Abstract: The recent developments in cobalt catalysis are compiled in this review covering the years 2000 through 2007. Special focus is directed towards cobalt-catalysed ring-formation reactions as well as towards cobalt-catalysed (cross-) coupling reactions and synthetically useful applications thereof in the synthesis of acyclic compounds.

1 Introduction

The application of the first-row transition metals, such as iron, cobalt and nickel, in synthetic organic transformations has attracted increasing interest for reasons other than simply their lower costs when compared to their higher homologues. A steadily growing number of contributions have appeared in the literature where benchmark transformations such as palladium-catalysed coupling reactions were conducted with these first-row transition metals. It became obvious that problems in palladium chemistry, such as the β-hydride elimination, are of reduced importance in the chemistry of iron, cobalt and nickel coupling reactions, probably because of lower rates for the β-hydride elimination pathway. Therefore, reactions with the first-row transition metals can provide an interesting alternative in established transformations and within this review we emphasise that cobalt, in particular, can open up new pathways to new products in catalysed reactions.

In this review we focus our attention upon the recent developments of the use of cobalt in organic synthesis in the years 2000 through 2007 and few selected examples from 2008. Uncovered are contributions concerning cobalt-catalysed Pauson–Khand reactions, Nicholas reactions and polymerisation reactions. For such applications, recent reviews exist¹ and herein we provide an update to earlier overviews of this field.²

2 Cobalt-Catalysed Cycloaddition Reactions

2.1 Cyclopropanation

Metal-catalysed cyclopropanation of double bonds with carbenoids obtained from diazo compounds is a well-known reaction in organic synthesis. The control of both the diastereoselectivity and the enantioselectivity has drawn much attention over the past years. There are various catalysts, such as copper, cobalt, ruthenium and rhodium complexes, that exhibit excellent stereoselectivities and, in general, result in the formation of the trans products.³

Recently Katsuki studied metallosalen complexes, which are known to be efficient catalysts for oxene and nitrene transfer reactions.⁴ He reported the use of chiral cobalt(salen) complexes for the analogous carbenoid transfer reaction (Scheme 1).⁵ Various styrene derivatives 1 reacted with simple α-diazo esters 2 with diverse salen-derived cobalt complexes to produce the cyclopropanation products 3 in excellent yield, diastereoselectivity and enantioselectivity.

The cis/trans relationship is influenced by the nature of the ligand and the cobalt centre. Cobalt(III) complexes seem to favour the generation of the trans isomer, and cobalt(II) complexes, the cis isomer.⁶

![Scheme 1](image-url)
Gao reported the use of dinuclear Robson-type coupled chiral salen complexes for the same purpose. These complexes catalysed the cyclopropanation of styrene with ethyl diazoacetate in high yields (49–94%) and excellent enantioselectivities (up to 94% ee) but only with moderate diastereoselectivities for the \( \text{trans} \) isomer (1:1 to 3:1).\(^7\) The same model transformation was applied by Charette in investigating the reaction of a cobalt(salen) complex in water, but only moderate yields and selectivities were reported.\(^8\) Yamada used the cyclopropanation of styrenes with \( \beta \)-ketiminato cobalt(II) complexes for the investigation of the influence of the reaction parameters, diverse alcohols as solvents, and nitrogen-containing heteroaromatics on the selectivity. The yield in all tested alcohols was very good and an increase in diastereoselectivities (up to 83:17 for the \( \text{trans} \) isomer) and enantioselectivities (up to 96% ee) with increasing dielectric constants was noted.\(^9\) It was also shown that the addition of \( \text{N,N}' \)-dimethylimidazole accelerated the reaction and enhanced the enantioselectivity.

Pozzi and O’Hagan studied chiral fluorinated diamine and diimine cobalt complexes along with copper complexes for use in fluorous solvent systems. Acceptable enantioselectivities were obtained; however, the yields were unsatisfactory with these complexes.\(^10\) The copper complexes were undoubtedly superior under such conditions.

Zhang reported the use of cobalt(porphyrin) complexes for the asymmetric cyclopropanation of styrene derivatives \( 4 \) with ethyl diazoacetate \( 5 \) under mild reaction conditions (Scheme 2).\(^11\)

\[
\begin{align*}
\text{Ph} & \quad \text{OEt} \\
\text{O} & \\
\text{N}_2 & \\
\text{Ph} & \\
\text{H} & \\
\text{Co(porphyrin)} \\
\end{align*}
\]

\( 83\%, \quad 75\% \text{ ee} \)

\( \text{trans/cis} \quad 94:6 \)

Scheme 2

A great number of structurally diverse porphyrin ligands were investigated and in general a preference for the \( \text{trans} \) product was shown.\(^12\) Excellent yields and selectivities were obtained, and these were significantly enhanced in the presence of catalytic amounts of nitrogen-containing aromatics, such as \( \text{N,N}' \)-dimethylaminopyridine (DMAP).

### Biographical Sketches

**Wilfried Hess** was born in Wiesbaden (Germany) in 1979 and studied chemistry at the Philipps-Universität Marburg. He obtained his Diploma with A. Studer in 2003 and his PhD with G. Hilt in 2007. Currently he is working in the group of M. Schlitzer, at the same university, on the synthesis of pharmacologically interesting enzyme inhibitors.

**Jonas Treutwein** was born in Werneck (Germany) in 1978 and studied chemistry at the Philipps-Universität Marburg (Germany). He obtained his diploma in 2006 and is currently working as a PhD student in the group of G. Hilt on cobalt(I)-catalysed reactions and their application in organic synthesis.

**Gerhard Hilt** was born in Andernach (Germany) in 1968. He studied chemistry in Bonn, where he obtained his diploma in 1992 and his PhD in 1996 with E. Steckhan on indirect electrochemical regeneration of enzymatic cofactors in asymmetric biosynthesis. From 1996 to 1998, he worked as a postdoctoral fellow with M. F. Semmelhack (Princeton, USA) on stoichiometric organometallic chemistry and from 1998 to 1999 in the group of R. Noyori (Nagoya, Japan) on mechanistic investigations in asymmetric catalysis. From late 1999 to 2002 he was at the Ludwig-Maximilians-Universität (Munich, Germany) for his habilitation, associated with the group of P. Knochel. In 2002 he moved to Marburg to his current position as an associate professor in organic chemistry. His research interests are electron-transfer-activated transition-metal complexes of cobalt and iron and their application as catalysts in organic synthesis.
With the use of chiral porphyrins, good to excellent enantioselectivities were achieved. Zhang recently reported the use of chiral cobalt(porphyrin) complexes for the asymmetric cyclopropanation of electron-deficient olefins such as 6 under very mild conditions, showing excellent selectivities (Scheme 3). This demonstrates the usefulness of the reaction by generating electrophilic cyclopropanes 7 which are versatile building blocks for organic synthesis.

**Scheme 3**

Caselli and Cenini additionally reported on the course of an investigation regarding nitrene transfer reactions, the asymmetric cyclopropanation of olefins with diazoacetates under cobalt(porphyrin) catalysis. The reaction proceeds under very mild conditions with good yields, yet poor selectivities.

### 2.2 Four-Membered-Ring Formation

The supra-suprafacial [2+2]-cycloaddition reaction of alkenes or alkynes is thermally forbidden by the Woodward–Hoffmann rules. Nevertheless, they are possible photochemically, by radical mechanisms, by Lewis acid catalysis, or by transition-metal catalysis, and are used routinely in organic synthesis.

**Dimerisation of Alkenes**

Krische reported the first example of an intramolecular, diastereoselective [2+2] cycloaddition of bis-enones 8 to cyclobutanes 9 (Scheme 4). The catalytically active species was supposed to be cobalt(I), which is isoelectronic to nickel(0), a known catalyst for [2+2] cycloadditions.

**Scheme 4**

The reaction is restricted to aryl-substituted ketones and the formation of bicyclo[3.2.0] backbones but the yields of this new and promising reaction are moderate to good and only one diastereomer is obtained.

**Reaction of Alkenes with Alkynes**

The [2+2] cycloaddition of alkynes with alkenes is a valuable reaction for the construction of four-membered rings, although the catalysis of such transformations with transition metals, such as iron or nickel complexes, is rather limited. There are only a few reactions described under cobalt catalysis. Cheng reported the reaction (Scheme 5) of terminal as well as internal alkynes with bicyclic alkenes such as benzooxonorbornadiene (10) to highly functionalised cyclobutenes 11 with the inexpensive and versatile CoI₂(PPh₃)₂, triphenylphosphine and zinc catalyst system.

**Scheme 5**

The yields of the desired polycyclic products are good to excellent but only some oxobenzonorbornadiene derivatives were investigated, while a broad variety of terminal and internal alkynes were applied. Unfortunately, when substituted alkenes were used, diastereomeric mixtures with a ratio of nearly 1:1 were obtained.

As an extension of this methodology, Hilt reported very recently on a simple cobalt catalyst system [CoBr₂(dppp), Zn, ZnI₂] whereby not only could norbornyl derivatives be used as starting materials, but alsoacenaphthylene and even cyclopentene (Scheme 6) could be applied for the synthesis of cyclobutene derivatives such as 12.

**Scheme 6**

However, only internal alkynes could be used, because with terminal alkynes, the concurrent cyclotrimerisation of the alkyne to the corresponding benzene derivative became the predominant reaction pathway.

