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Competitive Silyl-Prins Cyclization *vs* Tandem Sakurai-Prins Cyclization: interesting substitution effect

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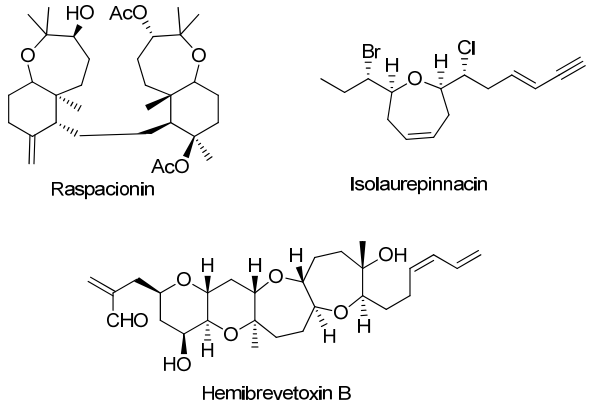
Abstract: Two different mechanism pathways are observed for the reaction of allylsilyl alcohols **1** and aldehydes in the presence of TMSOTf. In the case of allylsilyl alcohols without allylic substituents, the reaction gives dioxaspirodecanes, which are the products of a tandem Sakurai-Prins cyclization. In contrast, allylsilyl alcohols with an allylic substituent $R^2 \neq H$ selectively provide oxepanes, corresponding to a direct silyl-Prins cyclization. Both type of products are obtained with excellent stereoselectivity. Theoretical studies have been performed to get some rationalization for the observed stereoselectivity.

Introduction

Different sized oxacycles are structural motifs present in a wide range of natural products with important biological activities. Especially abundant are the corresponding 7-membered oxacycles, which occur in a great number of mono- and poliethers such as isolaurepinnacin,[1] insecticidal component of the marine red alga *Laurencia pinnata Yamada*, rogiolenyne,[2] acetogenin isolated from the red seaweed *Laurencia microcladia*, raspacionin,[3] main triterpenoid from the marine sponge, *Raspaciona aculeuta Johnston*, with anti-cancer activity against MCF-7 tumor cell line, 3-*epi*-sodwanone K 3-acetate,[4] triterpene from the marine sponge Axinella sp., which shows cytotoxic activity to T47D cells or Hemibrevetoxin B,[5] polyether produced by marine dinoflagellate *Karenia breve* which exhibits important cytotoxic activity and it's a sodium channel activator (Scheme 1).



Scheme 1. Natural products containing oxepane rings

Several approaches have been developed for the stereoselective synthesis of substituted oxacycles. Within them, Prins[6] or the so called silyl-Prins[7] Cyclization have emerged as promising tools for the construction of these units in a simple and efficient manner.

However, while Prins Cyclization has been extensively used for the preparation of 5- and 6-oxacycles, less frequent are the examples described for the synthesis of oxepanes.

For instance, Overman has used an application of the Prins-type cyclization in the synthesis of natural halogenated oxepane isolaurepinnacin.[8] Another example reported by Furman[9] shows the synthesis of 3-vinylidene oxepanes by acid-catalyzed reaction of secondary homopropargylic alcohols with aldehydes. Recently, Padrón et al. have reported a short synthesis of natural (+)-isolaurepan, where the key step is the Prins cyclization of bis-homoallylic alcohols with aldehydes catalyzed by Fe (III) salts.[10]

Following our interest in the synthesis of different sized carbo-[11,12] and heterocycles[13] using silicon-containing substrates, we have recently reported an approach towards the synthesis of oxacycles based in the intramolecular Prins reaction.[14]

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In this paper, we present the full study on the different factors that influence both the chemo- and the stereoselectivity of the Prins cyclization of allylsilyl alcohols.

Results and Discussion

Scope of the process

For that purpose we have synthesized different substituted allylsilyl alcohols using our methodology of silylcupration of allenes.[15]

Thus, the reaction of allylsilyl alcohol **1a** (1 mmol) with benzaldehyde (1.2 mmol), in the presence of 1.2 mmol of TMSOTf gave the desired oxepane **2a** in excellent yield (Table 1, entry 1). The starting alcohol is completely transformed in a very short time (within 5 min.). In addition, the reaction proceeded with excellent stereoselectivity providing a single *cis*-2,5,7-trisubstituted oxepane.

The scope of this process was then explored using different substituted aldehydes and allylsilyl alcohols. As it can be seen in Table 1, the reaction works well both for electron-rich and electron-poor aromatic aldehydes. Vinyl aldehydes give also good results in the Prins cyclization.

Table 1. Reaction of allylsilyl alcohols **1a-b** with aldehydes in the presence of TMSOTf.

