The fascinating construction of pyridine ring systems by transition metal-catalysed [2 + 2 + 2] cycloaddition reactions

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Cycloaddition reactions compose one of the most important classes of reactions when it comes to the simultaneous formation of several bonds in one reaction step. The *de novo* construction of carbocyclic aromatic systems from acetylenes was also found as an excellent possibility for the assembly of heteroaromatic systems. The transition metal-catalysed [2 + 2 + 2] cycloaddition reaction constitutes a fascinating tool for the synthesis of pyridines from nitriles and the most recent developments demonstrate the ability to control the substitution pattern as well as the possibility of introducing chirality by the use of achiral substrates and a chiral catalyst under mild conditions.

In this *tutorial review* we are focusing on the *de novo* construction of pyridine ring systems by the transition metal-catalysed [2 + 2 + 2] cycloaddition reaction. After surveying the mechanistic features and intermediates of the reaction depending on the different metal complexes used, we depict the preparation of achiral pyridine derivatives. The last section describes the advances in the synthesis of chiral pyridines and biaryls using the cyclotrimerisation method. The various possibilities of introducing chirality by catalytic means are presented and illustrated by instructive examples.

This review will be of interest for people active in: Organic Chemistry, Organometallic Chemistry, Transition Metal Chemistry, Stereoselective Synthesis, Heterocyclic Chemistry

1 Introduction

In the area of synthetic organic chemistry, the evolution of newly found reactions into practical and broad instruments for the synthetic chemist's toolbox, often requires a certain span of time. This statement is also true for transition metal-catalysed cyclotrimerisation reactions, beginning with the discovery of Reppe's trimerisation of acetylenes to yield benzene nearly 60 years ago.[1] Nowadays, the [2 + 2 + 2] cycloaddition reaction of alkynes, diynes and oligoynes has become an established tool for the construction of highly functionalised carbo- and heterocycles.

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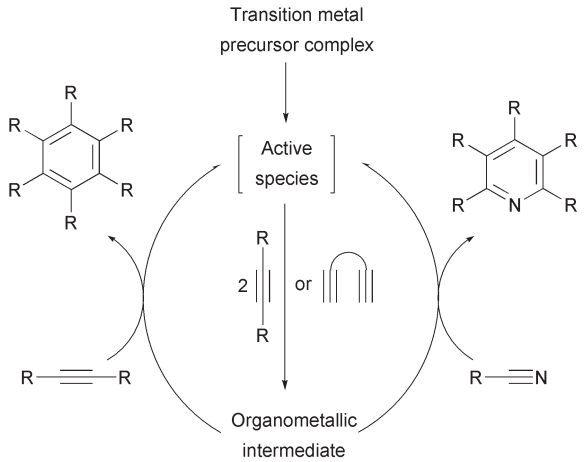
The research performed from the initial observations has uncovered many basic features of the transition metal-catalysed cycloaddition process, leading to a deepened understanding of mechanistic details, outcome of the reaction in terms of regio- and stereoselectivity and tolerance of functional groups. Today the [2 + 2 + 2] cycloaddition reaction belongs to the group of strategic reactions, essential in the total synthesis of complex molecules because they give the ability to perform a number of bond connections in only one step thus increasing the complexity of the target molecule significantly.[2] Moreover due to the aromatic nature of the products, the *de novo* synthesis of substituted arene systems establishes an access that has found broad interest recently as an exciting alternative for, *e.g.* often multi-step electrophilic and nucleophilic substitution sequences.

The [2 + 2 + 2] cycloaddition reactions in intermolecular as well as intramolecular fashion have been recently covered in several reviews, which detail the advantages of the different transition metal catalysts, possible substrates, products and regioselectivity issues.[3–9] The synthesis of pyridines, as one of the most important classes of heterocyclic aromatic compounds, by this method has already been explored by several groups and results have been discussed in detail in recent reviews by Varela and Saá, and by Henry.[10,11] In this review, we will focus on recent developments in the synthesis of pyridines by transition metal-catalysed [2 + 2 + 2] cycloaddition reactions, paying special attention to the discussion of mechanistic details and the synthetic access to chiral derivatives.

2 Mechanistic features of the [2 + 2 + 2] cycloaddition reaction

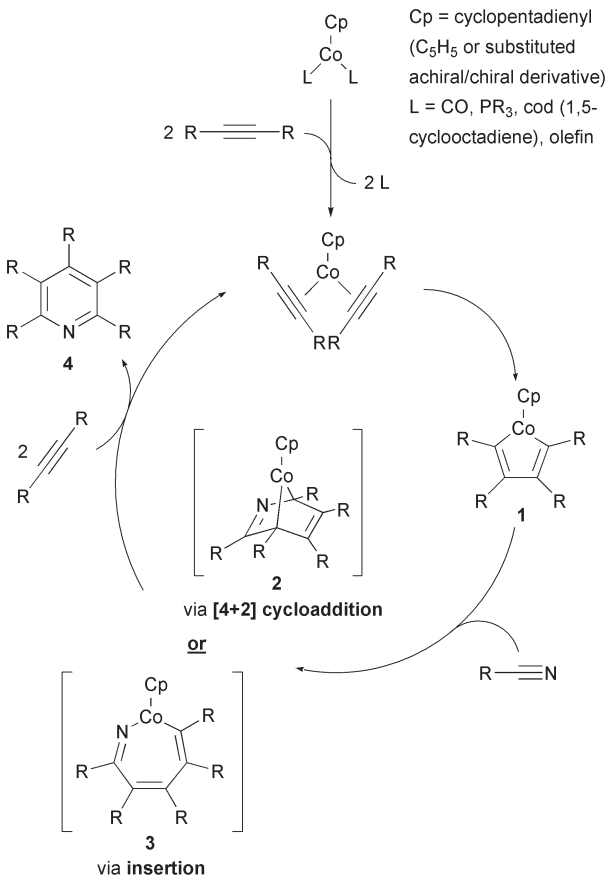
A number of different metal complexes derived from the whole range of transition metals can be used for the catalysis of cycloaddition reactions, varying in reactivity and different functional group tolerance. Interestingly, the mechanisms for the catalytic systems of the often used metals (cobalt, rhodium, ruthenium, nickel, zirconium) were proposed to have some common features. A general overview of the catalytic cycle is shown in Scheme 1.

