Transition Metal Catalyzed [2+2+2] Cycloaddition and Application in Organic Synthesis

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The [2+2+2] cycloaddition strategy is complementary to the well known Diels–Alder reaction for the generation of polycyclic compounds. This [2+2+2] approach is atom-economical and, with the availability of new catalysts to effect the [2+2+2] cycloaddition reaction, synthesis of a wide variety of highly functionalized polycycles is possible. This review deals with some recent advances relating to [2+2+2] cycloaddition reactions involving the syntheses both of polycycles and of heterocycles. More specifically, syntheses of various biologically active molecules, unusual amino acids, and theoretically interesting molecules are described. An attempt has also been made to give an overview of recent advances in the achievement of chemo-, regio-, and stereoselectivity in cyclotrimerization reactions.

1. Introduction

The development of novel reactions, useful reagents, and efficient catalysts to enable the formation of carbon-carbon bonds is an important activity in organic chemistry. More specifically, the use of carbon-carbon bond formation reactions to generate new ring systems is a key part of contemporary organic synthesis. In this respect, cycloaddition reactions are considered to be strategically useful where more than one carbon-carbon or carbon-heteroatom bonds are formed. With this as a goal, several researchers have developed new reaction pathways aimed towards the synthesis of complex organic molecules with cycloaddition reactions as key steps. Novel catalysts and new reaction conditions addressing the chemo- and regioselectivity aspects of these cycloaddition reactions have been discovered.

Strategically, [2+2+2] cycloaddition involving alkynes to generate annulated benzene derivatives is one of the more elegant methods for the construction of polycyclic aromatics. Since the discovery of benzene formation by thermal cyclization of three acetylene molecules by Bertholet in 1866, several advances have appeared in the literature. More specifically, the transition metal catalyzed cyclotrimerization of acetylenes to benzene derivatives reported by Reppe et al. in 1948[1a] accelerated the utility of metal catalysts in this area. Since then, various transition metal catalysts based on Ni, Co, Pd, Cr, Rh, Fe, Zr, Nb, Ir, and Ta have been developed for the trimerization reaction involving alkynes. Recently, Heiz and co-workers have reported that even a single palladium atom supported on MgO (100) films can catalyze the production of benzene from acetylene at low temperature (300 K).[1b] In addition to alkynes, other unsaturated components such as nitriles, isocyanates, olefins, carbonyl compounds, imines, and diimides have been shown to participate in cyclotrimerizations with alkynes to deliver useful end products. With the development of various catalysts these applications continue to grow: a significant number of reports have recently focused on the application of the alkyne trimerization reaction for the construction of new carbo- and heterocyclic frameworks useful in the synthesis of natural products and complex polycyclic aromatic compounds.[2–7] This review focuses on recent aspects of cyclotrimerization reactions, and examples appearing in previous reviews are not presented in detail, although some earlier examples are included as and when necessary.

The most common product of the acetylene cyclotrimerization is benzene (**1**; Scheme 1). Acetylene trimerization by a symmetry-allowed [2+2+2] cycloaddition reaction is an exothermic process (ΔH = –594 kJ mol^{-1}), but requires higher temperature or a catalyst because of entropic and kinetic considerations. If two alkynes were tethered, an-

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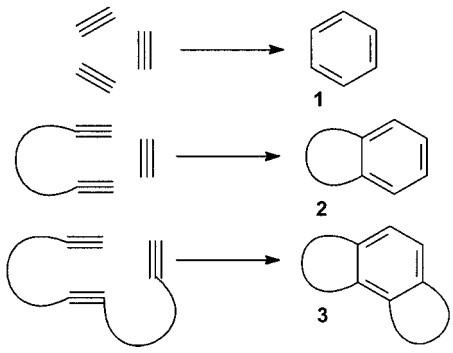
MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

nulated benzene derivative **2** would be generated, whilst if all three alkynes were connected a tricyclic ring **3** would be formed.

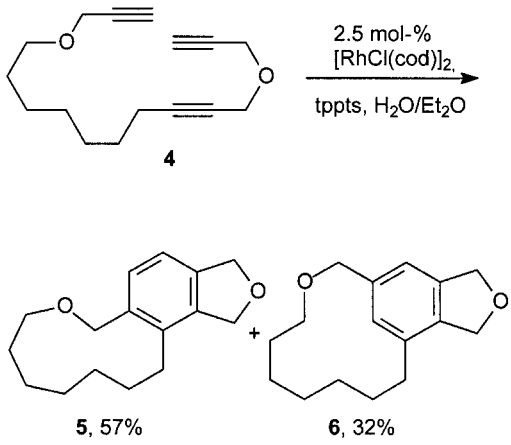


Scheme 1.

Cyclotrimerization of suitably placed alkyne derivatives can provide otherwise difficult to prepare highly substituted aromatic compounds. For a long time the regioselectivity of the product was a primary concern for this type of reactions,[5] but little success was achieved despite enormous efforts to control regioselectivity in these types of reactions.

In general, these reactions can be performed in common organic solvents at temperatures ranging from room temp. upwards. Cobalt-catalyzed alkyne trimerizations can be performed in supercritical water[8] or in supercritical carbon dioxide:[9] co-trimerization reactions involving mono-substituted alkynes in supercritical water as the solvent, for example, yielded products regioselectively comparable to those found in organic solvents, but the utility of supercritical water as the solvent was severely limited by significant hydrolysis of nitrile derivatives in cyclizations of two alkynes and a nitrile under similar conditions.

Eaton and co-workers reported the cyclization of hydrophilic alkynes in a water/methanol solvent system,[10] Butenschön et al. have recently reported cobalt-catalyzed alkyne cyclotrimerization reactions in aqueous solution (water/ethanol 80:20) at room temp. without any additional activation,[11] whilst a biphasic aqueous organic system appears to be useful for certain cyclotrimerized products, especially for medium- or large-ring systems (Scheme 2).[12]



Scheme 2.

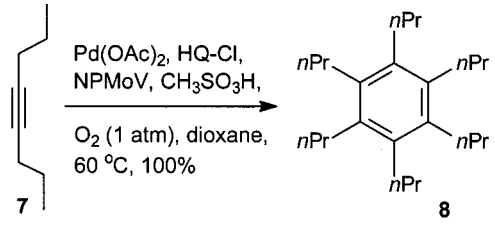
Sambasivarao Kotha was born in Amarthalur, Guntur District, AP, India. He received his B.Sc. degree from Nagarjuna University in 1977 and his M.Sc. degree from the University of Hyderabad in 1979. In 1985 he obtained his Ph.D. degree under the supervision of Professor G. Mehta at the University of Hyderabad. Subsequently, he worked with Professor R. J. Stoodley (1986–1987) at UMIST, Manchester, UK, and Professor J. M. Cook (1987–1989) at the University of Wisconsin, Milwaukee, as a research associate. Later, he joined Cornell University as a visiting scientist and worked in Professor A. Kuki's group on AIB peptide synthesis. In 1992–1993 he worked at Hoechst Celanese, Corpus Christi, Texas, as a research chemist. In 1994 he joined IIT Bombay as an Assistant Professor and was promoted to Professor in 2001. He was a recipient of the B. M Birla prize in Chemical Sciences (1996), the Professor N. S. Narasimhan endowment award (2000), and the CRSI bronze medal (2004). He has been elected as a member of the editorial board of the Indian Journal of Chemistry. His current research interests include methods in organic synthesis, unusual amino acids, peptide modifications, Suzuki coupling, metathesis, and theoretically interesting molecules.

Enugurthi Brahmachary was born in Aloor, Andhra Pradesh in India. After his early education in Aloor and Nirmal he obtained a B.Sc. degree from Kakatiya University in 1992, followed by a M.Sc. degree from Osmania University in 1994. He then moved to the Indian Institute of Technology-Bombay to pursue graduate study, receiving his Ph.D. degree in Organic Chemistry in 2000 under the direction of Prof. Sambasivarao Kotha for research that focused on development of new methodologies for the synthesis of unnatural amino acids. After his graduation he joined Prof. J. M. J. Fréchet's research group at the Department of Chemistry, University of California, Berkeley, as a postdoctoral fellow. At Berkeley, his research focused on combinatorial approaches for chiral recognition and preparation of new polymeric materials for the resolution of racemic compounds. He is currently a research scientist at the Medicinal Chemistry division at ChemBridge Research Laboratories in San Diego. California. His current research interests include chemistry and biology of amino acids and peptides, combinatorial chemistry, and medicinal chemistry.

Kakali Lahiri (née Chakraborty) was born in Hooghly, West Bengal. She obtained her B.Sc. degree in chemistry from Burdwan University, West Bengal in 1993 and her M.Sc. degree in organic chemistry from Burdwan University in December 1995. In 2002 she obtained her Ph.D. degree under the guidance of Professor S. Kotha from the Department of Chemistry, Indian Institute of Technology Bombay. Presently she is working as a Research Associate in the Department of Chemistry, Indian Institute of Technology Bombay. Her research interests are the development of new methodologies for the synthesis of interesting molecular frameworks and the modification of peptides.

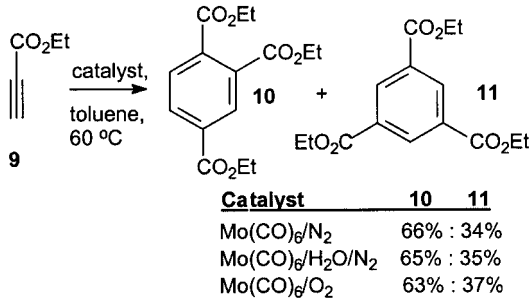
2. Intermolecular [2+2+2] Cycloaddition: Cyclotrimerization of Alkynes

Both homogeneous and heterogeneous catalyst systems have been used for cyclotrimerization of alkynes. New catalysts generally appear to be combinations of known and unknown metal complexes: an activated zirconium-titanium mixture, for example, has been found to catalyze alkyne trimerization in good yields.[13a] This highly reactive metal catalyst was prepared by reduction of zirconium(IV) chloride and titanium(III) chloride with lithium powder in a dry dimethoxyethane/tetrahydrofuran mixture, alkyne was added directly to the reaction mixture containing the metal complex, and the product was isolated by simple filtration. Both terminal and internal alkynes have been cyclotrimerized, but no significant regioselectivity was observed. Takahashi and co-workers have recently used zirconacyclopentadienes as attractive intermediates for the synthesis of six-membered heterocycles, with zirconacyclopentadienes prepared in situ from Cp_2ZrEt_2 and two symmetrical or unsymmetrical alkynes or diynes reacting with C=O, C=N, and N=N moieties containing electron-withdrawing groups to give pyran, pyridine, and dihydropyridazine derivatives, respectively, in good yields.[13b] For the synthesis of pyran and dihydropyridazine derivatives the presence of a metal salt such as $BiCl_3$ or CuCl is essential. The same strategy was used for selective preparation of pyridones and iminopyridines from two different alkynes via azazirconacycles,[13c] whilst a low-valent tantalum system derived from $TaCl_5$ and Zn has also been reported for this purpose.[14] Notably, the reactivity and the yields are found to depend mainly on the solvent system and the substituents on the alkyne. Ishii and co-workers reported cyclotrimerization of alkynes (e.g., **7**) with use of a multi-catalytic system involving $Pd(OAc)_2$, chlorohydroquinone (HQ-Cl), and molybdovanadophosphate (NPMoV) in the presence of dioxygen (Scheme 3).[15] No products were formed without an oxygen source, and temperature above 60 °C were necessary for the success of the reaction. Interestingly, some internal alkynes converted into aromatized products in quantitative yields under these conditions and terminal alkynes gave exclusively 1,3,5-trisubstituted benzenes.



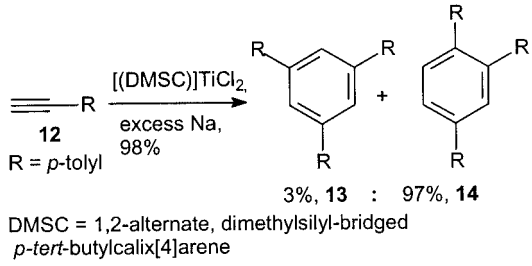
Scheme 3.

Several transition metal catalysts are known to effect the cyclotrimerization reaction, but chemo- and regioselectivity appear to be serious problems, a significant number of reports having focused recently on this important aspect. Phosphane complexes of Co^I, Rh^I, and Ir^I are generally used for the dimerization and cyclotrimerization of acetylenes.[16] Molybdenum(0) complexes were investigated for the cyclotrimerization of "electron-poor" alkynes such as ethyl propiolate (**9**) and dimethyl acetylenedicarboxylate (DMAD) (Scheme 4).[17] Parent molybdenum carbonyl complexes under nitrogen atmosphere induce cyclotrimerization of ethyl propiolate in good yields with about a 2:1 ratio of 1,2,4- and 1,3,5-carboethoxybenzene (Scheme 4), whilst an *N*-methylimidazole (1-Meim) complex of molybdenum carbonyl $[Mo(CO)_3(1\text{-Meim})_3]$ proved to be efficient for the selective formation of the 1,3,5-regioisomer as the major product. A similar selectivity has been observed for phenylacetylene and ethyl propiolate.



Scheme 4.

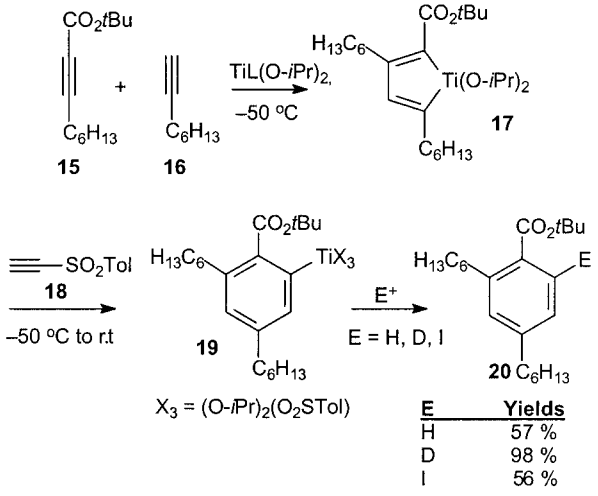
Recent efforts in this area have focused on the application of various catalysts to achieve regio- and chemoselectivity in the cyclotrimerization of alkynes. Ladipo et al. have reported the use of a calixarene-bound titanium complex to induce 1,2,4-regioselectivity in the trimerization of terminal alkynes (Scheme 5):[18] in the presence of excess amounts of sodium and the catalyst, several mono-substituted alkynes were trimerized to give 1,2,4-substituted benzene derivatives such as **14** as the major products. Aryl- and trimethylsilyl-substituted acetylenes gave the 1,2,4-isomers regioselectively (> 98%). The same group has further investigated the scope and mechanism of the reaction;[19] their mechanistic studies indicated that the steric demand of the calixarene cavity is responsible for the observed selectivity.



Scheme 5.

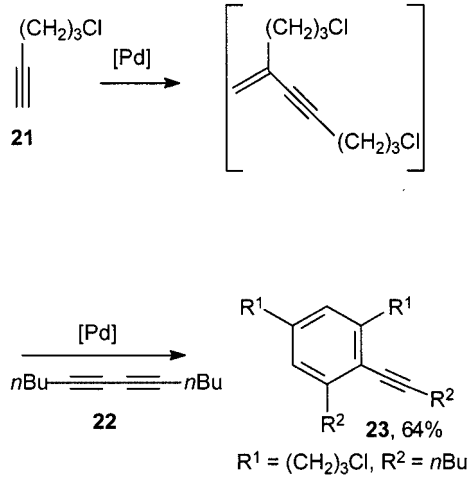
Sato and co-workers reported a novel Reppe-type cyclotrimerization method for the preparation of aryltitanium compounds, three different unsymmetrical acetylenes and one molecule of a specific metallic species being combined together in a highly controlled manner to give aromatic organometallic compounds directly.[20] As shown in Scheme 6, a dialkoxytitanocyclopentadiene **17** was prepared from two different acetylenes (**15** and **16**) and a divalent titanium alk-

oxide reagent. Treatment of **17** with ethynyl tolyl sulfone (**18**) gave aryl titanium compound **19**, which could be treated with various electrophiles to produce other substituted aromatic compounds such as **20**.



Scheme 6.