1a-b **2a-k**

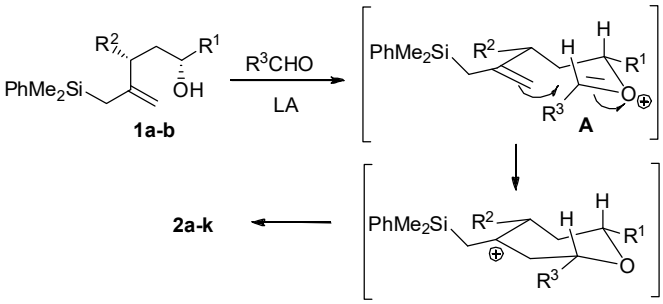
Entry	**1**	R^1	R^2	R^3	dr	Product[a] (yield, %)
1	**1a**	Me	Ph	C_6H_5	>95:5	**2a** (89)
2	**1a**	Me	Ph	4-$MeOC_6H_4$	>95:5	**2b** (93)
3	**1a**	Me	Ph	4-MeC_6H_4	>95:5	**2c** (92)
4	**1a**	Me	Ph	4-ClC_6H_4	>95:5	**2d** (91)
5	**1a**	Me	Ph	(*E*)-PhCH=CH	>95:5	**2e** (90)
6	**1a**	Me	Ph	(*E*)-MeCH=CH	>95:5	**2f** (87)
7	**1b**	Ph	Ph	C_6H_5	>95:5	**2g** (93)
8	**1b**	Ph	Ph	4-MeC_6H_4	>95:5	**2h** (91)
9	**1b**	Ph	Ph	4-ClC_6H_4	>95:5	**2i** (88)
10	**1b**	Ph	Ph	CH_2=CH	>95:5	**2j** (71)
11	**1b**	Ph	Ph	(*E*)-PhCH=CH	>95:5	**2k** (90)

[a] Conditions: **1a-b** (1.0 mmol), aldehyde (1.2 mmol), TMSOTf (1.2 mmol), at -78 ºC.

Very high stereocontrol is observed in every example of the Prins' cyclization (Table 1, entries 1-11). The stereochemistry of compounds **2a-k** was established on the basis of ^{1}H-NMR and NOE experiments.

The mechanism involving this cyclization implies the initial formation of an oxocarbenium ion **A**, by the acid-catalyzed reaction of the secondary homoallylic alcohol with an aldehyde. Subsequent 7-*endo* cyclization would give an oxepanyl carbocation, which is also a stable carbocation β to silicon. Final elimination of silicon would form the exocyclic double bond (Scheme 2).

The formation of the all-*cis* isomers is consistent with Alder's computational calculations,[16] which predict a preferred chair like transition state in which the substituents adopt an equatorial position for minimal energy.



Scheme 2. Mechanism for the obtention of oxepanes **2**.

Influence of the configuration of the allylsily alcohol

Next, we screened this cyclization using secondary homoallylic alcohols with a *trans*-relationship between R^1 and R^2, to see the influence of this factor in the selectivity of the process. The results are shown in Table 2.

Table 2. Reaction of allylsilyl alcohols **1c-d** with aldehydes in the presence of TMSOTf.

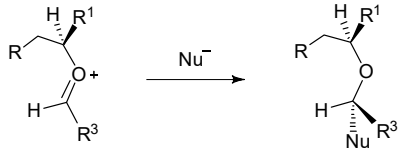
1c-d **3a-m**

Entry	**1**	R^1	R^2	R^3	dr	Product[a] (yield, %)
1	**1c**	Me	Ph	C_6H_5	>95:5	**3a** (92)
2	**1c**	Me	Ph	4-MeC_6H_4	>95:5	**3b** (90)
3	**1c**	Me	Ph	4-ClC_6H_4	>95:5	**3c** (91)
4	**1c**	Me	Ph	(*E*)-PhCH=CH	>95:5	**3d** (91)
5	**1c**	Me	Ph	(*E*)-MeCH=CH	>95:5	**3e** (92)
6	**1d**	Ph	Ph	C_6H_5	>95:5	**3f** (92)
7	**1d**	Ph	Ph	4-MeC_6H_4	>95:5	**3g** (93)
8	**1d**	Ph	Ph	4-ClC_6H_4	>95:5	**3h** (91)
9	**1d**	Ph	Ph	4-$MeOC_6H_4$	>95:5	**3i** (87)
10	**1d**	Ph	Ph	CH_2=CH	>95:5	**3j** (72)
11	**1d**	Ph	Ph	(*E*)-PhCH=CH	>95:5	**3k** (90)
12	**1d**	Ph	Ph	(*E*)-MeCH=CH	>95:5	**3l** (91)
13	**1d**	Ph	Ph	C_6H_{11}	>95:5	**3m** (81)

[a] Conditions: **1c-d** (1.0 mmol), aldehyde (1.2 mmol), TMSOTf (1.2 mmol), at -78 ºC.

As shown, the cyclization of **1c-d** again proceeds with excellent stereoselectivity and high yields. We now may think in a

competition between substituents R^1 and R^2 to adopt a pseudoequatorial orientation in the transition state. Noteworthy, the unique isomer isolated is the one that has an axial Ph (R^2) group, despite Ph (R^2) being a bulkier group than Me (R^1). Presumably, the closer proximity of R^1 to the C=O$^+$ bond determines this stereocontrol effect. This hypothesis is reinforced by Houk's computational calculations[17] which suggest that nucleophilic attack on an oxocarbenium ion adjacent to a stereogenic center would occur with stereofacial selectivity, anti to the neighbouring substituent (R^1) on the chiral center (Scheme 3).

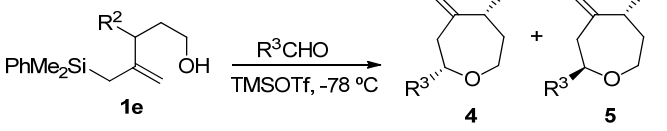


Scheme 3. Stereoselectivity on the nucleophilic attack to an oxocarbenium ion.

