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Palladium catalyzed ring expansion reaction of isoxazolones with isocyanides: synthesis of 1,3-oxazin-6-one derivatives

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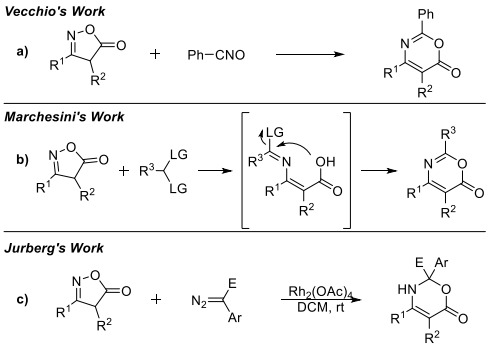
Abstract: A palladium catalyzed ring expansion reaction of isoxazolones with isocyanides was disclosed. In the reaction, a cascade process involving ring-opening/cyclization was suggested. The reaction features high atomic economy due to no elimination of CO_2 occurred. Moreover, products obtained demonstrate aggregation-induced emission properties with relatively high solid-state emission efficiencies.

Keywords: palladium, ring expansion, isoxazolone, isocyanide, aggregation-induced emission

Introduction

The 1,3-oxazine-6-one skeleton often occurs in natural products and drug molecules.[1] For example, Discoipyrroles A, B, and D were proved to show anticancer property,[1a] while Cetilistat ATL-962 could inhibit pancreatic lipase activity and be used as an anti-obesity drug.[1d] The alkaloids Spinoxazine A and B, which were separated and purified recently by Kwon's group, also have oxazinone frameworks.[1b, 1c]

Over the past decades, organic chemists developed many methods to construct the 1,3-oxazine-6-one skeleton.[2-6] Meanwhile, isoxazolones, as a kind of readily available starting material for the synthesis of 1,3-oxazin-6-ones, have attracted much attention in synthetic community. In 1979, Vecchio *et al.*[2] successfully constructed 1,3-oxazin-6-one derivatives by using isoxazolones and aryl nitrile oxides. However, the tedious work-up limited its application (Scheme 1a). Moreover, the procedure was less atom-economic since the loss of HNO_2 and PhCN as by-products. Marchesini's group[3] developed a new pathway from isoxazolones to 1,3-oxazin-6-ones through the ring-opening/cyclization cascade strategy (Scheme 1b). However, the use of toxic reagents and low reaction efficiency made the protocol less practical. Recently, a Rh-catalyzed carbene insertion reaction was reported by Jurberg's group (Scheme 1c).[6] The combination of transition-metal-catalysis and Marchesini's strategy not only improved the efficiency of reaction, but also enriched the types of products. Moreover, a Ag-catalyzed ring expansion strategy was developed by Wei's group, in which a oxazineone intermediate was experienced, followed by a Mumm-type rearrangement.[11a]



Scheme 1. Strategies from isoxazolones to 1,3-oxazine-6-ones.

Even so, more stable and versatile insertion reagents anticipated to be explored to expand the structural diversity of products. As a synthon with similar property to carbene intermediate, isocyanide is often stable, and has also been widespread used in organic synthesis.[7]

Therefore, we wonder if isocyanide could serve as insertion reagent in ring expansion reaction of isoxazolone. Indeed, there were certain reactions involving isocyanides and isoxazolones, which were mainly initiated by nucleophilic attack from methylene groups of isoxazolones[8] or carbon atoms of isocyanides[9]. To the best of our knowledge, elimination of CO_2 often occurs in the reactions of isoxazolones when meeting with transition-metal-

catalysts.[10] Reactions without the loss of CO_2 are rarely reported.[6, 11]

As an ongoing work about the palladium-catalyzed isocyanide insertion reactions in our group,[12, 8b] herein, we report an efficient Pd-catalyzed ring expansion reaction of isoxazolones with isocyanides for the synthesis of 1,3-oxazin-6-one derivatives.

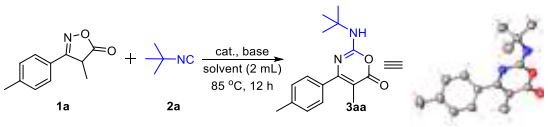
Results and Discussion

At the setout of our investigation, isoxazolone **1a** and *tert*-butyl isocyanide **2a** were chosen as reaction partners, $PdCl_2$ (5 mol %) as catalyst, NaOAc (1 equiv) as additive, and DCE (1,2-dichloroethane) as solvent. The mixture was stirred at 85 °C for 12 h. To our delight, target product **3aa** could be isolated with a yield of 47%. Structure of the product was confirmed by NMR, HRMS, IR and single-crystal X-ray diffraction. With this unambiguous result in hand, we further optimized the reaction conditions, and the results are summarized in **Table 1**.

First, several Pd catalysts and their dosages were screened (Table 1, entry 1-7), and $PdCl_2$ with a loading of 10 mol % was found to be the best choice giving a yield of 58% (Table 1, entry 6). After that, additives were investigated (Table 1, entry 8-12). Results showed that sodium benzoate could efficiently increase the yield to 83% (Table 1, entry 12), which was further increased to 86% upon dosage optimization (Table 1, entry 14). The screen of solvents shown that chlorine-containing solvents were better than others. Using TCE as solvent, a 95% yield of product could be obtained (Table 1, entry 19).

Finally, reaction time and temperature were investigated to determine the optimal reaction condition (Table 1, entry 20): **1a** (0.2 mmol), **2a** (2.0 equiv), $PdCl_2$ (10 mol %), PhCOONa (20 mol %), TCE (2 mL), 85 °C, 6 h.

Table 1. Optimization of the Reaction Conditions.[a]



Entry	Catalyst [mol %]	Additive [equiv]	Solvent	Yield[b] [%]
1	$PdCl_2$ (5)	NaOAc (1)	DCE	47
2	$Pd(OAc)_2$ (5)	NaOAc (1)	DCE	44
3	$Pd(PPh_3)_4$ (5)	NaOAc (1)	DCE	34
4	$Pd_2(dba)_3$ (5)	NaOAc (1)	DCE	37
5	$PdCl_2$ (2.5)	NaOAc (1)	DCE	36
6	$PdCl_2$ (10)	NaOAc (1)	DCE	58
7	$PdCl_2$ (15)	NaOAc (1)	DCE	55
8	$PdCl_2$ (10)	DBU (1)	DCE	trace
9	$PdCl_2$ (10)	Pyridine (1)	DCE	25
10	$PdCl_2$ (10)	Cs_2CO_3 (1)	DCE	trace
11	$PdCl_2$ (10)	PivONa (1)	DCE	59
12	$PdCl_2$ (10)	PhCOONa (1)	DCE	83
13	$PdCl_2$ (10)	PhCOONa (0.5)	DCE	81
14	$PdCl_2$ (10)	PhCOONa (0.2)	DCE	86
15	$PdCl_2$ (10)	PhCOONa (0.1)	DCE	77
16	$PdCl_2$ (10)	PhCOONa (0.2)	Toluene	71
17	$PdCl_2$ (10)	PhCOONa (0.2)	DMSO	trace
18	$PdCl_2$ (10)	PhCOONa (0.2)	MeCN	36
19	$PdCl_2$ (10)	PhCOONa (0.2)	TCE[c]	95
20[d]	**$PdCl_2$ (10)**	**PhCOONa (0.2)**	**TCE**	**95**
21[e]	$PdCl_2$ (10)	PhCOONa (0.2)	TCE	86
22[f]	$PdCl_2$ (10)	PhCOONa (0.2)	TCE	41

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), solvent (2 mL), 85 °C, 12 h. [b] Isolated yields. [c] TCE means 1,1,2-Trichoroethane. [d] The reaction time was 6 h. [e] The reaction time was 4 h. [f] The reaction temperature was 60 °C.

