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CuI-catalyzed cycloisomerization of propargyl amides†

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The synthesis of substituted dihydrooxazoles by the CuI-catalyzed cycloisomerization of terminal propargyl amides is reported. The reaction has been shown to have good substrate scope and experiments to delineate the mechanism have been performed. Substrates containing a benzylic methylene were oxidized to the ketone under the reaction conditions.

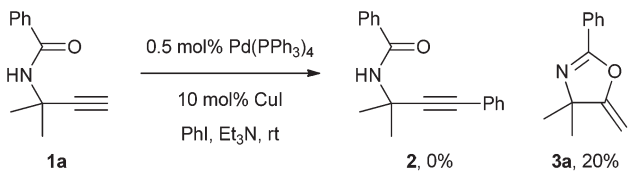
Introduction

Oxazole and oxazoline rings are found in a multitude of natural and non-natural compounds with useful biological properties, such as antibacterial, antifungal, antiviral and antiproliferative activities.[1] Oxazoles and oxazolines are also useful as intermediates in organic synthesis,[2] ligands for catalysts[3] and as protecting groups.[4]

A popular strategy for the construction of oxazole and oxazoline rings is the cycloisomerization of propargyl amides.[5–9] Gold-catalysis has been shown to be particularly effective for this process,[6] but catalytic systems employing silver,[7] copper,[8] molybdenum[9] and tungsten[9] salts have also been reported.

Results and discussion

Whilst attempting to prepare disubstituted alkyne **2** by a Sonogashira reaction on propargyl amide **1a**, heterocycle **3a** was isolated in 20% yield (Scheme 1). Coupled product **2** was not observed in the crude reaction mixture and the phenyl group from iodobenzene was not incorporated into the product. Jin and co-workers reported a similar phenomenon in a series of steroids.[8]



Scheme 1 Unexpected cycloisomerization under Sonogashira cross-coupling conditions.

Intrigued by this process, we investigated the reaction conditions for the cyclization of **1a** (Table 1). To determine whether the Cu or Pd catalysts were responsible for the cyclization, each was tested individually. The Pd catalyst led to no conversion of **1a** (entry 1) whereas the CuI led to 13% conversion (entry 2). Changing the solvent from triethylamine to CH_2Cl_2 led to an improvement in conversion and complete consumption of **1a** was observed (entry 3). Using CuCl as catalyst led to complete conversion (entry 4) and several Cu(II) salts led to complete conversion also (entries 5–7). Using one equivalent of either NaI or KO*t*-Bu both led to about 20% conversion (entries 8 and 9).

It was decided to continue with CuI as it is cheap, air stable, non-hygroscopic and easy to handle. With these conditions in hand, the scope of this reaction was investigated (Table 2). However, it soon became apparent that there were significant reaction rate differences between substrates, so the solvent was changed to the higher boiling 1,2-dichloroethane and the reactions were heated to reflux in all cases. A variety of substituted benzamides cyclized in very good yields (**3a–3d**), however substrate **1d**, bearing a nitro substituent, required 48 hours to reach completion. Unprotected indole derivative

Table 1 Optimization studies for formation of oxazoline **3a** from **1a**[a]

Entry	Catalyst	Solvent	Conversion[b]/%
1	0.5 mol% $Pd(PPh_3)_4$	Et_3N	0
2	10 mol% CuI	Et_3N	13
3	10 mol% CuI	CH_2Cl_2	99
4	10 mol% CuCl	CH_2Cl_2	99
5	10 mol% $Cu(OAc)_2$	CH_2Cl_2	99
6	10 mol% $Cu(OTf)_2$	CH_2Cl_2	99
7	10 mol% $CuSO_4$	CH_2Cl_2	99
8	1 equiv. NaI	CH_2Cl_2	20
9	1 equiv. KO*t*-Bu	CH_2Cl_2	18

[a] Reactions conducted at room temperature. [b] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture.

