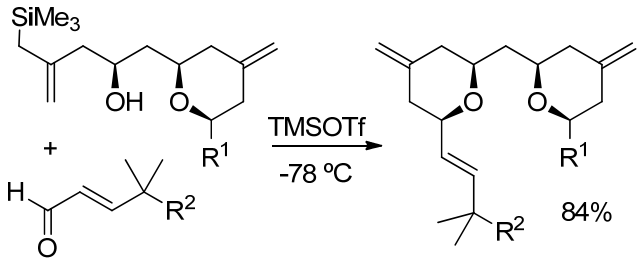
Multicomponent Prins-cyclization from allylsilyl alcohols leading to dioxaspirodecanes

ABSTRACT: A multicomponent reaction for the preparation of dioxaspirodecanes starting from allylsilyl alcohols was achieved. The one-pot sequence involves the sequential acid-catalyzed reaction of an allylsilane unit, which contains an alcohol, with an aldehyde to afford an alkenediol. The subsequent Prins-cyclization of the homoallylic alcohol moiety generates a tetrahydropyranyl carbocation which is intramolecularly trapped by the second hydroxyl group. The chemoselectivity of the process shows dependence on the nature of the aldehyde and the concentration of the catalyst.

The stereoselective synthesis of substituted tetrahydropyran and oxepane scaffolds has attracted considerable attention, due to the presence of these units in a wide range of natural products with important biological activities,[1] such as the marine tetracyclic ether Hemibrevetoxin B,[2] isolated from dinoflagellate *Gymnodinium breve*, or the bromotriterpene polyether Armatol F,[3] isolated from the red alga *Chondria armata*.

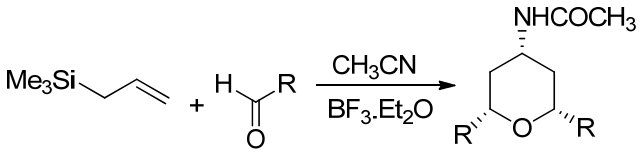
Among the many useful methods for the construction of these cyclic ethers, Prins cyclization has shown to be one of the most effectives.[4] Typically the process involves the acid-catalyzed reaction of an unsaturated alcohol with an aldehyde. The silyl-Prins modification has emerged as a very versatile approach for the synthesis of oxygenated heterocycles. Keck[5] and Wender[6] have applied this protocol to the synthesis of macrocycles containing pyran units. As shown in Scheme 1, the acid-catalyzed reaction of an allylsilyl alcohol with an aldehyde proceeds in high yield and with total stereocontrol to provide the methylene-tetrahydropyran derivative.

Scheme1



An even more powerful strategy consists on generating the homoallylic alcohol in situ. Minehan[7] has used this methodology in the synthesis of 4-methylene-tetrahydropyrans, via an initial Barbier-allylation to generate a silylated homoallylic alcohol intermediate, which then undergo indium-mediated Prins cyclization. Chan[8] and Saikia[9] have described a multicomponent reaction involving a Sakurai-allylation followed by an intramolecular silyl-Prins cyclization.

Scheme 2



On the other hand, there are rather few examples of Prins-cyclization involving internal trap of the pyranyl carbocation.[10] These strategies usually involve the intramolecular Prins cyclization of an alkene which contains a homoallylic alcohol or amide bearing another nucleophilic atom (either oxygen or nitrogen) to give fused diheterobicyclic compounds.[11]

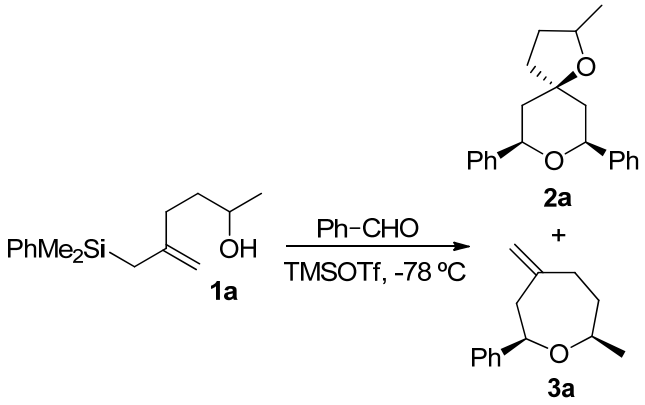
Following our interest in the development of new approaches to the synthesis of different sized carbo- and heterocycles, promoted by silicon-mediated cyclizations,[12] we now present our recent results on the extension of this methodology to the synthesis of oxacycles using the Prins-cyclization.

