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Merging the Ring Opening of Benzoxazoles with Secondary Amines and Iron-catalyzed Oxidative Cyclization toward the Environmentally Friendly Synthesis of 2-Aminobenzoxazoles

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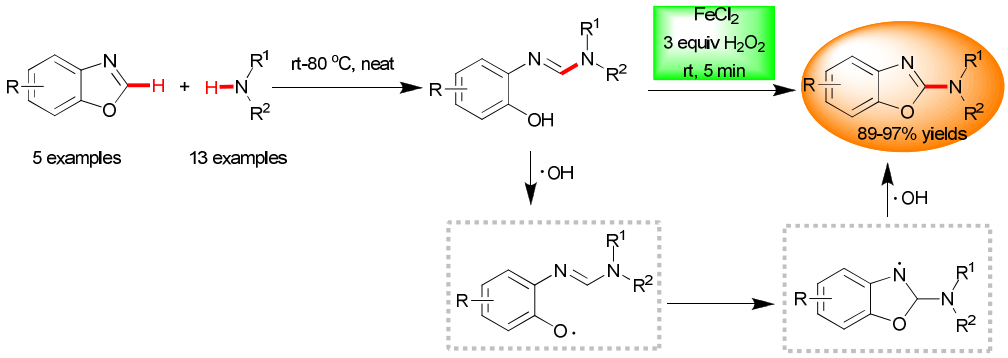

An environmentally friendly method was developed through iron-catalyzed oxidative cyclization with H_2O_2 as oxidant toward the synthesis of 2-aminobenzoxazoles.

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Merging the Ring Opening of Benzoxazoles with Secondary Amines and Iron-catalyzed Oxidative Cyclization toward the Environmentally Friendly Synthesis of 2-Aminobenzoxazoles

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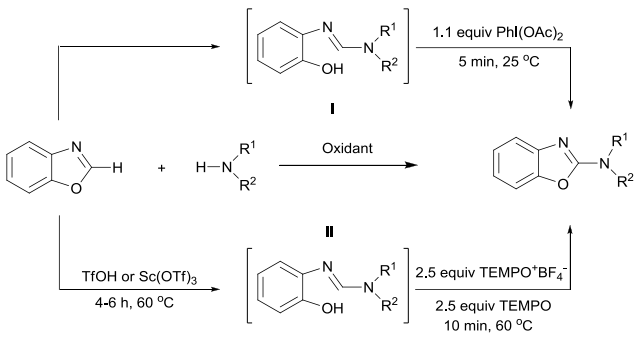
A facile and environmentally friendly method was developed through merging the ring opening of benzoxazoles with secondary amines and iron-catalyzed oxidative cyclization toward the synthesis of 2-aminobenzoxazoles. In the oxidative cyclization step, with catalytic amounts of $FeCl_2$, aqueous H_2O_2 as a green oxidant, highly desirable 2-aminobenzoxazoles were isolated in excellent yields of up to 97%. A plausible radical process is proposed for the oxidative cyclization on the basis of mechanistic studies.

Introduction

Oxazoles are extremely important structural motifs that feature prominently in pharmaceuticals, organic materials.[1] Among them, 2-aminobenzoxazoles have received much attention because of their high activity as partial antagonists for 5-HT receptors (5-HT = 5-hydroxy-tryptamine, seretonine) which are promising targets for the treatment of Alzheimer's disease and schizophrenia.[2] As a result, significant recent effort has focused on the development of new synthetic procedures for the generation of these compounds. Recently, transition-metal-catalyzed direct amination of oxazoles through C-H bond activation has been described.[3] Compared to the traditional selective C-N bond formation reaction that employed prefunctionalized building blocks, this method is quite beneficial. Various metal-based protocols, including copper, silver, manganese, iron, cobalt, nickel and other catalysts have been established.[4-6] However, the disadvantages associated with these methods are the utility of poisonous metals or expensive transition-metal catalysts. In some cases, reaction temperature greater than 100 ^oC and/or stoichiometric strong acids or bases are necessary.[6a,6d,6h] Recently, Chang and co-worker developed an alternative metal-free system for the amination of azoles with amines through a unique ring-opening and subsequent ring-closing strategy (Scheme 1, **I**).[7] Studer and co-worker also reported the amination of benzoxazoles and 1,3,4-oxadiazoles using 2,2,6,6-tetramethylpiperidine-*N*-oxoammonium tetrafluoroborate ($TEMPO^+BF_4^-$) as an organic oxidant (Scheme 1, **II**).[8] Both metal-free methods are very impressing, which provide the efficient and metal-free route to 2-aminooxazoles under very mild conditions.[9] However, both strategies needed the presence of rather expensive oxidants, iodobenzene diacetate or $TEMPO^+BF_4^-$, respectively. The development of catalytic oxidation reactions employing environmentally benign and inexpensive oxidants, are important trends in modern organic synthesis.[10] Hydrogen peroxide is probably the best terminal oxidant after dioxygen with respect to the above considerations, since water is the only side product.[11] As a result, oxidative cyclization of amidines using hydrogen peroxide in conjunction with catalytic amounts of cheap, relatively nontoxic metals are potentially viable for large-scale production of 2-aminooxazoles. Herein, we report an efficient method toward the synthesis of 2-aminobenzoxazoles, merging the ring opening of benzoxazoles with secondary amines and iron-catalyzed oxidative cyclization with H_2O_2 as a green oxidant.



