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Spiro-Cyclopropanation from Oxoallylsilanes

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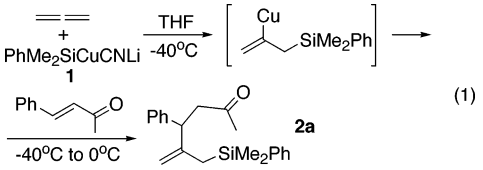
In the past years, organosilicon chemistry has become a cornerstone of organic synthesis.[1] Many valuable natural products have frequently been prepared, taking advantage of the outstanding chemical behavior of the silicon compounds.[2] Among them, allyl- and vinylsilanes are probably the most useful and widely used in synthesis.[3] It is not surprising, then, that a great deal of attention has been directed to development of efficient routes for the synthesis of these interesting building blocks. Silylmetalation of multiple bonds is one of the best strategies and provides an easy access to silicon-containing molecules.[4] In a recent review, we have reported the scope of the silylcupration of allenes, the relevancy of this methodology for the preparation of functionalized allylsilanes, and their application to the synthesis of naturally occurring products.[5]

Allylsilanes bearing an electrophilic group are readily obtained from allenes.[6] They easily undergo intramolecular cyclization due to the complementary electronic character of both functions, thus providing useful strategies for cycloalkane annulations.[6] Recently, we found that Lewis acid-catalyzed cyclization of epoxyallylsilanes follows an unusual rearrangement−cyclization pathway leading stereoselectively to methylenecyclohexanols contained in many terpenoid derivatives.[7]

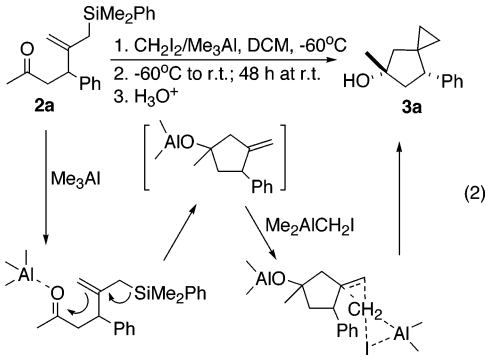
In an effort to find new alternatives for the silicon-assisted synthesis of natural products, we now report an unprecedented spiro-cyclopropanation reaction from allylsilane-containing ketones carried out in one step. Although huge advances have been made in the stereoselective synthesis of cyclopropane derivatives,[8] the recent discovery of new antibiotics, amino acids, and oligo-unsaturated fatty acids with linked cyclopropyl groups clearly demonstrates that research in this area is far from over.[9] Moreover, the spiro-cyclopropyl moiety is present in the skeleton of many biologically significant molecules such as illudin M and the taxane-AB fragment.[10]

Oxoallylsilanes of type **2** are readily available from silylcupration of allene (1,2-propadiene), followed by capture of the intermediate cuprate with α,β-unsaturated ketones, at low temperature (eq 1).[6a,7]



(1)

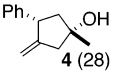
A lower-order cuprate such as **1** is required to ensure the correct regiochemistry of the addition to allene. The oxoallylsilane, in DCM, was treated consecutively with 2 equiv of CH_2I_2 and Me_3Al at −60 °C; then the mixture was left to warm and was stirred at room temperature around 48 h after workup to give the corresponding spiro-cyclopropanes of type **3** (eq 2). The reaction (one pot) proceeds under mild conditions and it is usually free from side reactions.



(2)

To optimize the procedure, a variety of combinations of solvent, temperature, time, and reagent-to-substrate ratio was carefully tested (Table 1). The use of different organometallics (Al or Zn) was also considered. From examination of Table 1, it can be concluded that conditions depicted in eq 2 seem to be the best choice. Times shorter than 24 h do not lead to completion (compound **4**, entry 2). Smaller reagent-to-substrate ratios result in poor efficiency and larger reaction times (entry 6). As revealed in Table 1, the Simmons−Smith reagent (Et_2Zn/CH_2I_2)[11] is much less effective than the Yamamoto version (Me_3Al/CH_2I_2),[12] the former leading to undesired cyclopropanated open-chain products (entry 7). Higher temperatures or nonpolar solvents reduce also the effectiveness of the process

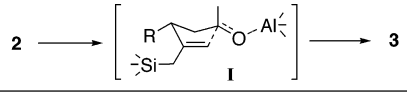
Table 1. Reactions' Conditions and Results

