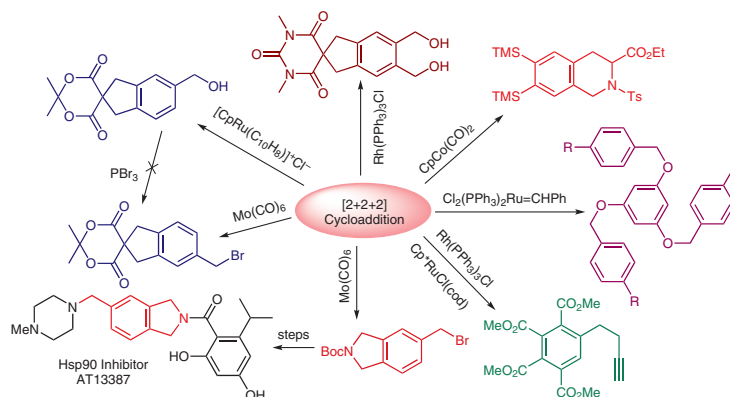


# Design and Synthesis of Aromatics through [2+2+2] Cyclotrimerization

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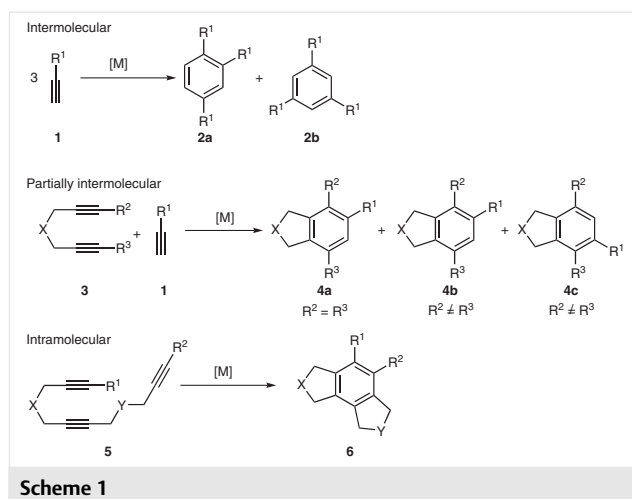
**Abstract** The [2+2+2] cycloaddition reaction is a useful tool to realize unusual chemical transformations which are not achievable by traditional methods. Here, we report our work during the past two decades that involve utilization of transition-metal complexes in a [2+2+2] cyclotrimerization reaction. 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
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- 3 Heteroanalogues of Indane
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- 13 Conclusions

**Key words** [2+2+2] cyclotrimerization, Diels–Alder, sultine, amino acids and peptides, spirocycles, Wilkinson’s catalyst, Vollhardt’s catalyst, alkyne surrogates

## 1 Introduction

[2+2+2] Cycloaddition is a useful tool to assemble densely functionalized aromatics in one step starting with alkynes. 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 alkynes (diyne **3**, monoynes **1**) were tethered, annulated benzene derivatives **4a–c** would be generated, whilst, if all three alkynes 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.<sup>1a</sup>



Scheme 1

In 1866, Bertholet first reported the thermal [2+2+2] cyclootrimerization of acetylene to benzene.<sup>1b</sup> The reaction is exothermic (experimental data  $\Delta H^0 = -143$  kcal/mol) and suffered from the formation of a large amount of byproducts. Despite a loss in entropy, the reaction occurs at high temperature to overcome the large energy barrier (activation barrier at least 36 kcal/mol) of the reaction. In 1948, Reppe reported the first transition-metal-mediated [2+2+2] cyclootrimerization, which occurs at low temperature with fewer byproducts.<sup>2</sup> 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 cyclootrimerization reaction of alkynes and some of them are included in the recent reviews.<sup>3</sup> 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 cyclootrimerization in the presence of another metal catalyst such as nickel. Recently, besides the development of transition-metal catalyzed [2+2+2] cyclootrimerization reactions, several transition-metal-free [2+2+2] cyclootrimerizations have also been reported.<sup>3c</sup>

Transition-metal complexes used in [2+2+2] cyclootrimerization 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] cyclootrimerization reaction allows multiple bond formation exhibiting a high de-

### Biographical sketches



**Sambasivarao Kotha** graduated with M.Sc. degree in chemistry from the University of Hyderabad and then obtained his Ph.D. in organic chemistry from the University of Hyderabad (1985). He continued his research at the University of Hyderabad as a postdoctoral fellow for one and half years. Later, he moved to UMIST Manchester, UK and the University of Wisconsin, USA as a research associate. Subsequently, he was appointed as a visiting scientist

at Cornell University and as a research chemist at Hoechst Celanese Texas prior to joining IIT Bombay in 1994 as an assistant professor. Later, in 2001, he was promoted to Professor. He has published 250 publications in peer-reviewed journals and is an elected fellow of various academies (FNASc, FASc, FRSC, and FNA). He was also associated with the editorial advisory board of several journals (Indian J. Chem., Sec-B, J. Amino Acids, Catal. J., Eur. J. Org. Chem., and

J. Chem. Sci.). His research interests include: Organic synthesis, green chemistry, development of new synthetic methods for unusual amino acids, peptide modification, cross-coupling reactions, metathesis, chemistry of benzocyclobutene, and theoretically interesting molecules. Currently, he occupies Pramod Chaudhari Chair Professor in green chemistry.



**Kakali Lahiri** (née Chakraborty) was born in Hooghly, West Bengal, India. She obtained her Ph.D. in 2002 under the guidance of Professor S. Kotha at IIT-Bombay. She worked as a research associate in the same department for sev-

en years. Her research interest is related to development of new synthetic methodologies. She received the ADANI Award for the Best Teaching Assistantship from the Department of Chemistry, IIT-Bombay. She was also the recipient of IIT-Bombay Best

Review Paper Award in 2005, 2010 and IIT-Bombay Research Dissemination Award 2016. Since 2009, she is working as Assistant Professor in V. K. K. Menon College, Bhandup, Maharashtra, India.



**Gaddamedi Sreevani** was born in Rimmanguda (village), Telangana. After her early education in Sree Triveni Junior College for Girls, Hyderabad, she joined Sri Sathya Sai Institute of Higher Learning (for Women), Anantapur for her B.Sc. (honors) in chemistry, and obtained her degree in 2006. Later, she

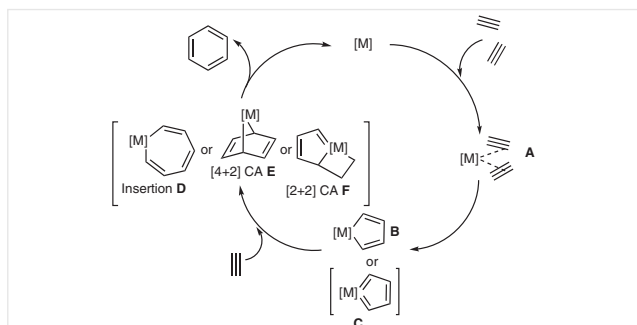
joined the Department of Chemistry, A. V. College Post Graduate Centre, Hyderabad (affiliated to the Osmania University) for her M.Sc. degree. In 2018, she obtained her Ph.D. degree under the guidance of Professor S. Kotha from the Department of Chemistry, Indian Institute of Technology Bombay,

Mumbai. Currently, she is working as a Research Associate in the Department of Biomedical Engineering, Indian Institute of Technology Hyderabad. Her current research interests are the synthesis of biopolymers for 3D bio printing, development of anticancer drugs, and drug release studies by 3D printing.

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-cyclohexadienes etc., in a single operation involving catalytic amounts of organometallic 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**.<sup>4</sup> 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.



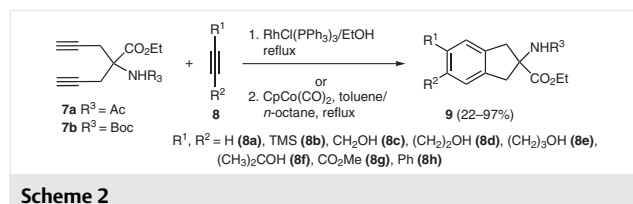
**Figure 1** A general mechanism to benzene derivatives by [2+2+2] cyclotrimerization

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”<sup>5f</sup> 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

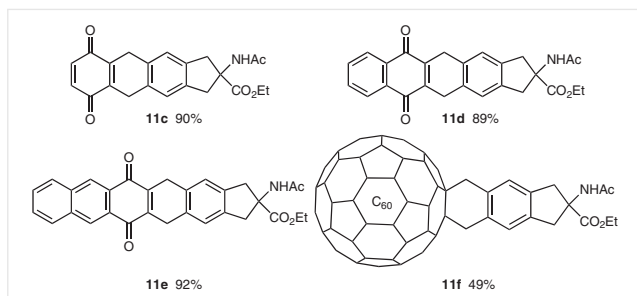
Indane-based  $\alpha$ -amino acid (AAA) is a constrained analogue of phenylalanine (Phe) and it is used extensively in the design and synthesis of a variety of bioactive peptides. Utilization of unusual AAAs in physical and life sciences continues to grow at an impressive rate. They are useful as building blocks for peptides, proteins, and natural products and used extensively in pharmaceutical, agrochemical, and food industry. The design and synthesis of peptides<sup>[5a-c]</sup> 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.<sup>5d,e</sup> 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.



