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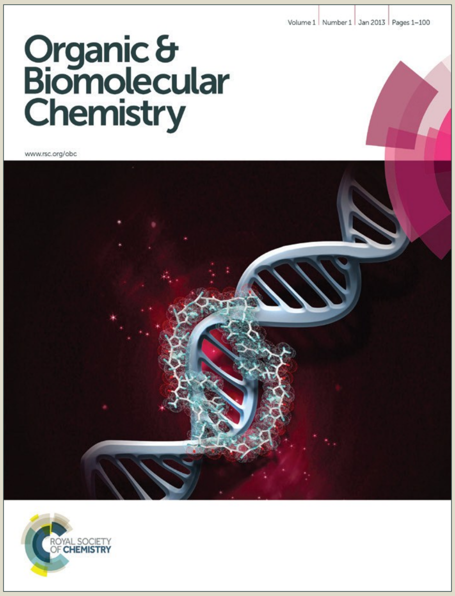

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ARTICLE

Recent developments and applications of Cadiot-Chodkiewicz reaction

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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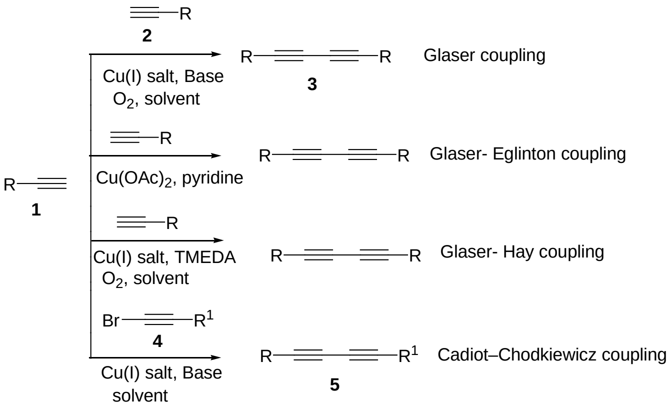
The classical heterocoupling of a 1-haloalkyne with a terminal alkyne catalyzed by copper salts in the presence of a base for the synthesis of unsymmetrical diynes is termed as Cadiot-Chodkiewicz coupling reaction. The diynes are of great importance due to their biological, optical and electronic properties. A number of modifications were developed recently to improve the efficiency of Cadiot-Chodkiewicz coupling reactions in terms of selectivity and yield. This is the first review on Cadiot-Chodkiewicz cross-coupling reaction which highlights the modern approaches and protocols developed for the synthesis and applications of unsymmetrical 1,3-diynes.

1. Introduction

The transition metal catalyzed reactions have turned out to be the most powerful tools in organic synthesis during the past several decades.[1] The metal catalysts are widely used to assemble carbon–carbon bonds between appropriately functionalized sp, sp^2, or sp^3 centers. Alongside the vast developments in Pd-catalyzed cross coupling reactions, advances were being made in the arena of copper-mediated catalysis also. Recently Cu salts have achieved particular success in performing a number of transformations in good yields, while maintaining low loading, mild reaction conditions and high functional group tolerance.[2] Cu-promoted coupling reactions have a longer history of about 150 years. Historically, it began in 1869 when Carl Glaser reported the air oxidation of Cu(I)phenyl acetylide to diphenyldiacetylene via dimerization.[3] The most important methods towards the synthesis of symmetrical diynes are still the Glaser oxidative acetylenic coupling[4], and its modified reactions such as the Eglinton[5] and the Hay coupling reactions.[6] The synthesis of unsymmetrical diynes is more challenging than that of the symmetrical diynes in terms of reactivity and selectivity. These 1,3-diynes are very important in synthetic organic chemistry and are common structural motifs of a large variety of biologically active molecules and supramolecular materials.[7] The most commonly used procedure for the preparation of unsymmetrical diyne and polyyne compounds is the Cadiot-Chodkiewicz reaction (Scheme 1). The copper-catalyzed cross-coupling reaction between terminal alkynes and haloalkynes is termed the Cadiot-Chodkiewicz reaction.[8] This reaction is known since the middle of the 1950s in which the terminal alkyne acts as the nucleophile and the 1-haloalkyne acts as the electrophile in the presence of an amine base. To the best of our knowledge, no review has so far been written specifically on this powerful and traditional reaction.[9] In this first review on Cadiot-Chodkiewicz cross-coupling reaction, we outline the developments, mechanism and modifications of the reaction along with its synthetic applications.



Scheme 1 The Glaser coupling modifications and Cadiot-Chodkiewicz coupling reaction

2. The Classical Cadiot-Chodkiewicz coupling reaction

In 1955, Cadiot and Chodkiewicz reported the first copper(I)-catalyzed coupling of bromoalkyne **6** with 2-Methyl-but-3-yn-2-ol **7** (Scheme 2).[8] Later, the C(sp)-C(sp) coupling of haloalkynes with terminal alkynes for the synthesis of unsymmetrical diynes is termed as the Cadiot-Chodkiewicz coupling reaction. Here, the procedure requires three components to achieve a selective cross-coupling product, an alkynyl halide, an alkyne and a copper source in stoichiometric or catalytic quantities. Usually Cu catalysts along with an amine, mostly, hydroxylamine, are used in this protocol and the reaction is generally carried out at room temperature.

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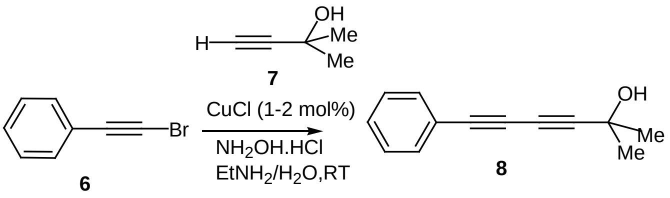


Scheme 2 The classical Cadiot-Chodkiewicz coupling reaction

The relatively high yields, low cost of catalyst, wide substrate scope, and mild reaction conditions are the advantages of this reaction. Eventhough the reaction is successful in many situations, the major limitation of this reaction is that sometimes the reaction suffers from reduced selectivity, yield and the formation of a significant amount of homocoupling byproducts when the alkynes are bulky or when the electronic properties of the substituents attached to the reactants are similar.[10] Excess of terminal alkynes are usually required to reduce the homocoupling and specific amines should be used as solvent. Often the coupling partners or precursors of bromoalkynes are not much stable also.[11] The reactivity of bromoalkynes can be enhanced by using oxygen substituted bromoalkyne moieties.[12] To overcome these challenges, many alternative methods have been explored.

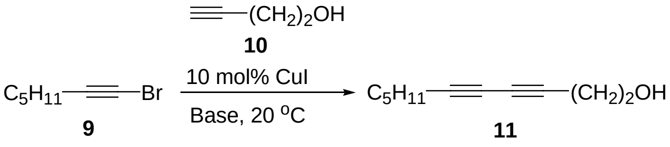
3. Modification of Cadiot-Chodkiewicz coupling reaction

Due to the importance of unsymmetrical 1,3-diynes, several research groups worked on the coupling of acetylenic precursors and many attempts have been made to invent mild, efficient and highly selective methods for the cross-coupling of alkynes and haloalkynes utilizing various catalytic systems and solvents.

Various factors such as nature of the base and the alkyne, solvent, reaction time and temperature affect the efficiency of heterocoupling reactions. A number of modifications are reported for these coupling reactions. These variations are helpful in suppressing the formation of the unwanted homocoupled products.

a. Changing the base

The amine base plays a crucial role for the improvement in the reaction rate and yield of the heterocoupling of alkynes and haloalkynes. The cyclic secondary amines like pyrrolidine gave quantitative yield for the cross coupling product **11** formed from 1-bromo hept-1-yne **9** and 3-butyn-1-ol **10** (Scheme 3). The efficiency decreased when secondary amines (Et_2NH, iPr_2NH etc) were used as the base and very low yield of the desired product was obtained when tertiary amine was used as the base.[13]



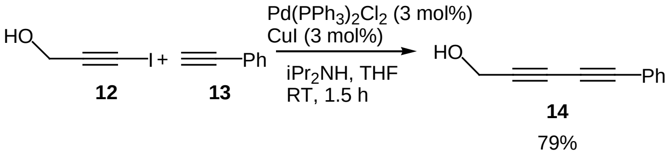
Base	Time	Isolated yield (%)
Et_3N	24h	20
Et_2NH	7h	35
$BuNH_2$	6h	54
i-Pr_2NH	3h	25
pyrrolidine	15 min	95

Scheme 3 The Cadiot-Chodkiewicz coupling reaction in presence of different bases

As expected, chloroacetylenes in presence of pyrrolidine as base showed lower reactivity and the corresponding iodides worked well. Even alkynols, which usually give the homocoupled product, also worked smoothly.

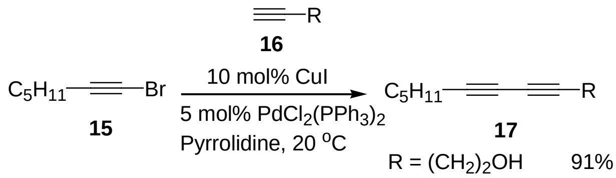
b. Addition of co-catalysts

The efficiency and scope of the hetero coupling reactions were improved further using Palladium catalysts along with Cu(I) salts.[14] Moreover, efficient heterocoupling of iodo and chloroalkynes took place in presence of Pd co-catalysts. In 1991, an improved CuI-catalyzed cross-coupling reaction of alkynyl iodides and terminal alkynes was reported by the addition of a $Pd(PPh_3)_2Cl_2$ co-catalyst.[15] Thus, 3-Hydroxy-1-iodopropyne **12** when coupled with phenyl acetylene **13** in presence of CuI, $Pd(PPh_3)_2Cl_2$ and diisopropylamine in THF afforded the corresponding diyne **14** in 79% yield (Scheme 4). This procedure is catalytic in both Pd and Cu (3 mol %) and provides high yields. Moreover, the homocoupling product was obtained in negligible amount.



