Small-Ring Compounds

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Zinc-Catalyzed Alkene Cyclopropanation through Zinc Vinyl Carbenoids Generated from Cyclopropenes

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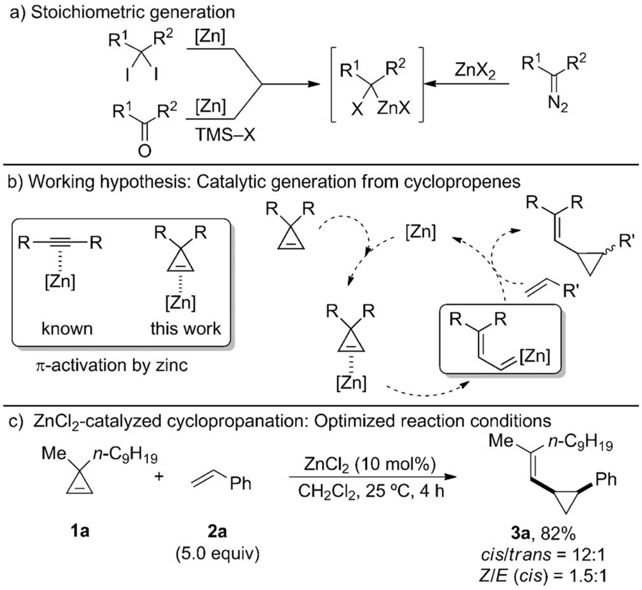
Dedicated to Professor Antonio Echavarren on the occasion of his 60th birthday

Abstract: *The zinc-catalyzed reaction of cyclopropenes with alkenes leading to vinylcyclopropane derivatives is reported. A broad range of alkenes (including highly substituted or functionalized alkenes) is compatible with this protocol. On the basis of trapping experiments and computational studies, this cyclopropanation reaction is proposed to proceed through initial formation of an electrophilic zinc vinyl carbenoid intermediate, which may be involved in a concerted cyclopropanation reaction. The reported protocol represents an unprecedented and simple strategy for the catalytic generation of zinc vinyl carbenoids, which are promising intermediates in organic synthesis.*

Ground-breaking reports on the generation of zinc carbenoids for the cyclopropanation of alkenes was already described by Simmons and Smith in 1958.[1,2] Nowadays, the Simmons–Smith cyclopropanation (SSC) still remains one of the most employed methods to synthesize cyclopropanes. In spite of the age of this venerable transformation, the standard procedures for the generation of these intermediates rely on the use of a large excess of zinc sources, generally Et_2Zn,[3] and diiodoalkanes, mainly CH_2I_2, as the carbenoid precursors (Scheme 1 a).[4] Less common stoichiometric approaches to zinc carbenoids make use of diazo compounds or carbonyl derivatives (including acetals and orthoesters; Scheme 1 a).[5,6]

Because of the growing significance of zinc catalysis in organic synthesis,[7] notable efforts to develop zinc-catalyzed cyclopropanations have been recently performed. Thus, Charette and co-workers reported the use of phenyldiazomethane to generate zinc carbenoids in a catalytic fashion.[8] Besides, considering the ability of zinc salts to activate alkynes towards nucleophiles,[9] we reported the catalytic generation of 2-furyl zinc carbenoids using conjugated enynones as the carbene source.[10] These intermediates were trapped by alkenes and other reagents.[11]

Despite these recent advances in zinc-catalyzed cyclopropanations, the development of catalytic versions of the SSC still remains a significant goal. In particular, the identification of alternative carbene sources and their implementation in organic synthesis would be very convenient.



Scheme 1. Zinc carbenoids: A) Classical stoichiometric approaches. B) Proposed catalytic approach using cyclopropenes as carbene source. C) Optimized reaction conditions. TMS = trimethylsilyl.

