EurJOC
European Journal of Organic Chemistry

Full Papers
doi.org/10.1002/ejoc.202100430

Chemistry Europe
European Chemical Societies Publishing

Divergent Rearrangements of Vinylcyclopropane into Skipped Diene and Cyclopentene: Mechanism, Scope, and Limitations

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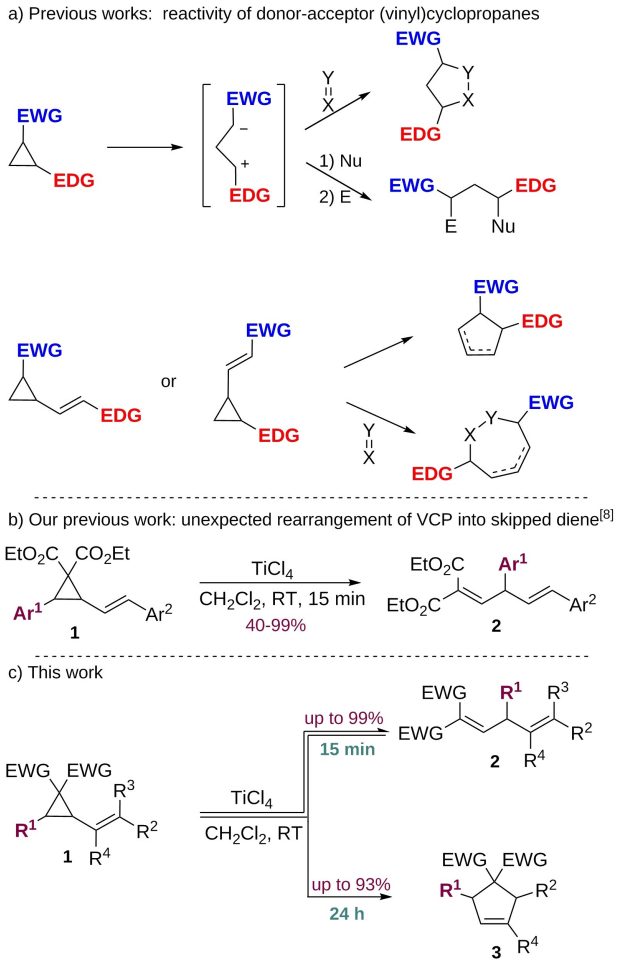
Vinylcyclopropanes are versatile intermediates in organic synthesis which undergo various rearrangements. We report a new rearrangement of vinylcyclopropane into skipped diene. A detailed mechanistic study revealed that this transformation involves regioselective ring-opening of the cyclopropane ring followed by 1,2-migration of one of the cyclopropane substituents. Interestingly, our investigations showed that skipped diene is the kinetic product of the process but formation of a more stable cyclopentene is also accessible. The fundamental understanding of the processes involved enabled the development of divergent methodologies allowing to obtain cyclopentene or skipped diene from vinylcyclopropane in a selective and controlled manner.

Introduction

The special reactivity of donor-acceptor cyclopropanes has been extensively studied over the last decades, showing their high versatility as building blocks in organic synthesis.[1] Indeed, the highly strained character of the ring and the polarization of the intracyclic C–C bond between the donor and the acceptor substituents favor the heterolytic ring-opening of the cycle to generate a 1,3-zwitterion intermediate. This latter can then be engaged into a variety of synthetically useful transformations such as (3+2),[1a,g,2] (3+3)[1a,d,g,3] or (4+3)[1a,4] cycloadditions, or reactions with nucleophiles and electrophiles[5] (Scheme 1a). In the case of vinylic substitution, i.e. vinylcyclopropane (VCP) derivatives, the cyclopropane can also rearrange into cyclopentene (CP) or be involved in (5+2) cycloadditions.[6] The synthetic interest of these specific reactivities of donor-acceptor cyclopropanes has been illustrated by their exploitation in key steps of total syntheses of many important targets, including natural products.[7]

Recently, serendipity led us to discover a new rearrangement of donor-acceptor vinylcyclopropane into skipped diene **2** (Scheme 1b).[8] In the course of its study, we observed that varying reaction conditions led in some cases to the formation of a cyclopentene **3** as the main product, instead of the skipped diene **2**. We now have carried out a comprehensive mechanistic study of the processes involved in these rearrangements which enables us to develop reaction conditions allowing to rearrange 1,1-dicarbonylester vinylcyclopropane **1** selectively into either skipped diene **2** or cyclopentene **3** (Scheme 1c).