The first step generates the reactive species from stable precursor molecules, which reacts with the substrate acetylenes or diynes in the next step under coordination. The most accepted mechanistic picture (also referred to in the literature as ''common mechanism'') then implements the oxidative coupling of the coordinated alkynes or diynes to yield the metallacyclopentadienes.[10,12] In the final step, these unsaturated metallacycles react with another triple bond from an acetylene or nitrile molecule in an insertion or cycloaddition reaction, followed by elimination from the metal center to furnish the final products, either benzene derivatives or pyridines. Beside these concerted reactions a few different mechanisms have been postulated such as the ''Sequential Insertion Route'' or the ''Metathesis Cascade Route'', albeit the ''Metallacycle Route'' described above is corroborated by the isolation of various metallacyclopentadiene complexes and their independent reactions with alkynes.[12]



Scheme 1 General overview of the mechanistic cycle of the [2 + 2 + 2] cycloaddition reaction of alkynes.

The mechanism of Co-catalysed cycloaddition reactions has been investigated during the last decades in great detail and the structural evidence of intermediates[13] as well as some computational work have thoroughly established the mechanistic conceivabilities, making it the standard model for the ''common mechanism'' (Scheme 2).

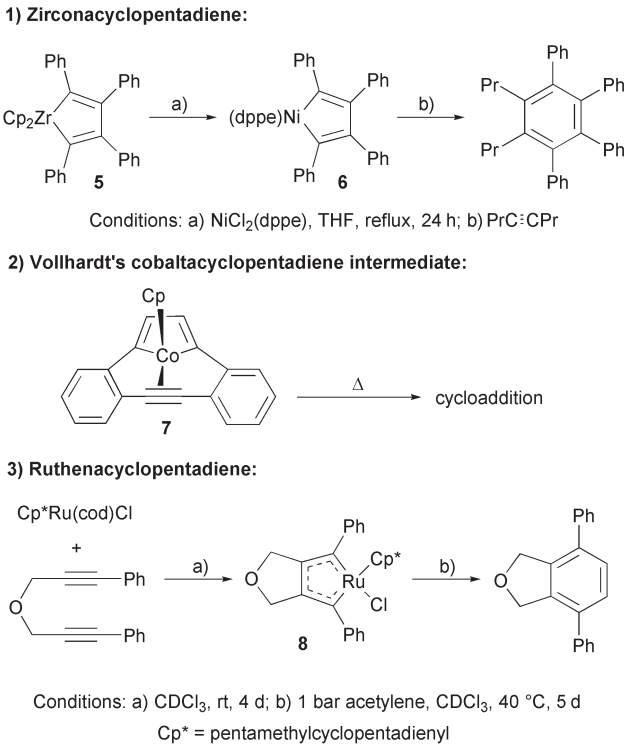


Scheme 2 Mechanism of the cobalt-catalysed pyridine synthesis from alkynes and nitriles.

Most of the investigations treat the pathway of pure carbocyclic product formation, but for the mechanism of pyridine formation it is reasonable to assume the same intermediates. In the latter case the metallacycle formation gave Co(III), which coordinates the nitriles lone-electron pair much more easily than the initial Co(I) species, leading to the preferred formation of pyridines. One advantage is the fact that the nitrile cyclotrimerisation is generally less favored in metal-catalysed reactions compared to the alkyne cyclotrimerisation.[10] The mechanism features the generation of the active cobalt species by displacement of dummy ligands with alkynes and the oxidative coupling to yield cobaltacyclopentadiene **1**. Coordination of the nitrile is followed by its incorporation into the metallacycle either by a [4 + 2] cycloaddition (**2**) or an insertion process (**3**). Finally the pyridinic product (**4**) is set free under aromatisation and regeneration of the catalyst species. Obviously, the mechanism can be influenced by the ability of the catalyst to make the ''right'' choice between the substrates during the cycle and therefore the nature of the cobalt catalyst species plays a crucial role for the success of the synthesis. The CpCo fragment (Cp = cyclopentadienyl) is the most often used catalytically active metal center, introduced into the reaction with a large number of dummy ligands like CO, phosphanes or olefins. Modifications of the Cp ring by different substituents have introduced new properties such as solubility in polar solvents (to perform the pyridine synthesis in water–ethanol mixtures), and the ability to introduce chirality into the catalyst backbone, that will give the possibility of stereoselection during the cycloaddition process, as we will discuss later.

While the advanced intermediates **2** and **3** are still subject to discussion and computational work, the nature of the metallacyclopentadienes (**1**) is established by sound experimental evidence. A wealth of these species have been isolated, as often stable compounds and their relevance as intermediates in the cycloaddition process been confirmed by subsequent reactions of the pure compounds with alkynes or nitriles. Moreover, while the outcome of the reaction is the same, the metal center in the metallacycle plays a striking role. Different examples for isolated intermediates from the same kind as **1** illustrate this fact (Scheme 3).

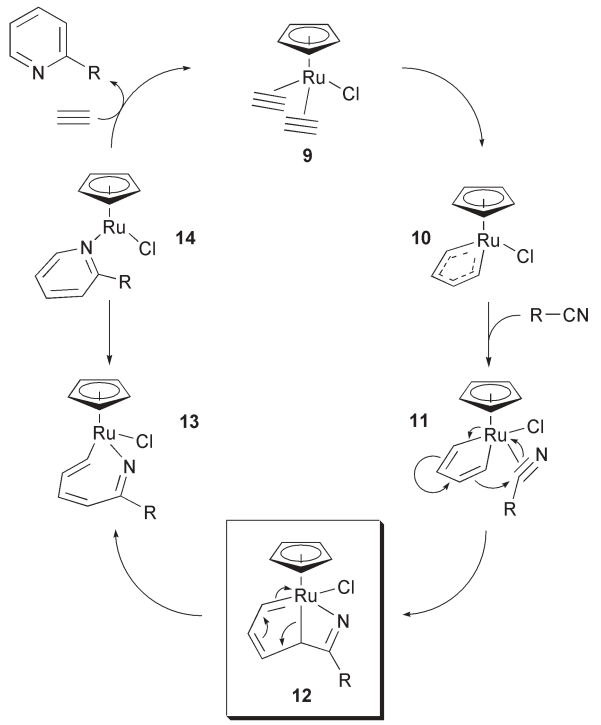
First, is the zirconacyclopentadiene **5**, which upon treatment with an alkyne under Ni catalysis forms a benzene derivative.[14] The metallacycle **5** does not undergo this reaction easily without the presence of late transition metal catalysts. Therefore, transmetalation to nickel, yielding the nickelacycle **6** was proposed as a first step in the formation of the aromatic products. Independent studies have confirmed the formation of nickelacycles by reactions of the isolated compounds.[15] Vollhardt *et al.* have been able to synthesise the intermediate **7** of the cobalt-catalysed alkyne trimerisation process, that yielded the cycloaddition product after thermal treatment. They used a substrate molecule, that contained three triple bonds to facilitate the formation of **7** under very moderate conditions.[13] The third example comes out of the vast area of ruthenacyclic chemistry.[16] Complex **8** was easily prepared from the corresponding diyne and could react with added acetylene to yield the appropriate benzene derivative.



