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Transition Metal-Mediated Synthesis of Monocyclic Aromatic Heterocycles

Anton V. Gulevich, Alexander S. Dudnik, Natalia Chernyak, and Vladimir Gevorgyan*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, 4500 SES, M/C 111, Chicago, Illinois 60607-7061

1. Introduction

Heterocycles constitute the largest and the most diverse family of organic compounds. Among them, aromatic heterocycles represent structural motifs found in a great number of biologically active natural and synthetic compounds, drugs, and agrochemicals. Moreover, aromatic heterocycles are widely used for synthesis of dyes and polymeric materials of high value.¹ There are numerous reports on employment of aromatic heterocycles as intermediates in organic synthesis.²

Although, a variety of highly efficient methodologies for synthesis of aromatic heterocycles and their derivatives have been reported in the past, the development of novel methodologies is in continuous demand. Particularly, development of new synthetic approaches toward heterocycles, aiming at achieving greater levels of molecular complexity and better functional group compatibilities in a convergent and atom economical fashions from readily accessible starting materials and under mild reaction conditions, is one of a major research endeavor in modern synthetic organic chemistry. Transition metal-catalyzed transformations, which often help to meet the above criteria, are among the most attractive synthetic tools.

Several excellent reviews dealing with transition metal-catalyzed synthesis of heterocyclic compounds have been published in literature during recent years. Many of them highlighted the use of a particular transition metal, such as gold,³ silver,⁴ palladium,⁵ copper,⁶ cobalt,⁷ ruthenium,⁸ iron,⁹ mercury,¹⁰ rare-earth metals,¹¹ and others. Another array of reviews described the use of a specific kind of transformation, for instance, intramolecular nucleophilic attack of heteroatom at multiple C–C bonds,¹² Sonogashira reaction,¹³ cycloaddition reactions,¹⁴ cycloisomerization reactions,¹⁵ C–H bond activation processes,¹⁶ metathesis reactions,¹⁷ etc. Reviews devoted to an application of a particular type of starting materials have also been published. Thus, for example, applications of isocyanides,¹⁸ diazocompounds,¹⁹ or azides²⁰ have been discussed. In addition, a significant attention was given to transition metal-catalyzed multicomponent syntheses of heterocycles.²¹ Finally, syntheses of heterocycles featuring formation of intermediates, such as nitrenes,²² vinylidenes,²³ carbenes, and carbenoids²⁴ have also been reviewed.

The main focus of the present review is a transition metal-catalyzed synthesis of aromatic *monocyclic* heterocycles. The organization of the review is rather classical and is based on a heterocycle, categorized in the following order: (a) ring size of heterocycle, (b) number of heteroatoms, (c) type of heterocycle, and (d) a class of transformation involved. A brief mechanistic discussion is given to provide information about a possible reaction pathway

*Corresponding Author vlad@uic.edu.

when necessary. The review mostly discusses recent literature, starting from 2004²⁵ until the end of 2011, however, some earlier parent transformations are discussed when needed.

2. Synthesis of Furans

The development of selective and general methods for a facile assembly of the diversely substituted furan core attracted a tremendous interest over the past decades.²⁶ Consequently, numerous reviews covering a large number of the existing synthetic methods toward furans via a modification of preexisting heterocyclic core^{2g,27} and assembly of the ring from acyclic precursors^{21b,28} have appeared. In this chapter, synthesis of furans via transition metal-catalyzed processes is discussed. All reactions are organized by a type of disconnection involved in the assembly of furan ring, including cycloisomerization and formal [4+1], [3+2], and [2+2+1] cycloaddition reactions (Figure 1).

2.1. Synthesis of Furans via Cycloisomerization-Type Reactions

2.1.1. Cycloisomerization of Unsaturated Carbonyl Compounds, Alcohols, and Esters—Transition metal-catalyzed cycloisomerization of allenyl ketones^{12c,d,12h} into furans was first introduced by Marshall et al. in 1990.²⁹ It was demonstrated that various alkyl-substituted furans **2-2** could be prepared in high yields via the Ag-^{4b} or the Rh(I)-catalyzed³⁰ cycloisomerization of allenyl ketones **2-1** (Scheme 1).

Later, the same group found a set of milder reaction conditions, which allowed for the Ag-catalyzed preparation of di- and tri-substituted functionalized furans **2-4** at room temperature (Scheme 2).³¹

According to the proposed mechanism, the Ag(I) first coordinates to the distal double bond of the allene moiety (**2-5**), triggering a nucleophilic attack of the carbonyl oxygen atom to produce the oxonium intermediate **2-6**. The latter, upon a proton loss, is converted into furan **2-4** either directly via the S_E2 type process or through a protonation/E1-type elimination sequence involving intermediate **2-8** (Scheme 3).^{31d}

Hashmi and others further elaborated the cycloisomerization of allenyl ketones type **2-3** into furans **2-4**. It was found that this transformation could efficiently be catalyzed by many transition metals, such as Cu(I), Ag, Rh(II), Pd(II), and Ru(II).³² The Pd(II) catalyst was shown to be efficient only for the cycloisomerization of allenyl ketones **2-3** possessing C-4 (R¹)^{32a} or bulky C-2 (R²)^{32d} substituents at the allene moiety. The Ag-catalyzed assembly of furans via the above cycloisomerization approach was featured as a key step in the syntheses of several naturally-occurring furanocycles, such as (±)-kallolide B,³³ (–)-kallolide B,³⁴ rubifolide,³⁵ kallolide A,³⁶ and unnatural polyhydroxylated piperidine.³⁷ In 2011, Liu et al. showed that [3]cumulenones could also undergo the Au(I)-catalyzed cycloisomerization into 2-vinyl furans.³⁸

Hashmi group also reported a very facile Au(III)-catalyzed cycloisomerization of allenyl ketones **2-9** into furans **2-10** (Scheme 4).³⁹ Furthermore, the same group extended this Au-catalyzed^{3b–d,12k,40} reaction to the cycloisomerization–formal Michael addition cascade of allenyl ketones **2-11** with enones **2-12** to produce 2,5-disubstituted furans **2-13** (Scheme 4).^{39b,41}

In contrast to the Au(III)-catalyzed cyclization–dimerization reaction leading to C2-functionalized furan derivatives, the Pd(II)-catalyzed cycloisomerization/homo-dimerization cascade reaction of allenones **2-14** produces C3-functionalized furylalkenones **2-16** (Scheme 5).^{32,42} Modest to excellent levels of selectivity toward the dimerization products **2-16** versus unfunctionalized furans **2-15** were achieved. Thorough mechanistic studies suggested

that this reaction proceeds via the generation of the furyl-palladium species [**2-17**↔**2-17a**]. The β-hydride elimination from the latter gives Pd(IV) intermediate **2-18**, which upon a subsequent carbopalladation reaction with allene **2-14**, followed by reductive elimination of Pd(II) in **2-19**, furnishes 3-furylalkenone **2-16** (Scheme 5). It should be noted, that the dimerization path is completely suppressed by introduction of substituents at the C4-position of the allenyl ketone.^{32a} A partial or complete inhibition of this process was also observed during the Pd(II)-catalyzed cycloisomerization of C2-functionalized allenes.^{32d}

Later, this methodology was utilized for the assembly of furanocycles **2-20** via an intramolecular mode of this reaction (Figure 2).⁴³

In 2000, Ma et al. developed a highly efficient two-component Pd-catalyzed synthesis of up-to-tetrasubstituted furans **2-22** from reaction of allenyl ketones **2-21** with organic halides (Scheme 6).⁴⁴ A variety of alkyl- and aryl-substituted allenyl ketones and aryl-, hetaryl-, or vinyl halides could be employed in this transformation, providing the corresponding furans **2-22** in moderate to excellent yields. According to the proposed mechanism, the carbopalladation of allenyl ketone **2-21** with organopalladium halide intermediate species affords the π-allyl palladium intermediate **2-23**, which, upon cyclization, produces cyclic oxocarbenium intermediate **2-24** and regenerates the Pd(0) catalyst. A subsequent proton loss in **2-24** furnishes furan **2-22** (Scheme 6).

The same group extended the scope of organic halides to allyl bromides **2-26** in this two-component Pd-catalyzed synthesis of furans (Scheme 7).^{44c,45} Thus, it was shown that this transformation could be achieved using Pd(0)- or Pd(II) catalysts and provides C3-allyl furans **2-27** in moderate to high yields. For the cycloisomerization of C4-substituted allenyl ketones, DMF was employed as a solvent to provide **2-27** in reasonable yields and good selectivities of the C3-allylated furans versus non-allylated products. In the case of Pd(II)-catalyst, reaction was proposed to proceed via allylation of transient furylpalladium(II) species **2-28**, through direct replacement of bromide by furyl ligand. Alternatively, for the Pd(0) catalyst, the initial oxidative addition of **2-26** to Pd(0) complex to form the π-allyl palladium intermediate **2-29**, followed by the 5-*endo-trig* cyclization yielding another π-allyl palladium **2-30 en route** to furan **2-27**, has been suggested. In 2011, Zhang also employed this transformation for the synthesis of furans.⁴⁶

Later, Ma developed a set of methodologies toward functionalized furans featuring a cycloisomerization/dimerization cascade reaction of two different allenyl compounds, particularly, allenyl ketones and various allenes tethered with nucleophilic functionalities. For instance, a facile reaction between allenyl ketone **2-32** and allenyl carboxylic acid **2-31** in the presence of the Pd(II) catalyst, provides an easy access to densely substituted 4-furylbutenolides **2-33**. A variety of alkyl- and aryl-substituted allenyl carboxylic acids could efficiently be employed in this process. However, the scope of the reaction appears to be limited to unfunctionalized simple alkyl allenyl ketones **2-32**. Mechanistically, this cascade transformation proceeds via a generation of the furylpalladium intermediate **2-34** (Scheme 8).^{44c,47}

Shortly after, it was also demonstrated that a perfect chirality transfer could be achieved for the cycloisomerization/dimerization cascade reaction of allenyl ketones with enantioenriched allenyl carboxylic acids **2-35** to prepare furans **2-36** (Scheme 9).^{47b}

More recently, the same group developed an analogous cycloisomerization/dimerization reaction of allenyl ketones with allenyl amides **2-37** proceeding under slightly modified conditions (Scheme 10).⁴⁸ This reaction provided functionalized furyl furanimines **2-38** in

moderate to high yields. The employment of benzoquinone additive allowed reducing both the Pd catalyst and allenyl ketone loadings.

Later, Kato and Akita reported a carbonylative homo-dimerization version of this chemistry. Thus, a very efficient Pd(II)-catalyzed two-fold cycloisomerization of allenyl ketones **2-39** under CO atmosphere afforded bis(3-furyl)ketones **2-40** efficiently. These products were employed later in the synthesis of a tamoxifen analogue. Mechanistically, the reaction proceeds via formation of the common furylpalladium intermediate **2-41**, followed by a coordination of the second allenyl ketone molecule to the Pd and insertion of CO into the C–Pd bond to produce the furoyl-Pd species **2-42**. A subsequent cycloisomerization step furnishes the corresponding furan products **2-40** (Scheme 11).⁴⁹

The Hg(II)-catalyzed cycloisomerization of allenyl ketones **2-43** into furans **2-44** was reported by Tius (Scheme 12).⁵⁰ A similar Hg(OTf)₂–tetramethylurea complex catalyst was employed for the synthesis of furans by Gosselin.⁵¹ Furthermore, Narasaka demonstrated that (Me₃N)Cr(CO)₅ complex could efficiently catalyze an analogous transformation leading to 2-monosubstituted furans.⁵²

More recently, Che and coworkers described a highly efficient cycloisomerization of allenones **2-45** into furans **2-46** using the porphyrinato-Au(III) catalyst, which had a TON of 850 and could be recycled up to nine times (product turnover number of 8300) without any notable loss of the catalytic activity (Scheme 13).⁵³

Interestingly, Gevorgyan and coworkers showed that the Cu-catalyzed cycloisomerization of 4-thio-substituted allenones **2-47** proceeded highly efficiently with a concomitant 1,2-migration of the phenylsulfanyl group,⁵⁴ providing 3-thio-substituted furan **2-48** (Scheme 14).⁵⁵

Based on these results, the same group developed a set of practical transformations toward furans which overcome the limitation of Marshall's protocol to the introduction of various groups at the C-3 position of a furan ring. Accordingly, a variety of multisubstituted 3-halofurans **2-50** could be accessed via the Au(III)-catalyzed cycloisomerization of haloallenyl ketones **2-49** proceeding with a 1,2-migration of iodine, bromine, and chlorine atoms. This chemistry represents a very efficient, selective, and mild approach for the synthesis of up-to-fully-substituted 3-halofurans (Scheme 15).⁵⁶ Iodo- and bromo-substituted substrates **2-49** were shown to be more reactive in this cycloisomerization than the corresponding chloro-substituted analogs.

In addition, in the case of cycloisomerization of ambident C4-monosubstituted haloallenones **2-51**, the authors demonstrated that simple switching of solvent from toluene to THF provided a regiodivergent formation of 2-halofurans **2-53**.⁵⁶ It was also shown that the use of Au complexes with counter-anions capable of assisting 1,2-H migration,⁵⁷ such as Et₃PAuCl⁵⁶ and Ph₃PAuOTf,⁵⁸ led to the formation of 2-halofurans **2-53** with high degree of regioselectivity (Scheme 15). On the other hand, similarly to AuCl₃ catalyst in toluene solvent, the use of cationic phosphine-Au(I) complexes, such as Ph₃PAuBF₄ or Ph₃PAuSbF₆, provided 3-halofurans **2-52** with an excellent selectivity.

Thorough mechanistic studies, including DFT calculations, indicated that both Au(I) and Au(III) catalysts activate distal double bond of the allene (**2-54**) to produce cyclic Au-carbene intermediate **2-55**, which in the case of cationic Au complexes (L = BF₄[−] or SbF₆[−]) undergoes a kinetically favored 1,2-halogen migration to give 3-bromofuran **2-53**. However, when Au(PR₃)₃L (L = Cl, OTf) catalysts were used, a stepwise counterion- or ligand-assisted proton-shift (**2-56**) was demonstrated to be the major process, leading to the 2-bromofuran

2-53. This observation indicates that the regioselectivity of the Au-catalyzed 1,2-H versus 1,2-Br migration processes can be ligand-controlled. (Scheme 16).^{56,58}

Next, aiming at the incorporation of 1,2-migration⁵⁹ of alkyl- or aryl groups into the cascade cycloisomerization of allenones, the same group disclosed an efficient cycloisomerization protocol for the synthesis of up-to-tetrasubstituted furans **2-58** and **2-60** from 4,4-disubstituted allenyl ketones **2-57** and **2-59**, respectively (Scheme 17).⁶⁰ In the case of transition metal catalysts, such as electrophilic Au(I)-, Ag-, Cu(I)-, and Cu(II)-complexes, the authors proposed the reaction mechanism analogous to that suggested for the transformation of halo-substituted allenones shown in Scheme 16.⁶⁰⁻⁶¹

Later, Gevorgyan developed a highly efficient regioselective Au(III)-catalyzed cycloisomerization of C4-silyl allenyl ketones **2-61** into synthetically valuable²⁷ C3-silylfurans **2-62** (Scheme 18).⁶² This cascade transformation features a 1,2-Si migration in a common Au-carbene intermediate **2-63**. Both experimental and computational results suggested that the 1,2-Si migration is kinetically favored over the 1,2-shifts of alkyl, aryl, and even H groups in the β -Si-substituted Au-carbene **2-63**. Notably, this methodology allows for a facile preparation of not so easily available C3-silylated furans lacking a substituent at C2 ($R^3 = H$), as well as for the synthesis of unsymmetrically 2,5-substituted C3-silylfurans.

More recently, Ferreira and coworkers reported an efficient synthesis of silylfurans featuring a selective 1,2-Si over 1,2-H migration to a platinum carbene center. Thus, the Pt(II)-catalyzed cycloisomerization of **2-64** in the presence of electron-neutral alkene ligand (1-octene) upon heating in toluene affords 3-silylfuran **2-67**. In this case, the cycloisomerization is accompanied by a predominant migration of the silyl group to the platinum carbene center **2-65**. On the other hand, cycloisomerization of **2-64** in the presence of electron-donating alkene ligand (ethyl vinyl ether) in THF at room temperature affords regioisomeric 4-silylfuran **2-70**, predominantly. Under these conditions (e.g., more Lewis basic THF solvent), dissociation of the chloride counterion is facilitated, which then could assist in hydrogen cleavage (**2-68**) to produce furan **2-70** upon protodemetalation of **2-69** (Scheme 19).⁶³ This observation is in agreement with the DFT computational studies evaluating the migratory processes of hydrogen and bromine in the Au-catalyzed cycloisomerizations (Scheme 16).⁵⁸

In 2011, Ma et al. reported the Rh-catalyzed cyclization of 1,5-bis(1,2-allenyl)ketones **2-71** into bicyclic furans **2-72** (for the Pd-catalyzed cyclizations, see Scheme 5 and Figure 2). The reaction proceeds via cycloisomerization of **2-73** into the 3-rhodafuran intermediate **2-74**, which undergoes a facile cyclization with the tethered allenyl moiety to produce the bicyclic furan **2-72** (Scheme 20).⁶⁴

In 2005, Kirsch reported the Au(I)-catalyzed cycloisomerization of vinyl propargyl ethers **2-75** into furans **2-77**. A variety of densely substituted furans could be prepared under very mild reaction conditions and using low catalyst loading. It is believed that this cascade process begins with the Au(I)-catalyzed Claisen-type rearrangement of **2-75** leading to the formation of skipped allenyl ketone **2-76**, which upon the Au(I)-catalyzed 5-*exo-dig*-cyclization provides furan **2-77** (Scheme 21).⁶⁵

A highly efficient Ru(II)- and Pt(II)-catalyzed cycloisomerization of skipped allenyl ketones **2-78** to produce densely functionalized furans **2-79** via a formal 1,4-migration of phenylsulfanyl- and phenylselenenyl groups was reported by Wang and co-workers.⁶⁶ The proposed mechanism for this cascade cycloisomerization features the initial attack of the phenylsulfanyl group at the terminal carbon atom of the activated allene moiety (**2-80**)

leading to a cyclic thiolanium intermediate **2-81**. Upon fragmentation, the latter undergoes a 1,4-migration of the thio group generating a metal carbene **2-82**, followed by its cyclization into the furan **2-79** (Scheme 22).

Huang et al. used conjugated propargyl ketones **2-83** in a fairly efficient Pd-catalyzed synthesis of disubstituted furans **2-84** (Scheme 23).⁶⁷ The authors suggested a possible intermediacy of the corresponding allenone **2-85**, which undergoes the 5-*endo-trig* cyclization into furan. Recently, a single example of an analogous Rh(I)-catalyzed cycloisomerization of alkynones similar to **2-83** into furans was documented by Hua.⁶⁸

Pd(0)- and Pd(II)-catalyzed cycloisomerizations of alkynones **2-86** leading to the assembly of furans **2-87** were further investigated by Ling. In many cases, this facile cyclization was complicated by a competitive oxidative dimerization process leading to 3,3'-bifurans **2-88**. (Scheme 24). The mechanism for dimerization reaction has not been established.⁶⁹

Gevorgyan et al. demonstrated that easily available conjugated alkynyl ketones^{121,21b,70} could indeed serve as highly versatile surrogates of somewhat unstable and not so simply accessible allenones, which are typically used in many efficient furan syntheses. Thus, it was shown that a Cu(I)-catalyzed cycloisomerization of alkynyl ketones **2-89** in the presence of tertiary amine base proceeded smoothly to provide furans **2-90** in high yields. This protocol allowed for a highly efficient preparation of 2-monosubstituted and 2,5-disubstituted furans possessing various labile groups (Scheme 25).⁷¹ The proposed mechanism involves the initial Cu(I)/base-assisted formation of allenyl ketone **2-91** followed by its facile Cu(I)-catalyzed 5-*endo-trig* cyclization.

This discovery guided the same group toward the development of a general concept of a transition metal-catalyzed cascade cycloisomerization involving 1,2-migrations of different functional groups in alkynyl- and allenyl systems as the key step in a rapid and very facile assembly of densely functionalized furan cores. For instance, it was shown that 3-sulfanyl-substituted furans **2-92** could efficiently be accessed via the Cu(I)-catalyzed migratory cycloisomerization of the corresponding propargyl sulfides **2-93** (Scheme 26).⁵⁵

As in the previous example, it is believed that this transformation occurs via the initial Cu/base-assisted prototropic rearrangement of **2-92** into allenyl sulfide **2-94**, followed by the intramolecular attack of a sulfanyl group at the activated enone moiety (**2-95**) to produce a thiirenium intermediate **2-96**.^{55,61} The latter undergoes cycloisomerization via either addition-elimination (Ad_N-E) or directly via S_N2 -*vin* substitution processes to give furan products **2-93** (Scheme 27). Notably, this methodology represents the first example of 1,2-migration of a thio-group⁵⁴ which occurs from an olefinic sp^2 carbon to an sp center.

Recently, the same group extended this protocol to the Cu(I)-catalyzed cycloisomerization of propargyl selenides **2-97** into 3-selenyl-substituted furans **2-99** proceeding with a 1,2-migration of arylselenyl groups. Remarkably, the 1,2-migration of seleno group (**2-98**) was more facile than that of the thio groups, allowing to perform the cycloisomerization reactions under significantly milder reaction conditions (Scheme 28).⁶¹

Gevorgyan and co-workers have also established a series of highly efficient, practical, and general 1,2-migration/cycloisomerization methodologies toward the assembly of 3-hydroxyfuran derivatives. Accordingly, conjugated propargyl acetates **2-100**⁷² and phosphates **2-104**⁷³ underwent a highly regioselective Cu(I)-catalyzed cycloisomerization to furnish regioisomeric 4- and 3-oxyfurans **2-101** and **2-105**, respectively (Scheme 29). Thus, in the case of conjugated acyloxy-substituted ketones **2-100**, the reaction involves a formation of the allene intermediate **2-102** via a prototropic rearrangement followed by a

cyclization into a dioxolenylium intermediate **2-103** and a subsequent formation of furan **2-101**.⁷³ In the case of propargyl phosphates **2-104**, the reaction sequence starts from the initial propargyl-allenyl isomerization, proceeding via a formal sigmatropic [3,3]-phosphatyloxy shift, followed by a cycloisomerization of allenyl ketone **2-106** into furan **2-105** (Scheme 29).⁷³

Skipped propargylic ketones can also undergo a transition metal-catalyzed cycloisomerization into furans. Thus, the Pd(II)-catalyzed synthesis of furan **2-108** via the cycloisomerization of skipped propargylic ketone **2-107** was first described by Utimoto in the 1980s (Scheme 30).⁷⁴ Later, Huang and co-workers expanded the scope of this transformation using the Pd(0)-catalyzed cycloisomerization of skipped propargyl ketones **2-109** into the corresponding furans **2-110** (Scheme 30).⁷⁵ Similarly, to their previous work on conjugated systems (*vide supra*), the authors proposed the generation of an allenyl ketone intermediate during this cascade process.

Next, Utimoto applied the above cycloisomerization methodology to a two-component tandem synthesis of trisubstituted 3-allylfurans **2-112** via the Pd(0)-catalyzed reaction of skipped propargyl ketones **2-111** with allyl chlorides. The authors took advantage of a facile coupling reaction of a furylpalladium intermediate **2-113**, generated upon oxypalladation reaction in **2-111**, with various allyl chlorides in the presence of oxirane as a proton scavenger (Scheme 31).^{74b}

A very mild and facile Au(III)-catalyzed version for the cycloisomerization of skipped alkynyl ketones **2-114** into 2,5-disubstituted furans **2-115** was first reported by Hashmi (Scheme 32).^{39a,b} Interestingly, this catalyst was shown to be completely inefficient for an analogous transformation of conjugated substrates.^{39b} In 2011, Moran et al. also reported the synthesis of furans via the Au(III)-catalyzed cycloisomerization of β -alkynyl β -ketoesters.³⁸

Toste and co-workers described the Au(I)-catalyzed synthesis of furan **2-117** from sulfoxide **2-116**.⁷⁶ In this interesting cascade transformation, sulfoxide **2-116** undergoes the Au(I)-catalyzed rearrangement into the homopropargylic ketone **2-118**, followed by its cycloisomerization into the furan product **2-117** (Scheme 33).

As an alternative to π -philic metal catalysts, Zn(II)-catalyzed cycloisomerization of 3-alkynyl ketones **2-119** into furans **2-120** was elaborated by Dembinski et al. This transformation proceeds under mild reaction conditions and provides a range of 2,5-di- and 2,3,5-trisubstituted furans **2-120** bearing several sensitive functional groups (Scheme 34).⁷⁷ In 2011, the same group described the Au(I)/Zn(II)-catalyzed halocyclization of 2-fluoro-3-alkynyl ketones in the presence of *N*-iodo- or *N*-bromosuccinimide to produce 3,4-fluorohalofurans under mild reaction conditions.⁷⁸

Gevorgyan disclosed a highly efficient route to tetrasubstituted and even fused furans via a transition metal-catalyzed migratory cycloisomerization of skipped propargylic systems. For instance, the Ag-catalyzed transformation of propargyl ketone **2-121** occurs with the involvement of an allenyl ketone intermediate and affords furan **2-122** as a product of a net 1,2-phosphatyloxy group migration. Interestingly, tosyloxy propargyl ketone **2-123** was shown to spontaneously isomerize into the allenyl ketone **2-124**. The latter could also undergo the Ag(I)-catalyzed cycloisomerization into the corresponding 3-tosyloxyfuran **2-125** (Scheme 35).^{72–73}

Cycloisomerization of alkynyl acetates **2-126** in the presence of the Ag-catalyst proceeds with a concomitant formal 1,2-acyloxy group migration to produce 3-acyloxyfurans **2-127** at room temperature (Scheme 35).^{72–73} Several other transition metals such as Cu(II), Pd(II),

Pt(II), and Au(III) were found to catalyze this transformation, as well. The mechanism for the cycloisomerization of skipped alkynyl ketones **2-128**, containing an acyloxy group, was found to follow a Rautenstrauch-type 1,2-migration of the acyloxy group to form vinyl carbenoid **2-129**, followed by its cycloisomerization into the furan **2-127a** (Scheme 36).^{73a} Very recently, Fang et al. confirmed the Rautenstrauch-type mechanism of the Au(III)-catalyzed cycloisomerization of **2-128** using DFT calculations.^{73b}

Gevorgyan group also reported a very efficient Au-catalyzed regiodivergent cycloisomerization/1,2-Si- or 1,2-H migration cascade transformation of silyl-substituted skipped alkynyl ketones **2-131** into silylfurans **2-132**. In the case of Ph₃PAuSbF₆ catalyst, it was suggested that the reaction proceeds via the initial propargyl–allenyl isomerization of **2-131** into allene **2-133**. A subsequent cyclization of the latter via an Au-carbene intermediate is followed by the 1,2-Si migration (*vide supra*). This cycloisomerization reaction could be applied to a variety of homopropargylic ketones **2-131**, possessing aryl-, alkyl-, as well as TMS-, TES-, and PhMe₂Si-, groups to afford 3-silylfurans **2-132** as sole regioisomers. However, for substrates bearing electron-deficient aryl substituents, the 1,2-H shift competes with the 1,2-Si migration, which results in the formation of regioisomeric C2-silylfurans with good to high degrees of regioselectivity favoring the C3-silylated isomers (Scheme 37).⁶²

Both experimental and computational mechanistic studies indicate that the 1,2-Si migration is kinetically more favored over the 1,2-shifts of H, alkyl, or aryl groups in the β-Si-substituted Au-carbenes. However, it was found that counterion and solvent effects might reverse this migratory preference. Accordingly, in the case of Au(I) catalyst possessing non-nucleophilic SbF₆[−] counterion, the initial propargyl–allenyl isomerization (**2-137**) followed by cyclization into the Au-carbene intermediate **2-138** and the subsequent 1,2-Si shift furnishes furan **2-135** regardless of the solvent used for the reaction. However, in the case of the TfO[−] counterion, the reaction course depends on the solvent. Thus, in the case of a polar solvent the reaction occurs via the initial 5-*endo-dig* cyclization to give a cyclic furyl-Au intermediate **2-139**, which undergoes a predominant β-to-Au protonation to form the Au-carbene intermediate **2-140**. A subsequent dissociation of the triflate ligand in the polar media, due to efficient solvation, facilitates formation of the 1,2-Si shift product **2-135**. On the other hand, in nonpolar solvents, the furyl-Au intermediate **2-139** undergoes an ipso-protodeauration, which is kinetically more favorable than the generation of the Au-carbene intermediate **2-140**. As a result, a predominant formation of the formal 1,2-H migration product **2-136** is observed (Scheme 38).⁶²

Following a CuI-catalyzed synthesis of dictamnine and 4-methoxyfuro[2,3-*b*]quinoline reported by Reisch in 1988,⁷⁹ Balme demonstrated a Pd(0)-catalyzed arylation cyclization reaction of 3-alkynylpyridones **2-141** to produce furo[2,3-*b*]pyridones **2-142** in good to excellent yields (Scheme 39).⁸⁰ In addition, a one-pot procedure toward **2-142** that involved an assembly of **2-141** from alkynes and 3-iodo-2-pyridones via Pd/Cu-catalyzed Sonogashira reaction was also developed.

More recently, Dembinski applied an analogous strategy for an efficient synthesis of furopyrimidine nucleosides **2-144** from enynones **2-143** using Zn(II)-^{77b} or Cu(I)-⁸¹ catalyst (Scheme 40). Agrofoglio⁸² and later Hudson⁸³ reported that several furo[2,3-*d*]pyrimidine-containing compounds with valuable properties could be assembled via an Ag-catalyzed version of this transformation.

In 2011, Kirsch reported a Pt(IV)-catalyzed cycloisomerization of alkynyl ketones **2-145** into furans **2-146**. The reaction proceeds via a cyclic oxonium ion intermediate **2-147**, which undergoes a ring-contracting 1,2-shift to form a spirocyclic intermediate **2-148**. A

subsequent Grob-type fragmentation of **2-148** followed by a protodemetalation leads to a formation of the furan core **2-146** bearing 4-oxobutyl group (Scheme 41).⁸⁴

Larock demonstrated that 2-alkynylenones^{15a,85} **2-149** underwent a facile transition metal-catalyzed cycloisomerization to give highly substituted furans **2-150** in the presence of external O- or C-nucleophiles.⁸⁶ Several transition metal catalysts, such as AgOTf, Cu(OTf)₂, and Hg(OTf)₂, provided good yields of furans, although AuCl₃ was proven to be superior in terms of reaction times. However, this method appears to be limited to aryl- or vinylalkynes only, as the cyclization of terminal- and alkyl- or silyl-substituted substrates failed to produce furans **2-150**. According to the proposed mechanism, the Au(III) catalyst activates the C–C triple bond in **2-151**, triggering a subsequent nucleophilic attack of the carbonyl function to produce a cyclic oxonium intermediate **2-152**. An intermolecular nucleophilic addition of an external nucleophile at the activated enone moiety in **2-152** leads to a furyl-Au species **2-153**. Finally, protodeauration of the latter produces furan **2-150** and regenerates the catalyst (Scheme 42).

Recently, Krafft et al. described the Au(III)-catalyzed cycloisomerization of alkynyl-substituted divinyl ketones **2-154** into a carbocycle-fused furans **2-155**. Similar to the above case, the reaction most likely begins with the Au-catalyzed cycloisomerization of **2-154** to give a cyclic intermediate **2-156**. The latter is then intercepted by a Nazarov-type cyclization to provide the corresponding furan **2-155** (Scheme 43).⁸⁷

Yamamoto used CuI catalyst for the cycloisomerization of 2-alkynylenones **2-157** into furans **2-158** in the presence of various alcohols (Scheme 44).⁸⁸ Recently, Liang discovered that a robust air-stable and recyclable Bu₄N[AuCl₄] catalyst⁸⁹ could be employed for an analogous cyclization of alkynyl alkenones into furans in ionic liquids.⁹⁰

Oh revealed the Pt(II)-catalyzed version of the above two-component cycloisomerization of alkynyl alkenones **2-159** to produce furans **2-160** with a significantly extended substrate scope. Under these new reaction conditions, a variety of previously unreactive O-, N-, and even C-nucleophiles, as well as terminal and silyl- or alkyl-substituted alkynes, could be employed to produce furan products **2-160** in typically high yields (Scheme 45).⁹¹

Recently, Zhang developed the Pd-catalyzed version of the above transformation coupled together with an allylation step. Thus, a very efficient three-component cascade cycloisomerization/allylation reaction of alkynyl alkenones **2-161**, allyl chlorides **2-162**, and nucleophiles furnished densely functionalized tetrasubstituted furans **2-163** (Scheme 46).⁹² A variety of substituted allyl chlorides and a broad scope of *O*-nucleophiles, such as benzyl alcohols, primary or secondary alcohols, phenols, and even *C*-nucleophile (dimethyl malonate) could efficiently be employed in this reaction. However, *N*-nucleophiles such as *N*-tosyl allylamine failed to produce the corresponding furan product. According to the proposed mechanism, the Pd-catalyzed cycloisomerization/nucleophile addition (**2-164**) leads to the furyl-palladium intermediate **2-165**, which undergoes a subsequent allylation (**2-166**), followed by a β-halide elimination to afford furan **2-163** (Scheme 46). An alternative mechanism featuring the generation of π-allyl-Pd species prior to the cyclization step has also been proposed.

The same group later extended this chemistry to a two-component Michael addition/cycloisomerization cascade of alkynyl alkenones **2-167** and dimethyl 2-allylmalonate **2-168** terminated by an intramolecular Heck reaction (Scheme 47).^{92b} A variety of C3–C4-fused furans **2-169** could be obtained in high yields using this methodology, albeit it could not be applied to substrates bearing a cyclic enone moiety. Two mechanisms have been suggested for this cascade reaction, both involving carbopalladation/β-hydride elimination steps in the

furyl-Pd intermediates **2-170** or **2-171**. Interestingly, allyl chloride was found to be the best oxidant for a conversion of Pd(0) to catalytically active Pd(II) species.

Furthermore, the same group also demonstrated that besides the Heck reaction, the furyl-Pd intermediate analogous of **2-170** could be intercepted with a variety of α,β -unsaturated compounds followed by the protidepalladation step, thus resulting in a net hydroarylation reaction (Scheme 48).⁹³ Accordingly, the Pd-catalyzed three-component coupling reaction between alkynyl alkenones **2-172**, activated alkenes **2-173**, and a wide array of O-nucleophiles, as well as *N*-methyl indole, afforded tetrasubstituted furans **2-174** efficiently.

Following the above chemistries, the Pd-catalyzed arylative cycloisomerization of 3-alkynyl-4*H*-chromen-4-ones **2-175** in the presence of aryl- or hetaryl iodides and primary or secondary alcohols was developed by Hu for the synthesis of furo[3,2-*c*]chromenes **2-176** (Scheme 49).⁹⁴ The best yields were achieved with electron-poor aryl iodides and electron-donating substituents at the alkyne moiety. Tertiary alcohols and phenols were not tolerated under the reaction conditions, providing complex mixtures of products. The proposed mechanism features the formation of the ArPdI intermediate, followed by its coordination to the alkyne moiety in **2-175** to induce a cyclization similar to that in the above-discussed examples.

Recently, Zhang developed a more general Pd(II)/Cu(I)-catalyzed three-component arylative cycloisomerization of alkynyl alkenones **2-177** for the synthesis of tetrasubstituted furans **2-178** using diaryliodonium salts as electrophilic coupling partners (Scheme 50).⁹⁵ The use of the Cu(I) co-catalyst was essential for achieving higher yields of products **2-178**. This reaction displays a broad scope, albeit the alkyne substituent in **2-177** appears to be limited to aromatic and vinylic, or vinylic in character group, such as cyclopropyl. Cyclic alkynyl alkenones also worked quite well providing moderate to good yields of the corresponding furan products. Besides, a variety of alcohols and even water could be employed in this cascade process as O-nucleophiles. The proposed reaction mechanism involves the formation of the common furyl-Pd(II) intermediate **2-179** followed by its reaction with iodonium salt to produce the Pd(IV) species **2-180**. A subsequent reductive elimination in the latter provides furan **2-178** and regenerates the Pd(II) catalyst (Scheme 50).

Following a similar design principle, the same group developed a mild Au(I)-catalyzed cycloisomerization/formal cycloaddition reaction of alkynyl alkenones **2-181** with nitrones **2-182**. This reaction proceeded with a high levels of regioselectivity and diastereoselectivity to produce densely substituted furo[3,4-*d*][1,2]oxazines **2-183**. The reaction scope appears to be quite broad as alkyl-, alkenyl-, aryl-, and hetaryl groups were tolerated at various substitution sites of both reaction components. The proposed reaction mechanism features the formation of the furyl-Au [1,3]-dipole intermediate **2-184** followed by its stepwise [3+3] cycloaddition reaction with nitrone and a subsequent cyclization (**2-185**) to afford the furan derivative **2-183**. (Scheme 51). In addition, the N–O bond in products **2-183** could be cleaved in the presence of SmI₂ to give furyl-containing aminoalcohols. Finally, moderate levels of enantioselectivity could be achieved in this cascade two-component transformation by using (*R*)-MeO-biphep-derived Au(I) catalyst.⁹⁶

Later, the reaction conditions were further optimized to achieve high levels of enantioselectivity (Scheme 52).⁹⁷ Similarly to the previous case, the Au(I) catalyst loading could be decreased to as low as 0.2 mol % on a large scale. This reaction is quite general in scope and allows for a very facile preparation of a variety of substituted furo[3,4-*d*][1,2]oxazines **2-188** in good to excellent yields. However, the employment of substrates with aliphatic R² and small R³ substituents provides the corresponding furan products with decreased levels of enantioselectivity.

Next, the same group reported the Rh(I)-catalyzed cycloisomerization reaction of alkynyl alkenones **2-189** in the presence of external nucleophiles terminated by a formal hydroarylation reaction of alkynes tethered to **2-189** to give fused furans **2-190** (Scheme 53).⁹⁸ A variety of substrates possessing terminal, aryl- and alkyl substituted alkyne moiety were tolerated in this reaction. Among nucleophiles tested, an array of alcohols and even water provided moderate to excellent yields of products **2-190**, whereas tertiary alcohols and *N*-based nucleophiles gave no reaction, probably likely due to a catalyst deactivation. Finally, malonate- and *N*-Ts-tethered substrates cyclized smoothly, while *O*-tethered substituents decomposed under the reaction conditions. Based on the D-labeling studies, two mechanisms have been proposed. In the cycle *a*, the intermediate **2-192**, undergoes tandem cyclization into the carbocation intermediate **2-194**, which could be rapidly trapped by the nucleophile to produce the intermediate **2-195**, followed by a subsequent protodemetalation to afford the bicyclic furan product **2-190** and regenerate the rhodium catalyst. According to the mechanism *b*, nucleophilic addition of nucleophile to the C=C double bond of intermediate **2-192**, followed by a subsequent cyclization gives a furanyl rhodium complex **2-193**, which undergoes the *syn*-addition of the C–Rh to the alkyne moiety to produce the intermediate **2-195** (Scheme 54).⁹⁸ Interestingly, a cyclization of **2-189** in the absence of nucleophile, leads to an insertion of CO with a formation of fused carbocyclic furans **2-191** in high yields.⁹⁹

Later, the above chemistry was extended further to the Rh(I)-catalyzed two-component cascade cycloisomerization/cycloaddition reaction between alkynyl alkenones **2-196** and alkynes **2-197** resulting in a net formal [3+2+2] process and leading to furan-containing 5,6,7-tricycles **2-198**. The regioselectivity of the reaction was shown to be dependent on the nature of alkyne substituents. Thus, both bulky and electron-donating substituents preferred to occupy the position away from R² group in **2-198**, whereas strong electron-withdrawing groups were placed next to R². Reaction with internal alkynes **2-197** provided furans **2-198** in lower yields, wherein electronic effects of the alkyne substituents controlled the regioselectivity of the insertion. High levels of the alkyne insertion regioselectivity were achieved with “push-pull” tolanes. Two catalytic cycles have been suggested for this reaction both featuring the generation of a rhodacycle analogous to **2-194** (see Scheme 54) followed by the migratory insertion of the alkyne into one of the Rh–C bonds and a subsequent reductive elimination (Scheme 55).¹⁰⁰

Zhang et al. also reported an interesting Au(I)-catalyzed cascade cyclization/[1,5]-hydride shift/cyclization reaction of alkynyl alkenones **2-199**, possessing *ortho* *N,N*-dialkylaniline substituent, to produce polycyclic tetrahydroazepine-fused furans **2-200** (Scheme 56).¹⁰¹ The cyclization of substrates with aryl substituents at the alkyne moiety gave higher yields of products **2-200** than that of the alkenyl- or alkyl substituted reactants. Amine components in **2-199**, cyclic morpholine and piperidine, as well as acyclic dibenzyl- and diethyl anilines, were tolerated in this reaction. Very recently, the same group developed an enantioselective version of this transformation.¹⁰²

The scope of the Pd-catalyzed cycloisomerization of alkynyl alkenones **2-203** with 1,3-dicarbonyl compounds as nucleophiles and in the absence of external electrophiles was investigated by Zhang (Scheme 57).¹⁰³ Among 1,3-dicarbonyl compounds tested, diketones and ketoesters were equally efficient in this transformation. Substrates **2-203** possessing an aryl-substituted alkene moiety provided furans in significantly higher yields than those having alkyl substituents; whereas alkyl- and aryl groups were perfectly tolerated at both the alkyne and carbonyl moieties.

More recently, the same group disclosed a mechanistically interesting Au(I)-catalyzed cycloisomerization/“4+3” cycloaddition cascade reaction between alkynyl alkenones **2-205**

and α,β -unsaturated imines **2-206**. A variety of rearranged furo[3,4-*c*]azepines **2-207** could be accessed via this methodology under mild reaction conditions in high yields and moderate to excellent diastereoselectivities.¹⁰⁴ The employment of *Z*-enriched instead of *E*-imines gave same *trans*-products **2-207** in this reaction. As in the previous example, substrates possessing aryl-substituted alkene moiety provided furans in significantly higher yields than those having alkyl substituents. Alkyne substituents in **2-205** could be either aromatic or aliphatic, although the latter gave relatively lower yields of the corresponding furan products. The proposed mechanism involves a generation of the common furyl-Au [1,3]-dipole intermediate **2-208** that reacts further with imine **2-206** to give iminium species **2-209**, suited for a spiro-cyclization into **2-210**. A subsequent ring opening in the latter via the cleavage of the C–C bond of a former alkenyl moiety produces an isomeric iminium intermediate **2-211**. A following cyclization between the iminium ion and the furyl-Au moieties furnishes furan **2-207**, thus resulting in a formal 1,2-alkyl shift (Scheme 58).

