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Oxidize Amines to Nitrile Oxides: One Type of Amine Oxidation and Its Application to Directly Construct Isoxazoles and Isoxazolines

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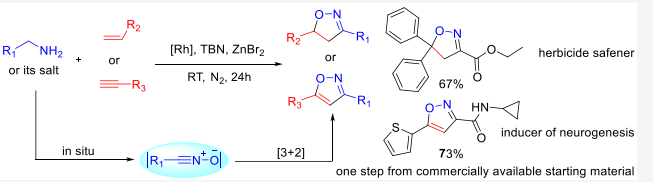
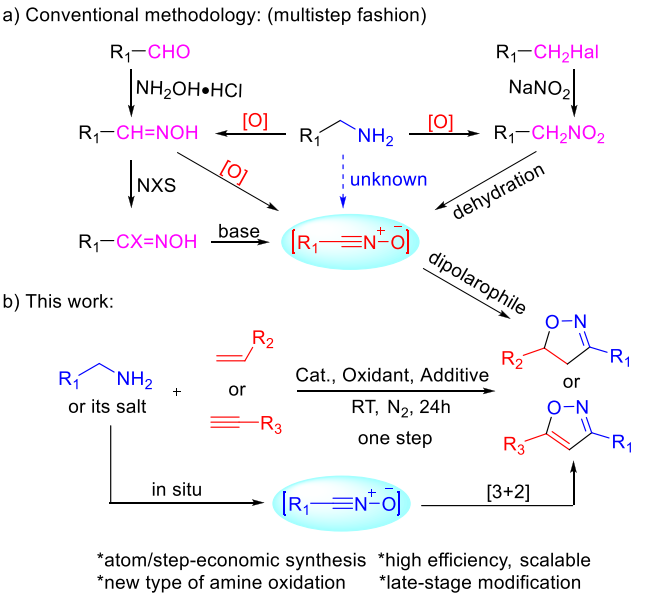
ABSTRACT: A facile oxidative heterocyclization of commercially available amines and *tert*-butyl nitrite with alkynes or alkenes leading to isoxazoles or isoxazolines is described. The unprecedented strategy of the oxidation of an amine directly to a nitrile oxide was used in this cyclization process. This reaction is highly efficient, regiospecific, operationally simple, mild, and tolerant of a variety of functional groups. Control experiments support a nitrile oxide intermediate mechanism for this novel class of oxidative cyclization reactions. Moreover, synthetic applications toward bioactive molecular skeletons and the late-stage modification of drugs were realized.



Nitrile oxides are valuable key intermediates that can undergo [3 + 2] cycloaddition to allow the construction of various heterocycles.[1] Isoxazolines and isoxazoles are privileged heterocyclic motifs found in various bioactive compounds and natural products.[1b,2] In addition, they can also be employed as efficient ligands[3] and eminent building blocks in organic synthesis.[4] The classic and well-established 1,3-dipolar cycloaddition of nitrile oxides with various alkenes and alkynes is a powerful C−C or C−O bond-forming transformation to deliver these five-membered heterocycles.[1] Thus, the generation of the nitrile oxides are critical to this [3 + 2] cycloaddition and is often achieved by one of the following three strategies: transformation from hydroximinoyl halides or aldoximes[5] or the dehydration of nitroalkanes.[6] Despite of their significance, most of the reported methods suffer from a low efficiency, a limited substrate scope, complicated operations, or harsh reaction conditions. More seriously, the multistep fashion is a common roadblock for accessing nitrile oxides. For example, such precursors always need to be synthesized from aldehydes, alkyl halides, or amines (Scheme 1a). Therefore, the development of practical and efficient approaches to construct nitrile oxides from stable, cheap, and readily accessible raw materials in one single step is highly valuable.

Amines are widespread chemicals and industrial raw materials because they are not only widely distributed but also cheap and commercially available. It would undoubtedly be a robust synthesis strategy if nitrile oxides could be synthesized by a one-step oxidation reaction using an amine as the starting material. Although there are many types of amines oxidations reported in the literature,[7] the direct transformation of amines to nitrile oxides has not yet been reported. To address the aforementioned limitations, we aim to develop a novel method that selectively oxidizes amines to nitrile oxides, which are in situ captured by alkenes or alkynes to construct isoxazolines or isoxazoles (Scheme 1b). However, there are two main challenges in this tandem oxidative/cyclization hypothesis. The primary amine might poison the transition

Scheme 1. Synthesize Isoxazoles and Isoxazolines via a Nitrile Oxide Intermediate



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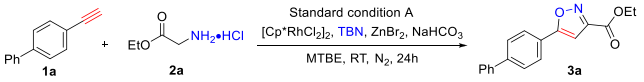
metal catalysts because of its strong coordination ability, thus blocking the catalytic process and leading to failure in the synthesis of heterocycles. Additionally, a suitable oxidant is required for this oxidative annulation strategy. Since amines are easily oxidized to imines,[8] nitriles,[9] oximes,[10] amides,[11] etc., and dipolarphiles are susceptible under strong oxidation conditions, a weak oxidant that does not cause the destruction of unstable substrates but can enable the oxidative and cyclization process should be found in this protocol. Herein, by using the *tert*-butyl nitrite (TBN) as the oxidant, we report a facile Rh-catalyzed oxidative heterocyclization of commercially available amines, alkynes, or alkenes, leading to isoxazoles or isoxazolines through a click reaction process.

We selected commercially available 4-ethynyl-1,1′-biphenyl **1a** with the ethyl glycinate hydrochloride salt **2a** as the model substrates for optimization. Extensive examinations (see the Supporting Information) revealed that a combination of $[Cp^*RhCl_2]_2/ZnBr_2/TBN/NaHCO_3$ at room temperature was optimal, with which the isoxazole product **3a** was obtained in a 97% yield (standard condition A, Table 1, entry 1). Very

Table 1. Evaluation of Reaction Conditions[a]



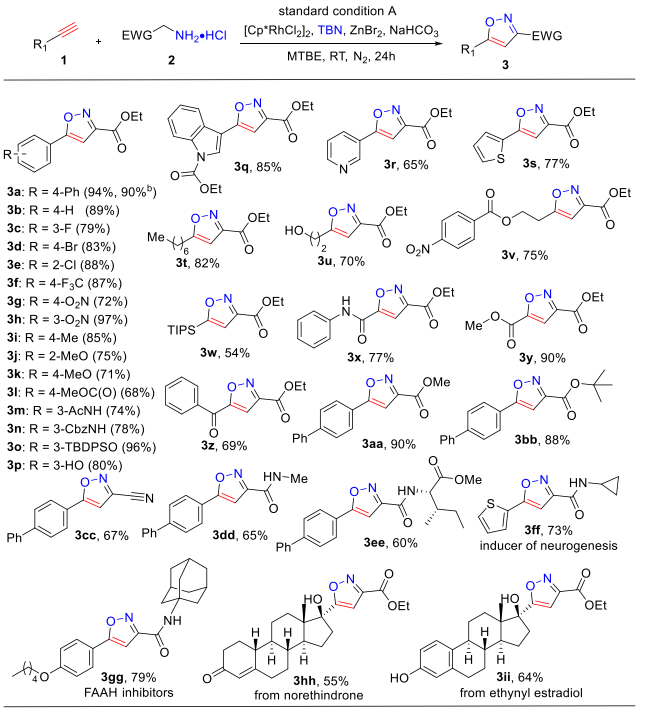
entry	variations from the standard conditions	1a (%)[b]	3a (%)[b]
1	**none**	**0**	**97 (94)**[c]
2	other oxidant instead of TBN[d]		0
3	$NaNO_2$ instead of TBN	64	19
4	without the [Rh] catalyst	88	0
5	0.5 mol % [Rh] was used	0	84
6	without $NaHCO_3$	44	26
7	1.5 equiv of $NaHCO_3$ was used	5	45
8	without $ZnBr_2$	80	0
9	1 equiv of $ZnBr_2$ was used	23	40
10	2 equiv of TBN and 2 equiv of **2a** were used	15	75
11	3 equiv of TBN and 2 equiv of **2a** were used	0	77
12	under air instead of N_2	0	85
13	1 mol % of $[Rh(OAc)_2]_2$ was used	60	27

[a]Standard conditions A are as follows: **1a** (0.3 mmol), **2a** (3 equiv), $[Cp^*RhCl_2]_2$ (1 mol %), TBN (3 equiv), $ZnBr_2$ (2 equiv), and $NaHCO_3$ (3 equiv) in methyl *tert*-butyl ether (3 mL); stirred for 24 h in a closed 10 mL vial at room temperature under a N_2 atmosphere. [b]Yields were determined by ^1H NMR spectroscopy with 1-bromo-3,5-bis(trifluoromethyl)benzene as an external standard. [c]Isolated yield. [d]In the place of TBN, 3 equiv of other oxidants was used; for details, see Table S3.

interestingly, when other oxidants were applied, no product could be detected except $NaNO_2$ with a 19% yield (Table 1, entries 2 and 3; see the Supporting Information for the details). Decreasing the amount of the catalyst slightly lower the yield, while no product was obtained without any catalyst (Table 1, entries 4 and 5, respectively). Only a 26% yield was obtained in the absence of a base, and a 45% yield was achieved when 1.5 equiv of $NaHCO_3$ was used (Table 1, entries 6 and 7, respectively). Since the yield of **3a** dropped sharply when reducing the amounts of $ZnBr_2$, 2 equiv of $ZnBr_2$ was necessary (Table 1, entries 8 and 9, respectively). Lowering the amounts of TBN or **2a** slightly influenced the yield (Table 1, entries 10 and 11, respectively). When the reaction was conducted under an air atmosphere, the yield slightly decreased to 85% (Table 1, entry 12). When 1 mol % $[Rh(OAc)_2]_2$ was used in place of $[Cp^*RhCl_2]_2$, the yield sharply decreased to 27% (Table 1, entry 13).