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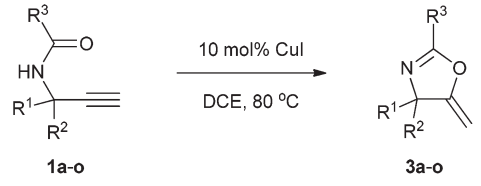
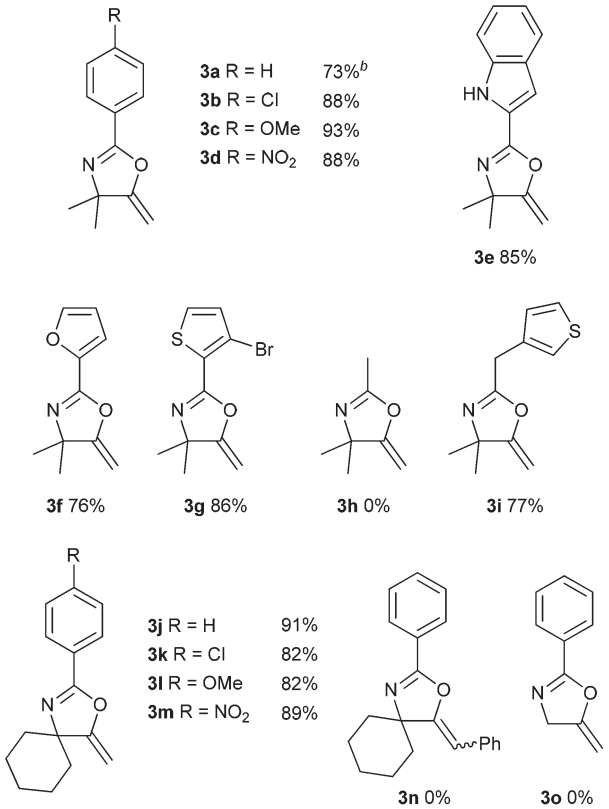
†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for new compounds. See DOI: 10.1039/c3ob42030b

Table 2 Scope of cyclization[a]



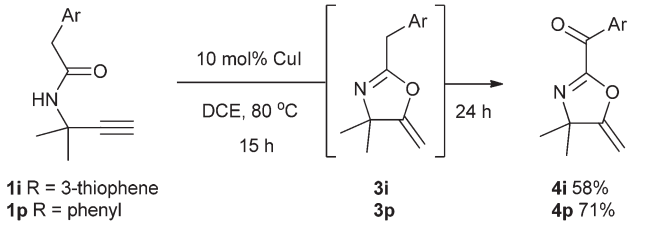
1a-o 3a-o



[a] Yields of pure isolated compounds. [b] Reaction performed at ambient temperature.

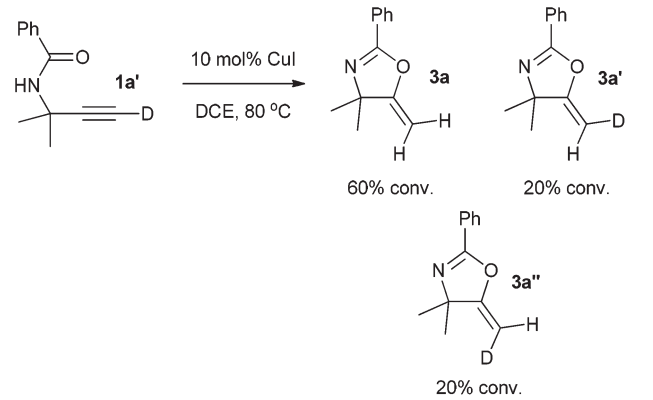
1e, furan **1f** and thiophene **1g** all cyclized in good yields. Acetamide **1h** did not cyclize under the reaction conditions, however **1i** did. Spirocycles **3j**, **3k**, **3l** and **3m** were formed in very good yields under these conditions. However, **1n**, containing an internal alkyne, did not cyclize and **1o** which lacks a *gem*-dialkyl group did not cyclize either.

Interestingly, compounds **3i** and **3p** underwent slow oxidation at the benzylic position to form ketones **4i** and **4p** (Scheme 2). Compound **3i** could be isolated in pure form; however, **3p** underwent faster benzylic oxidation and could not be isolated in pure form. Control experiments showed that the CuI was necessary for the oxidation to occur. The CuCl-catalyzed oxidation of diarylmethanes to benzophenones has been reported however an oxygen atmosphere and a dioxyl radical mediating agent was necessary for efficient conversion.[10] Addition of a radical inhibitor (galvinoxyl) to the reaction mixture did not lead to any noticeable differences in yield or rate for formation of **4p** from **1p** or **3a** from **1a**.