With optimal condition in hand, we investigated the scope of the reaction partners. First, the generality of isoxazolones were investigated, and the results were summarized in **Table 2**. Substituents on the benzene ring of isoxazolone were varied, and it showed that both electron withdrawing and electron donating groups could be well tolerated to give the products with good yields (**3aa-3ia**). Furthermore, when the benzene ring was replaced by heterocyclic rings such as thiophene (**3ka**), furan (**3la**), pyridine (**3ma**), the reactions proceeded smoothly to afford the products in moderate to high yields. When a methyl group (**3na**) other than benzene ring was introduced, only trace amount of product was detected. After that, compatibility of substituents at the 4-position of isoxazolone was investigated, and it was found that the desired products (**3oa-3qa**) could be isolated with ideal yields.

It is worth noting that when there are no substituents at 4-position of isoxazolones (**3ra-3va**), the reactions could proceed smoothly as well, providing the target products albeit in slightly lower yields, which differs from those in our previous work.[8b] It is suspected the property of different additive might answer for it. If two hydrogen atoms at 4-position of isoxazolone were substituted by two methyl groups (**3wa**), no reaction could be observed.

Subsequently, isoxazolone **1a** was used as a template to investigate the universality of isocyanide substrates. The results were summarized in **Table 3**. It turned out that alkyl isocyanides with greater steric

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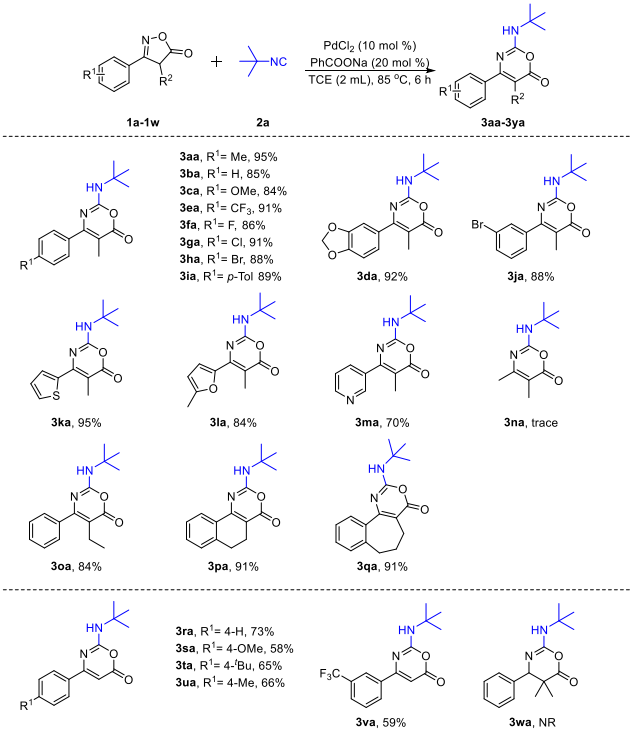
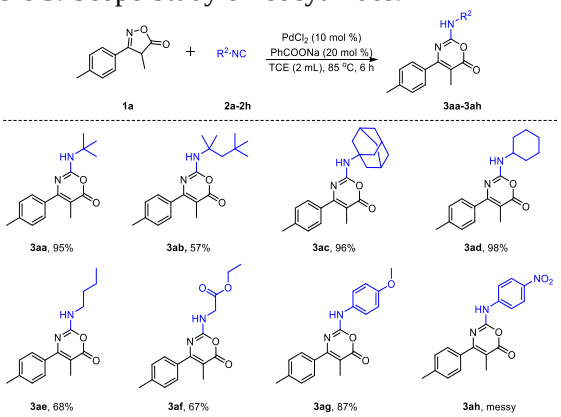
hindrance gave better results (**3aa**, **3ac**, **3ad**). Those with less steric hindrance such as *n*-butyl isocyanide (**3ae**), could only give the product in 68% yield. Reaction of functionalized isocyanide (**3af**) could also run smoothly, and the yield could be maintained at a moderate level. Attempts on aryl isocyanides indicated that electron-rich one demonstrated higher reactivity and produced target product (**3ag**) with higher yield, while electron-deficient one showed lower reactivity and only led to messy system.

Table 2. Scope Study of isoxazolones.[a, b]



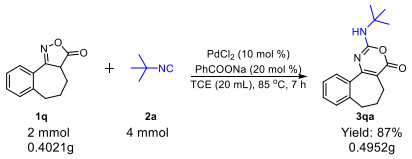
[a] Reaction conditions: **1a-1w** (0.2 mmol), **2a** (0.4 mmol), $PdCl_2$ (10 mol %), TCE (2 mL), PhCOONa (20 mol %), 85 °C, 6 h. [b] Isolated yields.

Table 3. Scope Study of isocyanides.[a, b]



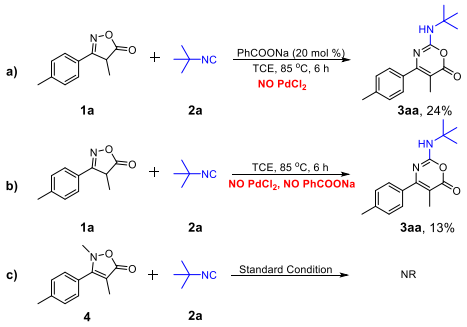
[a] Reaction conditions: **1a** (0.2 mmol), **2a-2i** (0.4 mmol), $PdCl_2$ (10 mol %), DCE (2 mL), PhCOONa (20 mol %), 85 °C, 6 h. [b] Isolated yields.

To evaluate the potential application of this protocol, a scale-up experiment was conducted (amplified by 10 times). As shown in **Scheme 2**, when 2 mmol of **1q** was introduced into the reaction, after 7 h stirring under standard conditions, 0.4952 g of **3qa** (87% yield) was obtained.

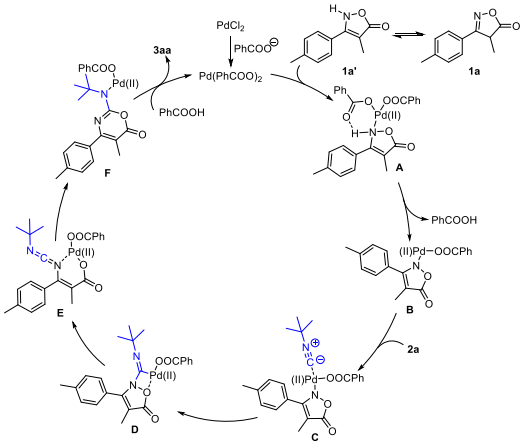


Scheme 2. Scale-up reaction.

