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Cobalt-catalyzed aerobic oxidative cyclization of β,γ-unsaturated oximes

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ABSTRACT

Cobalt complex $Co(nmp)_2$ can efficiently catalyze the aerobic oxidative 5-exo cyclization of β,γ-unsaturated oximes to afford isoxazolines. The key cyclization step involves the generation of carbon-centred radicals. The products are largely dependent on the reaction conditions. The oxidative termination products **2** were produced predominantly when the reaction was carried out in *i*-PrOH, whereas the reductive termination products **3** were selectively obtained in toluene in the presence of cyclohexa-1,4-diene.

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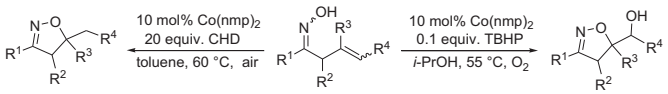
1. Introduction

Transition metal-catalyzed aerobic oxygenation of olefins is not only an important process in chemical industry, but also of great value in current organic synthesis.[1] The studies by Mukaiyama et al. have demonstrated that bis(β-diketonato) cobalt complexes can efficiently catalyze the aerobic oxygenation of olefins in the presence of a reductant, which is usually a secondary alcohol used as solvent.[2] The process was named as 'oxidation–reduction hydration'. When this methodology was applied to 5-hydroxy-1-alkenes, a highly stereoselective synthesis of 2-hydroxymethyl tetrahydrofurans was developed.[3,4] The reaction is largely dependent on the structural properties of cobalt catalysts, and yields can be improved by the addition of *tert*-butyl hydroperoxide (*t*BuOOH, TBHP). Hartung et al. later conducted a series of detailed investigations on this reaction with an aim to extend its synthetic scope and enhance the efficacy.[5] Their studies reveal that using bis{2,2,2-trifluoromethyl-1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*)bicyclo[2.2.1] hept-3-yliden] ethanolato-κ*O*}cobalt(II) (CoL^1_2) or bis{4-[3,5-bis(trifluoromethyl) phenyl]-2-(oxo-κ*O*)-but-3-en-4–olato-κ*O*}cobalt(II) as catalyst can obviate the use of TBHP. In addition, when the reaction is performed in toluene in the presence of cyclohexa-1,4-diene (CHD), the reductive termination products will be obtained in high yield. In another study, Pagenkopf et al. developed an improved procedure, which employs bis (5,5-dimethyl-1-(4- methylpiperazin-1-yl)hexane-1,2,4-trione) cobalt (II) ($Co(nmp)_2$) and 10 mol % of TBHP as catalyst.[6] The later procedure is advantageous in terms of simplified purification as well as high product yield.[6]

Isoxazolines are important intermediates in organic synthesis. Besides the commonly used 1,3-dipolar addition reactions between nitrile oxides and alkenes, isoxazolines can be accessed through the C–O forming cyclization of unsaturated oximes.[7,8] In this context, an aerobic oxidative cyclization of β,γ-unsaturated oximes has been recently achieved by using $Pd(OAc)_2$ as catalyst.[9] This protocol is attractive in that it employs the economical and environmentally benign oxygen as oxidant to realize the dioxygenation of alkenes. Considering the catalytic capacity of cobalt complexes in the oxygenation of olefins, we envisioned that cobalt catalysts would also be applicable to this type of oxidative cyclization. We examined the effects of several cobalt(II) salts and complexes, and found that $Co(nmp)_2$ was highly effective to prompt the reaction. Moreover, both oxidative termination products and reductive termination products can be selectively obtained, depending on the reaction conditions (Scheme 1).



Scheme 1. Cobalt-catalyzed cyclization of unsaturated oximes.

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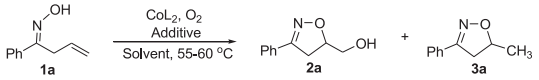
2. Results and discussion

We initiated this study by subjecting compound **1a** to several cobalt complexes and salts under oxygen atmosphere. The results are summarized in Table 1. Bis{2,2,2-trifluoromethyl-1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*)bicyclo[2.2.1] hept-3-yliden] ethanolato-κ*O*}cobalt(II) ($CoL^1{}_2$) and bis (5,5-dimethyl-1-(4- methylpiperazin-1-yl)hexane-1,2,4-trione) cobalt (II) ($Co(nmp)_2$) (Fig. 1), which can effectively prompt the oxidative cyclization of 5-hydroxy-1-alkenes as reported, respectively by Hartung et al.[5] and Pagenkopf et al.,[6] are capable of effecting the cyclization of **1a** in *i*-PrOH. Compound **2a** was obtained in good yield when the reaction was performed under Pagenkopf's conditions (Table 1, entry 6). Running the reaction in several other solvents led to inferior results. $Co(OAc)_2$, $Co(acac)_2$ and $CoBr_2$ also exhibited catalytic capacity, but they were not as effective as $Co(nmp)_2$. In some cases, a small amount of **3a** was isolated along with compound **2a**. Control experiments showed that the reaction also took place in the absence of cobalt catalyst when it was run in AcOH or toluene, but the yield of **2a** was low (Table 1, entries 17, 18).

As can be seen in Table 1, $Co(nmp)_2$ performed the best among the catalysts screened when used together with 0.1 equiv of TBHP (Table 1, entry 6). These conditions were then applied to a variety of differently substituted β,γ-unsaturated oximes (**2b**–**2m**) and α,β-unsaturated oxime **2n**. The results are shown in Table 2. The reaction proceeded smoothly for all the chosen substrates, resulting in the formation of 4,5-dihydroisoxazoles in good yields. The substituents did not influence the reaction consequence much, albeit that the yield was a little lower for **2d** and **2g**. When compounds **1i**, **1l** and **1m** were used, the corresponding isoxazolines were obtained as a mixture of two diastereoisomers. In the case of compound **2n**, 5-endo cyclization took place under the reaction conditions (Table 2, entry 14). It is noteworthy that both *E* and *Z* isomers of **1** can be converted to products **2**, and the initial configuration of the substrates has no apparent influence on the reaction rate.