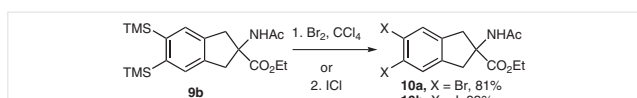
**Scheme 2**

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  $\text{CpCo}(\text{CO})_2$  with various monoynes **8a–h** delivers indane-based AAA derivatives such as **9** (Scheme 2).<sup>6</sup> 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*-xylylene intermediate **12** can be trapped with a suitable dienophile to produce new AAA derivatives **11**<sup>7a</sup> the attention was focused on the generation of the sultine derivative **13** (Scheme 4).

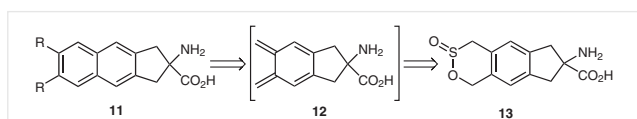


**Figure 2** List of indane derivatives prepared

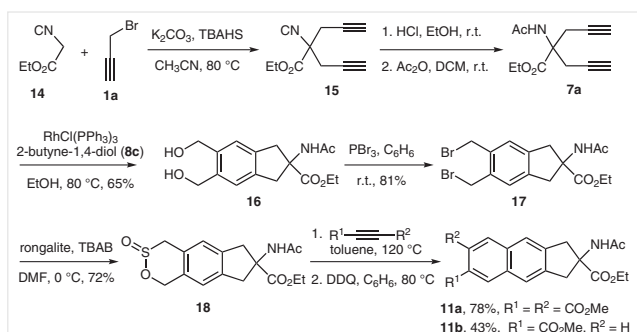


**Scheme 3**

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 dibromide **17** with use of  $\text{PBr}_3$ . Next, a reaction of dibromo compound **17** was performed with sodium hydroxymethanesulfonate (rongalite)<sup>7b</sup> 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-



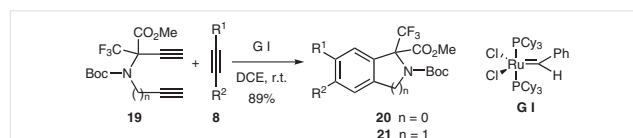
**Scheme 4**



**Scheme 5**

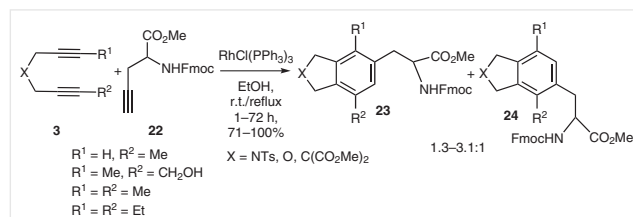
anthraquinone delivered the products **11c–e**. In view of various applications of fullerene-based AAA derivatives in bioorganic chemistry, we turned our attention to incorporate the AAA moiety in the fullerene system and successfully obtained compound **11f** in 49% yield (Figure 2). The hydrophobic 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  $\text{CF}_3$ -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  $\text{Cp}^*\text{Ru-Cl}(\text{cod})$  and the Grubbs catalyst (Scheme 6).<sup>8</sup>



**Scheme 6**

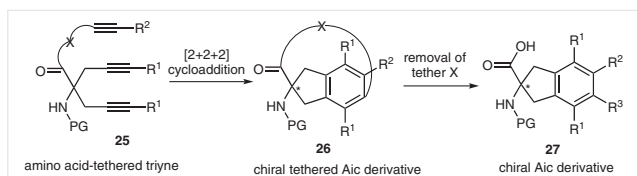
Along similar lines, Roglans and co-workers adopted this methodology to synthesize nonproteinogenic Phe derivatives using enantiopure and racemic propargylglycine **22** with different diynes **3** (Scheme 7).<sup>9</sup> When they used Wilkinson's catalyst or a cationic rhodium  $[\text{Rh}(\text{cod})_2]\text{BF}_4/\text{BINAP}$  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 aminoindane carboxylic acid (Aic) derivatives directly through a [2+2+2] cyclotrimerization using propargyl halides as co-partners with  $\text{Mo}(\text{CO})_6$  under microwave irradiation (MWI).<sup>10</sup>



**Scheme 7**

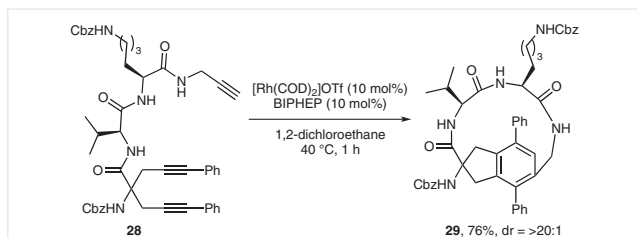
In 2016, Shibata et al. reported the enantioselective synthesis of Aic derivatives through a Rh-catalyzed intramolecular [2+2+2] cycloaddition reaction. When the intermolecular [2+2+2] cycloaddition was carried out in the presence of a Rh catalyst using (*S*)-BINAP as a chiral ligand, the enantioselectivity 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).<sup>11</sup>



Scheme 8

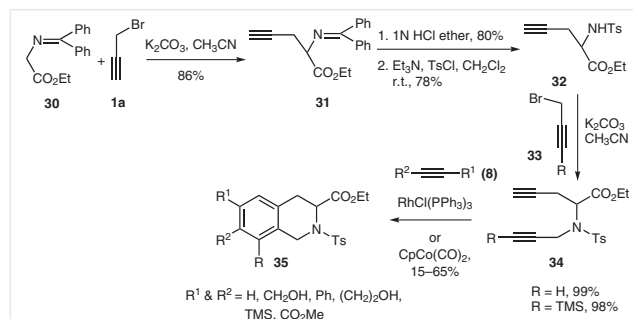
Similarly, they developed the synthesis of cyclic peptides. In this regard, they prepared the triynes from 1,6-diyne and alkyne connected by a di- or tri-, or tetrapeptide tether. Later, intramolecular [2+2+2] cycloaddition of the peptide-tethered triynes **28** in the presence of Rh(COD)<sub>2</sub>OTf/(*S*)-tolBINAP complex gave cyclic peptides **29** in moderate chemical yields and good diastereoselectivity. When they used bulky ligand (*S*)-xylBINAP a higher diastereoselectivity was achieved. However, (*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).<sup>12</sup>



Scheme 9

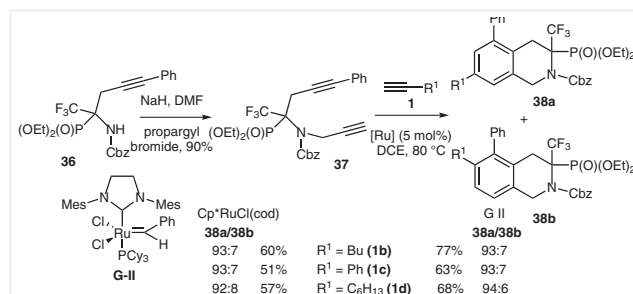
1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic),<sup>13a,b</sup> a constrained analogue of Phe, is an important structural component present in several biologically active natural products. Incorporation of Tic in opioid receptors enhances their affinity and selectivity. Tic can be prepared by traditional methods such as Bischler–Napieralski or Pictet–Spengler reaction, etc. These methods can accommodate limited functionalities in the aryl ring. Tic prepared by a [2+2+2] cycloaddition process provides an opportunity to incorporate various substituents in Tic derivatives in a predetermined manner.<sup>13c</sup> In this regard, the diyne **34** was prepared from the benzophenone Schiff's base derived from glycine ester by a four-step sequence (Scheme 10). Treatment of the diyne **34** with various monoynes **8** using Wilkinson's or Vollhardt's catalyst gave a variety of Tic-based AAA derivatives in good to moderate yields. It is

worth mentioning that similarly, Tic derivatives were also prepared by using enyne metathesis and DA reaction as the key steps.<sup>13c</sup>



Scheme 10

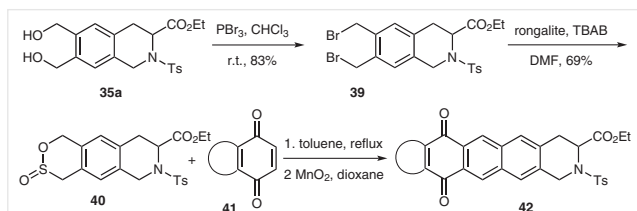
Recently, Zotova et al. demonstrated the trifluoromethyl-substituted phosphonate analogues of Tic derivatives **38** based on *N*-propargylation of  $\alpha$ -alkynyl- $\alpha$ -CF<sub>3</sub>- $\alpha$ -amino-phosphonates **36** to form 1,7-azadiynes **37**, followed by co-cyclotrimerization with terminal alkynes **1b–d** using two types of ruthenium catalysts: Cp<sup>\*</sup>RuCl(cod) and preferably the alkene-metathesis<sup>14a,b</sup> Grubbs second-generation catalyst (Scheme 11).<sup>14c</sup>



Scheme 11

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. The *o*-xylylene intermediate required for the DA reaction was prepared through the sultine methodology by using rongalite (Scheme 12, Figure 3).<sup>15</sup> 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.



