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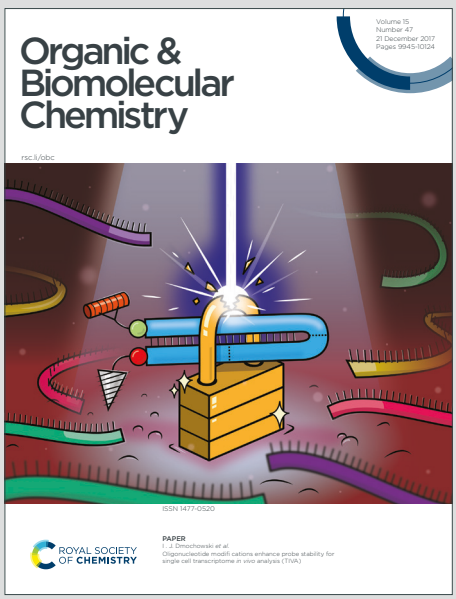

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ARTICLE

Room temperature iron(II)-catalyzed radical cyclization of unsaturated oximes with hypervalent iodine reagents

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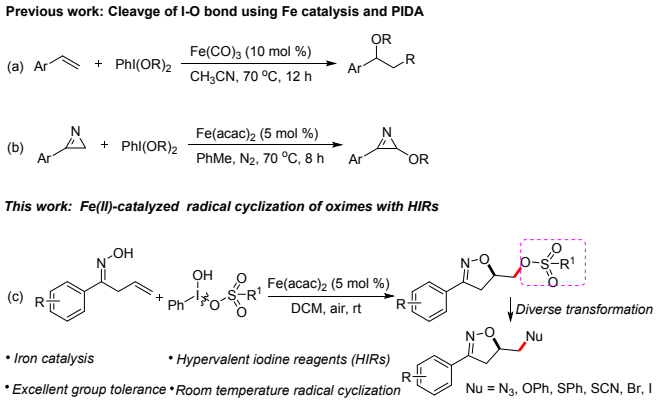
Here, we disclose an iron (II)-catalyzed I–O bond cleavage of Koser's hypervalent iodine reagents (HIRs) that initiated the radical cyclization of unsaturated oximes at room temperature. This strategy is successfully applied for the construction of isoxazoline backbone in an efficient way. In particular, the direct introduction of TsO group into products facilitates their late-stage transformations in organic synthesis.

Introduction

Over the past decades, hypervalent iodine reagents (HIRs) have been widely employed for the synthesis of complex organic molecules due to their easy preparation, ubiquitous property and synthetic versatility.[1] Classically, HIRs in reported works can function as reactive substrate, oxidant and both of them, as well as acting as a promoter in some reaction systems.[1-3] Among them, a number of the elegant reactions mainly depended on the combination of HIRs and transition metal catalysts. These metal catalysts include Pd,[3a,b] Cu,[3c] Fe,[3e-h] and some others,[3i-l] which have been found to be highly efficient in hypervalent iodine chemistry. Otherwise, the use of noble metal catalyst and toxic additives does not meet the requirement in current organic synthesis. In order to address this issue, as one of the efficient strategies, iron catalysis, have been successfully developed in organic synthesis, which also has achieved considerable advancement because of its economy and low toxicity.[4] To the best of our knowledge, only a handful of work by using iron catalysis and HIRs chemistry have been reported so far.[3e-h] For example, Kuninobu and coworkers reported the first $Fe(CO)_3$-promoted the cleavage of I–O bond within $PhI(OAc)_2$ (PIDA), yielding the hypervalent iodine radicals that triggered the subsequent radical addition of alkenes (Scheme 1a).[3g] Our group recently realized the selective oxidation of C(sp^3)–H of 2*H*-azirines using this strategy (Scheme 1b).[3h] Based on the previous work,[3] we envisioned that this strategy can be further extended to more challenging organic reactions.

As one of the most valuable five-membered *N*-containing heterocyclic compounds, the isoxazolines scaffold has been found in many biological natural products, agrochemicals and pharmaceuticals, natural and artificial products,[5a-f] as well as serving as chiral ligand in asymmetric catalysis.[5g-h] Massive research effort in past years has been devoted to isoxazoline synthesis, including transition metal catalysis and metal-free strategies.[6] Particularly, oximes bearing unactivated carbon-carbon double bond used as the precursor has been reported for its ability to access isoxazolines.[7] For an early example, Han's group realized the oxime radical promoted dioxygenation, oxyamination, and diamination of alkenes via the cyclization of α,ß-unsaturated oximes in the presence of equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the promoter, delivering a series of isoxazolines and cyclic nitrones.[7a] Then, the cyclizations of oximes using nucleophiles such as carbon, nitrogen oxygen, and some others via varied reaction modes demonstrated the powerful ability of this synthetic strategy.[6-7] Despite of these advances, most of the cyclizations are heavily restricted by the coordinating ability of hydroxyl unit, susceptibility toward oxygen (air), and excessive use of metal catalyst or external additives. Additionally, the late-stage transformation of the cyclization product is extremely important but not easy to fulfil in most cases.[8] In



Scheme 1. Fe-catalyzed cleavage of I–O within HIRs.

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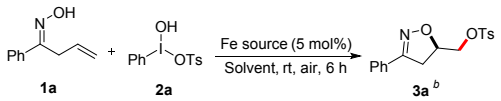
Table 1. Optimization of the reaction conditions.[a]

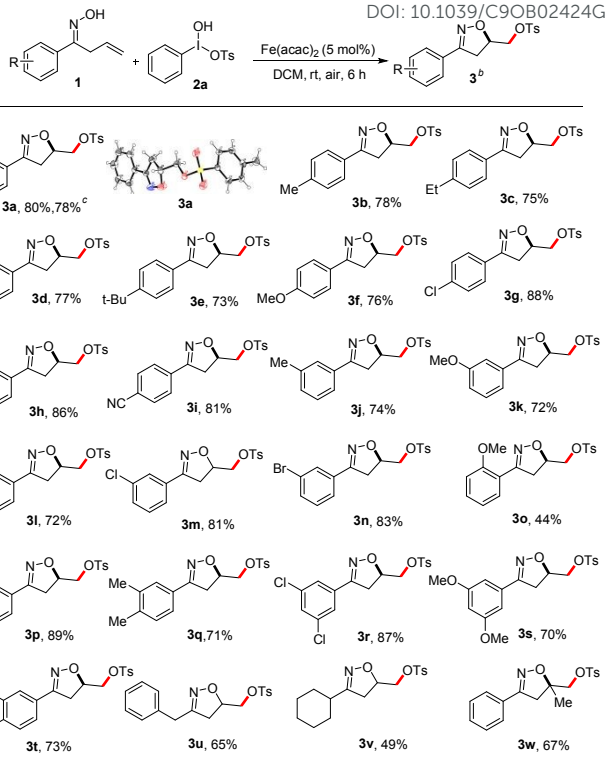


1a 2a 3a[b]