Scheme 3 Isolated metallacyclopentadiene complexes as intermediates of [2 + 2 + 2] cycloaddition type reactions.

However, this last cycloaddition sequence is nicely suited as a showcase for the twists and turns that come along with mechanistic considerations in this kind of cycloaddition reaction, especially when considering ruthenium-catalysed processes for pyridine synthesis. A good example is the recently published investigation of ruthenium-catalysed cycloaddition reactions of 1,6-diynes and nitriles by Yamamoto *et al.*[17] and the theoretical analysis by Kirchner *et al.*[18]

They elucidated the role of the nitrile substrate in terms of its coordinating ability during the catalytic cycle and performed experiments that excluded azaruthenacyclopentadienes from being intermediates in these reactions (which is true also for Co but different from Zr). While cationic ruthenium complexes are ineffective for alkyne trimerisation, due to formation of stable Ru arene complexes, they yield the pyridine products when using nitrile as a component of the cyclisation reaction. A key intermediate in their mechanistic considerations is an azaruthenabicycle, that is cleaved to give the pyridine product. An overall mechanistic picture of the catalytic cycle is presented in Scheme 4. The initiation is followed by the reaction of the ruthenium starting complex with acetylenes or diynes and results in formation of the complex **9**. The next step is considered to be the rate-determining step of the overall exothermic cycle in which the oxidative coupling of the two alkynes occurs to yield a ruthenacyclopentatriene **10**.[19] Coordination of a nitrile substrate molecule leads to the formation of ruthenacyclopentadiene molecule **11**, here shown in the most likely η^2-arrangement. Although the η^1-coordination end-on to the



Scheme 4 Mechanism of the ruthenium-catalysed synthesis of pyridines.

nitrogen of the nitrile is a more likely coordination mode, it is not considered essential in this mechanism. Intermediate **11** then reacts to give the azaruthenabicycloheptatriene **12**, which is a central intermediate in the Ru-catalysed cyclotrimerisation chemistry.[19] The importance of intermediate **12** has been uncovered only recently by calculations and a synthesised and isolated structurally analogous iridacycloheptatriene supports the structure of the proposed theoretical intermediate.[20] Bond scission between the ruthenium and the bridging carbon of the bicycle resulted in the formation of the azaruthenacycloheptatriene **13**. The following step is highly exothermic because an aromatic pyridine ring is formed. The pyridine coordinates the ruthenium (complex **14**), which is then displaced by the alkyne substrate, regenerating the catalyst back into the catalytic cycle.

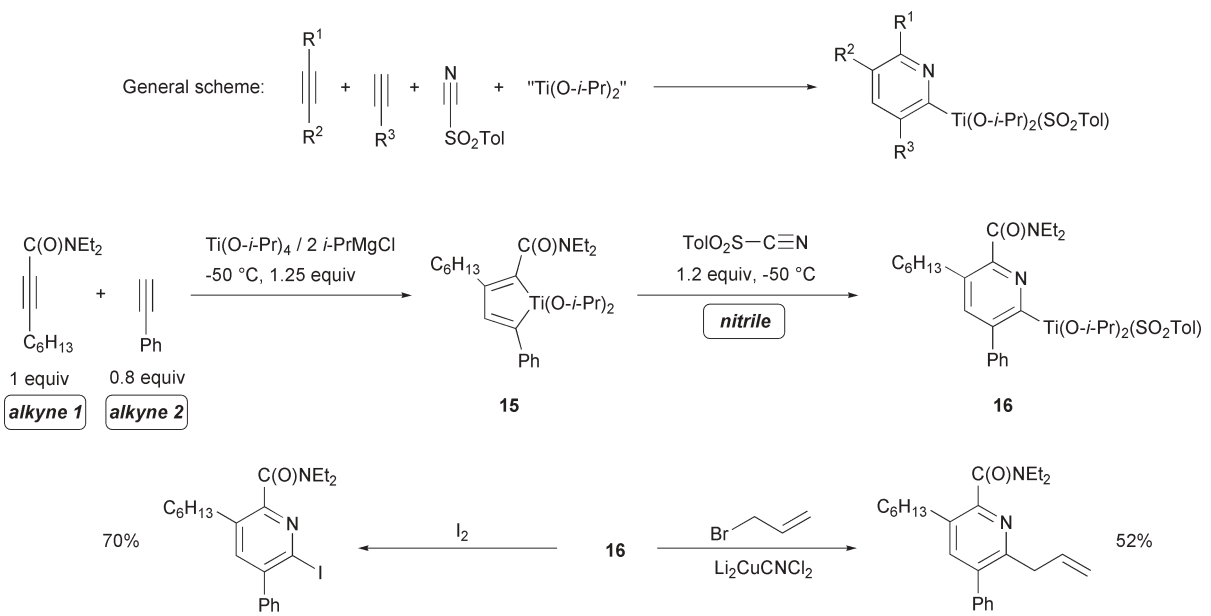
Along with the mechanistically puzzling catalytic cycles come regioselectivity issues. The easiest way for a predictable substitution pattern is the linkage of two or all three of the starting alkynes, either by a permanent or a temporary linker. For pure intermolecular reactions the outcome is more difficult to predict, but in the case of pyridines a certain amount of predictability is introduced by the nitrile, as we will see in the following sections.

