SYNTHESIS OF FUNCTIONALIZED FURAN DERIVATIVES BY GENERATION OF 2-(FURYL)CARBENE INTERMEDIATES

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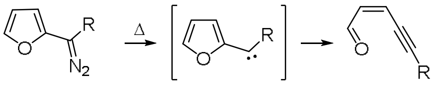
Abstract. *With a few notable exceptions, 2-furyl carbenes do not undergo any of the classical reactions of carbenes and for this reason they have traditionally been regarded as synthetically useless intermediates in the synthesis of functionalized furan derivatives. The use of enynones in combination with metal catalysts has dramatically changed this picture. In fact, the catalytic generation of metal (2-furyl)carbene complexes has evolved in the last decade into a powerful tool in heterocyclic chemistry. These intermediates display a typical carbenic reactivity that has been exploited in a plethora of useful synthetic applications. For this purpose, catalysts based on earth-abundant metals such as copper and zinc have proved particularly useful providing a straightforward methodology for the synthesis of an array of functionalized furan derivatives otherwise dificult to prepare.*

Contents

1. Introduction

Carbenes are intermediates featuring a rich and varied reactivity that has been exploited in a large variety of synthetically useful transformations. Classical reactions of carbenes include additions to unsaturated substrates, insertions into carbon-hydrogen and heteroatom-hydrogen bonds and rearrangements.

2-Furyl carbenes could serve as a convenient platform for accessing a variety of functionalized furan derivatives by exploiting the reactivity of the carbenic site. However, 2-furyl carbenes are elusive intermediates and, for this reason, they have traditionally been regarded as synthetically useless intermediates.[1] The main reason for the evasive character of these intermedies is that, once generated from a suitable precursor (2-furyl diazo compounds or 2-furyldiaziridine derivatives), they undergo a fast ring-opening reaction to provide enynones (Scheme 1), which precluded their capture when generated in the presence of potential trapping reagents.[2] As a result, with a few exceptions, 2-furyl carbenes do not undergo any of the classical reactions of carbenes.

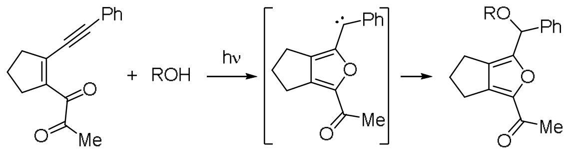


Scheme 1. Thermal ring-opening reaction of 2-furyl carbene intermediates.

In order to overcome this limitation, a plethora of transition metal-based alternatives have been reported in the last years.[3] In this personal account, we report on recent advances in the synthesis of functionalized furan derivatives based on the generation of 2-furyl carbene intermediates. This is an exciting field of research to which our group has actively contributed in the last years. We will mainly focus on those transformations involving catalysts based on earth-abundant metals such as copper and zinc. It should be noted that some early results discussed in this chapter were obtained in the course of a collaborative project of the senior author of this chapter (L.A.L.) with Professor José Barluenga at the University of Oviedo. We would like to pay a tribute to Professor Barluenga (1940-2016) for his outstanding contributions to the field of heterocyclic chemistry.

2. Metal-free approaches

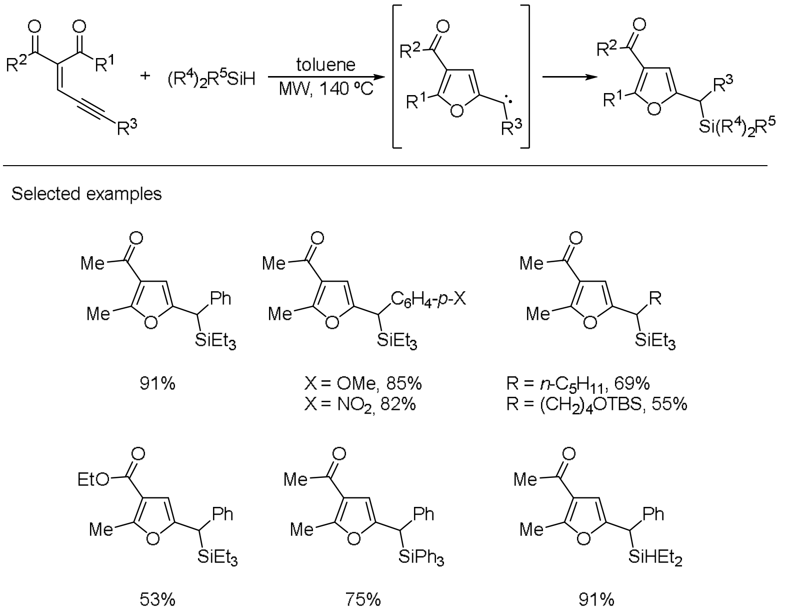
As stated before, the easy ring-opening of the 2-furyl carbene intermediate has hampered the use of these intermediates in organic synthesis. In 1995, Saito and co-workers reported the photochemical generation and subsequent intermolecular trapping by protic solvents of 2-furyl carbene intermediates arising from enynes featuring a conjugated α-diketone moiety (Scheme 2).[4] Of note, the α-diketone motif was found to be of fundamental importance for the success of this photochemical reaction. In fact, substrates lacking the additional carbonyl group failed to participate in this cyclization/insertion sequence.



Scheme 2. Photochemical generation and subsequent trapping of 2-furyl carbene intermediates.

Although conceptually interesting, the need of a multistep sequence for the preparation of the required enynones and the exclusive use of water and alcohols as trapping reagents represent significant limitations on the synthetic applicability of this methodology.

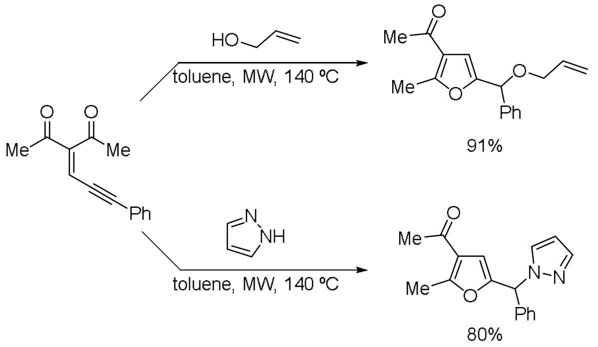
Inspired by a work of Bertrand and co-workers on the activation of Si-H bonds with singlet carbenes,[5] our group in 2016 reported an efficient and metal-free silicon-hydrogen bond functionalization based on the microwave-assisted reaction of readily available enynones and hydrosilanes (Scheme 3).[6] This transformation is believed to proceed through a 2-furyl carbene intermediate, which evolves to the final products through insertion into the silicon-hydrogen bond.



