Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2024, **22**, 759

A sequential reaction of picolinamide with benzaldehydes promoted by $Pd(TFA)_2$: rapid access to 4,5-disubstituted 2-(pyridin-2-yl) oxazoles in *n*-octane†

Taku Nakayama, Sayaka Fujiki, Tomokatsu Enda, Shoko Kikkawa, Hidemasa Hikawa * and Isao Azumaya *

Received 6th November 2023,
Accepted 16th December 2023

DOI: 10.1039/d3ob01815f

rsc.li/obc

We developed a synthetic method for obtaining 4,5-disubstituted 2-(pyridin-2-yl)oxazoles from picolinamide and aldehydes by employing $Pd(TFA)_2$ as the catalyst in *n*-octane. This cascade reaction involves the condensation of picolinamide and two aldehyde molecules promoted by trifluoroacetic acid (TFA) generated *in situ* from $Pd(TFA)_2$. This one-pot protocol provides rapid access to synthetically valuable triaryloxazoles from readily available starting materials under mild conditions. An ^{18}O labeling study revealed that this tandem reaction proceeded *via* a different reaction mechanism compared to the Robinson–Gabriel oxazole synthesis.

Introduction

Oxazole moieties, five-membered aromatic heterocycles containing one oxygen and one nitrogen atom, are found in a wide range of pharmaceuticals and fine chemicals including non-steroidal anti-inflammatory drugs (NSAIDs),[1] blue organic LEDs,[2] and antibacterial peptides[3] (Fig. 1).

Various classical methods for oxazole ring construction have been reported so far (Scheme 1A).[4–15] Although many efficient protocols have been developed, to the best of our knowledge, few methods exist to synthesize a range of highly functionalized oxazoles through one-pot tandem reactions using commercially available substrates. In 2015, Meng *et al.* achieved a Robinson–Gabriel type triaryloxazole synthesis from 2-cyanopyridine and benzaldehydes *via* α-acylaminoketone intermediates (Scheme 1B).[16] However, this method requires the use of acetic acid as a solvent under harsh reaction conditions. Our group recently developed a water-promoted borrowing hydrogen reaction between 2-aminopyridines and benzylic alcohols utilizing a π-benzylpalladium(II) species in *n*-heptane, leading to a series of *N*-benzylpyridin-2-amines[17] (Scheme 2A). Inspired by this discovery, we attempted to extend the method to more challenging electron-deficient amide nucleophiles for the direct substitution of alcohols (Scheme 2B). To our surprise, however, the attempted Pd-catalyzed *N*-benzylation of substrate **1a** yielded triaryloxazole **3a** instead of the *N*-benzylated product. Based on this result and our previous work, we hypothesized that the amide nucleophile **1a** reacted with the *in situ* generated aldehydes **2**, forming oxazoles **3**. To the best of our knowledge, the straightforward synthesis of multi-substituted oxazoles from readily available picolinamides and aldehydes without the use of stoichiometric amounts of acid has not been reported previously.

We herein present an example of the synthesis of 4,5-disubstituted 2-(pyridin-2-yl)oxazoles from picolinamide and aldehydes using $Pd(TFA)_2$ in *n*-octane (Scheme 2C). This cascade reaction was performed using TFA as the catalyst generated *in situ* from $Pd(TFA)_2$ under neutral reaction conditions,

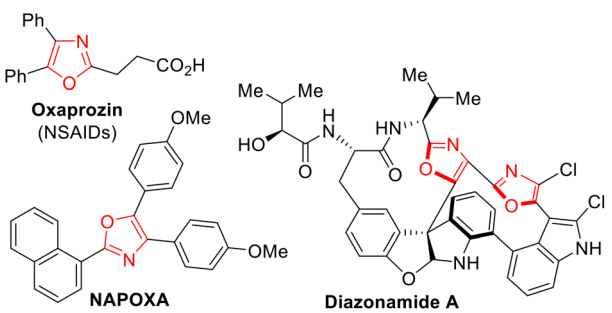
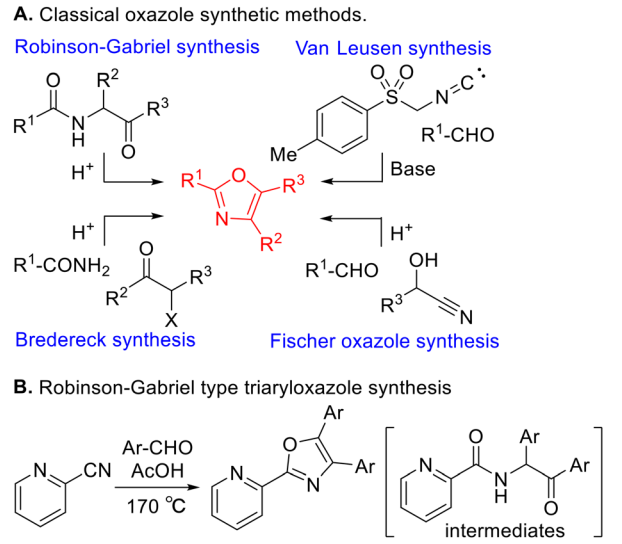


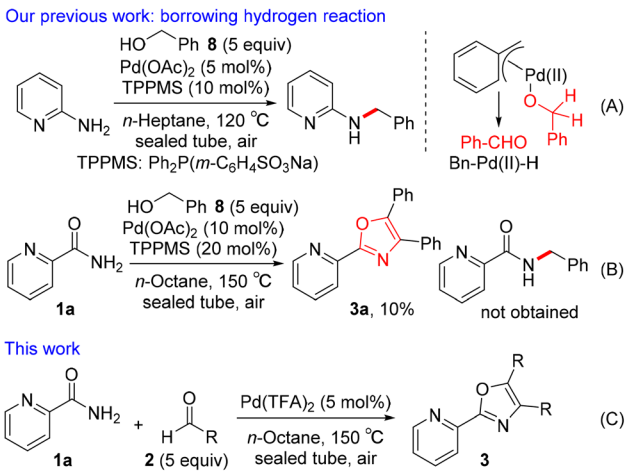
Fig. 1 Examples of drugs, a blue organic LED, and a marine natural product containing the oxazole moiety.

Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan. E-mail: hidemasa.hikawa@phar.toho-u.ac.jp, isao.azumaya@phar.toho-u.ac.jp

†Electronic supplementary information (ESI) available. CCDC 2305928. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ob01815f



Scheme 1 Classical oxazole synthetic methods.



Scheme 2 Straightforward Pd-catalyzed synthesis of triaryloxazoles **3**.

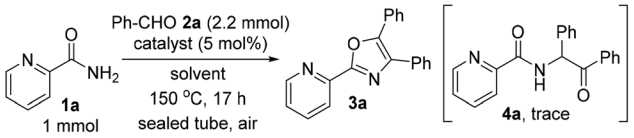
allowing rapid access to the valuable triaryloxazoles **3**. A plausible mechanism different from the Robinson–Gabriel reaction pathway was proposed based on an ^{18}O labeling study and several control experiments.

Results and discussion

Reaction optimization

Initially, a mixture of picolinamide (**1a**), benzaldehyde (**2a**, 2.2 equiv.) and $Pd(TFA)_2$ (5 mol%) was heated at 150 °C in *n*-octane in a sealed tube in air, furnishing the desired triaryloxazole **3a** in 62% yield (Table 1, entry 1). Replacing *n*-octane with *o*-xylene slightly diminished the yield (50%, entry 2). Polar solvents such as DMF or *n*-pentanol were not suitable for the oxazole synthesis (entries 3 and 4). No reaction occurred when using $(CHCl_2)_2$ as a solvent (entry 5). To investigate the

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	pK_a[b]	Solvent	Yield[c] (%)
1	$Pd(TFA)_2$	—	*n*-Octane	62
2	$Pd(TFA)_2$	—	*o*-Xylene	50
3	$Pd(TFA)_2$	—	DMF	0
4	$Pd(TFA)_2$	—	*n*-Pentanol	0
5	$Pd(TFA)_2$	—	$(CHCl_2)_2$	0
6	TFA	−0.25	*n*-Octane	54 (70)[d]
7	TfOH	−14	*n*-Octane	22
8	$TsOH{\cdot}H_2O$	−6.5	*n*-Octane	33
9	H_2SO_4	−3.0	*n*-Octane	32
10	MsOH	−2.6	*n*-Octane	40
11	AcOH	4.76	*n*-Octane	0
12	NaTFA	—	*n*-Octane	0
13	$Zn(TFA)_2$	—	*n*-Octane	26
14	AgTFA	—	*n*-Octane	56
15[d]	$Pd(TFA)_2$	—	*n*-Octane	86 (77)[e]

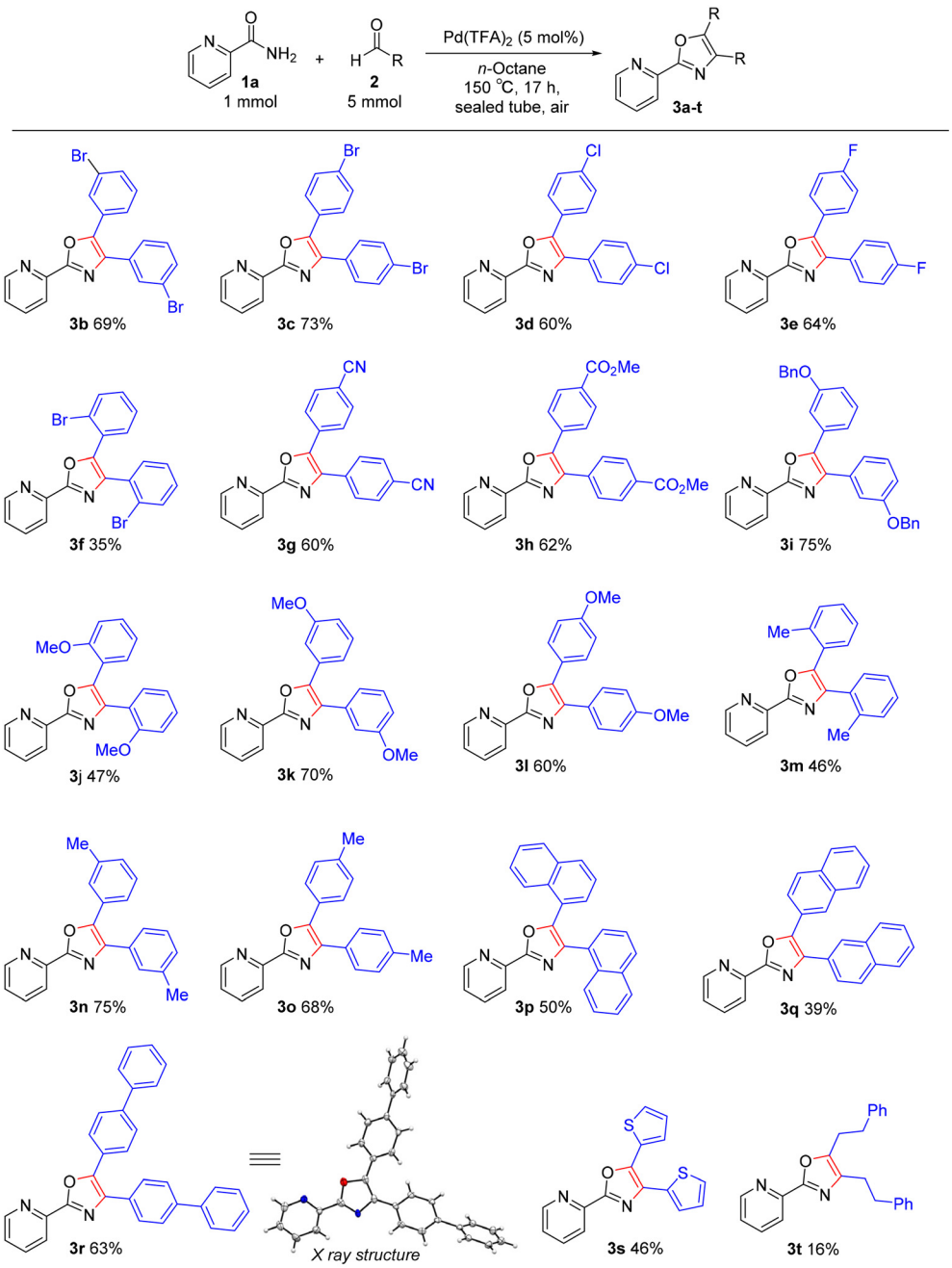
[a] Reaction conditions: amide **1a** (1.0 mmol), aldehyde **2a** (2.2 mmol), catalyst (5 mol%), solvent (4 mL), 150 °C, 17 h, sealed tube, in air. [b] pK_a values in H_2O. [c] The conversion was determined by ^1H NMR analysis of the crude product using 1,3,5-trimethoxybenzene (1 mmol) as an internal standard. [d] 5 equiv. of aldehyde **2a** was used. [e] Isolated yield in parenthesis.