1i R = 3-thiophene
1p R = phenyl
3i **3p**
4i 58%
4p 71%

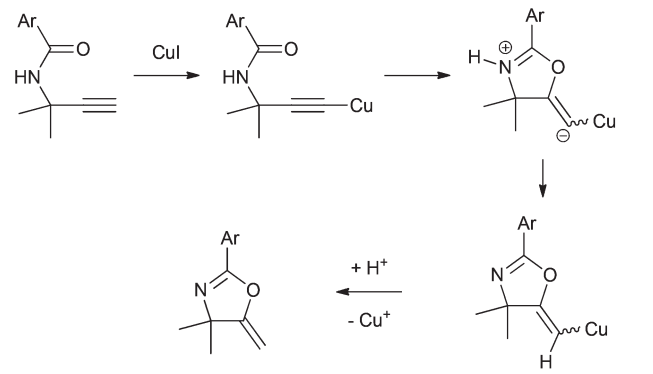
Scheme 2 Tandem CuI-catalyzed cyclization/benzylic oxidation.



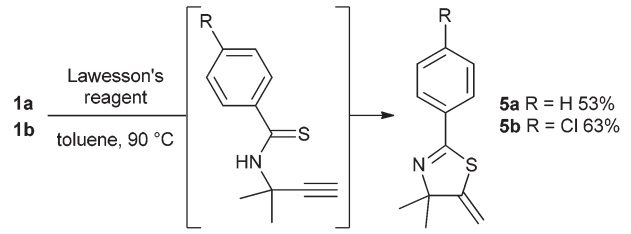
Scheme 3 Deuterium labelling experiment.

In order to investigate the mechanism of the cyclization, deuterated compound **1a′** was prepared and subjected to the standard reaction conditions (Scheme 3).[11] In the event, three compounds were observed by ^{1}H NMR analysis of the crude reaction mixture in a 3 : 1 : 1 ratio. The major product was **3a** with the two mono-deuterated compounds **3a′** and **3a″** formed in equal and minor amounts. This is in contrast to the analogous experiment conducted under Au(III)-catalysis reported by Hashmi and co-workers (**3a′** would be major in this case).[6f]

These results along with the inability of **1n** to cyclize led us to postulate that the mechanism proceeds through formation of a copper acetylide followed by cyclization, proton transfer and protonation to regenerate the Cu(I) catalyst (Scheme 4). The Cu-catalyzed azide alkyne cycloaddition reaction (click reaction) is believed to proceed through copper acetylide



Scheme 4 Postulated mechanism of cyclization.



Scheme 5 Formation of dihydrothiazoles.

formation and cyclization.[12] However, we cannot completely rule out the alternative mechanism of the Cu(I) catalyst activating the alkyne for cyclization with the CuI also causing H/D scrambling before cyclization. Our attempts to alkylate the Cu intermediates with iodomethane or allyl bromide were unsuccessful.

In order to expand the scope of this process, we attempted to prepare the thioamide analog of **1a** for use in a subsequent cyclization reaction. In the event, treatment of **1a** with Lawesson's reagent led to the direct formation of **5a** in moderate yield without any thioamide being observed or any copper catalyst present (Scheme 5).[13] Presumably, the thioamide is formed but it undergoes facile cyclization under the reaction conditions. Dihydrothiazole **5b** was also prepared under similar conditions.

Conclusions

The CuI-catalyzed cyclization of propargyl amides to dihydrooxazoles has been demonstrated. Mechanistic information has been obtained and concomitant benzylic oxidation has been observed in appropriate compounds. This reaction is efficient, easy to carry out and has good scope.

In addition, Lawesson's reagent has been shown to effect direct cyclization of propargyl amides in to the analogous dihydrothiazoles.

Experimental

General methods

^{1}H NMR spectra were recorded at 400 MHz. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). ^{13}C NMR were recorded with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.4 ppm). Mass spectrometry (*m*/*z*) was performed in ESI mode, with only molecular ions being reported. Infrared (IR) spectra ν_{max} are reported in cm^{-1}. Petroleum ether refers to the fraction boiling at 40–60 °C. All purchased reagents were used as received without further purification. All reactions were performed under a N_2 atmosphere.

General procedure for the synthesis of amides 1a–f, h and o

1,1-Dimethylpropargyl amine (0.96 mL, 9.1 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (10 mL) and the corresponding acyl chloride (1.89 equiv.) and triethylamine (2 equiv.) were added. The mixture was stirred overnight at room temperature. A saturated solution of NaCl (10 mL) was added and the mixture extracted with CH_2Cl_2 (10 mL × 2). The organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum to give the product.

4-Chloro-*N*-(1,1-dimethylprop-2-ynyl)benzamide (1b). White solid; yield: 92%; mp: 146–149 °C; $IR_{(neat)}$: 3328 (w), 3284 (m), 2990 (w), 1644 (s) cm^{-1}; ^{1}H: δ 1.76 (6H, s), 2.40 (1H, s), 6.15 (1H, s), 7.40 (2H, d, J = 8.5 Hz), 7.70 (2H, d, J = 8.5 Hz); ^{13}C: δ 29.3, 48.5, 69.9, 87.3, 128.7, 129.1, 133.5, 138.1, 165.7; HRMS: *m*/*z* calc'd for [M + Na] $C_{12}H_{12}ClNNaO$ 244.0500, found 244.0489.

