Palladium-catalyzed 1,4-addition of terminal alkynes to unsaturated carbonyl compounds promoted by electron-rich ligands

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The efficient palladium-catalyzed conjugate addition of terminal alkynes to α,β-unsaturated carbonyl compounds has been developed using electron-rich ligands, producing the corresponding γ,δ-alkynyl ketone and γ,δ-alkynyl esters in good yields.

1. Introduction

Within the past few decades, the development of palladium-catalyzed C–C bond formation reactions has dramatically advanced the 'state-of-the-art' of organic synthesis.[1] Well-known examples include the Heck reaction,[2] the Stille reaction,[3] the Suzuki reaction,[4] the Trost–Tsuji reaction,[5] and the Sonogashira coupling,[6] to name but a few. Furthermore, reactions involving overall addition provide an atom-economical way to construct more complex structures from simpler units.[7] Recently, there has been increased interest in the addition of terminal alkynes to compounds that involve sp^2 carbons such as C=O[8] or C=N bonds (Fig. 1, route a).[9] However, only a few examples of the addition of terminal alkynes to C=C bonds have been reported (Fig. 1, route b).[10]

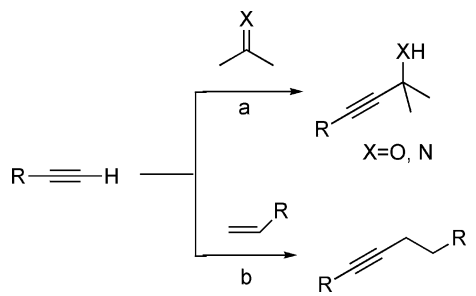
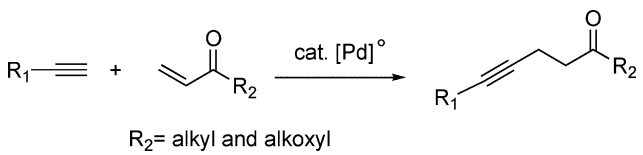


Fig. 1 Addition of terminal alkyne to C=X and C=C bonds.

Furthermore, although palladium is one of the most widely used metals in catalysis, palladium-catalyzed conjugate addition of alkynes to enones and alkene esters has not been previously reported.[11] We hypothesized that the failure of palladium in catalyzing such additions could be attributed to (1) either the facile homo- or heterodimerization of terminal alkynes (a well-known and synthetically useful process)[12] to form by-products or (2) the low reactivity of the alkynyl palladium intermediate towards enones and alkene esters. Conceivably, such obstacles can be overcome by tuning the electronic properties of the ligands coordinated to palladium.

Recently, we reported the preliminary results of a simple and highly efficient Pd-catalyzed addition of terminal alkynes to conjugated enones either in water or in acetone under air by using an electron-rich trimethylphosphine ligand.[13] Herein, we describe the detailed study of this reaction as well as its extension to alkene esters (Scheme 1).



Scheme 1 Conjugate addition of terminal alkynes to enones and alkene esters.

2. Results and discussion

2.1 General design

To begin with our study, we applied the rationale that the key to the success of the desired conjugate additions is to increase the reactivity of the alkynyl C–Pd bond (increasing the polarization of the σ-complex, Fig. 2) and decrease the reactivity of the C–C triple bond (decreasing π-complex formation, Fig. 2). The use of an electron-rich ligand[14] can potentially serve both purposes: the donation of electron density from the ligand to palladium will weaken the C–Pd bond and make alkyne coordination less favorable.

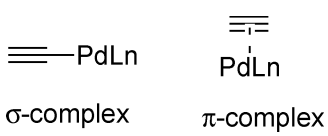


Fig. 2 Formation of σ- and π-palladium complexes with alkynes.

2.2 Conjugate addition of terminal alkynes to enones

We started by reacting phenylacetylene with ethyl vinyl ketone in the presence of 5 mol% of $Pd(OAc)_2$ and 10 mol% of the common ligand PPh_3 in water at 60 °C for 40 h. As expected, the reaction gave only a tiny amount of the desired product

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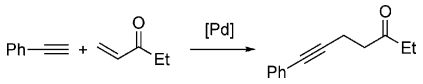
† L. Zhou and L. Chen contributed equally on this research.

Table 1 Addition of phenylacetylene to ethyl vinyl ketone catalyzed by various palladium catalysts in water[a]



Entry	Catalyst	L/C ratio	Yield (%)
1	$Pd(OAc)_2/PPh_3$	2	<10[b]
2	$Pd(OAc)_2$/tris(4-methoxyphenyl)phosphine	2	27
3	$Pd(OAc)_2$/tris(2,6-dimethoxyphenyl)phosphine	2	31
4	$Pd(OAc)_2$/tris(2,4,6-trimethoxyphenyl)phosphine	2	17
5	$Pd(OAc)_2/PMe_3$	2	77
6	$PdCl_2(PPh_3)_2$	—	<10[b]
7	$PdCl_2(PPh_3)_2/PMe_3$	2	<10[b]
8	$PdCl_2(O_2CCF_3)_2/PMe_3$	2	<10[b]
9	$Pd(0)(PPh_3)_4$	—	—[c]
10	$Pd(0)(PPh_3)_4/PMe_3$	2	32
11	$Pd(OAc)_2/PMe_3/Et_3N$ (1 equiv)	2	<10[b]
12	$Pd(OAc)_2/PMe_3$/NaOAc (1 equiv)	2	43
13	$Pd(OAc)_2$/trimethylphosphine oxide	2	<10[b]
14	PMe_3	—	—[c]
15	$Pd(OAc)_2$	0	15
16	$Pd(OAc)_2/Et_3N$ (1 equiv)	0	<10[b]
17	**$Pd(OAc)_2/PMe_3$**	**4**	**91**
18	$Pd(OAc)_2/PMe_3$	6	86

[a] All reactions were carried out using 1 mmol of phenylacetylene, 2 mmol of vinyl ethyl ketone, 5 mol% of palladium catalyst and the given amount of ligand in water at 60 °C for 40 h. [b] Measured by ^{1}H NMR. [c] Not detected by ^{1}H NMR.