Table 1
Screening of the conditions for the oxidative cyclization of **1a**



Entry	CoL_2 (mol %)	Additive (equiv)	Solvent	Products/yield (%)[a]
1	$Co(L^1)_2$ (10)	None	*i*-PrOH	**2a**/54, **3a**/—[b]
2	$Co(L^1)_2$ (10)	TBHP (1.0)	*i*-PrOH	**2a**/42, **3a**/—[b]
3	$Co(L^1)_2$ (10)	TBHP (0.1)	*i*-PrOH	**2a**/47, **3a**/—[b,c]
4	$Co(L^1)_2$ (10)	TBHP (0.1)	AcOH	**2a**/21, **3a**/—[b,c]
5	$Co(nmp)_2$ (10)	None	*i*-PrOH	**2a**/60, **3a**/6
6[f]	**$Co(nmp)_2$ (10)**	**TBHP (0.1)**	***i*-PrOH**	**2a/78, 3a/trace**[c]
7	$Co(nmp)_2$ (5)	TBHP (0.1)	*i*-PrOH	**2a**/21, **3a**/11
8	$Co(nmp)_2$ (10)	TBHP (0.1)	EtOH	**2a**/30, **3a**/—[b]
9	$Co(nmp)_2$ (10)	TBHP (0.1)	MeCN	**2a**/43, **3a**/6
10	$Co(nmp)_2$ (10)	TBHP (0.1)	AcOH	**2a**/31, **3a**/—[b]
11	$Co(OAc)_2$ (10)	TBHP (0.1)	*i*-PrOH	**2a**/40, **3a**/6
12	$Co(acac)_2$ (10)	TBHP (0.1)	*i*-PrOH	**2a**/37, **3a**/7
13	$Co(acac)_2$ (10)	None	*i*-PrOH	**2a**/29, **3a**/7
14	$CoCl_2$ (10)	TBHP (0.1)	*i*-PrOH	**2a**/10, **3a**/—[b]
15	$CoBr_2$ (10)	TBHP (0.1)	*i*-PrOH	**2a**/39, **3a**/10
16	None	TBHP (0.1)	*i*-PrOH	n.d.[c,d]
17	None	None	AcOH	**2a**/31, **3a**/—[b,e]
18	None	PPh_3 (1.0)	Toluene	**2a**/37, **3a**/5 +S.M.

[a] Isolated yields. The reaction time was 16 h unless otherwise specified.
[b] Not isolated.
[c] The reaction time was 5 h.
[d] With **1a** being recovered.
[e] Treated with PPh_3 after reaction.
[f] The optimal reaction conditions.

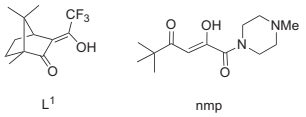
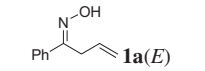
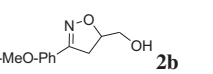
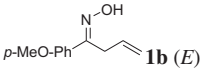
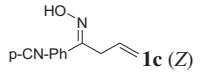
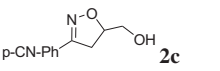
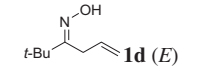
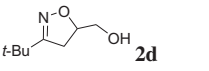
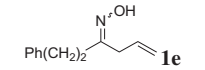
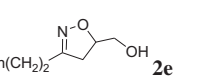
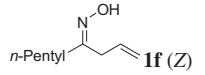
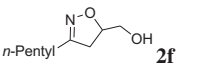
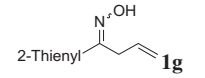
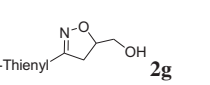
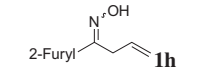
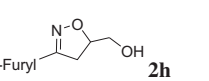
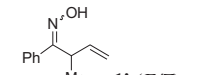
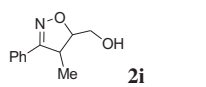
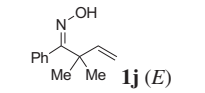
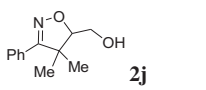
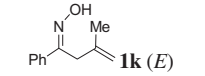
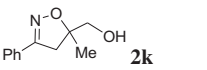
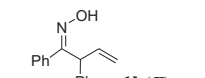
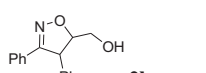
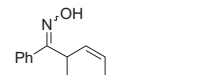
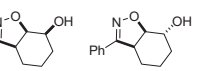
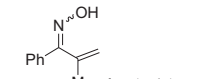
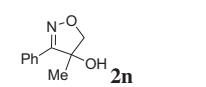


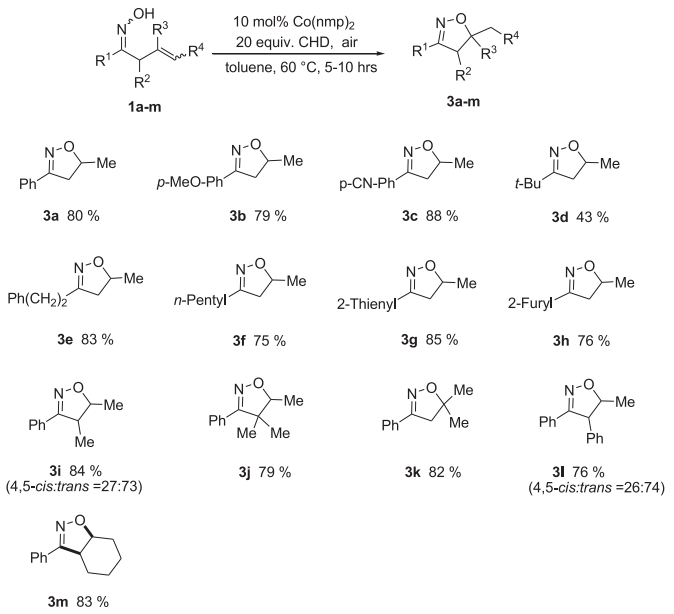
Fig. 1. Structures of ligand L^1 and nmp.

Table 2
$Co(nmp)_2$-catalyzed aerobic cyclization of unsaturated oximes[a]

Entry	Substrate	Product(s)	Yield (%)[b]
1	 **1a**(*E*)	 **2a**	78
2	 **1b** (*E*)	**2b**	76
3	 **1c** (*Z*)	 **2c**	92
4	 **1d** (*E*)	 **2d**	55
5	 **1e** (*E*/*Z*)	 **2e**	81
6	 **1f** (*Z*)	 **2f**	65
7	 **1g** (*E*/*Z*)	 **2g**	60
8	 **1h** (*E*/*Z*)	 **2h**	81
9	 **1i** (*E*/*Z*)	 **2i**	83 (*dr*=35:65)[c]
10	 **1j** (*E*)	 **2j**	77
11	 **1k** (*E*)	 **2k**	62
12	 **1l** (*E*)	 **2l**	65 (*cis*:*trans* =42:58)[c]
13	 **1m** (*E*/*Z*)	 **2m-1** **2m-2**	81 (**2m-1**:**2m-2** =35:65)[c]
14	 **1n** (*E*/*Z*)	 **2n**	73

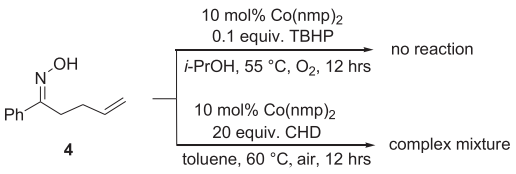
[a] The reaction was carried out on 1.0 mmol scale. Conditions: 10 mol % $Co(nmp)_2$, 10 mol % TBHP (70% in water), 5 mL *i*-PrOH, O_2 (in balloon), 55 °C.
[b] Isolated yields.
[c] Determined by GC–MS and ^1H NMR.

