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Synthesis of Furans – Recent Advances

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Synthesis of Furans – Recent Advances

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Introduction

Furans constitute an important class of aromatic heterocycles displaying a wide range of pharmacological activities.^{1–6} In addition, furans are the chief motifs of many natural products.^{7–9} Furans are used as flavor and fragrance compounds as well. They have been employed as reaction intermediates in widely divergent processes in both synthetic organic chemistry and materials science.^{10–14} Owing to the tremendous utility of furans, numerous methods for their construction have been reported and the topic has been widely reviewed.^{15–25,138–142} The relevance of the topic justifies a new review which highlights the most important methods. This review covers the literature from 2005 onwards, comprises 142 references and is divided into five major sections.

I. Name Reactions for Furan Synthesis

1. Paal-Knorr Synthesis

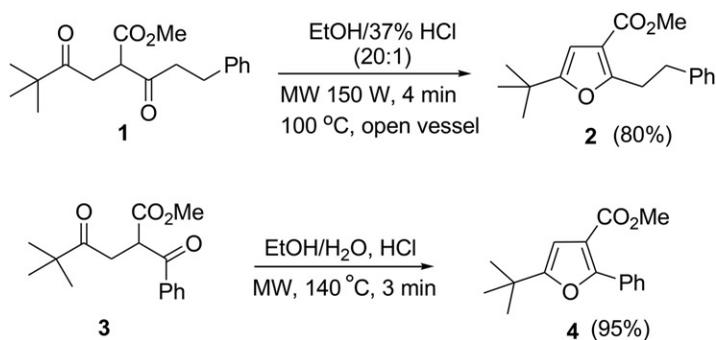
The acid catalyzed cyclization of 1,4-diones to furans is a reaction of historical importance and has been widely explored.²⁶ The frequently used catalysts include sulfuric acid, phosphorus (V) oxide, zinc chloride and amberlyst 15. Paal-Knorr chemistry was also used for the synthesis of furans from 1,4-dicarbonyl surrogates such as epoxy ketones²⁷ and 1,4-diol-2-ynes.²⁸

The harsh conditions required (such as prolonged heating in acid, which may degrade sensitive functionalities in many potential furan precursors) and the low availability of non-symmetrically substituted 1,4-dicarbonyl compounds are the major disadvantages of the classic Paal-Knorr synthesis. Both these points have been addressed by the use of microwave assisted methods which have led to decreased reaction times and better yields. The starting compounds for the cyclization were prepared by the homologation of β -keto esters using an aldehyde in the presence of CH_2I_2 and Et_2Zn followed by oxidation using pyridinium chlorochromate (PCC). Trisubstituted furans were obtained by the cyclization of these starting compounds in high yields as shown below (*Scheme 1*).²⁹

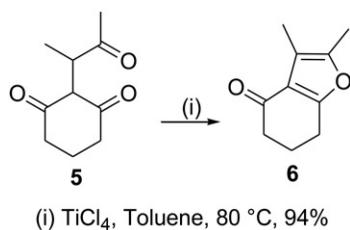
A smooth Paal-Knorr transformation of triketones of the type **5** to the corresponding furans was achieved by employing titanium tetrachloride as the dehydrating agent

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Scheme 1



Scheme 2

in toluene at 80 °C. Several symmetric tetracarbonyl compounds were also converted to the respective furans using this method (Scheme 2).³⁰

2. Feist-Benary Synthesis

The classical Feist-Benary reaction between an α -halo carbonyl compound and a 1,3-dicarbonyl compound catalyzed by amines is a versatile process owing to the flexibility of choices possible in the starting materials.^{31,32} The first step of this reaction affords hydroxy dihydrofurans by the condensation of the β -dicarbonyl compound with the α -haloketone. An exciting enantioselective method to produce these hydroxy dihydrofurans was reported in 2005 using a chiral catalyst.³³ The reaction proceeded through a hydrogen bonded intermediate between the protonated cinchona alkaloid catalyst and the electrophile. The enantioselectivity depends on the preferential attack of the nucleophile to the *Re* or *Si* face of the hydrogen bonded intermediate. The reaction scheme is depicted below (Scheme 3).

A more eco-friendly and efficient modification of the Feist-Benary synthesis was reported recently, using ammonium acetate in aqueous ethanol.³⁴ This reaction depends crucially on the structure of the α -halo carbonyl compound. For instance, the reaction of α -bromo phenacyl bromide with the 1,3-dicarbonyl compound resulted in the formation of the *O*-alkylated product **11** (Scheme 4) whereas the α -halo pyruvate **12** and α -halo 1,3-diketone **13** resulted in furan **14** and fused furan **15** respectively.

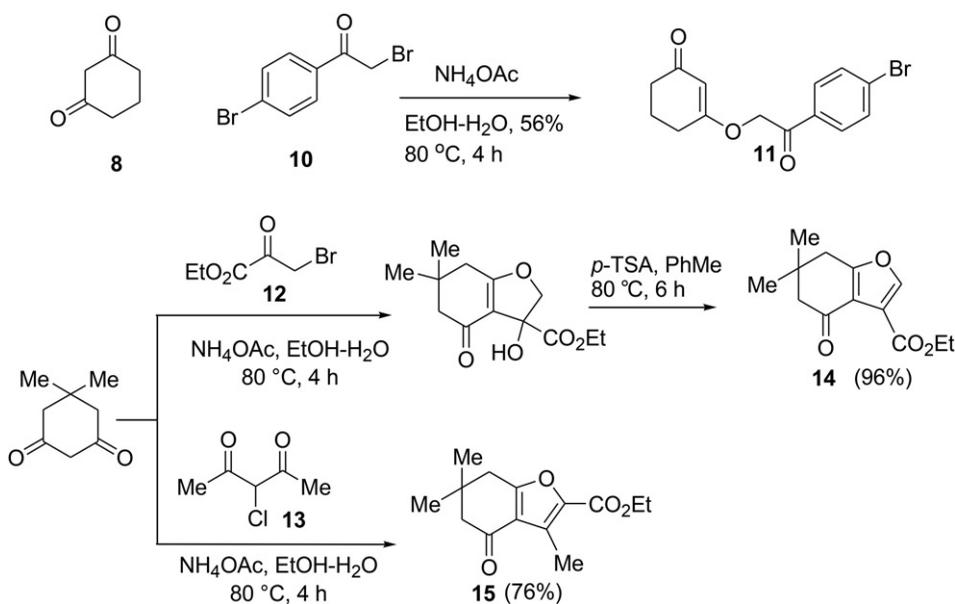
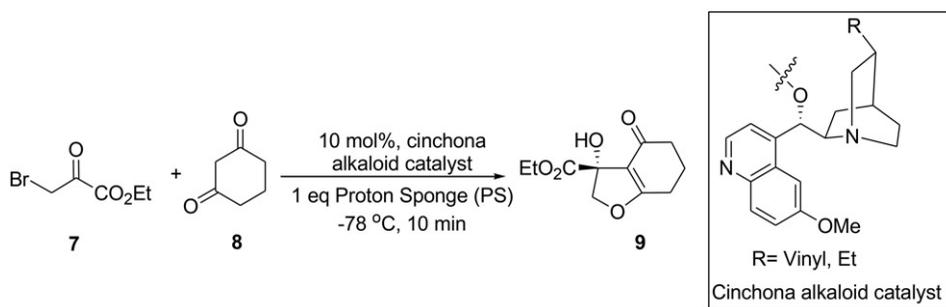
II. Synthesis of Furans via Catalysis by Gold and Silver Salts

A major route towards substituted furans includes the cyclization of acyclic precursors, and this generally proceeds under mild conditions. Exo-cyclization onto triple bonds or

cyclization of allenyl ketones are the two major routes which yield furans. Marshall and Dubay have shown that the protocol of cyclization onto triple bonds can be employed for the synthesis of the fragrance compound, rosefuran **16**. The latter is obtained by the potassium *tert*-butoxide mediated cyclization of dienynol **A** which in turn is obtained from the γ -alkynyl allylic alcohol **B** through palladium catalyzed coupling with the bromide **C** (Figure 1).³⁵

Transition metal catalysts have also been used for such cyclizations. Mercury had originally been used, but subsequently it was replaced by palladium or by platinum salts. More recently, the emergence of gold and silver catalysts has overshadowed the other catalysts. This owes to their mildness which allows greater flexibility for the reaction. Some of the new gold and silver catalyzed reactions are described below.

Intramolecular cyclization of alk-3-yn-1-ones was reported using gold catalysis in the year 2000.³⁶ Later it was demonstrated that such types of cyclizations can take place in the presence of zinc chloride at room temperature.³⁷ Intramolecular dehydrative cyclizations of



3-alkyne-1,2-diols to trisubstituted furans were achieved by two groups *via* gold catalysis (Scheme 5).^{38,39} The reaction proceeds rapidly under mild conditions and was also employed for the synthesis of pyrroles and thiophenes in high yields with low catalyst loading.

In a mechanistically related reaction, furans were prepared by the silver catalyzed reaction of alk-1-ynyl-oxiranes in the presence of *p*-toluenesulfonic acid (PTSA) and methanol.⁴⁰ The reaction takes place by the initial ring opening of the epoxide to an alkynyl alcohol, which in the presence of the silver salt yields the trisubstituted furan. Out of the various silver salts it was found that silver triflate was the most effective for this transformation (Scheme 6). This reaction was also found to proceed by employing a platinum catalyst in an aqueous medium⁴¹ as well as by using indium trichloride in toluene.⁴²

Perumal *et al.* described the efficient construction of structurally diverse fused furans by the gold catalyzed cycloisomerization of 2-alkynyl cycloalk-2-enols as shown below. The mild reaction conditions were found to be suitable for structurally diverse substrates yielding the product in good yields (Scheme 7).⁴³

Krafft *et al.* in 2011 reported a tandem Au(III) catalyzed synthesis of carbocycle fused furans **25** by the Nazarov cyclization of alkynyl-substituted divinyl ketones **23**.⁴⁴ A computational study was also done that complemented the experimental findings. It was proposed that the reaction proceeded through the formation of a cyclic oxonium intermediate **24**, which then underwent Nazarov-type cyclization to yield the product (Scheme 8).

Cyclization of allenyl ketones to furans is a strategy of great synthetic scope and utility. Marshall^{45–49} and Hashmi^{50–53} successfully utilized allenyl ketones for the synthesis of trisubstituted furans. It was reported that Ag(I)⁵⁴ or the Rh(I)-catalyzed⁵⁵ cycloisomerization of allenyl ketones gave alkyl substituted furans of the type **27** in high yields (Scheme 9).