Scheme 1. Indirect method for the amination of benzoxazoles.

Results and discussion

Optimization of the reaction conditions for oxidative cyclization towards the synthesis of 2-Aminobenzoxazole

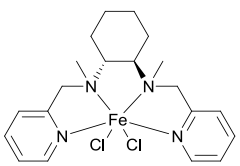


Fig. 1 *trans*-mcp-$FeCl_2$

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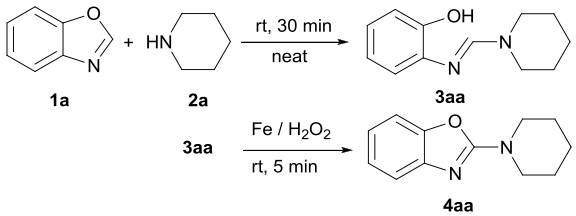
In line with our recent efforts on the non-heme iron or manganese complexes for oxidation reaction,[12] we wondered whether the non-heme iron catalysts could promote the oxidative cyclization of resulting amidines from the ring-opening of benzoxazoles with secondary amines.[7,8] Our initial investigations were started by testing the possibility with *trans*-mcp-$FeCl_2$ (Fig. 1, mcp = *N*,*N'*-dimethyl-*N*,*N'*-bis(2-pyridylmethyl)-cyclohexane-1,2-diamine) complex as catalyst in the presence of H_2O_2 as an oxidant, benzoxazole **1a** as the model substrate (Table 1). According to the procedure reported by Chang, the ring-opening amidine adduct (**3aa**) was obtained in high yield with piperidine.[7] To our delight, the further oxidative cyclization of the resulting amidine proceeded uneventfully within 5 min at room temperature to form 2-amino-benzoxazole (**4aa**) in 92% yield, employing 4.0 equiv of H_2O_2 as oxidant (Table 1, entry 1). Encouraged by the preliminary result, we subsequently investigated the activities of various iron sources such as $FeCl_3$, $FeCl_2$ and $Fe(OTf)_2$ (OTf = triflate). All employed iron salts furnished the desired product in very good yields in 10 mol % catalyst loadings (entries 2-4). Notably, further optimization of the amount of catalyst and oxidant demonstrated that the oxidative cyclization reaction could carry out in excellent yield in the presence of 2.0 mol % $FeCl_2$ and 3.0 equiv of H_2O_2 (entry 7). A screen of solvents revealed MeCN was the optimal choice for the reaction (entries 7-10). Interestingly, the present protocol can be efficiently carried out on a gram-scale synthesis and still 82% yield could be obtained under the optimized conditions (entry 11).

