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ARTICLE TYPE

CuI-catalyzed Cross-coupling of Terminal Alkynes with Dialkoxycarbenes: A General Method for the Synthesis of Unsymmetrical Propargylic Acetals

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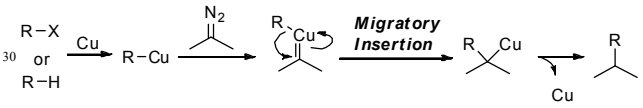
A general source of dialkoxycarbenes: 2,2-dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines have been successfully employed as the coupling partners in CuI-catalyzed cross-coupling reactions with terminal alkynes, which afforded various unsymmetrical propargylic acetals in good yields.

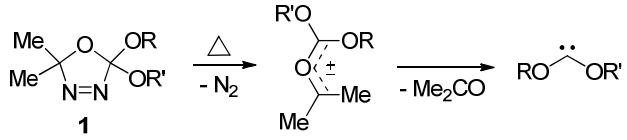
1. Introduction

Transition-metal-catalyzed coupling reactions are now serving as one of the most powerful tools in organic synthesis.[1] Through the gradual expansion of available nucleophilic and electrophilic coupling partners, various previously unknown synthetic disconnects are now realized. In the recent years, diazo compounds, which are commonly used as carbene precursors, have emerged as a new type of cross-coupling partner in transition-metal-catalyzed reactions.[2] In particular, with copper catalysts, diazo compounds or *N*-tosylhydrazones can be coupled with terminal alkynes,[3,4] 1,3-azoles,[5] *N*-iminopyridinium ylides,[6] and $TMSCF_3$.[7] In these transformations, the formation of Cu carbene and its subsequent migratory insertion are proposed as the characteristic steps in the mechanism (Scheme 1). Despite the progress in this field, carbenes bearing electron-donating substituents are difficult to derive from diazo compounds or *N*-tosylhydrazones because of their instability, which restricts the applications of these types of cross-coupling reactions with remarkable wide scopes.



Scheme 1 Migratory insertion of Cu carbene.

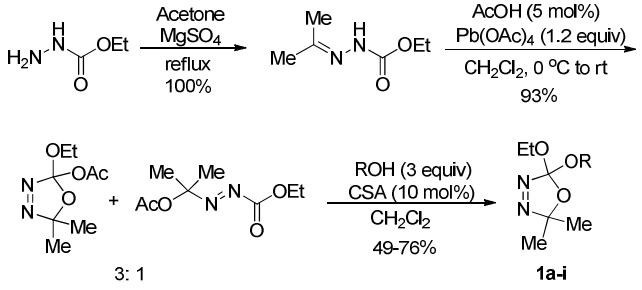
2,2-Dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines **1** are generally employed as a source of dialkoxycarbenes through thermal decomposition (scheme 2).[8] The chemical and mechanistic aspects of oxadiazolines **1** have been studied extensively by Warkentin and co-workers over the past decades.[9] These compounds are also widely used as dienophiles in Diels-Alder type [4 + 1] cycloaddition reactions.[10] However, to the best of our knowledge, the use of oxadiazolines **1** as coupling partners in transition-metal-catalyzed reactions has not been reported. As a continuation of our interest in cross-coupling reactions involving metal-carbenes,[3b,3g,11] we report a copper-catalyzed cross-coupling of oxadiazolines **1** with terminal alkynes, which gave a series of unsymmetrical propargylic acetals in good yields.



Scheme 2 Generation of dialkoxycarbene

2. Results and discussion

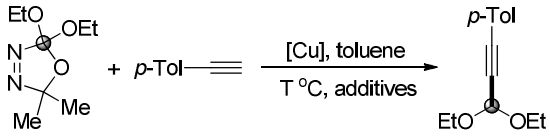
Initially, oxadiazolines **1a-i** were prepared via a three-step operation according to the reported procedure (Scheme 3).[10d] Then the reaction of oxadiazoline **1a** and 4-ethynyltoluene **2a** was carried out in the presence of 10 mol% of CuCl in toluene at 110 °C. To our delight, the desired cross-coupling product propargylic acetal **3a** was formed in 27% yield (Table 1, entry 1). After a comprehensive screening, we found that CuI was superior over other copper salts, such as $CuCl_2$, CuBr, and $CuBr_2$ with a high level of efficiency (Table 1, entries 2-5). It was observed that the use of inorganic bases such as ^{t}BuOK and Cs_2CO_3 disfavoured the reaction (Table 1, entries 6 and 7), while a slight increase in the yield was observed when 20% mol of pyridine was used as an additive (Table 1, entry 8). Generally, temperatures higher than 110 °C were necessary to effectively



Scheme 3 Synthesis of oxadiazolines **1a-h.**

promote the reaction. Lower temperatures slowed reaction rates and gave rise to low conversion ratios (Table 1, entries 9 and 10). However, diminished yield was obtained when the reaction was carried out at 120°C, which attributed to the fast decomposition of **1a** (Table 1, entry 11). There have been several reports on the metal-free direct O-H insertion reactions of dialkoxycarbenes with various alcohols.[12] The formal C−H insertion of *N*-heterocyclic carbene to acetylene was also reported by Arduengo and co- workers.[13] However, the control experiment showed that none of the desired propargylic acetal **3a** was detected in the absence of copper catalyst (Table 1, entry 12), which indicates the direct C-H insertion of carbene into terminal alkyne is less likely for the cross-coupling reaction described in this paper.