Scheme 3. Microwave-assisted reaction of enynones and hydrosilanes.

This fully atom-economical metal-free silicon-hidrogen bond functionalization exhibited a wide scope with respect to both components delivering the corresponding insertion products in good yields (Scheme 3).

The postulated furyl carbene intermediate could be trapped by other heteroatom-hydrogen bonds (Scheme 4). Specifically, we extended this cyclization/insertion sequence to alcohols. Indeed, the reaction with allylic alcohol provided the corresponding furyl ether derivative in excellent yield. Notably, this transformation takes place with complete chemoselectivity, since neither cyclopropanation of the olefinic moiety nor insertion into the allylic carbon-hydrogen bonds were observed. Moreover, some compounds with nitrogen-hydrogen bond demonstrated to be suitable substrates for this transformation. Thus, reaction with pyrazole led to the corresponding furyl- and pyrazolyl-containing triarylmethane derivative in good yield.



Scheme 4. Metal-free, microwave-assisted oxygen-hydrogen and nitrogen-hydrogen bonds functionalizations.

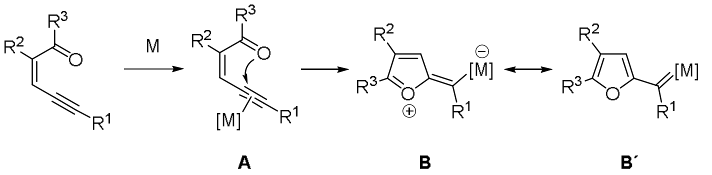
Although synthetically useful, the metal-free procedures discussed in this section exhibit important limitations with respect to the nature of the trapping reagent. In fact, the postulated furyl carbene intermediates were reactive exclusively toward compounds featuring heteroatom-hydrogen bonds, while failed to undergo addition reactions with unsaturated substrates. In this regard, the development of new methodologies for the generation of 2-furyl carbene intermediates susceptible of being intercepted by unsaturated substrates would be particularly appealing. As it will be displayed in the next Sections of this chapter, the use of metal-catalyzed transformations may overcome the limitations imposed by these metal-free protocols.

3. Transition metal-catalyzed transformations involving (2-furyl)carbene intermediates

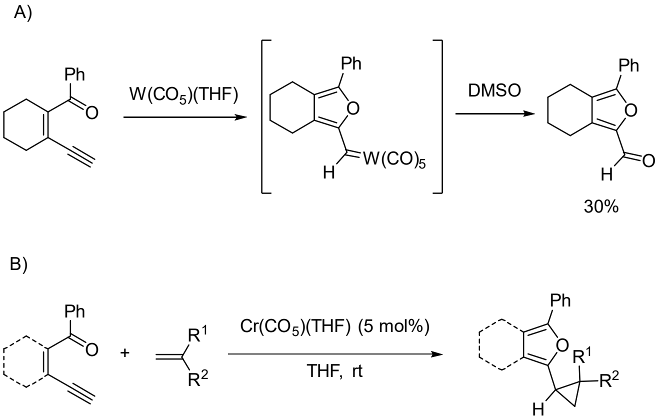
As stated in the introduction of this chapter, the catalytic generation of metal (2-furyl)carbene complexes has evolved in the last decade into a powerful synthetic methodology, because these reactive intermediates could be trapped *in situ* by suitable substrates affording functionalized furan derivatives in most cases in processes featuring full atom economy.

Enynones have been identified as the most common precursors for the catalytic generation of (2-furyl)carbene intermediates. The accepted mechanistic pathway for the generation of (2-furyl)carbene intermediates from enynones is depicted in Scheme 5. It involves initial activation of the C-C triple bond *via* complexation to the electrophilic catalyst to generate complex **A**. Subsequent 5-*exo*-dig cyclization by regioselective intramolecular nucleophilic attack of the carbonyl group to the activated alkyne would generate intermediate **B**, which can be also described as the carbene resonance formula **B′**. A number of transition metals including Cr, Cu, Zn, Au, Ag, Rh, Pd, among others were able to efficiently promote the catalytic generation of 2-furyl metal carbene complexes from enynones.

Seminal work on the generation of 2-furyl metal carbene intermediates was documented by Iwasava and co-workers, who in 2001 reported the preparation of furfural derivatives through $W(CO)_5(THF)$-catalyzed reaction of enynones and subsequent oxidation of the postulated carbene intermediate by DMSO (Scheme 6A).[7] One year later, Uemura, Ohe and co-workers reported the synthesis of cyclopropane derivatives using alkenes as trapping reagents (Scheme 6B).[8] This cyclopropanation reaction proceeded efficiently at room temperature in the presence of a catalytic amount of $Cr(CO)_5(THF)$.



Scheme 5. Pathway for the generation of 2-furyl metal carbene intermediates from enynones.

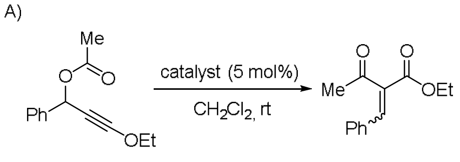


Scheme 6. Seminal contributions on the generation and synthetic applications of 2-furyl metal carbene intermediates.