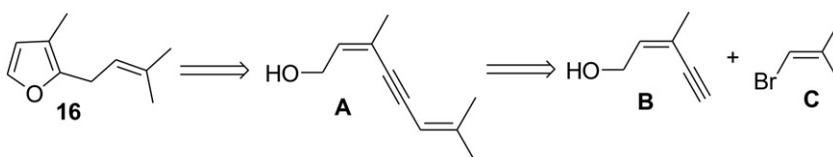
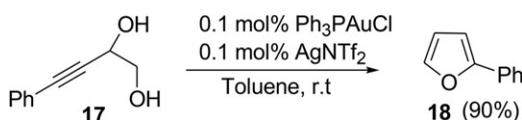
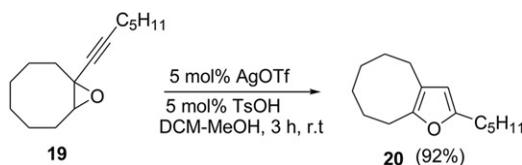


Figure 1. Rosefuran retrosynthesis.



Scheme 5

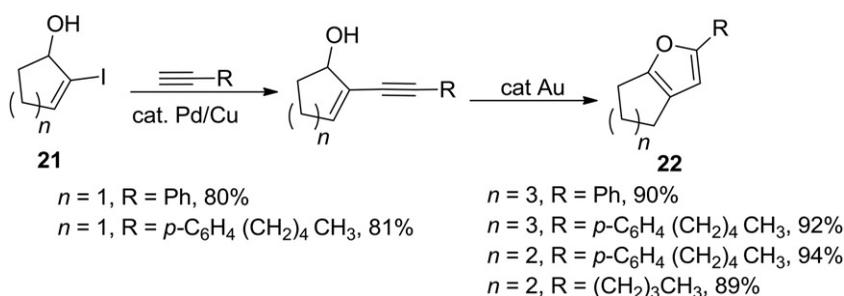


Scheme 6

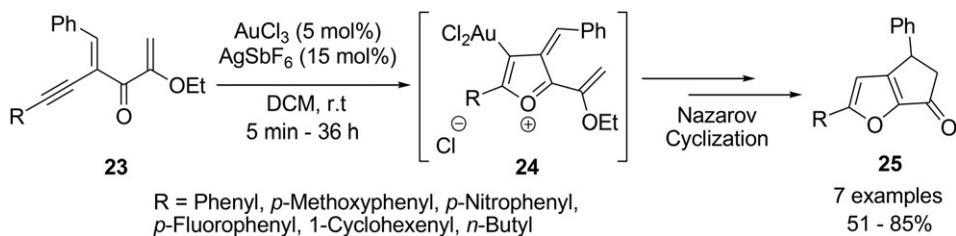
Very recently, Ma reported an efficient synthesis of 2-perfluoro alkyl furans **29** and **30** (Scheme 10) by the controlled cycloisomerization of *n*-perfluoro alkyl 1,2-allenyl ketones.⁵⁶ 3-Monoaryl allenone yielded the furan **29** in the presence of AuCl catalyst which was then efficiently converted into furan-2-yl *n*-perfluoro alkyl ketone **30** in the presence of catalytic amounts of TfOH and water.

Gevorgyan and co-workers synthesized 3-halofurans **32** via the Au(III)-catalyzed cycloisomerization of haloallenyl ketones **31** (Scheme 11). The reaction proceeded through a 1,2-migration of a halogen atom and was superior to Marshall's method in introducing a substituent at the C-3 position of the furan ring. Gold catalyzed selective 1,2-migration of halogen proceeds through a halirenium intermediate. This protocol proved to be more useful for yielding the bromo and iodo substituted furans rather than the chloro counterpart. It was also highly selective and efficient.⁵⁷

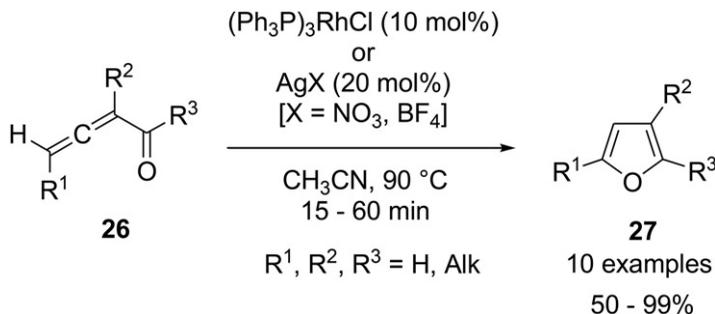
Gold(III)-porphyrin catalyzed cycloisomerization of allenones yielded the corresponding furans in good yields as shown below. In this reaction, the gold complex binds to the allene moiety and subsequently gets attacked by the carbonyl oxygen at the



Scheme 7



Scheme 8



Scheme 9

terminal allene carbon. Finally the acid catalyzed dimerization of the furyl gold species leads to the furan product (Scheme 12).⁵⁸

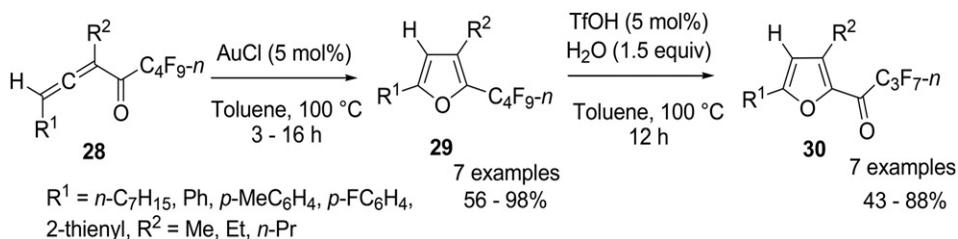
Gevorgyan used the allenyl ketone **35** for the preparation of multisubstituted and fused furans involving a cascade cycloisomerization reaction pathway.⁵⁹ The reaction proceeded through an unprecedented [1,2]-alkyl/aryl migration in the presence of both oxophilic Lewis acids such as indium, tin and silicon triflates, as well as with π -philic catalysts such as Ag(I), Cu(I) and Au(I) salts (Scheme 13).

Gevorgyan further utilized C-4 silyl allenyl ketones of the type **37** to prepare synthetically important C-3 silyl furans such as **39** by a Au(III) catalyzed regioselective cycloisomerization reaction (Scheme 14). Here, it is proposed that Au-carbene intermediate **38** underwent a 1,2-silicon shift. It was shown that compounds which had alkyl groups alpha to the silicon atom and unsubstituted allenes cyclized *via* 1,2-Si shift in preference to 1,2-H shift in both polar and non-polar solvents. The above result also was in good agreement with the computational studies, which suggested that 1,2-migration of the Si atom was the kinetically favored pathway over H, alkyl and aryl migrations.⁶⁰

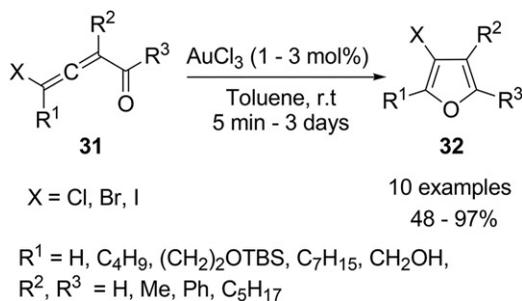
Gold-catalyzed cyclizations of diols and triols to the corresponding hetero- or spirocycles take place in an aqueous medium within nanomicelles. The reaction time and catalyst loading can be significantly decreased by the addition of simple salts such as sodium chloride (Scheme 15).⁶¹

Hydration of 1,3-diyne leading to 2,5-disubstituted furans occurs in the presence of a gold catalyst. The same methodology was adopted for the synthesis of substituted pyrroles as well (Scheme 16).⁶²

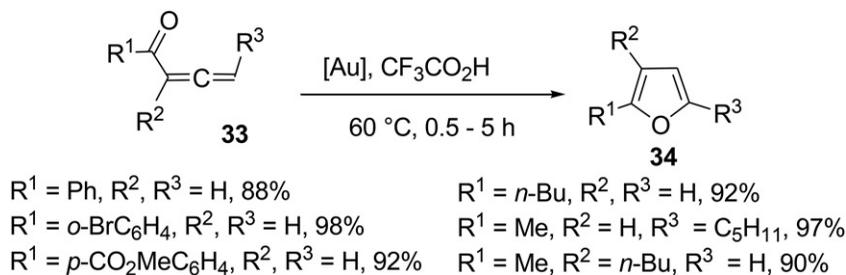
A mild gold catalyzed cascade reaction of cyclopropanes derived from enones led to the synthesis of highly substituted furans (Scheme 17).⁶³ Mechanistically furan formation takes place through the attack of a carbonyl oxygen lone pair on the alkyne followed by rearrangement. This atom economical gold (I) catalyzed process allows access to condensed ring systems *via* a ring expansion reaction.



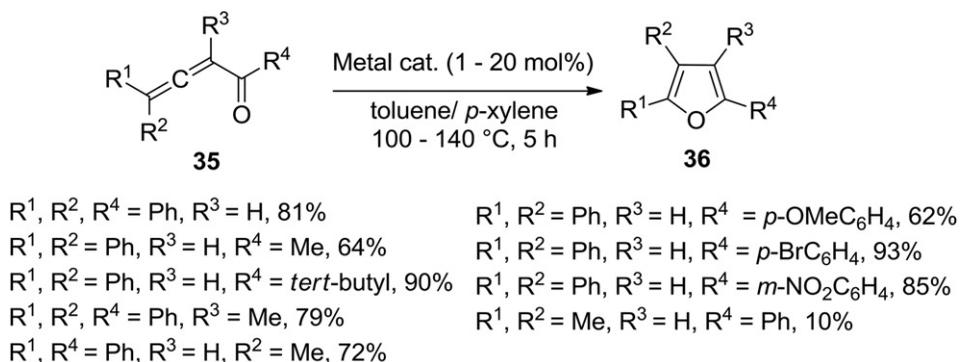
Scheme 10



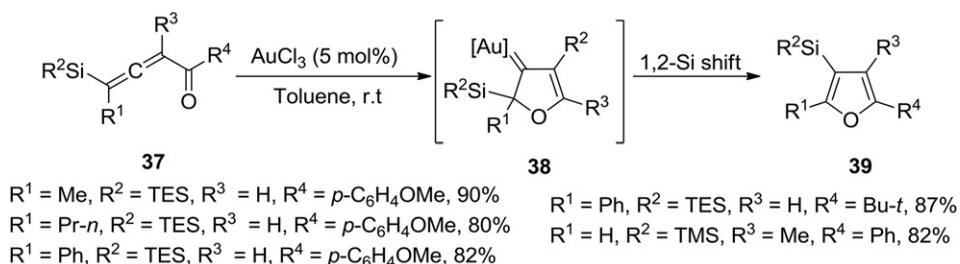
Scheme 11



Scheme 12



Scheme 13



Scheme 14

Propargyl vinyl ethers undergo propargyl-Claisen rearrangement and heterocyclization to afford furans through the intermediacy of an allene in the presence of cationic triphenylphosphine gold(I) catalyst. In this reaction an initial 6-endo-dig addition of the vinyl ether to the gold-alkyne complex leads to the formation of the intermediate allenyl ketone which subsequently undergoes a 5-exo-dig cyclization to deliver the furan **47** (Scheme 18).⁶⁴

