

Recent Advances in the Transition-Metal-Catalyzed Regioselective Approaches to Polysubstituted Benzene Derivatives

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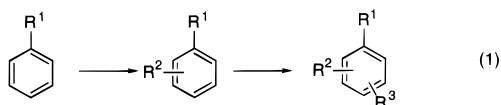
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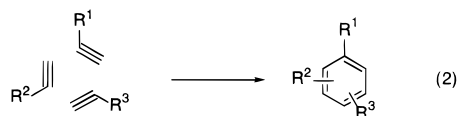
I. Introduction

Polysubstituted benzenes are highly useful compounds which are widely used in industry as well as in the laboratory. The regioselective construction of polysubstituted benzenes has been mainly achieved by stepwise introduction of the substituents via electrophilic substitution reactions such as the Friedel–Crafts reaction (eq 1).¹ This is a useful



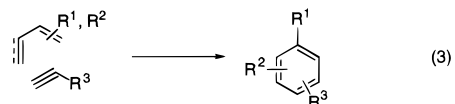
method for the synthesis of polysubstituted benzenes. However, high regioselectivity (and yield) can only be achieved by the careful choice of the reagents and synthetic route. Furthermore, it is usually necessary to convert and/or protect–deprotect the substituents properly. Directed *ortho* metalation is another synthetic method which has been studied extensively, and this approach is a useful method for the introduction of a substituent at the *ortho* position.² However, the scope of this reaction is clearly restricted by its nature. Compared to the following transition metal-catalyzed methods, these approaches have some drawbacks from the viewpoint of atom economy³ or environmental concern.

In 1948, Reppe et al. discovered the transition-metal-catalyzed [2+2+2] cyclotrimerization of alkynes,⁴ and this new synthetic method was applied to the synthesis of substituted benzenes (eq 2). In this

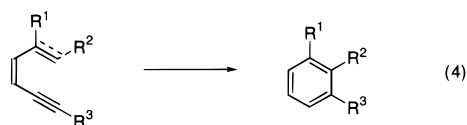


reaction, three C–C bonds of the aromatic ring are formed in one step. The regioselective synthesis of the compounds can be achieved especially when the reaction is carried out in a partially or totally intramolecular fashion, which provides another useful method for the synthesis of polysubstituted benzenes.

The construction of the benzene ring by the [4+2] approach is another promising methodology. For example, the intramolecular reaction of conjugated enynes with alkynes in the presence of Lewis acid or under thermal conditions has been reported,^{5,6} though the transition-metal-catalyzed reaction has not been reported in the literature.⁷ Recently, the [4+2] approach for the construction of benzene rings was realized by the transition-metal-catalyzed reaction of unsaturated hydrocarbons (eq 3).^{8,9} In this approach, the regioselective introduction of some substituents is guaranteed because the partial structure of the benzene ring is already built in the four-carbon moiety.



Some recent studies show that the benzene ring was also formed by the intramolecular cyclization of dienynes or enedienynes (eq 4). While the thermal benzannulation of these compounds such as Bergman cyclization has been extensively studied and reviewed,¹⁰ there are few examples of the transition-metal-catalyzed reactions.





Shinichi Saito was born in Japan in 1968. He studied at Tokyo University, where he obtained his B.Sc. degree in 1990 and his Ph.D. degree in 1995 under the supervision of Professor Koichi Shudo. In 1994, he had a chance to stay at the University of Utah as a Nagai Foundation Fellow under the supervision of Professor Peter J. Stang. After he spent one year as a postdoctoral fellow with Professor Yoshinori Yamamoto at Tohoku University, he moved to Toyama Medical and Pharmaceutical University as an Assistant Professor. In 1998, he returned to Tohoku University as an Assistant Professor. His current research interests are primarily directed toward the development of novel transition-metal-catalyzed reactions and their application to organic synthesis.



Yoshinori Yamamoto was born in Kobe, Japan, in 1942. He received his M.Sc. (1967) and Ph.D. (1970) degrees from Osaka University, Japan. He was appointed as an Instructor at Osaka University in 1970. While he was working as an Instructor at Osaka University, he went to Professor H. C. Brown's research group at Purdue University, as a Postdoctoral Associate (1970–1972). In 1977 he was appointed as an Associate Professor at Kyoto University, Japan, where he remained until 1985. In 1986 he moved to Tohoku University to take up his present position, Professor of Chemistry. He is also holding a Professorship at ICRS, Tohoku University, and a visiting Professorship at Kyushu University. He was a recipient of the Chemical Society of Japan Award for Young Chemists in 1976. More recently, he was awarded the Chemical Society of Japan Award (1995). He is a regional Editor of *Tetrahedron Letters*, and he is the President of the International Society of Heterocyclic Chemistry. He has a wide range of research interests in synthetic organic and organometallic chemistry. His recent work has focused on the use of transition-metal complexes as catalytic reagents in organic synthesis and synthesis of complex natural products.

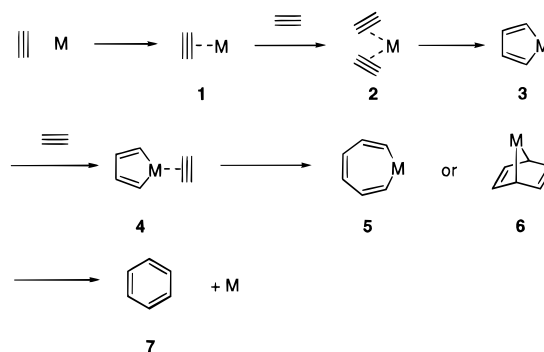
The purpose of this review is to cover the recent advances (1990 to early 2000) in the regioselective synthesis of polysubstituted benzenes achieved by the transition-metal-catalyzed [2+2+2] cyclotrimerization and [4+2] cycloaddition reactions.^{11,12} Other types of transition-metal-catalyzed benzannulation reactions are also discussed, but transition-metal-mediated reactions are not discussed in this review.

II. [2+2+2] Approach to the Regioselective Synthesis of Polysubstituted Benzenes

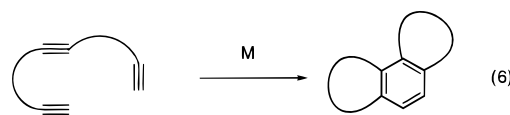
II.1. Reaction of Alkynes Which Involves Metallacyclopentadiene as an Intermediate

Transition-metal-catalyzed cyclotrimerization of alkynes is a useful method for the construction of substituted benzenes. Many transition-metal complexes have been used as catalysts (*vide infra*). This synthetic method has been reviewed repeatedly in the literature.¹³ The mechanism of this reaction has been considered as described in Scheme 1. Thus, two alkyne moieties coordinate to the metal, and then coupling reaction proceeds to give the metallacyclopentadiene **3**. Insertion or addition of an alkyne to the metallacycle takes place to give a metallacycle such as **5** or **6**. The benzene ring is formed by the reductive elimination of the metal (Scheme 1).

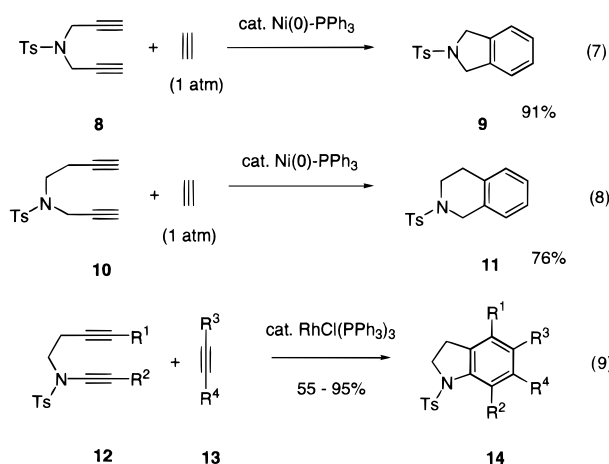
Scheme 1



In principle, it is possible to carry out the reaction in a regioselective manner by the selective formation of the metallacyclopentadiene, followed by the regioselective addition of the third alkyne. However, in most cases it has been difficult to carry out the intermolecular reaction in a highly regioselective manner, and a partially intramolecular approach (eq 5) or completely intramolecular approach (eq 6) was more successful and more applicable. In this section, we will first discuss the reaction of simple compounds, and proceed to the reaction of more complicated compounds which are of interest from a theoretical or biological point of view.



Cocyclization of aminodiyynes with alkynes proceeded in the presence of a Ni(0) catalyst¹⁴ (eqs 7 and 8) or Wilkinson's catalyst¹⁵ (eq 9, Table 1) to give bicyclic heterocycles. It is possible to introduce the nitrogen atom as well as the substituents at the desired position by choosing the appropriate amin-



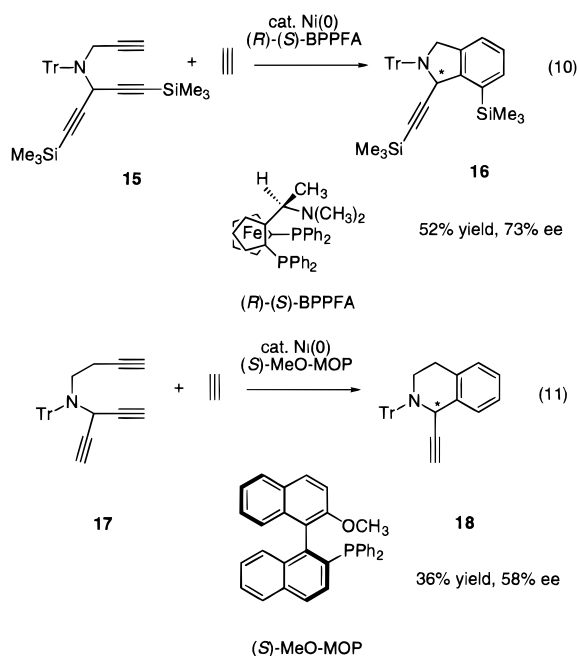
odiynes and the substituted alkynes. An asymmetric synthesis of these compounds has also been reported

Table 1. Rh-Catalyzed [2+2+2] Cyclotrimerization of Aminodiynes **12 with Alkynes **13****

| 12 | | 13 | | yield of 14 (%) |
|--------------------------------------|--------------------|------------------------------------|----------------|------------------------|
| R ¹ | R ² | R ³ | R ⁴ | |
| H | H | H | H | 91 |
| (CH ₂) ₂ OH | H | H | H | 70 |
| H | Ph | H | H | 85 |
| Ph | Me ₃ Si | H | H | 93 |
| H | Me ₃ Si | H | H | 68 |
| (CH ₂) ₂ OBzl | H | (CH ₂) ₂ OH | H | 88 ^a |

^a A mixture of isomers was isolated.

when the nickel-catalyzed reaction of **15** or **17** is carried out in the presence of chiral ligands (eqs 10 and 11).¹⁴ This is the first example of the application of this cyclotrimerization reaction to asymmetric synthesis.



