

# [2+2+2] Cycloaddition Reactions Catalyzed by Transition Metal Complexes

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**Abstract:** Recent progress in the synthesis of benzene and 1,3-cyclohexadiene derivatives, and heterocyclic compounds such as pyridines, pyridones, pyrans, pyrimidine diones, etc, has been reviewed. The general mechanistic aspects of the [2+2+2] cycloaddition reaction are discussed. The asymmetric variants of these reactions are also discussed along with the proposed models of asymmetric induction.

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**Keywords:** arenes; catalysis; cycloaddition; heterocycles; metallacycles; transition metals

## 1 Introduction

The significance and increasing popularity of [2+2+2] cycloaddition reactions is evident from the number of reviews that have recently appeared in the literature.<sup>[1–3]</sup> The [2+2+2] cycloaddition reaction is remarkable in terms of its ability to utilize various unsaturated substrates such as alkynes, diynes, alkenes, imines, isocyanates, isothiocyanates, and CO<sub>2</sub> in the synthesis of a broad variety of highly substituted cyclic molecules such as benzenes, pyridines, pyridones, 1,3-cyclohexadienes, pyrones, thiopyridones and cyclohexanes. Multisubstituted benzenes and pyridines have traditionally been synthesized by aromatic electrophilic substitution (AES) reactions and a varie-

ty of metal-mediated coupling reactions. Although, these reactions are extremely efficient, they generally involve multistep syntheses. The application of AES reactions in the synthesis of polysubstituted aromatic rings is limited by the effect of the substituent groups and, hence, it may be very difficult or even impossible to add various functionalities at a specific position on the aromatic ring. On the other hand, [2+2+2] cycloaddition reactions are extremely atom-efficient and involve the formation of several C–C bonds in a single step. Another important feature of the [2+2+2] cycloaddition reaction is tolerance of a myriad of functional groups such as alcohols, amines, alkenes, ethers, esters, halogens, and nitriles. Moreover, the availability of numerous catalytic systems that have

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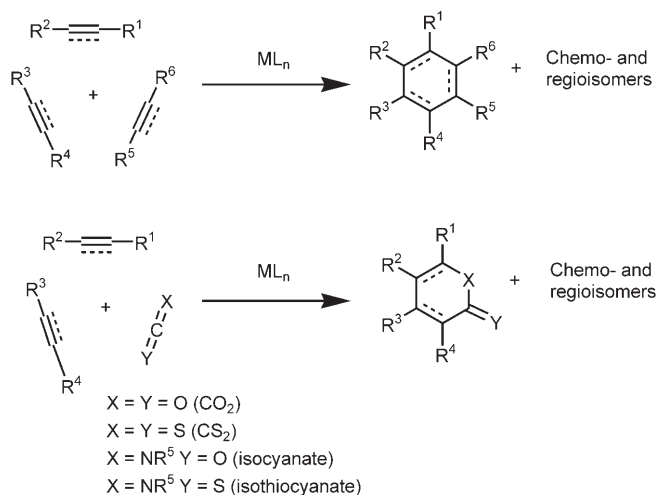


been efficient in tedious syntheses highlights the applicability of the [2+2+2] cycloaddition reaction. These are important requirements for the [2+2+2] cycloaddition reaction to become a universal synthetic tool for the synthesis of benzene, pyridine, and other cyclic derivatives. An important problem with the [2+2+2] cycloaddition reaction is the lack of chemo- and regioselectivity observed in earlier reported reactions. However, significant effort has been focused on attaining a high degree of chemo-, regio- and even

enantioselectivity with considerable success as evident from recent reports.

Excellent reviews on [2+2+2] cycloaddition reactions are available. Kotha and co-workers have reviewed the synthesis of benzene derivatives by the cyclotrimerization of three alkyne functionalities utilizing transition metal systems as catalysts.<sup>[1]</sup> Their review is divided into: (a) intermolecular reactions – in which the three pi (alkyne) systems are part of three different molecules, (b) partially intermolecular reactions – two pi systems are connected, and (c) totally intramolecular reactions – all three alkyne moieties are present in the same molecule. They have also discussed the application of the [2+2+2] cycloaddition reaction in the synthesis of amino acids, peptides, and natural products. Varela and Saá have reviewed the construction of pyridine rings by [2+2+2] cycloaddition.<sup>[2]</sup> They have discussed the utility of Co, Rh, Fe, Ru, Ti, and Ta metals and Zr/Ni, and Zr/Cu binary systems. The utility of Co, Ru, and Zr/Ni binary systems in the synthesis of pyridones has also been discussed. The intramolecular cycloaddition of  $\alpha,\omega$ -diynes with monoynes resulting in the formation of polysubstituted benzene derivatives was reviewed by Yamamoto.<sup>[3c]</sup> Malacria et al. have reviewed the recent progress in [2+2+2] cycloaddition reactions with a focus on Co-mediated reactions.<sup>[3f]</sup> The use of heteroatom-bearing alkynes in cycloaddition reactions has also been reviewed.<sup>[3g]</sup> This review will focus on the [2+2+2] cycloaddition reactions for the synthesis of benzene, pyridine, and pyridone derivatives that have appeared in the literature recently (after the publication of the aforementioned reviews) and other important molecules such as pyrones, indanones, indanes, thiopyranimines, dithiopyrones, cyclohexadienes, triazines, vinylogous amides, pyrans, etc. Every effort has been made to avoid repetition, even so, some overlap is unavoidable. This review is divided into sections based on the metal catalyst utilized in the [2+2+2] cycloaddition reaction, and subsections based on the type of molecule being synthesized.

A simplistic representation of a [2+2+2] cycloaddition reaction is shown in Scheme 1. It is clear that a broad variety of molecules can be assembled utilizing this methodology. Before we delve into the specific examples of [2+2+2] cycloaddition reactions, it is essential to gain some insight into its mechanistic aspects. Despite the large number of metal catalysts employed and an even larger number of substrates utilized in these reactions, the mechanism is relatively similar and straightforward in most cases (Scheme 2).<sup>[4]</sup> The reaction of two monoynes (or one  $\alpha,\omega$ -diyne) with the metal catalyst results in the formation of a metallacyclopentadiene system.<sup>[5]</sup> In the presence of a heteroatomic pi system, formation of a heteroatomic metallacyclopentadiene system is also reported. The third pi system is then inserted into a C–M bond re-



**Scheme 1.** [2+2+2] cycloaddition reactions.

sulting in the formation of a seven-membered metal-containing ring. Reductive elimination finally yields the cycloaddition product. Depending on the reaction system, catalyst, and substrates involved, subtle variations in the mechanism are observed. Also, the reaction may result in the formation of other intermediates, mainly complexes, involving coordination of the pi system with the metal center in the mechanistic pathway. Several computational calculations that provide valuable insight into various steps involved in cyclootrimerization reactions have been reported.<sup>[5c-g]</sup>

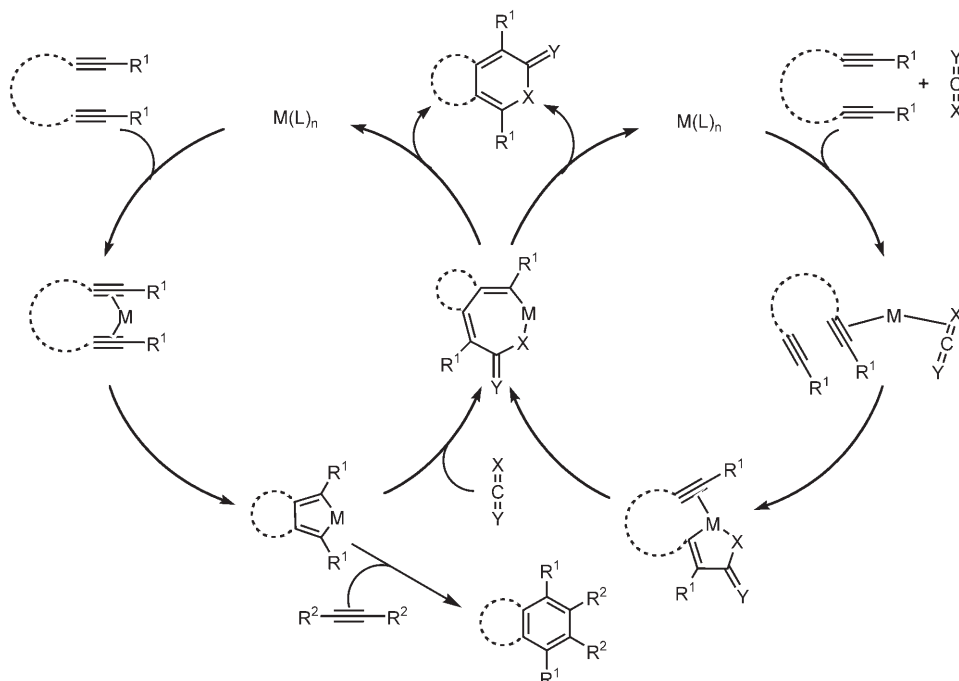
## 2 Cobalt-Catalyzed [2+2+2] Cycloaddition

Cobalt is one of the most commonly utilized metal catalysts in [2+2+2] cycloaddition reactions. The numerous applications of  $\text{CpCo}(\text{CO})_2$  in the preparation of natural products, pharmaceutically significant molecules and functional materials are well known.<sup>[6]</sup>

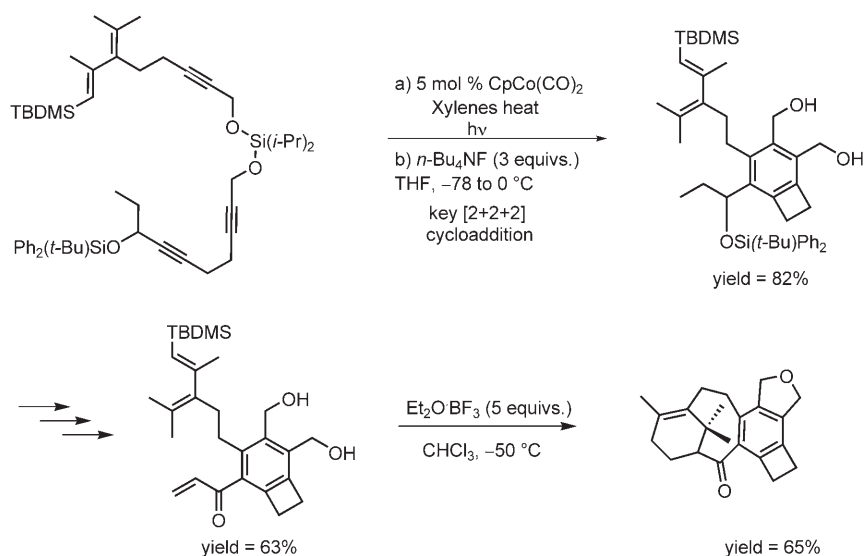
### 2.1 Synthesis of Substituted Benzene Derivatives

The application of the polycyclic taxane ring system has been reported by Malacria and co-workers.<sup>[7]</sup> A [4+2]/[2+2+2] cycloaddition of acyclic polyunsaturated substrates afforded the taxane core functionality in good yields. Although [4+2] cycloadditions have been utilized in other total synthesis of taxol, this is the first example of the use of cobalt-mediated [2+2+2] cyclization in conjunction with [4+2] cycloaddition (Scheme 3).