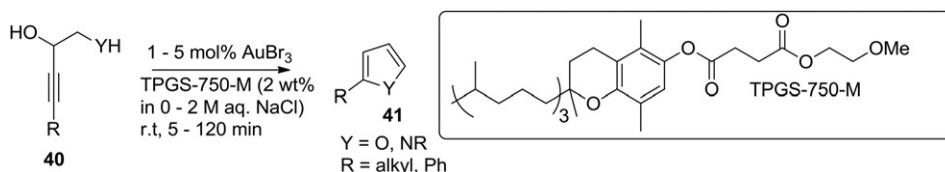
A gold catalyzed three component reaction of secondary amines, terminal alkynes and phenyl glyoxal led to the synthesis of 3-amino furan derivatives in moderate to good yields. In this reaction, the secondary amine reacts with glyoxal and alkyne in the presence of gold to form an intermediate in which the alkyne moiety is coordinated to gold. This is followed by cyclization and subsequent deprotonation and demetallation to provide the product (Scheme 19).⁶⁵

A tandem dual heterocyclization reaction of enynones with 1,3,5-triphenyl-[1,3,5]triazinane **53** is reported to yield furans as shown in *Scheme 20*. In this reaction the furanyl gold intermediate generated is attacked by the formalimine generated from the triazinane. Attack of one more molecule of formalimine followed by cyclization results in the product.⁶⁶

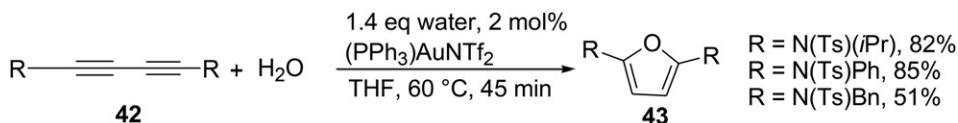
III. Synthesis of Furans *via* Catalysis by Rhodium and Palladium Salts

Zhao and Zhang synthesized fused furans **57**⁶⁷ and carbocyclic furans **56**⁶⁸ by the Rh(I) catalyzed cycloisomerization reaction of alkynyl alkenones **55**. The presence of external nucleophiles gave fused furans whereas their absence led to fused carbocyclic furans by the insertion of CO. Wide substrate scope with very few exceptions and the tolerance of nucleophiles including water are some of the highlights of this method (*Scheme 21*). Use of water as nucleophile led to the synthesis of hydroxy substituted furans which were amenable to further transformations. The alkyne terminus R³ can be H, alkyl, aryl and trimethylsilyl groups; the substituents alter only the reaction rates, not the yields.

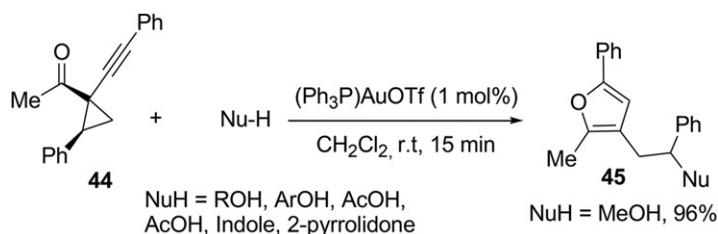
Ma reported a two component Pd-catalyzed synthesis of multisubstituted furans by the reaction of allenyl ketone and organic halides. The reaction is presumed to occur *via* the carbopalladation of allenyl ketone providing a wide substrate scope and moderate to excellent product yields.^{69,70} The versatility of the reaction provides the synthesis of 2,3,4 and 2,3,5-trisubstituted furans as well as 2,3,4,5-tetrasubstituted furans depending on the substituents on the allenyl ketone (*Scheme 22*).



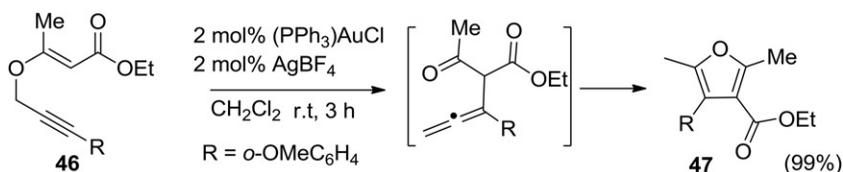
Scheme 15



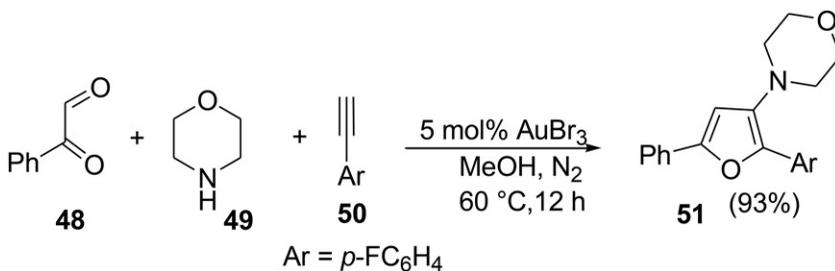
Scheme 16



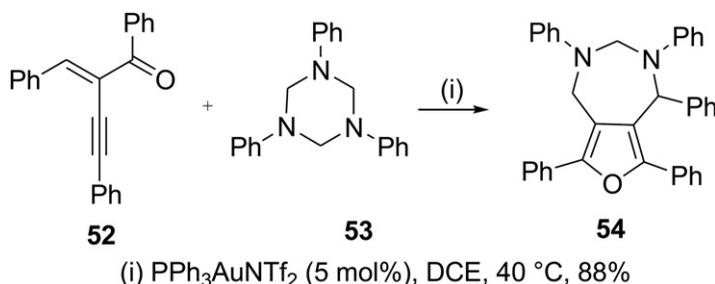
Scheme 17



Scheme 18



Scheme 19



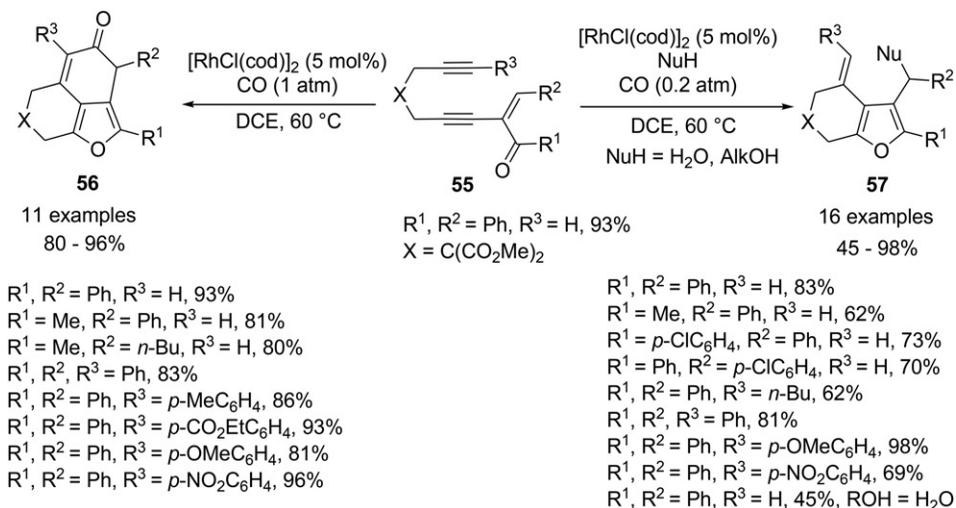
Scheme 20

The same group also reported the cascade reaction between allenyl ketones and allenyl carboxylic acids in the presence of $\text{Pd}(\text{II})$ catalyst yielding functionalized furans.^{71,72} The reaction proceeds through an oxidative cyclization followed by intermolecular dimerization and provides an efficient route to polysubstituted furanones which are otherwise not readily accessible (Scheme 23).

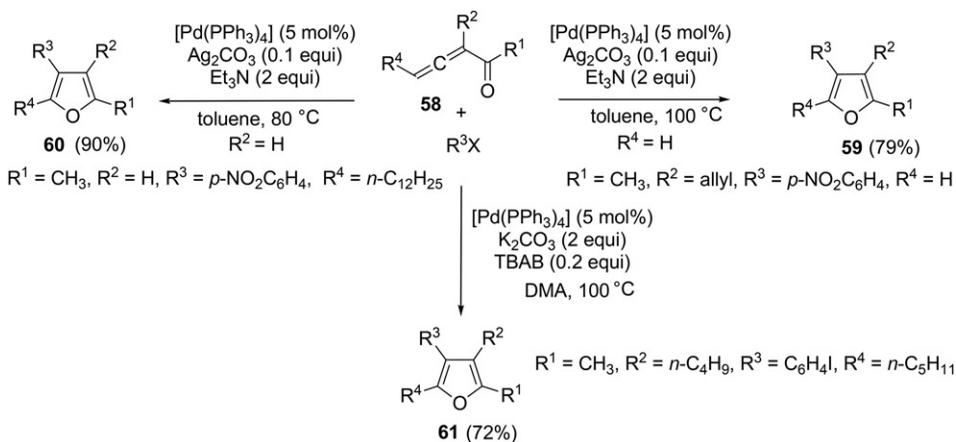
An analogous cycloisomerization reaction of allenyl ketone **65** with allenyl amide **66** was developed by modifying the reaction conditions.⁷³ Here benzoquinone was used as an additive, which helped in reducing both the substrate and catalyst loadings and produced functionalized furyl furanimines **67** in moderate to good yields (Scheme 24).

Alkyl enol ethers with pendant hydroxyl groups undergo intramolecular cyclization in the presence of 2.5 mol% palladium acetate and triphenylphosphine along with an oxidant benzoquinone (BQ) (Scheme 25). The reaction takes place by the initial coordination of the enol ether to palladium followed by attack of the alcohol. β -Hydride elimination from the alkylpalladium complex results in formation of the dihydrofuran. Aromatization of the dihydrofuran during acidic aqueous workup results in the formation of furan **69**.⁷⁴

A palladium catalyzed regioselective cascade reaction between aryloxy enynes and aryl halides was reported to yield 2,3,4-trisubstituted furans. The reaction takes place



Scheme 21



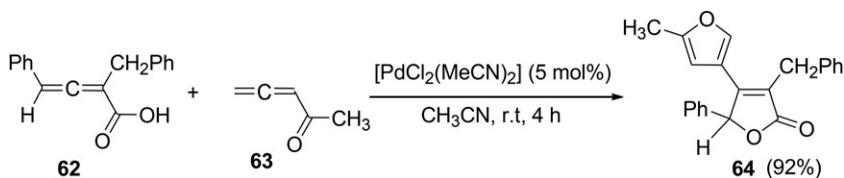
Scheme 22

by coordination of the alkynyl moiety to the Pd(II), in turn generated by the oxidative addition of the aryl halide to Pd(0). The enol oxygen then adds to the activated alkyne and finally leads to the furan product (Scheme 26).⁷⁵

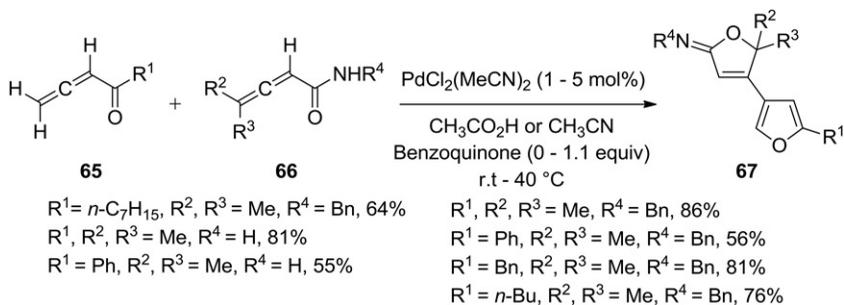
Enynes were also reported to undergo cyclization to furans using palladium acetate catalyst. It is felt that the reaction proceeds by the nucleophilic attack of the oxygen to the palladium activated alkyne to form a furyl palladium intermediate which subsequently undergoes protodepalladation to afford the 2,5-disubstituted furans (Scheme 27).⁷⁶

Zhu reported the Pd-catalyzed synthesis of 2-amino-5-alkyl furans **75** and 2-amino-5-formyl furans **76** by the cycloisomerization and aerobic oxidation of homoallenyl amides **74**.⁷⁷ The mechanistic studies suggested the role of peroxide as a key intermediate in this reaction (Scheme 28).