Influence of the substitution in the outcome of the process

We then examined the effect of the number and position of substituents on the secondary homoallylic alcohol in the outcome of the process. For that purpose we choose allylsilylalcohols where R^1 or R^2 are hydrogens. As it can be seen in Table 3, the Prins cyclization of allylsilyl alcohol **1e** (R^1=H) leads to methyleneoxepanes in high yield and with moderate to good stereoselectivity towards the 2,5-*cis* isomers. The ratios of isomers were determined by integration of the ^{1}H-NMR spectra of the crude reaction.

Table 3. Reaction of allylsilyl alcohols **1e** with aldehydes in the presence of TMSOTf.



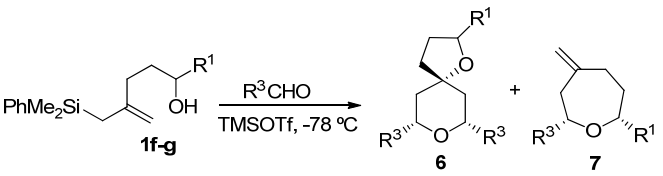
Entry	1	R^2	R^3	Ratio **4**/**5**	Product[a] (yield, %)
1	**1e**	Ph	C_6H_5	83:17	**4a+5a** (93)
2	**1e**	Ph	4-MeOC_6H_4	86:14	**4b+5b** (92)
3	**1e**	Ph	4-MeC_6H_4	80:20	**4c+5c** (91)
4	**1e**	Ph	4-ClC_6H_4	83:17	**4d+5d** (91)
5	**1e**	Ph	CH_2=CH	83:17	**4e+5e** (90)
6	**1e**	Ph	(*E*)-PhCH=CH	91:9	**4f+5f** (94)
7	**1e**	Ph	(*E*)-MeCH=CH	89:11	**4g+5g** (88)
8	**1e**	Ph	C_6H_{11}	75:25	**4h+5h** (89)

[a] Conditions: **1e** (1.0 mmol), aldehyde (1.2 mmol), TMSOTf (1.2 mmol), at -78 ºC.

As shown, the stereocontrol of the reaction is sensibly decreased when R^1=H, which again corroborates that in the absence of an α-sterogenic center to the C=O$^+$ bond, the distant R^2 group causes a less effective steric control in the approach of the allylsilane to the oxocarbenium ion.

While allylsilyl alcohols with a substituent on the allylic position (R^2≠H) selectively undergo direct silyl-Prins cyclization, providing oxepanes, we were surprised to find a completely different chemical behavior for allylsilyl alcohols with R^2=H. Now, the reaction of secondary homoallylic alcohols **1f-g** with aldehydes, in the presence of TMSOTf, [18] mainly provided the novel adducts **6a-p**, which were confirmed to be the shown dioxaspirodecanes (Table 4, entries 1-16).

Table 4. Reaction of allylsilyl alcohols **1f-g** with aldehydes in the presence of TMSOTf.



Entry	1	R^1	R^3	Ratio **6**[a]/**7**	Product[b] (yield, %)
1	**1f**	Me	C_6H_5	>95:5	**6a** (85)
2	**1f**	Me	4-MeOC_6H_4	92:8	**6b+7b** (89)
3	**1f**	Me	4-MeC_6H_4	>95:5	**6c** (85)
4	**1f**	Me	4-ClC_6H_4	74:26	**6d+7d** (75)
5	**1f**	Me	CH_2=CH	>95:5	**6e** (70)
6	**1f**	Me	(*E*)-PhCH=CH	94:6	**6f+7f** (88)
7	**1f**	Me	(*E*)-MeCH=CH	83:17	**6g+7g** (87)
8	**1f**	Me	*c*-C_6H_{11}	55:45	**6h+7h** (63)
9	**1g**	H	C_6H_5	>95:5	**6i** (86)
10	**1g**	H	4-MeOC_6H_4	89:11	**6j+7j** (80)
11	**1g**	H	4-MeC_6H_4	87:13	**6k+7k** (87)
12	**1g**	H	4-$NO_2C_6H_4$	40:60	**6l+7l**[c] (68)
13	**1g**	H	CH_2=CH	>95:5	**6m** (70)
14	**1g**	H	(*E*)-PhCH=CH	86:14	**6n+7n** (82)
15	**1g**	H	(*E*)-MeCH=CH	72:28	**6o+7o** (88)
16	**1g**	H	*c*-C_6H_{11}	40:60	**6p+7p** (76)

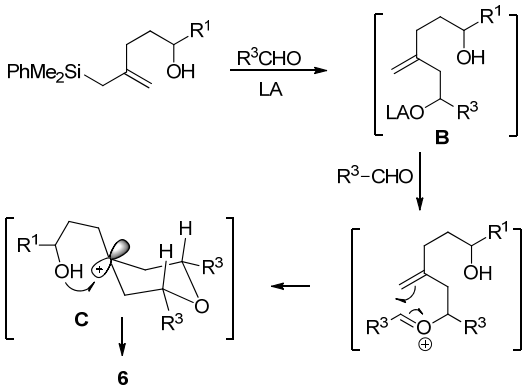
[a] No dihydropyrans were observed in the reaction mixture, as some authors have found in TMSOf catalyzed Prins cyclizations.[19] [b] Conditions: **1f-g** (1.0 mmol), aldehyde (2.2 mmol), TMSOTf (1.2 mmol), at -78 ºC.

