PART I

# [2 + 2 + 2] AND RELATED CYCLOADDITION REACTIONS

1

COBALT-MEDIATED [2 + 2 + 2] CYCLOADDITION

Vincent Gandon

1.1   INTRODUCTION

An expedient way to envisage the synthesis of conjugated six-membered rings such as benzenes, pyridines, pyridones, and related heterocycles is by a [2 + 2 + 2] cycloaddition retrosynthetic approach. These conjugated systems can indeed be viewed as cycloadducts of three readily available unsaturated partners, such as alkynes, nitriles, isothiocyanates, carbon disulfide, isocyanates, and carbodiimides (Scheme 1.1, $X = N, S; Y = N, O, S$). Although the thermal version of this reaction is usually hardly feasible [1], it becomes straightforward in the presence of the appropriate catalyst. The first example of transition-metal-catalyzed [2 + 2 + 2] cycloaddition was reported by Reppe and Schweckendiek in 1948 [2]. A nickel complex was used as a precatalyst to cyclotrimerize alkynes into benzenes. Until the early 1970s, it was shown that many other metals could be employed, notably cobalt. Afterward, led by Vollhardt, who reported a considerable number of applications, this chemistry clearly proved to be priceless in organic synthesis. Since the topic has already been thoroughly reviewed [3], in this chapter we emphasize the latest development of the cobalt-catalyzed [2 + 2 + 2] cycloaddition reaction over the past 10 years.
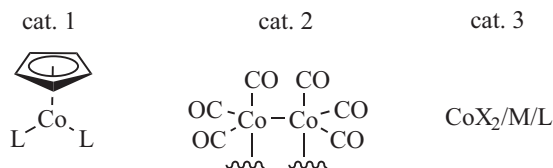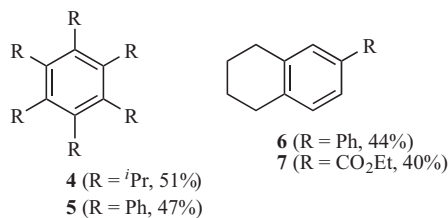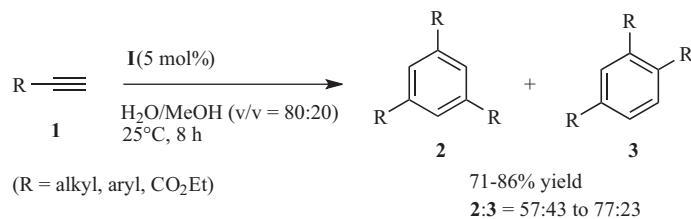
SCHEME 1.1
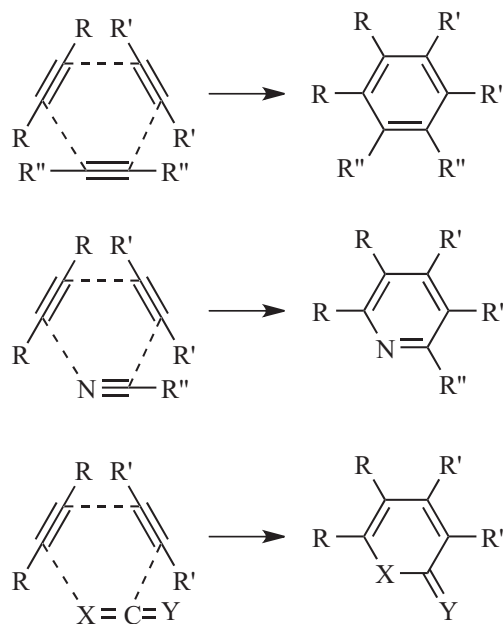
1.2 SYNTHESIS OF BENZENES

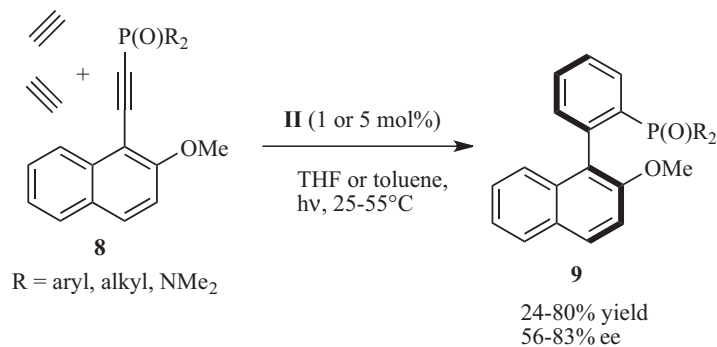### 1.2.1 New Catalytic Systems

The typical cobalt complexes used to form benzenes by $[2 + 2 + 2]$ cycloadditions can be classified into three categories (Figure 1.1). The first concerns those containing cyclopentadienyl ligands ($CpCoL_2$, Cp^*CoL_2, or other modified $Cp'CoL_2$). The most common ones are $CpCo(CO)_2$, $CpCo(C_2H_4)_2$, and $CpCo(COD)$, sometimes associated with a phosphine. $CpCoL_2$ catalysts can be used in a variety of organic solvents, as well as supercritical CO_2 or H_2O [3m]. The functionalization of the Cp (cyclopentadienyl) ring with a polar side chain allows the reaction to take place

FIGURE 1.1

in aqueous solution [4]. As shown below, new complexes of type CpCo(alkene)(L) have recently been used as catalysts. The second category deals with such cobalt carbonyls as $Co_2(CO)_8$, $Co_3(H)(CO)(PMe_3)_6$, and $Co_4(CO)_{12}$. A new versatile complex has also been developed. The third category contains cobalt halides of type $CoX(PR_3)_3$ or $CoX(PR_3)(CO)_2$ (X = Cl, Br; R = Ph, Me), as well as CoX_2/M/L catalytic systems (X = Cl, Br, I; M = Mn, Zn, NaBH$_4$, etc.; L = phosphines, imines, etc.). These systems, based on Co(II) sources, have aroused great enthusiasm in the past 10 years.

1.2.1.1   [CpCo] Complexes   Various problems associated with the synthesis of benzenes have been circumvented recently by using precatalysts **I** to **III**, displayed in Figure 1.2.

FIGURE 1.2

Yong and Butenschön succeeded in achieving alkyne cyclotrimerizations in an aqueous medium at room temperature using **I** [5]. While standard catalysts such as CpCo(COD) allow the formation of pyridines at room temperature in water [6], this feature has so far not been possible for benzenes, for which an elevated temperature is required [4]. Complex **I** was tested toward the cyclotrimerization of mono-substituted alkynes **1** and gave the expected regioisomeric mixture **2/3** in good yields and often good selectivities compared to reactions carried out in organic solvents (Scheme 1.2). The cyclotrimerization of the disubstituted alkynes 2,5-dimethyl-3-hexyne and diphenylacetylene to give **4** and **5**, respectively, was also reported, as well as bimolecular reactions between 1,7-octadiyne and phenylacetylene or ethyl propiolate to give **6** and **7**, respectively. Catalyst **I** could also be used to assemble pyridines (see Section 1.3.1.1).

The [2 + 2 + 2] cycloaddition reaction can give rise to chiral compounds, especially biaryls [3q]. Control of the enantioselectivity in such transformations is of prime importance, notably because biaryls can be used as ligands in asymmetric catalysis. This topic is covered in detail in Chapter 9. Nowadays, cobalt still looks like a poor relation in this field, which is largely dominated by rhodium. Nevertheless, a report from Heller et al. shows for the first time that phosphorus-bearing axially chiral biaryls **9** can be formed by enantioselective benzene formation using the neomenthyl-indenyl cobalt complex **II** as a catalyst (Scheme 1.3) [7]. Good yields

6   COBALT-MEDIATED [2 + 2 + 2] CYCLOADDITION
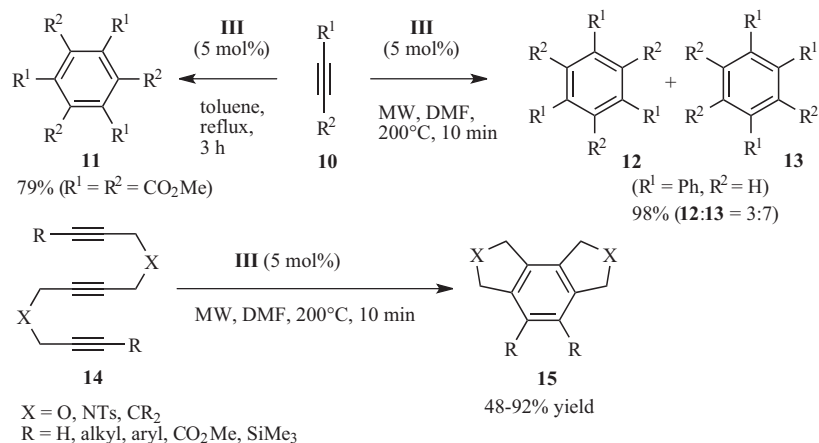

SCHEME 1.2

SCHEME 1.3

and ee values were obtained after the cycloaddition of 2 equiv of acetylene with alkynyl phosphine oxides **8**.

In many cases, standard catalysts such as CpCo(CO)$_2$ or CpCo(COD) necessitate heat and visible light irradiation to be active. Conversely, CpCo(C$_2$H$_4$)$_2$ turns over at room or lower temperatures [8]. However, these catalysts are sensitive to oxygen and usually require thoroughly degassed solvents. Complex **III** is a new air- and moisture-stable catalyst for [2 + 2 + 2] cycloadditions [9]. Heat is still necessary, but not irradiation. The reaction can be carried out in hot toluene or in microwaved dimethylformamide (DMF). Crude solvents can be used as found in the laboratory without purification. The catalyst is still active after months of storage in simple vials. Whereas the first report focused on simple cycloadditions of alkynes **10** or triynes **14** (Scheme 1.4), complex **III** proved useful as well with more sophisticated systems (see Section 1.2.2).

