2N (3.521 g). The nitrogen content was determined to be 1.86 mmol/g by elemental analysis.

In a Schlenk tube, MCM-41-2N (2.0 g) was mixed with Cu(OAc)$_2$ (0.236 g, 1.3 mmol) in anhyd DMF (30 mL). The reaction mixture was stirred at r.t. for 12 h under an argon atmosphere. The solid product was filtered by suction, washed with DMF and acetone, and dried at 60 °C under vacuum for 6 h, to afford the pale blue copper complex [MCM-41-2N-Cu(OAc)$_2$] (2.135 g). The copper content was determined to be 0.58 mmol/g by ICP-AES analysis.

The other heterogeneous copper catalysts MCM-41-2N-CuCl (**A**), MCM-41-2N-CuBr (**B**), MCM-41-2N-CuI (**C**), MCM-41-2N-CuCl$_2$ (**D**), and MCM-41-2N-CuBr$_2$ (**E**) were also prepared by using MCM-41-2N (2.0 g) and the corresponding copper salts (1.3 mmol) as the starting materials in the same manner; the copper content was determined to be 0.51 mmol·g^{-1}, 0.49 mmol·g^{-1}, 0.53 mmol·g^{-1}, 0.57 mmol·g^{-1}, and 0.61 mmol·g^{-1}, respectively.

Oxazoles 3; General Procedure

To a solution of benzylamine **1** (0.7 mmol) in DMF (3 mL) were successively added I_2 (0.6 mmol), 1,3-dicarbonyl compound **2** (0.5 mmol), MCM-41-2N-Cu(OAc)$_2$ (86 mg, 0.05 mmol), and TBHP (1 mmol). After the reaction mixture had been stirred for 3 h at 80 °C, another portion of benzylamine **1** (0.3 mmol) was added to the reaction mixture and the mixture was stirred at 80 °C for another 3 h. After being cooled to r.t., the mixture was diluted with EtOAc (15 mL) and filtered. The MCM-41-2N-Cu(OAc)$_2$ complex was washed with acetone (2 × 5 mL), followed by drying at 60 °C under vacuum for 2 h, and reused in the next run. The filtrate was washed with water (2 × 10 mL) and dried over $MgSO_4$. Then the organic phase was concentrated in vacuum and the residue was purified by column chromatography (silica gel, light PE/EtOAc = 2:1 to 10:1) to afford the desired product **3**.

Ethyl 5-Methyl-2-phenyloxazole-4-carboxylate (3a)[25]

Yield: 93.6 mg (81%); pale yellow solid; mp 47–48 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.03 (m, 2 H), 7.50–7.42 (m, 3 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 2.71 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 159.7, 156.1, 130.7, 128.8, 128.7, 126.6, 126.5, 61.0, 14.4, 12.2.

Methyl 5-Methyl-2-phenyloxazole-4-carboxylate (3b)[4c]

Yield: 94.5 mg (87%); pale yellow solid; mp 87–88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.04 (m, 2 H), 7.52–7.41 (m, 3 H), 3.95 (s, 3 H), 2.72 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 159.7, 156.4, 130.8, 128.8, 128.5, 126.6, 126.1, 52.0, 12.1.

tert-Butyl 5-Methyl-2-phenyloxazole-4-carboxylate (3c)[14b]

Yield: 115.4 mg (89%); pale yellow solid; mp 72–73 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.96 (m, 2 H), 7.41–7.34 (m, 3 H), 2.59 (s, 3 H), 1.55 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 159.5, 155.1, 130.6, 129.9, 128.7, 126.7, 126.5, 28.3, 28.0, 12.4.

Benzyl 5-Methyl-2-phenyloxazole-4-carboxylate (3d)[26]

Yield: 117.3 mg (80%); pale yellow solid; mp 91–93 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.04 (m, 2 H), 7.49–7.33 (m, 8 H), 5.41 (s, 2 H), 2.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 159.8, 156.4, 135.9, 130.8, 128.8, 128.7, 128.6, 128.4, 128.3, 126.6, 66.6, 12.3.

Ethyl 2-Phenyl-5-propyloxazole-4-carboxylate (3e)[14b]

Yield: 114.1 mg (88%); pale yellow solid; mp 52–54 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.04 (m, 2 H), 7.50–7.41 (m, 3 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 3.09 (t, *J* = 7.4 Hz, 2 H), 1.85–1.76 (m, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H), 1.02 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 159.9, 159.7, 130.7, 128.7, 128.6, 126.7, 126.6, 61.0, 28.0, 21.4, 14.4, 13.7.

