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OXIDATIVE REARRANGEMENT OF BENZYLAMINES TO 4*H*-3,1-BENZOXAZINES VIA Cu/Mn-PROMOTED INTRAMOLECULAR C–H AMINATION/ELECTROCYCLIC REACTION CASCADE

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Abstract – We have developed a copper/manganese-mediated oxidative rearrangement of benzylamines to 4*H*-3,1-benzoxazines of potent interest in medicinal applications. The reaction proceeds uniquely through the initial copper/manganese-promoted intramolecular C–H amination giving benzazetidine intermediates and subsequent 4π electrocyclic ring opening/6π electrocyclic ring closing cascade. The key to success is the introduction of picolinamide-based *N,N*-bidentate directing group. The obtained benzoxazines can also be readily hydrolyzed to the corresponding 2-aminobenzyl alcohols, thus indicating that the overall transformations is regarded as the *ortho*-aminative rearrangement of benzylamines to benzylic alcohols.

INTRODUCTION

4*H*-3,1-Benzoxazines uniquely have oxygen and nitrogen atoms in one ring system and thus constitutes an important class of heterocycles in various fields of organic chemistry. They are frequently occurring in pharmaceutical agents, bioactive molecules, and natural products.[1] Thus, synthetic chemists have developed numerous methodologies for the construction of benzoxazine framework.[2] However, most reported procedures rely on *ortho*-functionalized aniline derivatives as the starting substrates, which are often tedious and difficult to prepare.[3] On the other hand, the copper-mediated oxidative cyclization via C–H cleavage now receives significant attention in heterocycle synthesis because it can allow simpler starting materials to be adopted in the cyclization event and thus can be more atom- and step-economical than conventional protocols.[4] Our group also focused on the unique activity of less toxic, stable, and

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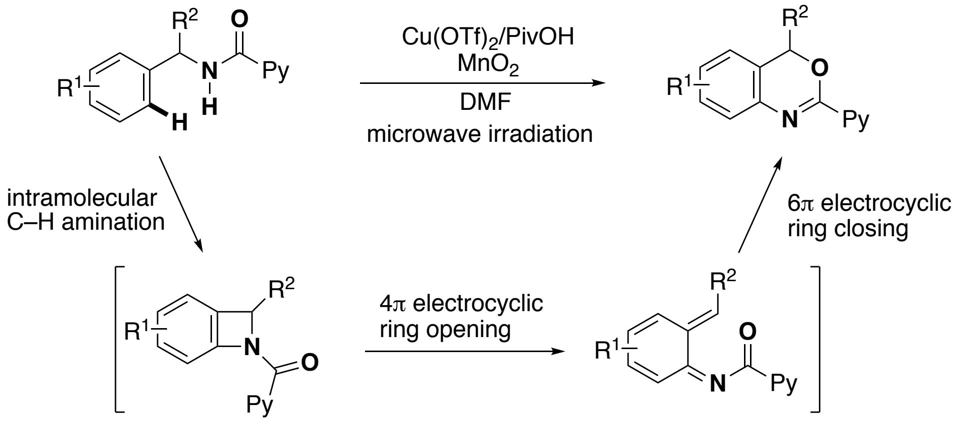
The paper is dedicated to Prof. Kiyoshi Tomioka on the occasion of his 70th birthday.

abundant copper salts and developed several copper-promoted intramolecular C–H amination reactions for the synthesis of *N*-heterocycles including carbazoles,[5a] indolines,[5b] isoindolinones,[5c] indoles, and oxazoles.[5d] During our continuous interest in this chemistry, we next investigated the reactivity of benzylamines under copper-mediated C–H activation conditions and serendipitously found the formation of 4*H*-3,1-benzoxazines via unique intramolecular C–H amination/electrocyclic reaction sequence (Scheme 1). This cascade reaction can provide the benzoxazine from the simpler and easily available mono-substituted benzylamine derivative. A related palladium-catalyzed benzazetidine formation was already developed,[6] but such a sequential reaction is not trivial, to the best of our knowledge. The detailed optimization studies and substrate scope are thus reported herein.



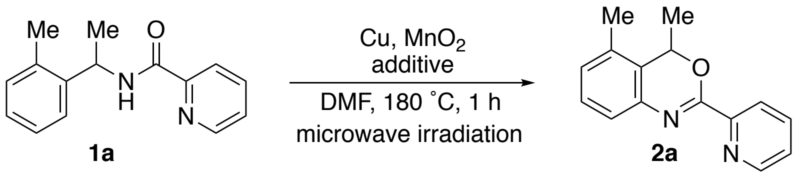
Scheme 1. Oxidative rearrangement of benzylamines to benzoxazines via Cu/Mn-mediated intramolecular C–H amination/electrocyclic reaction sequence (this work). Py = 2-pyridyl.

RESULTS AND DISCUSSION

Our optimization studies commenced with the *N*-picolinoylbenzylamine derivative **1a**, which is the representative *N*,*N*-bidentately coordinating substrate and originally developed by Daugulis.[7] We first found that treatment of **1a** with a $Cu(OAc)_2$ catalyst (20 mol%) and an MnO_2 oxidant (2.0 equiv) in DMF (1.0 mL) under microwave irradiation (180 °C, 1 h) afforded the oxidatively and uniquely rearranged 2-pyridyl-4*H*-3,1-benzoxazine **2a** in 29% ^{1}H NMR yield (Table 1, entry 1). Such a pyridine-substituted oxazine is the promising ligand framework for metal catalysts.[8] Screening of several acidic additives (100 mol%) revealed that PivOH increased the conversion (entries 2–4). Notably, the choice of copper salts was critical; $Cu(OTf)_2$ improved the ^{1}H NMR yield to 48% (entry 5) whereas acetate-type $Cu(OPiv)_2$ and $Cu(eh)_2$ (eh = 2-ethylhexanoate) as well as $Cu(BF_4)_2$ resulted in lower efficiency (entries 6–8). Subsequent fine tuning about amounts of catalyst, additive, and solvent (entries 9–12) identified a combination of 80 mol% $Cu(OTf)_2$, 50 mol% PivOH, and 0.60 mL DMF to be optimal, giving **2a** in 68% isolated yield (entry 12). The reaction was quite clean, and mass balance was almost perfect; unreactive **1a** was recovered in 30% ^{1}H NMR yield under conditions of entry 12. Even with 100 mol% of