Table 1 Optimization of Reaction Conditions.[a]



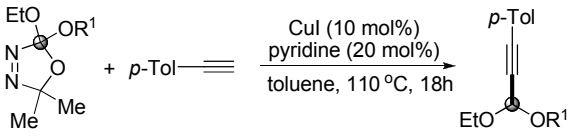
1a **2a** **3a**

entry	catalyst	T/°C	additive (equiv)	yield%[b]
1	CuCl	110	—	27
2	$CuCl_2$	110	—	13
3	CuBr	110	—	37
4	$CuBr_2$	110	—	22
5	CuI	110	—	71
6	CuI	110	^{t}BuOK (3)	24
7	CuI	110	Cs_2CO_3 (3)	21
8	CuI	110	pyridine (0.2)	81
9	CuI	90	pyridine (0.2)	7
10	CuI	100	pyridine (0.2)	37
11	CuI	120	pyridine (0.2)	53
12	none	110	pyridine (0.2)	0

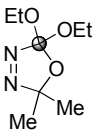
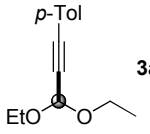
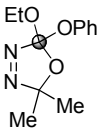
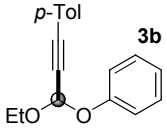
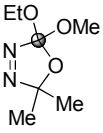
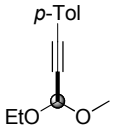
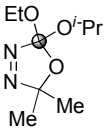
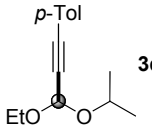
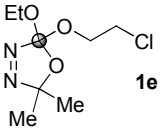
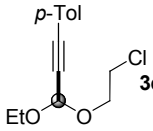
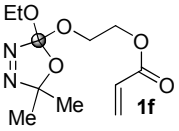
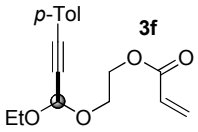
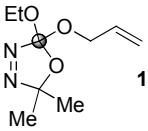
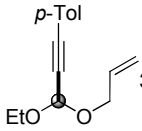
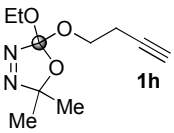
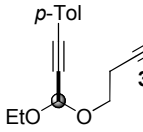
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Cu catalyst (10 mol%), toluene (2.5 mL), N_2 atmosphere, 18 h. [b] Yields were measured by ^{1}H NMR with $MeNO_2$ as internal standard.

The reaction of terminal alkynes with ortho esters in the presence of a zinc halide catalyst has become a routine method for the preparation of acetylenic acetals.[14] Other methods involving the use of $SnCl_4$, $TiCl_4$ as the catalysts have also been reported.[15] Although these methods have provided efficient routes for the preparation of symmetrical acetylenic acetals, general methods for the synthesis of unsymmetrical propargylic acetals are rare.[16] With the optimized reaction conditions for copper-catalyzed cross coupling of terminal alkynes with diethyoxylcarbene in hand, we next examined the scope of the reaction by using 4-ethynyltoluene **2a** with various unsymmetrical dialkoxycarbenes, which would give a series of unsymmetrical propargylic acetals. As shown in table 2, when one ethyl moiety in oxadiazoline **1a** was replaced by a simple phenyl group, the desired acetal **3b** was isolated in 63% yield (Table 2, entry 2). Similarly, unsymmetrical propargylic acetals **3c** and **3d** were obtained from corresponding oxadiazolines **1c** and **1d** in the yields of 67% and 80% respectively (Table 2, entries 3 and 4). A chloroethylated oxadiazoline **1e** was also a suitable substrate for the reaction under the optimal condition (Table 2, entry 5). In addition, the acryl group presented in oxadiazoline **1f** could be survived, yielded the cross-coupling

Table 2 Copper-catalyzed cross-coupling of 4-ethynyltoluene **2a** with various oxadiazolines[a]



1a-h **2a** **3a-3h**

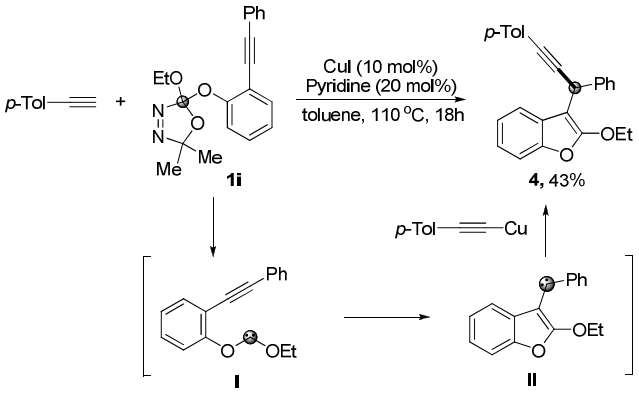
entry	oxadiazoline		product		yield(%)[b]
1		**1a**		**3a**	77
2		**1b**		**3b**	63
3		**1c**		**3c**	67
4		**1d**		**3d**	80
5		**1e**		**3e**	71
6		**1f**		**3f**	55
7		**1g**		**3g**	51
8		**1h**		**3h**	75

[a] Reaction conditions: oxadiazoline **1** (0.2 mmol), 4-ethynyltoluene **2a** (0.3 mmol), CuI (10 mol%), pyridine (20 mol%), toluene (2.5 mL), 110 °C, N_2 atmosphere, 18h. [b] Isolated yield.

product **3f** in 61% (Table 2, entry 6). This new method also provides opportunities for the construction of oxygen-containing 1,n-enynes and 1,n-diynes, which are important substrates in transition-metal catalyzed cycloisomerization reactions.[17] As exemplified in table 2, 1,6-enyne **3g** was smoothly prepared via CuI-catalyzed cross-coupling of 4-ethynyltoluene and oxadiazoline **1g** (Table 3, entry 7). Treatment of 4-ethynyltoluene

with oxadiazoline **1h** gave 1,7-diyne **3h** in the yield of 65% (Table 2, entry 8).

Interestingly, when oxadiazoline **1i** was employed to react with 4-tolylacetylene under the standard conditions, a benzofuran derivative **4** was isolated with a yield of 43% (Scheme 4). A possible pathway for the generation of **4** was proposed in scheme 4. First, the thermal decomposition of oxadiazoline **1i** formed aryloxyethxoycarbene **I**, which cyclized to give an exocyclic vinylcarbene **II**.[9e] The CuI-catalyzed cross-coupling of 4-tolylacetylene with the resulted benzofuryl carbene **II** afforded the benzofuran derivative **4**.



