FULL PAPER

Prins Cyclization Catalyzed by a Fe(III)/TMS System: A [2+2] Cycloaddition versus Oxocarbenium ion Pathway Study

Sixto J. Pérez,[a] Martín Purino,[a] Pedro O. Miranda,[c] Víctor S. Martín,*[a] Israel Fernández,*[b] and Juan I. Padrón*[a],[c]

Abstract: The different factors that control the alkene Prins cyclization catalyzed by iron(III) salts have been explored by means of a joint experimental-computational study. The system iron(III) salt/TMSX has proved to be an excellent promoter in the synthesis of crossed all-*cis* disubstituted tetrahydropyrans, minimizing the formation of products derived from side-chain exchange. In this iron(III)-catalyzed Prins cyclization reaction between homoallylic alcohols with non-activated alkenes two mechanistic pathways can be envisaged, namely the classical oxocarbenium route and the alternative [2+2]-cycloaddition based pathway. It is found that the [2+2]-pathway is disfavored for those alcohols having non-activated and non-substituted alkenes. In these cases, the classical pathway via the key oxocarbenium ion is preferred. In addition, the final products distribution strongly depends upon the nature of the substituent adjacent to the hydroxyl group in the homoallylic alcohol which can favor or hamper a side 2-oxonia-Cope rearrangement.

Introduction

Tetrahydropyrans (THPs) are common structural units present and widespread in many natural products,[1] from marine natural products such as brevetoxin B or gambierol to biological active macrolides and macrolactones such as dactylolide and bryostatin 1, respectively (Figure 1).[2,3] Therefore, THP derivatives represent a very attractive targets for synthetic organic chemists. Among the different methods and strategies to synthetize THP rings,[4] the so-called Prins cyclization reaction has emerged as a powerful tool allowing the efficient access to these oxacycles. For this reason, it is not surprising that this process has been widely applied to the synthesis of natural products.[5] This cyclization is based on the reaction between a homoallylic alcohol or derivative with aldehydes promoted or catalyzed by Brønsted as well as Lewis acids (Scheme 1).[6] The keystone in the widely accepted mechanism is the generation of an oxocarbenium ion which drives the cyclization. However, this species can also experience an oxonia-Cope rearrangement as a competitive pathway, leading to two deleterious problems, namely a mixture of products by side-chain exchange and racemization. These processes have been deeply studied by the groups of Rychnovsky and Willis.[7]

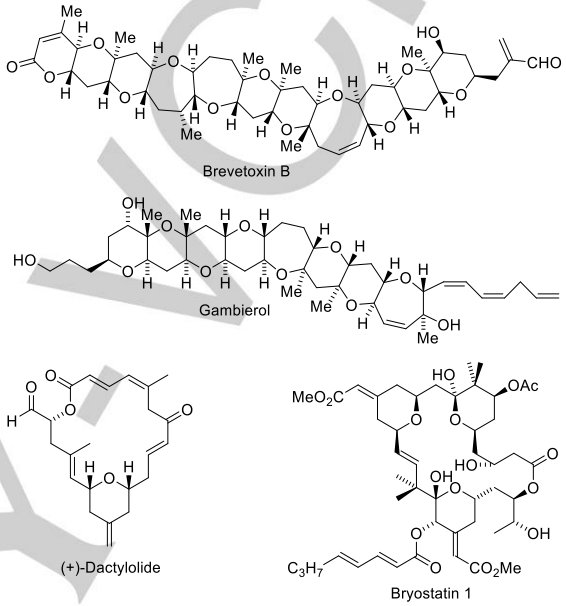
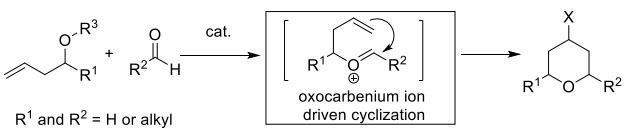


Figure 1. Selected examples of natural products containing tetrahydropyrans as subunits.

From the very beginning, this cyclization was promoted using strongly acidic conditions in stoichiometric amounts and mixed acetals as starting materials. This strategy ensured the mechanistic pathway through an oxocarbenium intermediate as the unique alternative.[7,8] At variance, many different Lewis acids have been recently used in the synthesis of substituted tetrahydropyrans with different substitution at the C-4 position, i.e. halogen,[9] and hydroxyl moieties.[6f,10] Strikingly, the combination of substoichiometric amounts of Lewis acid with trimethylsilyl halide (TMSX) led to a highlighted improvement of this cyclization reaction. Loh and co-workers have applied the combination of indium salts and chlorotrimethylsilane (TMSCl) as catalyst to the synthesis of 4-halo- tetrahydropyran rings.[11] Later on, the combination of TMSX with iron(III) salts (FeX_3 and $Fe(acac)_3$) permitted us to catalyze the Prins cyclization using non-activated alkenes and alkynes in a sustainable metal catalysis context (Scheme 1).[12]



R^1 and R^2 = H or alkyl
R^3 = H or $OC(OAc)R^2$ whithout R^2CHO
cat = MXn and/or TMSX, M = metal, X= Cl, Br, I
cat =TFA or M(OTf)n, X = OH

Scheme 1. Oxocarbenium ion drives Prins cyclization.

