Synthesis of Silylcyclopropanes through the Catalytic Generation of Zinc Silylcarbenoids from Enynones

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

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Abstract A simple methodology for the preparation of 1-furyl-1-(silyl)cyclopropanes is reported. ZnCl₂ serves as inexpensive, low-toxicity catalyst for the generation of silylcarbenes from enynones, which can be trapped by alkenes under mild reaction conditions. These cyclopropanations take place in high yields and selectivities, showing a remarkable scope.

Key words carbenes, cyclopropanation, silylcyclopropanes, silyl carbenes, zinc catalysis

Cyclopropane derivatives hold a significant position in synthetic and theoretical chemistry. Their electronic properties and high ring strains translate into an incomparable reactivity, which also serve as mechanistic probes. In particular, cyclopropylsilanes constitute latent versatile synthetic reagents merging two relevant synthons as the organosilane¹ and the cyclopropane components.² Unexpectedly, methodologies to prepare these compounds remain scarce and have limited scope.^{2a} Silyl-substituted cyclopropanes were prepared by the reaction of vinylsilanes with metal carbenoids,^{3,4} or by quenching cyclopropyllithium reagents with chlorosilanes.⁵ A different approach relies on the use of silylcarbenoid intermediates as C1-synthon for alkene cyclopropanation. Unsubstituted silylcarbenoids can be generated in situ from different easily available sources (Scheme 1, top): (i) by decomposition of Me₃SiCHN₂,⁶ (ii) by treatment of Me₃SiCH₂Cl with lithium amides,⁷ or (iii) by generation of a Simmons–Smith-type chromium carbenoid with stoichiometric amounts of CrCl₂ and Me₃SiCH₂.⁸ Thus, 1-(trimethylsilyl)cyclopropanes can be efficiently synthesized. In contrast, the preparation of 1-substituted 1-(silyl)cyclopropanes from the corresponding substituted silylcarbenoids is significantly more restricted,⁹ since the use of

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mercury-containing precursors is required,¹⁰ or involve the functionalization/manipulation of diazo compounds, which often show low stabilities or are difficult to handle.^{11,12}

In the recent years, we have studied the catalytic generation of zinc carbenoids from easily available substrates and their use in synthesis as an alternative to classical stoichiometric protocols.¹³ Taking advantage of the ability of zinc salts to activate alkynes,¹⁴ we used enynones as carbene source to generate in situ zinc carbene intermediates,¹⁵ which could be trapped by alkenes leading to the corresponding cyclopropanes. Remarkably, the transformation was accomplished with inexpensive, low-toxicity ZnCl_2 as catalyst (Scheme 1, top).^{13a} In light of these results, we envisioned that the use of properly substituted enynone, specifically when substituent **X** is a silyl group (**X** = SiR_3), might serve as the easily available precursor of a functionalized zinc silylcarbenoid intermediate, which eventually would lead to the corresponding silylcyclopropane derivative (Scheme 1, bottom). Herein, we disclose the results of this study.

Trimethylsilyl-substituted enynone **1a**, directly prepared from commercially available 3-(trimethylsilyl)propionaldehyde, was selected to test the feasibility of the proposed target. Under the previously described reaction conditions, styrene (**2a**, 6 equiv), ZnCl_2 (10 mol%) in CH_2Cl_2 (0.1 M) at ambient temperature,^{13a} did not lead to the formation of the desired silylcyclopropane **3a** (24 h), with the unaltered starting reagents being the only compounds observed by ^1H NMR analysis of the crude mixture (Scheme 2). This result could be anticipated considering the steric hindrance of the postulated intermediate that likely encumbers the approach of the alkene for the cyclopropanation. This difficulty could be surpassed by raising the reaction temperature to 50 °C in 1,2-dichloroethane (DCE). Under these reaction conditions, silylcyclopropane **3a** was obtained in excellent 90% isolated yield after 24 hours (Scheme 2).¹⁶ The

transformation occurred with high *trans* diastereoselectivity (>20:1), in agreement with bulkiness of the trimethylsilyl group.¹⁷ It is worth mentioning that, to our knowledge, there are no precedents of zinc-mediated synthesis of silylcyclopropanes by means of zinc silyl substituted carbenoids.

With suitable reaction conditions in hands, we studied the scope of this transformation (Scheme 3).¹⁶ Styrene derivatives with different electronic properties were evaluated. Under optimized conditions, silylcyclopropanes **3a–d** were obtained in good yields (81–90%) as single diastereoisomers. The use of 4-nitrostyrene led to the cyclopropane **3e** in lower yield (49%) after prolonged heating (50 h). This result agrees with the electrophilic character of the zinc carbene intermediate proposed.^{13a} 1,1-Disubstituted alkenes could be employed as illustrated with the preparation of compounds **3f–j**. With 1,1-diphenylethene, compound **3f** was obtained in a significant lower yield (35%) after a long reaction time, probably due to a detrimental effect of the steric hindrance.¹⁸ Dialkyl-substituted alkenes afforded the cyclopropanes **3g–j** in acceptable yields, including those with spirane cores in their structures. Importantly, the use of an alkyl monosubstituted alkene such as 1-heptene under standard conditions led to the formation of compound **3k** in low conversion (<30% conversion, 48 h). Despite the low yield, this result is relevant since this kind of alkenes proved unreactive with aryl- or alkyl-substituted enynones.¹⁹ Gratifyingly, **3k** could be isolated in 81% yield when microwave irradiation was employed as the heating source (μw , 120 °C, 12 h). Moreover, allyltrimethylsilane participated in the reaction leading to the formation of compound **3l** (75%; dr >20:1). Besides, the reaction with a 1,3-enyne allowed for the synthesis of 2-alkynyl-1-silylcyclopropane **3m** in a good yield (74%) with complete chemoselectivity for the alkene moiety. The employment of 3,4-dihydro-2H-pyran as electron-rich alkene resulted in the diastereoselective formation of alkoxy(silyl)cyclopropane **3n** in moderate yield (57%).²⁰ Then, we used enynones bearing different R^1/R^2 substituents, which served as zinc carbene source for the cyclopropanations of representative alkenes yielding the corresponding silylcyclopropanes **3o–3t** with similar efficiencies and complete selectivity. Next, we prepared enynones with silyl groups other than TMS. The reaction of triethylsilyl-substituted enynone with sty-

