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FUNCTIONALIZED ACETYLENES AS VERSATILE BUILDING-BLOCKS FOR THE MULTICOMPONENT ASSEMBLING OF POLYSUBSTITUTED FURANS AND PYRROLES

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Abstract – This review highlights the versatility of functionalized alkynes in the multicomponent construction of polysubstituted furan and pyrrole derivatives.

Dedicated to the memory of Professor Ivar Ugi

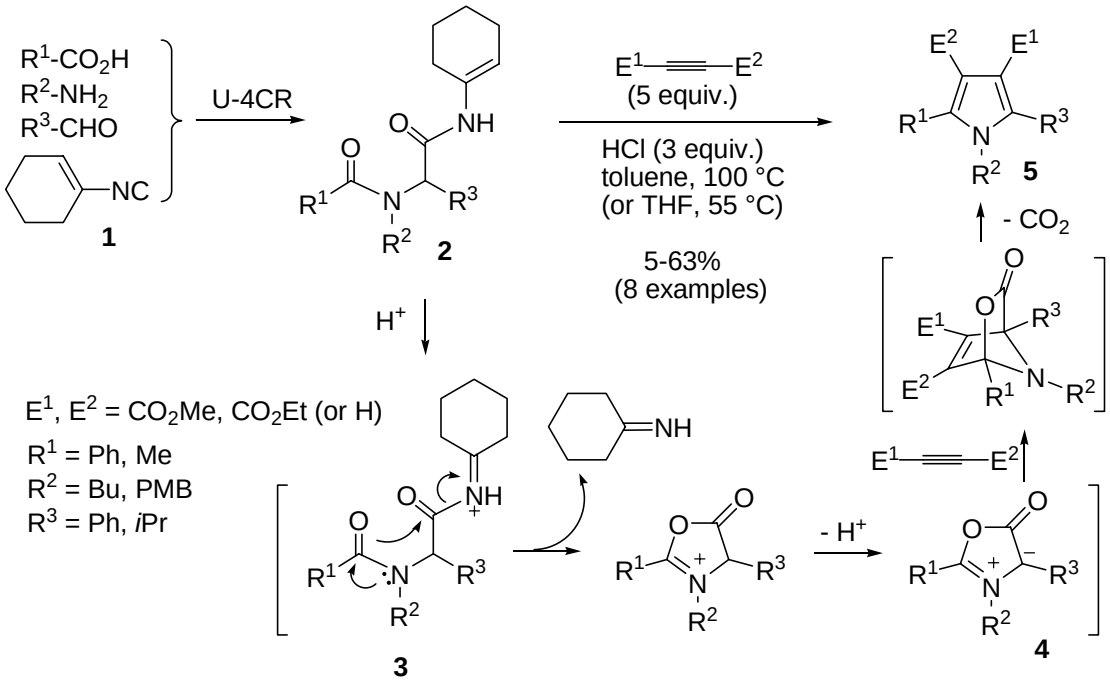
Introduction

Among numerous heterocycles, furans and pyrroles are the most prevalent since they are common structural motifs in many biologically active natural and synthetic compounds. The development of new approaches to produce these heterocyclic structures in a rapid, environmentally friendly way has become an important area of research nowadays.[1] Multicomponent strategies offer significant advantages over classical linear syntheses by combining a series of reactions from three or more simple and flexible building blocks in a one-pot operation.[2] In this review we report the preparation of pyrroles and furans by multicomponent strategies involving alkyne derivatives as versatile reaction partners. Indeed, alkynes hold a prominent place in multicomponent reactions since they constitute a very reactive class of intermediates. The attractive features of these building-blocks include their ease of preparation, the various selective transformations of the alkyne functionality as well as their versatility in metal-mediated organic synthesis.[3] The review is divided into sections relative to the specific role played by the alkyne moiety in the elaboration of the targeted heterocycles, and concerns essentially cycloaddition reactions, metal-catalyzed as well as uncatalyzed intramolecular cyclizations of alkynes, and carbometallation reactions.

MCRs based on cycloadditions of Münchnones and related intermediates with alkynes

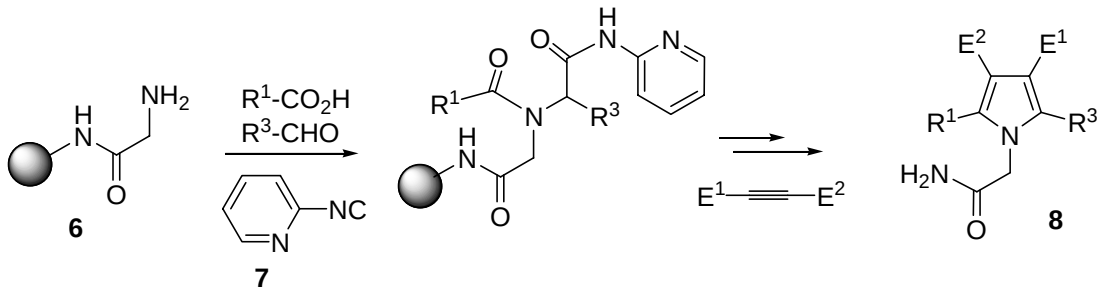
Many approaches for the synthesis of pyrrole derivatives are based on the 1,3-dipolar cycloaddition reaction of Münchnones with activated acetylenes.[4] These mesoionic 1,3-dipoles are usually generated by cyclodehydration of acylated amino acids. The main drawback of these approaches is associated with the necessity of preparation of the amino precursors.

The Ugi four-component reaction (Ugi 4CR) is a powerful process that allows the one-pot assembling of α-(acylamino)amides starting from a combination of an aldehyde, an amine, a carboxylic acid, and an isocyanide. Exploitation of Ugi condensation products through postcondensation modifications also offers numerous possibilities for molecular diversity.[5] For instance, 1-isocyanocyclohexene **1** may be used as a convertible isocyanide in the Ugi 4CR to enable postcondensation cyclization reactions.[6] Indeed, the cyclohexenamide products **2** are valuable precursors for oxazolinium-5-ones **4** (Münchnones) which may undergo *in situ* cycloaddition with acetylenic dipolarophiles and subsequent cycloreversion to liberate carbon dioxide and form fully substituted pyrroles (**5**) in low to moderate isolated yields (Scheme 1). The Münchnones are generated through protonation of the enamide to give the activated intermediates **3**, which then cyclize and eliminate cyclohexanimine.



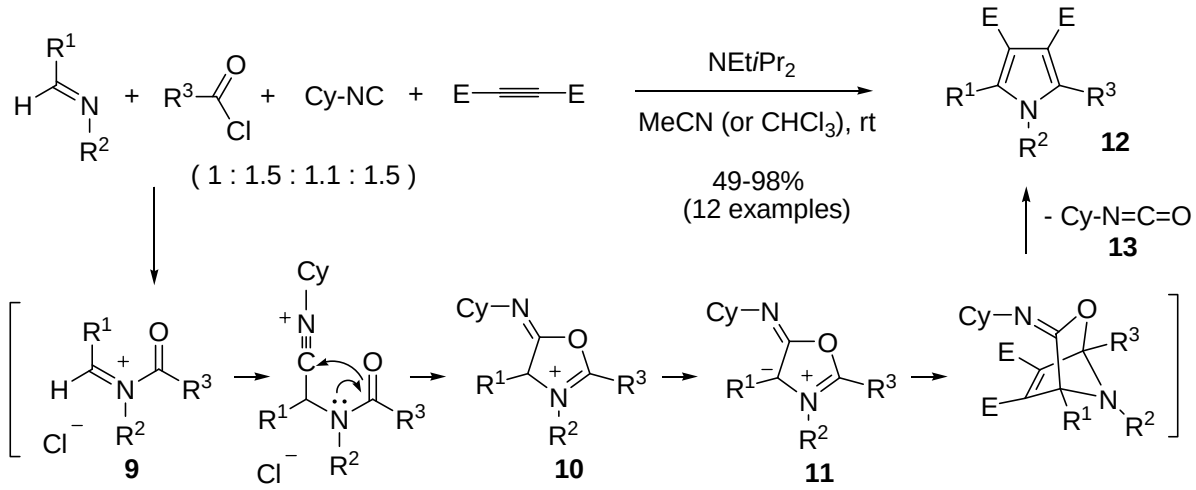
Scheme 1

A similar strategy has been developed to produce pyrroles **8** on solid support starting from NH_2-functionalized Rink resin (**6**) (Scheme 2). In this approach, the highly reactive 2-isocyanopyridine **7** was used as the convertible isocyanide.[7]



Scheme 2

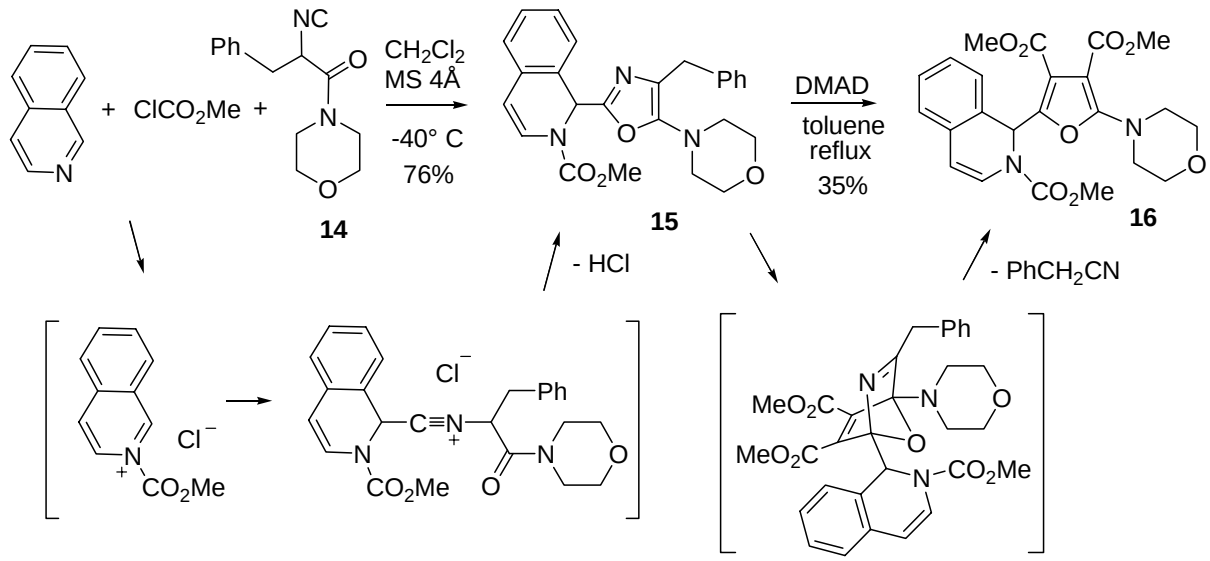
The contribution of isocyanides to the *in situ* generation of imino analogs of Münchnones has also been proposed for the direct synthesis of pyrroles from imines, acid chlorides, and alkynes.[8] Similarly to related Ugi-type reactions, the process presumably begins by nucleophilic attack of the isocyanide on a *N*-acyliminium salt **9,** generated here by reaction of the imine with the acid chloride, to form **10** (Scheme 3). In the presence of a base, the Münchnone analogs **11** are generated, which undergo cycloaddition followed by cycloreversion to form the desired pyrroles **12** with concomitant elimination of an isocyanate (**13**). As can be seen, the starting isocyanide is not incorporated in the final product but acts as a mediator of the reaction.



R1, R3 = aryl, alkyl R2 = Bn, allyl, propargyl, alkyl
E = CO2Me or COPh

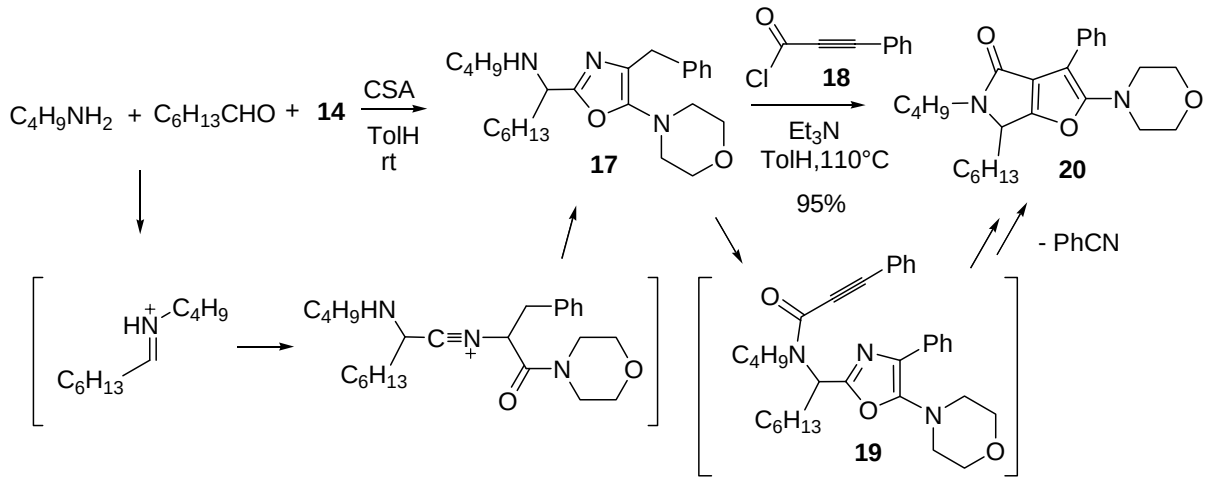
Scheme 3

A similar succession of events has been used in a two-step four-component approach of aminofurans based on the use of α-isocyanoacetamide **14** as the isocyanide input. The first step was designed to produce various 1,3-oxazol-2-yl-1,2-dihydro(iso)quinolines **15** prone to react with activated alkynes to form 2-aminofurans like **16** (Scheme 4).[9]



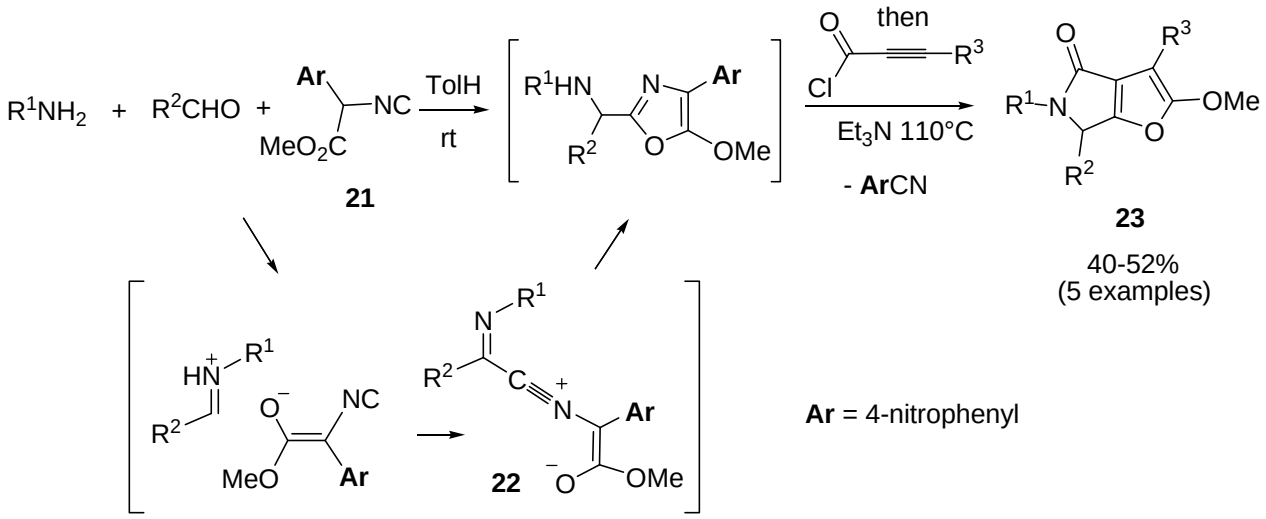
Scheme 4

The strategy may also be applied to the synthesis of fused 2-aminofurans via intramolecular cyclization of acetylenic oxazoles as illustrated by the synthesis of 5,6-dihydrofuro[3,2-*c*]pyrrol-4-one **20** (Scheme 5). For this purpose, **19** was generated *in situ* by reaction of 5-aminooxazole **17** with acyl chloride **18** in the presence of triethylamine in refluxing toluene.[10]



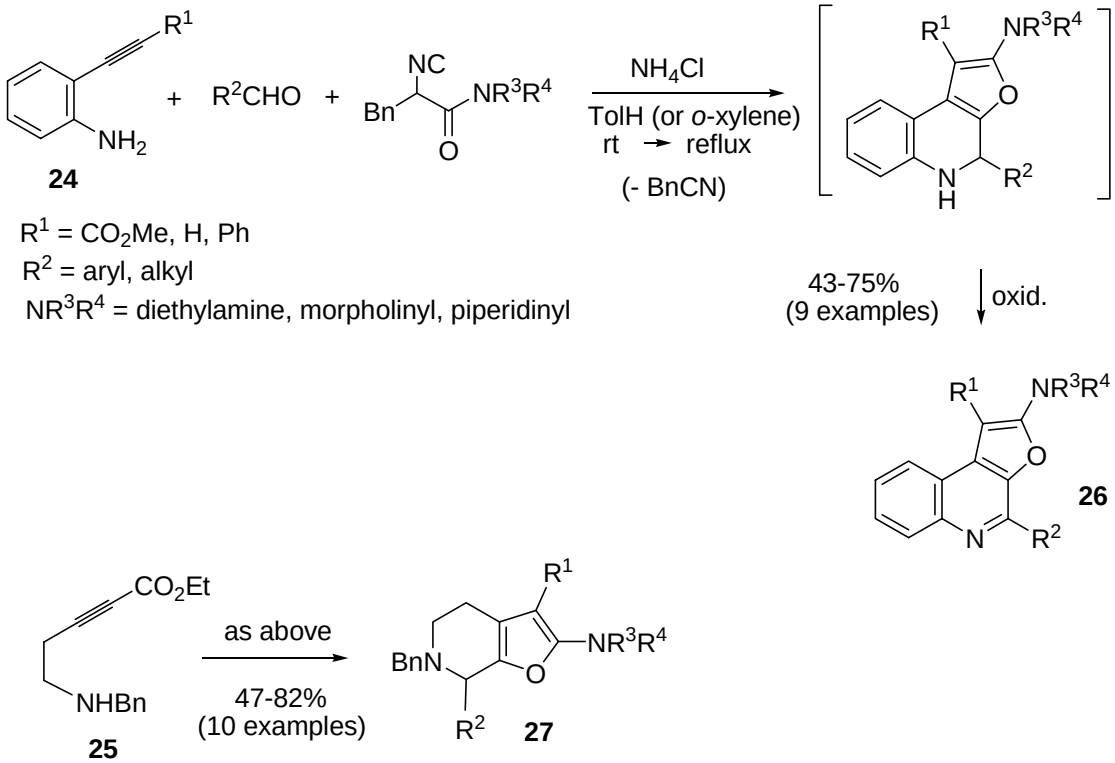
Scheme 5

Methyl α-(*p*-nitrophenyl)-α-isocyanoacetate **21** has been designed as a valuable isocyanide input for the synthesis of analogous fused 2-methoxyfurans **23** (Scheme 6).[11] The *p*-nitrophenyl group in **21** renders the α-CH acidic enough to facilitate the formation of enolate intermediates **22**. Importantly, in this process, the resulting oxazoles are not isolated but are treated *in situ* with various acyl chlorides to generate the desired furopyrrolones **23**.



