The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc **2021**, part viii, 0-0

Cu-Catalyzed solvent-free, pot-economic synthesis of 1,3-dynes from 1,1-dibromoalkenes in the presence of DBU•H_2O

Shiva Krishna Moodapelly,[a] Yerramsetti Nanaji,[b] Gangavaram V. M. Sharma,[a] Kanaparthy Suneeel,[c] and Venkata Ramana Doddi[a,e]*

[a]*Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, Telangana-500007, India*

[b]*Texas Tech University, Ophthalmology Department, Lubbock General, 3601 4th Street, Lubbock, TX 79430, USA*

[c]*Department of Chemistry, University of Delhi, Delhi-110007, India*

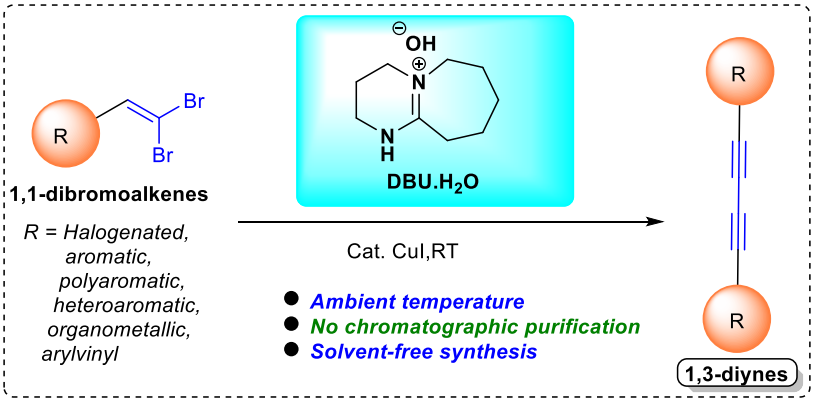
[d]*Department of Chemistry, Central University of Karnataka, Kadaganchi, Kalaburagi District, Karnataka-585367, India*

Email: venkatardoddi@cuk.ac.in

Received 01-10-2021 **Accepted** 04-01-2021 **Published on line** 04-25-2021

Abstract

An efficient synthesis of 1,3-diynes directly from 1,1-dibromoalkenes has been achieved by utilizing hydrated 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU.H_2O) as a sole reagent and a catalyst CuI. In general, 1,3-diynes were synthesized from corresponding terminal alkynes, which in turn were obtained from 1,1-dibromoalkenes. The DBU.H_2O allowed the synthesis of 1,3-diynes not only in a pot-efficient manner but also under solvent-free conditions at ambient temperature. A plausible mechanism is proposed via 1-bromoalkynes intermediate instead of terminal alkynes.

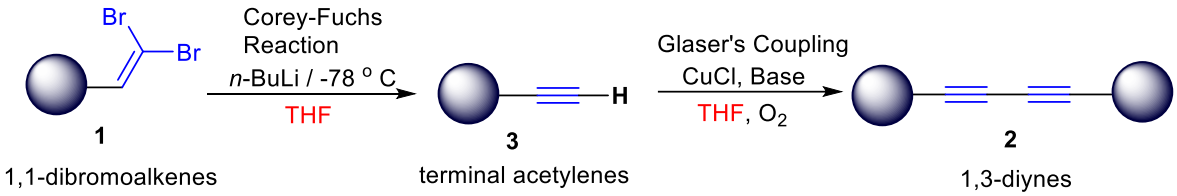


Keywords: 1,1-dibromoalkenes, Solvent-free, Bicyclic amidine, 1,3-Diynes, DBU, Pot-economic

Introduction

Symmetric and unsymmetric 1,3-Diynes are versatile structural motifs present in many natural products.[1-4] Some important natural products containing a 1,3-diynes system are Norcapillene,[5] Neocapillene,[6] Dihydro-PHT,[7] Atractylodin,[8] Enetriyne,[9] Triynol, Triynol acetate,[10] Repandiol,[11] Montiporyne,[12,13] and Cicutoxin.[14,15] In particular, aryl conjugated 1,3-diynes and their derivatives exhibit a broad spectrum of biological activity,[16-18] which has made them essential synthons in the synthesis of naturally occurring biologically active complex molecules and pharmaceuticals.[19-23] Besides, they have found numerous applications in supramolecular materials and electronic applications due to their unique electronic and thermal stability properties.[24-28] They are also useful in the preparation of π-conjugated acetylenic oligomers and anticancer drug delivery micelles.[29-31]

In view of their pharmacology and material science applications, the synthesis of aryl 1,3-diynes has received much attention in the recent development of organic chemistry.[32-36] Many methods have been developed to synthesize aryl 1,3-diynes **2** involving oxidative homocoupling of terminal alkynes **3**, first reported by Glaser in 1869 (Scheme 1).[37] In 1956, Eglinton and Galbraith developed base mediated $Cu(OAc)_2$ catalyzed oxidative coupling of terminal alkynes **3**.[38] Later, Hay et al. reported ligand assisted CuCl catalyzed synthesis of aryl 1,3-diynes.[39] Starting material terminal acetylenes **3** in these reactions, in turn, are usually synthesized from 1,1-dibromoalkenes **1** using Corey-Fuchs reaction.[40] Recently, a few domino synthetic protocols are also available to access aryl 1,3-diynes **2** directly from 1,1-dibromoalkenes **1**. Wang et al. synthesized 1,3-diynes **2** starting from 1,1-dibromoalkenes **1** using both palladium and copper catalysts in one pot.[41] Rao et al. developed copper-free conditions, used only palladium catalyst.[42] Satyanarayana et al. synthesized symmetrical 1,3-diynes **2** using Cu-catalyzed homocoupling of 1,1-dibromoalkenes **1**.[43] Few metal-catalyzed syntheses of symmetrical 1,3-diynes **2** from 1,1-dibromoalkenes **1** also have been reported in the recent literature.[44-49]



Scheme 1. Synthesis of 1,3-diynes in two steps.