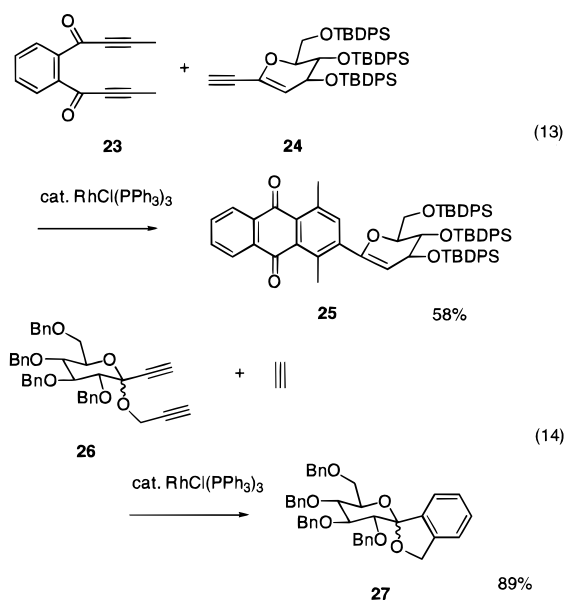
McDonald et al. reported the notable *meta* selectivity in the rhodium-catalyzed cyclotrimerization of diynes with alkynes (eq 12 and Table 2).¹⁶ The regioselectivity of the reaction and the reactivity of

Table 2. Rh-Catalyzed [2+2+2] Cyclotrimerization of Oxodiynes **19 with Alkynes **20****

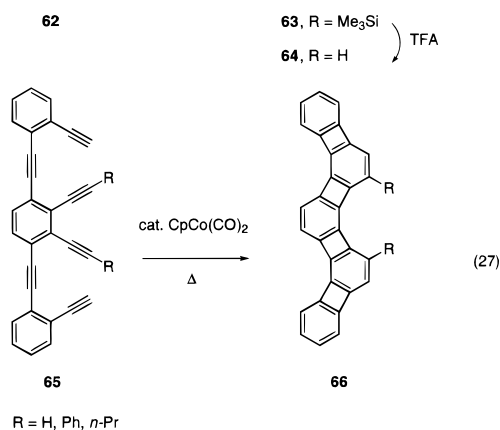
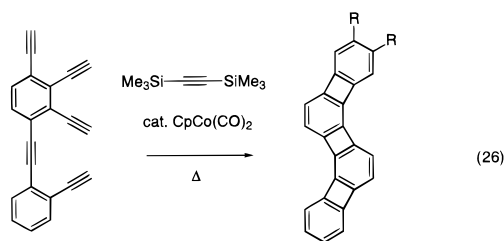
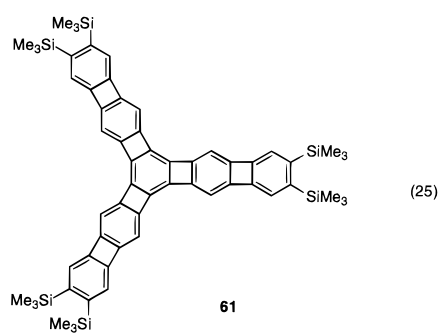
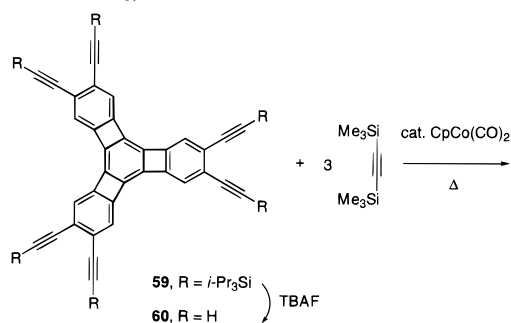
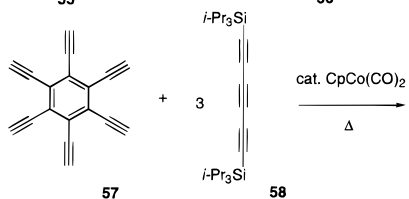
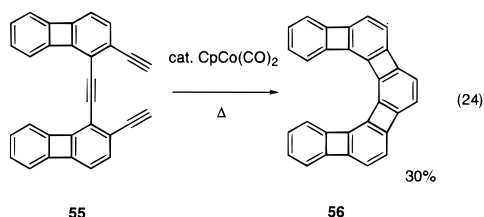
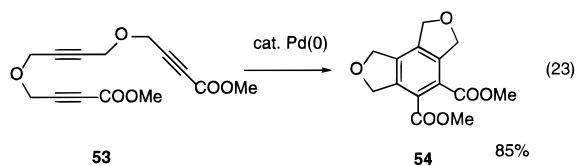
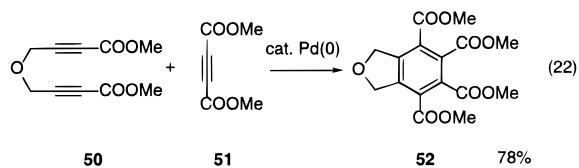
19 + **20** $\xrightarrow{\text{cat. RhCl(PPh}_3)_3}$ **21** + **22** (12)

| 19 | | 20 | combined yield of 21 + 22 (%) | ratio 21:22 |
|-------------------------------------|----------------|-------------------------------------|---|--------------------|
| R ¹ | R ² | R ³ | | |
| Me | H | <i>n</i> -Bu | 35 | 1.7:1 |
| Me | H | C(CH ₃) ₂ OH | 54 | 21 only |
| Me | H | CH ₂ OH | 53 | 1.8:1 |
| C(CH ₃) ₂ OH | H | <i>n</i> -Bu | 36 | 21 only |
| C(CH ₃) ₂ OH | H | C(CH ₃) ₂ OH | 60 | 21 only |
| OEt | Me | <i>n</i> -Bu | 61 | 4:1 |
| OEt | Me | C(CH ₃) ₂ OH | 53 | 21 only |

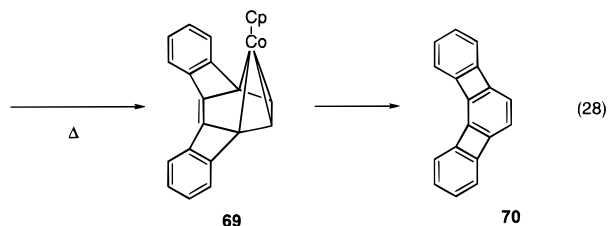
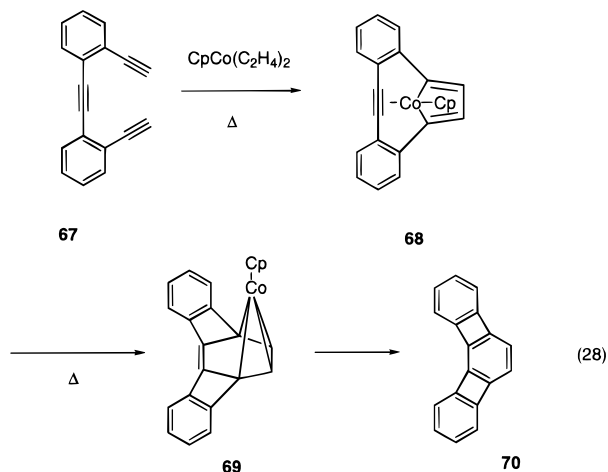
the substrate highly depend on the steric size of the substituents attached to the substrates **19** and **20**. An interesting application of this reaction to the synthesis of *C*-acyl glycoside has been reported: thus, they succeeded in the [2+2+2] cyclotrimerization of carbohydrate derivatives with alkynes (eqs 13 and 14).¹⁶ A Rh catalyst was also employed in the cyclotrimerization of perfluoroalkylated alkynes.¹⁷



It is well-known that nitriles could be used as an alkyne equivalent in the [2+2+2] cyclotrimerization,^{13d} and Saá and Vollhardt et al. studied the regioselectivity of the partially intramolecular reaction of the cyanoalkyne **28** with alkynes **29** in the presence of CpCo(CO)₂ (eq 15 and Table 3).^{18,19} High regioselectivity has been observed in some cases when a bulky trialkylsilyl group is introduced to the alkyne. They applied this methodology to the syntheses of ergot alkaloids such as lysergene (**36**, eq 16) and LSD. Castedo and Saá et al. reported the synthesis of



time (eq 28).^{23g} The structure of **69** was confirmed by X-ray crystallographic analysis.