Scheme 6

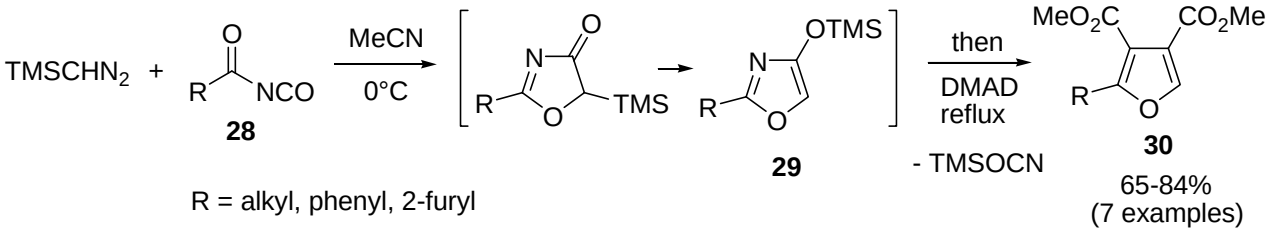
Other intramolecular versions of these reactions have been developed that involve amine inputs **24** and **25** already bearing a tethered acetylenic moiety. Furo[2,3-*c*]quinolines **26**[12] as well as furo[2,3-*c*]pyridines **27**,[13] respectively, have been prepared based on this strategy (Scheme 7).



Scheme 7

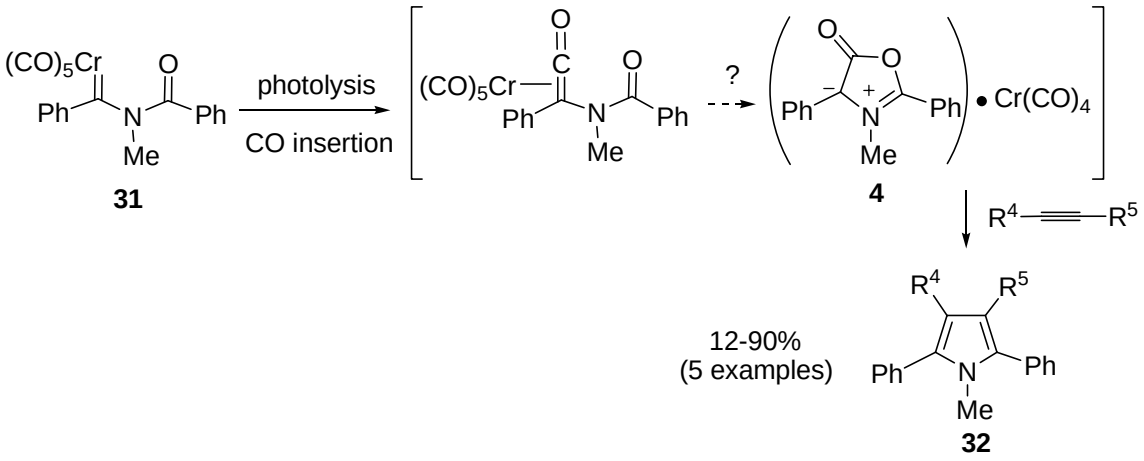
The reaction of trimethylsilyldiazomethane with acyl isocyanates **28** is another useful method to access oxazole precursors of furan derivatives. For instance, a series of 4-trimethylsiloxyoxazoles **29** have been

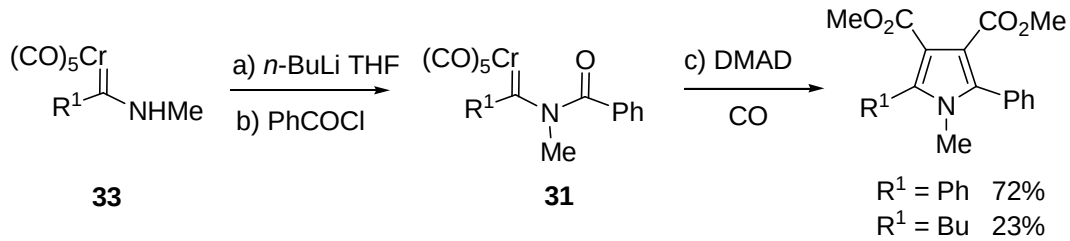
generated in acetonitrile at 0°C and were then treated *in situ* with two equivalents of DMAD at refluxing temperature to yield 2-substituted furans **30** in good yields (Scheme 8).[14]



Scheme 8

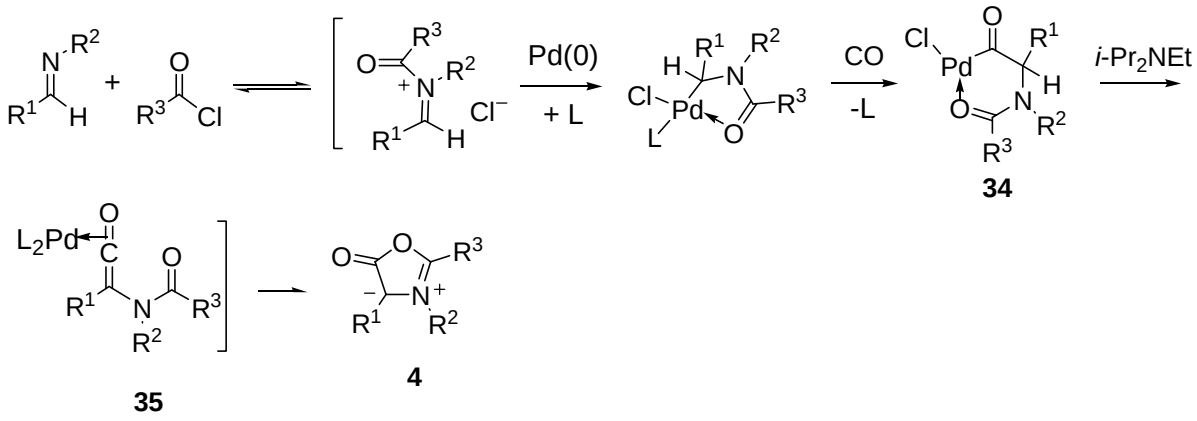
A conceptually new synthetic route to Münchnone or Münchnone complexes **4** from photolysis of a presynthesized acylamino chromium carbine complex **31** was recently developed. A subsequent *in situ* addition of electron-poor alkynes to these reactive intermediates led to the formation of pyrrole derivatives **32** in high yield. This strategy was further used to develop a new one-pot three-component synthesis of pyrroles. To do this, the acylamino chromium complexes **31** were prepared *in situ* from the condensation of stable aminocarbenes **33** with an acid chloride in the presence of a base. *In situ* addition of DMAD in the presence of CO gave the corresponding polysubstituted pyrroles (Scheme 9).[15]





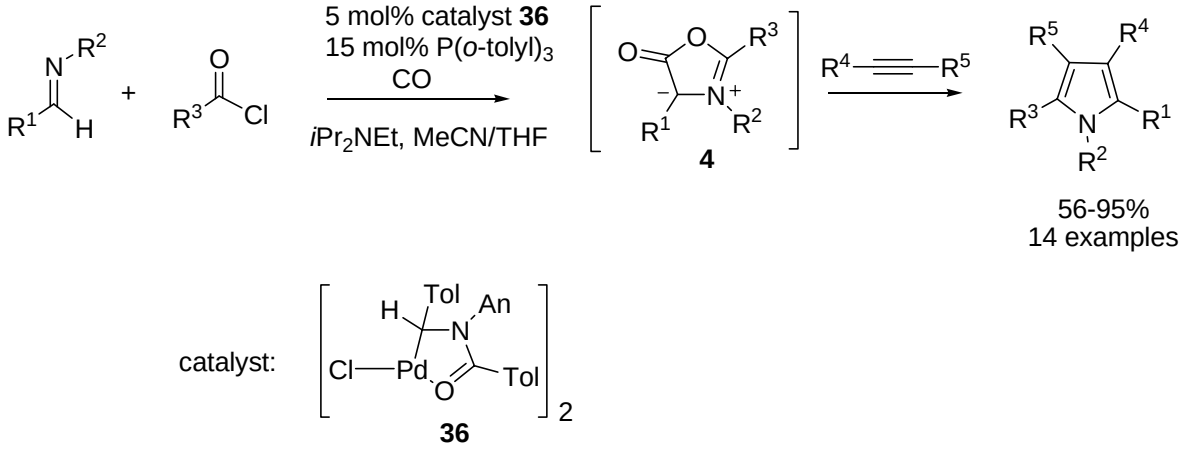
Scheme 9

More recently, the first catalytic synthesis of stable Münchnones was developed. This approach involves a palladium-mediated three-component coupling reaction of imines, carbon dioxide and acid chlorides. In this process, oxidative addition of imine and acid chloride to palladium(0) followed by CO coordination and insertion give the chelated complex **34**. A β-hydride elimination leads to the metal-free Münchnone **4** via the metalloketene complex **35**. (Scheme 10).[16]



Scheme 10

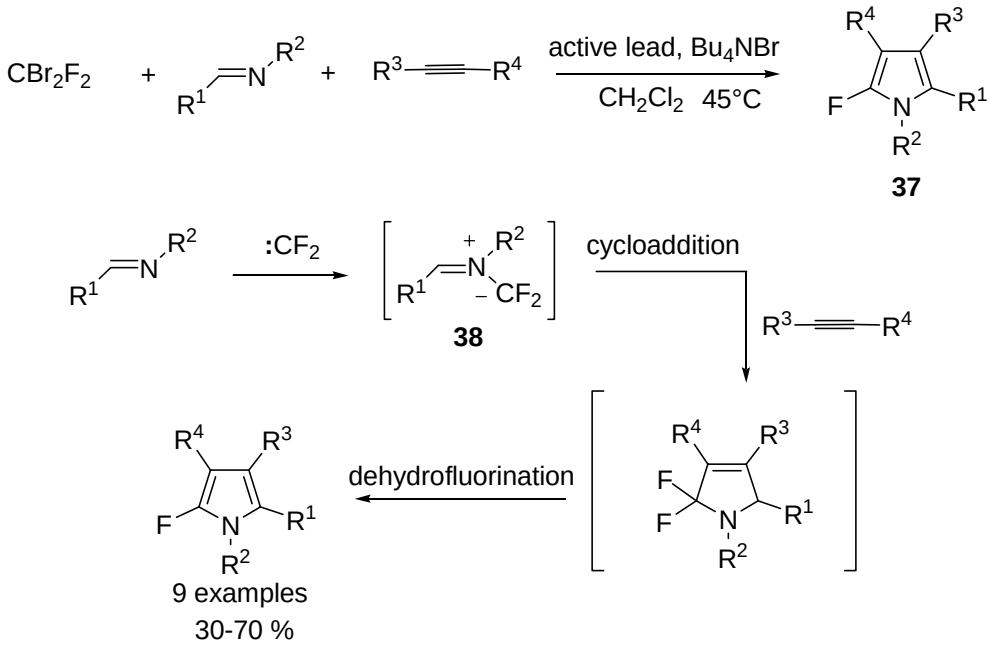
The combination of this catalytic synthesis of Münchnones with a cycloaddition process with activated alkynes leads to an efficient and elegant synthesis of highly substituted pyrrole derivatives. Alkyl, aryl, and heteroaryl substituents can be incorporated into the pyrrole structure from the acid chloride or imine and a variety of alkynes may be involved in this four component reaction (Scheme 11).[17]



Scheme 11

MCRs based on cycloadditions of azomethine ylides with alkynes

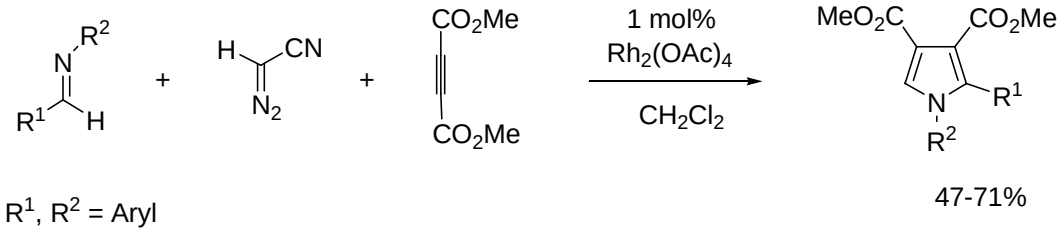
Several methods have been developed to generate azomethine ylids derived from imines. These ylids may be engaged in various 1,3-dipolar additions with dipolarophiles to prepare 5-membered heterocycles.[18] Cycloaddition of azomethine ylids with activated alkynes results in the formation of pyrrolines that can serve as valuable intermediates through aromatization to pyrroles. This methodology was applied to the one-pot synthesis of 2-fluoropyrrole derivatives **37** starting from imines, dibromodifluoromethane and electron-deficient alkynes. The initial step of this domino three-component reaction should consist of an *in situ* generation of difluorocarbene by reduction of dibromodifluoromethane with preformed active lead. The resulting difluorocarbene attacks on the nitrogen lone pair of the imine yielding fluoro substituted azomethine ylids **38**. Then a 1,3-dipolar cycloaddition to alkynes is followed by aromatization by means of dehydrofluorination. A wide range of structurally varied imines was coupled with several alkynes and dibromodifluoromethane. The best results were obtained with alkyne derivatives substituted by two electron-withdrawing groups (Scheme 12).[19]

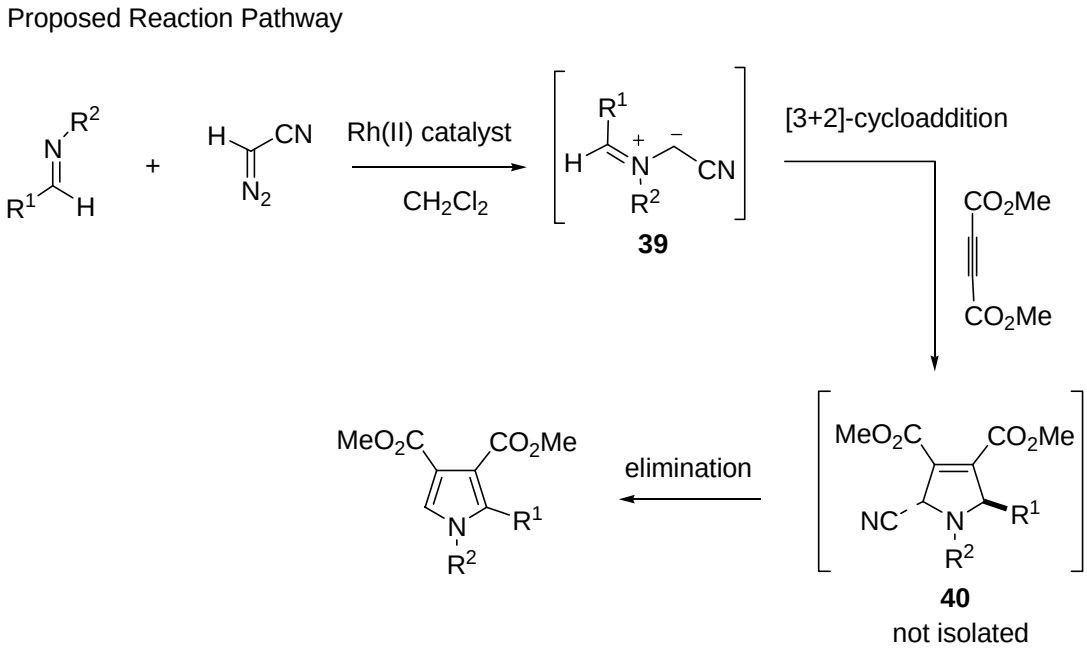


Scheme 12

A rhodium-mediated three-component reaction starting from diazoacetonitrile, an imine and DMAD, and leading to substituted 1,2-diarylpyrroles, has been recently developed. In this case, the transition metal-catalyzed decomposition of the diazo compound in the presence of an imine generates azomethine ylide intermediate **39** that undergoes a cycloaddition reaction with the activated alkyne. The resulting adduct **40** then undergoes an elimination of the cyano group to give the corresponding pyrrole. Only two diversity