Entry	Fe source	Solvent	Yield (%)[b]
1	–	DCM	14
2	$Fe(acac)_2$	DCM	81
3	$FeCl_2$	DCM	30
4	$FeBr_2$	DCM	32
5	$FeSO_4$	DCM	17
6	$Fe(acac)_3$	DCM	45
7	$FeCl_3$	DCM	20
8	$Fe(OAc)_3$	DCM	28
9	$Fe(acac)_2$	CH_3OH	17
10	$Fe(acac)_2$	Acetone	Trace
11	$Fe(acac)_2$	CH_3CN	32
12	$Fe(acac)_2$	$CHCl_3$	35
13	$Fe(acac)_2$	PhMe	51
14	$Fe(acac)_2$	DCE	65
15	$Fe(acac)_2$	THF	47
16	$Fe(acac)_2$	DCM	80[c]
17	$Fe(acac)_2$	DCM	82[d]
18	$Fe(acac)_2$	DCM	81[e]
19	$Fe(acac)_2$	DCM	75[f]

[a]Reaction conditions: Fe source (5 mol%), **1a** (0.20 mmol), **2a** (0.25 mmol) and distilled solvent (1.0 mL) at room temperature under air for 6 h. [b]Isolated yield. [c]N_2. [d]DCM (anhydrous). [e]7 h. [f]5 h.

Table 2. The scope of oximes.[a]



[a]Reaction conditions: $Fe(acac)_2$ (5 mol%), **1** (0.2 mmol), **2a** (0.25 mmol) and DCM (1 mL) at room temperature under air for 6 h. [b] Isolated yield. [c] gram-scale reaction.

this respect, exploration of mild approaches for highly efficient construction of structurally diverse isoxazolines under environment-benign reaction conditions is still highly desirable.

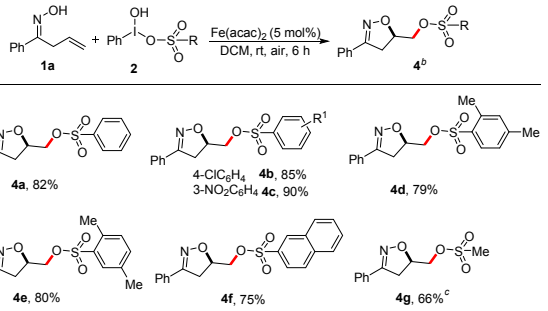
Herein, we will detail recent findings in our group with respect to the hypervalent iodine chemistry.[3h,9] Unlike the previous work on the oxidation of saturated C–H using PIDA,[3h] it is worth mentioning that a highly active sulfonyloxyl radical generated from Koser's HIRs using iron catalysis at room temperature is the key to the success of the radical cyclization of oximes, and which can be easily incorporated into the final products isoxazolines, therefore facilitating their late-stage transformations (Scheme 1c).

Results and discussion

We then began the work by optimizing the reaction conditions based on previously established catalytic radical chemistry involving hypervalent iodine reagents.[3h] Using oxime **1a** and hypervalent iodine reagent **2a** as reaction substrates, and using dichloromethane (DCM) as reaction medium, it is observed that the product **3a** was achieved in 14% isolated yield, and further confirmed by the single-crystal structure analysis (Table 1, entry 1).[10] Encouraged by this finding, we then employed $Fe(acac)_2$ as a catalyst to improve the radical cyclization, which could produce **3a** in 81% yield (entry 2). Furthermore, the use of some other iron(II) salts, including $FeCl_2$, $FeBr_2$ and $FeSO_4$, failed to improve the radical process (entries 3–5). We then continued to examined the iron(III) salts, such as $Fe(acac)_3$, $FeCl_3$ and $Fe(OAc)_3$, and which indicated that only slightly enhanced yield of **3a** was achieved (entries 6–8). Following that, some typical organic solvents were tested in the cyclization of **1a** with **2a** by using $Fe(acac)_2$ as a catalyst. Obviously, the use of methanol led to the formation of **3a** in 17% yield (entry 9). Even worse was only trace amount of **3a** was observed when using acetone as a solvent (entry 10). Performing the model reaction in CH_3CN or $CHCl_3$ did not enhance the isolated yield of **3a** (entries 11 and 12). The employment of toluene and 1,2-dichloroethane (DCE) led to the formation of **3a** in 51% and 65% yield, respectively (entries 13 and 14). Unfortunately, the employment of tetrahydrofuran (THF) did not achieve improved yield (entry 15). When the reaction was carried out under nitrogen atmosphere, comparable yield of **3a** was obtained (entry 2 *vs* entry 16). The reaction still proceeded in anhydrous DCM, and generated 82% yield of **3a** (entry 17). Finally, the optimization of reaction time indicated that the model reaction almost completed in 6 h, and produced **3a** in satisfactory yield (entries 18 and 19).