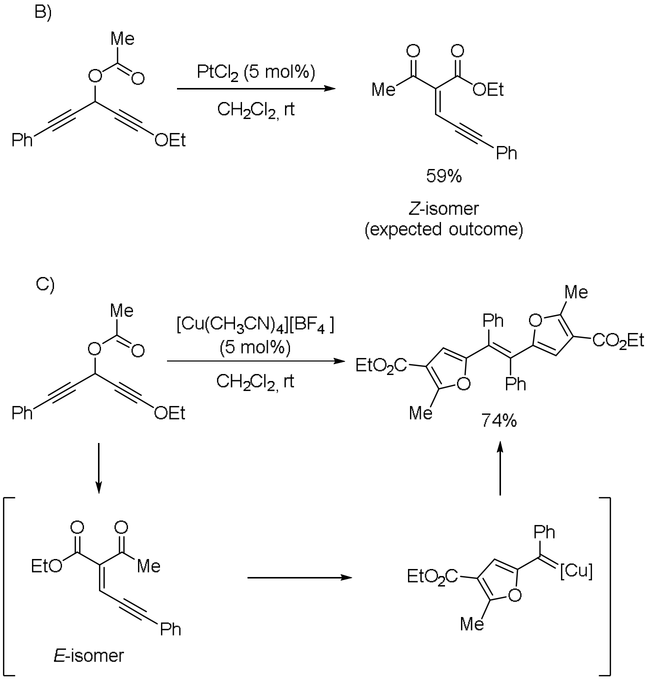
After these seminal works, 2-furyl metal carbene complexes have become versatile intermediates and a number of synthetic applications have been developed by trapping with suitable substrates. Specifically, 2-furyl metal carbene intermediates exhibit a rich chemistry in carbene transfer reactions such as cyclopropanation, aziridination, cyclopropenation, C-H and X-H insertions, cross-coupling, oxidation, etc. In this personal account we will mainly focus on those transformations developed in our research group using copper and zinc catalysts.

3.1. Copper-catalyzed synthesis of functionalized furans *via* (2-furyl)carbene complexes

Our interest in the generation and applications of (2-furyl)carbene intermediates started with an unexpected observation. In 2007, we reported the metal-catalyzed rearrangements of alkoxy-substituted propargylic esters to Knoevenagel adducts.[9] We found that the stereochemical outcome depended on the catalyst used. Specifically, we found that $PtCl_2$ and $[Cu(CH_3CN)_4][BF_4]$ performed the isomerization with complementary *Z*/*E* stereoselectivity; while the use of $PtCl_2$ as catalyst afforded exclusively the *Z*-isomer, $[Cu(CH_3CN)_4][BF_4]$ provided selectively the *E*-isomer (Scheme 7A). These transformations are supposed to proceed through initial 1,3-acyloxy migration with generation of an allene intermediate.[10] When a bis-propargylic ester was subjected to the isomerization conditions, the process was found to proceed with complete chemoselectivity through the alkoxy-substituted alkyne. Accordingly, the $PtCl_2$-catalyzed process led to the expected *Z*-configurated enyne Knoevengel adduct (Scheme 7B). Surprisingly, the reaction with $[Cu(CH_3CN)_4][BF_4]$ resulted in the formation of a dimeric compound (Scheme 7C). This unexpected outcome was rationalized in terms of initial generation of the expected *E*-configurated enyne Knoevenagel adduct and subsequent 5-*exo*-dig cyclization to give a 2-furyl copper carbene intermediate, which would evolve to the final olefinic compound through a dimerization reaction, a very common process in copper-carbenoid chemistry.



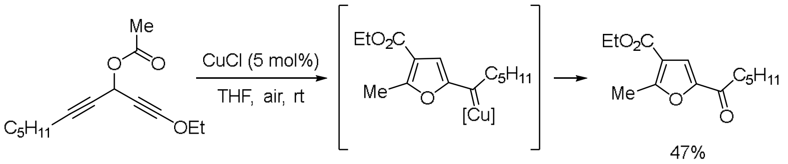
catalyst	yield	*Z*/*E*
$PtCl_2$	81%	> 95 : 5
$[Cu(CH_3CN)_4][BF_4]$	84%	10:90



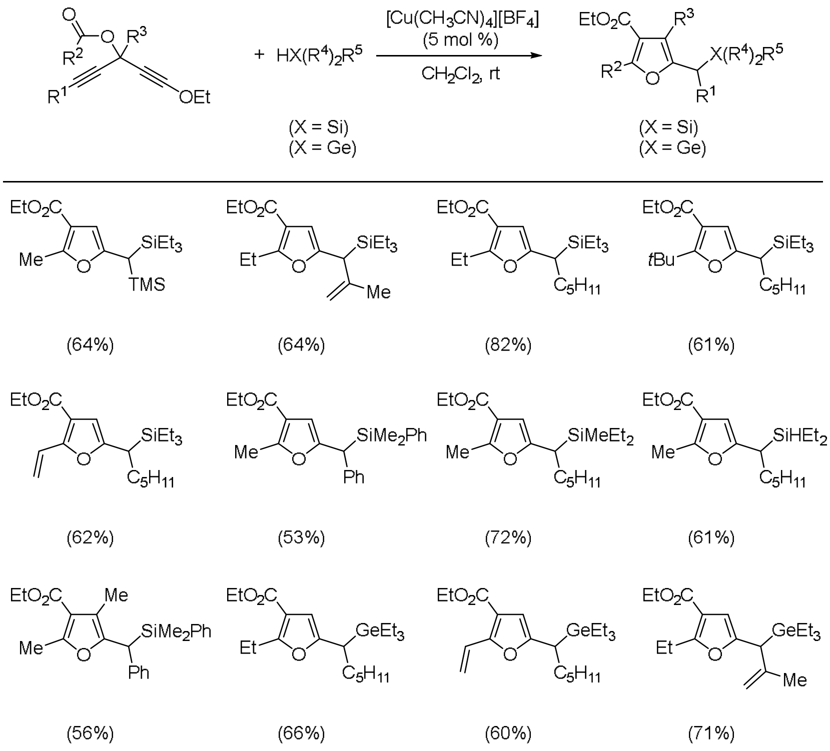
Scheme 7. A) Metal-based stereospecific rearrangement of propargylic esters. B) $PtCl_2$-catalyzed isomerization of a bis-propargylic ester. C) Unexpected outcome in the copper-catalyzed reaction of a bis-propargylic ester and proposed intermediates

Based on this unexpected outcome, we realized that the reactivity of the proposed Cu(I)-carbene complex could be exploited in order to access to functionalized furan derivatives. To this end, we initially found that treatment of the starting bis-propargylic esters with a catalytic amount of CuCl (5 mol%) under air delivered the corresponding 2-acylfurans resulting from a cycloisomerization/carbene oxidation sequence (Scheme 8).[11] In addition to the synthetic relevance of this transformation, this result would support the participation of a Cu(I)-carbene complex.

