Regioselectivity, Stereoselectivity and Catalysis in Intermolecular Pauson–Khand Reactions: Teaching an Old Dog New Tricks

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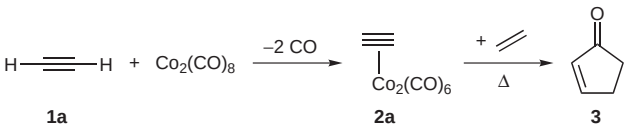
Dedicated to Prof. Henning Hopf on the occasion of his 65th birthday.

Abstract: Since its discovery in the early seventies the intermolecular Pauson–Khand reaction has made considerable progress towards a powerful synthetic method. This account describes the major accomplishments with respect to reactivity, stereoselectivity and catalytic versions, which have been achieved over the last decade and summarizes mechanistic information being obtained by theoretical and experimental studies.

Key words: Pauson–Khand reaction, metal-catalysis, stereoselectivity, theoretical studies

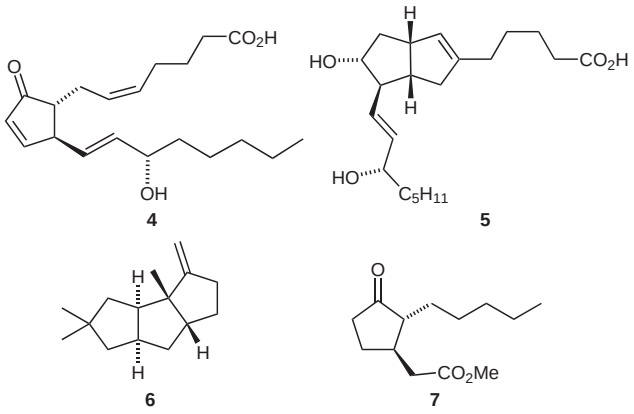
1 Introduction

During their studies of cobalt–alkyne complexes in 1971 Pauson and coworkers reported the formation of cyclopentenone **3** by treating acetylene dicobalthexacarbonyl **2a** with ethylene (Scheme 1).[1]



Scheme 1

Originally discovered by serendipity, the cobalt-mediated [2+2+1] cocyclization of an alkyne, an alkene and carbon monoxide to cyclopentenone, commonly known as the Pauson–Khand reaction, has grown into a powerful method in organic synthesis. Cyclopentenones are very versatile building blocks for natural products, pharmaceuticals and fine chemicals[2] such as prostaglandins **4**, isocarbacyclins **6**, sesquiterpenes **5**, and jasmonates **7** (Scheme 2).



Scheme 2

The mechanism of the Pauson–Khand reaction, initially proposed by Magnus,[3] has now been widely accepted (Scheme 3). In the presence of $Co_2(CO)_8$ the alkyne forms the tetrahedral dicobalt complex **8**. After loss of CO, the alkene is coordinated to give the alkene complex **9**, which undergoes insertion of the alkene moiety into the sterically least hindered Co–C bond. Subsequent CO insertion gives rise to the cobalt acyl complex **11**. Extrusion of one $Co(CO)_3$ fragment yields the cobaltacyclopropene complex **12**, which is finally converted to the cyclopentenone **13** by reductive cleavage of $Co_2(CO)_6$. Except the formation of the stable and isolable cobalt–alkyne complex **8**, however, there was no experimental evidence for this mechanism until recently.

Since the early reports by Pauson it was found that several other complexes containing transition metals such Fe,[4] Ru,[5] Rh,[6] Ni,[7] Cr,[8] Mo,[9] W, Ti,[10] and Zr[11] can be used for this cocyclization.

In 1981 Schore reported the first example of an intramolecular Pauson–Khand reaction (Scheme 4).[12] Despite this initial delay the intramolecular variant made much more progress over the last two decades particularly with regard to reactivity, stereoselectivity and catalysis as compared to the intermolecular counterpart.

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Based on our own research efforts in this area, the following article will focus on the various above-mentioned issues of the intermolecular Pauson–Khand reaction with some selected examples of the intramolecular version. Although the intermolecular Pauson–Khand reaction proceeds in a highly convergent fashion and tolerates a variety of functional groups such as ethers, alcohols, tertiary amines, thioethers, ketones, acetals, esters, amides, aryl and alkyl halides, heterocycles, vinylethers and -esters, it is limited to reactive alkenes such ethylene, allene and strained cyclic alkenes. Sterically hindered alkenes are disfavored. In many cases, yields are only moderate. Regio- and stereoselectivity are often difficult to control. And last but not least a catalytic version is out of sight.

2 Reactivity: Improvement by Additives

One of the earliest attempts to improve the reactivity was described by Smit[13a] (Scheme 5). By adsorption of the cobalt–alkyne complex **16** to silica gel and performing the reaction without any solvent (dry state adsorption conditions) reaction rate and yield of the intramolecular Pauson–Khand reaction could be dramatically increased.

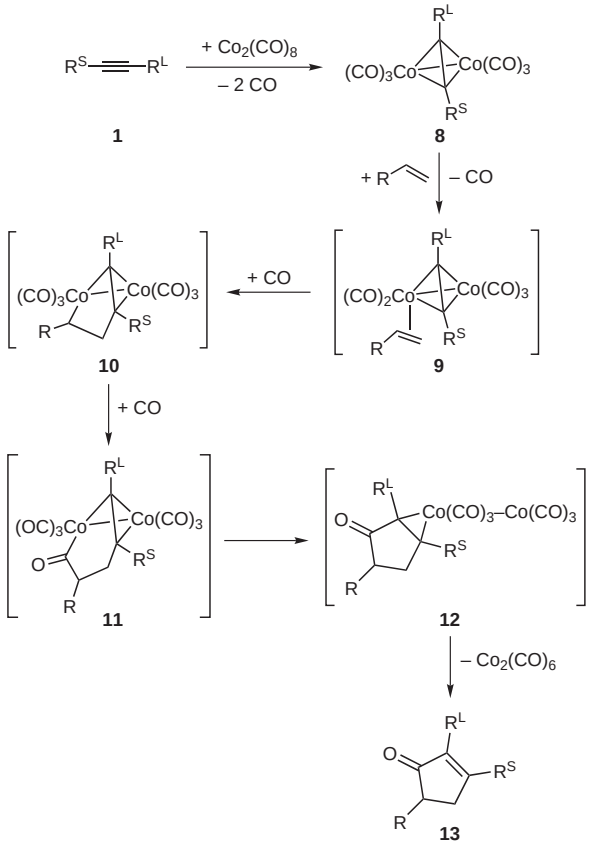
Biographical Sketches

Sabine Laschat studied chemistry at the Universität Würzburg from 1982–1987 and received her PhD at the Universität Mainz in 1991 under the supervision of Professor Horst Kunz. After a postdoc year in the group of Professor Larry Overman, she finished her habilitation at the Universität Münster (mentor: Professor Gerhard Erker) in 1996. Then she was appointed as an Associate Professor of Organic Chemistry at the Technische Universität in Braunschweig from 1997–2002. Since 2002 she holds a Chair in Organic Chemistry at the Universität Stuttgart.

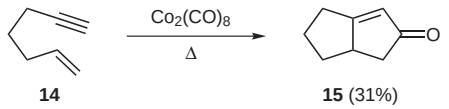
Armand G. Becheanu was born in 1977 in Lipova, Romania. He studied at the 'Politehnica' University Timisoara between 1995 and 2000, where he received his engineer diploma. He started his PhD on 'Pauson–Khand Reactions as Key Steps for Pharmaceutically Relevant Target Molecules' at the Technische Universität in Braunschweig, Germany, under the supervision of Professor Sabine Laschat and currently continues work in Stuttgart after the group moved there in 2002.

Thomas Bell was born in London, UK, in February 1981. He studied for a MChem (Europe) degree at the University of Leicester, UK, which included one year at the Technische Universität in Braunschweig, Germany, under the supervision of Professor Sabine Laschat. He graduated in 2003. He is currently studying at the University of Leicester for his PhD on 'Cellulose Modification Using Ionic Liquids' with Professor A. P. Abbott and Dr. S. Handa in cooperation with Procter and Gamble, UK.

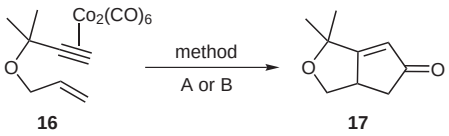
Angelika Baro was born in Stadtoldendorf, Germany. She studied chemistry at the Georg-August-Universität Göttingen, Germany, where she received her PhD in 1987 in Clinical Biochemistry under the supervision of Professor H. D. Söling. Since 1991 she is a scientific staff member at the Institut für Organische Chemie, Universität Stuttgart, Germany.



Scheme 3

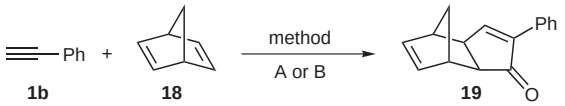


Scheme 4



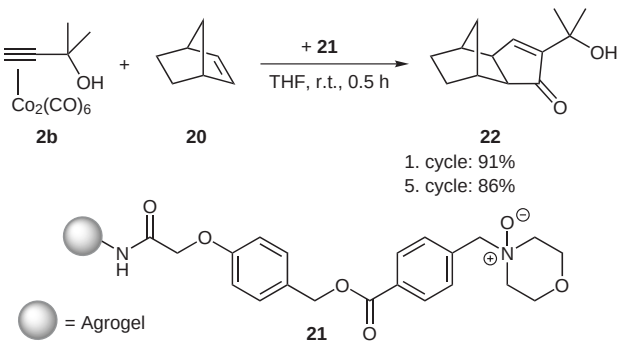
Scheme 5 *Reagents and conditions*: Method A: isooctane, 24 h, 60 °C, **17**: 29%; Method B: SiO_2, O_2, 0.5 h, 45 °C, **17**: 75%

Later Schreiber,[13b] Krafft,[14] and Chung[15] discovered the accelerating effect of tertiary amine *N*-oxides, which is probably due to the oxidative removal of one CO ligand from the cobalt–alkyne complex (Scheme 6).



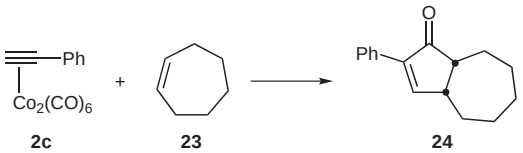
Scheme 6 *Reagents and conditions*: Method A: DME, 4 h, 60–70 °C, **19**: 45%; Method B: Me_3NO (3 equiv), CH_2Cl_2, 2 h, 0 °C, **19**: 80%

However, a disadvantage of the amine *N*-oxides is their need in large excess (3–6 equiv). A solution to this problem has been recently reported by Kerr, who developed a polymer-supported morpholine-*N*-oxide **21** which could be recycled up to five times by treatment with Davies reagent (Scheme 7).[16] This result is particularly relevant for the use and recycling of chiral amine *N*-oxides for stereoselective Pauson–Khand reactions (see chapter 4.4).



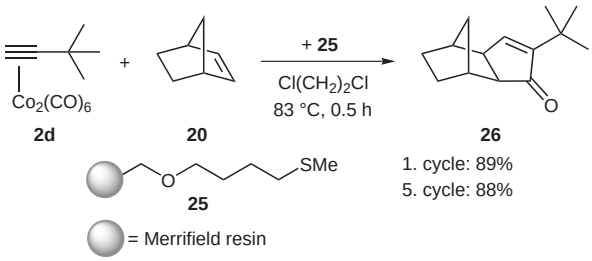
Scheme 7

A plethora of other Lewis bases such as dimethyl sulfoxide,[17] cyclohexylamine,[18,19] aqueous ammonium hydroxide (in dioxane),[18] and sulfides[20] has been developed in order to enhance Pauson–Khand reaction rates. Particularly *n*-butyl methyl sulfide turned out to be successful, where other additives failed (Scheme 8).[20]



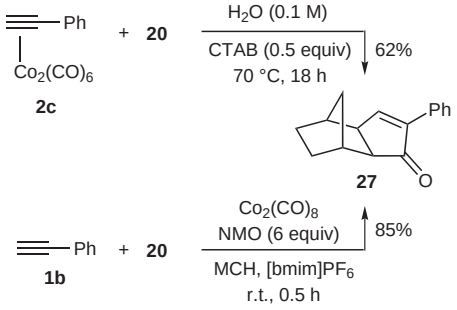
Scheme 8 *Reagents and conditions*: (i) Toluene, reflux, 3 d, **24**: 23%; (ii) NMO (6 equiv), CH_2Cl_2, r.t., 10 min, **24**: decomplexation; (iii) *n*-BuSMe (4 equiv), $Cl(CH_2)_2Cl$, 83 °C, 1.5 h, **24**: 85%

In order to circumvent the major disadvantage of *n*-butyl methyl sulfide, its unpleasant odor and high volatility, Kerr prepared a sulfide **25** tethered to a Merrifield resin (Scheme 9).[21] Even with sterically hindered cobalt–alkyne complexes such as **2d** high yields could be maintained over at least five cycles.



Scheme 9

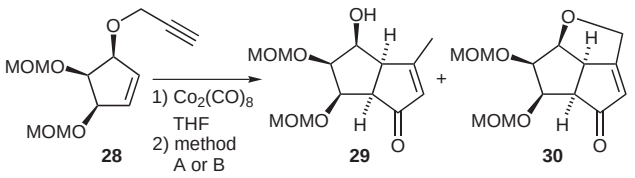
A completely different approach to rate enhancement utilizes solvent effects. Especially water has been identified as a useful reaction medium for many organic reactions.[22] In this respect recent results by Krafft should be mentioned. Thermal intermolecular cocyclization in aqueous solution in the presence of cetyltrimethylammonium bromide (CTAB) gave the desired enone **27** in good yield (Scheme 10).[23]



Scheme 10

We have explored the scope and limitations of ionic liquids as novel solvents for intermolecular Pauson–Khand reactions.[24,25] Although the amine *N*-oxide promoter could be circumvented by a ionic liquid such as [bmim]PF_6, a biphasic system of [bmim]PF_6/methylcyclohexane (MCH) not only made the use of low boiling CH_2Cl_2 obsolete, but also improved the work up, particularly the separation of the desired cyclopentenone from cobaltoxide and amine *N*-oxide residues, which remained in the polar phase (Scheme 10).