Table 1 Optimization of the oxidative cyclization reaction conditions.[a]



1a 2a 3aa 4aa

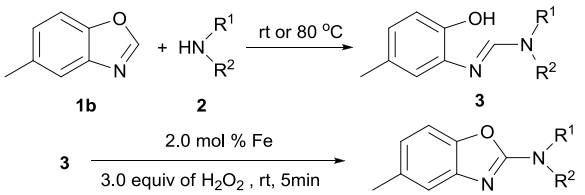
Entry	solvent	Cat. (X mol %)	H_2O_2 (equiv)	Yield of **4aa**(%)[b]
1	CH_3CN	*trans*-mcp-$FeCl_2$ (2)	4.0	92
2	CH_3CN	$FeCl_3$•$6H_2O$ (10)	4.0	90
3	CH_3CN	$Fe(OTf)_2$ (10)	4.0	93
4	CH_3CN	$FeCl_2$ (10)	4.0	94
5	CH_3CN	$FeCl_2$ (10)	3.0	94
6	CH_3CN	$FeCl_2$ (5)	3.0	94
7	CH_3CN	$FeCl_2$ (2)	3.0	95
8	CH_2Cl_2	$FeCl_2$ (2)	3.0	50
9	THF	$FeCl_2$ (2)	3.0	72
10	Dioxane	$FeCl_2$ (2)	3.0	75
11[c]	CH_3CN	$FeCl_2$ (2)	3.0	82

[a] Oxidative cyclization step: **3aa** (0.5 mmol) in MeCN (1.0 mL), 3.0 or 4.0 equiv of H_2O_2 (50 %) in 0.5 mL of MeCN was added dropwise in 1 min, and an additional 4 min of stirring was allowed at rt. [b] Isolated yield. [c] The gram scale of **3aa** (1 g, 4.9 mmol) was used as the substrate.

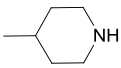
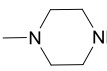
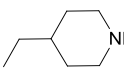
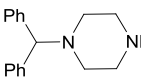
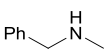
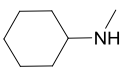
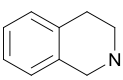
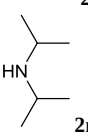
Synthesis of 2-Aminobenzoxazoles through iron-catalyzed oxidative cyclization protocol

We next applied this room temperature iron-catalyzed oxidative cyclization protocol to a variety of different secondary amine with 4-methylbenzoxazole **1b** as a reaction partner. As shown in Table 2, the secondary amine reagents generally afforded excellent yields under these conditions. In the case of piperidine derivatives containing methyl group in the different site, the

Table 2 Oxidative C–H amination of benzoxazoles with various amines.[a]



1b 2 3

Entry	Amine **2**	yield of **4**[b]
1	 **2a**	95(**4ba**)
2	 **2b**	97(**4bb**)
3	 **2c**	94(**4bc**)
4	 **2d**	95(**4bd**)
5	 **2e**	94(**4be**)
6	 **2f**	90(**4bf**)
7	 **2g**	89(**4bg**)
8[c]	 **2h**	93(**4bh**)
9[c]	 **2i**	92(**4bi**)
10[c]	 **2j**	92(**4bj**)
11	 **2k**	94(**4bk**)
12[d]	 **2l**	86(**4ab**)
13[e]	 **2m**	89(**4ac**)

[a] Ring opening step was conducted in neat according to Chang's procedure.[7] Oxidative cyclization step: **3** (0.5 mmol) and $FeCl_2$ (2.0 mol %) in MeCN (1.0 mL), 3.0 equiv of H_2O_2 (50 %) in 0.5 mL of MeCN was added dropwise in 1 min, and an additional 4 min of stirring was allowed at rt. [b] Isolated yield. [c] Ring opening step: **2h**, **2i,** or **2j** (0.5 mmol) and **1b** (0.5 mmol) in MeCN (1.0 mL), (**2h**, at rt for 2 hours; **2i**, at 80 °C for 2 hours; **2j**, at 80 °C for 10 hours). [d] Ring opening step was conducted according to Studer's method[8]: benzoxazole **1a** (0.5 mmol), **2l** (0.75 mmol) and 5.0 mol% of $Sc(OTf)_3$ under Ar atmosphere at 80 °C for 2 hours in MeCN (1.0 mL), 82% isolated yield of amidine. [e] Ring opening step: benzoxazole **1a** (0.5 mmol), **2m** (1.0 mmol) under Ar atmosphere at 80 °C for 12 hours in MeCN (1.0 mL), 87% isolated yield of amidine.

