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A Dual Gold-Iron Catalysis for a One-Pot Synthesis of 2,3-Dihydroisoxazoles from Propargylic Alcohols and N-Protected Hydroxylamines

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Abstract: A concise one-pot route for the synthesis of 2,3-dihydroisoxazoles *via* a dual gold-iron catalysis has been devised. The method, based on the addition of binucleophilic protected hydroxylamine to propargylic alcohols, enables a one-pot, highly selective synthesis of these heterocycles (10 examples, up to 86% yield).

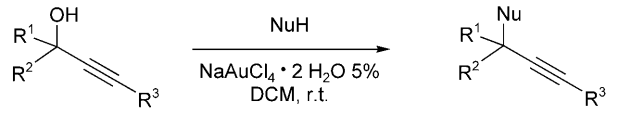
Keywords: gold; heterocycles; homogeneous catalysis; iron

Introduction

2,3-Dihydroisoxazoles (Δ^4-isoxazolines) are versatile heterocycles known for their potent biological activities,[1] but also as useful building blocks.[2] Although their efficacy in both chemistry and biology has been well established, only a few methods to obtain such scaffolds have been described so far. Among the most popular of these, the [3+2] cycloadditions between nitrones and alkynes,[3] oxaziridine ring opening,[4] and cyclization of propargylic *N*-hydroxylamine[5] are worthy of note. To the best of our knowledge, these approaches appear to be restricted to *N*-alkyl- or *N*-benzyl 2,3-dihydroisoxazoles, and so far no convenient method to obtain *N*-carbamate- or *N*-sulfonyl-protected derivatives has been described. Inspired by their potential in both chemistry and biology and our previous work on propargylic substitutions, we decided to devise a flexible route to obtain these heterocycles.

We have recently described that propargylic alcohols can be efficiently substituted under mild conditions using various nucleophiles (alcohols, thiols, allylsilanes, hydrides, electron-rich aromatics, sulfonamides) and gold(III) catalysts at room temperature (Scheme 1).[6]

By using a binucleophilic species HX–YH (such as hydroxylamine, hydrazines etc.), we anticipated that, after the first nucleophilic substitution (see **A**, Scheme 2), gold(III) will then be able to coordinate to the triple bond and thus promote the cyclization to furnish the unsaturated compound **B** (Scheme 2).



NuH = ROH, RSH, AllylTMS, Ar-H, $TsNH_2$, Et_3SiH
R^3 = Alkyl, Aryl, TMS
R^1, R^2 = (Aryl, H); (Aryl, Alkyl); (Alkyl, Alkyl)

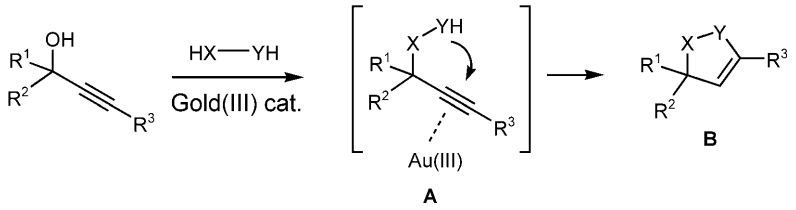
Scheme 1. Gold(III)-catalyzed propargylic substitution.

In this paper, we would like to disclose our results with protected hydroxylamines nucleophiles PNH–OH which in turn allows the preparation of protected 2,3-dihydroisoxazoles (Δ^4-isoxazolines).[7]

Results and Discussion

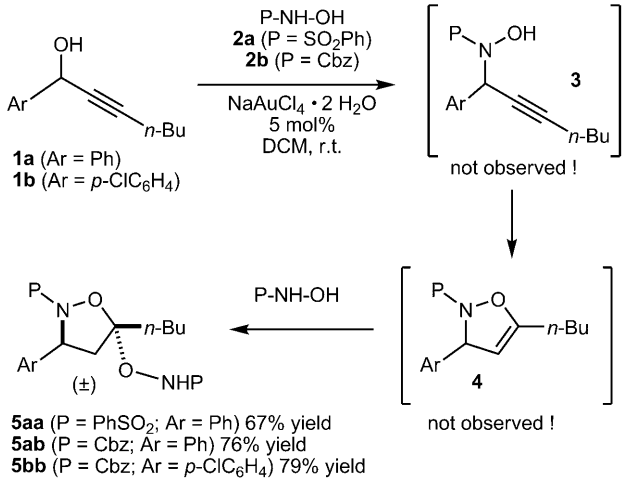
Gold-Catalyzed Reactions

Starting from model propargylic alcohol compounds **1a–b** and protected hydroxylamines **2a–b** (P = $PhSO_2$ or Cbz), the corresponding dihydroisoxazoles **4** could



Scheme 2. Propargylic substitutions with binucleophilic species.

not be observed in the crude product. Only a mixture of the starting propargylic alcohol **1a–b** and compounds **5** resulting from the formal addition of the protected hydroxylamine to **4** could be isolated. By using 2.1 equivalents of protected hydroxylamines, compounds **5aa**, **5ab** and **5bb** could be isolated in 67, 76 and 79% yields, respectively, as a single diastereomer (Scheme 3).



Scheme 3. Propargylic substitutions with binucleophilic species.

Determination of the structures of these compounds **5** appeared to be a challenging task. Indeed, two different substitution products **3** can be obtained depending on the nucleophilic site (O *vs.* N) of the hydroxylamine, thus leading to two different heterocycles **4**. These two heterocyles can in turn be attacked by the nitrogen or the oxygen sites of the hydroxylamine nucleophile thus leading to four potential structures **C–F** which are very similar (Figure 1).

By combining NMR and IR analysis, structure **C** was tentatively assigned to compounds **5**. This hypothesis could then be confirmed by an X-ray analysis (Figure 2) on compound **5bb** (P = Cbz, Ar = *p*-ClC_6H_4), thus also establishing the relative configurations.

