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FULL PAPER

In situ generation of alkynylzinc and its subsequent cross-coupling reaction in a flow reactor

Mohanraj Kandasamy, [a] Yu- Hsuan Huang, [a] Balaji Ganesan,[a] Gopal Chandru Senadi[c] and Wei-Yu Lin*[a, b]

Abstract: A highly efficient and convenient Negishi cross-coupling reaction has been developed for the synthesis of unsymmetrical alkynes and enynes in a continuous-flow process. The reaction proceeds through an *in situ* generated alkynylzinc reagent by the reaction of lithium acetylide with zinc halide at room temperature followed by a cross-coupling with aryl or vinyl iodides. The notable features of this work over the conventional benchtop method are mild reaction conditions, good to excellent yields, broad functional group compatibility, short residence time (73 sec) and especially desilylation of TMS group with the residence time of only 10.5 sec.

Introduction

Alkynes are valuable building blocks because of their versatile use in natural products, pharmaceuticals, and material sciences.[1] In this context, the alkynylation of aryl halides by Sonogashira reaction[2] has gained significant attention for the synthesis of functionalized alkynes.[3] However, the production of these alkynes on an industrial scale using the conventional method still remains a potential challenge.[4]

Continuous-flow mediated transition-metal catalysis has gained much attention in recent years as an alternative for benchtop chemistry because of the key benefits like enhanced mass and heat transfer, reduced reaction volumes, improved sample and reagents mixing.[5] Thus, the development of new synthetic methods under flow technology that could deliver the desired compounds in an environmentally benign manner on a larger scale with ease of operation is an essential area of research in the scientific community.

The pioneering work developed by Yoshida and co-workers on organolithium flash-chemistry has created a bench mark for the researchers to do synthetic transformations from *in situ* generated organolithium in the flow-process.[6] For instances, Buchwald and Yoshida independently developed the continuous-flow synthesis of biaryls enabled by multistep lithiation / borylation / Suzuki–Miyaura cross-coupling sequence.[7] Ryu et al developed the synthesis of metalloproteinase inhibitor having a high space time yield (STY) of 20.4 g/Lh,[8] by Sonogashira cross-coupling reaction. Similarly, James et al reported the drug-like 3-aminoindolizine derivatives with STY of 1.6 g/Lh[9] from milligram to gram scale.[8-10] Despite these significant advancements, some of the methods require copper as co-catalyst that may lead to the undesired homocoupled product (Glaser coupling), stoichiometric bases, high temperatures and long reaction times. To overcome the drawbacks, modified catalytic conditions has been reported in the literature,[4]but, those reagents are expensive or need to be prepared in the laboratories which may hamper the practicality in the large scale.

On the other hand, the formation of $C(sp^2)$-$C(sp)$ and $C(sp^3)$-$C(sp^3)$ bonds via the Negishi reaction using palladium- or nickel-catalyzed coupling of organozinc compounds with various halides[11] have been extensively studied because of its mild conditions and low toxicity of zinc salts.[12] However, the high reactivity and sensitivity of organozinc reagents to air/moisture makes it difficult to prepare under cryogenic conditions.[13] To date, only a few methodologies have been reported for the *in situ* generation of organozinc and its subsequent use in cross-coupling or electrophilic reactions in flow chemistry.[14] Knochel and co-workers demonstrated the *in situ* zincations of functionalized arenes and heteroarenes using $(Cy_2N)_2Zn{\cdot}2LiCl$ in a continuous flow system followed by a batch process.[14a] Buchwald and co-workers[15] reported the synthesis of aryloxirane derivatives via an *in situ* generated organozinc reagents followed by Negishi cross-coupling. Recently, Alcázar and co-workers reported the photoinduced[16] Pd or Ni catalyzed Negishi cross-couplings in a flow reactor using the zinc metal. Nevertheless, applying these methods for the preparation of organozinc by a lithium base still demands a low temperature conditions nor further transformation in a batch reactor and excessive amount of starting materials. By considering the above facts and our continuing interest in lithium acetylide chemistry[17] Herein, we designed an alternative approach for the synthesis of internal alkynes and enynes via Negishi cross-coupling between an *in situ* generated alkynylzinc reagents and aryl or vinyl iodides in a simple and robust flow system using commercial catalyst and ligand that can enable the gram scale synthesis.

Results and Discussion

A flow setup has been made using three T-shaped micromixers (M1, M2 and M3), three tubing reactors [(R1 (800 μm), R2 (1000 μm) and R3 (1000 μm), and a heating unit as presented in Scheme 1. We began our preliminary investigation by choosing phenylacetylene **1a** and iodobenzene **2a** as the model substrate for Negishi cross-coupling reaction. The active lithium phenylacetylide was generated according to our previous reported literature [17] using **1a** with *n*-butyllithium at mixer M1 at

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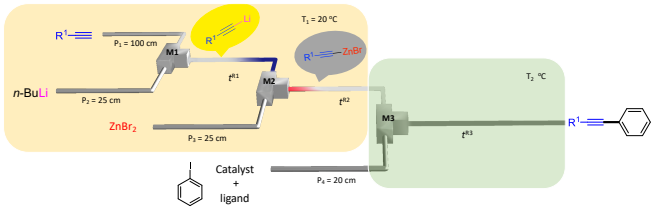
20 °C with the residence time (t^{R1}). Subsequent reaction of the lithium phenylacetylide with $ZnBr_2$ at M2 provided the corresponding alkynylzinc in reactor R2 with the residence time



Scheme 1. Optimization of Negishi cross coupling on flow reactor (M1, M2 and M3: 1000 μm of inner diameter) and three microtubing reactors (R1(1000 μm), R2(1000 μm) and R3(1000 μm)

Table 1. Optimization study [a]

