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Reaction Mechanisms |*Hot Paper*|

Prins Cyclization Catalyzed by a Fe^{III}/Trimethylsilyl Halide System: The Oxocarbenium Ion Pathway versus the [2+2] Cycloaddition

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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 iron(III) salt/trimethylsilyl halide system 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 and 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 product distribution strongly depends upon the nature of the substituent adjacent to the hydroxy group in the homoallylic alcohol, which can favor or hamper a side 2-oxonia-Cope rearrangement.

Introduction

Tetrahydropyrans (THPs) are common structural units present in many natural products,[1] from marine natural products such as brevetoxin B or gambierol to biologically active macrolides and macrolactones, such as dactylolide and bryostatin 1, respectively (Figure 1).[2,3] Therefore, THP derivatives represent 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 undergo 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 thoroughly studied by the groups of Rychnovsky and Willis.[7]

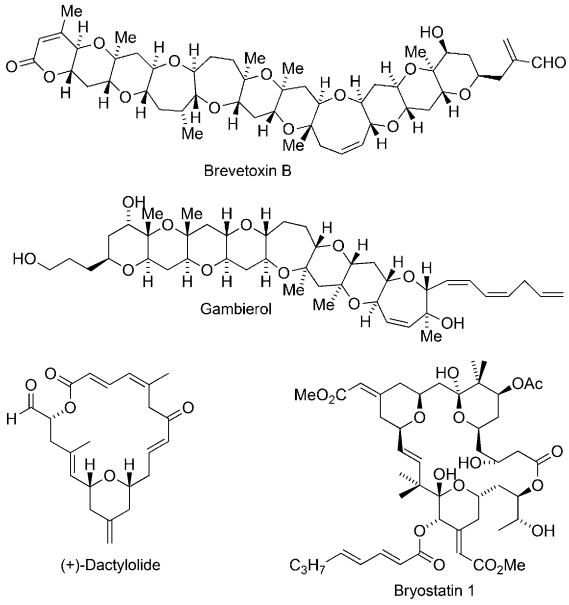

Figure 1. Selected examples of natural products containing tetrahydropyran subunits.

From the very beginning, this cyclization was promoted by using strongly acidic conditions in stoichiometric amounts and mixed acetals as starting materials. This strategy ensured the

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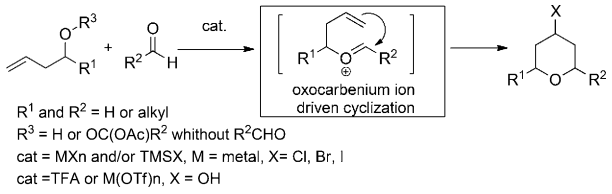


Scheme 1. Oxocarbenium ion-driven Prins cyclization.

reaction proceeded through an oxocarbenium intermediate as the unique mechanistic pathway.[7,8] Recently, many different Lewis acids have been used in the synthesis of substituted tetrahydropyrans with different substituents at the C4 position, that is, halide[9] and hydroxy moieties.[6f,10] Strikingly, the combination of substoichiometric amounts of Lewis acid with trimethylsilyl halide (TMSX) led to a significant improvement in this cyclization reaction. Loh and co-workers applied a combination of indium salts and chlorotrimethylsilane (TMSCl) as catalyst to the synthesis of 4-halotetrahydropyran rings.[11] More recently, the combination of TMSX with iron(III) salts (FeX_3 and $Fe(acac)_3$) permitted our group to catalyze the Prins cyclization with non-activated alkenes and alkynes in a sustainable metal catalysis context (Scheme 1).[12]

