# Multi-component syntheses of heterocycles by transition-metal catalysis†

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For a long time multi-component syntheses of heterocycles have undeniably been a domain of classical carbonyl condensation chemistry. However, the advent of transition-metal catalysis not only has fertilized strategies in heterocyclic synthesis by uni- and bimolecular transformations but the past decade has also witnessed a rapid development of transition-metal catalysis in new multi-component reactions (MCR). Expectedly, palladium catalyzed processes have received a dominant position, yet, other transition-metal complexes are catching up implying organometallic elementary steps that reach even further than cross-coupling and carbometallation. Besides domino MCRs that are purely based upon organometallic catalysis the sequential and consecutive combination with condensation, addition and cycloaddition steps opens a vast playground for the invention of new sequences in heterocyclic synthesis. This *tutorial review* outlines the underlying reaction based principles of transition-metal catalysis in multi-component syntheses of heterocycles, summarizes recent developments of palladium catalyzed MCR, and highlights the more recent contributions to MCR based heterocyclic synthesis by virtue of rhodium, ruthenium, and copper catalysis.

## 1 Introduction

Heterocycles are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. As a consequence, the ongoing interest for developing new versatile and efficient syntheses of heterocycles has always been a thread in the synthetic community. In the past decade the productive concepts of multi-component processes, domino reactions and sequential transformations, where complex and highly diverse structures are created in a one-pot fashion, have considerably stimulated both academia and industry.[1,2] As diversity oriented syntheses,[3] particularly multi-component reactions (MCR)[1,4] are masterpieces of synthetic efficiency and reaction design. Therefore, mastering unusual combinations and sequences of elementary organic reactions under similar

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conditions is the major conceptual challenge in engineering novel types of MCR. Most advantageously and practically, MCR can often be extended into combinatorial[5] and solid phase syntheses promising manifold opportunities for developing novel lead structures of active agents, catalysts and even novel molecule based materials. Inevitably, many classical heterocyclic syntheses are MCR that are based upon carbonyl group condensations. Hence, medicinal chemistry is largely founded on these easily accessible heterocyclic frameworks.

However, the advent of transition-metal catalyzed reactions as a modern and efficient tool in organic synthesis has not only exerted an important impact on the syntheses of well-established classes of heterocycles,[6] but by virtue of organometallic elementary reactions where reactive functionalities are generated *en route*,[7] also the formation of complex new heterocyclic scaffolds can be literally achieved in a programmed fashion.

Despite numerous elegant contributions in heterocyclic synthesis based upon transition-metal catalyzed key steps[6,7] this tutorial review will only focus on multi-component processes involving at least three components that are performed in a domino, sequential or consecutive fashion, yet, always as one-pot reactions. Intermediate workup or isolation of stable intermediates as well as the removal of undesired byproducts or catalysts shall be excluded as it interferes with the general idea of one-pot methodology. This means that purely transition-metal catalyzed domino-MCR will be treated as well as sequences where transition-metal catalysis and condensations, additions or cycloadditions are performed within the same reaction vessel. Most essentially, only transition-metal processes as well as their combinations with organic elementary reactions leading to the de novo formation of the heterocyclic core shall be covered.

Referring to the catalytically active metals in MCR synthesis of heterocycles it is no surprise that palladium catalysis adopts a key role, which has already been highlighted two and three years ago.[6,7] Therefore, only recent contributions in Pd catalysis in MCR synthesis of heterocycles will be discussed in the first part. Nevertheless, other catalytically active transition-metal complexes are catching up and quite astounding sequences have been published in the past years. Here, showing snapshots of a rapidly developing domain, the second part is devoted to elegant rhodium, ruthenium and copper catalysis in MCR synthesis of heterocycles.

## 2 Palladium catalysis in multi-component syntheses of heterocycles

Major reasons for the enormous success of Pd catalysis in complex molecules' synthesis are the mild reaction conditions, the excellent compatibility with many polar functional groups and the high degree of chemo-, regio- and even stereoselectivity.[8] As a logical consequence, MCRs taking advantage of Pd catalysis as a key step are predominantly founded on evergreens among organo-Pd elementary steps and Pd-catalyzed reactions. These are carbopalladation of allenes, alkynes or carbon monoxide, Heck type reactions, Sonogashira couplings and miscellaneous processes.

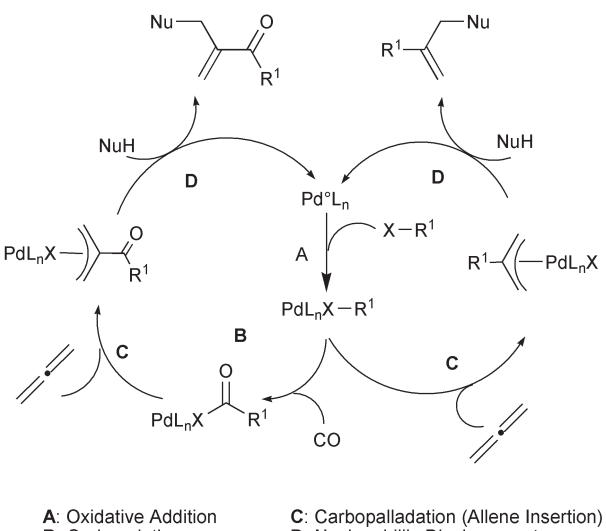
### 2.1 Insertion of allenes, alkynes, or carbon monoxide as a key step

Insertions of unsaturated functionalities are the most widespread organometallic elementary steps in Pd-catalyzed sequential, consecutive and domino processes.[9] In particular, the regioselective carbopalladation of allenes at the central carbon atom with aryl, heteroaryl, and vinyl halides opens a general entry to palladium allyl intermediates which, in turn, can be trapped with various nucleophiles at the allyl terminus giving rise to styryl derivatives as allylation products. Since carbon monoxide inserts even faster into Pd–C bonds the concurrent presence of carbon monoxide and allene first furnishes an aroyl–Pd intermediate that subsequently inserts allene, and finally concludes with the formation of α,β-unsaturated ketones (Scheme 1). In the past years Grigg and coworkers have significantly contributed to multi-component heterocycle synthesis based upon "cascade molecular queuing processes"[10] of allenes and/or carbon monoxide as reactive substrates. Both inter- and intramolecular variations endow a rich entry to heterocyclic chemistry.

This concept was successfully applied to the synthesis of annelated dihydrofurans **3** and **4** upon reacting an unsaturated halide, allene and heterocyclic enols **1** or **2** in the presence of a Pd(0) catalyst and base, followed by addition of trifluoroacetic acid to conclude the sequence by cyclization of the allylation product (Scheme 2).[11]

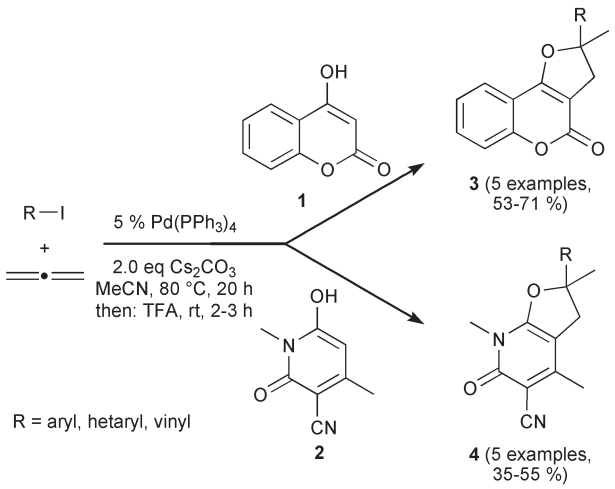
Mechanistically, the nucleophilic displacement at the allyl–Pd species can either occur by C- or O-allylation with a subsequent [3,3]-sigmatropic rearrangement.[12] The concluding acid catalyzed cyclization is very sensitive to the electronic nature of the aryl substituent. Expectedly, electron withdrawing groups hamper the cyclization by destabilizing the carbocation intermediate.

When aromatic *ortho*-halo aldehydes are chosen as aryl substrates, after allene insertion nitrogen nucleophiles **5**, such as amino acid esters, hydrazines or hydroxylamine, act as dinucleophilic substrates that undergo allylic substitution and condensation with aldehyde functionality to furnish




**Scheme 1**



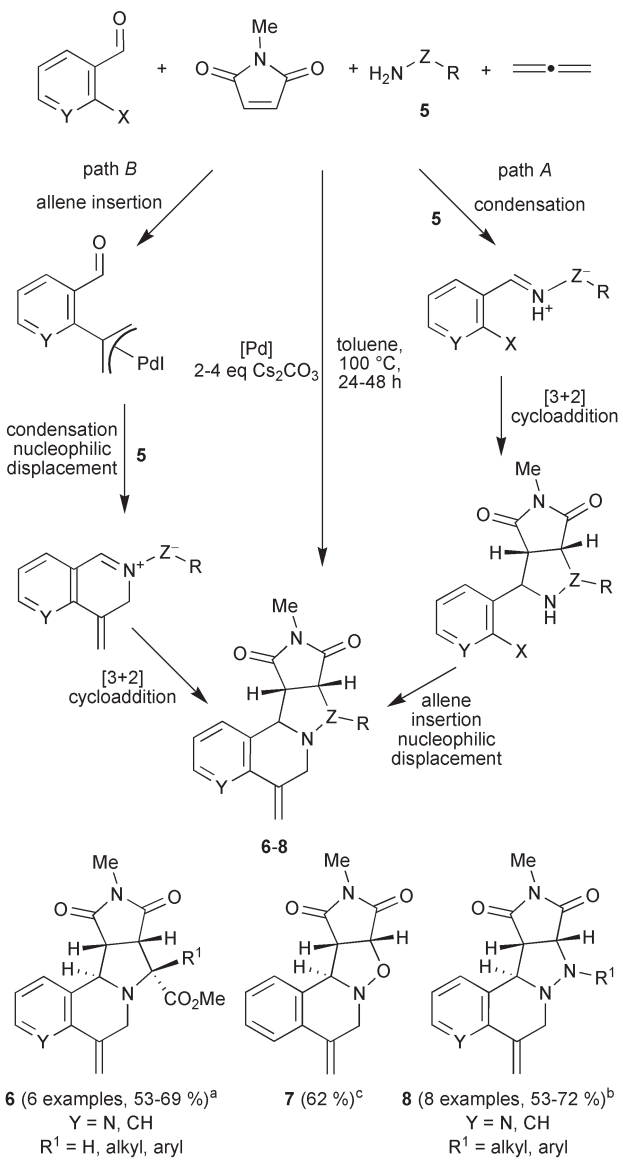

**Scheme 2**

1,3-dipoles. The dipolarophile *N*-methyl maleimide reacts in a [3 + 2]-cycloaddition to conclude the one-pot four-component reaction of annelated isoquinoline derivatives **6–8** (Scheme 3).[13] For this novel cascade both paths A or B represent plausible mechanistic rationales that are in agreement with the product analyses.