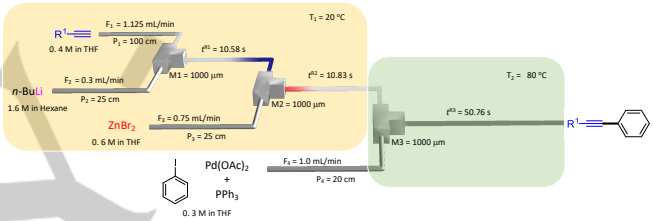
Entry	R^1	Catalyst (x, mol%)	$ZnBr_2$ (equiv.)	T_2 (°C)	Yield (%)[b]
1	Ph	$Pd(OAc)_2$(5.0)	2.0	20	24
2	Ph	$Pd(OAc)_2$(5.0)	2.0	50	48
3	Ph	$Pd(OAc)_2$(5.0)	2.0	60	63
4	Ph	$Pd(OAc)_2$(5.0)	2.0	70	77
5	Ph	$Pd(OAc)_2$(5.0)	2.0	80	99 (92)[c]
6	Ph	$Pd(OAc)_2$(5.0)	2.0[d]	80	68
7	Ph	$Pd(OAc)_2$(5.0)	2.0[e]	80	77
8	Ph	$Pd(OAc)_2$(2.5)	2.0	80	71[f]
9	Ph	$Pd(OAc)_2$(5.0)	1.5	80	96
10	Ph	$Pd(OAc)_2$(5.0)	1.25	80	89
11	Ph	$Pd(OAc)_2$(5.0)	1.0	80	81
12	Bu	$Pd(OAc)_2$(5.0)	2.0	50	41
13	Bu	$Pd(OAc)_2$(5.0)	2.0	80	83
14	Bu	$Pd(OAc)_2$(1.0)	1.5	80	99[g,h]
15	Bu	$Pd(OAc)_2$(0.5)	1.5	80	87[g,i]
16	Bu	$Ni(OAc)_2$(5.0)	2.0	80	N.R
17	Bu	$NiCl_2$(5.0)	2.0	80	N.R
18	Bu	$Co(OAc)_2$(5.0)	2.0	80	N.R
19	Bu	$Co(acac)_2$(5.0)	2.0	80	N.R

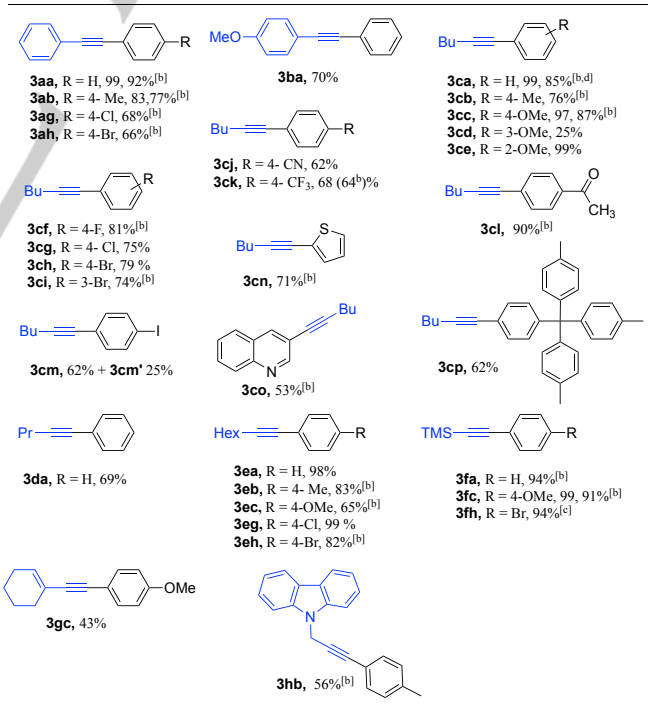
[a] Reaction conditions: Flow condition-A (alkyne, $ZnBr_2$ = 2.0 equiv, *n*-BuLi =2.16 equiv), residence time 20.34 s, catalyst (x mol %), PPh_3 (10 mol %) were maintained unless otherwise noted. [b] GC conversion yield. [c] Yields in the brackets corresponds to the isolated yields. [d] $ZnCl_2$. [e] ZnI_2. [f] PPh_3 = 5 mol %. [g] Flow condition-B (alkyne, $ZnBr_2$ =1.5 equiv, *n*-BuLi =1.6 equiv), residence time 72.17 s. [h] PPh_3 = 2 mol %. [i] PPh_3 = 1 mol %. phenylacetylene: **1a**, hexyne **1c**. Inner diameters of the tube (R1) 800 μm. N.R. = No Reaction.

(t^{R2}) at 20 °C. The *in situ* generated alkynylzinc reagent was reacted with iodobenzene **2a** in the presence of 5 mol% $Pd(OAc)_2$ and 10 mol % of PPh_3 at M3 to afford the desired cross-coupling product **3aa** in reactor R3 with the residence time of (t^{R3}). Further optimization studies were done by varying the residence (t^{R2}) in R2, cross-coupling temperature and the flow parameters.

At room temperature, the conversion of the desired product **3aa** by GC was found to be 24% without any traces of Glaser coupled product (Table 1, entry 1). When the temperature (T2) was gradually increased from 50 °C to 80 °C (Table 1, entries 2-5), the conversion of **3aa** was improved to 99% with an isolated yield of 92% (Table 1, entry 5). Changing to other zinc halides like $ZnCl_2$ and ZnI_2 ended up in low yields (Table 1, entries 6-7). Reducing the catalyst/ligand loading to 2.5 mol% and 5 mol% also decreased the yield of **3aa** (Table 1, entry 8). Equivalents studies of $ZnBr_2$ (Table 1, entries 9-11) revealed that the maximum yield of **3aa** can be achieved using 2.0 equiv. of $ZnBr_2$ (Table 1, entry 5).