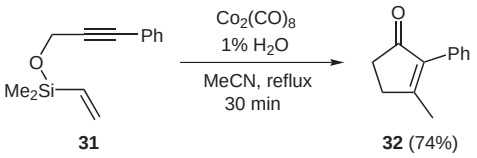
As mentioned in the introduction, the use of strained bicyclic alkenes and ethylene must be considered as serious limitation of substrates. Particularly, terminal alkynes could not be used in intermolecular Pauson–Khand reactions. Ogasawara presented a clever solution to this general problem (Scheme 11).[26]



Scheme 11 *Reagents and conditions*: Method A: Me_3NO, THF, –20 °C to r.t., 12 h, **30**: 56%; Method B: $cHexNH_2$, $Cl(CH_2)_2Cl$, reflux, 20 min, **29**: 40%

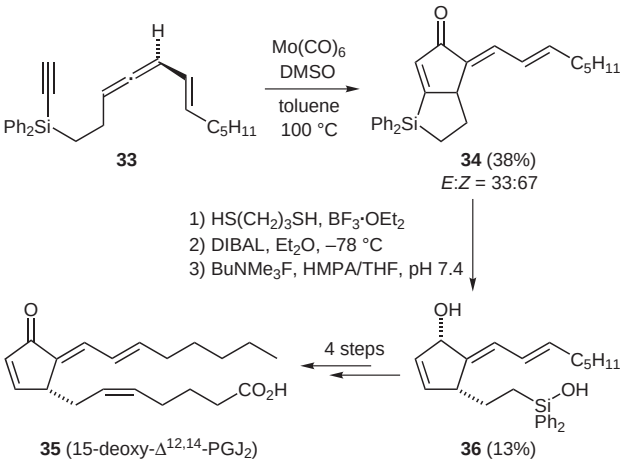
Alkene and alkyne were tethered via an ether moiety and thus, the overall Pauson–Khand reaction occurred intramolecularly. Careful choice of the reaction conditions allowed to accomplish a reductive cleavage of the tether in the final step giving the bicyclo[3.3.0]octenone **29** in 40% yield.

In a related work Pagenkopf employed silicon-tethered enynes **31** derived from propargylic alcohols and vinyl silanes for isoprostan synthesis (Scheme 12).[27] Surprisingly, the complete absence of water and additives, respectively, turned out to be deleterious for the Pauson–Khand reaction. In the presence of additives only decomposition products from enyne **31** were observed. However, when the reaction was carried out in acetonitrile with 1% of water, the cyclopentenone **32** was isolated, thus demonstrating the synthetic potential of silyloxy as a traceless linker.



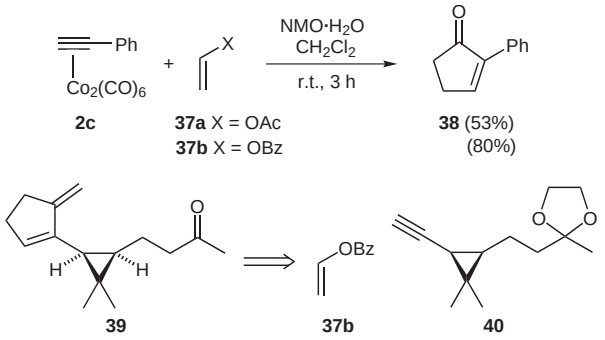
Scheme 12

Simultaneously, Brummond developed Mo-promoted [2+2+1] cocyclizations of silicon-tethered allenes (Scheme 13).[28] Tethered allene-yne **33** was converted to the bicyclic enone **34**. Subsequent *E*/*Z* isomerization with 1,3-propanedithiol provided the pure *E*-isomer, which was submitted to DIBAL reduction followed by fluoride-induced cleavage of the vinyl–silicon bond to give the allylic alcohol **36**. The latter was further converted to the prostaglandin derivative **35**.



Scheme 13

While looking for oxygenated cyclopentenone, Kerr and Pauson studied vinyl esters and ethers as starting materials.[29] However, treatment of cobalt–alkyne complex with vinyl benzoate **37b**[29] in the presence of NMO did not give the desired oxygenated product, but cyclopentenone **38** (Scheme 14). The reductive cleavage occurred only under inert conditions. After this unexpected outcome, Kerr and Pauson realized the potential of vinyl esters and even vinyl bromides as ethylene equivalents (Scheme 14). The strategy was applied in the total synthesis of (+)-taylorione (**39**).



Scheme 14

While a great deal of experimental effort has been spent on modified reaction conditions in order to enhance the rates, the observed large reactivity differences between various alkenes in intermolecular Pauson–Khand reactions still remained unclear. For example, in the intermolecular thermal version the following reactivity order was found: cyclohexene < cyclopentene < norbornene. Very recently, Milet, Greene and Gimbert shed some light on this important question by using DFT and ONIOM methods.[30] They anticipated that the insertion of the alkene into the Co–C bond (**9** → **10**, Scheme 3) is the rate-determining step and the LUMO (π* orbital) of the olefin plays an important role in olefin–Co back-donation and creation of the new carbon bond by overlapping with the HOMO of the alkyne $Co_2(CO)_5$ complex (Figure 1). Thus, transition states for cobaltacycle formation between propyne $Co_2(CO)_5$ and cyclopentene, cyclohexene and norbornene, respectively, were calculated and a strong correlation between HOMO/LUMO gaps and the relative reactivity of the olefin was found.

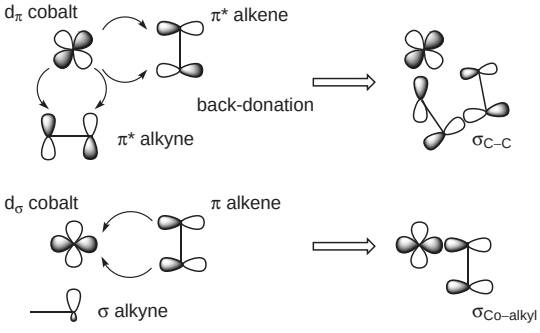
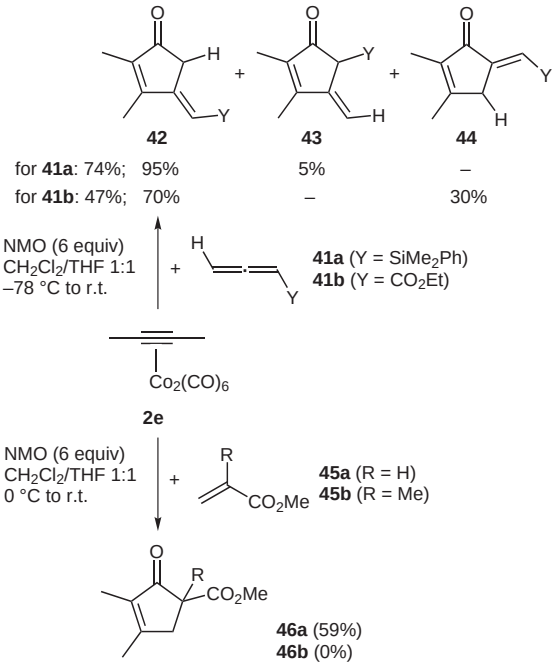


Figure 1 Schematic illustration of HOMO/LUMO orbital interactions in Co–C bonds

Although the majority of intermolecular Pauson–Khand reactions utilizes either cyclopentene, norbornene, norbornadiene and derivatives thereof, Cazes[31,32] and Pericas[33] demonstrated that allenes, electron-poor alkenes and even cyclopropene are useful substrates for the intermolecular cocyclization. For example, treatment of cobalt–alkyne complex **2e** with moderately electron-rich allene **41a** gave 74% of a 95:5 mixture of cyclopentenones **42** and **43**, while the corresponding electron-poor allene **41b** resulted in the formation of cyclopentenones **42** and **44** (47%, 70:30; Scheme 15).[31]



Scheme 15

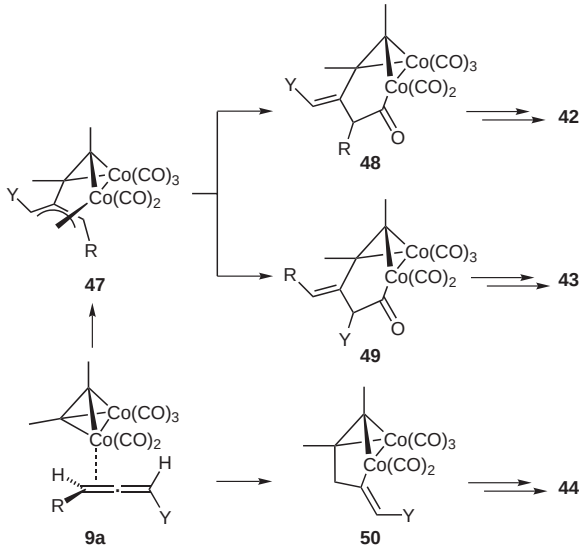
In order to explain the results three competing pathways were proposed (Scheme 16) starting from the allene complex **9a**. Allene insertion leads either to complex **48**, **49** or **50**. Further insertion of CO, reductive elimination and decomplexation gave the products **42**–**44**.

Cazes also investigated the reaction of cobalt–alkyne complexes with electron-poor alkenes (Scheme 15).[32] In contrast to previous observations Michael acceptors such as methyl acrylate **45a** gave under NMO activation the desired cyclopentenone **46a** in 59% yield. However, the reaction was very sensitive to steric effects and the corresponding methyl methacrylate **45b** did not give any trace of product **46b**.

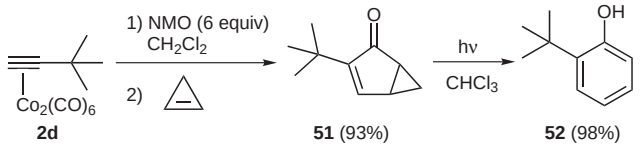
A rather surprising discovery was made by Pericas and Riera[33] regarding cyclopropene as a starting material for Pauson–Khand reactions (Scheme 17). While the NMO-promoted Pauson–Khand reaction of cobalt–alkyne complexes **2d** proceeded eventless, the obtained bicyclo[3.1.0]hex-3-en-2-one (**51**) underwent a photochemical rearrangement to an *ortho*-substituted phenol **52**.

3 Regioselectivity: Some Mechanistic Struggles

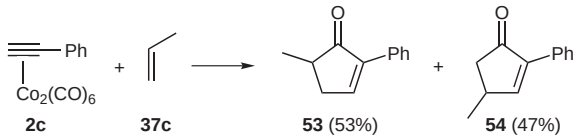
Whereas the intramolecular Pauson–Khand reaction results in only one regioisomer, the corresponding intermolecular version always leads to product mixtures. A typical example is given in Scheme 18.[34]



Scheme 16



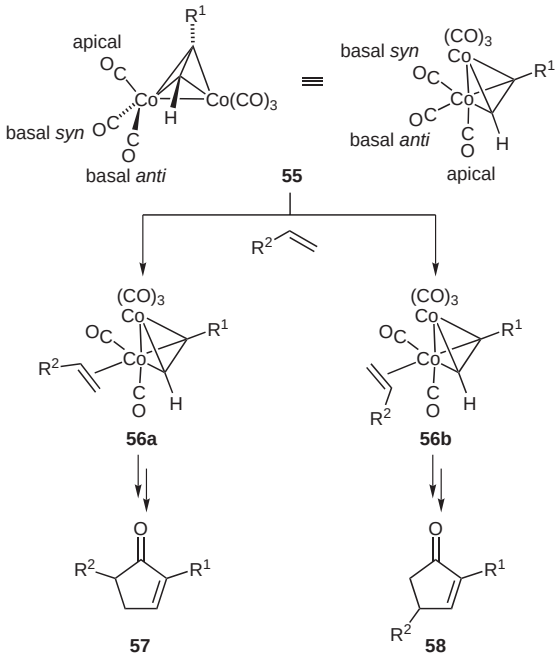
Scheme 17



Scheme 18

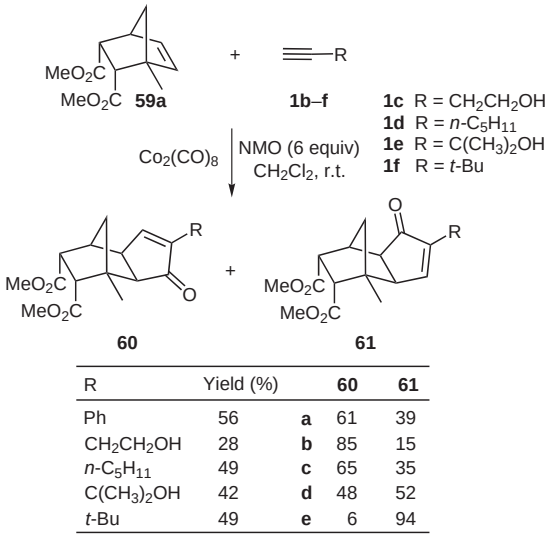
When we started our investigations on the regioselectivity of intermolecular Pauson–Khand reactions employing norbornenes, surprisingly little work has been done on unsymmetrically substituted bridged bicyclic alkenes.[35] According to the commonly accepted mechanism[36] the cocyclization is initiated by the formation of cobalt–alkyne complex **55** with a tetrahedral Co_2C_2 core (Scheme 19).

Under thermal conditions or in the presence of amine *N*-oxide promoters complex **55** is assumed to undergo decarbonylation at the basal (equatorial) carbon monoxide, which is oriented *anti* relative to R^1 followed by coordination of an alkene to give alkene complexes **56a** and **56b**. The regioselectivity with respect to the alkene is due to steric hindrance in the insertion step **56a** → **57** versus **56b** → **58**. The less hindered face of the alkene is inserted into the less hindered Co–C bond. For alkenes with sufficiently large substituents R^2, conformation **56a** and thus, cyclopentenone **57** is preferred. However, with most alkenes mixtures of regioisomers **57**, **58** are obtained.