Scheme 4 Cu/Pd-catalyzed coupling of 3-hydroxy-1-iodopropyne with phenyl acetylene

Later a similar protocol for the copper-catalyzed coupling reaction of terminal alkynes with 1-bromo alkynes in pyrrolidine was reported using 10 mol% CuI and 5 mol% co-catalyst $Pd(PPh_3)_2Cl_2$ (Scheme 5).[13]

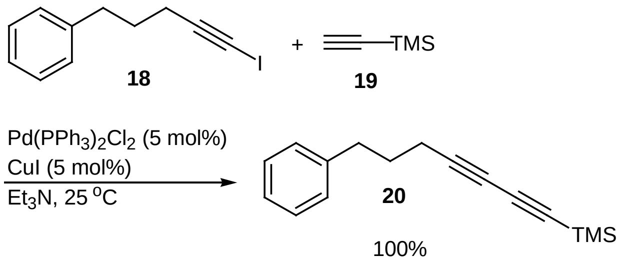


R =	
$(CH_2)_2OH$	91%
CH_2OH	80%
CH_2NMe_2	82%
C_8H_{17}	61%
C_6H_5	66%

Scheme 5 Cu/Pd-catalyzed coupling of haloalkyne with terminal alkyne in pyrrolidine

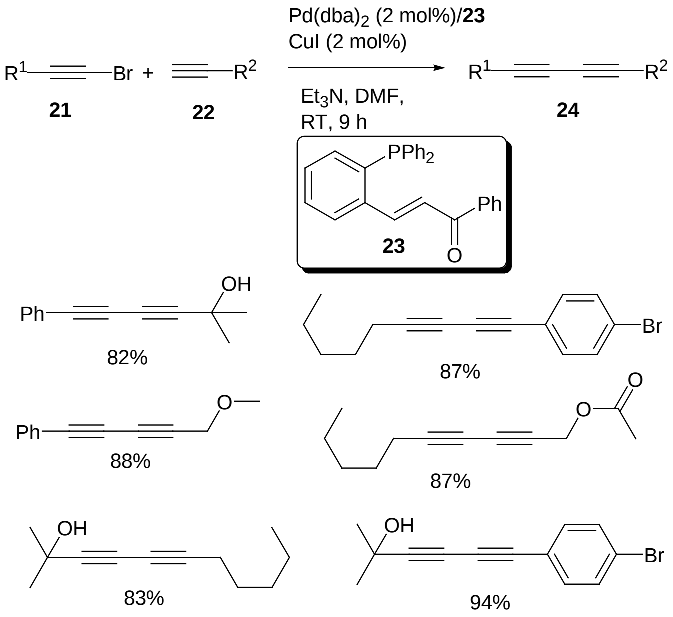
The yield of the coupling product **17** from 1-bromo alkyne **15** was found to be increased in the presence of Palladium co-catalyst. As expected, 1-chloro alkynes showed lower reactivity under similar conditions.

Another reaction in which Pd acts as a co-catalyst for the formation of diynes was observed by Lee *et al*.[16] The diyne **20** was generated in quantitative yield when the Pd-Cu catalytic system (5 mol% CuI and 5 mol% $Pd(PPh_3)_2Cl_2$) in triethylamine was used for the coupling of 1-iodo-5-phenyl-1-pentyne **18** and (trimethylsilyl)acetylene **19** (Scheme 6).



Scheme 6 Coupling of 1-iodo-5- phenyl-1-pentyne and (trimethylsilyl)acetylene in presence of CuI and Pd co-catalyst

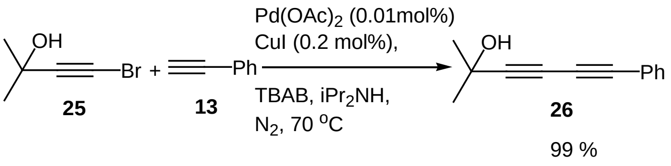
In 2008, Shi and co-workers developed another catalytic system comprising of $Pd(dba)_2$ and a phosphine ligand **23** for the synthesis of 1,3-conjugated diynes **24** with good yields (Scheme 7).[17]



Scheme 7 Coupling of bromoalkynes with terminal alkynes in presence of $Pd(dba)_2$ and phosphine ligand

Here, the reaction was found to be independent of substrates in most cases, and even alkynes with similar substituents were cross-coupled successfully with high yields.

Recently, a highly selective Cu/Pd-catalyzed cross-coupling reaction between terminal alkynes and 1-bromoacetylenes using tetrabutyl ammonium bromide (TBAB) as an additive was developed and utilized effectively for the Cadiot-Chodkiewicz reaction.[18] Cross-coupling of 4-bromo-2-methylbut-3-yn-2-ol **25** with phenylacetylene **13** gave the diyne **26** in almost quantitative yield (Scheme 8).

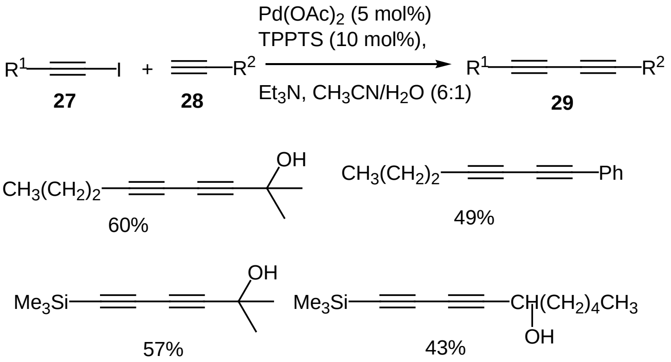


Scheme 8 Cross-coupling of 4-bromo-2-methylbut-3-yn-2-ol and phenylacetylene

By extensive kinetic studies, it was found that in the presence of TBAB, only 0.0001–0.01 mol% of Pd and less than 0.2 mol% of Cu were required for the coupling to afford the products in good to excellent yields.

c. Use of Pd catalysts

A few reports also illustrated that Cu salts are not mandatory for the coupling of the Cadiot-Chodkiewicz reactions. A water-soluble Pd catalytic system formed *in situ* from $Pd(OAc)_2$ and the water-soluble ligand TPPTS (triphenylphosphinetrisulfonate sodium salt) was reported by Amatore *et al*. for the heterocoupling reaction of alkynyl iodides **27** with terminal alkynes **28** in CH_3CN/water system (Scheme 9).[19] No Cu catalyst was used in this procedure.

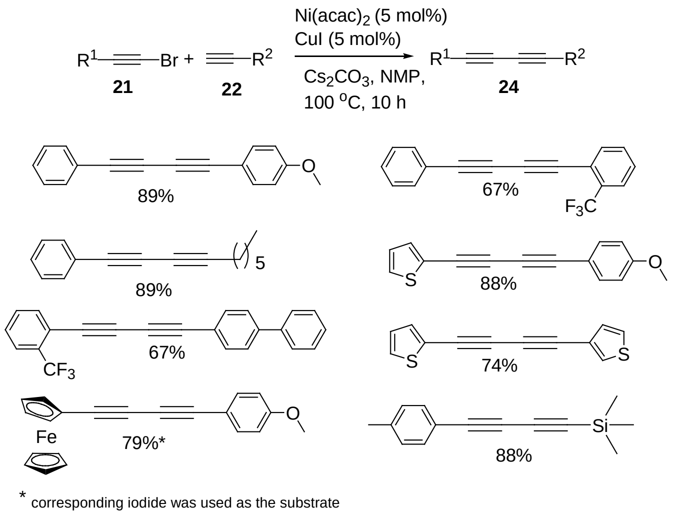


Scheme 9 Pd-catalyzed coupling of haloalkyne with terminal alkyne in presence of TPPTS

The conditions are very mild and the reaction proceeded smoothly for alkynyl iodides and alkynes that bear different functionalities like amines, alcohols etc. But the yield was moderate and homocoupled product was also formed.

d. Use of Nickel catalysts

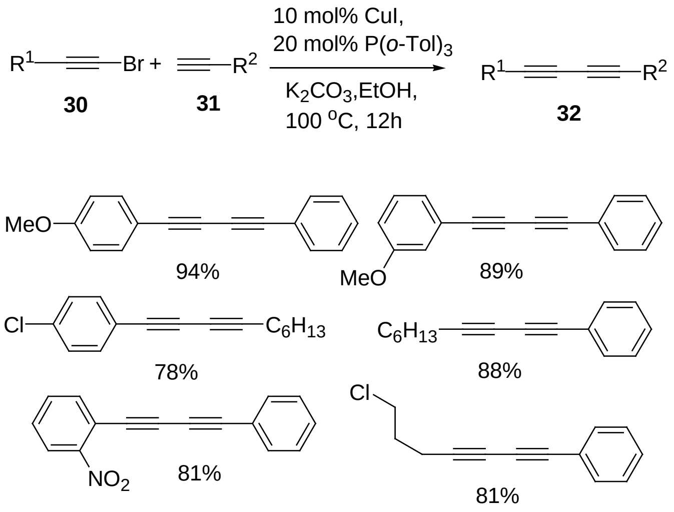
Very recently Nickel-copper catalytic system ($Ni(acac)_2$ and CuI) was reported for the cross-coupling of alkynyl halides **21** with alkynes **22** in the absence of any ligand (scheme 10).[20] A number of functionalised diaryl, aryl–alkyl, aryl–heteroaryl and diheteroaryl 1,3-diynes were produced with high yields. No product was observed when Ni or Cu catalyst was employed alone, and from the control experiments it was suggested that Ni is essential for initiation of the reaction and Cu acts in the transmetallation step. However, the protocol failed in the coupling of aliphatic alkynes with aliphatic halides.