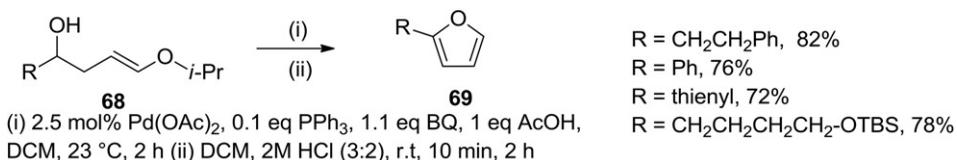
The same group reported the synthesis of multisubstituted 2-amino furans in good yields by the Pd-catalyzed oxygenative cycloisomerization of homoallenyl amides **77**



Scheme 23



Scheme 24

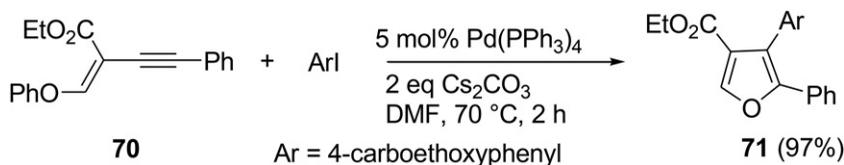


Scheme 25

(Scheme 29). Here hypervalent iodine reagent is used as the oxidant for the selective construction of acetoxyated, alkoxyated and hydroxylated 2-aminofurans **78**, **79** and **80** respectively.⁷⁸ The selective synthesis of different types of products from the same starting materials under mild reaction conditions makes this reaction particularly attractive for organic chemists. High efficiency, mildness of reaction conditions and tolerance of sterically demanding substituents are the major highlights of this process.

A palladium catalyzed three component reaction of propargyl acetates, α -keto carboxylic acids and aryl iodides result in the formation of substituted furans. The Pd(II) complex formed by the aryl iodide first coordinates with the propargyl acetate. Decarboxylation of the latter leads to formation of the π -allyl palladium complex which then reacts with the ketone to form the final product (Scheme 30).⁷⁹

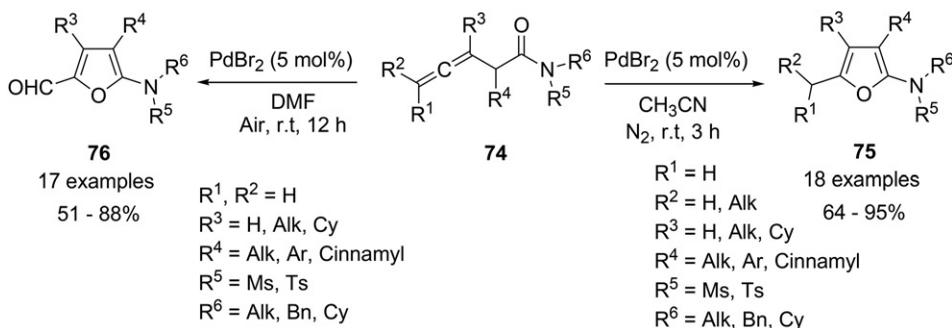
Dheur reported a reaction based on Rh(I)-catalyst to prepare mono and disubstituted furans in moderate to good yields. Here propargyl alcohols reacted with aryl boronic acids in the presence of carbon monoxide to yield the products.⁸⁰ Rhodium catalyzed synthesis of di- and trisubstituted furans were reported *via* intermolecular alkyne hydroacylation. This reaction has a 100% atom economic C-C bond forming step followed by simple dehydrative cyclization as depicted below and uses bis(norbornadiene)rhodium(I) tetrafluoroborate as the catalyst in conjunction with 1,2-bis(diphenylphosphino)ethane (Scheme 31).⁸¹



Scheme 26



Scheme 27

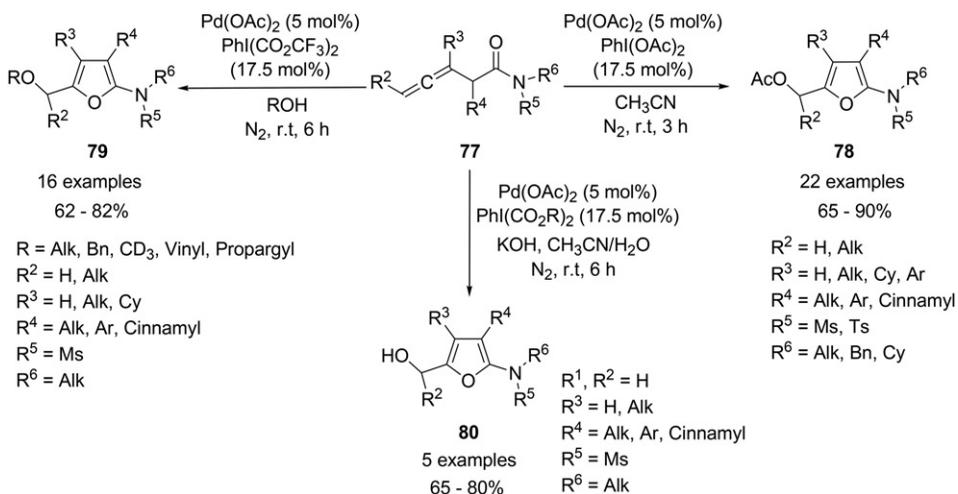


Scheme 28

Cycloaddition reactions constitute a very popular and highly convenient method for the construction of diversely substituted furan molecules. Early on, D'yakonov and Komendantov used this strategy to obtain 2-alkoxy furans using Cu(II) species.^{82–86} Later, numerous research groups expanded this reaction by using different transition metal catalysts for the efficient synthesis of furan molecules. Among these methods the [3 + 2] cycloaddition of α -carbonyl diazo compounds with alkynes is considered to be the most versatile and efficient.⁸⁷ The synthesis of fluorine-containing 1,2,4-trisubstituted furans was reported *via* the Rh₂(OAc)₄ catalyzed [3 + 2] cycloaddition reaction of fluoroacetyl diazo compound and aromatic alkynes (Scheme 32).⁸⁸

IV. Copper Catalyzed Furan Synthesis

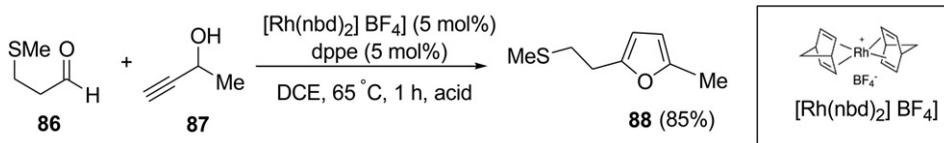
Wang reported a Cu(I)-catalyzed synthesis of 2,3,5-trisubstituted furans **95** by a cascade coupling of terminal alkynes **94** with α -alkyl substituted diazoesters **93**.⁸⁹ The copper carbenoid species generated during the reaction may insert into the triple bond to form the corresponding cyclopropenyl ester which then undergoes a ring-opening cycloisomerization to yield chemoselectively (>99:1) the 2,3,5-trisubstituted furans over the competing alkynoate (Scheme 33).



Scheme 29



Scheme 30

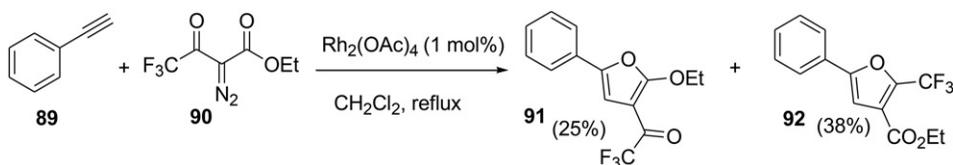


Scheme 31

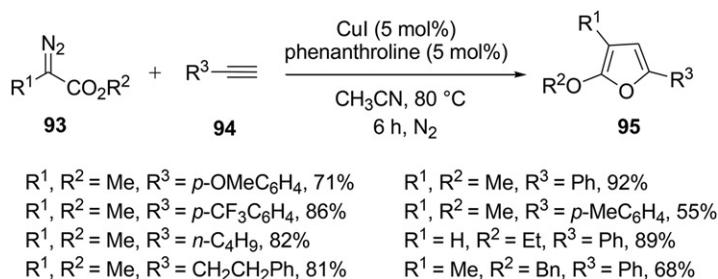
In another reaction, β -chlorovinyl ketones **96** underwent elimination in the presence of triethylamine leading to the formation of allenyl ketones and propargyl ketones. The latter then undergoes cyclization in the presence of 1 mol% CuCl to yield 2,5-disubstituted furans as shown below (Scheme 34).⁹⁰

A one-pot three-step cascade reaction for the synthesis of furans was reported by using a combination of triazole-gold catalyst and a copper catalyst. Propargylic alcohols reacted with substituted trialkynes in the presence of these catalysts to yield di-, tri- and tetrasubstituted furans in moderate to good yields as shown below (Scheme 35).⁹¹

A regioselective synthesis of multisubstituted furans was reported by the reaction of alkyl ketones and β -nitrostyrenes (Scheme 36). In this reaction the C-centered radical formed from the ketone in the presence of *tert*-butyl hydroperoxide (TBHP) adds to the β -position of the nitro alkene generating a new radical which through single electron transfer undergoes subsequent rearrangement and elimination to yield the final product.⁹²



Scheme 32



Scheme 33

1,3-Dicarbonyl compound **104** can undergo ring annulation with diethylene glycol in the presence of copper catalyst to yield 2,3-disubstituted furan **106**. The reaction takes place in the presence of TBHP *via* a sequential *O*- and *C*-functionalization of the β -ketoester (Scheme 37).⁹³

