



RECENT ADVANCES IN SYNTHESIS OF 1, 3-DIYNES FROM TERMINAL ALKYNES

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Abstract: Many molecules contain 1,3-diyne is an important core and shows important biological activities. The design and synthesis of these 1,3-diyne scaffolds using homo and heterocoupling of terminal alkynes have been very important methods for a very long period. In this review, we are highlighting some of the recent catalytic methods for the synthesis of 1, 3-diynes using terminal alkynes.

Keywords – 1,3-diyne, Terminal Alkynes, Homo and Hetero-coupling, Catalysis.

I. INTRODUCTION

Many molecules contain 1,3-diyne is an important core and widespread. Some of these molecules containing 1,3-diyne core show very important biological activities against the major diseases (Fig 1.1).¹ Also molecules containing 1,3-Diyne core have been extensively utilized in constructing molecular boxes as in supramolecular chemistry.² These conjugated 1,3-diyne scaffolds have been extensively used as core building blocks for the synthesis of advanced materials such as liquid crystals, conjugated polymers, and molecular wires.³

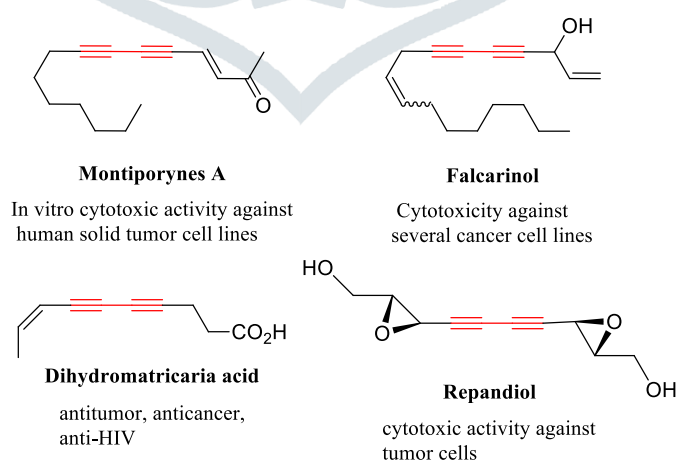


Fig 1.1 Bioactive 1,3-diynes

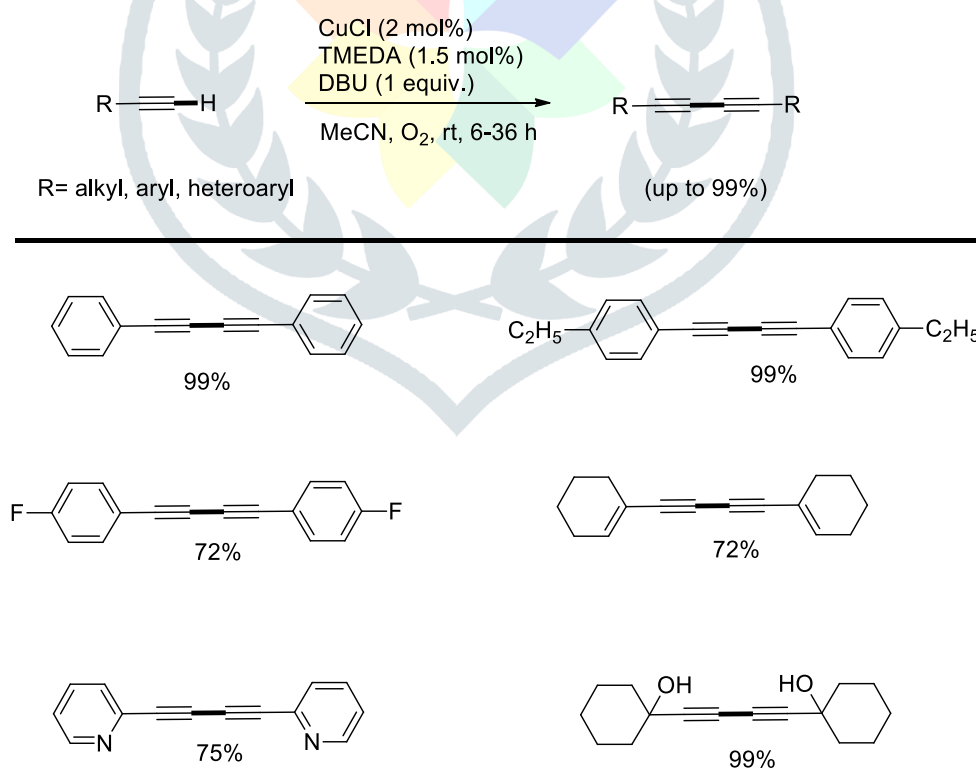
In organic chemistry, the carbon-carbon triple bond is one of the most versatile and well-explored functional and has tremendous synthetic importance.⁴ Therefore, the design and synthesis of compounds

