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Zinc-Catalyzed Cyclopropenation of Alkynes via 2-Furylcarbenoids

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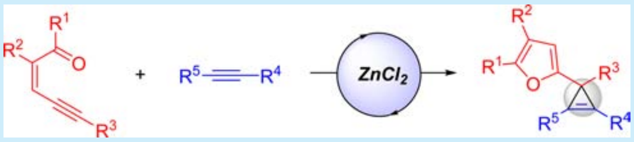
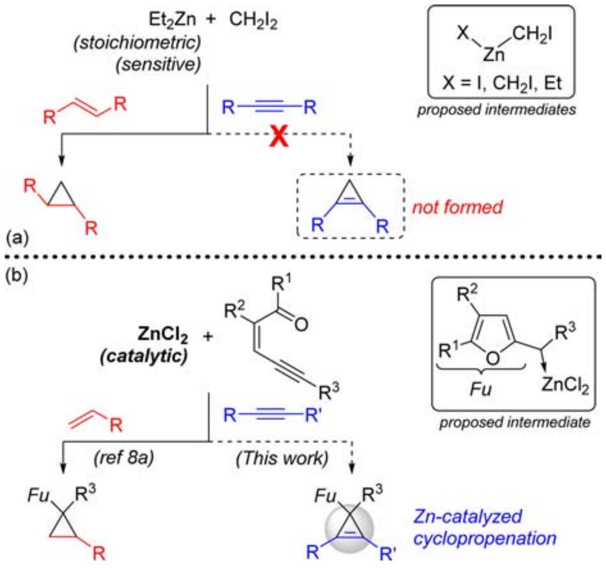
Ⓢ *Supporting Information*

ABSTRACT: An unprecedented cyclopropenation reaction of alkynes catalyzed by $ZnCl_2$ is reported. While Simmons–Smith-type carbenoids failed in the [2 + 1]-cycloaddition with alkynes, the use of enynones as the carbene source enables the preparation of substituted 2-furyl cyclopropene derivatives with remarkable scope.



Strained three-membered carbocycles, namely cyclopropanes and cyclopropenes, are a class of compounds that have fascinated chemists for years.[1] The particular physical properties of these compounds translate into an incomparable reactivity, which has been fruitfully exploited in organic synthesis.[2] The Simmons–Smith reaction, discovered in 1958,[3] described the first modular synthesis of cyclopropanes using alkenes and CH_2I_2 as C1 synthons in the presence of stoichiometric amounts of the zinc–copper couple. Subsequent studies on this transformation have enabled the establishment of broadly applicable and reproducible reaction conditions using an excess of Et_2Zn (Furukawa’s protocol).[4] Species such as XCH_2–ZnY or $(XCH_2)_2Zn$ (X = halogen) are now accepted as the zinc intermediates involved in the cyclopropanation reaction (Scheme 1, a).[5] In contrast to the reaction with alkenes, the Simmons–Smith reaction proved inapplicable to alkynes, making this synthetic strategy toward the corresponding cyclopropenes unrealizable.[6,7] Indeed, the use of terminal alkynes gives rise to C–H bond insertion products in low yields, while the corresponding cyclopropenes were not observed.[6a] Moreover, the reaction with internal alkynes led to complex reaction mixtures.[6b]

Scheme 1. Cyclopropanation vs Cyclopropenation Reactions Involving Zinc



In the last years, we have undertaken research devoted to the development of zinc-catalyzed processes with potential relevance to organic synthesis.[8,9] Among others, we reported the $ZnCl_2$-catalyzed cyclopropanation reaction of alkenes using enynones as carbene precursors (Scheme 1, b).[8a] Computational studies suggested the participation of a furyl Fischer-type zinc carbenoid intermediate. On the contrary, the involvement of a zinc intermediate structurally related to those proposed in the Simmons–Smith reaction is unlikely due to its higher energy compared to the furyl carbene. In addition, the absence of a reaction pathway connecting with the final cyclopropane argues against the role of Simmons–Smith-like intermediate in the transformation.[8a]

Considering the structural difference of both intermediates, we believed that this contrast might influence the reactivity toward alkynes allowing the access to cyclopropene derivatives. Herein, we report our findings on an unprecedented zinc-catalyzed cyclopropenation reaction with alkynes.

