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Jeffrey Bruffaerts, Alexandre Vasseur, Sukhdev Singh, Ahmad Masarwa, Dorian Didier, et al.. Zirconocene-Mediated Selective C–C Bond Cleavage of Strained Carbocycles: Scope and Mechanism. Journal of Organic Chemistry, 2018, 83 (7), pp.3497-3515. 10.1021/acs.joc.7b03115 . hal-03770459

HAL Id: hal-03770459

<https://hal.science/hal-03770459v1>

Submitted on 6 Sep 2022

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Zirconocene-Mediated Selective and Versatile C-C Bond Cleavage of Strained Carbocycles: Scope and Mechanism

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KEYWORDS. C-C bond cleavage – Allylic C-H bond activation – remote functionalization – organozirconium – quaternary carbon stereocenters

ABSTRACT: Several approaches using organozirconocene species for the remote cleavage of strained three-membered ring carbocycles such as ω -ene polysubstituted cyclopropanes, alkylidenecyclopropanes, ω -ene spiro[2.2]pentanes and ω -ene cyclopropyl methyl ethers, into stereodefined organometallic intermediates were successfully developed to access highly stereoenriched scaffolds in good yields. Two acyclic stereocenters including a quaternary carbon stereogenic carbon atom were easily obtained with very high diastereoselectivities. DFT calculations and isotopic labeling experiments were performed to delineate the origin of the observed stereoselectivities.

Initiated by the pioneering work of Breslow¹ and subsequent fundamental investigations by Schwarz,² the concept of *remote functionalization* – consisting in an initial interaction of a functional group with a reactant leading to a selective reaction at a distal position – has increasingly been regarded as a cornerstone in the general approach to efficiently solve challenging chemical problems in organic synthesis.³ This indirect activation of a site distant from the initial functional group allows the relay of chemical information across a molecular backbone strongly modifies our perception of retrosynthetic analysis. Not surprisingly, this concept has already sparked the development of numerous innovative transformations and nowadays represents a vibrant field of activity.⁴ Among those, transition-metal based methodologies and more particularly the metal-assisted alkene isomerization across a hydrocarbon chain have played a preponderant role in popularizing this conceptual approach.^{5,6} This property can be harnessed for the development of powerful cascade, tandem or sequential reactions involving a site distant from the initial double bond.⁷ An additional inherent advantage is that the chemical outcome is usually independent from the position and geometry of the initial double bond. Therefore, any geometrical or positional mixture of olefins should converge towards the same product, as the unsaturation is used as a versatile chemical handle to trigger a chain of events leading to a predetermined termination site. As alkenes are ubiquitous motifs in organic chemistry, remote functional-

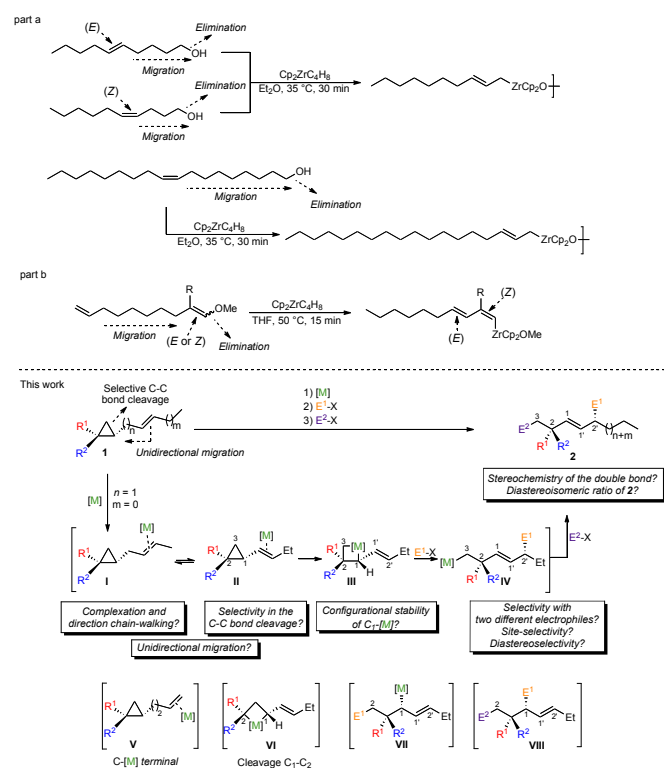
ization via transition-metal assisted olefin isomerization represents a highly promising synthetic tool.⁸

In this context, we have previously reported the zirconocene-mediated transformation of ω -unsaturated fatty alcohol derivatives into allylzirconocene species (Scheme 1, part a).⁹ This migration-elimination reaction, promoted by the Negishi reagent ($\text{Cp}_2\text{ZrC}_4\text{H}_8$),¹⁰ occurred through successive and reversible allylic C-H bond activations. Such isomerization that potentially occurs in all directions (process also called *Zr-walk* or *Zr-promenade*),¹¹ is terminated by a β -alkoxide elimination step acting as the driving force for the reaction. It should be stressed that neither the double-bond geometry (*E* or *Z*) nor its relative position towards the alcohol affects the chemical outcome. This tandem isomerization-elimination reaction was also successfully applied to transform ω -ene enol ethers into stereodefined polysubstituted conjugated (*E,Z*)-dienyl zirconocene derivatives (Scheme 1, part b).¹² Following this initial work, we anticipated that the release of a ring strain, provided by the zirconocene-mediated ring opening of a three-membered carbocycle¹³ such as in **1**,¹⁴ might also provide a sufficient driving force for an unidirectional zirconocene alkene-migration (Scheme 1, This work). However, the formation of the acyclic product **2** directly from **1** relies on the perfect control of a cascade of events (Scheme 1). More specifically, treatment of **1** with a single organometallic species could lead to a metal-alkene complex **I** (with $n = 1$ and $m = 0$ for the sake of simplicity) that would undergo the following sequence:

- 1) an unidirectional chain walking of the double bond producing vinylcyclopropane **II**.
- 2) a selective ring-opening leading to **III**.
- 3) a selective reaction with two different electrophiles leading to **2**.

However, many issues and pitfalls need to be circumvented to achieve the clean transformation of **1** into **2**. At first, to avoid the migration towards the terminal position of the alkenyl chain that would provide the thermodynamically stable organometallic compound **V**. If one assumes that **II** would be formed, two possibilities arise for the carbocycle metal insertion. A C₁-C₃ bond cleavage would provide **III** whereas the cleavage of the C₁-C₂ bond would give **VI**.

Scheme 1. Remote C-O bond activation in alkenyl ethers (path a) or alkenyl enol ethers (path b), and proposed sequence of metal-mediated isomerization – selective ring-opening – electrophilic functionalization (This work).



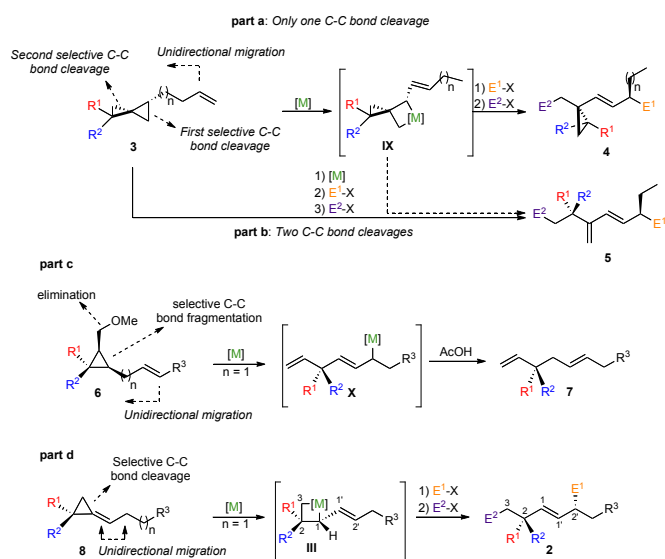
If one still assumes that the C-C bond cleavage would be selective (*i.e.* unique formation of **III**), then the issue of configurational stability of the sp^3 C₁-[M] of the metalacyclobutane **III** becomes of crucial importance for the diastereoselectivity of the reaction. One additional issue is the site selectivity for the reaction with different electrophiles. Would **III** first react through the C₁-[M] or C₃-[M] bond (formation of **IV** vs. **VII**)? Supposing that the site selectivity would be controlled (*i.e.* reaction of **III** with the first electrophile via the C₁-[M] bond), then the mode of reactivity would also need to be controlled. Would it provide **VIII** or

IV? What would the diastereoselectivity of the reaction after addition of the first electrophile be? What would the stereochemistry of the resulting double bond be? Could the remaining organometallic species **IV** be further functionalized with a second electrophile? All these potential synthetic pathways and pitfalls stress the overall difficulty of such strategy.