Scheme 2. Substrate scope for alkyne derivatives. [a]





[a] Flow condition: (Alkyne, $ZnBr_2$ =1.5 equiv, *n*-BuLi =1.6 equiv), residence time = 72.17 s, GC conversion yield. [b] Isolated Yield. [c] 3.0 mmol scale reaction (10 min). [d] 8.4 mmol scale reaction (28 min).

Based on the skeletal importance of alkyl substituted alkynes in natural product synthesis,[18] we next examined hexyne **1c** as a

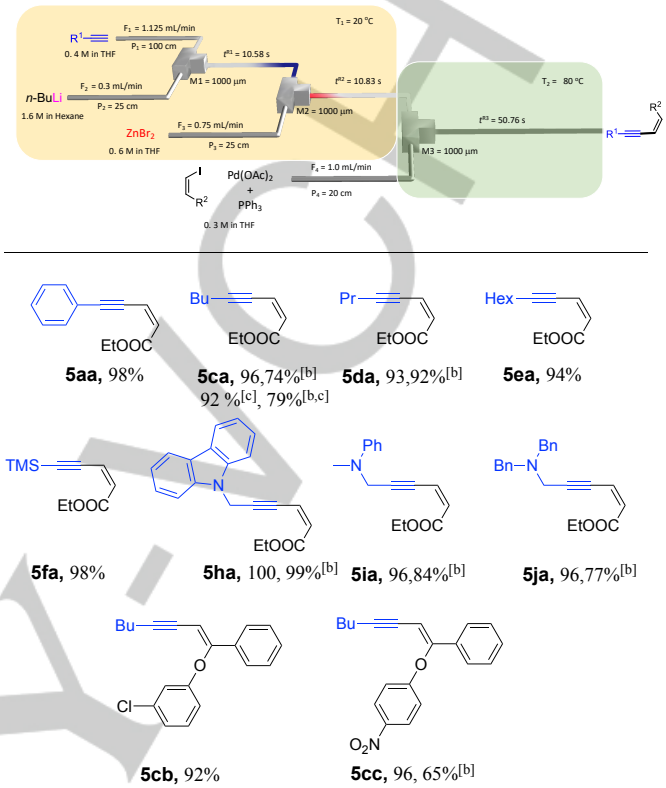
coupling partner with **2a** using 5 mol% of Pd catalyst, 10 mol% of PPh_3 and 2.0 equiv. of $ZnBr_2$ at 50 °C (T2). Unfortunately, the conversion of the expected compound was less (Table 1, entry 12), whereas at an elevated temperature the conversion of the product was drastically improved to 83% (Table 1, entry 13). To our surprise, quantitative conversion was obtained by decreasing the catalytic quantity to 1.0 mol% and increasing the residence time in order to increase the mixing efficiency, and the quantitative yield was almost observed (Table 1, entry 14). When the catalytic amount was reduced to 0.5 mol%, yield also dropped to 87%. The reaction was attempted with other catalysts, such as $Ni(OAc)_2$, $NiCl_2$, $Co(OAc)_2$ and $Co(acac)_2$, but failed to provide the desired product (Table 1, entries 16-19). Eventually, applying the same strategy to the Sonogashira cross-coupling resulted in heterogeneous solution and thereby leading to channel clogging. The probable reason for this observation could arise from the use of CuI catalyst.

With the optimized reaction conditions in hand for the synthesis of internal alkynes, the scope of the reaction was examined with different terminal alkynes and aryl iodides as presented in Scheme 2. The electron-donating substituents such as *p*-Me (**2b**), *p*-Cl (**2g**) and *p*-Br (**2h**) iodobenzenes reacted with **1a** to afford the desired products (**3ab**-**3ah**) in good to excellent yields. Similarly, *p*-Methoxyphenylacetylene (**1b**) also underwent smooth conversion with **2a** to give **3ba** in 70% yield. The reaction of electron-donating aryl iodides (**2b-e**) with aliphatic alkyne such as 1-hexyne (**1c**) gave the required internal alkyne scaffolds **3cb**-**3ce** in excellent yields except in the case of *m*-iodoanisole (**2d**). The practicality of the reaction was demonstrated on an 8.4 mmol scale to beget compound **3ca** within 28 minutes over 90% conversion and an isolated yield of 85% with a space time yield of 27.1 g/Lh (See Table S1). Whereas, the space time yield range is only 2.1 [19] to 6.2 [20] g/Lh in a commercial batch reactor for the synthesis alkynyl derivatives, suggesting that the flow system enables a 12.3 fold increase in throughput for a given reactor volume.

Electron-deficient groups such as -CN, and $-CF_3$ as well as halo- functional groups (**2f**-**2k**) were tolerated well to give the corresponding products **3cf**-**3ck**. Interestingly, when the di-iodo compound **2m** was employed, the desired mono- alkynylated **3cm** was obtained as a major product with a 62% yield, and di-alkynylated **3cm'** was observed with a 25% yield, which illustrated the precise control of reagent over the batch conditions.[21] Notably, acetyl functional groups, hetero aryl iodides and bulky substituents (**2l**, **2n**-**2p**) were proceeded smoothly and the cross-coupling products **3cl**, **3cn**-**3cp** were obtained in moderate to excellent yields. In addition, 1-pentyne (**1d**), 1-octyne (**1e**), TMS acetylene (**1f**), cyclic enyne (**1g**) and *N*-propargyl carbazole (**1h**) were efficiently coupled with various aryl iodides under these reaction conditions to afford the desired alkynes in moderate to excellent yields (49-99%).