Particularly interesting as trapping nucleophiles are azides, which upon nucleophilic displacement give rise to the formation of propargyl type 1,3-dipoles. As a consequence, annelated triazoles can be easily obtained. Therefore, the sequence of insertion of allenes **9**, allylic substitution and intramolecular 1,3-dipolar cycloaddition furnishes triazole derivatives **10** in a one-pot fashion (Scheme 4).[14] Releasing excessive allene ($R^2$ = H) and extended heating leads to the extrusion of nitrogen followed by an isomerization–aromatization to give isoquinolines **11** in good yields.

The incorporation of the $C^1$ synthon carbon monoxide in carbopalladation processes gives a competitive edge. In a three component reaction Grigg and co-workers reported a sequence of *ortho*-iodo cinnamic derivatives, primary amines and carbon monoxide under palladium catalysis furnishing 3-substituted isoindolinones **12** (Scheme 5). Two mechanistic pathways are plausible according to the product analysis. In path A, first a Michael addition occurs, followed by oxidative addition and CO insertion yielding an acylpalladium intermediate. The intramolecular nucleophilic attack at the adjacent amine gives the isoindolinone after reductive elimination of the catalyst. In path B, first the acylpalladium intermediate is formed and trapped by an intermolecular attack of the amine. The newly formed amide could undergo a base catalyzed intramolecular addition to the tethered Michael system (Scheme 5).[15]

A versatile catalytic strategy towards münchnones, substrates for the synthesis of biologically active molecules, was introduced by the group of Arndtsen. Starting from imines and acid chlorides oxidative addition furnishes a highly active palladium intermediate that subsequently incorporates carbon monoxide and gives after HCl elimination the münchnone skeleton **13** (Scheme 6).[16] Employing a palladacyclic dimer and $Bu_4NBr$ as a halide source for the stabilization of

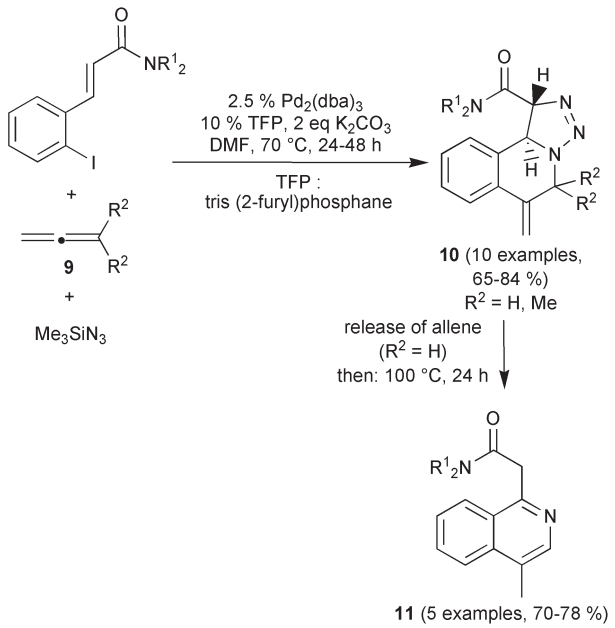



**Scheme 3**

intermediates and the non-nucleophilic base DIPEA and relatively high pressures of CO turned out to be most favorable. However, the addition of methanol to the reaction mixture gives α-amino acid derivatives **14** in nearly quantitative yields based upon the isolated münchnones.

As reactive 1,3-dipoles münchnones are known to readily undergo cycloaddition reactions with symmetrical und unsymmetrical substituted alkynes. In a 4-CR reaction Arndtsen and co-workers have incorporated imines, acid chlorides, carbon monoxide, and acetylene in a diversity-oriented synthesis of pyrroles **15** (Scheme 7).[17]

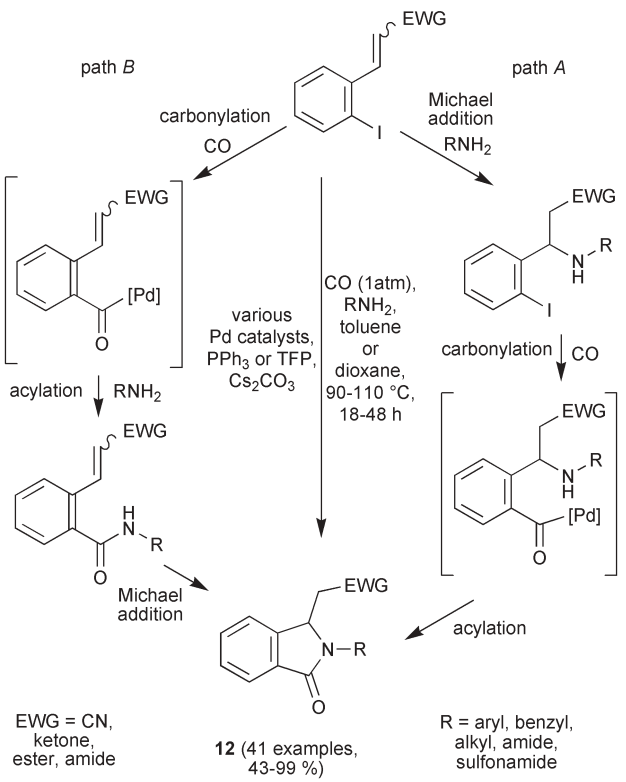
Here, sterically encumbered phosphanes like P(*o*-tolyl)$_3$ provoke a 7 times accelerated oxidative addition of the imine and acid chloride and CO insertion leading to the 1,3-dipole



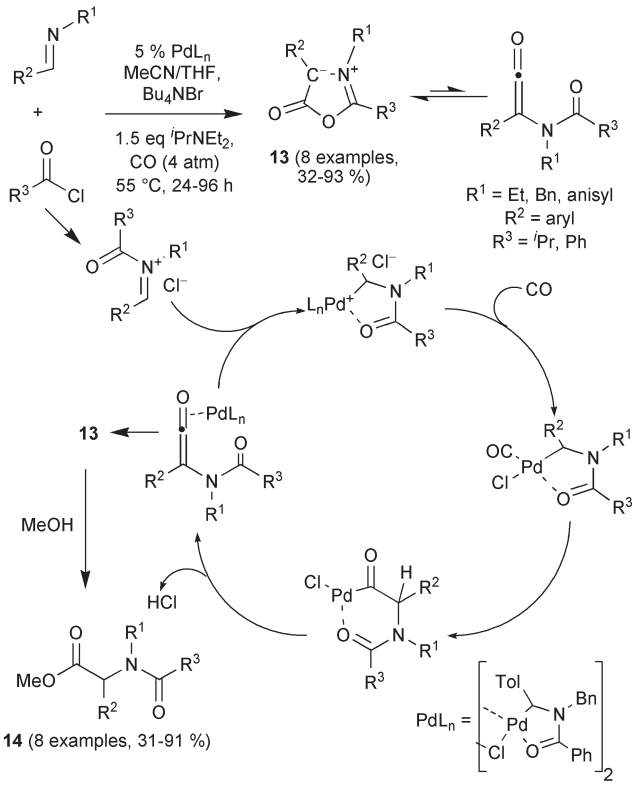

**Scheme 4**

**13**. In the presence of reactive dipolarophiles the preformation of **13** is required to prevent side reactions with the iminium ion.

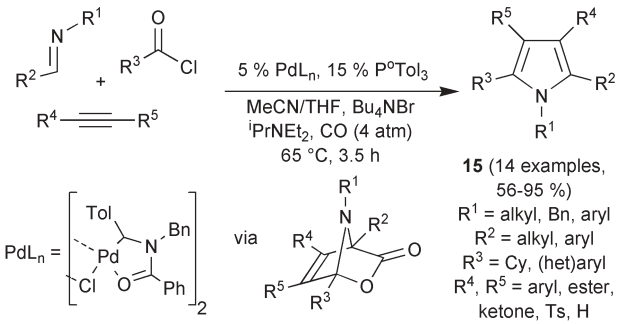
When the münchnones **13** are allowed to react with *N*-tosyl imines trisubstituted imidazoles **16** are obtained as products (Scheme 8).[18] The concurrent formation of *N*-(α-sulfonyl alkyl) amides was avoided at lower reaction temperatures and in the presence of P(*o*-tolyl)$_3$ and LiCl.