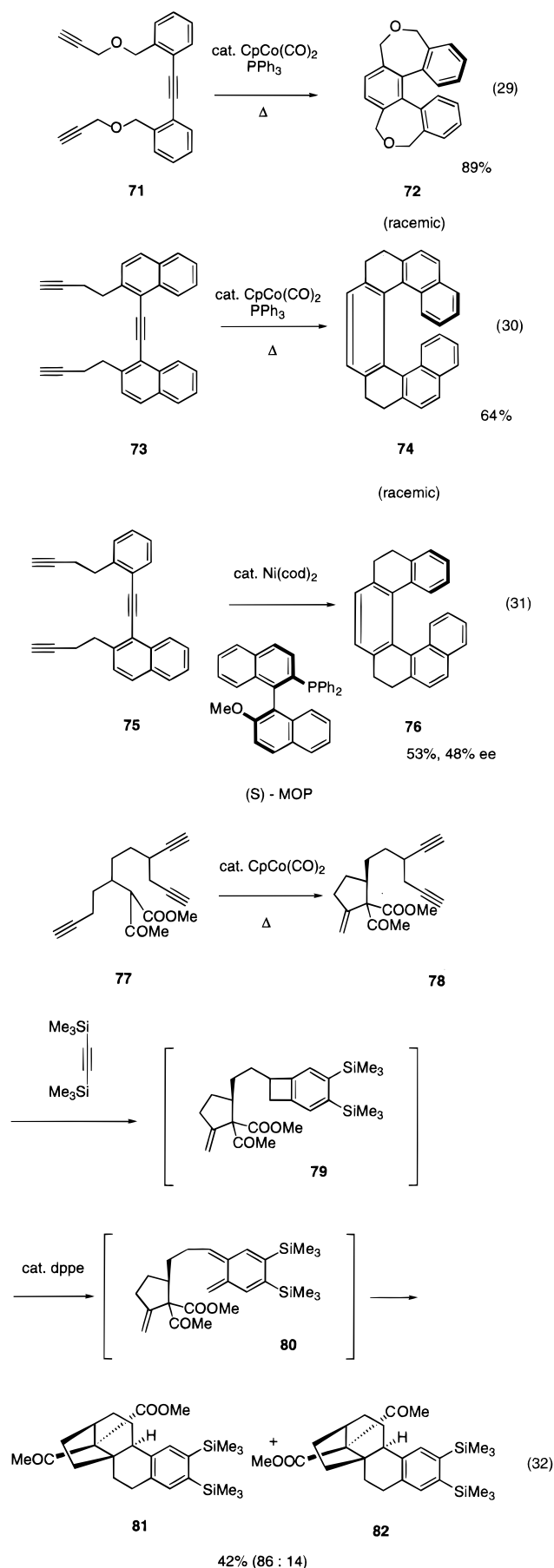


catalyzed reaction of triynes or the reaction of diynes (diethynylbenzene) with trimethylsilylacetylene, followed by the removal of the trimethylsilyl group. Recent applications include the synthesis of **56**,^{23b} **60**,^{23c} and **61**.^{23c} This reaction was also applied to the synthesis of zigzag [4]- and [5]phenylenes (eqs 26 and 27).^{23f}

During the study, they succeeded in the isolation of metallacyclopentadiene(alkyne) complexes and an η^4 -alkyne complex, the structures of which are closely related to important intermediates **4** and **6** (Scheme 1) in the cyclotrimerization of alkynes, for the first

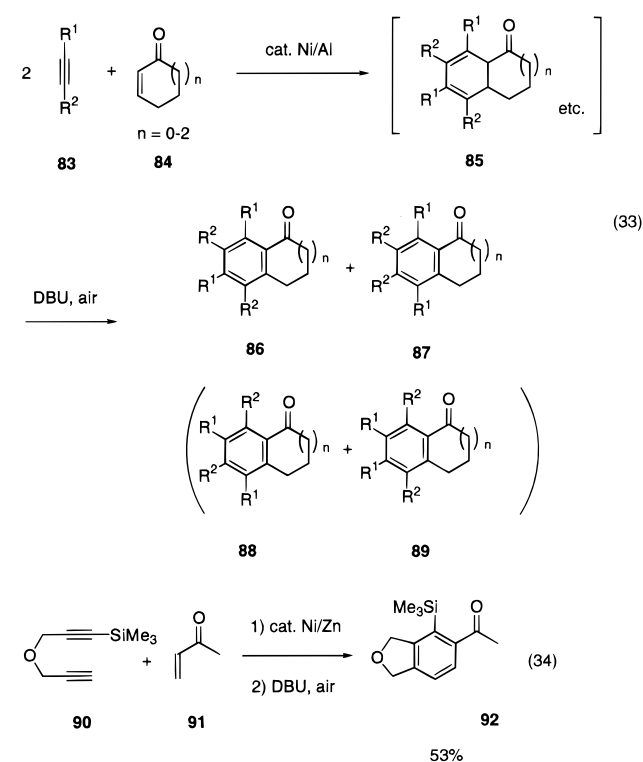
Stará and Starý et al. applied this [2+2+2] cyclotrimerization to the synthesis of helicenes.²⁴ Thus, they prepared triynes such as **71** and **73**, and treated the compounds with a catalytic amount of $\text{CpCo}(\text{CO})_2\text{-PPh}_3$ to obtain a series of helicenes such as **72** and **74** (eqs 29 and 30). They also reported the asymmetric synthesis of helicene **76** in the presence of chiral nickel catalyst (eq 31).^{24a} Cobalt-catalyzed cyclotrimerization of simple alkynes has also been carried out in supercritical water.²⁵

Malacria et al. applied the cyclotrimerization reaction to a new type of cascade reaction. Thus, they carried out the partially intramolecular reaction of diyne **78** with bis(trimethylsilyl)acetylene, followed by the treatment of the intermediate **79** with dppe to give a mixture of the tetracyclic products **81** and **82** in 42% yield (eq 32).²⁶ Six carbon-carbon bonds are formed in this one-pot sequence.

**Table 4. Nickel–Aluminum-Catalyzed Cotrimerization of Alkynes **83** with Enones **84****

| 83 R ¹ | 84 R ² | 84 <i>n</i> | combined yield of 86–89 (%) | ratio |
|---|-----------------------------|-----------------------|---------------------------------------|-------------------------|
| | | | | 86:87:88 + 89 |
| <i>n</i> -Bu | H | 0 | 71 | 82:14:4 |
| Et | Et | 0 | 62 | |
| CH ₂ OSi <i>t</i> -BuMe ₂ | H | 0 | 42 | 86 , >98% |
| (CH ₂) ₂ OSi <i>t</i> -BuMe ₂ | H | 0 | 81 | 92:<2:6 |
| <i>t</i> -Bu | H | 0 | 45 | 87 , 89 % |
| Me ₃ Si | H | 0 | 33 | 87 , >98% |
| <i>n</i> -Bu | H | 1 | 83 | 91:7:<2 |
| Me | H | 1 | 50 | 89:9:<2 |
| <i>n</i> -Bu | H | 2 | 70 | 85:0:15 |

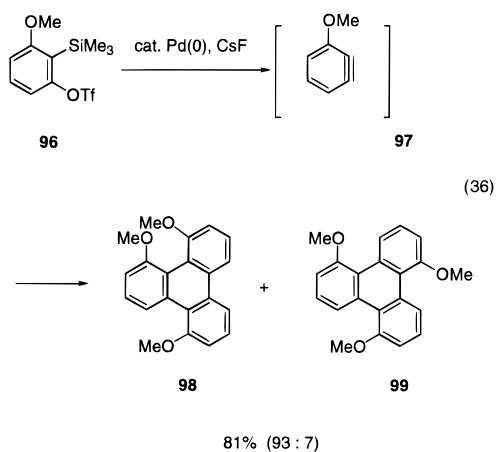
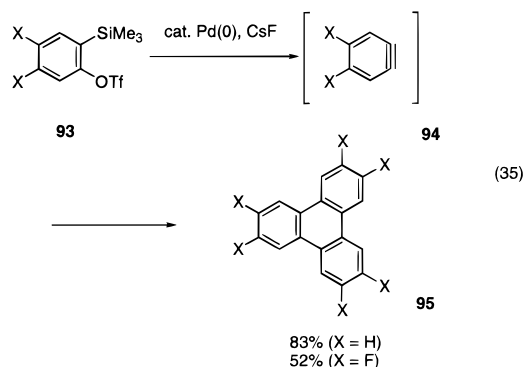
cotrimerization of α,β -enones **84** with alkynes **83**, followed by the aerobic oxidation of the intermediate **85** in the presence of DBU. Nickel–aluminum^{27a} (eq 33 and Table 4) and nickel–zinc^{27b} (eq 34) were



effective catalysts for these reactions. High regioselectivity has been observed in many examples. Similar reactions were also reported by Cheng et al.^{28a} The nickel–zinc catalytic system was also used in the cocyclotrimerization of oxa- and azabenzonorbornadienes with alkynes.^{28b}

Benzyne, which is a highly reactive alkyne, has recently been employed as a unique building block for the formation of fused aromatic compounds. Pérez and Guitián et al. have employed benzyne **94** in the palladium-catalyzed synthesis of triphenylenes **95** (eq 35).^{28a} They observed very high regioselectivity in the reaction of 3-methoxybenzyne **97** (eq 36). The reaction has been applied to the synthesis of hexabenzotriphenylene and other strained polycyclic aromatic compounds.^{29b} Cocyclization of arynes with alkynes was studied;^{29c,30a} for example, the reaction of benzyne **102** with alkynes **101** gave the phenanthrene