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This catalytic system is widely applicable and promotes the construction of substituted six-membered oxa- and azacycles, leading to the corresponding chloro, bromo and iodo heterocycles by the suitable combination of an iron(III) source, a trimethylsilyl halide and the solvent. The devised catalytic cycle relies on a ligand exchange between the iron complex and a halosilane, which regenerates the iron(III) halide due to the more oxophilic character of the silicon atom. This system presents several advantages such as the use of reduced amounts of metal, tolerance of functional groups present in the aldehyde, and cleaner reactions. Using this methodology, the synthesis of enantiomerically pure 4-hydroxyl-tetrahydropyran derivatives was successfully accomplished by Feng and co-workers recently, in an excellent study, through a sequential ene/Prins cyclization using $FeCl_3$/TBSCl as a catalyst.[6f]

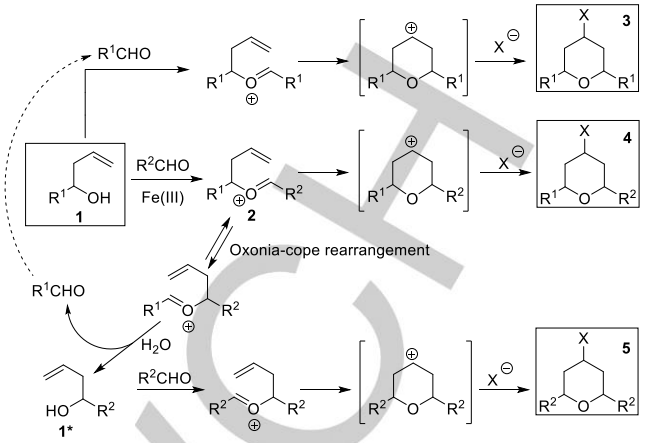
Herein, we describe the different factors that control the alkene Prins cyclization catalyzed by iron(III) salts in the presence of $SiMe_3X$ (X = Cl, Br) towards the synthesis of crossed disubstituted tetrahydropyrans. Density Functional Theory (DFT) calculations supports the preference of classical oxocarbenium ion pathway over the possible [2+2] pathway and explains the origin of the observed product distribution, which depends on the nature of the substituent at the homoallylic alcohol and the iron(III) source.

Results and Discussion

Influence of the oxonia-cope rearrangement in the alkene-Prins cyclization using the catalytic system Fe(III)/TMSX

As commented above, the Prins cyclization mechanism is based on the generation of an oxocarbenium ion intermediate **2** which drives the formation of the corresponding tetrahydropyrans (Scheme 2). However, this cationic intermediate may also undergo an oxonia-Cope rearrangement to generate a new homoallylic alcohol (**1***) and an aldehyde that can participate in a new Prins cyclization process thus generating the undesired species **3** and **5,** besides the tetrahydropyran **4** (Scheme 2). Furthermore, due to the involvement of an oxocarbenium ion, a mixture of diastereoisomers would be expected. Therefore, it was necessary to carry out a study on the influence of the oxonia-Cope rearrangement on the tetrahydropyrans distribution as well as their possible consequences using non-activated alkenes.

In a preliminary work, and using stoichiometric amounts of iron(III) chloride, we observed that the distribution of tetrahydropyrans mainly depends on two factors, namely the bulkiness of the substituent group at R^1 and the electronic effect of the substituents directly attached to the aromatic ring at R^1. An increment of the bulkiness of R^1 group (methyl, ethyl and cyclohexyl) increased the formation of the desired THP **4** with a subsequent decrease of THP **5**. This steric control therefore favored the Prins cyclization to **4** over the 2-oxonia-Cope rearrangement. Moreover, when R^1 is an aromatic ring the presence of electron-deficient substituents favors the Prins cyclization yielding the THP **4** as the major product.[13]



Scheme 2. Possible mixture of tetrahydropyrans in the Prins cyclization by participation of oxonia-Cope rearrangement.

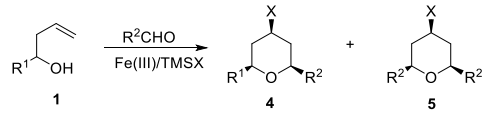
In order to have a better understanding of the effect of the catalytic system on the competitive processes (Prins cyclization vs oxonia-Cope rearrangement), different sources of Fe(III) salts as well as TMSX were evaluated. Moreover, these results, which are summarized in Table 1, can be compared to our previous studies using stoichiometric amounts of $FeCl_3$.[13]