$Cu(OAc)_2$, the yield of **2a** was much lower (entry 13), and $Cu(OTf)_2$ was thus confirmed to be superior. Additional several observations are to be noted: either $Cu(OTf)_2$ or MnO_2 alone did not promote the present transformation at all (entries 14 and 15); the corresponding *N*-benzoylbenzylamine showed no reactivity under identical conditions (data not shown), thus indicating necessity of cooper/manganese cooperation and *N*,*N*-bidentate coordination nature of **1a**.

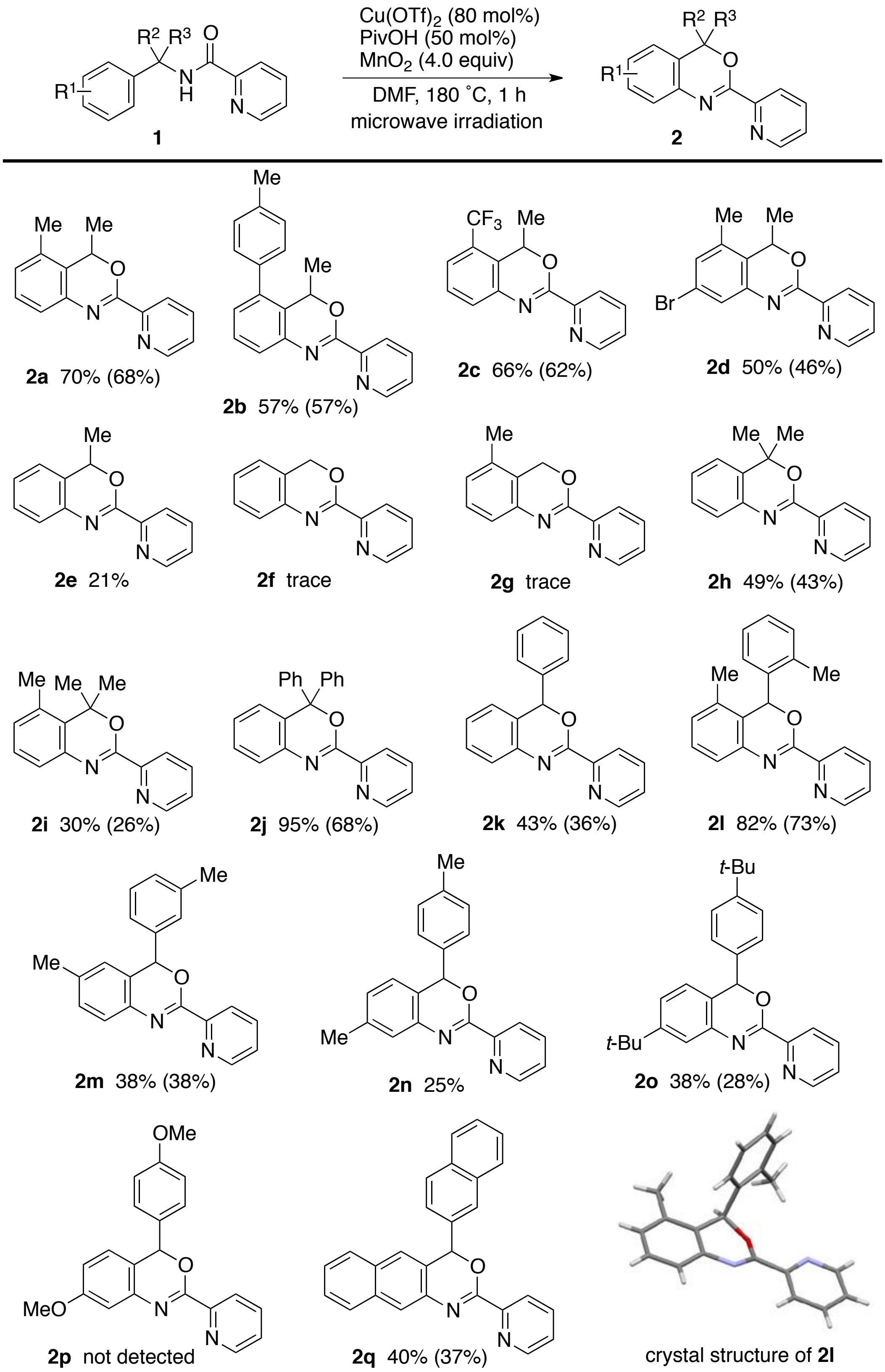
Table 1. Optimization studies for copper/manganese-mediated oxidative rearrangement of *N*-picolinoylbenzylamine **1a** to 4*H*-3,1-benzoxazine **2a**[a]



entry	Cu (mol%)	additive (mol%)	yield of **2a** (%)[b]
1	$Cu(OAc)_2$ (20)	none	29
2	$Cu(OAc)_2$ (20)	AcOH (100)	31
3	$Cu(OAc)_2$ (20)	1-AdCOOH (100)	28
4	$Cu(OAc)_2$ (20)	PivOH (100)	37
5	$Cu(OTf)_2$ (20)	PivOH (100)	48
6	$Cu(BF_4)_2$ (20)	PivOH (100)	23
7	$Cu(OPiv)_2$ (20)	PivOH (100)	23
8	$Cu(eh)_2$ (20)	PivOH (100)	26
9	$Cu(OTf)_2$ (100)	PivOH (100)	61
10	$Cu(OTf)_2$ (100)	PivOH (50)	64
11[c]	$Cu(OTf)_2$ (100)	PivOH (50)	68
12[c]	$Cu(OTf)_2$ (80)	PivOH (50)	70 (68)
13[c]	$Cu(OAc)_2$ (100)	PivOH (50)	40
14[d]	$Cu(OTf)_2$ (100)	PivOH (100)	0
15	none	PivOH (100)	0

