MECHANISTIC VIEWS OF
INTRAMOLECULAR HYDROXYCYCLOPROPANATION OF
ω-VINYL CARBOXYLIC ESTERS

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ABSTRACT

The overwhelming presentation of plenty of synthetic steps in a verbally reduced or succinct form as appearing in any paper is here focused in an extensive and particularly graphical manner; just to extend the screen when the reader is boarding a published series of synthesis. The Intramolecular Hydroxycyclopropanation of ω-Vinyl Carboxylic Esters appeared to us to be a fascinating synthesis thematic and served us as an example to propose didactical and mechanistic views.

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ANALYSIS AND MECHANISTIC PROPOSALS

As academics we are highly concerned with the didactical importance of covering the needs of debutant students in organic synthesis. This article presents an analytical and didactical approach to synthetic works by Jin Kun Cha and col. by means of reactions’ theoretical mechanisms. We are continuing the previously published: “A Theoretical Mechanistic Approach to Diasteroselective Synthesis of cis-1,2-dialkylcyclopropanols and Subsequent Oxy-Cope Rearrangement” (1) presenting now another synthesis by Cha and coworkers concerning Grignard reagents in the presence of transition metals (2). Cha worked with organotitanium compounds to effect cyclopropane-mediated natural product synthesis. Prof. Cha group became interested in the Kulinkovich hydroxycyclopropanation (3). They published first the treatment of a carboxylic ester with an excess (3 equiv) of Grignard reagent in the presence of Ti(O-i-Pr)4 (1 equiv) affording cis-1,2-dialkylcyclopropan-1-ols (4). We already proposed a mechanistic approach (1) about such article. The second related article by Cha and col. (2) reports an intramolecular version of the Kulinkovich hydroxycyclopropanation (4) and imposes the treatment of ω-vinyl carboxylates with n-BuMgCl in the presence of Ti(O-i-Pr)4 or ClTi(O-i-Pr)3. The Kulinkovich hydroxycyclopropanation’s scheme 1 (2) is reproduced here in Scheme 1 and it can be depicted through the next mechanistic proposal which has already been graphically and verbally described (1) and it is re-explained here.

Scheme 1. Kulinkovich’s Hydroxycyclopropanation virtual loop (2)
To depict this Kulinkovich hydroxycyclopropanation scheme we start with our 2 equiv of Grignard reagent or 2 R’CH₂CH₂MgX or 2 R’CH₂CH₂’MgX. A first interaction occurs between Grignard reagent and the titanium tetraisopropoxy derivative. Titanium is linked to the four alkoxy substituents. The reaction provokes the expulsion of two alkoxy residues to leave a Ti²⁺(OiPr)₂ species. The metal di-cationic charge is used by two carbanions each from 1 equiv of the Grignard reagent, to obtain a dialkoxy-dialkyl titanium derivative 3. (Figure 1).

Titanium receives temporarily an extra electron from an alkyl methylene to afford the Ti⁻¹(IV) (iPrO)₂ species and the carbonium ion R’CH₂CH₂⁺. A reductive nucleophilic attack by the anionic titanium leads to the apparition of the Ti 3-membered ring intermediate 4 (or a tatan cyclopropanoid or titanacyclopropane (2)). (Figure 2).

The next step in this pathway consists of the condensation of intermediate 4 with a carboxylic ester RCO₂R”. The carbonyl group of this ester drives the reaction by interacting with the Titanacyclopropane in a transition state that implies a co-planarity of both species. A nucleophilic attack by the nucleophile carbonyl oxygen over titanium dispatches the two electrons of the bond Ti-CH(R’)(CH₂) over that carbon. Hence the Titanacyclopropane splits to afford a carbanion and a cationic oxygen over the same molecule. A nucleophilic attack over the carbonyl carbon (with an exacerbated electrophilic character) leads to the formation of a titanium furanoid ring (Figure 3).