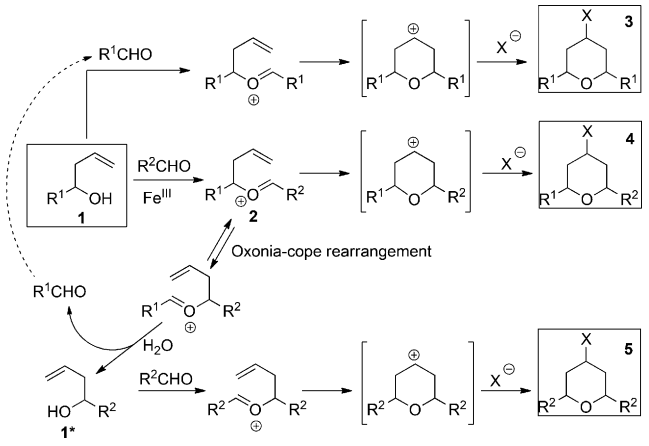
This catalytic system is widely applicable and promotes the construction of substituted six-membered oxa- and azacycles, leading to the corresponding chloro, bromo and iodo heterocycles by a suitable combination of an iron(III) source, a trimethylsilyl halide, and the solvent. The devised catalytic cycle 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 in the aldehyde, and cleaner reactions. By using this methodology, the synthesis of enantiomerically pure 4-hydroxytetrahydropyran derivatives was recently accomplished by Feng and co-workers in an excellent study, through a sequential ene/Prins cyclization with $FeCl_3$/TBSCl (TBS = *tert*-butyldimethylsilyl) 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 support the preference of the classical oxocarbenium ion pathway over the possible [2+2] cycloaddition pathway and explain 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 discussed 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



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

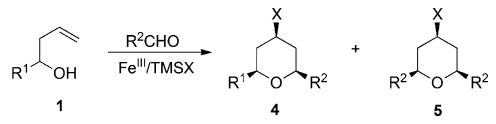
also undergo an oxonia-Cope rearrangement to generate a new homoallylic alcohol **1*** and an aldehyde that can participate in a new Prins cyclization process, thus generating the undesired species **3** and **5**, besides the tetrahydropyran **4** (Scheme 2). Furthermore, due to the involvement of an 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 tetrahydropyran distribution, as well as the possible consequences when using non-activated alkenes.

In a preliminary work 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 R^1 and the electronic effect of the substituents directly attached to R^1 if R^1 is an aryl group. An increase in the bulkiness of R^1 (methyl, ethyl and cyclohexyl) increased the formation of the desired THP **4** with a subsequent decrease in that of THP **5**. This steric control therefore favored the Prins cyclization to **4** over the 2-oxonia-Cope rearrangement. Moreover, when R^1 was an aromatic ring, the presence of electron-deficient substituents favored the Prins cyclization, yielding THP **4** as the major product.[13]

To better understand 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 (Table 1). Moreover, these results 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 *iso*-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, and electron-deficient substituents were not necessary to achieve this result (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

Table 1. Effect of catalytic system (Fe^{III}/TMSX) on the product distribution of direct Prins cyclization versus 2-oxonia-[3,3]-rearrangement.[a]



Entry	R^1	R^2	X	Fe^{III}	Selectivity [%][b,c] 4	5	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 detect any THP **3** product.

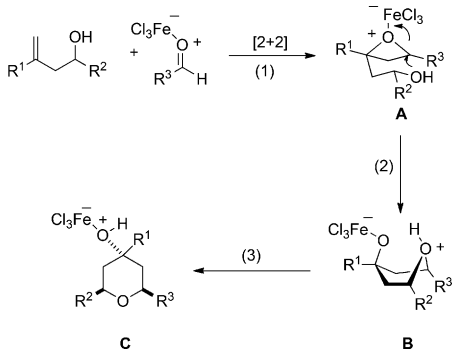
same product distribution.[7a] The cyclization works well with both iron(III) salts, $FeCl_3$ and $Fe(acac)_3$, leading to similar reaction yields. The combination of these conditions with a bulkier group at R^2 (*c*-Hex) results in a slight increase of the percentage of THP-**4** up to 89% (Table 1, entry 2). With homobenzyl as the 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 *iso*-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 with 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 the silyl additive did 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 eliminates 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.

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

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 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–$OFeCl_3$ center with concomitant ring opening to form intermediate **B**; 3) intramolecular proton transfer to produce compound **C** (Scheme 3). Step (2) occurs with an activation barrier of approximately 27 kcal mol^{-1} 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 undergo the Prins cyclization.[6f] In spite of this, 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 given in Figure 2, it seems that the pathway leading to the axial-hydroxy derivative **INT4** (**C** in Scheme 3) is feasible from the initially formed oxetane intermediate **INT2** (**A** in Scheme 3). However, the formation of the latter intermediate is clearly more difficult for systems lacking an aromatic substitu-