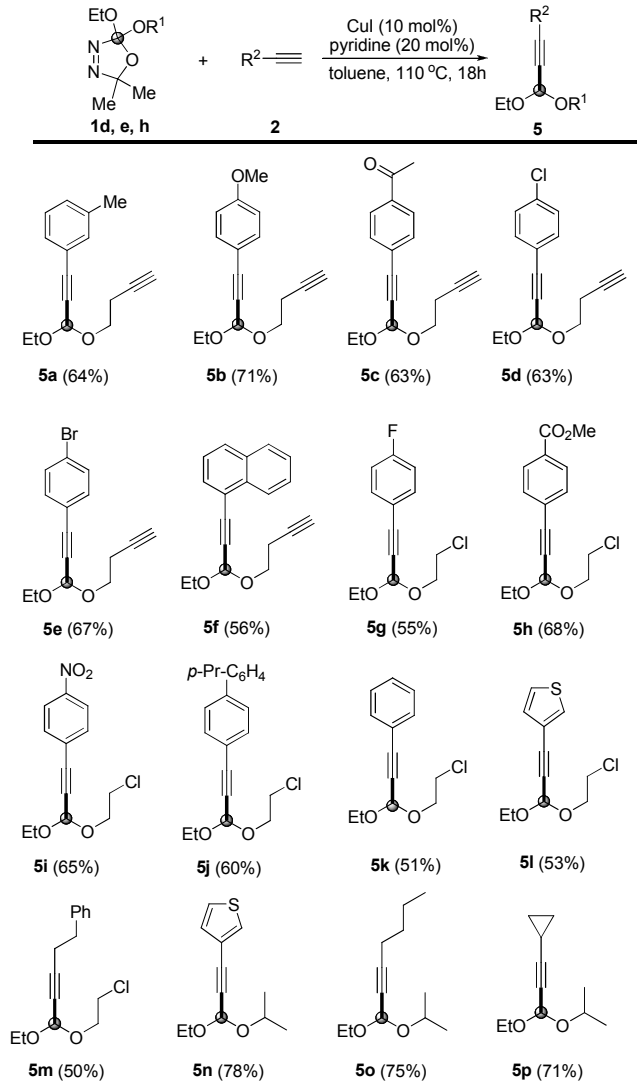
Scheme 4 CuI-catalyzed cross-coupling of 4-ethynyltoluene **2a** and oxadiazoline **1i**.

Next, the generality of these conditions for the reactions of various terminal alkynes was examined. As shown in table 3, the reactions proceeded smoothly with substrates having various functional groups, which included halogens (F, Cl, and Br), methoxy, ester, ketone, nitro, and aryl groups. Both electron-rich and electron-deficient aryl substituted alkynes were effective, furnishing the corresponding products in moderate to good yields. We were delighted to find that 1-ethynylnaphthalene and oxadiazoline **1h** coupled smoothly to form the propargylic acetal **5f** in 56% yield. A heterocyclic acetylene 3-ethynylthiophene also reacted with oxadiazolines **1d** and **1e** efficiently, affording the desired products **5l** and **5n** in good yields. It is worth mentioning that the alkyl terminal alkynes 1-hexyne and cyclopropyl acetylene were suitable substrates for the reaction, generating the corresponding propargylic acetals **5o** and **5p** with yields of 75% and 71%, respectively. In another case, the coupling of 4-phenyl-1-butyne and oxadiazolines **1e** gave the expected propargylic acetal **5m** with 50% yield.

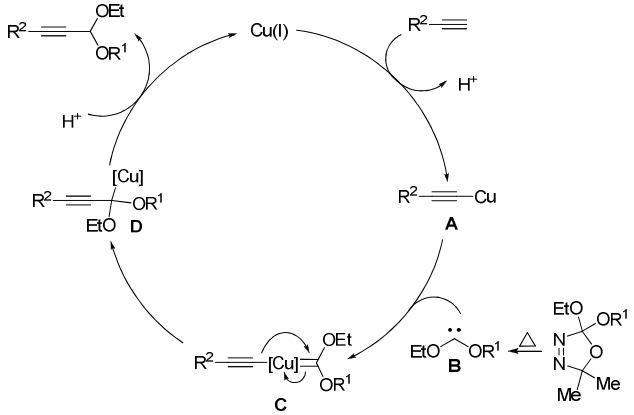
A plausible mechanism for this copper-catalyzed cross-coupling reaction of terminal alkynes with dialkoxycarbenes was described in scheme 5. First, copper acetylide **A** is formed from terminal alkyne. Reaction of copper acetylide **A** with dialkoxycarbene **B**, which is generated *in situ* from the thermal decomposition of oxadiazoline **1**, leads to the formation of copper carbene species **C**.[3,4] Migratory insertion of alkynyl group to the carbenic carbon gives intermediate **D**.[3-7] The final propargylic acetal product **3** is formed by protonation of intermediate **D,** in company with the regeneration of Cu(I) catalyst.

3. Conclusions

Table 3 The scope of terminal alkynes **2**.[a]



[a] Reaction conditions: oxadiazoline **1** (0.2 mmol), terminal alkyne **2** (0.3 mmol), CuI (10 mol%), pyridine (20 mol%), toluene (2.5 mL), 110 °C, N_2 atmosphere, 18h. [b] Isolated yield.



Scheme 5 Proposed Reaction Mechanism.

In conclusion, 2,2-dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines, a general source of dialkoxycarbenes, have been successfully employed as the coupling partners in CuI-catalyzed cross-coupling reactions with terminal alkynes. Various unsymmetrical propargylic acetals were obtained in moderate to good yields, which are difficult to synthesize by using previously reported methods. Moreover, this methodology also provides a novel route for the preparation of propargylic benzofuran derivatives via a sequential cyclization/coupling process. Further investigations on the substrate scopes, mechanism and their synthetic applications are currently underway in our laboratory.