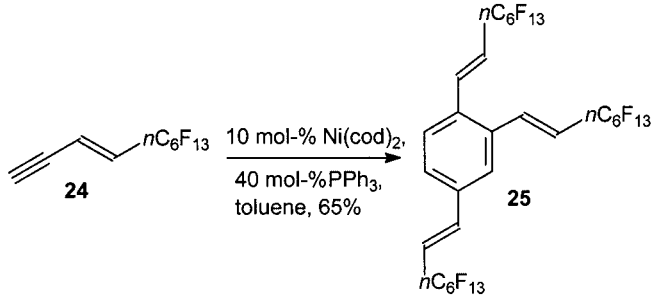
Recently, Gevorgyan and co-workers[21] have demonstrated aryl ring formation in a chemo- and regioselective manner through a palladium-catalyzed [2+2+2] sequential trimerization of alkynes (e.g., **21**; Scheme 7). This approach has delivered both tetra- (e.g., **23**) and pentasubstituted benzene derivatives in moderate yields. It was observed that the rate of the reaction could be accelerated significantly by the addition of a Lewis acid/phosphane ligand system. Jiang and co-workers reported $CuCl_2$-induced highly chemo- and regiospecific palladium-catalyzed cyclotrimerization in excellent yields.[22] Both symmetrical and unsymmetrical alkynes smoothly underwent cyclotrimerization in the presence of $PdCl_2/CuCl_2$ in a BuOH/benzene solvent system.



Scheme 7.

Takeuchi and Nakaya have observed that two molecules of DMAD react with one molecule of mono-yne to give 2:1 coupling products in the presence of $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene) catalyst and 1,2-bis(diphenylphosphanyl)-ethane (dppe) ligand. When 1,2-bis(dipentafluorophenylphosphanyl)ethane was used, one molecule of DMAD reacted with two molecules of mono-yne to give the 1:2 coupling product, so selective [2+2+2] cycloadditions of two different mono-ynes can be achieved by appropriate selection of the ligand.[23]

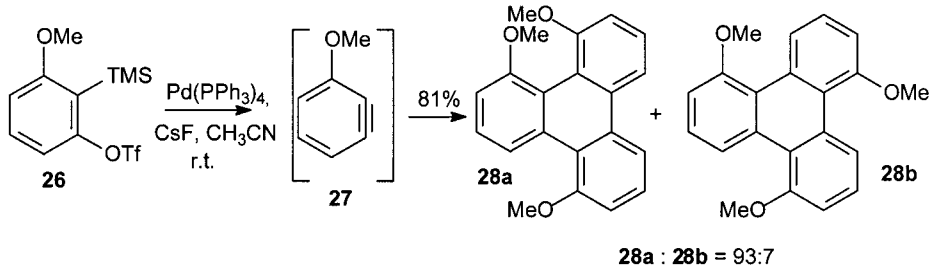
Yamamoto and co-workers have described a useful process involving nickel-catalyzed regioselective cyclotrimerization of 1-perfluoroalkylenynes.[24] The (*E*)-perfluorohexyl-enyne derivative **24**, for example, was cyclotrimerized in the presence of 10 mol-% $Ni(PPh_3)_4$, prepared from $Ni(cod)_2$ and PPh_3, to produce the 1,2,4-trisubstituted benzene derivative **25** in good yield (Scheme 8). The reaction proceeded smoothly in a highly regioselective manner, and only a trace amounts of 1,3,5-isomer were observed with most of the substrates.



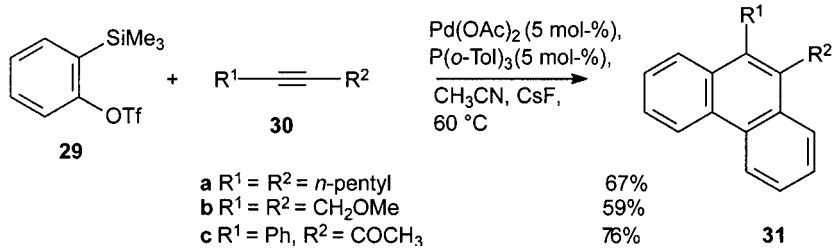
Scheme 8.

Tanaka et al. used cationic rhodium(I) and modified 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) complexes to achieve chemo- and regioselective cyclotrimerization of mono-substituted acetylenes with the electron-poor acetylene diethyl acetylenedicarboxylate (DEADC).[25a] The same methodology has been applied to assemble [6]metacyclophane and [7]-[12]paracyclophanes.[25b]

Benzyne and other substituted benzyne derivatives undergo chemoselective cyclotrimerization either with other acetylenes or with themselves to form synthetically useful triphenylenes. Palladium catalysis has been found to be effective for such cyclotrimerization under mild reaction conditions. Fluoride ion induces the generation of aryne **27** (Scheme 9), which undergoes cyclotrimerization to give a mixture of **28a** and **28b** in 93:7 ratio (81% overall yield);[26] the best results were found with 10 mol-% $Pd(PPh_3)_4$ and CsF in acetonitrile at room temp. They also reported co-cyclization of arynes with other mono-alkynes.[27] Benzynes derived from naphthalene or phenanthrene also underwent facile cyclotrimerization to give aromatic polycyclic ring systems.[28] Under the same reaction conditions, benzyne reacted with one or two molecules of a mono-alkyne such as DMAD to afford mixtures of phenanthrene and naphthalene derivatives in a ratio of 84:7, but when $Pd_2(dba)_3$ was employed as the catalyst the naphthalene derivatives were the major products (10:83 ratio). With electron-rich alkynes, phenanthrene derivatives were generally obtained in low yields. Yamamoto and co-workers have utilized a



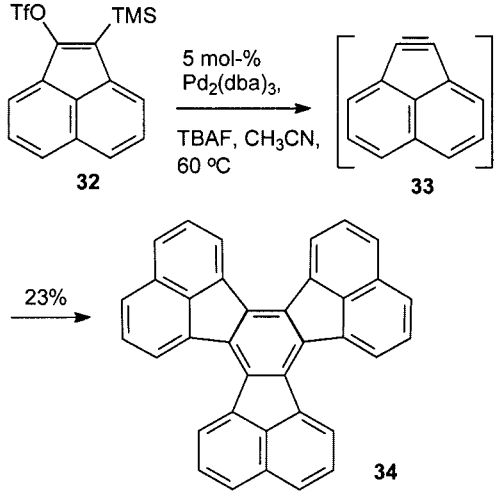
Scheme 9.



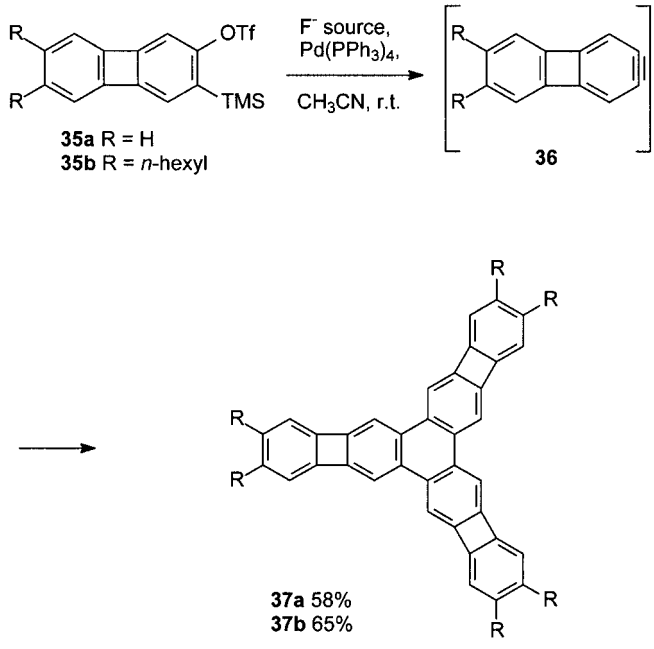
Scheme 10.

$Pd(OAc)_2$/(*o*-Tol)$_3$P catalyst system, with phenanthrene derivatives (e.g., **31)** being obtained in good yields regardless of the electronic nature of the alkyne (Scheme 10).[29]

Palladium-catalyzed trimerization has been applied for the synthesis of highly strained decacyclenes. Compound **32**, for example, gave a strained alkyne **33** in situ on treatment with tetrabutylammonium fluoride (TBAF) and 5 mol-% $Pd_2(dba)_3$ (dba = dibenzylideneacetone) in acetonitrile at 60 °C (Scheme 11), and this trimerized under the same reaction conditions to deliver dodecahydrotriphenylene **34** in 23% yield.[30] It was observed that generation and trimerization of compound **33** with CsF and $Pd(PPh_3)_4$ in CH_3CN gave very low yields of **34**. In another report, Vollhardt and co-workers synthesized tris(benzocyclobutadieno)triphenylene **37** by palladium-catalyzed trimerization of didehydrobiphenylenes **36** (Scheme 12).[31a] The embedded triphenylene unit in the C_3-symmetric trimer **37** was distorted to increase the aromaticity of the central benzene ring. Wegner and co-workers found that Ni^0 benzyne complexes delivered naphthalene derivatives when allowed to react with various alkynes.[31b] By the same methodology they have also prepared sulfur macrocycles, although the yield of the reaction was only moderate (45%), due to the unstable nature of the compound.[31c]



Scheme 11.

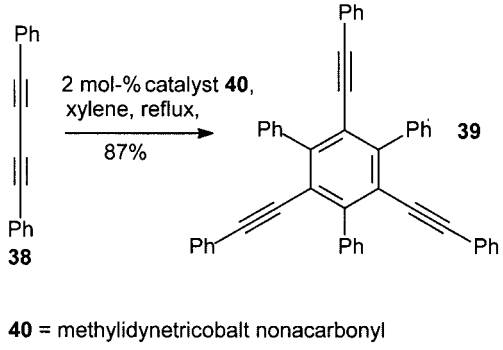


Scheme 12.

Ikeda and co-workers have investigated various cyclotrimerization reactions using Ni(acac or cod)$_2$-PPh_3–Et_2Zn–PhOH systems.[32] Competition of two different mono-alkynes for self-trimerization reactions was suppressed and in most cases the 1,2,4-isomer was formed with

up to 95% regioselectivity in good isolated yields. However, three different alkynes on reaction under similar conditions gave a mixture of regioisomers along with other benzene derivatives.

Sugihara et al. have reported that a methylidynetricobalt nonacarbonyl [$Co_3(CO)_9(\mu^3$-CH), **40**], a known catalyst for the Pauson–Khand reaction, also catalyzes the cyclotrimerization of mono- and disubstituted alkynes.[33] The conditions are relatively mild, and the reaction proceeded at low temperature to provide the trimerized product **39** in good yields, whilst up to 67% of the catalyst could be recovered (Scheme 13). The same group also showed that the trimerization reaction shown in Scheme 3 proceeded smoothly in toluene at reflux when methylidyne complex **40** was used as a catalyst (1 mol-%) to give hexa(*n*-propyl)-benzene in excellent yield (92%). Cyclotrimerization has also been used to prepare acetylene derivatives such as **42** and **43** (Scheme 14). These compounds have been characterized as nonlinear optical chromophores by hyper-Rayleigh scattering techniques.[34]

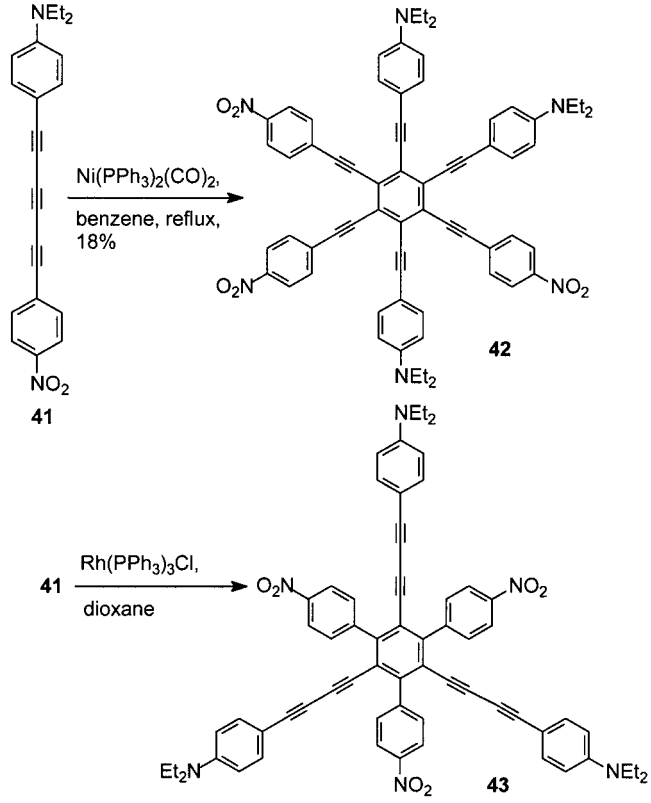


Scheme 13.

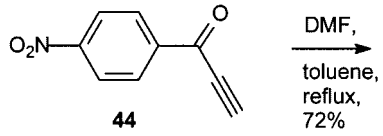
Tagliatesta and co-workers used different rhodium porphyrin catalysts for the solvent-free cyclotrimerization of arylethynes. Hindered catalysts favored the formation of less symmetrical isomers, whilst the selectivity of the reaction was also influenced by the nature of the substitution on the substrate.[35]

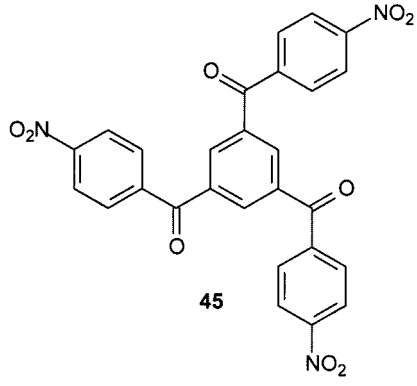
1,3,5-Tris(4-nitrobenzoyl)benzene (**45**) was synthesized from (4-nitrobenzoyl)acetylene (**44**) in good yield (Scheme 15). The C_3-symmetric compound **45** was found to form 1:1 crystalline inclusion complexes with CH_2Cl_2 and DMSO, as indicated by X-ray crystallographic studies.[36] Bis(1,3,5-triaroyl)benzene derivatives were prepared by an indirect route through condensation of linked bis(enaminones) with aryl ethynyl ketones, since the direct cyclotrimerization of linked aryl ethynyl ketones gave poor yields of the desired product.[37]

By a similar approach, a metal-free catalytic method for the preparation of optically pure 1,3,5-tris(1,1′-binaphthyl)-benzene derivatives through an amine-catalyzed alkyne trimerization has also been developed.[38,39] The cyclotrimerization proceeds smoothly in 54% yield and with complete regioselectivity. The reaction proceeds without epimerization of the starting chiral binaphthyl framework.



Scheme 14.





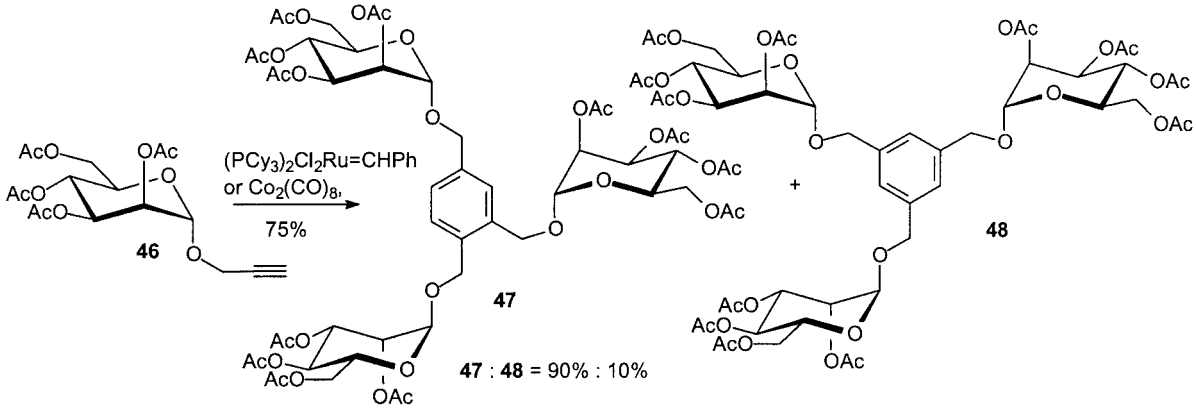
Scheme 15.

