# Highlights

# Beyond Reppe: Building Substituted Arenes by [2+2+2] Cycloadditions of Alkynes

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arenes · cycloaddition · homogeneous catalysis · multicomponent reactions

**T**ransition-metal-catalyzed cycloaddition reactions allow for the rapid construction of highly functionalized molecular frameworks in one step. The [2+2+2] cycloaddition reaction has become an effective tool for the synthesis of substituted arenes.[1] There are a number of excellent procedures published that have utilized various transition metals to synthesize these targets. Recent developments in this area have focused mainly on an intermolecular approach to ring synthesis, while still maintaining the ability to control the substitution pattern of the resulting products.[1] The purpose of this Highlight is to introduce the most recent attempts to solve the lingering problem of chemoselectivity in the intermolecular [2+2+2] cycloaddition reaction in the synthesis of arenes.

A nearly ideal synthesis of benzenoid rings involves the three-component coupling of alkynes. In 1948, Reppe and Schweckendiek discovered that transition metals can catalyze the cycloaddition of alkynes to form substituted benzenes [Scheme 1, Eq. (1)].[2] This discovery led to a paradigm shift in



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$$\text{(2)}$$
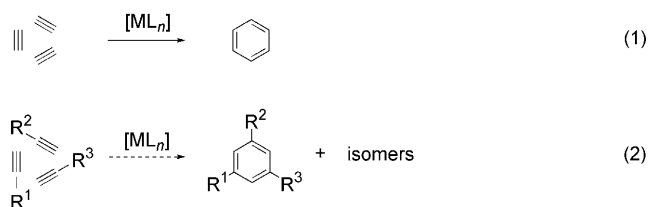
**Scheme 1.** Conceptual approach to benzene synthesis.

arene synthesis, moving beyond Friedel–Crafts approaches of derivatizing existing aromatics.[1b] However, the metal-catalyzed synthesis of arenes was inherently limited to alkyne trimerization; attempts at heterotrimerization (use of two or more different alkynes) led to complex mixtures [Eq. (2)].[1d,2]

Construction of substituted benzenes is problematic because of the difficulty in controlling the chemoselectivity during the initial metallacycle formation and subsequent regioselective insertion of the third alkyne.[1c,3] The most common strategy used to overcome this limitation has relied

on tethering two of the alkyne components [Scheme 2, Eq. (3)]. Metallacycle formation may be controlled by the geometric and entropic restrictions imparted by the tether. As a result, this partially intermolecular approach has been a



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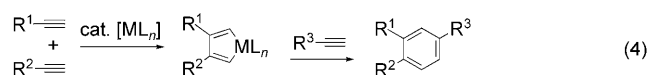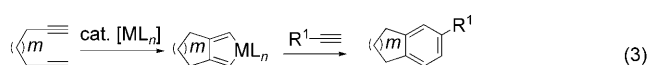
**Scheme 2.** Examples of intra- and intermolecular metal-catalyzed [2+2+2] cycloadditions.

powerful tool in assembling polycyclic frameworks from simple unsaturated precursors. Vollhardt et al. has had considerable success forming various benzenoid systems using [CpCo(CO)$_2$] (Cp = C$_5$H$_5$)to cyclotrimerize α,ω-diynes.[4] As a result, Co-catalyzed cycloadditions have become a versatile tool in ring synthesis of complex natural products.

A limitation of this strategy, however, is the presence of a secondary fused ring system in the resultant arene. A more general approach to substituted aromatics requires a fundamentally different strategy, one that completely eliminates the tether [Eq. (4)].

Over the last several years, promising new approaches to substituted arenes using transition-metal-catalyzed [2+2+2] cycloadditions have been reported. The selective "trimerization" of three different alkyne components has recently been reported using stoichiometric amounts of transition-metal complexes, for example, several based on zirconium[3] and titanium.[4,5] The stoichiometric approach avoids the potential pitfall of generating multiple different metallacycles by having the third alkyne added at the end, a solution that is impractical in a catalytic system.