(Table 1, entry 1). Then a more electron-rich ligand, tris(4-methoxyphenyl)phosphine, was tested, and the product yield increased significantly to 27% (Table 1, entry 2). Encouraged by this result, we tested other electron-rich ligands (Table 1, entries 3–5). The use of PMe_3, being both electron-rich and smaller, gave the coupling product in 77% yield (Table 1, entry 5). Other palladium salts were also tested; the results showed that the counter-ion of the palladium salt also had an effect on the reaction. With an electron-deficient trifluoroacetate or chloride as the counter-ion, the reaction was less effective (Table 1, entries 6–8). To examine whether the phosphine ligand served as a base or a real ligand, we also tested the catalyst system in the presence of an inorganic base as well as an organic base. The $Pd(OAc)_2/PMe_3$ combination generated less product in the presence of a base, especially in the case of NEt_3 (Table 1, entries 11 and 12), possibly because of competing coordination between triethylamine and the phosphine ligand. In the absence of a phosphine ligand, the $Pd(OAc)_2$/base system gave only a trace amount of the product. $Pd(OAc)_2$ alone as the catalyst was only slightly effective, whereas PMe_3 did not show any catalytic activity (although phosphines are known to catalyze conjugate additions with alcohols, amines, and activated methylene as nucleophiles).[15] Because PMe_3 is air-sensitive and easily oxidized to trimethylphosphine oxide, we also tested $Pd(OAc)_2$/trimethylphosphine oxide as a catalyst; however, almost no catalytic activity was observed (Table 1, entry 13); trimethylphosphine oxide alone did not show any catalytic activity either. Finally, when the ratio of $PMe_3/Pd(OAc)_2$ was increased from 2 : 1 to 4 : 1, the desired product was obtained in 91% yield (Table 1, entry 17). However, when the ratio of $PMe_3/Pd(OAc)_2$ was increased to 6 : 1, the product yield decreased, which can be attributed to the lower availability of coordination sites on palladium and the resulting decreased catalytic activity[16] (Table 1, entry 18).

Subsequently, a broad range of substrates were examined for this new palladium-catalyzed alkyne–enone addition, in water as well as in acetone (Table 2). It was shown that alkynes bearing silyl, alkenyl, aromatic, aliphatic or halid groups all reacted smoothly with vinyl ketone to afford good yields of the desired 1,4-addition products. With diyne as a substrate, a bis-addition adduct was the major product. In addition to ethyl vinyl ketone, methyl vinyl ketone also provided the corresponding product in this addition reaction, albeit in a lower yield. It should be noted that both water and acetone are effective as solvents, similar results being obtained with both.

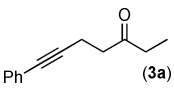
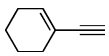
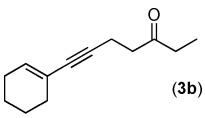
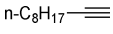
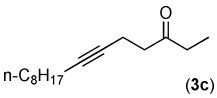
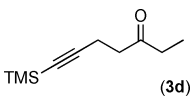
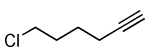
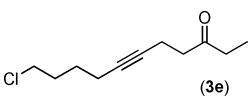
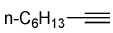
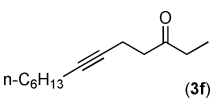
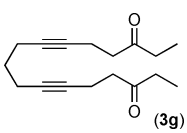
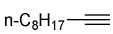
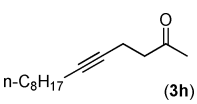
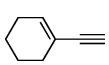
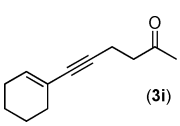
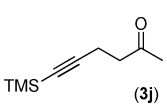
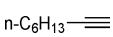
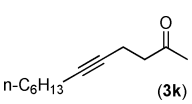
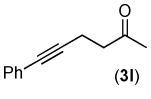
2.3 1,4-Addition of terminal alkynes to acrylate esters

The success of the $Pd(OAc)_2/PMe_3$-catalyzed conjugate addition of terminal alkynes to enones prompted us to explore the applicability of the catalytic method to less reactive substrates such as acrylate esters. Although there are a few reports on the 1,4-addition of terminal alkynes to unsaturated esters, the reactions are limited to the use of highly reactive diesters[17] or a specialized high-boiling point solvent.[18]

When phenylacetylene was reacted with methyl acrylate in the presence of 2.5 mol% of $Pd(OAc)_2$ and 5 mol% of PMe_3 as ligand under the alkyne–enone reaction conditions, only a trace amount of the desired product was observed. In order to further extend the scope of this addition, we hypothesized that by using an even more electron-donating ligand, such as N-heterocyclic carbenes (NHCs),[19] the reactivity of the alkynyl Pd–C bond can be increased further. Thus, various N-heterocyclic carbene ligands were tested and compared with the trimethylphosphine ligands under identical conditions. In order to solubilize the catalyst, the reactions were performed in THF (Table 3).