SCHEME 1.4

1.2.1.2   Cobalt Carbonyls   In 2002, Sugihara et al. showed that the cobalt carbonyl cluster $Co_3(CO)_9(\mu^3\text{-}CH)$ **IV** could serve as a $[2+2+2]$ cycloaddition catalyst for the construction of benzenes (Scheme 1.5) [10]. Of particular interest, **IV** is also air-stable and can be stored for a very long time without decomposition. A very low loading can be engaged, down to 1 mol %. Inter- and intramolecular reactions proceed with very good yields and selectivities. Actually, only the 1,2,4-regioisomer **13** was formed when phenylacetylene was used as a starting material.
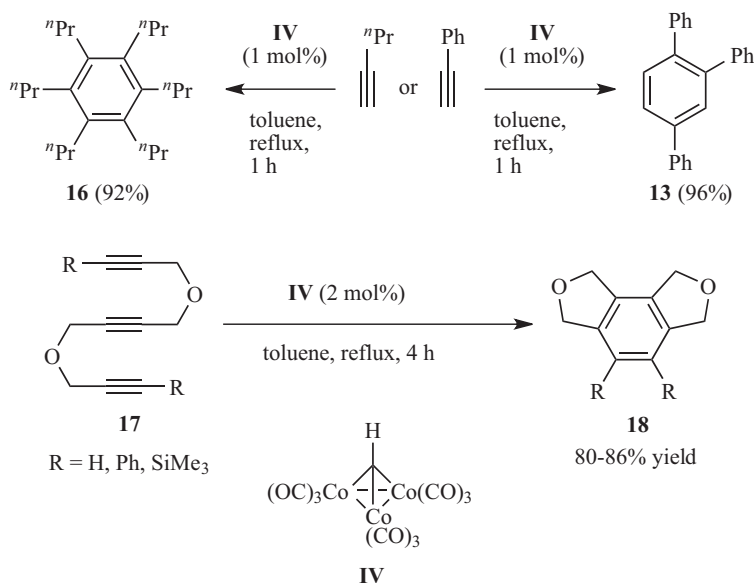
SCHEME 1.5

8   COBALT-MEDIATED [2 + 2 + 2] CYCLOADDITION

1.2.1.3   Cobalt Halides   As shown above, the formation of benzenes with CpCo or carbonyl catalysts often requires harsh conditions. Various research groups worked on the development of user-friendly Cp- and CO-free catalytic systems based on stable materials that would exhibit a high level of activity nonetheless. Early studies in this field by Bönnemann, Chiusoli, Slowinski, and co-workers identified precatalytic mixtures composed of a cobalt(II) halide ($CoCl_2$ and CoI_2) and a reducing agent such as $NaBH_4$ or manganese, sometimes in the presence of triphenylphosphine [11]. Figure 1.3 shows more recent precatalytic systems developed by Chang et al. (**V**) [12], Hilt et al. (**VI** and **VII**) [13], and Saino, Goswami, and co-workers (**VIII** and **IX**) [14].
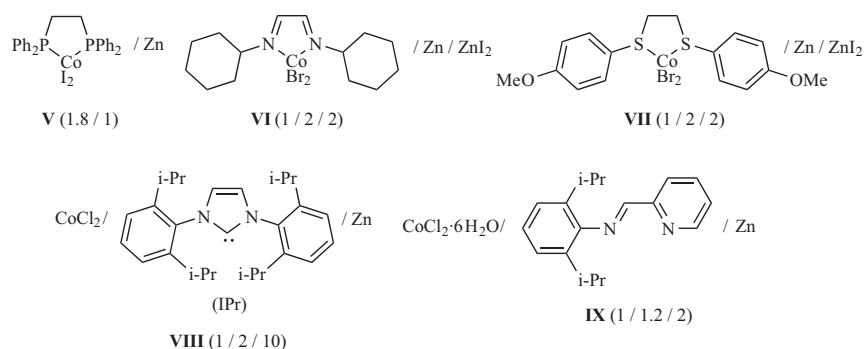
FIGURE 1.3

System **V** was used in a CH_3CN/THF mixture for the rapid and regioselective construction of benzolactones and lactams **21** from alkynyl alcohols or alkynylamides **19** and propiolates **20** (Scheme 1.6) [12]. An induction period of 1 h at room temperature is necessary to form the active species. The reaction mixture is then heated for 12 h at 80 °C. It is supposed that the [2 + 2 + 2] cycloaddition step precedes the transesterification. Remarkably, no pyridines form in the presence of CH_3CN.
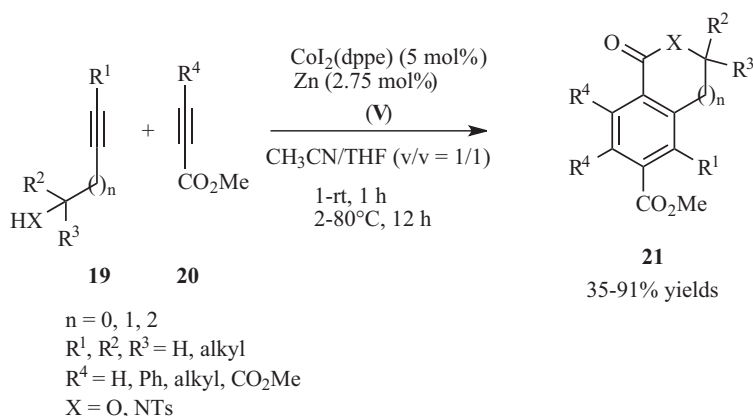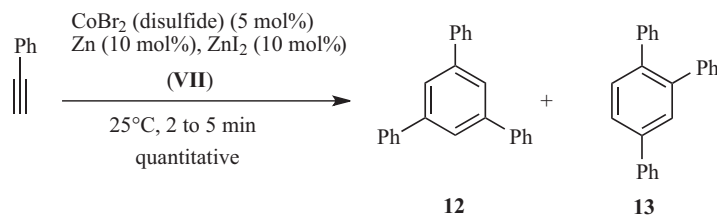

SCHEME 1.6

Excellent regiocontrol and high activity were also observed with the catalytic system **VI**, which comprises a Lewis acid to generate a cationic active species (Scheme 1.7) [13a and b]. The use of a ligand is not strictly necessary in this case, but it greatly reduces the reaction time. Again, whereas CH_3CN is used as a solvent, no pyridines are formed. Of particular interest, while most catalytic systems tend to give rise to the dissymmetrical cycloadduct of type **24** as the major regioisomer, it was shown that the outcome could be reversed when using **VII** in CH_2Cl_2 instead of CH_3CN [13c]. Such a case of regioselectivity switch is noteworthy since in most CpCo-catalyzed transformations the regioisomeric ratio is affected only moderately by the solvent.
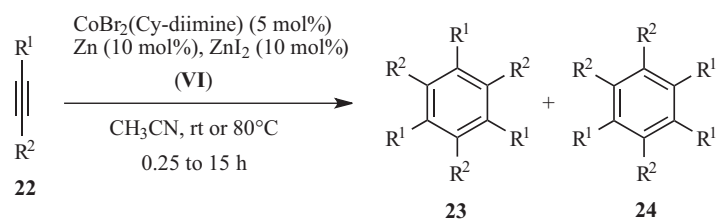
$R^1 = Ph$, $R^2 = H$, rt, 0.25 h, 99% yield, **23** : **24** = 5 : 95
$R^1 = {}^nBu$, $R^2 = H$, rt, 1 h, 90% yield, **23** : **24** = 8 : 92
$R^1 = Ph$, $R^2 = Ph$, 80°C, 15 h, 83% yield

CH_2Cl_2: **12** : **13** = 6.2 : 1.0
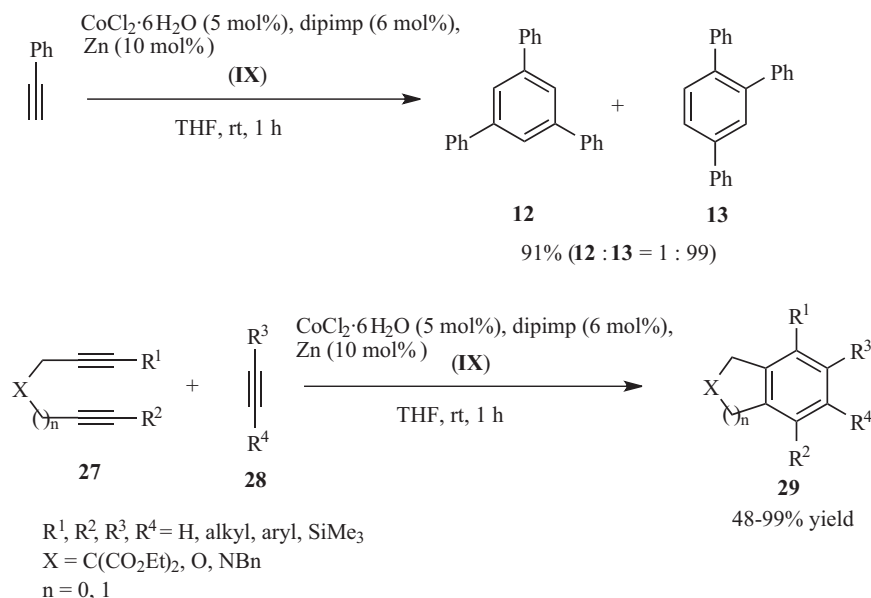CH_3CN: **12** : **13** = 1.0 : 22.9

SCHEME 1.7

The preparation of cobalt complexes can be avoided by choosing an "instant" catalyst protocol based on systems **VIII** and **IX**. For example, anhydrous $CoCl_2$ can be mixed directly with the IPr carbene (generated in situ from the corresponding imidazolium salt and n-BuLi) in a 1 : 2 ratio and zinc powder in excess. This mixture catalyzes the [2 + 2 + 2] cycloaddition of triynes **25** in tetrahydrofuran (THF) at 50 °C in good yields, except with R = R′ = Ph or SiMe_3, for which the yields did not exceed 5 and 20%, respectively (Scheme 1.8) [14a]. An even more appealing catalytic system, developed later [14b], comprises a bench-stable source of cobalt, $CoCl_2 \cdot 6H_2O$ and the air-stable Dipimp ligand. In addition to being very easy to carry out, the transformations are also possible at room temperature. Triynes substituted at both ends with R = R′ = Ph or SiMe_3 are now compatible with the reaction conditions, the cycloadducts being isolated in 82 and 97% yield, respectively.

CoCl$_2$ (1-5 mol%), IPr (2-10 mol%),
Zn (10 mol%)

(VIII)

THF, 50°C

5-98% yield

25

R, R' = H, alkyl, Ph, SiMe$_3$
Y, Z = O, C(CO$_2$Et)$_2$

CoCl$_2$·6 H$_2$O (5 mol%), dipimp (6 mol%),
Zn (10 mol%)

(IX)

THF, rt, 24 h

62-97% yield

26
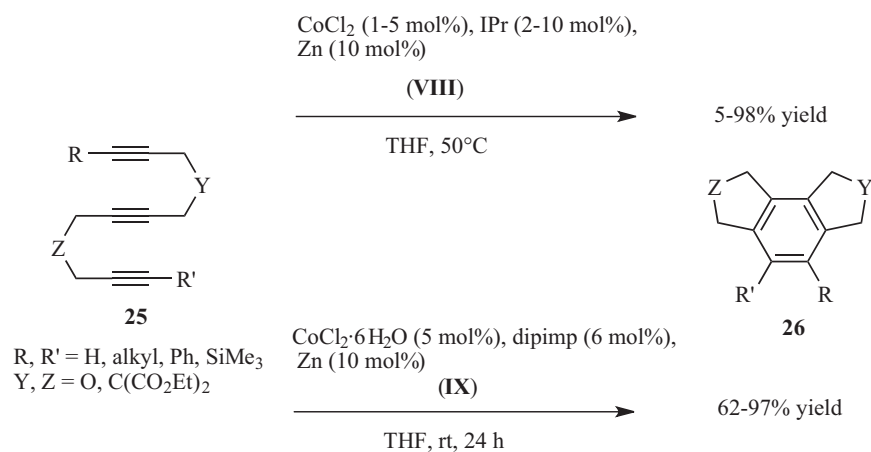
SCHEME 1.8

Importantly, the catalytic mixture **IX** is also able to cyclotrimerize monosubstituted alkynes such as phenylacetylene with excellent regiocontrol, and to cocyclize diynes with alkynes in good yields (Scheme 1.9). The latter category has recently been exploited for the synthesis of substituted anthracenes, pentaphenes, and trinaphthylenes [14d], as well as for quick access to diverse polymerizable molecules [15]. It is noteworthy that the reaction times can be decreased further by adding a silver salt such as AgOTf or AgSbF$_6$ [14c].


