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Metal-Catalyzed Metathesis of Fluorinated Alkenes: still a current major challenge.

Augustin Nouaille,^a Jan Lorkowski,^b Xavier Pannecoucke,^a Marc Mauduit,^{b} Thomas Poisson,^{a,c}
Samuel Couve-Bonnaire^{a*}*

^a Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France.

^b Univ Rennes, Ecole Nationale Supérieure de Chimie de Rennes, CNRS, ISCR UMR 6226, F-35000 Rennes, France.

^c Institut Universitaire de France, 1, rue Descartes 75231 Paris, France.

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ABSTRACT: Whereas the olefin metathesis is recognized as a powerful tool to produce alkene, the use of fluoroalkenes in metathesis catalyzed-reactions still remains a major current challenge. Herein, we presented the main developments in that field both in ring-closing- and cross-metathesis, highlighting the major improvements of these last years.

Introduction

Fluorinated alkenes,¹ designing herein alkenes bearing vinylic fluorine atom(s), have emerged as an important class of molecules, which can notably be found in various bioactive compounds.² In

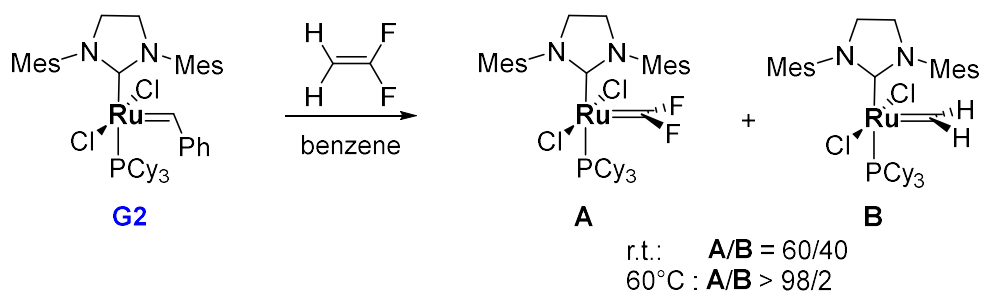
addition, they are important intermediates for the synthesis of organic materials,³ Teflon® or vinyl ether copolymers commonly used in the paint industry, being the most striking examples. The fluorolefin moiety is also known as a stable isosteric and isoelectronic mimic of the amide bond⁴ and can therefore be used *i)* as a bioisostere in structure-activity relationship studies in pharmaceutical or agrochemical domains⁵ or *ii)* to overcome problems associated to the instability of peptides.⁶ Among the numerous emerging catalytic reactions possessing enormous potential in industry, the olefin metathesis reaction stands at the top of the class.⁷ This catalytic reaction forges C–C double bonds from two entities to form cycles, polymers, novel alkenes in one step with well-defined catalysts. The savings in protection, deprotection and functionalization of olefins are simply astonishing as well as the shear savings in time, energy and economy of material. This reaction has attracted an enormous amount of interest and work towards the development of efficient catalysts and resulted in the 2005 Nobel Prize being awarded to three pioneers in the area (Chauvin, Grubbs and Schrock).⁸ The metathesis reaction could then be envisioned as a quick and efficient strategy to get fluoroalkenes. Despite the tremendous developments reported over the last years for the improvement of processes based on metathesis reactions to synthesize alkenes, the synthesis of fluorinated alkenes by olefin-metathesis reaction still remains a tremendous challenge for the scientific community. Indeed, among the countless reports dealing with metathesis reaction - between 300 and 600 research articles by year since 2000 - only sporadic examples reported olefin-metathesis with fluoroalkenes, due to the inherent challenges associated to the use of these reluctant substrates. Most of these reports deal with Ring-Closing Metathesis (RCM) and very few concerned the Cross Metathesis (CM) reaction, whereas the use of *gem*-alkylfluoroalkenes or trisubstituted fluoroalkenes, easily accessible substrates, could allow the formation of various

relevant fluorinated fine chemicals, including fluoropseudopeptides towards peptide-drug candidates.

In this review, we presented the results obtained in both ring-closing- and cross-metathesis reactions with fluorinated alkenes to date and suggested some perspectives in the area. To our knowledge, no other type of metathesis reaction with fluorinated alkenes (CEYM, ROMP, ADMET) has been reported in the literature. A more general review concerning the metathesis of fluorinated substrates has been published in 2015⁹ however new relevant results have been published since, especially concerning the challenging cross-metathesis reaction.

I) Problematic.

Early at the beginning of this new century, Grubbs was the first to test the olefin metathesis reaction with fluorinated olefins.¹⁰ The Grubbs II (**G2**) precatalyst was reacted with gaseous 1,1-difluoroethylene (boiling point: -84 °C) in a non-catalytic reaction, leading to the formation of Ruthenium difluorocarbene **A** as the major compound (Scheme 1). This compound could even be the sole product at higher temperature.

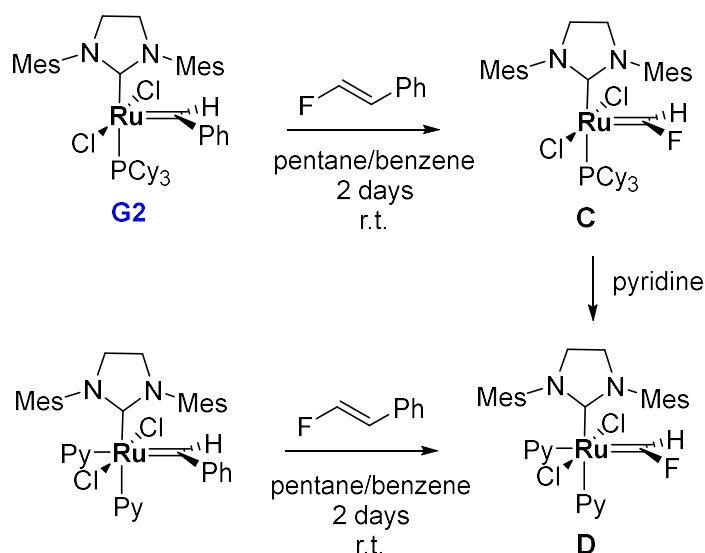


Scheme 1. First reaction of Ruthenium precatalyst with 1,1-difluoroethylene.

This preliminary study highlighted the possibility to use fluoroalkenes in olefin metathesis but also set the basis of the inherent difficulty of olefin metathesis with fluorinated olefins. Indeed, the characterized complex **A** can be assimilated to a Fischer carbene complex and proved to be a poor

catalyst. The main explanation remained on the difficult catalyst initiation, relying on phosphane dissociation which was not detected up to 100 °C upon $^{31}\text{P}\{^1\text{H}\}$ NMR magnetization-transfer experiments. Therefore, to preserve a decent catalytic activity, the formation of the stable and sluggish difluoromethylidene complex has to be avoided during the metathesis process.

Later in 2007, Johnson and co-workers drawn similar conclusion about complex **A** and its low efficiency to catalyze olefin metathesis reactions.¹¹ The authors also synthesized two new monofluoromethylidene complexes **C** and **D** from ruthenium precatalysts and β -fluorostyrene (Scheme 2). Compared to **A**, complexes **C** and **D** exhibited better olefin metathesis activity, albeit still lower than the parent compound **G2**. The authors reported several statements according to these new complexes: *i*) complex **C** was slowly initiating and underwent a gradual degradation to a terminal carbide complex, *ii*) complex **D** was fast initiating but was rapidly decomposed and *iii*) the quantitative formation of the thermodynamically favored monofluoromethylidene complexes **C** and **D** (no formation of the benzylidene complexes) during the reaction with β -fluorostyrene accounting for the limited formation of active alkylidene catalyst.



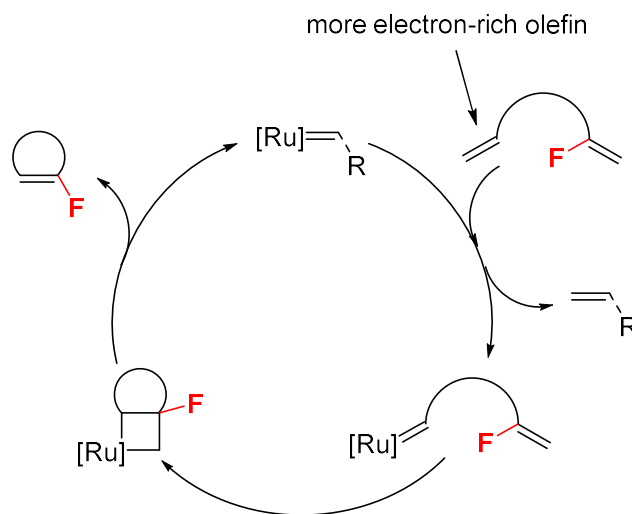
Scheme 2. Monofluoromethylidene complexes synthesized by Johnson and co-workers.

During the same period, several computational studies supported the difficulty of olefin metathesis reaction with fluoroalkenes.

Fomine, Tlenkopatchev and co-workers carried out computational studies about the cross-metathesis of norbornene with haloalkene.¹² They reported that the free Gibbs activation energy of the transformation of the transient ruthenacyclobutane into the new haloalkylidene complex decreased with the stability of the carbene complex. They also showed that the fluorine atom highly stabilized the Ru center by lone electron pairs donation and hampered its catalytic activity. The stabilization increased with the number of fluorine atom bearing by the carbene moiety.

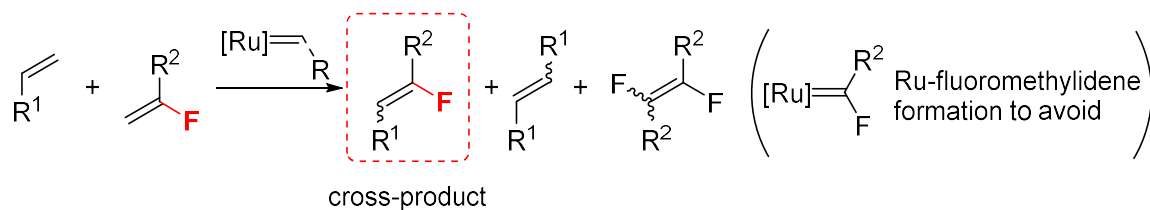
Dixon and co-workers reported computational studies using high level coupled cluster theory (CCSD(T)) calculations to study the role of the electronegative atoms bore by the carbenic carbon bound to the metal.¹³ From these studies, the same conclusion can be stated: the presence of fluorine atom on carbene moiety lowered the bond dissociation energy of metal-carbene for both molybdenum^{13a} and ruthenium,^{13b} the two most used metals in olefin metathesis, decreasing their effectiveness for metal-catalyzed metathesis reactions.

All of these drawbacks explain the poorly documented area of fluoroalkene metathesis. To resume, the metathesis reaction with fluoroalkene should preclude the formation of poorly catalytically active ruthenium-fluoromethylidene. The reaction seems easier to envision for RCM reaction for which the first metallacyclobutane should be formed by the reaction between the precatalyst and the more electron-rich and not fluorinated olefin and which might then be entropically favored by the intramolecular nature of the process (scheme 3).



Scheme 3: RCM with fluoroalkenes.

Regarding the CM reaction, the problem is more complicated and several parameters have to be tuned in order to get the cross-product as the major one compared to homodimer products or deactivation of catalysts (Scheme 4).

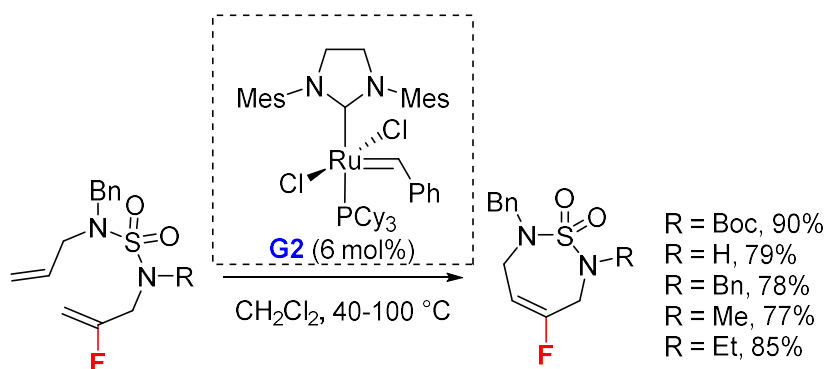


Scheme 4: CM with fluoroalkenes and challenges associated to the reaction.

Provided these principles, the first part of the manuscript will focus on the entropically favored RCM reaction of fluoroalkenes followed by the second part dedicated to the more challenging CM. All the yields given in the following schemes are isolated yields unless otherwise stated (GC or NMR).

II) Ring-Closing Metathesis.

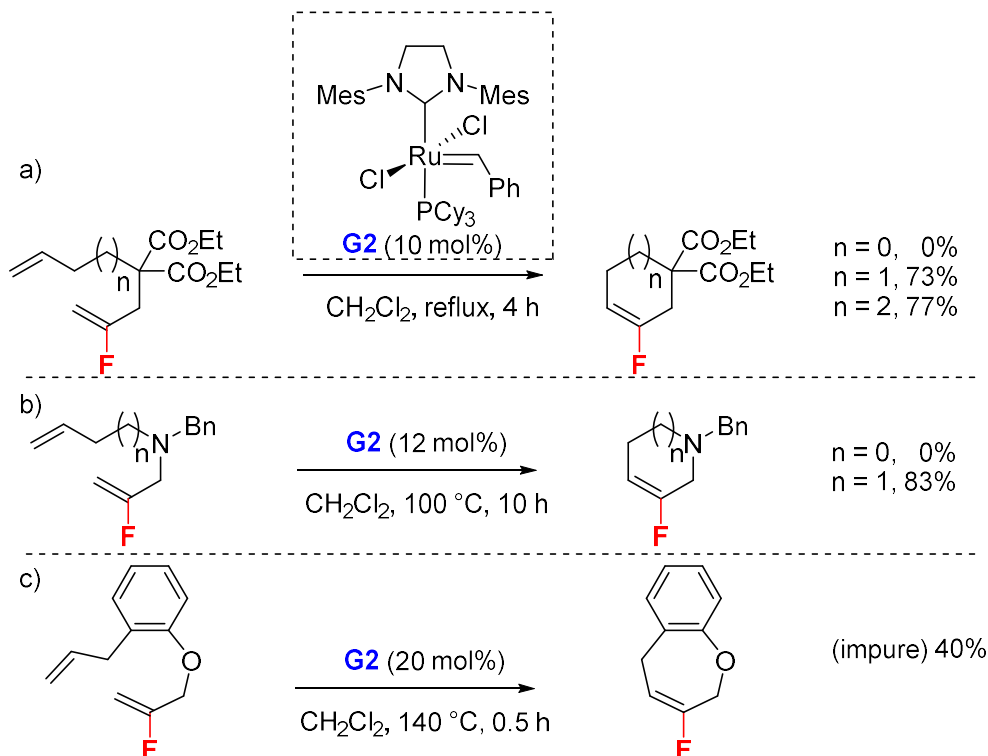
In 2003, Brown and co-workers investigated the RCM reaction of sulfamide-linked diene substrates, to provide fluorinated derivatives of a seven-membered cyclic scaffold present in a series of highly potent HIV protease inhibitors.¹⁴ The RCM was first carried out to form the *N*-Boc-protected cycle in 3 hours with 6 mol% of Grubbs-II (**G2**) catalyst loading in refluxing CH₂Cl₂ (Scheme 5). Under the same conditions, the mono-protected cycle was also obtained but required extended reaction time (7 h), whereas the *N*-alkyl sulfamides required higher temperature (100 °C) to be obtained. The authors also mentioned that no CM side reactions (formation of dimer) was observed.



Scheme 5. RCM of fluoralkenes with sulfonamides link (TON up to 15).

Then, taking into account the lack of report about the RCM of fluoroalkenes in the literature, the authors extended the scope of this reaction (Scheme 6). Surprisingly, the formation of the cyclopentane ring was not possible using these reaction conditions, while the six and seven-membered rings were obtained in good 73% and 77% yields, respectively (Scheme 6, Eq.a). In the case of the amine-linked precursors, the authors reported the deallylation side reaction, which completely prevent the formation of the five-membered nitrogen heterocycle,¹⁵ whereas the formation of the six-membered ring provided an excellent 83% yield (Scheme 6, Eq. b). Starting with ether-linked diene, the authors failed to obtain a pure sample of the oxygen heterocycle due to the instability and the volatility of the product (Scheme 6, Eq. c). A general observation claimed

by the authors is that RCM reactions of fluoroalkenes are typically slower than RCM reaction with their non-fluorinated congeners.