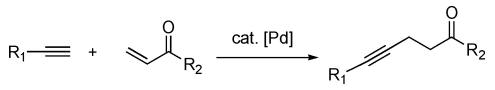
Mono-dentate N-heterocyclic carbene ligands, generated *in situ* from their commercially available precursors **4a** and **4b** in THF in the presence of 1.2 equiv of KO-*t*-Bu, were tested. The reactions led to promising yields of 65% and 42% respectively (Table 3, entries 2 and 3). Encouraged by these initial results, four other

Table 2 Addition of terminal alkynes **1** to vinyl ketones **2** catalyzed by $Pd(OAc)_2/PMe_3$ in water and in acetone[a]

Entry	Terminal alkyne **1**	Vinyl ketone **2**	Conditions	Product **3**	Isolated yield (%)
1			40 h, acetone	 (**3a**)	85
2			40 h, water		91
3			43 h, water	 (**3b**)	74
4			43 h, acetone	 (**3c**)	61
5			43 h, water		70
6			42 h, acetone	 (**3d**)	70
7			42 h, water		67
8			44 h, water	 (**3e**)	65
9			44 h, acetone	 (**3f**)	63
10			44 h, water		72
11[b]			44 h, acetone	 (**3g**)	57
12[b]			44 h, water		62
13			42 h, acetone	 (**3h**)	51
14			42 h, water		56
15			45 h, water	 (**3i**)	58
16			43 h, acetone	 (**3j**)	49
17			43 h, water		52
18			45 h, water	 (**3k**)	53
19			39 h, acetone	 (**3l**)	66
20			39 h, water		61

[a] The reactions were carried out using 1.0 mmol of a terminal alkyne, 2 mmol of a vinyl ketone, 5 mol% of $Pd(OAc)_2$ and 20 mol% of PMe_3 at 60 °C in water or acetone. The product structures were determined by ^1H NMR, ^{13}C NMR, MS, and IR. [b] 1.0 mmol of terminal alkyne was reacted with 4 mmol of vinyl ketone.

Table 3 Addition of phenylacetylene to methyl acrylate catalyzed by various palladium–NHC complexes[a]



Entry	Catalyst	Solvent[b]	Yield (%)[c]
1	$Pd(OAc)_2/PMe_3$	THF	<10
2	$Pd(OAc)_2$/**4a**	THF	65
3	$Pd(OAc)_2$/**4b**	THF	42
4	$Pd(OAc)_2$/**4c**	THF	55
5	$Pd(OAc)_2$/**4d**	THF	31
6	$Pd(OAc)_2$/**4e**	THF	15
7	$Pd(OAc)_2$/**4f**	THF	<10
8	$Pd(dba)_2$/**4a**	THF	Trace[d]
9	$[PdCl(allyl)]_2$/**4a**	THF	37
10	$Pd(OAc)_2$	THF	Trace[d]
11	**4a**	THF	—[d]
12	$Pd(OAc)_2$/**4a**	Acetone	79
13	$Pd(OAc)_2$/**4a**	DMF	61
14	$Pd(OAc)_2$/**4a**	Water	<10

[a] All reactions were carried out in sealed tubes using 0.5 mmol of phenylacetylene, 1 mmol of methyl acrylate, 2.5 mol% of palladium catalysts and 10 mol% of ligand in the desired solvent at 60 °C for 24 h. [b] N-Heterocyclic carbene ligands were generated *in situ* from their precursors in THF with 1.2 equiv of KO-*t*-Bu; when other solvents were used, THF was evaporated by pump slowly. [c] Measured by ^{1}H NMR. [d] Not detected by ^{1}H NMR.

N-heterocyclic carbene ligands were then prepared from their precursors **4c–f** (Fig. 3) and tested. The reaction with NHC generated from **4c** afforded product **5a** in 55% yield; whereas the reaction with NHC from **4d** (which coordinates to palladium by two six membered rings) gave product **5a** in only 31% yield (Table 3, entries 4 and 5).

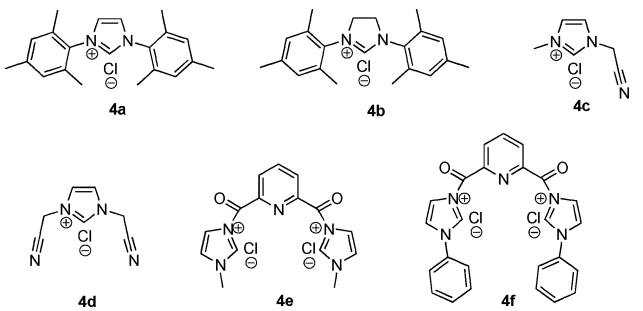


Fig. 3 Precursors of N-heterocyclic carbene ligands.

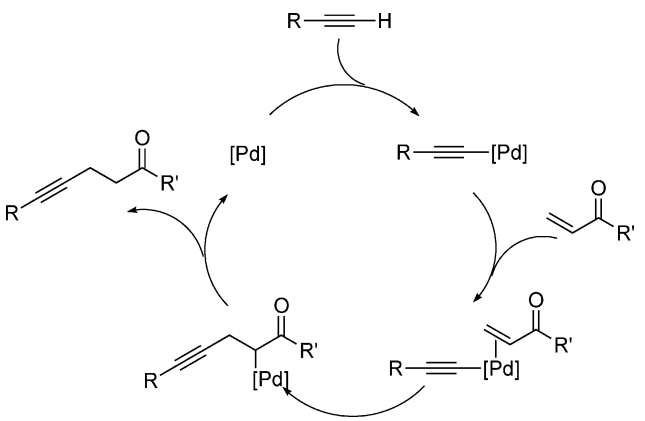
The use of the N-heterocyclic carbenes generated from **4e** and **4f** (both tridentate and sterically hindered ligands) afforded the desired **5a** in 15% and <10% yield respectively (Table 3, entries 6 and 7). The use of Pd(allyl)Cl dimer, instead of $Pd(OAc)_2$, gave 37% yield of the desired product, whereas the use of $Pd(dba)_2$ generated only a trace amount of **5a** (Table 3, entries 8 and 9). As a control, with $Pd(OAc)_2$ alone as the catalyst only a trace amount of the product was obtained, whereas N-heterocyclic carbene alone generated from **4a** did not show any catalytic activity (although NHCs have been shown to catalyze addition reactions with enols[20] and ketones[21]) (Table 3, entry 11). Having the preferred catalyst in hand, different solvents such as THF, DMF, acetone and water were examined. The use of THF or DMF as solvent gave only modest yields of **5a** (Table 3, entries 3 and 13). When water was used as solvent, <10% yield of **5a** was obtained (Table 3, entry 14). The best results were obtained by using acetone as solvent (Table 3, entry 12).