With the optimum conditions in hand, we subsequently proceeded to explore the substrate scope of this heterocyclization reaction. To our delight, various alkynes containing aryl, heteroaryl, alkyl, amide, ester, ketone, and other functional groups were compatible in this transformation, giving the desired product in good to high yields (Scheme 2, **3a**–**z**). A

Scheme 2. Synthesis of Isoxazoles[a]



[a]The standard condition A was adopted from Table 1, entry 1. Reaction yields refer to isolated yields. [b]Gram-scale yield.

gram scale reaction of **1a** was also realized with no impact on the yield or selectivity. Besides the simple ethyl glycinate hydrochloride salt, glycine methyl, *tert*-butyl ester hydrochloride, aminoacetonitrile hydrochloride, and some complex chiral amide containing hydrochlorides also gave the desired products in good yields (**3aa**–**gg**). It is worth noting that compound **3ff** is an inducer of neurogenesis, which triggered robust neuronal differentiation in adult neural stem cells that rapidly signaled to the neuronal genome via a Ca^{2+} influx;[2b] meanwhile, compound **3gg** is a fatty acid amide hydrolase (FAAH) inhibitor, which produced an anti-inflammatory effect in a dextran sulfate sodium (DSS)-induced acute colitis model in mice.[2c] Although an internal alkyne or compound **2** without an electron withdrawing-group (EWG) remained retarded in this condition, the late-stage modification of drugs was realized successfully. For example, norethindrone and ethyl estradiol were easily transformed to the corresponding isoxazoles derivatives **3hh** and **3ii** in 55% and 66% yields, respectively.

Furthermore, we prepared ethyl glycinate from its hydrochloride salt **2a** to test the scope of the free amine in our reaction, and only a 7% yield of **3a** was obtained in the standard condition A. However, the desired product could be

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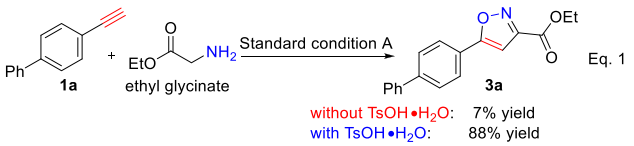
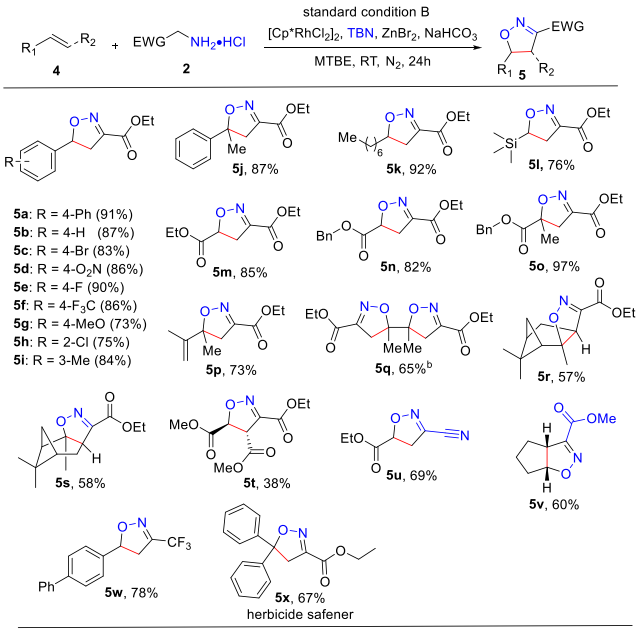
obtained in a comparable yield with the aid of *p*-toluenesulfonic acid monohydrate (eq 1).



To further demonstrate the potential utility of this reaction, we employed this method to synthesize isoxazolines (Scheme 3). With slightly lower equivalents of compound **2**, TBN, and

Scheme 3. Synthesis of Isoxazolines[a]

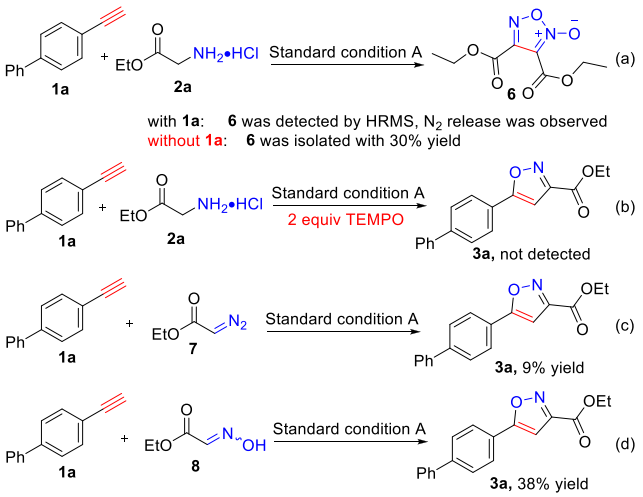


[a]Standard conditions B are as follows: **4** (0.3 mmol), **2** (2 equiv), $[Cp^*RhCl_2]_2$ (1 mol %), TBN (2 equiv), $ZnBr_2$ (2 equiv), and $NaHCO_3$ (2 equiv) in methyl *tert*-butyl ether (3 mL); stirred for 24 h in a closed 10 mL vial at room temperature under a N_2 atmosphere. Reaction yields refer to isolated yields. [b]Used 4 equiv of **2a**, TBN, and $NaHCO_3$.

$NaHCO_3$ (standard condition B), the desired isoxazoline products were still obtained with good to high yields. For example, various alkenes containing aryl [(with electron-withdrawing or electron-donoating functional groups (EWGs or EDGs, respectively) in different positions) or alkyl groups were compatible in this transformation (**5a**–**o**). When 2,3-dimethylbuta-1,3-diene was used in this standard conditions, compound **5p** was obtained in a 73% yield with specificity; meanwhile, the bisisoxazoline product **5q** was achieved in a 65% yield, and no **5p** was found when the equivalents of **2a**, TBN, and $NaHCO_3$ were doubled. The enantiomerically pure monoterpenes (1*R*)-(+)-*α*-pinene and (1*S*)-(−)-*α*-pinene reacted with **2a** to give 57% and 58% yields of thes isoxazoline **5r** and **5s**, respectively, as a single product. However, the internal alkene with two EWGs, such as dimethyl fumarate, only afforded product **5t** in a 38% yield. Other amino-acetonitrile, glycine methyl ester, or trifluoroethylamine hydrochloride were compatible with these conditions and gave the desired products in 60%–78% yields (**5u**–**w**, respectively). At last, this method was employed to synthesize the herbicide safener isoxadifen-ethyl[12] **5x** in a 67% yield from the commercially available 1,1-diphenylethylene in a single step.

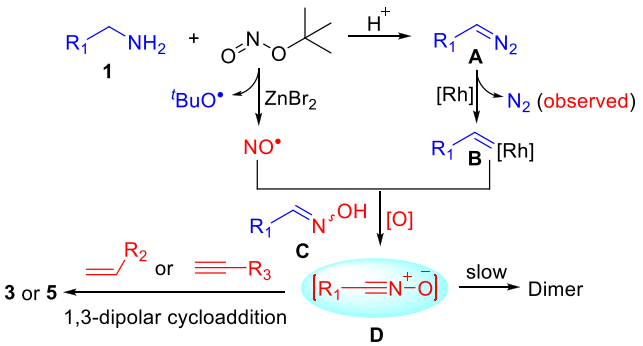
To gain insight into the mechanism, several control experiments were carried out (Scheme 4). A phenomenon of

Scheme 4. Control Experiments



slowly released nitrogen was observed,[13] and the dimer oxadiazole **6** was detected by HRMS in the model reaction. Next, **2a** was applied to the standard conditions in the absence of alkenes or alkynes, and oxadiazole **6** was isolated in a 30% yield (Scheme 4a). This result indicates that nitrile oxide could be the key intermediate in this reaction system.[14] In addition, the heterocyclization reaction was completely shut down when 2 equiv of TEMPO was added, suggesting that a radical intermediate may be involved in this transformation (Scheme 4b). Some possible intermediates were prepared and applied to this reaction system, such as ethyl diazoacetate (**7**) and ethyl 2-(hydroxyimino)acetate (**8**). Both of them afforded the desired product **3a** under the standard condition (Scheme 5c and d,

Scheme 5. Proposed Mechanism



respectively). Although the yield is relatively low, these compounds may still be intermediates considering that the reaction is sensitive to acid and alkali (Table 1, entries 6–9 and eq 1].

Although the detailed reaction pathway remains to be clarified, a plausible mechanism for this reaction was proposed on the basis of the above results and previous literature reports

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(Scheme 5).[15] The reaction is initiated by the formation of a Rh-carbene **B** from the diazo-compound **A**,[16] which was generated in situ via the reaction of the amine with *tert*-butyl nitrite. Meanwhile, the interaction of *tert*-butyl nitrite with $ZnBr_2$ gives rise to a nitroso radical, which is captured by the Rh-carbene **B** to either afford the nitrile oxide **D** directly or go preferentially through the intermediate **C**.[5a] Finally, intermediate **D** undergoes 1,3-dipolar cycloaddition with the alkene or alkyne to deliver the final product **3** or **5**, respectively.