An intramolecular nucleophilic attack by the ethereal oxygen of the “α-O-R” substituent group over the electrophilic titanium dispatches the two electrons of the Ti-CH₂ bond on intermediate 5 to afford the corresponding splat species bearing a carbanion and a cationic oxygen, which in turn recovers neutrality by splitting the four-membered, di-oxygenated (oxirane-type) ring. The result is the dipolar (a carbanion and carbonium ion) species that neutralizes the charged extremes into a substituted cyclopropane or intermediate 6 (Figure 4).
It is now time for two more equiv of Grignard reagent and for intermediate 6 to interact to afford species 2, closing thus our looping cycle. This meeting takes place by means of cationic interchange, or the cationic moiety of Grignard MgX′ that replaces cationic Ti′(OiPr)2(OH) through the temporary apparition of an anionic oxygen. The remaining Ti′(OiPr)2 species neutralizes the two anionic moieties liberated by the 2 equiv of Grignard reagent to form two new equiv of the species 3 to continue the cycle (Figure 5).

![Figure 5. Generation of Ti(IV) (OiPr)2(CH2CH2R′) 3, in the virtual cycle](image)

This synthetic pathway (Scheme 1) was largely applied by Cha and coworkers to produce a number of azulene sesquiterpene derivatives as published by these authors. Cyclisation (Scheme 1) goes on under stoichiometric or catalytic conditions involving the double alkylolation of the titanacyclopropane intermediate 4, itself formed by the reaction of Ti(OR′)4 or CTTi(OR′)3 and a Grignard reagent followed by elimination of the corresponding alkane (R′CH2CH3). The thesis that the putative intermediate 4 or the Titanacyclopropane intermediate could undergo a reversible exchange with an alkene has been thought. If a carboxylic ester is chained to the alkene moiety, then an intramolecular hydroxycyclopropanation is feasible. And this is the method currently under discussion. The numerous results afforded by Cha and coworkers include, structurally, two-fused cycles compounds all of them showing the cyclopropane feature, characteristic of the Kulinkovich synthesis. The second fused cycle comprises many models depending on the alkene used to be condensed to the Kulinkovich’s intermediate substrate. The following mechanisms correspond to entries 1 to 15 in table 1, page 292, (2).

**Entry 1.**

It regards the first intramolecular hydroxycyclopropanation achieved by the original paper authors. Methyl 5-hexenoate with 3 or 5 equiv of Grignard’s n-BuMgCl in the presence of 0.5 equiv of CTTi(OiPr)3 afforded the first intramolecular hydroxycyclopropanation product or cyclopropanol 8 (Scheme 2).

**Scheme 2. Intramolecular hydroxycyclopropanation: cyclopropanol 8 (2)**

To explicitly understand this reaction we must follow the mechanism exposed above as a model; however some different explanations must be given in order to achieve the reported results (4). This implies a modification of the section comporting the intermolecular interaction between the Titanacyclopropane derivative 4 and the carboxylic ester for now we must explain the apparition of the intramolecular process product. Thus, once generated intermediate 4 as shown mechanistically above what is provoked now contrasting with the intermolecular version is that before proceeding to a coplanar interaction between the Titanacyclopropane and the carboxylic ester, a splitting of 4 happens in order to generate the 1-butene residue (Figure 6).

![Figure 6. Splitting of 4 (Titanacyclopropane) into the 1-butene residue](image)
Titanium liberates one electron splitting so the bonding with its neighboring methylene which in turn receives the two bonding electrons acquiring an anionic character. Indeed, titanium becomes a cationic nucleus. Neutrality returns to the Ti nucleus by means of receiving an electron coming from the splitting of its bonding to the protoklene. The alkene appears due to the driving force derived from the re-accommodation of the electronic excess over the carbanion into a π bond. Titanium is now a neutralized nucleus; however there should be an electronic re-accommodation in different atomic orbitals generating so a dipolar situation giving titanium a nucleophilic character. This nucleophile will attack the terminal alkene of the ω-vinyl carboxylic ester. This fact collapses finally in the tricycle titanium derivative, some kind of epititanium (like epoxy) or a Titanacyclopropane appearing after addition over the double bond of the ω-vinyl ester (Figure 7).