3 Synthesis of non-chiral pyridine derivatives *via* [2 + 2 + 2] cycloadditions

The synthesis of mostly achiral pyridines by transition metal [2 + 2 + 2] cycloaddition reactions was extensively reviewed in 2003 by Saá and Varela, showing the complete range of transition metal complexes employed.[10] During the past few years further interesting developments have taken place, broadening the scope of the method.

Sato and Urabe reported on the modification of their method for the preparation of pyridines *via* titanacycles into an one-pot procedure, using different alkynes and nitriles.[21] Although not catalytic, the use of two different alkynes and a nitrile to assemble a pyridine core in a highly selective manner is still a challenging task to perform (Scheme 5).

The divalent titanium reagent is prepared *in situ* from Ti(O-*i*-Pr)$_4$ and a Grignard reagent and is then reacted with *alkyne 1* and *alkyne 2* at low temperature, yielding the titanacyclopentadiene intermediate **15**. This titanacycle is treated *in situ* with the *nitrile* to give titanated pyridine **16**. The order of addition

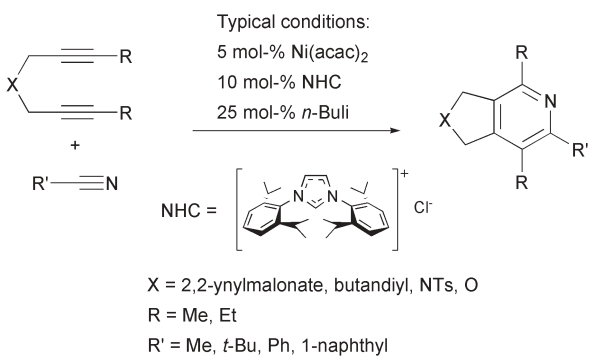


Scheme 5 Intermolecular titanium-mediated synthesis of metalated pyridines from two different alkynes.

of acetylenes and nitriles to the titanium reagent can be used to control the substitution pattern, dividing the reactions in four different types according to the resulting products. The resulting metallated species **16** can be easily subjected to further transformations, by quenching reaction with electrophiles like *e.g.* iodine, Michael-acceptor substrates and allylbromides, using a cuprate to facilitate the latter transformation (Scheme 5).

Albeit nickel complexes have found wide application in cyclisation reactions,[22] they have not been used in [2 + 2 + 2] cycloaddition reactions for the preparation of pyridines as single catalysts, but in combination with zirconium reagents (see Scheme 3). This combination features also the possibility of selectively performing the coupling of two different alkynes as already discussed with titanium above. However, the reaction still requires two steps: a) formation of the azazirconacyclopentadiene and b) transmetalation to nickel and cycloaddition with the second alkyne to yield the pyridine. Louie *et al.* recently reported a method that overcame this limitation and relies on a single nickel catalyst under very mild conditions (Scheme 6).[23] The key to success was the use of a N-heterocyclic carbene (NHC) ligand together with a nickel salt or precursor complex. While in a preceeding paper they used a combination of $Ni(cod)_2$ and free NHC ligand, a more user-friendly version was developed, consisting of $Ni(acac)_2$ and an imidazolium salt, from which the active catalyst was generated *in situ* by adding *n*-butyllithium as a base. This approach turned out to be very effective when using a diyne for the coupling reaction, although one example is reported, where untethered alkynes were successfully employed.

During the last couple of years ruthenium-catalysed [2 + 2 + 2] cycloadditions came to the fore and broadened the scope for the synthesis of pyridines. The groups of Saá and Yamamoto have performed extensive synthetic and mechanistic studies in this developing field. Moreover, Yamamoto and coworkers introduced methodology, developed for carbocyclic systems, which have the potential for application in the pyridinic systems, for example in the deployment of a temporary boron tether for the intermolecular coupling of three unsymmetrical alkynes.[24] This linker is not only useful for the achievement of selectivity but also enables further reactivity of the aromatic target molecule, which can subsequently be used for the introduction of further groups by cross-coupling methodology, Hayashi–Miyaura-type Michael additions or oxidation reactions.



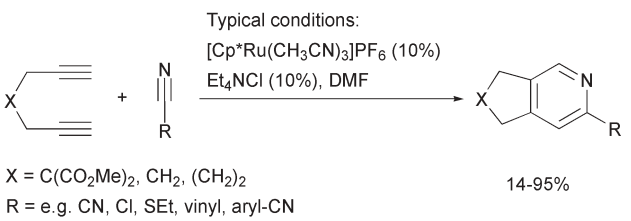
Scheme 6 Ni-carbene complex-catalysed synthesis of pyridines.

Overall, two different catalyst precursors have been used for the Ru-catalysed cycloaddition reactions. While Yamamoto *et al.* employed Cp*Ru(cod)Cl as the catalyst of choice, Saá *et al.* used a cationic complex, $[Cp^*Ru(CH_3CN)_3]PF_6$, for their studies. Both were focusing on the application of electron-deficient nitriles, which marks a significant difference to the cobalt-catalysed reactions, in which electron-neutral or more electron-rich nitriles have been applied. Also, the tolerance and possible steric and stereoelectronic effects were investigated leading to some surprising results. However, for the alkyne substrates they both have used symmetrical 1,6-diynes, which in most cases led to single cycloaddition products. In addition to the improved selectivity, the use of diynes, in general, facilitates the reaction because of a favorable entropy term compared to the completely intermolecular reaction with three alkynes.

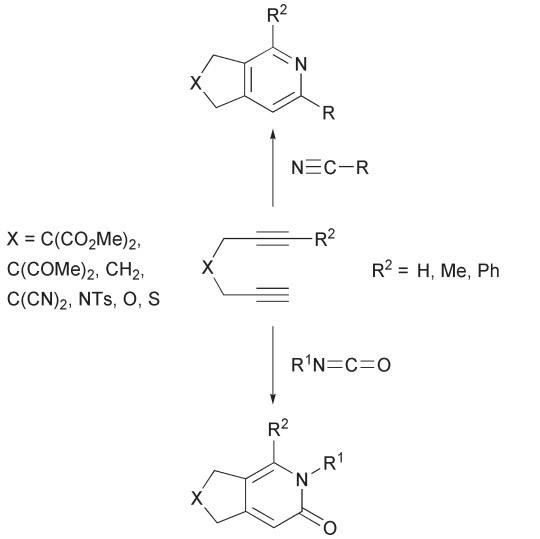
Saá *et al.* investigated the scope of the Ru-catalysed synthesis of pyridines using a broad range of mononitriles and dinitriles.[25] They found that no, or in certain cases, little to moderate yields in pyridine products were obtained in the reactions of a diyne with different mononitriles (Scheme 7).