The cyclodimerisation of alkynes to form cyclobutadienes yields only metal-bound products. Although these transformations are of great interest concerning reaction mechanisms and inorganic chemistry, they have not yet found broad application in organic synthesis.

### 2.3 Five-Membered-Ring Formation

The most valuable reaction in cobalt catalysis for the construction of five-membered rings is undoubtedly the Pauson–Khand reaction. This review concentrates, however, on reactions other than this versatile transformation because it has been extensively reviewed elsewhere.

Nevertheless, we would like to mention the work of Chung, who combined a cobalt-catalysed Pauson–Khand-type reaction in a tandem procedure with other cobalt-catalysed cycloaddition reactions. After a [2+2+1] cycloaddition, a cyclopentadienone intermediate formed and...
reacted with either 1,3-dienes in a Diels–Alder reaction or with two other alkynes in a [2+2+2]-cycloaddition reaction. Alternatively, a dimerisation to 13 by a Diels–Alder reaction (Scheme 7) and subsequent CO extrusion under rearrangement of the carbon backbone leads to the final product 14 in good yield. Dicobalt octacarbonyl or cobalt on carbon was employed as catalyst and the desired products were obtained in good to excellent yields.

Scheme 7

**Reaction of Allenes with Enones**

Cheng recently reported the diastereoselective reductive [3+2] cycloaddition of allenes with enones (Scheme 8). With the use of a CoI2(dppe), zinc and zinc iodide catalyst system, allenes and alkyl-substituted enones could be converted diastereoselectively, in refluxing aqueous acetonitrile, into the corresponding methylenecyclopentanol derivatives 15 in moderate to good yields.

Scheme 8

**Dipolar Cycloadditions with Nitrones**

The 1,3-dipolar cycloaddition of nitrones to alkenes is a very useful reaction for the construction of isoxazolidines such as 16 which are valuable synthetic intermediates (Scheme 9). The reaction can be catalysed by Lewis acids with or without ligands. One of the major goals is the control of diastereoselectivity and enantioselectivity in these transformations.

Recently, Desimoni, Kanemasa and Suga conducted studies with diverse Lewis acids, including cobalt salts, which were applied with moderate success. The work of Yamada focused mainly on the use of cationic 3-oxobutylideniminatocobalt(III) complexes for the enantioselective 1,3-dipolar cycloaddition reaction of nitrones with α,β-unsaturated aldehydes to form 16 (Scheme 9). He reported the application of these ligands for a diversity of aryl nitrones and alkyl-substituted α,β-unsaturated aldehydes under mild conditions and with high yields and medium to high enantioselectivities.

Additionally, Tang was the first to report the cycloaddition between nitrones and alkylidene malonates which could be accomplished with cobalt(trisoxazoline) complexes in high yields, diastereoselectivities and enantiomeric excesses.

2.4 **Six-Membered-Ring Formation**

The Diels–Alder reaction is a versatile reaction for the stereospecific construction of six-membered rings and is undoubtedly one of the most studied reactions in organic synthesis. The thermal, uncatalysed reactions sometimes have to be conducted under harsh reaction conditions; thus, many methods were studied to overcome this obstacle, such as Lewis or Brønsted acid catalysis, influence of solvents, pressure or transition-metal catalysis.

The metal-catalysed processes can be divided into two classes: Lewis acid catalysis by coordination to a Lewis basic group such as a carbonyl on either the diene or dienophile, or coordination of the π-bonds of the diene and dienophile. Both methods will be discussed briefly and the latest results regarding the use of cobalt are described.

**Lewis Acid Catalysed Diels–Alder Reaction**

The Diels–Alder reaction of α,β-unsaturated carbonyl compounds with 1,3-dienes can easily be catalysed by the addition of Lewis acids. Almost all possible Lewis acids have been used for this purpose and the use of diverse chiral ligands for enantioselective catalysis has been studied extensively by several groups. In the recent past, some studies have mentioned the use of cobalt complexes, but there are only few investigations that focused mainly on cobalt. For example, Suga studied chiral 2,2′-binaphthyldiimine nickel complexes for enantioselective Diels–Alder reactions. While similar cobalt catalysts also gave high yields, the enantioselectivity was somewhat low. Rawal investigated the use of chiral cobalt(III)salen complexes (Scheme 10) for the enantioselective Diels–Alder reaction of carbamate-substituted 1,3-dienes such as 17 with α,β-unsaturated aldehydes. The cyclohexene derivative 18 was obtained in high yield, excellent diastereoselectivity and excellent enantioselectivity.
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Cobalt-Catalysed Carbon–Carbon Bond-Formation Reactions

A drawback of the reaction is its narrow scope; to date, only the diene shown and a few simple aldehydes have been investigated (Scheme 10).

**Lewis Acid Catalysed Hetero-Diels–Alder Reaction**

The hetero-Diels–Alder reaction is a versatile tool for the construction of six-membered heterocycles, especially pyran derivatives. Several groups have reported Lewis acid catalysts for enantioselective versions of this reaction. Theoretical studies on the reaction were carried out by Yamada. The investigations pointed out the crucial role of the Lewis acidity of the applied complex and the coordination of an aldehyde as an additional axial ligand.

Jurczak reported the cobalt-catalysed enantioselective [4+2] cycloaddition of 1-methoxybuta-1,3-diene with simple glycolaldehyde-derived heterodienophiles to afford the oxygen-substituted dihydropyran in moderate yield (Scheme 11). The cis product was preferentially formed and good to excellent enantioselectivities were obtained with diverse salen ligands.

These products can be used for the synthesis of sugar derivatives, biologically active substances and polyhydroxylated compounds. Yamada used a 3-oxo-butylidenaminatocobalt complex for the hetero-Diels–Alder reaction of electron-rich 1,3-dienes, namely Danishefsky’s diene (20), with various aldehydes (Scheme 12) to afford the corresponding dihydropyran-4-ones with high yields and high enantioselectivities. Wu was the first to use chiral cobalt(salen) complexes for a comparable reaction (Scheme 13) and demonstrated the synthetic potential in the synthesis of 3-deoxy-D-manno-2-octulosonic acid (22).

An interesting new hetero-Diels–Alder reaction was described by Degl’Innocenti and Capperucci. In situ generated thiopropenone stannanes (Scheme 14) reacted with in situ generated thioaldehydes to obtain dithiins such as 24 in good yields, taking into account that the products are relatively unstable and difficult to purify.

**Cobalt-Catalysed Neutral Diels–Alder Reaction**

Most Diels–Alder reactions are conducted between 1,3-dienes and dienophiles with different electronic properties or with substituents which allow Lewis acid coordination and thus mild reaction conditions. Problems arise when electronically neutral substrates without coordinating groups, such as pure hydrocarbons, are used. Therefore, drastic reaction conditions must be applied, consequently leading to increased side reactions such as polymerisation of the starting materials. To circumvent this problem, π-coordinating metal catalysts can be used, and one of the promising developments of recent years is the cobalt catalyst system improved by Hilt, which is based on cobalt-catalyst systems described by Brunner, Lautens and Snyder utilised for cobalt-catalysed homo-Diels–Alder reactions (see below). The applied catalyst system, made up of CoBr₂(dppe), zinc iodide and zinc or tetrabutylammonium borohydride, is inexpensive and easy to both prepare and handle. With this catalyst, a great diversity of neutral dienes and internal as well as terminal alkynes (Scheme 15) can be used in the Diels–Alder reaction with neutral electron demand for the synthesis of dihydroaromatic compounds of type 25.

Scheme 10

[Diagram showing the reaction]

Scheme 11

[Diagram showing the reaction]

Scheme 12

[Diagram showing the reaction]

Scheme 13

[Diagram showing the reaction]

Scheme 14

[Diagram showing the reaction]
The resulting oxygen-sensitive cyclohexa-1,4-dienes of type 25 can be isolated or directly oxidised – for example, by dichlorodicyanoquinone (DDQ) – to the corresponding benzene derivates in good to excellent yields. The reaction proceeds with regioselectivities in the range of 80:20 to >98:2 for the para product such as 27 depending on the steric bulk of the substituents. Recently, Hilt reported a catalyst system for the regioselective synthesis of the corresponding meta-substituted products such as 26, by changing the ligand at the cobalt from the diphosphine ligand dppe (B) to pyridine-imine type ligands (A, Scheme 16).43

This extraordinary dependency of the regioselectivity can be rationalised by theoretical investigations reported by Hilt and Frenking.44

The scope and utility of the cobalt-catalysed Diels–Alder reaction was demonstrated by the application of a range of heteroatom-substituted substrates for the synthesis of valuable building blocks for organic synthesis. It is worth mentioning the application of alkynyl sulfides 28 in the cobalt-catalysed Diels–Alder reaction which was applied for the construction of highly functionalised diaryl sulfides such as 29 (Scheme 17) for the first time and which significantly broadens the scope of the reaction.45

A diversity of aryl-substituted alkynyl sulfides was investigated in this reaction and the desired products were obtained in good to excellent yields. A small drawback of such reactions is the ability of sulfur-containing compounds to poison the cobalt catalyst. Therefore, higher catalyst loadings were necessary.