Subsequently, various terminal alkynes and acrylate esters were used using the Pd–NHC catalyst under the optimized conditions in acetone (Table 4). Various aromatic alkynes with an electron-donating substituent such as the methyl, methoxy group, phenyl and dimethylamino on the *para*-positon of the benzene ring gave the corresponding esters in high yields (Table 4, entries 1–5), whereas aromatic alkynes with a substituent on the *ortho*-position gave the corresponding γ,δ-alkynyl esters only in modest yields, most likely due to the steric effect (Table 4, entries 6 and 7). It is worth mentioning that this catalytic system can tolerate a free amine in the reaction. The reaction of *m*-aminophenylacetylene with methyl acrylate gave the desired product smoothly without the need for functional group protection (Table 4, entry 8). The reaction of 2-ethynyl-6-methoxynaphthalene also proceeded smoothly and gave the corresponding γ,δ-alkynyl ester in 85% yield (Table 4, entry 9). When a diyne was used, a mono-addition adduct was obtained as a major product (Table 4, entry 10). *tert*-Butyl acrylate also reacted efficiently (Table 4, entries 11–14). When aliphatic alkynes such as 1-octyne were used as the substrates, only trace amounts of the desired products were detected.

2.4 Mechanistic studies

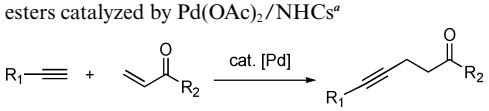
To gain insight into the mechanism of the reaction, when phenylacetylene-d_1 was reacted with ethyl vinyl ketone in dry THF, an α-deuterated alkynyl ketone product was obtained in 76% yield with 15% d-incorporation. On the other hand, in dry acetone (which has a relatively active α-H), the deuterated product was obtained in 79% yield with less than 10% d-incorporation. When phenylacetylene was reacted with ethyl vinyl ketone in the presence of 10 equiv D_2O in acetone, the addition product was obtained in 68% yield with 55% d-incorporation; while in D_2O solvent, the addition product was obtained in 52% yield with more than 95% d-incorporation. No deuterium incorporation was observed at any position when 7-phenyl-6-heptyn-3-one, a γ,δ-ynone product, was reacted in D_2O.

Based on these results, a tentative mechanism for the palladium-catalyzed 1,4-addition of terminal alkynes to conjugated enones and esters is illustrated in Scheme 2. The η^2-coordination of



Scheme 2 Tentative mechanism for the palladium-catalyzed 1,4-addition of terminal alkynes to unsaturated carbonyl compounds.

Table 4 Addition of terminal alkynes to acrylic esters catalyzed by $Pd(OAc)_2$/NHCs[a]



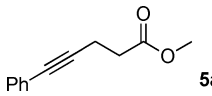
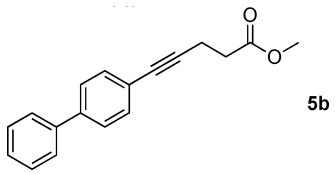
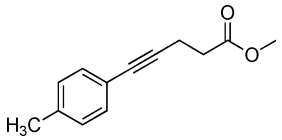
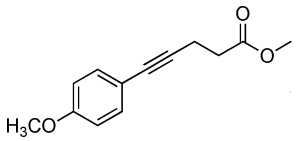
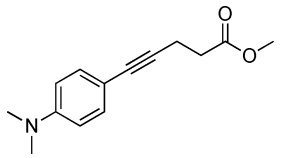
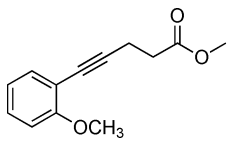
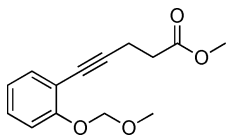
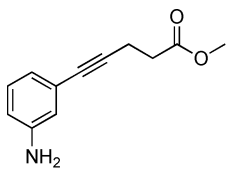
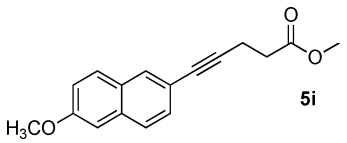
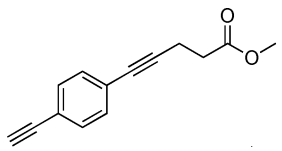
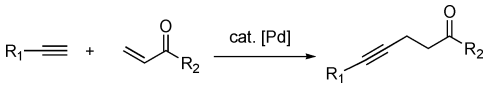
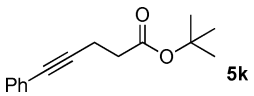
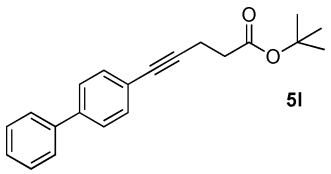
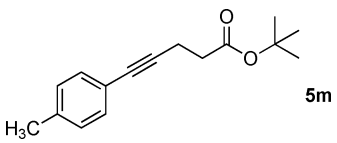
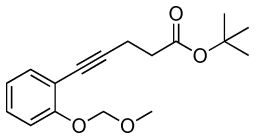
Entry	R_1	R_2	Time/h	Product **5**	Yield (%)[b]
1	Ph	OMe	24	 **5a**	76
2	*p*-Ph-C_6H_4	OMe	24	 **5b**	69
3	*p*-Me-C_6H_4	OMe	21	 **5c**	83
4	*p*-MeO-C_6H_4	OMe	18	 **5d**	80
5	*p*-Me_2N-C_6H_4	OMe	18	 **5e**	55
6	*o*-MeO-C_6H_4	OMe	23	 **5f**	71
7	*o*-$MeOCH_2O$-C_6H_4	OMe	28	 **5g**	52
8	*m*-H_2N-C_6H_4	OMe	24	 **5h**	41
9	6-Methoxynaphthalen-2-yl	OMe	20	 **5i**	85
10	*p*-Ethynyl-C_6H_4	OMe	45	 **5j**	58[c]