In the above-mentioned reactions, besides compounds **2**, a tiny amount of reductive termination products **3** were also generated in some cases. Further experiments showed that compounds **3** could became dominant when the reaction was performed in toluene in the presence of 20 equiv of CHD.[5b–d] As such, with the air as terminal oxidant, compounds **3** were generated mostly in good yields from **1** (Scheme 2). For the reactions of compounds **1i** and **1l**, a diasteroselectivity of roughly 3:1 was observed, respectively, which was higher than their counterparts shown in Table 2. On the other hand, when compound **1n** was used as the substrate, the expected **3n** did not form. Instead, the reaction afforded **2n** in yield of 71%.



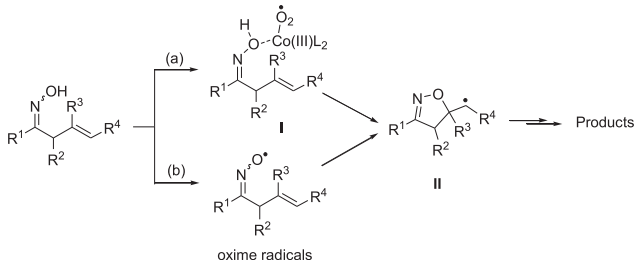
Scheme 2. The reaction of **1** in toluene under air in the presence of CHD.

Although these protocols are effective for the cyclization of β,γ-unsaturated oximes, they are not applicable to γ,δ-unsaturated oximes for similar transformations. When compound **4** was subjected to the reaction conditions shown in Table 2, no reaction took place, with only the starting materials being recovered. On the other hand, under the conditions of reductive termination, the reaction led to a complex mixture (Scheme 3).

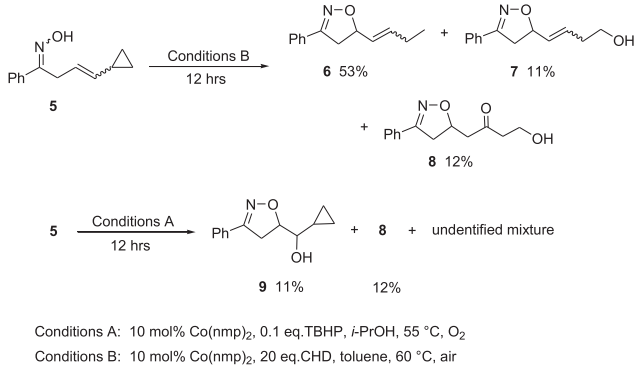


Scheme 3. The results with gamma,delta-unsaturated oxime 4 under the present conditions.

The mechanistic aspects of the cobalt-catalyzed aerobic oxygenation of olefins have been of much interest. It is believed that in general, the first step is the oxidation of Co(II) by oxygen, from which $Co(III)L_2OO^{\bullet}$ radical is produced.[2] Concerning the cobalt-mediated cyclization of 5-hydroxy-1-alkenes, Hartung proposes that the key step involves the single electron transfer (SET) from the double bond to the hydroxyl-binded $Co(III)L_2OO^{\bullet}$ radical.[5a] The tetrahydrofuran ring forms subsequently, affording the tetrahydrofuran-2-yl methyl radicals, which are then trapped by oxygen or CHD.[5b] The current cyclization of oximes might be rationalized by this mechanism as well (Scheme 4(a)). Indeed, when the protocol was applied to compound **5**, the cyclopropyl ring in **5** underwent ring opening under both conditions A and B, indicating that the cyclization step involves the generation of carbon-centred radicals (Scheme 5). However, apart from the SET mechanism, the radical II could also derive from the 5-exo-trig cyclization of oxime radicals (Scheme 4(b)). Our recent work shows that oxime radicals can be conveniently generated from the reaction of oximes with DEAD (diethyl azodicarboxylate).[10] As a matter of fact, Co(II) salts, such as $Co(OAc)_2$ and $Co(acac)_2$, have been well known to be capable of facilitating the generation of phthalimido-*N*-oxyl (PINO) radical from *N*-hydroxyphthalimide (NHPI) under aerobic conditions.[11] Considering the structural analogy of oxime radicals to PINO, it is possible that $Co(III)OO^{\bullet}$ radicals can convert oximes to oxime radicals as well. In fact, the bond dissociation energy (BDE) of the O–H bond in oximes is even lower (about 83 kcal/mol on average)[12] than in NHPI (about 88 kcal/mol).[11] Therefore, we assume that the transformations of **1** to 4,5-dihydroisoxazoles **2** and **3** follow, at least partly, the mechanism shown in path (b) of Scheme 4. This hypothesis is supported by the observations that the reaction of **1a** occurred moderately with $Co(OAc)_2$ as catalyst, or in AcOH and toluene in the absence of cobalt (Table 1). By contrast, $Co(OAc)_2$ is ineffective for the cyclization of 5-hydroxy-1-alkenes.

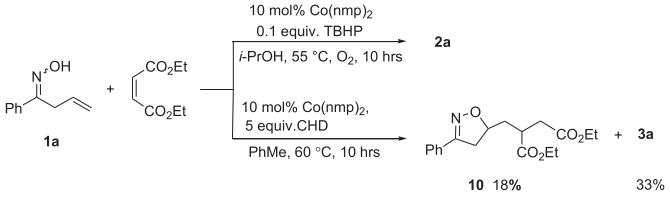


Scheme 4. Possible reaction mechanism.



Scheme 5. Evidence to support a free radical process.

In the case where conditions A were applied, compound **9** was also obtained along with the ring-opening product **8**. Probably the higher oxygen concentration here rendered the trapping of radical I by O_2 to be competitive with the ring opening process. This trend was reflected too when the reaction was carried out in the presence of activated alkenes. As shown in Scheme 6, when **1a** was subjected to



Scheme 6. Traping experiment with diethyl maleate.

$Co(nmp)_2$ in toluene in the presence of 5 equiv of CHD and 10 equiv of diethyl maleate at 60 °C in the air, compound **10** was obtained in 18% yield, together with compound **3a**. On the other hand, the reaction only led to the formation of compound **2a** under conditions A.

3. Conclusion

In summary, we have demonstrated that the aerobic oxidative cyclization of β,γ-unsaturated oximes can be achieved by using cobalt complex $Co(nmp)_2$ as catalyst. When the reactions are carried out in *i*-PrOH with 1 atm of O_2 as the oxidant, the major products are the oxidative termination products **2**. On the other hand, conducting the reaction in toluene in the air in the presence of 20 equiv of CHD would predominantly result in the formation of reductive termination products **3**. This work provides an alternative protocol for the synthesis of 4,5-dihydroisoxazoles.