Additionally, alkynyl phosphonium salts such as 30 were applied in cobalt-catalysed Diels–Alder reactions for the first time (Scheme 18). The intermediate phosphonium salts 31 were not isolated but directly converted, by way of a Wittig reaction and subsequent oxidation with DDQ, into stilbene derivatives 32 in moderate to excellent yields.46

In general, both $E/Z$ mixtures and regioisomeric mixtures were obtained when unsymmetrically substituted 1,3-dienes were applied.

Also, symmetrical as well as unsymmetrical 1,3-diynes can be used in a two-step procedure for the construction of highly substituted biphenyls 34 (Scheme 19). The first Diels–Alder reaction is significantly faster so that the intermediate mono-reacted product 33 can easily be obtained and the second reaction needs prolonged reaction time or elevated temperature.

The products were obtained in high yields and as single regioisomers, but only a limited number of functional groups were investigated and axially chiral derivatives could not be obtained because of the low reactivity of 33 towards the 1,3-diienes that would generate such products. In another reaction sequence, the scope of the Diels–Alder reaction of bromobenzene-substituted internal alkynes bearing a tosylate group, such as 35, for the modular construction of a variety of tricyclic compounds such as 36 was thoroughly investigated (Scheme 20). The two key steps were the cobalt-catalysed Diels–Alder reaction and the subsequent bromine–lithium exchange to initiate the Purham cyclisation to afford the desired products 36 in good yields.48
In addition to this reaction, the follow-up chemistry of the cyclohexa-1,4-dienes was studied with regard to regioselective carbenoid insertion under copper or rhodium catalysis.49

The use of boron-substituted substrates in the cobalt-catalysed Diels–Alder reaction was studied extensively by Hilt. Alkynyl boronic esters 37 reacted slowly in thermal Diels–Alder reactions, so rather harsh reaction conditions were needed for their efficient use. In contrast, they reacted very smoothly under the mild conditions of the cobalt-catalysed reaction, affording the boron-substituted cyclohexadiene 38 (Pin = pinacolyl; Scheme 21) in excellent yields.50 When 2-substituted 1,3-dienes, such as isoprene, were used, the regioisomer formed was that in which the boron functionality and the substituent from the 1,3-diene (e.g., the isoprenoid methyl group) emerged in a metarelationship to each other.51

The utility of the boron-substituted cyclohexadiene 39 was demonstrated by a palladium-catalysed Suzuki reaction to ultimately form the framework of the family of cannabinoid natural products 40 (Scheme 22).50 An analogous reaction scheme was applied for the construction of phenanthrenes, phenanthridines and tetrahydronaphthalenes.52,53

The application of 1-boron-substituted dienes 41 (Cat = catechol; Scheme 23) was also studied in a Diels–Alder and allylboration sequence affording cyclohexadienyl-substituted secondary alcohols such as 42 in good yields.54

The Diels–Alder reaction and the allylboration both proceed with excellent regioselectivity and diastereoselectivity but seem to be limited to aromatic aldehydes to give acceptable yields. The reaction was also performed with commercially available chiral diphosphine ligands such as Norphos and acceptable enantioselectivities of up to 78% ee were obtained.

The cobalt-catalysed Diels–Alder reaction tolerates a variety of functional groups and is a method with broad application. However, free amines cannot be used because of their ability to coordinate to the cobalt catalyst. Nevertheless, in the absence of NH-protons, their protected counterparts, such as 43 (Scheme 24), can successfully be applied in the reaction for the construction of protected benzylic imides and sulfonamides 44.55

The utility of the reaction was further demonstrated by a modular synthesis of dibenzoazepine derivatives, starting with the phthalimide-protected biphenyl derivatives.56 An interesting Diels–Alder dimerisation reaction of piperine derivatives was described by Nikaido, catalysed by cobalt(II) chloride hexahydrate, triphenylphosphine and zinc (Scheme 25).57 In this example, the cobalt catalyst is believed to act not as a classical Lewis acid but rather coordinates the double bonds within the ligand sphere and initiates the Diels–Alder reaction to form the product 45.
**Cobalt–Dienyl Complexes in Diels–Alder Reactions**

Welker\(^{58a}\) and Tada\(^{58b}\) have prepared air-stable cobalt-substituted dienes, mainly with cobaloxime substituents, and extensively investigated the rates, regioselectivities and stereoselectivities in [4+2]-cycloaddition reactions over the course of the last few years. These reactions show an unusual preference for the formation of the exo products. In the course of his studies, Welker prepared optically active cobalt(III)salen dienyl complexes and demonstrated their ability to undergo enantioselective Diels–Alder reaction with high selectivity of up to 98% ee.\(^{59}\) One goal in Welker’s research group is to establish a Diels–Alder process that is catalytic in the metal fragment. This has not been achieved yet, but a simple one-pot procedure for the cobaloxime diene formation/Diels–Alder reaction/demetallation reaction sequence was recently established. Accordingly, cyclohexene derivatives were generated upon Co–H exchange utilising dichloro(methyl)silane as reducing agent.\(^{60}\) The newest results by Welker included the preparation of aquocobaloxime dienyl complexes \(^{46}\) (dmg = dimethylglyoxime) and their successful application in Diels–Alder reactions in organic solvents as well as in water for the generation of cobaloxime-substituted cyclohexenes (Scheme 26).\(^{61}\)

![Scheme 26](image)

The reaction can also be performed under microwave irradiation but is in general restricted to electron-deficient alkenes. The desired products are selectively obtained in good to excellent yields.

Welker also reported the first exo-selective hetero-Diels–Alder reaction of cobaloxime-substituted dienes \(^{47}\) with some aldehydes to form cobaloxime-substituted dihydropyrans in moderate to good yields (Scheme 27).\(^{62}\) These were easily demetallated to the dihydropyrans \(^{48}\) and the obtained cobaloximes were recycled in the reaction process.

![Scheme 27](image)

**Homo-Diels–Alder Reaction**

The cobalt-catalysed [2+2+2] cycloaddition of alkenes with norbornadiene derivatives (homo-Diels–Alder reaction) is well known in organic synthesis. The catalyst is generated in situ from readily available cobalt(II) precursors \((\text{CoI}_2, \text{R}_3\text{P}, \text{Zn})\)\(^{63}\) or cobalt(III) precursors \((\text{Co}(\text{acac}))_3\), \(\text{Et}_2\text{AlCl})\).\(^{64}\) Independently, Hilt\(^{65a}\) and Snyder\(^{65b}\) reported the use of \(\text{CoBr}_2(\text{dppe})\) with zinc and zinc iodide as a catalyst system for the homo-Diels–Alder reaction of norbornadiene under mild reaction conditions for the synthesis of the deltacyclene backbone \(^{49}\) (Scheme 28).

![Scheme 28](image)

The cobalt-catalysed reaction is mostly restricted to neutral alkynyl-type dienophiles as well as electron-deficient alkenes and alkynes while oligomerised or cyclotrimerised side products were also observed.

Buono studied the enantioselective homo-Diels–Alder reaction with a cobalt(II) iodide, zinc and chiral ligand catalyst system.\(^{66}\) He reported the use of different chiral ligands and studied the variation of the enantiomeric excess depending on reaction temperature by making use of the isoconversion principle.\(^{67}\)

**[2+2+2] Cyclotrimerisation of Alkenes**

The transition-metal-catalysed cyclotrimerisation of alkenes is a valuable method for the efficient and atom-economical generation of arenes. Cobalt complexes of the type \(\text{CpCoL}_2\) \((\text{L} = \text{CO}, \text{R}_3\text{P}, \text{alkenes})\), in particular, have been extensively studied. Namely, Vollhardt investigated the use of \(\text{CoPc}(\text{CO})_2\) in such reactions and has contributed greatly to this area of research.\(^{68}\)

It is within the scope of this review to give a short overview of general developments in this rapidly growing field, but not to go into detail over the numerous catalyst systems applied for this reaction. So only a brief description of general trends and developments, of interest to the synthetic chemist for special applications, is given.

The mechanism of this seemingly simple reaction is not yet fully understood but has been investigated extensively by Vollhardt and others.\(^{69}\)

The intermolecular, chemo- and regioselective transformation of three different alkenes is today still beyond grasp. Recently, Aubert and Malacria reported the use of traceless silyl-based tethers for a formal [2+2+2] cycloaddition of three different alkenes, but the scope of the reaction was narrow.\(^{70}\)

In the literature, three types of alkyne trimerisation can be differentiated. The purely intermolecular reactions normally focus on the utilisation of one kind of alkyne. Second, the partly intermolecular reactions which make use of a covalently or coordinatively tethered diyne and the entropic preferred reaction of these two alkenes with a third. And finally, the fully intramolecular reactions, where the three triple bonds are within a single molecule.
The newest development in the field of purely intermolecular cyclotrimerisation includes the utilisation of borylated alkynes by Siebert\textsuperscript{71} and Vollhardt\textsuperscript{72} for the construction of polyborylated aromatic compounds 50 (Scheme 29, Cat = catechol), which are versatile building blocks in organic synthesis.