Interestingly, the reaction of alkynyl alkenone **2-212** with indolyl imine **2-213** furnishes furan **2-214** (Scheme 59).¹⁰⁴ In this case, the initially produced common furyl-Au intermediate generates reactive iminium ion species **2-215** upon a reaction with the imine nitrogen of **2-213**. A subsequent cyclization of **2-215** leads to the product **2-214**. In contrast, the Au(I)-catalyzed reaction of **2-212** with 3-styrylindoles **2-215** affords the corresponding cyclopenta[*c*]furans **2-216** via a cyclization of an intermediate **2-217** (Scheme 59).¹⁰⁵

In 1993, Cacchi and Larock described a two-component synthesis of furans **2-219** via the Pd-catalyzed reaction of 2-propynyl-1,3-dicarbonyl compounds **2-218** with aryl- or vinyl halides and pseudohalides.¹⁰⁶ Mechanistically, this reaction begins with the coordination of the initially generated organopalladium species R^3PdX to the acetylenic system (**2-220**) followed by the 5-*exo-dig* cyclization to produce a cyclic intermediate **2-221**. The latter upon a reductive elimination, followed by a tautomerization furnished furan **2-218**. This reaction tolerates a variety of alkynyl ketones and aryl- or vinyl halides and triflates affording trisubstituted furans in reasonable to high yields (Scheme 60). A carbonylative version of the above reaction of 2-propynyl-1,3-dicarbonyl compounds **2-218** with aryl halides was developed by Arcadi.¹⁰⁷ In addition, Cacchi also showed that alkyl 3-oxo-6-heptynoates **2-222** can undergo a similar arylative cyclization process to produce furylacetic acids **2-223**.¹⁰⁸ This transformation was later thoroughly investigated by groups of Cacchi and Arcadi.^{107b} In 2011, Saito and Hanzawa reported the synthesis of furans via the Pd-catalyzed cycloisomerization/allylation of β -alkynyl ketones with allyl carbonates as electrophilic partners.¹⁰⁹

In 2009, Yu developed a carbonylative cyclization of homopropargylic 1,3-diketones **2-224** with aryl iodides in the presence of CO to provide furans **2-225** (Scheme 61).¹¹⁰

Nishizawa reported that a range of 2-methylfurans **2-227** could be synthesized via a cycloisomerization of γ -ketoalkynes **2-226** in the presence of $Hg(OTf)_2$ catalyst under very mild reaction conditions with catalytic turnover numbers of up to 100 (Scheme 62).¹¹¹ The reaction is initiated by the π -activation of an alkynyl group with the $Hg(II)$ -catalyst toward an intramolecular attack of the carbonyl function. It should be noted that the employment of internal alkynes in this reaction provided poor to modest yields of products.

An analogous transformation of γ -ketoalkynes into furans was also studied by Hidai and Uemura¹¹² and by Arcadi¹¹³ in the presence of $PtCl_2$ and $Ph_3PAuOTf$ catalysts, respectively. Likewise, Krause et al. investigated the cycloisomerization of an array of γ -ketoalkynes **2-228** into furans **2-229** using a combination of an electrophilic Au(I) and Brønsted acid catalysts (Scheme 63).¹¹⁴ Furthermore, Cadierno and Gimeno reported

several examples of a similar Ru(II)-catalyzed reaction of terminal and internal γ -ketoalkynes leading to furan products.¹¹⁵

The synthesis of furans via a cycloisomerization of 2-en-4-yn-1-ols in the presence of mercuric sulphate catalyst was first reported by Heilbron et al. in 1946.^{116,117} One example of the 2,3-dimethylfuran synthesis via a Cu(II)-catalyzed cycloisomerization of (*Z*)-2-en-4-yn-1-ols was described by Végh et al. in 1990.¹¹⁸ A single example of the Rh-catalyzed version of the above cycloisomerization was described by Field and Messerle in 2000.¹¹⁹

The Ru(II)-catalyzed cycloisomerization of (*Z*)-pent-2-en-4-yn-1-ols **2-230** into a variety of 2,3,5-trisubstituted furans **2-231** was extensively studied by Dixneuf (Scheme 64).¹²⁰ The corresponding furans were obtained generally in good to high yields, although this reaction was specific to terminal alkynes only. The authors proposed a mechanism based on the electrophilic activation of the alkyne moiety by the Ru catalyst (**2-232**), followed by an intramolecular addition of the hydroxy function at the internal carbon atom of an alkyne to form intermediate **2-233**. A subsequent protodemetalation–isomerization sequence furnished furan **2-231** (Scheme 64). The same group also reported that the Pd(OAc)₂-catalyzed cycloisomerization of internal aryl-substituted enynols provided benzyl-substituted furans in moderate yields.

Alongside, Marshall et al. observed that this transformation involving internal alkynes occurred in the presence of 10 mol % AgNO₃-catalyst supported on a silica gel to provide furan products in good yields.¹²¹ Next, Hashmi demonstrated that the cycloisomerization of (*Z*)-pent-2-en-4-yn-1-ols could be achieved using 0.1 mol % AuCl₃ at room temperature.^{39b} This reaction could also be performed with high efficiency in aqueous solution in the presence of 1 mol % of several water-soluble Ru-, Rh-, and Ir-catalysts.¹²² More recently, the scope of the Au-catalyzed version was further investigated by Liu. Thus, it was shown that fully substituted furans **2-235** possessing a range of functional groups could efficiently be synthesized from enynols **2-234** (Scheme 65).¹²³ Perumal et al. employed the Au(III)-catalyzed cycloisomerization of 2-alkynylcycloalk-2-enols for an efficient synthesis of fused furans.¹²⁴ In 2011, Hashmi et al. employed Au(I)-carbene complexes for the synthesis of furans via the cycloisomerization of 2-alkynylallyl alcohols under very mild conditions.¹²⁵

Along this line, Gabriele and Salerno developed a general method for fully-substituted furan **2-237** synthesis based on the cycloisomerization of (*Z*)-2-en-4-yn-1-ols **2-236** using PdI₂ as a catalyst.¹²⁶ The reaction proceeds well with various substrates and gives the corresponding furans in high yields (Scheme 66).¹²⁷ The synthesis of furans via the Pd-catalyzed cycloisomerization of (*Z*)-2-en-4-yn-1-ols was also studied by Cadierno et al.¹²⁸ and Zeni et al.¹²⁹

Later, the same groups expanded the scope of this transformation. Thus, the Pd-catalyzed oxidative carbonylation of (*Z*)-2-en-4-yn-1-ols **2-238** in the presence of dioxygen in MeOH affords the corresponding 2-furylacetic acid esters **2-239** in good yields (Scheme 67).^{127a,130} Subsequently, it was also found that terminal (*Z*)-2-en-4-yn-1-ols **2-240** could efficiently be converted into the corresponding 2-furan-2-ylacetamides **2-241** in the presence of secondary amines via the PdI₂-catalyzed oxidative aminocarbonylation reaction (Scheme 67).¹³¹

In 2011, Gagosz et al. reported synthesis of furans **2-243** via the Au(I)-catalyzed cycloisomerization/Claisen type rearrangement of enynyl allyl ethers **2-242**. The reaction proceeds via the initial cycloisomerization (**2-244**) to form cyclic oxonium vinylgold intermediate **2-245** followed by its Claisen-type rearrangement into **2-246**. A subsequent aromatization and protiodeauration of the latter leads to the product **2-243** (Scheme 68).¹³²

Oi and Inoue disclosed the Rh(I)-catalyzed assembly of 3,4-disubstituted furans **2-248** from allyl propargyl ethers **2-247** in moderate yields (Scheme 69).¹³³

The Ag-catalyzed cycloisomerization of β -alkynyl allylic alcohols **2-249** was first investigated by Marshall. While various Ag salts provided quite high yields of trisubstituted furans **2-250**, it was found that performing the cycloisomerization reaction in the presence of 10 mol % of AgNO₃ supported on a silica gel in nonpolar hexane solvent provided highest yields of furans in shorter reaction times (Scheme 70).^{121,134}

The Pd-catalyzed version of the above process was utilized for the synthesis of 3-trifluoroethylfurans **2-252** from CF₃-alkynyl allylic alcohols **2-251** by Qing et al. (Scheme 71).¹³⁵ This method allows to obtain furan products **2-252** in yields comparable to those achieved under the Ag-catalyzed protocol.

Recently, Yuan reported the Ag-catalyzed synthesis of C2-trifluoromethylated furans **2-254** from the corresponding alkynyl allylic alcohols **2-253**. However, this reaction is limited to substrates bearing electron-withdrawing aromatic substituents (R²) (Scheme 72).¹³⁶

Later, Lee adopted this methodology for the cycloisomerization of allenynes-1,6-diols **2-255**. These ambident substrates readily underwent cyclization into 3-vinylfurans **2-256** in the presence of AgOTf catalyst (Scheme 73).¹³⁷

The same group recently reported a facile Au(I)-catalyzed cycloisomerization of alkynyl allylic alcohols **2-257**, possessing a tethered alkene moiety, to give trisubstituted furans **2-258** (Scheme 74).¹³⁸ Monosubstituted alkene moiety in **2-257** (R³=H) remained intact during the cycloisomerization reaction, whereas if 1,1-disubstituted alkene moiety is present (R³ = Me), it underwent a partial isomerization of the double bond, still favoring the formation of a terminal alkene.

In 2002, Ohe and Uemura described a novel Cr(0)-catalyzed approach for assembly of furan ring from enynones. Thus, the reaction of 1-benzoyl-1-buten-3-yne **2-259** with *tert*-butyl vinyl ether led to the formation of cyclopropyl furan **2-260** (Scheme 75).¹³⁹ This cascade reaction proceeds via 5-*exo-dig* cyclization involving a nucleophilic attack of carbonyl oxygen at the activated triple bond in complex **2-261**, which can also be represented as a polarized η^1 -complex **2-262**, to produce a relatively stable (2-furyl)carbene-metal complex **2-263**.¹⁴⁰ A subsequent [2+1] cycloaddition reaction of **2-263** with the double bond of *tert*-butyl vinyl ether yields the cyclopropyl furan **2-260** (Scheme 75). Besides *tert*-butyl vinyl ether, different mono-, di-, and trisubstituted alkenes can be tolerated in this transformation, wherein the stereoselectivity of the reaction depends on alkene substituents. It is worth mentioning that other group VI metals are also capable of catalyzing this transformation. Moreover, Ir and Rh catalysts were also found to be quite efficient. Finally, it was shown that the oxidation reaction of the (2-furyl)carbene-metal complexes **2-263**, obtained from stoichiometric reactions between enynones and metal carbonyls, provided 2-formyl furans in moderate yields.¹³⁹ A single example of an Au(III)-catalyzed version of the above cyclization/cyclopropanation reaction was demonstrated by Zhang.¹⁴¹

Most importantly, the generation of transient (2-furyl)carbene complex intermediates of type **2-263** opens a possibility for the incorporation into a sequence a wide array of other transformations characteristic for metal-carbene complexes. Thus, Uemura reported that related rhodium (2-furyl)carbenoid intermediates could be intercepted by C-H, O-H, N-H, Si-H, and S-H bond insertion processes furnishing functionalized furan derivatives **2-265** (Scheme 76).¹⁴² In addition, this chemistry was further expanded to a diazoalkane-free Doyle-Kirmse reaction wherein the Rh(II)-catalyzed cascade transformation of enynones

2-266 in the presence of allylic sulfides led to the corresponding 2-furylmethyl sulfides **2-267** (Scheme 76).¹⁴³ Along this line, it was also shown that the carbenoid species, generated *in situ* from the precursor **2-268**, could be trapped with PPh₃ to produce a phosphorous ylide intermediate. The latter then undergoes Wittig reaction with benzaldehyde to afford the 2-styrylfuran **2-269** in good yield (Scheme 76).¹⁴⁴

The above cascade transformations proceeding via the furyl metal-carbene intermediates were further applied to the synthesis of furan-containing polymers. Thus, the Rh(II)-catalyzed polymerization of enynones **2-270** possessing vinyl substituent in the benzene ring affords the corresponding cyclopropyl-linked polymers **2-271** in good yields with a degree of polymerization reaching 27 – 29. Likewise, *m*- and *p*-formyl derivatives **2-272** could be transformed into the corresponding polymers **2-273** with a similar degree of polymerization (Scheme 77).¹⁴⁴

Barluenga group described an alternative approach toward generation of the above-described key reactive (2-furyl)carbenoid intermediates (see also Scheme 75).¹⁴⁵ Thus, it was shown that the Cu(I)-catalyzed isomerization of diyne acetate **2-274** proceeds via a formation of enynone **2-276**, which upon a subsequent cycloisomerization step, furnishes the corresponding (2-furyl)carbene–Cu complex **2-277**. The latter could efficiently be trapped with a variety of electrophiles to give densely functionalized furan products. For instance, oxidation of transient (2-furyl)carbenoids with air gives access to 2-acyl furans **2-278**.¹⁴⁶ On the other hand, insertion of **2-277** into Si–H and Ge–H bonds produces the corresponding furan derivatives **2-279**.¹⁴⁶ Likewise, a carbene cross-dimerization reaction with ethyl diazoacetate leads to 2-alkenyl furans **2-280** in high yields.¹⁴⁶ In addition, the Cu(I)-catalyzed reaction of **2-274** with vinyl diazoacetates affords furyl-substituted cyclobutenes **2-281** in moderate to good yields (Scheme 78).¹⁴⁷

The synthesis of furans via the Au-catalyzed version of the enynone cyclization terminated by the intramolecular cyclopropanation reaction of a transient Au-carbenoid intermediate was described by Oh. Accordingly, the Au(III)-catalyzed cascade cycloisomerization of **2-282** bearing a double bond tethered by aliphatic or *N*-containing alkyl chain furnishes the corresponding bicyclo[3.1.0]hexane-substituted furans **2-283** (Scheme 79).¹⁴⁸

In 2007, Oh reported an interesting Pd-catalyzed cycloreduction reaction of conjugated enynals **2-284** bearing a tethered alkyne unit towards the synthesis of methylenecycloalkyl-substituted furans **2-285**. This cascade reaction occurs via a sequence of steps beginning with hydropalladation of the terminal alkyne moiety in **2-284** with HPdOCOH species, followed by carbopalladation of the internal alkyne with vinyl palladium species to afford intermediate **2-286**. A subsequent carbonyl oxygen attack at the Pd-center triggers fragmentation of the formate ligand into CO₂, concomitant with the 1,6-addition of hydride to the dienone unit in **2-286** from a sterically less-hindered site to form oxapalladacycle **2-287**. Finally, reductive elimination step in the latter gives the furan **2-285** and regenerates the Pd-catalyst (Scheme 80).¹⁴⁹

Ohe recently described the synthesis of α,β -unsaturated *N*-furylimines **2-290** via a catalytic vinylcarbene-transfer reaction to β -cyanoenone compounds **2-288**. It was shown that propargyl ester **2-289** undergoes a Rautenstrauch-type rearrangement in the presence of Pt(II) catalyst to generate carbenoid **2-291**, which upon a subsequent reaction with the nitrile group in **2-288**, followed by a cyclization step of resulting **2-292**, furnishes the furan product **2-290**. This methodology gives an efficient access to an array of 2-aminofuran derivatives (Scheme 81).¹⁵⁰

Cyclopropyl-containing alkynyl ketones could also undergo a transition metal-catalyzed cycloisomerizations into furans. Thus, Schmalz and co-workers recently reported an interesting highly efficient Au(I)-catalyzed cascade cycloisomerization of geminal acyl alkynyl cyclopropanes **2-291** in the presence of nucleophiles to give densely functionalized furans **2-292** (Scheme 82).¹⁵¹ This reaction proceeded under very mild reaction conditions and a variety of nucleophiles, such as alcohols, including *tert*-butanol, phenols, acetic acid, 2-pyrrolidone, and indole, were tolerated. In addition, this transformation could be catalyzed by Cu(II)- and Ag-triflates, albeit with somewhat lower efficiencies. According to the recent DFT calculations by Zhao¹⁵² and Li,¹⁵³ this reaction proceeds via the cycloisomerization of activated molecule **2-293** to produce cyclic intermediate **2-294**, which is better represented by a more delocalized species **2-294a**, followed by the attack of a nucleophile (**2-295**) and protodeauration step (Scheme 82).

In a recent report on the fused furan synthesis, Zhang and co-workers took an advantage of a facile ring opening of the cyclopropane ring in acyl alkynyl cyclopropanes **2-296** to generate a [1,4]-Au-containing dipole **2-299** that could be intercepted in a subsequent stepwise formal [4+2] cycloaddition reaction (Scheme 83). A range of annulated furans **2-300** were obtained in good yields using this Au(I)-catalyzed cycloisomerization–annulation cascade reaction in the presence of a variety of dipolarophiles **2-297**, including indoles, aldehydes, ketones, imines, and silyl enol ethers (Scheme 83).¹⁵⁴ A single example of this transformation with α,β -unsaturated imines ($R^4 = 2$ -(2-methyl)styrenyl) was also reported.¹⁰⁴

Later, Wang described a similar Cu(II)- or Au(III)-catalyzed formal [4+3] cycloaddition reaction of 1-(1-alkynyl) cyclopropyl ketones **2-302** and nitrones **2-301** to produce furan derivatives **2-303** in a stereoselective fashion in good yields (Scheme 84).¹⁵⁵

Recently, Zhang et al. also developed the Rh(I)-catalyzed cycloisomerization/carbonylation cascade transformation of 1-(1-alkynyl) cyclopropyl ketones **2-304** into the corresponding polysubstituted furans **2-307**.¹⁵⁶ Mechanistically, this reaction begins with a regioselective oxidative addition of the Rh(I) complex into the C1–C2 bond of a cyclopropane to generate rhodacyclobutane **2-305** that undergoes cyclization into a fused furan-derived rhodacyclopentane **2-306**. Subsequent carbonylation and reductive elimination of the Rh(I) catalyst processes gives furan **2-307** (Scheme 85). Using this method, a variety of substituted C3–C4-fused bicyclic furans bearing different functional groups could be obtained in good to excellent yields. Interestingly, the configuration of a substituted cyclopropane ring dramatically affects the reaction pathway. Thus, the cycloisomerization of (1*R**,2*R**)-*trans*-**2-304** yields normal carbonylation products **2-307**, whereas the reaction of (1*R**,2*S**)-*cis* isomers **2-308** produces C3-allyl-substituted furan **2-311**. Apparently, in the latter case, the initially formed rhodacyclobutane **2-309** undergoes β -hydride elimination/reductive elimination to produce allenyl ketone **2-310**. A subsequent Rh(I)-catalyzed cycloisomerization of **2-310** gives furan **2-311** (Scheme 85).

The first example of a transition metal-catalyzed cycloisomerization of cyclopropenes **2-312**¹⁵⁷ into furans **2-313** was demonstrated by Nefedov (Scheme 86).¹⁵⁸ It was proposed that this rearrangement proceeds via a carbenoid intermediate.¹⁵⁹ Formation of furan products during the Rh(II)-catalyzed cyclopropenation reaction of alkynes, which potentially involved generation of cyclopropene intermediates followed by their subsequent cycloisomerization, was later reported by several research groups, including Liebeskind, Davies, and Müller.¹⁶⁰

Later, Padwa reported a regioselective Rh(II)-catalyzed room temperature cycloisomerization of trisubstituted cyclopropenyl ketones into 2,3,4-trisubstituted furans **2-319**.¹⁶¹ In contrast, employment of a Rh(I) catalyst affords 2,3,5-trisubstituted furans

2-324 as single regioisomers in high yields (Scheme 87). It was proposed that in the case of the Rh(II) catalyst, a preferential electrophilic attack by bulky Rh(II) catalyst occurs at the cyclopropene double bond (**2-315**) to produce the most stabilized tertiary cyclopropyl carbocation **2-316** (Path A). A subsequent ring opening of the latter produced key Rh-carbenoid intermediate **2-317** that undergoes a cyclization into zwitterionic species **2-318**, wherein elimination of the Rh(II) catalyst affords “normal” product **2-319**. To account for the opposite regiochemistry in the case of Rh(I) catalyst, a formation of metallacyclobutene species **2-322**, available either via a direct oxidative addition of Rh(I) into the C1–C3 bond of a cyclopropene or through the cycloreversion–cycloaddition pathway, was suggested. A subsequent cyclization of **2-322** followed by a reductive elimination (**2-323**) furnished furan **2-324** (Scheme 87).

The recent study from Ma group demonstrated that the Cu(I)-catalyzed cycloisomerization of cyclopropenyl ketones **2-325** proceeded regioselectively providing the corresponding 2,3,4-trisubstituted furans **2-326a** (Scheme 88).¹⁶² A variety of functional groups could be tolerated under the reaction conditions. It should be noted that employment of a Pd(II)-catalyst completely changed the regioselectivity of this transformation, affording the isomeric 2,3,5-trisubstituted furans **2-326b** (Scheme 88).

According to the proposed mechanism, a regioselective iodocupration of the carbon-carbon double bond in cyclopropene **2-325** generates intermediate **2-327a**. A subsequent β -decarbocupration gives the copper enolate **2-328a**. Next, an intramolecular *endo*-mode insertion of the carbon-carbon double bond into the copper-oxygen bond of **2-328a** to generate **2-329a** is followed by a β -halide elimination to furnish product **2-326a**. In the case of Pd-catalyzed reaction, a regioselective chloropalladation of the double bond in the cyclopropenyl ketone **2-325** affords the palladium intermediate **2-327b**, which upon β -decarbopalladation produces species **2-328b**. A subsequent intramolecular *endo*-oxypalladation of the vinyl chloride moiety in the latter followed by the β -halide elimination (**2-329b**) gives the regioisomeric product **2-326b** (Scheme 89).

The same group also reported that, besides cyclopropenyl ketones, methylenecyclopropyl ketones could undergo a transition metal-catalyzed cycloisomerization to give furans.¹⁶³ Accordingly, the Pd-catalyzed cycloisomerization of **2-330** in the presence of NaI affords the corresponding furans **2-331** in high yields. Mechanistically, it was suggested that the nucleophilic attack of iodide anion at the Pd(II)-activated methylenecyclopropane C=C double bond (**2-332**) generates intermediate **2-333**. A subsequent ring opening of **2-333** affords Pd-enolate-type intermediate **2-334**, which undergoes intramolecular allylic substitution to form dihydrofuran **2-335**. Finally, isomerization of the double bond in **2-336** furnishes furan **2-331** (Scheme 90). Interestingly, the reaction could proceed in the presence of NaI and without the Pd catalyst, albeit with a slightly lower efficiency.¹⁶⁴

2.1.2. Synthesis of Furans via Cycloisomerization-Elimination Processes—In 1998, Wipf described the synthesis of furans via a cascade cycloisomerization–elimination reaction of alkynyl ketones **2-336** containing a leaving group. The reaction affords 2-alkenyl furans **2-337** in good yields (Scheme 91).¹⁶⁵ According to the mechanism proposed by the authors, the reaction occurs via a 5-*exo-dig* cyclization of **2-336** to generate allene intermediate **2-338**, followed by its stepwise prototropic aromatization via intermediate **2-339** into furan **2-337**. Consequently, the *E/Z*-stereoselectivity of the alkene fragment in **2-337** is governed by steric effects of substituents R² and R³.¹⁶⁶ Later, this approach was utilized in the total synthesis of furan-containing natural products by the same group.^{166–167}

Transformation of alkynyl glycols in the presence of stoichiometric amounts of Hg-salts into mercurated furan compounds was first demonstrated by Fabritsy in 1959.¹⁶⁸ Later,

cycloisomerization of alkynyl glycols, including monoprotected ones, in the presence of Pd(II) catalysts was studied by Utimoto.^{74a,169} These reactions usually proceed via 5-*endo-dig* cyclization involving a nucleophilic attack of the oxygen atom at the activated by a π -philic metal alkyne moiety in alkynyl glycols followed by elimination of the second hydroxy- or protected hydroxy functions. Analogous reactions could be performed using Ag(I)-, Au(I)-, or Cu(II) catalysts (*vide infra*).

In 2002, Miyashita described an example of the Ag(I)-catalyzed formation of furans **2-341** from the corresponding 3-alkynyl-1,2-diols **2-340**.¹⁷⁰ Later, Knight studied the cycloisomerization of alkynyl diols in the presence of catalytic amounts of AgNO₃ absorbed on a silica gel.¹⁷¹ The reaction affords a variety of trisubstituted furans in almost quantitative yields, however it is not efficient with terminal acetylenes (Scheme 92). Employment of electrophilic Au(I) catalyst by Aponick¹⁷² and Akai¹⁷³ allowed to significantly expand the scope of this reaction (Scheme 92). More recently, Gabriele group described the Cu(II)-catalyzed version of this cycloisomerization reaction (Scheme 92).¹⁷⁴ A single example of the Cu(II)-catalyzed iodocyclization process leading to the corresponding 3-iodofuran was described by Liang.¹⁷⁵ Moreover, Alcaide and Almendros demonstrated a single example of analogous cyclization/elimination reaction of isomeric to **2-340** allenyl glycerols in the presence of a Pt(II) catalyst.¹⁷⁶ In 2011, Deslongchamps reported a highly efficient Hg(II)-catalyzed cycloisomerization–elimination reaction of 3-alkynyl-1,2-diols into furans.¹⁷⁷

Along this line, Gabriele reported the Pd-catalyzed cycloisomerization–elimination–carbonylation cascade transformation of alkynyl diols **2-342** into furans **2-343**. Accordingly, the cyclization of **2-342** under CO-air atmosphere in methanol or ethanol affords the corresponding furan-3-carboxylic acid esters in good yields (Scheme 93).¹⁷⁸

Hammond developed an interesting approach toward 3-fluorofurans **2-345** based on the Ag(I)-catalyzed cycloisomerization of *gem*-difluoropropargyl alcohols **2-344**.¹⁷⁹ The initial cyclization of **2-344** leads to 3,3-difluoro-4,5-dihydrofuran intermediates **2-346** that are subsequently converted into the fluorinated furans **2-345** via elimination of HF in the presence of silica gel (Scheme 94). The same group also utilized this methodology in a two-component synthesis of 2,5-disubstituted furans from fluoropropargyl chlorides and aldehydes using In(0)- or InCl₃ catalysts along with 10 equivalents of Zn dust.¹⁸⁰

Metal complexes of Mo or Ru could catalyze the cycloisomerization of alkynyl glycols possessing terminal alkyne moiety via an alternative activation mode involving formation of the metal-allenylidene species. Thus, in 1993 McDonald described the Mo-mediated cycloisomerization of alkynyl glycols into the furans **2-347**. The reaction proceeds via formation of the allenylidene-metal complex **2-348**, followed by its subsequent cyclization.¹⁸¹ More recently, Nishibayashi studied the Ru-catalyzed version of the McDonald's cycloisomerization reaction of terminal 3-alkynyl-1,2-diols into the corresponding 2,3-disubstituted furans **2-349**. A variety of alkyl- and aryl-substituted furans could be obtained via this methodology. Similarly, this transformation proceeds via the formation of allenylidene-Ru intermediate **2-348a** (Scheme 95).¹⁸²

More recently, Ma et al. developed two cycloisomerization processes of 2-en-4-yne-1,6-diols **2-350** using Au(I) or Pd(II) catalysts. The Au(I)-catalyzed cycloisomerization–elimination–aromatization reaction of **2-350** affords alkenyl furans **2-351** efficiently (Scheme 96). On the other hand, performing the cycloisomerization reaction in the presence of Pd(II) catalyst allows efficient trapping transient Pd-species with electrophiles, such as allyl bromides **2-352**, to produce fully substituted alkenyl furans **2-353**. Mechanistically, the

Pd(II)-catalyzed transformation occurs via a cascade sequence of processes involving cyclization, cross-coupling, elimination, and aromatization steps (Scheme 96).¹⁸³

In 2007, Lu reported a facile and efficient Pd(II)-catalyzed cycloisomerization reaction of β -alkynyl allylic alcohols **2-354** into trifluoropropenyl-substituted furans **2-355** (Scheme 97).¹⁸⁴ During the cycloisomerization reaction, the siloxy group undergoes a concomitant elimination leading to formation of the C3-alkenyl substituent in **2-355**. Compounds **2-354** bearing Alkyl-, aryl-, and hetaryl substituents at both alkyne and alcohol moieties could be converted to furans under these reaction conditions.

In 1991, Fürstner reported an interesting method for the preparation of polysubstituted furans from β -acyloxyenones featuring a McMurry-type reaction mediated by a highly reactive Ti on graphite reagent.¹⁸⁵ In 1993, Lu disclosed an analogous approach to 2,5-disubstituted furans featuring the Pd₂(dba)₃•CHCl₃/resinsulfonic acid-catalyzed isomerization of but-2-yne-1,4-diols into γ -hydroxyenones followed by their subsequent cyclocondensation.¹⁸⁶

In 2007, Williams developed the Ru-catalyzed version of the above chemistry. The reaction is performed with only 1 mol% of Ru(PPh₃)₃(CO)H₂/xantphos (1:1) catalyst, providing various 2,5-disubstituted alkyl- and arylfurans **2-357** in moderate to high yields (Scheme 98). In contrast to the Lu's chemistry, this reaction was proposed to occur via formation of 1,4-diketone intermediate **2-358**, which was always observed as a byproduct, followed by the Paal-Knorr cyclocondensation step.¹⁸⁷

Alongside, Tanaka reported the synthesis of furans **2-360** via the Rh(I)-catalyzed cycloisomerization of monoprotected 2-butyne-1,4-diol derivatives **2-359**. This reaction occurs via the initial rearrangement of alcohol **2-359** into enone **2-361** that subsequently cyclizes and aromatizes to give furan **2-360** via cyclic oxonium intermediate **2-362** (Scheme 99).¹⁸⁸

In 2011, Ferreira et al. reported the Pt(II)-catalyzed cycloisomerization of skipped propargyl alcohols **2-364** into furans **2-365**. According to the proposed mechanism, the reaction proceeds via 5-*endo-dig* cyclization (**2-366**) and elimination of MeOH to form Pt-carbenoid **2-367**. A subsequent 1,2-H shift (**2-368**), followed by a tautomerization affords furan **2-365** (Scheme 100).⁶³ In the case of R² = Si, this transformation could also be accompanied by the 1,2-Si-migration to the platinum carbene center of **2-367** (see for details Scheme 19).

Several methods for the synthesis of furan derivatives from glycals or aldoses have been also developed. Accordingly, in 1999, Hayashi reported transformation of D-glucal into optically active furyl-substituted ethylene glycol in the presence of different metal catalysts such as Pd(II)-, Ru(II)-, Sm(III), and Yb(III) salts.¹⁸⁹ A similar process catalyzed by ZrCl₄/ZnI₂ system for D-glucal derivatives was recently disclosed by Shaw.¹⁹⁰ Finally, Nagarapu demonstrated a very efficient two component synthesis of polyhydroxyalkyl- and C-glycosylfurans from β -keto esters and unprotected sugar aldoses.¹⁹¹

Echavarren described an interesting cycloisomerization/elimination reaction of alkynyl ketone **2-369** into furan **2-370** catalyzed by cationic Au(I) complexes. Presumably, the reaction proceeds via a nucleophilic attack of the carbonyl oxygen atom at the Au(I)-activated triple bond of alkyne to form cyclic oxonium intermediate **2-371**. A subsequent debenzoylation, followed by protiodeauration and aromatization steps, affords furan product (Scheme 101).¹⁹²

Recently, Li reported the synthesis of furans via the Cu(I)-catalyzed intramolecular *O*-vinylation reaction of ketones. Thus, the Cu-catalyzed cyclization of halovinylketones **2-372**

gives multisubstituted furans **2-373** in good to excellent yields. Notably, ketones **2-372** containing both vinyl chloride and bromide moiety could equally well be employed in this transformation (Scheme 102).¹⁹³

Mioskowski, Falck and co-workers developed the Cr(III)-catalyzed radical cyclization/elimination approach toward C3-monosubstituted furans **2-375** possessing a variety of functional group. This method implies the use of trichloroethyl propargyl ethers **2-374**. (Scheme 103).¹⁹⁴

2.1.3. Synthesis of Furans via Cycloisomerization of Alkynyl Epoxides—The first report on cycloisomerization of alkynylepoxides into furan came from Miller group in 1969. It was shown that in the presence of the Hg(II) catalyst under acidic conditions alkynylepoxides **2-376** underwent cycloisomerization reaction into the corresponding 3-monosubstituted furans **2-377** (Scheme 104).¹⁹⁵

Later, McDonald and co-workers reported that 2-mono- and 2,3-disubstituted furans **2-379** could efficiently be synthesized from differently functionalized terminal alkynylepoxides **2-378** in the presence of *in situ* generated Et₃N:Mo(CO)₅ catalyst (Scheme 105).¹⁹⁶ The authors proposed a mechanism involving the initial alkyne–vinylidene isomerization^{23,197} of **2-378** into a reactive epoxyvinylidene-Mo complex **2-379**. The latter undergoes a concerted rearrangement into a cyclic alkenyloxacarbenoid **2-381**, which upon deprotonation with triethylamine ligand, gives a furyl-Mo zwitterionic intermediate **2-382**. A subsequent protodemetalation of the latter furnishes furan **2-379** and regenerates the Mo(0) catalyst (Scheme 105). Apparently, involvement of the alkyne–vinylidene isomerization step limits the applicability of this method to terminal alkynes only.

Liu group further elaborated the scope of this reaction with the Ru(II) catalyst (Scheme 106).¹⁹⁸ Thus, a variety of 2- or 3-mono- and 2,3-disubstituted furans **2-384** possessing a range of functional groups were synthesized in good to high yields from the corresponding terminal epoxyalkynes **2-383** using 1–2 mol% catalyst loadings. Mechanistic studies of this Ru(II)-catalyzed transformation using D-labeling experiments supported a mechanism analogous to that proposed by McDonald for the Mo(0)-catalyzed reaction (Scheme 106).

Hashmi proposed that the major limitation of the above chemistries (the use of terminal alkynes) could be alleviated if a different mode of substrate activation is engaged. Accordingly, the Au(III) catalyst was shown to be quite efficient in the cycloisomerization of internal epoxyacetylenes **2-385** into the corresponding 2,4-disubstituted furans **2-386** (Scheme 107).¹⁹⁹ Although, a variety of functional groups are tolerated under the Au(III)-catalyzed reaction conditions, the scope of this transformation is somewhat limited to substrates bearing nucleophilic hydroxyalkyl substituents. The proposed mechanism involves the initial activation of the alkyne moiety by a π -philic Au(III) catalyst (**2-387**) toward a subsequent cycloisomerization into furyl-Au intermediate **2-388**, followed by a proton elimination–protiodeauration (**2-389**) sequence (Scheme 107).

In a recent study, Yoshida demonstrated that the cycloisomerization of alkynylepoxides **2-390** into furans **2-391** could be achieved using the Pt(II) catalyst. Notably, the scope of this transformation was significantly improved, and high yields of 2,4-di- and fused 2,3,5-trisubstituted furans **2-391** were achieved in short (10 minutes) reaction time by using PtCl₂ catalyst in dioxane–water reaction media. In addition, it was demonstrated that the reactive furyl-Pt intermediate (analogous to **2-389**) could be intercepted with electrophiles such as NIS affording valuable tetrasubstituted 3-iodofuran **2-393** amenable for further functionalization reactions (Scheme 108).²⁰⁰

Along this line, Pale developed the Ag-catalyzed cycloisomerizations of alkynyl epoxides **2-394** into polysubstituted furans **2-395** (Scheme 109).²⁰¹ Thorough mechanistic studies performed by the authors suggested that during the AgOTf/*p*-TsOH-catalyzed reaction, epoxide **2-394** undergoes a ring opening reaction with methanol to produce alkynyl glycol derivative **2-396**, which in turn undergoes 5-*endo-dig* cyclization, followed by the elimination of MeOH to form furan **2-395** (Scheme 109).²⁰¹ The scope of the reaction is quite broad, however, it is limited to internal alkynes only.

In contrast, the use of Au(I) catalyst allowed to extend the scope and efficiency of this transformation. Thus, the Au(I)-catalyzed cycloisomerization of alkynyl epoxides **2-397** furnishes the corresponding furans **2-398** in high yields. It was shown that the reaction proceeds via a ring opening to form products **2-399a** and **2-399b**, both of which cyclize under the reaction conditions in the presence of the Au(I)-catalyst to provide furans **2-398** (Scheme 110).²⁰²

In 2001, Aurrecochea et al. introduced a sequential reaction for the synthesis of polysubstituted furans **2-401** beginning with the SmI₂-promoted reduction-elimination reaction of propargyl ester-derived epoxides **2-400** to give [3]cumulenol intermediates **2-402**. A subsequent Pd(II)-catalyzed 5-*endo-dig* cyclization of the latter produces Pd-species **2-403**, which upon tautomerization (**2-404**) and protonation steps finally furnishes furan **2-401** (Scheme 111).²⁰³ A variety of functionalized furans could be accessed in moderate to high yields by using this methodology. However, this approach is limited to the employment of substrates bearing aliphatic R³ and R⁴ substituents, as aryl-containing epoxides **2-400** give no furan products.

Later, the same group extended the above chemistry to a two-component stepwise arylative cascade transformation of alkynyl epoxides **2-405** with aryl halides to synthesize the C3-arylated furans **2-406** (Scheme 112).²⁰⁴ Among various electrophilic aryl cross-coupling components, both bromides and iodides, and even triflates, were quite efficient, providing up-to-fully-substituted furans **2-406** bearing an array of functional groups.

More recently, Aurrecochea demonstrated that the furyl-Pd species analogous to **2-404** (*vide supra*) could efficiently be intercepted with a range of α,β -unsaturated compounds. Depending on the choice of the reaction conditions, this two-component transformation provides either Heck- or conjugate-addition-type products **2-409** or **2-410**, respectively. Specifically, the use of a Pd(0) precatalyst under basic reaction conditions results in the formation of C3-vinyl furans **2-409**, whereas Pd(OAc)₂-catalyzed reaction in the absence of a base furnishes the C3-alkylated products **2-410** (Scheme 113).²⁰⁵

Following Liang's report (*vide supra*),²⁰⁶ Pale recently developed a mild and efficient Au(I)-catalyzed cycloisomerization/nucleophilic substitution cascade reaction of alkynyl epoxides **2-411**, possessing a leaving group at the propargyl position, into furans **2-412** (Scheme 114).²⁰⁷ Among nucleophiles tested in this transformation, primary, secondary, allylic, and benzylic alcohols and alkyl thiols were tolerated, furnishing furans **2-412** in moderate to excellent yields. In contrast, tertiary and unprotected propargyl alcohols, benzyl amine, and benzenesulfonamide did not provide any furan products. A single example of this reaction catalyzed by the AgOTf/TsOH system was later reported by the same group.²⁰²

In 2011, Zhang et al. reported the Rh-catalyzed tandem heterocyclization/[4+1] cycloaddition of 1-(1-alkynyl)oxiranyl ketones **2-415** in the presence of CO furnishing the corresponding furans **2-416** in good to excellent yields. Notably, this reaction represents a rare example of the Rh-catalyzed C–C bond cleavage of epoxide instead of a well known C–O bond cleavage process (Scheme 115).²⁰⁸

The first example of a transition metal-catalyzed cycloisomerization of skipped propargyl oxirane **2-417** into furans **2-418** was developed by Miller in 1969 (Scheme 116).¹⁹⁵

Later, Marson studied the cycloisomerization of skipped propargyl oxiranes **2-419** possessing a hydroxy group at the propargylic position into 2,5-di- and 2,3,5-trisubstituted furans in the presence of HgSO₄ (Scheme 117).²⁰⁹ The authors proposed that the initially formed common intermediate 2,3-dihydrofuran **2-420** undergoes different types of fragmentation processes to give functionalized furans **2-421** or **2-422**, depending on a substitution pattern. Accordingly, in the case when R³ is H, elimination of water molecule from **2-420** affords hydroxymethyl-substituted furan **2-421**, whereas a Grob-type fragmentation occurs for a spiro-containing **2-420** to provide furans **2-422**.

Transformation of skipped propargyl oxirane esters **2-423** into furans **2-425** was investigated by Aurrecoechea (Scheme 118).²¹⁰ Thus, treatment of **2-423** with stoichiometric amounts of SmI₂ in the presence of a Pd(0) catalyst first produced 2-en-4-yn-1-ol intermediates **2-424**, which upon a subsequent thermal cyclization provided furans **2-425** in moderate yields. Apparent limitation of this chemistry is the generation of *E/Z* isomeric mixtures of 2-en-4-yn-1-ols **2-424** at the first step, whereupon only the *Z*-intermediate could undergo the cyclization into furan. Consequently, this methodology could only be utilized for substrates where geometrical constraints impede formation of *E*-isomers, as exemplified by the synthesis of C3–C4 fused furans.

Recently, Liang reported the Au(III)-catalyzed cycloisomerization of a similar propargylic oxirane system into furans. Thus, propargylic acetates **2-426**, possessing an epoxide moiety, efficiently provided hydroxymethyl-substituted furan derivatives **2-427** in the presence of AuCl₃ catalyst and an external nucleophile (Scheme 119).²⁰⁶ The cycloisomerization reaction occurred under mild reaction conditions and with only 2 mol% of catalyst used. In addition, a variety of functionalized epoxides **2-426**, as well as an array of alcohols as O-nucleophiles, including sterically congested ones, could be employed in this transformation.

According to the proposed mechanism (Scheme 120), activation of the alkyne by the Au(III)-catalyst in **2-428** triggers a subsequent domino nucleophilic attack/*endo-dig* cyclization affording dihydrofuryl-Au intermediate **2-429**. The latter is transformed into the corresponding furan upon protodemetalation and aromatization steps (**2-430**). Alternatively, the reaction may proceed in a stepwise fashion with the involvement of a cyclic oxonium ion **2-428a**, followed by an epoxide ring opening initiated by an attack of the external O-nucleophile to produce the common intermediate **2-429**.

Similar transformations of epoxides bearing an alkyne unit were reported to proceed in the presence of HAuCl₄,²¹¹ Ph₃PAuBF₄,²¹² and Cu(II) triflate – iodine¹⁷⁵ catalytic systems. The first two protocols offer an attractive approach for the synthesis of differently substituted difurylmethanes via the Friedel–Crafts type homodimerization reaction, whereas the latter provides an easy and modular access to up-to-fully-substituted 3-iodofurans. More recently, Liang extended the dimerization reaction to a cross-dimerization process with a variety of nucleophiles, including furans, pyrroles, indoles, acetylacetone, and sodium azide.²¹³

2.1.4. Synthesis of Furans via Oxidative Cycloisomerizations—In 1982, Couturier reported the synthesis of furans **2-432** via the Pd(II)/Cu(II)-catalyzed oxidative cycloisomerization of 2-butene-1,4 diols **2-431** in the presence of oxygen as a terminal oxidant (Scheme 121).²¹⁴

Later, Widenhoefer disclosed the Pd(II)-catalyzed oxidative cyclization of 2-allyl-1,3-diketones and their homologs **2-433** into the corresponding furans **2-434**. The reaction proceeds in the presence of stoichiometric amounts of Cu(II) as an oxidant and affords C3-acylfurans in good yields (Scheme 122).²¹⁵

In 2009, Beller and Dixneuf reported the synthesis of furan **2-436** via an oxidative cycloisomerization of dienyl ether **2-435** in the presence of stoichiometric amount of CuCl₂ and 20 mol % of TsOH under air. According to the proposed mechanism, the reaction begins with a deprotection of methyl ether to produce enone **2-437**, which undergoes a subsequent oxidative cyclization into the corresponding furan **2-436** in the presence of Cu(II) salts (Scheme 123).²¹⁶ The catalytic version of this cycloisomerization reaction was used in a one-pot formal [2+2+1] furan synthesis (see Scheme 172). An example of furan synthesis involving a similar cycloisomerization in the presence of Ag(I) salts was also described by Padwa.²¹⁷

Ray et al. recently described a Cu(I)-catalyzed cycloisomerization of enynone **2-440** in the presence of water and oxygen, as a terminal oxidant, to produce the corresponding 2-acylfurans **2-441** in good yields (Scheme 124).²¹⁸ Zhang described a similar Au(III)-catalyzed transformation in the presence of hydrogen peroxide as a terminal oxidant. Thus, the oxidative cycloisomerization of **2-442** proceeded under very mild reaction conditions and afforded furans **2-443** in good yields (Scheme 124).¹⁴¹ The reaction scope is quite general, as both alkyl- and aryl-substituted alkynes and ketones are all perfectly competent in this reaction. In the case of symmetrically substituted 1,3-diketones **2-442** (e.g. R¹ = Me, R² = COMe), excellent yields of single-isomer furan products have been achieved, whereas for the unsymmetrical substrates, a regioselectivity of the product formation was dependent on the initial geometry of the alkene unit in **2-442** and its stability toward *E/Z*-isomerization under the reaction conditions. Notably, the oxidative cycloisomerization of β -ketoester- and sulfonyl-containing (R² = CO₂R or SO₂Ph, respectively) substrates **2-442** proceeded highly regioselectively placing R²-substituent at the C-4 position of the 2-acylfuran **2-442**. In addition, in the case of β -ketoesters, both *E*- and *Z*-isomers of the starting material produced the latter single regioisomers **2-442**. According to the proposed mechanisms, both of the above reactions proceed via cyclization of enynones into the (2-furyl)carbene–Au complexes followed by a subsequent carbene oxidation step.