As diastereoisomerically pure and enantiomerically enriched ω -ene polysubstituted cyclopropanes are easily accessible starting materials,¹⁵ if all the elementary steps described in Scheme 1 (This work) were controlled, this strategy would surely offer a powerful entry for the preparation of quaternary carbon stereocenters in acyclic systems.¹⁶ If our assumptions were to be validated, various extensions of this strategy could then be envisaged. For instance, this chemistry could be easily transposed to ω -ene alkenyl spiro[2.2]pentanes **3** (Scheme 2). Upon complexation, if the reaction sequence proceeds similarly, the unidirectional chain-walking of the double bond may promote a selective ring-opening of the spiro[2.2]pentane to initially afford **IX** (Scheme 2, for $n = 1$, part a). Subsequent reaction of **IX** with two different electrophiles may provide the appealing substituted vinylcyclopropanes **4** potentially possessing three stereogenic centers. Alternatively, if **IX** would undergo a second selective C-C bond cleavage, then acyclic product **5** would have been formed after reaction with two different electrophiles leading to a diene system possessing two distant stereocenters in a 1,5-relationship (Scheme 2, part b). On the other hand, ω -ene alkenyl cyclopropyl carbinol methyl ethers **6** (Scheme 2, part c) could be subjected to this combined isomerization - ring fragmentation sequence and should consequently provide metalated unconjugated diene fragments **X**. Addition of an electrophile may possibly lead to the formation of the skipped diene **7** possessing the initial quaternary carbon stereocenter but now in acyclic structure. Finally, as depicted in Scheme 2, part d, alkylidenecyclopropanes (ACPs) **8** should also represent ideal candidates for this transformation. Indeed, due to the ring strain imposed by the exocyclic double-bond, the binding of the zirconocene and subsequent isomerization should be favored and should similarly lead to a C-C bond cleavage to provide the intermediate **III** already discussed in Scheme 1. We and others have reported the synthesis of various acyclic scaffolds bearing quaternary stereocenters via selective fragmentation of alkylidenecyclopropanes using different strategies.¹⁷ Before performing the entire one-pot transformation as described in Scheme 1 (This work) on the ω -ene polysubstituted cyclopropanes **1** and then the one described in Scheme 2, we initially had to develop experimental conditions that would enable a high-yielding and 1,4-diastereoselective transformation of **1** into **2**. We first attempted to convert ω -ene-cyclopropane **1a** (with two identical groups as R^1 and R^2) into acyclic product **2a** by addition of the Negishi reagent $\text{Cp}_2\text{ZrC}_4\text{H}_8$,¹⁰ freshly prepared from Cp_2ZrCl_2 and 2 equiv of *n*-BuLi at low temperature in Et_2O as solvent (Scheme 3). We were pleased to observe that the Negishi reagent $\text{Cp}_2\text{ZrC}_4\text{H}_8$ could convert **1a** into **2a** as a single *E*-isomer after hydrolysis in a good isolated yield through the expected allylic C-H bond activation sequence

followed by a selective C-C bond cleavage (Scheme 3). Our mechanistic rationalization for the above transformation was that the π -allyl zirconocene hydride species **XII**, formed through an allylic C-H bond activation reaction of the zirconacyclopropane **XI**, would initiate the isomerization and would generate the new zirconacyclopropane **XIII** after readdition of the metal-hydride species onto the hydrocarbon chain.¹⁸ As β -metalated cyclopropyl species are known to undergo ring-opening reactions,¹⁹ the zirconacyclopropane **XIII** undergoes a selective C₁-C₃ bond cleavage to form the π -alkyl-allylzirconocene intermediate **III_a** (probably in haptotropic equilibrium with its σ -bonded form **III_b**) as described in Scheme 3. The origin of the selectivity for the ring cleavage (C₁-C₃ versus C₁-C₂) is kinetically and thermodynamically governed by the formation of the primary carbon zirconium bond (C₃-Zr, formation of **III**) rather than the formation of the tertiary carbon zirconium bond (C₂-Zr, formation of **V**), even though the activation could have otherwise occurred at the benzylic position (that is, **1a-e**).²⁰ The formation of a discrete bismetalated σ,π -allylzirconocene species **III_a** was confirmed by deuterolysis after the isomerization/ring-opening sequence and **2a_{d2}** was obtained with isotopic incorporation at the primary alkyl (C₃) and allylic (C₂) positions.

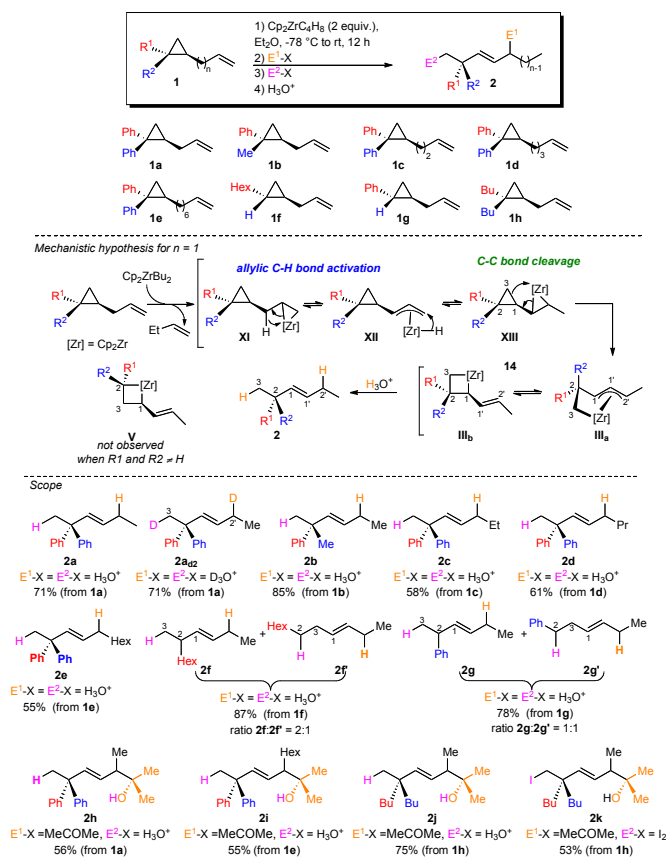
Scheme 2. Extension of the strategy of metal-mediated isomerization – ring-opening – functionalization