**Scheme 5**




**Scheme 6**



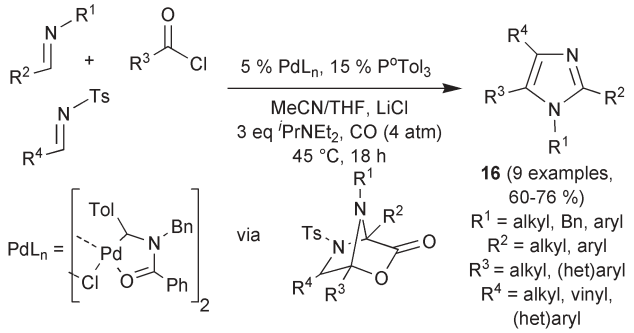

**Scheme 7**

## 2.2 Heck type reactions as a key step

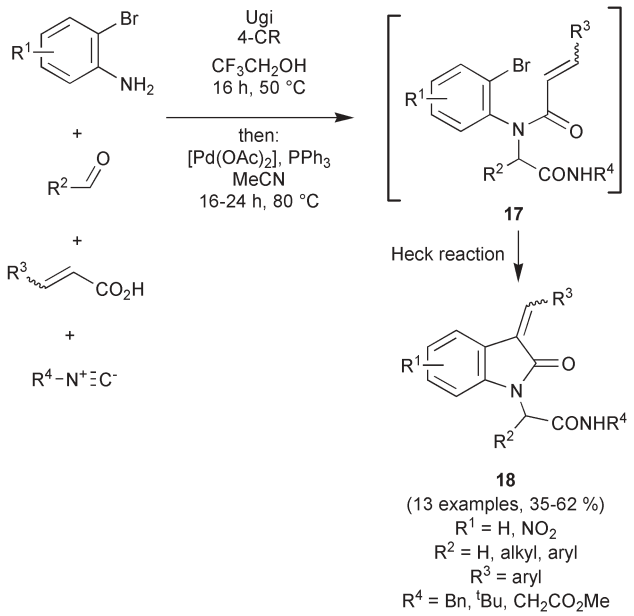
Besides for the preparation of complex substituted olefins, the Heck reaction has been applied in natural product synthesis by formation of carbo- and heterocycles.[19] Recently, Heck type transformations with subsequent organometallic transformations of "living" palladium intermediates giving access to indolone and benzofuranone skeletons have been published.[20]

A unique combination of the four component Ugi-reaction (U-4CR) and the intramolecular Heck reaction is an excellent showcase for diversity oriented syntheses of polysubstituted heterocycles. Combining the U-4CR with its enormous potential for generating acyclic compound libraries with a consecutive Heck sequence, Umkehrer *et al*. have reported a novel access to the pharmaceutically important class of indolones.[21] In a one-pot fashion the product of the Ugi step, an *N*-bromophenylacrylamide **17**, subsequently participates in




Scheme 8

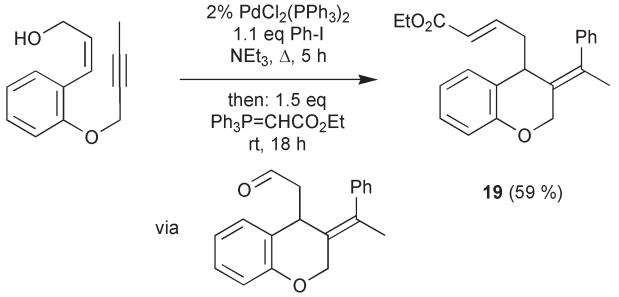



Scheme 9

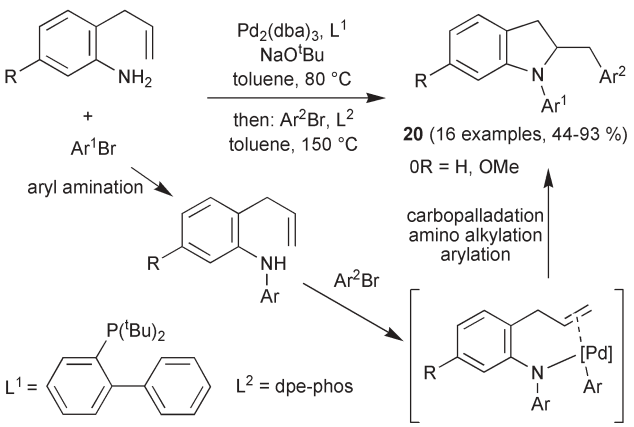
a cyclic carbopalladation reaction furnishing *N*-alkylated indolones **18** as isomer mixtures in moderate to good yields with a broad substitution pattern (Scheme 9).

Taking advantage of the formation of "living" vinyl palladium species by carbopalladation reactions of alkynes, Kressierer and Müller have recently introduced an intramolecular approach to an *exo*-methylene tetrahydrofurane skeleton. The incorporation of yne allyl alcohol derivatives in a Heck type insertion cyclization cascade furnishes enols as elusive intermediates which rapidly undergo a keto–enol tautomerism yielding aliphatic aldehydes as stable products. Based upon *in situ* trapping of aldehydes by a subsequent Wittig olefination a chromane derivative **19** with an α,β-unsaturated ester as a side chain was obtained in a one-pot fashion (Scheme 10).[22]

In contrast to carbopalladation sequences of alkynes, insertions of alkenes have to be combined with a rapid second reductive elimination step to overcome the nonproductive β-hydride elimination. Applying this concept, Wolfe and coworkers have invented a 3-CR with sequential *N*-arylation and carbopalladation as elementary steps.[23] The *N*-arylation proceeds with formation of an alkene-coordinating aryl




Scheme 10

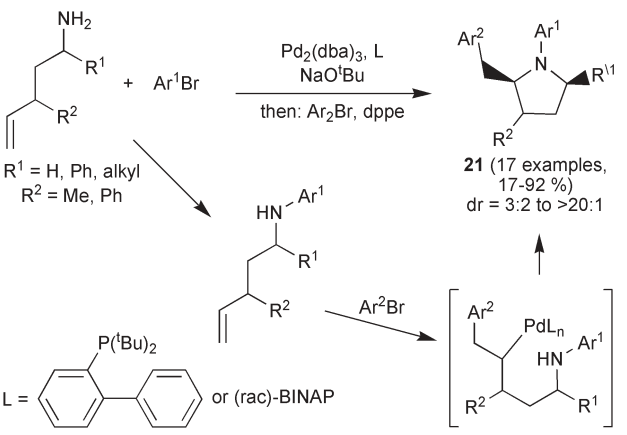



Scheme 11

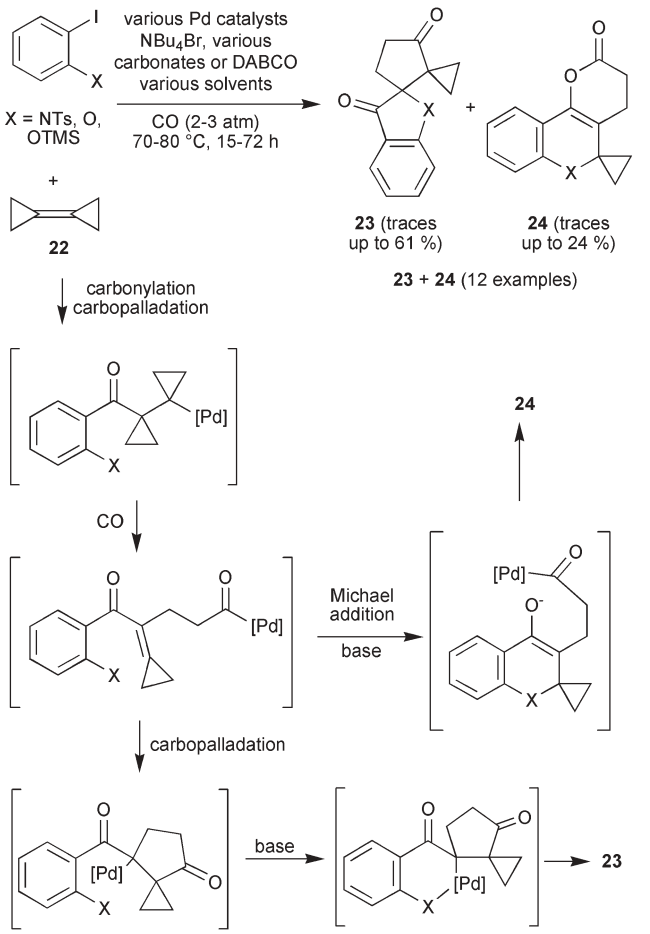
palladium complex. Insertion of the olefin fragment followed by a reductive elimination liberates the indoline **20** (Scheme 11).

Likewise Wolfe and his group have achieved a synthesis of pyrrolidines **21** starting from a terminally unsaturated amine and two different aryl bromides (Scheme 12).

An interesting multi-component reaction which actually can be described as a four-component domino reaction was discovered in de Meijere's and Grigg's laboratories. The authors have described a Heck type reaction cascade involving bicyclopropylidene (**22**) and carbon monoxide (Scheme 13).