After that, a number of oximes bearing different aryl groups were used to react with **2a**, affording the isoxazolines in varied yields (Table 2). Remarkably, electron-rich group at the *para*-position of phenyl ring within oximes, such as Me, Et, *i*-Pr, *t*-Bu and MeO, are well tolerated and afforded the desired products in moderate yields (**3b**–**3f**). The incorporation of halogens, including Cl and Br into the substrates gave the increasing yields of products when compared with those of the formers (**3g** and **3h**). Oximes with *meta*-substitution on phenyl ring

Table 3. The scope of Koser's reagents. [a]

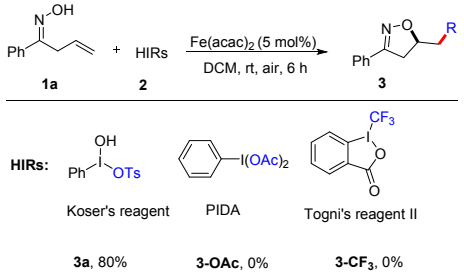


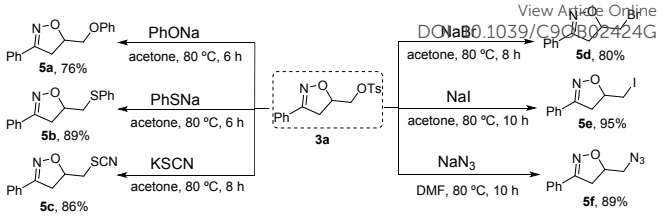
[a]Reaction conditions: $Fe(acac)_2$ (5 mol%), **1a** (0.20 mmol), **2** (0.25 mmol) and DCM (1 mL) at room temperature under air for 6 h. [b]Isolated yield. [c]15 h.

produced the relating products in acceptable yields (**3i**-**n**). In the case of the *ortho*-substituted substrate, only 44% yield of **3o** was obtained under the above optimal conditions, showing that strong steric hindrance existed in this reaction system (**3f** *vs* **3o**). Furthermore, the oximes bearing disubstitution on phenyl ring were employed as substrates to react with **2a**, moderate yields (70–89%) were achieved (**3p–3s**). Reactions with oxime possessing π-conjugated group gave the regarding product in 73% yield (**3t**). We then found that the oximes with alky group including Bn and Cy showed lower reactivity under optimal reaction conditions, generating desired products in 65% (**3u**) and 49% (**3v**) yield, respectively. Particularly, a steric oxime, (*E*)-3-methyl-1-phenylbut-3-en-1-one oxime, also efficiently react with **2a** to afford the cyclization product **3w** in 67% isolated yield. Notably, the reaction to form **3a** was allowed to be performed on a gram-scale, albeit with a slightly reduced yield (78%).

We continued to examine several Koser's HIRs, and which were then subjected to the cyclization of oxime **2a** under the optimal reaction conditions. Substitution on the benzene ring of HIRs was tolerated (Table 3). It was found that HIRs with electron-withdrawing group, such as Cl and NO_2, delivered the desired products in good yields (**4b** and **4c**). Installation of Methyl group both at the *ortho*- and *meta*-position was also allowed to react with **1a**, affording the relating products **4d** and **4e** in 79% and 80% yield, respectively. The reaction of HIRs having naphthyl group with **1a** proceeded smoothly to give **4f** in decreasing yield. Finally, hydroxy(phenyl)-λ³-iodanyl methanesulfonate was evaluated and the methanesulfonyl group could be built into the product **4g** with 66% isolated yield. Unfortunately, we further found that some other typical

Table 4. Radical cyclization of oxime **1a** with HIRs.



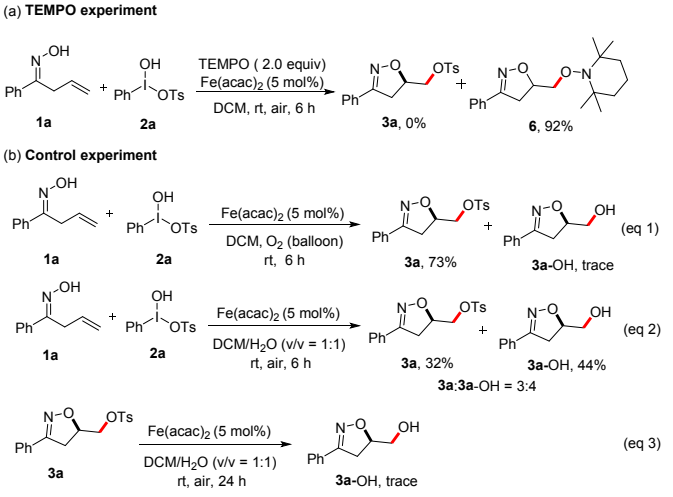


Scheme 2. Diverse transformations of **3a**.

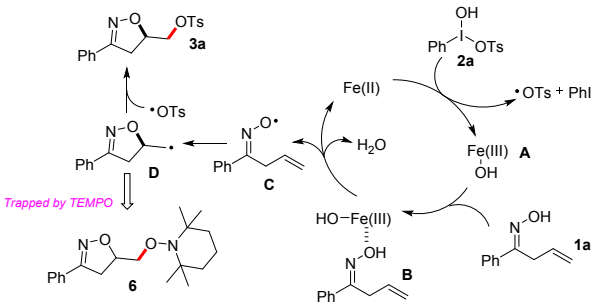
HIRs including PIDA[3m-n] and Togni's reagent were not reactive under the optimal conditions (Table 4), further indicating the unique activity of Koser's reagent.

The TsO group belongs to an extremely good leaving group in organic synthesis, which can be attacked by many kinds of nucleophiles to realize diverse transformations. Therefore, product **3a** was selected as a representative example for the following investigation (Scheme 2). The experiment results indicate that the nucleophiles including PhONa, PhSNa, KSCN, NaBr and NaI, can readily enable the substitution of TsO group using acetone as solvent at 80 °C, generating the according products (**5a–5e**) in good yields. In the case of NaN_3, the reaction of **3a** proceeded well in DMF under mild conditions, and afforded **5f** in 89% yield.

Next, some experiments were carried out to disclose the possible reaction pathway (Scheme 3). At first, 2.0 equiv. of radical scavenger TEMPO was directly added into the reaction **1a** with **2a**, and which proceeded under the optimal condition for 6 h (Scheme 3a). After that, only compound **6** was isolated in 92% yield and no **3a** was detected at all, showing that a radical cyclization was involved in the catalytic cycle (Scheme 4). The model reaction that carried out under O_2 atmosphere in freshly distilled DCM gave 78% yield of **3a** and trace amount of **3a**-OH[11], indicating that oxygen molecular does not affect this radical cyclization (Scheme 3b, eq. 1). Furthermore, performing the reaction **1a** with **2a** in DCM/H_2O (V/V = 1:1) obtain the mixture of **3a**/**3a**-OH with a ratio of 3:4 (Scheme 3b, eq. 2). Following that, we found the transformation of **3a** into **3a**-OH almost did not proceed in DCM/H_2O (V/V = 1:1)



Scheme 3. Mechanistic investigation.



Scheme 4. Proposed reaction mechanism.

(Scheme 3b, eq. 3). These experimental results show the presence of water would affect the formation of **3a**.