Groth and Kesenheimer have utilized the Co-mediated [2+2+2] cycloaddition in the synthesis of the core structure of several antibiotics, especially the angucyclines. They have reported the total synthesis of (-)-8-*O*-methyltetrangomycin (MM 47755), which belongs to the angucyclinone class of antibiotics.<sup>[8]</sup> This analogue has shown activity mainly against Gram-positive bacteria such as *Bacillus subtilis*. A totally intramolecular reaction involving a triyne system which undergoes cyclootrimerization to form a tetrasubstituted

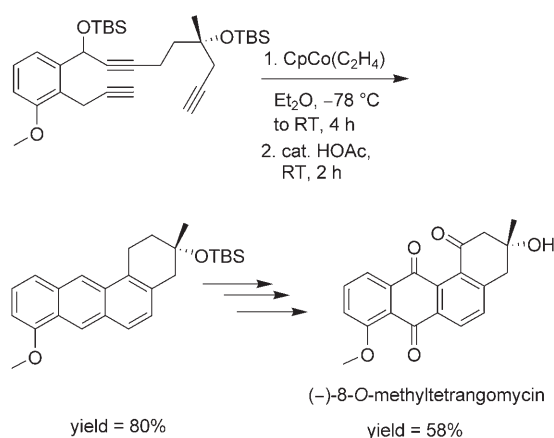


**Scheme 2.** A general mechanistic pathway for [2+2+2] cycloaddition reactions.



**Scheme 3.** Application of [2+2+2] cycloaddition in the synthesis of taxane core.

ed benzene derivative is the key step in this synthesis. A similar report from the same group had earlier demonstrated the utility of [2+2+2] cycloaddition in the synthesis of a benz[*a*]anthraquinone moiety by the totally intramolecular cyclotrimerization of three alkyne functionalities using  $\text{CpCo}(\text{ethene})_2$  complex (Scheme 4).<sup>[9]</sup>

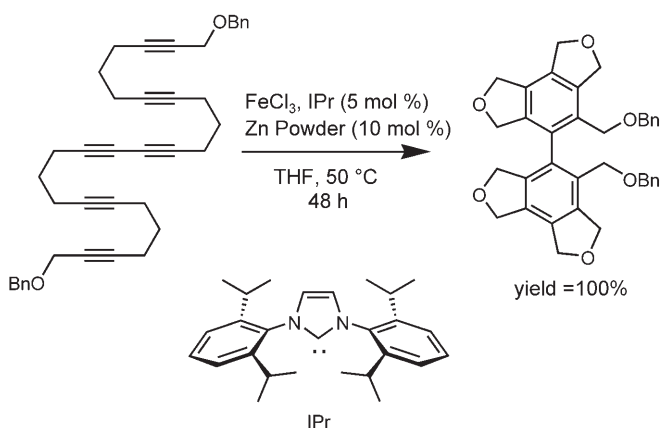


**Scheme 4.** Application of [2+2+2] cycloaddition in the total synthesis of (-)-8-*O*-methyltetragomycin (MM 47755) antibiotic.

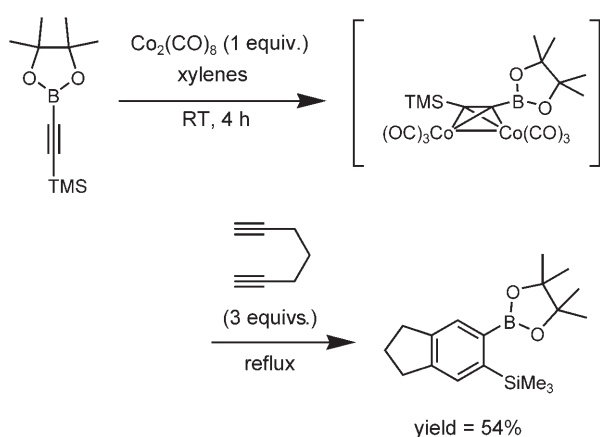
Although  $\text{CpCo}(\text{CO})_2$  is the most commonly utilized cobalt catalyst,<sup>[10]</sup> the use of CO-free Co catalysts has also been reported. Recently, Okamoto has described a novel Cp- and CO-free system for the cyclotrimerization of triynes which is catalyzed by an  $\text{FeCl}_3$ -imidazolium carbene reagent in the presence of Zn powder.<sup>[11]</sup> Salts of Co, Pd, and Ni have also been shown to catalyze this intramolecular cyclotrimeriza-

tion to afford substituted benzenes in varying yields. This reaction is proposed to be catalyzed by low-valent  $\text{MCl}_n$  ( $\text{M} = \text{Co}, \text{Fe}$ , and  $n = 0, 1$ ) + IPr complex [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]. The low-valent metal species is generated *in situ* from  $\text{Co}^{2+}$  and  $\text{Fe}^{3+}$  by Zn reduction (Scheme 5).

The cobalt-mediated cycloaddition of alkynylboronates with  $\alpha,\omega$ -diynes has been studied by Aubert and co-workers (Scheme 6).<sup>[12]</sup> It represents a straightforward synthesis of fused arylboronic esters which could be further derivatized by functional group transformations and coupling reactions. The application of  $\text{CpCo}(\text{CO})_2$  in the coupling of  $\alpha,\omega$ -diynes with substituted alkynes failed to provide the cycloadduct. Nevertheless, mixing the borylalkynes with stoichiometric amounts of  $\text{Co}_2(\text{CO})_8$  in xylenes at room temperature afforded a dicobalt tetrahedrane derivative



**Scheme 5.** Totally intramolecular cyclotrimerization of triynes.



**Scheme 6.** Use of borylalkynes in [2+2+2] cycloaddition reactions.

which reacted with diynes to afford the polysubstituted benzene derivatives.

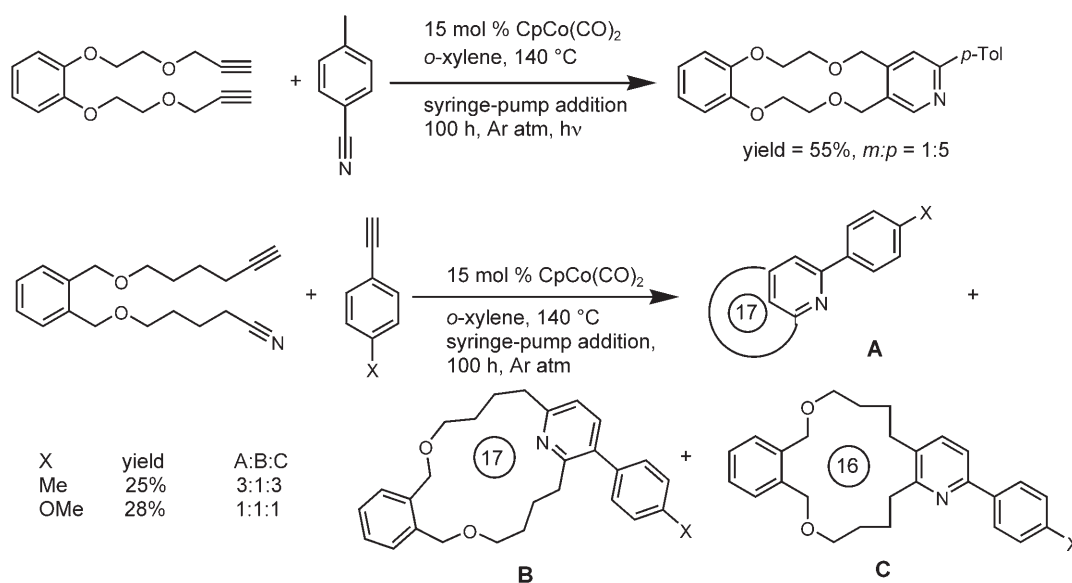
Due to the light sensitivity of the dicobalt-tetrahydride complexes, they were treated *in situ* with variously substituted diynes of varying length to afford benzene derivatives in 45–75% yields. Alkyl-, aryl-, and silyl-substituted alkynylboranes esters were successfully utilized in this transformation.

## 2.2 Synthesis of Pyridine and Pyridone Derivatives

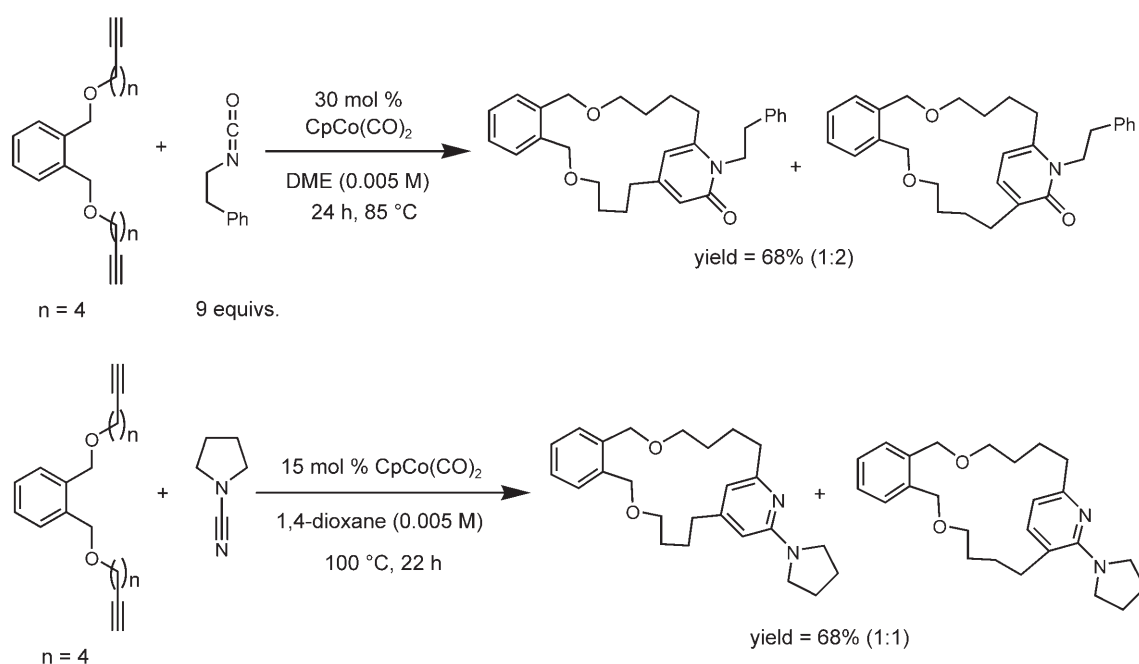
The cobalt-catalyzed [2+2+2] cycloaddition of  $\alpha,\omega$ -diynes with reactive molecules such as nitriles, isocyanates, cyanamides, and alkynes have been recently reported by Maryanoff and co-workers (Scheme 7 and

Scheme 8).<sup>[13a,b]</sup> Earlier reports stated that the cocyclo-trimerization of  $\alpha,\omega$ -diynes and an external alkyne catalyzed by cobalt has been largely unsuccessful due to a variety of possible side reactions that adversely affect the desired yields. These include oligomerization, polymerization, isomerization, decomposition, self-trimerization, and cyclobutadiene cobalt-complex formation. The formation of Co-cyclobutadiene complexes especially is commonly observed in Co-catalyzed cycloaddition reactions. This is possible due to the slow insertion of the third pi system into the organocobalt intermediate formed in the course of the reaction. Nitriles, being more reactive than alkynes, were successfully inserted into the reactive species to afford a variety of macrocyclic pyridine derivatives. Both terminal and internal diynes could be utilized in this reaction. Generally, nitriles conjugated to an arene, heteroarene, or alkene group underwent macrocyclization efficiently. The reaction of  $\omega$ -alkynyl nitriles with alkynes also afforded the macrocyclic pyridine derivatives. The use of a higher molar ratio of nitrile:diyne (*ca.* 5:1), 15 mol% of  $\text{CpCo}(\text{CO})_2$ , ether solvents and reflux resulted in higher yields.