In summary, we have developed an unprecedented Rh-catalyzed oxidative reaction of commercially available amines and *tert*-butyl nitrite with alkynes or alkenes as an efficient approach to the direct construction of isoxazoles or isoxazolines, respectively, with multiple bonds formation in a "click" manner. The salient features of this reaction include readily available materials, mild reaction conditions, good functional group tolerance, and the late-stage modification of drugs. In addition, this is the first example of using a cheap and commercially available amine as the nitrile oxide precursor. In a broader context, our results demonstrate an unprecedented control of the selectivity of amine oxidation to a nitrile oxide, which was enabled by a mild Rh-catalyzed reaction. This technology eliminates many problems inherent in the previous multistep fashion of preparing the nitrile oxide intermediate. It will create new opportunities to incorporate N−O heterocycles in drugs and biologics. Further novel applications using an amine as a safe and readily available nitrile oxide precursor can be expected in the near future.

EXPERIMENTAL SECTION

General Information. *tert*-Butyl nitrite was purified by distillation. Other purchased reagents were used without further purification unless otherwise noted. All solvents were dried over activated 4 Å molecular sieves. Chromatographic purification of products was carried out by flash column chromatography on silica gel (300−400 mesh). NMR spectra were measured in $CDCl_3$ (TMS, ^1H δ 0; $CDCl_3$, ^1H δ 7.26, ^{13}C δ 77.36), DMSO-d_6, or CD_3OD on a Bruker AV 400 (^1H at 400 MHz, ^{13}C at 100 MHz, and ^{19}F at 376 MHz) magnetic resonance spectrometer. High-resolution mass spectra (HRMS) were recorded on a SYNAPT G2Si High Definition MS system (ESI model).

General Procedure for the Synthesis of Isoxazoles. A solution of alkyne **1** (0.3 mmol, 1.0 equiv) in methyl *tert*-butyl ether (3 mL) and *tert*-butyl nitrite (0.9 mmol, 3.0 equiv) were added successively to a 15 mL Schlenk tube charged with $[Cp^*RhCl_2]_2$ (1 mol %), ammonium hydrochloride (0.9 mmol, 3.0 equiv), $NaHCO_3$ (0.9 mmol, 3.0 equiv), $ZnBr_2$ (0.6 mmol, 2.0 equiv), and a magnetic stirring bar under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 h, concentrated under vacuum, and purified by flash column chromatography.

General Procedure for the Synthesis of Isoxazolines. A solution of alkene **4** (0.3 mmol, 1.0 equiv) in methyl *tert*-butyl ether (3 mL) and *tert*-butyl nitrite (0.6 mmol, 2.0 equiv) were added successively to a 15 mL Schlenk tube charged with $[Cp^*RhCl_2]_2$ (1 mol %), ammonium hydrochloride (0.6 mmol, 2.0 equiv), $NaHCO_3$ (0.6 mmol, 2.0 equiv), $ZnBr_2$ (0.6 mmol, 2.0 equiv), and a magnetic stirring bar under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 h, concentrated under vacuum, and purified by flash column chromatography.

Gram-Scale Synthesis of 3a. A solution of 4-ethynyl-1,1′-biphenyl **1a** (1.07 g, 6.0 mmol, 1.0 equiv) in *tert*-butyl ether (25 mL) and *tert*-butyl nitrite (18.0 mmol, 3.0 equiv) were added successively to a 150 mL Schlenk tube charged with $[Cp^*RhCl_2]_2$ (1 mol %), glycine ethyl ester hydrochloride **2a** (2.51g, 18.0 mmol, 3.0 equiv), $NaHCO_3$ (18.0 mmol, 3.0 equiv), $ZnBr_2$ (12.0 mmol, 2.0 equiv), and a magnetic stirring bar under a nitrogen atmosphere. The mixture was stirred at room temperature (during the reaction, the slowly generated nitrogen needs to be released every few hours, otherwise the nitrogen ballon may burst.) After 24 h, the reaction mixture was filtered over a plug of Celite (EtOAc as the eluent), and the filtrate was washed with saturated aqueous sodium thiosulfate (30 mL) and dried over anhydrous magnesium sulfate. The organic phase was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography to afford the product **3a** (1.58 g, 90%).

*Ethyl 5-([1,1′-Biphenyl]-4-yl)isoxazole-3-carboxylate (**3a**).*[17a] Purified by flash column chromatography (petroleum ether/AcOEt = 70:1), pale yellow solid (82.5 mg, 94% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.3 Hz, 2 H), 7.71 (d, J = 8.3 Hz, 2 H), 7.63 (d, J = 7.5 Hz, 2 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.40 (t, J = 7.5 Hz, 1 H), 6.96 (s, 1 H), 4.48 (q, J = 7.1 Hz, 2 H), 1.45 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.8, 160.4, 157.3, 143.9, 140.1, 129.3, 128.4, 128.1, 127.4, 126.7, 125.7, 100.2, 62.6, 14.5; HRMS (ESI) m/z calcd for $C_{18}H_{16}O_3N^+$ $[M + H]^+$ 294.1125, found 294.1124.

*Ethyl 5-Phenylisoxazole-3-carboxylate (**3b**).*[6f] Purified by flash column chromatography (petroleum ether/AcOEt = 70:1), pale yellow solid (57.8 mg, 89% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.80−7.77 (m, 2 H), 7.47−7.45 (m, 3 H), 6.91 (s, 1 H), 4.45 (t, J = 7.2 Hz, 1 H), 1.42 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.0, 160.3, 157.2, 131.1, 129.4, 126.9, 126.2, 100.2, 62.5, 14.4.

*Ethyl 5-(3-Fluorophenyl)isoxazole-3-carboxylate (**3c**).*[15b] Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), colorless crystal (55.4 mg, 79% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.58−7.56 (m, 1 H), 7.50−7.42 (m, 2 H), 7.18−7.13 (m, 1 H), 6.93 (s, 1 H), 4.46 (q, J = 7.1 Hz, 2 H), 1.42 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ170.6 (C−F, $4J_{C-F}$ = 2.9 Hz), 163.2 (C−F, $1J_{C-F}$ = 247.0 Hz), 160.1, 157.3, 131.3 (C−F, $3J_{C-F}$ = 8.2 Hz), 128.7 (C−F, 3 J_{C-F} = 8.4 Hz), 122.0 (C−F, 4 J_{C-F} = 3.2 Hz), 118.1 (C−F, 2 J_{C-F} = 21.3 Hz), 113.2 (C−F, 2 J_{C-F} = 23.8 Hz), 101.0, 62.6, 14.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.13 to −111.19 (m, 1 F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −111.16 (s, 1 F).

*Ethyl 5-(4-Bromophenyl)isoxazole-3-carboxylate (**3d**).*[15b] Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), white solid (73.7 mg, 83% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.60 (m, 4 H), 6.92 (s, 1 H), 4.46 (q, J = 7.2 Hz, 2 H), 1.43 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.9, 160.1, 157.4, 132.7, 127.6, 125.8, 125.6, 100.6, 62.6, 14.5.

*Ethyl 5-(2-Chlorophenyl)isoxazole-3-carboxylate (**3e**).*[15b] Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), colorless oil (66.6 mg, 88% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.97−7.95 (m, 1 H), 7.53−7.50 (m, 1 H), 7.41−7.39 (m, 2 H), 7.33 (s, 1 H), 4.47 (q, J = 7.2 Hz, 2 H), 1.44 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.3, 160.2, 157.2, 132.2, 131.7, 131.3, 129.7, 127.6, 125.7, 105.1, 62.6, 14.5.

*Ethyl 5-(4-(Trifluoromethyl)phenyl)isoxazole-3-carboxylate (**3f**).*[17a] Purified by flash column chromatography (petroleum ether/AcOEt = 40:1), white crystalline solid (74.8 mg, 87% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 2 H), 7.73 (d, J = 8.2 Hz, 2 H), 7.02 (s, 1 H), 4.46 (q, J = 7.2 Hz, 2 H), 1.43 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.3, 160.0, 157.4, 132.7 (C−F, $2J_{C-F}$ = 33.0 Hz), 130.0, 126.5, 126.5 (C−F, $3J_{C-F}$ = 3.8 Hz), 123.9 (C−F, $1J_{C-F}$ = 273.0 Hz), 101.7, 62.7, 14.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.1 (s, 1 F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −63.1 (s, 1 F).

*Ethyl 5-(4-Nitrophenyl)isoxazole-3-carboxylate (**3g**).*[17b] Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), light yellow solid (56.5 mg, 72% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 8.8 Hz, 2 H), 8.00 (d, J = 8.8 Hz, 2 H), 7.11 (s, 1 H), 4.49 (q, J = 7.2 Hz, 2 H), 1.45 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 159.8, 157.6, 149.2, 132.3, 127.1, 124.9, 102.8, 62.9, 14.5; HRMS (ESI) m/z calcd for $C_{12}H_{10}O_5N_2Na^+$ $[M + Na]^+$ 285.0482, found 285.0482.