Methyl 5-Isopropyl-2-phenyloxazole-4-carboxylate (3f)[14b]

Yield: 116.5 mg (95%); pale yellow solid; mp 67–68 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.05 (m, 2 H), 7.50–7.43 (m, 3 H), 3.95 (s, 3 H), 3.90–3.82 (m, 1 H), 1.37 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 162.9, 159.4, 130.7, 128.8, 128.7, 126.7, 126.6, 52.0, 26.2, 20.7.

Ethyl 5-(*tert*-Butyl)-2-phenyloxazole-4-carboxylate (3g)[14b]

Yield: 118.9 mg (87%); pale yellow solid; mp 75–77 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.02 (m, 2 H), 7.49–7.41 (m, 3 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 1.52 (s, 9 H), 1.44 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 162.5, 157.8, 130.6, 128.8, 128.7, 126.7, 126.5, 61.2, 33.5, 28.2, 14.3.

Ethyl 2,5-Diphenyloxazole-4-carboxylate (3h)[27]

Yield: 129.1 mg (88%); pale yellow solid; mp 85–86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.02 (m, 4 H), 7.51–7.38 (m, 6 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 159.8, 155.1, 131.1, 130.3, 130.0, 128.8, 128.6, 128.4, 127.2, 126.9, 126.4, 61.5, 14.3.

Ethyl 2-Phenyl-5-(trifluoromethyl)oxazole-4-carboxylate (3i)

Yield: 91.3 mg (64%); pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.14 (m, 2 H), 7.59–7.47 (m, 3 H), 4.47 (q, *J* = 7.2 Hz, 2 H), 1.43 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 156.1, 139.9 (q, $^3J_{C-F}$ = 2.8 Hz), 136.7 (q, $^2J_{C-F}$ = 40.8 Hz), 132.4, 129.1, 128.8, 127.5, 119.8 (q, $^1J_{C-F}$ = 268.0 Hz), 62.5, 14.0.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{10}F_3NO_3$: 285.0613; found: 285.0618.

Methyl 5-(Methoxymethyl)-2-phenyloxazole-4-carboxylate (3j)

Yield: 106.3 mg (86%); pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.11 (m, 2 H), 7.51–7.43 (m, 3 H), 4.88 (s, 2 H), 3.98 (s, 3 H), 3.47 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 161.4, 154.2, 131.3, 131.1, 128.8, 127.0, 126.2, 63.6, 58.7, 52.3.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{13}NO_4$: 247.0845; found: 247.0838.

1-(5-Methyl-2-phenyloxazol-4-yl)ethanone (3k)[25]

Yield: 80.5 mg (80%); pale yellow solid; mp 78–79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.01 (m, 2 H), 7.50–7.43 (m, 3 H), 2.69 (s, 3 H), 2.60 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3, 158.6, 154.5, 135.8, 130.6, 128.8, 126.9, 126.4, 28.0, 12.4.

(2,5-Diphenyloxazol-4-yl)(phenyl)methanone (3l)[28]

Yield: 128.5 mg (79%); pale yellow solid; mp 79–81 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–7.96 (m, 6 H), 7.60–7.46 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8, 159.1, 154.6, 137.1, 133.4, 131.3, 130.6, 130.2, 129.9, 129.0, 128.5, 128.2, 127.9, 127.8, 127.2, 126.8.

5-Methyl-*N*,2-diphenyloxazole-4-carboxamide (3m)[14b]

Yield: 59.8 mg (43%); pale yellow solid; mp 90–91 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (s, 1 H), 8.09–8.02 (m, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H), 7.61–7.45 (m, 3 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 2.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 158.6, 153.8, 137.8, 130.8, 130.4, 129.0, 128.9, 126.7, 126.4, 124.3, 119.7, 12.0.

Ethyl 2-(4-Methoxyphenyl)-5-methyloxazole-4-carboxylate (3n)[14b]

Yield: 73.2 mg (56%); pale yellow solid; mp 78–79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.8 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 3.86 (s, 3 H), 2.69 (s, 3 H), 1.42 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 161.6, 159.8, 155.6, 128.8, 128.3, 119.4, 114.1, 61.0, 55.4, 14.4, 12.2.

Ethyl 2-(4-Methylphenyl)-5-methyloxazole-4-carboxylate (3o)[14b]

Yield: 82.2 mg (67%); pale yellow solid; mp 67–69 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 2.70 (s, 3 H), 2.40 (s, 3 H), 1.42 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 159.9, 155.9, 141.1, 129.4, 128.7, 128.6, 126.6, 61.0, 21.5, 14.4, 12.2.