Enynone **1a** and a terminal alkyne such as phenylacetylene **2a** were selected as model substrates to evaluate the feasibility of achieving zinc-promoted cyclopropenation reactions (Scheme 2). At the outset, we used reaction conditions analogous to those employed with alkenes,[8a] specifically $ZnCl_2$ (10 mol %), and an excess of **2a** (6.0 equiv) in CH_2Cl_2 at ambient temperature. Gratifyingly, we observed the formation of the desired cyclopropene **3a** in a moderate 48% yield. A subsequent study of the reaction conditions allowed us to isolate compound **3a** in 58% yield after column chromatography when the reaction temperature was decreased to 0 °C. At lower temperatures, the transformation occurred with very low conversions at long reaction times. Other commercially available zinc salts proved slightly less effective than $ZnCl_2$.

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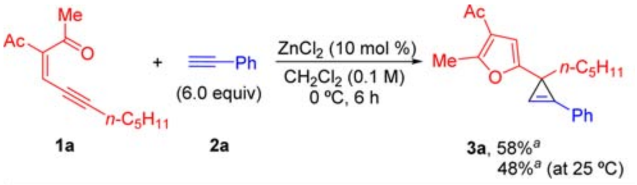
Scheme 2. Zinc-Catalyzed Cyclopropenation of 2a: Screening



Modifications of the standard conditions

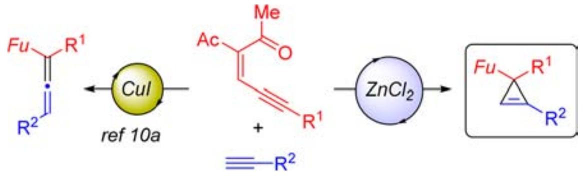
Catalyst	Solvent	Alkyne equiv
ZnBr$_2$; **3a**, 49%[b] (at 0 °C)	PhMe; **3a**, 55%[a]	**2a** (3.0 equiv); **3a**, 47%[b]
ZnI$_2$; **3a**, 50%[b] (at 0 °C)	THF; **3a**, 27%[b]	**2a** (1.5 equiv); **3a**, 39%[b]
Zn(OTf)$_2$; **3a**, 29%[b] (at 25 °C)		

[a] Isolated yield. [b] Yield estimated by ^{1}H NMR analysis using CH$_2$Br$_2$ as internal standard.

Among other solvents, only toluene provided similar results, while reducing the amount of **2a** led to a significant decrease in the yield. Remarkably, the preparation of compound **3a** represents the first example of a cyclopropenation of an alkyne using a zinc salt as the catalyst.

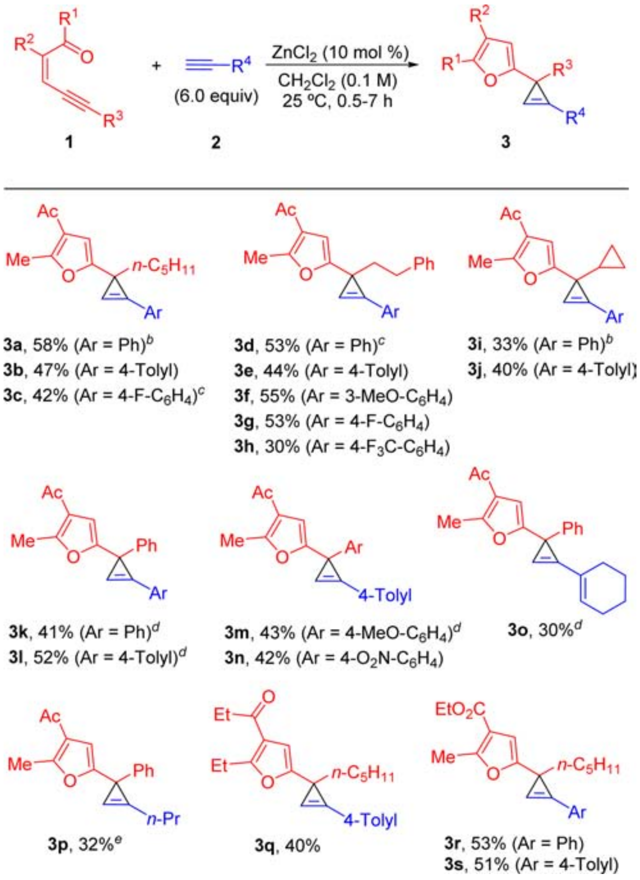
Moreover, this result shows a complementary reactivity of zinc salts with respect to copper ones in the reaction of enynones **1** with alkynes. Thus, while the use of CuI leads to the formation of a furyl allene, a known reactivity for copper carbenoids, ZnCl$_2$ enables the cyclopropenation (Scheme 3).[10−12]