As it's shown in Table 4, the reaction is general and high yielding, although in various examples small amounts of the oxepane derivatives were isolated together with the major dioxaspirodecane (entries 2,4,6-8,10-12,14-16). The chemoselectivity of the reaction is dependent on both the substituents and the nature (vinylic, arylic or alkylic) of the aldehyde. Thus, unsusbstituted aryl and vinyl aldehydes exclusively provide dioxaspirobicyclodecanes (Table 4, entries 1,5,9,13). Substituted vinyl aldehydes and electron-rich aryl aldehydes give a mixture of both dioxaspirobicyclodecane and oxepane derivatives, favoring the former with good to excellent selectivity (Table 4, entries 2,3,6,7,10,11,14,15). However,

electron-poor aryl aldehydes and alkyl aldehydes give moderate selectivity or an almost equimolar mixture of both **6** and **7**.

Mechanistic proposal

The most feasible mechanism for this tandem process leading to dioxaspirodecanes is an initial Sakurai reaction between the allylsilane unit and the aldehyde leading to a homoallylic alcohol **B**, which already has another hydroxyl group in a secondary homoallylic position. Further dehydrative condensation of the homoallylic alcohol with the aldehyde provides an oxocarbenium ion which is subsequently trapped by the alkenyl moiety to give a tetrahydropyranyl carbocation **C**. Final intramolecular addition of the secondary homoallylic alcohol to the intermediate carbocation affords the final product.



Scheme 4. Mechanistic proposal for the formation of dioxaspirodecanes **6**.

This process stands in sharp contrast with the reported observation that TMSOTf is not an efficient catalyst for the Sakurai reaction of allylsilanes and carbonilyc compounds.[20] So, we initially pressumed that the actual acid catalyst in the Sakurai reaction leading to **B** could be the trace of triflic acid present in the reaction media from the hydrolysis of TMSOTf. In order to examine this hypothesis we decided to carry out the reaction in the presence of 10% TfOH. However, when we performed the reaction of 1 mmol of allylsilyl alcohol **1g** with 2.2 mmol of p-methylbenzaldehyde, in the presence of 1.2 mmol of TMSOTf and 0.12 mmol of TfOH we obtained a 65:35 ratio of **6k** and **7k** (Table 5, entry 4). This result seems to indicate that the presence of TfOH facilitates the direct Prins cyclization leading to oxepanes, rather than the tandem reaction giving dioxaspirodecanes. To further explore this effect we decided to test the reaction under different amounts of TfOH. The results are shown in Table 5.

Table 5. Reaction of allylsilyl alcohols **1f-g** with aldehydes in the presence of TMSOTf and TfOH.

Entry	**1**	R^1	R^3	TfOH equiv	Ratio **6**/**7**[b]	Product[a] (yield, %)
1	**1f**	Me	(*E*)-MeCH=CH	0	83:17	**6g+7g** (87)
2	**1f**	Me	(*E*)-MeCH=CH	1.2	27:73	**6g+7g** (76)
3	**1g**	H	4-MeC_6H_4	0	87:13	**6k+7k** (87)
4	**1g**	H	4-MeC_6H_4	0.12	65:35	**6k+7k** (82)
5	**1g**	H	4-MeC_6H_4	1.2	28:72	**6k+7k** (75)
6	**1g**	H	(*E*)-PhCH=CH	0	86:14	**6n+7n** (82)
7	**1g**	H	(*E*)-PhCH=CH	0.12	74:26	**6n+7n** (80)
8	**1g**	H	(*E*)-PhCH=CH	1.2	36:64	**6n+7n** (74)

[a] Conditions: **1f-g** (1.0 mmol), aldehyde (2.2 mmol), TMSOTf (1.2 mmol), TfOH at -78 ºC.

As shown in Table 5, increasing the amount of TfOH has the effect of favoring the formation of oxepanes **6** over dioxaspirodecanes **7**. It's noteworthy that the use of 1.2 mmol of TfOH produces a chemoselectivity's inversion in the reaction, now obtaining oxepanes **6** as the major products.

The clear evidence that the traces of TfOH were not the catalyst for the initial Sakurai reaction of this tandem process let us to think that in the presence of TMSOTf the TMS ether derived from allylsilyl alcohol **1** could have been formed, and then the so called Silyl-Modified Sakurai (SMS) reaction could have taken place. Indeed, the SMS reaction reported by Markó[21] describes that while TMSOTf does not sufficiently activate carbonyl derivatives towards the addition of allylsilanes, the combination of TMSOTf and a silyl ether as coreactant readily promotes the reaction.

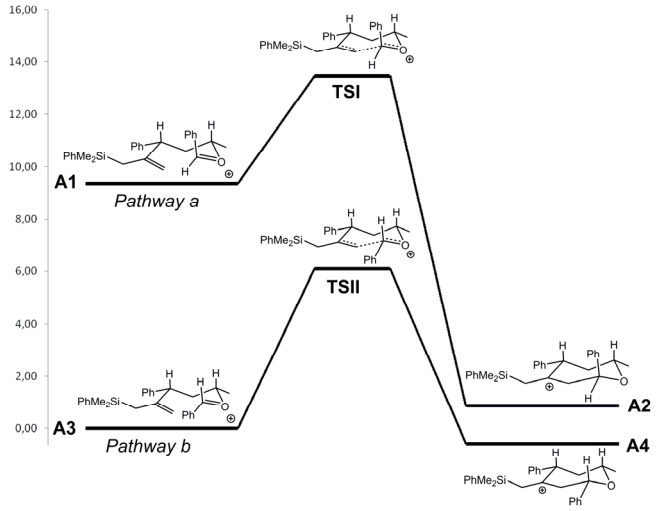
Moreover, the tandem reaction proceeds with complete diastereoselectivity. The stereoselectivity of the process could be explained by a preferential transition state in which both R^2 groups on C-2 and C-6 adopt a pseudoequatorial conformation for minimal repulsions. On the other hand, whereas Alder's model[15] predicts a favourable axial attack for the nucleophilic trapping of a tertiary tetrahydropyranyl cation, our dioxaspirodecanes **6** are generated by equatorial attack of the internal nucleophilic alcohol. The explanation for this unexpected stereocontrol could be due to steric factors. Thus, presumably the axial attack on **C** is more hindered than the equatorial one due to 1,3-destabilizating interactions.