Attempts to obtain the dihydroisoxazoles **4** from compounds **5**, under different reaction conditions, were unsuccessful in our hands. Therefore, we turned

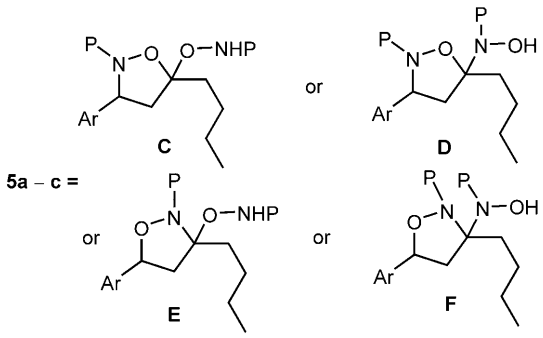


Figure 1. Potential structures for compounds **5**.

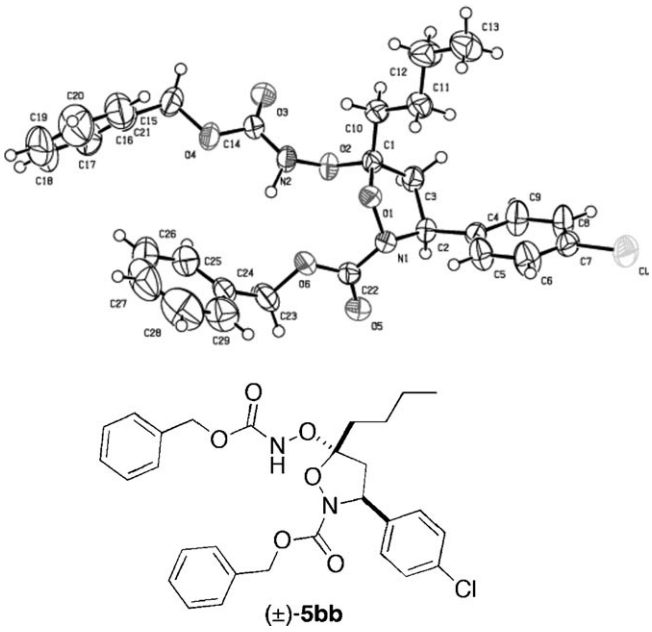
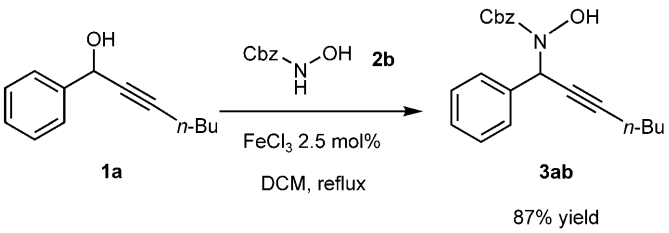


Figure 2. X-ray crystal structure of (±)-**5bb**.

our attention to the selective formation of dihydroxazoles **4**, under a different set of conditions.

Iron-Catalyzed Reactions

One alternative was to first obtain the substitution product **3** and then promote, in a separate step, the cyclization to obtain dihydroisoxazoles **4**. Among the recently described methodologies[8,9] to perform prop-



Scheme 4. Fe-catalyzed substitution of propargylic alcohols with protected hydroxylamines.

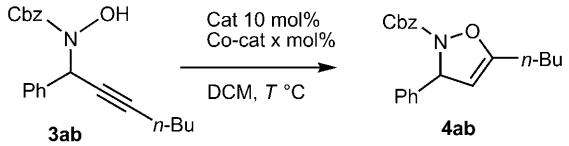
argylic substitutions, we focused primarily on iron-(III)-catalyzed reactions, recently described by Zhan and co-workers.[9] We anticipated that a less π-acidic metal, such as iron,[10,11] might selectively provide the propargylic substitution product.

Indeed, when **1a** and **2b** are refluxed, in the presence of $FeCl_3$ (2.5 mol%) in dichloromethane (DCM), the propargylic substitution product **3ab** is formed selectively in 87% yield, while neither cyclized **4ab**, nor diaddition product **5ab** could be observed (Scheme 4). Starting from **3ab**, the cyclization to dihydroisoxazole **4ab** was next investigated (Table 1). Surprisingly,[12] in the presence of iron(III) and gold(III) catalysts, no cyclization occurs (entries 1–3), and a low 8% yield could be observed in the presence of $Ph_3PAuOTf$ (Table 1, entry 3).[7a]

Under Carreira's conditions,[5] in the presence of ZnI_2 and DMAP, compound **4ab** was obtained in low yield (Table 1, entry 5), probably due to the electron-withdrawing character of the Cbz group.[13]

The intriguing role of DMAP in this cyclization prompts us to re-examine the gold- and iron-catalyzed cyclizations in the presence of DMAP. Whereas, no cyclization occurs in the presence of $FeCl_3$ and DMAP (Table 1, entry 6), gratifyingly the combination of $NaAuCl_4{\cdot}2H_2O$ and DMAP led to the desired 2,3-dihydroisoxazole **4ab** in 84% yield.

Table 1. Propargylic N-hydroxylamine cyclization.