4. Experimental section

General details

^{1}H NMR and ^{13}C NMR spectra were chemicals recorded on Varian 300 or Bruker 400 MHz spectrometer in $CDCl_3$ solution. Mass spectra were obtained on Micro mass ZAB-HS Magnetic mass spectrometer or ZAB-HS Double Focussing Mass Spectrometer, and HRMS were performed at analytical center of Sun Yat-Sen University on Thermo MAT95XP mass spectrometer. Compounds described in the literature were characterized by comparing their ^{1}H NMR and ^{13}C NMR to the reported values. Oxadiazolines **1a-i** were prepared according to literature known procedures.[10d] Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

2,2-Diethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (1a): light yellow liquid (76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74-3.59 (m, 4H), 1.46-1.44 (m, 6H), 1.20-1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 118.6, 60.5, 24.3, 15.4; EI-MS (m/z, relative intensity): 143 (M^+-OEt, 100), 131 (35), 119 (64), 102 (30), 71 (30), 59 (54); HRMS (EI) calcd. for $C_6H_{11}O_2N_2$ [M-OEt]$^+$ 143.0815, found: 143.0820.

2-Ethoxy-5,5-dimethyl-2-phenoxy-2,5-dihydro-1,3,4 - oxadiazole (1b): light yellow liquid (73%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-2.24 (m, 2H), 7.19-7.09 (m, 3H), 4.04-3.87 (m, 2H), 1.55-1.54 (m, 6H), 1.28 (t, *J*= 8.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 136.6, 129.3, 124.6, 121.8, 120.4, 61.6, 24.6, 15.5; EI-MS (m/z, relative intensity): 236 (M^+, 2), 191 (15), 167 (17), 143 (100), 121 (35), 91 (62), 77 (73), 71 (57); HRMS (EI) calcd. for $C_{12}H_{16}O_3N_2$ [M]$^+$ 236.1155, found: 236.1159.

2-Ethoxy-2-methoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (1c): light yellow liquid (66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (m, 2H), 3.43 (s, 3H), 1.52 (s, 6H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.01, 118.83, 60.43, 51.75, 24.04, 23.98, 15.08; EI-MS (m/z, relative intensity): 143 ([M-OMe]$^+$, 20), 129 (37), 104 (23), 59 (100); HRMS (EI) calcd. for $C_6H_{11}O_2N_2$ [M-OMe]$^+$ 143.0815, found: 143.0820.

2-Ethoxy-2-isopropoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (1d): light yellow liquid (76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06-4.26 (m, 1H), 3.61-3.75 (m, 2H), 1.52 (s, 6H), 1.22 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.24, 118.19, 68.41, 60.23, 24.08, 23.99, 23.66, 23.51, 15.07; EI-MS (m/z, relative intensity): 157 ([M-OEt]$^+$, 4), 149 (100), 143([M-O^{i}Pr]$^+$, 19), 87 (42); HRMS (EI) calcd. for $C_6H_{11}O_2N_2$ [M- O^{i}Pr]$^+$ 143.0815, found: 143.0816.

2-(2-Chloroethoxy)-2-ethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (1e): light yellow liquid (61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83-3.69 (m, 2H), 3.61-3.57 (m, 2H), 2.07-1.99 (m, 2H), 1.51-1.50 (m, 6H), 1.22 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 119.1, 61.4, 60.8, 41.7, 24.5, 24.4, 15.4; EI-MS (m/z, relative intensity): 223 (M^+, ^{37}Cl, 2), 221 (M^+, ^{35}Cl, 6), 191 (41), 193 (12), 167 (50), 143 (97), 115 (26), 91 (27), 71 (64), 59 (100); HRMS (EI) calcd. for $C_8H_{15}O_3N_2Cl$ [M]$^+$ 222.0766, found: 222.0774.

2-(2-Ethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yloxy) ethyl acrylate (1f): light yellow liquid (54%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32-6.26 (m, 1H), 6.05-5.96 (m, 1H), 5.75-5.71 (m, 1H), 4.25-4.21 (m, 2H), 3.93-3.85 (m, 2H), 3.68-3.53 (m, 2H), 1.46-1.41 (m, 6H), 1.47 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 136.6, 131.1, 128.2, 119.3, 62.8, 60.7, 60.5, 24.3, 15.3; EI-MS (m/z, relative intensity): 143 (M^+-$OCH_2CH_2OCOCH{=}CH_2$, 20), 99 (100), 59 (13), 55 (57); HRMS (EI) calcd. for $C_6H_{11}O_2N_2$ [M-$OCH_2CH_2OCOCH{=}CH_2$]$^+$ 143.0815, found: 143.0820.

2-(Allyloxy)-2-ethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (1g): light yellow liquid (67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94-5.81 (m, 1H), 5.26 (d, *J*= 10.2 Hz, 1H), 5.12 (d, *J*= 10.2 Hz, 1H), 4.28-4.13 (m, 2H), 3.80-3.65 (m, 2H), 1.51(s, 6H), 1.22 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.6, 119.1, 117.2, 65.8, 60.8, 24.4, 15.5; EI-MS (m/z, relative intensity): 200 (M^+, 10), 155 (5), 143 (68), 131 (44), 99 (17), 82 (18), 71 (27), 59 (100); HRMS (EI) calcd. for $C_9H_{16}O_3N_2$ [M]$^+$ 200.1155, found: 200.1155.

2-(But-3-ynyloxy)-2-ethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (1h): light yellow liquid (61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85-3.66 (m, 4H), 2.52-2.47 (m, 2H), 1.95 (t, *J*=2.4 Hz, 1H), 1.58-1.52 (m, 6H), 1.24 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 119.3, 69.9, 62.8, 24.5, 24.3, 20.3, 15.7, 15.4; EI-MS (m/z, relative intensity): 212 (M^+, 1), 167 (19), 155 (9), 143 (100), 115 (16), 98 (23), 82 (26), 71 (53), 59 (52); HRMS (EI) calcd. for $C_{10}H_{16}O_3N_2$ [M]$^+$ 212.1155, found: 212.1163.