***N*-(2-Methylbut-3-yn-2-yl)-4-nitrobenzamide (1d).** Yellow solid; yield: 39%; mp: 123–127 °C; $IR_{(neat)}$: 3278 (w), 2980 (m), 2184 (w), 1520 (m), 1343 (m) cm^{-1}; ^{1}H: δ 1.77 (6H, s), 2.42 (1 H, s), 6.29 (1H, s), 7.91 (2H, d, J = 7.7 Hz), 8.26 (2H, d, J = 7.1); ^{13}C: δ 29.2, 48.9, 70.3, 86.9, 124.2, 128.5, 140.7, 150.0, 164.8; HRMS: *m*/*z* calc'd for [M + Na] $C_{12}H_{12}N_2NaO_3$ 255.0740, found 255.0741.

General procedure for the synthesis of amides 1g, 1i and 1p

Thionyl chloride (0.22 mL, 2.93 mmol, 3.4 equiv.) was added to the corresponding carboxylic acid (2 equiv.) in $CHCl_3$ (3 mL) and stirred overnight at room temperature. The solvent was removed under vacuum to provide the acid chloride. 1,1-Dimethylpropargylamine (0.091 mL, 0.86 mmol, 1 equiv.) dissolved in $CHCl_3$ (10 mL) was added to the freshly prepared acid chloride followed by triethylamine (2 equiv.). The mixture was stirred overnight, then quenched with NaOH solution (3 M, 5 mL). The mixture was extracted with CH_2Cl_2 (10 mL × 2) and the organic layers were combined, dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc on silica gel) to give the product.

3-Bromo-*N*-(1,1-dimethylprop-2-ynyl)thiophene-2-carboxamide (1g). Orange oil; yield: 23%; $IR_{(neat)}$: 3399 (w), 3295 (w), 3082 (w), 2979 (w), 1647 (s), 1517 (s) cm^{-1}; ^{1}H: δ 1.69 (6H, s), 2.34 (1H, s), 6.95 (1H, d, J = 5.2 Hz), 7.17–7.25 (1H, m), 7.37 (1H, d, J = 5.2 Hz); ^{13}C: δ 29.4, 48.6, 70.0, 86.9, 108.7, 130.6, 132.3, 135.9, 159.6; HRMS: *m*/*z* calc'd for [M + Na] $C_{10}H_{10}BrNNaOS$ 293.9558, found 293.9559.

***N*-(1,1-Dimethylprop-2-ynyl)-2-(2-thienyl)acetamide (1i).** Yellow solid; yield: 53%; mp: 143–145 °C; $IR_{(neat)}$: 3304 (m), 3203 (m), 3009 (w), 2984 (w), 2935 (w), 1640 (s), 1548 (s) cm^{-1}; ^{1}H: δ 1.57 (6H, s), 2.30 (1H, s), 3.55 (2H, s), 5.49 (1H, s), 6.99 (1H, dd, J = 5.1, 4.8 Hz), 7.13 (1H, d, J = 2.38 Hz), 7.32 (1H, dd, J = 4.9 Hz); ^{13}C: δ 29.2, 39.2, 48.0, 69.6, 87.3, 123.7, 127.1, 128.7, 135.2, 169.9; HRMS: *m*/*z* calc'd for [M + Na] $C_{11}H_{13}NNaOS$ 230.0611, found 230.0615.

General procedure for the synthesis of amides 1j–m

1-Ethylcyclohexylamine (50 mg, 0.405 mmol, 1 equiv.) was dissolved in DMF (1 mL) and the corresponding acyl chloride (2 equiv.) and triethylamine (2 equiv.) were added. The mixture was stirred at 50 °C for an hour, then at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc with 5% Et_3N on silica gel) to give the product.

