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Note

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General 5-Halomethyl Isoxazolines Synthesis Enabled by Copper-Catalyzed Oxyhalogenation of Alkenes

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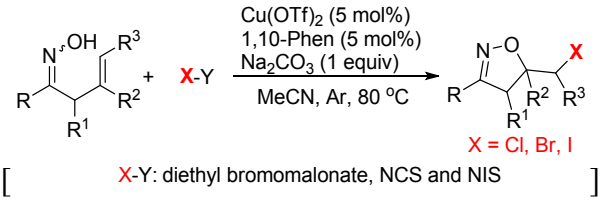
Supporting Information Placeholder



ABSTRACT: A general and efficient oxyhalogenation of unsaturated ketoximes has been achieved through copper catalysis with diethyl bromomalonate, NCS and NIS, yielding 5-chloromethyl, 5-bromomethyl as well as 5-iodomethyl isoxazolines in good to excellent yields.

5-Halomethyl isoxazolines represent a versatile building block for the rapid construction of valuable heterocycles and bioactive molecules. For instance, they can be transformed into isoxazole[1] and pyrrolidin-3-ol[2] via dehydrohalogenation and reduction, respectively. Furthermore, fused cyclopropyl-3-amino-2,4-oxazine BACE inhibitor can be synthesized with chloromethyl 3-(5-bromo-2-fluorophenyl) isoxazoline through multistep ring opening and cyclization sequences (Figure 1).[3] Conventional methods to synthesize 5-halomethyl isoxazolines use the 1,3-dipolar cycloaddition of nitrile oxides with allyl halide (Scheme 1a). However, the protocol suffers from moderate yields of the products.[3,4] Alternatively, oxyhalogenation of allylic oximes allows for efficient access to this valuable functionality (Scheme 1b).[2,5] Despite robust investigation, these methods are generally limited by the utilization of stoichiometric oxidants and a large excess of halides and the low halide atom economy. Thus, a general and cheap catalytic platform for oxyhalogenation of allylic oximes remains highly desired.

Recent progress toward the oxyfunctionalization of allylic Oximes[6] has employed copper catalysis as a versatile tool for radical rocesses. Han[7] and Wang[8], who through copper catalyzed single-electron-transfer (SET) processes have generated iminoxyl radical from allylic oximes and developed oxyalkynylation, oxyamination and oxytrifluoromethylthiolation with ethynylbenziodoxolone (EBX), amines and $AgSCF_3$, respectively. Liang[9], Liu[10] and Hu[11] have identified an array of Cu catalyzed protocols for oxytrifluoromethylation of allylic oximes. In these reactions, the role of copper catalysts was the generation of active CF_3-containing intermediates. Wang and co-workers have applied copper catalyzed atom transfer process to generate azido radicals from $TMSN_3$ and developed oxyazidation based on radical cross coupling.[12] Recently, we questioned whether 5-halomethyl isoxazolines synthesis might be accomplished in a general sense via copper catalysis with readily available halide source. Herein, we describe our work towards this goal, which has led to the development of a powerful platform for catalytic construction of chloromethyl, bromomethyl as well as iodomethyl isoxazolines (Schem 1c).

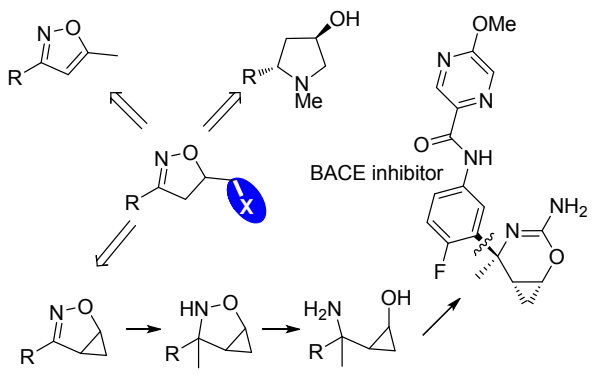
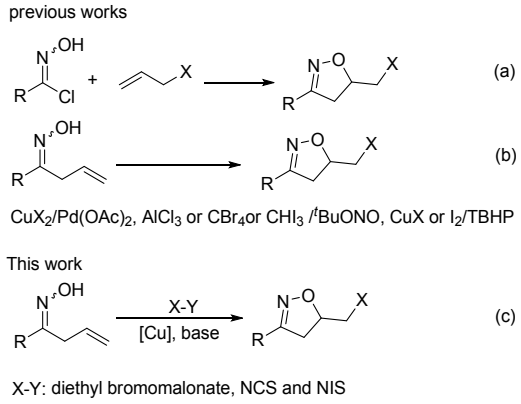
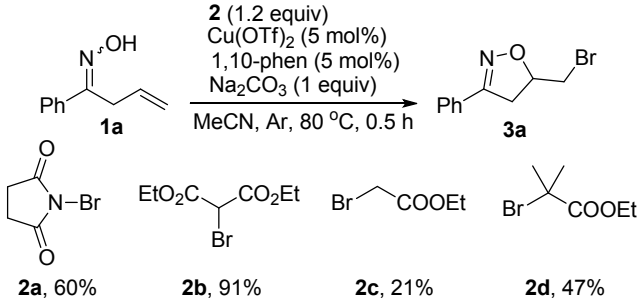


Figure 1. Transformation of 5-halomethyl isoxazolines.



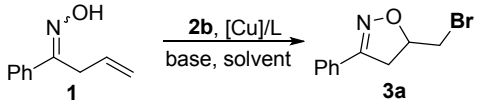
Scheme 1. Synthesis of 5-halomethyl isoxazolines.

We began our investigations into the proposed copper-catalyzed oxyhalogenation of allylic oximes by evaluating different Br source (Scheme 2). Upon stiring allylic oxime **1a** with N-Bromosuccinimide (NBS) in the presence of $Cu(OTf)_2$, 1,10-phenanthroline (1,10-phen), and Na_2CO_3, we observed 60% HPLC yield of the desired isoxazoline **3a**. Inspired by Leonori's work on iminobromogenation of olefins,[13] diethyl bromomalonate **2b** was then employed as bromo source. To our delight, 91% HPLC yield of the desired isoxazoline **3a** was obtained. Other commercially available α-bromoesters, such as ethyl bromoacetate **2c** and ethyl 2-bromoisobutyrate **2d** were less effective. We next explored the sensitivity of these reactions to various changes in the standard conditions. Other Cu salts were moderately successful (Table 1, entries 2−4), while other ligands uniformly less effective than 1,10-phen (Table 1, entries 5−7). Similarly, a number of bases were also effective in these reactions, but the reaction yields diminished with Cs_2CO_3 (Table 1, entries 8−11). Also, the reaction is moderately successful in THF and EtOH (Table 1,entry 12 and 14), but considerably less so in other solvents (Table 1, entries 14- 17). Control reactions of **1a** lacking $Cu(OTf)_2$ and 1, 10-phen were uniformly less effective (Table 1, entries 18−19), while lacking Na_2CO_3 was unsuccessful (Table 1, entry 20). Notably, 20 mol% of Na_2CO_3 could provide the desired isoxazoline **3a** in 86% HPLC yield (Table 1, entry 21).



