

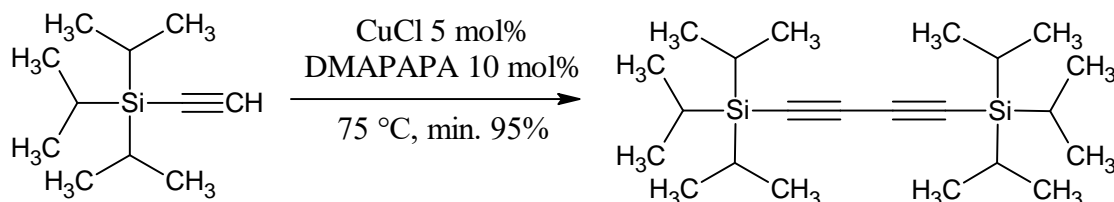
# Copper (I)-N, N-Dimethyldipropylenetriamine Catalyzed Robust Homocoupling of Terminal Alkynes

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**Abstract:** A robust catalytic system consisting of Cu (I)-salt and dimethyldipropylenetriamine for the synthesis of 1-4-disubstituted 1, 3-diyne have been developed. The new protocol involves homocoupling of terminal alkynes in the presence of CuI or CuCl and DMAPAPA as ligand in acetonitrile. A series of terminal alkynes having diverse functional groups are converted to corresponding 1, 3-diyne via homocoupling under ambient conditions within an hour in excellent yields upto 98%. The current protocol avoids stoichiometric amount of copper salt and high cost palladium salt, and harsher condition.