CoCl$_2$·6 H$_2$O (5 mol%), dipimp (6 mol%),
Zn (10 mol%)

(IX)

THF, rt, 1 h

12   **13**

91% (**12** : **13** = 1 : 99)

CoCl$_2$·6 H$_2$O (5 mol%), dipimp (6 mol%),
Zn (10 mol%)   **(IX)**

THF, rt, 1 h

27   **28**

29

48-99% yield

R^1, R^2, R^3, R^4 = H, alkyl, aryl, SiMe$_3$
X = C(CO$_2$Et)$_2$, O, NBn
n = 0, 1

SCHEME 1.9

A new "instant" catalyst exploiting guanidine as ligand with $CoCl_2/Zn/ZnI_2$ has recently been reported by Eichman et al. [16]. One must also keep in mind that a ligand is not always strictly necessary, as shown by Doszczak et al. in CoI_2/Zn-catalyzed co-cyclization of silicon-containing diynes with propargyl ethers and alcohols [17]. Lombardo et al. also reported ligand-free $CoBr_2/ZnI_2/NaBH_4$-catalyzed $[2 + 2 + 2]$ cycloadditions in ionic liquids [18].

1.2.2 New Cyclization Partners

Borylated and halogenated arenes are valuable compounds, notably in the context of cross-coupling reactions. Thus, rapid construction of such compounds by a $[2 + 2 + 2]$ cycloaddition strategy looks very appealing. In 1996, Maderna et al. reported the synthesis of a hexaborylbenzene derivative by cobalt-catalyzed cyclotrimerization of a diborylacetylene [19]. In 2000 and 2001, the same group described cobalt-catalyzed or cobalt-mediated $[2 + 2 + 2]$ cycloadditions involving monoborylacetylenes, giving rise to triborylbenzenes [20]. In 2004, cobalt-catalyzed cyclotrimerizations of arylborylacetylenes **30** were described (Scheme 1.10) [21].
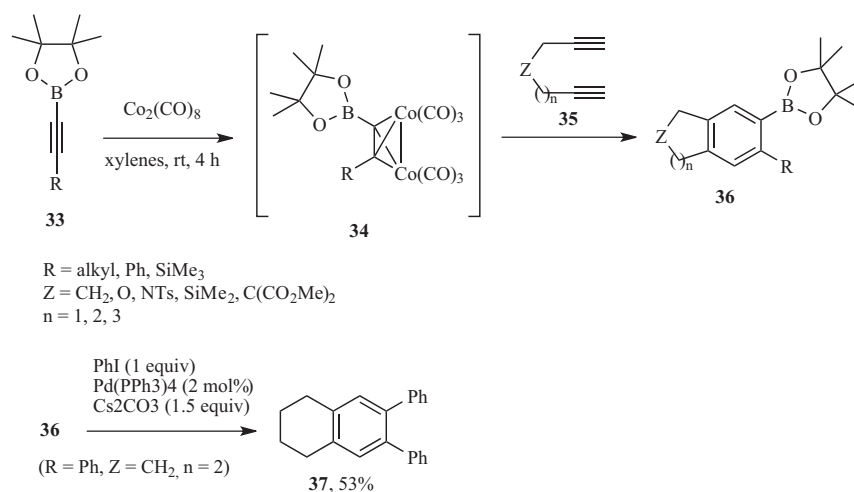

67-78% (not separated, ratio not determined)
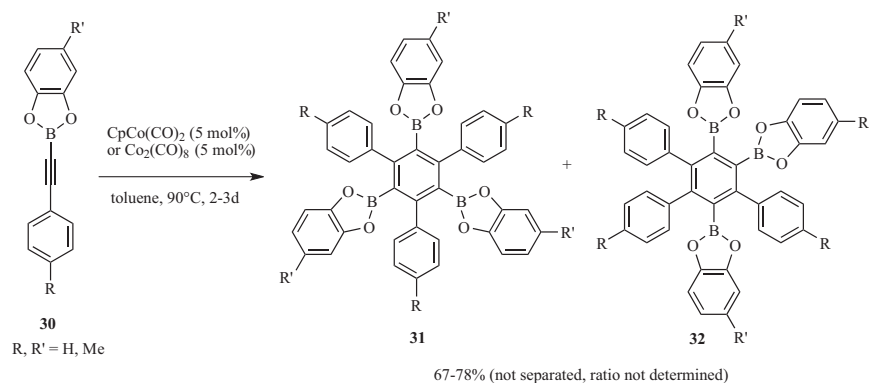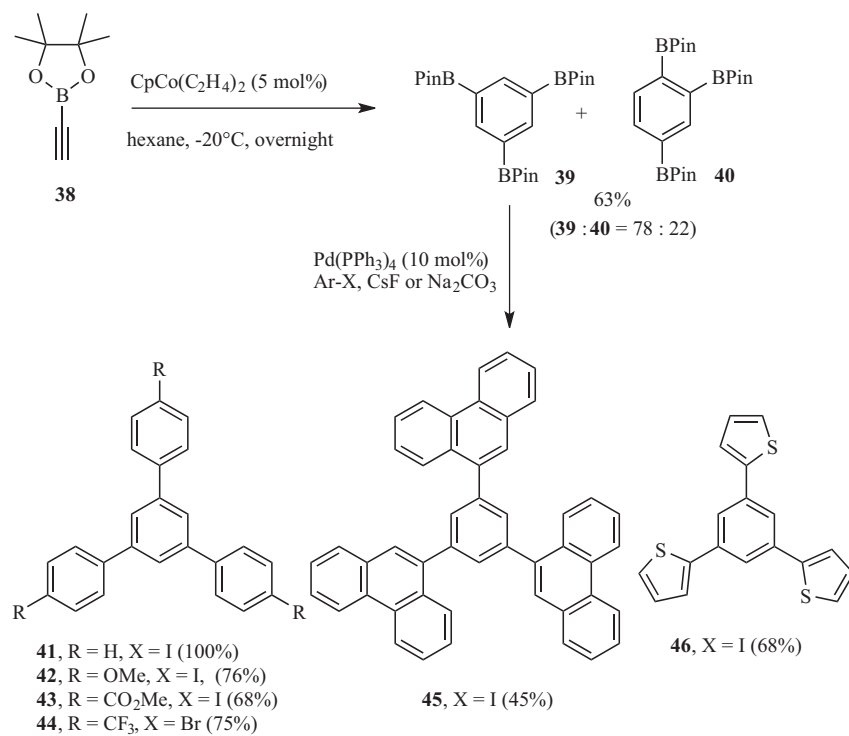
SCHEME 1.10

The same year, Gandon et al. reported the synthesis of fused arylboronic esters **36** via cobalt(0)-mediated cycloaddition of alkynylboronates **33** with diynes **35** (Scheme 1.11) [22]. The boronate is first reacted with $Co_2(CO)_8$ at room temperature for 4 h to generate the corresponding dicobaltatetrahedrane **34**. The diyne is then added and the mixture is refluxed for 2 h. To show the utility of the products, one of them was treated with phenyl iodide under Pd catalysis to give **37**. Complementary to these investigations, Ru-catalyzed $[2 + 2 + 2]$ cycloaddition of tethered alkynylboronic esters with alkynes was reported [23]. In this case, the borylated arene could not be isolated but was converted directly in situ by Suzuki–Miyaura coupling.

In 2011, Iannazzo et al. reported the construction of oligoaryls by Suzuki couplings of polyborylated platforms with aryl halides (Schemes 1.12 and 1.13) [24]. The platforms were obtained by using either $CpCo(C_2H_4)_2$ or **III** as catalyst. With the former, it was possible to carry out the cyclotrimerization of the borylacetylene **38** at
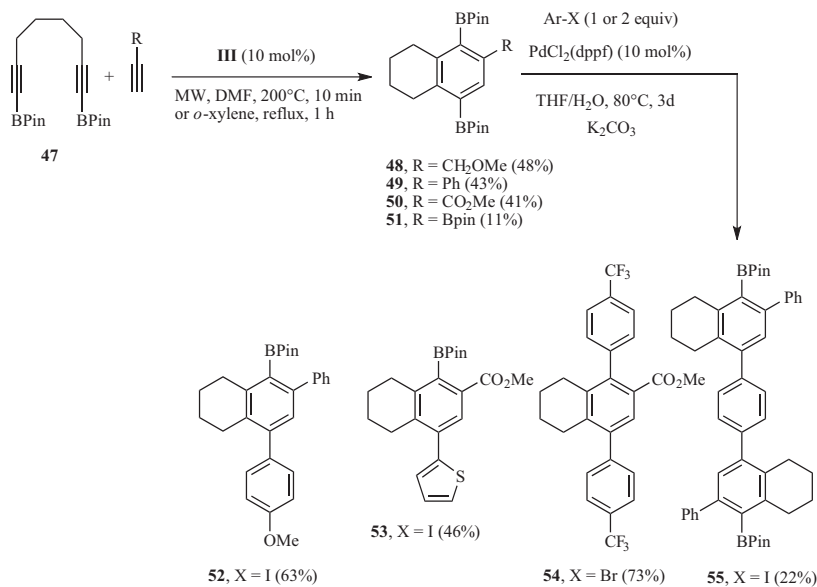
12   COBALT-MEDIATED [2 + 2 + 2] CYCLOADDITION

R = alkyl, Ph, SiMe$_3$
Z = CH$_2$, O, NTs, SiMe$_2$, C(CO$_2$Me)$_2$
n = 1, 2, 3

36 $\xrightarrow[\substack{(R = Ph, Z = CH_2, n = 2)}]{\substack{PhI\ (1\ equiv) \\ Pd(PPh3)4\ (2\ mol\%) \\ Cs2CO3\ (1.5\ equiv)}}$

37, 53%

SCHEME 1.11

CpCo(C$_2$H$_4$)$_2$ (5 mol%)

hexane, -20°C, overnight

38

PinB ... BPin

39

BPin ... BPin ... BPin

40

63%
(**39** : **40** = 78 : 22)

Pd(PPh$_3$)$_4$ (10 mol%)
Ar-X, CsF or Na$_2$CO$_3$

41, R = H, X = I (100%)
42, R = OMe, X = I, (76%)
43, R = CO$_2$Me, X = I (68%)
44, R = CF$_3$, X = Br (75%)

45, X = I (45%)

46, X = I (68%)

SCHEME 1.12

SCHEME 1.13

−20 °C and obtain the symmetrical regioisomer **39** as the major product. Unlike the regioisomeric mixtures of catechol-derived products shown in Scheme 1.10, those pinacol-derived triborylated benzenes could be separated. Thus, compound **39** could be obtained in pure form and submitted to various couplings to give oligoaryls **41** to **46**.

Diyne **47** bearing two sterically demanding boryl pinacolates at both ends could not be co-cyclized with alkynes when using $CpCo(C_2H_4)_2$. The desired products **48** to **51** could, nonetheless, be obtained in moderate yields when using **III** as a catalyst (Scheme 1.13) and cross-coupled with various aryl halides to give **52** to **55**.

It is worthy of note that polyborylated cyclohexadienes can also be formed by cobalt-catalyzed $[2+2+2]$ cycloaddition between alkynylboronates and alkenes after oxidation [25]. In this way, alkenes can be considered as substitutes of alkynes [26]. Liquid enol ethers might also advantageously replace acetylene gas in $[2+2+2]$ cycloadditions without oxidation [27]. This strategy has been applied to synthesis of the diborylated arenes **57** and **58** (Scheme 1.14) [28].