2-Ethoxy-5,5-dimethyl-2-(2-(phenylethynyl)phenoxy)-2,5-dihydro-1,3,4-oxadiazole (1i): light yellow liquid (49%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.47 (m, 3H), 7.39-7.32 (m, 4H), 7.28-7.22 (m, 1H), 7.12-7.07 (t, *J*=7.5 Hz, 1H), 4.20-3.72 (m, 2H), 1.56-1.55(m, 3H), 1.32-1.24 (m, 6H); ^{13}C NMR (75 MHz,) δ 152.73, 136.95, 133.20, 131.71, 129.23, 128.48, 124.39, 123.67, 121.78, 120.74, 117.62, 93.89, 85.89, 61.84, 60.70, 24.65, 23.78, 15.60; EI-MS (m/z, relative intensity): 336 (M^+, 2), 291 (2), 235 (37), 221 (78), 207 (57), 194 (68), 176 (42), 165 (84), 143 (93), 105 (29), 71 (100), 59 (8); HRMS (EI) calcd. for $C_{20}H_{20}O_3N_2$ [M]$^+$ 336.1468, found: 336.1463.

General procedure for the CuI-catalyzed cross-coupling of terminal alkynes with 2,2-Dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines:

CuI (3.8 mg, 10 mol%) was suspended in toluene (2.5 mL) in a 10 mL Schlenk tube under nitrogen. Then pyridine (3.2 mg, 20 mol%), alkynes **2** (0.3 mmol, 1.5 equiv) and oxadiazoline **1** (0.2 mmol) were added. The reaction mixture was stirred at 110 °C under nitrogen for 18 h. After cooling to room temperature, the resulting mixture was filtered through a short path of silica gel, eluting with ethyl acetate. The volatile compounds were removed in vacuo and the residue was purified by flash column chromatography (SiO_2, 1: 100 ethyl acetate: hexane).

1-(3,3-Diethoxyprop-1-ynyl)-4-methylbenzene (3a):[18] ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.36 (d, *J*= 9.1 Hz, 2H), 7.10 (d, *J*= 9.1 Hz, 2H), 5.48 (s, 1H), 3.88-3.77 (m, 2H), 3.71-3.61 (m, 2H), 2.35 (s, 3H), 1.31-1.26 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 131.9, 129.2, 119.0, 92.1, 85.7, 84.0, 61.2, 21.9, 15.6; EI-MS (m/z, relative intensity): 218 (M^+, 3), 173 (76), 145 (91), 115 (65), 91 (100), 65 (14).

1-(3-Ethoxy-3-phenoxyprop-1-ynyl)-4-methylbenzene (3b): ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.29 (m, 4H), 7.18-7.02 (m, 5H), 6.23-6.09 (m, 1H), 4.05-3.81 (m, 2H), 2.37(s, 3H), 1.32-1.27 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 144.5, 135.6, 130.8, 130.5, 129.6, 127.1, 123.2, 122.4, 119.5, 111.9; EI-MS (m/z, relative intensity): 221 (M^+- OEt, 13), 199 (9), 173 (100), 151 (31), 145 (74), 123 (19), 115 (26), 95 (22), 77 (12); HRMS (EI) calcd. for $C_{18}H_{18}O_2$ $[M]^+$ 266.1301, found: 266.1306, calcd. for $C_{16}H_{13}O$ $[M\text{-}OEt]^+$ 221.0961, found: 221.0960.

1-(3-Ethoxy-3-methoxyprop-1-yn-1-yl)-4-methylbenzene (3c): ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 5.47 (s, 1H), 3.90 - 3.79 (m, 1H), 3.72 – 3.62 (m, 1H), 3.48 (s, 3H), 2.38 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.05, 131.84, 129.04, 118.69, 92.70, 85.74, 83.22, 61.26, 52.27, 21.52, 15.13; EI-MS (m/z, relative intensity): 204 (M^+, 12), 173 (56), 159 (100), 145 (97), 115 (64); HRMS (EI) calcd. for $C_{13}H_{16}O_2$ $[M]^+$ 204.1145, found: 204.1133.

1-(3-Ethoxy-3-isopropoxyprop-1-yn-1-yl)-4-methylbenzene (3d): ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 5.57 (s, 1H), 4.16 (m, 1H), 3.87 (m, 1H), 3.70 (m, 1H), 2.37 (s, 3H), 1.30 - 1.26 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.87, 131.80, 129.00, 118.94, 118.82, 90.69, 85.12, 84.25, 68.64, 60.14, 23.31, 22.39, 21.50, 15.15, 15.13; EI-MS (m/z, relative intensity): 232 (M^+, 1), 173(49), 145 (100), 131 (8), 115 (26); HRMS (EI) calcd. for $C_{15}H_{20}O_2$ $[M]^+$ 232.1458, found: 232.1455.

1-(3-(2-Chloroethoxy)-3-ethoxyprop-1-ynyl)-4-methylbenzene (3e): ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J*= 8.1 Hz, 2H), 7.11 (d, *J*= 8.1 Hz, 2H), 5.48 (s, 1H), 3.94-3.80 (m, 2H), 3.76-3.62 (m, 2H), 2.35 (s, 3H), 2.09 (t, *J*= 6.6 Hz, 2H), 2.09 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (75 MHz,) δ 139.23, 132.00, 129.49, 129.21, 118.87, 92.29, 86.00, 83.66, 77.74, 77.33, 76.90, 61.76, 61.21, 42.17, 32.98, 21.86, 15.47; EI-MS (m/z, relative intensity): 207 (M^+-OEt, 3), 173 (84), 145 (100), 114 (43), 105 (7), 91 (11); HRMS (EI) calcd. for $C_{12}H_{12}OCl$ $[M\text{-}OEt]^+$ 207.0571, found: 207.0566.