When R^1 is a phenyl ring and R^2 an *i*-butyl group, the cyclization under stoichiometric conditions leads to a 50:50 mixture of tetrahydropyrans **4** and **5** in 70% yield.[13] We focused on this particular case as a starting point of our comparative study. In the case of allyl phenyl carbinol **1** (R^1= Ph) the percentage of the desired THP **4** was improved to 87% under catalytic conditions, being not necessary the presence of electron-deficient substituents (Table 1, entry 1).[7a] This is a remarkable result because Willis and co-workers had to introduce an electron-deficient substituent on the aromatic ring and use stoichiometric amounts of Lewis acid to obtain the same products distribution.[7a] The cyclization works well with both iron(III) salts, $FeCl_3$ and $Fe(acac)_3$, leading to similar reaction yields. The combination of these conditions with a bulkier group at R^2 (*c*-Hex) results in a slight increase of the percentage of THP-**4** up to 89% (Table 1, entry 2). With homobenzyl as substituent at R^1, the crossed 4-chloro-2,6-trisubstituted THP **4** was obtained almost exclusively, minimizing the competitive 2-oxonia-Cope rearrangement and side-chain exchange (Table 1, entry 3).[14] The best results were obtained when combining *n*-hexyl and *i*-butyl as R^1 with *c*-hexyl as R^2 (Table 1, entries 5 and 7). In these cases, the crossed THP-**4** was obtained exclusively with excellent yields. Similar results were obtained in the bromo-version of the catalytic system (Table 1, entries 8-12). The best ratios of crossed 4-bromo-2,6-trisubstituted THP **4** were obtained with *c*-hexyl as R^2 and $Fe(acac)_3$ as iron(III) source (Table 1, entries 10 and 12). The nature of silyl additive does not influence either the ratio or the yield of the Prins cyclization catalyzed by iron(III).[15]

At this moment, the combination of catalytic amounts of iron(III) salts and TMSCl as additive is effective and nearly cancels the 2-oxonia-Cope rearrangement favoring the direct Prins cyclization under the specified experimental conditions. We

have therefore solved some of the side reactions, avoiding the exchange of aldehyde and alcohol side chains.

Table 1. Catalytic system (Fe(III)/TMSX) effect on the products distribution of direct Prins Cyclization versus 2-oxonia-[3,3]-rearrangement.[a]



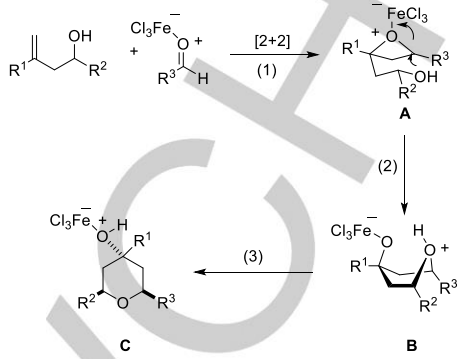
Entry	R^1	R^2	X	Fe(III)	**4**	:	**5**[b][c]	Yield %
1	Ph	*i*-Bu	Cl	$FeCl_3$	87		13	86
				$Fe(acac)_3$	87		13	80
2	Ph	*c*-Hex	Cl	$FeCl_3$	89		11	90
				$Fe(acac)_3$	85		15	90
3	$Ph(CH_2)_2$	*c*-Hex	Cl	$FeCl_3$	94		6	90
				$Fe(acac)_3$	94		6	88
4	$Ph(CH_2)_2$	Ph	Cl	$FeCl_3$	94		6	80
				$Fe(acac)_3$	93		7	75
5	*n*-Hex	*c*-Hex	Cl	$FeCl_3$	93		7	85
				$Fe(acac)_3$	100		0	75
6	*i*-Bu	*i*-Bu	Cl	$FeCl_3$	100		0	95
				$Fe(acac)_3$	100		0	96
7	*i*-Bu	*c*-Hex	Cl	$FeCl_3$	100		0	95
				$Fe(acac)_3$	100		0	95
8	Ph	*i*-Bu	Br	$FeBr_3$	80		20	87
				$Fe(acac)_3$	75		25	90
9	Ph	*c*-Hex	Br	$FeBr_3$	79		21	95
				$Fe(acac)_3$	89		11	90
10	*n*-Hex	*c*-Hex	Br	$FeBr_3$	95		5	74
				$Fe(acac)_3$	95		5	84
11	*i*-Bu	*i*-Bu	Br	$FeBr_3$	100		0	90
				$Fe(acac)_3$	100		0	87
12	*i*-Bu	*c*-Hex	Br	$FeBr_3$	95		5	95
				$Fe(acac)_3$	96		4	99

[a] reactions conditions: **1** (1.0 mmol), R_2CHO (1.2 mmol) and Fe(III) (0.1 mmol)/TMSX (1.1 mmol) in dry CH_2Cl_2 (10 mL) at rt for 15 h. [b] Yields of products after purification by silica gel column chromatography. [c] We did not observe any THP **3** product.

Theoretical calculations on Iron(III)-catalyzed alkene-Prins cyclization

Density Functional Theory (DFT) calculations were carried out (PCM(CH_2Cl_2)B3LYP/def2-TZVP//B3LYP/def2-SVP level)[16,17] to gain more insight into the reaction mechanism of the above iron(III)-catalyzed Prins cyclization reactions. To this end, we have selected the reaction between the model reactants **1** (R^1 = Me) and MeCHO in the presence of $FeCl_3$ as catalyst.