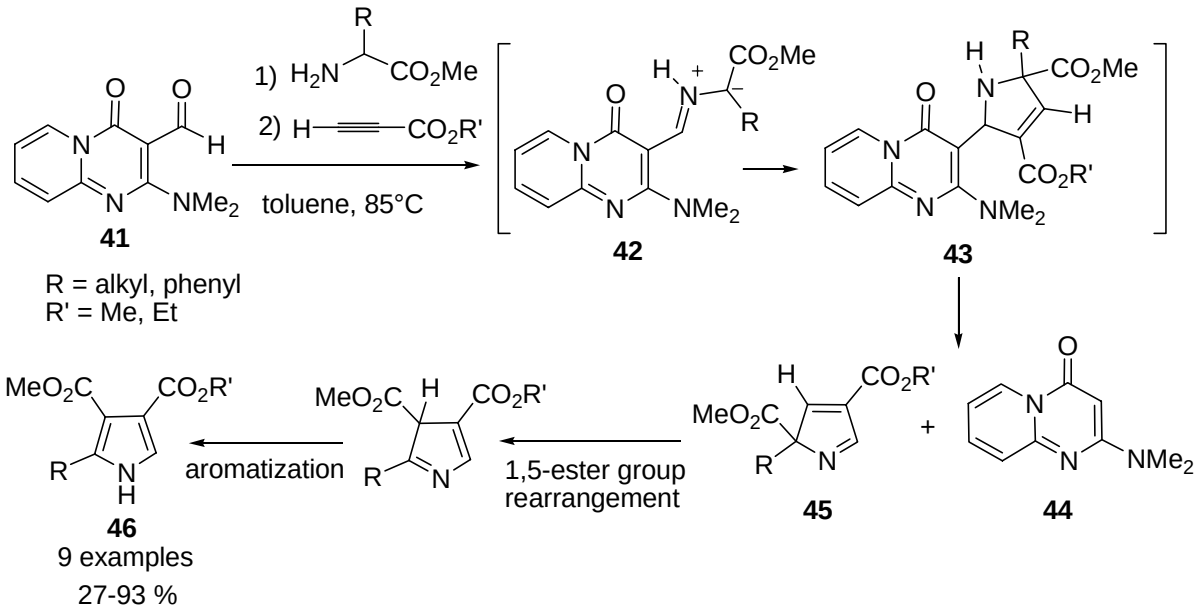
points of the imine component can be varied in this concise approach to substituted 1,2-diarylpyrroles, the other two starting materials being fixed in all reactions (Scheme 13).[20]





Scheme 13

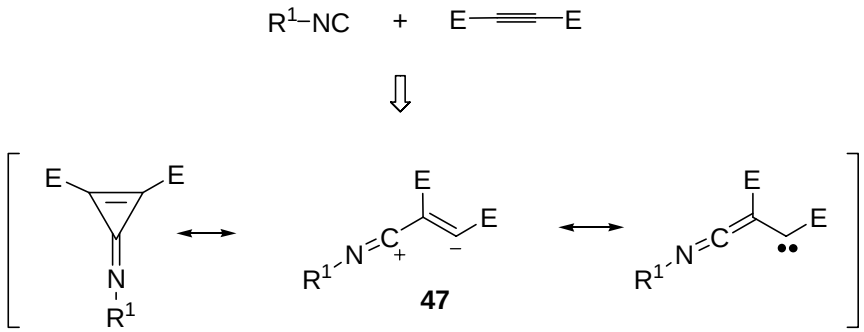
NH-azomethine ylides generated from heterocyclic aldehyde **41** and amino acid methyl esters can also enter into cycloaddition reactions with acetylenic dipolarophiles to produce functionalized 2*H*-pyrroles. In this process, there is first a 1,2-prototropic isomerization of the initially formed imines to give the corresponding azomethine ylides **42** as C-unsubstituted nitrile ylide equivalents. This is followed by a 1,3-dipolar cycloaddition with substituted alkynes. The resulting 2,5-dihydropyrrole cycloadducts **43** undergo a thermal fission reaction to give the expected 2*H*-pyrroles **45** and the parent heterocyclic system **44**. With monosubstituted acetylenic dipolarophiles, the corresponding 2*H*-pyrroles undergo a 1,5-ester group rearrangement followed by the aromatization to 1*H*-pyrrole **46**. In some cases, pyridinium *p*-toluene sulfonate (PPTS) was required for completing the reaction. This three-component reaction was carried out with a variety of amino esters and acetylenic dipolarophiles (Scheme 14).[21]



Scheme 14

MCRs based on cycloadditions of alkyne-derived zwitterionic species

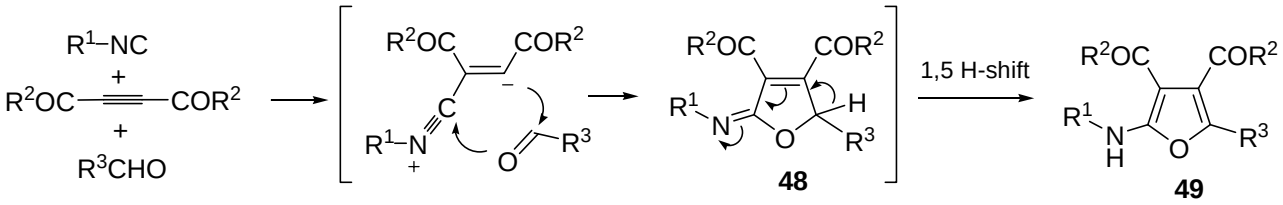
Addition of an isocyanide to an activated alkyne like DMAD generates a zwitterionic species **47** that can be trapped by a third component. This strategy has led to the development of diverse one-pot protocols for the construction of various heterocyclic compounds including furans and pyrroles (Scheme 15).[22]



Scheme 15

In his pioneering work, Nair has investigated the reactivity of the zwitterionic species against aldehydes which had the advantage of being inert toward both isocyanide and DMAD.[23] Various aldehydes, including benzaldehyde, furfural, and formaldehyde, were reacted with DMAD in refluxing benzene to generate the 1:1 zwitterionic intermediate (**47**) which was then treated with cyclohexyl isonitrile to yield a

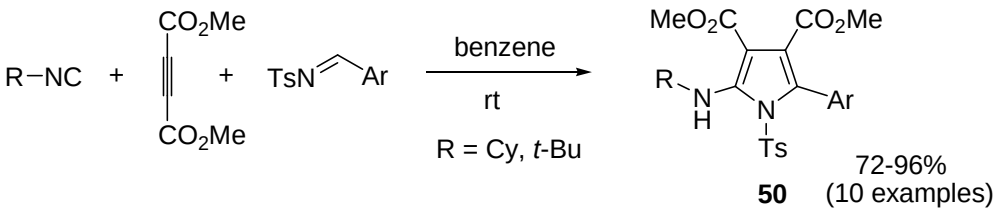
variety of 2-aminofuran derivatives **49** in moderate to good yields. A mechanistic rational for the reaction as depicted in Scheme 16 involves cycloaddition of the zwitterion to the aldehyde to give **48** which subsequently undergoes [1,5] hydrogen shift. The reaction has been applied to the synthesis of furylpyridines by 1:1:1 condensation of cyclohexyl (or *tert*-butyl) isocyanide, diaroylacetylenes, and pyridine carboxaldehydes in dichloromethane at room temperature.[24] Interestingly, related investigations by other research groups have since established new reaction conditions for this three-component reaction based on the use of "green" solvents like ionic liquids[25] or even water.[26]



Reaction conditions	R^1	R^2	R^3	Yield (examples)	ref.
A/ benzene, 80°C	Cy	OMe	aryl, furyl, H	35-74% (12)	23
B/ CH_2Cl_2, rt	Cy, *t*-Bu	OAr	pyridyl	82-93% (8)	24
C/ [bmim]BF_4, rt	Cy	OMe	aryl, furyl, thienyl, alkyl	78-89% (12)	25
D/ H_2O, rt	Cy	OMe	aryl	87-93% (10)	26

Scheme 16

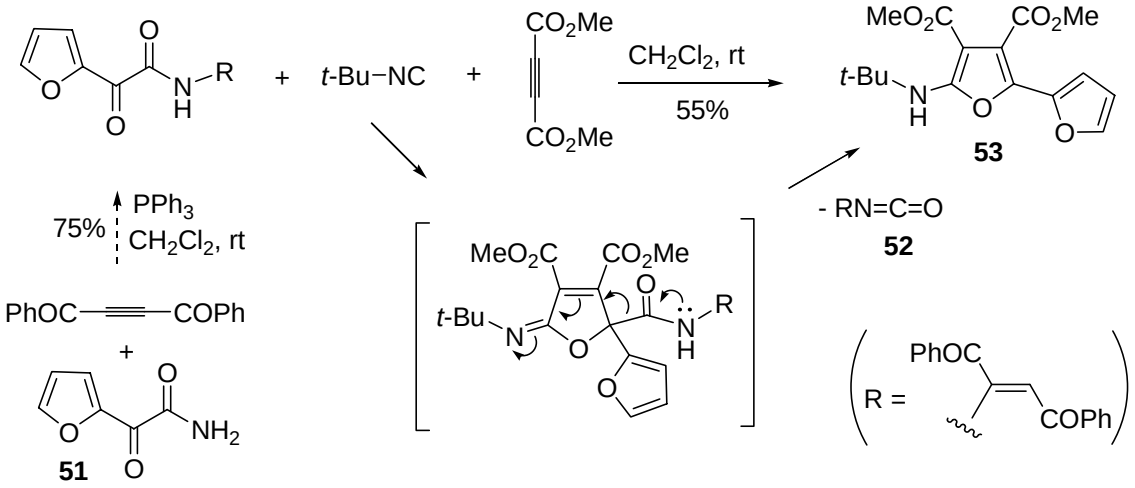
In the meantime, the group of Nair has applied the methodology to the synthesis of 2-aminopyrroles **50** by simply employing imines in lieu of aldehydes as trapping reagents, at room temperature (Scheme 17).[27]



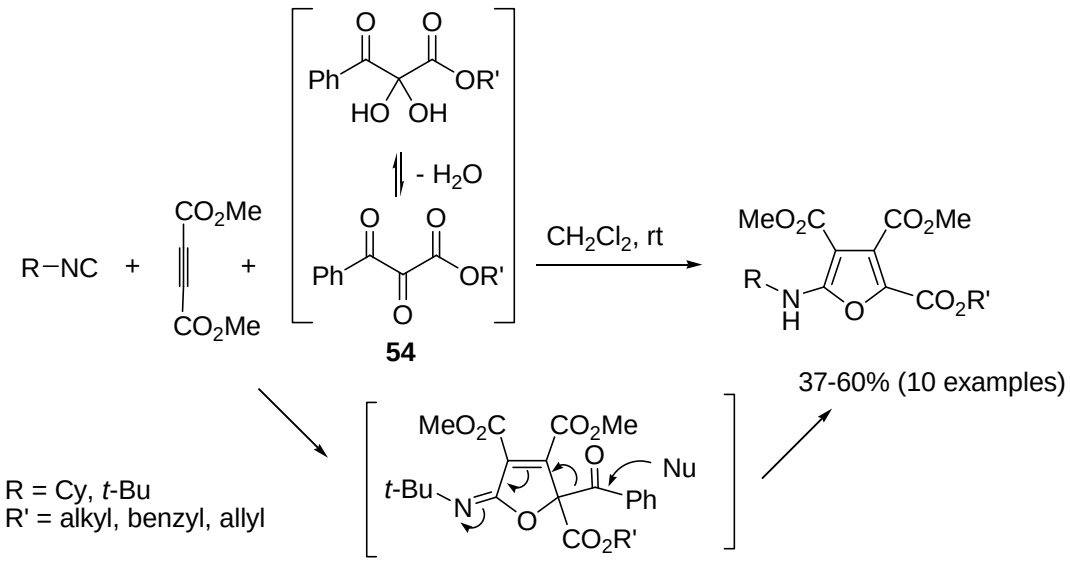
Scheme 17

Vicinal dicarbonyl and tricarbonyl compounds may also be effectively used as trapping reagents. However, despite the usefulness of these reactions, one drawback is that aromatization of the intermediate iminofurans results necessarily in the formation of side-products thus rendering the process less attractive in terms of atom economy. This may be illustrated by the production of isocyanate **52** as by-product

during the synthesis of bifurans **53** from 2-oxoacetamide derivative **51** (Scheme 18).[28] In the following example employing diketoesters **54** as trapping reagents, aromatization is the result of a debenzoylation process supposedly triggered by attack of excess isonitrile (Scheme 19).[29]

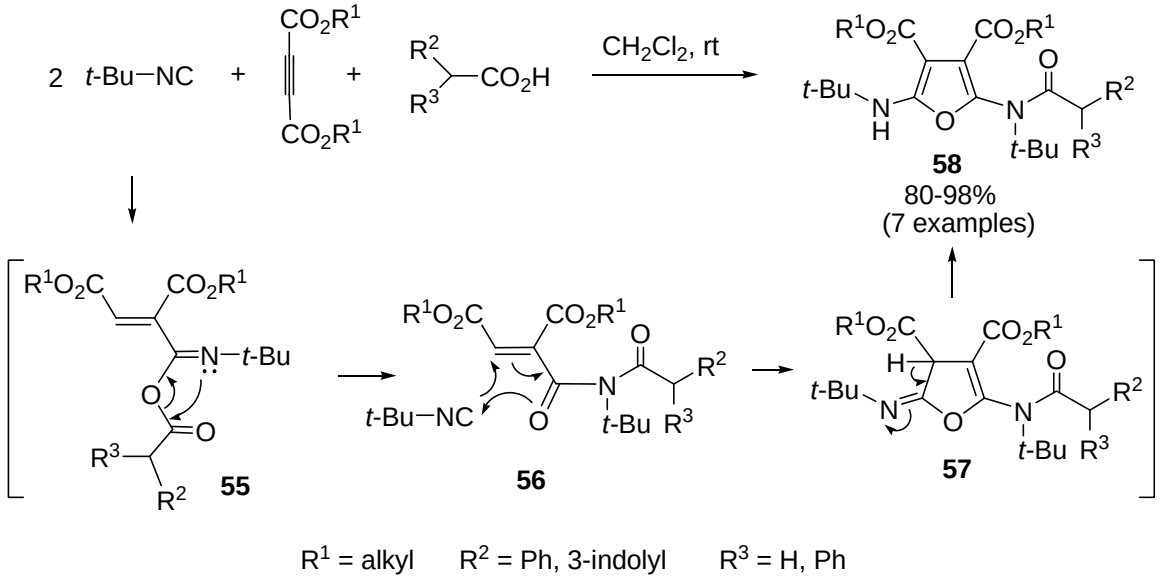


Scheme 18



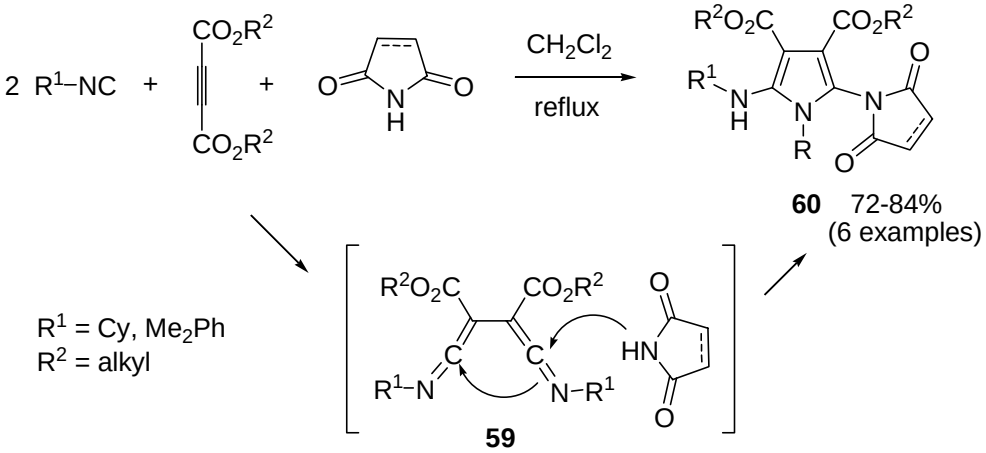
Scheme 19

It has been suggested that the zwitterionic intermediates may also be intercepted by aliphatic carboxylic acids thereby generating imidoyl carboxylate intermediates **55** that rearrange to produce acrylamides **56**. The latter is then trapped with a second isocyanide input to give intermediate iminofurans **57** which undergo isomerization. Overall this formal four-component 2:1:1 addition process furnishes a series of 2,5-diaminofurans **58** in high yields (Scheme 20).[30]



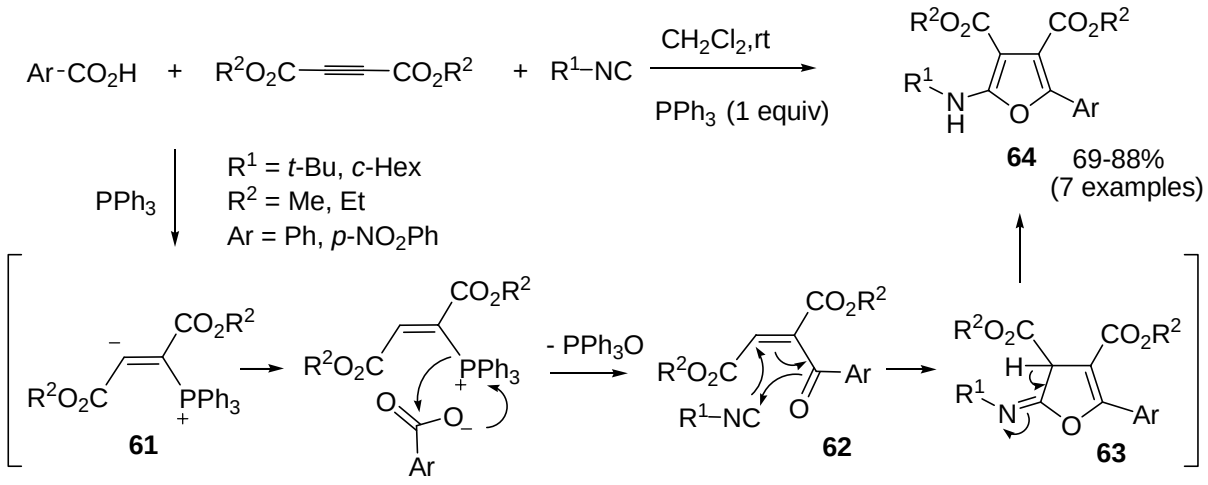
Scheme 20

The twofold addition of an isonitrile to an activated acetylene may also occur to generate a bis-ketimine intermediate of type **59** that may then react further with a fourth component. For instance, the formation of 2,5-diaminopyrroles **60** has been explained by reaction of succinimide or maleimide with such an intermediate (Scheme 21).[31]