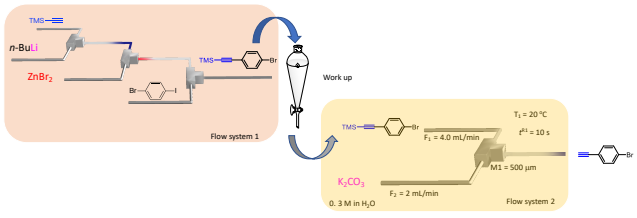
With the successful outcome of alkyne derivatives, we applied this methodology for the synthesis of various enynes, which are versatile building blocks in organic synthesis.[22] The reaction of **1a** with **4a** (ethyl *cis*-3-iodoacrylate) was performed under the standard conditions as presented in Scheme 3. Interestingly, the desired 1,3-enyne (Z)-**5aa** was obtained in 98% yield with full retention of stereochemistry. Further expansion of the scope with

Scheme 3. Substrate scope for enyne derivatives. [a]



[a] Flow condition: (Acetylene, $ZnBr_2$ =1.5 equiv, *n*-BuLi =1.6 equiv), residence time = 72.17 s, GC conversion. [b] Isolated Yield. [c] 3.0 mmol scale reaction (10 min): 427 mg (79 %) of desired product.

different alkyl acetylenes such as 1-hexyne (**1c**), 1-pentyne (**1d**), 1-octyne (**1e**), TMS (**1f**), *N*-propargyl carbazole (**1h**), *N*-methyl-*N*-propargylaniline (**1i**) and *N,N*-dibenzylpropargylamine (**1j**) with **4a** gave the corresponding products in good yields. The practicality of the reaction was demonstrated on a 3.0 mmol scale under the standard condition for 10 min and obtained 427 mg of **5ca** (79%). Next, we also investigated the feasibility of the reaction by changing the vinyl iodide derivatives such as (Z)-2-iodo-vinyl phenyl vinyl ether (3-Cl, **4b**) and (4-NO_2, **4c**) with **1b**; both were tolerated in this process, affording the corresponding (Z)-**5ab** and (Z)-**5ac** in good yield.



Scheme 4. Two flow microreactor systems for the stepwise Negishi cross-coupling and deprotection.

To show a broader application of this process, the deprotection of TMS protected alkynes was investigated by reacting alkyne **3fa** with K_2CO_3 as base using one T-shaped micromixer (M1), one tubing reactor [R1(800 μm)] at room temperature. The reaction underwent complete desilylation with a residence time of 10.5 s (See SI, Table S2, entry 1-3). With this success, two flow systems (Scheme 4 and see SI) were used to demonstrate the stepwise Negishi cross-coupling of TMS-protected alkyne and the deprotection of the corresponding TMS-alkyne. In this regards, compound **3fh** was synthesized in a 3 mmol scale using the first flow system and the resulting solution was worked up, re-dissolved in THF/MeOH to react with an aqueous solution of K_2CO_3 in the second flow system. This two-step reaction worked well to get the desired terminal alkyne **3fh'** in 92% yield (496 mg, 2.75 mmol).

Conclusions

In summary, we have successfully developed a C(sp)-C(sp^2) Negishi cross-coupling reaction in a continuous flow system using three T-shaped micromixers and three microtubular reactors. The reaction proceeds via an *in situ* generated alkynylzinc reagent from lithium acetylide and zinc bromide followed by a Pd-catalyzed cross-coupling with aryl iodides to form internal alkynes in good to excellent yields. The key advantages of this flow protocol are low catalyst/ligand, excellent conversion, short reaction time, highly controllable, broad substrate scope and desilylation of alkynes. Moreover, the synthesis of 1,3-enynes were achieved with retention of configuration using vinyl halides as the coupling partners.

Experimental Section

General information

Dry THF was freshly distilled under a nitrogen atmosphere over sodium and used for the reaction. All the compounds were commercially available and used without further purification unless otherwise noted. Compounds **1b**, **1g**, **1h**, **1i, 1j, 2o, 2p, 4a, 4b** and **4c** were prepared according to previous literature report.[23] *n*-BuLi was purchased from Rockwood Lithium company and $ZnBr_2$ was purchased from Alfa Aesar. $ZnBr_2$ solution (0.60 M in THF) was prepared by drying $ZnBr_2$ (8.10 g, 36 mmol) in a Schlenk-flask under flame dried for 5 minutes. After cooling to 25 °C, dry THF (60 mL) was added and stirred until the salts were dissolved. Micro mixture 500 μm was purchased from Sanko Seiki company, stainless tube and peek were purchased from Idex health & science. Harvard syringe pump model-11 elite were used for the reaction.

General procedure for synthesis of aromatic internal alkynes and 1,3-enynes: A microreactor system consist of three T-shaped micromixers (**M1**, **M2** and **M3**), three tubing reactors (**R1**, **R2** and **R3**) and two precooling units **P1** (inner diameter = 800 μm, length L = 50 cm), **P2** (inner diameter = 1000 μm, length L= 50 cm), and one preheating unit **P3** (inner diameter = 1000 μm, length L = 342 cm)) were used. A solution of terminal alkyne (0.40 M in THF) (flow rate: 1.125 mL/min) and a solution of *n*-BuLi (1.60 M in Hexane) (flow rate: 0.3 mL/min) were introduced into **M1** (Φ = 1.0 mm) by syringe pumps. The resulting solution was passed through **R1** (Φ = 0.8 mm, L = 50 cm, 251 μL) and was mixed with a solution of a $ZnBr_2$ (0.60 M in THF) (flow rate: 0.75 mL/min) at **M2** (Φ = 1.0 mm). The resulting solution was passed through **R2** (Φ = 1.0 mm, L = 50 cm, 392 μL) and introduced **M3** (Φ = 1.0 mm). A solution of aryl iodide or vinyl iodide, palladium acetate (1 mol %) and triphenyl phosphine (2 mol %) and introduced in **M3.** The resulting final solution passed through **R3** (Φ = 1.0 mm, L = 350 cm, 2749 μL) at 80 °C. After a steady state was reached (after 1 min), the final product solution was collected for 60 seconds in vial containing saturated solution of NH_4Cl.The reaction mixture was analysed by GC. The crude mixture was diluted with EA and water, organic phase was separated and the aqueous phase extracted twice with EA (2 × 20 mL). The combined organic layer was dried over $MgSO_4$, and purified by column chromatography and product was analysed by ^1H, ^{13}C NMR, IR and mass spectrometer.