*Ethyl 5-(3-Nitrophenyl)isoxazole-3-carboxylate (**3h**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1, R_f = 0.28), colorless crystal (76.4 mg, 97% yield): IR (KBr, cm^{-1}) ν 1728,

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1621, 1528, 1446, 1353, 1291, 1258, 1149, 1108, 1017, 942, 809, 781, 743, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (t, J = 1.8 Hz, 1 H), 8.32−8.30 (m, 1 H), 8.15−8.12 (m, 1 H), 7.71 (t, J = 8.0 Hz, 1 H), 7.09 (s, 1 H), 4.47 (q, J = 7.2 Hz, 2 H), 1.43 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 159.8, 157.6, 149.0, 131.7, 130.8, 128.4, 125.5, 121.2, 102.0, 62.8, 14.4; HRMS (ESI) m/z calcd for $C_{12}H_{11}O_5N_2^+$ [M + H]$^+$ 263.0662, found 263.0667.

*Ethyl 5-(p-Tolyl)isoxazole-3-carboxylate (**3i**).*[15b] Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), white solid (59.1 mg, 85% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.1 Hz, 2 H), 7.19 (d, J = 8.1 Hz, 2 H), 6.78 (s, 1 H), 4.38 (q, J = 7.2 Hz, 2 H), 2.31 (s, 3 H), 1.35 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.1, 160.3, 157.1, 141.5, 130.0, 126.1, 124.2, 99.6, 62.4, 21.8, 14.4.

*Ethyl 5-(2-Methoxyphenyl)isoxazole-3-carboxylate (**3j**).* Purified by flash column chromatography (petroleum ether/AcOEt = 30:1, R_f = 0.30), white solid (55.4 mg, 75% yield): IR (KBr, cm^{-1}) ν 1728, 1611, 1450, 1446, 1260, 1247, 1235, 1146, 1018, 779, 755, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 1.5, 7.8 Hz, 1 H), 7.46−7.41 (m, 1 H), 7.17 (s, 1 H), 7.08 (t, J = 7.6 Hz, 1 H), 7.02 (d, J = 8.4 Hz, 1 H), 4.47 (q, J = 7.2 Hz, 2 H), 3.97 (s, 3 H), 1.44 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.1, 160.8, 157.3, 156.6, 132.2, 128.0, 121.2, 115.9, 111.6, 104.2, 62.4, 55.9, 14.5; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_4N^+$ [M + H]$^+$ 248.0917, found 248.0925.

*Ethyl 5-(4-Methoxyphenyl)isoxazole-3-carboxylate (**3k**).*[15b] Purified by flash column chromatography (petroleum ether/AcOEt = 30:1), colorless crystal (52.7 mg, 71% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.9 Hz, 2 H), 6.98 (d, J = 8.9 Hz, 2 H), 6.78 (s, 1 H), 4.45 (q, J = 7.2 Hz, 2 H), 3.85 (s, 3 H), 1.42 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.0, 161.9, 160.5, 157.2, 127.9, 119.7, 114.9, 98.8, 62.4, 55.7, 14.5; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_4N^+$ [M + H]$^+$ 248.0917, found 248.0923.

*Ethyl 5-(4-(Methoxycarbonyl)phenyl)isoxazole-3-carboxylate (**3l**).* Purified by flash column chromatography (petroleum ether/AcOEt = 20:1, R_f = 0.35), white solid (53.0 mg, 68% yield): IR (KBr, cm^{-1}) ν 1732, 1718, 1590, 1438, 1278, 1255, 1151, 1102, 1017, 949, 827, 784, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 2 H), 7.85 (d, J = 8.4 Hz, 2 H), 7.00 (s, 1 H), 4.45 (q, J = 7.2 Hz, 2 H), 3.92 (s, 3 H), 1.42 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.7, 166.4, 160.0, 157.4, 132.3, 130.6, 130.6, 126.1, 101.7, 62.6, 52.7, 14.4; HRMS (ESI) m/z calcd for $C_{14}H_{14}O_5N^+$ [M + H]$^+$ 276.0866, found 276.0869.

*Ethyl 5-(3-Acetamidophenyl)isoxazole-3-carboxylate (**3m**).* Purified by flash column chromatography (petroleum ether/AcOEt = 1:1, R_f = 0.40), white solid (60.7 mg, 74% yield): IR (KBr, cm^{-1}) ν 3377, 1732, 1688, 1577, 1545, 1496, 1430, 1311, 1257, 1020, 939, 833, 782, 702; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1 H), 8.17 (s, 1 H), 7.61 (dd, J = 7.9, 21.7 Hz, 2 H), 7.43 (t, J = 7.9 Hz, 1 H), 7.31 (s, 1 H), 4.35 (q, J = 7.1 Hz, 2 H), 2.05 (s, 3 H), 1.31 (t, J = 7.1 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.4, 169.2, 159.7, 157.3, 140.5, 130.3, 126.8, 121.7, 121.2, 116.0, 101.2, 62.4, 24.5, 14.4; HRMS (ESI) m/z calcd for $C_{14}H_{15}O_4N_2^+$ [M + H]$^+$ 275.1026, found 275.1030.

*Ethyl 5-(3-(((Benzyloxy)carbonyl)amino)phenyl)isoxazole-3-carboxylate (**3n**).* Purified by flash column chromatography (petroleum ether/AcOEt = 5:1, R_f = 0.30), colorless crystal (85.6 mg, 78% yield): IR (KBr, cm^{-1}) ν 3338, 1724, 1577, 1544, 1499, 1409, 1251, 1222, 1068, 804, 775, 768, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1 H), 7.52−7.49 (m, 2 H), 7.43−7.34 (m, 6 H), 6.93 (s, 1 H), 6.91 (s, 1 H), 5.22 (s, 2 H), 4.46 (q, J = 7.2 Hz, 2 H), 1.43 (q, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.6, 160.3, 157.3, 153.5, 139.1, 136.1, 130.3, 129.0, 128.8, 128.7, 127.8, 121.3, 121.1, 116.2, 100.7, 67.7, 62.6, 14.5; HRMS (ESI) m/z calcd for $C_{20}H_{19}O_5N_2^+$ [M + H]$^+$ 367.1288, found 367.1282.

*Ethyl 5-(3-((Tert-butyldiphenylsilyl)oxy)phenyl)isoxazole-3-carboxylate (**3o**).*[2d] Purified by flash column chromatography (petroleum ether/AcOEt = 5:1), colorless oil (136.0 mg, 96% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.74 (m, 4 H), 7.47−7.38 (m, 6 H), 7.33−7.31 (m, 1 H), 7.23−7.22 (m, 1 H), 7.17 (t, J = 8.0 Hz, 1 H), 6.84−6.82 (m, 1 H), 6.71 (s, 1 H), 4.46 (q, J = 7.2 Hz, 2 H), 1.44 (t, J = 7.2 Hz, 3 H), 1.15 (s, 9 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.8, 160.3, 157.1, 156.4, 135.8, 132.7, 130.5, 130.3, 128.2, 127.9, 122.5, 119.0, 117.5, 100.3, 62.4, 26.8, 19.8, 14.4.

*Ethyl 5-(3-Hydroxyphenyl)isoxazole-3-carboxylate (**3p**).*[2d] Purified by flash column chromatography (petroleum ether/AcOEt = 2:1), white powder (55.8 mg, 80% yield): ^{1}H NMR (400 MHz, CD_3OD) δ 7.33−7.32 (m, 2 H), 7.27−7.26 (m, 1 H), 7.09 (s, 1 H), 6.94−6.91 (m, 1 H), 4.44 (q, J = 7.2 Hz, 2 H), 1.41 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 173.3, 161.2, 159.4, 158.3, 131.5, 129.0, 119.1, 118.1, 113.4, 101.0, 63.2, 14.4.

*Ethyl 5-(1-(Ethoxycarbonyl)-1H-indol-3-yl)isoxazole-3-carboxylate (**3q**).* Purified by flash column chromatography (petroleum ether/AcOEt = 20:1, R_f = 0.30), white solid (83.7 mg, 85% yield): IR (KBr, cm^{-1}) ν 1734, 1619, 1599, 1546, 1451, 1380, 1324, 1236, 1100, 1022, 828, 780, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.0 Hz, 1 H), 8.15 (s, 1 H), 7.90 (d, J = 7.7 Hz, 1 H), 7.45−7.36 (m, 2 H), 6.94 (s, 1 H), 4.54 (q, J = 7.2 Hz, 2 H), 4.49 (q, J = 7.2 Hz, 2 H), 1.50 (t, J = 7.2 Hz, 3 H), 1.45 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 160.3, 157.1, 150.7, 135.8, 126.4, 126.1, 125.6, 124.5, 120.5, 115.9, 109.2, 100.5, 64.4, 62.6, 14.7, 14.5; HRMS (ESI) m/z calcd for $C_{17}H_{16}O_5N_2Na^+$ [M + Na]$^+$ 351.0951, found 351.0950.

*Ethyl 5-(Pyridin-3-yl)isoxazole-3-carboxylate (**3r**).*[17c] Purified by flash column chromatography (petroleum ether/AcOEt = 2:1), colorless crystal (42.4 mg, 65% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, J = 1.7 Hz, 1 H), 8.71 (dd, J = 1.6, 4.8 Hz, 1 H), 8.12 (dt, J = 2.0, 8.0 Hz, 1 H), 7.47−7.43 (m, 1 H), 7.03 (s, 1 H), 4.48 (q, J = 7.2 Hz, 2 H), 1.44 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 160.0, 157.5, 151.9, 147.4, 133.4, 124.2, 123.3, 101.3, 62.8, 14.5; HRMS (ESI) m/z calcd for $C_{11}H_{11}O_3N_2^+$ [M + H]$^+$ 219.0764, found 219.0773.