Scheme 2. oxybromination of **1a** with various Br source. [a] HPLC yields using toluene as an internal standard are reported for reactions at 0.2 mmol scale.

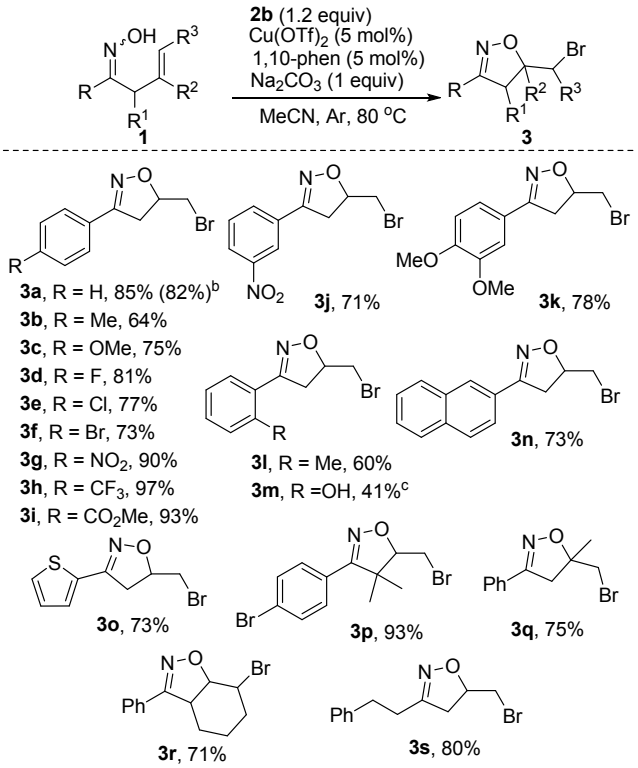
Table 1. Optimization of the reaction conditions [a]



Entry	Cu	Ligand	base	Sol.	Yield/% [b]
1	$Cu(OTf)_2$	1,10-phen	Na_2CO_3	MeCN	91(85)[c]
2	$Cu(OAc)_2$	1,10-phen	Na_2CO_3	MeCN	89
3	$CuCl_2$	1,10-phen	Na_2CO_3	MeCN	76
4	CuI	1,10-phen	Na_2CO_3	MeCN	88
5	$Cu(OTf)_2$	bpy	Na_2CO_3	MeCN	55
6	$Cu(OTf)_2$	TMEDA	Na_2CO_3	MeCN	68
7	$Cu(OTf)_2$	PPh_3	Na_2CO_3	MeCN	26
8	$Cu(OTf)_2$	1,10-phen	K_3PO_4	MeCN	78
9	$Cu(OTf)_2$	1,10-phen	Cs_2CO_3	MeCN	28
10	$Cu(OTf)_2$	1,10-phen	K_2CO_3	MeCN	82
11	$Cu(OTf)_2$	1,10-phen	$NaHCO_3$	MeCN	76
12	$Cu(OTf)_2$	1,10-phen	Na_2CO_3	THF	80
13	$Cu(OTf)_2$	1,10-phen	Na_2CO_3	H_2O	54
14	$Cu(OTf)_2$	1,10-phen	Na_2CO_3	EtOH	72
15	$Cu(OTf)_2$	1,10-phen	Na_2CO_3	DMA	40
16	$Cu(OTf)_2$	1,10-phen	Na_2CO_3	DCE	17
17	$Cu(OTf)_2$	1,10-phen	Na_2CO_3	PhMe	53
18	-	1,10-phen	Na_2CO_3	MeCN	31
19	$Cu(OTf)_2$	-	Na_2CO_3	MeCN	20
20	$Cu(OTf)_2$	1,10-phen	-	MeCN	0
21 [d]	$Cu(OTf)_2$	1,10-phen	Na_2CO_3	MeCN	86

[a] Reaction conditions: **1a** (0.2 mmol), **2b** (0.24 mmol), copper catalyst (0.01 mmol), base (0.2 mmol), solvent (1 mL), 80 °C, 0.5 h, under argon. [b] HPLC yields using toluene as an internal standard. [c] isolated yield. [d] 20 mol% of Na_2CO_3 used.

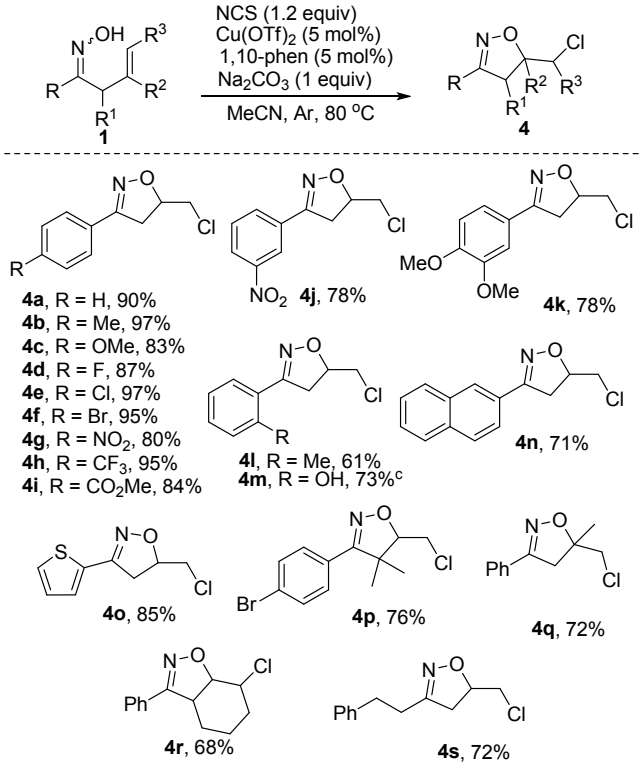
With optimal oxybromination conditions in hand, we probed the generality of this process with respect to the allylic oximes. As shown in Scheme 2, a diverse array of aromatic oximes with a variety of functional groups (methyl, methoxyl, fluoro, chloro, bromo, nitro, triflurormethyl and ester groups) performed well using this protocol (compounds **3a**–**3l**, 60–97% yield). Notably, we found that phenolic oxime could be bromooxygenated, though with modest reaction efficiency (**3m**, 41%). Moreover, naphthyl oxime was found to be a competent substrate in this transformation (**3n**, 73% yield). Furthermore, thiophenyl oxime could be employed without loss in efficiency (**3o**, 85% yield). With respect to substituted allylic group, we have found that a range of oximes with substitution at the R1, R2 and R3 positions were effective substrates in this protocol (**3p–3r**, 71–93% yield). Perhaps most importantly, this transformation is not limited to aromatic oximes. For example, phenethyl can be readily incorporated in this copper cyclization (**3s**, 80% yield). Scalability of this reaction was demonstrated through the preparation of **3a** on 6.5 mmol scale.