Scheme 19

Upon treatment of norbornene diester **59a** with various alkynes **1b**–**f** in the presence of NMO we observed a dependence of the regioselectivity on the steric hindrance (Scheme 20).[37]

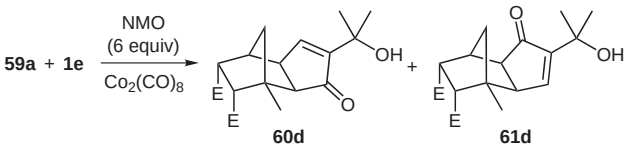


R	Yield (%)		60	61
Ph	56	**a**	61	39
CH_2CH_2OH	28	**b**	85	15
n-C_5H_{11}	49	**c**	65	35
$C(CH_3)_2OH$	42	**d**	48	52
t-Bu	49	**e**	6	94

Scheme 20

While linear unbranched alkynes yielded preferably regioisomer **60**, the ratio was reverted in favor of regioisomer **61**, when *tert*-butyl-substituted acetylene **1f** was employed. During these experiments an unexpected temperature effect was found (Scheme 21). For example, the Pauson–Khand reaction of norbornene diester **59a** with propargylic alcohol **1e** yielded at low temperature regioisomer **60d** as the major product, whereas at elevated temperatures regioisomer **61d** was favored. This reversal of

the regioisomeric ratio was observed in various solvents (toluene, CH_2Cl_2, THF), albeit at different temperature ranges.



Solvent	T (°C)	Yield (%)	**60d**	**61d**
CH_2Cl_2	–20	24	90	10
CH_2Cl_2	0	25	88	12
CH_2Cl_2	20	34	81	19
CH_2Cl_2	40	42	48	52
Toluene	–25	61	95	5
Toluene	20	59	23	77
Toluene	120	48	12	88

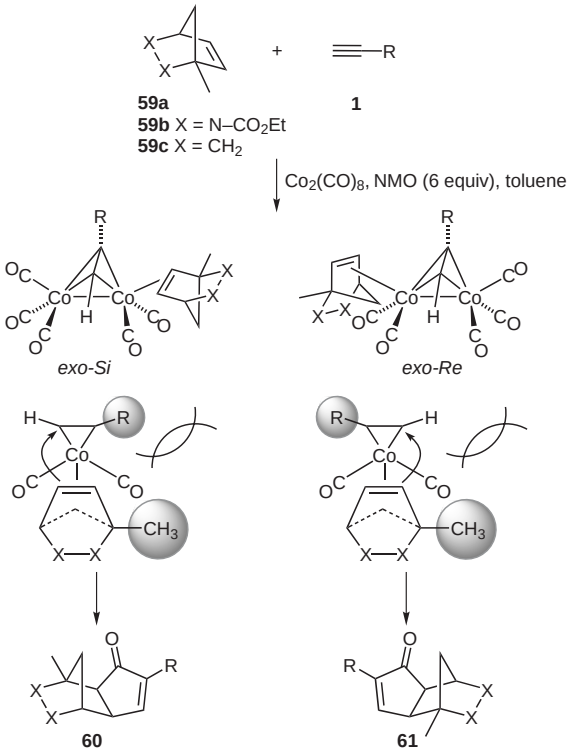
Scheme 21

From these results we have developed the following mechanistic rationale (Scheme 22). In contrast to the literature proposal we assumed removal of an axial CO ligand from the prochiral cobalt–alkyne complex resulting in the formation of diastereomeric alkene complexes *exo-Si* and *exo-Re*. Newman perspectives of these two complexes rationalize that due to the preference to insert the olefin into the least hindered alkyne carbon atom at low temperatures and with alkynes bearing small substituents R complex *exo-Si* should be favored, leading to product **60**. However, at elevated temperatures and with bulky substituents R complex *exo-Re* should be preferred giving product **61**. Our experimental results were further supported by Cazes,[38] who studied the regioselectivity of 7-oxanorbornenes. However, the question axial versus equatorial alkene complex still remained open.

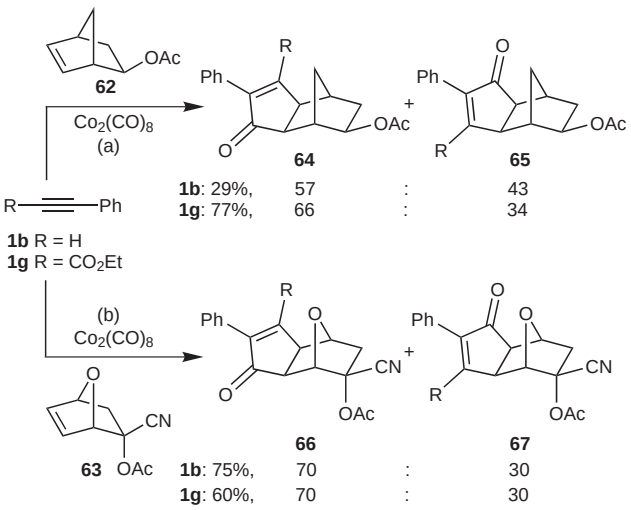
Almost simultaneously, Arjona, Plumet[39] and Tam[40] discovered remote substituent effects on the regioselectivity in Pauson–Khand reactions of 2-substituted norbornenes, 7-aza- and 7-oxanorbornenes. Moderate levels of regioselectivity were observed for norbornenes (Scheme 23),[40] while the regioisomeric ratio increased considerably for 7-oxanorbornenes **63**.[39a]

Moreover, the regioselectivity increases with increasing electron withdrawal by the remote substituent. Semi-empirical calculations indicated a polarization of the alkene which is controlled by the remote substituent.[40] Remarkably, the presence of a bromine atom in the alkene moiety of 7-oxa- and 7-azanorbornenes not only could be used to revert the regioisomeric ratio, but also a reductive dehalogenation step leads to removal of the bromine atom from the product during the progress of reaction. The bromine atom is thus acting as a traceless controller (Scheme 24).

According to Cazes[41] silyl groups at the alkyne are useful to control the regioselectivity in Pauson–Khand reactions employing allenes. While the cobalt–alkyne complex **71a** with one silyl group yielded a mixture of cyclopentenones **73**–**75**, the corresponding disilyl-substituted cobalt–



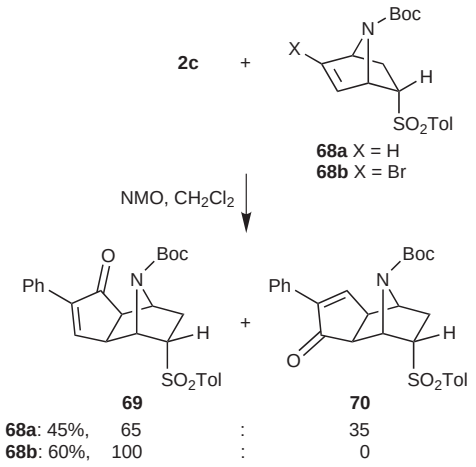
Scheme 22



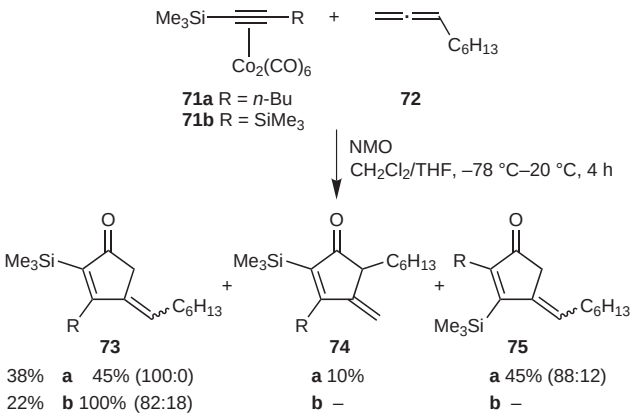
Scheme 23 *Reagents and conditions*: (a) $CyNH_2$, $Cl(CH_2)_2Cl$, 80 °C; (b) NMO, CH_2Cl_2, r.t.

alkyne complex **71b** gave exclusively regioisomer **73** (Scheme 25).

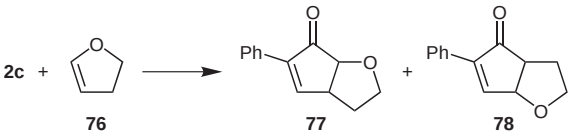
Concerning allene cocyclization Cazes proposed coordination of the allene on an axial vacant ligand site of the cobalt atom.[42] For Pauson–Khand reactions with vinylethenes the regioselectivity turned out to be strongly dependent on the reaction conditions.[43] Under thermal conditions dihydrofuran **76** gave a mixture of regioisomers **77**, **78**, whereas the NMO-promoted reaction yielded exclusively compound **77** as a single regioisomer (Scheme 26).



Scheme 24

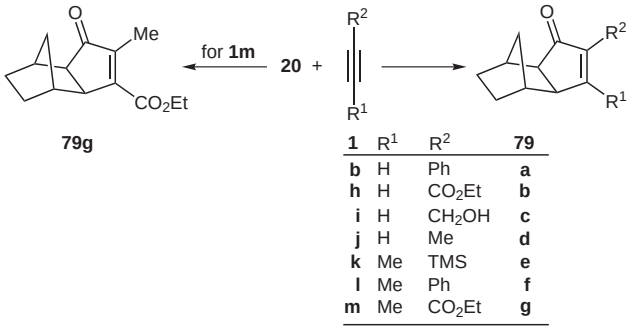


Scheme 25



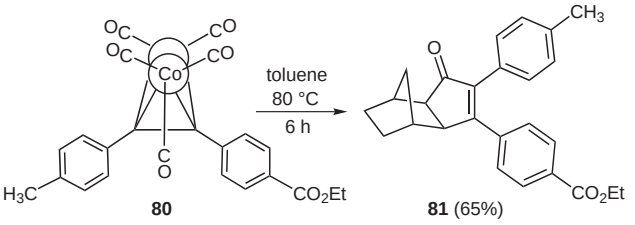
Scheme 26 *Reagents and conditions*: (a) Toluene, 70 °C, 20% yield (**77**: 78%, **78**: 22%); (b) NMO, CH_2Cl_2, US, 43% yield (**77**: 100%)

While the above-mentioned experimental work was in progress, Milet, Gimbert and Greene published two theoretical studies.[44,45] From DFT calculations of cobalt–propyne complexes bearing the alkene moiety either at an axial position or at one of the two equatorial positions it was concluded that the initial position of ethylene (and other olefins when pseudorotation is relatively facile) does not determine the regiochemistry in the Pauson–Khand reaction, because the barrier for pseudorotation of CO and ethylene can easily be overcome at room temperature.[44] However, for the insertion step the complex with the axially coordinated alkene runs through the lowest lying transition state and thus, must be considered seriously. The second study dealt with the regiochemical outcome of the Pauson–Khand reaction of substituted acetylenes with norbornene.[45] The experimentally observed regioisomeric preference shown in Scheme 27 cannot be explained simply by steric arguments.



Scheme 27

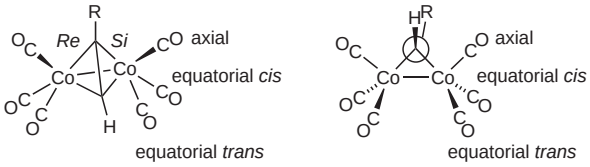
For example, while ethyl propiolate **1h** gave preferably isomer **79b**, ethyl butynoate **1m** afforded regioisomer **79g** as the major product. Therefore, Milet, Gimbert and Greene used DFT to examine whether electronic differences in the acetylenic substituents are involved in controlling the regioselectivity.[45] From calculations of atomic charges of the alkyne carbon atoms by natural population analysis it became evident that indeed propyne is strongly polarized, with the terminal alkyne carbon carrying a higher charge density as compared to the internal alkyne carbon. Ethyl propiolate **1h** is only weakly polarized and thus, steric effects are becoming predominant. In contrast, ethyl butynoate **1m** is strongly polarized in the opposite direction, resulting in a large charge density at the α-carbon relative to the ester group. In addition, electronegative substituents on the alkyne should strengthen the acceptor properties of the bridging ligand, which would result in reduced back-donation from the metal into the π* orbitals of the CO ligands. This proposal could be verified by examination of the CO absorptions in the IR spectra of the cobalt–alkyne complexes. The *trans*-effect together with the difference in electron density on the two acetylenic carbons in the complex should therefore be responsible for a discriminate loss of CO. The mechanism could be elegantly verified by employing an alkyne with two aryl substituents of similar size but with different electronic properties. As suggested by the calculations regioisomer **81** was obtained as the sole product (Scheme 28).



Scheme 28

4 Stereoselectivity

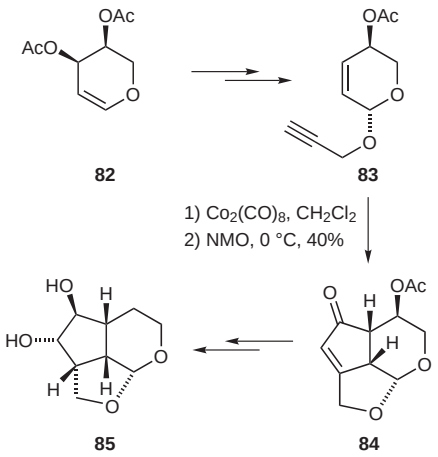
In order to differentiate between the enantiotopic faces of the prochiral cobalt–alkyne complex (Scheme 29), four different strategies are conceivable: i) chiral precursors (ex chiral pool), ii) chiral auxiliaries, iii) chiral cobalt complexes, and iv) chiral additives.



Scheme 29

4.1 Chiral Precursors

Marco-Contelles used an ex chiral pool strategy to obtain the iridoid aglycon **85** (Scheme 30).[46] Starting from the carbohydrate-derived enol ether **82** the enyne **83** was prepared, which underwent amine *N*-oxide-promoted cocyclization to the tricyclic cyclopentenone **84**, which was further converted to the target compound **85**.