*Ethyl 5-(Thiophen-2-yl)isoxazole-3-carboxylate (**3s**).*[15b] Purified by flash column chromatography (petroleum ether/AcOEt = 30:1), pale yellow solid (51.5 mg, 77% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 1.0, 3.7 Hz, 1 H), 7.47 (dd, J = 1.0, 5.0 Hz, 1 H), 7.11 (dd, J = 3.7, 5.0 Hz, 1 H), 6.75 (s, 1 H), 4.43 (q, J = 7.2 Hz, 2 H), 1.40 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 160.0, 157.1, 129.1, 128.5, 128.4, 128.0, 99.8, 62.5, 14.4.

*Ethyl 5-Hexylisoxazole-3-carboxylate (**3t**).*[17d] Purified by flash column chromatography (petroleum ether/AcOEt = 80:1), colorless oil (55.6 mg, 82% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 2.77 (t, J = 7.6 Hz, 2 H), 1.72−1.65 (m, 2 H), 1.39 (t, J = 7.2 Hz, 3 H), 1.37−1.23 (m, 6 H), 0.86 (t, J = 6.8 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.1, 160.6, 156.7, 101.7, 62.3, 31.7, 28.9, 27.7, 27.0, 22.8, 14.5, 14.3; HRMS (ESI) m/z calcd for $C_{12}H_{20}O_3N^+$ [M + H]$^+$ 226.1438, found 226.1446.

*Ethyl 5-(2-Hydroxyethyl)isoxazole-3-carboxylate (**3u**).*[17d] Purified by flash column chromatography (petroleum ether/AcOEt = 4:1), colorless oil (38.7 mg, 70% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 1 H), 4.39 (q, J = 7.2 Hz, 2 H), 3.94 (t, J = 6.2 Hz, 2 H), 3.04 (t, J = 6.2 Hz, 2 H), 2.54 (br s, 1 H), 1.37 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.1, 160.4, 156.7, 103.0, 62.5, 60.0, 30.5, 14.4; HRMS (ESI) m/z calcd for $C_8H_{11}O_4NNa^+$ [M + Na]$^+$ 208.0580, found 208.0586.

*Ethyl 5-(2-((4-Nitrobenzoyl)oxy)ethyl)isoxazole-3-carboxylate (**3v**).* Purified by flash column chromatography (petroleum ether/AcOEt = 4:1, R_f = 0.42), colorless crystal (75.1 mg, 75% yield): IR (KBr, cm^{-1}) ν 1729, 1718, 1532, 1461, 1277, 1253, 1115, 1003, 935, 882, 839, 787, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.9 Hz, 2 H), 8.14 (d, J = 8.9 Hz, 2 H), 6.56 (s, 1 H), 4.67 (t, J = 6.3 Hz, 2 H), 4.40 (q, J = 7.2 Hz, 2 H), 3.33 (t, J = 6.3 Hz, 2 H), 1.37 (t, J = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.3, 164.7, 159.3 (t, J = 30.0 Hz), 151.1, 135.2, 131.1, 124.0, 109.3 (t, J = 237.0 Hz), 99.5, 62.6, 27.0; HRMS (ESI) m/z calcd for $C_{15}H_{15}O_7N_2^+$ [M + H]$^+$ 335.0874, found 335.0862.

*Ethyl 5-(Triisopropylsilyl)isoxazole-3-carboxylate (**3w**).* Purified by flash column chromatography (petroleum ether/AcOEt = 100:1, R_f = 0.36), colorless oil (48.3 mg, 54% yield): IR (KBr, cm^{-1}) ν 2947, 2869, 1731, 1540, 1466, 1431, 1231, 1131, 1020, 883, 780, 686; ^{1}H

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NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1 H), 4.43 (q, J = 7.2 Hz, 2 H), 1.41 (t, J = 7.2 Hz, 3 H), 1.38−1.33 (m, 3 H), 1.11 (s, 9 H), 1.09 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.4, 160.9, 155.1, 114.9, 62.3, 18.6, 14.5, 11.2; HRMS (ESI) m/z calcd for $C_{15}H_{28}O_3N^+$ $[M + H]^+$ 298.1833, found 298.1833.

*Ethyl 5-(Phenylcarbamoyl)isoxazole-3-carboxylate (**3x**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1, R_f = 0.25), white solid (60.2 mg, 77% yield): IR (KBr, cm^{-1}) ν 3342, 1744, 1679, 1539, 1443, 1323, 1248, 1224, 1028, 759, 750, 689; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (br s, 1 H), 7.67−7.65 (m, 2 H), 7.40−7.36 (m, 3 H), 7.20 (t, J = 7.4 Hz, 1 H), 4.46 (q, J = 7.2 Hz, 2 H), 1.42 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 159.2, 157.8, 153.1, 136.6, 129.6, 126.0, 120.8, 108.4, 63.0, 14.4; HRMS (ESI) m/z calcd for $C_{13}H_{13}O_4N_2^+$ $[M + H]^+$ 261.0870, found 261.0876.

*3-Ethyl 5-Methyl Isoxazole-3,5-dicarboxylate (**3y**).* Purified by flash column chromatography (petroleum ether/AcOEt = 20:1, R_f = 0.32), colorless crystal (53.9 mg, 90% yield): IR (KBr, cm^{-1}) ν 1738, 1724, 1586, 1434, 1253, 1085, 1019, 927, 879, 831, 773; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1 H), 4.46 (q, J = 7.2 Hz, 2 H), 3.98 (s, 3 H), 1.42 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.9, 159.2, 157.3, 156.8, 110.1, 63.0, 53.5, 14.4; HRMS (ESI) m/z calcd for $C_8H_9O_5NNa^+$ $[M + Na]^+$ 222.0373, found 222.0379.

*Ethyl 5-Benzoylisoxazole-3-carboxylate (**3z**).* Purified by flash column chromatography (petroleum ether/AcOEt = 15:1, R_f = 0.34), colorless oil (50.6 mg, 69% yield): IR (KBr, cm^{-1}) ν 1735, 1666, 1599, 1448, 1242, 1186, 1019, 891, 798, 721, 681; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06−8.04 (m, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.51 (t, J = 7.8 Hz, 2 H), 7.33 (s, 1 H), 4.45 (q, J = 7.2 Hz, 2 H), 1.40 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.8, 168.1, 159.3, 156.9, 135.3, 134.7, 130.1, 129.2, 110.6, 62.9, 14.3; HRMS (ESI) m/z calcd for $C_{13}H_{12}O_4N^+$ $[M + H]^+$ 246.0761, found 246.0765.

*Methyl 5-([1,1′-Biphenyl]-4-yl)isoxazole-3-carboxylate (**3aa**).* Purified by flash column chromatography (petroleum ether/AcOEt = 80:1, R_f = 0.48), pale yellow solid (75.6 mg, 90% yield): IR (KBr, cm^{-1}) ν 1755, 1741, 1612, 1461, 1418, 1241, 1148, 1016, 805, 768, 726, 693; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 2 H), 7.69 (d, J = 8.3 Hz, 2 H), 7.61(d, J = 7.3 Hz, 2 H), 7.46 (t, J = 7.3 Hz, 2 H), 7.39 (t, J = 7.3 Hz, 1 H), 6.94 (s, 1 H), 4.00 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.8, 160.7, 156.9, 143.8, 140.0, 129.2, 128.4, 128.0, 127.3, 126.6, 125.6, 100.2, 53.1; HRMS (ESI) m/z calcd for $C_{17}H_{13}O_3NNa^+$ $[M + Na]^+$ 302.0788, found 302.0788.

*tert-Butyl 5-([1,1′-biphenyl]-4-yl)isoxazole-3-carboxylate (**3bb**).* Purified by flash column chromatography (petroleum ether/AcOEt = 80:1, R_f = 0.50), white solid (84.7 mg, 88% yield): IR (KBr, cm^{-1}) ν 2984, 1718, 1631, 1443, 1368, 1254, 1170, 1112, 995, 831, 769, 731, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 2 H), 7.70 (d, J = 8.4 Hz, 2 H), 7.64−7.61 (m, 2 H), 7.49−7.45 (m, 2 H), 7.41−7.37 (m, 1 H), 6.89 (s, 1 H), 1.65 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.5, 159.4, 158.5, 143.7, 140.2, 129.3, 128.4, 128.0, 127.4, 126.6, 125.9, 100.2, 84.0, 28.4; HRMS (ESI) m/z calcd for $C_{20}H_{19}O_3NNa^+$ $[M + Na]^+$ 344.1257, found 344.1248.

*5-([1,1′-Biphenyl]-4-yl)isoxazole-3-carbonitrile (**3cc**).* Purified by flash column chromatography (petroleum ether/AcOEt = 70:1, R_f = 0.45), colorless crystal (49.4 mg, 67% yield): IR (KBr, cm^{-1}) ν 1610, 1579, 1486, 1415, 1047, 1006, 949, 845, 802, 768, 722, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.5 Hz, 2 H), 7.75 (d, J = 8.5 Hz, 2 H), 7.64 (d, J = 7.5 Hz, 2 H), 7.50 (t, J = 7.3 Hz, 2 H), 7.43 (t, J = 7.3 Hz, 1 H), 6.84 (s, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.7, 144.7, 140.4, 139.8, 129.4, 128.7, 128.2, 127.4, 126.9, 124.5, 110.4, 101.7; HRMS (ESI) m/z calcd for $C_{16}H_{10}ON_2Na^+$ $[M + Na]^+$ 269.0685, found 269.0695.