Scheme 12

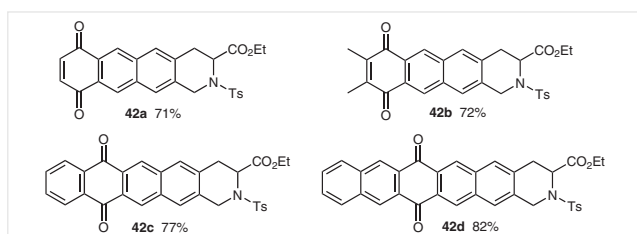
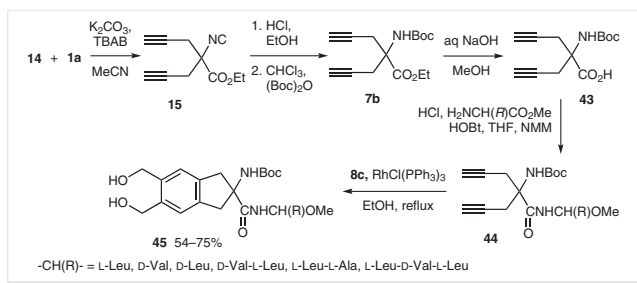


Figure 3 List of Tic derivatives prepared with use of rongalite

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.<sup>16</sup> 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 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 monoynone was chosen to avoid the formation of diastereomers and the representative constrained Phe peptides **45** were obtained in good yield.<sup>16</sup>

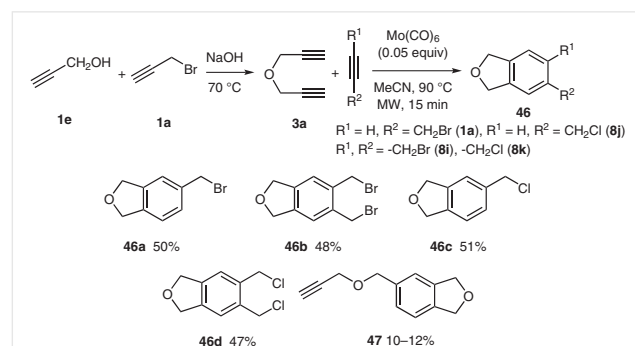


Scheme 13

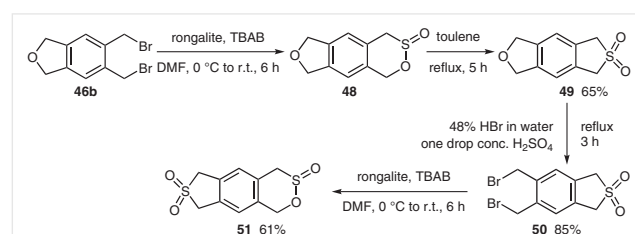
Later, the dihydroxy derivative **45** was treated with  $PBr_3$  in benzene to obtain the corresponding dibromide. However, several attempts could not deliver the desired product. Either, decomposed product or starting material was recovered under these conditions. However, recently we have developed a new protocol using a [2+2+2] cyclotrimerization 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.<sup>10</sup>

### 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).<sup>17a</sup> Benzosultine-sulfone **51** is a hybrid molecule which can participate in the DA reaction in a stepwise manner by opening the sultine or the sulfone fragment at different temperatures, and the respective *o*-xylylene intermediate can be trapped with different dienophiles. This approach delivers densely functionalized polycyclic compounds.



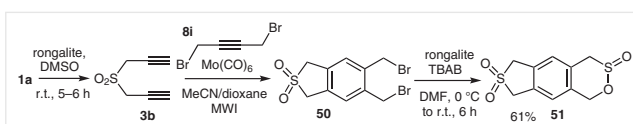
Scheme 14



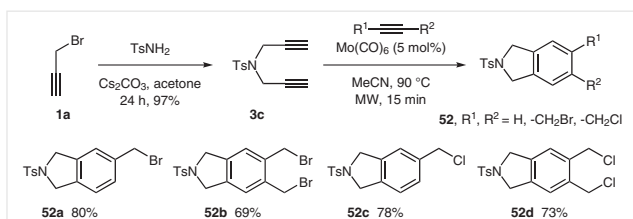
Scheme 15

Later on, Kotha and Sreevani have shown the synthesis of dipropargyl sulfone **3b** from ronalite 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)<sub>6</sub> as a catalyst in a short two-step synthetic sequence (Scheme 16).<sup>17b</sup>

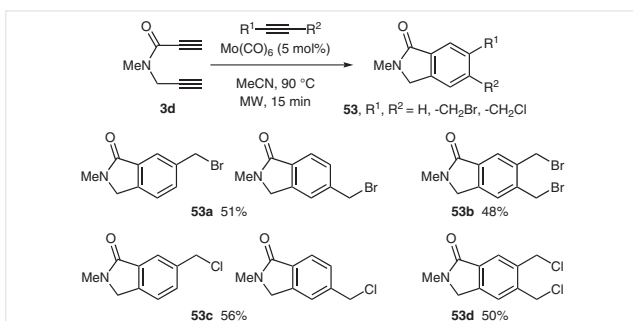
Furthermore, the methodology has been extended to prepare isoindoline and isoindolinone halide derivatives (Schemes 17 and 18).<sup>17c</sup>



Scheme 16

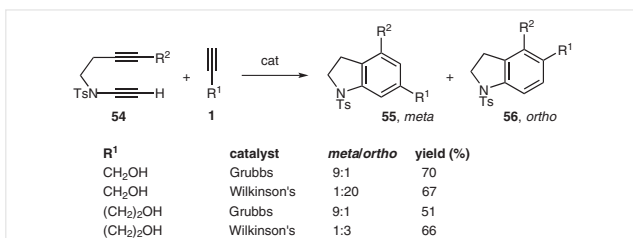


Scheme 17



Scheme 18

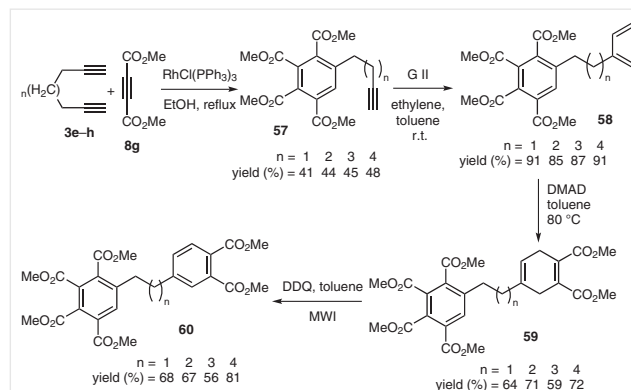
Witulski and co-workers reported a [2+2+2] cyclo-trimerization<sup>18a</sup> for the synthesis of 4,6- or 4,5-substituted indoline derivatives **55** and **56** using Grubbs and Wilkinson's catalysts, respectively (Scheme 19).



Scheme 19

## 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 antiestrogenic activity. In 1980, Ibuki et al. demonstrated a general method for the preparation of diphenylalkane derivatives of varied chain lengths using a benzenoid precursor.<sup>19a</sup> Recently, Kotha and Khedkar have developed a new approach to diphenylalkane derivatives using a [2+2+2] cycloaddition, cross-enyne metathesis (CEM), and DA reactions as the key steps.<sup>19b</sup> 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] cyclo-trimerization 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.

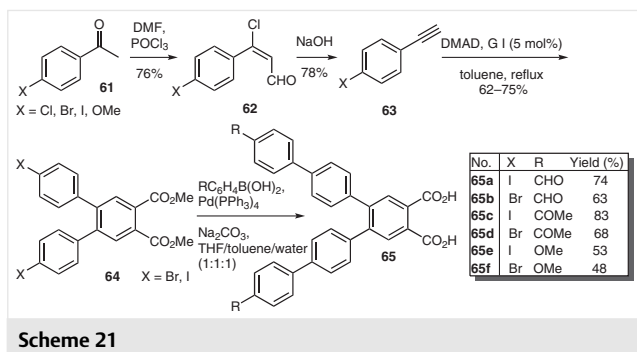


Scheme 20

## 5 Multi-Armed Aryl Benzene Derivatives

Kotha and co-workers have prepared bis- and trisaryl benzene derivatives through a [2+2+2] cyclo-trimerization reaction using the Grubbs first generation catalyst (G I).<sup>20a</sup> It was found that the G I catalyst is more suitable for cyclo-tri-

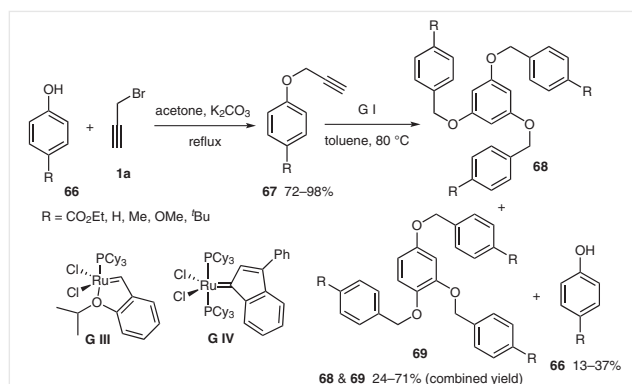
merization than the Grubbs second generation (G II) catalyst. The G I catalyst shows higher initiation and low propagation rates, whereas the G II catalyst has low initiation and high propagation rates. To this end, commercially available acetophenone derivatives **61** were converted into acetylenes **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-yne, 1,4-diacetylbut-2-yne, and 1,4-dihydroxybut-2-yne 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<sup>20b–d</sup> with different boronic acids such as 4-acetyl-, 4-formyl-, and 4-methoxyphenylboronic acid using Pd(PPh<sub>3</sub>)<sub>4</sub> catalyst (5–9 mol%) in a 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