The synthesis of pyridine derivatives can be carried out by the reaction of acetylene with nitriles using  $\text{CpCo}(\text{cod})$  as the catalyst.<sup>[13c]</sup> This reaction requires irradiation in the 350–500 nm range. Hence, lamps as well as sunlight can be used. A variety of simple aliphatic and aromatic nitriles were utilized in the cycloaddition reaction to afford pyridines in 70–90% yields. Nitriles with an amine moiety or a C=C bond resulted in lower yields due to deactivation of the catalyst. The synthesis of substituted pyridine derivatives by the reaction of  $\alpha,\omega$ -diynes with isocyanates was



**Scheme 7.** Large ring synthesis utilizing the [2+2+2] cycloaddition of a nitrile with a diyne.

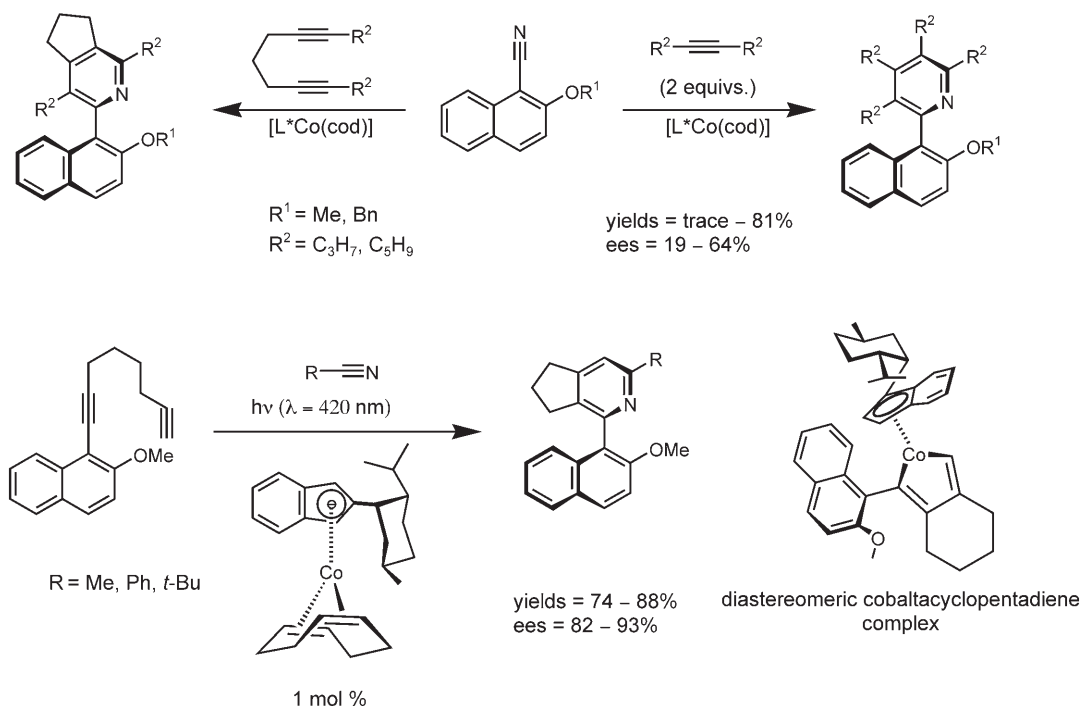


**Scheme 8.** Large ring synthesis utilizing [2+2+2] cycloaddition of isocyanates and cyanoamides with diynes.

also successful. Using similar conditions, the cyclotrimerization with alkynes afforded macrocyclic benzene derivatives in improved yields.

The synthesis of chiral 2-arylpyridines was efficiently performed by Gutnov, Heller and co-workers.<sup>[14]</sup> Chiral pyridines of this type are commonly utilized as ligands in numerous asymmetric transformations. The

[2+2+2] cycloaddition reaction of 2-substituted 1-naphthonitriles with variously substituted alkynes was catalyzed by chiral tartarate- and menthyl-derived cobalt complexes. The use of a bulkier diyne substrate resulted in better yields and higher *ees* (Scheme 9). The irradiation of the reaction mixture with visible light ( $\lambda = 350\text{--}500\text{ nm}$ ) or sunlight as the energy



**Scheme 9.** Synthesis of axially chiral pyridines using [2+2+2] cycloaddition.

source enabled the reaction to be performed under mild conditions. The formation of a diastereomeric cobaltacyclopentadiene intermediate is proposed to be the enantioselective step.

### 2.3 Synthesis of 1,3-Cyclohexadiene Derivatives

1,3-Cyclohexadienes are important substrates in natural product syntheses. The [2+2+2] cycloaddition of two monoynes (or one diyne) and one monoene functionality provides a cyclohexadiene moiety. The application of alkynylboronates and Co complexes as catalysts in the synthesis of cyclohexadienes has been described recently.<sup>[15]</sup> Treating  $\text{CpCo}(\text{C}_2\text{H}_4)_2$  with alkynylboronates under an atmosphere of ethene, resulted in the formation of 1,3- and 1,4-diboryl-( $\eta^4$ -1,3-cyclohexadiene), along with 1,2- and 1,3-diboryl-( $\eta^4$ -cyclobutadiene) complexes. These novel complexes were air-stable and purified by column chromatography. They can be subjected to oxidative demetalation with  $\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$  to form substituted 1,3-cyclohexadienes and demetalative aromatization with ceric ammonium nitrate to afford substituted benzene derivatives (Scheme 10). The Co-mediated [2+2+2] cycloaddition has also been utilized to synthesize substituted decahydrophenanthrenes by the intramolecular cyclotrimerization of enediynes.<sup>[16]</sup>

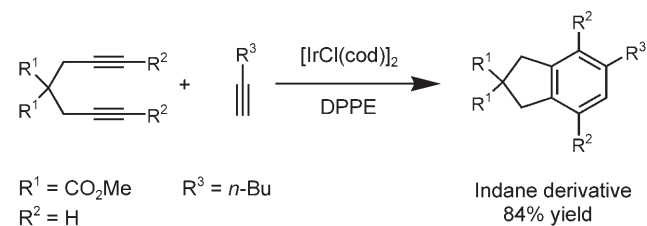
### 3 Iridium-Catalyzed [2+2+2] Cycloaddition

The first preparation of iridacyclopentadiene by the reaction of  $[\text{IrCl}(\text{N}_2)(\text{PPh}_3)_2]$  with dimethyl acetylenedicarboxylate (DMAD) was reported by Collman.<sup>[17]</sup> Since then several reports have appeared that describe the structure, stability,<sup>[18]</sup> and utility of Ir cata-

lysts in carbon-carbon bond formation, specifically the [2+2+2] cycloaddition reaction.<sup>[19]</sup>

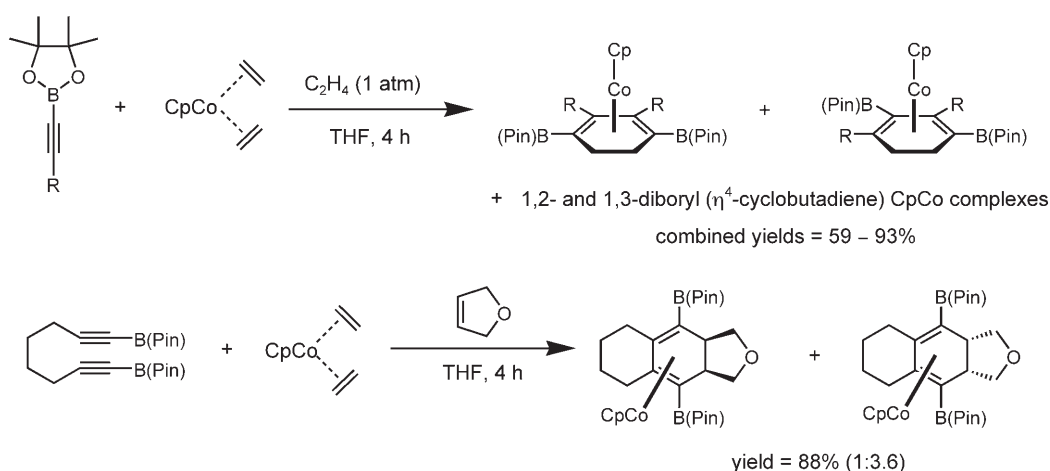
### 3.1 Synthesis of Substituted Benzene Derivatives

Takeuchi and co-workers have described the partially intramolecular cycloaddition of  $\alpha,\omega$ -diynes with monoynes and monoenes catalyzed by a variety of Ir complexes (Scheme 11).<sup>[20]</sup> Upon screening several Ir com-



**Scheme 11.** Iridium-catalyzed synthesis of indane derivatives.

plexes and ligands,  $[\text{IrCl}(\text{cod})_2]$  and 1,2-bis(diphenylphosphino)ethane (DPPE) mixture was found to be optimal at room temperature. Benzene was the solvent of choice compared to EtOH, THF, dioxane, acetone, and 1,2-dichloroethane. This is a common feature of several cycloaddition reactions. It is possible that the metallacyclopentadiene formed in the course of these reactions is stabilized by  $\pi$ -stacking with aromatic solvents such as benzene, toluene, and xylenes. These reactions proceed with good regioselectivity and are tolerant of hydroxy, amine, ether, alkyne functionalities. The yields in the reacted terminal as well as internal alkynes and terminal and internal diynes are comparable. An interesting aspect of this reaction system is the ligand-controlled regioselectivity observed in the products. In the reaction of 1,6-oc-

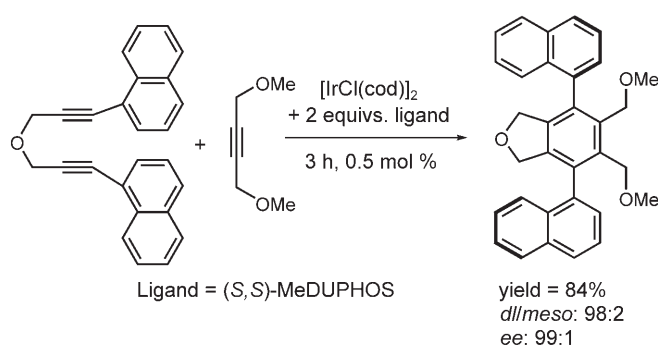


**Scheme 10.** Use of alkynylboronates in the synthesis of 1,3-cyclohexadienes.

tadiyne with terminal alkynes, the *ortho*-cycloaddition product predominates in the presence of DPPF as ligand, while the *meta*-product is the major product in presence of DPPE as ligand (Scheme 12). The *meta*-selectivity is rationalized on the basis of the chelating effect of DPPE. On the other hand, DPPF is proposed to coordinate (rather than chelate) in a monodentate fashion to Ir. This results in a vacant coordination site on the Ir atom. The monoynone occupies this site followed by insertion to form the *ortho*-product.

