Recent advances and applications of Glaser coupling employing greener protocols

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ARTICLE TYPE

Recent Advances and Applications of Glaser coupling employing Greener protocols

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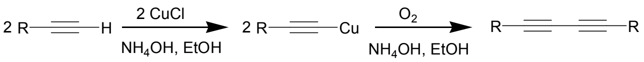
Symmetrical 1,3-diynes and their derivatives are useful motifs for the construction of complex molecules, and their excellent photochemical and material properties received greater attention in the last decades. They are used for the synthesis of a large variety of polymers, biologically active molecules, supramolecular materials and light harvesting systems. Glaser coupling is the most widely used procedure for the synthesis of 1,3-diynes through oxidative homocoupling of terminal alkynes. The classical homocoupling is catalysed by copper salts in the presence of a base and an oxidant. A number of modifications were developed recently to improve the efficacy of Glaser coupling reactions. Novel synthetic routes and approaches employing greener protocols are well appreciable. In addition to terminal alkynes, other susceptible substrates are also tested for the synthesis of 1,3-diynes. These recent advances and perspectives of Glaser coupling reactions are documented in this review. This review highlights the diverse and innovative strategies developed for the synthesis and applications of 1,3-diynes expending green chemistry.

1. Introduction

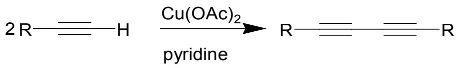
Copper catalysed acetylenic coupling reactions have a longer history of about 150 years. In 1869 Carl Glaser observed that air oxidation of Cu(I)phenyl acetylide led to diphenyldiacetylene via dimerization.[1-3] This strategy of oxidative homocoupling of terminal alkynes under the influence of copper catalyst and oxygen has been termed the Glaser coupling (scheme 1) and has attracted enduring attention in carbon-carbon bond formation in synthetic chemistry.



Scheme 1 Classical Glaser coupling reaction

The isolation and purification of Copper acetylides are tedious and therefore the original Glaser reactions failed to find wide applications. But recently Glaser reactions have been employed as key steps in the synthesis of shape persistent macrocycles, conjugated acetylenic polymers, molecular recognition processes etc with a number of modifications.[4, 5]

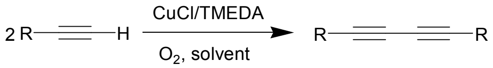
In 1956, Eglinton and Galbraith reported that stoichiometric amount of cupric salts in pyridine may also be used effectively for the coupling of terminal alkynes[6, 7] (scheme 2).



Scheme 2 Eglinton-Glaser coupling reaction

This has proven to be of great synthetic value and is particularly applicable to macrocyclizations. This modification of the Glaser reaction is now termed the Eglinton-Glaser reaction.

The Glaser coupling was further modified in 1962 by Hay who used a catalytic amount of N,N,N'N'-tetramethylethylenediamine (TMEDA) in the presence of O_2 as solubilising ligand for copper (I) halides[8] (scheme 3). The catalytic version of Glaser coupling using copper-TMEDA complex under air is termed as the Hay Coupling reaction or Glaser-Hay coupling.



Scheme 3 Glaser-Hay coupling reaction

The copper-TMEDA complex is soluble in a wide range of solvents which introduces more versatility to Hay coupling reactions.

In recent years also, many improvements and modifications were introduced in the methodology of homocoupling reactions for the synthesis of symmetrical 1,3-diynes from terminal alkynes and other substrates. These paved paths for the development of green processes in Glaser coupling. Each methodology has its own merits, scope and limitations and is discussed briefly in this review. Glaser coupling reactions are reviewed in time to time and the present review covers literature from 2000 to 2013. The synthesis and application of 1,3-diynes, which are common motifs in the synthesis of a large variety of polymers, biologically active molecules and supramolecular materials[9] with appreciable photoelectrical properties are also well documented.

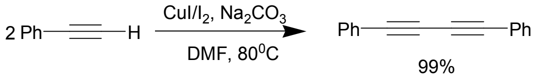
2. New strategies for the synthesis of symmetrical 1,3-diynes

Owing to the importance of 1,3-diynes, many research groups worked on the coupling of acetylenic components mediated by copper catalysts. Many attempts have been made to invent mild, efficient, selective and less expensive methods for the generation of 1,3-diynes utilizing various catalytic systems and solvents and are discussed below.

2.1. Copper mediated systems for Glaser coupling

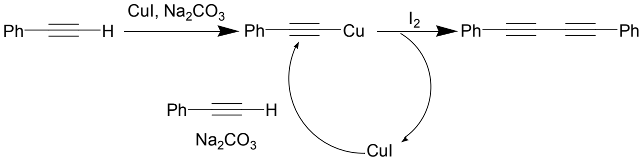
The original copper-mediated Glaser-type coupling reactions usually use excess amount of oxidants, inorganic bases, amines and are carried out in organic solvents at high temperature. Research has been focused on improving the classical procedure with mild reaction conditions and diverse substrates; but it is still challenging to find new promoting systems.

Jia et. al. developed a facile and simple CuI/iodine-mediated pathway for the homocoupling reaction of terminal alkynes to 1,3-diynes with good yields.[10] Quantitative conversion occurs when phenylacetylene is coupled in the presence of CuI, I_2 and a solid base Na_2CO_3 in DMF at 80 ^{0}C (scheme 4).



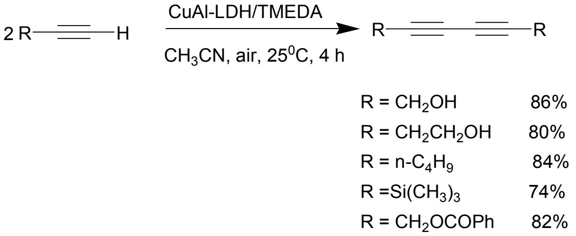
Scheme 4 CuI/Iodine-mediated homocoupling of phenylacetylene

The mechanism proposed by the authors involves the formation of alkynylcopper intermediate which undergoes oxidative dimerisation with Iodine (scheme 5).



Scheme 5 Mechanism proposed for CuI/Iodine-mediated homocoupling. Reprinted with permission from ref. 10 copyright 2008, Elsevier.

Jiang et al. investigated the use of CuAl–LDH (Copper (II) in the host layers of Layered Double Hydroxide or hydrotalcites) for homocoupling reactions (scheme 6).[11] The CuAl–LDH was synthesised by co-precipitation of copper and aluminum nitrates.



Scheme 6 CuAl-LDH mediated homocoupling of alkynes

CuAl–LDH with Cu:Al molar ratios of 3:1 and 4:1 were found to be effective at room temperature and were tested with a variety of substrates. Low cost and reusability of CuAl–LDH catalyst makes it suitable for commercial applications, but it requires an additional step for the preparation of the reagent.

The zeolites modified with cuprous ions in DMF offer another alternative catalyst in the Glaser coupling of a large number of alkynes including those containing carbohydrate moieties.[12] The catalyst was proved to be good due to the heterogeneous nature and appropriate pore size of zeolites.

Instead of copper salts, copper immobilised on a functionalised silica support also serves as an efficient heterogeneous catalyst for acetylenic homocoupling.[13] The catalyst was prepared by functionalizing the silica support by refluxing with 3-aminopropyltriethoxysilane followed by heating with an alcoholic solution of copper (I) chloride. The regeneration and recycling of the catalyst in the presence of air was very effective and thus emerged as a viable catalytic route. Copper nanoparticles supported on silica coated maghemite nanoparticles (MagSilica®) have also found to be an efficient, magnetically recoverable and easily reusable catalytic system. The simplicity of its preparation also adjoins to its utility.[14]

A series of heterobimetallic complexes $\{Cu^+–Co^{3+}–Cu^+\}$, $\{Cu^+–Fe^{3+}–Cu^+\}$, $\{Cu^{2+}–Co^{3+}–Cu^{2+}\}$ (**Fig 1**), can also be used as catalysts for the oxidative coupling of terminal alkynes.[15]

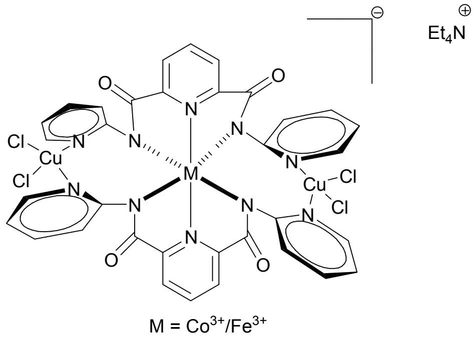
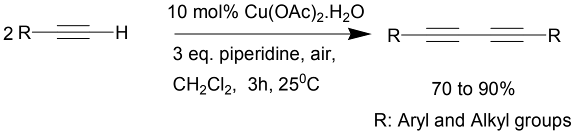


Fig 1 Heterobimetallic ligands used as catalysts in Glaser coupling. Reprinted with permission from ref. 15, copyright 2014, John Wiley and sons.

These complexes are used for better yields under mild and solvent free conditions and with O_2 as the only oxidant. The catalysts can be recoverded and reused effectively.

The use of copper(II) acetate in presence of stoichiometric amounts of piperidine was explored recently.[16] Oxidative dimerisation of various substrates bearing electron -donating and electron-withdrawing groups in presence of piperidine without any co catalyst proceeds with very good yields at ambient temperature (scheme 7).



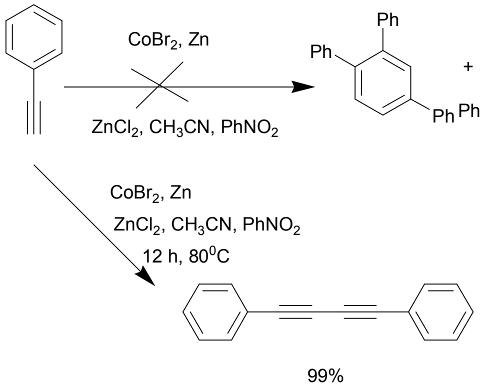
Scheme 7 Synthesis of conjugated 1, 3-diynes catalysed by $Cu(OAc)_2.H_2O$ in presence of piperidine

Glaser coupling was also achieved with CuI/NBS/DIPEA system in acetonitrile at room temperature.[17] Here N-Bromosuccinimide (NBS) acts as the oxidant, and sensitive functional groups such as acetal, ketal, TBDMS, ester and amide are tolerated in the reaction affording good amount of the coupling products.

A mild and base free method using di-tert-butyldiaziridinone as oxidant and CuBr as catalyst is also reported very recently for the homocoupling reaction.[18] Various aromatic and non-aromatic terminal alkynes with either electron-donating or electron-withdrawing substituents were smoothly coupled to give the corresponding 1,3-diynes in good yields.

2.2. Cobalt-catalysed alkyne homocoupling reaction

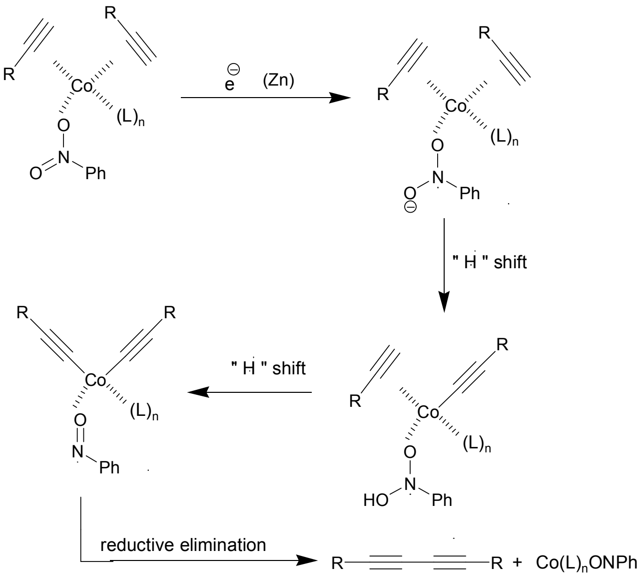
Glaser-type coupling of terminal alkynes was also attempted with cobalt catalysts.[19] When phenylacetylene was treated with a suspension of $CoBr_2$, Zn powder and nitrobenzene, the coupled product was obtained in quantitative yield instead of cyclotrimerisation product (scheme 8).



Scheme 8 Cobalt-catalysed alkyne homocoupling

It is evident that nitrobenzene can be used as a stoichiometric oxidant in the cobalt-catalysed Glaser coupling and acceptable yields were obtained with alkenyl, aliphatic, and silyl-substituted alkynes.

In contrast to the classical Glaser coupling reaction, the cobalt-catalysed reaction was performed under reductive conditions (zinc powder). Initial steps for cobalt-catalysed reactions proposed by Hilt et al. are shown below (scheme 9).