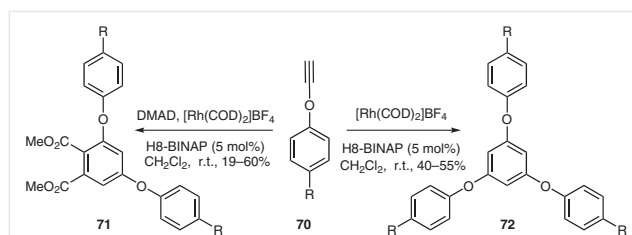
To synthesize 1,3,5-triaryloxymethylbenzene derivatives through a [2+2+2] methodology using Grubbs catalyst, (prop-2-ynyl)benzenes **67** were prepared by reaction of phenol derivatives **66** with propargyl bromide (**1a**) in acetone heated to reflux in the presence of K<sub>2</sub>CO<sub>3</sub>. 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).<sup>21</sup>

Along similar lines, Tanaka and co-workers found that a cationic rhodium(I)–H<sub>8</sub>-BINAP complex catalyzes the complete intermolecular homo- and a cross- [2+2+2] cycloaddi-



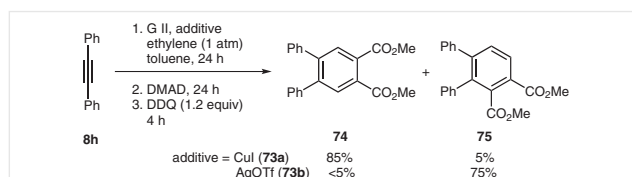
Scheme 22

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



Scheme 23

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**).<sup>18b</sup>



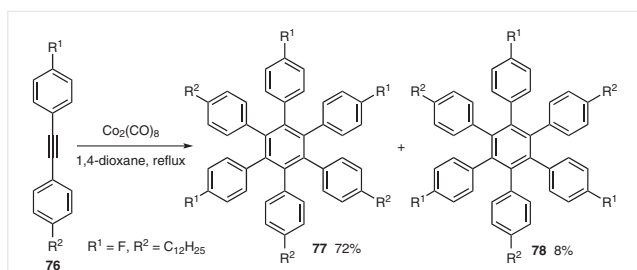
Scheme 24

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

## 6 Annulated Benzocycloalkanes

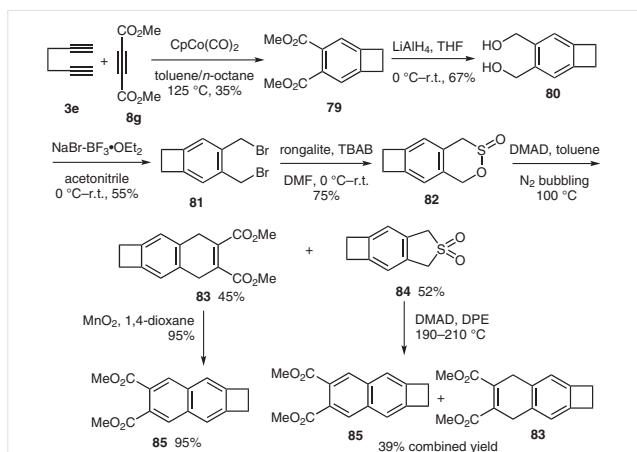
Kotha and Khedkar reported an interesting reactivity pattern of hybrid *o*-quinodimethane precursor **82**. This hybrid compound containing benzocyclobutane and benzo-





Scheme 25

sulfone moieties was prepared by a [2+2+2] cycloaddition reaction and utilization of rongalite (Scheme 26).<sup>23</sup> The DA reaction of *o*-quinodimethane precursor **82** can generate various annulated benzocycloalkanes. For example, the selective DA reaction was realized at the sulfone **82** or the sulfone **84** frame and not at the other end of *o*-quinodimethane precursor, i.e. the benzocyclobutane moiety. The DA reaction was studied under different conditions such as conventional heating, MWI, in the presence of an excess amount of dienophile, removal of SO<sub>2</sub> as it is generated in the reaction by continuous bubbling of N<sub>2</sub> gas. This hybrid system with differential reactivity pattern is likely to find interesting applications in organic synthesis.



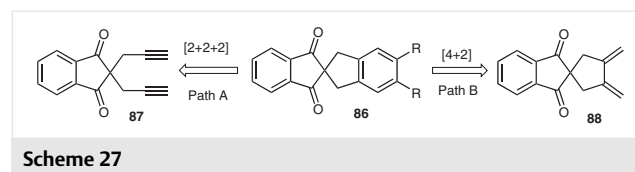
Scheme 26

## 7 Spirocycles

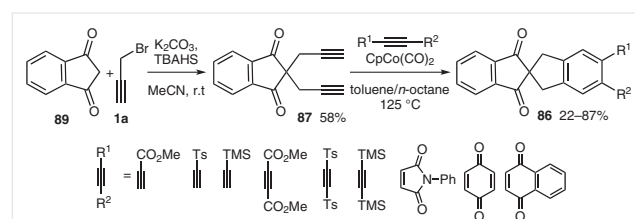
The spiro unit is an important structural element present in several natural products (e.g. terpenoids and alkaloids) and non-natural products. Recently, they have found important applications in materials science and also in medicinal chemistry. The attractive conformational feature of the spiro center 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 dif-

ficult task because it involves the generation of a quaternary center.<sup>24a</sup> There are many methods known in the literature for the synthesis of spirocyclic compounds<sup>24</sup> 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<sup>24c–f</sup> 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.<sup>24g</sup> 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 η<sup>5</sup>-cyclopentadienylcobalt complex CpCo(CO)<sub>2</sub> 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 cyclotrimerization reaction under these conditions.

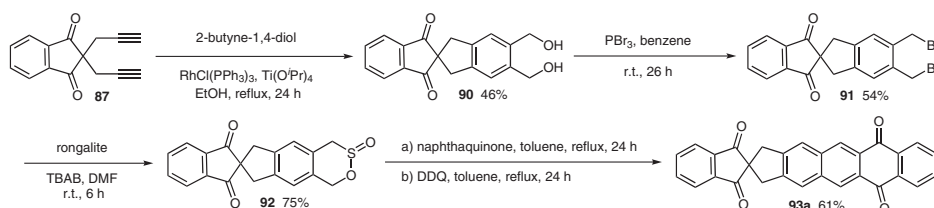


Scheme 27



Scheme 28

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.<sup>25</sup> The [2+2+2] cycloaddition of



Scheme 29

dipropargylated compound **87** with 2-butyne-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  $\text{Ti}(\text{O}^i\text{Pr})_4$  facilitates enyne metathesis,<sup>25c</sup> a similar role was anticipated in a [2+2+2] cycloaddition sequence. When  $\text{Ti}(\text{O}^i\text{Pr})_4$  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  $\text{PBr}_3$  in dry benzene at room temperature, and this dibromide was then converted into sultine derivative **92** by treatment with ronalite 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.

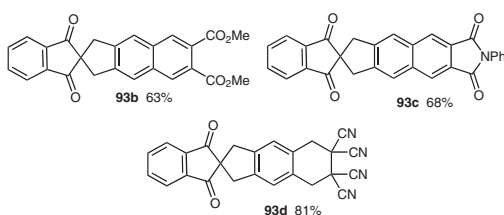
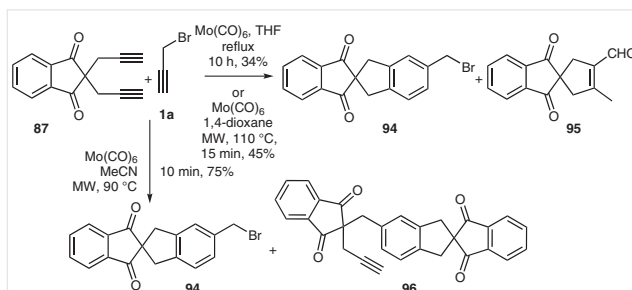


Figure 4 Linearly fused spiro derivatives

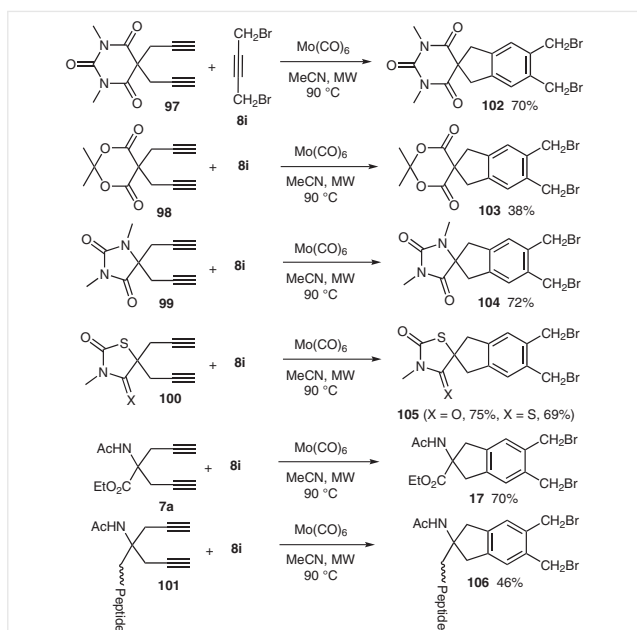
Although a [2+2+2] cycloaddition reaction has been applied with several substrates, limited examples are available where propargyl halides are used as co-partners. In all these examples propargyl diol is used as co-trimerized partner and the resulting dihydroxy derivative obtained in a [2+2+2] cycloaddition reaction is transformed into the corresponding bromide by using  $\text{PBr}_3$ . 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,  $\text{Mo}(\text{CO})_6$ , under MWI conditions.<sup>10a</sup> Mo com-

plexes 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 dione **87** was chosen as a model substrate (Scheme 30). Diyne **87** was then subjected to a [2+2+2] cycloaddition sequence with propargyl bromide (**1a**) in the presence of a catalytic amount of  $\text{Mo}(\text{CO})_6$  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  $(\text{CH}_3\text{CN})_3\text{Mo}(\text{CO})_3$  when  $\text{Mo}(\text{CO})_6$  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.



