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Tandem reaction of propargyl alcohols and *N*-tosyl hydroxylamine: switchable synthesis of 2,5-dihydroisoxazoles and 4-halo-2,5-dihydroisoxazoles

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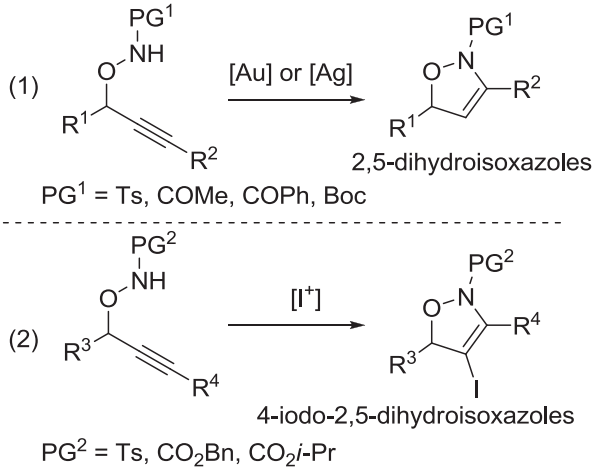
2,5-Dihydroisoxazoles, 4-iodo-2,5-dihydroisoxazoles, and 4-bromo-2,5-dihydroisoxazoles were efficiently constructed from propargylic alcohols and *N*-tosyl hydroxylamine using ytterbium triflate, iodine and *N*-bromosuccinimide, respectively. *N*-sulfonylallenamide is postulated to be the key intermediate for these tandem transformations. Moreover, the resulting 4-iodo-2,5-dihydroisoxazoles could be elaborated by palladium-catalyzed carbonylation to generate 4-methoxycarbonyl-4,5-dihydroisoxazoles.

1. Introduction

Isoxazole and dihydroisoxazole moieties are key substructures in both targets and building blocks for various pharmaceutical products,[1] chemosensor compounds,[2] and liquid crystals.[3] Much attention has been paid to the development of efficient methods for the synthesis of isoxazoles[4] and dihydroisoxazoles[5–7] due to their importance.

Although the construction of 2,3-[5] and 4,5-dihydroisoxazoles[6] has been well established, synthesis of 2,5-dihydroisoxazoles has been seldom reported. In few examples, 2,5-dihydroisoxazoles could be elegantly synthesized by π-acid catalyzed intramolecular cyclization of *O*-propargyl hydroxylamines[7a,b] (Scheme 1, Eq. 1). But to the disappointment, these methods require π-acid, such as gold and the protection groups for NH. As alternative methods, Knight[7c] and Wada[7d] reported efficient accesses to 4-iodo-2,5-dihydroisoxazoles via iodocyclization of *O*-propargyl hydroxylamines, respectively (Scheme 1, Eq. 2). The starting material, *N*-protected *O*-propynyl hydroxylamine, which was hard to be installed from propargylic alcohol,[7] should be pre-prepared in both cases. As a result, it is highly desirable to develop a new strategy that can be carried out under benign conditions without multi-step synthesis from propargyl alcohols.



Scheme 1. Previous works for the synthesis of 2,5-dihydroisoxazoles and 4-iodo-2,5-dihydroisoxazoles.

With our continuing research on the development of tandem reactions of allenamide intermediates,[8] we were interested in developing one-pot tandem approaches to 2,5-dihydroisoxazole skeleton from the readily available propargylic alcohols and *N*-tosyl hydroxylamine. Herein, we would like to report the results of this effort.

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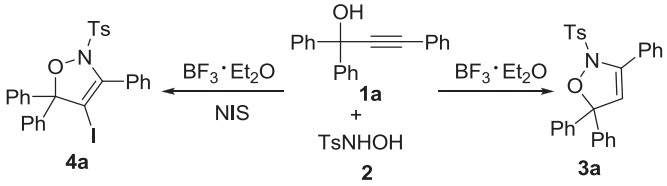
2. Results and discussion

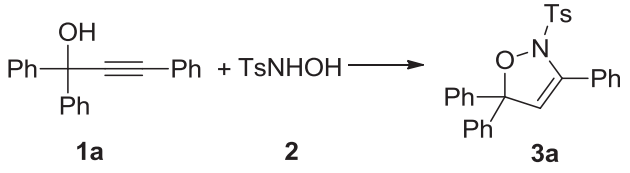
In our primary experiment, the Lewis acid catalyzed reaction of propargylic alcohol (**1a**) and *N*-tosyl hydroxylamine (**2**) was examined (Scheme 2). As we expected, 2,5-dihydroisoxazole (**3a**) was isolated in 54% yield when **1a** was treated with **2** in the presence of $BF_3 \cdot Et_2O$ in dichloromethane (DCM) at room temperature for a short time. To our delight, 4-iodo-2,5-dihydroisoxazole (**4a**) was obtained by supplementary addition of NIS. Structures of **3a** and **4a** were unambiguously confirmed by X-ray analysis.[9]



Scheme 2. Lewis acid catalyzed reactions between **1a** and **2**.

Due to the advantages of both reactions (without special π-acid catalysts, mild reaction conditions, and the commercially available starting materials), we optimized reaction conditions. Optimization of reaction conditions for the formation of **3a** was summarized in Table 1. By screening the various Lewis acids (Table 1, entries 1–4) and Brønsted acids (Table 1, entries 5 and 6), ytterbium triflate was observed to be the optimal catalyst. DCM was selected as the most suitable solvent among dichloroethane (DCE), acetonitrile, and toluene (Table 1, entries 2, and 7–9). Finally, the suitable reaction temperature and time were determined to be 25 °C and 3 h (Table 1, entries 2, and 10–13).

Table 1
Screening the reaction conditions for the formation of **3a**[a]

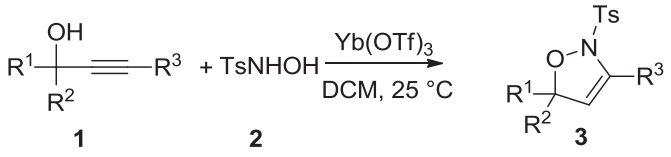


Entry	Catalyst	Temp (°C)	Time	Solvent	Yield[b] (%)
1	$BF_3 \cdot Et_2O$[c]	25	15 min	DCM	54
2	$Yb(OTf)_3$	25	3 h	DCM	82
3	AgOTf	25	30 min	DCM	65
4	$Cu(OTf)_2$	25	6 h	DCM	57
5	HOTf	25	15 min	DCM	50
6	$TsOH \cdot H_2O$	25	2 h	DCM	75
7	$Yb(OTf)_3$	25	6 h	DCE	78
8	$Yb(OTf)_3$	25	3 h	MeCN	15
9	$Yb(OTf)_3$	25	56 h	Toluene	81
10	$Yb(OTf)_3$	25	2 h	DCM	67
11	$Yb(OTf)_3$	25	4 h	DCM	81
12	$Yb(OTf)_3$	Reflux	1 h	DCM	73
13	$Yb(OTf)_3$	0	36 h	DCM	82

[a] Reaction conditions: Compound **1a** (0.6 mmol), **2** (0.5 mmol), catalyst (0.05 mmol), solvent (5 mL).
[b] Isolated yield referred to **2**.
[c] Catalyst (0.6 mmol) used.