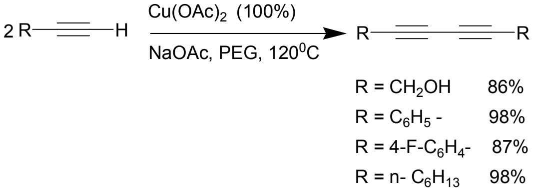


Scheme 9 Mechanism of Cobalt-catalysed alkyne homocoupling proposed by Hilt et al. Reprinted with permission from ref. 19, copyright 2009, Thieme.

2.3. Greener solvent alternatives for coupling reactions

The traditional oxidative homocoupling reactions are generally carried out in organic solvents such as DMF, THF, methanol, acetonitrile, pyridine, toluene etc. However, these solvents are harmful to environment and human beings. Often large volumes of solvents are required for smooth execution of the reaction and to achieve good selectivity. For designing environmentally benign process, commonly used organic solvents should be replaced by green solvents like supercritical fluids, ionic liquids, water etc. Even solvent free conditions would be attractive.

Poly ethylene glycol (PEG) is used as a green and efficient solvent replacement for homocoupling of terminal alkynes.[20] Here $Cu(OAc)_2$-polyethyleneglycol-NaOAc system was used in the homocoupling of terminal aryl and alkyl alkynes resulting in good yields of the products (scheme 10). In the optimized reaction condition, 100 mol% $Cu(OAc)_2$, 1.5 equivalents of NaOAc and PEG (4g for 1 mmol of alkyne) were used at 120 °C.



Scheme 10 Copper mediated homocoupling of alkynes using NaOAc and PEG

The chain length of PEG affects the yield of the product and best yields were obtained when PEG6000 was used. Increase or decrease of molecular weight from that of PEG6000 decreased the yield of the product considerably.

Only limited examples of aryl and alkyl alkynes were tested with this methodology. When the catalyst was recycled, the activity dropped drastically. The reason for this is attributable to the formation of Cu_2O from $Cu(OAc)_2$ during oxidative coupling. The activity of the catalyst was regained when the catalyst from the reaction was separated and treated with acetic acid. Use of one equivalent of Cu salt hampers the usefulness of this protocol. For performing the synthesis of industrially relevant macrocycles with varying ring sizes and functional groups in large scales, Collins and Bedard developed two strategies at higher concentrations.[21] One strategy uses PEG400 as an efficient solvent for Cu/pyridine complex in biphasic mixtures and the second approach uses T-PEG1900 which imparts a preference for the catalyst complex to solubilise in hydrophilic media.

The same group employed microwave irradiation for better efficiency in the macrocyclisation.[22] The rate of the reaction was accelerated when Cu/TMEDA catalyst and PEG400/MeOH solvent mixture were used under microwave irradiation. The duration of reaction could be decreased considerably (from 48 hours to 1-6 hours) and the reaction could be performed at concentrations up to 0.1 M though the yields of the products were somewhat less than that obtained with traditional heating. All these reactions emphasise the usefulness of PEG as a green solvent.

A recent report showed that a fluorous, oxime-based palladacycle[23] (fig. 2) could be used as an active pre-catalyst for homocoupling of terminal alkynes under microwave irradiation in either aqueous or organic medium. The MW irradiation increased the yield of the desired product considerably and reduced the reaction time significantly when used with a co-catalyst CuI.

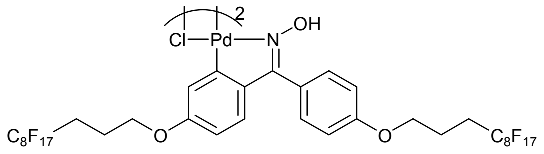
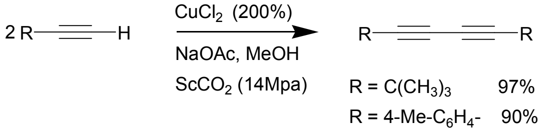


Fig 2 fluorous, oxime-based palladacycle

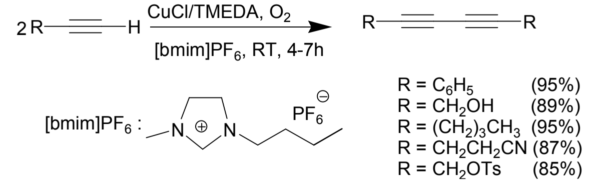
Supercritical CO_2 ($ScCO_2$) has emerged as a useful solvent in organic synthesis in recent days.[5] Jiang and Li demonstrated for the first time that Glaser coupling could be carried out smoothly in supercritical carbon dioxide as solvent (scheme 11). The homocoupling of terminal alkynes in $ScCO_2$ was achieved in the presence of 2 equivalents of $Cu(II)Cl_2$, sodium acetate and small quantities of methanol at 14 MPa CO_2 pressure.[24] Alkyl and aryl alkynes afforded the products in excellent yields.



Scheme 11. Cu-mediated homocoupling of alkynes in supercritical CO_2

Another Glaser coupling reaction was carried out by Li et al. in supercritical CO_2/PEG biphasic system or in PEG alone.[25] Here, the homocoupling of terminal alkynes occurred smoothly when the reaction was carried out in compressed CO_2/PEG biphasic system catalysed by $CuCl_2.2H_2O$ in the presence of O_2 under 15 MPa CO_2 pressure at 120 °C. Here the best result was observed when PEG 1000 was used. These reactions exemplify the utility of $ScCO_2$ and PEG as green solvents.

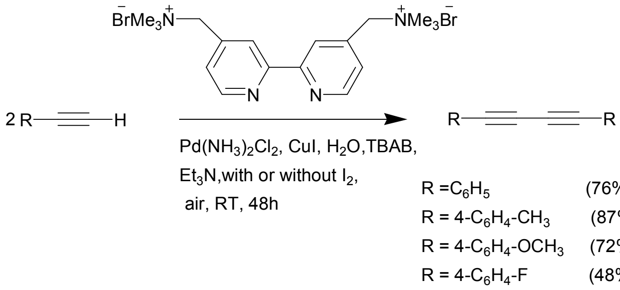
Yadav et al. reported a modification to the Glaser oxidative coupling for the synthesis of conjugated polyynes in which ionic liquids were used as solvents in mild conditions.[26] The reactivity of alkynes increased considerably, the reaction time reduced and the yields improved when ionic liquids were used as the solvent. Hydrophobic [bmim]PF_6 was used in the presence of CuCl-TMEDA and oxygen atmosphere for the oxidative dimerisation of terminal alkynes and the corresponding 1,3-diynes were produced in excellent yields(scheme 12).



Scheme 12 Copper-catalysed homocoupling of terminal alkynes in water

Ionic liquids allow the recycling and reuse of this catalytic system with simple procedures and thus pave path for green synthesis. [bmim]OH has also been tried as a solvent under atmospheric conditions for homocoupling of acetylenes.[27]

Water is considered to be the best environmentally benign solvent for any reaction. To address environmental concerns, impact of water as solvent was also explored.[28] The green process using water-soluble cationic 2,2'-bipyridyl palladium(II)/CuI catalytic system was successfully performed in water under aerobic conditions(scheme 13). The coupling of aliphatic terminal alkynes was carried out in presence of TBAB and I_2 to get better yields.



Scheme 13 Copper-catalysed homocoupling of terminal alkynes in water

2.4. Solvent free Glaser Coupling

The first solvent-free procedure for homocoupling of alkynes involved a $CuCl_2$–pyridine complex as the catalyst.[29] Kabalka et al. successfully performed the Glaser reactions by heating the substrates in a microwave oven in the presence of KF–Al_2O_3 (40 w% KF) and $CuCl_2$ to afford the coupling products in a very short time.[30] This reaction was optimized with 5 mol% Copper salt in neutral alumina and morpholine by Sharifi et al.[31] The strategy worked well for the homocoupling of aromatic acetylenes, propargyl amines and ethers and afforded the products in good yields within 10 minutes.

Another simple solvent free reaction was reported in which the homocoupling of terminal alkynes was carried out with catalytic amounts of $CuCl_2$ and triethylamine at 60 ^0C in air.[32] The reaction tolerated a variety of substrates and the catalyst was recycled successfully making it acceptable for industrial production.

Recently a continuous flow Glaser–Hay coupling mediated by dioxygen, based on a tube-in-tube gas or liquid reactor was reported.[33] The system utilises a semi-permeable Teflon AF-2400 membrane to achieve rapid contact in flow. The coupling generally proceeded in high yields, affording products in high purity without utilizing any chromatographic purification methods.

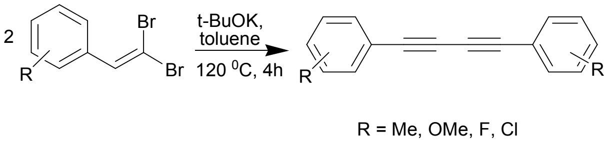
Terminal alkynes were effectively converted into the corresponding 1,4-substituted buta-1,3-diynes in a vibration ball mill using zirconia (ZrO_2) as the material for the milling beakers and balls.[34] This may be the first experimental reaction protocol for Cu-catalysed coupling reaction in a ball mill. Homocoupling of phenylacetylene was proved good with CuI catalyst and 60 w% KF and neutral alumina.[35] In presence of CuI catalyst and DABCO, 1,4-substituted buta-1,3-diyne was formed in good to excellent yields within 10 minutes. Reactions in ball mills were identified as powerful as irradiation with microwave from the performance base parameters like yield, selectivity, Turn over Number, Turn Over frequency etc.

3. Substrates susceptible to homocoupling – strategies to achieve clean reactions

The feasibility and selectivity of alkyne homocoupling proliferate on metallated alkynes and other related substrates. The use of these precursors promoted the exclusive formation of 1,3-diynes and prevented the formation of undesired products.

3.1. Dihaloolefinic substrates

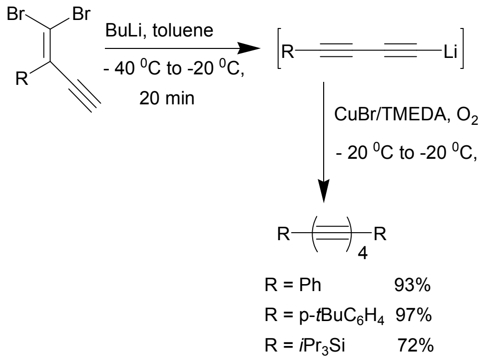
A simple and novel transition metal-free synthetic route has been developed by Jincan and Lie for the preparation of 1,3-diynes using Glaser type coupling of 1,1-dibromo-1-alkenes in the presence of *t*-BuOK and toluene in moderate to good yields (scheme 14).[36]



Scheme 14 Transition metal-free homocoupling of dihaloolefins

The reaction proceeded smoothly irrespective of the electronic nature of substituents and the substitution pattern on the aromatic rings. The reaction presumably proceeds through the debromination in the presence of *t*-BuOK to form the corresponding alkynyl bromide intermediate which subsequently couples with terminal alkyne or its derivative to generate the homocoupling product as in the case of a classic Glaser reaction.

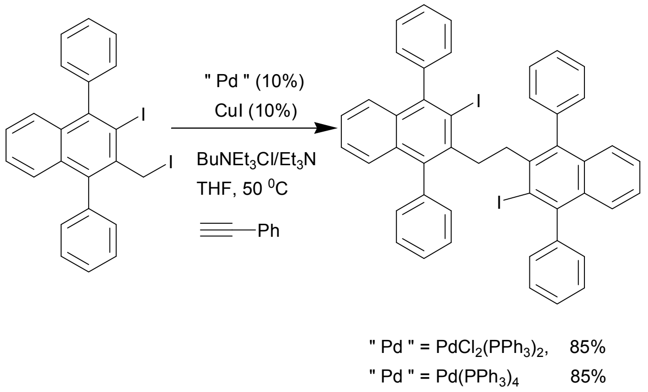
A divergent one pot synthesis of functionalised polyynes has been developed by Tykwinski and co workers.[37] The protocol involved the generation of lithium acetylide from 1,1 bromoolefines based on the Fritsch-Buttenberg-Wiechell rearrangement followed by transmetallation to Cu(I) by adding CuBr (1 eq.) and TMEDA (17 eq.) in presence of oxygen (scheme 15).



Scheme 15. One pot synthesis of diynes from substituted gem-dibromoolefins

The polyyne products were formed in one step with good to excellent yields. Acetylides from transition metals such as Zn, Sn, Pt are also were employed for the synthesis of similar products.

An unexpected homocoupling was observed by Shi and coworkers when Sonogashira coupling was tried between 2-iodo-3-iodomethyl-1,4-diphenylnaphthalene and phenyl acetylene in the presence of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$, CuI, Et_3N and $BuEt_3NCl$ in THF at 50 ^oC[38] (scheme 16).