In this communication we describe an exceptional multicomponent Prins-cyclization in which an alkenyl monoalcohol undergoes a tandem allylation-prins cyclization followed by internal trapping of the tetrahydropyranyl cation to give dioxaspirodecanes.

The requisite allylsilyl alcohols for this study were prepared by silylcupration of allene and capture of the intermediate cuprate with a,b-unsaturated aldehydes or ketones. Initially, we attempted the standard Prins-cyclization of allylsilyl alcohol **1a** (1.0 equiv) with benzaldehyde (1.0 equiv) in the presence of TMSOTf (1.2 equiv) at -78 ºC. Surprisingly, we didn't obtained the expected oxepane **3a**, from a direct Prins-cyclization. Instead, the reaction provided a product which turned out to be the shown dioxaspirodecane **2a**, along with unreacted hydroxyallylsilane **1a**. We then performed the same reaction using 2.0 equiv of benzaldehyde. The reaction then proceeded in high yield and with very high stereocontrol (>95:5) (a single stereoisomer could be detected in the reaction mixture).

Other Lewis acids, which are conventional in this type of cyclizations, were screened for this reaction. As shown in Table 1, AlCl3 gave dioxaspirodecane **2a** in low yield (entry 3), whereas TiCl4 gave a complex reaction mixture (entry 5) and Et2AlCl gave also a complex mixture from which oxepane **3a** could be isolate in very low yield (entry 4). From all, TMSOTf, at -78 ºC, showed to be the most effective catalyst. This catalyst and these conditions were used for the subsequent reactions.

Table 1

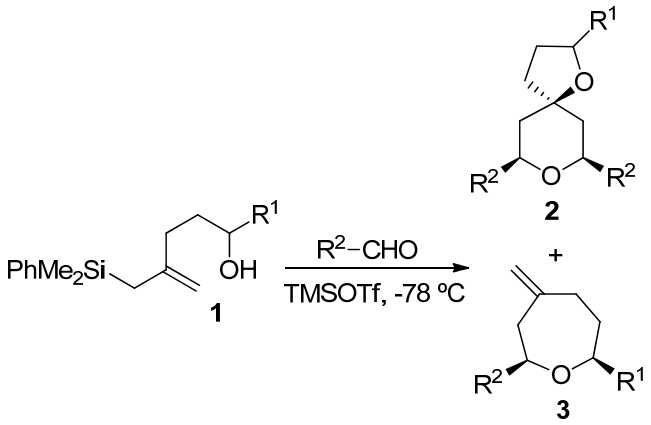


Entry	Catalyst	Temperature (ºC)	Ratio **2a**/**3a**	Yield[a] (%)
1	TMSOTf	-78	>95:5	85
2	TMSOTf	-40	>95:5	56
3	AlCl3	-78	>95:5	64
4	Et2AlCl	-78	<5:95	35
5	TiCl4	-78		---

[a]Conditions: **1a** (1.0 mmol), benzaldehyde (2.2 mmol), Lewis Acid (1.2 mmol).

We next evaluated the scope of this process by employing a variety of alkyl, aryl and □□□-unsaturated aldehydes and two different allylsilyl alcohols. The results are shown in Table 2.

Table 2



Entry	Allylsilyl alcohol	R^1	R^2	Ratio **2**/**3**[a]	Product,[b] yield (%)
1	**1a**	Me	C_6H_5	>95:5	**2a** (85)

2	**1a**	Me	4-MeOC$_6$H$_4$	92:8	**2b**+**3b** (89)
3	**1a**	Me	4-MeC$_6$H$_4$	>95:5	**2c** (85)
4	**1a**	Me	4-ClC$_6$H$_4$	74:26	**2d**+**3d** (75)
5	**1a**	Me	CH$_2$=CH	>95:5	**2e** (70)
6	**1a**	Me	(*E*)-PhCH=CH	94:6	**2f**+**3f** (88)
7	**1a**	Me	(*E*)-MeCH=CH	83:17	**2g**+**3g** (87)
8	**1a**	Me	*c*-C$_6$H$_{11}$	55:45	**2h**+**3h** (63)
9	**1b**	H	C$_6$H$_5$	>95:5	**2i** (86)
10	**1b**	H	4-MeOC$_6$H$_4$	89:11	**2j**+**3j** (80)
11	**1b**	H	4-MeC$_6$H$_4$	87:13	**2k**+**3k** (87)
12	**1b**	H	4-NO$_2$C$_6$H$_4$	40:60	**2l**+**3l**[c] (68)
13	**1b**	H	CH$_2$=CH	>95:5	**2m** (70)
14	**1b**	H	(*E*)-PhCH=CH	86:14	**2n**+**3n** (82)
15	**1b**	H	(*E*)-MeCH=CH	72:28	**2o**+**3o** (88)
16	**1b**	H	*c*-C$_6$H$_{11}$	40:60	**2p**+**3p** (76)