2-(1-Ethoxy-3-p-tolylprop-2-ynyloxy)ethyl acrylate (3f): ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J*= 8.1 Hz, 2H), 7.10 (d, *J*= 7.8 Hz, 2H), 6.44-6.39 (m, 1H), 6.18-6.09 (m, 1H), 5.84-5.80 (m, 1H), 5.53 (s, 1H), 4.37 (t, *J*= 7.8 Hz, 2H), 4.03-3.98 (m, 1H), 3.90-3.80 (m, 2H), 3.67-3.61 (m, 1H), 2.34 (s, 3H), 1.27 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 139.3, 131.9, 131.2, 129.2, 128.4, 118.7, 92.2, 86.2, 83.3, 63.9, 62.8, 62.0, 21.9, 15.4; EI-MS (m/z, relative intensity): 288 (M^+, 2), 197 (6), 173 (40), 145 (69), 115 (27), 99 (100), 55 (24); HRMS (EI) calcd. for $C_{17}H_{20}O_4$ $[M]^+$ 288.1356, found: 288.1355.

1-(3-(Allyloxy)-3-ethoxyprop-1-ynyl)-4-methylbenzene (3g): ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J*=8.1 Hz, 2H), 6.82 (d, *J*= 8.1 Hz, 2H), 6.02-5.91 (m, 1H), 5.52 (m, 1H), 5.38-5.31 (m, 1H), 5.23-5.19 (m, 1H), 4.28-4.12 (m, 2H), 3.84-3.70 (m, 1H), 3.70-3.64 (m, 1H), 2.35 (s, 3H), 1.29 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 134.6, 133.2, 131.9, 129.2, 118.9, 117.6, 91.7, 85.6, 83.7, 66.4, 61.5, 61.2, 21.9, 15.5; EI-MS (m/z, relative intensity): 230 (M^+, 4), 200 (6), 173 (93), 156 (89), 145 (100), 141 (59), 128 (16), 115 (83), 105 (8), 91(23); HRMS (EI) calcd. for $C_{15}H_{18}O_2$ $[M]^+$ 230.1301, found: 230.1243, calcd. for $C_{15}H_{18}O_2$ $[M\text{-}OEt]^+$ 185.0961, found: 185.0964.

1-(3-(But-3-ynyloxy)-3-ethoxyprop-1-ynyl)-4-methylbenzene (3h): ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J*= 8.1 Hz, 2H), 7.11 (d, *J*= 8.1 Hz, 2H), 5.52 (s, 1H), 3.91-3.64 (m, 4H), 2.58-2.52 (m, 2H), 2.35 (s, 3H), 2.00 (s, 1H), 1.29 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 131.9, 129.2, 118.8, 92.2, 86.1, 83.4, 81.5, 69.7, 63.3, 61.9, 21.8, 20.3, 15.5; EI-MS (m/z, relative intensity): 242 (M^+, 2), 197 (16), 173 (77), 145 (100), 115 (39), 91 (14); HRMS (EI) calcd. for $C_{16}H_{18}O_2$ $[M]^+$ 242.1301, found: 242.1297.

2-Ethoxy-3-(1-phenyl-3-p-tolylprop-2-ynyl)benzofuran (4): ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J*= 5.7 Hz, 2H), 7.52-7.48 (m, 1H), 7.35 (d, *J*= 6.0 Hz, 2H), 7.32-7.27 (m, 3H), 7.21 (t, *J*= 5.4 Hz, 1H), 7.11-7.08 (m, 4H), 5.40 (s, 1H), 4.44-4.38 (m, 2H), 2.33 (s, 3H), 1.44 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 148.7, 140.4, 137.9, 131.6, 128.9, 128.4, 127.4, 126.8, 122.7, 121.9, 120.5, 119.5, 110.2, 110.0, 94.8, 88.0, 68.4, 32.2, 21.4, 15.2; EI-MS (m/z, relative intensity): 366 (M^+, 83), 337 (100), 322 (32), 309 (34), 292 (31), 278 (56), 261 (45), 251 (33), 222 (82), 205 (72), 194 (36), 178 (19), 165 (51), 119 (31), 105 (16), 91 (24), 77 (10); HRMS (EI) calcd. for $C_{26}H_{22}O_2$ $[M]^+$ 366.1615, found: 366.1615.

1-(3-(But-3-yn-1-yloxy)-3-ethoxyprop-1-yn-1-yl)-3-methyl benzene (5a): ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.23 (m, 1H), 7.18 (m, 1H), 5.56 (s, 1H), 3.95-3.84 (m, 2H), 3.83-3.65 (m, 2H), 2.57 (dd, *J* = 9.4, 4.3 Hz, 2H), 2.35 (s, 3H), 2.03 (s, 1H), 1.31 (t, *J* = 7.1 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.98, 132.51, 129.79, 129.01, 128.18, 121.51, 91.95, 85.84, 83.50, 81.18, 69.40, 62.99, 61.63, 21.17, 19.92, 15.07; EI-MS (m/z, relative intensity): 213 (11), 197 ($[M\text{-}OEt]^+$, 22), 173 (74), 145 (100), 115 (43); HRMS (EI) calcd. for $C_{14}H_{13}O$ $[M\text{-}OEt]^+$ 197.0561, found: 197.0563.

1-(3-(But-3-yn-1-yloxy)-3-ethoxyprop-1-yn-1-yl)-4-methoxy benzene (5b): ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 2H), 5.55 (s, 1H), 3.95-3.75 (m, 6H), 3.73-3.62 (m, 1H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.03 (s, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.03, 133.45, 113.91, 113.74, 92.02, 85.72, 82.54, 81.21, 69.39, 62.91, 61.62, 55.29, 19.92, 15.08. EI-MS (m/z, relative intensity): 258 (M^+, 4), 213 (46), 189 (100), 161 (52), 149 (32); HRMS (EI) calcd. for $C_{16}H_{18}O_3$ $[M]^+$ 258.1250, found: 258.1254.