At this point, it is important to consider the recent work of Feng and co-workers based on labeling as well as DFT studies.[6f] These authors suggest a new mechanism for the $FeCl_3$-catalyzed Prins cyclization between homoallylic alcohols and aldehydes. It was proposed that the entire catalytic cycle proceeds via the following three consecutive steps: (1) initial [2+2] cycloaddition reaction leading to the oxetane intermediate **A**, (2) nucleophilic attack of the OH group at the electrophilic C–O$FeCl_3$ center with concomitant ring opening to form intermediate **B**, and (3) intramolecular proton transfer to produce compound **C** (Scheme 3). Step (2) occurs with an activation barrier of ca. 27 kcal/mol and constitutes the rate-determining step of the entire transformation.[6f]



Scheme 3. Feng´s mechanistic model for the $FeCl_3$-catalyzed Prins cyclization

This alternative reaction mechanism can be only considered as a special class of the Prins cyclization because of the particular nature of the substrates used by Feng and co-workers. These authors use a homoallylic alcohol with an activated alkene (typically R^1 = aromatic) having an ester group as R^2, which favors the initial stepwise [2+2]-cycloaddition step (Scheme 3). Feng and co-workers also showed that homoallylic alcohols with 4-unsubstituted alkenes but keeping the ester at R^2 did not produce the Prins cyclization.[6f] Despite that, we were curious to calculate an analogous reaction pathway for our substrates, where R^1 = H and $R^2 \neq$ ester. From the barrier energies shown in Figure 2, it seems that the pathway leading to the axial-hydroxyl derivative **INT4** (species C, Scheme 3) is feasible from the initially formed oxetane intermediate **INT2** (species A, Scheme 3). However, the formation of the latter intermediate is clearly more difficult for systems lacking an aromatic substituent at 4-position relative to the oxygen. Not surprisingly, the computed activation barrier for the second step of the [2+2]-cycloaddition (which produces **INT2**) is much higher (29.4 kcal/mol, corresponding free energy of 38.7 kcal/mol) than the analogous process reported by Feng and co-workers (4.7 kcal/mol, R^1 = Ph, R^2 = CO_2Et, R^3 = Et, at the similar PCM(CH_2Cl_2)//B3LYP/6-31G** level).[6f] In addition, all our attempts to locate the corresponding carbocationic intermediate **INT1** on the potential energy surface (even including the solvent during the geometry optimizations) met with no success, i.e. only dissociation into the initial reactants was found. These results suggest that the [2+2]-cycloaddition is disfavored when using homoallylic alcohols having non-activated and non-substituted alkenes. In the absence of substituents at the double bond (as it occurs in the substrates considered in the present work), this pathway can be ruled out and therefore, the so-called “classical” pathway seems to be operating. Further experimental support to this finding is given by the absence of the corresponding 4-hydroxy derivatives from **INT4** (no traces of this type of products were observed in the reaction crudes). Moreover, if the [2+2]-mechanism were operating, adding 4-hydroxy or 4-TMSO THP (compounds **6** and **7**, respectively) would produce the observed

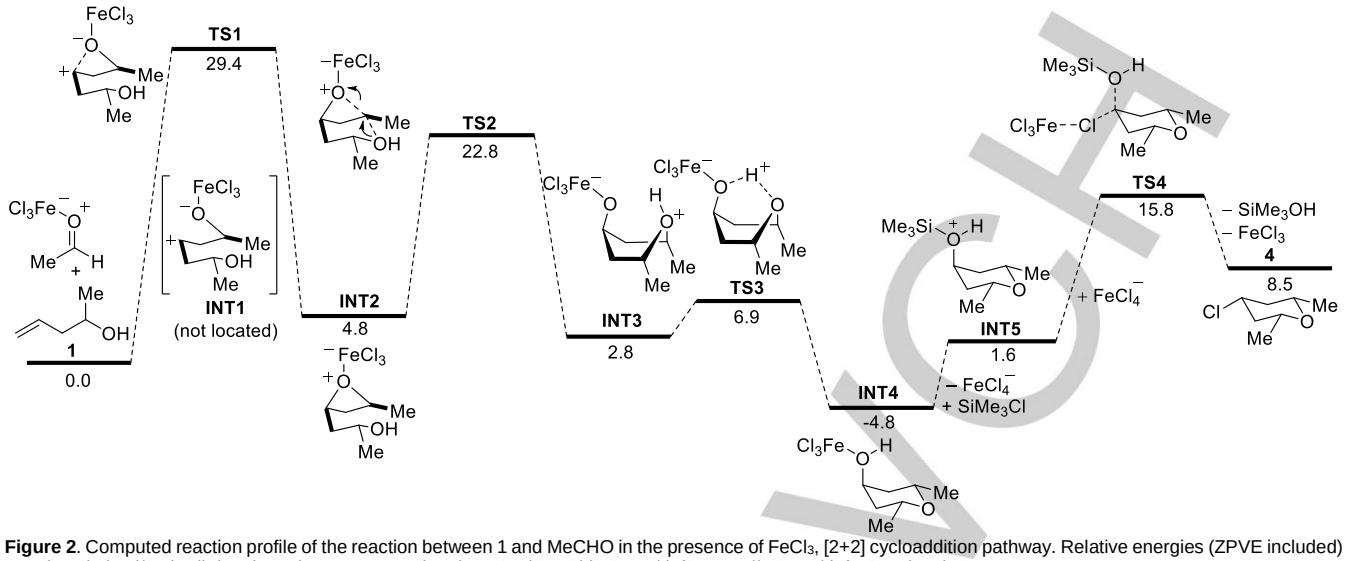
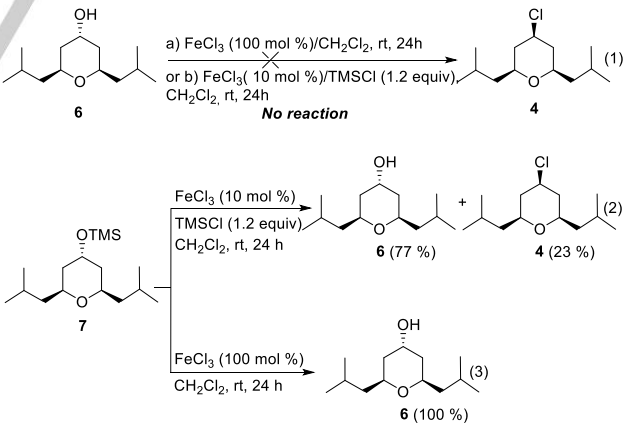