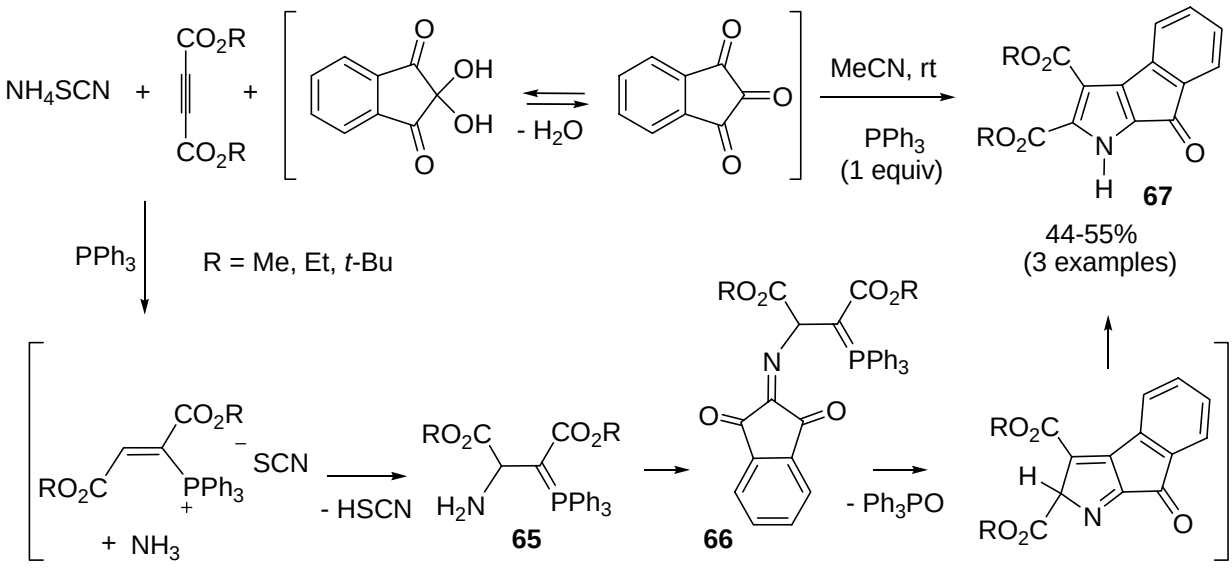
Scheme 21

Addition of triphenylphosphine to activated alkynes is another interesting way of generating zwitterionic intermediates that may be involved in the multicomponent assembling of furan and pyrrole derivatives.[22] For example, the intermediate **61** (Scheme 22) can be trapped by a carboxylic acid to produce dialkyl (*E*)-2-aroyl-2-butenedioate **62**. The latter can then react *in situ* with an isocyanide input to give the intermediate iminofuran **63** which undergoes isomerization to yield aminofurans **64** in good yields.[32]



Scheme 22

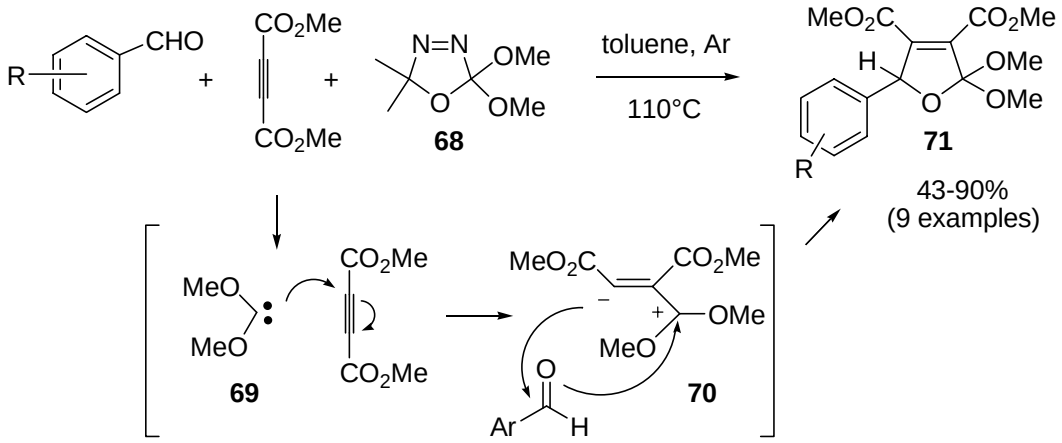
In the following example describing the synthesis of fused pyrroles **67** (Scheme 23), the zwitterionic intermediate was supposedly trapped by ammonium thiocyanate to generate phosphorane intermediate **65**. The latter would react with ninhydrin to produce phosphorane derivative **66** which would undergo intramolecular Wittig reaction followed by 1,5 H-shift to finally give pyrroles **67** in moderate yields. Ammonium acetate may also be used in place of ammonium thiocyanate in this process.[33]



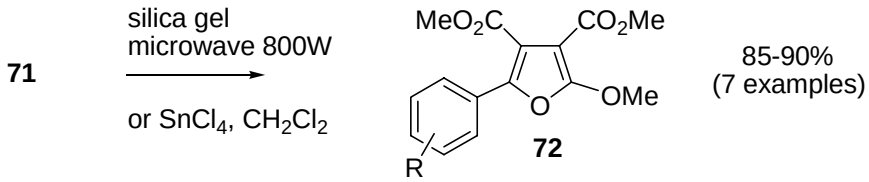
Scheme 23

The development of multicomponent reactions involving a nucleophilic carbene partner was first reported by Nair in 2001. Dimethoxycarbene **69**, generated *in situ* from the thermolysis of 2,2-dimethoxy-Δ^3-1,3,4-oxadiazoline **68** in refluxing toluene, is able to add to an activated alkyne like DMAD leading to a zwitterionic species **70** which can be trapped by diverse aromatic aldehydes (Scheme 24).[34] The resulting dihydrofuran derivatives **71** lose methanol slowly on standing for several hours at room temperature

affording furans **72**. Authors have shown that this step can be accelerated by a further treatment either under microwave irradiation or by addition of tin tetrachloride (Scheme 25).

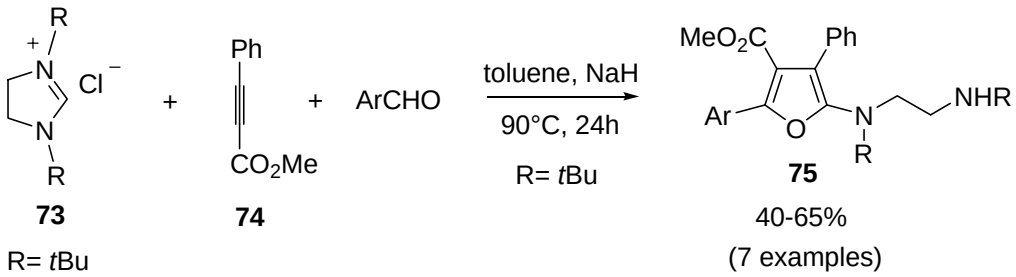


Scheme 24



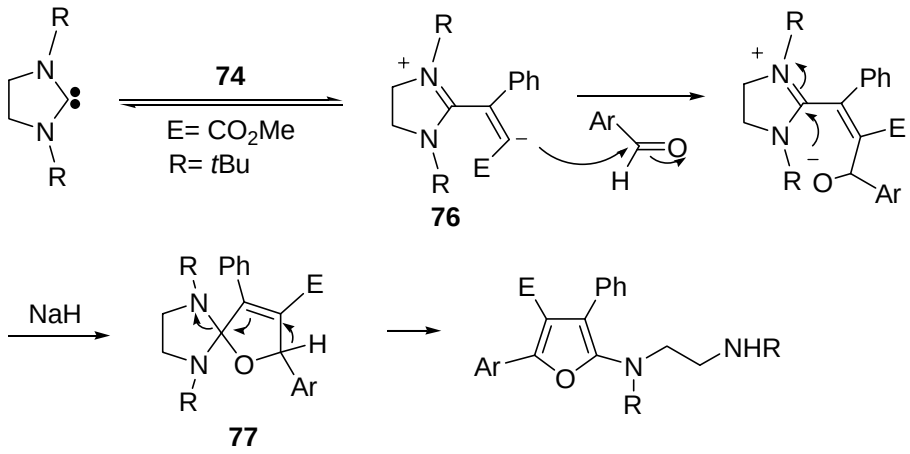
Scheme 25

N-Heterocyclic carbenes (NHCs) have known a growing interest in organic synthesis, and more particularly in the field of organometallic chemistry, since the isolation of a stable species in 1991 by Arduengo.[35] Their first application in MCRs was also reported by Nair which has developed a rapid access to a furanone moiety or to a 2-oxy maleate derivative by assembling a nucleophilic carbene, DMAD and an aromatic aldehyde. It has been demonstrated that the nature of the carbene was essential for the course of the reaction.[36] Following a similar strategy, they have further developed a rapid access to aminofurans **75** by simply replacing DMAD by methyl phenylpropiolate **74** as an activated alkyne, and using *tert*-butyl substituted imidazolin-2-ylidene **73** as a carbene precursor and an aromatic aldehyde (Scheme 26).[37]



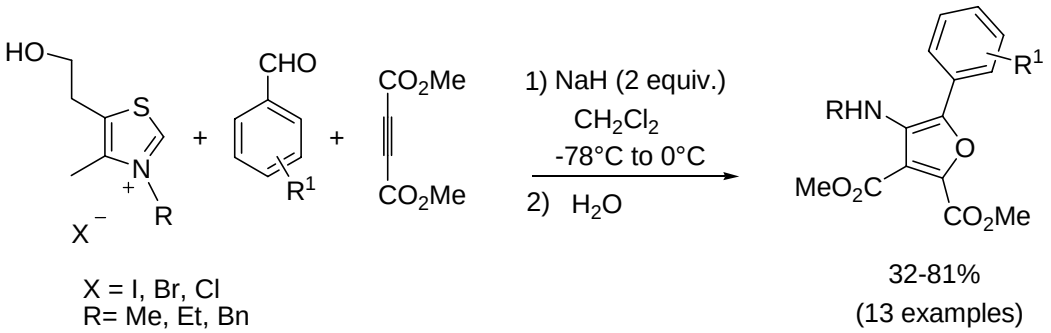
Scheme 26

The mechanism can be rationalized as follows: addition of the carbene, generated *in situ* with sodium hydride, to **74** leads to the dipole **76**. The latter undergoes a dipolar cycloaddition/cyclization with aldehyde to generate the intermediate **77** which evolves by ring opening to form aminofuran derivatives (Scheme 27).



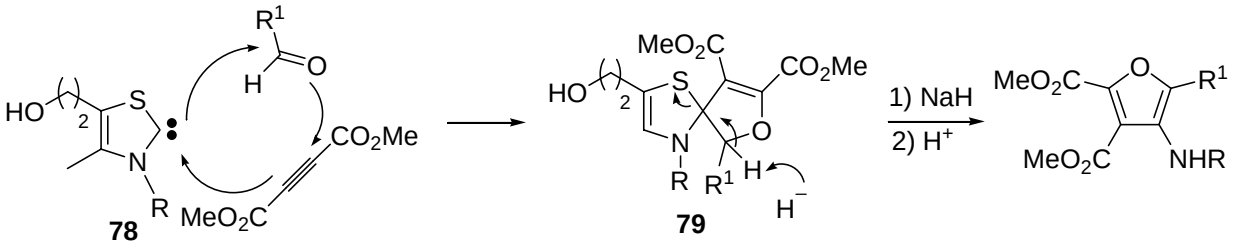
Scheme 27

Inspired by the work of Nair and co-workers, Ma has simultaneously reported a similar MCR involving a thiazolium carbene, DMAD and an aromatic aldehyde. The reaction works better with electron-deficient aldehydes than their electron-rich counterparts, giving moderate to excellent yields of aminofuran derivatives (Scheme 28).[38]



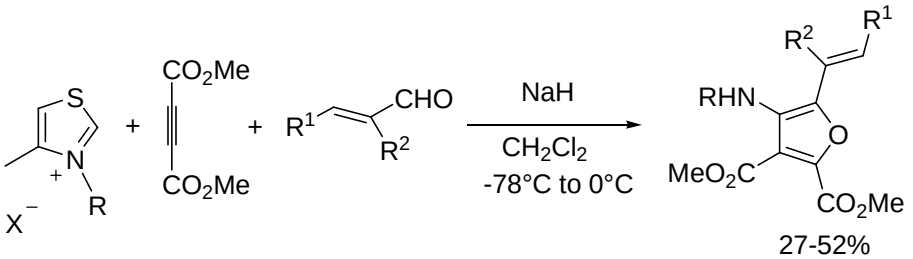
Scheme 28

Referring to previous studies by Nair,[36] Ma invokes in this case a first addition of the thiazolium carbene **78** to the aldehyde to form a zwitterion. This latter reacts with DMAD and a final cyclization step delivers the spirocycle **79**. Excess of base provokes selective ring opening of the latter, and subsequent hydrolysis of the resulting free thiol furnishes the furan derivative (Scheme 29).



Scheme 29

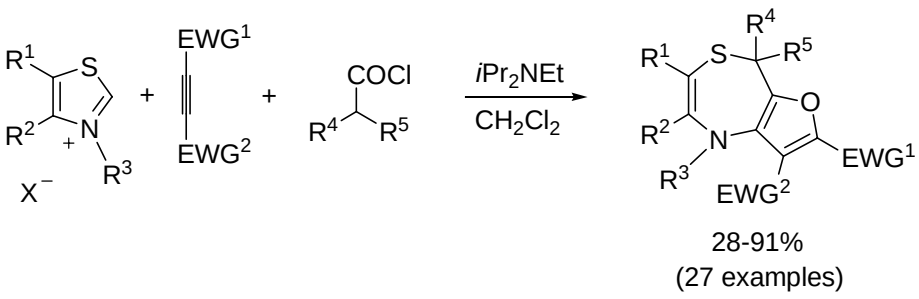
This methodology was subsequently extended to α,β-unsaturated aldehydes and to various thiazoliums salts to produce aminofurans in moderate yields (27-52%). This reaction can also be performed with terephthalaldehyde (52%) or even an aliphatic aldehyde such as butyraldehyde (42%). In this study authors have demonstrated that carbene **78** can be favorably replaced by more simple ones leading to a more efficient and economic overall process (Scheme 30).[39]



R= Me, Et, *n*-Bu
R^1= C_6H_5, 4-FC_6H_4, Me
R^2= H,Me
X= I, Br

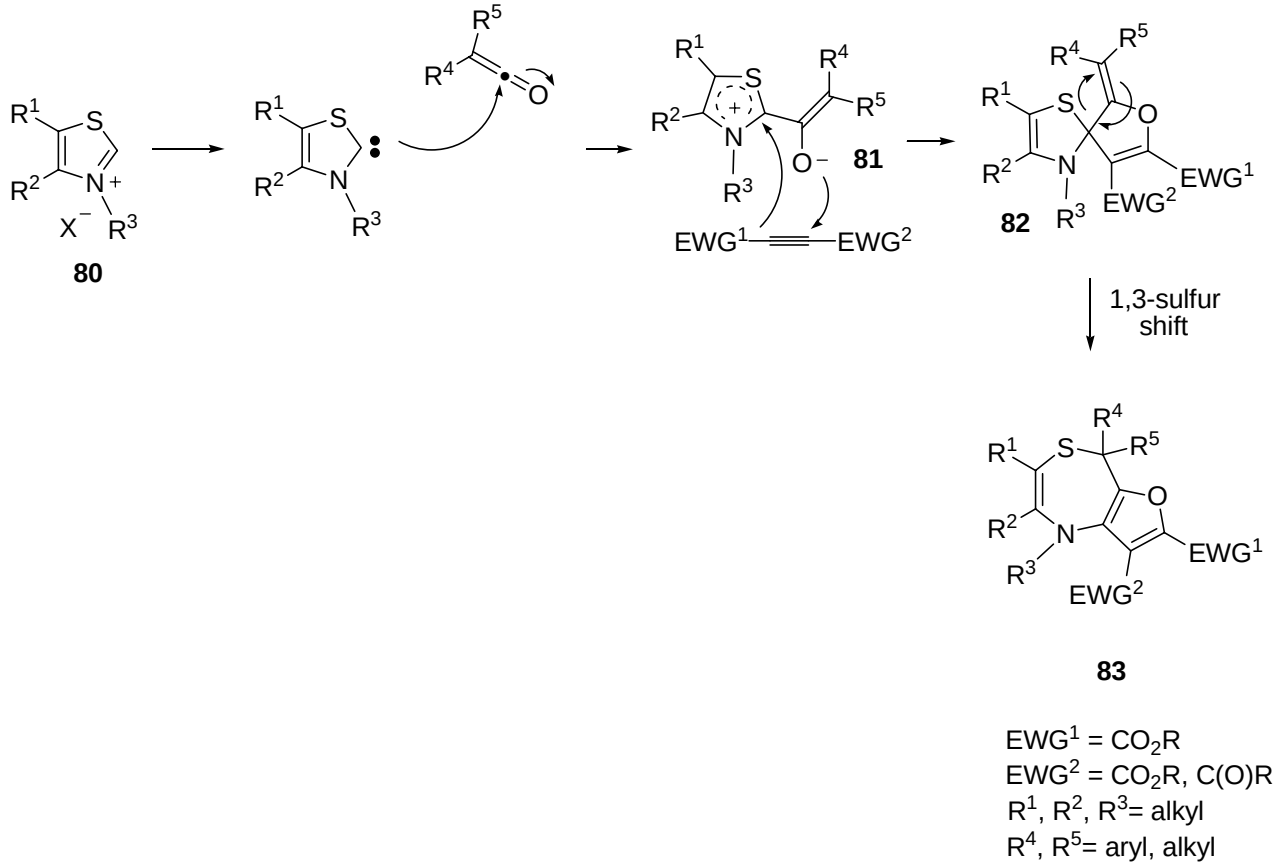
Scheme 30

Following the same strategy, Ma has developed another powerful multicomponent reaction employing a 1,1-disubstituted ketene instead of an aldehyde as electrophile. This method provides an access to unique polysubstituted furan-fused 1,4-thiazepine derivatives in excellent yields.[40] Authors have shown that NaH, used previously as base, can be efficiently replaced by diisopropylethylamine (Hunig's base) which acts to generate the carbene, as well as the ketene from acyl chloride precursor (Scheme 31).