Scheme 6. Further RCM involving fluoroalkenes (TON up to 7.7).

Concomitantly, Haufe and co-workers reported the RCM of fluoroalkenes.¹⁶ They failed to perform the cyclisation of various precursors, especially linked by an oxygen atom (ether or ester links), whereas their non-fluorinated analogues successfully achieved their cyclisation (Figure 1).

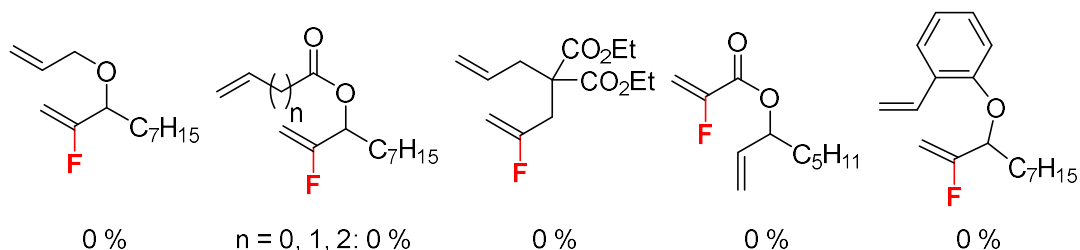
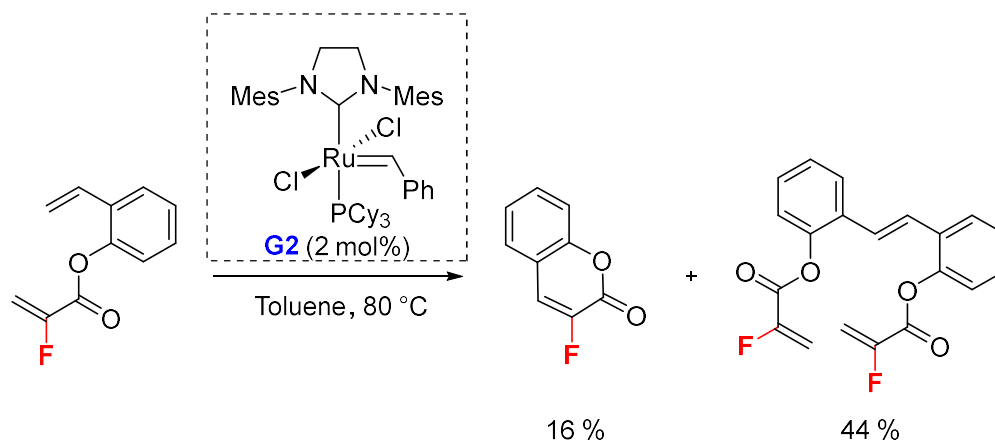


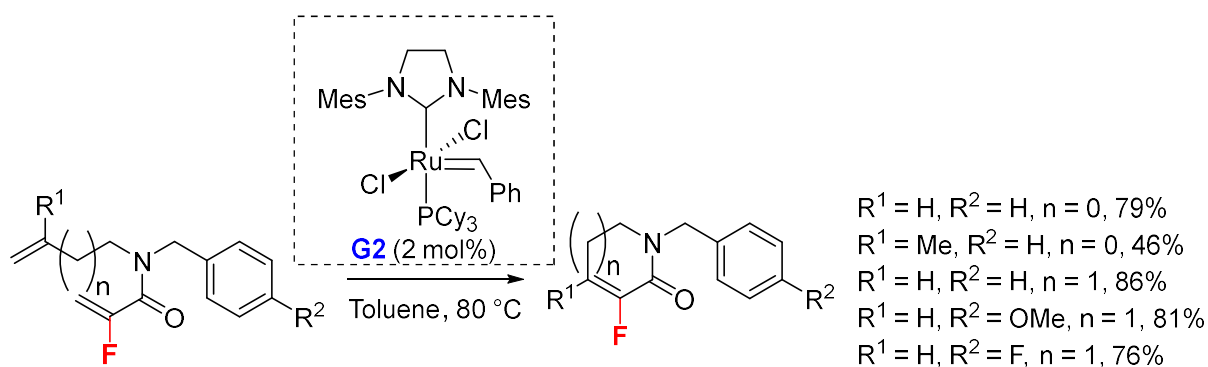
Figure 1. Non-reactive substrates in the RCM reaction.

In contrast, a rigid backbone was helpful in the reaction of a fluoroacrylate to give the desired 3-fluorocoumarin, in a poor 16 % yield, while 44 % of a homodimer side product resulting from the CM of the non-fluorinated double bond was isolated. Note that the high dilution conditions did not change the products ratio (Scheme 7).



Scheme 7. Synthesis of 3-fluorocoumarin by RCM.

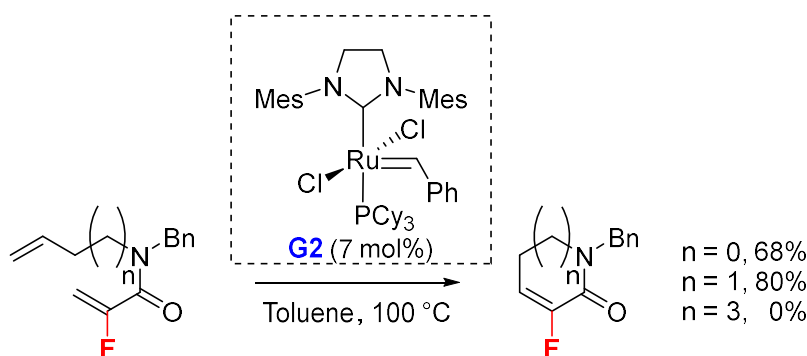
The authors noticed that the fluoroalkene part of a α,β -unsaturated carbonyl derivative seemed to be more suitable for RCM reactions. So the authors focused on the α -fluoroacrylamides moiety, which has a decreased π -electron density, as part of nitrogen-linked dienes and reported several examples of RCM reaction with this scaffold (Scheme 8).



Scheme 8. RCM of α -fluoroacrylamides (TON up to 43)

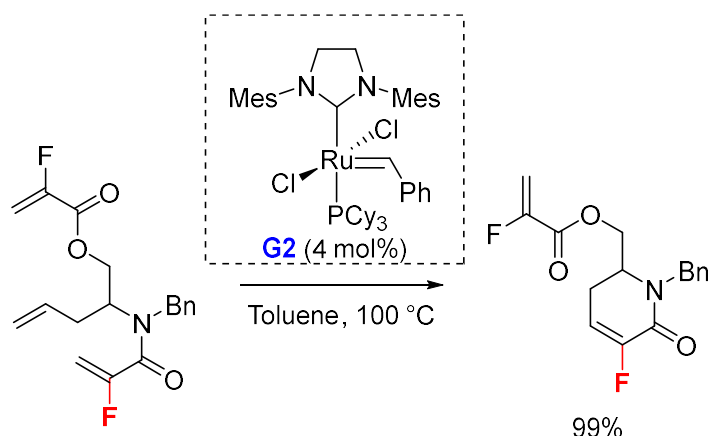
Five-membered rings γ -lactams, including one with a tetra-substituted fluoroalkenes, were successfully synthesized. In addition, the formation of six-membered rings afforded good yields (76-86%). Nevertheless, the precursors of the seven and eight-membered ring remained reluctant under these reaction conditions, and only the products resulting from the CM-homodimerisation of the non-fluorinated double-bond have been observed.

Simultaneously, Rutjes and co-workers performed the RCM reaction to obtain fluorolactams starting also from α -fluoroacrylamide substrates (Scheme 9).¹⁷



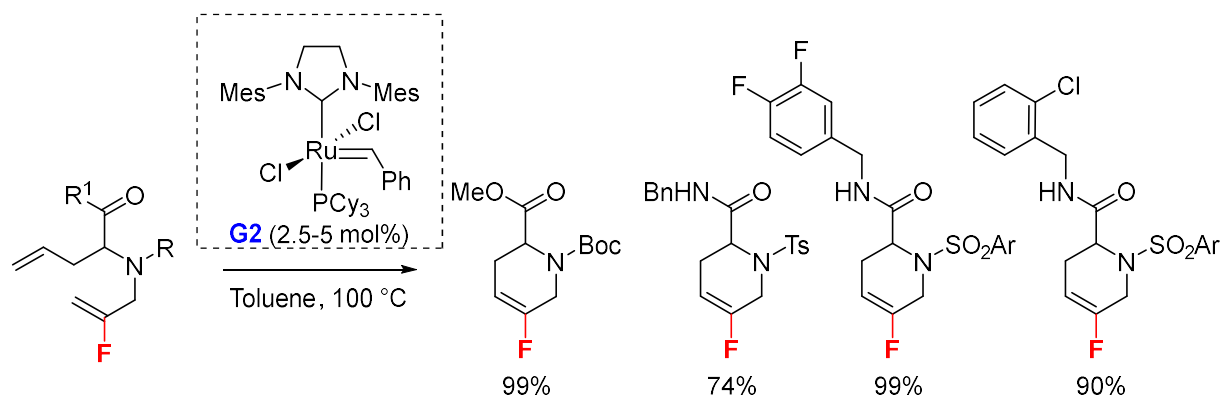
Scheme 9. Fluorolactams synthesis through RCM reaction (TON up to 11.4).

The five-membered ring was obtained with a good 68% yield without the presence of the side product resulting from the deallylation reaction, as previously reported by Brown and co-workers.¹⁴ The authors succeeded to form the six-membered ring with a good yield, but the reaction conditions did not afford the cyclisation towards an eight-membered ring. It appeared that the benzyl protecting group on the nitrogen atom was crucial for the cyclization to occur, the reaction being unsuccessful with non-protected amide. Furthermore, an allylglycinol-derived precursor underwent selective ring closure toward the six-membered lactam in an excellent 99 % yield (Scheme 10).



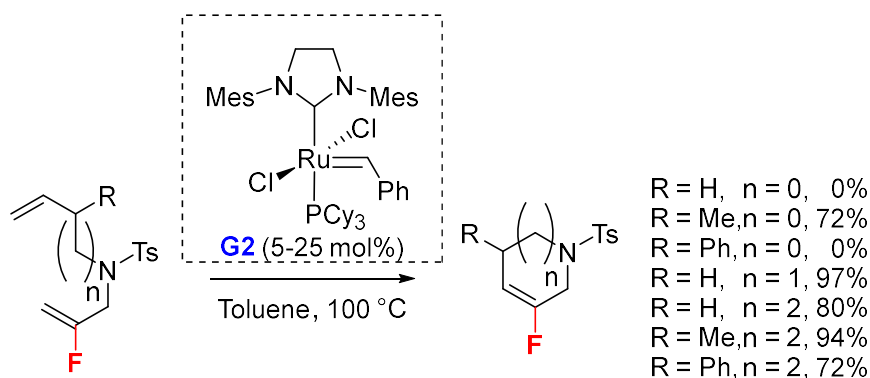
Scheme 10. Selective RCM of fluorolactam (TON = 24.75).

Few years later, Rutjes and co-workers reported additional RCM reactions with more functionalized new nitrogen-linked dienes.¹⁸ With the latter in hand, the authors successfully achieved the RCM reaction towards several novel fluorinated piperidines (Scheme 11). The product methyl-ester piperidine was obtained quantitatively using a lower catalyst loading. This may be explained by the nature of the side chain where the methyl ester did not interfere as much with the cyclization process as the more hindered amide substituents. This product was then used as a building-block toward further functionalization and formation of more elaborated heterocycles. The reaction carried out under microwave irradiations produced the *N*-tosyl benzamide piperidine in good yield, which constituted the first report of microwave-assisted RCM reaction with fluoroalkenes. Nevertheless, the authors noticed that the microwave activation did not lead to improved results in terms of kinetic and yield compared to conventional heating.



Scheme 11. RCM of nitrogen-linked dienes (TON up to 39.6).

The next year, the authors extended the scope of the RCM reaction to other fluorinated nitrogen heterocycles (Scheme 12).¹⁹

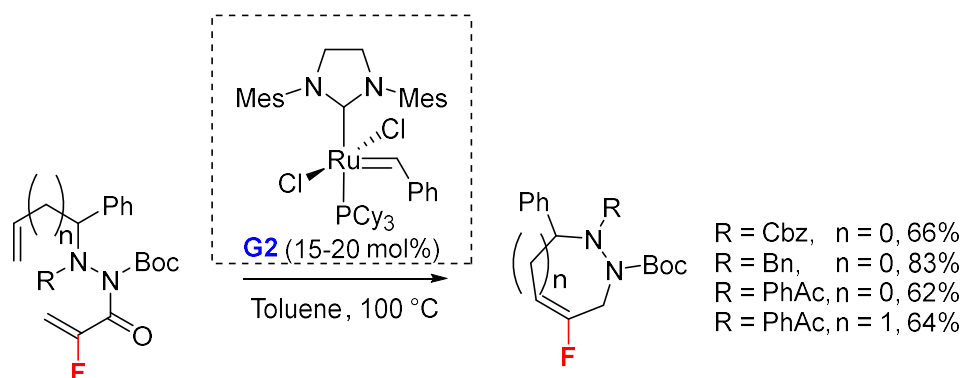


Scheme 12. Nitrogen heterocycles synthesis through RCM (TON up to 19.4).

The synthesis of non-substituted five-membered ring was not possible under these conditions and the precursors might be degraded by the deallylation reaction, already reported by Brown in 2003.¹⁴ Thanks to the introduction of a methyl substituent at the allylic position, the five-membered ring was obtained in a good 72% yield. However, the introduction of a phenyl ring at the allylic position did not afford the five-membered ring product. These results suggest that there is an optimum in the size of the allylic-substituent with respect to the cyclization event. Larger heterocycles could be obtained by this strategy. Regarding the formation of the eight-membered

ring, the expected product was not observed and the seven-membered ring was formed instead. This result might be explained by a faster isomerization of the terminal olefin to the internal position than the cyclization process. Then, the RCM of internal alkene and extrusion of propene led to the seven-membered ring. Finally, the formation of larger cycles was also investigated (twelve-, thirteen-membered rings) without success, even with higher catalyst loading or extended reaction time.

Later, the same group achieved RCM reaction of fluorinated cyclic hydrazines.²⁰ The presence of a phenyl moiety at the allylic position of the non-fluorinated olefin slowed down the isomerization process and increased the yield of the reaction. In order to propose a flexible pathway to post-functionalization, both nitrogen atoms were orthogonally protected (Cbz, Bn, PhAc) (Scheme 13).

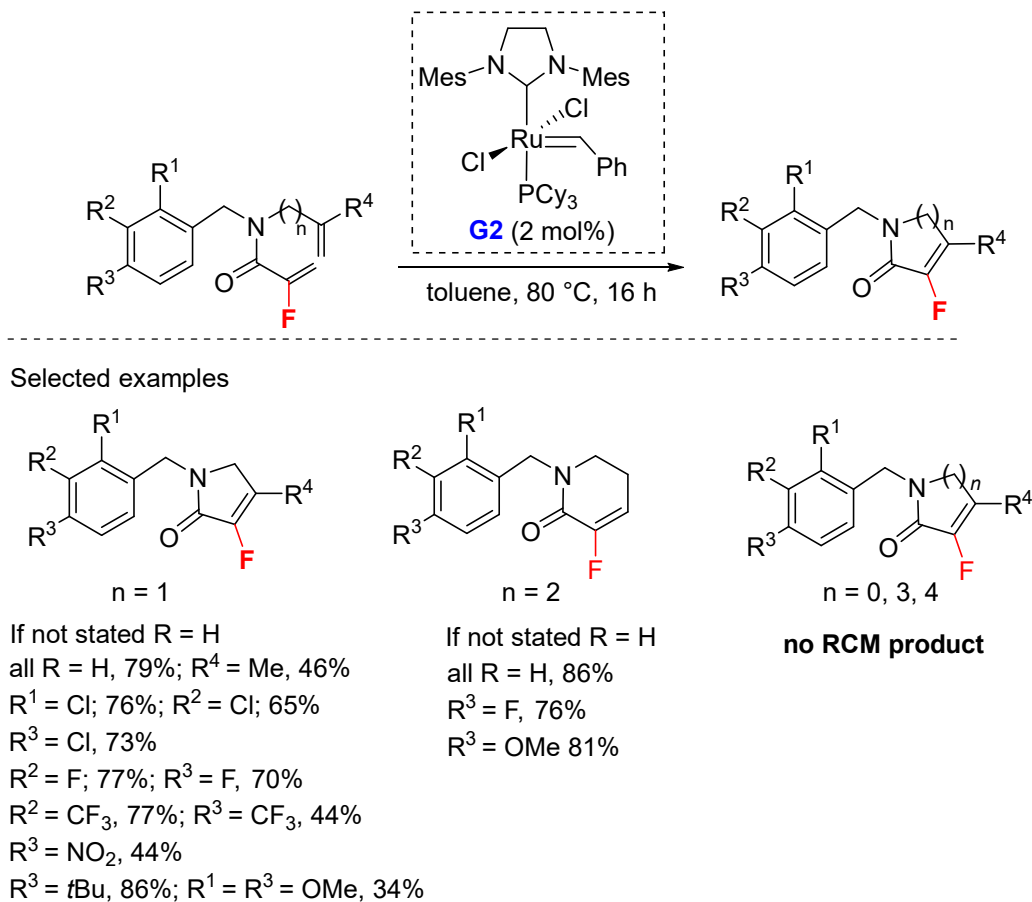


Scheme 13. RCM synthesis of fluorinated hydrazines (TON up to 5.5).