Based on these results and previous reports,[3] a plausible mechanism for this iron(II) catalyzed cyclization is depicted in Scheme 4. Firstly, the oxidization of iron(II) by **2a** afforded species iron(III) **A**[3g-h,12] and the reactive radical *p*-toluenesulfonyloxyl radical TsO•. Then oxime **1a** coordinated with **A** by hydroxyl group to complex **B**, which underwent a single electron transfer to generate iron(II) and a highly reactive species **C**. Then an intramolecular radical cyclization of **C** generated intermediate **D** that could be trapped by radical scavenger TEMPO to obtain **6**.[7a,11,13] Finally the radical coupling of TsO• with **D** delivered the product **3a**.

Conclusions

In summary, an iron(II)-catalyzed cyclization of oximes with HIRs at room temperature via a single electron transfer process has been developed, which provides an expedient access to isoxazolines. The current work using iron catalysis and hypervalent iodine chemistry complements the literature protocol, wherein a readily transformable *p*-toluenesulfonyloxyl group was incorporated into the target products in one-pot. The late-stage transformations of cyclization products have proved their practical applications in organic synthesis. Although a possible radical pathway for this iron-catalyzed cyclization was proposed, another reaction model via hypervalent iodine activated the double bond was not fully ruled out. The further exploration of this strategy in synthetic chemistry and mechanistic studies is underway in our laboratory.

Conflicts of interests

There are no conflicts to declare.

Experimental section

General: All ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz (or 600 MHz) Bruker FT-NMR spectrometers 400 MHz (or 600 MHz) and 100 MHz (or 150 MHz), respectively). All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectroscopy data of the products were collected on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS (ESI) and a Thermo Fisher Scientific LTQ FTICR-MS instrument. Melting points were determined in open capillary tube using WRS-1B digital melting point apparatus. All the solvents in this cyclization reaction were freshly distilled prior to use.

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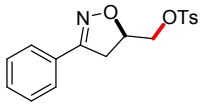
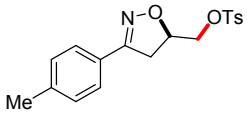
General procedure for the synthesis of 3a

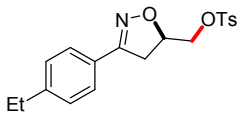
A 10 mL reaction tube was charged with (*E*)-1-phenylbut-3-en-1-one oxime (**1a**, 32.2 mg, 0.20 mmol), $Fe(acac)_2$ (2.5 mg, 5 mol%), DCM (1.0 mL) and [hydroxy(tosyloxy)iodo]benzene (**2a**, 98.1 mg, 0.25 mmol) was added to the resulted mixture. The reaction tube was placed at room temperature and stirred for 6 h. Then, the mixture in reaction tube was detected by TLC. After the reaction was completed, distilled water (10 mL) was added into the mixture, and extracted with dichloromethane (DCM, 3×10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 3:1 to 9:1), affording the desired product **3a** as a white solid (53.0 mg, 80% yield).



(3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (**3a**)**:** White solid; 53.0 mg, 80% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.63–7.61 (m, 2H), 7.44–7.38 (m, 3H), 7.34 (d, *J* = 7.8 Hz, 2H), 4.96–4.91 (m, 1H), 4.17–4.10 (m, 2H), 3.44 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.24 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.2, 145.2, 132.4, 130.4, 129.9, 128.8, 128.7, 128.0, 126.7, 77.4, 69.2, 37.3, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{17}H_{18}NO_4S]^+$: 332.0951, Found: 332.0949.



(3-(*p*-Tolyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3b): White solid; 53.9 mg, 78% yield; 1H NMR (400 MHz, CDCl3) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.94–4.87 (m, 1H), 4.16–4.08 (m, 2H), 3.42 (dd, *J* = 17.2, 10.8 Hz, 1H), 3.21 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.44 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 156.2, 145.2, 140.7, 132.5, 129.9, 129.4, 128.0, 126.7, 126.0, 77.2, 69.2, 37.4, 21.6, 21.4. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{18}H_{20}NO_4S]^+$: 346.1108, Found: 346.1108.



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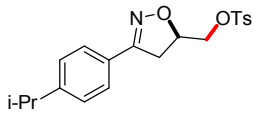
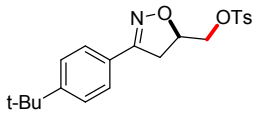
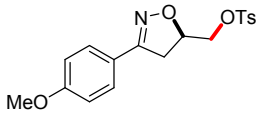
(3-(4-Ethylphenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3c): White solid; 53.9 mg, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.95–4.88 (m, 1H), 4.16–4.08 (m, 2H), 3.42 (dd, *J* = 16.8, 10.4 Hz, 1H), 3.22 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.44 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 147.0, 145.2, 132.4, 129.9, 128.3, 128.0, 126.8, 126.2, 77.2, 69.2, 37.4, 28.8, 21.6, 15.3. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{19}H_{22}NO_4S]^+$: 360.1264, Found: 360.1264.



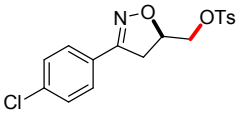
(3-(4-Isopropylphenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3d): White solid; 57.5 mg, 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.27–7.25 (m, 2H), 4.94–4.87 (m, 1H), 4.15–4.07 (m, 2H), 3.42 (dd, *J* = 16.8, 10.4 Hz, 1H), 3.22 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.98–2.88 (m, 1H), 2.43 (s, 3H), 1.26 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 151.6, 145.1, 132.5, 129.9, 128.0, 126.8, 126.3, 77.2, 69.2, 37.4, 34.0, 23.7, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{20}H_{24}NO_4S]^+$: 374.1421, Found: 374.1422.



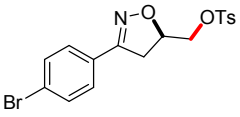
(3-(4-(*tert*-Butyl)phenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3e): White solid; 56.6 mg, 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.95–4.88 (m, 1H), 4.15–4.07 (m, 2H), 3.43 (dd, *J* = 17.2, 10.8 Hz, 1H), 3.23 (dd, *J* = 17.2, 6.8 Hz, 1H), 2.44 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 153.9, 145.1, 132.5, 129.9, 128.0, 126.6, 126.0, 125.7, 77.2, 69.2, 37.5, 34.9, 31.1, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{21}H_{26}NO_4S]^+$: 388.1577, Found: 388.1578.