Scheme 1. Reactivity of donor-acceptor (vinyl)cyclopropane and our divergent strategies toward skipped dienes and cyclopentenes.

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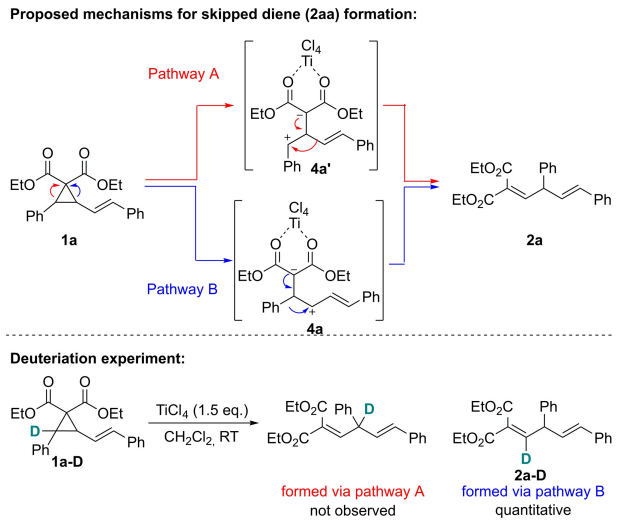
Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202100430

Results and Discussion

Mechanism

In order to get a fundamental understanding of the mechanism of observed rearrangements leading to **2** (see Scheme 1b–c),[8] we set up a combined experimental and computational study. We hypothesized that the rearrangement into skipped diene **2** could involve the heterolytic cleavage of the three-membered ring, to form a 1,3-zwitterion intermediate, followed by the 1,2-migration of the group in β position of the so-formed carbocation. This leaves us however with two possibilities: the ring-opening can occur either on the benzylic side with the 1,2-migration of the styryl group or instead on the styryl side with the phenyl group migrating (pathway A and B in Scheme 2, respectively). In order to support our mechanistic postulate and determine which group migrates, we carried out the rearrangement on a deuterium labelled VCP **1a-D**. Indeed, if this is pathway A which is operating, the deuterium atom will end up in the central benzilic position whereas in the case of pathway B it will be positioned on the double bond in the skipped diene. In fact, the rearrangement of **1a-D** led to the exclusive formation of **2a-D** providing support to our proposed mechanism and indicating that the ring opens on the styryl side with the phenyl group migrating (pathway B in Scheme 2).



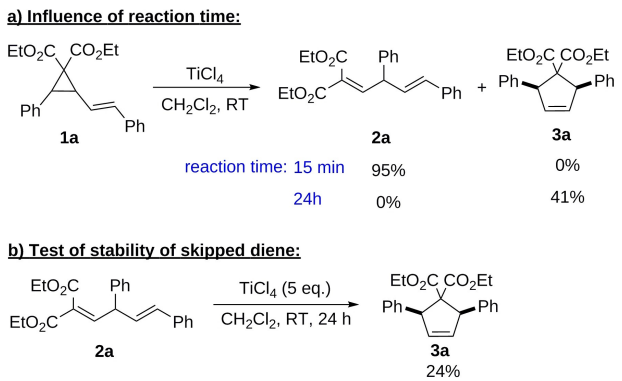
Scheme 2. Postulated mechanisms for skipped diene formation and deuteriation experiment.

In our search for optimal reaction conditions to perform the rearrangement of VCP **1** into skipped diene **2**, we found that extension of the reaction time leads to the formation of a cyclopentene **3** as the main product (Scheme 3a). This observation suggests that formation of skipped diene **2a** is reversible and that the cyclopentene **3a** is the thermodynamic product. In order to test this hypothesis, we isolated skipped diene **2a** and then subjected it to the reaction conditions. We found that, upon treatment with 5 eq. $TiCl_4$ for 24 h, skipped diene **2a** leads to cyclopentene **3a** (Scheme 3b). This control experiment demonstrates that cyclopentene **3a** can be formed from skipped diene **2a** and hence supports the fact that this latter is the kinetic product whereas the cyclopentene is the thermodynamic one. The monitoring of skipped diene and cyclopentene yields over time provided results which are also in good agreement with this proposition (see Supporting Information).