The formation of the six-membered rings was successfully achieved in moderate to good yield (62-83 %) and a seven-membered ring could also be obtained in 64% yield. However high catalyst loading (15-20 mol%) was required to reach full conversion.

Further, in 2014 Haufe and co-workers described the synthesis of several α -fluorinated α,β -unsaturated lactams, and lactones via an RCM of vinyl fluorides.²¹ Their initial focus was to

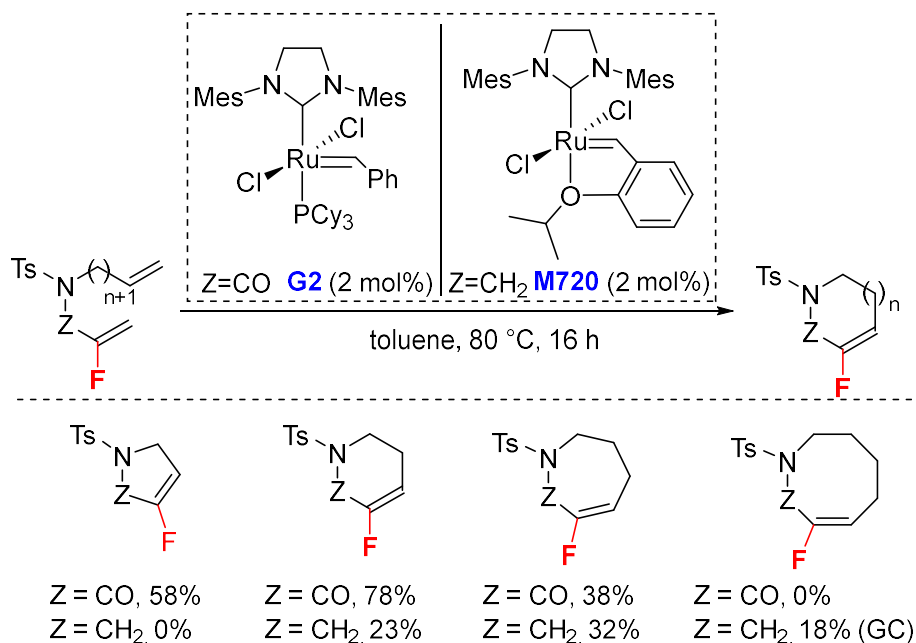
synthesize *N*-benzyl α,β -unsaturated α -fluoro γ - and δ -lactams starting from appropriate benzylamines with the use of second generation Grubbs catalyst **G2**. (Scheme 14)



Scheme 14. RCM of functionalized benzylamines (TON up to 43).

The RCM reactions leading to γ - and δ -lactams generally gave good to modest yields (ranging from 34% to 86%) depending on the starting material functionalization with a slightly better yield toward formation of a six-membered ring. It was noted that the introduction of electron-donating substituent on the phenyl ring of benzylamine increased the reaction yield, while electron-withdrawing groups hampered the efficiency of the reaction. Notably, the method failed to deliver seven- and eight-membered rings even using substrates bearing electron-donating groups, whereas these cycles can be easily reached for nonfluorinated analogues under similar conditions.²² The

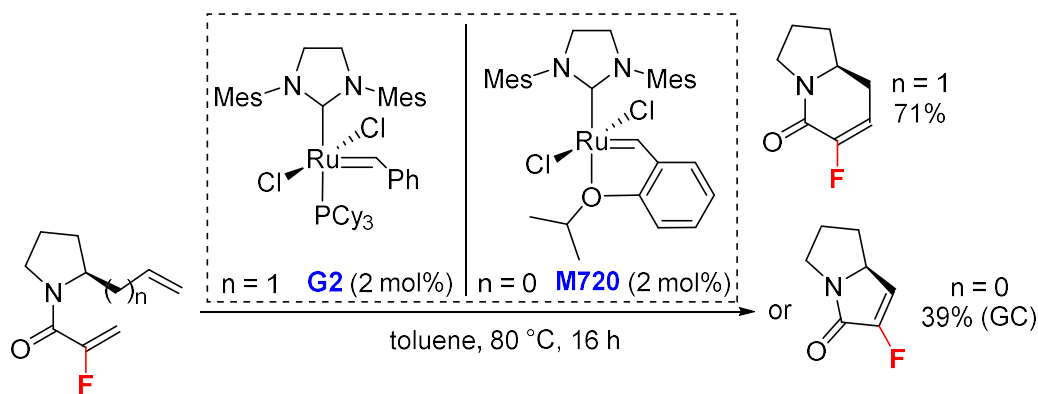
authors also disclosed the synthesis of fluorinated α,β -unsaturated *N*-tosyl lactams, using the second generation Grubbs catalysts **G2** and preparation of fluorinated *N*-tosyl heterocycles with the Hoveyda-Grubbs precatalyst **M720**. (Scheme 15)



Scheme 15. RCM of monofluorinated *N*-tosyl-substituted aza- α,ω -diene system (TON up to 39).

The applied methodology allowed for a facile preparation of γ - and δ -lactams, while ε -lactam was formed in a low yield and ζ -lactam was not formed and only the homodimer formation was observed. Interestingly, despite previous reports,¹⁹ the authors found **G2** complex as inefficient catalyst for the preparation of *N*-tosyl heterocycles, thus the more active **M720** catalyst was used for their preparation. Despite this enhanced activity of the catalyst, no formation of *N*-tosylpyrroline was observed and only six- and seven-membered ring heterocycles were isolated in very low yields. The eight-membered ring heterocycle was observed by GC but was not isolated, limiting the synthetic interest of the methodology. Accordingly, in light of these results, *N*-tosylamide functionality (Z=CO) seems to benefit RCM reaction compared to the *N*-tosylamines (Z=CH₂).

Additionally, Haufe and co-workers extended the scope of the RCM reaction toward fluorinated analogues of bicyclic alkaloids (Scheme 16), a class of desirable molecules due to their possible biological activity.²³

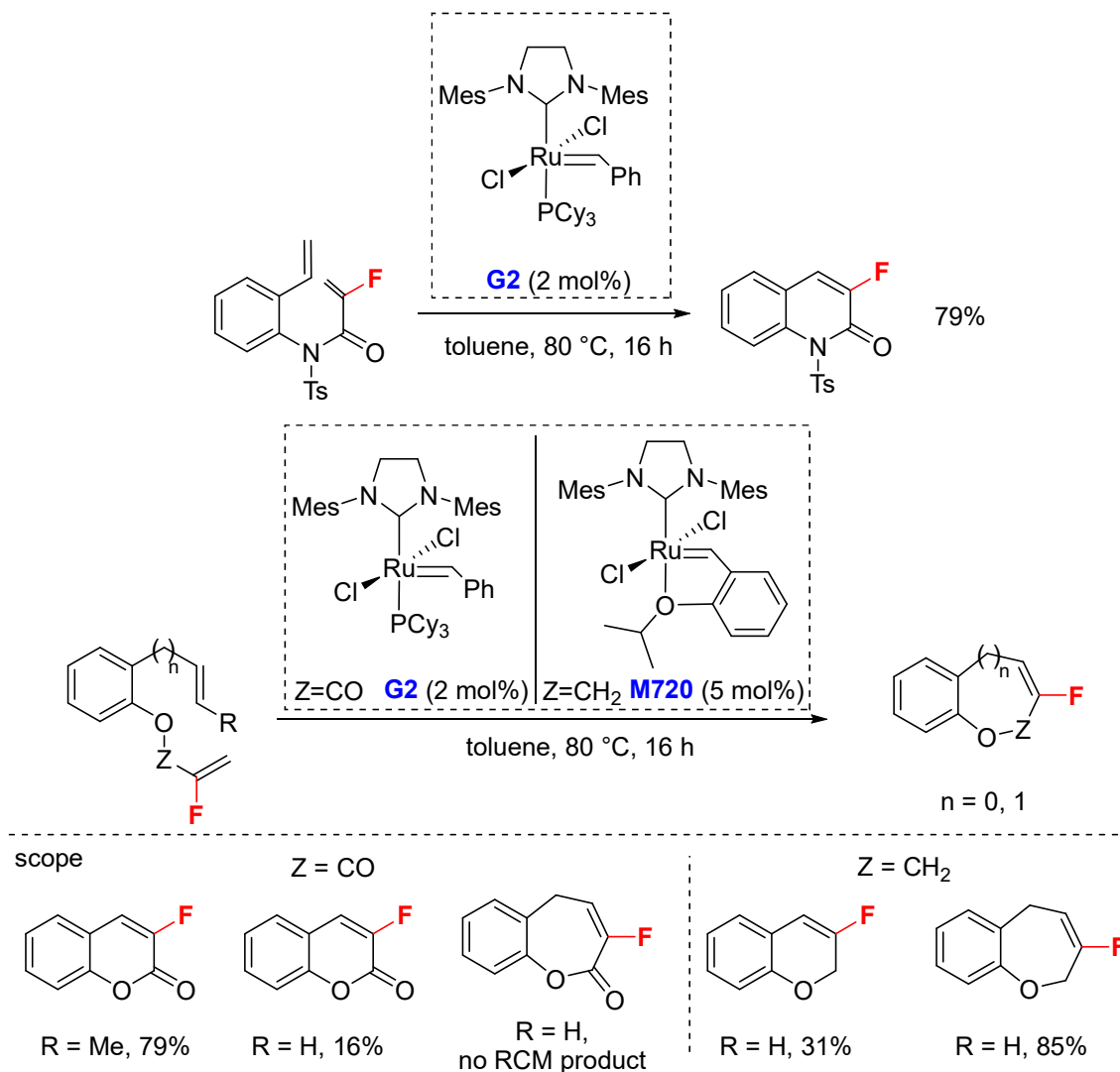


Scheme 16. Synthesis of fluorinated analogues of bicyclic alkaloids via RCM reaction (TON up to 35.5).

Starting from the appropriate enantiopure fluoroolefins, the formation of (*S*)-2-fluoro-5,6,7,7a-tetrahydropyrrolizin-3-one and (*S*)-6-fluoro-2,3,8,8a-tetrahydroindolizin-5(1H)-one was reported. The 5-membered ring lactam cannot be isolated due to a poor stability, while the six-membered ring analogue was isolated in 71% yield, and its structure was confirmed by the XRD. Noteworthy, the addition of a second carbonyl function at the α position of nitrogen, completely hampered the RCM reactions and the formation of the corresponding imides, limiting the presented methodology to the sole formation of the amide derivatives.

Additionally, the authors described an elegant 3-steps synthesis of the *N*-benzyl-3-fluoroquinolone, with a final RCM reaction catalysed by **G2** in a good 79% yield. Encouraged by these results, they further investigated analogues of fluorinated *O*-heterocycles synthesis (Scheme 12). For fluorinated lactams, **G2** was applied, giving a poor result for simple vinyl substrates. On the contrary, tri-substituted olefins as the starting material gave a good 74% yield, due to a low

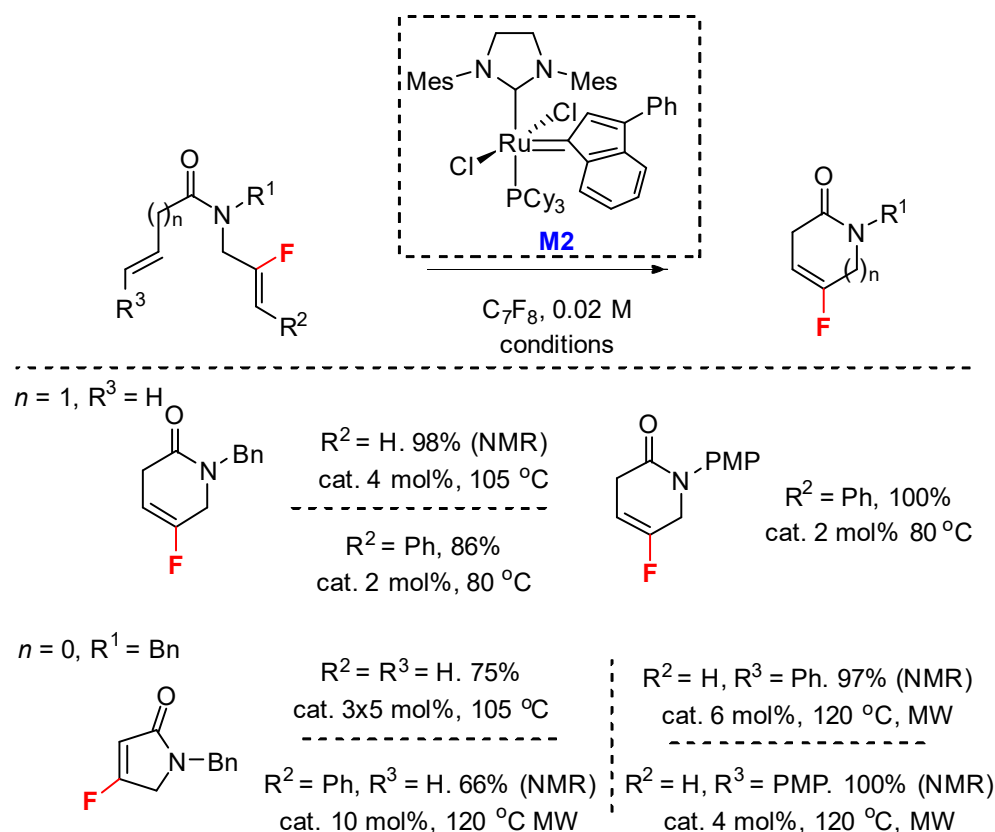
homodimerization side product formation. Note that the side homodimerization reaction was the main reaction observed by the authors when using fluorinated *gem*-disubstituted alkenes. Additionally, six- and seven-membered fluorinated *O*-heterocycles were prepared using the more active **M720** catalyst to facilitate the RCM reaction (Scheme 17).



Scheme 17. Preparation of *N*- and *O*-heterocycles with a fused benzene ring via RCM reaction (TON up to 39.5).

In 2014, our groups contributed to the field by developing the synthesis of relevant six- and five-membered fluorinated lactams via the RCM reaction, employing the **M2** precatalyst (Scheme

18).²⁴ Similarly to Haufe,²¹ we observed the beneficial use of a trisubstituted olefin as a substrate. Detailed kinetic studies revealed the higher efficiency of olefin bearing a bulky phenyl group with electron-donating substituent to facilitate RCM, although electronic and steric factors were not deconvoluted. The applied strategy allowed the preparation of six-membered ring lactams with a double bond not conjugated to the amide group in very good yields, under relatively mild reaction conditions. More challenging five-membered ring lactams required higher catalyst loading and reaction temperatures, as well as microwave irradiation. Although highly effective, the presented RCM reaction required octafluorotoluene as the solvent to enhance the performance of ruthenium catalysts²⁵ increasing both its cost and environmental fingerprint; nevertheless, this perfluorinated solvent could be recovered by distillation. In parallel, the additional sacrificial olefin substituents lost during RCM increase reaction output while decreasing atom efficiency of the process. To date, this study reported the highest TON value obtained in RCM reaction with fluoroalkenes.