Scheme 3. Scope of the oxybromination strategy. [a]Isolated yields are reported for reactions at 0.2 mmol scale for 0.5~2 h. [b]6.5 mmol scale, and product **3a** was obtained in 1.283 g. [c]2 equiv. of Na_2CO_3 used

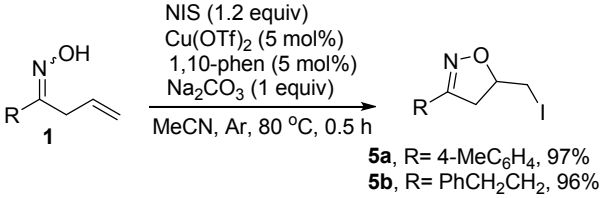
Inspired by the excellent results above, we next evaluated the ability of this copper catalysis to accommodate chlorooxygenation

of allylic oximes using N-chlorosuccinimide (NCS) as Cl source. As described in Scheme 4, with various oximes examined in the oxybromination reaction (scheme 3), the desired chloromethyl isoxazolines were successfully achieved in good to excellent yields under the optimal reaction conditions (**4a**-**4s**, 61-97%).



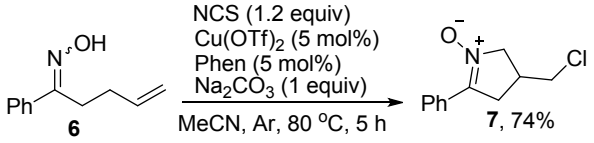
Scheme 4. Scope of the oxychrologenation strategy. [a]Isolated yields are reported for reactions at 0.2 mmol scale for 0.5~5 h. [c]2 equiv of Na_2CO_3 used

Although we recently developed the TBHP-induced iodocyclization of allylic oximes with I_2, the protocol is less effective for electron-rich aryl and aliphatic oximes.[5d] Therefore, we turned our attention to defining the capacity for copper catalyzed oxyiodo genation of allylic oximes in the presence of N-iodosuccinimide (NIS) (Scheme 5). To our delight, both methyl substituted aromatic (**5a**, 97%) and aliphatic (**5b**, 96%) isoxazolines were successfully achieved in excellent yields under the optimal reaction.



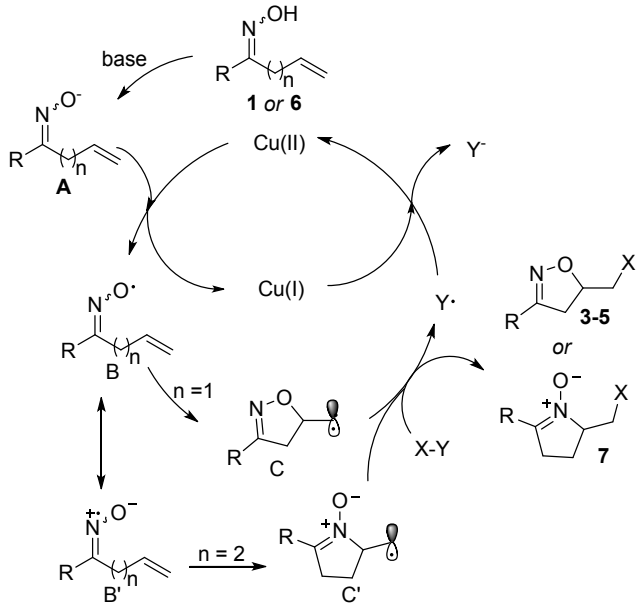
Scheme 5. oxyiodonalization of allylic oximes

As iminoxyl radical possesses an electronic structure with the single-electron spin density delocalized on both the O- and N-atom, iminoxyl radical-promoted cyclization of γ,δ-unsaturated ketoximes often affords nitrone products. [5c,7,14] To verify that this reaction experienced an iminoxyl radical involved process, γ,δ-unsaturated ketoxime **6** was subjected to the standard conditions with NCS. As expected, nitrones **7** was obtained in 74% yield (Scheme 6) .



Scheme 6. Control experiment

Based on these experiments and previous results, a plausible mechanism is proposed in Scheme 7. Cu(II) is SET reduced by the iminoxyl anion **A**, formed by deprotonation of substrates **1** or **6**, to generate the iminoxyl radical (resonance structures **B** and **B'**), along with Cu(I).[7,8] Then, iminoxyl radical **B (**or **B')** undergoes O- or N-atom 5-exo-trig radical cyclization relying on the length of carbon chain, delivering the radical intermediate **C** or **C'**. Subsequently, homolytic halide atom transfer with the polarized SOMOphile (X-Y) would furnish the targeted 5-halomethyl isoxazolines **3-5** or nitrone **7** as well as the electron-poor Y radicals.[13] Finally, single electron reduction of Y radicals by Cu(I) forms Y anion with the concomitant regeneration of Cu(II). Y anion can also act as a base to deprotonate the substrates **1** or **6**.



Scheme 7.Proposed mechanism

In conclusion, we have developed a highly efficient copper catalyzed oxyhalogenation of alkenes using readily available halide source, such as diethyl bromomalonate, NCS and NIS. This protocol serves as general and convenient approach for the rapid access of 5-halomethyl isoxazolines, which exhibited good substrate scope and function group compatibility. This transformation is predicated on a significant modification of the reported oxyhalogenation of allylic oximes as both stoichiometric amounts of oxidants and a large excess of halides are avoided.

EXPERIMENTAL SECTION

General method. Unless stated otherwise, all reactions were carried out under an argon atmosphere. All solvents were purified and dried according to standard methods prior to use. All commercial reagents were used without additional purification. Flash chromatography was carried out with silica gel (200-300 mesh). Melting points were determined without correction on a digital melting-point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz (or 600MHz) and 125 MHz (or 150

MHz) spectrometers in $CDCl_3$ using tetramethylsilane (TMS) as internal standard, respectively.[19]F NMR spectra were recorded at 400 MHz spectrometers. High-resolution mass spectra (HRMS) were recorded using ion trap (compounds **3-5** and **7**) and ICR (compound **1i**) with an positive-ion electrospray ionization (ESI^+) source, and ICR (compounds **1k** and **1m**) with an negative-ion electrospray ionization (ESI^-) source.

Synthesis of starting oximes 1. Oximes **1** were synthesized according to the reported procedures.[15] The starting substrates **1a-d, 1g-h**, **1n-o**, **1q**,[15a] **1e**, **1j**,[15b] **1f**,[15c] **1l**, **1r**,[15d] **1p**,[15e] **1s**[15f] are known compounds, and their NMR data were identical with those in the literature.

*methyl 4-(1-(hydroxyimino)but-3-en-1-yl)benzoate **(1i)***. The reaction of methyl 4-formylbenzoate (1.64 g, 10 mmol) give **1i** as white soild (1.50 g, 68%), mp 72-73 ℃, R_f = 0.22, (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.06 – 8.03 (m, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 5.98 – 5.85 (m, 1H), 5.22 – 5.09 (m, 2H), 3.93 (s, 3H), 3.60 (d, *J* = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 166.8, 156.2, 139.9, 131.7, 130.6, 129.8, 126.3, 117.4, 52.3, 30.8. HRMS (ESI) m/z calcd for $C_{12}H_{15}NO_3$ $[M+H]^+$: 222.1125, found 222.1128.