[a]The ratio of products was determined by ^{1}H NMR (400 MHz). [b]Conditions: **1** (1.0 mmol), aldehyde (2.2 mmol), TMSOTf (1.2 mmol), at -78 ºC. [c]The oxepane derivative was isolated as the regioisomeric 4-methyl-2-p-nitrophenyl-2,3,6,7-tetrahydrooxepine.

As shown in Table 2, the product outcome is dependent on both the (arylic, vinylic or alkylic) nature of the aldehyde and the electronic character of the substituents on it. Thus, there is a major predominance for the formation of the dioxaspirodecane derivatives **2** and the best diastereo-selectivities (>95:5) are found for unsubstituted vinylic and arylic derivatives (Table 2, entries 1, 5, 9 and 13)

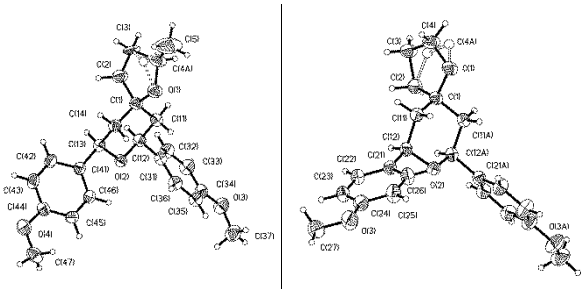
On the other hand, two different behaviours are found for arylic derivatives depending on the electronic character of the aromatic substituent. Thus, electron-rich aromatic aldehydes (Table 2, entries 2, 3, 10, 11) provide the corresponding dioxaspirodecanes **2b-c** and **2j-k** in high yield and with good to excellent diastereoselectivities.

However the reaction with electron-poor aromatic aldehydes led to a moderate selectivity towards **2** or even to a slight predominance of the oxepane derivative when nitrobenzaldehyde is used (Table 2, entries 4 and 12). Moreover, substituted vinylic aldehydes provided with good selectivities dioxaspirodecanes **2f-g** and **2n-o** (Table 2, entries 6, 7, 14 and 15). Interestingly, aliphatic aldehydes (Table 2, entries 8 and 16) furnished an almost equimolar mixture of both products **2** and **3**.

It has to be noted that the results with allylsilyl alcohols **1a** and **1b** are similar, although **1b** shows slightly lower selectivity towards the formation of the dioxaspirodecane derivatives.

The structures of **2b** and **2j** were unambiguously confirmed by NMR spectroscopy, HRMS analysis and X-ray crystal structure analysis (Figure 1).

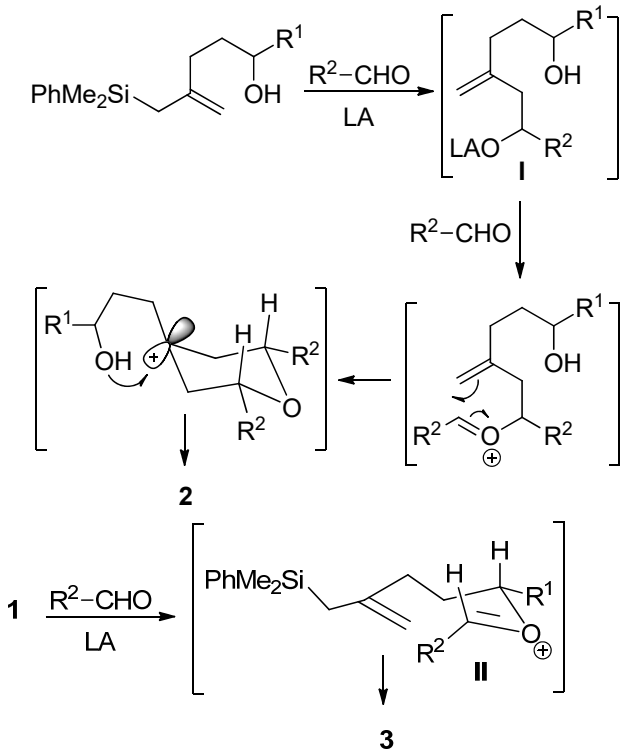
Figure 1. X-ray crystal structures of 2b and 2j



A mechanistical proposal for the formation of dioxaspirodecane **2** would involve the acid-catalyzed Sakurai reaction between the hydroxyallylsilane and benzaldehyde to provide an alkoxy-alkenol **I** which then will react with another molecule of aldehyde to form an oxocarbenium. Final cyclization will provide a pyranyl carbocation which in turn will be intramolecularly trapped by the neighboring hydroxy group.