Rendering the intermolecular [2+2+2] cycloaddition reaction catalytic has been the focus of more recent studies. A unique one-pot approach for the construction of polysubstituted aromatics from three unsymmetrical alkyne components catalyzed by [Cp\*RuCl(cod)] (Cp\* = C$_5$Me$_5$, cod = cyclooctadiene) has been realized by Yamamoto and Itoh et al. using a strategy based on a temporary boron tether.[6] In this innovative, although partially intramolecular, procedure a diyne intermediate is preformed in situ by reacting an

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alkynylboronate with propargyl alcohol which then undergoes metallacycle formation in the presence of [Cp*RuCl-(cod)]. This ruthenacycle regioselectively inserts a terminal alkyne to yield an arylboronate (Scheme 3). The arylboro-
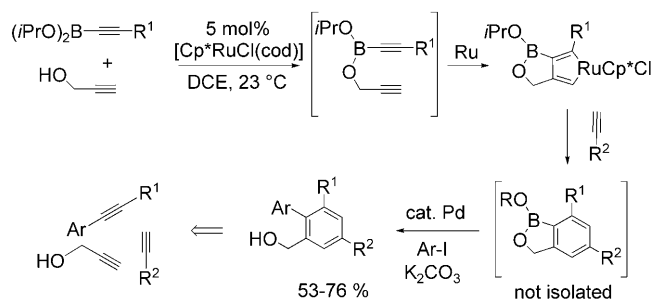


**Scheme 3.** Ru-catalyzed cycloaddition using a temporary boron tether. DCE = 1,2-dichloroethane.

nate, though not isolable, is further functionalized using Suzuki–Miyaura cross-coupling to yield the biphenyl product in satisfactory yields. Importantly, this one-pot two-step protocol achieves the equivalent of a three-component [2+2+2] cycloaddition (Scheme 3). A variety of terminal alkynes are well tolerated under the reaction conditions. Heterobiaryls are also accessible when 2-iodopyridine or 2-iodothiothene is used as the coupling partner. Further elaboration of this methodology by Yamamoto and Itoh et al. has broadened the synthetic utility of the reaction as the arylboronate is a versatile intermediate for other organic transformations. The arylboronate participates in Pd-catalyzed carbonylation to form phthalides in varying yields in the presence of Pd(OAc)$_2$/PPh$_3$, $p$-benzoquinone, and CO [Scheme 4, Eq. (5)].[6b] Imidates can also be synthesized when
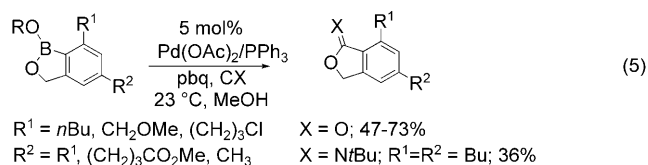


**Scheme 4.** Pd-catalyzed carbonylation of the arylboronate intermediate. pbq = $p$-benzoquinone.

an isocyanide is substituted for carbon monoxide. When the arylboronate derived from butynylboronate and propargyl alcohol is treated with *tert*-butylisocyanide under the reaction conditions, the imidate is isolated in low yield [Eq. (5)].

Yamamoto's temporary-tether strategy described above is a truly important breakthrough, but it, along with other similar strategies,[7] nevertheless suffers from the limitation of requiring a covalent linkage. Efforts at overcoming this limitation have met with some success, and often require addressing the simpler problem of regioselective trimerization of alkynes before one examines two or more alkyne partners.