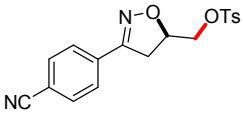
(3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3f): White solid; 54.9 mg, 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.93–4.86 (m, 1H), 4.18–4.07 (m, 2H), 3.84 (s, 3H), 3.42 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.22 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 155.8, 145.2, 130.0, 128.3, 128.0, 121.4, 114.2, 77.1, 69.2, 55.4, 37.6, 21.7. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{18}H_{20}NO_5S]^+$: 362.1057, Found: 362.1058.



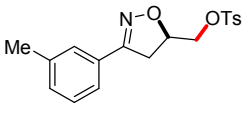
(3-(4-Chlorophenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3g): White solid; 64.4 mg, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.38–7.33 (m, 4H), 4.98–4.91 (m, 1H), 4.17–4.11 (, 2H), 3.41 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.22 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 145.2, 136.4, 132.5, 129.9, 129.0, 128.0, 127.9, 127.4, 77.7, 69.1, 37.1, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{17}H_{17}ClNO_4S]^+$: 366.0561, Found: 366.0561.



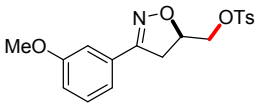
(3-(4-Bromophenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3h): White solid; 70.6 mg, 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.53–7.32 (m, 4H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.97–4.90 (m, 1H), 4.19–4.08 (m, 2H), 3.41 (dd, *J* = 17.2, 11.2 Hz, 1H), 3.21 (dd, *J* = 17.2, 7.2 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 145.2, 132.4, 131.9, 129.9, 128.1, 127.9, 127.8, 124.6, 77.8, 69.1, 36.9, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{17}H_{17}BrNO_4S]^+$: 410.0056, Found: 410.0056.



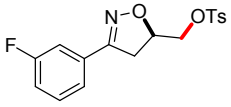
(3-(4-cyanophenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3i): White solid; 57.7 mg, 81% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 5.03–4.98 (m, 1H), 4.21–4.13 (m, 2H), 3.45 (dd, *J* = 16.8, 11.0 Hz, 1H), 3.27 (dd, *J* = 16.9, 7.0 Hz, 1H), 2.45 (s, 3H). NMR (150 MHz, $CDCl_3$) δ: 155.0, 145.3, 133.1, 132.4, 132.2, 129.9, 127.9, 127.1, 118.1, 113.6, 78.4, 69.0, 36.4, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{18}H_{16}N_2O_4S]^+$: 357.0904, Found: 357.0904.



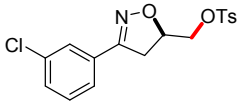
(3-(*m*-Tolyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3j): White solid; 51.1 mg, 74% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.45 (s, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 4.94–4.90 (m, 1H), 4.18–4.07 (m, 2H), 3.43 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.24 (dd, *J* = 16.8, 6.6 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 145.2, 138.5, 132.4, 131.2, 129.9, 128.7, 128.6, 127.3, 123.9, 77.3, 69.2, 37.4, 21.6, 21.3. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{18}H_{20}NO_4S]^+$: 346.1108, Found: 346.1109.



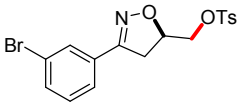
(3-(3-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3k): White solid; 52.0 mg, 72% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.30 (t, *J* = 8.4 Hz, 1H), 7.21–7.20 (m, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.98–6.96 (m, 1H), 4.95–4.90 (m, 1H), 4.19–4.10 (m, 2H), 3.82 (s, 3H), 3.42 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.21 (dd, *J* = 16.8, 6.6 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.7, 156.2, 145.2, 132.4, 130.0, 129.9, 129.7, 127.9, 119.4, 116.7, 111.4, 77.5, 69.2, 55.3, 37.3, 21.6. HRMS (ESI) ([M+H]$^+$) Calcd. For $[C_{18}H_{20}NO_5S]^+$: 362.1057, Found: 362.1057.



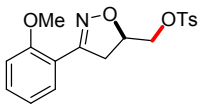
(3-(3-fluorophenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3l): White solid; 50.3 mg, 72% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.39–7.32 (m, 5H), 7.15–7.09 (m, 1H), 4.97–4.93 (m, 1H), 4.20–4.10 (m, 2H), 3.41 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.21 (dd, *J* = 16.8, 6.6 Hz, 1H), 2.44 (s, 3H). NMR (150 MHz, $CDCl_3$) δ: 162.67 (d, *J* = 245.3 Hz), 155.36 (d, *J* = 245.3 Hz), 145.3, 132.4, 130.9 (d, *J* = 8.3Hz), 130.4 (d, *J* = 8.4 Hz), 129.9, 127.9, 122.5 (d, *J* = 3.0 Hz), 117.3 (d, *J* = 21.5 Hz), 113.5 (d, *J* = 23.4 Hz), 77.8, 69.1, 37.0, 21.6. ^{19}F NMR (600 MHz, $CDCl_3$) δ: -111.94. HRMS (ESI) ([M+H]$^+$) Calcd. For $[C_{17}H_{16}FNO_4S]^+$: 350.0857, Found: 350.0858.



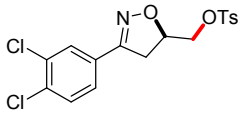
(3-(3-Chlorophenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3m): White solid; 59.3 mg, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.58 (s, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.39–7.31 (m, 4H), 4.98–4.92 (m, 1H), 4.20–4.11 (m, 2H), 3.40 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.19 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 145.2, 134.6, 132.3, 130.5, 130.2, 129.9, 129.8, 127.8, 126.6, 124.7, 77.8, 69.2, 36.7, 21.5. HRMS (ESI) ([M+H]$^+$) Calcd. For $[C_{17}H_{17}ClNO_4S]^+$: 366.0561, Found: 366.0561.



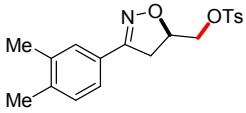
(3-(3-Bromophenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3n): White solid; 68.1 mg, 83% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.74 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 4.97–4.92 m, 1H), 4.19–4.10 (m, 2H), 3.42–3.37 (m, 1H), 3.21–3.17 (m, 1H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 145.2, 133.2, 132.3, 130.8, 130.2, 129.9, 129.6, 127.9, 125.2, 122.8, 77.8, 69.1, 36.8, 21.6. HRMS (ESI) ([M+H]$^+$) Calcd. For $[C_{17}H_{17}ClNO_4S]^+$: 410.0056, Found: 410.0057.