Scheme 3. Complementary Reactivity on Enynones toward Alkynes with Copper and Zinc Salts



The scope of this transformation was subsequently explored (Scheme 4). Enynones **1** bearing alkyl groups at the alkyne terminus were first evaluated using differently substituted aromatic alkynes, affording cyclopropenes **3a−h** in moderate yields. Interestingly, a cyclopropyl-substituted enynone afforded cyclopropenes **3i**,**j**, which contain an uncommon [1,1′-bi(cyclopropan)]-2-ene core.[13] Moreover, aryl-substituted enynones participated in the cyclopropenation reaction to afford compounds **3k−n**.[14] When a 1,3-enyne was employed, cyclopropene **3o** was chemoselectively obtained, as the alkene moiety did not participate in the reaction. The use of alkyl-substituted alkynes proved more challenging. Thus, enynones bearing alkyl groups at substituent R^3 did not give rise to the corresponding cyclopropene when using 1-pentyne yet afforded a complex reaction mixture. In contrast, the reaction of phenyl-substituted enynone **1d** with 1-pentyne led to cyclopropene **3p**, yet the yield was significantly lower and a stoichiometric amount of ZnCl$_2$ was required. Further modifications on the structure of the enynones were also evaluated. Thus, cyclopropenes **3q−s** were obtained in yields similar to those previously observed. As limitations, the present protocol proved unapplicable to other terminal alkynes such as (trimethylsilyl)acetylene or methyl propiolate, which gave rise to complex reaction mixtures.[15]

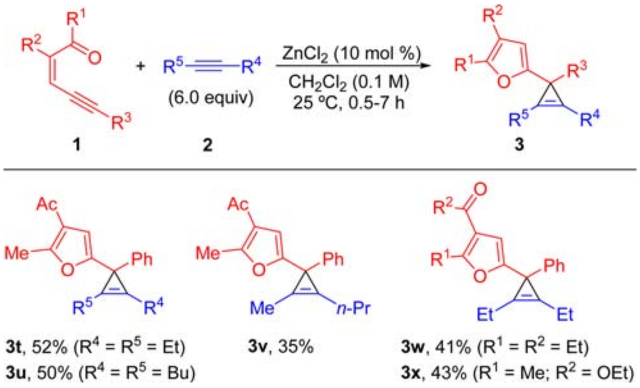
Scheme 4. Zinc-Catalyzed Cyclopropenation of Terminal Alkynes Using Enynones as Carbene Source: Scope[a]



[a] Reaction conditions: **1** (0.25 mmol), **2** (1.5 mmol, 6.0 equiv), ZnCl$_2$ (10 mol %), CH$_2$Cl$_2$ (0.1 M), 25 °C. Yields correspond to isolated products. [b] At 0 °C. [c] Using 20 mol % of ZnCl$_2$. [d] A byproduct was also obtained; see ref 14. [e] Using 100 mol % of ZnCl$_2$.