Heteroatom-substituted alkynes are of great interest in cyclotrimerisation reactions and most of the usual alkynes have already been investigated. Siebert was the first to report the high-yielding cyclotrimerisation of an aminothioacetylene with CpCo(CO)\textsubscript{2} or Co\textsubscript{2}(CO)\textsubscript{8} as catalyst.\textsuperscript{73}

Concerning the development of new catalysts or catalyst systems, Eaton described an altered CpCoL-catalyst system for the cyclotrimerisation of various alkynes in aqueous solution under mild conditions.\textsuperscript{74} Unprotected alcohols, amines and carboxylic acids can be used. A similar protocol was reported by Butenschön with another catalyst, which, in contrast, shows a slight preference for the 1,3,5- over the 1,2,4-substituted product.\textsuperscript{75} Trombini and Seddon used nitrile-substituted ionic liquids with a cobalt(II) bromide, zinc iodide and sodium borohydride catalyst system for the cyclotrimerisation of arylalkynes.\textsuperscript{76} Hilt recently investigated a simple system of CoBr\textsubscript{2}L, zinc and zinc iodide as catalyst in various solvents for the mild cyclotrimerisation of various terminal and internal alkynes.\textsuperscript{77} The regioselectivity of the reaction was greatly influenced by the choice of solvent and ligand. In general, the formation of the 1,2,4-substituted product was favoured with a selectivity of up to 97:3 with diimine-type ligands. In contrast, when electron-rich diynes, the catalyst system exhibits moderate to excellent regioselectivities and the products are formed in good to excellent yields.\textsuperscript{78} However, in general only one kind of alkyne is used in these reactions.

Cheng reported for the first time the chemo- and regioselective trimerisation of propiolates and alkynyl alcohols in a one-pot procedure (Scheme 30).\textsuperscript{79} In this reaction, a selective trimerisation of propiolates and alkynyl alcohols is used in these reactions.

The recent applications of intermolecular alkyne trimerisation include the work of Riant,\textsuperscript{80} who used bisarylacetylenes bearing planar-chiral ferrocenyl units for the construction of polyferrocene complexes, as well as the work of Amatore and Nierengarten,\textsuperscript{81} who constructed fullerene nanoclusters by cyclotrimerisation of bis(aryl) alkyne fullerenodendrimers.

The cyclotrimerisation of diynes with another alkyne has received much attention because the chemo- and regioselectivity of such reactions can easily be controlled so that, in principle, three different alkynes can be trimerised to yield only one, highly substituted benzene derivative. Vollhardt described the use of boron-substituted alkynes in a novel dicobalt octacarbonyl promoted reaction for the construction ofarylboronic esters 52 in moderate yields (Scheme 31), which are useful building blocks for cross-coupling reactions.\textsuperscript{82}

Okamoto recently described a versatile and inexpensive instant catalyst system for the cyclotrimerisation of alkynes (Scheme 32).\textsuperscript{83} His investigations focused on its use in partly intramolecular reactions for the synthesis of polysubstituted products such as 53. With unsymmetrical diynes, the catalyst system exhibits moderate to excellent regioselectivities and the products are formed in good to excellent yields.\textsuperscript{84} The addition of silver salts to increase the activity of the catalyst system was also described.\textsuperscript{84}

Tacke investigated extensively the use of silicon-tethered diynes for the construction of 1,4-disiladienes and 1,3-disila-1,3-dihydridosilobenzofurans with a cobalt(II) iodide and zinc catalyst system in acetonitrile.\textsuperscript{85} The target compounds were obtained in moderate to good yields (Scheme 33). The reaction was applied to the construction of the retinoid agonist disila-hexarotene 54 which was synthesised in a short reaction sequence.\textsuperscript{86}

The partly intramolecular cyclotrimerisation approach was recently applied to the construction of various highly functionalised benzene derivatives. Hudlicky described the synthesis of the deoxygenated pancratistatin core with CpCo(CO)\textsubscript{2} as catalyst.\textsuperscript{87} The same catalyst was ap-

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\textsuperscript{104} Synthesis 2008, No. 22, 3537–3562 © Thieme Stuttgart · New York
plied by Kotha for the construction of 2-indanyl glycine derivatives. However, only relatively low yields were obtained when compared with the simultaneously investigated rhodium-based catalysts.88 Kotora and Hocek investigated the cyclotrimerisation of 6-alkynylpurines with α,ω-dienes for the construction of biologically active 6-arylpurines by using CoBr(PPh₃)₃ as catalyst.89 The desired products were obtained in moderate to excellent yields. Kotora and Štepnička also described the use of CoBr(PPh₃)₃ as catalyst for the partly intramolecular reaction of ferrocenylalkynes with α,ω-dienes in good yields.90

Green used a cobalt-mediated [2+2+2] cycloaddition of cycloheptynes such as 55 for the construction of fused 7,6,5-ring systems represented by 56, which are known core structures of natural products, especially terpenes (Scheme 34).91 The cobalt-complexed cycloheptynes were prepared by ring-closing metathesis and subsequently transformed in acceptable yields into the desired products.

![Scheme 34](image)

**Scheme 34**

Fully intramolecular cyclotrimerisations of triynes are generally used for the construction of polycyclic compounds as intermediates for natural product synthesis, which was shown by the past work of Vollhardt. Only a few examples of such a reaction have been published recently and should briefly be described.

Chung described, in the course of his investigations concerning a cobalt-catalysed double carbonylative [2+2+1] cycloaddition (which is not within the scope of this review), the dicobalt octacarbonyl catalysted intramolecular [2+2+2] cycloaddition of triynes.92 The feasibility of the reaction was shown with some triynes, which were converted with moderate to good yields, but not studied in detail.

The fully intramolecular [2+2+2] cycloaddition of triynes 57 (Scheme 35) is mostly conducted with various cobalt-carbonyl complexes. Recently, some catalyst systems were reported to be easy to handle, inexpensive, mild and easily adaptable to the individual needs of generating products of type 58.

Sugihara enhanced the reactivity of cobalt-carbonyl complexes in such reactions by employing methylidyinetrio-

![Scheme 35](image)

**Scheme 35**

The intramolecular cyclotrimerisation of alkynes is a powerful method for the construction of highly substituted polycyclic compounds. Nevertheless, applications in natural product synthesis are relatively rare because of the sometimes-tedious synthesis of the required triynes. One of the few recent examples, reported by Groth, utilised a cobalt-catalysed cyclotrimerisation of triynes such as 61 to generate 62 as the key step (Scheme 37) in the synthesis of the augucyclinone core of rubiginone B₂.96

![Scheme 37](image)

**Scheme 37**

Another example for the application in natural product synthesis is the construction of the ABC core of the taxoid class of natural products as described by Aubert and Malacria (Scheme 38). The complex precursor 63 underwent a cobalt-mediated intermolecular [2+2+2] cycloaddition and a Diels–Alder reaction to provide the polycyclic product 64.97

**Phenylenes**

Vollhardt studied in detail the construction of phenylenes and heliphenes by either fully intramolecular cyclotrimerisation of triynes or partly intramolecular cyclotrimerisa-
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...tion of 1,2-diethynylbenzenes with bis(trimethylsilyl)acetylene and subsequent desilylation. By means of these processes, several phenylenes such as 65 (Scheme 39) were synthesised, characterised and their follow-up chemistry was investigated.98

[2+2+2] Cyclotrimerisation of Two Alkynes and One Double Bond

The 2:1 co-oligomerisation of two alkynes with one alkene is a powerful method for the construction of cyclohexa-1,3-dienes. Oxidation of the primary products generates benzene derivatives. Cobalt catalysts are well established for this co-oligomerisation reaction, which generally proceeds in high chemo-, regio- and stereoselectivity.

The reaction mechanism is proposed to be analogous to that of the alkyne trimerisation. Two alkynes react in the ligand sphere to give a cobaltacyclopentadiene intermediate. Insertion of the alkene into one of the cobalt–carbon bonds leads to a cobaltacycloheptadiene which undergoes a reductive elimination to the desired cyclohexadiene. A theoretical study concerning the reaction mechanism was recently conducted by Gandon and Aubert.99

The inter- and intramolecular co-oligomerisations of alkynes with alkene were also studied in the past and many protocols for this valuable reaction exist. Therefore, brief examples of recent developments are given in this review.

Aubert and Gandon recently studied the fully intermolecular CpCo(C2H4)2-mediated reaction of boron-substituted alkynes with alkene for the formation of polyborylated cyclohexadienes 66 (Scheme 40).100 The scope of the reaction was investigated with regard to the effect of the alkyl and alkene substituents on the chemo-, regio-, and stereoselectivity of the reaction.22 In general, the 1,3-diboron-substituted cyclohexadiene, as in 66, is formed. The relative position of the alkene substituent is determined by electronic rather than steric effects, so that it resides ortho and para relative to the boron substituents.

The cobalt-complexed polyborylated products were obtained with diverse monosubstituted or cyclic alkene in moderate to good yields and could be subsequently decomplexed with iron(III) The products are valuable building blocks for cross-coupling reactions and can be easily further modified.

Partly intramolecular reactions, where two of the reactants are covalently linked, are valuable methods for the construction of complex polycyclic molecules.