The intramolecular nucleophilic attack by the carbonyl oxygen in the methyl ester moiety occurs to produce a dipolar transition state. This nucleophilic attack exscinds heterolytically the bond Ti–C(H)(CH₂)(CH₂)CO₂Me and establishes a new link between oxygen an titanium. Stereochemistry in these mechanisms has a speculative character. A supraplanar attack over carbonyl electrophilic center (Cδ⁺=Oδ⁻) itself contained in a parallel plan to that containing the titanium derivative occurs placing the methoxy group upwards, adopting thus an axial position in the fusion bridge of the newest fused cycles compound. An isomerization towards a more comfortable conformer occurs changing all axial into equatorial bonds. The new conformer is particularly benefited by the absence of the previous through-space Van der Waals radii interaction of the axial methoxy and the axial isopropoxy substituents, all according to framework molecular models (Figure 8). All these steps conduct to the formation of the fused rings according to the reported reaction products (2). The polar attraction manifested by oxygen and titanium establishes a bridge for a much tensed four-side cycle including a highly stressing double oxy function. This tension incites the carbanion next to the stressed di-oxy ring to attack establishing a less tensed cycle a` trois. This enterprise generates the stable enough 3/5 fused rings compound, which is analog to intermediate 6 in the Scheme 1 of the present paper.

Figure 7. Apparition of epititanium after addition of (OiPr)₂Ti⁺, over the double bond of the ω-vinyl ester

Figure 8. Formation of a 3/5 fused cycles compound
We return now to Scheme 1 to observe that intermediate 6 will interact with the Grignard reagent that for entry 1 corresponds to nBu"MgCl. This happens first by means of exscinding the Ti-O-Cycles bond to generate an alcoxy function which in turn is neutralized by the Lewis acid from Grignard r. namely "MgCl giving rise to the intermediate to element 2 in the scheme. This Grignard adduct is finally destroyed in a protic medium to afford alcohol 8 (Figure 9).

What follows next is the different interactions for cation "Ti(OiPr)2(OMe). This is first neutralized by the basic moiety of the Grignard reagent or the nBu-carbanion (Figure 9). Next the basic –OMe is separated from titanium due to a better interaction with Lewis acid MgCl from a second equiv of Grignard r. The just formed Ti cation reacts with the basic moiety left by the second Grignard equiv to generate intermediate 3 (Figure 10) in Scheme 1 thus giving continuity to the virtual reacting loop.

*Entry 2.*

Under the standard conditions (5 equiv of nBuMgCl, 0.5 equiv of CITi(OiPr)3, ether, room temperature) the authors achieved the synthesis of bicyclic 10 out of the homologue 9. The mechanism is the same as the previously presented. This demarche is graphically described as follows in Figure 11.
**Entry 3.**
According to Cha and coworkers (2) a precipitous decrease in yield was observed for the intramolecular hydroxycyclopropanation of 11 to afford bicyclo[5.1.0]octan-1-ol 12 in a 11% yield. Now we start our discussion from the apparition of the transition state (Figure 12).

![Figure 12. Generation of compound 12 (entry 3, (2))](image)

As observed in the above graphics and after framework molecular models construction, the \( sp^3 \) carbons of the fusion bridge become very deformed from the tetrahedral geometry. It means that the instability of compound 12 is increased regarding that of compound 10. This could be a reason to explain the lower yield for compound 12 with respect to the yield of 10 and 8.

**Entries 4 and 5**
The original paper’s authors (2) mentioned that further extension to methyl 8-nonenoate and methyl 4-pentenoate failed to produce the corresponding bicyclic cyclopropanols 14 and 16 (0% yield for both). See Figure 13.

![Figure 13. Entries 4 and 5 (2)](image)

**Entries 6 and 7**
According to Cha and coworkers, as a rule, the intramolecular hydroxycyclopropanations are not much influenced as a result of the presence of different substituents in the chain (entries 6-13, (2)). We start this reaction graphic description from the nucleophilic attack over the terminal vinyl of the methyl carboxylate 17. This compound is actually being substituted at positions \( \alpha \) and \( \gamma \) from carbonyl (Figure 14).
In order to better propose the corresponding theoretical mechanism, we will imagine stereochemistry for the two chiral centers under a speculative scope (Figure 15).