Scheme 30

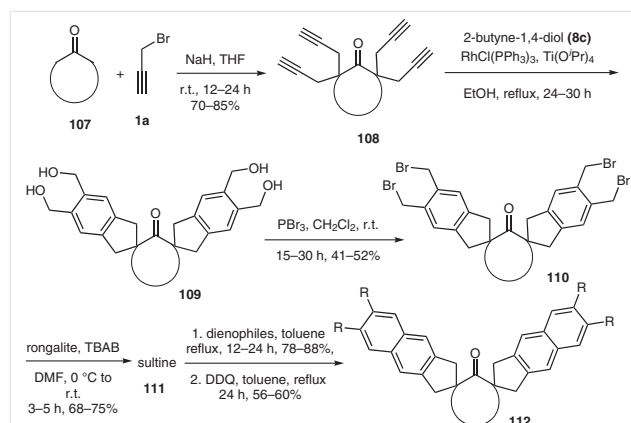
Later, this technology has been extended to barbituric acid, Meldrum's acid, hydantoin derivatives, thiazolidines, amino acids, and peptides to synthesize the corresponding halo(methyl)benzene derivatives **102–106** and **17** in moderate to good yields (Scheme 31).<sup>10b</sup>



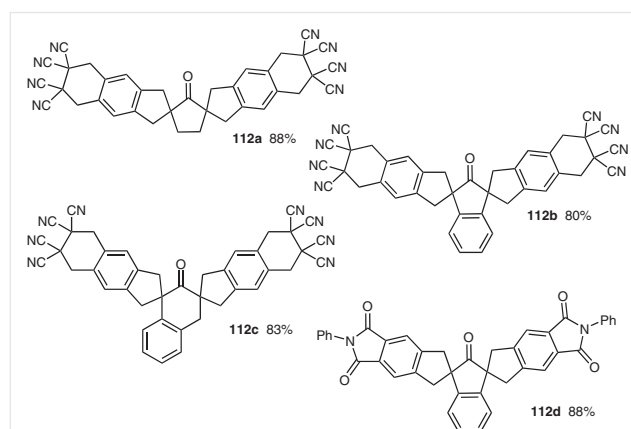
**Scheme 31** Preparation of halo(methyl)benzene derivatives containing different heterocycles

In continuation of our efforts to the synthesis of spirocycles, Kotha and Ali have developed a new strategy<sup>26a</sup> 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  $\text{Ti}(\text{O}^i\text{Pr})_4$  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 sultines **111** by using rongalite. Then, reactions of these sultines were performed with different dienophiles in a DA fashion to generate various complex bis-armed 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] cyclotrimerization followed by a DA reaction.<sup>26b</sup> The required tetrayne **114** was prepared by propargylation of dione **113** (Scheme 33), which was synthesized from commercially available hydroquinone. Further, the tetrayne **114** was treated with 1,4-dihydroxy-2-butyne (**8c**) in the presence of Wilkinson's catalyst to obtain tetraol **115**, which on treatment with  $\text{PBr}_3$  in  $\text{CH}_2\text{Cl}_2$



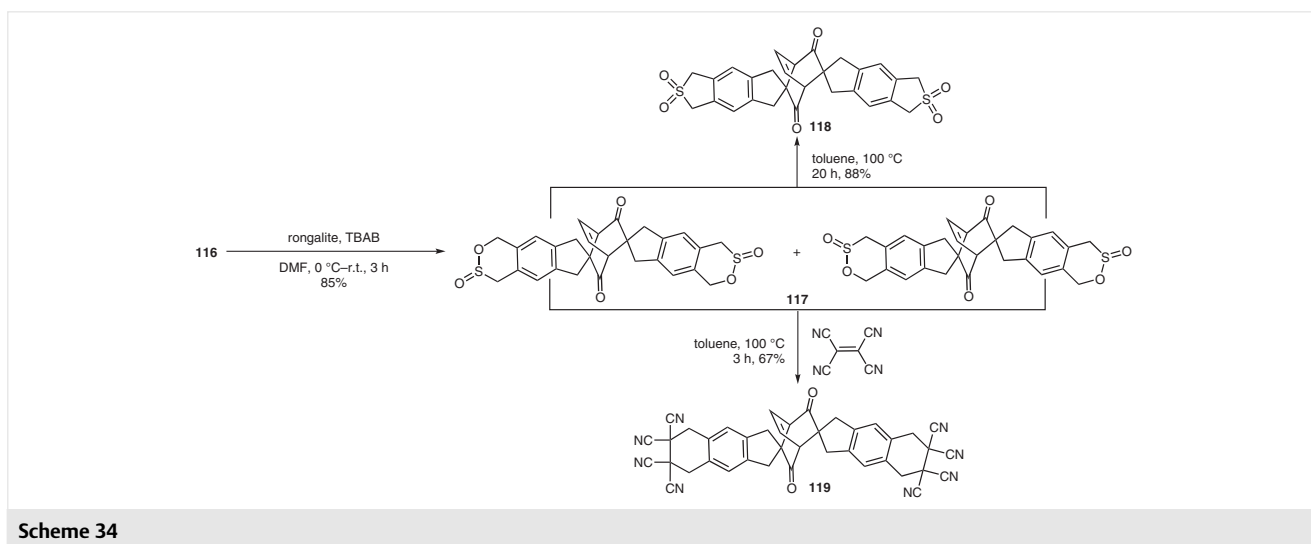
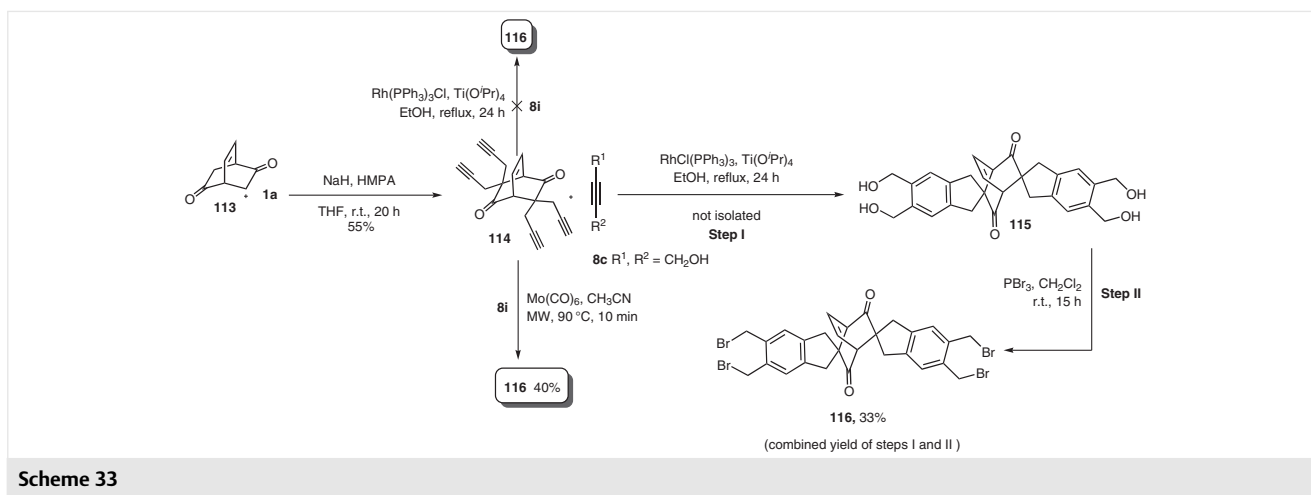
**Scheme 32**



**Figure 5** Bis-spirocycles prepared with use of rongalite and a DA strategy

without isolating the intermediate tetraol 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  $\text{Mo}(\text{CO})_6$  under MWI conditions in  $\text{CH}_3\text{CN}$  at  $90^\circ\text{C}$  and the spiro-annulated building block **116** was obtained in 40% yield. Next, tetrabromide **116** was successfully converted into the sultine 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 sultine 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-