Figure 2. Computed reaction profile of the reaction between 1 and MeCHO in the presence of $FeCl_3$, [2+2] cycloaddition pathway. Relative energies (ZPVE included) are given in kcal/mol. All data have been computed at the PCM(CH_2Cl_2)B3LYP/def2-TZVP//B3LYP/def2-SVP level

4-equatorial chloride **4** product under the same reaction conditions (Scheme 4). However, the latter reaction product **4** was only observed, in very low yield by treatment of the 4-OTMS THP **7** under catalytic conditions (Scheme 4, eq 2).

Therefore, it can be concluded that the [2+2]-pathway does not occur within the substrates and reaction conditions considered in this work. Once the classical pathway is confirmed to be preferred, we then computationally studied the formation of the key oxocarbenium ion **2** (Scheme 2). The computed reaction profile for the reaction between **1** (R^1 = Me) and the iron(III)-coordinated aldehyde MeCHO is depicted in Figure 3. Our calculations suggest that the process begins with the coordination of the initial reactants to the $FeCl_3$ to form **INT6**. This complex is stabilized by an intramolecular Cl···HO hydrogen bond which weakens the corresponding Fe–Cl bond. As a result, a molecule of HCl can be released to produce **INT7** in an endothermic process (ΔE = 14.8 kcal/mol). This intermediate is transformed into the metalla-1,3-dioxetane **INT8** through the transition state **TS5**, a saddle point associated with the formation of the new C–O bond, with an activation barrier of 12.5 kcal/mol. **INT8** evolves then into **INT9** via **TS6**, a transition state associated with the protonolysis of the Fe–O promoted by HCl. The ease of the latter reaction step is confirmed by the low computed activation barrier ($\Delta E^{\neq}$ = 6.2 kcal/mol) and high exothermicity (ΔE = –16.0 kcal/mol). It can be suggested that **INT9** is then converted into **INT10** in a slightly endothermic reaction (ΔE = 3.2 kcal/mol). This reaction very likely proceeds via decoordination of the $FeCl_3$ catalyst followed by nucleophilic substitution reaction between the readily formed alcohol and $SiMe_3Cl$ to produce the cation **INT10** and $FeCl_4^-$ as counteranion. We were not able to locate a transition state associated with the intramolecular nucleophilic addition of the C=C double bond with concomitant release of $SiMe_3OH$ in **INT10**. Instead, we found a S_N1-type mechanism which involves the initial release of the $SiMe_3OH$ fragment to produce the cationic intermediate **INT11**. This step is highly exothermic (ΔE = –14.9 kcal/mol) as a result of the stabilization of the carbocation by the adjacent oxygen atom. Then, the intramolecular cyclization reaction occurs via **TS7**, which is associated with the formation of the new C–C bond with an activation barrier of only 6.8 kcal/mol. This process leads to the formation of **INT12**, in which both methyl substituents are placed in equatorial positions. The geometry of this carbocation directs the subsequent nucleophilic attack, either by $FeCl_4^-$ or simply by Cl^-, from the equatorial position as the axial delivery is sterically hampered (see inset in Figure 3).



Scheme 4. Control experiments in the plausible hydroxy intermediates of the [2+2] cycloaddition pathway.

From the data in Figure 3, the initial C–O bond formation and subsequent Fe–O protonolysis constitute the rate-determining steps of the entire transformation. In addition, the overall relative reaction profile for this classical oxocarbenium-pathway is energetically favored over the alternative [2+2]-pathway (see Figure 2), which nicely agrees with the experimental observations.