Table 4 *(Contd.)*



Entry	R_1	R_2	Time/h	Product **5**	Yield (%)[b]
11	Ph	*t*-OBu	24	 **5k**	74
12	*p*-Ph-C_6H_4	*t*-OBu	24	 **5l**	62
13	*p*-Me-C_6H_4	*t*-OBu	20	 **5m**	77
14	*o*-$MeOCH_2O$-C_6H_4	*t*-OBu	25	 **5n**	48

[a] All reactions were carried out in sealed tubes by using 0.5 mmol of terminal alkynes, 1 mmol of acrylate, 2.5 mol% of palladium catalysts and 10 mol% of **4a** in acetone at 60 °C. [b] Isolated yield. [c] 7% of bis-addition adduct was detected by GC–MS.

the triple bond to the palladium center followed by direct deprotonation of the coordinated terminal alkyne to palladium catalyst[22] generated the alkynyl palladium intermediate. Then, η^2-coordination of the C=C double bond to the palladium center followed by carbopalladation[10b] and substitution of Pd with hydrogen (either from the solvent or terminal alkyne), produced the γ,δ-ynone product with concomitant regeneration of the Pd catalyst.

3. Conclusion

In conclusion, the first palladium-catalyzed conjugate addition of terminal alkynes to the C=C double bond of unsaturated carbonyl compounds under mild conditions has been developed. The corresponding γ,δ-alkynyl ketones and alkynyl esters were obtained in high yields. The asymmetric additions, mechanism and synthetic applications of this efficient addition reaction are under investigation.

4. Experimental

General details

^{1}H NMR spectra were recorded on Varian 300 and 400 MHz spectrometers in $CDCl_3$ solution and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained at 75 MHz and referenced to the internal solvent signals (central peak is 77.00 ppm). MS data were obtained by Agilent 6890 N Network GC System/Agilent 5973 Mass Selective Detector. HRMS analyses were carried out at the Chemistry Department of McGill University. Flash column chromatography was performed over SORBENT silica gel 30–60 μm. Thin layer chromatography was performed using Sorbent Silica Gel 60 F254 TLC plates and visualized with ultraviolet light. THF was dried under argon over sodium benzophenone; 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl, **4a**) and 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium chloride (SIMes·HCl, **4b**) were purchased from Aldrich and were used as received without further purification. 3-Cyanomethyl-1-methyl-3*H*-imidazolium chloride (**4c**),[23] 1,3-bis(cyanomethyl)-3*H*-imidazolium chloride (**4d**)[23], **4e**[24] and **4f**[24] were prepared according to the published procedures. Terminal alkynes (4-ethynylphenyl)dimethylamine, 1-ethynyl-2-(methoxy)methoxybenzene, 3-(ethynyl)phenylamine, and 1-ethynyl-2-(methoxy)methoxybenzene were prepared according to literature procedures.[25] Other reagents were purchased from Aldrich.

Experimental procedure for the 1,4-addition of terminal alkynes to enones

A mixture of 0.05 mmol $Pd(OAc)_2$ (11 mg, 5 mol%) and 0. 20 mL of PMe_3 solution (0.20 mmol, 1.0 M PMe_3 dissolved in toluene, 20 mol%) was stirred at 60 °C in an oil bath for 10 min until all palladium acetate was dissolved. Then 1 mL of water or acetone was added, followed by adding a mixture of terminal alkyne

(1 mmol) and vinyl ketone (2–3 mmol). The reaction mixture was then stirred at 60 °C in an oil bath. After the consumption of terminal alkyne starting material, as shown by TLC, the reaction mixture was extracted with ethyl ether (3 × 10 mL), dried over anhydrous $MgSO_4$ then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane–ethyl acetate = 4 : 1) to give the pure product **3**.

7-Phenyl-6-heptyn-3-one (3a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.27 (m, 2H), 7.19–7.17 (m, 3H), 2.64–2.57 (m, 4H), 2.38 (q, J = 7.6 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 209.7, 131.7, 128.4, 127.9, 123.8, 88.9, 81.1, 41.4, 36.2, 14.3, 8.0; IR (neat) cm^{-1}: 3055, 2971, 2240, 1712, 1481, 1363; GC–MS (relative intensity): 186 (M^+, 17), 171 (6), 157 (100), 128 (33), 115 (28), 102 (9), 89 (8).

7-Cyclohexenyl-6-heptyn-3-one(3b). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.94 (bs, 1H), 2.60 (t, J = 7.2 Hz, 2H), 2.50 (t, J = 7.2 Hz, 2H), 2.40 (q, J = 7.2 Hz, 2H), 2.03–1.99 (m, 4H), 1.56–1.50 (m, 4H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.8, 133.9, 120.9, 85.8, 82.9, 41.6, 36.2, 29.6, 25.7, 22.5, 21.7, 14.2, 7.9; IR (neat) cm^{-1} 2932, 2207, 1705, 1409, 1356; GC–MS (relative intensity) 190 (M^+, 21), 175 (9), 161 (100), 133 (20), 105 (28), 91 (66).