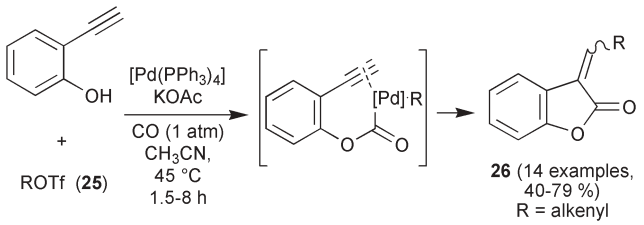

Scheme 12




**Scheme 13**

Starting from 2-iodophenol- or aniline derivatives, after the incorporation of two molecules of CO and one molecule of **22** generates an acyl palladium species as an intermediate. Acylcarbopalladation of the tetrasubstituted olefin, ring opening and intramolecular carbopalladation followed by heteroatom coordination and reductive elimination gives rise to the formation of spirocyclic products **23** in good yield. In a competitive reaction pathway the same intermediate can undergo an intramolecular Michael addition finally furnishing annelated lactones **24**.[24]

The palladium catalyzed cyclization of alkynes with nucleophilic centers in proximity to the triple bond is a versatile and convenient process for the preparation of heterocycles. In the sense of an intramolecular 5-*endo-dig* cyclization Balme and Young have synthesized benzofurans and furopyridones.[25] Recently, Cacchi could extend this methodology by a prefix oxidative addition of a vinyl triflate **25** followed by carbon monoxide insertion.[26] Unlike earlier observations under carbonylative conditions,[27] carbon monoxide is embedded in the heterocycle yielding 3-alkylidene-benzofuranones **26** as mixtures of *E*- and *Z*-isomers. A reasonable rationale accounts for an acylpalladium intermediate coordinating to the triple bond. After subsequent intramolecular alkyne insertion the reductive elimination terminates the sequence by formation of **26** (Scheme 14).



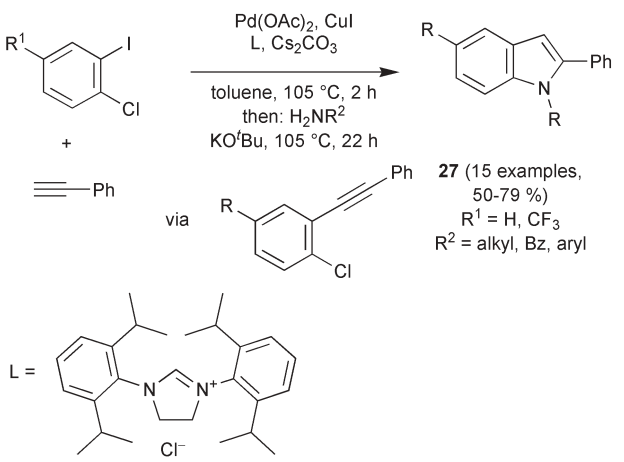

**Scheme 14**

### 2.3 Sonogashira coupling as a key step

The Sonogashira reaction is the most powerful catalytic alkynylation methodology. To date two major acetylene transformations are part and parcel of heterocyclic chemistry: carbopalladation sequences and Michael additions. The alkyne carbopalladation leads to the formation of ''living'' vinyl palladium intermediates, which can be trapped with nucleophiles under subsequent reductive elimination. Kaspar and Ackermann have developed a one-pot approach to indoles **27**, starting from *ortho*-iodo chloro arenes, terminal alkynes and primary amines (Scheme 15).[28]

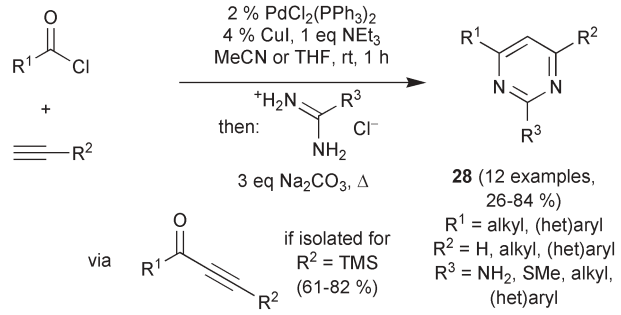
The Michael addition of nucleophiles to activated alkynes is a well established transformation in organic synthesis. Taking into account that ynones are the synthetic equivalents of β-keto aldehydes, and react readily with dinucleophiles, the entry to heterocycles by consecutive MCR lies at hand.

Recently, Karpov and Müller have established a catalytic access to the class of alkynones based upon the Sonogashira protocol: terminal acetylenes are transformed by the reaction with acid chlorides in the presence of only one equivalent of amine base and generate highly electrophilic ynones concomitantly consigning an essentially neutral reaction medium. Subsequent Michael additions can now selectively address the unsaturated functionality with a broad number of nucleophiles. The reaction of amidinium salts as amidine precursors in the presence of an excess of sodium carbonate leads to the formation of the pharmacologically important class of pyrimidines **28** (Scheme 16).[29] Interestingly, under the mild conditions even the ''notorious'' TMS alkynones were




**Scheme 15**

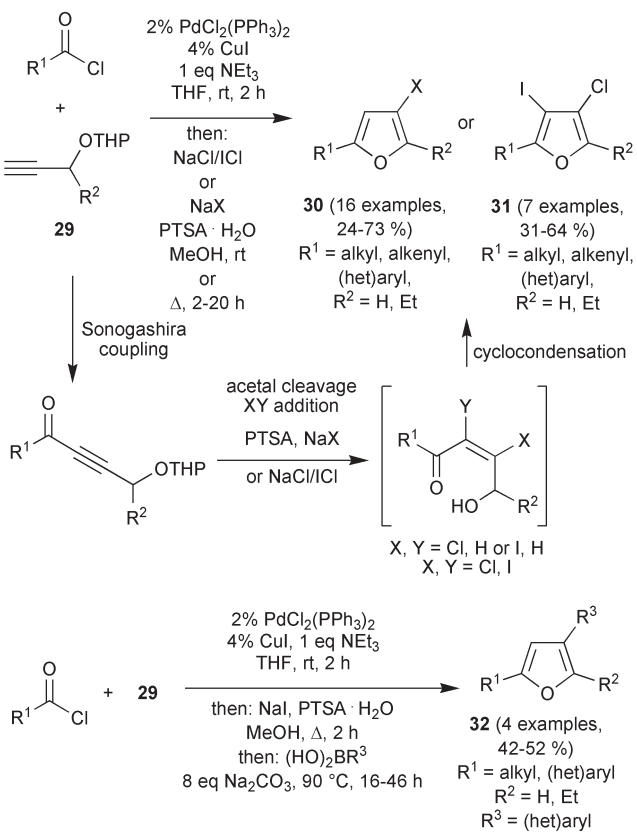
 



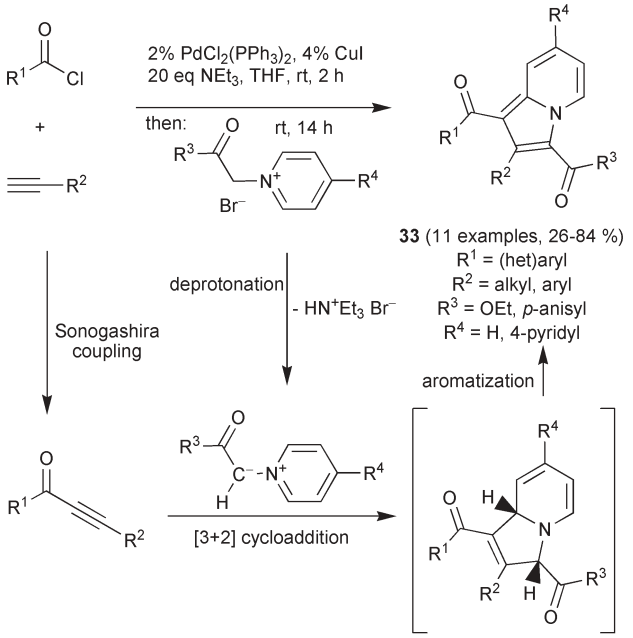

**Scheme 16**

successfully generated and transformed, leading to disubstituted derivatives as a consequence of TMS cleavage.

Interestingly, under the peculiar conditions of the alkynylation of acid chlorides the reaction medium can be easily conditioned to Lewis or Brønsted acidic reactions. Hence, Müller and co-workers have applied THP-protected propargyl alcohols **29** and sodium chloride/iodide or iodine monochloride, respectively, in a three-component reaction yielding the class of 3-halofurans **30** or 3-chloro-4-iodofurans **31** (Scheme 17).[30] After the ynone generation the acid catalyzed acetal cleavage liberates the hydroxyl ynone that undergoes an acid mediated Michael addition with concomitant cyclocondensation. Furthermore, the conditions are compatible with subsequent Suzuki reactions by simply adding the required boronic acids and excess of $Na_2CO_3$ to the reaction mixture




**Scheme 17**




**Scheme 18**

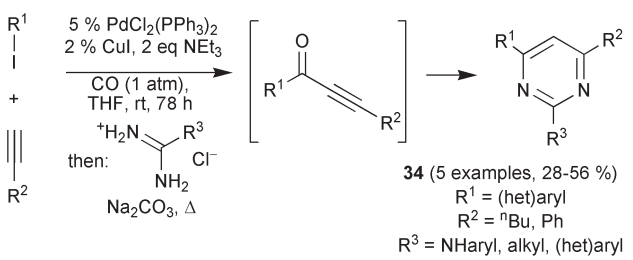
with the iodo furan giving rise to the formation of trisubstituted furans **32**.