*1-(3,4-dimethoxyphenyl)but-3-en-1-one oxime **(1k)***. The reaction of 3,4-dimethoxybenzaldehyde (1.66 g, 10mmol) give **1k** as colorless oil (1.22 g, 55%), R_f =0.17 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.26 (d, *J* = 4.1 Hz, 1H), 7.19 – 7.12 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 5.99 – 5.86 (m, 1H), 5.20 – 5.07 (m, 2H), 3.89 (d, *J* = 1.2 Hz, 7H), 3.57 (d, *J* = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 156.5, 150.2, 148.9, 132.5, 128.3, 119.5, 117.0, 110.7, 108.9, 55.9, 55.8, 30.9. HRMS (ESI) m/z calcd for $C_{12}H_{13}NO_3$ $[M-H]^-$: 218.0812, found 218.0835.

*1-(o-hydroxybenzene)but-3-en-1-one oxime **(1m)***. The reaction of 2-hydroxybenzaldehyde (1.22 g，20 mmol) give **1m** as white soild (0.90 g， 51%), mp 75-76 ℃, R_f = 0.36, (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.95 – 11.42 (m, 1H), 8.56 – 8.08 (m, 1H), 7.48 – 7.40 (m, 1H), 7.30 – 7.22 (m, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.00 – 5.88 (m, 1H), 5.24 – 5.10 (m, 2H), 3.70 – 3.63 (m, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 160.3, 157.6, 131.5, 130.9, 127.9, 119.5, 117.7, 117.6, 117.4, 29.1. HRMS (ESI) m/z calcd for $C_{10}H_{11}NO_2$ $[M-H]^-$:176.0706, found 176.0720.

General procedure for the synthesis of isoxazolines.

The general procedure A. A flame dry 8 mL tube was charged with oximes **1** (0.2 mmol), diethyl bromomalonate (**2b)** (57.4 mg, 0.24 mmol), Na_2CO_3 (21.2 mg, 0.2 mmol), $Cu(OTf)_2$ (3.6 mg, 0.01mmol), 1,10-Phen (1.0mg, 0.01 mmol) in anhydrous MeCN (1 mL) under argon atmosphere. The resulting suspension was stirred for 0.5-2 h at 80℃(block heaters). The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the products **3**.

The general procedure B. A flame dry 8 mL tube was charged with oximes 1or 6 (0.2 mmol), NCS (32.0 mg, 0.24 mmol), Na_2CO_3 (21.2 mg, 0.2 mmol), $Cu(OTf)_2$ (3.6 mg, 0.01mmol), 1,10-Phen (1.0mg, 0.01 mmol) in anhydrous MeCN (1 mL) under argon atmosphere. The resulting suspension was stirred for 0.5-5 h at 80 ℃(block heaters). The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the products **4** or **7**.

The general procedure C. A flame dry 8 mL tube was charged with oximes 1 (0.2 mmol), NIS (53.9 mg, 0.24 mmol), Na_2CO_3 (21.2 mg, 0.2 mmol), $Cu(OTf)_2$ (3.6 mg, 0.01mmol), 1,10-Phen (1.0mg, 0.01 mmol) in anhydrous MeCN (1 mL) under argon atmosphere. The resulting suspension was stirred for 0.5 h at 80℃ (block heaters). The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the products **5**.

Gram scale reaction. A flame dry 25 mL schlenk flask was charged with **1a** (1.05g, 6.5 mmol), diethyl bromomalonate (1.86 g, 7.8 mmol), Na_2CO_3 (689.0 mg, 6.5 mmol), $Cu(OTf)_2$ (117.6 mg, 0.33mmol), 1,10-Phen (64.4 mg, 0.33 mmol) in anhydrous MeCN (15 mL) under argon atmosphere. The resulting suspension was stirred for 2 h at 80℃ (block heaters). The mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the products **3a** (1.283 g, 5.34 mmol).

*5-(Bromomethyl)-3-phenyl-4,5-dihydroisoxazole **(3a)**.*[5b] Compound **3a** was prepared following the general procedure A. The reaction of **1a** (32.2 mg, 0.2 mmol) give **3a** as white soild (41 mg, 85%); mp 59-61 ℃, R_f = 0.65 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 2H), 7.45 – 7.37 (m, 3H), 5.05 – 4.95 (m, 1H), 3.58 (dd, *J* =10.4, 4.3 Hz, 1H), 3.51 (dd, *J* = 17.0, 10.5 Hz, 1H), 3.41 (dd, *J* = 10.4, 8.3 Hz, 1H), 3.33 (dd, *J* = 17.0, 6.4 Hz, 1H).

*5-(Bromomethyl)-3-(p-tolyl)-4,5-dihydroisoxazole **(3b)**.*[1] Compound **3b** was prepared following the general procedure A. The reaction of **1b** (35.0 mg, 0.2 mmol) give **3b** as white soild (32.4 mg, 64%); mp 88-89 ℃, R_f = 0.67 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.04 – 4.93 (m, 1H), 3.57 (dd, *J* = 10.3, 4.3 Hz, 1H), 3.50 (dd, *J* = 17.0, 10.4 Hz, 1H), 3.40 (dd, *J* = 10.3, 8.4 Hz, 1H), 3.31 (dd, *J* = 17.0, 6.3 Hz, 1H), 2.38 (s, 3H).

*5-(Bromomethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole **(3c)**.*[5b] Compound **3c** was prepared following the general procedure A. The reaction of **1c** (38.3 mg, 0.2 mmol) give **3c** as white soild (40.6 mg, 75%); mp 77-78 ℃, R_f = 0.42 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.9, 2H), 6.92 (d, *J* = 8.9, 2H), 5.01 – 4.91 (m, 1H), 3.83 (s, 3H), 3.57 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.49 (dd, *J* = 16.9, 10.4 Hz, 1H), 3.39 (dd, *J* = 10.3, 8.4 Hz, 1H), 3.29 (dd, *J* = 16.9, 6.3 Hz, 1H).

*5-(Bromomethyl)-3-(4-fluorophenyl)-4,5-dihydroisoxazole **(3d)**.* Compound **3d** was prepared following the general procedure A. The reaction of **1d** (35.8 mg, 0.2 mmol) give **3d** as white soild (42 mg, 81%); mp 49-50 ℃, R_f = 0.65 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.15 – 7.06 (m, 2H), 5.05 – 4.95 (m, 1H), 3.58 (dd, *J* = 10.4, 4.2 Hz, 1H), 3.50 (dd, *J* = 17.0, 10.5 Hz, 1H), 3.41 (dd, J = 10.4, 8.2 Hz, 1H), 3.31 (dd, *J* = 17.0, 6.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9 (d, J = 250.0 Hz), 155.1, 128.8 (d, J = 8.5 Hz), 125.4 (d, J = 3.4 Hz), 116.0 (d, J = 22.5Hz), 79.84, 39.7, 33.1. ^{19}F NMR (400 MHz, $CDCl_3$) δ -109.4. HRMS (ESI) m/z calcd for $C_{10}H_{10}BrFNO$ $[M+H]^+$: 257.9924, found 257.9927.

*5-(Bromomethyl)-3-(4-chlorophenyl)-4,5-dihydroisoxazole **(3e)**.*[1] Compound 3e was prepared following the general procedure A. The reaction of 1e (39.1 mg, 0.2 mmol) give 3e as white soild (42.3 mg, 77%); mp 104-105℃, R_f = 0.58 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 8.6, 2H), 7.37 (d, *J* = 8.6, 2H), 5.05 – 4.97 (m, 1H), 3.57 (dd, *J* = 10.4, 4.2 Hz, 1H), 3.48 (dd, *J* = 17.0, 10.5 Hz, 1H), 3.41 (dd, *J* = 10.4, 8.1 Hz, 1H), 3.29 (dd, *J* = 17.0, 6.5 Hz, 1H).