6-Pentadecyn-3-one (3c). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (t, J = 7.6 Hz, 2H), 2.42 (t, J = 7.6 Hz, 2H), 2.37 (m, 2H), 2.06 (m, 2H), 1.35–1.19 (m, 12H), 1.02 (t, J = 7.6 Hz, 3H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.0, 81.0, 78.7, 41.9, 36.2, 32.1, 29.4, 29.3, 29.2, 29.1, 22.9, 18.9, 14.3, 13.7, 7.9; IR (neat) cm^{-1}: 2920, 2850, 1719, 1461, 1369, 1106; GC–MS (relative intensity): 223 (M^+ + 1, 11), 207 (2), 193 (14), 165 (7), 150 (29), 135 (16), 123 (100), 121 (42), 109 (46), 95 (61), 81 (59).

7-Trimethylsilyl-6-heptyn-3-one (3d). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.64 (t, J = 8.0 Hz, 2H), 2.47 (t, J = 8.0 Hz, 2H), 2.34 (q, J = 7.2 Hz, 2H), 1.06 (t, J = 7.2 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.7, 106.0, 85.3, 41.4, 36.3, 14.8, 8.0, 0.3; IR (neat) cm^{-1}2958, 2207, 1705, 1455; GC–MS (relative intensity): 183 (M^+ + 1, 25), 167 (100), 153 (42), 109 (60).

11-Chloro-6-undecyn-3-one (3e). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.49 (t, J = 6.4 Hz, 2H), 2.55 (t, J = 8.0 Hz, 2H), 2.39 (q, J = 7.2 Hz, 2H), 2.35 (t, J = 8.0 Hz, 2H), 2.11 (m, 2H), 1.82–1.55 (m, 4H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.9, 79.9, 79.6, 44.8, 41.7, 36.2, 31.7, 26.2, 18.2, 13.6, 7.9; IR (neat): cm^{-1} 2932, 2859, 2213, 1725, 1448; GC–MS (relative intensity): 203 (M^+ + 3, 2), 201 (M^+ + 1, 8), 187 (4), 185 (14), 171 (18), 165 (29), 131 (6), 129 (14), 123 (100), 109 (28), 81 (80).

6-Tridecyn-3-one (3f). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (t, J = 7.6 Hz, 2H), 2.42–2.36 (m, 4H), 2.07 (m, 2H), 1.40 (m, 2H), 1.20–1.31 (m, 6H), 1.03 (t, J = 7.6 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.0, 81.0, 78.7, 41.9, 36.2, 31.6, 29.2, 28.7, 22.8, 18.9, 14.2, 13.7, 7.8; IR (neat): cm^{-1} 2952, 2886, 2174, 1718; GC–MS (relative intensity): 195 (M^+ + 1, 33), 165 (22), 123 (100), 109 (44), 95 (56), 81 (61).

6,11-Heptadecadiyne-3,15-dione (3g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (t, J = 7.2 Hz, 4H), 2.45–2.37 (m, 8H), 2.25–2.17 (m, 4H), 1.65 (m, 2H), 1.04 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 210.0, 79.9, 79.4, 41.8, 36.2, 28.0, 18.0, 13.7, 7.9; IR (neat): cm^{-1} 2938, 2331, 1712, 1429, 1363; GC–MS (relative intensity): 259 (M^+ − 1, 8), 243 (7), 231 (25), 189 (81), 175 (41), 159 (43), 131 (100), 117 (39), 105 (30).

5-Tetradecyn-2-one (3h). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60 (t, J = 7.2 Hz, 2H), 2.37 (m, 2H), 2.13 (s, 3H), 2.07 (m, 2H), 1.40 (m, 2H), 1.19–1.24 (m, 10H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.4, 81.1, 78.6, 43.2, 32.1, 31.8, 29.4, 29.3, 29.2, 29.1, 22.9, 18.9, 14.3, 13.6; IR (neat): cm^{-1} 2919, 2332, 1712; GC–MS (relative intensity) 209 (M^+ + 1, 5), 164 (9), 150 (17), 135 (13), 121 (33), 109 (100), 95 (49), 81 (59).

6-Cyclohexenyl-5-hexyn-2-one (3i). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.96 (bs, 1H), 2.64 (t, J = 7.2 Hz, 2H), 2.50 (t, J = 7.2 Hz, 2H), 2.13 (s, 3H), 2.04–2.00 (m, 4H), 1.58–1.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.2, 134.0, 120.9, 85.7, 82.9, 43.0, 30.2, 29.6, 25.7, 22.5, 21.7, 14.1. IR (neat): cm^{-1} 2932, 2219, 1712, 1429, 1356, 1158; GC–MS (relative intensity): 176 (M^+, 38), 161 (100), 133 (32), 105 (49), 91 (95).

6-Trimethylsilyl-5-hexyn-2-one (3j). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (t, J = 8.0 Hz, 2H), 2.46 (t, J = 8.0 Hz, 2H), 2.16 (s, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.9, 105.9, 85.4, 42.7, 30.2, 14.7, 0.3; IR (neat): cm^{-1} 2952, 2919, 2167, 1719, 835; GC–MS (relative intensity): 168 (M^+, not seen), 153 (100), 125 (27), 109 (23), 83 (31).

5-Dodecyn-2-one (3k). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.59 (t, J = 7.6 Hz, 2H), 2.37 (m, 2H), 2.13 (s, 3H), 2.07 (m, 2H), 1.40 (m, 2H), 1.20–1.31 (m, 6H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.4, 81.1, 78.6, 43.2, 31.6, 30.1, 29.1, 28.7, 22.8, 18.9, 14.3, 13.6; IR (neat): cm^{-1} 2925, 2853, 2200, 1712, 1461, 1356; GC–MS (relative intensity): 181 (M^+ + 1, 3), 165 (3), 151 (7), 137 (13), 122 (30), 109 (100), 95 (46).