1-(4-(3-(But-3-yn-1-yloxy)-3-ethoxyprop-1-yn-1-yl)phenyl) ethanone (5c): ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 5.57 (s, 1H), 3.89 (dd, *J* = 15.4, 7.8 Hz, 2H), 3.83-3.78 (m, 1H), 3.74-3.67 (m, 1H), 2.62 (s, 3H), 2.57 (dd, *J* = 9.2, 4.5 Hz, 2H), 2.04 (s, 1H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.27, 136.83, 132.12, 128.17, 126.50, 91.81, 86.95, 84.64, 81.06, 69.49, 63.11, 61.83, 26.65, 19.90, 15.05; EI-MS (m/z, relative intensity): 270 (M^+, 2), 225 (19), 201 (60), 173 (100), 149 (18); HRMS (EI) calcd. for $C_{17}H_{18}O_3$ $[M]^+$ 270.1250, found: 270.1253.

1-(3-(But-3-yn-1-yloxy)-3-ethoxyprop-1-yn-1-yl)-4-chloro benzene (5d): ^1H NMR (300 MHz,) δ 7.39 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.51 (s, 1H), 3.87 (m, 2H), 3.80-3.70 (m, 1H), 3.65 (m, 1H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.01 (s, 1H), 1.29 (t, *J*

= 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.06, 133.17, 128.69, 120.18, 91.83, 84.82, 84.47, 81.10, 69.48, 63.02, 61.74, 19.90, 15.05; EI-MS (m/z, relative intensity): 262 (M^+, 1), 217 (27), 193 (100), 187 (46), 152 (48), 101(46); HRMS (EI) calcd. for $C_{15}H_{15}O_2Cl$ $[M]^+$ 262.0755, found: 262.0757.

1-Bromo-4-(3-(but-3-yn-1-yloxy)-3-ethoxyprop-1-yn-1-yl) benzene (5e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.1 Hz, 2H), 7.36 (d, *J* = 6.6 Hz, 2H), 5.54 (s, 1H), 3.92-3.83 (m, 2H), 3.83-3.75 (m, 1H), 3.72 – 3.64 (m, 1H), 2.63-2.49 (m, 2H), 2.03 (d, *J* = 1.9 Hz, 1H), 1.32-1.28 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.36, 131.61, 123.32, 120.64, 91.84, 84.99, 84.52, 81.09, 69.47, 63.03, 61.75, 19.90, 15.05; EI-MS (m/z, relative intensity): 306 (M^+, 2), 263 (14), 239 (40), 209 (100), 152 (49), 101 (47); HRMS (EI) calcd. for $C_{15}H_{15}O_2Br$ $[M]^+$ 306.0250, found: 306.0244.

1-(3-(But-3-yn-1-yloxy)-3-ethoxyprop-1-yn-1-yl)naphthalene (5f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 7.1 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.58-7.52 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 5.73 (s, 1H), 3.99 (m, 2H), 3.89 (m, 1H), 3.78 (m, 1H), 2.63 (t, *J* = 6.8 Hz, 2H), 2.06 (s, 1H), 1.36 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.27, 133.07, 131.15, 129.44, 128.31, 126.98, 126.52, 126.05, 125.11, 119.36, 92.17, 88.72, 83.79, 81.21, 69.48, 63.15, 61.79, 19.99, 15.15; EI-MS (m/z, relative intensity): 278 (M^+, 3), 233 (30), 209 (64), 181 (100), 152 (87); HRMS (EI) calcd. for $C_{19}H_{18}O_2$ $[M]^+$ 278.1301, found: 278.1295.

1-(3-(But-3-yn-1-yloxy)-3-ethoxyprop-1-yn-1-yl)-4-fluoro benzene (5g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.5, 5.8 Hz, 2H), 7.03 (t, *J* = 8.4 Hz, 2H), 5.50 (s, 1H), 3.99 – 3.89 (m, 1H), 3.85 (m, 1H), 3.71 (m, 2H), 2.15-2.07 (m, 2H), 1.30 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.83 (d, *J* = 250.2 Hz), 133.92 (d, *J* = 8.5 Hz), 117.81 (d, *J* = 3.4 Hz), 115.64 (d, *J* = 22.2 Hz), 91.94, 84.47, 83.79, 61.48, 61.43, 41.82, 15.09; EI-MS (m/z, relative intensity): 225 (30), 177 ([M-OCH_2CH_2Cl]$^+$, 83), 149 (100), 101 (21); HRMS (EI) calcd. for $C_{11}H_{10}OF$ [M-OCH_2CH_2Cl]$^+$ 177.0710, found: 177.0713.

Methyl 4-(3-(2-chloroethoxy)-3-ethoxyprop-1-yn-1-yl) benzoate (5h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 7.8 Hz, 2H), 5.53 (s, 1H), 4.00-3.90 (m, 4H), 3.84 (m, 1H), 3.72 (m, 2H), 2.12 (m, 2H), 1.32 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.44, 131.90, 130.18, 129.44, 126.40, 91.88, 86.83, 84.59, 61.57, 52.30, 41.77, 15.08; EI-MS (m/z, relative intensity): 281 (8), 217 ([M-OCH_2CH_2Cl]$^+$, 68), 189 (100), 149 (34); HRMS (EI) calcd. for $C_{13}H_{13}O_3$ [M-OCH_2CH_2Cl]$^+$ 217.0859, found: 217.0856.

1-(3-(2-Chloroethoxy)-3-ethoxyprop-1-yn-1-yl)-4-nitro benzene (5i): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 2H), 5.54 (s, 1H), 4.01-3.91 (m, 1H), 3.86 (m, 1H), 3.72 (m, 2H), 2.18- 2.06 (m, 2H), 1.32 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.55, 132.78, 128.55, 123.57, 91.78, 89.07, 83.31, 61.78, 61.57, 41.71, 15.06; EI-MS (m/z, relative intensity): 252 (27), 204 ([M-OCH_2CH_2Cl]$^+$, 100), 176 (86); HRMS (EI) calcd. for $C_{11}H_{10}O_3N$ [M-OCH_2CH_2Cl]$^+$ 204.0655, found: 204.0653.