containing 1,3-diyne scaffold have been interesting topics for a long period since the discovery of oxidative coupling of copper acetylides by Glaser.⁵ Later on, this method was further modified and improved by Eglinton and Galbraith in the mid 20th century.⁶ Hay also made an important modification of this method by using the catalytic amount of copper salt to afford the 1,3-diyne in good yields.⁷ Homocoupling of terminal alkynes using copper-catalyst proved to be an important method as copper is readily available, comparatively less expensive, and less toxic.⁸ Different methods for the oxidative coupling of terminal alkynes have been optimized by utilizing different copper salts, bases, and ligands.

II. Recent methods for the synthesis of 1, 3-diynes from terminal alkynes

The design and synthesis of 1,3-diyne scaffold using homo and heterocoupling of terminal alkynes is an important method for a very long time since the discovery of oxidative dimerization of copper acetylides by Glaser in 1869.⁵ Some of the recent important methods of homo and heterocoupling of terminal alkynes are discussed here.

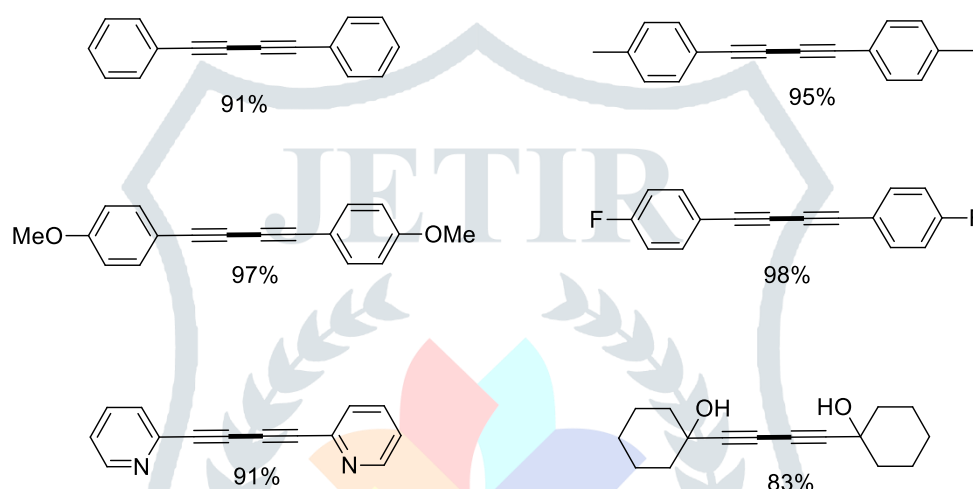
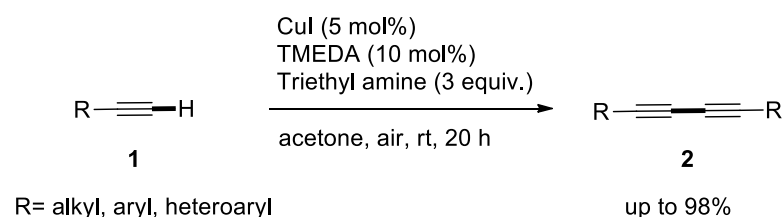
In 2009, Beifuss and co-workers reported a very interesting oxidative coupling reaction between terminal alkynes in the presence of a catalytic system containing copper (I) chloride and TMEDA as a ligand along with the DBU as a base in the oxygen atmosphere. Under this optimized condition, aliphatic as well as aromatic terminal alkynes underwent very effective oxidative homocoupling of terminal alkynes to afford the desired products symmetrical 1,3-diynes in good to excellent yields (Scheme 2.1).⁹



Scheme 2.1 Homocoupling of terminal alkynes using copper catalyst

In 2011, Zhang and co-workers demonstrated very effective homocoupling of terminal alkynes using catalytic amounts of CuI (5 mol%) and TMEDA (10 mol%) as a ligand to afford the product 1,3-diynes. To