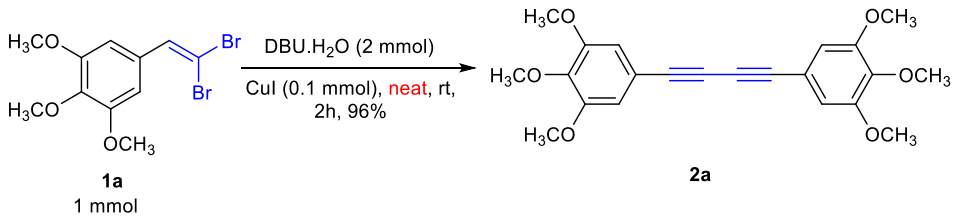
However, all these methods result in unsatisfactory yields or costly reagents, or harsh reaction conditions. Therefore, the development of new, improved methods for synthesizing aryl 1,3-diynes has gained much importance to current research. In our ongoing research on the development of improved methods for the synthesis of terminal acetylenes **2**,[50-53] we first explored nucleophilic reagent bicyclic imidine DBU in our laboratory to synthesize terminal acetylenes from 1,1-dibromoalkenes.[51] Very recently, we have revealed that 1-bromoalkynes can be synthesized using two molar equivalents of non-nucleophilic reagent DBU.H_2O under solvent-free conditions at room temperature.[53] However, Chunxiang et al. reported the ligand-free copper-catalyzed synthesis of symmetrical diynes from 1,1-dibromoalkenes using DBU in DMSO as a solvent.[54] One of DMSO's main disadvantages in organic reactions is its removal after a reaction, and the substance dissolved in DMSO is quickly absorbed by the skin.[55] Herein, we demonstrated the domino synthesis of aryl 1,3-diynes from 1,1-dibromoalkenes using DBU and its hydrate DBU.H_2O under solvent-free conditions at room

temperature. This effort resulted in an eco-friendly and environmentally benign solvent-free synthesis of 1,3-diynes from 1,1-dibromoalkenes.

Results and Discussion

We commenced our investigation by examining the reaction of 5-(2,2-dibromovinyl)-1,2,3-trimethoxybenzene **1a** employing DBU as base and CuI as catalyst under solvent-free conditions. We have observed very low yields of product **2a** (Entry 1, Table 1); this result is attributed to the observed exothermic reaction in the absence of solvent. Our attention then turned to milder base hydrated DBU (DBU.H_2O) as a base instead of a strong base dry DBU, which was previously employed for the controlled solvent-free synthesis of 1-bromoalkynes from 1,1-dibromoalkenes. Subsequently, 1,1-dibromolakene 1a was subjected to reaction with DBU.H_2O (2 mmol) and a catalytic amount of CuI (0.1 mmol) under solvent-free conditions at room temperature. To our delight, the reaction proceeded smoothly within 2 hours without forming any by-products and produced the only product **2a** with a 96 % yield (Entry 2, Table 1). Inspired by this result, we screened this organic transformation to test the efficiency of mild base DBU.H_2O and catalyst CuI with respect to time. When the reaction time was decreased to 1 hour and conducted the reaction by utilizing DBU.H_2O (2 mmol) and a catalytic amount of CuI (0.1 mmol), we observed a reduced yield of product **2a** (Entry 3, Table 1). Next, it was proved when this reaction was tested by reducing the Cu catalyst loading to 0.05 mmol gave further diminishing the yield of product **2a** (Entry 4, Table 1). Additionally, we also conducted the reaction by reducing the loading of DBU.H_2O to 1 mmol, gave the low yield of product **2a** (Entry 5, Table 1). Finally, the optimization reaction conditions revealed that using 2 mmol of DBU.H_2O and a catalytic amount of CuI (0.1 mmol) under the solvent-free condition at room temperature is a suitable condition to afford the desired product **2a** in excellent yields (Entry 2, Table 1).

Table 1. Optimization of the reaction conditions[a]