4. Experimental

4.1. General information

Chemicals and solvents were purified by standard methods. Reaction progress was monitored with thin layer chromatography (TLC) performed on GF254 silica gel plates. Flash chromatography was carried out with silica gel (200–300 mesh).

The ^1H and ^{13} C NMR spectra were recorded on a Bruker AM-400 MHz spectrometer. All the spectra were obtained in deuterated chloroform and were referred to residual chloroform at δ 7.27 ppm for ^1H spectra and the center peak of the triplet at δ 77.0 (t) for ^{13}C spectra. The EI-MS spectra were measured on an HP 5988A spectrometer by direct inlet at 70 eV. The high resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEX II 47e spectrometer by ESI. Melting points were measured on an XT-4 melting point apparatus and were uncorrected.

2-(2-Phenyltetrahydrofuran-2-yl)acetaldehyde,[13] bis{2,2,2-trifluoromethyl-1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*) bicyclo[2.2.1]hept-3-yliden]ethanolato-κ*O*} cobalt(II) (CoL'_2),[5a] and bis(5,5-dimethyl-1-(4- methylpiperazin-1-yl)hexane-1,2,4-trione) cobalt(II) ($Co(nmp)_2$)[6] were prepared according to the reported procedures. Compounds **1a**–**1n** were prepared as previously reported.[9]

4.2. General procedure for the syntheses of 2a–2m

β,γ-Unsaturated oxime **1** (1.0 mmol) was added into 5 mL of *i*-PrOH contained in a flask charged with $Co(nmp)_2$ (0.1 mmol) under 1 atm of O_2 (balloon) at room temperature. Then 0.1 mmol of *tert*-butyl hydroperoxide (TBHP) (70% in water) was added in one portion into the mixture under stirring, and the resulting solution was heated to 55 °C and stirred at that temperature for 5 h. The reaction mixture was cooled to room temperature, purged of O_2 with argon, and treated with methyl iodide (62 μL, 1.0 mmol, 1.0 equiv). After stirring for another 5 h, the mixture was concentrated under reduced pressure and the residual was dissolved in 20 mL of CH_2Cl_2, followed by addition of 20 mL of water. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure.[6] The residual was treated with flash chromatography to afford **2**. Compounds **2n** and **9** was obtained in the same way.

4.3. General procedure for the syntheses of 3a–3m

β,γ-Unsaturated oxime **1** (1.0 mmol) and cyclohexa-1,4-diene (CHD) (20 mmol) were consecutively added into 5 mL of toluene contained in a 10 mL round bottom flask charged with $Co(nmp)_2$ (0.10 mmol). The flask was then equipped with a condenser, and the resulting solution was stirred at 60 °C in the air. After the reaction finished as indicated by TLC, The reaction mixture was cooled to 20 °C and concentrated under reduced pressure. The residual was purified by chromatography to give product **3**.[5b] Compounds **6**, **7** and **8** were obtained in the same way.

4.4. Characterization data for the products

*4.4.1. (3-Phenyl–4,5-dihydroisoxazol-5-yl)methanol (**2a**).* White solid, mp 83–84 °C, R_f=0.30 (petroleum ether:ethyl acetate=1:1); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.68–7.66 (m, 2H), 7.41 (d, *J*=4.8 Hz, 3H), 4.91–4.84 (m, 1H), 3.89–3.86 (m, 1H), 3.72–3.66 (m, 1H), 3.39 (dd, *J*=16.8, 10.8 Hz, 1H), 3.29 (dd, *J*=16.4, 8.0 Hz, 1H), 2.30 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 157.1, 130.2, 129.3, 128.7, 126.7, 81.2, 63.6, 36.3; EI-MS *m*/*z* (rel int., %): 177 (M^+, 49.8), 146 (87.5), 118 (100.0), 91(30.9), 77 (80.4).

*4.4.2. (3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl)methanol (**2b**).* Pale yellow solid, mp 140–141 °C, R_f=0.26 (petroleum ether:ethyl acetate=1:1); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.59 (d, *J*=8.8 Hz, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 4.86–4.80 (m, 1H), 3.87–3.83 (m, 1H), 3.83 (s, 3H), 3.67 (dd, *J*=12.4, 4.8 Hz, 1H), 3.35 (dd, *J*=16.4, 10.4 Hz, 1H), 3.25 (dd, *J*=16.4, 8.0 Hz, 1H), 2.42 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 161.1, 156.6, 128.2, 121.8, 114.1, 80.9, 63.6, 55.3, 36.5; EI-MS *m*/*z* (rel int., %): 207 (M^+, 100.0), 176 (82.4), 148 (53.9), 121 (92.6), 107 (11.2), 92(15.5).

*4.4.3. 4-(5-(Hydroxymethyl)-4,5-dihydroisoxazol-3-yl)benzonitrile (**2c**).* White solid, mp 144–145 °C, R_f=0.35 (petroleum ether:ethyl acetate=1:1); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.78 (d, *J*=8.4 Hz, 2H), 7.70 (d, *J*=8.4 Hz, 2H), 4.98–4.92 (m, 1H), 3.97–3.91 (m, 1H), 3.74–3.68 (m, 1H), 3.39 (dd, *J*=16.4, 10.8 Hz, 1H), 3.32 (dd, *J*=16.4, 8.0 Hz, 1H), 1.93–1.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 155.8, 133.6, 132.4, 127.1, 118.2, 113.4, 82.2, 63.4, 35.5; EI-MS *m*/*z* (rel int., %): 202 (M^+, 28.7), 185 (2.0), 171 (69.3), 155 (16.7), 143 (100.0), 129 (52.4).

*4.4.4. (3-(tert-Butyl)-4,5-dihydroisoxazol-5-yl)methanol (**2d**).* Colourless oil, R_f=0.44 (petroleum ether:ethyl acetate=1:1); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): δ 4.67–4.61 (m, 1H), 3.74–3.70 (m, 1H), 3.57–3.52 (m, 1H), 3.00 (dd, *J*=16.8, 10.4 Hz, 1H), 2.86 (dd, *J*=16.8, 7.2 Hz, 1H), 2.36 (br, 1H), 1.19 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 166.5, 80.1, 63.7, 35.7, 33.0, 28.0; EI-MS *m*/*z* (rel int., %): 157 (M^+, 16.6), 142 (1.5), 126 (49.2), 84 (10.4), 57 (100.0).