Hence, two kinds of reaction pathways can be found in the Prins cyclization of allylsilyl alcohols **1**, one leading to oxepanes **2-5** and the other providing dioxaspirodecanes **6**. Apparently, the nature of the allylic substituent (R^2=H or R^2≠H) determines this change in the chemical outcome of the reaction.
This remarkable substitution effect[22] in the chemical pathway of the reaction could be presumably attributed to steric effects.

Thus, whether the most favorable process is the formation of intermediates **A** or **B** will determine the final obtention of oxepanes or dioxaspirodecanes. It's known that Sakurai reaction leading to intermediate **B** requires a perpendicular alignment between the silyl group and the double bond to allow the σ-p hyperconjugative stabilization of the intermediate carbocation by the C-Si bond.[23] This means that the electrophile attacks the allylsilane *anti* to the silyl group. We now presume that in the reactive conformation of allylsilanes **1a-e** the allylic phenyl group is partially blocking the lower surface of the double bond, through which the aldehyde should approach. This hypothesis is consistent with the observation that the Sakurai reaction, which is the first step of the tandem process leading to dioxaspirodecanes, is not favored when the allylsilyl alcohol **1** bears an allylic substituent.

Theoretical studies

In order to check if computational calculations can give some rationalization to the stereoselectivity observed for the formation of oxepanes **2**, *ab initio* calculations were performed at B3LYP/6-31G(d,p) level by first obtaining the Gibbs free energies in solution of two possible oxocarbenium ion intermediates in chair conformation (**A1** and **A3**) and then calculating their transition states leading to the oxepanyl carbocations **A2** and **A4**. The results are depicted in Scheme 5 and Tables 6 and 7.



Scheme 5. Reaction profile of the 7-*endo* cyclization step yielding oxepane **2a** (in kcal/mol)

Table 6. *Relative Gibbs free energy (in kcal/mol) for all stationary points calculated in solution at the 7-endo cyclization step leading to* ***2a****.*

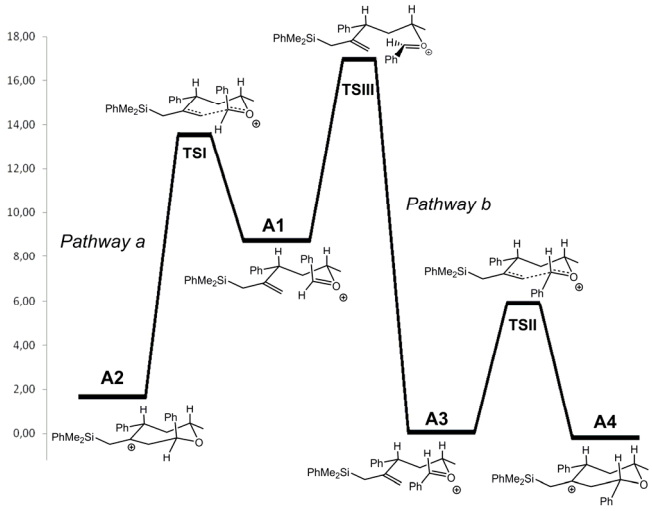
Stationary Point	*ΔG*
A1	*8.67*
A3	*0.00*
TSI	*13.48*
TSII	*5.86*
A2	*1.63*
A4	*-0.25*

Table 7. *Gibbs free energies calculated in solution (in kcal/mol) for Pathways* ***A*** *and* ***B***

Pathway	$\Delta G^{\neq}$	$\Delta G_{reaction}$
a	*4.81*	*-7.04*
b	*6.08*	*-0.25*

Both intermediates **A2** and **A4** are close in energy (**A4** being more stable by 1.88 kcal/mol). Similarly, the activation energy of **TSII** is 1.05 kcal/mo higher than **TSI**. However the energy difference between intermediates **A1** and **A3** is high (8.67kcal/mol), making *Pathway a* very unlikely at low temperatures, which is consistent with the experimental results concerning the total diastereoselectivity of the Prins cyclization leading to **2**. The larger difference in energy between **A1** and **A3** and Houk's *Z* and *E*-oxocarbenium ions[17] may be partly atributed to steric interactions. Thus, Houk et al. studied very simple systems, such as protonated acetaldehyde and O-methylacetaldehyde, and found an electronic difference between *trans* and *cis* isomers of 0.3 and 2.0 kcal/mol, respectively. This means one order of magnitude just by adding a methyl group. Our system is much more complex than those previously studied, having much bulkier groups. Moreover, our calculations have been performed in solution (Gibbs free energies in solution are given) and Houk et al. calculated electronic energies in gas phase. So, both factors may explain this difference in energy.