57, R = Ph, 59%
**58**, R = CH$_2$OMe, 88%
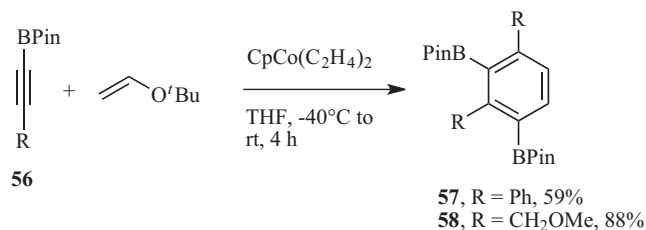
SCHEME 1.14

To close on the new cyclization partners used in cobalt-catalyzed [2 + 2 + 2] cycloaddition to give benzene derivatives, it is worth mentioning that alkynyl halides have been used for the first time in this transformation [29]. Until then, only ruthenium-based catalysts had been used with such substrates [30]. While the standard catalysts $CpCo(CO)_2$ and $CpCo(C_2H_4)_2$ did not allow the formation of cycloadducts, the new catalyst **III** proved able to accomplish this task efficiently starting from alkynyl bromides **59** and **62** (Scheme 1.15).

$Z = C(CO_2Me)_2,\ (CH_2)_2,\ O,\ NTs$
$R^1 = H,\ Et$
$R^2 = alkyl,\ aryl$

61

40–88% yield
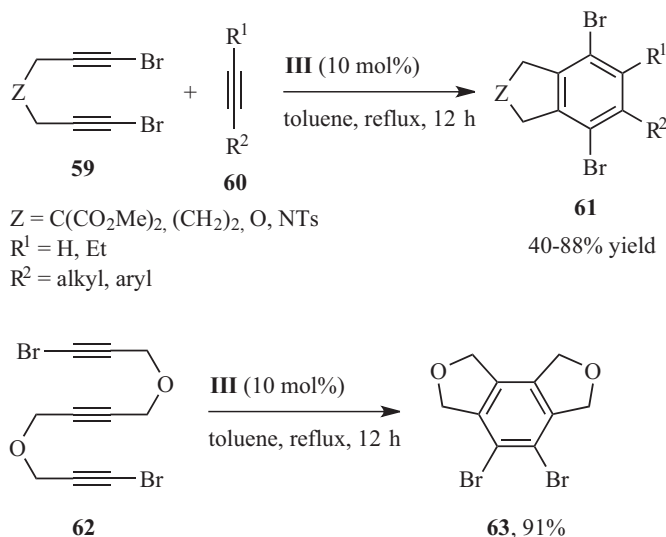
SCHEME 1.15

1.2.3   Chemo- and Regioselectivity Issues

Although most of the reactions described above show remarkable levels of chemo- and regioselectivities, these issues remain critical in many cases. The lack of selectivity can be circumvented by carrying out intramolecular cyclizations, or even bimolecular cyclizations, between diynes and alkynes in excess with the slow addition of one partner. For bi- or trimolecular cyclizations, another approach is to carry out solid-supported [2 + 2 + 2] cycloaddition in which one of the substrates is immobilized [31]. With cobalt, this field has been explored primarily for the synthesis of heterocycles (see Section 1.3.3). So far, control of the selectivity in intermolecular cyclization of three different partners to give benzenes remains highly challenging. In 2004, Chouraqui et al. reported an elegant way to get around this difficulty through the use of disposable linkers (Scheme 1.16) [32]. The three partners are connected with temporary silylated tethers as in **64**. Then an intramolecular cyclization is carried out. The resulting tricyclic products, such as **65**, are finally desilylated using a fluoride source. Only one product is obtained, whereas dozens are formed from the three untethered alkynes.
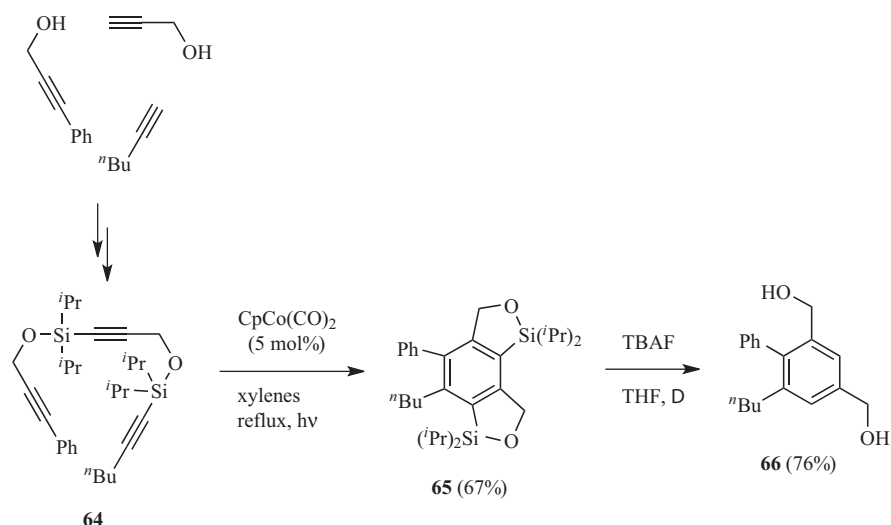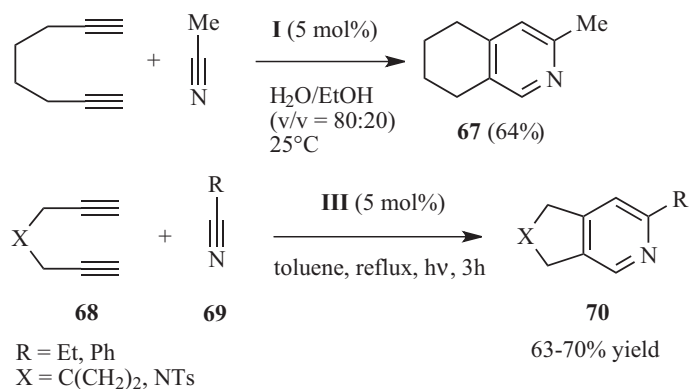
SCHEME 1.16

1.3   SYNTHESIS OF HETEROCYCLES

1.3.1   New Catalytic Systems

1.3.1.1   [CpCo] Complexes   The new catalytic systems **I** to **III** described in Figure 1.2 are also useful for the synthesis of pyridines (Scheme 1.17). With **I**, the formation of tetrahydroisoquilonine **67** could be achieved without irradiation in an aqueous medium at room temperature [5]. In that respect, complex **I** outperforms CpCo(COD), for which photochemical conditions were necessary [6]. It also proved more active than the hydrophilic cobalt catalyst developed by Fatland and Eaton,

SCHEME 1.17

with which synthesis of pyridines was achieved without irradiation but at 85 °C [33]. As for complex **III**, although the yields improved significantly under visible-light irradiation, the formation of bicyclic fused pyridines **70** could be achieved in neither degassed nor distilled toluene [9].

The synthesis of chiral racemic atropisomeric pyridines by cobalt-catalyzed [2 + 2 + 2] cycloaddition between diynes and nitriles was reported in 2006 by Hrdina et al. using standard CpCo catalysts [CpCo(CO)$_2$, CpCo(C$_2$H$_4$)$_2$, CpCo(COD)] [34]. On the other hand, chiral complexes of type **II** were used by Gutnov et al. in 2004 [35] and by Hapke et al. in 2010 [36] for the synthesis of enantiomerically enriched atropisomers of 2-arylpyridines (Scheme 1.18). This topic is described in detail in Chapter 9. It is noteworthy that the 2004 paper contains the first examples of asymmetric cobalt-catalyzed [2 + 2 + 2] cycloadditions. At that time, it had been preceded by only three articles dealing with asymmetric nickel-catalyzed transformations [37]. Then enantioselective metal-catalyzed [2 + 2 + 2] cycloadditions gained popularity, mostly with iridium- and rhodium-based catalysts, as shown in Chapter 9.
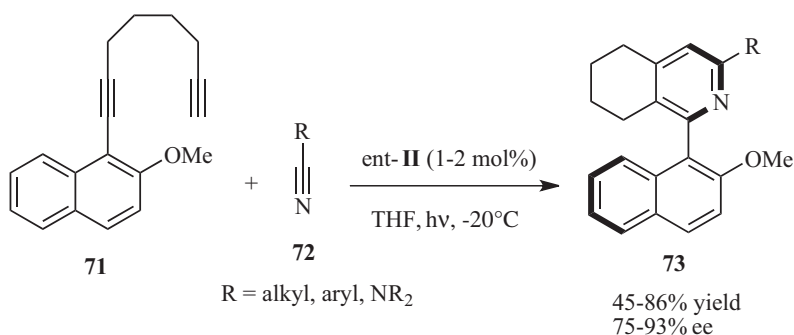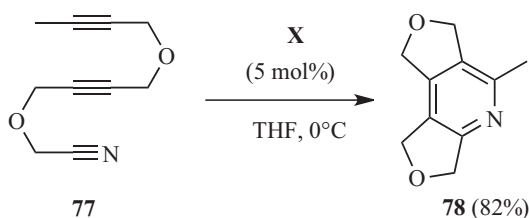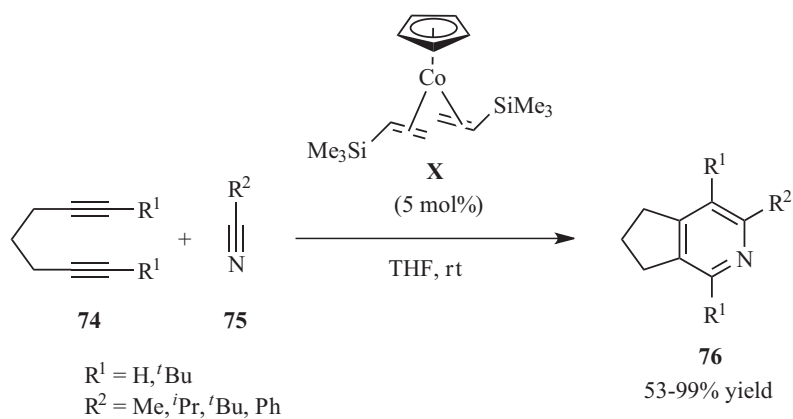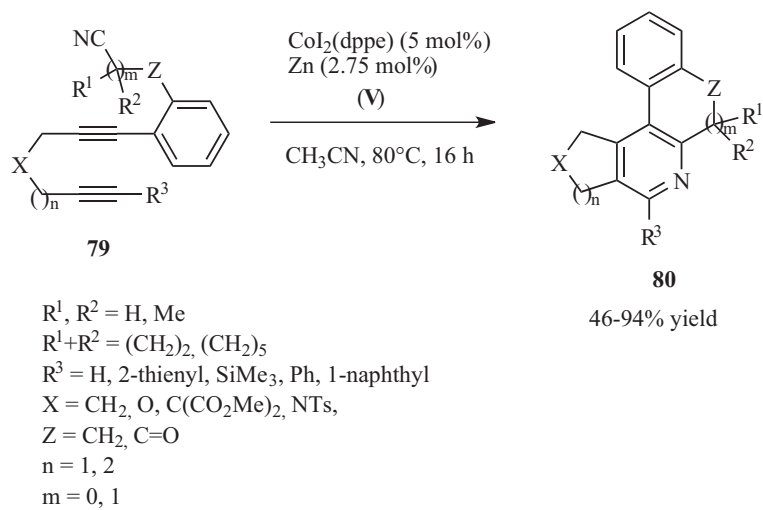

SCHEME 1.18

Recently, the highly reactive CpCo(C$_2$H$_3$SiMe$_3$)$_2$ complex **X** was used by Hapke et al. to catalyze the formation of pyridines under mild conditions (Scheme 1.19) [3u,38]. The co-cyclization of diynes **74** and nitriles **75** were carried out at room temperature without irradiation in good yields. On the other hand, cyclization of the cyanodiyne **77** could be achieved at 0 °C to give **78** in 82% yield. While catalyst **X** is particularly efficient for the construction of pyridines, it seems more reluctant in the case of benzenes, which are formed in low yields [38b].