[a] Conditions: **1a** (0.10 mmol), Cu, MnO_2 (0.40 mmol), additives, DMF (1.0 mL), microwave irradiation, 1 h, N_2. [b] Yields are estimated by ^1H NMR. Isolated yield is in parentheses. [c] In DMF (0.60 mL). [d] Without MnO_2.

Under the conditions of entry 12 in Table 1, we investigated the scope and limitations of benzylamine derivatives **1** (Scheme 2).

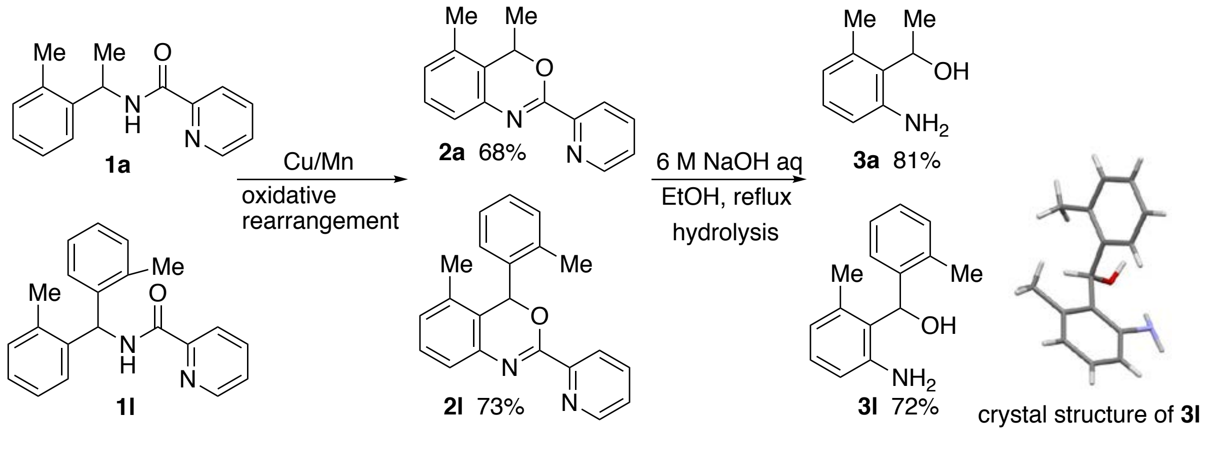


Scheme 2. Copper/manganese-mediated oxidative rearrangement of *N*-picolinoylbenzylamines **1** to 4*H*-3,1-benzoxazines **2**. ^{1}H NMR yields are shown. Isolated yields are in parentheses.

The substrates that bear 4-methylphenyl and trifluoromethyl groups at the ortho position also underwent the reaction to afford the corresponding oxazines **2b** and **2c** in 57% and 62% isolated yields, respectively.

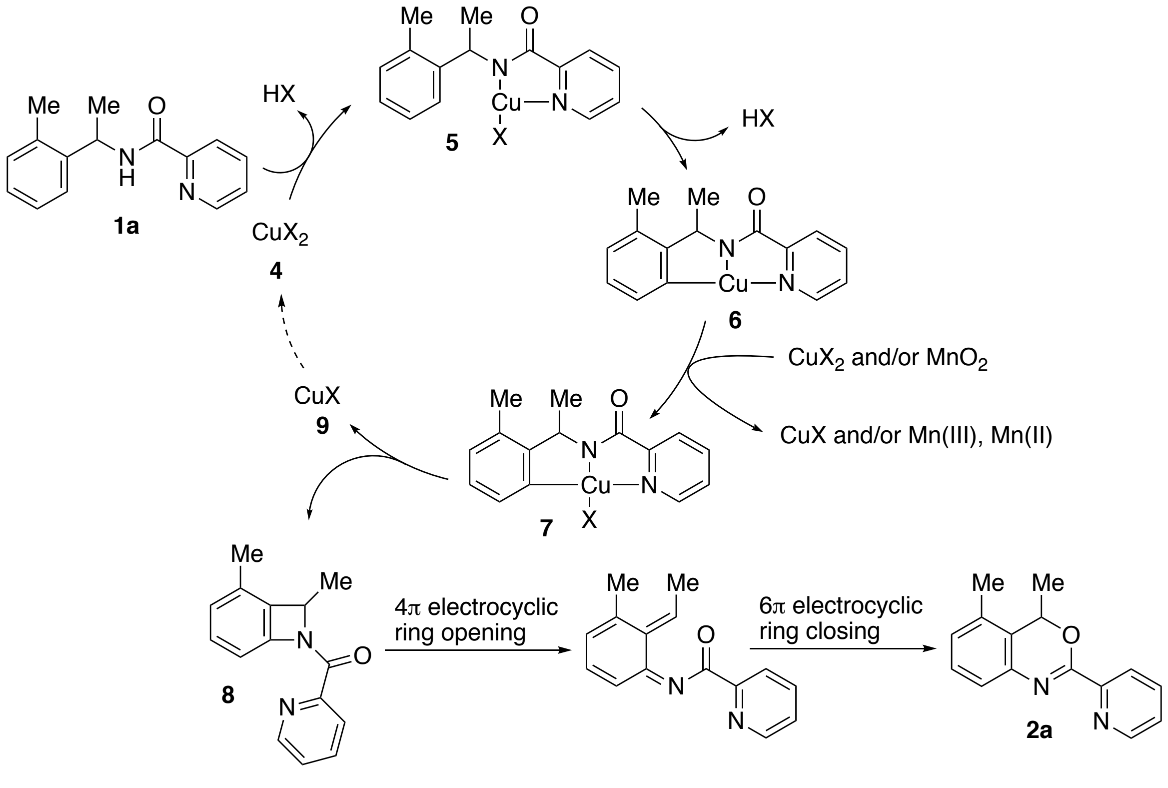
The conditions were compatible with the aryl-Br functional group, which can be a useful synthetic handle for further elaborations (**2d**). The ortho substituent apparently gave positive effects on reaction efficiency; the parent benzylamine **1e** resulted in lower conversion (**2e**), thus suggesting the important Thorpe-Ingold effect[9] in the C–H activation step (vide infra). Similar steric effects were observed with respect to the substitution pattern at the benzylic position α to nitrogen; the reaction of simple benzylamines **1f** and **1g** were sluggish (**2f** and **2g**) while tertiary benzyl-substituted **1h**, **1i**, and **1j** showed better reactivity (**2h**, **2i**, and **2j**). However, we have no explanation for the reason why the yield of **2i** was lower than that of **2h**. Additional investigation was performed with the diarylmethylamine structural motif. The reaction of diphenylmethylamine **1k** delivered the desired product **2k** in a moderate yield. Also in this case, sterically demanding substrates were more promising: the yield increased in order of *ortho*- > *meta*- > *para*-substituted diarylmethylamines (**2l**, **2m**, **2n**, and **2o**). Additionally, in the *meta*-substituted **1m**, more sterically accessible C–H was selectively functionalized. Unfortunately, the electron-donating methoxy group was detrimental (**2p**), but higher π-extended naphthoxazine **2q** was accessible under the standard conditions. Notably, the 4*H*-3,1-benzoxazine structure of **2l** was unambiguously confirmed by single-crystal X-ray diffraction.[10]