To explore the reaction mechanism, some control experiments were performed (Scheme 3). First, we removed $PdCl_2$ from the reaction system, and it was found that the yield decreased significantly to 24% (Scheme 3a). If sodium benzoate was removed as well, the yield dramatically reduced to 13% (Scheme 3b). This indicated that both palladium species and sodium benzoate could promote the reaction. A result similar to the one obtained with substrate **1wa** was observed upon transformation of the N-methyl substituted isoxazolone 4 (Scheme 3c). We suppose that the isomerization of isoxazolone to enamine format was crucial in this reaction.



Scheme 3. Control experiments.



Scheme 4. Plausible main path of reaction.

Table 4. Photophysical properties of selected compounds.

Compound	λ_{abs}[a] (nm)	λ_{em}[b] (nm)	Φ[c]$_{F,soln}$ (%)	Φ[d]$_{F,powder}$ (%)	T[e] (ns)
3aa	262/333	425	0.11	50.17	5.22
3ca	283/334	407	0.18	39.92	2.79
3da	282/313/338	455	0.06	31.73	3.39
3ea	256/336	455	0	33.64	16.59
3ma	258/335	440	0.03	23.43	5.57
3qa	260/340	431	4.86	69.48	6.86/5.22[f]

[a] Absorption wavelength (λ_{abs}) measured in DMSO at 50 μM. [b] Emission peaks (λ_{em}) measured in powder at room temperature. [c], [d] Absolute fluorescence quantum yield (Φ_F) measured by a calibrated integrating sphere in DMSO solution at 50 μM and powder respectively. [e] Decaying lifetimes (τ) of these emitters in powder. [f] Decaying lifetime (τ) of 3qa in DMSO.

Based on above results and previous literatures,[3, 6] a possible mechanism was proposed, which was shown in **Scheme 4**.[13] First, reaction of $PdCl_2$ and sodium benzoate produced $Pd(PhCOO)_2$, and then the Pd(II) species interact with the enamine-formatted isoxazolone **1a'** to give intermediate **A**. After loss of benzoic acid, intermediate **B** was formed. With the coordination of isocyanide **2a** to **B**, a cascade migration and insertion reaction occurred to afford intermediate **C** and **D**. After N-O bond cleavage of the strained ring in **D**, intermediate **E** was thus formed. Accompanying with nucleophilic addition of oxygen to diimine motif, **F** was generated. Then, protonolysis of **F** by benzoic acid produced the final product **3aa**, as well as the re-generated Pd-catalyst. Hereto, we suppose this cascade involving deprotonation/ coordination insertion/ ring-opening/ cyclization/ protonolysis would be a favored process when compared to a direct insertion of Pd to N-O bond because it often demonstrates elimination of CO_2 while not in the present case.

Although previous application of 1,3-oxazine-6-one mainly focused on the bioactivity study, during our experiments, we found that the 1,3-oxazine-6-one derivatives exhibited intense fluorescence in solid state under a 365 nm UV lamp (Figure 1c). To further explore its potential application, we selected several samples to investigate their photophysical properties. As shown in **Table 4**, 1,3-oxazine-6-ones with different functional groups, **3aa**, **3ca**, **3da**, **3ea**, **3ma** and **3qa** showed similar absorption maxima in a range of 333-340 nm in DMSO. The measured decaying lifetimes were of nanosecond magnitude, indicating a fluorescence rather than a phosphorescence decay process. Comparing to their low quantum yields (Φ_F) of 0-4.86% in solution, in powder state they emitted in a range of 407-455 nm with much higher Φ_F of 23.43-69.48%, demonstrating AIE (aggregation-induced emission) characteristics. It's worth noting that **3aa** and **3qa** showed higher Φ_F values of 50.17% and 69.48%, respectively, in solid state. We then systematically investigated their emission behaviors in solution and aggregated states. **Figure 1a** showed the photoluminescence (PL) spectra of **3aa** in DMSO and water mixtures with different water fractions (f_w) as an example. The PL curves of 3aa in DMSO and DMSO/water mixtures with f_w lower than 60% exhibit flat lines parallel to the abscissa, indicating that it is nearly non-emissive when molecularly dissolves. However, its PL intensities increased rapidly when f_w is higher than 60%. Notably, it reached the highest value at the f_w of 90% which was about 500 times higher than that in pure DMSO (Figure 1b). As water is a poor solvent for 3aa, the aggregates were formed in DMSO/water mixtures with higher f_w. Their emissions are induced by aggregation, further proving their AIE properties.

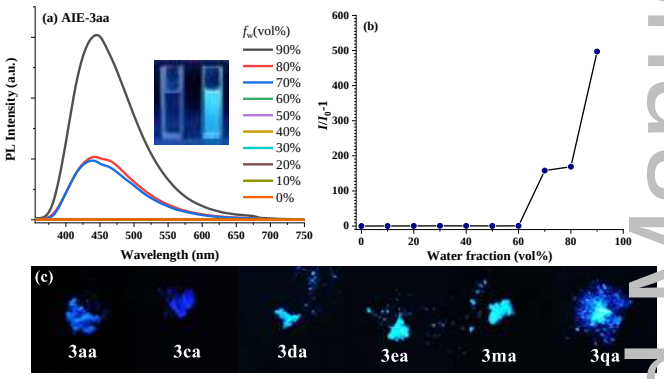


Figure 1. [a] Photoluminescence spectra of **3aa** in DMSO/water with different water fractions (f_w); c = 50 μM, λ_{ex} = 334 nm. [b] Variation in the PL intensity of **3aa** in water/DMSO with diff erent water fractions. [c] Photo images of the selected samples under UV light (λ_{ex} =365 nm).

Single crystal structure of **3aa** (Figure S1a) indicated a torsion angle between aromatic ring R^1 and oxazinone ring. In dilute solution, the dynamic rotations and vibrations of the aromatic rings and oxazinone rings dissipate energy in a non-radiatively manner, while in solid state the intermolecular C-H···π interactions (Figure S1b) may restrict the intramolecular motions, and thus resulted in an enhancement in emission.[14, 15] Besides, bulky R^2 group as well as the twisted molecular conformation could also contribute to the efficient fluorescence in solid state by suppressing close packing.[14, 16]

Over the past years, a lot of AIE luminogens with versatile functionalities have been developed.[17] However, most of them were derived from silole,[18] triphenylethene,[19] tetraphenylethene (TPE)[20] and tetraphenyl-1,4-butadiene (TPBD).[21] Exploration of AIE luminogens with new skeletons is thus highly

demanded.[14, 22] From this point of view, this work provided a simple and efficient method to prepare a type of AIE luminogens with high solid-state emission efficiencies.