**Figure 14. Nucleophilic attack over vinyl 17 toward the formation of 18 (entry 6, (2))**

**Figure 15. Generation of compounds 18 and 20 (entries 6 and 7, (2))**
Entry 8 and entry 9
Contrasting to entries six and seven, the intramolecular hydroxycyclopropanation in entries 8 and 9 becomes influenced by the presence of substituents at the allylic position in the side chain. This can be translated as a dramatic diminution in yields (14% for product 22, entry 8, and 0% for the expected 24a, entry 9). This entry is graphically described as follow in Figures 16, 17 and 18.

At this point a competitive elimination of the HOTIPS group takes place to give the corresponding tricycle alkene. This fact is responsible for the low yield in the intramolecular product 22 (Figure 17).

For entry 8:

For entry 9:
The expected intramolecular product 24a did not appear giving no yield. Instead product 24b (Figure 18) appeared as a result of a known intermolecular mechanism, it was yielded in a 61%. This result clearly shows that under the
given conditions, and with respect to eventual substituent groups present at the allyl position of the alkene, both mechanisms, have a competitive character.

![Diagram](image_url)

**Figure 18. Generation of 24b (entry 9, 2)**

**Entry 10**

Mechanism for entry 10 is the same as that proposed for entries 6, 7 and 8. As a practice for the novel, it should be done apart using entry 8 as a guide. However the apparition of a mixture of epimers as resulting products encourages us to develop graphically one of such reactions (Figure 19).

![Diagram](image_url)

**Figure 19. Generation of 26a (entry 10, 2)**
This same mechanistic demarche gives rise to epimer 26b with the only fact of departing from at the β-of-carbonyl inverted configuration position in the methyl ester compound.

**Entry 11**
Entry eleven presents new structural features and consequently new challenges in proposing a theoretical reaction mechanism. Now the side chain includes a substituted cyclohexane (Figure 20).

![Figure 20. Obtention of 28b (entry 11, (2))](image)

In order to obtain the isomer 28a (Figure 21), we must follow the mechanism below. We observe here that the stereochemical definition for one or the other isomer comes out just before establishing one or the other transition state. At that stage the free rotation about the sigma bond of the methyl ester group and the way for it to face the Lewis acid-base interaction between the carbonyl oxygen and the cationic titanium provokes a beta or alpha orientation for the tricycle. It is obvious that the most favored diasteroisomer in yielding was 28a due to an easier nucleophilic attack from the carbonyl oxygen to titanium in comparison to 28b (2:1).

![Figure 21. Obtention of 28a (entry 11, (2))](image)

**Entry 12**
The prodigious synthetic work by Cha and coworkers also permitted these authors to afford the trans-ring junction diasteroisomers 30a and 30b besides the cis-ring junction diasteroisomers 28a and 28b exposed in entry 11. The trans isomers resulted less favored in yielding due to the additional associated strain, all according to the original paper authors (2). No immediate references are given regarding the experimental conditions applicable in order to obtain cis or trans diasteroisomers. As expected the mechanistic proposal regards a close similarity to the ones expressed in entry 11 (Figure 22).

![Figure 22. Toward the obtention of the trans-ring junction diasteroisomers 30a and 30b](image)

At this point, the mechanism goes toward provoking an interaction between the ester moiety and titanium (Figure 23). To achieve such relationship an appropriate approaching of the ester function to titanium is necessary. Thus there must be a sigma bond free rotation of the tripod conformed by the cyclohexane and –OTBS as shown above in Figure 22.

![Figure 23. Interaction between the ester moiety and titanium (toward 30a)](image)
Once established the Ti-O link, the formation of a 5 membered cycle comes out from a nucleophilic attack from the carbanion faced to the carbonyl carbon avid itself of electronic charge (Figure 22). The result is apparent in the three-fused-cycles non-ionic intermediate in Figure 24. The proximity of an oxygen atom from a methoxy group to the titanium nucleus in such intermediate makes possible the continuation of the reaction by means of a nucleophilic attack over Ti. This splits the furanoid ring to give a highly instable 4-membered dioxy-titanium cycle and a methylene carbanion (Figure 25).