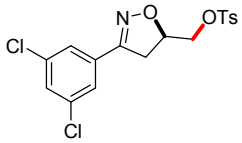
(3-(2-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3o) White solid; 31.8 mg, 44% yield; δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.65–7.63 (m, 1H), 7.38–7.36 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.96–6.91 (m, 2H), 4.88–4.83 (m, 1H), 4.14–4.06 (m, 2H), 3.83 (s, 3H), 3.54 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.32 (dd, *J* = 18.0, 6.6 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.4, 155.7, 145.0, 132.4, 131.5, 129.8, 129.3, 127.8, 120.7, 117.9, 111.3, 77.2, 69.5, 55.4, 39.8, 21.5. HRMS (ESI) ([M+H]$^+$) Calcd. For $[C_{18}H_{20}NO_5S]^+$: 362.1057, Found: 362.1057.



(3-(3,4-Dichlorophenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3p): White solid; 71.2 mg, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.67 (s, 1H), 7.49–7.46 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.00–4.93 (m, 1H), 4.21–4.10 (m, 2H), 3.40 (dd, *J* = 16.8, 11.2 Hz, 1H), 3.20 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 145.3, 134.5, 133.1, 132.4, 130.8, 130.0, 128.8, 128.4, 127.9, 125.8, 78.1, 69.0, 36.8, 21.6. HRMS (ESI) ([M+H]$^+$) Calcd. For $[C_{17}H_{16}Cl_2NO_4S]^+$: 400.0172, Found: 400.0173.

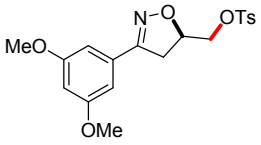


(3-(3,4-Dimethylphenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3q): White solid; 51.0 mg, 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.41 (s, 1H), 7.35–7.31 (m, 3H), 7.15 (d, *J* = 7.6 Hz, 1H), 4.93–4.86 (m, 1H), 4.18–4.14 (m, 2H), 3.42 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.21 (dd, *J* = 16.8, 6.4 Hz, 1H), 2.44 (s, 3H), 2.28 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 145.1, 139.4, 137.0, 132.5, 129.9, 128.0, 127.8, 126.3, 124.3, 77.2, 69.3, 37.5, 21.6, 19.7, 19.6. HRMS (ESI) ([M+H]$^+$) Calcd. For $[C_{19}H_{22}NO_4S]^+$: 360.1264, Found: 360.1262.

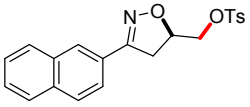


(3-(3,5-Dichlorophenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3r): White solid; 69.6 mg, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.47–7.46 (m, 2H), 7.39–7.34 (m, 3H), 5.00–4.94 (m, 1H), 4.20–4.11 (m, 2H), 3.38 (dd, *J*

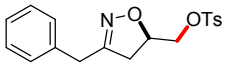
= 16.8, 11.2 Hz, 1H), 3.18 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 145.3, 135.4, 132.4, 131.7, 130.0, 129.9, 127.9, 125.0, 78.2, 69.0, 36.5, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{17}H_{16}Cl_2NO_4S]^+$: 400.0172, Found: 400.0172.



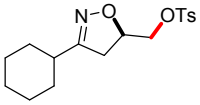
(3-(3,5-Dimethoxyphenyl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3s): White solid; 54.8 mg, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.75–6.74 (m, 2H), 6.50 (s, 1H), 4.95–4.88 (m, 1H), 4.19–4.06 (m, 2H), 3.40 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.17 (dd, *J* = 16.8, 6.4 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 156.2, 145.2, 132.4, 130.5, 129.9, 127.9, 104.7, 102.5, 77.5, 69.2, 55.4, 37.2, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{19}H_{22}NO_6S]^+$: 392.1162, Found: 392.1160.



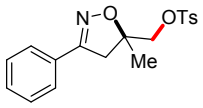
(3-(Naphthalen-2-yl)-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3t): White solid; 55.7 mg, 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.77 (m, 7H), 7.54–7.49 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.00–4.93 (m, 1H), 4.23–4.11 (m, 2H), 3.53 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.34 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 145.2, 134.0, 132.8, 132.4, 129.9, 128.5, 128.4, 127.9, 127.8, 127.2, 127.1, 126.7, 126.3, 123.4, 77.6, 69.2, 37.2, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{21}H_{20}NO_4S]^+$: 382.1108, Found: 382.1108.



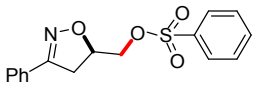
(3-benzyl-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3u): White solid; 44.9 mg, 65% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.31–7.29 (m, 4H), 7.26–7.24 (m, 1H), 7.18–7.17 (m, 2H), 4.69–4.64 (m, 1H), 3.96 (dd, *J* = 4.8, 1.2 Hz, 2H), 3.62 (d, *J* = 2.4 Hz, 2H), 2.88 (dd, *J* = 17.4, 11.4 Hz, 1H), 2.64 (dd, *J* = 17.4, 6.6 Hz, 1H), 2.41 (s, 3H). NMR (150 MHz, $CDCl_3$) δ: 157.3, 144.9, 135.1, 132.2, 129.7, 128.7, 128.5, 127.7, 126.9, 76.5, 69.4, 38.3, 33.5, 21.4. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{18}H_{19}NO_4S]^+$: 346.1108, Found: 346.1108.



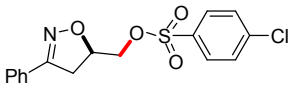
(3-Cyclohexyl-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3v): White solid; 33.1 mg, 49% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 4.71–4.69 (m, 1H), 4.06–3.94 (m, 2H), 3.02 (dd, *J* = 17.4, 10.8 Hz, 1H), 2.82 (dd, *J* = 17.4, 6.0 Hz, 1H), 2.45 (s, 3H), 2.37 (s, 1H), 1.82–1.76 (m, 4H), 1.69 (d, *J* = 12.6 Hz, 1H), 1.33–1.19 (m, 5H). NMR (150 MHz, $CDCl_3$) δ: 162.4, 145.1, 132.5, 129.9, 128.0, 75.8, 69.4, 37.7, 37.0, 30.3, 30.2, 25.7, 25.6, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{17}H_{23}NO_4S]^+$: 338.1421, Found: 338.1422.