On the other hand, formation of methyleneoxepanes **3** would proceed through initial formation of an (*E*)-oxocarbenium ion **II**, which would be trapped by the nucleophilic allylsilane.

Scheme 3



Presumably, whether the initial formation of intermediate **I** or **II** is the quickest process would determine the final outcome of the reaction. In this sense, the results shown in Table 2 seems to indicate that the reaction outcome depends on both steric and electronic factors. However, more investigation is needed to determine the real influence of these factors.

Moreover, in every case an excellent degree of diastereoselectivity was observed in the formation of both the 2,7-*cis*-oxepanes and the 7,9-*cis*-dioxaspirodecanes derivatives. The stereochemical outcome of Prins cyclization leading to tetrahydropyran derivatives has been rationalized by Alder,[13] using density functional calculations. This model suggests that Prins cyclization proceeds through a chair-like transition state in which the substituents on C-2 and C-6 are equatorial for minimal repulsions. Moreover, calculations show that equatorial nucleophilic attack to the tetrahydropyranyl cation will be favoured for secondary carbocations, while axial attack is predicted for tertiary pyranyl carbocations. It has to be noted that Alder's calculations have been done for intermolecular nucleophilic attack.

However, dioxaspirodecanes **2** show high selectivity for the equatorial trapping of the tertiary tetrahydropyranyl cation. The rationale for this unexpected selectivity could be found in steric reasons. Thus, the intramolecular trapping of the cation takes place on the less hindered face of the cyclic cation, since axial trapping will have an unfavourable 1,3-diaxial interaction.

We next decided to study the influence of the amount of catalyst in the outcome of the reaction. The results are shown in Table 3.

Table 3

Entry	**1** R^1	R^2-CHO R^2	TMSOTf equiv	Ratio **2**:**3**[a]	Yield[b] (%)
1	Me	(*E*)-MeCH=CH	0.8	78:22	89
2	Me	(*E*)-MeCH=CH	1.2	83:17	87
3	Me	(*E*)-MeCH=CH	2.4	87:13	85
4	Me	(*E*)-MeCH=CH	4.8	90:10	86
5	H	(*E*)-PhCH=CH	0.8	57:43	80
6	H	(*E*)-PhCH=CH	1.2	86:14	82

7	H	(*E*)-PhCH=CH	2.4	94:6	81
8	H	4-MeC$_6$H$_4$	0.8	79:21	89
9	H	4-MeC$_6$H$_4$	1.2	87:13	87
10	H	4-MeC$_6$H$_4$	2.4	91:9	86

[a]The ratio of products was determined by ^{1}H NMR (400 MHz). [b]Conditions: **1** (1.0 mmol), aldehyde (2.2 mmol), -78 ºC.

As shown in Table 3, the degree of selectivity towards the dioxaspirodecane derivatives is enhanced when the amount of catalyst increases. This fact seems to indicate that two molecules of TMSOTf are involved in the mechanism of the tandem reaction leading to dioxaspirodecane derivatives. Interestingly, the reaction of allylsilyl alcohol **1b** with (*E*)-cinnamaldehyde gives an almost equimolar mixture of compounds **2** and **3** when 0.8 equiv. of TMSOTf is used, but a 15:1 ratio when the catalyst load is increased to 2.4 equiv. As far as we know, this chemoselective dependence on the loading of catalyst has never been previously reported in Prins cyclizations.

In conclusion, we have reported an easy access to substituted dioxaspirodecanes in a very stereoselective manner, through a multicomponent Sakurai-Prins cyclization. To the best of our knowledge, this is the first described three-component Prins cyclization starting from an alkenyl alcohol. Moreover the chemoselectivity of this reaction towards the dioxaspirodecane (*vs* the oxepane derivative) is dependent on both stereoelectronic factors and the amount of catalyst used.

This multicomponent coupling allows the synthesis of complex dioxaspirodecanes in a sequence where three new stereogenic centers are created with excellent stereoselectivity.

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