Novel catalyst systems developed by Okamoto et al.[8] and Hilt et al.[9] utilize cobalt salts in the presence of easily prepared or commercially available ligands to effectively cyclotrimerize alkynes. Okamoto and his group have shown that iminomethylpyridine ligands in the presence of a CoCl$_2$·6H$_2$O/Zn catalyst system trimerize terminal alkynes to yield 1,2,4-trisubstituted benzene rings selectively in good to excellent yield [Scheme 5, Eq. (6)]. Similar results have been achieved by Hilt et al. when dicyclohexylimines are used as the ligand in the presence of a CoBr$_2$/Zn/ZnI$_2$ catalyst system [Eq. (7)].[9]
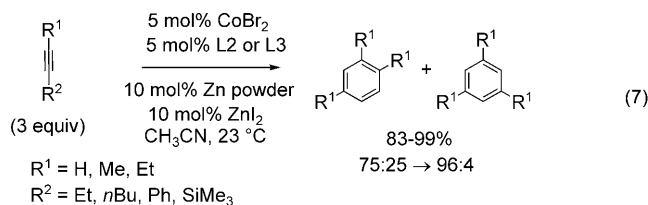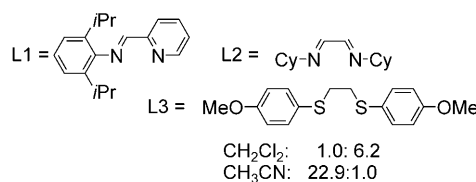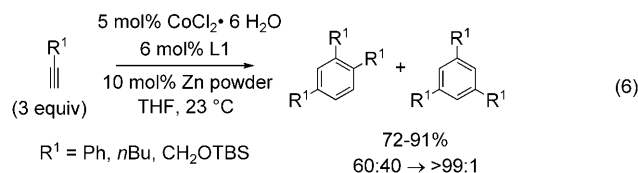


**Scheme 5.** Cobalt-catalyzed [2+2+2] cycloaddition. TBS = *tert*-butyldimethylsilyl, Cy = cyclohexyl.

Interestingly, when 1,2-bis(4-methoxyphenyl)thioethane (L3) is used as the ligand, the choice of solvent has a profound effect on the regioselective insertion of the third alkyne component.[9c] When CH$_3$CN is used as the solvent, product selectivity favors the 1,2,4-trisubstituted benzene; in contrast, reaction in CH$_2$Cl$_2$ selectively affords the 1,3,5 isomer. It has been rationalized that the coordinating ability of the solvent influences the regioselectivity of the reaction. Although the intermolecular cobalt-catalyzed reactions presented are operationally simple and extremely efficient, the substrate scope appears to be limited to aliphatic and aryl-terminal alkynes. Expanding the substrate scope while maintaining the desired selectivity remains a challenge.

In 2003, Tanaka et al. reported a highly regioselective intermolecular [2+2+2] homotrimerization of terminal alkynes catalyzed by a cationic Rh$^I$–biaryldiphosphine complex.[1d,10] Using 5 mol% [Rh(cod)$_2$]BF$_4$ and dtbm-segphos as a ligand, the cyclotrimerization of 1-dodecyne or cyclohexenyl acetylene was achieved in high yield giving predominantly the 1,2,4-substituted product over the 1,3,5 isomer [Scheme 6, Eq. (8)].[10] The use of neutral rhodium(I) or cationic iridium(I) complexes failed to yield a significant amount of product. Tanaka's attempts at facilitating an intermolecular heterotrimerization between two different alkynes relied on extreme electronic differentiation of the π components to control initial metallacycle formation. Upon
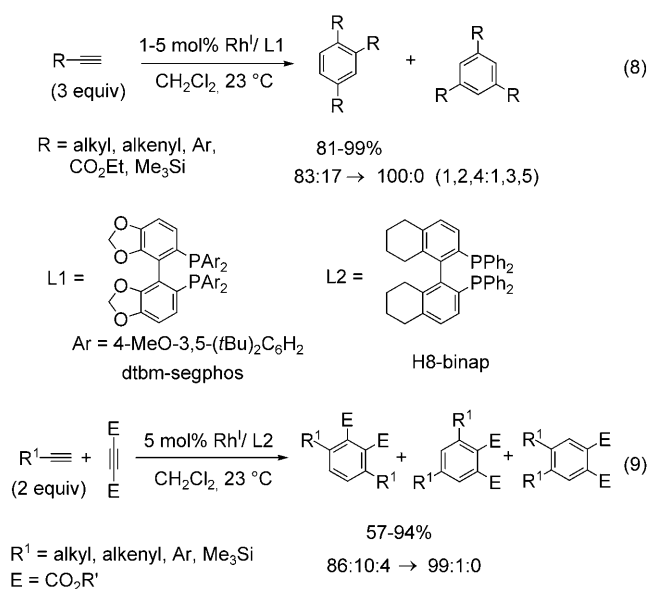
**Scheme 6.** Rh-catalyzed intermolecular [2+2+2] cycloaddition.