From this experiment, we can already suggest that the zirconocene complex allows not only an isomerization of the double bond (Zr-walk) but also a selective C₁-C₃ bond cleavage and site selective reactions with electrophiles.²¹ When the chain length between the cyclopropyl unit and the unsaturation increases ($n = 2, 3$ and 6 for **1c-e**), comparable yields were obtained (**2c-e**, respectively) albeit with a slight decrease for the longest alkyl chain (**2e**, $n = 6$, 55%).²¹ This allylic C-H bond activation with the subsequent combined C-C bond cleavage proceeds similarly for cyclopropanes possessing different substituents on C₂ (compare **2a**, **2b**, **2f**, **2g** and **2j**) although two isomers were obtained from 1,2-

disubstituted ω -ene cyclopropanes (**1f,g**) resulting from the unselective metal insertion (**2f,f'** and **2g,g'** respectively).²² It appeared that the selectivity of the ring opening might be limited to cyclopropane derivatives bearing a quaternary carbon center in C₂. Additionally, when two different electrophiles E¹-X and E²-X were added, the site selectivity for the functionalization is fully controlled (see formation of **2h-k** as unique isomer, Scheme 3). Indeed, the allylzirconocene fragment of **III**, whose reactivity has previously been established,²³ selectively reacts with carbonyl compounds such as acetone at the position C₂' (see **III_b**). Even in the presence of an excess of acetone, no trace of compounds resulting from the reaction of alkylzirconocene with ketone at C₃ could be detected. However, the subsequent addition of I₂ allows the functionalization of the remaining alkylzirconocene segment yielding **2k**. It should be emphasized that in all cases, the *E*-alkene was exclusively formed. Now that the sequence of allylic C-H activations and selective C-C bond cleavage is established, the potential of this transformation for the creation of two stereogenic centers in a 1,4-relationship was investigated (Scheme 4). When diastereomerically pure **1i** (R¹ = Me, R² = Bu) was treated with Cp₂ZrC₄H₈ under the same experimental condition, a similar process occurred to give the intermediate **III_b** that was subsequently treated with acetone and then iodine to yield **2l** as unique *E*-isomer. However, analysis of the crude reaction mixture by ¹H NMR showed that **2l** was formed as a mixture of two diastereoisomers in a 3:1 ratio (Scheme 4).

Scheme 3. Representative scope of the remote zirconocene-induced fragmentation of ω -ene cyclopropanes



To rationalize this low diastereoisomeric ratio, we hypothesized that a mixture of *trans*- and *cis*-allylzirconocene species might be responsible for this impediment (**III_{b-trans}** and **III_{b-cis}** respectively), both reacting with acetone and consequently leading to the two observed *sp*³-centered diastereoisomers. To improve this ratio, one needs to convert the *Z*-configured species **III_{b-cis}** into its more thermodynamically stable *E*-isomer **III_{b-trans}** prior to the addition of the first electrophile (path a).¹⁴ We were pleased to observe that this interconversion was effective by heating at 56 °C for 3 hours, under our pre-set experimental conditions. To allow the reaction mixture to reach the required temperature, addition of a cosolvent such as THF was primordial. Following this optimized procedure, the reaction of **ii** with Cp₂ZrC₄H₈ in Et₂O provided the product **2l** in an excellent 95:5 diastereomeric ratio, highlighting the relay of the stereochemical information from position C₁ to C₂' (Scheme 4).²⁴ Having in hands this improved protocol, various diastereomerically pure ω-ene-cyclopropanes **ii-n** were successfully treated with the Negishi reagent Cp₂ZrC₄H₈ to produce the corresponding functionalized acyclic products **2l-z**, bearing the expected quaternary carbon and allylic tertiary stereogenic centers with excellent diastereoselectivities (Scheme 4). In all cases, the reaction proceeded similarly and even when 4 carbon atoms are separating the unsaturation to the three-membered ring (*i.e.* **1n**), yields and diastereomeric ratios remained excellent. It should be noted that both diastereoisomers **2l** and **2m** could be obtained independently from the two diastereoisomers of the ω-ene cyclopropane (**ii** and **ij** respectively) with similar ratios. This transformation is not restricted to substrates with a terminal double bond as internal olefin **1m** provided **2p** as a single stereoisomer using our standard conditions. Importantly, the final stereochemical outcome of the double bond seemed independent of its initial geometry since both *E*- and *Z*-isomers of **1m** provide only the *E*-compound **2p**.

We should emphasize that the use of hindered or conformationally constrained electrophiles such as 4-methylcyclohexanone or 4-(*tert*-butyl)cyclohexanone respectively proved to be less efficient (**2z**) or totally unreactive, respectively. However, we were puzzled that one can isomerize the *cis* **III_{b-cis}** into *trans*-substituted allylzirconocene **III_{b-trans}** (isomerization at C₃) without inducing any scrambling of the stereochemistry at the C₁ position (see Figure 1). This notable high stereoelectronic control raises the question of its origin since the formation of a single product requires a large number of elementary steps during which stereochemical information could be altered. To get insights in the mechanism, DFT(Mo6) calculations with implicit SMD solvation (Et₂O) were carried out.²⁴⁻²⁶

One of the first issues that we wanted to clarify is the original formation of a zirconacyclopropane obtained by mixing the Negishi reagent with an external double bond (Scheme 5). In the literature a direct ligand exchange reaction is usually postulated²⁷ although a stepwise mechanism of addition-elimination has also been proposed.²⁸ The mechanism by which the zirconocene is transferred from the

Negishi reagent Cp₂Zr(η²-H₂C=CH₂Et) to the terminal π-bond of the substrate was first investigated using but-1-ene as model substrate (Scheme 5). This reaction is driven by the strong negative charge that is located at the α carbons of the butyl groups in **c1**.

Scheme 4. 1,4-diastereoselectivity in acyclic products 2 from ω-ene cyclopropanes 1

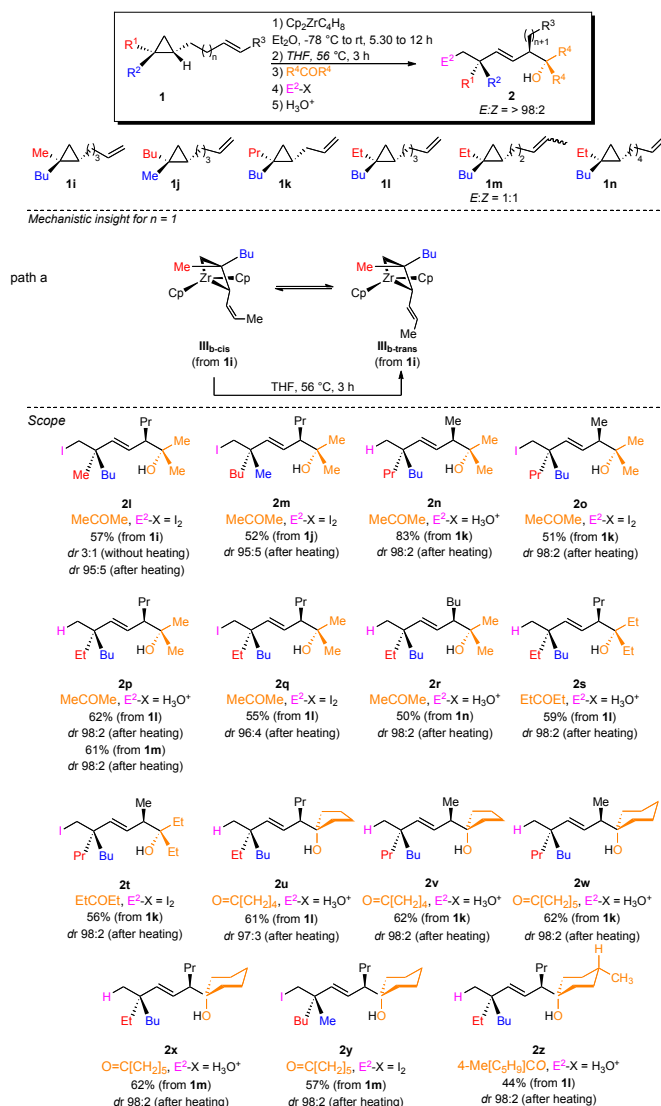
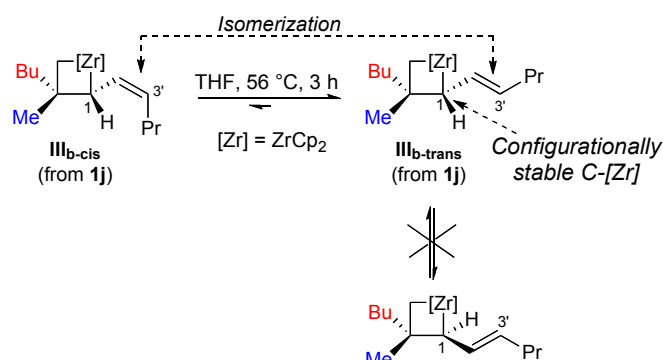
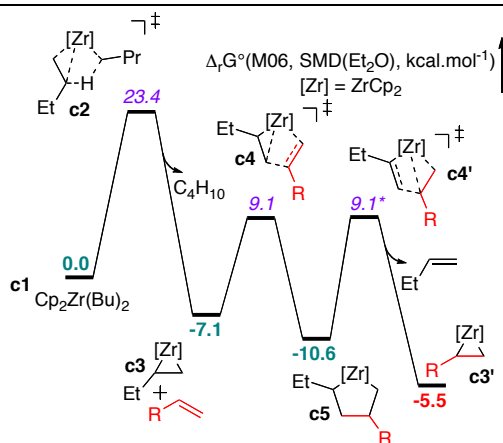
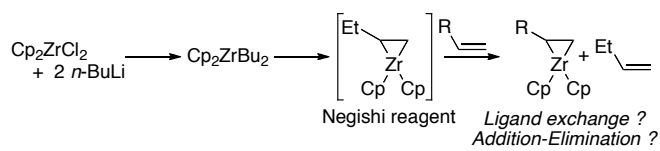