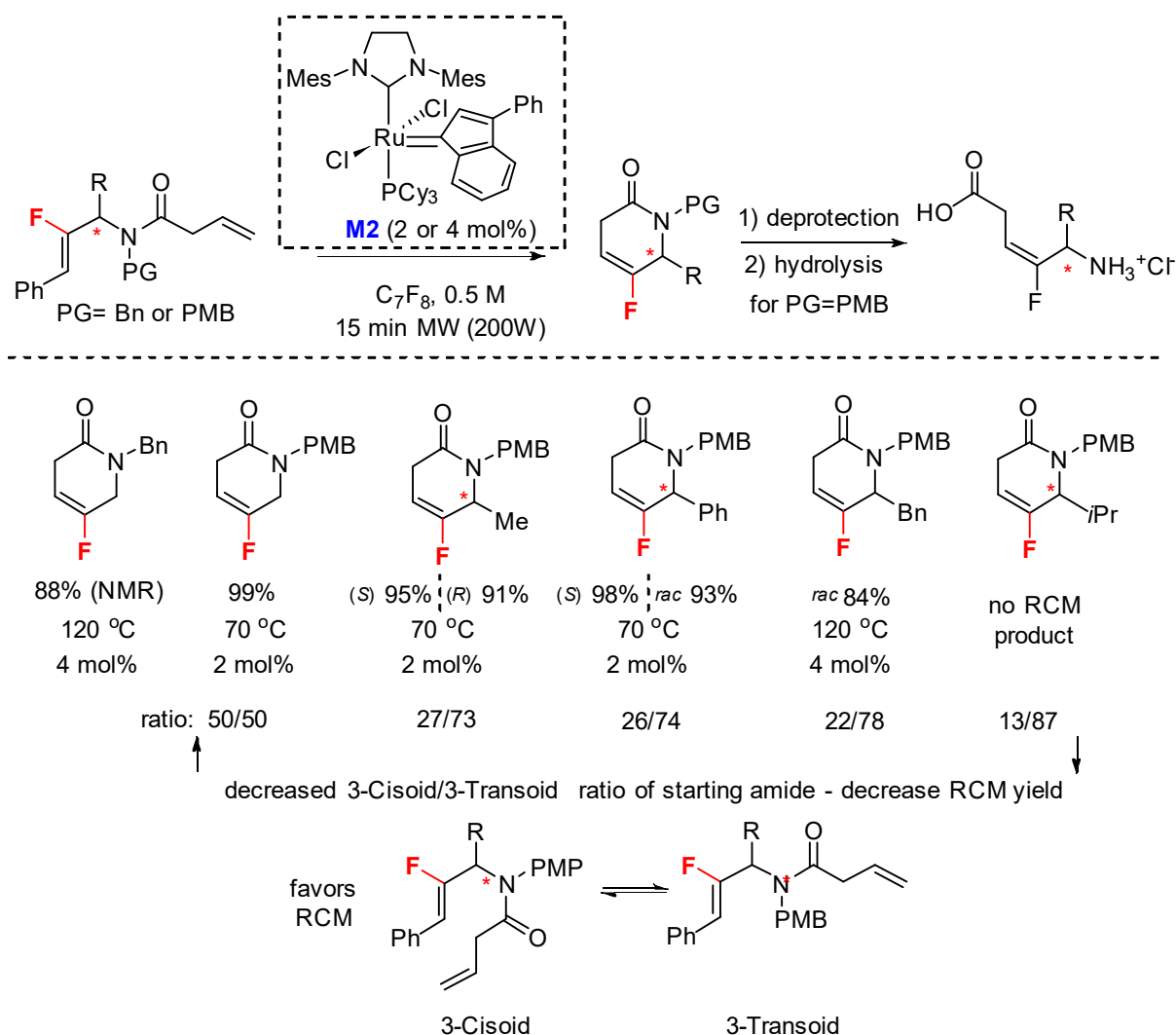


Scheme 18. Synthesis of six- and five-membered fluorinated lactams via the RCM reaction using **M2** catalyst (TON up to 100).

In 2016, we extended developed RCM reaction conditions, *i.e.*, **M2** catalyst, octafluorotoluene as the solvent, and microwave irradiation to get δ -lactams with additional substituents at the α -position of the nitrogen atom.²⁶ Interestingly, the size of the substituent had a significant impact on the yield of the metathesis reaction. This effect was attributed to the conformation of the starting olefin, which adopt a pseudo-3-cisoid form to facilitate the ring closure, as confirmed by NMR studies. Olefins, primarily in 3-transoid conformation, gave lower yields of desired products or did not engage in RCM reaction. Of note is that the olefin substrate bearing a non-protected amide functionality, strongly favouring the transoid form, was inactive, emphasizing the need for this functionality protection with benzyl or *para*-methoxyphenyl group. (Scheme 19). Additionally,

the obtained enantiopure δ -lactams were further converted into fluoropseudopeptides according to a straightforward deprotection/hydrolysis sequence, taking advantage of the bioisoterism of the fluoroalkene moiety to the peptide bond. Such molecules are plausible therapeutic agents²⁷ with increased *in vivo* half-life due to their tendency to stabilize peptides from enzymatic degradation.^{6a-}

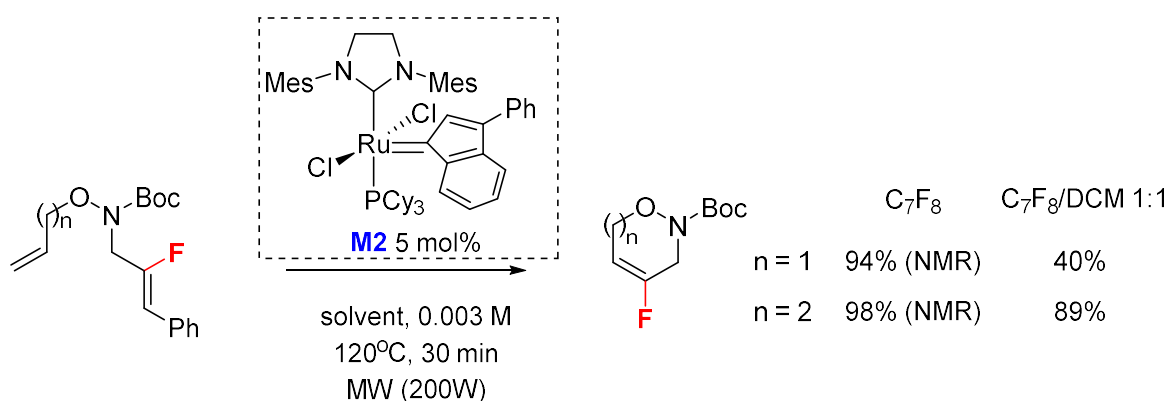
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Scheme 19. Synthesis of δ -lactams and influence of amide conformation on RCM reaction yield.

Application to the synthesis of fluoropseudopeptides (TON up to 49.5).

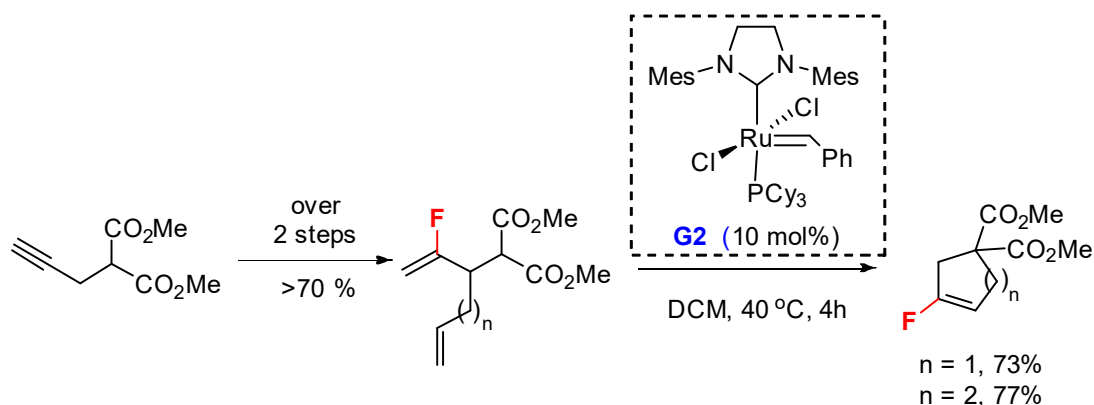
Further in 2018, we extended our methodology toward preparation of 4-fluoro-3,6-dihydro-1,2-oxazine and 4-fluoro-3,6,7-trihydro-1,2-oxazepine.²⁸ According to our previous results, using the **M2** precatalyst in perfluorinated toluene with trisubstituted olefins gave the desired products in almost quantitative yield. The drawback of this effective RCM reaction was the requirement of highly diluted media to avoid the homodimerization reaction, which therefore increase the amount of the expensive perfluorinated solvent. To address this problem, the RCM reaction was further optimized and a 1:1 mixture of DCM:octafluorotoluene was suitable, decreasing considerably the cost of the process at the cost of a slight decrease of the reaction yield (Scheme 20).



Scheme 20. Synthesis of fluorinated 1,2-oxazine and 1,2-oxazepine via RCM reaction (TON up to 17.8).

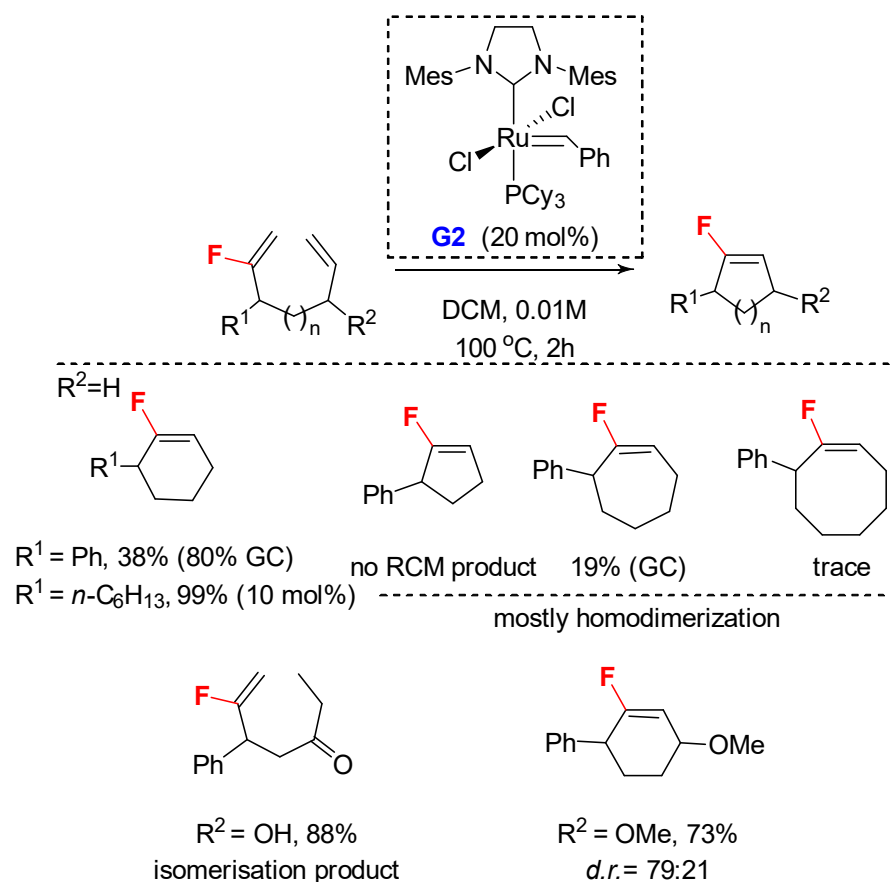
In 2014, Hammond, Xu and coworkers reported a new hydrofluorination reaction of alkynes, which allowed the easy preparation of RCM reaction starting materials.²⁹ To showcase the synthetic utility of the prepared compounds, the conditions developed by Brown¹⁴ were applied to furnish 5- and 6-membered fluorocarbocycle rings in ca 70% yield. (Scheme 21). The yield obtained for the 6-membered ring was similar to the one reported by Brown. Nevertheless, in sharp contrast to the previous report (see scheme 6), the successful formation of 5 membered-ring was

observed.¹⁴ It has to be highlighted that Brown used ethyl esters while Hammond and Xu used methyl ones, which might be the reason for such a drastic reactivity difference. Unfortunately, the authors omitted synthetic details and compounds characterization for RCM products what impede comparison between two methods.



Scheme 21. Synthesis 5- and 6-membered fluorocarbocycle rings (TON up to 7.7)

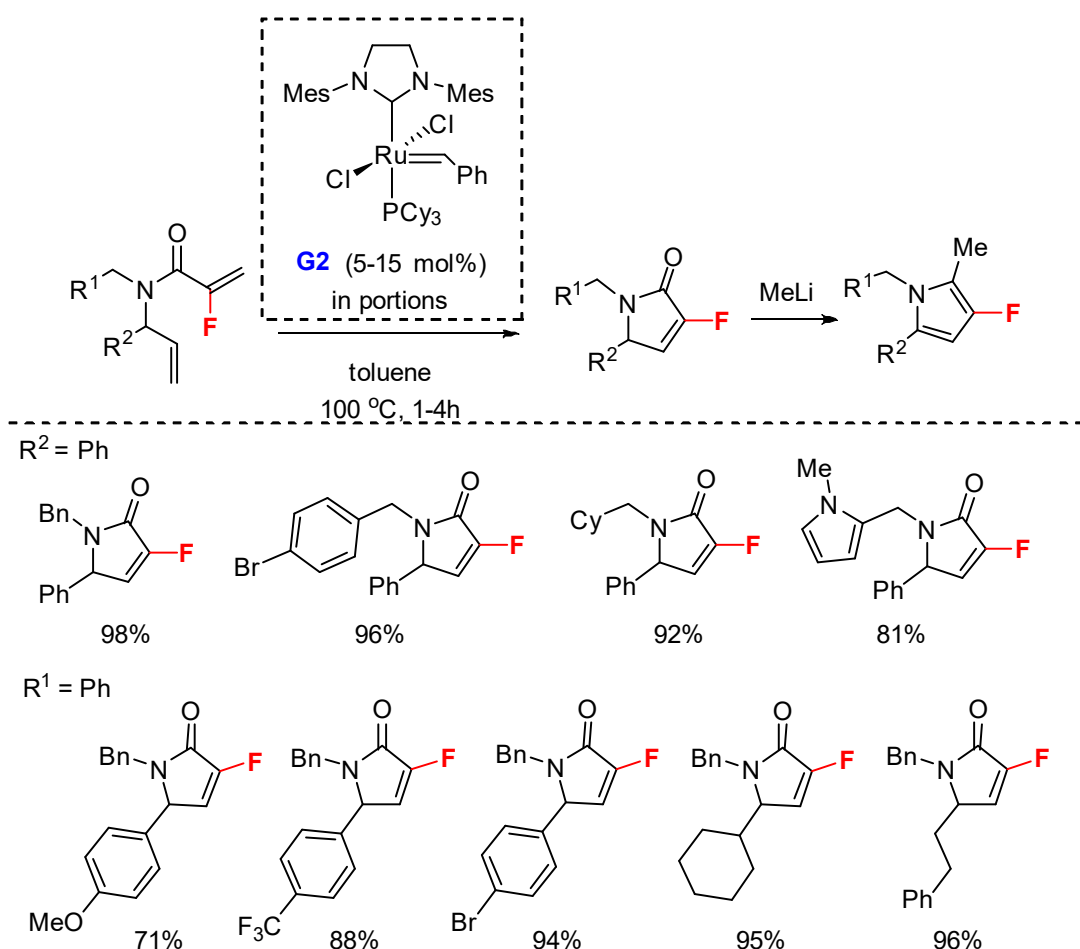
In 2014, Konno also developed a highly regioselective protocol for allylic substitution of β -fluoroallylic phosphates, which gave rise to structurally diverse olefins suitable as starting materials for the RCM reaction.³⁰ 6-Membered fluorocarbocycles were prepared and isolated in good yields, while attempts toward the formation of other ring sizes (5,7,8) mostly led to the homodimerization products. Interestingly, the authors attempted the RCM reaction with a substrate bearing an allylic hydroxy group, however only isomerization into the corresponding ketone was observed. However, the addition of a methoxy group at the allylic position allowed the smooth preparation of the desired product (Scheme 22). Of note is that this allylic ether functionality does not impact significantly the yield of the RCM reaction.