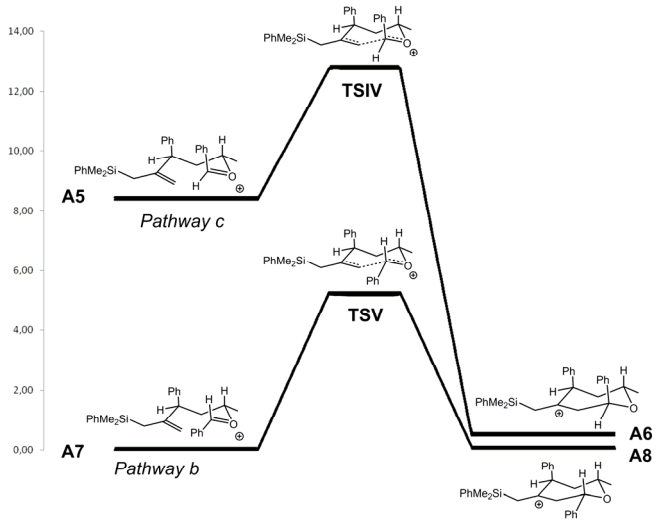
We next tried to connect both pathways by scanning the energy surface resulting from the rotation about the C─C═O⁺─C torsional angle. A new transition state was located and reoptimized so that the complete potential energy surface could be drawn.



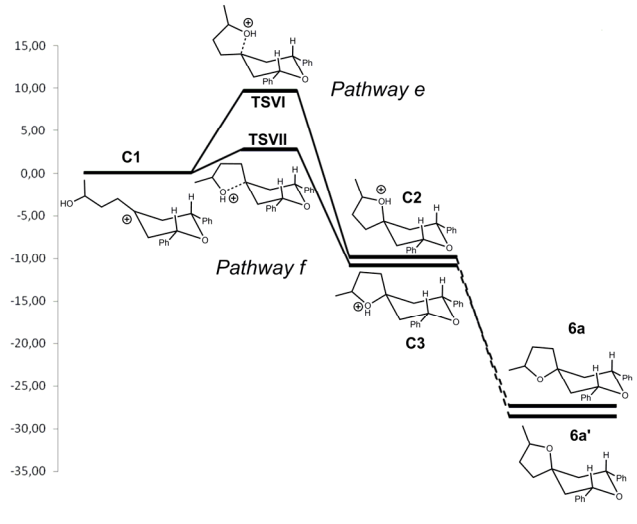
Scheme 6. Complete reaction profile of the 7-*endo* cyclization step yielding oxepane **2a** (in kcal/mol).

The free energy cost for the interconversion of **A3** into **A1** is 16.89 kcal/mol, while the energy barrier for its cyclization to **A4** is 5.86 kcal/mol. The large difference in activation energies (10.81 kcal/mol) between both pathways indicates that the interconversion process is not feasible. From all these data we can conclude that *Pathway b* is preferred over *Pathway a*.

The same protocol was followed for the computational study corresponding to the cyclization step leading to **3a**. The results obtained are very similar to those previously analysed and correlate well with the behavior suggested by Houk's computational study.[16]



Scheme 7. Reaction profile of the 7-*endo* cyclization step yielding oxepane **3a** (in kcal/mol).



Scheme 8. Reaction profile for the final attack of the hydroxyl group to the carbocation leading to two possible products **6a** and **6a'** (in kcal/mol).

Table 8. *Relative Gibbs free energy (in kcal/mol) for all stationary points calculated in solution at the 7-endo cyclization step leading to* ***3a****.*

Stationary Point	*ΔG*
A5	*8.38*
A7	*0.00*
TSIV	*12.76*
TSV	*5.27*
A6	*0.50*
A8	*0.11*

Table 9. *Gibbs free energies calculated in solution (in kcal/mol) for Pathways* ***c*** *and* ***d***

Pathway	$\Delta G^{\neq}$	$\Delta G_{reaction}$
c	*4.38*	*-7.88*
d	*5.27*	*0.11*

Thus, computational calculations show that the *trans* oxonium ion **A7** is 8.38 kcal/mol more stable that the *cis* **A5**, which explains why *Patway d* is preferred over *Pathway c* (Scheme 7, Table 8).[24]

Additionally, DFT calculations were performed to rationalise the preferred equatorial attack of the internal nucleophilic alcohol to the tertiary tetrahydropyranyl cation in the formation of dioxaspirodecanes **6**.

Thus, the tetrahydropyranyl carbocation intermediate **C1** was optimized and two transition states corresponding to the axial and equatorial attack by the hydroxyl group were found. [25] The results are sumarized in Scheme 8 and Table 10.

Table 10. *Gibbs free energies calculated in solution (in kcal/mol) for Pathways* ***e*** *and* ***f***

Pathway	$\Delta G^{\neq}$	$\Delta G_{reaction}$
e	*9.80*	*-9.92*
f	*2.88*	*-10.69*

As expected, the product corresponding to the axial trapping **6a'** is more stable (by 1.23 kcal/mol) than the product from the equatorial attack **6a** (Scheme 8). However their reaction pathways have different free energies of activation. The difference between both energies is 6.92 kcal/mol (Table 10), showing that *Pathway f* is more likely than *Pathway e* under kinetic conditions. On the other hand, Alder's calculations[15] predict a favourable axial attack on a cyclic tertiary carbocation when the trapping is intermolecular. Our experimental and theoretical results suggest a preference for the equatorial trapping when the process is intramolecular.