Use of another metal ion-free catalyst for cyclotrimerization of acetylenes has recently been reported. Si_2Cl_6-catalyzed cyclotrimerization of acetylene and other mono- and disubstituted acetylenes at elevated temperatures gave good yields and was claimed to be the first reported example of cyclotrimerization operating by a free-radical mechanism. No regioselectivity was observed with unsymmetrical alkynes.[40]

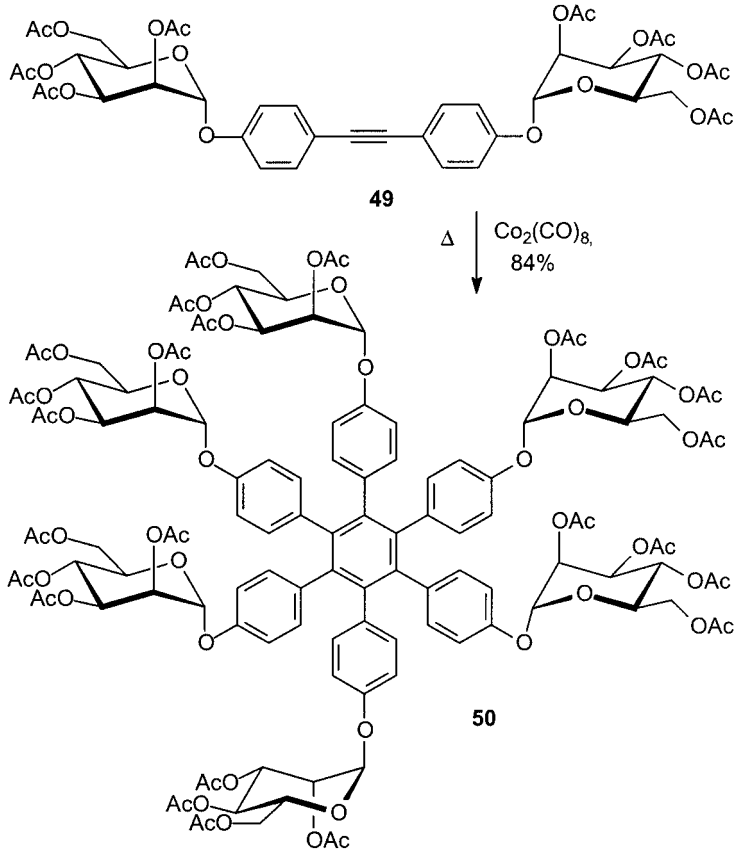
Roy and Das prepared a multivalent carbohydrate derivative by a Grubbs' ruthenium-catalyzed cyclotrimerization of terminal alkyne **46** (Scheme 16).[41] Interestingly, treatment of **46** with Grubbs' catalyst in dichloromethane at room temp. gave the desired trisubstituted derivatives (**47** and **48**), favoring the 1,2,4-isomer **47** as the major product. A similar result was observed when dicobalt octacarbonyl was used instead of the Grubbs' catalyst.[42] Deacetylation of **47** and **48** afforded water-soluble trimannosides that were shown to have protein cross-linker abilities. The same authors also prepared the hexamer **50** from a symmetrical internal alkyne **49** in good yield by a similar methodology (Scheme 17).[43]

Riant and co-workers produced a new family of conjugated hexaferrocenyl complexes by use of cyclotrimerization.[44] A [2+2+2] cycloaddition of alkyne **51**, bearing enantiopure ferrocene units at its periphery, was performed in the presence of dicobalt octacarbonyl $Co_2(CO)_8$ (10 mol-%) at reflux in dioxane to produce the desired product **52** in 85% yield (Scheme 18). From the NMR spectroscopic data and computational analysis it was proposed that the compound **52** favored a chiral helical structure in which all the ferrocene moieties were aligned in an all-*syn* conformation.

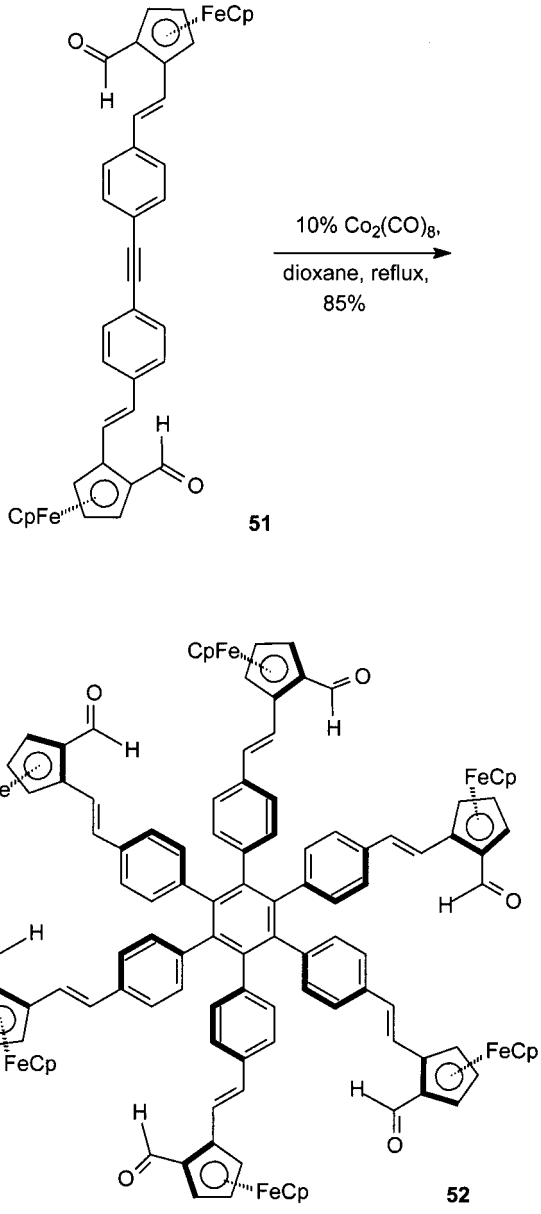
Müllen and co-workers reported a series of star-shaped hexaaryl or -heteroaryl benzene derivatives.[45] A represen-



Scheme 16.



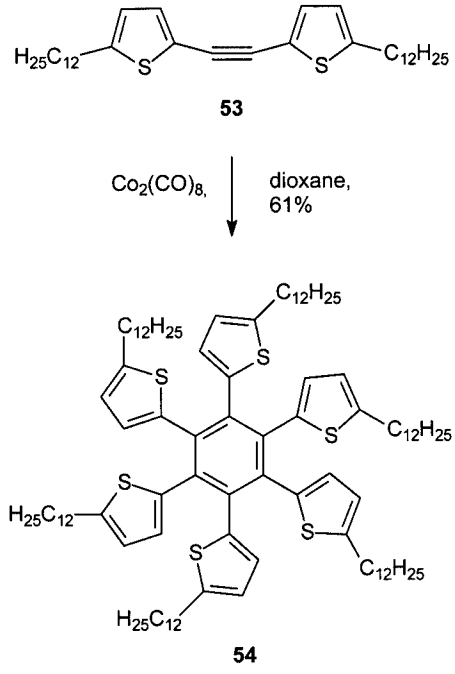
Scheme 17.



Scheme 18.

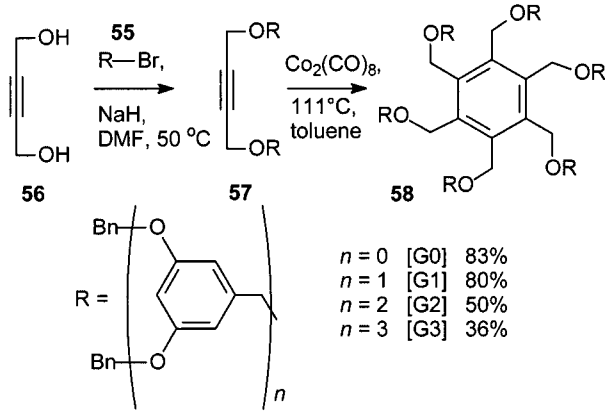
tative example, in which a symmetrical alkyne **53** substituted with two 2-alkylthienyl groups underwent cyclotrimerization in the presence of dicobalt octacarbonyl in dioxane to afford the trimerized products **54** in good yields, is shown in Scheme 19. When the alkyl groups were each replaced with a second thienyl unit, the yields of the products were low. Since the objective of this research was to investigate the formation of mesomorphic entities, all the substrates were decorated with flexible alkyl chains. Catalysts such as $Co_2(CO)_8$ have been used for the cyclotrimerization of bis(4-methoxyphenyl)acetylene to give hexakis(4-methoxyphenyl)benzene, which was further converted into hexakis(4-hydroxyphenyl)benzene.[46]

Fréchet and Hecht reported an elegant method for the convergent synthesis of dendrimers in which the dendrimer core is generated by an alkyne cyclotrimerization reaction



Scheme 19.

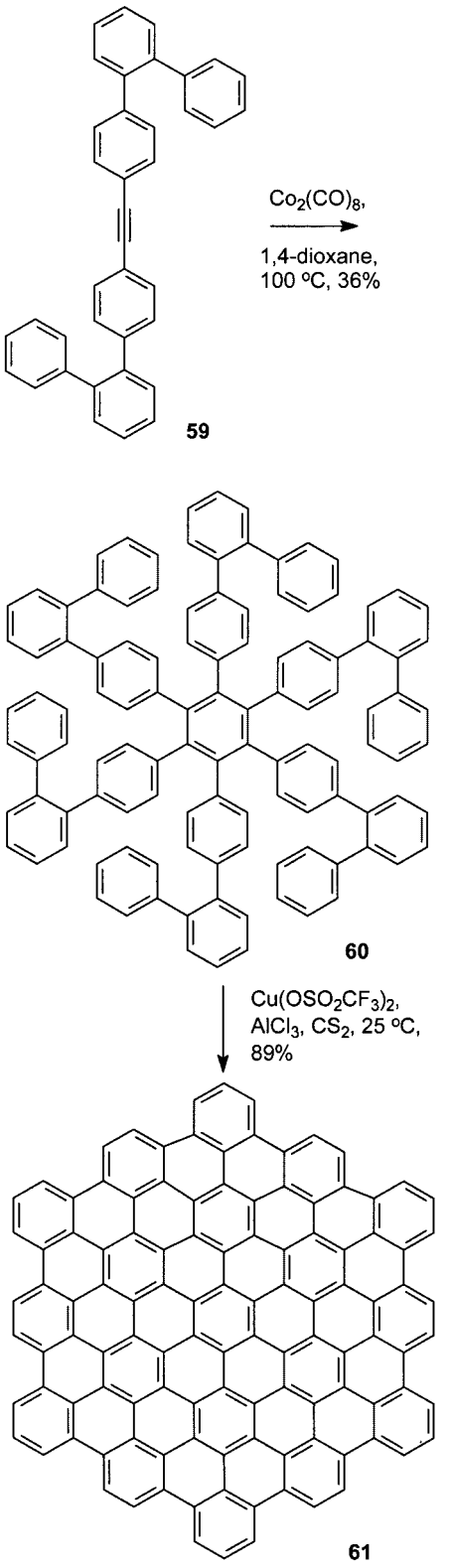
(Scheme 20). Here, the convergent dendrons, attached to an acetylene derivative, are cyclized in a [2+2+2] cycloaddition process to provide pure and monodispersed dendrimers in one-pot fashion.[47] The acetylenic precursor **57** was prepared from the commercially available but-2-yne-1,4-diol (**56**) by the Williamson ether coupling reaction with use of an appropriate polybenzyl ether-derived dendritic bromide (**55**). Cyclotrimerization of **57** in the presence of $Co_2(CO)_8$ at reflux in toluene afforded novel dendrimers **58** in good yields. As the size of the dendrons on the acetylene increases from generation one (G-1) to generation three (G-3) the time required for the complete trimerization increased, while the yield decreased as a result of steric crowding around the nascent core.



Scheme 20.

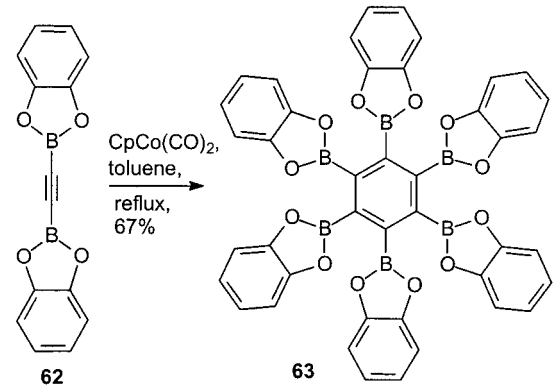
Novel polycyclic hydrocarbons were prepared by $Co_2(CO)_8$-catalyzed cyclotrimerization of an internal acetylene substituted with bulky aromatic groups.[48] Alkyne **59** was prepared by a palladium-mediated coupling reaction.

Cyclotrimerization of **59** at reflux in dioxane in the presence of $Co_2(CO)_8$ gave **60** in 36% yield, and this was then converted into the planar C_{114} hydrocarbon **61** in good yield (Scheme 21).



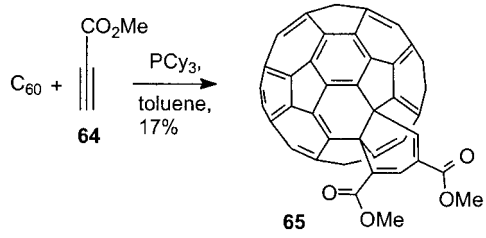
Scheme 21.

An interesting class of hexaborylbenzene derivatives has been prepared by cobalt-catalyzed trimerization of boryl-substituted alkynes.[49] Cyclotrimerization of a disubstituted alkyne **62** in the presence of $CpCo(CO)_2$ at reflux in toluene gave **63** in 67% yield (Scheme 22). The highly insoluble and air-stable **63** was purified by multiple washing with THF and dichloromethane. In contrast, alkyne **62** afforded a dicobalt complex on treatment with $Co_2(CO)_8$, and this complex was found to be useful for selective preparation of diboryl- and tetraborylbenzene derivatives.

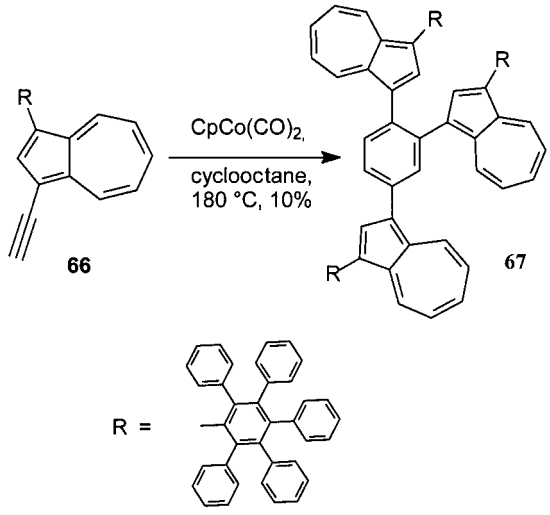


Scheme 22.

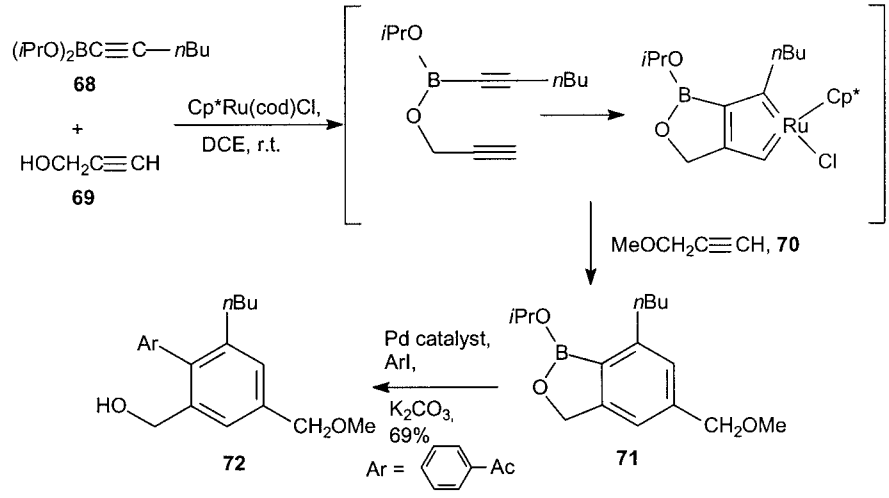
Cyclotrimerizations involving C_{60} fullerene were reported by Cheng and co-workers. Methyl propiolate (**64**) was treated with C_{60} fullerene in toluene in the presence of tricyclohexylphosphane (PCy_3), for example, to provide cycload-



Scheme 23.



Scheme 24.