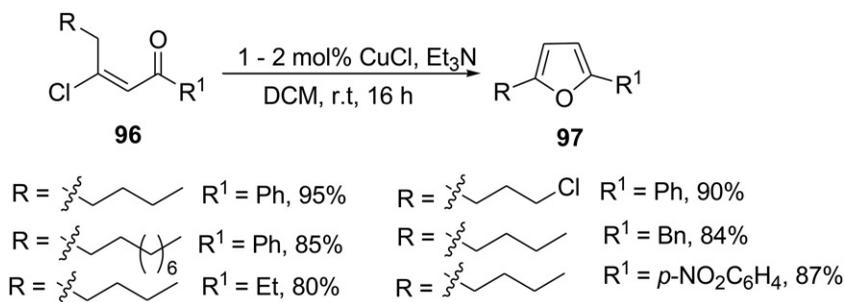
1,3-Dicarbonyl compounds undergo annulations with *gem*-difluoroalkenes in the presence of copper iodide catalyst and base to produce substituted furans in good yields as shown below (Scheme 38). The reaction occurs *via* formation of allenyl ketone in turn generated by the reaction of the 1,3-dicarbonyl compound with the difluoroalkene in the presence of CuI and Cs_2CO_3 .⁹⁴

An intermolecular *C*-allylation followed by an intramolecular Ullmann *O*-vinylation and a double bond isomerization occurs when a 1,3-dicarbonyl compound is treated with 2,3-dibromo-1-propene. The reaction takes place in DMF at 120°C using Cs_2CO_3 as a base and hydroquinone (HQ) as an additive delivering the 2,3,5-trisubstituted furans in good yields as shown below (Scheme 39).⁹⁵

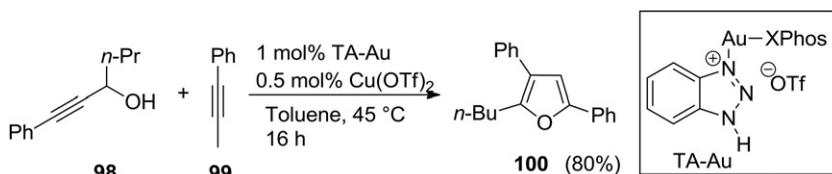
Trisubstituted furans were synthesized by the copper catalyzed reaction of 1,3-dicarbonyl compounds with propionaldehyde using air as the oxidant (Scheme 40). The reaction occurs *via* formation of an enyne intermediate which in turn coordinates with the Cu(I) species generating the copper carbene complex. The latter undergoes oxidation to yield the final product.⁹⁶

1,3-Dicarbonyl compounds undergo oxidative addition to alkynoates followed by cyclization in the presence of Sn(II) , Cu(I) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to yield polysubstituted furans. A representative example is shown below (Scheme 41). The reaction is presumed to take place by an initial activation of the 1,3-dicarbonyl compound by the copper catalyst and the alkynoate by a Lewis acid such as SnCl_2 . These intermediates then couple to form an addition product which undergoes subsequent rearrangement to yield the final product.⁹⁷

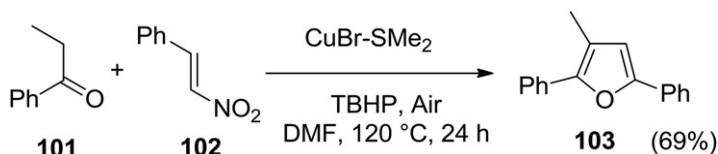
A convenient access to furans was reported by the reaction of readily available acetophenones and electron deficient alkynes. The reaction is catalyzed by Cu(I) salts using di-*tert*-butyl peroxide (DTBP) as the external oxidant (Scheme 42).⁹⁸



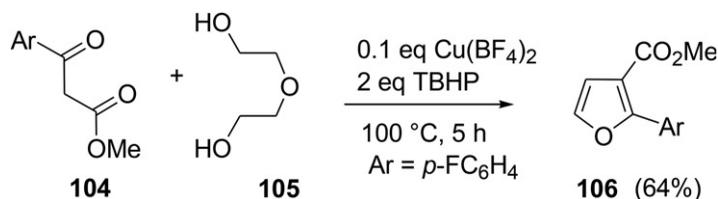
Scheme 34



Scheme 35



Scheme 36

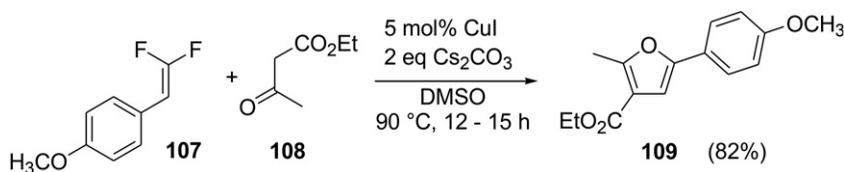


Scheme 37

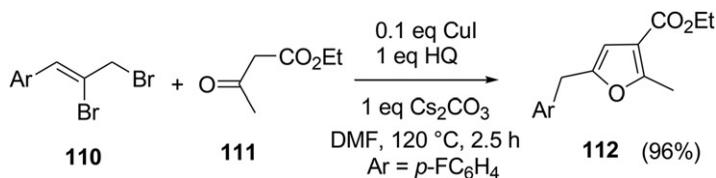
1,3-Dicarbonyl compounds also react with alkynoates in the presence of oxygen under copper catalysis to yield polysubstituted furans in good yields as shown below (Scheme 43).⁹⁹

2-Iodoprop-2-ene-1-ols undergo coupling and cyclization with terminal alkynes to generate tri- and tetrasubstituted furans in the presence of copper (I)/L-proline catalyst in good yields (Scheme 44).¹⁰⁰

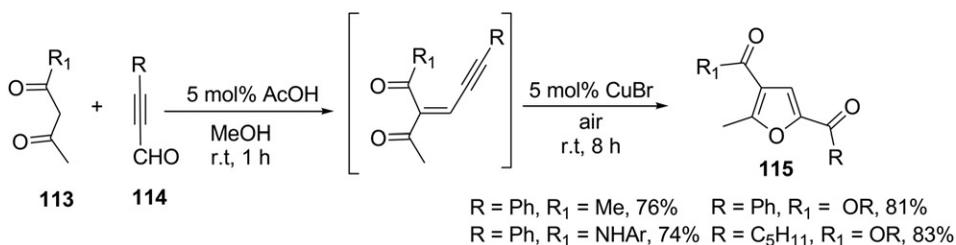
α -Bromo enamines undergo a cascade Sonogashira coupling followed by intramolecular cyclization with terminal alkynes to afford 3-formyl furans in the presence of a palladium-copper catalyst in moderate to good yields. The initial alkynylated enamine, produced by the Sonogashira coupling of the alkyne with the bromo ketone, undergoes cyclization and rearrangement to yield the final product (Scheme 45).¹⁰¹ This



Scheme 38



Scheme 39



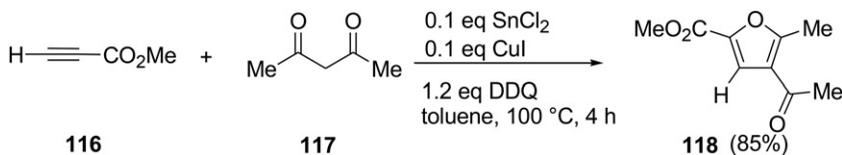
Scheme 40

was the first report of metal-mediated direct synthesis of trisubstituted furans with a C-3 formyl group.

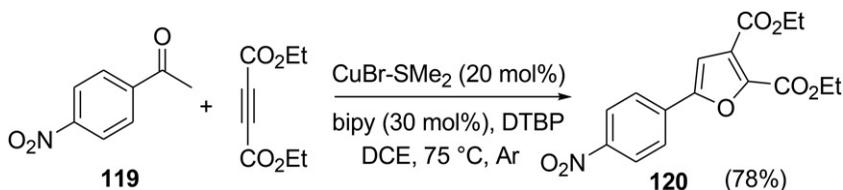
Gevorgyan synthesized 2-monosubstituted and 2,5-disubstituted furans by the Cu(I) catalyzed base-assisted cycloisomerization of alkynyl ketones.¹⁰² The reaction proceeded through the intermediary allenyl isomer which yielded furans bearing functional groups such as alkenes, ethers, acetals, esters and free hydroxyl groups. The latter methodology was subsequently utilized by the same group for the efficient synthesis of trisubstituted furans by using 4-thio- and 4-acyloxy but-2-ynones **128** and **129** as precursors (Scheme 46). The reaction proceeded through the 1,2-migration of the heteroatom-containing moiety and is initiated by a propargyl-allenyl isomerization. This is then followed by formation of aromatic thiirenium ions **130** or dioxolenylium zwitterions **131**. Cyclization of **130** and **131** by means of a nucleophilic addition-elimination (Ad_N-E) mechanism finally yields 3-thio-¹⁰³ and 3-acyloxy-substituted furans¹⁰⁴ **132** and **133** respectively (Scheme 46).

V. Miscellaneous Reactions

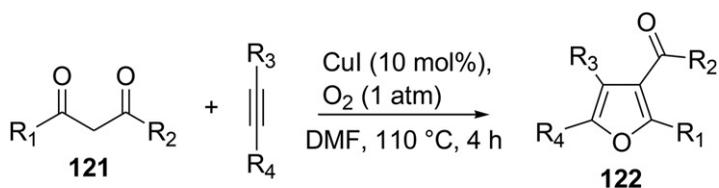
A 5-endo dig electrophilic cyclization of 1,4-diaryl-but-3-yne-1-one **134** with *N*-bromosuccinimide (NBS) [or *N*-iodosuccinimide (NIS) or iodine monochloride (ICl)] yielded 3-bromo [or 3-iodo] furans **135** in high yields as shown below (Scheme 47).¹⁰⁵ The same group demonstrated that but-3-yne-1-one substrates can also undergo



Scheme 41



Scheme 42



- $\text{R}_1, \text{R}_2 = \text{Ph}, \text{R}_3, \text{R}_4 = \text{CO}_2\text{Me}, 89\%$
 $\text{R}_1 = \text{Ph}, \text{R}_2 = \text{Me}, \text{R}_3, \text{R}_4 = \text{CO}_2\text{Me}, 62\%$
 $\text{R}_1 = \text{Ph}, \text{R}_2 = \text{Et}, \text{R}_3, \text{R}_4 = \text{CO}_2\text{Me}, 64\%$
 $\text{R}_1, \text{R}_2 = \text{Ph}, \text{R}_3, \text{R}_4 = \text{CO}_2\text{Et}, 86\%$
 $\text{R}_1 = \text{Ph}, \text{R}_2 = \text{Me}, \text{R}_3, \text{R}_4 = \text{CO}_2\text{Et}, 58\%$
 $\text{R}_1 = \text{Ph}, \text{R}_2 = \text{OEt}, \text{R}_3, \text{R}_4 = \text{CO}_2\text{Me}, 47\%$
 $\text{R}_1 = \text{PhNH}, \text{R}_2 = \text{Me}, \text{R}_3, \text{R}_4 = \text{CO}_2\text{Me}, 53\%$