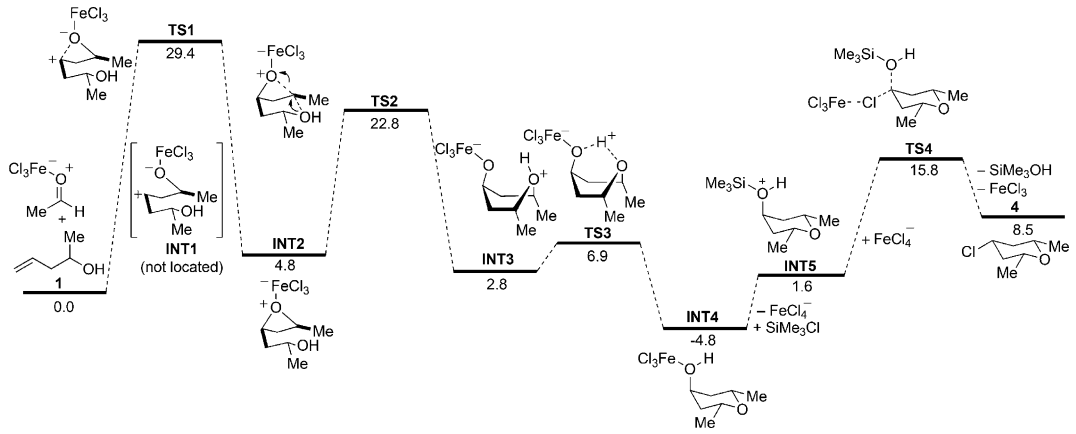
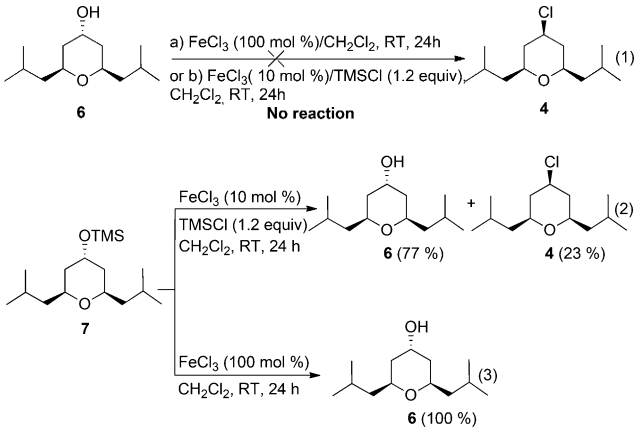


Figure 2. Computed reaction profile of the reaction between **1** and MeCHO in the presence of $FeCl_3$: [2+2] cycloaddition pathway. Relative energies (ZPVE included) are given in kcal mol^{-1}. All data were computed at the PCM(CH_2Cl_2)B3LYP/def2-TZVP//B3LYP/def2-SVP level

ent at the 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^{-1}, corresponding free energy of 38.7 kcal mol^{-1}) than the analogous process reported by Feng and co-workers (4.7 kcal mol^{-1}, 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 of 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, that is, only dissociation into the initial reactants was found. These results suggest that the [2+2] cycloaddition is disfavored when using homoallylic alcohols with non-activated and non-substituted alkenes. In the absence of substituents at the double bond, as 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 for this finding is given by the absence of the corresponding 4-hydroxy derivatives from **INT4** (no traces of this type of product were detected in the reaction crude product mixtures). Moreover, if the [2+2] mechanism were operating, adding 4-hydroxy or 4-OTMS THP (compounds **6** and **7**, respectively) would produce the observed 4-equatorial chloride product **4** 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 was 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



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

an endothermic process (ΔE = 14.8 kcal mol^{-1}). 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^{-1} (the total activation energy from **INT6** to **TS5** is 27.3 kcal mol^{-1}). **INT8** then evolves into **INT9** via **TS6**, a transition state associated with the protonolysis of 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^{-1}) and high exothermicity (ΔE = −16.0 kcal mol^{-1}). It can be suggested that **INT9** is then converted into **INT10** in a slightly endothermic reaction (ΔE = 3.2 kcal mol^{-1}). This reaction very likely proceeds via decoordination of the $FeCl_3$ catalyst followed by a 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