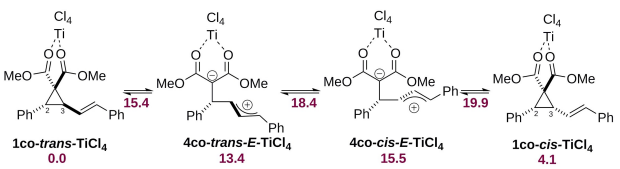
In order to give further support to our proposed mechanism for the transformation of vinylcyclopropane **1** into skipped diene **2** and understand how this latter rearranges into cyclopentene, we have explored the different possible pathways by computational means using the model vinylcyclopropane **1co** (Scheme 4). Calculations were carried out at the M06-2X/6-311 + G**//M06-2X/6-31 + G* level, including a continuum description of dichloromethane as the solvent (see the Supporting Information for computational details). Obtained results are in good agreement with our experimental results and shed light on the mechanism of observed rearrangements.

First, our calculations indicate that, in the presence of $TiCl_4$, a rapid isomerization ($\Delta G^{\ddagger} = 18.4$ kcal mol^{-1}) from *cis* to *trans* VCP must take place by epimerization of the allylic strereocenter, via a ring-opening/rotation/ring-closing sequence (Scheme 4). This epimerization is predicted to be much faster than any other transformation, as also supported by experimental observations showing full conversion of **1a-*cis*** into **1a-*trans*** in less than 1 min under the rearrangement conditions (see Supporting Information). Accordingly, only the reaction of the most stable *trans* isomer of VCP (**1co-*trans*-*E*-$TiCl_4$**) will be discussed further.

We modelled both possibilities for the ring-opening of the cyclopropane, pathways A and B in Scheme 2. Obtained results indicate that heterolytic cleavage of the C1–C3 bond between the diester substituted and the allylic carbon atoms is more



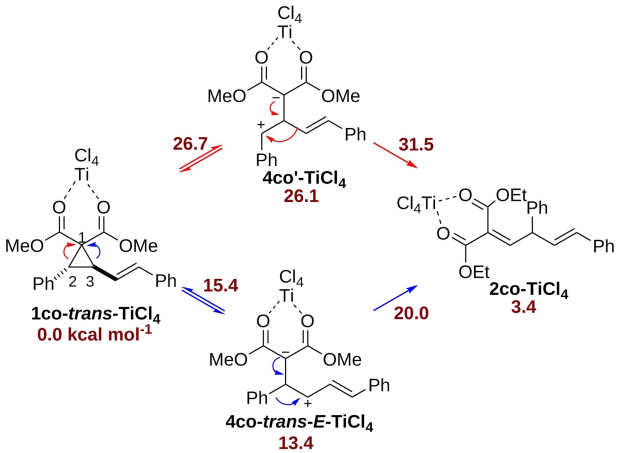
Scheme 3. Influence of reaction conditions on skipped diene/cyclopentene selectivity and rearrangement of skipped diene **2a**.



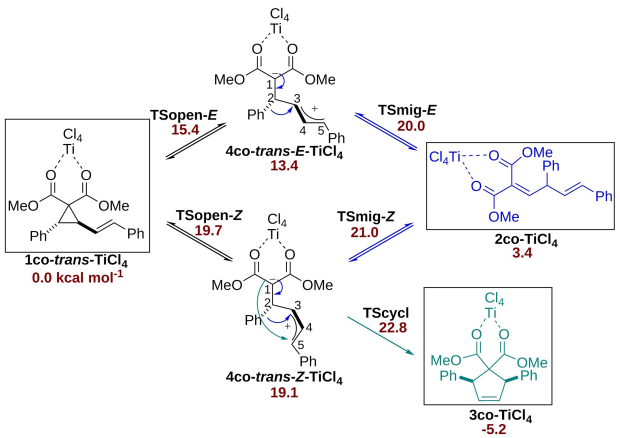
Scheme 4. *Cis-trans* isomerization mechanisms (free energy in kcal/mol relative to **1co-*trans*-$TiCl_4$**). See Supporting information for full details.