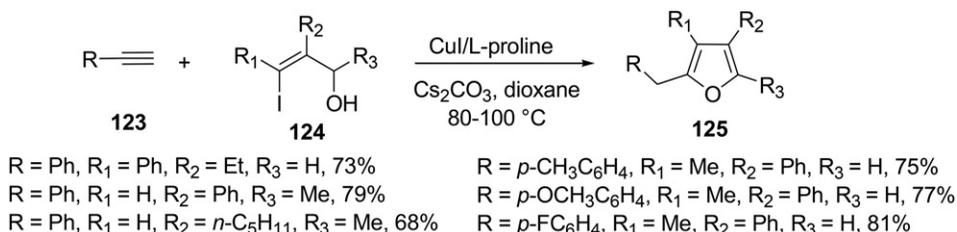
Scheme 43

cycloisomerization in the presence of zinc chloride in dichloromethane at room temperature to afford the corresponding furans in high yields.¹⁰⁶

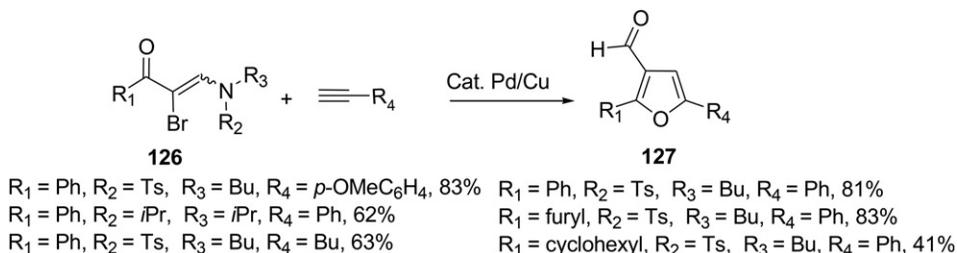
A very efficient method for the synthesis of 2,3,5-trisubstituted furans was developed recently using readily available aldehydes and 1,3-dicarbonyl compounds. The reaction proceeded through an acid-acid catalyzed tandem reaction in the presence of NBS as an oxidizing agent and AlCl_3 as catalyst (Scheme 48).¹⁰⁷

Jiang synthesized C-2 acylfurans from propargyl alcohols **139** and diethyl acetylenedicarboxylate **140** in a stepwise manner (Scheme 49). The first step involves a 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed Michael addition of propargyl alcohols to the activated alkyne followed by its rearrangement to afford allenyl ketones. The latter then underwent cycloisomerization and oxidation in the presence of Cu(I) species to yield substituted furans. Among alkynoates, only diethyl acetylenedicarboxylate underwent the above process.¹⁰⁸

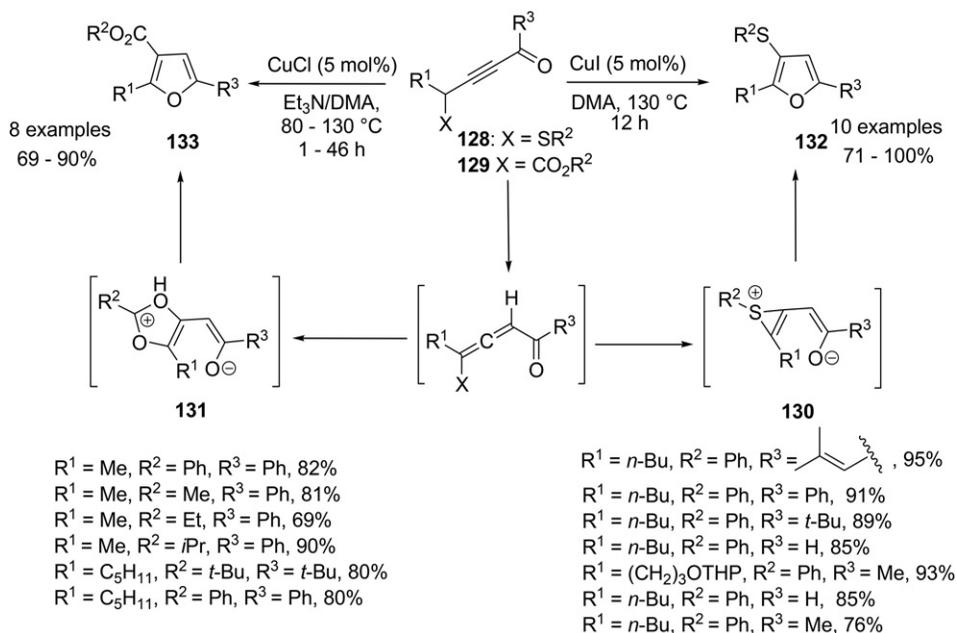
Later, a modified method was reported by the same group using PBu_3 as a catalyst instead of DABCO and a nano Cu_2O catalytic system instead of CuI (Scheme 50).¹⁰⁹ This reaction allowed the use of alkynoates such as ethyl 3-phenylpropiolate and aryl



Scheme 44



Scheme 45



Scheme 46

alkynyl ketones along with diethyl acetylenedicarboxylate. The above protocol was successfully employed using Fe(III)¹¹⁰ and Ag(I)-species¹¹¹ and also by a 'non-oxidative' version¹¹² by the same group.

Formation of 2,5-disubstituted furans by a sequence of Wittig reaction, conjugate reduction using trichlorosilane and Paal-Knorr cyclization has been reported employing

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as a coupling agent. The reaction demonstrates how the by-products from one step can be used in the next step of synthetic transformation. The Ph_3PO produced by the Wittig reaction of phosphorane **146** and 1,2-dicarbonyl compound **147** is used to catalyze the 1,4-reduction of enone intermediate in the presence of HSiCl_3 and the waste HCl thus generated promotes the cyclization reaction to yield the final furan product (Scheme 51).¹¹³

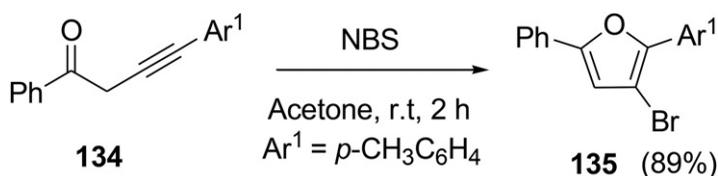
Iodocyclization of conjugated enyne acetates led to formation of iodine-containing furans, subsequently transformed to 2,3,5-trisubstituted furans. The reaction proceeds by the initial formation of the iodonium ion followed by an attack of the nucleophilic oxygen atom. Subsequent removal of the acetyl group by the iodide ion leads to the product (Scheme 52).¹¹⁴

Tri- and tetrasubstituted furans were synthesized by the cyclization of alkynyl ketones in turn produced from ferric chloride catalyzed reaction of propargyl acetates with silyl enol ethers. It is noteworthy that the reaction can occur under mild conditions and tolerates small amounts of air or moisture and furnishes the product in a very short time (Scheme 53).¹¹⁵

A triflic acid promoted reaction of propargylic alcohol with terminal alkynes leading to the synthesis of 2,3,5-trisubstituted furans has been reported. The reaction occurs by an initial activation of the propargylic alcohol by the acid followed by nucleophilic addition of the terminal alkyne. The resulting intermediate then undergoes cycloisomerization to afford the furan with 100% atom economy (Scheme 54).¹¹⁶

A metalloradical cyclization reaction mediated by cobalt carbene radicals (generated from activation of α -diazocarbonyls by Co(II)-porphyrin complexes) on addition to alkynes afforded furans. The reaction was found to have a wide substrate scope and a variety of terminal alkynes and α -diazocarbonyls furnished the furan product under the same conditions (Scheme 55).¹¹⁷

A regioselective synthesis of 2-acyl furans with diverse substitutions was effected by the reaction of *cis*-enynols using a combination of a hypervalent iodine(III) reagent, molecular iodine and a base. The reaction takes place by activation of the alkyne by



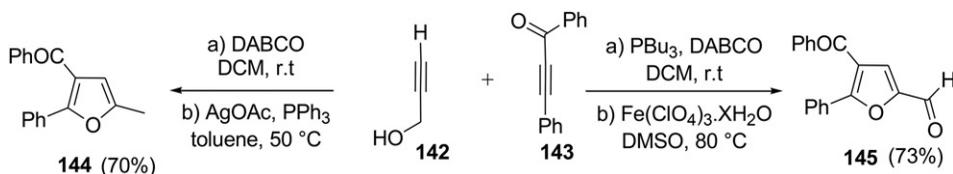
Scheme 47



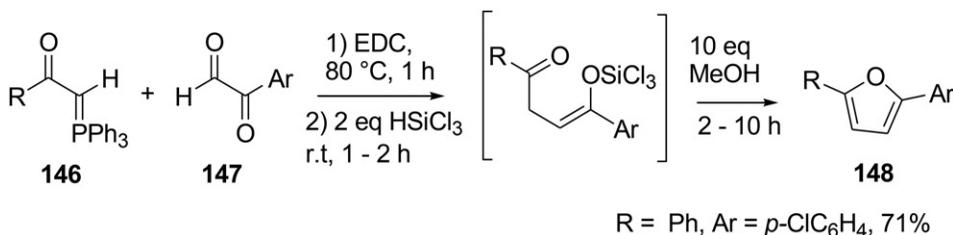
Scheme 48



Scheme 49



Scheme 50



Scheme 51

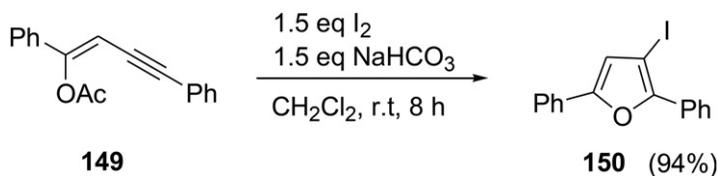
trifluoroacetyl hypoiodite (generated *in situ* by the reaction of PIFA and iodine) followed by nucleophilic attack of the oxygen atom of the hydroxyl group (Scheme 56).¹¹⁸

Propargylic alcohols and acetates react with 1,3-dicarbonyl compounds in the presence of ferric chloride catalyst to afford substituted furans in good yields. The propargylic cation formed by the ionization of the propargylic alcohol gets attacked by the enol to give the γ -alkynyl ketone. The latter is then rendered electrophilic by the complexation of iron. Subsequent nucleophilic attack by the hydroxyl group to the iron complex and successive protonolysis and isomerization steps generates the final product (Scheme 57).¹¹⁹

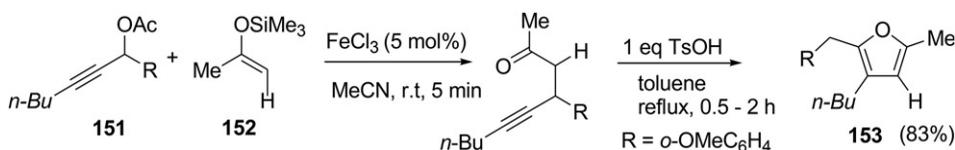
An efficient KOAc-promoted addition and cyclization protocol provides substituted furans. The enolate anion generated from the β -keto ester undergoes Michael addition to the nitro olefin which is followed by an oxidative cyclization to yield the final furan product (Scheme 58).¹²⁰

Decarboxylation of heteroaromatic carboxylic acids including furan carboxylic acid takes place in the presence of silver carbonate in acetic acid. The initially formed silver carboxylate undergoes decarboxylation to yield the silver arene complex which finally gets converted to the arene (Scheme 59).¹²¹