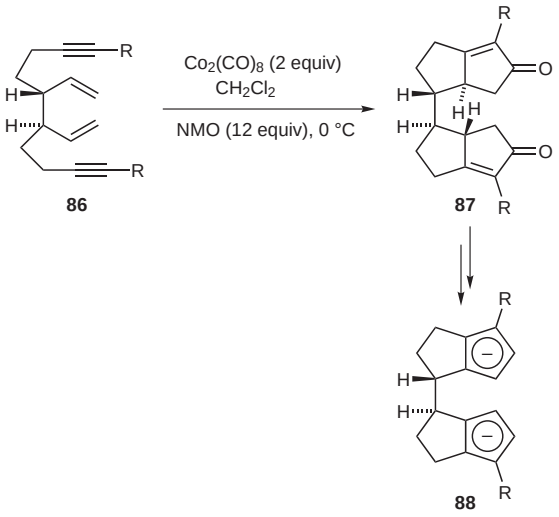


Scheme 30

As described by Grossman[47] the chiral C_2-symmetric bisenyne **86** was converted by a twofold Pauson–Khand reaction to the tethered pentalenedione **87**, which was further converted to the chiral cyclopentadienyl ligand **88** (Scheme 31).

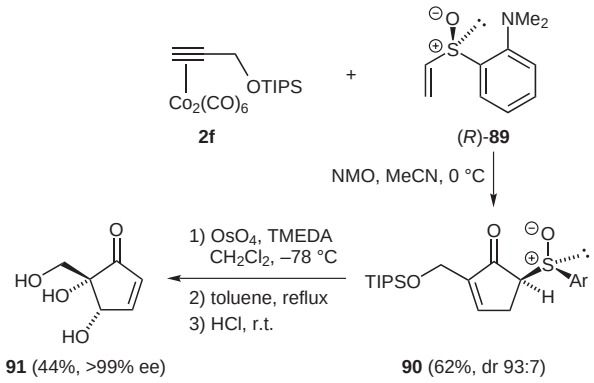
4.2 Chiral Auxiliaries

The vast majority of stereoselective intermolecular Pauson–Khand reactions is based on chiral auxiliaries, which are either attached to the alkene or the alkyne. For example, chiral sulfoxides have been successfully used for both alkenes and alkynes. Carretero[48] reported good to



Scheme 31

excellent diastereoselectivities for amine *N*-oxide-promoted cocyclizations of cobalt complexes and arylvinylsulfoxides such as (*R*)-**89** (Scheme 32).

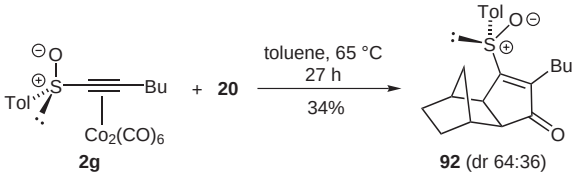


Scheme 32

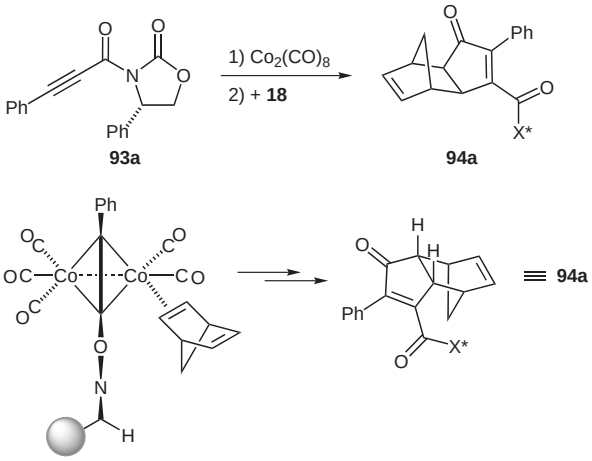
Treatment of alkyne complex **2f** with arylvinylsulfoxide (*R*)-**89** yielded the cyclopentenone **90** in 62% as a diastereomeric mixture (dr 93:7), which was converted in three steps into the antibiotic (–)-pentenomycin (**91**, 44% yield, >99% ee). Presumably the *N*,*N*-dimethylamino group chelates the cobalt atom which coordinates the alkene, thus increasing the steric bias in favor of one diastereomer. This hypothesis is supported by observations that arylvinylsulfoxides without an amino anchor gave lower diastereoselectivities.

In contrast, attaching the sulfoxide auxiliary to the alkyne gave rather disappointing results. Pericas and Riera unexpectedly found an easy racemization of alkynyl sulfoxide cobalt complex **2g** resulting in low diastereoselectivities of the corresponding cyclopentenone **92** (Scheme 33).[49]

Chiral oxazolidin-2-ones proved to be very useful auxiliaries for alkynes, as was shown by Moyano and Pericas (Scheme 34).[50]

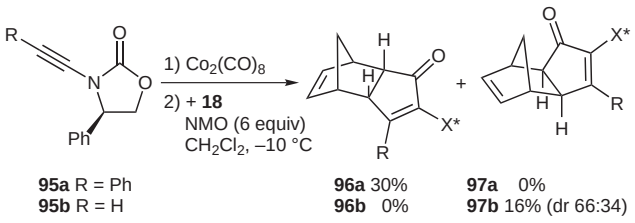


Scheme 33



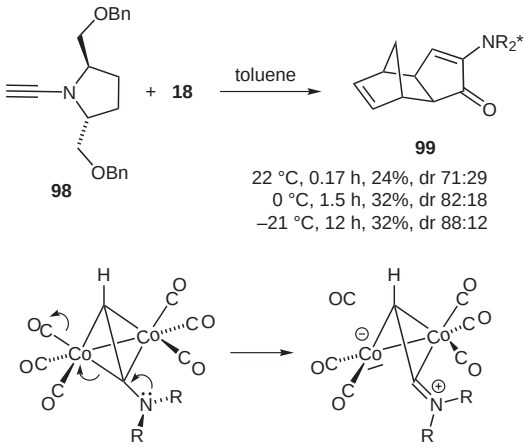
Scheme 34 *Reagents and conditions*: (i) Toluene, r.t., 21 h, **94a**: 91%, dr 84:16; (ii) NMO, CH_2Cl_2, –20 °C, **94a**: 100%, dr 79:21

Semiempirical calculations (PM3) of the cobalt–alkyne complexes clearly indicate that the *S*-configured chiral auxiliary effectively shields the *Re* face of the tetrahedral cobalt cluster, therefore directing the alkene to an equatorial *anti*-position of the *Si* face as depicted in Scheme 34. Subsequent insertion of the alkene, CO insertion and cleavage of the cobalt fragment gives the major diastereomer **94a**. It should be noted that similar yields and diastereoselectivities were obtained under both thermal and amine *N*-oxide-promoted conditions. When Hsung reexamined the Pauson–Khand reaction of chiral ynamides,[51] *endo*-products were observed as mixtures together with the expected *exo*-products. By careful optimization of the reaction conditions he was able to obtain either *endo*- or *exo*-products (Scheme 35). This result was later confirmed by Riera and Verdaguer.[52] Unfortunately, no clear mechanistic rationale could be drawn.



Scheme 35

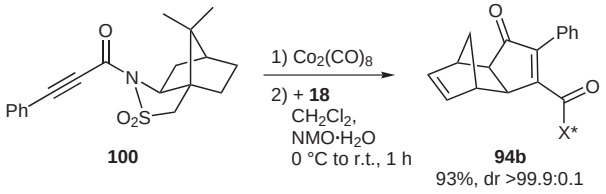
By using chiral C_2-symmetric ynamines **98** Pericas improved the reactivity in thermal Pauson–Khand reactions dramatically.[53] Despite the high instability of the cobalt–alkyne complexes the corresponding cyclopentenones **99** were obtained even at –21 °C with good diastereoselectivities (Scheme 36).



Scheme 36

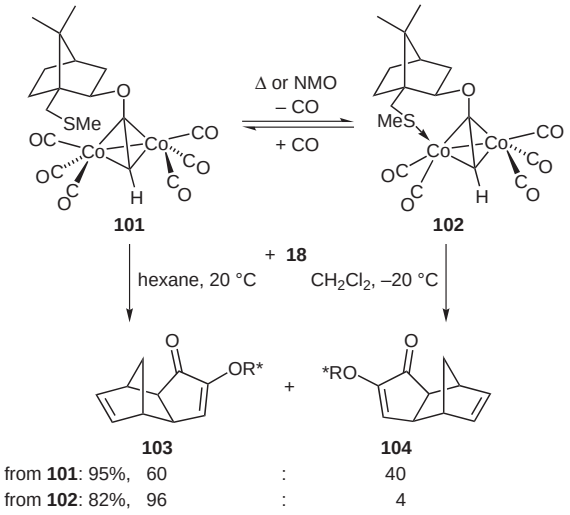
DFT calculations suggest that the dialkylamino substituent is assisting and directing the dissociative loss of CO through a *trans*-effect (Scheme 36).

Oppolzer's bornane-2,10-sultam (**100**, Scheme 37) proved to be a highly efficient auxiliary for intermolecular Pauson–Khand reactions giving exceptional diastereoselectivities.[54] Based on DFT calculations it was assumed that the extremely efficient chirality transfer is due to chelation of one of the cobalt atoms by the sulfoxide moiety and subsequent rate-determining formation of the alkene complex at this specific coordination site.



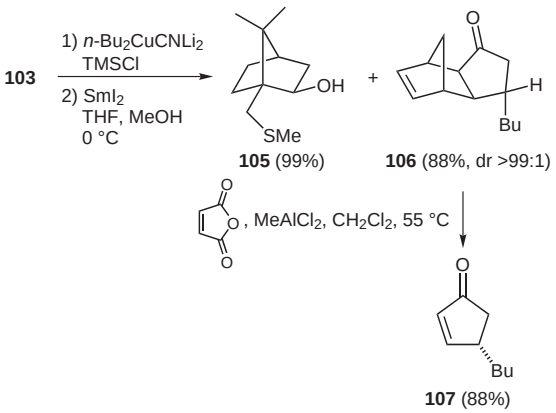
Scheme 37

Although previous studies by several groups have suggested that chelating effects of the chiral auxiliary might contribute to enhanced diastereoselectivity, this issue has not been thoroughly investigated until Pericas, Riera and Greene reported their results in a series of papers.[55] They anticipated that an additional thioether moiety at the chiral auxiliary would serve as an internal promoter which replaces one CO ligand and is further substituted by the alkene. When complex **101** bearing a camphor-derived auxiliary (Scheme 38) was generated at typical thermal conditions minimizing conversion to complex **102** and further treated with norbornene the desired cyclopentenones **103**, **104** were obtained with excellent yields albeit with a meager diastereoselectivity of 60:40 in favor of compound **103**.



Scheme 38

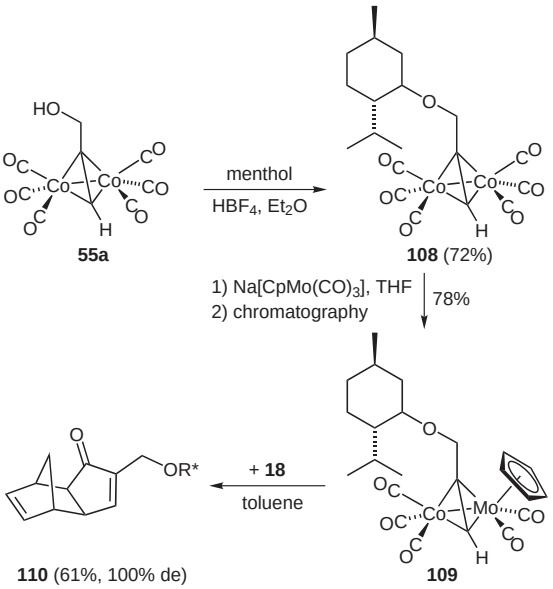
In contrast, conversion of complex **101** to the chelated complex **102** by treatment with NMO and subsequent addition of alkene resulted even at –20 °C in exceptional diastereoselectivities.[55a] From detailed studies, NMR investigations of the equilibrium between the two complexes **101**, **102** and DFT calculations a mechanistic picture emerges in which chelation of the axial position at the *Re* face is preferred and formation of the major diastereomer **103** occurs through a sequence of the most stable intermediates.[55b–f,56] Because even a slight excess of NMO had a deleterious influence on the diastereoselectivity, Pericas and Riera developed an amine *N*-oxide free method,[55f] in which the chelated complex **102** is formed under purely thermal conditions by simply heating to 55 °C prior to alkene addition and insertion at subambient temperatures. The chiral auxiliary could be further used for a stereocontrolled conjugate addition.[55d] The auxiliary was removed by treatment with SmI_2 and subsequent tandem retro Diels–Alder/Lewis acid catalyzed Diels–Alder reaction with maleic anhydride afforded the cyclopentenone **107** (Scheme 39).



Scheme 39

4.3 Chiral Cobalt Complexes

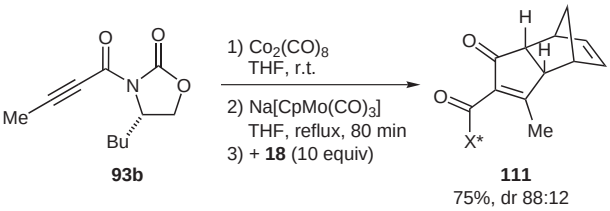
Chiral heterobimetallic alkyne complexes provide an additional tool to accomplish stereoselective intermolecular Pauson–Khand reactions, as was demonstrated first by Christie (Scheme 40).[9,57]



Scheme 40

The cobalt–alkyne complex **55a** was etherified with menthol to give complex **108**. Subsequent treatment with $Na[CpMo(CO)_3]$ gave a 1:1 mixture of heterobimetallic complex **109** and its diastereomeric counterpart which could be separated by chromatography. When complex **109** was heated with norbornadiene (**18**) the cyclopentenone **110** was obtained as a single diastereomer. Control experiments with the corresponding bis-cobalt–alkyne complex showed only a slight diastereomeric excess in the cyclopentenone product **110**.