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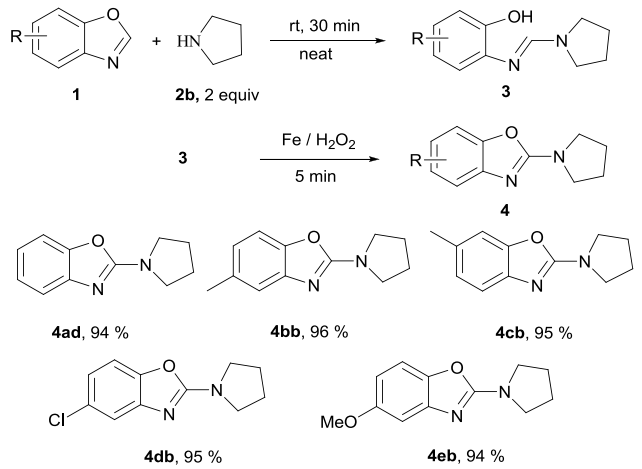
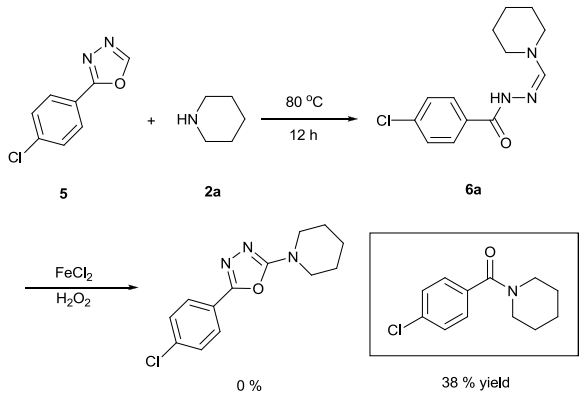
(entries 4 and 5). The reaction of piperazine derivatives bearing sterically hindered groups such as 1-benzhydrylpiperazine (**2h**) underwent the oxidative cyclization reaction smoothly to generate **4bh** in 93% isolated yield (entry 8). Several acyclic amines were also evaluated (**2j**, **2k**). In both cases, excellent yields were observed although the ring-opening step needed higher reaction temperatures (entries 10 and 11).[7] In addition, the liner aliphatic amines were also transformed into the desired 2-aminobenzoxazoles in good yields (entries 12 and 13). Notably, the Fe-catalyzed oxidative cyclization is quite efficient for the adduct of the diethylamine and benzoxazole, the desired product was obtained in 86% yield.[8] In contrast to benzoxazole, the ring-opening reaction didn't take place between benzothiazole and amine.[7]

With this catalytic system in hand, we also explored the scope of benzoxazole derivatives. The representative examples are shown in Scheme 2. In all employed benzoxazoles, the ring-opening amidine adducts were obtained in nearly quantitative yields (99 % yields). The resulting 2-aminobenzoxazoles were isolated in excellent yields via iron-catalyzed oxidative cyclization reaction.



Scheme 2 Substrate scope of benzoxazoles. (The total isolated yields for ring-opening and oxidative cyclization steps.)

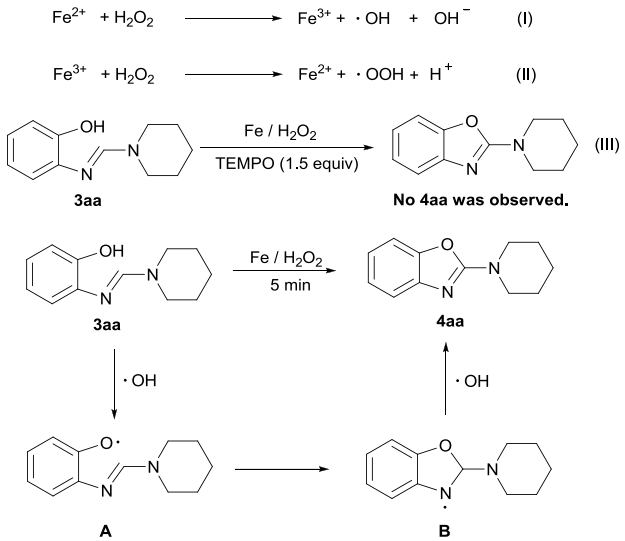


Scheme 3 2-Amination of arylated 1,3,4-oxadiazole.

Subsequently, the scope of heterocycles was expanded to test the generality of this synthetic protocol. 1,3,4-oxadiazoles were selected as substrates to proceed the ring-opening and oxidative cyclization reaction. Although the ring-opening step underwent smoothly, the Fe-catalyzed oxidative cyclization didn't occur to furnish the desired products. An amide was observed in 38% yield (Scheme 3).