In this regard, given that alkynes and cyclopropenes share a number of features,[12] we hypothesized that zinc salts could activate the π bond of a cyclopropene, thus triggering a ring-opening to generate a zinc vinyl carbenoid intermediate, which could be further trapped by alkenes and lead to the corresponding vinyl cyclopropane and catalyst turnover (Scheme 1 b).[13–15] From a synthetic standpoint, this method could represent a convenient catalytic entry to the vinylcyclopropane framework,[16] a key structural motif in relevant compounds such as sesquiterpenoids or chrysantemic acid derivatives.[17]

This working hypothesis was evaluated using the reaction of the easily accessible 3,3-dialkylcyclopropene **1a**[18] with different commercially available zinc salts in the presence of styrene (**2a**) as the alkene (Scheme 1 c). Various zinc salts proved capable of promoting the formation of the vinylcyclopropane **3a** under mild reaction conditions. The formation of **3a** points to the participation of a zinc vinyl carbenoid intermediate, thus supporting our hypothesis. Optimal results involved the use of inexpensive, low toxicity $ZnCl_2$ (10 mol%) and 5.0 equivalents of **2a** in CH_2Cl_2 at ambient

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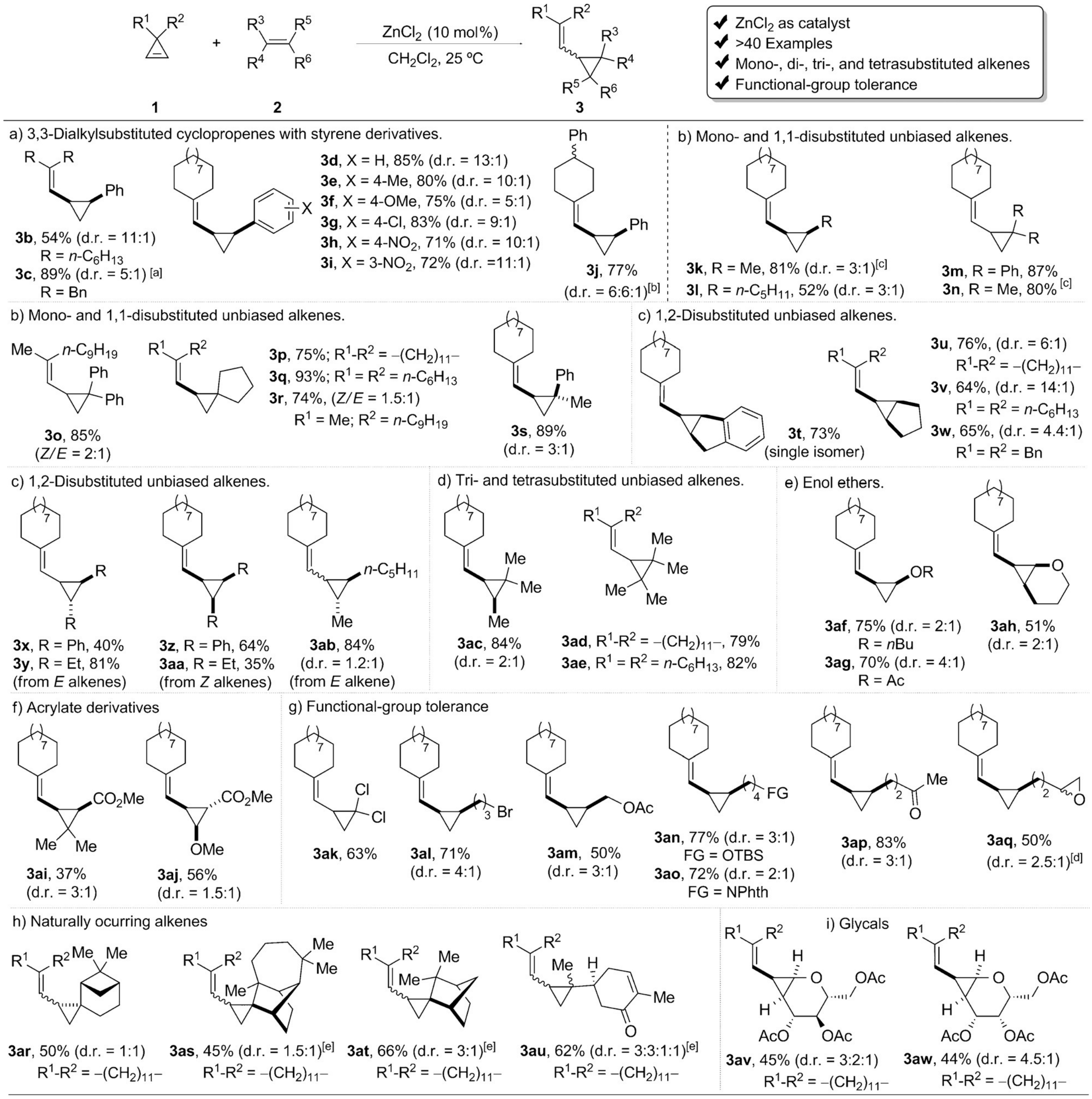
temperature, thus leading to **3a** in 82% yield upon isolation (*cis/trans* = 12:1; *Z/E* = 1.5:1).[19]