Likewise the alkynones can also enter a subsequent cycloaddition in a one-pot fashion. Müller and co-workers have reported a three-component coupling–[3 + 2] sequence where after the alkynone formation 1-(2-oxoethyl)pyridinium bromides are added to the reaction mixture, generating pyridinium ylides that react as allyl type 1,3-dipoles to give highly fluorescent indolizines **33** after oxidative aromatization (Scheme 18).[31]

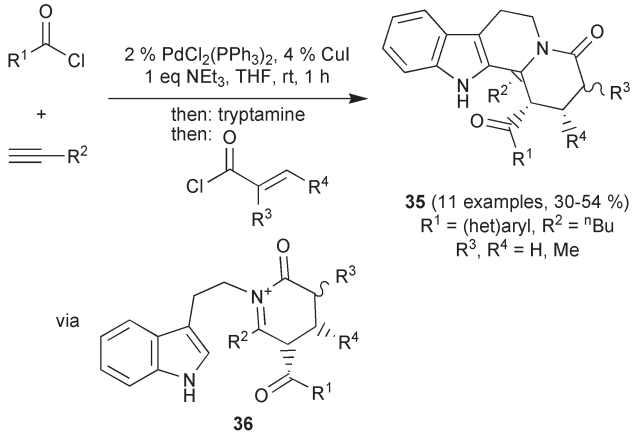
An alternative catalytic three-component access to ynones can be conceived by carbonylative alkynylation of aryl iodides, alkynes and carbon monoxide.[32] Upon subsequent addition of an amidinium salt polysubstituted pyrimidines **34** can be obtained in the sense of a four-component reaction (Scheme 19).[33] Likewise, Mori and co-workers have achieved a four-component pyrazole synthesis by applying hydrazine as a difunctional nucleophile in a domino fashion.[32]

Besides the reaction of ynones with difunctional substrates, the reaction with primary and secondary amines gives rise to β-enaminones that are extremely valuable building blocks in heterocyclic chemistry.[29]

Taking into account the enormous synthetic potential of β-enaminones and especially their unique ambiphilic reactivity,




**Scheme 19**

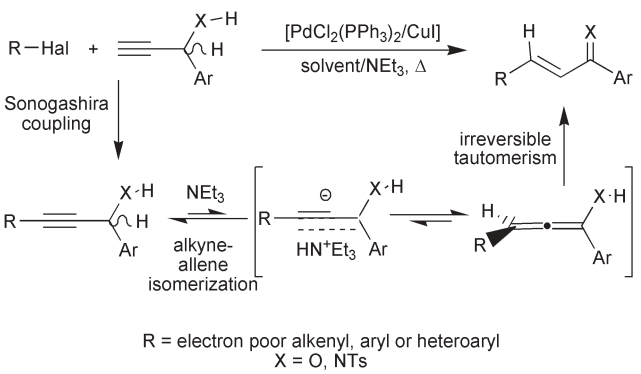



Scheme 20

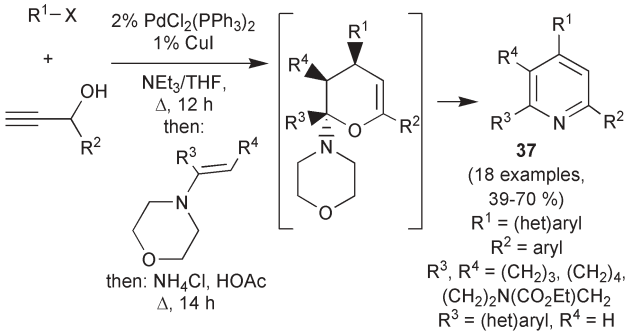
Müller and co-workers involved α,β-unsaturated acid chlorides as fourth component in a 4CR yielding tetrahydro-β-carbolines **35** in moderate to good yields (Scheme 20).[34] The final key step of this sequence is an aza-annulation reaction that presumably generates an acyliminium ion **36** which concludes in a Pictet–Spengler cyclization.

Under the mild conditions of Sonogashira coupling electron deficient (hetero)aryl halides and (hetero)arylpropargyl alcohols or *N*-tosylamines undergo a coupling–isomerization reaction (CIR) to furnish chalcones or enimines (Scheme 21).[35] Mechanistically, the CIR can be rationalized as a rapid palladium/copper-catalyzed alkynylation reaction, followed by the slow base-catalyzed isomerization of a propargyl alcohol or *N*-tosylamine into an enone or enimine, respectively.

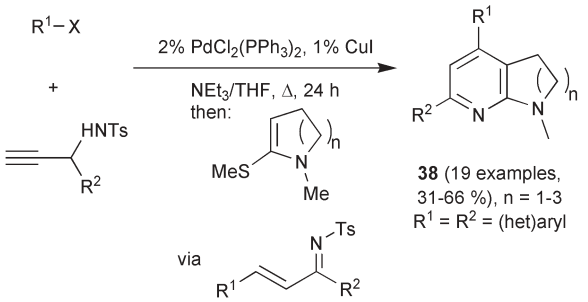
Addressing the Michael reactivity of the enone this new chalcone synthesis offers an excellent entry to novel multicomponent syntheses of heterocycles in the sense of consecutive one-pot processes. As heterodienes, chalcones can also be addressed by a subsequent Diels–Alder reaction with inverse electron demand giving rise to a cycloadduct that hydrolyses upon chromatographic isolation to furnish 1,5-diketones. However, upon addition of ammonium chloride and acetic acid the same cycloadduct can also be considered as a key intermediate in a consecutive CIR–cycloaddition–cyclocondensation sequence to highly substituted or annelated pyridines **37** (Scheme 22).[36]




Scheme 21




Scheme 22

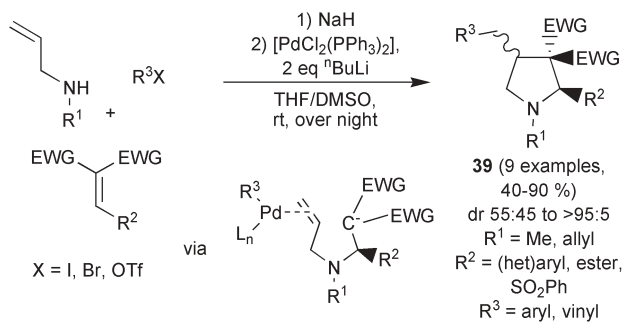



Scheme 23

Even more reactive than enones are *N*-tosyl enimines which can successfully applied in a CIR–[4 + 2]-cycloaddition–aromatization sequence applying very electron rich dienophiles such as *N*,*S*-ketene acetals to give annelated pyridines **38** (Scheme 23).[37] Interestingly, by this 3CR approach highly fluorescent pyrrolo[2,3-*b*]pyridines, [1,8]naphthyridines, and pyrido[2,3-*b*]azepines were obtained in excellent regioselectivities in moderate to good yields.

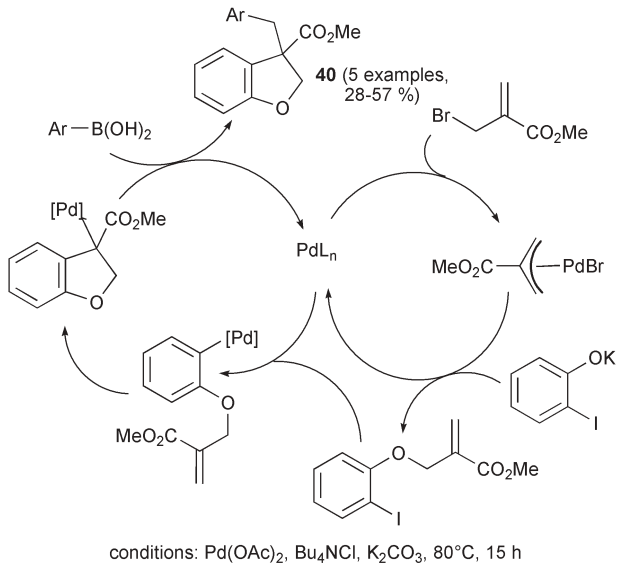
### 2.4 Miscellaneous processes

As many late transition-metal compounds, coordinatively unsaturated Pd complexes reveal a pronounced carbophilic Lewis acidity. Previously, Balme took advantage of this aspect by reacting propargyl amines or alcohols with activated alkenes and aryl or vinyl halides.[38] An extension of this peculiar palladium mediated sequence is the use of allyl derivatives (Scheme 24). A three-component reaction gives rise to diastereomeric mixtures of tetrasubstituted pyrrolidines **39**.




Scheme 24




**Scheme 25**

In the initial step the allyl amine derivative is deprotonated and undergoes an intermolecular Michael-addition to the activated alkene. The resulting stabilized carbanion with an alkene tether represents the ligand for the Pd species that triggers a 5-*exo*-trig cyclization to liberate after subsequent reductive elimination the pyrrolidine.

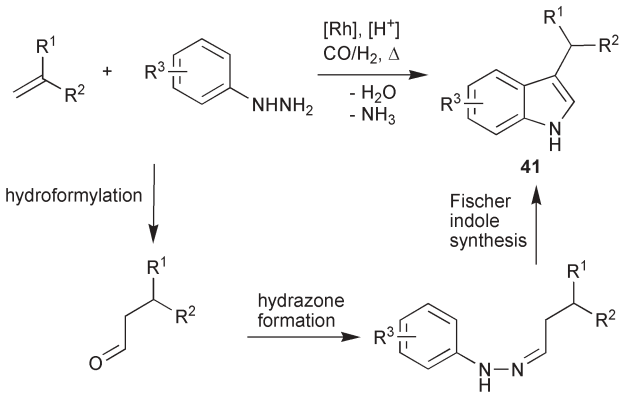
Allylic carbonates, esters or halides usually give linear products in Pd-catalyzed allylic substitutions as a result of steric and stereoelectronic reasons. Lamaty and co-workers have reported a three-component reaction based upon an allylation–carbopalladation–Suzuki-coupling sequence in a domino fashion. Combining palladium catalyzed allylation as the initial step with a subsequent Heck type transformation in a one-pot fashion gives rise to the formation of dihydrobenzofurans **40** (Scheme 25).[39]

## 3 Rhodium, ruthenium, and copper catalysis in multi-component syntheses of heterocycles

In contrast to Pd-catalyzed sequences multi-component syntheses of heterocycles catalyzed by other transition-metal complexes are less known so far. However, as a consequence of the rich organometallic chemistry and catalysis of a plethora of transition-metal derivatives a rapid development of this field can be already anticipated. Here, most prominent processes are based upon rhodium-, ruthenium-, and copper-catalyzed one-pot reactions.