*4.4.5. (3-Phenethyl-4,5-dihydroisoxazol-5-yl)methanol (**2e**).* Pale yellow oil, R_f=0.52 (petroleum ether:ethyl acetate=1:1); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.31–7.26 (m, 2H), 7.22–7.19 (m, 3H), 4.66–4.60 (m, 1H), 3.71 (dd, *J*=12.0, 3.2 Hz, 1H), 3.52 (dd, *J*=12.0, 4.8 Hz, 1H), 2.95–2.88 (m, 3H), 2.79 (dd, *J*=17.2, 7.6 Hz, 1H), 2.68–2.64 (m, 2H), 2.41 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 158.8, 140.4, 128.5, 128.2, 126.3, 80.0, 63.5, 38.6, 32.5, 29.3; EI-MS *m*/*z* (rel int., %): 205 (M^+, 47.1), 174 (66.9), 146 (72.5), 118 (20.2), 105 (57.3), 91 (100.0).

*4.4.6. (3-Pentyl-4,5-dihydroisoxazol-5-yl)methanol (**2f**).* Colourless oil, R_f=0.40 (petroleum ether:ethyl acetate=1:1); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 4.67–4.61 (m, 1H), 3.82–3.61 (m, 1H), 3.55 (dd, *J*=12.0, 4.0 Hz, 1H), 3.00–2.92 (m, 1H), 2.82 (dd, *J*=17.2, 7.6 Hz, 1H), 2.32 (t, *J*=7.6 Hz, 2H), 1.57–1.53 (m, 2H), 1.33–1.29 (m, 4H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 159.6, 79.8, 63.7, 38.4, 31.3, 27.5, 25.9, 22.2, 13.8; EI-MS *m*/*z* (rel int., %): 171 (M^+, 1.7), 149 (5.1), 115 (20.1), 71 (25.7), 43 (100.0).

*4.4.7. (3-(Thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)methanol (**2g**).* Yellow solid, mp 95–96 °C, R_f=0.36 (petroleum ether:ethyl

acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.39–7.37 (m, 1H), 7.21–7.20 (m, 1H), 7.06–7.05 (m, 1H), 4.88–4.83 (m, 1H), 3.86 (d, J=12.0 Hz, 1H), 3.68 (dd, J=12.0, 4.4 Hz, 1H), 3.49–3.27 (m, 2H), 2.44 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 152.8, 131.7, 128.6, 128.3, 127.3, 81.5, 63.4, 37.1; EI-MS m/z (rel int., %): 183 (M^+, 99.3), 152 (82.0), 124 (70.3), 105 (27.2), 97 (100.0).

*4.4.8. (3-(Furan-2-yl)-4,5-dihydroisoxazol-5-yl)methanol (**2h**) (new compound).* Pale yellow oil, R_f=0.34 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.50 (s, 1H), 6.70 (d, J=3.6 Hz, 1H), 6.47 (t, J=1.6 Hz, 1H), 4.85–4.79 (m, 1H), 3.84 (dd, J=12.4, 3.2 Hz, 1H), 3.66 (dd, J=12.0, 4.8 Hz, 1H), 3.34 (dd, J=16.8, 10.8 Hz, 1H), 3.24 (dd, J=16.8, 8.0 Hz, 1H), 2.48 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 149.2, 144.6, 144.4, 112.0, 111.6, 81.0, 63.3, 36.1; EI-MS m/z (rel int., %): 167 (M^+, 100.0), 136 (95.2), 108 (73.7), 81 (51.5), 53 (25.8); ESI-HRMS: m/z Calcd for $C_8H_9NO_3$+H^+: 168.0655, found 168.0650.

*4.4.9. (3-Phenyl-4-methyl-4,5-dihydroisoxazol-5-yl)methanol (**2i**, dr=35:65).* Colourless oil, R_f=0.27 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.69–7.66 (m, 3.20H), 7.42–7.41 (m, 4.17H), 4.75–4.69 (m, 0.24H) 4.46–4.43 (m, 1H), 3.97–3.95 (m, 0.59H), 3.79–3.70 (m, 1.32H), 3.67–3.60 (m, 2.14H), 2.14 (br, 1.18H), 1.35 (d, J=7.2 Hz, 3.37H), 1.27–1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 162.2, 130.1, 128.8, 128.6, 127.1, 127.1, 84.0, 60.7, 43.1, 11.5; EI-MS m/z (rel int., %): 191 (M^+, 40.3), 160 (81.8), 132 (86.2), 117 (100.0), 104 (35.8), 77(71.5).

*4.4.10. (4,4-Dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methanol (**2j**).* Colourless oil, R_f=0.50 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.63–7.60 (m, 2H), 7.43–7.39 (m, 3H), 4.32 (dd, J=6.8, 4.0 Hz, 1H), 3.91–3.78 (m, 2H), 2.38 (br, 1H), 1.46 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 164.9, 129.7, 128.9, 128.6, 127.5, 90.5, 60.9, 50.7, 25.9, 18.9; EI-MS m/z (rel int., %): 205 (M^+, 50.0), 175 (12.6), 174 (100.0), 147 (14.7), 131 (87.1), 104 (56.0).

*4.4.11. (5-Methyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methanol (**2k**).* Colourless oil, R_f=0.51 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.68–7.65 (m, 2H), 7.42–7.40 (m, 3H), 3.75 (d, J=12.0 Hz, 1H), 3.62–3.57 (m, 1H), 3.50 (d, J=16.8 Hz, 1H), 3.03 (d, J=16.4 Hz, 1H), 2.06 (br, 1H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 157.1, 130.0, 129.8, 128.7, 126.6, 87.4, 67.3, 42.0, 22.7; EI-MS m/z (rel int., %): 191 (M^+, 14.9), 160 (42.0), 118 (100.0), 77 (16.4), 43 (13.7).

4.4.12. ((4S,5S*)-3,4-Diphenyl-4,5-dihydroisoxazol-5-yl)methanol (**2l-1**).* White solid, mp 99–100 °C, R_f=0.63 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.59–7.57 (m, 2H), 7.34–7.24 (m, 8H), 4.71(d, J=6.0 Hz, 1H), 4.65–4.61 (m, 1H), 3.90 (d, J=11.6 Hz, 1H), 3.77 (d, J=12.0 Hz, 1H), 2.08 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 158.7, 139.0, 129.9, 129.3, 128.8, 128.5, 127.7, 127.6, 127.3, 90.5, 63.2, 55.7; EI-MS m/z (rel int., %): 253 (M^+, 41.5), 222 (34.6), 193 (100.0), 165 (25.0), 91 (65.8).