	Catalyst (10%)	*T* [°C]	Co-Cat [%]	Yield [%]
1	$FeCl_3$	reflux	–	–
2	$NaAuCl_4{\cdot}2\,H_2O$	r.t. or reflux	–	–
3	Ph_3PAuCl	r.t. or reflux	–	–
4	$Ph_3PAuCl/AgOTf$	reflux	–	8
5	ZnI_2	r.t. or reflux	DMAP (20%)	15–20
6	$FeCl_3$	reflux	DMAP (20%)	NR
7	$NaAuCl_4{\cdot}2H_2O$	reflux	DMAP (20%)	84%

Dual Iron-Gold Catalyzed Reactions

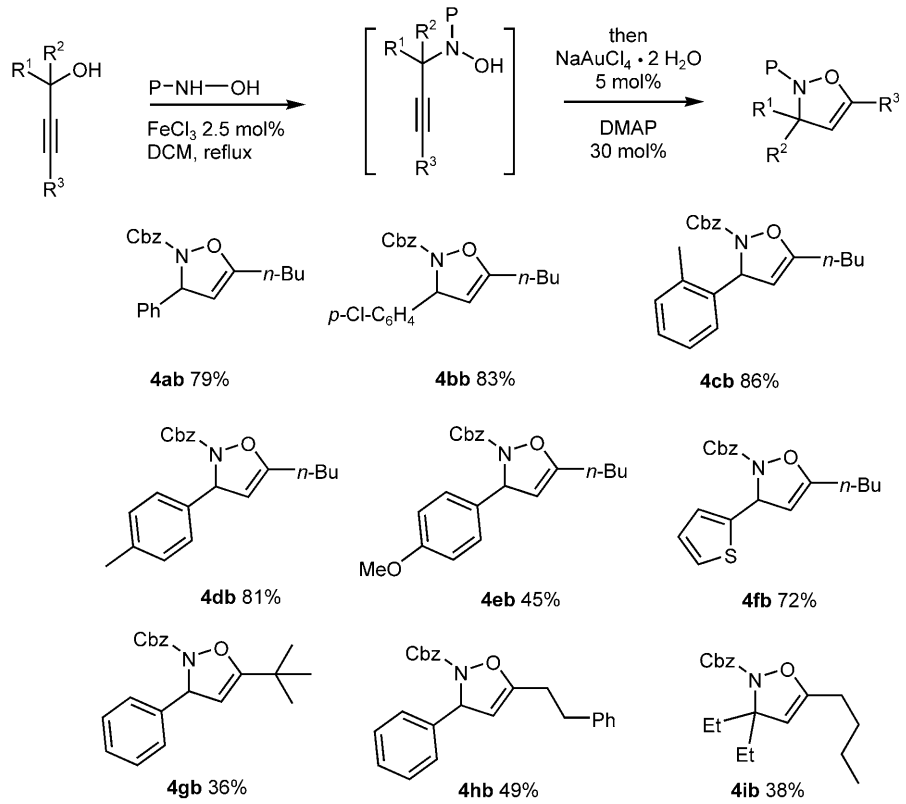
Finally, we thus turned our attention to a *one-pot* procedure to directly obtain the dihydroisoxazoles **4** from propargylic alcohols **1**. By performing the substitution in the presence of $FeCl_3$ and then (TLC monitoring) adding $NaAuCl_4{\cdot}2H_2O$ and DMAP to the reaction mixture, the corresponding dihydroisoxazoles **4** can be obtained selectively (Scheme 5). After optimization, we found that the amounts of iron and gold catalysts could be reduced to 2.5 and 5 mol%, respectively, but moving to 30% of DMAP was important in order to reduce reaction time and increase reaction yields.

On the propargylic position (R^1, R^2), various substituents [*ortho*, *meta* or *para* substituted aryl groups, heteroaromatic groups such as thiophene (**4fb**), or dialkyl groups ($R^1=R^2=Et$; **4ib**)] are well tolerated with the corresponding dihydroisoxazoles obtained in poor to good yields (Scheme 5). Dihydroisoxazoles bearing various alkyl groups on the alkyne position (R^3), including a *t*-Bu group (see **4gb**), are also obtained in good yields.

The structure of these 2,3-dihydroisoxazoles **4** could be further confirmed by an X-ray analysis on compound **4bb** (Figure 3).

Due to the inherent difficulties of promoting the **3**→**4** cyclization in the absence of DMAP (see reaction scheme in Table 1), we re-considered our initial mechanistic proposal, and complementary reactions were thus undertaken. First of all, the reaction of **4ab** with CbzNH–OH, in the presence of a catalytic amount of gold(III) at room temperature, efficiently leads to **5ab** in 74% yield [Scheme 6, Eq. (a)]. Knowing the Lewis properties of the gold catalyst, this transformation could be interpreted as the trapping of a transient gold(III)-**4ab** cationic complex by the oxygen pole of the hydroxylamine. The diastereoselectivity outcome in the formation of **5ab** can be explained through a reversible formation of the oxonium in the presence of gold Lewis acid [see Scheme 6, Eq. (a)] leading to the thermodynamic compound **5ab**.When **3ab** is, in turn, treated by CbzNH–OH in the presence of $NaAuCl_4{\cdot}2H_2O$, compound **5ab** is also stereoselectively obtained in two hours, at room temperature, and in 81% yield [Scheme 6, Eq. (b)].[14]

Different scenarios envisioned to explain the stereoselective formation of **5** are depicted in Scheme 7. Among all possibilities, two general ways are emerging, based on the initial step: a propargylic substitution (Scheme 7, path **A**) with the nitrogen pole of the protected hydroxylamine to give **3**, or an alkyne hydration (Scheme 7, path **B**) to furnish **7**. It is worth noting that the 'diaddition' product **5** is obtained as a single regioisomer [none of the alternative regioisomers (see Figure 1) are observed] and diastereomer. As this compound results from the condensation of hy-



Scheme 5. *One-pot* formation of 2,3-dihydroisoxazoles.