Chung described a new procedure for the construction of tetracyclic compounds such as 67 in a dicobalt octacarbonyl catalysed tandem [2+2+1]/[2+2+2]-cycloaddition reaction (Scheme 41), starting from simple diynes, in good to excellent yields.101

The [2+2+2] cycloaddition of norbornene derivatives with simple diynes led to the efficient and selective formation of polycyclic compounds in moderate to good yields utilising a catalyst system consisting of CoI2(PPh3)2 and zinc.102 The same catalyst system was applied to the [2+2+2] cycloaddition of hepta-1,6-diynes with allenes to generate the desired benzene derivatives such as 68 directly upon a double bond shift (Scheme 42).103

Vollhardt studied the cobalt-mediated [2+2+2] cycloaddition of diynes with heterocycles such as pyridones, pyrazinones and pyrimidines.104 Besides the desired cycloaddition process, dienylation at carbon and nitrogen was also observed, the latter especially favoured with unprotected nitrogen atoms. Nevertheless, the cycloaddition products such as 69 (Scheme 43) were obtained in moderate yields. The usefulness of this reaction was demonstrated by further transformation of 69 into anhydrolycorinone (70).
More complex natural products were targeted by Vollhardt in the stereoselective construction of the benzo-furan core by $[2+2+2]$ cycloaddition under $\text{CpCoL}_2$ catalysis, offering a new approach for the synthesis of morphinoids.\textsuperscript{105} Vollhardt also reported a short (14-step) synthesis of racemic strychnine (72) by constructing the tetracyclic core of intermediate 71 through a cobalt-catalysed $[2+2+2]$-cycloaddition process (Scheme 44).\textsuperscript{106}

Fully intramolecular co-oligomerisation reactions of alkynes with alkenes have not been thoroughly investigated. Recent developments were made by Malacria and Aubert who studied the diastereoselective reaction of substituted linear enediyne phosphine oxides.\textsuperscript{107} In general, a preference for the \textit{endo} product was observed, and moderate to excellent yields, depending on the structure of the reactant, were reported. The same authors also reported the use of (methylene-cyclopropyl)diynes for the construction of cyclopropanated oligocycles.\textsuperscript{108} The reaction proceeded well with electron-deficient acetylenes and achieved moderate to excellent yields. The extension towards the use of allene diynes gave, in a chemo-, regio- and diastereoselective fashion, the desired products in moderate to good yields. What is remarkable is that for the first time, a chirality transfer from axial to centred chirality was achieved.\textsuperscript{109} The reaction sequence was later applied in the synthesis of the 11-aryl steroid skeleton 73 (Scheme 45).\textsuperscript{110}

The relative \textit{trans} stereochemistry of the substituents at the cyclopentanone moiety is crucial because otherwise an Alder–ene reaction is the preferred reaction pathway.

\textbf{[2+2+2] Cyclotrimerisation of Alkynes and Nitriles}

Cobalt-catalysed $[2+2+2]$-cycloaddition reactions of two alkynes with one nitrile to form substituted pyridine derivatives are well known in organic synthesis. Theoretical and mechanistic considerations are not within the scope of this review and can be found in the literature.\textsuperscript{111} In general, cobalt complexes of the type $\text{CpCoL}_2$ are used for such chemo- and regioselective formations of various pyridine derivatives. Interestingly, even when just stoichiometric amounts of the nitrile are used, no benzene derivatives are formed. However, problems arise when two different alkynes should be incorporated in the pyridine product, because then eight possible regiosomers can be formed. Naturally, this can be circumvented by the use of partly or fully intramolecular reactions.

In this review, some of the newest developments on the field of intermolecular and intramolecular $[2+2+2]$-cycloaddition reactions of nitriles with alkynes are briefly discussed.

Heller studied the effects of irradiation, pressure, solvent, additives, ligand and substituent steric bulk on the chemoselectivity and regioselectivity of the reaction.\textsuperscript{112} Eaton prepared a catalyst system (74) which could be used in aqueous solution, thereby developing a mild, selective and broadly applicable reaction that affords pyridines such as 75 derived from propargylic alcohols in good to excellent yields (Scheme 46).\textsuperscript{113}

\textbf{Scheme 46}

Ward conducted a study in which a solution-phase combinatorial library of substituted pyridines were formed with the $\text{CpCo(CO)}_2$ catalyst from two different alkynes and one equivalent of nitrile. The reaction mixture was purified by ion-exchange chromatography and in general all eight possible isomers were detected.\textsuperscript{114} Deiters addressed the same problem in the intermolecular $[2+2+2]$ cycloaddition by investigating a solid-phase-supported reaction.
Propargylic alcohol was immobilised on a polystyrene resin utilising a trityl linker. With this method, the desired pyridines were obtained as regioisomeric mixtures of two or three isomers in good to excellent yields. The same concept was applied to the immobilisation of diynes or alkynyl nitriles. These then reacted under CpCo(CO)_2 catalysis and microwave irradiation. High yields and high selectivities were obtained under mild reaction conditions in a few minutes. In addition to the classical reaction partners, isocyanates and carbodiimide could be used with immobilised diynes in the preparation of pyridones such as 76 or iminopyridines (Scheme 47).  

![Scheme 47](image)

Okamoto described the application of the versatile cobalt(II) chloride hexahydrate, 1,2-bis(diphenylphosphino)ethane and zinc catalyst system for the generation of pyridines. Various α,ω-diynes can be used and transformed with different nitriles both chemo- and regioselectively, to the desired pyridines in high yields. However, the reactions demand, depending on the substrate, at least 1.5 equivalents – and up to 80 equivalents – of the nitrile, so that in general only simple nitriles can be used. Nevertheless, the catalyst system was applied in the synthesis of 2,2'-bipyridines and 2,2',6',2''-terpyridines starting from substituted α,ω-diynes. The desired products were obtained in good to excellent yields with exclusive regioselectivity and are valuable products for medicinal, synthetic and materials chemistry. Saá reported the reaction of ω-alkynyl nitrites with 1,3-diynes under CpCo(CO)_2 catalysis for the construction of bipyridines suitable as ligands. Unfortunately, this protocol was inferior because the yields were somewhat low and regioisomeric mixtures were generally obtained. However, Saá addressed the construction of spiropyridines such as 77 by starting from dialkynyl malodinitriles (Scheme 48). Although the yields were rather low, a new class of chiral ligands could be prepared in a simple one-step synthesis.  

Cyanamides were applied by Maryanoff in the [2+2+2] cycloaddition with α,ω-diynes under relatively mild and convenient conditions (Scheme 49). Accordingly, highly substituted aminopyridines such as 78 could be prepared from simple starting materials.  

![Scheme 49](image)

An extension of this methodology towards the synthesis of macrocyclic ring systems was realised by Maryanoff, utilising α,ω-diynes or ω-alkynyl nitriles in the cobalt-catalysed reaction with alkynes, nitriles, cyanamides and isocyanates. Thereby, 15- to 23-membered-ring systems were accessible in acceptable yield. However, in these transformations, regioisomeric mixtures of para- and meta-substituted products were also obtained. Attempts to control the regioselectivity were made by variations of the kind and length of the tether as well as by substituent effects.

Heller used the CpCo(cod) catalyst in partly intramolecular reactions for an improved synthesis of pyridoxine, starting from silyl-functionalised dipropargylic ether 79 (Scheme 50). The silyl substituents allowed for the necessary subsequent chemoselective transformations, namely protodesilylation and oxidation.

![Scheme 50](image)

Heller and Gutnov also reported an enantioselective partly intramolecular [2+2+2] cycloaddition for the preparation of enantiomerically enriched atropisomers of 2-arylpyridines 81 (Scheme 51) by using chiral derivatives of the well-known Cp*Co(cod) catalyst. Good yields and enantioselectivities of up to 93% ee were obtained in this fast and efficient synthesis of chiral ligands.

Snyder studied the [2+2+2] cycloaddition of nitrogen-linked alkynyl nitriles and diyne nitriles for the construction of 5,6,7,8-tetrahydro-1,6-naphthyridines under CpCo(CO)_2 catalysis and microwave irradiation. The partly intramolecular reaction proceeded with moderate yield, while the fully intramolecular reaction afforded the desired bicyclic products in good to excellent yield.

A fully intramolecular reaction was also used by Cheng for the construction of tetra- and pentasubstituted pyridine derivatives (Scheme 52). A simple, highly active cobalt catalyst generated from CoI₂(dppe) and zinc powder was used; this readily converted complex nitrile-substituted diynes such as 82 into the desired product 83.

Scheme 52

Groth demonstrated the intramolecular cobalt-catalysed cycloaddition of alkynes and nitriles by using silicon-tethered starting materials to provide functionalities for further modification (Scheme 53). The core of the ergot alkaloids, 84, was prepared, thereby showing the potential of such reactions in natural product synthesis.

Scheme 53

One of the newest applications of purely intramolecular cyclotrimerisation, reported by Stará and Star, is the synthesis of penta- and hexacyclic helically chiral aza- and diazahelicenes with one or two nitrogen atoms in the terminal rings. The desired products were obtained in good to excellent yields with the CpCo(CO)₂ catalyst, starting from suitable diaryl triynes. The same authors described the cycloaddition of triynes bearing a chiral centre for the diastereoselective synthesis of helicenes that have helical and central chirality.

2.5 Seven-Membered-Ring Formation

The synthesis of seven-membered rings is a prominent goal of organic synthesis because of their abundance in natural products. Nevertheless, there are only a few examples of cobalt-catalysed cycloaddition reactions for their straightforward generation.