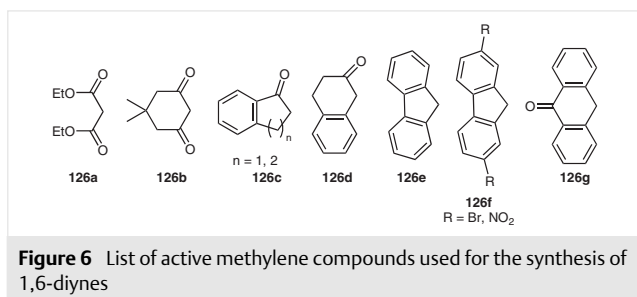
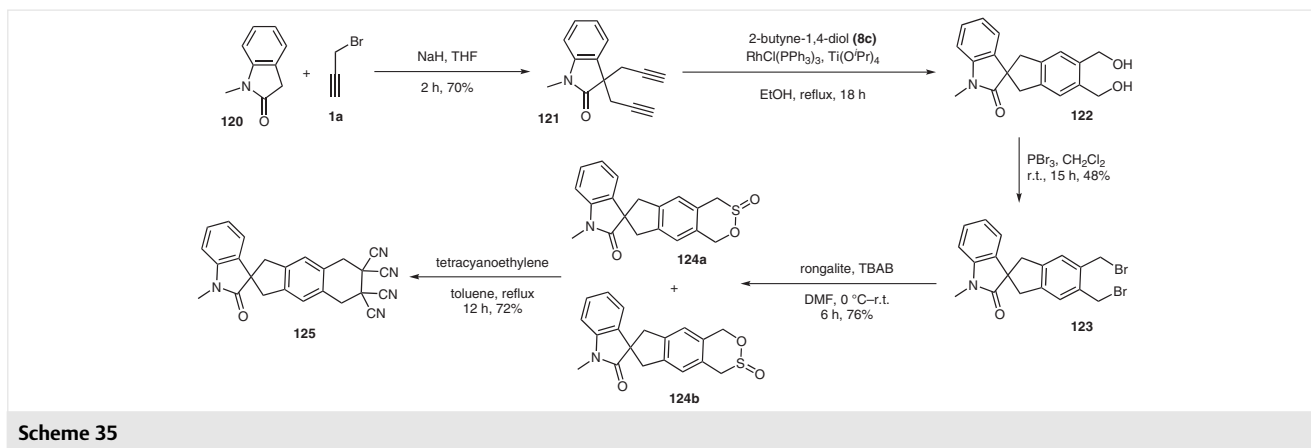


gy on the basis of a [2+2+2] cycloaddition and a DA reaction.<sup>27</sup> In this regard, *N*-methyl derivative of oxindole **120** was dipropargylated and subsequent [2+2+2] cycloaddition yielded diol **122**, which on treatment with  $\text{PBr}_3$  in  $\text{CH}_2\text{Cl}_2$  afforded the dibromo 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.<sup>28</sup> 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  $\text{Ti}(\text{O}^i\text{Pr})_4$  to afford the diol. Next, treatment with  $\text{PBr}_3$  delivered the dibromo compounds in good yield. Further, these dibromo

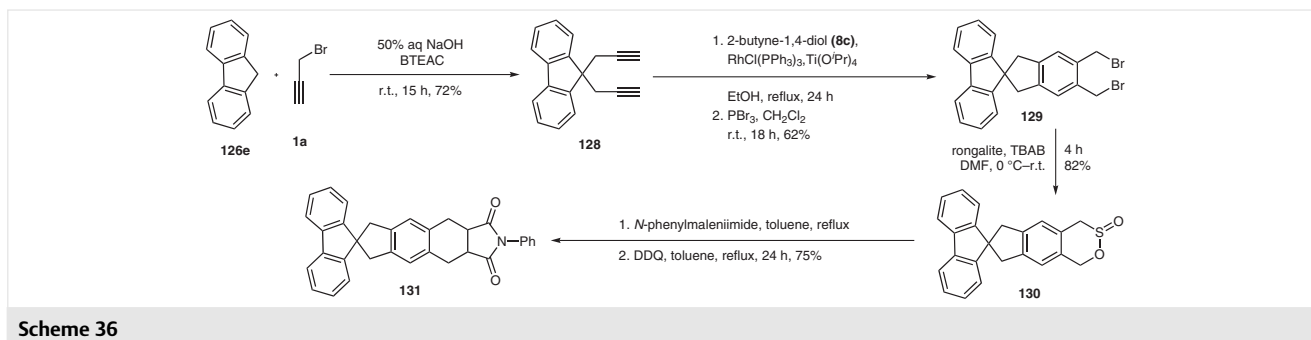
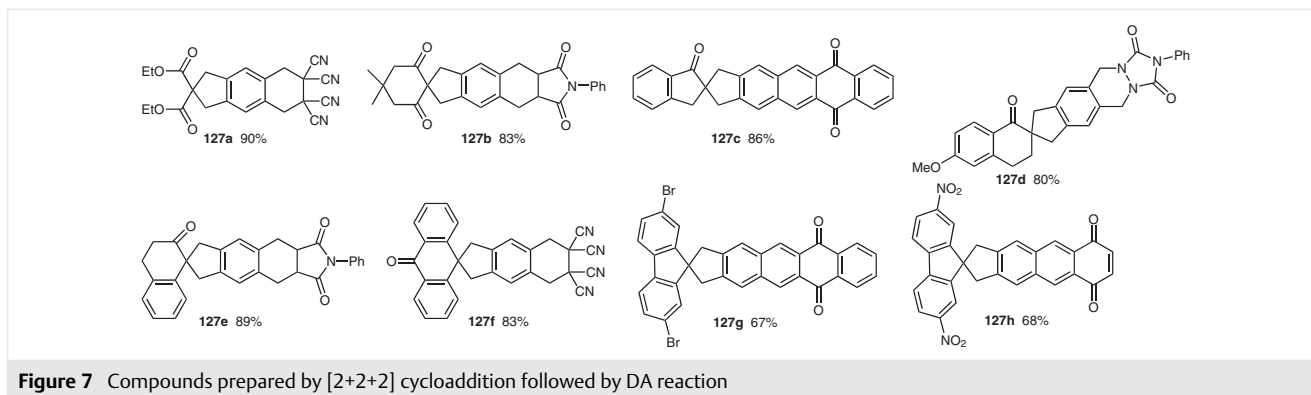
compounds were treated with rongalite in DMF to deliver the sultine derivatives, which on reaction with dienophiles in a DA fashion produced the cycloadducts. Finally, dehydrogenation delivered several linearly fused spirocycles **127a–h** (Figure 7). Interestingly, fluorenes are a unique class of blue-emitting 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.

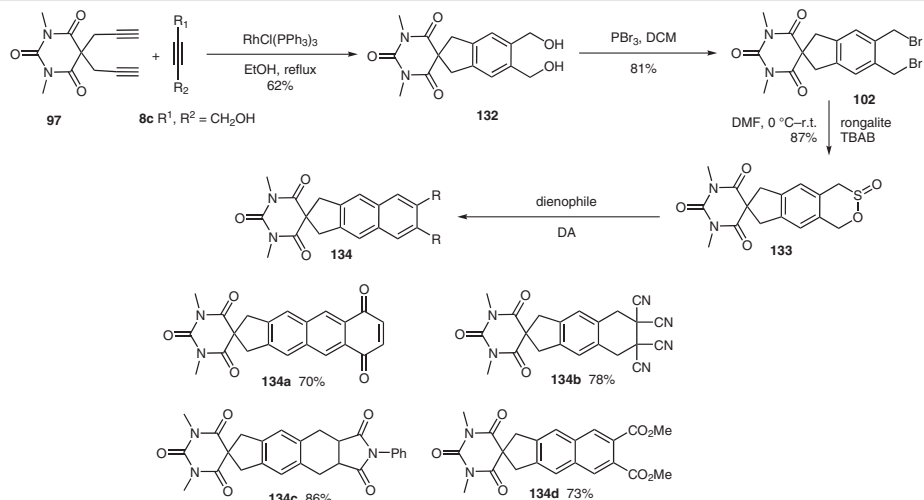
Kotha and co-workers also have reported spirobarbituric acid derivatives **134a–d** using a similar methodology starting from barbituric acid (Scheme 37).<sup>29</sup>



## 8 Selectivity in [2+2+2] Cycloaddition of Alkynes

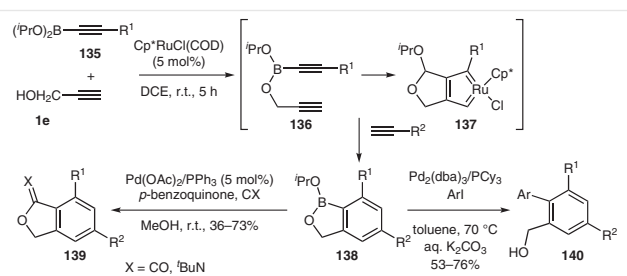
One of the disadvantages of a [2+2+2] cyclotrimerization reaction is the formation of regioisomeric products, i.e. the lack of selectivity. This problem can be addressed by using some of the strategies mentioned here. For example, use of a temporary tether to combine two alkynes allows overcoming the problems associated with the formation of regioisomers in intermolecular reactions or avoids the formation of isomers in partially intermolecular [2+2+2] cycloadd-