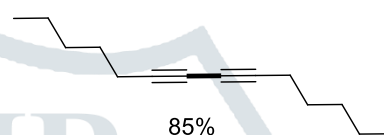
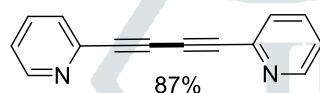
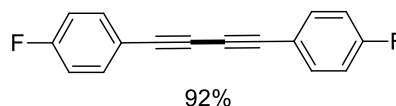
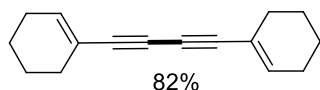
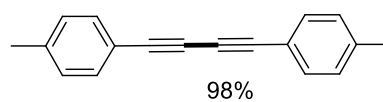
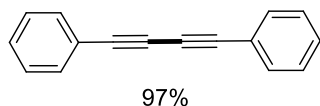
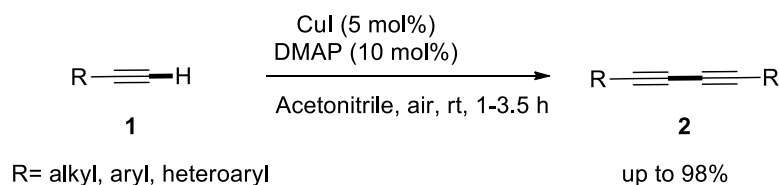
facilitate this reaction, an excess amount of base- Et_3N and air as an oxidant was required to furnish the desired product. A variety of aliphatic as well as aromatic terminal alkynes undergoes smooth oxidative homocoupling reactions to afford the corresponding desired symmetrical 1,3-diynes in good to excellent yields (Scheme 2.2).¹⁰



Scheme 2.2 Cu(I) iodide-catalyzed homocoupling of terminal alkynes

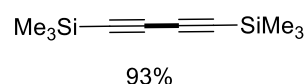
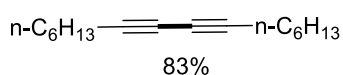
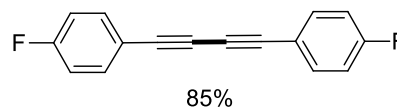
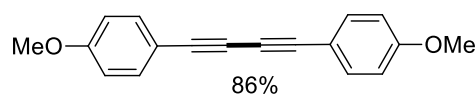
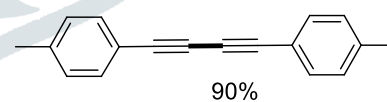
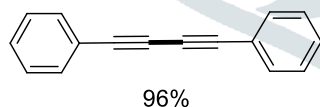
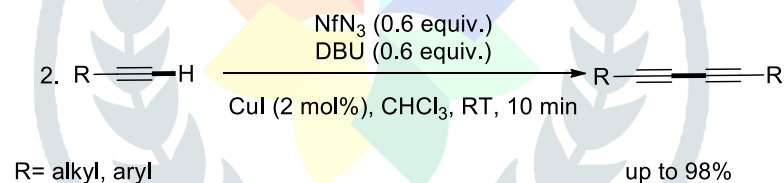
In 2013, Bhat and co-worker demonstrated efficient homocoupling of terminal alkynes using catalytic amounts of CuI (5 mol%) and DMAP (10 mol%) as a ligand to afford the symmetrical 1,3-diynes under an open atmosphere. Different aliphatic, as well as aromatic terminal alkynes, undergo smooth oxidative homocoupling reactions to afford the corresponding symmetrical 1,3-diynes in good to excellent yields (Scheme 2.3).¹¹

In 2015, Suarez et al. reported copper-catalyzed hom and heterocoupling of terminal alkynes using nonafluorobutanesulfonyl azide is a highly efficient reagent to afford 1,3-diynes in good to excellent yields