2.1.5. Synthesis of Furans via Ring-Closing Metathesis—Recently, an alternative methodology utilizing a ring-closing metathesis (RCM),^{8b,17a,219} has been developed for the synthesis of a variety of aromatic compounds,^{17b,c,220} including furans. Most commonly, in the case of furan synthesis, RCM first leads to the formation of dihydrofuran. A subsequent aromatization of RCM products can be achieved via several pathways: using substrates prefunctionalized with a double bond or a leaving group; application of cooperative catalysis for one-pot RCM/dehydrogenation tandem process; and a one-pot oxidation of intermediately formed dihydrofuran in the presence of an external oxidant (Figure 3).

In 1999, Harrity first reported the synthesis of furans using RCM–aromatization approach from starting materials incorporating diallyl ether moiety. For instance, cyclization of tetraene **2-444** or triene **2-445** catalyzed by the first-generation Grubbs catalyst produced spirocyclic acetal **2-446**, which was converted into C2-substituted furan **2-447** upon a subsequent *p*-TsOH-catalyzed ring opening reaction (Scheme 125).²²¹

Later, Donohoe reported an efficient synthesis of a variety of furans **2-449** from diallyl ethers **2-448**, using the second generation Grubbs catalyst (Scheme 126).²²² The aromatization step was achieved by the acid-mediated methanol elimination. This methodology was successfully applied for the preparation of pyrrolufuran **2-450** and bifuran **2-451**, as well as

for a facile assembly of the disubstituted furan moiety (**2-452**) in the total synthesis of (–)-*Z*-deoxypukalide (Scheme 126).²²³

More recently, the same group developed an efficient approach toward 2,5-di- and 2,3,5-trisubstituted furans **2-454** based on the RCM/aromatization sequence of homoallyl vinyl ethers **2-453** (Scheme 127).^{222b,224} The reaction produces furans in moderate yields and is more efficient for the synthesis of disubstituted products. Cyclization of substrates possessing 1,1-disubstituted double bond of the homoallyl moiety, as well as bulky R²-substituents at the vinyl ether double bond was not efficient.

Robertson et al. reported an RCM–oxidative aromatization two-step synthesis of pyrrolofuran **2-457** from the corresponding divinyl ether **2-456** (Scheme 128). The second, aromatization, step was accomplished by the use of 40 equiv of nickel(II) oxide.²²⁵ Along this line, Chattopadhyay reported the synthesis of unnatural furan-containing α -amino acids utilizing RCM reaction, catalyzed by the first generation Grubbs catalyst, followed by the aromatization of the dihydrofuran intermediate with DDQ.²²⁶

Schmidt demonstrated a sequential synthesis of furans involving RCM/isomerization, Heck–Matsuda, and aromatization reactions. It was shown that the isomerized intermediate dihydrofurans **2-458** could undergo the Pd(II)-catalyzed arylation followed by the oxidation with chloranil to produce the corresponding furans **2-459** in good yields (Scheme 129).²²⁷

Very recently, Schmidt also demonstrated an alternative strategy for the aromatization of RCM intermediates. Specifically, efficient RCM reaction of allyl acrylates **2-460** provided lactones **2-461** that were subsequently transformed into the corresponding phosphatyl oxy furans **2-462** using O-phosphatylation reaction (Scheme 130).²²⁸

Tae and co-workers developed an interesting approach toward di- and trisubstituted furans featuring a Fe(II)-catalyzed ring contraction reaction of 1,2-dioxines, which were prepared using a sequence consisting of an enyne-RCM and Diels–Alder reaction with dioxigen.²²⁹

2.2. Synthesis of Furans via Formal [4+1]-Cycloaddition Reactions

In 2010, Skrydstrup and co-workers reported the Au(I)-catalyzed double hydration of diynes **2-463** toward synthesis of 2,5-disubstituted furans **2-464** (Scheme 131). This transformation proceeds under relatively mild reaction conditions, affording furans in good yields.²³⁰

Liang et al. described the synthesis of furans via the Cu(I)-catalyzed formal [4+1] cycloaddition of α,β -alkynyl ketones **2-466** with diazo compounds **2-467**. Two mechanisms have been proposed for this transformation. According to the **Path A**, cyclopropanation reaction of the triple bond with the Cu(I)-carbenoid generated from diazoacetate leads to the acylcyclopropane **2-469**, which undergoes a subsequent ring-opening followed by the cycloisomerization reaction to produce furan **2-468**. In another scenario (**Path B**), the carbonyl group in **2-470** attacks the Cu-carbenoid to provide ylide intermediate **2-471**, cyclization of which furnishes the furan ring. The reaction tolerates various aryl substituted α,β -alkynyl ketones and gives furan products in moderate to high yields (Scheme 132).²³¹

Recently, Ma et al. described the synthesis of furans via the Cu(I)-catalyzed reaction of substituted 3-iodoprop-2-en-1-ols **2-472** with terminal alkynes. This methodology features the Cu(I)-catalyzed Sonogashira-type coupling, followed by a subsequent cycloisomerization of the *in situ* generated (*Z*)-pent-2-en-4-yn-1-ol intermediate, affording polysubstituted furans **2-473** (Scheme 133).²³²

Sauthier and Castanet disclosed an interesting “4+1” approach to furans **2-475** based on the Rh(I)-catalyzed reaction of propargyl alcohols **2-474** with arylboronic acids in the presence of carbon monoxide.²³³ The authors proposed generation of a γ -hydroxyenone **2-476** intermediate upon the Rh(I)-catalyzed carbonylative addition of boronic acids to the C–C triple bond of the propargyl alcohol, followed by its subsequent cyclocondensation into furan **2-475**. The reaction proceeds well with a range of arylboronic acids and gives mono- or disubstituted furans in moderate to good yields (Scheme 134).

In addition, several Mn(III)- and Ag(II)-mediated radical “4+1” methodologies have been developed for the synthesis of fused furans by Chuang.²³⁴

2.3. Synthesis of Furans via Formal [3+2]-Cycloaddition Reactions

Among many various formal [3+2] cycloaddition^{14a} approaches towards assembly of the furan core described in the literature, special attention was given to Rh- or Cu-catalyzed reactions between alkynes and α -diazocarbonyl compounds.^{19a,24a,235} This method quickly became very popular as a highly convenient and general tool for the construction of diversely substituted furans. Generally, this transformation, which is performed at elevated temperatures, affords furans directly in a single step without isolation or even observation of a possible cyclopropene intermediate (Section 2.1).

The first example of the Cu(II)-catalyzed reaction between α -diazooesters and internal alkynes leading to the corresponding 2-alkoxyfurans in moderate yields was demonstrated by D'yakonov in 1959.²³⁶ Later, Wang et al. reported optimized conditions for the Cu(I)-catalyzed dipolar cycloaddition reaction of diazocompounds **2-476** with terminal alkynes to prepare a variety of furans **2-477** in good to excellent yields (Scheme 135).²³⁷

Several research groups elaborated this transformation in the presence of different transition metal catalysts for an array of differently substituted α -diazocarbonyl compounds and alkynes. For instance, Davies reported that trisubstituted furans could be obtained via the Rh(II)-catalyzed formal [3+2] cycloaddition reaction between diazo-1,3-dicarbonyl compounds **2-478** and terminal alkynes (Scheme 136).^{160b} This protocol provided access to 2,3,5-trisubstituted furans **2-479** possessing various functional groups under relatively mild reaction conditions and low catalyst loading.

Synthesis of tetrasubstituted furans via intramolecular version of this methodology was developed by Padwa.²³⁸ Thus, alkyne-tethered diazoketones **2-480** and **2-482** underwent the Rh(II)-catalyzed formal [3+2] cycloaddition affording fused furans **2-481** and **2-483**, respectively (Scheme 137).

Later, Pirrung and co-workers investigated cyclic diazo-1,3-dicarbonyl compounds in the Rh(II)-catalyzed synthesis of fused furans (Scheme 138).²³⁹ Accordingly, diazocyclohexane-1,3-dione **2-484** underwent a formal [3+2] cycloaddition with a variety of terminal alkynes bearing labile functional groups in the presence of the Rh(II)-catalyst at room temperature to provide fused trisubstituted furans **2-485**. Expectedly, the use of unsymmetrical diazodiones led to the formation of mixtures of regioisomeric furans.

Many other research groups further investigated the scope of the Rh(II)-catalyzed synthesis of furans from alkynes and α -diazocarbonyl compounds.^{161b,240} Some representative results are summarized in Scheme 139. Tri- and tetrasubstituted furans possessing a wide array of functional groups and diverse substitution patterns could efficiently be accessed via this methodology. More recently, this methodology was used for the synthesis of fluorine-containing polysubstituted furans from fluoro-substituted diazocompounds and aromatic alkynes.²⁴¹ It was also demonstrated that iodonium ylides²⁴² and 2,2-dibromo-1,3-diones²⁴³

could be employed as carbene precursors instead of α -diazocarbonyl compounds in the above [3+2] cycloaddition reaction.²⁴⁴

Recently, Hsung utilized the above methodology for a facile synthesis of functionalized 2-amido-furans **2-489** from ynamides **2-487** and α -diazocarbonyl compounds or phenyl iodonium ylides **2-488** using the Rh(II) catalyst (Scheme 140).²⁴⁵

Several mechanistic possibilities were proposed to account for the formation of furan products in a Rh(II)-catalyzed [3+2] cycloaddition reaction between α -diazocarbonyl compounds and alkynes (Scheme 141). First, the reaction of diazo compound **2-487** with rhodium(II) carboxylate generates the Rh-carbenoid species **2-490**. According to the **Path A**, a direct nucleophilic attack²⁴⁶ of alkyne produces **2-491**, which then cyclizes to form furan **2-489** via a cyclic zwitterion **2-492**. Alternatively (**Path B**), [2+2] cycloaddition of **2-490** with alkyne leads to the metallacyclobutene **2-493**, which can also be formed via cyclization of **2-491**.^{240a} Rhodacycle **2-493** then undergoes metathesis reaction to produce Rh-carbenoid **2-494**, which upon 6π -electrocyclization and subsequent reductive elimination steps (**2-495**), furnishes product **2-489**. The [2+1] cycloaddition of **2-490** with alkyne (**Path C**) leading to the cyclopropene **2-496** in the presence of Rh(II) could also account for the formation of furan via a subsequent Rh(II)-catalyzed cycloisomerization reaction.^{160b,238b}

Wang et al. reported a sequential synthesis of furans from α -diazocarbonyl compounds **2-497** and propargyl sulfide (Scheme 142). This transformation begins with the initial Rh-catalyzed Doyle-Kirmse reaction leading to the formation of the skipped allenyl ketone **2-499**. The latter then undergoes a Ru-catalyzed cycloisomerization/sulfur migration cascade to afford furan **2-499** (see Scheme 22 for the cycloisomerization/migration of **2-499**).⁶⁶

In 2008, Tanaka developed an interesting Rh(I)-catalyzed reaction between two molecules of acetylenedicarboxylate **2-500** and an alkene **2-501** that leads to 3-cyclopropylfurans **2-502** in good yields and excellent diastereo- and enantioselectivities (Scheme 143).²⁴⁷ According to the proposed mechanism, alkyne **2-500** and alkene **2-501** react with the Rh(I) to produce rhodacyclopentene species **2-503**. A subsequent ring-contraction in the latter occurs to generate rhodium carbene **2-504** bearing a cyclopropane ring with the *cis* configuration of the former ester and alkene substituents. Next, insertion of the second molecule of alkyne into C=Rh bond in **2-504** gives intermediate **2-505**, which upon cyclization and elimination of the Rh(I) catalyst produces the cyclopropylfuran **2-502**.

Several “3+2” approaches for the assembly of furan core feature a transition metal-catalyzed propargylic substitution reaction in propargylic alcohols or their derivatives with a variety of C-nucleophiles to access key alkynyl ketone intermediates amenable for a further cycloisomerization step. Thus, Hidai and Uemura reported that propargylic alcohols **2-506** produce the corresponding furans **2-509** upon reaction with cyclic and acyclic carbonyl compounds **2-507** in the presence of bimetallic Ru/Pt(II) catalytic system (Scheme 144).¹¹² The authors proposed that the initial Ru-catalyzed propargylation reaction of **2-506**²⁴⁸ affords γ -ketoalkyne intermediate **2-508**. Further hydration/cyclization sequence of the latter catalyzed by the Pt/Ru catalytic system furnishes furan **2-509**. Although both good yields of tri- and tetrasubstituted furans and functional group compatibility can be achieved in this “3+2” cycloaddition reaction, the synthetic usefulness of this methodology is somewhat limited as a large excess of carbonyl compounds and high catalyst loadings are required.

An analogous Ru(II)-catalyzed transformation was investigated by Nebra and co-workers (Scheme 145).^{115,249} Hence, a formal [3+2] cycloaddition of propargylic alcohols with 1,3-dicarbonyl compounds afforded 3-acyl or 3-carbalkoxyfurans **2-510** in the presence of Ru(II) catalyst and substoichiometric amounts of trifluoroacetic acid. These new reaction conditions allowed achieving a significantly extended scope and perfect functional group tolerance for this transformation. It was demonstrated that a variety of terminal and internal propargylic alcohols, cyclic and acyclic, aromatic and aliphatic 1,3-diketones or β -ketoesters could efficiently be employed in this transformation providing up-to-tetrasubstituted furans **2-510**. Highly efficient Cu(OTf)₂²⁵⁰ and FeCl₃²⁵¹-catalyzed versions of this methodology were recently elaborated by Zhan, whereas the Au-catalyzed process was studied by Arcadi.¹¹³

In 2011, Jiang reported a two-component synthesis of furans **2-513** using quite similar starting materials but proceeding via a different reaction mode (Scheme 146). Thus, the Fe(III)-catalyzed reaction of 1,3-dicarbonyl compound **2-511** with propargyl alcohol **2-512** produces β -ketoenol propargyl ether **2-514**, which undergoes a Pd(II)/Cu(II)-catalyzed cycloisomerization reaction to give 2-formylfuran **2-513** in one-pot fashion (for a mechanism, see Scheme 148).²⁵²

Zhan also utilized a similar approach for the “3+2” synthesis of furan compounds from propargylic esters and carbon-centered nucleophiles, which overcomes the limitation of the Hidaï and Uemura’s methodology on employment of terminal alkynes only (Scheme 147).²⁵³ The use of a one-pot sequential Cu(II)-catalyzed nucleophilic substitution of propargylic acetates **2-515** with silyl enol ethers **2-516** to give the γ -alkynyl ketones allowed for a subsequent Cu(II)-catalyzed cycloisomerization of the latter upon addition of the *p*-toluenesulfonic acid co-promoter. It was shown that tri-, tetrasubstituted, as well as fused alkyl- or arylfurans **2-517** bearing various functionalities could be synthesized in high yields. In addition, bisfurylarenes could be accessed via this chemistry upon two-fold propargylic substitution–cycloisomerization sequence of bis(1-silyloxyvinyl)arenes. The same group also reported that this transformation could efficiently be catalyzed by Fe(III)⁹ salts.²⁵⁴ In addition, it was later demonstrated that the Cu(II)-catalyzed protocol does not require the use of the *p*-toluenesulfonic acid co-promoter.²⁵⁰

In 2009, Jiang reported a stepwise two-component synthesis of furans **2-519** from propargyl alcohols **2-518** and diethyl acetylenedicarboxylate (Scheme 148).²⁵⁵ A variety of propargyl alcohol-possessing alkyl- and aryl substituents could be employed in this reaction providing furan products in moderate to good yields. However, the reaction is limited to diethyl acetylenedicarboxylate, as the use of other alkynoates resulted in no product formation. Mechanistically, this reaction proceeds via the Michael addition of propargyl alcohols to activated alkynes to give vinyl propargyl ethers **2-520** followed by their rearrangement into skipped allenyl ketones **2-521**. A subsequent Cu-catalyzed cycloisomerization reaction gives Cu-carbene species **2-522**, which undergo oxidation of carbene center to furnish C2-acylfurans **2-519**.

Later, the same group reported that the second step of the above process could efficiently be catalyzed by nano-Cu₂O catalytic system, whereas the first Michael addition step in some cases requires the use of PBU₃ catalyst instead of DABCO (Scheme 149).²⁵⁶ This modified protocol allows employing not only diethyl acetylenedicarboxylate but also other alkynoates, such as ethyl 3-phenylpropiolate and aryl alkynyl ketones **2-523** as Michael acceptors. Furthermore, an array of alkyl- and aryl-substituted propargyl alcohols **2-524**, bearing a range of functional groups, could be used in this process to produce furans **2-525**. Notably, diyne-derived propargyl alcohols were also tolerated in this reaction, furnishing tetrasubstituted C3-alkynyl furans in synthetically useful yields. The employment of

unsymmetrically substituted aryl alkynyl ketones led to the formation of mixtures of regioisomeric keto-substituted furans with low levels of selectivity. The proposed formation of the putative Cu-carbene intermediate was supported by the trapping experiment with ethyl diazoacetate, leading to 3-(furan-2-yl)acrylate **2-526** (Scheme 149). More recently, an analogous Fe(III)-²⁵⁷ and Ag(I)-catalyzed²⁵⁸ modifications of this transformation were also reported by Jiang et al.

Later, Jiang also developed a “non-oxidative” version of this reaction leading to substituted furan-2,3-dicarboxylic acid esters **2-529** (Scheme 150).²⁵⁹ The reaction works well for either aryl-, hetaryl-, or alkyl-substituted propargylic alcohols **2-528**. Besides diethyl acetylenedicarboxylate, other alkynoates **2-528**, such as ethyl 3-phenylpropiolate and aryl alkynyl ketones, could also participate in this reaction, although they required the use of PBu₃ catalyst instead of DABCO at the first step of the sequence. As in the above process, this transformation begins with the Michael addition, followed by isomerization process, into skipped allenyl 1,3-dicarbonyl compound **2-530** and subsequent cycloisomerization in to furan **2-529**, similarly to the Au(I)-catalyzed process reported by Kirsch (Scheme 21).⁶⁵ It is worth mentioning that the use of unsymmetrically substituted aryl alkynyl ketones provided approximately 1:1 mixtures of regioisomeric aroyl-substituted furans. This is expected, since the first rearrangement step gives unsymmetrical skipped allenyl ketone **2-530** (R¹ R²) having both carbonyl groups suited for the next cycloisomerization step.

Recently, Alper et al. reported that primary propargylic alcohols **2-531** could serve as a three-carbon-atom components in the synthesis of furans (Scheme 151).²⁶⁰ Thus, the Rh(II)-catalyzed hydroformylation²⁶¹ of **2-531** resulted in the formation of γ -hydroxyenals, which upon a subsequent cyclocondensation provided 3-monosubstituted aryl- and hetarylfurans **2-532** possessing an array of functional groups.

In 2011, Willis reported another interesting approach toward furans based on a hydroacylation reaction of propargyl alcohols. Treatment of propargyl alcohols **2-533** with aldehydes **2-532** bearing β -SMe chelating group in the presence of the Rh(I) catalyst affords the corresponding furans **2-534**. The reaction proceeds via S-directed Rh(I)-catalyzed hydroacylation to initially produce 1,4-diketone intermediate **2-535**, followed by their Brønsted acid-catalyzed cyclization into furan. This method is suitable for the preparation of furans bearing alkyl, alkenyl, or aryl substituents (Scheme 152).²⁶²

In addition, one-pot “3+2” syntheses of furans featuring the generation of a key 2,3-dien-1-ol intermediate **2-537**, followed by its Hg(II)-mediated cyclization/elimination cascades to produce furan **2-538**, were reported by Tso (Scheme 153)²⁶³ and was later used by Luh.²⁶⁴

The synthesis of furans from α -bromoketones and copper(I) acetylides via a coupling–cyclization reaction was first introduced by Castro in the 1960s (Scheme 154).²⁶⁵ This discovery stimulated the development of an array of contemporary two-component “3+2” methodologies. A “3+2” approach toward furans from internal alkynes and 2-iodocyclohex-2-enols was also reported by Larock in 1998 (Scheme 154).²⁶⁶

In 2003, Balme reported a three-component one-pot stepwise Pd/Cu-catalyzed Sonogashira coupling – arylation cyclization cascade reaction between 3-iodo-2-pyridones **2-539**, terminal alkynes, and aryl- or hetaryl iodides and bromides to produce fused furans **2-540** in variable yields (Scheme 155).⁸⁰ Performing this reaction in integrated one-pot mode without isolation of any intermediates afforded furans **2-540** without loss of efficiency compared to a stepwise procedure (*vide supra*). Using a similar strategy, a regiodivergent coupling/cyclization transformation of 4-methoxy-3-iodo-2-pyridones **2-541** with alkynes to form fused furans **2-542** was reported by the same group. The use of triethylamine base in this

reaction induced the S_N2-type dealkylation process of Sonogashira coupling products, thus directing a subsequent cyclization at the demethylated oxygen atom. Besides pyridones, 3-iodo derivatives of coumarin and pyrone could also successfully undergo a similar transformation providing the corresponding furan derivatives **2-542** (Scheme 155).²⁶⁷

In 2011, Li described the Pd/Cu-catalyzed synthesis of 3-formylfurans **2-544** from bromo-substituted enaminoketones **2-543** and terminal alkynes. The reaction begins with the Sonogashira cross-coupling reaction followed by a cycloisomerization and hydrolysis of the enamine fragment into the aldehyde group (Scheme 156).²⁶⁸

Recently, Kim described a two-component coupling-isomerization protocol for the synthesis of furans **2-546** from terminal propargylic compounds **2-545** and acyl chlorides in the presence of stoichiometric amounts of ZnBr₂ promoter²⁶⁹ and tertiary amine base (Scheme 157).²⁷⁰ It is believed that the initial Zn(II)-mediated coupling reaction between alkynes and acyl chlorides provides the corresponding alkynones that are further isomerized into the allenyl ketones under the basic reaction conditions. Upon activation with the Zn(II) salt, the latter intermediates undergo a subsequent cycloisomerization to furnish the furan product. Furthermore, it was also demonstrated that this approach could be applied to the synthesis of bis-furyl-containing compounds, and that the corresponding propargylic ethers or amines could be substituted with simple alkynes.

Independently, Müller et al. reported a three-component synthesis of 3-halofurans **2-551** featuring the Pd/Cu-catalyzed Sonogashira coupling reaction between acyl chlorides and THP-protected propargyl alcohols (Scheme 158). The key assembly of furan ring was accomplished from the *in situ* generated 4-hydroxyalkenones **2-549** via a sequence consisting of acid-mediated THP-deprotection, Michael addition of halide to alkynones **2-549**, and cyclocondensation (**2-550**). Both substituted and unsubstituted THP-propargyl ethers as well as a variety of aryl-, hetaryl-, and alkenyl acyl chlorides could be employed in this reaction, providing up-to-tetrasubstituted furans **2-551**. Notably, synthesis of 3-chloro-4-iodofurans **2-551c** could be achieved by incorporating the iodine monochloride addition step into the above cascade sequence.²⁷¹

In 1985, Tsuji reported an efficient two-component Pd-catalyzed synthesis of furans **2-555** from propargyl halides or propargyl alcohol derivatives **2-552** and 1,3-dicarbonyl compounds **2-553** (Scheme 159).²⁷²

Recently, an arylative version of the Tsuji reaction was developed by Liang (Scheme 160).²⁷³ Thus, the Pd-catalyzed reaction between propargyl carbonates **2-556**, β-ketoesters **2-557**, and aryl- or hetaryl iodides or bromides furnished furans **2-558/2-559** in typically moderate to good yields. A variety of electron-withdrawing and mildly electron-donating aryl iodides participated in this transformation almost equally well, however, aryl bromides were notably less efficient. In the case of secondary propargyl carbonate **2-556** (R = Me), a mixture of furan products with low levels of selectivity has been obtained. The employment of β-ketoesters other than **2-557** or 1,3-diketones provided only trace amounts of the corresponding products.

The proposed reaction mechanism (Scheme 161) is similar to that proposed by Tsuji except for the presence of the Sonogashira coupling step preceding the formation of a key allenyl-Pd intermediate **2-561**. The selectivity of this reaction toward products **2-558** or **2-559** is governed by stereo-electronic effects of substituents at the π-allyl-Pd moiety in intermediate **2-563** which is formed during the cyclization sequence.

Along this line, an interesting formal [3+2] synthesis of substituted furans **2-566** via the Pd-catalyzed reaction of propargylic bromides or tosylates **2-565** with acylchromates **2-564** was reported by Narasaka et al. (Scheme 162).⁵² In general, this reaction tolerates a variety of alkyl- and aryl substituents at both coupling partners providing furans **2-566** in moderate to excellent yields. However, substitution at the terminal alkyne **2-565** with aryl- or alkyl groups gave mixtures of regioisomeric furan products. According to the proposed mechanism, the reaction is initiated by the oxidative addition of propargylic electrophiles to Pd(0) to give propargyl-Pd – allenyl-Pd complexes **2-567**, which further react with acylchromates **2-564** to give the key allenyl ketone intermediates **2-568**. A subsequent cycloisomerization of the latter mediated by the *in situ* generated Cr(CO)₅ complex affords furans **2-566**.

In 2000, Balme described an interesting synthesis of fused furans **2-572** based on the Pd-catalyzed reaction of α -sulfonyl ketones **2-570** with terminal propargyl alcohols or amines **2-571**. The reaction proceeds via the Michael addition to produce intermediate **2-573**, which undergoes the Pd-catalyzed cycloisomerization reaction with a concomitant elimination of the sulfonyl group to give furan **2-572** (Scheme 163).²⁷⁴

The same group described the Pd-catalyzed three-component synthesis of furans **2-576** from propargyl alcohols **2-574**, ethoxymethylene malonate, and aryl- or vinyl halides. The reaction proceeds via the Pd-catalyzed generation of tetrahydrofuran intermediate **2-577**, which then undergoes a subsequent one-pot deprotection, decarboxylation, and aromatization steps to furnish furan **2-576** (Scheme 164).²⁷⁵ The synthetic utility of this methodology was demonstrated by an efficient assembly of the furan core of ($\pm$)-burseran.²⁷⁵ In 2005, Morimoto described the total synthesis of novel modified furanoeremophilane-type sesquiterpenes using the same approach.²⁷⁶

Recently, several groups developed syntheses of furans from activated alkynes, such as alkynoates or aryl alkynes, and 1,3-dicarbonyl compounds (Scheme 165). It was shown that the transition metal-catalyzed Michael addition of 1,3-dicarbonyl compounds to activated alkynes produces β,γ -unsaturated ketone **2-578**, which the presence of oxidants undergoes a subsequent cycloisomerization to form the corresponding furans. Accordingly, Jiang employed a Cu(I)/Sn(II) catalytic system in the reaction of 1,3-dicarbonyl compounds with alkynes for the synthesis of furans **2-579** in the presence of DDQ as an oxidant.²⁷⁷ Huang and Liang utilized a Cu(I) catalyst and oxygen as a terminal oxidant for analogous transformation to produce furans **2-580**.²⁷⁸ Both reactions proceed quite efficiently with a variety of substrates and furnish furan products in good yields (Scheme 165).

Fe(III)-, Zn-, or In(III)-catalyzed “3+2” reactions that feature Michael addition/cyclocondensation cascade between 1,3-dicarbonyl compounds and but-2-ene-1,4-diones to provide tetra-substituted furans were reported by Jaisankar.²⁷⁹ Very recently, an oxidative CAN-mediated synthesis of 3-hydroxyfurans from terminal alkynes and 1,3-dicarbonyl compounds was reported by Deepthi et al.²⁸⁰

Komeyama and Takaki disclosed an interesting approach toward furans **2-583** via the Bi(III)-catalyzed formal [3+2] reaction of 1,3-dicarbonyl compounds **2-581** with acylloins **2-582**. The reaction proceeds via the formation of 1,4-diketone intermediate followed by a cyclocondensation to give furan **2-583** (Scheme 166). Notably, the reaction with nonsymmetrically-substituted acylloins furnishes furans in a regioselective manner.²⁸¹

2.3.1. Synthesis of Furans via Cross-Metathesis—Recently, Donohoe et al. employed cross-metathesis (CM) reaction for the synthesis of furans. Specifically, the reaction between allyl alcohols **2-585** and enones **2-584** catalyzed by Grubbs–Hoveyda

second-generation catalyst in the presence of acid furnished 2,5-disubstituted furans **2-586**. Initially, the CM reaction led to the formation of a stable *trans*- γ -hydroxyenone **2-587**. The latter underwent an acid-catalyzed isomerization into the *cis*-isomer **2-588** followed by a cyclocondensation step to form furan **2-586** (Scheme 167).²⁸²

In another acid free version of this methodology, the *trans*- γ -hydroxyenone **2-589** intermediate was subjected to a subsequent Heck reaction to give the arylated *cis*- γ -hydroxyenone **2-590**, which underwent a spontaneous cyclization into tri-substituted furan **2-591** (Scheme 168).²⁸²

2.4. Synthesis of Furans via Formal [2+2+1]-Cycloaddition Reactions

A number of transition metal-mediated formal [2+2+1] furan syntheses have been reported before 2004. For instance, in 1990, Takai and Utimoto developed a regioselective synthesis of highly substituted furans via a three-component reaction of tantalum-alkyne complexes with carbonyl compounds and isocyanides.²⁸³ In 1997, Iwasawa described a reaction of propargyl-W species with carbonyl compounds to produce furans.²⁸⁴

More recently, Sato and Urabe reported an example of the Ti(IV)-mediated synthesis of furans **2-593** from internal alkynes, nitriles **2-592**, and aldehydes. Thus, a consecutive addition of nitrile and alkyne to the Ti(IV) reagent led to azatitancyclopentadiene intermediate **2-594**, which underwent a subsequent insertion of aldehyde into the C–Ti bond to give adduct **2-595**. The latter, upon treatment with acid, afforded the corresponding furan **2-593** via a sequence of steps involving hydrolysis, cyclization, and aromatization processes. (Scheme 169).²⁸⁵

In 2007, Ishii disclosed the synthesis of substituted furans from aldehydes **2-596** and acrylates **2-597** using Pd(OAc)₂/HPMo₁₁V/CeCl₃/O₂ catalytic system. It was proposed that the initial Pd(II)-catalyzed acetalization of acrylates gives acetal **2-600** that represents a masked equivalent of a 1,3-dicarbonyl compound. A subsequent CeCl₃-catalyzed aldol-type reaction led to the formation of enone **2-601**, which underwent enolization to give a Pd(II)-enolate **2-602** followed by its cyclization into an intermediate **2-603**. Finally, aromatization of the latter under oxidative conditions provides the furan product and returns Pd(II) species to the catalytic cycle. The net transformation represents a formal [2+2+1] cycloaddition reaction wherein methanol serves as a source of oxygen atom in a furan ring. Notably, 1,3-dicarbonyl compounds **2-598** could also be employed in this transformation instead of acrylates. In this case, the reaction would begin from the aldol-type reaction (*step a*) and the overall reaction can be viewed as a formal [3+2] cycloaddition process (Scheme 170).²⁸⁶

Recently, Jiang demonstrated an interesting Pd(II)/Zn-catalyzed synthesis of furans **2-604** from diarylalkynes under oxygen atmosphere (Scheme 171).²⁸⁷ The reaction gives moderate to high yields of products and tolerates both electron-withdrawing and electron-donating aryl substituents at alkynes. However, it is limited to the preparation of symmetrical tetra-aryl-substituted furans only. It is believed that this reaction proceeds via the diketone intermediate **2-605**, formation of which was observed during the reaction course. Furthermore, when subjected to the standard reaction conditions, **2-605** underwent an efficient cyclization into furan **2-604**.

In 2009, Beller and Dixneuf developed a two-step one-pot synthesis of 2,5-disubstituted furans **2-606** from terminal alkynes and methanol. At the first step, the Ru-catalyzed reaction of two molecules of alkyne and one molecule of methanol produced (1*E*,3*E*)-dienyl ether **2-607**. A subsequent Cu(I)-catalyzed oxidative cycloisomerization (**2-608**) led to the corresponding furan **2-606** (see Scheme 123). The reaction proceeds in reasonable to good yields with a variety of aromatic alkynes (Scheme 172).²¹⁶ Very recently, Jiang et al.

described the Pd(II)/Zn(II)-catalyzed synthesis of tetrasubstituted furans from diaryl acetylenes in fluoruous media using molecular oxygen as a terminal oxidant.²⁸⁸

In conclusion, a variety of transition metal-catalyzed cycloisomerization reactions for synthesis of furans has been developed. Most of them include addition of an oxygen atom across a multiple C-C-bond, activated by a transition metal. A number of [3+2] cycloaddition methods are also available for assembly of furan core from simple starting materials. Among recently developed methodologies, synthesis of furans via metathesis reactions is worth mentioning. Notably, formation of furan using molecular oxygen as a source of oxygen for creating the furan skeleton was also impressively shown. Although, certain success in the development of multicomponent methodologies for synthesis of furan core has been achieved, this attractive and powerful approach is still in its infancy.

3. Synthesis of Pyrroles

A great interest caused by the importance and valuable properties of pyrroles have spawned a number of excellent recent reviews focused on their synthesis.^{21b,21d,289} Transition metal-catalyzed methodologies for chemo- and regioselective synthesis of pyrroles, which is among the most efficient approaches, still attract a tremendous attention. Often, advances in the construction of pyrroles are stimulated by the development of approaches towards the furan core. Thus, many protocols involve formation of reactive intermediates analogous to those used in the furan syntheses. However, there are several methods that can be considered as unique to pyrroles only. In this chapter, synthesis of pyrroles based on cycloisomerization approach as well as formal [4+1], [3+2], [3+1+1], and [2+1+1+1] cycloaddition reactions are discussed.

3.1. Synthesis of Pyrroles via Cycloisomerization-Type Reactions

Generally, construction of pyrrole ring via a cycloisomerization reaction or a related process requires a particular precursor, in which all 5 atoms required for the pyrrole formation, are pre-assembled in a specific order. Although not comprehensive, but the most general cycloisomerization modes toward pyrrole core are depicted in Figure 4.

3.1.1. Cycloisomerization reactions—In 2001, Dieter et al. reported a Pd-catalyzed arylylative cycloisomerization of skipped aminoallene **3-1** into pyrrole **3-2** (Scheme 173).²⁹⁰

Later, Reißig et al. described example of the Ag-catalyzed cycloisomerization of *tert*-butyl iminoallene **3-3** into pyrrole **3-4**, analogously to the method reported for the synthesis of furans from allenyl ketones (see Scheme 3). Iminoallenes bearing other substituents were found to be considerably less stable and more sensitive toward hydrolysis and oxidation; these issues limit application of this particular type of compounds for the pyrrole synthesis (Scheme 174).²⁹¹ However, iminoallenes could be easily generated *in situ* and used in subsequent transformations leading to multisubstituted pyrroles (*vide infra*).

Gevorgyan reported a practical method for the pyrrole synthesis where easily accessible and far more stable conjugated alkynyl imines **3-5** served as surrogates of the corresponding iminoallenes **3-7**. It was shown that propargyl imines **3-5** underwent the Cu(I)-catalyzed cycloisomerization reaction in the presence of triethylamine to provide 1,2-di- and 1,2,5-trisubstituted pyrroles **3-6** in good yields (Scheme 175).²⁹²

The same group reported an efficient approach toward 1,2,3-trisubstituted pyrroles based on cycloisomerization/1,2-S migration reaction. Accordingly, alkynyl imines **3-8** possessing a sulfanyl group at the propargylic position underwent the Cu(I)-catalyzed cycloisomerization reaction proceeding with a 1,2-migration of alkyl- or arylthio groups to afford 3-thiopyrroles

3-9 (Scheme 176).^{55,61} Later, this approach was adopted for an efficient synthesis of 1,2,3-trisubstituted 3-selenylpyrroles **3-10** via the Cu(I)-catalyzed cycloisomerization/1,2-Se migration cascade of propargyl selenides **3-11** (Scheme 176).⁶¹ In both cases, the proposed mechanism for the Cu(I)-catalyzed cycloisomerization of chalcogen-containing propargyl imines **3-8** and **3-10** is similar to that reported for an analogous migratory transformation of carbonyl compounds into furans (see Scheme 27).

Skipped propargyl imines and hydrazones could also undergo a cycloisomerization reaction into the corresponding pyrroles. Thus, in 1997, Arcadi described the Pd-catalyzed arylative cycloisomerization of homopropargyl hydrazones into *N*-aminopyrroles.²⁹³ Later, Palacios et al. reported the Pd-catalyzed arylative cycloisomerization of homopropargyl imines into pyrroles.²⁹⁴ More recently, Dake demonstrated the synthesis of *N*-fused pyrroles **3-13** from the corresponding cyclic homopropargylic imines **3-12** in reasonable yields in the presence of an Ag(I) catalyst (Scheme 177).²⁹⁵

In 2010, Malacria, Goddard, Fensterbank and co-workers described the Au(I)-catalyzed cycloisomerization of β -allenylhydrazones **3-14** into multisubstituted *N*-aminopyrroles **3-15**. The proposed mechanism includes a nucleophilic attack of the imine at the sp center of the allene activated by the Au(I) catalyst (**3-16**), followed by a [1,2]-alkyl or aryl shift in the zwitterion **3-17**, and a subsequent tautomerization of intermediate **3-18** into pyrrole **3-15** (Scheme 178). It was shown that alkyl, cycloalkyl and aryl groups can undergo the 1,2-migration. Interestingly, a highly selective 1,2-migration of ethyl and phenyl group over that of methyl group was observed.²⁹⁶

In 2010, Saito and Hanzawa reported formation of pyrroles **3-20** using the Au(I)-catalyzed amino-Claisen rearrangement of *N*-propargyl enamine derivatives **3-19**. It was suggested that this reaction proceeds via a cyclization of β -allenyl enamine intermediate **3-21** (Scheme 179).²⁹⁷

Aminodiyne derivatives could also be used for synthesis of pyrroles via a cycloisomerization processes. For instance, in 1988, Tsuda, Saegusa et al. described the Ni-catalyzed cyclization of amino-1,6-diynes to produce pyrroles.²⁹⁸ In 1996, Gleiter used the Pd-catalyzed cyclization of amino-1,6-diazacyclodeca-3,8-diynes for the synthesis of 3,3'-bispyrroles.²⁹⁹ Later, Tanaka et al. reported formation of pyrroles **3-23** via the Rh-catalyzed cycloisomerization of 1,6-diynes **3-22** containing a nitrogen heteroatom in the alkyl chain that tethers two alkyne moieties. According to the proposed mechanism, the reaction of **3-22** with Rh(I)/Segphos/1,2-cyclohexanedione catalyst system leads to the formation of a rhodacycle **3-24**. A subsequent β -hydride elimination followed by tautomerization in **3-25** yields pyrrole **3-23** (Scheme 180).³⁰⁰

The same group demonstrated that 1,6-enyne **3-26** bearing a monosubstituted alkene moiety could also undergo a cycloisomerization reaction into the pyrrole **3-27** under these conditions (Scheme 181).³⁰⁰⁻³⁰¹

In 2001, Gabriele, Salerno and co-workers reported the synthesis of substituted pyrroles **3-29** via the Pd-catalyzed cycloisomerization of readily available (*Z*)-(2-en-4-ynyl)amines **3-28**.³⁰² Later, it was found that Cu(I)- or Cu(II)-salts were equally efficient in this transformation.³⁰³ It was shown that di-, tri-, and tetrasubstituted pyrroles **3-29** with different substitution patterns could readily be synthesized using this method (Scheme 182). It should be noted that in the case of substrates **3-28** bearing terminal alkyne ($R^4 = H$), a spontaneous cycloisomerization was observed.³⁰⁴ The mechanism of this transformation is similar to that proposed for the transition metal-catalyzed synthesis of furans (see Scheme 64).

Gabriele and Salerno also developed an interesting heteroannulation–alkoxycarbonylation–aromatization cascade reaction of (*Z*)-(2-en-4-ynyl)amines **3-30** toward the synthesis of 2-pyrrolylacetic acids **3-31**. Apparently, the reaction occurs via a carbonylation of the initially formed vinylpalladium intermediate species **3-32**, followed by a subsequent alkoxylation of **3-33** (Scheme 183).³⁰⁵ Interestingly, a dramatic beneficial effect of CO₂ on the reaction rate was found for this transformation.³⁰⁶

An Au(I)-catalyzed version of the Gabriele's protocol for the synthesis of pyrroles was recently reported by Gagosz (Scheme 184).³⁰⁷ It was demonstrated that *N*-tosyl-protected (*Z*)-(2-en-4-ynyl)amines **3-34** could undergo a facile cycloisomerization into pyrroles **3-35** in the presence of the Au(I) catalyst. This methodology provides an easy access to tri- and tetrasubstituted pyrroles **3-35** in excellent yields and under very mild reaction conditions. Furthermore, *N,N*-disubstituted (*Z*)-(2-en-4-ynyl)amines **3-36**, possessing an allyl group at the nitrogen atom, underwent the Au(I)-catalyzed cycloisomerization with a concomitant 1,3-allyl shift (aza-Claisen type rearrangement) affording tri- and tetrasubstituted pyrroles **3-37** in excellent yields. This transformation allows for an efficient assembly of C2-homoallyl-substituted pyrroles bearing a range of functional groups (Scheme 184).³⁰⁷

An interesting approach toward the synthesis of M1–C2-fused pyrroles was recently developed by Zhang et al. (Scheme 185).³⁰⁸ Thus, a variety of tri- and tetrasubstituted pyrroles **3-39** were synthesized via the Au(I)-catalyzed cycloisomerization of (*Z*)-(2-en-4-ynyl)lactams **3-38**. According to the proposed mechanism, **3-38** undergoes a sequence of steps upon activation of the triple bond by the Au(I) catalyst to generate a key intermediate **3-41**. A subsequent lactam ring opening in the latter produces vinylgold species **3-42**, which, upon carbocyclization (**3-43**) and aromatization (**3-44**), furnishes pyrrole **3-39** (Scheme 185).³⁰⁸

Dovey utilized propargyl enamines **3-45** in the Ag(I)-catalyzed synthesis of tetrasubstituted *N*-functionalized 3-acylpyrroles **3-46** under a microwave irradiation conditions (Scheme 186).³⁰⁹ The reaction also proceeds in the presence of other group 12 metal catalysts.³¹⁰ This methodology was successfully applied for the synthesis of *N*-bridgehead pyrroles **3-48** (Scheme 186).³¹¹ Mechanistically this transformation follows the general mechanism proposed for an intramolecular nucleophilic addition of heteroatoms to transition metal-activated carbon–carbon multiple bonds (*vide supra*).