1,2-diphenylethyne (3aa)[24]**:** 49 mg, 92% yield. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.57-7.55 (m, 2H), 7.36-7.35 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.7, 128.4, 128.3, 123.3, 89.5.

1-methyl-4-(phenylethynyl)benzene (3ab)[24]**:** 44 mg, 77% yield. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.56-7.54 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.38-7.34 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 138.4, 132.5, 131.5, 129.1, 128.3, 128.0, 123.4, 120.2, 89.5, 88.7, 21.5.

1-chloro-4-(phenylethynyl)benzene (3ag)[24]**:** 43 mg, 68% yield. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.45-7.43 (m, 2H), 7.39-7.37 (m, 2H), 7.29-7.23 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 134.3, 132.8, 131.6, 128.7, 128.5, 128.4, 123.0, 121.8, 90.3, 88.32.

1-bromo-4-(phenylethynyl)benzene (3ah)[24]**:** 51 mg, 66% yield. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.46-7.43 (m, 2H), 7.41-7.39 (m, 2H), 7.32-7.26 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 133.1, 131.7, 133.6, 128.5, 128.4, 122.9, 122.5, 122.3, 90.5, 88.3.

1-methoxy-4-(phenylethynyl)benzene (3ba)[25]**:** ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.52-7.50 (m, 2H), 7.47 (d, *J* = 8.8Hz, 2H), 7.35-7.30 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.7, 133.1, 131.5, 128.4, 128.0, 123.6, 115.4, 114.1, 89.4, 88.1, 55.3.

hex-1-yn-1-ylbenzene (3ca)[26]**:** 42 mg, 89% yield. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.40-7.37 (m, 2H), 7.27-7.24 (m, 3H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.60-1.55 (m, 2H), 1.50-1.44 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 131.6, 128.2, 127.5, 124.1, 90.5, 80.6, 30.9, 22.1, 19.1, 13.7.

1-(hex-1-yn-1-yl)-4-methylbenzene (3cb)[24]**:**39 mg, 76% yield. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.28 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 2.40 (t, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 1.60-1.58 (m, 2H), 1.50-1.43 (m, 2H), 0.94 (t, *J*= 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 137.4, 131.4, 128.9, 120.9, 89.6, 80.5, 30.9, 22.0, 21.4, 19.1, 13.6.

1-(hex-1-yn-1-yl)-4-methoxybenzene (3cc)[26]**:** 49 mg, 87% yield. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.25 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 3.71 (s, 3H), 2.31 (t, *J* = 6.8 Hz, 2H), 1.52-1.46 (m, 2H), 1.42-1.36 (m, 2H), 0.86 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.0, 132.9, 116.3, 113.8, 88.8, 80.2, 55.3, 31.0, 22.1, 19.1, 13.7.

1-(hex-1-yn-1-yl)-3-methoxybenzene (3cd)[27]**:** ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.09 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.85-6.84 (m, 1H), 6.73 (m, 1H), 3.69 (s, 3H), 2.32 (t, *J* = 6.8 Hz, 2H), 1.52-1.37 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.3, 129.3, 125.1, 124.1, 116.4, 114.1, 90.3, 80.5, 55.2, 30.9, 22.1, 19.1, 13.7.

1-(hex-1-yn-1-yl)-2-methoxybenzene (3ce)[27]**:** ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.29 (d, *J* = 7.2, 1.2 Hz, 1H), 7.17-7.12 (m, 1H), 6.81-6.75 (m, 2H), 3.78 (s, 3H), 2.39 (t, *J* = 6.8 Hz, 2H), 1.57-1.49 (m, 2H), 1.46-1.38 (m,

2H), 0.86 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.8, 133.7, 128.9, 120.4, 113.2, 110.5, 94.7, 76.6, 55.8, 31.0, 22.1, 19.5, 13.7.

1-fluoro-4-(hex-1-yn-1-yl) benzene (3cf)[26]**:** 43 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.30-7.27 (m, 2H), 6.91-6.87 (m, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.52-1.37 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.0 (d, *J* = 246 Hz), 133.3 (d, *J* = 7.7 Hz), 120.2, 115.4 (d, *J* = 21.9 Hz), 90.0, 79.5, 30.8, 22.1, 19.0, 13.7.

1-chloro-4-(hex-1-yn-1-yl) benzene (3cg)[27]**:** ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.30 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 1.61-1.54 (m, 2H), 1.50-1.41 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 133.3, 132.7, 128.4, 122.6, 91.5, 79.5, 30.7, 22.0, 19.1, 13.6.

1-bromo-4-(hex-1-yn-1-yl)benzene (3ch)[27]**:** ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.38 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 2.37 (t, *J* = 6.8 Hz, 2H), 1.58-1.53 (m, 2H), 1.48-1.43 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 133.1, 131.4, 123.1, 121.6, 91.8, 79.6, 30.7, 22.1, 19.2, 13.7.

1-bromo-3-(hex-1-yn-1-yl)benzene (3ci) : 53 mg, 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (t, *J* = 1.6 Hz, 1H), 7.41-7.35 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.62-1.41 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 134.4, 130.6, 130.1, 129.2, 126.2, 12.0, 92.1, 79.2, 30.7, 22.0, 19.1, 13.7.