favoured than ring-opening on the benzylic side (C1–C2 bond), by 12.7 kcal mol^{-1} (Scheme 5). Formation of skipped diene from zwitterion **4co-*trans*-*E*-TiCl$_4$** is also predicted to be more favoured than via intermediate **4co'-TiCl$_4$**, in good agreement with our deuterium-labelling experiment (see Scheme 2).

Intermediate **4co-*trans*-*E*-TiCl$_4$** can in fact be formed in two isomeric forms, *E* and *Z* (Scheme 6). Both isomers are predicted to be accessible through a low free energy barrier ($\Delta G^{\neq}$ = 15.4 and 19.7 kcal mol^{-1}, respectively) with the *E* isomer being more stable than the *Z* one (ΔG = 13.4 and 19.1 kcal mol^{-1}, respectively). Our calculations show that both isomers, **4co-*trans*-*Z*-TiCl$_4$** and **4co-*trans*-*E*-TiCl$_4$**, can undergo 1,2-migration of the phenyl group to lead to skipped diene **2co-TiCl$_4$** through a low free energy barrier ($\Delta G^{\neq}$ = 20.0 and 21.0 kcal mol^{-1} for *Z* and *E* isomer, respectively). However, since the geometrical impossibility for the C1 atom to get close to the electrophilic C5 atom in **4co-*trans*-*E*-TiCl$_4$**, only the *Z* isomer (**4co-*trans*-*Z*-TiCl$_4$**) can ring-close to lead to cyclopentene **3co-TiCl$_4$** ($\Delta G^{\neq}$ = 22.8 kcal mol^{-1}). The ring-opening of **1co-*trans*-TiCl$_4$** being predicted to be reversible, the kinetic skipped diene/cyclopentene selectivity should be determined at the **TSmig** and **TScycl** level. The computed lower relative free energy of **TSmig-*E*** as compared to **TScycl** is in good agreement with the observed highly selective formation of skipped diene in the first minutes of the reaction (*vide supra*).



Scheme 5. Regioselectivity for ring-opening (free energies in kcal mol^{-1} relative to **1co-*trans*-TiCl$_4$**).



Scheme 6. Computed reaction pathways (free energy in kcal/mol relative to **1co-*trans*-TiCl$_4$**).

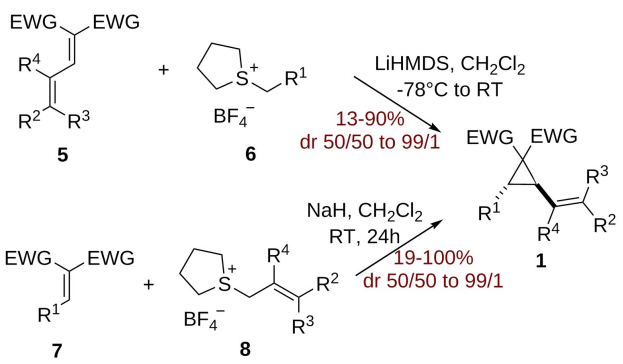
The nearly thermoneutral character of the skipped diene **2co-TiCl$_4$** formation presages its reversibility. This reversibility together with the computed higher stability of cyclopentene **3co-TiCl$_4$** as compared to skipped diene **2co-TiCl$_4$** provide strong support to our hypothesis that skipped diene is the kinetic product whereas formation of cyclopentene is the result of a thermodynamic selectivity.

Overall, our mechanistic study indicate that observed rearrangements proceed via a reversible ring-opening of the cyclopropane ring to form a 1,3-zwitterion. This latter can then undergo either 1,2-migration to lead to skipped diene or cyclization toward cyclopentene. The free energy barrier to 1,2-migration is however lower than the one to cyclization, accounting for the fact that skipped diene (**2**) is the first product formed during the reaction (kinetic selectivity). Yet, skipped diene formation is reversible what leads eventually to the accumulation of the more stable cyclopentene (**3**) (thermodynamic selectivity).