The obtained 4*H*-3,1-benzoxazines **2a** and **2l** could be readily hydrolyzed into the corresponding 2-aminobenzyl alcohols **3a** and **3l** in good yields (Scheme 3). The product **3a** was known compound, and its spectra data was in agreement with the reported values.[11] On the other hand, the structure of **3l** was determined by ^{1}H NMR, ^{13}C NMR, HRMS, and finally X-ray analysis.[10] Thus, the overall transformation can be regarded as the *ortho*-aminative rearrangement of benzylamines to benzyl alcohols.



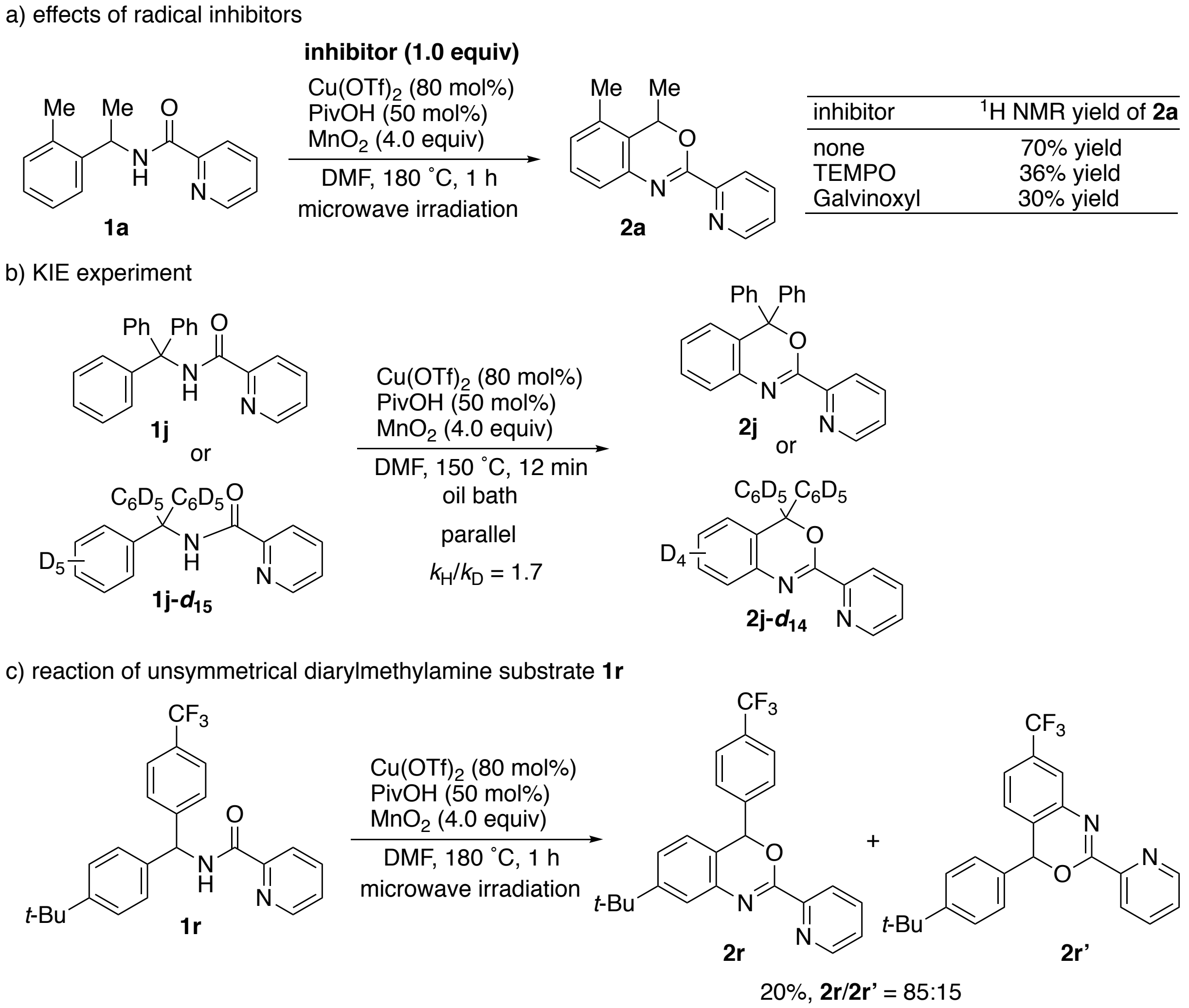
Scheme 3. The overall transformation of benzylamines **1a** and **1l** to 2-aminobenzyl alcohols **3a** and **3l** via Cu/Mn-mediated oxidative rearrangement and hydrolysis. Isolated yields are given.