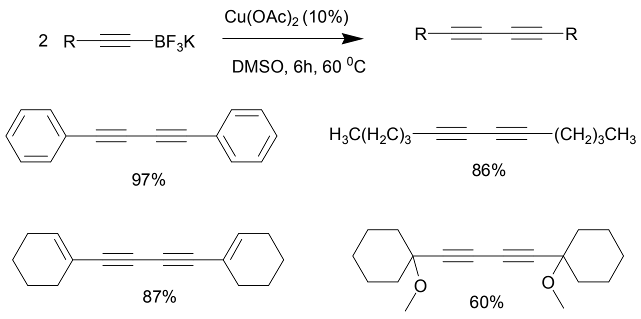
Scheme 16 Pd/Cu-catalysed coupling of 2-iodo-3-iodomethyl-1,4-diphenylnaphthalene and phenyl acetylene

Under the reaction conditions, Csp^3-Csp^3 homocoupling of the iodo derivative took place in 85% yield along with a small quantity of Csp-Csp homocoupling product. Low yield of the product was observed in the absence of copper iodide.

Interestingly, no Csp^3-Csp^3 homocoupling occurred in the absence of phenyl acetylene indicating its active role in the mechanism of the reaction. Substituted iodomethyldiphenyl naphthalene derivatives also gave Csp^3-Csp^3 homocoupling products (44-70%) under similar reaction conditions. The possibility of a radical mechanism for this reaction was ruled out by conducting control experiments in the presence of radical scavengers like TEMPO or BHT. In both cases, the yield of the homocoupling product was not altered. Simple benzyl iodide failed to give the homocoupled product indicating that the presence of a fused aromatic system is inevitable for the success of the reaction. A tentative mechanism for this reaction was proposed involving oxidative addition-transmetallation-reductive elimination sequence.

3.2. Alkynyl borates and boronates

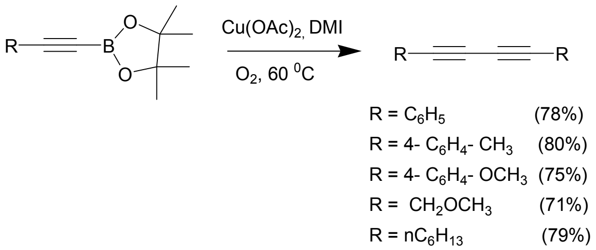
Homocoupling of alkynyl trifluoroborates to yield 1,3-diynes was reported by Paixao et al.[39] Potassium phenylethynyl trifluoroborate on reaction with Cu(OAc)$_2$ in DMSO in air at 60 °C afforded the homocoupled product in quantitative yield (scheme 17).



Scheme 17 Cu-catalysed homocoupling of Potassium alkynyltrifluoroborates using Cu(OAc)$_2$

This is an attractive method due to the simplicity of the reaction conditions. A variety of functional groups in the alkyne such as phenyl, tolyl, naphthyl, alkyl, alicyclic as well as sterically hindered quaternary carbon are tolerated in the reaction.

Homocoupling reactions of alkynylboronates in presence of Cu(I) or Cu(II) salt in aprotic polar solvent such as 1,3-dimethyl-2-imidazolidinone (DMI) and exposure to air was found to be synthetically useful for the preparation of symmetrical 1,3-butadiynes[40] (scheme 18). Alkynylboronates were prepared from isopropoxy(pinacol)borates by reaction with alkynyl lithium which in turn were prepared in situ from the corresponding terminal alkynes with n-BuLi at -78 °C.

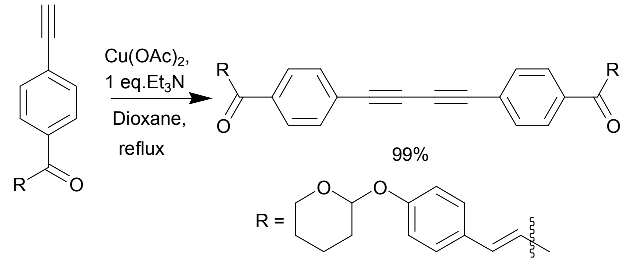


Scheme 18 Homocoupling of alkynylboronates in presence of Cu(OAc)$_2$ in DMI

Variuos derivatives of phenylethynylboronates with different substituents like 4-methyl, 4-methoxy, 3-trifluoromethyl, thio and oxo functionalities displayed excellent reactivity. This method involves the use of alkynes protected with the boron moiety, and thus the side reactions leading to enynes are avoided to a greater extent.

3.3. Acetylenic chalcones

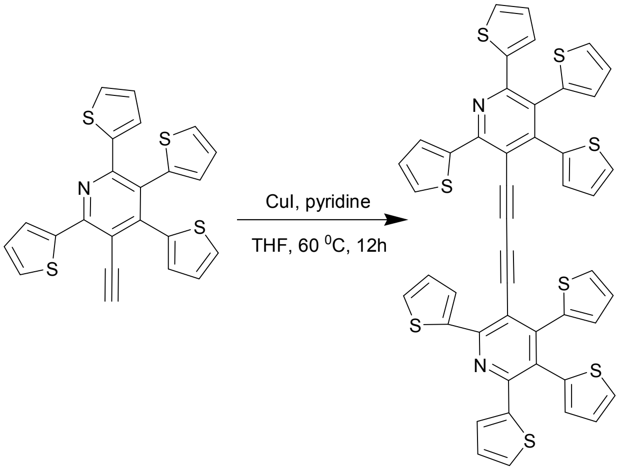
Chibale and co-workers observed the homocoupling of acetylenic chalcones during the synthesis of biologically active aryl acetylenic Mannich bases (scheme 19).[41] Dimerization of acetylenic chalcones were achieved effectively in high yields with 0.5 eq. of Cu(OAc)$_2$ (typical Cu-mediated Glaser reactions require an excess amount (10 eq.) of Cu(OAc)$_2$ in the absence of dioxygen) and 1.0 eq. of triethylamine in dioxane.



Scheme 19 Homocoupling of acetylenic chalcones with Cu(OAc)$_2$ and Et$_3$N in Dioxane

3.4. Thienyl pyridine derivatives

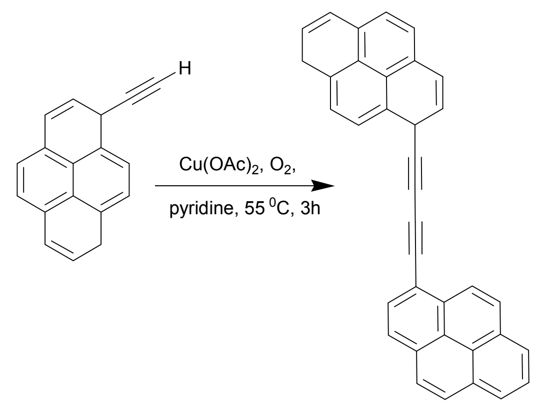
Glaser coupling was used as the key reaction in the synthesis of symmetrical per-(2-thienyl)pyridine derivatives from easily available pyridiols.[42] Alkyne substituted penta(2-thienyl)pyridine derivatives underwent Glaser coupling affording bis[penta-2-(thienyl)pyridyl]substituted butadiyne in good yields (scheme 20) which showed interesting photophysical and electrochemical properties.



Scheme 20 Homocoupling of thienyl pyridine derivatives

3.5. Pyrene derivatives

When cupric acetate was added to 1-ethynylpyrene in pyridine, 1,4-di(1-pyrenyl)butadiyne was obtained; here the linkage of the two pyrene units was established via a butadiynylene bridge (scheme 21).[43]

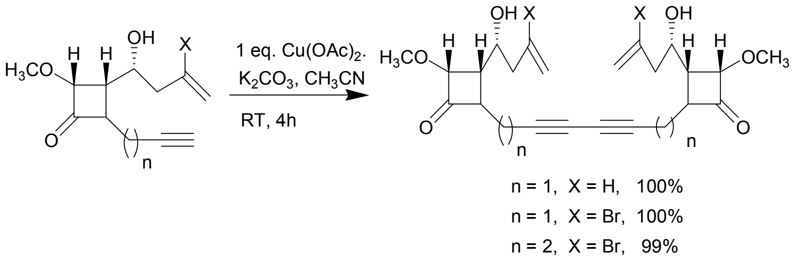


Scheme 21 Homocoupling of pyrene derivatives using Cu(OAc)$_2$

The dipyrene derivative showed intense fluorescence which was neither susceptible to self-quenching nor affected by the presence of molecular oxygen. . In the singlet state it can undergo both oxidative (*E*ox ≈1.4 eV) and reductive (*E*red ≈1.1 eV) electron transfer process which is in contrast to the property of pyrene which can only behave as a photoreductant. Other aromatic polycycles such as perylene also displayed photophysical properties.

3.6. Alkynyl β-lactams

Alkynyl β-lactams are good substrates for homocoupling reactions.[44] Copper-promoted homocoupling of alkynyl β-lactams in presence of stoichiometric quantities of Cu(OAc)$_2$ in acetonitrile and in the presence of O$_2$ and Et$_3$N or K$_2$CO$_3$ as base afforded quantitative yields of the product (scheme 22).

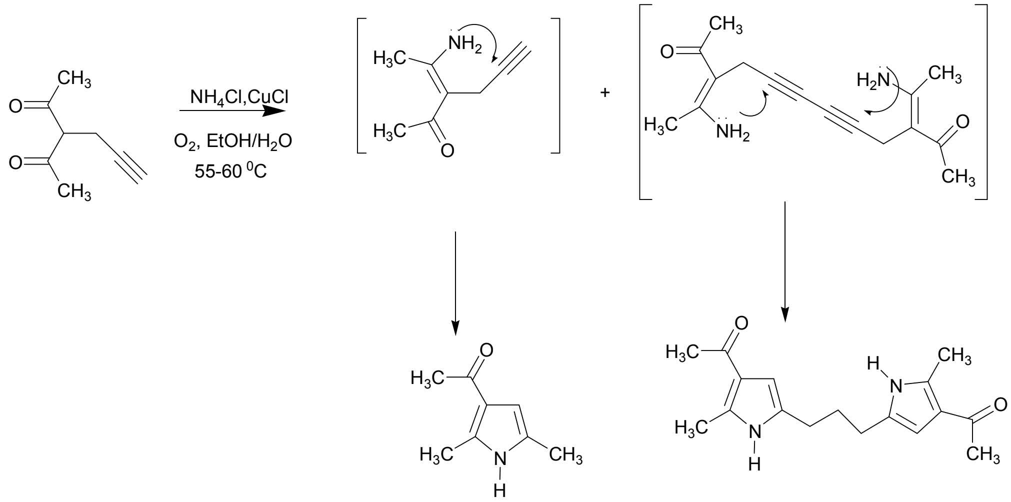


Scheme 22 Copper-mediated homocoupling of alkynyl β-lactams

The reaction was found to be general and an array of functional groups on the β-lactam ring such as alkenyl, alkoxy, hydroxyaryl, bromoaryl, carboxyalkyl, vinylbromide etc. are compatible with the reaction affording excellent yields of the products. The reaction went well irrespective of the position of the alkynyl group in the β-lactam ring. A radical mechanism involving one electron oxidation of copper acetylide to generate a free radical and subsequent dimerisation was proposed for this reaction.

3.7. 2-Propargyl-1,3-dicarbonyl compounds

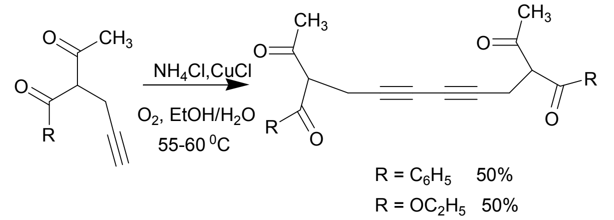
Synthesis of diacetylenes, substituted pyrroles and cumulenes were reported by Vizer and Yerzhanov using modified Glaser type reaction conditions.[45] Two products viz. 2,5-dimethyl-3-acetylpyrrole and the corresponding dipyrrole were formed during the oxidative dimerisation of 1,3-diketone in water–ethanol solution of ammonium chloride in presence of CuCl$_2$ and oxygen (scheme 23). When three times excess cuprous chloride and ten times excess ammonium chloride was used, substituted pyrrole was formed in 49% yield. But when palladium chloride was used instead of cuprous chloride dipyrrole was obtained in 65% yield.



Scheme 23 Glaser coupling of 3-acetylhex-5-yn-2-one. Reprinted with permission from ref. 45, copyright 2006, John Wiley and Sons.

3-Benzoylhex-5-yn-2-one and 2-acetylpent-4-ynic acid ethyl ester gave only diacetylenic compounds with 50% yield (scheme

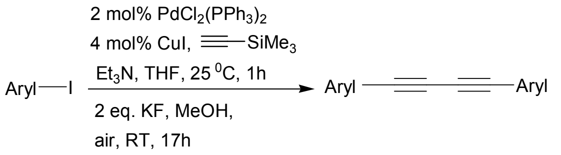
24).