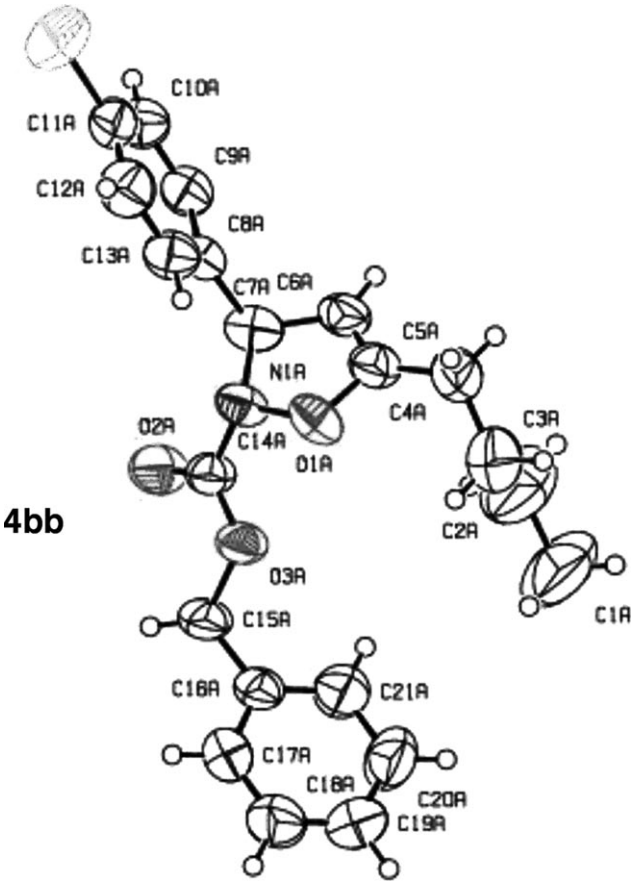
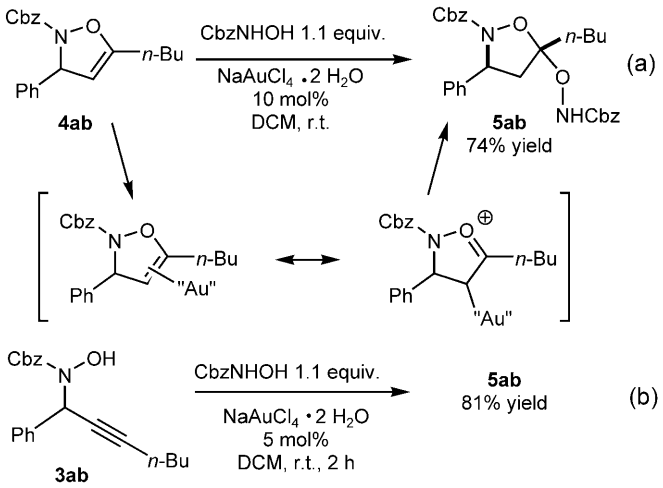
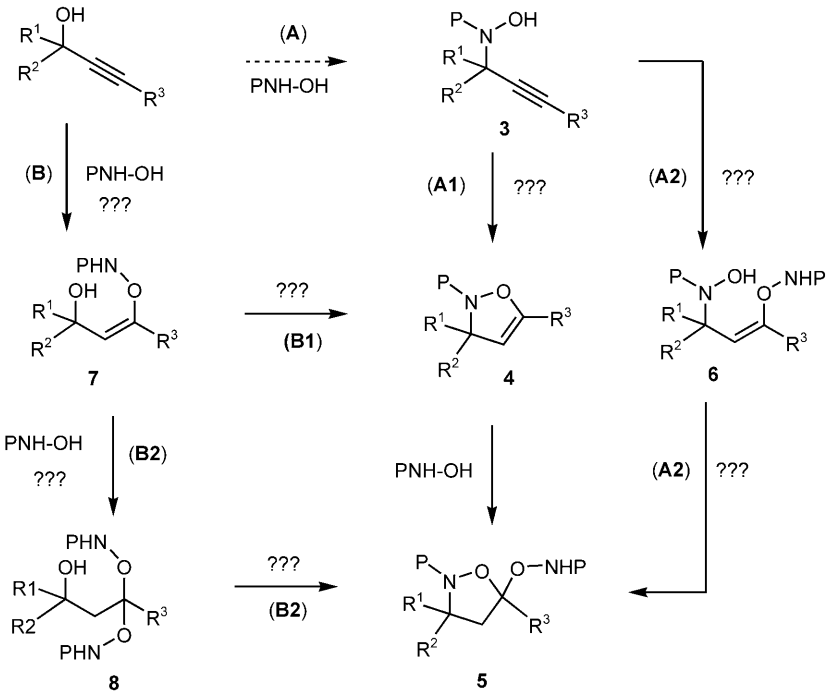


Figure 3. X-ray crystal structure of **4bb**.



Scheme 6.

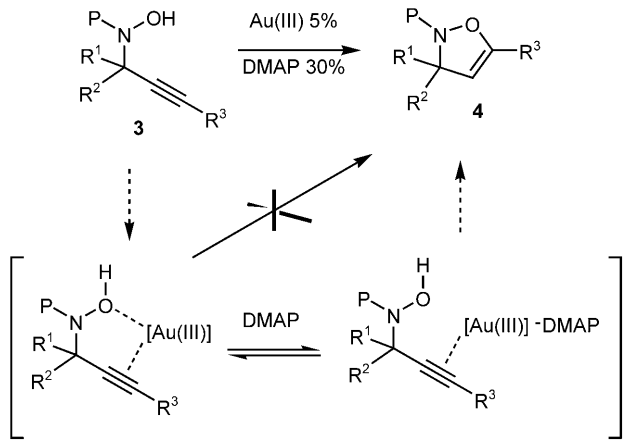
droxylamine **2b** to stabilized carbocationic intermediates,[6] it is reasonable to postulate that, in these conditions, O addition processes are preferred. If path A (Scheme 7) cannot be totally excluded [see Scheme 6, Eq. (b)], the alkyne hydration path (Scheme 7, path **B**) nevertheless seems more plausible. The gold-catalyzed triple bond 'hydration' will furnish **7** which can either cyclize to give **4** (Scheme 7, path **B1**) before the second addition of the protected hydroxylamine



Scheme 7. Mechanistic proposals.

[see Scheme 6, Eq. (a)] or a second equivalent of hydroxylamine (Scheme 7, path **B2**) could be re-added to **7** before cyclizing by an intramolecular benzylic subsitution.[15,16] We are currently not able to distinguish between the **B1** and **B2** paths, and theoretical studies have been initiated.