*5-([1,1′-Biphenyl]-4-yl)-N-methylisoxazole-3-carboxamide (**3dd**).* Purified by flash column chromatography (petroleum ether/AcOEt = 20:1, R_f = 0.28), colorless crystal (54.1 mg, 65% yield): IR (KBr, cm^{-1}) ν 3329, 1668, 1564, 1447, 1263, 974, 948, 862, 812, 766, 728, 696; ^1H NMR (400 MHz, DMSO-d_6) δ 8.77 (br s, 1 H), 8.02 (d, J = 8.2 Hz, 2 H), 7.86 (d, J = 8.2 Hz, 2 H), 7.76 (d, J = 7.5 Hz, 2 H), 7.51 (t, J = 7.5 Hz, 1 H), 7.44−7.40 (m, 1 H), 7.39 (s, 1 H), 2.82 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.5, 160.1, 159.4, 142.7, 139.4, 129.6, 128.7, 127.9, 127.3, 126.9, 125.7, 100.3, 26.4; HRMS (ESI) m/z calcd for $C_{17}H_{14}O_2N_2Na^+$ $[M + Na]^+$ 301.0947, found 301.0949.

*Methyl (5-([1,1′-Biphenyl]-4-yl)isoxazole-3-carbonyl)-L-isoleucinate (**3ee**).* Purified by flash column chromatography (petroleum ether/AcOEt = 8:1, R_f = 0.34), white solid (71.1 mg, 60% yield): IR (KBr, cm^{-1}) ν 3326, 2959, 2878, 1747, 1672, 1539, 1447, 1232, 1198, 1148, 843, 766, 723, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2 H), 7.71 (d, J = 8.3 Hz, 2 H), 7.63 (d, J = 7.4 Hz, 2 H), 7.47 (t, J = 7.4 Hz, 2 H), 7.39 (t, J = 7.4 Hz, 1 H), 7.34 (d, J = 8.7 Hz, 1 H), 6.99 (s, 1 H), 4.80 (dd, J = 5.1, 8.8 Hz, 1 H), 3.79 (s, 3 H), 2.08−2.01 (m, 1 H), 1.58−1.51(m, 1 H), 1.33−1.25 (m, 1 H), 1.01−0.95 (m, 6 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.9, 171.8, 159.1, 159.0, 143.8, 140.2, 129.3, 128.4, 128.1, 127.4, 126.7, 125.8, 99.5, 56.9, 52.6, 38.4, 25.5, 15.9, 11.9; HRMS (ESI) m/z calcd for $C_{23}H_{25}O_4N_2^+$ $[M + H]^+$ 393.1809, found 393.1804.

*N-Cyclopropyl-5-(thiophen-2-yl)isoxazole-3-carboxamide (**3ff**).*[2b] Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), white solid (51.2 mg, 73% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 1.0, 3.7 Hz, 1 H), 7.49 (dd, J = 1.0, 5.0 Hz, 1 H), 7.14 (dd, J = 3.7, 5.0 Hz, 1 H), 6.91 (br s, 1 H), 6.82 (s, 1 H), 2.93−2.87 (m, 1 H), 0.91−0.86 (m, 2 H), 0.69−0.65 (m, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 160.3, 159.3, 129.1, 128.8, 128.6, 128.0, 99.1, 22.9, 7.0; HRMS (ESI) m/z calcd for $C_{11}H_{10}O_2N_2SNa^+$ $[M + Na]^+$ 257.0355, found 257.0356.

*N-Adamantyl-5-(4-(pentyloxy)phenyl)isoxazole-3-carboxamide (**3gg**).*[2c] Purified by flash column chromatography (petroleum ether/AcOEt = 30:1), colorless crystal (97.2 mg, 79% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.6 Hz, 2 H), 6.96 (d, J = 8.6 Hz, 2 H), 6.77 (s, 1 H), 6.55 (br s, 1 H), 4.00 (t, J = 6.6 Hz, 2 H), 2.12 (s, 9 H), 1.82−1.69 (m, 8 H), 1.45−1.38 (m, 4 H), 0.94 (t, J = 7.0 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.8, 161.4, 160.4, 158.3, 127.8, 119.8, 115.3, 98.0, 68.5, 52.9, 41.8, 36.6, 29.8, 29.2, 28.5, 22.8, 14.3; HRMS (ESI) m/z calcd for $C_{25}H_{32}O_3N_2Na^+$ $[M + Na]^+$ 431.2305, found 431.2284.

*Ethyl 5-((8R,9S,10R,13S,14S,17S)-17-Hydroxy-13-methyl-3-oxo-2,3, 6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)isoxazole-3-carboxylate (**3hh**).* Purified by flash column chromatography (petroleum ether/AcOEt = 3:1, R_f = 0.22), white solid (67.9 mg, 55% yield): IR (KBr, cm^{-1}) ν 3313, 2930, 2912, 1737, 1653, 1573, 1454, 1272, 1245, 1198, 1191, 1133, 1014, 916, 830, 817, 775; ^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 1 H), 5.80 (s, 1 H), 4.43 (q, J = 7.1 Hz, 2 H), 2.49−2.46 (m, 1 H), 2.38−2.34 (m, 2 H), 2.28−2.17 (m, 3 H), 2.12−2.05 (m, 2 H), 1.87−1.73 (m, 4 H), 1.64−1.52 (m, 2 H), 1.43−1.39 (m, 5 H), 1.27−1.18 (m, 2 H), 1.06 (s, 3 H), 0.70−0.68 (m, 1 H), 0.59−0.53 (m, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.0, 179.0, 166.3, 160.1, 156.0, 124.7, 102.9, 83.5, 62.3, 48.8, 48.6, 48.2, 42.4, 40.9, 37.2, 36.5, 35.4, 32.8, 30.7, 26.5, 26.0, 23.6, 14.2, 14.0; HRMS (ESI) m/z calcd for $C_{24}H_{32}O_5N^+$ $[M + H]^+$ 414.2275, found 414.2258.

*Ethyl 5-((8R,9S,13S,14S,17S)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)isoxazole-3-carboxylate (**3ii**).* Purified by flash column chromatography (petroleum ether/AcOEt = 1:1, R_f = 0.35), white solid, (79.2 mg, 64% yield): IR (KBr, cm^{-1}) ν 3251, 2927, 2855, 1729, 1619, 1586, 1500, 1451, 1287, 1251, 1223, 1205, 1018, 871, 821, 778; ^1H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1 H), 6.95 (d, J = 8.5 Hz, 1 H), 6.72 (s, 1 H), 6.49−6.46 (m, 1 H), 6.42 (s, 1 H), 5.86 (s, 1 H), 4.36 (q, J = 7.1 Hz, 2 H), 2.73−2.69 (m, 2 H), 2.30−2.23 (m, 1 H), 2.14−2.11 (m, 1 H), 2.03−1.97 (m, 1 H), 1.87−1.81 (m, 3 H), 1.69−1.65 (m, 1 H), 1.48−1.36 (m, 3 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.26−1.22 (m, 2 H), 0.94 (s, 3 H), 0.62−0.56 (m, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 181.1, 160.1, 155.8, 155.4, 137.5, 130.6, 126.4, 115.4, 113.2, 103.2, 82.7, 79.6, 62.2, 48.9, 48.4, 43.5, 39.6, 37.1, 33.4, 29.6, 27.6, 26.4, 23.6, 14.4; HRMS (ESI) m/z calcd for $C_{24}H_{29}O_5NNa^+$ $[M + Na]^+$ 434.1938, found 434.1920.

*Ethyl 5-([1,1′-Biphenyl]-4-yl)-4,5-dihydroisoxazole-3-carboxylate (**5a**).*[17e] Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), pale yellow solid (80.8 mg, 91% yield): ^1H NMR

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(400 MHz, $CDCl_3$) δ 7.63−7.58 (m, 4 H), 7.47−7.35 (m, 5 H), 5.84 (dd, J = 8.9, 11.5 Hz, 1 H), 4.38 (q, J = 7.1 Hz, 2 H), 3.67 (dd, J = 11.5, 17.8 Hz, 1 H), 3.27 (dd, J = 8.9, 17.8 Hz, 1 H), 1.39 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.9, 151.5, 141.9, 140.7, 138.7, 129.1, 127.9, 127.9, 127.4, 126.7, 85.1, 62.5, 41.7, 14.4; HRMS (ESI) m/z calcd for $C_{18}H_{18}O_3N^+$ $[M + H]^+$ 296.1281, found 296.1287.

*Ethyl 5-Phenyl-4,5-dihydroisoxazole-3-carboxylate (**5b**).*[17e] Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), pale yellow oil (57.1 mg, 87% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.31 (m, 5 H), 5.79 (dd, J = 8.9, 11.6 Hz, 1 H), 4.36 (q, J = 7.2 Hz, 2 H), 3.64 (dd, J = 11.6, 17.8 Hz, 1 H), 3.22 (dd, J = 8.9, 17.8 Hz, 1 H), 1.38 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.9, 151.5, 139.9, 129.2, 129.0, 126.2, 85.3, 62.5, 41.8, 14.5.