Scheme 24 Synthesis of diacetylene derivatives from 3-benzoylhex-5-yn-2-one or 2-acetylpent-4-ynic acid ethyl ester

3.8. Aryl halides

In classical Glaser coupling reactions, terminal alkynes were used as substrates. But some of these terminal alkynes are unstable and thus susceptible to polymerisation. Müller et al. reported a one pot Pd/Cu-catalysed Sonogashira coupling and the catalytic Glaser coupling for the preparation of 1,4-disubstituted 1,3-butadiynes from aryl halides to avoid the shortcomings of isolating the alkynes[46] (scheme 25). The first step involved the preparation of trimethyl(phenylethynyl)silane by the reaction of iodobenzene with trimethylsilylacetylene (TMSA) in the presence of $[PdCl_2(PPh_3)_2]$, CuI and NEt_3. This was followed by deprotection of TMS group and exposure of the reaction to air with stirring to afford1,4-diphenylbuta-1,3-diyne in good yield. The yield decreases drastically in the absence of any one of the components of the catalytic system $(PdCl_2(PPh_3)_2/CuI/Et_3N)$.



Scheme 25 Cu/Pd-catalysed one pot synthesis of 1,4-disubstituted 1,3-diynes

The mechanistic basis of this one pot synthesis is the formation of TMS-protected (hetero)arylalkyne from Sonogashira coupling of aryl iodide and TMSA which is deprotected with fluoride to give the corresponding terminal alkyne. The alkyne then undergoes Glaser coupling by the catalytic Pd(II)/CuI pair. CuI ions are involved in transmetalation to Pd(II), and thus a dialkynyl Pd(II) complex is generated, which on reductive elimination furnishes the 1,3-butadiyne. The significant aspects of this sequence are the functional group tolerance and the possibility to react different types of electronically diverse six- and five-membered heterocyclic iodides.

4. Applications of alkyne homocoupling in diverse fields of Chemistry

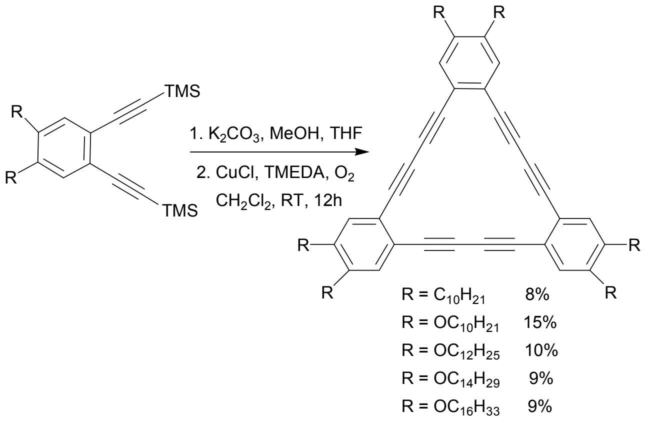
The Glaser coupling of terminal alkynes has been applied as a key step and viable procedure for carbon-carbon bond formation in many of the processes in polymer and supramolecular chemistry. The butadiynyl bridges formed from the homocoupling of alkynes act as the building blocks for shape persistent macrocycles, dendrimeric polyynes, interlocked compounds and many naturally occurring molecules.[47] Their unique electrical, optical, and structural properties make them potential components for electronic and optoelectronic devices and media. Since the applications of acetylenic scaffolds stretch out in diverse fields of chemistry, it is beyond the scope of the review to present all the works in this area. We focus mainly on the synthetic utility and recent applications of Glaser coupling in the field of supramolecular chemistry where complex molecular architecture is formed from simple building blocks.

4.1 Formation of Conjugated Macrocycles

The synthesis of macrocycles with fully conjugated and well defined shapes is one of the primary objectives of supramolecular chemistry. Some of the macrocycles are with inner cavities of nanometer range and some have specific interior and exterior sites; substitution at these sites can afford attractive structures, such as 1D,2D, and 3D supramolecular nanostructures.[48, 49] They show unique structural, electronic, and optical properties and thus used as media for electroluminescence, data storage, and nonlinear optics.[50]

4.1.1 Dehydrobenzoannulenes

Annulenes in which one or more of the double bonds have been replaced by triple bonds are termed dehydroannulenes.[51] The synthesis of hexa-substituteddodecadehydrobenzo[18]annulene ([18]DBA) derivatives[52] (scheme 26) were reported by Tahara, Tobe *et al.* focussing on their self-assembly at the interface between a liquid and graphite (HOPG).Copper-mediated coupling of silyl-protected diethynyl arenes under Hay conditions afford [18]DBA derivatives which are easily distinguishable in solution by colour and fluorescence under UV light.

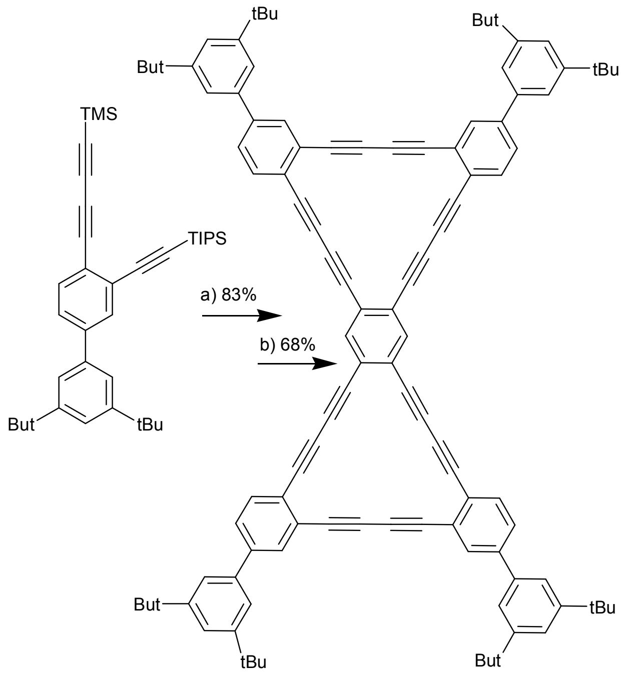


Scheme 26 The synthesis of [18] DBA derivatives using Hay conditions

Scanning Tunneling Microscopy (STM) investigations on self-assembled monolayers of these DBAs at the 1,2,4-trichlorobenzene (TCB) or phenyloctane/graphite interface [53]revealed that there are three types of structures; porous, linear, and lamella structures. The appearance of these structures was changed by altering the alkyl chain length, concentration, and the choice of solvent.

4.1.2. Construction of graphdiyne subunits

Glaser coupling with several modifications coupled with Sonogashira reaction was used by Haley and co-workers for the synthesis of networks of graphdiyne.[54] These molecules belong to complex annulenic systems composed of benzene rings and alkyne units having unique structural and optical properties. The same group investigated the synthesis and characterisation of a large number of expanded graphdiyne substructures such as dehydrobenzo[14], [16], [18] annulenes (scheme 27). The graphdiyne subunits were prepared in multi steps from polyynes with a final Cu-mediated intramolecular macrocyclisation step. The cyclooligomerization of 1,2 diethynyl benzene with CuCl and Cu(OAc)$_2$ in pyridine furnished the dimer and a 3:2 mixture of trimer and tetramer.



Reagents: (a) 1,2,4,5-tetraiodobenzene, KOH (aq), Pd(PPh3)4, CuI, i-Pr2NH, THF, 50 °C; then (b) [i] TBAF, THF, [ii] CuCl, Cu(OAc)2, pyridine, 60 °C

Scheme 27 Synthetic strategy for bis[18]annulene

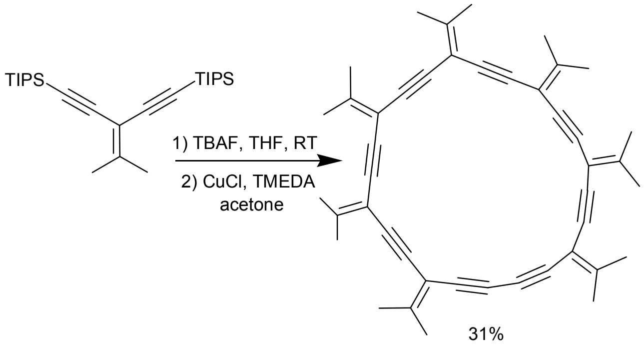
CT absorption and topological studies in relation with new properties were carried out extensively which suggested the strong dependence on the effective conjugation length of the subunits.

4.1.3 π Expanded Radialene macrocycles

Radialenes are the cyclic analogues of dendralenes, with the same number of exocyclic double bonds as that of ring atoms.[55] Several synthetic strategies have been reported for the formation of radialenes with different ring size and high functionalization over the past four decades. Several reviews have recently documented the synthesis and applications of such systems, and therefore discussion here will be limited to recent advances on “Expanded radialenes” aside from the interest in parent radialenes. Expanded radialenes are formed by insertion of an unsaturated spacer such as acetylenic, aryl, heteroatom, transiton metal[48, 56-59] between each pair of exo-methylene fragments into the cyclic skeleton of a radialene.

a) Expanded Radialenes with Acetylene Spacers

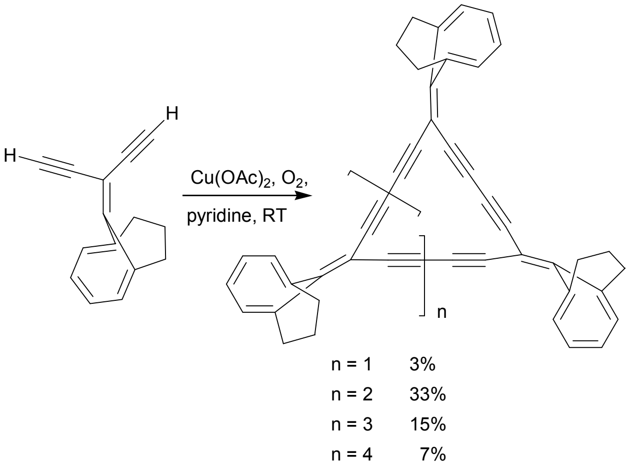
Glaser coupling plays a crucial role in the synthesis of macrocycles with π extended radialene frameworks. The synthesis of an expanded radialene based on inclusion of a single acetylene unit into the radialene framework was reported at first in 1999 by Tykwinski *et al.*[60].Later Zhao *et al*. reported the synthesis of expanded radialene1deliberately via the oxidative homocoupling of the protected heptamer in high dilution conditions using the Hay catalyst in dry acetone[59] (scheme 28). The cyclic enyneheptamer could be isolated in 31% yield as a colourless solid which was rather insoluble in most of the solvents.



Scheme 28 The synthesis of cyclic enyneheptamer under Hay conditions

b) Expanded Radialenes with Diacetylene Spacers

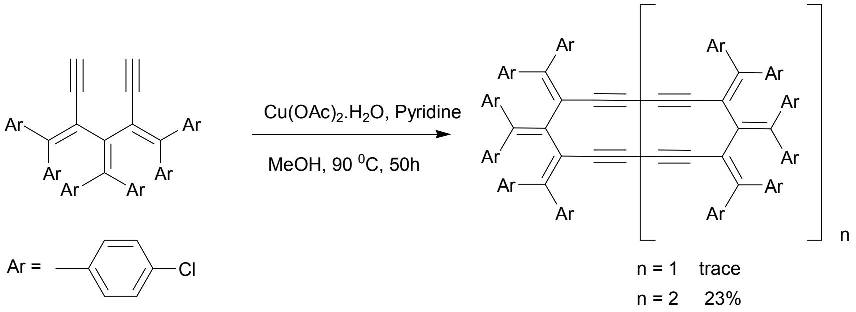
Tobe and co-workers have synthesised expanded radialenes (as a mixture of diastereomers) by copper(II)-mediated oxidative coupling of enediyne under dilute conditions[61] (scheme 29). Cyclic dehydrotetramer (n = 2) was obtained as the major product (33%) together with cyclic dehydrotrimer (n=1), dehydropentamer (n = 3) and dehydrohexamer (n = 4).



Scheme 29 Synthesis of cyclic dehydrooligomers with diacetylene Spacers

Electronic spectroscopic analysis of these structures revealed that the macrocycles with lowest ring size (*n* =1) showed the lowest energy absorption (*ì*max = 344 nm) as well as the smallest molar absorptivity. They exhibit poor solubility in organic solvents which make the spectroscopic analysis difficult. These expanded radialenes are used as precursors to the cyclo[*n*]-carbon anions with the loss of the aromatic indane fragments. .