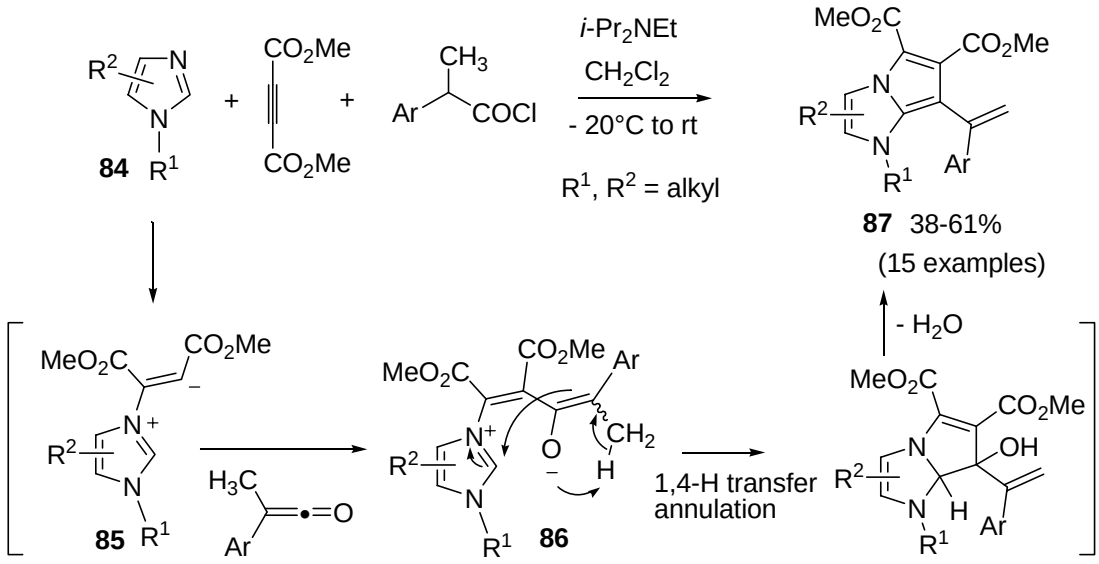
Scheme 31

A mechanistic rational for the reaction, as depicted in Scheme 32, involves generation of carbene species from thiazolium salt **80**, followed by a nucleophilic addition to the *in situ* generated 1,1-disubstituted ketene to afford the zwitterion **81**. Authors assume that for steric reasons, the latter would presumably undergo an oxa-Michael addition to the activated alkyne, followed by an intramolecular annulation to yield the spirocycle **82**. A ring expansion through a [1,3]-sigmatropic sulfur shift would finally provide the furan-fused 1,4-thiazepine **83**.



Scheme 32

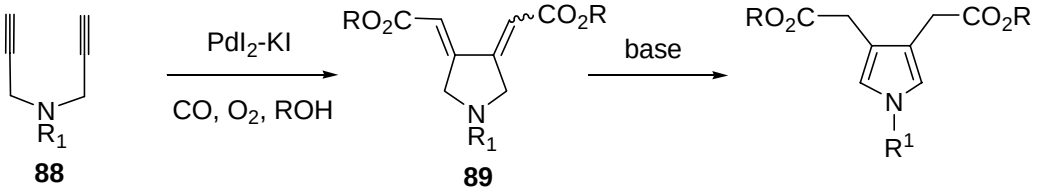
Ma and co-workers have also exploited the reactivity of ketenes to develop a similar MCR involving *N*-alkylimidazoles, DMAD and *in situ* generated aryl methyl ketenes. This reaction allows the one-step synthesis of 6-vinyl-1,3*a*-diazapentalene derivatives in moderate to good yields (Scheme 33).[41] It has been suggested that the reaction is initiated by addition of the *N*-alkylimidazoles **84** to DMAD affording the zwitterionic intermediates **85**. The latter react with aryl methylketenes, generated *in situ*, to furnish the enolates **86**. Substituted diazapentalene derivative **87** are finally obtained after a sequence involving 1,4-H transfer, attack onto the imidazolium ring, and finally elimination of water.



Scheme 33

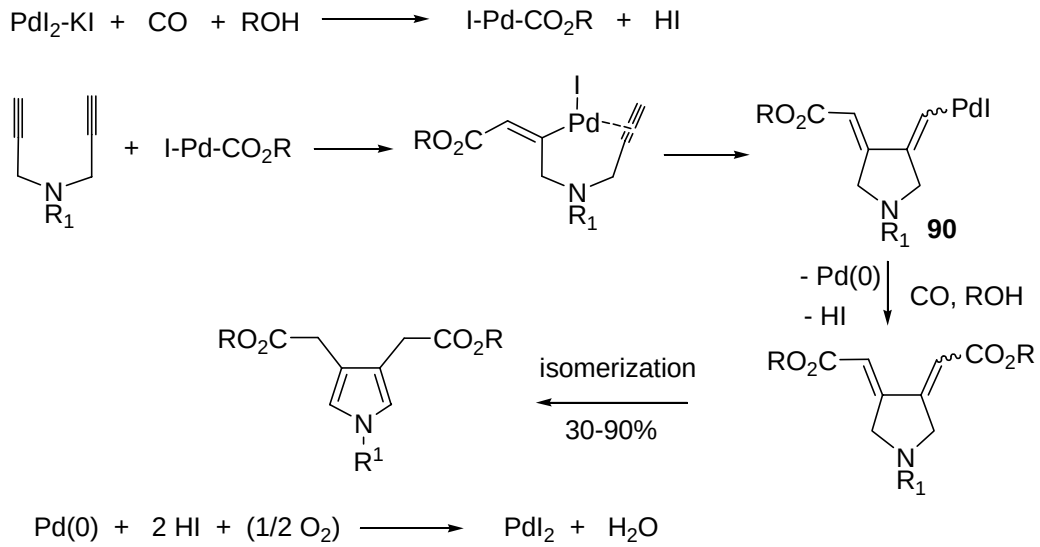
MCRs based on intramolecular cyclizations of alkynes

The PdI_2-catalyzed oxidative cyclization-alkoxycarbonylation of the readily accessible dipropargylamine and its N-substituted derivatives **88** gave 3,4-bis(alkoxycarbonyl)methylenepyrrolidines **89** (Scheme 34). This is followed by a base-catalyzed isomerization leading to the corresponding pyrroles, either in a separate step with triethylamine[42] or *in situ* with *N*,*N*-dimethylacetamide as co-solvent. [43]



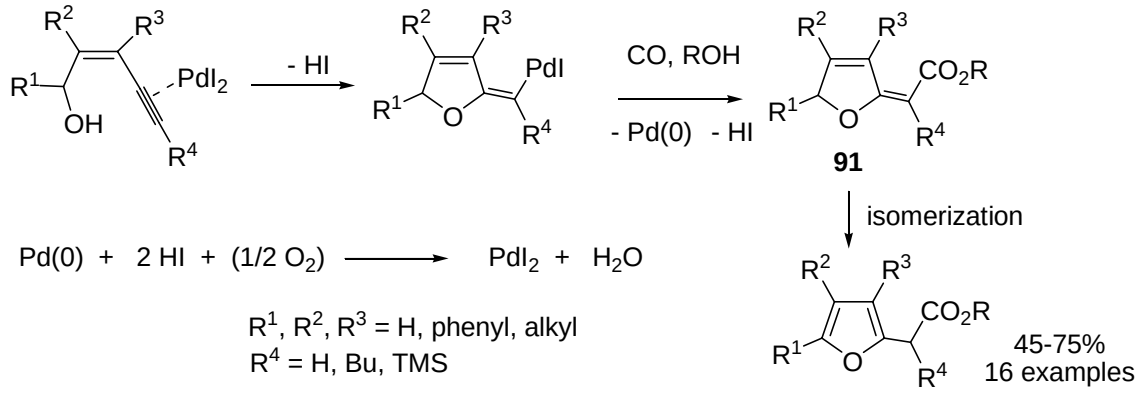
Scheme 34

This domino reaction is likely to be initiated by the formation of an I-Pd-CO_2R species. Then, a first carbonylation reaction occurs through triple bond insertion into the above palladium species and is followed by ring closure through an intramolecular Heck reaction. Alkoxycarbonylation of the resulting vinylpalladium intermediate finally leads to functionalized 1,3-bis-exocyclic dienic derivatives **90**. Reoxidation of the Pd(0) species resulting from this process occurs through oxidative addition by I_2 generated *in situ* through oxidation of HI by O_2 (Scheme 35).



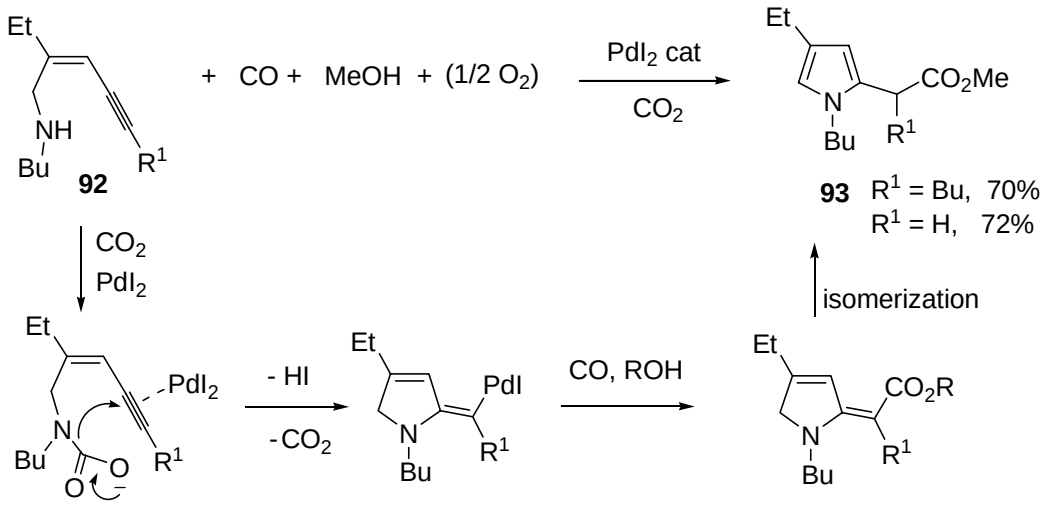
Scheme 35

When a similar reaction was performed by the same group on (*Z*)-2-en-4-yn-1-ols, a quite different reaction course was observed, since a PdI_2-catalyzed intramolecular attack of the oxygen nucleophile first occurs affording a vinylpalladium intermediate. This is followed by an alkoxycarbonylation. The initially non aromatic precursors **91** then undergo an *in situ* isomerization to give the corresponding furans (Scheme 36).[44]



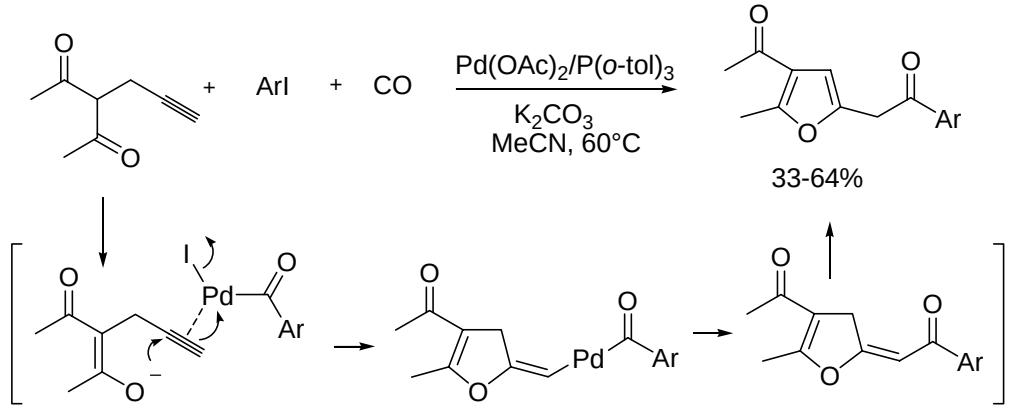
Scheme 36

An oxidative carbonylation reaction was also performed on the (*Z*)-2-en-4-ynylamines leading to the corresponding pyrrole-2-acetic esters in low yields. This is due to the basicity of enynamines **92**, which inhibits the cyclization/alkoxycarbonylation process by trapping the HI needed for the reoxydation of the palladium catalyst. The pyrrole derivatives **93** were obtained in good yields when the reaction was performed in the presence of excess of carbon dioxide. In this case, the oxidative carbonylation process may take place, the formation of a carbamate species buffering the basicity of the amino group (Scheme 37).[45]



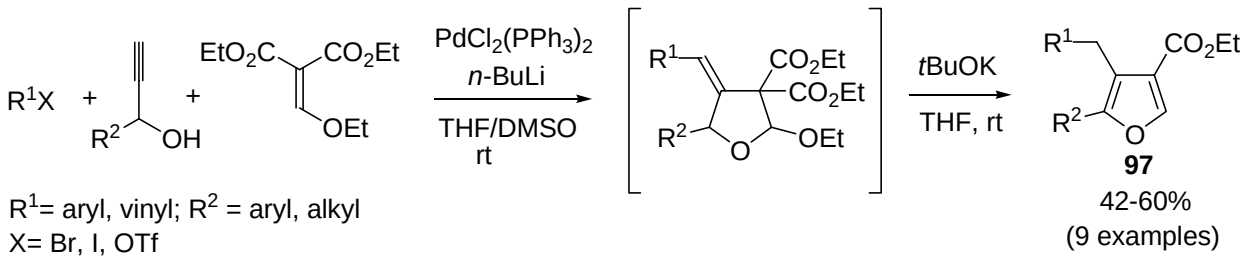
Scheme 37

The cyclization of acetylenes bearing a carbo- or heteronucleophile may be promoted by organopalladium complexes. The latter are in most cases generated *in situ* from oxidative addition of a palladium(0) complex to an unsaturated halide or triflate, but acylpalladium species may also be generated in the presence of carbon monoxide. This type of annulation involves an attack of the nucleophile onto the alkyne moiety from the opposite side of the activating σ-unsaturated palladium species. A reductive elimination gives the functionalized cyclization product and regenerates the catalyst.[46] For instance, the reaction of 3-acetyl-5-hexyn-2-one with various unsaturated halides and triflates under a CO atmosphere provided a valuable route to acetylfuran derivatives (Scheme 38). *Trans* addition of the oxygen nucleophile and the acylpalladium complex across the triple bond was followed by an isomerization of the *exo*-cyclic double bond to furnish the corresponding aromatized derivatives in moderate to good yields.[47]



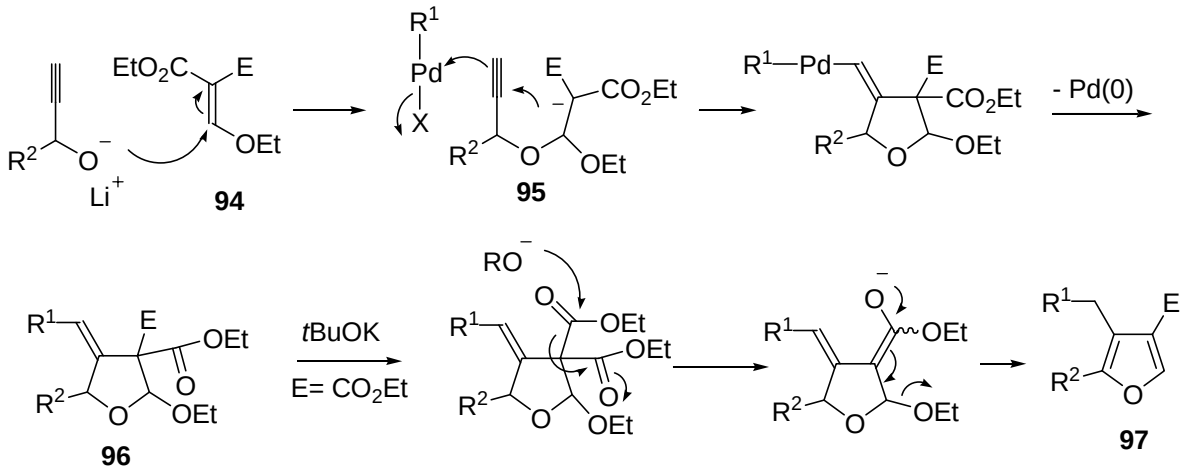
Scheme 38

Balme and co-workers reported the synthesis of highly substituted furans **97** by means of a MCR based on a related palladium-mediated cyclization process involving a carbonucleophile (Scheme 39).[48]