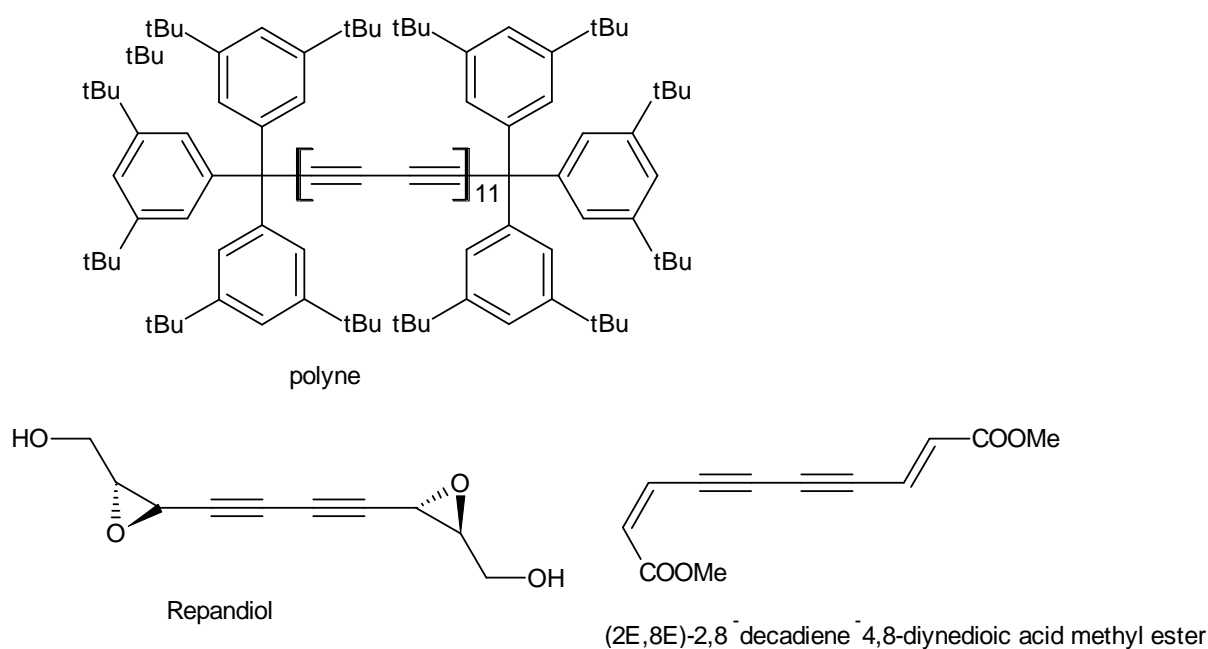


**Keywords:** homocoupling, copper catalysis, acetonitrile, terminal alkynes, 1, 3-diyne, DMAPAPA

## 1. Introduction

1, 4-disubstituted-1, 3-diyne have rod like structure and are found as an important structural motifs in natural products, pharmaceuticals bioactive compounds, electronic and optical materials and supramolecular molecules<sup>1-6</sup>. They have been isolated from various natural sources such as plants, fungi, corals, marine sponges and bacteria.<sup>7</sup> For example, symmetrical repandiol isolated from the hedgehog

mushroom (*Hydnumrepandum*) is found to display cytotoxic activity against several types of tumor cells.<sup>8</sup> Caryonencins (*Scheme 1*), isolated from waxcap mushroom (*pseudomonas caryophylli*) are polyne antibiotics having effective antibacterial activities.<sup>9-10</sup> (2E, 8E)-2, 8-decadiene-4, 6-diyne-1, 10-diol has also been isolated from the waxcap mushroom (*Hygrophorusvirginicus*).



**Scheme 1:** 1, 4-diyne isolated from natural sources

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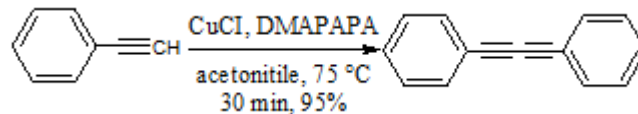
Copper and palladium complexes are widely used to prepare 1, 3-diynes by homocoupling of terminal alkynes. Palladium complexes as cocatalysts, in combination with Cu salts, are also traditionally employed.<sup>11-17</sup> Recently, catalysts, based on other transition metals such as Ni<sup>18</sup>, Co<sup>19</sup>, Au<sup>20</sup> and Ti<sup>21</sup> have also been employed in terminal alkyne homocoupling reactions. Literature survey showed that among all the cheap transition metal catalysts Cu-catalysts gave good results. We set out a project to study the performance of CuI and CuCl as catalyst inhomocoupling of terminal alkynes in the presence of various amine based ligands. As a result, herein, we report a mild, highly efficient Cu-salt catalysed homocoupling of terminal alkynes. Theoretical studies on homocoupling of terminal alkynes have been recently carried out S. Gosh<sup>22</sup> and A.C. Albenic et.al.

## 2. Results and Discussion

### Optimization of Homocoupling Conditions

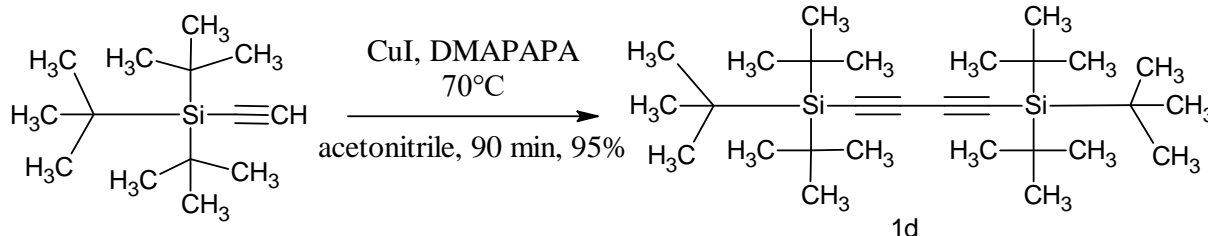
Initially, to optimize the conditions, a mixture of phenylacetylene (500mg, 5 mmol), CuI (93 mg, 0.48 mmol, 5 mol%), N, N, dimethyldipropylenetriamine (160 mg, 1 mmol, 20 mol%), and acetonitrile was stirred at room temperature under atmospheric air. Even after 6 hours of stirring the reaction was incomplete as shown by TLC. The desired product was obtained in 35% (isolated) yield. When the bath temperature was raised to 80°C, the reaction was complete after 25 min as shown by TLC. Although, different Cu-salts were screened for their catalytic activities in this study, CuI emerged as the winner (Scheme 1). Although, both CuCl and CuI showed similar results for aromatic