Figure 1. Isomerization reaction



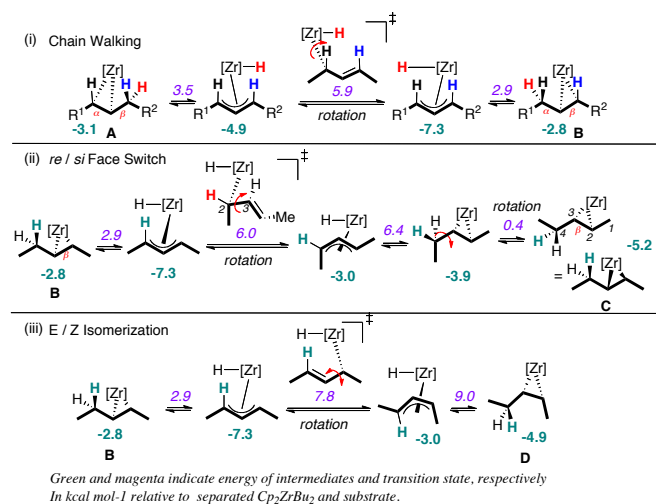
Scheme 5. Transfer mechanism of the metal fragment from Cp₂Zr(η²-H₂C=CH₂) to the substrate



Starting from Cp₂Zr(Bu)₂, an intramolecular β-H abstraction from one of the two butyl groups by the α carbon of the other one and subsequent elimination of butane (TS **c2**, ΔG[‡] = 23.4 kcal mol⁻¹) yields the Negishi reagent Cp₂Zr(η²-H₂C=CH₂) **c3**. A NBO analysis reveals that the charge on Zr remains almost constant during this step, suggesting that the formal Zr +IV oxidation state is unchanged from **c1** to **c3** and that Cp₂Zr(η²-H₂C=CH₂) is thus best viewed as a zirconacyclopentane [Zr(IV)]. Thereof, alkene exchange with the substrate is a two-step process that starts with a carbocation reaction [addition of the C=C double bond of the substrate to Cp₂Zr(η²-H₂C=CH₂)] via the transition state **c4** to yield a zirconacyclopentane intermediate **c5**. Ring-fragmentation of **c5** releases but-1-ene and the desired zirconacyclopentane.²⁹ The Gibbs energy barrier for this exchange reaction is moderate, and the irreversibility of the reaction is insured by but-1-ene elimination from the solution. The zirconacyclopentane character of **c3** clearly prevents direct alkene exchange towards **c3'**.³⁰ After transfer of Cp₂Zr to the terminal double bond of the substrate, migration of the metal fragment along the carbon skeleton can occur. During this migration, three types of isomerization were initially suggested:^{24a} (i) zirconacyclopentane walking along a σ-trans skeleton, (ii) facial interconversion of the zirconacyclopentane via the σ-cis allylic intermediate, (iii) *E* to *Z* double bond isomerization i.e. *syn/anti* allyl isomerization (Figure 2). Gibbs energy profiles of these transformations were computed using pent-1-ene as a model substrate. These transformations are initiated by the coordination of electron deficient zirconocene to the π C=C double bond which promotes the activation of the allylic C-H bond. This yields a zirconocene hydride η³-allyl complex, which is more stable than the initial zirconacyclopentane complex. This hydride allyl complex tuned to be the pivotal intermediate to the reactivity and dynamics of the overall reaction. The equilibrium between zirconacyclopentane

and allyl-hydride complexes enables the Zr-walk (Figure 2). Starting from the η³-allyl hydride complex, an η³- to η¹-haptotropic shift rotates Cp₂ZrH relative to the allyl group. Return to the η³-mode and reinsertion of the allyl group into a rotated Zr-H bond yields a π-C=C bond shifted by a methylene group. By this mechanism, zirconocene walks in the two directions along the carbon backbone. *E/Z* isomerization combines the above sequence and a rotation about the single C-C bond of the η¹-coordinated allyl complex.

Figure 2. Mechanism of the Zr-walk: (A) switch of prochiral faces (B) and (C) isomerization of stereochemistry. (A) has been computed for **ii, (B) and (C) for pent-2-ene. Free Gibbs energies are given in kcal mol⁻¹.**



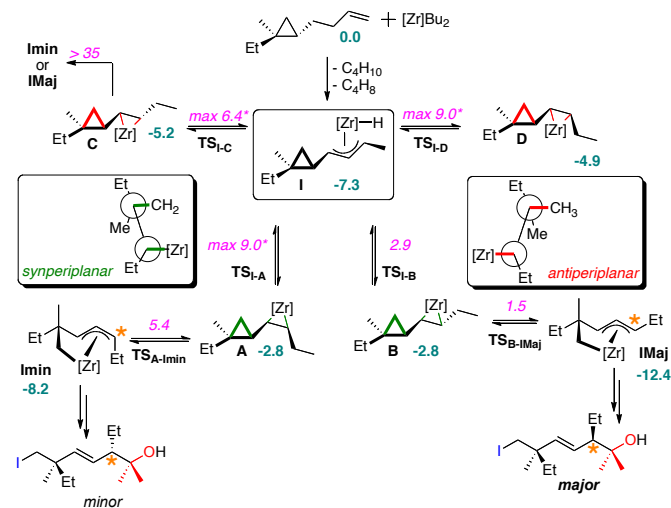
Similar types of isomerization steps are involved in the *re* to *si* face exchange. In this case, the initial C-H bond activation has to be performed on an allylic σ-cis conformation. On the overall, these transformations involve numerous elementary steps whose transition states are all low in energy (Δ_‡G[‡] < 15 kcal mol⁻¹ with respect to separate reactants Cp₂ZrC₄H₈ and but-1-ene) and all of similar energy (ΔΔ_‡G[‡] < 7 kcal mol⁻¹). The combination of these sequences, that have common intermediates and similar energy profiles, allows the coordination of zirconocene to all carbons without conformational restriction. The Gibbs energy profiles for these isomerizations are shown in Figures S2 to S4 in the SI.

