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Re-determination of the Structure of a Water-Soluble Hypervalent Iodine(V) Reagent AIBX and Its Synthetic Utility in the Oxidation of Alcohols and Synthesis of Isoxazoline *N*-Oxides

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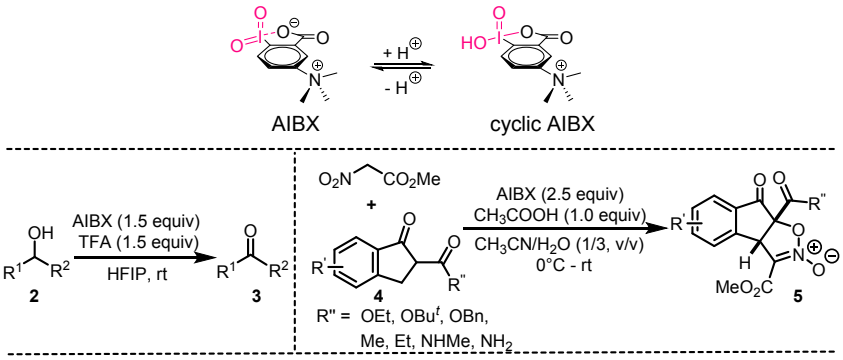


ABSTRACT: The structure of a water-soluble hypervalent iodine(V) reagent AIBX is re-examined through its single crystal X-ray analysis and theoretical calculation including Mayer bond order and localized orbital locator (LOL), and AIBX is believed to be a *pseudocyclic* iodylarene because of the strong electron-withdrawing nature of the trimethylammonium cation on its phenyl ring, which would decrease the electron density of carboxylic anion and make *ortho*-carboxyl oxygen anion incapable to form hypervalent bond with iodine atom. However, the cyclic benziodoxole structure of AIBX could be obtained by adding a Brønsted acid, which was supported by the calculation result including the increase of Mayer bond order and the shortening of I-O bond length. Moreover, the fact that the system of AIBX and TFA could oxidize various alcohols to their corresponding carbonyl compounds would indicate that AIBX constitute to be a cyclic benziodoxole structure under acidic conditions. In addition, an efficient method has been developed for the synthesis of isoxazoline *N*-oxides *via* AIBX-induced dehydrogenative cyclization using *β*-keto esters as substrates and methyl nitroacetate as a nucleophile.

Introduction

IBX is a commonly used hypervalent iodine(V) reagent owing to its rich reactivities including the efficient oxidation of alcohols.[1] It is worth noting that IBX has poor solubility in water. To improve the water-solubility of IBX, a hypervalent iodine(V) reagent called AIBX having trimethylammonium group on the phenyl ring was designed and synthesized by our

group in 2011,[2a] and we believed that AIBX was an IBX's derivative with a five-membered heterocyclic benziodoxole structure initially (Figure 1, **1A**), not to be *pseudocyclic* iodylarene (Figure 1, **1B**), and then we focused on the exploration of the reactivity of AIBX. Since the first reactivity of AIBX-mediated dehydrogenation of various six-membered *β*-keto esters was found, our group has reported methods of using AIBX-induced dehydrogenative *α*,*β*'-bifunctionalization of *β*-keto esters to construct 2,3-dihydrofurans, cyclopropanes and epoxides so far.[2b-f]

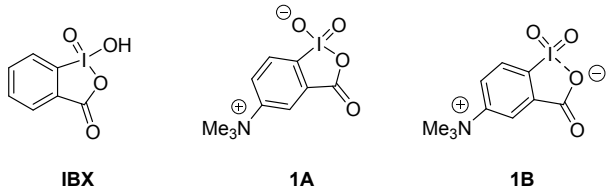
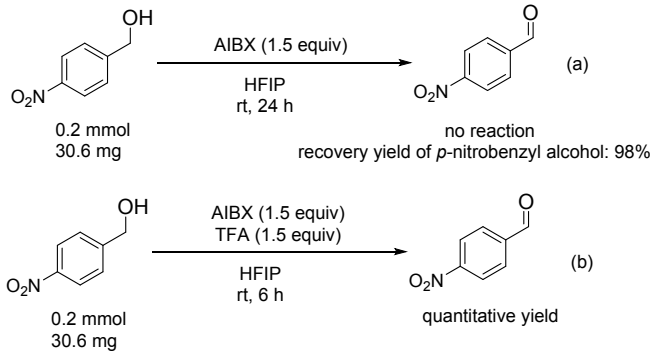


Figure 1. IBX and AIBX (heterocyclic benziodoxole 1A and *pseudocyclic* 1B)

Then, we tried the oxidation of alcohols by AIBX. The reaction was conducted with *p*-nitrobenzyl alcohol and AIBX in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at room temperature (Scheme 1a). To our surprise, it was found that the oxidation of *p*-nitrobenzyl alcohol by AIBX did not happen. However, when trifluoroacetic acid (TFA) was added into the system, the reaction did oxidize *p*-nitrobenzyl alcohol to its corresponding aldehyde in a quantitative yield (Scheme 1b). Notably, it is generally known that IBX can efficiently oxidize various alcohols to their corresponding carbonyl compounds.[3] On the other hand, noncyclic iodylarenes such as $PhIO_2$ are not effective oxidants toward alcohols without acid additives.[4] Because of the oxidative reactivity of AIBX in alcohol oxidation is identical to $PhIO_2$ rather than IBX having a five-membered heterocyclic benziodoxole structure,[4e] we speculated that AIBX would adopt a *pseudocyclic* structure **1B**.

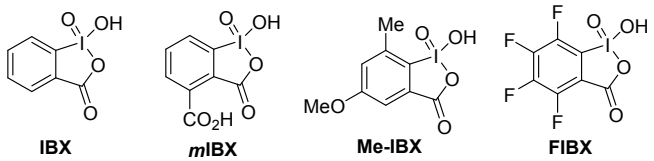
Scheme 1. The Oxidation of *p*-Nitrobenzyl Alcohol by AIBX



In general, IBX and its analogs with a bond distance between the iodine(V) atom and the *ortho*-carboxyl oxygen atom in the range of 2.00-2.48 Å can be classified as cyclic benziodoxole iodylarenes (Figure 2a) , such as IBX,[5a] *m*IBX,[5b] Me-IBX[5c] and FIBX;[5d] while iodylarenes with the intramolecular I···O bond distance longer than 2.50 Å are considered to be *pseudocyclic* iodylarenes[6] (Figure 2b), such as IBX-amides,[4b] IBX-esters[4c] and IBX-SO_3K.[4e] Therefore, for AIBX, it is uncertain whether

AIBX is cyclic benziodoxole **1A** or *pseudocyclic* iodylarenes **1B** if only the intramolecular I···O bond distance of 2.498 Å, which is a boundary value, is used as a criterion.

(a) Cyclic benziodoxole iodine(V) reagents with an *ortho*-carboxy group to the iodine



(b) *Pseudocyclic* iodine(V) reagents with an *ortho*-carboxy group to the iodine

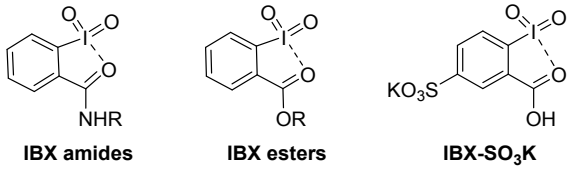


Figure 2. Five-Membered Heterocyclic and *Pseudocyclic* Iodine(V) Reagents

Results and Discussion

The intramolecular I(1)···O(1) distance is 2.498 Å shown in Figure 3, a critical value for determining whether AIBX is cyclic benziodoxole iodylarenes **1A** or not, which is longer than that in IBX (2.263 Å) but closer to that in IBX-SO_3K (2.61 Å) which is a *pseudocyclic* iodylarene. Therefore, we consider AIBX to be a *pseudocyclic* iodylarenes **1B**. As shown in Figure 4a, for the *pseudocyclic* iodylarenes,[7] the difference of bond length between I-O(2) and I-O(3) varies in the range of 0.001-0.030 Å; while it varies in the range of 0.036-0.141 Å for cyclic benziodoxole iodylarenes (Figure 4b). The difference between I-O (2) and I-O (3) bond length in AIBX is 0.014 Å, indicating that AIBX belongs to *pseudocyclic* iodylarenes. Therefore, it is more likely that AIBX is present as *pseudocyclic* iodylarene **1B**.

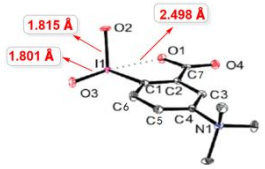
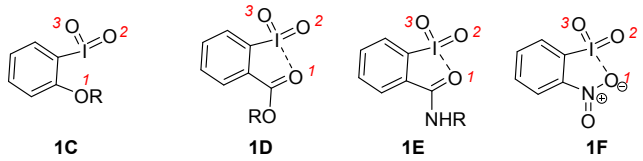
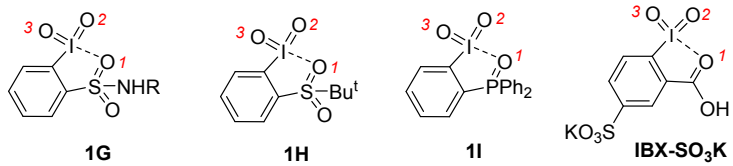


Figure 3. Perspective Drawing of AIBX with 50% Ellipsoid Probability

(a) Pseudocyclic iodylarenes

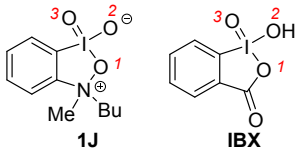


	1C		1D		1E	1F	
	R = *n*Bu	R = *i*Pr	R = Me	R = *i*Pr	R = (*S*)-CH(Bn)CO_2Me		
$d_{I\text{-}O1}$ (Å)	2.931	2.882	2.697	2.818	2.571	2.682	2.767 [a]
$d_{I\text{-}O2}$ (Å)	1.793	1.806	1.794	1.817	1.807	1.787	1.813
$d_{I\text{-}O3}$ (Å)	1.792	1.803	1.806	1.803	1.823	1.805	1.817
$\Delta d = \lvert d_{I\text{-}O2} - d_{I\text{-}O3} \rvert$ (Å)	0.001	0.003	0.012	0.014	0.016	0.018	0.004