With the optimized reaction conditions in hand, we subsequently tested the substrate diversity for this transformation. As shown in Table 2, the triaryl substituted propargyl alcohols **1a**–**f** (Table 2, entries 1–6) and **1h**–**m** (Table 2, entries 8–13) and the diaryl substituted propargyl alcohol **1n** (Table 2, entry 14) could undergo this cascade process to afford the corresponding 2,5-dihydroisoxazoles **3a**–**3f**, **3h**–**3n** and **3p** in moderate to excellent yields (30–95%). With different aryl groups (R^1, R^2, **1a**–**f**) occupied

Table 2
Tandem synthesis of **3**[a]



Entry	**1** ($R^1/R^2/R^3$)	Time (h)	Product/yield[b] (%)
1	**1a** (Ph/Ph/Ph)	3	**3a**/82
2	**1b** (4-$MeOC_6H_4$/4-$MeOC_6H_4$/Ph)	2	**3b**/57
3	**1c** (4-MeC_6H_4/4-MeC_6H_4/Ph)	3	**3c**/70
4	**1d** (4-MeC_6H_4/Ph/Ph)	3	**3d**/81
5	**1e** (4-ClC_6H_4/Ph/Ph)	3	**3e**/86[c]
6	**1f** (4-ClC_6H_4/4-ClC_6H_4/Ph)	6	**3f**/95[c]
7	**1g** (Ph/Me/Ph)	2	**3g**/nd[d]
8	**1h** (Ph/Ph/4-$MeOC_6H_4$)	3	**3h**/43
9	**1i** (Ph/Ph/4-MeC_6H_4)	3	**3i**/55
10	**1j** (Ph/Ph/4-FC_6H_4)	6	**3j**/86
11	**1k** (Ph/Ph/4-BrC_6H_4)	6	**3k**/85
12	**1l** (Ph/Ph/3-BrC_6H_4)	5	**3l**/82
13	**1m** (Ph/Ph/2-BrC_6H_4)	4	**3m**/30
14	**1n** (Ph/Ph/*n*-Bu)	3	**3n**/46
15	**1o** (Ph/Ph/H)	3	**3o**/nd[d]
16	**1p** (Ph/Ph/TMS)	2	**3p**/46

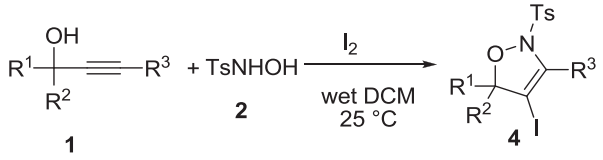
[a] Reaction conditions: Compound **1** (0.6 mmol), **2** (0.5 mmol), $Yb(OTf)_3$ (0.05 mmol), solvent (5 mL).
[b] Isolated yields refer to **2**.
[c] Run at reflux.
[d] nd=No desired product detected.

on the propargyl alcohols, reactions proceeded smoothly (Table 2, entries 1–6). Propargyl alcohols **1e** and **1f**, with the electron-withdrawing group substituted, could not be completely consumed at room temperature. Fortunately, by raising the reaction temperature, **3e** and **3f** could be obtained in 86% and 95% yields, respectively (Table 2, entries 5 and 6). When 2,4-diphenylbut-3-yn-2-ol (**1g**) was used as the substrate, no desired product was obtained (Table 2, entry 7) as **1g** was consumed completely. In cases of various substituents on R^3 (Table 2, entries 8–12), groups with the nature of the electron-withdrawing (**1j**–**l**, Table 2, entries 8–10) increased the yields in comparison with the electron-donating groups (**1h**, **1i**, Table 2, entries 11 and 12), while the sterically hindered 3-(2-bromophenyl)-1,1-diphenylprop-2-yn-1-ol (**1m**) gave relatively lower yield (Table 2, entry 13). Aliphatic alkyne **1n** could also afford the desired product **3n** in 46% yield (Table 2, entry 14). However, terminal alkyne **1o** failed to afford the desired product **3o** (Table 2, entry 15). TMS substituted alkyne **1p** could afford the desired product **3p** in 46% yield (Table 2, entry 16), but attempt to remove TMS for generation of **3o** by using $KF \cdot 2H_2O$ failed and the decomposition of **3p** occurred to yield benzophenone.

Screening of the reaction conditions for the formation of **4a** was summarized in Table S1. The best yield was obtained by mixing **1a** (0.6 mmol), **2** (0.5 mmol), and iodine (1.0 mmol) in wet DCM (5 mL) and reacting at room temperature for 4 h. With this procedure, we prepared various 4-iodo-2,5-dihydroisoxazoles **4a**–**n** as depicted in Table 3. The reaction could tolerate both electron-donating (Table 3, entries 1–4 and 7–9) and electron-withdrawing groups (Table 3, entries 5, 6 and 10–13). Aliphatic alkyne **1n** afforded **4n** in 35% yield (Table 3, entry 14). It is noteworthy that 2,4-diphenylbut-3-yn-2-ol (**1g**) could work to give the desired product **4g** in 27% yield (Table 3, entry 7). However, terminal alkyne **1o** also did not yield the desired product (Table 3, entry 15).

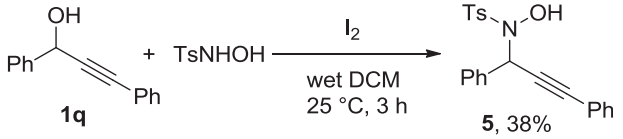
We also examined the secondary propargylic alcohol **1q** (Scheme 3). In this case, however, a direct N-propynylation of *N*-tosyl hydroxylamine occurred to form **5** in 38% yield. This result is similar to Campagne's work.[10]

Table 3
Tandem synthesis of **4**[a]



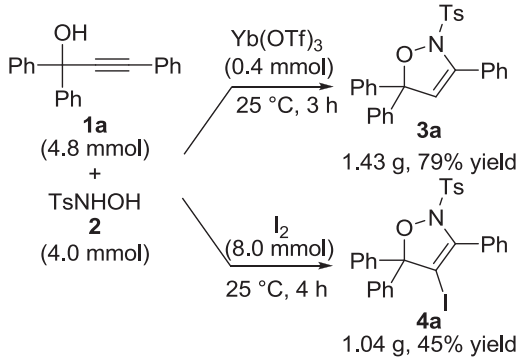
Entry	**1** ($R^1/R^2/R^3$)	Time (h)	Product/yield[b] (%)
1	**1a** (Ph/Ph/Ph)	4	**4a**/53
2	**1b** (4-$MeOC_6H_4$/4-$MeOC_6H_4$/Ph)	2	**4b**/41
3	**1c** (4-MeC_6H_4/4-MeC_6H_4/Ph)	4	**4c**/47
4	**1d** (4-MeC_6H_4/Ph/Ph)	4	**4d**/52
5	**1e** (4-ClC_6H_4/Ph/Ph)	12	**4e**/56[c]
6	**1f** (4-ClC_6H_4/4-ClC_6H_4/Ph)	20	**4f**/63[c]
7	**1g** (Ph/Me/Ph)	2	**4g**/27
8	**1h** (Ph/Ph/4-$MeOC_6H_4$)	4	**4h**/31
9	**1i** (Ph/Ph/4-MeC_6H_4)	4	**4i**/52
10	**1j** (Ph/Ph/4-FC_6H_4)	4	**4j**/64
11	**1k** (Ph/Ph/4-BrC_6H_4)	5	**4k**/67
12	**1l** (Ph/Ph/3-BrC_6H_4)	4	**4l**/71
13	**1m** (Ph/Ph/2-BrC_6H_4)	4	**4m**/59
14	**1n** (Ph/Ph/*n*-Bu)	3	**4n**/35
15	**1o** (Ph/Ph/H)	4	nd[d]

[a] Reaction conditions: Compound **1** (0.6 mmol), **2** (0.5 mmol), I_2 (1.0 mmol), solvent (5 mL).
[b] Isolated yields refer to **2**.
[c] Run at reflux.
[d] nd=No desired product detected.



Scheme 3. Synthesis of *N*-propargyl hydroxylamine **5**.