***N*-(1-Ethynylcyclohexyl)-4-nitrobenzamide (1m).** Light yellow solid; yield: 99%; mp: 137–140 °C; $IR_{(neat)}$: 3301 (w), 3244 (w), 2939 (w), 2853 (w), 1648 (s), 1522 (s), 1486 (s) cm^{-1}; ^1H: δ 1.21–1.33 (1H, m), 1.58–1.74 (5H, m), 1.83–1.89 (2H, m), 2.12–2.24 (2H, m), 2.45 (1H, s), 6.37 (1H, s), 7.88 (2H, d, J = 8.7 Hz), 8.19 (2H, d, J = 8.6 Hz); ^{13}C: δ 22.9, 25.5, 37.2, 53.0, 72.5, 85.1, 124.1, 128.5, 140.9, 149.9, 164.7; HRMS: m/z calc'd for [M + Na] $C_{15}H_{16}N_2NaO_3$ 295.1053, found 295.1053.

Synthesis of *N*-(1-(phenylethynyl)cyclohexyl)benzamide (1n)

1-Ethynylcyclohexylamine (100 g, 0.81 mmol, 1 equiv.) was dissolved in Et_3N (5 mL) then CuI (16 mg, 0.081 mmol, 10 mol%), PhI (91 μL, 0.81 mmol, 1 equiv.) and $Pd(PPh_3)_4$ (5 mg, 0.040 mmol, 0.5 mol%) were added. The mixture was left stirring overnight at room temperature then concentrated under reduced pressure. The residue was purified by flash chromatography (5 : 1 : 0.005 petroleum ether–EtOAc–Et_3N on silica gel) to provide the product as a brown oil (0.064 g, 45%). This was dissolved in DMF (5 mL) then benzoylchloride (84 μL, 0.72 mmol, 2 equiv.) and Et_3N (101 μL, 0.72 mmol, 2 equiv.) were added. The mixture was stirred overnight and concentrated under reduced pressure. The residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc on silica gel) to provide the product as a white solid; 0.096 g; yield: 84%; mp: 174–177 °C; $IR_{(neat)}$: 3285 (w), 3050 (w), 2913 (w), 2851 (w), 1786 (w), 1639 (s) cm^{-1}; ^1H: δ 1.30–1.39 (1H, m), 1.63–1.83 (5H, m), 2.08–2.22 (2H, m), 2.26–2.29 (2H, m), 6.22 (1H, s), 7.27–7.29 (3H, m), 7.40–7.50 (5 H, m), 7.77 (2 H, d, J = 7.3 Hz); ^{13}C: δ 23.3, 25.7, 37.3, 53.6, 84.2, 91.4, 123.5, 127.3, 128.4, 128.5, 128.9, 131.7, 132.2, 135.7, 166.7; HRMS: m/z calc'd for [M + Na] $C_{21}H_{21}NNaO$ 326.1515, found 326.1508.

Synthesis of 4,4-dimethyl-5-methylene-2-phenyl-4,5-dihydrooxazole (3a)[14]

N-(2,2-Dimethylpropyne)benzamide **1a** (50 mg, 0.27 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (5 mL). Then, copper(I) iodide (10 mol%) was added and the mixture was stirred at room temperature overnight. After concentration under vacuum, the residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc on silica gel) to give **3a** as a yellow oil (0.374 g, 73%); $IR_{(neat)}$: 2972.4 (w), 2971 (w), 2294 (w), 2851 (w), 1643 (m) cm^{-1}; ^1H: δ 1.47 (6H, s), 4.26 (1H, d, J = 2.9), 4.76 (1H, d, J = 2.9), 7.42–7.46 (2H, m), 7.49–7.7.55 (1H, m), 7.99–8.02 (2H, m); ^{13}C: δ 29.8, 69.1, 82.4, 127.1, 128.1, 128.5, 131.8, 160.0, 168.1; HRMS: m/z calc'd for [M + H] $C_{12}H_{14}NO$ 188.1070, found 188.1069.

General procedure for the synthesis of dihydrooxazoles 3b–3m

The corresponding amide (50 mg, 1 equiv.) was dissolved in 1,2-DCE (2 mL), and then CuI was added (10 mol%). The mixture was heated at reflux overnight. After concentration under vacuum, the residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc on silica gel) to provide the product.

2-(4-Chloro-phenyl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole (3b). Yellow oil; yield: 88%; $IR_{(neat)}$: 2974 (w), 2928 (w), 1674 (m), 1309 (s) cm^{-1}; ^1H: δ 1.47 (6H, s), 4.28 (1H, d, J = 2.8 Hz), 4.76 (1H, d, J = 2.8 Hz), 7.42 (2H, d, J = 8.6 Hz), 7.94 (2H, d, J = 8.6 Hz); ^{13}C: δ 30.1, 69.6, 83.2, 125.6, 129.2, 129.8, 138.4, 159.6, 167.9; HRMS: m/z calc'd for [M + H] $C_{12}H_{13}ClNO$ 222.0680, found 222.0680.