effect of $Pd(TFA)_2$ on oxazole synthesis, the reaction using TFA as a catalyst was carried out. Surprisingly, TFA showed almost the same effect as $Pd(TFA)_2$ (54%, entry 6), suggesting that the *in situ* generated Brønsted acid catalyst from $Pd(TFA)_2$ promoted this sequential reaction. Screening of Brønsted acid catalysts showed no linear correlation between the pK_a values and the yield of **3a**, and the use of TFA gave the best result (entries 6–11).

Although the use of other salts such as NaTFA and Zn $(TFA)_2$ was not effective (entries 12 and 13), AgTFA showed almost the same result as $Pd(TFA)_2$ (56%, entry 14). To our delight, increasing the amount of aldehyde **2a** to 5 equiv. was shown to increase the yield of triaryloxazole **3a** (86%, entry 15), although a trace amount of by-product **4a** was formed.

Reaction scope

The reaction scope of aldehydes **2** was explored under the optimal conditions for triaryloxazole synthesis (Scheme 3). Several benzaldehydes with halogen groups could be converted to oxazole products with the carbon–halogen moieties left intact, which would be useful for further synthetic conversions (**3b–e**). The use of 2-bromobenzaldehyde led to a lower yield of **3f**, probably due to steric hindrance. A wide variety of functional groups including electron-withdrawing groups (cyano and ester) and electron-donating groups (benzyloxy, methoxy, and methyl) were tolerated under our catalytic conditions, furnishing a series of oxazoles in moderate yields (**3g–o**). Advantageously, aldehydes containing acid-sensitive cyano or benzyloxy group led to the desired products. Even the hydro-

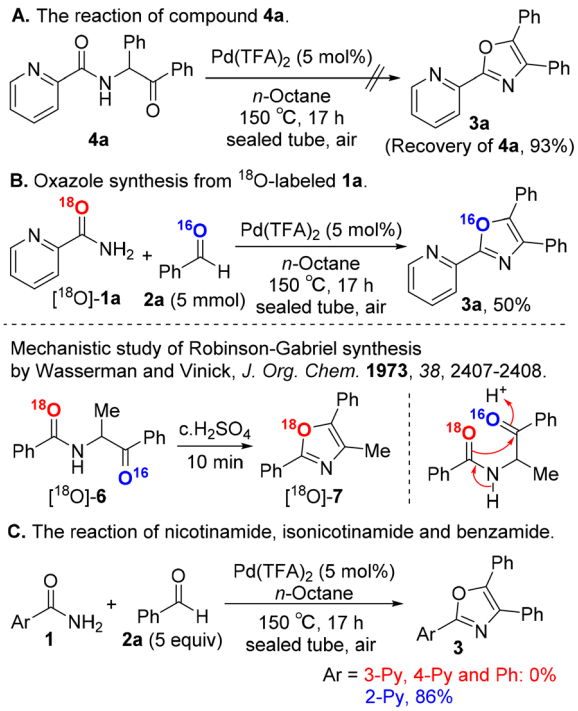


Scheme 3 Substrate scope of oxazole synthesis. Yields are those of isolated products **3**. Reaction conditions: amide **1a** (1.0 mmol), aldehyde **2** (5 mmol), $Pd(TFA)_2$ (5 mol%), *n*-octane (4 mL), 150 °C, 17 h, sealed tube, in air.

phobic and sterically hindered 4-phenylbenzaldehyde and naphthaldehydes led to the corresponding desired products (**3p–r**). The structure of **3r** was unambiguously confirmed by single-crystal X-ray diffraction analysis. Heterocyclic and aliphatic aldehydes were also converted to the corresponding oxazoles **3s** and **t**, albeit in poor yields. Unfortunately, 2-pyrazinecarboxamide and *N*,*N*-dimethylaminobenzaldehyde were not applicable to the TFA-catalyzed oxazole synthesis. These substrates are considered unsuitable for acid-catalyzed reactions due to their basicity.