	1G		1H	1I	IBX-SO_3K
	R = (*S*)-CH(*i*Pr)CO_2Me				
$d_{I\text{-}O1}$ (Å)	2.781	2.858 [a]	2.693	2.603	2.61
$d_{I\text{-}O2}$ (Å)	1.795	1.809	1.822	1.818	1.80
$d_{I\text{-}O3}$ (Å)	1.820	1.820	1.796	1.789	1.83
$\Delta d = \lvert d_{I\text{-}O2} - d_{I\text{-}O3} \rvert$ (Å)	0.025	0.011	0.026	0.029	0.03

(b) Cyclic benziodoxole iodylarenes



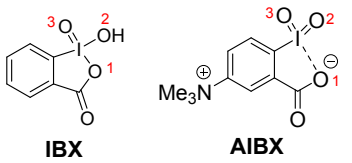
	1J	IBX
$d_{I\text{-}O1}$ (Å)	2.366	2.466 [a]	2.263
$d_{I\text{-}O2}$ (Å)	1.771	1.745	1.925
$d_{I\text{-}O3}$ (Å)	1.807	1.836	1.784
$\Delta d = \lvert d_{I\text{-}O2} - d_{I\text{-}O3} \rvert$ (Å)	0.036	0.091	0.141

[a] Data for two independent molecules in crystal unit cell.

Figure 4. I-O Bond Lengths and the Difference between I-O(2) and I-O(3) Bond Length in *Pseudocyclic* and Cyclic Benziodoxole Iodylarenes

To further determine the structure of AIBX, we started computational studies based on the X-ray structure of AIBX at the DFT M06-2X/[6-31+G(d) + Lanl2dz(I)] level of theory, especially Mayer bond order (MBO) and localized orbital locator (LOL).

Mayer bond order (MBO)[8] is established to inspect the electronic structures, and it is generally accepted that a lower value of MBO implies a lower bond strength. The hypervalent three-center-four-electron (3c-4e) bond has a theoretical bond order of 1.0, and the endocyclic I-O(1) bond in cyclic benziodoxole iodylarenes has a theoretical bond order of 0.5.[9] As shown in Figure 5, the endocyclic I-O(1) bond in IBX has an MBO value of 0.35, which is close to the theoretical bond order of 0.5. While the endocyclic I···O(1) bond in AIBX has a MBO value of 0.13, much smaller than the theoretical bond order of 0.5, indicating that the probability of forming a hypervalent bond is very small



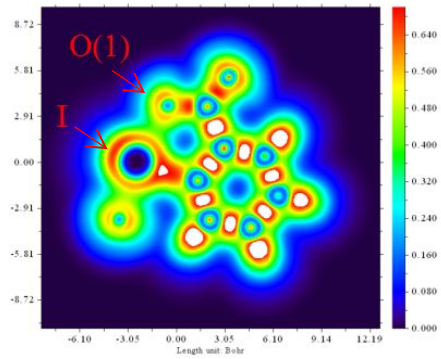
	IBX	AIBX
Mayer bond order	0.35	0.13
$d_{I\text{-}O1}$ from crystals (Å)	2.263	2.498

Figure 5. I-O(1) Mayer Bond Orders and Their Bond Lengths in IBX and AIBX

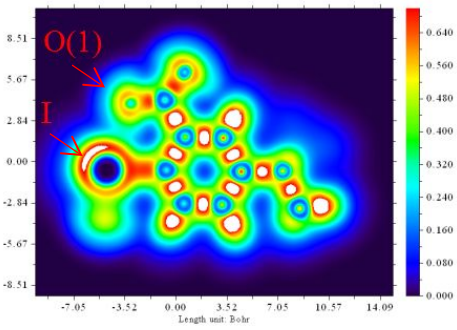
To observe characteristics of hypervalent iodine bond and localization of electron density of bonds, we calculated and visualized localized orbital locator (LOL)[10] of IBX and AIBX (Figure 6). The LOL values are visualized on a blue-green-red color scale, in which blue and red colors indicate no electron and high electron localization respectively, and the green region shows a certain degree of valence electron density between blue and red extremes. In IBX, the green color region between I and O(1) indicated that there was a certain degree of valence electron density between I and O(1), which participated in the formation of hypervalent iodine bond. However, in AIBX, there was a light blue color region between I and O(1), indicating that the electron density between I and O(1) was very low and the intramolecular interaction was thus weak. Consequently, it was most likely that a hypervalent bond was not formed between I and O(1) in AIBX and AIBX was present as *pseudocyclic* iodylarene **1B**, which was consistent with the MBO calculation result.

AIBX is believed to be a *pseudocyclic* iodylarene **1B** through its single crystal X-ray analysis and theoretical calculation including Mayer bond order and localized orbital locator (LOL). The reason for not forming a hypervalent bond between I and O(1) in AIBX was that the trimethylammonium cation inductively withdraws electron density from the aromatic ring, which would decrease the electron density of carboxylic anion and make *ortho*-carboxyl oxygen anion incapable to form hypervalent bond with iodine(V) atom.

Further computational studies showed that when the oxygen atom of the IO_2 in AIBX was protonated, the MBO of I-O(1) increased from 0.13 to 0.36, and the bond length of I-O(1) was shortened from 2.498 Å to 2.07 Å, which were similar to those of IBX, and this indicated that a cyclic benziodoxole structure of AIBX could be achieved by adding an external acid. This was because the iodine(V) center was thus more electrophilic upon protonation to form hypervalent bond with the *ortho*-carboxy oxygen atom. Thus, it was fully understood that the AIBX-TFA system in HFIP[11] had an excellent alcohol oxidation reactivity resulted from the cyclic benziodoxole structure of AIBX upon protonation (Scheme 1b).



IBX

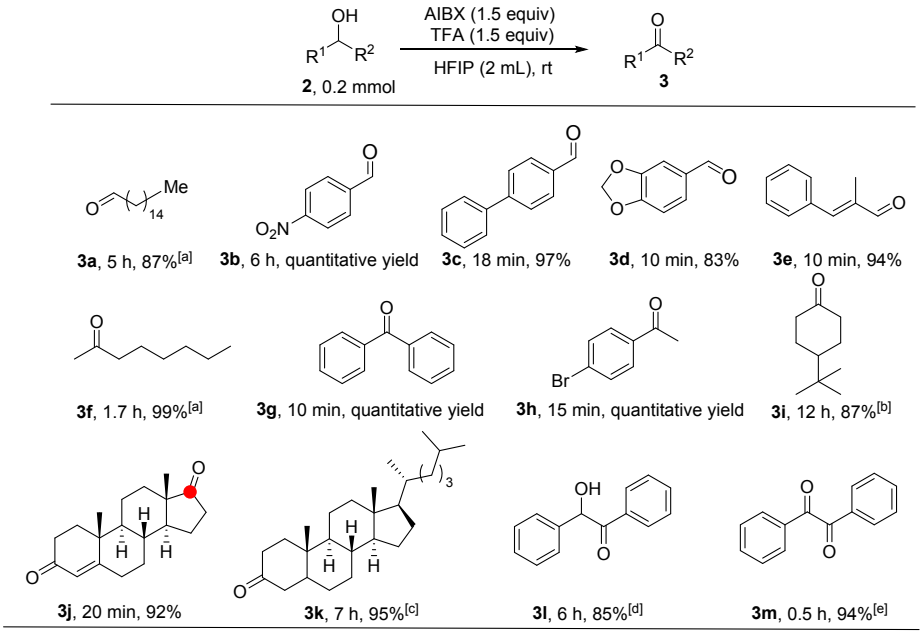


AIBX

Figure 6. Color-Filled Maps of Localized Orbital Locator for IBX and AIBX

A range of alcohols can be oxidized to their corresponding carbonyl compounds by the AIBX-TFA system (Scheme 2). Aliphatic primary alcohol (hexadecan-1-ol **2a**) and benzylic primary alcohols (**2b-d**) were readily oxidized to their corresponding aldehydes **3a-d** in excellent yields without overoxidation to the carboxylic acid. An allylic alcohol 2-methyl-3-phenyl-2-propenol (**2e**) was found to undergo oxidation in an excellent yield of 94% without oxidizing the carbon-carbon double bond. As for acyclic aliphatic secondary alcohol (**2f**), aromatic secondary alcohols (**2g-h**) and cyclic secondary alcohols (4-*tert*-butylcyclohexanol **2i**, testosterone **2j** and dihydrocholesterol **2k**), they were oxidized to their corresponding ketones **3f-k** in excellent yields. 1,2-Diphenylethane-1,2-diol (**2l**) could be oxidized to benzoin (**3l**) or benzil (**3m**) in excellent yield without detection of benzaldehyde from oxidative cleavage of the glycolic C-C bond. It should be noted that excess AIBX was employed to ensure complete conversion of alcohols with a satisfactory reaction rate (e.g., **2a**, **2f, 2i and 2k**). The oxidation of a fluorinated alcohol 1-phenyl-2,2,2-trifluoroethanol was also examined under the optimal conditions, however, no reaction took place after 55 h.

Scheme 2. Substrate Scope of the Oxidation of Alcohols by AIBX-TFA System

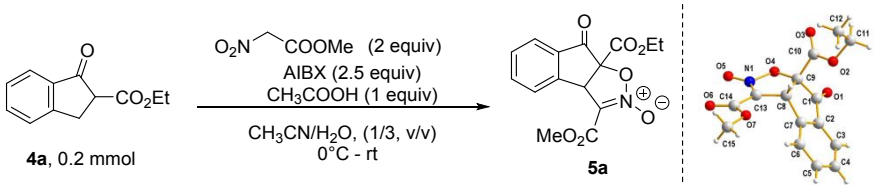


[a] 2.0 equiv AIBX and 2.0 equiv TFA were used. [b] 1.8 equiv AIBX and 1.8 equiv TFA were used. [c] 2.5 equiv AIBX and 2.5 equiv TFA were used. [d] 1.1 equiv AIBX and 1.1 equiv TFA were used. [e] 2.2 equiv AIBX and 2.2 equiv TFA were used.