Scheme 25.

duct **65** in 17% yield (recovered [60]fullerene in 74%; Scheme 23). No trimerized product was obtained in the absence of PCy_3 or in the presence of other phosphane ligands such as PPh_3 and $P(OPh)_3$.[50]

A new π system has been prepared by Elwahy by [2+2+2] cyclization of the 1-ethynylazulene derivative **66** (Scheme 24). Compound **67** was obtained in 10% yield and the symmetrical derivative was not obtained. The triazulenebenzene derivative **67** exhibits an absorption maximum at 617 nm.[51]

One-pot Ru-catalyzed intermolecular cyclotrimerization of three distinct unsymmetrical alkynes (**68**, **69**, and **70**) in a chemo- and regioselective manner has been achieved by use of a temporary tethering approach through a C–B–O linkage (Scheme 25).[52a] The crude arylboronates underwent Suzuki–Miyaura cross-coupling with various aryl iodides in the presence of a $Pd_2(dba)_3/PCy_3$ catalyst in aqueous toluene to afford biaryls. The same catalyst has also been found to be effective for the cycloaddition of 1,2-bis(propiolyl)benzene to provide anthraquinone derivatives at room temperature.[52b] McDonald and co-workers have utilized intramolecular cyclotrimerization of diyne and *C*-alkynylglycosides for the synthesis of anthraquinone *C*-glycosides,[52c] whilst Cheng and co-workers have studied a series of nickel-catalyzed [2+2+2] cyclizations of oxa- and azabenzonorbornadienes with terminal alkynes and bis-alkynes for construction of multi-fused ring systems.[53] It was noted that temperature control was necessary for the successful isolation of cyclotrimerized products. An additional phosphane ligand was essential to stabilize the Ni^0 catalyst and to obtain a higher yield of the product. These cycloaddition reactions are highly stereoselective.

3. Partial Intramolecular [2+2+2] Cycloaddition: Co-cyclotrimerization of Alkynes

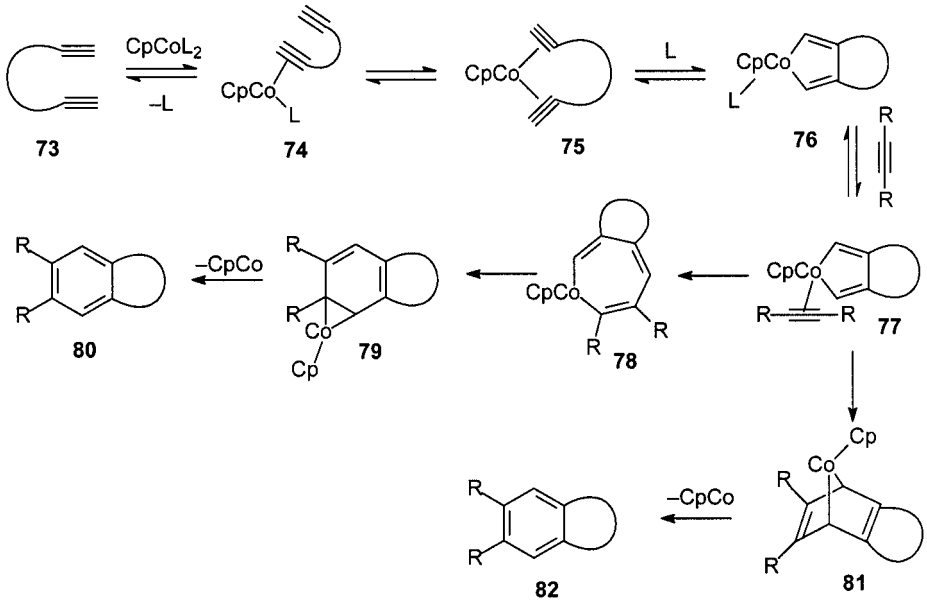
The most useful strategy for the construction of polycyclic ring systems is partial intramolecular cyclotrimerization or co-cyclotrimerization of alkynes. An α,ω-diyne undergoes cyclotrimerization with a third alkyne, yielding a bicyclic compound. A generally accepted mechanism of the cobalt-catalyzed co-cyclotrimerization reaction is shown in Scheme 26.[54a]

Initial complexation of catalyst $CpCoL_2$ with the dialkyne would give a complex **75**, which could undergo oxidative coupling to give the metallacyclopentadiene complex **76**. The third alkyne could then react to generate new complex **77**, which could be transformed either into a tricyclic complex **78** by an intramolecular Diels–Alder-type reaction or into a metallacyclopropane complex **79**. Finally, a reductive elimination process via **78** or **79** could afford the aromatized product **80**. Species **75**, **76**, and **77** have been isolated in some catalytic reactions. However, different mechanistic studies showed that the sequence for the formation of the final product depends on the catalyst system employed in the reaction.[54b–54d]

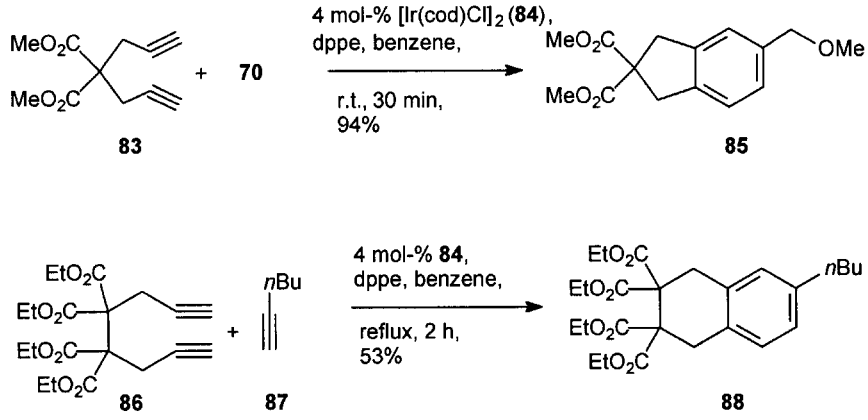
Several cyclotrimerization catalysts have been reported with a variety of dialkyne systems. Thanks to their usefulness in generating desired products exclusively and in eliminating unwanted oligomeric or self-trimerized products, partial intramolecular [2+2+2] reactions have attracted special attention in recent years. Several authors have reported regio- and chemoselective versions of these reactions, and these developments are summarized in the following section.

The iridium complex of $[Ir(cod)Cl_2]$ and dppe is reported to be effective for the co-trimerization of 1,6-diyne **83** with a range of functionalized mono-alkynes (e.g., **84**) to give indane derivatives (e.g., **85**) in excellent yields (Scheme 27).[55] Similarly, the octa-1,7-diyne **86** reacts with hex-1-yne (**87**) to yield the corresponding cyclotrimerized product **88** in a moderate yield. It was found that the other ligands such as PPh_3 and bidentate ligands such as 1,3-bis(diphenylphosphanyl)propane (dppp) afforded products in lower yields. The reaction mechanism may involve the formation of an iridiacyclopentadiene complex as an intermediate.[56]

Mori et al. have used Mortreux's catalyst system derived from $Mo(CO)_6$ and *p*-chlorophenol for alkyne co-trimeri-



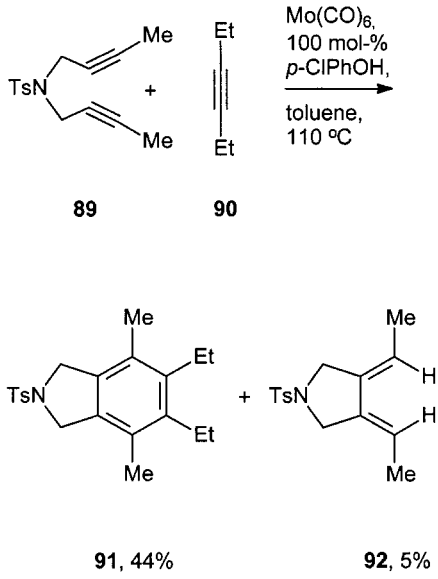
Scheme 26.



Scheme 27.

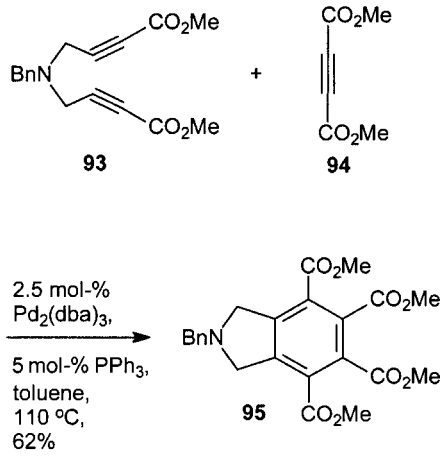
zation reactions to prepare isoindoline derivatives in moderate yields.[57] Under these conditions, mono-alkynes containing an *o*-hydroxyphenyl group gave trimerized products, whereas alkynes containing a *m*- or *p*-hydroxyphenyl group gave cross-alkyne metathesis products. The diyne **89** has recently been reported to undergo co-trimerization with various mono-alkynes (e.g., **90**) under similar reaction conditions to give the cyclized product **91** along with the byproduct **92** (Scheme 28).[58] Isolation of the byproduct **92** indicated that this catalytic reaction proceeded via a molybdenacyclopentadiene complex. Use of 15 equivalents of mono-alkyne gave improved yields of the desired trimerized products. A similar catalyst system was also found to be effective for totally intramolecular [2+2+2] cyclization reactions.

Palladium(0)-catalyzed intramolecular cyclotrimerization has been reported by Itoh et al. In the presence of $Pd_2(dba)_3$ and PPh_3, electron-deficient dialkynes such as **93** reacted with DMAD (**94**) to give highly substituted dihydroisoindole derivatives (e.g., **95**; Scheme 29). The method has been applied for the synthesis of phthalin and isoindoline deriva-



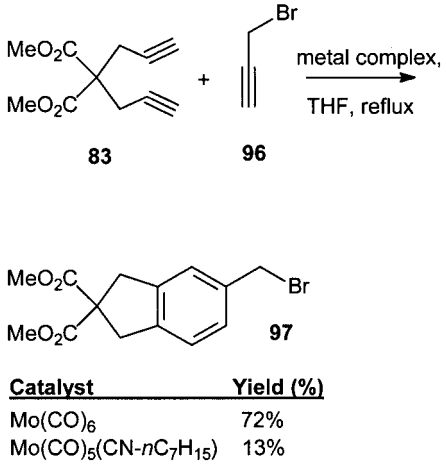
Scheme 28.

tives in moderate yields.[59] The strategy has also been efficiently extended to totally intramolecular cyclization of triynes to prepare tricyclic aromatic systems.



Scheme 29.

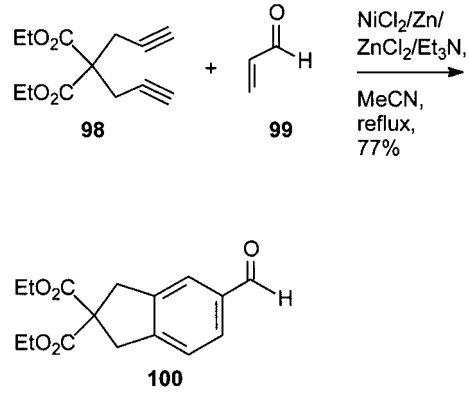
Sugihara et al. have investigated co-trimerization of alkynes by use of group-VI metal carbonyl complexes of isonitriles (Scheme 30).[60] Although isocyanide complexes of metal carbonyls are known to exhibit higher reactivity than the parent metal carbonyls in oxidative addition, these complexes gave poor yields when they were employed as mediators in alkyne co-trimerization reactions. In contrast, the parent metal carbonyls catalyzed a similar reaction with good yields. It is worth mentioning that such a highly reactive and advanced intermediate as propargyl bromide has been utilized as a partner in this trimerization reaction, which has additional advantage for further exploration.



Catalyst	Yield (%)
$Mo(CO)_6$	72%
$Mo(CO)_5(CN\text{-}nC_7H_{15})$	13%

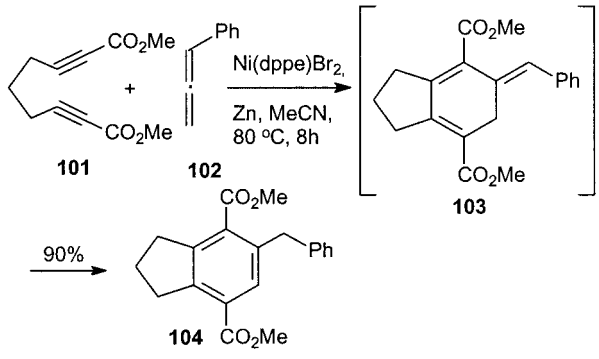
Scheme 30.

Sato et al. have investigated Ni- and Zn-promoted [2+2+2] cycloadditions of diynes with α,β-enones to give aromatic compounds directly in good yields. Under these conditions cyclic enones also cyclize with diynes.[61] As shown in Scheme 31, a dialkyne (e.g., **98**) can undergo a [2+2+2] cycloaddition reaction with an α,β-enone (e.g., **99**) in the presence of $NiCl_2/Zn/ZnCl_2/Et_3N$ in acetonitrile to provide the co-trimerized product (e.g., **100**) in good yield. Cheng and co-workers have reported a similar approach with a $Ni(PPh_3)_2X_2$ (X = Cl, I) /ZnI_2/Zn catalyst system[62] for regioselective co-trimerization of α,β-unsaturated cyclic and acyclic enones with alkynes.



Scheme 31.

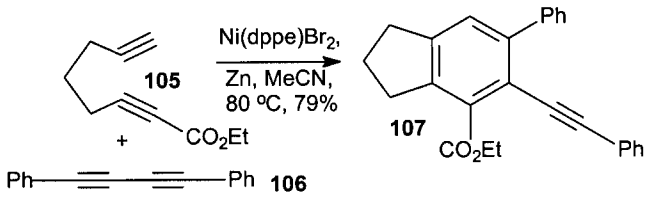
The same group has recently reported nickel-catalyzed regio- and chemoselective [2+2+2] cycloadditions between electron-deficient diynes and allenes.[63] The diyne **101**, for example, was treated with the unsymmetrical allene **102** in the presence of Ni(dppe)Br_2/Zn in acetonitrile to give the cyclized product **104**, presumably via compound **103**, in excellent yields and with good regioselectivity (Scheme 32). Under similar reaction condition, unsymmetrical diynes reacted with allene **102** to give exclusively the *meta* isomers in 73–86% yields. The reaction appears to be highly regio- and chemoselective with several dialkynes and has also shown excellent compatibility with various functional groups. Since allenes are synthetically equivalent to monosubstituted alkynes, this methodology may serve as a useful alternative for controlling regioselectivity.



Scheme 32.

Cheng and co-workers described a convenient and practical method for the preparation of various aryl alkynes under Ni(dppe)Br_2/Zn catalytic conditions.[64] Here, an unsymmetrical diyne **105** reacts regioselectively with a symmetrical alkyne **106** in the presence of Ni(dppe)Br_2/Zn in acetonitrile at 80 °C to afford **107** as a major product (Scheme 33). It appears that the chelating effect of the dppe ligand is crucial to effect the reaction, because it was found that use of $NiBr_2$ or $Ni(cod)_2$ afforded very low yields of the product. This methodology can be viewed as an alterna-

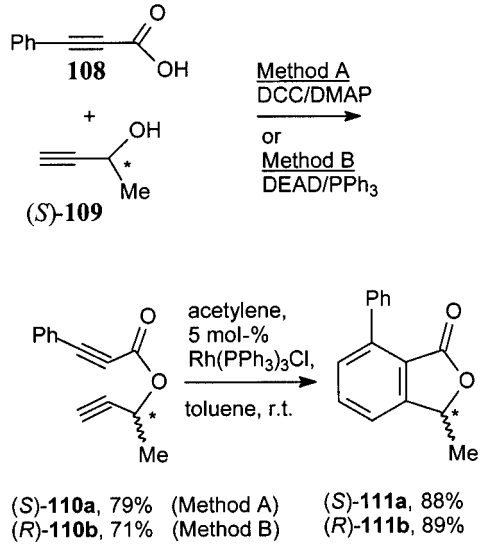
tive for the Sonogashira coupling of aryl halides with alkynes to deliver aryl alkynes.



Scheme 33.

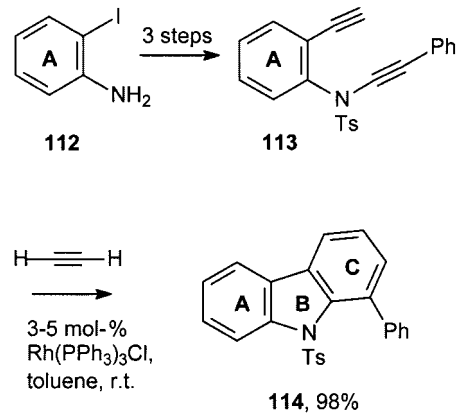
A nickel(0)-catalyzed asymmetric version of a [2+2+2] cycloaddition reaction has been reported.[65] Two alkyne groups of a triyne react with zero-valent Ni catalyst to form a chiral nickel cyclopentadiene, which then allows insertion of a third alkyne to form the final product with a benzylic chiral center. Among the chiral ligands investigated, a ferrocene-derived ligand gave very good yields and high enantiomeric excess during isoindoline synthesis.