Scheme **10** Ni/Cu-catalyzed synthesis of unsymmetrical 1,3-diynes

e. Use of ligands

Another important modification employed for the conventional Cadiot-Chodkiewicz coupling reaction is the use of phosphine based ligands. Recently Wang and co-workers reported that the Cadiot-Chodkiewicz reaction carried out in the presence of CuI and *tris*(*o*-tolyl)phosphine ligand afforded the unsymmetrical diynes **32** in excellent yields (Scheme 11).[21] Under the optimized reaction conditions, ethanol and potassium carbonate were used as the solvent and the base respectively. The coupling of terminal aliphatic alkynes with bromoalkynes was not successful with this protocol.

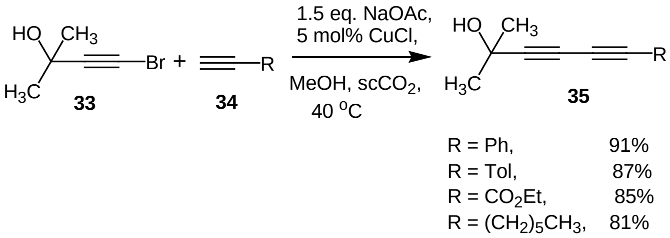


Scheme 11 Cadiot-Chodkiewicz coupling reaction of terminal alkynes with 1-bromoalkyne in presence of P(*o*-Tol)$_3$ ligand.

Very recently an amine-functionalized mesoporous silica SBA-15-supported palladium was used for the cross-coupling of acetylenic bromides and terminal alkynes with high selectivity and good yields.[22] Only minimal amounts of the homo-coupling by-products were formed with this phosphine free ligand.

f. Use of environmentally benign solvents

Beneficial effects are reported for Cadiot-Chodkiewicz coupling reactions when co-solvents like methanol, ethanol, DMF and THF are used. These co-solvents increase the solubility of alkyne moieties. Supercritical CO$_2$ (scCO$_2$) has emerged as an environmentally benign and efficient solvent in organic synthesis in recent days. A mild and environmentally friendly approach was reported for the synthesis of unsymmetrical diynes **35** in which the scCO$_2$ was used as the reaction medium and NaOAc as the base instead of the organic amine (Scheme 12).[23] This procedure was found to be highly efficient in the coupling of bromoalkynols with terminal alkynes using catalytic CuCl in scCO$_2$ and methanol co-solvent. Here, the reactions are limited to only bromoalkynols **33**.

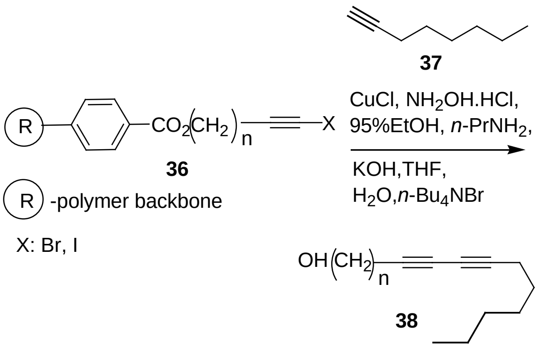


Scheme 12 Cadiot-Chodkiewicz coupling reaction carried out in supercritical CO$_2$

Some of the Pd-catalyzed hetero cross-coupling reactions are also carried out in presence of water. For example, a water-soluble Pd catalytic system comprising of Pd(OAc)$_2$ and the water-soluble ligand TPPTS (triphenylphosphinetrisulfonate sodium salt) was used for Cadiot-Chodkiewicz coupling reaction (Scheme 9).

g. Cadiot-Chodkiewicz coupling under solid support

Kurth and coworkers demonstrated a polymer-supported Cadiot-Chodkiewicz coupling to prevent the homocoupling of haloalkyne.[24] Copper (I) chloride catalyzed coupling reactions of polymer-bound bromo and iodo alkynes **36** with 1-octyne **37** were investigated. They observed that three- and four-carbon alkynol (i.e., n=1, 2) derived haloalkynes performed well under the usual solution-phase Cadiot-Chodkiewicz conditions in coupling reaction with 1-octyne **37** but when alkynols with n = 3 or 4 were used; approximately one third of the isolated product was the homocoupled product. When 2% cross-linked PS-DVB (polystyrene-divinylbenzene) haloalkynyl-esterified resin was used as the polymer support, the homocoupling was inhibited due to the diminished mutual interaction between the haloalkynes, though lower yield of the desired product was observed (Scheme 13).



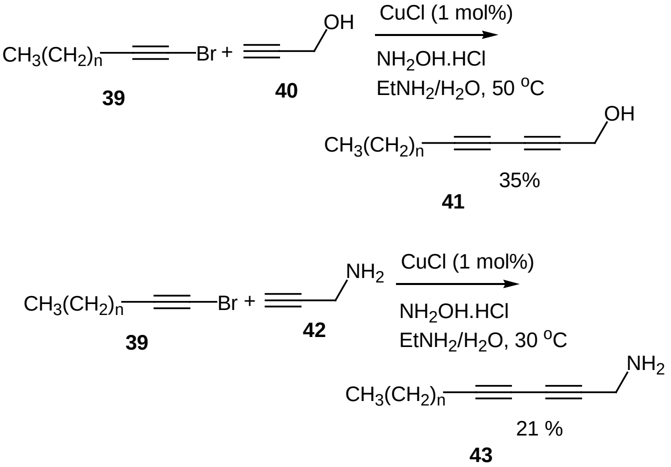
Scheme 13 Polymer supported Cadiot-Chodkiewicz coupling

4. Scope of Cadiot-Chodkiewicz coupling reaction

Cadiot-Chodkiewicz coupling reaction is extensively used for the synthesis of a wide range of aliphatic and aromatic diacetylenic compounds. The classical reaction work best for aromatic 1,3-butadienes, but the aliphatic counterparts are formed in lower yields. In general, less acidic alkynes have a tendency to undergo homocoupling rather than cross-coupling reactions. The Cadiot-Chodkiewicz coupling reaction has very high functional group tolerance and it enables the coupling of acetylene moieties containing alcohols,[25] epoxides,[26] amines,[27] amides,[28] carboxylates,[29] carboxylic esters,[30] disulfides,[31] silyl-protected acetylenes[32] and even nitroxyl radicals.[33]

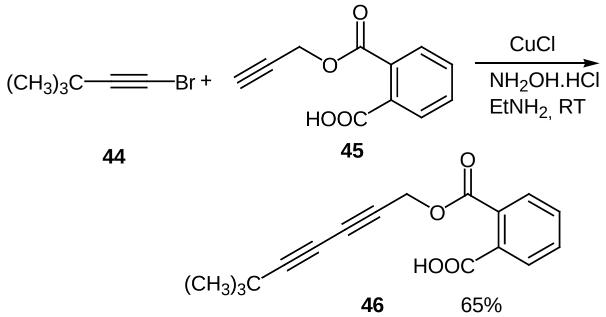
a. Alcohols, amines and carboxylate esters

1-bromoalkynes **39** were coupled with Propargyl alcohol **40** under normal Cadiot-Chodkiewicz reaction conditions at 50 °C affording the expected diacetylene in yields ranging from 23% to 31%.[25] The same group also reported the coupling of 1-bromoalkynes **39** with prop-2-ynyl amine **42** under normal Cadiot-Chodkiewicz reaction conditions.[27] Here also the yield of the desired product **43** was quite low.