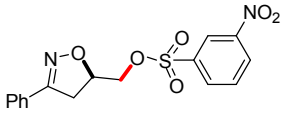
(5-Methyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl 4-methylbenzenesulfonate (3w): White solid; 46.3 mg, 67% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78–7.77 (m, 2H), 7.60–7.58 (m, 2H), 7.41–7.37 (m, 3H), 7.32 (d, *J* = 7.8 Hz, 2H), 4.01 (d, *J* = 2.4 Hz, 2H), 3.38 (d, *J* = 16.8 Hz, 1H), 3.05 (d, *J* = 16.8 Hz, 1H), 2.43 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 145.2, 132.4, 130.2, 129.9, 129.2, 128.7, 128.0, 126.6, 84.4, 72.2, 43.0, 22.9, 21.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{18}H_{20}NO_4S]^+$: 346.1108, Found: 346.1109.



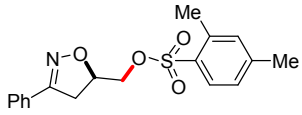
(3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl benzenesulfonate (4a): White solid; 52.0 mg, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.90 (m, 2H), 7.68–7.60 (m, 3H), 7.55 (t, *J* = 8.0 Hz, 2H), 7.42–7.37 (m, 3H), 4.98–4.91 (m, 1H), 4.22–4.11 (m, 2H), 3.45 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.25 (dd, *J* = 16.8, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 134.1, 130.4, 129.3, 128.7, 127.9, 126.7, 77.4, 69.4, 37.2. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{16}H_{16}NO_4S]^+$: 318.0795, Found: 318.0794.



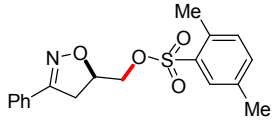
(3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl 4-chlorobenzenesulfonate (4b): White solid; 59.6 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.62–7.60 (m, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.43–7.38 (m, 3H), 4.98–4.91 (m, 1H), 4.20–4.15 (m, 2H), 3.46 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.24 (dd, *J* = 17.2, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 140.8, 134.0, 130.5, 129.7, 129.3, 128.8, 126.7, 69.7, 37.1. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{16}H_{15}ClNO_4S]^+$: 352.0405, Found: 352.0405.



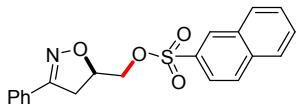
(3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl 3-nitrobenzenesulfonate (4c): White solid; 65.2 mg, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74–8.72 (m, 1H), 8.51–8.48 (m, 1H), 8.24–8.22 (m, 1H), 7.78 (t, *J* = 8.0 Hz, 1H), 7.59–7.57 (m, 2H), 7.45–7.37 (m, 3H), 4.98–4.92 (m, 1H), 4.36–4.28 (m, 2H), 3.48 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.25 (dd, *J* = 16.8, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 148.2, 137.8, 133.4, 130.8, 130.5, 128.8, 128.5, 128.4, 126.7, 123.3, 70.6, 36.9. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{16}H_{15}N_2O_6S]^+$: 363.0645, Found: 363.0645.



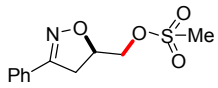
(3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl 2,4-dimethylbenzenesulfonate (4d): White solid; 54.5 mg, 79% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 1H), 7.62–7.60 (m, 2H), 7.43–7.38 (m, 3H), 7.15 (s, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 4.95–4.90 (m, 1H), 4.13–4.06 (m, 2H), 3.44 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.24 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.59 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 145.0, 138.4, 133.4, 130.7, 130.3, 130.1, 128.8, 128.7, 126.7, 126.6, 77.5, 69.2, 37.1, 21.3, 20.1. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{18}H_{20}NO_4S]^+$: 346.1108, Found: 346.1109.



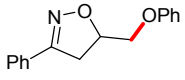
(3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl 2,5-dimethylbenzenesulfonate (4e): White solid; 55.2 mg, 80% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.63–7.61 (m, 2H), 7.43–7.38 (m, 3H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 4.97–4.92 (m, 1H), 4.15–4.07 (m, 2H), 3.45 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.26 (dd, *J* = 16.8, 6.6 Hz, 1H), 2.58 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 136.2, 135.4, 134.7, 133.4, 132.6, 130.4, 130.3, 128.8, 128.7, 126.7, 77.5, 69.2, 37.2, 20.7, 19.7. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{18}H_{20}NO_4S]^+$: 346.1108, Found: 346.1109.



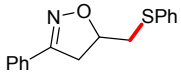
(3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl naphthalene-2-sulfonate (4f): White solid; 55.0 mg, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.99–7.91 (m, 3H), 7.86–7.84 (m, 1H), 7.70–7.61 (m, 2H), 7.58–7.56 (m, 2H), 7.42–7.34 (m, 3H), 4.98–4.91 (m, 1H), 4.25–4.14 (m, 2H), 3.43 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.24 (dd, *J* = 17.2, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 135.4, 132.2, 131.9, 130.4, 129.9, 129.8, 129.5, 129.3, 128.7, 128.0, 127.9, 126.7, 122.4, 77.4, 69.5, 37.2. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{20}H_{18}NO_4S]^+$: 368.0951, Found: 368.0952.



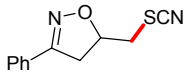
(3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl methanesulfonate (4g): White solid; 33.7 mg, 66% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67–7.65 (m, 2H), 7.45–7.39 (m, 3H), 5.03–4.98 (m, 1H), 4.40–4.32 (m, 2H), 3.49 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.28 (dd, *J* = 17.4, 7.2 Hz, 1H), 3.07 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.5, 130.4, 128.8, 128.7, 126.7, 77.7, 69.4, 37.6, 36.8. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{11}H_{14}NO_4S]^+$: 256.0638, Found: 256.0638.



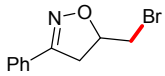
5-(Phenoxymethyl)-3-phenyl-4,5-dihydroisoxazole (5a):[14] White solid; 38.5 mg, 76% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70–7.69 (m, 2H), 7.41–7.40 (m, 3H), 7.28 (t, *J* = 7.2 Hz, 2H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.13–5.08 (m, 1H), 4.17 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.04 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.50 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.38 (dd, *J* = 16.8, 7.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.4, 156.4, 130.2, 129.5, 129.3, 128.7, 126.7, 121.3, 114.6, 78.7, 68.4, 37.6. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{16}H_{16}NO_2]^+$: 254.1176, Found: 254.1174.