To raise insight into the thermally induced interconversion described in Scheme 4 (path a) and Figure 1, we completed our initial computational study (See Scheme 6).^{24a} Based on the equilibria shown in Figure 2, four isomers (A-D, Scheme 6) of zirconocene β-ene-cyclopropane are produced in equilibrium via a common zirconocene-allyl-hydride intermediate **I**. Ring opening from these four isomers was considered resulting in a deeper understanding of the *syn-* vs *anti*-periplanar relationship required between the cyclopropane methylene unit and the zirconocene.^{20a} In intermediates **C** and **D**, zirconocene is *trans*-periplanar to the less substituted cyclopropane C-C bond. Thus, cyclopropane ring opening requires a large distortion that is kinetically prohibitive (Δ_‡G[‡] > 35 kcal mol⁻¹) (Scheme 6). In contrast, in intermedi-

ates **A** and **B**, a *syn*-periplanar relationship between these bonds lowers the energy barrier by 30 kcal mol⁻¹, yielding $\Delta_{\text{G}}^{\ddagger}$ of 1.5 and 5.4 kcal mol⁻¹ for **TS_{B-IMaj}** and **TS_{A-IMin}**, respectively. **TS_{A-IMin}** accounts for the formation of the final minor diastereoisomer. Hence, the most stable complex **IMaj** is kinetically favored over **IMin** and accounts for the major final diastereoisomer. In order to explain the epimerization in favor of **IMaj** observed upon heating, all plausible routes that connect **IMin** to **IMaj** were explored. The most favorable pathway entails the η^3 -allylic intermediate **I** and relies on the reversible formation of **IMaj** from **IMin** via **I** using the elementary steps described previously in Figure 2. Since **IMin** is 8.2 kcal mol⁻¹ lower in energy than the reactants, heating is required to overcome the exoergicity and pass through the transition states and intermediates that link **IMin** to **IMaj**.²⁴

The high diastereoselectivity observed in this transformation results from a dynamic thermodynamic process in which heating increases the stereocontrol of the reaction. Remarkably, this stereocontrolled remote functionalization results from unselective C–H bond activations and reversible cyclopropane ring opening enabling a micro-reversibility of all events until the lowest energy minimum is fully reached.

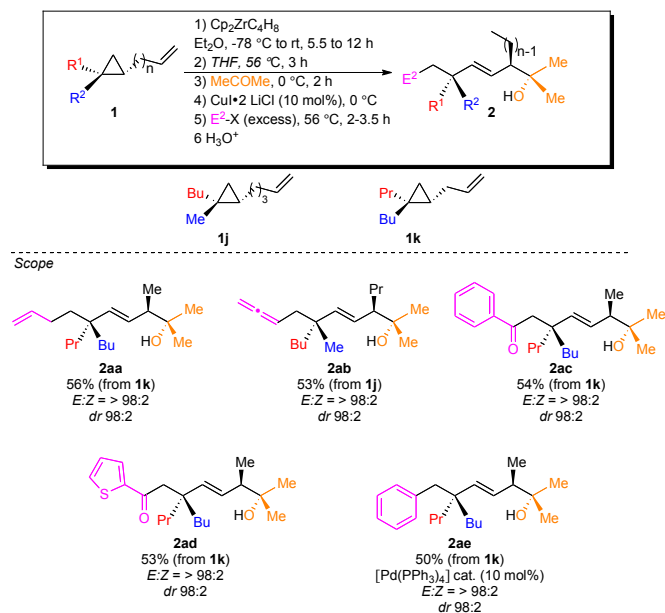
Scheme 6. Diastereoisomeric cyclopropane ring opening: a Dynamic Kinetic Resolution



Having now a better understanding of the chemical process, we decided to further increase the versatility and scope of this approach by functionalizing the remaining sp³ carbon-zirconium bond with carbon electrophiles. Although the ionic character of the sp³ C–[Zr] bond is similar to a C–Mg bond, only small size electrophiles such as proton or very reactive electrophilic reagents such as I₂ proved to efficiently react with the sp³ C–[Zr] bond, presumably owing to the steric shielding of the two cyclopentadienyl ligands at the metal center. To circumvent the lack of reactivity of this σ -carbon-metal bond, transmetalation to copper was required. Gratifyingly, after addition of the first electrophile, the introduction of a catalytic amount of CuI•2LiCl in the reaction mixture allowed to considerably expand the scope

of the second functionalization.^{24,31} For instance, S_N2'-type processes could be carried out with allyl or propargyl bromide to give **2aa** and **2ab** respectively. C(sp³)–C(sp²) bonds were directly formed using acyl chlorides (**2ac** and **2ad**), or indirectly via a Pd-catalyzed cross-coupling reaction with phenyl iodide (**2ae**) (Scheme 7).

Scheme 7. Functionalization of the remaining sp³ C–[Zr] bond via a catalytic transmetalation to copper

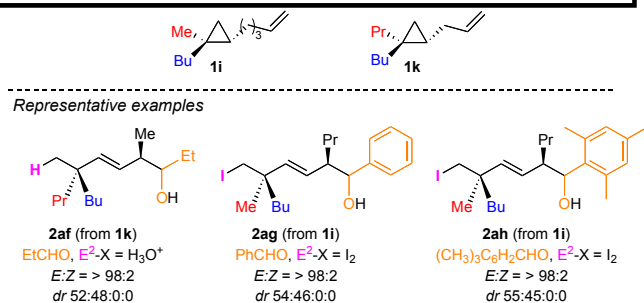
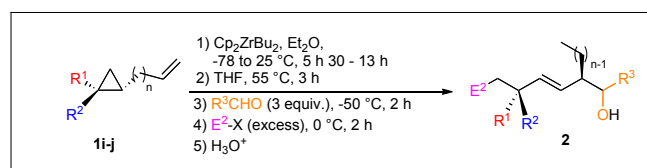


As our strategy led to products bearing stereogenic centers in a highly stereodefined 1,4-relationship, we attempted to add one additional level of stereochemical complexity by studying the addition of prochiral substrates such as aldehydes or imines. Whereas *N*-(tosyl)benzylideneimine and *N*-(diphenylphosphinyl)benzaldimine proved to be unreactive towards the intermediate **III** (described in Scheme 4), the use of aliphatic or aromatic aldehydes with **ii,k** led to the linear products **2af-h** in good yields but with a disappointing diastereoisomeric ratio (Scheme 8). Extensive efforts to improve this ratio by further tuning the experimental conditions turned out to be fruitless. As the stereoselective reaction with aldehydes proved to be unsuccessful to build a third stereogenic center in decent diastereoisomeric ratio, we then envisaged an alternative approach where the third stereocenter would result from a selective ring opening of 1,1,2,3-tetrasubstituted cyclopropane such as **1o** (Scheme 9).

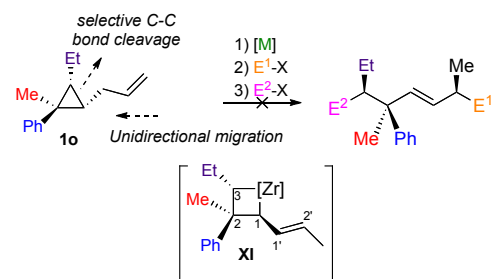
As we previously noticed that the ring-opening of 1,2-disubstituted ω -ene cyclopropane **1f** was not fully selective and could lead to the formation of the two products **2f** and **2f'** in a 2:1 ratio (see Scheme 3), we hypothesized that the combined reactions of allylic C–H bond activation followed by ring opening of the polysubstituted cyclopropanes **1o** should proceed and be selective towards the formation of a secondary sp³ organozirconocene species,³² which has been reported to be configurationally stable³³ (see Scheme 9). However, all attempts to promote the isomerization fol-

lowed by selective C-C bond cleavage of **10** led to a complex reaction mixture and could therefore not be synthetically valuable.