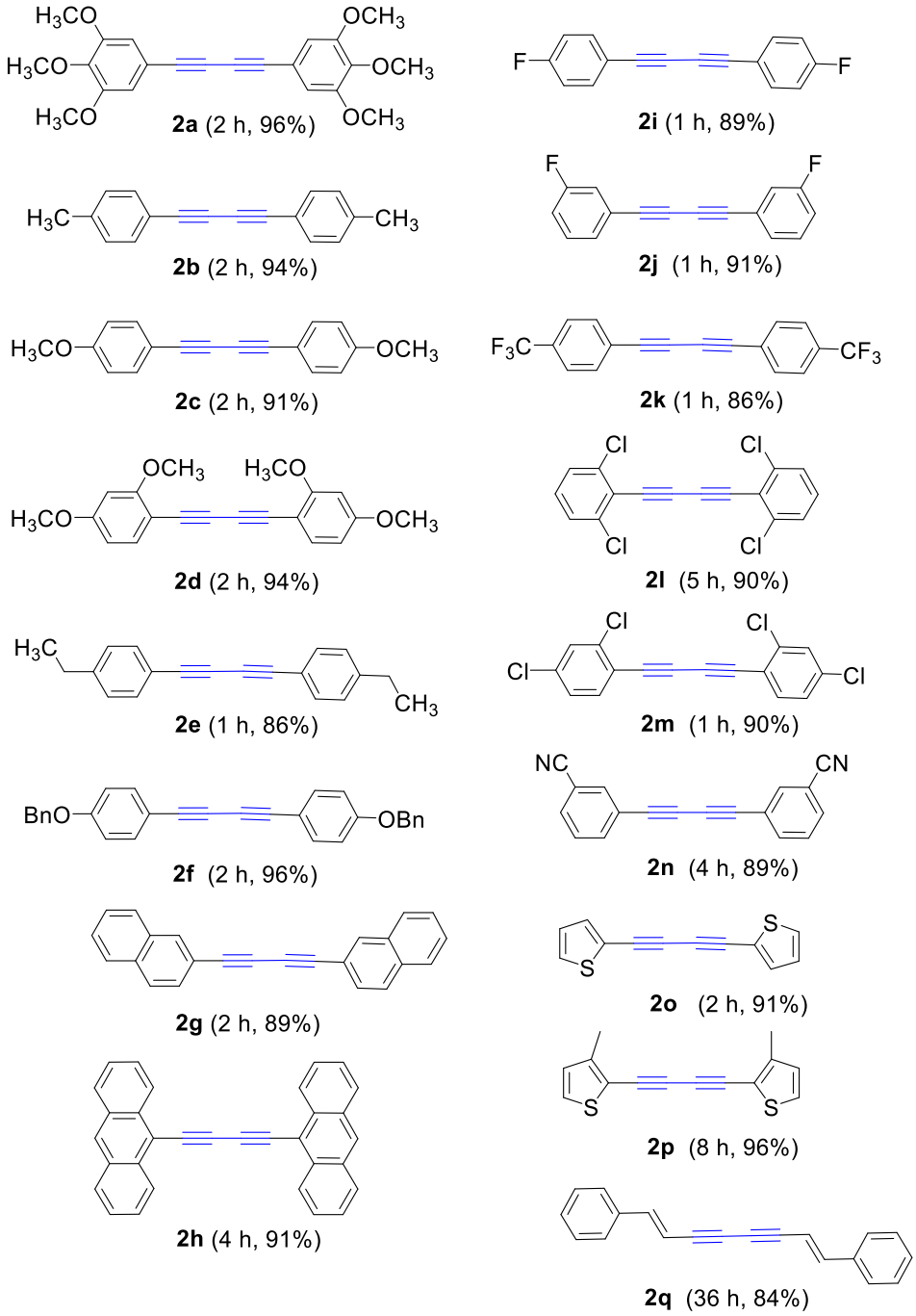
1a
1 mmol

2a

Entry	Base (equiv.)	CuI (equiv.)	Time [h]	Yield[b]
1	Dry DBU (2)	0.1	2	12
2	**DBU.H_2O (2)**	**0.1**	**2**	**96**
3	DBU.H_2O (2)	0.1	1	87
4	DBU.H_2O (2)	0.05	2	71
5	DBU.H_2O (1)	0.1	2	56

[a] Reaction conditions: all reactions were carried out with 1a and CuI in the presence of DBU.H_2O at RT;
[b] Yields of the isolated product.

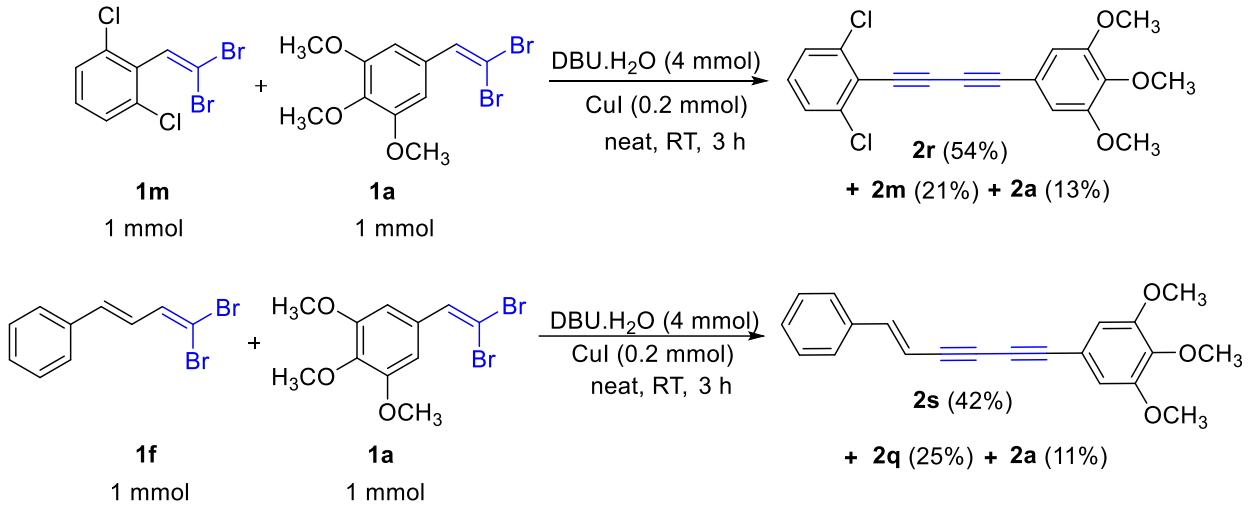
Table 2. Substrate Scope **2**[a]



[a]Reaction conditions: all reactions were carried out at room temperature, **1a** (2 mmol) and CuI (0.1 mmol) in the presence of DBU.H_2O; Yields are for isolated products.

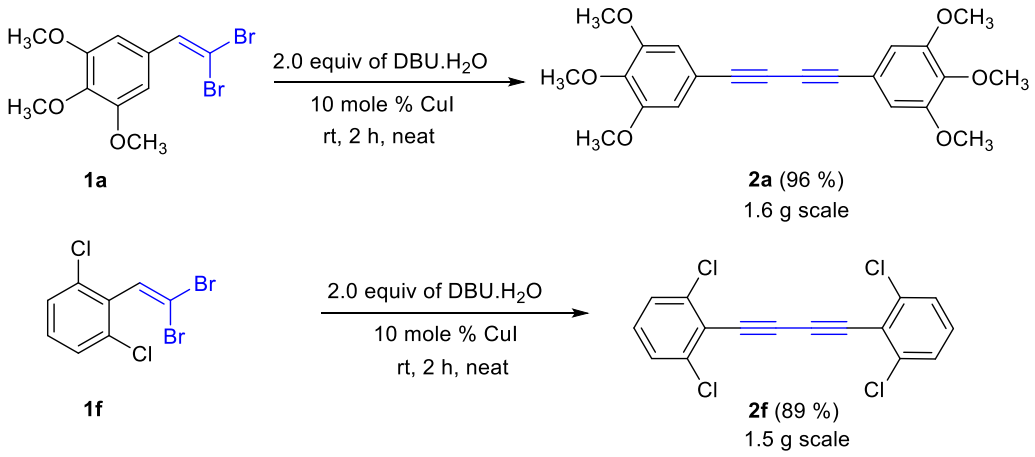
In order to evaluate the substrate scope, various 1,1-dibromoalkenes **1a-q** were treated with DBU.H_2O and a catalytic amount of CuI using developed solvent-free conditions. All the reactions proceeded smoothly afforded the desired products **2a-q** in good to excellent yields (Table 2). The reactions with substituted 1,1-dibromoalkenes **1a-f** having electron-donating group gave the desired products **2a-f** in very good yields. Importantly, substrates bearing polyaromatic groups like naphthalene **1g** and anthracene **1h** also compatible with the conditions and gave the products **2g** and **2h** in 89% and 91% yields. The substrates containing electron-withdrawing groups substitution **1i-n** were also well-tolerated and provided the corresponding