Ethyl 2-(4-Fluorophenyl)-5-methyloxazole-4-carboxylate (3p)[14b]

Yield: 98.4 mg (79%); pale yellow solid; mp 70–71 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.04 (m, 2 H), 7.14 (t, *J* = 8.6 Hz, 2 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 2.70 (s, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (d, $^1J_{C-F}$ = 250.1 Hz), 162.4, 158.8, 156.2, 128.7 (d, $^3J_{C-F}$ = 8.6 Hz), 123.0 (d, $^4J_{C-F}$ = 3.2 Hz), 115.9 (d, $^2J_{C-F}$ = 22.0 Hz), 61.1, 14.4, 12.2.

Ethyl 2-(4-Chlorophenyl)-5-methyloxazole-4-carboxylate (3q)[14b]

Yield: 108.9 mg (82%); pale yellow solid; mp 80–81 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 2.71 (s, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 158.7, 156.3, 136.9, 129.1, 128.9, 127.9, 125.1, 61.1, 14.4, 12.2.

Ethyl 5-Methyl-2-[4-(trifluoromethyl)phenyl]-oxazole-4-carboxylate (3r)

Yield: 112.2 mg (75%); pale yellow solid; mp 48–49 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 2.73 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 158.2, 156.8, 132.3 (q, $^2J_{C-F}$ = 32.5 Hz), 129.7, 129.3, 126.8, 125.8 (q, $^3J_{C-F}$ = 3.7 Hz), 123.7 (q, $^1J_{C-F}$ = 270.6 Hz), 61.2, 14.4, 12.3.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{12}F_3NO_3$: 299.0769; found: 299.0766.

Ethyl 2-(3-Bromophenyl)-5-methyloxazole-4-carboxylate (3s)

Yield: 117.8 mg (76%); pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1 H), 8.00 (d, *J* = 7.6 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 2.72 (s, 3 H), 1.43 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 158.2, 156.6, 133.6, 130.3, 129.5, 129.1, 128.4, 125.1, 122.9, 61.2, 14.4, 12.3.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}BrNO_3$: 309.0001; found: 309.0005.

Ethyl 2-(2-Chlorophenyl)-5-methyloxazole-4-carboxylate (3t)[14b]

Yield: 91.7 mg (69%); pale yellow solid; mp 65–66 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.97 (m, 1 H), 7.51–7.47 (m, 1 H), 7.41–7.32 (m, 2 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 2.73 (s, 3 H), 1.42 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 157.8, 156.7, 132.7, 131.5, 131.4, 131.0, 128.7, 126.8, 125.8, 61.0, 14.4, 12.3.

Ethyl 2-(2-Methoxyphenyl)-5-methyloxazole-4-carboxylate (3u)

Yield: 92.8 mg (71%); pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.92 (m, 1 H), 7.46–7.40 (m, 1 H), 7.05–6.97 (m, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 3.94 (s, 3 H), 2.71 (s, 3 H), 1.42 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 162.5, 158.3, 157.7, 155.9, 132.1, 130.6, 120.5, 115.8, 111.7, 60.9, 55.9, 14.4, 12.2.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{15}NO_4$: 261.1001; found: 261.0997.

Ethyl 2-(2,6-Difluorophenyl)-5-methyloxazole-4-carboxylate (3v)

Yield: 78.8 mg (59%); pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.40 (m, 1 H), 7.05–7.00 (m, 2 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 2.73 (s, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 160.9 (d, $^1J_{C-F}$ = 256.0 Hz), 157.2, 150.9, 132.4 (t, $^3J_{C-F}$ = 10.3 Hz), 128.9, 112.1 (d, $^2J_{C-F}$ = 20.5 Hz), 112.1 (dd, $^2J_{C-F}$ = 20.0 Hz, $^4J_{C-F}$ = 5.1 Hz), 61.1, 14.4, 12.1.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{11}F_2NO_3$: 267.0707; found: 267.0705.

Ethyl 5-Methyl-2-(naphthalene-1-yl)oxazole-4-carboxylate (3w)[25]

Yield: 78.7 mg (56%); pale yellow solid; mp 80–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.19 (d, *J* = 8.4 Hz, 1 H), 8.21–8.18 (m, 1 H), 7.98–7.86 (m, 2 H), 7.69–7.50 (m, 3 H), 4.45 (q, *J* = 7.2 Hz, 2 H), 2.77 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 159.5, 156.0, 133.8, 131.6, 130.1, 128.5, 128.2, 127.8, 126.4, 126.1, 124.8, 123.2, 61.0, 14.5, 12.3.