On the other hand, dinitriles gave good to very good yields of the resulting cyanopyridines, without reacting the second nitrile group. This unusual result was explained by the assumption that the catalyst $[Cp^*Ru(CH_3CN)_3]PF_6$ dimerises under the reaction conditions to $[Cp^*Ru(CH_3CN)Cl]_2$, which can be split into monomers by the dicyanides. The catalytic system was applied to the complete intermolecular [2 + 2 + 2] co-cyclisation of two different alkynes and a nitrile and yields up to 89% could be obtained when methyl propiolate was reacted with electron-deficient nitriles.

The most thorough investigations on Ru-catalysed [2 + 2 + 2] cycloadditions of 1,6-diynes and nitriles have been performed by the Yamamoto group.[17,26,27] In their investigations they reacted different 1,6-diynes with electron-deficient carbon-heteroatom multiple bonds such as nitriles, isocyanates and isothiocyanates, the latter yielding substituted pyridones and thiacycles.[27] However, the focus of their work was on the synthesis of achiral pyridines and the mechanism of the reaction, which they elucidated with computational methods, supported by some experimental evidence. In the synthetic investigations the regioselectivity issue became especially interesting, when the diynes were differently substituted at the alkyne parts as well as at the connection between both triple bonds. The reactions were performed in 1,2-dichloroethane at 60–90 °C, normally with 5 mol% Cp*Ru(cod)Cl as catalyst, giving pyridines and pyridones in good to excellent yields and also good selectivity (Scheme 8).[17]



Scheme 7 Synthesis of bicyclic pyridines after Saá *et al.*

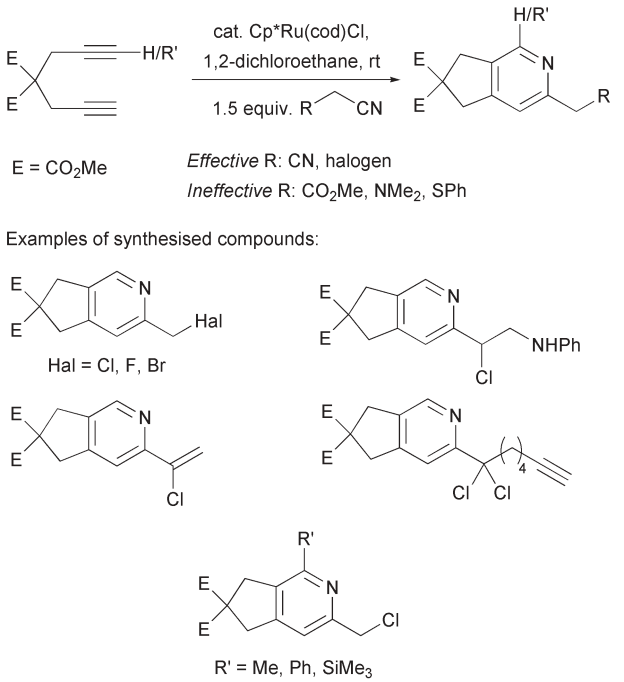


Reaction conditions: cat. Cp*Ru(cod)Cl, 1,2-dichloroethane, 60-90 °C

N≡C–R : R = CO_2Et, COPh, CO-2-furyl, COMe, Ts, CCl_3, C_6F_5

R^1N=C=O : R^1 = Ph, 1-naphthyl, 2-furyl, Bn, Pr, Cy

Scheme 8 Synthesis of pyridines and pyridones.



Scheme 9 Synthesis of pyridines from α-haloalkylnitriles.

They have also found an unprecedented halide effect in the Cp*RuCl-catalysed reaction of diynes with α-halonitriles, which depends on the position of the halide with respect to the cyano group.[26] The mechanistic picture is not clear yet, but the ability of the halonitrile to act as a bidentate ligand with both halide and cyano group coordinating to a cationic ruthenacyclic intermediate was proposed. These reactions can be performed under mild conditions at room-temperature significantly within 24 h, yielding haloalkylpyridines, that are useful building blocks for substituted pyridines and potential herbicides.

In the most recent paper on that topic, Yamamoto *et al.* expanded the scope of the nitriles, using dinitriles and nitriles, which incorporate electron-deficient and electron-rich substituents as well as further unsaturation (*e.g.* alkylidene, alkyne) and heteroatomic (*e.g.* amine) groups (Scheme 9).[27] Comparable to the results of Saá *et al.* in the cycloaddition reaction with dicyanides only one nitrile group reacted, leaving the other one unchanged. Most of the reactions could also be performed at room temperature and within reasonable reaction times, giving excellent yields. The screening of a rather large number of different nitrile compounds gave insight into the importance of certain structural features required for the successful cycloaddition reaction. The high reactivity of the dinitriles was thus linked to the donor ability of the carbon–nitrogen bond rather than the nitrogen lone pair, presumably in the activation of the catalyst. Other applications explored were the preparation of fully substituted pyridines and the synthesis of *C*-pyridyl-glycosides.

Despite the advances of the above mentioned transition metals new accomplishments using cobalt complexes have been reported. Maryanoff *et al.* synthesised a series of pyridine-containing macrocycles like *meta*- and *para*-pyridinophanes, and optimised their reaction conditions in terms of optimal selectivity and flexibility of the approach.[28] Two further interesting approaches combining the [2 + 2 + 2] cycloaddition reaction with other synthetic techniques are worth mentioning. Brändli and Ward applied the cobalt-catalysed cycloaddition of alkynes and nitriles to solution-phase combinatorial synthesis, yielding a small library of pyridines.[29] Yet another approach is the solid phase-supported cross-cyclotrimerisation, developed by Deiters *et al.*[30] They circumvented chemoselectivity issues by linking one alkyne to the polystyrene resin, and reacting with the second alkyne and the nitrile under cobalt catalysis. After work-up and cleavage under mild conditions a mixture of regioisomers of the desired pyridine was obtained. This method could also be used for rapidly assembling small pyridine derivative libraries.

