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

Sergio Mata
Luis A. López*
Rubén Vicente*

Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Química Organometálica ‘Enrique Moles’, Universidad de Oviedo, c/ Julián Clavería 8, 33006 Oviedo, Spain
lalg@uniovi.es
vicenteruben@uniovi.es

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

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.³ Silyl-substituted cyclopropanes were prepared by the reaction of vinylsilanes with metal carbenoids,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 CrCl₃ and Me₃SiCHI₂.⁸ 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

Received: 03.07.2015
Accepted after revision: 21.10.2015
Published online: DOI: 10.1055/s-0035-1560590; Art ID: st-2015-b0496-l

Sergio Mata was born in 1991 in Avilés, Spain. He studied chemistry at the University of Oviedo (2009–2013) and obtained his Master’s degree in 2014 with work on the development of new zinc-catalyzed multicomponent processes. He is currently pursuing PhD studies under the supervision of Dr. L. A. López and Dr. R. Vicente. His work focuses on the use of simple zinc salts as catalysts in organic synthesis.

Luis A. López studied chemistry at the Universidad de Oviedo, where he also earned his PhD in 1990 working in the field of heterocyclic chemistry under the supervision of Prof. J. Barluenga and Prof. M. Tomás. As an Alexander von Humboldt postdoctoral fellow he then carried out research on group 4 organometallic chemistry at the Organisch-Chemisches Institut der Universität Münster (Germany) with Prof. G. Erker. In 1993, he took a position as a Research Associate at the Universidad de Oviedo, where he was promoted to Associate Professor in 2000. His current research is focused on the development of new selective synthetic methodologies based on the use of transition metal catalysts.

Rubén Vicente studied chemistry at the Complutense University in Madrid. He got his PhD from the University of Oviedo in 2006 with Prof. J. Barluenga, developing synthetic applications of Fischer carbenes. After short research stays at the University of Bonn and Boston College, he spent three years as a Postdoctoral Researcher sponsored by the Humboldt Foundation in the group of Prof. L. Ackermann (Georg-August-Universität, Göttingen, 2007–2009), working on C–H bond functionalizations. He returned to Oviedo in 2010 within the ‘Juan de la Cierva’ program and since 2012 he is a ‘Ramón y Cajal’ Fellow. In 2014, he was awarded with the Young Investigator Award from the Spanish Royal Chemical Society. His interests include the discovery of new reactivity patterns and sustainable catalysis.
mercury-containing precursors is required,\textsuperscript{10} or involve the functionalization/manipulation of diazo compounds, which often show low stabilities or are difficult to handle.\textsuperscript{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.\textsuperscript{13} Taking advantage of the ability of zinc salts to activate alkenes,\textsuperscript{14} we used enynones as carbene source to generate in situ zinc carbene intermediates,\textsuperscript{15} which could be trapped by alkenes leading to the corresponding cyclopropanes. Remarkably, the transformation was accomplished with inexpensive, low-toxicity ZnCl\textsubscript{2} as catalyst (Scheme 1, top).\textsuperscript{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\textsubscript{3}), might serve as the easily available precursor of a functionalized zinc silylcyclopropanoid intermediate, which eventually would lead to the corresponding silylcyclopropane derivative (Scheme 1, bottom). Herein, we disclose the results of this study.

With suitable reaction conditions in hands, we studied the scope of this transformation (Scheme 3).\textsuperscript{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.\textsuperscript{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.\textsuperscript{18} Dialkyl-substituted alkenes afforded the cyclopropanes 3g–j in acceptable yields, including those with spiran 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.\textsuperscript{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-enzyme 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%).\textsuperscript{20} Then, we used enynes bearing different R\textsubscript{1}/R\textsubscript{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 enynes 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-butylidemethylsilyl-substituted enyne was also tested leading to 3v in lower yield (38%). Finally, cyclopropanes bearing PhMe2Si and BnMe2Si 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 enyne 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, bis(silylated) 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 enyne, whose synthesis proved unsuccessful in our hands. Besides, treatment of compound 3w with HBF4 (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 ZnCl2 to generate a carbene intermediate from enynes capable of reacting with alkenes to afford cyclopropanes. In particular, the silyl substituent attached at the alkyne terminus of the enyne 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-

---

1. **Scheme 3** Zinc-catalyzed synthesis of silylcyclopropanes 3: scope. Isolated yields are given. *Reaction was performed under microwave irradiation (120 °C, 15 h).*

2. **Scheme 4** Reactivity of silyl-substituted enyne 1a with 1,3-butadiene 4a.

3. **Scheme 5** Derivatization of cyclopropanes 3.1. Major isomer was not determined.
erating the carbeneoid intermediate. Importantly, an economic and low-toxicity salt such as ZnCl₂ served as catalyst.

**Acknowledgment**

Financial support from MINECO of Spain (grant no. CTQ2013-41511-P) and the Principado de Asturias (‘Severo-Ochoa’ Program, fellowship to S.M.) is gratefully acknowledged. R.V. is a Ramón y Cajal fellow.

**Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560590.

**References and Notes**


(12) For the reactivity of enyne carbenoids bearing other substituents with related 1,3-diene derivatives, see: Song, B.; Li, L.-H.; Song, X.-R.; Qiu, Y.-F.; Zhong, M.-J.; Zhou, P.-X.; Liang, Y.-M. Chem. Eur. J. 2014, 20, 5910. (b) Signals attributable to the silycyclopropane were not observed by ¹H NMR analysis. Nevertheless, formation of cyclopropane followed by ring expansion cannot be ruled out.
(22) For related silicon-to-carbon migrations of phenyl groups, see:

(23) Unfortunately, attempts to obtain cyclopropanols by Tamao–Fleming oxidation (on compounds 3w–x) through various standard procedures failed, leading to complex mixtures or hydrodesilylation product. Various attempts to perform Hiyama couplings were also unsuccessful.