4.4.13. ((4S,5R*)-3,4-Diphenyl-4,5-dihydroisoxazol-5-yl)methanol (**2l-2**) (new compound).* White solid, mp 88–89 °C, R_f=0.52 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.57 (d, J=6.8 Hz, 2H), 7.32–7.26 (m, 6H), 7.17 (d, J=7.2 Hz, 2H), 4.96–4.90 (m, 1H), 4.78 (d, J=10.0 Hz, 1H), 3.56–3.44 (m, 2H), 1.57 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 159.6, 133.4, 130.0, 129.1, 128.7, 128.6, 128.1, 127.3, 85.2, 61.6, 55.4; EI-MS m/z (rel int., %): 253 (M^+, 41.4), 222 (99.0), 193 (13.9), 165 (18.5), 91 (100.0); ESI-HRMS: m/z Calcd for $C_{16}H_{15}NO_2$+H^+: 254.1176, found 254.1181.

4.4.14. (7S, 7aR*)-3-phenyl-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazol-7-ol (**2m-1**).* White solid, mp 86–87 °C, R_f=0.37 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.66–7.63 (m, 2H), 7.42–7.41 (m, 3H), 4.44 (dd, J=8.4, 4.8 Hz 1H), 4.13–4.10 (m, 1H), 3.68 (dd, J=15.2, 8.0 Hz, 1H), 2.57 (br, 1H), 1.96–1.92 (m, 1H), 1.85–1.80 (m, 1H), 1.68–1.62 (m, 2H), 1.55–1.41 (m, 2H), 1.40–1.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 162.9, 130.1, 128.8, 128.8, 127.0, 84.8, 66.9, 44.5, 28.4, 24.7, 17.7; EI-MS m/z (rel int., %): 217 (M^+, 100.0), 188 (12.3), 158 (28.6), 132 (47.7), 104 (63.0).

4.4.15. (7R, 7aR*)-3-phenyl-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazol-7-ol (**2m-2**).* Pale yellow solid, mp 114–115 °C, R_f=0.36 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.71–7.69 (m, 2H), 7.42–7.41 (m, 3H), 4.63 (dd, J=7.6, 4.0 Hz, 1H), 4.04–4.01 (m, 1H), 3.54–3.50 (m, 1H), 2.32 (br, 1H), 1.96–1.90 (m, 2H), 1.82–1.75 (m, 1H), 1.71–1.61 (m, 1H), 1.44–1.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 163.4, 130.2, 128.8, 128.7, 126.9, 82.3, 68.9, 46.1, 28.7, 25.4, 21.3; EI-MS m/z (rel int., %): 217 (M^+, 67.3), 188 (11.3), 158 (33.4), 132 (51.2), 104 (100.0).

*4.4.16. 4-Methyl-3-phenyl-4,5-dihydroisoxazol-4-ol (**2n**).* White solid, mp 83–84 °C, R_f=0.74 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.80–7.78 (m, 2H), 7.42–7.34 (m, 3H), 4.38 (d, J=9.6 Hz, 1H), 4.21 (d, J=10.0 Hz, 1H), 3.30 (br, 1H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 160.6, 130.0, 128.6, 127.5, 127.4, 85.2, 82.0, 23.2; EI-MS m/z (rel int., %): 177 (M^+, 39.0), 149 (4.6), 135 (5.4), 104 (97.5), 43 (100.0).

*4.4.17. 5-Methyl-3-phenyl-4,5-dihydroisoxazol (**3a**).* White solid, mp 51–52 °C, R_f=0.44 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.69–7.66 (m, 2H), 7.41–7.39 (m, 3H), 4.93–4.84 (m, 1H), 3.43 (dd, J=16.4, 10.0 Hz, 1H), 2.93 (dd, J=16.4, 8.0 Hz, 1H), 1.44 (d, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 156.4, 129.9, 129.8, 128.6, 126.5, 77.4, 41.5, 20.9; EI-MS m/z (rel int., %): 161(M^+, 100.0), 147 (4.8), 131 (9.1), 118 (33.1), 91 (17.3).

*4.4.18. 3-(4-Methoxyphenyl)-5-methyl-4,5-dihydroisoxazole (**3b**).* White solid, mp 104–105 °C, R_f=0.19 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.63–7.59 (m, 2H), 6.94–6.90 (m, 2H), 4.90–4.81 (m, 1H), 3.85 (s, 3H), 3.41 (dd, J=16.4, 10.0 Hz, 1H), 2.91 (dd, J=16.0, 8.0 Hz, 1H), 1.43 (d, J=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 160.9, 156.0, 128.1, 122.5, 114.1, 77.3, 55.3, 41.8, 20.9; EI-MS m/z (rel int., %): 191 (M^+, 100.0), 176 (15.4), 161 (8.4), 148 (21.9), 121 (40.0).

*4.4.19. 4-(5-Methyl-4,5-dihydroisoxazol-3-yl)benzonitrile (**3c**) (new compound).* White solid, mp 91–92 °C, R_f=0.17 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.74 (d, J=8.4 Hz, 2H), 7.67–7.64 (m, 2H), 4.98–4.88 (m, 1H), 3.42 (dd, J=16.4, 10.4 Hz, 1H), 2.92 (dd, J=16.4, 8.4 Hz, 1H), 1.43 (d, J=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 155.1, 134.1, 132.3, 126.9, 118.2, 113.0, 78.4, 40.7, 20.8; EI-MS m/z (rel int., %): 186 (M^+, 100.0), 171 (25.3), 143 (98.1), 129 (25.9), 102 (54.6); ESI-HRMS: m/z Calcd for $C_{11}H_{10}N_2O$+H^+: 187.0866, found 187.0860.

*4.4.20. 3-(tert-Butyl)-5-methyl-4,5-dihydroisoxazole (**3d**) (new compound).* Colourless oil, R_f=0.47 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 4.71–4.62 (m, 1H), 3.03 (dd, J=16.4, 9.6 Hz, 1H), 2.53 (dd, J=16.4, 8.0 Hz, 1H), 1.31 (d, J=6.0 Hz, 3H), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 165.9, 76.4, 40.9, 32.9, 28.0, 20.7; EI-MS m/z (rel int., %): 141 (M^+, 38.4), 126 (100.0), 97 (42.4), 82 (64.9), 57 (22.4); ESI-HRMS: m/z Calcd for $C_8H_{15}NO$+H^+: 142.1226, found 142.1224.

*4.4.21. 5-Methyl-3-phenethyl-4,5-dihydroisoxazole (**3e**).* White solid, mp 35–36 °C, R_f=0.27 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.33–7.29 (m, 2H), 7.24–7.21 (m,

3H), 4.71–4.62 (m, 1H), 2.99–2.90 (m, 3H), 2.69–2.65 (m, 2H), 2.47 (dd, J=16.8, 7.6 Hz, 1H), 1.30 (d, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 158.2, 140.6, 128.5, 128.2, 126.3, 76.2, 43.9, 32.6, 29.6, 20.7; EI-MS m/z (rel int., %): 189 (M^+, 29.8), 174 (8.6), 145 (12.8), 129 (2.3), 91 (100.0).