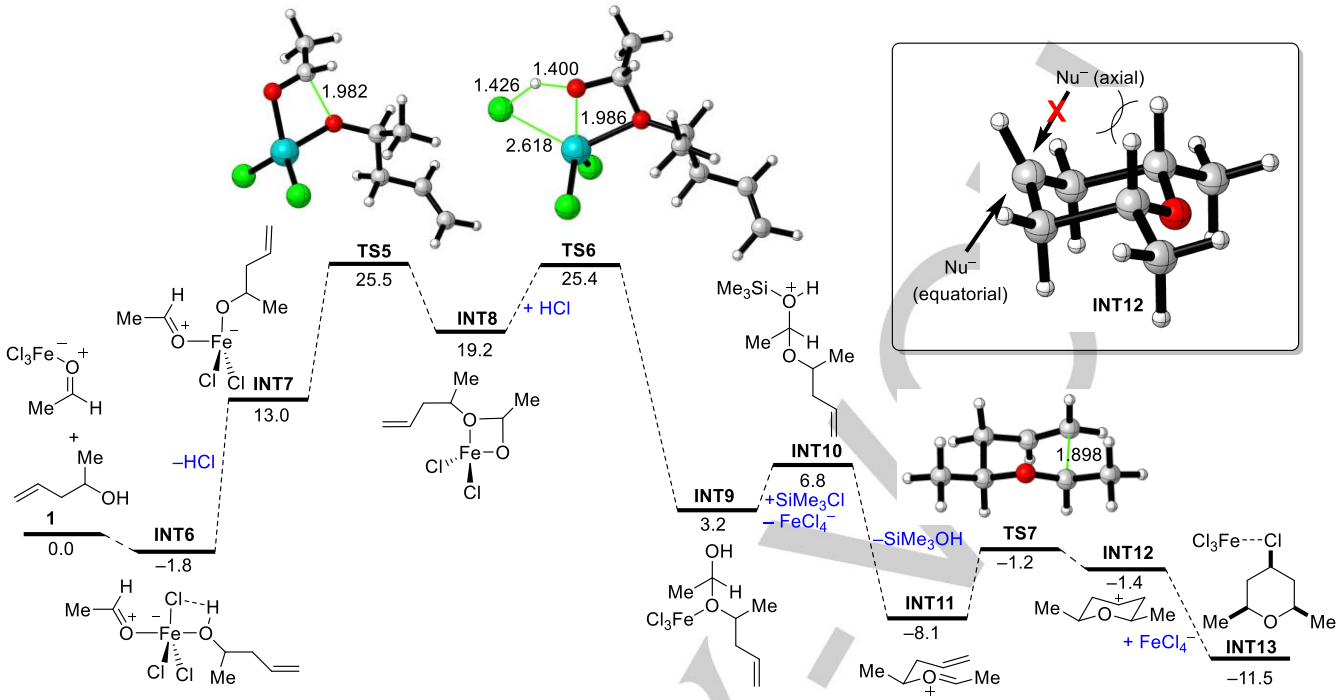
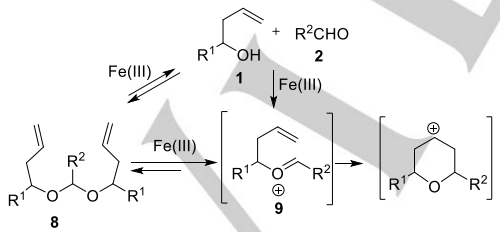


Figure 3. Computed reaction profile of the reaction between **1** and MeCHO in the presence of $FeCl_3$ and $SiMe_3Cl$, oxocarbenium ion pathway. Relative energies (ZPVE included) are given in kcal/mol and bond distances in angstroms. All data have been computed at the PCM(CH_2Cl_2)B3LYP/def2-TZVP//B3LYP/def2-SVP level.

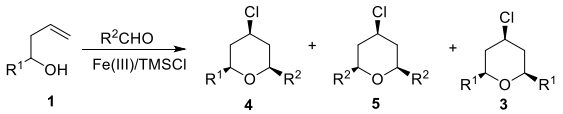
The occurrence of mixture of products (**3**, **4** and **5,** Scheme 2) by means of competitive 2-oxonia-Cope rearrangement and side-exchange reaction is fully compatible with the above described classical pathway via the key oxocarbenium ion. Despite that, the final product distribution strongly depends on the experimental conditions, type of alkene and iron(III) salts. For instance, we observed significant differences when using stoichiometric instead of catalytic conditions. Thus, the relative amount of **5** is in general higher under stoichiometric amounts of iron(III) salts than under catalytic conditions. Moreover, acetal **8**, which contributes to the oxocarbenium ion formation **9**, is only present under stoichiometric conditions (Scheme 5).



Scheme 5. Contribution of the acetal to the oxocarbenium ion pathway.