Ikeda et al. reported the regioselective synthesis of benzenes, which was achieved by the regioselective



derivatives **103** as the major products (eq 37 and Table 5). The reaction of benzyne **102** with π -al-

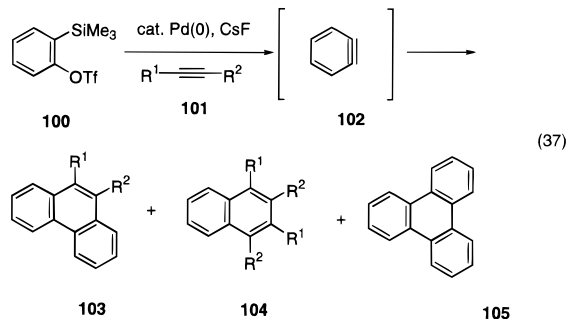


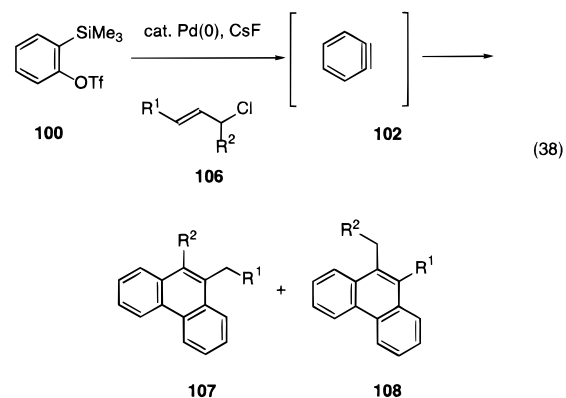
Table 5. Palladium-Catalyzed Cocyclization of Benzenes with Alkynes

| 101 | | yield (%) | | |
|-----------------|-----------------|-----------|-----|-----|
| R ¹ | R ² | 103 | 104 | 105 |
| COOMe | COOMe | 84 | 7 | 2 |
| CF ₃ | CF ₃ | 65 | | 20 |
| COOEt | Me | 63 | 8 | 10 |
| Et | Et | 28 | | 23 |
| Ph | Ph | 34 | 2 | 26 |

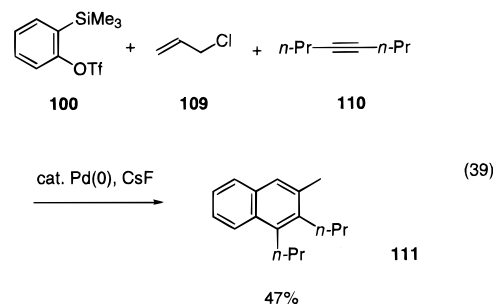
lypalladium species derived from **106** afforded a mixture of **107** and **108** (eq 38 and Table 6).^{30b} The

Table 6. Palladium-Catalyzed Cocyclization of Benzenes with Allyl Chlorides

| 106 | | combined yield of 107 + 108 (%) | ratio 107:108 |
|----------------|----------------|---|----------------------|
| R ¹ | R ² | | |
| H | H | 70 | |
| Me | H | 66 | 58:42 |
| H | Me | 70 | 35:65 |
| Ph | H | 73 | 73:27 |



controlled trimerization of benzyne–alkene–alkyne was accomplished (eq 39).^{30b} The latter two reactions



(eqs 38 and 39) would not proceed through a palladacyclopentadiene intermediate but would proceed via a sequential carbopalladation process. These methods provide interesting pathways for the construction of fused aromatic compounds.

II.2. Miscellaneous Reactions

Grubbs catalyst, which has been widely used in the olefin metathesis reaction,³¹ was used as a catalyst for the cyclotrimerization of alkynes. Blechert et al. reported for the first time that the Grubbs catalyst was an efficient catalyst for the intramolecular cyclotrimerization of alkynes such as **112** (eq 40).³² This catalyst was also an effective catalyst for the intermolecular reaction of alkynes **114** (eq 41 and

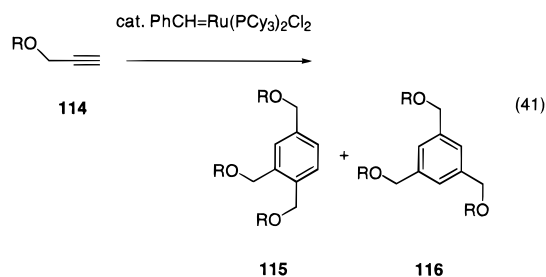
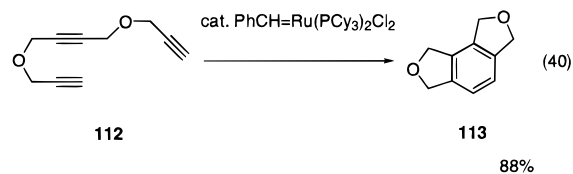
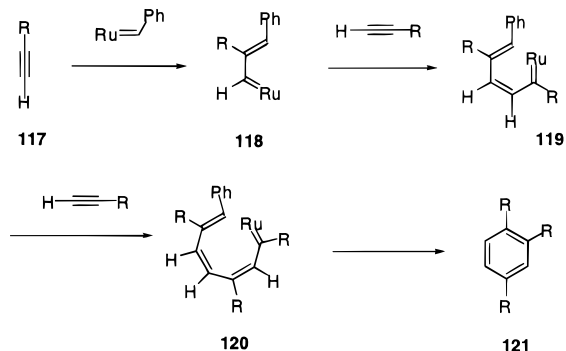


Table 7).³³ In this case, however, the mechanism of the reaction should be quite different, and vinyl

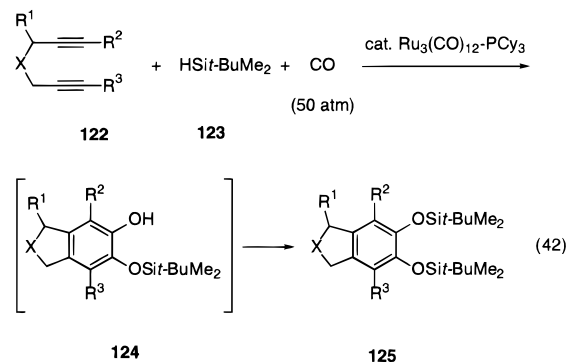
Table 7. Ru-Catalyzed Cyclotrimerization of 2-Propynyl Derivatives

| R | combined yield of | |
|--------------------------------|-------------------|-------------------|
| | 115+116 (%) | ratio (115 : 116) |
| | 75 | 90 : 10 |
| | 72 | 90 : 10 |
| | 66 | 90 : 10 |
| Ac | 70 | 95 : 5 |
| <i>t</i> -BuMe ₂ Si | 82 | 75 : 25 |
| Piv | 81 | 95 : 5 |

Scheme 2

carbene complexes such as **118–120** would be the intermediates of this reaction (Scheme 2). The consecutive intramolecular ring closing metathesis reaction should follow.

Another interesting method for the construction of the benzene ring **125** has been reported by Murai et al. They carried out the ruthenium-catalyzed [2+2+1+1] reaction of 1,6-diyne **122** with a hydrosilane **123** and carbon monoxide (eq 42 and Table 8).³⁴

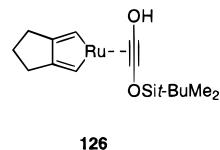


They assume that two molecules of carbon monoxide

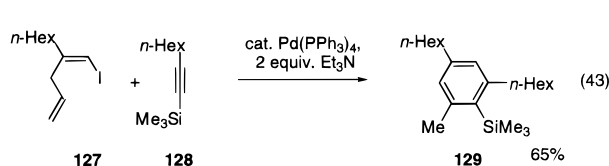
Table 8. Synthesis of Benzene Derivatives by the Ruthenium-Catalyzed Reaction of Diynes with HSi*t*-BuMe₂ and CO

| X | R ¹ | R ² | R ³ | yield (%) of 125 |
|----------------------------------|---------------------------------|----------------|----------------|-------------------------|
| C(COMe) ₂ | H | H | H | 71 |
| CH ₂ | H | H | H | 45 |
| O | H | H | H | 40 |
| TsN | H | H | H | 45 |
| C(CH ₃) ₂ | OSi <i>t</i> -BuMe ₂ | H | H | 73 |
| C(COOEt) ₂ | H | Me | H | 62 |
| C(COOEt) ₂ | H | Me | Me | 53 |

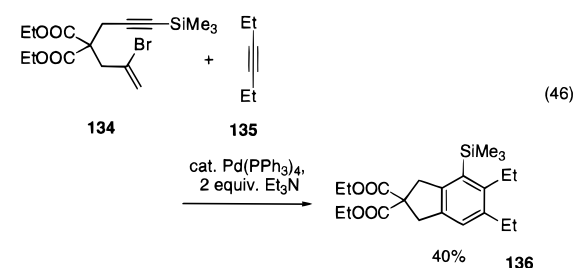
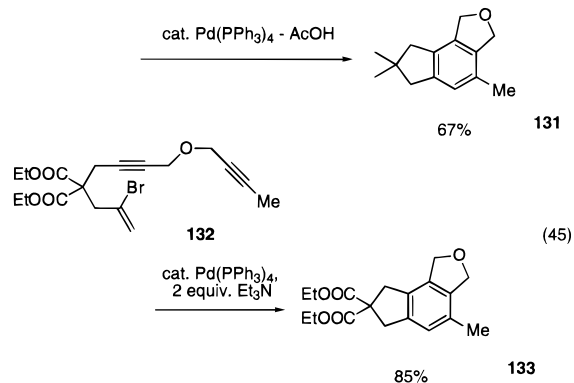
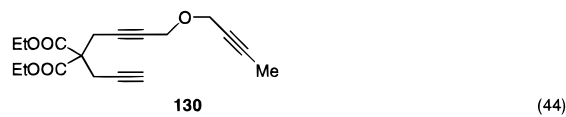
were reduced in situ to give a Ru–alkyne complex **126**, which further reacted to give the final product.



