

Copper-catalyzed radical oxyallylation of olefins for the construction of alkene-containing isoxazolines

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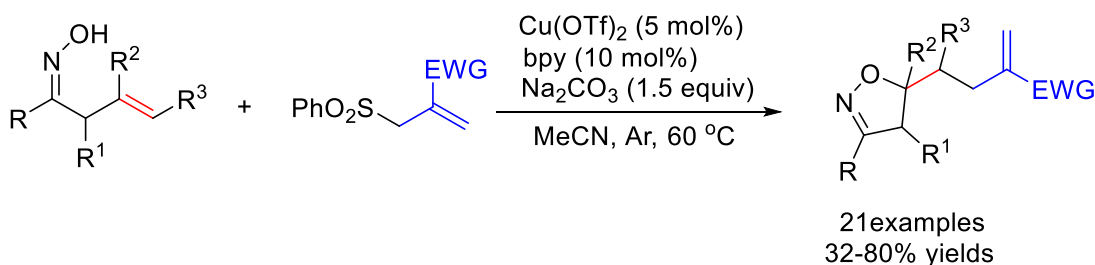
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Abstract

A radical-mediated approach to alkene oxyallylation using allylic oximes is described. The reaction proceeds under copper-catalytic redox-neutral conditions and tolerates various functional groups. This protocol thus enables the synthesis of structurally valuable isoxazolines and the introduction of a versatile olefin motif in a single step.

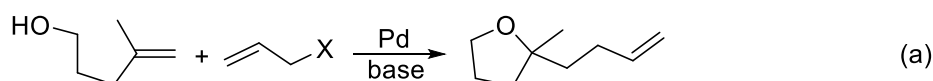


Keywords: allylic oximes, copper-catalytic, oxyallylation, isoxazolines, allyl sulfones

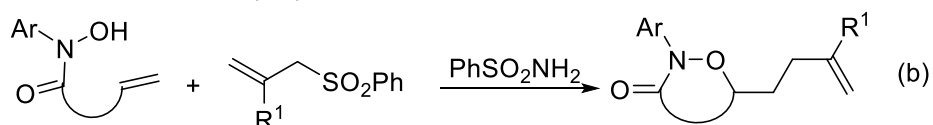
Introduction

The direct difunctionalization of alkenes, a valuable and readily available feedstock, represents one of the most effective strategies for increasing molecular complexity in synthetic organic chemistry.¹⁻¹⁶ Among them, the oxyallylation of alkenes is a particularly useful reactions, because the alkenes motif in the resulting products offer rich possibilities for synthetic manipulations. Despite significant advances in the oxyfunctionalization of alkenes,¹⁷⁻²⁶ oxyallylation of alkenes have been little explored. France and co-workers developed the palladium-catalyzed oxyallylation of unactivated alkenes using phenols, alcohol and carboxylic acid as the nucleophiles (Scheme 1a).²⁷ However, monosubstituted alkene are not tolerated under the given reaction conditions, because of the β -hydride elimination of the putative σ -alkyl Pd(II) intermediate. Alternatively, Alexanian and co-workers demonstrated the radical-mediated oxyallylation of alkenes with allyl sulfones using hydroxamic acids as the radical precursor with the assistance of PhSO₂NH₂ (Scheme 1b).²⁸ Although highly practical, the types of oxygen-centered radicals remain limited. Encouraged by the works of Han,^{29,30} Wang,³¹ and our group³² on the copper-catalyzed iminoxyl radical-mediated oxyfunctionalization of alkenes, we envisioned that iminoxyl radical may also be involved in the oxyallylation with allyl sulfones. Herein, we describe more convenient method, which has led to the construction of useful isoxazolines³³⁻⁴³ and the installation of versatile alkenyl groups in one transformation. It is expected that the resulting C=C bond will serve as a useful precursor for obtaining other isoxazoline-containing compounds.

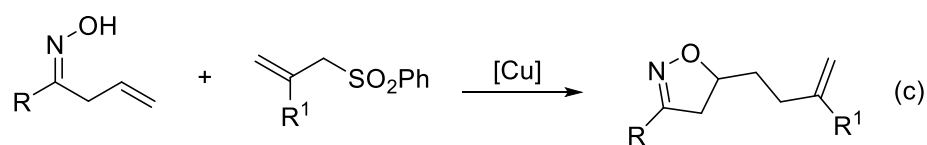
Palladium-catalyzed oxyallylation of alkenes



Radical-mediated oxyallylation of alkenes



This work



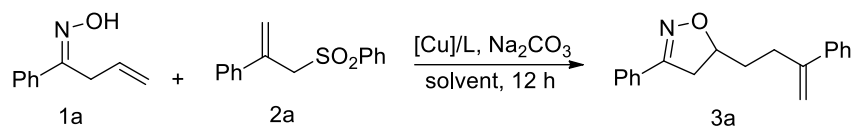
Scheme 1. Oxyallylation of alkenes.

Results and Discussion

The initial experiments were carried out with allylic oxime **1a** and allyl sulfone **2a** as the model substrates (Table 1 and S1). When the standard reaction conditions developed by our previous work revealed that using (Cu(OTf)₂, 1,10-phen and Na₂CO₃ were used as catalyst, ligand and base respectively in MeCN at 80 °C), the desired isooxazoline **3a** was produced in 57% NMR yield. Inspired by these result, various reaction parameters were changed to explore the sensitivity of this reaction. Cu(II) catalysts were generally more effective than Cu(I) sources (entries 1-3 vs entries 4-6). Bpy was also effective ligand (entry 7), but the reaction yield diminished with TMEDA (entry 8). Other solvents, such as DCE, EtOH, toluene, THF and DMF uniformly less

effective than MeCN (entries 9-13). Importantly, the loading of **2a** had significant effect on the reactions. Increasing the loading to 3 equiv provides **3a** in 84% NMR yield (entry 14). It is noteworthy that the remaining **2a** could be recovered quantitatively. Finally, the reaction temperature could be reduced to 60 °C without the loss the reaction efficiency (entry 15). In the absence of Cu(OTf)₂ and base, the reactions could hardly occur (entries 16-17), while control experiment lacking ligand was less effective (entry 18).