Mechanism study

After exploration of a satisfying substrate scope, we turned our attention to elucidate the mechanism. To our knowledge, the mixture of Fe^{2+} and H_2O_2 is the typical Fenton's reagent, which can generate a very powerful oxidizing agent such as hydroxyl radical ($^{\bullet}OH$) (Scheme 4, Eq. I). According to this accepted mechanism, the chain reactions may either propagate through the production of superoxide radical ($^{\bullet}OOH$) (Scheme 4, Eq. II).[13] On the basis of the nature of Fenton process, the present oxidation cyclization of amidine may undergo a radical initiation pathway. Indeed, we found that this cyclization was completely inhibited by the addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), which was a traditional radical scavenger (Scheme 4, Eq. III). Based on these experiments and previous studies about Fenton process, the mechanism of this transformation is proposed as shown in Scheme 3. Intermediate **A** is initially generated via single-electron transfer (SET) from amidine **3aa** and hydroxyl radical. Then the cyclization of radical **A** will take place to give the radical **B**. Subsequently, the desired product is formed through another SET process.[8,14]



Scheme 4 Proposed mechanism for the oxidative cyclization of amidines.

Conclusions

In summary, we have developed a facile and environmentally friendly method for the amination of benzoxazoles with secondary amines, merging the ring opening of benzoxazoles with secondary amines and iron-catalyzed oxidative cyclization with H_2O_2 as a green oxidant. The mild reaction conditions, lower amounts of cheap and nontoxic $FeCl_2$ as catalyst, and H_2O_2 as oxidant make this indirectly amination protocol highly practical

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for future applications. A plausible radical process is proposed for the oxidative cyclization of amidines on the basis of mechanistic studies.

Experimental section

General remarks

NMR spectra were obtained on a Bruker Avance III 400 MHz spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in $CDCl_3$. The chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. High resolution mass spectra (HRMS) were recorded by Bruker micrOTOFQ-II (ESI). GC-MS was recorded by an Agilent 7890A/5975C using an HP/5MS column. Column chromatography was generally performed on silica gel (200-300 mesh) and TLC inspections were on silica gel GF_{254} plates.

$FeCl_2$, all amines and benzoxazole were purchased from Aldrich or Alfa Aeser and used as received. Other substituted benzoxazoles were obtained according to the reported procedures.[6-8] The synthesis of *trans*-mcp-$FeCl_2$ was according to the reported procedures.[12b,15]

Compound 1b

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.57 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 148.2, 140.2, 134.4, 126.7, 120.41, 110.2, 21.4. GC-MS calcd for C_8H_7NO: 133.1, found: 133.1

Compound 1c

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.38 (s, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 150.2, 137.8, 136.0, 125.8, 119.8, 111.0, 21.7. GC-MS calcd for C_8H_7NO: 133.1, found: 133.1

Compound 1d

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.46-7.39 (m, 1H), 7.34-7.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 148.5, 141.1, 130.1, 126.0, 126.05, 120.6, 111.7. GC-MS calcd for C_7H_4ClNO: 153.0, found: 153.0

Compound 1e

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.27 (s, 1H), 6.99 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 152.2, 143.6, 139.8, 113.5, 110.0, 102.1, 54.9. GC-MS calcd for $C_8H_7NO_2$: 149.0, found: 149.1

General procedure for indirect amination of benzoxazoles

Ring opening step was conducted in neat according to Chang's procedure.[7] To a 10 mL reaction tube, benzoxazole (0.5 mmol) and amine **2** (1 mmol, 2 equiv) were added. And the reaction mixture was stirred in neat condition for the specified temperature and time in air. After the reaction detected by TLC was completed, the excessive amine was evaporated by oil pump to obtain **3**. Oxidative cyclization step: $FeCl_2$ (1.3 mg, 2 mol%) in 1 mL of CH_3CN was directly added into **3**. And 3 equiv H_2O_2 in 0.5 mL CH_3CN was added dropwise into the above mixture in 1 min and another 4 min was allowed at room temperature in air. When the reaction was completed, the crude mixture was extracted with dichloromethane. Then the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the desired product was obtained by column chromatography using appropriate eluent.