1.3.1.2 Cobalt Halides   Chang et al.'s precatalytic mixture **V** (Figure 1.3) is also efficient for the construction of pyridines [39]. Tetra- and pentacyclic pyridines derivatives **80** were obtained by cobalt-catalyzed [2 + 2 + 2] cycloaddition of cyanodiynes **79** in good yields (Scheme 1.20). This time, the reaction is carried out in pure acetonitrile. The presence of a sterically demanding substituent at the alkyne terminus (R^3) proved to be beneficial in most cases.
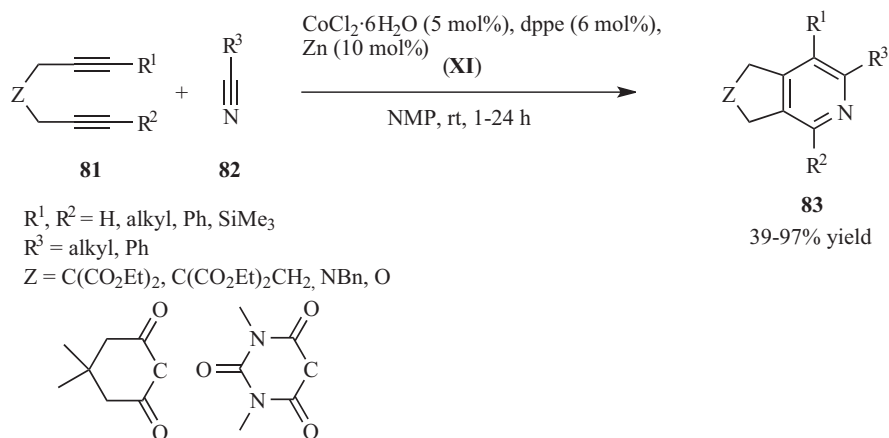
SCHEME 1.19

R^1 = H, ^{t}Bu
R^2 = Me, ^{i}Pr, ^{t}Bu, Ph

76
53–99% yield

78 (82%)

R^1, R^2 = H, Me
R^1+R^2 = (CH$_2$)$_2$, (CH$_2$)$_5$
R^3 = H, 2-thienyl, SiMe$_3$, Ph, 1-naphthyl
X = CH$_2$, O, C(CO$_2$Me)$_2$, NTs,
Z = CH$_2$, C=O
n = 1, 2
m = 0, 1

80
46–94% yield

SCHEME 1.20

Kase et al.'s "instant" catalyst based on the catalytic mixture **IX** (Figure 1.3) was tested for the construction of pyridines from diynes and nitriles but proved inefficient [40]. Oligomers of the starting diynes were obtained instead of the products desired. To circumvent this problem, the Dipimp ligand was replaced by bis(diphenylphosphino)ethane (DPPE), and the reaction was carried out in *N*-methylpyrrolid-2-one (NMP) at room temperature. In this case, diynes **81** and nitriles **82** co-cyclized to give the expected bicyclic pyridines **83** in good yield (Scheme 1.21).

R^1, R^2 = H, alkyl, Ph, SiMe$_3$
R^3 = alkyl, Ph
Z = C(CO$_2$Et)$_2$, C(CO$_2$Et)$_2$CH$_2$, NBn, O

SCHEME 1.21

Importantly, incorporation of the nitrile proved regioselective when dissymmetrical diynes were used (Figure 1.4).

84
R = H, ^{n}Bu, Ph
39-91% yield
regioselectivity > 99:1

85 (96%)
regioselectivity = 85:15
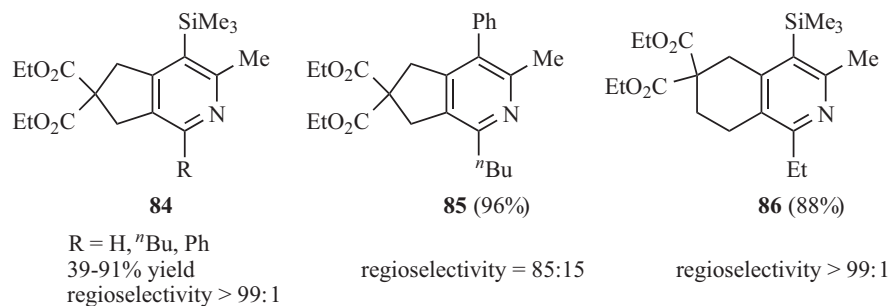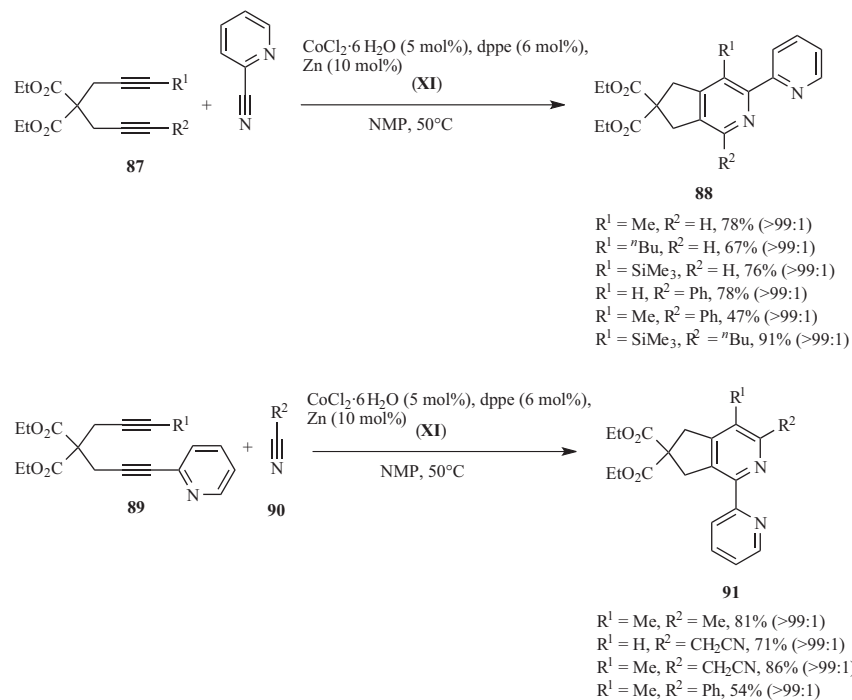
86 (88%)
regioselectivity > 99:1

FIGURE 1.4

The reaction was latter applied to picolinonitrile and 2-pyridyl-substituted diynes **89** so as to synthesize 2,2′-bipyridine frameworks **88** and **91** (Scheme 1.22) [41]. Again, almost perfect regiocontrol was observed, which is a great improvement compared to procedures reported previously.
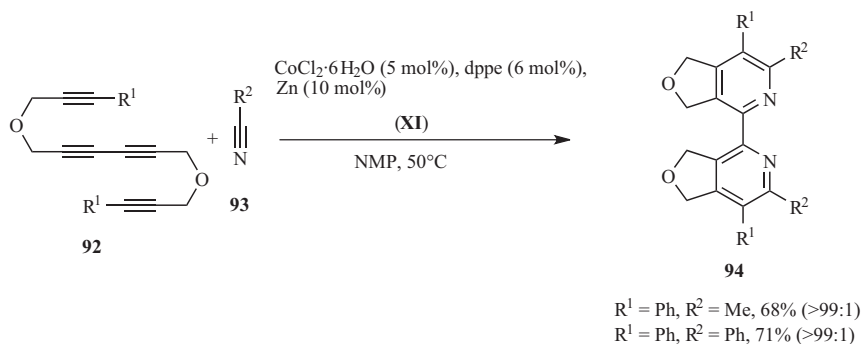
SCHEME 1.22

Tetraynes **92** were also reacted with nitriles to give symmetrical bipyrines **94**, again with excellent regiocontrol (Scheme 1.23). The selectivities observed in all of these transformations were explained in terms of electronic effects.

Finally, as in the case of benzenes described in Section 1.2.1.3, this reaction was used to rapidly build a library of polymerizable pyridines [15a].
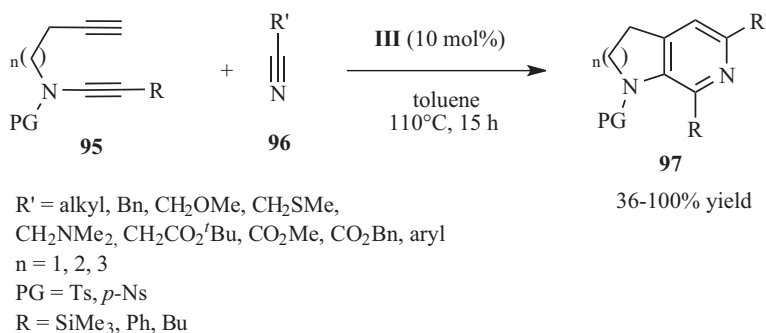

R^1 = Ph, R^2 = Me, 68% (>99:1)
R^1 = Ph, R^2 = Ph, 71% (>99:1)
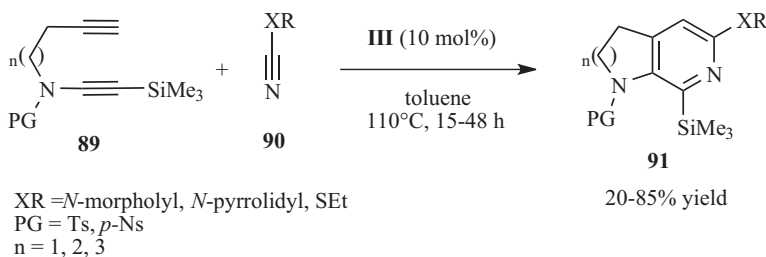
SCHEME 1.23

1.3.2 New Cyclization Partners

Synthetic efforts directed toward the formation of aminopyridine frameworks have been made in recent years. Indeed, nitrogen-substituted pyridines represent an important class of compounds displaying promising biological activities. In that respect, Zhou et al. reported in 2007 the synthesis of tetrahydronaphthyridines by cobalt-catalyzed [2 + 2 + 2] cycloaddition using $CpCo(CO)_2$ or CpCo(COD) as a catalyst under microwave irradiation [42]. On the other hand, Garcia et al. used ynamides as cocyclization partners to construct 3-aminopyridines [43]. Although it has been quite some time since ynamides [44] were used in [2 + 2 + 2] cycloaddition to build aniline derivatives [45], they had not been used before to form pyridines. The reaction of yne-ynamides **95** with nitriles and cyanoformates **96** was carried out in hot toluene using the new catalyst **III** (Figure 1.2). In most cases, the incorporation of **96** proceeded in a regioselective fashion to give 3-aminopyridines **97** in moderate to quantitative yields (Scheme 1.24).