products **2i-n** in good yields. Heteroaromatic substituted substrates **1o**, and **1p** underwent this reaction smoothly and gave the desired products **2o** and **2p** in 91% and 96% yields, respectively. Significantly, the substrate, which has aryl-vinyl substitution **1q**, afforded the desired product **2q** in 84% yield without affecting the reaction rate. Further, we examined this organic transformation's scope to synthesize unsymmetrical diynes **2r** and **2s** (Scheme 2). Experiments were conducted by utilizing substrates containing two different substituted dibromides like **1m** (1 mmol) and **1a** (1 mmol) reacted to give the corresponding unsymmetrical diyne **2r** in 54% yield. Due to the formation of some amounts of the corresponding homo coupled by-products 21% of 2m & 13% of **2a** along with unsymmetrical diyne 54 % of **2r**, chromatography was necessitated to separate the products. A similar reaction was carried out with substrates like enyne **1f** with **1a**, giving unsymmetrical enediyne product **2s** in 42% and homocoupled products **2f** and **2a** in 25% and 11%, respectively.



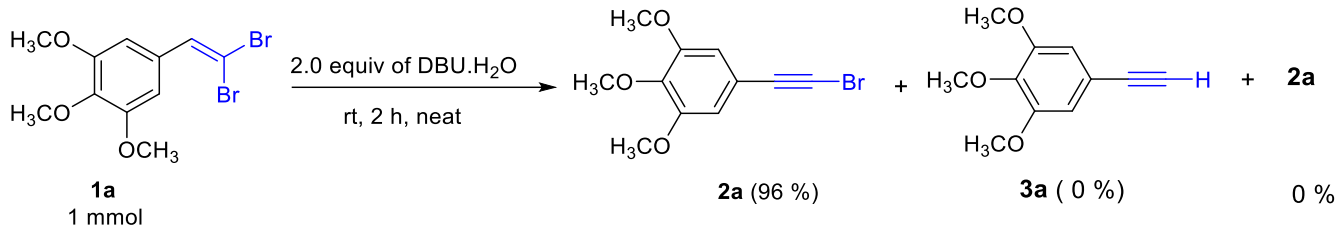
Scheme 2. Synthesis of unsymmetrical diynes **2r** & **2s**.

On the other hand, we also conducted experiments on a gram scale to confirm the present protocol's efficiency and robustness. Treatment of **1a** and **1f** under the optimized conditions gave the desired products **2a** and **2f** in excellent yields (Scheme 3).



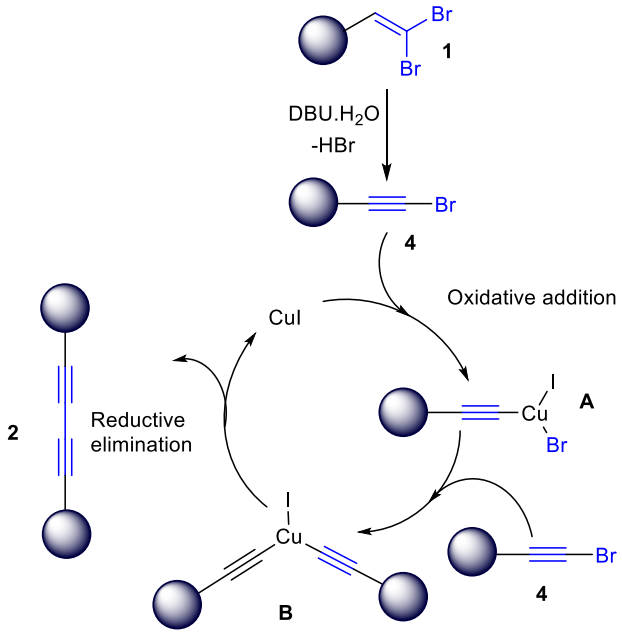
Scheme 3. Gram scale synthesis of representative 1,3-diynes **2a** & **2f**.

It is well known from literature[37] that 1,3-diynes can be straightforwardly obtained by treating terminal alkynes **3** using the Glaser-Hay coupling reaction. Further, based on the above results, our interest turned on to confirm the possible intermediate terminal alkyne or 1-bromoakyne involved in the reaction (Scheme 4). The developed solvent-free and pot-economic reaction was performed with 1,1-bromoalkyne **1a** and base DBU.H_2O alone without using copper catalyst at ambient temperature. Interestingly, only corresponding 1-bromoalkyne **4a** formed in good yield and there was neither 1,3-diyne **2a** not expected terminal alkyne **3a** formed. These results indicated that the reaction proceeds via alkynyl bromide **2a** intermediate and not through terminal alkyne intermediate **3a**.



Scheme 4. Mechanistic investigations.

Based on the above experimental results and previous reports, a plausible catalytic mechanism can be proposed for this organic transformation (Scheme 5). We assume this reaction proceeds through the formation of 1-bromoalkyne **4** instead of terminal acetylene **3**. Initially, the DBU.H_2O acts as a base and eliminates HBr from dibromoalkene **1** would form bromoalkyne **4**, which would further convert to complex **A** with Cu(I). Then, complex **A** added by another molecule of bromoalkyne **4** to generate dialkyne iodo complex **B** with Cu(III) and subsequently undergo reductive elimination to produce 1,3-diyne **2** and release the copper catalyst Cu(I).



Scheme 5. A plausible reaction mechanism through 1-bromoalkyne intermediate.

Conclusions

In conclusion, we have developed a green and straightforward synthetic method to access 1,3-diynes at ambient temperature. The products can be obtained in pure form without chromatography purification technique leads to save time and solvents. The usage of hydrated DBU as the sole reagent can be evidenced as a better reagent than dry DBU.[56] This method avoids the costly palladium catalysts, harsh reaction conditions, and usage of phosphine reagents/ligands. This method proves to be an efficient synthetic approach than the existing methods in the literature.