*5-(Bromomethyl)-3-(4-bromophenyl)-4,5-dihydroisoxazole **(3f)**.*[5b] Compound **3f** was prepared following the general procedure A. The reaction of **1f** (48.0 mg, 0.2 mmol) give **3f** as white soild (48.1 mg, 73%); mp 109-110℃, R_f = 0.54 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 4H), 5.06 – 4.96 (m, 1H),

3.58 (dd, J = 10.4, 4.2 Hz, 1H), 3.53 -3.37 (m, 2H), 3.29 (dd, *J* = 17.0, 6.5 Hz, 1H).

*5-(Bromomethyl)-3-(4-nitrophenyl)-4,5-dihydroisoxazole (**3g**).*[5b] Compound **3g** was prepared following the general procedure A. The reaction of **1g** (41.2 mg, 0.2 mmol) give **3g** as yellow soild (51.5 mg, 90%); mp 159-160 ℃, R_f = 0.41 (petroleum ether/ethyl acetate 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 – 8.21 (m, 2H), 7.90 – 7.77 (m, 2H), 5.16 – 5.06 (m, 1H), 3.61 (dd, J = 10.6, 4.1 Hz, 1H), 3.55 (dd, J = 17.0, 10.7 Hz, 1H), 3.47 (dd, J = 10.6, 7.9 Hz, 1H), 3.36 (dd, J = 17.0, 6.7 Hz, 1H).

*5-(Bromomethyl)-3-(4-(trifluoromethyl)phenyl)-4,5-dihydroisoxazole (**3h**).* Compound **3h** was prepared following the general procedure A. The reaction of **1h** (45.8 mg, 0.2 mmol) give **3h** as white soild (59.8 mg, 97%); mp 68-69 ℃, R_f = 0.48 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 5.11 – 5.01 (m, 1H), 3.60 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.53 (dd, *J* = 17.0, 10.6 Hz, 1H), 3.45 (dd, *J* = 10.5, 7.9 Hz, 1H), 3.34 (dd, J = 17.0, 6.6 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.1, 132.5, 132.0(q, *J* = 32.4 Hz), 127.0, 125.7 (q, *J* = 3.8 Hz), 124.8, 122.7, 80.2, 39.3, 33.1. ^{19}F NMR (400 MHz, $CDCl_3$) δ -62.9. HRMS (ESI) m/z calcd for $C_{11}H_{10}F_3BrNO$ $[M+H]^+$: 307.9898, found 307.9894.

*Methyl4-(5-(Bromomethyl)-4,5-dihydroisoxazol-3-yl)benzoate (**3i**).*[16] Compound **3i** was prepared following the general procedure A. The reaction of **1i** (43.8 mg, 0.2 mmol) give **3i** as white soild (55.6 mg, 93%); mp 135-137℃, R_f = 0.40 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4, 2H), 7.72 (d, *J* = 8.5, 2H), 5.10 – 4.96 (m, 1H), 3.92 (s, 3H), 3.58 (dd, *J* = 10.4, 4.2 Hz, 1H), 3.52 (dd, *J* = 17.0, 10.6 Hz, 1H), 3.43 (dd, *J* = 10.4, 8.1 Hz, 1H), 3.33 (dd, *J* = 17.0, 6.6 Hz, 1H).

*5-(Bromomethyl)-3-(3-nitrophenyl)-4,5-dihydroisoxazole (**3j**).* Compound **3j** was prepared following the general procedure A. The reaction of **1j** (41.2 mg, 0.2 mmol) give **3j** as white soild (40.6 mg, 71%); mp 72-73 ℃, R_f = 0.48 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (t, *J* = 1.9 Hz, 1H), 8.29 – 8.24 (m, 1H), 8.12 – 8.02 (m, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 5.15 – 5.05 (m, 1H), 3.64 – 3.52 (m, 2H), 3.47 (dd, *J* = 10.6, 7.7 Hz, 1H), 3.38 (dd, *J* = 17.0, 6.7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.5, 148.5, 132.3, 130.9, 129.9, 124.8, 121.6, 80.4, 39.2, 33.0. HRMS (ESI) m/z calcd for $C_{10}H_{10}BrN_2O_3$ $[M+H]^+$: 284.9869, found 284.9868.

*5-(Bromomethyl)-3-(3,4-dimethoxyphenyl)-4,5-dihydroisoxazole (**3k**).* Compound **3k** was prepared following the general procedure A. The reaction of **1k** (44.2 mg, 0.2 mmol) give **3k** as white soild (47.1 mg, 78%); mp 92-93 ℃, R_f = 0.32 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.9 Hz, 1H), 7.04 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 5.02 – 4.93 (m, 1H), 3.90 (s, 6H), 3.57 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.49 (dd, *J* = 16.9, 10.4 Hz, 1H), 3.39 (dd, *J* = 10.3, 8.4 Hz, 1H), 3.30 (dd, *J* = 16.9, 6.3 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.8, 151.1, 149.3, 121.9, 120.5, 110.6, 108.8, 79.6, 56.0 (d, J = 3.8 Hz), 39.8, 33.2, 29.7. HRMS (ESI) m/z calcd for $C_{12}H_{15}BrNO_3$ $[M+H]^+$: 300.0229, found 300.0223.

*5-(Bromomethyl)-3-(o-tolyl)-4,5-dihydroisoxazole (**3l**).* Compound **3l** was prepared following the general procedure A. The reaction of **1l** (35.0 mg, 0.2 mmol) give **3l** as pale brown oil (30.4 mg, 60%); R_f = 0.57 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 4H), 5.00 – 4.91 (m, 1H), 3.63 – 3.52 (m, 2H), 3.47 – 3.33 (m, 2H), 2.56 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.9, 138.2, 131.7, 129.6, 128.9, 128.2, 1259, 78.6, 42.2, 33.3, 23.0. HRMS (ESI) m/z calcd for $C_{11}H_{13}BrNO$ $[M+H]^+$: 254.0175, found 254.0178.

*5-(Bromomethyl)-3-(o-hydroxybenzene)-4,5-dihydroisoxazole (**3m**).* Compound **3m** was prepared following the general procedure A with 0.4 mmol of Na_2CO_3 (42.4 mg). The reaction of **1m** (35.4 mg, 0.2 mmol) give **3m** as pale brown oil (21.0 mg, 41%); R_f = 0.48 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.39 – 7.30 (m, 1H), 7.21 (dd, J = 7.8, 1.6 Hz, 1H), 7.05 (dd, J = 8.3, 0.9 Hz, 1H), 6.99 – 6.88 (m, 1H), 5.03 – 4.94 (m, 1H), 3.66 – 3.54 (m, 2H), 3.48 – 3.38 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.1, 157.4, 132.1, 128.5, 119.7, 117.2, 113.5, 78.6, 39.8, 32.7. HRMS (ESI) m/z calcd for $C_{10}H_{11}BrNO_2$ $[M+H]^+$: 255.9977, found 255.9968.