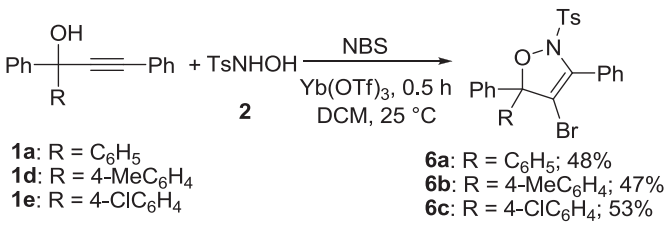
In order to test the scalability and to demonstrate the practical utilities of these two tandem transformations, reactions were performed on gram scale. As shown in Scheme 4, reactions proceeded well to afford **3a** (1.43 g, 79% yield) and **4a** (1.04 g, 45% yield), respectively.



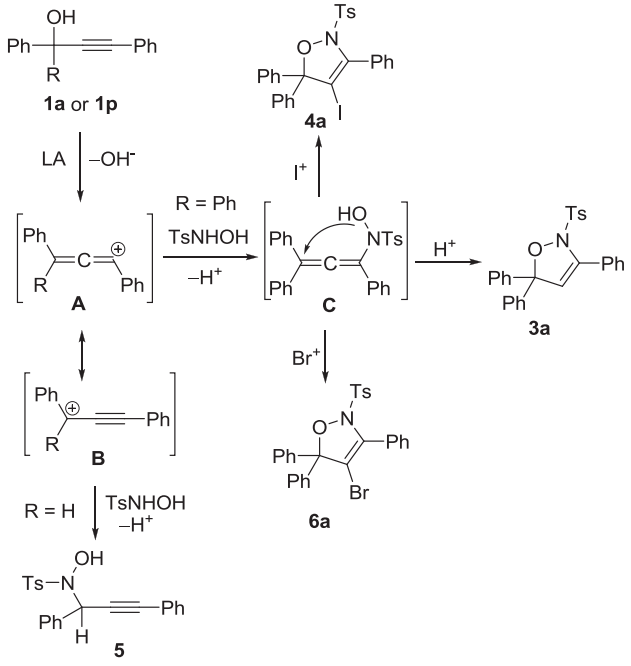
Scheme 4. Reactions on gram scale.

This protocol could also be used to prepare 4-bromo-2,5-dihydroisoxazoles **6a**–**c** (Scheme 5) with the combination of NBS and ytterbium triflate.

On the basis of the aforementioned experiments, a plausible mechanism is outlined in Scheme 6. Cooperated with Lewis acid, **1** can undergo a Meyer–Schuster rearrangement[11] to form allenic carbocation **A** (R=Ph) or a direct dehydration to generate propargylic carbocation **B** (R=H), depending on the pendant group R. According to theoretical calculation, the resonance structure **A** is more stable than the resonance structure **B** when R=Ph, while **B** is more stable than **A** when R=H.[12] Attributed to the tosyl group on the hydroxylamine, nitrogen presented stronger nucleophilicity than oxygen did.[13] As a result, *N*-sulfonylallenamide **C**[14] and **5** can be obtained by trapping **A** and **B** with *N*-sulfonyl hydroxylamine, respectively. In the presence of different electrophiles, such as H^+, I^+, or Br^+, the active *N*-sulfonylallenamide **C** is further converted into isolable **3a**, **4a**, or **6a** in a cascade way. In the cases where I_2 was used as electrophile (Table 3), additional Lewis acid was not necessary because molecular iodine is actually a well known Lewis acid.[8c,15]

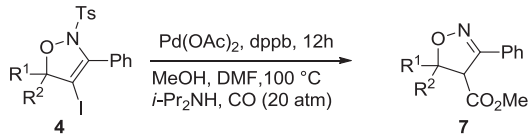


Scheme 5. Formation of 4-bromo-2,5-dihydroisoxazoles.



Scheme 6. Proposed mechanism for the tandem transformation.

As aryl halide is an important family in transition metal catalyzed coupling reactions, we tested 4-iodo-2,5-dihydroisoxazoles for palladium catalyzed carbonylation.[16] Thus, **4a**, **4c**, and **4d** were, respectively, loaded in autoclave (Scheme 7). To our surprising, **7a**, **7b**, and **7c** were constructed in moderate yields. It



4a: R^1 = C_6H_5, R^2 = C_6H_5 **7a**: R^1 = C_6H_5, R^2 = C_6H_5; 58%
4c: R^1 = 4-MeC_6H_4, R^2 = 4-MeC_6H_4 **7b**: R^1 = 4-MeC_6H_4, R^2 = 4-MeC_6H_4; 51%
4d: R^1 = 4-MeC_6H_4, R^2 = C_6H_5 **7c**: R^1 = 4-MeC_6H_4, R^2 = C_6H_5; 51%

Scheme 7. Further elaboration of compounds **4**.

indicated that the palladium catalyzed carbonylation occurred in accompany with the detosylation. Besides, the constructed 4-methoxycarbonyl-4,5-dihydroisoxazole is the subunit of biologically active compounds.[17]

3. Conclusions

In conclusion, we have developed an efficient protocol for the preparation of 2,5-dihydroisoxazoles and 4-halo-2,5-dihydroisoxazoles from readily available and simple starting materials. Moreover, the resulting 4-iodo-2,5-dihydroisoxazoles could be converted into 4-methoxycarbonyl-4,5-dihydroisoxazoles via palladium catalyzed carbonylation and detosylation. Further researches on the chemistry of allenamide are ongoing in our laboratory.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded on 500 MHz or 400 MHz spectrometer. The chemical shifts were reported relative to internal standard TMS (0 ppm) in $CDCl_3$. The following abbreviations were used to describe peak patterns where appropriate: b=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants were reported in hertz (Hz). ^{13}C NMR were recorded on 125 MHz or 100 MHz and referenced to the internal solvent signals (77.27 ppm for $CDCl_3$). Infrared spectra were obtained on an FTIR spectrometer. Low-resolution MS were obtained by ESI ionization. high-resolution mass spectra (HRMS) data were obtained by using ESI ionization on ion cyclotron resonance (ICR) mass spectrometer or EI ionization on time-of-flight (TOF) mass spectrometer. Melting points were measured with micro melting point apparatus.

CH_2Cl_2, MeCN, and 1,2-dichloroethane were distilled from CaH_2. The propargyl alcohols[18] and *N*-tosyl hydroxylamine[19] were prepared according to the published methods. 1,1-Diphenylprop-2-yn-1-ol (**1o**) and other materials were purchased from common commercial sources and used without additional purification.

4.2. General procedure for the synthesis of 3

To a solution of propargyl alcohol **1** (0.6 mmol) and *N*-tosyl hydroxylamine **2** (0.5 mmol) in dry DCM (5 mL) was added $Yb(OTf)_3$ (0.05 mmol) slowly at 25 °C, and the reaction mixture was stirred at the shown temperature for an indicated period of time shown in text. Saturated aqueous brine was added to quench the reaction and the mixture was extracted with DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel with DCM/hexane as eluent to give **3**.

*4.2.1. 3,5,5-Triphenyl-2-tosyl-2,5-dihydroisoxazole (**3a**).* White solid (186 mg, 82%); mp 183–184 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70–7.62 (m, 2H), 7.43–7.37 (m, 3H), 7.24–7.15 (m, 8H), 7.07–7.00 (m, 4H), 6.79 (d, *J*=8.0 Hz, 2H), 5.70 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 144.3, 141.8, 130.2, 130.0, 129.1, 128.9, 128.5, 128.4, 128.3, 127.7, 126.8, 116.9, 95.6, 21.9; IR (film): 3056, 2922, 1596, 1489, 1364, 1168, 1049 cm^{-1}; MS (ESI) *m*/*z* ([M+H]$^+$): 454; HRMS (EI) calcd for $C_{28}H_{23}NO_3S$: 453.1399; found: 453.1398.