Experimental Section

General. All reactions were carried out in oven-dried reaction flasks under nitrogen atmosphere, and dry solvents and reagents were transferred by oven-dried syringes to ambient temperature. TLC was performed on Merck silica gel aluminium sheets, and solvents were removed under reduced pressure. Columns were packed as slurry of silica gel in hexane and ethyl acetate solvent mixture. The elution was assisted by applying pressure with an air pump. ^{13}C NMR spectra were recorded on 101 MHz spectrometers. ^{1}H NMR spectra were recorded on 400 and 500 MHz spectrometers in appropriate solvents using TMS as an internal standard. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet. All reactions were performed at room temperature. Reagents were obtained from Aldrich, Alfa Aesar, and TCI used without further purification. All compounds are characterized by ^{1}H and ^{13}C NMR. Additionally, unknown compounds are characterized by HRMS analysis. All known compounds data are in consistent with the given literature report.

Typical procedure for the preparation of 1,3-Diynes. Synthesis of 1,4-bis(3,4,5-trimethoxyphenyl)buta-1,3-diyne (2a). To a 5 mL screw cap vial containing dibromoalkene **1a** (0.34 g, 0.1 mmol) and CuI (19 mg, 0.2 mmol), freshly prepared DBU.H_2O (0.334 mL, 2.0 mmol) was added dropwise over a period of 1 min against the walls of vial at ambient temperature (25-30 °C) and stirred for 2h. The reaction mixture was quenched by the addition of water (10 mL) and extracted with EtOAc (2 x 10 mL). Organic layers were washed with 5N aqueous HCl (10 mL), water (10 mL), dried (Na_2SO_4), and evaporated to afford pure 2,5-dihydrofuran derivative **2a** (0.36 g, 96%) as colorless solid. Similar experimental procedure was adopted for the synthesis of all the 1,3-diyne derivatives **2b-q**.

1,4-Bis(3,4,5-trimethoxyphenyl)buta-1,3-diyne (2a). Mp 187–189 °C, Yield 96%. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ 6.76 (4H, s, C_6H_2), 3.87 (6H, s, OCH_3), 3.86 (12H, s, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 153.14, 139.92, 116.61, 109.72, 81.72, 73.06, 61.04, 56.21. MS (ESI, 70 eV) *m*/*z* 383 ($M+H^+$, 100%).

1,4-Di-*p*-tolylbuta-1,3-diyne (2b). Mp 184–187 °C, Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ 7.44 – 7.40 (d, 4H), 7.14 (d, *J* 7.9 Hz, 4H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 139.52, 132.41, 129.24, 118.82, 81.57, 73.48, 21.66. MS (ESI, 70 eV) *m*/*z* 231 ($M+H^+$, 100 %).

1,4-Bis(4-methoxyphenyl)buta-1,3-diyne (2c). Mp 130–133 °C, Yield 91%. ^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 7.48 – 7.44 (d, 4H), 6.87 – 6.84 (d, 4H), 3.82 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 160.26, 134.07, 114.16, 113.97, 81.27, 72.99, 55.37. MS (ESI, 70 eV) *m*/*z* 263 ($M+H^+$,100%).

1,4-Bis(2,4-dimethoxyphenyl)buta-1,3-diyne (2d). Mp 186-189 °C, Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ 7.40 (m, 2H), 6.46 – 6.42 (m, 4H), 3.87 (s, 6H), 3.82 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 162.61,

161.71, 153.28, 105.09, 104.08, 98.40, 78.33, 76.72, 55.86, 55.51. HRMS (EI) *m*/*z* calculated for $C_{20}H_{18}O_4$ $(M)^+$ 322.121, found 322.121.

1,4-Bis(4-ethylphenyl)buta-1,3-diyne (2e). Mp 115–118 °C, Yield 86%. ^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 7.39 (d, *J* 8.1 Hz, 4H), 7.13 (d, *J* 8.0 Hz, 4H), 2.64 (q, *J* 7.6 Hz, 4H), 0.91 (t, *J* 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 145.37, 132.52, 127.94, 119.25, 84.51, 73.74, 31.06, 22.20. HRMS (EI) *m*/*z* calculated for $C_{20}H_{18}$ $(M)^+$ 258.141, found 258.141.

1,4-Bis(4-(benzyloxy)phenyl)buta-1,3-diyne (2f). Mp 184–186 °C, Yield 96%.; ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ 7.43 – 7.31 (m, 14H), 6.92 – 6.88 (m, 4H), 5.06 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 159.08, 136.52, 133.50, 128.63, 128.16, 127.50, 115.11, 114.90, 79.93, 70.07, 48.02. HRMS (EI) *m*/*z* calculated for $C_{30}H_{22}O_2$ $(M)^+$ 414.162, found 414.162.

1,4-Di(naphthalen-2-yl)buta-1,3-diyne (2g). Mp 172–174 °C, Yield 89%.;^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 8.43 (d, *J* 8.2 Hz,2H,), 7.89 (dd, *J* 8.2, 4.5 Hz,4H), 7.83 (dd, *J* 7.2, 1.0 Hz, 2H), 7.65 – 7.62 (m, 2H), 7.56 (ddd, *J* 8.1, 6.9, 1.2 Hz, 2H), 7.47 (dd, *J* 8.2, 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 133.95, 133.16, 132.10, 129.81, 128.49, 127.28, 126.75, 126.19, 125.28, 119.57, 81.01, 78.75. MS (ESI, 70 eV) *m*/*z* 303 ($M+H^+$, 100%).

1,4-Di(anthracen-9-yl)buta-1,3-diyne (2h). Mp 187–189 °C, Yield 91%. ^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 8.71 (d, *J* 8.7 Hz, 4H), 8.51 (s, 2H), 8.06 (d, *J* 8.5 Hz, 4H), 7.70 – 7.66 (m, 4H), 7.58 – 7.54 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 134.07, 131.17, 128.94, 127.32, 126.72, 125.98, 115.84, 85.12, 81.71. HRMS (EI) *m*/*z* calculated for $C_{32}H_{18}$ $(M)^+$ 402.141, found 402.141.

1,4-Bis(4-fluorophenyl)buta-1,3-diyne (2i). Mp 86–89 °C, Yield 89%. ^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 7.55 – 7.36 (m, 4H), 7.09 – 6.93 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 164.19, 161.79, 134.69, 115.95, 115.76, 89.34, 74.48. HRMS (EI) *m*/*z* calculated for $C_{16}H_8F_2$ $(M)^+$ 238.059, found 238.059.