The fundamental understanding of the different pathways provided by this study allows envisioning the selective divergent synthesis of skipped diene and cyclopentene from vinylcyclopropane. We thus decided to capitalize on this and on our experience in vinylcyclopropane synthesis to develop short strategies toward skipped diene and cyclopentene from sulfonium ylides and activated olefins or 1,3-dienes.

Synthesis of VCPs

Vinylcyclopropanes **1** were synthesized in one step according to two strategies previously developed in our group.[9] Both strategies use sulfonium ylides but in the first case that are benzylic sulfonium ylides which are reacted with 1,3-dienes whereas the second methodology involves allylic sulfonium ylides and activated olefins (Scheme 7). These methodologies enabled the synthesis of differently substituted vinylcyclopro-



Scheme 7. Synthesis of VCPs (**1**).

panes in good to excellent yields (see Supporting Information for details).

Synthesis of skipped dienes

Our mechanistic studies showed that, in the presence of $TiCl_4$, skipped diene **2** forms very fast from VCP **1** whereas cyclopentene **3** formation is observed only in a second phase of the reaction. Accordingly, our optimization of reaction conditions using **1a** (R^1,R^2 = Ph; R^3,R^4 = H) showed that a reaction time of 15 min in the presence of 1 eq. $TiCl_4$ in dichloromethane is optimal to obtain skipped diene **2a** in excellent yield (entry 1, Table 1). Other Lewis acids were also tested and shown to mediate the rearrangement but $TiCl_4$ was found to be the most efficient one as well as the easiest to handle (See Supporting Information).

With optimized reaction conditions in hand, we next explored the scope of this transformation (see Table 1). First, we evaluated a range of VCP **1** with variously substituted double bonds (R^2, R^3 and R^4).[10] This transformation exhibits good tolerance to diverse aromatic substitutions (see entries 1–6 in Table 1), alkyl groups (entry 7) or polysubstitution (entries 10–12). We observed one limitation however with highly electron-rich aromatic groups. Indeed, in the case of R^2 = *p*-$MeOC_6H_4$ (entry 6), formation of skipped diene could not be observed, the only isolated product being cyclopentene (*vide infra*). Our computational results suggest that this limitation can be accounted for by the increased stabilization of the zwitterion (**4**) by conjugation and hence the facilitation of the cyclization (see Supporting Information).

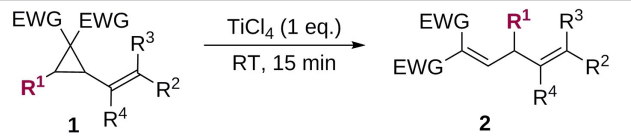
Next, we turned our attention to the nature of the migrating group (R^1). The reaction works nicely with aryl bearing electron-donating (entries 13–16 in Table 1) and slightly electron-withdrawing (entry 17) substituents as well as with heteroaromatic and cyclopropyl[11] groups (entries 19–20). In the case of electron-poor aryl (entry 18) and alkyl (entries 22–23) groups however no skipped diene could be observed. Instead exclusive formation of cyclopentene (**3**) was obtained (*vide infra*). This observation is in line with the generally observed low migratory aptitude of these groups in pinacol[12] and Wagner-Meerwein[13] rearrangements. Indeed, their low migratory aptitude leads to a slowing down of the migration whereas the nature of R^1 has no significant impact on the cyclization, this latter thus becoming the faster pathway (see Supporting Information for computational results supporting this analysis).

With respect to the nature of the electron-withdrawing groups (EWGs), our attempt to change the ester groups by cyano groups led to exclusive formation of corresponding cyclopentene (entry 24; Table 1).

In order to observe the migration of electron-poor aryl and alkyl groups despite their low migratory aptitude, we thought of disfavouring the competing cyclization to cyclopentene (**3**). We reasoned that this could be achieved by increasing the steric bulk at the C5 position and/or by having no aryl substituents in this position. Indeed, the cyclization toward cyclopentene is made possible according to Baldwin's rules[14] only because of the delocalization of the positive charge in **5** into the aryl substituent (R^2) which leads to a partial 5-*exo*-trig character of the cyclization (Scheme 8).