In 2009, Xu et al. reported an efficient synthesis of pyrrolocoumarins **3-50** via the Pd-catalyzed intramolecular hydroamination of the corresponding alkynyl-substituted aminocoumarins **3-49** (Scheme 187). This method works equally well for the preparation of a range of pyrrolocoumarins bearing both alkyl and aryl substituents.³¹² The same transformation can also be performed using a Fe(III)/Pd(II) catalyst system.³¹³

In 2009, Zhao and Li developed the synthesis of trisubstituted pyrroles **3-52** based on the Au(III)-catalyzed cyclization of the corresponding amino-functionalized enynes **3-51**. The reaction provides *N*-alkyl-, *N*-arylsulfonyl-, as well as carbamoyl and benzoyl-protected pyrroles **3-52** bearing C2-aminomethyl group, in good yields (Scheme 188).³¹⁴ The same cycloisomerization reaction, but catalyzed by Pd(OTFA)₂, was recently described by the Trost group.³¹⁵ Zhou et al. reported the Ga(III)-catalyzed cycloisomerization of amino-substituted enynes into pyrroles.³¹⁶

Recently, several examples of cycloisomerization reactions that proceed via metal–carbenoid species have also been developed. For instance, in 2003, an interesting Rh-catalyzed cycloisomerization–cyclopropanation reaction sequence between iminoenynes compounds **3-53** and alkenes **3-54** that leads to 2-cyclopropyl-substituted pyrroles **3-55** was

developed by Ohe, Uemura and co-workers.³¹⁷ The reaction proceeds via cyclopropanation of the alkene **3-54** by the (2-pyrrolyl)carbene-Rh intermediate **3-56**, which is generated via the Rh-catalyzed cycloisomerization of **3-53**. 2-Cyclopropylpyrroles **3-55** were obtained in good yields and with high diastereoselectivity for almost all cases, except for *N*-*t*-Bu pyrrole, which was obtained in a lower yield (Scheme 189).

In 2004, Liu reported the Ru-catalyzed two-component synthesis of pyrroles **3-58** from iminoenynes **3-57**. This methodology relies on a facile generation of (2-pyrrolyl)carbene-Ru intermediate **3-59**, similar to its Rh-derived analog described above, which is subsequently trapped by insertion into O–H or N–H bond of external nucleophiles. The reaction easily accommodates a variety of nucleophiles such as H₂O, alcohols, and amines to provide a range of 1,2,5-trisubstituted pyrroles **3-58** (Scheme 190).³¹⁸

An analogous Cr(0)-mediated transformation was disclosed by Herndon and co-workers. Accordingly, reaction of enyne derivatives **3-60** with stoichiometric amounts of Cr-Fisher carbene complex **3-61** leads to the formation of pyrroles **3-62**. According to the proposed mechanism, the coupling of alkyne moiety with the carbene complex first affords a divinylcarbene–Cr intermediate **3-63**, which undergoes an intramolecular nitrogen atom attack at the carbene center to form ylide intermediate **3-64**. A subsequent elimination of the Cr(0) catalyst, followed by acidic hydrolysis of thus formed enol ether **3-65**, leads to the pyrrole product **3-62** (Scheme 191).³¹⁹

Very recently, Hu and Wang reported the Pd-catalyzed arylation/cycloisomerization cascade transformation of enynes **3-66** in the presence of aryl bromides to form 1,3,4-trisubstituted pyrroles **3-67**. The reaction is triggered by a carbopalladation of an enyne **3-66** with an arylpalladium halide species to generate intermediate **3-68**, which undergoes an intermolecular 5-*exo-trig* carbopalladation process to give cyclized intermediate **3-69**. A subsequent β-hydride elimination and isomerization of the exocyclic double bond furnishes pyrrole **3-67** (Scheme 192). This reaction works well with aromatic bromides containing an array of electron-withdrawing groups, whereas reaction with electron-neutral and electron-donating aryl bromides is less efficient.³²⁰

3.1.2. Synthesis of Pyrroles via Ring-Expansion of Alkynyl and Alkenyl

aziridines—Transition metal-catalyzed cycloisomerization of functionalized alkynyl aziridines recently provided a new platform for the synthesis of pyrroles.^{3j} For instance, Davies and Martin developed a regiodivergent Au(I)-catalyzed ring-expansion of alkynyl aziridines **3-70** to access regioisomeric trisubstituted pyrroles **3-71** or **3-72**.³²¹ Specifically, the cycloisomerization reaction of **3-70** in the presence of Ph₃PAuOTf catalyst furnishes 2,5-disubstituted pyrroles **3-71** as sole regioisomer in excellent yields (**Path A**). According to the proposed mechanism, a ring-opening/nucleophilic attack of the N-atom at the distal carbon atom of the Au(I)-activated alkyne intermediate **3-73** generates a five-membered cyclic cation **3-74**. A subsequent proton loss in the latter, followed by protiodeauration step gives 2,5-disubstituted pyrrole product **3-71** (Scheme 193). In contrast, when Ph₃PAuOTf was used as the catalyst, regioisomeric 1,4-disubstituted pyrroles **3-72** were obtained as major or the only products (**Path B**). Recent isotope labeling studies showed that the reaction most likely proceeds via a cyclization of alkynyl aziridine to give intermediate **3-75**; subsequent selective ring opening (involving R²C–N) produces a benzylic cation intermediate **3-76** with adjacent 4-membered dihydroazete ring. The latter undergoes a ring-expanding 1,2-shift of vinyl-Au moiety to the benzylic cation to form a 5-membered cyclic cationic intermediate **3-77** that is regioisomeric to **3-74**. As in the previous case, subsequent proton loss and protiodeauration steps furnish 2,4-disubstituted pyrrole **3-72** (Scheme 193).³²² Shortly after, Hou reported that the Au(I)-catalyzed cycloisomerization reaction of

alkynyl aziridines **3-70** could be accelerated in the presence of protic additives (e.g., methanol) to produce a range of 1,2,4-trisubstituted pyrroles **3-78**, including C2-TMS derivatives (Scheme 193).³²³ In addition, Yoshida et al. disclosed that this reaction proceeds quite efficiently in the presence of PtCl₂ catalyst in aqueous dioxane media to afford alkyl- or aryl-substituted *N*-benzylpyrroles **3-79** (Scheme 193).^{200b} Very recently, the same group expanded this methodology to the synthesis of 3-iodopyrroles by performing the Pt-catalyzed cycloisomerization reaction of *N*-tosyl alkynyl aziridines in the presence of iodine.³²⁴

In 2011, Yoshida et al. also reported the synthesis of C2–C3-fused pyrroles **3-81** via the Pt(II)-catalyzed cascade cycloisomerization/ring expansion reaction of 2-alkynyl-1-azaspiro[2–3]hexanes or [2–4]heptanes **3-80** (Scheme 194).³²⁵ This methodology tolerates a range of functional groups, including an alkene, an alkyne, and an alcohol, and can also be efficiently applied for the preparation of tricyclic fused pyrroles. Two mechanisms have been proposed for this transformation, both featuring a 1,2-alkyl shift/ring expansion process either after the initial cyclization in a spirocyclic five-membered cationic intermediate analogous to **3-74** (Scheme 193), or in aziridine **3-80** prior to a cyclization step.

In 2010, Liu and coworkers reported that 1,2,3,5-tetrasubstituted *N*-phthalymidyl-containing pyrroles **3-83** could be prepared via the Au(I)-catalyzed cycloisomerization of the corresponding functionalized alkynyl aziridines **3-82** (Scheme 195).³²⁶ *N*-Phthalyl protecting group could efficiently be removed with hydrazine from the products **3-83** providing an easy access to *NH*-pyrroles. Notably, both R¹ and alkynyl substituents in an ester-containing aziridine **200** should be *cis* to each other, as no product was obtained in the reaction of the *trans*-isomer.

Very recently, a two-component Au(I)-catalyzed cascade cycloisomerization/nucleophilic substitution reaction of propargyl aziridines **3-84** containing an acyloxy group was reported by Blanc and Pale. This reaction provides pyrroles **3-85** in good yields in the presence of alcohols as nucleophiles (Scheme 196).²⁰⁷

The utility of aziridines for the synthesis of pyrroles was further demonstrated by Tu. It was shown that the Au-catalyzed cycloisomerization of homopropargylaziridines **3-86** affords polysubstituted fused pyrroles **3-87**.³²⁷ A plausible mechanism includes a 5-*endo-dig* cyclization of **3-88** to produce an ammonium cation intermediate **3-89**, which undergoes an aziridine ring-opening between the N atom and C-2, followed by elimination of the β-proton to form a spirocyclic intermediate **3-90**. A subsequent elimination of a siloxy group produces a cation **3-91**, which gives bicyclic species **3-92** upon a 1,2-vinyl group migration/ring expansion. The sequence is completed after a proton loss in **3-92** to furnish pyrrole **3-87**. A range of C-5 alkyl-, aryl-, and heteroaryl substituted pyrroles **3-87** were easily prepared via this method (Scheme 197).

Padwa reported an interesting cycloisomerization reaction of 2-alkenyl-2*H*-azirines **3-93** in the presence of Grubbs I catalyst to give the corresponding pyrroles **3-94** in good yields (Scheme 198).³²⁸

3.1.3. Synthesis of Pyrroles via Cycloisomerization of Azides—An assembly of the pyrrole core via transition metal-catalyzed cycloisomerization reactions of organic azides has received some attention over the last decade. In their pioneer work, Toste and co-workers demonstrated that homopropargylic azides **3-95** undergo an acetylenic Schmidt reaction in the presence of a cationic Au(I) catalyst to provide pyrroles **3-96** (Scheme 199).³²⁹ According to the proposed mechanism, activation of the alkyne moiety in **3-97** by the Au(I) catalyst triggers a nucleophilic attack by the proximal nitrogen atom of the azide

followed by a loss of dinitrogen in **3-98** to afford a cationic intermediate **3-99**, which can also be represented as a pyrrolydene-Au carbene. The latter undergoes a formal 1,2-migration of the R³-group to the Au-carbene center to furnish the 2*H*-pyrrole **3-100** and regenerate the Au(I) catalyst. Finally, tautomerization of **3-100** gives *MH*-pyrrole **3-96** (Scheme 199). This protocol is efficient for a rapid assembly of *N*-unprotected pyrroles possessing a variety of labile functional groups.

Later, Hiroya et al. reported that the cycloisomerization of homopropargylic azides **3-101** into pyrroles **3-102** could be achieved with a Pt(IV)–pyridine catalyst system (Scheme 200).³³⁰ Various mono-, di-, and trisubstituted pyrroles were obtained in good yields under these reaction conditions. Recently, mechanisms of the Au(I)- and Pt(IV)-catalyzed pyrrole synthesis via the intramolecular acetylenic Schmidt reaction were thoroughly investigated by DFT computations.³³¹ In 2009, Dembinski et al. developed the Zn-catalyzed version of the above transformation. This methodology allows for the preparation of a variety of alkyl- and aryl-substituted pyrroles **3-103** in good yields under microwave irradiation at 105–130 °C (Scheme 200).³³² Very recently, Yamamoto et al. developed a solid-supported Hg(II)-based catalyst for the cycloisomerization of homopropargyl azides into pyrroles at room temperature.³³³

In 2011, Driver and co-workers employed 1,3-dienone azides **3-104** for the Zn(II)- or Rh(II)-catalyzed synthesis of *MH*-pyrroles **3-105** (Scheme 201).³³⁴ Using this method, a range of di- and trisubstituted alkyl- and arylpyrroles, possessing an array of different functional groups, could be prepared. It was demonstrated that this reaction could also be efficiently catalyzed by CuOTf and Cu(OTf)₂. The Rh-catalyzed reaction most likely proceeds via a nitrogen atom transfer through a nitrenoid^{22a} **3-106**, followed by its cyclization into an intermediate **3-107**. A subsequent metal elimination and isomerization (**3-108**) affords pyrrole **3-105**. Alternatively, in case of Lewis acidic Zn(II)-catalyst, an initial activation of the azide followed by a cyclization into **3-107** with the loss of dinitrogen could be operating. Recently, RuCl₃ was used successfully as a catalyst for this transformation.³³⁵

3.1.4. Synthesis of Pyrroles via Cycloisomerization-Elimination Processes—In

1981, Utimoto described the synthesis of pyrroles **3-110** via the Pd-catalyzed cycloisomerization of 1-amino-3-alkyn-2-ols **3-109** (Scheme 202).³³⁶ Compounds containing either hydroxy or methoxy leaving group undergo this transformation under fairly mild reaction conditions.^{74a}

Later, other metals were tested as catalysts in this transformation. Thus, stoichiometric W³³⁷ and catalytic Ru¹⁸² were used to promote this reaction. A cationic Au(I) catalyst was also efficiently used for the synthesis of pyrroles **3-112** from the corresponding 1-amino-3-alkyn-2-ols **3-111** by Aponick et al.¹⁷² and Akai et al.¹⁷³ (Scheme 203). In the most recent work, Gabriele and co-workers.¹⁷⁴ reported an efficient ligand-free Cu(II)-catalyzed cycloisomerization toward pyrroles **3-112** (Scheme 203). In 2011, Knight et al. used recoverable and reusable AgNO₃/SiO₂ heterogeneous catalyst for efficient synthesis of pyrroles via this transformation.³³⁸

Knight et al. reported 3-hydroxy-dihydropyrroles **3-114**, which were found to be main products in the cycloisomerization of *N*-tosyl-1-amino-3-alkyn-2-ols **3-113**, containing a carboxylic group. The corresponding pyrrole-2-carboxylates were formed only as by-products (0–29%) even in the presence of stoichiometric amounts of Cu, Pd or Hg salts (Scheme 204).³³⁹

Recently, the Au(III)-catalyzed cycloisomerization of fluorinated 1-amino-3-alkyn-2-ols **3-115** was used for the synthesis of 2-aryl-3-fluoropyrroles **3-116** by De Kimpe and co-workers. In this case, the F[−] serves as a requisite leaving group for the aromatization process. A number of fluorosubstituted pyrroles **3-116** were obtained using this mild and efficient transformation (Scheme 205).³⁴⁰ Dixon reported formation of pyrrole **3-118** from 3-nitro-3-alkynyl amine **3-117** featuring elimination of the nitro group during the aromatization step (Scheme 205).³⁴¹

Allenes also can undergo this type of transformation. Thus, in 2006, Reissig et al. observed the Au-catalyzed cyclization of allene derivatives **3-119** to form the corresponding pyrroles **3-120** (Scheme 206). Elimination of the siloxy group is observed in this transformation.³⁴²

Later, Alcaide, Almendros et al. reported formation of pyrroles **3-122** via an Ag(I)-mediated cycloisomerization of allenes **3-121**. Likewise, this reaction features elimination of the methoxy group during aromatization step (Scheme 207).³⁴³

Recently, the Pd(II)-catalyzed ring expansion of 2-azidocyclobutanol **3-123** to form 2-phenyl pyrrole **3-124** via a selective cleavage of the C-C bond was observed by Chiba and co-workers. The proposed mechanism presumes the β-carbon elimination of the Pd(II)-alcoholate **3-125**, followed by elimination of N₂ to give **3-126**, which undergoes subsequent intramolecular nucleophilic attack of the iminyl palladium fragment into cyclic intermediate **3-127**. A subsequent protonation/dehydration leads to the pyrrole **3-124** (Scheme 208).³⁴⁴

In 2000, Grigg described an interesting Pd-catalyzed cyclization of enamines **3-128** into pyrroles **3-129**. The reaction proceeds via an oxidative addition, followed by a cyclization, a reductive elimination and isomerization steps (Scheme 209).³⁴⁵

In 2011, Urabe disclosed the Pd-catalyzed Heck-type cyclization of enamines **3-130** into pyrroles **3-131**. The reaction affords 1,2,4-trisubstituted pyrroles **3-131** in good from simple reagents, as the corresponding enamine precursors **3-130** are easily available from allyl sulfonamides and bromoacetylenes. (Scheme 210).³⁴⁶

Wang reported the synthesis of pyrroles **3-133** via the Rh- or Cu-catalyzed cyclization of δ-(*N*-Tosyl)amino-β-keto-α-diazo carbonyl compounds **3-132**.³⁴⁷ The reaction proceeds via intramolecular N-H insertion of the Rh-carbenoid **3-134**, subsequent elimination of *p*-toluenesulfonic acid TsH from the intermediate **3-135**, followed by a 1,5-H shift in **3-136** (Scheme 211).³⁴⁸

Later, Zhu used similar transformation for the synthesis 3-fluorosubstituted pyrroles. Accordingly, it was found that δ-(*N*-Tosyl)amino-β-keto-α-diazo carbonyl compounds **3-137** underwent cyclization to produce β-fluoropyrroles **3-138** in excellent yields. The reaction proceeds via the Rh-catalyzed intramolecular N-H insertion of the carbenoid **3-139**, followed by a subsequent elimination of HF from (**3-140**). Moreover, the scope of this transformations was extended to 3-fluoro-4-pyrroloacetonitriles **3-142** when the corresponding vinyl diazometanes **3-141** were used (Scheme 212).³⁴⁹

3.1.5. Synthesis of Pyrroles via Oxidative Cyclizations with Internal Oxidant—

In 1999, Narasaka reported formation of pyrroles **3-144** via an oxidative cyclization of *O*-pentafluorobenzoximes of γ,δ-unsaturated ketones **3-143**. This Heck-type intramolecular amination of olefinic moiety occurs via the oxidative addition to form *N*-Pd-species **3-145**. A subsequent intramolecular carbopalladation, followed by the β-hydride elimination (**3-146**) leads to cyclic imine **3-147**, which gives pyrrole **3-144** after isomerization of the crude reaction product with TMSCl (Scheme 213).³⁵⁰ A number of polysubstituted pyrroles **3-144**

bearing alkyl, aryl, carbethoxy and methoxy group, can be obtained using this methodology. It should be noted that the stereochemistry of the oximes **3-143** exhibited no significant effect on the reaction course.³⁵¹ The main limitation of this method is a substituent at the double bond (R^4), which is limited to H, Me, and CO_2Me .^{351a} Trimethylhydrazonium salts of γ,δ -unsaturated ketone were also used in this transformation, however without significant advantages.³⁵²

Later, Fürstner and co-workers used this methodology for the synthesis of the pyrrole-containing natural product butylcycloheptylprodigiosin **3-151**. (Scheme 214). Thus, the bicyclic pyrrole-containing core fragment **3-149** was obtained from the corresponding precursor **3-148** via the $\text{Pd}(0)$ -catalyzed cycloisomerization. The initially formed intermediate **3-150** was then isomerized into aromatic **3-149** under strongly basic conditions using KAPA (potassium 3-aminopropylamide).³⁵³

This cycloisomerization was recently extended to the γ,δ -unsaturated ketone *O*-diethylphosphinyloximes **3-152**, which are more stable under column chromatography conditions compared to the previously employed *O*-pentafluorobenzoximes. Thus, a variety of 2,5-disubstituted pyrroles **3-153** could be obtained upon a Pd-mediated cyclization of **3-152**. Moreover, it was shown that β,γ -unsaturated ketone derivative **3-154** also undergoes intramolecular cyclization to afford fused pyrrole **3-155** (Scheme 215).³⁵⁴

Recently, Anderson and co-workers described cycloisomerization of *O*-allyl oximes into pyrroles catalyzed by the $\text{Ir}(\text{I})/\text{Ag}(\text{I})$ -combined system.³⁵⁵ This reaction represents a transition metal catalyzed version of the Trofimov reaction, where *o*-vinyl oximes are cyclized under strongly basic conditions.³⁵⁶ *O*-allyl oximes are more stable precursors than the corresponding *O*-vinyl oximes and, therefore, are more convenient starting materials. Thus, cycloisomerization of α -cyano substituted *O*-allyl oximes **3-156** gives 2,3,4-trisubstituted pyrroles **3-157** in good yields. The reaction proceeds via a successive isomerization of α -cyano *O*-allyl oxime **3-156** into *O*-vinyl oxime **3-158**, followed by a facile tautomerization and formation of intermediate **3-159**. A subsequent [3,3] sigmatropic rearrangement leads to the 1,4-imino aldehyde **3-160**, which undergoes cyclocondensation into 2,3,4-trisubstituted pyrrole **3-157**. On the other hand, in the case of *O*-allyl oximes, containing other α -substituents (H, Alk, Ar), the reaction starts with the formation of *O*-vinyl oxime **3-158a**, which is not prone to [3,3] rearrangement due to the high enolization barrier. A [1,3] rearrangement of *O*-vinyl oxime **3-158a** into the iminoaldehyde **3-162** occurs instead. A subsequent nucleophilic cyclization affords regioisomeric 2,3,5-trisubstituted pyrrole **3-161**. In the case of α -aryl or α -carbmethoxy *O*-allyl oximes **3-165** the reaction can be driven to the 1,2,5-trisubstituted pyrroles **3-164** by addition of a base, which facilitates imine-enamine tautomerization, followed by a subsequent [3,3] rearrangement pathway (Scheme 216). Therefore, the regioselectivity of pyrrole formation in this transformation can be controlled by either the nature of the α -substituent or by addition of a base.³⁵⁷

In 2011, Camp et al. reported the analogous gold(I)-catalyzed cycloisomerization of *O*-vinyl oximes **3-165** into polysubstituted pyrroles **3-166**. Importantly, the reaction can be performed in one-pot fashion from the corresponding oxime **3-167** and acetylenedicarboxylate to produce 2,3-pyrroledicarboxylic acid derivatives **3-168** (Scheme 217).³⁵⁸

3.1.6. Synthesis of Pyrroles via Oxydative Cyclizations with External Oxidant

—In 2000, Katritzky reported the synthesis of pyrroles **3-170** via the Pd-catalyzed oxidative cycloisomerization of β -alkenyl amines **3-169**, bearing benzotriazole residue. However, the reaction requires stoichiometric amount of $\text{Cu}(\text{II})$ as a terminal oxidant.³⁵⁹

Later, Imhof observed formation of pyrroles along with γ -lactams in the Ru-catalyzed reaction of α,β -unsaturated aldehydes and amines. As an example, the aldehyde **3-170** undergoes reaction with methylamine in the presence of CO and ethylene, to produce the corresponding pyrrole **3-171** in mixture with a γ -lactam **3-172**. A formation of γ -lactam **3-172** can be suppressed in certain cases by using less polar solvent (Scheme 219). Although, the mechanism of this transformation was not investigated in details, the authors suggested the Ru-assisted activation of the C-H bond in the β -position of the intermediately formed imine as a possible reaction pathway.³⁶⁰

In 2004, Knölker and co-workers developed the Ag(I)-promoted oxidative cyclization of homopropargyl amines **3-173** into pyrroles **3-174**.³⁶¹ The reaction requires stoichiometric amount of AgOAc to form pyrroles in good yields. This cyclization was used to assemble a pyrrole fragment in a total syntheses of alkaloids Crispine A³⁶² and Harmicine³⁶³ by the same research group (Scheme 220).

Later, Wang et al. developed an Aza-Wacker oxidative cyclization of aminoalkenes **3-175**, derived from natural amino acids, to form the corresponding pyrroles **3-176** in the presence of the Pd-catalyst, and Cu(II) as a terminal oxidant. A variety of 1,2,3,5-tetrasubstituted pyrroles **3-176** could be prepared in moderate to good yields using this method (Scheme 221).³⁶⁴

In 2009, Prandi et al. described a similar Pd(II)-catalyzed transformation using O₂ as a terminal oxidant. Thus, a number of *N*-tosyl 3-ethoxypyrroles **3-178** were obtained in good yields via oxidative cyclization of alkoxydienylamines **3-177** under these mild conditions (Scheme 222).³⁶⁵

Takeya, Ohta, and co-workers developed the synthesis of pyrroles **3-180** via the Pd-catalyzed oxidative cyclization of hydroxy-enamines **3-179**. It is believed, that this reaction proceeds via oxidation of hydroxy enamine **3-179** into keto-enamine **3-181** (by Pd(0)/MesBr system), followed by its subsequent intramolecular cyclization to produce pyrrole **3-180**. A variety of polysubstituted *NH*-pyrroles **3-180** bearing aliphatic or aromatic substituents can be synthesized using this methodology (Scheme 223).³⁶⁶

In 2011, Chiba et al. described the Cu-catalyzed synthesis of 4-carbonyl pyrroles **3-183** via the oxidative cycloisomerization of *N*-allyl enamine carboxylates **3-182** using oxygen as a terminal oxidant. The reaction provides moderate yields of 2-arylpyrrole-3-carbaldehydes **3-183** (Scheme 224).³⁶⁷

3.1.7. Synthesis of pyrroles via Ring-Closing Metathesis—Ring-Closing Metathesis (RCM) has been extensively used in the synthesis of various carbo- and heterocyclic compounds of varying sizes and types.^{220a} It has also been used efficiently for the synthesis of the pyrrole core. The main problem of this approach is necessity of a subsequent oxidative transformation of the obtained intermediate dehydropyrrolidine species into aromatic pyrroles (Figure 5). There are several ways to overcome this obstacle, including the use of substrates, prefunctionalized with a double bond or a leaving group, application of a cooperative catalysis for the one-pot RCM/dehydrogenation tandem process, and one-pot oxidation of the intermediately formed 3-pyrroline with external oxidant.

In 1998, Fürstner developed a two-step synthesis of pyrrole core via the Pt-catalyzed enyne RCM and subsequent isomerization/aromatization of the metathesis product with KAPA.³⁶⁸ An example of the one step pyrrole formation using an enyne RCM was described by Hsung and Grebe,³⁶⁹ in which an enyne RCM reaction of **3-184** gave pyrrole **3-185** via a one-pot isomerization of the initially formed pyrroline derivative **3-186** (Scheme 225). Pérez-Castels

et al. reported formation of pyrrole **3-188** from 2-vinylindole **3-187** via the RCM reaction, followed by a subsequent isomerization of the double bond in the intermediate **3-189** (Scheme 225).³⁷⁰ The two-step synthesis of pyrrole in a similar system by RCM/Ru-catalyzed isomerization was performed by Mori.³⁷¹

Donohoe developed a metathesis approach toward pyrroles **3-191** starting from divinylamines **3-190**, containing a leaving group.²²² After the RCM reaction was complete, the addition of acid promotes an elimination of methanol from **3-192** to form pyrrole product **3-191** (Scheme 226). The same approach was used for the synthesis of 4-CF₃-pyrrole by Rutjes et al.³⁷²

In 1999 Grigg observed formation of pyrroles from divinylamines at elevated temperatures via the RCM/aromatization reaction sequence.³⁷³ Later, Wilson reported the synthesis of pyrrole **3-194** under microwave irradiation via the Grubbs I-catalyzed RCM of diallylamine **3-193**, containing an aliphatic substituent at the nitrogen atom. In case of other substituents at nitrogen, the corresponding 3-pyrrolidines were formed as main products. On the other hand, Xiao et al. observed exclusive formation of pyrroles **3-196** from *N*-aryl divinylamines **3-195**, whereas *N*-alkyl derivatives gave mixtures of pyrroles and 3-pyrrolines (Scheme 227).³⁷⁴ Therefore, selective formation of pyrroles via this approach is limited to a particular substitution pattern.

In order to overcome this limitation, Stevens used Grubbs I/RuCl₃ catalyst system for the one-pot RCM/dehydrogenation synthesis of pyrroles **3-198** from divinylamines **3-197**. Thus 1,3-disubstituted pyrroles bearing different substituents at the nitrogen atom were prepared in good yields using these protocol (Scheme 228).³⁷⁵

Later, Stevens et al. suggested the RCM/oxidation protocol for synthesis of 2-phosphonopyrroles **3-200** from the corresponding phosphonates **3-199** using tetrachloro-1,4-benzoquinone (TCQ) as an oxidant (Scheme 229).³⁷⁶ An enyne-RCM was also applied for the pyrrole synthesis by the same research group. Thus, pyrroles **3-202** were prepared in reasonable yields from the corresponding precursors **3-201** via the enyne-RCM/oxidation sequence (Scheme 229).³⁷⁷

In conclusion, a cycloisomerization approach is a powerful tool for the synthesis of various pyrrole derivatives. Cycloisomerization reactions can be especially efficient for the synthesis of particular pyrrole skeleton from specific starting materials. However, an application of cycloisomerization approaches for a diversity-oriented synthesis of pyrrole derivatives is quite limited, since these approaches require a pre-assembly of precursors bearing all 5 atoms.

3.2. Synthesis of pyrroles via Formal [4+1]-cycloaddition reactions

Synthesis of pyrroles via formal [4+1] cycloaddition processes is discussed in this chapter. The reactions are divided into two modes: 'Addition of Nitrogen' and 'Addition of Carbon' processes (Figure 6).

3.2.1. Formal [4+1] Nitrogen Addition Reactions—In 1960's Schulte et al. reported the Cu(I)-mediated synthesis of symmetrical 2,5-diarylpyrroles **3-204** from conjugated diaryldiynes **3-203** and primary amines.³⁷⁸ Later, Makhsumov³⁷⁹ and Chalk³⁸⁰ described catalytic version of this pyrrole synthesis. The reaction is believed to proceed via the transition metal-catalyzed hydroamination,^{12a,12e,f,12i,12m} leading to the formation of a transient tautomeric aminoenyne **3-205** or homopropargylic imine **3-206**, which further undergoes 5-*endo-dig* cyclization to furnish the pyrrole product **3-204** (Scheme 230). The scope of this transformation is quite broad, however, stoichiometric amounts of CuCl and

relatively high temperature often requires for achieving good yields.³⁸¹ In 2010, Hua found that this reaction can be performed at lower temperature in the presence of 10% CuCl using DMF as a solvent, producing 1,2,5-triarylsubstituted pyrroles in high yields.³⁸² An example of the Ti-catalyzed modification of this reaction has been reported by Ackermann and co-workers in 2004.³⁸³

In 2008, Bertrand disclosed the Au(I)-catalyzed reaction of diyne **3-207** with ammonia to afford 2,5-diphenylpyrrole **3-208** under harsh conditions.³⁸⁴ Later, Skrydstrup et al. developed an Au(I)-catalyzed amination of diynes **3-210** under very mild conditions to afford 1,2,5-trisubstituted pyrroles **3-211** (Scheme 131). In case of diaminosubstituted diynes, the reaction gives excellent yields of the corresponding 2,5-diaminopyrroles **3-208** at 30 °C. However the reaction with di-alkyl or arylsubstituted diynes requires higher temperature.²³⁰ Consequently, general amination of diversely substituted diynes into pyrroles under mild conditions still remains a challenging task.

Odom and co-workers extended this methodology to the Ti(IV)-catalyzed syntheses of pyrroles using skipped 1,*n*-diynes.³⁸⁵ Thus, monohydroamination of 1,4-diynes **3-212** occurs with the Markovnikov selectivity, to afford propargylic imine intermediates **3-214**, followed by a 5-*endo-dig* cyclization into pyrroles **3-213**. Similarly, the reaction of 1,5-diynes **3-215** with primary amines gave the corresponding pyrroles **3-216**. Both reactions tolerate various primary amines, providing moderate to high yields of 1,2,5-trisubstituted pyrroles (Scheme 232).

The Au(I)-catalyzed hydroamination of skipped diynes toward *NH* pyrroles was described by Bertrand. Accordingly, diyne **3-217** is converted pyrroles **3-218** and **3-219** upon the reaction with ammonia,³⁸⁴ and hydrazine³⁸⁶ respectively (Scheme 233).

In 2001, Ogura et al. reported the synthesis of pyrroles **3-221** from the corresponding 2-sulfonyl-1-alken-3-ynes **3-220** using the Cu(I)/Cu(II) catalyst system.³⁸⁷ The reaction proceeds via the Michael addition of an amine to an activated double bond, followed by a cycloisomerization/elimination reaction of **3-222** to form pyrrole **3-221** (Scheme 234).³⁸¹

Recently Liang disclosed a convenient protocol for the synthesis of pyrroles **3-224** based on the Au(III)-catalyzed reaction of 1-en-4-yn-3-ols **3-223** with sulfonamide. The reaction proceeds under mild conditions providing fused pyrroles **3-224** in moderate to good yields (Scheme 235).³⁸⁸

Liu et al. developed the Au(I)-catalyzed formal [4+1] approach toward pyrroles **3-226** via the reaction of (*Z*)-enynols **3-225** with amines, bearing electron withdrawing substituents. The reaction occurs via amination of (*Z*)-enynols **3-225**, followed by a cycloisomerization of the *in situ* generated (*Z*)-(2-en-4-ynyl)amines **3-227** into pyrroles **3-226** (Scheme 236).³⁸⁹ Alkyl- or aryl amines **3-229** undergo the reaction with more active acetoxy-(*Z*)-enynols **3-228** providing the corresponding *N*-arylsubstituted pyrroles **3-230** in good yields (Scheme 236).³⁹⁰

In 2011, Ray reported the synthesis of 2-acylpyrroles **3-233** via the Cu(I)-catalyzed reaction of *Z*-enynones **3-231** and aromatic hydroxylamines **3-232**. The reaction affords multisubstituted pyrroles **3-233** in good yields (Scheme 237).³⁹¹

Buchwald elaborated the Cu(I)-catalyzed protocol for the synthesis of pyrroles **3-235** from haloenynes **3-234** and *tert*-butyl carbamate (Scheme 238). Initially, the Cu(I)-catalyzed amidation of haloenynone **3-234** produces enyne **3-236**, which undergoes 5-*endo-dig* cyclization into pyrrole **3-235** (see Scheme 186 for the related cycloisomerization).³⁹²

the scope of this approach was expanded by Ackermann et al., who employed a Ti(IV)-catalyzed amination of (*E/Z*)-chloroenynes **3-237** with different amines. Thus, the Ti(IV)-catalyzed reaction of **3-237** with aryl- or benzylamines in presence of TiCl₄ affords pyrroles **3-238** in moderate to good yields (Scheme 239). Moreover, it was found that α -haloalkynols **3-239**, available via a nucleophilic addition of acetylides to a α -halo ketones, could also be used for the synthesis of pyrroles **3-240**. In this case, one additional equivalent of TiCl₄ is necessary for dehydration of **3-239** into haloenynes (type **3-237**). Pyrroles **3-241**, obtained after initial cyclization, can be functionalized with AcCl in a one-pot fashion to give the pentasubstituted pyrroles **3-240**. In contrast to the Buchwald protocol (Scheme 238), this transformation proceeds via an amination of the triple bond (**3-242**), followed by an intermolecular nucleophilic substitution in **3-243** (Scheme 239).³⁹³

In 2007, Williams and co-workers reported the Ru-catalyzed synthesis of pyrroles **3-245** from the corresponding 1,4-alkynediols **2-244** and aromatic or aliphatic amines (Scheme 240).³⁹⁴ Apparently, the reaction proceeds via a formation of diketone **3-246** and a subsequent Paal-Knorr reaction with amines to produce pyrrole **3-245**. In general, the reaction is more efficient with aliphatic alkynediols and amines.^{187b}

In 1983 Utimoto described the Pd-catalyzed synthesis of pyrroles **3-248** from 2-alkynyl ketones **3-247** and methyl amine (Scheme 241). The reaction proceeds via an imine formation and a subsequent cycloisomerization.^{74a}

In 2001, Arcadi et al. reported the similar synthesis of pyrrole employing the Au(III)-catalyzed reaction of 3-alkynyl ketones **3-248** with primary amines. (Scheme 242).³⁹⁵ An array of 1,2,3,5-tetrasubstituted pyrroles **3-249**, possessing various functional groups, are available in good yields via this method. According to the proposed mechanism, the Au(III)-catalyzed amination of 1,3-diketone **3-248** initially produces the corresponding imine **3-250**, which undergoes the Au(III)-catalyzed cycloisomerization into the pyrrole product **3-249**. The use of enantiomerically pure chiral amines, β -amino alcohols, and α -amino esters in this protocol gave the corresponding pyrroles **3-249** with complete preservation of chirality.³⁹⁶ Similarly, Hidai and Uemura reported that this reaction can successfully be performed in the presence of Pt(II) catalyst.¹¹²

Dake and co-workers extended the scope of this approach to the synthesis of pyrroles **3-252** from internal 2-alkynyl ketones **3-251** and amines using either an Au(I) or Ag(I) catalyst, leading to pyrroles **3-252** in moderate to high yields (Scheme 242). In 2010, this method was substantially improved by Bi, Zhang, who employed Fe(III)-catalyst for this transformation. Thus, a variety of tetra- and penta-substituted pyrroles **3-254** were prepared in excellent yields from the corresponding propargyl ketones **3-253** and amines (Scheme 242).³⁹⁷ In 2011, Tsuji and Nakamura reported the efficient synthesis of pyrroles from 2-alkynyl ketones and amines in the presence of In(III)-catalyst.³⁹⁸

Zhan et al. recently described the Zn(II)-catalyzed intramolecular formal [4+1] cyclization of β -alkynyl ketones **3-255** containing a tethered amino group. Thus, an amination/5-*exo-dig*-cyclization affords *N*-fused pyrroles **3-256** in good yields in under these conditions (Scheme 243).³⁹⁹

In 2007, Oh described the synthesis of 2-(2-methylenecycloalkyl)pyrroles **3-258** via the Pd-catalyzed cascade reaction of enediynals **3-257** with amines. Initially, imine **3-259** formed via reaction of **3-257** with an amine undergoes hydropalladation of the terminal triple bond with in situ generated HPdOCOH. Carbopalladation of the internal alkyne unit by the resulting vinylpalladium species affords intermediate **3-259**. An intramolecular imine attack, release of CO₂, and intramolecular hydride transfer from the less sterically hindered face

leads to the palladacycle **3-260**. The latter, upon reductive elimination, forms pyrrole **3-258**. Thus, a variety of highly functionalized fused pyrroles can be obtained via this methodology.⁴⁰⁰

Skipped allenyl aldehydes can also be used for synthesis of pyrroles. Thus, Wang reported the assembly of pentasubstituted pyrroles **3-263** via an acid-catalyzed cascade transformation of allenyl aldehydes **3-262** with aniline. It was also demonstrated that this transformation can efficiently be catalyzed by an Au(I)- or Ag(I)-salts. During this reaction, the sulfanyl group in the intermediate **3-264** underwent an intramolecular 1,2-migration yielding the corresponding 2-thiopyrroles **3-263** (Scheme 245).⁴⁰¹

Kirsch et al. reported the synthesis of substituted pyrroles **3-267** via the Ag/Au(I)-catalyzed successive [3,3]-migration/condensation/cycloisomerization reaction of vinyl propargyl ethers **3-265** with anilines. In this transformation, substrates **3-265** serve as surrogates of skipped allenyl ketones **3-266**. The latter forms a skipped allenyl imine in reaction with amine, followed by the Au(I)-catalyzed 5-*exo-dig*-cyclization providing pyrrole **3-267** (Scheme 246).⁴⁰²

A number of formal 4+1 protocols for the synthesis of pyrrole cores utilizing the Cu(I)-mediated vinylation of primary amines or amides have been reported recently. Thus, Li et al. reported the Cu(I)-catalyzed double alkenylation of amides with 1,4-diiodo-1,3-dienes **3-268** to obtain tri- and tetrasubstituted *N*-acylpyrroles **3-269a** (Scheme 247).⁴⁰³ Alkylcarbamates can also be employed in this reaction, however, in this case stoichiometric amounts of CuI are required. Recently, this methodology was extended to aromatic amines. Thus, Xi et al. showed that a variety of anilines undergo a Cu(I)-catalyzed double *N*-vinylation to afford pyrroles **3-269b** in good yield in presence of CuI and TMEDA (Scheme 247).⁴⁰⁴

Buchwald reported a highly efficient synthesis of pyrroles **3-271** via the Cu(I)-catalyzed double vinylation of *tert*-buthyl carbamate with 1,4-diiodo-1,3-dienes **3-270**. This methodology showed an excellent functional group compatibility toward multisubstituted pyrroles (Scheme 248).⁴⁰⁵

It was also shown by Li and co-workers that bromoenones **3-273** enable to produce the corresponding pyrroles **3-274** via the Cu(I)-catalyzed reaction with various amines. The reaction is substantially accelerated by the addition of NH₄OAc to the reaction mixture (Scheme 249).⁴⁰⁶

In 1997, Fürstner et al. developed the synthesis of pyrrole **3-276** via the Pd(0)-catalyzed reaction of α,β -unsaturated ketone **3-275** with benzyl amine (Scheme 250).⁴⁰⁷ The reaction was applied by the same group for the construction of the pyrrole ring in the total syntheses of roseophilin.⁴⁰⁸

Very recently, Demir reported a cooperative Au(I)/Zn(II)-catalyzed tandem hydroamination/annulation of 4-yne-nitriles **3-277** with amines, as a new route to 2-aminopyrroles **3-278**. According to the proposed mechanism, a coordination of Zn(II) to the nitrile group (**3-279**) facilitates a nucleophilic attack of an amine to form intermediate **3-280**. A subsequent activation of the triple bond in **3-280** by the Au(I) triggers an intramolecular attack by the nitrogen atom, which, according to the routes *a* and *b*, would lead to a formation of two regioisomeric pyrroles **3-278a** and **3-278b**. Formation of **3-278a** is predominant with regioselectivity in some cases up to 100% (Scheme 251).⁴⁰⁹

Yamamoto and co-workers described interesting example of the Rh-catalyzed reaction of 1,6-diyne **3-281** and *N*-thionylaniline to form pyrrole **3-282**. The reaction proceeds via

[2+2] cycloaddition followed by a extrusion of S=O from the intermediate cycloadduct **3-283** (Scheme 252).⁴¹⁰

In 2011, Yan et al. developed the Co(II)-catalyzed reaction of 1,1-dicyano-2,3-diarylcyclopropanes **3-284** with aromatic aldehydes and anilines to afford polysubstituted pyrrole-3-carbonitriles **3-285**. A plausible mechanism implies ring-opening reaction of cyclopropane with aniline, followed by a cyclization of the intermediate **3-286** into the cyclic 2-iminopyrrolidine **3-287**. A subsequent oxidation and condensation with aldehyde furnishes pyrrole derivative **3-288** (Scheme 253).⁴¹¹

3.2.2. Carbon Addition Reactions—In 1989, Pedersen and co-workers reported the synthesis of pyrroles **3-290** via the Nb(III)-catalyzed reaction of α,β -unsaturated imines **3-289** with dimethylformamide (or carboxylic esters) as a formal [4+1] process including addition of a carbon atom (Scheme 254).⁴¹²

Recently, Iwasawa developed the Rh(I) catalyzed [4+1] cycloaddition of α,β -unsaturated imines **3-291** with terminal acetylenes to afford tetrasubstituted pyrroles **3-292** (Scheme 255). According to the suggested mechanism, the reaction proceeds via the formation of the carbenoid **3-293** followed by a subsequent nucleophilic attack of the imine nitrogen to form a zwitterionic intermediate **3-294**, which undergoes cyclization into rhodocycle **3-295**. A subsequent reductive elimination gives enamine **3-296**, which yields pyrrole **3-292** via subsequent desilylation and isomerization. The reaction proceeds smoothly with aliphatic alkynes and a variety of α,β -unsaturated imines.⁴¹³

Konakahara et al. described a new approach to 3-aminopyrroles **3-298** via the Yb(III)-catalyzed cyclization of enimes **3-297** with TMSCN. According to the proposed mechanism, the Yb(III)-catalyzed allylcyanation of imine leads to intermediate **3-299**, which undergoes cyclization into the imine intermediate **3-300**. A subsequent isomerization and a hydrolysis of the TMS group affords 3-aminopyrrole **3-298**. This method allows for an efficient synthesis of scarcely available 3-aminopyrroles (Scheme 256).⁴¹⁴

Very recently, Chuang and co-workers described an interesting heterocyclization reaction, which involved radical intermediates generated by Ag(II)-species. Thus, 2-substituted-1,4-naphthoquinones **3-302** reacted with ketoacids **3-303** to afford polysubstituted pyrroles **3-304** in the presence of an Ag(I) and sodium persulphate. At the first step, the Ag(II)-mediated decarboxylation of ketoacid **3-303** produces acyl radical **3-305**, which attacks quinone **3-302**, followed by an oxidation of the formed intermediate into **3-306**. A subsequent intramolecular condensation and isomerization of **3-306** furnishes pyrrole **3-304** (Scheme 257). The reaction gives reasonable yields with variety of aliphatic ketoacids **3-303**, whereas aromatic ketoacids proved to be less efficient.^{234c}

In conclusion, a formal [4+1] nitrogen addition processes can serve as efficient tools for the synthesis of pyrroles with various substituents at the nitrogen atom. The analogues carbon addition reactions, though much less developed, could also be used for the synthesis of pyrrole structures with particular substitution pattern.