By virtue of its three-component nature the rhodium catalyzed hydroformylation of olefins with syngas ($CO/H_2$) generates aldehydes that are excellent functional group in condensation based chemistry. Independently, Eilbracht and Beller have introduced a one-pot four-component indole synthesis that is based upon a sequence of hydroformylation, hydrazone formation, and subsequent Fischer indole formation giving rise to a number of substituted indoles **41** (Scheme 26).[40]

In continuation of their extended studies on Rh catalysis based sequences[41] Eilbracht and Schmidt have extended the

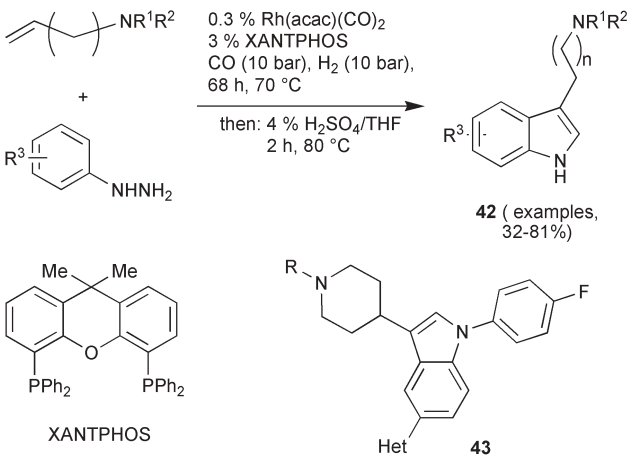



**Scheme 26**

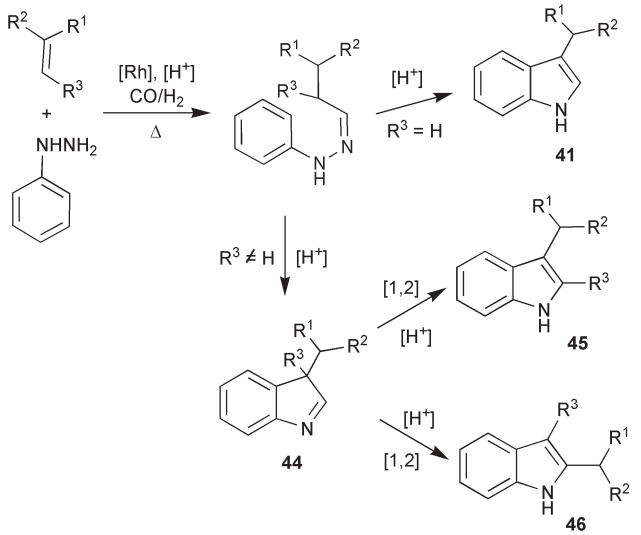
sequential indole syntheses by using allyl amines and amides as substrates to the formation of biologically interesting tryptamide derivatives **42** or the optimized lead of antipsychotic sertindole **43** (Scheme 27).[42]

Furthermore, the same group reported an intriguing access to 2,3-disubstituted indoles from olefins and hydrazines *via* a sequential hydroformylation-Fischer indole synthesis and skeletal rearrangement.[43] After hydroformylation of selected olefins to form α-branched aldehydes and condensation with phenylhydrazine to give hydrazones, the acid-catalyzed [3,3]-sigmatropic rearrangement of indolenine intermediates **44** with quaternary centers in the 3-position undergo a selective Wagner–Meerwein-type rearrangement of one of the substituents from the 3- to the 2-position, lead to 2,3-disubstituted indoles **45** and/or **46** in good to excellent yields (Scheme 28).

Cyclic olefins **47** can be transformed into 2,3-annelated indoles **48** and 3-spiro-indolines **49** with remarkable selectivity depending on the reaction conditions giving also rise to the reduction of the imine **44** (Scheme 29). The formation of **50** can be rationalized by the nucleophilic character of the indoline nitrogen as a hydroformylation–Fischer indole synthesis–hydroaminomethylation with excessive aldehyde, generated in the hydroformylation step. Starting from bicyclic or heterocyclic olefins polycyclic heterocyclic frameworks such as tetrahydrocarbazoles **51** and **52**, and tetrahydro-β-carbolines



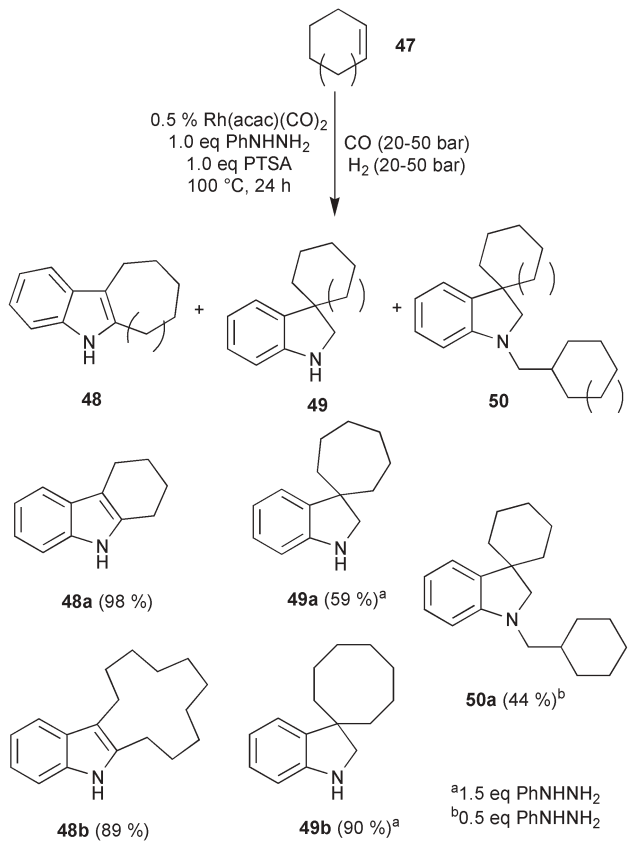

**Scheme 27**



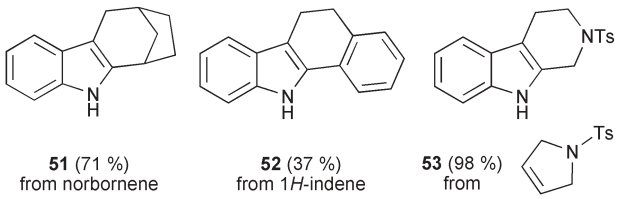

Scheme 28

**53** are accessible in a one-pot fashion and in moderate to excellent yields (Scheme 30).

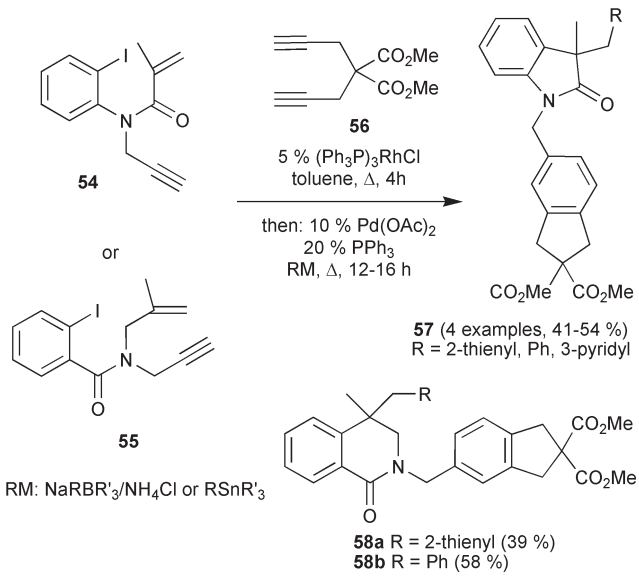
Rhodium and palladium catalysis can be sequentially combined as demonstrated by Grigg *et al.* with the development of one-pot [2 + 2 + 2]-cyclotrimerization–cross-coupling reactions (Scheme 31).[44] Starting from alkynyl enamides **54** or **55**, diynes **56**, and organostannanes (Stille coupling) or organoboron compounds (Suzuki–Miyaura coupling)




Scheme 29




Scheme 30




Scheme 31

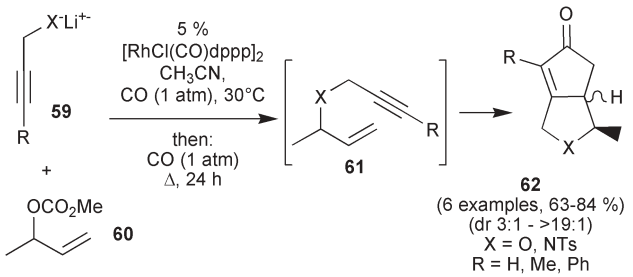
Wilkinson's catalyst and Pd(0) catalysts work harmoniously in sequence to form indolones **57** or isoquinolones **58** in reasonable yields. In addition, performing the sequence under an atmosphere of carbon monoxide in the Pd-catalyzed step a carbonylative cross-coupling paves the way to four-component reactions.

Rh-catalyzed allylic substitutions occur with selective formation of the branched substitution product. Hence, Evans and Robinson have developed two captivating sequences to fused heterocycles initiated by Rh-catalyzed allylic substitution.[45] In the same pot the lithium salts of propargyl alcohols or propargyl *N*-tosyl amides **59** and 3-buten-2-yl methyl carbonate (**60**) in the presence of a rhodium catalyst and under an atmosphere of carbon monoxide give rise to the formation of the heteroatom tethered enyne **61** that subsequently reacts in the sense of a Pauson–Khand reaction to the hetero bicyclic enone **62** in good to excellent yields and with reasonable to excellent levels of diastereoselectivity (Scheme 32).