On the basis of the literature information, we propose the reaction mechanism of **1a** as shown in Scheme 4. An initial *N*,*N*-bidentate coordination of *N*-picolinoylbenzylamine **1a** to CuX_2 **4** with the liberation of HX forms the chelated Cu species **5**. Subsequent C–H cupration generates the metalacycle **6**, which can be sterically accelerated by the substituents at the ortho and benzylic positions (Thorpe-Ingold effect). The 4-membered benzazetidine intermediate **8** follows from the oxidation (disproportionation)-induced reductive elimination via Cu(III) **7**.[12] The higher oxidation state of Cu(III) **7** enables such a challenging, small ring-constructing reductive elimination. As mentioned in the introduction part, the related process was recently developed under Pd(II) catalysis by Chen and coworkers.[6] The formed benzazetidine **8** then undergoes thermal 4π electrocyclic ring opening/6π electrocyclic ring closing cascade to furnish the observed 4*H*-3,1-benzoxazine **2a**.[6,13] If the concurrently formed Cu(I) species **9** was reoxidized with MnO_2 to the starting CuX_2 **4**, the copper catalytic cycle could be completed. However, the product, 2-pyridyl-3,1-oxazine **2a**, can be a good ligand to copper and thus retard the catalytic turnover due to its tight coordination.[14]



Scheme 4. Plausible mechanism of oxidative rearrangement of *N*-picolinoylbenzylamine **1a** to 4*H*-3,1-benzoxazine **2a**. X = OTf or OPiv.

Previously, we[15] and Wang and coworkers[16] reported related copper-promoted reactions of benzylamines through the benzazetidine intermediate **8**, in which *N*-centered radical species was believed to take part in the 4-membered ring construction. To determine whether a similar radical species is involved or not in the present case, we conducted control experiments with radical inhibitors (Scheme 5a). The yield of **2a** decreased, but the reaction was not completely shut down. Additionally, a primary kinetic isotope effect (KIE) value of k_H/k_D = 1.7 was observed in the parallel reaction of **1j** and **1j-*d*$_{15}$** (Scheme 5b).[17] These outcomes support the organometallic pathway involving the rate-limiting C–H cupration proposed in Scheme 4, rather than the reported radical pathway. Although the detailed C–H cupration mechanism (**5** to **6** in Scheme 4) still remains unclear, the electrophilic metalation pathway[18] is likely, which can explain the higher performance with $Cu(OTf)_2$ of cationic nature. Actually, the unsymmetrical diarylmethylamine substrate **1r** underwent the reaction preferably at the more electron-rich *t*-Bu-substituted benzene ring (Scheme 5c).



inhibitor	^1H NMR yield of **2a**
none	70% yield
TEMPO	36% yield
Galvinoxyl	30% yield

Scheme 5. Experiments for mechanistic considerations

CONCLUSION

We have developed a unique oxidative rearrangement of benzylamines to 4*H*-3,1-benzoxazines via picolinamide-directed, copper/manganese-promoted intramolecular C–H amination/electrocyclic reaction cascade. The obtained benzoxazines are among representative *N*-heterocycles of potent interest in medicinal and pharmaceutical chemistry. Additionally, subsequent hydrolysis forms the corresponding 2-aminobenzyl alcohols; the overall transformation thus can be regarded as *ortho*-aminative rearrangement of benzylamines to benzyl alcohols. While still limited in scope, this protocol can provide an additional approach to otherwise synthetically challenging *N*-heterocycles and new insight to further development and design of C–H activation catalysis based on copper.

EXPERIMENTAL

General. ^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra were recorded at 400, 100, and 376 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by APCI using TOF. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or a CBP-1 capillary column (i. d. 0.5 mm x 25 m). TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F$_{254}$. Silica gel (Wakosil C-200) was used for column chromatography. Microwave irradiation was conducted with Initiator^{+} (Biotage), and the reaction temperature was measured by an internal probe. Unless otherwise noted, materials obtained from commercial suppliers were used as received. DMF was dried on a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.) prior to use. The starting *N*-picolinoylbenzylamines **1** were prepared from the corresponding primary amines and picolinoyl chloride.[5b] The deuterium-labeled **1j-*d*$_{15}$** was synthesized according to the following procedure.

Preparation of 1j-*d*$_{15}$. *n*BuLi (1.55 M in hexanes, 20 mL, 32 mmol) was added at –78 °C to a solution of bromobenzene-d_5 (3.2 mL, 30 mmol) in THF (50 mL), and the solution was stirred for 30 min. Diethyl carbonate (1.2 mL, 10 mmol) was added dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for an additional 3 h. The solution was then quenched with water and extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/EtOAc (20/1, v/v) afforded tris(pentadeuteriophenyl)methanol (2.5 g, 90% yield) as a white solid.