3.3. Synthesis of Pyrroles via Formal [3+2]-Cycloaddition Reactions

Syntheses of pyrroles via formal 3+2 cycloaddition reactions are discussed in this Chapter. The most general modes of [3+2] cycloaddition (disconnections a,b, and c) are shown in Figure 7.

3.3.1. Synthesis of Pyrroles Using α -Acidic Isocyanides—Isocyanides has long been recognized as important building blocks for synthesis of nitrogen-containing

heterocycles.^{18b,c} Moreover, α -acidic isocyanides, such as isocyanoacetic acid derivatives, are especially attractive as a partners for formal [3+2] cycloaddition reactions in the synthesis of heterocycles.^{18d}

Thus, Murahashi et al. reported the synthesis of pyrrole **3-309** via the Rh(0)-catalyzed reaction of 1,3-dicarbonyl compounds **3-307** and ethyl isocyanoacetate **3-308** (Scheme 258). The proposed mechanism involves a Rh(0)-catalyzed α -C-H bond activation of isocyanide followed by an attack at the carbonyl group of **3-307**, leading to intermediate **3-310**. The latter undergoes the Rh-catalyzed decarbonylation to form **3-311**, which produces the corresponding pyrrole **3-309** upon cyclocondensation. The regioselectivity of the reaction with unsymmetrical 1,3-diones is controlled by stereo- and/or electronic effects of the substituents at acyl groups.⁴¹⁵

In 2005, Yamamoto developed new synthetic procedures for the Cu-catalyzed formation of pyrroles **3-313** via a formal [3+2] cycloaddition of isocyanides **3-312** with activated alkynes. (Scheme 259).⁴¹⁶ It is believed that this transformation starts with the C-H activation of isocyanide by the Cu(I)-catalyst to form organocopper intermediate **3-314**. This intermediate **3-314**, or its tautomer **3-315**, undergoes a 1,4-addition at the alkyne, followed by an intramolecular cyclization to give the cyclic organocopper intermediate **3-316**. The latter provides pyrrole **3-313** upon protonation, followed by a subsequent [1,5]-H shift (Scheme 259).

De Meijere group independently discovered analogous transformation. Thus, the use of Cu(I) benzenethiolate or pre-activated nanosized copper powder (Cu⁰-NP) catalysts is allowed for synthesis of various pyrroles **3-318**. However, the acetylenic component of the reaction was limited to terminal activated alkynes only (Scheme 260).⁴¹⁷

In 2009, De Meijere has extended this methodology to unactivated terminal alkynes, which underwent the Cu(I)-promoted formal [3+2] cycloaddition reaction with isocyanides **3-319** to produce the corresponding 2,3-disubstituted pyrroles **3-320** in moderate to high yields. The proposed mechanism includes a carbocupration of the copper acetylenide **3-321** by Cu(I)-isocyanide species **3-322**, followed by cyclization of thus formed intermediate **3-323** into the 2H-pyrrole-4,5-dicopper intermediate **3-324**. A subsequent protonation and aromatization furnishes pyrrole **3-320** (Scheme 261).^{417b}

Very recently, the Cu(I)-catalyzed reaction of alkynes **3-325**, containing iodoaryl fragment, with α -acidic isocyanides **3-326** have been used for the synthesis of 2,3-fused pyrroles **3-327** by Cai and Ding. The reaction proceeds via a formation of the Cu-intermediate **3-328**, followed by an intermolecular arylation reaction with aryl iodide to form the product **3-327**. Isocyanides **3-326** containing different electron-withdrawing groups could be tolerated in this transformation, providing pyrroles in good yields (Scheme 262).⁴¹⁸ The Cu-catalyzed synthesis of pyrroles **3-330** from the corresponding iodoarylenones **3-329** and isocyanides was also disclosed by the same group. According to the proposed mechanism, intermediate **3-331** undergoes cyclization into dihydropyrrole **3-332**, which furnishes pyrrole **3-327** upon oxidation step (Scheme 262).⁴¹⁹

Similarly, the Cu(I)-catalyzed synthesis of pyrrolo[3,2-c]quinolin-4-ones **3-334** from the corresponding *N*-(2-haloaryl)propiolamides **3-333** and C-H acidic isocyanides has been developed by the same group (Scheme 263).⁴²⁰

3.3.2. Synthesis of Pyrroles from Vinyl Azides—Recently, an efficient synthesis of multisubstituted pyrroles employing vinyl azides was reported by Chiba, Narasaka, and coworkers. Hence, it was shown that α -azidoacrylates **3-335**, upon the Cu(II)-catalyzed

reaction with ethyl acetoacetate afforded tri- and tetrasubstituted pyrroles **3-336**. According to the proposed mechanism, the 1,4-addition of the copper enolate **3-338** to a Cu(II)-activated vinyl azide **3-337** affords an alkylidene iminocopper intermediate **333**, which undergoes an intramolecular cyclization into the cyclic hemiaminal intermediate **3-340**. The latter, upon dehydration-isomerization sequence, furnishes pyrrole **3-336** (Scheme 264). The presence of a carbalkoxy group (R^1), geminal to the azide function in **3-335**, is requisite to achieve high yields (Scheme 264).⁴²¹

Later, Chiba and Narasaka expanded the scope of this transformation by using the Mn(III) catalyst. Thus, the reaction tolerates simple non-activated alkyl-, aryl-, hetaryl- and even cyclic vinyl azides **3-341** to provide pyrroles **3-342** in good to excellent yields (Scheme 265). In addition, previously unreactive 1,3-diketones **3-344** now react with vinyl azides **3-343** to afford 3-acylpyrroles **3-345** (Scheme 265). The Mn(III)-catalyzed reaction is believed to occur via a radical mechanism.⁴²²

3.3.3. Synthesis of Pyrroles from Vinyl Halides—Buchwald and co-workers disclosed the synthesis of pyrroles via the Cu(I)-catalyzed reaction of 1,2-bis-Boc-hydrazines **3-346** and vinyl iodides **3-347**. The reaction is similar to the Piloty-Robinson pyrrole synthesis involving [3,3]-rearrangement of divinylhydrazides of type **3-349**. Thus, **3-349**, which is formed via a Cu(I)-catalyzed vinylation of bis-Boc-hydrazine **3-346** with vinyl iodide **3-347**, undergoes a subsequent [3,3]-rearrangement to give the intermediate **3-350**. The latter produces pyrrole **3-348** upon cyclization and elimination of BocNH_2 (Scheme 266). When electron-withdrawing groups were attached to the pyrrole core, the carbamate group was cleaved under the reaction conditions, affording the corresponding MH-pyrrole products.⁴²³

In 2006, Crawley et al. developed the synthesis of pyrroles **3-352** via the Pd-catalyzed annulation of 2-amino-3-iodoacrylate derivatives **3-351** and symmetrically-substituted alkynes. When unsymmetrically substituted alkynes were employed, a mixture of regioisomeric pyrroles was formed. In some cases, acetyl group was deprotected under the reaction conditions, affording the corresponding MH-pyrrole products (Scheme 267).⁴²⁴ Queiroz et al. extended this methodology for terminal alkynes. Thus, pyrroles **3-354** were formed from the corresponding iodoacrylates **3-353** and aryl acetylenes using Pd/Cu catalysts system. The reaction proceeds via the Sonogashira reaction followed by the 5-*endo-dig*-cyclization of intermediate **3-355** to produce pyrrole **3-354**. Pyrroles, containing amino-, methoxy- or halo-aryl substituents, as well as thienyl and pyridyl rings, can be prepared in good yields using this methodology (Scheme 267).⁴²⁵

In 2011, Zhou et al. reported the synthesis of pyrroles **3-356** via the Pd/Cu catalyzed cascade reaction of amino vinyl bromides **3-355** and terminal alkynes. The reaction proceeds via the Sonogashira coupling followed by a cycloisomerization of aminoenyne **3-357** into pyrrole **3-356** bearing hydrogen, alkyl, or aryl group at the nitrogen atom (Scheme 268). In the case of electron withdrawing substituent at the nitrogen of **3-355** ($R^1 = \text{Ac, Ts, Ms}$), the cyclization step requires additional Ga(III)-catalyst.³¹⁶

3.3.4. Synthesis of Pyrroles from Imines—Ishii group reported the Sm(III)-catalyzed [3+2] cyclocondensation between imines **3-358** and nitroalkenes **3-359** *en route* to various tri- and tetrasubstituted pyrroles **3-360**. (Scheme 269). The nitro-group plays a double role, by activating the alkene toward addition reaction and serves as a leaving group during aromatization step in this transformation.⁴²⁶

Carretero described the Cu(I)-catalyzed reaction of glycine aldimines **3-362** and *trans*-bisulfonyl ethylene **3-361** into pyrroles **3-363** (Scheme 270). The reaction proceeds via the

[3+2] cycloaddition reaction to form bis-sulfone adduct **3-364**, followed by a subsequent double elimination of sulfone moieties under basic conditions. This reaction represents a convenient method for the synthesis of pyrrolocarboxylates from aldehydes (via aldimines **3-362**).⁴²⁷

Park reported the Ag-catalyzed regioselective synthesis of tetrasubstituted pyrroles by a 1,3-dipolar cycloaddition of α,β -unsaturated benzofuran-3(2*H*)-ones **3-366** and oxazolones **3-365** (Scheme 271). According to the proposed mechanism, the Lewis acid catalyzed [3+2] cycloaddition forms polycyclic adduct **3-368**, which undergoes a spontaneous decarboxylation into pyrrole **3-367**.⁴²⁸

Wang and co-workers developed the Cu-catalyzed synthesis of pyrrolo [2,1-a] tetrahydroisoquinolines **3-371** and **3-373** via oxidation/cycloaddition of *N*-carbomethoxymethyl tetrahydroisoquinolines **3-369** and alkynes or alkenes. These reactions proceed via an oxidation of **3-369** to azomethine **3-374**, which undergoes a subsequent [3+2] cycloaddition with activated alkenes **3-370**, as well as alkynes **3-372**, to produce pyrroles **3-371** and **3-373**, respectively (Scheme 272). Shortly after, Xiao et al. employed visible light photocatalytic⁴²⁹ oxidation for this transformation. Thus, the reactive intermediate **3-374** is formed in the presence of Ru(bpy)₃²⁺ and visible light using air oxygen as a terminal oxidant. A subsequent cycloaddition of activated alkene (alkyne), followed by aromatization with NBS, affords the final pyrrole product. As an example, pyrrole **3-375** was prepared from the corresponding tetrahydroisoquinoline **3-369** and *N*-benzylsuccinamide in high yield using this protocol (Scheme 272).⁴³⁰

Very recently, Dixon reported a one-pot synthesis of pyrroles **3-378** via the nitro-Mannich/hydroamination cascade reaction of aromatic tosyl-imines **3-376** with 4-nitrobutyne **3-377** (Scheme 273). The initially formed Mannich adduct **3-379** in the presence of the Au(III)-catalyst underwent cycloisomerization/elimination into pyrrole **3-378** (see also Scheme 205 for the related cycloisomerization).³⁴¹

3.3.5. Synthesis of Pyrroles via Transannulation of Triazoles—Thus, in 2009, Murakami and co-workers reported the Ni-catalyzed transannulation^{431,432} reaction of *N*-sulfonyl-1,2,3-triazoles **3-380** with the internal alkynes **3-381**, leading to *N*-sulfonyl pyrroles **3-382**. It is believed that the initially formed Ni-carbenoid **3-383**, which may exist in cyclic form **3-384**, undergoes an insertion of the internal alkyne into the Ni-C bond to afford the corresponding six-membered nickelacycle **3-385**, giving the product **3-382** after a reductive elimination. The reaction requires Lewis acid, apparently, for the formation of the σ -imino diazo compound and/or accelerating the reductive removal of the Ni(0). The scope of reaction is limited to 4-aryl triazoles **3-380**, as well as to the symmetrical internal alkyl- or aryl alkynes. Unsymmetrical internal alkynes gave mixtures of regioisomeric pyrroles, whereas terminal C-H alkynes failed to react under those conditions at all (Scheme 274).⁴³³

Shortly after, Gevorgyan group expanded the scope of this transformation to terminal alkynes. Thus, combination of the Rh-catalyst and the Lewis acid (AgOCOCF₃) allowed obtaining the corresponding pyrroles **3-388** in good to excellent yields. The reaction most likely proceeds via the formation of Rh-iminocarbene **3-389**, followed by a direct nucleophilic attack of the terminal alkyne to form ylide **3-390**, which undergoes cyclization into intermediate **3-391**. A subsequent elimination of Rh(II) furnishes pyrrole **3-388** (Scheme 275). Silver trifluoroacetate could possibly act as a Lewis acid, which activates the electrophilic Rh carbene moiety of **3-389** toward the nucleophilic attack by the alkyne **3-387** via coordination to the nitrogen atom of the imine. It was also shown that tosyl azide and terminal alkynes could be directly employed in the Cu-click/Rh-transannulation reaction

sequence in a semi-one-pot fashion to produce pyrroles without significant loss of efficiency.⁴³⁴

In 2010, Park et al. reported the synthesis of fully substituted pyrroles **3-394** via the Cu-catalyzed cycloaddition of β -dimethylamino acrylates **3-393** with diazocompounds **3-392a**, which exist in an equilibrium with of N-alkoxy triazoles **3-392b** (Scheme 276). The reaction proceeds via a [3+2] cycloaddition followed by an aromatization of the pyrroline derivative **3-395** via an elimination of dimethylamine upon acidic treatment. A variety of polysubstituted *N*-alkoxy pyrroles **3-394** can be prepared using this methodology.⁴³⁵

3.3.6. Synthesis of Pyrroles via C-H Activation Processes—Transition metals-catalyzed C-H activation is one of the most extensively growing fields in modern organic and organometallic chemistry. Especially, cleavage of an aromatic C-H bond is useful for the building different fused heterocyclic skeletons such as indole or benzofuran. Very recently, synthesis of monocyclic heterocycles, including pyrroles, via this approach has also been developed. For instance, pyrroles can be obtained via reactions featuring cleavage of an allylic or a vinylic C-H bond and N-H bond.

Thus, in 2010, Glorius et al. reported the Rh-catalyzed synthesis of pyrroles **3-398** via the reaction of *N*-acetyl vinylamines **3-396** with internal alkynes **3-397**. Apparently, the reaction proceeds via the ester-(acetyl) group directed C-H activation to form rhodacycle **3-399**, followed by a subsequent reaction with alkyne (Scheme 277). A variety of internal aryl alkynes **3-397** were successfully employed, while α -aryl pyrroles were formed as a single regioisomer from unsymmetrical aryl-alkyl substituted alkynes ($R^4 = \text{Alk}$). In the case of unsymmetrically-substituted alkynes with two aryl groups ($R^4 = \text{Ar}$), a mixture of regioisomeric pyrroles was obtained.⁴³⁶

This methodology was extended by the same group for the synthesis of pyrroles **3-401** via the Rh(I)/Ag(I)/Cu(II)-catalyzed cleavage of vinylic C-H bond in activated vinylamine **3-400**. Thus, reaction of **3-400** with internal alkynes leads to a regioselective formation of polysubstituted pyrroles **3-401** (Scheme 278).⁴³⁶ Stuart and co-workers used oxygen as a terminal oxidant for a similar transformation. Hence, reaction of vinyl amines **3-402** with internal alkynes produces tetrasubstituted pyrroles **3-403** regioselectively. The reaction occurs under mild conditions in the presence of Rh(I)/Cu(II) catalyst system under an oxygen atmosphere. This reaction shows good functional group compatibility and allows to obtain a variety of substituted pyrroles (Scheme 278).⁴³⁷

3.3.7. Synthesis of Pyrroles via Ring-Opening of 3-Membered Rings—In 1985, Binger reported synthesis of pyrroles via Ni- and Pd-catalyzed cycloaddition of methylenecyclopropane with ketenimines. For example, the reaction of ketenimine **3-404** with methylenecyclopropane furnishes pyrrole **3-405** in excellent yield.⁴³⁸

In 2004, Yamamoto et al. developed a simple and efficient approach to pyrroles **3-408** based on the Pd-catalyzed reaction of acetophenones **3-406** with methyleneaziridines **3-407** (Scheme 280). According to the proposed mechanism, oxidative insertion of Pd(0) into the C-H bond of acetyl group gives hydridopalladium species **3-409**. A subsequent hydropalladation of methyleneaziridine **3-407**, followed by a reductive elimination of Pd(0) from **3-410a** leads to the ketoaziridine intermediate **3-410b**. An intramolecular nucleophilic attack and elimination of water from cyclic intermediate **3-411** affords pyrrole **3-408**. A variety of 1,2,4-trisubstituted pyrroles **3-408**, containing aromatic or heteroaromatic substituents, can be synthesized in good yields using this efficient methodology (Scheme 283). Definitely, the high acidity of the α -C-H bond in the carbonyl compound is essential for this transformation.⁴³⁹

Later, Nakamura and Yamamoto employed 1,3-diketones **3-412**, containing acidic CH₂ fragment, as a keto-component in the Pd-catalyzed reaction with methyleneaziridines **3-413**. Thus, various 3-acyl pyrroles **3-414** were prepared in good yields using this approach (Scheme 281). In case of unsymmetrical 1,3-diketones, a nearly equal mixture of regioisomeric pyrroles was formed.⁴⁴⁰

In 1977, Schuchardt described synthesis of pyrroles via Ni metal-catalyzed reaction of aryl-2*H*-azirines with carbonyl compounds, containing acidic CH₂ group.⁴⁴¹ Recently, Suárez extended the scope of this transformation and applied it for the synthesis of bis-glycosylated pyrroles. Thus, the V(V)-catalyzed reaction of 1,3-dicarbonyl compounds (or malonates) **3-415** with 2*H*-azirines **3-416** afforded 3-acetylpyrroles **3-417** in good yields. A regiochemistry of this reaction is controlled by substituents in 1,3-dicarbonyl compounds (Scheme 282).⁴⁴² Notably, as was described by Chiba, Narasaka, and co-workers, the reaction of a carbomethoxy-2*H*-azirine with acetylacetone proceeds without catalyst, producing the corresponding pyrrole in quantitative yield.⁴²¹

3.3.8. Synthesis of Pyrroles via Olefin Metathesis—It was recently shown that along with a ring closing metathesis (RCM),^{17c} an olefin cross-metathesis (CM)^{220b} is applicable for the synthesis of heteroaromatic compounds, including pyrroles. Thus, Donohoe developed a CM/cyclization sequence for synthesis of pyrroles **3-421** and **3-422** (Scheme 283). At the first step, the CM reaction of allylic amines **3-418** and enones **3-419** produces *trans*- γ -aminoenones **3-420** in good yields using the Hoveyda-Grubbs 2nd generation catalyst. Products **3-420**, containing amino- and carbonyl functions can be easily cyclized either in acidic media (to afford *N*-protected 2,5-disubstituted pyrroles **3-421**) or under the Heck-arylation conditions, to provide *N*-protected 2,3,5-trisubstituted pyrroles **3-422** in regioselective fashion (Scheme 283).⁴⁴³

Subsequently, Grela and co-workers reported a one-pot protocol for the direct synthesis of pyrroles **3-425** from the corresponding allylic amines **3-423** and enones **3-424** (Scheme 284). The reaction catalyzed by the Hoveyda-Grubbs 2 generation catalyst in the presence of Lewis acid directly furnishes pyrroles **3-425** in good yields.⁴⁴⁴

3.3.9. Miscellaneous [3+2] reactions—In 1999, Periasamy et al. developed a condensation of aryl methyl ketimines **3-426** to 2,5-diarylpyrroles **3-427** using stoichiometric amounts of TiCl₄/Et₃N (Scheme 285).⁴⁴⁵

In 2009, Cie reported the synthesis of pyrrole-2,5-dicarboxylic esters **3-429** via the Ti(IV)-mediated dimerization of 2-azidocarboxylic esters **3-428**. It was proposed, that Ti(IV) complex with iminoester **3-430** undergoes oxidative coupling to give open chain 1,4-diimines **3-431**. A subsequent cyclization, elimination of NH₃, and subsequent isomerization furnishes pyrroles **3-429**. This reaction is quite sensitive to the bulkiness of substituents at the ester group, (R²) and β -carbon atom (R¹) in starting azidocarboxylates **3-428** (Scheme 286).⁴⁴⁶

Liu and co-workers described the synthesis of trisubstituted pyrroles **3-433** via the Mn(III)-catalyzed dimerization of aroyl hydrazones of 1,3-dicarbonyl compounds **3-432** (Scheme 287). It is believed, that the reaction proceeds via a radical mechanism.⁴⁴⁷

In 1988, Marks described formation of pyrroles **3-435** via the lanthanides-catalyzed dimerization of 2-butyne-1-amine **3-434** (Scheme 288).⁴⁴⁸

Very recently, Trost et al. developed the Pd-catalyzed synthesis of 1,2,4-trisubstituted pyrroles **3-437** operating via the reaction of propargyl amines **3-436** with terminal alkynes.

At the first step, the corresponding amino enynes **3-438** are formed under the conditions *a*. A subsequent addition of Pd(OTFA)₂ (conditions *b*) trigger the cycloisomerization of **3-438** into pyrroles **3-437** via intermediate **3-439**. A variety of pyrroles **3-437** containing different aliphatic or aromatic substituents can be prepared in good to excellent yields under these mild conditions (Scheme 289).³¹⁵

Arndtsen and co-workers developed the Pd-catalyzed synthesis of multisubstituted pyrroles **3-443** from α -amidoesters **3-440** and alkynes **3-441** in presence of CO as a reductant. Thus, it was found that Pd(0) inserts into a C-OPy bond of **3-440** to give the palladacycle **3-444**, which undergoes a subsequent carbonylation to afford intermediate **3-445**. A reductive elimination leads to the münchone **3-446**, which could undergo various 1,3-dipolar cycloaddition reactions.^{21c} In that case, the reaction with alkyne forms adduct **3-447** producing the corresponding pyrrole **3-443** upon a loss of CO₂. A variety of pyrroles **3-443**, containing different substituents, are accessible in moderate to good yields using this method (Scheme 290). In the case of unsymmetrically-substituted alkynes, regioselectivity is controlled by both steric and electronic effects.⁴⁴⁹ A three-component modification of this transformation was also developed by the same group (see Scheme 317).

Very recently, Zhan developed the synthesis of *N*-fused pyrroles **3-450** via the Ag(I)-catalyzed reaction of indoles **3-448** with propargyl alcohols **3-449**. The reaction followed the Fridel—Crafts type propargylation to form **3-451**, which then undergoes cycloisomerization into **3-450**. A number of aryl-substituted pyrroles **3-450** were prepared using this transformation. In case of nonaromatic substituent at the acetylene **3-449** (R³ = TMS or *n*-Bu), a complete isomerization to pyrrole did not occur, and *N*-fused indoles **3-452** were formed exclusively (Scheme 291).⁴⁵⁰

In 2009 Müller developed a one-pot two-step synthesis of iodopyrroles **3-455** from acyl chlorides **3-453** and *N*-Boc-protected propargylamine **3-454**. The reaction proceeds via the Sonogashira coupling and subsequent I⁺-mediated cycloisomerization into 3-iodopyrroles **3-455**. Both aliphatic and aromatic acid chlorides **3-453** are tolerated under these reaction conditions affording 3-iodopyrroles **3-455** in good yields (Scheme 292).⁴⁵¹

In 1988, Kascheres developed the synthesis of pyrroles via the Cu(II)-catalyzed cycloaddition of enamines and diazoketones. Thus, the reaction of enamine **3-456** and diazoketone **3-457** furnishes pyrrole **3-458** in good yield. The reaction proceeds via an insertion of diazocompound into enamine C-H bond followed by a cyclization of the intermediate **3-459** into pyrrole. However, the reaction sometimes accomplished by an N-H insertion first, which produces a mixture of regioisomeric pyrroles if unsymmetrically substituted diazoketones were used (Scheme 293).⁴⁵²

Recently, Doyle et al. reported formation of pyrroles via the Rh(II)/Cu(II)-catalyzed reaction of *N*, α -diarylnitrones **3-461** with unsaturated diazocompounds **3-460**. The reaction proceeds via the Cu(II)-catalyzed Mannich reaction to produce diazocompound **3-463**. A subsequent Cu(II)/Rh(II)-catalyzed insertion of carbenoid into the N-O bond furnishes pyrrolidin-3-one **3-464**, diastereoselectively. The latter can be converted into pyrrole **3-462** under acidic conditions in a one-pot fashion (Scheme 294).⁴⁵³

In 1995, Ila and Junjappa described the synthesis of pyrroles **3-466** via the Cu(I)-mediated reaction of enamines **3-465** with propargyl bromide. The reaction proceeds via a formation of allenyl imine **3-467**, followed by the Cu(I)-catalyzed 5-*exo-dig* cyclization into pyrrole **3-466** (Scheme 295).⁴⁵⁴

In 2010, Huang and Liang reported the Cu(I)-catalyzed reaction of β -enamino ketones **3-468** and activated alkynes producing pentasubstituted pyrroles **3-469** (Scheme 296). According to the proposed rationale, the first step involves the coupling of **3-468** with alkyne to produce Michael addition-type intermediate **3-470**, which undergoes hydride abstraction with oxidant to form radical **3-471**. A subsequent 5-*endo-trig* cyclization gives cyclic radical **3-472**, which upon hydrogen loss transforms into pyrrole **3-469**.⁴⁵⁵

Recently, Guan reported formation of pyrroles **3-475** via the Fe(III)-catalyzed reaction of enamine **3-473** with nitroalkenes **3-474**. According to the proposed mechanism, the Michael addition produces the adduct **3-476**, which undergoes cyclization into intermediate **3-477**, followed by a elimination of HNO and water to form pyrrole **3-475**. The reaction affords tetrasubstituted pyrroles bearing a variety of aryl substituents at the C4 atom, in good yields (Scheme 297).⁴⁵⁶ This transformation was also done in four-component fashion (see Scheme 324).

Attanasi, Langer and co-workers developed the synthesis of *N*-aminopyrroles **3-480** via the Zn-catalyzed condensation of 1,2-diaza-1,3-butadienes **3-478** with 1,3-bis(silyl enol)ethers **3-479**. As proposed, the reaction proceeds via the Zn(II)-catalyzed conjugate addition and subsequent deprotection/cyclization of the intermediate **3-481** in acidic media. A large collection of *N*-aminopyrroles **3-480**, containing different substituents, were prepared via this methodology (Scheme 296).⁴⁵⁷

Very recently, Liu et al. reported formation of pyrroles **3-484** via the Ag-promoted reaction of 5-imidazolecarbaldehyde, secondary amines **3-482**, and alkynes **3-483**. According to the proposed mechanism, the reaction begins with formation of alkynyl amine **3-485**, which undergoes the Ag-catalyzed cycloisomerization (**3-486**) into the intermediate **3-487**. A subsequent hydrogen shift (**3-488**), followed by a hydrolysis (**3-489**) furnishes the corresponding pyrrole **3-484**, formaldehyde and ammonia. Oxidation of formaldehyde by Ag(I)/ammonia facilitates hydrolysis of **3-489**. The reaction proceeds with various aromatic and aliphatic alkynes **3-483** affording the corresponding 2-pyrrolecarbaldehydes **3-484** in moderate yields (Scheme 299).⁴⁵⁸

3.4. Synthesis of Pyrroles via Formal [2+2+1]-Cycloaddition Reactions

Multicomponent reactions are efficient instruments for building various heterocyclic cores, including pyrroles.^{21f,459} An application of a formal [2+2+1] cycloaddition reactions opens great opportunities for multicomponent assembly of pyrroles and pyrrole-containing molecules in one step. In this section, [2+2+1] cycloaddition processes can be divided into two modes: a) addition of nitrogen and b) addition of carbon reactions.

3.4.1. Addition of Nitrogen—In 2005, Shi and co-workers developed the synthesis of 1,3,4-trisubstituted pyrroles **3-490** via the Pd(II)-catalyzed trimerization of aryethylamines **3-489**, utilizing Cu(II) as a terminal oxidant. In this reaction, at least, twelve C-H and C-N bonds were cleaved, whereas five new bonds were assembled during multiple deprotonation and deamination processes. Different aryethylamines containing electron-neutral, electron-donating and slightly electron withdrawing substituents underwent this reaction to afford pyrroles **3-190** in reasonable yields (Scheme 300). A mechanism of this transformation is not clearly understood at this point.⁴⁶⁰

Very recently, Jia et al. suggested a simple method for the synthesis of pyrroles via the Ag(I)-mediated condensation reaction of aldehydes **3-491**, containing α -CH₂ fragment, with amines **3-492**. Both aliphatic and aromatic aldehydes and amines can be used in this reaction to produce pyrroles **3-493** mostly in good yields. Using ammonia as an amine component *N*-

unsubstituted pyrrole can be prepared, however, in diminished yield (25%). The reaction proceeds via the formation of imine **3-494**, which equilibrates with enamine **3-495**. A single-electron oxidation of the latter with AgOAc produces α -imine radical cation **3-496**. A subsequent dimerization and aromatization with the loss of one amine molecule furnishes pyrrole **3-493** (Scheme 301).⁴⁶¹ This transformation was used for construction of pyrrole ring in the synthesis of natural product purpurone (a potent ATP-citrate lyase inhibitor),⁴⁶¹ as well as alkaloids lamellarin (D,H,R forms) and ningalin B.⁴⁶²

Jiang and coworkers developed a one-pot Ag-catalyzed synthesis of polysubstituted pyrroles **3-500** via the sequential reaction of alkynes **3-497** and **3-498** with amines **3-499** in presence of PIDA (PhI(OAc)₂) as an oxidant. At the first step, the Ag-catalyzed amination of alkyne **3-497** yields enamine **3-501**, which undergoes oxidation with PIDA to form intermediate **3-502**. The latter reacts with another molecule of alkyne **3-498**, activated with Ag(I), to produce intermediate **3-503**, followed by protodemetalation to form nitrenium ion **3-504**. A subsequent cyclization produces carbocation **3-505**, which yields pyrrole **3-500** upon proton loss. When only one alkyne used, there is no regioselectivity issue and thus all reagents are loaded in the reaction vessel together. In the case of different alkynes, successive addition of alkynes and PIDA is required to achieve selective formation of unsymmetrically substituted pyrroles **3-500** (Scheme 302).⁴⁶³

In 2011, Wu et al. described an interesting synthesis of polysubstituted pyrroles via the Ni-catalyzed reaction of 1-ethynyl-8-iodonaphthalenes **3-506** and nitriles **3-507**, producing pyrroles **3-508**, accompanied by traces of diarylzethrene **3-509**. According to the proposed reaction mechanism, the oxidative addition of Ni(0) to **3-506** gives intermediate **3-510**, which undergoes addition to the C-N triple bond of nitrile to form imine derivative **3-511**. A subsequent migratory insertion of alkynyl moiety yields **3-512**, which reacts with another molecule of **3-506** to form intermediate **3-513**. A migratory insertion of imine moiety, followed by an oxidative addition furnishes **3-514**. A reductive elimination of Ni(II) from **3-514** followed by a reduction of Ni(II) by Zn affords pyrrole **3-508** and Ni(0) for the next catalytic cycle. Alternatively, the reaction of the intermediate **3-510** with another molecule of 1-ethynyl-8-iodonaphthalene **3-506** yields diphenylzethrene **3-509** as a by-product (Scheme 303).⁴⁶⁴

Hidai and Uemura reported that the bimetallic Ru/Pt catalyst system could be applied to the [2+2+1] synthesis of pyrroles **3-518** from propargylic alcohols **3-515**, enolizable ketones **3-516**, and anilines **3-517** (Scheme 304).¹¹² Up-to-fully substituted pyrroles **3-518** could be obtained via this approach in moderate yields. A large excess of carbonyl compound and aniline was required to achieve a complete conversion. This transformation is believed to proceed via the Ru-catalyzed propargylic substitution of **3-515** with **3-516** (*vide infra*) to give doubly skipped alkynyl ketone **3-519**, which, upon amination, furnishes γ -iminoalkyne **3-520**. The latter undergoes a Pt(II)-catalyzed cycloisomerization into the pyrrole product **3-518** (Scheme 304).

More recently, Cadierno, Gimeno et al. applied the same concept to the synthesis of pentasubstituted 3-acylpyrroles **3-524** from 1,3-dicarbonyl compounds **3-523**.⁴⁶⁵ Efficiency of this transformation was significantly improved by employment of the Ru(II) catalyst in the presence of trifluoroacetic acid. Reaction tolerates various secondary propargylic alcohols **3-521**, aromatic and aliphatic amines **3-522**, and 1,3-diketones or β -ketoesters **3-523** (Scheme 305). In addition, the authors demonstrated that this protocol could be further extended to the syntheses of 1,2,3,5-tetrasubstituted- and NH-pyrroles by *in situ* removal of various N- and C-protecting groups. It was also shown that *tert*-butyl carbamate can be employed instead of amine **3-522** to afford NH-pyrroles via the *in situ* removal of the Boc-group.⁴⁶⁶

Zhan developed the Zn-catalyzed version of this transformation. Thus, a one-pot reaction of propargylic acetates **3-523**, enoxysilanes **3-524**, and primary amines **3-525** afforded polysubstituted pyrroles **3-526** possessing different aliphatic and aromatic substituents (Scheme 306).³⁹⁹

Very recently, Das and co-workers developed the synthesis of tetrasubstituted pyrroles **3-529** via the Fe(III)-catalyzed three-component condensation of acetylenedicarboxylates **3-527**, phenacyl bromides **3-528** and amines (Scheme 307). According to proposed mechanism, reaction of amine and alkyne produces intermediate **3-530**, which then reacts with phenacyl bromide to produce aminoketone **3-531**. A subsequent cyclocondensation of **3-531** affords pyrrole **3-529**. Notably, the corresponding *NH*-pyrrole derivative is available via this transformation in 84% yield using NH_4OAc as an amine source.⁴⁶⁷

Mantellini reported the Zn(II)-catalyzed three-component reaction of α,β -unsaturated hydrazides **3-532** with amines and activated alkynes, producing pyrroles **3-533**. First, the double Michael addition of amine with **3-532** and alkyne produces α -(*N*-enamino)-hydrazone **3-534**, which undergoes cycloisomerization into pentasubstituted pyrrole **3-533**. The reaction is triggered by a Lewis acid activation of the hydrazone moiety toward intramolecular nucleophilic attack by the enamine (**3-535**) to produce cyclic intermediate **3-536**. A subsequent elimination of the hydrazino moiety furnishes pyrrole **3-533** (Scheme 308).⁴⁶⁸

Parrain and Duchêne described the Pd/Cu-catalyzed synthesis of pyrroles **3-540** via a one-pot allylic amination/Sonogashira/heterocyclization sequence under very mild conditions. Thus, reaction of (*E*)-3,4-diiodobut-2-enoic acid **3-537** with terminal acetylenes **3-538** and amines **3-539** affords β -pyrroloacetic acid **3-540** containing aliphatic or aromatic substituents. According to the proposed mechanism, an amination leads to the intermediate **3-541**, which undergoes the Sonogashira reaction with alkyne **3-538**. A subsequent cycloisomerization of **3-542**, followed by an aromatization of the cyclic intermediate **3-543** yields pyrrole **3-540** (Scheme 309).⁴⁶⁹

In 2008, Yadav et al. developed the In(III)-catalyzed three-component synthesis of annulated pyrroles **3-547** from aldose sugars (e.g. D-glucose **3-544**), aromatic amines **3-545** and 1,3-diones **3-546**. Apparently, the reaction proceeds via an aldol condensation followed by a subsequent cyclodehydration and aromatization. Noteworthy, other sugars, such as mannose, fructose, arabinose and others, also react efficiently to form the corresponding pyrroles in good to excellent yields (Scheme 310).⁴⁷⁰ The same reaction of aldehyde, amine and 1,3-diketones, induced by a low-valent titanium reagent, was described by Shi et al.⁴⁷¹

3.4.2. Carbon Addition Reactions—In 2007 Scheidt devised the Rh(II)-catalyzed reaction of imines **3-548**, activated alkynes **3-549** and diazoacetone nitrile (DAN) leading to pyrrolo-3,4-dicarboxylates **3-550** in good yields (Scheme 311).⁴⁷² The authors proposed that DAN reacts with the Rh(II) catalyst to generate the corresponding metalcarbenoid **3-551**, which upon a reaction with imine **3-548** produces the reactive transient azomethine ylide **3-552**, which is intercepted via a Huisgen [3+2]-cycloaddition with an activated alkynyl dipolarophile **3-549**. Next, the 2,5-dihydropyrrole adduct **3-553** undergoes elimination of HCN to furnish pyrrole **3-550** (Scheme 311).

Yamamoto group disclosed a transition metal-catalyzed four-component coupling approach toward tricyclic pyrroles **3-558** in a semi one-pot fashion from terminal acetylenes **3-554**, ethyl glyoxylate, benzylallylamine, and activated alkenes **3-557** (Scheme 312). At the first step, the Cu-catalyzed three-component Mannich reaction gives enyne **3-555**. Crude **3-555** underwent an Ir-catalyzed cycloisomerization into diene **3-556** with exocyclic double bonds.

A subsequent Diels-Alder reaction with dienophile **3-557**, followed by a dehydrogenative aromatization furnishes pyrrole **3-558** (Scheme 312).⁴⁷³

In 1986, Chatani⁴⁷⁴ and Ogata⁴⁷⁵ described synthesis of pyrroles **3-559** via the Pd-, Ni-, or Co-catalyzed reaction of trimethylsilyl cyanide with alkynes. Chatani et al. also described the formation of pyrrole **3-560** in a Co(0)-catalyzed reaction of alkyne, TMS-CN and *tert*-buthyl isocyanide (Scheme 313).⁴⁷⁶

In 2009, Tsukada and Inoue reported the Pd-catalyzed synthesis of 2-amino-5-cyanopyrroles **3-562** from *tert*-buthyl isocyanide and alkynes. Interestingly, the reaction of alkyne with 3 equivalents of *tert*-buthyl isocyanide, catalyzed by Pd-dinuclear complex, leads to formation of pyrrole **3-562**, where, 2 molecules of isocyanide are consumed to build the pyrrole ring and the third molecule serves as a source of the cyano group. In the case of unsymmetrically-substituted alkyne, a mixture of regioisomeric pyrroles is formed. According to the proposed mechanism, (Scheme 314). According to the proposed mechanism, an alkyne would insert into the Pd-Pd bond to form **3-561**, which undergoes insertion of two isocyanides to produce **3-561b**. A subsequent intramolecular cyclization of **3-561b** would afford iminopyrrolinyl complex **3-561c**. A subsequent cyanation of **3-561c** with a cyanide ligand generated by C-N bond cleavage [17] of third *tert*butylisocyanide on palladium would form intermediate **3-561d**. A subsequent reductive elimination would give **3-561e** producing pyrrole upon tautomerization **3-562**.⁴⁷⁷

Sato and Urabe described the Ti(IV)-mediated synthesis of pyrroles **3-565** from internal alkynes **3-563**, nitriles **3-564**, and methoxyacetone nitrile. Thus, successive addition of a nitrile to a complex of Ti(IV) and an alkyne **3-563** affords pyrrole **3-565** regioselectively in synthetically useful yields (Scheme 315).²⁸⁵

In 1996, Sato reported the synthesis of pyrroles **3-566** from alkyne, imine and carbon monoxide in the presence of stoichiometric amount of the Ti(IV)-reagent (Scheme 316).⁴⁷⁸

Later, Arndtsen group developed the Pd-catalyzed multicomponent synthesis of pentasubstituted pyrroles **3-572** from imines **3-567**, alkynes **3-568**, and acyl chlorides **3-569**. Conceptually, the reaction is based on the [2+3] cycloaddition of alkynes and münchnones **3-571**. Thus, acylation of imine with acyl chloride produces iminium salt **3-573**, which undergoes oxidative addition of Pd(0), subsequent carbonylation and reductive elimination into münchnones **3-574**. A following reaction with acetylenes furnishes pyrroles **3-572** upon CO₂ loss (see Scheme 290). The reaction tolerates a wide range of functional groups producing pyrroles in good yields. In the reaction with unsymmetrical alkynes, the regioselectivity is controlled by steric and electronic effects (Scheme 317).⁴⁷⁹

In 2011, Lu, Wang, and co-workers reported the Cu(I)-catalyzed three-component synthesis of pyrroles **3-549** from α -diazoketones **3-576**, nitroalkanes **3-577** and amines **3-578**. The cascade processes involves an N-H insertion of carbene to form secondary amine **3-580**, followed by a Cu-catalyzed oxidative dehydrogenation and a subsequent [3+2] cycloaddition of the formed azomethine ylide **3-581** with nitroalkene **3-577** to produce pyrrolidine **3-582**. A thermal extrusion of HNO₂ from pyrrolidine **3-582** accompanied by a dehydrogenative aromatization furnishes pyrroles **3-579**. The reaction represents an efficient multicomponent synthesis of 2-acylpyrroles **3-579** from simple precursors (Scheme 318).⁴⁸⁰

3.4.3. Synthesis of Pyrroles via Formal [3+1+1]-Cycloaddition reactions—In 2001, Müller et al. developed the synthesis of pyrroles **3-587** from propargyl alcohol **3-583**, aryl halides, aldehydes **3-584**, and amines **3-585** via a one-pot Sonogashira coupling/isomerization/Stetter/Paal-Knorr reaction sequence. Thus, at the first step, the Sonogashira

reaction/isomerization gives α,β -unsaturated ketone **3-588**, which undergoes the Stetter reaction with aldehyde **3-584** catalyzed by the thiazolium salt **3-586**. The formed 1,4-diketone **3-589** is converted to pyrrole upon the Paal-Knorr reaction with amine **3-585** (Scheme 319).⁴⁸¹

Okamoto described the synthesis of pyrroles **3-592** via a one-pot reaction of aromatic aldehydes **3-590**, amines **3-591** and 3,3-diethoxypropyne in presence of $\text{Ti}(\text{O}i\text{-Pr})_4/i\text{-PrMgCl}$. Thus, at the first step, (η^2 -imine)titanium complex **3-593** is formed. A subsequent reaction of **3-593** with 3,3-diethoxypropyne affords Ti-intermediate **3-594**, which after aqueous workup furnishes pyrrole via intermediately formed aminoallene **3-595** (Scheme 320). Thus, 1,2-disubstituted pyrroles **3-592** can be prepared in reasonable yields using this methodology.⁴⁸²

3.5. Synthesis of Pyrroles via Formal [2+1+1+1]-Cycloaddition Reactions

Several transition metal-catalyzed [2+1+1+1] reactions for synthesis of pyrroles were described. Thus, Eilbracht observed formation of pyrroles via the Rh-catalyzed hydroformylation of 1,4-diene **3-596** in the presence of primary amines **3-597**. Interestingly, two molecules of CO serve as carbon atom source for construction of the pyrrole ring in this transformation. Thus, the first hydroformylation produces the Rh-alkyl intermediate **3-599**, which undergoes insertion of another molecule of carbon monoxide to form rhodium 1,4-diketone species **3-600**, capable to undergo a subsequent Paal-Knorr reaction with amine to produce pyrrole **3-598** (Scheme 321).⁴⁸³

In 2009, Odom and co-workers disclosed an interesting Ti-catalyzed [2+1+1+1] type transformation. Thus, rear 2,3-diaminopyrrole **3-603** is formed by the reaction of alkynes **3-601**, anilines **3-602** and two molecules of *tert*-BuNC. According to the proposed mechanism, the Ti-catalyst and aniline **3-602** form Ti-nitrenoid **6-604**, which produces azatitanacycle **3-605** after cycloaddition with alkyne **3-601**. A subsequent insertion of two isocyanide molecules forms the corresponding 5-membered and six-membered azatitanacycles **3-606** and **3-607**, respectively. A protolytic cleavage of **3-607** releases enamine intermediate **3-608** that gives the pyrrole **3-603** upon cyclization and isomerization (Scheme 322). Terminal alkynes ($R_2 = \text{H}$) react smoothly to form one pyrrole regioisomer exclusively in good yields. The reaction with symmetrical internal alkynes gives diminished yields of pyrroles even after longer reaction time.⁴⁸⁴

In 1998, Ishii reported a formal [2+1+1+1] synthesis of pyrroles **3-612** via the Sm(III)-catalyzed three-component reaction of aldehydes **3-609**, amines **3-610** and nitroalkanes **3-611**. According to the proposed mechanism, the imine **3-613** undergoes condensation with another molecule of aldehyde to form α,β -unsaturated imine **3-614**. A subsequent Michael addition of **3-611** at the latter produces the intermediate **3-615**, which furnishes pyrrole **3-612** upon cyclocondensation and loss of the nitro group (Scheme 323).⁴⁸⁵

Later, Jana used two different aldehydes in the similar transformation. Thus, polysubstituted pyrroles **3-620** were formed in a multicomponent fashion from 1,3-dicarbonyl compounds **3-616**, aldehydes **3-617**, amines **3-618**, and nitroalkanes **3-619** in the presence of a Fe(III)-catalyst (see also Scheme 297). Thus, the Michael reaction of the one-pot formed β -ketoenamines **3-621** with nitroalkene **3-622** affords adduct **3-623**, which undergoes an intramolecular cyclization to form cyclic intermediate **3-624**. The latter converts into pyrrole **3-620** upon subsequent aromatization (Grob—Camendish type reaction). The reaction tolerates a variety of aliphatic and aromatic substituents producing pyrroles in regioselective fashion (Scheme 324).⁴⁸⁶ In 2011, Pal reported a more versatile Pd-catalyzed version of this transformation.⁴⁸⁷

In conclusion, a variety of transition metal-catalyzed methodologies are available for assembly of the pyrrole core. Thus, cycloisomerization reactions, as well as formal [3+2] syntheses, open almost unlimited opportunities for synthesis of diversely substituted pyrroles. Those methodologies use elemental reactions such as attack of nitrogen across activated multiple C-C bond, C-N bond forming cross-coupling reactions, insertion of metal-carbenoids into N-H bond, and cyclocondensation reaction of amine and carbonyl compounds. A number of multicomponent methodologies are also available for preparation of pyrroles. In addition, synthesis of pyrroles via metathesis reactions, as well as C-H activation processes, has been extensively developed. Further improvement of transition metal-catalyzed formation of pyrroles could be based on development of new catalytic system to achieve higher efficiency and selectivity.