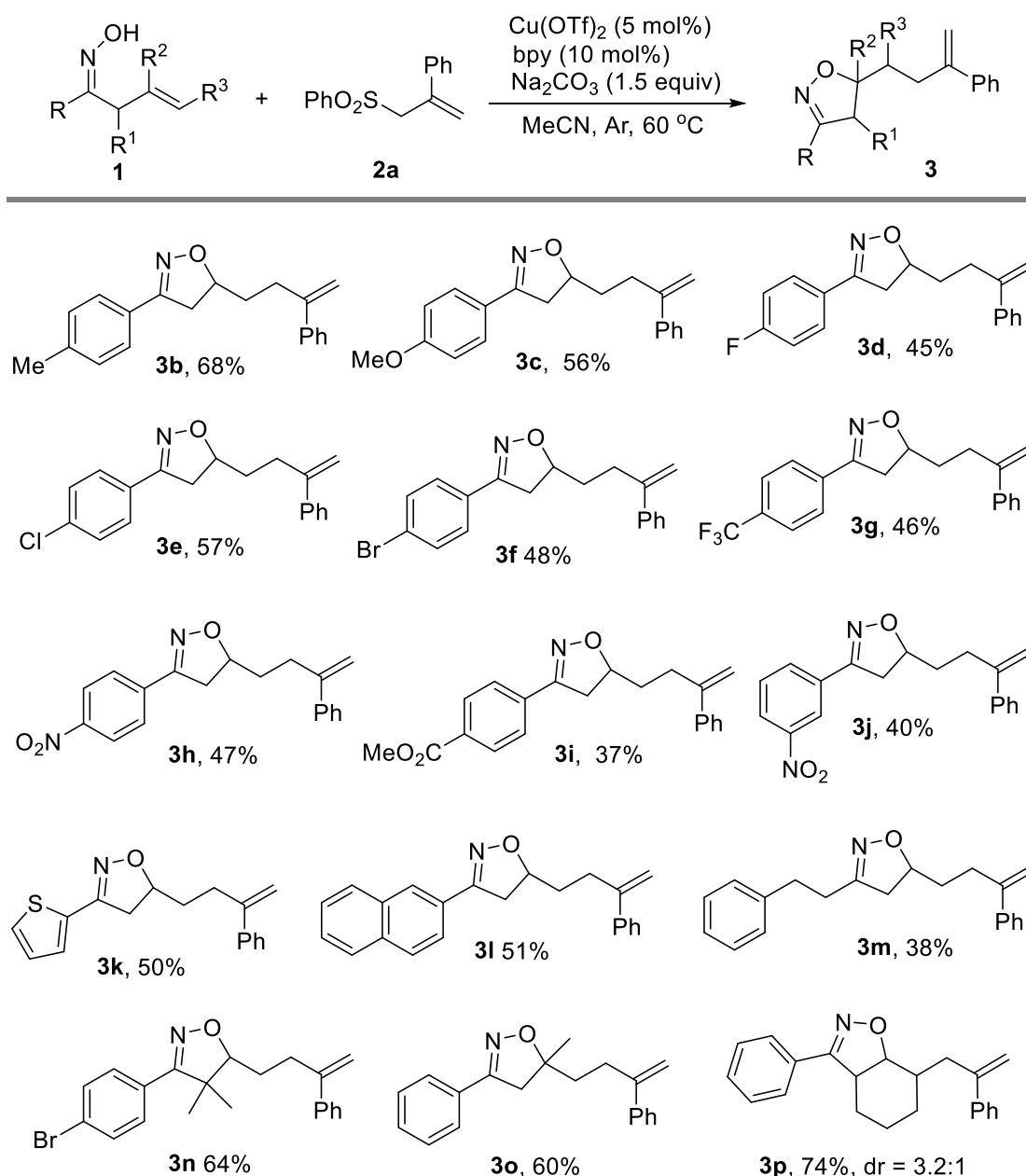
Table 1. Optimization of reaction conditions ^{a,b}



Entry	Cat.	Ligand	Sol.	Yield/(%) ^b
1	Cu(OTf) ₂	1,10-phen	MeCN	57
2	Cu(acac) ₂	1,10-phen	MeCN	56
3	Cu(OAc) ₂	1,10-phen	MeCN	48
4	CuI	1,10-phen	MeCN	37
5	Cu ₂ O	1,10-phen	MeCN	10
6	CuBr	1,10-phen	MeCN	30
7	Cu(OTf) ₂	bpy	MeCN	58
8	Cu(OTf) ₂	TMDE A	MeCN	44
9	Cu(OTf) ₂	bpy	DCE	27
10	Cu(OTf) ₂	bpy	EtOH	16
11	Cu(OTf) ₂	bpy	toluene	38
12	Cu(OTf) ₂	bpy	THF	6
13	Cu(OTf) ₂	bpy	DMF	5
14 ^d	Cu(OTf) ₂	bpy	MeCN	84
15 ^e	Cu(OTf) ₂	bpy	MeCN	86(80) ^c
16	-	bpy	MeCN	trace
17	Cu(OTf) ₂	-	MeCN	38
18 ^f	Cu(OTf) ₂	bpy	MeCN	trace

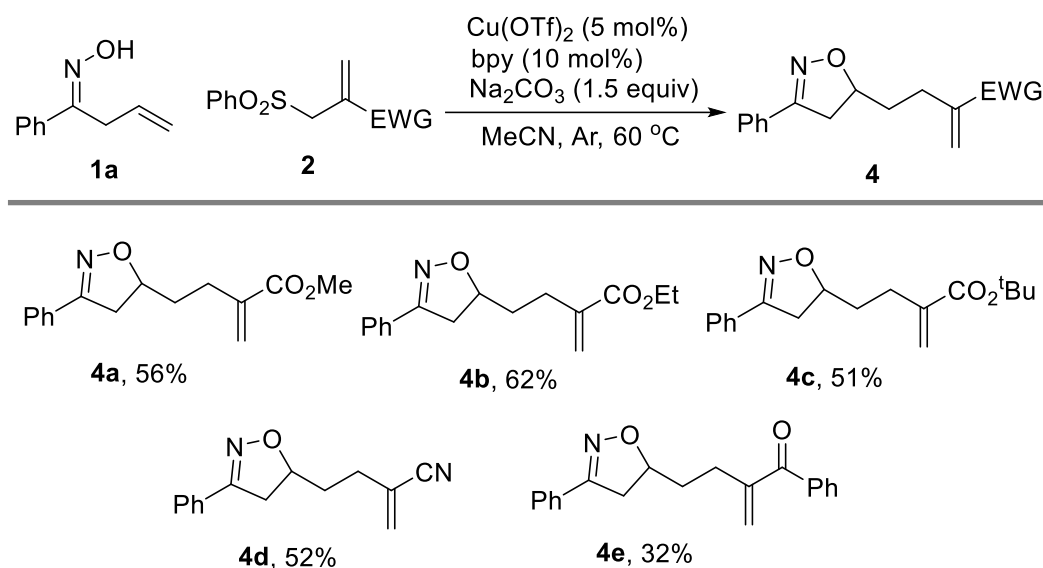
^aReaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), copper catalyst (0.005 mmol), Ligand (0.01 mmol), base (0.15 mmol), solvent (1 mL), at 80 °C under argon. ^bHPLC yields using naphthalene as an internal standard. ^cIsolated yield. ^d0.30 mmol of **2a** was used. ^e60 °C. ^fwithout base.