*4.4.22. 3-Pentyl-5-methyl-4,5-dihydroisoxazole (**3f**).* Pale yellow oil, R_f=0.44 (petroleum ether:ethyl acetate=10:1). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 4.70–4.60 (m, 1H), 2.98 (dd, J=16.4, 10.0 Hz, 1H), 2.48 (dd, J=16.4, 8.0 Hz, 1H), 2.32 (t, J=7.6 Hz, 2H), 1.58–1.51 (m, 2H), 1.33–1.29 (m, 7H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 159.0, 76.0, 43.6, 31.3, 27.7, 26.0, 22.2, 20.8, 13.8; EI-MS m/z (rel int., %): 155 (M^+, 100.0), 140 (45.9), 129 (29.6), 112 (37.8), 99 (73.7).

*4.4.23. 5-Methyl-3-(thiophen-2-yl)-4,5-dihydroisoxazole (**3g**) (new compound).* Light red oil, R_f=0.29 (petroleum ether:ethyl acetate=10:1). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.38 (dd, J=5.2, 0.8 Hz, 1H), 7.19 (dd, J=3.6, 0.8 Hz, 1H), 7.06 (dd, J=5.2, 3.6 Hz, 1H), 4.93–4.84 (m, 1H), 3.45 (dd, J=16.4, 10.0 Hz, 1H), 2.95 (dd, J=16.4, 8.0 Hz, 1H), 1.44 (d, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 152.2, 132.5, 128.0, 128.0, 127.2, 77.8, 42.4, 20.8; EI-MS m/z (rel int., %): 167 (M^+, 100.0), 152 (19.1), 124 (25.6), 111 (18.2), 97 (43.8); ESI-HRMS: m/z Calcd for $C_8H_9NOS+H^+$: 168.0478, found 168.0475.

*4.4.24. 3-(Furan-2-yl)-5-methyl-4,5-dihydroisoxazole (**3h**) (new compound).* Pale yellow oil, R_f=0.33 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.50 (d, J=1.2 Hz, 1H), 6.68 (d, J=3.6 Hz, 1H), 6.48 (dd, J=3.6, 1.6 Hz, 1H), 4.88–4.79 (m, 1H), 3.38 (dd, J=16.4, 10.0 Hz, 1H), 2.89 (dd, J=16.4, 8.0 Hz, 1H), 1.41 (d, J=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 148.7, 145.2, 144.1, 111.6, 111.4, 77.3, 41.4, 20.7; EI-MS m/z (rel int., %): 151 (M^+, 100.0), 129 (7.1), 108 (23.1), 91 (17.0), 81 (28.4); ESI-HRMS: m/z Calcd for $C_8H_9NO_2+H^+$: 152.0706, found 152.0702.

*4.4.25. 4,5-Dimethyl-3-phenyl-4,5-dihydroisoxazole (**3i**, 4.5 cis:trans =27:73).* Colourless oil, R_f=0.51 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.72–7.66 (m, 2.61H), 7.43–7.37 (m, 3.91H), 4.71–4.65 (m, 0.26H), 4.48–4.42 (m, 1H), 3.50–3.45 (m, 0.25H), 3.33–3.26 (m, 1H), 1.44 (d, J=6.4 Hz, 0.78H), 1.35 (d, J=6.0 Hz, 3H), 1.29 (d, J=7.2 Hz, 3H), 1.12 (d, J=7.6 Hz, 0.83H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 162.7, 160.4, 129.8, 129.6, 129.2, 129.1, 128.7, 128.6, 126.8, 126.8, 84.7, 80.5, 48.5, 43.8, 20.1, 17.3, 13.1, 11.5; EI-MS m/z (rel int., %): 175 (M^+, 88.8), 160 (8.0), 130 (100.0), 117 (34.7),77 (37.8).

*4.4.26. 4,4,5-Trimethyl-3-phenyl-4,5-dihydroisoxazole (**3j**) (new compound).* White solid, mp 53–54 °C, R_f=0.56 (petroleum ether:ethyl acetate=10:1). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.68–7.64 (m, 2H), 7.42–7.36 (m, 3H), 4.24 (q, J=6.4 Hz, 1H), 1.34–1.33 (m, 6H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 165.0, 129.7, 129.4, 128.4, 127.1, 86.7, 50.7, 23.7, 19.2, 12.4; EI-MS m/z (rel int., %): 189 (M^+, 74.3), 174 (5.3), 144 (100.0), 131 (18.3), 105 (15.2); ESI-HRMS: m/z Calcd for $C_{12}H_{15}NO+H^+$: 190.1226, found 190.1232.

*4.4.27. 5,5-Dimethyl-3-phenyl-4,5-dihydroisoxazole (**3k**).* White solid, mp 58–59 °C, R_f=0.55 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.68–7.64 (m, 2H), 7.41–7.38 (m, 3H), 3.11 (s, 2H), 1.50 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 156.2, 130.3, 129.7, 128.6, 126.4, 84.9, 46.7, 27.3; EI-MS m/z (rel int., %): 175 (M^+, 56.5), 160 (36.3), 143 (5.7), 118 (100.0), 91 (13.1).

4.4.28. (4S,5R*)-5-Methyl-3,4-diphenyl-4,5-dihydroisoxazole (**3l-1**).* White solid, mp 99–100 °C, R_f=0.60 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.58 (dd, J=7.6, 1.6 Hz, 2H), 7.33–7.21 (m, 8H), 4.67–4.61 (m, 1H), 4.30 (d, J=5.6 Hz, 1H), 1.47 (d, J=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 157.9, 139.1, 129.6, 129.2, 128.5, 128.4, 127.6, 127.5, 127.2, 86.8, 61.2, 20.6; EI-MS m/z (rel int., %): 237 (M^+, 15.2), 193 (100.0), 165 (24.1), 117 (26.8), 91 (13.4).

4.4.29. (4S,5S*)-5-Methyl-3,4-diphenyl-4,5-dihydroisoxazole (**3l-2**) (new compound).* White solid, mp 97–98 °C, R_f=0.48 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.63–7.61 (m, 2H), 7.36–7.16 (m, 6H), 7.15 (d, J=7.2 Hz, 2H), 4.98–4.91 (m, 1H), 4.54 (d, J=9.2 Hz, 1H), 1.08 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 160.4, 134.3, 129.8, 129.4, 128.9, 128.7, 128.6, 127.8, 127.1, 81.9, 57.1, 14.4; EI-MS m/z (rel int., %): 237 (M^+, 15.2), 193 (100.0), 165 (24.1), 91 (13.4), 77 (13.1); ESI-HRMS: m/z Calcd for $C_{16}H_{15}NO+H^+$: 238.1226, found 238.1230.