Conclusion

In summary, we reported a palladium-catalyzed ring expansion reaction of isoxazolones with isocyanides to synthesize 1,3-oxazin-6-one compounds, during which no CO_2 elimination was observed, and it exhibited extremely high atom economy. Besides, this protocol features relatively mild condition, wide substrate scope, as well as excellent yield. For the function of the product point of view, it provided a new skeleton with AIE characters when compared to conventional framework.

Experimental Section

General Information

All commercially available compounds were used without further purification, unless otherwise noted. Solvents for chromatography were analytical grade and used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel, visualized by irradiation with UV light. 200-300 mesh silica gel was used for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on BRUKER 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) were reported according to an internal tetramethylsilane (TMS) standard or the $CDCl_3$ residual peak (δ 7.26) for ^{1}H NMR (For DMSO-d_6, peak at δ 2.50 was used). Chemical shifts of ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16) or DMSO-d_6 (δ 39.52). Data were reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (J) are in Hertz (Hz). IR spectra were recorded on a BRUKER VERTEX 70 spectrophotometer and are reported in terms of frequency of absorption (cm^{-1}). HRMS spectra were obtained by using BRUKER micrOTOF-Q III instrument with ESI source. UV-*vis* absorption spectra were obtained with Agilent Cary Series UV-Vis-NIR Spectrophotometer at room temperature. Photoluminescence spectra (PL) were measured by Edinburgh FLS 980 fluorescence spectrometer at room temperature. Absolute PL quantum yields (Φ_F) were measured by Edinburgh FLS 980 fluorescence spectrometer with a calibrated integrating sphere. Fluorescence lifetime was collected by Edinburgh LifeSpec II L041.

Preparation of Starting Materials

Take 1a as example, 4-methyl-3-(*p*-tolyl)isoxazol-5(4*H*)-one (1a) were synthesized according to the methods of previous lectures without modifications.[23]

Procedure 1: To a suspension of NaH (0.5600 g, 23.3 mmol) in toluene (20 mL) was added 1-(*p*-tolyl)propan-1-one (0.75 mL, 5.00 mmol), the resulting mixture was stirred at room temperature for 30 minutes. After that, $(MeO)_2CO$ (0.85 mL, 10 mmol) was added when the mixture was heated at 110 ℃ oil bath. After 12 hours, the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed under reduced pressure.

Procedure 2: A suspension of $NH_2OH{\cdot}HCl$ (0.5291 g, 7.51 mmol) and NaOAc (0.6214 g, 7.57 mmol) in ethanol (20 mL) was stirred at room temperature for 5 minutes, and then the product of last step was dissolved in ethanol and added dropwise. The mixture was heated at 78 ℃ oil bath overnight. After cooling to room temperature, the suspension was concentrated in vacuo, and purified by flash column chromatography over a short plug of silica gel.

Isocyanides were synthesized according to the published methods with minor modifications.[24]

General procedure for synthesis of products:

Take **3aa** as example, in a test tube loaded with **1a** (0.2 mmol), $PdCl_2$ (10 mol %), PhCOONa (20 mol %), 2 mL of 1,1,2-trichoroethane was added, followed by the injection of **2a** (2 equiv). Then the reaction system was sealed and heated with oil bath at 85 ℃ for 6 h. After completion and cooled to room temperature, solvent was removed under vacuum. Product **3aa** was obtained through purification by flash column chromatography with petroleum ether and ethyl acetate (V_{PE}/V_{EA} = 10/1), over a short plug of silica gel.

Procedure for gram scale synthesis of 3qa:

In a round bottom flask loaded with **1q** (0.4021g, 2 mmol), $PdCl_2$ (0.0352g, 10 mol %), PhCOONa (0.0576g, 20 mol %), 20 mL of 1,1,2-trichoroethane was added, followed by the injection of **2a** (0.45 mL, 4 mmol). Then the reaction system was sealed and heated with oil bath at 85 ℃ for 7 h. After completion and cooled to room temperature, solvent was removed under vacuum. Product **3qa** (0.4952g, 87% yield) was obtained as white solid through purification by flash column chromatography with petroleum ether and ethyl acetate (V_{PE}/V_{EA} = 10/1), over a short plug of silica gel.

For spectra information of **1a**,**1c**, **1e**, **1f**, **1g**, **1o** one can refer to published document.[25] For spectra information of **1b**, one can refer to published document.[10f] For spectra information of **1n**, one can refer to published document.[26] For spectra information of **1p**, one can refer to published document.[27] For spectra information of **1r**, **1s**, **1t**, **1u**, **1v**, one can refer to published document.[8b] For spectra information of **1w**, one can refer to published document.[10d]

CCDC-2004329 (**3aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

3-(benzo[*d*][1,3]dioxol-5-yl)-4-methylisoxazol-5(4*H*)-one (1d) Yield: 71% (0.7734 g). White Solid. M.p. 177.8-179.1 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.21 – 7.14 (m, 2H), 7.12 – 7.08 (m, 1H), 6.13 (s, 2H), 1.87 (s, 3H) ppm. ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 173.0, 160.7, 149.4, 148.0, 122.2, 121.5, 108.9, 107.3, 101.9, 93.6, 7.4 ppm. HRMS (ESI) *m/z*: calcd for $C_{11}H_{10}NO_4^+$ $[M+H]^+$ 220.0604, found: 220.0599. IR (neat, ν) = 3107, 2210, 1690, 1590 cm^{-1}.

3-(4-bromophenyl)-4-methylisoxazol-5(4*H*)-one (1h) Yield: 43% (0.5417 g). White Solid. M.p. 172.7-174.2 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 7.79 – 7.75 (m, 2H), 7.60 – 7.56 (m, 2H), 1.88 (s, 3H) ppm. ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 172.6, 160.1, 160.0, 132.2, 129.4, 127.2, 124.4, 7.2 ppm. HRMS (ESI) *m/z*: calcd for $C_{10}H_8BrN\ NaO_2^+$ $[M+Na]^+$ 275.9631, found: 275.9621. IR (neat, ν) = 3080, 2363, 2335, 1691, 1604 cm^{-1}.

4-methyl-3-(4'-methyl-[1,1'-biphenyl]-4-yl)isoxazol-5(4*H*)-one (1i) Yield: 46% (0.6053 g). White Solid. M.p. 150.8-152.5 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s,

1H), 7.90 – 7.79 (m, 2H), 7.77 – 7.67 (m, 2H), 7.67 – 7.57 (m, 2H), 7.36 – 7.21 (m, 2H), 2.35 (s, 3H), 1.94 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 173.0, 160.6(0), 160.5(7), 160.5(5), 142.3, 137.7, 136.0, 129.7, 127.9, 127.0, 126.7, 20.7, 7.5 ppm. HRMS (ESI) *m/z*: calcd for $C_{17}H_{16}NO_2^+$ $[M+H]^+$ 266.1176, found: 266.1187. IR (neat, ν) = 3021, 2810, 2363, 2349, 1666, 1597 cm^{-1}

3-(3-bromophenyl)-4-methylisoxazol-5(4*H*)-one (1j) Yield: 44% (0.5581 g). White Solid. M.p. 140.8-142.5 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 7.79 – 7.77 (m, 1H), 7.76 – 7.72 (m, 1H), 7.66 – 7.63 (m, 1H), 7.53 – 7.48 (m, 1H), 1.89 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 172.5, 159.6, 152.6, 133.4, 131.2, 130.3, 129.7, 126.6, 122.3, 7.2 ppm. HRMS (ESI) *m/z*: calcd for $C_{10}H_9BrNO_2^+$ $[M+H]^+$ 253.9811, found: 253.9817. IR (neat, ν) = 3039, 1689, 1610 cm^{-1}.