*4.2.2. 5,5-Bis(4-methoxyphenyl)-3-phenyl-2-tosyl-2,5-dihydro-isoxazole (**3b**).* White solid (146 mg, 57%); mp 93–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70–7.62 (m, 2H), 7.43–7.37 (m, 3H), 7.26–7.20 (m, 2H), 6.94 (d, *J*=8.5 Hz, 4H), 6.85 (d, *J*=8.0 Hz, 2H), 6.70 (d, *J*=8.5 Hz, 4H), 5.65 (s, 1H), 3.78 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 144.8, 141.4, 136.8, 130.3, 130.2, 129.9, 129.4, 129.0, 128.4, 128.3, 128.2, 117.5, 113.6, 95.3, 55.5, 21.9; IR (film): 2929, 1608, 1510, 1364, 1251, 1168, 1031 cm^{-1}; MS (ESI) *m*/*z* ([M+H]$^+$): 514; HRMS (EI) calcd for $C_{30}H_{27}NO_5S$: 513.1610; found: 513.1625.

*4.2.3. 3-Phenyl-5,5-di-p-tolyl-2-tosyl-2,5-dihydroisoxazole (**3c**).* White solid (168 mg, 70%), mp 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68–7.62 (m, 2H), 7.43–7.35 (m, 3H), 7.21 (d, *J*=8.0 Hz, 2H), 6.97 (d, *J*=8.0 Hz, 4H), 6.91 (d, *J*=8.0 Hz, 4H), 6.79 (d, *J*=8.0 Hz, 2H), 5.67 (s, 1H), 2.33–2.29 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 141.6, 141.5, 137.4, 130.3, 130.2, 129.9, 129.2, 129.0, 128.9, 128.4, 128.3, 126.7, 117.3, 95.6, 21.9, 21.3; IR (film): 2917, 1596, 1506, 1367, 1171, 1049 cm^{-1}; MS (ESI) *m*/*z* ([M+H]$^+$): 482; HRMS (EI) calcd for $C_{30}H_{27}NO_3S$: 481.1712; found: 481.1724.

*4.2.4. 3,5-Diphenyl-5-(p-tolyl)-2-tosyl-2,5-dihydroisoxazole (**3d**).* White solid (189 mg, 81%), mp 163–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68–7.62 (m, 2H), 7.45–7.37 (m, 3H), 7.24–7.14 (m, 5H), 7.08–7.02 (m, 2H), 6.98 (d, *J*=8.0 Hz, 2H), 6.90 (d, *J*=8.0 Hz, 2H), 6.80 (d, *J*=8.0 Hz, 2H), 5.69 (s, 1H), 2.32 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 144.5, 141.7, 141.5, 137.4, 130.3, 130.2, 129.9, 129.00, 128.99, 128.4, 128.3, 128.3, 127.6, 126.74, 126.71, 117.1, 95.6, 21.9, 21.3; IR (film): 1593, 1489, 1444, 1364, 1168, 1087 cm^{-1}; MS (ESI) *m*/*z* ([M+H]$^+$): 468; HRMS (EI) calcd for $C_{29}H_{25}NO_3S$: 467.1555; found: 467.1559.

*4.2.5. 5-(4-Chlorophenyl)-3,5-diphenyl-2-tosyl-2,5-dihydro-isoxazole (**3e**).* White solid (210 mg, 86%); mp 166–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70–7.62 (m, 2H), 7.45–7.37 (m, 3H), 7.24–7.18 (m, 5H), 7.14 (d, *J*=8.5 Hz, 2H), 7.08–7.02 (m, 2H), 6.95 (d, *J*=8.5 Hz, 2H), 6.84 (d, *J*=8.0 Hz, 2H), 5.66 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.3, 143.8, 142.9, 142.2, 133.7, 130.18, 130.15, 130.0, 129.1, 128.9, 128.53, 128.50, 128.3, 128.2, 127.9, 126.6, 116.2, 95.1, 21.9; IR (film): 3060, 1596, 1489, 1367, 1174, 1087 cm^{-1}; MS (ESI) *m*/*z* ([M+H]$^+$): 488; HRMS (EI) calcd for $C_{28}H_{22}ClNO_3S$: 487.1009; found: 487.1004.

*4.2.6. 5,5-Bis(4-chlorophenyl)-3-phenyl-2-tosyl-2,5-dihydro-isoxazole (**3f**).* White solid (248 mg, 95%); mp 111–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68–7.62 (m, 2H), 7.45–7.40 (m, 3H), 7.22 (d, *J*=8.5 Hz, 2H), 7.16 (d, *J*=8.5 Hz, 4H), 6.96 (d, *J*=9.0 Hz, 4H), 6.88 (d, *J*=8.0 Hz, 2H), 5.62 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.6, 142.6, 142.4, 134.0, 130.3, 130.2, 129.7, 129.1, 129.0, 128.7, 128.6, 128.3, 128.2, 115.5, 94.6, 21.9; IR (film): 2922, 1593, 1489, 1367, 1168, 1090, 814 cm^{-1}; MS (EI) *m*/*z* ([M−Ts]$^+$): 366; HRMS (EI) calcd for $C_{28}H_{21}Cl_2NO_3S$: 521.0619; found: 521.0623.

*4.2.7. 3-(4-Methoxyphenyl)-5,5-diphenyl-2-tosyl-2,5-dihydro-isoxazole (**3h**).* White solid (104 mg, 43%); mp 134–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J*=8.5 Hz, 2H), 7.23–7.14 (m, 8H), 7.07–7.00 (m, 4H), 6.93 (d, *J*=8.0 Hz, 2H), 6.79 (d, *J*=8.0 Hz, 2H), 5.60 (s, 1H), 3.84 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 144.8, 144.5, 141.5, 130.2, 129.7, 129.1, 129.0, 128.3, 127.6, 126.8, 122.4, 115.1, 113.9, 95.5, 55.6, 21.9; IR (film): 2920, 1608, 1507, 1367, 1257, 1171, 1046 cm^{-1}; MS (ESI) *m*/*z* ([M+Na]$^+$): 506; HRMS (EI) calcd for $C_{29}H_{25}NO_4S$: 483.1504; found: 483.1503.

*4.2.8. 5,5-Diphenyl-3-(p-tolyl)-2-tosyl-2,5-dihydroisoxazole (**3i**).* White solid (129 mg, 55%); mp 148–149 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J*=7.5 Hz, 2H), 7.25–7.14 (m, 10H), 7.08–7.00 (m, 4H), 6.79 (d, *J*=8.0 Hz, 2H), 5.65 (s, 1H), 2.38 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 144.4, 141.9, 140.1, 130.2, 129.2,

129.1, 129.0, 128.3, 128.2, 127.6, 127.3, 126.8, 116.0, 95.5, 21.9, 21.7; IR (film): 3051, 3027, 1596, 1489, 1450, 1367, 1168, 1046 cm^{-1}; MS (ESI) *m*/*z* ($[M+Na]^+$): 490; HRMS (EI) calcd for $C_{29}H_{25}NO_3S$: 467.1555; found: 467.1563.

*4.2.9. 3-(4-Fluorophenyl)-5,5-diphenyl-2-tosyl-2,5-dihydro-isoxazole (**3j**).* White solid (203 mg, 86%); mp 158–159 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.68–7.60 (m, 2H), 7.25–7.16 (m, 8H), 7.10 (t, *J*=8.5 Hz, 2H), 7.05–7.00 (m, 4H), 6.80 (d, *J*=8.0 Hz, 2H), 5.67 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7 (d, $^1J_{CF}$=248 Hz), 145.0, 144.3, 140.8, 130.22, 130.16, 129.2, 128.9, 128.4, 127.7, 126.7, 126.3, 116.6, 115.6 (d, $^2J_{CF}$=22 Hz), 95.7, 21.9; IR (film): 2917, 1650, 1601, 1504, 1364, 1171, 1049 cm^{-1}; MS (ESI) *m*/*z* ($[M+Na]^+$): 494; HRMS (EI) calcd for $C_{28}H_{22}FNO_3S$: 471.1304; found: 471.1320.