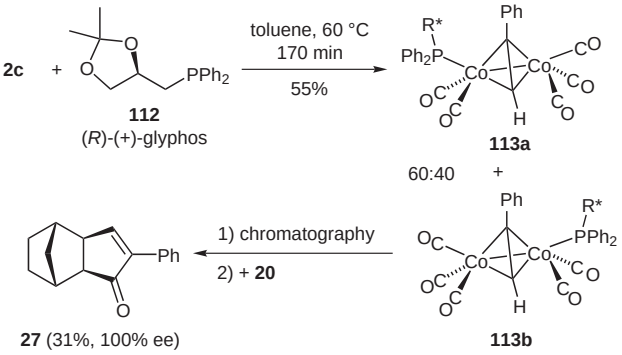
When studying heterobimetallic W–Co[58] and Mo–Co complexes[59] of alkynoates, Pericas and Moyano were surprised to find *endo*-adducts (Scheme 41).[59]



Scheme 41

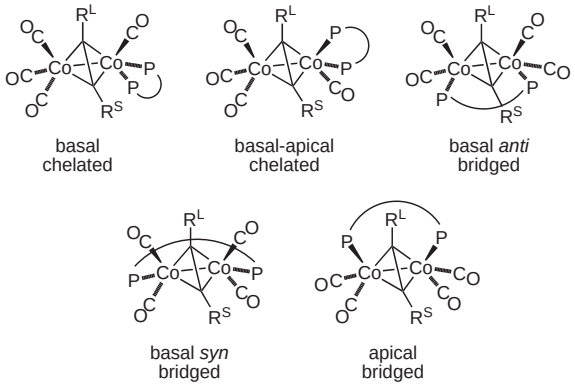
The chirality of the tetrahedral C_2CoMo core appears to control the diastereoselectivity of the *endo*-products such as **111**. The analogous $[MoCp(CO)_2]_2$ complexes did not react with norbornadiene (**18**) to the cyclopentenone, thus indicating that the cobalt atom is the 'active' species in these heterobimetallic complexes.

An alternative approach towards chiral cobalt–alkyne complexes utilized chiral phosphine ligands. This access dates back to 1988 when Pauson and Brunner[60] employed (*R*)-(+)-glyphos (**112**) to prepare a 60:40 diastereomeric mixture of the cobalt complexes **113a**,**b** which could be separated by chromatography (Scheme 42). Subsequent reaction with norbornene (**20**) yielded the enantiomerically pure cyclopentenone **27**. Kerr modified the original methodology by using mild decarbonylation with amine *N*-oxides[61] and thus, obtaining the chiral complexes in high yields.



Scheme 42

However, even under these very mild conditions two serious limitations could not be overcome. First no enantiofacial differentiation of the two enantiotopic cobalt atoms in the prochiral cobalt–alkyne complex could be achieved and secondly the diastereomeric cobalt–alkyne phosphine complexes required tedious chromatographic separations. Because in some cases, even preparative HPLC is necessary, this route is not accessible to large-scale synthesis.



Scheme 43

Encouraged by the promising stereoselectivities of cobalt–alkyne complexes bearing chiral phosphines we initiated a study of various diphosphines. Depending on the distance of the two P atoms and the flexibility of the tether bidentate phosphines should give access to five different cobalt–alkyne complexes, i.e. basal chelated, basal-apical chelated, basal *anti*-bridged, basal *syn*-bridged, and apical bridged (Scheme 43).

It was known from Bonnet,[62] Bird,[63] and Cullen[64] that monophosphines such as PPh_3 usually coordinate at the apical position, diphosphines with small bite angles such as $f_6$fos prefer the basal chelated geometry, while the basal bridged orientation was obtained for diphosphines with an increased bite angle and a more flexible tether such as dppm or dppe. Diphosphines with a very large bite angle (e.g. dppb) gave apical bridged complexes. At the outset of our experiments we anticipated that a chiral C_2-symmetrical diphosphine such as BINAP should prefer a basal bridged coordination mode.[65] By treating (3,3-dimethylbutyne)$Co_2(CO)_6$ and (*R*)-BINAP in refluxing THF followed by recrystallization from diethyl ether the corresponding (3,3-dimethylbutyne)[(*R*)-BINAP]$Co_2(CO)_4$ complex was obtained as a crystalline solid, which fortunately was suitable for X-ray crystal structure determination. As shown in Figure 2 indeed a basal *anti*-bridged coordination mode was found. Further work with achiral diphosphines confirmed that, for example, (phenylacetylene)(dppm)$Co_2(CO)_4$ also contains a basal *anti*-bridged diphosphine ligand (Figure 3).

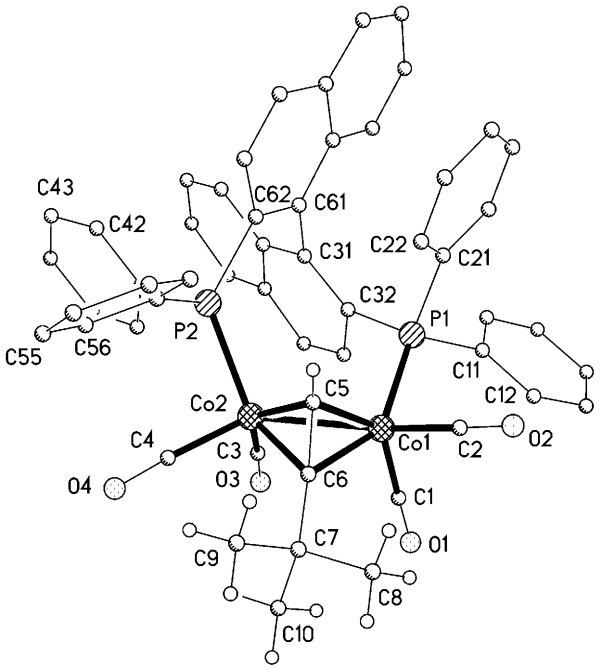


Figure 2 X-ray crystal structure of (3,3-dimethylbutyne)[(*R*)-BINAP]$Co_2(CO)_4$

Surprisingly, upon treatment with norbornene (**20**) both the (*R*)-BINAP and the dppm complex turned out to be completely unreactive, and neither thermal conditions nor amine *N*-oxides resulted in the formation of the desired cyclopentenone. In order to get a deeper insight we carried out some qualitative rate experiments (Scheme 44).

(3,3-Dimethylbutyne)$Co_2(CO)_6$ (**114a**) and the corresponding complex **114b**, where one CO ligand has been replaced by PPh_3, were submitted to thermal and amine *N*-oxide-promoted Pauson–Khand reactions. The rate-determining influence of PPh_3 is clearly visible. The effect is

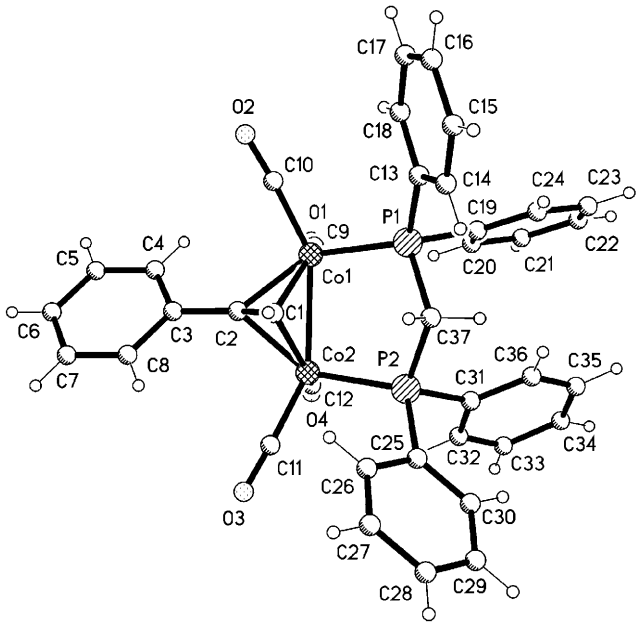
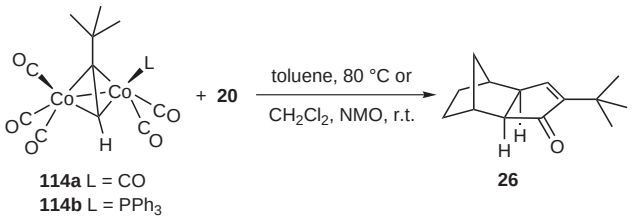


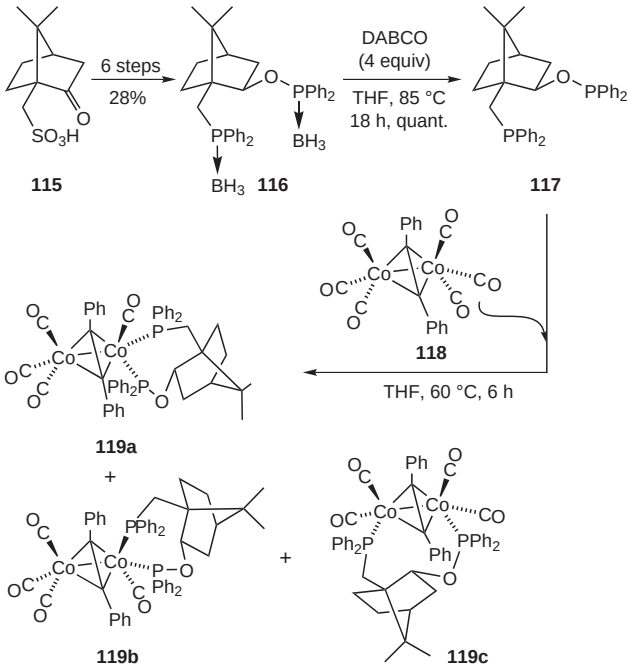
Figure 3 X-ray crystal structure of (phenylacetylene)-(dppm)$Co_2(CO)_4$



Scheme 44

even more pronounced when two CO ligands were replaced by PPh_3 or a diphosphine such as dppm. In this case, less than 1% conversion was observed. The decreased reaction rate of the phosphine complex is probably due to the replacement of carbon monoxide by a poorer π-acceptor ligand thus increasing back-donation between cobalt and the remaining carbon monoxide. This should lead to a retardation of the initial decarbonylation step in the Pauson–Khand reaction. According to the mechanistic scheme proposed for the cocyclization the carbon monoxides in the basal position *anti* to the larger substituent are usually supposed to be most prone to undergo decarbonylation and subsequent coordination of the alkene. The inertness of the (*R*)-BINAP complex and the corresponding dppm (and dppe) complexes towards the reaction conditions support this mechanism. The only carbon monoxide that might be accessible for the cocyclization is the basal coordinated C1–O1 and C3–O3. However, the insertion step is very sensitive to steric hindrance and thus, insertion from a basal position such as C3–O3 is disfavored due to steric interactions with the *tert*-butyl group. In contrast, the other two basal positions are occupied by the phosphine ligand and thus, the Pauson–Khand reaction is completely suppressed. As a consequence, the shutdown of the cocyclization pathway is caused by the decrease of the reaction rate due to the phosphine and the coordination of the bidentate ligand at the 'wrong' position, i.e. basal *anti* instead of basal *syn*. Another implication of these results is that in the Pauson–Khand reaction of (alkyne)[(*R*)-glyphos]$Co_2(CO)_6$ the coordination and insertion step presumably takes place at the phosphine-free cobalt atom. The $Co(CO)_2$glyphos moiety is thus acting as a chiral neighbour that directs the stereoselectivity.

The results obtained so far with (*R*)-BINAP prompted us to look for chiral diphosphine ligands which would meet the following requirements: a) diastereoselective complexation and b) formation of a chelated complex instead of a bridged one in order to overcome the limitation with (*R*)-BINAP. We anticipated that the phosphine phosphinite ligand **117** might serve this purpose (Scheme 45).[66]

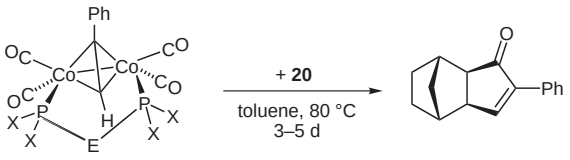


Scheme 45

Ligand **116** can be prepared in 6 steps followed by deprotection from (*S*)-(+)-camphorsulfonic acid (**115**). Heating of phosphine phosphinite **117** in the presence of tolane cobalt complex **118** yielded two cobalt complexes **119a**,**b** (20%) and **119c** (21%) with a chelated and bridged geometry. Unfortunately, the spectroscopic data gave no evidence for either apical-basal chelated (**119a**,**b**) or basal chelated (**119c**) geometry and subsequent Pauson–Khand reactions were therefore expected to be of less mechanistic value. Nevertheless, these bidentate ligands proved to be useful in catalytic asymmetric hydrogenation of methylacetamidocinnamates reaching complete conversion with up to 89% ee.[67] Our mechanistic assumptions were further supported by very recent results by Gibson,[68] who found conditions to obtain the chelated BINAP cobalt–alkyne complexes, which indeed could be used for enan-

tioselective Pauson–Khand reactions. While our above-mentioned basal *anti*-bridged BINAP cobalt–alkyne complex was obtained by mixing the cobalt–alkyne complex with (*R*)-BINAP,[65] Gibson first prepared a precatalyst from either $Co_2(CO)_8$ or $Co_4(CO)_{12}$ and (*R*)-BINAP and then added the alkyne[68] in order to get the chelated complex. Thus, the order of addition seems to play an important role. Gibson speculated that the bridged complex might be an intermediate during epimerization of the chelated complex.

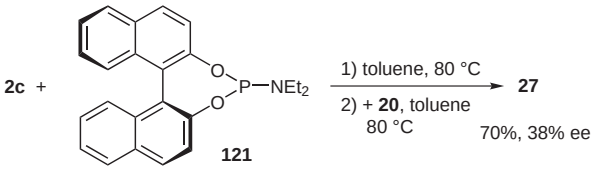
To overcome the deleterious effect of phosphine ligands on the reactivity of the cobalt center Gimbert and Greene pursued a different approach maintaining the excellent stereocontrol.[69,70] The reactivity in Pauson–Khand reactions of cobalt–alkyne complexes **120** bearing bidentate diphosphinoamine ligands with norbornene (**20**) increased with increasing electron-withdrawal from the phosphorus atoms (Scheme 46).[69] The replacement of the bridging *N*-methyl group by (+)-α-methylbenzylamine yielded the cyclopentenone **27** with 16% ee.