It is possible to prepare polysubstituted benzenes by utilizing the cyclic cascade carbopalladation reaction. Negishi et al. reported that the palladium-catalyzed reaction of a halodiene **127** with an alkyne **128** afforded a polysubstituted benzene **129** in good yield (eq 43).^{35a} They have also shown that this



reaction could be applied to the synthesis of various benzene derivatives (eqs 44–46).^{35b} A vinyl palladium



Scheme 3

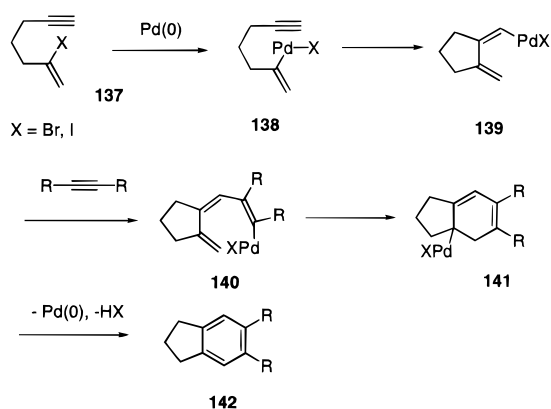


Table 9. Synthesis of Benzene Derivatives by the Rhodium-Catalyzed Silylcarbonyl Cyclization of Triynes

| X | combined yield of 144 + 145 (%) | ratio 144 : 145 |
|--|---|-------------------------------|
| C(COOEt) ₂ | 95 | 88:12 |
| C(CH ₂ O) ₂ C(CH ₃) ₂ | 90 | 93:7 |
| C(CH ₂ OMe) ₂ | 75 | 92:8 |
| C(CH ₂ OBn) ₂ | 94 | 91:9 |

species such as **139** would be formed as an intermediate in these reactions (Scheme 3).

Ojima et al. have also reported a similar cascade reaction initiated by the metallasilylation of triynes (eq 47, Table 9).³⁶ This reaction proceeded in the presence of rhodium catalyst, and the silylbenzenes **144**, together with benzenes **145** produced by the normal [2+2+2] cyclotrimerization of the alkyne **143**, were obtained as the major products.

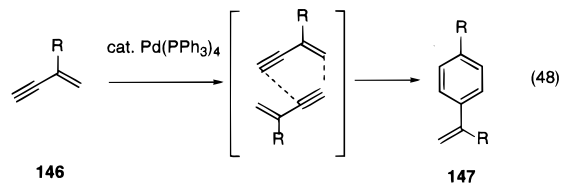
III. [4+2] Approach and Other Approaches to the Regioselective Synthesis of Polysubstituted Benzenes

III.1. Reaction of Conjugated Enynes

Though the [4+2] approach is an alternative and attractive method for the regioselective construction of the benzene ring, few examples have been reported in the literature. The intramolecular reaction of conjugated enynes with alkynes in the presence of Lewis acid or under thermal conditions has been reported,^{5,6} but the intramolecular reaction has never been reported. The finding of the transition-metal-catalyzed reaction has changed the situation dramatically. In this section we examine the scope of these reactions first, and then the application of the reactions is discussed.

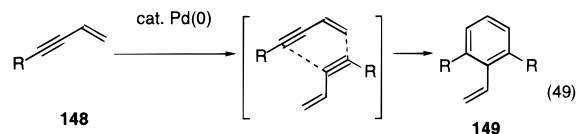
Yamamoto et al. discovered that the conjugated enynes **146** were excellent substrates for the formal

[4+2] cycloaddition in the presence of palladium catalyst (eq 48 and Table 10).^{8a} The reaction pro-

Table 10. Palladium-Catalyzed Homobenzannulation of 2-Substituted Enynes **146**

| R | yield of 147 (%) | R | yield of 147 (%) |
|---------------|-------------------------|--|-------------------------|
| <i>n</i> -Hex | 77 | (CH ₃) ₂ C(OH)CH ₂ CH ₂ | 81 |
| Me | 70 | CH ₃ COCH ₂ CH ₂ | 82 |

ceeded in a highly regioselective manner, and the product was obtained as a single isomer: when 2-substituted enynes **146** cyclodimerized, 1,4-disubstituted benzenes **147** were obtained as the single isomers. 4-Substituted enynes **148** also cyclodimerized efficiently to give 1,2,3-trisubstituted benzenes **149** (eq 49 and Table 11).^{8b} The reactivity of other conjugated enynes such as 1-alkylenynes or dialkylenynes was much lower, and the attempted homodimerization did not give satisfactory results.

Table 11. Palladium-Catalyzed Homobenzannulation of 4-Substituted Enynes **148**

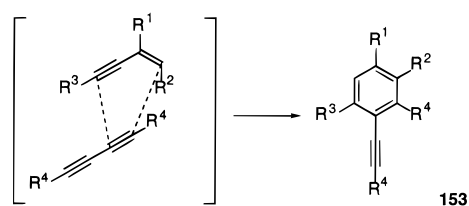
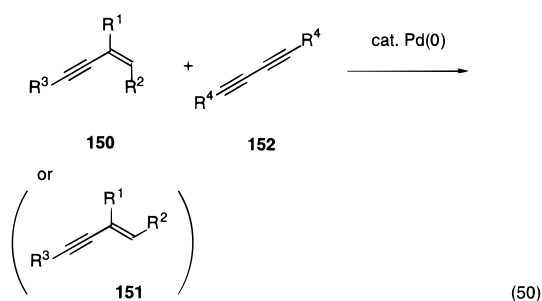
| R | yield of 149 (%) | R | yield of 149 (%) |
|-------------------------------------|-------------------------|----------------------------------|-------------------------|
| <i>n</i> -Hex | 86 | MeOCH ₂ | 100 |
| <i>n</i> -decyl | 92 | Et ₂ NCH ₂ | 100 |
| HO(CH ₂) ₃ | 81 | Ph | 71 |
| Cl(CH ₂) ₃ | 30 | 2-furanyl | 69 |
| MeCO(CH ₂) ₃ | 51 | 2-thiophenyl | 81 |

The scope of the benzannulation reaction was extended significantly by introducing conjugated diynes as the partner for the cross-benzannulation reaction. The conjugated enynes **150** (or **151**) reacted

Table 12. Palladium-Catalyzed Cross-Benzannulation of Enynes with Diynes (**1**)

| enyne | 150 (151) | | | diyne (152) | yield of 153 (%) | |
|------------|---------------------------|-------------------------------------|----------------------------------|----------------------|-------------------------|----|
| | R ¹ | R ² | R ³ | R ⁴ | | |
| 150 | Me | H | H | <i>n</i> -Bu | 89 | |
| | H | H | Ph | Me | >99 | |
| | H | H | SiMe ₃ | Me | 92 | |
| | H | H | CH(OEt) ₂ | <i>n</i> -Hex | 88 | |
| | H | H | CH ₂ NET ₂ | <i>n</i> -Hex | 88 | |
| | H | MeCO(CH ₂) ₃ | <i>n</i> -Bu | H | 24 | |
| | H | <i>n</i> -Hex | <i>n</i> -Bu | Me | 69 | |
| | H | 1-hexenyl | <i>n</i> -Bu | Me | 71 | |
| | H | Ph | <i>n</i> -Bu | Ph | 98 | |
| | Me | Ph | <i>n</i> -Bu | H | 77 | |
| | COOMe | Ph | <i>n</i> -Bu | Me | 72 | |
| | CN | Ph | <i>n</i> -Bu | Me | 81 | |
| | 151 | Me | COOMe | Ph | <i>n</i> -Bu | 55 |
| | | CN | Ph | <i>n</i> -Bu | Me | 65 |

with conjugated diynes **152** in the presence of Pd(0) catalysts to give the polysubstituted benzenes **153** in good yields (eq 50 and Table 12).⁹ In this case, too,



the product was formed in a highly regioselective manner, and the other isomeric benzene was not isolated. It is noteworthy that di- or trisubstituted enynes reacted with conjugated diynes fairly smoothly, since the homobenzannulation of these enynes was very sluggish. Unsymmetrical diynes **155** were also used as the substrates, and the products were formed with various selectivity (eq 51 and Table 13).^{9a,b} The

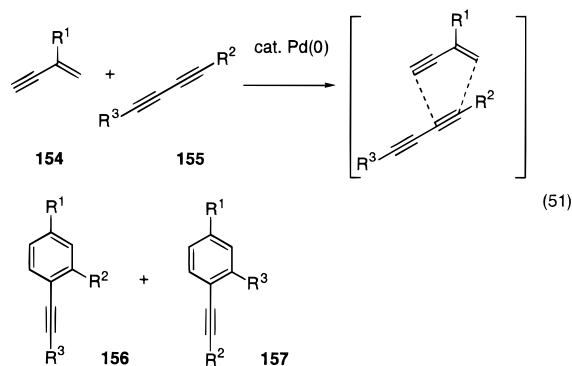


Table 13. Palladium-Catalyzed Cross-Benzannulation of Enynes with Diynes (2)

| 154 R ¹ | 155 | | yield (%) | |
|-----------------------|--------------------------------------|---|-----------|-------|
| | R ² | R ³ | 156 | 157 |
| Me | <i>n</i> -Hex | H | 50 | 28 |
| Me | <i>t</i> -Bu | H | 52 | trace |
| Me | MOMOC(CH ₃) ₂ | H | 80 | |
| Me | <i>n</i> -Bu | Ph | 54 | 46 |
| Me | Me ₃ Si | Ph | 78 | |
| <i>n</i> -Hex | Ph | CH ₂ OH | 44 | 36 |
| <i>n</i> -Hex | HOC(CH ₃) ₂ | <i>n</i> -Bu | 54 | trace |
| <i>n</i> -Hex | <i>n</i> -Bu | CH ₂ OSi(<i>i</i> -Pr) ₃ | 50 | 26 |

regioselective reaction of enynes **158** with triynes **159** has also been reported (eq 52 and Table 14).^{9a} In most cases the enynes **158** reacted with the “terminal” triple bond of the triynes.