*4.2.10. 3-(4-Bromophenyl)-5,5-diphenyl-2-tosyl-2,5-dihydro-isoxazole (**3k**).* White solid (226 mg, 85%); mp 169–170 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.57–7.50 (m, 4H), 7.22–7.13 (m, 8H), 7.02 (d, *J*=6.5 Hz, 4H), 6.80 (d, *J*=7.0 Hz, 2H), 5.72 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 144.1, 140.8, 131.7, 130.1, 129.7, 129.2, 129.1, 128.7, 128.4, 127.8, 126.7, 124.2, 117.3, 95.8, 21.9; IR (film): 3060, 2920, 1650, 1596, 1489, 1364, 1171, 1046 cm^{-1}; MS (ESI) *m*/*z* ($[M+Na]^+$): 554; HRMS (EI) calcd for $C_{28}H_{22}BrNO_3S$: 531.0504; found: 531.0508.

*4.2.11. 3-(3-Bromophenyl)-5,5-diphenyl-2-tosyl-2,5-dihydro-isoxazole (**3l**).* Pale gray solid (218 mg, 82%); mp 183–184 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.77–7.74 (m, 1H), 7.62 (d, *J*=8.0 Hz, 1H), 7.54–7.50 (m, 1H), 7.31–7.26 (m, 1H), 7.25–7.15 (m, 8H), 7.07–6.98 (m, 4H), 6.82 (d, *J*=8.0 Hz, 2H), 5.75 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 144.0, 140.4, 132.9, 132.2, 130.8, 130.2, 130.0, 129.2, 128.7, 128.4, 127.8, 127.1, 126.7, 122.4, 118.0, 95.8, 21.9; IR (film): 3062, 3021, 1595, 1561, 1491, 1366, 1172, 1088, 1050 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 532; HRMS (EI) calcd for $C_{28}H_{22}BrNO_3S$: 531.0504; found: 531.0502.

*4.2.12. 3-(2-Bromophenyl)-5,5-diphenyl-2-tosyl-2,5-dihydro-isoxazole (**3m**).* White solid (80 mg, 30%); mp 169–172 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, *J*=7.5, 1.5 Hz, 1H), 7.66 (d, *J*=8.0 Hz, 1H), 7.40–7.31 (m, 3H), 7.25–7.15 (m, 7H), 7.10–7.04 (m, 4H), 6.82 (d, *J*=8.0 Hz, 2H), 6.05 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 144.1, 137.9, 134.0, 132.6, 130.7, 130.6, 130.4, 129.2, 129.0, 128.4, 127.8, 127.3, 127.0, 121.7, 120.6, 96.8, 21.9; IR (film): 3057, 3027, 1653, 1593, 1367, 1170, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 532; HRMS (EI) calcd for $C_{28}H_{22}BrNO_3S$: 531.0504; found: 531.0508.

*4.2.13. 3-Butyl-5,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**3n**).* White solid (100 mg, 46%); mp 106–107 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J*=8.5 Hz, 2H), 7.22–7.16 (m, 6H), 6.97 (d, *J*=7.5 Hz, 4H), 6.83 (d, *J*=8.5 Hz, 2H), 5.36 (s, 1H), 2.60 (t, *J*=8.0 Hz, 2H), 2.31 (s, 3H), 1.70–1.60 (m, 2H), 1.43–1.32 (m, 2H), 0.92 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 144.5, 141.4, 129.8, 129.4, 129.2, 128.2, 127.5, 126.8, 114.9, 94.8, 30.1, 27.8, 22.5, 21.8, 14.0; IR (film): 1596, 1489, 1447, 1364, 1174, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+K]^+$): 472; HRMS (EI) calcd for $C_{26}H_{27}NO_3S$: 433.1712; found: 433.1717.

*4.2.14. 5,5-Diphenyl-2-tosyl-3-(trimethylsilyl)-2,5-dihydroisoxazole (**3p**).* White solid (103 mg, 46%); mp 131–133 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J*=7.6 Hz, 2H), 7.22–7.10 (m, 6H), 6.96 (d, *J*=7.6 Hz, 4H), 6.83 (d, *J*=8.0 Hz, 2H), 5.73 (s, 1H), 2.28 (s, 3H), 0.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 144.3, 141.5, 130.1, 129.9, 129.7, 129.1, 128.3, 127.4, 126.9, 95.4, 21.8, 0.02; IR (film): 3054, 1593, 1492, 1447, 1355, 1168, 1084 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 450; HRMS (EI) calcd for $C_{25}H_{27}NO_3SSi$: 449.1481; found: 449.1481.

4.3. General procedure for the synthesis of 4 and 5

To a solution of propargyl alcohol **1** (0.6 mmol) and *N*-tosyl hydroxylamine **2** (0.5 mmol) in wet DCM (5 mL) was added I_2 (1.0 mmol) slowly at 25 °C, and the reaction mixture was stirred at a shown temperature for an indicated period of time shown in text. Saturated aqueous $Na_2S_2O_3$ was added to quench the reaction and the mixture was extracted with DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated. The residue was purified flash column chromatography on silica gel with DCM/hexane as eluent to give **4** or **5**.

*4.3.1. 4-Iodo-3,5,5-triphenyl-2-tosyl-2,5-dihydroisoxazole (**4a**).* White solid (153 mg, 53%); mp 185–186 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.78–7.70 (m, 2H), 7.53–7.43 (m, 3H), 7.30–7.18 (m, 8H), 7.17–7.12 (m, 4H), 6.89 (d, *J*=8.5 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 143.1, 142.3, 130.4, 130.3, 130.0, 129.8, 129.5, 128.7, 128.3, 128.2, 128.0, 98.1, 82.7, 22.0; IR (film): 3054, 1596, 1492, 1444, 1367, 1174, 1084 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 580; HRMS (EI) calcd for $C_{28}H_{22}INO_3S$: 579.0365; found: 579.0363.

*4.3.2. 4-Iodo-5,5-bis(4-methoxyphenyl)-3-phenyl-2-tosyl-2,5-dihydroisoxazole (**4b**).* White solid (131 mg, 41%), mp 184–185 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.76–7.70 (m, 2H), 7.50–7.43 (m, 3H), 7.30–7.22 (m, 2H), 7.07 (d, *J*=9.0 Hz, 4H), 6.93 (d, *J*=8.0 Hz, 2H), 6.72 (d, *J*=9.0 Hz, 4H), 3.81 (s, 6H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 145.1, 142.6, 134.6, 130.34, 130.31, 130.2, 130.1, 130.0, 129.4, 128.3, 113.3, 98.0, 84.0, 55.5, 22.0; IR (film): 1608, 1513, 1373, 1257, 1174, 1087, 1034 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 640; HRMS (EI) calcd for $C_{30}H_{26}INO_5S$: 639.0576; found: 639.0566.

*4.3.3. 4-Iodo-3-phenyl-5,5-di-p-tolyl-2-tosyl-2,5-dihydro-isoxazole (**4c**).* White solid (143 mg, 47%); mp 172–173 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.77–7.70 (m, 2H), 7.50–7.43 (m, 3H), 7.24 (d, *J*=8.0 Hz, 2H), 7.06–6.96 (m, 8H), 6.89 (d, *J*=8.5 Hz, 2H), 2.39 (s, 3H), 2.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 142.7, 139.5, 138.0, 130.3, 130.2, 130.1, 129.9, 129.3, 128.6, 128.3, 98.2, 83.4, 22.0, 21.4; IR (film): 3030, 1590, 1513, 1447, 1367, 1168, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 608; HRMS (EI) calcd for $C_{30}H_{26}INO_3S$: 607.0678; found: 607.0670.