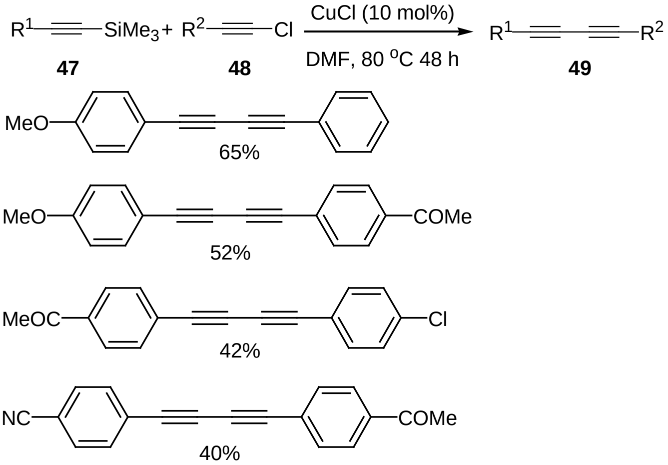
Scheme 14 Synthesis of unsymmetrically substituted diacetylenes containing alcohol and amine functionalities

Even carboxylic esters also successfully underwent Cadiot-Chodkiewicz coupling reactions. The reaction of 1-bromo-3,3-dimethyl-1-butyne **44** with 2-propynyl hydrogen phthalate **45** in presence of CuCl and $EtNH_2$ at room temperature afforded the product 6,6-dimethyl-2,4-heptadiynyl hydrogen phthalate **46** in 65% yield (scheme 15).[30]



Scheme 15 Reaction of 2-propynyl hydrogen phthalate with 1-bromo-3,3-dimethyl-1-butyne under Cadiot-Chodkiewicz reaction conditions

Bromoacetylenes are used more frequently and the more reactive acetylenic iodides are used sparsely. Usually the coupling of chloroalkynes with terminal alkynes furnishes the diynes in poor yields. As expected, the low reactivity is attributed to the inertness of chloroalkynes compared to their bromo and iodo analogues obviously due to strong C-Cl bond. As an exceptional case, Mori *et al*. reported a base free procedure for the formation of unsymmetrical conjugated diynes by the copper(I)-catalyzed cross-coupling reaction using alkynylsilanes and 1-chloroalkynes.[4a,34] Cu-catalyzed cross-coupling reaction of alkynylsilanes **47** with 1-chloroalkyne **48** in presence of 10 mol% CuCl in DMF at 80 °C afforded excellent yield of the product **49**. Alkynylsilanes bearing electron donating groups afforded high yield of the coupled product (Scheme 16). The advantage of this method is that the reaction can be carried out in neutral conditions, without any base and also moderate to good yields of the products were obtained.

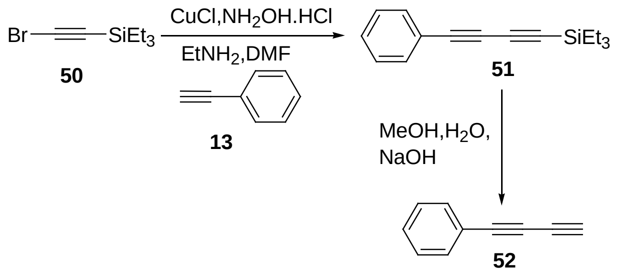


Scheme 16 Cadiot-Chodkiewicz coupling of alkynylsilane with 1-chloroalkyne

b. Silylated alkynes

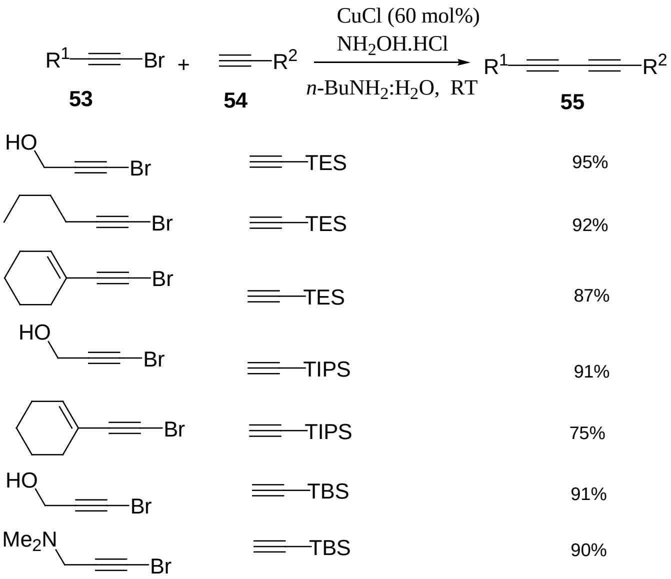
Silyl motifs are used as protective groups in the synthesis of terminal diynes. The protecting group is required because the cross-coupling products are more acidic than the coupling partners. Thus silylation can be used as a preventive measure to avoid the homo coupling in Cadiot-Chodkiewicz reaction.[35]

Walton demonstrated that a triethylsilyl group is the suitable group for protection. The Cu(I) catalyzed reaction of bromoethynyl(triethyl)silane **50** with aryl acetylene **13** afforded the silylated diyne **51** in moderate yield. The reaction was carried out using CuCl in presence of $NH_2OH.HCl$ and $EtNH_2$ as the base in DMF at 25°C.



Scheme 17 Cadiot-Chodkiewicz coupling of aryl acetylene with bromoethynyl(triethyl)silane.

Since the silyl group can be easily deprotected with aqueous methanolic alkali, such type of cross-coupling reactions can be envisaged for the synthesis of unique linear conjugated polyynes. Under the similar conditions, the advantage of bulky trialkylsilyl groups such as triethylsilyl or triisopropylsilyl group in terms of both yields and easy handling was described by Marino *et al.*[36] The cross-coupling reaction between bromoalkyne **53** and trialkylsilyl acetylene **54** was catalyzed by CuCl and $NH_2OH.HCl$ in 30% *n*-butyl amine in water system affording excellent yields of the diyne **55** which is a useful synthon for polyynes possessing excellent electronic and optical properties (Scheme 18).

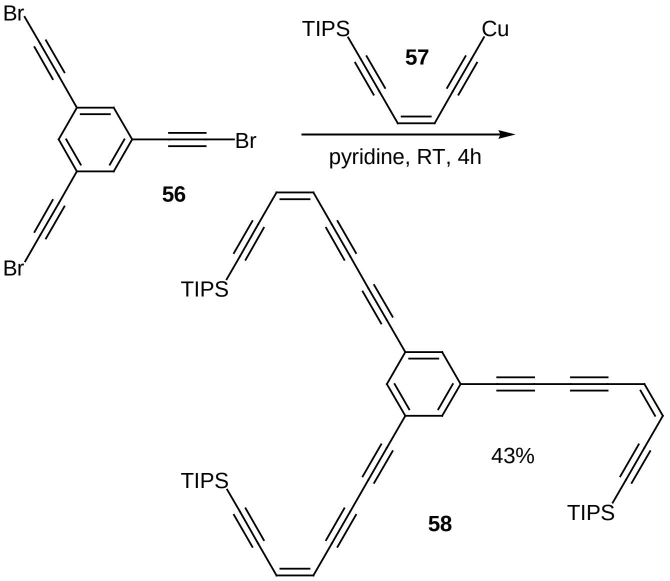


Scheme 18 Cadiot-Chodkiewicz coupling of trialkyl silane with bromoalkyne

Bromoalkynes containing polar functional groups such as hydroxyl and amino groups afforded good yield of the product within 5 minutes.

c. Use of metal acetylides

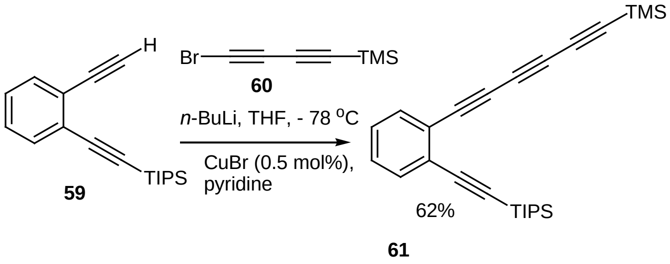
Copper acetylides are sometimes used instead of the terminal alkyne as coupling partner in Cadiot–Chodkiewicz reactions. Rubin and co-workers used such a copper acetylide for the synthesis of acetylenic cyclophane $C_{60}H_{18}$.[37] The copper acetylide **57** was obtained by selectively deprotecting 1-(triisopropylsilyl)-6-(trimethylsilyl)-3-hexen-1,5-diyne with K_2CO_3/MeOH, and then deprotonation with LHMDS, followed by addition of CuBr. The copper acetylide **57** was coupled with the *tris*(bromoalkyne) **56** at room temperature yielding the stable protected triyne **58** (Scheme 19).



Scheme 19 The coupling of copper acetylide with *tris*(bromoalkyne) in presence of pyridine

The reaction is usually carried out in pyridine and is promising, but because of its exothermic nature, the metal acetylides are less preferred compared to terminal alkynes.

Another modification to this reaction involves the use of *n*-BuLi for metal exchange process. The diyne **59** was coupled with silyl protected 1-bromo-1,3-butadiyne **60** to form the phenylhexatriyne synthon **61** which could be used as a precursor for the synthesis of dehydrobenzoannulenes (scheme 20).[38]

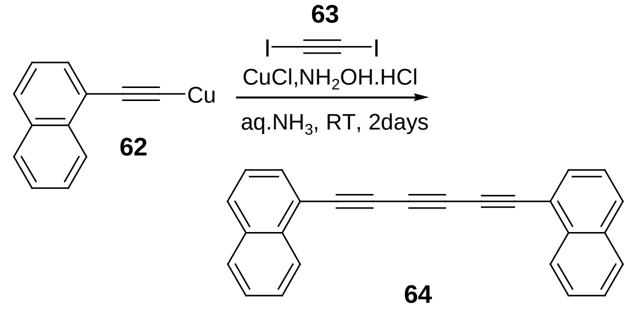


Scheme 20 Modified Cadiot-Chodkiewicz coupling of 1-bromo-1,3-butadiyne and alkyne with *n*-BuLi

This modification makes Cadiot-Chodkiewicz reaction one of the most efficient active template cross-coupling reactions and this strategy is used for active metal template synthesis of rotaxanes and catananes (see section 5.c).