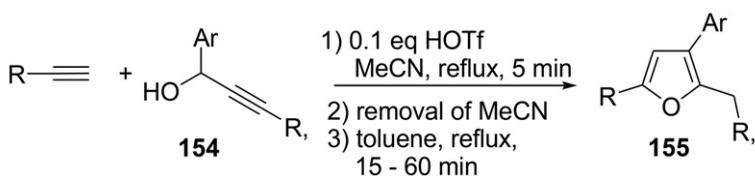
In(OTf)₃ or In(NTf₂)₃ effectively catalyze the cycloisomerization reaction of α -propargyl- β -keto esters and their imine analogs to afford trisubstituted furans and pyrroles respectively. Both terminal and internal alkynes react to yield the corresponding



Scheme 52



Scheme 53

R = *p*-OMeC₆H₄, Ar = Ph, R₁ = H, 73%R = *p*-OMeC₆H₄, Ar = Ph, R₁ = TMS, 80%R = *p*-OMeC₆H₄, Ar = Ph, R₁ = *n*-Bu, 78%R = Ar = Ph, R₁ = *n*-Bu, 71%R = *p*-BrC₆H₄, Ar = Ph, R₁ = H, 64%

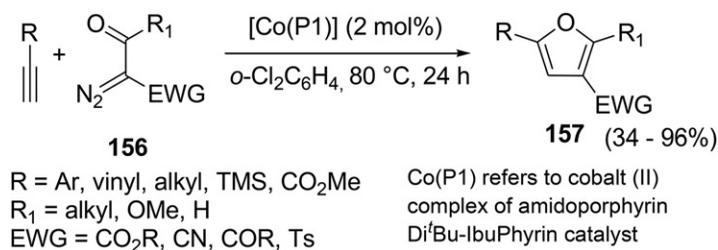
Scheme 54

product. Electrophilic activation of the carbon-carbon triple bond followed by cyclization and rearrangement yields the product (Scheme 60).¹²²

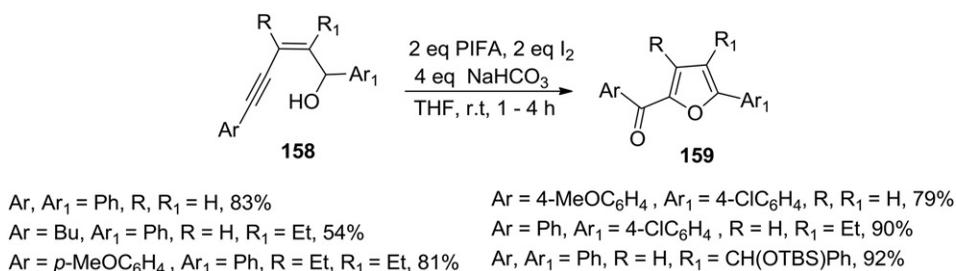
An intramolecular Wittig reaction and cyclization leads to formation of furans from acyl chlorides and electron deficient alkenes mediated by tributylphosphine catalyst. The reaction takes place by the initial addition of the tributylphosphine to the alkene forming zwitterions which then react with the acid chloride to generate a carboxylic ester intermediate. Deprotonation of the latter by triethylamine followed by intramolecular Wittig reaction yields the final product (Scheme 61).¹²³

DABCO catalyzed reaction of α -halo ketones with DMAD leads to substituted furans and highly functionalized 2*H*-pyrans in good yields. The reaction is triggered by the S_N2 displacement of the halide by DABCO to form a quaternary ammonium salt which then gets deprotonated by the potassium carbonate base. The anion thus formed adds in a Michael fashion to DMAD to give an intermediate which finally rearranges to the product (Scheme 62).¹²⁴

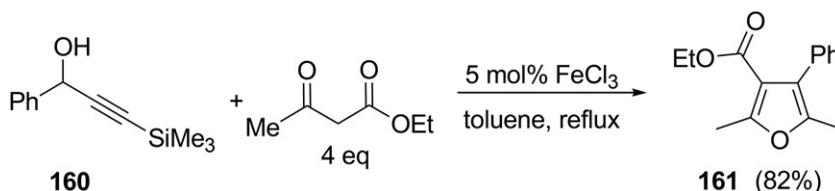
Cycloisomerization of homoallenyl amides to yield 2-amino furans was reported using hypervalent iodine reagent in the presence of palladium acetate catalyst in good yields at room temperature. The intramolecular oxypalladation of the starting material followed by deprotonation leads to a furfuryl palladium intermediate which undergoes subsequent oxidation by PIFA to form a higher valent palladium species. The latter then undergoes reductive elimination and rearrangement to form the final product (Scheme 63).¹²⁵



Scheme 55



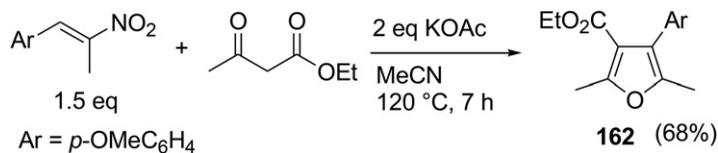
Scheme 56



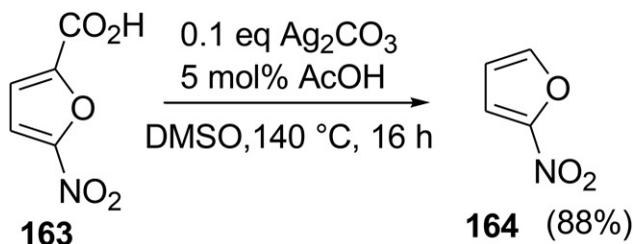
Scheme 57

A facile unprecedented reaction of β -diketones with DDQ resulted in the formation of 2,3-dicyanofurans in very good yields. The reaction takes place by the addition of the α -carbonyl radical to DDQ followed by a C-C cleavage (Scheme 64).¹²⁶ Substrates containing heterocyclic moieties such as furan, thiophene and pyridine were also used for this kind of transformation which afforded the corresponding furan containing scaffold in moderate to excellent yields. The synthesized heteroaryl dicyano compound has potential applications in the fields of dyes and pigments and as photoelectric materials.

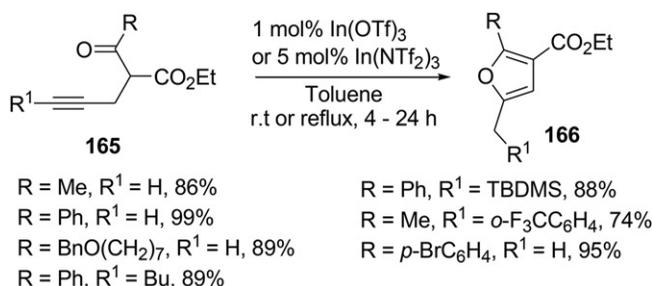
Tetrasubstituted furans were formed in a regioselective manner by the reaction of acetylenes with nitriles in the presence of a titanium catalyst. The reaction proceeds through formation of an azatitanacyclopentadiene intermediate which on subsequent reaction with aldehydes generates the furans in good yields. The reaction can also be used for the synthesis of other heterocycles by varying the reaction conditions and reagents. For instance, the azatitanacyclopentadiene intermediate on reaction with sulfonylacetylene and suitable electrophile affords substituted pyridines. In another reaction, nitrile addition to azatitanacyclopentadiene intermediate generates diazatitanacycloheptatriene, which on subsequent hydrolysis and ring closure finally yields pyrrole derivatives. The generation of tetrasubstituted furans is depicted in Scheme 65.¹²⁷



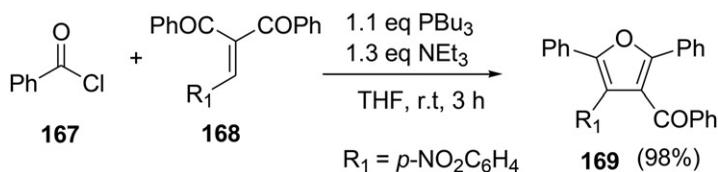
Scheme 58



Scheme 59



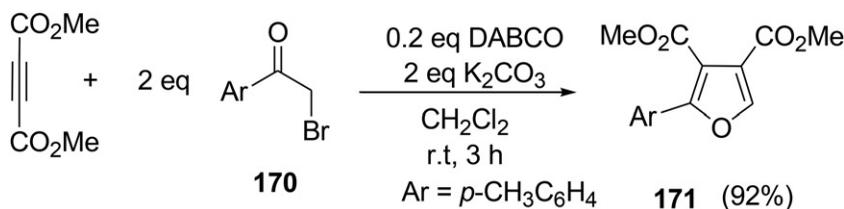
Scheme 60



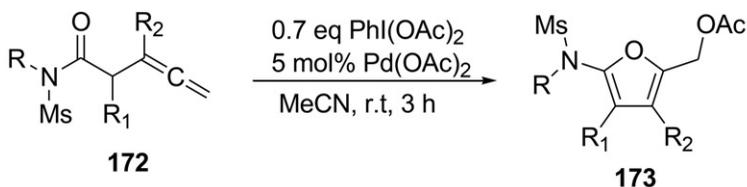
Scheme 61

A bismuth triflate promoted reaction of 1,3-dicarbonyl compounds and acyloins was reported to yield tetrasubstituted furans by a tandem condensation/cyclization sequence (Scheme 66).¹²⁸

The oxidative addition of 1,3-dicarbonyl compounds to terminal acetylenes in the presence of stoichiometric amounts of cerium (IV) ammonium nitrate in acetonitrile solvent was reported to yield multisubstituted or fused furans in moderate to good yields. The reaction takes place by the oxidative addition of the 1,3-dicarbonyl compound to the terminal acetylene generating a vinyl radical species which then undergoes a second oxidation followed by cyclization to yield the furan. It is presumed that

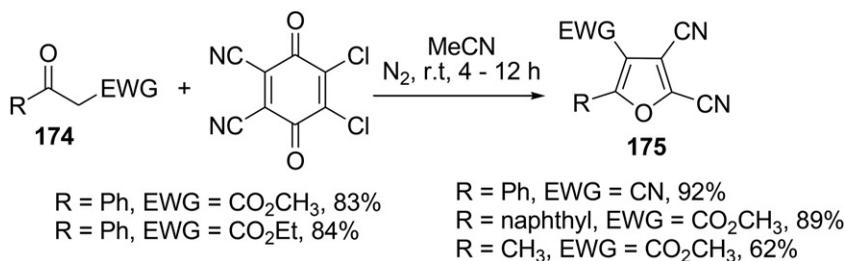


Scheme 62



$\text{R} = n\text{-Bu}$, $\text{R}_1 = \text{Ph}$, $\text{R}_2 = \text{Me}$, 83% $\text{R} = \text{Me}$, $\text{R}_1 = \text{Ph}$, $\text{R}_2 = \text{H}$, 65%
 $\text{R} = n\text{-Bu}$, $\text{R}_1 = \text{C}_6\text{H}_{13}$, $\text{R}_2 = \text{Me}$, 75% $\text{R} = \text{Cy}$, $\text{R}_1 = \text{Ph}$, $\text{R}_2 = \text{Me}$, 81%
 $\text{R} = n\text{-Bu}$, $\text{R}_1 = (E)\text{-styrenyl}$, $\text{R}_2 = \text{Me}$, 80% $\text{R} = n\text{-Bu}$, $\text{R}_1 = p\text{-BrC}_6\text{H}_4$, $\text{R}_2 = \text{Me}$, 85%