4-methyl-3-(thiophen-2-yl)isoxazol-5(4*H*)-one (1k) Yield: 76% (0.6924 g). Pale yellow Solid. M.p. 120.3-122.0 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 7.97 – 7.88 (m, 1H), 7.61 – 7.55 (m, 1H), 7.33 – 7.26 (m, 1H), 1.94 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 172.6, 155.9, 154.5, 130.4, 128.8, 128.4, 7.4 ppm. HRMS (ESI) *m/z*: calcd for $C_8H_8NO_2S^+$ $[M+H]^+$ 182.0270, found: 182.0269. IR (neat, ν) = 3039, 2925, 2848, 2362, 2340, 1691, 1611 cm^{-1}.

4-methyl-3-(5-methylfuran-2-yl)isoxazol-5(4*H*)-one (1l) Yield: 65% (0.5819 g). White Solid. M.p. 160.1 - 161.8 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.11 – 6.81 (m, 1H), 6.56 – 6.20 (m, 1H), 2.38 (s, 3H), 1.91 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 172.8, 155.3, 151.9, 140.8, 114.8(8), 114.8(5), 108.8, 13.4, 7.2 ppm. HRMS (ESI) *m/z*: calcd for $C_9H_{10}NO_3^+$ $[M+H]^+$ 180.0655, found: 180.0660. IR (neat, ν) = 3083, 2363, 2360, 1092, 1630 cm^{-1}.

1,4,5,6-tetrahydro-3*H*-benzo[6,7]cyclohepta[1,2-*c*]isoxazol-3-one (1q) Yield: 70% (0.7038 g). White Solid. M.p. 175.8-177.7 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.61 – 7.53 (m, 1H), 7.47 – 7.40 (m, 1H), 7.38 – 7.31 (m, 2H), 2.87 (t, J = 6.7 Hz, 2H), 1.90 (dt, J = 10.6, 6.6 Hz, 2H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 173.1, 159.2, 143.6, 131.0, 130.2, 126.6, 126.3, 125.8, 101.6, 34.5, 24.5(2), 24.4(5) ppm. HRMS (ESI) *m/z*: calcd for $C_{12}H_{12}NO_2^+$ $[M+H]^+$ 202.0863, found: 202.0864. IR (neat, ν) = 3060, 2952, 2843, 2356, 2335, 1687, 1613 cm^{-1}.

4-methyl-3-(pyridin-3-yl)isoxazol-5(4*H*)-one (1m) Yield: 53% (0.4665 g). White Solid. M.p. 126.6-128.5 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.91 – 8.80 (m, 1H), 8.79 – 8.66 (m, 1H), 8.16 – 7.98 (m, 1H), 7.66 – 7.53 (m, 1H), 1.90 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 172.5, 158.8(9), 158.8(7), 151.3, 147.9, 135.1, 124.7, 124.2, 7.1 ppm. HRMS (ESI) *m/z*: calcd for $C_9H_9N_2O_2^+$ $[M+H]^+$ 177.0659, found: 177.0661. IR (neat, ν) = 3336, 2060, 2380, 2355, 1620 cm^{-1}.

2-(tert-butylamino)-5-methyl-4-(*p*-tolyl)-6*H*-1,3-oxazin-6-one (3aa) Yield: 95% (51.7 mg). White Solid. M.p. 183.8 - 185.3 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.41 (m, 2H), 7.26 – 7.16 (m, 2H), 5.18 (s, 1H), 2.40 (s, 3H), 2.05 (s, 3H), 1.44 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 162.9, 162.8, 162.5, 139.6, 135.2, 128.9, 128.8, 102.9, 52.1, 28.9, 21.5, 12.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{16}H_{20}N_2NaO_2^+$ $[M+Na]^+$ 295.1417, found: 295.1411. IR (neat, ν) = 3255 (N-H), 3068, 2967, 2925, 2858, 2363, 2338, 1704, 1600, 1563 cm^{-1}.

2-(tert-butylamino)-5-methyl-4-phenyl-6*H*-1,3-oxazin-6-one (3ba) Yield: 85% (43.8 mg). White Solid. M.p. 173.2-174.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.52 (m, 2H), 7.49 – 7.40 (m, 3H), 5.18 (s, 1H), 2.04 (s, 3H), 1.44 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 162.9, 162.4, 151.0, 138.1, 129.4, 128.9, 128.1, 103.3, 52.2, 28.9, 12.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{19}N_2O_2^+$ $[M+H]^+$ 259.1441, found: 259.1445. IR (neat, ν) = 3245, 3068, 2970, 2927, 2362, 2340, 1712, 1605 cm^{-1}.

2-(tert-butylamino)-4-(4-methoxyphenyl)-5-methyl-6*H*-1,3-oxazin-6-one (3ca) Yield: 84% (48.4 mg). White Solid. M.p. 165.8-167.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.37 (m, 2H), 7.04 – 6.82 (m, 2H), 5.27 (s, 1H), 3.84 (s, 3H), 2.07 (s, 3H), 1.43 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 162.6, 162.2, 160.6, 155.1, 130.7, 130.4, 113.4, 102.2, 55.4, 52.0, 28.9, 13.0 ppm. HRMS (ESI) *m/z*: calcd for $C_{16}H_{20}N_2NaO_3^+$ $[M+Na]^+$ 311.1366, found: 311.1356. IR (neat, ν) = 3250, 3065, 2961, 2926, 2871, 2361, 2339, 1701, 1599 cm^{-1}.

4-(benzo[*d*][1,3]dioxol-5-yl)-2-(tert-butylamino)-5-methyl-6*H*-1,3-oxazin-6-one (3da) Yield: 92% (55.5 mg). White Solid. M.p. 176.2-177.3 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.03 (m, 2H), 6.92 – 6.75 (m, 1H), 5.99 (s, 2H), 5.35 (s, 1H), 2.04 (s, 3H), 1.42 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 169.5, 162.5, 162.1, 148.6, 147.4, 131.9, 123.6, 109.4, 107.8, 102.5, 101.4, 52.0, 28.8, 13.0 ppm. HRMS (ESI) *m/z*: calcd for $C_{16}H_{18}N_2NaO_4^+$ $[M+Na]^+$ 325.1159, found: 325.1160. IR (neat, ν) = 3255, 3069, 2959, 2907, 2362, 2341, 1708, 1602 cm^{-1}.