The obtained perdeuteriotriphenylmethanol was placed in a two-necked reaction flask with a reflux condenser, and the flask was flushed with nitrogen. Dry toluene (6.0 mL) was sequentially injected via a syringe. The mixture was heated to 80 °C. Acetyl chloride (640 μL, 9.0 mmol) was added with a dropping funnel while stirring vigorously with a magnetic stirrer. Once the solid had dissolved, additional acetyl chloride (960 μL, 14 mmol) was added over 10 min. The solution was heated for an additional 30 min. After concentration under reduced pressure, choloro{tris(pentadeuteriophenyl)}methane was obtained, which was used for the next step without further purifications.

The residual solid was placed in a two-necked reaction flask, and the flask was flushed with nitrogen. CH_2Cl_2 (14 mL) and ammonia solution (25% in water, 15 mL) were sequentially injected via a syringe. The resulting solution was stirred for 2 days vigorously at room temperature. The solution was then extracted with CH_2Cl_2 and washed two times with water. The organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with CH_2Cl_2 afforded tris(pentadeuteriophenyl)methylamine (2.2 g, 89% yield) as a white solid.

The obtained perdeuteriotriphenylmethylamine (2.2 g, 8.1 mmol), pyridine-2-carbonyl chloride hydrochloride (1.4 g, 8.1 mmol), and *N*,*N*-dimethyl-4-aminopyridine (DMAP; 290 mg, 2.4 mmol) were placed in a 50 mL two-necked reaction flask, and the flask was flushed with nitrogen. Anhydrous CH_2Cl_2 (16 mL) and Et_3N (3.3 mL, 24 mmol) were added at 0 °C, and the resulting solution was stirred at room temperature for 4 h. The mixture was quenched with water (30 mL) and extracted three times with CH_2Cl_2. Combined organic phase was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/EtOAc (3/1, v/v) afforded *N*-{tris(pentadeuteriophenyl)methyl}picolinamide (**1j-d_{15}**; 2.8 g, 7.4 mmol, >99% D) in 91% yield.

Copper/Manganese-promoted oxidative rearrangement of *N*-picolinoylbenzylamines 1 to 4*H*-3,1-benzoxazines 2. The reaction of **1a** is representative (Table 1, entry 12). $Cu(OTf)_2$ (29 mg, 0.080 mmol), *N*-(1-(*o*-tolyl)ethyl)picolinamide (**1a**; 24 mg, 0.10 mmol), pivalic acid (5.1 mg, 0.050 mmol), and MnO_2 (35 mg, 0.40 mmol) were placed in a microwave vessel, and the vessel was flushed with nitrogen. DMF (0.60 mL) was sequentially injected via a syringe. The mixture was irradiated under microwave reactor conditions at 180 °C for 1 h. The resulting mixture was then quenched with water, and a small amount of ethylenediamine was added to dissolve the residual copper salts in the aqueous phase. The mixture was extracted with EtOAc three times, and the combined organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/EtOAc (1/2, v/v) afforded 4,5-dimethyl-2-(pyridin-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**2a**; 16 mg, 0.068 mmol) in 68% yield.

Hydrolysis of 4*H*-3,1-benzoxazines 2. The reaction of **2a** is representative (Scheme 3, top). 4,5-Dimethyl-2-(pyridin-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**2a**; 29 mg, 0.12 mmol), EtOH (3 mL), and 6 M aqueous NaOH (1 mL) were placed in a 50 mL recovery flask equipped with a reflux condenser, and the flask was flushed with nitrogen. The resulting solution was stirred at 100 °C for 4 h. The resulting mixture was diluted with water and extracted three times with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/EtOAc (3/1, v/v) afforded 1-(2-amino-6-methylphenyl)ethan-1-ol (**3a**; 15 mg, 0.097 mmol) in 81% yield.

Characterization Data for Products

4,5-Dimethyl-2-(pyridin-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**2a**) colorless liquid; 16 mg (68%); IR (neat, cm^{-1}) 1242, 1435, 1467, 1581, 1618; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, J = 6.6 Hz, 3H), 2.27 (s, 3H), 5.77 (q, J = 6.6 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.21-7.29 (m, 2H), 7.40 (ddd, J = 1.2, 4.8, 7.6 Hz, 1H), 7.81 (dt, J = 1.8, 7.8 Hz, 1H), 8.25 (td, J = 1.0, 7.8 Hz, 1H), 8.78 (ddd, J = 1.0, 1.8, 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 17.4, 21.0, 71.4, 123.5, 123.6, 125.3, 125.8, 128.3, 129.2, 132.1, 136.6, 138.1, 149.8, 150.8, 154.6; HRMS (APCI) *m/z* ([M+H]$^{+}$) calcd for $C_{15}H_{15}N_2O$: 239.1179, found: 239.1180.

4-Methyl-2-(pyridin-2-yl)-5-(*p*-tolyl)-4*H*-benzo[*d*][1,3]oxazine (**2b**) colorless liquid; 18 mg (57%); IR (neat, cm^{-1}) 1240, 1355, 1438, 1467, 1514, 1570, 1624; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 7.0 Hz, 3H), 2.42 (s, 3H), 5.78 (q, J = 7.0 Hz, 1H), 7.11 (dd, J = 1.3, 7.6 Hz, 1H), 7.21-7.26 (m, 4H), 7.33-7.45 (m, 3H), 7.81 (dt, J = 1.7, 7.6 Hz, 1H), 8.22 (td, J = 1.0, 8.0 Hz, 1H), 8.78 (ddd, J = 1.0, 1.7, 4.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.2, 21.7, 71.6, 123.5, 124.9, 125.1, 125.4, 128.3, 128.8, 129.0, 129.2, 136.3, 136.6, 137.2, 138.3, 138.5, 149.8, 150.7, 154.9; HRMS (APCI) *m/z* ([M+H]$^{+}$) calcd for $C_{21}H_{19}N_2O$: 315.1492, found: 315.1489.