terminal alkynes, CuCl fared better for aliphatic alkynes as the reaction. Other copper salts such as CuCl<sub>2</sub>, Cu (acac)<sub>2</sub> took longer reaction time even to achieve 35% yield (isolated). The results of current protocol proved the homocoupling can be achieved even in the absence of palladium and base.



Scheme 2: optimization of conditions

With the optimized conditions, the scope the protocol was further investigated for a variety of aromatic and aliphatic terminal alkynes having different functional groups and the result is collected. It was observed that while aromatic alkynes underwent coupling within 30 min, aliphatic alkynes took about 1 hr for the completion of the reaction (Table 1). Aromatic alkynes with electron donating and electron withdrawing groups did not show noticeable difference in the reaction time. However, 1-ethynylcyclohexan-1-ol (**1a**) underwent coupling in less than 30 min to afford 1, 1'-(buta-1, 3diyne-1, 4-diyl)di (cyclohexan-1-ol) whereas ethynylcyclohexane (**1f**) took 1 hr for the completion of the reaction. While, trisopropylsilylacetylene (**1d**) underwent coupling smoothly to give the product. In general, the homocoupling of aromatic alkynes required relatively less time than aliphatic alkynes. However, as expected the homocoupling of 1-nonyn (**1h**) took rather longer time (6hr).



Scheme 3: homocoupling of trisopropylsilylacetylene5

## 3. Experimental

All chemicals used were purchased from Sigma-aldrich, and the solvents were procured from Merck India. The progress of the reaction was monitored by TLC on pre-coated Merck silica gel 60 F-255. Column chromatography was performed using silica gel 60-120 mesh and solvents were removed

using Buchi Rotavapor-R 300 under reduced pressure. Melting points observed using automatic melting point apparatus. <sup>1</sup>HNMR spectra were recorded on 300 MHz spectrometer, 400 MHz bruker or agilent spectrometer and <sup>13</sup>CNMR spectra at 75 MHz in (CDCl<sub>3</sub>), and 100 (DMSO-d<sub>6</sub>) MHz and J values were recorded in hertz. Mass spectral data were obtained using MS (ESI) or MS (EI).

**Table 1:** CuI-DMAPAPA Catalyzed homocoupling of terminal alkynes

S. No	substrate	Product	Time	Temp <sup>o</sup> C	Yield %	#
1a			30min	75	95	
1b			30min	75	97	
1c			30min	75	93	
1d			30min	75	96	
1e			40min	75	93	
1f			30 min	75	95	
1g			40 min	75	95	
1h			40min	75	95	
1i			60 min	75	93	
1j			4 hr	85	65	
1k			30 min	75	95	
1l			45 min	80	85	

# All yields are isolated yields after column chromatographic separation

#### General procedure

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A mixture of CuCl or CuCuI (5mol%), terminal alkyne (5mmol), and N, N-dimethyldipropylenetriamine (10mol%) in acetonitrile (8 mL) was taken to a Schelenk tube and fitted with water condenser and guard tube. The mixture was stirred at 75°C -85°C. The progress of the reaction was monitored by TLC. The solvent was evaporated under pressure. Column chromatography was performed without any further work up using eluents petroleum ether, ether, chloroform, and in some cases methanol. The results are collected in the **Table 1**.

#### 4. Spectral Data

##### 1, 4-Diphenylbuta-1, 3-diyne: (1a)

White crystalline solid: yield: 95%, mp: 86°C, (lit. 86-87 °C). <sup>1</sup>H NMR (300 MHz) CDCl<sub>3</sub>: δ 7.35-7.45 (m, 6H), 7.5-7.6 (m, 4H). <sup>13</sup>C (CDCl<sub>3</sub>): δ 73.98, 81.58, 121.88, 128.43, 129.17, 132.51, EI (MS): 202.