With the optimized conditions in hand, we next tested the reaction scope with respect to the allylic oximes, keeping allyl sulfone **2a** as the substrate (Scheme 2). Allylic oximes bearing various electronically different substituents (methyl, methoxyl, fluoro, chloro, bromo, trifluoromethyl, nitro, and ester groups) proved to be suitable substrates and provided products **3b-j** in moderate yields. In addition, naphthyl and thien-2-yl oxime were converted smoothly to the corresponding products (**3k-l**). Importantly, aliphatic oxime, such as phenethyl oxime was suitable substrate, delivering the isoxazoline (**3m**) in useful yield. Then, oximes with substituted allylic group were tested. Oxime with double-methyl substitution at R¹ position (**3n**, 64% yield) showed higher reactivity than unsubstituted one (**3f**, 48% yield). Moreover, oxime with steric 1,1-disubstituted alkene group was converted smoothly to the corresponding product (**3o**, 60% yield). Finally, oxime of phenyl cyclohex-2-enyl methanone, having a cyclic allyl unit also proved to be a reactive substrate, transforming into the product **3p** in 74% yield.



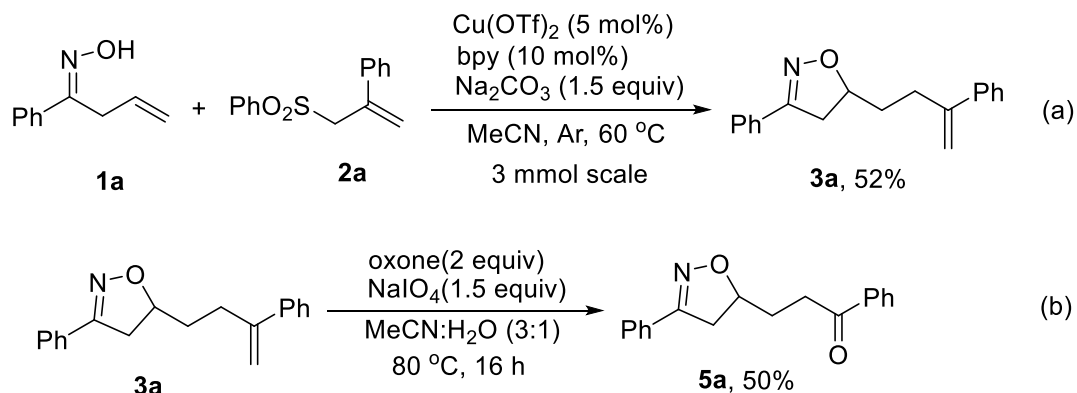
Scheme 2. Substrate scope of allylic oximes. ^aReaction conditions: **1** (0.20 mmol), **2a** (0.60 mmol), $\text{Cu}(\text{OTf})_2$ (5 mol%), bpy (10 mol%) and Na_2CO_3 (0.30 mmol) in MeCN (2.0 mL) at 60 °C for 12 h, under argon. ^bIsolated yields.

Next, we surveyed various allyl sulfones. As summarized in Scheme 3, when the phenyl group in **1a** was replaced by ester group, isoxazoline with useful α,β -unsaturated ester groups **4a-c** were prepared in 51-62% yields. Similarly, cyano and benzoyl substituted allyl sulfones were successfully engaged in the cyclization to yield products **4d-e** in 52% and 32% yields, respectively.



Scheme 3. Substrate scope of allyl sulfones. ^aReaction conditions: **1a** (0.20 mmol), **2a** (0.60 mmol), $\text{Cu}(\text{OTf})_2$ (5 mol%), bpy (10 mol%) and Na_2CO_3 (0.30 mmol) in MeCN (2 mL) at 60 °C for 12 h, under argon. ^bIsolated yields.

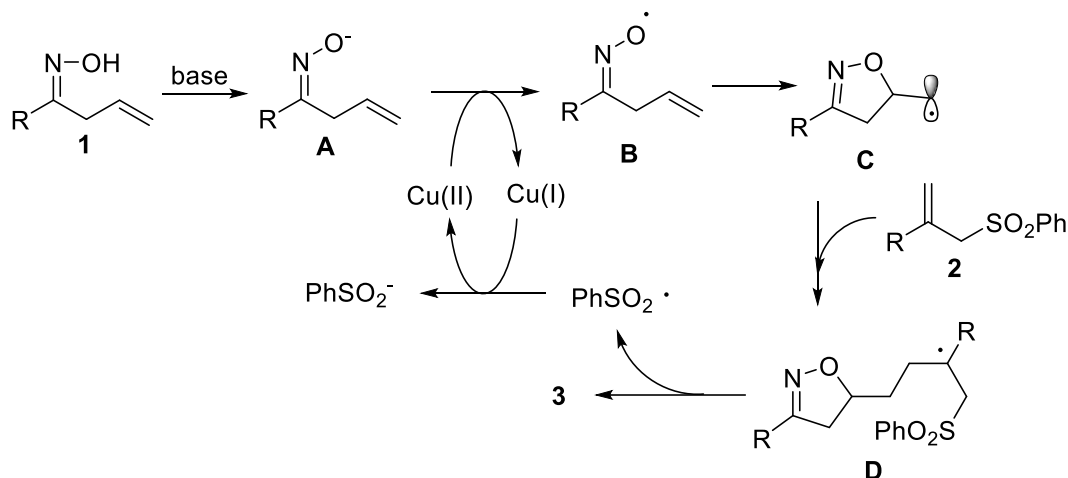
To show practicality of this protocol, we scaled up the reaction to 3 mmol, and the isoxazoline **3a** was isolated in 52% yield (0.43 g) (Scheme 4a). The synthetic utility of the alkene-containing isoxazoline was exemplified by the oxidative cleavage of C=C double bond⁴⁴ into isoxazoline with ketone side chain. Treatment of **3a** with 2 equiv of oxone and 1.5 equiv of NaIO_4 under 80 °C led to the isolation of **5a** in 50% yield (Scheme 4b).