2-(4-Methoxy-phenyl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole (3c). Colorless oil; yield: 93%; $IR_{(neat)}$: 2972 (w), 2930 (w), 1643 (m), 1609 (s) cm^{-1}; ^1H: δ 1.44 (6H, s), 3.84 (3H, s), 4.22 (1H, d, J = 2.6 Hz), 4.71 (1H, d, J = 2.8 Hz), 6.92 (2H, d, J = 9.1 Hz), 7.93 (2H, d, J = 9.0); ^{13}C: δ 30.2, 55.7, 69.3, 82.3, 114.2, 119.7, 130.2, 160.0, 162.7, 168.4; HRMS: m/z calc'd for [M + Na] $C_{13}H_{15}NNaO_2$ 240.0995, found 240.0995.

2-(4-Nitro-phenyl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole (3d). Yellow solid; mp: 103–107 °C; yield: 88%; $IR_{(neat)}$: 3108 (w), 2974 (w), 1679 (m), 1644 (m), 1524 (s) cm^{-1}; ^1H: δ 1.46 (6H, s), 4.31 (1H, d, J = 3.0 Hz), 4.78 (1H, d, J = 3.1 Hz), 8.15 (2H, d, J = 8.9 Hz), 8.28 (2H, d, J = 9.0 Hz); ^{13}C: δ 30.0, 70.0, 83.9, 124.0, 129.5, 133.2, 150.0, 158.6, 167.7; HRMS: m/z calc'd for [M + H] $C_{12}H_{13}N_2O_3$ 233.0921, found 233.0937.

2-(1*H*-Indol-2-yl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole (3e). Colorless oil; yield: 85%; $IR_{(neat)}$: 3126 (w), 3066 (w), 2968 (m), 1698 (m), 1650 (s) cm^{-1}; ^1H: δ 1.46 (6H, s), 4.29 (1H, d, J = 3.0 Hz), 4.78 (1H, d, J = 3.0 Hz), 7.13 (1H, s), 7.25 (1H, d, J = 7.5 Hz), 7.29 (1H, d, J = 7.3 Hz), 7.38 (1H, d, J = 8.2 Hz), 7.68 (1H, d, J = 8.0 Hz), 9.34 (1H, s); ^{13}C: δ 30.2, 69.2, 83.3, 107.3, 111.9, 121.0, 122.4, 124.8, 125.1, 128.1, 137.5, 155.4, 167.7; HRMS: m/z calc'd for [M + H] $C_{14}H_{15}N_2O$ 227.1178, found 227.1186.

2-(Furan-2-yl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole (3f). Brown oil; yield: 76%; $IR_{(neat)}$: 3649 (w), 2981 (w), 2170 (w), 2156 (w), 2039 (m) cm^{-1}; ^1H: δ 1.26 (6H, s), 4.07 (1H, d, J = 3.1 Hz), 4.54 (1H, d, J = 3.0 Hz), 6.32 (1H, dd, J = 3.4, 4.0 Hz), 6.82 (1H, d, J = 3.4 Hz), 7.38 (1H, d, J = 1.5); ^{13}C: δ 29.7, 69.0, 83.0, 111.7, 115.0, 142.1, 145.7, 152.4, 167.2; HRMS: m/z calc'd for [M + Na] $C_{10}H_{11}NNaO_2$ 200.0682, found 200.0689.

2-(3-Bromothiophen-2-yl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole (3g). Brown oil; yield: 87%; $IR_{(neat)}$: 3082 (w), 2973 (w), 2927 (w), 1696 (w), 1637 (s) cm^{-1}; ^1H: δ 1.45 (6H, s), 4.25 (1H, d, J = 3.0 Hz), 4.75 (1H, d, J = 2.9 Hz), 7.06 (1H, d, J = 5.3 Hz), 7.40 (1H, d, J = 5.3 Hz); ^{13}C: δ 26.1, 30.1, 69.6, 83.3, 114.2, 129.8, 133.1, 154.9, 167.6; HRMS: m/z calc'd for [M + Na] $C_{10}H_{10}BrNNaOS$ 293.9558, found 293.9524.