1,4-Bis(3-fluorophenyl)buta-1,3-diyne (2j). Mp 130–133 °C, Yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ 7.34 – 7.29 (m, 4H), 7.24 – 7.19 (m, 2H), 7.13 – 7.05 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 163.52, 161.06, 130.22, 130.13, 128.51, 128.49, 123.45, 123.36, 119.36, 119.13, 117.05, 116.84, 80.68, 80.65, 74.45. HRMS (EI) *m*/*z* calculated for $C_{16}H_8F_2$ $(M)^+$ 238.059, found 238.059.

1,4-Bis(4-(trifluoromethyl)phenyl)buta-1,3-diyne (2k). Mp 163–166 °C, Yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ 77.67 – 7.60 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 132.83, 133.25, 130.56, 125.50, 125.46, 125.28, 125.06, 122.35, 82.58, 75.65. HRMS (EI) *m*/*z* calculated for $C_{18}H_8F_6$ $(M)^+$ 338.053, found 338.053.

1,4-Bis(2,6-dichlorophenyl)buta-1,3-diyne (2l). Mp 192–195 °C, Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ 7.38 – 7.32 (m, 4H), 7.25 – 7.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 138.61, 130.12, 127.81, 122.04, 83.02, 77.81. HRMS (EI) *m*/*z* calculated for $C_{16}H_6Cl_4$ $(M)^+$ 337.922, found 337.922.

1,4-Bis(2,4-dichlorophenyl)buta-1,3-diyne (2m). Mp 185–187 °C, Yield 90%. ^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 7.49 (d, *J* 8.4 Hz, 2H), 7.45 (d, *J* 2.0 Hz, 2H), 7.25 – 7.23 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 137.83, 135.98, 134.92, 129.59, 127.22, 120.31, 79.06, 78.90. HRMS (EI) *m*/*z* calculated for $C_{16}H_6Cl_4$ $(M)^+$ 337.922, found 337.922.

3,3'-(Buta-1,3-diyne-1,4-diyl)dibenzonitrile (2n). Mp 229–231 °C, Yield 89%. ^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 7.81 (q, *J* 1.1 Hz, 2H), 7.76 – 7.74 (m, 2H), 7.67 (dt, *J* 7.8, 1.4 Hz, 2H), 7.51 – 7.48 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 136.50, 135.83, 132.65, 129.55, 123.07, 117.65, 113.28, 79.97, 75.54. HRMS (EI) *m*/*z* calculated for $C_{18}H_8N_2$ $(M)^+$ 252.069, found 252.069.

1,4-Di(thiophen-2-yl)buta-1,3-diyne (2o). Mp 98–100 °C, Yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ 7.38 – 7.32 (m, 4H), 7.25 – 7.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 134.43, 128.94, 127.24, 121.96, 77.80, 76.67. MS (ESI, 70 eV) *m*/*z* 214 ($M+H^+$, 100%).

1,4-Bis(3-methylthiophen-2-yl)buta-1,3-diyne (2p). Mp 88–89 °C, Yield 96%. ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ 7.19 (d, *J* 5.1 Hz, 2H), 6.85 (d, *J* 5.1 Hz, 2H), 2.37 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 167.37, 145.73, 129.36, 127.53, 117.63, 80.02, 15.23. HRMS (EI) *m/z* calculated for $C_{14}H_{10}S_2$ (M)$^+$ 242.359, found 242.359.
(1*E*, 7*E*)-1,8-Diphenylocta-1,7-dien-3,5-diyne (2q). Mp 130–132 °C, Yield 84%. ^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 7.41 – 7.39 (m, 4H), 7.36 – 7.31 (m, 6H), 7.10 (d, *J* 16.1 Hz, 2H), 6.29 – 6.24 (d, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 144.45, 135.82, 129.27, 128.83, 126.48, 106.89, 82.08, 76.41. HRMS (EI) *m/z* calculated for $C_{20}H_{14}$ (M)$^+$ 254.110, found 254.110.

Typical procedure for the preparation of unsymmetrical diynes. Synthesis of 5-((2,6-dichlorophenyl)buta-1,3-Diyn-1-yl)-1,2,3-trimethoxybenzene (2r). To a 5 mL screw cap vial containing dibromoalkenes 1m (0.32 g, 1 mmol), 1a (0.34 g, 1 mmol) and CuI (38 mg, 0.2 mmol), freshly prepared DBU.H2O (0.668 mL, 4.0 mmol) was added dropwise over a period of 1 min against the walls of vial at ambient temperature (25-30 °C) and stirred for 3 h. The reaction mixture was quenched by the addition of water (10 mL) and extracted with EtOAc (2 x 10 mL). Organic layers were washed with 5N aqueous HCl (10 mL), water (10 mL), dried (Na2SO4), evaporated, and purified by column chromatography (60 – 120 mesh silica gel, 2% ethyl acetate in pet ether) to afford the diyne **2r** (0.19 g, 54%) as a colorless solid. Similar experimental procedure was adopted for the synthesis of **2s**.
5-((2,6-Dichlorophenyl)buta-1,3-diyn-1-yl)-1,2,3-trimethoxybenzene (2r). Mp 196–198 °C, Yield 54%. ^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 7.34 (d, *J* 8.2 Hz, 2H), 7.23 – 7.19 (m, 1H), 6.81 (s, 2H), 3.88 (s, 3H), 3.86 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ 153.14, 140.19, 138.40, 129.72, 127.65, 122.33, 116.17, 109.85, 84.87, 83.72, 76.61, 74.90, 72.72, 61.04, 56.22. HRMS (EI) *m/z* calculated for $C_{19}H_{14}Cl_2O_3$ (M)$^+$ 361.218, found 361.218.
(*E*)-1,2,3-Trimethoxy-5-(6-phenylhexa-5-en-1,3-diyn-1-yl)benzene (2s). Mp 84–86 oC, Yield 42%. 1H NMR (500 MHz, CDCl3, 298K): δ 7.42 – 7.31 (m, 5H), 7.12 (d, J 16.3 Hz, 1H), 6.75 (s, 2H), 6.27 (d, J 16.2 Hz, 1H,), 3.87 (d, J 1.6 Hz, 3H), 3.86 (d, J 2.2 Hz, 6H). 13C NMR (101 MHz, CDCl3, 298K): δ 153.12, 144.59, 139.87, 135.76, 129.32, 128.84, 126.48, 116.74, 109.69, 106.75, 82.34, 81.40, 76.50, 73.41, 61.04, 56.20. HRMS (EI) *m/z* calculated for C21H18O3 (M)+ 318.365, found 318.365.