Scheme 63



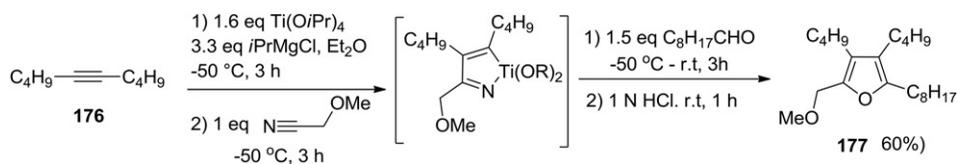
Scheme 64

hydrolysis of the nitrate during work-up yields the hydroxylated product which is strongly intramolecularly H-bonded (Scheme 67).¹²⁹

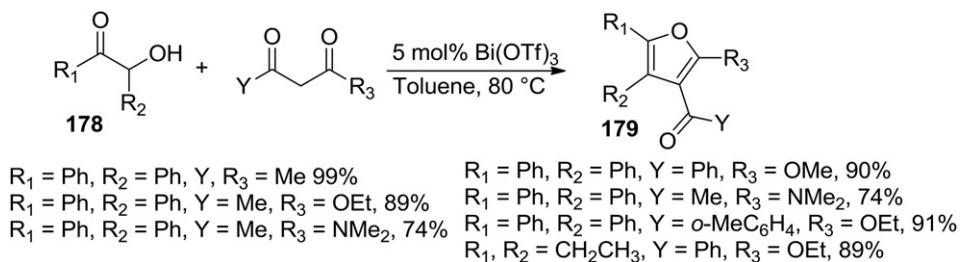
The above reaction was also found to be extendable to cyclic 1,3-dicarbonyl compounds. The stability of the fused furan formed as the product in this case is probably the reason why the tetrasubstituted furan is not formed as with the reaction of the acyclic counterpart. The scheme below shows the reaction of a cyclic 1,3-dicarbonyl compound (Scheme 68).¹²⁹ It was also observed that terminal acetylenes with electron-withdrawing groups attached to phenyl ring were found to be sluggish in reactivity.

Very recently, a mild method for the synthesis of polysubstituted furans was reported by the reaction of bromo nitromethane and oxodienes in the presence of DABCO. The anion generated from bromo nitromethane undergoes Michael addition to the oxodiene which is followed by the subsequent enolization and cyclization of the intermediate. Elimination of nitric acid from the dihydrofuran in the presence of DABCO leads to the polysubstituted furan (Scheme 69).¹³⁰

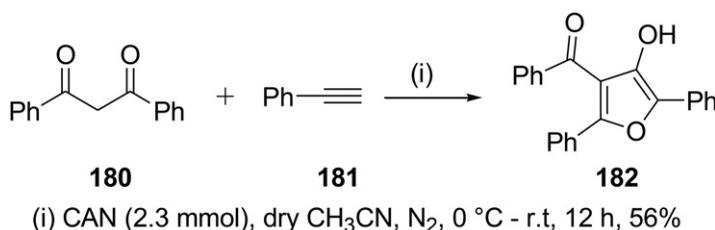
Another reaction reported recently for the synthesis of tetrasubstituted furans involves the participation of Cp_2TiCl_2 as a catalyst for the formation of 1,4-dicarbonyl compounds from alkyl carboxylates and unsymmetrical alkynes. The 1,4-diones thus



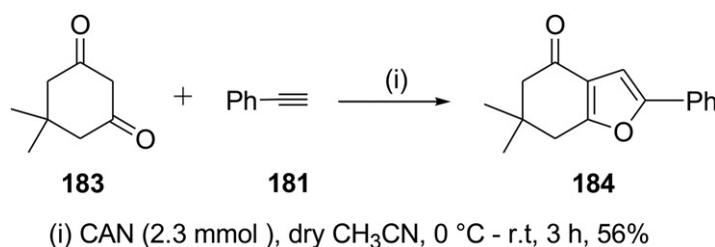
Scheme 65



Scheme 66



Scheme 67

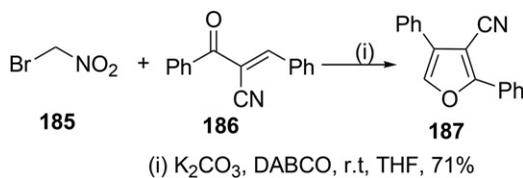


Scheme 68

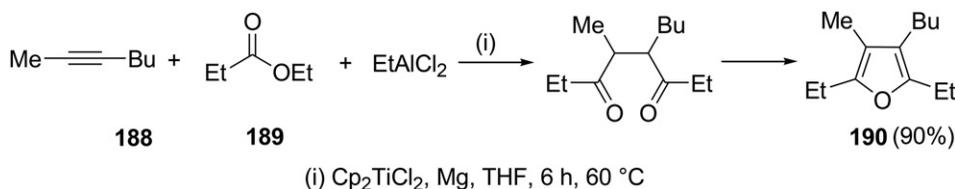
formed are converted to the tetrasubstituted furans by the action of EtAlCl_2 using the Paal-Knorr strategy (Scheme 70).¹³¹

The phosphine catalyzed transformation of ynenones to furans was also reported recently. The reaction involves an initial 1,6-addition of the trialkyl phosphine to the ynenone followed by a 5-exo-dig cyclization to afford a phosphonium ylide intermediate. The latter is finally converted to the 2-acyl furan by the action of oxygen (Scheme 71).¹³²

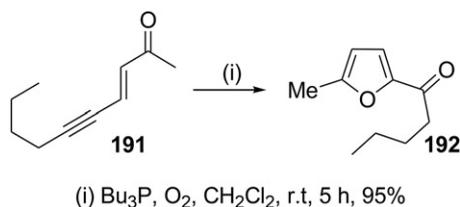
The conversion of endoperoxides to the corresponding multisubstituted furans under Appel reaction conditions were reported recently (Scheme 72).¹³³ The procedure was efficient for the total synthesis of a furan fatty acid as well.



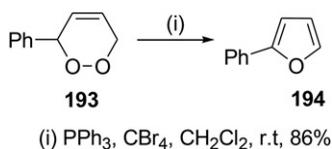
Scheme 69



Scheme 70



Scheme 71

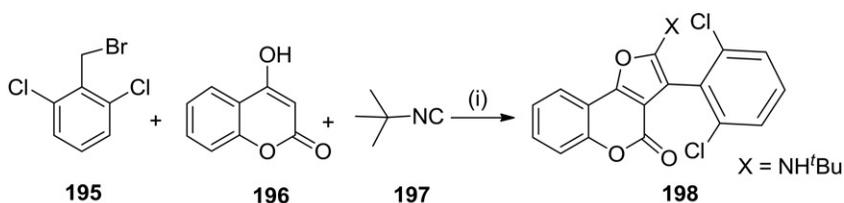


Scheme 72

A one-pot reaction of *tert*-butyl isocyanide, 4-hydroxy coumarin and benzyl halides was reported to yield furochromenes of the type **198**. The reaction proceeds by an initial Kornblum oxidation of the benzyl halide to benzaldehyde followed by condensation with 4-hydroxy coumarin and subsequent cycloaddition with the isocyanide (Scheme 73).¹³⁴

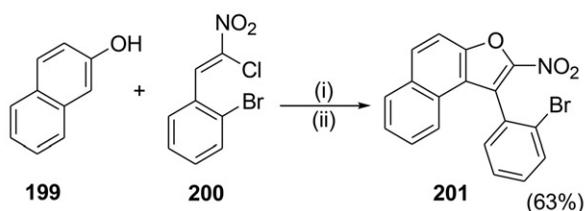
An organocatalyzed reaction of 1,3-dicarbonyl compounds or naphthols with bulky β -substituted nitro olefins led to the synthesis of enantiopure dihydrofurans. The latter was then carefully converted to the corresponding furans by mild and selective oxidation using manganese dioxide. Axially chiral furan molecules could be obtained by this strategy (Scheme 74).¹³⁵

The Friedel-Crafts reaction of dimethoxy benzene with the α,β -unsaturated ketone leads to the formation of a 1,4-dione intermediate which in turn can undergo acid promoted intramolecular cyclization to yield the furan in the absence of any solvent. Using this novel strategy several polysubstituted furans could be synthesized by varying the starting compounds (Scheme 75).¹³⁶

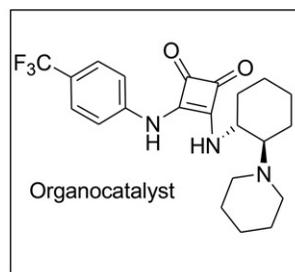


(i) DMSO, K₂CO₃, 3 h, 90 °C, 92%

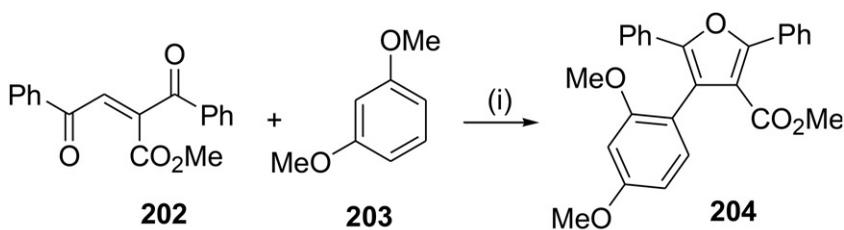
Scheme 73



(i) organocatalyst (10 mol%), K₂HPO₄·3H₂O, CHCl₃, -10 °C, 48 h
 (ii) MnO₂, Toluene, -5 °C

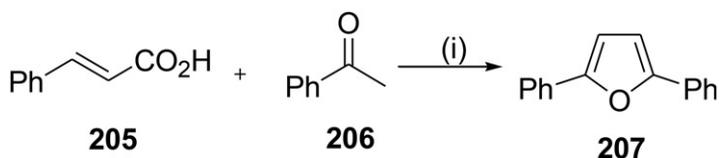


Scheme 74



(i) Triflic acid, neat, 90 °C, 2 h, 94%

Scheme 75



(i) CoFe₂O₄, visible light, water, r.t., 3 h, 91%

Scheme 76

Synthesis of poly-functionalized furans by photocatalysis using white LED light was reported recently. The reaction takes place by the excitation of the Co²⁺ ion. The excited state thus generated is reductively quenched by the enol form of acetophenone. The vinyloxy radical thereby generated reacts with cinnamic acid; subsequent cyclization and electron transfer leads to furans (*Scheme 76*).¹³⁷

VI. Conclusion

The appearance of so many new papers on furan synthesis periodically is a testimony to the importance and relevance of the heterocycle.^{138–142} This review highlights a variety of synthetic methodologies adopted for furan synthesis and focuses on the literature from 2005 onwards. The main goal of the review is to provide a convenient one-source reference for the practicing organic chemist on important methods for synthesizing furans.

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