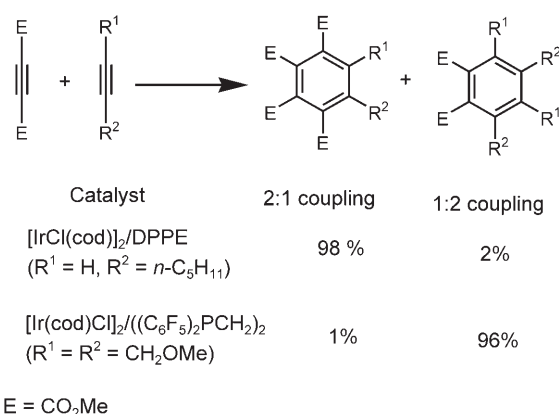
Shibata and co-workers have utilized the [2+2+2] cycloaddition of an  $\alpha,\omega$ -diyne (possessing an *ortho*-substituted aryl on its terminus) and a disubstituted alkyne in the synthesis of axially chiral aryl compounds.<sup>[21]</sup> They postulated the formation of an axially chiral teraryl compound due to the restricted rotation across the central C–C bond as a result of steric hindrance between the *ortho*-substituents on the diyne aryl functionality and the substituents on the newly formed benzene ring. As expected, the use of a chiral ligand in this reaction afforded axially chiral diols in high enantiomeric excess (Scheme 13). Various other diyne systems and oxygen-rich alkynes also provided teraryl compounds in good yields and excellent diastereo- and enantioselectivity.

In another interesting report, Takeuchi and Nakaya have utilized  $[\text{IrCl}(\text{cod})_2]$  in the cross [2+2+2] cycloaddition of two different monoynes (Scheme 14).<sup>[22]</sup> Understandably, selectivity was a major issue in this cyclotrimerization. The reaction of DMAD with a variety of monoynes was reported. They observed the formation of a polysubstituted benzene derivative in the presence of DPPE as ligand. The benzene derivative is formed by 2:1 coupling (two molecules of DMAD and one molecule of alkyl-substituted alkyne such as 1-hexyne). On the other hand, use of  $[\text{IrCl}(\text{cod})_2]$  and 1,2-bis(dipentafluorophenylphosphino)ethane in place of DPPE gave the 1:2 coupling product involving one molecule of DMAD and 2 molecules of monoynone. This 2:1 *versus* 1:2 selectivity dependent on ligand is rationalized based on the electronic effect of the monoynes and ligands. Normally,



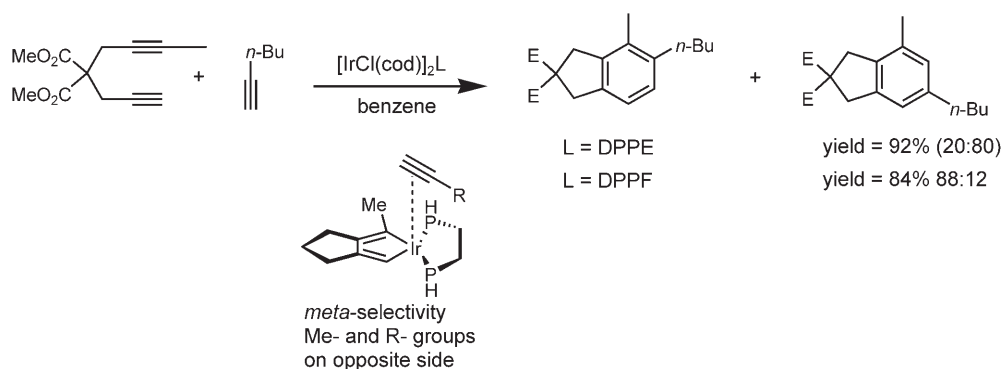
(S,S)-MeDUPHOS = 1,2-bis(2,5-dimethylphospholano)benzene

**Scheme 13.** Iridium-catalyzed synthesis of axially chiral teraryl compounds.



**Scheme 14.** Ligand-based chemoselectivity in Ir-catalyzed intermolecular [2+2+2] cycloaddition.

in the presence of DPPE, two molecules of DMAD react with the Ir center to form a tetracarboxymethoxy-substituted iridacyclopentadiene as the kinetic intermediate, which then reacts with an electron-rich monoynone leading to 2:1 coupling. However, when the ligand is a strong electron-withdrawing group such as 1,2-bis(dipentafluorophenylphosphino)ethane, the catalyst prefers to undergo oxidative cyclization with the



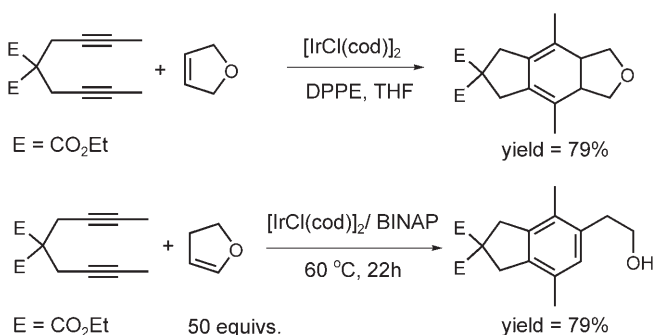
**Scheme 12.** Regioselectivity in Ir-catalyzed [2+2+2] cycloaddition.



electron-rich monoyne rather than the electron-deficient DMAD leading to 1:2 coupling.

### 3.2 Synthesis of 1,3-Cyclohexadiene Derivatives

$[\text{IrCl}(\text{cod})]_2/\text{DPPE}$  catalyzes the [2+2+2] cycloaddition of internal 1,6-diynes with 2,5-dihydrofuran to afford variously substituted 1,3-cyclohexadienes. The same reaction involving 2,3-dihydrofuran resulted in a novel aromatization reaction involving cleavage of C–O bond (Scheme 15).<sup>[23]</sup> The cycloaddition of 1,6-enynes and monoynes also results in the formation of 1,3-cyclohexadienes.  $[\text{IrCl}(\text{cod})]_2$  in conjunction with DPPE is known to catalyze the partially intramolecular cycloaddition.<sup>[24]</sup>



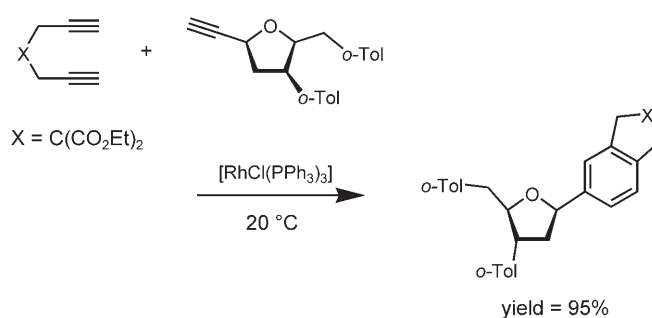
**Scheme 15.** An example of novel aromatization involving cleavage of C–O bond.

## 4 Rhodium-Catalyzed [2+2+2] Cycloaddition

Muller first reported the stoichiometric reaction of rhodacyclopentadienes which were formed by the reaction of  $[\text{RhCl}(\text{PPh}_3)_3]$  with  $\alpha,\omega$ -diynes and monoynes to form substituted benzene derivatives.<sup>[25]</sup> Several examples of Rh catalysis in [2+2+2] cycloaddition have been reported since.<sup>[26]</sup>

### 4.1 Synthesis of Substituted Benzene Derivatives

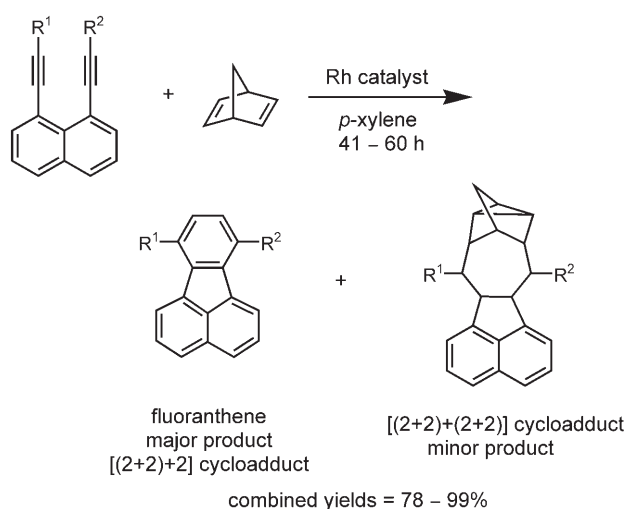
The application of [2+2+2] cycloaddition in the synthesis of natural and biologically active compounds is well documented.<sup>[27]</sup> Recently, Kotora, Hocek, and co-workers reported the catalytic [2+2+2] cyclotrimerization of  $\alpha,\omega$ -diynes with *C*-ethynyldeoxyriboside under mild reaction conditions to form variously substituted *C*-aryldeoxyriboside derivatives (Scheme 16).<sup>[28]</sup> Several transition metal catalysts such as Rh, Ni, Ru, and Co complexes were utilized for



**Scheme 16.** Synthesis of aryl substituted deoxyribosides.

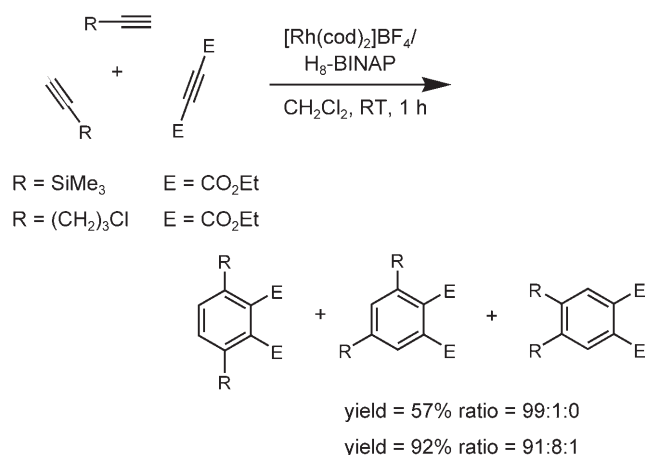
these reactions. Wilkinson's catalyst  $[\text{RhCl}(\text{PPh}_3)_3]$  afforded optimum yields for variously substituted  $\alpha,\omega$ -diynes. Yamamoto and co-workers have also reported the catalytic cyclotrimerization of 1,6-diynes with *C*-alkynylglycosides to afford *C*-arylglycosides in the presence of  $\text{Cp}^*\text{RuCl}(\text{cod})$  at ambient temperature.<sup>[29]</sup>

Siegel and co-workers have reported the Rh-catalyzed cycloaddition of norbornadiene (that acts as an acetylene equivalent) to 1,8-dialkynyl naphthalenes to form fluoranthenes by a formal [(2+2)+2] cycloaddition (Scheme 17).<sup>[30]</sup> The use of 2.5 mol% of  $\text{Rh}_2(\text{OAc})_4 \cdot 2 \text{H}_2\text{O}$  gave exclusively the fluoranthene product while  $[\text{RhCl}(\text{PPh}_3)_3]$  afforded a mixture of fluoranthene and the [(2+2)+(2+2)] cycloadduct. The preparation of (a)symmetric 7,8,9,10-substituted fluoranthenes from the reaction of 1,8-dialkynyl naphthalene derivatives and alkynes catalyzed by  $[\text{RhCl}(\text{PPh}_3)_3]$  has also been reported. A working mechanism for this reaction involves cycloaddition of the two alkynes to form a rhodacyclopentadiene intermediate followed by insertion of one pi bond of norbornodiene. Reductive elimination of Rh, and thermal elimination of cyclopentadiene results in formation of fluoranthene.