6-Phenyl-5-hexyn-2-one (3l). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.31 (m, 2H), 7.22–7.15 (m, 3H), 2.69 (dt, ^tJ = 8.0 Hz, ^dJ = 1.6 Hz, 2H), 2.60 (dt, ^tJ = 8.0 Hz, ^dJ = 1.6 Hz, 2H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.0, 131.7, 128.4, 128.0, 123.8, 88.8, 81.1, 42.6, 30.1, 14.2; IR (neat): cm^{-1} 3057, 2899, 2226, 1719, 1481, 1363; GC–MS (relative intensity): 172 (M^+, 28), 171 (30), 157 (75), 129 (68), 128 (83), 115 (64), 102 (26), 77 (25), 63 (22), 51 (22), 43 (100).

Experimental procedure for the 1,4-addition of terminal alkynes to acrylate esters

1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride (34 mg, 1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and *t*-BuOK(13.5 mg, 1.2 mmol) were added to a 10 mL Schlenk tube under N_2. Dry THF (1.5 mL) was injected and the mixture was stirred at rt for 2 h; then THF was slowly removed *in vacuo*, followed by the addition of acetone (2 mL), phenylacetylene (102 mg, 1 mmol) and methyl acrylate (172 mg, 2 mmol). The mixture was stirred at 60 °C until the reaction had reached completion (as determined by TLC analysis). The solvent was evaporated and the crude reaction mixture was then purified by flash chromatography on silica gel with EtOAc–hexane (1 : 10) as the eluant.

5-Phenylpent-4-ynoic acid methyl ester (5a). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.40 (m, 2H), 7.26–7.29 (m, 3H), 3.72(s, 3H), 2.73

(t, $J = 6.3$ Hz, 2H), 2.64 (t, $J = 6.39$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 166.3, 131.8, 128.4, 128.0, 123.7, 88.2, 81.4, 52.1, 33.7, 15.6; MS (70 eV) m/z: 188 (M^+), 173, 160, 145, 128 (100), 115; HRMS(EI) calc. for $C_{12}H_{12}O_2$ [M^+]: 188.08373, found: 188.08342.

5-(*p*-(Phenyl)phenyl)pent-4-ynoic acid methyl ester (5b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.59 (m, 5H), 7.41–7.46 (m, 4H), 3.73 (s, 3), 2.76 (t, $J = 7.8$ Hz, 2H), 2.65 (t, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 140.2, 132.6, 128.8, 127.7, 127.1, 127.0, 126.9, 123.2, 89.3, 80.6, 51.9, 33.3, 15.8; MS (70 eV) m/z: 264 (M^+,100), 249, 236, 205, 191, 178, 165, 148; HRMS(EI) calc. for $C_{18}H_{16}O_2$ [M^+]: 264.11503, found: 264.11524.

5-(*p*-Tolyl)pent-4-ynoic acid methyl ester (5c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, $J = 6.0$ Hz, 2H), 7.08 (d, $J = 6.0$ Hz, 2H), 3.72 (s, 3H), 2.71 (t, $J = 6.0$ Hz, 2H), 2.65 (t, $J = 6.3$ Hz, 2H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 138.0, 131.7, 129.2, 120.6, 87.4, 81.4, 51.9, 33.7, 21.7, 15.6; MS (70 eV) m/z: 202 (M^+), 187, 174, 159 (100),141, 129,115; HRMS(EI) calc. for $C_{13}H_{14}O_2$ [M^+]: 202.09938, found: 202.09916.

5-(*p*-Methoxyphenyl)pent-4-ynoic acid methyl ester (5d). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, $J = 6.6$ Hz, 2H), 6.80 (d, $J = 6.6$ Hz, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 2.73 (t, $J = 5.4$ Hz, 2H), 2.62 (t, $J = 5.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 159.1, 132.9, 115.6, 113.8, 86.3, 80.9, 55.2, 51.8, 33.5, 15.3; MS (70 eV) m/z: 218 (M^+), 203, 190, 175, 159, 144, 115 (100).

5-(4-(Dimethylamino)phenyl)pent-4-ynoic acid methyl ester (5e). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, $J = 8.4$ Hz, 2H), 6.59 (d, $J = 8.4$ Hz, 2H), 3.70 (s, 3H), 2.94 (s, 6H), 2.71 (t, $J = 7.5$ Hz, 2H), 2.61 (t, $J = 7.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 150.0, 132.8, 112.1, 110.8, 85.5, 82.0, 51.9, 40.5, 34.0, 15.7; MS (70 eV) m/z: 231 (M^+), 216, 202, 188, 158 (100); HRMS(EI) calc. for $C_{14}H_{17}O_2N$ [M^+]: 231.1293, found: 231.12564.

5-(2-Methoxyphenyl)pent-4-ynoic acid methyl ester (5f). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, $J = 7.8$ Hz, 1H), 7.25 (t, $J = 7.8$ Hz, 1H), 6.83–6.90 (m, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 2.78 (t, $J = 7.8$ Hz, 2H), 2.67 (t, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 160.3, 134.0, 129.4, 120.6, 112.8, 110.8, 92.3, 76.8 56.0, 52.0, 33.7, 15.9; MS (70 eV) m/z: 218 (M^+), 203, 190, 175, 159, 144, 115 (100); HRMS(EI) calc. for $C_{13}H_{14}O_3$ [M^+]: 218.09429, found: 218.09397.