4,4-Dimethyl-5-methylene-2-(thiophen-2-ylmethyl)-4,5-dihydrooxazole (3i). Dark green oil; yield: 76%; $IR_{(neat)}$: 3108 (w), 2972 (m), 2927 (w), 1667 (s) cm^{-1}; ^1H: δ 1.35 (6H, s), 3.71

(2H, s), 4.15 (1H, d, J = 3.0 Hz), 4.57 (1H, d, J = 3.3 Hz), 7.04 (1H, d, J = 5.0, Hz), 7.16 (1H, d, J = 1.8, Hz), 7.28 (1H, d, J = 5.0,); ^{13}C: δ 29.8, 29.9, 69.0, 82.5, 123.0, 126.3, 128.5, 134.4, 162.0, 168.4; HRMS: m/z calc'd for [M + H] $C_{11}H_{14}NOS$ 208.0790, found 208.0789.

2-(4-Chlorophenyl)-4-methylene-3-oxa-1-azaspiro[4.5]dec-1-ene (3k). Colorless oil; yield: 82%; $IR_{(neat)}$: 2929 (m), 2852 (w), 1654 (s), 1489 (m) cm^{-1}; ^{1}H: δ 1.47–1.89 (10H, m), 4.23 (1H, d, J = 2.8 Hz), 4.72 (1H, d, J = 2.8 Hz), 7.38 (2H, d, J = 8.5 Hz), 7.91 (2H, d, J = 8.6 Hz); ^{13}C: δ 22.5, 26.0, 39.5, 72.5, 83.2, 126.3, 129.1, 129.9, 138.0, 158.8, 168.5; HRMS: m/z calc'd for [M + H] $C_{15}H_{17}ClNO$ 262.0993, found 262.0991.

2-(4-Methoxyphenyl)-4-methylene-3-oxa-1-azaspiro[4.5]dec-1-ene (3l). Colorless oil; yield: 99%; $IR_{(neat)}$: 2929 (m), 2852 (w), 1646 (s), 1510 (s) cm^{-1}; ^{1}H: δ 1.38–1.5 (10H, m), 3.84 (3H, s), 4.22 (1H, d, J = 2.4 Hz), 4.71 (1H, d, J = 2.7 Hz), 6.92 (2H, d, J = 9.1 Hz), 7.95 (2H, d, J = 9.0 Hz); ^{13}C NMR: δ 22.5, 25.9, 39.5, 55.7, 72.1, 82.8, 114.1, 120.0, 130.2, 159.6, 162.5, 168.6; HRMS: m/z calc'd for [M + H] $C_{16}H_{20}NO_2$ 258.1488, found 258.1488.

2-(4-Nitrophenyl)-4-methylene-3-oxa-1-azaspiro[4.5]dec-1-ene (3m). brown solid; mp: 68–71 °C; yield: 89%; $IR_{(neat)}$: 3301 (w), 2932 (s), 2853 (m), 1708 (m) cm^{-1}; ^{1}H: δ 1.68–1.90 (10H, m), 4.29 (1H, d, J = 3.0 Hz), 4.78 (1H, d, J = 3.0 Hz), 8.17 (2H, d, J = 8.7 Hz), 8.28 (2H, d, J = 9.7 Hz); ^{13}C: δ 22.4, 25.9, 39.6, 73.0, 83.9, 123.9, 129.5, 133.6, 149.9, 157.9, 168.2; HRMS: m/z calc'd for [M + H] $C_{15}H_{17}N_2O_3$ 273.1234, found 273.1239.

Synthesis of (4,4-dimethyl-5-methylene-oxazol-2-yl)-(2-thienyl)methanone (4i)

4,4-Dimethyl-5-methylene-2-(thiophen-2-ylmethyl)-4,5-dihydrooxazole **3i** (30 mg, 0.14 mmol, 1 equiv.) was dissolved in 1,2-DCE (2 mL) and CuI was added (3 mg, 10 mol%). The mixture was heated at reflux overnight and then concentrated under vacuum. The residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc on silica gel) to provide the product **4i** as a yellow oil (18 mg, 58%) $IR_{(neat)}$: 2975 (w), 2930 (w), 2360 (w), 1671 (s), 1634 (m) cm^{-1}; ^{1}H: δ 1.48 (6H, s), 4.32 (1H, d, J = 3.2 Hz), 4.84 (1H, d, J = 2.9 Hz), 7.33 (1H, dd, J = 5.2, 5.1), 7.81 (1H, dd, J = 5.2, 5.1), 8.90 (1H, dd, J = 2.9, 3.0); ^{13}C: δ 27.7, 57.9, 95.3, 125.9, 127.6, 131.0, 136.2, 150.1, 154.1, 158.2; HRMS: m/z calc'd for [M + Na] $C_{11}H_{11}NNaO_2S$ 244.0402, found 244.0402.