4 Synthesis of chiral pyridine derivatives *via* [2 + 2 + 2] cycloadditions

Chiral pyridines have been established as an important class of chiral building blocks not only in natural products but also in asymmetric synthesis. The stereogenic center is most often attached to the pyridine core, but in recent decades atropisomers play an increasingly important role, especially in stereoselective catalysis, in which the pyridine itself is part of the stereogenic element. The general strategies and concepts of atroposelective synthesis of axially chiral compounds have been recently covered by an excellent overview of Bringmann and Breuning *et al.*[31]

Apart from diastereoselective methods and those involving an optical resolution stage, there are only few direct catalytic asymmetric approaches to non-racemic axially chiral biaryls. The most popular examples are known from asymmetric cross-coupling reactions of Grignard reagents or aryl boronic acids with aryl halides or triflates as well as oxidative coupling

reactions.[32] However, the synthesis of chiral biaryls normally requires the substituted aryls, because the atropisomers must be stable against the reaction conditions, that is, the rotation barrier needs to be high enough, so that racemisation cannot occur. The possibility of a *de novo* synthesis using a cycloaddition of arylpropiolates with gaseous acetylene in the presence of a nickel(0)/triphenylphosphane catalyst was first realised by Mori and co-workers, who synthesised a racemic biaryl in one elegant step.[33] This reaction was recently taken to the next stage by introducing stereoselectivity, thus giving access to biaryls with a defined stereochemistry.

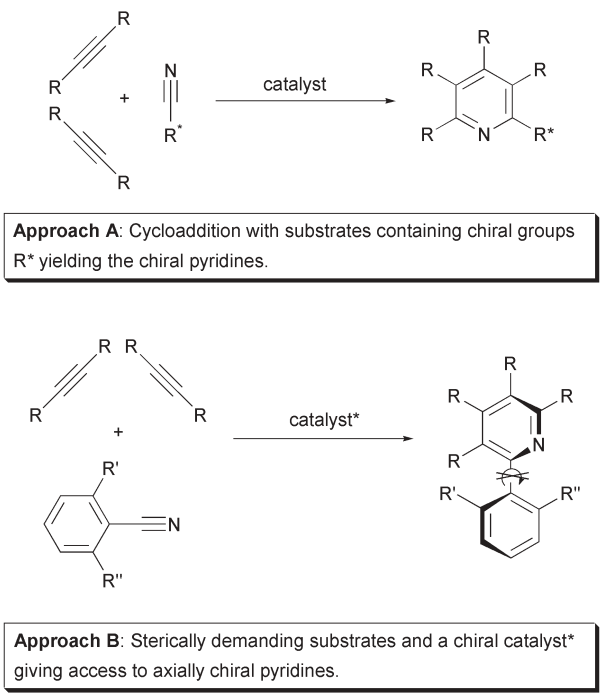
The synthetic approach to chiral pyridines by [2 + 2 + 2] cycloaddition reactions can be divided into two routes: A) acetylenes or nitriles bearing a chiral group, useful for the introduction of chirality, and B) sterically demanding acetylenic or nitrilic substrates were used together with a chiral catalyst to give axially chiral pyridines (Scheme 10).

Approach A requires the starting materials to be enantiomerically pure and the assembling reaction and its reaction conditions to be compatible with the stereogenic center, so that no racemisation can occur. Approach B is the more elegant route to introduce chirality because it starts with achiral substrates and transfers the stereochemical information from the chiral catalyst to the axially chiral product over the course of the reaction.

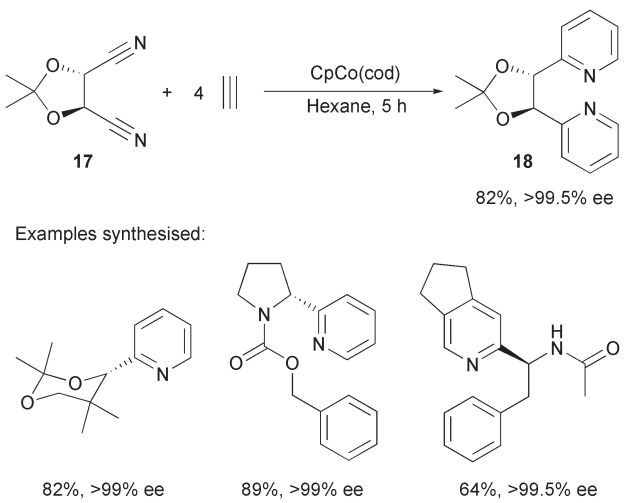
In recent years, we developed practical and efficient synthetic procedures for both aforementioned principles. The thermally initiated variant for Approach A was already known, but required high acetylene pressure (above 10 bar), reaction temperatures above 100 °C, long reaction times and high catalyst loadings to achieve acceptable yields. Under these conditions (Approach A) a noticeable decrease of enantiomeric purity with respect to the starting material (nitrile) was observed. Our approach aimed at the application of the photochemical Co(I)-complex-catalysed variant that we had already successfully deployed for the synthesis of achiral mono- to pentasubstituted pyridine derivatives.[34] The Co(I)-catalysed [2 + 2 + 2] cycloaddition of alkynes with nitriles can be carried out under very mild conditions (ambient temperature and pressure) and the required energy is delivered in form of light. The light energy can be supplied as artifical visible light or even as sunlight since the wavelength range between 350 to 500 nm was found optimal for the promotion of the catalytic process.

We first demonstrated the potential of this process for stereoselective reactions in the racemisation-free conversion of chiral nitriles into pyridine derivatives, following Approach A (Scheme 11).[35] The cobalt(I)-complex CpCo(cod) was the catalyst of choice and the reaction could be performed in organic solvents (toluene or hexane) or even water within 6 hours. A broad variety of versatile functionalised (*e.g.* ester, ketones, amines) chiral mono- as well as dinitriles were used as substrates for the reaction with acetylene, internal alkynes or diynes. In Scheme 11, the process is exemplified by the reaction of dinitrile **17**, a protected chiral diol, yielding the bispyridine product **18** with excellent yield and stereoselectivity. In general, the obtained yields for these mostly intermolecular cycloadditions were good to excellent, accompanied by complete retention of chirality.