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##### 1, 4-bis (3-fluorophenyl)buta-1, 3-diyne (1b)

<sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>) δ 7.05–7.1 (m, 2H), 7.2-7.3 (m, 2H), 7.4-7.45 (m, 4H). <sup>13</sup>C NMR, (100 Hz) δ 74.4, 80.6, 116.76, 117, 119.1, 119.37, 123.3, 123.41, 128.44, 128.49, 130.1, 160.62, 163.9.

##### 1, 4-bis (3-fluorophenyl)buta-1, 3-diyne

<sup>1</sup>H NMR (300Hz, CDCl<sub>3</sub>)δ:7.10 (ddd, 2H, 5.8, 11.8 Hz), 7.19–7.25 (m, 2H), 7.32 (ddd, 4H, ).  
<sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>)δ:74.39, 80.59, 116.77, 117.05, 119.07, 119.37, 123.29, 123.41, 128.44, 128.49, 130.08, 130.19, 160.61, 163.89. EI-MS: 238

##### 1, 4-Bis (4-fluorophenyl)buta-1, 3-diyne (1c)

White crystalline solid: yield: 97%, mp: 111°C, (lit. 86-87 °C). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7-7.1 (m, 4H), 7.48-7.54 (m, 4H). <sup>13</sup>C (CDCl<sub>3</sub>): δ 164.78, 161.44, 134.58, 134.46, 117.94, 117.91, 116.1, 115.75, 80.44, 73.608.  
© E(MS):238.

##### 1, 1'-(Buta-1, 3-diyne-1, -diyl)dicyclohexanol (1e)

White amorphous solid: yield: 95%, mp: 167°C, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7-7.1 (m, 4H), 7.48-7.54 (m, 4H).  
<sup>13</sup>C (CDCl<sub>3</sub>): δ 164.78, 161.44, 134.58, 134.46, 117.94, 117.91, 116.1, 115.75, 80.44, 73.608.  
EI (MS):238.

##### 1, 1'-(buta-1, 3-diyne-1, 4-diyl)dicyclohexane (1f)

White crystalline solid: yield 93%. mp: 100 °C, <sup>1</sup>H NMR (400 MHz) DMSO-d<sub>6</sub>: δ 1.5-1.6 (d, 4H), 1.43-1.46 (m, 8H), 1.65-1.77 (m, 8H), 2.39-2.41 (2H).

<sup>13</sup>C DMSO-d<sub>6</sub>:

24.72, 25.68, 29.42, 30.89, 32.21, 65.00, 76.66, 76.98, 77.29, 81.8

##### Bis-2, 6- ( tertiarybutyl, dimethylsilyloxy) octa-3, 5-diyne (1k)

Colorless viscous liquid: <sup>1</sup>H NMR (400 MHz) DMSO-d<sub>6</sub>: δ 0.0-0.15 (m, 12 H), 0.8-0.9 (s, 18 H), 1.35-1.4 (d, 6 H), 4.5-4.6 (q, 2H). <sup>13</sup>C (DMSO-d<sub>6</sub>, 100MHz): δ -5.089, -4.70, 0.959, 18.124, 24.971, 25.691, 59.248, 67.633, 76.631, 76.949, 77.266, 81.321.

#### 5. Conclusion

In conclusion, it is demonstrated that CuI-DMAPAPA-acetonitrile as a versatile robust catalytic system for homocoupling of terminal alkynes with diverse nature and functional groups. The coupling is achieved under ambient conditions that avoid high temperature, inorganic bases, high cost palladium, and oxygen atmosphere. Further, the current methodology is superior to existing methodologies as it significantly minimizes the reaction time and therefore has very high turnover frequency (TNF). The procedure also avoids tedious isolation procedures. Further, in a short reaction time the homocoupling is achieved in excellent yields

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