*4.3.4. 4-Iodo-3,5-diphenyl-5-(p-tolyl)-2-tosyl-2,5-dihydro-isoxazole (**4d**).* White solid (154 mg, 52%); mp 160–161 °C (decomposition); ^1H NMR (500 MHz, $CDCl_3$): δ 7.77–7.71 (m, 2H), 7.52–7.44 (m, 3H), 7.30–7.18 (m, 5H), 7.16 (d, *J*=7.5 Hz, 2H), 7.05–6.97 (m, 4H), 6.89 (d, *J*=8.0 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 142.9, 142.4, 139.4, 138.1, 130.4, 130.3, 130.0, 129.4, 128.75, 128.68, 128.6, 128.3, 128.2, 127.9, 98.2, 83.1, 22.0, 21.5; IR (film): 1596, 1489, 1447, 1373, 1174, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 594; HRMS (EI) calcd for $C_{29}H_{24}INO_3S$: 593.0522; found: 593.0528.

*4.3.5. 5-(4-Chlorophenyl)-4-iodo-3,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**4e**).* White solid (172 mg, 56%); mp 173–174 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.77–7.70 (m, 2H), 7.52–7.44 (m, 3H), 7.32–7.20 (m, 5H), 7.20–7.12 (m, 4H), 7.07 (d, *J*=8.5 Hz, 2H), 6.93 (d, *J*=8.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.5, 143.4, 141.9, 141.0, 134.4, 130.6, 130.2, 130.0, 129.94, 129.91, 129.5, 128.7, 128.5, 128.4, 128.3, 128.1, 97.7, 81.9, 22.0; IR (film): 3056, 1602, 1486, 1444, 1373, 1171, 1093 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 614; HRMS (EI) calcd for $C_{28}H_{21}ClINO_3S$: 612.9975; found: 612.9969.

*4.3.6. 5,5-Bis(4-chlorophenyl)-4-iodo-3-phenyl-2-tosyl-2,5-dihydroisoxazole (**4f**).* White solid (204 mg, 63%); mp 189–190 °C; ^1H NMR

(500 MHz, $CDCl_3$): δ 7.76–7.70 (m, 2H), 7.52–7.45 (m, 3H), 7.27–7.22 (m, 2H), 7.20–7.15 (m, 4H), 7.10–7.03 (m, 4H), 6.96 (d, *J*=8.0 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 143.7, 140.5, 134.7, 130.7, 130.2, 129.93, 129.89, 129.8, 129.5, 128.45, 128.38, 97.2, 81.0, 22.0; IR (film): 3069, 1596, 1489, 1370, 1171, 1093, 1010 cm^{-1}; MS (ESI) *m*/*z* ($[M+Na]^+$): 670; HRMS (EI) calcd for $C_{28}H_{20}Cl_2INO_3S$: 646.9586; found: 646.9599.

*4.3.7. 4-Iodo-5-methyl-3,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**4g**).* White solid (70 mg, 27%); mp 151–152 °C (decomposition); ^1H NMR (500 MHz, $CDCl_3$): δ 7.72–7.65 (m, 2H), 7.56 (d, *J*=8.0 Hz, 2H), 7.50–7.42 (m, 3H), 7.32–7.23 (m, 5H), 7.21 (d, *J*=8.0 Hz, 2H), 2.44 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.6, 141.9, 141.3, 130.9, 130.3, 130.2, 130.0, 129.9, 129.7, 128.5, 128.4, 128.3, 127.0, 95.4, 85.0, 25.9, 22.0; IR (film): 3060, 1593, 1495, 1450, 1370, 1171, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+Na]^+$): 540; HRMS (EI) calcd for $C_{23}H_{20}INO_3S$: 517.0209; found: 517.0200.

*4.3.8. 4-Iodo-3-(4-methoxyphenyl)-5,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**4h**).* White solid (94 mg, 31%); mp 177–178 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.73–7.67 (m, 2H), 7.30–7.25 (m, 2H), 7.24–7.17 (m, 6H), 7.15–7.10 (m, 4H), 7.00 (d, *J*=9.0 Hz, 2H), 6.88 (d, *J*=8.0 Hz, 2H), 3.87 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 145.0, 142.9, 142.5, 131.8, 129.9, 129.5, 128.7, 128.2, 128.0, 122.1, 113.7, 97.9, 81.2, 55.6, 22.0; IR (film): 3060, 1608, 1510, 1447, 1373, 1257, 1174, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 610; HRMS (EI) calcd for $C_{29}H_{24}INO_4S$: 609.0471; found: 609.0473.

*4.3.9. 4-Iodo-5,5-diphenyl-3-(p-tolyl)-2-tosyl-2,5-dihydroisoxazole (**4i**).* White solid (154 mg, 52%); mp 174–175 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J*=8.0 Hz, 2H), 7.31–7.17 (m, 10H), 7.15–7.10 (m, 4H), 6.88 (d, *J*=8.0 Hz, 2H), 2.42 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 143.2, 142.4, 140.7, 130.2, 130.0, 129.8, 129.5, 129.1, 128.7, 128.2, 128.0, 127.2, 98.0, 82.0, 22.0, 21.9; IR (film): 3057, 3036, 2923, 1596, 1492, 1447, 1370, 1174, 1084 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 594; HRMS (EI) calcd for $C_{29}H_{24}INO_3S$: 593.0522; found: 593.0518.

*4.3.10. 3-(4-Fluorophenyl)-4-iodo-5,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**4j**).* White solid (192 mg, 64%), mp 175–176 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.78–7.70 (m, 2H), 7.33–7.26 (m, 2H), 7.24–7.10 (m, 12H), 6.89 (d, *J*=8.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8 (d, $^1J_{CF}$=250 Hz), 145.3, 142.18, 142.16, 132.3 (d, $^3J_{CF}$=8 Hz), 129.9, 129.7, 129.6, 128.7, 128.3, 128.0, 126.2 (d, $^4J_{CF}$=3 Hz), 115.6 (d, $^2J_{CF}$=22 Hz), 98.2, 82.8, 22.0; IR (film): 3060, 1629, 1593, 1507, 1444, 1370, 1170, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 598; HRMS (EI) calcd for $C_{28}H_{21}FINO_3S$: 597.0271; found: 597.0262.

*4.3.11. 3-(4-Bromophenyl)-4-iodo-5,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**4k**).* White solid (221 mg, 67%); mp 178–179 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.64–7.57 (m, 4H), 7.33–7.17 (m, 8H), 7.16–7.10 (m, 4H), 6.90 (d, *J*=8.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.3, 142.2, 142.1, 131.72, 131.69, 129.9, 129.7, 129.6, 129.1, 128.7, 128.4, 128.0, 124.8, 98.4, 83.3, 22.0; IR (film): 3060, 3024, 1593, 1483, 1367, 1168, 1087, 1010 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 658; HRMS (EI) calcd for $C_{28}H_{21}BrINO_3S$: 656.9470; found: 656.9474.

*4.3.12. 3-(3-Bromophenyl)-4-iodo-5,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**4l**).* White solid (234 mg, 71%); mp 176–177 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 7.59 (d, *J*=8.0 Hz, 1H), 7.40–7.32 (m, 1H), 7.32–7.18 (m, 8H), 7.17–7.10 (m, 4H), 6.91 (d, *J*=8.0 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.4, 142.0, 141.7, 133.4, 133.0, 132.2, 129.9, 129.68, 129.65, 128.9, 128.7, 128.4, 128.1, 122.2, 98.4, 84.0, 22.0; IR (film): 3063, 1596, 1492, 1447, 1370, 1170, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 658; HRMS (EI) calcd for $C_{28}H_{21}BrINO_3S$: 656.9470; found: 656.9473.