120	E	X	27, Yield (%)
a	CH_2	Ph	24
b	NMe	Ph	65
c	NMe	F	92
d	NMe	$(CF_3)_2CHO$	>98
e	NMe	Pyrrolyl	90
f		Pyrrolyl	98, 16% ee

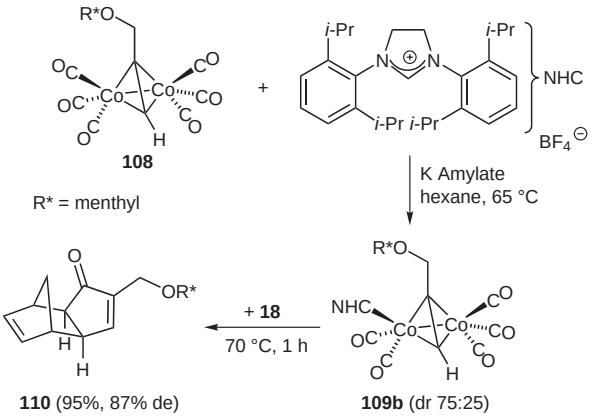
Scheme 46

X-ray crystal structures reveal that the bridging diphosphinoamine ligand occupies the basal *anti*-position. This strongly suggests that the apical (axial) CO ligand is replaced by the alkene. Although later work by Moyano and Pericas[71] confirmed the high reactivity of trispyrrolylphosphine containing cobalt–alkyne complexes, the enantioselectivity of the diphosphinoamine ligand could not be improved.[70] After considerable experimentation, two equivalents of (*R*)-BINOL-derived phosphoramidite **121** were found to increase the enantiomeric excess of the reaction with norbornene (**20**) up to 38% (Scheme 47).



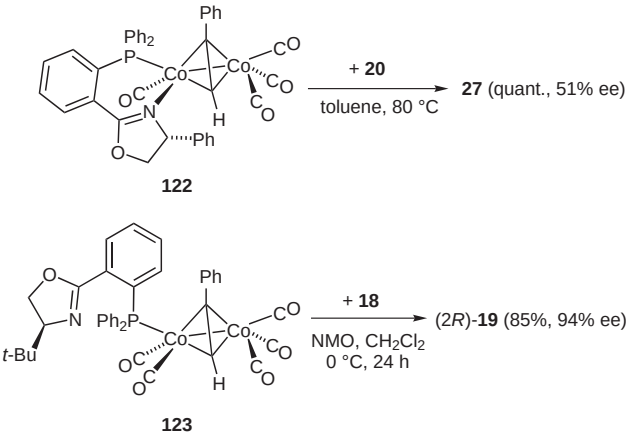
Scheme 47

The problems associated with phosphine ligands motivated two other groups to put further efforts in this issue. Christie prepared diastereomeric cobalt–alkyne complexes **109b** with menthyl auxiliary and N-heterocyclic carbene ligand (NHC, Scheme 48).[72] The obtained yields and diastereoselectivities of the Pauson–Khand product **110** were excellent, however, the presence of a chiral auxiliary was still necessary. In addition, partial migration of the NHC ligand was observed creating some loss of stereochemical integrity.



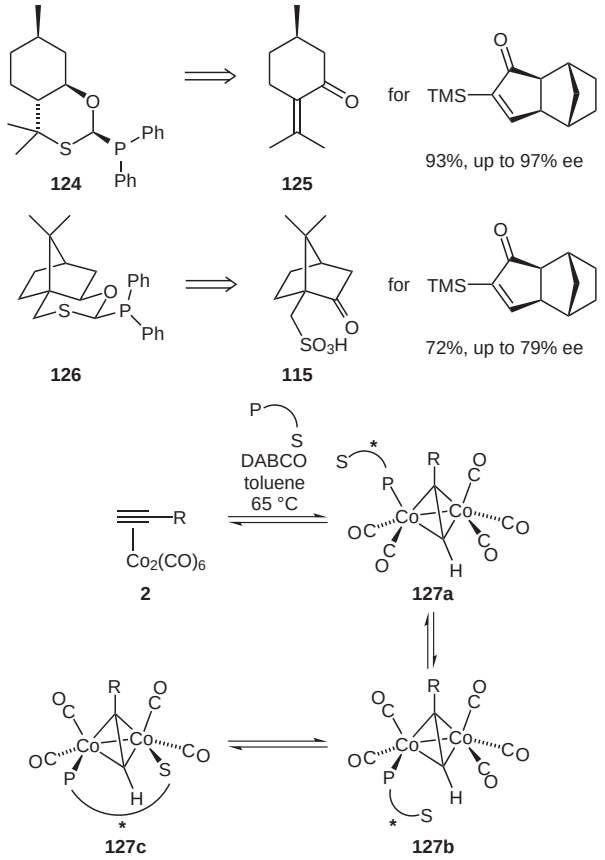
Scheme 48

Moyano, Pericas and Riera reexamined the possibilities of bidentate phosphinooxazoline ligands on the cobalt atoms (Scheme 49).[73] Depending on the steric bulkiness of the substituents at the alkyne and at the oxazoline moiety either chelated complex **122** or complex **123** with monodentate phosphine was observed, which could be interconverted under certain conditions. However, the non-chelated complexes such as **123** gave much better enantioselectivities than the corresponding chelated species (Scheme 49). By using circular dichroism the absolute configuration of the non-chelate complex **123** could be correlated with the absolute configuration of the cyclopentenone product **19**. Coordination of the phosphine to the *Re* face of **123** resulted in 2*R*-configured cyclopentenone **19**.



Scheme 49

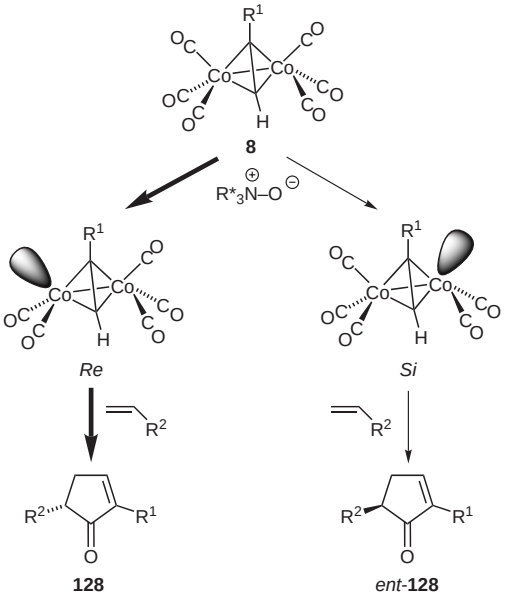
The epimerization rate of complexes such as **123** is strongly dependent on the alkyne substituent and the rate increases in the order Ph < *n*-Bu < $SiMe_3$ << *t*-Bu. Further experiments showed that the intermolecular Pauson–Khand reaction of the pure diastereomeric complexes is stereospecific.[73b] The only requisite for obtaining high enantioselectivities is that the rate of the cocyclization must be higher as compared to the epimerization. Furthermore, the use of amine *N*-oxides allowed convenient recycling of the ligand as phosphine oxide. Based on their ground-breaking results with camphor-derived auxiliaries with a tethered thioether promoter Pericas and Riera developed new hemilabile (P,S) ligands named PuPHOS (**124**)[74] and CamPHOS (**126**)[75,76] which are generated from (+)-pulegone (**125**) and (+)-camphorsulfonic acid (**112**), respectively (Scheme 50). The authors assumed a coordination pathway, which is also depicted in Scheme 50. The incoming ligand preferably coordinates via P at the axial position. The phosphine then undergoes migration to the equatorial position yielding complex **127b**. Final replacement of an equatorial CO at the second cobalt atom should give bridged complex **127c**.



Scheme 50

4.4 Chiral Amine *N*-Oxides

Despite the progress in stereoselective Pauson–Khand reactions utilizing chiral auxiliaries or chiral P-ligands, introduction, removal and/or recycling of the auxiliary or ligand must be considered as major limitation. In a completely different approach the prochiral cobalt–alkyne complex **8** is desymmetrized by a chiral amine *N*-oxide which should lead to the preferred decarbonylation of either *Re* face or *Si* face ultimately resulting in the formation of one of the two enantiomeric cyclopentenones **128** (Scheme 51).

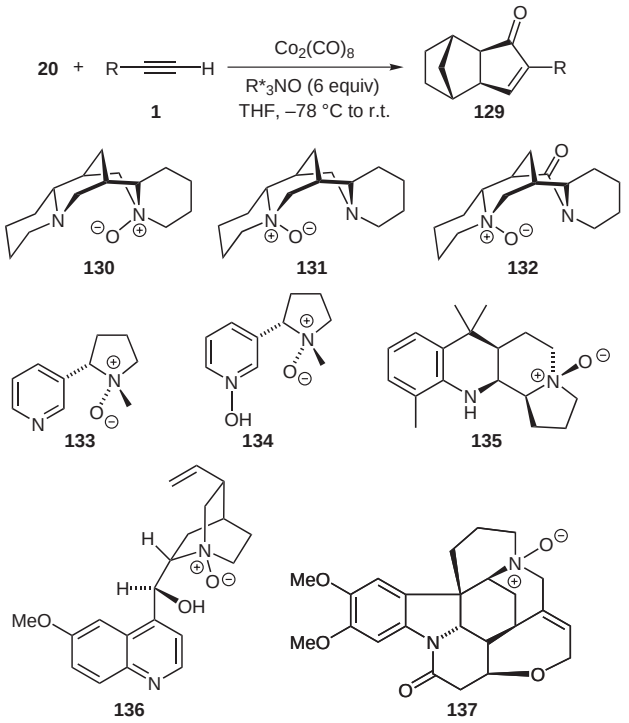


Scheme 51

In a seminal paper Kerr demonstrated for the first time that brucine *N*-oxide could be used for this purpose giving 72–78% ee for the reaction of (1,1-dimethyl-prop-2-ynol)$Co_2(CO)_6$ with norbornene (**20**).[77] Because nothing was known about the scope and limitation of Pauson–Khand reactions in the presence of chiral amine *N*-oxides, we investigated the intermolecular cocyclization of norbornene (**20**) with terminal alkynes **1** in the presence of various chiral amine *N*-oxides in more detail (Scheme 52).[78,79]

As shown in Table 1, (–)-sparteine *N*16-oxide (**130**), (+)-sparteine *N*1-oxide (**131**), (–)-17-oxosparteine *N*-oxide (**132**), (–)-nicotine *N*1-oxide (**133**) as well as (–)-nicotine *N*1,*N*1′-bisoxide (**134**) resulted only in low enantioselectivities (up to 16% ee) regardless of the alkyne. Remarkably, the enantioselectivities could be considerably improved up to 42% ee by using amine *N*-oxides with additional donor functionalities such as (–)-quinine *N*-oxide (**136**), the tetracyclic *N*-oxide (**135**) and (–)-brucine *N*-oxide (**137**).

Sterically hindered alkynes (e.g. **1f**) and alkynes with hydroxy groups (**1c**,**e**) gave higher enantioselectivities. Therefore, hydrogen bonding between the alkyne and the *N*-oxide seems to play an important role in controlling the enantioselectivity. In order to rationalize the stereochemical results, we assumed hydrogen bonding between the alkyne hydroxy group and the *N*-oxide preferably at the *Si*



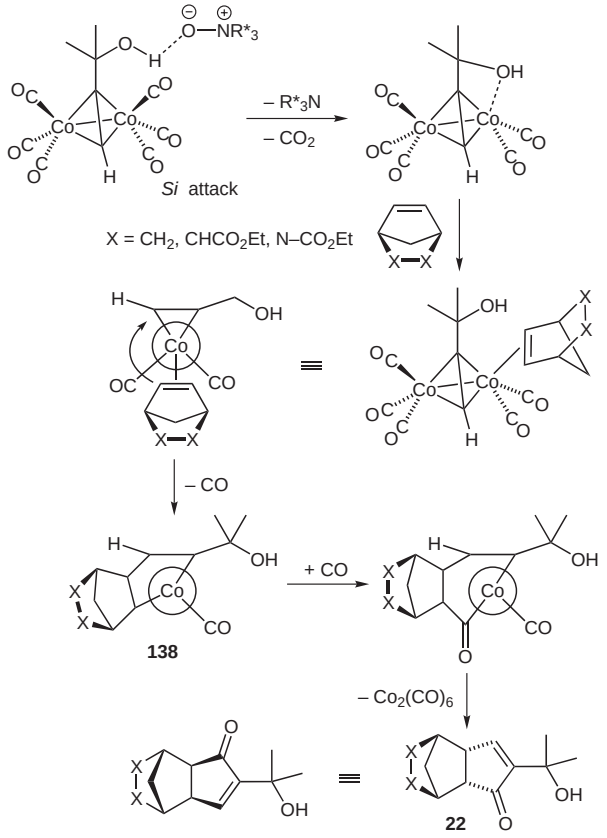
Scheme 52

face due to the steric bias provided by the amine *N*-oxide (Scheme 53).

The complex undergoes decarbonylation of the axial CO ligand assisted by the hydroxy group of the alkyne moiety acting as a labile ligand, which is replaced by norbornene, norbornene ester or aza-norbornenes. As can be seen from the Newman perspective insertion preferably takes place at the least hindered Co–C-bond, resulting in the formation of complex **138**, which undergoes CO insertion and decomplexation to give cyclopentenone **22**. Although this mechanistic proposal caused controverse discussions, DFT calculations by Gimbert, Milet and Greene strongly supported this suggested scheme.[44] Despite the modest enantioselectivities obtained with amine *N*-oxides, Nicholas[80] and Kerr[81] independently pushed the desymmetrization of cobalt–alkyne complexes with chiral amine *N*-oxides one step further. Remarkably, both enantiomers of cyclopentenone **22** could be received by using a single source of chirality. That means, while brucine *N*-oxide (**137**) resulted in decarbonylation at the *Si* face, subsequent alkene insertion should give enantiomer **22**. However, if PPh_3 is added to the mixture directly after decarbonylation, the empty coordination site is immediately occupied by PPh_3 and the opposite cobalt complex results. Further treatment with NMO leads to decarbonylation at the more reactive phosphine-free *Re* cobalt giving the opposite enantiomer *ent*-**22** after alkene insertion.