Scheme 2.3 Cu(I) iodide-DMAP catalyzed homocoupling of terminal alkynes

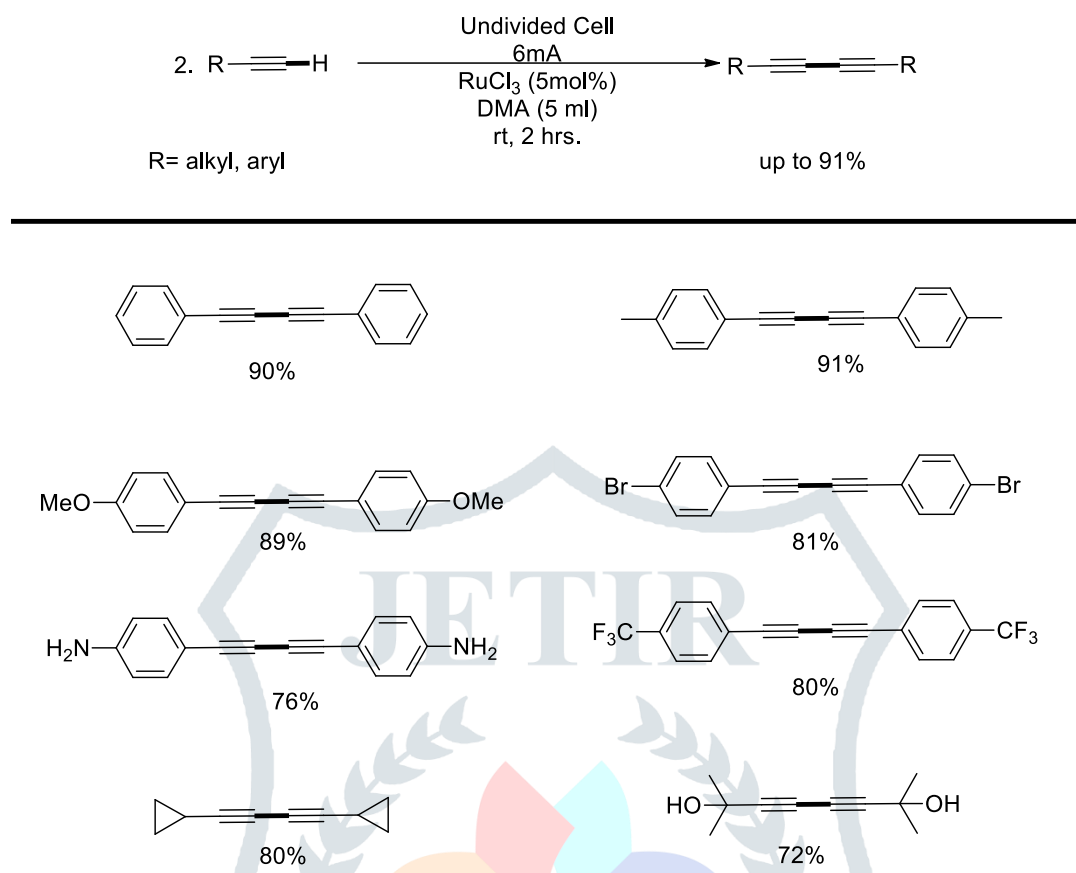
and with good functional group compatibility. The reaction is very fast and requires catalytic amounts of a simple copper(I) or copper(II) salt (2–5 mol %) and an organic base (0.6 mol %) (Scheme 2.4).¹²



Scheme 2.4 Synthesis of 1,3-diynes using Copper catalyst and nonafluorobutanesulfonyl azide

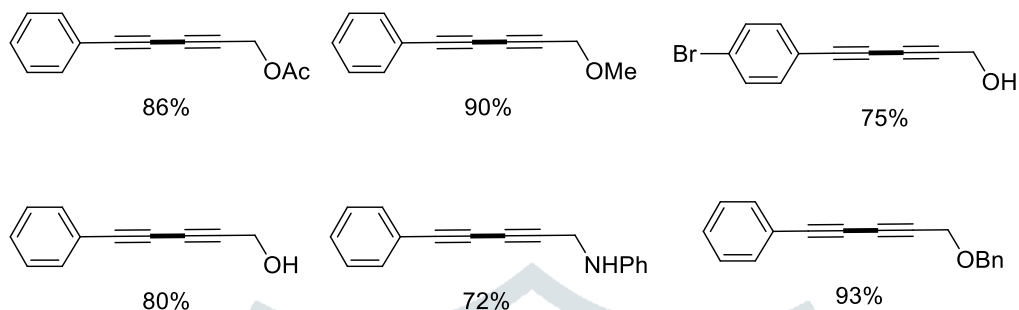
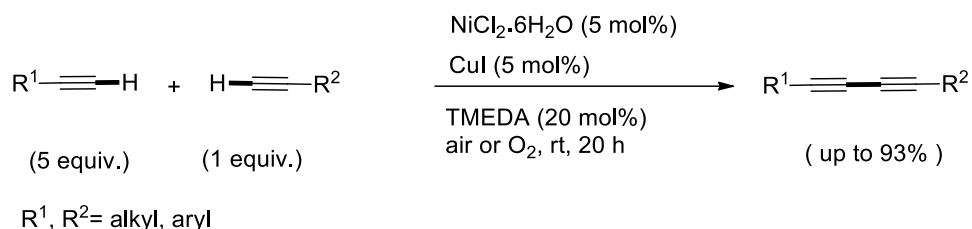
In 2023, Bordoloi and co-workers demonstrated a highly efficient Ru-catalyzed electrochemical homo- and heterocoupling reaction of terminal alkynes via a simple undivided cell reaction setup. Under the optimized reaction conditions aliphatic as well as aromatic terminal alkynes undergo smooth oxidative