*5-(Bromomethyl)-3-(naphthalen-2-yl)-4,5-dihydroisoxazole (**3n**).*[2] Compound **3n** was prepared following the general procedure A. The reaction of **1n** (42.2 mg, 0.2 mmol) give **3n** as white soild (42.8 mg, 73%); mp 87-88 ℃, R_f = 0.61 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.91 (s, 1H), 7.86 (dd, *J* = 8.3, 4.7 Hz, 3H), 7.57 – 7.50 (m, 2H), 5.10 – 5.02 (m, 1H), 3.68 – 3.58 (m, 2H), 3.50 – 3.41 (m, 2H).

*5-(Bromomethyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole (**3o**).*[1] Compound **3o** was prepared following the general procedure A. The reaction of **1o** (33.4 mg, 0.2 mmol) give **3o** as yellow oil (36.2 mg, 73%); R_f = 0.41 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.23 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.07 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.04 – 4.95 (m, 1H), 3.61 – 3.48 (m, 2H), 3.40 (dd, *J* = 10.4, 8.4 Hz, 1H), 3.34 (dd, *J* = 16.8, 6.4 Hz, 1H).

*5-(Bromomethyl)-3-(4-bromophenyl)-4,4-dimethyl-4,5-dihydroisoxazole (**3p**)* . Compound **3p** was prepared following the general procedure A. The reaction of **1p** (53.6 mg, 0.2 mmol) give **3p** as white soild (64.8 mg, 93%); mp 71-72 ℃, R_f = 0.62 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.50 – 7.46 (m, 2H), 4.48 (t, *J* = 6.7 Hz, 1H), 3.60 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.52 (dd, *J* = 10.8, 6.8 Hz, 1H), 1.48 (s, 3H), 1.32 (s, 3H). ^{13}C{^{1}H}C NMR (125 MHz, $CDCl_3$) δ 164.1, 132.0, 129.0, 127.8, 124.4, 89.5, 51.6, 27.5, 25.6, 18.9. HRMS (ESI) m/z calcd for $C_{12}H_{14}Br_2NO$ $[M+H]^+$: 345.9437, found 345.9442.

*5-(Bromomethyl)-5-methyl-3-phenyl-4,5-dihydroisoxazole (**3q**).*[1] Compound **3q** was prepared following the general procedure A. The reaction of **1q** (35.0 mg, 0.2 mmol) give **3q** as colorless oil (38 mg, 75%); R_f = 0.58 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.57 (m, 2H), 7.49 – 7.31 (m, 3H), 3.58 – 3.45 (m, 3H), 3.13 (d, *J* = 17.0 Hz, 1H), 1.66 (s, 3H).

*7-Bromo-3-phenyl-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazole (**3r**).* Compound **3r** was prepared following the general procedure A. The reaction of **1r** (40.2 mg, 0.2 mmol) give **3r** as white soild (39.9 mg, 71%); mp 109-111℃, R_f = 0.63 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 2H), 7.46 – 7.38 (m, 3H), 4.73 – 4.65 (m, 2H), 3.65 – 3.57 (m, 1H), 2.17 – 2.01 (m, 3H), 1.88 – 1.75 (m, 1H), 1.60 – 1.50 (m, 1H), 1.42 – 1.31 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 130.4, 128.9, 128.6, 127.1, 84.11, 47.1, 42.6, 29.7, 25.8, 18.0. HRMS (ESI) m/z calcd for $C_{13}H_{15}BrNO$ $[M+H]^+$: 280.0332, found 280.0331.

*5-(Bromomethyl)-3-phenethyl-4,5-dihydroisoxazole (**3s**).*[17] Compound **3s** was prepared following the general procedure A. The reaction of **1s** (37.8 mg, 0.2 mmol) give 3s as colorless oil (42.9 mg, 80%); R_f = 0.57 (petroleum ether/ethyl acetate 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 4.84 – 4.70 (m, 1H), 3.43 (dd, J = 10.3, 4.2 Hz, 1H), 3.22 (dd, J = 10.3, 8.3 Hz, 1H), 3.04 (dd, J = 17.4, 10.3 Hz, 1H), 2.97 – 2.87 (m, J = 8.0, 2.8 Hz, 2H), 2.84 (dd, J = 17.4, 6.1 Hz, 1H), 2.68 (dd, J = 14.8, 7.1 Hz, 2H).

*5-(Chloromethyl)-3-phenyl-4,5-dihydroisoxazole (**4a**).*[5c] Compound **4a** was prepared following the general procedure B. The reaction of **1a** (32.2 mg, 0.2 mmol) give **4a** as white soild (39.3 mg. 81%); mp 51-52 ℃, R_f = 0.37 (petroleum ether/ethyl acetate 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ7.68 – 7.66 (m, 2H), 7.43 – 7.40 (m, 3H), 5.02 – 4.69 (m, 1H), 3.71 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.58 (dd, *J* = 11.2, 7.4 Hz, 1H), 3.42 (dd, *J* = 17.0, 10.5 Hz, 1H),3.35 (dd, *J* = 17.0, 6.3 Hz, 1H).

*5-(Chloromethyl)-3-(p-tolyl)-4,5-dihydroisoxazole (**4b**).*[1] Compound **4b** was prepared following the general procedure B. The reaction of 1b (35.0 mg, 0.2 mmol) give **4b** as white soild (45.0 mg. 97%); mp 76-77 ℃, R_f = 0.33 (petroleum ether/ethyl acetate 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 4.92 – 4.86 (m, 1H), 3.49 (dd, *J* = 17.0, 10.3 Hz, 1H), 3.40 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.18 – 3.24 (m, 2H),2.38 (s, 3H).

*5-(Chloromethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**4c**).*[1] Compound **4c** was prepared following the general procedure B. The reaction of **1c** (38.2 mg, 0.2 mmol) give **4c** as white soild (36.9 mg. 83%); mp 72-74 ℃, R_f = 0.36 (petroleum ether/ethyl acetate 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.59 (d, *J* = 8.8 Hz, 2H), 6.92 – 6.90 (d, *J* = 8.8 Hz, 2H), 4,96 – 4.91 (m, 1H), 3.83 (s, 1H), 3.69 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.55 (dd, *J* = 11.2, 7.5 Hz, 1H), 3.36 (dd, *J* = 16.9, 10.5 Hz, 1H), 3.30 (dd, *J* = 16.9, 6.3 Hz, 1H).

*3-(4-fluorophenyl)-5-(Chloromethyl)-4,5-dihydroisoxazole (**4d**).*[1] Compound **4d** was prepared following the general procedure B. The reaction of **1d** (35.8 mg, 0.2 mmol) give **4d** as white soild (37.0 mg. 87%); mp 58-59 ℃, R_f = 0.30 (petroleum ether/ethyl acetate 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.66 (m, 1H), 7.07 – 7.14 (m, 1H), 4.96 – 5.01 (m, 1H), 3.71 (dd, *J* = 11.3, 4.2 Hz, 1H), 3.57 (dd, *J* = 11.3, 7.3 Hz, 1H), 3.47 (dd, *J* = 16.9, 10.5 Hz, 1H), 3.32 (dd, *J* = 16.9, 6.5 Hz, 1H).