*4.3.13. 3-(2-Bromophenyl)-4-iodo-5,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**4m**).* White solid (194 mg, 59%); mp 177–178 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J*=8.0 Hz, 1H), 7.58–7.52 (m, 1H), 7.47–7.40 (m, 3H), 7.35–7.16 (m, 11H), 6.89 (d, *J*=8.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 142.3, 142.05, 142.00, 133.9, 133.0, 131.7, 131.5, 130.7, 130.2, 129.3, 129.0, 128.9, 128.38, 128.35, 128.1, 128.0, 127.3, 123.4, 98.5, 86.7, 21.9; IR (film): 3057, 1593, 1492, 1447, 1373, 1174, 1084 cm^{-1}; MS (ESI) *m*/*z* ($[M+Na]^+$): 680; HRMS (EI) calcd for $C_{28}H_{21}BrINO_3S$: 656.9470; found: 656.9469.

*4.3.14. 3-Butyl-4-iodo-5,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**4n**).* White solid (98 mg, 35%), mp 148–149 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J*=8.0 Hz, 2H), 7.28–7.21 (m, 2H), 7.16 (t, *J*=7.5 Hz, 4H), 7.02 (d, *J*=8.0 Hz, 4H), 6.91 (d, *J*=8.0 Hz, 2H), 2.84 (t, *J*=7.5 Hz, 2H), 2.37 (s, 3H), 1.80–1.70 (m, 2H), 1.42–1.32 (m, 2H), 0.95 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 143.4, 141.9, 129.6, 129.5, 129.4, 128.3, 127.8, 127.7, 96.1, 82.5, 29.8, 29.7, 22.1, 21.7, 13.9; IR (film): 1599, 1489, 1447, 1367, 1171, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+H]^+$): 560; HRMS (EI) calcd for $C_{26}H_{26}INO_3S$: 559.0678; found: 559.0677.

*4.3.15. N-(1,3-Diphenylprop-2-yn-1-yl)-N-hydroxy-4-methylbenzenesulfonamide (**5**).* White solid (72 mg, 38%); mp 113–114 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J*=8.5 Hz, 2H), 7.63 (d, *J*=7.5 Hz, 2H), 7.40–7.17 (m, 8H), 7.05 (d, *J*=7.5 Hz, 2H), 6.32 (s, 1H), 5.99 (s, 1H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 136.2, 131.9, 131.8, 130.2, 129.6, 128.77, 128.75, 128.70, 128.68, 128.2, 122.3, 89.1, 81.6, 57.4, 21.7; IR (film): 3378, 3066, 1599, 1486, 1346, 1168, 1087 cm^{-1}; MS (ESI) *m*/*z* ($[M+K]^+$): 416; HRMS (ESI) calcd for $C_{22}H_{19}NO_3SNa$: 400.0980; found: 400.0971.

4.4. General procedure for the synthesis of 6

To a solution of propargyl alcohol **1** (0.6 mmol) *N*-tosyl hydroxylamine **2** (0.5 mmol), and NBS (0.6 mmol) in dry DCM (5 mL) was added $Yb(OTf)_3$ (0.05 mmol) slowly at 25 °C, and the reaction mixture was stirred at 25 °C for 0.5 h. Saturated aqueous $Na_2S_2O_3$ was added to quench the reaction and the mixture was extracted with DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel with DCM/hexane as eluent to give **6**.

*4.4.1. 4-Bromo-3,5,5-triphenyl-2-tosyl-2,5-dihydroisoxazole (**6a**).* White solid (128 mg, 48%); mp 181–182 °C (decomposition); ^1H NMR (500 MHz, $CDCl_3$): δ 7.80–7.73 (m, 2H), 7.52–7.43 (m, 3H), 7.32–7.18 (m, 8H), 7.16–7.08 (m, 4H), 6.89 (d, *J*=8.5 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 141.9, 139.1, 130.4, 130.0, 129.9, 129.5, 129.3, 129.0, 128.31, 128.27, 128.1, 107.9, 96.9, 22.0; IR (film): 3057, 1593, 1489, 1441, 1367, 1171, 1084 cm^{-1}; MS (ESI) *m*/*z* ($[M+Na]^+$): 556; HRMS (ESI) calcd for $C_{28}H_{22}BrNO_3SNa$: 556.0393; found: 556.0374.

*4.4.2. 4-Bromo-3,5-diphenyl-5-(p-tolyl)-2-tosyl-2,5-dihydro-isoxazole (**6b**).* White solid (128 mg, 47%); mp 98–100 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.80–7.73 (m, 2H), 7.50–7.43 (m, 3H), 7.30–7.18 (m, 5H), 7.14 (d, *J*=8.0 Hz, 2H), 7.05–6.95 (m, 4H), 6.89 (d, *J*=8.0 Hz, 2H), 2.39 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 142.0, 139.0, 138.9, 138.1, 130.4, 130.0, 129.9, 129.5, 129.4, 129.1, 128.7, 128.4, 128.3, 128.2, 128.0, 108.1, 96.9, 22.0, 21.4; IR

(film): 3057, 1593, 1492, 1444, 1367, 1171, 1082 cm^{-1}; MS (ESI) *m/z* ($[M+Na]^+$): 570; HRMS (ESI) calcd for $C_{29}H_{24}BrNO_3SNa$: 570.0550; found: 570.0523.

*4.4.3. 4-Bromo-5-(4-chlorophenyl)-3,5-diphenyl-2-tosyl-2,5-dihydroisoxazole (**6c**).* White solid (150 mg, 53%); mp 167–168 °C (decomposition); ^1H NMR (500 MHz, $CDCl_3$): δ 7.80–7.72 (m, 2H), 7.52–7.45 (m, 3H), 7.30–7.20 (m, 5H), 7.17 (d, *J*=8.5 Hz, 2H), 7.12 (d, *J*=7.5 Hz, 2H), 7.05 (d, *J*=8.5 Hz, 2H), 6.93 (d, *J*=8.5 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.6, 141.4, 140.6, 139.4, 134.4, 130.6, 130.0, 129.9, 129.6, 129.5, 129.4, 128.8, 128.6, 128.4, 128.32, 128.26, 128.2, 107.1, 96.4, 22.0; IR (film): 3060, 1593, 1489, 1444, 1370, 1171, 1087 cm^{-1}; MS (ESI) *m/z* ($[M+Na]^+$): 590; HRMS (ESI) calcd for $C_{28}H_{21}BrClNO_3SNa$: 589.9997; found: 589.9966.

4.5. General procedure for the synthesis of 7

A solution of **4** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), dppb (0.02 mmol), *i*-Pr_2NH (0.8 mmol) in DMF (10 mL) and MeOH (1 mL) was stirred under CO atmosphere (20 atm) at 100 °C for 12 h. When the reaction was complete, the mixture was filtered and the methanol was removed under vacuum. The DMF residue was diluted with H_2O and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel with DCM/hexane as eluent to give **7**.

*4.5.1. Methyl 3,5,5-triphenyl-4,5-dihydroisoxazole-4-carboxylate (**7a**).* White solid (42 mg, 58%); mp 181–182 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.72–7.64 (m, 4H), 7.48–7.42 (m, 2H), 7.42–7.35 (m, 5H), 7.34–7.27 (m, 3H), 7.26–7.21 (m, 1H), 5.13 (s, 1H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 155.2, 143.5, 139.8, 130.6, 129.1, 129.0, 128.8, 128.5, 128.23, 128.16, 127.0, 126.8, 126.3, 95.3, 63.8, 52.6; IR (KBr): 1739, 1617, 1498, 1460, 1314, 1171, 1126 cm^{-1}; MS (ESI) *m/z* ($[M+H]^+$): 358; HRMS (EI) calcd for $C_{23}H_{19}NO_3$: 357.1365; found: 357.1363.