Compound 4aa[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 10.3, 4.6 Hz, 1H), 7.28-7.21 (m, 1H), 7.15 (dd, *J* = 15.7, 8.0 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 3.66 (s, 4H), 1.68 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 148.7, 143.3, 123.9, 120.3, 116.0, 108.6, 46.6, 25.3, 24.1. HRMS (ESI) calcd. for $C_{12}H_{14}N_2O$ [M+1]: 203.1179, found: 203.1170.

Compound 4ba[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.79 (dd, *J* = 8.0, 0.8 Hz, 1H), 3.64 (s, 4H), 2.38 (s, 2H), 1.67 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 146.8, 143.4, 133.4, 120.9, 116.4, 107.9, 46.6, 25.2, 24.1, 21.5. HRMS (ESI) calcd for $C_{13}H_{16}N_2O$ $[M+H]^+$: 217.1335, found: 217.1331.

Compound 4bb[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.79 (dd, *J* = 8.1, 0.9 Hz, 1H), 3.69-3.57 (m, 1H), 2.38 (s, 1H), 2.07-1.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 147.1, 143.6, 133.5, 120.7, 116.4, 107.9, 47.4, 25.6, 21.5. HRMS (ESI) calcd for $C_{12}H_{14}N_2O$ $[M+H]^+$: 203.1179, found: 203.1173.

Compound 4bc[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 3.87-3.76 (m, 4H), 3.76-3.62 (m, 4H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 153.2, 146.8, 133.9, 121.8, 116.8, 108.3, 66.2, 45.8, 21.5. HRMS (ESI) calcd for $C_{12}H_{14}N_2O_2$ $[M+H]^+$: 219.1128, found: 219.1124.

Compound 4bd[6j]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.26 (s, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 2H), 2.25 (s, 3H), 1.72 (d, *J* = 13.8 Hz, 2H), 1.66-1.57 (m, 1H), 1.28-1.11 (m, 3H), 0.99 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 147.8, 137.0, 128.9, 123.7, 116.3, 112.8, 58.4, 31.3, 21.7, 20.9, 18.5. HRMS (ESI) calcd for $C_{14}H_{18}N_2O$ $[M+H]^+$: 231.1492, found: 231.1496.

Compound 4be

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 4.24-4.07 (m, 2H), 3.01 (td, *J* = 12.5, 2.8 Hz, 1H), 2.75-2.60 (m, 1H), 2.38 (s, 3H), 1.91-1.81 (m, 1H), 1.75 (m, 2H), 1.67-1.50 (m, 1H), 1.20-1.06 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 146.8, 143.5, 133.5, 120.9, 116.4, 107.9, 53.0, 46.0, 32.7, 30.6, 24.8, 21.6, 18.9. HRMS (ESI) calcd for $C_{14}H_{18}N_2O$ $[M+H]^+$: 231.1492, found: 231.1487.

Compound 4bf[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 3.77-3.64 (m, 4H), 2.58-2.46 (m, 4H), 2.39 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 146.9, 143.2, 133.6, 121.5, 116.7, 108.1, 54.3, 46.3, 45.5, 21.5. HRMS (ESI) calcd for $C_{13}H_{17}N_3O$ $[M+H]^+$: 232.1444, found: 232.1440.

Compound 4bg

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.8 Hz, 1H), 7.25 (s, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 3.78-3.70 (m, 4H), 2.60-2.55 (m, 4H), 2.49 (q, *J* = 7.2 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 148.8, 143.1, 123.9, 120.7, 116.3, 108.7, 52.4, 52.0, 45.5, 11.9. HRMS (ESI) calcd for $C_{14}H_{19}N_3O$ $[M+H]^+$: 246.1601, found: 246.1605.

Compound 4bh[9b]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 4H), 7.30 (t, *J*

= 7.5 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 7.14-7.06 (m, 2H), 6.80 (d, *J* = 7.4 Hz, 1H), 4.28 (s, 1H), 3.71-3.67 (m, 4H), 2.52-2.48 (m, 4H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 146.9, 143.6, 142.2, 133.6, 128.7, 127.9, 127.2, 121.2, 116.7, 108.0, 76.0, 51.2, 45.8, 21.5. HRMS (ESI) calcd for $C_{25}H_{25}N_3O$ $[M+H]^+$: 384.2070, found: 384.2066.