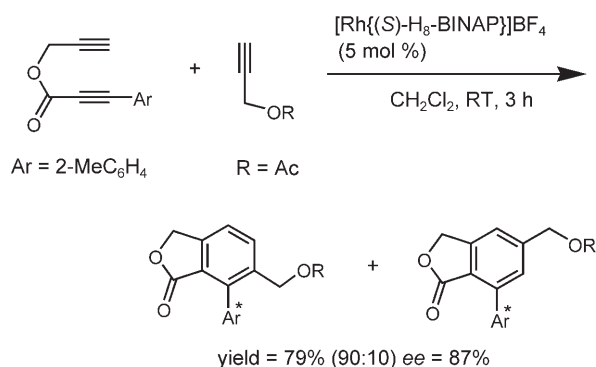
**Scheme 17.** Rh-catalyzed synthesis of complex fluoranthene derivatives.

Tanaka and co-workers had earlier described a highly chemo- and regioselective intermolecular cyclootrimerization of three alkyne moieties.<sup>[31]</sup> Generally, similar reactions lack a high degree of regioselectivity, however in the presence of a cationic rhodium(I)/modified H<sub>8</sub>-BINAP complex, excellent regioselectivity was observed (Scheme 18).



**Scheme 18.** High degree of regioselectivity in Rh-catalyzed [2+2+2] cyclootrimerization.

Recently, an asymmetric variant of this cross alkyne cyclootrimerization reaction has also been reported by the same group.<sup>[32]</sup> The synthesis of axially chiral phthalides was reported using the cross alkyne trimerization of unsymmetrical  $\alpha,\omega$ -diynes and (un)symmetrical terminal monoynes catalyzed by the cationic [Rh(I)(H<sub>8</sub>-BINAP)] complex. Excellent regioselectivity and enantioselectivity were obtained. The *ee* was higher in the case of symmetrical monoynes as compared to unsymmetrical monoynes (Scheme 19). In a similar report, the use of internal alkynes in asymmetric cross-cyclootrimerization has also been effective in the synthesis of axially chiral biaryl substrates.<sup>[33a]</sup> The enantioselective synthesis of tetra-*ortho*-substituted



**Scheme 19.** Rh-catalyzed synthesis of axially chiral biaryl compounds.

axially chiral biaryl compounds has also been reported recently.<sup>[33b]</sup>

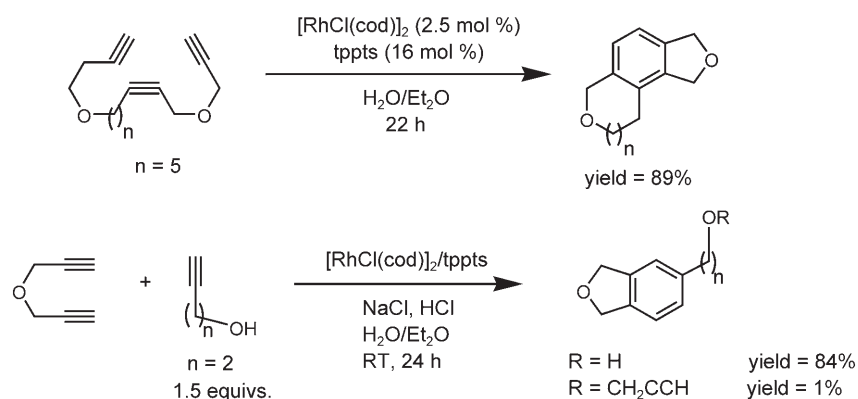
The solvent plays a very important role in [2+2+2] cycloaddition reactions. Generally non-polar solvents such as benzene, toluene, THF, DCE, etc. are preferred in these reactions. Oshima and co-workers have reported the use of an aqueous-organic biphasic solvent system in which, surprisingly, the aqueous phase is the reaction phase.<sup>[34]</sup> The [2+2+2] cyclootrimerization of alkynes was catalyzed by [RhCl(cod)]<sub>2</sub> and the trisodium salt of the tris(*m*-sulfonatophenyl)phosphine (tppts) ligand. A major drawback of the cyclootrimerization of a diene and monoyne moiety is the formation of the homoannulation product as opposed to the desired cross-annulation product. High degree of dilution, slow addition techniques and a large excess of the monoyne enhance the yields of the cross-addition product. In the aqueous-ether biphasic system reported by Oshima, a simpler alternative is described. A mixture of ([RhCl(cod)]<sub>2</sub> + tppts) a water-soluble catalyst and water-soluble monoyne (e.g., propargyl alcohol) is treated with a diyne molecule that is partially soluble in water. Thus, a large excess of monoyne to diyne is achieved in the water phase. Moreover, the lower solubility of the diyne results in a lower concentration and hence a higher dilution. Both intra- and partially intramolecular cyclootrimerizations have been successfully carried out in water (Scheme 20).

## 4.2 Synthesis of Substituted 1,3-Cyclohexadiene Derivatives

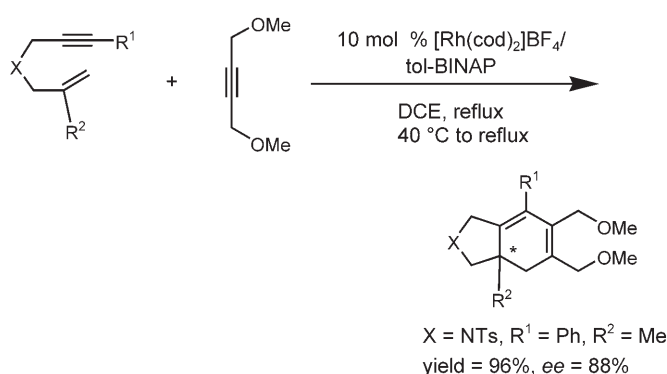
The [2+2+2] cycloaddition of two monoyne (or one diyne) functionalities with one monoene functionality results in the formation of cyclohexadienes. Numerous examples of transition metal-catalyzed syntheses of cyclohexadienes by the [2+2+2] cycloaddition pathway are known.<sup>[35]</sup> Recently, Shibata and co-workers have reported the use of chiral rhodium catalysts in the enantioselective [2+2+2] cycloaddition reaction of 1,6-enynes and alkynes to afford substituted bicyclic 1,3-cyclohexadienes containing quaternary carbon stereocenters.<sup>[36]</sup> Terminal and internal alkynes could be utilized in this reaction. The use of symmetrical monoynes resulted in higher *ees* compared to unsymmetrical monoynes (Scheme 21).

## 4.3 Synthesis of Substituted Pyridine Derivatives

The general procedure for the synthesis of pyridones is the reaction of diynes with isocyanates.<sup>[37]</sup> An example of this methodology is reported by Tanaka and co-workers.<sup>[38]</sup> The [2+2+2] cycloaddition of alkynes (and diynes) with isocyanates was catalyzed by a



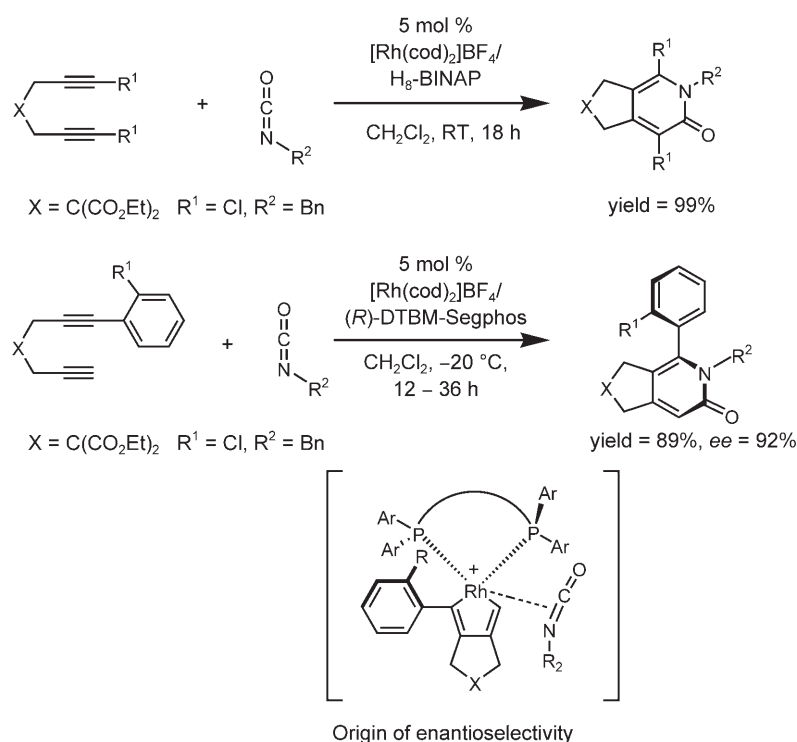
**Scheme 20.** Use of water-ether biphasic solvent system in [2+2+2] cycloadditions.



**Scheme 21.** Synthesis of optically active 1,3-cyclohexadienes by [2+2+2] cycloaddition.

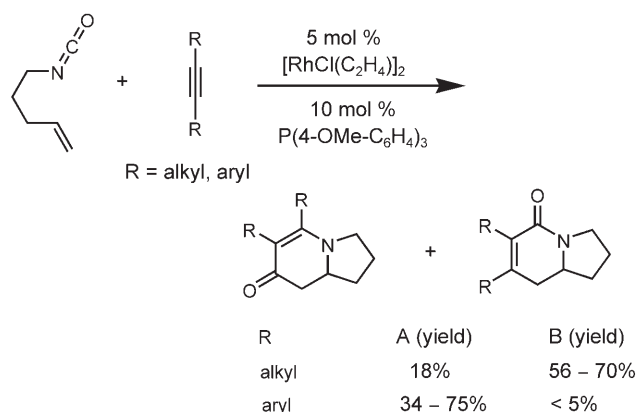
Rh(I)/modified complex to afford pyridone derivatives. Various substituted isocyanates and diynes were utilized in this study. The resulting polysubstituted pyridones were obtained in good yields (48–99%). Excellent chemo- and regioselectivities were observed in these reactions. The asymmetric variant of this reaction utilizing unsymmetrical 1,6-diynes, isocyanates, and  $[Rh(cod)_2]BF_4/(R)-DTBM-Segphos$  furnished an axially chiral regioisomer as the major product. The observed enantioselectivity is explained on the basis of the selective formation of a rhodacyclopentadiene complex (Scheme 22).