Witulski et al. synthesized chiral 3-substituted phthalides by use of Wilkinson's catalyst. Several α,ω-dialkynes such as **110** were prepared either by standard dicyclohexylcarbodiimide (DCC) coupling reactions or through Mitsunobu coupling reactions between the corresponding propargyl alcohol and propargylic acid derivatives. Treatment of dialkyne **110** with acetylene in the presence of Wilkinson's catalyst gave chiral phthalide derivative **111** in good to excellent yields (Scheme 34). The best results were obtained when the reactions were carried out in toluene in the presence of acetylene gas and 5 mol-% of Wilkinson's catalyst.[66]



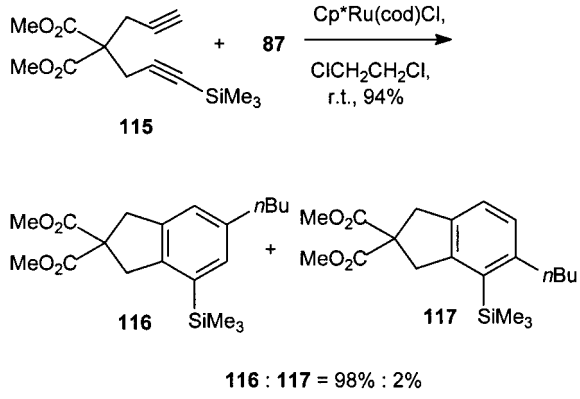
Scheme 34.

The same group has also reported a highly efficient synthesis of substituted carbazoles. The synthesis involved the assembly of the carbazole nucleus through an A to ABC ring formation (Scheme 35).[67] Diynes were prepared in three steps starting from the readily available 2-iodoanilines **112** with the Sonogashira reaction as a key step. Cyclotrimerization of dialkynes (e.g., **113**) with mono-alkynes (e.g., acetylene) proceeded smoothly in the presence of Wilkinson's catalyst under mild reaction conditions. A range of functional groups were tolerated under the reaction conditions, allowing the synthesis of a diverse set of carbazoles (e.g., **114**) in good yields.



Scheme 35.

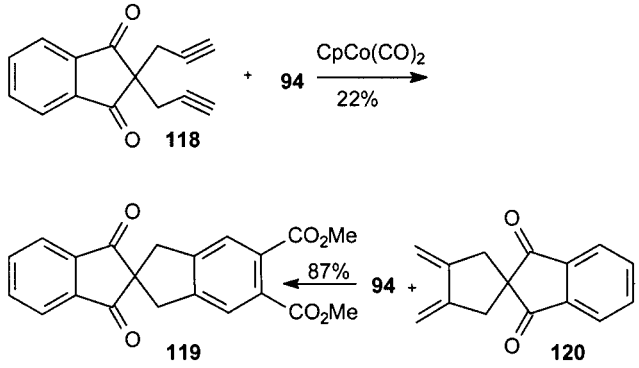
Cyclotrimerization of 1,6-diynes (e.g., **115**) with monosubstituted alkynes (e.g., **87**) with the aid of Cp*Ru(cod)Cl catalyst gave products (**116** and **117**) with *meta*:*ortho* regioselectivity as high as 98:2 (Scheme 36).[68] An insertion mechanism has been proposed to explain the *meta*-selectivity in this reaction.



Scheme 36.

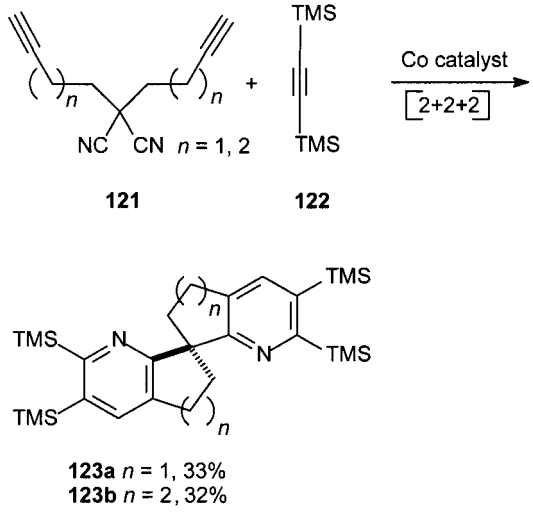
Witulski and co-workers reported that 4,6-disubstituted indolines could be prepared from α,ω-diynes with high regioselectivity by use of ruthenium-derived Grubbs' catalyst. In contrast, when the same dialkyne was treated with mono-alkynes in CH_2Cl_2 in the presence of Wilkinson's catalyst, 4,5-substituted indolines were formed as major products.[69]

Substituted spiro-indane-1,3-dione derivatives (e.g., **119**) were prepared through cobalt-catalyzed co-cyclotrimerization reactions.[70] Under high-dilution conditions, diyne **118** underwent co-cyclotrimerization with both mono- and disubstituted alkynes (e.g., **94**) to afford spiro-indane derivatives (e.g., **119**) in moderate yields (Scheme 37). An alternative strategy by a Diels–Alder approach involving diene **120** for the synthesis of similar products in good yields was also described.



Scheme 37.

Saá and co-workers have utilized cobalt-catalyzed [2+2+2] cycloadditions between bis-alkynenitriles (e.g., **121**) and alkynes such as **122** in one-step syntheses of spiropyridines such as **123**, a novel class of C_2-symmetric ligands (Scheme 38).[71] The same group have also performed a one-step, regioselective synthesis of symmetric and asymmetric 3,3′-disubstituted 2,2′-bipyridines by a cobalt-catalyzed [2+2+2] cycloaddition of the hex-5-ynenitrile and 1,3-diyne.[72]

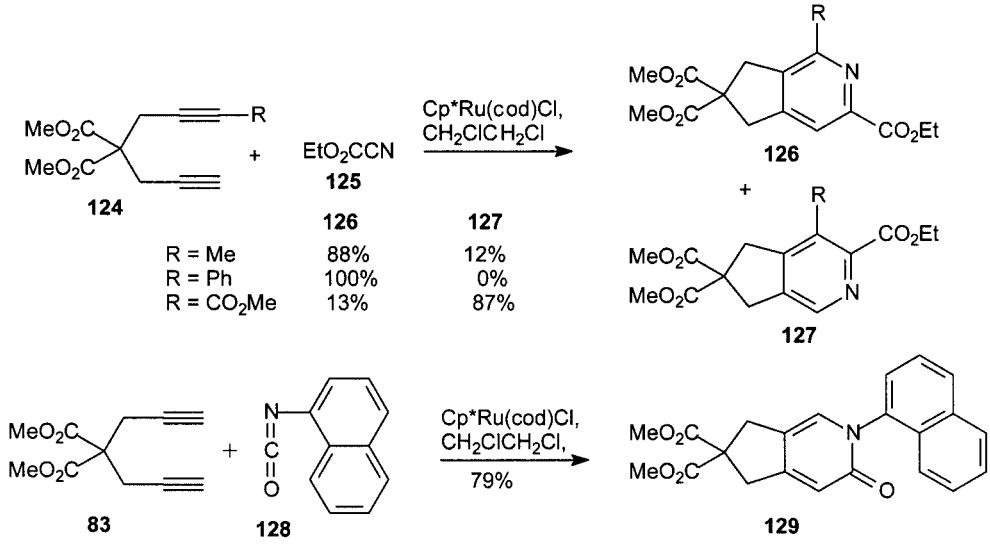


Scheme 38.

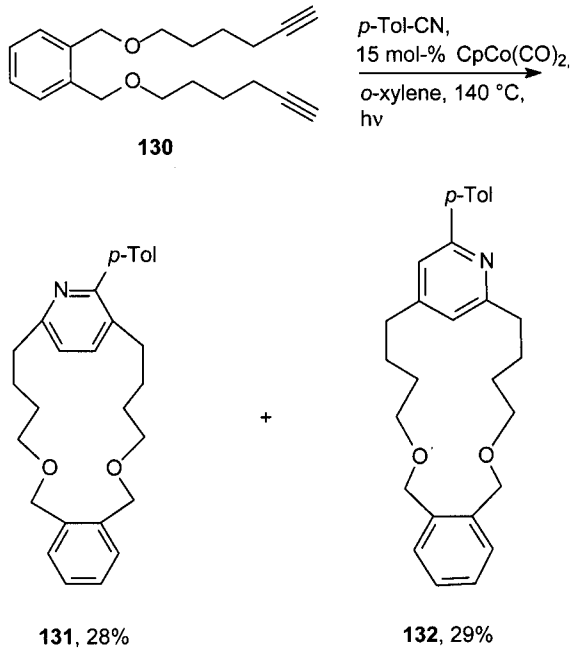
Yamamoto et al. have used Cp*Ru(cod)Cl catalyst for selective cyclotrimerization of unsymmetrical diynes (e.g., **124**) with electron-deficient nitriles (e.g., **125**; Scheme 39) to generate pyridine derivatives **126** and **127**.[73] The same catalyst has been used to catalyze [2+2+2] cycloadditions between 1,6-diynes such as **83** and isocyanates such as **128** to afford bicyclic pyridones such as **129** in 79% yield (Scheme 39).[74] When the reaction was carried out with use of cobalt catalyst[75] or nickel catalyst[76] either the yield of the reactions was low or no pyridone was formed. The same group has also studied the chemo- and regioselectivity of different Ru^{II} catalysts in [2+2+2] cycloadditions between 1,6-diynes and dicyanides for pyridine annulation.[77] This catalyst system appears to tolerate a wide range of functional groups and the trimerization reaction proceeds at room temp. in dichloromethane and does not require any special conditions.

Pyridine-cyclophanes of types **131** and **132** (Scheme 40) were prepared by macrocyclization of long-chain bis-alkynes **130** with nitriles or alkyne-nitriles and alkyne.[78] The regioselectivity of the product was dependent on the substitution on the bis-alkynes. Grigg and co-workers have synthesized intricate heterocyclic derivatives by rhodium-catalyzed [2+2+2] cycloaddition in combination with imine cycloaddition.[79] It was observed that solvent plays an important role in this process. When THF was used as a solvent the [2+2+2] cycloaddition reaction was able to occur at room temp., but the dimer was formed to a large extent. Surprisingly, the dimer was obtained as a minor product in toluene, but cyclotrimerization could be achieved in good yield at 110 °C.

Interestingly, [2+2+2] cycloaddition of alkynes has been found to be applicable in the preparation of long-chain molecules useful in materials science. A novel synthesis of oligo-*p*-phenylenes **134**, involving a rhodium-catalyzed alkyne trimerization as a key step, was recently reported by McDonald



Scheme 39.



Scheme 40.

and co-worker (Scheme 41).[80] Some of the phenylene products are remarkably soluble in organic solvents and are useful in the preparation of organic conducting and light-emitting polymers. It is worth mentioning that this type of multiple [2+2+2] cyclotrimerization reaction is so far a unique example.

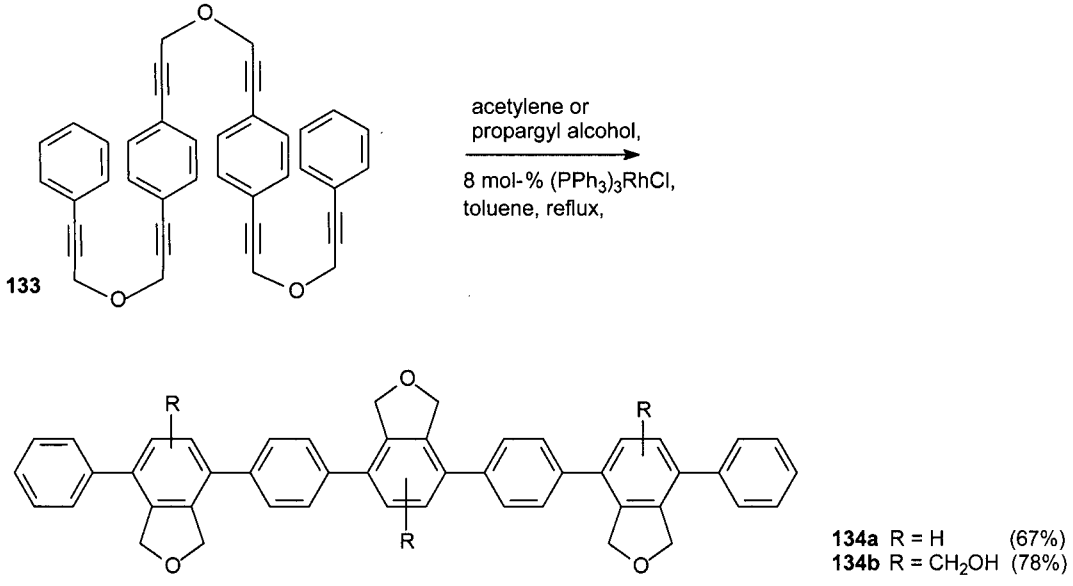
Therien and Fletcher reported the synthesis of a series of cofacial porphynato zinc(II) complexes **137** and **139** by sequential palladium-mediated cross-coupling and [2+2+2] cyclotrimerization of alkynes.[81] Later on, they disclosed electrochemical studies of these interesting molecules.[82] Quite remarkably, these structurally large and hindered alkynes gave cyclotrimerized products in good yields under $Co_2(CO)_8$ catalyst conditions (Scheme 42).

Several 6-aryl purines have been prepared by co-trimerization of 6-alkynylpurines (e.g., **140**) with diynes such as **141**.[83] The key co-trimerization reaction was catalyzed by Ni or Rh or Co-phosphane derived catalysts. The choice of the catalyst depends on the substitution patterns of both dialkyne and mono-alkyne (Scheme 43). Compounds containing the pyrimidine nucleus exhibit diverse physiological activities and this motif is present in a large number of biologically active molecules, including nucleic acids. Selective modification of the pyrimidine nucleus in nucleosides is a challenging task. With this as a goal, Vollhardt and coworkers studied the chemo-, regio-, and stereoselective participation of pyrimidine derivatives (e.g., **143** and **146**) in cobalt-mediated [2+2+2] cycloaddition reactions (Scheme 44).[84]

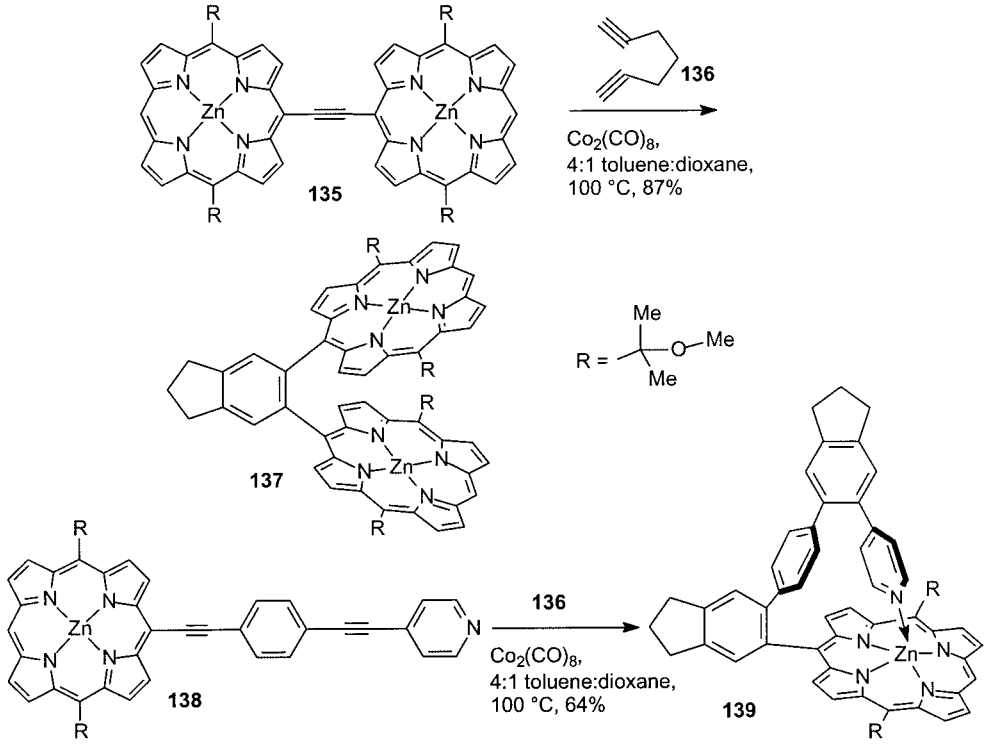
Vollhardt and co-workers have also used a [2+2+2] cycloaddition to prepare fused arylboronates. In this regard, $Co_2(CO)_6$-complexed alkynyl pinacolborane derivatives (e.g., **148**) have been shown to undergo cycloaddition to α,ω-diynes to generate fused arylboronates (e.g., **149**, Scheme 45).[85] Unlike conventional aryl boronic acid syntheses, this reaction tolerates a wide range of functional groups.