Synthesis of (4,4-dimethyl-5-methylene-4,5-dihydrooxazol-2-yl)-(phenyl)methanone (4p)

N-(2-Methylbut-3-yn-2-yl)-2-phenylacetamide **1p** (50 mg, 0.25 mmol, 1 equiv.) was dissolved in 1,2-DCE (2 mL) and CuI (5 mg, 10 mmol%) was added. The mixture was heated at reflux for 48 h and then concentrated under vacuum. The residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc on silica gel) to provide the product **4p** as a yellow solid (38 mg, 71%); mp: 53–56 °C; $IR_{(neat)}$: 2975 (w), 2930 (w), 2360 (w), 1671 (s), 1634 (m) cm^{-1}; ^{1}H: δ 1.50 (6H, s), 4.34 (1H, d, J = 3.4 Hz), 4.84 (1H, d, J = 3.1 Hz), 7.47–7.51 (2H, m), 7.61–7.65 (1H, m), 8.28–8.31 (2H, m); ^{13}C: δ 29.8, 70.9, 84.9, 128.9, 131.1, 134.8, 134.8, 155.9, 166.2, 182.8; HRMS: m/z calc'd for [M + Na] $C_{13}H_{13}NNaO_2$ 238.0838, found 238.0841.

General procedure for the synthesis of thiazoles (5a–b)

The requisite benzamide (1.1 mmol, 1 equiv.) and Lawesson's reagent (1.1 mmol, 1 equiv.) were dissolved in dry toluene (10 mL) and heated at 90 °C overnight. The solvent was removed under vacuum and the residue was purified by flash chromatography (5 : 1 petroleum ether–EtOAc on silica gel) to give the product.

4,4-Dimethyl-5-methylene-2-phenyl-thiazole (5a). Yellow oil; yield: 53%; $IR_{(neat)}$: 2972 (m), 2927 (w), 1604 (m), 1447 (m) cm^{-1}; ^{1}H: δ 1.53 (6H, s), 5.18 (1H, d, J = 1.7 Hz), 5.27 (1H, d, J = 1.9 Hz), 7.39–7.45 (3H, m), 7.77–7.80 (2H, m); ^{13}C: δ 29.8, 82.8, 103.2, 128.3, 128.9, 131.5, 133.5, 156.7, 161.0; HRMS: m/z calc'd for [M + H] $C_{12}H_{14}NS$ 203.0841, found 203.0853.

2-(4-Chlorophenyl)-4,4-dimethyl-5-methylene-thiazole (5b). Yellow oil; yield: 63%; $IR_{(neat)}$: 2973 (m), 2928 (w), 1606 (m), 1489 (m) cm^{-1}; ^{1}H: δ 1.50 (6H, s), 5.17 (1H, d, J = 1.8 Hz), 5.25 (1H, d, J = 1.5 Hz), 7.34–7.38 (2H, m), 7.67–7.70 (2H, m); ^{13}C: δ 29.7, 82.9, 103.5, 129.1, 129.6, 132.0, 137.6, 156.6, 159.6; HRMS: m/z calc'd for [M + H] $C_{12}H_{13}ClNS$ 238.0451, found 238.0459.

Synthesis of *N*-(2-methylbut-3-yn-2-yl)benzamide-d^1 (1a′)

N-(2,2-Dimethylpropyne)benzamide **1a** (0.2 g, 1.06 mmol, 1 equiv.) was dissolved in MeCN (1 mL) and K_2CO_3 (0.22 g, 1.59 mmol, 1.5 equiv.) was added to the mixture. After 30 min of stirring, D_2O (0.96 mL, 53 mmol, 50 equiv.) was added and the mixture was stirred overnight at rt. The mixture was extracted with CH_2Cl_2 (10 mL × 2) and the organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue was stirred with HCl (0.5 M, 2 mL) for 7 days, and then extracted with CH_2Cl_2 (10 mL × 2). The organic layers were combined and dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum to give the product as white solid; yield: 0.132 g, 66%; mp: 155–158 °C; IR: 3485 (w), 3238 (w), 2980 (w), 2583 (w), 1639 (s), 1514 (s) cm^{-1}; ^{1}H: δ 1.77 (6H, s), 6.13 (1H, s), 7.40–7.70 (3H, m), 7.75 (2H, d, J = 7.1 Hz); ^{13}C: δ 29.4, 48.4, 127.2, 128.9, 131.9, 135.2, 166.8; HRMS: m/z calc'd for [M + Na] $C_{12}H_{12}DNNaO$ 211.0952, found 211.0959.

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