The exact role of DMAP as agent to promote the **3**→**4** cyclization remains unclear (Table 1 and Scheme 5). One possible explanation could be the formation of a stable chelate resulting from the complexation of gold to both the triple bond and the oxygen, thus preventing the cyclization process by depletion of the oxygen atom nucleophilicity (Scheme 8). Complexation of DMAP to the metal center[17] would break the chelate by displacing the Au(III)–O interaction, restoring the oxygen lone pair and thus allowing the cyclization.



Scheme 8.

Conclusions

In conclusion, we took advantage of the different reactivities between gold and iron,[19] and of their compatibility, to develop an efficient gold-iron catalyzed one-pot synthesis of 2,3-dihydroisoxazole from propargylic alcohols: iron(III) to promote the propargylic substitution, and then, in a *one-pot* procedure, gold(III) (in the presence of a co-catalytic amount of DMAP) to ensure the cyclization. When gold(III) is used as the sole catalyst, the disubstitution products **5** are selectively obtained in good yields. Further applications of such iron-gold sequential catalytic[20] reactions are currently under development.

Experimental Section

General Remarks

Unless otherwise stated all commercial materials were used without further purification. Reactions were carried out in round-bottom flasks equipped with a magnetic stirring bar. Dichloromethane was distilled over CaH_2. TLC analysis of all reactions was performed on silica gel 60 F_{254} TLC plates. Chromatography was carried out on silica gel 60 A (35–70 μm). FT-IR spectra were recorded with a Perkin–Elmer

Spectrum 1000. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Ultra shield 400 plus and referenced to $CDCl_3$ unless otherwise noted. Mass spectra and high resolution mass spectra were obtained using the mass spectrometers operated by the Centre Commun de Spectrométrie de Masse of University Claude Bernard Lyon 1 and Laboratoire de Mesure Physique of University Montpellier 2.

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 720996 and CCDC 720997. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for Preparation of Compounds 5

To a solution of propargylic alcohol (1 mmol) in 5 mL of dichloromethane were added protected hydroxylamine (2.1 mmol) and $NaAuCl_4{\cdot}2H_2O$ (0.1 mmol). The mixture was stirred at room temperature during 6 h. After reaction completion (TLC monitoring), the mixture was concentrated under vacuum and the crude material loaded on to a silica gel column and chromatographed with a mixture of cyclohexane and diethyl ether.

General Procedure for Preparation of Compounds 3

To a solution of propargylic alcohol (1 mmol) in 5 mL of dichloromethane were added protected hydroxylamine (1.2 mmol) and $FeCl_3$ (0.1 mmol). The mixture was refluxed for 1 hour. After reaction completion (TLC monitoring), the mixture was concentrated under vacuum and the crude material loaded on to a silica gel column and chromatographed with a mixture of cyclohexane and diethyl ether.

General Procedure for Preparation of Compounds 4

To a solution of propargylic alcohol (1 mmol) in 5 mL of dichloromethane were added protected hydroxylamine (0.9 mmol) and $FeCl_3$ (0.025 mmol). The mixture was refluxed for 1 hour, then $NaAuCl_4{\cdot}2H_2O$ (0.05 mmol) and DMAP (0.25 mmol) were added and the reflux was maintained for additional 2 h. After reaction completion (TLC monitoring), the mixture was concentrated under vacuum and the crude material loaded on to a silica gel column and chromatographed with a mixture of cyclohexane and diethyl ether.

Benzyl hydroxy(1-phenylhept-2-ynyl)carbamate (3ab): According to the general procedure, compound **3ab** is obtained in 87% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.92$ (t, $J = 7.3$ Hz, 3H), 1.38–1.47 (m, 2H), 1.50–1.56 (m, 2H), 2.29 (td, $J = 2.1$ Hz and $J = 7.1$ Hz, 2H), 5.26 (s, 2H), 5.65 (s, 1H), 6.13 (t, $J = 2.0$ Hz, 1H), 7.31–7.4 (m, 8H), 7.52–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 13.59$, 18.46, 21.97, 30.62, 55.79, 68.38, 74.52, 87.58, 127.92 (2C), 128.19 (2C), 128.21, 128.38 (3C), 128.55 (2C), 135.58, 136.22, 157.15; IR-FT (film): $\nu = 3366$, 3062, 3032, 2956, 2931, 2871, 1702, 1495, 1453, 1406, 1351, 1287, 1097, 1029, 962, 912, 831, 746, 696, 632 cm^{-1}; MS (ES+): $m/z =$ 338 (85), 314 (8), 289 (26), 261 (7), 217 (9), 189 (38), 171 (22), 152 (4), 84 (3), 81(100); HR-MS (ES+): $m/z =$ 338.1766, calcd. for $C_{21}H_{23}NO_3 + H^+$: 338.1756.

Benzyl 5-butyl-3-phenylisoxazole-2(3*H*)-carboxylate (4ab): According to the general procedure, compound **4ab** is obtained in 79% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.92$ (t, $J = 7.3$ Hz, 3H), 1.34–1.44 (m, 2H), 1.54–1.61 (m, 2H), 2.29 (t, $J = 7.49$ Hz, 2H), 4.81 (dt, $J = 1.0$ Hz and $J = 2.0$ Hz, 1H), 5.21 (s, 2H), 5.91 (dd, $J = 1.5$ Hz and $J = 3.5$ Hz, 1H), 7.27–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 13.73$, 22.24, 25.27, 28.64, 68.01, 68.51, 96.54, 126.8 (2C), 127.99 (2C), 128.06, 128.20, 128.45 (2C), 128.58 (2C), 135.67, 140.95, 155.47; IR-FT (film): $<\iota\tau>\nu<\iota\tau> = 3064$, 3032, 2957, 2931, 2872, 1715, 1682, 1590, 1496, 1455, 1393, 1324, 1231, 1123, 1076, 1028, 1022, 938, 910, 823, 751, 697 cm^{-1}; MS (ES+): $m/z = 675$ [2M+H$^+$] (20), 338 (100), 294 (29), 255 (24), 189 (19), 91 (3); HR-ESI-MS: $m/z = 337.1674$, calcd. for $C_{21}H_{23}NO_3$: 337.1678.