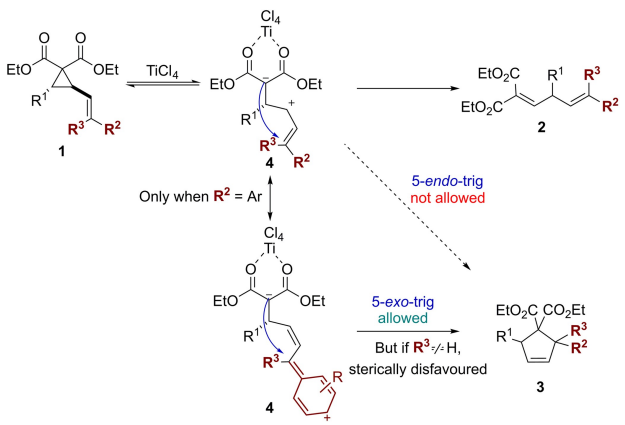
Satisfyingly, both of these strategies proved to be efficient. Indeed, rearrangement of VCPs substituted on the double bond by an isopropyl group (R^2 = *i*-Pr) showed that this substitution allows preventing cyclopentene **3** formation. However, instead of the formation of the desired skipped diene (**2**), we observed

Table 1. Synthesis of skipped dienes from VCPs.



Entry	EWG	R^1	R^2	R^3	R^4	Yield [%][a]
1	CO_2Et	Ph	Ph	H	H	95
2[b]	CO_2Et	Ph	Ph	H	H	95
3	CO_2Et	Ph	*p*-$CO_2MeC_6H_4$	H	H	quant.
4	CO_2Et	Ph	*p*-FC_6H_4	H	H	71
5	CO_2Et	Ph	*p*-MeC_6H_4	H	H	40
6	CO_2Et	Ph	*p*-$MeOC_6H_4$	H	H	0[c]
7	CO_2Et	Ph	*i*-Pr	H	H	15(90)
8[d]	CO_2Et	Ph	H	H	H	(41)
9	CO_2Et	Ph	Ph	H	Me	54
10	CO_2Et	Ph	Ph	Ph	H	81
11	CO_2Et	Ph	Me	Me	H	25
12	CO_2Et	CH=CHPh	Me	Me	H	54
13	CO_2Et	*p*-MeC_6H_4	Ph	H	H	95
14[d]	CO_2Et	*p*-$MeOC_6H_4$	Ph	H	H	quant.
15	CO_2Et	*m*-$MeOC_6H_4$	Ph	H	H	28(37)
16	CO_2Et	*o*-MeC_6H_4	Ph	H	H	25(39)
17	CO_2Et	*p*-FC_6H_4	Ph	H	H	71
18	CO_2Et	*p*-$CO_2MeC_6H_4$	Ph	H	H	0[c]
19	CO_2Et	2-furyl	Ph	H	H	quant.
20	CO_2Et	cyclopropyl	Ph	H	H	50
21	CO_2Et	CH=CHPh	Ph	H	H	80
22	CO_2Et	*i*-Pr	Ph	H	H	0[c]
23	CO_2Et	*t*-Bu	Ph	H	H	0[c]
24	CN	Ph	Ph	H	H	0[c]

[a] Yield in isolated, analytically pure, material. In brackets, yield determined on the crude mixture by ^1H NMR using an internal standard. [b] Reaction performed on isolated *trans* VCP. [c] Exclusive formation of cyclopentene was observed. See Table 4. [d] 0.4 eq $TiCl_4$.



Scheme 8. Influence of substitution on the 1,2-migration/cyclization selectivity.

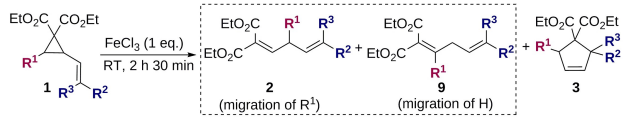
quenching of the zwitterionic intermediate **4** by a chloride ion providing from the catalyst, $TiCl_4$ (see Supporting Information). Accordingly, in order to reduce this quenching, we tried to perform the rearrangement with $FeCl_3$, the other Lewis acid which was identified by our screening (*vide supra*). Under these reaction conditions, skipped dienes resulting from the migration of *t*-Bu and electron-poor aryl groups could be obtained, with no trace of corresponding cyclopentene (see entries 1–2 in Table 2). Interestingly, the presence of an electron-poor aryl substituent in R^2 position is also sufficient to hamper the cyclization by decreasing its partial 5-*exo*-trig character and observe the migration of *t*-Bu and H (entries 3 and 7).