R' = alkyl, Bn, CH_2OMe, CH_2SMe,
CH_2NMe_2, $CH_2CO_2{}^tBu$, CO_2Me, CO_2Bn, aryl
n = 1, 2, 3
PG = Ts, *p*-Ns
R = $SiMe_3$, Ph, Bu

36-100% yield

SCHEME 1.24

Cyanamides [33,36,46] and ethyl thiocyanate **90** could be used as well in such bimolecular cyclizations (Scheme 1.25).

XR = *N*-morpholyl, *N*-pyrrolidyl, SEt
PG = Ts, *p*-Ns
n = 1, 2, 3

20-85% yield

SCHEME 1.25

Tricyclic fused 3-aminopyridines **93** could also be assembled via intramolecular $CpCo(C_2H_4)_2$-catalyzed [2 + 2 + 2] cycloaddition between ynamides, nitriles, and alkynes (Scheme 1.26) [47]. Of particular interest, one of the cycloadducts could be used in a rare type of silylated pyridine Hiyama cross-coupling to give **95** in 77% yield.

X = NCbz, CH$_2$, (CH$_2$)$_2$, C(CO$_2$Me)$_2$, O
n = 1, 2, 3
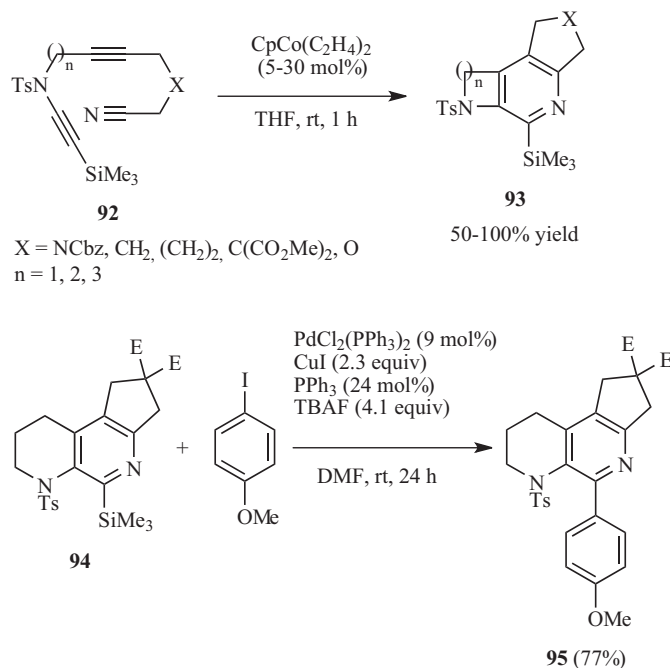
SCHEME 1.26

1.3.3   Chemo- and Regioselectivity Issues

As stated above for benzenes (see Section 1.2.3), the chemo- and regioselective assembly of three distinct cyclization partners constitutes a great challenge. In the case of pyridines, this issue could be addressed by carrying out solid-supported [2 + 2 + 2] cycloadditions. In 2006, Senaiar et al. reported cobalt-catalyzed [2 + 2 + 2] cycloaddition between trityl resin-supported propargyl alcohol **96**, alkynes **97**, and nitriles **98** to give pyridines **100** after acidic cleavage (Scheme 1.27)


R^1 = alkyl, Ph
R^2 = H, alkyl
R^3 = Me, Et, Ph
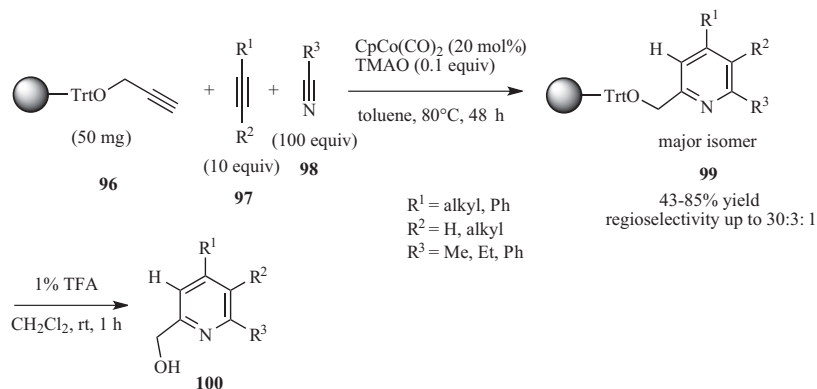
SCHEME 1.27

[48]. The nitrile was used in large excess to avoid competitive benzene formation. Excellent chemoselectivities were observed, and in various cases, impressive regioselectivities as well, in favor of the 2,4,6-regioisomer.

Solid-supported [2 + 2 + 2] cycloadditions were also tested by Young and Deiters in the case of bimolecular cyclizations leading to fused pyridines (Scheme 1.28) [49]. This procedure avoids oligomerization of the starting diyne. The nitrile is used in excess (10 equiv) and mixed directly with the derivatized resin in toluene. After addition of the cobalt catalyst, the mixture is irradiated at 300 W for 10 min. With no solid support, the product desired, **103**, is obtained only as traces (R = Ph). With dissymmetrical diynes **104**, the reaction proved perfectly regioselective.
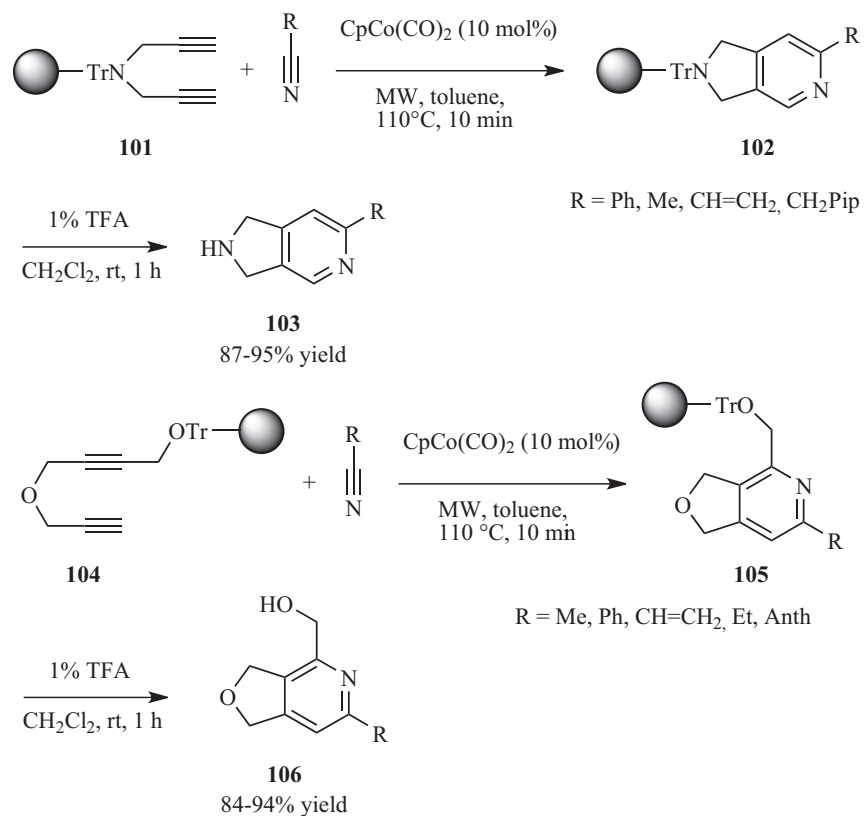
SCHEME 1.28

Isocyanates and carbodiimides were also tested, leading to compounds of type **109** in high yields (Scheme 1.29). Under standard conditions, such reactions usually give rise to poor selectivities, especially in the case of carbodiimides. On the other hand, the solid-supported version allows the formation of pyridones and 2-iminopyridines in high yields.
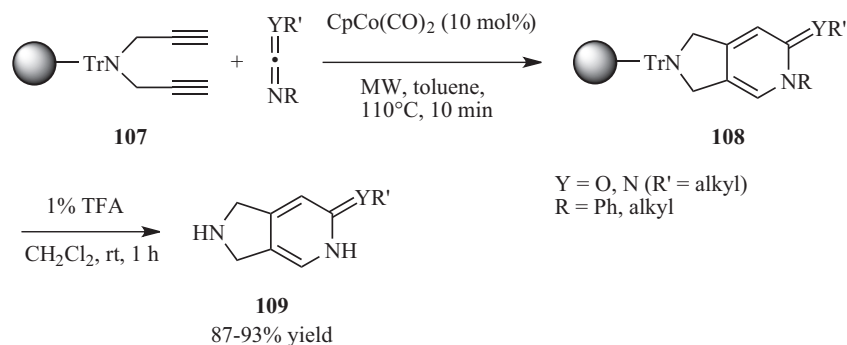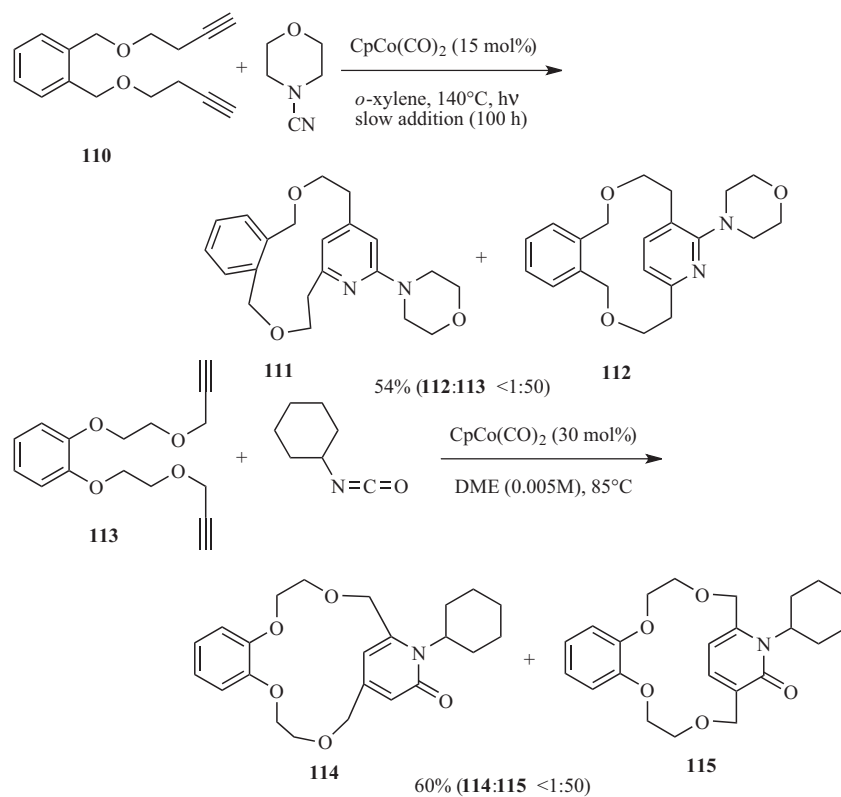
SCHEME 1.29

Young et al. also reported in 2009 that some chemoselectivity issues could be solved without solid support under open-vessel microwave conditions [50].