Cheng and co-workers have also developed a method for the construction of a fused cyclohexadiene ring on C_{60} (e.g., **150**) through nickel-catalyzed [2+2+2] cycloaddition between 1,6-diyne **83** and fullerene (Scheme 46).[86] Further, the cycloaddition product **150** was shown to undergo a [4+4] cycloaddition on irradiation at 350 nm, with the corresponding bisfulleroids being obtained in excellent yield.

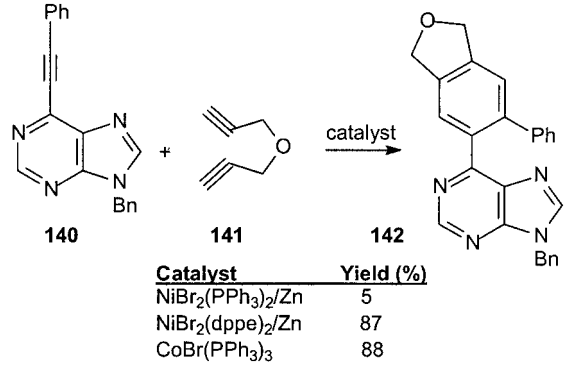
Co-cyclotrimerization of ferrocenylalkynes **151** with α,ω-diynes **98** to give functionalized ferrocenylarenes **152** has recently been studied under different catalyst conditions (Scheme 47).[87] It was observed that Wilkinson's catalyst



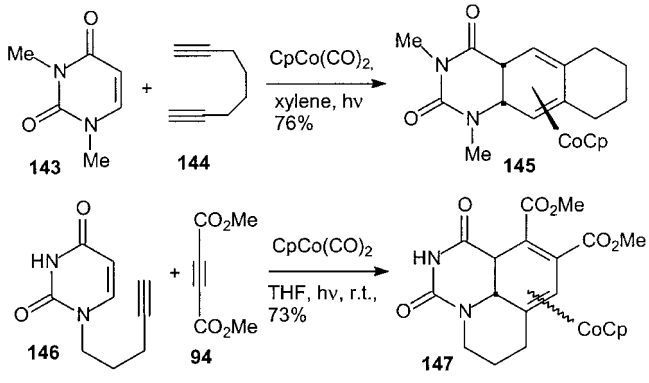
Scheme 41.



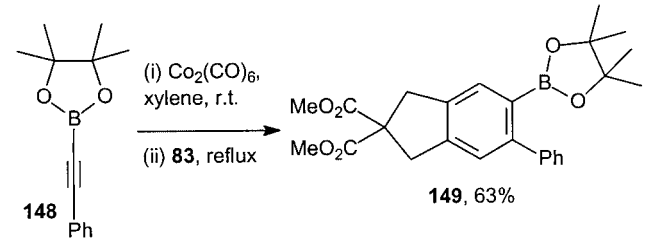
Scheme 42.



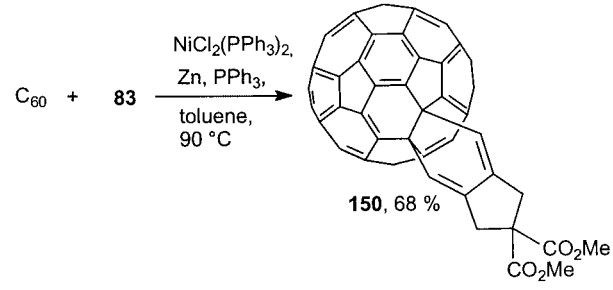
Scheme 43.



Scheme 44.



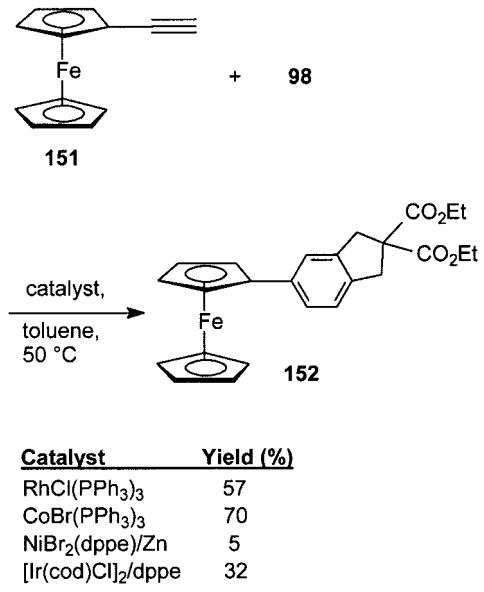
Scheme 45.



Scheme 46.

afforded the ferrocenylarenes in good yields and under mild conditions irrespective of the natures of the functional groups present.

Axially chiral biaryl compounds are useful ligands and they usually exhibit interesting biological activities. Gutnov,

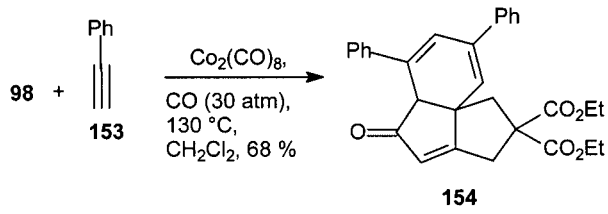


Catalyst	Yield (%)
$RhCl(PPh_3)_3$	57
$CoBr(PPh_3)_3$	70
$NiBr_2(dppe)/Zn$	5
$[Ir(cod)Cl]_2/dppe$	32

Scheme 47.

Heller, and co-workers reported the synthesis of chiral 2-arylpyridines through asymmetric [2+2+2] cycloadditions between nitriles and alkynes in the presence of chiral cobalt complexes such as $[Cp^RCo(cod)]$ (Cp^R = substituted cyclopentadienyl, cod = cycloocta-1,5-diene).[88a] Shibata and co-workers reported the synthesis of chiral teraryl compounds through iridium complex-catalyzed [2+2+2] cycloadditions of α,ω-diynes possessing *ortho*-substituted aryls on their termini and disubstituted alkynes. The high enantio- and diastereoselectivities were attributed to the steric hindrance between the substituents.[88b] Tanaka and co-workers have synthesized chiral phthalides bearing one or two oxymethylene functionalities through $[Rh(H_8\text{-binap})]$-catalyzed cross alkyne trimerization of unsymmetrical 1,6-diynes, with both terminal and internal alkynes.[88c]

The tricyclic enone **154** was synthesized through dicobaltoctacarbonyl-catalyzed [2+2+1] and [2+2+2] cycloaddition reactions in the presence of CO (Scheme 48). The reaction proceeds through a Pauson–Khand-type carbonylative cycloaddition between diyne **98** and CO to form the bicyclic cyclopentadienone, which further undergoes a [2+2+2] cycloaddition with two phenylacetylenes (**153**) to give the tricyclic product **154**. With diynes containing quaternary centers at the 4-position, the tricyclic enones are the sole products, but with other diynes the cycloaddition reaction took a different course.[88d] Cycloheptane-fused benzene compounds are generally difficult to synthesize. Green and co-workers synthesized $Co_2(CO)_6$-complexed cycloheptyne analogues that underwent cycloadditions with various alkynes to give cycloheptane-fused benzene derivatives in good yields.[88e]

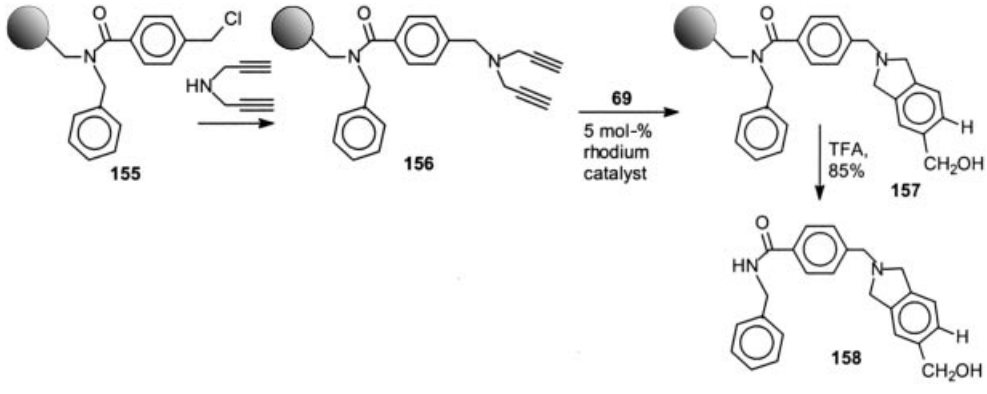


Scheme 48.

3.1 [2+2+2] Cycloaddition Reactions Involving Solid Supports

[2+2+2] Cycloaddition reactions on solid-phase have yet to be fully explored. Sun and co-workers have recently reported a rhodium-catalyzed [2+2+2] cycloaddition reaction under solid-phase conditions for the synthesis of a variety of isoindolines (Scheme 49).[89] A key dipropargyl substrate **156** was prepared from the commercially available 4-(4-formyl-3-methoxyphenoxy)-butyrylaminomethylated resin. Treatment of **156** with various mono-alkynes (e.g., **69**) under rhodium-catalyzed [2+2+2] cycloaddition conditions gave a series of isoindoline derivatives (e.g., **157**) in good yields, the trimerized products (e.g., **158**) being obtained after cleavage from the solid support with trifluoroacetic acid (TFA). Although the product **158** contained a trace amount of the linker, the method successfully demonstrated the application of a [2+2+2] cycloaddition reaction on a solid support.

Since cycloaddition reactions, like many other solid-phase reactions, are often plagued with steric hindrance problems, it is necessary to find an appropriate support,



Scheme 49.

linker, and monitoring protocol for this approach to become synthetically useful in a combinatorial fashion. Blümel and co-workers recently reported cyclotrimerizations of acetylenes catalyzed by silica-immobilized Ni catalyst. The catalyst could be recycled a dozen times and the final substrate conversion was around 30% to 40%, with turnover numbers (TONs) around 1500. Solid-state ^{31}P NMR spectroscopic data were used to optimize the stability and to minimize leaching of Ni catalyst for alkyne cyclotrimerization.[90]

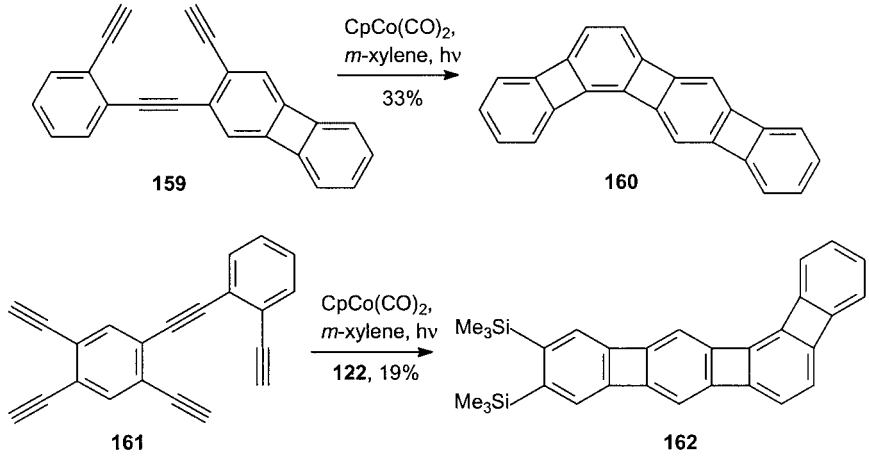
4. Totally Intramolecular Trimerization Reactions of Alkynes

The CpCo system has been a promising catalyst since pioneering work by Yamazaki and Hagihara.[91a] In this context, Vollhardt and co-workers have developed a synthetic strategy involving an intramolecular cyclotrimerization of a trialkyne for the synthesis of several natural products and theoretically interesting molecules.[91b] They have developed a simple strategy based on use of a bulky alkyne partner – bis(trimethylsilyl)acetylene (BTMSA) – that cannot undergo self-trimerization. Since then, a combination of $CpCo(CO)_2$ and the BTMSA reaction pathway has served as an attractive tool for the synthesis of many natural products and strained aromatic systems. Despite its efficiency in producing desired products, low yields (sometimes) and the use of special reaction conditions, such as high-dilution conditions and the requirement for BTMSA as solvent for the best results, have limited its utility in organic synthesis.

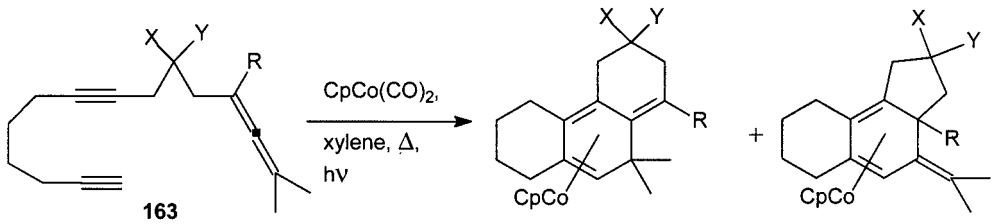
Syntheses of bent phenylene molecules through cobalt-mediated cyclotrimerization reactions have recently been described. The properties of such bent phenylene frameworks reflected the combined effects of linear and angular components of the [3]phenylene substructures (Scheme 50).[92] Triyne **159** underwent cobalt-catalyzed cyclization to give phenylene **160** in 33% yield. Similarly, compound **161** underwent simultaneous intra- and intermolecular [2+2+2] cycloaddition in BTMSA to produce phenylene derivative **162** in 19% yield. Some of the limitations of this approach are multistep synthetic sequence and low yields in the final step.

Along similar lines, the same group has reported syntheses of angular [4]phenylene,[93] *anti*-[5]phenylene derivatives,[94] and *syn*-doubly bent [5]phenylene derivatives[94] by cobalt-catalyzed cyclization of suitably constructed multiynes. Among the angular phenylene molecules for $n > 5$, the structures become helical and have attracted the attention of theoretical chemists. Vollhardt and co-workers have synthesized the helical phenylenes (heliphenes) angular [6]-, [7]-, [8]-, and [9]phenylene by a cobalt-catalyzed cyclotrimerization strategy.[95a–95b] They have also synthesized C_{3h}-symmetric [7]phenylene by cobalt-catalyzed cycloisomerization of an appropriate nonayne. These molecules represent the substructure of archimedene, C_{120}.[95c]

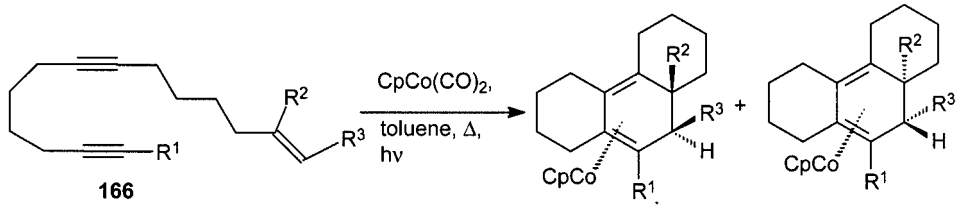
Malacria and co-workers have used the $CpCo(CO)_2$ complex for an intramolecular [2+2+2] cyclization of allenediyne **163** (Scheme 51).[96] The reaction occurred with high regio- and diastereoselectivity. The regioselectivity of the reaction varies, resulting in either η^4 complexed tricyclic [6.6.6] or [6.6.5] compounds depending on the situation of the allene. This method has been extended further to study of the intramolecular [2+2+2] approach with optically active allenediynes, and a high degree of optical induction was observed.[97] The same group has reported that the diastereoselectivity of cobalt-mediated [2+2+2] cyclizations of enediynes (Scheme 51) can be improved by substitution of the triple or the double bond with ester, phosphane oxide, or sulfoxide moieties (e.g., **166**).[98a] Among these, the ester and phosphane oxide groups are more suitable for asymmetric studies, due to the stability of the complexed cycloadduct and high yield of the cyclization. This strategy was further extended to derivatives based on chiral esters and chiral phosphane oxides.[98b] It was observed that a high degree of asymmetric induction could be achieved during the cyclization through proper choice of the substituent on the chiral phosphane oxide. With a chiral ester the level of asymmetric induction was low; initial coordination be-



Scheme 50.