The increase of the steric bulk at the C5 position by double phenyl substitution allows also observing skipped dienes resulting from the migration of *p*-$CO_2MeC_6H_4$ with no trace of corresponding cyclopentene (see entry 8 in Table 2).

However, in the case of methyl, isopropyl and isobutyl migrating groups (entries 4–7; Table 2), no migration of the alkyl group could be observed, even if cyclopentene (**3**) was still not formed. Instead, that is a skipped diene **9** resulting from the migration of the hydrogen atom which was isolated, indicating that in this rearrangement H is a better migrating group than Me, *i*-Bu and *i*-Pr.

Last, we searched for a one-pot procedure allowing to perform the synthesis of the VCP by cyclopropanation and rearrangement in one synthetic step. Using 1,3-diene **5a** (R^2 = Ph) and sulfonium salt **6a** (R^1 = Ph) as model substrates, various one-pot reaction conditions were explored. In the event, we found that deprotonation of the ylide by NaH to provoke the cyclopropanation followed by addition of $TiCl_4$, at room temperature, enables isolating skipped diene **2a** in 90% yield (entry 1, Table 3). This one-pot methodology proved to be applicable to various substrates (entries 1–5).

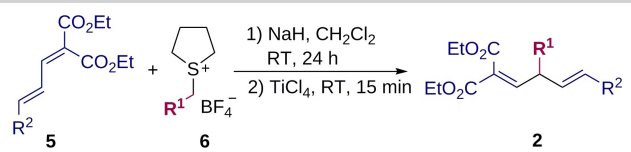
Table 2. Disfavouring cyclization to allow migration of poor migrating groups.



Entry	R^1	R^2	R^3	Yield [%][a] 2	9	3
1	*t*-Bu	*i*-Pr	H	57	0	0
2	*p*-$CO_2MeC_6H_4$	*i*-Pr	H	12	5	0
3	*t*-Bu	*p*-$CO_2MeC_6H_4$	H	33	0	7
4	*i*-Pr	*i*-Pr	H	0	26	0
5	Me	*i*-Pr	H	0	39	0
6	*i*-Bu	*i*-Pr	H	0	49	0
7	*i*-Pr	*p*-$CO_2MeC_6H_4$	H	0	23	0
8	*p*-$CO_2MeC_6H_4$	Me	Me	30	6	0

[a] Yield determined on the crude mixture by ^{1}H NMR using an internal standard.

Table 3. One-pot synthesis of skipped dienes from benzyic sulfonium ylides and 1,3-dienes.



Entry	R^1	R^2	Yield [%][a]
1	Ph	Ph	90
2	*p*-$MeOC_6H_4$	Ph	95
3	*p*-MeC_6H_4	Ph	80
4	*p*-FC_6H_4	Ph	(43)
5[b]	Ph	*p*-$CO_2MeC_6H_4$	45

[a] Yield in isolated, analytically pure, material. In brackets, yield determined on the crude mixture by ^{1}H NMR using an internal standard. [b] 45 min of reaction.

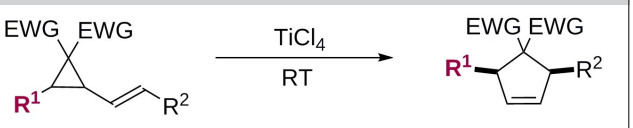
Synthesis of cyclopentenes

In accordance with our mechanistic understanding, our optimized reaction conditions to obtain cyclopentene **3** involve 24 h reaction at room temperature in the presence of $TiCl_4$ (Table 4). Investigation of the reaction scope showed that the rearrangement into cyclopentene is not very sensitive to the nature of the R^1 group (see entries 1–6). Interestingly, a total diastereoselectivity in favor of the *cis* isomer is observed in all cases, except when an electron-rich (hetero)aromatic group is present on the cyclopentene (see entries 7–9). Indeed, in these cases, the *cis* isomer is formed but it was found to isomerize to the more stable *trans* isomer under reaction conditions (see Supporting Information).