Benzyl 5-butyl-3-(4-chlorophenyl)isoxazole-2(3*H*)-carboxylate (4bb): According to the general procedure, compound **4bb** is obtained in 83% yield as a white solid; mp 65.8 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.89$ (t, $J = 7.3$ Hz, 3H), 1.30–1.40 (m, 2H), 1.49–1.57 (m, 2H), 2.25 (t, $J = 7.7$ Hz, 2H), 4.74 (dd, $J = 1.1$ Hz and $J = 2.2$ Hz, 1H), 5.18 (s, 2H), 5.84 (s, 1H), 7.21–7.32 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 13.72$, 22.22, 25.25, 28.59, 67.86, 68.15, 96.10, 128.12 (2C), 128.23 (2C), 128.31, 128.49 (2C), 128.72 (2C), 133.78, 135.50, 139.47, 155.84; IR-FT (film): $\nu = 2959$, 2928, 2848, 1741, 1712, 1675, 1494, 1454, 1391, 1325, 1236, 1089, 1019, 934, 835, 805, 742, 694 cm^{-1}; MS (EI): $m/z = 371$ (10), 298 (2), 280 (3), 236 (61), 192 (9), 152 (11), 139 (4), 125 (14), 91 (100); HR-MS (ES+): $m/z = 372.1356$, calcd. for $C_{21}H_{22}ClNO_3 + H^+$: 372.1366.

Benzyl 5-butyl-3-*o*-tolylisoxazole-2(3*H*)-carboxylate (4cb): According to the general procedure, compound **4cb** is obtained in 86% yield as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.90$ (t, $J = 7.3$ Hz, 3H), 1.32–1.41 (m, 2H), 1.51–1.59 (m, 2H), 2.27 (t, $J = 7.7$ Hz, 2H), 2.36 (s, 3H), 4.78 (dd, $J = 1.1$ Hz and $J = 2.0$ Hz, 1H), 5.20 (s, 2H), 6.12 (s, 1H), 7.10–7.36 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 13.73, 18.82, 22.24, 25.27, 28.58, 65.75, 68.01, 96.65, 126.54, 126.71, 127.64, 128.03 (2C), 128.20, 128.44 (2C), 130.45, 134.54, 135.64, 138.89, 155.17; IR-FT (film): $\nu = 3065$, 3031, 2956, 2929, 2871, 1742, 1718, 1682, 1490, 1458, 1389, 1322, 1230, 1103, 1053, 938, 910, 872, 850, 823, 750, 697 cm^{-1}; MS (EI): $m/z = 351$ (21), 278 (3), 228 (3), 216 (43), 186 (2), 172 (3), 132 (40), 117(5), 105 (8), 91 (100), 57 (19); HR-MS (ES+): $m/z = 352.1919$, calcd. for $C_{22}H_{25}NO_3 + H^+$: 352.1913.

Benzyl 5-butyl-3-*p*-tolylisoxazole-2(3*H*)-carboxylate (4db): According to the general procedure, compound **4bb** is obtained in 81% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.91$ (t, $J = 7.3$ Hz, 3H), 1.32–1.43 (m, 2H), 1.53–1.61 (m, 2H), 2.28 (t, $J = 7.7$ Hz, 2H), 2.33 (s, 3H), 4.78 (s, 1H), 5.21 (s, 2H), 5.87 (s, 1H), 7.14 (d, $J =$ 8 Hz), 7.23 (d, $J = 8$ Hz), 7.29–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 13.73$, 21.13, 22.24, 25.27, 28.63, 67.94, 68.27, 96.62, 126.77 (2C), 128.06 (2C), 128.17, 128.43 (2C), 129.43 (2C), 135.07, 137.76, 138.00, 155.3; IR-FT (film): $\nu = 3028$, 2958, 2927, 2869, 1716, 1682, 1609, 1515, 1497, 1450, 1389, 1320, 1227, 1179, 1125, 1082, 937, 916, 818, 749, 695 cm^{-1}; MS (EI): $m/z = 351$ (22), 278 (2), 260 (3), 216 (52), 172 (6), 132 (38), 119 (4), 105 (18), 91 (100), 77 (5), 57 (12), 41 (3); HR-MS (ES+): $m/z = 352.1891$, calcd. for $C_{22}H_{25}NO_3 + H^+$: 352.1913.

Benzyl 5-butyl-3-(4-methoxyphenyl)isoxazole-2(3*H*)-carboxylate (4eb): According to the general procedure, compound **4eb** is obtained in 45% yield as a pale yellow oil. ^{1}H NMR (DMSO, 400 MHz): $\delta = 0.88$ (t, $J = 7.2$ Hz, 3H), 1.30–1.38 (m, 2H), 1.45–1.54 (m, 2H), 2.26 (t, $J = 7.4$ Hz, 2H), 3.74 (s, 3H), 5.04 (s, 1H), 5.18 (s, 2H), 5.86 (s, 1H), 6.91 (d, $J = 8.5$ Hz, 1H), 7.21 (d, $J = 8.6$ Hz, 1H), 7.32–7.39 (m, 5H); ^{13}C NM;R (DMSO, 100 MHz): $\delta = 13.74$, 22.25, 25.29, 28.65, 55.30, 67.95, 68.03, 96.52, 113.91 (2C), 128.08 (2C,), 128.20, 128.22 (2C), 128.45 (2C), 133.06, 135.04, 155.38, 159.40; IR-FT (film): $\nu = 3028$, 2966, 2928, 2870, 1738, 1713, 1682, 1609, 1511, 1456, 1380, 1336, 1303, 1248, 1173, 1107, 1032, 930, 842, 750, 697 cm^{-1}; MS (EI): $m/z = 367$ (15), 281 (7), 232 (63), 207 (13), 188 (28), 160 (5), 148 (22), 135 (21), 121 (20), 91 (100), 77 (15) , 57 (10), 44 (40); HR-MS (ES+): $m/z = 368.1862$, calcd. for $C_{22}H_{25}NO_4 + H^+$: 368.1860.