*4.4.30. 3-Phenyl-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazole (**3m**).* White solid, mp 86–87 °C, R_f=0.43 (petroleum ether:ethyl acetate=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.74–7.70 (m, 2H), 7.43–7.38 (m, 3H), 4.52–4.48 (m, 1H), 3.30–3.24 (m, 1H), 2.27 (dd, J=15.2, 2.8 Hz, 1H), 2.01–1.96 (m, 1H), 1.82–1.50 (m, 4H), 1.32–1.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 163.9, 129.9, 129.4, 128.7, 126.8, 80.3, 44.4, 26.4, 25.0, 22.3, 20.2; EI-MS m/z (rel int., %): 201 (M^+, 100.0), 184 (9.1), 172 (19.8), 158 (25.9), 144 (28.0).

*4.4.31. 5-(But-1-en-1-yl)-3-phenyl-4,5-dihydroisoxazole (**6**) (new compound).* White solid, R_f=0.57 (petroleum ether:ethyl acetate=10:1). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.69–7.66 (m, 2H), 7.40 (t, J=3.2 Hz, 3H), 5.89 (dt, J=15.2, 6.4 Hz 0.88H), 5.63–5.61 (m, 0.13H), 5.59 (ddt, J=8.0, 7.6, 2.0 Hz, 1H), 5.53–5.45 (m, 0.12H), 5.13 (dd, J=18.4, 8.8 Hz, 0.88H), 3.49–3.42 (m, 1H), 3.13–3.06 (m, 1H), 2.15–2.07 (m, 2H), 1.03 (t, J=7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 156.5, 137.2, 129.9, 129.7, 128.6, 126.9, 126.6, 82.4, 41.1, 40.5, 25.1, 21.1, 14.2, 13.0; EI-MS m/z (rel int., %): 201 (M^+, 69.8), 172 (58.0), 145 (22.7), 117 (73.4), 91 (29.2); ESI-HRMS: m/z Calcd for $C_{13}H_{15}NO+H^+$: 202.1226, found 202.1221.

*4.4.32. 4-(3-Phenyl-4,5-dihydroisoxazol-5-yl)but-3-en-1-ol (**7**) (new compound).* White solid, R_f=0.37 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.68–7.66 (m, 2H), 7.42–7.40 (m, 3H), 5.90–5.83 (m, 1H), 5.76–5.71 (m, 1H), 5.16 (dd, J=18.0, 8.4 Hz, 1H), 3.72 (t, J=6.4 Hz, 2H), 3.48 (dd, J=16.4, 6.4 Hz, 1H), 3.12 (dd, J=16.4, 8.8 Hz, 1H), 2.37 (dd, J=13.2, 6.4 Hz, 2H), 1.62 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 156.5, 131.3, 130.8, 130.1, 129.6, 128.7, 126.7, 81.9, 61.7, 40.6, 35.5; EI-MS m/z (rel int., %): 217 (M^+, 39.4), 187 (10.5), 172 (50.6), 146 (39.7), 117 (100.0); ESI-HRMS: m/z Calcd for $C_{13}H_{15}NO_2+Na^+$: 240.0995, found 240.0999.

*4.4.33. 4-Hydroxy-1-(3-phenyl-4,5-dihydroisoxazol-5-yl)butan-2-one (**8**) (new compound).* White solid, mp 71–72 °C, R_f=0.17 (petroleum ether:ethyl acetate=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.67–7.65 (m, 2H), 7.42–7.40 (m, 3H), 5.16–5.08 (m, 1H), 3.91–3.86 (m, 2H), 3.58 (dd, J=16.8, 10.4 Hz, 1H), 3.11–3.00 (m, 2H), 2.82–2.74 (m, 3H), 2.37 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 208.5, 156.8, 130.2, 129.3, 128.7, 126.7, 80.3, 57.7, 48.2, 45.5, 40.4; EI-MS m/z (rel int., %): 233 (M^+, 1.2), 215 (0.4), 189 (1.0), 161 (1.2), 146 (100.0); ESI-HRMS: m/z Calcd for $C_{13}H_{15}NO_3+H^+$: 234.1125, found 234.1120.

*4.4.34. Cyclopropyl (3-phenyl-4,5-dihydroisoxazol-5-yl) methanol (**9**) (new compound).* Colourless oil, R_f=0.67 (petroleum ether:ethyl acetate=1:1): ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ 7.71–7.67 (m, 2H), 7.42–7.41 (m, 3H), 4.88–4.79 (m, 1H), 3.54 (dd, J=16.8, 8.8 Hz, 0.72H), 3.38–3.28 (m, 1.87H), 2.97 (dd, J=8.4, 4.8 Hz, 0.34H), 2.02 (s, 1H), 1.29–1.24 (m, 2H), 1.08–1.06 (m, 0.55H), 0.90–0.88 (m, 1H),

0.63–0.59 (m, 2H), 0.47–0.39 (m, 1H), 0.39–0.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 157.3, 157.1, 130.2, 130.1, 129.5, 128.7, 128.7, 126.7, 84.3, 83.9, 77.3, 77.2, 75.5, 37.0, 34.7, 14.0, 13.0, 2.7, 2.5, 2.4, 2.0; EI-MS *m*/*z* (rel int., %): 217 (M^+, 7.1), 146 (7.2), 134 (19.2), 119 (96.1), 104 (100.0); ESI-HRMS: *m*/*z* Calcd for $C_{13}H_{15}NO_2$+Na^+: 240.0995, found 240.0999.

*4.4.35. Diethyl 2-((3-phenyl-4,5-dihydroisoxazol-5-yl)methyl) succinate (**10**) (new compound).* Pale yellow oil, R_f=0.26 (petroleum ether:ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ 7.68–7.65 (m, 2H), 7.42–7.40 (m, 3H), 4.85–4.78 (m, 1H), 4.23–4.12 (m, 4H), 3.51–3.43 (m, 1H), 3.11–2.96 (m, 2H), 2.84–2.72 (m, 1H), 2.67–2.59 (m, 1H), 2.45–2.17 (m, 0.69H), 2.07–2.04 (m, 0.35H), 1.94–1.83 (m, 1H), 1.30–1.24 (m, 6H), 4.85–4.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): δ 174.2, 174.0, 171.6, 171.5, 156.5, 130.1, 129.5, 128.7, 126.6, 79.3, 78.8, 61.0, 60.7, 40.6, 40.3, 38.6, 38.4, 37.4, 36.7, 35.7, 14.1; EI-MS *m*/*z* (rel int., %): 333 (M^+, 0.2), 289 (3.8), 261 (0.9), 187 (5.1), 146 (100.0); ESI-HRMS: *m*/*z* Calcd for $C_{18}H_{23}NO_5$+Na^+: 356.1474, found 356.1699.

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Supplementary data

The general experimental methods, all the characterization data and copies of ^{1}H NMR, ^{13}C NMR spectra for compounds **1**, **2**, **3**, **5**–**10** are available in Supplementary data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.02.032.

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