Rovis and Yu have reported a unique Rh-catalyzed [2+2+2] cycloaddition involving alkenyl isocyanates



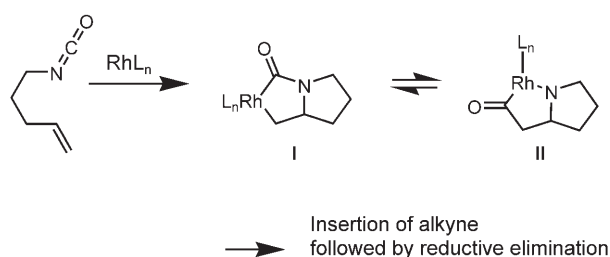
**Scheme 22.** Rh-catalyzed synthesis of enantioenriched axially chiral aryl-substituted pyridones by [2+2+2] cycloaddition.

and alkynes (Scheme 23).<sup>[39]</sup> The expected indolizine product formed by a straightforward [2+2+2] cycloaddition was obtained in very small quantities,



**Scheme 23.** Synthesis of vinylamides by the reaction of alkenyl isocyanates with alkynes.

while the bicyclic vinylogous amide formed by a rare fragmentation of the isocyanate was obtained as the major product. A variety of alkyl- and aryl-substituted alkyne substrates gave the vinylamide in moderate to good yields. A proposed mechanism to explain the formation of the rearranged product involves metal-catalyzed [2+2] cycloaddition of the isocyanate and alkene functionalities to form a bicyclic metalloamide intermediate that could rearrange by CO migration (I $\rightleftharpoons$ II). The insertion of the alkyne into these two intermediates followed by reductive elimination of the metal gives the two products (Scheme 24).

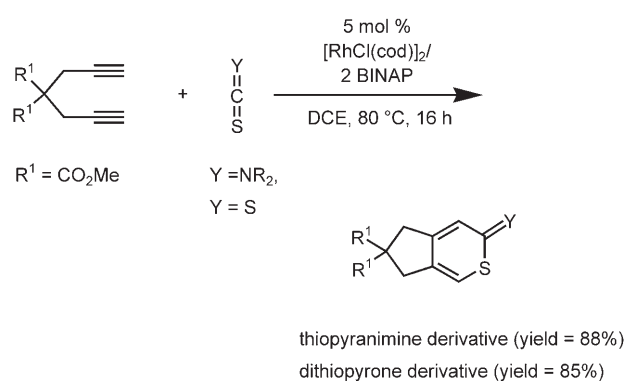


**Scheme 24.** A rare example of CO migration in a metalloamide intermediate.

#### 4.4 Synthesis of Substituted Thiopyranimine and Dithiopyrone Derivatives

The [2+2+2] cycloaddition of alkynes with isothiocyanates was first reported by Wakatsuki and Yamazaki.<sup>[40]</sup> The catalytic version of this reaction using 10 mol % of [Cp\**Ru*Cl(cod)] as catalyst was reported by Yamamoto, Itoh, and co-workers.<sup>[41]</sup> Tanaka and co-workers have described a neutral rhodium(I)/BINAP

complex-catalyzed [2+2+2] cycloaddition of alkynes with isocyanates and CS<sub>2</sub> (Scheme 25).<sup>[42]</sup> This reaction gave good yields of bicyclic thiopyranimines (59–



**Scheme 25.** Rh-catalyzed [2+2+2] cycloaddition of diynes and isothiocyanates/CS<sub>2</sub>.

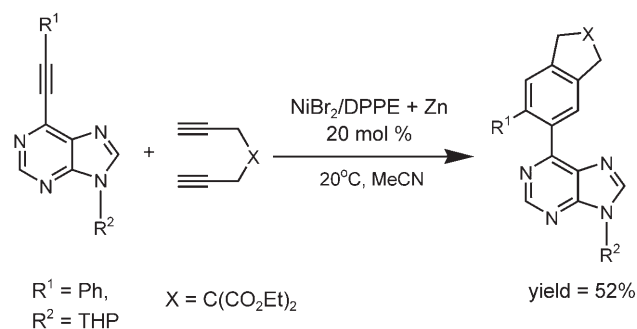
89%) for both aryl and alkyl thiocyanates. The use of CS<sub>2</sub> also gave dithiopyrones in good yields (75–85%). The asymmetric variant of this reaction using (*R*)-BINAP (and phenyl isocyanate) gave enantio-enriched pyranimine in 98% yield and 61% *ee*. Interestingly, the proposed mechanism involves the initial formation of a rhodacyclopentadiene complex from CX<sub>2</sub> and one alkyne functionality, followed by insertion of the other pendant alkyne group.

## 5 Nickel-Catalyzed [2+2+2] Cycloaddition

The cyclotrimerization of alkynes to form a benzene derivative reported by Reppe was the first example of a [2+2+2] cycloaddition.<sup>[43]</sup> The catalyst used in this pioneering report was a NiBr<sub>2</sub> and CaC<sub>2</sub> mixture. Since then, the application of Ni catalysts has been studied in a variety of substrates.<sup>[44]</sup>

### 5.1 Synthesis of Substituted Benzene Derivatives

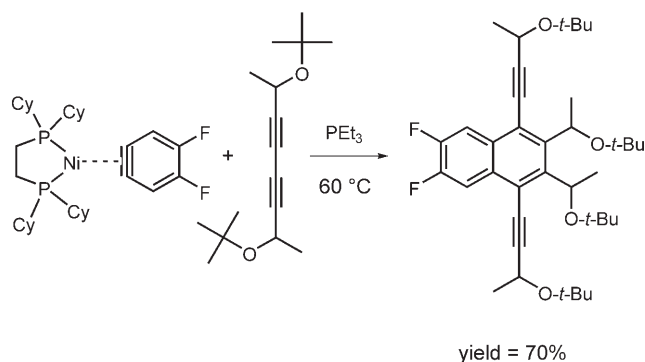
The Ni-catalyzed co-cyclotrimerization of 6-alkynylpurines with  $\alpha,\omega$ -diynes is a novel approach to the synthesis of variously substituted 6-arylpurines.<sup>[45]</sup> Although Co is also an effective catalyst in this reaction, optimal yields were obtained in the presence of the NiBr<sub>2</sub>(DPPE) complex in combination with Zn powder. The generation of the catalytically active Ni(0) species occurs *in situ* by Zn-mediated reduction of Ni(II) to Ni(0). The commonly utilized Wilkinson's catalyst, [RhCl(PPh<sub>3</sub>)<sub>3</sub>] failed to catalyze this transformation (Scheme 26). A variety of alkynylpurines and



**Scheme 26.** Ni(0)-catalyzed synthesis of aryl-substituted purines.

$\alpha,\omega$ -diynes were effective in this reaction. The synthesis of axially chiral arylpurines should be possible utilizing the same protocol and a chiral ligand-Ni complex. Several 6-arylpurines synthesized by the [2+2+2] cycloaddition showed considerable *in vitro* cytotoxic activity against human promyelocytic leukemia HL60 cells and human T lymphoblastoid CCRF-CEM cells.

Ni-benzyne complexes also act as alkyne equivalents in a [2+2+2] cycloaddition reaction. The first example of the use of an Ni-benzyne complex in a [2+2+2] cycloaddition reaction was reported by Bennett in which two monoynes react with benzyne- and difluorobenzyne-Ni complexes to form substituted naphthalenes.<sup>[46]</sup> Gin and Deaton have utilized substituted conjugated 1,3-diynes as substrates in their reaction with Ni-benzyne.<sup>[47]</sup> However, the incorporation of the benzyne moiety was low. Rather the homo-cyclotrimerization of the alkynes to substituted benzenes was the major pathway. The slow addition of freshly prepared 4,5-difluorobenzyne (which is more stable than benzyne) enhanced the yields of the desired naphthalene derivatives (Scheme 27). Excellent regioselectivity was observed in these reactions. The formation of the 2,3-dialkynyl versus 1,4-dialkynyl products was dependent on steric and electronic

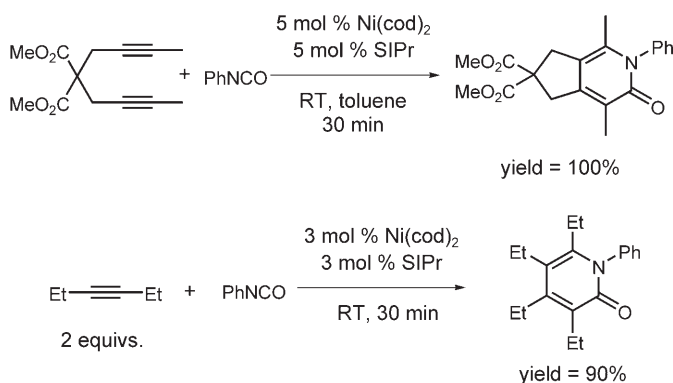


**Scheme 27.** Application of an Ni-benzyne complex as an alkyne equivalent.

factors of the dialkynyl terminal substituents. The naphthalene products are chromophoric and fluorescent and hence could be applicable as fluorescent materials. Other applications of Ni catalysts in [2+2+2] cycloaddition of diynes with allenes to afford polysubstituted benzene derivatives are also known.<sup>[48]</sup>

## 5.2 Synthesis of Substituted Pyridone, Isocyanurate and Pyridine Derivatives

The application of Ni(0) metal and N-heterocyclic carbenes (NHCs) as ligands in [2+2+2] cycloaddition reaction has been studied extensively by Louie and co-workers. They have recently reported the cycloaddition of diynes and isocyanates to afford various 2-pyridones in excellent yields and selectivity (Scheme 28).<sup>[49]</sup> Although a variety of phosphines and



**Scheme 28.** Nickel-NHC catalyzed efficient syntheses of multisubstituted pyridones.

NHCs were screened as Ni ligands for catalytic activity, SIPr and IPr were the most effective [SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolin-2-ylidene]. Under reported reaction conditions, alkyne cyclotrimerization is largely inhibited in the presence of the Ni-SIPr or Ni-IPr catalytic systems. Both alkyl and aryl isocyanates, as well as internal and external diyne substrates containing diverse functional groups are effective substrates in this transformation. Elevated temperatures are not required. Generally, intermolecular, three component cycloaddition reactions lack a high degree of chemoselectivity. However, the reaction of an alkyne with 2 equivalents of isocyanate in the presence of the Ni(0)-SIPr system at room temperature afforded the 2-pyridone in excellent yields.

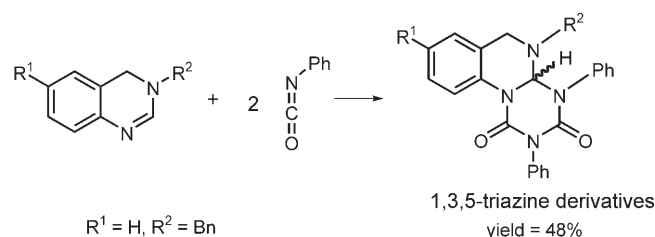
Recently, Louie and co-workers have shown that the cycloaddition of alkynes and isocyanates can also afford pyrimidinediones.<sup>[50]</sup> The Ni-IPr-catalyzed [2+2+2] cycloaddition reaction of a monoynes with excess quantities of an isocyanate functionality resulted in the formation of pyrimidinediones rather than

the expected pyridones. The oxidative coupling between an alkyne and one isocyanate moiety leads to the formation of a nickelacycle intermediate. At high concentrations of isocyanate, a second molecule of isocyanate is preferentially inserted into the nickelacycle (*in lieu* of an alkyne functionality) to form pyrimidinediones. Thus, steric factors play an important role in this transformation, with bulky substituents on the monoynone and a bulky ligand such as IPr favoring the formation of pyrimidinediones (Scheme 29).