To close, it is worth mentioning the work of Boñaga et al. regarding the formation of macrocycles via cobalt-catalyzed pyridine or pyridone formation (Scheme 1.30) [3k,46c and d,51]. Using long-tethered diynes, only two pyridinophanes are actually
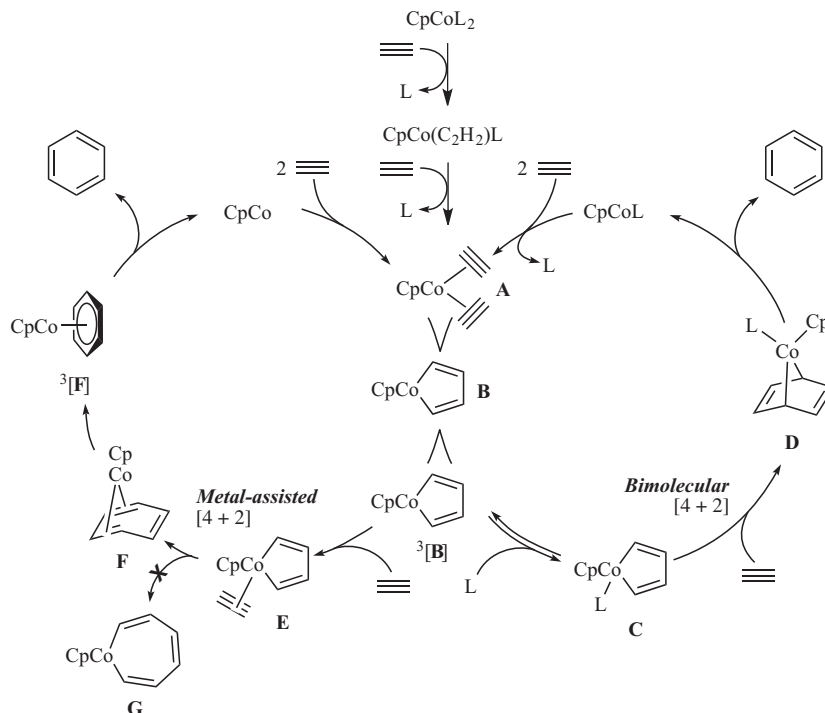

SCHEME 1.30

obtained (para and meta macrocycles). The regioselectivity is affected by the nature of the tether (length and type), as well as by stereoelectronic factors.

1.4   MECHANISTIC ASPECTS

The mechanism of CpCo-catalyzed [2 + 2 + 2] cycloaddition to give benzene derivatives has been the subject of many experimental studies. Theoretical work of Hardesta et al. [52], Dahy et al. [53], and Agenet et al. [54] has unified all these experimental findings together in two overlapped catalytic cycles (Scheme 1.31). In both cycles, a bisalkyne complex **A** undergoes oxidative addition to a singlet cobaltacyclopentadiene **B**, which relaxes to the triplet ground state ^{3}[**B**]. That species can be trapped rapidly by strongly donating ligands (PR$_3$, CO, THF) to give the singlet 18-electron complex **C**. Therefore, for reactions carried out in coordinating solvents or employing CpCo(PR$_3$)$_2$ or CpCo(CO)$_2$, the species **C** is a likely intermediate. Strongly dienophilic alkynes react with **C** by intermolecular [4 + 2] cycloaddition to furnish the cobaltanorbornadiene **D**. A change in the spin state results in formation of the free arene and triplet CpCoL. In the absence of strong donors and electron-poor alkynes, another catalytic cycle takes place: ^{3}[**B**] reacts with the alkyne to give the singlet species **E**, which subsequently transforms into the CpCo(η^4-arene) complex **F** via intramolecular metal-assisted [4 + 2] cycloaddition. A spin change transforms **F** into
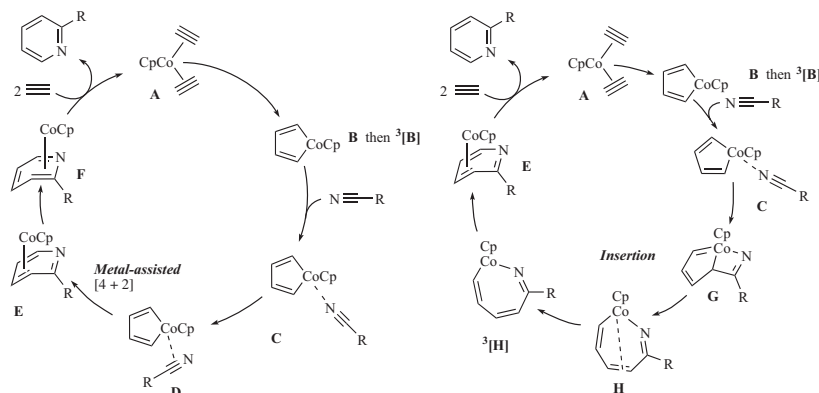

SCHEME 1.31

the 20-electron sandwich complex ^{3}[**F**], whose dissociation provides the free arene and CpCo.

Importantly, one can note that the frequently invoked cobaltacycloheptadienes of type **G**, which would arise from insertion of the alkyne into the cobaltacyclopentadiene are not part of any of the mechanistic pathways computed.

In the case of pyridines, catalytic cycles have been proposed on the basis of theoretical studies of Dazinger et al. [55], Dahy et al. [56], Garcia et al. [43b], and Rodriguez et al. [57]. The main difference in the case of benzenes shown above is that the insertion mechanism leading to seven-membered cobaltacycles can be modeled in some cases. Thus, two pathways are possible (metal-assisted [4 + 2] and insertion), the prevalence of one over the other depending on the nature of the cyclization partners involved (Scheme 1.32). In the [4 + 2] pathway, the intermediate metallacycle **B** reacts in its triplet ground state ^{3}[**B**] with the nitrile to give the singlet η^1-complex **C**, which subsequently rearranges into the η^2-nitrile complex **D**. The latter undergoes [4 + 2] cycloaddition to give singlet **E** and then **F**. This pathway is favored with acetonitrile (R = Me). However, it seems that acetonitrile may prefer the insertion pathway with cobaltacyclopentadiene derived from ynamides [43b].

SCHEME 1.32

In the insertion pathway, carbene **G** transforms into the seven-membered complex **H**, which collapses to its triplet ground state before reductively eliminating to give **E**. This pathway was found to be the most favored one with hydrogen cyanide (R = H) and trifluoroacetonitrile (R = CF$_3$). Thus, it was concluded that electron-rich nitriles rather follow the [4 + 2] mechanism, whereas electron-poor nitriles follow the insertion mechanism [56]. The case of benzonitrile was studied recently and led to the [4 + 2] pathway as the best option [57]. Thus, in the case of pyridines, the two options are possible and the switch between them seems to depend on subtle electronic variations.

Finally, in the case of cobalt halides (see Section 1.2.1.3), although such systems did not receive much attention experimentally and theoretically with regard to the mechanism of the cycloaddition, metallacyclopentadienes of type **B** and **D** are also invoked [13c,41].

1.5   SYNTHETIC APPLICATIONS

1.5.1   Natural Products and Naturally Occurring Scaffolds

Because the synthesis of natural products via [2 + 2 + 2] cycloaddition constitutes the topic of Chapter 7, only a rapid overview is given in this section. The first total synthesis involving a cobalt-catalyzed [2 + 2 + 2] cycloaddition is that of (rac)-estrone, reported by Funk and Vollhardt in 1980 [58]. Then followed the total syntheses of protoberberines (1983) [59], camptothecin (1983 and 1984) [60], vitamin B_6 (1985) [61], and (rac)-lysergene and (rac)-LSD (1994) [62]. These syntheses rely on benzene, pyridine, or pyridone ring formation. In 1990, Chelucci et al. reported the cobalt way to 2-nicotine by pyridine construction [63]. In 1993 and 1996, Aubert, Cruciani, and co-workers described cascade approaches involving a cobalt-catalyzed [2 + 2 + 2] cycloaddition leading to phyllocladane and kaurane basic skeletons [64]. The title reaction was also used in the synthesis of Steganone analogs reported by Bradley et al. in 1999 [65]. Over the last 10 years, at least 14 more papers involving a cobalt-catalyzed benzene formation as a key step in the synthesis of natural scaffolds have been published [66], and at least seven involving a cobalt-catalyzed pyridine formation [67]. As a first illustrative example, Kesenheimer et al. reported in 2010 the asymmetric total synthesis of the antibiotics (+)-rubiginone B_2, (–)-tetrangomycin, and (–)-8-O-methyltetrangomycin (Scheme 1.33) [66m]. Triyne **116** was cyclized in the presence of 1 equiv of $CpCo(C_2H_4)_2$ at low temperature to afford the intermediate **117**, which was converted into the aromatic tratrahydrobenzo[a]anthracene **118** by acidic treatment. The latter was used as a precursor of the antibiotics desired.

The total synthesis of (+)-complanamide A relies on two cobalt-mediated [2 + 2 + 2] cycloadditions to give pyridine rings (Scheme 1.34) [67f]. This cyclization