[3+2+2] Cycloaddition

Recently, Stryker reported a [3+2+2]-cycloaddition reaction of neutral η⁵-allyl cobalt triflate complexes 85 with alkynes to afford the η⁵-cycloheptadienyl complex intermediates such as 86 in moderate to excellent yields (Scheme 54). These intermediates can be transformed easily into cycloheptadiene derivatives such as 87 by a nucleophilic alkylation and oxidative decomplexation sequence.

Scheme 54

The reaction is presumed to proceed via a η⁵-pentadienyl cobalt complex which is generated by reaction with the first alkyne. Reaction of this primary intermediate with the second alkyne then affords 86.

[5+2] Cycloaddition

Based on his investigations concerning the [3+2+2]-cycloaddition reaction, Stryker developed a novel [5+2]-cycloaddition reaction of preformed η⁵-pentadienyl cobalt complexes 88 (Scheme 55) with alkynes to form η⁵-, η²,η⁵-cycloheptadienyl cobalt complexes 90 and 89 in moderate to excellent yields respectively.

Scheme 55

The η⁵-pentadienyl cobalt complexes of type 90 are formed from a limited number of simple 1,4-alkadien-3-ols and the alkynes are restricted to alkyl- or silyl-substituted derivatives.

Tanino reported a new [5+2]-cycloaddition reaction of silyl enol ethers with cobalt-complexed propargyl cations (Scheme 56). This Nicholas-type cyclisation reaction was highly stereoselective and the desired cobalt-complexed cycloheptyne derivatives such as 91 were obtained in excellent yields.

Scheme 56

[4+3] Cycloaddition

For the synthesis of seven-membered rings, [4+3] cycloadditions are an attractive approach and have attracted much attention. The most widely encountered methods
are the reactions between allyl or oxyallyl cations and 1,3-dienes, or those between bis(trimethylsilyl) enol ethers and 1,4-diones.

Nevertheless, examples of cobalt-catalysed \([4+3]\) cycloadditions are rare. Green reported the cobalt-assisted reaction of 1,4-dialkoxybut-2-ynyl cobalt complexes such as 92 with 1,3-bimetallic allyl species 93 (Scheme 57). Essentially, the cobalt complex is necessary for the reaction to proceed utilising the geometric non-linearity of the alkylnyl cobalt complex and the stabilisation of the intermediate carbocation 94 in the double Nicolas-type cyclisation process. The cyclohept-4-en-1-ynyl cobalt complexes such as 95 are prepared in moderate to good yields.

Substitution of the 1,3-bimetallic allyl species for allyl(trimethyl)silane (Scheme 58) leads to the generation of a secondary cation, 96, which can subsequently react with nucleophiles such as benzene to form products of type 97 in moderate to good yields.

Substitution of the 1,3-bimetallic allyl species for allyl(trimethyl)isilane (Scheme 58) leads to the generation of a secondary cation, 96, which can subsequently react with nucleophiles such as benzene to form products of type 97 in moderate to good yields.

**Scheme 57**

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{Co}_2(\text{CO})_6 & \quad \text{Bu}_3\text{Sn} \\
+ & \quad \text{BF}_3\cdot\text{OEt}_2 \\
\text{Et}_3\text{Si} & \quad \text{OMe} \\
\text{Co}_2(\text{CO})_6 & \quad \text{Et}_3\text{Si} \\
\text{BF}_3\cdot\text{OEt}_2 & \quad \text{Et}_3\text{Si} \\
\end{align*}
\]

**Scheme 58**

[4+2+2] Cycloaddition

The [4+2+2]-cycloaddition reaction between norbornadiene derivatives such as 100 with buta-1,3-dienes is a powerful method for the construction of polycyclic products 101 from simple starting materials (Scheme 60). The reaction does not proceed under thermal conditions, and therefore transition-metal catalysis is the method of choice. Some catalyst systems are restricted by their narrow scope, expressed in their low functional group tolerance. Also, low selectivities for the desired cycloaddition reaction were encountered, owing to polymerisation of the educts.

Significant improvements were reported by Snyder in the reaction of an efficient cobalt catalyst system consisting of a mixture of cobalt(II) iodide with 1,2-bis(diphenylphosphino)ethane, zinc and zinc iodide (1:1:1:3 ratio) for the mild [4+2+2] cycloaddition and thus the generation of a variety of products such as 101 (Scheme 60).

A further expansion of this methodology was contributed by Snyder in the successful application of bicyclo[2.2.2]octadienes as the 1,4-diene component in this
reaction.\textsuperscript{140} Intensive investigations by Snyder addressed the follow-up chemistry of the complex polycyclic products.\textsuperscript{141} Through treatment with $[\text{Pt}(\text{C}_3\text{H}_5)_2\text{Cl}]_2$ (Zeise’s dimer), the cyclopropane ring is opened and, with subsequent ozonolysis, bicyclo[5.3.0]decanes can be prepared; the latter are suitable precursors for the synthesis of natural products such as guaianolides or pseudoguaianolides.\textsuperscript{142} Consequently, Snyder demonstrated a straightforward application of this strategy in the natural product synthesis of the functionalised hydroazulene core of portulal.\textsuperscript{143} The outcome of the ring opening with Zeise’s dimer could also be altered such that bicyclo[4.2.1]nonanes were generated; these are at the core of some natural products, including the mediterraneols.\textsuperscript{144}

The intermolecular synthesis of eight-membered-ring systems is not a strength of cobalt catalysis. More favourable are processes where, upon reductive elimination, six-membered rings are formed. Therefore, it is quite unusual that a simple cobalt catalyst consisting of CoBr$_2$(pyrrolidine), zinc, iron and zinc iodide is capable of directing a highly regioselective, atom-economic reaction in moderate to good yields (Scheme 61).

Electron-deficient terminal and internal alkynes such as methyl propynoate, in combination with an electron-rich 1,3-diene, gave the best results for the regioselective formation of the cycloocta-1,3,6-triene derivatives. When 2-trimethylsilyloxybuta-1,3-diene was used, the enol ether intermediate was transformed into ketone 102 under mild conditions in very good overall yield.\textsuperscript{145} The alkyl amine substituent, as well as the iron powder additive, proved to be beneficial for the chemoselectivity and therefore also for the yields of the reaction. However, the role of the iron powder remains speculative.

2.7 Ten-Membered-Ring Formation

The synthesis of ten-membered-ring systems by a cycloaddition process is more of a curiosity than a well-established methodology. Nevertheless, bridged ten-membered-ring systems became accessible when cobaltoxime dienyl complexes were used in Diels–Alder reactions with tropone derivatives (Scheme 62). Besides the already described [4+2] cycloadditions of electron-deficient tropone derivatives such as 103 to afford the complex bicyclic structure 104, Welker also observed the [6+4]-cycloaddition product 105 in the transformation with tropone itself in excellent yield.\textsuperscript{146}

![Scheme 62](image)

Although this seems to have been a single observation, complex molecules and new reaction pathways often open up when even rather small changes are made.

3 Cobalt-Catalysed Synthesis of Acyclic Compounds

3.1 Coupling Reactions between Alkenes and Alkynes

A broadly applicable reductive intermolecular coupling of alkynes with activated alkenes (Scheme 63) was reported by Cheng.\textsuperscript{147} The reaction led to $\gamma,\delta$-unsaturated carbonyls, acids, sulfones or nitriles such as 106. In the intramolecular version of this reaction, a wide variety of nitrogen, oxygen, silicon or sulfur-containing functional groups were tolerated.

![Scheme 63](image)

Besides this broad tolerance shown by the cobalt catalyst towards functional groups, this method has the further advantages of being highly chemo-, regio-, and stereoselective, and it can also be used in an intramolecular reaction to generate six- and seven-membered lactones. Thus, a powerful method for carbon–carbon bond formation under reductive coupling, suitable for use in the total synthesis of more complex products, has been established. The intramolecular coupling of alkynes and alkynes was reported by Malacria,\textsuperscript{148} whereas the intermolecular version at ambient temperatures and anhydrous conditions utilising catalytic amount of reducing agent (zinc powder) was carried out by Hilt only recently (Scheme 64).\textsuperscript{149}

Therein, a formal Alder–ene reaction leads to 1,4-dienes (107) in good to excellent yields and the process thus represents an alternative to other transition-metal-catalysed methodologies.\textsuperscript{150} In the cobalt-catalysed Alder–ene reaction, the double bonds are generated in a highly regio- and
stereoselective fashion, giving rise almost exclusively to E-configured double bonds. However, when an allylic boron functionalised alkene was used (R₃ = pinacolyl boronate), the vinyl boronic double bond was generated predominantly with Z-configuration, most likely because of cobalt–oxygen interactions between the catalyst and the reacting pinacolyl boronate. The application of such polyfunctionalised and regioselectively generated intermediates in palladium-catalysed cross-coupling reactions generates very interesting products in a very short reaction sequence.

3.2 Cross-Coupling Reactions

There are various reactions in which organocobalt compounds are coupled to aryl halides, alkenes, or alkynes. Among these, the synthesis of biaryls such as 108 by coupling electron-deficient aryl triflates or aryl halides with other aryl halides (Scheme 65) was recently reported by Gosmini.¹⁵¹ In these reactions, the homocoupled biaryl products were obtained in minor amounts as side products because in these side reactions, both the nucleophilic and the electrophilic coupling components were generated from the same precursor.