Scheme 4. Gram scale reaction and product derivatization.

According to the above experimental results and previous reports, a plausible mechanism is proposed (Scheme 5). Firstly, iminoxyl anion **A**, formed by deprotonation of

substrates **1** were SET oxidized by Cu(II), to generate the iminoxyl radical **B**.³² Then, iminoxyl radical **B** undergoes 5-exo-trig radical cyclization, delivering the carbon-centered radical intermediate **C**. The addition of the radical **C** onto the C=C bond of allyl sulfone **2** followed by desulfonation leads to the product **3** and a sulfonyl radical. Finally, SET reduction of sulfonyl radical by Cu(I) forms the benzenesulfinic acid anion with the concomitant regeneration of Cu(II).



Scheme 5. Proposed mechanism.

Conclusions

We have developed an efficient copper-catalyzed radical oxyallylation of alkenes with allylic sulfones using oximes as the oxygen-centered radical precursor. This new method provided a practical approach to isoxazolines containing an alkene moiety in moderate to good yields, which may act as a versatile platform allowing further downstream diversification.

Experimental Section

General. Unless stated otherwise, all reactions were carried out under an argon atmosphere. All commercial reagents were used without additional purification. Flash chromatography was carried out with silica gel (200–300 mesh). Melting points were determined without correction on a digital melting-point apparatus. ¹H NMR, ¹³C NMR and ¹⁹F NMR spectra were recorded at 500 (600) MHz, 125 (150) MHz and 400 MHz spectrometers in CDCl₃ using tetramethylsilane (TMS) as internal standard, respectively. High resolution mass spectra (HRMS) were obtained by the ESI ionization sources.

Experimental procedures and characterization of products. To a dried reaction tube was added allyl oxime **1** (0.20 mmol), **2** (0.60 mmol), Cu(OTf)₂ (5 mol%), bpy (10 mol%), Na₂CO₃ (0.30 mmol). The tube was evacuated and backfilled with argon (three times). Then, anhydrous MeCN (2.0 mL) was injected into the tube by syringe. The solution was kept at 60 °C for 12 h. The reaction mixture was partitioned with EtOAc and water. The organic layer was separated and washed with brine, dried over anhydrous Na₂SO₄ and concentrated under

reduced pressure. The crude mixture was purified by silica gel column chromatography (PE/EA 30:1, v/v) to give the corresponding product **3** or **4**.

3-Phenyl-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3a). Colorless liquid (80%, 48 mg), R_f 0.49 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.60–7.56 (m, 2 H), 7.42 (m, 2 H), 7.39–7.32 (m, 4 H), 7.30–7.26 (m, 1 H), 5.33 (d, J 0.8 Hz, 1 H), 5.13 (d, J 1.2 Hz, 1 H), 4.78 (dtd, J 10.4, 7.9, 5.3 Hz, 1 H), 3.36 (dd, J 16.4, 10.4 Hz, 1 H), 2.92 (dd, J 16.4, 8.1 Hz, 1 H), 2.77 (m, 1 H), 2.65 (m, 1 H), 2.00–1.85 (m, 1 H), 1.87–1.70 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.4, 147.4, 140.7, 129.9, 128.7, 128.4, 127.6, 126.6, 126.1, 113.0, 80.7, 77.3, 77., 76.8, 40.0, 34.1, 31.3. HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{20}\text{NO}^+$ ($\text{M}+\text{H}$) $^+$ 278.1539, found 278.1548.

4-Phenyl-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3b). White solid (40 mg, 68%), mp 45–47 °C, R_f 0.53 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.55 (d, J 8.2 Hz, 2 H), 7.44 (d, J 7.5 Hz, 2 H), 7.35 (dd, J 10.2, 4.8 Hz, 2 H), 7.29 (m, 1 H), 7.20 (d, J 8.0 Hz, 2 H), 5.33 (s, 1 H), 5.14 (d, J 1.1 Hz, 1 H), 4.75 (dtd, J 10.3, 7.8, 5.3 Hz, 1 H), 3.38 (dd, J 16.4, 10.3 Hz, 1 H), 2.94 (dd, J 16.4, 8.0 Hz, 1 H), 2.77 (m, 1 H), 2.71–2.59 (m, 1 H), 2.38 (s, 3 H), 1.99–1.90 (m, 1 H), 1.83–1.74 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.4, 147.4, 140.8, 140.1, 129.4, 128.4, 127.5, 127.0, 126.5, 126.1, 112.9, 80.5, 77.3, 77.0, 76.8, 40.1, 34.0, 31.3, 21.4. HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{21}\text{NONa}^+$ ($\text{M}+\text{Na}$) $^+$ 314.1515, found 314.1517.

3-(4-Methoxyphenyl)-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3c). White solid (36 mg, 56%), mp 72–74 °C, R_f 0.32 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.63–7.54 (m, 2 H), 7.43 (m, 2 H), 7.36–7.31 (m, 2 H), 7.28 (m, 1 H), 6.93–6.89 (m, 2 H), 5.32 (d, J 0.9 Hz, 1 H), 5.13 (d, J 1.2 Hz, 1 H), 4.73 (dtd, J 10.3, 7.8, 5.3 Hz, 1 H), 3.83 (s, 3 H), 3.36 (dd, J 16.3, 10.3 Hz, 1 H), 2.93 (dd, J 16.4, 8.0 Hz, 1 H), 2.76 (m, 1 H), 2.65 (m, 1 H), 2.00–1.86 (m, 1 H), 1.84–1.70 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 161.0, 156.0, 147.4, 140.8, 128.4, 128.1, 127.5, 126.1, 122.4, 114.1, 112.9, 80.4, 77.3, 77.0, 76.8, 55.3, 40.2, 34.0, 31.4. HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_2\text{Na}^+$ ($\text{M}+\text{Na}$) $^+$ 330.1470, found 330.1469.