In 2004, Iyoda *et al.* reported the synthesis of polyenyne macrocycles with π-extended [9]- and [12]radialene frameworks from suitable dendralene precursors.[56] Homocoupling reaction of bis(ethynyl)[3]dendralene with $Cu(OAc)_2.2H_2O$ in pyridine-methanol afford the dimer and trimer (scheme 30)

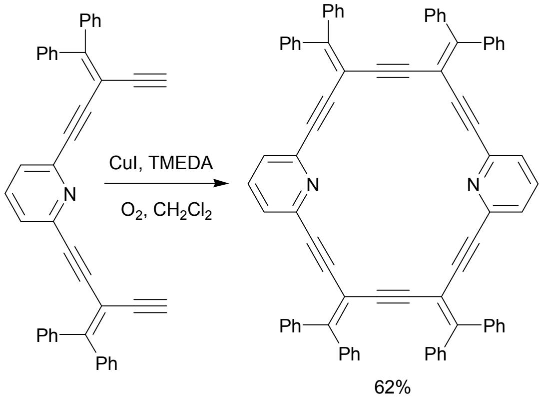


Scheme 30 Synthesis of π extended radialenes from dendralenes

The dimer was detected only by MS Analysis. The highly symmetrical trimer with a small inner cavity (2.6A^o) could be isolated and characterized by ^{1}H NMR spectroscopy and MALDI TOF-MS analysis. The trimer is capable of incorporate a silver cation when treated with $AgOCOCF_3$ or $AgClO_4$.

c) Expanded Radialenes with Arylene Ethynylene Spacers

These series of expanded radialenes are obtained by inserting Arylene Ethynylene groups between each pair of methylene units of radialenes C_nH_n. Tykwinski and co-workers have synthesized fully conjugated macrocycles based on 3,5-diethynylpyridyl subunits by oxidative acetylenic coupling strategies[62] (scheme 31).



Scheme 31 Synthesis of expanded radialenes with pyridyl Spacer

The pyridyl moiety was oriented endocyclic and exocyclic with respect to the macrocyclic core and adopted a nearly planar conformation in the solid state without any ring strain. They readily function as macrocyclic analogues of bipyridines and participate in self-assembly into highly ordered systems, by axial coordination to metalloporphyrins.[63] When the solution of macrocycle in DCM was added to cis-$(TfO)_2Pt(PEt_3)$, an assembly with bidirectional porosity was obtained within 2 days. X-ray analysis of the crystals confirmed that these solids are capable of selective uptake of small organic molecules into the molecular channels. [64] From hyperpolarised ^{129}Xe NMR spectroscopy, it is found that the channel structure remains unhurt even upon removal of the co-crystallised guest molecules.[65]

d) Radiaannulenes

Diederich and co-workers developed a novel class of planar, highly conjugated, all carbon macrocycles called radiaannulenes which represent a hybrid of traditional annulenes and expanded radialenes.[66, 67] Bicyclic radiaannulene (Fig 3) was prepared from tetraethynylethene (TEE) building blocks via an oxidative homocoupling reaction.

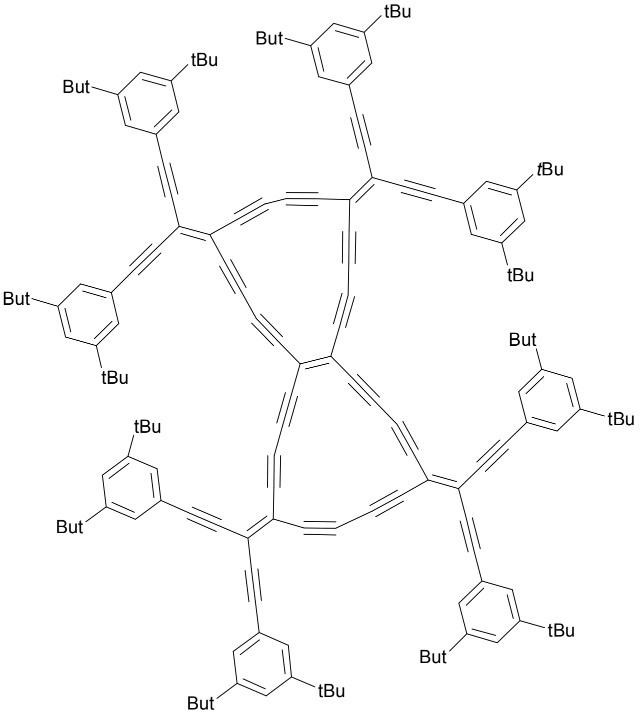


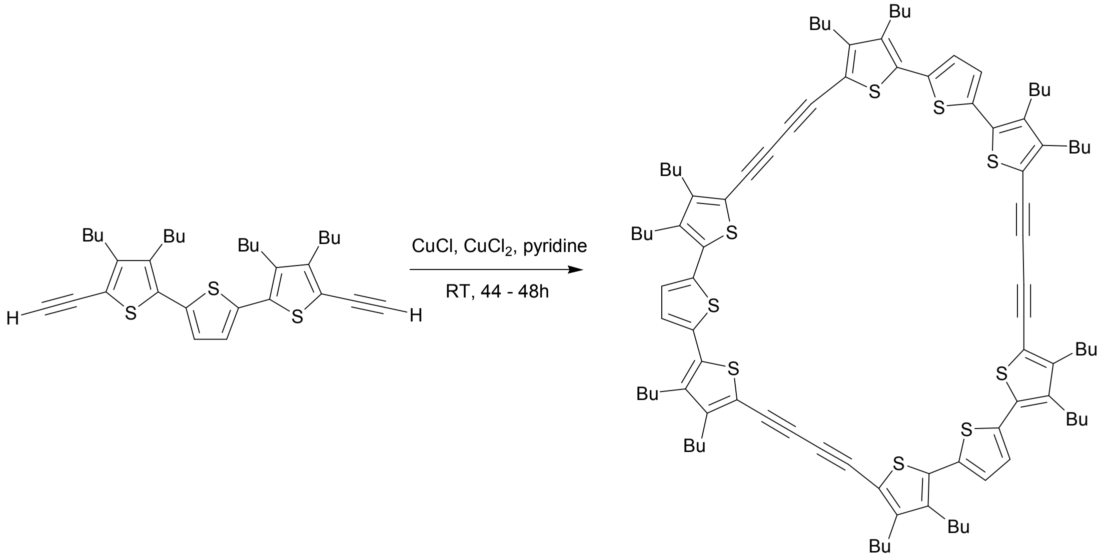
Fig 3 Bicyclic radiaannulene

These types of structures are considered as powerful electron acceptors with a remarkably low first reduction potential at -0.81 V. Upon peripheral substitution with electron-donating *N,N*-dialkylanilino groups, a very strong intramolecular charge transfer was displayed with a low-energy end-absorption at 850 nm, which is the lowest energy known for any other TEE oligomers.

4.3 Macrocyclic oligothiophenes

Poly- and oligo- thiophenes are efficient and most promising materials in the field of electronics and photonics due to their easier polarizability and stability in various redox states, and tunable electronic properties.[68-70] They are extensively used in electronic devices such as organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs), and organic solar cells.[71, 72]

The syntheses of π-Expanded oligothiophenes by copper-mediated oxidative coupling of butylated thiophenes under high dilution conditions was first reported by Bauuerle *et al.* in 2000.[73] Macrocyclic cyclo[n]thiophene (n = 12, 16, and 18) have been synthesised from 3,4- dibutyl-2,5-diethynylthiophene by modified Glaser-Eglington or Glaser-Hay coupling conditions (scheme 32).



Scheme 32 Macrocyclization of thiophenediyne to cyclothiophene diacetylene under modified Glaser-Eglington conditions

This reaction has been applied to the synthesis of cyclic oligothiophenes containing thienylene, ethynylene, and vinylene units also. Synthesis of fully conjugated oligothiophenediacetylenes having dibutyl substituents on alternate thiophene units were also investigated by the same group.[74] These cyclic oligothiophenes are capable of enfolding guest molecules and thus are highly useful for molecular recognition by utilising the inner cavities of known dimensions which usually in the nanometer range.[75, 76]

Recently, Aso and co-workers synthesised rectangular oligothiophenes from substituted ethynylbenzothiophenes[77] (scheme 33). Intramolecular Eglinton-Galbraith coupling by using excess amount of $Cu(OAc)_2$ in high dilution conditions is the key step in the formation of both the diacetylene precursor and rectangular oligomer. The oligomer dissolves in common organic solvents and has comparable electrochemical properties and thus making the oligomer suitable for the production of solution-processable semiconducting materials.

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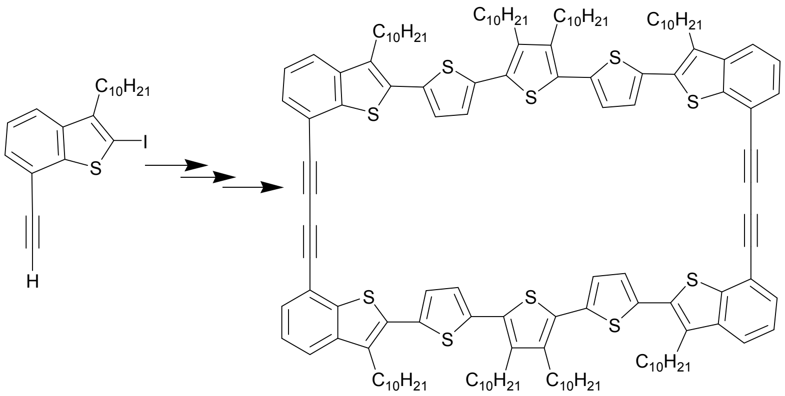

Scheme 33 Synthesis of rectangular oligothiophene bearing benzothiophene units at the corner positions

Mayor and Didschies reported a giant conjugated molecular ring (Fig. 4) with a diameter of about 12 nm with periphery comprising of conjugation active sub units like ethynylene, butadiynylene, 2,5-thienylene, and 1,4-phenylene moieties.[78] 2,5-Diethynylthiophene with two acetylene units at the para position turned out to be the ideal corner unit.

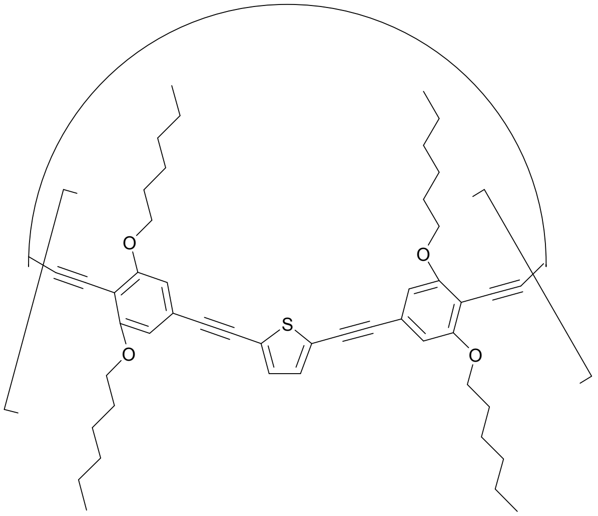

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Fig 4 A giant molecular ring with 2,5-Diethynylthiophene as the corner unit. Reprinted with permission from ref. 78, copyright 2003, John Wiley and Sons.

The multistep synthesis involved four sequential oxidative acetylenic coupling of subunits derived from hydroquinone and 2,5-dibromothiophene. The optical investigations indicate that the observed absorption maximum (461nm) is very close to the theoretical value (462 nm) and thus these structures are good candidates for supporting persistent currents at low temperatures.

4.4 Pyridine containing macrocycles

Pyridine containing macrocycles have attracted much attention as a consequence of their interesting structural and optical properties. Pyridine containing macrocycles such as butadiyne-bridged (2,6)-pyridinophane derivatives were first reported by Tobe et al. [79] The synthesis is based on a Cu-catalysed acetylenic dimerisation strategy. Oxidative coupling of bis-(trimethylsilyl)ethynyl derivative obtained by condensation of dichlorocitrazinic acid with 1-octanol afforded the dimer which on deprotection and stepwise intramolecular oxidative coupling using Hay's and Eglinton's methods under high dilution conditions gave the corresponding tetramer and hexamer with 50% and 29% yield respectively (scheme 34).