Both the iron ligand and the reaction temperature have also a direct effect on the tetrahydropyran distribution when the homoallylic alcohol **1** bears at R^1 a phenyl group (Table 2). For instance, with $Fe(OTf)_3$/TMSCl as catalytic system, the decrease of the amount of THP **4** involves the increase of the amounts of THPs **5** and **3,** the latter being observed for the first time (Table 2, entry 3).

Table 2. Iron ligand and temperature effect on the ratio of direct Prins Cyclization versus product derived from the 2-oxonia-[3,3]-rearrangement.[a]



Entry	R^1	R^2	Temp.	FeL_3	**4**	**5**	**3**[b]	Yield %
1	*i*-Bu	*i*-Bu	rt	$Fe(OTf)_3$	100	0	0	90
2	*i*-Bu	*c*-Hex	rt	$Fe(OTf)_3$	100	0	0	>99
3	Ph	*i*-Bu	rt	$Fe(OTf)_3$	30	45	25	74
4	Ph	*i*-Bu	0 ºC	$FeCl_3$	22	59	19	75
5	Ph	*i*-Bu	0 ºC	$Fe(acac)_3$	23	62	15	87
6	Ph	*i*-Bu	0 ºC	$Fe(OTf)_3$	15	85	0	75
7	*i*-Bu	*c*-Hex	0 ºC	$FeCl_3$	100	0	0	80
8	*i*-Bu	*c*-Hex	0 ºC	$Fe(acac)_3$	100	0	0	84
9	*i*-Bu	*c*-Hex	0 ºC	$Fe(OTf)_3$	100	0	0	73
10	Ph	*i*-Bu	40 ºC	$FeCl_3$	10	90	0	80
11	Ph	*i*-Bu	40 ºC	$Fe(acac)_3$	25	75	0	75
12	Ph	*i*-Bu	40 ºC	$Fe(OTf)_3$	28	57	14	64
13	*i*-Bu	*c*-Hex	40 ºC	$FeCl_3$	100	0	0	>99
14	*i*-Bu	*c*-Hex	40 ºC	$Fe(acac)_3$	100	0	0	95
15	*i*-Bu	*c*-Hex	40 ºC	$Fe(OTf)_3$	100	0	0	>99

[a] reactions conditions: **1** (1.0 mmol), R^2CHO (1.2 mmol) and Fe(III) (0.1 mmol)/TMSCl (1.1 mmol) in dry CH_2Cl_2 (10 mL) at rt for 15 h and 24 h at 0ºC. [b] Yields of products after purification by silica gel column chromatography.

Similar results are obtained when using allyl phenyl carbinol (**1**, R^1 = Ph) and a reaction temperature of 0 ºC. In this case, we obtained a mixture of THPs **3**, **4** and **5** regardless of the iron(III) salt used (Table 2, entries 4-6).[18] When using $Fe(OTf)_3$ the major compound is the THP **5** (Table 2, entry 6). This behavior was also observed when changing the temperature of the reaction to 40ºC (Table 2, entries 10-12). However, when the homoallylic alcohol **1** bears an aliphatic substituent, the Prins cyclization leads exclusively to the THP **4** regardless of the reaction temperature or iron ligands (Table 2, entries 1-2, 7-9 and 13-15).

From all this data in Table 2, it becomes clear that the oxonia-Cope rearrangement is favored when using allyl phenyl carbinols, triflate as iron ligand and modifying the temperature of the cyclization.

At this point, we tried to rationalize the finding of the formation of the mixture of THPs when R^1 = Ph. To this end, we decided to carry out a theoretical study comparing the oxonia-Cope rearrangement with phenyl and *iso*-butyl as R^1 substituents (Figure 4). Although the computed activation barrier is quite similar in both cases ($\Delta\Delta E^{\neq}$ of only 0.2 kcal/mol), the process is greatly thermodynamically favored ($\Delta\Delta E$ = 9.3 kcal/mol) for the oxocarbenium ion having a phenyl substituent (**2-Ph**, Figure 4). This can be of course ascribed to the stabilization by π-conjugation exerted by the phenyl group in **2'-Ph**, which constitutes the driven force for the rearrangement. At variance, the stabilization by hyperconjugation exerted by the isobutyl group is comparatively much weaker, making the rearrangement much more difficult (i.e. **2'-iBu** is practically isoenergetic to **2-iBu**, which suggests an equilibrium between both species). Therefore, our computational data indicate that the oxonia-Cope rearrangement is favored when R^1 = Ph, which is in agreement with the experimental results gathered in Table 2.