homo-coupling reactions to afford the desired symmetrical 1,3-diynes in good to excellent yields (Scheme 2.5).¹³



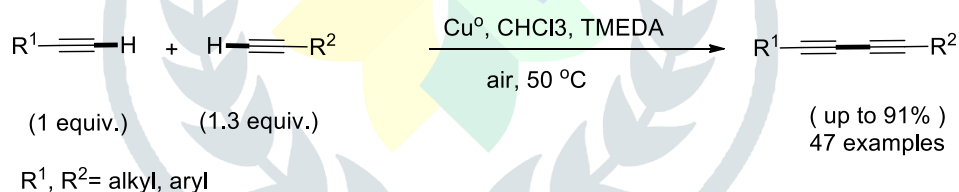
Scheme 2.5 Electrochemical homo-coupling reaction of terminal alkynes

In comparison to homocoupling, heterocoupling is relatively more challenging. In heterocoupling of two different terminal alkynes, there is the formation of unwanted homocoupling reaction products. To obtain desired cross-coupled products in good yields, the synthetic chemist has to use one of the terminal alkynes in excess amounts. In 2009, Lei and co-workers reported a method for the synthesis of unsymmetrical 1,3-diynes by using a co-catalytic system using NiCl_2 and CuI as catalysts in the presence of TMEDA under an open atmosphere to obtain the desired product unsymmetrical 1,3-diynes in good to excellent yields (Scheme 2.6).¹⁴



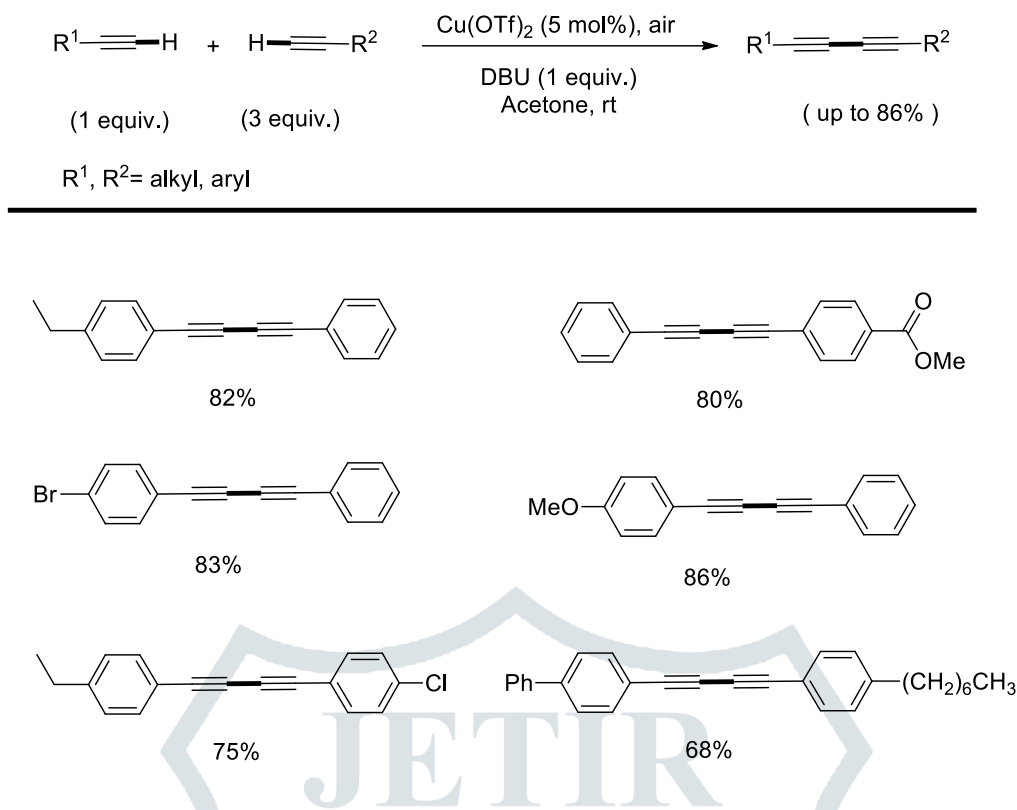
Scheme 2.6 Heterocoupling of terminal alkynes using Ni and Cu catalyst