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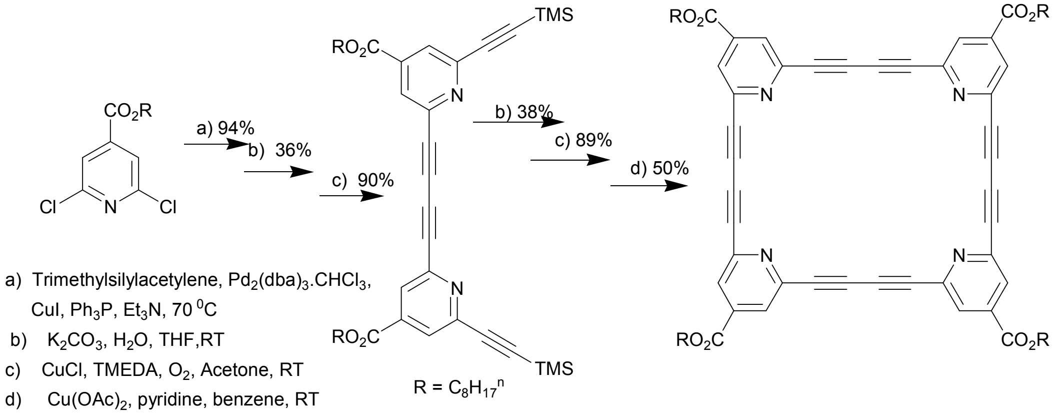
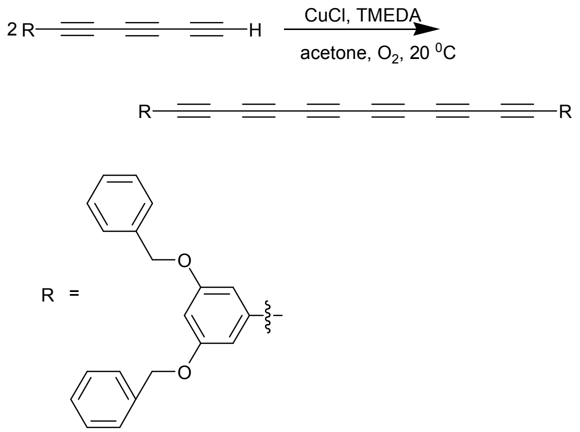


Scheme 34 Synthesis of Butadiyne-bridged (2,6)-pyridinophane

These butadiyne-bridged pyridinophanes have no tendency to self-aggregate in solution but form hetero-aggregates with the corresponding metacyclophanes, and have the ability to bind with large organic cations like tropylium to form 1:1 and 2:1 complexes.

4.5 Generation of macrocyclic and dendrimeric polyynes

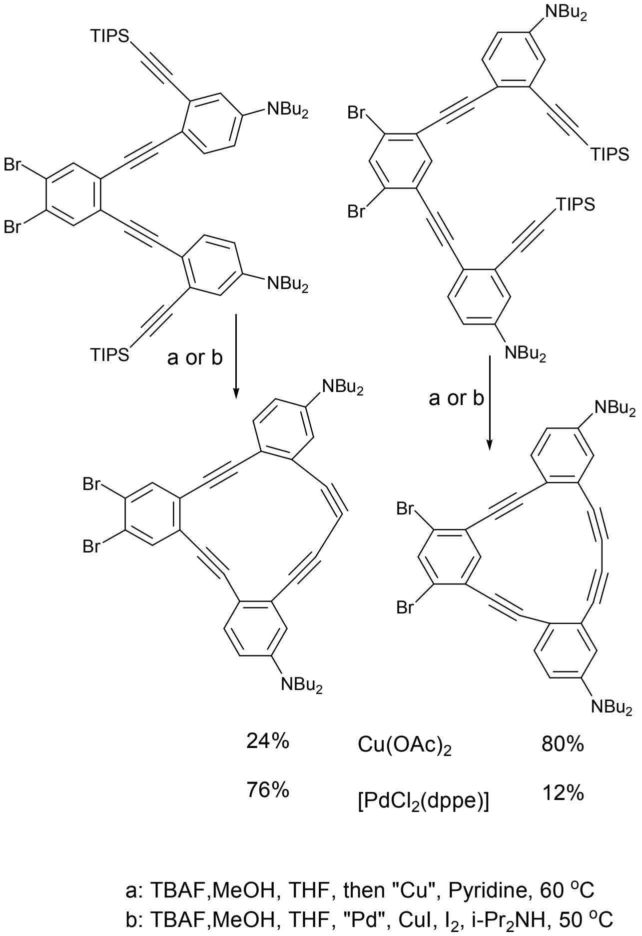
Many generations of dendrimeric polyynes containing even number of acetylene units were prepared by the Hay modified Glaser coupling.[80] An example for a first generation product is shown below (scheme 35).



Scheme 35 CuCl-catalysed homocoupling of terminal alkynes using TMEDA

All of the long symmetrical polyynes exhibit an indefinite stability in solution and to air, whereas in the solid state they display different behaviour; for example, the hexayne decomposes to black polymeric material.

Homocoupled products were obtained under typical Sonogashira cross coupling conditions (Pd, CuI, base) by the addition of a suitable oxidant and avoiding organic electrophile.[81] (scheme 36). Macrocycle formation by intramolecular homocoupling of terminal alkynes was also reported in this article.



Scheme 36 Pd/Cu-catalysed intramolecular homocoupling of terminal alkynes

It is observed that the geometry and the ring size of the macrocycle could be controlled by choosing the right catalyst. Thus $Cu(OAc)_2$ gave [15]annulene in 80% and [14]annulene in 24% yields. On the other hand when $[PdCl_2(dppe)]$ was used, 12 % of [15]annulene and 76% of [14]annulene were formed.

The reason for the formation of different products was attributed to the difference in the structure and shape of the intermediate metal acetylides. Here copper forms a dimeric Cu(I)acetylide, which exists in a pseudo trans configuration. But for Pd catalyst, the intermediate metal acetylide has a cis configuration. Certain systems cannot attain the pseudo trans configuration due to strain. Systems which can easily form intermediates with cis configuration will favour Pd catalysis.

4.6 Shape persistent macrocycle formation

Synthetically challenging targets like shape persistent macrocycles and tubular or more complex molecular structures were synthesized by oxidative Glaser coupling of two acetylene-terminated precursors under pseudo high-dilution conditions and the synthesis and applications of these shape persistent macrocycles were reviewed recently.[82, 83] Macrocycles have interesting photophysical, light harvesting and material properties.[84] Nano-sized shape persistent macrocycles containing appropriate functional groups in intra-annular sites can act as biological receptors too. These are of great scope and can be synthesised by the intermolecular oxidative Glaser coupling of bisacetylenes.

The first synthesis of a nano-sized shape-persistent macrocycle was reported by Höger.[4] The macrocycle (Fig. 5) contains two intra annular carboxylic acid groups and four (S)-2-methylbutoxy groups which provide enough solubility and scope for further functionalisation.

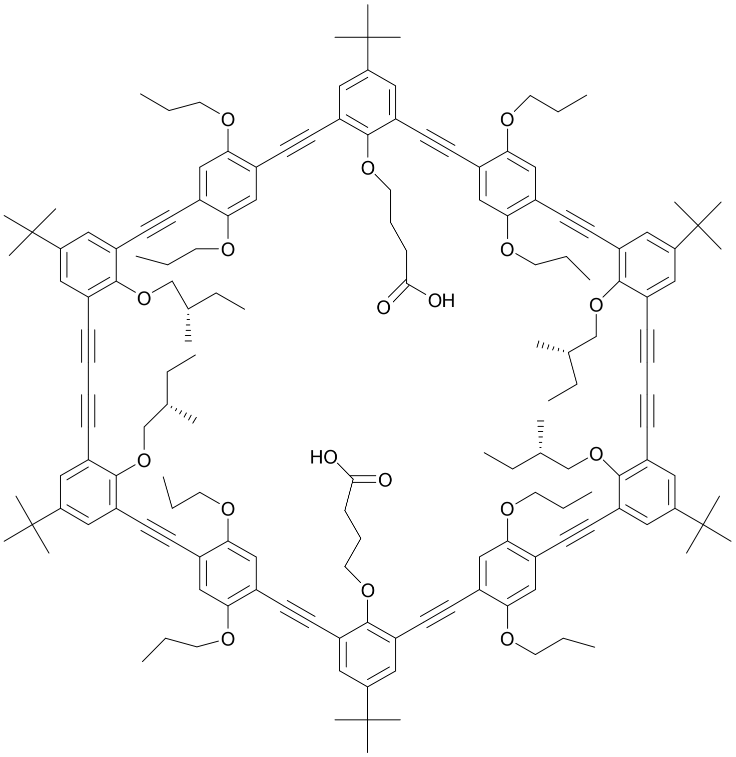


Fig.5 Nano-sized shape-persistent macrocyclic diacid. Reprinted with permission from ref. 4, copyright 1997, American Chemical Society.

Another recent investigation carried out by the Höger's group is based on the synthesis and characterisation of a shape-persistent triphenylene–butadiynylene macrocycle.[85] The method utilizes oxidative coupling of bisacetylenes derived from 3,6-dibromophencyclone and bis-(4-methoxyphenyl)acetylene by Glaser-Eglinton conditions (scheme 37).

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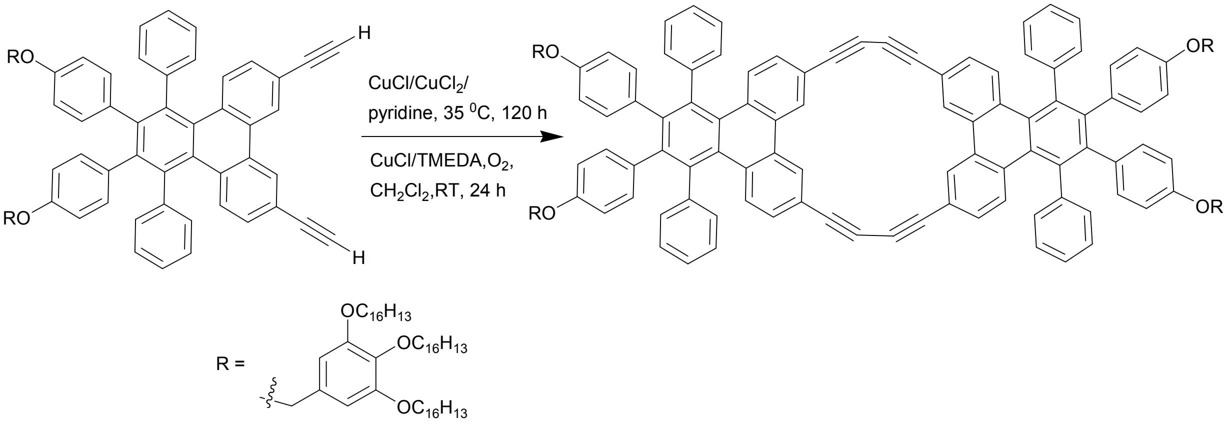
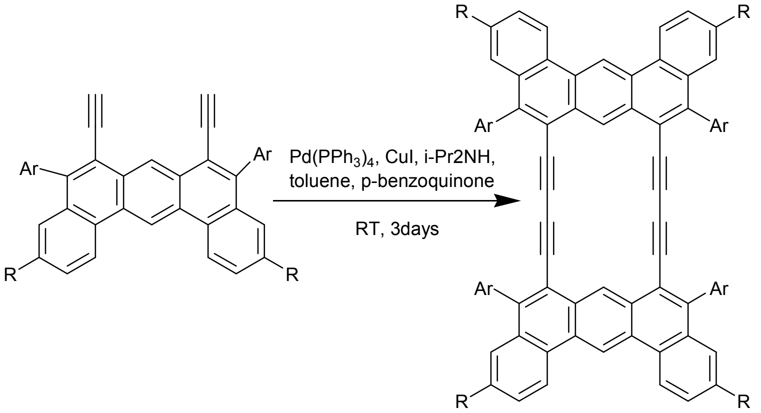


Scheme 37 Synthesis of triphenylene–butadiynylene macrocycle

Since the diacetylene bending in the macrocycle has a constrained topology, the macrocycle is more conjugated in the ground state and less so in the excited state on comparison with its open dimer. The flexible side groups allow more solubility to the macrocycle even in nonpolar solvents like cyclohexane.

There are a large variety of shape-persistent macrocycles like shape-persistent elliptic macrocycles composed of polycyclic aromatic hydrocarbons[86], poly(*p*-phenyleneethynylene)s, (polyPPEs), oligo(*p*-phenylenebutadiynylene)s, (oligoPPBs) etc. which are used as light-harvesting systems and photochemical sensors.[87]

Synthesis of J-aggregating dibenz[*a,j*]anthracene-based macrocycles[88] was reported recently by Swager which displays amazing photophysical properties and find use in optoelectronic devices. Functionalised dibenz[*a,j*]anthracene units with alkyne substituents were prepared first and the macrocyclic system was realised by a modified Glaser coupling under high-dilution techniques (scheme 38).



Scheme 38 Synthesis of J-aggregating dibenz[a,j]anthracene-based macrocycles. Reprinted with permission from ref. 88, copyright 2009, American Chemical Society.

4.7. Formation of cyclic polymers through ring closure

Glaser coupling was successfully used as a new intramolecular ring closure technique for linear precursors by Huang and co-workers in the synthesis of a variety of cycle-based polymers.[89] Synthesis of a polymer of monocyclic poly(ethylene oxide) (PEO) and polystyrene (PS) was achieved with high efficiency by the intramolecular cyclisation of the linear propargyl-telechelic precursors(1-PEO and l-PS) in pyridine/CuBr/PMDETA system at room temperature.

The synthesis of cyclic poly(ethylene oxide) with two hydroxyl groups in the middle of the chain was reported from the α,ω–dialkyne poly(ethylene oxide) containing two hydroxyl groups and was used in the synthesis of biocompatible tadpole shaped co-polymer.[90] (scheme 39). No intermolecular by-products were observed during cyclisation.