Disappointingly, when the Cu(I)-catalyzed cycloisomerization of the bis-propargylic ester substrate was conducted in the presence of both activated and non-activated alkenes no cyclopropanation occurred. Instead, alkenes arising from the dimerization of the corresponding carbene intermediates were in all the cases obtained. By contrast, the $[Cu(CH_3CN)_4][BF_4]$-catalyzed reaction of bis-propargylic esters in the presence hydrosilanes resulted in the formation of furan derivatives resulting from a cycloisomerization/carbene Si-H bond insertion (Scheme 9).[11] This transformation exhibited a good scope with respect to both components. We also found that the proposed Cu(I) carbene intermediate is smoothly captured by triethylgermanium hydride.



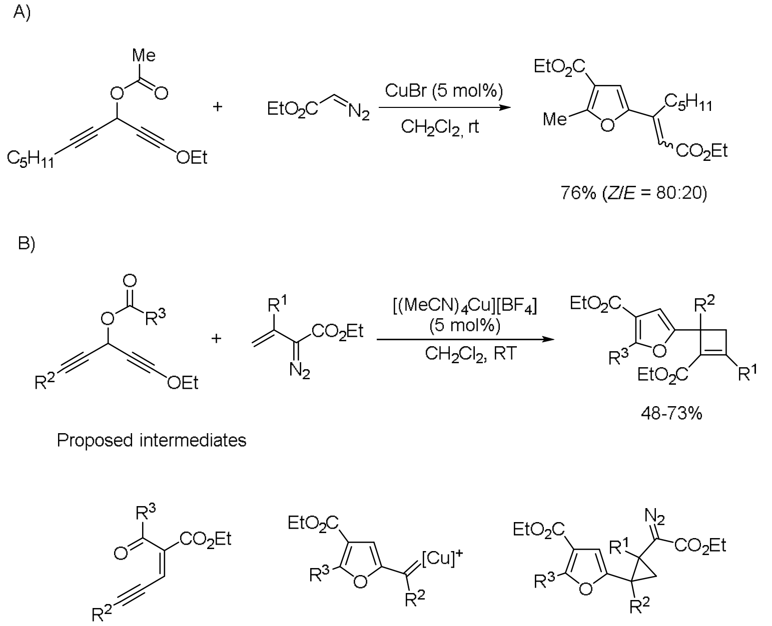
Scheme 8. Synthesis of acylfurans through a cycloisomerization/carbene oxidation sequence



Scheme 9. Cu(I)-catalyzed synthesis of furan derivatives from hydrosilanes and trietylgermanium hydride

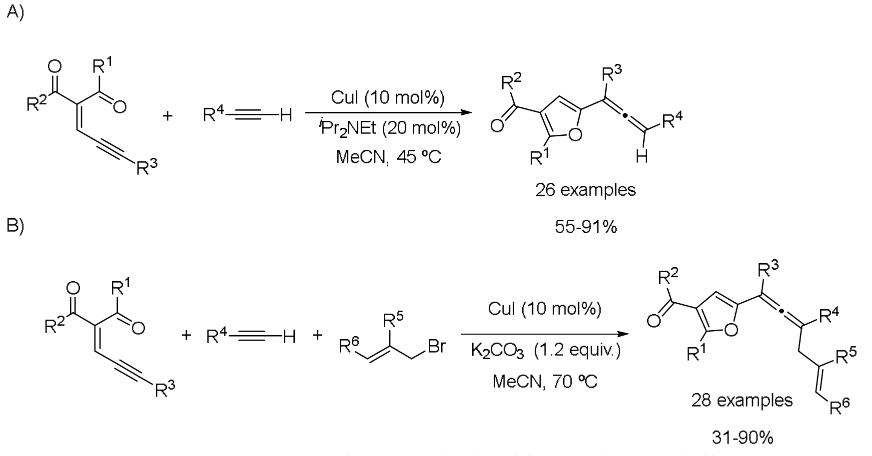
Next, we briefly investigated the viability of a heterocoupling reaction in order to form a carbon-carbon double bond. To this end, bis-propargylic esters were reacted with 2.5 equivalents of ethyl diazoacetate (EDA) in the presence of CuBr (5 mol%) leading to the corresponding furan derivatives featuring a vinyl moiety at C-2 along with variable amounts of maleate and fumarate esters arising from the dimerization of EDA (Scheme 10A).[11] This heterocoupling reaction proceeds in good yields and moderate selectivity with a preference for *Z* isomer formation.

To further expand the synthetic utility of this unusual heterocoupling reaction, we extended the study to vinyldiazo compounds. Surprisingly, the expected cross-coupling conjugated diene was not formed. Instead, furyl-substituted cyclobutenes were isolated in moderate to good yields (Scheme 10B).[12] These compounds are proposed to result from a cascade process involving: i) initial isomerization of the bis-propargylic substrate to the *E* Knoevenagel adduct, ii) 5-*exo*-dig cyclization to generate a 2-furyl copper(I) carbene species, iii) cyclopropanation of the carbon-carbon double bond of the vinyldiazo compound with generation of a cyclopropyldiazo intermediate, and iv) regioselective ring expansion to the final cyclobutene derivative.[13] It should be noted that this reactivity pattern of the vinyldiazo compound component with participation of its carbon-carbon double bond is extremely infrequent, and contrasts with the commonly carbene formation observed in most of the metal-catalyzed transformations of these diazo compounds.[14]



Scheme 10. Cu(I)-catalyzed synthesis of vinylfuran derivatives by hetero-coupling reaction

In 2014, Wang and co-workers reported the synthesis of furan-substituted allenes through CuI-catalyzed cross-coupling of enynones and terminal alkynes (Scheme 11A).[15]