Furthermore, it was also in the presence of acid (AcOH) that AIBX could effectively facilitate the synthesis of isoxazoline *N*-oxides using *β*-keto esters as substrates and methyl nitroacetate as a nucleophile (Scheme 3). Isoxazoline *N*-oxides are useful heterocyclic structures,[12] and several approaches to isoxazoline *N*-oxides have been developed, such as a tandem nitroaldol-intramolecular cyclization of *α*-haloketones/*α*-haloaldehydes and epoxides,[13] intramolecular oxidative N-O coupling of *β*-hydroxy ketoximes,[14] and [4+1] annulation of nitroalkenes and a carbon nucleophiles.[15] To the best of our knowledge, in the oxidative coupling reactions to synthesize isoxazoline *N*-oxides, other types of substrates have never been reported except for *β*-hydroxy ketoximes.

Scheme 3. Synthesis of Isoxazoline *N*-Oxides Promoted by AIBX

and X-ray crystallography with 50% Ellipsoid Probability

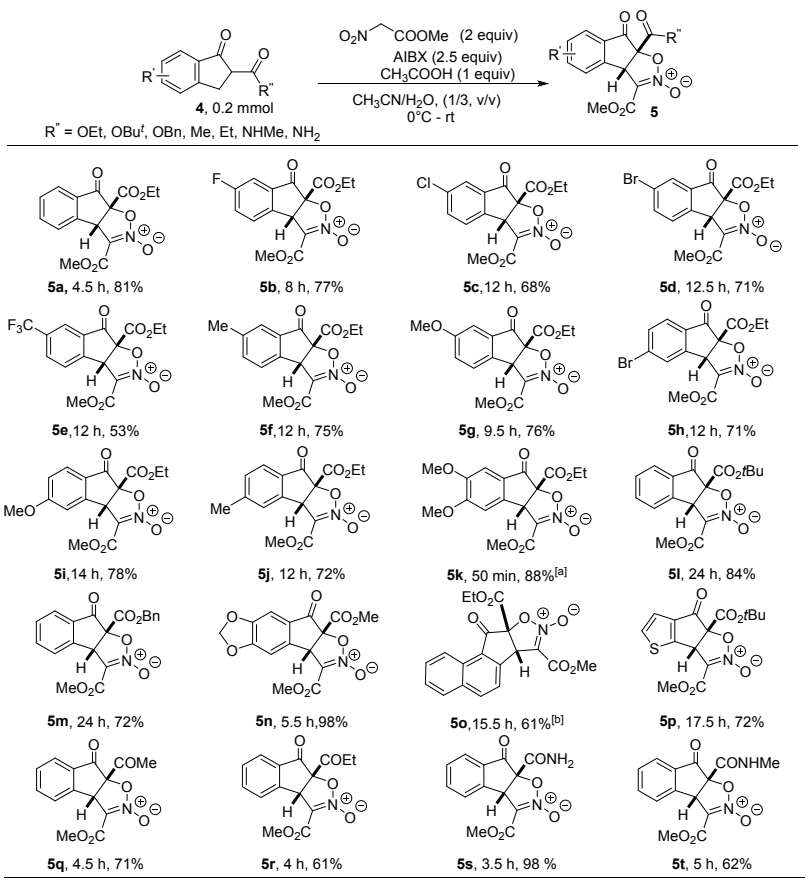


We began our exploration by using starting material **4a** with methyl nitroacetate (2.0 equiv) in the presence of 2.5 equiv of AIBX in a solution of 1:3 (v/v) CH_3CN/H_2O at room temperature, which affording the product **5a** in 56% yield within 6 h, and the structure of **5a** was confirmed by X-ray crystallography. The reaction was also tried with 1.2 equivalents of AIBX and afforded only 45% yield of **5a** after 32 h. Further investigation of reaction conditions revealed that a system of 2.0 equiv of methyl nitroacetate, 2.5 equiv of AIBX, and 1.0 equiv of AcOH in 1:3 (v/v) CH_3CN/ H_2O at 0°C to room temperature was

optimal (for details, see Table S1 of the supporting information. Notably, 2-iodoxybenzoic acid (IBX) was employed as the oxidant under the otherwise identical reaction conditions, and the yield was only 3%. It showed the difference in the chemical structure of IBX and AIBX. When other water-soluble hypervalent iodine reagents, such as *m*IBX, PIBS, IBX-SO_3K, PISA, HTIB and AIBA, were subjected to the standard reaction conditions, the results were disappointing).

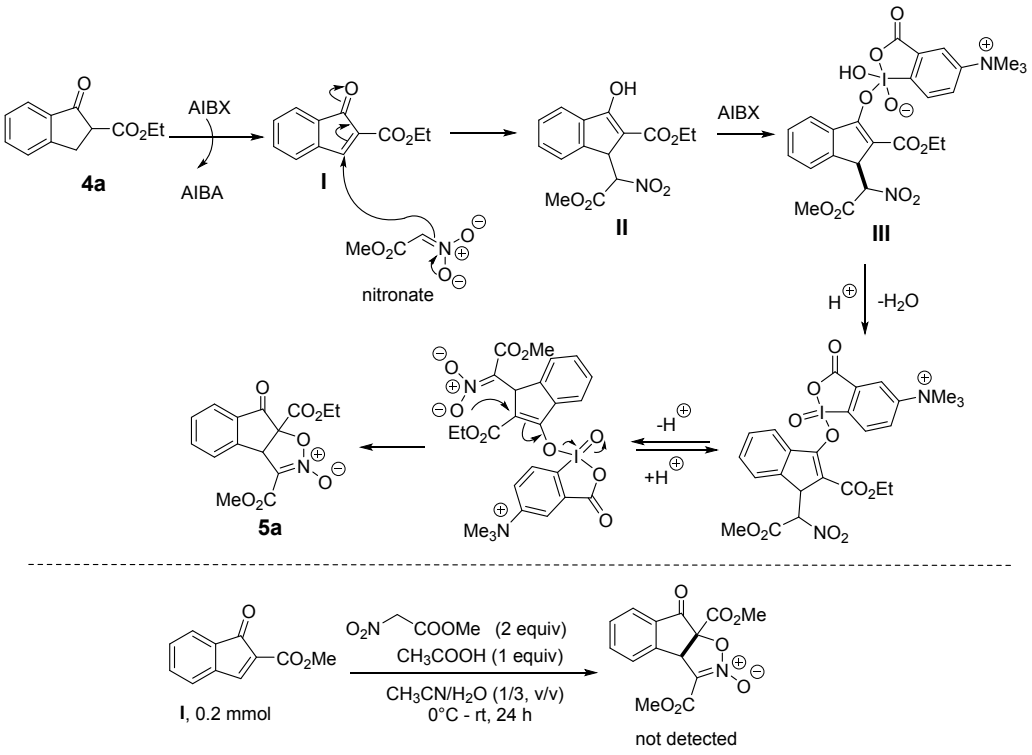
We investigated the generality of the reaction by using various *β*-keto esters, *β*-diketones and *β*-keto amides as substrates (Scheme 4). As expected, *β*-keto esters with electron-donating or -withdrawing groups on the phenyl ring smoothly gave products in high yields (**5b**-**k**), which suggested that the electronic properties of the phenyl ring had little influence on the outcome of the reaction. Substrates bearing *tert*-butyl and benzyl ester groups could also generate the corresponding products **5l** and **5m** (84% and 72% yields, respectively). Substrates with a piperonyl moiety, a naphthalene ring and a thiophene moiety, all of which are oxidizable, were compatible with the present reaction conditions, providing **5n**, **5o** and **5p** (98%, 61% and 78% yields, respectively). Moreover, the reaction of *β*-diketones **4q** and **4r** proceeded smoothly to afford the desired products **5q** and **5r** (71% and 61% yields, respectively). In addition, *β*-keto amides proved to be good substrates for this transformation, and gave the corresponding products **5s** and **5t** in 98% and 62% yields, respectively.

Scheme 4. Substrate Scope of AIBX-Mediated Synthesis of Isoxazoline *N*-Oxides



[a] The reaction was carried out at 40℃. [b] CH_3CH_2COOH was used as additive instead of AcOH.

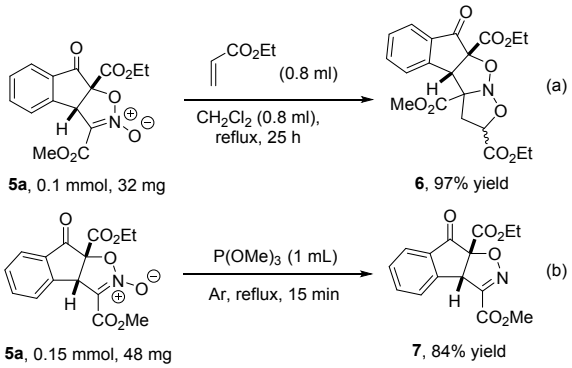
On the basis of our previous work on AIBX-initiated reactions[2b-d], we proposed the mechanism shown in Scheme 5. Firstly, enone **I** was generated *via* AIBX-mediated dehydrogenation. Under the acidic condition, Michael addition of methyl nitroacetate to enone **I** could readily happen. Then the yielding adduct **II** would attack the iodine center of another molecule of AIBX to give a reactive iodine(V) complex **III**. Finally, after removal of one molecule of water, the intramolecular oxidative cyclization would take place which was driven by the release of one AIBA molecule to give **5a**. It was feasible that enone **I** would directly provide a cycloadduct with methyl nitroacetate which would subsequently be oxidized by a hypervalent iodine reagent. In order to check this mechanistic feasibility, enone **I** was prepared separately and was treated with methyl nitroacetate under the standard reaction conditions except for the absence of AIBX. The desired product **5a** was not detected after 24 h, which indicating that an isoxazoline *N*-oxide product might not be obtained from the sequence of [3+2] cycloaddition of enone **I** with methyl nitroacetate first followed by the oxidation by a hypervalent iodine reagent in the reaction system. In addition, AIBX could be regenerated (91%) with dimethyl dioxirane after reaction. Notably, the dehydrogenation of *β*-keto esters mediated by AIBX was a key step, and it was well known that the dehydrogenation of ketones was a typical reactivity of IBX. This also indicated that AIBX was present as a cyclic benziodoxole structure under acidic conditions.