The substitution of the double bond showed, on the contrary, some limitations. Indeed, as discussed above, substitution by an alkyl group prevents the cyclisation (entry 10, Table 2).

In this case, the electron-withdrawing groups (EWG) can also be varied. Indeed, the biscyano cyclopropane derivatives (EWG = CN) led to corresponding cyclopentene in excellent yield (see entry 11; Table 4).

Table 4. Synthesis of cyclopentenes from VCPs



Entry	EWG	R^1	R^2	Yield [%][a]	*cis*/*trans*[b]
1	CO_2Et	Ph	Ph	41	>98/2
2	CO_2Et	*p*-$CO_2MeC_6H_4$	Ph	26	>98/2
3	CO_2Et	*p*-FC_6H_4	Ph	27	>98/2
4	CO_2Et	*i*-Bu	Ph	70	>98/2
5	CO_2Et	*t*-Bu	Ph	93	>98/2
6	CO_2Et	*i*-Pr	Ph	82	>98/2
7	CO_2Et	Ph	*p*-MeC_6H_4	79	88/12
8	CO_2Et	Ph	2-furyl	86	80/20
9	CO_2Et	Ph	*p*-$MeOC_6H_4$	(39)	>2/98
10	CO_2Et	Ph	*i*-Pr	0[c]	–
11	CN	Ph	Ph	90	50/50

[a] Yield in isolated, analytically pure, material. [b] Determined by ^{1}H NMR on the crude reaction mixture. [c] Exclusive formation of skipped diene **2** is observed (see Table 1).

All our attempts to develop reaction conditions allowing to prepare cyclopentenes **3** in one synthetic step from activated olefins **7** and allylic sulfonium salts **8** led only to poor yields (< 10%).

Conclusion

We have discovered a new rearrangement of vinylcyclopropane which opens a way to skipped diene. This rearrangement is very selective and proceeds rapidly (15 min) at room temperature under $TiCl_4$ or $FeCl_3$ catalysis. Interestingly, we showed that extending the reaction time enables obtaining instead cyclopentene as the main product. A combined experimental and computational study of the mechanism of these rearrangements showed that the first step consists in the ring-opening of the cyclopropane yielding a zwitterion intermediate. A 1,2-migration of one of the cyclopropyl substituent can then occurs to lead to a skipped diene. This 1,2-migration is however reversible and cyclization of zwitterionic intermediate to a more stable cyclopentene is eventually observed if the reaction is left a sufficiently long time.

The fundamental understanding of mechanisms involved enabled us to identify factors controlling skipped diene/cyclopentene selectivity and develop divergent strategies toward skipped dienes substituted on the central center and polysubstituted cyclopentenes from vinylcyclopropanes just by changing the reaction conditions.

Experimental Section

Full details on synthetic methods and analytical data, along with full computational details and data can be found in the Supporting Information.

Acknowledgements

This work was supported by the Fonds de la Recherche Scientifique-FNRS (F.R.S-FNRS), the Fonds pour la formation à la Recherche dans l'industrie et dans l'Agriculture (PhD fellowship to MR) and the Fonds Spéciaux de Recherche (PhD fellowship to AD). Computational resources have been provided by the supercomputing facilities of the Université catholique de Louvain (CISM/UCL) and the Consortium des Équipements de Calcul Intensif en Fédération Wallonie Bruxelles (CÉCI) funded by the F.R.S.-FNRS under convention 2.5020.11 and by the Walloon Region. We thank S. Ouk, through the Fondation Louvain, for very kind financial support. We thank Gabriella Barozzino-Consiglio, Guillaume Dassy and Tran Trieu-Van for their technical assistance. RR is a Maître de Recherche of the F.R.S.-FNRS.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cyclopentenes · Density functional calculations · Rearrangement · Skipped dienes · Vinylcyclopropanes

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Manuscript received: April 9, 2021
Revised manuscript received: April 22, 2021