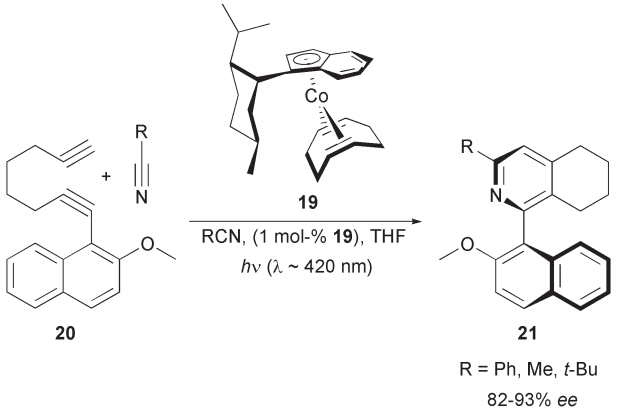
Our group has been the first to accomplish the asymmetric transition metal-catalysed [2 + 2 + 2] cycloaddition by the more elegant Approach B. This discovery was closely connected to the design and synthesis of chiral Co(I)-complexes, that we have prepared.[36,37] We synthesised chiral Co(I)-complexes $Cp^{chiral}Co(cod)$, that possess tartrate or menthyl derived cyclopentadienyl (Cp^{chiral}) ligands in the catalyst backbone (see **19** in Scheme 12). It was found that the "dummy" ligand cod was superior to CO or PR_3 in terms of reaction rate and the yield of the pyridine. Another requirement to obtain two stable atropisomers is that bulky



Scheme 10 General principles of synthesising chiral pyridines by [2 + 2 + 2] cycloaddition.



Scheme 11 Synthesis of pyridines by [2 + 2 + 2] cycloaddition reactions with retention of stereochemistry.



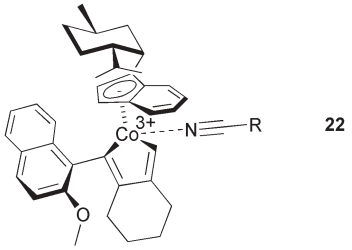
Scheme 12 Co-catalysed enantioselective cycloaddition to pyridines.

substituents must be attached to the *ortho* positions of the 2-arylpyridine derivatives. In our initial experiments we expected that the chiral ligand in the cobalt complex would be able to provide the preferential formation of only one atropisomer. We first screened the transformation by reacting 2-substituted 1-naphthonitriles with several alkynes and also different chiral cobalt(I)-complexes as catalysts.[38] The obtained yields and enantioselectivities were low to moderate, but proved the general feasibility of the idea. It turned out that neither the solvents used (hexane, toluene, dioxane and THF), nor the irradiation period or the amount of catalyst have a measurable influence on the enantioselectivity.

We modified the reaction conditions by choosing bulkier substrates for the reaction and synthesised 2-methoxy-1-(1,7-octadiynyl)naphthalene (**20**) by a palladium-catalysed arynylation of the appropriate iodonaphthalene with a diyne. This substrate was reacted with a nitrile like benzonitrile, acetonitrile or pivalonitrile together with the Co-complex **19** and finally yielded the atropisomers **21** in 82–93% ee (Scheme 12).

The yields of the reaction were also very good after 24 h (74–86%) and only a little temperature effect was observed in the range between 3 and 20 °C. The enantioselectivity indeed became better when turning to lower temperatures; using PhCN as the nitrile at 20 °C 82% ee was observed while at 3 °C 89% ee could be reached. At −20 °C, an even higher enantioselectivity of 93% ee was achieved. The optimised reaction conditions were applied to a number of different nitriles and gave very good yields with substituted benzonitriles, carrying electron-donating (–OMe) and electron-withdrawing ($–CF_3$) groups. With heterocyclic nitriles poor results were obtained, because the bidentate ligands resulting from the cycloaddition reaction are efficiently complexing the cobalt catalyst to form a stable and catalytically inactive complex.

From a mechanistic standpoint the intermediate is a diastereomeric cobaltacyclopentadiene complex, that forms from the diyne or acetylenes in the first step (intermediate **22**, Scheme 13). The reason for this selectivity was already discussed in the mechanistic section: the metallacycle formation gave Co(III), which coordinates the nitriles lone-electron pair much easier than the initial Co(I) species. The sterical repulsion of the chiral catalyst backbone and the groups incorporated in the cobaltacycle are responsible for the



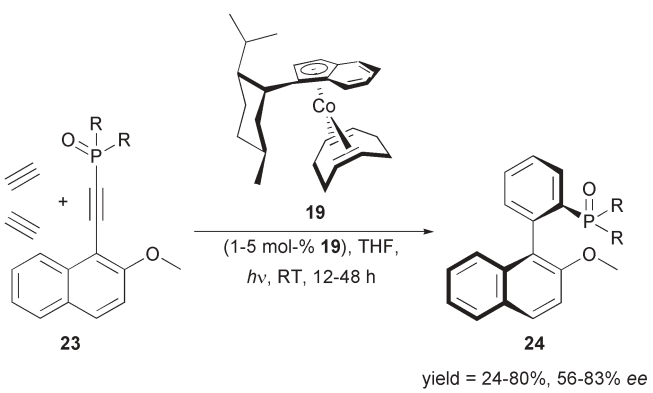
Scheme 13 Cobaltacyclic intermediate (**22**).

selective introduction of chirality. The nitrile is not involved in the stereoselection process and with the coordination of the nitrile to the cobaltacycle only the conformation in the final pyridine is fixed. This perception is corroborated by the finding, that sterically and electronically different nitriles have no influence on the stereochemically course of the reaction.