screening two different alkynes, it was found that the cationic rhodium(I)/H8-binap system is effective in the chemo- and regioselective cycloaddition of terminal alkynes with acetylene dicarboxylates giving the 1,2,3,4-substituted benzenes in excellent yield [Eq. (9)]. It is also important to note that the reaction is tolerant of many functional groups including alkyl halides, ethers, and alkenes. The selectivity of the reactions above [Eqs. (8) and (9)] contrasts that of the work reported by Patrick et al. in which a titanium complex, supporting a *p-tert*-butylcalix[4]arene ligand, yields primarily the 1,2,4-substituted isomer in 95% yield when terminal arylacetylenes or trimethylsilylacetylenes are used.[11]

Although a cationic iridium(I) complex was not successful in the cycloadditions performed by Tanaka et al.,[10] Takeuchi and Nakaya have shown that neutral iridium(I) systems are capable of facilitating the cyclization of dimethylacetylene dicarboxylate (DMAD) with terminal alkynes.[12] The choice of ligand was shown to have a profound effect on the chemoselectivity of this reaction. For example, when 1,2-bis(diphenylphosphino)ethane (dppe) is used as the ligand, two molecules of DMAD are incorporated into the product [Scheme 7, Eq. (10)]. However, when the perfluoroaryl derivative of dppe is used as the ligand, one molecule of DMAD reacts with two molecules of the acetylene.

Polysubstituted benzenes are produced in high yields (up to 98%) when a variety of substituted terminal and internal alkynes are used with the dppe ligand. Regioselectivity decreases when terminal aliphatic alkynes are used with the
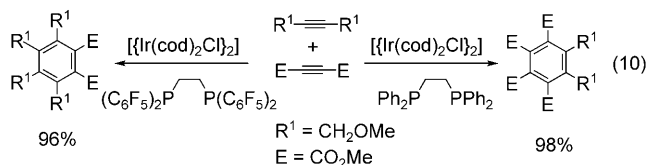


**Scheme 7.** Ligand-controlled product formation in an Ir-catalyzed [2+2+2] cycloaddition.

perfluoroaryl derivative. For example, 1-hexyne gives a mixture of 1,2,4,5- and 1,2,3,5-substituted benzenes in a 64:36 ratio and 95% yield. Chemoselectivity was rationalized based on the electronics of the metal center. An electron-rich iridium(I) center, arising from the coordination of dppe, would lead to more effective binding of an electron-deficient alkyne such as DMAD. When an electron-withdrawing ligand, such as the perfluoroaryl dppe, is used coordination of the acetylene over DMAD is preferred.

The strategy of electronic differentiation between alkynes fails in cases where similar substituents are desired. For that reason, a complementary approach has recently been advanced that relies on the use of an alkyne surrogate as one of the π components. In 2008, a coupling reaction of β-keto esters with terminal alkynes was reported by Nakamura and Tsuji et al. as well as by Takai and Kuninobu et al.[13,14] Both groups have reported the manganese-catalyzed dehydrative [2+2+2] coupling of 1,3-dicarbonyl compounds with arylacetylenes. The enol form of the β-keto ester mimics the role of an alkyne and undergoes a cycloaddition followed by dehydration to yield *p*-terphenyl derivatives. Using 10 mol% [MnBr(CO)$_5$], 10 mol% *N*-methylmorpholine *N*-oxide (NMO), and 20 mol% MgSO$_4$, Nakamura, Tsuji, and co-workers were able to successfully couple 1,3-dicarbonyls with phenylacetylene [Scheme 8, Eq. (11)].[13]
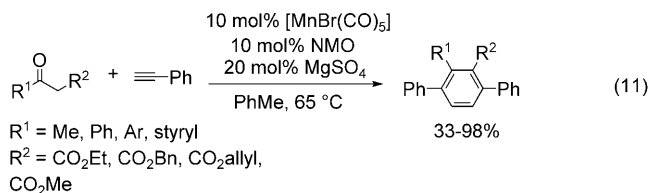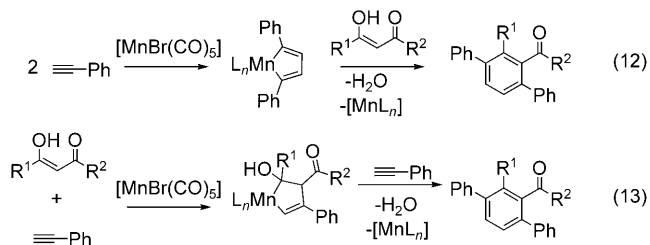