Table 1 Amine *N*-Oxide-Promoted Pauson–Khand Reaction of Various Terminal Alkynes **1**

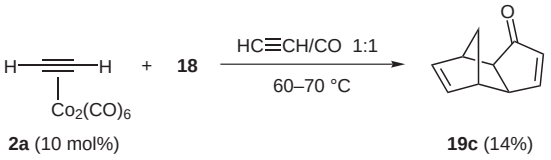
N-Oxide	Alkyne **1**	R	Product **129**	Yield (%)	ee (%)
130	**1n**	Pr	**a**	46	13
131	**1f**	*t*-Bu	**b**	62	12
132	**1b**	Ph	**c**	73	16
133	**1f**	*t*-Bu	**b**	47	10
134	**1f**	*t*-Bu	**b**	48	10
135	**1e**	CMe_2OH	**e**	57	18
	1f	*t*-Bu	**b**	37	33
	1n	Pr	**a**	42	12
136	**1n**	Pr	**a**	28	2
	1c	$(CH_2)_2OH$	**d**	68	30
137	**1e**	CMe_2OH	**e**	67	42
	1n	Pr	**a**	75	0



Scheme 53

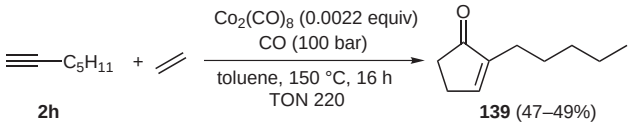
5 Catalysis

One of the earliest examples of catalytic intermolecular cocyclizations was developed by Pauson (Scheme 54).[82] While treating norbornadiene (**18**) with 10 mol% of (acetylene)$Co_2(CO)_6$ (**2a**) in the presence of acetylene and carbon monoxide at 60–70 °C the corresponding cyclopentenone **19c** was isolated in 14% yield.



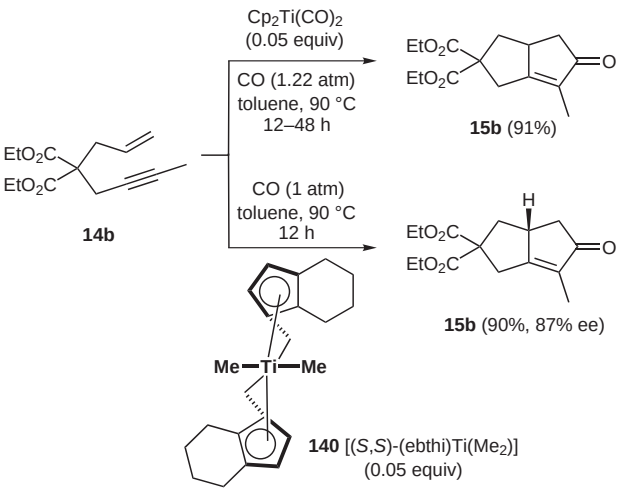
Scheme 54

Almost 20 years later a truly catalytic system was reported by Rautenstrauch (Scheme 55),[83] in which a TON of 220 for $Co_2(CO)_8$ was realized in the preparation of 2-pentylcyclopent-2-en-1-one (**139**) as a precursor for methyl dihydrojasmonate. Rautenstrauch proposed that the formation of cobalt clusters such as $Co_4(CO)_{12}$ might induce a shutdown of the catalytic cycle. Despite the high turnover the scope of this catalytic version was rather limited.



Scheme 55

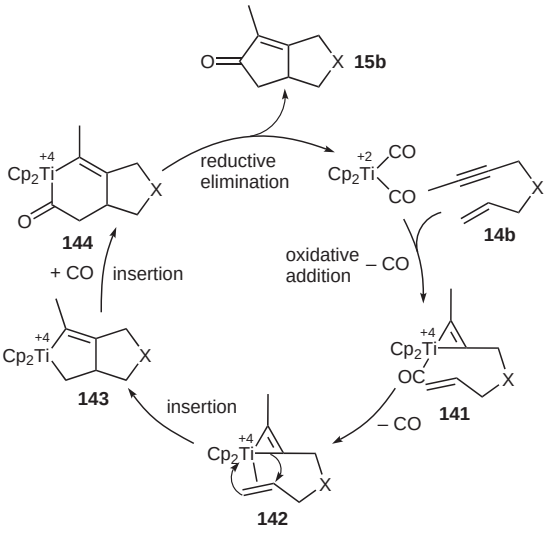
A remarkable breakthrough was achieved, when Buchwald demonstrated in 1996 that titanocene complexes are capable of catalyzing the intramolecular Pauson–Khand reaction of enynes such as **14b**.[84] Shortly after that Buchwald developed an enantioselective version by utilizing a chiral *ansa*-titanocene **140** (Scheme 56) which has previously been used for stereoselective Ziegler–Natta polymerization.[85,86]



Scheme 56

The following catalytic cycle was proposed (Scheme 57).[86] Oxidative addition of the enyne **14b** to the titanocene dicarbonyl complex which may be either directly used or in situ formed from titanocenedimethyl complex under CO pressure, gave the titanacyclopropene complex **141**. Decarbonylation to **142** followed by insertion of the alkene should give the titanocyclopentene complex **143**, which undergoes CO insertion and reductive elimination to yield the final cyclopentenone **15b**.

Unfortunately, chiral metallocenes were not amenable to catalytic intermolecular Pauson–Khand reactions. At this point further improvement in catalytic intramolecular reactions are reported continuously,[2b] while the intermolecular reactions are still lagging behind. Nevertheless, various attempts towards a catalytic intermolecular reaction have been performed, which can be categorized according to the metal, i.e. reactions employing i) cobalt, ii) ruthenium, iii) rhodium and iv) iridium.



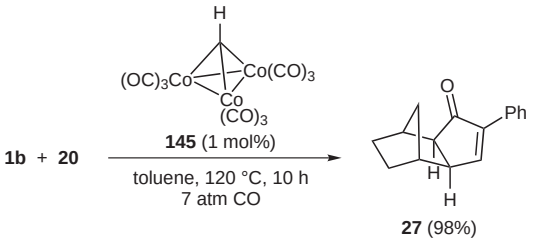
Scheme 57

5.1 Cobalt-Catalyzed Reactions

It should be noted that Livinghouse discovered a catalytic intramolecular version of the Pauson–Khand reaction employing $Co_2(CO)_8$ under ultrapure conditions.[87] In order to avoid the use of $Co_2(CO)_8$ which decomposes upon prolonged storage, Chung developed an in situ method, where the cobalt carbonyl is formed from $Co(acac)_2$ and $NaBH_4$ under CO pressure,[88] and by reacting norbornadiene (**18**) the desired cyclopentenone **19** was obtained almost quantitatively. A related substoichiometric system was described by Periasamy[89] utilizing $CoBr_2$ and Zn. Sugihara reported that methylidenetricobalt nonacarbonyl (**145**) catalyzed intra- and intermolecular Pauson–Khand reactions (Scheme 58).[90]

Even $Co_2(CO)_8$ can be used as a catalyst under suitable conditions. For example, Jeong used supercritical CO_2 as a solvent for catalytic Pauson–Khand reactions of norbornene (**20**) with terminal alkynes in the presence of 3 mol% of $Co_2(CO)_8$.[91] However, when employing ethylene instead of norbornene (**20**) these conditions gave less than 10% of the cyclopentenone.[92] Fortunately, by running the reaction of **1b** in supercritical ethylene in the presence of $Co_4(CO)_{11}[P(OPh)_3]$ or $Co_4(CO)_{12}$, 2-phenylcyclopentenone was obtained in good yield without any alkyne

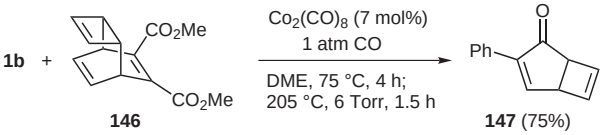
trimerization as the by-product. The results by Jeong also disproved Rautenstrauch's notion that $Co_4(CO)_{12}$ poisons the catalytic cycle.



Scheme 58

Both $Co_2(CO)_8$- and $Co_4(CO)_{12}$-catalyzed reactions are promoted by Lewis basic solvents (e.g. DMF, H_2O) or additives (e.g. cyclohexylamine, tributylphosphanesulfide) as was independently reported by Sugihara,[93] Krafft,[94] and Hashimoto.[95] Catalytic reactions were also possible by microwave irradiation according to results by Groth.[96,97]

Very recently, the cyclobutadiene equivalent **146** was successfully employed in catalytic cocyclizations by Gibson (Scheme 59).[98]



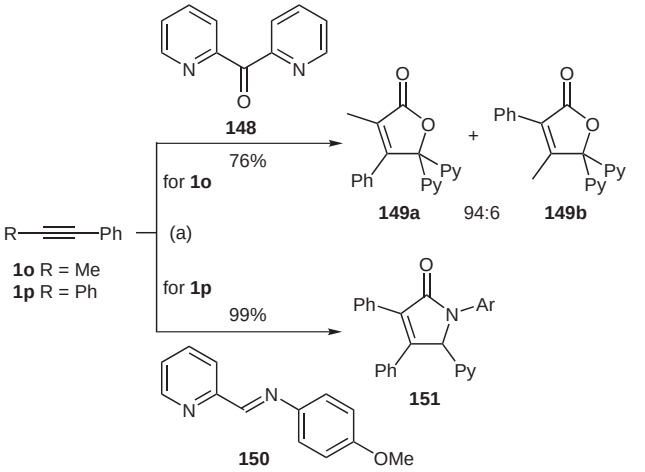
Scheme 59

When considering the decreased reactivity of cobalt–alkyne complexes bearing phosphine ligands, it was quite surprising that $(PPh_3)Co_2(CO)_7$ catalyzed the Pauson–Khand reaction without any problems.[99] Moreover, this monophosphine complex turned out to be much more stable than $Co_2(CO)_8$.

Hiroi studied catalytic reactions of phenylacetylene (**1b**) and norbornene (**20**) in the presence of $Co_2(CO)_8$ and chiral ligands such as (*S*)-BINAP, (*R*,*R*)-DIOP, (*S*,*R*)-BPPFOH and (*S*,*R*)-PPFA.[100] However, with neither ligand an enantiomeric excess exceeding 10% could be achieved. With regard to immobilization a very promising result was obtained by Chung.[101] Although the yields for intermolecular cocyclizations were much lower as compared to the corresponding intramolecular reactions, cobalt on mesoporous silica proved to be a suitable heterogeneous catalyst.

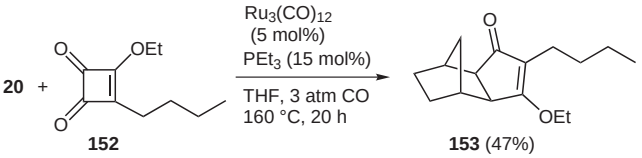
5.2 Ruthenium-Catalyzed Reactions

The use of Ru catalysts allowed access to unusual substrates. A hetero Pauson–Khand reaction was described by Murai.[102] Dipyridylketone **148** reacted with alkyne **1o** to give the (5*H*)-furanones **149a**,**b** (Scheme 60). The conversion of the corresponding imine **150** with alkyne **1p** afforded under similar conditions the unsaturated γ-lactam **151**.[103]



Scheme 60 *Reagents and conditions*: (a) $Ru_3(CO)_{12}$ (2.5 mol%), $P(4\text{-}CF_3C_6H_4)_3$ (7.5 mol%), 5 atm CO, toluene, 160 °C, 20 h

According to Mitsudo $Ru_3(CO)_{12}$ could also be employed in the catalytic cocondensation of squaric acid derivatives such as **152** and norbornene (**20**) to yield the cyclopentenone **153** as a single regioisomer (Scheme 61).[104]



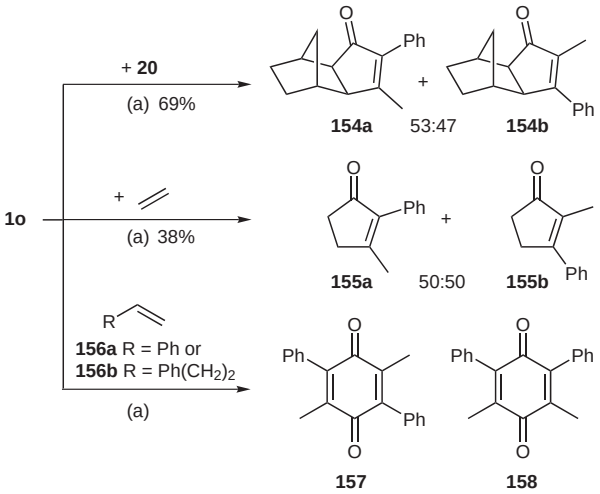
Scheme 61

Mitsudo also showed that alkynes could be replaced by allylic carbonates in intermolecular Pauson–Khand reactions catalyzed by $[RuCl_2(CO)_3]_2$ in the presence of Et_3N.[105]

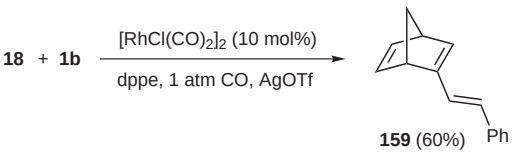
5.3 Rhodium-Catalyzed Reactions

With $[RhCl(CO)_2]_2$ as a catalyst, Narasaka was able to perform intramolecular Pauson–Khand reactions with excellent yields.[106] In contrast, yields for intermolecular reactions were much lower, and unstrained terminal alkenes **156a**,**b** only resulted in the formation of quinones **157** and **158** (Scheme 62).