Scheme 22. Preparation of various size phenyl substituted fluorocarbocycles with **G2** (TON up to 9.9).

In 2015, the group of Marquez disclosed the synthesis of a small library of relevant fluorinated δ -lactams as potential building blocks for medicinal chemistry.³¹ The RCM reaction of fluorinated olefins with amide functionality protected with *para*-methoxyphenyl group bearing various substituents at the α -position of the nitrogen atom was carried out using 2.5 mol% of the **G2** precatalyst. Several substituted RCM substrates were tested, including aryl, bromoaryl, alkyl, furan, and tosyl protected pyrrole, giving desired products in very good yields. Moreover, the synthetic utility of the fluorinated products was further emphasized through Suzuki-Miyaura cross-coupling (for bromoaryl derivative), *para*-methoxyphenyl group deprotection, and

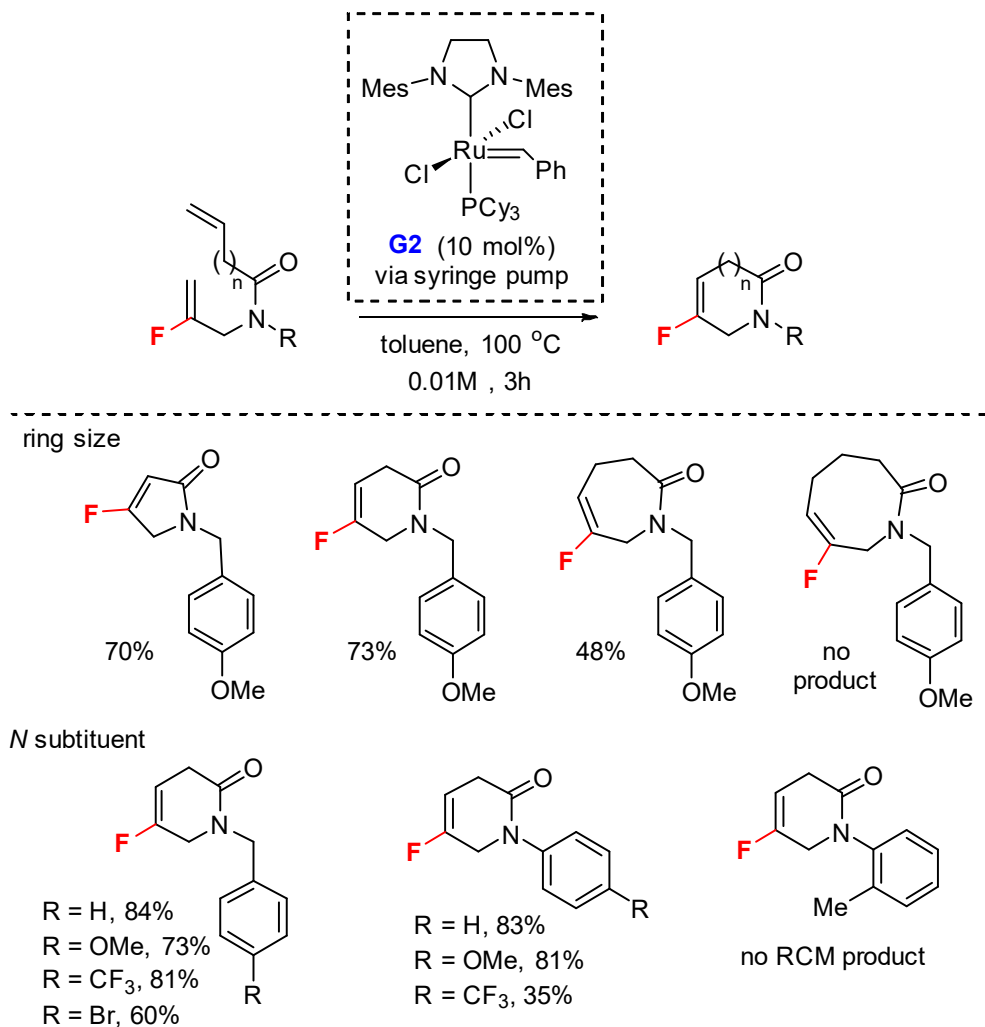
relevant tetrafunctionalized 3-fluoropyrroles in good yields,³³ after reaction with methyllithium. These results again indicated the challenging formation of the 5- vs 6-membered ring via RCM of fluoroalkene. In comparison to the previous work of the same group where δ -lactams were prepared with the use of 2.5 mol% mol Ru-catalyst loading, γ -lactams required at least 5 mol% of catalysts portion wised. The effect of the electron-withdrawing substituents can be noted from the two reports from Marquez and co-workers. Regarding the preparation of geometrically favoured 6-membered ring, the substituents did not impact the reaction efficiency, whereas the formation of the more challenging 5-membered rings required a higher catalyst loading (15% for compound with CF₃ group and 10% for Br atom, respectively). This difference suggested the crucial role of electronic properties of the olefins for the formation of the challenging 5-membered ring.



Scheme 24. Synthesis of γ -lactams via RCM reaction and their further transformation into tetra-functionalized 3-fluoropyrroles (TON up to 19.2).

A new straightforward and cost-effective protocol for the synthesis of *N*-substituted 2-fluoroallyl amines starting from methyl 2-fluoroacrylate was developed by Lei and co-workers in 2016.³⁴ These molecules were subsequently used by the authors as starting materials in RCM reaction to obtain the fluorovinyl-decorated five-, six- and seven-membered ring lactams (Scheme 25). A careful screening of the RCM reaction conditions revealed that the slow addition of a toluene solution of the **G2** precatalyst at 100 °C under an inert atmosphere allowed for the enhancement of activity and life-time of catalyst, providing the desired products in good yields. Surprisingly, usually considered as better-performing, the 2nd generation Hoveyda-Grubbs precatalyst **M720** and 3rd generation Grubbs catalyst bearing 3-bromopyridines **M300** were not able to surpass the **G2** catalyst activity. The substrate scope highlighted that both γ - and δ -lactams were easily accessible with the developed conditions in ca 70% yield, while a seven-membered ring example was reported in a modest 48% yield and the eight-membered ring was not accessible. Additionally, the influence of nitrogen atom substituents on the RCM reaction yields was evaluated. Varying groups at the *ortho* position of the phenyl ring of benzyl moiety did not have a significant effect on the reaction outcome. Nevertheless, when the aromatic ring bearing an electron-withdrawing CF₃ substituent in the *para* position was directly connected to the nitrogen atom, a significant drop of the yield occurred. It was also observed that the presence of an *ortho* methyl substituent on the phenyl ring hampered the cyclization. Although no details for this phenomenon were provided, a plausible explanation for such a reactivity would be a preferential transoid geometry of the starting olefin due to the bulkiness of nitrogen atom substituent, which prevents the RCM reaction.²⁶ The authors also attempted RCM reaction with starting materials having two fluoroalkene moieties to

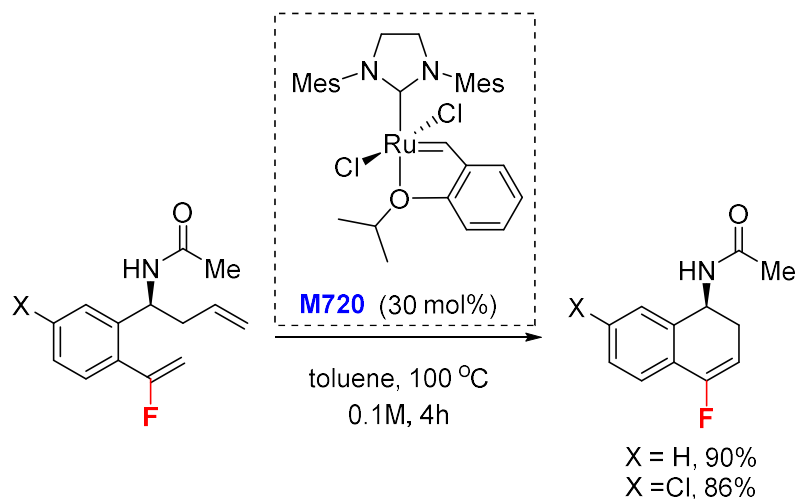
deliver the tetrasubstituted olefin with two fluoride substituents, however the reaction failed to provide the desired product, highlighting a further challenge to overcome in the reviewed area.



Scheme 25. RCM of N-substituted 2-fluoroallyl amines and their products (TON up to 8.4).

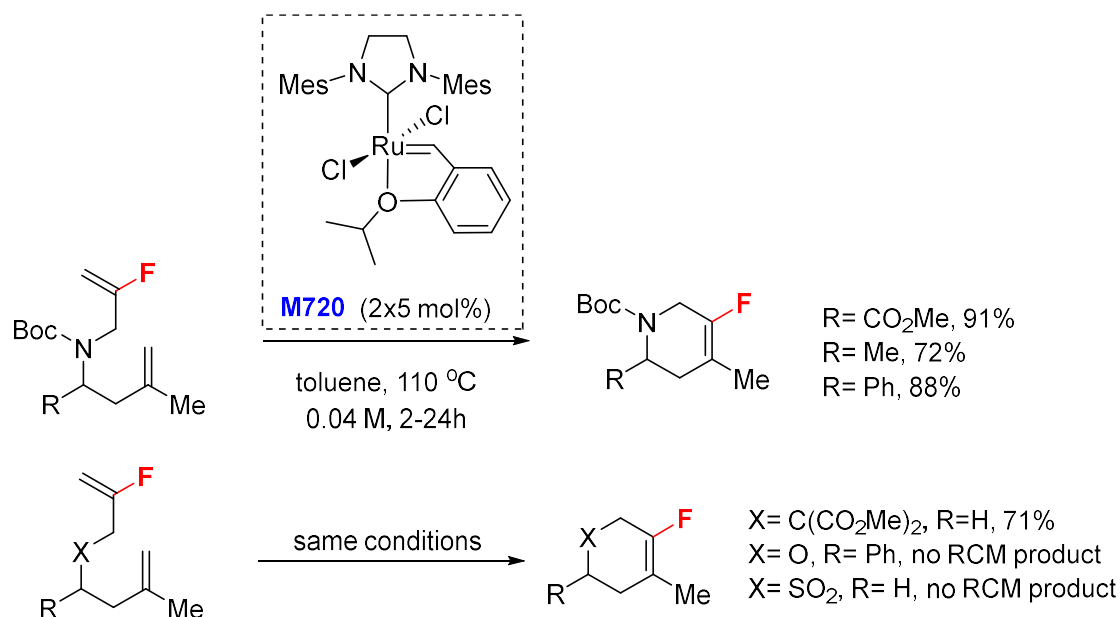
Another example of the RCM reaction with fluoralkenes was reported by Barrio, Fustero and co-workers in collaboration with Haufe in 2016.³⁵ A substoichiometric amount of the 2nd generation Hoveyda-Grubbs precatalyst **M720** was used to synthesize two 1-amino-1,2-dihydronaphthalene derived vinyl fluorides (Scheme 26). Although a high catalyst loading (30 mol%) was used, which could be explain by the presence of a non-protected amide residue, the

desired products were isolated in very good yields, 86% and 90%, respectively. The RCM reaction of the analogue bearing a *tert*-butanesulfinamide moiety, instead of an acetamide group, failed to give the desired product further highlighting the importance to tailor the amide function for receiving desirable synthetic outcomes in RCM transformation.



Scheme 26. Synthesis of 1-amino-1,2-dihydronaphthalenederived vinyl fluorides via the RCM reactions (TON up to 9).

Among a series of tetrasubstituted olefin prepared via the RCM reaction by Michelet, Starck and co-workers in 2020, several compounds bearing a fluoroalkene moiety were prepared (Scheme 27).³⁶ The use of the 2nd generation Hoveyda-Grubbs **M720**, which was better catalyst than **G2**, allowed the synthesis of three fluorinated tetrahydropyridines and one. Unfortunately, this methodology failed to deliver *O*-heterocycles and cyclic sulfone. The developed methodology is a good atom-economical example, giving fluorinated tetrahydropyridine scaffold as valuable building blocks for medicinal chemistry.³⁷ However further investigations of both the substrate scope, as well as the suitable ring size, is required to demonstrate its synthetic utility.



Scheme 27. Synthesis of fluorine containing tetrasubstituted olefin via the RCM reactions (TON up to 9.1).

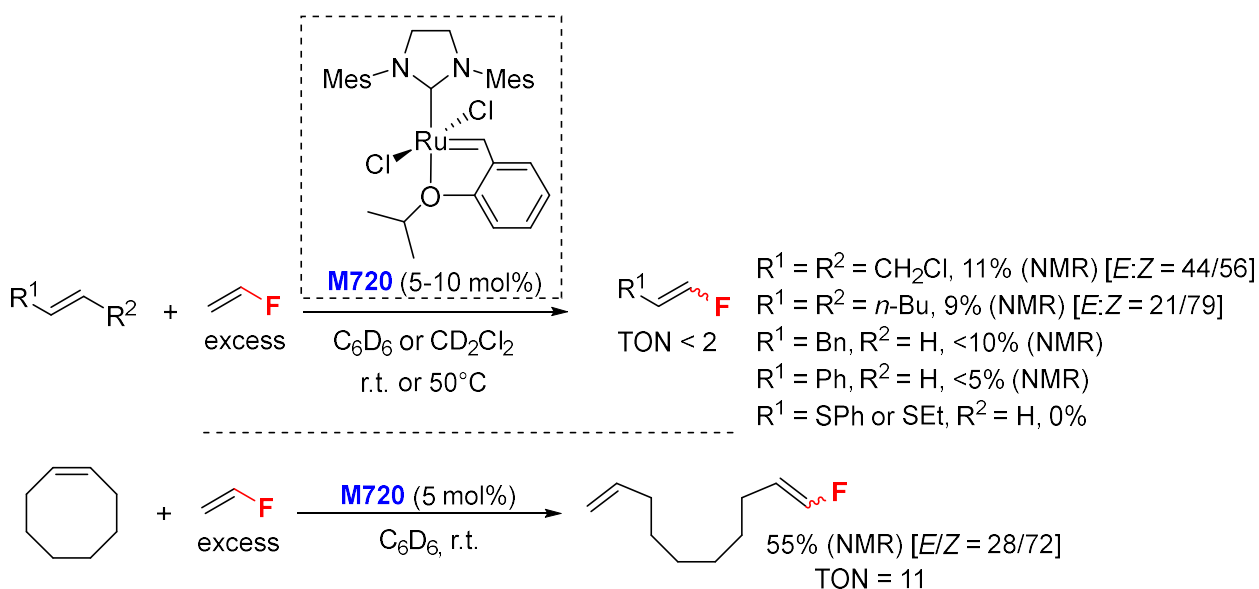
II) Cross-Metathesis

Reports dealing with metal-catalyzed CM reaction of fluoroalkenes are very scarce in the literature and can be divided in two categories: the Ruthenium- and Molybdenum-catalyzed reactions.