Scheme 11. Copper-catalyzed synthesis of furan-substituted allenes

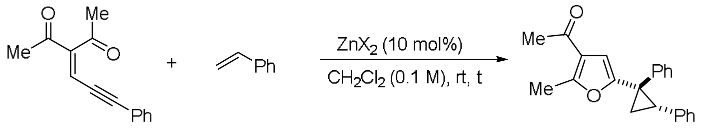
This transformation was supposed to proceed through a sequence involving copper alkynylation, copper carbene formation, migratory insertion and final protonation. In a subsequent report, the same group extended the use of other coupling partner in this cross-coupling reaction. Specifically, they found that allyl halides are also suitable electrophiles providing the corresponding tetrasubstituted allene derivatives (Scheme 11B).[16]

3.2. Zinc-catalyzed synthesis of functionalized furans *via* (2-furyl)carbene complexes

As a continuation of our interest in the development of sustainable synthetic applications based on the catalytic generation of (2-furyl)carbene intermediates we decided to explore the use of zinc salts as catalysts.[17] There were various reasons for our interest in this research. First, zinc is an abundant and non-toxic metal and its salts are generally stable towards air and moisture. Despite this, at the time the use of zinc salts in catalytic transformations involving organometallic intermediates remained almost unexplored. This fact is really surprising if one considers that the organometallic chemistry of zinc is an old subject. On the other hand, since the seminal work by Simmons and Smith in 1958,[18] the reaction of zinc carbenoids with olefins (the so called Simmons-Smith cyclopropanation reaction) represents arguable one of the most important methodologies for the synthesis of the cyclopropane ring,[19] a common structural motif in numerous natural products and bioactive compounds. At the beginning of our research on this topic in 2012, the number of available precursors for the generation of zinc carbenoids was very limited. In fact, more than fifty years after the seminal work by Simmons and Smith, diiodoalkanes, specifically diiodomethane, remained the most common precursors for the generation of zinc carbenoids. Occasionally, carbonyl compounds[20] and diazo compounds[21] were also used for the generation of these useful intermediates. Regarding the reactivity of zinc carbenoids, we would like to point out two general features. The first one is that the reactivity of these intermediates has been extensively studied toward olefinic derivatives (cyclopropanation reaction) but studies involving other organic substrates are very scarce. On the other hand, almost all synthetic applications based on the participation of zinc carbenoids required the use a stoichiometric amount of the corresponding zinc source.[22]

In this context, we thought that the development of new zinc-catalyzed cyclopropanation reactions would be very interesting from a synthetic point of view. Based on the experience gained in the previously discussed copper-catalyzed transformations, we envisioned enynones as convenient precursors for the generation of zinc carbenoids.

To test the viability of this hypothesis first we studied the reaction of the model enynone depicted in Scheme 12 with styrene as the trapping reaction in the presence of a catalytic amount (5 mol%) of several zinc salts in dichloromethane as the solvent at room temperature.

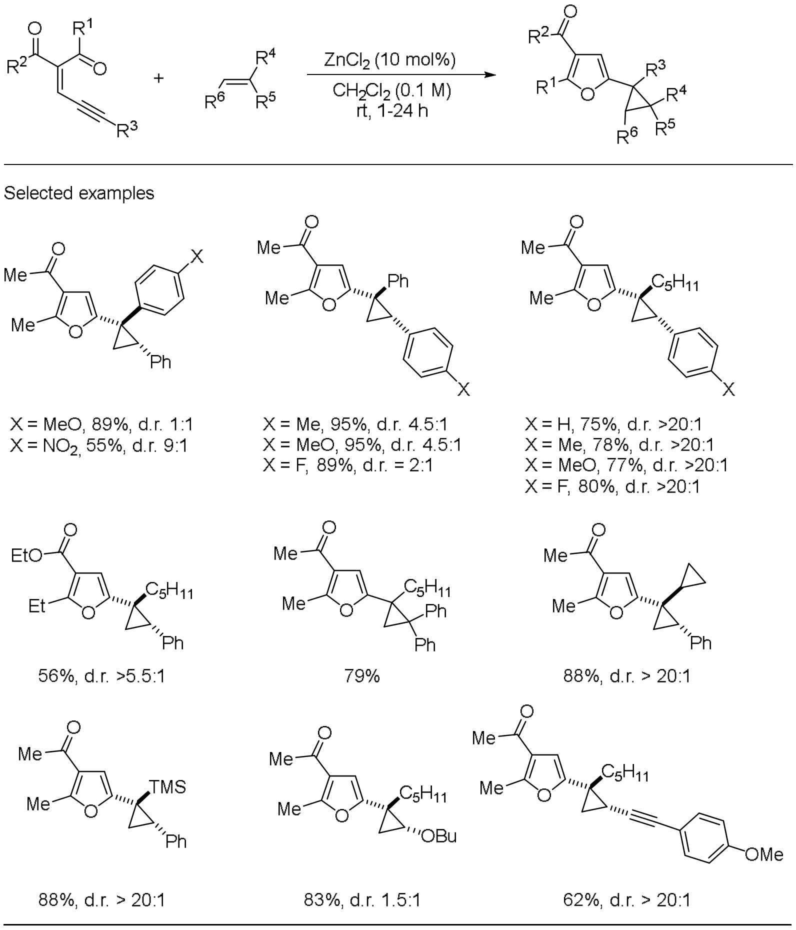


ZnX$_2$	t (h)	Yield (%)	d.r.
Zn (OAc)$_2$	48	-	-
Zn (OTf)$_2$	48	40	3.0:1
ZnI$_2$	2	74	3.5:1
ZnBr$_2$	2	85	3.5:1
ZnCl$_2$	1.5	99	3.5:1
AuCl$_3$	24	56	1.2:1

Scheme 12. Zinc-catalyzed cyclopropanation reaction using enynones as carbenoid precursors: initial screening

As shown in Scheme 12, a number of zinc salts were able to catalyze this transformation. The best result was obtained with $ZnCl_2$. In this case we were able to isolate the target cyclopropane derivative in almost quantitative yield as a 3.5:1 mixture of stereoisomers. Noteworthy, in this transformation $ZnCl_2$ performed better in terms of both chemical yield and stereoselectivity than $AuCl_3$, whose use had been previously reported.[23]

Having demonstrated the validity of our hypothesis, next we studied the scope of this zinc-catalyzed cyclopropanation reaction. We found that the reaction was compatible with a number of enynones and alkenes providing the corresponding cyclopropane derivatives in good yields and selectivities (Scheme 13).[24,25] For example, the reaction tolerated aryl, alkyl, cycloalkyl and silyl groups at the alkyne. Regarding the olefinic component, the cyclopropanation reaction worked well with mono- and di-substituted alkenes. Enol ethers were also suitable substrates for this cyclopropanation reaction. Finally, the reaction with an enyne proceeded with complete chemoselectivity with exclusive participation of the olefinic moiety.