4-(3-(2-Chloroethoxy)-3-ethoxyprop-1-yn-1-yl)-4'-propyl-1,1'-biphenyl (5j): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 4H), 7.53 (d, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 2H), 5.54 (s, 1H), 4.01-3.83 (m, 2H), 3.73 (m, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.16 (m, 2H), 1.71 (dd, *J* = 14.7, 7.3 Hz, 2H), 1.35 (d, *J* = 7.3 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.47, 141.62, 137.52, 132.33, 129.00, 126.84, 126.75, 120.23, 92.08, 85.56, 84.51, 64.37, 64.12, 40.92, 37.70, 24.52, 14.25, 13.85; EI-MS (m/z, relative intensity): 325 (25), 277 ([M-OCH_2CH_2Cl]$^+$, 100), 249 (96), 219 (50); HRMS (EI) calcd. for $C_{20}H_{21}O$ [M-OCH_2CH_2Cl]$^+$ 277.1587, found: 277.1580.

(3-(2-Chloroethoxy)-3-ethoxyprop-1-yn-1-yl)benzene (5k): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.35 (m, 3H), 5.52 (s, 1H), 3.90-3.75 (m, 2H), 3.72 (m, 2H), 2.17-2.04 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.94, 128.89, 128.28, 121.75, 92.02, 85.54, 84.05, 61.49, 61.44, 41.83, 15.10; EI-MS (m/z, relative intensity): 207 (22), 159 ([M-OCH_2CH_2Cl]$^+$, 36), 131 (100), 103 (24); HRMS (EI) calcd. for $C_{11}H_{11}O$ [M-OCH_2CH_2Cl]$^+$ 159.0804, found: 159.0808.

3-(3-(2-Chloroethoxy)-3-ethoxyprop-1-yn-1-yl)thiophene (5l): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.29 (m, 1H), 7.17 (d, *J* = 4.6 Hz, 1H), 5.50 (s, 1H), 3.98-3.81 (m, 2H), 3.71 (m, 2H), 2.15-2.09 (m, 2H), 1.30 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.93, 129.91, 125.39, 120.77, 92.02, 83.71, 80.80, 61.49, 61.45, 41.83, 15.08; EI-MS (m/z, relative intensity): 213 (24), 165 ([M-OCH_2CH_2Cl]$^+$, 60), 137 (100), 109 (20); HRMS (EI) calcd. for C_9H_9OS [M-OCH_2CH_2Cl]$^+$ 165.0369, found: 165.0367.

(5-(2-Chloroethoxy)-5-ethoxypent-3-yn-1-yl)benzene (5m): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 13.5, 6.4 Hz, 2H), 7.24 (t, *J* = 5.8 Hz, 3H), 5.26 (s, 1H), 3.83-3.76 (m, 1H), 3.75- 3.69 (m, 1H), 3.65 (m, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.08-2.01 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.34, 128.42, 126.37, 91.60, 85.97, 76.10, 61.16, 61.13, 41.89, 34.61, 20.77, 15.07; EI-MS (m/z, relative intensity): 235 (34), 187 ([M-OCH_2CH_2Cl]$^+$, 100), 154 (34), 129 (44), 91 (95); HRMS (EI) calcd. for $C_{13}H_{15}O$ [M-OCH_2CH_2Cl]$^+$ 187.1117, found: 187.1114.

3-(3-Ethoxy-3-isopropoxyprop-1-yn-1-yl)thiophene (5n): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.28 (d, *J* = 3.1 Hz, 1H), 7.16 (d, *J* = 4.1 Hz, 1H), 5.55 (s, 1H), 4.15 (m, 1H), 3.86 (m, 1H), 3.75 – 3.64 (m, 1H), 1.31 – 1.25 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.92, 129.71, 129.58, 125.29, 121.02, 90.61, 84.54, 80.19, 68.75, 60.14, 23.29, 22.34, 15.10; EI-MS (m/z, relative intensity): 224 (M^+, 1), 179 (14), 137 (100), 109 (15); HRMS (EI) calcd. for $C_{12}H_{16}O_2S$ $[M]^+$ 224.0866, found: 224.0863.

1-Ethoxy-1-isopropoxyhept-2-yne (5o): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 1H), 4.08 (m, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 2.26 (t, *J* = 7.0 Hz, 2H), 1.53 (dt, *J* = 14.4, 7.1 Hz, 2H), 1.43 (dq, *J* = 14.4, 7.1 Hz, 2H), 1.22 (m, 9H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 90.26, 86.16, 76.10, 68.24, 59.75, 30.38, 23.27, 22.30, 21.97, 18.34, 15.11, 15.08, 13.56; EI-MS (m/z, relative intensity): 153 ([M-OEt]$^+$, 24), 139 (69), 111 (100); HRMS (EI) calcd. for $C_{10}H_{17}O$ [M-OEt]$^+$ 153.1274, found: 153.1271.

(3-Ethoxy-3-isopropoxyprop-1-yn-1-yl)cyclopropane (5p): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.07 (m, 1H), 3.81 – 3.70 (m, 1H), 3.64-3.52 (m, 1H), 1.35-1.29 (m, 1H), 1.26-1.17 (m, 9H), 0.84-0.69 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 90.25, 89.02, 88.89, 68.27, 59.74, 23.26, 22.28, 15.07, 8.17, 8.15, -0.65; EI-MS (m/z, relative intensity): 167 (52), 149 (100), 123 (37), 137 ([M-OEt]$^+$, 19), 95 (79); HRMS (EI) calcd. for $C_9H_{13}O$

[M-OEt]$^+$ 137.0961, found: 137.0958.

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