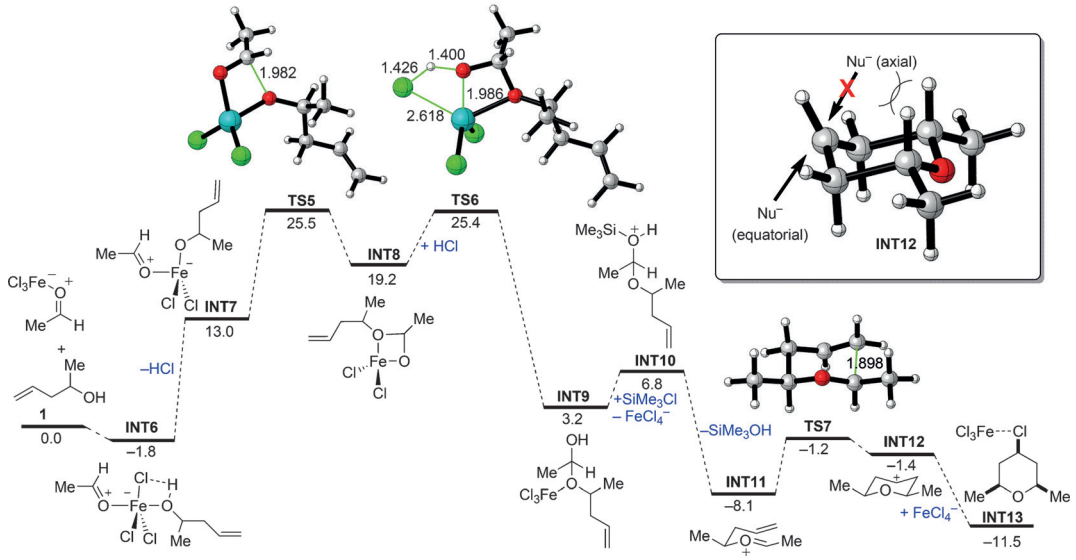


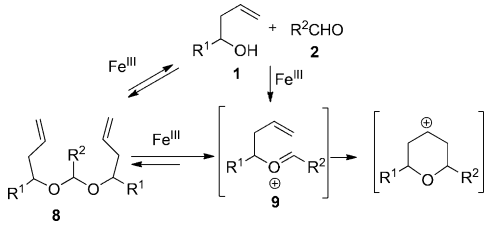
Figure 3. Computed reaction profile of the reaction between **1** and MeCHO in the presence of $FeCl_3$ and $SiMe_3Cl$: oxocarbenium ion pathway. Relative energies (ZPVE included) are given in kcal mol^{-1} and bond distances in angstroms. All data were computed at the PCM(CH_2Cl_2)B3LYP/def2-TZVP//B3LYP/def2-SVP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

($\Delta E = -14.9$ kcal mol^{-1}) 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^{-1}. 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).

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] cycloaddition pathway (see Figure 2), which is in good agreement with the experimental observations.

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

The iron ligand and the reaction temperature both also have a direct effect on the tetrahydropyran distribution when the homoallylic alcohol **1** bears at R^1 a phenyl group (Table 2). For



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

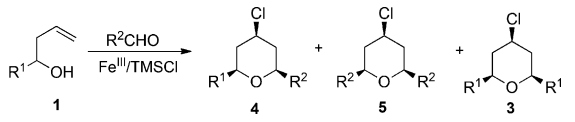
instance, use of $Fe(OTf)_3$/TMSCl as the catalytic system leads to a decrease in the amount of THP **4** and an increase in the amounts of THPs **5** and **3**, the latter being observed for the first time (Table 2, entry 3).

Similar results were obtained when using allyl phenyl carbinol (**1**, R^1 = Ph) and a reaction temperature of 0 °C. 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 product was THP **5** (Table 2, entry 6). This behavior was also observed when the temperature of the reaction was changed to 40 °C (Table 2, entries 10–12). However, when the homoallylic alcohol **1** bore an aliphatic substituent, the Prins cyclization led 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 is clear that the oxonia-Cope rearrangement is favored when using allyl phenyl carbinols, triflate as the iron salt, and when the temperature of the cyclization is modified from room temperature.