Mechanistic investigations

To gain mechanistic insights into our oxazole synthesis, we performed several control experiments. The Robinson–Gabriel reaction generally proceeds *via* α-acylaminoketone intermediates **4** to afford oxazoles **3**. Surprisingly, compound **4a** was not converted to oxazole **3a** in our catalytic system (Scheme 4A). Next, we conducted an oxygen-18 tracer examination using ^{18}O-labeled picolinamide, and the resulting oxazole product was measured by high resolution mass spectrometry. The ^{18}O-



Scheme 4 Control experiments.

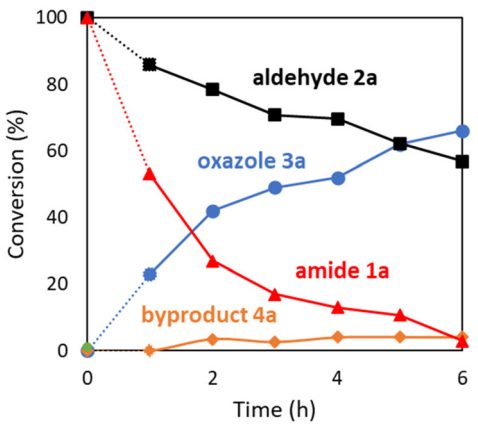


Fig. 2 Time course of the reaction for oxazole synthesis: amide **1a** (1 mmol), aldehyde **2a** (5 mmol), $Pd(TFA)_2$ (5 mol%), *n*-octane (4 mL), 150 °C, sealed tube, in air.

labeled substrate [^{18}O]-**1a** was prepared from picolinonitrile and $H_2{}^{18}O$, based on Sharley's method[18] (see the ESI†). The substrate [^{18}O]-**1a** was successfully transformed into the corresponding oxazole compound, leading to the non-^{18}O-labeled **3a** with a corresponding *m*/*z* value of 298.1106 (calcd mass for $[M]^+$: 298.1106) (Scheme 4B). In contrast, Wasserman and Vinick reported that the cyclization of substrate [^{18}O]-**6** gave oxazole [^{18}O]-**7**, clearly showing that the amide oxygen is incorporated in the oxazole ring.[19] These results exclude the Robinson–Gabriel reaction pathway *via* intermediate **4a** in our oxazole synthesis.

When replacing picolinamide (**1a**) with other amide substrates **1** such as nicotinamide, isonicotinamide and benzamide, the corresponding oxazole products **3** were not obtained under the standard conditions,[20] suggesting that the nitrogen atom in the pyridine ring of **1a** plays an important role in oxazole synthesis (Scheme 4C).

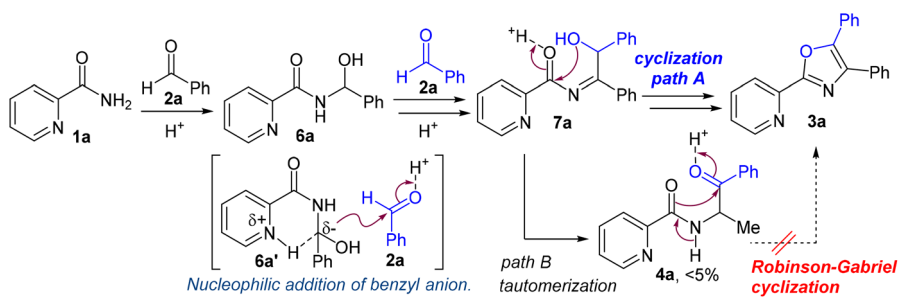
Reaction progress

The oxazole synthesis of **3a** was monitored over time by ^{1}H NMR spectroscopy to understand reaction progress (Fig. 2). The coupling reaction of amide **1a** with aldehyde **2a** proceeded smoothly to generate the triaryloxazole **3a**. Notably, the Robinson–Gabriel intermediate **4a** was not formed (<5%), ruling out the possibility of the Robinson–Gabriel reaction pathway (see Scheme 4B).

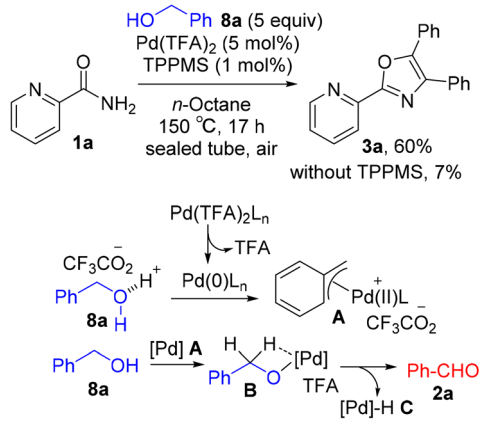
Proposed reaction mechanism

On the basis of several control experiments and previous reports, a plausible mechanism for the 4,5-disubstituted 2-(pyridin-2-yl)oxazole synthesis between picolinamide (**1a**) and benzaldehyde (**2a**) was proposed, as illustrated in Scheme 5. First, the nucleophilic amide nitrogen of **1a** attacks the electrophilic carbon of aldehyde **2a** to generate the aminal **6a**.

The benzylic proton of **6a** is removed by the neighboring pyridine base. The resulting benzyl anion **6a′** is stabilized by the adjacent substituents (carboxamide, hydroxy and phenyl groups) and the hydrogen bond in the pyridine ring. Subsequently, the nucleophilic addition of nucleophile **6a′** to a second aldehyde followed by dehydration proceeds to form intermediate **7a**. Finally, the cyclocondensation of **7a** affords the desired oxazole **3a** (path A). Following path B, the tautomerization of intermediate **7a** generates the Robinson–Gabriel



Scheme 5 Proposed mechanism for triaryloxazole synthesis.