R = Me, R' = H ((+)-Rubiginone B2)
R = Me, R' = OH ((-)-Tetrangomycin)
R = H, R' = OH ((-)-8-O-Methyltetrangomycin)
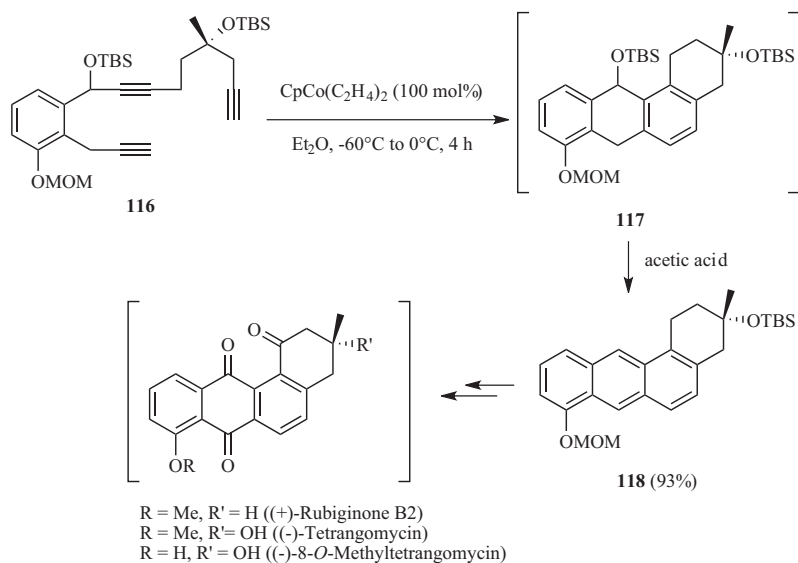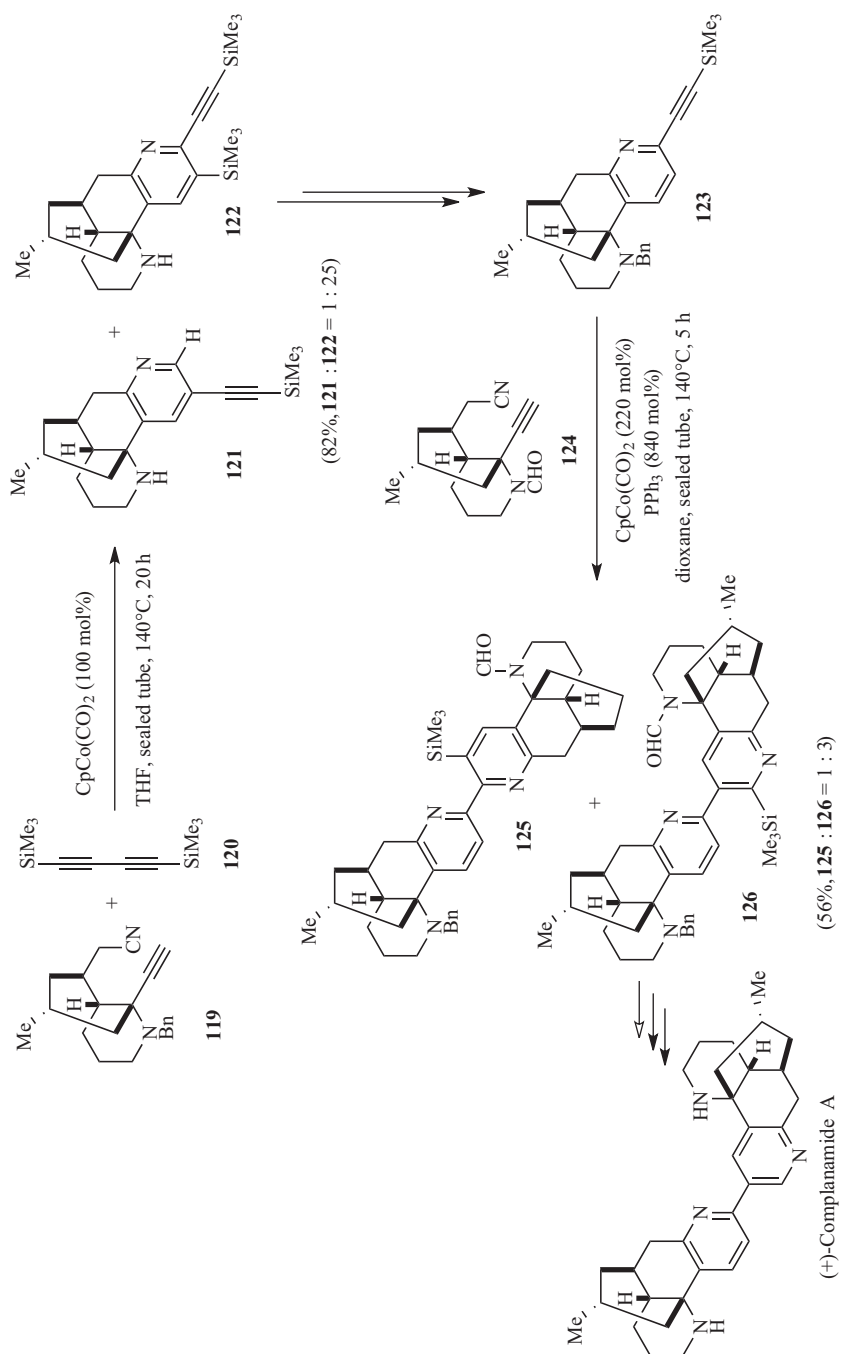
SCHEME 1.33

SCHEME 1.34

of cyanoyne **119** with the 1,2-diyne **120** led to **121**, which suffers from protodelilyla-tion, and its regioisomer **122**, which is the major product. It was transformed in two steps into **123**, which was engaged in another cycloaddition, this time with cyanoyne **124**. Without triphenylphosphine, regioisomer **125** was the major product (3.3 : 1). With an excess of triphenylphosphine, the key intermediate **126** became the major product and was converted into the target compound in three steps.

1.5.2 Polyphenylenes

1.5.2.1 Helicenes   Helicenes are fascinating molecules displaying a broad range of properties. The cobalt-catalyzed [2 + 2 + 2] cycloaddition allows the construction of such angularly fused polycyclic compounds [68]. Stará et al. reported various applications, using $CpCo(CO)_2$ or $CpCo(C_2H_4)_2$ as a catalyst, like the one depicted in Scheme 1.35 [68b]. This topic is covered in detail in Chapter 10.
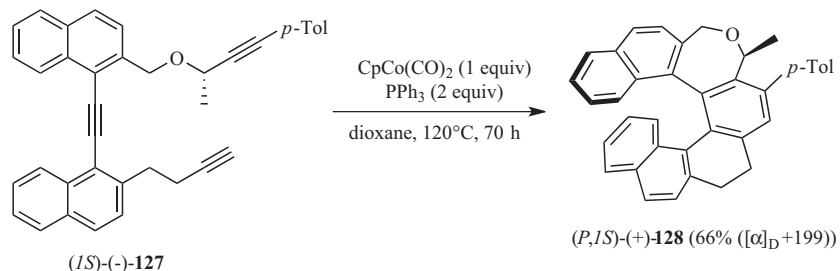
SCHEME 1.35

1.5.2.2 [N]-Phenylenes   [*N*]-Phenylenes have received considerable attention because of their unique combination of aromatic and antiaromatic properties and their potential as molecular magnets, conducting materials, and precursors of fullerenes [69]. Among various intriguing properties, the σ- and π-ring strain in triangular C3-symmetric [4]-phenylenes act in concert, causing their cores to behave spectroscopically and chemically as true cyclohexatrienes [70]. Biphenylenes, linear [3]-phenylenes, and higher analogs can be formed by cobalt-catalyzed [2 + 2 + 2] cycloaddition involving 1,2-bis(alkynyl)arenes such as **130** or 1,2,4,5-tetra(alkynyl)arenes such as **132** (Scheme 1.36) [71].
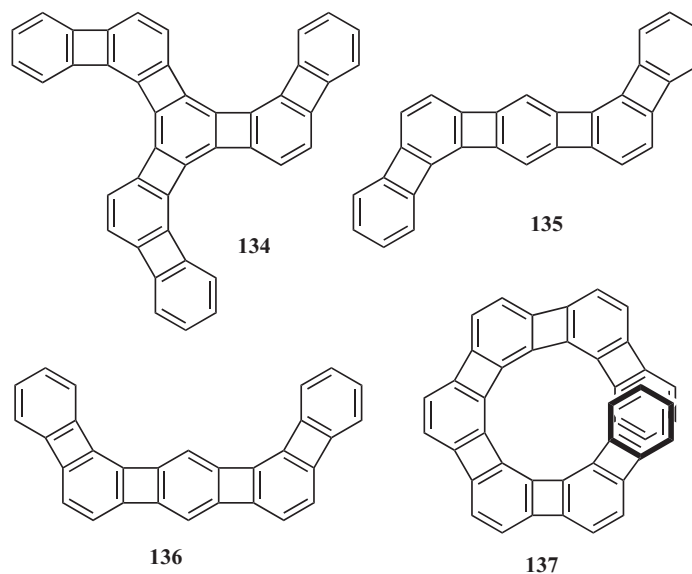

SCHEME 1.36

134

135

136

137
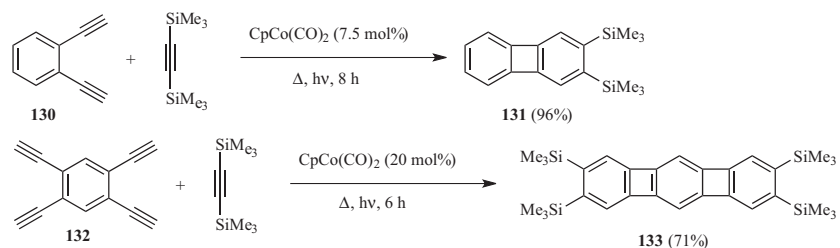
FIGURE 1.5

Numerous linear and angular [*N*]-phenylenes can be obtained rapidly by this methodology [72]. For example, the C3*h*-symmetric [7]-phenylene **134** has been synthesized via cobalt-mediated triple cycloisomerization of a nonayne (Figure 1.5) [73]. The syn and anti double bent [5]phenylenes **135** and **136** have been assembled via double cobalt-catalyzed cyclization of hexaynes [74]. Helical [7]-, [8]-, and [9]phenylenes (heliphenes) such as **137** have also been prepared via cobalt-mediated multiple cycloisomerization of polyynes [75].

1.5.2.3 Polyaryls The ease with which the cobalt-catalyzed [2 + 2 + 2] cycloaddition delivers quater- or higher oligoaryls has been exploited for the preparation of materials displaying interesting photophysical or electrochemical properties (Scheme 1.37).

SCHEME 1.37

FIGURE 1.6

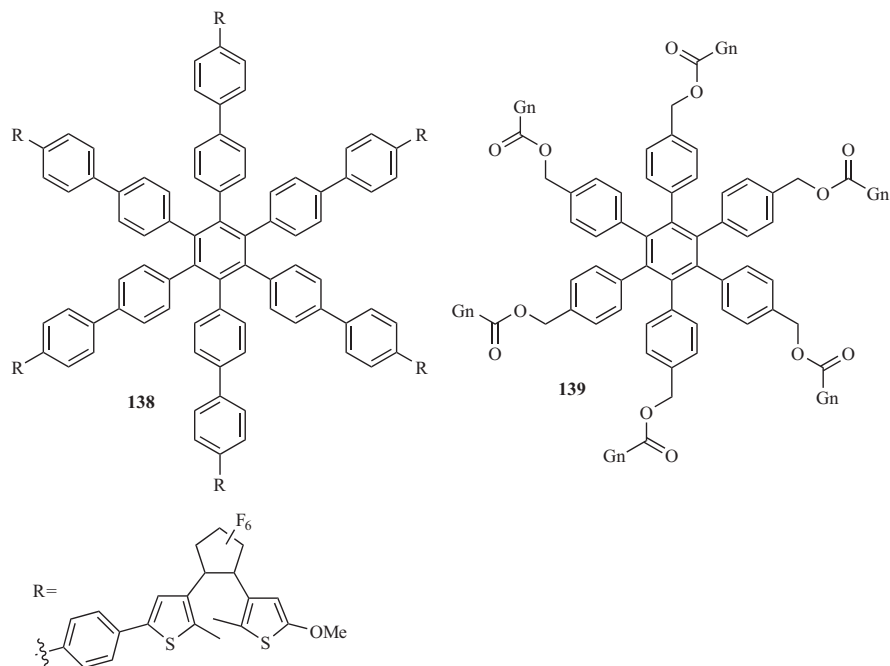For example, regioisomers of tris(azulen-1-yl)benzene (Ar = azulen-1-yl) and tris(ferrocenyl)benzene have recently been prepared by this methodology and characterized [76]. Porous organic polymers have also been synthesized in this way [77]. Electrochemical switches **138** [78], as well as fullerodendrimers **139** [79], were assembled rapidly by cobalt-catalyzed [2 + 2 + 2] cycloaddition (Figure 1.6).

1.5.2.4   Other Systems   Other examples of carbon-rich molecules prepared by this reaction, including fluorescent anthracenes and azaanthracenes [80] and quadrannulene [81], have recently been described.

1.6   SUMMARY AND OUTLOOK

This chapter covers in detail new findings dealing with cobalt-catalyzed [2 + 2 + 2] cycloaddition over the period 2002–2012. In terms of methodology, this decade has witnessed the discovery of new practical and inexpensive catalysts. The first asymmetric reactions were also reported. Important progress has been made regarding control of the chemo- and regioselectivities. New partners have been tested, leading to valuable functionalized compounds. In terms of applications, the cobalt-catalyzed [2 + 2 + 2] cycloaddition did not fall short of its reputation. Many complex molecules, including natural products, have been synthesized in an expedient fashion.

Compounds that present interesting properties for material science have also been prepared with this reaction.

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