d. Use of diiodoacetylenes

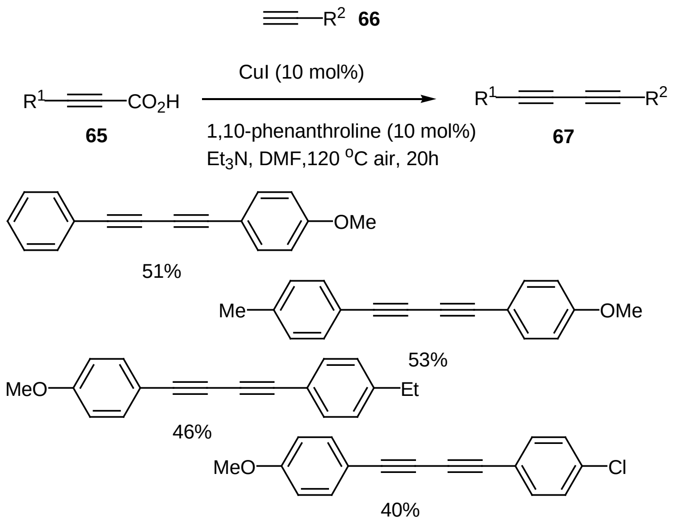
A series of sp hybridised carbon chains terminated by naphthyl groups (dinaphthyl polyynes) were synthesized through a new route by the reaction of copper (I) ethynyl naphthalide **62** with diiodoacetylene **63** under Cadiot-Chodkiewicz reaction condition[39] (Scheme 21). The reaction using diiodoacetylenes simplifies the synthetic route to long polyyne chains with tailor-made end caps, thus making this procedure applicable for the general synthesis of α,ω-diarylpolyynes. The unusual photophysical and spectroscopic properties of the dinaphthyl polyynes **64** make them promising building blocks in electronic devices.



Scheme 21 Synthesis of dinaphthyl polyyne using Cadiot-Chodkiewicz coupling

e. Decarboxylative Cross-coupling

A copper-catalyzed decarboxylative cross-coupling reaction of propiolic acids with terminal alkynes was reported in 2010 by Yu *et al.* which is considered as an extension of the classical Cadiot-Chodkiewicz reaction.[40] Substituted arylpropiolic acids **65** reacted with arylacetylenes **66** in presence of CuI, 1,10-phenanthroline and Et_3N at 120°C in DMF under air affording the unsymmetrical conjugated diynes **67** in moderate yields (Scheme 22). Only a slight excess of the propiolic acid was used in this method. Since only carbon dioxide is produced as the by-product instead of organic halides, the process can be considered as a green variant of the Cadiot-Chodkiewicz coupling reaction. However the reaction temperature is high and the yields are not satisfactory.



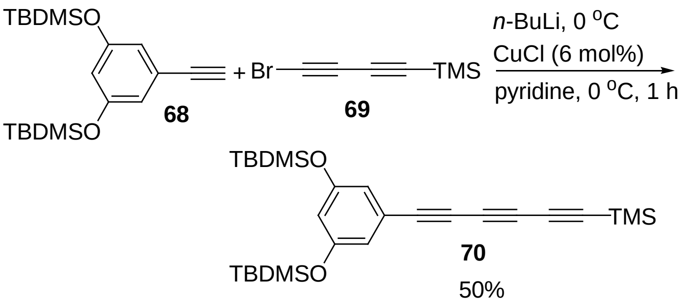
Scheme 22 Decarboxylative cross-coupling reaction of propiolic acids with terminal alkynes

5. Applications of Cadiot-Chodkiewicz coupling reactions in diverse fields

The Cadiot-Chodkiewicz coupling of terminal alkynes and 1-haloalkynes has been regarded as a key step for the carbon-carbon bond-formation in many of the processes in polymer and supramolecular chemistry. The reaction together with the modified processes are used in the synthesis of natural products, natural and synthetic polyynes, interlocked compounds, highly conjugated molecules for use in electronic and as optical materials. An attempt is made to provide a flavour of the generality and functional group tolerance of this reaction.

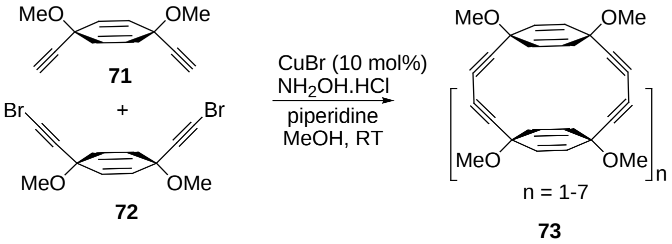
a. Generation of precursors for macrocyclic and dendrimeric polynes

Many precursors for the generation of dendrimeric polyynes containing odd number of acetylene units were prepared by Cadiot-Chodkiewicz reaction. An example of this type of reaction is given below. The coupling of alkyne **68** and alkynyl bromide **69** was carried out in the presence of CuI/*n*-BuLi to yield **70** in good yield which is used for the synthesis of longer sp carbon chains (Scheme 23).[41]



Scheme 23 Cu-catalyzed Cadiot-Chodkiewicz coupling of dendrimer-bound alkynes

An efficient method for the synthesis of tub shaped cyclohexadiene-based acetylenic macrocycles was reported by Sankararaman *et al.*[42] Synthesis of a mixture of acetylenic macrocycles **73** ranging from dimer to octamer was performed using the coupling of cis-1,4-diethynyl-1,4-dimethoxy cyclohexa-2,5-diene **71** and the corresponding ethynyl bromide **72** (Scheme 24). It is found that the tetrameric macrocycle (n=3) was obtained as the major product in 33% yield followed by the hexameric macrocycle (n=5) in 13% yield. These macrocycles find application in the areas of molecular recognition and guest-host chemistry.

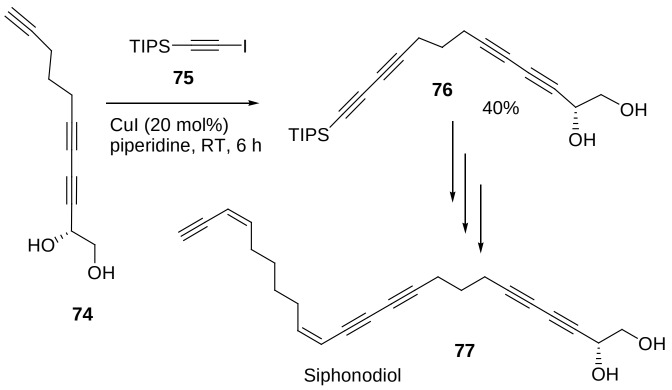


Scheme 24 Cu-catalyzed synthesis of macrocycles via Cadiot-Chodkiewicz reaction

b. Natural polyacetylenes

A large number of polyynes have been isolated from fungi and higher plants. They exhibit excellent biological properties including antimicrobial, cytotoxic, antitumor, antiviral, and enzyme inhibitory activity. Their synthetic routes are based primarily on Cu-catalyzed heterocoupling reactions especially Cadiot-Chodkiewicz reaction to assemble the polyyne skeleton. In 2006, Tykwinski *et al.* reviewed the total syntheses of these challenging natural polyynes, including the copper-mediated diyne bond formation reactions.[43]

Cadiot-Chodkiewicz reaction was used in the synthesis of the marine natural product, Siphonodiol **77** which is a C_{23} polyacetylene diol (Scheme 25).[44] Siphonodiol shows antimicrobial, cytotoxic, antiviral and enzyme inhibitory activity. It also acts as an environmentally harmless antifoulant.



Scheme 25 Synthesis of Siphonodiol via Cadiot-Chodkiewicz coupling

The preparation of a key intermediate in the synthesis of Callyberynes **78** and **79** (Figure 1) which are C_{21} hydrocarbon polyacetylenes and structurally related to Siphonodiols was also achieved by Cadiot-Chodkiewicz reaction.[45] These Callyberynes show biological activity and play ecological role such as (1) induce metamorphosis of sessile marine animals (2) act as antifoulant and (3) inhibit fertilization of starfish gametes.

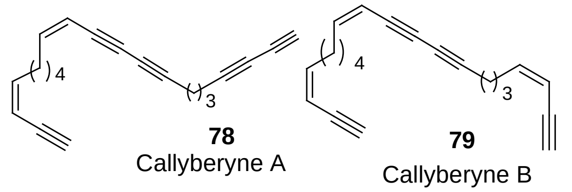
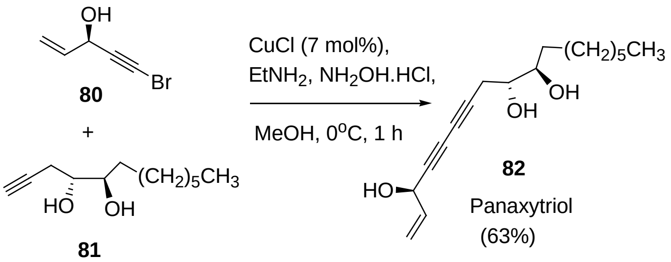


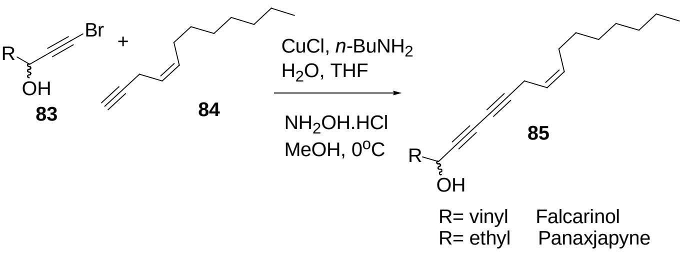
Fig 1 Callyberyne A and Callyberyne B

One of the active components of red Ginseng, the Panaxytriol **82,** mostly found in North America which is used as a traditional medicine, was synthesized by Cu-catalyzed Cadiot-Chodkiewicz coupling (Scheme 26).[46] It acts as analeptic and erythropoietic.