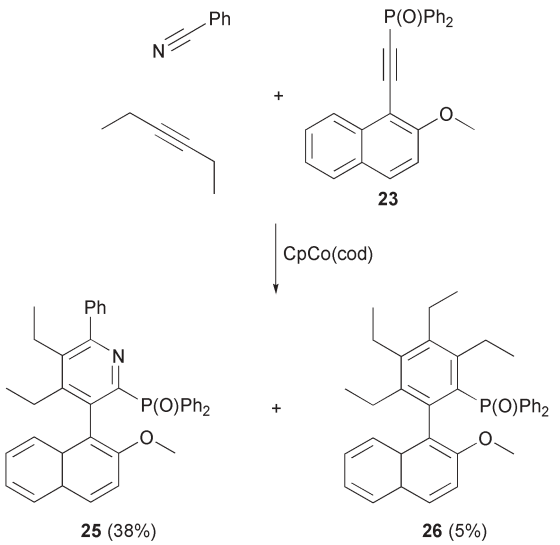
We have further proven this concept as very valuable for the synthesis of chiral pure carbocycles that act as skeletal structure for atropisomeric phosphane ligands (**24**), by the reaction of an alkyne bearing a naphthyl, phosphoryl group (**23**) and simple acetylene (Scheme 14).[39] After deoxygenation of the phosphorus the resulting phosphane was used as an efficient ligand for the palladium-catalysed asymmetric hydrosilylation of alkenes.

In an interesting cross-coupling experiment alkyne **23**, benzonitrile and 1-hexyne (1 : 1 : 1 ratio) and CpCo(cod) were reacted in order to clarify the origin of the stereochemical induction and the nature of the intermediates (Scheme 15). We observed that only the pyridine **25** was formed with 38% yield and only a small amount of a carbocyclic side product (**26**, 5%). The ratio observed between pyridine **25** and carbocycle **26** contributes to the proposed mechanism according to which one single metallacyclopentadiene intermediate reacts faster with the nitrile than with the additional alkyne (compare to Scheme 13).

The asymmetric cross-cyclotrimerisation of alkynes with Ir or Rh complexes was demonstrated to be a powerful tool for the construction of axially chiral carbocyclic biaryl derivatives shortly after our initial report. Two selected recent examples should be mentioned in the following to illustrate the progress



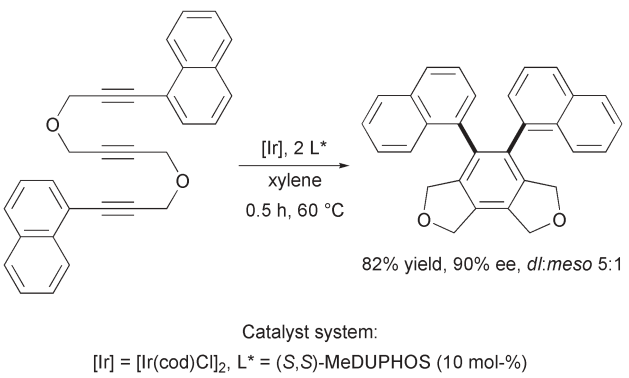
Scheme 14 Synthesis of chiral phosphane oxides by intermolecular enantioselective cross-cyclotrimerisation.



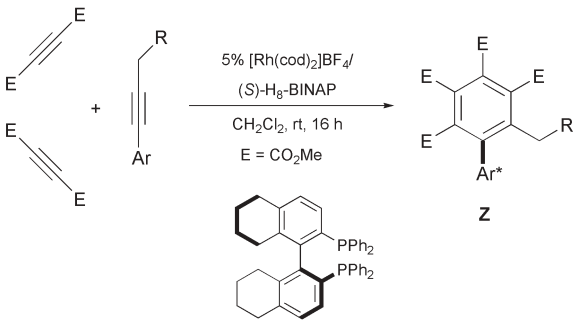
Scheme 15 Cross-cyclisation experiment for the evaluation of mechanistical features.

with these different catalyst systems. The group of Shibata developed the enantioselective Ir-catalysed cycloaddition of diynes or oligoynes with alkynes, partially creating several axial chirality elements in one molecule.[40] The reaction could also be performed in an entirely intramolecular fashion (Scheme 16).[41] The substrate triyne was conveniently prepared from the alkyne and the appropriate aryl halide by the Sonogashira cross-coupling protocol. The catalyst is generated *in situ* from $[Ir(cod)Cl]_2$ and the chiral bisphosphane (*S*,*S*)-MeDUPHOS and reacted with the triyne within only 0.5 h to give the chiral *ortho*-diarylbenzene derivative in excellent yield and good stereoselectivity.

Another impressive example for the preparation of axially chiral biaryls that are assembled in a completely intermolecular fashion and that are comparable to our systems (see Scheme 14) was reported in 2005 by Tanaka *et al.* (Scheme 17).[42] Two molecules of acetylenecarboxylates participate in a rhodium-catalysed cycloaddition with an unsymmetrical arylalkyne to yield the axially chiral biaryl. After screening several chiral diphosphane ligands they evaluated the necessary structural features of the arylalkyne



Scheme 16 Ir-catalysed enantioselective synthesis of *ortho*-diarylbenzenes.



Ar*	R	Z	Yield (%)	ee (%)
2-MeC_6H_4	OCOEt	**Z-1**	73	91
2-EtC_6H_4	OAc	**Z-2**	70	92
2-ClC_6H_4	OAc	**Z-3**	67	84
2-BrC_6H_4	OAc	**Z-4**	61	91
1-naphthyl	OAc	**Z-5**	89	95

Scheme 17 Rh-catalysed enantioselective cross-cyclotrimerisation.

and found an acetoxymethyl and an *ortho*-substituted aryl group as necessary structural elements to reach high yields and also high enantioselectivities. The optimised catalyst system contains a rhodium tetrafluoroborate complex and a partially hydrogenated BINAP derivative. An advantage of the aforementioned iridium- as well as rhodium-based catalyst systems compared to manufactured chiral complexes is the *in situ* preparation of the catalyst complex, thus making the handling more convenient.

5 Conclusions

The *de novo* construction of pyridine ring systems by the transition metal-catalysed [2 + 2 + 2] cycloaddition reaction has evolved in recent years as a very valuable member of the synthetic chemist's toolbox. Compared with the already impressive assembly of pyridines from the reaction of diynes and oligoynes with nitriles in a more or less intramolecular fashion, the completely intermolecular reaction between acetylenes and nitriles is another great improvement. The possibility of incorporating a wide variety of functional groups into the substrates gives access to pyridinic products that are versatile starting materials for further transformations. Furthermore, many facets of the mechanistic background of this fascinating reaction have been uncovered, showing the similarities and differences in the reaction performance of the different metals. A very recent development is the introduction of chirality into the cycloaddition reaction, especially by using chiral metal complexes, that yield atropisomeric biaryls.

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