4-(hex-1-yn-1-yl)benzonitrile (3cj)[28]**:** ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.48 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 2.35 (t, *J* = 6.8 Hz, 2H), 1.54-1.48 (m, 2H), 1.42-1.37(m, 2H), 0.87 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 132.1, 131.9, 129.2, 118.7, 110.8, 95.7, 79.5, 30.5, 22.1, 19.2, 13.6.

1-(hex-1-yn-1-yl)-4-(trifluoromethyl)benzene (3ck)[29]**:** 43 mg, 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.45 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 2.35 (t, *J* = 6.8 Hz, 2H), 1.54-1.49 (m, 2H), 1.45-1.37 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 131.8, 129.3 (d, *J* = 33 Hz), 128.0, 125.4, 125.1 (d, *J* = 4 Hz), 93.3, 79.5, 30.6, 22.1, 19.2, 13.7.

1-(4-(hex-1-yn-1-yl)phenyl)ethan-1-one (3cl)[30]**:** 54 mg, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.83 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 2.54 (s, 3H), 2.39 (t, *J* = 7.2 Hz, 2H), 1.60-1.52 (m, 2H), 1.49-1.41 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 197.4, 135.6, 131.7, 129.2, 128.2, 94.4, 80.1, 30.7, 26.6, 22.1, 19.2, 13.7.

1-(hex-1-yn-1-yl)-4-iodobenzene (3cm): ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.60 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 2.39 (t, *J* = 7.0 Hz, 2H), 1.54-1.62 (m, 2H), 1.40-1.50 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 137.3, 133.1, 123.6, 93.0, 92.0, 79.7, 30.7, 22.0, 19.1, 13.6.

1,4-di(hex-1-yn-1-yl)benzene (3cm')[31]**:** ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.22 (s, 4H), 2.33 (t, *J* = 6.8 Hz, 4H), 1.53-1.47 (m, 4H), 1.44-1.36 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 131.4, 123.2, 91.9, 80.4, 30.8, 22.1, 19.2, 13.7.

2-(hex-1-yn-1-yl)thiophene (3cn)[32]**:** 35 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.07 (d, *J* = 5.6 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 6.84 (dd, *J* = 4.8, 4.0 Hz, 1H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.54-1.47 (m, 2H), 1.43-1.35 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 130.9, 126.8, 125.9, 124.3, 94.5, 73.7, 30.7, 22.1, 19.4, 13.7.

3-(hex-1-yn-1-yl)quinoline (3co)[33]**:** ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.85 (d, J = 1.6 Hz, 1H), 8.13 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.66 (td, J = 7.8, 1.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 2.46 (t, J = 7.1 Hz, 2H), 1.65-1.44 (m, 4H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 152.6, 146.5, 138.0, 129.6, 129.3, 127.4, 127.1, 118.3, 94.1, 77.9, 30.7, 22.1, 19.3, 13.7.

4,4',4''-((4-(hex-1-yn-1-yl)phenyl)methanetriyl)tris(methylbenzene) (3cp):

Brown solid. m.p: 146-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.30 (d, *J* = 8.0 Hz, 2H), 7.19-7.07 (m, 2H), 2.43 (t, *J*= 6.8 Hz, 2H), 2.35 (s, 9H), 1.63-1.59 (m, 2H), 1.54-1.48 (m, 2H), 0.98 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 146.8, 143.9, 135.3, 132.9, 130.5, 128.1, 127.3, 121.3, 90.2, 80.4, 63.8, 30.8, 21.9, 20.9, 19.1, 13.6. HRMS (EI) calcd for $C_{34}H_{34}$[M]+442.2661, found for 442.2668.

pent-1-yn-1-ylbenzene (3da)[32]**:** ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.33-7.31 (m, 2H), 7.21-7.18 (m, 3H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.60-1.51 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 131.6, 128.2, 127.5, 124.1, 90.3, 80.7, 22.3, 21.4, 13.6.

oct-1-yn-1-ylbenzene (3ea)[34]**:** ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.39-7.36 (m, 2H), 7.27-7.23 (m, 3H), 2.38 (t, *J* = 7.6 Hz, 2H), 1.62-1.54 (m, 2H), 1.47-1.40 (m, 2H), 1.34-1.28 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 131.6, 128.2, 127.5, 124.1, 90.5, 80.6, 31.4, 28.8, 28.7, 22.6, 19.5, 14.1.

1-methyl-4-(oct-1-yn-1-yl)benzene (3eb) [34]**:** 53 mg, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.29 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 2.39 (t, *J* = 6.8 Hz, 2H), 2.33 (s, 3H), 1.62-1.55 (m, 2H), 1.49-1.41 (m, 4H), 1.35-1.30 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 137. 4, 131.4, 129.0, 121.1, 89.7, 80.6, 31.5, 28.9, 28.7, 22.6, 21.4, 19.5, 14.1.

1-methoxy-4-(oct-1-yn-1-yl)benzene (3ec)[35]**:** 45 mg, 65% yield ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.25 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 3.72 (s, 3H), 2.30 (t, *J* = 7.2 Hz, 2H), 1.55-1.48 (m, 2H), 1.40-1.35 (m, 2H), 1.28-1.22 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.0, 132.9, 116.3, 113.8, 88.9, 80.2, 55.3, 31.4, 28.9, 28.7, 22.6, 19.5, 14.1.

1-(4-chlorophenyl)oct-1-yn-3-one (3eg)[34]**:** ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.29 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 1.61-1.54 (m, 2H), 1.46-1.38 (m, 2H), 1.34-1.23 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 133.4, 132.8, 128.5, 122.6, 91.6, 79.5, 31.4, 29.7, 28.7, 22.6, 19.4, 14.1.