Compound 4bi[9b]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.08 (m, 5H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.75-6.73 (m, 1H), 4.76 (s, 2H), 3.86 (t, *J* = 5.9 Hz, 2H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 145.9, 142.2, 133.0, 132.6, 131.4, 127.7, 125.7, 125.5, 125.3, 120.2, 115.6, 107.1, 46.1, 42.0, 27.4, 20.5. HRMS (ESI) calcd for $C_{17}H_{16}N_2O$ $[M+H]^+$: 265.1335, found: 265.1332.

Compound 4bj[6j]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.24 (m, 5H), 7.18 (s, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.75 (s, 2H), 3.11 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 147.2, 143.6, 136.5, 133.6, 128.7, 127.7, 127.7, 121.0, 116.6, 108.1, 53.8, 35.2, 21.6. HRMS (ESI) calcd for $C_{16}H_{16}N_2O$ $[M+H]^+$: 253.1335, found: 253.1331.

Compound 4bk[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.66 (dd, *J* = 8.1, 0.4 Hz, 1H), 4.04-3.97 (m, 1H), 2.92 (s, 3H), 2.27 (s, 3H), 1.75-1.70 (m, 4H), 1.58 (d, *J* = 13.1 Hz, 1H), 1.43-1.26 (m, 4H), 1.07-0.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 146.8, 143.7, 133.3, 120.5, 116.2, 107.8, 56.6, 29.9, 29.4, 25.6, 25.4, 21.5. HRMS (ESI) calcd for $C_{15}H_{20}N_2O$ $[M+H]^+$: 245.1648, found: 245.4645.

Compound 4ab[8]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.3 Hz, 1H), 7.28 – 7.18 (m, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.02 – 6.91 (m, 1H), 3.58 (q, *J* = 7.1 Hz, 4H), 1.28 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 148.8, 143.6, 123.7, 119.9, 115.8, 108.4, 42.9, 13.4. GC-MS (EI):190.1

Compound 4ac[6f]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 6.4 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 4.24 (dt, *J* = 13.4, 6.7 Hz, 2H), 1.38 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 148.4, 123.7, 119.8, 115.5, 108.4, 58.4, 20.8. GC-MS (EI): 218.1.

Compound 4ad[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 12.1, 4.8 Hz, 1H), 7.28-7.21 (m, 1H), 7.19-7.08 (m, 1H), 7.04-6.86 (m, 1H), 3.79-3.51 (m, 4H), 2.11-1.93 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 149.0, 143.6, 123.8, 120.0, 115.9, 108.5, 47.41, 25.6. HRMS (ESI) calcd for $C_{11}H_{12}N_2O$ $[M+H]^+$: 189.1022, found: 189.1025.

Compound 4cb[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 7.9 Hz, 1H), 7.07 (s, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 3.63 (s, 4H), 2.39 (s, 3H), 2.02 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 149.2, 141.1, 129.9, 124.4, 115.3, 109.1, 47.3, 25.6, 21.4. HRMS (ESI) calcd for $C_{12}H_{14}N_2O$ $[M+H]^+$: 203.1179, found: 203.1175.

Compound 4db[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 1.9 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.96-6.91 (m, 1H), 3.67-3.63 (m, 4H), 2.06-1.97 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 147.6, 144.9, 129.1, 119.8, 116.0, 109.0, 47.4, 25.5. HRMS (ESI) calcd for $C_{11}H_{11}ClN_2O$ $[M+H]^+$: 223.0633, found: 223.0630.

Compound 4eb[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.55 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.80 (s, 3H), 3.67-3.55 (m, 4H), 2.02 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 156.9, 144.4, 143.5, 108.4, 106.4, 101.2, 55.8, 47.4, 25.5. HRMS (ESI) calcd for $C_{12}H_{14}N_2O_2$ $[M+H]^+$: 219.1128, found: 219.1125.

N-(4-Chlorobenzoyl)piperidine [16]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 4H), 3.71 (d, *J* = 4.1 Hz, 2H), 3.33 (s, 2H), 1.73 – 1.57 (m, 4H), 1.53 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 134.4, 133.8, 127.6, 127.3, 47.7, 42.2, 28.6, 24.5, 23.5.

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Notes and references

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