Scheme 6 Pd-catalyzed dehydrogenative coupling of **1a** with **8a**.

intermediate **4a** as a minor product (<5% yield), which cannot be converted to the desired oxazole **3a** in our catalytic system.

Direct use of benzyl alcohol 8a for the construction of oxazole 3a

Pd-catalyzed oxidative coupling of picolinamide **1a** with the *in situ* generated benzaldehyde **2a** from benzyl alcohol **8a** enables the atom-economical synthesis of triaryloxazole **3a** along with H_2 and H_2O as the co-products. Encouraged by the finding of this oxazole synthesis (Scheme 2B), we examined the optimization of the Pd-catalyzed oxidative coupling of amide **1a** with alcohol **8a**. To our delight, decreasing the amount of TPPMS to 1 mol% improved the yield of **3a** to 60% (Scheme 6). In contrast, a lower yield was obtained in the absence of TPPMS (7%). The mechanism for Pd-catalyzed dehydrogenation of alcohol **8a** to aldehyde **2a** is proposed as follows: (1) reduction of $Pd(TFA)_2L_n$ (L = TPPMS) with alcohol **8a** leads to an active $Pd(0)L_n$ species along with TFA; (2) alcohol **8a** undergoes oxidative addition to $Pd(0)L_n$ (the C–O bond of **8a** is activated by the *in situ* generated TFA catalyst), forming π-benzylPd(II) **A**; and (3) β-hydride elimination of Pd(II)–alkoxide **B** generates aldehyde **2a**.

Conclusions

In summary, we developed a sequential reaction between picolinamide and aldehydes, which affords a series of 4,5-disubstituted 2-(pyridin-2-yl)oxazoles in *n*-octane. This one-pot protocol features, namely, practical simplicity, broad substrate scope, and easily available starting materials. Based on an ^{18}O labeling study, it was shown that the reaction mechanism differs from the Robinson–Gabriel synthetic pathway that relies on a stoichiometric amount of Brønsted acid under harsh reaction conditions. Therefore, this mild protocol is compatible with the substrate scope of aldehydes containing acid-sensitive functional groups. Further investigations on the detailed mechanism and extension towards other motifs are underway in our laboratory.

Experimental section

General comments

All starting materials and solvents were purchased from Aldrich, Wako, nacalai, and TCI Co., Ltd, Tokyo, Japan. All commercially available reagents and solvents were used without further purification. FT-IR spectra were recorded on a JASCO FT/IR-4100 spectrometer using KBr tablets. ^{1}H-NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) spectrometer. Chemical shifts (δ) are given from TMS (0 ppm) in $CDCl_3$ and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddd = double double doublet, dt = double triplet, td = triple doublet and m = multiplet. ^{13}C-NMR spectra were recorded on a JEOL ECS400 (100 MHz) spectrometer. Chemical shifts (δ) are given from $^{13}CDCl_3$ (77.0 ppm). Mass spectra and high-resolution mass spectra were measured on a JEOL JMS700 MStation.

Synthesis and spectroscopic and analytical data of 3a–3r

General procedure. A mixture of 2-picolinamide (**1**) (1 mmol), palladium(II) trifluoroacetate (16 mg, 0.05 mmol) and benzaldehyde **2** (5 mmol) in *n*-octane (4 mL) was heated for 17 h in a sealed tube in air. After cooling, $CHCl_3$ was added to the reaction mixture and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give the desired product **3**.

4,5-Diphenyl-2-(pyridin-2-yl)oxazole (3a).[16] Yield: 230 mg (0.77 mmol), 77%; light yellow solid; mp: 112.0–113.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.42 (m, 7H), 7.71–7.77 (m, 4H), 7.84 (td, J = 7.5, 1.8 Hz, 1H), 8.24 (ddd, J = 8.0, 1.1, 0.9 Hz, 1H), 8.78 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.3, 124.7, 127.2, 128.2, 128.4, 128.7, 128.7, 128.8, 129.0, 132.3, 137.0, 137.2, 146.2, 147.0, 150.2, 159.1; FT–IR (KBr, cm^{-1}): 3051, 1586, 1551; MS (FAB): m/z 299 $[M + H]^+$.

4,5-Bis(3-bromophenyl)-2-(pyridin-2-yl)oxazole (3b).[16] Yield: 314 mg (0.69 mmol), 69%; white solid; mp: 156.2–157.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, J = 8.0 Hz, 2H), 7.41 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.50–7.53 (m, 2H), 7.59–7.64 (m, 2H), 7.87 (td, J = 7.7, 1.8 Hz, 1H), 7.91 (t, J = 1.83 Hz, 1H), 7.97 (t, 1.8 Hz, 1H), 8.24 (ddd J = 7.7, 1.1 0.9 Hz, 1H), 8.80 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.5, 123.0, 123.0, 125.1, 125.7, 126.6, 130.0, 130.2, 130.2, 130.4, 131.2, 131.8, 132.3, 133.8, 136.5, 137.1, 145.8, 145.8, 150.3, 159.6; FT–IR (KBr, cm^{-1}): 3058, 1554; MS (FAB): m/z 457 $[M + H]^+$.

4,5-Bis(4-bromophenyl)-2-(pyridin-2-yl)oxazole (3c).[16] Yield: 333 mg (0.73 mmol), 73%; white solid; mp: 154.0–155.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.65–7.55 (m, 8H), 7.88 (td, J = 7.8, 1.8 Hz, 1H), 8.24 (dt, J = 8.0, 1.1 Hz, 1H), 8.81 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.3, 122.7, 123.3, 124.8, 127.2, 128.5, 129.6, 130.8, 131.9, 132.1, 136.5, 137.0, 145.8, 146.0, 150.2, 159.3; FT–IR (KBr, cm^{-1}): 3060, 1587 MS (FAB): m/z 457 $[M + H]^+$.