Scheme 8. Non diastereoselective reaction of aldehydes with allylzirconocene originating from ω -ene cyclopropanes **1**



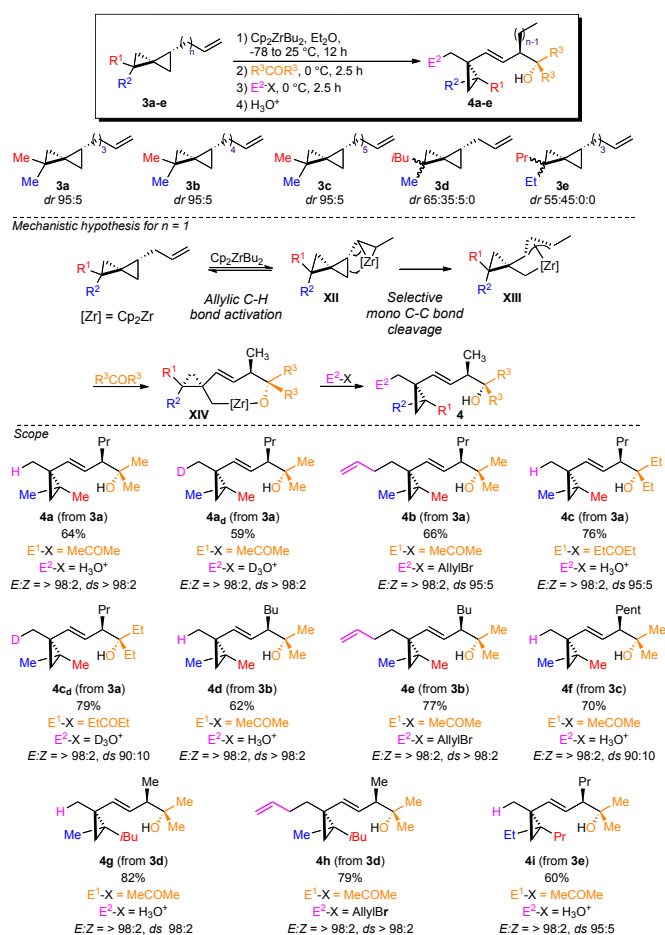
Scheme 9. Attempt to extend the sequence to 1,1,2,3-tetrasubstituted ω -ene cyclopropane **10**



Based on these results, the remote functionalization of ω -ene cyclopropane efficiently proceeds through isomerization of a double bond and selective C-C bond cleavage only for ω -ene 1,1,2-trisubstituted cyclopropanes **1a-n** possessing a quaternary stereocenter. We were then interested to extend this approach to ω -ene alkenyl spiro[2.2]pentanes **3**. These smallest encountered spirocarbocycles³⁴ have a higher ring strain energy (63 kcal.mol) than two cyclopropanes taken separately (27.5 kcal.mol) suggesting an even higher propensity towards fragmentation.³⁵ Moreover, unlike thermal, radical, ionic or carbene-induced cleavage of spiro[2.2]pentanes, the transition-metal assisted transformations of these entities usually lead to selective transformations, therefore potentially becoming of synthetic use. For instance, selective single or double ring opening procedures of spiro[2.2]pentanes were already reported, although the single-ring opening mode being less encountered. As an example, de Meijere initially showed the possibility of inducing a single ring-opening mode through the [Co₂(CO)₈]-catalyzed carbonylation of vinyl spiro[2.2]pentanes³⁶ and of 4-methylenespiro[2.2]pentanyl methanols.³⁷ In parallel, a

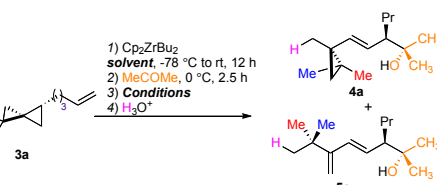
double ring-opening modes of spiro[2.2]pentanes were previously shown to be triggered either by a Heck arylation,³⁸ a Rh(I)-catalyzed carbonylation³⁹ or a Ru(II)-catalyzed full ring-opening followed by a subsequent [4+2] dimerization reaction.⁴⁰ Following the development of a straightforward access⁴¹ to various ω -ene alkenyl spiro[2.2]pentanes **3** in good to excellent diastereoisomeric ratios (see Supplementary Material), we then focused on their behavior in our zirconocene-mediated isomerization followed by selective C-C bond cleavage. When **3a** was treated with the Negishi reagent, we were gratified to observe a rapid and clean isomerization reaction followed by a selective single C-C bond cleavage to provide, after reaction with acetone and subsequent hydrolysis, **4a** in 64% yield as a single *E*-isomer without any trace of second C-C bond cleavage product (Scheme 10). Notably, the diastereospecificity of the conversion of **3a** into **4a** is quantitative (*ds* > 98:2) as the 95:5 diastereomeric ratio of **3a** is recovered for **4a** (*dr* 95:5).

Scheme 10. Combined isomerization-selective mono C-C bond cleavage of ω -ene alkenyl spiro[2.2]pentanes **3a-e**.



The presence of the remaining sp^3 carbon-zirconium bond enabled the functionalization by addition of deuterium (formation of **4a**) or by allylation reaction after transmetalation reaction with a catalytic amount (10 mol%) of $CuI \cdot 2LiCl$ (formation of **4b**). This tandem sequence was applied to various ω -ene alkenyl spiro[2.2]pentanes **3a-e** and as previously discussed, longer alkyl chain between the strained ring –namely here the spiro[2.2]pentane unit- and the unsaturation's relative positioning did not hamper the overall transformation. Yields resulting from the isomerization followed by the selective mono- C-C bond cleavage of **3a**, **3b** and **3c** (with $n = 3, 4$ and 5 respectively) were indeed comparable. This approach allowed the formation of (1,1,2,2-*E*)-vinyltetrasubstituted cyclopropanes motifs seemingly challenging to prepare otherwise by more conventional strategies. As previously observed with alkenyl cyclopropanes (see Scheme 8), the addition of aldehyde such as isobutyraldehyde also proceeded smoothly but without any diastereocontrol (**4j**), stereochemistry at the carbinol center is not controlled as already depicted in Scheme 8, compound not reported in Scheme 10). Following the development of this straightforward approach for a selective mono- C-C bond cleavage, we then turned our attention to promote the second C-C bond cleavage to give **5**. All our attempts to directly cleave the two rings of the spiro[2.2]pentane failed as the σ - π -zirconocene complex **XIII** resulting for the first scission did not induce the desired second ring-cleavage, most probably due to rotational constraints. We presumed that a suitable solution would be to disengage the zirconocene complex from its π -system after addition of the first electrophile. The gained flexibility should then allow rotations over the C-Zr bond, necessary to optimally perform the second C-C bond cleavage.