Being the 4-membered dioxy-titanium cycle besides an electronic deficient charged species, this reacts by splitting the 4-membered cycle by the attack of the nucleophile basic methylene. An important feature of the electronic movement at this stage of the intramolecular interactions is that the nucleophilic attack taking place between the already mentioned nucleophilic carbanion ($\cdot$CH$_2$) and the dioxygenated carbon at the just formed 4-membered dioxytitanio cycle, implies as a result the apparition of the fused tricycle in an $\alpha$ orientation all through the inversion of the configuration of this chiral carbon [(iPrO)$_2$TiO(MeO$^+$)C] (Figure 26). The complementing mechanism to obtain the alcohol derivative form out from the titanium intermediate is shown in Figure 27.

![Figure 24. A three-fused-cycles non-ionic Intermediate (toward 30a)](image)

![Figure 25. Splitting of the furanoid ring, apparition of the instable 4-membered dioxy-titanium cycle (toward 30a)](image)

![Figure 26. Apparition of the fused tricycle in an $\alpha$ orientation all through configuration inversion of the chiral carbon [(iPrO)$_2$TiO(MeO$^+$)C], (toward 30a)](image)

![Figure 27. Obtaining of alcohol form derivative out from the titanium intermediate, or final product 30a](image)
In order to propose a mechanistic explanation for product $30b$ we must observe at model A (Figures 23 and 28) that the two electrons are in the inner position, ready for a nucleophilic attack over the electrophilic carbon of carbonyl in the ester moiety actually linked to titanium through the carbonyl oxygen. To achieve the attended inverted (relative to the $\alpha$ position of the tricycle in $30a$) stereochemistry for the 3-membered cycle as shown in $30b$ (2), we locate temporarily the two electrons in the outer position just as shown in Model B (Figure 28). Afterwards there must be an accommodation of the two electrons on that carbanion, currently at a $sp^2$ hybrid state, in order to be located (the 2 $e^-$) again in the inner position. So, model B must be turned for the 2 $e^-$ to regain the inner position being thus ready again for the nucleophilic attack over the carbonyl carbon. The result of turning atoms through bonds is shown below on model C (Figure 28).

![Figures 28 and 29](image)

**Figure 28. Positioning demarche of 2 electrons of one cyclic carbanion methyne to obtain product $30b$**

This conformer (Model C, Figure 28) presents already the hydrogen of this carbanion ($sp^2$) in an alpha position differing from the same cycle junction hydrogen in diastereoisomer $30a$, where it appears in the beta position.

Let us proceed now to the nucleophilic attack by the electrons from the inner position into the carbonyl carbon. This provokes indeed the displacement of the $\pi$ electrons of carbonyl to compensate the cationic charge over oxygen, deriving thus in an ether cyclic ether function (Figure 29).

**Figure 29. The nucleophilic attack by the electrons from the inner position in Model C to drive reaction to the obtention of compound $30b$**

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The remaining operations regards the replacement of the titanium moiety by the Grignard’s cation and the final alcoholic water residue to afford 30b (Figure 30). This intramolecular nucleophilic attack driving to the apparition of the β-oriented-three-membered cycle characterizing compound 30b, happens with inversion of configuration at the chiral centre supporting the °OMe and OTi residues.

**Figure 30. Successive replacement of the titanium moiety by the Grignard’s cation and of this by H⁺ to afford 30b**

**Entry 13**

Even though the failure to accomplish derivative 32 (0% yielding (2)) we propose with a didactical purpose how such reaction should happen from a strictly theoretical standpoint (Figure 31).

**Figure 31. Speculative mechanism to obtain 32 (entry 13, (2))**
The constructed model at this stage shows partially our molecule, particularly the conjugated C=C and C=O(OCH\(_3\)) systems. We do also identify the methine carbanion as well as the Ti\(^+\)(OiPr)\(_2\) cation. The next electronic movement comports the nucleophilic attack C=O\(\rightarrow\)Ti\(^+\) (Figure 31). This gives rise to an eight-membered cycle which according to the constructed model exhibits annular tension because of failing to reach the previous and normally expected co-planarity of both \(\pi\) conjugated systems (Figure 32). Isn’t this the cause for the reaction failure? However still theorizing we can suppose from there on another nucleophilic intramolecular attack from the methine carbanion to the electrophilic carbonyl carbon. As a result we’ve got a three fused cycles system 6-5-5 (Figure 31).