4,5-Bis(4-chlorophenyl)-2-(pyridin-2-yl)oxazole (3d).[16] Yield: 221 mg (0.6 mmol), 60%; white solid; mp: 151.3–152.4 °C; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.36–7.42 (m, 5H), 7.62–7.69 (m, 4H), 7.85 (td, 7.7, 1.8 Hz, 1H), 8.22 (ddd, J = 8.0, 1.1, 0.9 Hz, 1H), 8.79 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.4, 125.0, 126.9, 128.4, 129.0, 129.2, 129.5, 130.5, 134.5, 135.2, 136.5, 137.1, 145.9, 146.1, 150.3, 159.3; FT–IR (KBr, cm^{-1}): 3067, 3049, 1588; MS (FAB): m/z 367 $[M + H]^+$.

4,5-Bis(4-fluorophenyl)-2-(pyridin-2-yl)oxazole (3e).[16] Yield: 214 mg (0.64 mmol), 64%; white solid; mp: 172.0–172.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–7.07 (m, 4H), 7.39 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.65–7.73 (m, 4H), 7.85 (td, J = 7.5, 1.8 Hz, 1H), 8.22 (dt, J = 8.0, 1.1 Hz, 1H), 8.78 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.7 (d, J_F = 22.0 Hz), 116.0 (d, J_F = 22.0 Hz), 122.2, 124.6, 124.7, 128.0, 129.1 (d, J_F = 8.6 Hz), 129.9 (d, J_F = 8.6 Hz), 136.0, 136.9, 145.8, 145.9, 150.2, 159.0, 162.7 (d, J_F = 248.2 Hz), 163.0 (d, J_F = 250.2 Hz); FT–IR (KBr, cm^{-1}): 3055, 1587, 1552; MS (FAB): m/z 335 $[M + H]^+$.

4,5-Bis(2-bromophenyl)-2-(pyridin-2-yl)oxazole (3f).[16] Yield: 159 mg (0.35 mmol), 35%; white solid; mp: 139.5–140.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.34 (m, 4H), 7.38–7.41 (m, 2H), 7.49 (dd, J = 7.6, 1.6 Hz, 1H), 7.60 (dd, J = 8.0, 1.1 Hz, 1H), 7.64 (dd, J = 7.7, 0.9 Hz, 1H), 7.85 (dt, J = 7.6, 1.8 Hz, 1H), 8.26 (ddd, J = 7.7, 1.1, 0.9 Hz, 1H), 8.78 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.4, 123.4, 123.5, 124.9, 127.3, 127.4, 129.9, 130.2, 131.0, 132.2, 132.2, 133.1, 133.3, 133.6, 137.1, 138.5, 146.1, 147.3, 150.3, 159.6; FT–IR (KBr, cm^{-1}): 3062, 1586, 1560; MS (FAB): m/z 457 $[M + H]^+$.

4,4′-(2-(Pyridin-2-yl)oxazole-4,5-diyl)dibenzonitrile (3g). Yield: 210 mg (0.6 mmol), 60%; white solid; mp: 256–257 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.75–7.70 (m, 4H), 7.81–7.92 (m, 5H), 8.25 (ddd, J = 8.0, 1.1, 0.9 Hz, 1H), 8.81 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.7, 113.0, 118.3, 118.5, 122.8, 125.5, 127.5, 128.8, 132.2, 132.7, 132.8, 136.1, 137.3, 137.6, 145.3, 146.1, 150.5, 160.4; FT–IR (KBr, cm^{-1}): 3062, 2225, 1735, 1608; MS (FAB): m/z 349 $[M + H]^+$; anal. calcd for $C_{22}H_{12}N_4O{\cdot}0.2H_2O{\cdot}0.3CHCl_3$: C, 69.07; H, 3.30; N, 14.45. Found: C, 69.47; H, 3.67; N, 14.27.

Dimethyl 4,4′-(2-(pyridin-2-yl)oxazole-4,5-diyl)dibenzoate (3h). Yield: 258 mg (0.62 mmol), 62%; white solid; mp: 198.5–199.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H), 3.95 (s, 3H), 7.43 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.78–7.90 (m, 5H), 8.08 (td, J = 8.2, 1.8 Hz, 4H), 8.26 (dt, J = 8.3, 1.1 Hz, 1H), 8.81 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, 52.3, 122.5, 125.0, 126.8, 128.1, 129.9, 130.0, 130.1, 132.3, 136.2, 137.0, 137.6, 145.6, 146.7, 150.3, 159.8, 166.4, 166.7; FT–IR (KBr, cm^{-1}): 2954, 1716, 1609; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{24}H_{19}$ 415.1294; found: 415.1294.

4,5-Bis(3-(benzyloxy)phenyl)-2-(pyridin-2-yl)oxazole (3i). Yield: 383 mg (0.75 mmol), 75%; brown solid; mp: 135.5–135.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.01 (s, 2H), 5.06 (s, 2H), 6.96–7.00 (m, 2H), 7.28–7.44 (m, 17H), 7.85 (td, J = 7.7, 1.8 Hz, 1H), 8.23 (ddd, J = 7.7, 1.1, 0.9 Hz, 1H), 8.78 (ddd, J = 4.8, 1.1, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.2, 70.2, 113.3, 114.4, 115.5, 116.0, 120.0, 121.1, 122.4, 124.7, 127.6, 128.1, 128.1, 128.7, 128.7, 129.7, 129.8, 129.9, 133.6, 136.8, 137.0, 137.2, 146.2, 146.9, 150.3, 159.0, 159.0, 159.1; FT–IR (KBr, cm^{-1}): 3032, 2916, 1588, 1496; MS (FAB): m/z 511 $[M + H]^+$; anal. calcd for $C_{34}H_{26}N_2O_3{\cdot}0.9H_2O$: C, 77.52; H, 5.32; N, 5.32, found: C, 77.45; H, 5.07; N, 5.21.