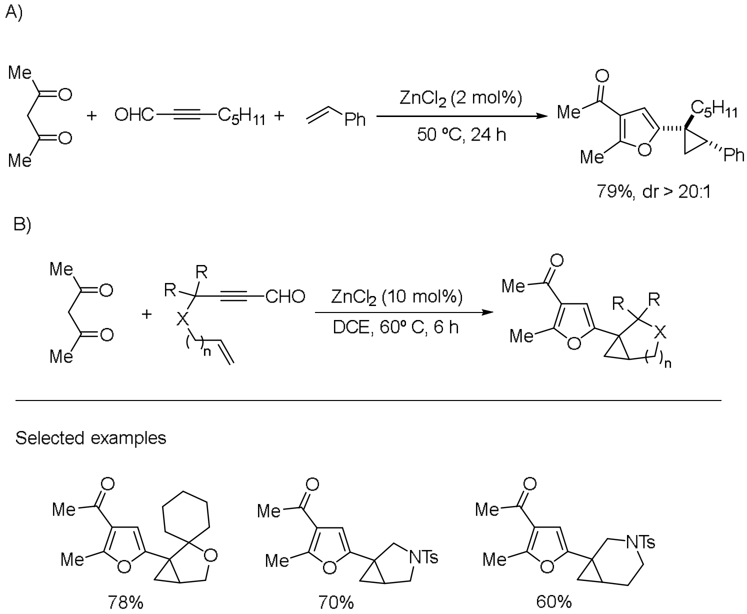


Scheme 13. Zinc-catalyzed cyclopropanation reaction using enynones as carbenoid precursors: scope.

Taken into account that the starting enynone derivatives used in this work were prepared by a conventional base-promoted Knoevenagel condensation and considering the ability of $ZnCl_2$ to catalyze some condensation reactions,[26] we decided to investigate the feasibility of preparing the cyclopropylfuran derivatives in a more straightforward manner through a multicomponent reaction involving initial

$ZnCl_2$-catalyzed Knoevenagel condensation.[27] This plan worked out rather well, and a representative example is provided in Scheme 14A. So, heating a mixture of 2,4-pentanedione, 2-octynal and styrene in the presence of just 2 mol% of $ZnCl_2$ afforded the desired furan derivative in good yield and complete selectivity. In this nice multicomponent reaction, three commercially available starting materials were converted into a quite complex product resulting from two cyclization reactions in a single experimental operation. In most cases, this multicomponent reaction, in which water is the only by-product formed, worked efficiently under solvent-free conditions. The reaction exhibited a notable scope with respect to the three components. Finally, we were able to perform this reaction on a gram-scale without any erosion of its efficiency and selectivity.

To further increase the synthetic utility of this one-pot protocol we also investigated the intramolecular variant. The selected results provided in Scheme 14B demonstrate the potential of this methodology for the synthesis of structurally complex polycyclic scaffolds from readily available starting materials in a single experimental operation.

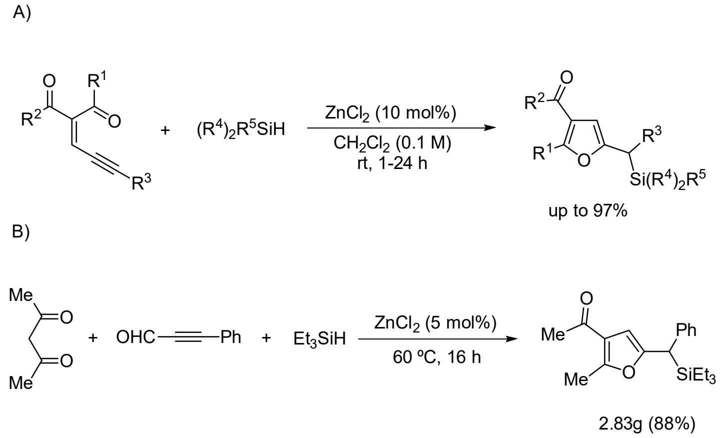


Scheme 14. A) Zinc-catalyzed multicomponent variant: Representative example. B) Intramolecular version.

To gain further information about the structure of the intermediates involved in these cyclopropanation reactions we decided to study the reactivity of our systems toward hydrosilanes. We thought this reaction could provide valuable information because the insertion into the silicon-hydrogen bond is a quite general process for many metal carbene complexes, although virtually unexplored in zinc carbenoid chemistry.[28]

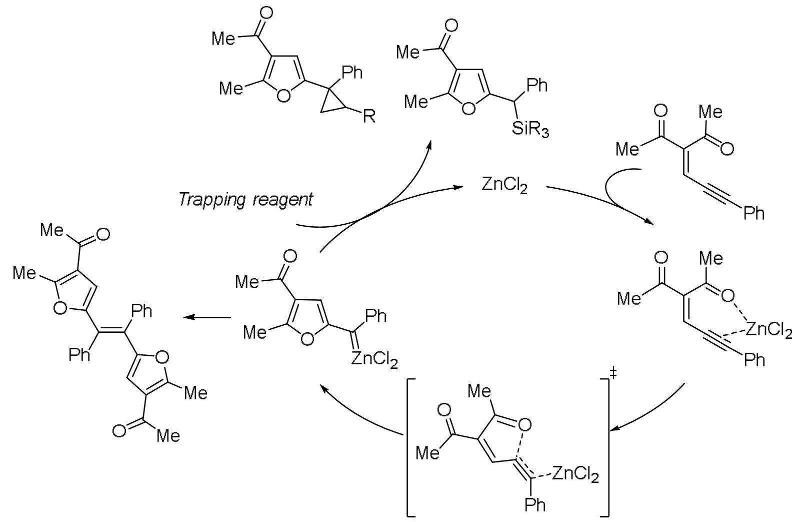
In line with our expectations, treatment of enynones with hydrosilanes in the presence of 10 mol% of $ZnCl_2$ delivered the corresponding functionalized furan derivatives in good yields (Scheme 15A). This silicon-hydrogen bond functionalization exhibited a good scope with respect to both components. Even cyclic and linear polysiloxanes were able to participate in this transformation affording the corresponding furan-containing oligomers.