Conclusion

In conclusion the reaction of allylsilyl alcohols **1** with aldehydes in the presence of TMSOTf affords two different kinds of products depending on the structure of **1**. Apparently the nature of the allylic substituent on **1** causes an important effect in the chemoselectivity of the reaction. Thus, allylsilyl alcohols having no substituents on the allylic position provide dioxaspirodecanes, from a tandem Sakurai-Prins cyclization. In contrast, allylsilyl alcohols with an allylic substituent $R^2 \neq H$ give selectively oxepanes, which correspond to a direct silyl-Prins cyclization. A mechanistical proposal is provided for both pathways.

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Experimental Section

Representative procedure for the synthesis of oxepanes 2-5. To a stirred solution of the allylsilyl alcohols **1a-e** (1 mmol) and the corresponding aldehyde (1.2 mmol) in CH_2Cl_2 (13 mL) at -78 °C was added dropwise TMSOTf (1.2 mmol). The mixture was stirred for 10 min at -78 °C. Aqueous NaOH (2 M) was added and the mixture extracted with ether. The combined organic layer was dried, concentrated to dryness and chromatographed on silica gel (hexanes/ethyl acetate), (v/v) to afford oxepanes **2-5.**

Representative procedure for the synthesis of dioxaspirodecanes 6. To a stirred solution of the allylsilyl alcohols 1f-g (1 mmol) and the aldehyde (2.2 mmol) in CH_2Cl_2 (13 mL) at -78 °C was added dropwise TMSOTf (1.2 mmol). The mixture was stirred for 10 min at -78 °C. Aqueous NaOH (2 M) was added and the mixture extracted with ether. The combined organic layer was dried, concentrated to dryness and cromatographied on silica gel (hexanes/ethyl acetate), to afford the corresponding products (Table 4).

Computational details. DFT calculations were carried out by using the GAUSSIAN09 package.[26] B3LYP method (Becke Three Parameter Hybrid Functionals) was applied[27] A split-valence double-zeta basis set with polarization functions 6-31G(d,p) was used for C, H, O and Si.[28] Geometry optimizations were performed in gas-phase on the full potential energy surface without symmetry restrictions and confirmed by vibrational analysis. Transition States were obtained by first scanning the Potential Energy Surface along the bond expected to be formed and then applying the synchronous transit-guided quasi-Newton method QST3 at the approximate geometry of the TS.[29] Once located, they were confirmed by vibrational analysis. Solvent effects were taken into account by single-point calculations at geometries previously optimized in gas-phase by using PCM algorithm with Dichloromethane (ε=8.93) as a solvent.[30]

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Keywords: Prins • Sakurai • tandem • oxepane • silanes

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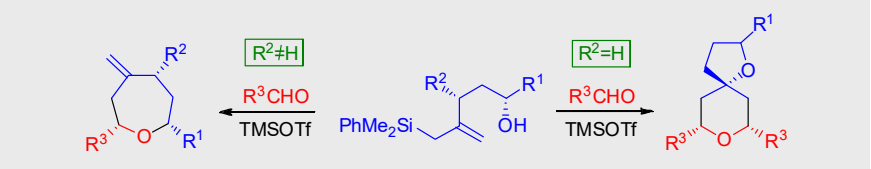

Different chemoselectiviy *is observed in the reaction of allylsilyl alcohols with aldehydes in the presence of TMSOTf. Apparently the nature of the substituents on the allylic position of the silane plays a determinant role in the outcome of the reaction, affording either dioxaspirodecanes or oxepanes in a very selective manner. The stereoselectiviy of both processes is very high.*

Prins

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■■ – ■■

Competitive Silyl-Prins Cyclization vs Tandem Sakurai-Prins Cyclization: interesting substitution effect