Table 1. Screening of experimental conditions for the second ring-opening mode converting ω -ene spiro[2.2]pentane **3a into diene **5a**.**

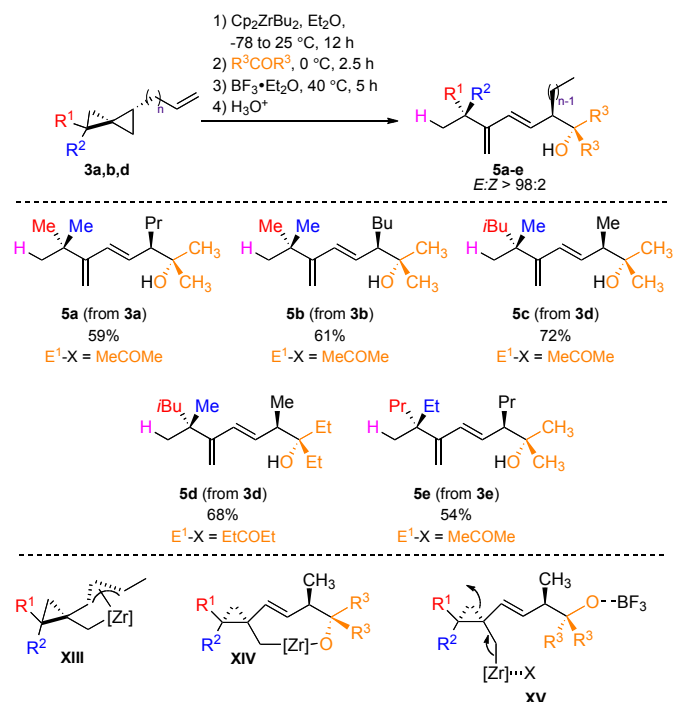


Entry	Solvent	Additive (2.5 equiv)/ Temperature (°C)/ Time (h)	Yield (4a + 5a) ^a	Ratio (4a : 5a) ^b
1	Et ₂ O	none / 0 / 2.5	64	100:0
2	THF	none / 55 / 12	<10	0:100
3	Et ₂ O/THF	none / 55 / 12	58	82:18
4	Et ₂ O/2-MeTHF	none / 80 / 12	40	80:20
5	Et ₂ O/THF	MeLi / 55 / 12	61	95:5
6	Et ₂ O/THF	ZnCl ₂ / 55 / 12	51	95:5
7	Et ₂ O/THF	TMSCl / 25 / 12	50	75:25
8	Et ₂ O/THF	TMSCl / 55 / 12	51	0:100
9	Et ₂ O	TMSOTf / 25 / 12	/	/
10	Et ₂ O	BF ₃ ·Et ₂ O / 25 / 6	67	13:87
11	Et ₂ O	BF ₃ ·Et ₂ O / 40 / 6	59	2:98

^a Combined yields after column chromatography. ^b Determined by ¹H NMR spectroscopy on the crude reaction mixture

For instance, we observed that the reaction could lead to a second ring-cleavage product **5a**, albeit in very low yield, when the complete sequence of isomerization - first C-C bond fragmentation and reaction with acetone was performed in more polar solvent such as THF (Table 1, compare entries 1 and 2). This result underlined that a more polar solvent might break the presumed aggregate described in **XIV** and induce the second ring fragmentation. However, THF was clearly not an appropriate solvent for the zirconium-walk reaction (Table 1, entry 2). As it became rapidly clear that the most suitable solvent for the Zr-walk was Et₂O, we further screened the influence of various parameters on the ring-opening of intermediate **XIV** (Table 1). As adding THF or 2-MeTHF as cosolvent after the first ring-opening and heating the reaction mixture slightly increased the ratio in favor of the double-opening product (Table 1, entries 3-4), we opted for additives to weaken or transmetalate the O-[Zr] bond. Addition of a Lewis base such as MeLi in the reaction mixture to produce the more reactive "organozirconate" complex (Table 1, entry 5) or adding Zn(II) salt to promote a transmetalation into an alkylzinc species (Table 1, entry 6) was not successful in promoting the second ring-opening reaction. Only the addition of a Lewis acid such as TMSCl at room temperature slightly proved to be beneficial (Table 1, entry 7). Heating the reaction mixture to reflux over 12 hours led to a complete full ring-opening of the initial spiro[2.2]pentane substrate (Table 1, entry 8). Whereas TMSOTf induced the elimination of the alcohol moiety in **5a** (Table 1, entry 9), BF₃·OEt₂ was found to be the most efficient additive affording the desired 4,6-diene **5** in satisfactory yields and still excellent *E*-selectivity (Table 1, entries 10 and 11).

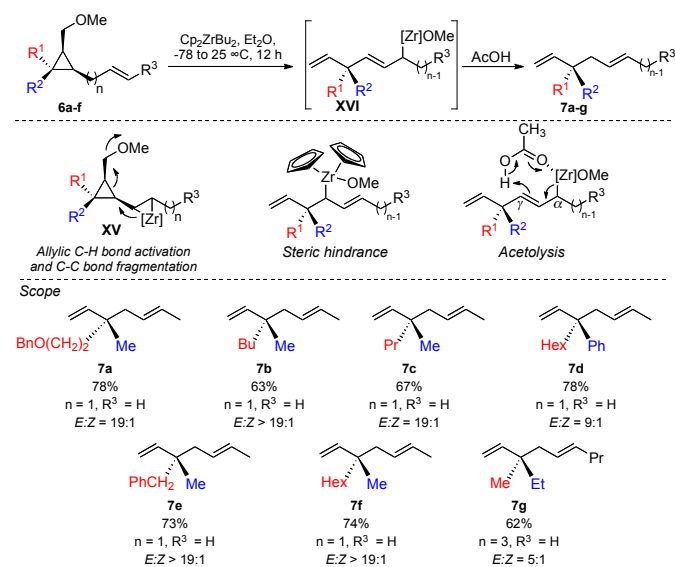
Scheme 11. Scope of the remote and selective double ring-opening of ω -ene spiro[2.2]pentane



Various ω -ene spiro[2.2]pentanes **3a,b,d** were then subjected to these optimized conditions (Scheme 11). As already mentioned, the reaction proceeded invariably of the chain length ($n = 1$ to 4) affording products **5** after reaction with ketone and hydrolysis. Besides the isomerization, this study provided a unique, flexible and selective multiple C-C bond cleavage of ω -ene spiro[2.2]pentanes leading either to **4** or **5** selectively.

Similar isomerization/carbocycle fragmentation sequence could also be applied to ω -ene cyclopropane possessing a strategically placed methoxy group on the cyclopropyl ring. When diastereopure cyclopropyl methyl ethers **6**, also potentially obtained enantiomerically enriched,¹⁵ were treated with the Negishi reagent, a sequence of isomerization followed by a C-C bond fragmentation as depicted in **XV** gave the corresponding allylzirconocene species and after acetolysis, the dienes **7** with an excellent *E:Z* ratio as described in Scheme 12.

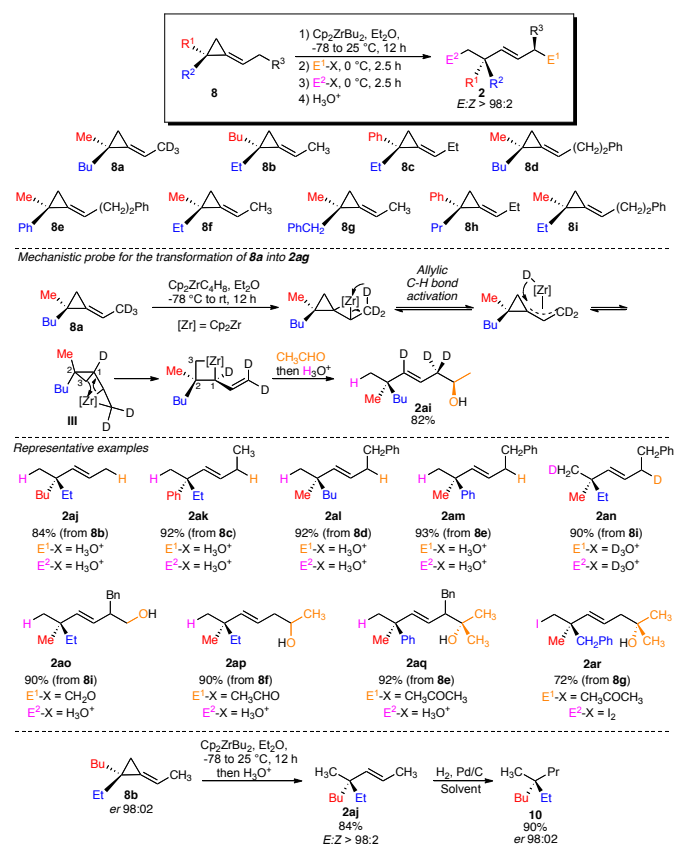
Scheme 12. Combined zirconocene-induced migration of alkene with C-C bond fragmentation