Ethyl 2-(Furan-2-yl)-5-methyloxazole-4-carboxylate (3x)[25]

Yield: 84.1 mg (76%); pale yellow solid; mp 74–75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.56 (m, 1 H), 7.10 (d, *J* = 3.6 Hz, 1 H), 6.55–6.53 (m, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 2.70 (s, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 155.7, 152.3, 144.6, 142.0, 128.5, 112.3, 111.9, 61.0, 14.3, 12.0.

Ethyl 5-Methyl-2-(thiophen-2-yl)oxazole-4-carboxylate (3y)

Yield: 87.8 mg (74%); pale yellow solid; mp 71–72 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.71 (m, 1 H), 7.46–7.43 (m, 1 H), 7.11 (t, *J* = 4.2 Hz, 1 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 2.69 (s, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 155.9, 155.7, 128.9, 128.8, 128.7, 128.5, 127.9, 61.1, 14.4, 12.1.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{11}NO_3S$: 237.0460; found: 237.0455.

Ethyl 5-Methyl-2-(pyridin-2-yl)oxazole-4-carboxylate (3z)

Yield: 67.3 mg (58%); brown solid; mp 81–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 4.8 Hz, 1 H), 8.24 (d, *J* = 8.0 Hz, 1 H), 7.83–7.79 (m, 1 H), 7.39–7.35 (m, 1 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 2.76 (s, 3 H), 1.42 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 162.2, 158.3, 149.9, 145.4, 137.0, 128.8, 125.0, 122.5, 61.1, 14.4, 12.4.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}N_2O_3$: 232.0848; found: 232.0851.

[2-(4-Fluorophenyl)-5-phenyloxazol-4-yl]phenylmethanone (3a′)

Yield: 133.9 mg (78%); pale yellow solid; mp 88–90 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.05 (m, 4 H), 7.98–7.93 (m, 2 H), 7.51 (t, *J* = 7.4 Hz, 1 H), 7.42–7.35 (m, 5 H), 7.11 (t, *J* = 8.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7, 164.4 (d, $^1J_{C-F}$ = 250.7 Hz), 158.2, 154.6, 137.4, 135.0, 133.1, 130.6, 130.3, 129.8, 129.0 (d, $^3J_{C-F}$ = 8.7 Hz), 128.6, 128.2, 127.8, 127.3, 116.2 (d, $^2J_{C-F}$ = 22.0 Hz).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{14}FNO_2$: 343.1009; found: 343.1016.

1-[2-(3-Bromophenyl)-5-methyloxazol-4-yl]ethanone (3b′)

Yield: 112.1 mg (80%); pale yellow solid; mp 93–94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (t, *J* = 1.6 Hz, 1 H), 7.95 (d, *J* = 7.6 Hz, 1 H), 7.60–7.56 (m, 1 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 2.69 (s, 3 H), 2.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 157.1, 154.8, 135.9, 133.5, 130.4, 129.3, 128.7, 124.8, 122.9, 27.9, 12.4.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{10}BrNO_2$: 278.9895; found: 278.9893.

Methyl 2-(4-Chlorophenyl)-5-isopropyloxazole-4-carboxylate (3c′)

Yield: 127.3 mg (91%); pale yellow solid; mp 87–88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.00 (m, 2 H), 7.45–7.42 (m, 2 H), 3.95 (s, 3 H), 3.91–3.81 (m, 1 H), 1.37 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 162.7, 158.5, 136.9, 129.1, 127.9, 126.7, 125.2, 52.1, 26.2, 20.7.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}ClNO_3$: 279.0662; found: 279.0657.

Ethyl 2-(Furan-2-yl)-5-propyloxazole-4-carboxylate (3d′)[14b]

Yield: 88.5 mg (71%); pale yellow solid; mp 77–78 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.55 (m, 1 H), 7.10 (d, *J* = 3.6 Hz, 1 H), 6.55–6.52 (m, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 3.08 (t, *J* = 7.6 Hz, 2 H), 1.84–1.75 (m, 2 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.01 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 159.5, 152.4, 144.6, 142.2, 128.3, 112.3, 111.9, 61.0, 27.9, 21.3, 14.4, 13.7.

Ethyl 5-Propyl-2-(thiophen-2-yl)oxazole-4-carboxylate (3e′)

Yield: 91.5 mg (69%); pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 1 H), 7.39–7.35 (m, 1 H), 7.04 (t, *J* = 4.2 Hz, 1 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 2.99 (t, *J* = 7.4 Hz, 2 H), 1.75–1.65 (m, 2 H), 1.34 (t, *J* = 7.0 Hz, 3 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 159.5, 155.9, 129.0, 128.8, 128.5, 128.4, 127.9, 61.0, 27.9, 21.3, 14.3, 13.7.

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{13}H_{15}NO_3S$: 265.0773; found: 265.0776.

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Supporting Information

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