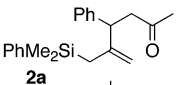
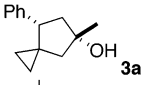
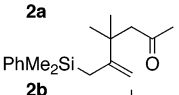
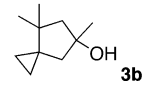
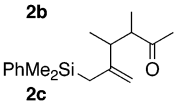
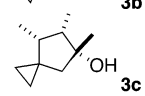
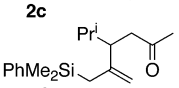
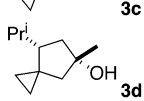
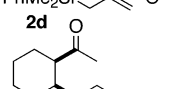
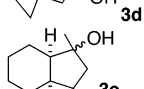
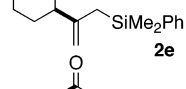
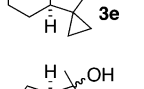
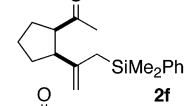
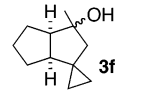
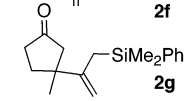
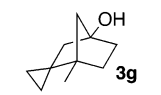
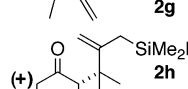
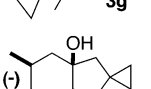
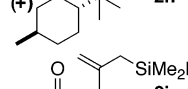
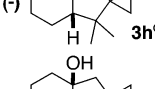
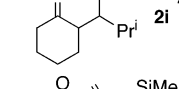
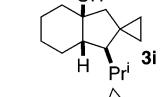
Entry	Comp.[a]	Reagent ratio Solvent	T (°C) t (h)	Products[b] (yield)
1	**2a**	CH_2I_2/Me_3Al (2:2), DCM	-60 48	**3a** (75)
2	**2a**	CH_2I_2/Me_3Al (2:2), DCM	-60 24	**3a** (43) +  **4** (28)
3	**2a**	CH_2I_2/Me_3Al (2:2), DCM	-40 48	**3a** (30) +  **5** (44)
4[c]	**2a**	CH_2I_2/Me_3Al (2:2), Toluene	-60 48	**3a** (21) + **5** (46) + **2a** (15)
5	**2a**	CH_2I_2/Me_3Al (2:3), DCM	-60 48	**3a** (12) +  **6** (70)
6[c]	**2a**	CH_2I_2/Me_3Al (1:1), DCM	-60 60	**3a** (17) + **4** (11) + **5** (33) + **2a** (19)
7	**2a**	CH_2I_2/Et_2Zn (2:2), DCM	-60 48	**3a** (43) +  **7** (35)
8	**2a**	Me_3Al (2 eq.) DCM	-60 2	**5** (90)
9	**2a**	CH_2I_2/Et_2Zn/TFA (2:2:2), DCM	0 4	**7** (88)

[a] One equivalent used. [b] DMPSi = $PhMe_2Si$. [c] Yield determined by GC.

10.1021/ja051967b CCC: $30.25

Table 2. Spiro-Cyclopropanes from Oxoallylsilanes



Entry	Oxoallylsilane	Spiro-cyclopropane	Yield (%)[a]
1	 **2a**	 **3a**	(75)
2	 **2b**	 **3b**	(92)
3	 **2c**	 **3c**	(88)
4[b]	 **2d**	 **3d**	(52)
5	 **2e**	 **3e**	(72)[c]
6	 **2f**	 **3f**	(77)[c]
7	 **2g**	 **3g**	(58)
8	 **2h**	 **3h**[d]	(79)
9	 **2i**	 **3i**	(88)
10	 **2j**	 **3j**	(80)
11	 **2k**	 **3k**	(72)

[a] Isolated pure compounds. [b] Reagent used: CH_2I_2/Et_2Zn. [c] Epimeric ratio 3:1. [d] **3h**: $[\alpha]_D = +12.4$.

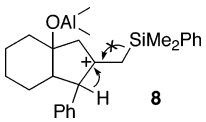
because of the increasing importance of organometallic addition to the carbonyl group (entries 3 and 4).

Formation of spiro-cyclopropanes **3a**−**j** (Table 2) seems to proceed by a two-step pathway, involving silicon-assisted cyclization of the starting oxoallylsilane, followed by cyclopropanation of the resulting methylenecyclopentanol (eq 2). The first step (cyclization) is induced by the presence of the organoaluminum compound; the second one (cyclopropanation) takes place by reaction with an in situ formed iodomethylaluminum intermediate (eq 2). The actual catalyst in the first step may be either Me_3Al or the iodomethylaluminum species.

This unique tandem mechanism is probably the most remarkable feature of the reaction, enabling the construction of spiro-bicyclic systems from open-chain allylsilanes in one step, a process of undoubted interest from a synthetic point of view. Moreover, the significance of the overall process becomes obvious when one realizes that each component of the reagent (Me_3Al or CH_2I_2) leads separately to results different from the general reaction (Table 1, entries 8−9, compare **5** and **7**).

The procedure herein described is quite general, providing an efficient route for the design and construction of hydroxylated bi-, tri-, and tetracyclic systems bearing the spiro-cyclopropyl group (Table 2). High levels of diastereoselectivity were found in all cyclizations studied with the exception of **3e,f** which were isolated as a mixture of epimeric alcohols in 3:1 ratio.

The stereochemistry observed might indicate a preference for the transition state **I**, where bulky groups attain an equatorial conformation which minimizes steric repulsions. The high stereocontrol with which the reaction proceeds allows the preparation of enantiomerically pure compounds such as **3h**, starting from a chiral building block such as (+)-pulegone. It should be noted that the β-phenyl-substituted oxoallylsilane **2k** affords the fused cyclopropane **3k** instead of the former spiro compound, maintaining the silyl group unchanged. This interesting result seems to point to the intermediacy of a stabilized β-silyl cation **8** in which the loss of a



proton competes favorably with the leaving of silyl group, perhaps due to the formation of highly stabilized tetrasubstituted alkene. This observation might be useful in the future for directing the reaction in either sense, on the basis of the type of substitution.

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Supporting Information Available: Experimental procedures and characterization data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) A modification of the original procedure due to Furukawa, see: Nishimura, J.; Furukawa, J.; Kawabata, N.; Kitayama, M. *Tetrahedron* **1971**, *27*, 1799; see also: Lorenz, J. C.; Long, J.; Yang, Z.; Xue, S.; Xie, Y.; Shi, Y. *J. Org. Chem*. **2004**, *69*, 327.

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