3-(4-Fluorophenyl)-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3d). White solid (26 mg, 45%), mp 79–80 °C, R_f 0.41 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.55–7.49 (m, 4 H), 7.44–7.40 (m, 2 H), 7.37–7.31 (m, 2 H), 7.30–7.26 (m, 1 H), 5.33 (d, J 0.9 Hz, 1 H), 5.13 (d, J 1.2 Hz, 1 H), 4.78 (dtd, J 10.4, 7.9, 5.3 Hz, 1 H), 3.36 (dd, J 16.4, 10.4 Hz, 1 H), 2.92 (dd, J 16.5, 8.1 Hz, 1 H), 2.76 (m, 1 H), 2.65 (m, 1 H), 2.01–1.85 (m, 1 H), 1.86–1.70 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 163.7 (d, J 251.8 Hz), 155.5, 147.3, 140.7, 128.5 (d, J 8.3 Hz), 128.4, 127.6, 126.1, 115.9 (d, J 21.4 Hz), 113.0, 80.8, 77.3, 77.0, 76.8, 40.0, 34.0, 31.3. ^{19}F NMR (400 MHz, CDCl_3) δ 112.7. HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{18}\text{FNONa}^+$ ($\text{M}+\text{Na}$) $^+$ 318.1265, found 318.1267.

3-(4-Chlorophenyl)-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3e). White solid (36 mg, 57%), mp 82–84 °C, R_f 0.54 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.60–7.56 (m, 2 H), 7.42 (m, 2 H), 7.39–7.31 (m, 4 H), 7.30–7.26 (m, 1 H), 5.33 (d, J 0.8 Hz, 1 H), 5.13 (d, J 1.2 Hz, 1 H), 4.78 (dtd, J 10.4, 7.9, 5.3 Hz, 1 H), 3.36 (dd, J 16.4, 10.4 Hz, 1 H), 2.92 (dd, J 16.4, 8.1 Hz, 1 H), 2.77 (m, 1 H), 2.65 (m, 1 H), 2.00–1.89 (m, 1 H), 1.85–1.71 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 155.5, 147.3, 140.7, 135.9, 128.9, 128.4, 127.8, 127.6, 126.1, 113.0, 81.0, 77.3, 77.0, 76.8, 39.8, 34.0, 31.3. HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{18}\text{ClNONa}^+$ ($\text{M}+\text{Na}$) $^+$ 334.0975, found 334.0975.

3-(4-Bromophenyl)-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3f). White solid (34 mg, 48%), mp 94–95 °C, R_f 0.45 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.55–7.49 (m, 4 H), 7.44–7.40 (m, 2 H), 7.37–7.31 (m, 2 H), 7.30–7.26 (m, 1 H), 5.33 (d, J 0.9 Hz, 1 H), 5.13 (d, J 1.2 Hz, 1 H), 4.78 (dtd, J 10.4, 7.9, 5.3 Hz, 1 H), 3.36 (dd, J 16.4, 10.4 Hz, 1 H), 2.92 (dd, J 16.5, 8.1 Hz, 1 H), 2.76 (m, 1 H), 2.65 (m, 1 H), 2.01–1.85 (m, 1 H), 1.86–1.70 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 155.6, 147.3, 140.7, 131.9, 128.8, 128.4, 128.0, 127.6, 126.1, 124.2, 113.0, 81.0, 77.3, 77.0, 76.8, 39.8, 34.0, 31.3. HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{18}\text{BrNONa}^+$ ($\text{M}+\text{Na}$) $^+$ 378.0464, found 378.0465.

5-(3-Phenylbut-3-en-1-yl)-3-(4-(trifluoromethyl)phenyl)-4,5-dihydroisoxazole (3g). White solid (32 mg, 46%), mp 99-100 °C, *R*_f 0.46 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, *J* 8.1 Hz, 2 H), 7.67 (d, *J* 8.3 Hz, 2 H), 7.63-7.26 (m, 5 H), 5.35 (d, *J* 1.0 Hz, 1 H), 5.16 (d, *J* 1.2 Hz, 1 H), 4.82 (dtd, *J* 10.5, 7.9, 5.3 Hz, 1 H), 3.40 (dd, *J* 16.5, 10.5 Hz, 1 H), 2.96 (dd, *J* 16.5, 8.1 Hz, 1 H), 2.78 (m, 1 H), 2.67 (m, 1 H), 2.04-1.92 (m, 1 H), 1.88-1.76 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 155.4, 147.2, 140.6, 133.2, 131.7 (d, *J* 1.0 Hz) (q, *J* 32.8 Hz), 128.4, 127.6, 126.8, 126.1, 125.6 (q, *J* 3.7 Hz), 124.9 (q, *J* 272.9 Hz), 113.1, 81.4, 77.3, 77.0, 76.8, 39.6, 34.01, 31.3. ¹⁹F NMR (400 MHz, CDCl₃) δ 63.9. HRMS (ESI): *m/z* calcd for C₂₀H₁₈F₃NONa⁺ (M+Na)⁺ 368.1238, found 368.1231.

3-(4-Nitrophenyl)-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3h). Yellow solid (30 mg, 47%), mp 73-75 °C, *R*_f 0.29 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 8.28-8.21 (m, 2 H), 7.85-7.75 (m, 2 H), 7.46-7.38 (m, 2 H), 7.37-7.32 (m, 2 H), 7.31-7.26 (m, 1 H), 5.34 (d, *J* 1.1 Hz, 1 H), 5.14 (d, *J* 1.2 Hz, 1 H), 4.86 (dtd, *J* 10.6, 8.0, 5.3 Hz, 1 H), 3.41 (dd, *J* 16.5, 10.6 Hz, 1 H), 2.97 (dd, *J* 16.5, 8.2 Hz, 1 H), 2.83-2.72 (m, 1 H), 2.71-2.61 (m, 1 H), 2.02-1.90 (m, 1 H), 1.89-1.76 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 154.9, 148.4, 147.1, 140.6, 135.9, 128.5, 127.6, 127.2, 126.1, 124.0, 113.2, 82.0, 77.3, 77.0, 76.8, 39.4, 34.0, 31.2. HRMS (ESI): *m/z* calcd for C₁₉H₁₉N₂O₃⁺ (M+H)⁺ 323.1390, found 323.1391.