Scheme 5. Proposed mechanism

We investigated the transformations of the isoxazoline *N*-oxides **5**. [3+2] cycloaddition of **5a** as a 1,3-dipolar substrate with electron-poor dipolarophile ethyl acrylate readily produced the fused polycyclic isoxazoline **6** in a yield of 97% (Scheme 6). **5a** was treated with excessive $P(OMe)_3$ to give the deoxygenated isoxazoline **7** in an excellent yield (Scheme 6b).

Scheme 6. Transformations of isoxazoline *N*-oxide 5a



Trifluoroacetic acid was successfully employed in the oxidation of alcohols with AIBX, while acetic acid was used in the efficient formation of isoxazoline *N*-oxides. Can the use of these two acids be interchanged? The reaction was conducted with *p*-nitrobenzyl alcohol under the standard reaction conditions, except for acetic acid in replace of trifluoroacetic acid. After the reaction ran for 24 h, the *p*-nitrobenzaldehyde was obtained in a yield of 23%. Compared with the reaction using trifluoroacetic acid (Scheme 1b), the use of acetic acid significantly reduced the reaction rate and yield. The results showed that trifluoroacetic acid could activate AIBX and improve the oxidation performance of AIBX better than acetic acid. The reason for this phenomenon is that trifluoroacetic acid (pK_a: 3.5 in DMSO) would release more protons to protonate AIBX and thus lead to more cyclic benziodoxole structure of AIBX than that with acetic acid (pK_a: 12.6 in DMSO). Moreover, to observe the influence of the acid for the synthesis of isoxazoline *N*-oxides, the reaction was conducted under the standard reaction conditions, except for trifluoroacetic acid in replace of acetic acid, which affording the desired isoxazoline *N*-oxide in a yield of 22% (Table S1, entry 5). The results showed that acetic acid was suitable for the synthesis of isoxazoline *N*-oxides because the reaction with acetic acid gave 81% yield of the isoxazoline *N*-oxide product (Table S1, entry 2). The conjugated base of an acid can abstract proton of methyl nitroacetate at the α-position to form the corresponding resonance stabilized anion (nitronate), which would react with enone **I** to give a Michael addition product **II** (Scheme 5). It is known that the conjugate base ($CH_3COO^{\ominus}$) of acetic acid is a stronger one than $CF_3COO^{\ominus}$, consequently, $CH_3COO^{\ominus}$ could better abstract proton of methyl nitroacetate at the α-position to produce more nitronate.

Conclusion

In summary, AIBX was re-determined to be a *pseudocyclic* iodylarene **1B** by studying the difference between I-O(2) and I-O(3) bond length in iodylarenes and theoretical calculation including Mayer bond order and localized orbital locator. However, the cyclic benziodoxole structure of AIBX could be achieved by adding a Brønsted acid like TFA. From our work on re-determination of AIBX structure, it was understood that judging whether the hypervalent iodine reagent is cyclized or not is not an easy task. To determine whether the cyclization or not only by a single criterion would be misleading sometimes, however, using a combination of various means including the comprehensive analysis of X-ray crystallography

of reagents, theoretical calculation, and even the comparison of reagent's reactivity is more reliable to give the right structure. This set of methods should be useful for the determination of similar iodine(III/V) heterocyclic structures. As far as reactivity was concerned, AIBX could effectively facilitate the oxidation of alcohols and the synthesis of isoxazoline *N*-oxides under acidic conditions.

Experimental Section

General Information. All the reactions were carried out under atmosphere without any special protection. The distilled CH_3CN and deionized water were used as solvents. The known compounds were synthesized by reported procedures and identified by the comparison of their NMR spectra with reported data in the literatures. The ^1H NMR spectra were recorded at 400 MHz and $^{13}C\{^1H\}$ NMR spectra were measured at 100 MHz using Bruker AV 400 as instrument; $CDCl_3$ was used as the solvent. ^1H NMR spectra are reported as follows: chemical shift in ppm (δ) relative to the chemical shift of $CDCl_3$ at 7.26 ppm, multiplicities, coupling constants (Hz) and integration. $^{13}C\{^1H\}$NMR spectra are reported in ppm (δ) relative to the central line of triplet of $CDCl_3$ at 77.00 ppm. IR spectra were recorded with a FT-IR Bruker EQUINOX55 spectrometer in KBr pellets. High-resolution mass spectroscopy (HRMS) was performed with a high resolution ESI–FTICR mass spectrometer (Varian 7.0 T). The X-ray diffraction data were collected on Bruker SMART-1000 CCD diffractometer.

Typical procedure for alcohols oxidation. To a solution of alcohols (0.2 mmol) in HFIP (2 mL) was added AIBX (101 mg, 1.5 equiv) and TFA (23 μL, 1.5 equiv). The reaction mixture was stirred at room temperature and monitored by TLC. After the starting material was completely consumed, the reaction was quenched with sat. aqueous $NaHCO_3$ (1 mL) and $Na_2S_2O_3$ (1 mL). The separated aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography to afford carbonyl compounds, identical in all respects with a commercial sample.

Hexadecanal (3a).[16] Colorless solid, 41.7 mg, 87% yield, m.p. 32-34 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 2.33-2.37 (m, 2H), 1.53-1.57 (m, 2H), 1.18-1.22 (m, 24 H), 0.81 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.8, 43.9, 31.9, 29.6, 29.3, 29.1, 22.7, 22.1, 14.1.

4-Nitrobenzaldehyde (3b).[17] Beige solid, 31 mg, quantitative yield, m.p. 104-105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.40 (d, *J* = 8.6 Hz, 2H), 8.08 (d, *J* = 8.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.3, 151.1, 140.0, 130.5, 124.3.

4-Biphenylcarboxaldehyde (3c).[17] Colorless solid, 35 mg, 97% yield, m.p. 57-58 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.9, 147.2, 139.7, 135.2, 130.2, 129.0, 128.4, 127.7, 127.3.

Piperonal (3d).[3c] Colorless solid, 32 mg, 83% yield, m.p. 36-38 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.33 (s, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.07 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.3, 153.1, 148.7, 131.8, 128.7, 108.3, 106.9, 102.1.

2-Methylcinnamylaldehyde (3e).[18] Yellow liquid, 41.3 mg, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.43 (m, 3H), 7.27 (s, 1H), 2.08 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.5, 149.8, 138.3, 135.1, 130.0, 129.5, 128.7, 10.9.

2-Octanone (3f).[16] Liquid, 38 mg, 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (t, J = 7.4 Hz, 2H), 2.13 (s, 3H), 1.28 (m, 8H), 0.88 (t, J = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 209.24, 43.71, 31.51, 29.74, 28.76, 23.73, 23.41, 13.93.

Benzophenone (3g).[17] Oil, 38 mg, quantitative yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 4H), 7.59 (t, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.7, 137.5, 132.4, 130.0, 128.2.

Para-bromoacetophenone (3h).[17] Colorless solid, 45 mg, quantitative yield, m.p. 50-51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 2.59 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.0, 135.8, 131.9, 129.8, 128.3, 26.5.

4-Tert-butylcyclohexan-1-one (3i).[19] Colorless solid, 33 mg, 87% yield, m.p. 47-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45-2.20 (m, 4H), 2.12-2.02 (m, 2H), 1.55-1.36 (m, 3H), 0.90 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 212.5, 46.7, 41.3, 32.4, 27.6.

Androstenedione (3j).[20] Colorless solid, 39.5 mg, 92% yield, m.p. 170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (s, 1H), 2.52-2.29 (m, 5H), 2.16-1.93 (m, 4H), 1.87 (d, *J* = 12.9 Hz, 1H), 1.78-1.39 (m, 6H), 1.33-1.24 (m, 2H), 1.21 (s, 3H), 1.17-1.06 (m, 1H), 0.92 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 220.2, 199.1, 170.2, 124.0, 53.7, 50.7, 47.4, 38.5, 35.6, 35.6, 35.0, 33.8, 32.5, 31.2, 30.6, 21.6, 20.2, 17.3, 13.6.

Coprostanone (3k).[19] Colorless solid, 40 mg, 95% yield, m.p. 126-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46-2.20 (m, 3H), 2.12-1.93 (m, 3H), 1.85-1.77 (m, 1H), 1.73-1.65 (m, 1H), 1.64-1.45 (m, 5H), 1.45-1.03 (m, 17H), 1.00 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.6, 1.6 Hz, 7H), 0.67 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 212.2, 56.3, 56.2, 53.8, 46.7, 44.7, 42.6, 39.9, 39.5, 38.5, 38.2, 36.1, 35.8, 35.6, 35.4, 31.7, 29.0, 28.2, 28.0, 24.2, 23.8, 22.8, 22.5, 21.4, 18.6, 12.0, 11.5.

Benzoin (3l).[16] Colorless solid, 36 mg, 85% yield, m.p. 135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2H), 7.54-7.50 (m, 1H), 7.42-7.38 (m, 2H), 7.34-7.26 (m, 5H), 5.95 (s, 1H), 4.56 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.9, 138.9, 133.9, 133.4, 129.1, 129.1, 128.7, 128.6, 127.7, 76.2.

Benzil (3m).[16] Yellow solid, 40 mg, 94% yield, m.p. 94-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.2 Hz, 4H), 7.67 (t, *J* = 7.4 Hz, 2H), 7.52 (t, *J* = 7.7 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.5, 134.9, 133.0, 129.9, 129.0.

Ethyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4a).[2b] Yellow oil, 857 mg, 84% yield; the ratio of keto form to enol form is 5:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.33 (brs, 0.2H), 7.78 (d, *J* = 7.6 Hz, 1.0H), 7.61-7.65 (m, 1.2H), 7.38-7.52 (m, 2.6H), 4.33 (q, *J* = 7.2 Hz, 0.4H), 4.25 (d, *J* = 5.4 Hz, 2.0H), 3.71 (dd, *J* = 4.0 Hz, 8.4 Hz, 0.9H), 3.53-3.59 (m, 1.4H), 3.38 (dd, *J* = 8.4 Hz, 17.2 Hz, 1.1H), 1.37 (t, *J* = 7.2 Hz, 0.6H), 1.31 (t, *J* = 7.2 Hz, 3.1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.5, 169.1, 153.6, 135.3, 135.2, 129.2, 127.7, 126.7, 1265, 124.6, 124.6, 120.6, 102.4, 61.6, 60.0, 53.2, 32.5, 30.2, 14.4, 14.1.

Ethyl 6-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4b).[21] Yellow oil, 833 mg, 75% yield; the ratio of keto form to enol form is 2.3:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.33 (brs, 0.2H), 7.47 (dd, *J* = 8.4, 4.5 Hz, 1.0H), 7.43-7.28 (m, 2.7H), 7.13-7.08 (m, 0.4H), 4.32 (q, *J* = 7.1 Hz, 0.9H), 4.24 (q, *J* = 7.1 Hz, 2.0H), 3.75 (dd, *J* = 8.2, 4.0 Hz, 0.9H), 3.56-3.45 (m, 1.9H), 3.33 (dd, *J* = 17.1, 8.2 Hz, 1.0H), 1.36 (t, *J* = 7.1 Hz, 1.3H), 1.30 (t, *J* = 7.1 Hz, 3.0H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.4, 168.9, 168.6, 168.3, 163.6, 163.3, 161.1, 160.9, 148.9, 138.7, 138.6, 138.3, 137.0, 136.9, 127.9, 127.8, 125.7, 125.6, 123.1, 122.9, 116.4, 116.1, 110.3, 110.1, 107.5,

107.3, 104.3, , 61.7, 60.1, 54.0, 31.9, 29.6, 14.3, 14.0.

Ethyl 6-chloro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4c).[21] Colorless solid, 1.1 g, 92% yield, m.p. 100-101 °C; the ratio of keto form to enol form is 2.2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.34 (brs, 0.1H), 7.73 (d, *J* = 1.9 Hz, 0.9H), 7.61 (t, *J* = 1.2 Hz, 0.4H), 7.59 (d, *J* = 2.0 Hz, 0.4H), 7.57 (d, *J* = 2.1 Hz, 0.5H), 7.46 (s, 0.5H), 7.44 (s, 0.4H), 7.38 (d, *J* = 1.2 Hz, 0.8H), 4.32 (q, *J* = 7.1 Hz, 0.9H), 4.25 (q, *J* = 7.2 Hz, 2.0H), 3.75 (dd, *J* = 8.2, 4.0 Hz, 0.9H), 3.55 (d, *J* = 4.0 Hz, 0.4H), 3.50 (d, *J* = 4.7 Hz, 1.5H), 3.34 (dd, *J* = 17.4, 8.2 Hz, 1.1H), 1.36 (t, *J* = 7.1 Hz, 1.3H), 1.31 (t, *J* = 7.1 Hz, 3.0H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.2, 168.6, 151.6, 141.1, 138.6, 136.7, 135.4, 134.2, 132.9, 129.2, 127.7, 125.7, 124.3, 120.8, 103.9,61.9, 60.3, 53.7, 32.2, 29.8, 14.4, 14.1.

Ethyl 6-bromo-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4d).[21] Colorless solid, 991 mg, 70% yield, m.p. 92-93 °C; the ratio of keto form to enol form is 2.2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.30 (brs, 0.1H), 7.89 (d, *J* = 1.8 Hz, 0.9H), 7.77 (d, *J* = 1.8 Hz, 0.4H), 7.73 (d, *J* = 1.9 Hz, 0.4H), 7.71 (d, *J* = 1.9 Hz, 0.5H), 7.52 (dd, *J* = 8.0, 1.8 Hz, 0.4H), 7.40 (s, 0.5H), 7.38 (s, 0.4H), 7.34 (s, 0.2H), 7.32 (s, 0.2H), 4.32 (q, *J* = 7.1 Hz, 0.9H), 4.25 (q, *J* = 7.1 Hz, 2.0H), 3.74 (dd, *J* = 8.2, 4.0 Hz, 0.9H), 3.52 (d, *J* = 4.0 Hz, 0.4H), 3.48 (d, *J* = 4.2 Hz, 1.5H), 3.32 (dd, *J* = 17.4, 8.2 Hz, 1.0H), 1.36 (t, *J* = 7.1 Hz, 1.4H), 1.31 (t, *J* = 7.1 Hz, 3.0H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.1, 168.6, 152.1, 141.7, 139.0, 138.1, 137.1, 132.0, 128.1, 127.5, 126.1, 123.8, 122.0, 120.8, 103.8, 61.9, 60.3, 53.6, 32.3, 29.9, 14.4, 14.2.

Ethyl 1-oxo-6-(trifluoromethyl)-2,3-dihydro-1H-indene-2-carboxylate (4e).[21] Light brown solid, 748 mg, 55% yield, m.p. 68–69 °C; the ratio of keto form to enol form is 1.3:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.33 (brs, 0.7H), 8.02 (s, 1.0H), 7.87 (s, 0.7H), 7.85 (d, *J* = 8.2 Hz, 1.0H), 7.63-7.66 (m, 1.7H), 7.55 (d, *J* = 7.9 Hz, 0.7H), 4.33 (q, *J* = 7.1 Hz, 1.5H), 4.22-4.28 (m, 2.0H), 3.77 (dd, *J* = 8.3 Hz, *J* = 4.0 Hz, 1.0H), 3.62 (dd, *J* = 17.7 Hz, *J* = 3.4 Hz, 1.0H), 3.56 (s, 1.5H), 3.43 (dd, *J* = 17.7 Hz, *J* = 8.3 Hz, 1.0H), 1.37 (t, *J* = 7.1 Hz, 2.3H), 1.31 (t, *J* = 7.1 Hz, 3.0H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.4, 168.6, 156.9, 146.6, 137.7, 135.8, 132.0, 130.9, 129.8, 127.5, 125.2, 124.3, 123.7, 122.1, 117.9, 104.2, 62.2, 60.6, 53.6, 32.9, 30.5, 14.6, 14.3.

Ethyl 6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4f).[21] Yellow oil, 928 mg, 85% yield; the ratio of keto form to enol form is 6.7:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 0.9H), 7.45 (d, *J* = 7.8 Hz, 1.1H), 7.39 (d, *J* = 7.9 Hz, 1.0H), 4.32 (q, *J* = 7.1 Hz, 0.3H), 4.24 (q, *J* = 7.7 Hz, 2.0H), 3.71 (dd, *J* = 8.2, 4.0 Hz, 1.0H), 3.52 (d, *J* = 4.1 Hz, 0.4H), 3.47 (d, *J* = 3.0 Hz, 0.9H), 3.32 (dd, *J* = 17.0, 8.2 Hz, 1.0H), 2.43 (s, 0.4H), 2.40 (s, 3.0H), 1.36 (t, *J* = 7.1 Hz, 0.4H), 1.31 (t, *J* = 7.1 Hz, 3.0H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.6, 169.2, 151.0, 140.4, 137.8, 137.1, 136.64, 135.4, 130.3, 128.8, 126.2, 124.5, 124.4, 121.0, 102.6, 61.6, 60.0, 53.6, 32.1, 29.9, 21.3, 21.0, 14.4, 14.2.

Ethyl 6-methoxy--1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4g).[21] Colorless solid, 1.07 g, 91% yield, m.p. 58-60 °C; the ratio of keto form to enol form is 6.7:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.44 (brs, 0.1H) 7.40 (s, 0.4H), 7.38 (s, 0.5H), 7.36-7.33 (m, 0.1H), 7.23 (d, *J* = 2.6 Hz, 0.5H), 7.20 (dd, *J* = 7.2, 2.5 Hz, 1.4H), 7.15 (d, *J* = 2.4 Hz, 0.1H), 4.32 (q, *J* = 7.1 Hz, 0.3H), 4.25 (q, *J* = 7.0 Hz, 2.0H), 3.86 (s, 0.4H), 3.83 (s, 3.0H), 3.74 (dd, *J* = 8.1, 3.8 Hz, 0.9H), 3.48 (d, *J* = 3.7 Hz, 0.4H), 3.46-3.43 (m, 0.9H), 3.30 (dd, *J* = 16.9, 8.0 Hz, 1.0H), 1.36 (t, *J* = 7.1 Hz, 0.4H), 1.31 (t, *J* = 7.1 Hz, 3.0H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.4, 169.2, 169.1, 159.5, 159.0, 146.4, 137.9, 136.3, 135.3, 127.1, 125.2, 124.7, 116.8, 105.5, 104.3, 103.4, 61.5, 59.9, 55.5, 53.9, 31.7, 29.5, 14.3, 14.0.

Ethyl 5-bromo-1-oxo-2,3-dihydro-1H-indene-2-carboxylate(4h).[21] Colorless solid, 1.23 g, 87% yield, m.p. 47-49 °C; the ratio of keto form to enol form is 3.3:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (s, 0.9H), 7.64 (s, 0.4H), 7.62 (s, 0.8H), 7.55-7.49 (m, 1.5H), 4.32 (q,

J = 7.1 Hz, 0.6H), 4.25 (q, *J* = 7.0 Hz, 2.0H), 3.71 (dd, *J* = 8.3, 4.0 Hz, 0.9H), 3.57 (d, *J* = 4.0 Hz, 0.4H), 3.53 (d, *J* = 4.0 Hz, 0.6H), 3.50 (s, 0.6H), 3.35 (dd, *J* = 17.4, 8.3 Hz, 1.0H), 1.37 (t, *J* = 7.1 Hz, 0.9H), 1.31 (t, *J* = 7.1 Hz, 3.0H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 198.2, 168.6, 155.1, 144.9, 135.9, 134.1, 131.5, 130.9, 130.1, 129.9, 128.0, 125.8, 123.8, 121.9, 102.8, 61.9, 60.3, 53.3, 32.4, 29.9, 14.4, 14.2.