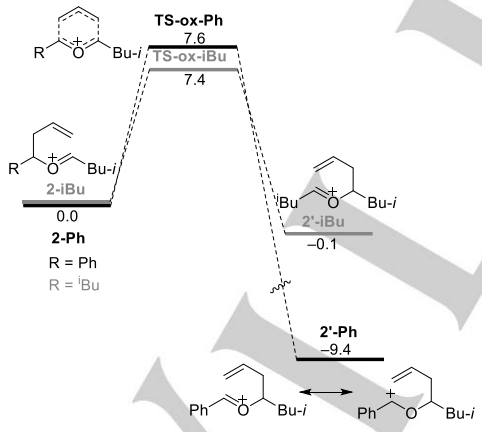
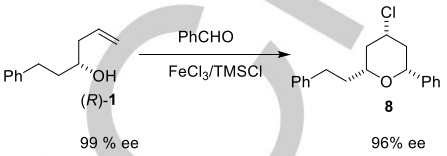


Figure 4. A comparative computed reaction profile for the oxonia-Cope rearrangement with phenyl and alkyl as R^1 substituents. Relative energies (ZPVE included) are given in kcal/mol. All data have been computed at the PCM(CH_2Cl_2)B3LYP/def2-TZVP//B3LYP/def2-SVP level.

Finally, racemization in the Prins cyclization has been also suggested to be an indicator for the participation of the oxonia-Cope rearrangement in the process.[7] Thus, the next step was to check the level of racemization in the process under our catalytic conditions that, in principle, should be low based on the data commented above on Table 1. For this purpose, we carried out the Prins cyclization between alcohol (*R*)-**1** and benzaldehyde using our catalytic system (Scheme 6). The use of 10 mol % of $FeCl_3$ yielded the desired product **8** with a 96% ee, which nicely indicates that no competitive 2-oxonia-Cope rearrangement or side-chain exchanged occurred.



Scheme 6. Iron(III) salt/TMSCl system catalyzes Prins cyclization preventing racemization.

Conclusions

We have established a method to obtain almost exclusively crossed 2,4,6-trisubstituted tetrahydropyrans by using the catalytic system iron(III) salts and TMSX and avoiding side-chain exchange and racemization processes. In this iron(III)-catalyzed Prins cyclization reaction between homoallylic alcohols with non-activated alkenes two mechanistic pathways can be envisaged, namely the classical oxocarbenium route and the alternative [2+2]-cycloaddition based pathway. Our joint experimental and computational study clearly confirms that the [2+2]-pathway is disfavored for those alcohols having non-activated and non-substituted alkenes. In these cases, the classical pathway via the key oxocarbenium ion **2** is preferred. Furthermore, the nature of the substituent adjacent to the hydroxyl group in the homoallylic alcohol is decisive to control the possible oxonia-Cope rearrangement of the corresponding oxocarbenium ion. Thus, whereas alkyl substituents do not favor this side-rearrangement and therefore, lead almost exclusively to crossed tetrahydropyran derivatives, the 2-oxonia-Cope rearrangement is strongly thermodynamically favored in the presence of a phenyl group. As a result, a mixture of tetrahydropyrans is observed in these cases.

Experimental Section

General methods and computational details are given in the Supporting Information.

General procedure by the iron(III) salt/TMSX catalyzed Prins cyclization: To a solution of homoallylic alcohol (1.0 equiv) in anhydrous CH_2Cl_2 (0.1 M) was added the corresponding aldehyde (1.2 equiv) and then the iron(III) salt (0.1 equiv) and TMSX (1.1 equiv) in this order. The reaction mixture was stirred at room temperature for 15h. The reaction was quenched by addition of water with stirring for 90 min, and the mixture extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulphate, filtered and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

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Keywords: cyclization • heterocycle • iron • Lewis catalysis • DFT calculations

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[14] This data is in agreement with the Loh results except in the meso type compound obtained. In our case, 5% yield of the *meso*-product **5** was obtained. However, 5% of the meso product **3** was obtained by Loh and co-worker using In(III) salt instead Fe(III) salts. Ref 11a.

[15] We have obtained the same results using TMSCl or TBSCl as silyl additive. No difference in the ratio **4**:**5** and yields were observed.

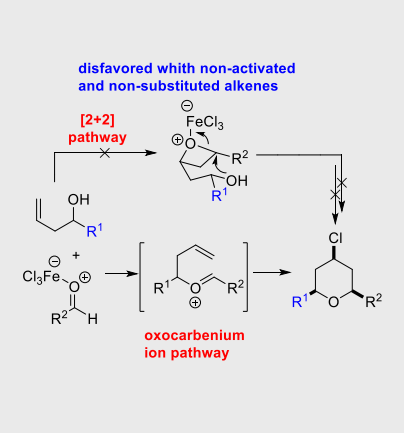
[16] This level has been selected because a similar level (PCM(CH_2Cl_2)/B3LYP/6-31G**) was used by Feng and co-workers in a related study (see reference [6f]).

[17] See computational details in the Supporting Information.

[18] We have not detected benzyl chloride as result to benzyl carbocation formation.

FULL PAPER

Two mechanistic pathways: In this iron(III)-catalyzed Prins cyclization between homoallylic alcohols with non-activated alkenes two mechanistic pathways can be envisaged, namely the classical oxocarbenium and the [2+2] cyclization. Our joint experimental-DFT study supports the classical route.



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Prins Cyclization Catalyzed by a Fe(III)/TMS System: A [2+2] Cycloaddition versus Oxocarbenium ion Pathway Study