Methyl-4-(5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazol-3-yl)benzoate (3i). White solid (18 mg, 37%), mp 103-105 °C, *R*_f 0.28 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 8.09-8.03 (m, 2 H), 7.73-7.69 (m, 2 H), 7.42 (m, 2 H), 7.37-7.31 (m, 2 H), 7.28 (m, 1 H), 5.33 (d, *J* 1.0 Hz, 1 H), 5.13 (d, *J* 1.2 Hz, 1 H), 4.81 (dtd, *J* 10.5, 7.9, 5.4 Hz, 1 H), 3.93 (s, 3 H), 3.40 (dd, *J* 16.5, 10.5 Hz, 1 H), 2.96 (dd, *J* 16.5, 8.1 Hz, 1 H), 2.77 (m, 1 H), 2.66 (m, 1 H), 2.01-1.88 (m, 1 H), 1.87-1.73 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 166.5, 155.8, 147.3, 140.7, 134.0, 131.2, 129.9, 128.4, 127.6, 126.4, 126.1, 113.1, 81.3, 77.3, 77.0, 76.8, 52.3, 39.6, 34.0, 31.3. HRMS (ESI): *m/z* calcd for C₂₁H₂₁NO₃Na⁺ (M+Na)⁺ 358.1419, found 358.1434.

3-(3-Nitrophenyl)-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3j). Pale yellow oil (16 mg, 40%), *R*_f 0.27 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 8.39 (t, *J* 1.9 Hz, 1 H), 8.25 (m, 1 H), 8.10-8.04 (m, 1 H), 7.59 (t, *J* 8.0 Hz, 1 H), 7.46-7.40 (m, 2 H), 7.37-7.32 (m, 2 H), 7.30-7.26 (m, 1 H), 5.33 (d, *J* 1.0 Hz, 1 H), 5.14 (d, *J* 1.2 Hz, 1 H), 4.86 (dtd, *J* 10.5, 7.9, 5.4 Hz, 1 H), 3.43 (dd, *J* 16.5, 10.5 Hz, 1 H), 3.00 (dd, *J* 16.5, 8.1 Hz, 1 H), 2.82-2.73 (m, 1 H), 2.67 (m, 1 H), 2.02-1.92 (m, 1 H), 1.87-1.76 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 154.8, 148.5, 147.2, 140.6, 132.1, 131.69, 129.8, 128.5, 127.6, 126.1, 124.4, 121.4, 113.2, 81.7, 77.3, 77.0, 76.8, 39.5, 34.0, 31.3. HRMS (ESI): *m/z* calcd for C₁₉H₁₈N₂O₃Na⁺ (M+Na)⁺ 345.1215, found 345.1212.

5-(3-Phenylbut-3-en-1-yl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole (3k). Brown oil (27mg, 50%), *R*_f 0.38 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 7.44-7.39 (m, 2 H), 7.39-7.30 (m, 3 H), 7.28 (d, *J* 7.4 Hz, 1 H), 7.16 (d, *J* 3.6 Hz, 1 H), 7.05 (dd, *J* 5.0, 3.7 Hz, 1 H), 5.32 (s, 1 H), 5.13 (d, *J* 1.0 Hz, 1 H), 4.76 (dtd, *J* 10.3, 7.8, 5.4 Hz, 1 H), 3.40 (dd, *J* 16.3, 10.3 Hz, 1 H), 2.96 (dd, *J* 16.3, 8.0 Hz, 1 H), 2.76 (m, 1 H), 2.69-2.58 (m, 1 H), 2.05-1.86 (m, 1 H), 1.83-1.70 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 128.4, 128.1, 127.6, 127.2, 126.1, 113.0, 81.0, 77.3, 77.0, 76.8, 40.8, 33.9, 31.3. HRMS (ESI): *m/z* calcd for C₁₇H₁₇NOSNa⁺ (M+Na)⁺ 306.0923, found 306.0924.

3-(Naphthalen-2-yl)-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3l). White solid (30 mg, 51%), mp 114-114 °C, *R*_f 0.46 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 7.98 (dd, *J* 8.7, 1.6 Hz, 1 H), 7.85 (m, 4 H), 7.57-7.47 (m, 2 H), 7.47-7.41 (m, 2 H), 7.36 (dd, *J* 10.2, 4.8 Hz, 2 H), 7.32-7.27 (m, 1 H), 5.35 (s, 1 H), 5.16 (d, *J* 1.1 Hz, 1 H), 4.83 (dtd, *J* 10.4, 7.8, 5.4 Hz, 1 H), 3.51 (dd, *J* 16.3, 10.4 Hz, 1 H), 3.08 (dd, *J* 16.3, 8.0 Hz, 1 H), 2.80 (m, 1 H), 2.73-2.63 (m, 1 H), 2.07-1.91 (m, 1 H), 1.91-1.76 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 156.6, 147.4, 140.8, 134.0, 133.0, 128.4, 127.8, 127.5, 127.0, 126.7, 126.1, 123.5, 113.0, 80.9, 77.3, 77.0, 76.77, 39.9, 34.1, 31.3. HRMS (ESI): *m/z* calcd for C₂₃H₂₁NONa⁺ (M+Na)⁺ 350.1521, found 350.1521.

3-Phenethyl-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3m). Pale yellow oil (29 mg, 38%), R_f 0.36 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.40 (m, 2 H), 7.36-7.32 (m, 2 H), 7.31-7.27 (m, 3 H), 7.21 (m, 3 H), 5.31 (d, J 1.2 Hz, 1 H), 5.09 (d, J 1.3 Hz, 1 H), 4.54 (dtd, J 10.2, 7.7, 5.4 Hz, 1 H), 2.98-2.86 (m, 3 H), 2.67 (m, 3 H), 2.60-2.51 (m, 1 H), 2.47 (m, 1 H), 1.81 (m, 1H), 1.67-1.61 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.2, 147.5, 140.8, 140.6, 128.6, 128.3, 127.5, 126.4, 126.1, 112.8, 79.5, 77.3, 77.0, 76.8, 42.4, 33.9, 32.7, 31.3, 29.6. HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{23}\text{NONa}^+$ ($\text{M}+\text{Na}$) $^+$ 328.1672, found 328.1676.