4. Synthesis of Thio-, Seleno- and Tellurophenes

Transition-metal catalyzed C-S bond formation has been recognized as an important method for synthesis of organosulfur compounds.⁴⁸⁸ However, only a limited examples of halohenophene synthesis using transition-metals were developed. The possible reason is that organosulfur compounds such as thiols, sulfides and disulfides usually strongly coordinate to a metal atom, which could deactivate the catalyst. Nevertheless, a number of thiophene synthesis using stoichiometric amount of transition metals was reported. Thus, Fagan and Nugent described formation of thiophenes via a metallacycle transfer from zirconium to sulfur atom.⁴⁸⁹ Later, Kim reported synthesis of thiophenes **4-3** via a reaction of thioaroylketene *S,N*-acetals **4-1** with 1,3-dicarbonyl compounds **4-2**, promoted by a stoichiometric amounts of Hg(II) (Scheme 325).⁴⁹⁰

One of the first transition metal-catalyzed synthesis of thiophene was reported by in 1991 by Hartke, who observed formation of thiophene via the Pd/Cu-catalyzed cycloisomerization of propargyl thionester derivatives.⁴⁹¹ Later, Gabriele and Salerno described the synthesis of substituted thiophenes **4-5** via the Pd-catalyzed cycloisomerization of (*Z*)-2-en-4-yne-1-thiols **4-4** (Scheme 326).⁴⁹²

Marson and co-workers described the synthesis of thiophenes **4-7** via the Hg(II)-catalyzed cycloisomerization of substituted episulfides **4-6** in the presence of sulfuric acid.⁴⁹³

Later, Ma et al. developed the synthesis of polysubstituted thiophenes **4-10** via the Cu(I)-catalyzed tandem reaction of alkylidenethiiranes **4-8** with terminal alkynes **4-9** (Scheme 328). Apparently, the reaction proceeds via a ring-opening reaction (**4-11**), followed by a subsequent cycloisomerization into thiophenes **4-10**.⁴⁹⁴

In 2010, Xi and co-workers developed an efficient approach to polysubstituted thiophenes **4-13** via the Cu-catalyzed tandem S-alkenylation of 1,4-diiodo-1,3-dienes **4-12** with potassium sulfide (Scheme 329). The reaction tolerates a variety of alkyl and aryl substituents, including those posing TMS group, to afford thiophenes **4-13** in good to excellent yields.⁴⁹⁵

Alves, Zeni, and co-workers, described the synthesis of seleno- and tellurophenes⁴⁹⁶ via the Cu(I)-catalyzed reaction of (*Z*)-chalcogenoenynes **4-14** with *n*-butyl- or phenyldichalcogenides **4-15**. The reaction produces functionalized seleno- and tellurophenes **4-16** in good to excellent yields. According to the proposed mechanism, the Cu(I)-catalyzed cycloisomerization forms the furyl copper intermediate **4-17**, which undergoes a reductive elimination (**4-18**), followed by a formation of the final product (i.e. **4-19**) (Scheme 330).⁴⁹⁷

In 2011 Zeni also developed formation of 3-halo-chalcogenophenes **4-21** via the aerobic Cu(II)-promoted cycloisomerization of chalcogenoenynes **4-21**. The reaction proceeds under

mild conditions producing the corresponding thio- and selenophenes **4-21** efficiently (Scheme 331).⁴⁹⁸

Recently, Müller group reported a one-pot formal [1+1+1+1+1] multicomponent synthesis of thiophenes **4-22** based on the sequentially Pd/Cu-catalyzed Sonogashira-Glaser reaction, followed by a microwave-assisted cyclization in the presence of Na₂S (Scheme 332).⁴⁹⁹

5. Synthesis of 5-Membered Heterocycles with Two or More Heteroatoms

5.1. Synthesis of Oxazoles

5.1.1. Synthesis via cycloisomerization or related processes—N-

Propargylamides are valuable precursors for the synthesis of oxazoles via cycloisomerization reaction (Figure 9). Accordingly, propargylic amides may be cyclized to the corresponding oxazoles under acidic⁵⁰⁰ or basic conditions.^{500b,501} Silica gel,⁵⁰² as well as PhI(OAc)₂⁵⁰³ were also used to promote cyclization of propargylamides into oxazoles. The first transition metal-catalyzed reaction was described in 1973 by Eloy and Deryckere, who used Hg(II)-promoted cycloisomerization reaction for preparation of oxazoles.^{500b} This reaction has been used for the synthesis of oxazole-containing biologically active and drug-like molecules.⁵⁰⁴ Subsequently, in order to avoid toxic Hg(II)-salts and increase efficiency of the cycloisomerization reaction, other transition metals were tested for synthesis of oxazoles from propargylamides.

In 2004, Nishibayashi, Uemura⁵⁰⁵ and Hashmi et al.⁵⁰⁶ independently described the Au(III)-catalyzed 5-*exo-dig* cyclization (**5-3** to **5-4**) of propargylamides **5-1** into oxazole **5-2**. The reaction proceeds through formation of dihydrooxazole **5-5**, which is a main product when Au(I)-catalyst is used (Scheme 333).^{506–507} A variety of oxazoles containing aliphatic or aromatic substituents are easily available using this methodology.⁵⁰⁸ The same transformation was also observed by Padwa,^{217,509} and Zhao and Li.³¹⁴ Urriolabeitia employed an air- and moisture-stable Au(III) iminophosphorane complexes as a catalyst for synthesis of oxazoles from propargylamides.⁵¹⁰

In 2001 Cacchi and co-workers developed the synthesis of 2,5-disubstituted oxazoles **5-7** via the Pd-catalyzed cyclization/arylation tandem reaction of N-propargylamides **5-6** with aryl iodides (Scheme 334). The reaction proceeds efficiently with a variety of aryl substituted propargylamides and aryl iodides, producing oxazoles **5-7** in reasonable to good yields under mild conditions.⁵¹¹ Later, Saito and Hanzawa developed a tandem Pd-catalyzed cyclization/allylation reaction of N-propargylamides **5-8** with allyl carbonate to afford allylated oxazoles **5-9** (Scheme 334).⁵¹²

Broggini reported the Pd-catalyzed oxidative cyclization of N-propargylamides **5-10** into 5-oxazolecarbaldehydes **5-11** using benzoquinone or CuCl₂/O₂ as a terminal oxidant. The reaction produces a variety of oxazolecarbaldehydes containing aliphatic, aromatic, or heteroaromatic substituents in good yields (Scheme 335).⁵¹³

Isocyanoacetic acid derivatives are perfectly set for cyclization into oxazole ring, therefore, they are widely used for the multicomponent synthesis of oxazoles.^{18a,18d} Surprisingly, TM-catalyzed transformations were developed not so extensively compared to metal free reactions. Thus, Orru et al. reported a single example of the Ag-catalyzed cycloisomerization of isocyanoacetamide **5-12** into oxazole **5-13** (Scheme 336).⁵¹⁴

It is known, that isocyanoacetic acid derivatives could undergo Lewis Acid-assisted Ugi- or Passerini-type heterocyclizations in presence of carbonyl compounds or imines respectively.⁵¹⁵ It was shown by Ganem that isocyanoacetate or isocyanoacetamides **5-15**

reacts with carbonyl compounds **5-14** to produce oxazoles **5-16** in the presence of $\text{Zn}(\text{OTf})_2$ and silylating agent. A plausible mechanism involves a nucleophilic attack of isocyanide at the carbonyl group to form nitrilium ion **5-17**, which can exist in closed cyclic oxonium ion form (**5-18**). Aromatization of the latter produces oxazoles **5-16**. (Scheme 337).⁵¹⁶

In 2007, Wang and Zhu reported the $\text{Sn}(\text{II})$ -catalyzed cyclization of isocyanoacetamides with aldehydes into oxazoles. In general, linear or α -branched aliphatic aldehydes give the corresponding oxazoles in high yields, whereas aromatic aldehydes furnish the corresponding oxazoles in diminished yields. Moreover, enantioselective version of this transformation (ees up to 80%) using $\text{Sn}(\text{OTf})_2$ and a PyBox ligand was developed. As an example, oxazole **5-21** was obtained from the corresponding isocyanoacetamide **5-20** and aldehyde **5-19** in good yield and moderate enantioselectivity (Scheme 338).⁵¹⁷

5.1.2. Synthesis of Oxazoles via Formal [3+2]-Cycloaddition Reactions—

Formal [3+2] cycloaddition of α -diazocarbonyl compounds with nitriles represents an important method for synthesis of oxazoles. Initially, Huisgen found that the reaction can proceed upon heating, however, only trace amounts of oxazole were formed. Notably, in the presence of the Cu-catalyst, formation of reasonable amounts of oxazole was observed.⁵¹⁸ In 1974 Kitatani, Hiyama, and Nozaki described reaction of diazocarbonyl compounds with benzonitrile promoted by stoichiometric amount of WCl_6 .⁵¹⁹ Teyssie developed the Pd -⁵²⁰ and the Cu-catalyzed⁵²¹ version of this transformations. Later Helquist and Åkermark used Rh-catalysts for this transformation, which allowed to obtain oxazoles in higher yields under mild conditions.⁵²² This chemistry was extensively developed by Åkermark,⁵²³ Xu,⁵²⁴ Moody,⁵²⁵ Yoo,⁵²⁶ Ibata,⁵²⁷ Marsden,⁵²⁸ and Zhu,⁵²⁹. The reaction proceeds via formation of the Rh-carbenoid **5-25**, which undergoes a nucleophilic attack by the nitrile to form ylide intermediate **5-26**, which cyclizes into oxazole **5-24** (Scheme 339).⁵³⁰ Unfortunately, the reaction usually requires the use of large excess of nitrile (solvent) and therefore is only applicable to simple nitriles. Nevertheless, the reaction was successfully applied for construction of oxazole fragment in total synthesis of natural products by Lee,^{240f,g} Hoffmann,⁵³¹ Kozmin,⁵³² and Moody.⁵³³ Very recently, CpRu-catalyst was employed in this transformation by Lacour.⁵³⁴ Interestingly, Regitz showed that the $\text{Rh}(\text{II})$ -catalyzed reaction of α -diazocarbonyl compounds with *tert*-butylphosphaacetylene furnishes 1,3-oxaphospholes.⁵³⁵

Noteworthy, formation of metal carbenoid type **5-25** can be achieved not only from a diazocompound, but also from iodonium ylides or alkynes, which offers more synthetic flexibility and significantly increases efficiency of the reaction toward synthesis of oxazoles. Thus, Hadjiarapoglou et al. described the synthesis of oxazoles, based on the Cu-⁵³⁶ and Rh-catalyzed^{242b,c} reaction of nitriles with carbenoids **5-30**, generated from iodonium ylides. As an example, a Rh-catalyzed decomposition of iodonium ylide **5-27** in presence of nitriles **5-28** led to formation of oxazoles **5-29** in moderate yields (Scheme 340). Nevertheless, this reaction requires the use of a nitrile compound as a solvent, and suffers from poor yields and low functional group tolerance.

Very recently, it was impressively shown by Zhang's group that the corresponding gold-carbenoid could be generated from a simple terminal alkyne, gold catalyst and pyridine *N*-oxide.⁵³⁷ Using this concept, they developed an Au(I)-catalyzed synthesis of oxazoles **5-33** in the presence of *N*-oxide **5-32** from terminal alkynes **5-31** and nitriles as a solvent. The reaction proceeds via an oxidation of alkyne **5-31** into the gold carbene intermediate **5-34**, followed by a reaction with nitrile and subsequent cycloisomerization of the intermediate **5-35** into oxazole **5-33**. The reaction tolerates a variety of alkynes and nitriles producing oxazoles **5-33** in good to excellent yields (Scheme 341). Notably, a big excess of a nitrile is

not always necessary of this transformation. Thus, for some case, the reaction proceeds well with only 3 equiv of a nitrile.⁵³⁸

In 1996, Moody suggested an alternative route to oxazoles, based on the reaction of diazocarbonyl compounds **5-37** with amides **5-36**. First, an insertion of the Rh-carbenoid into N-H bond of amide produces intermediate **5-38**, which undergoes an iodine-mediated cyclization into oxazole **5-39** (Robinson-Gabriel oxazole synthesis).⁵³⁹ The reaction tolerates a variety of aliphatic and aromatic amides **5-36**, as well as different diazocompounds **5-37**, giving access to a wide range of oxazoles **5-39** (Scheme 342).⁵⁴⁰ In contrast to the nitrile-based synthesis (see Scheme 339), the reaction with amides does not require excess of an amide. Interestingly, the same group showed that the use of a more electrophilic $\text{Rh}_2(\text{NHCOC}_3\text{F}_7)_4$ catalyst in this transformation gives regioisomeric oxazole **5-42** via the reaction of aryl amides **5-40** with diazocarbonyl compounds **5-41**. (Scheme 342) Presumably, formation of oxazoles arises from OH insertion of intermediately formed Rh-carbenoid. In this case, regioselectivity of N-H versus O-H insertion is controlled by ligand at the rhodium catalyst.⁵⁴¹ Notably, thioamides also undergo the Rh(II)-catalyzed reaction with diazocompounds to produce thiazoles (see Scheme 359 for details).

Very recently, Nicasio and Pérez developed a new route to oxazoles **5-45** based on the Cu(I)-catalyzed cycloaddition of aryl azides **5-43** and terminal alkynes **5-44**. Interestingly, the reaction produces trisubstituted oxazoles instead of expected triazoles. According to the proposed mechanism, the Cu-catalyzed cycloaddition leads to copper triazolyl intermediate **5-46**, which could be transformed into the ketenimide species **5-47**. Protonation of the later (**5-48**), followed by a subsequent cycloisomerization furnishes oxazole **5-45**. The reaction proceeds smoothly with aromatic substrates, whereas aliphatic alkynes react less efficiently (Scheme 343).

Glorius developed the synthesis of trisubstituted oxazoles from amides **5-49** and 1,2-dibromoalkenes **5-50**, which are easily available via bromination of alkynes (Scheme 344). Apparently, two bromine atoms show comparable reactivity towards Cu-catalyzed amination, therefore, the reaction produces mixture of 2,5- and 2,4-disubstituted oxazoles (ratios up to 14:1). The stereochemistry of dibromoalkenes show almost no influence on the reaction course. The use of diiodoalkenes instead of dibromoalkenes also did not improve both the reaction yield and regioselectivity.⁵⁴² To overcome the regioselectivity issue, Buchwald used 1,2-iodo-bromoalkene **5-53** in the reaction with aryl amides **5-52** under Cu-catalysis to produce single regioisomer of disubstituted oxazoles **5-54** in excellent yields. In this case, the regioselectivity is controlled by the selective amination of C-I bond in place of C-Br bond. However, limitation of this method is the lack of general route for the synthesis of 1,2-iodo-bromoalkenes of type **5-53** (Scheme 344).⁵⁴³ In 2010, Moses reported the synthesis of oxazoles from amides and α -bromoketones in the presence of one equivalent of an Ag(I) salt.⁵⁴⁴

Buchwald also suggested another efficient one-pot approach toward trisubstituted oxazoles via the Cu-catalyzed vinylation/cyclization sequential reaction. Thus, a Cu-catalyzed reaction of aliphatic or aromatic amides **5-55** with bromoalkenes **5-56** leads to formation of enamides **5-58** which can cyclize into oxazole **5-57** in the presence of iodine and base via formation of a cyclic intermediate **5-59**. Using this method, a variety of alkyl- and aryl-substituted oxazoles **5-57** could efficiently be prepared from simple starting materials via a one-pot fashion (Scheme 345).⁵⁴³

Nishibayashi and Uemura developed a one-pot Ru/Au-catalyzed sequential synthesis of oxazoles **5-62** from amides **5-60** and propargylic alcohols **5-61** (Scheme 346). The reaction

proceeds via formation of propargyl amide **5-63**, followed by the Au(III)-catalysed cycloisomerization (see also Scheme 333) into oxazole **5-62**.⁵⁰⁵

Later, Liu described the Zn/Ru-catalyzed reaction of amides **5-64** with propargylic alcohols **5-65** into trisubstituted oxazoles **5-66**, which are regioisomeric to oxazoles **5-63**, obtained via the Ru/Au-catalysis (Scheme 346). It was found that the reaction proceeds via the Zn-catalyzed amination of triple bond of propargyl alcohols and an isomerization to produce α -amidoketone **5-67**. A subsequent Zn/Ru-catalyzed cycloisomerization of the latter leads to oxazole **5-66**. The reaction proceeds well with both aromatic and aliphatic amides and aromatic propargyl alcohols, affording oxazoles **5-66** in excellent yields (Scheme 347).⁵⁴⁵ Notably, this transformation could also be efficiently performed using TsOH as a catalyst.⁵⁴⁶

Very recently, Wang et al. described the synthesis of polysubstituted oxazoles **5-70** via the Cu-catalyzed tandem oxidative cyclization of benzyl amines **5-68** and 1,3-dicarbonyl compounds **5-69**. The reaction proceeds via an iodination/amination sequence to form secondary amine derivative **5-71**, which then undergoes oxidation into imine **5-72**, followed by a cyclization into oxazoline **5-73**. A subsequent oxidation of **5-73** affords oxazole **5-70** (Scheme 348). The reaction tolerates broad variety of benzyl amines and 1,3-dicarbonyl compounds, forming oxazoles **5-70** under mild conditions.⁵⁴⁷

In 2011, Davies developed the synthesis of oxazoles **5-76** via the Au-catalyzed reaction of pyridine-*N*-amidines **5-74** with activated alkynes **5-75** (ynamides or ynol ethers). The reaction proceeds well with a variety of diversely-substituted reactants, providing the corresponding oxazoles **5-76** in good to excellent yields (Scheme 349).⁵⁴⁸

5.2. Synthesis of Isoxazoles

5.2.1. Synthesis of Isoxazoles via Cycloisomerization Reactions—In 1973, Moritani and Murahashi described formation of isoxazoles **5-78** via the Pd-mediated oxidative cycloisomerization of α,β -unsaturated ketoximes **5-77**. The major drawback of this method is the requirement of stoichiometric amounts of a palladium salt (Scheme 350).⁵⁴⁹

In contrast, cycloisomerization of alkynyl oximes seems a more reasonable alternative as it would lead to the desired oxazoles without necessity of an oxidation step. Along this line, in 1993, Ziegler described the synthesis of isoxazoles via cyclization of β -alkynyl oximes under basic conditions.⁵⁵⁰ Later, Larock et al. described cyclization of β -alkynyl oximes using electrophilic reagents (I_2 , ICl).⁵⁵¹ In 2005, Mori reported the multicomponent synthesis of isoxazoles including a Pd-catalyzed cycloisomerization of formed in situ β -alkynyl oximes (see Scheme 358 for details).⁵⁵²

In 2010, the Au-catalyzed cycloisomerization of β -alkynyl oximes was reported by Perumal. Thus, a variety of oximes **5-79** can be converted to the corresponding isoxazoles **5-80** in excellent yields under mild conditions (Scheme 351).⁵⁵³ Recently, Studer used the Au(III)-catalyzed cycloisomerization of β -alkynyl oximes in sequential synthesis of isoxazoles from nitrones and alkynes.⁵⁵⁴ In 2011, the Ag(I)-catalyzed cycloisomerization of benzyl ethers of β -alkynyl oximes into isoxazoles was reported by Miyata.⁵⁵⁵

Very recently, the scope of this transformation was expanded to synthesis of trisubstituted isoxazoles. Thus, Miyata described the Au-catalyzed cycloisomerization reaction of allylic ethers of alkynyl oxime **5-81** into tetrasubstituted oxazoles **5-82**. The reaction proceeds via cycloisomerization (**5-83**), followed by a Claisen-type rearrangement into oxazole **5-82** (Scheme 352).⁵⁵⁶

A single example of efficient cycloisomerization of azirinecarbaldehyde **5-84** into the corresponding oxazole **5-85** in the presence of Grubbs I catalyst was reported by Padwa (Scheme 353).³²⁸

5.2.2. Synthesis of Isoxazoles via Formal [3+2]-Cycloaddition Reactions—Very recently, Vrancken and Campagne described a versatile Fe(III)-catalyzed synthesis of disubstituted isoxazoles **5-88**. Accordingly, the Fe-catalyzed reaction of propargylic alcohols **5-86** with *N*-sulfonyl protected hydroxylamine **5-87** produced the propargyl hydroxylamine **5-89**, which undergoes a subsequent elimination of PhSO₂H, followed by a cyclization of the formed oxime **5-90** into the oxazole **5-88** (Scheme 354).⁵⁵⁷

Cycloadditions of nitrile oxide are widely used for synthesis of heterocyclic compounds.⁵⁵⁸ Thus, [3+2] cycloaddition of nitrile oxides with alkynes, leading to formation of isoxazoles, was first described by Huisgen in 1973.⁵⁵⁹ The reaction sometimes gives two regioisomeric isoxazoles. However, steric effects control the regioselectivity placing the more encumbered carbon atom of the alkyne next to the oxygen of the nitrile oxide. Subsequently, Müller developed a one-pot three component synthesis of oxazoles **5-94** from acyl chlorides **5-91**, terminal alkynes **5-92**, and hydroxymoyl chlorides **5-93**. First, the Sonogashira reaction produces acylalkyne **5-95**, which undergoes a microwave-assisted regioselective cycloaddition with nitrile oxide **5-96** (formed in situ from hydroximoyl chloride **5-93**) to form the isoxazole **5-94** (controlled by kinetic factors). The reaction proceeds with variety of alkynes and acyl chlorides, but is limited to aromatic hydroximoyl chlorides **5-93** (Scheme 355).⁵⁶⁰ Later, this method was applied by the same group for synthesis of ferrocenyl isoxazoles.⁵⁶¹

Noodleman, Sharpless, and Fokin developed the Cu-catalyzed synthesis of isoxazoles **5-99** via the cycloaddition of terminal alkynes **5-98** and nitrile oxides, which were formed in situ from the corresponding hydroximoyl chlorides **5-97**. The use of the Cu-catalyst gives significant improvements, in comparison with the noncatalyzed process, in terms of both yields and regioselectivity. According to the proposed mechanism, the Cu-acetylide **5-101** coordinates to the nitrile oxide **5-100** via the Cu(I) atom, this facilitating the cycloaddition reaction to give cyclic species **5-102**. A subsequent reductive elimination furnishes the corresponding isoxazoles **5-99** (Scheme 356).⁵⁶² Later Fokin developed an efficient and general one-pot protocol for synthesis of disubstituted isoxazoles **5-104** starting from aldehydes **5-103**. At the first step, aldehyde **5-103** is converted to an aldoxime, which is transformed to a nitrile oxide via treatment with Chloramine-T. A subsequent Cu(II)-catalyzed cycloaddition reaction with alkynes affords isoxazoles **5-104** (Scheme 356).⁵⁶³ This reaction was also efficient with ynammides, as shown by Hsung.⁵⁶⁴

Analogously to the alkyne-azide cycloaddition (see Chapter 5.7.1), Fokin developed the Ru-catalyzed cycloaddition of nitrile oxides and alkynes, leading to formation of isomer 3,4-disubstituted isoxazoles. Thus, the Ru-catalyzed reaction of hydroximoyl chlorides **5-105** with terminal alkynes **5-106a** afforded 3,4-disubstituted oxazoles **5-107**. The reaction mechanism is similar to a Ru-catalyzed synthesis of 1,5-disubstituted triazoles (see Scheme 404). Importantly, these process is not limited to terminal alkynes only. Thus, the reaction of **5-105** with internal alkynes **5-106b** affords trisubstituted isoxazoles **5-108** in good yields and regioselectivity. Notably, when alkyne containing a hydrogen-bond donors is used, the cycloaddition reactions are especially regioselective and efficient, leading to single regioisomer of isoxazole. Generally, the corresponding isoxazoles **5-107** and **5-108** are formed in good yields under mild conditions (Scheme 357).⁵⁶⁵

5.2.3. Synthesis of Isoxazoles via Formal [2+2+1]-Cycloaddition Reactions—

An example of formal [2+2+1] synthesis of isoxazoles was described by Mori. Thus,

isoxazoles **5-110** were obtained via the Pd-catalyzed multicomponent reaction of terminal alkyne **5-109**, hydroxylamine, and aryl iodide under the CO atmosphere. First, carbonylative Sonogashira reaction produces alkynyl ketone **5-111**, which reacts with hydroxylamine to form alkynyl oxime **5-112**. A subsequent cycloisomerization of **5-112** (see also Scheme 351) affords the corresponding isoxazole **5-110** (Scheme 358).⁵⁵²

5.3. Synthesis of Thiazoles and Selenazoles

Similarly to the preparation of oxazoles from amides and diazocarbonyl compounds (see Chapter 5.1.2.), thiazoles can also be prepared from the corresponding thioamides. Thus, Yadav developed an efficient synthesis of 2-aminothiazoles **5-515** via a Cu(II)-catalyzed cyclocondensation of thiourea **5-113** with α -diazocarbonyl compounds **5-114**. The reaction affords 2-aminothiazoles in excellent yields under mild conditions using inexpensive Cu(II) catalyst (Scheme 359).⁵⁶⁶ Analogously to the oxazole synthesis (see Scheme 342 for details), Moody and co-workers reported efficient and regioselective formation of thiazoles **5-118** via the Rh(II)-catalyzed reaction of aryl thioamides **5-116** with diazocarbonyl compounds **5-117** (Scheme 359).⁵⁶⁷

In 2009, Yoshimatsu developed the synthesis of thiazoles and selenazoles **5-121** from thio- or selenoamides **5-119** and propargyl alcohol derivatives **5-120** (for synthesis of oxazoles see Scheme 346). At the first step, an ionization and isomerization of propargyl alcohol would lead to an allenyl cation **5-123**, stabilized by S or Se atom. A subsequent nucleophilic attack of amide **5-119** would produce intermediate **5-124**, which undergoes a Sc(III)-catalyzed cycloisomerization into a cyclic intermediate **5-125**, finally producing the corresponding aromatic heterocycle **5-121** upon tautomerization (Scheme 360).⁵⁶⁸

In 2010, Zhan extended the scope of this approach using the Ag-catalyzed reaction of propargyl alcohols **5-127** and thioamides **5-126**, to form thiazoles **5-128**. (Scheme 361). The same research group suggested the Fe(III)-catalyzed one-pot protocol for direct synthesis of thiazoles **5-131** from amides **5-129** and propargyl alcohols **5-130**. Thus, the Fe-catalyzed propargylation of amide led to the formation of an alkynyl-amide **5-132**, which is converted into alkynyl-thioamide **5-133** via treatment with the Lawesson's reagent. A subsequent spontaneous cyclization of **5-133** furnishes the corresponding thiazole **5-131** (Scheme 361).⁵⁶⁹

To the best of our knowledge, a single example of isothiazole synthesis using transition metal catalyst was described by Kumagai and Shibasaki in 2011. Thus, the Cu(I)-catalyzed cyclization of α,β -unsaturated nitriles **5-134**, containing a tethered thioamide fragment, produced fused isothiazoles **5-135** in good yields. The reaction proceeds via a base-induced 6-*exo-dig* cyclization (*Z*-configuration of the double bond in **5-134** is crucial) to form the Cu(I) complex **5-136**, which undergoes oxidation into the Cu(II) complex **5-137**. A subsequent reductive elimination furnishes fused isothiazole **5-135** (Scheme 362).⁵⁷⁰

5.4. Synthesis of Imidazoles

Recent developments of catalytic synthesis of imidazoles were discussed in 2007 in excellent review by Kamijo and Yamamoto.⁵⁷¹ Accordingly, in this section generally most recent methods are discussed.

5.4.1. Synthesis of Imidazoles via Cycloisomerization-Type processes—An efficient synthesis of imidazoles **5-139** from amidoximes **5-138** based on the Pd-catalyzed imino-Heck reaction (for the synthesis of pyrroles via the similar transformation, see Scheme 213) was developed by Abell. (Scheme 363).⁵⁷²

It deserves mentioning, that a somewhat related Cu-mediated synthesis of imidazoles **5-141** from imines **5-140** was reported by Arcadi in 1994 (Scheme 364).⁵⁷³

Later, Abbiati and Arcadi reported the Pd/Cu-catalyzed synthesis of 4-substituted-2-phenylimidazoles **5-143** via an arylative cyclization of *N*-propargyl-benzylamidines **5-142** with aryl iodides. The reaction most likely proceeds via intermolecular aminopalladation (**5-144**) to produce cyclic intermediate **5-145**, followed by a reductive elimination and aromatization of the intermediate **5-146** (Scheme 365). On the other hand, the Sonogashira reaction and subsequent cycloisomerisation could be an alternative pathway for this transformation.⁵⁷⁴

Looper developed the synthesis of 2-aminoimidazoles **5-149** via the La(III)-catalyzed addition-hydroamination reaction of propargyl cyanamines **5-147** with dialkyl or diallyl amines **5-148** (Scheme 366).⁵⁷⁵ Notably, starting cyanamines **5-147** can be easily prepared by three-component coupling reaction of aldehyde, amine, and alkyne,⁵⁷⁶ followed by a subsequent cyanation.

Van der Eycken developed an efficient synthesis of 2-aminoimidazoles **5-152** via the Ag-catalyzed cycloisomerization of propargyl guanidines **5-150**. At the first step, protected 2-aminoimidazole precursors **5-151** are formed in quantitative yields. Subsequently, the Boc group is easily removed under acidic conditions to afford 2-aminoimidazoles **5-152** (Scheme 367).⁵⁷⁷

5.4.2. Synthesis of Imidazoles via Formal [3+2]-Cycloaddition Reactions—

Isocyanoacetic acid derivatives^{18d} are valuable building blocks for synthesis of heterocyclic compounds, including imidazoles. Thus, Grigg developed an efficient Ag-catalyzed cyclization of isocyanoacetates **5-153** into imidazoles **5-154** under mild conditions. According to the proposed mechanism, the coordination of an Ag(I) salt to the isocyanide group (**5-155**) facilitates deprotonation of CH₂-group to form carboanion **5-156**. The latter attacks another molecule of isocyanoacetate **5-153** to form intermediate **5-157**, which undergoes ring closure, followed by aromatization and protodemetalation (**5-158**) to furnish the corresponding bis-carbalkoxy imidazole **5-154** (Scheme 368).⁵⁷⁸

Later, Yamamoto developed the synthesis of imidazoles **5-161** via the Cu-catalyzed cross-cycloaddition of isocyanides **5-159**, containing acidic CH₂ fragment, with aryl isocyanides **5-160**. A variety of isocyanoacetates and aromatic isocyanides could be reactants for this transformation. Less acidic isocyanides, containing amide and diethylphosphate group, give imidazoles in diminished yields (Scheme 369). On a related note, Roy et al. developed a direct semi-one-pot protocol for the synthesis of 1-arylimidazole-4-carboxylates **5-164** starting from the corresponding *N*-formylglycine esters **5-162** and *N*-arylformamides **5-163**. At the first step, a mixture of two formamides is converted into a crude mixture of two isocyanides, followed by Cu-catalyzed reaction to form imidazole **771**. Importantly, a new catalytic system (10% Cu₂O/20% proline) allowed reaction to proceed at room temperature with variety of aryl isocyanides (Scheme 369).⁵⁷⁹

In 2008, Gevorgyan and Fokin developed the synthesis of imidazoles **5-167** via the Rh-catalyzed transannulation reaction⁴³² of *N*-sulfonyl-1,2,3-triazoles **5-165** with nitriles **5-166** (for related synthesis of pyrroles via transannulation reaction see Section 3.3.5).⁵⁸⁰ The reaction can be performed under both microwave and conventional heating conditions, possessing high functional group tolerance with respect to a triazole and nitrile component (Scheme 370).

Clapham and Janda reported the Rh(II)-catalyzed one-pot synthesis of imidazolones via the reaction of α -diazocarbonyl compounds **5-168** and ureas **5-169**.⁵⁸¹ Thus, an insertion of Rh-carbenoid into N-H bond of urea produces ketourea **5-171**. A subsequent cyclization under acidic conditions furnishes imidazole **5-170**. The reaction represents a general method for synthesis of imidazolones **5-170** bearing a variety of substituents and functional groups. Moreover, the reaction was adapted for solid-phase synthesis using insoluble polymer resins, connected to α -diazocarbonyl compounds **5-170** via a carboxylic linker (Scheme 371).⁵⁸²

In 2010, Xie described the Ti-catalyzed synthesis of imidazoles via the reaction of propargyl amines **5-172** with nitriles **5-173**. Thus, the reaction regioselectively produces 1,2,4-trisubstituted imidazoles **5-175** in the presence of titanacarborane monoamide catalyst **5-174**. Generally, aromatic nitriles react smoothly, whereas the reaction with aliphatic nitriles requires prolonged heating and produces the corresponding imidazoles in diminished yields (Scheme 372).⁵⁸³

Very recently, the same group applied the Ti-catalyst **5-174** for the synthesis of 2-aminoimidazoles **5-178** via amination of carbodiimides **5-177** with primary propargylamines **5-176**. Thus, 2-aminoimidazoles **5-178** were obtained in good to excellent yields when aromatic or aliphatic carbodiimides were used (Scheme 373).⁵⁸⁴

5.4.3. Synthesis of Imidazoles via Formal [2+2+1]-Cycloaddition Reactions—

Arndtsen developed a multicomponent synthesis of imidazoles via the Pd-catalyzed reaction of acyl chlorides **5-179** with two different imines (**5-180** and **5-181**). The reaction proceeds via formation of münchone **5-183**, followed by a subsequent [2+3] cycloaddition reaction with imine (for synthesis of pyrroles via formation of münchone see Scheme 290 and Scheme 317). Thus, reaction of more nucleophilic imine **5-181** with acyl chloride **5-179** in the presence of Pd(0)-catalyst and carbon monoxide produces münchone **5-183** (see Scheme 317 for details). A subsequent [2+3] cycloaddition reaction with less nucleophilic tosyl imine **5-180** furnishes imidazole **5-182** upon elimination of TsOH. The reaction tolerates a range of functional groups, affording imidazoles in good yields (Scheme 374). Recently, this efficient transformation was also used by the same group for the synthesis of imidazole-based oligomers.⁵⁸⁵

5.4.4. Synthesis of Imidazoles via Formal [2+1+1+1]-Cycloaddition Reactions

—The reaction of dicarbonyl compounds, aldehydes and ammonia (or amine) is widely used for synthesis of imidazoles.⁵⁸⁶ However a noncatalyzed transformations require harsh reaction conditions and often suffer from poor yields and low selectivity. Therefore, transition metal-catalysis was applied to this transformation in order to achieve more efficient and selective synthesis of imidazoles.⁵⁷¹

Thus, Wang et al. developed the Yb-catalyzed reaction of benzyl with aromatic aldehydes **5-184** and ammonium acetate to produce 2,4,5-trisubstituted imidazoles **5-185** in high yields. According to the proposed mechanism, benzyl and the aldehyde **5-184** form imines **5-186** and **5-187** respectively. A subsequent reaction of imine **5-184** with the carbonyl function of **5-186** produces intermediate **5-188**, which undergoes cyclization into iminium species **5-189**, producing imidazole **5-185** upon dehydration (Scheme 375).⁵⁸⁷

Sharma improved this protocol by using ZrCl₄ catalyst. The reaction of benzyl, aldehydes **5-190**, ammonia (or amine **5-191**) produces imidazoles **5-192** in excellent yields under mild conditions. Notably, tri- or tetrasubstituted imidazoles could be prepared via this method by using an appropriate amine **5-191** (Scheme 376).⁵⁸⁸ Later, Jadhav showed that phosphomolybdic acid is also capable catalyst for this transformation.⁵⁸⁹ Provot and Alami

described a DMSO-PdI₂-catalyzed oxidation of diphenylacetylene to dibenzyl, followed by a one-pot reaction with aldehyde and ammonium acetate to afford imidazole.⁵⁹⁰

5.5. Synthesis of Pyrazoles

5.5.1. Synthesis of Pyrazoles via Cycloisomerization Reactions and Related Processes—In 1997 Cacchi described the synthesis of pyrazoles via a one-pot arylation/cyclization/elimination reaction sequence. Hence, arylation of propargyl hydrazine **5-193** with aryl halides and enol triflates under Sonogashira conditions led to hydrazine **5-195**. A subsequent *one-pot* Pd(II)-catalyzed cyclization of the latter, followed by an elimination of TsH under basic conditions affords pyrazoles **815** in reasonable to good yields (Scheme 377).⁵⁹¹

Later, Knight described the synthesis of pyrazole *N*-oxides **5-197** via an Ag-catalyzed cycloisomerization of alkynyl nitrosamines **5-196**. The reaction proceeds at room temperature, producing pyrazole *N*-oxides **5-197** in quantitative yields (Scheme 378). A subsequent deoxygenation of **5-197** with phosphorus trichloride furnishes pyrazoles in high yields.⁵⁹²

An example of cycloisomerization of alkenylazirinecarbaldehyde imine **5-198** into the corresponding pyrazole **5-199** in the presence of Grubbs I catalyst was reported by Padwa et al. (Scheme 379).³²⁸

Shi described formation of pyrazolium organogold complexes **5-201** via cycloisomerization of 2-propargyl triazoles **5-200** in presence of stoichiometric amounts of Au-salt. Thus, a series of complexes **5-201** containing an acid stable Au-C bond were obtained in excellent yields (Scheme 380).⁵⁹³

Driver developed the synthesis of *N*-methoxy pyrazoles **5-203** via the Fe-catalyzed cyclization of unsaturated azide oximes **5-202** (Scheme 381). It was proposed that the reaction proceeds via an activation of the azide (**5-204**), followed by the cyclization and extrusion of N₂ (**5-205**) to form pyrazole **5-203** (Scheme 381).⁵⁹⁴

In 2011, Zora reported the Cu(I)-mediated cycloisomerization of alkynyl hydrazones **5-206** into pyrazoles **5-207** (Scheme 382). It was shown that albeit slower this reaction also proceeds in the presence of 10% of CuI.⁴⁵³ Liu and Xu also showed that this reaction can be efficiently catalyzed by the Au(I)-catalyst.⁵⁹⁵ Moreover, the same group developed the Au(I)-catalyzed fluorinative cycloisomerization of alkynyl hydrazones **5-208** into 4-fluoropyrazoles **5-209a** in the presence of selectfluor. The reaction leads to predominant formation of fluorinated pyrazoles **5-209a**, however formation of a significant amounts of nonfluorinated products **5-209b** was also observed (Scheme 382).⁵⁹⁵

5.5.2. Synthesis of Pyrazoles via Formal [3+2]-Cycloaddition Reactions—The 1,3-dipolar cycloaddition of diazo compounds with alkynes is a commonly used method for synthesis of pyrazoles.^{14b} Thus, in 1995, Kende described the Ag(I)-catalyzed cyclization of azides **5-210**, bearing tethered terminal alkyne group, into pyrazoles **5-211** in reasonable yields. It was shown that two methyl substituents at the α -position to the carbonyl group in diazocompound **5-210** are crucial for successful reaction (Scheme 383).⁵⁹⁶

Later, Ready developed intermolecular version of this transformation using Cu(I)-catalysis. Thus, the Cu-acetylide, generated from Li-acetylide **5-213** and stoichiometric amounts of Cu-salt, undergoes cycloaddition with diazoacetate **5-212** to afford pyrazole **5-214**. This method is efficient with a variety of acetylenes and diazoacetates, producing pyrazoles **5-214** in good yields under mild conditions (Scheme 384).⁵⁹⁷ Later, Liang described the Zn-

catalyzed cycloaddition of diazoacetates **5-215** with alkynes **5-216**, furnishing pyrazoles **5-217** in moderate to good yields (Scheme 384).⁵⁹⁸

In 2011, Frantz reported the synthesis of pyrazoles **5-220** via a one-pot tandem cross-coupling/electrocyclization of enol triflates **5-218** and diazoacetates **5-219**. The reaction proceeds via formation of a cross-coupled product **5-221**, followed by electrocyclization into pyrazole **5-220** (Scheme 385).⁵⁹⁹

Glorius reported the synthesis of fully substituted pyrazoles **5-223** via the Cu-mediated [3+2] cycloaddition of enamines **5-222** with excess amount of nitriles. The reaction proceeds in the presence of 1.5-6 equiv of Cu(II)-salt under air atmosphere, to give polysubstituted pyrazoles **5-223** in good to excellent yields. According to the proposed mechanism, enamine **5-222** attacks nitrile **5-224**, activated by a Cu(II), to form 1,3-bisimine **5-225**. A subsequent formation of the Cu(II)-chelate **5-226**, followed by a reductive elimination of Cu(0) furnishes pyrazole **5-223** (Scheme 386). It was also shown that the reaction can be performed in a one-pot fashion via the *in situ* formation of enamines **5-222** from the corresponding imines.⁶⁰⁰