These functionalized furan derivatives were also available by means of a multicomponent reaction involving a 1,3-diketone, an acetylenic aldehyde and the corresponding hydrosilane.[29] Pleasingly, we found that this multicomponent reaction proceeded uneventfully on a gram-scale. A representative example of this multicomponent approach is provided in Scheme 15B.



Scheme 15. A) Zinc-catalyzed synthesis of furan derivatives from enynones and silanes. B) Multicomponent version.

All these transformations involving alkenes and silanes pointed to a zinc carbene intermediate. As depicted in Scheme 16, the formation of this key intermediate would involve initial coordination of the substrate to $ZnCl_2$, where the metal is coordinated to a carbonyl group and the alkyne.[30] This complex would then undergo a 5-*exo-dig* cyclization by nucleophilic attack of the carbonyl oxygen atom to the C4 carbon atom, thus generating the corresponding zinc carbene intermediate which would be intercepted by the alkene or silane to give the final products. The structure of the final products after reaction with the trapping reagent in fully consistent with the participation of a carbene intermediate because additions and insertions are typical carbenoid reactions. On the other hand, the isolation of a dimeric compound in the control experiment performed in the absence of trapping reagent is also congruent with the participation of a carbenic intermediate because the dimerization is another common pathway in carbenoid chemistry.



Scheme 16. Proposed mechanism for the zinc-catalyzed reaction of enynones with alkenes and silanes.

A computational study provided further support for this mechanistic pathway. In particular, our DFT calculations would rule out the participation of a carbenoid intermediate featuring a classical

Simmons-Smith structure. Indeed, according to our calculations the Fischer-type carbene complex is predicted to be almost 20 kcal/mol more stable than the carbenoid with the classical structure (Figure 1).

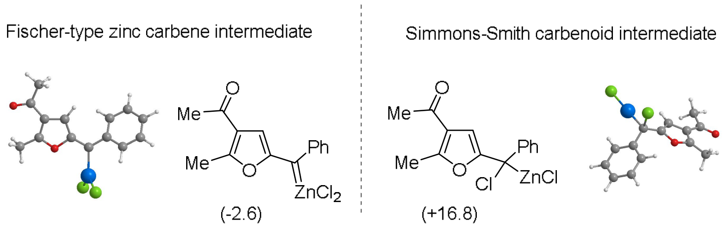
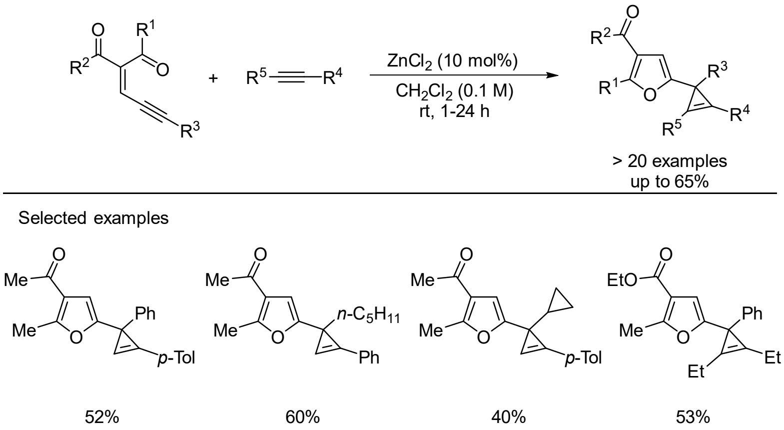


Figure 1. Relative energies of Fischer-type zinc carbene and Simmons-Smith carbene intermediates.

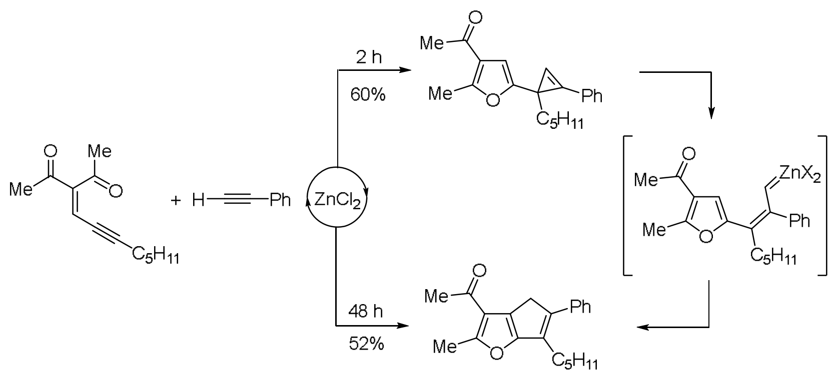
Based on these computational predictions, we realized that the different structure of the intermediate involved in our transformations could give rise to a different reactivity, thus opening up new opportunities in zinc carbenoid chemistry. With this idea in mind, we investigated the generation of the postulated zinc carbene intermediate in the presence of alkynes. The main reason for this interest was that alkynes are not suitable substrates toward zinc carbenoids generated under classical Simmons-Smith conditions. In other words, the Simmons-Smith reaction represents a powerful methodology for the synthesis of cyclopropane derivatives, but it is useless for the preparation of cyclopropenes when using alkynes as trapping reagents. For this reason, we were very happy when we found that the reaction of enynones with alkynes provided cyclopropene derivatives featuring a furyl substituent (Scheme 17).[31] Once again, $ZnCl_2$ was the most efficient catalyst for this transformation. As shown in the selected examples depicted in Scheme 17, both terminal and internal alkynes participated in this transformation with a similar efficiency. A preliminary computational study supported also in this case the participation of a zinc carbene intermediate. Even though the yields reached are in all the cases moderate, this transformation represents the first zinc catalyzed cyclopropenation reaction, a challenging process in zinc carbenoid chemistry.



Scheme 17. Zinc-catalyzed synthesis of cyclopropene derivatives.