	Yield (%)	164	165
a X,Y = H, R = H	72	0%	100%
b X,Y =  , R = *t*Bu	80	0%	100%
c X,Y = " , R = Ph	87	100%	0%
d X, Y = " , R = Me	70	100%	0%

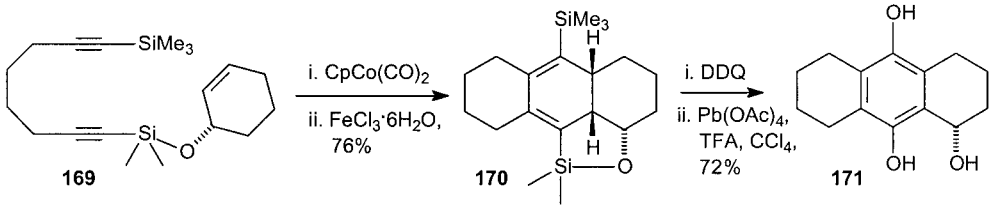


R^1	R^2	R^3	Yield (%)	*exo*	*endo*
CO_2Me	H	H	94	60%	40%
$Ph_2P(O)$	H	H	96	75%	25%
p-TolS(O)	H	H	31	76%	24%

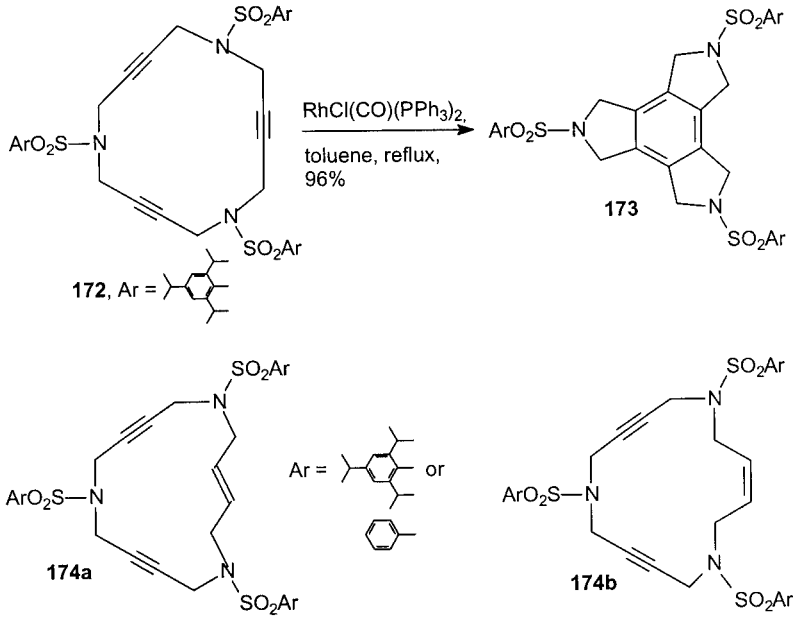
Scheme 51.

tween the cobalt moiety and the chelating site of the substituent on phosphorus appear to be the determining factor for *endo*/*exo* selectivity. Another example of enantioselective synthesis involves the synthesis of optically active helicene compounds through nickel(0) [$Ni(cod)_2$]-mediated intramolecular [2+2+2] cyclization of the triynes in the presence of chiral phosphane ligands.[98c,98d] Under these conditions the absolute stereochemistry can be controlled during the helix-formation stage. Initially, the reaction was attempted with Grubbs catalyst, but that reaction failed. The desired cyclization was achieved with the aid of $Co_2(CO)_8$ and $CpCo(CO)_2$, and the helicene compound was obtained in a moderate yield.

In the field of the synthesis of linear annelated polycyclics such as 1,9,10-trihydroxy octahydro anthracene (**171**), Groth and co-workers have used a cobalt-mediated [2+2+2] cycloaddition of enediynes **169** (Scheme 52).[99a] These compounds (e.g., **171**) represent the ABC ring systems of many anthracyclin antibiotics such as daunomycin. Prior to the cyclization, the diyne and the olefin were linked through a temporary silicon tether (e.g., **170**), which accelerated the reaction with high regioselectivity. The silicon tether was cleaved either by oxidation or by hydrolysis. Malacria and coworkers have used disposable silylated tethers for chemo- and regioselective cobalt-mediated [2+2+2] cyclizations of three different alkynes in boiling xylene under irradiation.[99b] Cyclotrimerization and subsequent displacement of the silylated groups gave functionalized polysubstituted arenes in high yield. The same group has developed an alternative catalyst (in situ generation of catalyst from CoI_2, PPh_3, and Mn) that can effect the cyclization at room temp.[99c] Depending on the size of the alkyl chain, benzene ring fused with four-, five-, and six-membered rings were obtained. Recently, Roglans and co-workers have studied [2+2+2] cyclizations of nitrogen-containing macrocyclic triynes and macrocyclic enediynes under different catalyst conditions.[100] It was found that the $RhCl(CO)(PPh_3)_2$ complex catalyzed the cycloisomerization reaction more efficiently than all other catalysts.



Scheme 52.



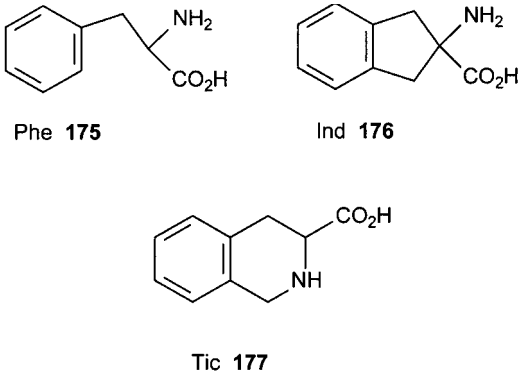
Scheme 53.

Cycloisomerization of **172** with 5 mol-% $RhCl(CO)(PPh_3)_2$ in toluene at reflux, for example, afforded the triazaindane derivative **173** in 96% yield (Scheme 53). This methodology was extended to macrocyclic *trans*- and *cis*-enediynes of types **174a** and **174b** respectively.

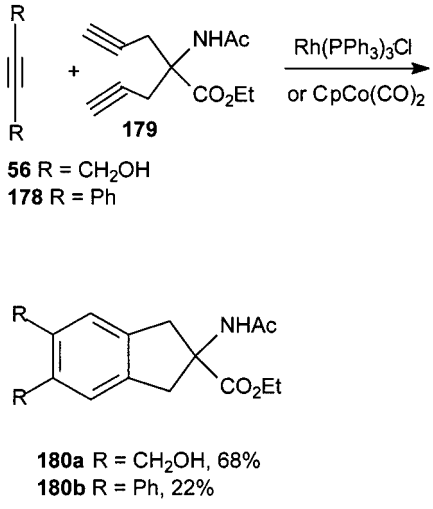
5. Application of [2+2+2] Cycloadditions in Organic Synthesis

5.1 Synthesis of Unusual Amino Acids and Peptides

Synthetic α-amino acids (AAAs) bearing unusual side chains have found widespread use in peptide design. In particular, α,α-disubstituted AAAs are used as a means of controlling the secondary structure of a peptide. Incorporation of unusual AAAs into peptides may provide unique analogues, biologically more active and resistant to enzymatic degradation. As part of a general program directed towards the synthesis of unusual AAAs, we conceived a "Building Block Approach" involving cycloaddition, metathesis, and Suzuki coupling reactions as key steps.[101] Our early approaches for the synthesis of 2-indanylglycine (**176**, Ind) and tetrahydroisoquinoline-3-carboxylic acid (**177**, Tic) derivatives involve a [2+2+2] cycloaddition reaction as a key step. The Ind- and Tic-based AAAs are constrained analogue of phenylalanine (**175**, Phe), and the former has been utilized in the synthesis of peptides with agonistic and antagonistic activity towards the angiotensin II receptor.



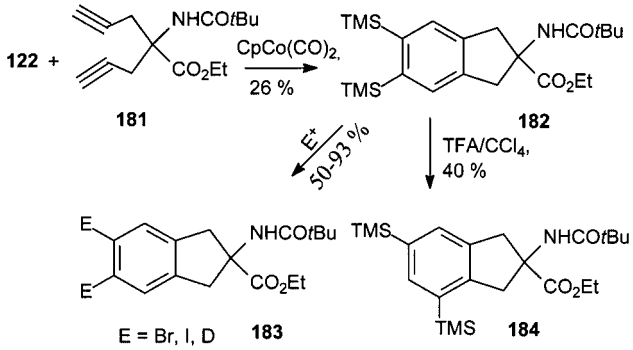
As shown in Scheme 54, the dialkyne building block **179**, containing an AAA moiety, underwent co-cyclotrimerization with various alkynes (e.g., **56**) in the presence of Wilkinson's catalyst to generate various Ind derivatives **180a**.[102] Diyne building block **179** can readily be prepared by dipropargylation of ethyl isocyanoacetate and a subsequent hydrolysis and protection sequence. Wilkinson's catalyst was found to be effective for both symmetrical and unsymmetrical mono-alkynes containing the hydroxy functionality. For other alkynes devoid of hydroxy substitution



Scheme 54.

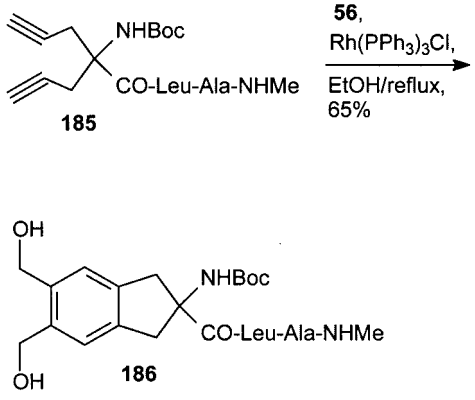
(e.g., **178**), cobalt catalyst $CpCo(CO)_2$ was found to be suitable (Scheme 54).[103a] Under cobalt catalyst conditions, bulky alkynes such as BTMSA and diphenylacetylene also gave the required co-trimerized products. The dihydroxy derivative **180a** was found to be useful for production of the *o*-xylylene intermediate[103b] suitable for further annulation sequence.[103c,103d]

The silyl derivative **182**, prepared through the reaction between BTMSA and dialkyne **181**, underwent electrophilic substitution reactions *ipso* to the silicon with various electrophiles to generate other AAA derivatives (Scheme 55).[104] Treatment of **182** with bromine or iodine chloride, for example, afforded the corresponding halogen derivatives **183**, substrates with great potential for further modification, such as through palladium-mediated cross-coupling reactions.[105] In the presence of TFA in CCl_4, the *ortho* silyl compound **182** rearranged to the *meta* silyl derivative **184**.



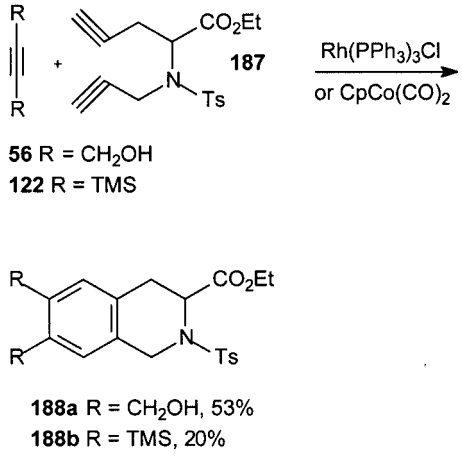
Scheme 55.

To expand the scope of the above methodology for peptide modification, building block **181** has been incorporated in tripeptide **185**. Under rhodium-catalyzed conditions, peptide **185** underwent co-cyclotrimerization with, for example, the mono-alkyne but-2-yne-1,4-diol (**56**), to give compound **186** in good yield (Scheme 56).[106] Various other di- and tripeptides were also found to be suitable for this method.

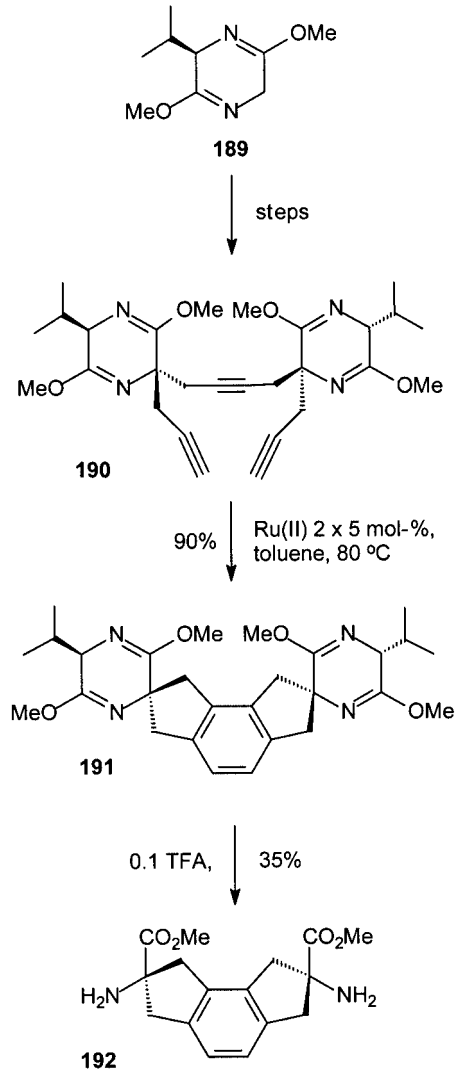


Scheme 56.

Tic (**177**) is an important constrained analogue in the design of δ-opioid peptide antagonists with useful therapeutic applications. The Tic moiety is also an important structural element present in alkaloids and some medicinally interesting molecules. A series of Tic derivatives **188** have been synthesized by alkyne co-trimerization reactions.[107–108] Diyne **187**, the starting material for the synthe-



Scheme 57.



Scheme 58.

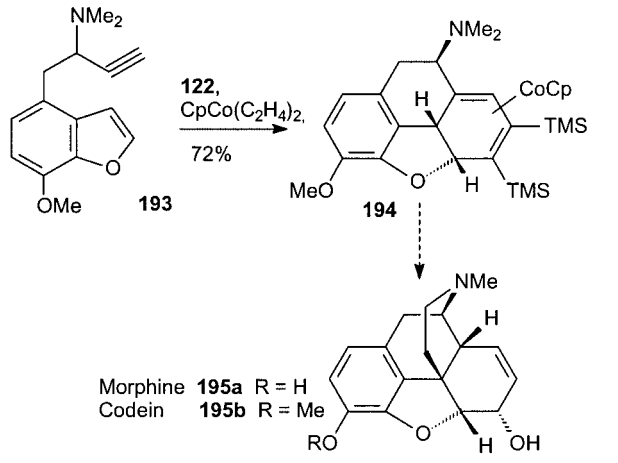
sis of Tic derivatives, was synthesized from benzophenone Schiff's base ester by a four-step sequence. Treatment of the diyne **187** with various mono-alkynes (e.g., **56**, **122**) in the presence of Wilkinson's catalyst or $CpCo(CO)_2$ proceeded smoothly to afford various Tic derivatives **188** in good to moderate yields (Scheme 57). Alkynes with hydroxy substituents gave good yields of Tic derivatives under Wilkinson's catalyst conditions, while $CpCo(CO)_2$ catalyst was effective for other alkynes, including silyl-substituted alkynes. Recently, Yamamoto and co-workers have used [2+2+2] cycloadditions for the synthesis of conjugated amino acid–sugar hybrids. In this regard, an *N*-dipropargylated glutamic acid derivative was treated with *C*-alkynylglycosides at room temp. to provide amino acid–sugar hybrid molecules in 83% yield.[109a]

Undheim and co-workers reported a Ru^{II}-catalyzed cascade ring-closing metathesis (RCM) approach for the construction of bis-indane-based AAA derivatives (Scheme 58).[109b] Trialkyne **190** was prepared stereoselectively from a chiral auxiliary **189** – (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine – by initial construction of an alkyne bridge and subsequent introduction of a propargyl group on each of the chiral auxiliary moieties. Highly constrained trialkyne **190** underwent a cascade of RCM sequence in the presence of ruthenium catalyst to afford the pentacyclic product **191** in 90% yield. Mild hydrolysis of compound **191** afforded the amino ester **192** in 35% yield.