**Scheme 8.** Mn-catalyzed [2+2+2] cycloaddition of 1,3-dicarbonyls with terminal acetylenes.

The Mn-catalyzed [2+2+2] cycloaddition reaction proved to be sensitive to the steric and electronic properties of the $R^1$ group of the 1,3-dicarbonyl. Substrates bearing a bulky substituent such as cyclohexyl or *tert*-butyl failed to give product. This is most likely because of the inability of a sterically encumbering enol to coordinate to an already congested metal center. Likewise, electron-donating groups at the $R^1$ position, such as *p*-methoxyphenyl, led to slightly lower yields of product. Electron-rich alkynes were found to react more rapidly than electron-deficient alkynes. A reasonable argument is that electron-rich alkynes coordinate more readily to the electron-deficient Mn center. Although the reaction is tolerant of acetylene functionalization, internal alkynes and *o*-methyl-substituted phenylacetylene gave no desired product. The substrate scope of this reaction appears to be limited to aromatic terminal alkynes.

Takai and Kuninobu et al. have also shown that the cycloaddition between β-keto esters and terminal alkynes is facile under neat reaction conditions at 80 °C in the presence of molecular sieves (4 Å).[14] While the mechanism is not well understood, they have suggested that it proceeds via one of two metallacycle intermediates [Scheme 9, Eqs. (12) and

(13)]. In first case [Eq. (12)], two equivalents of alkyne undergo a cycloaddition to form a manganacyclopentadiene, which subsequently intercepts the enol form of the β-keto ester and upon reductive elimination and dehydration gives the desired product. Alternately, manganacyclopentadiene formation could occur by means of an oxidative cyclization between the β-keto ester and an alkyne [Eq. (13)]. A second equivalent of alkyne inserts to give the benzene product.



**Scheme 9.** Proposed pathway of the Mn-catalyzed [2+2+2] cycloaddition of β-keto esters with terminal acetylenes.[13]

Intriguingly, the use of a rhenium catalyst in lieu of manganese with 1,3-dicarbonyls and alkynes results in the formation of pyrone adducts instead of benzenes, as recently reported by Kuninobu, Takai, and co-workers [Scheme 10, Eq. (14)].[15] A subsequent addition of electron-deficient alkyne results in a [4+2]/retro-[4+2] sequence to form benzenoid rings (Scheme 10). The overall strategy, while involving two distinct steps, introduces the equivalent of three different cycloaddition components and affords product selectively. Manipulating the alkyl substituents on the keto
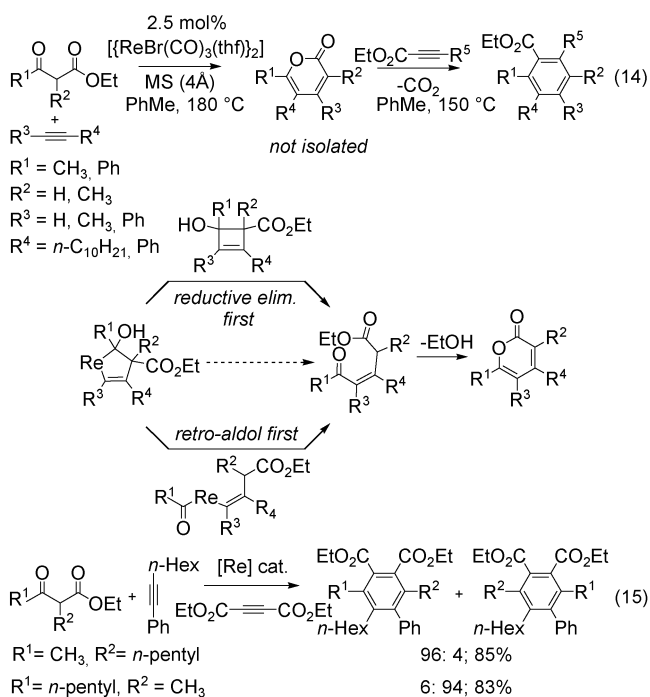