While exploring the scope of this transformation, we found that in some cases the final outcome depended on the reaction time. For example, in the reaction of the enynone shown in Scheme 18 with phenylacetylene standard chromatographic work-up after two hours afforded the expected cyclopropene derivative in 60% yield. By contrast, running the reaction for 48 h led to a tetrasubstituted furan derivative in moderate yield.

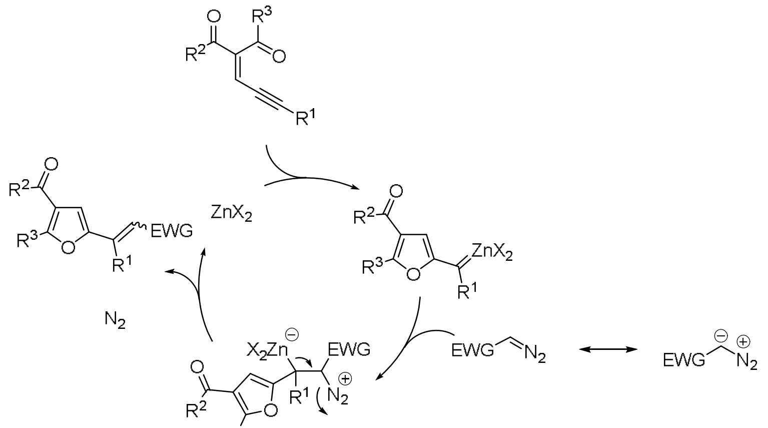
As expected, in the formation of this new product the cyclopropene is an intermediate as demonstrated a control experiment in which it was converted into the final product. The formation of this product would involve initial ring-opening of the cyclopropene with generation of a zinc carbene intermediate, which in turn would evolve to the final product through an electrophilic Friedel-Crafts cyclization.



Scheme 18. Synthesis of tetrasubstituted furan derivatives.

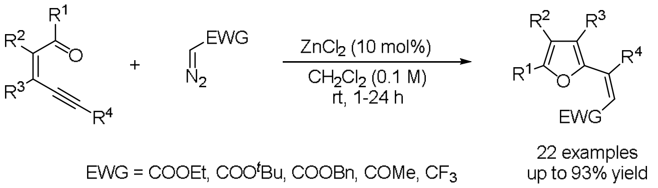
It should be noted that the generation of vinylcarbene intermediates from cyclopropenes has been documented but mainly in the presence of gold- or rhodium based catalysts.[32] This unexpected result opened up a completely new research line in our group focused on the generation of zinc carbenoids from simple cyclopropenes.[33]

Next, we decided to study the reactivity of enynones towards stabilized diazo compounds under zinc catalysis. The most relevant synthetic application of this type of diazo compounds relies on the decomposition in the presence of transition metal catalysts to generate electrophilic metal carbene intermediates. Many transition metals are able to promote this transformation and many synthetic applications have been developed on the basis of this chemical behavior. However, in general zinc salts do not decompose stabilized diazo compounds.[34] We thought that this apparent limitation could make diazo compounds suitable reagents for the nucleophilic trapping of the postulated zinc carbene intermediate. In fact, carbon-carbon bond formation by attack of the nucleophilic carbon atom of the diazo compound to the electrophilic one of the carbene intermediate would generate an intermediate, which through an elimination reaction would render the process catalytic (Scheme 19). This reactivity would furnish relevant 2-alkenyl furan derivatives in a straightforward way.



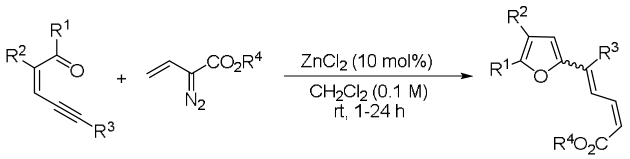
Scheme 19. Synthesis of vinylfuran derivatives by coupling of enynones with diazo compounds under zinc catalysis: working hypothesis.

As anticipated, reaction of enynones with diazo compounds in the presence of a catalytic amount of $ZnCl_2$ (5 mol%) led to the desired alkenylfurans in good yields and selectivities (Scheme 20).[35] This process was compatible with diazo compounds such as diazoesters with different substitution pattern, diazoketones or even trifluoromethyldiazomethane. In this last case, the required diazo compound was generated *in situ* according to a protocol developed by the group of Carreira.[36]



Scheme 20. Synthesis of vinylfuran derivatives by coupling of enynones with diazo compounds under zinc catalysis.

Soon later, we extended this unusual cross-coupling reaction to vinyldiazo compounds.[37] This study allowed us to prepare a family of furyl-substituted dienoate derivatives in good yield (Scheme 21). Notably, this coupling reaction takes place through the γ-carbon atom of the vinyldiazo compound. Interestingly, the reactivity found in this zinc-catalyzed transformation differs from that previously observed for the copper-catalyzed reaction, which yielded cyclobutene derivatives (see Scheme 10B).



Scheme 21. Zinc-catalyzed coupling of enynones and vinyldiazo compounds.

4. Conclusions

When generated from 2-furyl diazo or 2-furyldiazirine derivatives in the presence of potential trapping reagents, 2-furyl carbenes do not undergo any of the typical carbenic reactions. In the last decade, this limitation has been overcome by using readily available enynones as substrates in combination with several metal catalysts. The generated 2-furyl metal carbene complexes exhibit a rich chemistry which has been widely exploited for synthetic purposes. To this end, catalysts based on precious transition metals such as rhodium and gold have been extensively studied providing access to diverse furan derivatives. In this field, our group focused mainly on the use of catalysts based on earth-abundant metals. The examples described above demonstrate the potential and versatility of this approach in heterocyclic chemistry. A critical analysis of the current state of the art provided in this personal account allows for the identification of some areas in which there is yet room for improvements. For example, so far, enantioselective transformations remain underexplored and advances in this field can be foreseen. On the other hand, efforts aimed at the elucidation of the actual structure of the intermediates involved in these transformations would be very helpful in order to achieve a better understanding of the reactivity profiles observed.

In summary, we are convinced that 2-furyl metal carbene intermediates will play an important role in heterocyclic chemistry evolving into a more and more powerful synthetic tool.

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