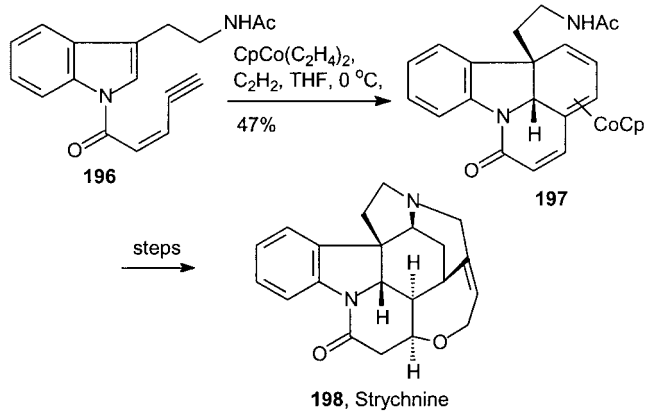
5.2 Synthesis of Natural Products

In continuation of their earlier studies,[110] Vollhardt's group recently reported a stereoselective cobalt-mediated [2+2+2] cycloaddition reaction for the synthesis of morphine (**195a**), a framework also present in other opioid alkaloids such as thebaine and codeine (**195b**) (Scheme 59).[111] The key tetracyclic complex **194** was obtained through a [2+2+2] addition reaction between BTMSA and a suitably functionalized benzofuran derivative **193** in the presence of $CpCo(C_2H_4)_2$ as catalyst. It appears that the formation of complex **194** was completely stereospecific under the reaction conditions, as only one of four possible diastereomers was isolated.

A similar strategy has been employed in the formal total synthesis of isostrychnine and strychnine **198** through a $CpCo(C_2H_4)_2$-mediated [2+2+2] cycloaddition reaction (Scheme 60).[112a] Various approaches for the racemic synthesis of strychnine based on [2+2+2] cycloaddition reactions between an alkynylindole moiety and acetylene have been reported. Earlier, the same group studied regioselective [2+2+2] cycloadditions of the 2,3-double bonds of acetyl- or phenylsulfonylindole with various terminally substituted α,ω-diynes.[112b] A 14-step convergent synthesis directed towards the synthesis of strychnine (**198**) begins with tryptamine derivative **196**, which is converted into the tetracyclic lactam framework **197** of strychnine in the presence of $CpCo(C_2H_4)_2$ and acetylene gas. The reaction proceeded with complete diastereoselectivity, producing a key intermediate **197** as a single diastereomer in 47% yield, the intermediate **197** subsequently being converted into strychnine (**198**).

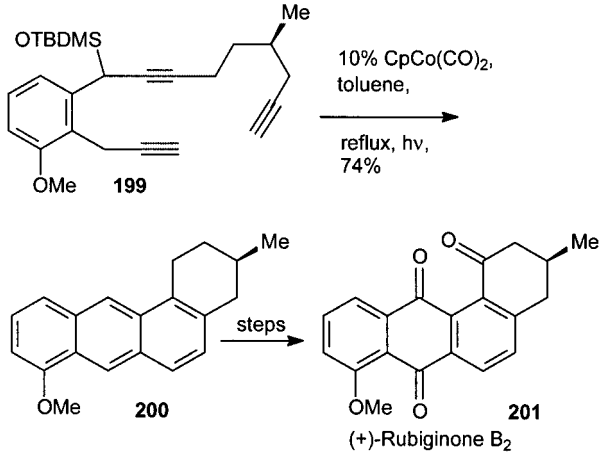


Scheme 59.



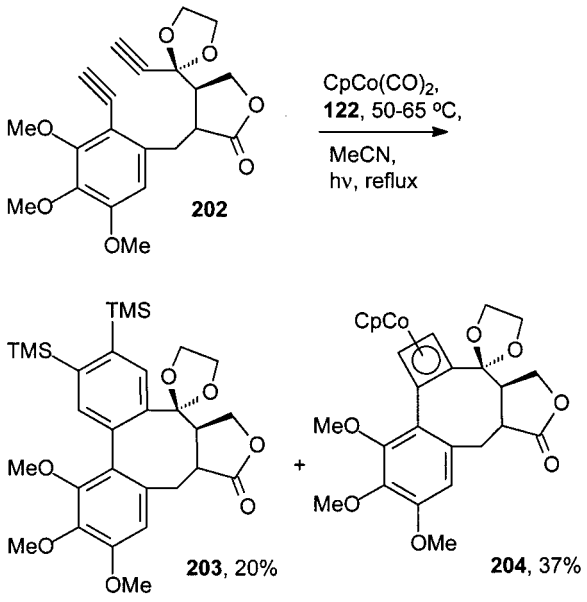
Scheme 60.

Groth and co-workers have reported a novel approach to the angucyclinone antibiotic (+)-rubiginone B_2 (**201**) from *R*-(+)-citronellal through an intramolecular cobalt-mediated [2+2+2] cycloaddition of the triyne precursor **199** (Scheme 61).[113] The chiral synthesis of (+)-rubiginone B_2 was achieved in 11 steps and in 15% overall yield.



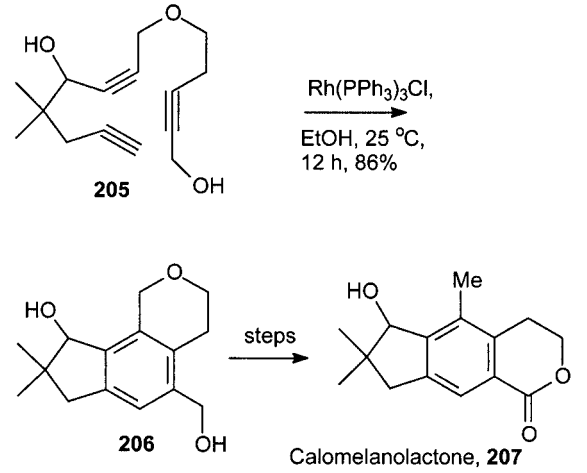
Scheme 61.

Motherwell and co-workers have reported a concise and elegant approach to the synthesis of steganone analogues (Scheme 62).[114] Here, a cobalt-mediated partially intramolecular [2+2+2] cycloaddition reaction was used as a key step. As shown in Scheme 62, a tethered deca-1,9-diyne **202** was treated with BTMSA under photochemical conditions in the presence of $CpCo(CO)_2$ and acetonitrile at 50–65 °C. Along with the required product **203** (20% yield), an unwanted byproduct **204** was also formed (37% yield). Later on, deprotection and selective mono- or diprotodesilylation of **203** in the presence of TFA generated steganone analogues in good yields.



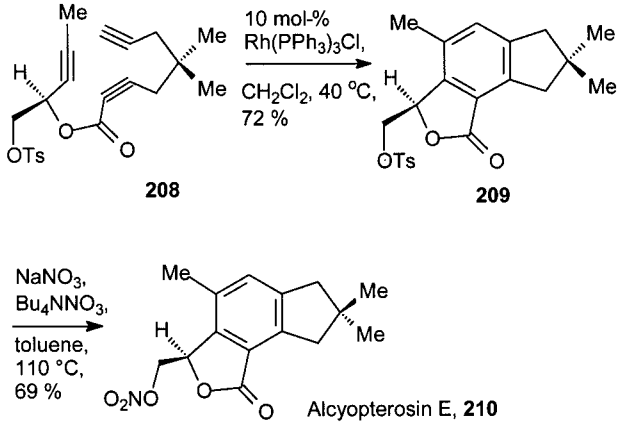
Scheme 62.

Stevenson used Wilkinson's catalyst for the total synthesis of sesquiterpenoid calomelanolactone (**207**).[115] The triyne **205** underwent a fully intramolecular trimerization in the presence of Wilkinson's catalyst to give compound **206** in 86% yield, and this was further elaborated to the required natural product **207** (Scheme 63).



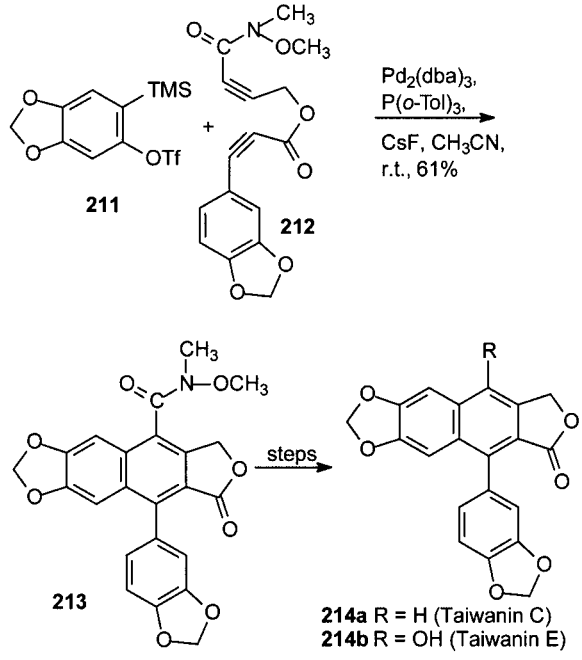
Scheme 63.

Recently, Witulski et al. have reported Wilkinson's catalyst-mediated intramolecular cyclization of alkynes for the total synthesis of the sesquiterpenoid alcyopterosin E (**210**), an illudalane-type sesquiterpenoid isolated from marine sources.[116] Their approach involves assembly of the tricyclic core **209** by a concise ABC ring formation through an intramolecular rhodium(I)-catalyzed alkyne cyclotrimerization reaction, the key building block trialkyne **208** thus being prepared from commercially available isophorone and a chiral propargylic alcohol. Enantiomerically pure trialkyne ester **208** was treated with 10 mol-% of Wilkinson's catalyst in CH_2Cl_2 at 40 °C to afford cyclotrimerized product **209** in 72% yield, and this was converted into alcyopterosin E (**210**; Scheme 64).



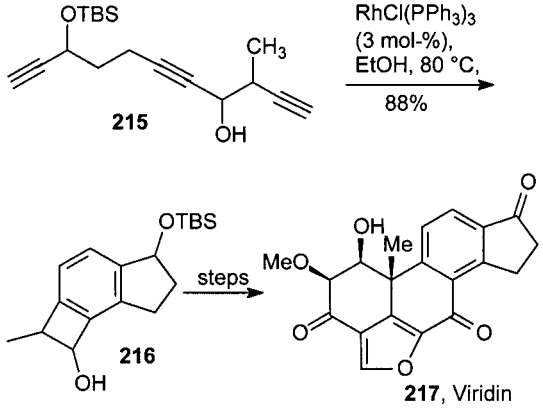
Scheme 64.

The key intermediate aryl naphthalene derivative **213** required for the total synthesis of taiwanins C and E (**214a** and **214b** respectively) was synthesized by palladium(0)-cat-



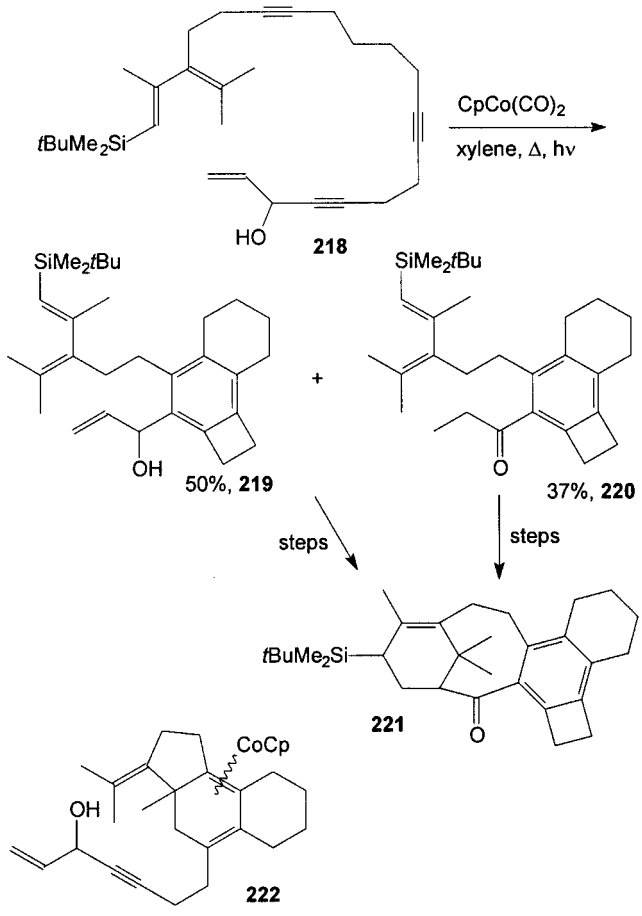
Scheme 65.

alyzed [2+2+2] cocyclization of diyne **212** and the benzyne species derived from **211** (Scheme 65).[117] Viridin, a furanosteroidal antibiotic, is used for the treatment of neoplasms and other diseases. Sorensen and co-workers have synthesized (±)-viridin (**217**) by use of a [2+2+2] cycloaddition reaction as a key step (Scheme 66).[118] This step also provides an efficient approach to the formation of the aromatic C-ring of an eventual steroid skeleton.



Scheme 66.

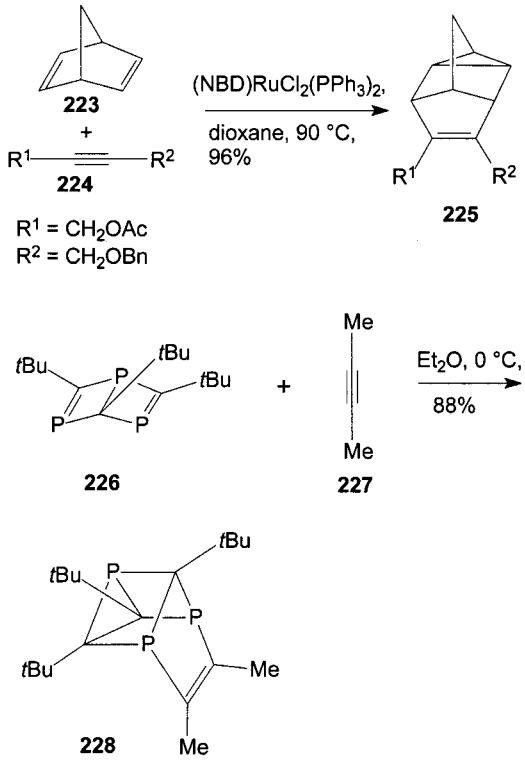
Malacria and co-workers have developed an efficient route to construct the taxoid ABC core by employing stepwise [2+2+2] and [4+2] cycloaddition reactions.[119] The intramolecular cyclotrimerization of polyenyne precursor **218** in the presence of $CpCo(CO)_2$ gave the expected product **219** along with minor product **220**. Both products were converted into taxoid **221** by use of intramolecular Diels–Alder reactions as key steps. The presence of the TBDMS group prevented the intramolecular [4+2] diyne–alkene cycloaddition in **218** and suppressed the formation of complex **222** (Scheme 67).



Scheme 67.

5.3 Miscellaneous Approaches to Polycyclic Systems Based on [2+2+2] Cycloaddition Reactions

Transition metal catalyzed [2+2+2] homo-Diels–Alder (HDA) reactions are important reactions in nonconjugated systems, one example being that of norbornadiene to generate a tetracyclic structure such as a deltacyclene. Lautens and co-worker have reported several examples of HDA [2+2+2] cycloaddition on norbornadiene systems.[120] The same group has also shown that HDA reactions can be used as key reactions to synthesize a number of natural products containing diquinane and triquinane units.[121] Generally Ni and Co catalysts are used for HDA reactions.[120] Tenaglia and Giordano have recently reported that HDA reactions between functionalized disubstituted alkynes such as **224** and norbornadiene (NDA, **223)** can be achieved through the use of readily available phosphane ruthenium(II) complexes as catalysts (Scheme 68).[122] Triphospha-bishomoprismanes, (e.g. **228**) were prepared in good yields by HDA cycloadditions between 2,4,6-tri-*tert*-butyl-triphospha-



Scheme 68.

Dewar-benzene **226** and substituted and unsubstituted acetylenes (e.g., **227**).[123]

6. Conclusions

The [2+2+2] cycloaddition strategy is complementary to the well known Diels–Alder approach. It appears that [2+2+2] cycloaddition is useful for the design of a variety of molecular frames ranging from intricate natural products to theoretically interesting molecular entities. With the design of new catalyst systems, several labile partners not previously amenable towards [2+2+2] cycloaddition have been shown to undergo cyclotrimerization. With these advances in hand, several regiochemical problems have been solved. The problem associated with the [2+2+2] cycloaddition strategy is that the preparation of the key building blocks necessary for the total synthesis of target molecule generally requires a lengthy synthetic sequence. We anticipate that several new catalysts and interesting targets will continue to appear in the literature[124] at an accelerating rate.

Acknowledgments

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