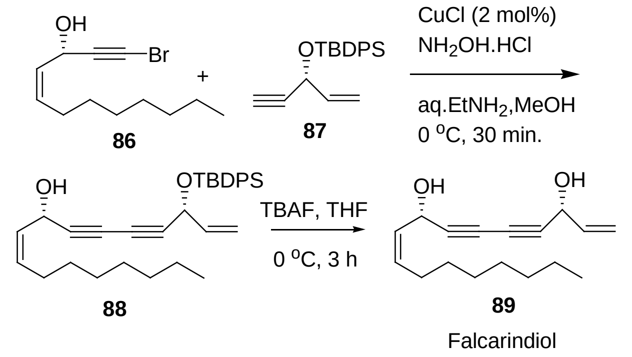
Scheme 26 Cu-catalyzed synthesis of panaxytriol via Cadiot-Chodkiewicz reaction.

The synthesis of similar chiral polyacetylenic alcohols such as (*S*)-and (*R*)-Falcarinol and Panaxjapyne A **85** also includes the linkage between a chiral bromoalkynol **83** and an enyne **84** which is accomplished by Cadiot-Chodkiewicz cross-coupling reaction (scheme 27).[47]



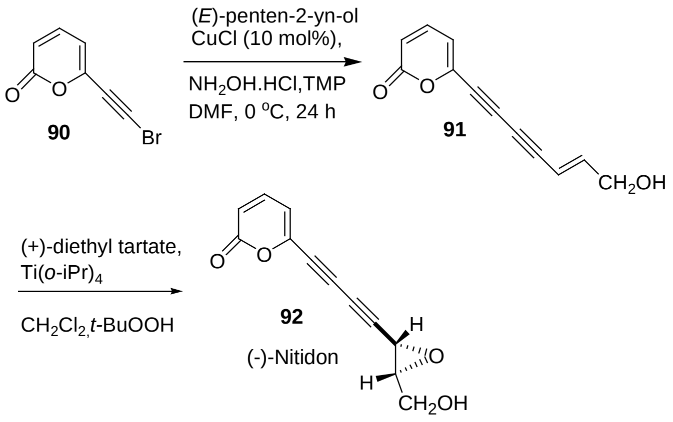
Scheme 27 Cu-catalyzed synthesis of Falcarinol and Panaxjapyne A via Cadiot-Chodkiewicz reaction.

The synthesis of (3*R*,8*S*)-Falcarindiol **89** was also achieved using Cadiot-Chodkiewicz coupling conditions by the reaction between (3*S*,4*Z*)-1-bromododec-4-en-1-yn-3-ol **86** and 3(*R*)-(*tert*-butyldiphenylsilyloxy)-1-pentene-4-yne **87** (Scheme 28).[48] Falcarindiol shows antifungal and antitumor activity.



Scheme 28 Synthesis of Falcarindiol via Cadiot-Chodkiewicz coupling

Cu-catalyzed Cadiot-Chodkiewicz coupling is also used in the synthesis of naturally occurring and highly unsaturated pyranone derivative (-)-Nitidon **92** (Scheme 29).[49] (-)-Nitidon induces morphological and physiological differentiation of certain tumor cell lines and also exhibits antibacterial and antifungal activities.



Scheme 29 Synthesis of (-)-Nitidon via Cu-catalyzed Cadiot-Chodkiewicz coupling

Synthesis of anticancer agents like Minquartynoic acid[50] **93** and (*S*)-(-)-(*E*)-15,16-dihydrominquartynoic acid **94**,[12] was also achieved using Cadiot-Chodkiewicz procedure (Figure 2). The key step in the synthesis of these compounds is the one-pot Cadiot-Chodkiewicz coupling to construct the tetrayne unit, which on further modifications yielded the products in good yields and selectivity.

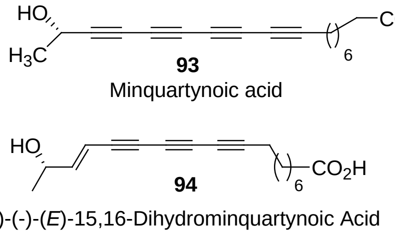


Fig 2 Minquarynoic acid and dihydrominquartynoic acid

The following biologically active natural products, Ivorenolide B **95** [51], Oplopandiol **96** [52], Oploxyne A **97**, Oploxyne B **98** [53], Virol C **99**, [54] (+)-Gymnasterkoreayne F **100**,[55] (-)-Gummiferol **101**,[56] (-)-Petrosiol D **102**[57] and Peyssonenyne B **103**[58] were prepared following a strategy featuring the Cadiot-Chodkiewicz reaction (Figure 3).

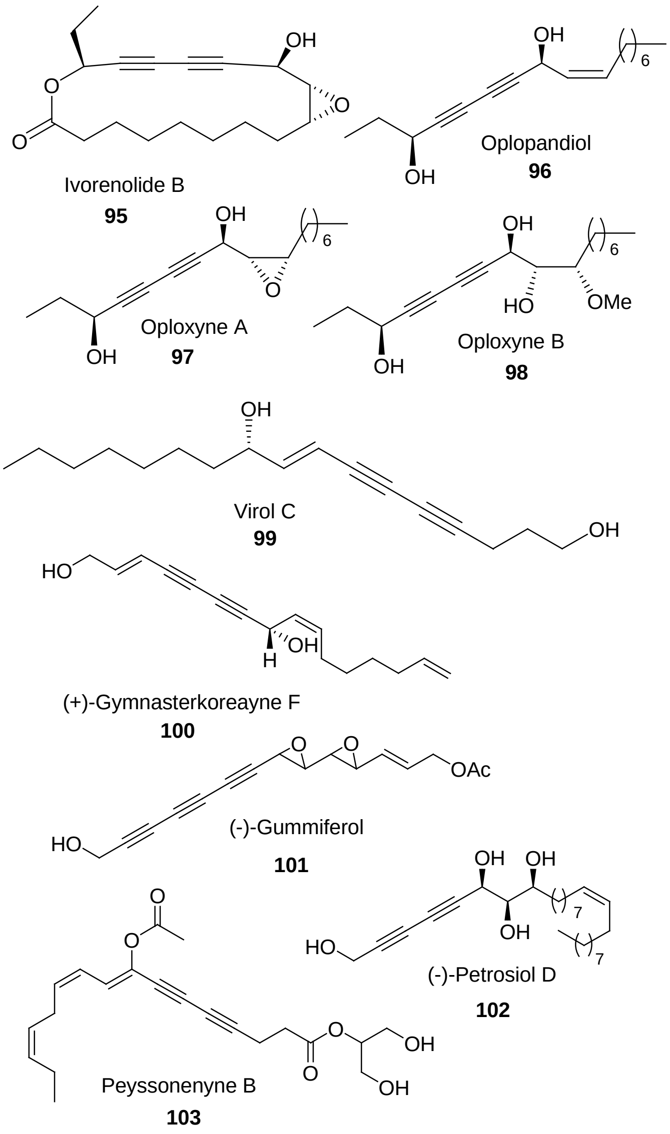
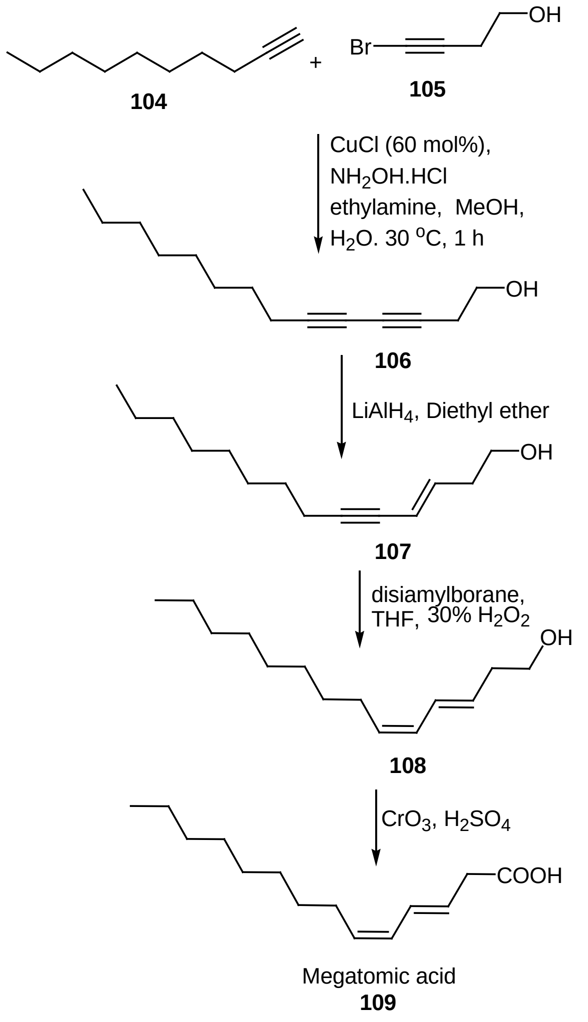


Fig 3 Some natural products prepared using Cadiot-Chodkiewicz reaction

The synthesis of conjugated dienic pheromone components was achieved by a route which involves the Cadiot-Chodkiewicz coupling reaction and successive dialkylborane reduction as the key steps.