*Ethyl 5-(4-Bromophenyl)-4,5-dihydroisoxazole-3-carboxylate (**5c**).*[17e] Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), pale yellow oil (74.5 mg, 83% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.5 Hz, 2 H), 7.19 (d, J = 8.5 Hz, 2 H), 5.73 (dd, J = 8.7, 11.6 Hz, 1 H), 4.35 (q, J = 7.2 Hz, 2 H), 3.64 (dd, J = 11.6, 17.8 Hz, 1 H), 3.16 (dd, J = 8.7, 17.8 Hz, 1 H), 1.37 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.7, 151.4, 138.9, 132.3, 127.8, 123.0, 84.4, 62.6, 41.8, 14.4.

*Ethyl 5-(4-Nitrophenyl)-4,5-dihydroisoxazole-3-carboxylate (**5d**).*[17e] Purified by flash column chromatography (petroleum ether/AcOEt = 8:1), pale yellow oil (68.0 mg, 86% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.8 Hz, 2 H), 7.51 (d, J = 8.8 Hz, 2 H), 5.89 (dd, J = 8.2, 11.8 Hz, 1 H), 4.36 (q, J = 7.2 Hz, 2 H), 3.75 (dd, J = 11.7, 17.8 Hz, 1 H), 3.19 (dd, J = 8.2, 17.8 Hz, 1 H), 1.37 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 151.4, 148.3, 147.0, 126.9, 124.5, 83.6, 62.8, 42.2, 14.4; HRMS (ESI) m/z calcd for $C_{12}H_{12}O_5N_2Na^+$ $[M + Na]^+$ 287.0638, found 287.0640.

*Ethyl 5-(4-Fluorophenyl)-4,5-dihydroisoxazole-3-carboxylate (**5e**).*[17e] Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), pale yellow oil (64.2 mg, 90% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.28 (m, 2 H), 7.08−7.04 (m, 2 H), 5.76 (dd, J = 8.9, 11.5 Hz, 1 H), 4.36 (q, J = 7.1 Hz, 2 H), 3.63 (dd, J = 11.5, 17.8 Hz, 1 H), 3.18 (dd, J = 8.9, 17.8 Hz, 1 H), 1.37 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.1 (C−F, $1J_{C-F}$ = 247.7 Hz), 160.8, 151.5, 135.6 (C−F, $4J_{C-F}$ = 3.2 Hz), 128.1 (C−F, $3J_{C-F}$ = 8.3 Hz), 116.2 (C−F, 2 J_{C-F} = 21.7 Hz), 84.6, 62.5, 41.8, 14.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.97 to −111.05 (m, 1 F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −113.01 (s, 1 F).

*Ethyl 5-(4-(Trifluoromethyl)phenyl)-4,5-dihydroisoxazole-3-carboxylate (**5f**).*[17e] Purified by flash column chromatography (petroleum ether/AcOEt = 15:1), white solid (73.8 mg, 86% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 2 H), 7.43 (d, J = 8.2 Hz, 2 H), 5.83 (dd, J = 8.5, 11.6 Hz, 1 H), 4.34 (q, J = 7.1 Hz, 2 H), 3.69 (dd, J = 11.7, 17.8 Hz, 1 H), 3.17 (dd, J = 8.4, 17.8 Hz, 1 H), 1.35 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.5, 151.4, 143.9, 131.0 (C−F, $2J_{C-F}$ = 32.6 Hz), 126.4, 126.1 (C−F, $3J_{C-F}$ = 3.8 Hz), 124.1 (C−F, $1J_{C-F}$ = 272.0 Hz), 84.1, 62.6, 42.0, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.70 (s, 1 F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −62.70 (s, 1 F); HRMS (ESI) m/z calcd for $C_{13}H_{12}O_3NF\ _3Na^+$ $[M + Na]^+$ 310.0661, found 310.0662.

*Ethyl 5-(4-Methoxyphenyl)-4,5-dihydroisoxazole-3-carboxylate (**5g**).*[15a] Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), yellow oil (54.5 mg, 73% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 5.73 (dd, J = 9.4, 11.3 Hz, 1 H), 4.37 (q, J = 7.1 Hz, 2 H), 3.81 (s, 1 H), 3.59 (dd, J = 11.5, 17.8 Hz, 1 H), 3.20 (dd, J = 9.2, 17.8 Hz, 1 H), 1.38 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0, 160.2, 151.5, 131.6, 127.8, 114.5, 85.3, 62.4, 55.6, 41.4, 14.4.

*Ethyl 5-(2-Chlorophenyl)-4,5-dihydroisoxazole-3-carboxylate (**5h**).*[17e] Purified by flash column chromatography (petroleum ether/AcOEt = 30:1), colorless oil (57.2 mg, 75% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.45 (m, 1 H), 7.40−7.38 (m, 1 H), 7.32−7.25 (m, 2 H), 6.07 (dd, J = 7.8, 11.7 Hz, 1 H), 4.35 (q, J = 7.2 Hz, 2 H), 3.79 (dd, J = 11.7, 17.9 Hz, 1 H), 3.09 (dd, J = 7.8, 17.9 Hz, 1 H), 1.37 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 151.6, 138.0, 131.4, 130.0, 129.8, 127.6, 126.7, 82.1, 62.5, 41.6, 14.4.

*Ethyl 5-(m-Tolyl)-4,5-dihydroisoxazole-3-carboxylate (**5i**).*[17e] Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), colorless oil (58.9 mg, 84% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.24 (m, 1 H), 7.15−7.10 (m, 3 H), 5.75 (dd, J = 8.9, 11.5 Hz, 1 H), 4.36 (q, J = 7.2 Hz, 2 H), 3.62 (dd, J = 11.6, 17.8 Hz, 1 H), 3.21 (dd, J = 8.9, 17.8 Hz, 1 H), 2.36 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.9, 151.4, 139.8, 139.0, 129.7, 129.1, 126.8, 123.3, 85.3, 62.4, 41.7, 21.7, 14.4; HRMS (ESI) m/z calcd for $C_{13}H_{16}O_3N^+$ $[M + H]^+$ 234.1125, found 234.1128.

*Ethyl 5-Methyl-5-phenyl-4,5-dihydroisoxazole-3-carboxylate (**5j**).*[17e] Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), colorless oil (60.7 mg, 87% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.35 (m, 4 H), 7.31−7.27 (m, 1 H), 4.33 (q, J = 7.1 Hz, 2 H), 3.42−3.30 (m, 2 H), 1.77 (s, 3 H), 1.36 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0, 151.3, 144.6, 128.9, 128.0, 124.7, 91.5, 62.3, 47.4, 28.4, 14.4.

*Ethyl 5-Hexyl-4,5-dihydroisoxazole-3-carboxylate (**5k**).*[15a] Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), colorless oil (62.5 mg, 92% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 4.82−4.74 (m, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 3.23 (dd, J = 11.0, 17.5 Hz, 1 H), 2.82 (dd, J = 8.5, 17.5 Hz, 1 H), 1.78−1.70 (m, 1 H), 1.59−1.53 (m, 1 H), 1.43−1.39 (m, 1 H), 1.37−1.33 (m, 4 H), 1.31−1.27 (m, 6 H), 0.87 (t, J = 6.9 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2, 151.7, 84.5, 62.3, 38.7, 35.4, 31.9, 29.3, 25.3, 22.8, 14.4, 14.3.

*Ethyl 5-(Trimethylsilyl)-4,5-dihydroisoxazole-3-carboxylate (**5l**).*[17f] Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), light yellow oil (49.2 mg, 76% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 (q, J = 7.2 Hz, 2 H), 4.16 (dd, J = 12.4, 15.7 Hz, 1 H), 3.31 (dd, J = 12.4, 16.7 Hz, 1 H), 2.92 (dd, J = 15.7, 16.7 Hz, 1 H), 1.33 (t, J = 7.2 Hz, 3 H), 0.10 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3, 151.6, 77.6, 62.2, 36.5, 14.4, −3.9; HRMS (ESI) m/z calcd for $C_9H_{18}O_3NSi^+$ $[M + H]^+$ 216.1050, found 216.1059.

*Diethyl 4,5-Dihydroisoxazole-3,5-dicarboxylate (**5m**).*[17g] Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), colorless oil (55.0 mg, 85% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 5.14 (t, J = 10.0 Hz, 1 H), 4.30 (q, J = 7.2 Hz, 2 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.44 (d, J = 10.0 Hz, 2 H), 1.31 (t, J = 7.2 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.1, 160.0, 151.3, 80.1, 62.5, 62.4, 37.8, 14.3, 14.2.

*5-Benzyl 3-Ethyl 4,5-Dihydroisoxazole-3,5-dicarboxylate (**5n**).*[6d] Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), pale yellow oil (68.1 mg, 82% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 5 H), 5.24−5.17 (m, 3 H), 4.32 (q, J = 7.1 Hz, 2 H), 3.50−3.43 (m, 2 H), 1.34 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.9, 160.0, 151.3, 135.0, 128.9, 128.9, 128.6, 80.0, 67.9, 62.6, 37.8, 14.3.