*3-(4-chlorophenyl)-5-(Chloromethyl)-4,5-dihydroisoxazole (**4e**).*[1] Compound **4e** was prepared following the general procedure B. The reaction of **1e** (39.1 mg, 0.2 mmol) give **4e** as white soild (45.0 mg. 97%); mp 85-86 ℃, R_f = 0.32 (petroleum ether/ethyl acetate 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d. *J* =7.1 Hz, 2H), 7.37 (d, *J* = 7.1 Hz, 2H), 4.97 – 5.02 (m, 1H), 3.70 (dd, *J* = 9.5, 3.6 Hz, 1H), 3.58 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.46 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.30 (dd, *J* = 14.0, 5.4 Hz, 1H).

*3-(4-bromophenyl)-5-(Chloromethyl)-4,5-dihydroisoxazole (**4f**).*[1] Compound **4f** was prepared following the general procedure B. The reaction of **1f** (48.0 mg, 0.2 mmol) give **4f** as white soild (51.7 mg, 95%); mp 105-106 ℃, R_f = 0.30 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 4H), 3.30 (dd, *J* = 16.9, 6.5 Hz, 1H), 5.02 – 4.96 (m, 1H), 3.70 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.58 (dd, *J* = 11.3, 7.2 Hz, 1H), 3.46 (dd, *J* = 16.9, 10.5 Hz, 1H).

*5-(Chloromethyl)-3-(4-nitrophenyl)-4,5-dihydroisoxazole (**4g**).*[18] Compound **4g** was prepared following the general procedure B. The reaction of **1g** (41.2 mg, 0.2 mmol) give **4g** as white soild (38.0 mg, 80%); mp 154-155℃, R_f= 0.38 (petroleum ether/ethyl acetate 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 – 8.20 (m, 2H), 7.89 – 7.79 (m, 2H), 5.12 – 5.07 (m, *J* = 10.9, 6.8, 4.1 Hz, 1H), 3.75 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.65 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.53 (dd, *J* = 17.0, 10.7 Hz, 1H), 3.39 (dd, *J* = 17.0, 6.7 Hz, 1H).

*5-(Chloromethyl)-3-(4-(trifluoromethyl)phenyl)-4,5-dihydroisoxazole (**4h**).*[18] Compound 4h was prepared following the general procedure B. The reaction of **1h** (45.8 mg, 0.2 mmol) give **4h** as white soild (50.3 mg, 95%); mp 79-80 ℃, R_f = 0.36 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 5.06 (m, 1H), 3.74 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.62 (dd, *J* = 11.4, 7.2 Hz, 1H), 3.52 (dd, *J* = 17.0, 10.7 Hz, 1H), 3.37 (dd, *J* = 17.0, 6.6 Hz, 1H).

*methyl 4-(5-(Chloromethyl)-4,5-dihydroisoxazol-3-yl)benzoate (**4i**).* Compound **4i** was prepared following the general procedure B. The reaction of **1i** (43.8 mg, 0.2 mmol) give **4i** as white soild (42.5 mg, 84%); mp 124-126℃, R_f= 0.26 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.7 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 4.99 – 5.04 (m, 1H), 3.91 (s, 3H), 3.71 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.60 (dd, *J* = 11.3, 7.1 Hz, 1H), 3.50 (dd, *J* = 16.9, 10.6 Hz, 1H), 3.34 (dd, *J* = 16.9, 6.6 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.3, 155.5 , 133.1 , 131.4 , 129.9 , 126.6, 80.2 , 52.2 , 44.7 , 38.1 .HRMS (ESI) m/z calcd for $C_{12}H_{13}ClNO_3$ $[M+H]^+$: 254.0578, found 254.0577.

*5-(Chloromethyl)-3-(3-nitrophenyl)-4,5-dihydroisoxazole (**4j**).* Compound **4j** was prepared following the general procedure B. The reaction of **1j** (41.2 mg, 0.2 mmol) give **4j** as white soild (37.2 mg, 78%); mp 84-85℃, R_f= 0.29 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (t, *J* = 1.9 Hz, 1H), 8.26 (m, 1H), 8.11 – 8.00 (m, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 5.13 – 5.08 (m, 1H), 3.74 (dd, *J* = 11.5, 4.2 Hz, 1H), 3.65 (dd, *J* = 11.5, 6.8 Hz, 1H), 3.55 (dd, *J* = 17.0, 10.7 Hz, 1H), 3.40 (dd, *J* = 17.0, 6.7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) *δ* 154.5, 148.4, 132.2, 130.8, 129.8, 124.7, 121.5, 80.5, 44.8, 37.9. HRMS (ESI) m/z calcd for $C_{10}H_{10}ClN_2O_3$ $[M+H]^+$: 241.0375, found 241.0373.

*3-(3,4-dimethoxyphenyl)-5-(Chloromethyl)-4,5-dihydroisoxazole (**4k**).* Compound **4k** was prepared following the general procedure B. The reaction of **1k** (44.2 mg, 0.2 mmol) give **4k** as white soild (39.8 mg, 78%); mp 74-76 ℃, R_f = 0.21 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 1.9 Hz, 1H), 7.04 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 4.99 – 4.91 (m, 1H), 3.90 (s, 6H), 3.69 (dd, *J* = 11.2, 4.3 Hz, 1H), 3.55 (dd, *J* = 11.2, 7.5 Hz, 1H), 3.47 (dd, *J* = 16.8, 10.4 Hz, 1H), 3.30 (dd, *J* = 16.8, 6.3 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) *δ* 155.8, 151.0, 149.1, 121.7, 120.4, 110.5, 108.7, 79.6, 55.8 (d, J = 3.2 Hz), 44.8, 38.6, 29.6. HRMS (ESI) m/z calcd for $C_{12}H_{15}ClNO_3$ $[M+H]^+$: 256.0735, found 256.0739.

*5-(chloromethyl)-3-(o-tolyl)-4,5-dihydroisoxazole (**4l**).* Compound **4l** was prepared following the general procedure B. The reaction of **1l** (35.0 mg, 0.2 mmol) give **4l** as light yellow oil (25.4 mg, 61%); R_f= 0.28 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.33 – 7.23 (m, 3H), 4.96 – 4.91 (m, 1H), 3.61 – 3.53 (m, 2H), 3.72 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.39 (dd, *J* = 16.9, 6.2 Hz, 1H), 2.56 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.9, 138.1, 131.6, 129.6, 128.9, 128.1, 125.9, 78.7, 44.9, 41.1, 22.8. HRMS (ESI) m/z calcd for $C_{11}H_{13}ClNO$ $[M+H]^+$: 210.0680, found 210.0680.

*2-(5-(Chloromethyl)-4,5-dihydroisoxazol-3-yl)phenol (**4m**).* Compound **4m** was prepared following the general procedure B with 0.4 mmol of Na_2CO_3 (42.4 mg). The reaction of **1m** (35.4 mg, 0.2 mmol) give **4m** as white soild (30.6 mg, 73%); mp 67-68℃, R_f = 0.37 (petroleum ether/ethyl acetate 10:1);^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.38 – 7.30 (m, 1H), 7.21 (dd, J = 7.8, 1.6 Hz, 1H), 7.04 (dd, J = 8.3, 1.0 Hz, 1H), 6.94 (m, 1H), 5.01 – 4.96 (m, 1H), 3.73 (dd, J = 11.4, 4.4 Hz, 1H), 3.65 – 3.53 (m, 2H), 3.45 (dd, J = 16.9, 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.1, 157.3, 132.0, 128.4, 119.6, 117.1, 113.5, 78.6, 44.5, 38.7. HRMS (ESI) m/z calcd for $C_{10}H_{11}ClNO_2$ $[M+H]^+$: 212.0472, found 212.0474.