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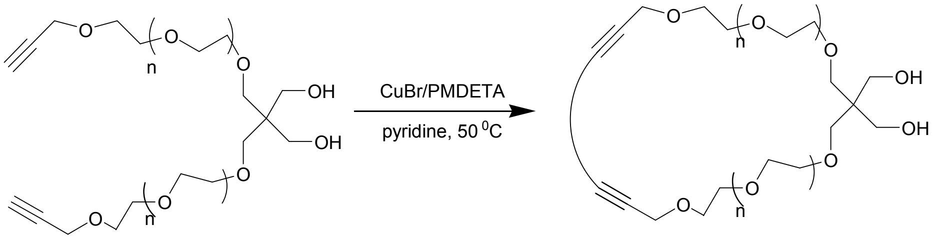


Scheme 39 Synthesis of cyclic poly(ethylene oxide) with two hydroxyl groups

Synthesis of eight-shaped poly (ethyleneoxide) was also achieved by intramolecular cyclisation of the four armed poly (ethylene oxide) with alkyne end groups with 100% efficiency.[91] The cyclisation of $(PEO\text{-}alkyne)_4$ was carried out in pyridine/CuBr/ PMDETA system at room temperature in air.

Recently the synthesis of cyclic block copolymers like amphiphilic cyclic poly(ethylene oxide)-block polystyrene [c-(PEO-b-PS)], twin-tail tadpole-shaped (cyclic polystyrene)-block-[linear poly (*tert*-butyl acrylate)]$_2$ [(c-PS)-b-(l-PtBA)$_2$][92] and biocompatible tadpole-shaped copolymer with one poly(ethylene oxide) (PEO) ring and two poly(ἐ-caprolactone) (PCL) tails[90] were reported by the same group using Glaser coupling in combination with ring opening polymerisation.

4.8 Formation of rotaxanes and catananes

Glaser coupling reactions are widely employed in the synthesis of rotaxanes and catananes,[93-95] which are mechanically-interlocked molecules and challenging synthetic targets and are expected to be important components of molecular machines[96] and switches.[97, 98] The synthesis of [2] rotaxanes and [2] catananes can be achieved successfully by Cu(I) catalysed oxidative intramolecular coupling of diynes with macrocyclic phenanthroline complexes. Saito *et al.* developed a new method for the synthesis of [2] rotaxane (Fig. 6) by intramolecular homocoupling of alkyne with tris(4-biphenyl)methyl group as the blocking group in presence of a stable Cu-phenanthroline macrocycle complex. [99]

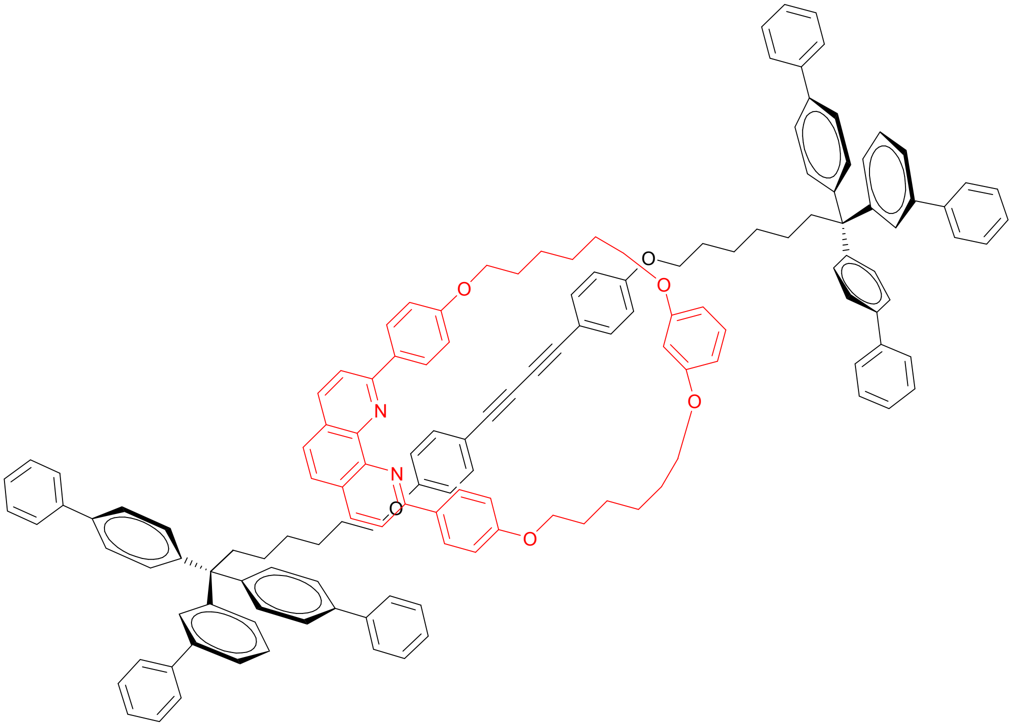
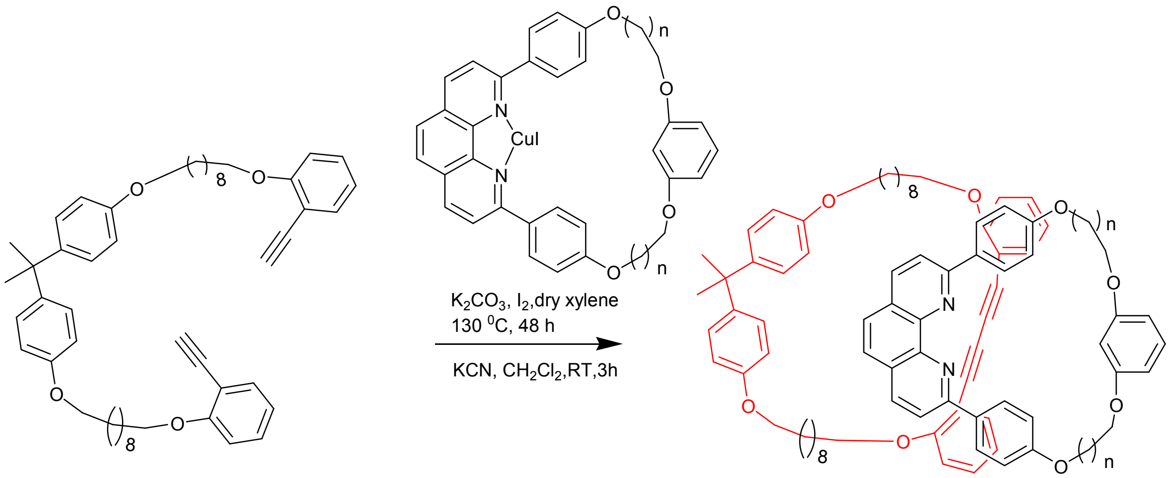


Fig 6 [2]rotaxanes from a macrocyclic Cu(I)-phenanthroline complex. Reprinted with permission from ref. 99, copyright 2006, American Chemical Society.

This methodology used only a small excess of diynes and the product was obtained in good yields without the formation of cross coupled products.

Synthesis of [2] catananes was also known by the same template strategy.[100] α,ω-diynes with 4,6-dihydroxy dibenzofuran linker undergo intramolecular cyclisation in presence of Cu complex of phenanthroline macrocycle to form the [2]catanane (scheme 40).

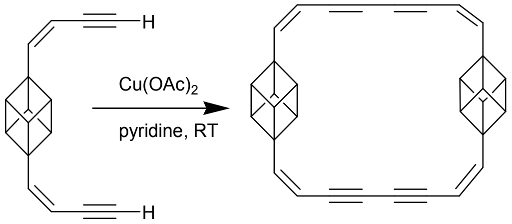


Scheme 40 Synthesis of [2]catenanes based on phenanthroline. Reprinted with permission from ref. 100, copyright 2009, John Wiley and Sons.

The yield of the product was found to be low and has decreased with increasing size of the macrocycle. However the yield can be improved by using excess amount of diynes.

4.9. The modular synthesis of cyclophanes

The Glaser-Eglinton coupling was also applied in the macrocyclisation of strained 1,4-annulated cyclooctatetraene-based cyclophanes from 1,4-disubstituted cubane precursors.[101] Oxidative coupling of cubyldienyne (1,4-bis[(*Z*,*Z*)-but-1-en-3-ynyl]cubane) with Cu(OAc)$_2$ in dry pyridine under pseudo-high dilution conditions produced cyclic dimer (4-[8-cuban-4-yl-octa-(*Z*,*Z*)-1,7-dien-3,5-diynyl]-1-nona-(*Z*,*Z*)-1,7-dien-3,5-diynylcubane) in 50% yield (scheme 41).



Scheme 41 Synthesis of [8,8](1,4)-cubanophane. Reprinted with permission from ref. 101, copyright 2004, American Chemical Society.

Formation of rigid cyclophane macrocycles is sometimes difficult. An inexpensive and readily available additive like Quinolinium salt (Fig. 7) solves the problem and acts as a conformation control element (CCE) to promote macrocyclisation.[102]

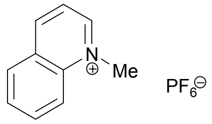
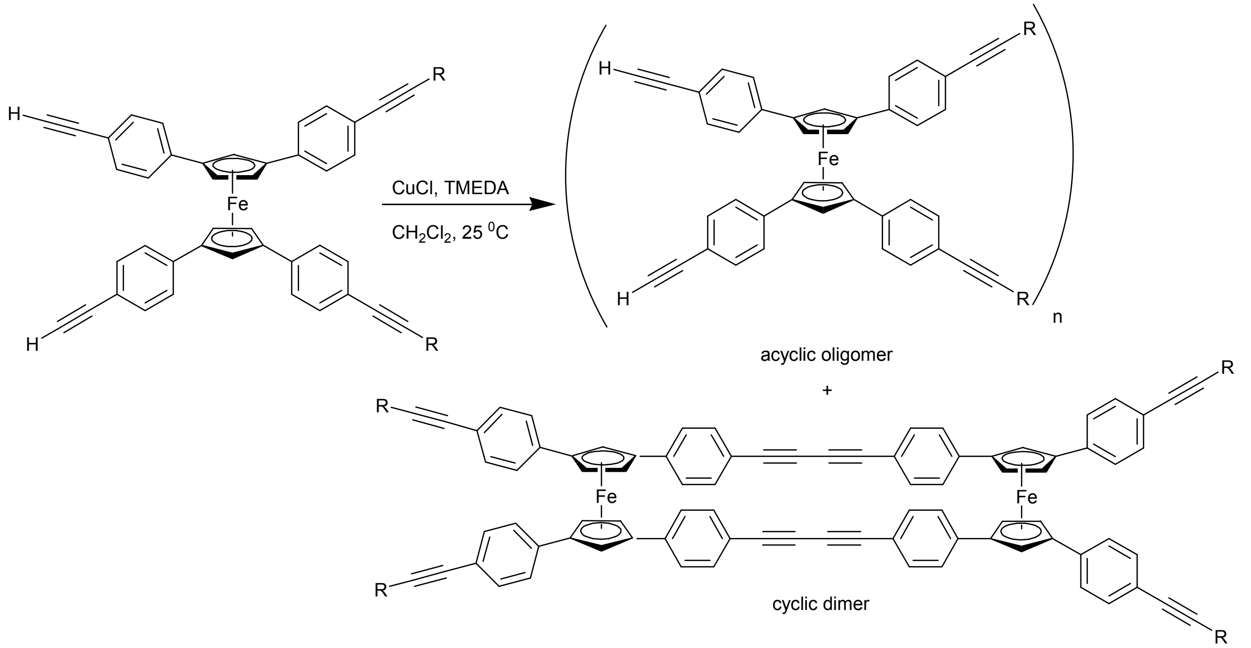


Fig. 7 Quinolinium salt as a conformation control element

4.10. Synthesis of Ferrocenophanes

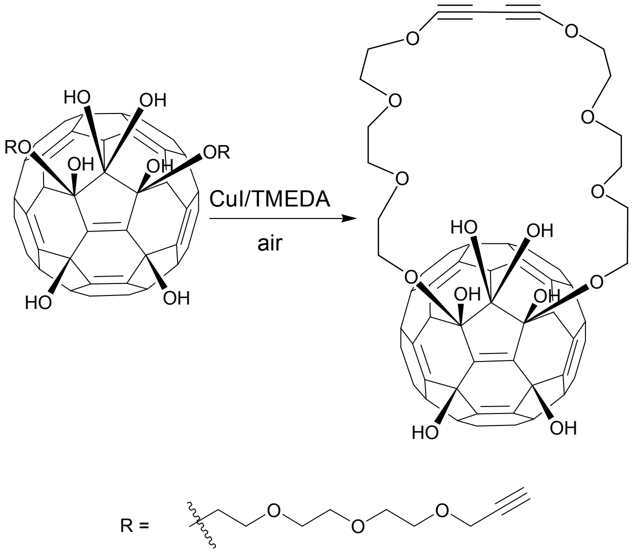
Enantiopure *C*2-chiral tetrasubstituted ferrocenes carrying phenylalkynyl groups underwent Cu(I)-mediated Glaser-Hay coupling at a high [CuCl]/[ferrocene] ratio producing cyclic oligomers having defined geometries and showed excellent chiroptical properties[103] (scheme 42). These compounds are the first chiral ferrocenophanes that bear *C*2-chiral ferrocenyl joints connected by a π-conjugated rigid bridge. Cyclic trimer resembles the Escher's endless staircase and is formed as a single conformer.