Ethyl 5-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4i).[21] Yellow oil, 707 mg, 61% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74-7.66 (m, 1H), 6.97-6.89 (m, 2H), 4.24 (q, *J* = 6.7 Hz, 2H), 3.90 (s, 3H), 3.70 (dd, *J* = 8.2, 3.9 Hz, 1H), 3.51 (dd, *J* = 17.3, 3.9 Hz, 1H), 3.30 (dd, *J* = 17.3, 8.2 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 197.3, 169.2, 165.6, 156.5, 128.1, 125.9, 115.7, 109.3, 61.3, 55.5, 53.3, 30.0, 13.9.

Ethyl 5-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4j).[21] Yellow oil, 786 mg, 72% yield; the ratio of keto form to enol form is 20:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, *J* = 7.9 Hz, 1.0H), 7.53 (d, *J* = 7.5 Hz, 0.1H), 7.30 (s, 1.0H), 7.20 (d, *J* = 7.9 Hz, 1.0H), 4.31 (q, *J* = 7.2 Hz, 0.1H), 4.24 (q, *J* = 6.9 Hz, 2.0H), 3.70 (dd, *J* = 8.2, 4.0 Hz, 0.9H), 3.50 (dd, *J* = 17.3, 3.8 Hz, 1.2H), 3.31 (dd, *J* = 17.2, 8.2 Hz, 1.0H), 2.45 (s, 3.0H), 2.44 (s, 0.2H), 1.36 (t, *J* = 7.1 Hz, 0.2H), 1.31 (t, *J* = 7.1 Hz, 3.0H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 199.0, 169.3, 154.1, 146.7, 133.0 129.0, 127.7, 126.8, 125.4, 124.4, 120.4, 100.0, 61.6, 53.5, 30.1, 22.1, 14.2.

Ethyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4k).[21] Colorless solid, 1.24 g, 94% yield, m.p. 141-142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18 (s, 1H), 6.91 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 3.70 (dd, *J* = 7.9, 3.6 Hz, 1H), 3.45 (dd, *J* = 17.0, 3.5 Hz, 1H), 3.27 (dd, *J* = 17.0, 7.9 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 198.1, 169.4, 156.0, 149.7, 149.2, 128.0, 107.2, 104.8, 61.6, 56.3, 56.1, 53.6, 30.0, 14.2.

Tert–butyl 1-oxo-2,3-dihydro-1H -indene-2-carboxylate (4l).[2b] Yellow solid, 760 mg, 66% yield, m.p. 49-51 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 3.62 (dd, *J* = 3.9 Hz, 8.1 Hz, 1H), 3.47-3.54 (m, 1H), 3.32 (dd, *J* = 8.1 Hz, 17.1 Hz, 1H), 1.49 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 200.0, 168.3, 153.7, 143.0, 137.1, 135.4, 135.2, 134.6, 129.0, 127.6, 127.2, 126.6, 126.5, 124.6, 124.5, 123.67, 120.5, 104.0, 82.0, 80.9, 54.3, 32.8, 30.3, 28.4, 28.0.

Benzyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4m).[2b] Colorless solid, 600 mg, 45% yield, m.p. 43-45 °C; the ratio of keto form to enol form is 4:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 0.8H), 7.63 (t, *J* = 7.4 Hz, 1.0H), 7.54-7.29 (m, 7.7H), 5.32 (s, 0.4H), 5.24 (d, *J* = 1.8 Hz, 1.6H), 3.79 (dd, *J* = 8.3, 4.2 Hz, 0.8H), 3.62-3.53 (m, 1.3H), 3.39 (dd, *J* = 17.2, 8.3 Hz, 0.9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 199.2, 168.9, 153.5, 143.3, 136.8, 136.1, 135.5, 135.4, 135.2, 129.5, 128.6, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 126.8, 126.5, 124.7, 120.8, 102.2, 67.3, 65.7, 53.3, 32.6, 30.2.

Methyl 5-oxo-6,7-dihydro-5H-indeno[5,6-d][1,3]dioxole-6-carboxylate (4n).[21] Yellow solid, 646 mg, 69% yield, m.p. 95-97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (s, 1H), 6.85 (s, 1H), 6.08 (s, 2H), 3.78 (s, 3H), 3.73 (dd, *J* = 7.9, 3.5 Hz, 1H), 3.43 (dd, *J* = 17.1, 3.4 Hz, 1H), 3.24 (dd, *J* = 17.1, 7.9 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 197.1, 169.6, 154.9, 151.4, 148.6, 129.7, 105.5, 102.8, 102.4, 53.5, 52.6, 30.1.

Ethyl 1-oxo-2,3-dihydro-1H-cyclopenta[a]naphthalene-2-carboxylate (4o).[2c] Colorless solid, 335 mg, 88% yield, m.p. 82-83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.08 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.68-7.70 (m, 1H), 7.54-7.59 (m, 2H), 4.26-4.29 (m, 2H), 3.84 (dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 3.65 (dd, *J* = 4.0 Hz, 16.0 Hz, 1H), 3.45 (dd, *J* = 8.0 Hz, 16.0 Hz, 1H), 1.33 (t, *J*

= 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 199.9, 169.4, 157.3, 136.7, 129.6, 129.4, 129.3, 128.3, 126.9, 123.9, 123.7, 61.8, 53.9, 30.6, 14.3.

Tert-butyl 4-oxo-5,6-dihydro-4H-cyclopenta[b]thiophene-5-carboxylate (4p).[2b] Slightly yellow solid, 762 mg, 64% yield, mp 62-64 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, *J* = 5.1 Hz, 1H), 7.13 (d, *J* = 5.1 Hz, 1H), 3.90 (dd, *J* = 3.0 Hz, 7.2 Hz, 1H), 3.53 (dd, *J* = 3.0 Hz, 17.4 Hz, 1H), 3.36 (dd, *J* = 7.2 Hz, 17.4 Hz, 1H), 1.50 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 191.2, 169.9, 167.8, 144.2, 131.3, 119.9, 82.3, 59.6, 28.5, 28.0.

2-Acetyl-2,3-dihydro-1H-inden-1-one (4q).[2b] Yellow solid, 230mg, 44% yield, m.p. 76-77 °C; the ratio of keto form to enol form is 1:6, ^1H NMR (400 MHz, $CDCl_3$) δ 13.67 (brs, 0.8H), 7.80 (d, *J* = 7.6 Hz, 0.9H), 7.70 (t, *J* = 8.7 Hz, 0.2H), 7.66-7.45 (m, 2.4H), 7.40 (t, *J* = 7.4 Hz, 1.1H), 3.96 (dd, *J* = 7.7, 3.3 Hz, 0.2H), 3.72 (dd, *J* = 17.4, 3.2 Hz, 0.2H), 3.57 (s, 2.0H), 3.12 (dd, *J* = 17.4, 7.7 Hz, 0.2H), 2.49 (s, 0.5H), 2.17 (s, 3.0H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.3, 199.7, 191.4, 177.4, 154.1, 147.5, 138.2, 135.4, 135.0, 132.7, 127.6, 127.3, 126.6, 125.7, 124.5, 123.1, 110.4, 61.9, 30.2, 30.0, 27.8, 21.0.

2-Propionyl-2,3-dihydro-1H-inden-1-one (4r).[2b] Yellow solid, 338 mg, 60% yield, m.p. 39-40 °C; the ratio of keto form to enol form is 1:2.7, ^1H NMR (400 MHz, $CDCl_3$) δ 13.67 (brs, 1.0H), 7.81 (d, *J* = 7.6 Hz, 0.9H), 7.72 (d, *J* = 7.7 Hz, 0.4H), 7.63-7.49 (m, 2.8H), 7.45-7.33 (m, 1.4H), 3.96 (dd, *J* = 7.7, 3.3 Hz, 0.3H), 3.73 (dd, *J* = 17.3, 3.1 Hz, 0.4H), 3.59 (s, 2.0H), 3.19-3.10 (m, 0.7H), 2.72-2.58 (m, 0.4H), 2.48 (q, *J* = 7.6 Hz, 2.0H), 1.25 (t, *J* = 7.6 Hz, 3.0H), 1.10 (t, *J* = 7.2 Hz, 1.1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.0, 199.9, 190.2, 183.0, 154.3, 147.1, 138.1, 135.3, 135.0, 132.5, 127.5, 127.2, 126.5, 125.6, 124.4, 122.9, 109.5, 60.9, 36.1, 30.0, 28.3, 28.1, 9.7, 7.5.

1-Oxo-2,3-dihydro-1H-indene-2-carboxamide (4s).[22] Colorless solid, 35 mg, 10% yield, m.p. 178-180 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.16 (brs, 1H), 5.57 (brs, 1H), 3.77 (dd, *J* = 17.7, 3.9 Hz, 1H), 3.62 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.37 (dd, *J* = 17.7, 8.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.7, 168.7, 154.1, 135.6, 135.2, 127.6, 126.7, 124.4, 52.9, 28.5. IR (KBr) ν = 3372, 3083, 2349, 1715, 1648, 1417, 1310, 1203, 1007, 798, 711 cm^{-1}.

N-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (4t).[22] Colorless solid, 133 mg, 35% yield, m.p. 150-151 °C;^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.15 (brs, 1H), 3.78 (d, *J* = 17.6 Hz, 1H), 3.54 (dd, *J* = 7.8, 3.3 Hz, 1H), 3.35 (dd, *J* = 17.6, 8.2 Hz, 1H), 2.87 (d, *J* = 4.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.6, 167.0, 154.3, 135.7, 135.3, 127.6, 126.7, 124.3, 52.7, 28.8, 26.5. IR (KBr) ν = 3291, 3172, 2407, 2031, 1643, 1406, 1269, 1094, 754 cm^{-1}.