2-(tert-butylamino)-5-methyl-4-(4-(trifluoromethyl)phenyl)-6*H*-1,3-oxazin-6-one (3ea) Yield: 91% (59.3 mg). White Solid. M.p. 198.2-199.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.61 (m, 4H), 5.38 (s, 1H), 2.02 (s, 3H), 1.44 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 162.1, 161.4, 161.3, 141.6, 131.2 (q, $J_{C\text{-}F}$ = 32.4 Hz), 129.2, 125.1 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.0 (q, $J_{C\text{-}F}$ = 270.5 Hz), 104.1, 52.3, 28.8, 12.6 ppm. HRMS (ESI) *m/z*: calcd for $C_{16}H_{17}F_3N_2NaO_2^+$ $[M+Na]^+$ 349.1134, found: 349.1138. IR (neat, ν) = 3268, 3069, 2975, 2926, 2361, 2340, 1709, 1603 cm^{-1}.

2-(tert-butylamino)-4-(4-fluorophenyl)-5-methyl-6*H*-1,3-oxazin-6-one (3fa) Yield: 86% (47.4 mg). White Solid. M.p. 186.2-188.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.45 (m, 2H), 7.21 – 7.01 (m, 2H), 5.28 (s, 1H), 2.03 (s, 3H), 1.43 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 163.3 (d, $J_{C\text{-}F}$ = 248.2 Hz), 162.4, 161.7, 155.3, 134.1 (d, $J_{C\text{-}F}$ = 3.3 Hz), 131.0 (d, $J_{C\text{-}F}$ = 8.4 Hz), 115.1 (d, $J_{C\text{-}F}$ = 21.6 Hz), 103.1, 52.2, 28.9, 12.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{18}FN_2O_2^+$ $[M+H]^+$ 277.1347, found: 277.1344. IR (neat, ν) = 3243, 3068, 2978, 2965, 2928, 2863, 2362, 2335, 1712, 1602 cm^{-1}.

2-(tert-butylamino)-4-(4-chlorophenyl)-5-methyl-6*H*-1,3-oxazin-6-one (3ga) Yield: 91% (53.2 mg). White Solid. M.p. 192.4-193.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.46 (m, 2H), 7.45 – 7.34 (m, 2H), 5.18 (s, 1H), 2.02 (s, 3H), 1.43 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 165.1, 162.2, 161.5, 136.5, 135.5, 130.3, 128.4, 103.5, 52.2, 28.9, 12.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{18}ClN_2O_2^+$ $[M+H]^+$ 293.1051, found: 293.1049. IR (neat, ν) = 3244, 3067, 2970, 2927, 2362, 2340, 1712, 1604 cm^{-1}.

4-(4-bromophenyl)-2-(tert-butylamino)-5-methyl-6*H*-1,3-oxazin-6-one (3ha) Yield: 88% (59.1 mg). White Solid. M.p. 201.6-203.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.52 (m, 2H), 7.50 – 7.35 (m, 2H), 5.21 (s, 1H), 2.02 (s, 3H), 1.43 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 162.2, 161.6, 159.5, 136.9, 131.4, 130.6, 123.8, 103.5, 52.2, 28.9, 12.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{17}BrN_2NaO_2^+$ $[M+Na]^+$ 359.0366, found: 359.0371. IR (neat, ν) = 3243, 3062, 2971, 2957, 2926, 2361, 2341, 1711, 1606 cm^{-1}.

2-(tert-butylamino)-5-methyl-4-(4'-methyl-[1,1'-biphenyl]-4-yl)-6*H*-1,3-oxazin-6-one (3ia) Yield: 89% (62.0 mg). White Solid. M.p. 210.5-212.1 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.58 (m, 4H), 7.57 – 7.46 (m, 2H), 7.31 – 7.18 (m, 2H), 5.24 (s, 1H), 2.40 (s, 3H), 2.10 (s, 3H),

1.45 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 165.6, 162.5, 160.4, 142.2, 137.7, 137.6, 136.6, 129.7, 129.5, 127.1, 126.5, 103.2, 52.2, 28.9, 21.2, 12.9 ppm. HRMS (ESI) *m/z*: calcd for $C_{22}H_{24}N_2NaO_2^+$ $[M+Na]^+$ 349.1911, found: 349.1918. IR (neat, ν) = 3264, 3070, 2964, 2925, 2361, 2341, 1710, 1603 cm^{-1}.

4-(3-bromophenyl)-2-(tert-butylamino)-5-methyl-6*H*-1,3-oxazin-6-one (3ja) Yield: 88% (59.2 mg). White Solid. M.p. 142.3-144.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 1H), 7.57 – 7.50 (m, 1H), 7.50 – 7.43 (m, 1H), 7.33 – 7.27 (m, 1H), 5.23 (s, 1H), 2.01 (s, 3H), 1.43 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 162.1, 161.3, 161.2, 140.1, 132.4, 131.8, 129.7, 127.5, 122.2, 103.8, 52.3, 28.9, 12.7 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{17}BrN_2NaO_2^+$ $[M+Na]^+$ 359.0366, found: 359.0375. IR (neat, ν) = 3252, 3066, 2974, 2929, 2362, 2341, 1711, 1606 cm^{-1}.

2-(tert-butylamino)-5-methyl-4-(thiophen-2-yl)-6*H*-1,3-oxazin-6-one (3ka) Yield: 95% (50.2 mg). Pale yellow Solid. M.p. 170.4 - 172.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.58 (m, 1H), 7.56 – 7.48 (m, 1H), 7.21 – 7.11 (m, 1H), 5.38 (s, 1H), 2.26 (s, 3H), 1.49 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 162.7, 154.3, 154.0, 143.2, 130.4, 128.4, 100.5, 52.1, 28.7, 12.6 ppm. HRMS (ESI) *m/z*: calcd for $C_{13}H_{16}N_2NaO_2S^+$ $[M+Na]^+$ 287.0825, found: 287.0829. IR (neat, ν) = 3252, 3068, 2969, 2929, 2873, 2362, 2340, 1693, 1603 cm^{-1}.

2-(tert-butylamino)-5-methyl-4-(5-methylfuran-2-yl)-6*H*-1,3-oxazin-6-one (3la) Yield: 84% (44.0 mg). White Solid. M.p. 189.2 - 190.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 6.96 (m, 1H), 6.31 – 6.04 (m, 1H), 5.11 (s, 1H), 2.38 (s, 3H), 2.26 (s, 3H), 1.44 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 162.9, 156.0, 151.4, 151.3, 150.1, 117.5, 108.6, 99.6, 52.0, 28.8, 14.2, 11.3 ppm. HRMS (ESI) *m/z*: calcd for $C_{14}H_{19}N_2O_3^+$ $[M+H]^+$ 263.1390, found: 263.1396. IR (neat, ν) = 3250, 3072, 2980, 2962, 2925, 2361, 2339, 1689, 1605 cm^{-1}.