A) Ruthenium-catalyzed Cross-Metathesis

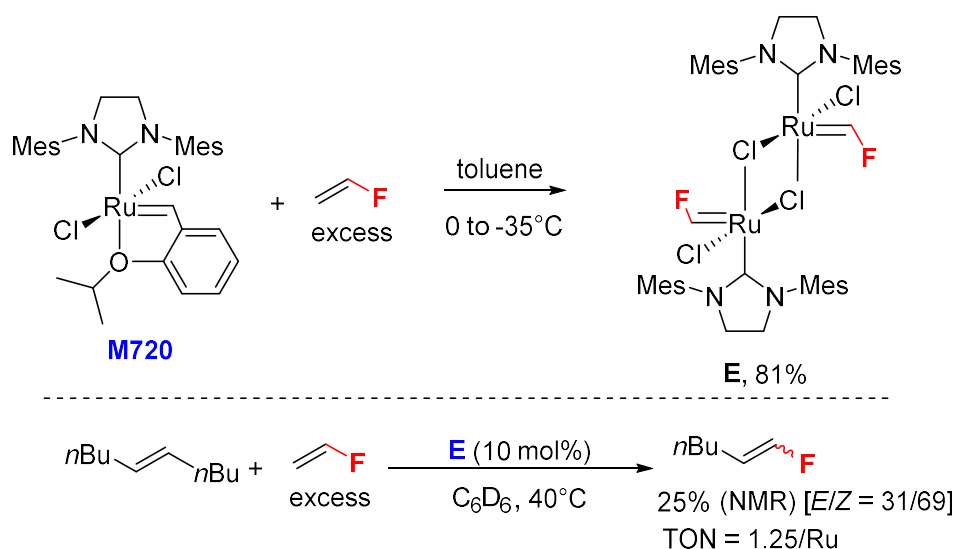
In 2009, Johnson and co-workers studied the CM of vinyl halides and reported the first examples of CM involving vinyl fluoride (boiling point: -72°C).³⁸ Several catalysts were tested and the Grubbs II (**G2**) and Hoveyda-Grubbs II (**M720**) precatalysts allowed to obtain fluoroalkenes from productive CM, albeit in low yields and poor turnover numbers (Scheme 28). From internal or terminal alkenes, yields were up to 11% with a TON up to 2. The authors only identified a monofluoroalkylidene as a newly formed carbene in the reaction, too stable to continue the CM process. Heating the reaction media to circumvent this issue did not

improve the yields but only led to the decomposition of the catalyst. The ring opening CM of cyclooctene allowed to get 55% of the desired product thanks to the ring strain release, providing an enthalpic driving force towards the alkylidene form of the catalyst.



Scheme 28. First examples of CM with vinyl fluoride (TON up to 11).

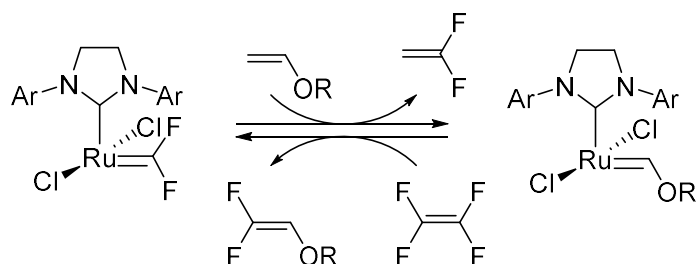
Mixing **M720** with an excess of vinyl fluoride allowed to isolate a new monofluoromethylidene complex **E** (Scheme 29). The latter can be used in CM reaction and could be a possible intermediate of the metathesis process. Nevertheless, this complex only furnished low yields due to a poor solubility, as well as a poor stability (complete decomposition within twenty minutes at room temperature).



Scheme 29. Synthesis and reactivity of a monofluoromethylidene dimer complex.

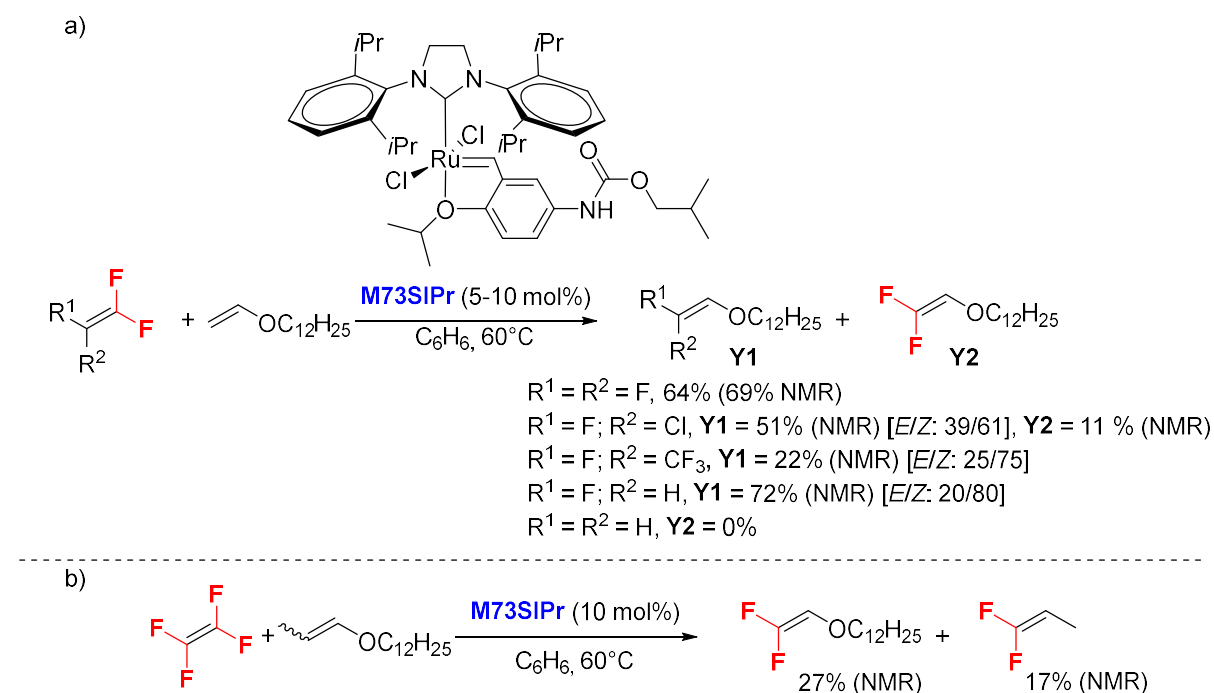
To resume, only fair to low yields of fluoroalkenes have been obtained, with a TON up to 11, using gaseous vinyl fluoride as reagent. Nevertheless, these results showed that the difficult CM process with fluoroalkenes was possible and opened the way to improvements.

In 2015, Takahira and Morizawa developed an elegant CM reaction with polyfluoroalkenes.³⁹ First, they submitted the tetrafluoroethylene in reaction with the **G2** precatalyst, allowing to obtain the difluorocarbene complex **A** in 86%. This result prompted them to study the reactivity of tetrafluoroethylene and analogues in CM reaction. Taking into account the stability of the difluorocarbene complex **A**, the authors developed a Fischer carbenes⁴⁰ interconversion between difluorocarbene and alkoxycarbene to synthesize new fluoroalkene derivatives (Scheme 30).



Scheme 30. Principle of Fischer carbenes interconversion.

After a screening of catalysts, the M73SiPr precatalyst was selected to carry out the CM reaction (Scheme 31).



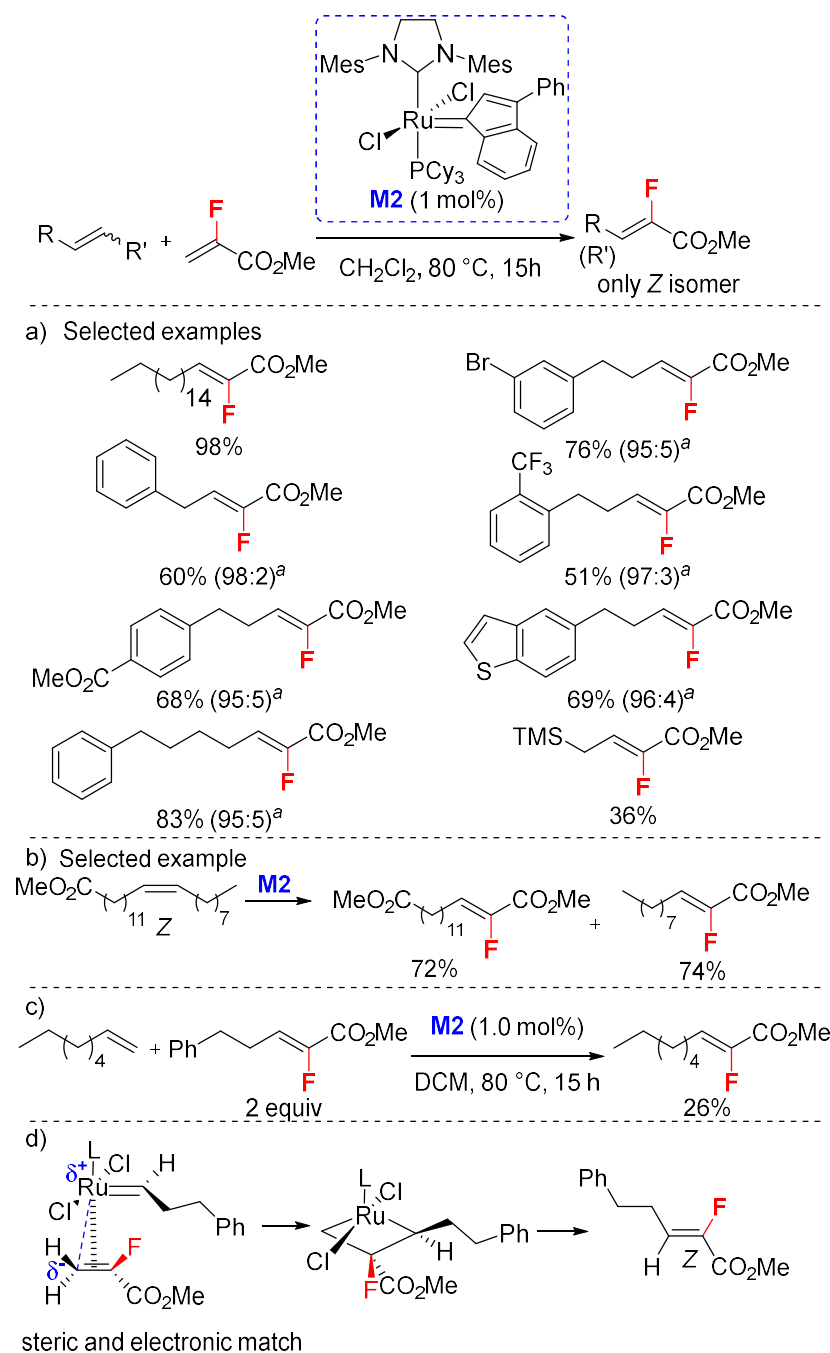
Scheme 31. CM reaction with tetrafluoroethylene and analogues through Fischer carbenes interconversion (TON up to 7.2).

Four different fluoroalkenes have been synthesized in a range of yields from 22 to 72% with a TON up to 7.2 (Scheme 31, Eq. a). Worthy of note that unsymmetrical fluorinated alkenes led to

a *E/Z* mixture of products. A last reaction called fluoroethenolysis has also been described providing two difluoroalkenes in low yields (Scheme 31, Eq. b). Results from the mechanistic studies confirmed the Fischer carbene interconversion between difluorocarbene and alkoxycarbene suggested by the authors. This very appealing strategy, nevertheless required the use of hazardous and difficult-to-handle chemicals. Moreover, the reaction has only been developed with alkylvinylether as reagents with fluoroalkenes, which restricted the scope of the reaction.

Very recently, our research group succeeded to synthesize, for the first time, trisubstituted monofluoroalkenes by ruthenium-catalyzed metathesis.⁴¹ Type I olefins⁴² were reacted with ethyl 2-fluoroacrylate, a commercially available, inexpensive (0.52 \$/mmol) and liquid reagent (boiling point: 95°C), convenient to use. Constrained olefins are poor substrates for the reaction, while more flexible olefin revealed to be excellent substrates. Indeed, as reported by Grela few years ago,^{7b} put further the reactive olefin from a moiety being able electronically or sterically to destabilize the substrate, allowed to succeed in performing CM reaction with fluoroalkenes. More than forty *Z*-fluoroalkenes have been stereoselectively synthesized from terminal, cyclic or internal olefins with 1%mol of the **M2** precatalyst (Scheme 32). For the first time a TON of 175 has been reached with fluoroalkenes. The reaction tolerated the presence of various substituents (OMe, Cl, Br, CO₂Me...) at any position of the (hetero)aromatic moiety, which can be in α , β , γ or δ position from the olefin moiety (Scheme 32, Eqs. a & b). Some side-isomerisation reactions occurred during the metathesis process leading to the formation of undesired products in very low amount (from 0 to 11%). Two side-products, one with a subtracted carbon, and the other with an additional carbon, in low amount, were identified as a result of a prior alkene isomerization during the CM

process.^{7,43} Worthy of note that this reaction did not tolerate the presence of substituents bearing an acidic hydrogen or the use of too crowded olefins.

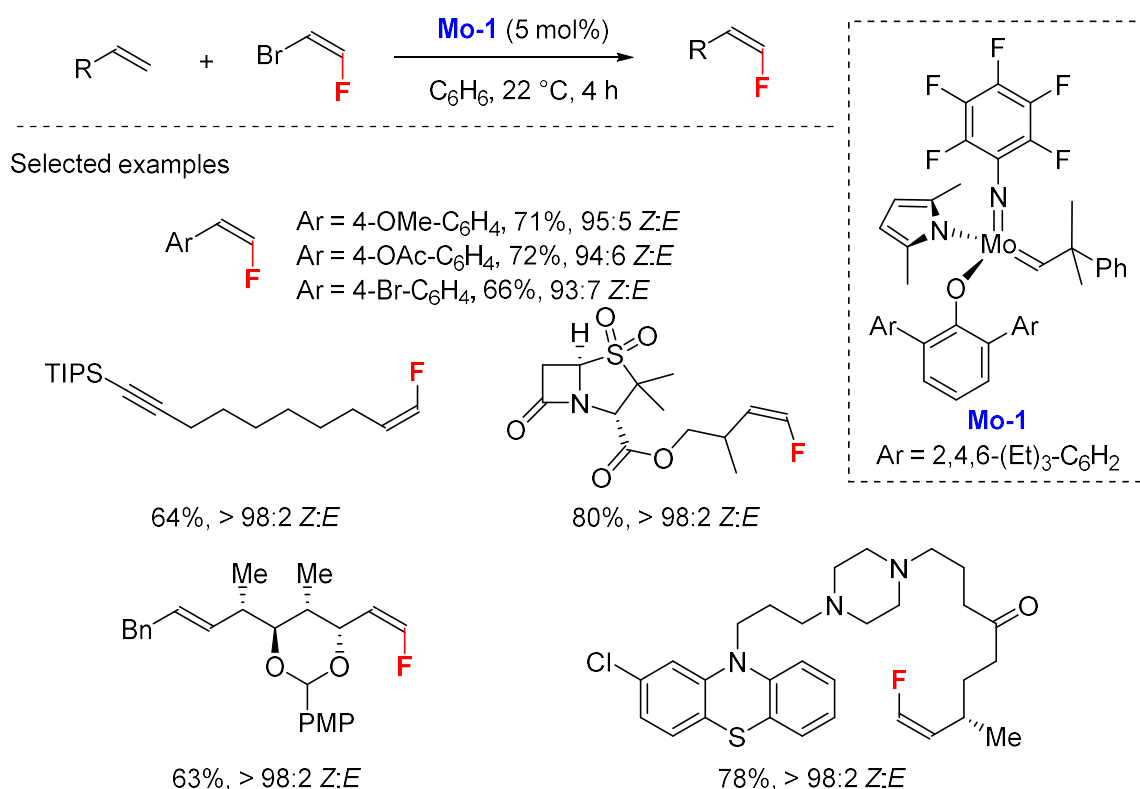


Scheme 32. Ruthenium-catalyzed CM reaction with 2-fluoroacrylate (^aRatio desired product:side isomerized products; TON up to 175).

We also showed that CM reaction of internal olefin with flexible tri-substituted fluoroalkene was possible, leading to the formation of the desired CM-product bearing the fluoroacrylate moiety, albeit in low yield (Scheme 32, Eq c). We suggested a model explaining the stereoselectivity of the reaction thanks to i) a less hindered approach of the fluoroalkene, ii) an electronically match between the metal and the β -carbon of the 2-fluoroacrylate and iii) the formation of a less hindered ruthenacyclobutane (Scheme 32, Eq d). Although this study represents the first access to tri-substituted fluoroalkenes by CM, it still suffers from limitations such as isomerisation issues or too much reluctant substrates. However, it showed that the appropriate choice of the suitable alkene partners allowed to develop efficient CM reaction under ruthenium catalysis.

B) Molybdenum-catalyzed Cross-Metathesis

In 2016, Hoveyda and co-workers reported a milestone with regards to the synthesis of the difficult to access *Z*-alkenyl halides using a well-designed Mo-catalyst.⁴⁴ Through this report, the authors overcome the intrinsic limitation of halo-substituted Ru-carbene, well-known to quickly decompose or to be catalytically inefficient (*vide supra*). As part of their study, the synthesis of *Z*-alkenyl fluorides was carried out using the easy-to-handle *Z*-bromo-2-fluoroethene (boiling point: 36 °C) as the fluorinated building block. The reaction was fully selective toward the formation of the *Z*-alkenyl fluoride (Scheme 33). Although restricted to terminal olefins, the reaction was applied to a large panel of substrates: styrenes, terminal alkyl-substituted alkenes and biorelevant molecules, with good to excellent yields and outstanding *Z*-selectivity.