Several possible mechanisms have been proposed for the [4+2] benzannulation reaction (Scheme 4). A

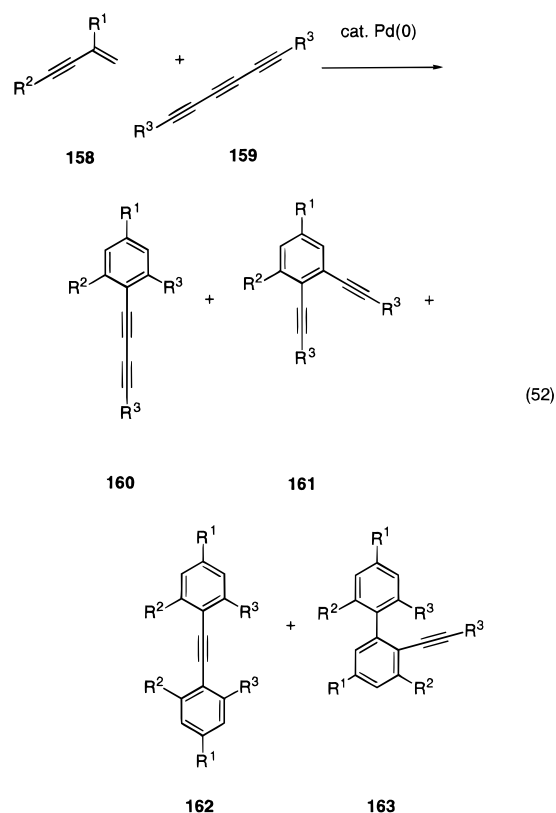
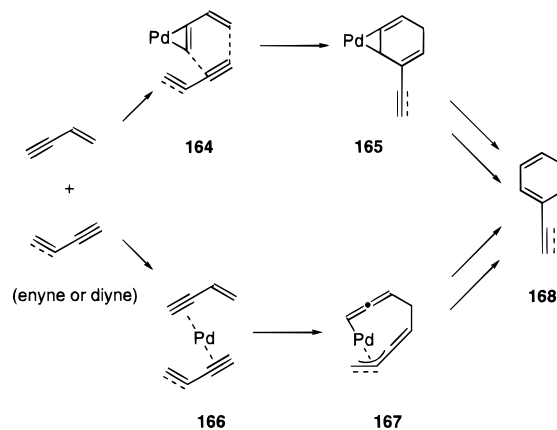


Table 14. Palladium-Catalyzed Cross-Benzannulation of Enynes with Triynes

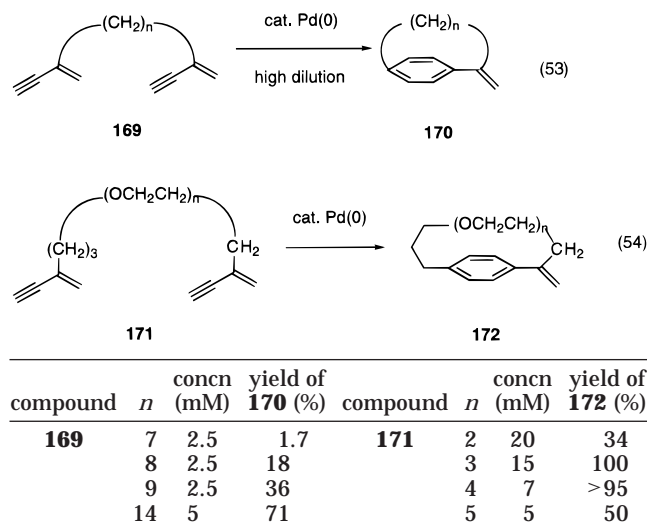
| 158 | | 159 | yield (%) | | | |
|-------------------|----------------|--------------------------------------|-----------|-----|-----|-----|
| R ¹ | R ² | R ³ | 160 | 161 | 162 | 163 |
| Me | H | <i>n</i> -Bu | 24 | 22 | 10 | 10 |
| <i>n</i> -Hex | H | Ph | 44 | 28 | | |
| <i>n</i> -Hex | H | MOMOCCH ₂ | 22 | 50 | | 6 |
| <i>n</i> -Hex | H | MOMOC(CH ₃) ₂ | 84 | | | |
| PhCH ₂ | H | Me ₃ Si | 86 | | | |
| H | <i>n</i> -Hex | Ph | 36 | 9 | | |
| H | <i>n</i> -Hex | MOMOC(CH ₃) ₂ | 29 | | | |

Scheme 4



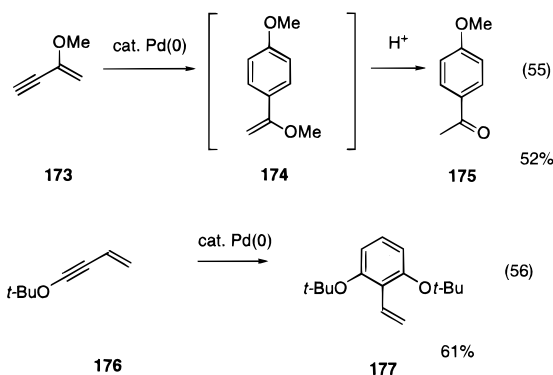
palladacyclopropane such as **165** might be an intermediate of the reaction.⁸ Alternatively, a palladacycle such as **167** could be an intermediate.⁹ The mechanistic details of this reaction are still unknown.

These regioselective [4+2] benzannulation reactions were applied to the synthesis of various phane derivatives. For example, the efficient short-step syntheses of paracyclophanes **170** have been achieved

Table 15. Palladium-Catalyzed Intramolecular Benzannulation of Bisenyne **169 and **171****

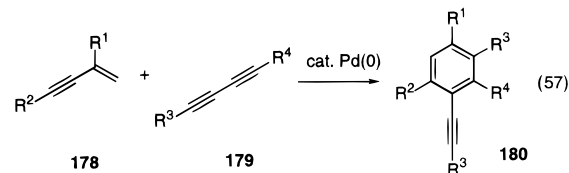
by the intramolecular benzannulation of conjugated enynes **169** (eq 53 and Table 15).³⁷ It is possible to prepare highly strained paracyclophanes by this method, and even under these conditions, the less strained metacyclophanes were not isolated. The result again confirmed the highly regioselective *para*-directive characteristics of the [4+2] benzannulation reaction.^{37a} This method was further applied to the preparation of oxaparcyclophanes **172** (eq 54 and Table 15).^{37b} The use of cyclic diynes and other types of cyclic enynes led to the synthesis of ortho- and metacyclophanes.^{12,38}

The synthesis of phenol and aniline derivatives was also reported by the palladium-catalyzed benzannulation of some substituted enynes and diynes. For example, phenol derivatives **175**, **177**, and **180** were synthesized by the reaction between alkoxyenyne or between enynes and alkoxydiynes, as shown in eqs 55–57 and Table 16.³⁹ The aryl *tert*-butoxy ethers

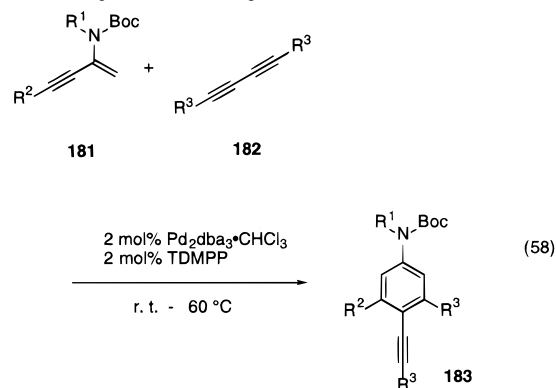


180 bearing an *o*-(*tert*-butoxy)ethynyl substituent were further converted to coumaranones by protonolysis.^{39b} It is also possible to synthesize polysubstituted anilines **183** by the reaction of aminoenyne **181** with diynes **182** (eq 58, Table 17).⁴⁰

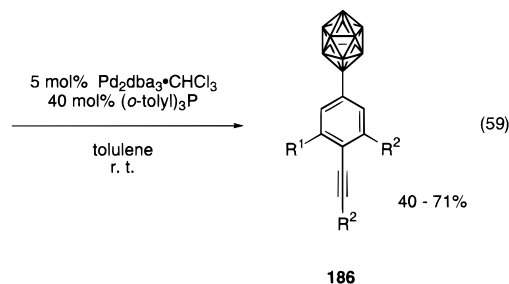
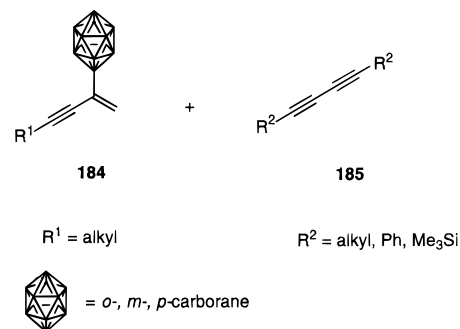
This reaction was also applied to the synthesis of carboranylbenzenes. 2-Carboranylenynes **184** reacted with conjugated diynes **185** to give the polysubstituted carboranylbenzenes **186** in good yields (eq 59).⁴¹