1-(4-chlorophenyl)oct-1-yn-3-one (3eh)[36]**:** 69 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.33 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.17 (dt, *J* = 9.2, 2.0 Hz, 2H), 2.30 (t, *J* = 6.8 Hz, 2H), 1.55- 1.48 (m, 2H), 1.40-1.18 (m, 6H), 0.83 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 133.0, 131.4, 123.1, 121.5, 91.8, 79.6, 31.4, 29.7, 28.6, 22.6, 19.5, 14.1.

trimethyl(phenylethynyl)silane (3fa)[37]**:** 49 mg, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.48-7.46 (m, 2H), 7.32-7.29 (m, 3H), 0.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 131.9, 128.5, 128.2, 123.1, 105.1, 94.1, -0.04.

((4-methoxyphenyl)ethynyl)trimethylsilane (3fc)[37]**:** 56 mg, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.33 (d, *J* = 9.2 Hz, 2H), 6.74 (d, *J* = 9.2 Hz, 2H), 3.72 (s, 3H), 0.16 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.8, 133.6, 115.3, 113.9, 105.3, 92.5, 55.3, 0.2.

((4-bromophenyl)ethynyl)trimethylsilane (3fh)[37]**:** 714 mg, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.41(d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 0.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 133.4, 131.5, 122.8, 122.1, 103.9, 95.6, -0.03.

1-(cyclohex-1-en-1-ylethynyl)-4-methoxybenzene (3gc)[25]**:** ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.28 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H),

6.10-6.08 (m, 1H), 3.72 (s, 3H), 2.16-2.04 (m, 4H), 1.63-1.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 134.5, 132.9, 120.9, 115.9, 113.9, 89.9, 86.7, 55.3, 29.4, 25.8, 22.4, 21.6.

9-(3-(p-tolyl)prop-2-yn-1-yl)-9H-carbazole (3hb): Pale yellow solid. 50 mg, 56% yield. m.p: 114-116 ^{o}C.^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.51 (td, J = 7.7, 1.2 Hz, 2H), 7.30-7.24 (m, 4H), 7.05 (d, J = 7.6 Hz, 2H), 5.25 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 138.6, 131.7, 129.0, 125.9, 123.3, 120.4, 119.4, 119.3, 109.0, 84.2, 82.6, 33.3, 21.5. IR (KBr) ν 1698, 1598, 1508, 1484, 1454, 1327, 1259, 1207, 1150 cm^{-1}. HRMS (APCI) calcd for $C_{22}H_{17}N$ $[M+H]^+$: 296.1439, found 296.1436.

ethyl (Z)-5-phenylpent-2-en-4-ynoate (5aa)[38]**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.50 (m, 2H), 7.33-7.30 (m, 3H), 6.33 (d, J = 11.4 Hz, 1H), 6.11 (d, J = 11.4 Hz, 1H), 4.24 (q, J = 6.8 Hz, 1H), 1.30 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 132.1, 129.2, 128.4, 128.3, 122.9, 122.7, 101.2, 86.4, 60.5, 14.3. IR (neat) ν 2982, 2204, 1721, 1609, 1490, 1443, 1412, 1180 cm^{-1}.

ethyl (Z)-non-2-en-4-ynoate (5ca)[39]**:** 427 mg, 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (dt, J = 11.3, 2.5 Hz, 1H), 5.99 (d, J = 11.2 Hz, 1H), 4.20 (q, J = 6.8 Hz, 2H), 2.43 (td, J = 7.1, 2.3 Hz, 2H), 1.62-1.37 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 127.4, 124.0, 104.2, 77.7, 60.3, 30.5, 22.0, 22.0, 19.8, 14.3, 13.6.

ethyl (Z)-oct-2-en-4-ynoate (5da): Colourless liquid. 46 mg, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (dt, J = 11.2, 2.4 Hz, 1H), 5.79 (d, J = 11.6 Hz, 1H), 3.98 (q, J = 7.2 Hz, 2H), 2.19 (td, J = 6.8, 2.4 Hz, 2H), 1.39 (sex, J = 6.8 Hz, 2H), 1.07 (t, J = 7.6 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 127.4, 123.9, 104.0, 77.8, 60.2, 22.0, 21.9, 14.2, 13.5. IR (neat) ν 2965, 2935, 2905, 2873, 2208, 1726, 1608 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{23}NO_2$ $[M+Na]^+$: 189.0627, found 189.0623.

ethyl (Z)-6-oxoundec-2-en-4-ynoate (5ea)[38]**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (dt, J = 11.2, 2.4 Hz, 1H), 5.79 (d, J = 11.2 Hz, 1H), 4.18 (q, J = 6.8 Hz, 2H), 2.41 (td, J = 7.2, 2.4 Hz, 2H), 1.55 (q, J = 7.2 Hz, 2H), 1.42-1.35 (m, 2H), 1.31-1.23 (m, 7H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 127.4, 124.0, 104.3, 77.7, 60.3, 31.3, 28.7, 28.4, 22.5, 20.1, 14.3, 14.1.

ethyl (Z)-5-(trimethylsilyl)pent-2-en-4-ynoate (5fa)[40]**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (d, J =11.2 Hz, 1H), 6.04 (d, J =11.2 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 2H), 0.20 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 129.5, 122.4, 108.1, 100.7, 60.6, 14.3, -0.2.