5-(*o*-(Methoxymethoxy)phenyl)pent-4-ynoic acid methyl ester (5g). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, $J = 7.5$ Hz, 1H), 7.22 (t, $J = 6.6$ Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.94 (t, $J = 7.8$ Hz, 1H), 5.22 (s, 2H), 3.71 (s, 3H), 3.51 (s, 3H), 2.78 (t, $J = 7.5$ Hz, 2H), 2.65 (t, $J = 7.5$ Hz, 2H; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 166.3, 157,9, 133.9, 129.3, 122.1, 115.6, 96.8, 95.3, 92.2, 56.4, 52.0, 33.8, 15.9; MS (70 eV) m/z: 248 (M^+), 233, 216, 201, 175, 157 (100); HRMS(EI) calc. for $C_{14}H_{16}O_4$ [M^+]: 248.10486, found: 248.10457.

5-(3-Aminophenyl)pent-4-ynoic acid methyl ester (5h). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (t, $J = 7.8$ Hz, 1H), 6.79 (d, $J = 6.0$ Hz, 1H), 6.70 (s, 1H), 6.59 (d, $J = 8.1$ Hz, 1H), 3.69 (s, 3H), 3.65 (br, 2H), 2.71 (t, $J = 7.8$ Hz, 2H), 2.61 (t, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 146.4, 129.4, 124.4, 122.2, 118.2, 115.1, 87.5, 81.6, 52.0, 33.7, 15.7; MS (70 eV) m/z: 203 (M^+,100), 188, 174, 144, 130, 115; HRMS(EI) calc. for $C_{12}H_{13}O_2N$ [M^+]: 203.09463, found: 203.09422.

5-(6-Methoxynaphthalen-2-yl)pent-4-ynoic acid methyl ester (5i). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (s, 1H), 7.65 (t, $J = 8.1$ Hz, 2H), 7.40 (d, $J = 5.1$ Hz, 1H), 7.08–7.15 (m, 2H), 3.92 (s, 3H), 3.74 (s, 3H), 2.78 (t, $J = 7.8$ Hz, 2H), 2.67 (t, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 166.3, 158.3, 134.0, 131.3, 129.43,129.40, 128.7, 126.9, 119.5, 105.9, 87.7, 81.8, 55.5, 52.0, 33.8, 15.7; MS (70 eV) m/z: 268 (M^+,100), 253, 239, 209, 195, 165, 152; HRMS(EI) calc. for $C_{17}H_{16}O_3$ [M^+]: 268.10994, found: 268.11020.

5-(4-Ethynylphenyl)pent-4-ynoic acid methyl ester (5j). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, $J = 7.5$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 3.72 (s, 3H), 3.13 (s, 1H), 2.74 (t, $J = 6.8$ Hz, 2H), 2.65 (t, $J = 6.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 132.2, 131.7, 124.3, 121.7, 90.4, 83.5, 80.9, 78.8, 52.1, 33.5, 15.6; MS (70 eV) m/z: 212 (M^+),197, 184, 152, 139 (100); HRMS(EI) calc. for $C_{14}H_{12}O_2$ [M^+]: 212.08373, found: 212.08347.

5-Phenylpent-4-ynoic acid *tert*-butyl ester (5k). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.38 (m, 2H), 7.26–7.29 (m, 3H), 2.68 (t, $J = 6.9$ Hz, 2H), 2.53 (t, $J = 6.9$ Hz, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 131.8, 129.1, 128.4, 123.9, 88.5, 81.7, 35.1, 29.9, 28.3, 15.8; MS (70 eV) m/z: 230 (M^+),215, 174, 157, 146(100),128, 115; HRMS(EI) calc. for $C_{15}H_{18}O_2$ [M^+]: 230.13068, found: 230.13040.

5-(*p*-(Phenyl)phenyl)pent-4-ynoic acid *tert*-butyl ester (5l). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54–7.60 (m, 5H), 7.41–7.47 (m, 4H), 2.72 (t, $J = 7.8$ Hz, 2H), 2.56 (t, $J = 7.8$ Hz, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 140.7, 132.2, 129.0, 127.73, 127.67, 127.21, 127.12, 122.9, 89.3, 81.1, 35.1, 28.3, 15.1; MS (70 eV) m/z: 306 (M^+), 250 (100), 222, 191, 154; HRMS(EI) calc. for $C_{21}H_{22}O_2$ [M^+]: 306.16198, found: 306.16164.

5-(*p*-Tolyl)pent-4-ynoic acid *tert*-butyl ester (5m). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, $J = 6.0$ Hz, 2H), 7.07 (d, $J = 6.0$ Hz, 2H), 3.72 (s, 3H), 2.67 (t, $J = 6.3$ Hz, 2H), 2.54 (t, $J = 6.3$ Hz, 2H), 2.32 (s, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 137.9, 131.6, 129.7, 120.8, 87.7, 80.9, 35.1, 28.3, 21.6, 15.8; MS (70 eV) m/z: 244 (M^+), 229, 188, 171, 160, 145(100), 129, 115; HRMS(EI) calc. for $C_{16}H_{20}O_2$ [M^+]: 244.14633, found: 244.14599.

5-(2-(Methoxymethoxy)phenyl)pent-4-ynoic acid *tert*-butyl ester (5n). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, $J = 7.5$ Hz, 1H), 7.22 (t, $J = 6.6$ Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.94 (t, $J = 7.8$ Hz, 1H), 5.23 (s, 2H), 3.51 (s, 3H), 2.71 (t, $J = 7.5$ Hz, 2H), 2.57 (t, $J = 7.5$ Hz, 2H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.7, 166.3, 158.0, 133.9, 129.2, 122.1, 115.7, 95.3, 92.2, 81.4, 35.1, 28.3, 16.1; MS (70 eV) m/z: 290 (M^+), 234, 202 (100), 189, 174, 157; HRMS(EI) calc. for $C_{17}H_{22}O_4$ [M^+]: 290.15181, found: 290.15152.

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