2-(tert-butylamino)-5-methyl-4-(pyridin-3-yl)-6*H*-1,3-oxazin-6-one (3ma) Yield: 70% (36.3 mg). White Solid. M.p. 182.6 - 184.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 – 8.78 (m, 1H), 8.69 – 8.59 (m, 1H), 7.94 – 7.81 (m, 1H), 7.43 – 7.32 (m, 1H), 5.27 (s, 1H), 2.05 (s, 3H), 1.44 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 162.4, 161.9, 159.8, 150.3, 149.9, 136.2, 133.9, 123.0, 104.3, 52.3, 28.9, 12.6 ppm. HRMS (ESI) *m/z*: calcd for $C_{14}H_{18}N_3O_2^+$ $[M+H]^+$ 260.1394, found: 260.1398. IR (neat, ν) = 3251, 3072, 2974, 2360, 2340, 1721, 1604 cm^{-1}.

2-(tert-butylamino)-5-ethyl-4-phenyl-6*H*-1,3-oxazin-6-one (3oa) Yield: 84% (45.7 mg). White Solid. M.p. 113.8 - 114.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 2H), 7.45 – 7.40 (m, 3H), 5.19 (s, 1H), 2.42 (q, J = 7.3 Hz, 2H), 1.43 (s, 9H), 1.15 (t, J = 7.4 Hz, 3H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 163.3(3), 163.2(8), 161.7, 138.3, 129.3, 128.2, 109.5, 52.2, 29.0, 20.2, 13.9 ppm. HRMS (ESI) *m/z*: calcd for $C_{16}H_{22}N_2NaO_2^+$ $[M+Na]^+$ 295.1417, found: 295.1423. IR (neat, ν) = 3263, 3066, 2968, 2928, 2872, 2362, 2338, 1709, 1602 cm^{-1}.

2-(tert-butylamino)-5,6-dihydro-4*H*-naphtho[1,2-*d*][1,3]oxazin-4-one (3pa) Yield: 91% (49.2 mg). White Solid. M.p. 166.5-168.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 7.95 (m, 1H), 7.43 – 7.27 (m, 2H), 7.25 – 7.14 (m, 1H), 5.49 (s, 1H), 2.90 (t, J = 7.8 Hz, 2H), 2.70 (t, J = 7.7 Hz, 2H), 1.52 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 161.3, 158.1, 156.4, 139.6, 132.1, 131.0, 127.9, 126.8, 126.0, 102.4, 52.1, 28.8, 27.6, 19.6 ppm. HRMS (ESI) *m/z*: calcd for $C_{16}H_{18}N_2NaO_2^+$ $[M+Na]^+$ 293.1260, found: 293.1262. IR (neat, ν) = 3249, 3073, 2964, 2926, 2362, 2340, 1709, 1604 cm^{-1}.

2-(tert-butylamino)-6,7-dihydrobenzo[6,7]cyclohepta[1,2-*d*][1,3]oxazin-4(5*H*)-one (3qa) Yield: 91% (51.7 mg). White Solid. M.p. 174.5-176.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.57 (m, 1H), 7.41 – 7.29 (m, 2H), 7.27 – 7.19 (m, 1H), 5.31 (s, 1H), 2.64 (t, J = 7.0 Hz, 2H), 2.32 (t, J = 7.0 Hz, 2H), 2.19 (p, J = 6.8 Hz, 2H), 1.46 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 164.3, 162.8, 161.4, 141.3, 138.2, 130.0, 129.2, 128.1, 126.5, 106.5, 52.3, 33.2, 32.1, 29.0, 21.5 ppm. HRMS (ESI) *m/z*: calcd for $C_{17}H_{21}N_2O_2^+$ $[M+H]^+$ 285.1598, found: 285.1601. IR (neat, ν) = 3314, 2968, 2931, 2361, 2341, 1711, 1659 cm^{-1}.

2-(tert-butylamino)-4-phenyl-6*H*-1,3-oxazin-6-one (3ra) Yield: 73% (35.6 mg). White Solid. M.p. 158.0-159.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 2H), 7.50 – 7.43 (m, 3H), 6.08 (s, 1H), 5.58 (s, 1H), 1.53 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 165.7, 161.2, 161.1, 135.9, 131.5, 128.8, 127.3, 91.9, 52.5, 28.9 ppm. HRMS (ESI) *m/z*: calcd for $C_{14}H_{17}N_2O_2^+$ $[M+H]^+$ 245.1285, found: 245.1294. IR (neat, ν) = 3232, 3070, 2970, 2361, 2339, 1723 cm^{-1}.

2-(tert-butylamino)-4-(4-methoxyphenyl)-6*H*-1,3-oxazin-6-one (3sa) Yield: 58% (31.8 mg). White Solid. M.p. 155.6-157.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.76 (m, 2H), 7.07 – 6.82 (m, 2H), 5.99 (s, 1H), 5.65 (s, 1H), 3.85 (s, 3H), 1.51 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 165.3, 165.2, 162.4, 161.4, 129.1, 128.3, 114.1, 90.1, 55.5, 52.4, 28.9 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{19}N_2O_3^+$ $[M+H]^+$ 275.1390, found: 275.1380. IR (neat, ν) = 3266, 3055, 2983, 2964, 2362, 2335, 1727 cm^{-1}.

4-(4-(tert-butyl)phenyl)-2-(tert-butylamino)-6*H*-1,3-oxazin-6-one (3ta) Yield: 65% (39.0 mg). White Solid. M.p. 175.8-177.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 2H), 7.51 – 7.46 (m, 2H), 6.06 (s, 1H), 5.53 (s, 1H), 1.52 (s, 9H), 1.35 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 165.5, 161.3, 157.2, 155.1, 133.1, 127.2, 125.8, 91.3, 52.5, 35.1, 31.3, 28.9 ppm. HRMS (ESI) *m/z*: calcd for $C_{18}H_{24}N_2NaO_2^+$ $[M+Na]^+$ 323.1730, found: 323.1728. IR (neat, ν) = 3254, 3054, 2966, 2930, 2905, 2868, 2361, 2340, 1712 cm^{-1}.

2-(tert-butylamino)-4-(p-tolyl)-6*H*-1,3-oxazin-6-one (3ua) Yield: 66% (34.1 mg). White Solid. M.p. 175.5-178.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.74 (m, 2H), 7.31 – 7.18 (m, 2H), 6.04 (s, 1H), 5.65 (s, 1H), 2.41 (s, 3H), 1.52 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 165.7, 161.3, 159.7, 142.0, 133.1, 129.5, 127.3, 91.2, 52.4, 28.9, 21.6 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{18}N_2NaO_2^+$ $[M+Na]^+$ 281.1260, found: 281.1259. IR (neat, ν) = 3232, 3064, 2971, 2361, 2341, 1720 cm^{-1}.