ethyl (Z)-6-(9H-carbazol-9-yl)hex-2-en-4-ynoate (5ha): Red oily liquid. 86 mg, 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 3.6 Hz, 4H), 7.17-7.10 (m, 2H), 5.92 (d, J = 12.0 Hz, 1H), 5.87 (dt, J = 12.0, 2.0 Hz, 1H), 5.10 (s, 2H), 3.98 (q, J = 6.8 Hz, 2H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 139.9, 129.5, 126.0, 123.3, 122.2, 120.5, 119.6, 108.9, 95.6, 80.5, 60.6, 33.4, 14.2. IR (neat) ν 3053, 2982, 1722, 1613, 1486, 1456, 1330, 1189 cm^{-1}. HRMS (APCI) calcd for $C_{22}H_{23}NO_2$ $[M+H]^+$: 303.1338, found 304.1335.

ethyl (Z)-6-(methyl(phenyl)amino)hex-2-en-4-ynoate (5ia): Dark red oily liquid. 61 mg, 84% yield. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.82-6.78 (m,1H), 6.09 (dt, J = 11.4, 1.6 Hz, 1H), 6.04 (d, J = 11.4 Hz, 1H), 4.28 (d, J = 1.6 Hz, 2H), 4.17 (q, J = 6.8 Hz, 2H), 3.01 (s, 3H), 1.26 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 149.1, 129.2, 128.7, 122.8, 118.3, 114.3, 98.1, 80.8, 60.4, 43.6, 38.8, 14.3. IR (neat) ν 2981, 1723, 1600, 1505, 1184 cm^{-1}.

ethyl (Z)-6-(dibenzylamino)hex-2-en-4-ynoate (5ja): Yellow oily liquid. 77 mg, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.41 (m, 4H), 7.33-7.29 (m, 4H), 7.26-7.22 (m, 2H), 6.22 (dt, J = 11.6, 2.0 Hz, 1H), 6.11 (d, J = 11.6 Hz, 1H), 4.24 (q, J = 7.6 Hz, 2H), 3.75 (s, 3H), 3.48 (d, J = 1.6 Hz, 2H), 1.30 (t, J = 7. 2Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 138.9, 129.1, 128.4, 128.3, 127.1, 123.0, 98.2, 82.6, 60.4, 57.6, 42.5, 14.3. IR (neat) ν 3029, 1723, 1608, 1495, 1454, 1410 cm^{-1}. HRMS (APCI) calcd for $C_{22}H_{23}NO_2$ $[M+H]^+$: 334.1807, found 334.1800.

(Z)-1-chloro-3-((1-phenyloct-1-en-3-yn-1-yl)oxy)benzene (5cb): Yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.48 (m, 2H), 7.34-7.30 (m, 3H), 7.15 (t, J = 8.0 Hz, 1H), 7.04-7.02 (m, 1H), 6.95 (d, J = 1.2 Hz, 1H), 6.90-6.87 (m, 1H), 5.92 (q, J = 2.0, 4.4 Hz, 1H), 2.24 (t, J = 7.2 Hz, 2H), 1.30-1.21 (m, 4H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 157.8, 134.8, 134.0, 130.2, 129.3, 128.8, 125.2, 122.2, 116.7, 114.4, 99.5, 97.5, 75.4, 30.6, 21.8, 19.5, 13.6. IR (neat) ν 3065, 2958, 2871, 2218, 1737, 1590, 1519, 1473, 1343, 1239,1165 cm^{-1}. HRMS (APCI) calcd for $C_{20}H_{19}ClO$ $[M+H]^+$: 311.1203, found 311.1206.

(Z)-1-nitro-4-((1-phenyloct-1-en-3-yn-1-yl)oxy)benzene(5cc): Light yellow liquid. 63 mg, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 9.2 Hz, 2H), 7.49-7.46 (m, 2H), 7.33-7.32 (m, 3H), 7.07 (d, J = 9.2 Hz, 2H), 6.00 (t, J = 2.4 Hz, 1H), 2.20 (td, J = 2.0, 6.8 Hz, 2H), 1.30-1.17 (m, 4H), 0.76 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 157.1, 142.4, 133.2, 129.7, 128.9, 125.9, 124.9, 116.1, 100.4, 98.2, 75.0, 30.5, 21.7, 19.4, 13.5. IR (neat) ν 3081, 2958, 2871, 2217, 1737, 1591, 1518, 1447, 1343, 1238, 1165, 1111 cm^{-1}. HRMS (APCI) calcd for $C_{20}H_{19}NO_3$ $[M]^+$: 321.1365, found 321.1363.

1-bromo-4-ethynylbenzene (3fh'): 496 mg, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 2.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.6, 131.6, 123.2, 121.1, 82.6, 78.4.

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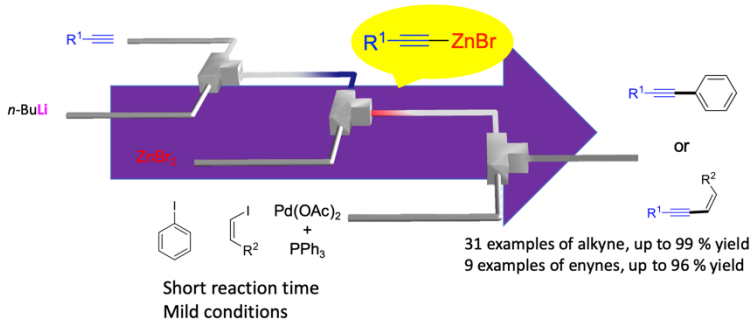

Key Topic*

*Mohanraj Kandasamy, Yu- Hsuan Huang, Balaji Ganesan Gopal Chandru Senadi and Wei-Yu Lin**

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Title

***In situ* generation of alkynylzinc and its subsequent cross-coupling reaction in a flow reactor**

* Mild and highly efficient method for synthesis of internal alkynes or 1,3-enynes was achieved in a continuous flow system through the generation of alkynylzinc reagent from lithium acetylide and zinc bromide followed by a Pd-catalyzed cross-coupling with aryl or vinyl iodides.