Yadav *et al*. prepared (3*E*,5*Z*)-3,5-tetradecadienoic acid (Megatomic acid) **109**, the sex attractant of the black carpet beetle, following the customary procedure of the Cadiot-Chodkiewicz cross-coupling reaction of 1-decyne **104** and 4-bromo-3-butyn-1-ol **105** in the presence of CuCl affording 3,5-tetradecadiyn-1-ol **106** in 90% yield (Scheme 30). [59] Reduction of **106** with lithium aluminium hydride gave (*E*)-tetradeca-3-en-5-yn-1-ol **107** which on stereoselective hydrogenation with disiamylborane yielded the dienol **108** with 99% stereoselectivity and 85% yield. Oxidation of dienol **108** with Jones reagent gave Megatomic acid **109** in 83% yield. The reaction was carried out at room temperature or a little higher to achieve a reasonable reaction rate.



Scheme30 Synthesis of Megatomic acid using Cadiot-Chodkiewicz reaction

Several other *Z*,*Z*- and *Z*,*E*-dienic pheromone compounds such as (8*Z*,10*Z*)-8,10-dodecadien-1-ol **110**, (*Z*,*E*)-3,5-tetradecadienyl acetate **111**, (3*Z*,5*Z*)-3,5-dodecadienyl and (8*Z*,10*Z*)-8,10-tetradecadienyl acetates **112** and **113** were prepared following a related strategy (Figure 4).[60]

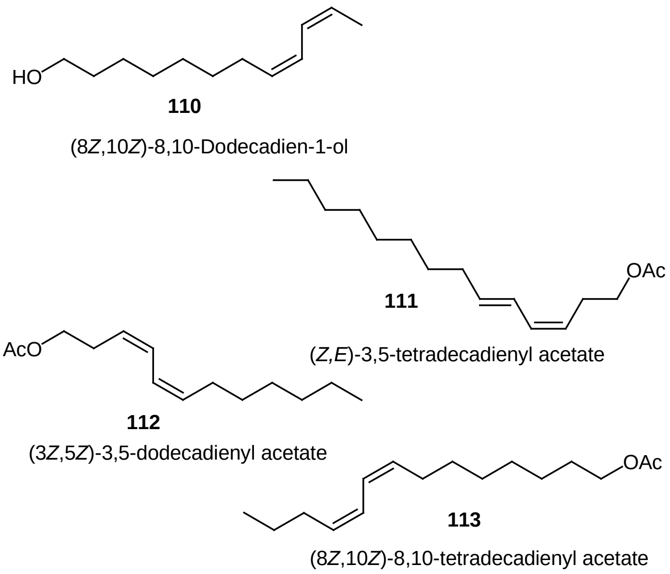
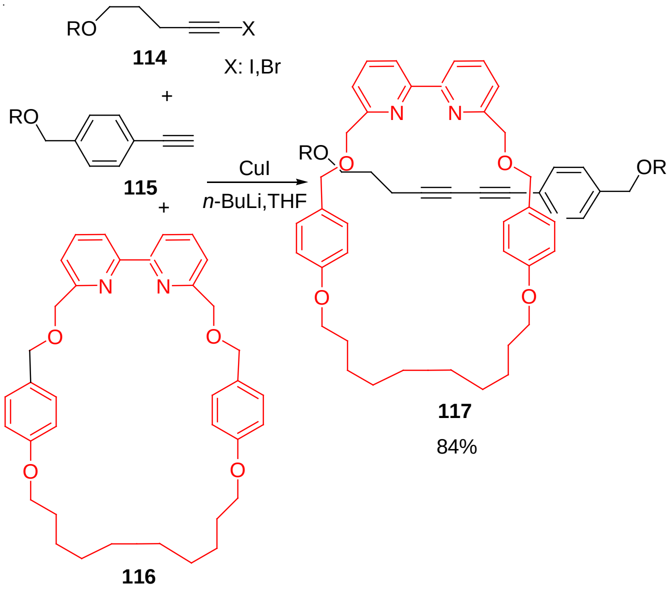


Fig 4 Some dienic pheromones synthesized using Cadiot-Chodkiewicz reaction

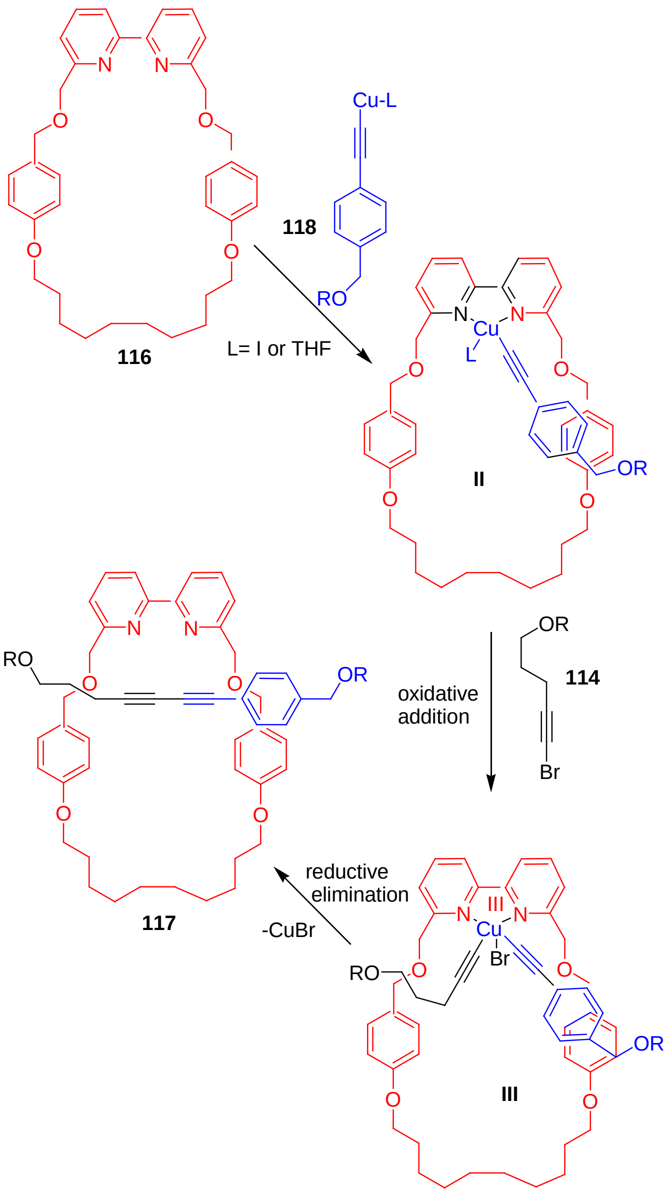
c. Catenanes and rotaxanes

The synthesis of interlocked compounds especially catenanes and rotaxanes was revolutionalized by active metal template synthesis using the Cadiot-Chodkiewicz reaction. Rotaxanes and catenanes were used to create molecular electronic devices and molecular sensors.[61] Leigh *et al*. reported a new rotaxane forming reaction with unsymmetrical threads using Cadiot-Chodkiewicz reaction utilizing *n*-BuLi as the base (Scheme 31).[62]



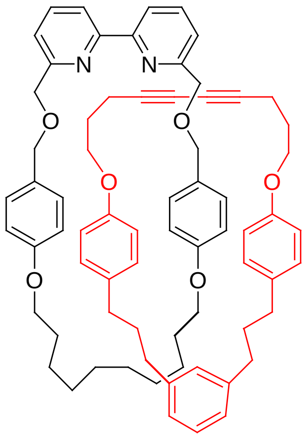
Scheme 31 Synthesis of [2] rotaxane using Cadiot-Chodkiewicz coupling

Here, the copper (I) acetylide **118** generated from the terminal acetylene **115** was captured by the bipyridine macrocycle **116** (Scheme 32). Oxidative addition of bromoacetylene **114** to the opposite face of the macrocycle produces Cu(III) intermediate **III** and subsequent reductive elimination furnishes the heterocoupled [2]rotaxane **117**.



Scheme 32 Mechanism of Cadiot-Chodkiewicz active metal template synthesis of [2]rotaxane proposed by Liegh *et al*. [Reproduced with permission from Angew. Chem. Int. Ed., 2008, 47, 4392]

Cadiot-Chodkiewicz reaction has also been applied in the synthesis of [2]Catenanes **119** using [Cu(CH_3CN)$_4$]PF_6 in dichloromethane in acceptable yield (Figure 5).[63]

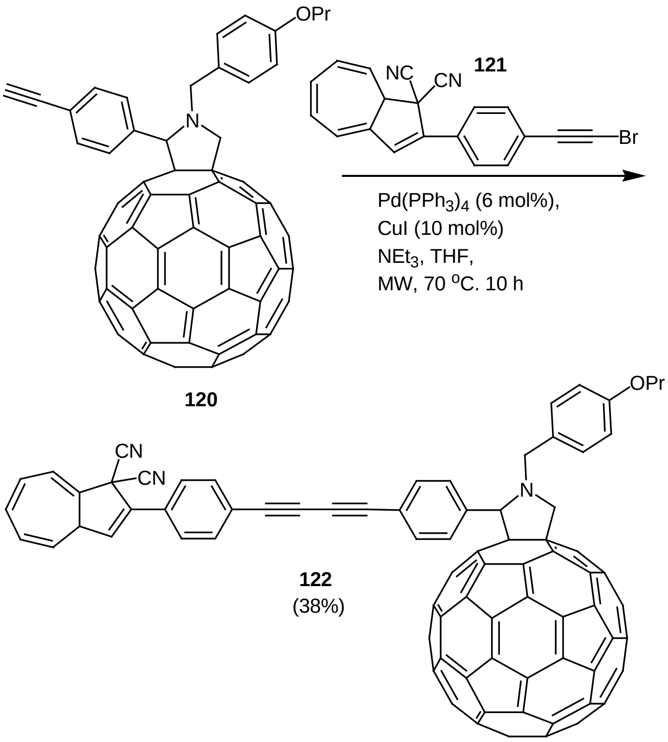


119

Fig 5 [2]Catenane from bipyridyl macrocycle and bromoalkyne.

d. Buckminsterfullerene conjugates

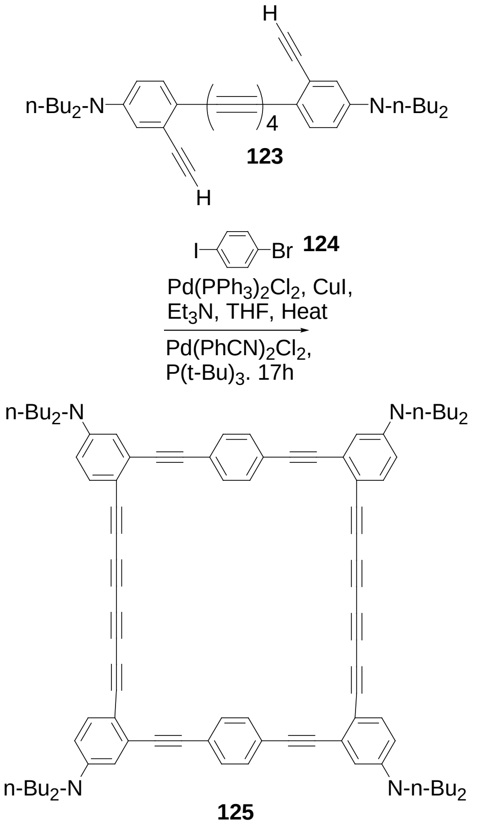
An efficient synthetic protocol for making covalently linked dihydroazulene-Buckminsterfullerene conjugates **122** using Cadiot-Chodkiewicz reaction was developed by Nielsen *et al.*[64] These conjugates are used as light-triggered conductance switches in single-molecule devices. The coupling of fulleropyrrolidine aryl-ethynyl alkyne **120** with dihydroazulene (DHA) **121** using Pd(PPh_3)$_4$/CuI catalyst system under microwave heating (70 °C) resulted in the formation of the product **122** in moderate yields (Scheme 33).



Scheme 33 Synthesis of DHA-C_{60} conjugate by Pd-catalyzed Cadiot-Chodkiewicz reaction

e. Cyclophanes

Modified Cadiot-Chodkiewicz cross-coupling plays a crucial role in the design and synthesis of suitable building blocks of novel cyclophanes,[65] dihydroazulenes[66] and dehydrobenzo[n]annulenes ([n]DBAs) (in which n denotes the number of π electrons in the cyclic pathway).[67] The dehydroannulenes annelated by propellatriene units exist in different shapes and supramolecular geometries. The preparation of an acetylenic 60-carbon atom macrocyclic cyclophanes with *para*- and *meta*-substituted capping groups was reported by Fallis *et al*.[65] The key step in the synthesis is the Cadiot-Chodkiewicz coupling of an aminosubstituted acetylenic precursor **123** and a substituted bromide **124**. The structure of the cyclophane **125** is shown in scheme 34.

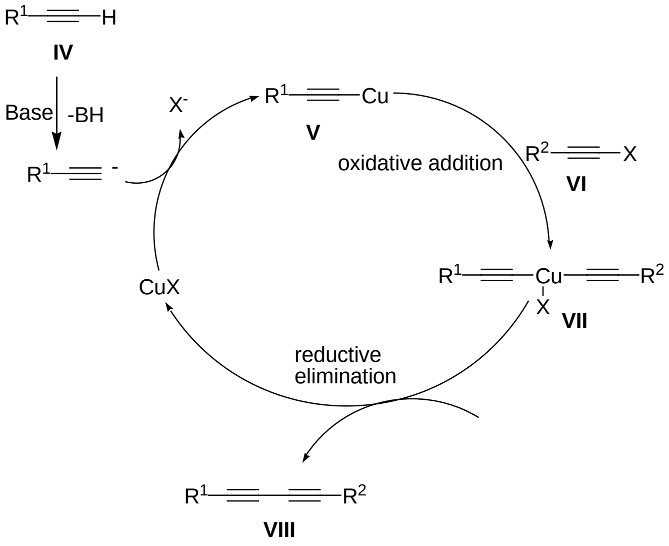


Scheme 34 Formation of an acetylenic 60-carbon atom macrocyclic cyclophane

Synthesis of poly(triacetylene)-derived oligomers with very high fluorescence intensities also utilized Cadiot-Chodkiewicz cross-coupling reactions on solid support.[68]

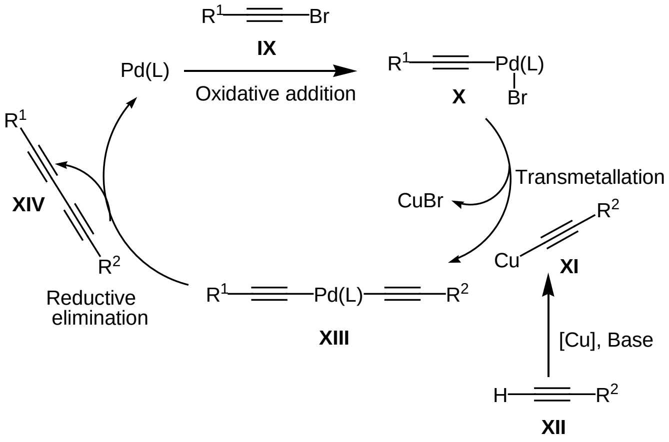
6. Mechanistic study of Cadiot-Chodkiewicz reaction

Only a few mechanistic studies have been conducted on the process of C(sp)-C(sp) bond formation of the Cadiot-Chodkiewicz coupling. The reaction mechanism involves deprotonation of the acetylenic proton from the terminal alkyne **IV** by a base followed by formation of a copper acetylide **V** (Scheme 35).[69] The ability of deprotonation of terminal acetylene is believed to be due to the high proportion of s character of carbon atom. Oxidative addition of copper acetylide on haloalkyne **VI** affords a bis alkynyl copper species **VII** which undergoes reductive elimination producing the new C-C bond to give the 1,3-diyne **VIII**, regenerating the Cu(I) species and thus the catalytic cycle continues.



Scheme 35 Mechanism of Cu-catalyzed Cadiot-Chodkiewicz coupling reaction

The mechanism of palladium-catalyzed Cadiot-Chodkiewicz coupling reactions was proposed by Lei *et al*.[17] At first the bromoalkyne **IX** undergoes oxidative addition to Pd(0) species to form an intermediate **X** followed by transmetallation with alkynylcopper **XI** to afford **XIII** (Scheme 36). The alkynylcopper **XI** is generated from the Cu(I) salt and terminal alkyne **XII** in presence of a base. Finally, reductive elimination takes place and the target diyne **XIV** is formed along with the regeneration of the Pd(0) species. If the reductive elimination is slow, the intermediate will react with another alkynylcopper and the homocoupled side product is formed.



Scheme 36 Mechanism of Pd-catalyzed Cadiot-Chodkiewicz coupling reaction

7. Conclusion

1,3-Diynes serve as building blocks and intermediates for the synthesis of a large variety of compounds in different fields like supramolecular chemistry, organic synthesis and material science. These unsymmetrical diynes can be easily synthesized using Cadiot-Chodkiewicz reaction. Cadiot-Chodkiewicz coupling reaction can also be successfully applied as the key step in the synthesis of natural products, many of which exhibit excellent biological activities, and in the synthesis of electronic and optical materials as well as in molecular recognition systems. This is an old but very useful reaction and attempts to improve the yield are still under investigation. This review gives an overview of recent developments in the coupling reactions of terminal alkynes with haloalkynes particularly focused on the exploration of the modified strategies and their applications. The advantage of the coupling reaction includes the relatively good yields, low cost of catalyst and mild reaction conditions. The reaction will increasingly find advantages by the use of Pd co-catalysts. This protocol tolerates numerous functionalized starting materials including alcohols, carboxylates, acetals etc. Despite the many significant discoveries and developments in Cadiot-Chodkiewicz reaction, there still remain the issues of selectivity and formation of considerable amounts of homocoupling by-products. In addition, in many cases the precursors of this reaction are less stable. It is presumed that the next breakthroughs in this area will be the improvement in the efficiency of the catalyst at lower catalyst loading, enhancement of the selectivity and yields by fine tuning of the reaction conditions, and further insight into the mechanism of Cadiot-Chodkiewicz reaction. This reaction also awaits the development of more practical and economical conditions and procedures for application in large-scale syntheses.

Acknowledgements

The authors are thankful to the Kerala State Council for Science, Technology and Environment (KSCSTE), Trivandrum for a research grant (Order No. 341/2013/KSCSTE dated 15.03.2013). KSS and APT thank the University Grants Commission (UGC), New Delhi and KSCSTE, Trivandrum for junior research fellowships.

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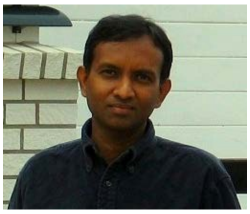

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