Typical procedure for synthesis of isoxazoline *N*-oxides. To a solution of starting materials *β*-keto esters **4** (0.2 mmol) and methyl nitroacetate (47.6 mg, 0.4 mmol) in 1:3 (v/v) CH_3CN/water (5.3 mL) were added AcOH (11.4 μL, 0.2 mmol) and AIBX (168 mg, 0.5 mmol) successively. The reaction mixture was stirred at 0°C to room temperature and monitored by TLC. After the starting material **4** was completely consumed, the reaction was quenched with sat. aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL). The separated aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography to afford the

product **5**. The aqueous phase was evaporated under vacuum to afford the white solid which was reoxidized by freshly prepared dimethyldioxirane to regenerate AIBX in 91% yield.

8a-(Ethoxycarbonyl)-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5a). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 55 mg, 81% yield, m.p. 132-133 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 5.40 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 192.3, 165.9, 159.1, 149.6, 137.3, 133.0, 130.4, 127.3, 126.3, 108.0, 81.9, 53.2, 52.5, 14.0; IR (KBr) ν = 2957, 2352, 1736, 1640, 1447, 1380, 1244, 1067, 747 cm^{-1}; HRMS(ESI): calcd for $C_{15}H_{13}NNaO_7$ [M+Na]+ 342.0584, found 342.0588.

8a-(Ethoxycarbonyl)-6-fluoro-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-inde-no[1,2-d]isoxazole 2-oxide (5b). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 52 mg, 77% yield, m.p. 148-149 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (dd, *J* = 8.5, 4.4 Hz, 1H), 7.57 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.49 (td, *J* = 8.4, 2.4 Hz, 1H), 5.36 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 191.5, 165.5, 165.0, 62.5, 159.1, 145.3, 135.2, 135.2, 129.3, 129.2, 125.2, 124.9, 112.1, 111.9, 107.7, 82.3, 63.5, 53.2, 52.1, 14.0; IR (KBr) ν = 2954, 1739, 1641, 1479, 1444, 1258, 1063, 978, 867, 746 cm^{-1}; HRMS(ESI): calcd for $C_{15}H_{12}FKNO_7$ [M+K]$^+$ 376.0229, found 376.0232.

6-Chloro-8a-(ethoxycarbonyl)-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5c). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v); 48 mg, 68% yield, m.p. 135-137 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90-7.86 (m, 2H), 7.73 (d, *J* = 8.3 Hz, 1H), 5.36 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 1.32 (t, *J* =7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 191.3, 165.4, 159.0, 147.7, 137.2, 137.1, 134.6, 128.7, 125.8, 107.5, 82.0, 63.5, 53.2, 52.2, 14.0; IR (KBr) ν = 2963, 2356, 1740, 1642, 1446, 1379, 1247, 1203, 1061, 972, 860, 739 cm^{-1}; HRMS(ESI): calcd for $C_{15}H_{12}ClKNO_7$ [M+K]$^+$ 391.9934, found 391.9938.

6-Bromo-8a-(ethoxycarbonyl)-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5d). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 56 mg, 71% yield, m.p. 138-139 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 5.33 (s, 1H), 4.35 (q, *J* = 6.9 Hz, 2H), 3.97 (s, 3H), 1.32 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 191.2, 165.4, 156.0, 148.2, 140.1, 134.8, 129.0, 128.9, 124.9, 107.5, 81.9, 63.5, 53.3, 52.2, 14.0; IR (KBr) ν = 2954, 2351, 1738, 1640, 1446, 1245, 1112, 1065, 977, 858, 741 cm^{-1}; HRMS(ESI): calcd for $C_{15}H_{12}BrNNaO_7$ [M+Na]$^+$ 419.9689, 421.9669, found 419.9689, 421.9670.

8a-(Ethoxycarbonyl)-3-(methoxycarbonyl)-8-oxo-6-(trifluoromethyl)-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5e). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 43 mg, 53% yield, m.p. 140-141 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 5.45 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 191.4, 165.3, 159.0, 152.4, 133.7, 133.7, 133.4, 133.0, 130.9, 128.8, 128.5, 124.4, 123.4, 121.7, 107.2, 81.8, 63.7, 53.3, 52.5, 14.0. IR (KBr) ν = 3402, 2961, 1745, 1641, 1445, 1382, 1325, 1250, 1199, 1130, 1063, 977, 862, 748 cm^{-1}; HRMS(ESI): calcd for $C_{16}H_{12}F_3NNaO_7$ [M+Na]$^+$ 410.0458, found 410.0462.

8a-(Ethoxycarbonyl)-3-(methoxycarbonyl)-6-methyl-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5f). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 50 mg, 75% yield, m.p. 144-145 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 - 7.73 (m, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 5.34 (s, 1H), 4.34 (q, *J* = 7.0 Hz, 2H), 3.97 (s, 3H), 2.47 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 192.4, 165.9, 159.0, 147.1, 140.9, 138.5, 133.2, 127.0, 126.1, 108.2, 82.2, 63.3, 53.1, 52.2, 21.1, 14.0; IR (KBr) ν = 3397, 2960, 2352, 1734, 1640, 1444, 1382, 1252, 1105, 749, 610 cm^{-1}; HRMS(ESI): calcd for $C_{16}H_{15}NNaO_7$ $[M+Na]^+$ 356.0741, found 356.0745.

8a-(Ethoxycarbonyl)-6-methoxy-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5g). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 53 mg, 76% yield, m.p. 137-139 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.32 (d, *J* = 2.3 Hz, 1H), 5.31 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 3.88 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 192.4, 165.8, 161.4, 159.0, 143.0, 134.6, 128.0, 126.5, 108.2, 106.9, 82.4, 63.2, 55.8, 53.1, 51.9, 14.0; IR (KBr) ν = 2949, 2407, 1734, 1637, 1484, 1445, 1387, 1245, 1063, 1017, 971, 860, 747 cm^{-1}; HRMS(ESI): calcd for $C_{16}H_{15}KNO_8$ $[M+K]^+$ 388.0429, found 388.0431.

5-Bromo-8a-(ethoxycarbonyl)-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5h). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 56 mg, 71% yield, m.p. 149-151 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 5.37 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 191.3, 165.4, 158.9, 150.9, 134.1, 132.9, 131.9, 130.8, 127.2, 107.4, 81.8, 63.9, 53.9, 52.1, 14.0; IR (KBr) ν = 2961, 1738, 1643, 1582, 1444, 1383, 1246, 1059, 975, 908, 855, 747 cm^{-1}; HRMS(ESI): calcd for $C_{15}H_{12}BrNNaO_7$ $[M+Na]^+$ 419.9689, 421.9669, found 419.9692, 421.9672.

8a-(Ethoxycarbonyl)-5-methoxy-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5i). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 54 mg, 78% yield, m.p. 134-136 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, *J* = 8.6 Hz, 1H), 7.34 (s, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 5.33 (s, 1H), 4.35 (q, *J* = 7.0 Hz, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 190.3, 167.1, 166.0, 159.3, 152.8, 128.0, 125.9, 118.2, 110.7, 108.1, 82.6, 63.3, 56.1, 53.1, 52.1, 14.0; IR (KBr) ν = 3443, 2962, 2032, 1724, 1639, 1598, 1448, 1381, 1264, 1089, 1002, 857, 753 cm^{-1}; HRMS(ESI): calcd for $C_{16}H_{15}NNaO_8$ $[M+Na]^+$ 372.0690, found 372.0695.

8a-(Ethoxycarbonyl)-3-(methoxycarbonyl)-5-methyl-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5j). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 51 mg, 72% yield, m.p. 122-124 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 7.8 Hz, 1H), 7.67 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 5.34 (s, 1H), 4.35 (q, *J* = 6.4 Hz, 2H), 3.98 (s, 3H), 2.52 (s, 3H), 1.32 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.7, 166.0, 159.2, 150.1, 149.3, 131.6, 130.6, 127.6, 126.1, 108.1, 82.3, 63.3, 53.1, 52.3, 22.5, 14.0; IR (KBr) ν = 3438, 2953, 2034, 1732, 1638, 1445, 1380, 1247, 1064, 980, 857, 752 cm^{-1}; HRMS(ESI): calcd for $C_{16}H_{15}NNaO_7$ $[M+Na]^+$ 356.0741, found 356.0743.

8a-(Ethoxycarbonyl)-5,6-dimethoxy-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5k). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 5/1-3/1, v/v): 71 mg, 88% yield, m.p.

160-162 ℃; A gram-scale synthesis of **5k**: 1.27g, 83% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (s, 1H), 7.27 (s, 1H), 5.28 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 190.9, 166.0, 159.5, 157.3, 151.5, 145.6, 126.0, 108.4, 108.0, 105.6, 82.5, 63.2, 56.6, 56.3, 53.1, 52.0, 14.0; IR (KBr) ν = 3000, 2885, 2818, 2351, 1721, 1637, 1499, 1450, 1375, 1247, 1105, 979, 741, 669 cm^{-1}; HRMS(ESI): calcd for $C_{17}H_{17}NNaO_9$ $[M+Na]^+$ 402.0796, found 402.0801.

8a-(Tert-butoxycarbonyl)-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5l). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 62 mg, 84% yield, m.p. 138-140 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.77 (t, *J* = 7.0 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 5.33 (s, 1H), 3.98 (s, 3H), 1.49 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 192.9, 164.6, 159.2, 149.7, 137.1, 133.2, 130.3, 127.3, 126.2, 108.2, 85.4, 81.9, 53.1, 52.3, 27.8; IR (KBr) ν = 3000, 2886, 2351, 1739, 1640, 1452, 1378, 1256, 1154, 975, 747, 670 cm^{-1}; HRMS(ESI): calcd for $C_{17}H_{17}NNaO_7$ $[M+Na]^+$ 370.0897, found 370.0901.

8a-(Benzyloxy)carbonyl)-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5m). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 58 mg, 72% yield, m.p. 113-115 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 4.2 Hz, 5H), 5.37 (s, 1H), 5.31 (dd, *J* = 20, 12 Hz, 2H), 3.97 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 192.1, 165.8, 159.0, 149.5, 137.3, 134.2, 133.0, 130.4, 128.8, 128.7, 128.3, 127.4, 126.3, 107.9, 82.0, 68.6, 53.2, 52.4; IR (KBr) ν = 3454, 2352, 1737, 1641, 1449, 1380, 1257, 1075, 975, 745 cm^{-1}; HRMS(ESI): calcd for $C_{20}H_{15}NNaO_7$ $[M+Na]^+$ 404.0741, found 404.0745.