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 carried out a theoretical study, comparing the oxonia-Cope rearrangement with phenyl and *iso*-butyl as R^1 substituents

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	T [°C]	FeL_3	Selectivity [%] 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	$FeCl_3$	22	59	19	75
5	Ph	*i*Bu	0	$Fe(acac)_3$	23	62	15	87
6	Ph	*i*Bu	0	$Fe(OTf)_3$	15	85	0	75
7	*i*Bu	*c*-Hex	0	$FeCl_3$	100	0	0	80
8	*i*Bu	*c*-Hex	0	$Fe(acac)_3$	100	0	0	84
9	*i*Bu	*c*-Hex	0	$Fe(OTf)_3$	100	0	0	73
10	Ph	*i*Bu	40	$FeCl_3$	10	90	0	80
11	Ph	*i*Bu	40	$Fe(acac)_3$	25	75	0	75
12	Ph	*i*Bu	40	$Fe(OTf)_3$	28	57	14	64
13	*i*Bu	*c*-Hex	40	$FeCl_3$	100	0	0	>99
14	*i*Bu	*c*-Hex	40	$Fe(acac)_3$	100	0	0	95
15	*i*Bu	*c*-Hex	40	$Fe(OTf)_3$	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 or 0 °C at 24 h; 4 h at 40 °C. [b] Yields of products after purification by silica gel column chromatography.

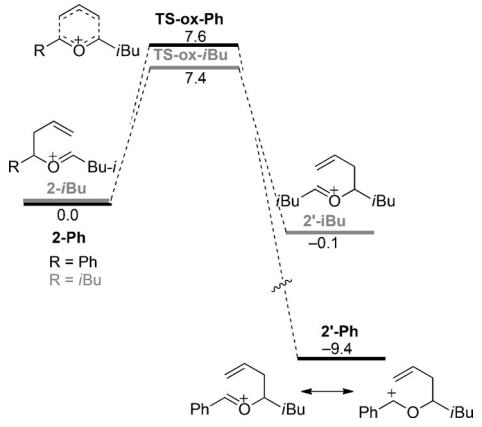
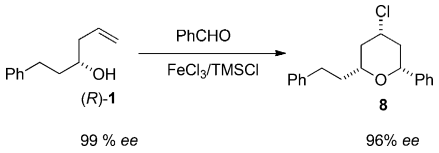


Figure 4. Comparative computed reaction profiles for the oxonia-Cope rearrangement with phenyl and alkyl as R^1 substituents. Relative energies (ZPVE included) are given in kcal mol^{-1}. All data were computed at the PCM(CH_2Cl_2)B3LYP/def2-TZVP//B3LYP/def2-SVP level.

(Figure 4). Although the computed activation barrier is quite similar in both cases ($\Delta\Delta E^{\neq}$ of only 0.2 kcal mol^{-1}), the process is greatly thermodynamically favored ($\Delta\Delta E = 9.3$ kcal mol^{-1}) for the oxocarbenium ion with a phenyl substituent (**2-Ph**, Figure 4). This can of course be ascribed to the stabilization by π-conjugation exerted by the phenyl group in **2′-Ph**, which constitutes the driving force for the rearrangement. In contrast, the stabilization by hyperconjugation exerted by the isobutyl group is comparatively much weaker, making the rearrangement much more difficult (i.e., **2′-*i*Bu** is practically isoenergetic to **2-*i*Bu**, 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.

Finally, racemization in the Prins cyclization has also been suggested as an indicator for 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 in 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 96% *ee*, which nicely indicates that no competitive 2-oxonia-Cope rearrangement or side-chain exchange occurred.



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

Conclusion

We have established a method to obtain almost exclusively crossed 2,4,6-trisubstituted tetrahydropyrans, avoiding side-chain exchange and racemization processes, by using a catalytic system of iron(III) salts and TMSX. Two mechanistic pathways can be envisaged for this iron(III)-catalyzed Prins cyclization reaction between homoallylic alcohols and non-activated alkenes, namely the classical oxocarbenium route and the alternative [2+2] cycloaddition-based pathway. Our joint experimental and computational study clearly indicates that the [2+2] pathway is disfavored for 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 hydroxy group in the homoallylic alcohol is decisive in controlling the possible oxonia-Cope rearrangement of the corresponding oxocarbenium ion. Thus, whereas alkyl substituents do not favor this side reaction 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 for 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 15 h. 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 sulfate and filtered and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc solvent systems).

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[14] This data is in agreement with the results of Chan and Loh 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 Chan and Loh using In^{III} salt instead of Fe^{III} salts. See ref. [11a].

[15] We obtained the same results using TMSCl and TBSCl as silyl additive with no difference in the **4**/**5** ratio or yields.

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

[17] For computational details, see the Supporting Information.

[18] We did not detect benzyl chloride resulting from benzyl carbocation formation.

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