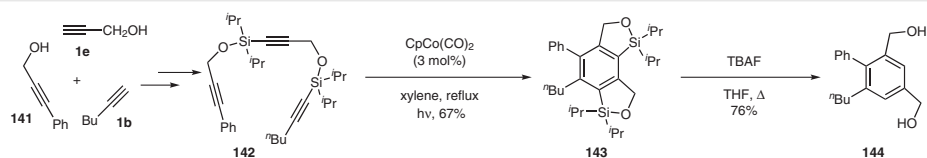
Scheme 37

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  $\text{Cp}^*\text{RuCl}(\text{cod})$  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 carbonylation reaction (Scheme 38).<sup>30</sup>



Scheme 38

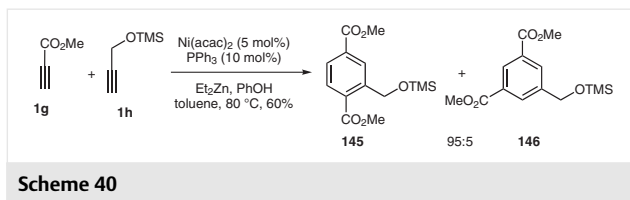
Selectivity in intermolecular cyclization of different partners (**1b**, **1e**, and **141**) can be achieved by using disposable linkers such as temporary silyl tethers. In this context, Malacria and co-workers utilized silicon tether **142** that al-



Scheme 39

lowed the transformation of intermolecular reactions into intramolecular versions in the presence of a cobalt(I) catalyst, generating a highly chemo- and regioselective product **143**. Finally, the tethers could be selectively removed after the reaction heading to the creation of functionalized arenes **144** (Scheme 39).<sup>31</sup>

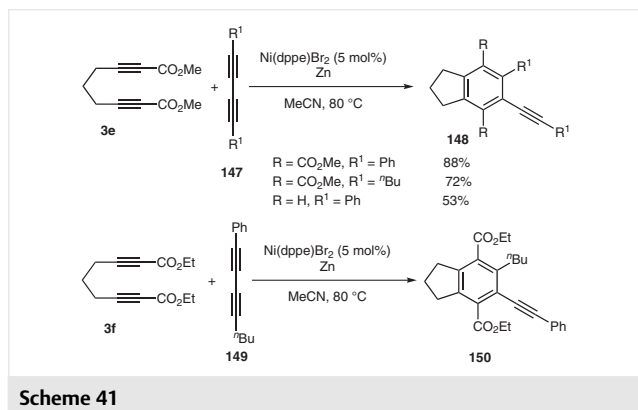
Mori et al. have reported a highly regioselective Ni-catalyzed [2+2+2] cycloaddition of two distinct alkynes using additives such as diethyl zinc and phenol. Reaction of methyl propiolate (**1g**) with trimethylsilyl protected propargylic alcohol **1h** afforded the cycloadducts **145** and **146** in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



Scheme 40

The regioselectivity problem was addressed by a reaction of alkynes together with a suitable linker (e.g. 1,6-diyne or 1,7-diyne). 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-

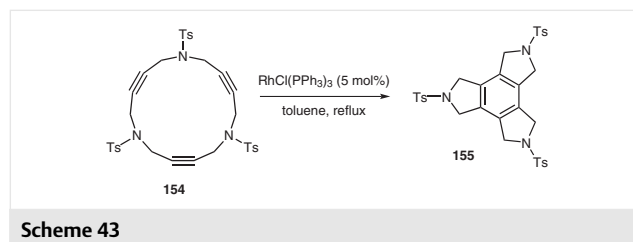
lent yields. Furthermore, unsymmetric 1,3-diyne **149** coupled regioselectively with 1,6-diyne **3f** to give arylalkyne **150** (Scheme 41).<sup>33</sup>



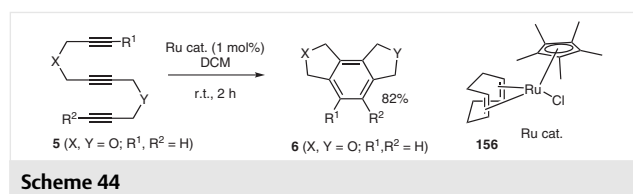
Deiters and co-workers developed solid-supported diyne substrates for controlling the regioselectivity during a [2+2+2] cyclotrimerization sequence. A variety of diynes were immobilized on polystyrene resin by using trityl or carboxy linkers, and a [2+2+2] cyclotrimerization was conducted with various symmetric as well as unsymmetric alkynes in the presence of Wilkinson's catalyst or Cp<sup>\*</sup>RuCl(cod) catalyst. Unsymmetric alkynes in the presence of Wilkinson's catalyst showed poor regioselectivity; however, using Cp<sup>\*</sup>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.<sup>34a</sup> Later, the same group reported solid-supported [2+2+2] cycloaddition reactions under MWI conditions using Cp<sup>\*</sup>RuCl(cod) catalyst.<sup>34b</sup>

By an intramolecular cycloaddition 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.<sup>34c,d</sup> 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.

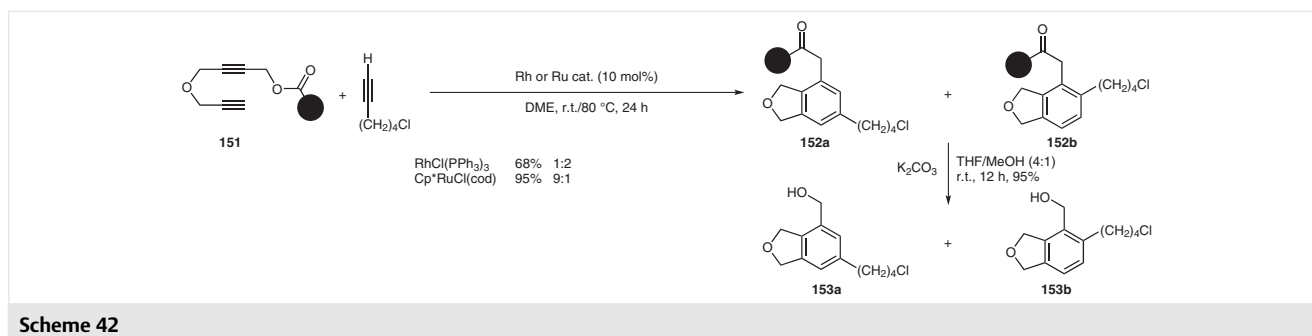


Peters and Blechert were the first to report fully intramolecular cyclotrimerization using Grubbs catalyst.<sup>35a</sup> The mechanistic explanation for the reaction involves a cascade of four metathesis reactions occurring to isomerize the triynes to benzene derivatives using Grubbs catalyst.<sup>35a</sup> Yamamoto and co-workers demonstrated that 1,6,11-triyne **5** on cyclization in the presence of 1 mol% catalyst **156** produced the tricyclic compound **6** in 82% yield (Scheme 44).<sup>35b</sup>

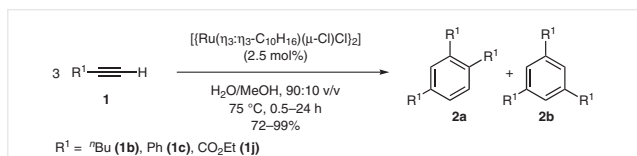


## 9 [2+2+2] Cycloaddition Reactions under Environmentally Friendly Conditions

Despite several advances in metal-catalyzed [2+2+2] cycloaddition 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.<sup>36a</sup> Later, Cadierno et al. have report-

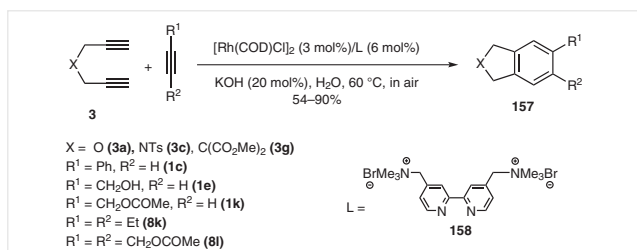


ed intermolecular cyclotrimerization of alkynes (**1b**, **1c**, and **1j**) in aqueous medium using a commercially available ruthenium(IV) dimer (Scheme 45).<sup>36b</sup>



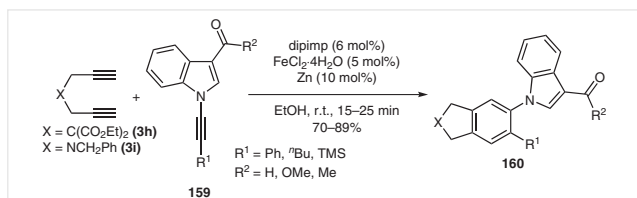
Scheme 45

In 2010, Tsai and co-workers demonstrated a [2+2+2] cycloaddition of  $\alpha,\omega$ -diynes (**3a**, **3c**, and **3g**) catalyzed by  $[\text{Rh}(\text{COD})\text{Cl}]_2$ /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.<sup>36c</sup>