*5-(chloromethyl)-3-(naphthalen-2-yl)-4,5-dihydroisoxazole (**4n**).*[1] Compound **4n** was prepared following the general procedure B. The reaction of **1n** (42.2 mg, 0.2 mmol) give **4n** as white soild (34.9 mg, 71%); mp 78-79 ℃, R_f = 0.30 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.91 (s, 1H), 7.88 – 7.81 (m, 3H), 7.57 – 7.48 (m, 2H), 5.07 – 5.00 (m, 1H), 3.75 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.65 – 3.58 (m, 2H), 3.46 (dd, *J* = 16.8, 6.5 Hz, 1H).

*5-(chloromethyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole (**4o**).*[1] Compound **4o** was prepared following the general procedure B. The reaction of **1o** (33.4 mg, 0.2 mmol) give **4o** as light yellow oil (34.2 mg, 85%); R_f= 0.26 (petroleum ether/ethyl acetate 10:1);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.23 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.07 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.01 – 4.96 (m, 1H), 3.71 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.60 – 3.49 (m, 2H), 3.35 (dd, *J* = 16.8, 6.4 Hz, 1H).

*3-(4-bromophenyl)-5-(chloromethyl)-4,4-dimethyl-4,5-dihydroisoxazole (**4p**).* Compound **4p** was prepared following the general procedure B. The reaction of **1p** (53.6 mg, 0.2 mmol) give

4p as white soild (45.5 mg, 76%); mp 61-62 ℃, R_f = 0.30 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.52 (m, 2H), 7.51 – 7.47 (m, 2H), 4.42 (t, *J* = 6.5 Hz, 1H), 3.78 (dd, *J* = 11.6, 6.2 Hz, 1H), 3.71 (dd, *J* = 11.6, 6.8 Hz, 1H), 1.48 (s, 3H), 1.33 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 131.9, 128.9, 127.6, 89.5, 51.3, 40.6, 25.5, 18.9. HRMS (ESI) m/z calcd for $C_{12}H_{14}BrClNO$:$[M+H]^+$: 301.9941, found 301.9943.

*5-(chloromethyl)-5-methyl-3-phenyl-4,5-dihydroisoxazole (**4q**).*[1] Compound **4q** was prepared following the general procedure B. The reaction of **1q** (35.04 mg, 0.2 mmol) give **4q** as colorless oil (30.0 mg, 72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 2H), 7.43 – 7.27 (m, 3H), 3.61 (q, *J* = 11.2 Hz, 2H), 3.53 (d, *J* = 16.9 Hz, 1H), 3.16 – 3.05 (m, 1H), 1.62 (s, 3H).

*7-iodo-3-phenyl-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazole (**4r**).*[18] Compound **4r** was prepared following the general procedure B. The reaction of **1r** (40.2 mg, 0.2 mmol) give **4r** as white soild (31.9 mg, 68%); mp 89-90℃, R_f = 0.50 (petroleum ether/ethyl acetate 10:1);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.68 (m, 2H), 7.42 (dd, *J* = 5.1, 1.9 Hz, 3H), 4.59 – 4.53 (m, 2H), 3.61 – 3.56 (m, 1H), 2.13 – 1.93 (m, 3H), 1.86 – 1.72 (m, 1H), 1.56 – 1.46 (m, 1H), 1.42 – 1.31 (m, 1H).

*5-(chloromethyl)-3-phenethyl-4,5-dihydroisoxazole (**4s**).* Compound **4s** was prepared following the general procedure B. The reaction of **1s** (37.8 mg, 0.2 mmol) give **4s** as colorless oil (32.2 mg,72%); R_f = 0.50 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.23 (dd, *J* = 10.5, 4.5 Hz, 3H), 4.76 (m, 1H), 3.57 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.39 (dd, *J* = 11.2, 7.4 Hz, 1H), 3.03 (dd, *J* = 17.3, 10.4 Hz, 1H), 2.93 (td, *J* = 8.0, 2.9 Hz, 2H), 2.85 (dd, *J* = 17.3, 6.1 Hz, 1H), 2.69 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.8, 140.2, 128.5, 128.2, 126.4, 78.6, 44.7, 40.8, 32.5, 29.1. HRMS (ESI) m/z calcd for $C_{12}H_{15}ClNO$ $[M+H]^+$: 224.0836, found 224.0838.

*5-(iodomethyl)-3-(p-tolyl)-4,5-dihydroisoxazole (**5a**).*[19] Compound **5a** was prepared following the general procedure C. The reaction of **1b** (35.0 mg, 0.2 mmol) give **5a** as white soild (58.0 mg, 97%); mp 87-89℃, R_f = 0.43 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.94 – 4.88 (m, 1H), 3.50 (dd, *J* = 17.0, 10.3 Hz, 1H), 3.42 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.26 – 3.18 (m, 2H), 2.38 (s, 3H).

*5-(iodomethyl)-3-phenethyl-4,5-dihydroisoxazole (**5b**).* Compound **5b** was prepared following the general procedure C. The reaction of **1s** (37.8 mg, 0.2 mmol) give **5b** as white soild (60.4 mg, 96%); mp 54-55℃, R_f = 0.54 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.23 (dd, *J* = 10.6, 4.6 Hz, 3H), 4.69 (m, 1H), 3.27 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.07 – 2.99 (m, 2H), 2.93 (td, *J* = 8.0, 2.3 Hz, 2H), 2.74 (dd, *J* = 17.4, 6.2 Hz, 1H), 2.70 – 2.62 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.5, 140.2, 128.6, 128.2, 126.4, 79.2, 43.2, 32.5, 29.2, 7.8. HRMS (ESI) m/z calcd for $C_{12}H_{15}INO$ $[M+H]^+$: 316.0192, found 316.0193.

*3-(chloromethyl)-5-phenyl-3,4-dihydro-2H-pyrrole 1-oxide (**7**).* Compound **7** was prepared following the general procedure B. The reaction of **6** (35.0 mg, 0.2 mmol) give **7** as brown soild (30.9 mg, 74%); mp 90 – 91℃, R_f = 0.51 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 – 8.30 (m, 2H), 7.45 (dd, *J* = 5.3, 2.0 Hz, 3H), 4.54 (s, 1H), 4.38 (dd, *J* = 11.6, 4.3 Hz, 1H), 3.84 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.27 – 3.03 (m, 2H), 2.45 – 2.33 (m, 1H), 2.28 (ddd, *J* = 15.7, 11.7, 5.7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 139.4, 130.1, 128.3, 126.89, 74.1, 45.6, 28.4, 18.9. HRMS (ESI) m/z calcd for $C_{11}H_{13}ClNO$ $[M+H]^+$: 210.0683, found 210.0680.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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