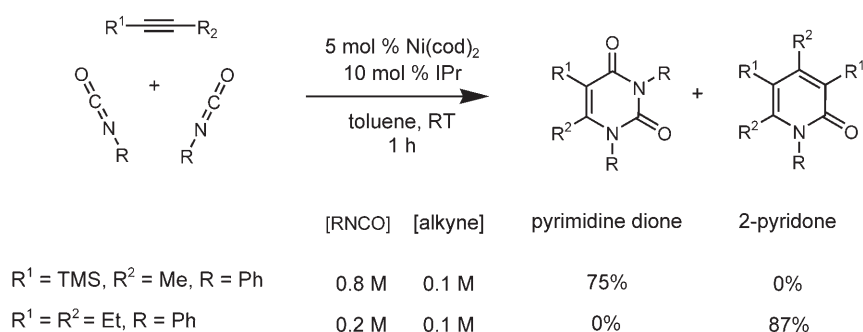
N-Heterocyclic carbenes are also capable of catalyzing [2+2+2] cycloadditions individually.<sup>[51]</sup> The SIPr-catalyzed cyclotrimerization of isocyanates to isocyanurates has been reported. Isocyanurates are the aromatic products obtained by the cyclotrimerization of three isocyanate molecules. Isocyanurates and their polymers are extremely resistant to heat and chemicals and hence are especially useful in flame retardation materials. Aryl as well as alkyl isocyanates readily undergo trimerization in the presence of SIPr as catalyst. Formation of a tetracyclic dimer was also observed. Treatment of a diisocyanato substrate with SIPr resulted in the formation of a polyamide solid containing exclusively an isocyanurate-linked backbone (Scheme 30).

The utility of the Ni-NHC catalytic system has been extended to the synthesis of substituted pyridines. The [2+2+2] cycloaddition of variously substi-

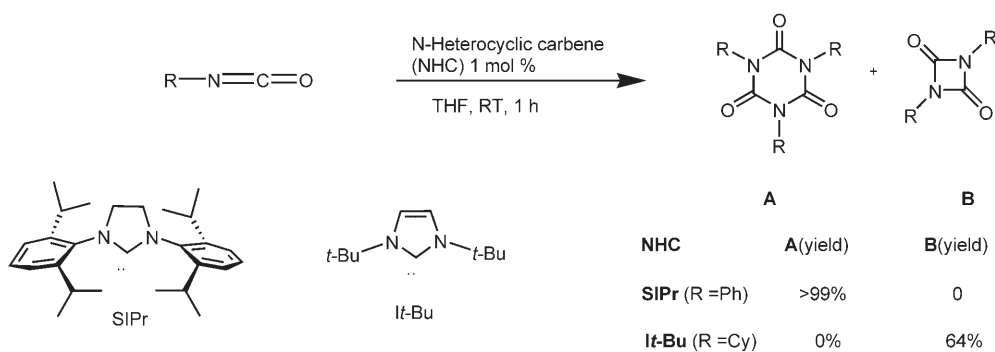
tuted diynes and nitriles afforded substituted pyridine derivatives in good yields under ambient reaction conditions. Similar to earlier reports, the Ni(0)-SIPr system was the most efficient. Use of unsymmetrical diynes can potentially give two regioisomeric pyridine derivatives. In this study, formation of a single regioisomer was observed.<sup>[52]</sup> The co-cyclotrimerization of two monoynone derivatives with a nitrile functionality (as opposed to alkyne cyclotrimerization to form benzene) proceeded smoothly (Scheme 31).



**Scheme 31.** Nickel-NHC catalyzed efficient synthesis of multisubstituted pyridines.



**Scheme 29.** Synthesis of pyrimidine diones from monoynes and excess amount of isocyanates.

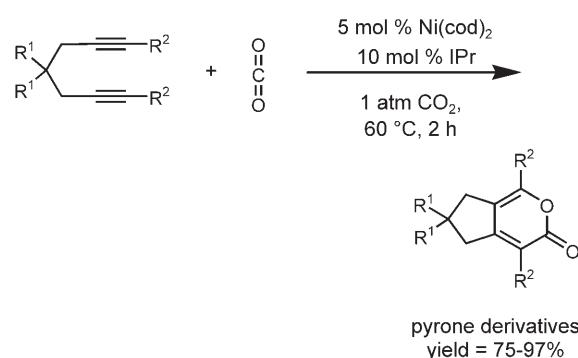


**Scheme 30.** [2+2+2] Co-cyclotrimerization of isocyanates to useful isocyanurates.

### 5.3 Synthesis of Substituted Pyrone, Pyran, and Cyclohexadiene Derivatives

The [2+2+2] cycloaddition of monoene moieties to a 1,6-diyne to form substituted benzenes or 1,3-cyclohexadienes is well precedented. Cycloaddition of diynes to heteroatomic pi systems such as nitriles and isocyanates is also common. A variety of transition metal catalytic systems are available for these reactions. However, the cycloaddition of a C=O pi system (as in CO<sub>2</sub> or carbonyl compounds) to diynes is rare, possibly due to the difficulty associated with their ability to undergo insertion or oxidative coupling. Nevertheless, the Ni-NHC catalytic systems have been shown to be effective in the [2+2+2] cycloaddition of CO<sub>2</sub> and diynes to form polysubstituted pyrones.<sup>[53]</sup> Excellent regioselectivity was observed in these reactions along with excellent yields in case of internal diynes. These reactions were fast and completed at atmospheric pressure of CO<sub>2</sub> (Scheme 32).

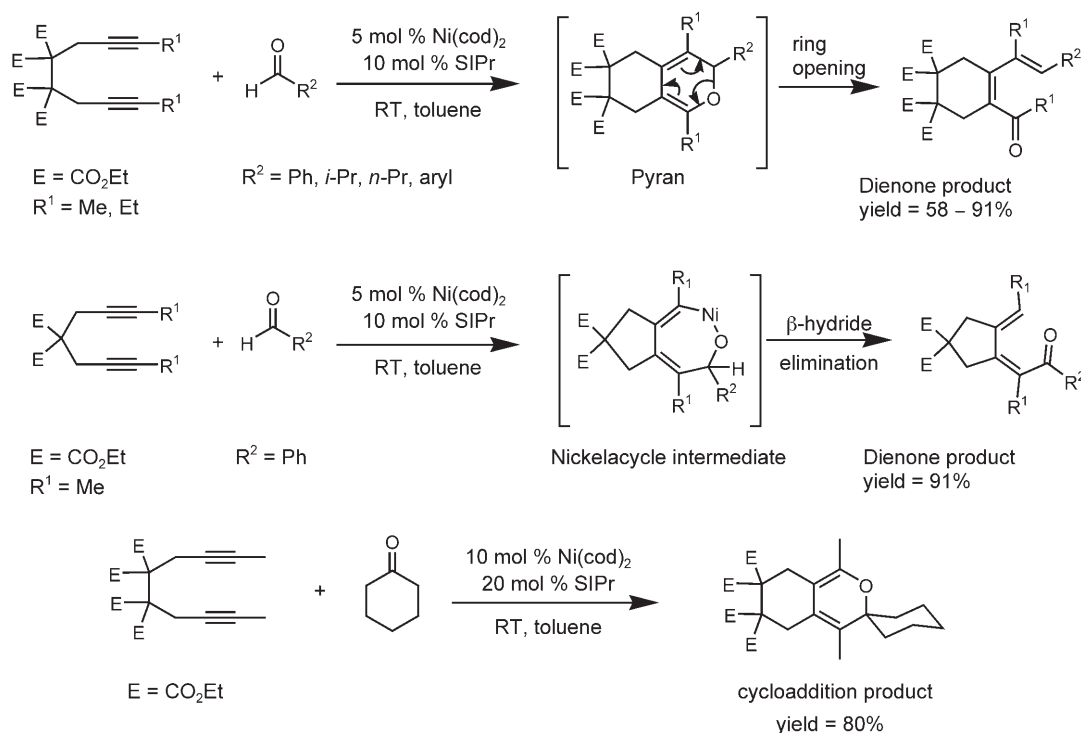
In general, [2+2+2] cycloaddition reactions are thought to proceed through the formation of a metalacyclopentadiene intermediate (see Scheme 2). However, in the Ni-catalyzed addition of CO<sub>2</sub> to diynes, experimental evidence suggests the [2+2] addition of CO<sub>2</sub> to one alkyne moiety, followed by activation and insertion of the second alkyne moiety. This mechanistic pathway explains the formation of a single regioisomer of pyrone.<sup>[54]</sup> Although the formation of a nickelacyclopentadiene intermediate followed by in-



**Scheme 32.** CO<sub>2</sub> fixation using Ni(cod)<sub>2</sub> and IPr catalytic systems to afford pyrones.

sertion of a C=O bond is unlikely, it cannot be entirely ruled out.<sup>[55]</sup> The application of the Ni(0)-NHC system to the [2+2+2] cycloaddition of carbonyl compounds to diynes gave surprising results. Rather than the expected pyrans, dienone systems were obtained, either by electrolytic ring opening or β-hydride elimination. The use of ketones provided the cycloaddition product in good yields (Scheme 33).

The pioneering report on catalytic and enantioselective syntheses of chiral cyclohexa-1,3-dienes by [2+2+2] cycloaddition of two monoynes and one monoene functionality in the presence of chiral nickel catalysts came from Ikeda and co-workers.<sup>[56]</sup>



**Scheme 33.** Ring opening of cycloaddition products.

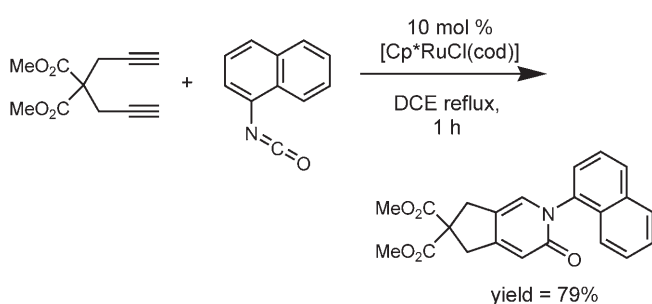
## 6 Ruthenium-Catalyzed [2+2+2] Cycloaddition

### 6.1 Synthesis of Substituted Benzene Derivatives

The [2+2+2] cyclotrimerization of alkynes to benzene derivatives is well-documented and reviewed earlier.<sup>[57]</sup>

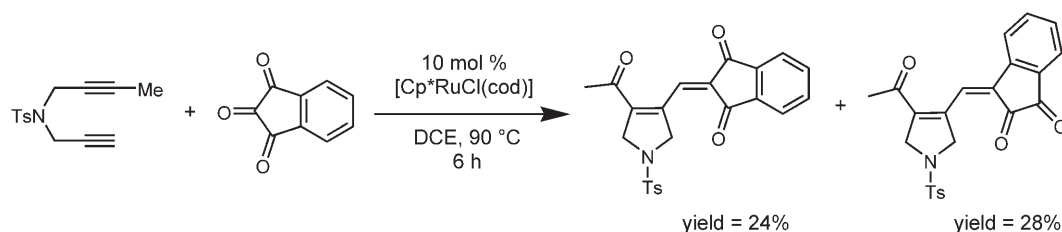
### 6.2 Synthesis of Substituted Pyridone and Pyridine Derivatives

Ruthenium-based catalytic systems are useful in the [2+2+2] cycloaddition of 1,6-diynes with isocyanates to afford bicyclic pyridones in good yields. Screening of several Ru catalysts indicated that [Cp\*RuCl(cod)] (10 mol%) in refluxing 1,2-dichloroethane was the most efficient.<sup>[58]</sup> Several *N*-aryl- and *N*-alkyl-substituted pyridones were obtained from the respective isocyanates (Scheme 34).