[1] A. Fukuzawa, T. Masamune, *Tetrahedron Letters* **1981**, *22*, 4081–4084.
[2] G. Guella, F. Pietra, *Helv. Chim. Acta* **1991**, *74*, 47–54
[3] a) G. Cimino, A. Madaio, E. Trivellone, *J. Nat. Prod.* **1994**, *57*, 784–790; b) G. Cimino, A. Crispino, A. Madaio, E. Trivellone, *J. Nat. Prod.* **1993**, *56*, 534–538; c) G. Cimino, R. D. A. Epifanio, A. Madaio, R. Puliti, E. Trivellone, *J. Nat. Prod.***1993**, *56*, 1622–1626.
[4] J. Q. Dai, J.A. Fishback, Y. D. Zhou, D. G. Nagle, *J. Nat. Prod.* **2006**, *69*, 1715–1720.
[5] A. V. K. Prasad, Y. Shimizu, J. *Am. Chem. Soc.* **1989**, *111*, 6476–6477.
[6] a) C. Olier, M. Kaafarani, S. Gastaldi, M. P. Bertrand, *Tetrahedron*, **2010**, *66*, 413–445; b) I. Pastor, M. Yus, *Curr. Org. Chem.* **2007**, *11*, 925–957; c) I. Pastor, M. Yus, *Curr. Org. Chem.* **2012**, *16*, 1277–1312; d) X. Han, G. Peh, P. E. Floreancig, *Eur. J. Org. Chem.* **2013**, 1193–1208.
[7] See within others: a) A. P. Dobbs, R. J. Parker, J. Skidmore, *Tetrahedron Lett.*, **2008**, *49*, 827–831; b) A. P. Dobbs, J. Dunn, *Tetrahedron Lett.*, **2012**, *53*, 2392–2395; c) A. P. Dobbs, S. A. Martinovic, *Tetrahedron Lett*., **2002**, *43*, 7055–7057.
[8] a) D. Berger, L. E. Overman, P. A. Renhowe, *J. Am. Chem. Soc.* **1993**, *115*, 9305–9306; b) D. Berger, L. E. Overman, P. A. Renhowe, *J. Am. Chem. Soc.* **1997**, *119*, 2446–2452.
[9] B. Furman, M. Dziedzc, I. Justyniak, *Tetrahedron* **2008**, *64*, 3103–3110.
[10] M. A. Purino, M. A. Ramírez, A. H. Daranas, V. S. Martín, J. I. Padrón, *Org. Lett.* **2012**, *14*, 5904–5907.
[11] a) A. Barbero, F. J. Pulido, *Chem. Soc. Rev.* **2005**, *34*, 913–920; b) A. Barbero, P. Cuadrado, A. M. González, F. J. Pulido, R. Rubio, I. Fleming, *Tetrahedron Lett.* **1992**, *33*, 5841–5842.
[12] a) A. Barbero, F. J. Pulido, *J. Am. Chem. Soc.* **2005**, *127*, 8022–8023; b) A. Barbero, A. Blanco, F. J. Pulido, *J. Org. Chem.* **2005**, *70*, 6876–6883; c) A. Barbero, A. Blanco, F. J. Pulido, *Chem. Commun*. **2001**, 1606–1607; d) F. J. Pulido, A. Barbero, P. Castreño, *J. Org. Chem.* **2011**, *76*, 5850–5855.
[13] a) F. J. Pulido, A. Barbero, Y. Blanco, *Org. Biomol. Chem.* **2011**, *9*, 1454–1458; b) F. J. Pulido, A. Barbero, P. Val, A. Diez, A. González-Ortega, *Eur. J. Org. Chem.* **2012**, 5350–5356.
[14] A. Barbero, A. Diez-Varga, F. J. Pulido, *Org. Lett.* **2013**, *15*, 5234–5237.
[15] A. Barbero, F. J. Pulido, *Synthesis* **2004**, 779–785.
[16] R. W. Alder, J. N. Harvey, M. T. Oakley, *J. Am. Chem. Soc.* **2002**, *124*, 4960–4961.
[17] J. L. Broeker, R. W. Hoffmann, K. N. Houk, *J. Am. Chem. Soc.* **1991**, *113*, 5006–5017.
[18] From various Lewis acids screened in this reaction (see ref 14), TMSOTf was the one that provided better yields and selectivities towards the dioxaspirodecane derivatives.
[19] F. K. Chio, J. Warne, D. Gough, M. Penny, S. Green, S. J. Coles, M. B. Hursthouse, P. Jones, L. Hassall, T. M. McGuire, A. P. Dobbs, *Tetrahedron*, **2011**, *67*, 5107–5124.
[20] S. Murata, M. Suzuki, R. Noyori, *Tetrahedron*, **1988**, 44, 4259–4275.
[21] a) A. Mekhalfia, I. E. Markó, *Tetrahedron Lett.* **1992**, *32*, 4779–4782; b) I. E. Markó, A. Mekhalfia, D. J. Bayston, H. Adams, *J. Org. Chem.* **1992**, *57*, 2211–2213; c) I. E. Markó, D. J. Bayston, *Tetrahedron* **1994**, 50, 7141–7156.
[22] Marko has also reported an interesting substitution effect in a Prins cyclization: B. Leroy, I. E. Marko, *J. Org. Chem.* **2002**, *67*, 8744–8752.
[23] M. G. Organ, V. Dragan, M. Miller, R. D. J. Froese, J. D. Goddard, *J. Org. Chem.* **2000**, *65*, 3666–3678.
[24] In a few cases the minor diasteroisomer, corresponding to the loss of silicon from **A2** or **A6**, could be isolated (Table 1 and 2).
[25] Although intermediate **C1** is the only one considered in this discussion, other intermediate having a *trans*-relationship between the Ph substituents, and its possible pathways, were calculated showing a similar profile but much higher in energy.
[26] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.
[27] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
[28] a) R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.* **1971**, *54*, 724; b) W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257; c) P. C. Hariharan, J. A. Pople, *Theor. Chem. Acc.* **1973**, *28*, 213–222; d) P. C. Hariharan, J. A. Pople, *Mol. Phys.* **1974**, *27*,

209–214; e) M. S. Gordon, *Chem. Phys. Lett,* **1980**, *76*, 163–168; f) M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, D. J. DeFrees, J. A. Pople, M. S. Gordon, *J. Chem. Phys.* **1982**, *77*, 3654–3665; g) R. C. Binning Jr., L. A. Curtiss, *J. Comp. Chem.* **1990**, *11*, 1206–1216; h) J.-P. Blaudeau, M. P. McGrath, L. A. Curtiss, L. Radom, *J. Chem. Phys.* **1997**, *107*, 5016–5021; i) V. A. Rassolov, J. A. Pople, M. A. Ratner, and T. L. Windus, *J. Chem. Phys.* **1998**, *109*, 1223–1229; j) V. A. Rassolov, M. A. Ratner, J. A. Pople, P. C. Redfern, L. A. Curtiss, *J. Comp. Chem.* **2001**, *22*, 976–984.

[29] a) C. Peng, H. B. Schlegel, *Israel J. Chem.* **1993**, *33*, 449–454; b) C. Peng, P. Y. Ayala, H. B. Schlegel, M. J. Frisch, *J. Comp. Chem.* **1996**, *17*, 49–56.

[30] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev*. **2005**, *105*, 2999–3093.