Scheme 46

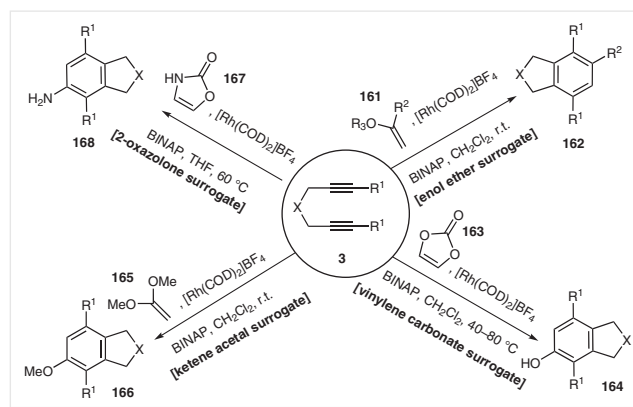
Recently, Goswami and co-workers prepared an iron-based catalytic system  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ /dipimp/Zn to accomplish [2+2+2] cycloaddition reactions. They reported an eco-friendly [2+2+2] partially intramolecular reaction using the same catalytic system in ethanol to prepare *N*-substituted 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-diisopropylphenyl)iminomethyl]pyridine (dipimp) as the ligand, and zinc as the reducing agent.<sup>37</sup>



Scheme 47

## 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<sup>38a</sup> **161**, vinylene carbonates<sup>38b</sup> **163**, or 2-oxazolones<sup>38c</sup> **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] cyclotrimerization reaction with 1,6-diynes.<sup>38d</sup>

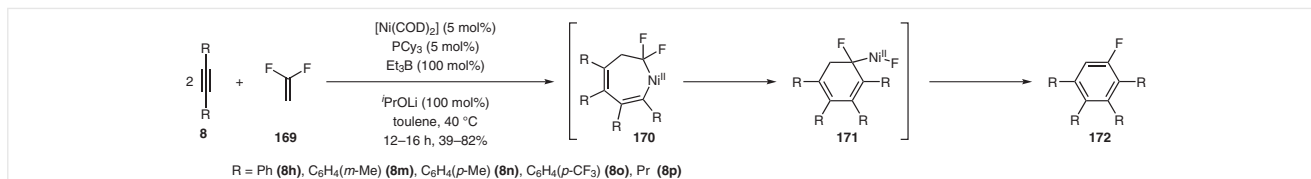


Scheme 48

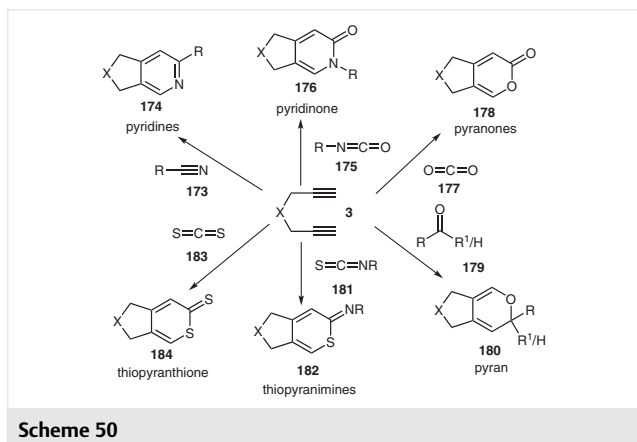
In 2015, Ichikawa and co-workers demonstrated the synthesis of fluorobenzene derivatives **172** through a nickel-catalyzed intermolecular [2+2+2] cycloaddition reaction using 1,1-difluoroethylene **169** as an alkyne surrogate (Scheme 49). They have also demonstrated that this reaction works with 1,6-enynes in a partially intramolecular fashion.<sup>38e</sup>

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 co-partner with two acetylenes in the presence of a cobalt catalyst leading to the formation of pyridines **174**.<sup>39a</sup> Later on,





Scheme 49



Scheme 50

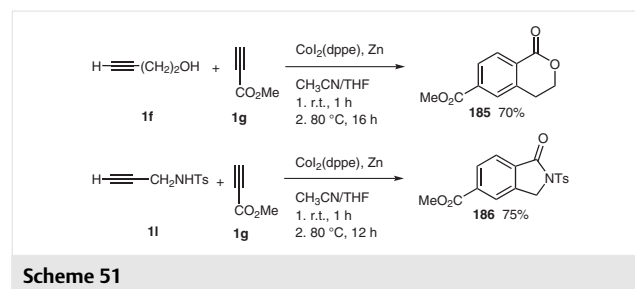
it was found that not only acetylenes and nitriles, but also other partners such as cyanates, isocyanates **175**, carbonyls **179**, and carbon disulfide (**183**) etc.<sup>39b</sup> participate in the [2+2+2] cycloaddition reaction, thereby enabling the formation of a variety of heterocyclic aromatic as well as non-aromatic compounds such as pyridones, pyrans, pyranones, etc. (Scheme 50).<sup>39</sup>

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,  $\pi$ -enriched systems, such as furans,<sup>40a</sup> thiophenes,<sup>40a,b</sup> pyrroles,<sup>40c</sup> and imidazoles<sup>40d</sup> deliver fused dihydro heterocycles. Recently, this methodology has been extended to indoles,<sup>41</sup> pyrimidines,<sup>42a,b</sup> pyridines, and pyrazinones.<sup>42c</sup>

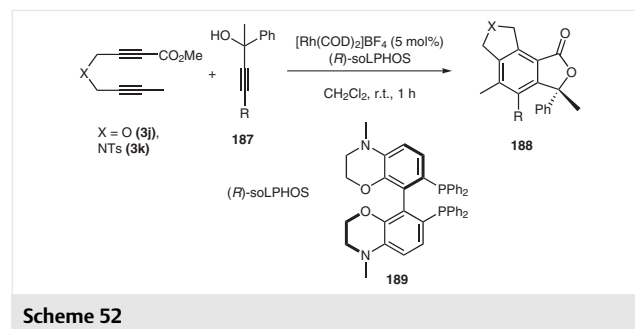
## 11 Domino Reactions Involving [2+2+2] Cycloaddition

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.<sup>43a</sup> Chang and co-workers demonstrated a one-pot synthesis of ben-

zolactone **185** and lactam **186** through a cobalt-catalyzed regioselective [2+2+2] cyclotrimerization and trans-esterification of alkynyl alcohols **1f** and amines **1l** with propiolates **1g** (Scheme 51).<sup>43b</sup> Tanaka and co-workers have prepared enantioenriched tricyclic phthalide derivatives **188** by a cationic Rh(I)/SOIPHOS complex-catalyzed asymmetric one-pot trans-esterification and a [2+2+2] cycloaddition reaction (Scheme 52).<sup>44</sup>

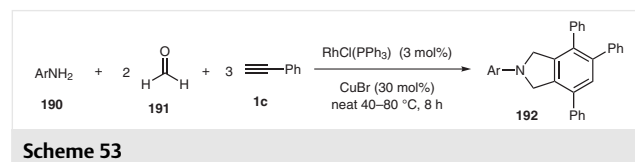


Scheme 51



Scheme 52

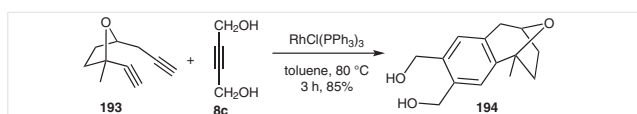
Li and Bonfield have prepared isoindoline derivatives **192** by treating amines **190** with aldehyde **191** and alkynes **1c** (Scheme 53). Three consecutive reactions take place in a single synthetic operation. First, one molecule of amine combines with two molecules of aldehyde and two molecules 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.<sup>45</sup>



Scheme 53

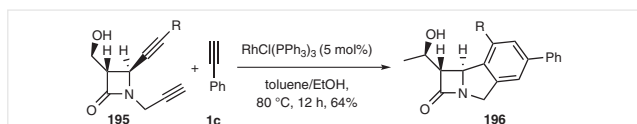
## 12 Biologically Important Targets/ Total Synthesis

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 benzanulated 8-oxabicyclo[3.2.1]octane systems **194** (Scheme 54) and this strategy was applied for the synthesis of (–)-bruguierol A.<sup>46a</sup>



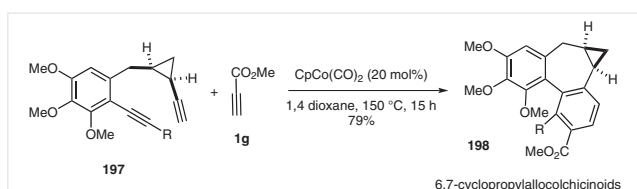
Scheme 54

A similar strategy was employed to construct the central 4/5/6 tricyclic framework of 6-(1-hydroxyethyl)-cyclo-nocardicin trinems **196** (Scheme 55).<sup>46b</sup>



Scheme 55

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



Scheme 56

## 13 Conclusions

In this account, we have demonstrated that a [2+2+2] cycloaddition sequence is a useful tool to assemble various

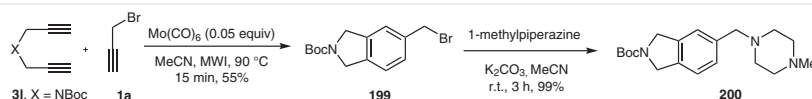
carbo- and heterocycles, spirocycles and polycycles including unusual amino acids and peptides. In this regard, we have used Wilkinson's catalyst, Vollhardt's catalyst, and Grubbs catalyst. More interestingly, we found that propargyl halides can be useful co-partners when Mo(CO)<sub>6</sub> is applied as a catalyst. For the first time, we have used Ti(O<sup>i</sup>Pr)<sub>4</sub> 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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Scheme 57

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