Scheme 42 Copper-mediated Glaser coupling of enantiopure tetra substituted ferrocene in the formation of cyclic oligomers. Reprinted with permission from ref. 103, copyright 2010, American Chemical Society.

4.11. Synthesis of fullerenol derivatives

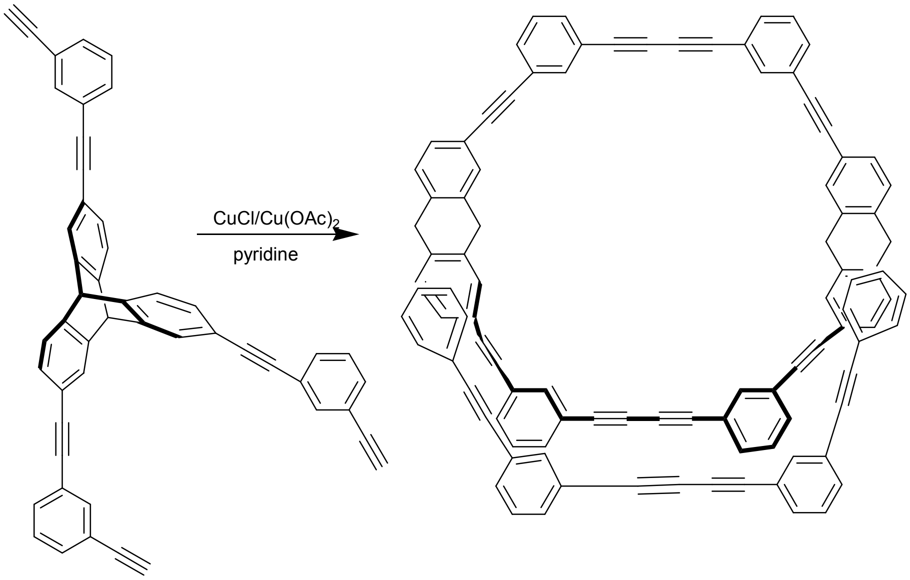
Glaser-Hay coupling has been proven as a useful strategy even for the synthesis of fullerene derivatives. An interesting intramolecular oxidative coupling of fullerenol derivatives with terminal alkynes was reported by Gan and co-workers.[104] The coupling of two terminal alkynyl groups of fullerenol derivative in presence of cuprous iodide and TMEDA afforded a fullerenyl crown ether derivative with a crown size comparable to that of 24-crown-8 (scheme 43).



Scheme 43 Glaser-Hay coupling for the synthesis of fullerenyl crown ether

4.12. Construction of molecular cages

A triptycene-based nano-sized molecular cage with rigid phenyldiacetylenic bridge units was prepared with 2, 7, 14-triiodotriptycene as the starting material by an Eglinton-Glaser coupling reaction[9] (scheme 44). 2,7,14-triiodotriptycene was coupled with protected 1,3-diethynylbenzene to yield triethynylation product which on deprotection and oxidative coupling with CuCl/Cu(OAc)$_2$ in pyridine, afforded the molecular cage in 58% yield.

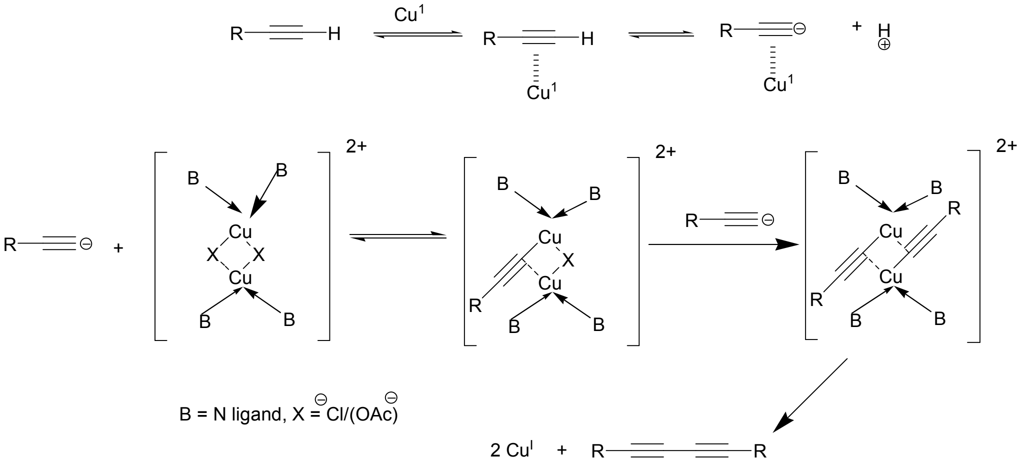


Scheme 44 Eglinton-Glaser coupling for the synthesis of molecular cage compounds

5. Mechanistic Investigations of Glaser coupling

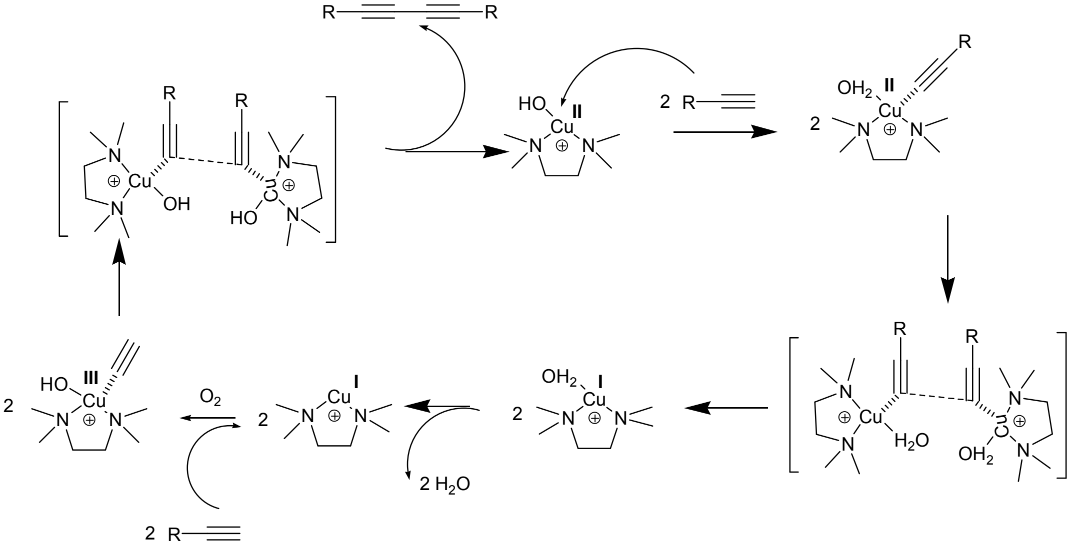
Though the copper-mediated homocoupling of alkynes is the oldest of the many coupling reactions and proceeds through very simple procedure, there is no mechanistic investigation that clearly states the complex mechanism of the process. The studies indicate ranges from pure radical processes to π complex formation. None of them are directly comparable as the mechanism is highly dependent on experimental set up and reaction conditions.

Of the many mechanisms available, [3] the most widely accepted one is published in 1964 by Bohlmann *et al.*[105] They suggested a copper(II) acetylide product which collapses to the product (scheme 45). The reaction follows a second-order kinetics and the rate-limiting step is the formation of a dicopper(II)–diacetylide complex based on the relationship between the conjugation length of the acetylenic precursor and the reaction rate, and on the inevitability of Copper(I) salt when the reaction is carried out at P^H 3. Many of the studies conducted later confirmed the results obtained by Bohlmann even though they differ in the formation of the π complex and its subsequent collapse to the product.



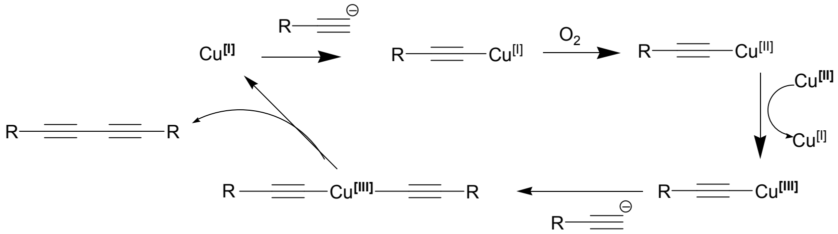
Scheme 45 The Bohlmann's mechanism for Glaser coupling

Recently Fomina *et al.* reported a detailed mechanism for the Hey modification of the Glaser oxidative coupling based on DFT calculations.[106] The mechanism includes Cu(I)/Cu(III)/Cu(II)/Cu(I) catalytic cycle. The first step is the generation of the acetylide followed by the formation of dicopper-dioxo complex with $[Cu_2(\mu-O_2)]^{2+}$ core from acetylide and molecular oxygen (scheme 46). This is the key step which serves as an intermediate for the Cu(III) species. In the next step two molecules of the complex is added to a molecule of diacetylene and two molecules of paramagnetic Cu(II) mononuclear complex. The dissociation of complexes completes the catalytic cycle.



Scheme 46 Mechanism of Glaser coupling suggested by Fomina based on DFT study. Reprinted with permission from ref. 106, copyright 2002, Elsevier.

In 2013, Vilhelmsen *et al.* reported a detailed study on the reaction mechanism of Glaser-Hay coupling using both ^{13}C NMR and UV/Vis spectroscopic methods.[107] The authors used the integrals of the carbon resonances from ^{13}C NMR to study the kinetics of Hay coupling of aryl substituted alkynes since the aryl carbon resonances of the reactants and products have similar NOEs and relaxation times. They studied the kinetics on a preparatory scale at room temperature and with oxygen uptake from the air rather than supplied as a neat gas. Under these conditions, the reaction follows zero-order with respect to the acetylenic reactant. A change to lower reaction kinetics is observed during the course of reaction which mainly depends on the catalyst load. The rate-limiting step is the oxidation of copper(I) species by oxygen before coordination of the acetylene. The mechanism (scheme 47) suggested involves the formation of Cu(I) acetylide which is subsequently oxidised to Cu(II) species. This complex is disproportionated and another Cu(II) species generates a Cu(III) complex and a Cu(I) species. The Cu(III) complex is coordinated to another acetylide and the product is reductively eliminated from the Cu(III) species. The Cu(I) species enters a new cycle or oxidized to Cu(II).



Scheme 47 Mechanism of Glaser-Hay coupling suggested by Vilhelmsen *et al.* Reprinted with permission from ref. 107, copyright 2013, John Wiley and Sons.

Effect of metal surfaces in Glaser coupling

Very recently Gao et al. reported the effect of metal surfaces in surface Glaser coupling.[108] They investigated the covalent coupling of the dimers of 1,4-diethynyl benzenes at various metal surfaces (Au, Ag, Cu) experimentally by STM and also by theoretical DFT calculations to address the role of metal substrate in the C-C bond forming process. It was found that the on-surface coupling was not efficient on Cu and Au surfaces. Ag surface is best suited for the coupling of alkynylated arenes by direct C-C bond formation via alkynyl activation through π complex formation. Subsequently, they moved on to the photochemical homo coupling process.[109] Here also they explored the importance of mobility of the molecules at the Ag surface on coupling reaction and self-assembled dimers were obtained after coupling.

Conclusion

1,3-butadiynes serve as building blocks and intermediates for the synthesis of a large variety of compounds in different fields of chemistry. Homocoupled products of these alkynes by copper-mediated Glaser reactions are highly constructive and useful in different fields like supramolecular chemistry, organic synthesis and material sciences. This review gives an extensive overview of recent developments in acetylenic coupling reactions particularly focused on the exploration of new catalytic systems, oxidants and substrates towards greener protocols. The efforts to make the processes greener and environmentally friendly are on an upward curve. The applications of Glaser coupling in polymer chemistry, supramolecular chemistry, electronics, material chemistry, electrochemistry, host-guest studies, optoelectronics etc. are discussed in this review. Assessment of different protocols is difficult since it involves the determination of different performance based parameters. The selectivity of the catalytic systems for different substrates, the improvement in the efficiency of catalysts to lower loading and better yields, the recovery and reuse of the catalysts, investigations and further studies on the mechanism of coupling are the advances likely to appear in the near future. More general approaches should be derived from experimental and mechanistic studies so that the future synthetic challenges could be easily met with. Thus, a wide pathway is opened for researchers to innovate more efficient, inexpensive and simple methods for conducting coupling reactions.

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