rene under the standard conditions for the preparation of cyclopropane **3u** showed low conversion (<50% conversion, 48 h). Again, microwave irradiation (μw , 120 °C, 12 h) improved the results enabling the preparation of compound **3u** in a reasonable yield (60%). More sterically hindered *tert*-butyldimethylsilyl-substituted enynone was also tested leading to **3v** in lower yield (38%). Finally, cyclopropanes bearing PhMe_2Si and BnMe_2Si substituents (**3w–x**) were prepared in very good yields (88% and 94%, respectively) under standard conditions.

In addition, we preliminarily explored the reactivity of conjugated dienes as the alkene counterpart. In this case, treatment of benchmark enynone **1a** with an excess of 1,3-butadiene (**4a**) under standard conditions led to the formation of bicycles **5a,b** (45% combined yield, not optimized), arising from a formal [4+3] cycloaddition with partial desilylation (Scheme 4).²¹

Finally, we preliminarily attempted the derivatization of cyclopropanes **3**. Using standard reaction conditions for silyl groups removal, representative silylated compounds **3a** and **3h** were transformed into the corresponding cyclopropanes **6a** and **6h** in very good yields, albeit with low diastereoselectivity in the case of **6a** (Scheme 5, top). Moreover, bissilylated compound **3l** was converted into cyclopropane **6l** by chemoselective deprotection of one TMS group. It is noteworthy that the overall process is equivalent to the use of the H-substituted enynone, whose synthesis proved unsuccessful in our hands. Besides, treatment of compound **3w** with HBF_4 (4.4 equiv) in DCE at 60 °C, led to compound **7** (76%), in which a phenyl group migrated from silicon to carbon with a concomitant ring opening (Scheme 5, bottom).^{22,23}

In summary, we have reported an easy protocol to prepare valuable 1-substituted 1-silylcyclopropane derivatives. This methodology is based on the ability of ZnCl_2 to generate a carbene intermediate from enynones capable of reacting with alkenes to afford cyclopropanes. In particular, the silyl substituent attached at the alkyne terminus of the enynone enables the in situ generation of a zinc silylcarbene intermediate, which, to our knowledge, has not been previously proposed in the case of zinc catalysis. This approach operates under mild reaction conditions, avoiding the use of diazo compounds or highly reactive reagents when gen-

erating the carbenoid intermediate. Importantly, an economical and low-toxicity salt such as ZnCl_2 served as catalyst.

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Supporting Information

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- (16) **Representative Procedure:** To a solution of enynone **1** (0.30 mmol) and alkene **2** (1.8 mmol, 6.0 equiv) in 1,2-dichloroethane (3.0 mL, 0.10 M), ZnCl_2 (4.0 mg, 10 mol%) was added at ambient temperature. The Schlenk flask was placed in a preheated oil bath at 50 °C and the reaction mixture was stirred until consumption of **1** (TLC analysis). After elimination of the solvent, purification by flash column chromatography (SiO_2 , hexane-EtOAc) afforded the corresponding cyclopropanes **3**. Characterization data for compound **3a**: ^1H NMR (300 MHz, CDCl_3): δ = 7.05–7.23 (m, 3 H), 6.92–7.03 (m, 2 H), 5.86 (s, 1 H), 2.37 (s, 3 H), 2.34 (dd, J = 7.9, 6.1 Hz, 1 H), 2.25 (s, 3 H), 1.63 (dd, J = 6.0, 4.8 Hz, 1 H), 1.39 (dd, J = 7.8, 4.8 Hz, 1 H), 0.09 (s, 9 H). ^{13}C NMR (75 MHz, CDCl_3): δ = 194.4 (C), 156.6 (C), 153.9 (C), 138.3 (C), 127.9 (CH), 127.6 (CH), 125.9 (CH), 121.6 (C), 107.5 (CH), 29.0 (Me), 26.9 (CH), 17.7 (C), 15.1 (CH_2), 14.2 (Me), –2.9 (Me). HRMS (ESI): m/z [M] $^+$ calcd for $\text{C}_{19}\text{H}_{24}\text{O}_2\text{Si}$: 312.1546; found: 312.1543.
- (17) The *trans* configuration of cyclopropanes **3** was established by NOESY experiments and was not affected during the purification.
- (18) Higher temperatures or longer reaction times did not influence the yield.
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