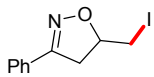
3-Phenyl-5-((phenylthio)methyl)-4,5-dihydroisoxazole (5b):[15] White solid; 47.9 mg, 89% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66–7.64 (m, 2H), 7.42–7.39 (m, 5H), 7.32–7.29 (m, 2H), 7.24–7.22 (m, 1H), 4.89–4.84 (m, 1H), 3.45–3.35 (m, 2H), 3.26 (dd, *J* = 16.8, 6.6 Hz, 1H), 2.98 (dd, *J* = 13.8, 9.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.2, 134.7, 130.1, 130.0, 129.3, 129.1, 128.7, 126.8, 126.7, 79.5, 39.5, 37.7. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{16}H_{16}NOS]^+$: 270.0947, Found: 270.0946.



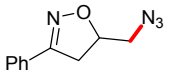
3-Phenyl-5-(thiocyanatomethyl)-4,5-dihydroisoxazole (5c):[7g] White solid; 37.5 mg, 86% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68–7.66 (m, 2H), 7.46–7.41 (m, 3H), 5.10–5.05 (m, 1H), 3.64–3.60 (m, 1H), 3.32–3.24 (m, 2H), 3.17 (dd, *J* = 13.8, 6.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 130.6, 128.8, 128.6, 126.8, 111.5, 78.7, 39.4, 37.0. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{11}H_{11}N_2OS]^+$: 219.0587, Found: 219.0586.



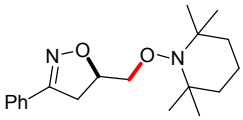
5-(Bromomethyl)-3-phenyl-4,5-dihydroisoxazole (5d):[16] White solid; 38.4 mg, 80% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69–7.65 (m, 2H), 7.44–7.39 (m, 3H), 5.02–4.97 (m, 1H), 3.57 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.51 (dd, *J* = 16.8, 10.2 Hz, 1H), 3.41 (dd, *J* = 10.2, 8.4 Hz, 1H), 3.32 (dd, *J* = 17.4, 6.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0, 130.3, 129.0, 128.7, 126.7, 79.6, 39.5, 33.1. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{10}H_{11}BrNO]^+$: 240.0019, Found: 240.0018.



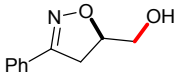
5-(Iodomethyl)-3-phenyl-4,5-dihydroisoxazole (5e):[17] White solid; 54.5 mg, 95% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69–7.65 (m, 2H), 7.44–7.39 (m, 3H), 4.95–4.90 (m, 1H), 3.52 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.42 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.25–3.21 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8, 130.3, 129.0, 128.7, 126.7, 80.4, 41.0, 7.5. HRMS (ESI) ($[M+H]^+$) Calcd. For $[C_{10}H_{11}INO]^+$: 287.9880, Found: 287.9879.



5-(Azidomethyl)-3-phenyl-4,5-dihydroisoxazole (5f):[7d] White solid; 36.0 mg, 89% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68–7.67 (m, 2H), 7.42–7.41 (m, 3H), 4.94–4.90 (m, 1H), 3.54–3.43 (m, 3H), 3.22 (dd, *J* = 16.8, 6.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 130.3, 129.1, 128.7, 126.7, 79.1, 53.5, 37.8. HRMS (ESI) ([M+H]$^+$) Calcd. For $[C_{10}H_{11}N_4O]^+$: 203.0927, Found: 203.0928.



3-Phenyl-5-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-4,5-dihydroisoxazole (6):[7a] White solid; 58.2 mg, 92% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62–7.59 (m, 2H), 7.32–7.31 (m, 3H), 4.81–4.76 (m, 1H), 3.92–3.87 (m, 2H), 3.29 (dd, *J* = 16.2, 10.8 Hz, 1H), 3.17 (dd, *J* = 16.2, 7.2 Hz, 1H), 1.46-1.35 (m, 5H), 1.23–1.21 (m, 1H), 1.11 (s, 6H), 0.99 (d, *J* = 4.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.06, 129.8, 129.7, 128.6, 126.6, 79.1, 77.5, 60.0, 59.9, HRMS (ESI) ([M+H]$^+$) Calcd. For $[C_{19}H_{29}N_2O_2]^+$: 317.2224, Found: 317.2227.



(3-Phenyl-4,5-dihydroisoxazol-5-yl)methanol (3a-OH):[18] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67–7.65 (m, 2H), 7.42–7.38 (m, 3H), 4.89–4.84 (m, 1H), 3.87 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.69 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.33 (m, 2H), 2.23 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.06, 130.16, 129.29, 128.68, 126.69, 81.22, 63.65, 36.30.

Acknowledgements

This work is financially supported by the National Science Foundation of China (21772062, 21572078, 21772061), the Natural Science Foundation of Anhui Province (1708085QB28).

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Room temperature iron(II)-catalyzed radical cyclization of unsaturated oximes with hypervalent iodine reagents

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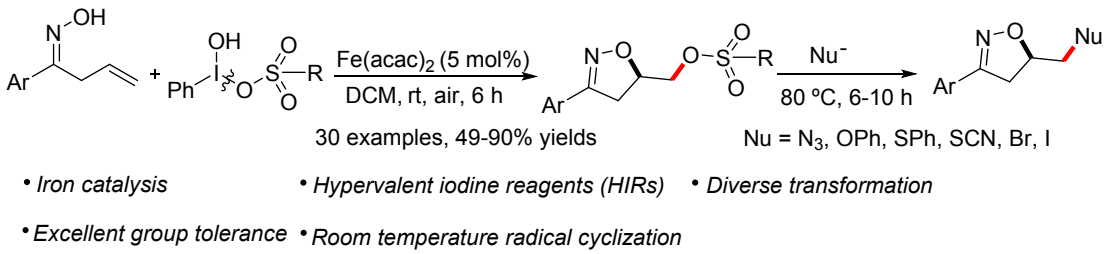
Abstract **:** An iron (II)-catalyzed radical cyclization of oximes with hypervalent iodine reagents was developed, which enabled the construction of isoxazoline backbone.



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