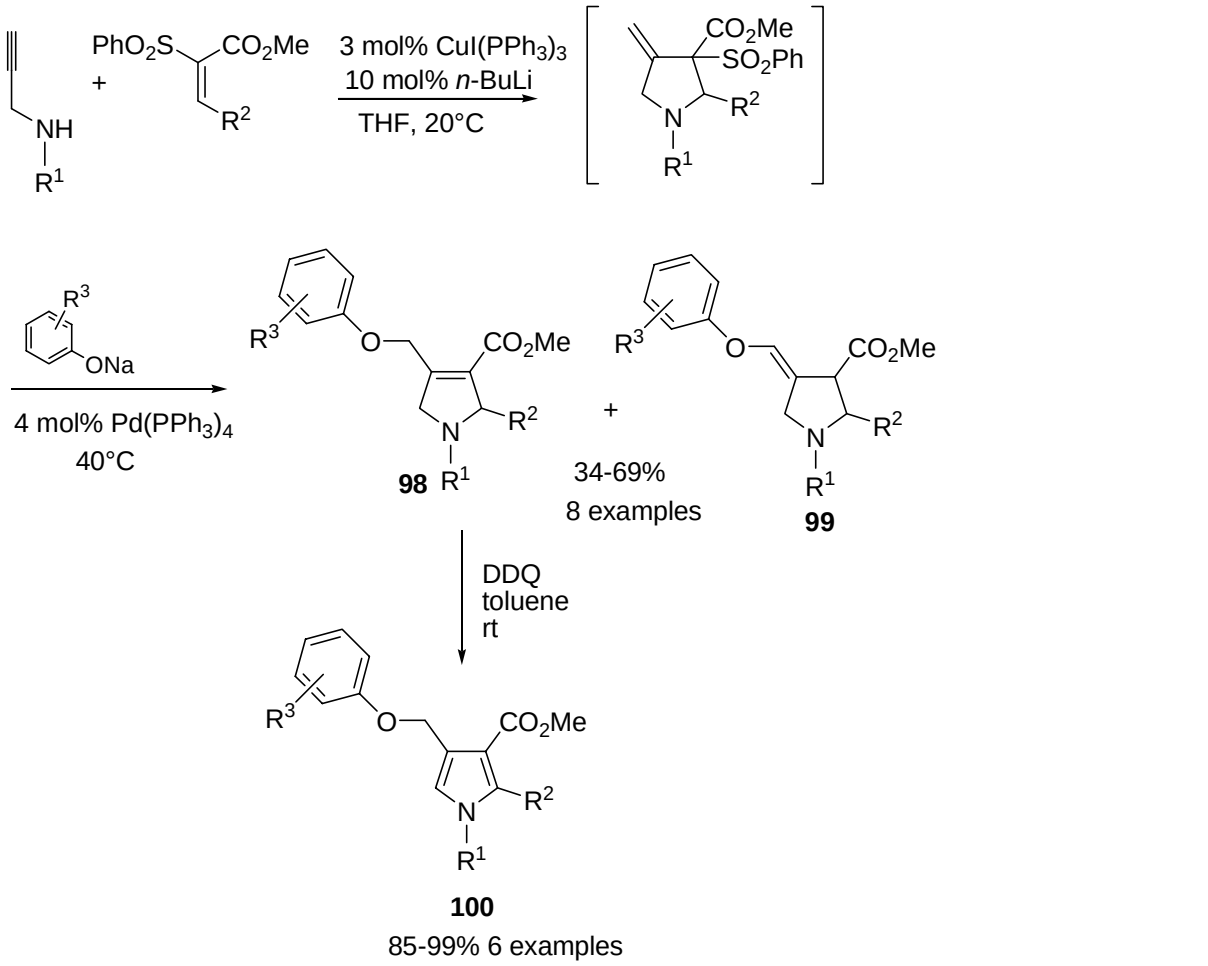
Scheme 39

In this reaction, formation of enolate **95** by the initial 1,4-addition of a propargyl lithium alkoxide to the conjugate acceptor **94** is followed by a palladium-mediated cyclization reaction involving the unsaturated halide. The resulting tetrahydrofurans **96** can be easily converted into furan derivatives **97** by simple treatment with a slight excess of potassium *t*-butoxide, via a base-induced eliminative decarboxylation and double bond isomerization (Scheme 40).



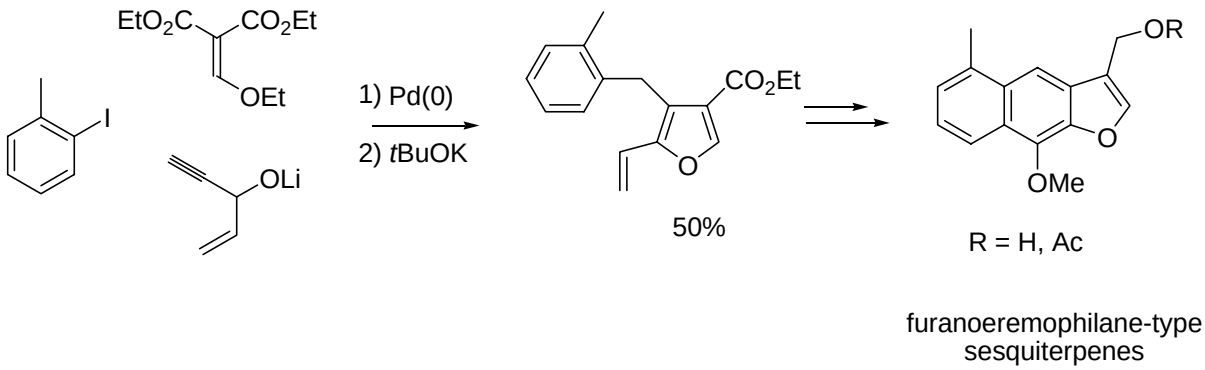
Scheme 40

A similar strategy was employed in order to obtain the pyrrole nucleus. To this end, Balme and coworkers have developed a MCR based on a sequence of two metal-catalyzed reactions. In the first step, reaction of a propargylamine with a Michael acceptor bearing a sulfonyl group, under base and copper complex catalysis, leads to a methylene pyrrolidine. When the reaction has gone to completion, *in situ* addition of sodium phenoxide and of 4 mol% of $Pd(PPh_3)_4$ leads to the displacement of the allylic sulfone via a π-allylpalladium intermediate. This methodology allows the one-pot synthesis of a mixture of 4-(phenoxymethyl)-3-pyrrolines **98** and their isomeric 4-(phenoxymethylene)-3-pyrrolidines **99**.[49] Authors have established, in a following paper, that pyrrolines **98** can be easily transformed into pyrrole derivatives **100** upon treatment with DDQ (Scheme 41).[50]



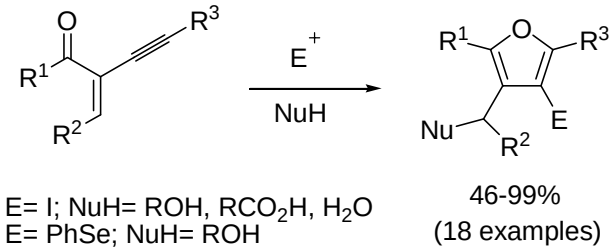
Scheme 41

The MCR involving propargylic alcohols, as developed by Balme's group, has been utilized by Morimoto to develop highly convergent total syntheses of 13-hydroxy- and 13-acetoxy-14-nordehydrocacalohastines, two novel modified furanoeremophilane-type sesquiterpenes with potential biological activities (Scheme 42).[51]



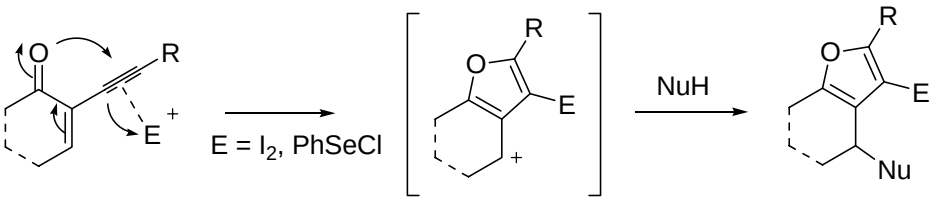
Scheme 42

A new and efficient MCR leading to highly substituted furans has been developed by Larock and co-workers using 2-(1-alkynyl)-2-alken-1-ones, various nucleophiles (alcohols, H_2O, 1,3-diketones and carboxylic acids) and diverse electrophiles (iodine, NIS, PhSeCl) (Scheme 43).[52]



Scheme 43

To rationalize the reaction, the following mechanism is proposed: after nucleophilic attack of the oxygen of the ketone onto the triple bond activated by the electrophile, a carbocation was generated which can be intercepted by an external nucleophile (Scheme 44).

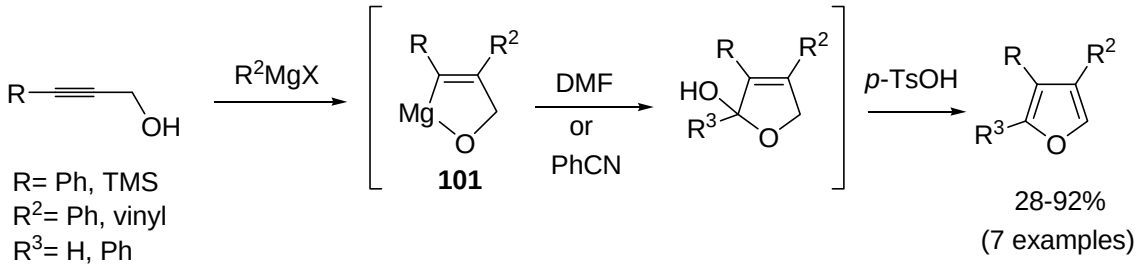


Scheme 44

Simultaneously, a similar work was reported by Liu and co-workers giving access to the same kind of furan derivatives.[53]

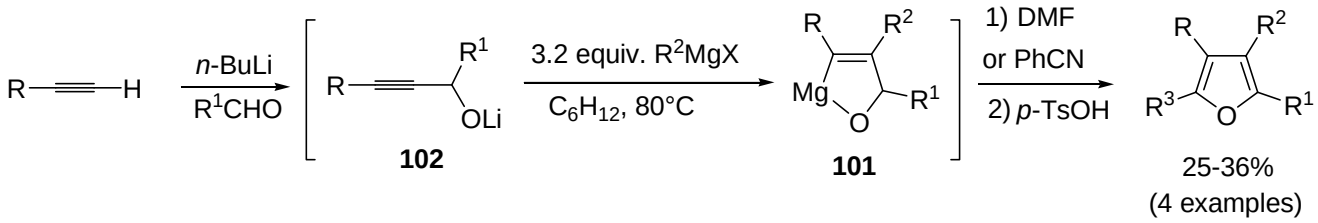
MCRs based on carbometallations of alkynes

The group of Fallis has described a new access to substituted furans via a magnesium-mediated carbometallation of a propargylic alcohol.[54] Treatment of the latter with an excess of a Grignard reagent (3.2 equiv.), in refluxing cyclohexane, generates the intermediate magnesium chelate **101** which can be trapped either by DMF or benzonitrile. The resulting lactols can be easily transformed into furans by a further acidic treatment. In this process, authors postulate a regiocontrolled *anti*-addition of the R^2 group (vinyl or aryl) with respect to the formation of the carbon-magnesium bond leading to the metallacycle **101** (Scheme 45).



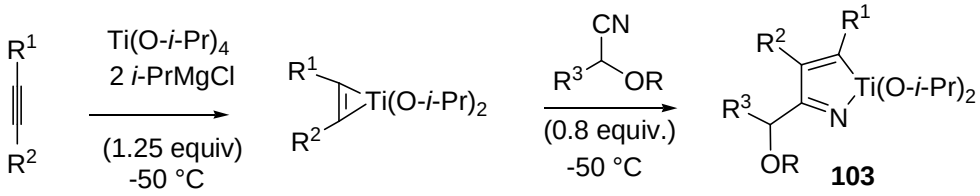
Scheme 45

To extend the versatility of this reaction, another process has been developed to permit introduction of substituents at the C-5 position of the furan. Thus, the lithium alkoxide **102,** prepared by addition of an alkynyl lithium salt to an aldehyde, was reacted with vinyl magnesium chloride leading to chelate **101** by a transmetallation step, the latter being trapped as previously described. However, this strategy gave relatively low yields of furan derivatives (Scheme 46).



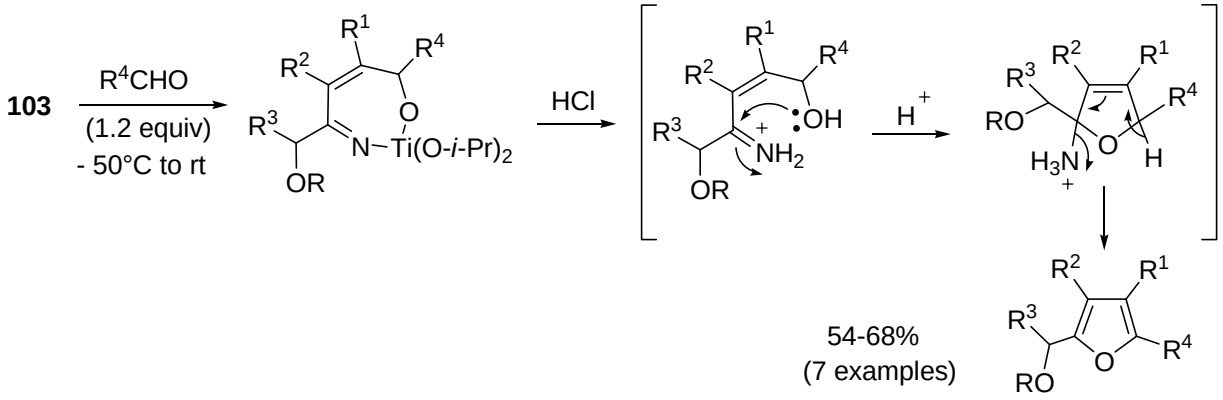
Scheme 46

Development of a new MCR involving the use of azatitanacyclopentadiene as one partner of the reaction has been reported by Sato and Urabe. Authors have obtained fully substituted furan or pyrrole derivatives depending on the nature of the electrophile (aldehyde or nitrile) used to trap the metallacyclopentadiene. The cornerstone of this strategy relies on the generation of the azatitanacyclopentadiene **103** reputed unsuccessful with alkanenitrile or benzonitrile. To overcome this difficulty, Sato and Urabe have used α-heterosubstituted nitriles which allow the formation of **103** in good yields (Scheme 47).[55]



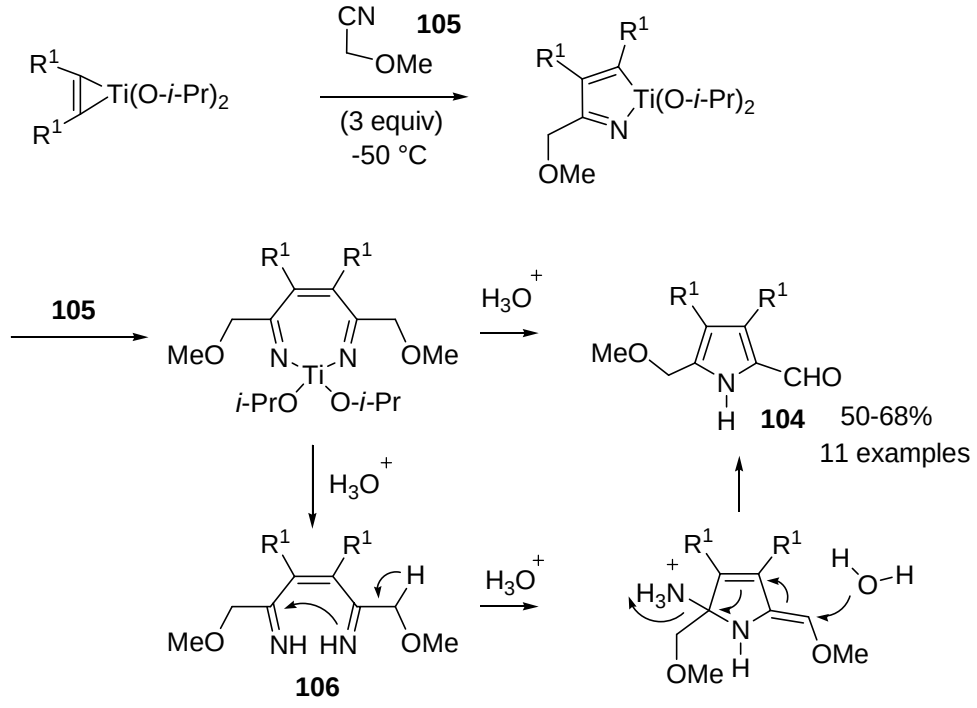
Scheme 47

The carbon-titanium bond can react with an aromatic or an aliphatic aldehyde to provide, after quenching with HCl, polysubstituted furans. A rational mechanism is illustrated in Scheme 48:



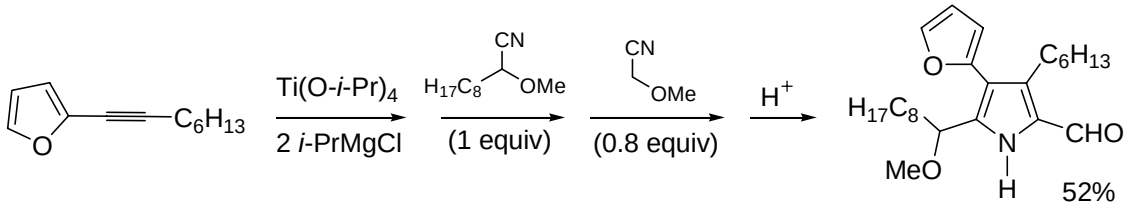
Scheme 48

This strategy can also be applied to the synthesis of pyrrolecarboxaldehydes **104**. It has been observed that addition of three equivalents of nitrile **105** to the acetylene-titanium complex led after acidic workup to a pyrrole derivative. Authors have presumed the formation of a diazatitanacycloheptatriene via a double addition of the nitrile **105** to the alkyne-titanium complex, which was converted to diimine **106** by hydrolysis. This step was followed by a ring closure via an enamine intermediate, and subsequent elimination of the ammonium group with a simultaneous addition of water to the vinyl ether moiety, giving rise to the pyrrolecarboxaldehyde **104** (Scheme 49).