Acknowledgements

We are thankful to Srivari Chandra Sekhar, Director, and CSIR-IICT for the congenial atmosphere and continuous support. The reported study was funded by DST-India according to the research project (ECR/2017/000419)

Supplementary Material

^{1}H and ^{13}C NMR Spectra for compounds **2a-s** can be found using the link “Supplementary Material” in the journal issue contents page.

References

1. Chinchilla, R.; Najera, C. *Chem. Rev*. **2014**, *114*, 1783–1826. https://doi.org/10.1021/cr400133p

2. Mukherjee, N.; Kundu, D.; Ranu, B. C. *Chem. Commun*. **2014**, *50*, 15784–15787. https://doi.org/10.1039/C4CC07413K
3. Shi, W.; Lei, A. Tetrahedron Lett. **2014**, *55*, 2763–2772. https://doi.org/10.1016/j.tetlet.2014.03.022
4. Doucet, H.; Hierso, J.-C. *Angew. Chem. Int. Ed.* **2007**, *46*, 834–871. https://doi.org/10.1002/anie.200602761
5. Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F.-T. *J. Org. Chem*. **1984**, *49*, 2629–2632. https://doi.org/10.1021/jo00188a025
6. Wrangham, R. W.; Nishida, T. *Primates.* **1983**, *24*, 276–282. https://doi.org/10.1007/BF02381090
7. Bohlmann, F.; Ahmed, M.; Grenz, M.; King, R. M.; Robinson, H. *Phytochemistry*. **1983**, *22*, 2858–2859. https://doi.org/10.1016/S0031-9422(00)97716-1
8. Bohlmann, F.; Von Kap-Herr, W.; FanghPnel, L.; Arndt, C. *Chem. Ber*. **1965**, *98*, 1411–1415. https://doi.org/10.1002/cber.19650980509
9. Bohlmann, F.; Bornowski, H.; Kleine, K.-M. *Chem. Ber*. **1964**, *97*, 2583–2585. https://doi.org/10.1002/cber.19640970924
10. Takahashi, A.; Endo, T.; Nozoe, S.; *Chem. Pharm. Bull*. **1992**, *40*, 3181–3184. https://doi.org/10.1248/cpb.40.3181
11. Bae, B. H.; Im, K. S.; Choi, W. C.; Hong, J.; Lee, C.-O.; Choi, J. S.; Son, B.W.; Song, J.-I.; Jung, J. H. *J. Nat. Prod*. **2000**, *63*, 1511–1514. https://doi.org/10.1021/np0002076
12. Anet, E. F. L. J.; Lythgoe, B.; Silk, M. H.; Trippett, S. *J. Chem. Soc*. **1953**, 309–322. https://doi.org/10.1039/JR9530000309
13. Bohlmann, F.; Rode, K.-M. *Chem. Ber.* **1968**, *101*, 1163–1175. https://doi.org/10.1002/cber.19681010405
14. Zhang, Y.; Zhong, H.; Wang, T.; Geng, D.; Zhang M.; Li, K. Eur. *J. Med. Chem*. **2012**,*48*, 69–80. https://doi.org/10.1016/j.ejmech.2011.11.036
15. Buchta, V.; Pour, M.; Kubanová, P.; Silva, L.; Vortuba, I.; Vopršálová, M.; Schiller, R.; Fáková, H.; Špulák, M. *Antimicrob. Agen. Chemother*. **2004**, *48*, 873. https://doi.org/10.1128/AAC.48.3.873-878
16. Matsuoka, Y.; Mutoh, Y.; Azumaya, I.; Kikkawa, S.; Kasama, T.; Saito, S. *J. Org. Chem*. **2016**, *81*, 3479–3514. https://doi.org/10.1021/acs.joc.5b02911
17. Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem. Int. Ed*. **2006**, *45*, 1034–1057. https://doi.org/10.1002/anie.200502071
18. Ratnayake, A. S.; Hemscheidt, T. Org. Lett. 2002, 4, 463–466. https://doi.org/10.1021/ol017229j
19. Kanikarapu, S.; Marumudi, K.; Kunwar,A. C.; Yadav, J. S.; Mohapatra, D. K. *Org. Lett*. **2017**, *19*, 4167–4170. https://doi.org/10.1021/acs.orglett.7b01620
20. Heydenreuter, W.; Kunold, E.; Sieber, S. A. *Chem. Commun*. **2015**, *51*, 15784–15787. https://doi.org/10.1039/C5CC06424D
21. Mohapatra, D. K.; Umamaheshwar, G.; Rao, R.; Srinivasarao, T.; Sudheer Kumar R.; Yadav, J. S. *Org. Lett*. **2015**, *17*, 979–981. https://doi.org/10.1021/acs.orglett.5b00138