4-Methyl-2-(pyridin-2-yl)-5-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazine (**2c**) white solid; mp 57.3-58.2 ^{o}C; 18 mg (62%); IR (neat, cm^{-1}) 1271, 1323, 1421, 1587, 1618; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (d, J = 6.3 Hz, 3H), 6.00 (q, J = 6.3 Hz, 1H), 7.44-7.46 (m, 2H), 7.54 (d, J = 7.4 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.85 (dt, J = 1.7, 7.8 Hz, 1H), 8.24 (td, J = 1.0, 8.0 Hz, 1H), 8.81 (ddd, J = 1.0, 1.7, 4.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.2, 70.8 (q, J = 2.3 Hz), 123.7, 123.9 (q, J = 273.7 Hz), 124.4 (q, J = 5.6 Hz), 125.1 (q, J = 31.4 Hz), 125.77 (q, J = 1.5 Hz), 125.82, 128.7, 129.4, 136.8, 139.9, 150.0, 150.1, 155.9; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -59.0; HRMS (APCI) *m/z* ([M+H]$^{+}$) calcd for $C_{15}H_{12}F_3N_2O$: 293.0896, found: 293.0902.

7-Bromo-4,5-dimethyl-2-(pyridin-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**2d**) colorless liquid; 15 mg (46%); IR (neat, cm^{-1}) 1263, 1309, 1359, 1436, 1465, 1566, 1585, 1620; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, J = 6.7 Hz, 3H), 2.25 (s, 3H), 5.73 (q, J = 6.7 Hz, 1H), 7.21-7.22 (m, 1H), 7.40-7.44 (m, 2H), 7.82 (dt, J = 1.8, 7.8 Hz, 1H), 8.25 (td, J = 0.9, 7.8 Hz, 1H), 8.78 (ddd, J = 0.9, 1.8, 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 17.2, 20.9, 71.3, 121.5, 123.7, 124.7, 125.6, 126.4, 131.6, 134.0, 136.7, 139.7, 149.8, 150.4, 155.6; HRMS (APCI) *m/z* ([M+H]$^{+}$) calcd for $C_{15}H_{14}BrN_2O$: 317.0284, found: 317.0286.

4,4-Dimethyl-2-(pyridin-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**2h**) colorless liquid; 10 mg (43%); IR (neat, cm^{-1}) 1271, 1334, 1365, 1471, 1481, 1566, 1598, 1620; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (s, 6H), 7.16 (dd, J = 1.4, 7.5 Hz, 1H), 7.23 (dt, J = 1.4, 7.5 Hz, 1H), 7.31 (dt, J = 1.4, 7.5 Hz, 1H), 7.39 (ddd, J = 1.1, 4.8, 7.5 Hz, 1H), 7.44 (dd, J = 1.2, 7.8 Hz, 1H), 7.81 (dt, J = 1.7, 7.7 Hz, 1H), 8.20 (td, J = 1.0, 8.0 Hz, 1H), 8.81 (ddd, J = 1.0, 1.7, 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 28.6, 79.1, 122.3, 123.4, 125.2, 125.9, 127.3, 128.6, 131.4, 136.6, 138.2, 149.9, 150.9, 155.4; HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{15}H_{15}N_2O$: 239.1179, found: 239.1181.

4,4,5-Trimethyl-2-(pyridin-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**2i**) colorless liquid; 6.6 mg (26%); IR (neat, cm^{-1}) 1240, 1273, 1334, 1429, 1465, 1566, 1633, 1691; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 6H), 2.43 (s, 3H), 7.03 (dd, J = 0.6, 7.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.33 (dd, J = 0.8, 7.6 Hz, 1H), 7.39 (ddd, J = 1.2, 4.8, 7.6 Hz, 1H), 7.81 (dt, J = 1.7, 7.6 Hz, 1H), 8.18 (td, J = 1.0, 7.9 Hz, 1H), 8.81 (ddd, J = 1.0, 1.7, 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 22.5, 28.6, 80.4, 123.3, 124.9, 125.2, 128.1, 129.5, 131.2, 132.4, 136.6, 139.1, 149.9, 150.8, 154.7; HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{16}H_{17}N_2O$: 253.1335, found: 253.1337.

4,4-Diphenyl-2-(pyridin-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**2j**) white solid; mp 212.0-213.9 °C; 25 mg (68%); IR (neat, cm^{-1}) 1271, 1327, 1421, 1570, 1618; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (dd, J = 1.3, 7.7 Hz, 1H), 7.19 (dt, J = 1.3, 7.7 Hz, 1H), 7.25-7.31 (m, 10H), 7.34-7.41 (m, 2H), 7.56 (dd, J = 1.1, 7.9 Hz, 1H), 7.77 (dt, J = 1.7, 7.7 Hz, 1H), 8.22 (td, J = 0.9, 7.9 Hz, 1H), 8.78 (ddd, J = 0.9, 1.7, 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 86.7, 123.6, 125.4, 125.8, 126.8, 126.9, 128.0, 128.3, 128.4, 128.9, 129.3, 136.7, 139.5, 142.6, 150.1, 150.4, 155.5; HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{25}H_{19}N_2O$: 363.1492, found: 363.1493.