Scheme 49

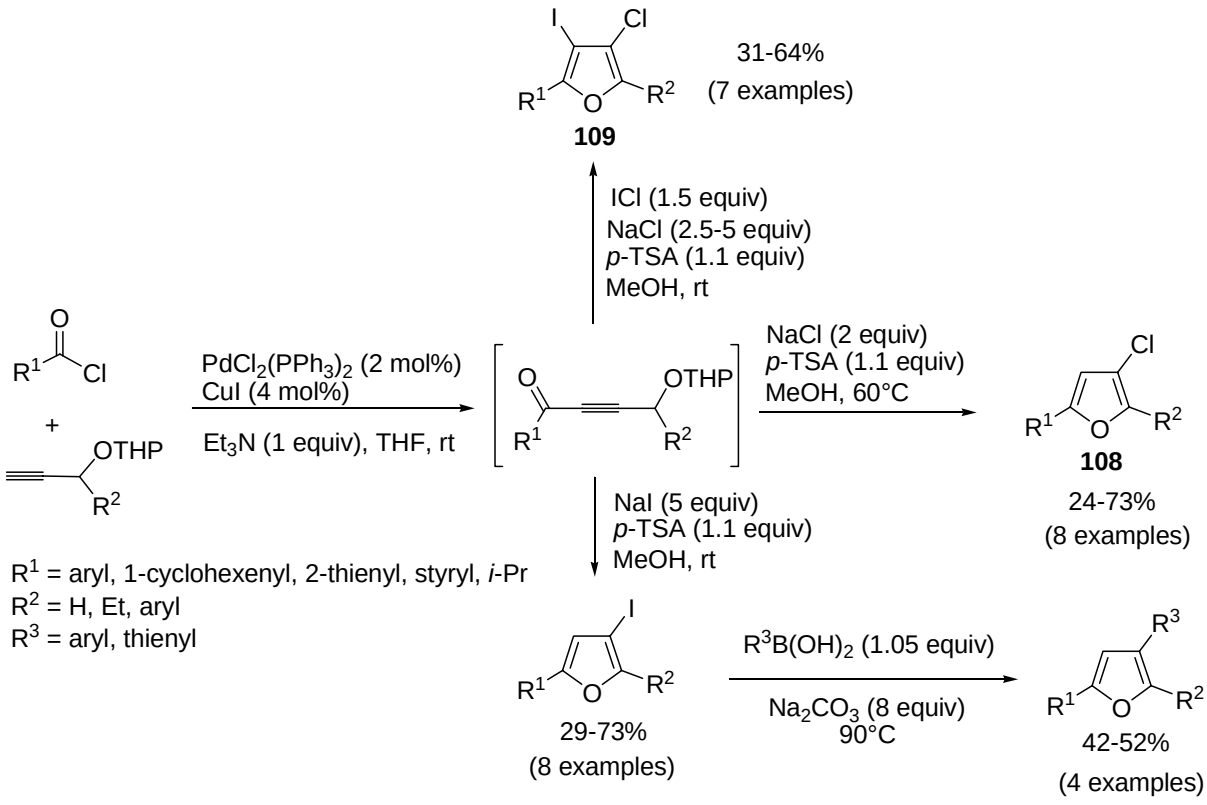
However, when the reaction was performed with an unsymmetrical alkyne, a 1:1 ratio of two regioisomers of **104** was obtained, demonstrating that the cyclization could not be controlled by the substituents on the alkyne partner. Interestingly, when two different nitriles were sequentially added, the reaction led to a single regioisomer even when an unsymmetrical alkyne was used as starting material. This efficient four-component reaction allowed the selective formation of pyrroles having four different substituents, as illustrated in one example in Scheme 50.



Scheme 50

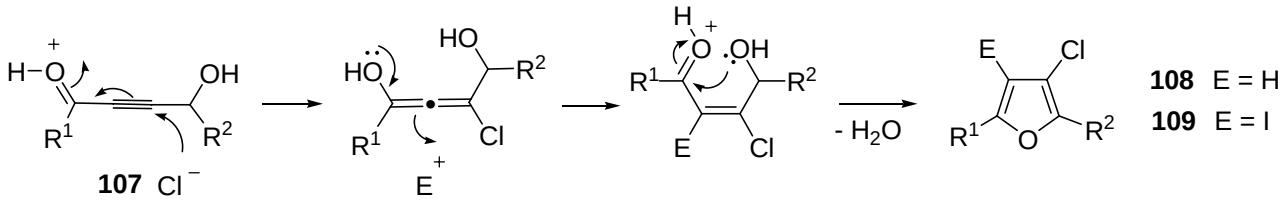
Miscellaneous

Müller and co-workers have developed a new access to 3-halofurans and 3-chloro-4-iodofurans via a MCR involving an acid chloride, a protected propargyl alcohol and a halide salt. Taking advantage of the presence of the halide in the synthesized furan substrate, this methodology has been easily extended to a four-component reaction, by sequential, *in situ* addition of an arylboronic acid to the resulting 3-iodofuran (Scheme 51).[56]



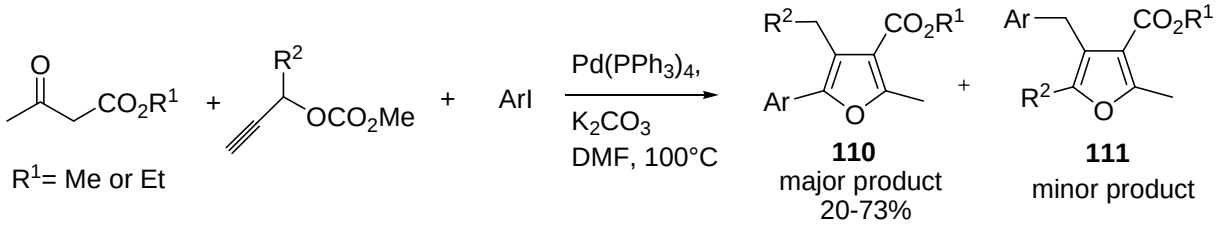
Scheme 51

The first step of this MCR was based on a Sonogashira coupling reaction between an acid chloride and a THP-protected propargyl alcohol in the presence of only one equivalent of triethylamine. After completion of this coupling reaction, the reaction medium was virtually free of base, and was subjected to a sequential addition of p-TSA and NaCl. Acidic conditions were used to liberate the hydroxy function giving rise to a γ-hydroxy alkynone **107**, which was subjected to an acid-catalyzed Michael addition of chloride anion and subsequent cyclocondensation to furnish the 3-chlorofuran derivatives **108**. Furthermore, when iodine monochloride was used instead of sodium chloride, very useful chloro(iodo) furans **109** were obtained in a one-pot operation (Scheme 52).

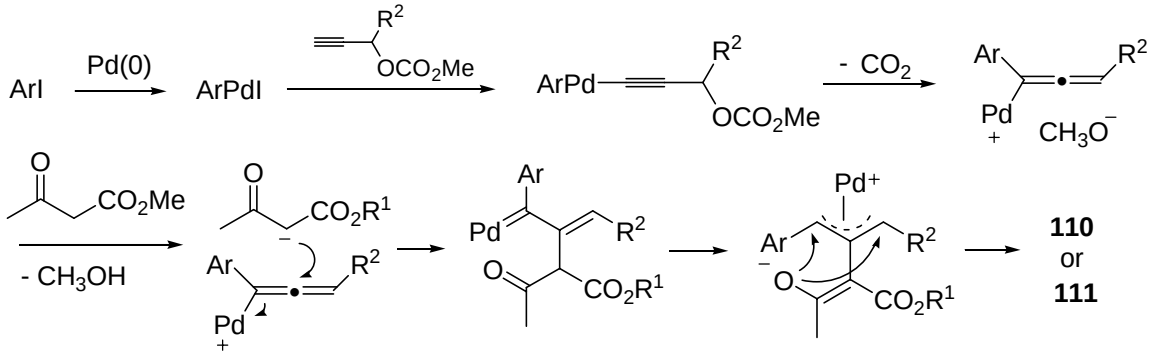


Scheme 52

A palladium-mediated three-component cyclization-coupling reaction has been elaborated by Liang and co-workers in order to synthesize furan derivatives (Scheme 53).[57] This strategy relies on the combination of three readily available and inexpensive materials, β-ketoester, propargylcarbonate and aryl iodide. When the reaction was conducted with a primary carbonate (R^2 = H), excellent yields and regioselectivities were obtained in favor of furan **110**. Unfortunately, when a secondary carbonate (R^2 = Me) was used, mixtures of isomeric furans **110** and **111** were obtained. Authors have proposed a tentative mechanism as depicted in Scheme 54.

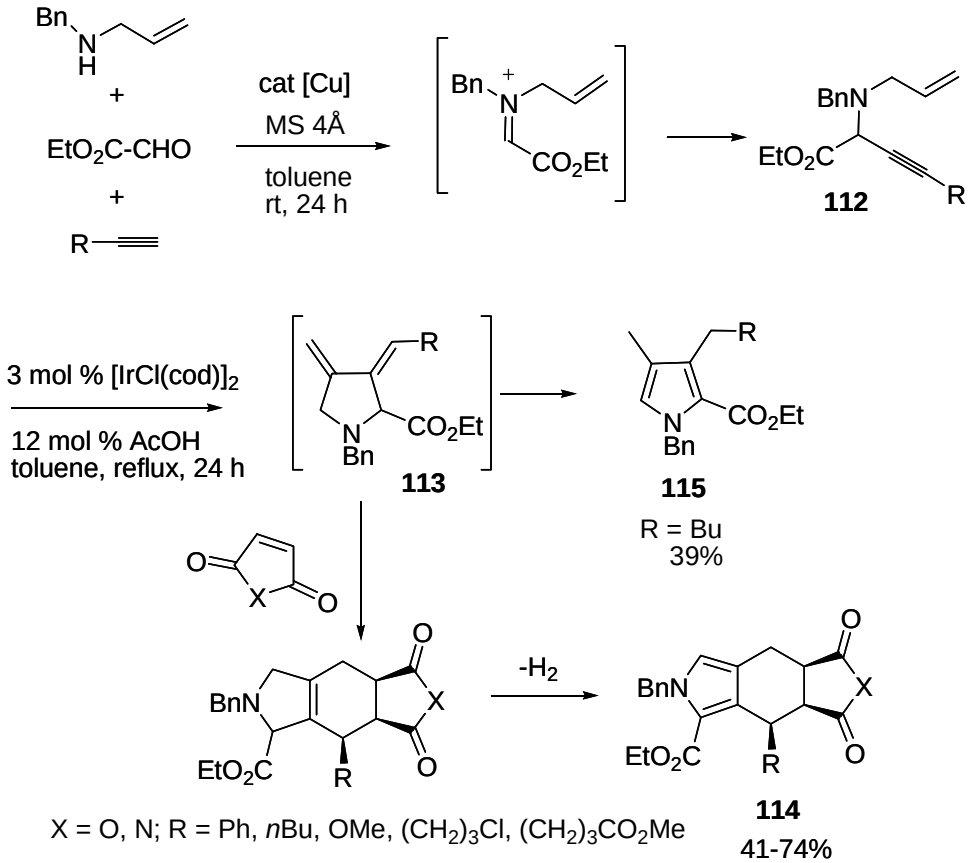


Scheme 53



Scheme 54

Nucleophilic additions of alkynes to imines generate propargylamines that are widely used as intermediates for the preparation of complex amino derivatives.[58] Recently, an efficient copper-catalyzed three-component coupling reaction of alkynes, aldehydes and amines to generate propargylamines in good yields was developed.[59] According to this report, a novel four-component coupling strategy to prepare polycyclic pyrrole-2-carboxylates was explored. This approach first involves a Cu-catalyzed Mannich condensation of *N*-benzylallylamine, ethyl glyoxalate, and terminal alkynes. This is followed by Ir-catalyzed cycloisomerization of the resulting glycinate-tethered 1,6-enynes **112** in the presence of reactive dienophiles which trap the newly formed exocyclic diene intermediates **113** via Diels-Alder reactions. Finally, a dehydrogenative aromatization of the resulting 3,4-dehydroprolines by Ir species lead to polycyclic pyrrole-2-carboxylates **114**. When the Ir-catalyzed cycloisomerization was performed in the absence of a dienophile, the pyrrole-2-carboxylate **115** was obtained, albeit in rather low yield (Scheme 55).

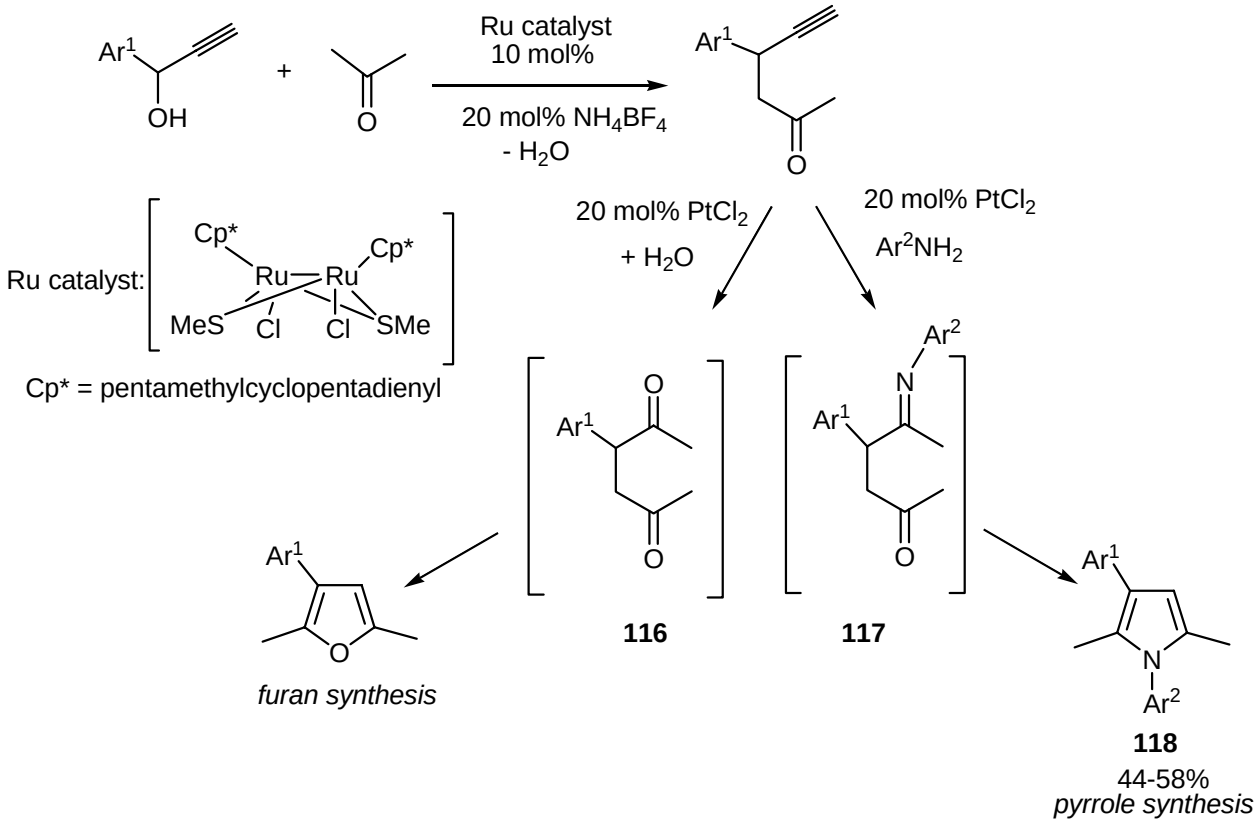


Scheme 55

Syntheses of pyrroles or furans starting from Paal-Knorr cyclocondensation of 1,4-dicarbonyl systems are among the most common approaches to these heterocycles.[60] In this context, an original development of ruthenium- and platinum-catalyzed sequential reactions to the synthesis of substituted furans and pyrroles

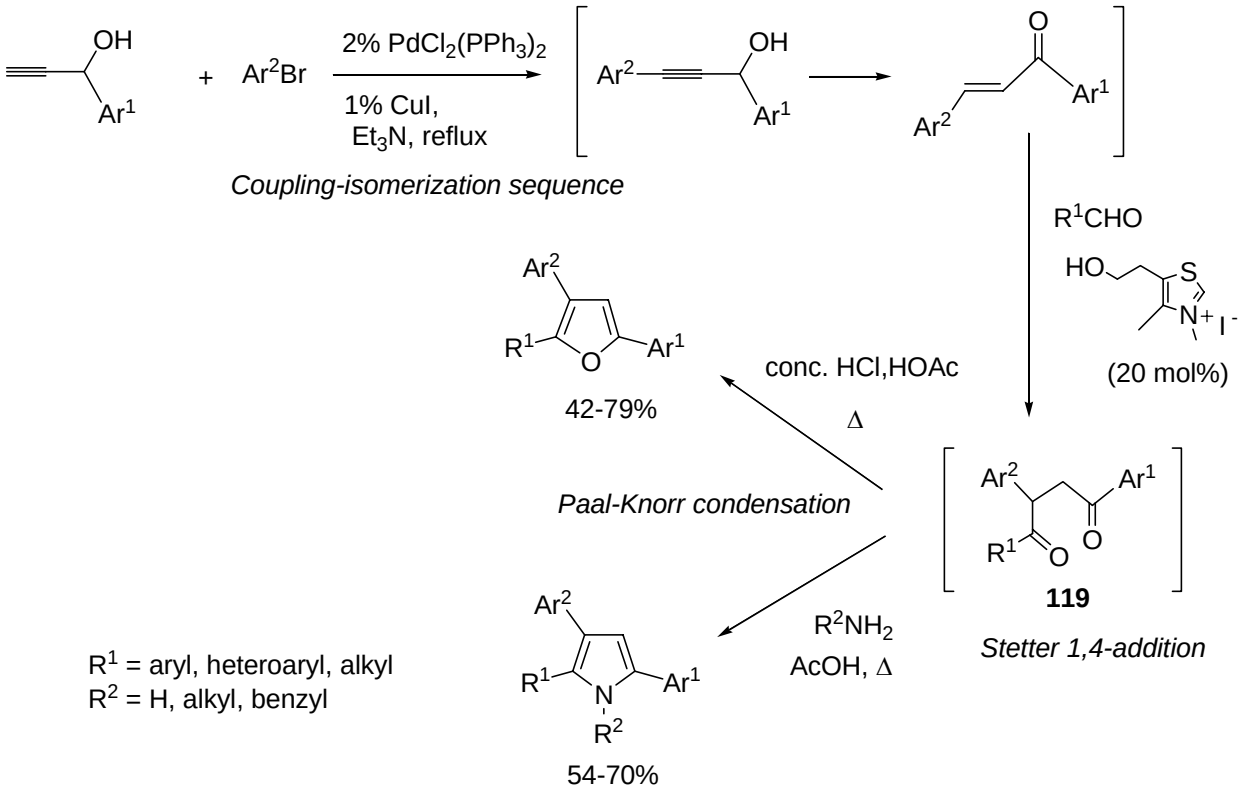
has been recently reported.[61] The method involves a ruthenium-catalyzed propargyl alkylation of propargylic alcohols with acetone leading to the corresponding γ-ketoacetylene with production of water during the process. Regioselective hydration of the alkyne then occurs by the produced water in the presence of catalytic amount of $PtCl_2$ and the resulting 1,4-diketone **116** undergoes an *in situ* intramolecular cyclization promoted by the platinum catalyst.