Benzyl 5-butyl-3-(thiophen-2-yl) isoxazole-2(3*H*)-carboxylate (4fb): According to the general procedure, compound **4fb** is obtained in 72% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.92$ (t, $J = 7.2$ Hz, 3H), 1.35–1.43 (m, 2H), 1.54–1.62 (m, 2H), 2.29 (t, $J = 7.5$ Hz, 2H), 4,87 (s, 1H), 5.25 (s, 2H), 6.20 (s, 1H), 6.95 (dd, $J = 3.52$ Hz and $J = 4.8$ Hz, 1H), 7.03 (d, $J = 3.39$ Hz, 1H), 7.26 (d, $J = 5.1$ Hz, 1H), 7.25–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 13.73$, 22.17, 25.29, 28.55, 63.64, 68.20, 95.56, 125.40, 125.79, 126.84, 128.17 (2C), 128.30, 128.49 (2C), 135.52, 145.10, 156.68; IR-FT: $\nu = 3114$, 3033, 2957, 2931, 2871, 1739, 1716, 1682, 1497, 1455, 1393, 1320, 1242, 1115, 1064, 968, 718, 698 cm^{-1}; MS (EI): $m/z = 343$ (16), 208 (79), 164 (3), 124 (14), 111 (6), 91 (100), 70 (3), 57 (8), 41 (4); HR-ESI-MS: $m/z = 343.1302$, calcd. for $C_{19}H_{21}NSO_3$: 343.1320.

Benzyl 5-*tert*-butyl-3-phenylisoxazole-2(3*H*)-carboxylate (4gb): According to the general procedure, compound **4gb** is obtained in 36% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.23$ (s, 9H), 4.77 (s, 1H), 5.19 (ab, $J_{ab} = 12.41$ Hz, 1H), 5.25 (ab, $J_{ab} = 12.41$ Hz, 1H), 7.28–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 27.97$ (3C), 31.47, 67.90, 68.54, 94.25, 126.71 (2C), 127.85, 127.96 (2C), 128.12, 128.43 (2C), 128.59 (2C), 135.75, 141.03, 163.32; IR-FT (film): $\nu = 3033$, 2968, 2932, 2872, 1749, 1719, 1669, 1588, 1496, 1456, 1393, 1321, 1230, 1203, 1093, 1029, 926, 734, 696 cm^{-1}; MS (EI): $m/z = 337$ (17), 278 (2), 202 (54), 186 (7), 160 (24), 117 (12), 105 (6), 91 (100), 77 (3), 57 (19), 41 (5); HR-MS (ES+)MS: $m/z = 338.1779$, calcd. for $C_{21}H_{23}NO_3 + H^+$: 338.1756.

Benzyl 5-phenethyl-3-phenylisoxazole-2(3*H*)-carboxylate (4hb): According to the general procedure, compound **4hb** is obtained in 49% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 2.63$ (t, $J = 7.7$ Hz, 2H), 2.92 (t, $J = 7.8$ Hz, 2H), 4.77 (dd, $J = 1.0$ Hz and $J = 2.1$ Hz), 5.22 (ab, $J = 12.4$ Hz, 1H), 5.24 (ab, $J = 12.4$ Hz, 1H), 5.88 (s, 1H), 7.19–7.34 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 27.41$, 32.53, 68.10, 68.49, 97.45, 126.26 (2C), 126.88 (2C), 128.02, 128.15, 128.27, 128.40 (2C), 128.46 (2C), 128.49 (2C), 128.54 (2C), 135.59, 140.25, 140.59, 154.15; IR-FT (film): $\nu = 3063$, 3030, 2929, 2875, 1745, 1714, 1683, 1603, 1496, 1455, 1392, 1324, 1233, 1110, 1076, 1029, 937, 910, 818, 751, 697 cm^{-1}; MS (EI): $m/z = 385$ (14), 294 (4), 250 (32), 208 (2), 194 (3), 158 (12), 145 (13), 117 (22), 105 (12), 91 (100), 77 (5), 65 (6), 44 (3); HR-MS (ES+): $m/z = 386.1726$, calcd. for $C_{25}H_{23}NO_3 + H^+$: 386.1756.

Benzyl 5-butyl-3,3-diethylisoxazole-2(3*H*)-carboxylate (4ib): According to the general procedure, compound **4gb** is obtained in 38% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.85$–0.90 (m, 9H), 1.28–1.38 (m, 2H), 1.46–1.59 (m, 4H), 1.63–1.72 (m, 2H), 2.51 (t, $J = 7.6$ Hz, 2H), 4.68 (s, 1H), 5.23 (s, 2H), 7.29–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 8.02$ (2C), 13.83, 22.18, 27.56, 29.71, 31.35 (2C), 67.38, 93.08, 107.61, 128.09 (2C), 128.13, 128.43 (2C), 136.04, 140.64, 152.4; IR-FT (film): $\nu = 3065$, 2963, 2932, 2874, 1738, 1707, 1455, 1411, 1350, 1264, 1099, 944, 916, 745, 697 cm^{-1}; MS (EI): $m/z = 317$ (2), 288 (6), 244 (29), 91 (100), 70 (6), 57 (5), 41 (3); HR-MS (ES+): $m/z = 318.2046$, calcd. for $C_{19}H_{27}NO_3 + H^+$: 318.2069.