Scheme 33. Mo-catalyzed synthesis of Z-fluoroalkenyl fluoride (TON up to 16).

The authors explained this complete selectivity thanks to the stronger π -donation and σ -withdrawing inductive effect of the fluorine atom, which favor its interaction with the Lewis acidic Mo center of the catalyst. In addition, the Z-selectivity was explained through the formation of low steric repulsion between the fluorine and the bromine atoms, which favor the formation of the transient all *cis*-metallocyclobutane, as the reaction intermediate (Figure 2).

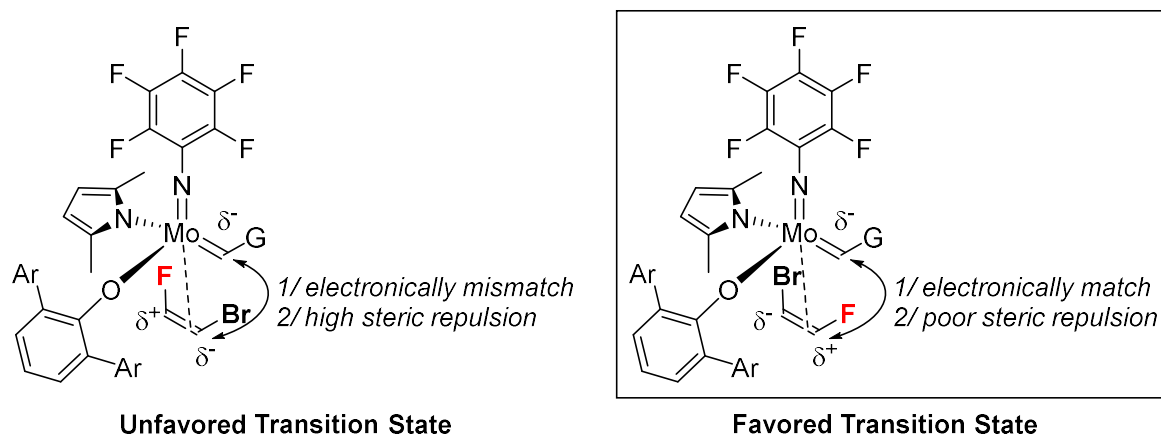
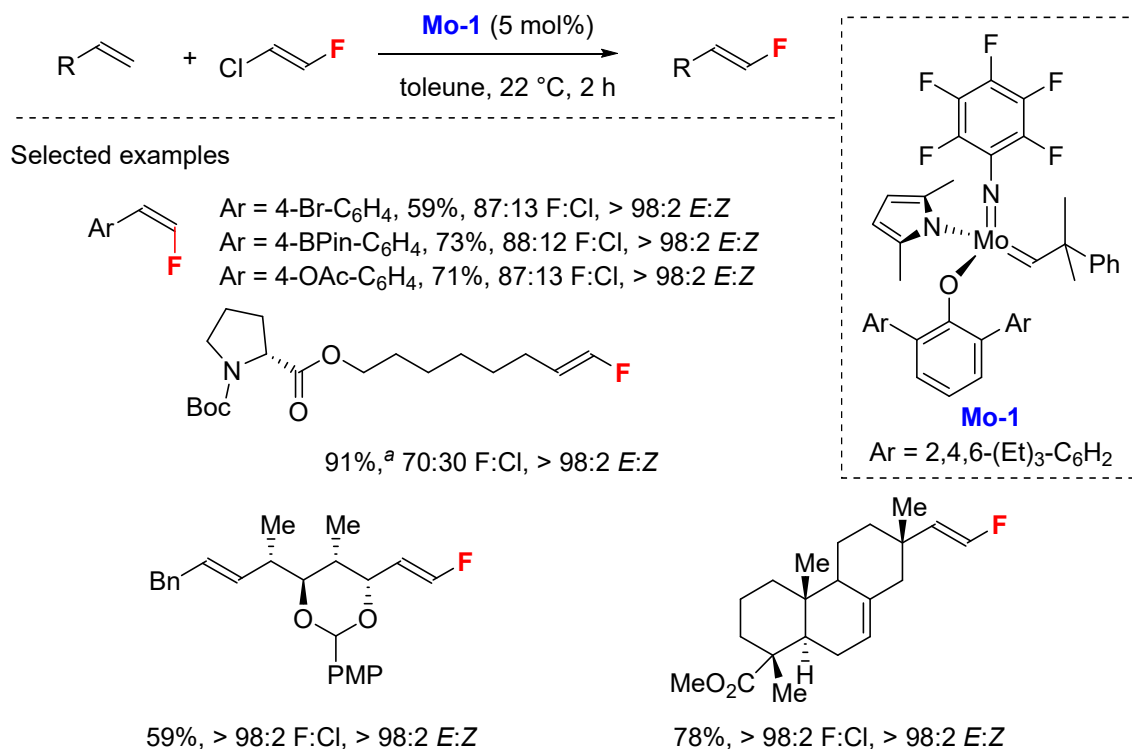


Figure 2. Explanation of the selectivity of the Mo-catalyzed synthesis of *Z*-fluoroalkenyl fluoride.
 Ar = 2,4,6-(Et)₃-C₆H₂.

Shortly after this study, Hoveyda and co-workers reported the *E*-selective metathesis reaction to access the *E*-alkenyl fluoride.⁴⁵ Using the same catalyst **Mo-1** and thanks to a simple change of the fluorinated building blocks, using the *Z*-1-bromo-2-fluoroethene instead of the *E*-1-chloro-2-fluoroethene (boiling point: -4 °C), the reaction was applied to a large panel of substrates including styrene derivatives, terminal alkyl-substituted alkenes and biorelevant molecules. The corresponding *E*-alkenyl fluorides were obtained in good to excellent yields, excellent selectivity in favor of the fluorinated olefin and outstanding *E*-selectivities (Scheme 34). Similarly to their previous report, this reaction remains restricted to terminal olefin, restricting the scope of the transformation and opening room for further improvements.



Scheme 34. *E*-selective synthesis of alkenyl fluoride using *E*-1-chloro-2-fluoroethene and **Mo-1** as the catalyst (TON up to 16.4).

In 2019, Hoveyda and co-workers reported an extension of these two protocols to the previously reluctant hydroxy- or carboxylic acid-containing molecules, using a traceless protection strategy.⁴⁶ Thanks to the astute *in situ* protection of the alcohol, phenol or carboxylic acid functions as boronates using the commercially available H-Bpin or H-B(trip)₂, prior to the metathesis event, a panel of four *Z*- and *E*-alkenyl fluorides was synthesized in good to excellent yields and a remarkable selectivity (Figure 3).

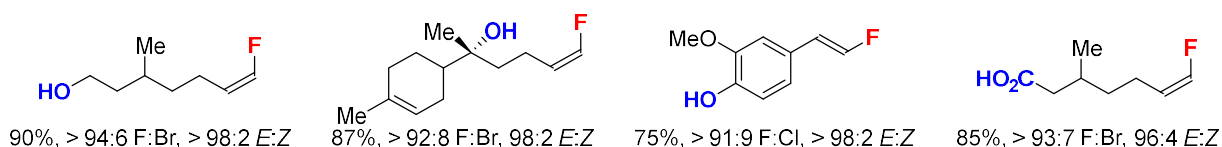


Figure 3. Alcohols and carboxylic acid derivatives synthesized thanks to the *in situ* protection protocol (TON up to 112.5).

Conclusion and Perspectives

This review reported the results obtained in metathesis of fluorinated alkenes since the first attempt twenty years ago. Obviously, two decades later, efficient metathesis reactions have been developed with reluctant fluoroalkenes, but still remains in its infancy. Indeed, the RCM reaction of fluoroalkenes has been studied by several authors and a lot of cyclic compounds of different size can be obtained. Nevertheless, the almost exclusive cycles bearing a fluoroalkene moiety formed are nitrogen-containing ones, with sporadic examples of carbocycles. The few examples of dienes linked by an oxygen moiety (ether or ester groups) remained reluctant, excepted some *ortho*-phenolic substrates. In light of the recent results in RCM reaction, fluoroalkenes are obviously not trivial substrates for RCM reaction. To date, RCM reaction of fluoroalkenes towards heterocycles containing heteroatom such as a sulfur, a phosphorous or a silicon... remained elusive and still have to be developed. Concerning the CM reaction of fluoroalkenes, results are scarcely reported in the literature and until very recently remained a poorly productive process. Pioneering work of Johnson led to interesting preliminary results of fluoroalkenes formation by CM reaction, albeit giving low yields. Indeed, the ruthenium-catalyzed CM of fluoroalkenes had to deal with the formation of a stable ruthenium-fluoromethylidene complex unable to initiate the reaction, hampering the catalyst activity. Takahira and Morizawa developed elegant strategy based on interconversion of Fischer-carbene between fluorinated alkenes and alkyl vinyl ether. Nevertheless, this work had a limited scope of reaction. More recently, Couve-Bonnaire and co-workers reported promising results of ruthenium-catalyzed CM reaction with the inexpensive and convenient-to-use methyl 2-fluoroacrylate, paving the way for further developments. The appropriate choice of substrates allowed the formation of CM products from terminal, cyclic and internal olefins with unprecedented turnover number with fluoroalkene (up to 175). The used

catalyst loading of 1 mol% might appear high compared to other metathesis reaction developed but it was the first time that such low catalyst loading has been used and high TON have been obtained with fluoroalkenes. This study highlighted the possibility to use the ruthenium in the efficient formation of fluoroalkenes. Nevertheless, sterically hindered substrates, as well as substrates bearing labile-hydrogen are unreactive in their experimental conditions, highlighting a limitation. During the process, some side-isomerization reaction occurred, implying the formation of undesired products in low proportion. The use of ruthenium precatalysts known to prevent isomerization could address this issue.⁴⁷ In front of the recent successes in various metathetic transformations gained by ruthenium complexes featuring cyclic (alkyl)(amino)carbenes (CAACs) as ancillary ligands, which lead to enhanced catalytic activities,⁴⁸ improved results are expected in metathesis of fluoroalkenes with this novel class of robust precatalysts. Improvements have also to be done with more constrained or acidic alkene partner. Hoveyda, Schrock and coworkers synthesized several molybdenum-catalyst, one of them leading to astonishing results in molybdenum-catalyzed CM reactions towards either the *E* or *Z* fluoroalkenes. Terminal fluoroalkenes have been obtained in high yields and remarkable selectivities. Nevertheless, these reactions only led to terminal disubstituted fluoroalkenes and required, most often, to work using glovebox conditions. The fluorinated reagents used, including the less practical to use gaseous *E*-1-chloro-2-fluoroethene, are also quite expensive. This molybdenum-catalyzed reaction can also be improved towards the formation of tri- or tetra-substituted fluoroalkenes.

Hence, taking into account this current state of the art regarding the metathesis reaction toward the formation of fluoroalkenes, there is still room for improvement and strategic developments. For instance, substrates scopes still have to be broaden to fulfill the synthetic utility criterion and will probably require the development of original catalysts. The intrinsic properties of the fluorine atom

and more specifically of fluorinated carbene to inhibit the catalyst efficiency is probably the main key feature to address to develop competent metathesis catalyst.

In conclusion, we hope that this review will inspire the community to address this current challenge and to reach significant milestones that will push the metathesis reaction with fluorinated alkenes at the forefront of the synthetic methods to build up complex and highly functionalized fluorinated alkenes.

AUTHOR INFORMATION

Corresponding Author

*samuel.couve-bonnaire@insa-rouen.fr

marc.mauduit@ensc-rennes.fr

Present Addresses

†If an author's address is different than the one given in the affiliation line, this information may be included here.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

Any additional relevant notes should be placed here.

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ABBREVIATIONS

CM cross-metathesis; RCM ring-closing metathesis; CEYM cross enyne metathesis ; ROMP ring opening metathesis polymerization; ADMET acyclic diene metathesis; MW microwave.

REFERENCES

1. (a) Hara, S. in *Stereoselective Alkene Synthesis*, (Ed.: Jianbo Wang), Springer Berlin Heidelberg, Berlin, Heidelberg, **2012**, pp 59-86. (b) Yanai, H.; Taguchi, T. Synthetic Methods for Fluorinated Olefins. *Eur. J. Org. Chem.* **2011**, 5939-5954. (c) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. Synthetic approaches to monofluoroalkenes. *Chem. Soc. Rev.* **2011**, *40*, 2867-2908. (d) Zhang, X.; Cao, S. Recent advances in the synthesis and C-F functionalization of gem-difluoroalkenes. *Tetrahedron Lett.* **2017**, *58*, 375-392. (e) Drouin, M.; Hamel, J.-D.; Paquin, J.-F. Synthesis of Monofluoroalkenes: A Leap Forward. *Synthesis* **2018**, *50*, 881-955. (f) van Steenis, J. H.; van der Gen, A. Synthesis of terminal monofluoro olefins. *J. Chem. Soc. Perkin 1* **2002**, 2117-2133.

2. See for example: (a) Asahina, Y.; Iwase, K.; Iinuma, F.; Hosaka, M.; Ishizaki, T. Synthesis and Antibacterial Activity of 1-(2-Fluorovinyl)-7-substituted-4-quinolone-3-carboxylic Acid Derivatives, Conformationally Restricted Analogues of Fleroxacin. *J. Med. Chem.* **2005**, *48*, 3194–3202. (b) Edmonson, S. D.; Wei, L.; Xu, J.; Shang, J.; Xu, S.; Pang, J.; Chaudhary, A.; Dean, D. C.; He, H.; Leiting, B.; Lyons, K. A.; Patel, R. A.; Patel, S. B.; Scapin, G.; Wu, J. K.; Beconi, M. G.; Thornberry, N. A.; Weber, A. E. Fluoroolefins as amide bond mimics in dipeptidyl peptidase IV inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2409–2413. (c) Alloatti, D.; Giannini, G.; Cabri, W.; Lustrati, I.; Marzi, M.; Ciacci, A.; Gallo, G.; Tinti, M. O.; Marcellini, M.; Riccioni, T.; Guglielmi, M. B.; Carminati, P.; Pisano, C. Synthesis and Biological Activity of Fluorinated Combretastatin Analogues. *J. Med. Chem.* **2008**, *51*, 2708–2721. (d) Oishi, H.; Kaminati, H.; Kodera, Y.; Watanabe, K.; Kobayashi, K.; Narumi, T.; Tomita, K.; Ohno, H.; Naito, T.; Kodama, E.; Matsuoka, M.; Fujii, N. Peptide bond mimicry by (*E*)-alkene and (*Z*)-fluoroalkene peptide isosteres: synthesis and bioevaluation of α -helical anti-HIV peptide analogues. *Org. Biomol. Chem.* **2009**, *7*, 2872–2877. (e) Osada, S.; Sano, S.; Ueyama, M.; Chuman, Y.; Kodama, H.; Sakaguchi, K. Fluoroalkene modification of mercaptoacetamide-based histone deacetylase inhibitors. *Bioorg. Med. Chem.* **2010**, *18*, 605–611. (f) Chang, W.; Mosley, R. T.; Bansal, S.; Keilman, M.; Lam, A. M.; Furman, P. A.; Otto, M. J.; Sofia, M. J. Inhibition of hepatitis C virus NS5A by fluoro-olefin based γ -turn mimetics. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2938–2942. (g) Nadon, J.-F.; Rochon, K.; Grastilleur, S.; Langlois, G.; Dao, T. T. H.; Blais, V.; Guérin, B.; Gendron, L.; Dory, Y. L. Synthesis of Gly- ψ [(*Z*)CF₂CH]-Phe, a Fluoroalkene Dipeptide Isostere, and Its Incorporation into a Leu-enkephalin Peptidomimetic. *ACS Chem. Neurosci.* **2017**, *8*, 40–49.