Table 16. Palladium-Catalyzed Benzannulation of Oxoenyne or Oxodiynes

| 178 | | 179 | | yield of 180 (%) |
|----------------|----------------|----------------|----------------|-------------------------|
| R ¹ | R ² | R ³ | R ⁴ | |
| PhO | H | <i>n</i> -Bu | <i>n</i> -Bu | 56 |
| PhO | H | Ph | Ph | 65 |
| PhO | <i>n</i> -Hex | <i>n</i> -Bu | <i>n</i> -Bu | 83 |
| PhO | <i>n</i> -Hex | Ph | Ph | 73 |
| Me | H | <i>t</i> -BuO | <i>t</i> -BuO | 91 |
| MeO | H | <i>t</i> -BuO | <i>t</i> -BuO | 78 |
| H | <i>t</i> -BuO | <i>t</i> -BuO | <i>t</i> -BuO | 66 |
| Me | H | <i>t</i> -BuO | <i>n</i> -Bu | 72 |
| H | <i>t</i> -BuO | <i>t</i> -BuO | <i>n</i> -Bu | 52 |

Table 17. Palladium-Catalyzed Crossbenzannulation of Aminoenyne with Diynes

| 181 | | 182 | yield of 183 (%) |
|----------------|----------------|----------------|-------------------------|
| R ¹ | R ² | R ³ | |
| H | H | <i>n</i> -Bu | 53 |
| H | H | Ph | 37 |
| H | H | Me | 60 |
| Me | H | <i>n</i> -Bu | 40 |
| Me | Me | <i>n</i> -Bu | 62 |
| Me | Me | Ph | 64 |



A formal [2+2+2] cyclization was achieved by the reaction of the alkynes with the conjugated diynes (eq 60, Table 18).⁴² Initially the alkynes **187** dimerize

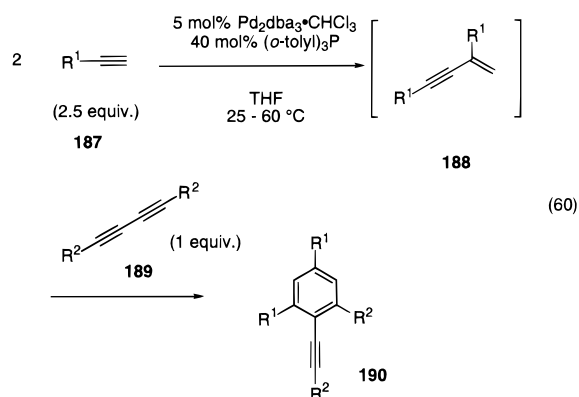
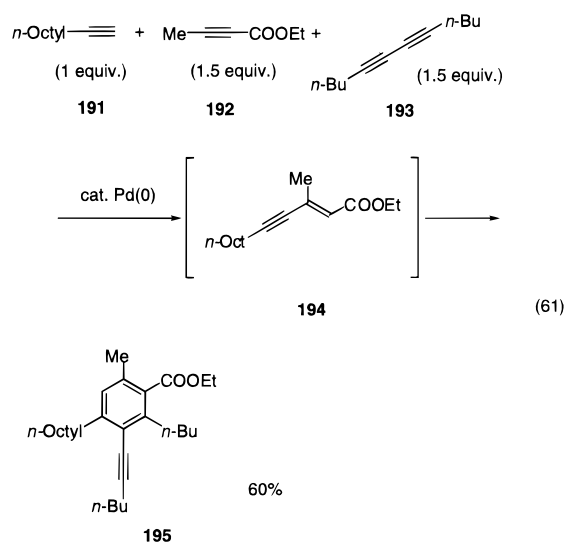


Table 18. Palladium-Catalyzed Coupling of Alkynes **187 with Diynes **189****

| R ¹ | R ² | yield of 190 (%) | R ¹ | R ² | yield of 190 (%) |
|-----------------------------------|----------------|-------------------------|-------------------------------------|----------------|-------------------------|
| Ph | <i>n</i> -Bu | 89 | MeOCH ₂ | <i>n</i> -Bu | 56 |
| Ph(CH ₂) ₂ | <i>n</i> -Bu | 56 | MeOCH ₂ | Ph | 48 |
| <i>n</i> -Bu | <i>n</i> -Bu | 59 | MOMO(CH ₂) ₂ | <i>n</i> -Bu | 54 |
| Ph | Ph | 65 | Cl(CH ₂) ₃ | <i>n</i> -Bu | 64 |

to give the substituted enynes **188**,⁴³ and the enynes **188** further react with the diynes **189** to give the final products **190**. In this case, too, the regioselectivity is perfectly controlled. It is possible to carry out the reaction of the alkynes **191**, electron-deficient alkynes **192**, and a conjugated diyne **193** to synthesize the polysubstituted benzenes **195** in moderate yields (eq 61).⁴² Selective dimerization of the alkynes to give the disubstituted enyne **194**⁴³ is a key reaction to achieve the high regioselectivity.



The scope of this reaction is still expanding, and recently the homobenzannulation of the alkoxy-carbonyl- and cyanoenynes was reported (eq 62 and Table 19).⁴⁴ The high reactivity of these enynes was clearly demonstrated by the fact that disubstituted enynes bearing an electron-withdrawing group are more reactive than dialkylenyne in the homobenz-

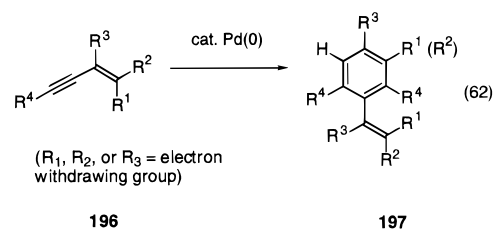
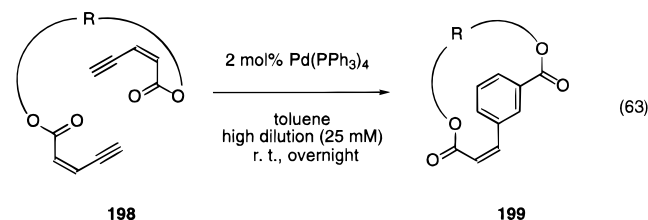


Table 19. Homobenzannulation of Alkoxy-carbonyl- and Cyanoenynes

| entry | 196 | | | | yield of 197 (%) |
|-------|----------------|----------------|--|----------------|-------------------------|
| | R ¹ | R ² | R ³ | R ⁴ | |
| 1 | COOEt | H | H | H | 88 |
| 2 | H | COOEt | H | H | 43 |
| 3 | CN | H | <i>n</i> -C ₅ H ₁₁ | H | 78 |
| 4 | H | CN | <i>n</i> -C ₅ H ₁₁ | H | 49 |
| 5 | H | H | COOMe | <i>n</i> -Bu | 68 |

annulation: while dialkylenyne does not cyclodimerize in the presence of palladium catalysts, disubstituted enynes bearing an alkoxy-carbonyl group or a cyano group cyclodimerized smoothly, and the formation of substituted benzenes was observed. (*Z*)-Enynes were more reactive compared to (*E*)-enynes. This reaction was also applied to the synthesis of metacyclophanes (eq 63, Table 20).⁴⁵

Table 20. Intramolecular Benzannulation of Bisenynes



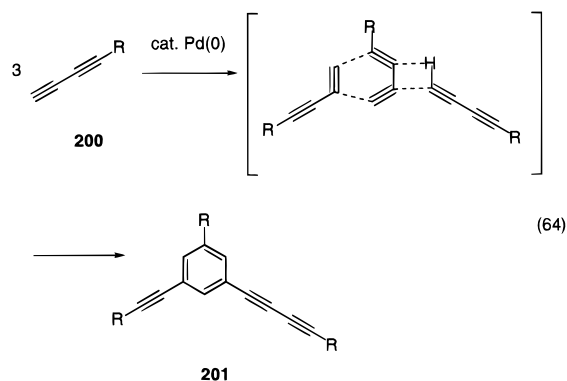
| R | yield of 199 (%) | R | yield of 199 (%) |
|---------------------------------|-------------------------|---|-------------------------|
| (CH ₂) ₅ | 92 | (CH ₂) ₂ O(CH ₂) ₂ | 65 |
| (CH ₂) ₈ | 70 | (CH ₂) ₂ O(CH ₂) ₂ O(CH ₂) ₂ | 68 |
| (CH ₂) ₄ | 85 | | |

III.2. Miscellaneous Reactions

The palladium-catalyzed trimerization of conjugated diynes was also reported in the literature, which might be related to the benzannulation of conjugated enynes. Thus, the conjugated diynes **200** cyclotrimerize in the [4+2] manner to give the 1,3,5-trisubstituted benzenes **201** regioselectively (eq 64, Table 21).⁴⁶ In this reaction, three different substituents (R-, R-C≡C-, and R-C≡C-C≡C-) were introduced in one step at the 1,3,5-positions of the benzene ring.