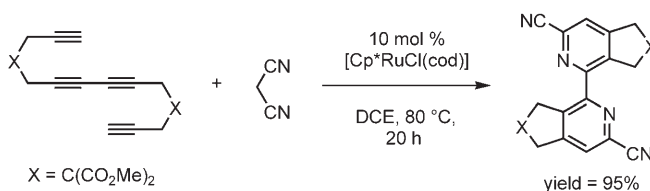
**Scheme 34.** Ru-catalyzed partially intramolecular cycloaddition reaction.

The first Ru-catalyzed cycloaddition of 1,6-diynes with a nitrile functionality was reported by Itoh and co-workers.<sup>[59]</sup> Dicyanides afforded optimal yields of the pyridine derivatives. However, unactivated and electron-rich nitriles such as acetonitrile were ineffective in this transformation. [Cp\*RuCl(cod)] provides the best yields due to the planer ligand, (Cp\*) and a readily leaving ligand (cod). Interestingly, undesired cyclotrimerization of the alkynes was restrained.



**Scheme 36.** Use of a tricarbyl substrate in [2+2+2] cycloaddition reactions.

After the consumption of one -CN group in the dicyanide, the other -CN functionality is unactivated and therefore unreactive. This could be an efficient methodology for the synthesis of axially chiral dipyrindines that could be further functionalized (Scheme 35).



**Scheme 35.** Application of dicyanides as unsaturated functionalities in [2+2+2] cycloaddition.

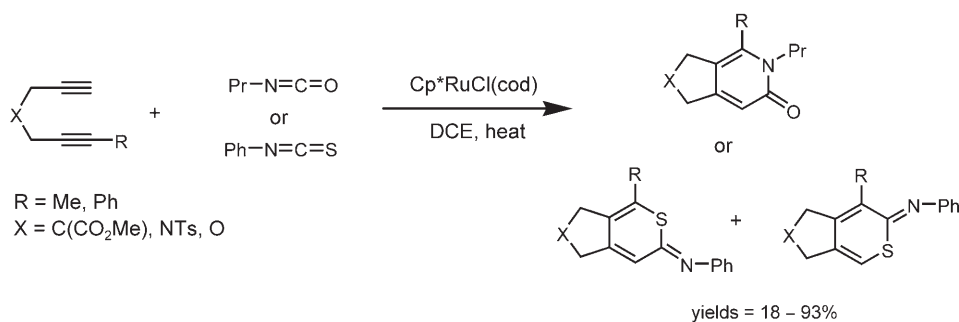
### 6.3 Synthesis of Substituted Pyran Derivatives

The utility of the [Cp\*RuCl(cod)] system in the [2+2+2] cycloaddition of 1,6-diynes with tricarbonyl substrates has also been described by Itoh and co-workers.<sup>[60]</sup> Although the pyran derivative was not isolated, a dienone formed by electrolytic ring opening of the expected pyran derivative was the major product. Various diynes with diverse substituents were effective in this transformation. Functionalities such as ether, tosylamide, hydroxy, ketone, and ester are well tolerated. The carbonyl substrates, however, are limited to a highly electron-deficient tricarbonyl that could potentially chelate to the Ru center. Elevated temperatures are required (Scheme 36).

### 6.4 Synthesis of Substituted Thiopyridones and Dithiopyrones

A recent example of catalytic [2+2+2] cycloaddition of diynes to isothiocyanates and carbon disulfide utilized [Cp\*RuCl(cod)] as the catalyst.<sup>[61]</sup> The concomitant cyclotrimerization of alkynes to a benzene was minimal. Elevated temperatures and the presence of a Cp\* ligand on the Ru center were required conditions for effective cycloaddition (Scheme 37).



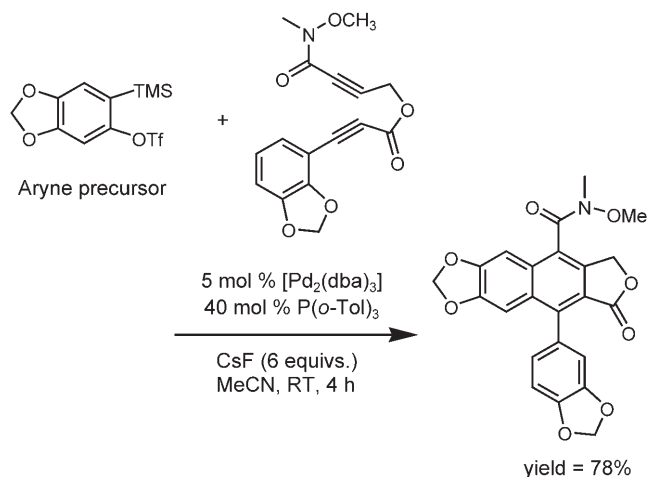


**Scheme 37.** [2+2+2] Cycloaddition of isocyanates and isothiocyanates to diynes.

## 7 Palladium-Catalyzed [2+2+2] Cycloaddition

### 7.1 Synthesis of Substituted Benzene Derivatives

Sato, Mori and co-workers have reported the total synthesis of taiwanins C and E utilizing the [2+2+2] cycloaddition as a key step.<sup>[62]</sup> The cyclotrimerization of a diyne species with a benzyne precursor was subjected to catalysis by [Ni(acac)<sub>2</sub>]/PPh<sub>3</sub> and DIBAL-H mixture, and [Pd<sub>2</sub>(dba)<sub>3</sub>] with PPh<sub>3</sub>/DPPB/P(Otol)<sub>3</sub> as ligands. The [Pd<sub>2</sub>(dba)<sub>3</sub>]/P(Otol)<sub>3</sub> complex was found to be most effective, which was utilized in the total synthesis of taiwanins C and E (Scheme 38). Other



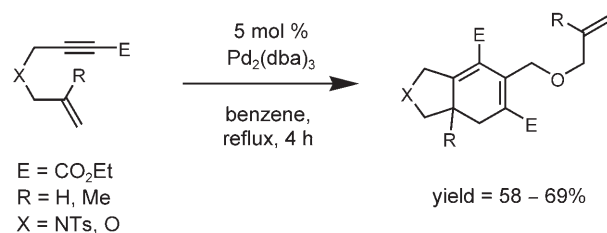
**Scheme 38.** Application of [2+2+2] cycloaddition in the synthesis of taiwanins C and E.

examples of Pd catalysis in the synthesis of benzene derivatives include the use of Pd(PPh<sub>3</sub>)<sub>4</sub> to form 1,2,3,5-tetrasubstituted benzenes,<sup>[63]</sup> the Pd<sub>2</sub>(dba)<sub>3</sub>-catalyzed cycloaddition of benzyne to 1,6-diyne to afford benzo[*b*]fluorenones,<sup>[64]</sup> and the PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>-mediated co-cyclotrimerization of benzyne with bicyclic alkenes to form anellated 9,10-dihydrophenan-

threne derivatives.<sup>[65]</sup> These reports have been reviewed earlier.<sup>[3]</sup>

### 7.2 Synthesis of Substituted 1,3-Cyclohexadiene Derivatives

The cyclotrimerization of enyne esters was efficiently catalyzed by 5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub> to afford 1,3-cyclohexadiene derivatives in good yields (Scheme 39).<sup>[66]</sup>



**Scheme 39.** Pd-catalyzed synthesis of cyclohexene derivatives.

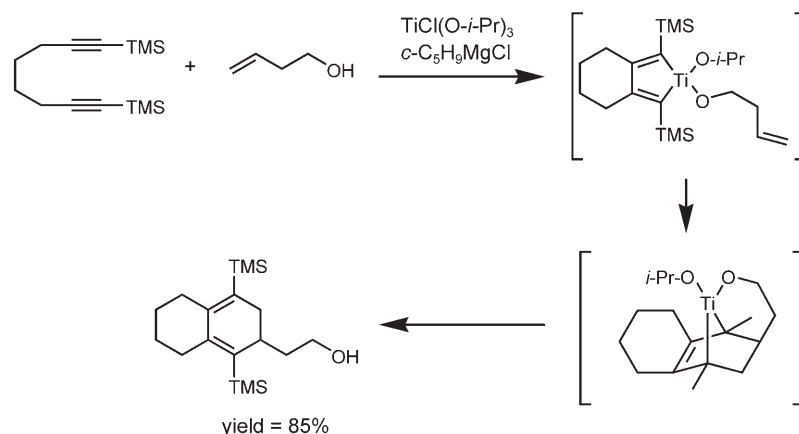
## 8 Other [2+2+2] Cycloaddition Reactions

### 8.1 Titanium-Catalyzed [2+2+2] Cycloaddition Reactions

Late transition metals and/or soft metals are the most common catalysts utilized in [2+2+2] cycloaddition. However, Cha and co-workers have reported the use of a strong Lewis acid, TiCl(O-*i*-Pr)<sub>3</sub> as a catalyst for the [2+2+2] coupling of diynes with homoallylic alcohols (Scheme 40).<sup>[67]</sup>

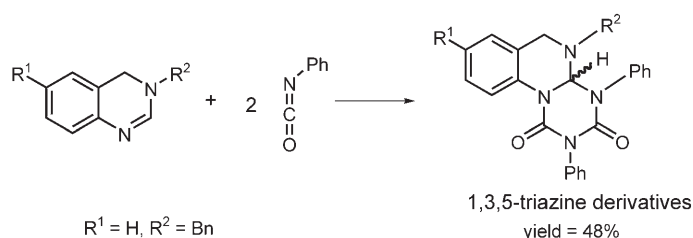
### 8.2 Uncatalyzed [2+2+2] Cycloaddition Reactions – Synthesis of Triazine Derivatives

Tietz and co-workers have reported a unique reaction involving 3-substituted 3,4-dihydroquinazolines with



**Scheme 40.** Ti-catalyzed [2+2+2] cycloaddition.

phenyl isocyanate.<sup>[68]</sup> At low temperatures, [2+2+2] cycloaddition resulted in the formation of 1,3,5-triazine derivatives for the preferred pathway. At high temperatures, a mixture of different cycloadducts was obtained (Scheme 41).



**Scheme 41.** Synthesis of 1,3,5-triazines by uncatalyzed [2+2] cycloaddition.

## 9 Conclusion

The efficiency, atom-economy, and ease of [2+2+2] cycloaddition reactions are clearly evident from the above examples. The catalysts utilized in these reactions are easily handled under inert gas conditions *via* Schlenk line or in a glove box. The catalyst loading generally ranges between 5–10 mol%. In most reactions, mild conditions provide desired products in excellent yields. These reactions are excellent alternatives to the traditional aromatic electrophilic substitution and metal coupling reactions. The development of novel transition metal catalysts and novel applications of known catalysts have enhanced the utility of this extremely useful reaction. Late transition metals such as Co, Ni, Rh, Ru, Pd, Ir, are commonly utilized in the synthesis of highly substituted carbocyclic and heterocyclic ring systems. The reactions generally proceed *via* formation of a metallacyclopentadiene intermediate followed by insertion of another unsaturated bond.

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