\[\text{Figure 32. Speculative mechanism to obtain 32: non-coplanarity of } \pi \text{ conjugated systems. Formation of 6-5-5 fused tricycle (entry 13, (2))}\]

We can describe these steps inverting the order of the nucleophilic attacks episodes (Figure 33): we first propose an CH: attack on C=O and then, once free from the contracting non-planarity of the \(\pi\) conjugated systems (now existing only the C=C system), the second nucleophilic attack of C-O\(^-\) to the Ti\(^+\)(OiPr)\(_2\) cation. Anyway the first attack may never happen because of the currently absence of the Lewis acid catalytic action of Ti\(^+\)(OiPr)\(_2\), once linked to C=O as it was our first option. The problem arising from these mechanistic proposals is the trans disposition reached by the 1,2-trans-H-OMe group at the ring junction after the methine attack on the carbonyl carbon of the ester moiety. This does not conduct to the expected stereochemistry at the ring junction of the final structure comporting the 5- and 3-membered fused rings. The good structure (2) 32 (Figure 31) presents a cis disposition for the just mentioned groups. It forces to another pre-disposition of the methine before attack on the C=O. For solving this we will only consider the case of a first nucleophilic attack on titanium by the carbonyl oxygen and then a second by the carbanion methine on the carbonyl carbon of the ester moiety. The transition state has already been described as we can see in Figure 34.

\[\text{Figure 33. Speculative mechanism to obtain 32: Inverting the order of the nucleophilic attacks episodes}\]
Figure 34. Speculative mechanism to obtain 32: Transition state, the case of a first nucleophilic attack on titanium by the carbonyl oxygen and then a second by the carbanion methine on the carbonyl carbon of the ester moiety

Nevertheless, the intramolecular carbanion attack on C=O as just described, proved to give rise to the 1,2-trans-H-OMe isomer. This TS shows the methine hydrogen in an outer position regarding the 8-membered ring. Thus it becomes necessary to employ the opposite position for that methine hydrogen before the carbanion attack, or the inner hydrogen position on the carbanion. For that purpose the 8-sided cycle must be re-accommodated throughout restricted sigma bonding rotation. The result can be drawn and constructed as follows (Figure 35):

Figure 35. Speculative mechanism to obtain 32: Re-accommodation of the 8-sided cycle throughout restricted sigma bonding rotation, recovery of co-planarity in the conjugated π-systems (cf. Figure 34)

This TS shows after rotation the inner hydrogen which means the electron pair placed in an outer position. It signifies that there is no spatial disposition for the nucleophilic intramolecular action of the Lewis base (CH: - ). This TS needs anyway the electron pair in an inner or well disposed situation. In order to place the electron pair inside the 8-sided cycle, the sp² carbon (CH: - ) hybridize to sp³ and then to sp³ inside the 8-sided cycle to place the electron pair again resulting all in a configuration inversion of the chiral centre and thus the electron pair placed inside the ring ready for a nucleophilic attack (Figure 36).

Figure 36. Speculative mechanism to obtain 32: Hybridization of the sp³ carbon (CH: - ) to sp³ and then to sp³ inside the 8-sided cycle to place the electron pair again resulting all in a configuration inversion of the chiral centre to make possible a nucleophilic attack
The next steps would involve the formation of the highly tensioned dioxotitano 4 membered ring and the formation of the three membered fused ring by the carbanion attack over the electrophilic carbon supporting the MeO⁺ function. All this is followed by the known steps leading to the final alcohol form of the hypothetic product 32 (Figure 37).

Entries 14 and 15
According to Cha and col. esters of ω-alken-1-ols, particularly 3-buten-1-ols, seem to be amenable to intramolecular hydroxycyclopropanations. Thus, Cha and col. also effected the reaction of benzoate 33 to give a 7:1 mixture of the cyclopropanols 34a and 34b. A further extension to the homologue 35, lacked of good yield. These reaction entries can be mechanistically envisaged as follow (Figure 38).

For entry 14:
Figure 38 (Cont.). Views of the synthesis of 34a and 34b (entry 14 (2))

For entry 15: The mechanistic approach for the 33-homologue 35 is the same as for 33 (see entry 14 mechanistic approach for details).

REFERENCES