3,9a-Bis(methoxycarbonyl)-9-oxo-3a,9a-dihydro-9H-[1,3]dioxolo[4',5':5,6]indeno [1,2-d]isoxazole 2-oxide (5n). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 5/1-3/1, v/v): 73 mg, 98% yield, m.p. 189-190 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (s, 1H), 7.22 (s, 1H), 6.17 (d, *J* = 4.3 Hz, 1H), 5.27 (s, 1H), 3.97 (s, 3H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 190.0, 166.3, 159.0, 156.3, 150.5, 147.8, 128.0, 108.0, 106.5, 103.9, 103.3, 82.5, 53.7, 53.2, 52.0; IR (KBr) ν = 2354, 1718, 1637, 1461, 1381, 1241, 1098, 1032, 949, 877, 792, 667 cm^{-1}; HRMS(ESI): calcd for $C_{15}H_{11}NNaO_9$ $[M+Na]^+$ 372.0326, found 372.0330.

9a-(Ethoxycarbonyl)-7-(methoxycarbonyl)-10-oxo-6b,9a-dihydro-10H-benzo[4,5]indeno[1,2-d]isoxazole 8-oxide (5o). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 10/1-5/1, v/v): 45 mg, 61% yield, m.p. 174-175 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.07 (d, *J* = 8.3 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 5.49 (s, 1H), 4.47 – 4.27 (m, 2H), 4.00 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 192.7, 166.0, 159.2, 152.9, 138.7, 133.7, 130.3, 129.6, 128.6, 128.3, 127.9, 124.4, 123.3, 108.1, 82.3, 63.3, 53.2, 52.2, 14.1; IR (KBr) ν = 2996, 2352, 1713, 1637, 1514, 1443, 1377, 1245, 1092, 975, 830, 752, 671 cm^{-1}; HRMS(ESI): calcd for $C_{19}H_{15}NNaO_7$ $[M+Na]^+$ 392.0741, found 392.0742.

7a-(Tert-butoxycarbonyl)-3-(methoxycarbonyl)-7-oxo-3a,7a-dihydro-7H-thieno[3',2':4,5]cyclopenta[1,2-d]isoxazole 2-oxide (5p). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 54 mg, 72%

yield, m.p. 137-139 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, *J* = 5.1 Hz, 1H), 7.28 (d, *J* = 5.2 Hz, 1H), 5.32 (s, 1H), 3.97 (s, 3H), 1.51 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 184.7, 165.9, 164.0, 158.5, 143.0, 134.5, 120.7, 107.3, 86.6, 85.6, 53.1, 50.8, 27.8; IR (KBr) ν = 3513, 3001, 2911, 2845, 2353, 1986, 1731, 1644, 1513, 1463, 1381, 1263, 1103, 975, 749 cm^{-1}; HRMS(ESI): calcd for $C_{15}H_{15}NNaO_7S$ $[M+Na]^+$ 376.0461, found 376.0465.

8a-Acetyl-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5q). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 44 mg, 72% yield, m.p. 52-53 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (t, *J* = 8.4 Hz, 2H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 5.49 (s, 1H), 3.98 (s, 3H), 2.59 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 201.8, 193.9, 158.9, 150.3, 137.3, 132.8, 130.3, 127.5, 126.1, 109.0, 87.5, 53.1, 50.7, 27.5; IR (KBr) ν = 2355, 1726, 1637, 1444, 1371, 1255, 1201, 969, 862, 729 cm^{-1}; HRMS(ESI): calcd for $C_{14}H_{11}NNaO_6$ $[M+Na]^+$ 312.0479, found 312.0481.

3-(Methoxycarbonyl)-8-oxo-8a-propionyl-3a,8a-dihydro-8H-indeno[1,2-d] isoxazole 2-oxide (5r). A colorless liquid after purification by flash column chromatography (petroleum ether/EtOAc = 20/3-5/1, v/v): 40 mg, 61% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (t, *J* = 8.6 Hz, 2H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 5.48 (s, 1H), 3.97 (s, 3H), 3.00 (qd, *J* = 7.1, 1.8 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 204.6, 194.0, 158.9, 150.4, 137.2, 132.9, 130.3, 127.5, 126.2, 109.0, 87.6, 53.1, 51.1, 33.5, 6.7; IR (KBr) ν = 2947, 2357, 1724, 1638, 1446, 1379, 1250, 746 cm^{-1}; HRMS(ESI): calcd for $C_{15}H_{13}NNaO_6$ $[M+Na]^+$ 326.0635, found 326.0640.

8a-Carbamoyl-3-(methoxycarbonyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d] isoxazole 2-oxide (5s). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 3/1-2/1, v/v): 61 mg, 98% yield, m.p. 174-175 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 6.92 (brs, 1H), 6.33 (brs, 1H), 5.56 (s, 1H), 3.99 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 193.6, 167.7, 158.8, 150.2, 137.3, 133.1, 130.3, 127.3, 126.3, 108.7, 82.7, 53.3, 52.1; IR (KBr) ν = 3368, 3151, 2925, 2352, 2034, 1732, 1686, 1622, 1388, 1256, 1100, 976, 817, 746 cm^{-1}; HRMS(ESI): calcd for $C_{13}H_{10}N_2NaO_6$ $[M+Na]^+$ 313.0431, found 313.0436.

3-(Methoxycarbonyl)-8a-(methylcarbamoyl)-8-oxo-3a,8a-dihydro-8H-indeno[1,2-d]isoxazole 2-oxide (5t). A colorless solid after purification by flash column chromatography (petroleum ether/EtOAc = 3/1-2/1, v/v): 41 mg, 62% yield, m.p. 204-205 ℃ (decomp.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 6.89 (brs, 1H), 5.56 (s, 1H), 3.99 (s, 3H), 2.97 (d, *J* = 5.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 193.9, 165.6, 158.8, 150.3, 137.3, 133.2, 130.3, 127.3, 126.2, 108.8, 82.8, 53.7, 52.0, 26.5; IR (KBr) ν = 3273, 2929, 2355, 2030, 1732, 1636, 1536, 1381, 1298, 1230, 1150, 971, 855, 795, 716 cm^{-1}; HRMS(ESI): calcd for $C_{14}H_{12}N_2NaO_6$ $[M+Na]^+$ 327.0588, found 327.0592.

Typical procedure for [3+2] cycloaddition of isoxazoline *N*-oxides 5a and ethyl acrylate. Isoxazoline *N*-oxide **5a** (0.1 mmol, 32.0 mg) was dissolved in a mixture of ethyl acrylate (0.8 mL) and dichloromethane (0.8 mL). The resulting mixture was stirred under reflux until **5a** was consumed completely, as monitored by TLC. The solvent and volatile components were removed on a rotary evaporator under reduced pressure, and the residue was subjected to column chromatographic isolation on silica gel (petroleum ether/EtOAc = 3/1-2/1, v/v) to give the product **6** as colorless oil in 97% yield (40.5 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ

7.88 (d, *J* = 7.7 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 5.26 (dd, *J* = 9.8, 4.5 Hz, 1H), 4.59 (s, 1H), 4.34-4.14 (m, 4H), 3.47 (s, 3H), 3.26 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.92 (dd, *J* = 13.0, 9.9 Hz, 1H), 1.26 (m, 7H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 196.1, 168.9, 167.8, 166.4, 145.0, 136.1, 135.0, 130.1, 126.4, 125.6, 86.9, 86.7, 80.9, 62.9, 62.0, 56.0, 52.8, 38.9, 14.0, 13.9; IR (KBr) ν = 2921, 2352, 1738, 1596, 1453, 1373, 1272, 1205, 1098, 1029, 923, 831, 752, 673 cm^{-1}; HRMS(ESI): calcd for $C_{20}H_{21}NNaO_9$ $[M+Na]^+$ 442.1109, found 442.1113.

General procedure for transformation of isoxazoline *N*-oxide 5a to the corresponding isoxazolines 7: Isoxazoline *N*-oxide **5a** (0.15 mmol, 48.0 mg) was dissolved in trimethyl phosphite (1.0 mL) in a flask equipped with a condenser. The solution was well degassed and heated at reflux under Ar. After **5a** was completely consumed, the reaction was quenched with 1 N HCl (2.0 mL) and water (5 mL). The separated aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography (petroleum ether/EtOAc =5/1) to afford the product isoxazolines **7** as colorless oil in 84% yield (38 mg). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, *J* = 7.4 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 5.36 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 192.9, 166.0, 160.0, 150.4, 149.2, 137.0, 133.0, 130.1, 127.3, 126.5, 93.4, 63.1, 56.9, 53.3, 14.0; IR (KBr) ν = 2920, 2352, 1730, 1529, 1227, 1039, 910, 749, 671 cm^{-1}; HRMS(ESI): calcd for $C_{15}H_{13}NNaO_6$ $[M+Na]^+$ 326.0635, found 326.0640.

COMPUTATIONAL DETAILS

All calculations were carried out with the GAUSSIAN 16 packages.[23] Geometry optimizations were performed with M06-2X,[24] in which 6-31G(d)[25] basis set was used for C, H, O, N and LANL2DZ[26] basis set was used for I atom. Frequency analysis calculations were subsequently performed to verify the optimized geometries to be minima (no imaginary frequency). Localized orbital locator (LOL) was calculated by Multi WFN 3.5.[27]

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interests.

Supporting Information

Reaction optimization, X-ray crystallography data, ^{1}H NMR, $^{13}C\{^{1}H\}$ NMR spectra and computational details. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC: 632351-632352(**1C**); 222124-222125(**1D**); 200547(**1E**); 207068 (**1F**); 268074(**1G**); 137693(**1H**); 271726(**1I**); 1050503(**IBX-SO_3K**); 696745(**1J**); 683965(**IBX**).

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