Nevertheless, various polysubstituted biaryl products of type 108 were synthesised in good to very good yields, including those with trifluoromethyl, ether, ester, and sulfone functionalities. In addition, Cheng reported the carbon–heteroatom coupling of thiophenols and alkyl thiols with aryl iodides and aryl bromides to generate the corresponding thioethers in good to excellent yields.¹⁵² This remarkable reaction is of great importance because it demonstrates the explicit tolerance of cobalt catalysts towards sulfur-containing reactants.

Cheng also demonstrated that low-valent cobalt catalysts can be used for an oxidative addition to aryl iodides and for subsequent insertion processes of alkenes and acceptor-substituted alkenes.¹⁵³ The proposed arylcobalt intermediate can be used for the synthesis of indenols and indenones. To this end, the coupling of functionalised 2-iodobenzaldehydes and 2-iodophenyl ketones such as 109 (Scheme 66) with internal alkynes or acrylates led to indenols such as 110 and indene derivatives like 111 in good to excellent yields.

Besides the shown ketone 109, several other dimethoxy-, butyl-, or phenyl-substituted ketones and aldehydes were efficiently coupled to internal alkynes bearing aryl, alkyl, ester or trimethylsilyl functionalities. The use of unsymmetrical alkynes led to a mixture of regioisomers, the ratio of which varied between 50:50 and >99:1 depending on the steric bulk of the substituents. The use of acrylates instead of alkynes led, in moderate to good yields (41–75%), to indene derivatives such as 111 as a result of the alcohol intermediate eliminating water under the reaction conditions. Surprisingly, the reaction of acrylonitrile with 109 led to 3-methyl-6-methoxyindene in 95% yield upon a reductive decyanation reaction, so that acrylonitrile could be seen as a masked ‘ethylene’ equivalent.

3.3 Cobalt-Catalysed Coupling Reactions Using Grignard Reagents

A large number of cobalt-catalysed coupling reactions between alkylhalides and allyl-, alkenyl-, aryl- and trimethylsilylmethylmagnesium halides have been reported by Oshima over the last years. A representative example for the radical-type cyclisation reaction of an iodo-functionalised alkene 112 to form lactone 113 is given in Scheme 67.¹⁵⁴

The methodology was also applied in Heck-type reactions utilising alkyl halides with styrene derivatives. Also, highly silylated olefins are accessible starting from dibromodimethylmethane and trimethylsilylmethylmagnesium bromide. In a similar way, the cobalt-catalysed coupling of alkynyl Grignard reagents with alkynyl triflates was realised by Shirakawa and Hayashi.¹⁵⁵ The cobalt(III)
acetylated reaction was used in the synthesis of various enynes in a stereoselective fashion in good to excellent yields.

### 3.4 Hydrocyanation, Hydrophosphinination, Hydroisilylation and Hydrovinylation Reactions

The regioselective hydrocyanation of various alkenes to form products of type 114 (Scheme 68) can be catalysed by cobalt(salen) complexes utilising tosylcyanide and phenylsilane as a source of hydrogen cyanide (Scheme 68), as reported by Carreira.156

![Scheme 68](image)

Under the mild reaction conditions, the hydrocyanation products are generated in good to excellent yields. Besides the shown substrates, 1,2- and 1,1-disubstituted cyclic and bicyclic alkenes were also converted into the corresponding cyanoaldehydes.

The hydrophosphinination of internal alkynes with diphenylphosphine can be catalysed by cobalt(II) acetylacetonate (10 mol%) and butyllithium (20 mol%) in dioxane, as reported by Oshima.157 The diphenyl(vinyl)phosphine intermediates were oxidised in situ with sulfur to give a variety of different diphenyl(vinyl)phosphine sulfides as much more stable products which could then be isolated in high yields (62–89%).

The hydroisilylation of isoprene with triethoxysilane was catalysed by a system comprised of cobalt(II) bromide, tri(n-butyl)phosphine, tetraethylammonium borohydride and zinc iodide to give 1-triethoxysilyl-3-methylbut-2-ene in 90% yield on a ten-gram scale as shown by Hilt.158 The hydroisilylation of alkynes was reported by Butenschön, who used a tethered cyclopentadienylphosphine cobalt complex.159 Noteworthy was the selectivity observed in the hydroisilylation of internal alkynes. While the use of triethylsilane gave exclusively the cis-addition product, the application of triethoxysilane led predominantly to the trans-addition product. However, the regioselectivity concerning the hydroisilylation of unsymmetrical internal alkynes was rather low, and terminal alkynes gave nearly 1:1 mixtures of regioisomers.

A cobalt catalyst system consisting of Co(dppe)Br₂, zinc iodide and zinc powder was efficient in the regioselective 1,4-hydrovinylation of 1,3-dienes with terminal alkynes (Scheme 69) to afford 1,4-dienes of type 115; this was also investigated by Hilt.160

![Scheme 69](image)

Various terminal non-activated as well as acceptor-substituted alkenes reacted with isoprene, myrcene, 2,3-dimethylbuta-1,3-diene or norbornadiene in good to excellent yields. The reaction gave predominantly the branched 1,4-dienes 115a where the new carbon–carbon bond was formed at the internal carbon of the terminal alkene. In contrast, acceptor-substituted alkenes gave exclusively the linear hydrovinylation products 115b with the new carbon–carbon bond generated at the terminal carbon of the alkene component.

The 1,2-hydrovinylation of styrene with ethane, producing 3-phenylbut-1-ene, was carried out by Vogt, who used cobalt(II) chloride with bidentate diphosphine ligands activated by tetraethylammonium borohydride or diethylaluminium chloride.161 Various diphosphine complexes catalysed this reaction, and with the use of chiral ligands, (R)-3-phenylbut-1-ene could be generated in up to 74% yield and up to 47% ee.

### 3.5 Nucleophilic Substitution with Organocobalt Reagents

An electrochemical cobalt(II) bromide catalysed reductive Michael addition of aryl halides to methyl vinyl ketone in N,N-dimethylformamide and pyridine was reported by Gosmini.162 The yields of different functionalised electron-rich and electron-deficient 4-arylbutan-2-ones varied between 20% and 70%. A similar reaction, reported by Cheng, used CoCl₂(dppe) as a catalyst and zinc powder as stoichiometric reducing agent in acetonitrile and water.163 Therein, the scope of the reaction was enlarged so that various alkyl and aryl halides underwent the 1,4-addition to acceptor-substituted alkenes such as acrylates, vinyl cyanide, vinyl ketones and vinyl sulfones in high yields (60–92%).

An efficient cobalt-catalysed Reformatsky reaction using α-chloro esters was introduced by Lombardo, who applied cobalt(II) chloride with 1,2-bis(diphenylphosphino)ethane and zinc iodide as the catalyst system (Scheme 70).164

![Scheme 70](image)
Accordingly, different 3-hydroxy esters **116** were obtained in high to excellent yields. However, the range of functional groups tolerated by the reaction conditions has still to be examined.

A cobalt(II) chloride catalysed regio- and stereoselective allylzincation of internal alkynes followed by nucleophilic addition to electrophiles was realised by Oshima (Scheme 71).[^165]

![Scheme 71](image)

Besides the shown transformations towards regio- and stereoselectively uniform iodo-functionalised 1,4-dienes such as **117**, otherwise-functionalised 1,4-dienes and even complex 1,4,7-trienes could be generated from simple non-functionalised alkynes. Other electron-rich and electron-deficient 1-arylalk-1-ynes reacted smoothly under the shown reaction conditions.

An interesting application of a methylene-bridged bis[co-balt(salen)] complex (**118**), for the reductive coupling of benzyl bromide under photoelectrochemical conditions (Scheme 72) was reported by Hisaeda.[^166]

![Scheme 72](image)

In this reaction, the cobalt complex undergoes an electrochemical reduction followed by an oxidative addition of the low-valent cobalt centre into the carbon–bromine bond. Irradiation with visible light initiates the homolytic cobalt–carbon bond cleavage and the dimeric structure of the cobalt catalyst favours the formation of diphenylethane in up to 75% yield. In contrast, with a comparable monomeric catalyst system, toluene was formed as the major product, in up to 87% yield, under otherwise identical reaction conditions.

### 3.6 Cobalt-Catalysed Carbonylative Ring-Expansion and Ring-Opening Reactions

The cobalt-catalysed formation of β-hydroxybutyrate **119** from propylene oxide, carbon monoxide and methanol has been known since the early 1960s and was introduced by Eisenmann.[^167] The reaction (Scheme 73) was catalysed by dicobalt octacarbonyl and generated the desired product in 40% yield, albeit under conditions of drastically high pressure and temperature.