*5-Benzyl 3-Ethyl 5-Methyl-4,5-dihydroisoxazole-3,5-dicarboxylate (**5o**).* Purified by flash column chromatography (petroleum ether/AcOEt = 15:1, R_f = 0.38), pale yellow oil (84.8 mg, 97% yield): IR (KBr, cm^{-1}) ν 2984, 2941, 1719, 1595, 1381, 1342, 1269, 1130, 1018, 941, 859, 781, 747, 736; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.23 (m, 5 H), 5.13 (s, 1 H), 4.24 (q, J = 7.2 Hz, 2 H), 3.62 (d, J = 18.0 Hz, 1 H), 2.99 (d, J = 18.0 Hz, 1 H), 1.58 (s, 3 H), 1.26 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.6, 160.2, 151.2, 135.2, 128.8, 128.7, 128.3, 88.7, 67.9, 62.4, 43.6, 23.5, 14.3; HRMS (ESI) m/z calcd for $C_{15}H_{18}O_5N^+$ $[M + H]^+$ 292.1179, found 292.1179.

*Ethyl 5-Methyl-5-(prop-1-en-2-yl)-4,5-dihydroisoxazole-3-carboxylate (**5p**).* Purified by flash column chromatography (petroleum ether/AcOEt = 50:1, R_f = 0.40), colorless oil (43.3 mg, 73% yield): IR (KBr, cm^{-1}) ν 1719, 1588, 1446, 1340, 1261, 1127, 1018, 956, 810; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (s, 1 H), 4.90 (s, 1 H), 4.33 (q, J = 7.1 Hz, 2 H), 3.19 (d, J = 17.6 Hz, 1 H), 2.97 (d, J = 17.6 Hz, 1 H), 1.79 (s, 3 H), 1.54 (s, 3 H), 1.36 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2, 151.0, 145.5, 111.9, 92.3, 62.3, 44.2, 25.5,

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18.8, 14.5; HRMS (ESI) m/z calcd for $C_{10}H_{16}O_3N^+$ $[M + H]^+$ 198.1125, found 198.1126.

*Diethyl 5,5′-Dimethyl-4,4′,5,5′-tetrahydro-[5,5′-biisoxazole]-3,3′-dicarboxylate (**5q**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1, R_f = 0.52), light yellow oil (61.2 mg, 65% yield): IR (KBr, cm^{-1}) ν 2959, 2941, 1740, 1596, 1455, 1381, 1267, 1132, 928, 748, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36−4.29 (m, 4 H), 3.48 (d, J = 17.8 Hz, 1 H), 3.17 (d, J = 17.8 Hz, 1 H), 2.92 (dd, J = 12.6, 18.0 Hz, 2 H), 1.50 (s, 3 H), 1.45 (s, 3 H), 1.37−1.33 (m, 6 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8, 160.7, 151.4, 151.2, 93.0, 93.0, 62.6, 62.4, 42.3, 41.1, 23.4, 22.3, 14.4, 14.4; HRMS (ESI) m/z calcd for $C_{14}H_{21}O_6N_2^+$ $[M + H]^+$ 313.1394, found 313.1394.

*Ethyl (3aS,5S,7S,7aS)-6,6,7a-Trimethyl-3a,4,5,6,7,7a-hexahydro-5,7-methanobenzo[d]isoxazole-3-carboxylate (**5r**).*[5g] Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), light yellow oil (43.1 mg, 57% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 4.38−4.30 (m, 2 H), 3.24 (dd, J = 4.0, 10.9 Hz, 1 H), 2.33−2.22 (m, 2 H), 2.18−2.15 (m, 1 H), 1.97−1.93 (m, 1 H), 1.75 (dt, J = 3.6, 14.0 Hz, 1 H), 1.38−1.35 (m, 6 H), 1.29 (s, 3 H), 1.01 (d, J = 10.9 Hz, 1 H), 0.92 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4, 155.1, 95.6, 62.1, 49.9, 44.3, 39.4, 38.2, 30.7, 27.3, 27.2, 26.8, 23.4, 14.5.

*Ethyl (3aR,5R,7R,7aS)-6,6,7a-Trimethyl-3a,4,5,6,7,7a-hexahydro-5,7-methanobenzo[d]isoxazole-3-carboxylate (**5s**).* Purified by flash column chromatography (petroleum ether/AcOEt = 50:1, R_f = 0.44), light yellow oil (43.3 mg, 58% yield): IR (KBr, cm^{-1}) ν 2927, 2873, 1718, 1583, 1457, 1378, 1269, 1248, 1142, 1111, 1024, 955, 800, 771; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38−4.30 (m, 2 H), 3.24 (dd, J = 4.0, 10.9 Hz, 1 H), 2.33−2.22 (m, 2 H), 2.18−2.15 (m, 1 H), 1.97−1.93 (m, 1 H), 1.75 (dt, J = 3.6, 14.0 Hz, 1 H), 1.38−1.35 (m, 6 H), 1.29 (s, 3 H), 1.01 (d, J = 10.9 Hz, 1 H), 0.92 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4, 155.1, 95.6, 62.1, 49.9, 44.3, 39.4, 38.2, 30.7, 27.3, 27.2, 26.8, 23.4, 14.5; HRMS (ESI) m/z calcd for $C_{14}H_{22}O_3N^+$ $[M + H]^+$ 252.1594, found 252.1598.

*3-Ethyl 4,5-Dimethyl (4S,5S)-4,5-Dihydroisoxazole-3,4,5-tricarboxylate (**5t**).*[17h] Purified by flash column chromatography (petroleum ether/AcOEt = 6:1), pale yellow oil (29.7 mg, 38% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (d, J = 6.2 Hz, 1 H), 4.64 (d, J = 6.2 Hz, 1 H), 4.37−4.30 (m, 2 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 1.33 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 168.0, 159.3, 149.4, 83.8, 63.0, 55.5, 53.8, 53.7, 14.3; HRMS (ESI) m/z calcd for $C_{10}H_{13}O_7NNa^+$ $[M + Na]^+$ 282.0584, found 282.0590.

*Ethyl 3-Cyano-4,5-dihydroisoxazole-5-carboxylate (**5u**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1, R_f = 0.42), colorless oil (34.9 mg, 69% yield): IR (KBr, cm^{-1}) ν 2245, 1735, 1574, 1438, 1321, 1233, 937, 886, 806; ^1H NMR (400 MHz, $CDCl_3$) δ 5.26 (dd, J = 7.6, 11.8 Hz, 1 H), 4.28 (q, J = 7.2 Hz, 2 H), 3.55−3.41 (m, 2 H), 1.33 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.0, 134.8, 110.3, 80.5, 63.1, 39.0, 14.3; HRMS (ESI) m/z calcd for $C_7H_9O_3N_2^+$ $[M + H]^+$ 169.0608, found 169.0615.

*cis-Methyl 3a,5,6,6a-tetrahydro-4H-cyclopenta[d]isoxazole-3-carboxylate (**5v**).*[17i] Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), colorless oil (30.5 mg, 60% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 5.20−5.17 (m, 1 H), 3.81−3.76 (m, 4 H), 2.09−2.05 (m, 1 H), 1.96−1.91 (m, 1 H), 1.77−1.60 (m, 3 H), 1.38−1.29 (m, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4, 153.3, 90.5, 52.7, 51.0, 35.7, 31.6, 23.2.

*5-([1,1′-Biphenyl]-4-yl)-3-(trifluoromethyl)-4,5-dihydroisoxazole (**5w**).* Purified by flash column chromatography (petroleum ether/AcOEt = 50:1, R_f = 0.50), colorless oil (68.0 mg, 78% yield): IR (KBr, cm^{-1}) ν 1630, 1488, 1395, 1260, 1180, 1153, 1137, 1085, 925, 852, 832, 769, 730, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.58 (m, 4 H), 7.48−7.44 (m, 2 H), 7.42−7.38 (m, 3 H), 5.89 (dd, J = 9.2, 11.2 Hz, 1 H), 3.64 (dd, J = 11.5, 17.5 Hz, 1 H), 3.23 (dd, J = 8.9, 17.5 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.8 (C−F, $2J_{C-F}$ = 37.2 Hz), 142.4, 140.6, 138.0, 129.2, 128.1, 128.0, 127.5, 126.7, 120.0 (C−F, $1J_{C-F}$ = 272.0 Hz), 85.0, 40.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.26 (s, 1 F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −66.26 (s, 1 F); HRMS (ESI) m/z calcd for $C_{16}H_{13}ONF_3^+$ $[M + H]^+$ 292.0944, found 292.0950.

*Ethyl 5,5-Diphenyl-4,5-dihydroisoxazole-3-carboxylate (**5x**).*[17j] Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), colorless solid (59.5 mg, 67% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 10 H), 4.33 (q, J = 7.1 Hz, 2 H), 3.84 (s, 2 H), 1.35 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.9, 151.4, 143.3, 128.8, 128.3, 126.3, 95.1, 62.5, 47.1, 14.4; HRMS (ESI) m/z calcd for $C_{18}H_{17}O_3NNa^+$ $[M + Na]^+$ 318.1101, found 318.1104.

*3,4-Bis(ethoxycarbonyl)-1,2,5-oxadiazole 2-Oxide (**6**).*[5g] Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), colorless oil (31.2 mg, 30% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 4.49 (q, J = 7.1 Hz, 2 H), 4.44 (q, J = 7.1 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H), 1.38 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.0, 155.5, 148.7, 107.1, 64.0 (2C), 14.3, 14.2; HRMS (ESI) m/z calcd for $C_8H_{10}O_6N_2Na^+$ $[M + Na]^+$ 253.0431, found 253.0436.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02281.

^1H, ^{13}C, and ^{19}F NMR spectra and HRMS spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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