In order to explore the scope of $[RhCl(CO)_2]_2$ in more detail, we studied intermolecular reactions of norbornadiene (**18**) and terminal alkynes such as phenylacetylene (**1b**). While the use of $[RhCl(CO)_2]_2$ alone did not give any conversion, the presence of the chelating diphosphine dppe and a Ag(I) salt resulted in the formation of the conjugated diene **159** accompanied by some polymeric by-products (Scheme 63). No trace of the desired cyclopentenone was found. Obviously the CO insertion step is somewhat



Scheme 62 *Reagents and conditions*: (a) $[RhCl(CO)_2]_2$ (5 mol%), 1 atm CO, Bu_2O, 130 °C, 60 h

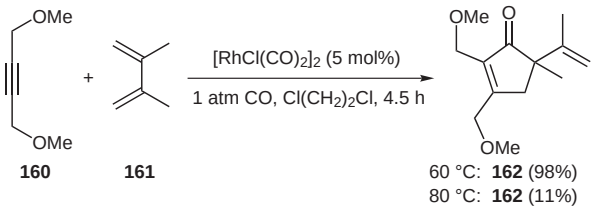


Scheme 63

blocked. Change of stoichiometry and CO pressure did not change the outcome of the reaction.

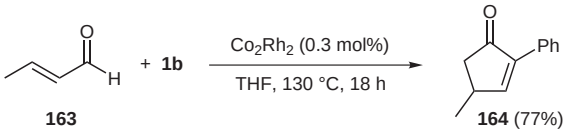
The different catalytic activity of Rh complexes in intra- versus intermolecular reactions was also noticed by Chung,[107] when treating norbornene (**20**) and phenylacetylene (**1b**) with entrapped $[Rh(COD)Cl]_2$. Only 6% of the desired cyclopentenone **27** could be isolated, whereas intramolecular reactions yielded 79–93% of the product.

Recently, Wender investigated Rh-catalyzed competing [2+2+1], [4+2], and [2+2+2] cycloadditions.[108] The product ratio turned out to be strongly temperature dependent. By simply decreasing the temperature from 80 °C to 60 °C the reaction of alkyne **160** and 2,3-dimethylbutadiene (**161**) gave 98% of the cyclopentenone **162** as compared to meager 11% at 80 °C (Scheme 64).



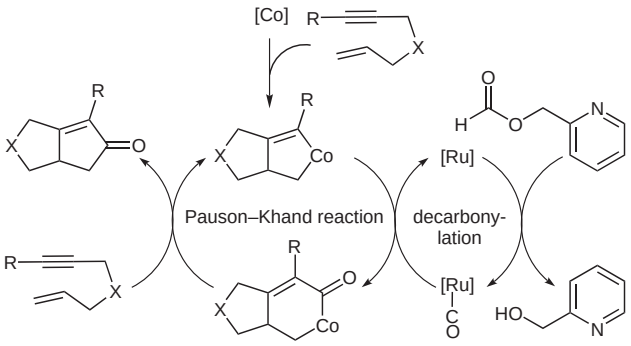
Scheme 64

A major limitation of the above-mentioned catalytic processes is the need of carbon monoxide. Chung elegantly addressed this problem by using an α,β-unsaturated aldehyde instead of an alkene and CO.[109] For this purpose heterobimetallic nanoparticles derived from $Co_2Rh_2(CO)_{12}$ were used as catalysts (Scheme 65). The nanoparticles could be recycled at least five times without any loss of activity. Surprisingly, this catalytic system was completely unreactive towards enynes.



Scheme 65

A further modification employing Ru/Co nanoparticles immobilized on charcoal and 2-pyridyl formate as a CO source allowed both inter- and intramolecular cocyclization in excellent yields.[110] For intermolecular reactions Chung proposed a mechanism involving a Co-catalyzed Pauson–Khand cycle coupled with a Ru-catalyzed decarbonylation cycle (Scheme 66).

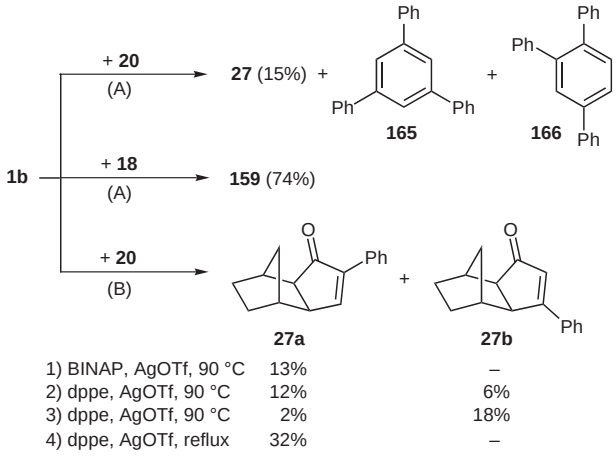


Scheme 66

5.4 Iridium-Catalyzed Reactions

Based on Shibata's promising results with Ir catalysts in intramolecular Pauson–Khand reactions[111] we investigated intermolecular Pauson–Khand reactions of alkyne **1b** and **1o** with norbornadiene (**18**) and norbornene (**20**). For example, the reaction of phenylpropyne (**1o**) and norbornene (**20**) in the presence of catalytic amounts of $[Ir(COD)Cl]_2$ and tol-BINAP in toluene under 1 atm CO gave only 0.3% of the cyclopentenone **154**. Mainly unreacted phenylpropyne was recovered after work up. When norbornadiene (**18**) was used instead, no conversion was observed.

As shown in Scheme 67, the situation changed when phenylacetylene (**1b**) was employed. The reaction of **1b** with **20** gave 15% of the cyclopentenone **27** together with the regioisomeric alkyne trimerization products **165**, **166** in 16% and 10% yield, respectively. Employing **18** under the same conditions, the conjugated diene **159** was isolated in 74% yield. Although Ir-catalyzed C–C coupling between alkyne and alkene is obviously much faster for norbornadiene (**18**) as compared to norbornene (**20**) and even the competing alkyne trimerization is completely suppressed,



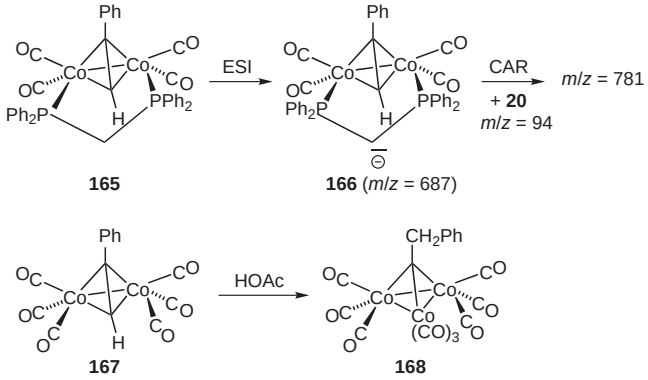
Scheme 67 *Reagents and conditions*: Method A: $[Ir(COD)Cl]_2$, BINAP, toluene, 1 atm CO, 110 °C, 12 h; Method B: $[Ir(COD)Cl]_2$, THF, 1 atm CO, 12 h

the final CO insertion is too slow. In order to improve the catalytic activity of the Ir catalyst, AgOTf was added to the reaction mixture.[112] In addition, the coordination properties of the solvent were improved by using THF instead of toluene. It turned out that the quality of the Ag(I) salt and the solvent was very critical. In the presence of BINAP and AgOTf the Ir-catalyzed reaction of phenylacetylene with norbornene (**20**) gave cyclopentenone **27a** in 13% as a single regioisomer. Use of dppe instead of BINAP gave a mixture of the regioisomers **27a** and **27b** in 18–20% overall yield. Upon lowering the reaction temperature from 90 °C to reflux the yield of cyclopentenone **27a** could be further improved to 32%. Unfortunately, the use of BINAP or tol-BINAP under these modified conditions did not give the desired cyclopentenone. Both Rh and Ir catalysts appeared to be not suitable to promote C–C coupling and CO insertion efficiently and thus, allow a full catalytic cycle for the intermolecular Pauson–Khand reaction.

6 Theoretical Studies and Some Mechanistic Curiosities

As discussed earlier the original mechanism for the stoichiometric Pauson–Khand reaction which was proposed by Magnus in 1985[3] was commonly accepted despite some disputes about the coordination mode of the alkene. Surprisingly, little theoretical and experimental mechanistic information existed until 2001 a very detailed DFT study by Nakamura appeared.[113] The results from DFT calculations clearly indicated, for example, that the initial CO loss is rather energy consuming and thus, irradiation[87,114] or promoters (Lewis bases, tethered donor ligands, etc.) acting as weak ligands enhance the rate of this step. It was also found that the alkene insertion step is the critical stereo- and regiochemistry determining step of the Pauson–Khand reaction. Another result was that migratory insertion of CO at the alkene terminus is energetically favored over competing/alternative pathways. The most important mechanistic finding was that, while the bond-forming events occur only on one metal atom, the other metal atom acts as an anchor and also exerts electronic influences on the other through the metal–metal bond.

Shortly after that, theoretical studies by Milet, Gimbert and Greene[44,45] emphasized the importance of the *trans*-effect in govering the regioselectivity. Koch and Schmalz investigated the configurational stabilities of cationic, radical and anionic $Co_2(CO)_6$ complexed propargylic species by DFT and found a surprisingly high racemization barrier for the anionic intermediate.[115] However, experimental evidence was still sparse until Gimbert, Greene and Milet[116] were able to detect the decarbonylated intermediate **166** by tandem mass spectrometry using negative ion electrospray ionization. Subsequent collision-activated reaction (CAR) with norbornene (**20**) yielded a molecular ion with *m*/*z* = 781, i.e. the corresponding alkene complex (Scheme 68). Complementary DFT calculations revealed the chronology of the early events of the Pauson–Khand reaction in the gas phase. The results perfectly support Nakamura's calculations and the original Magnus mechanism.

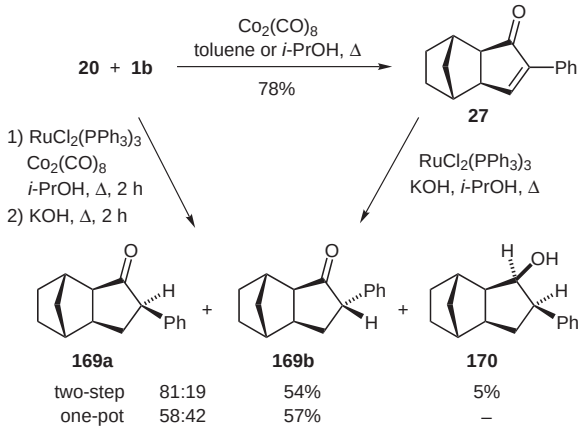


Scheme 68

Another combined theoretical and experimental mechanistic study by McGlinchey dealt with the acid-catalyzed rearrangement of cobalt–alkyne complexes such as **167** to alkylidene nonacarbonyl tricobalt clusters **168** (Scheme 68).[117]

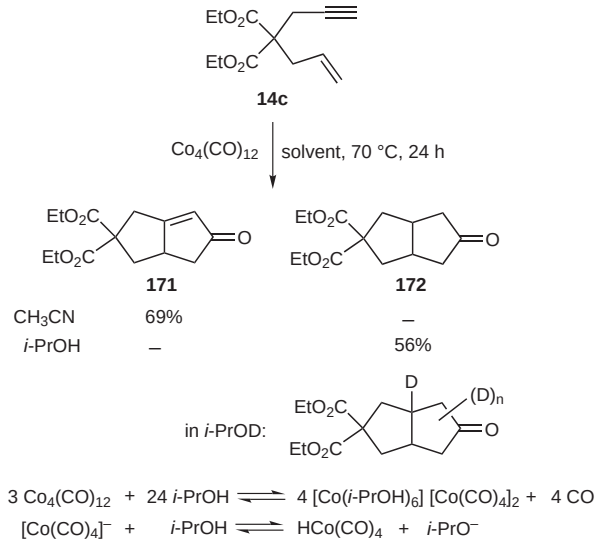
While tandem catalysis employing intramolecular Pauson–Khand reactions has been recently explored in several cases,[118] only little information was known about intermolecular tandem processes. Towards this goal we investigated the sequential Pauson–Khand reaction/transfer hydrogenation outlined in Scheme 69. We anticipated that the transfer hydrogenation with $RuCl_2(PPh_3)_3$ should be compatible with the preceeding Pauson–Khand reaction conditions.[119] While the two-step process yielded 54% of the diastereomeric ketones **169a**,**b** (dr 81:19) together with 5% of the saturated alcohol **170**, the corresponding one-pot reaction was only successful when the base KOH was added after a certain induction period of 2

hours. Monitoring by GC indicated clean conversion to the cyclopentenone **27** within two hours. Subsequent addition of KOH resulted in the formation of diastereomeric ketone **169a**,**b** (dr 58:42) in 57%. The results indicated that in accordance with observations by Sasson[120] and Wilkinson[121] $Ru(H)Cl(PPh_3)_3$ as the major active species preferably adds to the C=C bond rather than to the ketone.



Scheme 69

In contrast, the outcome of this sequential reaction might be also due to an intermediate cobalt hydride species, which is acting as a reducing agent. In the intramolecular Pauson–Khand reactions of enyne **14c** in the presence of $Co_4(CO)_{12}$ Krafft isolated in acetonitrile the desired bicyclic enone **171** in 69% yield.[122] However, in *i*-PrOH only the saturated ketone **172** was obtained in 56% (Scheme 70). Deuterium-labeling experiments demonstrate that a hydridocobalt species was involved and that the hydride comes from the solvent isopropanol.



Scheme 70

7 Conclusions

During the last couple of years the intermolecular Pauson–Khand reaction has seen tremendous achievements concerning reactivity, novel substrates, regio- and stereoselectivity. In particular, theoretical studies using DFT methods have provided very detailed insight into the mechanism, which not long ago appeared more or less like a black box. However, one of the most urgent problems, i.e. a catalytic and hopefully enantioselective version has not yet been solved to fully satisfy synthetic chemist requirements. From the preliminary results it seems that cobalt–carbonyl complexes are still much better suited to promote both C–C coupling of alkyne and alkene, and CO insertion as compared to other transition metal catalysts. But maybe we and others have not yet looked carefully enough. So, there is still plenty of work to do in the future.

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