*4.5.2. Methyl 3-phenyl-5,5-di-p-tolyl-4,5-dihydroisoxazole-4-carboxylate (**7b**).* White solid (39 mg, 51%); mp 150–152 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.70–7.65 (m, 2H), 7.52 (d, *J*=8.5 Hz, 2H), 7.40–7.34 (m, 3H), 7.30 (d, *J*=8.0 Hz, 2H), 7.17 (d, *J*=8.0 Hz, 2H), 7.09 (d, *J*=8.0 Hz, 2H), 5.08 (s, 1H), 3.24 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 155.2, 140.8, 138.2, 137.8, 136.9, 130.5, 129.4, 129.2, 129.1, 128.9, 126.9, 126.8, 126.1, 95.4, 63.6, 52.6, 21.28, 21.25; IR (film): 1733, 1516, 1447, 1358, 1194, 918 cm^{-1}; MS (ESI) *m/z* ($[M+H]^+$): 386; HRMS (EI) calcd for $C_{25}H_{23}NO_3$: 385.1678; found: 385.1680.

*4.5.3. Methyl 3,5-diphenyl-5-(p-tolyl)-4,5-dihydroisoxazole-4-carboxylate (**7c**) mixture of Z and E form.* White solid (38 mg, 51%); mp 149–150 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.72–7.62 (m, 3H), 7.54 (d, *J*=8.0 Hz, 1H), 7.43 (d, *J*=7.5 Hz, 1H), 7.41–7.35 (m, 4H), 7.33–7.20 (m, 3H), 7.18 (d, *J*=8.0 Hz, 1H), 7.10 (d, *J*=8.0 Hz, 1H), 5.10 (s, 1H), 3.23 (d, *J*=22 Hz, 3H), 2.31 (d, *J*=16 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 155.21, 155.18, 143.7, 140.6, 140.0, 138.3, 137.9, 136.8, 130.6, 129.4, 129.1, 129.0, 128.7, 128.2, 126.9, 126.8, 126.20, 126.18, 95.4, 95.3, 63.72, 63.68, 52.63, 52.59, 21.28, 21.26; IR (KBr): 1617, 1558, 1447, 1314, 1194, 1171 cm^{-1}; MS (ESI) *m/z* ($[M+H]^+$): 372; HRMS (EI) calcd for $C_{24}H_{21}NO_3$: 371.1521; found: 371.1520.

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Supplementary data

The Supplementary data contains copies of ^1H and ^{13}C NMR spectra along with other experimental details. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.09.092.

References and notes

1. (a) Giomi, D.; Cordero, F. M.; Machetti, F. In *Comprehensive Heterocyclic Chemistry III*; Alan, R. K., Christopher, A. R., Eric, F. V. S., Richard, J. K. T., Eds.; Elsevier: Oxford, 2008; p 365; (b) Habeeb, A. G.; Praveen Rao, P. N.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 2921; (c) Niho, N.; Kitamura, T.; Takahashi, M.; Mutoh, M.; Sato, H.; Matsuura, M.; Sugimura, T.; Wakabayashi, K. *Cancer Sci.* **2006**, *97*, 1011.
2. Matsumoto, M.; Sakuma, T.; Watanabe, N. *Tetrahedron Lett.* **2002**, *43*, 8955.
3. Haino, T.; Tanaka, M.; Ideta, K.; Kubo, K.; Mori, A.; Fukazawa, Y. *Tetrahedron Lett.* **2004**, *45*, 2277.
4. For examples on access to isoxazoles, see: (a) Burkhard, J. A.; Tchitchanov, B. H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5379; (b) Murarka, S.; Studer, A. *Org. Lett.* **2011**, *13*, 2746; (c) Waldo, J. P.; Mehta, S.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2008**, *10*, 658; (d) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643; (e) Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. *Org. Lett.* **2010**, *12*, 2594.
5. For examples on access to 2,3-dihydroisoxazoles, see: (a) Yu, X.; Du, B.; Wang, K.; Zhang, J. *Org. Lett.* **2010**, *12*, 1876; (b) Gonzalez-Cruz, D.; Tejedor, D.; Armas, P.; Morales, E. Q.; Garcia-Tellado, F. *Chem. Commun.* **2006**, 2798; (c) Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 2331.
6. For examples on access to 4,5-dihydroisoxazoles, see: (a) Zhu, M. K.; Zhao, J. F.; Loh, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 6284; (b) Cecchi, L.; Sarlo, F. D.; Machetti, F. *Chem.—Eur. J.* **2008**, *14*, 7903.
7. For examples on access to 2,5-dihydroisoxazoles, see: (a) Knight, D. W.; Proctor, A. J.; Clough, J. M. *Synlett* **2010**, 628; (b) Yeom, H. S.; Lee, E. S.; Shin, S. *Synlett* **2007**, 2292; (c) Foot, O. F.; Knight, D. W.; Low, A. C. L.; Li, Y. *Tetrahedron Lett.* **2007**, *48*, 647; (d) Okitsu, T.; Sato, K.; Potewar, T. M.; Wada, A. *J. Org. Chem.* **2011**, *76*, 3438.
8. (a) Zhu, Y. X.; Yin, G. W.; Hong, D.; Lu, P.; Wang, Y. G. *Org. Lett.* **2011**, *13*, 1024; (b) Zhu, Y. X.; Wen, S.; Yin, G. W.; Hong, D.; Lu, P.; Wang, Y. G. *Org. Lett.* **2011**, *13*, 3553; (c) Yin, G. W.; Zhu, Y. X.; Zhang, L.; Lu, P.; Wang, Y. G. *Org. Lett.* **2011**, *13*, 940.
9. CCDC 889064 and 889065 contain the supplementary crystallographic data of **3a** and **4a**, respectively.
10. (a) Debleds, O.; Zotto, C. D.; Vrancken, E.; Campagne, J. M.; Retailleau, P. *Adv. Synth. Catal.* **2009**, *351*, 1991; (b) Debleds, O.; Gayon, E.; Ostaszuk, E.; Vrancken, E.; Campagne, J. M. *Chem.—Eur. J.* **2010**, *16*, 12207; (c) Gayon, E.; Quinonero, O.; Lemouzy, S.; Vrancken, E.; Campagne, J. M. *Org. Lett.* **2011**, *13*, 6418.
11. For reviews, see: (a) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429; (b) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149 For recent examples, see; (c) Zhu, H. T.; Ji, K. G.; Yang, F.; Wang, L. J.; Zhao, S. C.; Ali, S.; Liu, X. Y.; Liang, Y. M. *Org. Lett.* **2011**, *13*, 684; (d) Hao, L.; Wu, F.; Ding, Z. C.; Xu, S. X.; Ma, Y. L.; Chen, L.; Zhan, Z. P. *Chem.—Eur. J.* **2012**, *18*, 6453.
12. Andres, J.; Cardenas, R.; Silla, E.; Tapia, O. *J. Am. Chem. Soc.* **1988**, *110*, 666.
13. Bohm, S.; Exner, O. *Org. Biomol. Chem.* **2003**, *1*, 1176.
14. For a review, see: Wei, L. L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773.
15. For recent examples, see: (a) Khan, A. T.; Ghosh, A.; Khan, M. M. *Tetrahedron Lett.* **2012**, *53*, 2622; (b) Reddy, C. R.; Ramesh, P.; Rao, N. N.; Ali, S. A. *Eur. J. Org. Chem.* **2011**, 2133; (c) Lin, X. F.; Cui, S. L.; Wang, Y. G. *Tetrahedron Lett.* **2006**, *47*, 4509; (d) Jareb, M.; Vrazic, D.; Zupan, M. *Tetrahedron* **2010**, *67*, 1355; (e) Nath, J.; Patel, B. K.; Jamir, L.; Sinha, U. B.; Satyanarayana, K. V. V. V. *Green Chem.* **2009**, *11*, 1503.
16. For recent reviews, see: (a) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114; (b) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095.
17. Zadrożna, I.; Kurkowska, J.; Kruszewska, H.; Makuch, I. *IL Farmaco* **2000**, *55*, 499.
18. Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027.
19. Banerjee, R.; King, S. B. *Org. Lett.* **2009**, *11*, 4580.