4-Phenyl-2-(pyridin-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**2k**) colorless liquid; 10 mg (36%); IR (neat, cm^{-1})1263, 1431, 1450, 1521, 1685; ^1H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.87 (d, J = 7.4 Hz, 1H), 7.19 (dt, J = 1.1, 7.4 Hz, 1H), 7.33-7.42 (m, 7H), 7.51 (d, J = 8.0 Hz, 1H), 7.77 (dt, J = 1.7, 7.7 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.78 (d, J =4.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 78.8, 123.6, 125.2, 125.3, 125.4, 125.8, 127.3, 127.8, 128.8, 128.9, 129.2, 136.7, 138.8, 139.8, 150.0, 150.3, 155.3; HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{19}H_{15}N_2O$: 287.1179, found: 287.1181.

5-Methyl-2-(pyridin-2-yl)-4-(*o*-tolyl)-4*H*-benzo[*d*][1,3]oxazine (**2l**) white solid; mp 186.6-187.9 °C; 23 mg (73%); IR (neat, cm^{-1}) 1263, 1350, 1465, 1558, 1579, 1616; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.76 (s, 3H), 6.73 (d, J = 7.5 Hz, 1H), 6.84 (s, 1H), 6.99 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.17 (dt, J = 1.1, 7.5 Hz, 1H), 7.24-7.34 (m, 3H), 7.46 (d, J = 7.9 Hz, 1H), 7.69 (dt, J = 1.8, 7.9 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 8.71 (d, J = 4.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 17.7, 19.4, 72.9, 122.7, 123.2, 123.8, 125.1, 126.4, 128.4, 128.9, 129.0, 129.2, 130.8, 133.6, 136.1, 136.5, 137.1, 139.5, 149.9, 150.5, 154.4; HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{21}H_{19}N_2O$: 315.1492, found: 315.1493. The single crystal suitable for X-ray analysis was grown from hexane/CH_2Cl_2.

6-Methyl-2-(pyridin-2-yl)-4-(*m*-tolyl)-4*H*-benzo[*d*][1,3]oxazine (**2m**) colorless liquid; 12 mg (38%); IR (neat, cm^{-1}) 1267, 1435, 1492, 1583, 1598, 1625; ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.25 (s, 3H), 6.38 (s, 1H), 6.58 (s, 1H), 7.07-7.20 (m, 5H), 7.28 (ddd, J = 1.1, 4.7, 7.6 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.68 (dt, J = 1.7, 7.6 Hz, 1H), 8.04 (td, J = 1.0, 8.0 Hz, 1H), 8.69 (ddd, J = 1.0, 1.7, 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 21.3, 21.5, 79.0, 123.4, 125.0, 125.2, 125.7, 125.8, 128.5, 128.61, 128.62, 129.7, 129.8, 136.4, 136.6, 137.3, 138.5, 140.0, 149.9, 150.5, 154.7; HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{21}H_{19}N_2O$: 315.1492, found: 315.1490.

7-(*tert*-Butyl)-4-(4-(*tert*-butyl)phenyl)-2-(pyridin-2-yl)-4*H*-benzo[*d*][1,3]oxazine (**2o**) colorless liquid; 11 mg (28%) on a 0.10 mmol scale; IR (neat, cm^{-1}) 1265, 1363, 1419, 1467, 1571, 1610, 1651, 1680; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.34 (s, 9H), 6.50 (s, 1H), 6.80 (d, J = 7.7 Hz, 1H), 7.21 (dd, J = 2.0, 8.0 Hz, 1H), 7.32-7.38 (m, 5H), 7.57 (d, J = 2.0 Hz, 1H), 7.76 (dt, J = 2.0, 7.8 Hz, 1H), 8.13 (td, J = 0.9, 7.8 Hz, 1H), 8.78 (ddd, J = 0.9, 1.7, 4.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 31.28, 31.30, 34.6, 34.7, 78.7, 122.4, 123.2, 123.5, 124.2, 124.8, 125.3, 125.6, 127.5, 136.6, 137.1, 138.4, 150.0, 150.5, 151.8, 152.4, 155.3; HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{27}H_{31}N_2O$: 399.2431, found: 399.2433.

4-(Naphthalen-2-yl)-2-(pyridin-2-yl)-4*H*-naphtho[2,3-*d*][1,3]oxazine (**2q**) colorless liquid; 14 mg (37%); IR (neat, cm^{-1}) 1265, 1410, 1440, 1616, 1654, 1685; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 7.31 (s, 1H), 7.36-7.41 (m, 2H), 7.45-7.52 (m, 3H), 7.61 (dd, J = 1.7, 8.4 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.78 (dt, J = 1.7, 7.7 Hz, 1H), 7.81-7.90 (m, 5H), 8.00 (s, 1H), 8.21 (td, J = 1.0, 8.0 Hz, 1H), 8.80 (ddd, J = 1.0, 1.7, 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 79.4, 123.65, 123.68, 124.9, 125.41, 125.43, 125.6, 126.0, 126.5, 126.6, 126.7, 127.6, 127.7, 127.8, 128.2, 128.3, 129.0, 132.6, 133.0, 133.5, 134.2, 136.66, 136.68, 136.9, 150.0, 150.4, 155.6; HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{27}H_{19}N_2O$: 387.1492, found: 387.1489.

(2-Amino-6-methylphenyl)(*o*-tolyl)methanol (**3l**) white solid; mp 116.6-118.3 °C; 16 mg (72%); IR (neat, cm^{-1}) 1265, 1357, 1458, 1602, 1710; ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.45 (s, 3H), 6.25 (s, 1H), 6.59-6.62 (m, 2H), 7.03 (t, J = 7.7 Hz, 1H), 7.10 (dt, J = 2.4, 6.8 Hz, 1H), 7.11-7.25 (m, 3H): $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 19.6, 20.0, 71.1, 116.3, 121.2, 124.5, 126.0, 127.0, 128.0, 128.4, 131.0, 136.7, 137.3, 138.5, 145.9; HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{15}H_{18}NO$: 228.1383, found: 228.1379. The single crystal suitable for X-ray analysis was grown from hexane/CH_2Cl_2.

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