2-(tert-butylamino)-4-(3-(trifluoromethyl)phenyl)-6*H*-1,3-oxazin-6-one (3va) Yield: 59% (36.8 mg). White Solid. M.p. 130.4-131.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.18 (m, 1H), 8.15 – 8.04 (m, 1H), 7.77 – 7.70 (m, 1H), 7.63 – 7.54 (m, 1H), 6.10 (s, 1H), 5.88 (s, 1H), 1.53 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 164.2, 160.9, 157.5, 136.8, 131.3 (q, $J_{C\text{-}F}$ = 32.5 Hz), 130.3, 129.3, 127.8 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.2 (q, $J_{C\text{-}F}$ = 3.9 Hz), 124.0 (q, $J_{C\text{-}F}$ = 270.0 Hz), 92.6, 52.7, 28.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{15}F_3N_2NaO_2^+$ $[M+Na]^+$ 355.0978, found: 335.0977. IR (neat, ν) = 3238, 3067, 2976, 2939, 2361, 2341, 1724, 1590 cm^{-1}.

5-methyl-4-(*p*-tolyl)-2-((2,4,4-trimethylpentan-2-yl)amino)-6*H*-1,3-oxazin-6-one (3ab) Yield: 57% (37.4 mg). White Solid. M.p. 149.3-151.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.39 (m, 2H), 7.26 – 7.20 (m, 2H), 5.06 (s, 1H), 2.40 (s, 3H), 2.05 (s, 3H), 1.82 (s, 2H), 1.48 (s, 6H), 1.01 (s, 9H) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 162.8, 162.6, 139.6, 135.2, 129.0, 128.8, 102.8, 55.9, 51.5, 31.8, 31.6, 29.4, 21.5, 12.9 ppm. HRMS (ESI) *m/z*: calcd for $C_{20}H_{28}N_2NaO_2^+$ $[M+Na]^+$ 351.2043, found: 351.2043. IR (neat, ν) = 3257, 3071, 2977, 2947, 2928, 2893, 2864, 2361, 2340, 1693, 1603 cm^{-1}.

2-(adamantan-1-ylamino)-5-methyl-4-(*p*-tolyl)-6*H*-1,3-oxazin-6-one (3ac) Yield: 96% (67.2 mg). White Solid. M.p. 205.7-207.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.38 (m, 2H), 7.26 – 7.19 (m, 2H), 4.99 (s, 1H), 2.40 (s, 3H), 2.14 – 2.08 (m, 3H), 2.06 (d, J = 3.8 Hz, 9H), 1.68 (t, J = 3.0 Hz, 6H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 162.9, 162.5(2), 162.4(8), 139.6, 135.2, 129.0, 128.8, 102.8, 52.6, 41.7, 36.3, 29.5, 21.5, 12.9 ppm. HRMS (ESI) *m/z*: calcd for $C_{22}H_{27}N_2O_2^+$ $[M+H]^+$ 351.2067, found: 351.2067. IR (neat, ν) = 3244, 3070, 2904, 2845, 2360, 2334, 1711, 1604 cm^{-1}.

2-(cyclohexylamino)-5-methyl-4-(*p*-tolyl)-6*H*-1,3-oxazin-6-one (3ad) Yield: 98% (58.4 mg). White Solid. M.p. 152.0-153.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.37 (m, 2H), 7.27 – 7.18 (m, 2H), 5.34 (s, 1H), 3.73 (s, 1H), 2.39 (s, 3H), 2.04 (s, 3H), 1.97 (s, 2H), 1.70 (dt, J = 13.7, 4.1 Hz, 2H), 1.60 (dt, J = 12.6, 4.0 Hz, 1H), 1.41 – 1.29 (m, 2H), 1.18 (s, 3H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 163.5, 162.4, 139.7, 135.1, 128.8, 128.5, 102.4, 50.3, 32.8, 25.4, 24.7, 21.5, 12.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{18}H_{22}N_2NaO_2^+$ $[M+Na]^+$ 321.1573, found: 321.1580. IR (neat, ν) = 3251, 3956, 2926, 2892, 2361, 2340, 1703, 1598 cm^{-1}.

2-(butylamino)-5-methyl-4-(*p*-tolyl)-6*H*-1,3-oxazin-6-one (3ae) Yield: 68% (37.0 mg). White Solid. M.p. 90.2-92.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.36 (m, 2H), 7.29 – 7.19 (m, 2H), 5.33 (s, 1H), 3.66 – 2.80 (m, 2H), 2.39 (s, 3H), 2.02 (s, 3H), 1.65 – 1.40 (m, 2H), 1.38 – 1.24 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 171.0, 163.6, 139.7, 135.1, 130.0, 128.9, 128.7, 41.1, 31.5, 21.5, 19.9, 13.8, 12.8. ppm. HRMS (ESI) *m/z*: calcd for $C_{16}H_{20}N_2NaO_2^+$ $[M+Na]^+$ 273.1598, found: 273.1607. IR (neat, ν) = 3253, 2957, 2930, 2870, 2363, 2336, 1703, 1607 cm^{-1}.

ethyl (5-methyl-6-oxo-4-(*p*-tolyl)-6*H*-1,3-oxazin-2-yl)glycinate (3af) Yield: 67% (40.4 mg). White Solid. M.p. 120.4-122.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.29 (m, 2H), 7.25 – 7.17 (m, 2H), 5.97 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.08 (br, 2H), 2.39 (s, 3H), 2.01 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 169.3, 162.6, 155.8, 139.9, 134.6, 128.9, 128.8, 61.7, 42.8, 21.5, 14.2, 12.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{16}H_{19}N_2O_4^+$ $[M+H]^+$ 303.1339, found: 303.1338. IR (neat, ν) = 3389, 2987, 2955, 2924,2362, 2340, 1721, 1604 cm^{-1}.

2-((4-methoxyphenyl)amino)-5-methyl-4-(*p*-tolyl)-6*H*-1,3-oxazin-6-one (3ag) Yield: 87% (56.1 mg). White Solid. M.p. 188.4-189.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.53 – 7.50 (m, 2H), 7.50 – 7.39 (m, 2H), 7.27 – 7.24 (m, 2H), 6.90 – 6.83 (m, 2H), 3.79 (s, 3H), 2.41 (s, 3H), 2.11 (s, 3H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 162.8, 162.2, 156.6, 153.7, 140.0, 134.8, 129.9, 129.0(4), 128.9(7), 122.0, 114.4, 104.8, 55.6, 21.6, 13.1 ppm. HRMS (ESI) *m/z*: calcd for $C_{19}H_{19}N_2O_3^+$ $[M+H]^+$ 323.1390, found: 323.1399. IR (neat, ν) = 3273, 2362, 2336, 1709, 1604 cm^{-1}.

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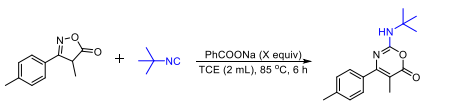
[13] According to one of the reviewer's suggestion, reactions using stoichiometric amount of PhCOONa without Pd catalyst were conducted. As shown below, when 1 equiv. PhCOONa was introduced, **3aa** could be isolated in 55% yield. Further increase the amount to 1.5 equiv. led to a bit lower yield. Thus, we think the reaction ran under our conditions mainly promoted by Pd catalyst.



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FULL PAPER

Palladium catalyzed ring expansion reaction of isoxazolones with isocyanides: synthesis of 1,3-oxazin-6-one derivatives

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