Then we turned our attention to internal alkynes, whose reactivity in cyclopropenation reactions using metal carbenoids is significantly more restricted compared to terminal acetylenes.[16] Interestingly, we found that the present approach could be extended in some cases to the use of internal alkynes (Scheme 5). Thus, treatment of enynones **1** bearing a phenyl

Scheme 5. Zinc-Catalyzed Cyclopropenation Using Internal Alkynes[a]



[a] Yields are referred to isolated product.

group at R^3 with various dialkyl-substituted alkynes under analogous reaction conditions (10 mol % $ZnCl_2$, 6.0 equiv of the alkyne, CH_2Cl_2 at 25 °C) allowed the preparation of fully substituted cyclopropenes **3t−x** in moderated yields (35−52%). Unsymmetrically substituted alkynes could also be employed as exemplified with the preparation of compound **3v**. In contrast, the procedure is at this stage limited to alkynes bearing primary alkyl groups since we observed complex reaction mixtures or degradation of the starting materials when using internal alkynes bearing secondary/tertiary alkyl or aromatic substituents.

According to previous proposals, we believe that the formation of cyclopropenes **3** might occur through the formation of a zinc furyl carbene intermediate (see Scheme 1).[8] The particular structure of this carbenoid, when compared with the one proposed for the Simmons−Smith reaction, seems to be the key for the subsequent steps. In analogy with the cyclopropanation reaction,[8a] the formation of cyclopropenes **3** might occur via a concerted while asynchronous transition state in which bond formation to the terminal carbon proceeds earlier than the one involving the internal acetylenic carbon.[17] However, different mechanisms could be operating, especially when using internal alkynes.

In summary, we have herein presented the first zinc-catalyzed cyclopropenation reaction of alkynes, an unprecedented reactivity pattern in the chemistry of zinc carbenoids. This procedure makes use of easily available enynones **1** as the zinc carbenoid source and both terminal and internal alkynes. The results depicted in this work are in sharp contrast to previous studies involving zinc carbenoid-like species, which were incapable of promoting cyclopropenation reactions. This preliminary study showed that the present transformation occurs with a remarkably ample scope, including challenging internal alkynes. Thus, a variety of relevant highly substituted cyclopropene derivatives **3** can be accessed in a simple manner. Interestingly, inexpensive and less toxic $ZnCl_2$ served as the catalyst, which operates under very mild reaction conditions. Further studies concerning mechanistic issues and the extension of the scope are currently ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) The use of rhodium catalysts under otherwise identical reaction conditions leads to a cascade sequence involving the participation of cyclopropenes, which could be isolated only in few cases; see: González, M. J.; López, E.; Vicente, R. *Chem. Commun.* **2014**, 5379.

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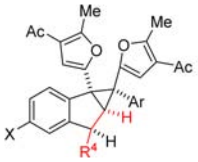
(13) An enynone bearing a *tert*-butyl group at the alkyne terminus did not react with the alkyne under similar reaction conditions.

(14) Compounds **4** (major diastereoisomer shown below) were in some cases obtained. The formation of **4** involves the coupling of two molecules of the corresponding enynone (in black) and one of the alkyne (in red). Attempts to increase the yield of compounds **4** using an excess of the corresponding enynone were unsuccessful. It should be noted that compounds **4** do not arise from the corresponding cyclopropenes **3**. See the Supporting Information for further details.



4k, 20% (R^4 = Ph; Ar = Ph; X = H)
4l, 15% (R^4 = 4-tolyl; Ar = Ph; X = H)
4m, 14% (R^4 = 4-tolyl; Ar = 4-MeO-C_6H_4; X = OMe)
4o, 19% (R^4 = cyclohex-1-en-1-yl; Ar = Ph; X = H)

(15) Attempts to accomplish a zinc-catalyzed one-pot cascade sequence through the generation of the enynone **1** via Knoevenagel condensation proved unsuccessful since complex reaction mixtures were obtained under a variety of reaction conditions.

(16) For a silver-catalyzed cyclopropenation of internal alkynes with diazocompounds as the carbene source, see: Briones, J. F.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 3984.

(17) A similar mechanism has been proposed in the cyclopropenation of terminal alkynes with rhodium carbenoids; see: Nowlan, D. T., III; Singleton, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 6190.