In 2016, Su et al. reported highly selective copper-catalyzed aerobic heterocoupling of terminal alkynes which enables the synthesis of unsymmetrical 1,3-diynes in good to excellent yields. Under the optimized reaction conditions aliphatic as well as aromatic terminal alkynes undergo smooth oxidative hetero-coupling reactions to afford the desired unsymmetrical 1,3-diynes in good to excellent yields (Scheme 2.7).¹⁵



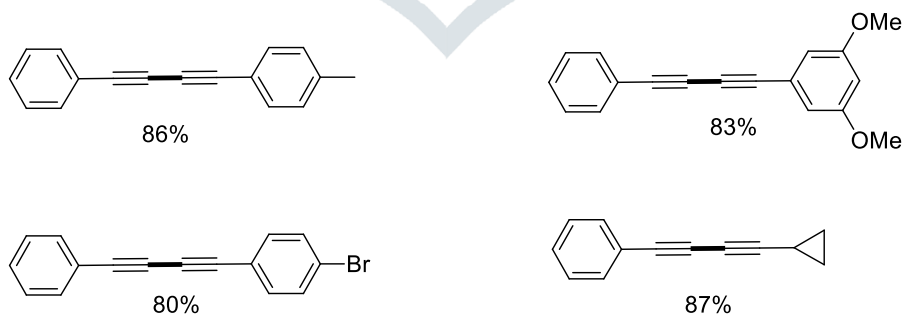
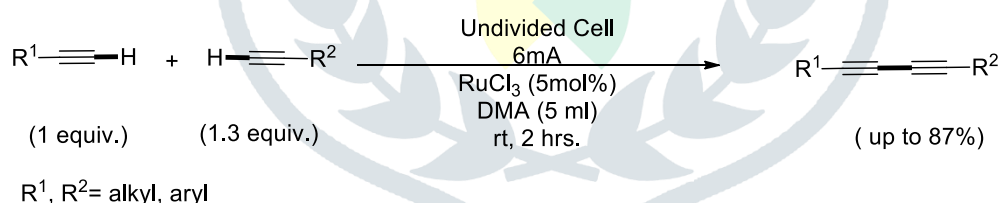
Scheme 2.7 Selective heterocoupling of terminal alkynes using Cu catalyst

In 2019, Xing and co-workers developed $\text{Cu}(\text{OTf})_2$ catalyzed homo- and heterocoupling of aromatic and aliphatic terminal alkynes in the presence of an organic base DBU under an aerobic condition to afford symmetric and unsymmetric 1,3-diynes in good yields. During this reaction, they utilized one of the alkynes in excess to afford the desired product in good yield (Scheme 2.8).¹⁶



Scheme 2.8 Heterocoupling of terminal alkynes using Cu(OTf)_2 catalyst

In 2023, Bordoloi and co-workers reported highly efficient Ru-catalyzed electrochemical heterocoupling of terminal alkynes via a simple undivided cell reaction setup. Under the optimized reaction conditions aliphatic as well as aromatic terminal alkynes undergo smooth oxidative hetero-coupling reactions to afford the desired unsymmetrical 1,3-diynes in good to excellent yields (Scheme 2.9).¹³



Scheme 2.9 Electrochemical hetero-coupling reaction of terminal alkynes

III. Conclusions

Synthesis of 1,3-diynes from terminal alkynes requires careful selection of the catalyst, and ligand-base combination for the efficient homo and heterocoupling of terminal alkynes. Heterocoupling of terminal alkynes is comparatively more challenging than homocoupling. Due to this, there is always great scope for the development of novel and efficient protocols for the homo- and hetero-coupling of terminal alkynes to afford the synthesis of 1,3-diynes.

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V. Notes

The authors declare no competing financial interest.

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