4,5-Bis(2-methoxyphenyl)-2-(pyridin-2-yl)oxazole (3j). Yield: 169 mg (0.47 mmol), 47%; white solid; mp: 142.1–143.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (s, 3H), 3.43 (s, 3H), 6.81–6.86 (m, 2H), 6.96–7.06 (m, 2H), 7.27–7.36 (m, 3H), 7.59 (ddd J = 7.6, 1.8, 1.6 Hz, 1H), 7.71 (dd J = 7.5, 1.8 Hz, 1H), 7.81 (td J = 7.7, 1.8 Hz, 1H), 8.23 (ddd J = 8.0, 1.1, 0.9 Hz, 1H), 8.76 (ddd J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.8, 55.0, 110.3, 110.5, 119.7, 120.2, 120.3, 122.2, 123.0, 124.3, 129.2, 129.8, 130.1, 130.5, 135.5, 136.8, 146.1, 146.6, 150.1, 156.8, 156.8, 159.2; FT–IR (KBr, cm^{-1}): 3068, 1584, 1502; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_3$ 359.1; found: 359.1.

4,5-Bis(3-methoxyphenyl)-2-(pyridin-2-yl)oxazole (3k). Yield: 250 mg (0.7 mmol), 70%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.80 (s, 3H), 6.88–6.91 (m, 1H), 6.92 (ddd J = 2.7, 1.6 Hz, 1H), 7.26–7.34 (m 6H), 7.38 (ddd J = 7.5, 4.8, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 112.3, 113.3, 114.8, 115.2, 119.8, 120.8, 122.4, 124.7, 129.6, 129.8, 129.8, 133.5, 137.0, 137.2, 146.2, 146.9, 150.2, 158.9, 159.7, 159.8; FT–IR (KBr, cm^{-1}): 3057, 3001, 2938, 2835, 1589; MS (FAB): m/z 359 $[M + H]^+$: anal. calcd for $C_{22}H_{18}N_2O_3{\cdot}0.2CHCl_3$: C, 69.75; H, 4.80; N, 7.33, found: C, 69.77; H, 4.97; N, 7.31.

4,5-Bis(4-methoxyphenyl)-2-(pyridin-2-yl)oxazole (3l).[16] Yield: 215 mg (0.6 mmol), 60%; light yellow solid; mp: 129.5–130.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 6H), 6.90–6.94 (m, 4H), 7.36 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.63–7.68 (m, 4H), 7.82 (td, J = 7.7, 1.8 Hz, 1H), 8.72 (dt, J = 7.9, 0.9 Hz, 1H), 8.77 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 55.3, 114.0, 114.1, 121.3, 122.0, 124.3, 124.8, 128.5, 129.3, 135.8, 129.3, 135.8, 136.8, 146.2, 146.3, 150.1, 158.4, 159.5, 160.0; FT–IR (KBr, cm^{-1}): 2960, 1597, 1578; MS (FAB): m/z 359 $[M + H]^+$.

2-(Pyridin-2-yl)-4,5-di-*o*-tolyloxazole (3m). Yield: 150 mg (0.46 mmol), 46%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.21 (s, 3H), 7.17–7.12 (m, 2H), 7.20–7.33 (m, 6H), 7.37 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.83 (td, J = 7.7, 1.8 Hz, 1H), 8.22 (ddd, J = 8.0, 1.1, 0.9 Hz, 1H), 8.76 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 20.5, 122.2, 124.6, 125.9, 128.1, 128.5, 129.4, 130.2, 130.3, 130.8, 131.6, 137.0, 137.2, 138.4, 146.4, 148.2, 150.2, 159.3; FT–IR (KBr, cm^{-1}): 3058, 1589, 1457; MS (FAB): m/z 327 $[M + H]^+$; anal. calcd for $C_{22}H_{18}N_2O{\cdot}0.3CHCl_3$: C, 73.95; H, 5.09; N, 7.73, found: C, 74.17; H, 5.14; N, 7.62.

2-(Pyridin-2-yl)-4,5-di-*m*-tolyloxazole (3n). Yield: 246 mg (0.75 mmol), 75%; white solid; mp: 125.8–127.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 1H), 2.38 (s, 1H), 7.16–7.18 (m, 2H), 7.25 (t, J = 7.5 Hz 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.38 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.48–7.52 (m, 2H), 7.59–7.60 (m, 1H), 7.64–7.65 (m, 1H), 7.84 (td, J = 7.7, 1.8 Hz, 1H), 8.24 (ddd, J = 8.0, 1.1 Hz, 1H), 8.79 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 21.5, 122.3, 124.3, 124.6, 125.2, 127.7, 128.4, 128.5, 128.6, 128.9, 129.1, 129.8, 132.2, 137.0, 137.2, 138.3, 138.5, 146.3, 147.1, 150.2, 158.9; FT–IR (KBr,

cm^{-1}): 2919, 2345, 1589; MS (FAB): *m*/*z* 327 [M + H]$^+$; anal. calcd for $C_{32}H_{22}N_2O$: C, 80.96; H, 5.56; N, 8.58, found: C, 80.70; H, 5.56; N, 8.47.