**Scheme 10.** Re-catalyzed pyrone synthesis: [4+2] cycloaddition/retro-[4+2] cycloaddition.

ester results in complementary access to either substitution pattern [Eq. (15)].

Tanaka et al. have shown that enol acetates are competent alkyne surrogates in intermolecular rhodium-catalyzed [2+2+2] cycloadditions.[16] The use of 10 mol% of a [Rh-(cod)$_2$]BF$_4$/rac-binap catalyst system yields a tetrasubstituted benzene as a single regioisomer [Scheme 11, Eq. (16)]. Importantly, they succeed in coupling three distinct "alkynes" in this transformation.
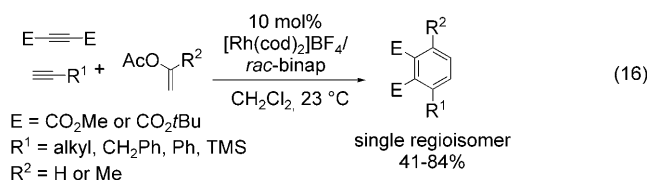


**Scheme 11.** Rh-catalyzed cycloaddition using enol acetates as alkyne surrogates.

Terminal aliphatic, aryl, and silyl alkynes are well tolerated providing benzenes in varying yields as single regioisomers. Mechanistically, it is hypothesized that the regioselectivity of the enol insertion is controlled by the coordination of the enol carbonyl moiety to the cationic Rh$^I$ center as illustrated in Scheme 12. Insertion of the third
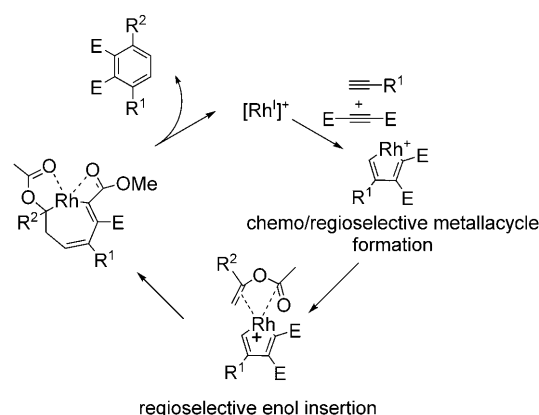


**Scheme 12.** Cationic rhodium-catalyzed cycloaddition using enol acetate.

alkyne component yields a cationic rhodacycle in which the rhodium center is stabilized by the carbonyl functionality of the enol carbonyl as well as the dicarboxylate carbonyl. Reductive elimination and aromatization by loss of acetic acid closes the catalytic cycle and affords the desired product.

The reports highlighted above are clear advances to more general [2+2+2] cycloadditions en route to polysubstituted benzenoid systems. That said, significant challenges still remain. Expanding the substrate scope to include more diverse alkynes and alkyne surrogates as well as solving the regioselectivity problem in reactions of aliphatic alkynes will lead to a truly general, intermolecular [2+2+2] cycloaddition reaction. Although the reaction and substrate scope of each reaction presented above are still being investigated, the

intermolecular approach to polysubstituted benzenes will certainly find a broader application in the synthesis of small molecules.

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