Buchwald developed the synthesis of pyrazoles via the Cu-catalyzed domino amidation/hydroamination reaction sequence (for an analogous pyrrole synthesis, see Scheme 238). Thus, the Cu-catalyzed amidation of iodo enynes **5-227** with 1,2-bis(Boc)hydrazine, followed by a subsequent 5-*exo-dig* cyclization and deprotection affords diversely substituted pyrazoles **5-228** in good to excellent yields (Scheme 387).³⁹²

Cho and co-workers reported the Pd-catalyzed synthesis of 1-aryl-1*H*-pyrazoles **5-231** from β -bromovinyl aldehydes **5-229** and aryl hydrazines **5-230**. Thus, a variety of 1,2,3-trisubstituted pyrazoles **5-231** are available via this methodology in reasonable to good yields (Scheme 388).⁶⁰¹

Recently, Skrydstrup et al. described formation of pyrazoles **5-232** as a mixture of regioisomers via the Au-catalyzed amination of diphenyldiyne with phenylhydrazine (Scheme 389).²³⁰ Bertrand and co-workers employed the Au(I)-carbene complex for the reaction of symmetrical diynes **5-233** with hydrazine, producing pyrazoles **5-234** (Scheme 389).³⁸⁶

It is known that the the formation of pyrazoles via the reaction of certain hydrazines with 1,3-dicarbonyl compounds often proceeds well under conventional heating in the presence of protic acids. However hydrazines, bearing electron withdrawing groups, are less reactive in this transformation. Aiming to overcome this limitation, Curini and Rosati described the synthesis of pyrazoles **5-237** via reaction of 1,3-dicarbonyl compounds **5-235** with hydrazines **5-236** in the presence of a heterogeneous Zr-catalyst. Thus, the reaction proceeds well with different hydrazines containing electron withdrawing substituents, forming pyrazoles **5-237** in good yields under solvent-free conditions (Scheme 390). In the case of unsymmetrically substituted 1,3-dicarbonyl compounds, the mixtures of a regioisomeric pyrazoles are formed.⁶⁰²

Recently, Beveridge reported a one-pot Cu-catalyzed synthesis of polysubstituted pyrazoles via the reaction of 1,3-dicarbonyl compounds **5-238**, *tert*-Buthyl azodicarboxylate **5-239**, and arylboronic acids **5-240**. First, the Cu-catalyzed reaction of arylboronic acid **5-240** with **5-239** affords *bis*-Boc-hydrazine **5-242**, which undergoes deprotection in acidic media, followed by a cyclocondensation with 1,3-dicarbonyl compound **5-238** to yield pyrazole **5-243** (Scheme 391).⁶⁰³

Franchini showed that pyrazoles can be obtained via the Sc(III)-catalyzed cycloaddition of nitrile imines, generated from hydrazidoyl chlorides **5-243** and alkynes **5-244**. Generally, nitrile imines react with alkynes without catalyst, producing the corresponding pyrazole as a mixture of regioisomers. However, the Sc(III)-catalyzed transformation proceeded with higher yields and better regioselectivity, especially, when starting nitrile imine and alkyne, bearing functional groups, allowed for coordination to a metal. Thus, the reaction of hydrazidoyl chlorides **5-243** and alkynes **5-244** furnished pyrazoles in excellent yields with predominant formation of the 3,4-regioisomer **5-245a**, whereas noncatalyzed process affords **5-245b** as a main product, but in lower overall yield. It was proposed that Sc(III) chelates nitrile imine and alkyne to form intermediate **5-246a**, producing 3,4-disubstituted regioisomer **5-245a** upon cycloaddition. In the case of noncatalyzed transformation, the transition state **5-246b**, yielding 1,5-pyrazole **5-245b**, is favored. (Scheme 392).⁶⁰⁴

5.5.3. Synthesis of Pyrazoles via Formal [2+2+1]-Cycloaddition Reactions—An

example of [2+2+1] synthesis of pyrazoles was described by Mori and co-workers, who showed that pyrazole **5-247** can be obtained via the Pd-catalyzed multicomponent reaction of terminal alkyne, aryl iodide, and hydrazine, under the CO atmosphere (see also Scheme 351 and Scheme 358, for analogous synthesis of isoxazoles). The reaction represents an efficient method for preparation of 3,5-disubstituted pyrazoles, however it is limited to unsubstituted hydrazine or methyl hydrazine, whereas phenyl hydrazine is unreactive (Scheme 393).⁵⁵² Later, Stonehouse used Mo(CO)₆ as a source of carbon monoxide for this transformation. The reaction was used for parallel plate-based synthesis of pyrazoles **5-248**. Moreover, this reaction is more general with respect to the hydrazine component (Scheme 393).⁶⁰⁵

Jiang synthesised pyrazoles **5-252** via one-pot sequential reaction of aroyl chlorides **5-249**, aryl iodides **5-250**, and hydrazines **5-251**.⁶⁰⁶ At the first step, the Sonogashira reaction afforded an alkynyl ketone, which then underwent a cyclocondensation with hydrazine in *one-pot* fashion to afford pyrazoles in moderate to good yields. (Scheme 394) Müller and co-workers observed increased yields of pyrazoles **5-253** and widen scope of the transformation using microwave irradiation (Scheme 394).⁶⁰⁷ Recently, they also shown that glyoxylyl chloride (R¹ = COAr) can be also involved in this sequence to produce the corresponding 5-acyl pyrazoles.⁶⁰⁸

In 2011, Beller reported the synthesis of pyrazoles **5-255** from phenyl bromide, styrene, carbon monoxide, and hydrazines **5-254**. At the first step, the carbonylative Heck-type reaction formed α,β -unsaturated ketone **5-256**. A subsequent cyclocondensation reaction with hydrazine (**5-257**), followed by oxidation furnished pyrazole **5-255** (Scheme 395).⁶⁰⁹

Cao and Quian developed the synthesis of fully substituted pyrazoles **5-259** via the aerobic Yb(III)-catalyzed three-component reaction of aldehydes, phenyl hydrazine, and 1,3-dicarbonyl compounds **5-258**. According to the proposed mechanism, the reaction proceeds via cycloaddition of an activated hydrazide **5-260** and 1,3-dicarbonyl compound **5-261** to produce cyclic intermediate **5-262**. The latter undergoes dehydration (**5-263**), followed by an oxidation into the pyrazole **5-259** (Scheme 396).⁶¹⁰ In 2011, Mohammadpoor-Baltork and Khosropour reported this transformation in the presence of Zn(OTf)₂ catalyst.⁶¹¹

In 2011, Huang synthesized pyrazoles **5-265** via the Cu(I)-catalyzed reaction of aryl hydrazones **5-264** with dialkyl ethylenedicarboxylates. The reaction provides a variety of pyrazoles in good yields under mild conditions (Scheme 397).⁶¹²

Odom and co-workers reported an isocyanide-based one-pot Ti-catalyzed synthesis of pyrazoles. Thus, the Ti-catalyzed reaction of alkyne **5-266** with *t*-Bu-isocyanide and

cyclohexylamine affords 1,3-diimine **5-269**, which undergoes reaction with hydrazine **5-267** to afford pyrazole **5-268** in a one-pot fashion. The formed pyrazoles **5-268** are obtained regioselectively in reasonable yields. It is noteworthy that internal alkynes, including unsymmetrically substituted alkynes, also suitable reactants for this transformation. Thus, as an example, reaction of alkyne **5-270** with hydrazine affords disubstituted pyrazole **5-271** regioselectively. The latter was used for synthesis of the natural product with asomnine **5-272** (Scheme 398).

5.6. Synthesis of Oxadiazoles

A general method for 1,2,4-oxadiazole synthesis is based on the acylation of amidoximes **5-273** with suitably activated carboxylic acid derivative, followed by a cyclization of the intermediate **5-274** upon heating. In 1998, Young used Pd(0)-catalyst for generation of the intermediate type **5-274** from the corresponding amidoximes and aryl iodides. 1,2,4-Oxadiazoles **5-275** were obtained in reasonable yields using this method.⁶¹³ In 2002, Chen utilized diaryliodonium salts for the Pd-catalyzed synthesis of 1,2,4-oxadiazoles **5-276** (Scheme 399).⁶¹⁴

In 1997, Kraft synthesized oxadiazole **5-278** via the Pd-catalyzed reaction of an aryl iodide with tetrazole **5-277** in the presence of base and carbon monoxide (Scheme 400). The reaction proceeds via a Pd(0)-catalyzed carbonylative acylation of tetrazole **5-277** to produce N-acyl tetrazole **5-279**, which produces oxadiazole **2-278** upon the loss of dinitrogen (as described by Huisgen in 1960⁶¹⁵). Although, the yields of this transformation are quite low, the reaction was applied for the synthesis of oxadiazole-containing dendrimers.⁶¹⁶

A thermal cycloaddition of benzamideoxime and organic nitriles, producing 1,2,4-oxadiazoles, was described by Yarovenko and co-workers in 1986. This transformation, however, required a prolonged heating in a sealed tube.⁶¹⁷ In 2009, Augustine reported the Zn(II)/TsOH-catalyzed synthesis of 1,2,4-oxadiazoles **5-281** via the reaction of amidoximes **5-280** with nitriles. The reaction proceeds via initial formation of nitrile oximes **5-282**, followed by its Zn(II)-catalyzed cycloaddition reaction with a nitrile. A variety of alkyl- and aryl substituted oxadiazoles **5-281** can be prepared in high yields using this method (Scheme 401).⁶¹⁸

In 1999, Couturier reported the synthesis of 1,3,4-oxadiazoles **5-284** via the Pd(0)-catalyzed intramolecular condensation of *N,N'*-diacylhydrazines **5-283** upon heating in decalin (Scheme 402).⁶¹⁹

It was shown that the Cu(II)-catalyzed oxidative cyclization of hydrazides **5-285** produces 2,6-diaryl 1,3,4-oxadiazoles **5-286** in good to excellent yields. The reaction most likely proceeds via a C-H activation pathway (Scheme 403).⁶²⁰ This transformation was used before by Jiang in a highly selective turn-on fluorescent chemodosimeters for the Cu(II)-ion.⁶²¹

5.7. Synthesis of Triazoles

5.7.1. Synthesis of 1,2,3-Triazoles—Among methods for synthesis of 1,2,3-triazoles, the 1,3-dipolar cycloaddition of organic azides with alkynes is arguably the most widely useful approach.⁶²² The thermal reaction of organic azides and alkynes was developed by Huisgen in 1960s–1970s.⁶²³ Usually, the thermal reaction requires prolonged heating and results in mixtures of both 1,4 and 1,5-regioisomers **5-287a,b** (Figure 10). In 2002 Meldal⁶²⁴ and Sharpless⁶²⁵ independently disclosed dramatic effect of Cu(I)-catalyst on cycloaddition of azides with terminal alkynes. Thus, the Cu-catalyzed alkyne-azide

cycloaddition (CuAAC) proceeds at room temperature to afford 1,4-disubstituted triazole **5-287a** regioselectively in high yield. According to the simplified mechanism, the reaction operates via coordination of azide to the intermediately formed Cu(I)-acetylide **5-288** followed by the formation of a strained copper metalocycle **5-289** and a subsequent formation of the Cu-triazolyl complex **5-290**. At the last step, a protodemetalation yields 1,4-disubstituted triazole **5-287a**. The CuAAC reaction is exceptionally general and practical, as is working well with broad range of substrates. Moreover, it proceeds in most protic and aprotic solvents, including water.

Due to exceptional efficiency, CuAAC «click-reaction», has become broadly useful across the chemical disciplines. For example, CuAAC was applied in the synthesis of drugs and biologically active compounds,⁶²⁶ in polymer chemistry,⁶²⁷ in materials sciences,⁶²⁸ in supramolecular chemistry,⁶²⁹ in electrochemistry,⁶³⁰ and in many other fields. Importantly, CuAAC is extensively used for conjugation of peptides,⁶³¹ nucleotides,⁶³² nucleic acids,⁶³³ glycosides,⁶³⁴ carbohydrates,⁶³⁵ with other molecules. A comprehensive information about scope and mechanism of the CuAAC «click-reaction» can be found in excellent detailed reviews,^{14f,636} therefore, this reaction is not discussed here.

The CuAAC reaction of terminal alkynes and azides furnishes 1,4-disubstituted 1,2,3-triazoles exclusively. Notably, 1,5-disubstituted triazoles can also be prepared via the reaction of alkynes and azides under different conditions. Thus, Akimova⁶³⁷ and later Fokin⁶³⁸ showed that formation of 1,5-disubstituted triazoles could be achieved via a conventional cycloaddition of bromomagnesium acetylides with organic azides. On the other hand, 1,5-diaryl triazoles could be also prepared from the corresponding azides and alkynes in the presence of catalytic amounts of tetraalkylammonium hydroxide.⁶³⁹

In 2005, Fokin, Jia, and Sharpless reported the cycloaddition of azides **5-291** and terminal alkynes **5-292** in the presence of the Cp*Ru-catalyst producing 1,5-disubstituted triazoles **5-294**, complementary to the CuAAC, producing 1,4-triazoles. The Ru-catalyzed cycloaddition (RuAAC) exhibits good functional group compatibility, producing 1,5-disubstituted triazoles in good to excellent yield (Scheme 404).⁶⁴⁰ According to experimental and computational studies, the reaction proceeds via the coordination of alkyne and azide to the Ru-center to produce intermediate **5-294**. A regioselectivity of the reaction is determined by a nucleophilic attack of the C-atom of coordinated alkyne at the terminal electrophilic nitrogen of the coordinated azide. Both steric and electronic factors favor the nucleophilic attack pathway in the intermediate **5-294**, which leads to the observed experimentally 1,5-regioselectivity. In addition, it was found that internal alkynes **5-295** could also undergo the Ru-catalyzed cycloaddition reaction with azides producing triazoles **5-296**. In the case of unsymmetrically substituted alkynes, the substituent at the more electronegative and less sterically-demanding carbon of the alkyne ends up at the C4 position of the formed triazole (Scheme 404).⁶⁴¹

In 2009, Hein, Fokin, and Sharpless reported the Cu(I)-catalyzed cycloaddition of azides and iodoalkynes **5-297**, leading to formation of iodotriazoles **5-298**. It was proposed that, this reaction proceeds via a coordination of azide and alkyne to copper (**5-299**), followed by a cyclization into a vinylidene-like intermediate **5-300** and a reductive elimination into the triazole product. The reaction shows good functional group tolerance, providing valuable iodotriazoles **5-298** in good to excellent yields (Scheme 405).⁶⁴²

The Cu- and Ru-catalyzed cycloaddition reactions of alkynes and organic azides are extremely efficient for preparation of *N*-substituted-1,2,3-triazoles, however, synthesis of *NH*-triazoles via this approach requires an additional step of *N*-deprotection. On the other hand, *NH*-triazoles can be obtained via the thermal cycloaddition of activated alkynes and

hydrazoic acid, trimethylsilylazide, or sodium azide. However, conventional cycloaddition reactions require the use of activated alkyne, harsh reaction conditions, and harmful reagents. In order to overcome these limitations, transition metal-catalyzed reactions for synthesis of *NH*-triazoles were explored extensively.

Thus, in 2004, Yamamoto reported the Cu(I)-catalyzed cycloaddition of terminal alkynes and TMSN₃ to produce triazoles **5-301**. The reaction proceeds via the formation of Cu-acetylides followed by a cycloaddition reaction with the *in situ* formed hydrazoic acid. This protocol allows for preparation of diversely-substituted triazoles **5-301** in good to excellent yields (Scheme 406).⁶⁴³ Later, Yang reported efficient Cu(I)-mediated cycloaddition of terminal alkynes with sodium azide affording *NH*-triazoles **5-302** (Scheme 406).⁶⁴⁴ Subsequently, Kuan showed that cycloaddition of terminal alkyne with sodium azide could potentially be performed using catalytic amount of the Cu(I)-catalyst (Scheme 406).⁶⁴⁵

A number of the Pd-catalyzed reactions for the synthesis of triazoles were also described. Thus, Barluenga developed synthesis of *NH*-triazoles **5-305** via the Pd(0)-catalyzed reaction of vinyl bromides **5-304** with sodium azide. According to the proposed mechanism, the reaction proceeds via formation of the vinyl-palladium complex **5-306**, which undergoes a [3+2] cycloaddition reaction with azide ion to form the dihydrotriazolylpalladium intermediate **5-307**. A subsequent β -hydride elimination forms triazolide-anion **5-308**, affording triazole **5-305** upon protonation, and hydrido-palladium complex **5-309** (Scheme 407).⁶⁴⁶

Later, Kuang reported the Pd(0)-catalyzed formation of aryl *NH*-triazoles **5-311** via the reaction of *anti*-3-aryl-2,3-dibromopropanoic acids **5-310** with sodium azide (Scheme 408). According to the proposed pathway, the reaction proceeds via a debrominative decarboxylation, followed by the formation of a vinyl-palladium complex **5-312** (see also Scheme 407).⁶⁴⁷ The same group also reported the Cu(I)-catalyzed modification of this transformation, which features slightly higher yields of triazoles **5-312**, shorter reaction times, and the use of inexpensive CuI catalyst. In this case, the reaction most likely proceeds via debrominative decarboxylation and elimination of HBr with the formation of Cu-acetylide **5-313**, followed by its cycloaddition reaction with the azide-ion (Scheme 408).⁶⁴⁵

Chen developed a one-pot procedure for synthesis of 4,5-disubstituted *NH*-triazoles **5-314** via a Sonogashira/cycloaddition reaction sequence. The reaction starts with the formation of an alkynyl ketone, followed by its facile cycloaddition reaction with sodium azide. The described method works well with a wide range of alkynes and acyl chlorides furnishing *NH*-triazoles in excellent yields (Scheme 409).⁶⁴⁸

Yamamoto also developed an efficient three-component synthesis of 2-allyl-1,2,3-triazoles **5-316** via the Pd-catalyzed reaction of activated internal alkynes **5-315**, allyl carbonate, and TMSN₃. According to the proposed mechanism, the reaction is triggered by the formation of π -allylpalladium azide complex **5-317**, which undergoes a cycloaddition reaction with alkyne to form intermediate **5-318**, followed by a reductive elimination to produce the *N*-allyl triazole **5-316**. However, this reaction is efficient with activated internal alkynes only.

Later, the same group expanded the scope of this transformation to terminal alkynes **5-319** by employing the cooperative Pd/Cu-catalyst. The reaction works via the cycloaddition of the π -allylpalladium azide complex (of type **5-317** Scheme 410) with the copper acetylide to form triazolyl-copper intermediate **5-321**, giving triazole **5-320** upon protodemetalation. The reaction tolerates a variety of alkynes, furnishing triazoles **5-320** in good yields (Scheme 411).⁶⁴⁹ Analogously, trisubstituted triazoles **5-323** are available via the Pd/Cu-

catalyzed reaction of silyl alkynes **5-322**, TMS azide, and excess allyl carbonate (Scheme 411).⁶⁵⁰

5.7.2. Synthesis of 1,2,4-Triazoles—A number of 1,2,4-triazole syntheses using stoichiometric amount transition metal have been developed. Thus, cyclization of triazene derivatives into 1,2,4-triazoles was described by Buzykin, who used the H₂O₂/KOH oxidation system.⁶⁵¹ In 2000 Paulvannan reported improved protocol for synthesis of 1,2,4-triazoles **5-325** via the Ag(I)-mediated oxidative cyclization of triazene derivatives **5-324** (Scheme 412).⁶⁵²

Recently, Fehrentz reported the synthesis of 1,2,4-triazoles **5-328** from tioamides **5-326** and acyl hydrazines **5-327** in the presence of stoichiometric amounts of Hg(II)⁶⁵³ or Ag(I)⁶⁵⁴ salts (Scheme 413).

Staben developed the Pd-catalyzed four-component one-pot synthesis of fully substituted 1,2,4-triazoles **5-331** based on the Einhorn-Brunner reaction. Thus, carbonylative amination of aryl iodides with amidines **5-329** affords acyl amidine **5-331**, which undergoes nucleophilic substitution reaction with hydrazine **5-330** to form intermediate **5-332**. Cyclocondensation of the latter produces 1,2,4-triazole. This reaction offers a straightforward approach toward pharmaceutically relevant triazoles (Scheme 414).⁶⁵⁵

In 2009, El Kaim and Grimaud reported the three-component synthesis of 1,2,4-triazoles from acyl chlorides, isocyanides, and tetrazoles **5-333** based on Nef/Huisgen reaction sequence.⁶⁵⁶ First, the Nef reaction produces imidooyl chloride **5-335**, which undergoes a reaction with tetrazole under the Lewis acid activation to form intermediate **5-336**. A subsequent Zn(II)-catalyzed Huisgen rearrangement of **5-336** furnishes 1,2,4-triazole **5-334** upon loss of dinitrogen. The reaction produces the corresponding 1,2,4-triazoles **5-334** in reasonable to good yields (Scheme 415).

5.8. Synthesis of Tetrazoles

5.8.1. Cycloaddition of Nitriles and Azide Ion: Synthesis of 1H-Tetrazoles—The most convenient route to the 1H-tetrazoles is based on the [3+2]-cycloaddition between nitriles with the azide ion, which generally proceeds in the presence of Lewis or Brønsted acid. However, it often requires harsh reaction. Some of the methods imply the *in-situ* generating of highly toxic and explosive hydrazoic acid.⁶⁵⁷

In 2001, Sharpless developed the Zn(II)-mediated synthesis of 5-substituted tetrazoles **5-337** from nitriles and sodium azide in water. It was shown that 0.5 equiv of Zn(II)-salt is required in most cases for completion of the reaction. The reaction proceeds smoothly with a variety of nitriles, however sometimes high temperatures (150–170 °C in a sealed vessel) are required (Scheme 416). Computations indicated that the reaction proceeds via a coordination of the nitrile to Zn(II), which substantially lowers the barrier for nucleophilic attack of the azide.⁶⁵⁸ Sharpless also used this protocol for the Zn(II)-catalyzed synthesis of tetrazole analogues of α -amino acids **2-339** from the corresponding α -amino nitriles **5-338**. The reaction proceeds smoothly under mild conditions affording tetrazoles in excellent yields. In the case of chiral nitriles, the reaction usually proceeds without racemization of the chiral center (Scheme 416).⁶⁵⁹ Later, Fmoc-⁶⁶⁰ and Boc-protected⁶⁶¹ amino nitriles were involved in tetrazole synthesis via the Zn-mediated reaction of nitriles with sodium azide.

In 2006, Fang reported a one-pot synthesis of tetrazoles from aldehydes or alcohols via the *in-situ* formation of nitriles, followed by a microwave-assisted Zn(II)-mediated reaction with sodium azide. It was shown that microwave-assisted reaction is more efficient than the process operating under conventional heating conditions.⁶⁶² The Zn(II)-mediated reaction of

nitriles and azides was extensively used for synthesis of different types of tetrazoles. Thus, Bolm described the Zn-mediated synthesis of *NH*-Tetrazole Sulfoximines from the corresponding nitriles.⁶⁶³ Nasrollahzadeh reported the Zn-mediated synthesis of arylaminotetrazoles from arylcyanamides.⁶⁶⁴ The reaction of nitriles with sodium azide was also used for incorporation of a tetrazole moiety into various bioactive molecules.⁶⁶⁵

In 2008 Jin and Yamamoto developed the Cu(I)-catalyzed synthesis of tetrazoles **5-340** via the cycloaddition of nitriles with trimethylsilyl azide. Thus, tetrazoles **5-340** were formed in excellent yields in the case of aromatic nitriles, whereas aliphatic nitriles gave diminished yields (Scheme 417). Bolm et al. reported the Fe(II)-catalyzed (was used Fe(OAc)₂ with the purity of 95%, containing traces of copper impurities) cycloaddition of aromatic nitriles and trimethylsilyl azide producing *NH*-tetrazoles **5-341** (Scheme 417).⁶⁶⁶

Notably, heterogeneous catalysis is also an efficient tool for the synthesis of tetrazoles from nitriles and sodium azide. Thus, Kantam proposed the reactions of nitriles and sodium azide via the heterogeneous catalysis by a nanocrystalline ZnO,⁶⁶⁷ Zinc Hydroxyapatite,⁶⁶⁸ and Zn/Al hydrotalcite.⁶⁶⁹ Recently, Xu employed a mesoporous ZnS nanospheres for catalytic synthesis of tetrazoles from nitriles and sodium azide.⁶⁷⁰ Nasrollahzadeh used FeCl₃ supported on SiO₂ for heterogeneous synthesis of tetrazoles. In all cases, reaction performs on heating in DMF at 120–130°C forming the desired aryl- or benzyl substituted tetrazoles in high yields. In 2011 magnetically recoverable and reusable CuFe₂O₄ nanoparticles were used by Sreedhar for the reaction of aromatic nitriles with sodium azide.⁶⁷¹ Laali employed Cu–Zn alloy nanopowder for synthesis of tetrazoles from aromatic nitriles and sodium azide.⁶⁷² Reusable CoY Zeolite was used for synthesis of tetrazoles by Pitchumani.⁶⁷³

Very recently, Jiao and co-workers reported a new approach toward diarylsubstituted tetrazoles **5-343** via the Cu(I)-catalyzed reaction of alkenes **5-342** and TMSN₃. According to the proposed mechanism, the reaction proceeds via the formation of stabilized allyl cation **5-344**, followed by a reaction with azide-ion to produce allyl azide **5-345**. The latter could undergo oxidation into azido allylic cation **5-346**, followed by isomerization (**5-347**) and aryl migration to form nitrilium cation **5-348**. A subsequent cycloaddition reaction of **5-348** with azide-ion produces tetrazole **5-343** (Scheme 418). The reaction is efficient with a variety of aromatic substituents producing the corresponding tetrazoles in good yields. In addition, it was shown that the diarylmethanes **5-349**, posing electron-rich aromatics, are also capable substrate for synthesis of tetrazoles **5-350** (Scheme 418).⁶⁷⁴

5.8.2. Cycloaddition of Nitriles and Organic Azides: Synthesis of Disubstituted Tetrazoles—In 1962, Carpenter showed that nitriles, possessing electron-withdrawing group (such as CCl₃, R_F, and others) undergo thermal cycloaddition with aliphatic or aromatic azides at 130–150°C to afford 1,5-disubstituted tetrazoles.⁶⁷⁵ Later Klaubert used thermal cycloaddition of alkyl cyanoformates and benzyl azides to build tetrazole moiety in the synthesis of antiallergy agents.⁶⁷⁶ Sharpless showed that sulfonyl cyanides⁶⁷⁷ and acyl cyanides⁶⁷⁸ undergo cycloaddition with various azides upon heating at 80–120 °C. Ganem used 1 equiv of ZnBr₂ to promote cycloaddition of azides and enolizable pyruvonnitrile (which was unstable during prolonged heating under Sharpless conditions) for synthesis of various disubstituted tetrazoles.⁶⁷⁹ Sureshbabu used ZnBr₂-promoted reaction of nitriles and sodium azide to prepare 5-Substituted *S/Se*-linked Tetrazoles.⁶⁸⁰

Bearing in mind the development of milder and safer conditions for cycloaddition of nitriles and azides, Vilarrasa developed the Cu(I)-catalyzed synthesis of 1,5-disubstituted tetrazoles. It was found that the Cu(I)-catalyzed reaction of activated nitriles **5-351** and benzyl- or alkyl azides produces tetrazoles **5-352** under mild conditions at room temperature or using microwave irradiation at 80°C. The reaction proceeds regioselectively with the formation of

1,5-disubstituted tetrazoles **5-352**, however, in some cases, 1,4-disubstituted compounds are formed minor regioisomer (Scheme 419).⁶⁸¹

In conclusion, cycloaddition of azides and nitriles is an important method for synthesis of tetrazoles, however, it is limited by application of activated nitriles. Consequently, development of mild and general method for cycloaddition of unactivated nitriles with azides toward tetrazoles is still warranted.

5.8.3. Miscellaneous Tetrazole Syntheses—Yamamoto and co-workers developed the regioselective synthesis of 2-allylated-5-substituted tetrazoles **5-255** via a Pd-catalyzed reaction of allyl acetates **5-253**, activated nitriles, and TMS azide.⁶⁸² Later, allyl carbonates were used as the allylic component in this transformation. Thus, oxidative addition of the Pd(0) at allylic compound in presence of azide upon elimination of TMSOMe and CO₂ forms the π -allylpalladium azide complex **5-255**. A subsequent [3+2] cycloaddition reaction of **5-255** with an activated nitrile gives π -allylpalladium tetrazole intermediate **5-256**, which undergoes reductive elimination to form tetrazole **5-254** (Scheme 420).⁶⁸³

In 2007, Wanner observed a significant catalytic effect of Zn(II) in the Passerini-type synthesis of tetrazoles via reaction of protected aminoaldehydes with TMSN₃, originally described by Nixey and Hulme.⁶⁸⁴ Thus, the reaction of Boc-aminoaldehydes **5-257**, isocyanides, and TMS azide in the presence of Zn(II) affords tetrazoles **5-258** in moderate to good yields (Scheme 421).⁶⁸⁵

In 2000, Batey and co-workers developed a general synthesis of 5-aminotetrazoles **5-260** using the Hg(II)-mediated cycloaddition of thioureas **5-259** with sodium azide.⁶⁸⁶ Recently, Wang et al. used this transformation for synthesis of fused tetrazoles.⁶⁸⁷

6. Synthesis of Six-Membered Aromatic Heterocycles

6.1. Synthesis of Pyridines and Pyridones

Although not comprehensive, but the most general formal cycloaddition modes toward the pyridine core are depicted in Figure 11.

6.1.1. Synthesis of pyridines via cycloisomerization reactions—In 1976, Murahashi et al. reported the synthesis of 2-substituted pyridines **6-2** via the Pd-mediated cycloisomerization of dienone oximes **6-1** (Scheme 423).⁶⁸⁸

In 2001, Narasaka developed modification of this process featuring an amino-Heck reaction. Specifically, it was demonstrated that the conjugated 1,3-dienyl phenyl ketoxime derivative **6-3** undergoes the Pd(0)-catalyzed cyclization to produce 2-phenylpyridine **6-4** in 61% yield. According to the proposed mechanism, the reaction proceeds via the insertion of an active Pd(0) catalyst into the N–O bond of the ketoxime to produce intermediate **6-5**. A subsequent 6-*endo-trig* cyclization of the latter via an aminopalladation reaction of the terminal double bond, followed by a β -hydride elimination (amino-Heck reaction) produces pyridine **6-4** (Scheme 424). A range of dienyl ketoximes **6-3** could be generated *in situ* from alkoxy- or ester-containing precursors **6-6**. A subsequent cycloisomerization reaction affords 2,3,4,6-tetrasubstituted pyridines **6-7** in moderate to good yields (Scheme 424).^{351a}

Following the work by Narasaka, Zhu developed the Pd-catalyzed amino-Heck type cyclization of homoallyl *O*-phosphinyloximes **6-8** and their homologs **6-10** to produce upon oxidation the corresponding pyridines **6-9** and **6-11** in moderate yields (Scheme 425).⁶⁸⁹

In 2009, Zhang reported the Au(I)-catalyzed formation of pyridines **6-13** via the cycloisomerization of oxime derivatives **6-12** (Scheme 426).⁶⁹⁰ The authors showed that AgOTf additive alone can catalyze this process, albeit resulting in significantly lower yields. The authors proposed a mechanism for the formation of pyridine product **6-13** involving the Au(I)-catalyzed 6-*endo-dig* cyclization of **6-12** to produce 1-methoxypyridinium intermediate followed by its deprotonative demethoxylation via loss of formaldehyde.

In 2006, Movassaghi reported an elegant approach toward pyridine ring via the Ru-catalyzed cycloisomerization of 3-azadienynes. An array of *N*-vinyl trimethylsilylalkynyl ketimines **6-14** undergo the Ru-catalyzed cycloisomerization to produce 2,5,6-trisubstituted pyridines **6-15** in good to excellent yields. It was proposed that the reaction begins with the Ru-catalyzed alkyne–vinylidene isomerization featuring a 1,2-silyl shift to form a silyl-substituted Ru-vinylidene intermediate **6-16**. A subsequent protodesilylation of the latter (**6-17**) and cycloisomerization gives a Ru-carbene species **6-18**. Finally, a 1,2-hydride shift to the Ru-carbene center in **6-18** furnishes pyridine **6-15** (Scheme 427).⁶⁹¹

In 2008, Cacchi and Fabrizi reported the synthesis of pyridines **6-20** via the Cu-catalyzed cycloisomerization of *N*-propargyl- β -enaminones **6-19**. The proposed mechanism involves the coordination of the copper catalyst at the alkyne moiety (**6-21**), followed by an 6-*endo-dig* cyclization into the vinyl copper **6-22** species. A subsequent protodemetalation (**6-23**), followed by an oxidation step furnishes pyridine **6-20**. The reaction proceeds under mild conditions and affords pyridine products in good yields (Scheme 428).⁶⁹²

Wang developed the Cu(II)-promoted iodocyclization of *N*-propargylaminoquinones **6-24** for the synthesis of the corresponding chloro-containing pyridine derivatives **6-25**. The reaction proceeds via the formation of an organocopper(II) intermediate **6-26**, which undergoes a subsequent reductive elimination (**6-27**) and aromatization into fused pyridine **6-25** (Scheme 429).⁶⁹³

Recently, Nakamura disclosed an interesting Cu-catalyzed cascade cycloisomerization of *O*-propargyl oximes of α,β -unsaturated aldehydes **6-28** into polysubstituted pyridine *N*-oxides **6-29**. The reaction is triggered by a 5-*endo-dig* attack of the oxime nitrogen atom at the activated triple bond (**6-30**) to produce cyclic intermediate **6-31**. A subsequent heterolytic C–O bond cleavage (**6-32**), followed by an elimination of the copper catalyst, produces allenyl nitron species **6-33**. A 6π -3-azatriene electrocyclization of its conformer **6-34** provides pyridine *N*-oxide **6-29**. This reaction tolerates a variety of substituents at the unsaturated oxime group, as well as at the propargyl moiety, providing access to a range of multisubstituted pyridine *N*-oxides **6-29** in good yields (Scheme 430).⁶⁹⁴

Ring closing metathesis is a powerful method for construction of carbo- and heterocyclic compounds. Along with the syntheses of furans and pyrroles (see Chapter 2.1.5. and Chapter 3.1.7., respectively), this reaction was recently used for the preparation of pyridines. Thus, Donohoe reported an RCM-based approach toward pyridines **6-37** and **6-40**. Specifically, the RCM reaction of α,β -unsaturated amide **6-35** produced cyclic product **6-36**, which was easily converted into multisubstituted 2-pyridones **6-37** in the presence of DBU.⁶⁹⁵ On the other hand, 3-hydroxypyridines **6-40** can be obtained from the corresponding precursors **6-38** via a similar RCM/elimination reaction sequence (Scheme 431).^{695b} Very recently, Donohoe also incorporated a cross-metathesis^{220b} process into an elegant two-step synthesis of pyridines featuring initial formation of unsaturated 1,5-diketones, followed by their reaction with ammonia.⁶⁹⁶

6.1.2. Synthesis of Pyridines and Pyridones via Formal [4+2]-Cycloaddition Reactions—

In 1997, Padwa disclosed a formal [4+2]-cycloaddition approach for the

synthesis of pyridones featuring a Rh(II)-catalyzed reaction of diazoimide **6-41** with activated alkenes **6-42**. The reaction proceeds via the formation of mesoionic dipole **6-44**, cycloaddition reaction with alkene **6-42**, and a ring-opening step of cycloadduct **6-45** with the subsequent aromatization via elimination of PhSO₂H (Scheme 432).⁶⁹⁷

In 1998, Larock reported the synthesis of pyridines **6-47** using the Pd-catalyzed reaction of halovinyl imines **6-46** with internal alkynes.⁶⁹⁸ The proposed mechanism includes an oxidative addition of vinyl halide to an active Pd(0) catalyst, the migratory insertion of the vinyl-Pd into an acetylene to produce a second vinylogous vinyl-Pd intermediate **6-48**, a ring closure into a seven-membered ammonium-salt-containing palladacycle **6-49**, a reductive elimination (**6-50**), and the cleavage of *t*-Bu group to furnish pyridine **6-47** (Scheme 433). Regioselectivity of the reaction is controlled by the steric and the electronic properties of the substituents at alkyne molecule.^{698–699} Later, Frühauf described the synthesis of the pyridine ring via the Pd-catalyzed reaction of imines of 3-halo-2-alkenals, similar to **6-46**, with allenes.⁷⁰⁰

In 2000, Tkachev described a simple and practical synthesis of pyridines **6-53** via the Fe-catalyzed reaction of α,β -unsaturated oximes **6-51** with ethyl acetoacetate. This reaction proceeds via a Michael addition followed by the cyclization and the aromatization processes (Scheme 434).⁷⁰¹

Arcadi developed the Au- or Cu-catalyzed annulation reaction of polysubstituted aryl or alkyl ketones **6-54** with propargylamine for efficient synthesis of 2,3- disubstituted pyridines **6-55** (Scheme 435).⁷⁰² The reaction begins with the initial formation of enamine **6-56**, and followed by its 6-*endo-dig* cyclization (**6-57**), subsequent protodemetalation (**6-58**), and aromatization reactions.

In 2006, Müller and co-workers developed a three-component one-pot synthesis of pyridines **6-61** via the Sonogashira/[4+2]-cycloaddition/elimination reaction cascade. Accordingly, Sonogashira cross-coupling reaction between *N*-tosyl propargyl amines **6-59** and aryl halides, followed by isomerization forms 1-aza-1,3-diene **6-62**, which readily undergoes a [4+2]-cycloaddition reaction with *N,S*-ketene acetal **6-60** to give annulated tetrahydropyridine cycloadduct **6-63**. The following aromatization via a two-fold base-assisted elimination of *p*-tolylsulfonate and methyl mercaptane affords pyridine **6-61** (Scheme 436).⁷⁰³

In 2008, Lebeskind reported a two-step modular synthesis of polysubstituted pyridines **6-66**. Thus, the first step of this process utilizes an interesting Cu-catalyzed cross-coupling reaction between an *N*-perfluorobenzoyl derivative of α,β -unsaturated ketoxime **6-64** with vinyl boronic acid **6-65** to form a reactive azatriene intermediate **6-67**. The latter upon a 6π -electrocyclization, followed by an oxidation, affords pyridine **6-66** (Scheme 437). The method features relatively mild reaction conditions and exhibits good functional group compatibility.⁷⁰⁴

Saito and Hanzawa reported the Rh(I)-catalyzed intramolecular formal [4+2]-cycloaddition reaction of ω -alkynyl-substituted vinyl methyl ketoximes **6-68** toward bicyclic pyridine derivatives **6-69** (Scheme 438). This transformation provides fused pyridines in good to excellent yields under fairly mild reaction conditions. Although the actual mechanism was not investigated, it was suggested that the transformation occurs via a coordination of the cationic Rh(I) catalyst to the unsaturated system of the 1-aza-1,3-diene.⁷⁰⁵

Recently, a number of methodologies featuring various C–H activation processes have also been used for the synthesis of pyridines. For instance, Bergman, Ellmann et al. reported a

Rh-catalyzed one-pot synthesis of pyridines **6-73** from α,β -unsaturated *N*-benzyl imines **6-70** and alkynes **6-71**. It was proposed that this reaction proceeds via the imine-directed C–H insertion of the Rh(I) catalyst into the alkenyl C–H bond to produce the rhodacycle **6-74**. A subsequent hydorrhodation of an alkyne generates a vinyl-Rh intermediate **6-76**, which undergoes a reductive elimination to produce 1-azatriene **6-77**, which is a subject to a 6- π electrocyclization into dihydropyridine **6-72**. The latter is efficiently converted into the corresponding pyridine **6-73** in a one-pot fashion under debenzylolation conditions. This methodology allows for the preparation of highly substituted pyridines, possessing up to five substituents around the ring (Scheme 439).⁷⁰⁶

Along this line, Cheng and co-workers developed the Rh(I)-catalyzed reaction between a range of alkyl- or aryl-substituted α,β -unsaturated ketoximes **6-78** and alkynes **6-79** to provide an easy access to polysubstituted pyridines **6-80** (Scheme 440).⁷⁰⁷ The authors suggested a mechanism for this cascade transformation analogous to that proposed by Bergman and Ellmann (Scheme 439). In this case however, aromatization of the 6- π electrocyclization product, dihydropyridine intermediate **6-83**, occurred upon elimination of the water molecule. A similar Rh(III)-catalyzed transformation featuring milder reaction conditions was recently described by Chiba et al.⁷⁰⁸ The above-mentioned Rh-catalyzed protocols are limited to symmetrically substituted or terminal alkynes, whereas in the case of unsymmetrically substituted alkynes, a mixture of regioisomeric pyridines is formed. Rovis and co-workers found that the employment of different bulky cyclopentadienyl-containing ligands in the Rh(III)-catalyzed reaction can be used to enhance the selectivity of the reaction with unsymmetrically substituted alkynes.⁷⁰⁹

A similar transformation was employed for the synthesis of pyridones. Particularly, in 2010, Song and Li reported the Rh(III)-catalyzed reaction of acrylamides **6-84** with alkynes **6-85** for the preparation of pyridones **6-86** (Scheme 441). This reaction is quite efficient for the synthesis of a number of pyridone derivatives, however, the scope of the process is limited to symmetrically substituted alkynes **6-85**.⁷¹⁰ In the case of unsymmetrically substituted acetylenes, a mixture of regioisomers is formed. Rovis employed a bulky cyclopentadienyl ligand in order to improve selectivity of this transformation with unsymmetrically substituted alkynes **6-88**. Indeed, it was found that the corresponding pyridines **6-89** could be obtained in both good yields and regioselectivity (up to 19:1) using Cp^t-ligand (Scheme 441).⁷¹¹

Very recently, Ackermann reported an analogous Ru-catalyzed synthesis of pyridones **6-92**. The reaction tolerates a variety of alkyl- or aryl-substituted α,β -unsaturated amides **6-90** and alkynes **6-91**, providing good to excellent yields of products **6-92**. It was also shown that certain unsymmetrically substituted alkynes **6-91a** produce the corresponding pyridones **6-92a** in moderate yields as single regioisomers (Scheme 442).⁷¹²

Nitriles could also be used as formal dienophiles in the [4+2]-cycloaddition reactions. For instance, Barluenga and Aguilar reported the Au(I)-catalyzed intermolecular hetero-dehydro-Diels-Alder cycloaddition reaction of 1,3-dien-5-ynes **6-93** with unactivated nitriles **6-94** for the synthesis of 3-vinylpyridine derivatives **6-95**. The reaction works well with an array of alkyl and aryl nitriles affording the corresponding pyridine derivatives **6-95** in good yields. According to the proposed mechanism, the reaction of the methoxyalkyne moiety in **6-93** with the Au(I)-catalyst produces intermediate **6-96**, possessing a push-pull diene core. The latter undergoes a regioselective nucleophilic attack by the nitrile to form nitrilium species (**6-97**→**6-98**), which then could undergo cyclization into dihydropyridine **6-99**. A subsequent proton loss/protodemetalation sequence provides the final product **6-95** and regenerates the Au(I) catalyst. (Scheme 443)

Recently, Ogoshi reported a regioselective synthesis of pyridines **6-101** via the Ni-catalyzed dehydrogenative [4+2]-cycloaddition of 1,3-dienes **6-100** with nitriles. In one of the possible mechanistic scenarios, the reaction may proceed via an oxidative cyclization of a nitrile and a diene with the Ni(0)-catalyst to give an η^3 -allyl-iminonickel intermediate **6-102**, which undergoes isomerization into enamine tautomer **6-103**. A reductive elimination from the latter produces dihydropyridine **6-104**. A subsequent dehydrogenation leads to pyridine product **6-101** (Scheme 444). This methodology could also be successfully applied to reactions with di- and tricyano-containing compounds, thus, producing potentially useful polypyridine ligands.⁷¹³

In conclusion, employment of the formal [4+2]-cycloaddition processes is an efficient strategy for the synthesis of an array of pyridine derivatives. However, the lack of regioselectivity in these processes could be an important issue in several cases, especially when unsymmetrical alkynes are used as dienophiles. On the other hand, recent transition metal-catalyzed pyridine syntheses based on an alternative [4+2]-cycloaddition disconnection approach and exploiting nitriles as formal dienophiles allow alleviating this problem.

