Zinc-Catalyzed Cyclopropenation of Alkynes via 2-Furylcarbenoids

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Supporting Information Placeholder

ABSTRACT: An unprecedented cyclopropenation reaction of alkynes catalyzed by ZnCl₂ 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 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 CH₂I₂ as Cl₁ synthon 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 Et₂Zn (Furukawa’s protocol).⁴ Species such as XCH₂–ZnY or (XCH₂)₂Zn (X = halogen) are nowadays 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 towards 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

In the last years, we have started a research devoted to the development of zinc-catalyzed processes with potential relevance to organic synthesis.⁸,⁹ Among others, we reported the ZnCl₂-catalyzed cyclopropagation reaction of alkenes using enynones as carbene precursor (Scheme 1, b).⁹a 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. Also, the absence of a reaction pathway connecting with the final cyclopropane argues against the role of Simmons-Smith-like intermediate in the transformation.⁹a

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

Scheme 1. Cyclopropanation vs cyclopropenation reactions involving Zinc.

Enynone 1a and a terminal alkyne as phenyl acetylene 2a were selected as model substrates to evaluate the feasibility to achieve zinc-promoted cyclopropenation reactions (Scheme 2). At the outset, we used reaction conditions analogous to
those employed with alkenes, specifically ZnCl₂ (10 mol %), an excess of 2a (6.0 equiv) in CH₂Cl₂ 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 decreasing the reaction temperature to 0 ºC. At lower temperatures, the transformation occurred with very low conversions at long reaction times. Other commercially available zinc salts proved slightly less effective than ZnCl₂. 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.

Scheme 2. Zinc-catalyzed cyclopropenation of 2a: Screening.

![Scheme 2](image1.png)

<table>
<thead>
<tr>
<th>Modifications of the standard conditions</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Alkyne equiv</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnBr₂; 2a, 3a, 49% (at 0 ºC)</td>
<td>PhMe; 3a, 55%</td>
<td>3a, 47%</td>
<td></td>
</tr>
<tr>
<td>ZnCl₂; 10 mol %, 3a, 50% (at 0 ºC)</td>
<td>THF; 3a, 27%</td>
<td>3a, 39%</td>
<td></td>
</tr>
</tbody>
</table>

" Isolated yield. b Yield estimated by ¹H NMR analysis using CH₂Br₂ as internal standard.

Moreover, this result shows a complementary reactivity of zinc salts with respect to copper ones in the reaction of enynones 1 with alkynes. Thus, the use of CuI leads to the formation of a furyl allene, a known reactivity for copper carbenoids, ZnCl₂ enables the cyclopropenation (Scheme 3).

Scheme 3. Complementary reactivity on enynones towards alkynes with copper and zinc salts.

![Scheme 3](image2.png)

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'-bicyclo[2.2.1]hept-2-ene] core. Moreover, ary substituted enynones participated in the cyclopropenation reaction affording compounds 3k-n. 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 R³ 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 ZnCl₂ was required. Further modifications on the structure of the enynones were also evaluated. Thus, cyclopropenes 3q-s were obtained in similar yields to those previously observed. As limitations, the present protocol proved not applicable to other terminal alkynes such as trimethylsilylacetylene or methyl propiolate, which gave rise to complex reaction mixtures.

Scheme 4. Zinc-catalyzed cyclopropenation of terminal alkynes using enynones as carbene source: Scope.

![Scheme 4](image3.png)

" Reaction conditions: 1 (0.25 mmol), 2 (1.5 mmol, 6.0 equiv), ZnCl₂ (10 mol %), CH₂Cl₂ (0.1 M), 25 ºC. Yields correspond to isolated products. b At 0 ºC. c Using 20 mol % of ZnCl₂. d A by product was also obtained, see ref 14. e Using 100 mol % of ZnCl₂.

Then, we turned our attention to internal alkynes, whose reactivity in cyclopropenation reactions using metal carbenoids is significantly more restricted compared to terminal acetylenes. 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...
group at \( R^3 \) with various dialkyl-substituted alkynes under analogous reaction conditions (10 mol % \( \text{ZnCl}_2 \), 6.0 equiv of the alkyne, \( \text{CH}_2\text{Cl}_2 \) 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.

This preliminary study showed that the present transformation of internal alkynes bearing secondary/tertiary alkyl or aromatic substituents.

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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(3) Simmons, H. E.; Smith, R. D. J. Am. Chem. Soc. 1958, 80, 5323.


(10) (a) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. Org. Lett. 2014, 16, 4082. For other examples of the reactivity of copper carbenes with alkynes to yield allenes, see: (b) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. Angew. Chem. Int. Ed. 2011, 50, 1114. (c) Hossain, M. L.; Ye, F.; Zhang, Y.; Wang, J. J. Org. Chem. 2013, 78, 1236. When the reaction was accomplished with ZnCl₂ in the presence of bases (K₂CO₃ or i-Pr₃NE), allene derivatives were not detected, yet significantly lower yields of cyclopropene 3α were observed.

(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.


(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.

(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 diazo compounds 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 III, D. T.; Singleton, D. A. J. Am. Chem. Soc. 2005, 127, 6190.