By using the optimized reaction conditions, the scope of this zinc-catalyzed vinylcyclopropane synthesis was next evaluated. As shown in Scheme 2, the present protocol shows a remarkably broad scope. First, 3,3-dialkylsubstituted cyclopropenes, employed as the carbenoid source, were initially trapped with various styrene derivatives to afford the compounds **3b–j** in good yields (Scheme 2a). The method tolerated a variety of substitution patterns on the phenyl group without significantly influencing the reaction outcome. In general, the reaction showed a noticeable preference for the formation of the *cis* isomer.[20] Mono- and 1,1-disubstituted alkenes were converted into the corresponding compounds **3k–s**, mostly in good yields (52–89%) and moderate *cis/trans* selectivity (ca. 3:1 for **3k–l,s**; Scheme 2b). Notably, economically relevant raw materials such as propylene and isobutylene could be processed under these reaction conditions. The use of cyclic or acyclic 1,2-disubstituted alkenes was next explored (Scheme 2c). Under the optimized reaction conditions, the corresponding 1,2,3-trisubstituted cyclopropanes **3t–ab** were obtained in yields ranging from moderate to



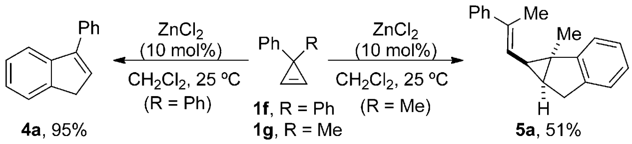
Scheme 2. ZnCl$_2$-catalyzed cyclopropanation using cyclopropenes **1** as a vinyl carbene source: Scope (e–i). Yields are those of the isolated products. The d.r. value was determined by ^{1}H NMR spectroscopy. [a] At 50 °C in 1,2-DCE. [b] **3j** has axial chirality. [c] Alkene was condensed (ca. 1 mL) and the reaction was accomplished in a sealed tube. [d] d.r. = 1:1 with respect to the chiral carbon at the epoxide. [e] Major isomer(s) not determined. NPhth = phthalamide, TBS = *tert*-butyldimethylsilyl.

good (35–85 %). Interestingly, as observed in the classical stoichiometric SSC, these transformations took place with complete stereospecificity with respect to the starting alkene. Moreover, increasing substitution in the alkene had no deleterious effect on the reaction outcome. Thus, tri- and tetrasubstituted alkenes were employed and lead efficiently to the compounds **3 ac–ae** (Scheme 2 d). Once the ability of styrene derivatives and electronically unbiased alkenes to participate in this zinc-catalyzed cyclopropanation reaction was demonstrated, the role of the electronic properties of the alkene was next studied. Hence, electron-rich alkenes such as enol ethers were converted into the alkoxycyclopropanes **3 af–ah** in useful yields with moderate selectivity (Scheme 2 e). In contrast, methyl vinyl ketone and methyl acrylate, representative electron-deficient alkenes, were unreactive.