2-(Pyridin-2-yl)-4,5-di-*p*-tolyloxazole (3o). Yield: 221 mg (0.68 mmol), 68%; white solid; mp: 118.0–119.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 6H), 7.17–7.20 (m, 4H), 7.35 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.82 (td, J = 7.8, 1.1 Hz, 1H), 8.77 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 21.4, 122.1, 124.4, 125.9, 127.0, 128.0, 129.2, 129.3, 129.4, 136.6, 136.8, 138.0, 138.9, 146.2, 146.8, 150.1, 158.6; FT–IR (KBr, cm^{-1}): 2918, 2860, 1699; HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2O$: 327.1497; found: 327.1496.

4,5-Di(naphthalen-1-yl)-2-(pyridin-2-yl)oxazole (3p). Yield: 199 mg (0.5 mmol), 50%; white solid; mp: 174.5–175.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.50 (m, 9H), 7.79–7.90 (m, 5H), 8.05 (d, J = 8.5 Hz, 1H), 8.26 (d, J = 8.9 Hz, 1H), 8.34 (dt, J = 8.0, 0.9 Hz, 1H), 8.81 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.3, 124.7, 125.1, 125.2, 125.5, 125.9, 126.1, 126.4, 126.9, 128.2, 128.3, 128.4, 129.0, 130.0, 133.6, 133.9, 137.0, 138.6, 146.3, 148.5, 150.2, 159.8; FT–IR (KBr, cm^{-1}): 3053, 2362, 1698; HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{19}N_2O$: 399.1497; found: 399.1498.

4,5-Di(naphthalen-2-yl)-2-(pyridin-2-yl)oxazole (3q). Yield: 155 mg (0.39 mmol), 39%; white solid; mp: 169.8–170.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.47–7.55 (m, 4H), 7.76–7.91 (m, 9H), 8.31–8.37 (m, 3H), 8.83 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm): δ 122.5, 124.5, 126.0, 126.5, 126.8, 127.6, 127.8, 127.9, 128.2, 128.4, 128.5, 133.3, 133.4, 133.6, 137.0, 137.6, 146.2, 147.4, 150.3, 159.4; FT–IR (KBr, cm^{-1}): 3052, 1698, 1587; HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{19}N_2O$: 399.1497; found: 399.1497.

4,5-Di([1,1′-biphenyl]-4-yl)-2-(pyridin-2-yl)oxazole (3r). Yield: 285 mg (0.63 mmol), 63%; white solid; mp: 219.5–220.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.41 (m, 3H), 7.44–7.48 (m, 4H), 7.63–7.68 (m, 8H), 7.84–7.90 (m, 5H), 8.27 (ddd, J = 7.79, 1.14, 0.92 Hz, 1H), 8.80 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.4, 124.7, 127.1, 127.1, 127.4, 127.4, 127.5, 127.6, 127.8, 128.7, 128.9, 129.0, 131.3, 137.0, 137.1, 140.3, 140.7, 141.2, 141.7, 146.2, 146.9, 150.3, 159.2; FT–IR (KBr, cm^{-1}): 3647, 3035, 2355, 1588, 1483; MS (FAB): *m*/*z* 451 [M + H]$^+$; anal. calcd for $C_{32}H_{22}N_2O$: C, 85.31; H, 4.92; N, 6.22, found: C, 85.47; H, 5.00; N, 6.27.

2-(Pyridin-2-yl)-4,5-di(thiophen-2-yl)oxazole (3s). Yield: 143 mg (0.46 mmol), 46%; brown solid; mp: 128.6–129.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (dd, J = 5.2, 3.6 Hz, 1H), 7.13 (dd, J = 5.0, 3.6 Hz, 1H), 7.37–7.41 (m, 2H), 7.45 (dd, J = 5.2, 1.1 Hz, 1H), 7.58 (dd, J = 3.6, 1.1 Hz, 1H), 7.61 (dd, J = 3.6, 1.1 Hz, 1H), 7.84 (td, J = 7.7, 1.6 Hz, 1H), 8.22 (ddd, J = 8.0, 1.1, 0.9 Hz, 1H), 8.78 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.6, 124.9, 126.5, 126.6, 127.5, 127.5, 127.7, 127.9, 129.1, 132.1, 133.6, 137.0, 141.6, 145.7, 150.3, 158.7; FT–IR (KBr, cm^{-1}): 3078, 1588, 1455; MS (FAB): *m*/*z* 311 [M + H]$^+$; anal. calcd for $C_{16}H_{10}N_2O_1S_2 \cdot 0.15H_2O$: C, 61.38; H, 3.32; N, 8.95, found: C, 61.45; H, 3.37; N, 8.73.

4,5-Diphenethyl-2-(pyridin-2-yl)oxazole (3t). Yield: 57 mg (0.16 mmol), 16%; brown solid; mp: 98.8–99.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61–2.65 (m, 2H), 2.77 (s, 4H), 2.80–2.84 (m, 2H), 7.07–7.12 (m, 4H), 7.15–7.21 (m, 2H), 7.23–7.28 (m, 4H), 7.34 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.82 (td, J = 7.9, 1.8 Hz, 1H), 8.09 (ddd, J = 8.0, 1.1, 0.9 Hz, 1H), 8.74 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.0, 28.1, 34.6, 35.2, 121.7, 124.2, 126.1 126.3, 128.4, 128.5, 128.6, 128.7, 136.6, 137.0, 140.8, 141.7, 146.5, 148.4, 150.1, 158.6; FT–IR (KBr, cm^{-1}): 3029, 2920, 1634, 1591, 1456; MS (FAB): *m*/*z* 355 [M + H]$^+$; anal. calcd for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90, found: C, 81.10; H, 6.30; N, 7.70.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Dr Katsuyoshi Mitsunaga (Faculty of Pharmaceutical Sciences, Toho University) for recording the high-resolution mass spectra. This work was supported by JSPS KAKENHI, Grant Number 19K07003. The authors thank FORTE Science Communications (https://www.forte-science.co.jp/) for English language editing.

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