![Scheme 73](image)

The reaction proceeds via a cobalt-catalysed formation of the corresponding β-lactone, which is then opened by way of a nucleophilic attack by methanol to generate the product. Extensive mechanistic studies have been conducted by Rieger.[^168] Various different groups have worked on the optimisation of this reaction. The additions of different Lewis acids or of various nitrogen- or phosphorus-containing donor ligands have been investigated by Cheon[^169] and Chen.[^170] The most effective system was described by Jacobsen, who used 5 mol% of a chiral cobalt(salen) complex and 3-hydroxypyridine as a co-catalyst to form β-hydroxybutyrate in 92% yield.[^171] The reaction was highly regioselective and, with the use of chiral epoxides, was also highly stereoretentive. Nevertheless, harsh conditions [high pressures of carbon monoxide (40 bar) and elevated temperatures] were still required. It was also shown by Jacobsen that the formation of various β-hydroxy morpholine amides such as **120** can be carried out at room temperature under atmospheric pressure of carbon monoxide with *N*-(trimethylsilyl)morpholine, catalysed by 2.5 mol% dicobalt octacarbonyl (Scheme 74).[^172]

![Scheme 74](image)

It was not until recently that Denmark reported the formation of β-hydroxybutyrate from propylene oxide catalysed by dicobalt octacarbonyl (5 mol%) and 3-hydroxypyridine with an atmospheric pressure of carbon monoxide with *N*-(trimethylsilyl)morpholine, catalysed by 2.5 mol% dicobalt octacarbonyl (Scheme 74).[^172]

[^165]: A cobalt(II) chloride catalysed regio- and stereoselective allylzincation of internal alkynes followed by nucleophilic addition to electrophiles was realised by Oshima (Scheme 71).

[^166]: An interesting application of a methylene-bridged bis[co-balt(salen)] complex for the reductive coupling of benzyl bromide under photoelectrochemical conditions was reported by Hisaeda.

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[^170]: It was not until recently that Denmark reported the formation of β-hydroxybutyrate from propylene oxide catalysed by dicobalt octacarbonyl (5 mol%) and 3-hydroxypyridine with an atmospheric pressure of carbon monoxide. The reaction could be carried out with a wide number of epoxides bearing ether, ester, halide or phthalimide functionalities. A carbonylative ring-opening reaction of cyclic ethers with trialkylsilanes catalysed by dicobalt octacarbonyl was shown by Murai.

[^171]: A large number of different silylated diols of type **121** can be generated at room temperature under atmospheric pressure of carbon monoxide in high yields (56–92%). A lot of different functionalities such as chlorides, esters, and acetals are tolerated in this reaction. The use of alcohol-functionalised cyclic ethers led to silyl-protected products under the reaction conditions. When the reaction was car-
ried out at higher temperatures and with higher pressures of carbon monoxide, the corresponding hydroxy aldehydes 122, instead of the diols 121, were generated in moderate yields.

In the early 1990s, Watanabe showed that cyclic ethers like epoxides or oxetanes can also be opened by trimethylsilylamines under insertion of carbon monoxide at atmospheric pressure (Scheme 76).175

According to this procedure, various unsymmetric epoxides like propylene oxide underwent carbonylative ring opening to generate trimethysilyloxy amides 123 in high yields (60–89%) with excellent regioselectivities. The formation of β-lactones from epoxides and β-lactams from aziridines was first reported by Alper.176 For the synthesis of β-lactones 124, Alper used a bis(triphenylphosphine)iminium cobalt tetracarbonyl complex in combination with a Lewis acid (BF₃ OEt₂) as the catalyst system (Scheme 77).

Besides various alkyl-, alkenyl-, aryl-, alcohol-, ether- or halide-functionalised epoxides, which generated the corresponding β-lactams from aziridines is also possible with the same catalyst system. This work was optimised by Coates, who used a bimetallic aluminium porphyrin cobalt tetracarbonyl catalyst system, with inversion of the stereogenic centre (Scheme 79).179

A wide range of substituted epoxides have been used successfully in this reaction. The catalyst loadings are again very low, which allows for easier purification of the generated products.

Besides the shown cobalt-catalysed ring-expansion and ring-opening reactions, various copolymerization reactions between epoxides, aziridines and carbon monoxide are also well described in the literature. Recent developments in the formation of polyesters and polyketides were made by the research groups of Jia180 and Sen.181

Zhang182 reported the intermolecular C–H amination of indene with bromamine-T using a cobalt tetra(dichlorophenyl)porphyrin complex as catalyst to afford 128 (Scheme 80). Aside from indene, a couple of other aromatic compounds with benzyl hydrogen atoms, like 9H-fluorene or tetrahydronaphthalene, were aminated in moderate to low yields.

An interesting application of the CpCo(C$_2$H$_4$)$_2$ complex was described by Vollhardt in the intermolecular synthesis of dienyl amides from α,ω-diyne and an amide. The cyclisation gave five- and six-membered rings with excellent Z-selectivities for the formation of the enamide unit. For example, product 129 (Scheme 81) was obtained in good yield under mild reaction conditions.

A cobalt tetraphenylporphyrin catalysed olefination of aldehydes and ketones with ethyl diazoacetate in the presence of triphenylphosphine to generate predominantly E-configured alkenes was presented by Zhang. A cobalt-catalysed dimerisation of alkenes was described by Cheng, who achieved the reductive homocoupling of acceptor-substituted alkenes and styrenes (Scheme 82) to yield branched products (130) as well as linear products such as 131.

The reaction was carried out with acrylates, acrylamides, acrylonitrile, vinyl ketones and electron-rich and electron-deficient styrenes, and generated the corresponding products in high yields.

The enantioselective carbonyl–Alder–ene reactions catalysed by chiral cobalt(salen) complexes were described by Rawal. Starting from ethyl glyoxylate and various 1,1-disubstituted and trisubstituted alkenes, the reaction gave rise to γ,δ-unsaturated α-hydroxy esters in high yields (84–99%) with excellent stereoselectivities (92 to >99%). However, the use of a wide variety of carbonyl compounds in this cobalt-catalysed reaction has not yet been achieved.

A sol-gel entrapped Rh$_6$Co$_4$(CO)$_{12}$ catalyst precursor for the hydrogenation of aromatic, olefinic or carbonylic substrates was described by Avnir. For example, the hydrogenation of ethylbenzene with the catalyst and hydrogen (14 bar) generated ethylecyclohexane in 92% yield. In hydrogenation reactions of styrene or diphenylacetylene, complex mixtures of partially or fully hydrogenated products were obtained, thus diminishing the broad utility of the methodology.

A very interesting hydrogen shift reaction catalysed by a Cp$^+$Co(vinylsilane)$_2$ complex was described by Brookhardt (Scheme 83). Therein, hydrogen was abstracted from amine 132 and transferred to the nitrogen’s vinylsilane protecting group to generate the enamine 133. Various nitrogen-containing heterocycles were dehydrogenated in up to quantitative yields in NMR tube experiments.

An oxidation of secondary alcohols to ketones catalysed by a square-planar cobalt(III)tetraamine complex, dioxygen and pivalylaldehyde was established by Pedro and Journaux. This reaction was carried out with aliphatic, aromatic and cyclic alcohols and led, for example, to 1-acetyl-4-nitrobenzene in 95% yield starting from 1-(4-nitrophenyl)ethanol.

An enantioselective Michael addition catalyst by cobalt(II) perchlorate hydrate and (R,R)-4,6-dienobenzofuranyl-2,2′-bis(4-phenyloxazoline) [(R,R)-DBFOX-Ph] in a 1:1 mixture of tert-butyl alcohol and tetrahydrofuran was introduced by Kanemasa to generate chiral polyfunctionalised ketones such as 134 (Scheme 84). This reaction can also be conducted with nickel(II) perchlorate hexahydrate and further investigations concerning an enantioselective double Michael addition were carried out only with the nickel complex.

The enantioselective alkylation of Schiff base derived benzaldehyde and the isopropyl ester of racemic alanine with benzyl bromide catalysed by chiral metal(salen) complexes were described by Belokon. The results for different transition metals showed that the reaction can be carried out with cobalt(II) as central ion to give the desired product in 84% yield in 15% ee. Because copper(salen) complexes led to far better results with regard to yield and...
enantioselectivity in this reaction, no further investigations were carried out with the cobalt system.

An unusual ring-expansion reaction of benzosilacyclobutenes was recently contributed by Gandon, Malacria and Aubert. The insertion of the cobalt fragment into the silicon–carbon bond of the silacyclobutene ring in Scheme 85 initiated the process and either an intramolecular or an intermolecular insertion of a triple or a double bond led to bicyclic and tricyclic products in moderate to good yields. A representative example is shown in Scheme 85 for the intramolecular synthesis of the tricyclic product 136.

Scheme 85

5 Conclusions and Outlook

The growing interest in first-row transition-metal catalysis and the increasing number of interesting and astonishing reactivities and new reaction pathways prompted us to compile this review since we ourselves entered the inspiring field of cobalt catalysis years ago. It is clear that cobalt has a high potential for catalysing various cycloaddition reactions over a wide range of ring sizes. Some of the cobalt-based methodologies are quite competitive with existing alternatives, while other reactions, such as the cyclotrimerisation of alkynes and the Diels–Alder reactions of non-activated starting materials and several other transformations, are clearly a stronghold of cobalt catalysis. In addition, the progress in the field concerning mild, efficient and selective coupling reactions to generate acyclic products can not be overlooked. The impact of this research area ourselves.

As German-speaking chemists, we have to admit that the name for this element, with respect to its rich organometallic chemistry, was appropriately chosen. The German word ‘Kobold’ depicts a friendly ghost (protecting the house) who sometimes plays tricks on you. In this respect, the progress in the field concerning mild, efficient and selective coupling reactions to generate acyclic products can not be overlooked. The impact of this research area ourselves.

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(173) Denmark, S. E.; Ahmad, M. J. Org. Chem. 2007, 72, 9630.