3-(4-Bromophenyl)-4,4-dimethyl-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3n). Pink oil (49 mg, 64%), R_f 0.55 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.55-7.50 (m, 4 H), 7.46-7.43 (m, 2 H), 7.37-7.33 (m, 2 H), 7.31-7.27 (m, 1 H), 5.35 (s, 1 H), 5.17 (d, J 1.1 Hz, 1 H), 4.14 (dd, J 10.4, 2.6 Hz, 1 H), 2.95 (m, 1 H), 2.68-2.60 (m, 1 H), 1.92-1.82 (m, 1 H), 1.72-1.63 (m, 1 H), 1.28 (s, 3 H), 1.15 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.3, 147.6, 140.7, 131.8, 128.8, 128.6, 128.4, 127.5, 126.1, 124.0, 113.1, 90.29, 77.3, 77.0, 76.8, 50.6, 32.2, 26.8, 24.0, 19.5. HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{BrNONa}^+$ ($\text{M}+\text{Na}$) $^+$ 406.0777, found 406.0780.

5-Methyl-3-phenyl-5-(3-phenylbut-3-en-1-yl)-4,5-dihydroisoxazole (3o). Colorless oil (35 mg, 60%), R_f 0.54 (petroleum ether/ethyl acetate 10:1). ^1H NMR (600 MHz, CDCl_3) δ 7.69-7.64 (m, 2 H), 7.45-7.38 (m, 5 H), 7.37-7.31 (m, 2 H), 7.30-7.25 (m, 1 H), 5.30 (d, J 0.9 Hz, 1 H), 5.12 (d, J 1.2 Hz, 1 H), 3.19 (d, J 16.5 Hz, 1 H), 3.06 (d, J 16.5 Hz, 1 H), 2.71-2.62 (m, 2 H), 1.95-1.86 (m, 2 H), 1.49 (d, J 7.0 Hz, 3 H). ^{13}C NMR (150 MHz, CDCl_3) δ 156.1, 147.9, 140.9, 130.2, 129.8, 128.7, 128.4, 127.5, 126.5, 126.1, 112.6, 87.0, 77.3, 77.1, 76.9, 45.2, 39.0, 30.1, 25.9. HRMS (ESI) : m/z calcd for $\text{C}_{20}\text{H}_{21}\text{NONa}^+$ ($\text{M}+\text{Na}$) $^+$ 314.1515, found 314.1513.

3-Phenyl-7-(2-phenylallyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazole (3p). major isomer: Colorless oil (36 mg, 56.3%), R_f 0.46 (petroleum ether/ethyl acetate 10:1). ^1H NMR (600 MHz, CDCl_3) δ 7.67-7.62 (m, 2 H), 7.48-7.43 (m, 2 H), 7.39 (dd, J 6.7, 3.6 Hz, 3 H), 7.35 (dd, J 10.4, 4.8 Hz, 2 H), 7.31-7.27 (m, 1 H), 5.36 (d, J 1.3 Hz, 1 H), 5.10 (d, J 0.7 Hz, 1 H), 4.34 (dd, J 8.0, 5.2 Hz, 1 H), 3.46 (dd, J 15.9, 7.8 Hz, 1 H), 3.00-2.90 (m, 1 H), 2.46 (dd, J 14.2, 9.3 Hz, 1 H), 2.16-2.04 (m, 1 H), 1.90 (m, 1 H), 1.66 (m, 1 H), 1.52-1.42 (m, 2 H), 1.35 (m, 1 H), 1.30-1.22 (m, 1 H). ^{13}C NMR (150 MHz, CDCl_3) δ 162.8, 146.2, 140.4, 129.9, 129.4, 128.7, 128.4, 127.6, 127.0, 126.3, 114.4, 84.7, 77.3, 77.0, 76.8, 44.1, 39.0, 32.9, 24.9, 24.6, 18.7. HRMS (ESI) : m/z calcd for $\text{C}_{22}\text{H}_{23}\text{NONa}^+$ ($\text{M}+\text{Na}$) $^+$ 340.1672, found 340.1671.

minor isomer: Colorless oil (11 mg, 17.3%), R_f 0.58 (petroleum ether/ethyl acetate 10:1). ^1H NMR (600 MHz, CDCl_3) δ 7.72-7.68 (m, 2 H), 7.44 (m, 2 H), 7.40-7.37 (m, 3 H), 7.35 (m, 2 H), 7.28 (m, 1 H), 5.36 (d, J 1.6 Hz, 1 H), 5.24 (d, J 1.1 Hz, 1 H), 4.37 (dd, J 6.9, 3.4 Hz, 1 H), 3.18 (dt, J 10.3, 6.9 Hz, 1 H), 2.92 (dd, J 14.1, 7.5 Hz, 1 H), 2.72 (dd, J 14.1, 7.3 Hz, 1 H), 1.94-1.80 (m, 2 H), 1.74-1.60 (m, 2 H), 1.41-1.32 (m, 1 H), 1.22-1.15 (m, 2 H). ^{13}C NMR (150 MHz, CDCl_3) δ 164.1, 145.8, 140.9, 129.9, 129.4, 128.8, 128.4, 127.4, 126.8, 126.3, 115.0, 82.5, 77.2, 77.0, 76.8, 45.2, 38.9, 35.1, 26.5 (d, J 13.1 Hz), 22.9. HRMS (ESI) : m/z calcd for $\text{C}_{22}\text{H}_{23}\text{NONa}^+$ ($\text{M}+\text{Na}$) $^+$ 340.1672, found 340.1673.

Methyl-2-methylene-4-(3-phenyl-4,5-dihydroisoxazol-5-yl)butanoate (4a). Yellow oil (29 mg, 51%), R_f 0.22 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.69-7.62 (m, 2 H), 7.42-7.37 (m, 3 H), 6.20 (s, 1 H), 5.63 (d, J 1.0 Hz, 1 H), 4.82-4.68 (m, 1 H), 3.76 (s, 3 H), 3.42 (dd, J 16.5, 10.4 Hz, 1 H), 3.01 (dd, J 16.5, 7.9 Hz, 1 H), 2.57-2.49 (m, 1 H), 2.49-2.41 (m, 1 H), 1.98-1.89 (m, 1 H), 1.84 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.4, 156.4, 139.4, 132.2, 130.0, 129.7, 129.2, 128.7, 128.4, 128.3, 127.0, 126.6, 126.3, 125.7, 117.0, 80.5, 77.3, 77.0, 76.8, 51.9, 39.9, 34.2, 28.1. HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_3\text{Na}^+$ ($\text{M}+\text{Na}$) $^+$ 282.1106, found 282.1109.