Table 21. Palladium-Catalyzed Trimerization of Diynes **200**

| R | yield of 201 (%) | R | yield of 201 (%) |
|---------------|-------------------------|---------------------------------------|-------------------------|
| <i>n</i> -Hex | 64 | <i>p</i> -tolyl | 46 |
| <i>t</i> -Bu | 21 | MOMO(CH ₃) ₂ C | 56 |
| cyclohexenyl | 40 | | |



Murakami and Ito et al. reported the [4+2] cycloaddition of vinylallenes **202** with alkynes **203** (eq 65, Table 22).⁴⁷ This reaction is also an efficient

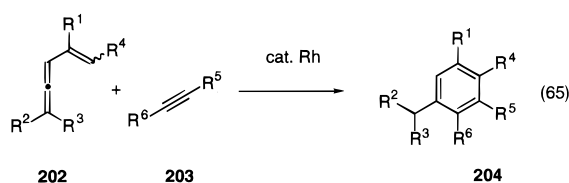
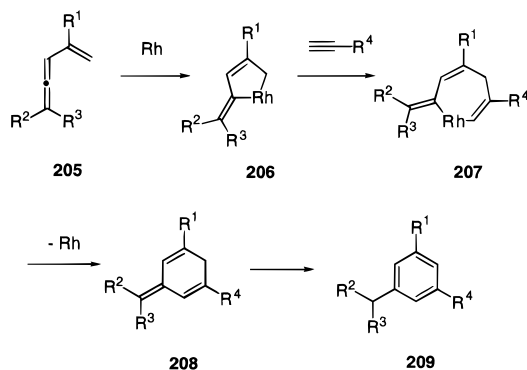


Table 22. Rh-Catalyzed [4+2] Cycloaddition of Vinylallenes **202 with Alkynes **203****

| 202 | | | | 203 | | yield of 204 (%) |
|--------------------|----------------|----------------|----------------|-----------------------------------|----------------|-------------------------|
| R ¹ | R ² | R ³ | R ⁴ | R ⁵ | R ⁶ | |
| Me ₃ Si | H | H | Me | H | H | 93 |
| Me ₃ Si | Me | Me | H | <i>n</i> -Bu | H | 87 |
| Ph | Me | Me | H | H | H | 81 |
| Ph | Me | Me | H | <i>n</i> -Bu | H | 84 |
| Ph | Me | Me | H | Ph | H | 55 |
| Ph | Me | Me | H | HO(CH ₂) ₂ | H | 94 |
| Ph | Me | Me | H | Cl(CH ₂) ₃ | H | 93 |
| Ph | Me | Me | H | Et | Et | 65 |
| Ph | H | Me | H | <i>n</i> -Bu | H | 24 |
| Ph | H | H | H | <i>n</i> -Bu | H | 15 |

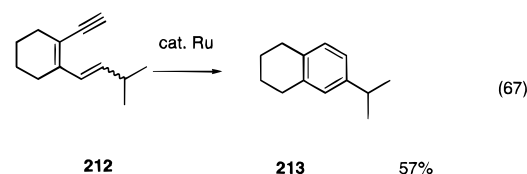
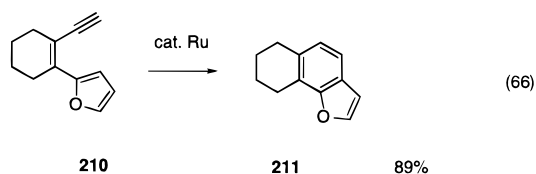
method for the regioselective construction of polyalkylated benzenes. The mechanism of this reaction was considered as shown in Scheme 5. A metallacyclopentene such as **206** would be an intermediate of this reaction.

Scheme 5



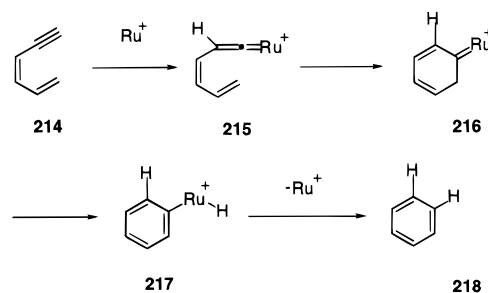
clopente such as **206** would be an intermediate of this reaction.

Ruthenium-catalyzed intramolecular cyclizations of dienylalkynes have been reported by Merlic et al. (eqs 66 and 67).⁴⁸ This reaction, which presumably pro-



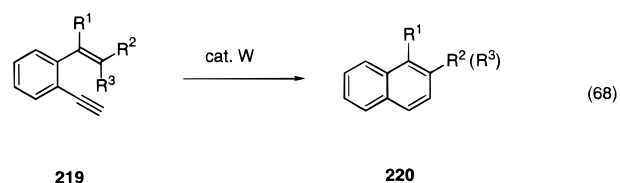
ceeds via the vinylidene intermediate **215** (Scheme 6), is a useful method for the regioselective construc-

Scheme 6



tion of fused aromatics. This reaction was also catalyzed by a tungsten complex, and polyaromatic compounds **220** were prepared (eq 68 and Table 23).⁴⁹

Table 23. Tungsten-Catalyzed Cyclization of Aromatic Enynes



| 219 | | | isolated yield of 220 (%) |
|---------------------------------|----------------|----------------|----------------------------------|
| R ¹ | R ² | R ³ | |
| Me | H | H | 81 |
| COOMe | H | H | 84 |
| OSi <i>t</i> -BuMe ₂ | H | H | 100 |
| H | H | H | 68 |
| Me | COOEt | H | 100 |
| Me | H | COOEt | 88 |
| OSi <i>t</i> -BuMe ₂ | Me | H | 90 |

IV. General Trends and Choice of the Catalyst in the [2+2+2] and [4+2] Cycloaddition Reactions

In this section we discuss the general trends in the [2+2+2] and [4+2] cycloaddition reactions, on the basis of reactions mentioned in this review, to provide hints for the selection of the catalyst for the reactions described in sections II.1 and III.1. Other reactions are much less investigated, and the scope and limitation of the reactions have not been established.

IV.1. [2+2+2] Cyclotrimerization of Alkynes

Though many transition metals have been employed for the cyclotrimerization of alkynes, the

number of practically useful catalysts is rather small. Among them, the Co catalysts have been most widely used, and they are the compounds of primary choice for the [2+2+2] cyclotrimerization. For the preparation of pyridine from alkynes and nitriles, the Co catalysts are the only compounds of choice, since this type of reaction has not been reported or gave less satisfactory results⁵⁰ in the presence of other catalysts. The general regioselectivity in the reaction has already been established,^{13d} and by the proper choice of the substrate or protective groups, it is possible to carry out the cocatalyzed reactions in highly regioselective manner.

Ni catalysts are also reactive catalysts for this transformation. The reaction of alkynes with acetylene seems to be a quite general method for the construction of the benzene ring. However, the activity of the Ni catalysts seems to be lower compared to that of Co or Rh catalysts, since most disubstituted alkynes did not react with diynes in the presence of Ni catalysts.¹⁴ The facile introduction of chiral ligands to the catalytic system is another notable feature of the Ni-catalyzed reaction: so far, the asymmetric reactions have only been carried out in the presence of chiral Ni catalysts.^{14,24a}

Rh complexes are effective catalysts for the synthesis of substituted benzenes. The Rh catalysts have been used for the reactions of 1,5- and 1,6-diynes with acetylene or alkynes, and in some reactions high regioselectivity has been reported. It is possible to achieve high regioselectivity by considering the steric effect of the substrates.^{15,16} Compared with the Ni catalysts, the Rh catalysts might tolerate a larger number of functional groups.

Though it has been shown that some Pd(II) compounds are good catalysts for the formation of benzene rings,^{13e-f} the synthetic usefulness of this catalyst remains to be examined. The activity of Pd(0) complexes seems to be lower compared to that of other catalysts, and these catalysts have been used only for highly reactive substrates such as benzyne.

The electronic and steric effects of alkynes are also important factors to carry out the reaction successfully. The rate of the reaction is generally affected by the steric factor, less substituted alkynes showing higher reactivity. On the other hand, the lower¹⁶ or higher²² reactivity of electron-deficient alkynes in the reactions has been reported, and it is difficult to generalize the electronic effect of the substrates on the reaction. The reactivity of conjugated alkynes seems to be higher compared to that of nonconjugated alkynes.²¹

IV.2. [4+2] Benzannulation of Enynes

So far this reaction proceeds only in the presence of some Pd(0) catalysts, and the Pd(0) catalysts are the only compounds of choice for this reaction. The reaction did not proceed in the presence of other transition-metal catalysts, except for some Pt complexes, the catalytic activity of which was very low.⁵¹ Tetrakis(triphenylphosphine)palladium (Pd(PPh₃)₄) is the compound of primary choice for this reaction. Other compounds such as Pd₂(dba)₃·CHCl₃-(*o*-tolyl)₃P are employed as the catalysts. The Pd(PPh₃)₄-(*o*-

tolyl)₃P system is an efficient catalyst especially when the reaction is carried out at higher temperature: in certain cases, the presence of a larger amount of phosphine ligand prevents the decomposition of the catalyst.^{9c}

The reactivity of the enynes is controlled by steric as well as electronic factors. The reactivity of less substituted enynes is higher compared to that of polysubstituted enynes.¹² However, it is necessary to consider the electronic effect on the reactivity of the enynes, and the enhanced reactivity of electron-deficient enynes has been observed.⁴⁴

V. Conclusion

Transition-metal-catalyzed reactions of unsaturated hydrocarbons are very useful in organic synthesis, and the applications of the reactions are shown in many papers. The reactions described in this review clearly demonstrate the high ability of the transition-metal catalysts to carry out the regioselective preparation of polysubstituted benzenes.

Though the highly regioselective formation of benzene derivatives has been mainly achieved in intramolecular reactions, the high regioselectivity has also been observed in some intermolecular reactions. Especially, the transition-metal-catalyzed [4+2] approach seems to be very promising for the intermolecular regioselective construction of polysubstituted benzenes. The wide scope of the transition-metal-catalyzed synthesis of the benzene ring has been demonstrated by the facile synthesis of natural products, theoretically interesting compounds, and sterically congested benzenes, which cannot be easily prepared by other synthetic methods. Considering the importance of benzene derivatives in the vast field of basic and applied chemistry, these methods are highly useful in organic synthesis.

VI. References

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