Owing to the potential harmful steric interaction between the Cp groups of the zirconocene and the quaternary carbon stereocenter, we hypothesized that the allylzirconocene **XVI** should be the predominant isomer among all the possible haptotropic forms. Surprisingly, only acetolysis provided a good selectivity for the protonation reaction at the γ -position as addition of H_3O^+ gave a mixture of α and γ -isomers. One possible explanation could be the formation of a 6-membered ring intermediate that would only react through an allylic rearrangement as depicted in Scheme 12. Several ω -ene cyclopropyl carbinol methyl ethers **6a-f** were subjected to these conditions and in all cases unconjugated dienes **7a-g** were obtained with excellent positional selectivity of the internal double bond. This reaction was not restricted to short alkenyl chain ($n = 1$) as longer alkyl chain ($n = 3$) also successfully led to the unconjugated diene **7g** in a good yield although with a slightly lower *E:Z* ratio. Spurred by our previous results, we then attempted to extend this

strategy to a different family of small strained ring derivatives, namely alkylidenecyclopropane (ACPs) species.^{42,43} These substrates should be excellent candidates for this transformation as we have already reported the metal-catalyzed hydroboration,⁴⁴ hydrostannylation,⁴⁴ hydrosilylation⁴⁴ and hydroformylation⁴⁵ reactions with subsequent selective ring-opening of ACPs.⁴⁶ Based on the high reactivity of the exoalkylidene moiety of ACPs,³⁵ we reckoned that the Negishi zirconocene species should first induce the isomerization of the double bond to release the strain. The resulting zirconocyclopropane would then undergo a selective C₁-C₃ bond cleavage (Scheme 13) to give the previously mentioned intermediate **III** already discussed for the transformation of ω -ene cyclopropanes **1** into acyclic fragments **2** (Scheme 1).

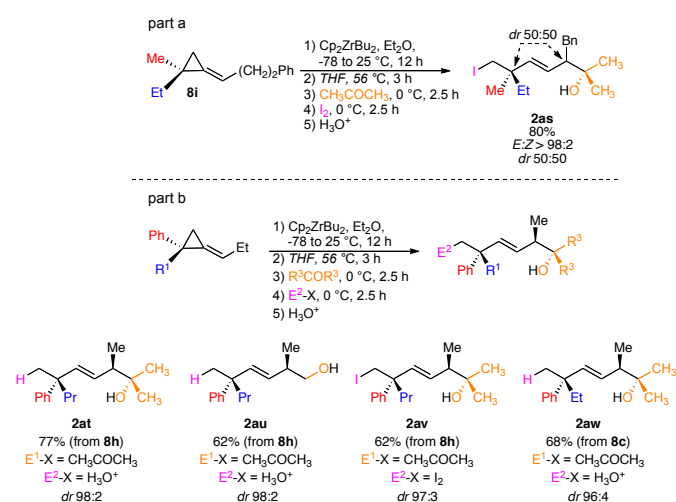
Scheme 13. Isomerization followed by C-C bond cleavage of ACPs



To further probe our mechanistic understanding, we used the allylic CD₃-labelled **8a** as starting ACP and the product resulting from this combined allylic C-H bond activation and C-C bond cleavage gave **2ai** in excellent yield possessing two deuterium atoms at the allylic and one deuterium atom at the vinylic positions supporting our mechanistic hypothesis. In all cases, the combined allylic C-H bond activation followed by the selective C₁-C₃ bond cleavage proceeded smoothly to afford a large variety of linear products **2ai-2ar** in excellent yields.²¹ As enantiomerically enriched ACPs are easily accessible⁴³ and because the quaternary carbon stereocenter is at no risk of epimerization during the process, the

optical purity of **2ai** can be assumed to be identical to the initial ACP. When enantiomerically enriched **8b** (*er* 98:2)^{43c-e} was treated under our experimental conditions, the acyclic product **2ai** possessing the quaternary carbon stereocenter was indeed obtained in excellent yields as unique *E*-isomer. The enantiomeric ratio of (*2E,4R*)-4-ethyl-4-methyl-octene **2ai** was determined by correlation with an authentic sample.⁴⁷ As expected, **2ai** was obtained with the same enantiomeric ratio (*er* 98:2) than the starting material **8b** confirming that the overall reaction proceeds without altering the stereochemistry of the quaternary carbon stereocenter. By a hydrogenation reaction of the double bond of **2ai**, the simplest crypto-optically active saturated hydrocarbon **10** with a quaternary carbon stereocenter was successfully prepared.⁴⁸ Finally, we were interested to use ACPs to create a new and distant stereogenic center (1,4-relationship from the initial quaternary carbon stereocenter). When ACP **8i**, possessing two alkyl groups at the quaternary stereocenter, was treated in our experimental conditions, the product **2as** was obtained in excellent yield as a single *E*-isomer but as two diastereoisomers in a 1:1 ratio (Scheme 14, path a).

Scheme 14. Diastereoselective reaction with ACPs



However, changing one alkyl by a phenyl group at the quaternary stereocenter of the alkylidenecyclopropane (Scheme 14, path b) led to an outstanding diastereoselectivity as **2at** was now obtained in 77% yield in a diastereoisomeric ratio higher than 98:2. Several other electrophiles were added and in all cases, the acyclic products **2as-2aw** were obtained with constantly high diastereoselectivities as unique *E*-isomer. The unique diastereoselectivity for the reaction of alkylidenecyclopropanes possessing an aromatic group and not an alkyl group was investigated with computations. Considering the minimum steric difference between the two alkyl groups (Me and Et) of **8i**, one could hypothesized that the two faces of the ACP were equally accessible for reaction with the zirconocene complex while one of the two faces of **8c** was preferred when an aryl group was present. However, this hypothesis was not supported by the calculations as the coordination of the two faces with the zircono-

cene reagent for **8i** as well as for **8h** was found to be energetically equivalent with $\Delta\Delta_r G^\circ \leq 0.8$ kcal mol⁻¹. As the complexation essentially proceeds equally on the two faces, we then imagined that the lowest energy pathway could originate from differences between the backward chain-walking processes on the two prochiral faces. However, this hypothesis was supported neither by the calculations as no difference in the energy profiles was found between the two diastereoisomeric pathways. Moreover, no significant differences were pinpointed between substrates **8i** and **8h**. Although it could not be computationally confirmed, the phenyl group most likely prevents (or enables) some rotations allowing the zirconocene to change from a diastereotopic face to the other one.⁴⁹

Conclusion

Several approaches using organozirconocene species for the remote cleavage of strained three-membered ring carbocycles such as ω -ene polysubstituted cyclopropanes, alkylidenecyclopropanes, ω -ene spiro[2.2]pentanes and ω -ene cyclopropyl methyl ethers, into stereodefined organometallic intermediates were successfully developed to access highly stereoenriched scaffolds in good yields. Two acyclic stereocenters including a quaternary carbon stereocenter were easily obtained in acyclic systems with very high diastereoselectivities. Theoretical calculations and isotopic labeling were performed to delineate the origin of the obtained stereoselectivities.

ASSOCIATED CONTENT

The supporting information is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENT

This research is supported by the European Research Council under the European Community's Seventh Framework Program (ERC agreement no. 338912). S.S. thanks the Planning and Budgeting Committee (PBC) of the Council for Higher Education for providing financial support. LP thanks CCIR of ICBS and CALMIP for providing computational resources and technical support. L.P. and O.E. thank the CNRS and the Université Claude Bernard and Université de Montpellier for support. I.M. holds the Sir Michael and Lady Sobell Academic Chair.

ABBREVIATIONS

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