Ethyl-2-methylene-4-(3-phenyl-4,5-dihydroisoxazol-5-yl)butanoate (4b). Colorless oil (34 mg, 62%), R_f 0.26 (petroleum ether/ethyl acetate 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.68-7.64 (m, 2 H), 7.42-7.37 (m, 3 H), 6.19 (d, J 0.4 Hz, 1 H), 5.61 (d, J 1.2 Hz, 1 H), 4.81-4.71 (m, 1 H), 4.21 (q, J 7.1 Hz, 2 H), 3.42 (dd, J 16.5, 10.4 Hz, 1 H),

3.01 (dd, *J* 16.5, 7.9 Hz, 1 H), 2.56-2.48 (m, 1 H), 2.48-2.40 (m, 1 H), 1.94 (m, 1 H), 1.84 (m, 1 H), 1.30 (t, *J* 7.1 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 167.0, 156.4, 139.7, 130.0, 129.7, 129.1, 128.7, 128.4, 126.6, 126.3, 125.4, 80.6, 77.3, 77.0, 76.8, 60.7, 39.9, 34.2, 28.1, 14.2. HRMS (ESI): *m/z* calcd for C₁₆H₁₉NO₃Na⁺ (M+Na)⁺ 296.1263, found 296.1265.

tert-Butyl-2-methylene-4-(3-phenyl-4,5-dihydroisoxazol-5-yl)butanoate (4c). Yellow oil (31 mg, 51%), *R_f* 0.36 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 7.69-7.64 (m, 2 H), 7.44-7.34 (m, 3 H), 6.09 (d, *J* 1.3 Hz, 1 H), 5.54 (d, *J* 1.3 Hz, 1 H), 4.76 (dtd, *J* 10.4, 7.4, 5.9 Hz, 1 H), 3.42 (dd, *J* 16.5, 10.4 Hz, 1 H), 3.01 (dd, *J* 16.5, 7.9 Hz, 1 H), 2.53-2.34 (m, 2 H), 1.94 (m, 1 H), 1.83 (m, 1 H), 1.49 (s, 9 H). ¹³C NMR (125 MHz, CDCl₃) δ 156.4, 141.2, 130.0, 129.8, 128.7, 126.6, 124.5, 80.7 (d, *J* 5.7 Hz), 77.3, 77.0, 76.8, 39.9, 34.3, 28.1. HRMS (ESI): *m/z* calcd for C₁₈H₂₃NO₃Na⁺ (M+Na)⁺ 324.1576, found 324.1572.

2-Methylene-4-(3-phenyl-4,5-dihydroisoxazol-5-yl)butanenitrile (4d). Orange solid (24 mg, 52%), mp 44-45 °C, *R_f* 0.14 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 7.72-7.61 (m, 2 H), 7.46-7.36 (m, 3 H), 5.90 (s, 1 H), 5.82 (s, 1 H), 4.76 (dtd, *J* 10.5, 7.7, 4.9 Hz, 1 H), 3.48 (dd, *J* 16.5, 10.4 Hz, 1 H), 3.02 (dd, *J* 16.5, 7.5 Hz, 1 H), 2.57-2.39 (m, 2 H), 2.03-1.86 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 156.5, 131.3, 130.2, 129.4, 128.8, 126.7, 122.0, 118.4, 79.4, 77.3, 77.0, 76.8, 40.2, 33.4, 30.9. HRMS (ESI): *m/z* calcd for C₁₄H₁₄N₂ONa⁺ (M+Na)⁺ 249.0998, found 249.1000.

2-Methylene-1-phenyl-4-(3-phenyl-4,5-dihydroisoxazol-5-yl)butan-1-one (4e) White solid (20 mg, 32%) ; mp 87-88 °C, *R_f* 0.21 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 7.75 (m, 2 H), 7.70-7.64 (m, 2 H), 7.57-7.52 (m, 1 H), 7.47-7.37 (m, 5 H), 5.95 (s, 1 H), 5.68 (s, 1 H), 4.86-4.76 (m, 1 H), 3.45 (dd, *J* 16.5, 10.4 Hz, 1 H), 3.05 (dd, *J* 16.5, 7.9 Hz, 1 H), 2.72-2.58 (m, 2 H), 2.03-1.85 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 198.1, 156.5, 147.0, 137.7, 132.3, 130.0, 129.8, 129.5, 128.7, 128.2, 126.7, 80.7, 77.3, 77.0, 76.8, 40.0, 34.0, 28.5. HRMS (ESI): *m/z* calcd for C₂₀H₁₉NO₂Na⁺ (M+Na)⁺ 328.1308, found 328.1307.

Phenyl-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propan-1-one (5a). White solid (28 mg, 50%) ; mp 78-79 °C, *R_f* 0.12 (petroleum ether/ethyl acetate 10:1). ¹H NMR (500 MHz, CDCl₃) δ 8.04-7.92 (m, 2 H), 7.70-7.62 (m, 2 H), 7.61-7.51 (m, 1 H), 7.46 (dd, *J* 10.6, 4.7 Hz, 2 H), 7.43-7.38 (m, 3 H), 4.86 (m, 1 H), 3.48 (dd, *J* 16.5, 10.3 Hz, 1 H), 3.23 (t, *J* 7.2 Hz, 2 H), 3.09-3.01 (m, 1 H), 2.19 (m, 1 H), 2.14-2.02 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 199.3, 156.7, 136.8, 133.2, 130.1, 129.6, 128.7, 128.1, 126.6, 80.2, 77.3, 77.0, 76.8, 40.3, 34.4, 29.7. HRMS (ESI): *m/z* calcd for C₁₈H₁₇NO₂Na⁺ (M+Na)⁺ 302.1157, found 302.1138.

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Supplementary Material

Supplemental material such as substrate preparation, optimization details, references and ¹H NMR, ¹³C NMR, ¹⁹F NMR spectra for compounds **3a-3p**, **4a-4e** and **5a** for this article is available online.

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