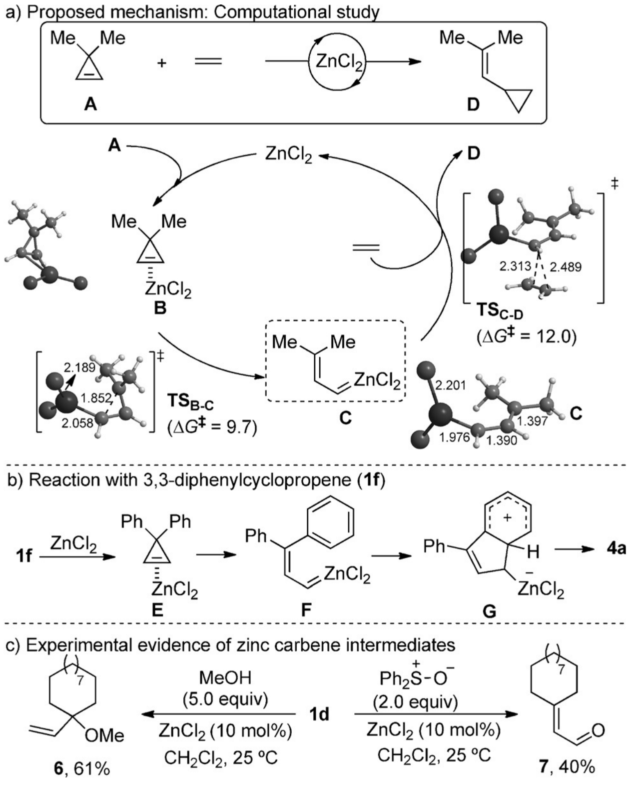
Remarkably, substituted acrylates as methyl 3,3-dimethylacrylate or methyl 3-methoxyacrylate participated in the reaction, thus providing the cyclopropane **3 ai** (37 %) and push-pull cyclopropane **3 aj** (56 %), respectively (Scheme 2 f). Functional-group compatibility was also addressed (Scheme 2 g). As shown, a broad range of functional groups were found to be compatible under the standard reaction conditions, including chloride, bromide, protected alcohol or amine, ketone, and ester, thus affording the corresponding cyclopropanes **3 ak–ap** in moderate to good yields (50–83 %). Even Lewis acid sensitive functionalities such as epoxides were also tolerated as demonstrated the preparation of cyclopropane derivative **3 aq** in a passable 50 % yield.

Taking advantage of this remarkably broad scope, we attempted the modification of representative naturally occurring alkenes (Scheme 2 h). Under the standard reaction conditions, β-pinene was transformed into the cyclopropane **3 ar** in moderate yield (50 %; d.r. = 1:1) without the observation of rearrangement byproducts. Similarly, (+)-longifolene or (+)-camphene were converted into the corresponding cyclopropanes **3 as–at**. In line with our expectations, the most electron-rich alkene was in L-(−)-carvone chemoselectively cyclopropanated to afford **3 au** in good yield (62 %, d.r. = 3:3:1:1). Interestingly, O-acetyl-protected glycals such as D-glucal and D-galactal were suitable alkenes as illustrated by the preparation of the cyclopropanes **3 av–3 aw** in decent yields as a mixture of diastereoisomers (Scheme 2 i).

Aryl substituents in the 3-position of the cyclopropene have a remarkable effect on reactivity (Scheme 3). Thus, when using **1 f** (R = Ph) with or without styrene (**2 a**), under standard reaction conditions, the indene **4 a** was the only isolated product.[21,22] Interestingly, the reaction with **1 g** (R = Me) led to the indane derivative **5 a** (51 %) as a single isomer.[23]



Scheme 3. Reactivity of 3-phenyl-substituted cyclopropenes (**1 f–g**).



Scheme 4. Mechanistic studies. Bond lengths in Å, $\Delta G^{\neq}_{rel}$ in kcal mol^{-1}.