22. Zhang, B.; Wang, Y.; Yang, S.-P.; Zhou, Y.; Wu, W.-B.; Tang, W.; Zuo, J.-P.; Li, Y.; Yue, J.-M. *J. Am. Chem. Soc*. **2012**, *134*, 20605–20608. https://doi.org/10.1021/ja310482z
23. Ladika, M.; Fisk, T. E.; Wu W. W.; Jons, S. D. *J. Am. Chem. Soc*. **1994**, *116*, 12093–12094. https://doi.org/10.1021/ja00105a076
24. Yang, W.; Bam, R.; Catalano, V. J.; Chalifoux, W. A. *Angew. Chem. Int. Ed*. **2018**, *57*, 4773–14777. https://doi.org/10.1002/anie.201808043
25. Rietsch, P.; Soyka, J.; Brulls, S.; Hoffmann, J. Er, K.; Beerhues, J.; Sarkar, B.; Resch-Genger, U.; Eigler, S. *Chem. Commun*. **2019**, *55*, 10515–10518. https://doi.org/10.1039/C9CC05451K
26. Arnaboldi, S.; Benincori, T.; Penoni, A.; Vaghi, L.; Cirilli, R.; Abbate, S.; Longhi, G.; Mazzeo, G. ; Grecchi, S.; Panigati, M.; Mussini P. R. *Chem. Sci*. **2019**, *10*, 2708–2717. https://doi.org/10.1039/C8SC04862B
27. Liu, J.; Yang, J.; Baumann, W.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed*. **2019**, *58*, 10683–10687. https://doi.org/10.1002/anie.201903533
28. Yuanyuan, L.; Yunxiang, L.; Lichao, D.; Longlong Z.; Junge, Z.; Jianbing S.; Bin, T.; Yuping, D. *Chem. Eur. J*. **2019**, *25*, 573–581. https://doi.org/10.1002/chem.201804074
29. Fukushima, S.; Ashizawa, M.; Kawauchi, S.; Michinobu, T. *Helv. Chim. Acta*. **2019**, *102*, e1900016. https://doi.org/10.1002/hlca.201900043
30. Carrera, E. I.; Lanterna, A. E.; Lough, A. J.; Scaiano, J. C.; Seferos, D. S. *J. Am. Chem. Soc*. **2016**, *138*, 2678–2689. https://doi.org/10.1021/jacs.5b11649
31. Hao, N.; Sun, C.; Wu, Z.; Xu, L.; Gao, W.; Cao, J.; Li, L.; He, B. *Bioconjugate Chem*. **2017**, *28*, 1944–1966. https://doi.org/10.1021/acs.bioconjchem.7b00274
32. Karmakar, R.; Lee, D. Chem. Soc. Rev. **2016**, *45*, 4459–4470. https://doi.org/10.1039/C5CS00835B
33. Diamond, O. J.; Marder, T. B. *Org. Chem. Front*. **2017**, *4*, 891–910. https://doi.org/10.1039/C7QO00071E
34. Li, W.; Zhou, L.; Zhang, J. *Chem. Eur. J*. **2016**, *22*, 1558–1571. https://doi.org/10.1002/chem.201503571
35. Holden, C.; Greaney, M. F. *Angew. Chem. Int. Ed*. **2014**, *53*, 2–6. https://doi.org/10.1002/anie.201402405
36. Guolin, C.; Hong, Z.; Xiuling, C. *RSC Adv*. **2014**, *4*, 1849–1852. https://doi.org/10.1039/C3RA43873B
37. Glaser, C. *Ber. Dtsch. Chem. Ges*. **1869**, *2*, 422–424. https://doi.org/10.1002/cber.186900201183
38. Eglinton, G.; Galbraith, A. R. *J. Chem. Soc*. **1959**, 889–896. https://doi.org/10.1039/JR9590000889
39. Hay, A. *J. Org. Chem*. **1960**, *25*, 1275–1276. https://doi.org/10.1021/jo01077a633
40. Corey, E. J.; Fuchs,P. L. *Tetrahedron Lett*. **1972**, *13*, 3769–3772. https://doi.org/10.1016/S0040-4039(01)94157-7

41. Shen, W.; Thomas, S. A. *Org. Lett*. **2000**, *2*, 2857–2860. https://doi.org/10.1021/ol006282p
42. Rao, M. L. N.; Priyabrata, D.; Ramakrishna, B. S.; Murty, V. N. *Tetrahedron Lett*. **2014**, *55*, 3529–3533. https://doi.org/10.1016/j.tetlet.2014.04.092
43. Mahendar L.; Venkat Ramulu, B.; Satyanarayana, G. *Synthetic Communications*. **2017**, *47*, 1151-1158. http://dx.doi.org/10.1080/00397911.2017.1315732
44. Coste, A.; Couty, F.; Evano, G. *Synthesis* **2010**, 1500. https://doi.org/10.1055/s-0029-1218688
45. Suzuki, H.; Aihara, M.; Yamamoto, H.; Takamoto, Y.; Ogawa, T. *Synthesis* **1988**, 236. https://doi.org/10.1055/s-1988-27527
46. Huang, Z..; Shang, R.; Zhang, Z. -R.; Tan, X. -D. Xiao, X.; Fu, Y. *J. Org. Chem.* **2013**, *78*, 4551. https://doi.org/10.1021/jo400616r
47. Yan, J.; Wang, L. *Synth. Commun.* **2005**, *35*, 2333. https://doi.org/10.1080/00397910500187191
48. Vanderesse, R.; Fort, Y.; Becker, S.; Caubere, P. *Tetrahedron Lett.* **1986**, *27*, 3517. https://doi.org/10.1016/S0040-4039(00)84838-8
49. Galamb, V.; Gopal, M.; Alper, H. *Organometallics.* **1983**, *2*, 801. https://doi.org/10.1021/om50001a003
50. Thummala, Y.; Karunakar, G. V.; Doddi, V. R. *Adv. Synth. Catal*. **2019**, *361*, 611–616. https://doi.org/10.1002/adsc.201801334
51. Morri, A. K.; Thummala, Y.; Doddi, V. R. *Org. Lett*. **2015**, *17*, 4640–4643. https://doi.org/10.1021/acs.orglett.5b02398
52. Thummala, Y.; Morri, A. K.; Karunakar, G. V.; Doddi, V. R. *Eur. J. Org. Chem*. **2018**, *45*, 6280–6285. https://doi.org/10.1002/ejoc.201801143
53. Moodapelly, S. K.; Sharma, G. V. M.; Doddi, V. R. *Adv. Synth. Catal*. **2017**, *359*, 1535–1540. https://doi.org/10.1002/adsc.201601279
54. Hui, J.; Chunxiang, K. *Chin. J. Chem*. **2011**, *29*, 592–594. https://doi.org/10.1002/cjoc.201190128
55. Capriotti, K.; Capriotti, J. A. *J Clin Aesthet Dermatol*. **2012**, *9*, 24–26. PMID 23050031
56. Cota, I.; Chimentao, R.; Sueiras, J.; Medina, F. *Catal. Commun*. **2008**, *9*, 2090–2094. https://doi.org/10.1016/j.catcom.2008.03.047