***N*-[5-Butyl-3-phenyl-2-(phenylsulfonyl)isoxazolidin-5-yloxy]benzenesulfonamide (5aa):** According to the general procedure, compound **5aa** is obtained in 67% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.87$ (t, $J = 7.13$ Hz, 3H), 1.14–1.36 (m, 3H), 1.49–1.59 (m, 1H), 1.79 (ddd, $J = 4.6$ Hz and $J = 12.6$ Hz and $J = 14.2$ Hz, 1H), 2.19 (ddd, $J = 4.4$ Hz and $J = 12.2$ Hz and $J = 14.4$ Hz, 1H), 2.28 (dd, $J = 11$ Hz, $J = 13.4$ Hz, 1H), 2.68 (dd, $J = 7.1$ Hz and $J = 13.4$ Hz, 1H), 5.19 (dd, $J = 7.0$ Hz and $J = 11$ Hz, 1H), 7.27–7.36 (m, 5H), 7,54 (t, $J = 7.8$ Hz, 2H), 7.63 (t, $J = 7.6$ Hz, 2H), 7.64 (dd, $J = 7.6$ Hz and $J = 15.3$ Hz, 1H), 7.70 (dd, $J = 7.6$ Hz and $J = 14.8$ Hz, 1H) , 7.87 (d, $J = 7.5$ Hz, 2H), 7.97 (d, $J = 7.4$ Hz, 2H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 13.85$, 22.62, 26.35, 30.83, 46.61, 61.83, 115.48, 126.38 (2C), 128.1, 128.28 (2C), 128.58 (2C), 128.74 (2C), 129.09 (2C), 129.14 (2C), 133.68, 134.02, 136.86, 137.01, 139.18; IR-FT (film): $\nu = 3233$, 2960, 2856, 1448, 1388, 1343, 1324, 1170, 1092, 1023, 964, 857, 754, 698, 600, 573, 554 cm^{-1}; MS (ES+): $m/z = 517$ (50), 391 (27), 344 (100), 204 (6); HR-MS (ES+): $m/z = 517.1455$, calcd. for $C_{25}H_{28}N_2O_6S_2 + H^+$: 517.1467.

Benzyl 5-(benzyloxycarbonylaminooxy)-5-butyl-3-phenylisoxazolidine-2-carboxylate (5ab): According to the general procedure, compound **5ab** is obtained in 76% yield, as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.83$ (t, $J = 7.2$ Hz, 3H), 1.22–1.30 (m, 3H), 1.49–1.55 (m, 1H), 1.74 (ddd, $J = 4.3$ Hz and $J = 12.4$ Hz and $J = 14.3$ Hz, 1H), 2.14 (ddd, $J = 4.1$ Hz and $J = 11.6$ Hz and $J = 14.4$ Hz, 1H), 2.28 (dd, $J = 6.4$ Hz and $J = 13.4$ Hz, 1H), 2.92 (dd, $J = 9.1$ Hz and $J = 13.4$ Hz, 1H), 5.11–5.22 (m, 4H), 5.34 (dd, $J = 6.6$ Hz and $J = 8.8$ Hz, 1H), 7.26–7.37 (m, 15H), 8.07 (b, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 13.72$, 22.63, 26.13, 29.78, 45.32, 63.10, 67.38, 68.64, 115.47, 125.68 (2C), 127.59, 128.04, 128.31 (2C), 128.38 (2C), 128.47, 128.51 (2C), 128.63 (2C), 128.77 (2C), 135.12, 135.68, 141.34, 156.57, 159.60; IR-FT (film): $\nu = 3306$, 3072, 3033, 2959, 2927, 2871, 1758, 1718, 1497, 1455, 1387, 1310, 1252, 1227, 1102, 1028, 980, 866, 755, 698 cm^{-1}; MS (ES+): $m/z = 1010$ (5), 505 (90), 338 (27), 289 (24), 271 (100), 217 (5), 204 (11), 189 (50), 168 (11), 124 (6), 83 (78); HR-MS (ES+): $m/z = 505.2322$, calcd. for $C_{29}H_{32}N_2O_6 + H^+$: 505.2339.

Benzyl 5-(benzyloxycarbonylaminooxy)-5-butyl-3-(4-chlorophenyl) isoxazolidine-2-carboxylate (5bb): According to the general procedure, compound **5bb** is obtained in 79% yield, as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.83$ (t, $J = 7.13$ Hz, 3H), 1.19–1.31 (m, 3H), 1.46–1.55 (m, 1H), 1.73 (ddd, $J = 4.3$ Hz and $J = 12.6$ Hz and $J = 14.2$ Hz, 1H), 2.13 (ddd, $J = 4.4$ Hz and $J = 11.8$ Hz and $J = 14.4$ Hz, 1H), 2.22 (dd, $J = 6.3$ Hz, $J = 13.4$ Hz, 1H), 2.91 (dd, $J = 9.1$ Hz

and $J=13.4$ Hz, 1H), 5.11–5.24 (m, 4H), 5.31 (dd, $J=6.6$ Hz and $J=8.8$ Hz, 1H), 7.22–7.39 (m, 14H), 8.01 (b, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=13.71$, 22.61, 26.11, 29.74, 45.24, 62.53, 67.43, 68.79, 115.48, 127.14 (2C), 128.12, 128.33 (2C), 128.37 (2C), 128.52 (2C), 128.58, 128.67 (2C), 128.93 (2C), 133.45, 135.03, 135.65, 139.90, 156.6, 159.48; IR-FT (film): $\nu=3306$, 3033, 2959, 2929, 2871, 1757, 1718, 1492, 1457, 1388, 1334, 1304, 1227, 1101, 981, 826, 789, 753, 697 cm^{-1}; MS (EI): $m/z=539$ (100), 495 (8), 374 (11), 330 (13), 328 (35), 223 (15); HR-ESI-MS: $m/z=539.1943$, calcd. for $C_{29}H_{31}ClN_2O_6$: 539.1949.

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