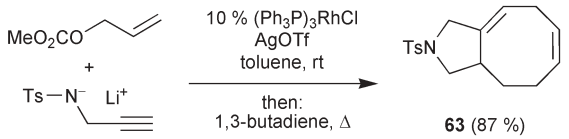
Likewise, Evans and co-workers have succeeded in combining the allylic amination and a [4 + 2 + 2] cycloaddition, both are sequentially rhodium catalyzed reactions (Scheme 33). Here, the amide tethered enyne is generated by an *in-situ* generated cationic rhodium complex and upon placing an atmosphere of 1,3-butadiene on the reaction vessel the hexahydro-1*H*-cycloocta[*c*]pyrrole **63** is formed in excellent yield.

Besides ruthenium complexes Wilkinson's catalyst also has proven to catalyze a direct *ortho*-alkenylation of aromatic




**Scheme 32**




**Scheme 33**

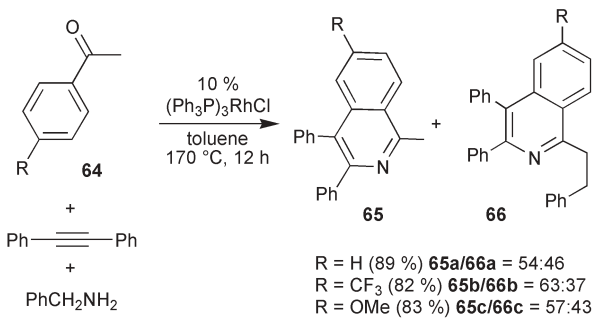
ketimines.[46] Interestingly, starting from acetophenones **64**, benzyl amine, and tolane Jun and co-workers have elaborated an elegant three-component synthesis of isoquinoline derivatives **65** and **66** (Scheme 34).

The tentative mechanism of the three-component process comprises an imine formation, a rhodium-catalyzed *ortho*-alkenylation (*ortho*-metallation, alkyne insertion, and β-elimination as elementary steps), electrocyclization of the resulting alkenyl imine, benzyl transfer, and oxidative aromatization. In particular, the formation of the unexpected product **64** accounts for a complex intermolecular benzyl transfer mechanism that has not been elucidated yet.

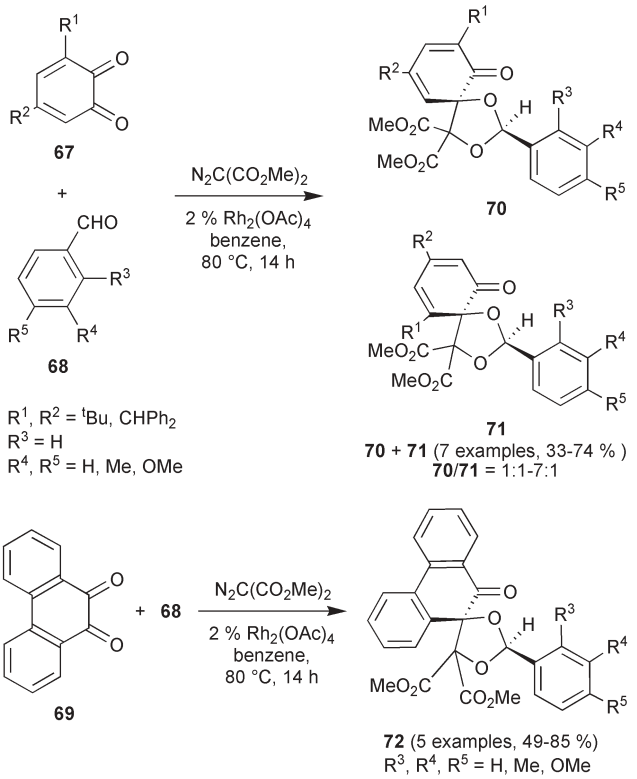
Rhodium carbenoids are well suited to initiate uni- or bimolecular domino reactions.[47] However, it was not before 2003 that Nair and co-workers have introduced a rapid and facile three-component synthesis of spiro-dioxolanes and tetrahydrofurans.[48] The Rh(II)-catalysed decomposition of dimethyl diazomalonate in the presence of *o*-quinones **67** or **69** and aromatic aldehydes **68** afforded regioisomeric mixture of dioxolanes **70** and **71**, or **72** (Scheme 35).

This three-component reaction probably involves the formation of a carbonyl ylide through the reaction between a carbene and the aldehyde and the sequence concludes by a 1,3-dipolar cycloaddition (Scheme 36).

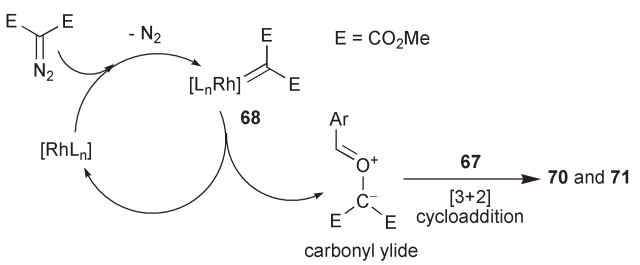
Recently, Nair and co-workers have expanded this concept to β-nitrostyrenes **73** as dipolarophiles, providing highly




**Scheme 34**



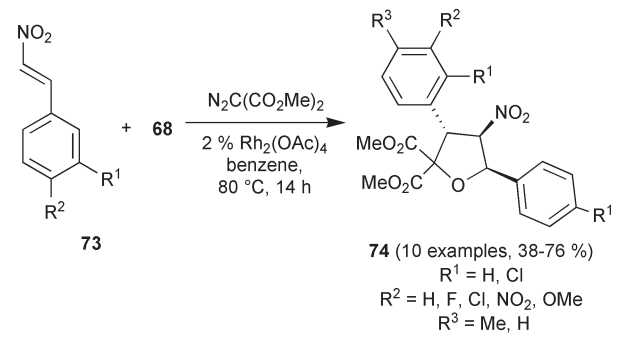

**Scheme 35**



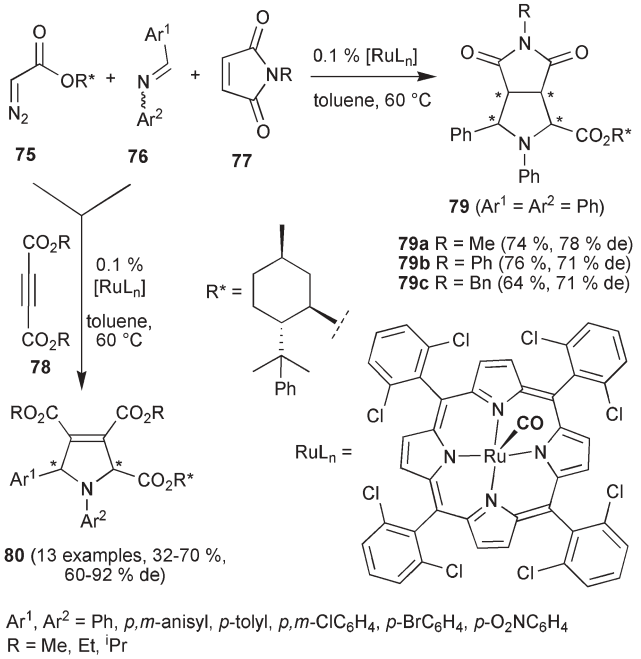

**Scheme 36**

substituted tetrahydrofuran derivatives **74** in moderate to good yields and with excellent diastereoselectivity (Scheme 37).

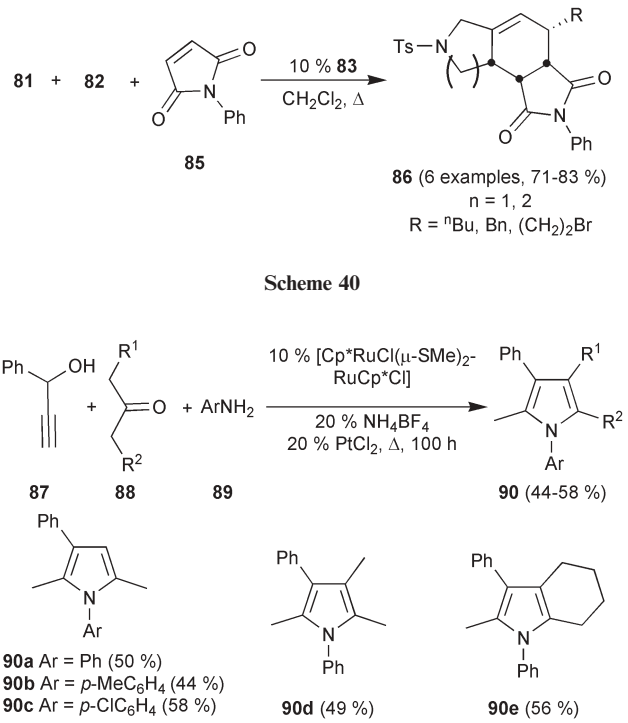
Just recently, Che and co-workers have reported an asymmetric three-component reaction based upon a Ru-prophyrine catalyzed decomposition of a chiral diazo ester **75** in the presence of Schiff bases **76** and maleimides **77** or




**Scheme 37**




Scheme 38

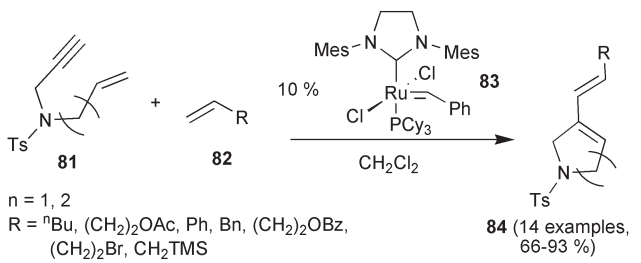



Scheme 41

acetylene dicarboxylic esters **78** as dipolarophiles giving rise to multifunctionalized chiral pyrrolidines **79** or pyrrolines **80** in good yields and high diastereoselectivity (Scheme 38).[49] Presumably, the ruthenium carbenoid reacts with the imine to furnish a chiral azomethine ylide, which, in turn undergoes an asymmetric 1,3-dipolar cycloaddition with the alkene or alkyne.