6.1.3. Synthesis of Pyridines via Formal [3+3]-Cycloaddition Reactions—The Bohlmann-Rahtz reaction of enamines with alkynyl ketones represents one of the first formal [3+3] pyridine syntheses.⁷¹⁴ However, the conventional protocol requires two steps, as well as high temperature to induce this cyclization reaction. In order to improve synthetic procedure, Bagley explored Lewis and Brønsted acid catalysts for this transformation. It was found that a catalytic modification of the Bohlmann-Rahtz reaction now occurs under milder conditions and exhibits a better functional group tolerance.⁷¹⁵ Specifically, Zn(II)- or Yb(III)-catalyzed reaction of enamines **6-105** with alkynyl ketone **6-106** produces the corresponding pyridines in good to excellent yields in a one-step fashion (Scheme 445).⁷¹⁶ Notably, the reaction could also be performed in a three-component mode when enamine **6-105** is formed *in situ* from a 1,3-dicarbonyl compound and ammonia (see, Scheme 451).

Konakahara developed the synthesis of tetrasubstituted pyridines **6-110** via an Yb(III)-catalyzed cycloaddition of *N*-silylenamines **6-108** and 1,3-diketone derivatives **6-109**. According to the proposed mechanism, the reaction operates via formation of activated α,β -unsaturated carbonyl compound **6-111**, which undergoes Michael addition of enamine to form intermediate **6-112**. A subsequent cyclization produces cyclic imine species **6-113**, which furnishes pyridine **6-110** upon elimination of silanol and oxidation step (Scheme 446).⁷¹⁷

In 2008, Wang reported the Fe(III)-mediated synthesis of pyridones **6-116** from α,β -unsaturated ketones **6-114** and malonamides **6-115** (Scheme 447). This transformation occurs via the Fe(III)-catalyzed Michael addition reaction followed by a cyclocondensation and oxidative aromatization steps.⁷¹⁸

Davies and co-workers developed an interesting one-pot synthesis of pyridines **6-119** via the Rh-catalyzed formal [3+3]-cycloaddition of 3,5-disubstituted isoxazoles **6-117** with vinyl-substituted α -diazocarbonyl compounds **6-118**. First, diazocompound is converted into a donor-acceptor-substituted Rh-carbene that undergoes an insertion into the O–N bond of isoxazole, presumably via an ylide mechanism, to produce the ring expansion product **6-120**. The latter undergoes a thermal [3,3]-rearrangement (**6-121**) followed by a tautomerization into the 1,4-dihydropyridine **6-122**. A subsequent one-pot oxidation of **6-122**, provides multisubstituted pyridine **6-119** (Scheme 448). A variety of 3-carbonyl-containing pyridines could be prepared using this methodology in good yields.⁷¹⁹

Chiba developed the Mn(III)-mediated synthesis of pyridines **6-125** from cyclopropanols **6-123** and vinyl azides **6-124**. The proposed reaction mechanism involves a one-electron oxidation of cyclopropanol with Mn(III) salt to form a radical species **6-126**. The latter undergoes radical addition to the vinyl azide affording upon loss of dinitrogen iminyl radical **6-127**. A subsequent 6-*exo-trig* radical cyclization of **6-127** produces alkoxy radical **6-128**. Reduction of the latter with Mn(II) followed by protonation provides tetrahydropyridine **6-129**, which undergoes elimination of water and aromatization to furnish pyridine **6-125**. An array of pyridines bearing different substituents and a range of functional groups could be obtained using this method (Scheme 449).⁷²⁰

6.1.4. Synthesis of Pyridines via Formal [3+2+1]-Cycloaddition Reactions—In 2002, Müller developed the Pd/Cu-catalyzed synthesis of pyridines from propargyl alcohols **6-130**, aryl bromides, enamines **6-131**, and ammonia in a formal one-pot [3+2+1] cycloaddition process. Initially, the Sonogashira–isomerization tandem reaction between the propargyl alcohol and an aryl bromide generates chalcone **6-133**, which undergoes Stork–enamine reaction with **6-131** followed by a reaction with amine to furnish pyridine **6-132** upon condensation/aromatization sequence (Scheme 450). Enamines derived from cyclic ketones or acetophenones are capable reactants for this reaction conditions.^{703,721}

Bagley reported Lewis- or Brønsted acid-catalyzed three-component synthesis of pyridines. Thus, the Zn(II)-catalyzed reaction of 1,3-dicarbonyl compounds **6-135** with alkynyl ketone **6-136** in the presence of ammonium acetate produces the corresponding pyridines **6-137** in good to excellent yields (Scheme 451). The reaction proceeds via formation of enamine followed by its Michael addition reaction to **6-136** and cyclization (for 2-CC reaction starting from enamine and alkynyl ketone, see Scheme 445).⁷¹⁵

In 2008, Kantewari et al. used $K_5CoW_{12}O_{40} \cdot 3H_2O$ as a catalyst for synthesis of 2,3,6-trisubstituted pyridine derivatives **6-140** from enaminones **6-139**, 1,3-dicarbonyl compounds **6-138**, and ammonia (Scheme 452).⁷²² This reaction can efficiently be performed under the microwave irradiation.⁷²³

Cheng developed the synthesis of pyridinium derivatives **6-142** using the Ni-catalyzed intermolecular multicomponent annulation reaction of 3-iodo-3-phenylacrolein (**6-141**) with *p*-toluidine and internal alkynes. According to the proposed mechanism, the oxidative addition of the Ni(0) with vinyl iodide in imine **6-143** produces Ni(II) azacycle **6-144**, which after a regioselective alkyne insertion (**6-145**), followed by a reductive elimination, furnishes pyridinium salt **6-142** (Scheme 453). The latter could be transformed into the corresponding *N*-substituted 2-pyridones upon an oxidation reaction.⁷²⁴

A multicomponent synthesis of pyridines **6-146** using the Zn(II)-catalyzed reaction of aldehydes, two molecules of malononitrile, and thiophenol was developed by Shridar. Initially, condensation of aldehyde with malononitrile produces a Knoevenagel adduct **6-147**, which after 1,2-addition of a sulfide **6-148** undergoes reaction with another molecule of malononitrile, activated by the Zn(II) catalyst, to produce an intermediate **6-148**. The latter undergoes cyclization into dihydropyridine **6-150**, followed by isomerization and aromatization to give pyridine **6-146** (Scheme 454).⁷²⁵ In comparison with a base-promoted modification of this transformation,⁷²⁶ the Zn(II)-catalyzed reaction⁷²⁵ features slightly higher yields and better functional group tolerance.

Very recently, Guan developed the Cu(I)-catalyzed synthesis of symmetrically-substituted pyridines **6-153** from aldehydes **6-151** and two molecules of oxime *O*-acetates **6-152**. A range of aromatic aldehydes and even paraformaldehyde could be involved in this transformation producing pyridines in good to excellent yields (Scheme 455). The authors

suggested that the reaction proceeds via formation of imine radical, formed by the cleavage of the N–O bond of the oxime.⁷²⁷

6.1.5. Synthesis of Pyridines via Formal [2+2+2]-Cycloaddition Reactions—

Transition metal-catalyzed [2+2+2]-cycloaddition^{14c,d,728} represents an efficient and atom economic method to construct a variety of 6-membered carbo- and heterocyclic molecules. Particularly, [2+2+2] cycloaddition reaction between two alkynes and a nitrile (or isocyanate) is a very powerful strategy for the construction of pyridine derivatives. Arguably, the [2+2+2] cycloaddition is currently the most convenient approach to pyridine core. Mechanistic details, scope, and applications of this [2+2+2] synthesis of pyridines have been recently reviewed by Henry,⁷²⁹ Varela and Saá,⁷³⁰ Heller and Hapke.^{14e} In addition, in 2011, Dominges and Pérez-Castellas reviewed recent advances in the [2+2+2] cycloaddition reactions, including synthesis of pyridines.⁷³¹ Therefore, only the most recent examples of the [2+2+2] formation of pyridines are discussed in this Chapter. Generally, two most challenging problems are associated with transition metal-catalyzed [2+2+2] pyridine synthesis: a) regioselectivity in entirely intermolecular reaction, and b) development of new catalytic systems to achieve milder reaction conditions, better functional group tolerance and even to make reaction enantioselective.

In spite of great efforts, totally intermolecular [2+2+2] cycloaddition reaction of two alkynes and a nitrile usually leads to a mixture of regioisomeric pyridines, as well as a products of alkyne cyclotrimerization.⁷³² As a general solution of this problem, Takahashi and co-workers developed regioselective synthesis of pyridines **6-155** via a sequential reaction of alkyne and nitrile with Cp_2ZrEt_2 to form azazirconocyclopentadiene **6-154**, followed by a transmetallation with Ni(II) and a reaction with the second alkyne (Scheme 456). The reaction can also be performed regioselectively using two different unsymmetrically-substituted alkynes. In addition, under these reaction conditions the use of isocyanates and carbodiimides instead of nitriles leads to pyridone and iminopyridine derivatives, respectively.⁷³³ Subsequently, Sato and Urabe developed a one-pot sequential pyridine synthesis via the formation of azatitanacyclopentadiene intermediates **6-156**, followed by a reaction with TsCN to produce 2-titanated pyridine **6-157**, which can be quenched with different electrophiles to produce pyridines **6-158** (Scheme 456).^{285,734} However, the major drawback of these powerful methodologies is the use of stoichiometric amounts of transition-metals.

Another approach to solve regioselectivity issue is based on the use of temporary/removable tether to preassemble two, or even three components. In 1977, Vollhardt developed the Co(I)-catalyzed synthesis of pyridines from tethered diynes and nitriles.⁷³⁵ Nowadays, Aubert and Malacria used Si-tethered alkynes for synthesis of benzenes via a [2+2+2] cycloaddition reaction.⁷³⁶ Tacking advantage of this concept, Groth developed the Co(I)-catalyzed synthesis of pyridines **6-160** from the precursor **6-159**, containing preassembled alkynes and nitrile under very mild conditions (in the case of terminal alkyne). Notably, pyridine product can be easily desilylated to form hydroxymethyl pyridine **6-161**, or oxidized into 4-hydroxypyridine derivative **6-162**. To demonstrate the usefulness of this methodology, the authors prepared polycyclic indolylpyridine **6-164** with ABCD ring annelation pattern typical for ergot alkaloids (Scheme 457).⁷³⁷

Later, Schreiber reported the synthesis of pyridines via the Co(I)-catalyzed cycloaddition of nitriles with Si-tethered alkynes **6-165**.⁷³⁸ The reaction tolerates a variety of aliphatic and aromatic nitriles, providing pyridine derivatives **6-166** in regioselective fashion. Notably, the Si-tether can be removed from the products **6-166** to produce pyridines **6-167** efficiently. In 2011, the temporary Si-tether approach was used by Deiters to construct the pyridine core in

synthesis of **6-172**, a structural fragment of thiopeptide antibiotic Cyclothiazomycin (Scheme 458).⁷³⁹

The recent developments in area of [2+2+2] synthesis of heterocycles were directed toward developments of new catalytic systems to achieve milder reaction conditions, higher regio- and enantioselectivity, and better functional group tolerance. Co, Rh, Ru, Ti, Ta, Zr/Mi, Zr/Cu, and Ni-complexes can catalyze the reaction.^{14e,730–731} Among them, the CpCo(CO)₂-catalyzed reaction has been widely used in recent years. However, the CpCo(CO)₂-catalyzed reactions usually require harsh reaction conditions (T>120 °C).⁷⁴⁰ It was shown that milder reaction conditions could be achieved with the help of ligands and additives.⁷³¹

Thus, in 2007, Cheng⁷⁴¹ and Okamoto⁷⁴² independently developed efficient system for Co(I)-catalyzed synthesis of pyridines based on Co(II)-salt, dppe, and Zn. Thus, reaction of diynes **6-173** with unactivated nitriles produces pyridines **6-174** under mild conditions in the presence of CoCl₂•6H₂O, dppe, and Zn, according to the Okamoto's protocol. In the case of unsymmetrically-substituted diynes, the regiochemistry is efficiently controlled by steric and electronic factors. As an example, diyne **6-173a** produces pyridine **6-174a** in excellent yield and good regioselectivity (Scheme 459).^{742–743} However, this reaction requires the employment of significant excess of a nitrile, therefore, is limited to simple nitriles only.

Later, Malacria, Aubert, and Gandon developed air stable CpCo(CO)(dimethylfumarate) complex⁷⁴⁴ to catalyze [2+2+2] synthesis of pyridine. Thus, the reaction of ynamides **6-175** with nitriles produces pyridines **6-176** under relatively mild reaction conditions. The regioselectivity is controlled by substitution pattern in an ynamide (Scheme 460).⁷⁴⁵

Notably, a number of the Ru-catalyzed [2+2+2] cycloaddition reactions for synthesis of pyridine were developed recently by Yamamoto and Itoh,^{410,746} and Saá group.⁷⁴⁷ In addition, Ni(0)-based catalytic systems for [2+2+2] synthesis of pyridines were recently reported. Thus, the application of Ni(0) metal and *N*-heterocyclic carbenes as ligands were extensively used by Louie and co-workers, who reported the Ni-catalyzed [2+2+2] cycloaddition of diynes with isocyanates⁷⁴⁸ and nitriles,⁷⁴⁹ to produce pyridone and pyridine derivatives respectively under mild conditions in a highly regioselective fashion. The Ni/NHC-catalyzed reaction of diynes with cyanamides *en route* to 2-aminopyridines was described recently by the same group.⁷⁵⁰ Likewise, Louie group recently reported a highly efficient Ni(0)/Xantphos-catalyzed [2+2+2] cycloaddition of diynes **6-177** with nitriles. This reaction produces pyridines **6-178** in excellent yields at room temperature. Both high yields and regioselectivity were obtained in the reaction with unsymmetrically-substituted alkyne **6-177a** (Scheme 461).⁷⁵¹

A number of efficient Rh-catalyzed [2+2+2] cycloaddition were also recently reported.⁷⁵² Thus, Tanaka developed the Rh(I)-catalyzed intermolecular [2+2+2] cycloaddition of electron-rich aryl ethynyl ethers with nitriles, providing single regioisomer of pyridine **6-179** under mild conditions. In addition, employment of isocyanates in this transformation furnishes pyridones **6-180** efficiently (Scheme 462).⁷⁵³

Fe-catalyzed [2+2+2] methods for synthesis of pyridines have been recently reported. Thus, in 2011, Wan et al. reported an efficient Fe-catalyzed synthesis of pyridines **6-182** via the partially intermolecular [2+2+2] cycloaddition of tethered diynes **6-181** with nitriles. The reaction features mild reaction conditions, high yields, and regioselectivity. For example, unsymmetrically substituted diyne **6-81a** undergoes regioselective reaction with nitriles to provide pyridine product **6-182a** (Scheme 463).⁷⁵⁴ Independently, Louie developed the Fe-catalyzed [2+2+2] cycloaddition of tethered alkynenitriles with alkynes, featuring the use of a hindered pyridyl ligand.⁷⁵⁵

Another important challenge in the [2+2+2] synthesis of pyridines is a development of asymmetric version of the reaction for synthesis of chiral pyridines. It is known that the [2+2+2] cycloaddition with chiral nitriles could be performed without racemization.⁷⁵⁶ Moreover, Gutnov, Heller, and co-workers developed the Co(I)-catalyzed asymmetric [2+2+2] cycloaddition reaction producing axially chiral 2-arylpyridines. As an example, pyridines **6-185** were prepared from diyne **6-183** and nitriles using chiral Co(I)-catalyst **6-184** in enantioselective manner (Scheme 464).⁷⁵⁷ The reaction could also be potentially used for synthesis of chiral phosphorous-bearing 2-arylpyridine ligands.⁷⁵⁸

Later, Tanaka developed the Rh-catalyzed asymmetric intermolecular [2+2+2] cycloaddition reaction. Thus, polyalkyne **6-186**, bearing two nitrile groups, was converted pyridine derivatives **6-187** in high yields and moderate level of enantioselectivity (Scheme 465).⁷⁵⁹

Notably, not only alkynes, but also alkenes could be used in [2+2+2] synthesis of pyridines. Thus, Barluenga, Valdés, and co-workers developed the synthesis of pyridines based on the Pd-catalyzed cross-coupling/cycloaddition reaction sequence. Thus, the reaction of two different vinyl bromides **6-188** and **6-189**, *N*-TMS imine **6-190** and morpholine produces triarylsubstituted pyridines **6-191** in a one-pot fashion. The reaction begins with the Pd-catalyzed cross-coupling reaction of the bromide **6-189** with morpholine to produce enamine **6-192**. On the other hand, cross-coupling of the bromide **6-188** with *N*-TMS imine forms imine **6-193**. A subsequent Yb(III)-catalyzed aza-Diels-Alder reaction between **6-192** and **6-193** produces tetrahydropyridine **6-194**, furnishing pyridine product upon elimination of morpholine and oxidation (Scheme 466). This reaction is allowed for regioselective multicomponent synthesis of pyridines bearing three different aryl substituents.⁷⁶⁰

In conclusion, the [2+2+2] cycloaddition approach is a very important tool for synthesis of pyridines. In spite of lack of general and selective fully intermolecular reaction, some ways to overcome this obstacle exist. Among them, the use of temporary or permanent tethers to preassemble two alkynes or alkyne and nitrile in one molecule. On the other hand, a number of new catalytic systems based on Co, Ni, Rh, Ru, and Fe were recently developed for efficient and regioselective synthesis of pyridines under mild reaction conditions.

6.1.6. Synthesis of Pyridines via Formal [2+2+1+1]-Cycloaddition Reactions—

In 2011, Wang showed that 2-amino-3-cyanopyridines **6-198** could be prepared via a formal [2+2+1+1]-cycloaddition reaction of aldehydes with ketones, malononitrile, and ammonium acetate. First, aldehyde undergoes a Knoevenagel condensation reaction with malononitrile to give alkylidenemalononitrile intermediate **6-196**. The enamine **6-195**, which is formed from ketone and ammonium acetate, undergoes the Stork-enamine reaction with **6-196**, followed by a 6-*exo-dig* cyclization to produce dihydropyridine **6-197**. A subsequent aromatization furnishes 2-amino-3-cyanopyridine **6-198** (Scheme 467). This simple protocol allows for the synthesis of an array of pyridines in high yields under mild reaction conditions. Moreover, the Yb(III) catalyst could be recovered after the reaction.⁷⁶¹

6.2. Synthesis of Six-membered Heterocycles Containing Two or More Nitrogen Atoms

6.2.1. Synthesis of Pyrimidines, Pyridazines, and Pyrazines—In 2003, Müller demonstrated the synthesis of pyrimidines **6-201** using a formal [3+2+1]-cycloaddition reaction between acyl chlorides **6-199**, terminal acetylenes, and amidinium or guanidinium salts **6-200**. At first, Sonogashira reaction between an alkyne and an acyl chloride affords alkynyl ketone **6-202**, which undergoes a base-induced condensation with amidinium salt to furnish a 2,6-disubstituted pyrimidine **6-201** (Scheme 468). In the case of a TMS-substituted acetylene, the reaction produces the corresponding 2,6-disubstituted products due to the loss of the TMS group.^{608,762} Shortly after, Müller and co-workers reported a similar four-

component synthesis of pyrimidines starting from aryl iodides, terminal alkynes, and amidines under a carbonylative Sonogashira cross-coupling reaction conditions. In this case, alkynyl ketone intermediates **6-202** are formed from an aryl iodide, alkynes, and carbon monoxide during the reaction course.⁷⁶³ Later, Stonehouse et al. used Mo(CO)₆ as the carbon monoxide source for the carbonylative synthesis of pyrimidines.⁶⁰⁵

In 2010, Hu reported the synthesis of benzopyrano[4,3-*d*]pyrimidines **6-205** via a formal [3+3]-reaction between iodochromones **6-203**, terminal alkyne, and amidines **6-204** under Sonogashira cross-coupling reaction conditions. Thus, initially formed alkynyl-substituted enone **6-206** undergoes a condensation with amidine to produce pyrimidine intermediate **6-207**. A subsequent 6-*exo-dig* cyclization of the phenol hydroxy group at the pendant alkyne furnishes fused pyrimidine product **6-205**. The reaction is performed in a three-component fashion (R³ = OMe), or as a sequential one-pot process (for R = Alk, Ar, SMe) affording fused pyrimidines in variable yields (Scheme 469).⁷⁶⁴

Zhan developed a formal [3+3] synthesis of pyrimidines **6-209** using the Cu(II)-catalyzed reaction of propargyl alcohols **6-208** with phenyl amidine. The reaction presumably proceeds through a generation of propargyl cation **6-210** that further reacts with amidine to produce intermediate **6-211**. The latter undergoes a Cu(II)-catalyzed 6-*endo-dig* cyclization to furnish dihydropyrimidine **6-212**, and a subsequent aromatization to yield pyrimidine **6-209**. In the case of TMS-acetylene, the corresponding 2,6-disubstituted pyrimidines are formed via a loss of TMS group during the reaction course (Scheme 470).⁷⁶⁵

In 2010, Fu et al. disclosed the synthesis of pyrimidones via the Cu-catalyzed formal [3+3]-cycloaddition reaction of 2-bromocycloalk-1-enecarboxylic acids **6-213** and amidinium hydrochlorides **6-214**. The reaction proceeds via the Cu-catalyzed vinyl bromide amination-cyclocondensation sequence affording a variety of fused pyrimidones **6-215** in good yields under mild reaction conditions (Scheme 471).⁷⁶⁶

Odom and co-workers reported the Ti-catalyzed one-pot multicomponent synthesis of pyrimidines employing a formal [3+2+1]-cycloaddition process. Accordingly, the reaction of an alkyne **6-216**, cyclohexylamine, and *t*-BuNC in the presence of the Ti-catalyst affords intermediate **6-219** (for a similar synthesis of pyrazoles, see Scheme 398). A subsequent one-pot reaction with amidines **6-217** produces pyrimidines **6-218** in moderate yields (Scheme 472).⁷⁶⁷

In 2005, Lejon and co-workers developed a formal [2+2+2] synthesis of pyrimidines **6-221** from ketones **6-220** and formamide in the presence of Pd(0) and iodobenzene. Interestingly, a thermal reaction of ketones and formamide (Leuckart reaction) produces formamide derivatives **6-223** accompanied by trace amounts of pyrimidine (*path b*, Scheme 473). In the presence of Pd-catalyst and aryl iodide, however, up to good yields of pyrimidine product were obtained. The authors suggest that the Pd(0)/PhI system serves as an oxidant for removal of ammonium formate from the reaction mixture, thus suppressing the side Leuckart reaction (*path b*). Instead, *N*-alkylideneformamide **6-222** undergoes a cyclocondensation reaction with formamide to produce pyrimidine **6-221** (*path a*). This reaction represents an interesting example when a transition metal catalyst is used to prevent a competing side process.⁷⁶⁸

Konakahara reported a formal [3+1+1+1] synthesis of 5,6-disubstituted pyrimidines **6-225** featuring a Zn(II)-catalyzed reaction of enamines **6-224** with triethyl orthoformate and ammonia. According to the proposed mechanism, the Zn(II)-catalyzed reaction of enamine with orthoester forms imine intermediate **6-226**, which undergoes an amination reaction with ammonia to produce isolable *N*-vinylamidine intermediate **6-227**. A subsequent Zn(II)-

catalyzed reaction of **6-227** with another molecule of orthoester leads to the corresponding pyrimidine **6-225** via cyclization of the intermediate **6-228**. In addition, enamines **6-224** could be generated *in situ* from the corresponding ketones and ammonia. In this case, the reaction represents a formal [2+1+1+1+1] synthesis of the pyrimidine core.⁷⁶⁹

An example of pyridazine synthesis via a transition-metal catalyzed reaction was described by Williams. It was shown that the Ru-catalyzed isomerization of alkyne-1,4-diols **6-229** followed by a one-pot reaction with hydrazine affords pyridazines **6-230** in reasonable yields (Scheme 475).^{187b} Donohoe et al. employed an RCM strategy for the synthesis of pyridazinones **6-232** from the corresponding *N*-allylacrylohydrazide precursors **6-231** via a one-pot procedure (Scheme 475).^{695b}

Milstein et al. reported the Ru-catalyzed synthesis of pyrazines **6-235** using a dehydrogenative dimerization of aminoalcohols **6-234**, which proceeds at high temperature in the presence of the Ru-pincer complex (Scheme 476).⁷⁷⁰

6.2.2. Synthesis of Triazines—A limited number of triazine syntheses using transition-metal catalyzed transformations were reported. In 1984, Vollhardt et al. developed a partially intramolecular synthesis of fused 1,2,4-triazines **6-236** employing the Fe-catalyzed cyclotrimerization of adiponitrile **6-235** with nitriles. The reaction tolerates alkyl, benzyl, and phenyl nitriles, providing triazines **6-236** in good yields (Scheme 477).⁷⁷¹

Moody and co-workers demonstrated synthesis of 1,2,4-triazines via a sequential two-step procedure. First, the Cu-catalyzed insertion of diazoacetate **6-238** into the N–H bond of acyl hydrazine **6-237** provides intermediate **6-240**, which undergoes a microwave-promoted cyclocondensation reaction with ammonia to produce triazine **6-239** (Scheme 478).⁷⁷²

In 2010, Vasu reported the Hg(II)-mediated one-pot synthesis of 1,3,5-triazines from isothiocyanates **6-242**, diethylamidines **6-241**, and carbamidines **6-243**. Initially, the reaction of isothiocyanate with amidine **6-241** produces the corresponding amidinothiourea **6-245**. A subsequent Hg(II)-mediated condensation of the latter with carbamidine **6-243** furnishes triazine **6-244** (Scheme 479).⁷⁷³

7. Conclusion

In conclusion, this review clearly indicates a growing application of transition-metal catalysis in synthesis of aromatic heterocycles. Evidently, transition metals can be used to increase efficacy of traditional non-catalyzed transformations used for synthesis of heterocycles, such as addition of nucleophilic heteroatoms to multiple bonds, reaction of nucleophilic heteroatoms with carbonyl compounds, cycloaddition reactions, Michael addition reaction, and other types of transformations. On the other hand, the use of transition metal-catalysts is allowed to use novel transformations, such as cross-coupling reactions, olefin metathesis, insertion of carbenoids into heteroatom-H bond, C-H activation, alkyne-allene rearrangement, a ring-opening of small cycles. A significant progress was achieved in the field of complex cascade cycloisomerization reactions, leading to regiodivergent formation of diversely substituted heteroaromatic molecules. It was also shown that small unreactive molecules such as CO, CO₂, or ethylene could be efficiently used for construction of heteroaromatic structures in transition metal-catalyzed processes. Despite the impressive progress of the transition metal-catalyzed chemistry of aromatic heterocycles made, there is still a high demand for general and efficient, as well as sustainable methodologies, for synthesis of these important molecules. This can be achieved by developing novel catalytic systems, which would allow for more efficient formation of carbon-carbon and carbon-heteroatom bonds.

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11. Abbreviations

%	mol %
acac	acetylacetonate
aq	aqueous
atm	atmosphere
BINOL	1,1'-bi-2-naphthol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
H₈-BINAP	(R)-(+)-2,2'-Bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl
Boc	<i>tert</i> -butylcarbonyl
BQ	1,4-benzoquinone
Bz	Benzoyl
cat	catalytic
Cbz	carboxybenzyl
Cp	cyclopentadienyl
cod	1,5-cyclooctadiene
coe	<i>cis</i> -cyclooctene
cymene	1-Methyl-4-(1-methylethyl)benzene
DABCO	1,4-diazabicyclo[2.2.2]octane
DavePhos	2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	N,N-Diisopropylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	<i>N,N</i> -dimethylformamide
Dmfu	dimthylfumarate
Dmpm	3,4-Dimethoxybenzyl
DMSO	Dimethyl sulfoxide
dnb	1,3-dinitrobenzyl

(S)-dosp	1-[[4-alkyl(C11-C13)phenyl]sulfonyl]-(2S)-pyrrolidinecarboxylate
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppm	1,1-bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
DTBMP	di- <i>t</i> -Buthyl-4-Methylpyridine
EDG	electron-donating group
equiv	equivalent
ex	excess
EWG	electron-withdrawing
hfacac	Hexafluoroacetylacetone
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
JohnPhos	(2-biphenyl)di- <i>tert</i> -butylphosphine
KAPA	potassium salt of 1,3-diaminopropane
LDA	lithium diisopropylamide
Mes	mesityl
MOM	methoxymethyl
MS	molecular sieves
MW	microwave
nbd	norbornadiene
NEM	<i>N</i> -ethylmorpholine
NIS	<i>N</i> -iodosuccinimide
NMM	<i>N</i> -methylmorpholine
NMP	<i>N</i> -Methyl-2-pyrrolidone
NP	nanoparticles
Nu	nucleophile
oct	octanoate
pfb	perfluorobutyryl
pfo	perfluorooctanoate
Ph	phenyl
Pht	phthalimide
Piv	pivalyl
phen	1,10-phenanthroline
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl
Py	pyridine
PIDA	phenyliodine(II) diacetate

Pic	picrate
rt	room temperature
S-Phos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
SegPhos	4,4'-Bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane)
TBAB	tetrabutylammonium bromide
TBHP	<i>tert</i> -Butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TCQ	tetrachloro-1,2-benzoquinone
TDMPP	1,1,3,3-tetrakis(3,5-dimethyl-1-pyrazole)propane
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	triethylsilane
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TM	transition metal
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	tolyl
Tp	trispyrazolylborate
Ts	tosyl
TTTA	Thenoyltrifluoroacetone
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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Biographies

Anton Gulevich was born in Chelyabinsk, Russia. He received a B.S. in Chemistry from M. V. Lomonosov Moscow State University in 2006. In 2009, he obtained his Ph.D. in Organic Chemistry working in the group of Prof. Nenajdenko at the M. V. Lomonosov Moscow State University. In 2010 he joined the group of Prof. Gevorgyan at the University of Illinois at Chicago as a postdoctoral fellow. His research interests include transition-metal catalyzed C-H activation reactions, multicomponent reactions, and heterocyclic chemistry.

Alexander S. Dudnik was born in Krasnodar, Russia. He received a B.S. in Chemistry from the M. V. Lomonosov Moscow State University in 2005. Between 2003 and 2005, he worked as a visiting researcher at the Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. He obtained his Ph.D. in Organic Chemistry from the University of Illinois at Chicago in 2011, where he was working under the direction of Prof. Gevorgyan. He is currently a postdoctoral associate in the laboratory of Prof. Gregory C. Fu at the California Institute of Technology.

Natalia Chernyak was born in Riga, Latvia. She obtained her B.S. degree in 2002 and M.S. degree in 2005 from the Riga Technical University. In 2000–2005 she was a visiting researcher at the Latvian Institute of Organic Chemistry. In 2011, she received a Ph.D. in Organic Chemistry from the University of Illinois at Chicago under the supervision of Prof. Gevorgyan. After postdoctoral studies in the laboratories of Prof. Stephen L. Buchwald at

the Massachusetts Institute of Technology, she joined Prof. Chad A. Mirkin group at Northwestern University as a postdoctoral associate.

Vladimir Gevorgyan has received his BSc from Kuban State University in 1978 and his PhD from the Latvian Institute of Organic Synthesis in 1984, where he was promoted to Group Leader in 1986. He spent two years (1992–1994) in Tohoku University in Sendai, Japan, the first as the JSPS Postdoctoral Fellow and the second as the Ciba-Geigy International Postdoctoral Fellow. In the following year (1995) he worked as a Visiting Professor at CNR, Bologna, Italy. He returned to Tohoku University in 1996 as an Assistant Professor and was promoted to Associate Professor in 1997. In 1999 he moved to The University of Illinois at Chicago as an Associate Professor. He was promoted to the rank of Full Professor in 2003. He is currently Distinguished Professor of Liberal Arts and Sciences. Prof. Gevorgyan's current research interests cover several main areas, including: development of highly regio- and chemoselective transition metal-catalyzed annulation reactions; development of cycloisomerization reactions for the synthesis of heterocyclic compounds; development of novel direct and directed C-H functionalization methods; and development of novel robust methodologies amenable for synthesis of small molecules libraries for wide biological screening.

Figure 1.

Figure 2.

Figure 3.

CHAPTER 3.1.1 Cycloisomerizations and Related processes

Figure 4.

G = substituent or functionality which will either be transformed during a heterocycle core assembly or will be lost (e.g. via elimination)

Figure 5.

Figure 6.

Chem Rev. Author manuscript; available in PMC 2014 May 08.

Figure 8.

Figure 9.

Huisgen 1960s-1070s *Meldal; Sharpless 2002* **Figure 10.**

Figure 11.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.

Scheme 11.

Scheme 12.

Scheme 13.

Scheme 14.

Scheme 15.

Scheme 16.

Scheme 17.

Scheme 18.

Scheme 19.

Scheme 20.

Scheme 21.

Scheme 22.

Scheme 23.

Scheme 24.

Scheme 25.

Scheme 26.

Scheme 27.

Scheme 28.

Scheme 29.

Utimoto 1983 *Huang 1987*

Scheme 30.

Scheme 31.

Scheme 32.

Scheme 33.

Scheme 34.

Scheme 35.

Scheme 36.

Scheme 37.

Scheme 38.

Scheme 39.

Scheme 40.

Scheme 42.

Scheme 43.

Scheme 44.

Scheme 45.

Scheme 46.

Scheme 47.

Scheme 48.

Scheme 49.

Scheme 50.

Scheme 51.

(*R*)- C_1 -tunephos

20 examples

61 - 99%

>20:1 dr

28 - 98% *ee* (*R*)-MeO-dtbm-biphepAr = 3,5-(*t*-Bu)₂-4-MeO-C₆H₂

20 examples

51 - 99%

>20:1 dr

4 - 99% *ee* R^1 = Me, -(CH₂)₃-, Ph R^2 = *n*-Bu, -(CH₂)₃-, Ph R^3 = *n*-Bu, 1-cyclohexenyl, 1-hexenyl, Ph, 4-Tol, 4-MeO-C₆H₄ R^4 = styryl, Ph, 4-Br-C₆H₄, 4-MeO-C₆H₄, 4-O₂N-C₆H₄, 1-furanyl R^5 = Ph, Bn

Scheme 52.

Scheme 53.

Scheme 54.

Scheme 55.

Scheme 56.

Scheme 57.

Scheme 58.

Scheme 59.

Arcadi et al. 1993 *Cacchi et al. 1997*

Scheme 60.

Scheme 61.

Scheme 62.

Scheme 63.

Scheme 64.

Scheme 65.

Scheme 66.

Scheme 67.

Scheme 68.

Scheme 69.

Scheme 70.

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Scheme 72.

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Scheme 82.

Scheme 83.

Scheme 84.

Scheme 85.

Scheme 86.

Scheme 87.

Scheme 88.

Scheme 89.

Scheme 90.

Scheme 91.

Scheme 92.

Scheme 93.

Scheme 94.

McDonald et al. 1993 *Nishibayashi et al. 2008*

Scheme 95.

Scheme 96.

Scheme 97.

Scheme 98.

Scheme 99.

Scheme 100.

Scheme 101.

Scheme 102.

Scheme 103.

Scheme 104.

Scheme 105.

$\text{R}^1 = \text{H, Alk}$ $\text{R}^2 = \text{H, Me, CH}_2\text{OBn, CH}_2\text{N(Ts)Bn}$

10 examples

45 - 91%

Tp = trispyrazolylborate

Scheme 106.

Scheme 107.

R¹, R² = H, Alk, Ph
R³ = Alk, Bn, Ar

Scheme 108.

Scheme 109.

Scheme 110.

Scheme 111.

Scheme 112.

Scheme 114.

Scheme 115.

Scheme 116.

Scheme 117.

Scheme 118.

Scheme 119.

Scheme 120.

Scheme 121.

Scheme 122.

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Scheme 125.

Scheme 126.

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Scheme 153.

Scheme 154.

Scheme 155.

Scheme 156.

Scheme 158.

Scheme 159.

Scheme 160.

Scheme 161.

Scheme 162.

Scheme 163.

Scheme 164.

Jiang 2010

Huang and Liang 2010

Scheme 165.

Scheme 166.

Scheme 167.

Scheme 168.

Scheme 169.

Scheme 170.

Scheme 171.

Scheme 172.

Scheme 173.

Scheme 174.

Scheme 175.

Scheme 176.

Scheme 177.

Scheme 178.

Scheme 179.

Scheme 180.

Scheme 181.

1% PdCl₂
2% KCl
DMA, 25-50 °C, 4-6 h

7 examples
53-88%

R = H, Alk
R¹ = H, Alk
R² = H, Alk, Ph
R³ = H, Me
R⁴ = Bu

1 - 10%
CuCl₂ or CuI•2KI
DMA, 100 °C, 2-26 h

10 examples
59-90%

R = H, *n*-Bu, Bn, *t*-Bu
R¹ = H, *n*-Bu
R² = H, Et
R³ = Alk, Ph
R⁴ = *n*-Bu, vinyl

Scheme 182.

Scheme 183.

Scheme 184.

Scheme 185.

Scheme 186.

Scheme 187.

Scheme 188.

Scheme 189.

Scheme 190.

Scheme 191.

Scheme 192.

Scheme 193.

Scheme 194.

Scheme 195.

Scheme 196.

Scheme 197.

Scheme 198.

Scheme 199.

Hiroya et al. 2006 *Dembinsky et. al. 2009*

Scheme 200.

Scheme 201.

Scheme 202.

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Scheme 219.

Scheme 220.

Scheme 221.

Scheme 222.

Scheme 223.

Scheme 224.

Scheme 225.

Scheme 226.

Scheme 227.

Scheme 228.

Scheme 229.

Scheme 230.

Bertrand et al. 2008

Skrydstrup et al. 2010

1% $(\text{PPh}_3)\text{AuNTf}_2$
DCE, 30 $^\circ\text{C}$, 0.5h

$\text{R}^1 = \text{N}(\text{Ts})\text{R}$
 $(\text{R} = \text{Bn, Ph, } n\text{-Pr})$
 $\text{R}^2 = \text{Ar}$
 8 examples
 90-96%

5% $2\text{-PhC}_6\text{H}_4\text{P}(i\text{-Bu})_2\cdot\text{Au}(\text{CH}_3\text{CN})\text{SbF}_6$
PhMe, 80 $^\circ\text{C}$, 24h

$\text{R}^1 = \text{Ar, } n\text{-Hex, N}(\text{Ts})i\text{-Pr}$
 $\text{R}^2 = \text{Ph, NHPh}$
 4 examples
 24-58%

Scheme 231.

Scheme 232.

Scheme 233.

Scheme 234.

Scheme 235.

Scheme 236.

Scheme 237.

Scheme 238.

Scheme 239.

Scheme 240.

Scheme 241.

Scheme 242.

Scheme 243.

Scheme 244.

Scheme 245.

Scheme 246.

Li 2007

$\text{RNH}_2 = \text{R}^5\text{CONH}_2$
 20-100% CuI,
 20% **L**, 2 equiv Cs_2CO_3
 dioxane, 100 °C
 3-24 h

3-269a
 12 examples
 32-95%

$\text{R}^1 = \text{H, Alk, Ph}$
 $\text{R}^2, \text{R}^3 = \text{Alk, Ph}$
 $\text{R}^4 = \text{H, R}^5 = \text{Alk, Ar, OEt}$

Xi 2010

$\text{R} = \text{Aryl}$
 10% CuI, 20% DMEDA
 3 equiv NaOt-Bu,
 toluene, 140 °C, 48-60 h

3-269b
 18 examples
 32-95%

$\text{R}^1 = \text{H, Alk, Ph}$
 $\text{R}^2, \text{R}^3 = \text{H, Alk, Ph}$
 $\text{R}^4 = \text{H, Alk, Ph}$
 $\text{R}^5 = \text{Ar, 2-Py}$

Scheme 247.

Scheme 248.

Scheme 249.

Scheme 250.

Scheme 251.

Scheme 252.

Scheme 253.

Scheme 254.

Scheme 255.

Scheme 256.

Scheme 257.

Scheme 258.

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Scheme 332.

Scheme 333.

Cacchi et al. 2001 *Saito and Hanzawa 2010*

Scheme 334.

Scheme 335.

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Scheme 343.

Scheme 344.

Scheme 345.

Scheme 346.

Scheme 347.

Scheme 348.

$R^1 = \text{Alk, Ar, HetAr, Alkenyl, OMe}$

$R^2 = \text{Alk, Ar, vinyl, alkynyl, allenyl}$

30 examples

38-98%

$R^4 = \text{Me, Tol, 4-NO}_2\text{C}_6\text{H}_4$

$R^5 = \text{Alk, Ar, allenyl, propargyl}$

Scheme 349.

Scheme 350.

Scheme 351.

Scheme 352.

Scheme 353.

Scheme 354.

Scheme 355.

Scheme 356.

Scheme 357.

Scheme 358.

Yadav 2008 *Moody 2010*

Scheme 359.

Scheme 360.

Scheme 361.

Scheme 362.

Scheme 363.

Scheme 364.

Scheme 365.

Scheme 366.

Scheme 367.

Scheme 368.

Yamamoto 2006 *Roy 2007*

Scheme 369.

Scheme 370.

Scheme 371.

30 examples
20-92%

Scheme 372.

Scheme 373.

Scheme 374.

Scheme 375.

Scheme 376.

Scheme 377.

Scheme 378.

Scheme 379.

Scheme 380.

Scheme 381.

Zora et al. 2011 *Liu, Xu et al. 2011*

Scheme 382.

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Scheme 390.

Scheme 391.

Scheme 392.

Mori 2005 *Stonehouse 2008*

Scheme 393.

Scheme 394.

Scheme 395.

Scheme 396.

Scheme 397.

Scheme 398.

Young 1998

Chen 2002

Scheme 399.

Scheme 400.

Scheme 401.

Scheme 402.

Scheme 403.

Scheme 404.

Scheme 405.

Yamamoto 2004 *Yang 2008* *Kuang 2010*

Scheme 406.

Scheme 407.

Scheme 408.

Scheme 409.

Scheme 410.

Scheme 411.

Scheme 412.

Scheme 413.

Scheme 414.

Scheme 415.

Scheme 416.

Yamamoto 2008 *Bolm 2009*

Scheme 417.

Scheme 418.

Scheme 419.

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Scheme 431.

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Scheme 435.

Scheme 436.

Scheme 437.

Scheme 438.

Scheme 439.

Scheme 440.

Song and Li 2010 *Rovis 2011* R¹ = AlkR² = H, Me, Ar, NHAcR³ = Ar, HetArR⁴/R⁵ = Alk/Ph, CO₂Me/Ph, Et/alkenyl, *i*-Pr/Me, Ph/SiEt₃regioselectivity (R⁴ vs R⁵): 2.7/1 to 19/1**Scheme 441.**

Scheme 442.

Scheme 443.

Scheme 444.

Scheme 445.

Scheme 446.

Scheme 447.

Scheme 448.

Scheme 449.

Scheme 450.

Scheme 451.

Scheme 452.

Scheme 455.

Takahashi et al. 2000 *Urabe and Sato 2002*

Scheme 456.

Scheme 457.

Scheme 458.

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Scheme 461.

Scheme 462.

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Scheme 468.

Scheme 469.

Scheme 470.

Scheme 471.

Scheme 472.

Scheme 473.

Scheme 474.

Williams et al. *Donohoe et al. 2009*

Scheme 475.

Scheme 476.

Scheme 477.

Scheme 478.

Scheme 479.