To gain support for the mechanism proposed in Scheme 1, we carried out a computational study, at the B3LYP/6-31G* level of theory,[24] on the model reaction of 3,3-dimethylcyclopropene (**A**) and ethylene with ZnCl$_2$. (Scheme 4 a). According to our calculations, coordination of **A** to ZnCl$_2$ forms the π-type complex **B**, which is 2.4 kcal mol^{-1} more stable than the reactants. Interestingly, this complex evolves by cleavage of C2−C3 bond as can be seen in the analysis of the transition state (**TS**$_{B\text{-}C}$) identified for this reaction, whose activation free energy is 9.7 kcal mol^{-1}. The normal mode associated with the imaginary vibrational frequency of **TS**$_{B\text{-}C}$ shows an elongation of the C2−C3 bond and a sp^3 to sp^2 hybridization change for C3. The intrinsic reaction coordinate (IRC) algorithm indicates that this first-order saddle point is connected with a minimum (**C**), whose structure could be viewed as an electrophilic carbene intermediate. Then, transition state **TS**$_{C\text{–}D}$, showing an activation free energy of 12 kcal mol^{-1}, was found for the [2+1]-cycloaddition reaction of zinc carbenoid intermediate **C** with ethylene, and evolves into the vinylcyclopropane **D**. While **TS**$_{C\text{-}D}$ is a slightly asynchronous transition structure, the cycloaddition is a concerted process according to the IRC.[25] This result is in good agreement with the stereospecificity observed experimentally, and the absence of rearrangements in the reaction with β-pinene. An important piece of evidence about the nature of the intermediate involved in these reactions comes from the ZnCl$_2$-promoted ring-opening of 3,3-diphenylcyclopropene (**1 f**). Transition structures for a Nazarov-type intramolecular cyclization of the corresponding carbene intermediate **F** (Scheme 4 b), thus leading to **4 a**, and those for the cycloaddition to styrene were found. According to our calculations, the transition structure corresponding to the intramolecular cyclization is significantly (ca. 6 kcal mol^{-1}) more stable than those located for the cycloaddition to styrene. This result is in line with the experimental results.

Additional experiments were performed to support the predicted structure of the zinc carbenoid intermediate **C** (Scheme 4c). Its electrophilic nature was established by trapping with a nucleophile such as methanol, and afforded the ether **6a**, likely by 1,4-addition to species **C**. Moreover, the use of diphenylsulfoxide led to the aldehyde **7**, supporting again the participation of a carbene-like species.[26]

In summary, we have reported a novel strategy for the catalytic generation of zinc vinyl carbenoid intermediates. This approach relies on the ability of zinc to promote the ring-opening of cyclopropenes, which serve as a reliable and easy-to-handle vinyl carbene source. The carbene intermediates generated can be efficiently trapped with alkenes to yield valuable vinyl cyclopropane derivatives. The remarkably broad scope includes raw olefins to highly substituted and densely functionalized alkenes, thus highlighting the potential of this transformation in organic synthesis. Moreover, the use of inexpensive, low toxicity $ZnCl_2$ as the catalyst is attractive when considering large-scale applications. Preliminary studies on the structure of the involved intermediate pointed to an electrophilic zinc vinylcarbenoid, which shows a different structure from those haloalkylzinc intermediates proposed in the classical Simmons–Smith reaction. Accordingly, we hope that this feature will enable the development of new catalytic transformations using a non-noble metal as zinc. Further studies on the nature of the involved intermediates as well as new synthetic applications are currently underway.

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[23] The use of a large excess of **2a** (25 equiv) allowed the formation of the corresponding vinylcyclopropane in low yield (21 %, d.r. = 10:1). For additional information, see the Supporting Information.

[24] See the Supporting Information for details of the computational study.

[25] Participation of a typical SSC intermediate with haloalkylzinc structure was also evaluated. Even though the Simmons–Smith-type carbenoid structure could be formed from the structure **C**, after an extensive search, no transition structure was located for the cycloaddition with ethylene. Accordingly, we believe that SSC-type species are not involved in this process. See the Supporting Information for further details.

[26] For additional trapping and competition experiments, see the Supporting Information.

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