Besides Ru-catalyzed ring-closing metathesis of dienes the metathesis of enynes[50] has become a new and valuable tool. As a consequence of heteroatom tethering of enyne substrates the reaction products of these cycloisomerizations are heterocyclic conjugated dienes that can readily undergo in a following [4 + 2]-cycloaddition. As an extension of enyne metathesis Lee and co-workers have developed a domino enyne–diene–ene metathesis where an amide tethered enyne **81** and a terminal alkene **82** are cycloisomerized and metathesized in the presence of a Grubbs catalyst **83** to give substituted five- and six-membered heterocyclic conjugated dienes **84** in good to excellent yields (Scheme 39).[51]

Mechanistically, either the diene metathesis of **81** and **82** occurs followed by an enyne metathesis of the product to give **84**, or the enyne metathesis starts the sequence that is concluded by the diene cross-metathesis. Conceptually, the stage

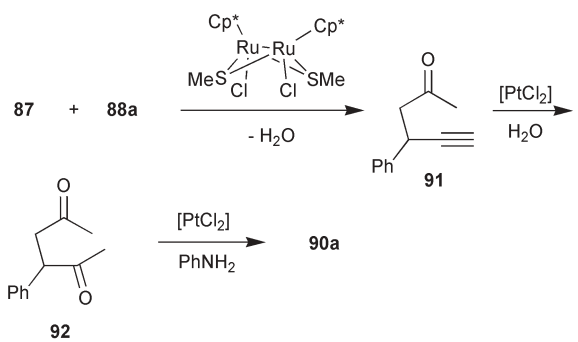



Scheme 39

was then set for a three-component enyne-diene-ene metathesis-Diels–Alder domino reaction of **81**, **82**, and phenyl maleimide (**85**) as dienophile to give the tricyclic products **86** with four contiguous stereocenters in very good yields (Scheme 40).

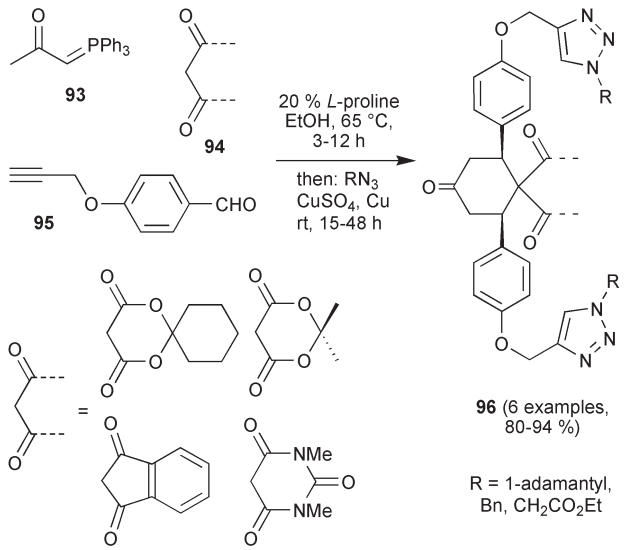
Dinuclear ruthenium complexes have been found to efficiently catalyze propargylations of carbon and heteroatom nucleophiles with propargyl alcohols as substrates. Therefore, Uemura and co-workers have succeeded in developing a ruthenium- and platinum-catalyzed sequential three-component synthesis of tri- and tetrasubstituted pyrroles **90** starting from 1-phenylpropyn-1-ol (**87**), ketones **88**, and anilines **89** (Scheme 41).[52]

The mechanistic rationale suggests that first a propargylation of acetone (**88a**, $R^1 = R^2 = H$) with **87** catalyzed by the dinuclear ruthenium complex furnishes the ynone **91** (Scheme 42). Then, platinum dichloride catalyzes both, the hydration of the triple bond to the 1,4-diketone **92** and the subsequent Paal–Knorr cyclocondensation with aniline to give the pyrrole **90a**.

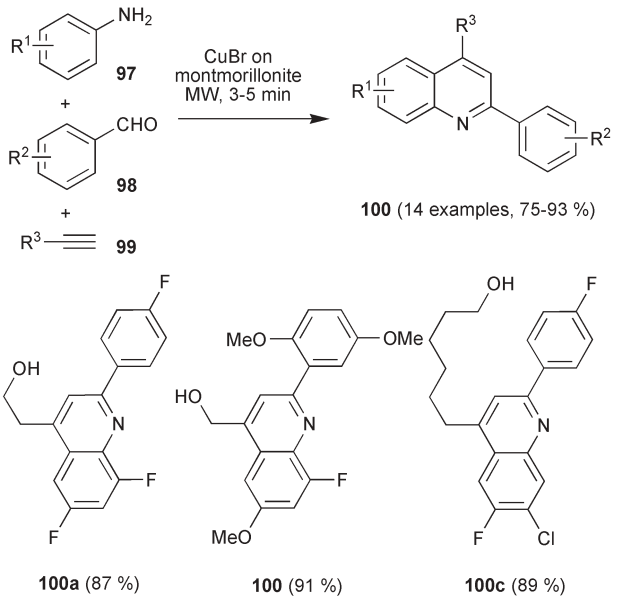



Scheme 42

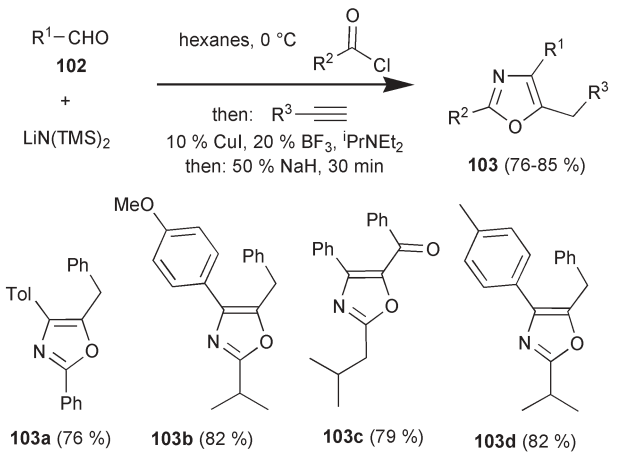
 




Scheme 43




Scheme 44




Scheme 45

Finally, copper catalyzed multi-component syntheses of heterocycles remain to be discussed. As an impressive show case for an organocatalytic, copper-catalyzed one-pot sequence consisting of Wittig, Knoevenagel, Diels–Alder, and copper reactions, Barbas and Ramachary have presented a high yielding, stereospecific synthesis of polysubstituted triazoles **96** (Scheme 43).[53] The sequence commences with a simultaneous Wittig olefination of the ylide **93** and the aldehyde **95**, and a proline catalyzed Knoevenagel condensation of **95** and the CH-acidic compound **94**. Again, proline catalyzes a Diels–Alder reaction of the Knoevenagel condensation product and the Wittig product *via* formation of a vinyl enamine to give a spirocyclic intermediate. Then, this diyne reacts smoothly with the azide in the presence of a copper catalyst to give the pseudo-six-component product **96**.

A concise three-component synthesis of 2,4-disubstituted quinolines was reported by Yadav and co-workers.[54] A microwave assisted reaction of anilines **97**, aldehydes **98**, and alkynes **99** that is catalyzed by montmorillonite clay doped with copper(I) bromide the quinoline derivatives **100** are obtained with 3–5 min in good to excellent yields (Scheme 44). Presumably, the sequence is initiated by an amino alkylation of the terminal alkyne followed by a cycloisomerization and an oxidative aromatization.

Recently, Arndtsen and Black have shown that oxazoles **103** can be very efficiently synthesized in a consecutive four-component reaction starting with the in situ generation of silylimines from aldehydes **102** and lithium hexamethyl disilazanide (Scheme 45).[55] Subsequent addition of an acid chloride furnishes an acylimine that reacts in a copper-catalyzed alkynylation to give a secondary propargylamide. Upon addition of sodium hydride the propargylamide cycloisomerizes to form the oxazoles **103** in very good yields.

## Conclusions

Transition organometallic catalysis has considerably contributed to the development of diversity oriented synthesis of heterocycles, namely by disclosing new transition-metal catalyzed MCR. Besides purely insertion based processes sequential and consecutive one-pot reactions have expanded the playground for reaction design. Therefore, the combination of organic and organometallic elementary steps opens numerous options for devising new multi-component methodologies in heterocyclic chemistry that are diversity oriented and increase complexity of molecular scaffolds. Conceptually, many applications such as in natural product synthesis, medicinal chemistry, functional materials design or ligand synthesis for catalysis can be tackled by transition-metal catalyzed MCR of heterocycles. Still many other transition-metal complexes that are known to catalyze uni- and bimolecular transformations are waiting to be discovered for inventing a new MCR. Undoubtedly, the future holds surprising sequences in store.

## Acknowledgements

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