3. (a) *Handbook of Fluoropolymer Science and Technology*, Smith, D. W., Iacono, S. T., Iyer, S. S., Eds; John Wiley & Sons: Hoboken, NJ, 2014. (b) Ameduri, B. Fluoropolymers: The Right Material for the Right Applications. *Chem. Eur. J.* **2018**, *24*, 18830–18841.
4. (a) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I, Ed; Wiley – Blackwell, Chichester, 2009. (b) Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. Chiral dipeptide mimics possessing a fluoroolefin moiety: a relevant tool for conformational and medicinal studies. *Org. Biomol. Chem.* **2007**, *5*, 1151-1157.
5. Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822–5880.
6. (a) Lin, J.; Toscano, P. J.; Welch, J. T. Inhibition of dipeptidyl peptidase IV by fluoroolefin-containing N-peptidyl-O-hydroxylamine peptidomimetics. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 14020–14024. (b) Pierry, C.; Couve-Bonnaire, S.; Guilhaudis, L.; Neveu, C.; Marotte, A.; Lefranc, B.; Cahard, D.; Ségalas-Milazzo, I.; Leprince, J.; Pannecoucke, X. Fluorinated Pseudopeptide Analogues of the Neuropeptide 26RFa: Synthesis, Biological, and Structural Studies. *ChemBioChem* **2013**, *14*, 1620–1633. (c) Drouin, M.; Arenas, J. L.; Paquin, J.-F. Incorporating a Monofluoroalkene into the Backbones of Short Peptides: Evaluating the Impact on Local Hydrophobicity. *ChemBioChem* **2019**, *20*, 1817-1826.
7. (a) *Handbook of Metathesis*, 2nd ed.; Grubbs, R. H., Wenzel, A. G., Eds.; Wiley-VCH: Weinheim, Germany, 2015. (b) *Olefin Metathesis: Theory and Practice*; Grela, K., Ed.; John Wiley & Sons: Hoboken, NJ, 2014.
8. (a) Chauvin, Y. Olefin Metathesis: The Early Days (Nobel Lecture 2005). *Adv. Synth. Catal.* **2007**, *349*, 27–33. (b) Grubbs, R. H. Olefin-Metathesis Catalysts for the Preparation of

- Molecules and Materials (Nobel Lecture 2005). *Adv. Synth. Catal.* **2007**, *349*, 34–40. (c) Schrock, R. R. Multiple Metal–Carbon Bonds for Catalytic Metathesis Reactions (Nobel Lecture 2005). *Adv. Synth. Catal.* **2007**, *349*, 41–53.
9. Fustero, S.; Simón-Fuentes, A.; Barrio, P.; Haufe, G. Olefin Metathesis Reactions with Fluorinated Substrates, Catalysts, and Solvents. *Chem. Rev.* **2015**, *115*, 871–930.
 10. Trnka, T. M.; Day, M. W.; Grubbs, R. H. Olefin Metathesis with 1,1-Difluoroethylene. *Angew. Chem., Int. Ed.* **2001**, *40*, 3441–3444.
 11. Macnaughtan, M. L.; Johnson, M. J. A.; Kampf, J. W. Synthesis, Structure, and Olefin Metathesis Activity of Two Ruthenium Monofluoromethylidene Complexes. *Organometallics* **2007**, *26*, 780–782.
 12. (a). Fomine, S.; Ortega, J. V.; Tlenkopatchev, M. A. Metathesis of halogenated olefins A computational study of ruthenium alkylidene mediated reaction pathways. *J. Mol. Catal. A: Chem.* **2007**, *263*, 121–127. (b) Fomine, S.; Tlenkopatchev, M. A. Metathesis of fluorinated olefins by ruthenium alkylidene catalysts. Fluorine substituent effects on a Ru-carbene (alkylidene) complex stability: A computational study. *Appl. Catal., A* **2009**, *355*, 148–155.
 13. (a) Vasiliu, M.; Shenggang, L.; Arduengo, A. J., III; Dixon, D. Bond Energies in Models of the Schrock Metathesis Catalyst. *J. Phys. Chem. C* **2011**, *115*, 12106–12120 (b) Vasiliu, M.; Arduengo, A. J., III; Dixon, D. A. Role of Electronegative Substituents on the Bond Energies in the Grubbs Metathesis Catalysts for M = Fe, Ru, Os. *J. Phys. Chem. C* **2014**, *118*, 13563–13577.

14. Salim, S. S.; Bellingham, R. K.; Satcharoen, V.; Brown, R. C. D. Synthesis of Heterocyclic and Carbocyclic Fluoro-olefins by Ring-Closing Metathesis. *Org. Lett.* **2003**, *5*, 3403-3406.
15. Cadot, C.; Dalko, P. I.; Cossy, J. Olefin isomerization by a ruthenium carbenoid complex. Cleavage of allyl and homoallyl groups. *Tetrahedron Lett.* **2002**, *43*, 1839-1841.
16. Marhold, M.; Buer, A.; Hiemstra, H.; van Maarseveen, J. H.; Haufe, G. Synthesis of vinyl fluorides by ring-closing metathesis. *Tetrahedron Lett.* **2004**, *45*, 57-60.
17. De Matteis, V.; van Delft, F. L.; de Gelder, R.; Tiebes, J.; Rutjes, F. P. J. T. Fluorinated (hetero)cycles via ring-closing metathesis of fluoride- and trifluoromethyl-functionalized olefins *Tetrahedron Lett.* **2004**, *45*, 959-963.
18. De Matteis, V.; van Delft, F. L.; R.; Tiebes, J.; Rutjes, F. P. J. T. A Ring-Closing Metathesis Pathway to Fluorovinyl-Containing Nitrogen Heterocycles. *Eur. J. Org. Chem.* **2006**, 1166-1176.
19. De Matteis, V.; Dufay, O.; Waalboer, D. C. J.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T. An Improved Ring-Closing Metathesis Approach to Fluorinated and Trifluoromethylated Nitrogen Heterocycles. *Eur. J. Org. Chem.* **2007**, 2667-2675.
20. De Matteis, V.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T. RCM-Mediated Synthesis of Fluorinated Cyclic Hydrazines. *Synlett* **2008**, 351-354.
21. Marhold, M.; Stillig, C.; Fröhlich, R.; Haufe, G. Ring-Closing Metathesis of Vinyl Fluorides towards α -Fluorinated α,β -Unsaturated Lactams and Lactones. *Eur. J. Org. Chem.* **2014**, 5777-5785.

22. Maier, M. E. Synthesis of Medium-Sized Rings by the Ring-Closing Metathesis Reaction. *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077.
23. (a) Liddell, J. R. Pyrrolizidine alkaloids. *Nat. Prod. Rep.* **2002**, *19*, 773–781. (b) Michael, J. P. Indolizidine and quinolizidine alkaloids. *Nat. Prod. Rep.* **2008**, *25*, 139–165.
24. Guerin, D.; Gaumont, A.-C.; Dez, I.; Mauduit, M.; Couve-Bonnaire, S.; Pannecoucke, X. Access to Fluorinated Lactams through Ring-Closing Metathesis of Reluctant Fluoroalkenes Promoted by Appropriate Substitution of a Double Bond. *ACS Catal.* **2014**, *4*, 2374–2378.
25. (a) Samojłowicz, C.; Bieniek, M.; Zarecki, A.; Kadyrov, R.; Grela, K. The doping effect of fluorinated aromatic hydrocarbon solvents on the performance of common olefin metathesis catalysts: application in the preparation of biologically active compounds. *Chem. Commun.* **2008**, 6282–6284. (b) Samojłowicz, C.; Bieniek, M.; Pazio, A.; Makal, A.; Woźniak, K.; Poater, A.; Cavallo, L.; Wójcik, J.; Zdanowski, K.; Grela, K. The Doping Effect of Fluorinated Aromatic Solvents on the Rate of Ruthenium-Catalysed Olefin Metathesis. *Chem. Eur. J.* **2011**, *17*, 12981–12993. (c) Rost, D.; Porta, M.; Gessler, S.; Blechert, S. A hexafluorobenzene promoted ring-closing metathesis to form tetrasubstituted olefins. *Tetrahedron Lett.* **2008**, *49*, 5968–5971. (d) Grandbois, A.; Collins, S. K. Enantioselective Synthesis of [7]Helicene: Dramatic Effects of Olefin Additives and Aromatic Solvents in Asymmetric Olefin Metathesis. *Chem. Eur. J.* **2008**, *14*, 9323–9329.
26. Guerin, D.; Dez, I.; Gaumont, A.-C.; Pannecoucke, X.; Couve-Bonnaire, S. Access to Constrained Fluoropseudopeptides via Ring-Closing Metathesis of Fluoroalkenes. *Org. Lett.* **2016**, *18*, 3606–3609.

27. (a) Guarna, A.; Trabocchi, A. *Peptidomimetics in Organic and Medicinal Chemistry*; John Wiley & Sons, Ltd.: Chichester, 2014. (b) *Pseudo-Peptides in Drug Discovery*; Nielsen, P. E., Ed.; Wiley–VCH: Weinheim, 2004. (c) Avan, I.; Hall, C. D.; Katritzky, A. R. Peptidomimetics via modifications of amino acids and peptide bonds. *Chem. Soc. Rev.* **2014**, *43*, 3575-3594.
28. Guerin, D.; Dez, I.; Gaumont, A.-C.; Pannecoucke, X. ; Couve-Bonnaire, S. Ring-closing metathesis of fluoroalkenes toward the synthesis of fluorinated heterocycles containing an oxaza bond. *C. R. Chimie* **2018**, *21*, 740–748.
29. Okoromoba, O. E.; Han, J.; Hammond, G. B.; Xu, B. Designer HF-Based Fluorination Reagent: Highly Regioselective Synthesis of Fluoroalkenes and gem-Difluoromethylene Compounds from Alkynes *J. Am. Chem. Soc.* **2014**, *136*, 14381-14384.
30. Nihei, T.; Kubo, Y.; Ishihara, T.; Konno, T. Highly regioselective SN2' reaction of β -fluoroallylic phosphates with organocopper reagents and its application to the synthesis of fluorine-containing carbocycles. *J. Fluor. Chem.* **2014**, *167*, 110-121.
31. Cogswell, T. J.; Donald, C. S.; Long, D.-L.; Marquez, R. Short and efficient synthesis of fluorinated δ -lactams. *Org. Biomol. Chem.* **2015**, *13*, 717-.
32. Cogswell, T. J.; Donald, C. S.; Marquez, R. Flexible synthesis of polyfunctionalized 3-fluoropyrroles. *Org. Biomol. Chem.* **2016**, *14*, 183-190.
33. (a) Onda, H.; Toi, H.; Aoyama, Y.; Ogoshi, H. Fluoropyrroles and tetrafluoroporphyrins. *Tetrahedron Lett.* **1985**, *26*, 4221–4224. (b) De Laszlo, S. E.; Liverton, N. J.; Ponticello, G. S.; Selnick H. G.; Mantlo, N. B. 2,5-substituted aryl pyrroles, compositions containing such

- compounds and methods of use. US5837719A19981117, 1998. (c) Zhu, B.-Y.; Su, T. Li, W.; Goldman, E. A.; Zhang, P.; Jia, Z. J.; Scarborough, R. M. Piperazin-2-one amides as inhibitors of factor Xa. WO2002026734 A1 20020404, 2002.
34. Li, Y.; Li, K.; Wu, Y.; Ma, Q.; Lei, X. Facile synthesis of fluorovinyl-containing lactams via ring-closing metathesis of N-substituted 2-fluoroallylamides. *Tetrahedron* **2016**, *72*, 4845-4853.
35. Lázaro, R.; Román, R.; Sedgwick, D. M.; Haufe, G.; Barrio, P.; Fustero, S. Asymmetric Synthesis of Monofluorinated 1-Amino-1,2-dihydronaphthalene and 1,3-Amino Alcohol Derivatives. *Org. Lett.* **2016**, *18*, 948-951.
36. Heinrich, C. F.; Durand, D.; Starck, J.; Michelet, V. Ruthenium Metathesis: A Key Step To Access a New Cyclic Tetrasubstituted Olefin Platform. *Org. Lett.* **2020**, *22*, 7064-7067.
37. (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of fluorine in medicinal chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257-10274. (c) Brown, B. S.; Keddy, R.; Zheng, G. Z.; Schmidt, R. G.; Koenig, J. R.; McDonald, H. A.; Bianchi, B. R.; Honore, P.; Jarvis, M. J.; Surowy, C. S.; Polakowski, J. S.; Marsh, K. C.; Faltynek, C. R.; Lee, C. H. Tetrahydropyridine-4-carboxamides as novel, potent transient receptor potential vanilloid 1 (TRPV1) antagonists. *Bioorg. Med. Chem.* **2008**, *16*, 8516-8525.

38. Macnaughtan, M. L.; Gary, J. B.; Gerlach, D. L.; Johnson, M. J. A.; Kampf, J. W. Cross-Metathesis of Vinyl Halides. Scope and Limitations of Ruthenium-Based Catalysts. *Organometallics* **2009**, *28*, 2880–2887.
39. Takahira, Y.; Morizawa, Y. Ruthenium-Catalyzed Olefin Cross-Metathesis with Tetrafluoroethylene and Analogous Fluoroolefins. *J. Am. Chem. Soc.* **2015**, *137*, 7031–7034.
40. Louie, J.; Grubbs, R. H. Metathesis of Electron-Rich Olefins: Structure and Reactivity of Electron-Rich Carbene Complexes. *Organometallics* **2002**, *21*, 2153–2164.
41. Nouaille, A.; Pannecoucke, X.; Poisson, T.; Couve-Bonnaire, S. Access to trisubstituted fluoroalkenes by ruthenium-catalyzed cross-metathesis. *Adv. Synth. Catal.* **2021**, *363*, 2140–2147.
42. Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
43. (a) Hong, S. H.; Day, M. W.; Grubbs, R. H. Decomposition of a Key Intermediate in Ruthenium-Catalyzed Olefin Metathesis Reactions. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415. (b) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. Decomposition of Ruthenium Olefin Metathesis Catalysts. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968. (c) Herbert, M. B.; Lan, Y.; Keitz, B. K.; Liu, P.; Endo, K.; Day, M. W.; Houk, K. N.; Grubbs, R. H. Decomposition Pathways of Z-Selective Ruthenium Metathesis Catalysts. *J. Am. Chem. Soc.* **2012**, *134*, 7861–7866. (d) I. W. Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. Searching for the Hidden Hydrides: The Competition between Alkene Isomerization and Metathesis with Grubbs Catalysts. *Eur. J. Org. Chem.* **2012**, 5673–5677.

44. Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. Direct synthesis of Z-alkenyl halides through catalytic cross-metathesis. *Nature* **2016**, *531*, 459–465.
45. Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. Kinetically controlled E-selective catalytic olefin metathesis. *Science* **2016**, *352*, 569–575.
46. Mu, Y.; Nguyen, T. T.; Van der Mei, F. W. Schrock, R. R.; Hoveyda, A. H. Traceless protection for more broadly applicable olefin metathesis. *Angew. Chem. Int. Ed.* **2019**, *58*, 5365-5370.
47. For a review, see: (a) V. Paradiso, V.; C. Costabile, C.; F. Grisi, F. Ruthenium-based olefin metathesis catalysts with monodentate unsymmetrical NHC ligands. *Beilstein J. Org. Chem.* **2018**, *14*, 3122-3149. See also : (b) M. Rouen, M.; P. Queval, P.; E. Borré, E.; L. Falivene, L.; A. Poater, A.; M. Berthod, M.; F. Hugues, F.; L. Cavallo, L.; O. Baslé, O.; H. Olivier-Bourbigou, H.; M. Mauduit, M. Selective Metathesis of α -Olefins from Bio-Sourced Fischer–Tropsch Feeds. *ACS Catal.* **2016**, *6*, 7970-7976. (c) T. Nienałowski, T.; P. Szczepanik, P.; P. Małeck, P.; i, D. Czajkowska-Szczykowska, D.; S. Czarnocki, S.; J. Pawłowska, J.; A. Kajetanowicz, A.; Grela, K.. Large-Scale Synthesis of a Niche Olefin Metathesis Catalyst Bearing an Unsymmetrical N-Heterocyclic Carbene (NHC) Ligand and its Application in a Green Pharmaceutical Context. *Chem. Eur. J.* **2020**, *26*, 15708-15717.
48. For a review, see: Morvan, J.; Mauduit, M.; Bertrand, G.; Jazzar, R. Cyclic (Alkyl)(amino)carbenes (CAACs) in Ruthenium Olefin Metathesis. *ACS Catal.* **2021**, *11*, 1714-1748.

TOC Scheme:

