Design and Synthesis of Aromatics through [2+2+2] Cyclotrimerization

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Abstract The [2+2+2] cycloaddition reaction is a useful tool to realize unusual chemical transformations which are not achievable by traditional methods. Here, we report our work during the past two decades that involve utilization of transition-metal complexes in a [2+2+2] cyclotrimerization reaction. Several key “building blocks” were assembled by a [2+2+2] cycloaddition approach and they have been further expanded by other synthetic transformations to design unusual amino acids and peptides, diphenylalkanes, bis- and trisaryl benzene derivatives, annulated benzocycloalkanes, spirocycles, and spirooxindole derivatives. Furthermore, we have also discussed about alkyne surrogates, environmentally friendly, and stereoselective [2+2+2] cycloaddition reactions. Application of the [2+2+2] cycloaddition reaction in total synthesis is also covered. In this review we also included others work to give a balanced view of the recent developments in the area of [2+2+2] cycloaddition.

1 Introduction

[2+2+2] Cycloaddition is a useful tool to assemble densely functionalized aromatics in one step starting with alkyynes. Moreover, this method is also applicable to annulated benzenes by precise selection of the starting materials. The most common product of the acetylene cyclotrimerization is benzene. Regioisomers 2a, 2b are generated when substituted alkyne 1 is used. If two different alkyynes (diyne 3, monoyne 1) were tethered, annulated benzene derivatives 4a–c would be generated, whilst, if all three alkyynes were connected such as 5, a tricyclic ring 6 would be formed (Scheme 1). The driving force for the [2+2+2] cyclotrimerization reactions is the gain of aromaticity, and the reaction is exothermic. This intramolecular approach is effective for the synthesis of sterically demanding molecules such as helicenes.12

Scheme 1
In 1866, Bertholet first reported the thermal [2+2+2] cyclotrimerization of acetylene to benzene.\(^2\) The reaction is exothermic (experimental data \(\Delta H^0 = -143 \text{ kcal/mol}\)) and suffered from the formation of a large amount of byproducts.\(^2\) Since then, seventeen transition-metal cyclotrimerization, which occurs at low temperature with a low reaction barrier at least 36 kcal/mol) of the reaction. In 1948, Reppe reported the first transition-metal-mediated [2+2+2] cyclotrimerization, which occurs at low temperature with fewer byproducts.\(^2\) Since then, seventeen transition-metal catalysts based on Ni, Co, Pd, Cr, Rh, Ru, Fe, Zr, Nb, Ir, Ta, Ti, Re, etc. have been used for the cyclotrimerization reaction of alkynes and some of them are included in the recent reviews.\(^3\) These transition-metal catalysts are not used to the same extent. Transition-metal catalysts of group 9 such as Co, Rh, and Ir are mostly used in this reaction. Zirconium only allows cyclotrimerization in the presence of another metal catalyst such as nickel. Recently, besides the development of transition-metal catalyzed [2+2+2] cyclotrimerization reactions, several transition-metal-free [2+2+2] cyclotrimerizations have also been reported.\(^3\)

Transition-metal complexes used in [2+2+2] cyclotrimerization have emerged as indispensable tools in synthetic organic chemistry because they can tolerate a variety of functional groups, and this process allows incorporation of diverse substituents at a late stage of the synthetic sequence. Interestingly, the [2+2+2] cyclotrimerization reaction allows multiple bond formation exhibiting a high de-
gree of selectivity in some cases. It is an efficient protocol for assembling aromatic compounds, which can act as functional materials. This operation is an atom-economic process leading to the formation of unsaturated six-membered, highly substituted carbo- and heterocycles such as benzenes, pyridines, pyridones, and 1,3-cyclohexitritenes etc., in a single operation involving catalytic amounts of organo-metallic complexes. Owing to the several advantages of a [2+2+2] cycloaddition sequence, this strategy has been expanded into several areas and found diverse applications in organic synthesis.

Traditional methods to generate functionalized aromatic rings rely on stepwise electrophilic or nucleophilic aromatic substitution reactions. These approaches have several limitations with regard to regiochemical issues and functional-group tolerance. The [2+2+2] cycloaddition strategy seems to be a better option to design substituted benzenes because of its convergent nature. In addition, functionalization of the aromatic ring by this method can be achieved in a predetermined manner and this approach provides better regiocontrol while incorporating various substituents in the benzenoid systems.

The exact mechanism for [2+2+2] cyclotrimerization depends on the nature of the metal and alkyne partners. A general mechanism is shown in Figure 1. When two alkynes coordinate to a metal center, oxidative cyclization occurs forming metallacyclopentadiene intermediate B or metallacyclopentatriene intermediate C. Coordination of the third alkyne generates a new complex, which could be transformed either into metallacycloheptane complex D or a bicyclic complex E by an intramolecular Diels–Alder (DA)-type reaction or complex F through a [2+2] cycloaddition reaction. Finally, a reductive elimination process affords the aromatized product, by completing the catalytic cycle.

![Figure 1](image-url) A general mechanism to benzene derivatives by [2+2+2] cyclotrimerization

To test the scope and limitations of the [2+2+2] cycloaddition approach we have prepared new building blocks, and utilized them during the past two decades in a diversity-oriented synthesis. This approach has now widespread use in pharmaceutical industry. In this review, we would like to demonstrate how the “building block approach” has been used to prepare several complex targets using the [2+2+2] cycloaddition reaction as a key step. Some relevant approaches described in the literature are also covered.

2 Unusual Amino Acids and Peptides

Indane-based α-amino acid (AAA) is a constrained analogue of phenylalanine (Phe) and it is used extensively in the design and synthesis of a variety of bioactive peptides. Utilization of unusual AAAs in physical and life sciences has continued to grow at an impressive rate. They are useful as building blocks for peptides, proteins, and natural products and used extensively in pharmaceutical, agrochemical, and food industry. The design and synthesis of peptides with predetermined structure is a challenging task in the present day peptide chemistry. In this regard, conformationally restricted Phe analogues have proven to be useful tools as they can control the secondary structure of a peptide. Moreover, incorporation of unusual AAAs into peptides may provide unique analogues which are biologically more active and resistant to enzymatic degradation. To synthesize diverse unusual AAA derivatives, we have adopted the “building block approach” involving a [2+2+2] cycloaddition as a key step.

This methodology involves the preparation of diyne building block 7 containing an AAA moiety which on [2+2+2] cycloaddition reaction in the presence of Wilkinson’s catalyst or Vollhardt’s catalyst CpCo(CO)2 with various monynes 8a–h delivers indane-based AAA derivatives such as 9 (Scheme 2). This methodology is strategically different from the other routes because the benzene ring is generated during the cycloaddition sequence, while the other methods involve manipulation of preformed benzene derivatives. Since the cycloaddition reaction can generate complex targets by judicious selection of the reacting partners, we obtained a variety of unusual AAA derivatives. Silylated benzene derivatives underwent electrophilic substitution reactions ipso to the silyl group, and therefore the modification of the bis-silyl indane derivative 9b was also explored (Scheme 3).

Since o-xyllylene intermediate 12 can be trapped with a suitable dienophile to produce new AAA derivatives 11a the attention was focused on the generation of the sultine derivative 13 (Scheme 4).
Towards the synthesis of 11, the required indane derivative 16 was synthesized through a [2+2+2] cycloaddition of 2-butyne-1,4-diol (8c) and the diyne derivative 7a, obtained from ethyl isocyanoacetate 14. The dihydroxy indane derivative 16 was then converted into the corresponding dibromo 17 with use of PBr3. Next, a reaction of dibromo compound 17 was performed with sodium hydroxymethanesulfinate (rongalite)7b in the presence of tetrabutylammonium bromide (TBAB) in DMF at 0 °C, and the two isomeric sultine-based AAA derivatives 18 were obtained in 72% combined yield (1:1) (Scheme 5). Having the sultines 18 in hand, we explored their DA chemistry with various dienophiles to produce DA adducts. Subsequent oxidation of the DA adducts with DDQ gave benzoannulated derivatives (11a,b). The DA reaction of 18 with other dienophiles such as 1,4-benzoquinone, 1,4-naphthaquinone, and 1,4-anthraquinone delivered the products 11c-e. In view of various applications of fullerene-based AAA derivatives in bioorganic chemistry, we turned our attention to incorporate the AAA moiety in the fullerene system and successfully obtained compound 11f in 49% yield (Figure 2). The hydrophobic character of the fullerene moiety and its ability to act as an electron sink may make the fullerene-based AAA derivative an attractive building block for biological applications.

Dixneuf and co-workers have developed an impressive approach to CF3-substituted benzoproline and tetrahydroisoquinoline-3-carboxylic acid derivatives 20 and 21, which is based on ruthenium-catalyzed cyclotrimerization of 1,6- and 1,7-azadiynes 19 and alkynes 8 with Cp*RuCl(cod) and the Grubbs catalyst (Scheme 6).8

Along similar lines, Roglans and co-workers adopted this methodology to synthesize nonproteinogenic Phe derivatives using enantiopure and racemic propargylglycine 22 with different diynes 3 (Scheme 7).9 When they used Wilkinson’s catalyst or a cationic rhodium [Rh(cod)2]BF4/BINAP catalyst the required product was not formed; only homo-coupling product was observed. However, Wilkinson’s catalyst in ethanol heated to reflux gave the desired cycloaddition product in good yields. The reaction worked well with symmetric as well as unsymmetric 1,6-diynes; however, the regioselectivity was poor in the case of unsymmetric diynes. Very recently, our group has shown the synthesis of benzyl halo derivatives of aminooindane carboxylic acid (Aic) derivatives directly through a [2+2+2] cyclotrimerization using propargyl halides as co-partners with Mo(CO)6 under microwave irradiation (MWI).10

In 2016, Shibata et al. reported the enantioselective synthesis of Aic derivatives through a Rh-catalyzed intramolecular [2+2+2] cycloaddition reaction. When the intermolecular [2+2+2] cycloaddition was carried out in the presence of a Rh catalyst using (S)-BINAP as a chiral ligand, the enantioselectivity was very poor. Hence, they realized that the
enantioselectivity could be improved by intramolecular [2+2+2] cycloaddition. Starting with triynes 25, the tethered Aic derivatives 26 were generated. Subsequently, removal of the tether gave chiral Aic derivatives 27 (Scheme 8).\textsuperscript{11}

Similarly, they developed the synthesis of cyclic peptides. In this regard, they prepared the triynes from 1,6-diyne and alkyne connected by a di- or tri-, or tetrapeptide tether. Later, intramolecular [2+2+2] cycloaddition of the peptide-tethered triynes 28 in the presence of \( \text{Rh(COD)}_2\text{OTf} \) (10 mol%) toluBINAP complex gave cyclic peptides 29 in moderate chemical yields and good diastereoselectivity. When they used bulky ligand \( \text{(S)-xylBINAP} \) a higher diastereoselectivity was achieved. However, \( \text{(R)-tolBINAP} \) also gave the same stereoisomer suggesting that the stereoselectivity was controlled by the chiral peptide tether, but not by chiral Rh catalysts. Moreover, achiral ligand BIPHEP provided similar results (Scheme 9).\textsuperscript{12}

Recently, Zotova et al. demonstrated the trifluoromethyl-substituted phosphate analogues of Tic derivatives based on N-propargylation of \( \alpha\)-alkynyl-\( \alpha\)-CF\(_3\)-\( \alpha\)-amino-phosphonates 36 to form 1,7-azadiynes 37, followed by cocyclotrimerization with terminal alkynes 1b-d using two types of ruthenium catalysts: \( \text{CpRuCl(cod)} \) and preferably the alkene-metathesis\textsuperscript{14c} Grubbs second-generation catalyst (Scheme 11).\textsuperscript{14c}

Kotha and Banerjee have developed a short and efficient synthetic route to Tic-quinone hybrids 42a–d using a [2+2+2] and a [4+2] cycloaddition reaction as the key steps.\textsuperscript{13c} The \( \alpha\)-xylylene intermediate required for the DA reaction was prepared through the sultine methodology by using rongalite (Scheme 12, Figure 3).\textsuperscript{15} The required diol building block 35a used for the preparation of sultine 40, was prepared by following a [2+2+2] procedure starting with alkyne building block 34, which in turn can be obtained from benzophenone imine 30. The starting material 32 is commercially available in enantiomerically pure form. The method can be easily extended to the preparation of optically active Tic derivatives 42a–d (Figure 3). The compounds prepared here may find further applications in drug design and peptide modifications. They can be used as...
building blocks in pharmaceutically active molecules, ligands for catalysis, liquid crystals, organic semiconductor, polymers, and sensors.

Later, the dihydroxy derivative 45 was treated with PBr₃ in benzene to obtain the corresponding dibromide. However, several attempts could not deliver the desired product. Either, decomposed product or starting material was recovered under these conditions. However, recently we have developed a new protocol using a [2+2+2] cycloaddition reaction with propargyl halides to generate halide derivatives directly in a one-step procedure without the formation of the hydroxy derivative. By using this protocol, dipropargyl peptide was treated with propargyl halides in the presence of Mo(CO)₆ under MWI conditions to generate the trimerized halo derivatives.¹⁰

### 3 Heteroanalogues of Indane

Kotha and co-workers synthesized 1,3-dihydroisobenzofuran 46 derivatives starting with propargyl halides (1a, 8i, 8j, 8k) and dipropargylether 3a through a [2+2+2] cycloaddition reaction (Scheme 14). In this regard a minor amount of dimer 47 is observed. Furthermore, the dibromo derivative of 1,3-dihydroisobenzofuran 46b was used to prepare benzosultine-sulfone 51 by using rongalite (Scheme 15).¹⁵ Benzosultine-sulfone 51 is a hybrid molecule which can participate in the DA reaction in a stepwise manner by opening the sulfine or the sulfone fragment at different temperatures, and the respective o-xylene intermediate can be trapped with different dienophiles. This approach delivers densely functionalized polycyclic compounds.

![Scheme 12](image1)

**Figure 3** List of Tic derivatives prepared with use of rongalite

A general goal of peptide research is to design modified peptides that may enhance the pharmacological profile of the native peptide. In this connection, Kotha and co-workers were interested in peptide modifications by adapting the “building block approach” to generate a large number of compounds starting with a common precursor.¹⁶ For the first time, a new strategy for the modification of Phe peptides by a [2+2+2] cycloaddition reaction was developed and these peptides might be useful in developing combinatorial libraries of peptidomimetics. In this regard, the dipeptide precursor 44 was easily synthesized by a standard peptide synthesis protocol starting with the dipropargyl glycine 43 as the key amino acid building block. The dipropargyl glycine was prepared from ethyl isocyanoacetate 14 in a four-step sequence (Scheme 13). The dipeptide precursor 44 was treated with five-fold excess of but-2-yn-1,4-diol (8c). Here, the monoyne was chosen to avoid the formation of diastereomers and the representative constrained Phe peptides 45 were obtained in good yield.¹⁶

![Scheme 13](image2)
Later on, Kotha and Sreevani have shown the synthesis of dipropargyl sulfone \(3b\) from rongalite and propargyl bromide in a single step. The building block \(3b\) was also converted into benzosultine-sulfone \(51\) through \([2+2+2]\) cyclo-trimerization reaction by using 1,4-dibromo-2-butyne (8i) and Mo(CO)\(_6\) as a catalyst in a short two-step synthetic sequence (Scheme 16).\(^{17b}\)

Furthermore, the methodology has been extended to prepare isoindoline and isoindolinone halide derivatives (Schemes 17 and 18).\(^{17c}\)

![Scheme 16](image)

![Scheme 17](image)

![Scheme 18](image)

Witulski and co-workers reported a [2+2+2] cyclo-trimerization\(^{15a}\) for the synthesis of 4,6- or 4,5-substituted indoline derivatives \(55\) and \(56\) using Grubbs and Wilkinson’s catalysts, respectively (Scheme 19).

![Scheme 19](image)

4 Diphenylalkane Derivatives

The diphenylalkane moiety is present in a variety of natural products and in biologically important molecules. For example, 1,3-diphenylpropane (viscoline) isolated from hemiparasitic herb is used in Chinese medicine for a number of diseases such as haemorrhage, gout, heart diseases, epilepsy etc. 1,2-Diphenylethane derivatives possess cytotoxic activity towards genital fibroblasts and also show anti-angiogenic activity. In 1980, Ibuki et al. demonstrated a general method for the preparation of diphenylalkane derivatives of varied chain lengths using a benzenoid precursor.\(^{15a}\) Recently, Kotha and Khedkar have developed a new approach to diphenylalkane derivatives using a [2+2+2] cyclodaddition, cross-enyne metathesis (CEM), and DA reactions as the key steps.\(^{18}\) In this connection, various \(\alpha,\omega\)-diynes such as 1,5-hexadiyne (3e, \(n = 0\)), 1,6-heptadiyne (3f, \(n = 1\)), 1,7-octadiyne (3g, \(n = 2\)), and 1,8-nonadiyne (3h, \(n = 3\)) were subjected to a [2+2+2] cyclotrimerization reaction with dimethyl acetylenedicarboxylate (DMAD, 8g) using Wilkinson’s catalyst, and the polysubstituted benzene derivatives \(57\) were produced in 41–48% yield. Alkynes \(57\) were subjected to CEM with ethylene in the presence of a G II catalyst, by using toluene as the solvent, and the diene derivatives \(58\) were obtained in excellent yields. Microwave irradiation of the reaction mixture with DDQ delivered the corresponding aromatized diphenylalkane derivatives \(60\) in good yields (Scheme 20). The methodology is suitable for a diversity-oriented approach to synthesize densely functionalized diphenylalkane derivatives. The two different polysubstituted aromatic rings are built at the two ends of the \(\alpha,\omega\)-diyne scaffold in a stepwise manner.

![Scheme 20](image)

5 Multi-Armed Aryl Benzene Derivatives

Kotha and co-workers have prepared bis- and trisaryl benzene derivatives through a [2+2+2] cyclotrimerization reaction using the Grubbs first generation catalyst (G I).\(^{20a}\) It was found that the G I catalyst is more suitable for cyclotrimerization.
merization than the Grubbs second generation (G II) catalyst. The G I catalyst shows higher initiation and low propagation rates, whereas the G II catalyst has low initiation and high propagation rates. To this end, commercially available acetophenone derivatives 61 were converted into acetylenes 63 through the Vilsmeier reaction. Acetylenes 63 were subjected to a [2+2+2] cyclotrimerization with DMAD in the presence of the G I catalyst (5 mol%) in toluene heated to reflux to deliver the terphenyl systems 64 in 62–75% yield (Scheme 21). The [2+2+2] cycloaddition reaction of acetylenes 63 was also studied with other acetylenic partners, such as 1,4-dibromobut-2-yn, 1,4-diacyetylbut-2-yn, and 1,4-dihydroxybut-2-yn but the desired [2+2+2] cyclotrimerized product was not observed. Therefore, acetylene derivatives with electron-withdrawing groups such as DMAD are required for the successful implementation of the [2+2+2] cyclotrimerization reaction with phenylacetylene derivatives. As an extension to the above methodology, products 64 were subjected to a Suzuki–Miyaura (SM) cross-coupling reaction with different boronic acids such as 4-acetyl-, 4-formyl-, and 4-methoxyphenylboronic acid using Pd(PPh3)4 catalyst (5–9 mol%) in tetrahydrofuran/toluene/water (1:1:1) mixture in the presence of sodium carbonate as a base. The SM cross-coupling products (65a–f) were hydrolyzed during the course of the reaction.

![Scheme 21](image)

To synthesize 1,3,5-triaryloxyethylbenzene derivatives through a [2+2+2] methodology using Grubbs catalyst, (prop-2-ynyloxy)benzenes 67 were prepared by reaction of phenol derivatives 66 with propargyl bromide (1a) in acetone heated to reflux in the presence of K2CO3. The propargylated compounds 67 were then treated with G I catalyst (7.5 mol%) in toluene at 80 °C. A mixture of symmetric 1,3,5- and unsymmetric 1,2,4-triaryl benzene derivatives 68 and 69 were obtained as white solids along with depropargylated product 66. It was observed that the G I catalyst was more effective for the [2+2+2] cyclotrimerization than the G II catalyst. With catalysts G III and G IV the depropargylated product 66 was obtained as a major product (Scheme 22).21

Along similar lines, Tanaka and co-workers found that a cationic rhodium(I)–H8-BINAP complex catalyzes the complete intermolecular homo- and a cross- [2+2+2] cycloaddi-

![Scheme 22](image)

tion of aryl ethynyl ethers 70 at room temperature, with electron-deficient internal monoalkynes, leading to tri- and diaryloxybenzenes, respectively (Scheme 23).22

![Scheme 23](image)

Feng et al. reported the synthesis of two different tetra-substituted benzenes 74 and 75 (Scheme 24) from the same starting material 8h simply by catalysis with G II in the presence of an additive CuI (73a) or AgOTf (73b).18b

![Scheme 24](image)

Chen and co-workers reported the intermolecular cyclotrimerization of unsymmetric diarylalkynes 76 in the presence of Co2(CO)8 to produce the corresponding 1,2,4-regioisomers 77 or 1,3,5-regioisomers 78 with excellent yields and high regioselectivity (Scheme 25).18c

6 Annulated Benzocycloalkanes

Kotha and Khedkar reported an interesting reactivity pattern of hybrid o-quinodimethane precursor 82. This hybrid compound containing benzocyclobutane and benzo-
difficult task because it involves the generation of a quaternary center. There are many methods known in the literature for the synthesis of spirocyclic compounds but many of these methods have several limitations such as low functional group tolerance, restriction to particular substitution patterns etc. In this regard, there is a compelling need to develop new methods to form spirocycles. During the past few years, Kotha and co-workers have made continuous effort to prepare diverse spirocycles using the “building block approach” and some of them are described here.

Kotha and Manivannan envisaged the spiro compound 86 as a useful precursor for the synthesis of unsymmetric benzoannulated systems. They have found that there are two possible retrosynthetic routes for the preparation of 86; one using a [2+2+2] cycloaddition (path A, Scheme 27) and the other using [4+2] cycloaddition (path B, Scheme 27). These routes are strategically different and, using the above methodologies, they have shown that [2+2+2] and [4+2] cycloaddition strategies are useful to prepare various 2,2-spirobisindane-1,3-dione derivatives. To realize the [2+2+2] strategy the key intermediate was prepared by bis-propargylation of 1,3-indanedione (89) with propargyl bromide (1a) by using a phase-transfer catalyst (Scheme 28). With the prepared compound 87 a [2+2+2] cycloaddition sequence was performed with use of n^2-cyclopentadienylcobalt complex CpCo(CO)2 as a catalyst. Here, slow addition of diyne 87 and catalyst in dry toluene to a solution of alkyne heated to reflux under inert conditions gave the required linear spiro derivatives 86. Various monoynes underwent the cycloretimerization reaction under these conditions.

Starting with same material (1,3-indanedione, 89) Kotha and co-workers have prepared several angularly as well as linearly fused spirocyclic derivatives. To this end, a [2+2+2] cycloaddition and DA reaction were used sequentially as the key steps.

7 Spirocycles

The spiro unit is an important structural element present in several natural products (e.g. terpenoids and alkaloids) and non-natural products. Recently, they have found important applications in materials science and also in medicinal chemistry. The attractive conformational feature of the spiro center is responsible for the biological activity. Because of the presence of an axial chirality, these compounds are useful in designing new chiral ligands and catalysts applicable in asymmetric synthesis. Hudlicky has once remarked that the generation of a spiro center is a highly difficult task because it involves the generation of a quaternary center. There are many methods known in the literature for the synthesis of spirocyclic compounds but many of these methods have several limitations such as low functional group tolerance, restriction to particular substitution patterns etc. In this regard, there is a compelling need to develop new methods to form spirocycles. During the past few years, Kotha and co-workers have made continuous effort to prepare diverse spirocycles using the “building block approach” and some of them are described here.

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dipropargylated compound 87 with 2-butylene-1,4-diol in dry ethanol in the presence of Wilkinson’s catalyst gave diol 90 in 39% yield along with a small amount (4%) of the dimer (Scheme 29). Since Ti(OPr)i activates enyne metathesis,25c a similar role was anticipated in a [2+2+2] cyclodaddition sequence. When Ti(OPr)i was used in catalytic amount, the yield of diol 90 increased to 46% along with a minor amount (7%) of the dimer. Diol 90 was then converted into the dibromo derivative 91 by using PBr3 in dry benzene at room temperature, and this dibromide was then converted into sultine derivative 92 by treatment with rongalite in dimethylformamide. The diene intermediate was generated from sultine 92 in toluene heated to reflux and was trapped with 1,4-naphthoquinone to deliver the corresponding DA adduct. Dehydrogenation of the DA adduct with DDQ in toluene heated to reflux produced the aromatized product 93a. Other linearly fused spirocycles 93b–d prepared by this methodology are shown in Figure 4.

Although a [2+2+2] cycloaddition reaction has been applied with several substrates, limited examples are available where propargyl halides are used as co-partners. In all these examples propargyl diol is used as co-trimerized partner and the resulting dihydroxy derivative obtained in a [2+2+2] cycloaddition reaction is transformed into the corresponding bromide by using PBr3. This strategy could not be extended to sensitive substrates such as Meldrum’s acid, peptides, ethers, and these substrates decompose during the bromination sequence. To expand its utility in organic synthesis, we have studied the use of propargyl halides in a [2+2+2] cycloaddition under different catalysts/conditions. Kotha and Sreevani have demonstrated a [2+2+2] cycloaddition strategy with propargyl halides using a Mo catalyst, Mo(CO)i0, under MWI conditions.10a Mo complexes are not the regular catalysts for a [2+2+2] cyclotrimerization sequence. The mechanism may involve the formation of molybdenacyclopentadiene which would react with the alkyne partner to produce the cyclotrimerized product. In this context dipropargylated 1,3-indane diene 87 was chosen as a model substrate (Scheme 30). Dyne 87 was then subjected to a [2+2+2] cycloaddition sequence with propargyl bromide (1a) in the presence of a catalytic amount of Mo(CO)i0 in THF heated to reflux for 10 hours. The desired [2+2+2] cycloaddition product 94 was obtained (34%) along with self-dimerized product 96 (5%) and the unsaturated aldehyde 95. After considerable amount of experimentation, it was found that the reaction was successful with acetonitrile under MWI conditions at 90 °C. The yield of the trimerized product 94 was improved to 75%. This may be due to in situ formation of the air-sensitive catalyst (CH3CN)i0Mo(CO)i0 when Mo(CO)i0 was heated with acetonitrile, and this could facilitate the reaction. Additionally, the high dielectric constant of acetonitrile facilitates the absorption of MW radiation to enhance the rate of the reaction. The [2+2+2] cyclotrimerization was achieved with a variety of active methylene-based diynes and different propargyl halides under similar reaction conditions and the corresponding benzyl halide derivatives were isolated in good yields.

Later, this technology has been extended to barbituric acid, Meldrum’s acid, hydantoin derivatives, thiazolidines, amino acids, and peptides to synthesize the corresponding halomethylbenzene derivatives 102–106 and 17 in moderate to good yields (Scheme 31).10b
In continuation of our efforts to the synthesis of spirocycles, Kotha and Ali have developed a new strategy involving a sequential usage of [2+2+2] and [4+2] cycloadditions. To design intricate spirocycles, readily available carbonyl compounds (i.e. mono ketones 107) were tetrapropargylated. Later, reactions of the tetrapropargyl ketones 108 with 2-butyne-1,4-diol (8c) were performed in the presence of Wilkinson’s catalyst and a catalytic amount of Ti(O\textit{Pr})4 to deliver [2+2+2] cycloaddition products 109 (Scheme 32). Next, the tetraol derivatives 109 were directly converted into tetra-bromides 110 so that they can be transformed into sulphines 111 by using rongalite. Then, reactions of these sulphines were performed with different dienophiles in a DA fashion to generate various complex bisarmed spirocycles 112 (Figure 5) in excellent yield. Unexpectedly, the DA reaction with 1,4-naphthaquinone and DMAD (8g) gave the corresponding mono-DA adducts which on subsequent dehydrogenation furnished the aromatized products.

Later on, this strategy has been extended to bis-armed spirocycles 115 and 116 containing a bicyclo[2.2.2]octane system through a [2+2+2] cyclotrimORIZATION followed by a DA reaction. The required tetryne 114 was prepared by propargylation of dione 113 (Scheme 33), which was synthesized from commercially available hydroquinone. Further, the tetryne 114 was treated with 1,4-dihydroxy-2-butyne (8c) in the presence of Wilkinson’s catalyst to obtain tetaol 115, which on treatment with PBr3 in CH2Cl2 without isolating the intermediate tetaol afforded the desired tetrabromo derivative 116. In this context, we directly treated the tetrapropargylated compound 114 with 2-butyne-1,4-dibromide (8i) in the presence of Wilkinson’s catalyst; however, unfortunately, we did not achieve the desired product. Later on, we treated the propargyl building block 114 with 8i and Mo(CO)6 under MWI conditions in CH3CN at 90 °C and the spiro-annulated building block 116 was obtained in 40% yield. Next, tetrabromide 116 was successfully converted into the sulfine derivative 117 by using rongalite followed by the DA sequence with tetracyanoethylene, which delivered the cyclo adduct 119 in 67% yield (Scheme 34). Moreover, the sulfine derivative 117 was rearranged to bis-sulfone derivative 118 in toluene heated to reflux in good yield.

The spirooxindole moiety is a critical structural unit present in drugs, which show antimalarial, anticancer, and antimicrobial activity. To this end, to synthesize various spirooxindole derivatives, Kotha and Ali conceived a strate-
gy on the basis of a [2+2+2] cycloaddition and a DA reaction.\(^{27}\) In this regard, N-methyl derivative of oxindole \(120\) was dipropargylated and subsequent [2+2+2] cycloaddition yielded diol \(122\), which on treatment with \(\text{PBr}_3\) in CH\(_2\)Cl\(_2\) afforded the dibromo building block \(123\). Later, the dibromo derivative \(123\) was converted into the sultine derivative \(124\) (76%), and subsequent treatment with tetracyanoethylene delivered the DA adduct \(125\) (72%, Scheme 35).

Kotha and Ali reported several linearly annulated spirocyclic compounds starting with inexpensive and commercially available active methylene compounds (AMCs) \(126a\)–\(g\) (Figure 6). These AMCs were dipropargylated; the selection of the base used during the dipropargylation step depends on the acidity of the AMCs.\(^{28}\) The dipropargylated compounds were further subjected to a [2+2+2] cycloaddition reaction with 2-butyne-1,4-diol with the aid of Wilkinson’s catalyst and a catalytic amount of Ti(O\(_{\text{i}}\)Pr\(_4\)) to afford the diol. Next, treatment with \(\text{PBr}_3\) delivered the dibromo compounds in good yield. Further, these dibromo compounds were treated with rongalite in DMF to deliver the sultine derivatives, which on reaction with dienophiles in a DA fashion produced the cycloadducts. Finally, dehydrogenation delivered several linearly fused spirocycles \(127a\)–\(h\) (Figure 7). Interestingly, fluorenes are a unique class of blue-emitting molecular entities used in polymer light-emitting diodes (PLEDs). Moreover, they also found useful applications as sensors, and their remarkable quantum efficiency has made them important in the field of optoelectronics. Recently, much attention has been paid towards the synthesis of ladder-type oligomers and polymers of fluorenes with a rigid spiro linkage in their structures. Therefore, these fluorene-based spirocycles (e.g. \(131\)) prepared by this simple methodology (Scheme 36) may find useful application in polymer chemistry and materials science.

Kotha and co-workers also have reported spirobarbituric acid derivatives \(134a\)–\(d\) using a similar methodology starting from barbituric acid (Scheme 37).\(^{29}\)
8 Selectivity in [2+2+2] Cycloaddition of Alkynes

One of the disadvantages of a [2+2+2] cyclotrimerization reaction is the formation of regioisomeric products, i.e. the lack of selectivity. This problem can be addressed by using some of the strategies mentioned here. For example, use of a temporary tether to combine two alkynes allows overcoming the problems associated with the formation of regioisomers in intermolecular reactions or avoids the formation of isomers in partially intermolecular [2+2+2] cycload-
dition reactions. Yamamoto and co-workers reported a chemo- and regioselective ruthenium-catalyzed intermolecular cyclotrimerization of three different unsymmetric alkynes by means of a temporary tethering approach involving boron. Alkynylboronates 135, propargylic alcohol 1e, and terminal alkynes were cyclotrimerized in the presence of Cp*RuCl(cod) generating an arylboronate intermediate 138 which could be isolated or subjected to further synthetic manipulations such as Suzuki–Miyaura coupling with various aryl iodides or palladium(II)-catalyzed carbon–iodination reaction (Scheme 38).30

Mori et al. have reported a highly regioselective Ni-catalyzed [2+2+2] cycloaddition of two distinct alkynes using additives such as diethyl zinc and phenol. Reaction of methyl propiolate (1g) with trimethylsilyl protected propargyl alcohol 1h afforded the cycloadducts 145 and 146 in 95:5 regioselectivity (Scheme 40).32

The regioselectivity problem was addressed by a reaction of alkynes together with a suitable linker (e.g. 1,6-diynes or 1,7-diynes). The 1,2-bis(diphenylphosphino)ethane (DPPE)-bound Ni catalyst can facilitate the reaction of 1,6 diynes 3e with 1,3-diyne 147. The diynes bearing electron-withdrawing ester groups on the termini gave excel-
lent yields. Furthermore, unsymmetric 1,3-diyne 149 coupled regioselectively with 1,6-diyne 3f to give arylalkyne 150 (Scheme 41).

Deiters and co-workers developed solid-supported diyne substrates for controlling the regioselectivity during a [2+2+2] cyclotrimerization sequence. A variety of diynes were immobilized on polystyrene resin by using trityl or carboxy linkers, and a [2+2+2] cyclotrimerization was conducted with various symmetric as well as unsymmetric alkynes in the presence of Wilkinson’s catalyst or Cp*RuCl(cod) catalyst. Unsymmetric alkynes in the presence of Wilkinson’s catalyst showed poor regioselectivity; however, using Cp*RuCl(cod) catalyst, high regioselectivity was observed (meta/ortho 9:1) (Scheme 42). This method avoids self-coupling reaction of diynes and facilitates easy separation of cross-cycloaddition products. The compounds were obtained in good to excellent yields and with high purities after cleavage from the solid support. Later, the same group reported solid-supported [2+2+2] cyclodaddition reactions under MWI conditions using Cp*RuCl(cod) catalyst.

By an intramolecular cyclodaddition strategy, one can solve selectivity issues (Scheme 43). Totally intramolecular [2+2+2] cyclotrimerization was observed in 15- and 25-membered polyacetylenic azamacrocycles with Wilkinson’s catalyst. The expected cyclotrimerized compound was obtained in 54 and 50% yield, respectively. However, 20-membered azamacrocycle gave no product because of the lack of reactivity. This reaction is very attractive and of high synthetic potential because of its chemo- and regioselectivity. Limited reports are available, which is due to the difficulty in designing of the triyne substrate.

Peters and Blechert were the first to report fully intramolecular cyclotrimerization using Grubbs catalyst. The mechanistic explanation for the reaction involves a cascade of four metathesis reactions occurring to isomerize the triynes to benzene derivatives using Grubbs catalyst. Yamamoto and co-workers demonstrated that 1,6,11-triyne on cyclization in the presence of 1 mol% catalyst produced the tricyclic compound 6 in 82% yield (Scheme 44).35b

Despite several advances in metal-catalyzed [2+2+2] cyclodaddition processes for laboratory uses, this process still needs additional improvements with respect to the development of environmentally friendly and scalable procedures that are applicable on industrial scale. In this regard, Oshima and co-workers, in 2003, reported a rhodium-catalyzed [2+2+2] cyclotrimerization of triynes in a water-organic biphasic system. Later, Cadierno et al. have report-
ed intermolecular cyclotrimerization of alkynes (1b, 1c, and 1j) in aqueous medium using a commercially available ruthenium(IV) dimer (Scheme 45).36b

![Scheme 45](image)

In 2010, Tsai and co-workers demonstrated a [2+2+2] cycloaddition of α,ω-dienes (3a, 3c, and 3g) catalyzed by [Rh(COD)Cl]2/cationic 2,2'-bipyridyl system 158, with terminal (1c, 1e, and 1k) and internal alkynes (8k and 8l) in water in the presence of air at 60 °C (Scheme 46). After separation of the organic products from the reaction mixture by extraction, the residual aqueous solution could be reused for further reactions until complete degradation of its catalytic activity.36c

![Scheme 46](image)

Recently, Goswami and co-workers prepared an iron-based catalytic system FeCl3·4H2O/dipimp/Zn to accomplish [2+2+2] cycloaddition reactions. They reported an eco-friendly [2+2+2] partially intramolecular reaction using the same catalytic system in ethanol to prepare N-substituted indolyl-aryl derivatives 160 in good yields (Scheme 47). Here, the reaction was carried out in ethanol as the solvent and iron(II)chloride tetrahydrate acts as the metal source, 2-[(2,6-disopropylphenyl)iminomethyl]pyridine (dipimp) as the ligand, and zinc as the reducing agent.37

![Scheme 47](image)

10 Alkyne Surrogates

Synthesis of fused benzene rings can also be accomplished by using alkyne surrogates during the [2+2+2] cycloadDITION reaction with diynes. This alternate method avoids the selectivity problems. Several groups have reported the use of enol ethers or easily enolizable ketones as alkyne equivalents that undergo dehydration after the cyclotrimerization giving the aromatic products. Some recent examples, depicted in Scheme 48, show diynes reacting with rhodium(I)/BINAP catalyst system with enolethers 161, vinylene carbonates 163, or 2-oxazolones 167. The regioselectivity of the enol ether insertion is thought to be controlled by coordination of the enol carbonyl moiety to the cationic Rh center in the metallacyclopentadiene intermediate. If the enol ether component is replaced by vinylene carbonate 163, a phenol derivative 164 is obtained, whereas the reaction with ketene acetal 165 gives aromatic ether 166, and the reaction with 2-oxazolones 167 gives anilines 168. In addition, Matsuda and co-workers showed that substituted maleic anhydride functioned as synthetic equivalent of alkynes in a rhodium(III)-catalyzed [2+2+2] cycloaddition reaction with 1,6-diynes.36d

![Scheme 48](image)

In 2015, Ichikawa and co-workers demonstrated the synthesis of fluorobenzene derivatives 172 through a nickel-catalyzed intermolecular [2+2+2] cycloaddition reaction using 1,1-difluoroethylene 169 as an alkyne surrogate (Scheme 49). They have also demonstrated that this reaction works with 1,6-enynes in a partially intramolecular fashion.39e

For the first time in 1973, Yamazaki reported the application of a [2+2+2] cycloaddition reaction for the synthesis of heterocycles where nitrile 173 has been used as a copartner with two acetylenes in the presence of a cobalt catalyst leading to the formation of pyridines 174.39a Later on,
it was found that not only acetylenes and nitriles, but also other partners such as cyanates, isocyanates, carbonyls, and carbon disulfide participate in the [2+2+2] cycloaddition reaction, thereby enabling the formation of a variety of heterocyclic aromatic as well as non-aromatic compounds such as pyridones, pyrans, pyranones, etc. (Scheme 50).39b

Double bonds that form parts of heterocycles are also known to participate in the [2+2+2] cycloaddition reaction with alkynes. Although they are resonance stabilized, cobalt-mediated heterocyclic activation allows these systems to participate readily in cyclization reactions. Thus, π-enriched systems, such as furans, thiophenes, pyrroles, and imidazoles deliver fused dihydro heterocycles. Recently, this methodology has been extended to indoles, pyrimidines, pyridines, and pyrazinones.41c

11 Domino Reactions Involving [2+2+2] Cycloaddition

A useful approach to accomplish molecular complexity in one step is the domino reaction. This theme has drawn increasing attention in recent years. However, unfortunately only a limited number of domino reactions are known where a [2+2+2] cycloaddition is used in combination with other reactions. Benzolactones and lactams are found in plants and they show pharmacological activity. Chang and co-workers demonstrated a one-pot synthesis of benzolactone and lactam through a cobalt-catalyzed regioselective [2+2+2] cyclotrimerization and trans-esterification of alkynyl alcohols and amines with propiolates (Scheme 51).43b Tanaka and co-workers have prepared enantioenriched tricyclic phthalide derivatives by a cationic Rh(I)/SOIPHOS complex-catalyzed asymmetric one-pot trans-esterification and a [2+2+2] cycloaddition reaction (Scheme 52).44

Li and Bonfield have prepared isoindoline derivatives by treating amines with aldehyde and alkynes (Scheme 53). Three consecutive reactions take place in a single synthetic operation. First, one molecule of amine combines with two molecules of aldehyde and two molecules of alkyne to give the starting diyne which on cycloaddition with a third alkyne gives the final isoindoline derivative. The first coupling reaction is catalyzed by CuBr and the cycloaddition reaction is catalyzed by Wilkinson’s catalyst. Therefore, both are added from the beginning.45
12 Biologically Important Targets/Total Synthesis

Ramana and co-workers also used a [2+2+2] cycloaddition to synthesize bicyclic and tricyclic derivatives. They reported the application of intermolecular [2+2+2] alkyne cyclotrimerization reactions for the construction of benzannelated 8-oxabicyclo[3.2.1]octane systems 194 (Scheme 54) and this strategy was applied for the synthesis of (−)-bruguierol A.46a A similar strategy was employed to construct the central 4/5/6 tricyclic framework of 6-(1-hydroxyethyl)-cyclocardinicin trinems 196 (Scheme 55).46b

The same group has also synthesized 6,7-cyclopropylallocolchicinoids 198 using cobalt-catalyzed [2+2+2] cyclotrimerization to construct the ABC ring system (Scheme 56).46c Along similar lines, they have also shown the total synthesis of (±)-alcolchicine and its analogues.46d Kotha and Sreevani have demonstrated a formal total synthesis of (±)-allocolchicine and its analogues.46d,46e Kotha and Sreevani have demonstrated a formal total synthesis of an isoindoline derivative of Hsp90 inhibitor AT13387 (Scheme 57).17c

13 Conclusions

In this account, we have demonstrated that a [2+2+2] cycloaddition sequence is a useful tool to assemble various carbo- and heterocycles, spirocycles and polycycles including unusual amino acids and peptides. In this regard, we have used Wilkinson’s catalyst, Vollhardt’s catalyst, and Grubbs catalyst. More interestingly, we found that propargyl halides can be useful co-partners when Mo(CO)₆ is applied as a catalyst. For the first time, we have used Ti(OPr)₄ to improve the [2+2+2] cycloaddition with Wilkinson’s catalyst. We also included the work of others to keep a balanced view of the theme. The strategies and the compounds developed here are likely to find useful applications in materials science and in the design of pharmaceutically important drugs. Since a [2+2+2] cycloaddition is considered as an atom-economic process, our results may be of interest to several chemists working in the area of green chemistry. Although this strategy has witnessed several advances, its application on industrial scale is yet to be seen.

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