When the above Ru-Pt bimetallic reaction was carried out in the presence of various aniline derivatives, the corresponding substituted pyrroles **118** were obtained with complete regioselectivity via the initially formed imine **117** (Scheme 56).



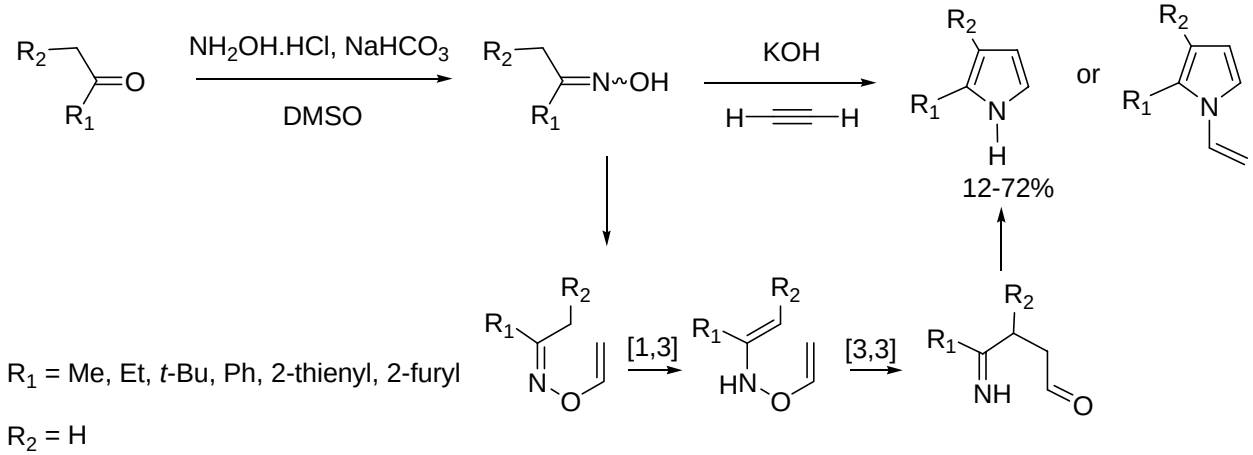
Scheme 56

Another elegant multicomponent strategy for the preparation of various furans and pyrroles via the initial formation of 1,4 dicarbonyl systems has been recently reported.[62] This approache takes advantage of a previously developed palladium-copper coupling-isomerization sequence of electron-deficient aryl or heteroaryl halides and 1-aryl prop-2-yn-1-ols leading to the corresponding chalcones.[63] Thus, by combining the above sequence with a Stetter reaction, the resulting 1,4-diketones **119** can be engaged in a subsequent Paal-Knorr cyclocondensation, leading to various substituted furans or pyrroles, depending on the reaction conditions: acidic condition for the furan synthesis, addition of primary amines or ammonium chloride in the presence of acetic acid for pyrrole synthesis (Scheme 57).[64]



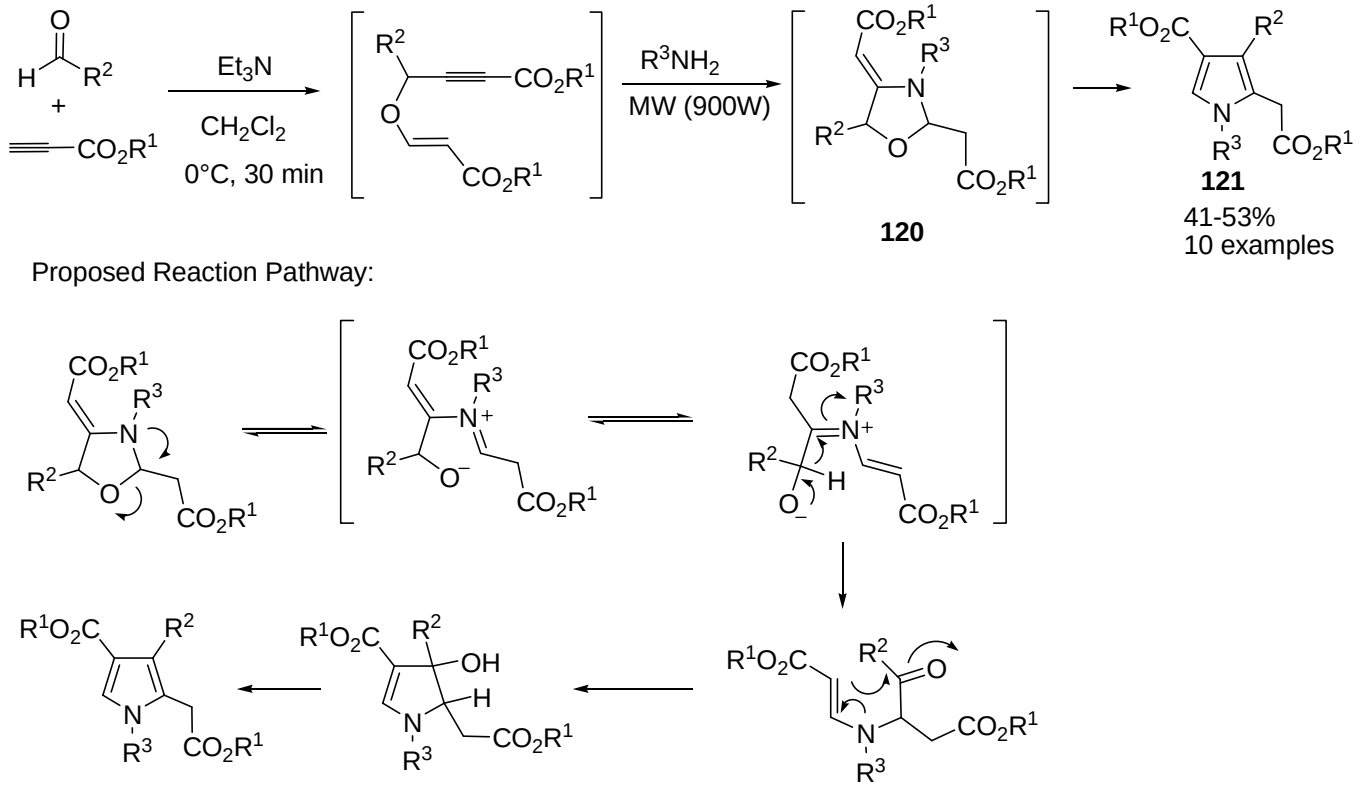
Scheme 57

The reaction of ketoximes with terminal alkenes leading to pyrrole derivatives, *via* the rearrangement of O-vinyloxime intermediates, is known as the Tropimov reaction.[65] A novel version of this reaction allowing the one-pot preparation of *NH*-pyrroles and *N*-vinylpyrroles by the sequential addition of hydroxylamine and acetylene to various ketones was recently developed. The three-component reaction is performed in a superbasic system (KOH/DMSO). This sequence eliminates the necessity for prior formation of the ketoxime. In this reaction, there is only one variable component, the ketone but a range of diversely substituted ketones may be engaged and this route provides an easy access to 2,3-substituted pyrroles (Scheme 58).[66]



Scheme 58

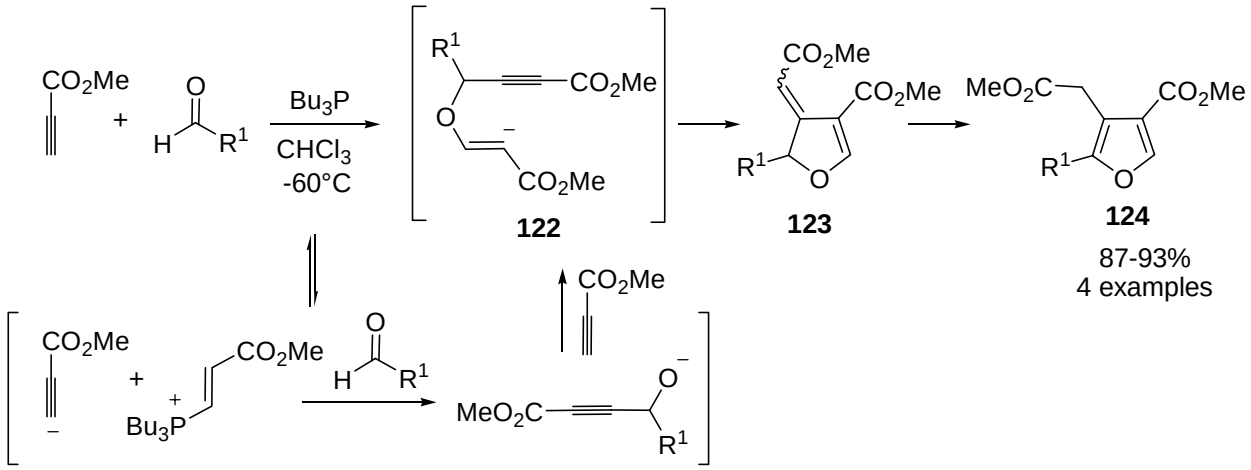
Recently, a triethylamine-triggered reaction of activated terminal alkynes with aldehydes leading to enol-protected functionalized propargylic alcohols was reported.[67] These highly functionalized adducts incorporate two units of the alkynoate and one of the aldehyde. The potential of this three-component reaction to access various heterocyclic systems was further explored by the same group.[68] In particular, the above first domino process was combined with an *in situ* microwave-assisted (160 W) tandem Michael addition-cyclization reaction involving primary amines. This one-pot two-step operation allowed the formation of tetrasubstituted 1,3-oxazolidines **120** (Scheme 58). When the second domino process was performed under microwave irradiation with a higher power, a spontaneous rearrangement of 1,3-oxazolidines to pyrroles was observed. In this two coupled domino processes, two carbon-carbon bonds, two carbon-nitrogen bonds and an aromatic ring are formed in a regioselective manner. This multicomponent reaction showed structural diversity with respect to the aldehyde and amine components and a range of tetrasubstituted pyrroles **121** were obtained in moderate yield (Scheme 59).



Scheme 59

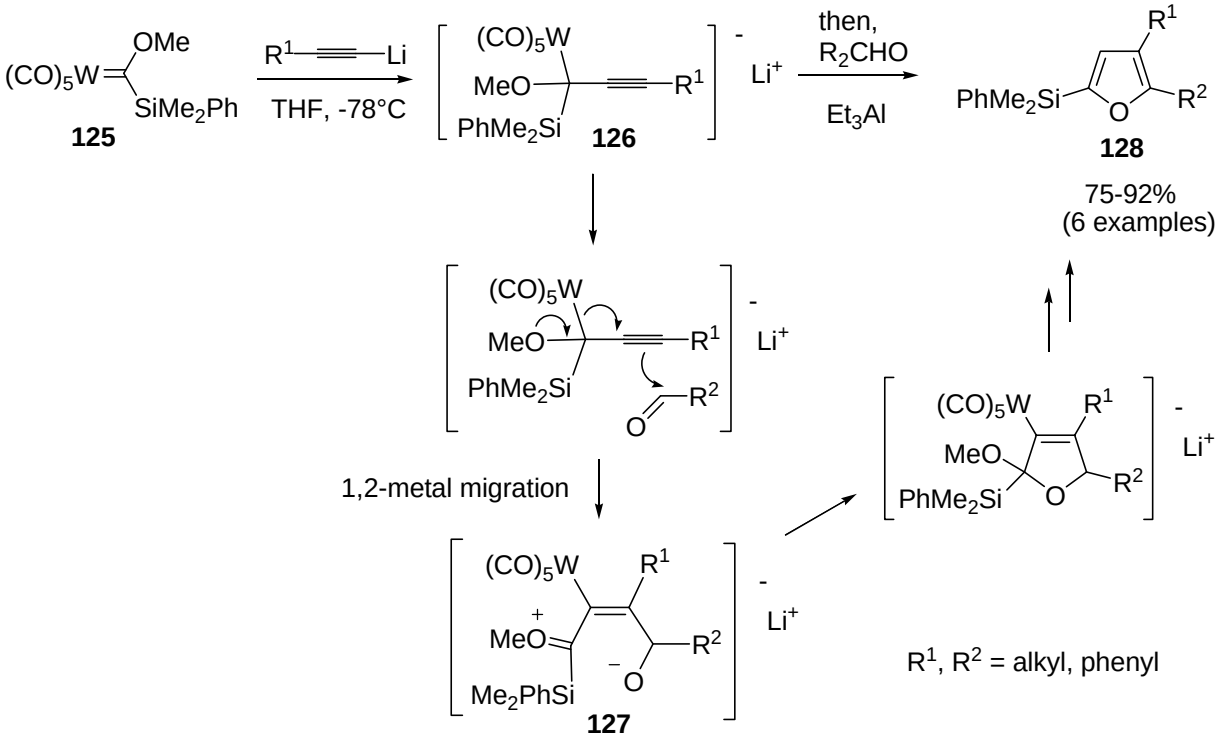
A new access to trisubstituted furans from terminal conjugated alkynes and aldehydes was also developed by the same group. In this case, the organocatalysts are tertiary phosphines with pK_a values around 8.5 and the reaction is performed in halogenated solvent. Using these conditions, the linear adducts **122** were not isolated and a new process occurred leading to dihydrofurans **123**, isolated as a mixture of *E*,*Z*

isomers. A subsequent isomerization of the exocyclic double bond allowed the formation of 2,3,4-trisubstituted furans **124** in moderate yields (Scheme 60).[69]



Scheme 60

The addition of an alkynyl lithium to the tungsten carbene complex **125** was reported to generate propargyltungsten species **126** which react with aldehydes in the presence of Et_3Al, supposedly through 1,2-migration of $W(CO)_5$, to give zwitterionic addition intermediates **127**. Nucleophilic attack of the Et_3Al-coordinated oxyanion on the oxonium moiety would then lead to the formation of furan derivatives **128** (Scheme 61).[70]



Scheme 61

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Didier Bouyssi was born in Valence, France, in 1964 and studied chemistry at the University of Lyon where he obtained his PhD degree in 1992 under the guidance of Prof. Jacques Goré and Dr. Geneviève Balme for research on new palladium-mediated cyclisation processes. After a one-year period as "ATER" (Attaché Temporaire d'Enseignement et de Recherche) in the same university, he was appointed by University of Lyon as a "Maître de Conférences" in the group of Geneviève Balme. His current research interests cover the development of organic synthetic methods using transition metal complexes as catalytic reagents, multi-components reactions and the synthesis of natural or unnatural bioactive compounds.

Nuno Monteiro was born in Marinha Grande, Portugal, in 1965 and grew up in France. He studied chemistry at the University of Lyon where he obtained his Ph.D. degree in 1992 under the guidance of Prof. Jacques Goré and Dr. Geneviève Balme for research on new palladium-mediated cyclisation processes. Following a one-year period as "A.T.E.R." (Attaché Temporaire d'Enseignement et de Recherche) in the same university, he joined in the fall of 1993 the team of Prof. Varinder K. Aggarwal (University of Sheffield, U.K.) as a Marie Curie post-doctoral fellow to work on the synthesis of carbocyclic analogues of polyoxins and nikkomycins, a family of nucleoside-like antibiotics. In 1996 he returned to Lyon where he was appointed by the CNRS as a "Chargé de Recherches" in the group of Geneviève Balme. His current research interests concern the use of

transition metal complexes as catalytic reagents in organic synthesis, the development of diversity-oriented synthetic methods directed toward heterocycles, and the synthesis of bioactive natural products and structural analogues.